DESIGN AND SYNTHESIS OF 4-(HYDROXY-(1*H*-1,2,3-TRIAZOL-4-YL))METHYL PHENOL DERIVATIVES AS ANTITUBERCULOSIS AGENTS

By
Miss Ei Ei THIN

A Thesis Submitted in Partial Fulfillment of the Requirements
for Doctor of Philosophy (PHARMACEUTICAL SCIENCES)
Graduate School, Silpakorn University
Academic Year 2019

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MissEi Ei THIN

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MISS EI EI THIN : DESIGN AND SYNTHESIS OF 4-(HYDROXY-(1*H*-1,2,3-TRIAZOL-4-YL))METHYL PHENOL DERIVATIVES AS ANTITUBERCULOSIS AGENTS THESIS ADVISOR : ASSISTANT PROFESSOR SATHIT NIRATISAI, Ph.D.

The design and synthesis of 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives (compounds 7a-m, 8) were developed and evaluated for their antituberculosis activities. The design strategy was based on combination of scaffold structures of the chemical compound from *Alpinia galangal* rhizome possessed anti-tubercular activity, 1′-Acetoxychavicol acetate (ACA) and 1,2,3-triazole derivatives to get the target compounds. Compounds 7a-m, 8 were synthesized in 4 steps i.e. (1) The protection of hydroxyl group of 4-hydroxybenzaldehyde with *t*-butyldimethylsilyl group, (2) Grignard reaction between protected hydroxybenzaldehyde and ethynyl magnesium bromide to get protected hydroxypropynyl phenol, (3) click reactions between the alkynes and various aryl, aralkyl, and alkyl azides in mild condition with the aid of copper (I) catalyst, and (4) deprotections of the hydroxyl groups. The click reactions were performed not only under conventional way at room temperature but also the microwave irradiation condition to accelerate the chemical reactions. A one-pot two-step synthesis of these compounds under microwave irradiation has also performed by (1) microwave-assisted synthesis involved *in situ* generating of corresponding azides without purification to avoid explosive nature of azide extraction procedure, and (2) coupling reactions with terminal alkyne to generate 1,2,3-triazole derivatives, 6g-m. In the one-pot two-step procedure, the percent yields from microwave-assisted reactions of all azides, 5g-m were ranged from 82.54% to 96.18%. This method provided the comparable percent yields with conventional method. In addition to one-pot two-step, all microwave-assisted reactions offered better yields of the desired products 6a-m within short period of time (5 to 15 min) than conventional method at room temperature for overnight. Therefore, it was concluded that microwave-assisted click reaction synthesis strategy is simple, practical, efficient, safe, eco-friendly, and provided the newly synthesized compounds in a short reaction time with good yields when compared with conventional one. The overall yields of compounds 7a-m ranged from 25.99% to 48.73% and compound 8 was obtained as 27.33% overall yield. The structures of desired compounds were elucidated by FT IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic methods. Those synthesized compounds 7a-m and 8 were evaluated for antituberculosis activities by agar-dilution method and it was found that they possessed lower activities than control drug kanamycin. The MIC values of compounds 7a-m displayed 80 µg/mL when compared with kanamycin with MIC value 10 µg/mL on 20 clinical isolates and MTB H37Rv reference strains (ATCC 27294).

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LIST OF ABBREVIATIONS

ACA	acetoxychavicol acetate
AIDS	acquired immunodeficiency syndrome
cm^{-1}	per centimeter
cLog*P*	calculated logarithm of partition coefficient between *n*-octanol and water
^{13}C NMR	carbon nuclear magnetic resonance
CuAAC	copper-catalyzed azide-alkyne cycloaddition
d	doublet
dd	doublet of doublet
δ	chemical shift
decompn	decomposition
DMSO	dimethyl sulfoxide
DCC	dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)-pyridine
DR-TB	drug-resistant TB
EtOAc	ethyl acetate
equiv	equivalent(s)
FT IR	Fourier transform infrared
g	gram
h	hour(s)
HCl	hydrochloric acid
Hex	*n*-hexane
^{1}H NMR	proton nuclear magnetic resonance
HIV	human immunodeficiency virus
Hz	hertz
HRMS	high resolution mass spectrometry
HOMO	highest occupied molecular orbital
J	coupling constant
KBr	potassium bromide

LIST OF ABBREVIATIONS (conti.)

LUMO	lowest unoccupied molecular orbital
Mtb	Mycobacterium tuberculosis
mp	melting point
m	multiplet
mg	milligram
min	minute(s)
mL	milliliter
mmol	millimole
m/z	mass to charge ratio
MAOS	microwave-assisted organic synthesis
MIC	minimum inhibitory concentration
MDR-TB	multidrug-resistant TB
q	quartet
quint	quintet
rt	room temperature
RR-TB	rifampicin-resistant TB
s	singlet
sext	sextet
st.	stretching
t	triplet
tt	triplet of triplet
TBAF	*tetra-n*-butylammonium fluoride
TBS-Cl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TB	tuberculosis

LIST OF ABBREVIATIONS (conti.)

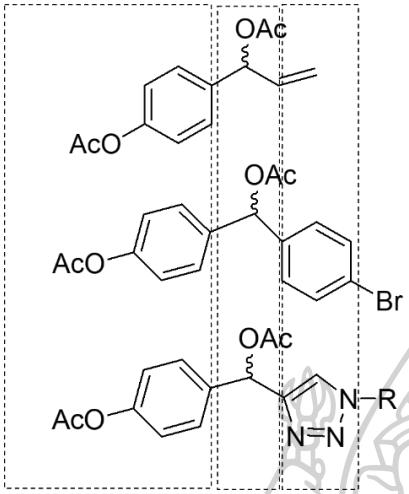
TDR-TB	totally drug-resistant TB
µM	micromolarity
µg/mL	microgram per milliliter
UV	ultraviolet
XDR-TB	extensively drug-resistant TB

CHAPTER I
INTRODUCTION

Tuberculosis (TB) is one of the top ten causes of death all over the world and still standing as a major global health problem (1). The latent TB was notified in one-quarter of the world's population. Since 1940s, chemotherapy was started to combat TB, however, drugs for treatment of TB do not completely effective in order to achieve radical cure. The occurrence of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), totally drug-resistant TB (TDR-TB) and co-infection with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are more complicated to combat this disease. Until 50 years, there are handful of drugs in clinical trial for tuberculosis treatment. For that reason, it is still necessary to develop new structural classes of anti-tubercular agents for efficient TB treatment. Those new chemical entities should be able to unique and divergent chemical structures, synthesize easily, shorten the duration of treatment, avoid drug-drug interactions with current regimens, efficacious against MDR-TB and XDR-TB and preferably operate via a new mode of action (2).

1′-Acetoxychavicol acetate (ACA) is a chemical constituent of *Alpinia galangal* rhizome and possesses anti-tuberculosis activity (3). A literature survey described that not only acetoxychavicol acetate but also 1,4-disubstituted-1,2,3-triazole compounds possess against tuberculosis with promising minimum inhibitory concentration (MIC) values on *Mycobacterium.tuberculosis (Mtb)* strains (4). This fact highlights for developing new chemical compounds which containing both of these structural fragments. ACA is still needed to modify its physicochemical properties and reduce toxicity as anti-tuberculosis agent. However, only a few literature on ACA based analogs synthesis have been reported. One attempt has been found that phenyl group was substituted in place of vinyl group of ACA in order to increase solubility without affecting the desirable biological activity of that compound (5). Therefore, it draws more attention to search novel for ACA analogs and the drug design study began to investigate the replacement effect of the phenyl on ACA with 1*H*-1,2,3-triazole as

shown in Figure 1. Proposed scaffold is one unit of compound but two different active units; ACA and 1-*H*-1,2,3-triazole.



1′-Acetoxychavicol acetate (ACA)

Bromobenzhydrol diacetate

Proposed 1,4-disubstituted-1,2,3 triazole derivatives

Figure 1. Design strategy used for 1,4-disubstituted 1,2,3-triazole derivatives.

A large number of 1,4-disubstituted-1,2,3-triazole derivatives are being synthesized and investigated by means of various *in vivo* and *in vitro* tests for anti-tubercular activity because scientific research publications mentioned that 1,2,3-triazole can be a good pharmacophore due to its aromatic character and nature of hydrogen bond donor and acceptor that can contribute as intermolecular interactions with different binding sites of biological targets (6). Besides, mechanism of actions of those promising compounds containing 1,2,3-triazole nucleus have also been extensively researched and it is still standing as a challenging task.

According to previous scientific findings, with the hope of promising anti-TB activities of ACA and 1,2,3-triazole, various chemical compounds those containing ACA fragment joined at 4 position of 1,2,3-triazole were synthesized conventionally and microwave-assisted methods. Various types of substituents such as phenyl ring, electron withdrawing such as fluorine and electron donating groups at the para position of aromatic ring, carbon units to extend the length between triazole and phenyl ring, various change length of aliphatic groups and alicylic structure were inserted at N-1 position of 1,2,3-triazole ring (Figure 2).

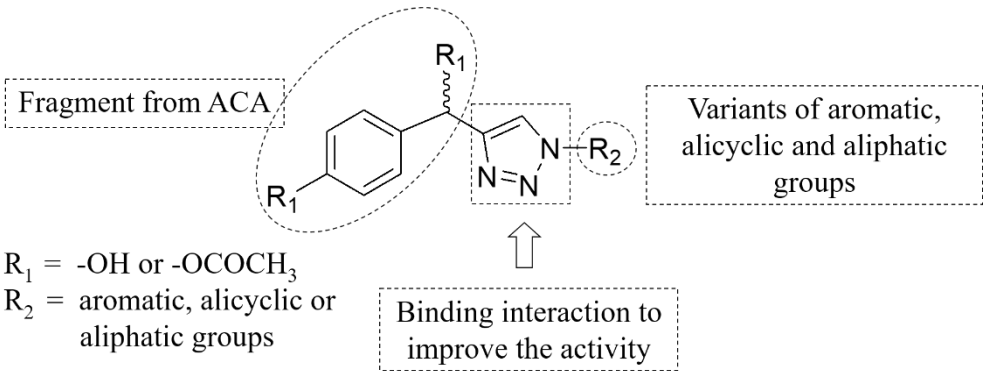


Figure 2. Design of 1,4-disubstituted 1,2,3-triazole derivatives.

All synthesized compounds were investigated for their MIC values by agar dilution method as pharmacodynamics measurement in compare with control drug against *Mtb* strains. To the best of knowledge, there is no synthesized structure that mimic ACA joining with 1,2,3-triazole as anti-tuberculosis agent to combat this deadly disease. From structure activity relationship study, nature and possible structural characteristics of binding sites for eliciting anti-tubercular activity were predicted because binding site exhibit chemical specificity complementary to ligands by means of intermolecular interactions.

CHAPTER II
LITERATURE REVIEW

2.1 Tuberculosis

TB is a deadly infectious disease caused by the bacillus *Mycobacterium tuberculosis* (*Mtb*) that affects the lung or other sites of the body. It is the ninth leading cause of worldwide death and ranking above HIV/AIDS. According to World Health Organization (WHO) 2018 report, it was found that 9.0 to 11.1 million people were infected with TB. Among TB infected people, 5.8 million people were accounted for men, 3.2 million and 1.0 million people were women and children. The new cases of TB were up to 6.4 million in 2017 from 6.1 million in 2015. In addition, an approximate 1.2 to 1.4 million mortalities caused by TB were documented in HIV-negative people and 300 000 deaths in HIV-positive people because TB was frequently co-infected with HIV/AIDS (1).

Drug-susceptible TB is curable by standard four-drug regimen for six months. However, the management of TB is still a challenging task because of the emergence of drug resistance strains. Drug-resistant in TB treatment was recognized by Pyle in 1947 in which mortality rate of streptomycin therapy and untreated patient was similar (7). In the early 1990s, multidrug-resistant TB (MDR-TB), TB caused by strains resistant to at least isoniazid and rifampicin, incidence in the United States drew attention as a catastrophic challenge to effective TB treatment. In 2017, WHO reported that there were 558 000 people with resistance to the most active first line drug rifampicin (RR-TB) in which 82% cases were MDR-TB (1). Extensively drug-resistant (XDR) tuberculosis is defined as a MDR-TB plus additional resistance to any fluoroquinolone and to ≥1 injectable second-line drugs (capreomycin, kanamycin, or amikacin). Fluoroquinolone-resistant or second-line injectable drug-resistant MDR-TB is known as pre-XDR-TB. The term totally drug-resistant (TDR) TB is used to define first-line and second-line drugs resistant TB and extremely drug-resistance (XXDR) TB is TDR-TB with additional drugs resistant such as rifabutin, clofazimine, dapsone, clarithromycin and thiacetazon. The selection of the term is dependent on the severity of resistance (8, 9). In 2017, RR-TB was 558 000 in TB patients and globally,

MDR/RR-TB was notified in 3.5% of new TB cases and 18% of formerly treated cases. Furthermore, 8.5% of MDR-TB was estimated as XDR-TB (1). The major causes of MDR-TB include the individual or operational sub-optimal management in susceptible TB patients. In addition, conflicting and lacking suitable resources and programmatic failures also facilitate the occurrence of resistance (10).

2.2 Treatment guidelines for drug susceptible and drug resistance TB

Guideline for treating drug-susceptible TB patients is either a 6-month regimen in which 2-month of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4-month of isoniazid and rifampicin or 8-month regimen of including 2-month of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 6-month of isoniazid and ethambutol.

According to the WHO guideline, drug regimens for patients with RR-TB or MDR-TB include at least five effective TB medicines from four groups of anti-TB drugs A to D. One drug must be selected from each group except from group D in which two drugs is needed to be chosen. Group A: Levofloxacin, Moxifloxacin, Gatifloxacin. Group B: Amikacin, Capreomycin, Kanamycin, Streptomycin. Group C: Ethionamide, Prothionamide, Cycloserine, Terizidone, Linezolid, Clofazimine. Group D. Add-on agents. D1: Pyrazinamide, Ethambutol, High-dose isoniazid. D2: Bedaquiline, Delamanid. D3: *p*-Aminosalicylic acid, Imipenem-cilastatin, Amoxicillin clavulanate, Thioacetazon. In addition, the new guidelines for MDR/RR-TB treatment described that levofloxacin or moxifloxacin, bedaquiline, linezolid, clofazimine, cycloserine or terizidone, ethambutol, delamanid, pyrazinamide may be included for longer regimens, however, clavulanic acid should not be included (11-13).

2.3 Development of anti-tuberculosis drugs

It is hard to believe that tuberculosis has been haunted to human beings for thousands of years and drug discovery for anti-TB drug is still challenging. Chemotherapy for TB was started from using natural product streptomycin in 1944. Then, discovery of alternative synthetic compounds isoniazid and pyrazinamide were developed in the early 1950s and followed by ethambutol and rifampicin in 1961 and

1963 (14, 15). Then, there were not new anti-tubercular drug development after approval of rifampicin in 1967 until bedaquiline was introduced as anti-tubercular drug in 2012. There was a 40-year gap for drug discovery of novel compounds for the treatment of this disease. Despite the recent advances in searching for new anti-TB compounds, TB is considered as a priority disease for the discovery and development of novels safe compounds because MDR and XDR strains is emerging at a fast rate, it is the synergistic of HIV pandemic, pharmacokinetic interaction between anti-TB and anti-retroviral drugs, complexing regimens for MDR-TB, longer treatment duration, relapse, occurrence of toxic side effects, co-morbidity with non-communicable diseases and the number of patients with untreatable TB is also increasing (16).

First approach to find promising anti-tubercular compounds is screening of synthetic small molecule libraries. An adenosine triphosphate (ATP)-synthase inhibitor, bedaquiline and delaminid affected on mycolic acid synthesis are two Food and Drug Administration (FDA)-approved drugs emerging from this approach. However, there are few number of druggable targets, similar resistance-associated mutation from diverse chemical hits, forming bias in the *in vitro* screening process and failure *in vivo* situation preclude the usefulness of promising compounds. Host cell-based anti-tubercular drug discovery is one of the alternative novel based screening methods that can overcome these limitation mention above. In this approach, drugs are tested on *Mtb* in mammalian host cell, therefore, condition is much similar with real antibiotic treatment. Drug in phase I clinical trials, Q203 is the outcome of this intracellular drug screening method using *Mtb* infected RAW 246.7 macrophages. One of the anti-TB project is finding previously published *in vivo* data available compounds with poor absorption, distribution, metabolism and excretion (ADME) profile. Then, computational models and *in vitro* testing will be applied to fix the flaw, increase solubility and metabolic stability of those compounds (15).

In addition, higher quality leads with unique mechanism of action are also obtained by means of repurposing, antimicrobial drugs that are not used to treat TB and rekindling, neglected antibiotics whose development was not track, approach from small natural product libraries containing diverse chemical structures, for example spectinomycin (17). The Medical Research Council Trials Unit started the first trials

for tuberculosis in 1948 and compared with streptomycin. According to the global TB drug pipeline 2017, there are eight drugs in phase II and III clinical trials. Delamanid and Betaquiline are in phase III clinical trial for MDR-TB and sutezolid and pretomanid are also new anti-TB compounds in phase II trial. The repurposed drug clofazimine previously used for leprosy was evaluated for MDR-TB with standardized regimen and it was found that relapse-free cure of approximate 90% and less than 1% failure in Bangladesh patients. Carbapenem was proposed for the treatment of patients in MDR-TB and XDR-TB. According to the *in vitro* susceptibility, other repurposed drugs studying for anti-tubercular activity are mefloquine, phenothiazine, metronidazole, doxycycline, disulfiram, tigecycline and co-trimoxazole. Repurposed drugs have been used for drug resistance tuberculosis in the interim period before development of new drug and universal regimen (10, 18, 19).

As first and foremost, new drugs required to fight TB must possess bactericidal activity on both drug susceptible and drug resistant *Mtb* strains and effective in real world situation. Generally, novel and safe anti-TB agents are designed to achieve shorten treatment duration, new mechanisms of actions against drug resistance strains, be efficacious against MDR-TB and XDR-TB and avoid problematic drug-drug interactions with current regimens and minimize toxic side effect. In addition, new anti-TB drugs must be oral-only regimens in adults, children, HIV patients and in term of posology, it is needed to once daily or less frequently in order to be well-tolerated for treatment course. The next challenge is to be cost competitive with current drugs. In 1999, the estimated cost for getting new anti-TB drug in the market was about 650 dollars and affordability of medicines in the countries is one of the major concerns in drug development (10, 20, 21).

According to the database of drugs for tuberculosis, there are 40 drugs in which 28 drugs have been approved and 12 drugs are candidate in different phases of drug discovery and development process. Among 40 drugs, targets of 33 drugs have been known and biological process for the rest 7 drugs were completely or partially known (22). The chemical class, mechanism of action, MIC and stage of chemical development are shown in Table 1 (22, 23). Identification and validation of novel targets in *Mtb*, the target-to-drug and drug-to-target approaches are primarily used (24, 25). There are four

major drugs targets responsible for vital biological functions of *Mtb* and those targets include cell wall synthesis, information pathway (DNA replication, transcription or translation), oxidative phosphorylation and folic acid synthesis (22). The new anti-tubercuosis agents are targeting mycolic acid biosynthesis, peptidoglycan biosynthesis or arabinogalactan biosynthesis, amino acid biosynthesis, cofactor biosynthesis, mycothiol biosynthesis, terpenoid biosynthesis, menaquinone biosynthesis, ATP biosynthesis, the glyoxylate shunt, regulatory proteins and the stringent response enzyme (26). Some approaches are being applied in order to search drugs and targets to fight TB. The whole-genome sequencing after isolation of resistant mutants is an example of finding target approach for bedaquiline. Transcriptional profiling before and after drug exposure and proteomics and metabolomics are also valuable tactics for revealing or validating drug targets in mycobacteria (15). Nowadays, novel drug discovery to fight TB drugs is improved by rapid advancement in the field of genomics, bioinformatics, computer-aided drug design and high-throughput screening and biochemical assays (27).

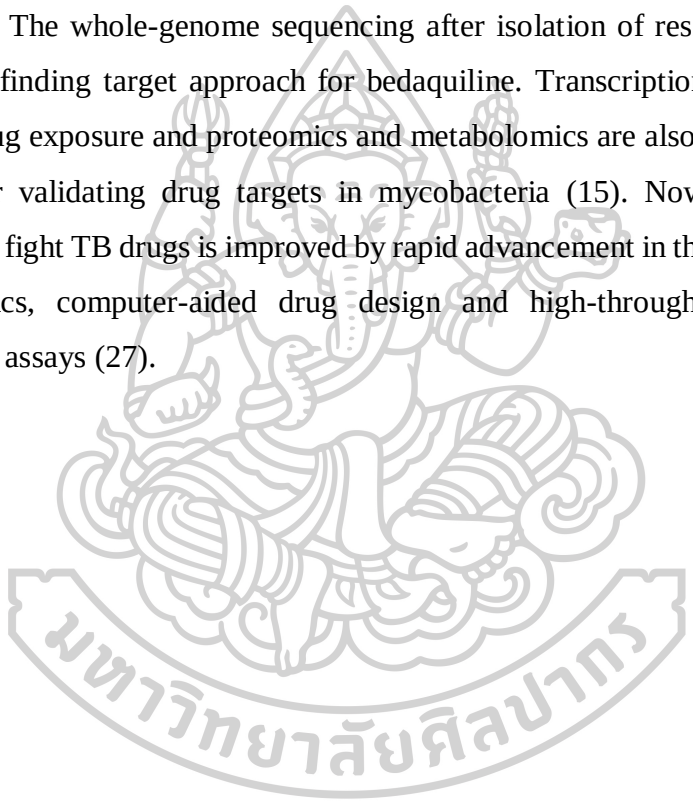


Table 1. Anti-TB drugs.

No.	Drug	Chemical class	Mechanism of action	MIC (µg/mL)	Stage of clinical development	Reference
1	Isoniazid	Isonicotinic acid derivative	Inhibits cell wall mycolic acid biosynthesis	0.02-020	Developed as first-line drug	(10)
2	Rifampicin	Amide	Inhibits of RNA synthesis	0.05-0.50	Developed as first-line drug	(10)
3	Pyrazinamide	Niacinamide derivative	Depletion of membrane energy	10.0-100.0 (in acid pH 5.5 or 6)	Developed as first-line drug	(10)
4	Ethambutol	Ethylenediamine	Inhibits cell-wall arabinogalactan synthesis	1.0-5.0	Developed as first-line drug	(10)
5	Streptomycin	An amino-glycoside	Inhibits protein synthesis	1.0-8.0	Developed as first-line drug	(10)
6	Kanamycin	An amino-glycoside	Inhibits protein synthesis	1.0-4.0	Developed to treat MDR-TB	(10)
7	Amicacin	Semi-synthetic aminoglycoside	Inhibits protein synthesis	1.0-4.0	Developed as second-line drug	(10)
8	Capreomycin	Cyclic peptide	Inhibits protein synthesis	2.0-4.0	Developed to treat MDR-TB	(10)

Table 1. Anti-TB drugs (continued).

No.	Drug	Chemical class	Mechanism of action	MIC (μg/mL)	Stage of clinical development	References
9	Levofloxacin	Fluroquinolone	Inhibits DNA replication and transcription	1	Developed to treat MDR-TB	(28)
10	Moxifloxacin	Fluroquinolone	Inhibits DNA replication and transcription	0.12-0.5	Developed to treat MDR-TB	(28)
11	Gatifloxacin	Fluroquinolone	Inhibits DNA replication and transcription	0.20-0.25	Developed to treat MDR-TB	(28)
12	Ofloxacin	Fluroquinolone	Inhibits DNA replication and transcription	1.0-2.0	Developed to treat MDR-TB	(28)
13	Ethionamide	Isonicotinic acid-derivative	Inhibits mycolic acid synthesis	2.5-10.0	Developed to treat MDR-TB	(10)
14	Prothionamide	Thioamide derivative	Disrupts cell wall biosynthesis	~ 0.5	Developed to treat MDR-TB	(29)
15	Para-amino salicylic acid	Salicylic acid	Inhibits folate biosynthesis	0.50-8.0	Developed to treat XDR-TB	(10)

Table 1. Anti-TB drugs (continued).

No.	Drug	Chemical class	Mechanism of action	MIC (µg/mL)	Stage of clinical development	References
16	D-cycloserine	Structural analogue of D-analine	Inhibits peptidoglycan biosynthesis in the cell wall	1.5-40.0	Developed to treat DR-TB	(10)
17	Terizidone	Structural analogue of cycloserine	Inhibits peptidoglycan biosynthesis in the cell wall	15-30	Used to treat MDR-TB and XDR-TB	(30)
18	Clofazimine	A lipophilic riminophena-zine antibiotic	Probably acts on membrane transport	0.01-0.25	Used to treat MDR-TB and XDR-TB	(10)
19	Rifabutin	A rifamycin class	Inhibits RNA synthesis	0.015 - 0.125	First-line anti-TB drug in HIV patients	(31)
20	Rifapentine	Cyclopentyl rifampicin	Inhibits RNA synthesis	0.06-0.5	Used with isoniazid to prevent TB in high risk subject	(32)
21	Bedaquiline	Diarylquinoline	Inhibits ATP synthesis	0.03-0.12	Used in the regimen of MDR-TB	(33)
22	Delamanid	Dihydro-nitroimidazo oxazole derivative	Probably inhibiting cell wall	0.006-0.024	Used in the regimen of MDR-TB	(34)

Table 1. Anti-TB drugs (continued).

No.	Drug	Chemical class	Mechanism of action	MIC (µg/mL)	Stage of clinical development	References
23	Linezolid	Oxazolidinone	Inhibits protein synthesis	0.06-1.0	Used to treat MDR-TB and XDR-TB	(35)
24	Amoxicillin and clavulanate	Beta lactam Carboxylic acid	Inhibits peptidoglycan biosynthesis	2-16	Used in the regimen of DR-TB	(36)
25	Imipenem and cilastatin	Beta lactam Carboxylic acid	Inhibits peptidoglycan biosynthesis	< 100 (imipenem)	Used in the regimen of DR-TB	(37)
26	Meropenem and clavulanate	Beta lactam Carboxylic acid	Inhibits peptidoglycan biosynthesis	0.125-2	Used to treat MDR-TB and XDR-TB	(38)
27	Thioacetazone	Thiosemi-carbazone	Inhibits cell wall synthesis	0.1	Used to treat DR-TB	(39)
28	Clarithromycin	Semisynthetic macrolide	Inhibits protein synthesis	4 - >16	Used to treat DR-TB	(40)
29	Pretomanid	Nitroimidazole	Probably inhibition of cell wall synthesis and causing respiratory poisoning	0.015-0.25	Phase III candidate	(34)
30	AZD-5847	Oxazolidinone	Inhibits protein synthesis	0.25–0.5	Phase II candidate	(41)
31	Sutezolid	Oxazolidinone	Inhibits protein synthesis	≤0.062	Phase II candidate	(42)

Table 1. Anti-TB drugs (continued)

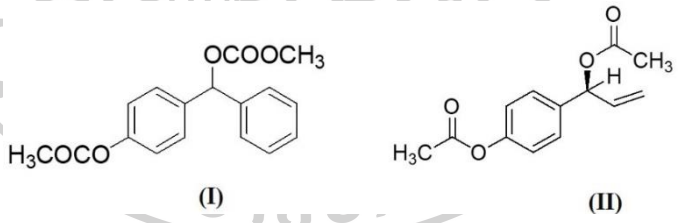
No.	Drug	Chemical class	Mechanism of action	MIC (μg/mL)	Stage of clinical development	References
32	SQ 109	1,2-ethylenediamine	Inhibits cell wall synthesis	0.7-1.56 (μM)	Phase II candidate	(43)
33	TBA-354	Pyridine-containing biaryl nitroimidazole	Inhibits cell wall synthesis and causing respiratory poisoning	0.011	Phase I candidate	(44)
34	CPZEN-45	Caprazamycin derivative (nucleoside antibiotic)	Inhibits cell wall biosynthesis	1.56	Preclinical candidate	(45)
35	DC-159a	Fluoquinolone	Acts on DNA replication and transcription	0.03-0.125	Preclinical candidate	(46)
36	Q203	Imidazopyridine amide	Oxidative phosphorylation	10 nM	Phase I candidate	(47)
37	SQ609	Dipiperidine	Inhibits cell wall biosynthesis	4	Preclinical candidate	(48)
38	SQ641	Carboxamide	Inhibits cell wall biosynthesis	1	Preclinical candidate	(48)
39	TBI-166	Riminophenazine	Acts on membrane transport	0.016	Preclinical candidate	(49)
40	PBTZ-169	Benzothiazine	Inhibits cell wall biosynthesis	0.3 ng/mL	Preclinical candidate	(50)

2.4 Acetyoxychavicol acetate

1′-S-1′-Acetoxychavicol acetate **(I)** is a chemical constituent of *Alpinia galanga* or *in Thai* "Khar". The chemical configuration of ACA from natural source was the *S*-form (51, 52). In contrast, there was no *R*-form in nature and synthetic ACA compound was found as racemic (53). In China and Thailand, it is widely used as food condiment due to its pungent, hot and spicy taste and in ethnomedicine. In the literature, ACA was reported to possess various biological activities (54) such as xanthine oxidase inhibitory activity, antitumor, anti-inflammatory, antiallergic, antioxidative, antifungal, antiHIV, and antituberculosis activities (3, 52, 55-60).

The protective effect of ACA against 4-nitroquinoline 1-oxide-induced oral carcinogenesis has proved by Koshimizu K et al. in male rats. Xanthine oxidase is oxygen radical-generating compounds responsible for tumor development and ACA was regarded as xanthine oxidase enzyme inhibitor (61). The dietary feeding of ACA during the initiation or post initiation phase caused to reduce cell proliferation with no clinical or morphological signs of toxicity. Although exact mechanism for chemopreventive action of ACA is not clear, this compound was predicted to inhibit the conversion step of 4-nitroquinoline 1-oxide to 4-hydroxyaminoquinoline 1-oxide (55). The cytotoxic and apoptotic-inducing activity of ACA from the extract of *A. galanga* fresh rhizomes was firstly reported by Quick and coworkers in 2013. It was observed that ACA promoted the caspase 3-activated glioblastoma cell death by overcoming enhanced cytokine expression and weakened migratory ability of glioblastoma cells by reducing their adhesive properties (56). Anti-inflammatory effect of ACA was investigated by Nagasaki et al. on contact dermatitis models of male mice. They used β-1,3-glucans as stabilization agent in order to improve the water solubility of less soluble compound, ACA. After detection of tumor necrosis factor alpha from plasma, it was concluded that ACA complex with β-1,3-glucans possess promising anti-inflammatory activity for the treatment of chronic dermatitis (60). Muraoka et al. synthesized and studied structure activity relationship on acetoxybenzhydrol. Active and stable analogues of 1′-S-1′-acetoxychavicol for type I antiallergic activity by testing the release of antigen-IgE-mediated degranulation in RBL-2H3 cells marker, β-hexosaminidase. Among benzhydrol analogues, it was observed that **compound I**

inhibited the release of β-hexosaminidase (IC_{50} 6.5 µM). The structural requirements of ACA for displaying activity have described that phenyl acetate moiety was important, substitution of vinyl group by phenyl **(compound II)** still possessed the activity and the chirality was not influential factor for eliciting the response (57). Masuda A. and coworkers reported the antioxidant activity of ACA and its related compounds such as 1′-hydroxychavicol acetate, *p*-acetoxy cinnamyl alcohol and *p*-ccoumaryl diacetate from *A. galanga* fresh rhizomes imported from Thailand. They heated rhizomes in aqueous medium or lard and antioxidant assay was investigated by ferric thiocyanate and thiobarbituric acid (TBA) method. It was found that even after cooking in aqueous medium or lard, ACA and its degraded compounds of *A. galanga* rhizomes still had significant antioxidant activity toward the auto-oxidation of linoleic acid (58). Scheffer J.J.C. and Janssen A.M. studied the antifungal activity of Alpinia galangal against different fungi and found that ACA was the antifungal compound as moderate potency with broad activity (59). Ye and Li reported that ACA isolated from *Alpinia galangal* inhibited HIV replication by blocking Rev HIV-1 regulatory protein transport process *in vitro* yeast model. In addition, it has synergic antiviral effect on currently used anti-HIV drugs (52).



(I) (II)

2.4.1 Anti-tuberculosis activity of ACA

Anti-tuberculosis activity of ACA was well investigated and reporte (3, 5, 62). In 2002, Palittapongarnpim et al. first patented ACA as anti-TB agent for preventive and tuberculosis treatment. Although mechanism for anti-tuberculosis activity is not clear, authors reported that MIC value of ACA against *M.tb* H37Ra (ATCC 25166) was 0.1 µgmL^{-1} and 0.6-1.6 µgmL^{-1} for H37Rv strains on 30 in clinical isolates (3, 63). In contrast, MIC of synthetic racemic L-and D-form of ACA against with *M.tb* H37Ra and *M.tb* H37Rv strains were 0.4 and 2.7 µgmL^{-1}. It was also tested for toxicity and the

concentration levels were 7-8.5 μgmL^{-1} (L929, mouse lung cells and BHK 21, Hamster kidney cell) and 2-3.4 μgmL^{-1} on HepG2 (human liver cell). According to the toxicity testing, natural extract of ACA on Vero cells (African green monkey kidney cell line from American Type Culture collection USA) was 2.0 μgmL^{-1} which was 20 time higher than its MIC value of ACA from natural sources, however, it is close with MIC value from synthetic ACA and alarms side effects of this compound (3, 63).

In the development of ACA as anti-tuberculosis agent, there are some limitations for clinical applications. ACA was not stable in aqueous medium and can easily be hydrolyzed into 1′-hydroxy chavicol acetate, *p*-coumaryl diacetate and *p*-acetoxy cinnamic alcohol (Figure 3). It can also be postulated that ACA is metabolically unstable compound. Palittapongarnpim et al. also tested the enantiopure and racemic form of acetoxychavicol acetate against drug susceptible and drug resistant clinical isolates. According to the MIC values, it was observed that *S*-form was more potent than racemic form and it was responsible for potent antiTB activity (64).

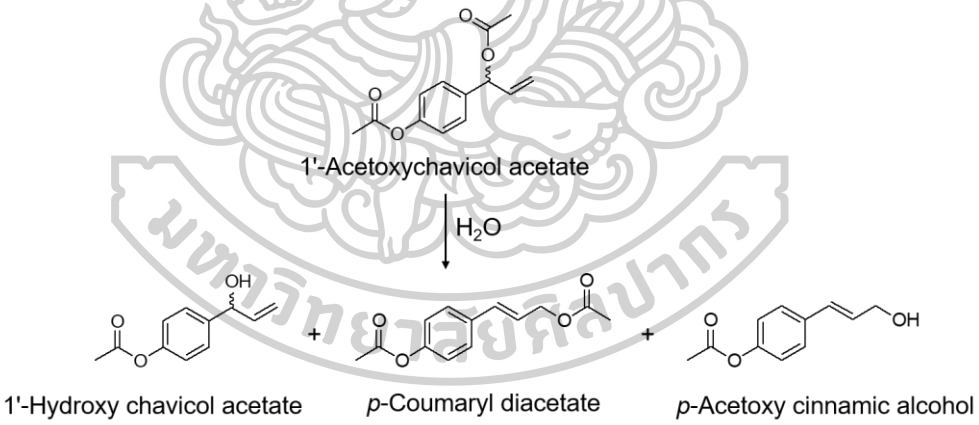


Figure 3. Hydrolysis of 1′-Actetoxychavicol acetate.

As hydrolysis products, *p*-acetoxycinnamic alcohol is resulted from S_N1 reaction mechanism of ACA and formation of *p*-coumaryl diacetate is derived from isomerization by [3,3]-sigmatropic rearrangement (Figure 4) (65). In addition, ACA has poor solubility in water (0.12 mgmL^{-1}).

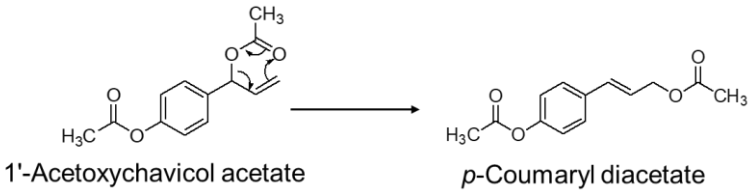
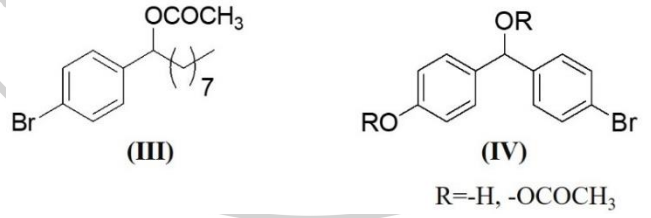
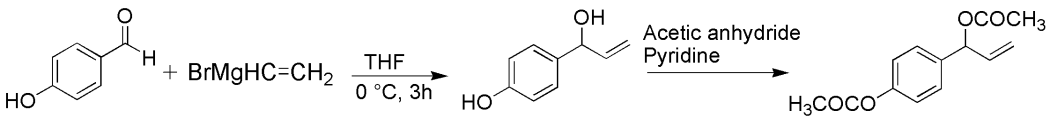


Figure 4. Proposed sigmatropic rearrangement of 1'-Acetoxychavicol acetate.

Therefore, it is still needed to modify its physicochemical properties and reduce toxicity of ACA. In order to increase solubility, various solubilizing and stabilizing techniques such as preparing water-soluble complex of ACA with cyclodextrins or β-1,3-glucan were developed (60, 66). To the best of knowledge, in the chemical synthesis field, there are two published literature concerned with the study of structure activity relationship on racemic ACA analogues as antitubercular candidates and indicated that those analogues showed possibility as new lead compounds. The most active **compound (III)** possessed MIC value 12.5 μgmL^{-1} in compared to rifampicin (MIC 0.003-0.012 μgmL^{-1}) (62). One attempt has been found that phenyl group was substituted in place of vinyl group of ACA in order to increase solubility without affecting the desirable biological activity of that compound. New **compound (IV)** and its analogues are ongoing process for anti-tuberculosis activity testing (5).



2.4.2 Synthesis of *dl*-1′-Acetoxychavicol acetate

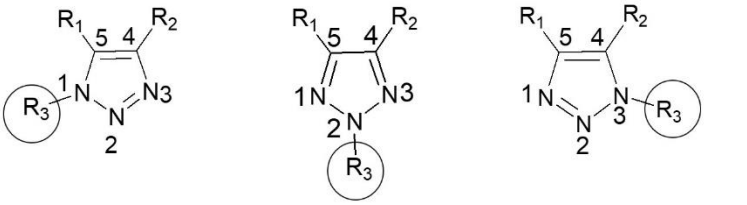


Scheme 1. Synthesis of *dl*-1′-Acetoxychavicol acetate.

The synthesis pathway of *dl*-1′-Acetoxychavicol acetate was reported by Ogiso et al. Under ice-cooling, *p*-hydroxybenzaldehyde was added to a solution of vinyl magnesium bromide in dry tetrahydrofuran (THF) and reaction mixture was run for additional 3 h at room temperature (Scheme 1). Reaction was quenched with ammonium hydroxide and oily product was acetylated by acetic anhydride and pyridine, then crude product was purified by column chromatography (53).

2.5 1,2,3-Triazole

Triazole (1,2,3-triazole) is a five-membered diunsaturated heterocyclic organic compound containing three nitrogen and two carbon atoms. It can be divided into three groups according to the position of substituent at nitrogen atom. Among three isomers, 1-*H* isomer and 2*H*-isomer can be differentiated according to the polarity because the dipole moment of 1*H*-1,2,3-triazole is significantly higher than 2*H*-isomer and 3(1)*H*-1,2,3-triazole was found in rare cases (67).



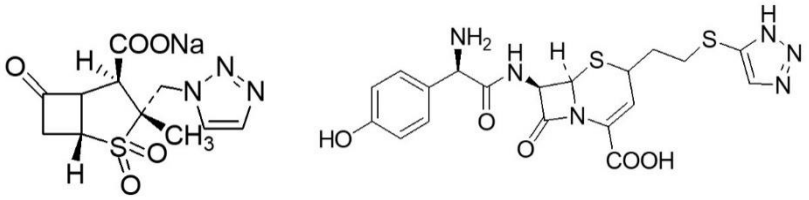
1*H*-1,2,3-triazole 2*H*-1,2,3-triazole 3(1)*H*-1,2,3-triazole

1,2,3-triazole,$C_2H_3N_3$ (molecular mass 69.0654), is a color liquid, density 1.192 gcm^{-3}, boiling point 203 °C, melting point 23-15 °C and vapor pressure 0.4 mmHg (at 25 °C). Triazole has p*K*b 9.4 and p*K*a 1.2 and it can behave as a weak acid or a weak base due to its amphoretic property. Furthermore, it is very soluble in water which is one of the interesting physical properties of 1,2,3-triazole ring moiety for using this ring in conjunction with poorly soluble compounds in order to increase their solubility (68).

2.5.1 Medicinal attributes of 1,2,3-triazole

The medicinal chemists develop new leads containing 1,2,3-triazoles nucleus due to their extensive biological activities such as anti-inflammatory, anticancer, antileishmanial, antimicrobial and antiviral activities and has promising effect for the

treatment of Alzheimer's disease (69-76). Some compounds containing 1,2,3-triazole moiety with therapeutic efficacy are showed in Figure 5.



Tazobactum sodium (β-lactamase inhibitor) Cefatrizine (Antibiotic)

Figure 5. 1,2,3-triazole containing compounds in clinical use.

In 2017, Jain et al. reported the new structural classes of anti-TB agents (77). There are many heterocyclic ring structures i.e; pyrrole, pyrrolidine, piperidine, pyridine, pyrimidine, triazole, pyrazole, pyrazoline, furan, imidazole, oxazole, isoxazole, thiazole, oxadiazole, thiadiazole, thiophene, piperazine, pyrazine, oxazine, thiazine, indole, purine, quinoline, acridine, phenazine, phenothiazine and thiomorpholine those all have been contributed in the antitubercular drug design (78). However, 1,2,3-triazole containing compounds have attracted attention to medicinal chemists as new class of ant-TB candidates because of their promosing antitubercular activity and unique features of triazole moiety (4, 79).

Generally, small and rigid 1,2,3-triazole core is regarded as the basic of small molecule pharmaceutical lead (6). Moreover, Massarotti et al. demonstrated the pharmacophoric role of 1,4- and 1,5-disubstituted 1,2,3-triazoles by studying X-ray crystal structural complexes of 1,2,3-triazole and either protein or DNA. Firstly, 1,2,3-triazole can able to bind with biological targets by means of different interactions. The presence of lone pairs in N-2 and N-3 nitrogen, 1,2,3-triazole can behave as hydrogen bond acceptor and acidic C-H group displays as hydrogen bond donor. These hydrogen bond acceptor and donor properties are responsible for the formation of hydrogen bond interaction with target molecules. As benzene, 1,2,3-triazole possesses aromatic character, therefore, 1,2,3-triazole aromatic core can participate in the π- π stacking

interactions with aromatic side chain of amino acids in the active site. In addition, the experimental dipole moment of unsubstituted 1,2,3-triazole tautomeric mixture is high in which 1*H*-1,2,3-triazole displays 1.85 D at 25 °C and 2*H*-1,2,3-triazole is 2.08 D at 45 °C. The dipole moment of 1,4- and 1,5-disubstituted 1,2,3-triazoles are 4.18 and 5.06 D. In brief, this high dipole moment can enhance the hydrogen bond and π-π stacking interactions of triazoles with binding pocket to elicit the response. However, 1,2,3-triazole does not always involved in direct binding with molecules in active site and in that case, triazole moiety can serve as a connection unit (linker) between two chain structures. In addition, these hydrogen bonding and dipole interactions contribute to improve the solubility of the compound.

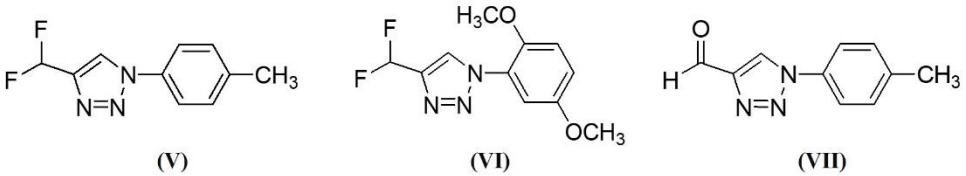
1H-1,2,3-triazole 2H-1,2,3-triazole

1,2,3-triazoles containing compounds are reported to be stable towards hydrolysis, oxidative/reductive conditions and enzymatic degradation. In addition, this unit is important for amide bond isoster because of similarity of structural features in distance, planarity and hydrogen bond acceptor and donor capacity between 1,2,3-triazole and amide bond. The distance between substituents in amide is 3.8–3.9 Å and 5.0–5.1 Å in triazoles and the dipole characters for amide and triazole are ~ 4 Debye and ~ 5 Debye. Amide oxygen has lone pair as in triazole nitrogen for hydrogen bond acceptor capacity and amide N-H can behave hydrogen bond donor as N-H in triazole. Nowadays, 1,2,3-triazole are being widely used as biosteric replacement not only for the amide but also for ester and heterocycles isosters (80, 81). The development of novel antiTB agents incorporating 1,2,3-triazole nucleus are still continuing. According to published articles, 1,2,3- triazole containing chemical entities with antitubercular activity were presented.

2.5.2 1,4-Disubstituted 1,2,3-triazole for the treatment of tuberculosis

Various substituents were used at N-1 position of 1,2,3- triazole in order to study the structure activity relationship on anti-tuberculosis activity. Aromatic phenyl (-C_6H_5)

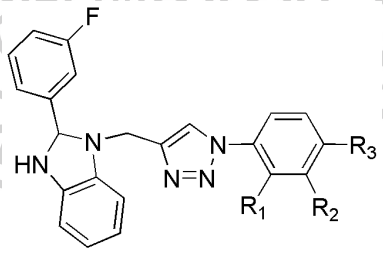
is commonly selected group as a substituent at N-1 position of triazole ring. Compounds containing electron donating and withdrawing substituents at the different positions of phenyl ring were also designed. The literature indicates that planarity of triazole and phenyl ring in the compound is important and it should be same plane for acquiring activity because out of plane conformation of triazole and phenyl ring can lose the activity. According to the study of Skakle and coworkers, the geometry of 4-difluoromethyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole **(V)** could be discovered with the aid of PLATON. In this study proved that the methyl group is coplanar with the aryl ring, with a torsion angle C7—C8—C9—C91 = 178.2 (3°) and aryl ring and triazole is also planar with an angle between the planes 0.34 (17) Å to possess inhibitory activity against *M.tb* (87% of inhibition at a concentration of 40.0 μgmL^{-1}) (82). If methoxy group ($-OCH_3$) was substituted instead of methyl ($-CH_3$) at ortho position on aryl ring (4 difluoromethyl-1-(2,5-dimethoxyphenyl)-1*H*-1,2,3-triazole, **VI**), ortho substituents can lead to torsion of the aromatic ring and deviation from coplanarity. Therefore, inhibitory activity of compound **VI** was reduced (74% of inhibition at a concentration of 80.0 μgml^{-1}) in compared to 4-difluoromethyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole (83). This un-derirable *ortho* effect has seen in the study of SAR and tuberculosis inhibitory activity for N-substituted-phenyl-1,2,3-triazole derivatives by Ferreira et al. They synthesized twenty four compounds, among them, 1-(4-methylphenyl)-1,2,3-triazole-4-carbaldehyde, **VII** showed the best inhibition with MIC value of 2.5 μgmL^{-1} that was comparable to currently useful drugs rifampicin (MIC 1 μgmL^{-1}) and ethambutol (3.25 μgmL^{-1}) (84). In addition to phenyl ring, researchers studied the importance of same planar conformation of pyridine ring and triazole by AutoDock4 molecular docking study (85).



(V) (VI) (VII)

Bioisosteric replacement of hydrogen by halogen in phenyl ring is important in drug design because halogen substitution on phenyl ring can alter the physical, chemical

and biological properties of lead compounds by modifying their steric and electronic effect of compounds (86). The monovalent isosteric replacement of hydrogen by fluorine is commonly used in drug design because hydrogen and fluorine have similar steric parameters and van der Waal's radii (1.2 and 1.35 Å) (87). In the periodic table, fluorine is the most electronegative element and its electron-withdrawing effect can be contributed to change the acidity, lipophilicity and conformation and modify the interaction of fluorinated compounds with biological receptor or enzyme those all will influence on biological and/or pharmacological properties. In addition, fluorinated compounds can prevent the undesired metabolic pathways by blocking the potential oxidation site. In recent year, it was found that 30% of administered drugs including biopharmaceutical products contain fluorine because of the advantages (88, 89). In the drug design of 1,4-disubstituted 1,2,3-triazole antiTB agents, Gill synthesized clubbed [1,2,3] triazoles by fluorine benzimidazole. As lead modification, fluorine heteroatom was incorporated at the different position of phenyl ring and it was observed that antituberculosis activities were related to the highly electronegative parts containing fluorine because **compound VIII** to **X** were most active compounds (MIC 0.32 to 0.58 µM) in compared to rifampicin (MIC 0.015-0.125 $mgmL^{-1}$) at 96% inhibition of H37Rv strains (90).



(VIII) $R_{1,=}$ -H, R_2, R_3 = -F

(IX) R_1, $R_{3\,=}$ -H, R_2, = -F

(X) R_1, $R_{3\,=}$ -F, R_2, = -H

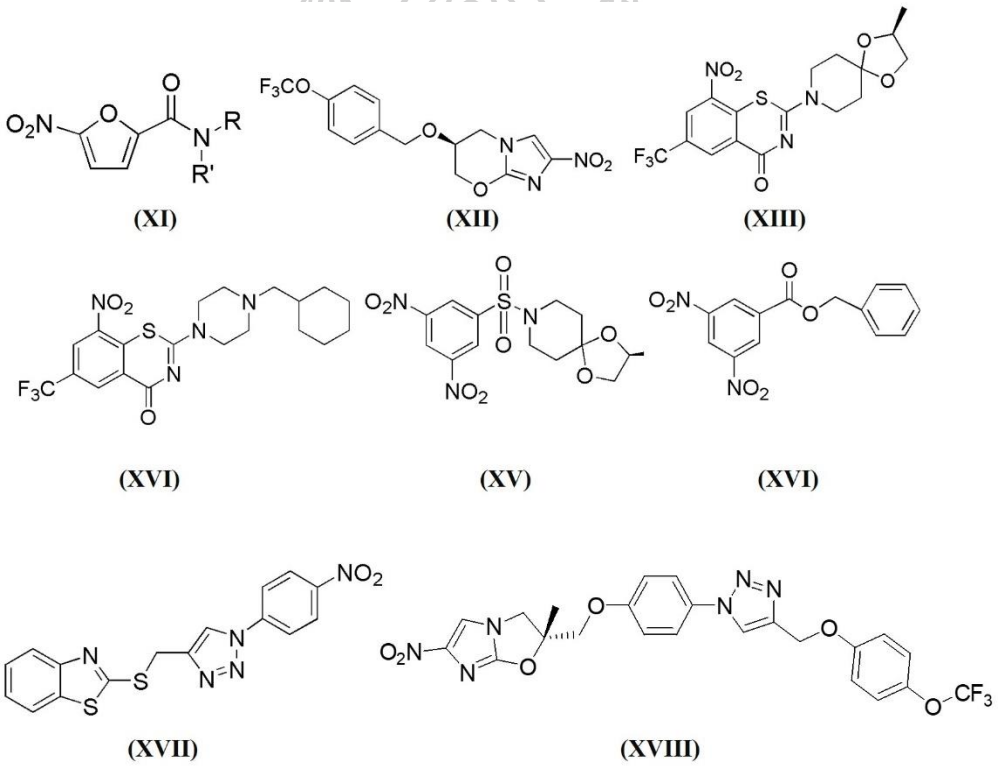
Nitroaromatic compounds are organic molecules that has at least one nitro (-NO_2) group which is very important functional group in drug design. There are many well-known drugs containing nitroaromatic structure such as antibiotic

chloramphenicol, amoebicide metronidazole, immunosuppressant azathioprine, tranquilizer nitrazepam, androgen receptor antagonist nilutamide and analgesic nimesulide. They have various chemical and biological actions and are useful for the treatment of various kind of diseases although detail mechanism of notroaromatic compounds are still unknown. Chemically, it is a very strong electron withdrawing group and it can create localized or regional electron deficient regions within the molecules by attracting electrons nearby. In the living system, this electrophilic nitro groups can react with biological nucleophiles such as proteins, amino acids, enzymes and nucleic acids. As molecular level, nucleophilic addition, displacement, one electron transfer (oxidation or reduction) are contributed to form covalent bond between electrophilic nitrogroup and nucleophilic biological molecules or can form complex between electrophile and nucleophile without forming covalent bond and these all reactions will lead to form biological changes which may be desirable or harmful. Although nitroaromatic compounds are regarded as hazardous compounds, selective toxicity in bacteria, parasite or tumor cell without affecting host organism or normal cell becomes one reason to explain the usefulness of those nitroaromatic containing compounds in medicinal chemistry (91).

In the discovery of leads as new anti-tuberculosis agents, nitroaromtic group containing compounds are well documented such as nitrofuran **(XI)**, nitroimidazole (PA824) **(XII)**, benzothiazinone (BTZ043) **(XIII)** (92). **Compound (XII)** is a prodrug and the mode of action is intracellular releasing nitric oxide (NO) as the active agent from nitro group (93) and it was also active for both replicating and non-replicating *Mtb* by inhibiting cell wall synthesis and respiratory poisoning (94). At present, it is undergoing phase III clinical trial. **Compound (XIII)** is highly selective for mycobacterial species and it inhibits mycobacterium cell wall synthesis and it stands in preclinical development. The nitro group of BTZ043 was reduced to its nitroso intermediate by cofactor flavin adenine dinucleotide (reduced form), $FADH_2$ and can form covalent adduct with cysteine moiety of decaprenyl-phosphoribose-2′-epimerase (DprE1) which is essential for the synthesis of arabinoglactan and arabinomannan components, D-Arabinofuranose (95). The nitroaromatic group of PBTZ 169 **(XIV)** is also inhibitor of DprE1 enzyme as BTZ 043 but it is slightly more potent and currently

undergoing phase I clinical trial (96). Miller and coworkers synthesized nitroaromatic sulfonamide and nitroaromatic ester classes of compounds based on BTZ043 by using a scaffold simplification strategy and evaluated the antitubercular activity on H37Rv strain and found that dinitro substituents of sulfonamide **compound (XV)** showed MIC 1.53 µM and nitroaromatic ester **compound (XVI)** had MIC 13.03 µM in compared with BTZ043 (MIC <0.02 µM). This finding highlight the importance of electronic character of nitroaromatic ring because **compound (XV)** is more electron deficient than **compound (XVI)**. In addition to these finding, Khan et al. synthesized sulfur rich 2-mercaptobenzothiazole and 1,2,3-triazole conjugates as lead compounds and it was found that **compound (XVII)** that has nitro substitution on aromatic ring showed the promising results (Compound **XIV** MIC 8 µgmL^{-1}, INH MIC 0.125 µgmL^{-1}) on H37Rv strains against tuberculosis. According to the molecular docking studies, this ligand was assumed as DprE1 inhibitor for the treatment of drug susceptible and multidrug resistance strain (97). Singh PP synthesized triazole containing 6-nitro-2,3-dihydroimidazooxazoles as anti-TB agents and **compound (XVIII)** showed MIC of 0.23 µM in compare with MIC of rifampicin 0.07 µM against *Mtb* H37 Rv. It was found that this compound possessed synergistic to additive effects with first line anti-tuberculosis drugs and no CYP inhibition (98).

Generally, nitrobenzenes are carcinogenic, potent environmentally toxic and mutagenic compounds. In addition, bone marrow depression, formation of methemoglobin, allergic reactions are inevitable side effects of nitroaromatic containing compounds. Although reductive metabolism of nitro group ($ArNO_2$) to nitroso (ArNO) to hydroxylamine (ArNHOH) to primary amine ($ArNH_2$) has been well investigated, the fate of most nitroaromatic compounds and their detail physiological effects in humans are still limited (99). However, the nitro group is important for medicinal chemists in drug designing process because its electron attracting ability for eliciting desirable biological effects.



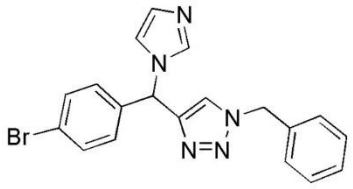
(XI) **(XII)** **(XIII)**

(XVI) **(XV)** **(XVI)**

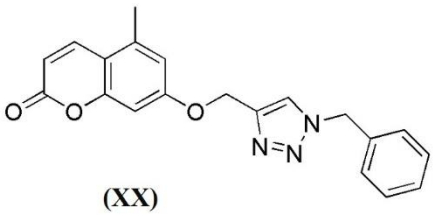
(XVII) **(XVIII)**

The literature indicates that the substitution of phenyl ring with one carbon extension (benzyl) to N-1 position of 1,2,3-triazole were synthesized and evaluated for anti-tuberculosis activity. In the new class of azole derivative, **compound (XIX)** showed good anti-tuberculosis activity with MIC value 16 μgmL^{-1} in compare to INH (0.2 μgmL^{-1}) (100). A new coumarin-based 1,2,3-triazole derivatives were synthesized by Shinde and it was found that **compound (XX)**, 4-Methyl-7-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-*2H*-chromen-2-one possessed antitubercular activity IC_{50} 1.8 μgmL^{-1} as compared to the standard drug INH (IC_{50} 0.0023 μgmL^{-1}) on *Mtb* H37Ra

strain. In addition to this, molecular docking study pointed out that **compound (XX)** has a high affinity to the active site of DprE1 enzyme (101).



(XIX)



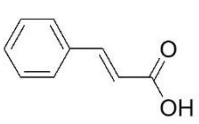
(XX)

Cinnamic acid **(XXI)** has been recorded as a traditional anti-tuberculosis agent in the 19th century before the emergence of antimycobacterial chemotherapy (102). It is a naturally occurring compound presented in cinnamon (*Cinnamomum verum*). Both *tran*-and *cis*-isoform of cinnamic acid are found in the plant but *trans*-cinnamic acid is a major compound due to its high stability. Chemically it is composed of phenyl ring substituted with an acrylic acid group. Most of the naturally occurring compounds are generally regarded as non-toxic and safe to human exposure, for that reason, cinnamic acid was explored in drug design.

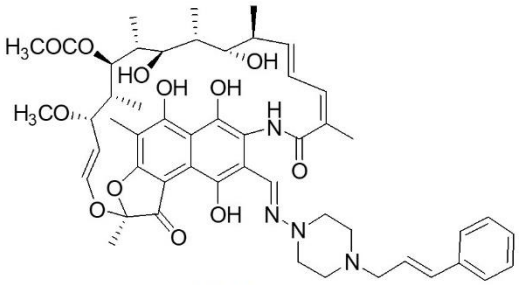
In 1995, Reddy and coworkers developed 3-(4-cinnamylpiperazinyl iminomethyl) rifamycin SV **(XXII)** and it was the first report describing synergistic effect of cinnamyl moiety on the piperazinyl group of currently existing antituberculosis drug rifammycin. In general, the radiometric MICs of **(XXII)** were two to eight times lower than those of rifamycin on most drug-sensitive and drug-resistant strain of *Mtb* (103). This study was supported by augmenting activity of *trans*-cinnamic acid in drug combination with various antibiotics such as rifampin, amikacin, clofazimine for tuberculosis infection (104). The molecular hybridization approach between isoniazid and *trans*-cinnamic acid was reported and MIC of the developed **compound (XXIII)** was 3.12 μgmL^{-1} in compare to isoniazid (0.2 μgmL^{-1}) (105). In order to identify potential anti-tuberculosis agents, Degani et al. described novel molecular hybrids of cinnamic acid and guanylhydrazone as **compound (XXIV)** which showed MIC of 6.49 µM (Isoniazid MIC 1.8 µM) against *Mtb* H37Rv with good safety profile (106). As continuously, the same authors designed and synthesized cinnamide compound containing ethylenediamine fragment from ethambutol and it was found that

compound (XXV) possessed MIC 5.1 µM (Ethambutol MIC 15.3 µM). Besides, it has the synergistic effect with rifampicin. The MIC of rifampicin was 0.125 μgmL^{-1} and it was reduced to 16-fold (0.0078 μgmL^{-1}) after combination with rifampicin and **compound (XXV)** (107). Promising traizolophthalazine derivatives of 4-alkoxy cinnamic acid have been synthesized by Baltas et. al and evaluated their antituberculosis activities. **Compound (XXVI)**, a 4-isopentenyloxycinnamyl triazolophthalazine derivative (MIC 0.4 µM) was found to be 1800 times more active than isoniazid (MIC 729 µM) against isoniazid-resistant *Mtb* 1400 strain and possessed good selectivity index. This fact pointed out that **compound (XXVI)** does not inhibit mycolic acid synthesis and it may has new mode of action (108). In 2014, Tevekar et al. designed and synthesized the analogs of N-[4-(piperazin-1-yl)phenyl]cinnamamide and trifluoromethyl substituted compound analog **(XXVII)** and it was exhibited good antitubercular activity (MIC 3.125 μgmL^{-1}) in compare to reference drug isoniazid (MIC 0.39 μgmL^{-1}) (109).

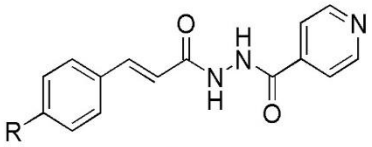
According to the published literature indicate that *trans*-cinnamic acid containing compounds possessed synergistic effect on currently existing antibiotics and promising activities on resistance strains. Therefore, cinnamic derivatives can be potential leads in the design and synthesis of antimycobacterial agents.



(XXI)

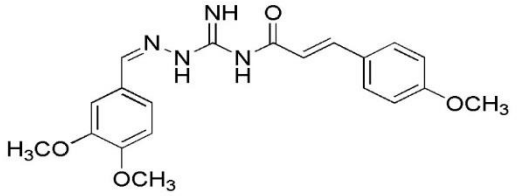


(XXII)

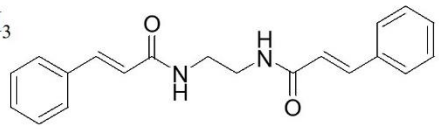


(XXIII)

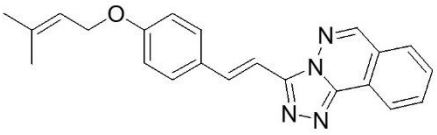
R = -H, -NO_2, -OCH_3



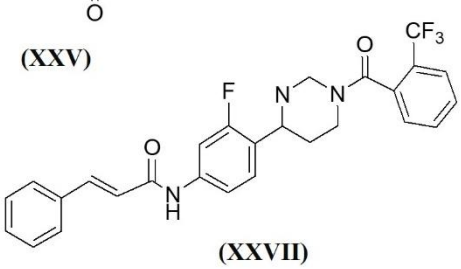
(XXIV)



(XXV)



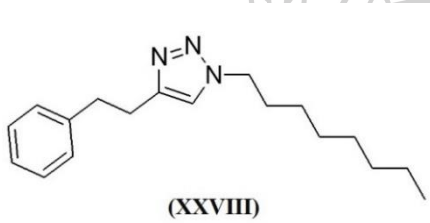
(XXVI)



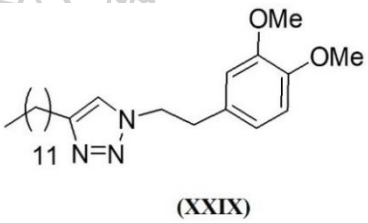
(XXVII)

Baltas et al. synthesized the triazole derivatives to inhibit the enoylreductase enzyme (InhA) which is essential for the type II fatty acid biosynthesis pathway of mycobacterial mycolic acid. The most active **compound (XXVIII)** exhibited MIC value of 35 µM for *Mtb* growth in compared to triclosan (MIC 34.5 µM) (110). By following InhA inhibitors, they tried to synthesized triazole derivatives in order to study the effect of alkyl chain length and it was observed that **compound (XXIX)** possesses good anti-tuberculosis activity with MIC value 0.6 µM (triclosan MIC 34.5 µM) but this compound has no inhibition on InhA at 50 µM concentration. Therefore, it was postulated that **compound (XXIX)** has unknown biological target as anti-TB agent (111).

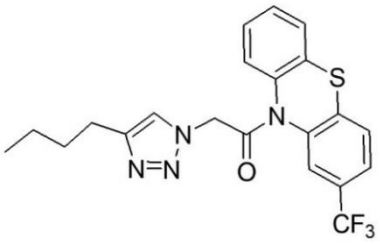
Furthermore, Kantevari and coworkers synthesized a series of novel 2-(trifluoromethyl)phenothiazine-1,2,3-triazoles designing by molecular hybridization strategy and **compound (XXX)** exhibited as most potent antitubercular agent (MIC 6.25 μgmL^{-1}) with lower toxicity (selectivity index >10) when in compared to first line antiTB drug isoniazid (MIC 0.1 μgmL^{-1}) (112). The similar strategy was being following, they continued to demonstrate click-based synthesis and antitubercular evaluation of dibenzofuran tethered thiazolyl-1,2,3-triazolyl acetamides as drug-like hit analogues. The most active **compound (XXXI)** showed *in vitro* antimycobacterial activity against *Mtb* H37Rv with MIC value 1.56 μgmL^{-1} in compared to isoniazid (MIC 0.1 μgmL^{-1}) and provided lower cytotoxicity (113).



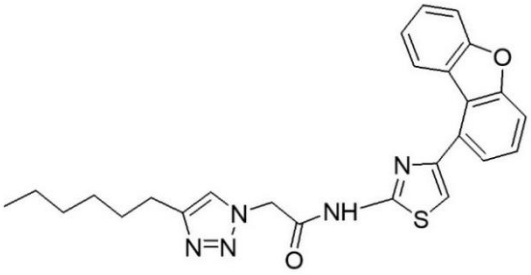
(XXVIII)



(XXIX)



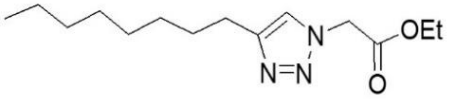
(XXX)



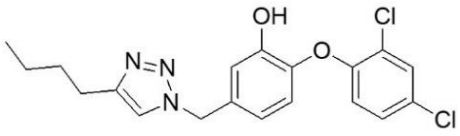
(XXXI)

Mycobacteria cell walls are composed of very long chain (C60-C90) a-branched chain fatty acids esterified to the arabinogalactan component of the cell wall or to trehalose. It is thick cell wall contributes as one of the limiting factors of antibiotics to reach the mycobacterial cytoplasm. Generally, lipophilic drugs pass more easily through the cell wall and more active (114). Therefore, chemical modification of the compound structure to increase the permeability property of cell wall is quite challenging task. Labadie et al. synthesized 1,2,3-triazolyl fatty acid derivatives such as methyl carboxylate, free carboxylic acid, and alcohols and evaluated antitubercular activity. It was observed that alcohol derivatives were less active than acid and ester containing **compound (XXXII)** possessed the best activity with MIC value of 0.5

µgmL^{-1} which has similar MIC value of rifampicin against *Mtb* (115). Furthermore, Stec J et al. synthesized the triclosan derivatives to inhibit the enoyl-acyl carrier protein reductase InhA of *Mtb* drug-sensitive and drug-resistance strains. It was found that *n*-butyl attached triazole ring containing **compound (XXXIII)** showed the promising activity with MIC value 0.6 µgmL^{-1} when in compare with triclosan (12.5 µgmL^{-1}) (116).



(XXXII)



(XXXIII)

According the above-published data, it was observed that 1,4-disubstituted 1,2,3-triazole containing compounds have potent antiTB activity and design and development of more selective, drug likeness and good pharmacokinetics properties of those derivatives are still continuing for effective tuberculosis treatment (79).

2.6 1,3-Dipolar cycloaddition and click chemistry

In synthetic organic chemistry, a cycloaddition is a chemical reaction in which two or more unsaturated molecules combine to construct cyclic or heterocyclic structure and the reaction scope and mechanism was introduced by Huisgen in early 1960s. This reaction can be classified according to the formation of new σ bond number or size of the ring. 1,3 dipole is a dipolar compound possessing delocalized electron and charge will be separated over three atoms and dipolarophile is a compound (double or triple bond) that can react with 1,3-dipole in the cycloaddition reaction. However, uncharged 5-membered ring cannot be formed from octet-stabilized reactants. In can be seen in Figure 6, *a* has an electron sextet and *c* has an unshared electron pair. This *a-b-c* 1,3-dipole react by cyclic electron displacement to form 5-membered ring. This reaction is known as 1,3-dipolar cycloaddition and IUPAC recommend 3+2 cycloaddition in terms of atom involvement in reactants.

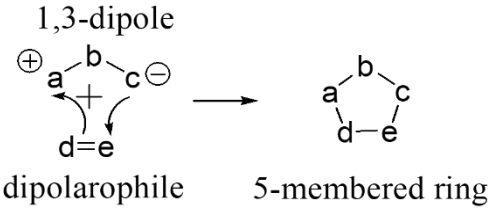
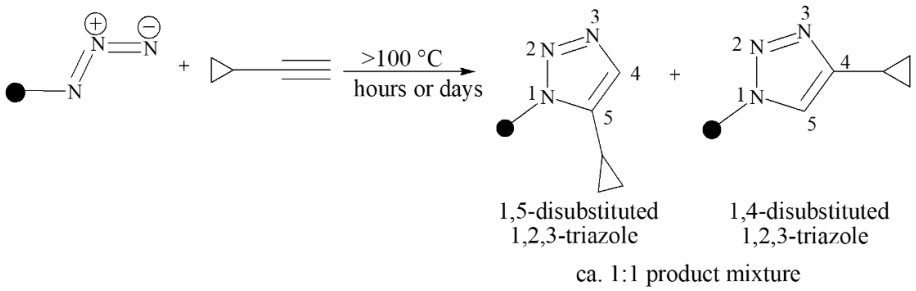


Figure 6. 3+2 cycloaddition reaction.

Thermal reaction of 1,3-dipole (azide, $N\equiv\overset{\oplus}{N}-\overset{\ominus}{N}-$) and dipolarophile (alkyne) for the preparation of 1,2,3-triazole was reported by A.Michael in 1893. In this reaction, phenyl azide and acetylenedicarboxylic ester were used as reactants to prepare 1-phenyl-1,2,3-triazole-4,5-dicarboxylic ester (117).

Azides and alkynes are regarded as the most energetic species but they are the least reactive functional groups in organic chemistry. Although, irreversible reaction for synthesizing triazole from azide and alkyl is highly exothermic (ΔH^{θ} between −50 and −65 kcal mol^{-1}), the rate of reaction is quite slow because of its high activation barrier that can hide the close proximity of reactants to happen reaction under uncatalyzed condition (118). Therefore, azide-alkyne catalyst-free 1,3-dipolar cycloaddition reaction is usually carried out at elevated temperature. Ambient temperature can be possible only for very reactive substrate for example, alkyne with electron withdrawing group and prolong reaction time is needed for all cases. Furthermore, highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO-LUMO) energy levels differences for azides and alkynes are comparable and contribution of dipole HOMO and dipole LUMO pathways in this reaction leads to regioisomeric mixture of 1,2,3-triazole product (Scheme 2) (119).

However, electron-deficient terminal alkyne favors the formation of more 1,4-regiosomer. Longer reaction time, higher reaction temperature and lacking reagioselectivity are limiting factors for the effectiveness of uncatalyzed cycloaddition reaction. In order to overcome these limitations, alternative approach of using copper catalyst in Huisgen cycloaddition reaction had been developed as new chemical discipline and termed click chemistry.

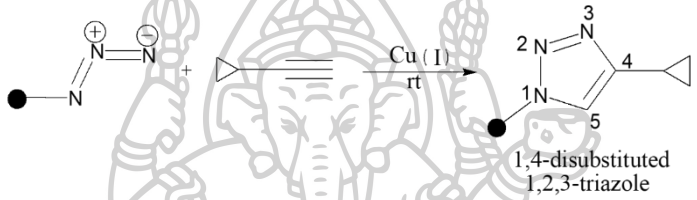


Scheme 2. Huisgen 1,3-dipolar cycloaddition between azide and alkyne.

Click chemistry is a chemical philosophy to generate substances quickly and reliably by joining small units together with heteroatom links (C-X-C). This new strategy for organic synthesis was introduced by Professor K. Barry Sharpless of the Scripps Research Institute in 2001 (120). The goal of click reaction is powerful, selective modular set of compounds for small and large scale applications. Nowadays, it is highly applicable in areas of classical organic synthesis, *in situ* click chemistry, lead finding through combinatorial chemistry to proteomics and DNA research (121). In order to be a click reaction, it is needed be modular, wide in scope, stereospecific, simple reaction condition from readily available starting materials and reagents to used benign solvent (water) or in solvent free condition or easily removed solvent. Furthermore, it can provide high yields and atom economy, inoffensive byproducts and simple product isolation and the product must be stable under physiological conditions due to irreversible bonding connection (122, 123). The advantages of click reaction also includes that it is pH insensitive and can work in pH between 4 to 12 (124), it can be performed at room temperature in order to avoid very high or very low reaction temperature condition (125). This reaction does not interfere with other chemical functionalities i.e., orthogonal. In summary, click chemistry can be defined in one sentence; “all searches must be restricted to molecules that are easy to make” (126). However click reaction has some limitation such as explosive nature of azides and side effects of copper in the body (127).

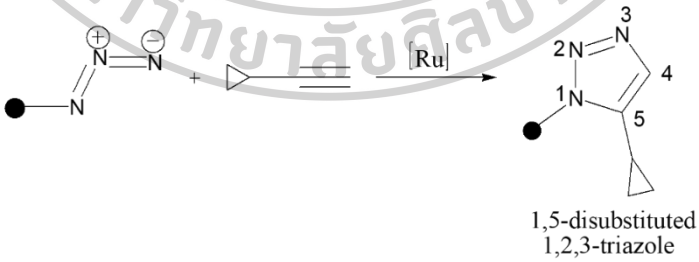
Click reaction can be classified as cycloaddition click reaction, ring opening nucleophilic substitution reaction, ‘non-aldol” type carbonyl chemistry and carbon-carbon multiple bonds additions (120). Among various types of click reactions,

copper-catalyzed Huisgen's 1,3-dipolar cycloaddition of alkynes and azides to synthesize 1,2,3-triazoles was first example of click reaction and has regarded as "cream of the crop" (122). In the presence of copper catalyst, azide and alkyne were easily joined and reaction rate was accelerated ~10^6 or 10^7 times than uncatalyzed procedure. This ligation reaction can form in aqueous media, happen straightforwardly without using protection groups for most common functional groups such as ester, ether, amide and thioether. Besides, because of its specificity, it can avoid structural uncertainties and the formation of regioisomers and produces 1,4-disubstituted 1,2,3-triazole exclusively with high yield (Scheme 3).



Scheme 3. Copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction.

Therefore, this copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction is compliance with click status (121). The complementary regioisomer (1,5-disubstituted 1,2,3-triazole) can be synthesized by ruthenium catalyzed reaction of organic azides with terminal or internal alkynes (Scheme 4) (128, 129).



Scheme 4. Ruthenium catalyzed azide-alkyne cycloaddition reaction.

The common sources of copper for CuAAC reaction includes elemental copper; Cu (0) from wire, turnings, powder or nanoparticles, CuI and CuBr are suitable for polymer ligations. In order to increase solubility in organic solvents, ($[Cu(CH_3CN)_4]PF_6$, $(EtO)_3P$:CuI, $Cu(CH_3CN)_4OTf$) can be used and $Cu(OAc)_2$ can

also improve the reactivity. The oxidation state of catalytically active species for the reaction is +1 irrespective of copper element or copper salt or copper species (124). One important factor is that during reaction, it is needed to maintain copper (I) at high level at all times. A large excess amount (three to ten-fold excess) of sodium ascorbate can reduce copper (II) sulfate pentahydrate *in situ* to copper (I) and reaction will less susceptible to oxygen due to this reducing agent and can run this type of reaction under open-air conditions. If copper (I) catalyst is used directly, it can be oxidized to oxidized copper (II) species which has non-catalytic property. Therefore, use of copper (II) sulfate in conjunction with reducing agent; sodium ascorbate is highly efficient, cost effective, more cleaner and favorable than Cu (I) for CuAAC reaction (119, 130).

Although click reaction is impressive scope in synthesis field, catalytic mechanism is complex and still unclearity. First experimental investigation by ligand free process of *in situ* copper (I) species from copper (II) and ascorbate proposed that there are two copper centers needed to form azide-alkyne cycloaddition reaction (131). A detail mechanism of copper-catalyzed azide-alkyne cycloaddition was firstly described in 2006 by means of kinetic studies and discrete Fourier transform (DFT) calculations (132). It was extensively investigated by real time infrared analysis technique based on attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) principles and also predicted the rate limiting step of the CuAAC reaction (133). Generally, it is a stepwise mechanism as mentioned below (Figure 7) (132, 134, 135).

(1) Formation of π bond between copper and alkyne (Cu-alkyne π complex).
(2) Deprotonation of the alkyne proton (formation of Cu acetylide).
(3) Copper ion coordinates with azide nitrogen and activates it that can cause cyclization reaction in the complex by nucleophilic attack of terminal nitrogen of the azide group on the internal carbon of alkyne and forms metallacycle.
(4) A transannular interaction between the lone pair of electrons on the substituted nitrogen of azide and C=Cu bond makes ring contraction that can cause metallacycle to Cu triazolide.
(5) 1,4-disubstituted 1,2,3-triazole will be formed after protonation to alkyne carbon.

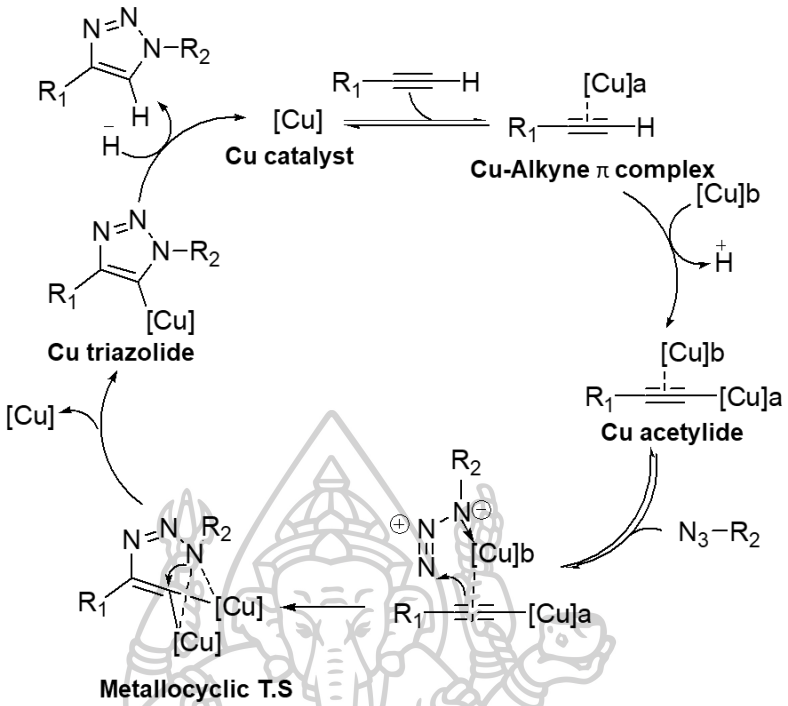


Figure 7. Proposed catalytic model for the CuAAC with two copper atoms.

The successful reaction cannot be expected for all type of azide and alkyne reaction. N-unsubstituted 1,2,3-triazole (NH-1,2,3-triazoles) cannot be formed by means of copper-catalyzed [3+2] cycloaddition strategy because of its high activation barrier and requires prolong heating time (67, 136). When acetylene react highly electron deficient fluorine-substituted azides, product yield was very low and with sulfonyl substituted azides, no triazole product will be formed. It indicates that more electron rich azides, alkynes with electron withdrawing group favor the smoothness of click reaction by facilitating the formation of metallocycle. α –carbonyl-alkynes are more reactive than alkyl-alkynes and organic azides are more active than the anion itself (119). Steric effect may also affect the success of click reaction (132). Click chemistry (CuAAC) is beneficial for 1,3-dipolar cycloaddition reaction at ambient temperature to obtain 1,2,3-triazole containing structure and highest yield, however, medicinal chemists still concern about the safety of azide moiety. Nowadays, *in situ* generated azides in one-pot tandem azidation-cycloaddition reaction by using microwave energy are being interested not only for the reason of azide safety but also for the shorter reaction time.

2.7 Microwave-assisted click chemistry

In drug discovery and lead optimization processes, the main target of medicinal chemistry is to synthesize compounds or compound libraries within a short period of time (137). Apart from conventional synthesis, there are many strategies and methods such as combinatorial, parallel, solid-phase and microwave-assisted organic syntheses which are being used to achieve the desired compounds. Mostly, chemical reactions are needed to apply heat to occur chemical transformation. In 1855, Robert Bunsen inverted Bunsen burner and thermal energy from burner could be used for heating reaction mixture. Later, other heating sources, for example; oil bath, sand bath, hot plate, heating mantle are more popular than burner in the scientific field. However, one of the major drawbacks of thermal or electric sources is very slow heating rate and takes several hours or days to complete the reaction that can retard the optimization processes of organic synthesis. In order to synthesize complex organic structures, short and efficient synthesis is a dream of each and every chemist (138-140). Organic synthesis by microwave irradiation was known as microwave-assisted organic synthesis (MAOS) and introduced by groups of Gedye and Giguere/Majetich in 1986. They studied four types of reactions such as hydrolysis, oxidation, esterification and S_N2 reaction by using domestic microwave and compared the results from microwave heating with conventional reflux heating method. It was found that microwave oven experiment increased rate of reaction in contrast with classical method (141).

Microwave is a part of electromagnetic spectrum with wavelength between 1 mm to 1 m and corresponding frequency range 300 to 0.3 GHz. Basic principle of microwave heating is resulted from the interaction of charged particle of reaction matter and electric field portion of microwave. Microwave can provide heat to reaction by means of two heating mechanisms. When reaction mixture is irradiated by microwave, solvent or reagent with dipole will attempt to align itself with the oscillating field. This alignment causes rotation, which results in friction and ultimately generates heat energy and such kind of heat generating mechanism is known as dipolar polarization mechanism. In conduction, dissolved and charged particles (ions) in reaction mixture can oscillate back and forth under the influence of microwave irradiation. It can cause collisions of the charged particles with molecules or atoms nearby and generates heat

energy. Conduction mechanism has stronger interaction among charged particles and large heat generating capacity than dipolar polarization mechanism (142, 143). Microwave reactor is an instrument used for MAOS. Currently there are two types of reactors; single-mode (monomode) and multimode reactor. In single-mode instrument, microwave irradiation is directly focused on the reaction mixture and provides exceeding heating rate. In multimode reactor, microwave entered in the cavity is reflected from the wall of the cavity and interact with cavity load. The decision making for selecting reactor type is largely dependent on types of research and reaction scales. Generally, small scale of synthesis can be done in single-mode reactor and large scale can be possible in multimode reactor (144). For reaction optimization in MAOS, microwave reaction is similar to the conventional one. Reaction time and temperature are key parameters to be changed and other parameters such as solvent, reagent, catalyst, molar ratios and concentration can also be varied. However, one parameter should be changed at a time in order to make systematic optimization and to check the parameter that affect the reaction (138).

Although MAOS is not suitable for some chemical reactions such as reaction with short reaction time and temperature sensitive reaction, it has many advantages. Microwave-assisted reactions are simple, efficient, economical, available temperature and pressure measurement and it allows reaction scale up to milligram to kilogram scale, using solvent-free reaction method or recycled solvents and provides cleaner reaction for greener chemistry (145). The most significant benefit of microwave heating is rapid reaction rate. The conventional heating process provides less efficient energy because vessel wall is the source of heat loss and it is needed to use high boiling point solvent for higher temperature condition. In sealed vessel of microwave heating, temperature of solvent can be increased more than 100 °C of boiling point of selected solvent. Reaction vessel wall is also transparent to the microwave and it can irradiate directly to the reaction mixture for effective heating (146, 147).

Selective heating is responsible for microwave heating that can produce less side products, high purity and improved yield (148, 149). Strongly microwave absorbing heterogeneous catalysts or reagents can be used for less polar reaction medium, microwave energy can directly transfer to that reactive species and it can form

chemical transformation that cannot occur in conventional ways. Generally, there are three effects proposed in microwave heating process i.e; thermal, non-thermal and specific microwave effects. Selectivity effect of microwave irradiation has been reported in the synthesis of cyclodextrin methacrylate in which conventional heating produced regioisomeric mixture while 1,4-regioselectivity was the exclusive product under microwave irradiation (150). However, in 2013, researchers pointed out that there is no non-thermal microwave effect in organic synthesis. Specific microwave effect is based on uniqueness of dielectric microwave heating that include the superheating effect of solvent at atmospheric pressure, selective heating of microwave in reaction mixture, formation of microscopic hotspots and elimination of wall effects (151-153).

Nowadays, chemists are trying to protect the environment by using environmental friendly solvents in organic synthesis. Water is the best of choice because abundant, non-toxic, non-corrosive, non-flammable and easiest handling. At atmospheric temperature and pressure, water boils at 100 ℃ and it cannot dissolve many organic compounds. However, temperature between at 200 ℃ to 300 ℃, water can be near critical water and can acts as pseudo-organic solvent. Many reactions have been carried out in water instead of organic solvents. For example, Fisher indole synthesis in sealed vessel condition by microwave heating at 270 ℃ has completed in 30 minutes when water is used as solvent and in conventionally, it took hours and needed catalyst (154, 155).

MAOS can be applied in various types of chemical reactions. Among them, microwave-assisted click chemistry cycloaddition reaction is highly beneficial not only to reduce reaction time but also to increase product yields, purities, avoid polymerization and decomposition of sensitive reagents (156). Generally, reaction condition for click reaction is very simple. It can be done at room temperature in an open flask. However, microwave irradiation achieves some form of process intensification in organic synthesis especially for click reaction that needs longer reaction times under room temperature condition (157). Click reaction can be compatible with both classical and non-classical methods such as microwave, ultrasound, continuous flow processing, polymer support, room temperature ionic liquids and *in situ* click chemistry methods (158, 159). In 2004, microwave was first

successfully applied for CuAAC reactions to synthesize 1,4-disubstituted 1,2,3-triazoles by mean of *in situ* tandem-azidation cycloaddition (160). Besides, *in situ* generation of organic azides by microwave heating simplify experimental procedure and reduce the explosion hazard (161). In recent years, many references had been reported microwave-assisted synthesis of 1,2,3-triazole containing compounds by copper catalyzed 1,3-dipolar cycloaddition (162-165). Furthermore, conventional and microwave synthesis have been studied in order to make the comparison between both methods based on total reaction time and percentage yield. It was found that microwave-promoted click reactions are shorter reaction time, higher yields, user-friendly and safe (166-168).

CHAPTER III
OBJECTIVES OF THE STUDY

The goal of the study is synthesis of 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives as antituberculosis agents. Objectives of research in order to achieve this goal are

1. To design and synthesis of 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives
2. To evaluate antitubercular activities of synthesized 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives
3. To determine the structure activity relationship of synthesized 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives after evaluation of MIC values against *M.tb* strains

CHAPTER IV
EXPERIMENTAL

4.1 Material

4.1.1 Equipment

Name	Source
Analytical balance	Satorius, Germany
Infrared spectrophotometer (FTIR 4700)	Thermo Scientific Nicolet, USA
Magnetic stirrer heating plate (IKA®C-MAG HS7)	IKA, USA
Mass spectrometer (micrOTOF-Q II)	Bruker, USA
Melting point apparatus (M-560)	BÜCHI, Switzerland
Microwave™ Synthesis System Discover® SP	CEM, USA
Nuclear magnetic resonance spectrophotometer (300 MHz)	Bruker, USA
Rotary evaporator BÜCHI Heating Bath B 490 BÜCHI Rotavapor R-205	BÜCHI, Switzerland

4.1.2 Chemicals

Name	Source
4-Aminophenol	Sigma Aldrich, Germany
Ammonium chloride	QRëC™, Newzealand
Aniline	BDH, England
Benzophenone	Fluka, Switzerland
Benzyl alcohol	P.C Drug Center Co., Ltd, Thailand
t-Butanol	Sigma Aldrich, Germany
tertra-n-Butylammonium fluoride	Sigma Aldrich, Germany
tert-Butyldimethylsilyl chloride	Sigma Aldrich, Germany
1-Bromobutane	Fluka, Switzerland

(1-Bromoethyl) benzene	Sigma Aldrich, Germany
1-Bromohexane	Sigma Aldrich, Germany
1-Bromooctane	Sigma Aldrich, Germany
3-Bromo-1-phenyl-1-propene	Sigma Aldrich, Germany
Chloroform	Honeywell, Burdick&Jackson, USA
Copper sulphate	Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Silpakorn University, Thailand
Cyclohexyl bromide	Sigma Aldrich, Germany
N,N' Dicyclohexylcarbodiimide	Sigma Aldrich, Germany
Diethylether	J.T. Baker, USA
Dimethyl aminopyridine	Fluka, Switzerland
Dimethyl sulfoxide	Loba Chemie PVT. Ltd. India
Ethanol 99.99%	Honeywell, Burdick&Jackson, USA
Ethyl acetate	Burdick&Jackson, Korea
Ethynylmagnesium bromide	Sigma Aldrich, Germany
4-Fluoroaniline	Sigma Aldrich, Germany
n-Hexane	QRëC™, Newzealand
Hydrochloric acid, concentrated	Ajax FineChem Pty Ltd. Australia
4-Hydroxybenzaldehyde	Sigma Aldrich, Germany
Imidazole	Fluka, Switzerland
Iodine	VWR, BDH, Prolabo®, England
Methanol	Honeywell, Burdick&Jackson, USA
Molecular sieve (4Å beads 8-12 mesh)	Sigma Aldrich, Germany
4-Methoxyaniline	Sigma Aldrich, Germany
Nitrogen gas	Masser Speciality Gas Co.Ltd, Thailand
4-Nitroaniline	Sigma Aldrich, Germany
2-Propanol	Scharlau, Spain
Silica gel 60 (0.063-0.2 mm)	Merck, Germany

Silica gel 60 (0.04-0.06 mm)	Merck, Germany
Sodium metal, sticks PRS	Panreac, Spain
Sodium ascorbate	Sigma Aldrich, Germany
Sodium azide	Sigma Aldrich, Germany
Sodium nitrite	Carlo Erba Reagents, Italy
Sodium sulfate, anhydrous	Sigma Aldrich, Germany
Tetrahydrofuran	Carlo Erba, France
TLC silica gel 60 F_{254}	Merck, Germany
Toluidine	Carlo Erba, France

4.2 Chemical preparations

4.2.1 General chemistry methods

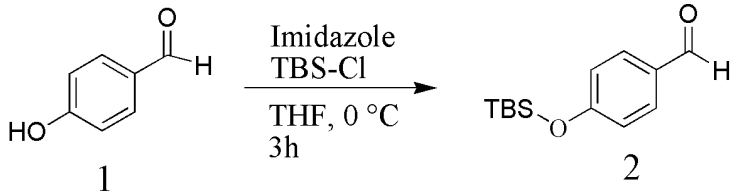
All chemical reactions for this protocol were performed by using reagent grade chemicals purchased from Sigma-Aldrich without further purification except benzyl chloride was synthesized in our laboratory. DMSO for making azides was stored over molecular sieves 4Å. All microwave-assisted experiments were conducted in a Activent closed reaction vial using a Microwave TM Synthesis System Discover® SP monomode microwave apparatus working at a frequency of 2.45 GHz with continuous irradiation power programmable from 0 to 300 W (CEM, USA). The progress of reactions was monitored by TLC on pre-coated silica gel plates (Merck 60 F254, 0.25 mm thickness) with a fluorescence indicator visualized by UV inspection and/or exposed to iodine vapor (stained with iodine vapor). Column chromatography was performed with silica gel 60 (0.063-0.2 mm and 0.04-0.06 mm, Merck) by using stated solvent systems and equilibrated with those systems prior to use. IR spectra of synthesized compounds were recorded (Neat or KBR pellets or nujol mulets) on a Thermo Scientific Nicolet FI IR spectrophotometer (USA) and reported as a wave number (cm^{-1}). ^{1}H NMR spectra were verified on a Bruker (300 MHz) using $CDCl_3$ or CD_3COCD_3 and tetramethylsilane (TMS) was used as internal standard. ^{13}C NMR spectra were verified on a Bruker (75 MHz) using CD_3COCD_3. Chemical shifts were reported in ppm (δ) or coupling constants (*J*) were reported as Hertz (Hz). Abbreviations to indicate the multiplicity of a individual signal are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), dd (doublet of doublet), tt

(triplet of triplet), m (multiplet), app (apparent) and br (broad). High resolution mass spectrometry (HRMS) measurements were recorded on a quadrupole time-of-flight mass spectrometer (Bruker Daltonics micrOTOF-Q II™ ESI-Qq-TOF, USA) with an electrospray ionization (ESI) source. The dry gas flow 8.0 L/min, positive ion polarity and capillary voltage 4000 V were used for accurate mass measurement. Melting points were determined in capillary tubes using digital visual melting point apparatus M-560 (BÜCHI, Switzerland) and were reported as uncorrected values.

4.2.2 Synthesis of designed compounds

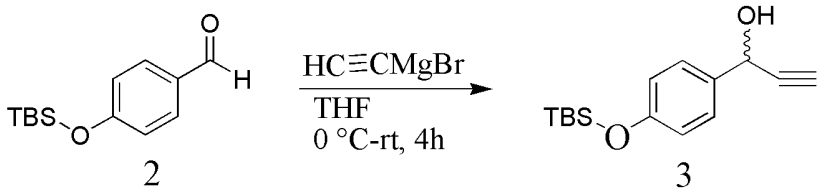
The total fifteen 1,4-disubstituted-1,2,3-triazole compounds (**7a-m**) were synthesized from the starting material, 4-hydroxybenzaldehyde **2**.

4.2.2.1 Synthesis of 4-(tert-Butyldimethylsilyloxy)benzaldehye 2



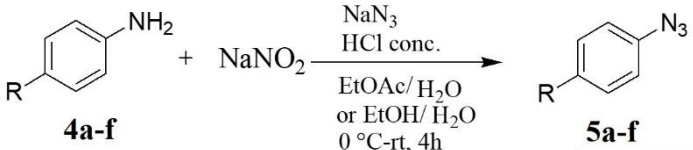
Oven-dried glasswares were used for the reaction. 4-Hydroxybenzaldehyde **1** (857.40 mg, 7 mmol, 1 equiv), imidazole (1.26 g, 21 mmol, 3 equiv) and *tert*-butyldimethylsilyl chloride (TBS-Cl) (2.14 mg, 14 mmol, 2 equiv) were dissolved in dry THF and stirred. Reaction was run at 0 °C under inert gas nitrogen and monitored by TLC to complete the reaction. After 3 h, the reaction mixture was quenched with water and it was evaporated the solvent. Aqueous layer was extracted with EtOAc and it was washed the organic layer by water and dried over anhydrous sodium sulphate. Organic layer was filtered and concentrated under reduced pressure and it was purified by column chromatography (SiO_2, EtOAc/*n*-Hex 1:1) to afford compound **2** (1.33 g, 80.93 %) as pale yellow oil. FT IR (Neat), *v*: 1700.8 cm^{-1} (C=O stretching), 2732.2 cm^{-1} (C-H stretching). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.25 (6H, s, Si-$(CH_3)_2$), 1.00 (9H, s, C-$(CH_3)_3$), 6.94 (2H, d, *J* = 6.0 Hz, H-3, H-5), 7.79 (2H, d, *J* = 6.0 Hz, H-2, H-6), 9.89 (1H, s, CHO) (5, 169).

4.2.2.2 Synthesis of 4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl) phenol 3



Oven-dried glasswares were used for the reaction. 4-(*tert*-Butyldimethylsilyloxy)benzaldehye, **2** (1.08 g, 4.60 mmol, 1 equiv) was dissolved in dry THF 5 mL in round-bottomed flask and cooled in ice-salt bath for 15 min. Ethynylmagnesium bromide (0.5M in THF) (24 mL, 11.97 mmol, 2.6 equiv) was added drop by drop to the flask. Reaction was run in a close system for 2 h. After that the reaction mixture was warmed to room temperature and stirred for additional 2 h. Then, saturated ammonium chlorides was added and shaken manually for a while and it was evaporated the solvent. Extraction was preceded with diethyl ether. Collected ether layer was washed with brine solution. Residual water was removed by anhydrous sodium sulphate. Finally, solution was concentrated under rotary evaporator. Crude product was purified by column chromatography (SiO_2, EtOAc/*n*-Hex 1:1) to obtain compound **3** (1.06 g, 88.40%) as pale yellow oil. FT IR (Neat), *v*: 2118.3 cm^{-1} (C=C stretching), 3309.9 cm^{-1} (=CH stretching, O-H stretching). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.20 (6H, s, Si-$(CH_3)_2$), 0.98 (9H, s, C-$(CH_3)_3$), 2.65 (1H, d, *J* = 3.0 Hz, C=CH), 5.41 (1H, s, CH-OH), 6.84 (2H, d, *J* = 9.0 Hz, H-3, H-5), 7.42 (2H, d, *J* = 9.0 Hz, H-2, H-6) (170).

4.2.2.3 General procedure A for syntheses of 5a-f



4a,5a; R = -H
4b,5b; R = -F
4c,5c; R = -NO_2
4d,5d; R = -CH_3
4e,5e; R = -OH
4f,5f; R = -OCH_3

Aniline and substituted aniline derivatives were used to get desired compounds. Aniline or 4-substituted aniline derivatives were dissolved in suitable solvent and it was cooled at 0 °C in ice-bath for 15 min. Then, concentrated hydrochloric acid (conc. HCl) was added to the solution with cooling and stirring. Then, solution of sodium nitrite in water was added dropwisely with stirring and reaction was run for 1 h. After that, solution of sodium azide in water was added drop by drop to the reaction mixture with stirring and temperature was maintained at 0 °C. An immediate emission of nitrogen was observed as white foam. The reaction mixture was warmed to room temperature and stirred for additional 3 h. Reaction was quenched with water, evaporated the organic solvent and azide product was extracted with EtOAc (3 × 50 mL). Then, organic layer was washed with water and dried over anhydrous sodium sulphate. It was filtered and concentrated under reduced pressure. In order to prevent degradation, crude azide was used directly in the next step without purification by column chromatography (170). **Caution:** Sodium azide and hydrazoic acicd are potentially explosive.

Azidobenzene 5a

Compound **5a** was obtained as reddish brown oily liquid (293.7 mg, 82.1%) by reaction of aniline **4a** (273.37 mg, 0.28 mL, 3 mmol, 1 equiv) in EtOAc with HCl conc. (1.034 g, 0.9 mL, 10.5 mmol, 3.5 equiv), sodium nitrite (208 mg, 3 mmol, 1 equiv) and sodium azide (195.4 mg, 3 mmol, 1 equiv) according to general procedure A. FT IR (Neat), *v*: 2129.0 cm^{-1} (asymmetric stretching N_3).

4-Fluorophenyl azide 5b

Compound **5b** was obtained as brown oily liquid (260 mg, 63.20%) by reaction of 4-fluoroaniline **4b** (336.36 mg, 0.29 mL, 3 mmol, 1 equiv) in ethanol with HCl conc. (1.034 g, 0.9 mL, 10.5 mmol, 3.5 equiv), sodium nitrite (311.1 mg, 4.5 mmol, 1.5 equiv) and sodium azide (297.1 mg, 4.5 mmol, 1.5 equiv) according to general procedure A. FT IR (Neat), *v*: 2114.6 cm^{-1} (asymmetric stretching N_3).

4-Nitrophenyl azide 5c

Compound **5c** was obtained as yellow powder (320 mg, 97.48%) by reaction of 4-nitroaniline **4c** (275.7 mg, 2 mmol, 1 equiv) in ethanol with HCl conc. (0.696 g, 0.6 mL, 7 mmol, 3.5 equiv), sodium nitrite (166.2 mg, 2.4 mmol, 1.2 equiv) and sodium azide (155.5 mg, 2.4 mmol, 1.2 equiv) according to general procedure A. FT IR (Nujol mull), *v*: 2121.6 cm^{-1} (asymmetric stretching N_3).

4-Methylphenyl azide 5d

Compound **5d** was obtained as orange oily liquid (322.4 mg, 80.70%) by reaction of 4-methylaniline **4d** (326.7 mg, 3 mmol, 1 equiv) in ethanol with HCl conc. (1.044 g, 0.9 mL, 10.5 mmol, 3.5 equiv), sodium nitrite (310.6 mg, 4.5 mmol, 1.5 equiv) and sodium azide (293.4 mg, 4.5 mmol, 1.5 equiv) according to general procedure A. FT IR (Neat), *v*: 2104.1 cm^{-1} (asymmetric stretching N_3).

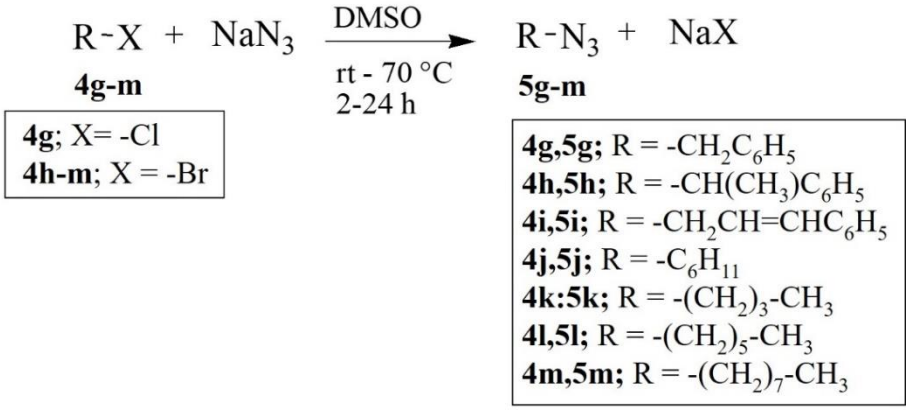
4-Hydroxyphenyl azide 5e

Compound **5e** was obtained as brown oily liquid (244.8 mg, 90.58%) by reaction of 4-amino phenol **4e** (218.7 mg, 2 mmol, 1 equiv) in ethanol (containing small amount of MeOH) with HCl conc. (0.696 g, 0.6 mL, 7 mmol, 3.5 equiv), sodium nitrite (165.7 mg, 2.4 mmol, 1.2 equiv) and sodium azide (155.4 mg, 2.4 mmol, 1.2 equiv) according to general procedure A. FT IR (Neat), *v*: 2114.3 cm^{-1} (asymmetric stretching N_3).

4-Methoxyphenyl azide 5f

Compound **5f** was obtained as brown oily liquid (533.6 mg, 89.44%) by reaction of *p*-anisidine **4f** (490.5 mg, 4 mmol, 1 equiv) in ethanol with HCl conc. (1.171 g, 1.010 mL, 12 mmol, 3 equiv), sodium nitrite (415.0 mg, 6 mmol, 1.5 equiv) and sodium azide (390.5 mg, 6 mmol, 1.5 equiv) according to general procedure A. FT IR (Neat), *v*: 2104.7 cm^{-1} (asymmetric stretching N_3).

4.2.2.4 General procedure B for syntheses of 5g-m



To a solution of 0.5M sodium azide (1.1 equiv) in DMSO (32.50 mg of sodium azide in 1 mL of DMSO), chloro or bromo alkyl, aralkyl or alicyclic bromide (1 equiv) was added. The solution was stirred according to the specified temperature and duration to complete the reaction which was checked by exposing of TLC plate to iodine vapour for alkyl azides without having chromophores. After completion, water was added to quench the reaction. This step was done in the ice bath due to the reaction was exothermic. After cooling down the reaction mixture to room temperature, the aqueous solution was extracted with diethyl ether (3 × 20 mL). The organic layers was merged and it was washed with cool water (5 × 20 mL). After drying over anhydrous sodium sulphate, diethyl ether was removed under reduced pressure or atmospheric pressure at room temperature to yield desired product. In order to prevent degradation, crude azide was used directly in the next step without purification by column chromatography (171).

Benzyl azide 5g

Benzyl chloride was synthesized from benzyl alcohol in our laboratory. Benzyl alcohol (4.8 mL, 5g, 0.046 mole, 1 equiv) was added to 10 M HCl (18.39 mL, 6.71 g, 0.184 mol, 4 equiv) to give white and cloudy solution. The reaction was slowly heated into 65 °C in an oil bath for 1½ h. Then, the reaction mixture was allowed to cool to room temperature (172). Benzyl chloride was extracted with hexane (3 × 20 mL) and washed with 5% sodium hydrogen carbonate until the aqueous layer was pH 8. After

washed with brine, organic layer was dried over anhydrous sodium sulphate and evaporated hexane layer to afford benzyl chloride as colorless oily liquid (5.37 g, 92.28%). This crude benzyl chloride was used directly in the next step without purification by column chromatography. **Caution:** Benzyl chloride is a lachrymatory agent.

Compound **5g** was obtained as colorless clear liquid (368.10 mg, 92.15%) by reaction of benzyl chloride **4g** (379.74 mg, 3 mmol, 1 equiv) with 6.6 mL of 0.5 M sodium azide (214.53 mg, 3.3 mmol, 1.1 equiv). The reaction mixture was stirred under room temperature for 2 h. The rest of the preparation method was followed as general procedure B. FTIR (Neat), *v*: 2097.3 cm^{-1} (asymmetric stretching N_3).

(1-Azidoethyl)benzene 5h

Compound **5h** was obtained as pale yellow liquid (819.70 mg, 81.66%) by reaction of (1-bromoethyl)benzene **4h** (1.26 mg, 6.82 mmol, 1 equiv) with 15 mL of 0.5 M sodium azide (487.57, 7.5 mmol, 1.1 equiv). The reaction mixture was stirred under room temperature for 2½ h. The rest of the preparation method was followed as general procedure B. FT IR (Neat), *v*: 2105.0 cm^{-1} (asymmetric stretching N_3).

Cinnamyl azide 5i

Compound **5i** was obtained as pale yellow liquid (759.10 mg, 79.47%) by reaction of 3-bromo-1-phenyl-1-propene **4i** (1.18 g, 6 mmol, 1 equiv) with 13.2 mL of 0.5 M sodium azide (429.06 mg, 6.6 mmol, 1.1 equiv). The reaction mixture was stirred under room temperature for 1½ h. The rest of the preparation method was followed as general procedure B. FT IR (Neat), *v*: 2099.7 cm^{-1} (asymmetric stretching N_3).

Cyclohexyl azide 5j

Compound **5j** was obtained as pale yellow liquid (474.80 mg, 63.22%) by reaction of cyclohexyl bromide **4j** (978.36 mg, 0.75 mL, 6 mmol, 1 equiv) with 13.2 mL of 0.5 M sodium azide (429.06 mg, 6.6 mmol, 1.1 equiv). The reaction mixture was stirred at 75 °C for 1½ h. The rest of the preparation method was followed as general procedure B. FT IR (Neat), *v*: 2090.7 cm^{-1} (asymmetric stretching N_3).

Butyl azide 5k

Compound **5k** was obtained as colourless liquid (1.12 g, 94.40%) by reaction of butyl bromide **4k** (1.64 g, 1.3 mL, 12 mmol, 1 equiv) with 26.4 mL of 0.5 M sodium azide (858.13 mg, 13.2 mmol, 1.1 equiv). The reaction mixture was stirred at 55 °C for 24 h. The rest of the preparation method was followed as general procedure B. Butyl azide is easy to volatile due to its low carbon content nature and does not tolerate to vacuum evaporation. Therefore, it is needed to isolate by removing the organic solvent under atmospheric pressure at room temperature. FT IR (Nujol mull), *v*: 2094.7 cm^{-1} (asymmetric stretching N_3).

Hexyl azide 5l

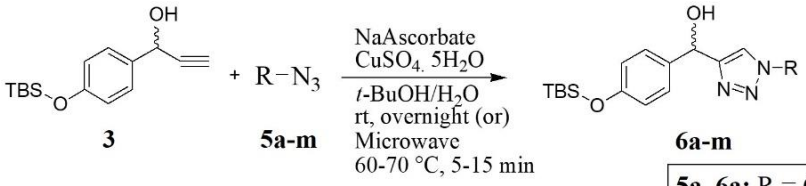
Compound **5l** was obtained as colourless liquid (879.9 mg, 86.62%) by reaction of hexyl bromide **4l** (1.32 mg, 1.13 mL, 8 mmol, 1 equiv) with 17.6 mL of 0.5 M sodium azide (572.088 mg, 8.8 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 4 h. The rest of the preparation method was followed as general procedure B. FT IR (Neat), *v*: 2095.6 cm^{-1} (asymmetric stretching N_3).

Octyl azide 5m

Compound **5m** was obtained as colourless liquid (966.6 mg, 77.80%) by reaction of octyl bromide **4m** (1.54 g, 1.4 mL, 8 mmol, 1 equiv) with 17.6 mL of 0.5 M sodium azide (572.08 mg, 8.8 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 4 h. The rest of the preparation method was followed as general procedure B. FT IR (Neat), *v*: 2095.8 cm^{-1} (asymmetric stretching N_3).

4.2.2.5 Syntheses of 6a-m

Compounds **6a-m** were synthesized conventionally and microwave-assisted methods from 4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl) phenol **3** by means of click reactions.



5a, 6a; R = C_6H_5-
5b, 6b; R = 4″F-C_6H_4-
5c, 6c; R = 4″NO_2-C_6H_4-
5d, 6d; R = 4″H_3-C_6H_4-
5e, 6e; R = 4″OH-C_6H_4-
5f, 6f; R = 4″OCH_3-C_6H_4-
5g, 6g; R = -$CH_2C_6H_5$
5h, 6h; R = -$CH(CH_3)C_6H_5$
5i, 6i; R = -CH_2CH=CHC_6H_5
5j, 6j; R = -C_6H_{11}
5k, 6k; R = -$(CH_2)_3$-CH_3
5l, 6l; R = -$(CH_2)_5$-CH_3
5m, 6m; R = -$(CH_2)_7$-CH_3

4.2.2.5.1 General procedure C for conventional syntheses of 6a-m

4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol **3** was dissolved in solvent (*t*-BuOH:H_2O) and it was mixed with organic azide solution in solvent. Powder of sodium ascorbate was added and stirred (100). Then, copper sulphate was added immediately. Reaction was run over night at room temperature under nitrogen. After that, it was quenched with water and solvent was concentrated in rotary evaporator. The aqueous phase was extracted with EtOAc (3 × 20 mL). The organic components were combined and washed with water (3 × 20 mL) and brine. Then, organic phase was dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by column chromatography on silica gel by using EtOAC:*n*-Hex 1:1 as an eluent afforded title compounds **6a to 6m**.

(1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6a)

To a solution of phenyl azide **5a** (60.57 mg, 0.50 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (119.7 mg, 0.45 mmol, 1 equiv), sodium ascorbate (40.5mg, 0.20 mmol, 0.45 equiv) and copper sulphate (17.4 mg, 0.06 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 14 h to

afford compound **6a** as reddish brown oil (94.4 mg, 54.28%). FT IR (Neat), *v*: 3148.2 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.20 (6H, s, Si-$(CH_3)_2$), 0.98 (9H, s, C-$(CH_3)_3$), 6.05 (1H, s, CH-OH), 6.85 (2H, d, *J* = 6.0 Hz, H-3′, H-5′), 7.36 (2H, d, *J* = 6.0 Hz, H-2′, H-6′), 7.42-7.44 (1H, m, H-4″), 7.47-7.52 (2H, m, H-3″, H-5″), 7.67-7.70 (2H, m, H-2″, H-6″), 7.69 (1H, s, triazole-H).

(1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6b)

To a solution of 4-flourophenyl azide **5b** (74.8 mg, 0.53 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (128.5 mg, 0.48 mmol, 1 equiv), sodium ascorbate (46.0 mg, 0.22 mmol, 0.45 equiv) and copper sulphate (18.9 mg, 0.07 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 14 h to afford compound **6b** as orange solid (151.9 mg, 77.65%). FT IR (KBr pellet), *v*: 3150.2 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.19 (6H, s, Si-$(CH_3)_2$), 0.98 (9H, s, C-$(CH_3)_3$), 6.04 (1H, s, CH-OH), 6.84 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 7.14-7.22 (2H, m, H-2″, H-6″), 7.33 (2H, d, *J* = 9.0 Hz, H-2′, H-6′), 7.61-7.68 (2H, m, H-3″, H-5″), 7.67 (1H, s, triazole-H).

(1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6c)

To a solution of 4-nitrophenyl azide **5c** (22.3 mg, 0.13 mmol, 1 equiv) in *t*-BuOH:H_2O 3:1 were added compound **3** (60.4 mg, 0.23 mmol, 1.7 equiv), sodium ascorbate (12.3 mg, 0.06 mmol, 0.45 equiv) and copper sulphate (151.9 mg, 0.60 mmol, 4.5 equiv). Reaction was performed according to general procedure C for 26 h to afford compound **6c** as yellowish brown oil (27.67 mg, 50.62%) (173). FT IR (Neat), *v*: app 3150.0 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.19 (6H, s, Si-$(CH_3)_2$), 0.98 (9H, s, C-$(CH_3)_3$), 3.01 (1H, s, br, CH-OH), 6.06 (1H, s, CH-OH), 6.85 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.35 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.84 (1H, s, triazole-H), 7.93 (2H, d, *J* = 9.2 Hz, H-2″, H-6″), 8.39 (2H, d, *J* = 9.1 Hz, H-3″, H-5″).

(1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl) methanol (6d)

To a solution of 4-methylphenyl azide **5d** (63.0 mg, 0.46 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (112.2 mg, 0.42 mmol, 1 equiv), sodium ascorbate (38.9 mg, 0.19 mmol, 0.45 equiv) and copper sulphate (16.3 mg, 0.06 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 12 h to afford compound **6d** as brown solid (124.20 mg, 73.53%). FT IR (KBr pellet), *v*: 3142.5 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.19 (6H, s, Si-$(CH_3)_2$), 0.99 (9H, s, C-$(CH_3)_3$), 2.40 (3H, s, 4′′-CH_3), 6.04 (1H, s, C<u>H</u>-OH), 6.84 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 7.27 (2H, d, *J* = 9.0 Hz, H-2′, H-6′), 7.35 (2H, d, *J* = 9.0 Hz, H-3′′, H-5′′), 7.54 (2H, d, *J* = 9.0 Hz, H-2′′, H-6′′), 7.66 (1H, s, triazole-H).

(1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyl oxy)phenyl)methanol (6e)

To a solution of 4-hydroxyphenyl azide **5e** (49.7 mg, 0.35 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (85.2 mg, 0.32 mmol, 1 equiv), sodium ascorbate (29.7 mg, 0.14 mmol, 0.45 equiv) and copper sulphate (12.3 mg, 0.04 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 14 h to afford compound **6e** as yellowish brown oil (88.50 mg, 68.58%). FT IR (Neat), *v*: 3152.1 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.16 (6H, s, Si-$(CH_3)_2$), 0.94 (9H, s, C-$(CH_3)_3$), 6.02 (1H, s, C<u>H</u>-OH), 6.79 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 6.85 (2H, d, *J* = 8.8 Hz, H-3′′, H-5′′), 7.29-7.32 (4H, m, H-2′, H-6′, H-2′′, H-6′′), 7.58 (1H, s, triazole-H).

(1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6f)

To a solution of 4-methoxyphenyl azide **5f** (129.3 mg, 0.82 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (196.7 mg, 0.74 mmol, 1 equiv), sodium ascorbate (67.2 mg, 0.33 mmol, 0.45 equiv) and copper sulphate (28.8 mg, 0.11 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 17 h to

afford compound **6f** as brown oil (234.60 mg, 76.10%). FT IR (Neat), *v*: 3146.4 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.18 (6H, s, Si-$(CH_3)_2$), 0.98 (9H, s, C-$(CH_3)_3$), 3.84 (3H, s, 4′′-OC<u>H</u>$_3$), 6.03 (1H, s, C<u>H</u>-OH), 6.82 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 6.94 (2H, d, *J* = 9.0 Hz, H-3′′, H-5′′), 7.34 (2H, d, *J* = 9.0 Hz, H-2′, H-6′), 7.53 (2H, d, *J* = 9.0 Hz, H-2′′, H-6′′), 7.63 (1H, s, triazole-H).

(1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6g)

To a solution of 4- benzyl azide **5g** (154.45 mg, 1.16 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (280.0 mg, 1.06 mmol, 1 equiv), sodium ascorbate (93.2 mg, 0.47 mmol, 0.45 equiv) and copper sulphate (39.9 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 24 h to afford compound **6g** as brown oil (253.70 mg, 60.50%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.17 (6H, s, Si-$(CH_3)_2$), 0.96 (9H, s, C-$(CH_3)_3$), 5.42 (2H, s, benzyl C<u>H</u>$_2$), 5.91 (1H, s, C<u>H</u>-OH), 6.78 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.17 (1H, s, triazole-H), 7.19-7.22 (2H, m, H-2′, H-6′), 7.23-7.26 (2H, m, H-2′′, H-6′′), 7.30-7.33 (3H, m, H-3′′, H-4′′ H-5′′).

(1-(Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6h)

To a solution of (1-Azidoethyl)benzene **5h** (162.0 mg, 1.10 mmol, 1.1 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (262.9 mg, 1.00 mmol, 1 equiv), sodium ascorbate (90.2 mg, 0.45 mmol, 0.45 equiv) and copper sulphate (37.5 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 24 h to afford compound **6h** as brown oil (171.50 mg, 41.87%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.17 (6H, s, Si-$(CH_3)_2$), 0.97 (9H, s, C-$(CH_3)_3$), 1.90 (3H, d, *J* = 7.1 Hz, CH_3), 3.68 (1H, s, br, CH-O<u>H</u>), 5.72 (1H, q, *J* = 7.0 Hz, C<u>H</u>-CH_3), 5.91 (1H, s, C<u>H</u>-OH), 6.78 (2H, d, *J* = 8.4 Hz, H-3′, H-5′), 7.16 (1H, s, triazole-H), 7.18-7.22 (2H, m, H-2′, H-6′), 7.24-7.27 (2H, m, H-2′′, H-6′′), 7.28-7.35 (3H, m, H-3′′, H-4′′ H-5′′).

(1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6i)

To a solution of cinnamyl azide **5i** (177.6 mg, 1.11 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (266.1 mg, 1.01 mmol, 1 equiv), sodium ascorbate (90.01 mg, 0.45 mmol, 0.45 equiv) and copper sulphate (37.71 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 24 h to afford compound **6i** as brown oil (222.10 mg, 52.15%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring). ^{1}H NMR (300 MHz), $CDCl_3$, δ: 0.18 (6H, s, Si-$(CH_3)_2$), 0.96 (9H, s, C-$(CH_3)_3$), 3.47 (1H, s, br, CH-OH), 5.05 (2H, dd, *J* = 1.2, 6.6 Hz, CH_2), 5.95 (1H, s, CH-OH), 6.23-6.32 (1H, m, CH_2-CH=CH), 6.61 (1H, d, *J* = 15.7 Hz, CH_2-CH=CH), 6.80 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.33 (1H, s, triazole-H), 7.22-7.40 (7H, m, H-2′, H-6′, H-2″, H-3″, H-4″ H-5″, H-6″).

(1-(Cyclohexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6j)

To a solution of cyclohexyl azide **5j** (133.3 mg, 1.05 mmol, 1.5 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (179.9 mg, 0.7 mmol, 1 equiv), sodium ascorbate (63.10 mg, 0.31 mmol, 0.45 equiv) and copper sulphate (26.80 mg, 0.10 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 16 h to afford compound **6j** as brown oil (160.50 mg, 59.15%). FT IR (Neat), *v*: 3131.4 cm^{-1} (C-H stretching in triazole ring). ^{1}H NMR (300 MHz), $CDCl_3$, δ: 0.19 (6H, s, Si-$(CH_3)_2$), 0.98 (9H, s, C-$(CH_3)_3$), 1.17-1.31 (1H, m, H-4″), 1.34-1.49 (2H, m, H-3″, H-5″), 1.61-1.77 (3H, m, H-3″ H-4″, H-5″), 1.86-1.92 (2H, m, H-2″, H-6″), 2.14-2.18 (2H, m, H-2″, H-6″), 4.38 (1H, tt, *J* = 3.8, 11.7 Hz, H-1″), 5.95 (1H, s, CH-OH), 6.82 (2H, d, *J* = 8.6 Hz, H-3′, H-5′), 7.21 (1H, s, triazole-H), 7.30 (2H, d, *J* = 8.6 Hz, H-2′, H-6′).

(1-(Butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6k)

To a solution of butyl azide **5k** (304.7 mg, 3.07 mmol, 3 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (268.9 mg, 1.02 mmol, 1 equiv), sodium ascorbate (91.4

mg, 0.46 mmol, 0.45 equiv) and copper sulphate (38.20 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 22 h to afford compound **6k** as yellow oil (191.2 mg, 51.64%). FT IR (Neat), *v*: 3141.8 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.19 (6H, s, Si-$(CH_3)_2$), 0.92 (3H, t, *J* = 7.3 Hz, H-4″), 0.97 (9H, s, C-$(CH_3)_3$), 1.32 (2H, sext, *J* = 7.5 Hz, H-3″), 1.83 (2H, quint, *J* = 7.4 Hz, H-2″), 3.55 (1H, s, br, CH-O<u>H</u>), 4.27 (2H, t, *J* = 7.3 Hz, H-1″), 5.95 (1H, s, C<u>H</u>-OH), 6.79-6.84 (2H, m, H-3′, H-5′), 7.20 (1H, s, triazole-H), 7.28-7.32 (2H, m, H-2′, H-6′).

(1-(Hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6l)

To a solution of hexyl azide **5l** (320.6 mg, 2.51 mmol, 2.5 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (263.7 mg, 1.00 mmol, 1 equiv), sodium ascorbate (89.2 mg, 0.45 mmol, 0.45 equiv) and copper sulphate (37.60 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 24 h to afford compound **6l** as brown oil (221.0 mg, 56.49%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.18 (6H, s, Si-$(CH_3)_2$), 0.86 (3H, t, *J* = 6.6 Hz, H-6″), 0.97 (9H, s, C-$(CH_3)_3$), 1.27-1.31 (6H, m, H-3″, H-4″, H-5″), 1.83 (2H, quint, *J* = 7.1 Hz, H-2″), 3.45 (1H, s, br, CH-O<u>H</u>), 4.26 (2H, t, *J* = 7.3 Hz, H-1″), 5.95 (1H, s, C<u>H</u>-OH), 6.79-6.84 (2H, m, H-3′, H-5′), 7.20 (1H, s, triazole-H), 7.28-7.31 (2H, m, H-2′, H-6′).

(1-(Octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6m)

To a solution of octyl azide **5m** (207.9 mg, 1.26 mmol, 1.1 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (302.3 mg, 1.15 mmol, 1 equiv), sodium ascorbate (104.7 mg, 0.51 mmol, 0.45 equiv) and copper sulphate (43.40 mg, 0.17 mmol, 0.15 equiv). Reaction was performed according to general procedure C for 12 h to afford compound **6m** as orange oil (282.9 mg, 58.90%). FT IR (Neat), app 3140.0 cm^{-1} (C-H stretching in triazole ring). ^1H NMR (300 MHz), $CDCl_3$, δ: 0.19 (6H, s, Si-$(CH_3)_2$), 0.87 (3H, t, *J* = 6.9 Hz, H-8″), 0.97 (9H, s, C-$(CH_3)_3$), 1.18-1.26 (10H, m, H-

3″, H-4″, H-5″, H-6″, H-7″), 1.86 (2H, quint, *J* = 7.2 Hz, H-2″), 4.27 (2H, t, *J* = 7.2 Hz, H-1″), 5.95 (1H, s, CH-OH), 6.79-6.84 (2H, m, H-3′, H-5′), 7.20 (1H, s, triazole-H), 7.28-7.32 (2H, m, H-2′, H-6′).

4.2.2.5.2 Conventional synthesis of 6g by thermal heating method

To a solution of benzyl azide **5g** (150.90 mg, 1.13 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (270.6 mg, 1.03 mmol, 1 equiv), sodium ascorbate (91.3 mg, 0.46 mmol, 0.45 equiv) and copper sulphate (38.5 mg, 0.15 mmol, 0.15 equiv). The reaction mixture was heated at 70 °C in silicone bath for 15 min. Then, the reaction mixture was quenched with water and the solvent was evaporated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The organic components were combined and it was washed with water (3 × 20 mL) and brine. Then, organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a desired crude product which was purified by column chromatography on silica gel (EtOAC:Hex 1:1 v/v) as eluent afforded title compounds **6g** as brown oil (209.60 mg, 51.44%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

4.2.2.5.3 General procedure D for microwave-assisted syntheses of 6a-m

4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol **3**, organic azide, sodium ascorbate, and copper sulphate were added to a CEM design 10 mL or 35 mL ActiVent reaction vial with snap on ActiVent cap containing *t*-BuOH:water and small magnetic bar. The reaction mixture was transferred to the CEM monomode microwave system and subjected to microwave irradiation at a power level of 150 watt and at specified constant temperature 60 °C or 70 °C and time. During the reaction time, microwave power was automatically limited when specified temperature was reached and the built up pressure in the closed reaction vessel was cautiously examined. Pre-stirring time 30 second and medium stirring speed were used for the whole process. After the irradiation, the sealed reaction vial was cooled down to room temperature by passing high-pressure compressed air through the microwave cavity until the temperature was decreased to 60 °C (ca. 0 to 54 second). Then, the reaction mixture was quenched with water and the solvent was evaporated. The aqueous phase was

extracted with EtOAc (3 × 20 mL). The organic components were combined and it was washed with water (3 × 20 mL) and brine. Then, organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a desired crude product which was purified by column chromatography on silica gel (EtOAC:Hex 1:1 v/v) as eluent afforded title compounds **6a to 6m**.

(1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6a)

To a solution of phenyl azide **5a** (54.70 mg, 0.44 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (107.3 mg, 0.4 mmol, 1 equiv), sodium ascorbate (36.1mg, 0.18 mmol, 0.45 equiv) and copper sulphate (15.0 mg, 0.06 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 60 °C, 5 min to afford compound **6a** as reddish brown oily liquid (118.40 mg, 75.22%). FT IR (Neat), *v*: 3149.5 cm^{-1} (C-H stretching in triazole ring).

(1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6b)

To a solution of 4-fluorophenyl azide **5b** (75.50 mg, 0.55 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (132.4 mg, 0.5 mmol, 1 equiv), sodium ascorbate (44.8mg, 0.22 mmol, 0.45 equiv) and copper sulphate (18.8 mg, 0.07 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 60 °C, 5 min to afford compound **6b** as orange solid (166.80 mg, 83.50%). FT IR (KBr pellet), *v*: 3150.2 cm^{-1} (C-H stretching in triazole ring).

(1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6c)

To a solution of 4-nitrophenyl azide **5c** (26.00 mg, 0.15 mmol, 1 equiv) in *t*-BuOH:H_2O 3:1 were added compound **3** (69.9 mg, 0.26 mmol, 1.7 equiv), sodium ascorbate (14.1 mg, 0.07 mmol, 0.45 equiv) and copper sulphate (175.3 mg, 0.70 mmol, 4.5 equiv). Reaction was performed according to general procedure D under microwave

irradiation at 60 °C, 10 min to afford compound **6c** as yellowish brown semisolid (38.20 mg, 57.44%). FT IR (Neat), *v*: 3151.1 cm^{-1} (C-H stretching in triazole ring).

(1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6d)

To a solution of 4-methylphenyl azide **5d** (71.3 mg, 0.52 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (125.8 mg, 0.47 mmol, 1 equiv), sodium ascorbate (43.6 mg, 0.21 mmol, 0.45 equiv) and copper sulphate (18.1 mg, 0.07 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 60 °C, 5 min to afford compound **6d** as brown solid (161.20 mg, 85.11%). FT IR (KBr pellet), *v*: 3142.5 cm^{-1} (C-H stretching in triazole ring).

(1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*butyldimethylsilyloxy) phenyl)methanol (6e)

To a solution of 4-hydroxyphenyl azide **5e** (58.0 mg, 0.42 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (100.9 mg, 0.38 mmol, 1 equiv), sodium ascorbate (34.5 mg, 0.17 mmol, 0.45 equiv) and copper sulphate (14.5 mg, 0.05 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 60 °C, 15 min to afford compound **6e** as brown oil (106.30 mg, 69.65%). FT IR (KBr pellet), *v*: 3152.2 cm^{-1} (C-H stretching in triazole ring).

(1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6f)

To a solution of 4-methoxyphenyl azide **5f** (123.2 mg, 0.82 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (196.8 mg, 0.75 mmol, 1 equiv), sodium ascorbate (67.2 mg, 0.33 mmol, 0.45 equiv) and copper sulphate (28.1 mg, 0.11 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 60 °C, 5 min to afford compound **6f** as brown oil (249.50 mg, 80.83%). FT IR (KBr pellet), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6g)

To a solution of benzyl azide **5g** (212.00 mg, 1.5 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (375.8 mg, 1.43 mmol, 1 equiv), sodium ascorbate (128.0 mg, 0.64 mmol, 0.45 equiv) and copper sulphate (55.7 mg, 0.21 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6g** as brown oil (435.40 mg, 76.70%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6h)

To a solution of (1-Azidoethyl)benzene **5h** (170.8 mg, 1.16 mmol, 1.1 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (277.0 mg, 1.05 mmol, 1 equiv), sodium ascorbate (94.2 mg, 0.47 mmol, 0.45 equiv) and copper sulphate (40.5 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6h** as brown oil (242.30 mg, 56.07%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6i)

To a solution of cinnamyl azide **5i** (162.1 mg, 1.01 mmol, 1.1 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (243.9 mg, 0.92 mmol, 1 equiv), sodium ascorbate (82.5 mg, 0.41 mmol, 0.45 equiv) and copper sulphate (34.5 mg, 0.13 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6i** as brown oil (281.90 mg, 72.69%). FT IR (Neat), *v*: 3144.2 cm^{-1} (C-H stretching in triazole ring).

(1-(Cyclohexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6j)

To a solution of cyclohexyl azide **5j** (61.95 mg, 0.49 mmol, 1.5 equiv) in *t*-BuOH:H_2O 1:1 were added compound **3** (88.0 mg, 0.33 mmol, 1 equiv), sodium

ascorbate (29.5 mg, 0.14 mmol, 0.45 equiv) and copper sulphate (12.7 mg, 0.04 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6j** as brown oil (82.80 mg, 64.73%). FT IR (Neat), *v*: 3132.1 cm^{-1} (C-H stretching in triazole ring).

(1-(Butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6k)

To a solution of butyl azide **5k** (283.60 mg, 2.85 mmol, 3.0 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (253.0 mg, 0.95 mmol, 1 equiv), sodium ascorbate (85.1 mg, 0.42 mmol, 0.45 equiv) and copper sulphate (34.8 mg, 0.14 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6k** as yellow oil (205.80 mg, 59.91%). FT IR (Neat), *v*: 3141.8 cm^{-1} (C-H stretching in triazole ring).

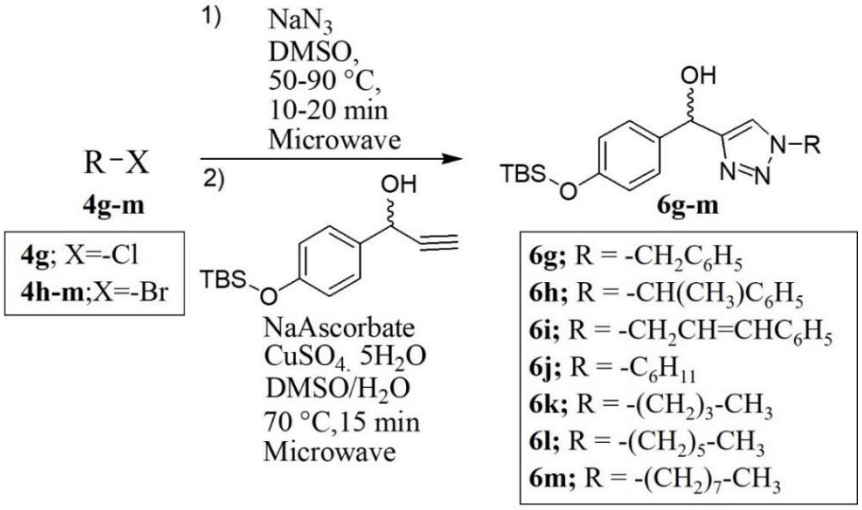
(1-(Hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6l)

To a solution of hexyl azide **5l** (321.70 mg, 2.52 mmol, 2.5 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (266.6 mg, 1.01 mmol, 1 equiv), sodium ascorbate (90.7 mg, 0.45 mmol, 0.45 equiv) and copper sulphate (38.2 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6l** as brown oil (266.70 mg, 67.77%). FT IR (Neat), *v*: 3141.8 cm^{-1} (C-H stretching in triazole ring).

(1-(Octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6m)

To a solution of octyl azide **5m** (170.90 mg, 1.10 mmol, 1.1 equiv) in *t*-BuOH:H_2O 2:1 were added compound **3** (264.2 mg, 1.00 mmol, 1 equiv), sodium ascorbate (90.3 mg, 0.45 mmol, 0.45 equiv) and copper sulphate (37.6 mg, 0.15 mmol, 0.15 equiv). Reaction was performed according to general procedure D under microwave irradiation at 70 °C, 15 min to afford compound **6m** as orange oil (286.40 mg, 68.58%). FT IR (Neat), *v*: 3142.2 cm^{-1} (C-H stretching in triazole ring).

4.2.2.6 One-pot two-step microwave-assisted reactions



Scheme 5. One-pot, two-step synthesis of **6g-m**.

The overall reaction scheme for one-pot, two-step synthesis was described in Scheme 5. It has two-step procedure including microwave-assisted synthesis of azide and those desired azides reacted with alkyne to afford compound **6g-m**.

4.2.2.6.1 General procedure E for microwave-assisted syntheses of azides 5g-m

To a solution of 0.5M sodium azide (1.1 equiv) in DMSO (32.505 mg of sodium azide in 1 mL of DMSO) in CEM design 10 mL or 35 mL ActiVent reaction vial with snap on ActiVent cap and small magnetic bar, alkyl, arylalkyl or alicyclic halide (1 equiv) was added. The reaction mixture was transferred to the CEM monomode microwave system and subjected to microwave irradiation at a power level of 150 watt and at specified constant temperature and time. During the reaction time microwave power was automatically limited when specified temperature was reached and the built up pressure in the closed reaction vessel was cautiously examined. Pre-stirring time 30 second and medium stirring speed was used for the whole process. Completion of the reaction was checked by exposing of TLC plate to iodine vapour for alkyl azides without having chromophore. After the irradiation, the sealed reaction vial was cooled down to room temperature by passing high-pressure compressed air through the microwave cavity until the temperature was decreased to 60 ℃ (ca. 1 second to 1 minute). Then, the reaction mixture was quenched with water. After cooling down the reaction mixture to room temperature, the aqueous solution was extracted with diethyl

ether (3 × 50 mL). The organic layers was merged and washed with cool water (5 × 50 mL). After drying over anhydrous sodium sulphate, diethylether was removed under reduced pressure or atmospheric pressure at room temperature to yield desired product. In order to prevent degradation, crude azide was used directly in the next step without purification by column chromatography.

Benzyl azide 5g

Compound **5g** was obtained as colorless clear liquid (379.40 mg, 94.98%) by reaction of benzyl chloride **4g** (379.74 mg, 3 mmol, 1 equiv) with 6.6 mL of 0.5 M sodium azide (214.53 mg, 3.3 mmol, 1.1 equiv). The reaction mixture was stirred at 50 °C for 10 min. The rest of the preparation method was followed as general procedure E. FT IR (Neat), *v*: 2097.2 cm^{-1} (asymmetric stretching N_3).

(1-Azidoethyl)benzene 5h

Compound **5h** was obtained as pale yellow liquid (1.01 g, 86.52%) by reaction of (1-bromoethyl)benzene **4h** (1.48 g, 8 mmol, 1 equiv) with 17.6 mL of 0.5 M sodium azide (572.08 mg, 8.8 mmol, 1.1 equiv). The reaction mixture was stirred at 50 °C for 10 min. The rest of the preparation method was followed as general procedure E. FT IR (Neat), *v*: 2104.5 cm^{-1} (asymmetric stretching N_3).

Cinnamyl azide 5i

Compound **5i** was obtained as pale yellow liquid (525.60 mg, 82.54%) by reaction of cinnamyl bromide **4i** (790.70 mg, 4 mmol, 1 equiv) with 8.8 mL of 0.5 M sodium azide (286.04 mg, 4.4 mmol, 1.1 equiv). The reaction mixture was stirred at 50 °C for 10 min. The rest of the preparation method was followed as general procedure E. FT IR (Neat), *v*: 2099.4 cm^{-1} (asymmetric stretching N_3).

Cyclohexyl azide 5j

Compound **5j** was obtained as pale yellow liquid (330.30 mg, 65.9%) by reaction of cyclohexyl bromide **4j** (625.24 mg, 0.5 mL, 4 mmol, 1 equiv) with 8.8 mL of 0.5 M sodium azide (286.04 mg, 4.4 mmol, 1.1 equiv). The reaction mixture was

stirred at 90 °C for 20 min. The rest of the preparation method was followed as general procedure E. FT IR (Neat), *v*: 2090.5 cm^{-1} (asymmetric stretching N_3).

Butyl azide 5k

Compound **5k** was obtained as colourless liquid (1.14 mg, 96.18%) by reaction of butyl bromide **4k** (1.64 g, 1.3 mL, 12 mmol, 1 equiv) with 26.4 mL of 0.5 M sodium azide (858.13 mg, 13.2 mmol, 1.1 equiv). The reaction mixture was stirred at 80 °C for 10 min. The rest of the preparation method was followed as general procedure E. The solvent diethylether was removed at 500 mbar and at room temperature due to intolerance of butyl azide to vacuum evaporation. FT IR (Nujol mull), *v*: 2102.1 cm^{-1} (asymmetric stretching N_3).

Hexyl azide 5l

Compound **5l** was obtained as colourless liquid (891.30 mg, 87.59%) by reaction of hexyl bromide **4l** (1.32 g, 1.2 mL, 8 mmol, 1 equiv) with 17.6 mL of 0.5 M sodium azide (572.08 mg, 8.8 mmol, 1.1 equiv). The reaction mixture was stirred at 80 °C for 10 min. The rest of the preparation method was followed as general procedure E. FT IR (Neat), *v*: 2095.8 cm^{-1} (asymmetric stretching N_3).

Octyl azide 5m

Compound **5m** was obtained as colourless liquid (1.06 mg, 85.36%) by reaction of octyl bromide **4m** (1.54 g, 1.4 mL, 8 mmol, 1 equiv) with 17.6 mL of 0.5 M sodium azide (572.088 mg, 8.8 mmol, 1.1 equiv). The reaction mixture was stirred at 80 °C for 10 min. The rest of the preparation method was followed as general procedure E. FT IR (Neat), *v*: 2095.8 cm^{-1} (asymmetric stretching N_3).

4.2.2.6.2 General procedure F for microwave-assisted syntheses of 6g-m

4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol **3** was added to substituted azide solution in DMSO which was prepared by general procedure B. Then, solution of sodium ascorbate in water and copper sulphate were added to a CEM design 10 mL or 35 mL ActiVent reaction vial with snap on ActiVent cap and small magnetic

bar. The reaction mixture was transferred to the CEM monomode microwave system and subjected to microwave irradiation at a power level of 150 watt and at specified constant temperature and time. The During the reaction time microwave power was automatically limited when specified temperature was reached and the built up pressure in the closed reaction vessel was cautiously examined. Pre-stirring time 30 second and medium stirring speed were used for the whole process. After the irradiation, the sealed reaction vial was cooled down to room temperature by passing high-pressure compressed air through the microwave cavity until the temperature was decreased to 60 ℃ (ca. 12 to 54 second). Then, more water was added to the reaction mixture when it was reached to room temperature and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine and dried over anhydrous sodium sulphate and evaporated the solvent under reduced pressure to obtain a desired crude products **6g-m** which was purified by column chromatography on silica gel (EtOAC:*n*-Hex 1:1) as eluent.

(1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6g)

To a 0.5M NaN_3 in DMSO 2.9 mL (94.39 mg), benzyl chloride 0.16 mL (175.70 mg, 1.32 mmol, 1.29 equiv) was added. Reaction was performed according to general procedure B to obtain compound **5g** by microwave energy at 50 ℃, 10 min. Then, compound **3** (269.90 mg, 1.02 mmol, 1 equiv), sodium ascorbate (90.9 mg, 0.459 mmol, 0.45 equiv) solution in water and copper sulphate (38.3 mg, 0.15 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F under microwave irradiation at 70 ℃, 15 min to obtain compound **6g** as pale yellow oil (242.8 mg, 60.17%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6h)

To a 0.5M NaN_3 in DMSO 2.82 mL (91.53 mg), 1-bromoethyl benzene 0.18 mL (236.87 mg, 1.25 mmol, 1.47 equiv) was added. Reaction was performed according to general procedure B to obtain compound **5h** by microwave energy at 50 ℃, 10 min. Then, compound **3** (230.5 mg, 0.87 mmol, 1 equiv), sodium ascorbate (77.60 mg, 0.39

mmol, 0.45 equiv) solution in water and copper sulphate (32.6 mg, 0.13 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F under microwave irradiation at 70 °C, 15 min to obtain compound **6h** as pale yellow oil (245.0 mg, 68.75%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6i)

To a 0.5M NaN_3 in DMSO 3.28 mL (106.47 mg), cinnamyl bromide (304.9 mg, 1.48 mmol, 1.52 equiv) was added. Reaction was performed according to general procedure B to obtained compound **5i** by microwave energy at 50 °C, 10 min. Then, compound **3** (256.0 mg, 0.975 mmol, 1 equiv), aqueous solution of sodium ascorbate (87.4 mg, 0.43 mmol, 0.45 equiv) solution and copper sulphate (36.45 mg, 0.14 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F under microwave irradiation at 70 °C, 15 min to obtain compound **6i** as pale yellow oil (242.80 mg, 59.06%). FT IR (Neat), *v*: 3144.2 cm^{-1} (C-H stretching in triazole ring).

(1-(Cyclohexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6j)

To a 0.5M NaN_3 in DMSO 6.0 mL (194.37 mg), cyclohexyl bromide (445.0 mg, 0.34 mL, 2.72 mmol, 2.72 equiv) was added. Reaction was performed according to general procedure B to obtained compound **5j** by microwave energy at 90 °C, 20 min. Then, compound **3** (263.30 mg, 1.00 mmol, 1 equiv), aqueous solution of sodium ascorbate (89.2 mg, 0.45 mmol, 0.45 equiv) solution and copper sulphate (37.5 mg, 0.15 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F under microwave irradiation at 70 °C, 15 min to obtain compound **6j** as white solid (175.5 mg, 45.27%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6k)

To a 0.5M NaN_3 in DMSO 8.31 mL (270.31 mg), butyl bromide (517.97 mg, 3.78 mmol, 3.74 equiv) was added. Reaction was performed according to general procedure B to obtained compound **5k** by microwave energy at 80 °C, 10 min. Then, compound **3** (267.6 mg, 1.01 mmol, 1 equiv), aqueous solution of sodium ascorbate (90.80 mg, 0.454 mmol, 0.45 equiv) solution and copper sulphate (37.70 mg, 0.151 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F under microwave irradiation at 70 °C, 15 min to obtain compound **6k** as pale yellow oil (199.9 mg, 54.74%). FT IR (Neat), *v*: 3129.7 cm^{-1} (C-H stretching in triazole ring).

(1-(Hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6l)

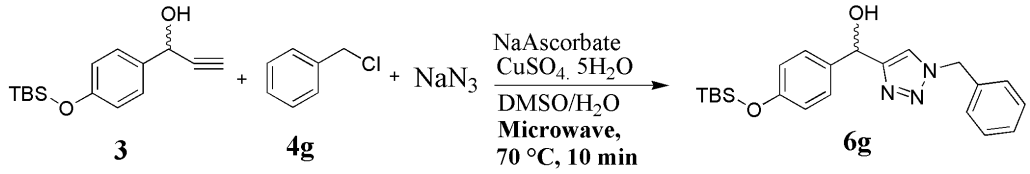
To a 0.5M NaN_3 in DMSO 2.82 mL (91.53 mg), bromo hexane 0.3 mL (359.50 mg, 2.17 mmol, 3.57 equiv) was added. Reaction was performed according to general procedure B to obtained compound **5l** by microwave energy at 80 °C, 10 min. Then, compound **3** (161.1 mg, 0.61 mmol, 1 equiv), aqueous solution of sodium ascorbate (54.3 mg, 0.274 mmol, 0.45 equiv) solution and copper sulphate (22.9 mg, 0.09 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F under microwave irradiation at 70 °C, 15 min to obtain compound **6l** as pale yellow oil (137.1 mg, 57.70%). FT IR (Neat), *v*: app 3140.0 cm^{-1} (C-H stretching in triazole ring).

(1-(Octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6m)

To a 0.5M NaN_3 in DMSO 2.9 mL (92.96 mg), bromo octane 0.23 mL (251.05 mg, 1.3 mmol, 1.48 equiv) was added. Reaction was performed according to general procedure B to obtained compound **5m** by microwave energy at 80 °C, 10 min. Then, compound **3** (233.2 mg, 0.88 mmol, 1 equiv), aqueous solution of sodium ascorbate (78.5 mg, 0.396 mmol, 0.45 equiv) solution and copper sulphate (33.0 mg, 0.13 mmol, 0.15 equiv) were added. Reaction was performed according to general procedure F

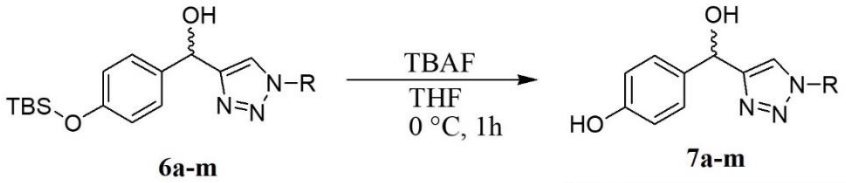
under microwave irradiation at 70 °C, 15 min to obtain compound **6m** as pale yellow oil (208.0 mg, 56.59%). FT IR (Neat), *v*: 3142.2 cm^{-1} (C-H stretching in triazole ring).

4.2.2.7 Multicomponent synthesis of 6g



4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol **3** (285.9 mg, 1.08 mmol, 1 equiv) was added to benzyl chloride (187.60 mg, 0.17 mL, 1.40 mmol, 1.3 equiv) in 3.1 mL of 0.5 M sodium azide (100.70 mg, 1.54 mmol, 1.43 equiv) in DMSO which was prepared by general procedure B. Then, solution of sodium ascorbate (97.20 mg, 0.49 mmol, 0.45 equiv) in water and copper sulphate (40.40 mg, 0.163 mmol, 0.15 equiv) were added to a CEM design 10 mL ActiVent reaction vial with snap on ActiVent cap and small magnetic bar. The reaction mixture was transferred to the CEM monomode microwave system and subjected to microwave irradiation at a power level of 150 watt. Reaction was performed according to general procedure F under microwave irradiation at 70 °C, 15 min to obtain compound **6g** as pale yellow thick oil (89.20 mg, 20.88%). FT IR (Neat), *v*: 3141.7 cm^{-1} (C-H stretching in triazole ring).

4.2.2.8 General procedure G for syntheses of 7a-m



6a-m **7a-m**

6a,7a:R= C_6H_5-
6b,7b:R= 4F-C_6H_4-
6c,7c:R= 4NO_2-C_6H_4-
6d,7d:R= 4CH_3-C_6H_4-
6e,7e:R= 4OH-C_6H_4-
6f,7f:R= 4OCH_3-C_6H_4-
6g,7g:R= -$CH_2C_6H_5$
6h,7h:R= -$CH(CH_3)C_6H_5$
6i,7i:R= -CH_2CH=CHC_6H_5
6j,7j:R= -C_6H_{11}
6k,7k:R= -$(CH_2)_3$-CH_3
6l,7l:R= -$(CH_2)_5$-CH_3
6m,7m:R= -$(CH_2)_7$-CH_3

Oven-dried glasswares were used for the deprotection reaction. To a solution of (1-(substituted)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol in dry THF 10 mL cooled at 0 ℃ of ice-bath for 15 min, a solution of *terta-n*-butyl ammonium fluoride (TBAF) was added. The reaction mixture was stirred at 0 ℃ for 1h and the reaction was quenched with water. The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic components were combined and it was washed with water (3 × 20 mL). Then, organic phase was dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by column chromatography on silica gel with gradient elution by using EtOAC:*n*-Hex 2:1 to 100% EtOAc as eluent afforded title compounds **7a to 7m** (5, 169).

4-(Hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7a)

To a solution of (1-(phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol **6a** (366.4 mg, 0.96 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 ℃ of ice-bath for 15 min, a solution of TBAF (502.0 mg, 2 mL, 1.92 mmol, 2 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7a** as pale yellow solid (232.3 mg, 90.56%), mp 180 °C (decompn).

FT IR (KBr pellet), *v*: 3157.0 cm^{-1} (C-H stretching in triazole ring), 3448.3 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 4.88 (1H, s, br, CH-OH), 5.96 (1H, s, CH-OH), 6.80 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 7.34 (2H, d, *J* = 9.0 Hz, H-2′, H-6′), 7.44-7.79 (1H, m, H-4″), 7.57 (2H, t, *J*=9.0, H-3″, H-5″), 7.89 (2H, d, *J* = 9.0 Hz, H-2″, H-6″), 8.33 (1H, s, triazole-H). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 69.68 (CH-OH), 115.84 (C-3′, C-5′), 120.31 (C-5), 121.00 (C-3″, C-5″), 128.84 (C-2′, C-6′), 129.26 (C-4″), 130.68 (C-2″, C-6″), 135.67 (C-1″), 138.40 (C-1′), 154.31 (C-4), 157.69 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{15}H_{13}N_3O_2$ is 290.0906 and observed $[M+Na]^+$ at 290.0913.

4-(Hdroxyl-(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7b)

To a solution of (1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol **6b** (96.6 mg, 0.24 mmol, 1 equiv) in dry THF (5 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (94.50 mg, 0.4 mL, 0.36 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7b** as pale yellow solid (55.80 mg, 81.16%), mp 165 °C (decompn). FT IR (KBr pellet), *v*: 1234.3 cm^{-1} (C-F stretching), 3154.1 cm^{-1} (C-H stretching in triazole ring), 3462.8 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 4.94 (1H, s, br, CH-OH), 5.96 (1H, s, CH-OH), 6.80 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.32-7.37 (4H, m, H-2′, H-6′, H-2″, H-6″), 7.91-7.96 (2H, m, H-3″, H-5″), 8.32 (1H, s, triazole-H). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 69.63 (CH-OH), 115.85 (C-3′, C-5′), 117.36 (C-3″, C-5″, *J* = 23.2 Hz), 120.62 (C-5), 123.27 (C-2″, C-6″, *J* = 9.0 Hz), 128.83 (C-2′, C-6′), 134.84 (C-1″, *J* = 3.0 Hz), 135.58 (C-1′), 154.34 (C-4), 157.70 (C-4′), 163.04 (C-4″, *J* = 244.5 Hz). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{15}H_{12}FN_3O_2$ is 308.0812 and observed $[M+Na]^+$ at 308.0813.

4-(Hydroxyl-(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7c)

To a solution of (1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol **6c** (552.1 mg, 1.29 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (504.61 mg, 2.2 mL, 1.93 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure

G to obtained compound **7c** as yellow solid (370.70 mg, 92.02%), mp 193 °C (decompn). FT IR (KBr pellet), *v*: 1342.0 cm^{-1}, 1523.0 cm^{-1} (NO_2 stretching), 3094.6 cm^{-1} (C-H st. in triazole ring), 3409.5 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 5.01 (1H, s, br, CH-OH), 5.98 (1H, s, CH-OH), 6.80 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.34 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 8.24 (2H, d, *J* = 9.1 Hz, H-2″, H-6″), 8.34 (1H, s, br, 4′-OH), 8.44 (2H, d, *J* = 9.1 Hz, H-3″, H-5″), 8.55 (1H, s, triazole-H). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 69.57 (CH-OH), 115.90 (C-3′, C-5′), 120.80 (C-5), 121.39 (C-3″, C-5″), 126.30 (C-2″, C-6″), 128.88 (C-2′, C-6′), 135.32 (C-1″), 142.55 (C-1′), 147.99 (C-4), 155.01 (C-4′), 157.81 (C-4″). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{15}H_{12}N_4O_4$ is 335.0757 and observed $[M+Na]^+$ at 335.0753.

4-(Hydroxyl-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7d)

To a solution of (1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol **6d** (153.0 mg, 0.38 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (151.30 mg, 0.6 mL, 0.57 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7d** as pale yellow solid (80.90 mg, 74.50%), mp 175 °C (decompn). FT IR (KBr pellet), *v*: 3125.1 cm^{-1} (C-H stretching in triazole ring), 3345.1 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 2.39 (3H, s, 4″-CH_3), 4.87 (1H, s, br, CH-OH), 5.95 (1H, s, CH-OH), 6.80 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 7.31-7.38 (4H, m, H-2′, H-6′, H-3″, H-5″), 7.75 (2H, d, *J* = 9.0 Hz, H-2″, H-6″), 8.27 (1H, s, triazole-H). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 21.02 (4″-CH_3), 69.66 (CH-OH), 115.84 (C-3′, C-5′), 120.25 (C-5), 120.91 (C-3″, C-5″), 128.82 (C-2′, C-6′), 131.06 (C-2″, C-6″), 135.65 (C-1″), 136.09 (C-4″), 139.25 (C-1′), 154.13 (C-4), 157.67 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{16}H_{15}N_3O_2$ is 304.1062 and observed $[M+Na]^+$ at 304.1058.

4-(Hydroxyl-(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7e)

To a solution of (1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol **6e** (595.9 mg, 1.49 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (587.50 mg, 2.3 mL,

2.24 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7e** as pale yellow solid (258.40 mg, 60.90%), mp 111 °C (decompn). FT IR (KBr pellet), *v*: around 3100.0 cm^{-1} (C-H st. in triazole ring), 3288.0 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: app 3.20 (1H, s, br, CH-O<u>H</u>), 4.90 (1H, s, 4″-OH), 5.95 (1H, s, C<u>H</u>-OH), 6.80 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 6.99 (2H, d, *J* = 9.0 Hz, H-3″, H-5″), 7.33 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.67 (2H, d, *J* = 9.0 Hz, H-2″, H-6″), 8.17 (1H, s, triazole-H), 8.65 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 69.65 (<u>C</u>H-OH), 115.83 (C-3′, C-5′), 116.97 (C-3″, C-5″), 120.40 (C-5), 122.86 (C-2″, C-6″), 128.79 (C-2′, C-6′), 130.86 (C-1′), 135.63 (C-1″), 153.88 (C-4), 157.66 (C-4′), 158.62 (C-4″). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{15}H_{13}N_3O_3$ is 306.0855 and observed $[M+Na]^+$ at 306.0847.

4-(Hydroxyl-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7f)

To a solution of (1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol **6f** (222.9 mg, 0.54 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (212.35 mg, 0.8 mL, 0.81 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7f** as pale yellow solid (128.79 mg, 78.88%), mp 161 °C (decompn). FT IR (KBr pellet), *v*: 3126.2 cm^{-1} (C-H stretching in triazole ring), 3422.5 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 3.87 (3H, s, 4″-OCH_3), 4.87 (1H, s, br, CH-O<u>H</u>), 5.95 (1H, s, C<u>H</u>-OH), 6.80 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 7.10 (2H, d, *J* = 9.0 Hz, H-3″, H-5″), 7.33 (2H, d, *J* = 9.0 Hz, H-2′, H-6′), 7.78 (2H, d, *J* = 9.0 Hz, H-2″, H-6″), 8.21 (1H, s, triazole-H). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 56.05 (4″-OCH_3), 69.65 (<u>C</u>H-OH), 115.64 (C-3′, C-5′), 115.83 (C-3″, C-5″), 120.35 (C-5), 122.66 (C-2″, C-6″), 128.76 (C-2′, C-6′), 131.79 (C-1′), 135.64 (C-1″), 154.09 (C-4), 157.74 (C-4′), 160.64 (C-4″). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{16}H_{15}N_3O_3$ is 320.1011 and observed $[M+Na]^+$ at 320.1016.

4-(Hydroxyl-(1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7g)

To a solution of (1-(benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy) phenyl)methanol **6g** (1.06 g, 2.69 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (4.5 mL, 4.03 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7g** as off-white solid (662.80 mg, 87.59% yield), mp 137 °C (decompn). FT IR (KBr pellet), *v*: 3145.6 cm^{-1} (C-H stretching in triazole ring), 3294.3 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 4.82 (1H, s, br, CH-O<u>H</u>), 5.56 (2H, s, benzyl CH_2), 5.86 (1H, s, C<u>H</u>-OH), 6.77 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.26 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.32-7.40 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.72 (1H, s, triazole-H), 8.35 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 54.16 (benzyl C<u>H</u>$_2$), 69.59 (<u>C</u>H-OH), 115.77 (C-3′, C-5′), 122.28 (C-5), 128.64 (C-2′, C-6′), 128.94 (C-4″), 129.08 (C-2″, C-6″), 129.69 (C-3″, C-5″), 135.81 (C-1′), 137.15 (C-1″), 153.56 (C-4), 157.56 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{16}H_{15}N_3O_2$ is 304.1062 and observed $[M+Na]^+$ at 304.1057.

4-(Hydroxyl-(1-(ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7h)

To a solution of (1-(ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol **6h** (1.03 g, 2.53 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (4.2 mL, 3.79 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G afforded desired compound. After consecutive washing the crude compound with *n*-hexane, chloroform and then EtOAc, pure compound **7h** was precipitated and it was dried under vacuum to afford the desired compound as off-white solid (513.20 mg, 68.68% yield), mp 180 °C (decompn). FT IR (KBr pellet), *v*: 3148.3 cm^{-1} (C-H stretching in triazole ring), 3454.0 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 1.93 (3H, d, *J* = 6 Hz, CH_3), 4.82 (1H, s, br, CH-O<u>H</u>), 5.88 (1H, q, *J* = 6.9 Hz, C<u>H</u>-CH_3), 5.89 (1H, s, C<u>H</u>-OH), 6.77 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.26 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.30-7.38 (5H, m, H-2″, H-3″ H-4″, H-5″ H-6″), 7.74 (1H, s, triazole-H), 8.38 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 21.71 (CH-<u>C</u>H$_3$), 60.75 (<u>C</u>H-CH_3), 69.65 (<u>C</u>H-OH), 115.77 (C-3′, C-5′), 121.12 (C-5), 127.37 (C-2″, C-6″), 128.66 (C-2′, C-6′), 128.94 (C-

4″), 129.64 (C-3″, C-5″), 135.82 (C-1′), 142.25 (C-1″), 153.13 (C-4), 157.55 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{17}H_{17}N_3O_2$ is 318.1219 and observed $[M+Na]^+$ at 318.1216.

4-(Hydroxyl-(1-(cinnamyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7i)

To a solution of (1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl) methanol, **6i** (928.28 mg, 2.2 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (3.6 mL, 3.3 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7i** as off-white solid (485.80 mg, 71.84% yield), mp 147 °C (decompn). FT IR (KBr pellet), *v*: 3157.5 cm^{-1} (C-H stretching in triazole ring), 3439.4 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 4.93 (1H, s, br, CH-O<u>H</u>), 5.13 (2H, dd, *J* = 1.0, 6.4 Hz, CH_2), 5.91 (1H, s, C<u>H</u>-OH), 6.43-6.52 (1H, m, CH_2-C<u>H</u>=CH), 6.69 (1H, d, *J* = 15.8 Hz, CH_2-CH=C<u>H</u>), 6.77-6.82 (2H, m, H-3′, H-5′), 7.23-7.35 (5H, m, H-2′, H-6′, H-3″, H-4″, H-5″), 7.41-7.45 (2H, m, H-2″, H-6″), 7.75 (1H, s, triazole-H), 8.48 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 52.55 (CH_2), 69.58 (<u>C</u>H-OH), 115.79 (C-3′, C-5′), 122.09 (C-5), 124.19 (-CH_2-CH=<u>C</u>H-), 127.53 (C-2″, C-6″), 128.63 (C-2′, C-6′), 129.00 (C-4″), 129.52 (C-3″, C-5″), 135.14 (-CH_2-<u>C</u>H=CH-), 135.75 (C-1′), 137.02 (C-1″), 153.40 (C-4), 157.57 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{18}H_{17}N_3O_2$ is 330.1219 and observed $[M+Na]^+$ at 330.1223.

4-(Hydroxyl-(1-(cyclohexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7j)

To a solution of (1-(cyclohexy)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl) methanol, **6j** (853.8 mg, 2.20 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (3.65 mL, 3.3 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7j** as off-white solid (478.9 mg, 79.64% yield), mp 133 °C (decompn). FT IR (KBr pellet), *v*: 3121.7 cm^{-1} (C-H stretching in triazole ring), 3260.9 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 1.26-1.36 (1H, m, H-4″), 1.39-1.55 (2H, m, H-3″, H-5″), 1.68-1.90 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 2.05-2.15 (2H, m, H-2″, H-6″), 4.44 (1H, tt, *J* = 3.8, 11.5 Hz, H-1″), 4.93 (1H, s, br, CH-O<u>H</u>), 5.89 (1H, s, C<u>H</u>-OH), 6.80 (2H,

d, *J* = 8.6 Hz, H-3′, H-5′), 7.29 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.73 (1H, s, triazole-H), 8.53 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 25.84 (C-3″, C-4″, C-5″), 34.05 (C-2″, C-6″), 60.49 (C-1″), 69.64 (CH-OH), 115.78 (C-3′, C-5′), 120.13 (C-5), 128.64 (C-2′, C-6′), 135.80 (C-1′), 152.66 (C-4), 157.56 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{15}H_{19}N_3O_2$ is 296.1375 and observed $[M+Na]^+$ at 296.1375.

4-(Hydroxyl-(1-(butyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7k)

To a solution of (1-(butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyl oxy)phenyl) methanol, **6k** (851.20 mg, 2.35 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (3.9 mL, 3.52 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7k** as pale yellow solid (545.60 mg, 93.88% yield), mp 96 °C (decompn). FT IR (KBr pellet), *v*: 3142.7 cm^{-1} (C-H stretching in triazole ring), 3371.6 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 0.90 (3H, t, *J* = 7.3 Hz, H-4″), 1.29 (2H, sext, *J* = 7.5 Hz, H-3″), 1.82 (2H, quint, *J* = 7.3 Hz, H-2″), 4.34 (2H, t, *J* = 7.1 Hz, H-1″), 5.12 (1H, s, br, CH-OH), 5.91 (1H, s, CH-OH), 6.80 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.27 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.73 (1H, s, triazole-H), 8.70 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 13.72 (C-4″), 20.20 (C-3″), 32.91 (C-2″), 50.30 (C-1″), 69.46 (CH-OH), 115.80 (C-3′, C-5′), 122.26 (C-5), 128.58 (C-2′, C-6′), 135.55 (C-1′), 152.94 (C-4), 157.55 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{13}H_{17}N_3O_2$ is 270.1219 and observed $[M+Na]^+$ at 270.1223.

4-(Hydroxyl-(1-(hexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7l)

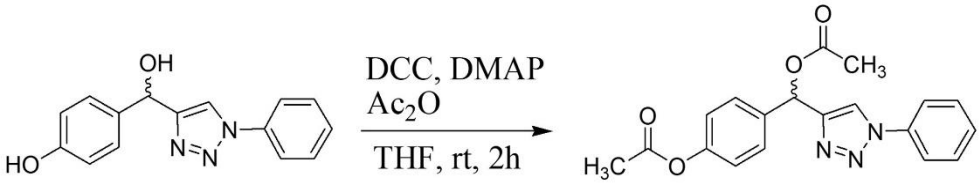
To a solution of (1-(hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol, **6l** (771.2 mg, 1.97 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (3.3 mL, 2.95 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7l** as off-white solid (410.40 mg, 75.65% yield), mp 82 °C (decompn). FT IR (KBr pellet), *v*: 3122.8 cm^{-1} (C-H stretching in triazole ring), 3241.1 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6, δ: 0.86 (3H, t, *J* = 6.9 Hz, H-6″), 1.22-1.29 (6H, m, H-3″, H-4″, H-5″), 1.85 (2H, quint, *J* = 6.9 Hz, H-2″), 4.34 (2H,

t, *J* = 7.1 Hz, H-1″), 4.88 (1H, s, br, CH-O<u>H</u>), 5.87 (1H, s, C<u>H</u>-OH), 6.78 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.26 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.70 (1H, s, triazole-H), 8.48 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 14.27 (C-6″), 23.12 (C-5″), 26.80 (C-3″), 30.98 (C-2″), 31.88 (C-4″), 50.57 (C-1″), 69.58 (-<u>C</u>H-OH), 115.77 (C-3′, C-5′), 122.13 (C-5), 128.62 (C-2′, C-6′), 135.82 (C-1′), 153.05 (C-4), 157.57 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{15}H_{21}N_3O_2$ is 298.1532 and observed $[M+Na]^+$ at 298.1533.

4-(Hydroxyl-(1-(octyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7m)

To a solution of (1-(octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyl oxy)phenyl)methanol, **6m** (871.1 mg, 2.08 mmol, 1 equiv) in dry THF (10 mL) cooled at 0 °C of ice-bath for 15 min, a solution of TBAF (3.45 mL, 3.12 mmol, 1.5 equiv) was added. Reaction was performed according to general procedure G to obtained compound **7m** as off-white bulky solid (334.3 mg, 52.97% yield), mp 95 °C (decompn). FT IR (KBr pellet), *v*: 3125.0 cm^{-1} (C-H stretching in triazole ring), 3238.4 cm^{-1} (O-H stretching). ^{1}H NMR (300 MHz), Acetone-d_6) δ: 0.87 (3H, t, *J* = 6.5 Hz, H-8″), 1.26-1.29 (10H, m, H-3″, H-4″, H-5″, H-6″, H-7″), 1.87 (2H, quint, *J* = 6.9 Hz, H-2″), 4.34 (2H, t, *J* = 7.1 Hz, H-1″), 4.92 (1H, s, br, CH-O<u>H</u>), 5.87 (1H, s, C<u>H</u>-OH), 6.78 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 7.26 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 7.70 (1H, s, triazole-H), 8.53 (1H, s, br, 4′-OH). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 14.39 (C-8″), 23.28 (C-7″), 27.14 (C-3″), 29.66 (C-2″), 29.84 (C-4″), 31.02 (C-5″), 32.47 (C-6″), 50.58 (C-1″), 69.56 (<u>C</u>H-OH), 115.76 (C-3′, C-5′), 122.13 (C-5), 128.61 (C-2′, C-6′), 135.78 (C-1′), 153.04 (C-4), 157.57 (C-4′). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{17}H_{25}N_3O_2$ is 326.1845 and observed $[M+Na]^+$ at 326.1849.

4.2.2.9 4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl acetate 8



To a solution of 4-(hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol **7a** (312.1 mg, 1.16 mmol, 1 equiv) in dry THF were added DCC (602.50 mg, 2.91 mmol, 2.5 equiv), acetic anhydride (417.20 mg, 3.8 mL, 4.08 mmol, 3.5 equiv) and DMAP (285.10 mg, 2.33 mmol, 2 equiv). Reaction was stirred at room temperature for 2 h and quenched with water. THF was evaporated and filtered dicyclohexylurea (DCU). Aqueous layer was extracted with EtOAc (3 × 20 mL), washed with water (3 × 20 mL) and brine. Then, organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a desired crude product which was purified by column chromatography on silica gel (EtOAC:Hex 1.5:1 v/v) as eluent afforded title compounds **8** as white solid (230.10 mg, 56.09% yield), mp 119 °C (decompn). FT IR (KBr pellet), *v*: 1206 cm^{-1} (C-O stretching), 1637 cm^{-1} (aromatic, skeletal C=C stretching), 1763, 1741 cm^{-1} (C=O stretching), 3136.45 cm^{-1} (C-H stretching of triazole ring). ^{1}H NMR (300 MHz), $CDCl_3$, δ: 2.16 (3H, s, CH-OCOC$\underline{H}_3$), 2.29 (3H, s, Ar-OCOC$\underline{H}_3$), 7.10 (1H, s, C$\underline{H}$-OCOCH_3), 7.10-7.13 (2H, m, H-3′, H-5′), 7.42-7.56 (5H, m, H-2', H-6′, H-3″, H-4″, H-5″), 7.68-7.71 (2H, m, H-2″, H-6″), 7.86 (1H, s, triazole-H). ^{13}C NMR (75 MHz), Acetone-d_6, δ: 50.75 (CH-OCO$\underline{C}$H$_3$), 54.93 (4″-OCO$\underline{C}$H$_3$), 70.40 ($\underline{C}$H-OCOCH$_3$), 121.17 (C-3′, C-5′), 121.95 (C-5), 122.78 (C-2″,C-6″), 129.35 (C-2′,C-6′), 129.55 (C-4″), 130.68 (C-3″, C-5″), 137.28 (C-1″), 148.77 (C-1′), 151.84 (C-4), 155.07 (C-4′), 169.67 (4′ C=O), 170.14 (CH-O$\underline{C}$=O) (174). HRMS (ESI) (m/z) calculated $[M+Na]^+$ $C_{19}H_{17}N_3O_4$ is 347.1117 and observed $[M+Na]^+$ at 347.1117.

4.3 Evaluation of antituberculosis activities

The evaluation of anti-tuberculosis activities of all synthesized compounds 7a-m and 8 was performed by Tuberculosis Research Laboratory, National Center for Genetic Engineering and Biotechnology, the National Science and Technology Development Agency (NSTDA), Thailand.

4.3.1 Determination of minimum inhibitory concentration by agar dilution method

Synthesized chemical compounds was evaluated for their anti-tuberculosis activity against *Mtb* H37Rv and 20 MTB clinical isolates. It was performed on agar dilution method. This method is still regarded as gold standard method to find minimum inhibitory concentration (MIC) for antimycobacterial drug-susceptibility testing. In agar dilution method, MIC means lowest concentration of drug that can prevent visible growth of bacteria *Mtb* on solid Middlebrook agar medium within 21 days of incubation at 37 °C. This method is whole cell screening on bacterial growth and not target-based screening approach; therefore, it cannot give information concern with mechanism of action. However, this *in vitro* bioassay method for investigating MIC-based structure activity relationship of different synthesized compounds is one of the promising methods in the early stage of drug discovery process. Proposed general protocol for agar dilution method is presented as follows (175) .

4.3.1.1 Preparation of inoculums

Inoculums was prepared by scraping colonies of exponential growth *Mtb* H37Rv/ H37Ra from solid medium, disperse colonies in a 20x150 mm screw-cap tube containing 2 to 3 mL of Middlebrook*7H9* broth supplemented with 10% oleic acid-albumin-dextrose-catalase (OADC) and 0.05% Tween 80 and 5-8 glass beads (diameter of 6 mm), vortex for 2-3 min, and stand for 20 min to allow large clumps of cells to settle. Cell suspension was transferred to a new sterile tube and adjust to a turbidity equivalent to a 1 McFarland Standard (ca. 3×10^7 cells/mL) with *M7H9* broth. Then, it was diluted to reach standard inoculums (ca. 1.5×10^5 cells/mL).

4.3.1.2 Preparation of test compounds and antibiotic-containing Middlebrook 7H10 agar dilution plates

Middlebrook 7H10-10% oleic acid-albumin-dextrose-catalase (OADC) (Difco, USA) agar plates with different concentrations of test compounds (Final concentration: 0 to 64 or 128 μgmL^{-1}) and antibiotics was used.

4.3.1.3 Inoculation of 7H10 agar plates

McFarland No. 1 (1.5×10^5 cells) of each *Mtb* strain standard inoculums 5 μL was spotted onto both test compound, antibiotic containing and drug-free control *7H10* agar plates. Plates was sealed in CO_2-permeable polyethylene bags and incubated at 37 °C for 3 weeks.

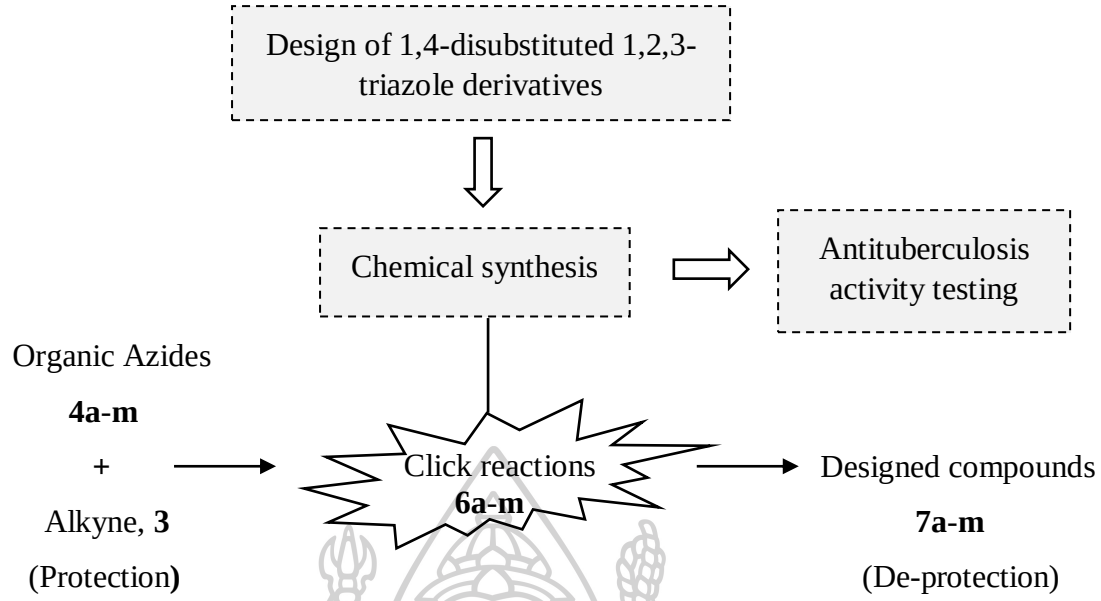
4.3.1.4 Determination of MIC

MIC was determined as the concentration that do not found colonies (% resistance bacteria) compared with the control plate without drug.

$$\% \text{ Resistance bacteria} = \frac{\text{Number of colonies on drug containing medium}}{\text{Number of colonies on Drug free medium}} \times 100$$

CHAPTER V
RESULTS AND DISCUSSION

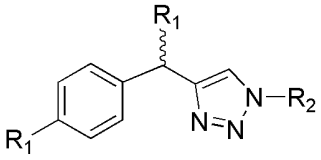
This research was included two experimental portions as chemical synthesis and activity testing for antituberculosis activity. The scope of the research project was illustrated in Figure 8. Total fourteen 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives compounds were designed and synthesized. The chemical structures, molecular weights and formulae of proposed 1,4-disubstituted-1,2,3-triazole compounds are displayed in Table 2. In order to synthesize those compounds, firstly, 4-hydroxybenzaldehyde was used as starting material. Its hydroxyl group was protected by hydroxyl protecting group, *tert*-butyl-dimethylsilyl chloride (TBS-Cl) and protected hydroxybenzaldehyde was changed to alcohol group by means of Grignard reaction using ethynyl magnesium bromide as a reagent. In order to synthesize 1,4-disubstituted-1,2,3-triazole derivatives, copper catalysed alkyne and azide click reaction was applied by using various methods. Therefore, alkyne was reacted with desired azide in the presence of sodium ascorbate and copper sulphate pentahydrate catalysts to form protected 1,4-disubstituted-1,2,3-triazole derivatives. De-protection reaction was done by using *tetra*-*n*-butyl ammonium fluoride (TBAF). Further di-acetylation was continued if needed with *N*,*N'*-dicyclohexylcarbodiimide (DCC), dimethylamino pyridine (DMAP) and acetic anhydride. Each and every synthesized designed compound was purified by column chromatography using silica gel and pure synthesized compound was elucidated by means of FT IR, ^{1}H NMR, ^{13}C NMR and HR-MS spectroscopic methods. General reaction pathways for synthesizing compounds **7a-m** and **8** are showed in Scheme 6 and 7. Then, the synthesized designed compounds **7a-m** and **8** were investigated for their antituberculosis activities.

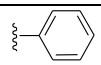
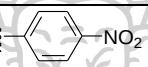
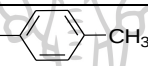
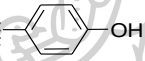
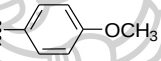
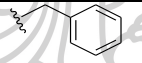
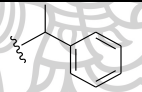
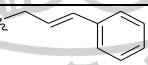
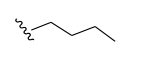
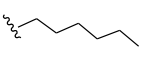
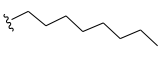


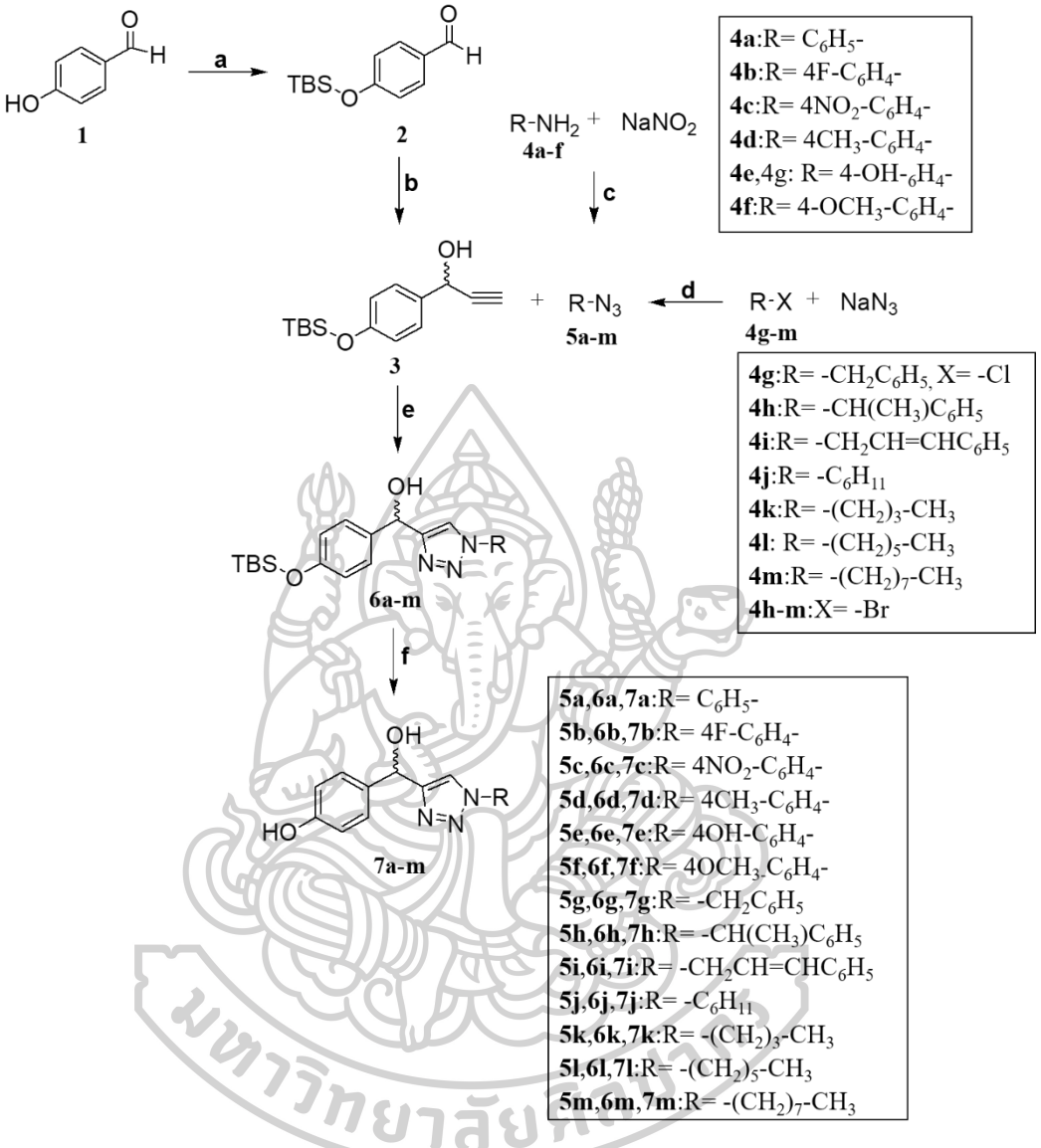
1. Conventional synthesis (room temperature)
2. Conventional synthesis (thermal heating)
3. Microwave assisted organic synthesis
4. One-pot, two-step microwave assisted organic synthesis
5. Multicomponent microwave assisted organic synthesis

Figure 8. The scope of research project.

Table 2. Proposed 1,4-disubstituted-1,2,3-triazole compounds.

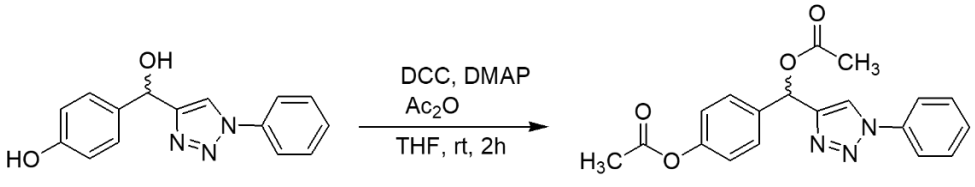


Entry	Compd code	R_1	R_2	Molecular formula	Molecular weight	Exact mass
1	7a	-OH		$C_{15}H_{13}N_3O_2$	267.28	267.1008
2	8	-$OCOCH_3$		$C_{19}H_{17}N_3O_4$	351.36	351.1219
3	7b	-OH		$C_{15}H_{12}FN_3O_2$	285.27	285.0914
4	7c	-OH		$C_{15}H_{12}N_4O_4$	312.28	312.0859
5	7d	-OH		$C_{16}H_{15}N_3O_2$	281.31	281.1164
6	7e	-OH		$C_{15}H_{13}N_3O_3$	283.28	283.0957
7	7f	-OH		$C_{16}H_{15}N_3O_3$	297.31	297.1113
8	7g	-OH		$C_{16}H_{15}N_3O_2$	281.31	281.1164
9	7h	-OH		$C_{17}H_{17}N_3O_2$	295.34	295.1321
10	7i	-OH		$C_{18}H_{17}N_3O_2$	307.35	307.1321
11	7j	-OH		$C_{15}H_{19}N_3O_2$	273.33	273.1477
12	7k	-OH		$C_{13}H_{17}N_3O_2$	247.29	247.1321
13	7l	-OH		$C_{15}H_{21}N_3O_2$	275.35	275.1634
14	7m	-OH		$C_{17}H_{25}N_3O_2$	303.40	303.1947



Scheme 6. General reaction pathway for compound **7a-m**.

Reaction and conditions: (a) imidazole, *tert*-butyldimethylsilyl chloride, THF, 0 °C, 3 h. (b) ethynylmagnesium bromide, THF, 0 °C to rt, 4 h. (c) concentrated hydrochloric acid, NaN_3, H_2O/EtOAc or H_2O/EtOH, 0 °C to rt, 4 h. (d) NaN_3, DMSO, rt-75 °C, 1½ to 24 h. (e) sodium ascorbate, $CuSO_4.5H_2O$, *t*-BuOH/H_2O, rt, overnight (or) microwave irradiation with suitable temperature and duration. (f) *tetra-n*-butylammonium fluoride, THF, 0 °C, 1 h.



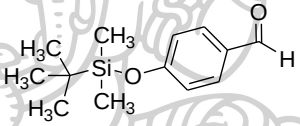
7a **8**

Scheme 7. Reaction pathway for compound **8**.

Reaction and conditions: *N*,*N′*-dicyclohexylcarbodiimide (DCC), dimethylamino pyridine (DMAP), acetic anhydride (AC_2O), rt, 2 h.

5.1 Chemical synthesis

5.1.1 4-(*tert*-Butyldimethylsilyloxy)benzaldehye 2



In this reaction, 4-Hydroxybenzaldehyde was used as starting material to afford compound **2**. The aim of this step was to protect the active hydroxyl group of 4-hydroxybenzaldehyde before the next step to prevent the undesirable reaction. As a protecting group, *tert*-butyldimethylsilyl chloride (TBS-Cl) was selected because silicon protecting group can be introduced efficiently to starting material, stable in quenching and column chromatographic purification procedures and cleavage of this group can be achieved readily in deprotection step. The reaction rate of silylation to phenolic hydroxy can be reduced due to the bulky and steric nature of TBS-Cl, therefore, basic imidazole was used to accelerate the reaction of forming *tert*-butyldimethylsilyl ether (176, 177). This reaction was performed in polar aprotic solvent, dry tetrahydrofuran (THF) and it was completed at 0 °C for 3h with or without nitrogen to provide good percent yield, 80.93%. The reaction mechanism for introduction of TBS-Cl protecting group to phenolic hydroxyl was described in Figure 9.

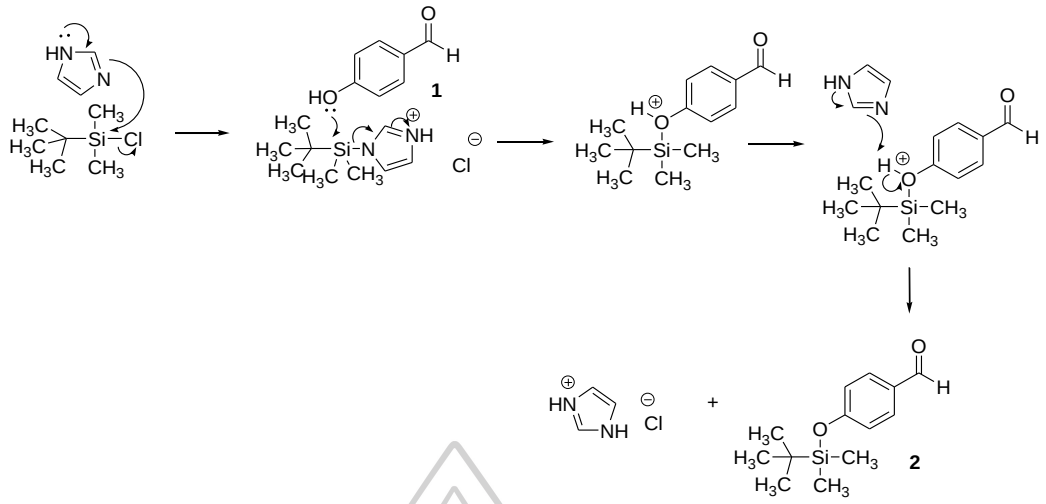


Figure 9. Reaction mechanism of compound **2** synthesis.

The availability of dry and oxygen free organic solvent is a critical part of some chemical reactions. Generally, the laboratory THF contains high content of water. In this research, the solvent, dry THF means THF was dried and deoxygenated by using vertical distillation apparatus containing sodium-benzophenone combination in which benzophenone was reduced by sodium to ketal radical (Figure 10). The sodium benzophenone ketal anion radical (deep blue color) has oxygen-scavenging activity and can react with water to form colorless products. Therefore, the deep blue color of ketal indicator in THF still showed the solvent is deoxygenated and contains very low level of water content about 10 ppm (178).

Caution: THF drying still is hazardous because of its hot vapor of highly flammable solvent during reflux operation. This apparatus should be paid of special attention by experienced chemist.

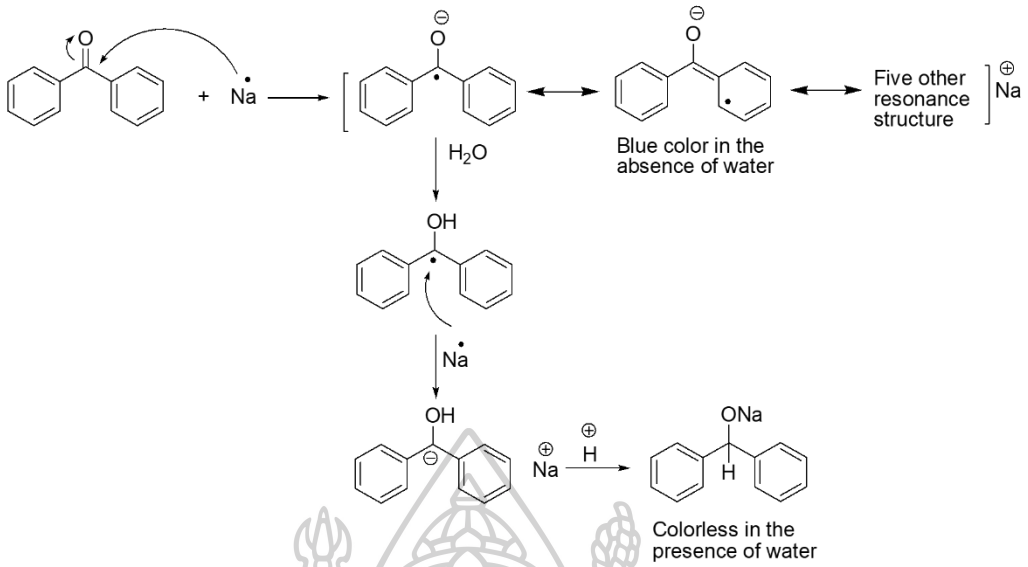
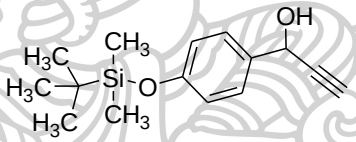


Figure 10. The reaction of sodium with benzophenone.

5.1.2 4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl) phenol 3



The aim of this step was to convert the function group and the creation of new carbon-carbon bond by mean of Grignard reaction. Oven-dried glasswares, needles, stir bar and septum (110 °C, overnight) were used for this reaction. The Grignard reagent, ethynylmagnesium bromide (0.5M in THF) 2.6 equiv was needed to proceed the reaction efficiently in a close system with 1 equiv of previously cooled 4-(*tert*-Butyldimethylsilyloxy)benzaldehye, **2** in dry THF to stabilize the reaction. The compound **3** was obtained in good percent yield (88.40%) as pale yellow oil. The less equiv of ethynylmagnesium bromide (~1.5 equiv) produced unsatisfactory percent yield of product or reaction had not happened readily. The strong basic nature of reagent can react with acid hydrogen in water, so polar protic solvent must be avoided. As reaction mechanism, the Grignard reagent is a strong carbon nucleophile, therefore, it can attack to electrophilic aldehyde functional group of compound **2** to form a new carbon-carbon bond. The saturated ammonium chloride was used in quenching

procedure to protonate the negative charge oxygen to form hydroxyl group. The reaction mechanism to generate compound **3** was described in Figure 11.

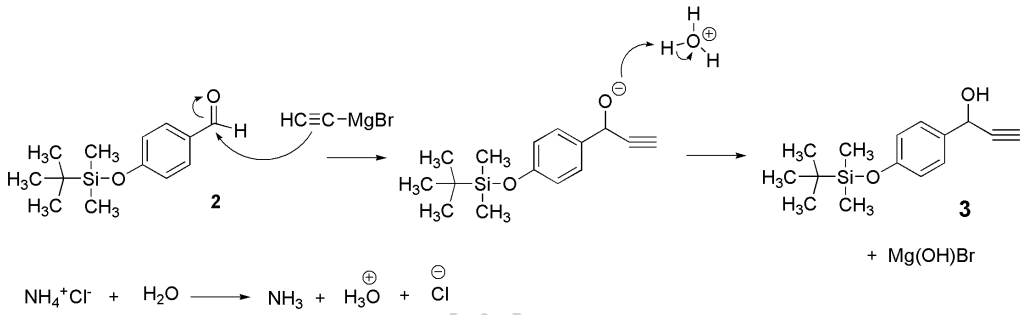


Figure 11. Reaction mechanism of compound **3** synthesis.

5.1.3 Organic azides 5a-m

Phenyl azide was first discovered by Grieβ since more than 140 years ago and organic azides are important substrates for making useful compounds in various fields such as chemistry, biology, medicine, and materials science (179). Besides, azides are versatile functional groups and useful intermediates for synthesizing nitrogen containing chemical compounds as triazoles in click chemistry. In this research, aryl azides, primary and secondary alkyl azides were synthesized in order to use them as starting materials for next click reaction steps to form 1,2,3-triazole nucleus containing compounds **6a-m**.

5.1.3.1 Aryl azides 5a-f

The reaction of an aromatic amine with sodium nitrite in acid solution to form diazonium salt at low temperature (below 5 °C) is known as diazotization. In this step, aryl azides **5a-f** were synthesized from sodium nitrite, hydrochloric acid and sodium azides by diazotization reaction. Firstly, the sodium nitrite reacted with hydrochloric acid to form nitrous acid, HNO_2 which reacted with acidic proton followed by tautomerization of the nitrous acidium ion (H_2ONO^+) to form nitrosonium. Aromatic primary amine reacted with this nitrosonium and decomposition of its diazohydroxide to afford diazonium salt (180).

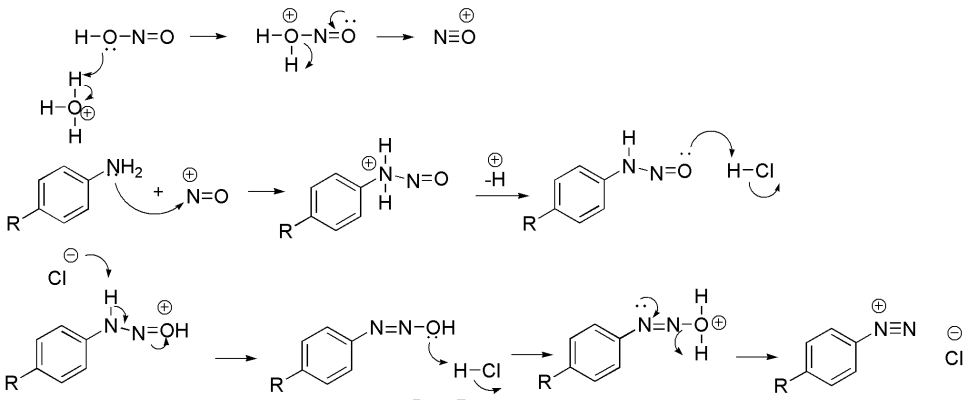


Figure 12. Reaction mechanism of diazotization.

After that, diazonium salt reacted with sodium azide to form aryl azide. However, the mechanism for the preparation of aryl azide was still unclear and controversy. There are three possible mechanisms of forming aryl azide were described (181) as the following proposed mechanisms. The mechanism (A) included S_N2 aromatic substitution reaction that is similar to the diazonium salt solvolysis. The second mechanism (B) consisted of a thermal (3+2) cycloaddition reaction that generated a 1*H*-pentazole cycloadduct followed by a second retro-(3+2) reaction to form an aryl azide product. The final mechanism (C) involved addition-elimination process via an acyclic intermediate. The reaction mechanisms of diazotization and azidation were described in Figure 12 and 13.

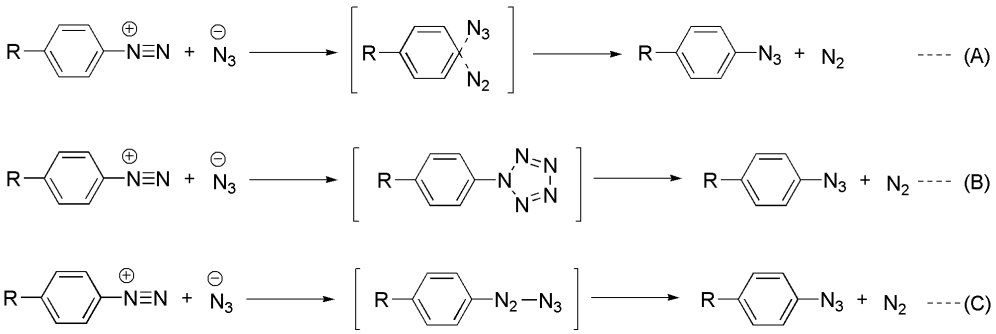


Figure 13. Reaction mechanism of azidation.

Conversion of aromatic primary amines to their corresponding azides has been completed via diazotization and azidation within 4h at 0 °C-rt. The reaction solvents were selected according to the solubility of starting material. The quenching procedure with water was needed to perform in ice bath because of its exothermic nature. As a result, compound **5a-f** were formed in good percent yields in the range of 63.20 to 97.48% as oily liquid except 4-nitrophenyl azide which was bright yellow solid form. The physical properties and percent yield of synthesized compound **5a-m** are summarized in Table 3.

5.1.3.2 Aralkyl and alkyl azides 5g-m

In the literature, general applicable synthetic strategy of alkyl azides had limitations such as it needed multi-step procedure and high temperature, used uncommon solvent type, formation of azeotropes when distilled and lower percent yield. Generally, aliphatic azides are prepared by S_N2 type nucleophilic substitution reaction (Figure 14) of high nucleophilic properties of alkali azide, NaN_3 and good leaving halide groups (182-184).

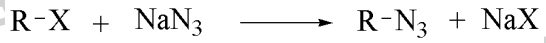


Figure 14. The nucleophilic substitution reaction of alkali azide.

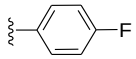
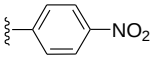
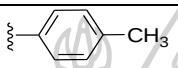
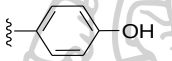
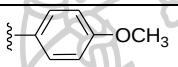
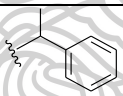
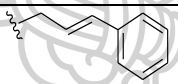
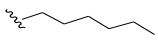
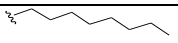
Previous published synthetic approaches toward making alkyl azides used carbitol, propyl alcohol or methanol as solvents and could form azeotrope with alkyl azides. Moreover, it was needed fractional distillation to separate desired products (185, 186) and which could explode while distilling. The selection of solvents is important for this azide displacement reaction. Halogenated solvents as dichloromethane and chloroform should be avoided because of forming diazomethane or triazidomethane that can cause violent explosion in high concentrated solution especially during rotary evaporation of that solvent (187). Here in this case, polar aprotic solvent DMSO was selected because the nucleophilicity of the azide anion is the largest in DMSO than acetonitrile, methanol and ethanol (188). Synthetic methodology used for making

organic azides **5g-m** in this protocol was modified the practical procedure of Alvarex SG and Alvarez MT in 1997 (171). In this method, 0.5M of sodium azide in DMSO was used to get high yield of azides under convective heating or at room temperature. According to the conventional reaction results, all organic azides **5g-m** were successfully synthesized at room temperature or 55 to 75 °C for 1½ to 24h. All azides except cyclohexyl and butyl azide were formed at room temperature. Cyclohexyl azide was generated at 75 °C, 1½ h, whereas, n-hexyl azide was afforded at room temperature.

As starting materials, alkyl bromides were commercially available and used to convert alkyl azides. However, benzyl chloride was lachrymatory and banned chemical for importation. Therefore, it was synthesized in the laboratory from benzyl alcohol (189) with 10M hydrochloric acid to afford benzyl chloride as colorless oily liquid and 92.28% yield.

Table 3. The physical properties and percent yields of synthesized compounds **5a-m**.

R-N_3

Entry	Compd	R	Molecular formula	Molecular weight	Physical state	Yield (%)[a]
1	5a		$C_6H_5N_3$	119.12	brown oily liquid	82.10
2	5b		$C_6H_4FN_3$	137.11	brown oily liquid	63.20
3	5c		$C_6H_4N_4O_2$	164.12	yellow powder	97.48
4	5d		$C_7H_7N_3$	133.15	orange oily liquid	80.70
5	5e		$C_6H_5N_3O$	135.12	brown oily liquid	90.58
6	5f		$C_7H_7N_3O$	149.15	brown oily liquid	89.44
7	5g		$C_7H_7N_3$	133.15	colorless clear liquid	92.15
8	5h		$C_8H_9N_3$	147.18	pale yellow liquid	81.66
9	5i		$C_9H_9N_3$	159.19	pale yellow liquid	79.47
10	5j		$C_6H_{11}N_3$	125.17	pale yellow liquid	63.22
11	5k		$C_4H_9N_3$	99.13	colourless liquid	94.40
12	5l		$C_6H_{13}N_3$	127.19	colourless liquid	86.62
13	5m		$C_8H_{17}N_3$	155.24	colourless liquid	77.80

[a] Percent yield in crude

5.1.4 Microwave-assisted syntheses of azides 5g-m

Organic azides are notorious for explosion hazardous, therefore, more simpler, efficient and safe synthetic methodology for making azide is still needed (190).

Microwave-assisted methods can alleviate some difficulties encountered in conventional ways in making azides. The azidation by microwave irradiation was inspired by the published work of Gudmundsdóttir AD et.al in 2003 in which the synthesis of azidoaryl ketones alkyl halogens and sodium azides had been done by conventional microwave oven to reduce the reaction time (191).

Firstly, conventional reactions for generating azides were investigated with a total seven diverse primary and secondary alkyl chloride or bromides. In addition to the largest nucleophilicity of the azide anion in DMSO, it has good solvent-reagent ability to absorb microwave energy and possess high dielectric constant. For that reason, DMSO was also used for microwave-assisted reactions of azides as in case of conventional method. According to the conventional reaction results, specified temperature and duration for microwave irradiation reaction were created by applying time prediction chart for microwave-assisted synthesis. According to the results, the azides **5g-m** were successfully synthesized by using microwave energy within 20 minutes in the temperature range 50-90 °C.

On the basic of FTIR results of all azides **5g-m** by means of microwave-assisted reactions, it was observed that characteristic peaks due to strong asymmetric stretching and symmetric stretching of the azido group were in the region of 2105-2090 cm^{-1} and 1266 -1236 cm^{-1}. All frequencies were compliance with the literature value (192). Moreover, the percent yields from microwave-assisted reactions of all azides are higher than conventional method results within specified conditions (Table 4). The reaction was easily conducted for butyl azide synthesis in which reaction time was largely reduced from 24h at 55 °C by conventional heating with 94.40 percent yield to 10 min at 80 °C with 96.18 percent yield by microwave irradiation method. Butyl azide can be volatile at room temperature, therefore, sealed condition of microwave reaction is another additional advantage. After extraction, removal of ethyl ether have done around atmospheric pressure at room temperature because butyl azide cannot stand under vacuum evaporation. As a rule of thumb, the azido compound should not have larger number of nitrogen atoms than carbon and oxygen $(N_C+N_O)/N_N \geq 3$ (N= number of atom) to be nonexplosive and handle (179). In this research, butyl and hexyl azides were synthesized more safely by applying microwave radiation in sealed vials. Then,

the crude organic azides **5a-m** were used in next step for the preparing compounds **6a-m** without purification because azides are potentially explosive and unstable compounds.

Caution: Sodium azide and hydrazoic acid are potentially explosive. Azide displacement reaction should not be performed in the presence of halogenated solvent in laboratories. Every reactivity of azide and reactant should be checked before reaction starts and carefully planned for reaction scale and follow the safety rule for handling azides. The use of ice-water bath is recommended for quenching step of compounds **5a-m** because this step is exothermic (193).

Table 4. Conventional and microwave-assisted synthesis of organic azides **5g-m**.

$$\underset{\textbf{4g-m}}{R\text{-}X} + NaN_3 \xrightarrow{DMSO} \underset{\textbf{5g-m}}{R\text{-}N_3} + NaX$$

Compd	R-X	Conventional			Microwave		
		Temp (°C)	Time (h)	Yield (%)[a]	Temp (°C)	Time (min)	Yield (%)[a]
5g	C_6H_5-CH_2-Cl	rt	2	92.15	50	10	94.98
5h	C_6H_5-(CH)Br-CH_3	rt	2½	81.66	50	10	86.52
5i	C_6H_5-CH=CH-CH_2-Br	rt	1½	79.47	50	10	82.54
5j	C_6H_{11}-Br	75	1½	63.22	90	20	65.90
5k	C_4H_9-Br	55	24	94.40	80	10	96.18
5l	C_6H_{13}-Br	rt	4	86.62	80	10	87.59
5m	C_8H_{17}-Br	rt	4	77.80	80	10	85.36

[a] Percent yield in crude

5.1.5 Click compounds 6a-m

The aim of this step is to create the formation of 1,4-disubstituted 1,2,3-triazole ring and it is one of the critical reaction steps of the chemical synthesis in this study. In the laboratory experiment, the Grignard product compound **3** was used as dipolarophile which reacted with 1,3 dipole of organic azide **5** to generate heterocyclic ring and this reaction is known as 1,3-dipolar cycloaddition reaction. As alternative term, (3+2) cycloaddition reaction was also used according to the number of atom involvement in the reactants. In brief, this reaction generated 5-membered herterocyclic structure by joining small units together with heteroatom links (C-N-C) and this chemical philosophy was regarded as click chemistry. Therefore, here in this case, the triazole containing products **6a-m** are referred to as click compounds. In order to avoid the formation of regioisomers and increase the reaction rate, the reaction was performed in aqueous media *t*-BuOH/H_2O using copper (II) sulphate as a source of copper catalyst.

The detail mechanism of azide-alkyne cycloaddition reaction is still unclear, however, the proposed stepwise mechanism was described in Figure 15. Firstly, copper I species was formed in situ from copper (II) sulphate with the aid of reducing agent sodium ascorbate. There were two copper centers needed to proceed the reaction. Then, this copper (I) attacked with π bond of dipolarophile alkyne formed copper-alkyne π complex. After that copper (I) attacked again to alkyne and its proton was deprotonated and formed copper acetylide. The second step involved coordination of copper ion azide nitrogen and activation to form cyclization reaction in the complex by nucleophilic attack of terminal nitrogen of the azide group on the internal carbon of alkyne and formed metallacycle. The later step consisted the transformation of metallacycle to Cu triazolide via ring contraction of the lone pair of electrons on the substituted nitrogen of azide and C=Cu bond as a transannular interaction. Finally, 1,4-disubstituted 1,2,3-triazole was formed after protonation to alkyne carbon (194).

The click reactions of azide and alkyne were studied in various conditions such as at room temperature, thermally-assisted, microwave irradiation, one-pot two-step and multicomponent as the followings.

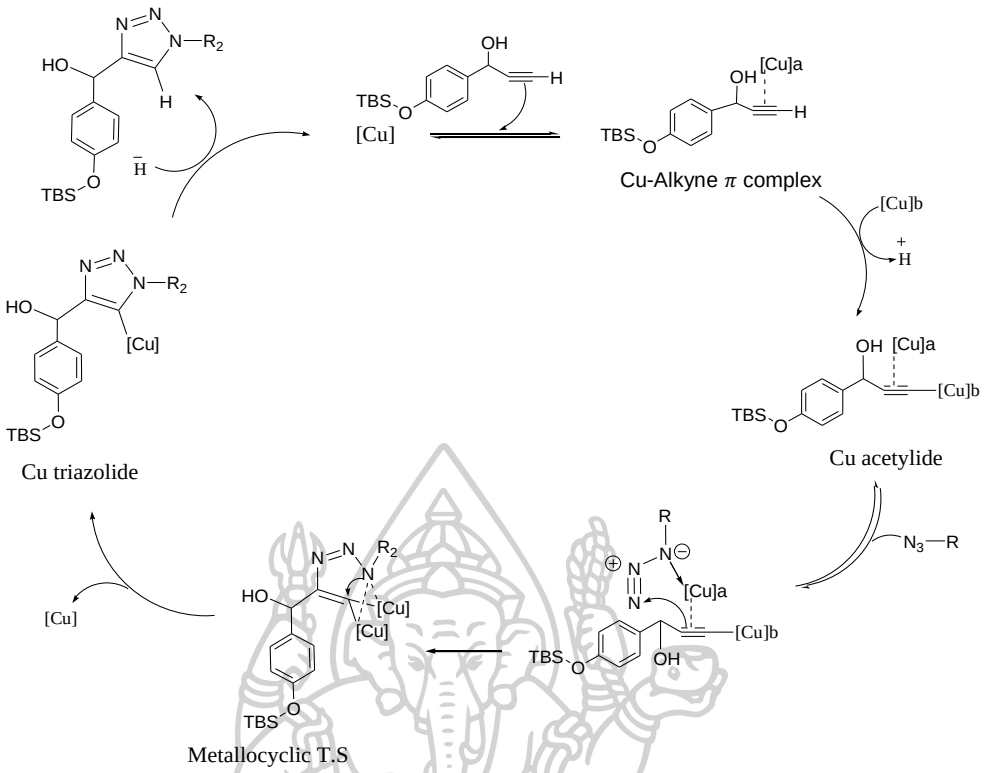


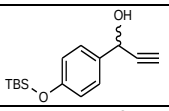
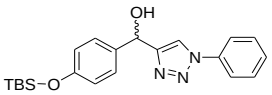
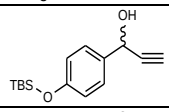
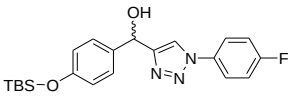
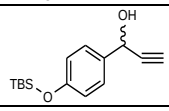
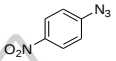
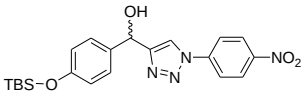
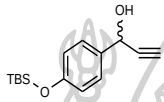
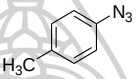
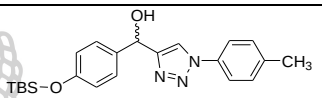
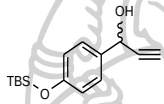
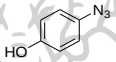
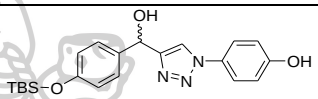
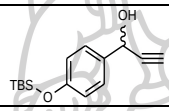
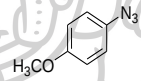
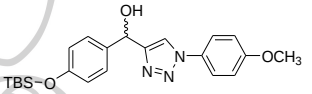
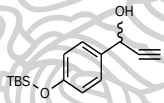
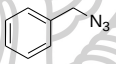
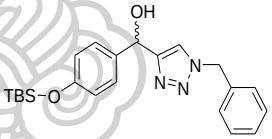
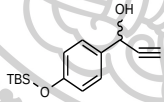
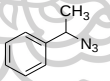
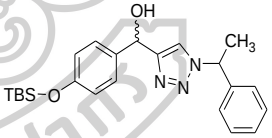
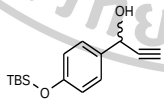
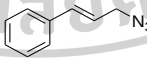
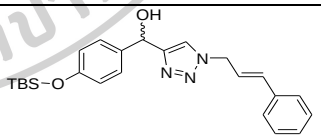
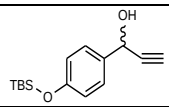
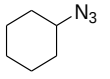
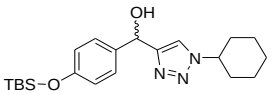
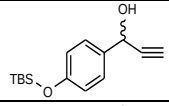
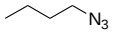
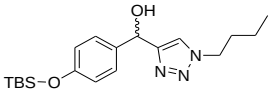
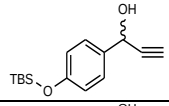
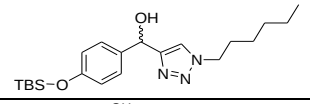
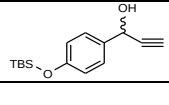
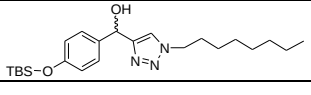
Figure 15. Reaction mechanism of azide-alkyne cycloaddition.

5.1.5.1 Conventional syntheses of compounds 6a-m

One of the advantages of copper-catalyzed azide-alkyne cycloaddition reaction is that this reaction can be successfully performed at room temperature to obtain 1,2,3-triazole containing structure with highest yield. Therefore, designed compounds **6a-m** were synthesized by the reaction between compound **3** and various organic azides **5a-m** with the aid of copper catalyst in aqueous solvent at room temperature. According to the results, all click compounds **6a-m** were generated with moderate to high yield (41.87-77.65%) within 24 h (except for compound **6c**). The alkyne, different organic azides, products and percent yields and physical properties were described in Table 5 and 6.

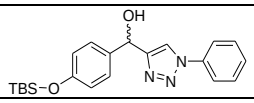
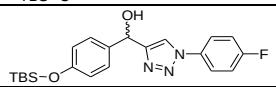
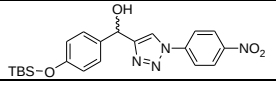
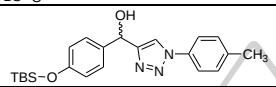
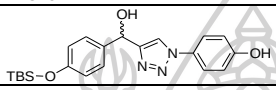
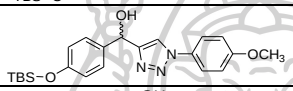
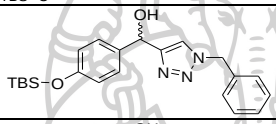
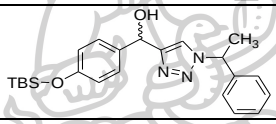
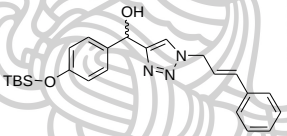
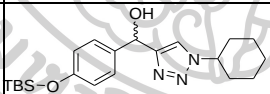
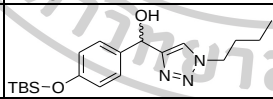
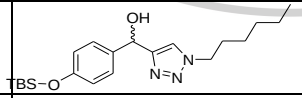
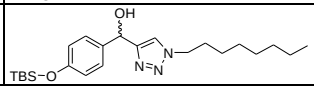
The reaction time, solvent, molar ratio and concentrations of reagents and catalysts were studied. In order to check the effect of those parameters on reaction, one parameter have changed at a time.

Table 5. The synthesis of 1,4-disubstituted 1,2,3-triazoles **6a-m** from organic azides and alkyne.

Entry	Compd	Alkyne	Organoazide	Product	Yield (%)[a]
1	6a				54.28
2	6b				77.65
3	6c				50.62
4	6d				73.53
5	6e				68.58
6	6f				76.10
7	6g				60.50
8	6h				41.87
9	6i				52.15
10	6j				59.15
11	6k				51.64
12	6l				56.49
13	6m				58.90

[a]Yield refer to the isolated product

Table 6. The physical properties of synthesized compounds **6a-m**.

Entry	Compd	Product	Molecular Formula	Molecular Weight	Physical state
1	6a		$C_{21}H_{27}N_3O_2Si$	381.54	Reddish brown oil
2	6b		$C_{21}H_{26}FN_3O_2Si$	399.53	Orange solid
3	6c		$C_{21}H_{26}N_4O_4Si$	426.54	Yellowish brown oil
4	6d		$C_{22}H_{29}N_3O_2Si$	395.57	Brown oil
5	6e		$C_{21}H_{27}N_3O_3Si$	397.54	Yellowish brown oil
6	6f		$C_{22}H_{29}N_3O_3Si$	411.569	Brown oil
7	6g		$C_{22}H_{29}N_3O_2Si$	395.57	Brown oil
8	6h		$C_{23}H_{31}N_3O_2Si$	409.59	Brown oil
9	6i		$C_{24}H_{31}N_3O_2Si$	421.60	Brown oil
10	6j		$C_{21}H_{33}N_3O_2Si$	387.59	Brown oil
11	6k		$C_{19}H_{31}N_3O_2Si$	361.55	Yellow oil
12	6l		$C_{21}H_{35}N_3O_2Si$	389.60	Brown oil
13	6m		$C_{23}H_{39}N_3O_2Si$	417.66	Orange oil

This synthesis strategy was modified from the published work (100, 170) for the preparation of 1,4-disubstituted 1,2,3-triazoles for different biological activities. After setting reaction under nitrogen, its progress was monitored by TLC on pre-coated silica plate with a fluorescence indicator visualized by UV inspection and run it overnight. After that, it was quenched with water, removed *t*-BuOH in rotary evaporator

and extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulphate and evaporated the organic solvent. The resulted crude product was purified by column chromatography and percent yields were calculated as mentioned in experimental section.

Generally, total reaction time for overnight reaction lasted approximate 12 to 18 h. The reaction of (1-Azidoethyl)benzene **5h** and compound **3** for 18 h provided only 37.63% yield of compound **6h** which was increased to 41.87% for 24 h. The percent yield of compound **6i** was also increased from 32.24% for 12 h to 52.15% for 24 h reaction. It was found that, steric nature of methyl group in **5h** and longer chain of **5i** hampered the reaction rate of azide and alkyne and needed longer duration to complete the reactions.

As reaction solvent, *t*-BuOH/H_2O (1:1) was generally used. However, the ratio of water to *t*-BuOH depends on the solubility of reagents in selected solvents. The reaction mixture of compound **3** and **5c** needed *t*-BuOH/H_2O (3:1) and compound **3** and phenyl ethyl azide **5h**, butyl azide **5k**, hexyl azide **5l**, octyl azide **5m** needed *t*-BuOH/H_2O (2:1).

The selection of equivalents used in reagents was decided based on the FT IR characterization result of the crude product. The loss of starting materials were also checked by TLC. The compound **3** was regarded as limiting substance, therefore, 1 equiv of compound **3** and 1.1 equiv of phenyl azide were used to afford the compound **6a**. Then, crude product was checked by FT IR to investigate the characteristic band and it was found that asymmetric N_3 stretching of azide band was still appeared. This finding showed 1.1 equiv of azide was enough for this reaction. This study showed 1.5 equiv of cyclohexyl azide, 3 equiv of butyl azide and 2.5 equiv of hexyl azide were selected for the reactions to produce good percent yields of corresponding products shown in Table 5.4. In the reaction to prepare compound **6k**, 1.1 equiv of butyl azide was not enough to react with compound **3** and provided only 15.67% yield of **6k**. In the consideration of volatile nature of low carbon content butyl azide, its equivalent was increased to **3** and observed percent yield of compound **6k** was 51.64%. For hexyl azide, N_3 stretching peak was lost in IR spectrum for 1.5 equiv and 2.5 equiv of azide generated 56.49% yeld of compound **6l**.

For catalyst, copper (II)-sodium ascorbate system was used as copper source to accelerate the reaction. The sodium ascorbate reduced copper (II) to active catalyst copper (I) *in situ* is more widely used than using copper (I) catalyst that it can be oxidized to Cu (II) which has no catalytic activity. According to the literature, equiv of sodium ascorbate used was two to ten time greater than equiv of sodium ascorbate (122, 195). In this research, 0.45 equiv of sodium ascorbate and 0.15 equiv of copper sulphate were used to proceed as click reaction. The overall reaction and percent yields could not be affected by oxygen in copper copper (II)-sodium ascorbate system, therefore, this click reaction was carried out well with or without nitrogen atmosphere.

According to the results, it was found that click compounds **6a-m** have prepared in good percent yield by applying general experimental procedure except for compound **6c**. As for synthesizing other click compounds, 1 equiv of compound **3** reacted with 1.1 equiv of nitrophenyl azide **5c** in the presence of reducing agent 0.45 equiv of sodium ascorbate and 0.15 equiv of copper (II) sulphate as catalyst in *t*-BuOH/H_2O (1:1) at room temperature for overnight and observed that reaction was failed. It was assumed that electron withdrawing nitro group of **5c** preclude the reactivity of azide and alkyne. In order to happen the reaction, 1 equiv of nitrophenyl azide **5c**, 1.7 equiv of compound **3** were dissolved in *t*-BuOH/H_2O (3:1) in the presence of 0.45 equiv of sodium ascorbate and 4.5 equiv of copper (II) sulphate. Reaction was run for at least 26 h at room temperature to prepare the compound **6c** successfully as 50.62% yield. This condition needed more molar ratio of starting material alkyne, catalyst amount, *t*-BuOH and longer duration than general reaction methods for preparing other click compounds.

Here in this work, aniline holding electron withdrawing or electron donating group and alicyclic, aralkyl or alkyl halides were smoothly transformed into corresponding azides and those all organic azides were well tolerated to occur the click reaction with alkyne **3**. All click reactions for different substituent were carried out at room temperature for overnight to create 1,4-disubstituted 1,2,3-trizoles in good percent yields. The next step was continued to reduce the reaction time by applying heat-assisted method on this reaction.

5.1.5.2 Conventional synthesis of compound 6g by thermal heating

The aim of this study was to investigate the thermal effect on click reaction to prepare compound **6g**. In the series of azides **5g-m**, compound **5g** was more widely useful azide to prepare benzyl substituted 1,2,3-triazole, **6g** in compare with the rest of other compounds. Therefore, click compound **6g** was subjected to this experiment.

It can be seen that conventional method took approximate 24 h at room temperature to complete the reaction between benzyl azide and compound **3** in the presence of copper sulphate and sodium ascorbate in *t*-butanol and water (1:1) as solvent and produced 60.50 percent yield. The longer reaction time was reduced to min by heat-assisted way. The silicone bath was used as heat source and exact temperature setting via digital display was at 70 °C. The selection of temperature was based on time prediction chart for microwave-assisted synthesis and preliminary experiment of heating catalyst that charred if reaction time was longer and higher temperature about 80 °C. This reaction was run under light protected condition. After purification by column chromatography, isolated pure compound **6g** was obtained as orange oil in 51.44% and characterized by FT IR band at app 3140.0 cm^{-1} due to C-H stretching in triazole ring. Both method used same mmol of limiting substrate compound **3** that was 1.06 mmol in conventional and 1.03 mmol in thermal-assisted reaction. It was found that reaction rate was dramatically decreased from 24h to 15 min with comparable yields by applying heat to this kind of cycloaddition reaction. According to the result, percent yield (51.44%) of compound **6g** by thermal heating method was lower than 24 h reaction at room temperature convention method percent yield (60.50%). However, this finding disclosed the valuable information to prepare all click compounds **6a-m** by using microwave irradiation energy instead of convective heating.

5.1.5.3 Microwave-assisted organic syntheses of compounds 6a-m

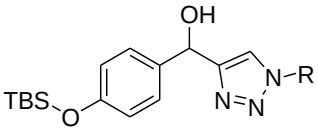
The aim of this step was to synthesize click compounds **6a-m** by means of microwave radiation in a specified temperature and time with the hope of reducing reaction time and increasing percent yields in compare with the results from conventional ways described in section 4.2.2.5.1. This work began with an attempt to find the suitable temperature and time as key parameters for microwave irradiation. As

mentioned in experimental section 4.2.2.5.3, microwave-assisted reactions were performed in CEM monomode microwave system with CEM design 10 mL or 35 mL ActiVent reaction vial with snap on ActiVent cap small magnetic bar. The solvent system, mole ratio of reagents and catalysts for this microwave-assisted reactions were same as described in conventional ways.

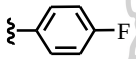
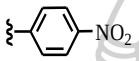
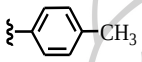
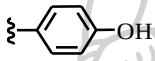
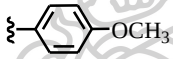
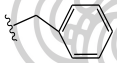
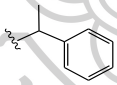
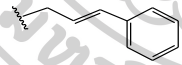
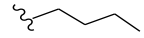
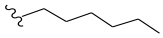
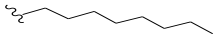
On the basic of these data from conventional synthesis, the temperature and time required for microwave reactions were carefully determined by using Arrhenius equation based time/temperature prediction chart (196). Firstly, all reagents needed to afforded compound **6f** were placed in 10 mL ActiVent reaction vial and it was subjected to microwave irradiation at 120 °C for 2 min with pre-stirring time 30 second and medium stirring speed at 150 watt power level. It was found that brown powder formed during extraction procedure due to decomposition of catalyst at high temperature 120 °C. According to FTIR result of product, C-H stretching in triazole ring have not been observed and the designed product was not obtained. As a result, radiation temperature was reduced to 60 °C and the reaction was run again for 5 min. The compound **6f** was generated from this condition with high percent yield (80.83%). With these results in hand, temperature 60 °C and reaction time 5 min was applied for preparing other click compounds **6a** to **6e**. However, 10 min reaction time at 60 °C was not enough to afford compound **6e** and it required longer reaction time to complete the reaction. The yield of compound **6e** was increased from 46.88% for 10 min to 69.65% for 15 min at 60 °C by microwave irradiation. For compound **6c** was obtained in 57.44% under the condition at 60 °C for 10 min. The reactions were carried out well for the rest of the compounds **6g-m** at 70 °C for 15 min with good percent yield.

As expected, all reactions of microwave-assisted syntheses gave better yields of the designed products **6a-m** within short period of time (5 to 15 min) than conventional method. The comparative study of reaction temperature, reaction time and percent yields of compounds **6a-m** by conventional and microwave-assisted methods were described in Table 7.

Table 7. Comparison of conventional and microwave irradiation methods for click compounds **6a-m**.



6a-m

Compound	R	Conventional			Microwave		
		Temp (°C)	Time (h)	Yield[a] (%)	Temp (°C)	Time (min)	Yield[a] (%)
6a		rt	14	54.28	60	5	75.22
6b		rt	14	77.65	60	5	83.50
6c		rt	26	50.62	60	10	57.44
6d		rt	12	73.53	60	5	85.11
6e		rt	14	68.58	60	15	69.65
6f		rt	17	76.10	60	5	80.83
6g		rt	24	60.50	70	15	76.70
6h		rt	24	41.87	70	15	56.07
6i		rt	24	52.15	70	15	72.69
6j		rt	16	59.15	70	15	64.73
6k		rt	22	51.64	70	15	59.91
6l		rt	24	56.49	70	15	67.77
6m		rt	12	58.90	70	15	68.58

[a] Yield refer to the isolated product

5.1.5.4 One-pot, two-step microwave-assisted organic synthesis

In this study, synthesis strategy of the one-pot, two-step microwave-assisted organic synthesis of both alkyl azides and designed click compounds by microwave irradiation was developed. This work was encouraged due to in hand results from

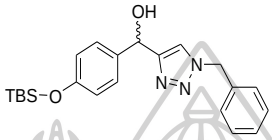
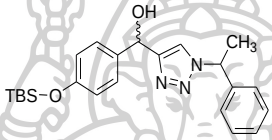
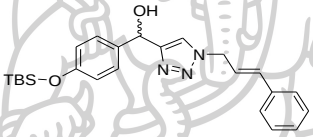
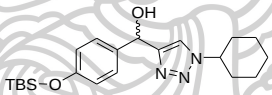
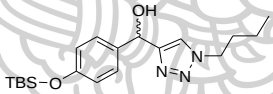
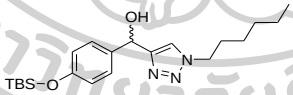
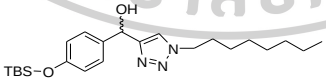
azidation by microwave irradiation to generate primary and secondary alkyl azides **5g-m** described in experimental section 4.2.2.6.1 and the advantages of microwave irradiation to prepare click compounds **6a-m** mentioned in experimental section 4.2.2.5.3. The aim of this step was to prepare the click compounds **6g-m** in one-pot to diminish exposure of explosive nature of azides, to reduce reaction time and to increase percent yield in compare with conventional and two-pot microwave irradiation methods.

As published works, one-pot, two-step reactions by microwave radiation were largely applied in organic synthesis of pyrazolopyrimidines (197), aminoimidazoles (198), and 1,2,3-triazole (199) in order to reduce reaction time, lessen the formation of side products and ease of operation. According to the name, overall reaction process involved two steps. First step is nucleophilic substitution reaction of forming azide and second step is introducing of the diversity elements to prepared azide without further purification and continue subsequent reaction at 70 ℃ for 15 min to complete CuAAC reaction in one-pot. As in azidation by microwave energy, 0.5M sodium azide in DMSO was used for reaction of primary or secondary alkyl halides. Based on the previous studied percent yields of forming azides **5g-m**, equiv of sodium azide and alkyl halides were carefully calculated to produce approximate 1.1 equiv of corresponding azides which were excess amount to react with alkyne, copper sulphate and sodium ascorbate as conventional click reactions.

Under the selected conditions it was found that click reactions of all compounds were formed within 15 min with good percent yields (45.27% to 68.75%) (Table 8) those all were comparable with percent yields from conventional methods except for higher yield in compound **6h** and lower yield in compound **6j.** It have been demonstrated that this one-pot two-step procedure was safe in synthesizing organic azides intermediates, reaction was completed in a short period of time with significant energy saving with acceptable percent yield and also advantages for synthesis of a large number of triazole chemical entities in drug discovery laboratories. In addition, all click compounds **6g-m** were directly synthesized from alkyl halides and completed as multicomponent reaction in one-pot including of forming explosive nature of azides *in situ*, therefore, this procedure could be avoided azide extraction procedure with diethyl

ether as in experimental section 4.2.2.4 that made ease of synthesis operation to prepare designed compounds.

Table 8. One-pot two-step microwave-assisted synthesis of **6g-m**.

Entry	Compd	Product	Temp (°C)	Time (min)	Yield (%)[a]	Physical state
1	6g		70	15	60.17	Pale yellow oil
2	6h		70	15	68.75	Pale yellow oil
3	6i		70	15	59.06	Pale yellow oil
4	6j		70	15	45.27	White sticky solid
5	6k		70	15	54.74	Pale yellow oil
6	6l		70	15	57.70	Pale yellow oil
7	6m		70	15	56.59	Pale yellow oil

[a] Yield refers to the isolated product after column chromatography

5.1.5.5 Multicomponent microwave-assisted organic synthesis

In this study was inspired by the published work of Fokin VV et.al in 2004 describing microwave-assisted three-component reaction to synthesize 1,4-disubstituted 1,2,3-triazoles from alkynes, alkyl halides and sodium azide. It was found that the developed synthetic strategy provided the designed product within 10 to 15

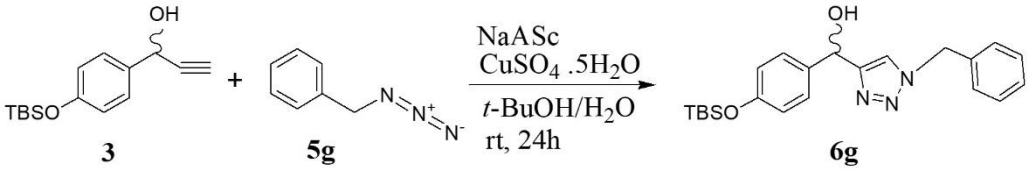
minutes with regioselective manner, good yields and avoided chromatographic purification.

Here in this study, the one-pot three components microwave-assisted reaction to afford the compound **6g** was easily conducted under microwave irradiation at 70 °C, 15 min as the same temperature and time for other microwave-assisted reaction methods. According to the result, IR band of the compound appeared at 3141.7 cm^{-1} due to C-H stretching in the triazole ring that indicated the formation of designed compound **6g**. However, the percent yield of compound was only 20.88%. Generally, the solvent DMSO used for making azides was dried in molecular sieve 40Å and it provided better yields than DMSO without drying by molecular sieve. Therefore, the solvent water used to dissolve sodium ascorbate and copper sulphate in the reaction can terminate the dry condition of DMSO and interfere the formation of azide. For that reason, the reaction between alkyne and incomplete formation of azides was hampered and reduced the percent yield of compound **6g**.

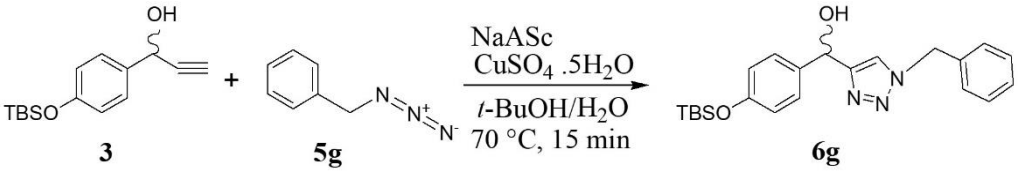
In summary, the click reactions were carried out well at room temperature for overnight in good percent yields. The longer reaction time can be largely reduced by applying thermal energy to afford designed compound although percent yield was slightly lower in compare with conventional method. The microwave irradiation was used instead of thermal heating provided great advantages. All compounds could be synthesized within short period of time with highest percent yields by using microwave energy. In convention heating by using silicone bath as heat source, heating mechanism is conduction and there is physical contact between energy source and reaction vessel. Therefore, the wall of the reaction vessel wall is the source of heat loss in conventional heating. In contrast, there is no need to contact energy source and reaction vessel and heating can proceed directly inside the reaction mixture. In addition, the electric filed component of microwave interacts with the matrix by dipolar polarization mechanism. On the other hand, the formation of more dipolar activated complex favors dipole-dipole interaction with electric field of microwave that can reduce the activation energy and lead to enhance reaction rate (146). Although it is still controversial, specific microwave effect also contributed as a reason to increase percent yields of designed products in microwave-assisted reactions (151). The one-pot, two-step procedures were

worked well for various primary or secondary alkyl substituents at 1-position of 1,2,3-triazoles. The percent yields of compound **6g-m** were comparable with conventional method except compound **6g** and **6j**. This method allowed *in situ* formation of azide and to avoid crude isolation of organic azide during extraction procedure. As multicomponent reaction by microwave energy, it was still needed to be modified. The click product **6g** was synthesized by applying those all conditions as in Figure 16 and percent yields from various methods were displayed in Table 9.

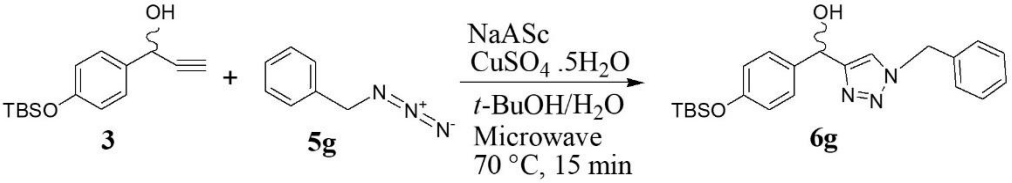
(1) Conventional reaction at room temperature



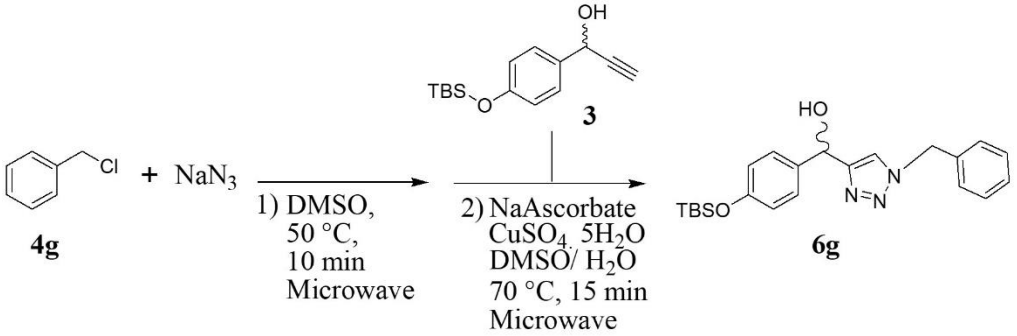
(2) Conventional reaction with heating at 70 °C



(3) Reaction with microwave irradiation at 70 °C



(4) Microwave-assisted one-pot two-step synthesis



(5) Microwave-assisted three-component synthesis

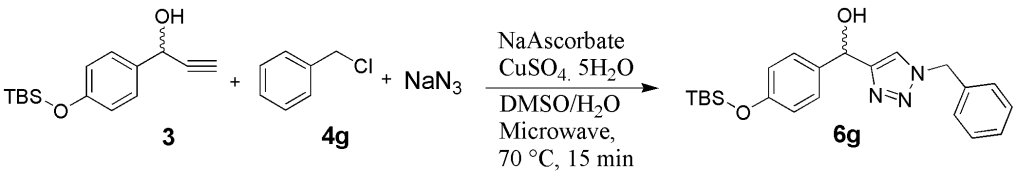


Figure 16. Click reaction conditions for compound **6g**.

Table 9. The reaction conditions and percent yields of click compound **6g** (Also see **Figure 16**).

No.	Reaction	Temperature (°C)	Time	Yield (%)[a]
(1)	Conventional	Room temperature	24 h	60.50
(2)	Convective heating (Silicone bath)	70 °C	15 min	51.44
(3)	Microwave heating	70 °C	15 min	76.70
(4)	Microwave-assisted one-pot two-step synthesis	50 °C 70 °C	10 min 15 min	94.98[b] 60.17[c]
(5)	Microwave-assisted three-component synthesis	70 °C	15 min	20.88

[a] Yield refers to the isolated product after column chromatography and all the percent yields for click reaction step was calculated based on compound **3** as limited substance.

[b] The first step of one-pot two-step reaction in which benzyl azide (**5g**) was synthesized from benzyl chloride (**4g**) and sodium azide by microwave heating for 10 min at 50 °C. Percent yield in crude was calculated from previous study after evaporation solvent.

[c] The second step of one-pot two-step reaction in which compound (**6g**) was synthesized from compound (**3**) and first step forming azide without extraction by mean of microwave heating for 15 min at 70 °C. The percent yields for step 2 (click reaction) was calculated based on compound **3** as limited substance. Yield refers to the isolated product after column chromatography of **6g**.

5.1.6 Deprotection

The aim of this step is to cleave the temporary organic functional groups from compound **6a-m** to afford the compounds **7a-m**. The protecting group, *tert*-butyldimethylsilyl chloride (TBS-Cl) is acid or base labile and it can be removed by acid or base hydrolysis. However, the high thermodynamic affinity of silicon for fluorine allowed fluoride-induced cleavage of Si-O bond by using tetra-*n*-butylammonium fluoride (TBAF) in THF. The pentavalent fluorosiliconate was formed

by attacking of fluoride ion to silicon of TBS group (176). After quenching procedure, the fluoro *tert*-butyldimethylsilane, tetra-*n*-butylammonium salt were loss to liberate products **7a-m**. The reaction mechanism of deprotection step was described in Figure 17.

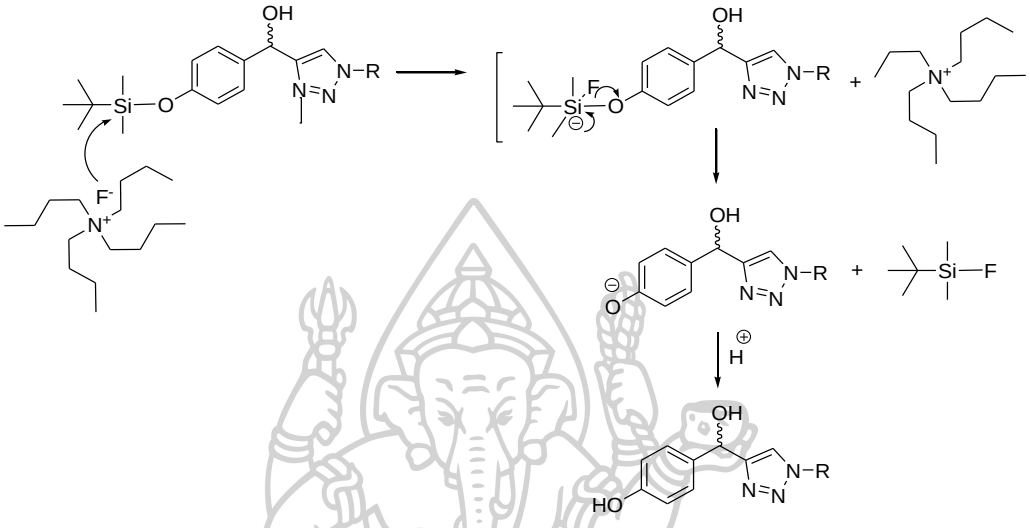
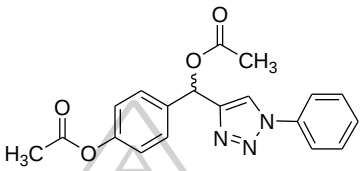


Figure 17. The reaction mechanism of the deprotection.

Oven-dried glasswares were used for the deprotection reaction. A solution of TBAF 1.5 equiv (2 equiv for **7a**) was used to deprotect TBS protecting group of compound **6** at 0 °C for 1 h in dry THF. After quenched with water and evaporated out of the THF from reaction mixture, the product was separated by extraction with ethyl acetate. The nitro group containing compound **7c** was very polar and not easily soluble in THF at 1 h reaction and it was difficult to detect whether the reaction was completed or not. Therefore, it was checked after dissolving the reaction mixture in methanol. Moreover, purification of all compounds have been done by column chromatography using different proportion of ethyl acetate and hexane as eluents. Before sample loading in column, the crude compound was needed to dissolve in the small amount of methanol and ethyl acetate. As exception, the product **7h** was easily purified as off-white solid by successive washing the crude compound with *n*-hexane, chloroform and ethyl acetate. The results revealed that this general deprotection method was easily conducted to afford the compounds **7a-m** with moderate to good percent yields (60.90% to 93.88%) as solid formed products. The synthesized compounds **7a-m** were confirmed

by characterization of melting point, FT IR, ^{1}H NMR, ^{13}C NMR and HR MS and subjected to antituberculosis activities. The physical properties and percent yield of synthesized compound **7a-m** are summarized in Table 10.

5.1.7 Synthesis of 4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl acetate 8



The aim of this step was to change the active hydroxyl group of compound 4-(hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol, **7a** to ester group in order to mimic the structure of ACA (I), chemical constituent of *Alpinia galanga*. For acetylation, the acetic anhydride was used as a source of acyl group for acylation of alcohol. The reaction was accelerated by the presence of carbodiimide activator, dicyclohexylcarbodiimide (DCC) with catalytic amount of dimethylamino pyridine, (DMAP) in THF (174). The reaction was completed at room temperature for 2 h to afford compound **8** as white solid in 56.09% yield. The reaction mechanism for esterification was described in Figure 18 (200).

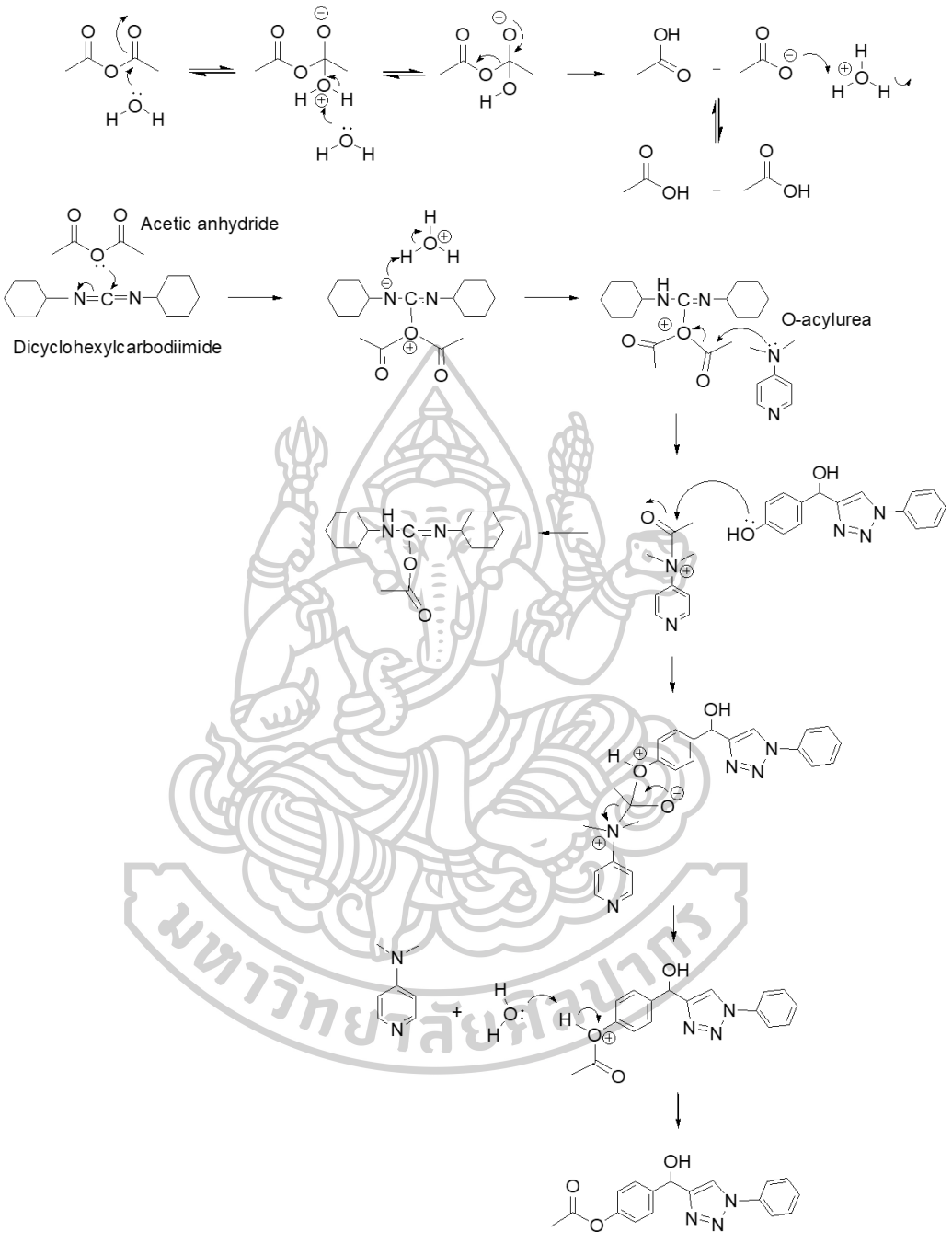
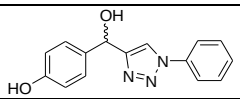
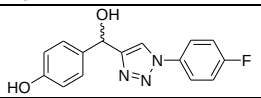
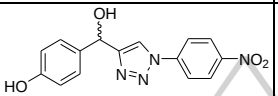
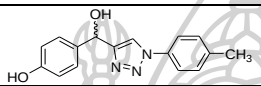
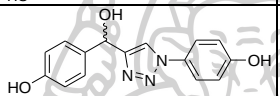
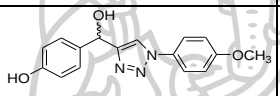
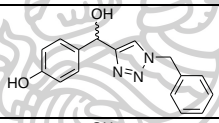
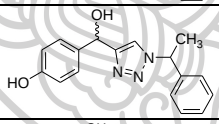
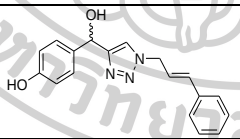
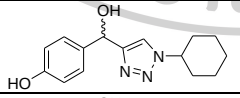
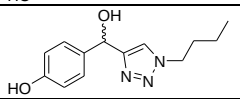
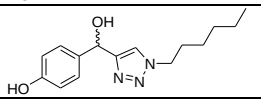
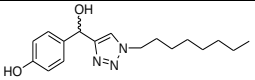


Figure 18. The reaction mechanism of the esterification.

Table 10. The physical properties and percent yield of synthesized compounds **7a-m**.

Entry	Compd	Product	Physical State	Melting Point (°C)	Yield (%)[a]	Overall Yield (%)[b]
1	7a		pale yellow solid	180	90.56	48.73
2	7b		pale yellow solid	165	81.16	48.48
3	7c		yellow solid	193	92.02	41.70[c]
4	7d		pale yellow solid	175	74.50	45.36
5	7e		pale yellow solid	111	60.90	30.35
6	7f		pale yellow solid	161	78.88	45.61
7	7g		off-white solid	137	87.59	48.06
8	7h		off-white solid	180	68.68	27.55
9	7i		off-white solid	147	71.84	37.36
10	7j		off-white solid	133	79.64	36.88
11	7k		pale yellow solid	96	93.88	40.24
12	7l		off-white solid	82	75.65	36.68
13	7m		off-white solid	95	52.97	25.99

[a] Yield refers to the isolated product after column chromatography

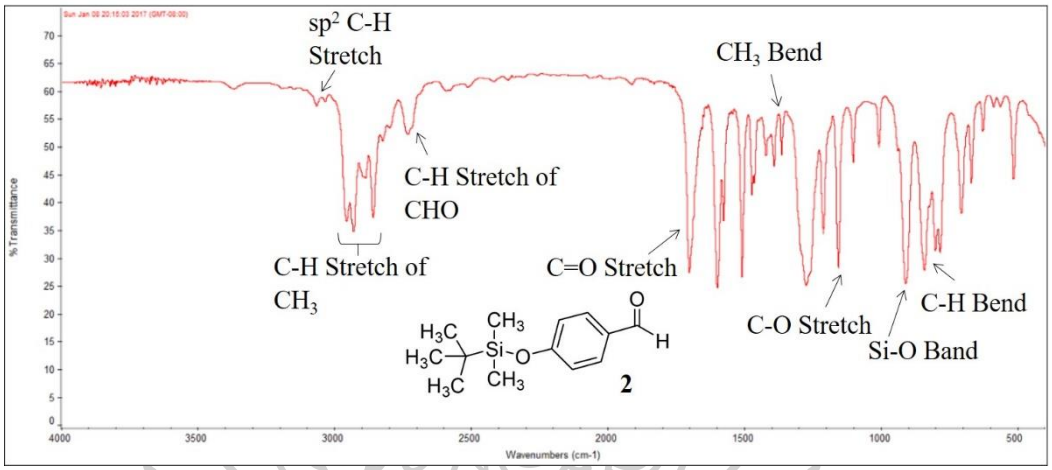
[b] The overall yield of this convergent synthesis was calculated based on overall steps starting from compound 1 to afford final product and percent yield for click reaction step was the result of using microwave energy.

[C] In the click reaction to synthesize compound (**6c**), 4-nitrophenyl azide (**5c**), was used as limiting substance instead of compound (**3**) and this percent yield was used to calculate the overall yield of final product **(7c)**.

5.2 Structural characterizations

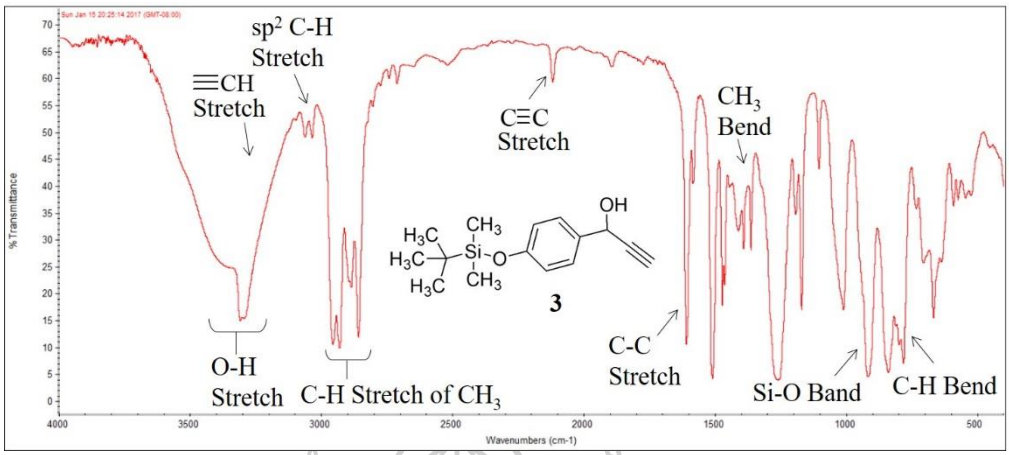
5.2.1 IR spectroscopic characterization

4-(*tert*-Butyldimethylsilyloxy)benzaldehye (2)



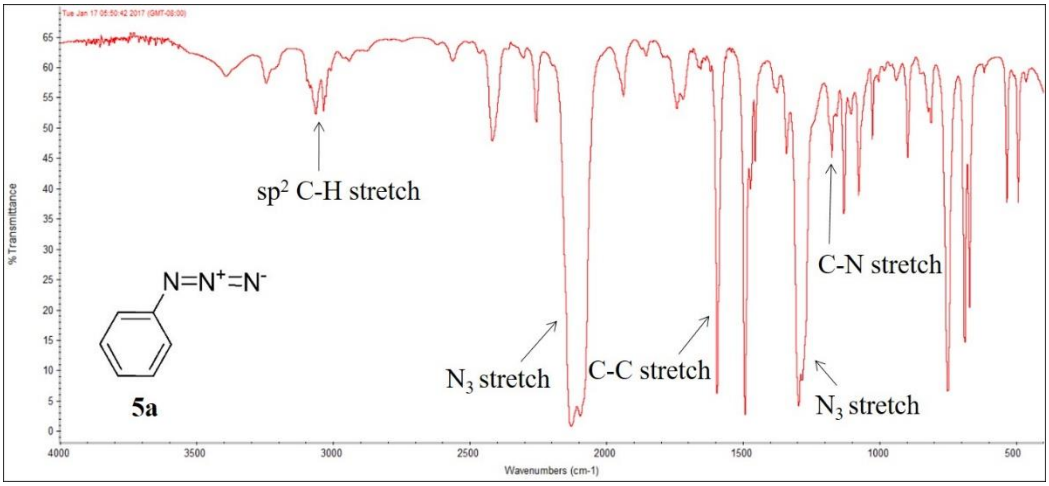
IR spectrum of TBS-protected 4-hydroxybenzaldehyde **2** showed characteristic vibration bands of stretching and bending of functional groups. The bands of aldehyde moiety were displayed C-H stretching at 2732 cm^{-1}, carbonyl C=O stretching at 1700 cm^{-1}. The bands of aromatic ring included aromatic C-H stretching band at 3066 cm^{-1}, C-H out of plane bending at 840 cm^{-1}, skeletal C-C stretching at 1598 cm^{-1}. The strong Si-O stretching band was showed at 908 cm^{-1} and symmetric C-H stretching bands in methyl were seen at 2956, 2930 cm^{-1}.

4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl) phenol (3)

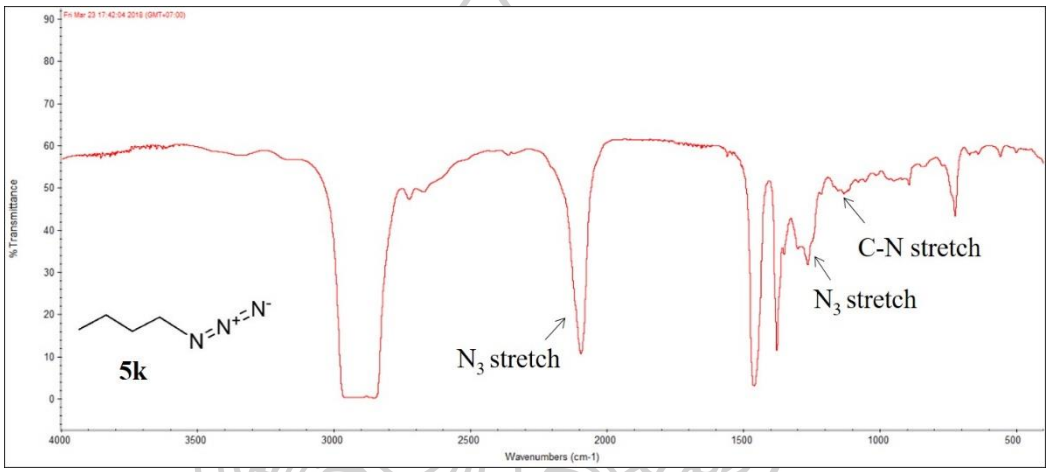


Characteristic vibration bands of functional groups were displayed in IR spectrum of 4-(*tert*-butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol. Banding of C=O group for aldehyde was lacked in this compound. The two bands of alkyne were showed at 3309 cm^{-1} and 2118 cm^{-1} for ≡C-H stretching and C≡C stretching of acetylene. The characteristic O-H stretching for intramolecular hydrogen bonding of alcohol was displayed in the range of 3550-3200 cm^{-1}. It is the good evidence of the formation of alcohol. The bands of aromatic ring included aromatic C-H stretching band at 3062 cm^{-1}, C-H out of plane bending at 839 cm^{-1}, skeletal C-C stretching at 1608 cm^{-1}. The strong Si-O stretching band was showed at 915 cm^{-1} and C-H stretching bands in methyl were seen at 2956, 2930 cm^{-1}.

Organic azides 5a-m



There are two IR spectra of aryl azide **5a** and primary alkyl azide **5k** were showed as representative spectra. In the IR spectrum of phenyl azide showed typical vibration bands of functional groups. Azide group was displayed as doublet and asymmetric stretching strong band at 2129 cm^{-1} and symmetric stretching frequency at 1296 cm^{-1}. The bands of aromatic ring included aromatic C-H stretching band at 3064 cm^{-1}, C-H out of plane bending at 810 cm^{-1}, skeletal C-C stretching at 1594 cm^{-1}. For butyl azide **5k** in nujol mulet, azide group was displayed as asymmetric stretching sharp band at 2094 cm^{-1} and symmetric stretching frequency at 1263 cm^{-1}.



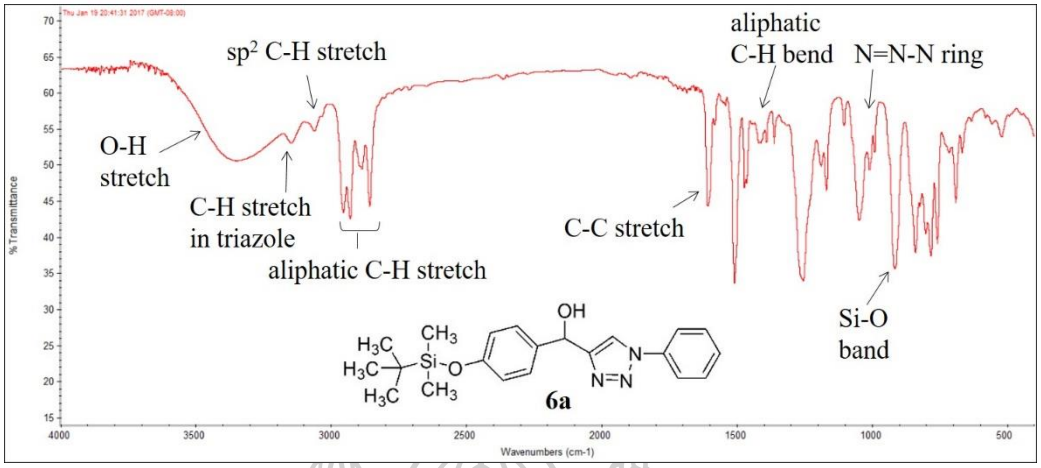
On the basic of FTIR results of all azides **5a-m**, it was observed that infrared spectra showed characteristic peaks due to strong asymmetric stretching and symmetric stretching of the azido group in the region of 2138-2090 cm^{-1} and 1299-1234 cm^{-1}. Furthermore, C-N stretching of azides displayed moderate to weak absorption band in the region of 1246-1121 cm^{-1}. The aromatic C-H stretching of compounds **5a-i** appeared at 3000 cm^{-1} except in compound **5c** in which this absorption band disappeared due to overlapping band of nujol's absorption around 3000-2854 cm^{-1}. The bending vibration of aliphatic C-H for **5d**, **5f-m** displayed at 1466-1448 cm^{-1}. All frequencies were compliance with the literature values. In addition, the N_3 symmetric stretching of azido group, C-N stretching and other low frequencies formed Fermi interactions that lead to unusual band splitting. Therefore, the doublet band can be observed in each spectrum of all compounds and one weak band in this doublet appeared as a shoulder of the main band (192, 201). The IR spectra of synthesized compounds **5c** and **5k** were recorded as nujol mulets and the absorption bands at 2925, 2854, 1459, 1376 and 722 cm^{-1} are also

contributed by nujol's absorption itself. The characteristic IR bands of important functional group of synthesized organic azide **5a-m** were presented in Table 11.

Table 11. Characteristic IR bands of important functional group of synthesized organic azides **5a-m**.

Compd	Wave number (cm^{-1})								
	O-H st	**Ar C-H st.**	**Alip C-H st.**	**N_3 asym st.**	**N_3 sym st.**	**C-N st.**	**C-F st.**	**NO_2 st.**	**C-O st.**
5a	-	3064	-	2129	1296	1174	-	-	-
5b	-	app 3000	-	2114	1283	1155	1229	-	-
5c	-	-	2921	2121	1299	1176	-	1528, 1342	-
5d	-	3029	2923	2138	1298	1181	-	-	-
5e	3356	3029	-	2114	1234	1129	-	-	1104
5f	-	3039	2955, 2836	2104	1285	1246	-	-	1035
5g	-	3065	2979, 2878	2097	1256	1202	-	-	-
5h	-	3064	2980 2895	2105	1247	1202	-	-	-
5i	-	3060	2927, 2869	2099	1235	1156	-	-	-
5j	-	-	2935, 2858	2090	1255	1145	-	-	-
5k	-	-	2853	2094	1263	1130	-	-	-
5l	-	-	2958, 2860	2095	1266	1121	-	-	-
5m	-	-	2928 2857	2095	1260	1124	-	-	-

Click compounds 6a-m



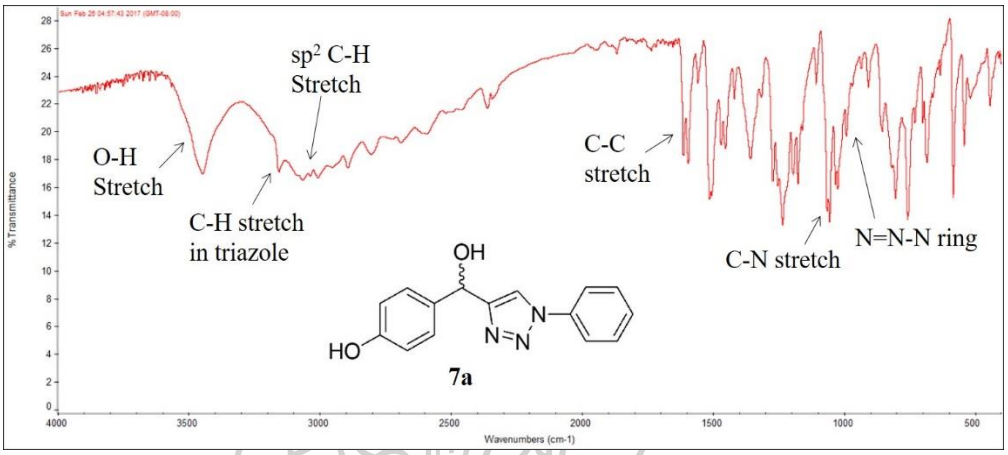
IR spectrum of (1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol, **6a** was used as representative spectrum in order to explain the characteristic vibration bands of functional groups in the compound. The significant O-H stretching for intramolecular hydrogen bonding of alcohol was displayed at 3347cm^{-1}. The bands of aromatic ring included aromatic sp^2 C-H stretching band at 3062 cm^{-1}, C-H out of plane bending at 839 cm^{-1} and skeletal C-C stretching at 1607 cm^{-1}. The strong Si-O stretching band was showed at 914 cm^{-1} and sp^3 C-H stretching bands in methyl were seen at 2956, 2930 cm^{-1}. The aliphatic C-H bending vibration was observed at 1471 cm^{-1}. In the spectrum, the absorption band of =C-H stretching around 3100 cm^{-1}, C-N stretching at 1047 cm^{-1} and N=N-N stretching at 990 cm^{-1} indicated the presence of 1,2,3-triazole ring.

According to the FT IR rspectra of all click compounds **6a-m** illustrated in the Appendix, it was found that the characteristic O-H stretching band for intramolecular hydrogen bonding of alcohol was displayed in the region of 3200- 3482cm^{-1}. The bands of aromatic ring included aromatic sp^2 C-H stretching band in the region of apparent 3064-3000 cm^{-1} and skeletal C-C stretching in the region of 1637-1599 cm^{-1}. Furthermore, the strong Si-O stretching band was showed in the region of 928-913 cm^{-1} and aliphatic sp^3 C-H stretching bends were seen in the region of 2958-2855 cm^{-1}. The aliphatic C-H banding vibration was observed in the region of 1471-1464 cm^{-1}. In the spectrum, the absorption band of =C-H stretching around 3100 cm^{-1}, C-N stretching in

the region of 1054-1041 cm^{-1} and N=N-N stretching around 1000 cm^{-1} indicated the presence of 1,2,3-triazole ring (202, 203). The characteristic IR bands of important functional group of synthesized organic azide **6a-m** were presented in Table 12.

4-(Hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives 7a-m

4-(Hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol 7a

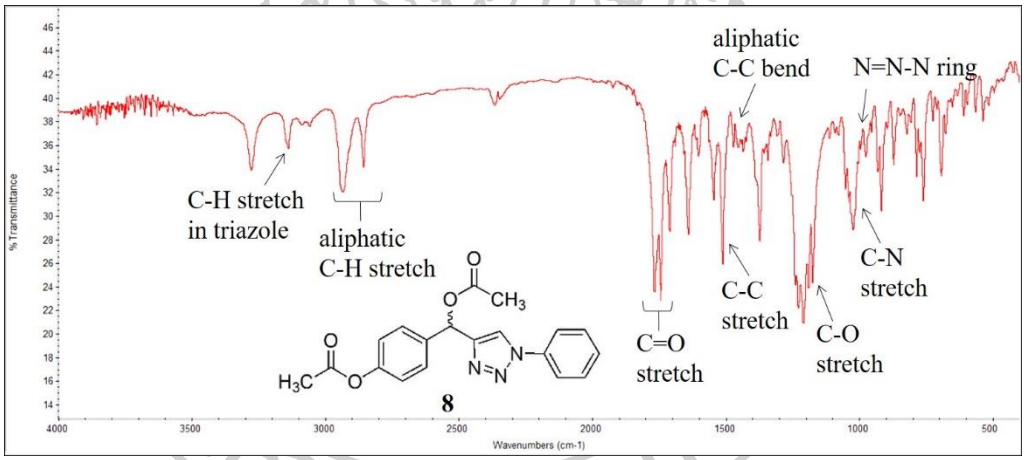


Characteristic vibration bands of functional groups were displayed in IR spectrum of 4-(hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol, **7a** used as representative spectrum for the explanation of the significant vibration bands of functional groups in the compound. The characteristic O-H stretching for intra-molecular hydrogen bonding of alcohol was displayed at 3348 cm^{-1}. The bands of aromatic ring included aromatic C-H stretching band at 3067 cm^{-1}, C-H out of plane bending at 854 cm^{-1}, skeletal C-C stretching at 1613 cm^{-1}. The strong Si-O stretching band was lost at 914 cm^{-1} and C-H stretching bends in alkane were also disappeared at 2955, 2855 cm^{-1}. In the spectrum, the absorption band of C-H stretching at 3157 cm^{-1}, C-N stretching at 1055 cm^{-1} and N=N-N stretching at 991 cm^{-1} indicated the presence of 1,2,3-triazole ring.

According to the FT IR results of all click compounds **7a-m** showed in Appendix, The characteristic O-H stretching band for intramolecular hydrogen bonding of alcohol was displayed in the region of 3238-3462 cm^{-1}. The bands of aromatic ring included aromatic sp^2 C-H stretching bend in the region of approximate 3064-3000 cm^{-1} and skeletal C-C stretching in the region of 1637-1611 cm^{-1}. The aliphatic sp^3 C-H

stretching bands were seen in the region of 2983-2812 cm^{-1} in compound **7d**, **7f** and **7g-m**. The aliphatic C-H bending vibration was observed in the region of 1462-1447 cm^{-1}. In the spectrum, the absorption band of =C-H stretching around 3100 cm^{-1}, C-N stretching in the region of 1055-1041 cm^{-1} and N=N-N stretching around 1000 cm^{-1} indicated the presence of 1,2,3-triazole ring (202, 203). In addition, the strong Si-O stretching band observed in the region of 928-913 cm^{-1} were lost and C-H stretching bands in alkane were also disappeared in the region of 2958-2855 cm^{-1}. Those all finding were strong evidences from FT IR results in order to prove the formation of designed compounds **7a-m**. The characteristic IR bands of important functional group of synthesized organic azide **7a-m** were presented in Table 13.

4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl acetate (8)



Characteristic vibration bands of functional groups were displayed in IR spectrum of 4-(acetyloxy(1-phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl acetate, **8.** The bands of aromatic ring included aromatic C-H stretching bend at about 3000 cm^{-1}, C-H out of plane bending at 868 cm^{-1}, skeletal C-C stretching at 1637 cm^{-1}. The aliphatic sp^3 C-H stretching bands were seen at 2934, 2854 cm^{-1} and aliphatic C-H bending was displayed at 1467 cm^{-1}. The stretching of C=O at 1763 cm^{-1}, 1741 cm^{-1} and C-O stretching at 1205 cm^{-1} indicated the presence of ester groups. In the spectrum, the absorption band of =C-H stretching at 3136 cm^{-1}, C-N stretching at 1019 cm^{-1} and ring breathing vibration of N=N-N stretching at 972 cm^{-1} indicated the

Table 12. Characteristic IR bands of important functional group of synthesized compounds **6a-m**.

	Wavenumber (cm^{-1})											
Compd	O-H st.	=C-H st. (triazole ring)	Aromatic C-H st.	Aliphatic C-H st.	Aromatic C=C st.	Aliphatic C-H bend	C-N st.	N=N-N st.	C-F st.	NO_2 st.	C-O st.	S-O vibration
6a	3347	3148	3062	2955, 2885	1607	1471	1047	990	-	-	-	914
6b	3482	3150	app 3000	2958, 2895	1637	1471	1050	app 990	1257	-	-	921
6c	3357	app 3150	app 3000	2955, 2885	1599	1471	1041	988	-	1525, 1342	-	913
6d	3493	3142	app 3000	2956, 2886	1604	1471	1054	991	-	-	-	923
6e	app 3400	3152	app 3000	2955, 2886	1607	1471	1054	992	-	-	1168	915
6f	3348	3146	app 3000	2956, 2895	1608	1471	1041	989	-	-	1169	915
6g	3356	app 3140	3064	2955, 2885	1607	1471	1047	1009	-	-	-	915
6h	3346	app 3140	3063	2955, 2885	1607	1471	1042	1009	-	-	-	916
6i	3347	App 3140	3060	2955, 2885	1607	1471	1047	967	-	-	-	915
6j	3200	3131	app 3000	2930, 2858	1637	1464	1047	app 1000	-	-	-	928
6k	3346	3141	app 3000	2957, 2858	1608	1471	1047	1009	-	-	-	916
6l	3354	app 3140	app 3000	2956, 2858	1608	1471	1048	1009	-	-	-	916
6m	3347	app 3140	app 3000	2955, 2857	1608	1470	1048	1009	-	-	-	916

Table 13. Characteristic IR bands of important functional group of synthesized compounds **7a-m**.

	Wavenumber (cm^{-1})										
Compd	O-H st.	=C-H st. (triazole ring)	Aromatic C-H st.	Aliphatic C-H st.	Aromatic C=C st.	Aliphatic C-H bend	C-N st.	N=N-N st.	C-F st.	NO_2 st.	C-O st.
7a	3448	3157	3067	-	1613	-	1055	991	-	-	-
7b	3462	3154	app 3000	-	1613	-	1053	992	1234	-	-
7c	3409	app 3140	3094	-	1637	-	1049	990	-	1523 1342	-
7d	3345	3125	app 3000	app 2900	1615	1452	1045	993	-	-	-
7e	3288	app 3140	app 3000	-	1613	-	1054	992	-	-	1170
7f	3422	3126	app 3000	2958, 2836	1611	1451	1048	990	-	-	1170
7g	3294	3145	3087	2815	1614	1456	1045	910	-	-	-
7h	3454	3148	app 3000	2983, 2812	1612	1456	1050	935	-	-	-
7i	3439	3157	app 3000	2856	1614	1451	1045	app 950	-	-	-
7j	3261	3121	app 3000	2925, 2857	1614	1450	1046	997	-	-	-
7k	3371	3142	app 3050	2955, 2871	1614	1462	1041	944	-	-	-
7l	3241	3122	app 3050	2954, 2869	1614	1447	1041	959	-	-	-
7m	3238	3125	app 3050	2957, 2869	1637	1447	1045	958	-	-	-

5.2.2 NMR spectroscopic characterization

4-(*tert*-Butyldimethylsilyloxy)benzaldehye (2)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.25 ppm and 1.00 ppm as singlets for six and nine protons intensity respectively. The resonances of two aromatic protons at positions of 3 and 5 showed at 6.94 ppm resulting from the coupling with neighboring protons H-2, H-6 at 7.79 ppm with the same coupling constant of 6.0 Hz and both signals showed doublet splitting patterns. The characteristic chemical shift for aldehyde proton showed at 9.89 pm as singlet.

4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol (3)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.25 ppm and 0.98 ppm as singlets for six and nine protons intensity respectively. The characteristic chemical shift for alkyne proton showed at 2.65 pm as singlet. The C-H proton α to the alcohol showed singlet signal at 5.41 ppm. The resonances of two aromatic protons at positions of 3 and 5 showed at 6.84 ppm as doublet splitting pattern resulting from the coupling with neighboring protons H-2, H-6 at 7.42 ppm as doublet with the coupling constants of 9.0 Hz.

(1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6a)

According to the ^{1}H NMR spectrum, it was found that the resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl appeared in the alkyl (methyl) region with the chemical shift 0.20 ppm and 0.98 ppm as singlets for six and nine protons intensity respectively. The C-H proton α to the alcohol showed singlet signal at 6.05 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.85 ppm resulting from the coupling with neighboring protons H-2′, H-6′ at 7.36 ppm with the same coupling constant of 6.0 Hz and both signals showed doublet splitting patterns. The phenyl ring proton in 4″ position

appeared signal between 7.42-7.44 ppm as multiplet. The resonances of 3″, 5″ protons and 2″, 6″ in this aromatic ring were 7.47-7.52 and 7.67-7.70 respectively. The multiplet splitting patterns for those protons at positions 3″, 5″ and 2″, 6″ were be observed. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 7.69 ppm as singlet.

(1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6b)

The ^{1}H NMR spectrum of compound **6b** showed the resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.19 ppm and 0.98 ppm as singlets for six and nine protons intensity respectively.

The C-H proton α to the alcohol showed singlet signal at 6.04 ppm. The resonances of aromatic protons at positions of 3′, 5′ and 2′, 6′ showed at 6.84 ppm and 7.33 ppm as doublet splitting patterns with coupling constant 9.0 Hz, respectively. The chemical shifts of protons at 2″, 6″ appeared in the aromatic region of 7.14 to 7.22 ppm as multiplet. The resonances of 3″ and 5″ protons were appeared in the more downfield region between 7.61 to 7.68 ppm as multiplet due to electron withdrawing effect of fluorine. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.67 ppm as singlet.

(1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6c)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.19 ppm and 0.98 ppm as singlets for six and nine protons intensity respectively. The proton signal for OH of CH-OH appeared at 3.01 ppm as a singlet. The C-H proton α to the alcohol showed singlet signal at 6.06 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.85 ppm as doublet splitting pattern resulting from the coupling with neighboring protons H-2′, H-6′ at 7.35 ppm as doublet with the same coupling constants of 8.5 Hz. The resonance of 3″, 5″ nitro group substituted

aromatic protons appeared at 8.39 ppm which was more downfield than signal of 2″, 6″ at 7.93 ppm resulting from the electron withdrawing effect of NO_2 at para position of aromatic ring that made deshielding effect on neighboring protons. The coupling constants 9.1 Hz, 9.2 Hz and doublet splitting patterns for those protons at positions 3″, 5″ and 2″, 6″ were be observed. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 7.84 ppm as singlet.

(1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl) methanol (6d)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.19 ppm and 0.99 ppm as singlets for six and nine protons intensity respectively. The chemical shift of methyl proton in aromatic 4″-CH_3 showed at 2.40 ppm as singlet for three protons intensity. The C-H proton α to the alcohol showed singlet signal at 6.04 ppm. The resonances of aromatic protons at positions of 3′, 5′ and 2′, 6′ showed at 6.84 ppm and 7.27 ppm as doublet splitting patterns with coupling constant 9.0 Hz, respectively. The chemical shifts of protons at 3″, 5″ appeared in the aromatic region of 7.35 as doublet with the coupling constant 9.0 Hz. The signal of 2″ and 6″ protons were appeared in the more downfield region at 7.54 ppm due to resonance effect of electron donating methyl group. The doublet splitting pattern with the same coupling constant 9.0 Hz were be observed. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.66 ppm as singlet.

(1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl) methanol (6e)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.16 ppm and 0.94 ppm as singlets for six and nine protons intensity respectively.

The C-H proton α to the alcohol showed singlet signal at 6.02 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.79 ppm as doublet splitting pattern with coupling constant 8.5 Hz. The resonance of 3″, 5″

aromatic protons appeared at upfield region of 6.85 ppm with coupling constant 8.8 Hz resulting from the electron donating effect of OH at para position of aromatic ring that made shielding effect on neighboring protons. The multiplet splitting pattern of 2′, 6′, 2″, 6″ proton signals appeared at 7.29 to 7.32 ppm resulting from the coupling of each other. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 7.58 ppm as singlet.

(1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6f)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.18 ppm and 0.98 ppm as singlets for six and nine protons intensity respectively. The chemical shift of methoxy proton in aromatic 4″-OCH_3 at 3.84 ppm as singlet for three protons intensity. The C-H proton α to the alcohol showed singlet signal at 6.03 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.82 ppm as doublet splitting pattern with coupling constant 9.0 Hz. The chemical shifts of protons at 2′, 6′ appeared in the aromatic region at 7.34 ppm as doublet with coupling constant 9.0 Hz. The signal of 3″ and 5″ protons were appeared in the more upfield region at 6.94 ppm as doublet resulting from shielding effect of electron donating methoxy group when in compared with chemical shift of protons in the region of 2″ and 6″. In this position, the signal appeared at 7.53 in downfield region as doublet. The same coupling constant 9.0 Hz was observed for both 3″, 5″ and 2″, 6″ protons. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.63 ppm as singlet.

(1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6g)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.17 ppm and 0.96 ppm as singlets for six and nine protons intensity respectively. A singlet signal at 5.42 ppm indicated the presence of benzylic proton. The C-H proton

α to the alcohol showed singlet signal at 5.91 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.78 ppm as doublet splitting pattern with coupling constant of 8.5 Hz. The chemical shifts of protons at 2′, 6′ appeared in the aromatic region between 7.19 to 7.22ppm as multiplet. It was found that signals of two protons at 2″, 6″ positions appeared in the aromatic region with chemical shift between 7.23-7.26 as multiplet due to coupling with each other. The multiplet splitting pattern of H-3″, H-4″ H-5″ protons signal appeared at 7.30-7.33 due of coupling of each other. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.17 ppm as singlet.

(1-(Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6h)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.17 ppm and 0.97 ppm as singlets for six and nine protons intensity respectively. The chemical shift of methyl proton in CH-CH_3 at 1.90 ppm as a doublet with coupling constant 7.1 Hz due to coupling with neighboring CH proton. The resonance of OH proton in CH-OH appeared at 3.68 ppm as a broad singlet. A quartet signal at 5.72 ppm was resulting from the presence of proton in CH that attached to CH_3 with coupling constant 7.0 Hz. The C-H proton α to the alcohol showed singlet signal at 5.91 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.78 ppm as doublet splitting pattern with coupling constant of 8.4 Hz. The chemical shifts of protons at 2′, 6′ appeared in the aromatic region at 7.18-7.22 ppm as multiplet. It was found that signals of protons at 2″, 6″ and 3″, 4″, 5″ positions appeared in the aromatic region with chemical shift between 7.24-7.27 and 7.28-7.35 as multiplet. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.16 ppm as singlet.

(1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6i)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.18 ppm and 0.96 ppm as singlets for six and nine protons intensity respectively. The resonance of OH proton in CH-OH appeared at 3.47 ppm as a broad singlet. A doublet of doublet signal at 5.05 ppm was resulting from the presence of methylene proton of compound **6i** with coupling constant 1.2 and 6.6 Hz. The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The protons at position H-d and H-e showed their signals at 6.23 ppm to 6.32 ppm and at 6.61 ppm. The splitting patterns of both observed signals were multiplet and doublet resulting from coupling of proton in H-e with coupling constant 15.7 Hz that indicated H-d and H-e protons were in *trans* configuration. The chemical shifts of seven protons in the region of 2′, 6′, 2″, 3″ 4″, 5″, 6″ appeared in the aromatic region between 7.22-7.40 ppm as multiplet due to coupling of each other. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.33 ppm as singlet.

(1-(Cyclohexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy) phenyl)methanol (6j)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.19 ppm and 0.98 ppm as singlets for six and nine protons intensity respectively. The signal of 1″ proton in cyclohexyl ring appeared at 4.38 ppm as triplet of triplet with coupling constant 3.8 and 11.7 Hz resulting from the coupling of neighboring protons. According to the nature of cyclohexane ring, it can be formed axial and equatorial conformations. The signals of axial protons at 2″, 6″ appeared at the chemical shift of 1.86-1.92 ppm and equatorial protons at this position appeared in the region of 2.14-2.18. The resonances of axial protons at 3″, 5″ appeared at the chemical shift of 1.34-1.49 ppm and equatorial protons at this position appeared in the region of 1.61-1.77 ppm. The chemical shifts 1.17-1.31 ppm indicated the presence of 4″ axial proton and 1.61-1.77 ppm was responsible for equatorial 4″ proton.

The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The resonances of aromatic protons at positions of 3′, 5′ and 2′, 6′ showed at 6.82 ppm and 7.30 ppm. The splitting patterns of 3′, 5′, 2′, 6′ were doublet with the same coupling constant 8.6 Hz. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.21 ppm as singlet.

1-(Butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6k)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.19 ppm and 0.97 ppm as singlets for six and nine protons intensity respectively. The signal of proton at position 4″ showed at the chemical shift of 0.92 ppm as triplet with coupling constant 7.3 Hz. Two protons at position 3″ appeared resonance at 1.32 ppm as sextet resulting from the coupling of neighboring protons with coupling constant 7.5 Hz. The splitting pattern of 2″ proton was quintet due to coupling of 1″ and 3″ protons and its signal appeared at 1.83 ppm with coupling constant 7.4 Hz. The proton of 1″ showed chemical shift of 4.27 ppm as triplet with coupling constant 7.3 Hz. The resonance of OH proton in CH-OH appeared at 3.55 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The resonances of aromatic protons at positions of 3′, 5′ and 2′, 6′ showed at 6.79-6.84 ppm and 7.28-7.32 as multiplets. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.20 pm as singlet.

(1-(Hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6l)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.18 ppm and 0.97 ppm as singlets for six and nine protons intensity respectively. The signal of proton at position 6″ showed at the chemical shift of 0.86 ppm as triplet with coupling constant 6.6 Hz. Six protons at position 3″, 4″ and 5″ appeared resonance at 1.27-1.31 ppm as multiplet resulting from the coupling of each other. The splitting

pattern of 2″ proton was quintet due to coupling of 1″ and 3″ protons and its signal appeared at 1.83 ppm with coupling constant 7.1 Hz. The proton of 1″ showed chemical shift of 4.26 ppm as triplet with coupling constant 7.3 Hz. The resonance of OH proton in CH-OH appeared at 3.45 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The resonances of two aromatic protons at positions of 3′, 5′ and 2′, 6′ showed at 6.79-6.84 ppm and 7.28-7.31 as multiplets. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.20 ppm as singlet.

(1-(Octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6m)

The resonances of six hydrogen atoms H-a and nine hydrogen atoms H-b from *tert*-butyldimethylsilyl were observed in the alkyl (methyl) region with the chemical shift 0.19 ppm and 0.97 ppm as singlets for six and nine protons intensity respectively. The signal of proton at position 8″ showed at the chemical shift of 0.87 ppm as triplet with coupling constant 6.9 Hz. Ten protons at position 3″, 4″, 5″, 6″ and 7″ appeared resonance at 1.18-1.26 ppm as multiplet resulting from the coupling of each other. The splitting pattern of 2″ proton was quintet due to coupling of 1″ and 3″ protons and its signal appeared at 1.86 ppm with coupling constant 7.2 Hz. The proton of 1″ showed chemical shift of 4.27 ppm as triplet with coupling constant 7.2 Hz. The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The resonances of aromatic protons at positions of 3′, 5′ and 2′, 6′ showed at 6.79-6.84 ppm and 7.28-7.32 as multiplet. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.20 ppm as singlet.

4-(Hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7a)

According to the ^{1}H NMR spectrum, it was found that proton signal for OH of CH-OH appeared at 4.88 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.96 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet splitting pattern resulting from the coupling with neighboring protons H-2′, H-6′ at 7.34 ppm which was doublet with the same

coupling constant of 9.0 Hz. The phenyl ring proton in 4″ position appeared signal between 7.44-7.79 ppm as multiplet. The resonances of 3″, 5″ protons in this aromatic ring coupling to H-2″, H-6″ were 7.57 as triplet and 7.89 as doublet respectively. The same coupling constant 9.0 Hz and doublet splitting patterns for those protons at positions 3″, 5″ and 2″, 6″ were observed. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 8.33 ppm as singlet.

The ^{13}C NMR spectrum showed signals of CH-OH carbon at 69.68 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.84 to 157.69 ppm. The signals of carbons for aromatic ring substituted at N-1 position of triazole were observed in the region with the chemical shifts 121.00 to 135.67 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 120.31 ppm and 154.31 ppm, respectively.

4-(Hydroxyl-(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7b)

The ^{1}H NMR spectrum of compound **7b** showed the resonance of OH proton in CH-OH at 4.94 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.96 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet splitting pattern with coupling constant 8.5 Hz. The chemical shifts of protons at 2′, 6′, 2″, 6″ appeared in the aromatic region of 7.32 to 7.37 ppm as multiplet. The fluorine has strong coupling with proton and the resonances of 3″ and 5″ protons were appeared in the more downfield region between 7.91-7.96 ppm as multiplet due to electron withdrawing effect of fluorine. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 8.32 ppm as singlet.

The ^{13}C NMR spectrum showed signals of CH-OH carbon at 69.63 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.85 to 157.70 ppm. The signals of carbons in 3″, 5″ positions were observed at 117.36 ppm with the coupling constant of 23.2 Hz due to coupling of fluorine atom and its carbon atoms at ortho positions. The chemical shift of C-2″, C-6″ was 123.27 ppm with coupling constant 9.0 Hz resulting from C-F coupling of meta carbons, 2″, 6″ and fluorine. The carbon at 1″ position was para position of fluorine atom and its signal appeared at 134.84 ppm as

two split peaks with coupling constant 3.0 Hz due to C-F coupling. The chemical shift at 163.04 ppm was responsible for 4″ carbon which attached directly to fluorine with large coupling constant 244.5 Hz. The ^{19}F has two spin states +½ and -½ and its nuclear magnet can be aligned or disaligned relative to applied mangnetic field of NMR instrument. That is the reason why ^{19}F splits ^{13}C peaks in the compound containing carbon bonded with fluorine atom as shown in the NMR spectrum. The signals of C-5 and C-4 from triazole moiety appeared at 120.62 ppm and 154.34 ppm, respectively.

4- (Hydroxyl-(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7c)

The proton signal for OH of CH-OH appeared at 5.01 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.98 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet splitting pattern resulting from the coupling with neighboring protons H-2′, H-6′ at 7.34 ppm which was doublet with the same coupling constant of 8.5 Hz. The resonance of 3″, 5″ nitro group substituted aromatic protons appeared at 8.44 ppm which was more downfield than signal of 2″, 6″ at 8.24 ppm resulting from the electron withdrawing effect of NO_2 at para position of aromatic ring that made deshielding effect on neighboring protons. The same coupling constant 9.1 Hz and doublet splitting patterns for those protons at positions 3″, 5″ and 2″, 6″ were observed. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 8.55 ppm as singlet.

The ^{13}C NMR spectrum showed signals of CH-OH carbon at 69.57 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.90 to 155.01 ppm. The signals of carbons for aromatic ring substituted at N-1 position of triazole were observed in the region with the chemical shifts 121.39 to 157.81 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 120.80 ppm and 147.99 ppm, respectively.

4-(Hydroxyl-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7d)

The ^{1}H NMR spectrum of compound **7d** showed the chemical shift of methyl proton in aromatic 4″-CH_3 at 2.39 ppm as singlet for three protons intensity. The resonance of OH proton in CH-OH at 4.87 ppm as a broad singlet. The C-H proton α

to the alcohol showed singlet signal at 5.95 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet splitting pattern with coupling constant 9.0 Hz. The chemical shifts of protons at 2′, 6′, 3″, 5″ appeared in the aromatic region of 7.31 to 7.38 ppm as multiplet. The signal of 2″ and 6″ protons was appeared in the more downfield region at 7.75 ppm as doublet due to resonance effect of electron donating methyl group. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 8.27 ppm as singlet.

The ^{13}C NMR spectrum showed that the carbon of methyl group in 4″ position of aromatic ring appeared chemical shift at 21.02 ppm. The signals of CH-OH carbon at 69.66 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.84 to 157.67 ppm. The signals of carbons for aromatic ring substituted at N-1 position of triazole were observed in the region with the chemical shifts 120.91 to 136.09 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 120.25 ppm and 154.13 ppm, respectively.

4-(Hydroxyl-(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7e)

The proton signal for OH of CH-OH and 4″-OH appeared at apparent app 3.20 ppm and 4.90 ppm as broad singlets. The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet splitting pattern resulting from the coupling with neighboring protons H-2′, H-6′ at 7.33 ppm which was also doublet with coupling constants of 8.5 Hz. The resonance of 3″, 5″ aromatic protons appeared at 6.99 ppm which was more upfield than signal of 2″, 6″ at 7.67 ppm resulting from the electron donating effect of OH at para position of aromatic ring that made shielding effect on neighboring protons. The same coupling constant 9.0 Hz and doublet splitting patterns for those protons at positions 3″, 5″ and 2″, 6″ were observed. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 8.17 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.65 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the signals of CH-OH carbon at 69.65 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.83 to 157.66 ppm. The signals of carbons for aromatic ring substituted at N-1 position of triazole were observed in the region with the chemical shifts 116.97 to 158.62 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 120.40 ppm and 153.88 ppm, respectively.

4-(Hydroxyl-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7f)

The ^{1}H NMR spectrum of compound **7f** showed the chemical shift of methoxy proton in aromatic 4″-OCH_3 at 3.87 ppm as singlet for three protons intensity. The resonance of OH proton in CH-OH at 4.87 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.95 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet splitting pattern with coupling constant 9.0 Hz. The chemical shifts of protons at 2′, 6′ appeared in the aromatic region at 7.33 ppm as doublet with coupling constant 9.0 Hz. The signal of 3″ and 5″ protons were appeared in the more upfield region at 7.10 ppm as doublet resulting from shielding effect of electron donating methoxy group when in compared with chemical shift of protons in the region of 2″ and 6″. In this position, the signal appeared at 7.78 in downfield region as doublet. The same coupling constant 9.0 Hz was observed for both 3″, 5″ and 2″, 6″ protons. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 8.21 ppm as singlet.

The ^{13}C NMR spectrum showed that the carbon of methoxy group in 4″ position of aromatic ring appeared chemical shift at 56.05 ppm. The signals of CH-OH carbon at 69.65 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.64 to 157.74 ppm. The signals of carbons for aromatic ring substituted at N-1 position of triazole were observed in the region with the chemical shifts 115.83 to 160.64 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 120.35 ppm and 154.09 ppm, respectively.

4-(Hydroxyl-(1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7g)

The resonance of OH proton in CH-OH appeared at 4.82 ppm as a broad singlet. A singlet signal at 5.56 ppm was resulting from the presence of benzylic proton of compound **7g**. The C-H proton α to the alcohol showed singlet signal at 5.86 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.77 ppm as doublet splitting pattern with coupling constant of 8.5 Hz. The chemical shifts of protons at 2′, 6′ appeared in the aromatic region at 7.26 ppm as doublet with coupling constant 8.5 Hz. It was found that signals of all five protons at 2″ to 6″ positions appeared in the aromatic region with chemical shift between 7.32-7.40 as multiplet due to coupling with each other. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.72 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.35 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the chemical shift of benzylic carbon appeared at 54.16 ppm. The signals of CH-OH carbon at 69.59 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.77 to 157.56 ppm. The signals of aromatic ring carbons at position of 1″ to 6″ were observed in the chemical shift region between 128.94 to 137.15 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 122.28 ppm and 153.56 ppm, respectively.

4-(Hydroxyl-(1-(ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7h)

The ^{1}H NMR spectrum of compound **7h** showed the chemical shift of methyl proton in CH-CH_3 at 1.93 ppm as a doublet with coupling constant 6.0 Hz due to coupling with neighboring CH proton. The resonance of OH proton in CH-OH appeared at 4.82 ppm as a broad singlet. A quartet signal at 5.88 ppm was resulting from the presence of proton in CH that attached to CH_3 with coupling constant 6.9 Hz. The C-H proton α to the alcohol showed singlet signal at 5.89 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.77 ppm as doublet splitting pattern with coupling constant of 8.5 Hz. The chemical shifts of protons at 2′, 6′ appeared in the aromatic region at 7.26 ppm as doublet with coupling constant 8.5 Hz. It was found that signals of all five protons at 2″ to 6″ positions appeared in the aromatic region with

chemical shift between 7.30-7.38 as multiplet. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.74 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.38 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the chemical shifts of methyl carbon in CH-CH_3 appeared at 21.71 ppm and carbon that attached to methyl group was 60.75 ppm. The signals of CH-OH carbon at 69.65 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.77 to 157.55 ppm. The signals of aromatic ring carbons at position of 1″ to 6″ were observed in the chemical shift region between 127.37 to 142.25 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 121.12 ppm and 153.13 ppm, respectively.

4-(Hydroxyl-(1-(cinnamyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7i)

The resonance of OH proton in CH-OH appeared at 4.93 ppm as a broad singlet. A doublet of doublet signal at 5.13 ppm was resulting from the presence of methylene proton of compound **7i** with coupling constant 1.0 and 6.4 Hz. The C-H proton α to the alcohol showed singlet signal at 5.91 ppm. The protons at position H-b and H-c showed their signals at 6.43 ppm to 6.52 ppm and at 6.69 ppm. The splitting patterns of both observed signals were multiplet and doublet resulting from coupling of proton in H-c with coupling constant 15.8 Hz that indicated H-b and H-c protons were in *trans* configuration. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.77 ppm to 6.82 ppm as multiplet. The chemical shifts of five protons in the region of 2′, 6′, 3″, 4″, 5″ appeared in the aromatic region between 7.23-7.35 ppm as multiplet due to coupling of each other. It was found that signals of 2″ to 6″ protons appeared at 7.41 ppm to 7.45 ppm as multiplet. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.75 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.48 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the chemical shift of methylene carbon, C-a appeared at 52.55 ppm. The signals of CH-OH carbon at 69.58 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.79 to 157.57 ppm. The signals of aromatic ring carbons at position of 1″ to 6″ were observed in the chemical shift region

between 127.53 to 137.02 ppm. The resonances of carbons in C-b and C-c were observed at 135.14 ppm and 124.19 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 122.09 ppm and 153.40 ppm, respectively.

4-(Hydroxyl-(1-(cyclohexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7j)

The signal of 1″ proton in cyclohexyl ring appeared at 4.44 ppm as triplet of triplet with coupling constant 3.8 and 11.5 Hz resulting from the coupling of neighboring protons. According to the nature of cyclohexane ring, it possesses chair and boat conformations and both of which contain six equatorial hydrogens and six axial hydrogens. At room temperature, chair form can flip rapidly and chair-char conformation interconvert those axial and equatorial protons in the ring. Therefore, the chemical shift assignments of axial and equatorial protons at that temperature showed in average resonance values. In order to assign axial and equatorial proton by ^{1}H NMR, the temperature of the sample must be lowed (-100 °C) that show the splitting pattern for protons. Here in this structure **7j**, it was postulated that the bulky group locked the chair ring flipping and formed mono-substituted rigid cyclohexane ring. The generic chemical shift values for equatorial is 1.60 ppm which is more downfield than axial proton at 1.12 ppm. Therefore, the assignment of predicted chemical shift in structure **7j** was assigned as the following. The signals of axial protons at 2″, 6″ appeared at the chemical shift of 1.68-1.90 ppm and equatorial protons at this position appeared in the region of 2.05-2.15. The resonances of axial protons at 3″, 5″ appeared at the chemical shift of 1.39-1.55 ppm and equatorial protons at this position appeared in the region of 1.68-1.90 ppm. The chemical shifts 1.26-1.36 ppm indicated the presence of 4″ axial proton and 1.68-1.90 ppm was responsible for equatorial 4″ proton. It was impossible to predict the exact chemical shift values, however, the four-bond coupling (W coupling) as *J* value 1.5-2 Hz could be observed in this rigid cyclohexane ring. The resonance of OH proton in CH-OH appeared at 4.93 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.89 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet with coupling constant 8.6 Hz. Two protons at position 2′ and 6′ appeared signals at 7.29 ppm as doublet with coupling constant 8.5 Hz. The characteristic chemical shift for 5-H proton attached to triazole ring showed at

7.73 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.53 and it was observed as broad singlet (201, 202, 204).

The ^{13}C NMR spectrum showed that the signals of CH-OH carbon at 69.64 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.78 to 157.56 ppm. The signals of carbons from cyclohexyl ring appeared in the region of 25.84 ppm to 60.49 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 120.13 ppm and 152.66 ppm, respectively (205).

4-(Hydroxyl-(1-(butyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7k)

The signal of proton at position 4″ showed at the chemical shift of 0.90 ppm as triplet with coupling constant 7.3 Hz. Two protons at position 3″ appeared resonance at 1.29 ppm as sextet resulting from the coupling of neighboring protons with coupling constant 7.5 Hz. The splitting pattern of 2″ proton was quintet due to coupling of 1″ and 3″ protons and its signal appeared at 1.82 ppm with coupling constant 7.3 Hz. The proton of 1″ showed chemical shift of 4.34 ppm as triplet with coupling constant 7.1 Hz. The resonance of OH proton in CH-OH appeared at 5.12 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.91 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.80 ppm as doublet with coupling constant 8.5 Hz. Two protons at position 2′ and 6′ appeared signals at 7.27 ppm as doublet with coupling constant 8.5 Hz. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.73 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.70 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the signals of CH-OH carbon at 69.46 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.80 to 157.55 ppm. The signals of carbons from butyl side chain appeared in the region of 13.72 ppm to 50.30 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 122.26 ppm and 152.94 ppm, respectively.

4-(Hydroxyl-(1-(hexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7l)

The signal of proton at position 6″ showed at the chemical shift of 0.86 ppm as triplet with coupling constant 6.9 Hz. Six protons at position 3″, 4″ and 5″ appeared resonance at 1.29 ppm as multiplet resulting from the coupling of each other. The splitting pattern of 2″ proton was quintet due to coupling of 1″ and 3″ protons and its signal appeared at 1.85 ppm with coupling constant 6.9 Hz. The proton of 1″ showed chemical shift of 4.34 ppm as triplet with coupling constant 7.1 Hz. The resonance of OH proton in CH-OH appeared at 4.88 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.87 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.78 ppm as doublet with coupling constant 8.5 Hz. Two protons at position 2′ and 6′ appeared signals at 7.26 ppm as doublet with coupling constant 8.5 Hz. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.70 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.48 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the signals of CH-OH carbon at 69.58 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.77 to 157.57 ppm. The signals of carbons from hexyl side chain appeared in the region of 14.27 ppm to 50.57 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 122.13 ppm and 153.05 ppm, respectively.

4-(Hydroxyl-(1-(octyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7m)

The signal of proton at position 8″ showed at the chemical shift of 0.87 ppm as triplet with coupling constant 6.5 Hz. Ten protons at position 3″, 4″, 5″, 6″ and 7″ appeared resonance at 1.26-1.29 ppm as multiplet resulting from the coupling of each other. The splitting pattern of 2″ proton was quintet due to coupling of 1″ and 3″ protons and its signal appeared at 1.87 ppm with coupling constant 6.9 Hz. The proton of 1″ showed chemical shift of 4.34 ppm as triplet with coupling constant 7.1 Hz. The resonance of OH proton in CH-OH appeared at 4.92 ppm as a broad singlet. The C-H proton α to the alcohol showed singlet signal at 5.87 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed at 6.78 ppm as doublet with coupling

constant 8.5 Hz. Two protons at position 2′ and 6′ appeared signals at 7.26 ppm as doublet with coupling constant 8.5 Hz. The characteristic chemical shift for 5-H proton attached to triazole ring showed at 7.70 ppm as singlet. The chemical shift of phenolic hydroxyl at 4′ position was 8.53 and it was observed as broad singlet.

The ^{13}C NMR spectrum showed that the signals of CH-OH carbon at 69.56 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 115.76 to 157.57 ppm. The signals of carbons from octyl side chain appeared in the region of 14.39 ppm to 50.58 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 122.13 ppm and 153.04 ppm, respectively.

Generally, thermal condition of azide-alkyne catalyst-free 1,3-dipolar cycloaddition reaction produced regioisomers. In contrast, the CuAAC process provided 1,4-regioisomer and the ruthenium-catalyzed cycloaddition of alkyne and azide generated complementary 1,5-regioisomer of 1,2,3-triazole (128, 206, 207). The structural assignments of substituted 1,2,3-triazoles have been studied in order to discriminate the signals of these structures (208, 209). In the research, the formation of 1,4-disubstituted 1,2,3-triazole rings in the synthesized compounds was confirmed by ^{1}H NMR in which the chemical shift values of H-5 triazolyl proton were in the region of 7.86-8.55 ppm and this peak appeared as a singlet in every spectrum.

In addition, ^{13}C NMR was used to identify the establishment of triazole ring. One study verified that the resonance of C-5 showed at ~120 ppm (120 ±3) for 1,4-disubstituted-1*H*-1,2,3-triazole and C-4 appeared at ~133 (133±3) ppm for 1,5-disubstituted-1*H*-1,2,3-triazole by using one-dimensional ^{13}C NMR. The emergence of upfield signal for C-5 allowed more easily differentiation from its C-4 regioisomer (209). After analyzing the signals of synthesized compounds **7a-m** in this research, it was observed that signal of 1,2,3-triazolyl carbon C-5 exhibited in the region 120.25-122.28 and this characteristic chemical shift value for carbon atom of triazole moiety that was consistent with literature value of experimental investigation.

In order to discriminate 1*H*-1,4-disubstituted 1,2,3-triazole and 2*H*-1,4-disubstituted 1,2,3-triazole, homonuclear NOE (Nuclear Overhauser Enhancement)

difference spectroscopy can also be applied. The strong NOE was observed in 1*H*-1,4-disubstituted-1,2,3-triazole and 2*H*-1,4-disubstituted-1,2,3-triazole showed only small through-space interaction with lack of NOE. In addition, the 2 substituted-2*H*-1,2,3-triazole can be synthesized by mean of 1,3-dipolar cycloaddition reaction using copper catalyst and obtained as a tautomer of 1*H*-1,2,3-triazole (210). It was clear that the chemical shifts of the signals of triazoles protons in 1 substituted-1*H*-1,2,3-triazole and 2 substituted-2*H*-1,2,3-triazole were not the same. In this research, only a singlet signal of triazole proton resonance in ^{1}H NMR and chemical shift of ^{13}C NMR were be observed for each designed compounds and those all findings indicated that the synthesized compounds were 1,4-disubstituted-1*H*-1,2,3-triazole compounds.

In the ^{1}H NMR spectra, the loss of hydroxyl peak in CH-OH was due to the deuterium exchange of labile proton with deuterated solvents $CDCl_3$ or acetone-d_6. The chemical shifts at 2.98 to 3.20 were resulted from the residual water peaks of acetone-d_6 which appeared more downfield region in compare with literature value 2.84 ppm because the synthesized compounds contained good hydrogen bond donor OH that could react with hydrogen bond acceptor solvent, acetone-d_6 in order to form hydrogen bond and the signal appeared at large downfield shift. The solvent residual peaks of CH in $CDCl_3$ or CH_3 in acetone-d_6 were observed at 7.26 ppm and 2.06 to 2.08 ppm in ^{1}H NMR. The resonance of the signals of CO and CH_3 appeared around 205.87 and 30.60 ppm as acetone-d_6 solvent signal in ^{13}C NMR spectra (205, 211). The residual chromatographic solvents of ethyl acetate and hexane signals were also observed inevitably in some ^{1}H NMR spectra and chemical shifts value of those signals were consistent with literature values.

4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl acetate (8)

The signal of methyl proton in CH-$OCOCH_3$ and Ar-$OCOCH_3$ showed at the chemical shift of 2.16 ppm and 2.29 ppm as singlet. The C-H proton α to the acetate showed singlet signal at 7.10 ppm. The resonances of two aromatic protons at positions of 3′ and 5′ showed in the region of 7.10-7.13 as multiplet. The splitting pattern resulting from the coupling with neighboring protons H-2′, H-6′, H-3″, H-4″, H-5″ was multiplet and chemical shift appeared in the region of 7.42-7.56. The reason of upfield region

chemical shift was due to shielding effect of acetyl groups. The resonances of H-2″, H-6″ protons appeared in the downfield region at 7.68-7.71 ppm as multiplet. The characteristic chemical shift for 1,4-disubstituted 5-H triazolyl proton showed at 7.86 ppm as singlet.

The ^{13}C NMR spectrum showed methyl carbon signals of CH-$OCOCH_3$ and 4′-$OCOCH_3$ were 50.75 and 54.93 ppm. The carbon signal bearing acetyl group at 70.40 ppm and aromatic ring carbons at position 1′ to 6′ in the region of 121.17 to 155.07 ppm. The signals of carbons for aromatic ring substituted at N-1 position of triazole were observed in the region with the chemical shifts 122.78 to 137.28 ppm. The signals of C-5 and C-4 from triazole moiety appeared at 121.95 ppm and 151.84 ppm, respectively. The resonances of carbonyl in 4′ C=O and CH-OC=O were 169.67 and 170.14.

5.2.3 Mass spectroscopic characterization

The high-resolution mass spectra and the accurate mass measurements were obtained on a Brucker-Daltonics micrOTOF-Q II mass spectrophotometer with positive mode electrospray ionization. According to the results of mass spectra, the sodium adduct $[M+Na]^+$ peaks of compound **7a-m** were observed in agreement with their molecular formula. The accuracy of mass for every compound was determied based on the the mass measurement parts per million (ppm) error. As described in Table 14, the mass errors were less than 5 ppm (in the range of -2.613649 ppm to 2.413039). For compound **8**, the experimental mass and theoretical mass of sodium adduct $[M+Na]^+$ was observed at 374.1117 and there was mass error with zero ppm. In summary, mass error values of those all compounds **7a-m** and **8** were compliance with a 5 ppm criterion of mass spectrometric dtermination by HRMS (212).

Table 14. The mass errors of synthesized compounds **7a-m**.

Entry	Compd	Molecular formula	Proposal ions	Theoretical Mass (m/z) $[M+Na]^+$	Experimental mass (m/z) $[M+Na]^+$	Mass error (ppm)
1	7a	$C_{15}H_{13}N_3O_2$	$[M+Na]^+$	290.0906	290.0913	2.413039
2	7b	$C_{15}H_{12}FN_3O_2$	$[M+Na]^+$	308.0812	308.0813	0.324590
3	7c	$C_{15}H_{12}N_4O_4$	$[M+Na]^+$	335.0757	335.0753	-1.193760
4	7d	$C_{16}H_{15}N_3O_2$	$[M+Na]^+$	304.1062	304.1058	-1.315330
5	7e	$C_{15}H_{13}N_3O_3$	$[M+Na]^+$	306.0855	306.0847	-2.613649
6	7f	$C_{16}H_{15}N_3O_3$	$[M+Na]^+$	320.1011	320.1016	1.562007
7	7g	$C_{16}H_{15}N_3O_2$	$[M+Na]^+$	304.1062	304.1057	-1.644162
8	7h	$C_{17}H_{17}N_3O_2$	$[M+Na]^+$	318.1219	318.1216	-0.943035
9	7i	$C_{18}H_{17}N_3O_2$	$[M+Na]^+$	330.1219	330.1223	1.211674
10	7j	$C_{15}H_{19}N_3O_2$	$[M+Na]^+$	296.1375	296.1375	0.000000
11	7k	$C_{13}H_{17}N_3O_2$	$[M+Na]^+$	270.1219	270.1223	1.480813
12	7l	$C_{15}H_{21}N_3O_2$	$[M+Na]^+$	298.1532	298.1533	0.335398
13	7m	$C_{17}H_{25}N_3O_2$	$[M+Na]^+$	326.1845	326.1849	1.226300

5.3 Structure-activity relationship of synthesized compounds and anti-tuberculosis activity

The synthesized compounds **7a-m** and compound **8** were investigated for antituberculosis activity on 20 clinical isolates and MTB H37Rv reference strains (ATCC 27294) according to the procedure described in section 4.3. Firstly, compound **7a** and **8** were tested on inhibitory activity against mycobacteria in order to access the importance of alcohol and ester type functional group. The results showed that the MIC value of compound **7a** was observed at 80 µg/ml for all 20 MTB clinical isolates and MTB H37Rv reference strains. It was found that two hydroxyl groups containing compound **7a** showed better antimycobacterial activity than ester, compound **8**. The insertion hydrophobic ester group to imitate ACA diminished desired activity. Therefore, two hydroxyl groups containing compounds **7b-m** were synthesized by the insertion of various side chains containing electron withdrawing and electron donating groups and other chemical groups at the N-1 position of triazole rings and subjected for inhibitory activities on tuberculosis. The results were presented in Table 15.

In order to study structure-activity relationship **(**SAR), the compound hydrophilicity by means of calculated logarithm of partition coefficient between n-octanol and water (cLog*P*) calculation, molecular weight and MIC values were evaluated. The clog*P* vaues of **7a** and **8** were 1.332, 2.204 and control drug kanamycin was -3.88. Those data indicated that hydrophilic hydroxyl group is necessary for antituberculosis activity. All compounds might act with different mode from kanamycin.

The chemical constituent of ACA from natural source responsible for antituberculosis activity is S-configuration i.e., 1′-S-1′-Acetoxychavicol acetate. According to the literature, MIC of synthetic ACA was higher than natural S-form of ACA on *M.tuberculosis* stains (63). Therefore, it can be postulated that the racemic form of synthetic *dl*-4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives contributed to lower antituberculosis activity and chirality may play an important role in the intermolecular interaction with binding sites of biological targets. In addition, the control drug for determination of MIC was kanamycin and its MIC value was 10 µg/mL. The Global Program for the Discovery of New Anti-Tuberculosis Drugs

postulated that 6.25 µg/mL should be an upper threshold for the evaluation of new anti-tuberculosis therapy (213). Another approach is that MIC value of single drug resistant strain should not be more than ten times of the MIC of non-resistant strains (214). According to the results, it is concluded that synthesized compounds possessed low activity and their structural modifications and stereoselective ligands are necessary to afford as specific agents to combact MDR-strains.

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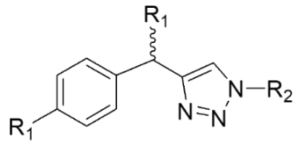
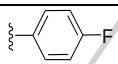
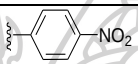
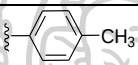
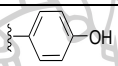
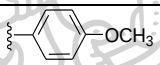
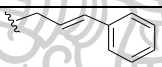
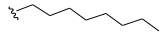
Table 15. In vitro antitubercular activities of synthesized compounds against M. tuberculosis[a].



No.	R_1	R_2	MIC (μg/mL)	MW	cLog*P*
7a	OH		80	267.28	1.33
7b	OH		80	285.27	1.64
7c	OH		80	312.28	1.44
7d	OH		80	281.31	1.83
7e	OH		80	283.28	1.09
7f	OH		80	297.31	1.56
7g	OH		80	281.31	0.88
7h	OH		80	295.34	1.19
7i	OH		80	307.35	1.48
7j	OH		80	273.33	1.14
7k	OH		80	247.29	0.70
7l	OH		80	275.35	1.75
7m	OH		80	303.40	2.81
8	$OCOCH_3$		>80	351.36	2.204
Kanamycin (control)			10	484.49	-3.88[b]

[a] 20 MTB clinical isolates and MTB H37Rv reference strains (ATCC 27294).

[b] Data is available on the website (http://drugcentral.org).

CHAPTER VI
CONCLUSION

The structure-based design and synthesis of 4-(hydroxy-(1*H*-1,2,3-triazol-4-yl))methyl phenol derivatives have been developed and assessed for their *in vitro* antituberculosis activity. The various substituents such as aryl, aralkyl, cycloalkyl and alkyl derivatives were installed at the N-1 positions of 1,2,3-triazole rings. The electron withdrawing groups such as fluorine and nitro at the para position of phenyl ring can create the electron deficient regions that might act on nucleophilic regions of binding sites. The electron donating groups of methyl and methoxy might have electronic effects on site of actions. The aryl alkyl side chains such as benzyl, phenyl ethyl were also studied. The different chain lengths of aliphatic groups at the N-1 position of 1,2,3-triazole were selected in order to mimic the high fatty acid content of cell wall of tuberculosis strains due to hydrophobic nature of compounds.

The synthesis pathways to afford designed products **7a-m** included five steps. The active hydroxy group was protected by *tert*-butyldimethylsilyl chloride to provide compound **2** with 80.93 percent yield. Next step was new carbon-carbon bond formation by Grignard reaction to obtain alkyne product **3** with 88.40 percent yield. The coupling of alkyne, azide click reaction catalyzed by copper catalyst was continued by conventional way and microwave irradiation. The microwave-assisted one-pot two-step reaction was also developed. The organic azides **5g-m** were prepared by microwave synthesizer in safe manner and it could avoid tedious extraction procedure and handling of potentially explosive azides. After that triazole ring closure was completed in a short period of time by means of microwave energy in one-pot and their percent yields were comparable with conventional one. In addition, the microwave-assisted reactions for synthesizing compounds **6a-m** from prepared alkyne and organic azides were completed within the temperature ranging from 60 to 70 °C for 5 to 15 minutes and provided higher percent yields (56.07% to 85.11%) than conventional reactions (41.87% to 77.65%) at room temperature for overnight. It was found that the developed microwave-assisted synthesis reactions were simple, practical, efficient and safe to generate designed compounds within a short period of time in compare with

conventional reactions. The deprotection step was completed by *tetra*-n-butylammonium fluoride in THF within one hour with moderate to good percent yields, 60.90% to 93.88%. The overall percent yields of compound **7a**-**m** were 25.99% to 48.73%. The compound **7a** was acetylated by DCC, DMAP and acetic anhydride to generate compound **8** and its overall yield was 27.33%. All the structures of synthesized designed compounds were confirmed by FT IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic methods and evaluated for antituberculosis activities. The MIC of compounds **7a-m** showed 80 µg/mL in compare with compound **8** was >80 µg/mL. It was observed that the synthesized products possessed lower activity than control drug kanamycin (MIC 10 µg/mL). This could imply that extending the structure with 1,2,3-triazole ring might be steric to the site of action. Furthermore, possible stereoisomeric nature of synthesized products can also influence on the activity. It can be pointed out that the binding site might possess stereogenic center and compound chirality is important to elicit the response.

According to the result, it is possible that there are more than one parameters of synthesized compounds influenced on the inhibitory activity of tubercular strains. It is difficult to discover active molecule that meet with full structural requirements as new tuberculosis agent in order to combact MDR-TB. However, this study suggested that modifying chemical structure of substituent on N-1 or other positions might be needed.

In this case, chirality of compound might necessary to generate the active compound which possesses chemical specificity for ligand as a future drug candidate for TB.

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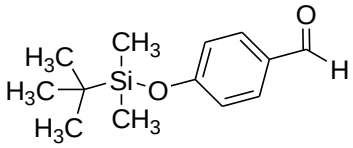
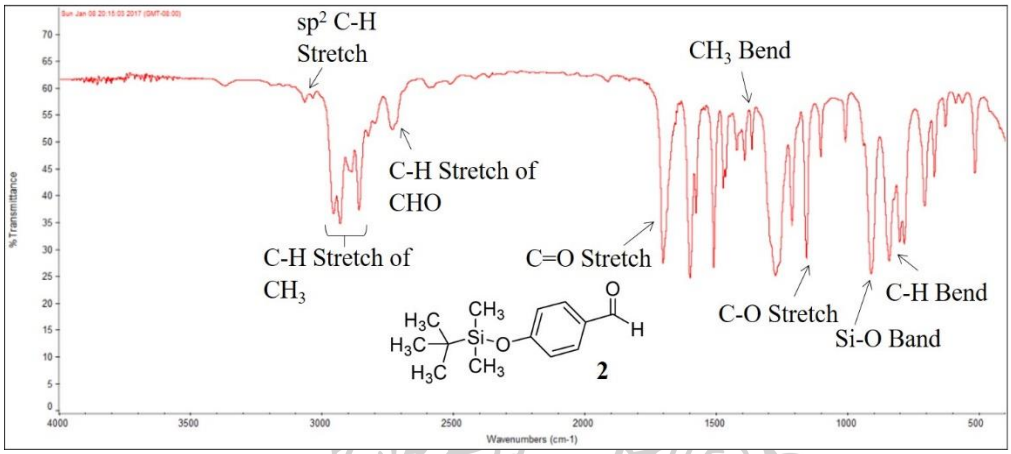
APPENDIX

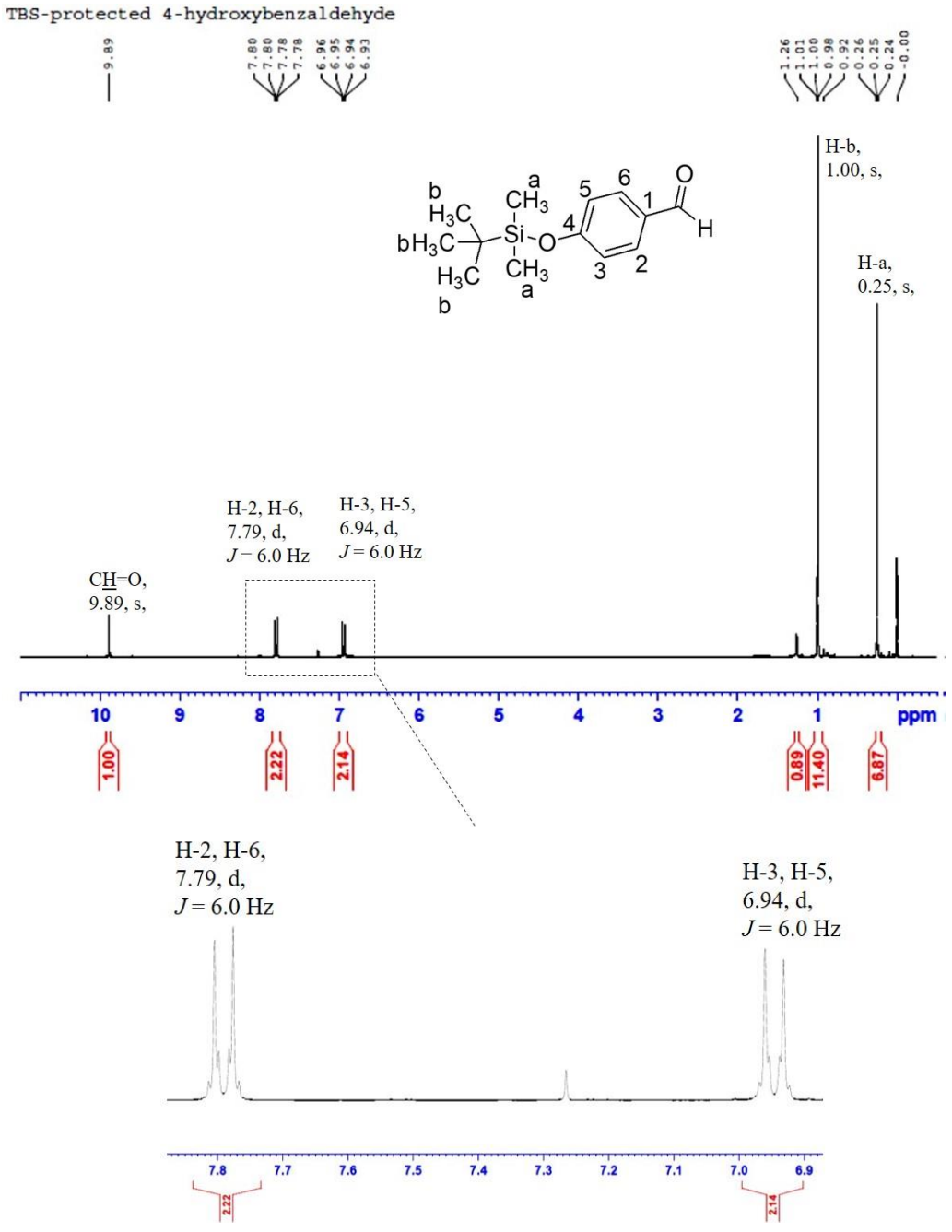
4-(*tert*-Butyldimethylsilyloxy)benzaldehye (2)



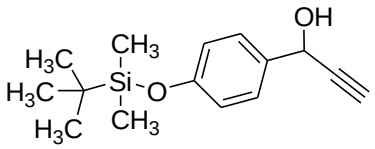
IR spectrum



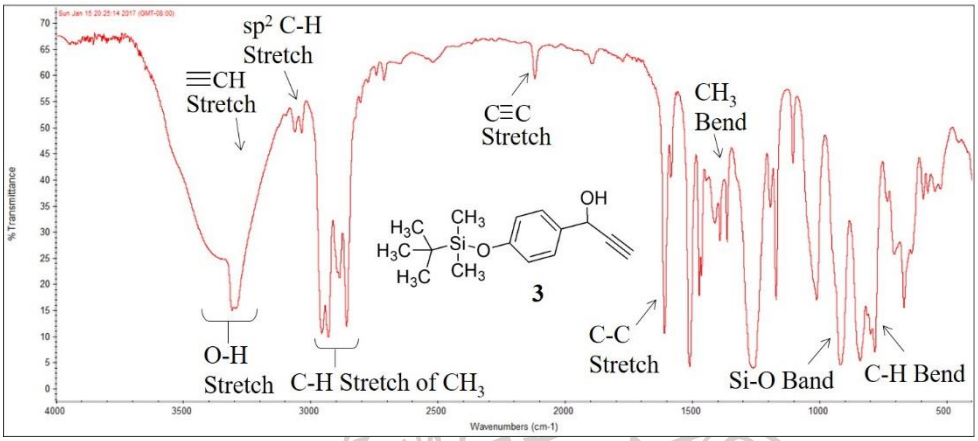
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 4-(*tert*-Butyldimethylsilyloxy) benzaldehye (2)



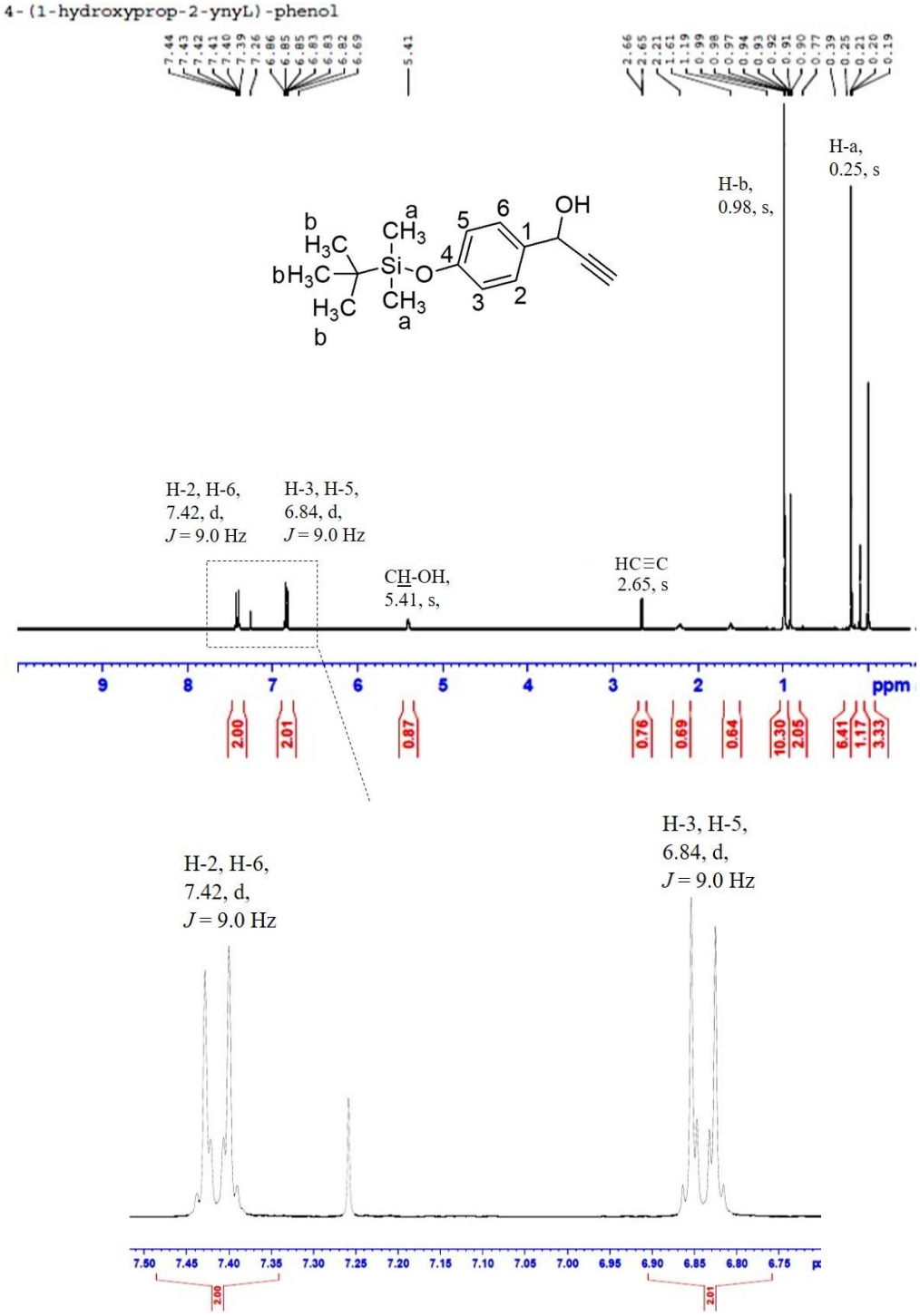
4-(*tert*-Butyldimethylsilyl-1-hydroxyprop-2-ynyl)phenol (3)



IR spectrum

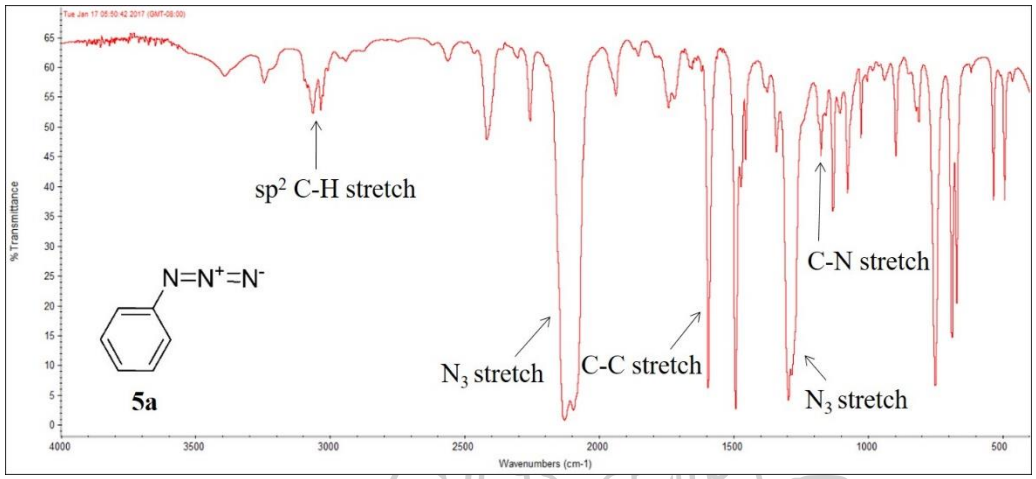


^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 4-(*tert*-Butyldimethylsilyl-1-hydroxy prop-2-ynyl)phenol (3)



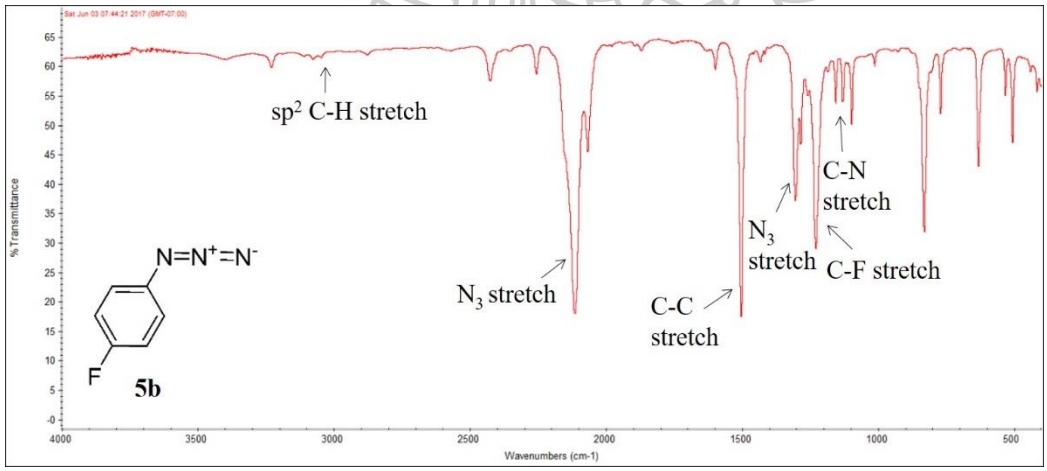
Azidobenzene 5a

IR spectrum



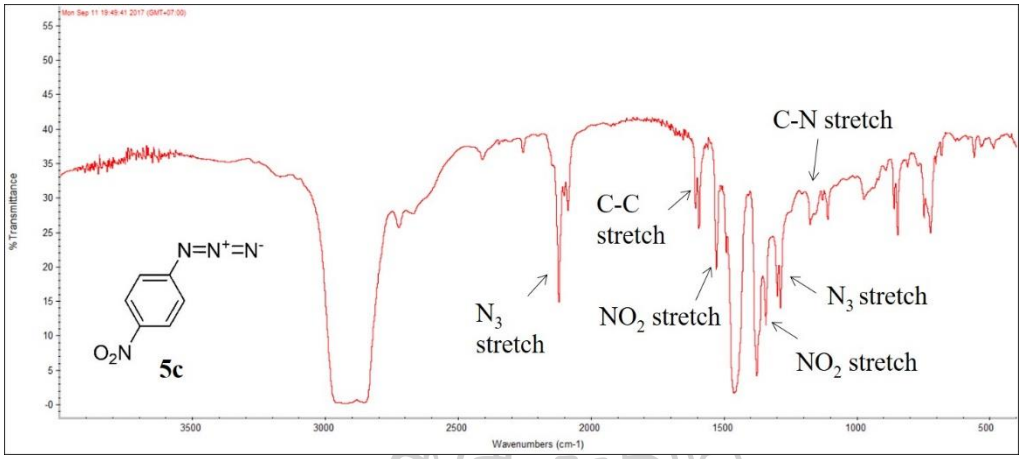
4-Fluorophenyl azide 5b

IR spectrum



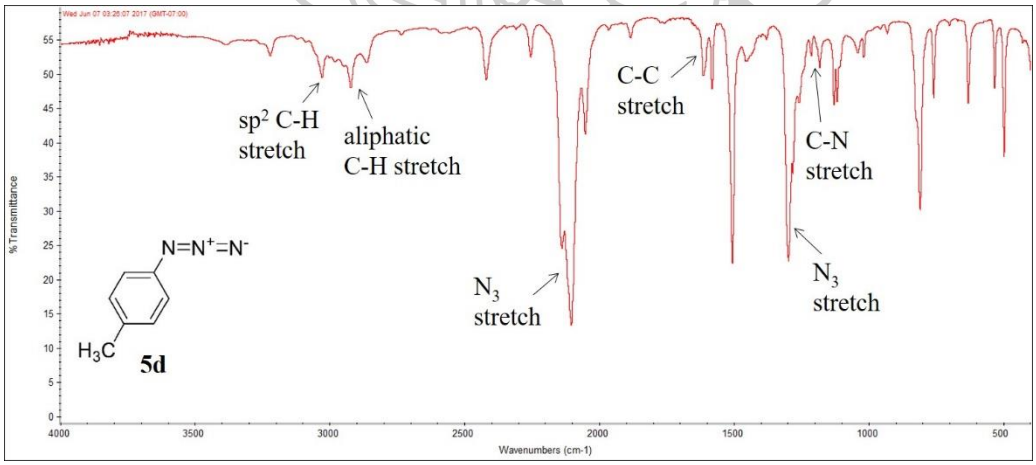
4-nitrophenyl azide 5c

IR spectrum



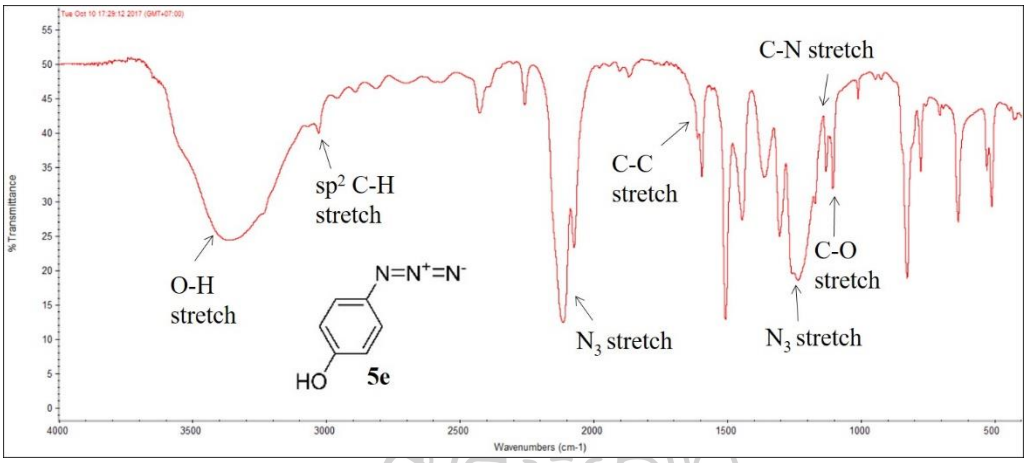
4-methylphenyl azide 5d

IR spectrum



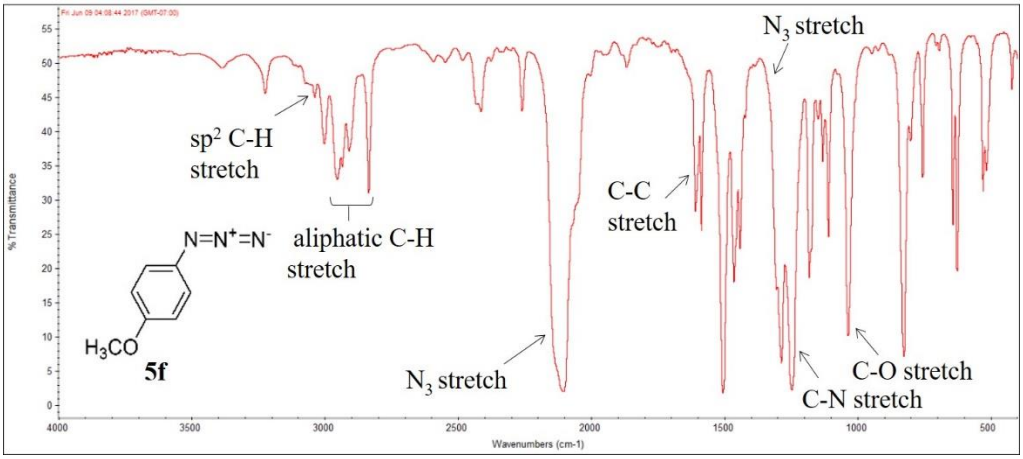
4-hydroxyphenyl azide 5e

IR spectrum



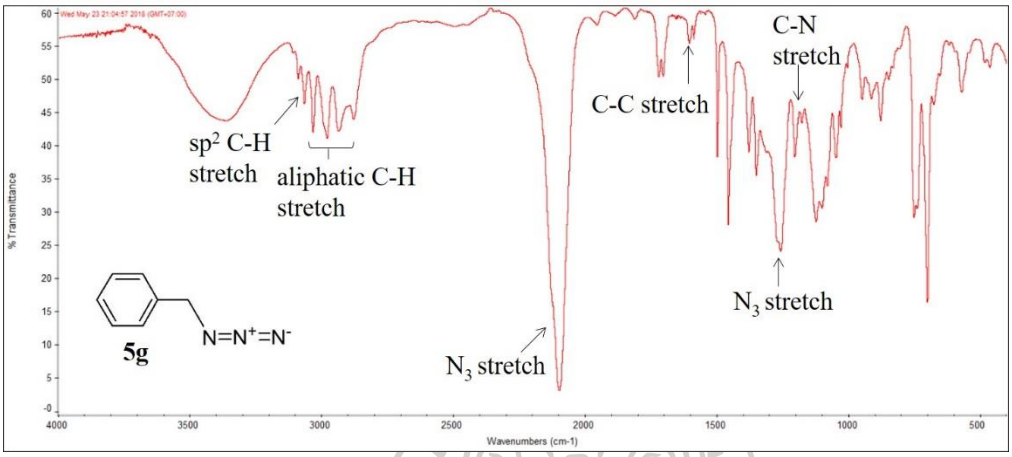
4-methoxyphenyl azide 5f

IR spectrum



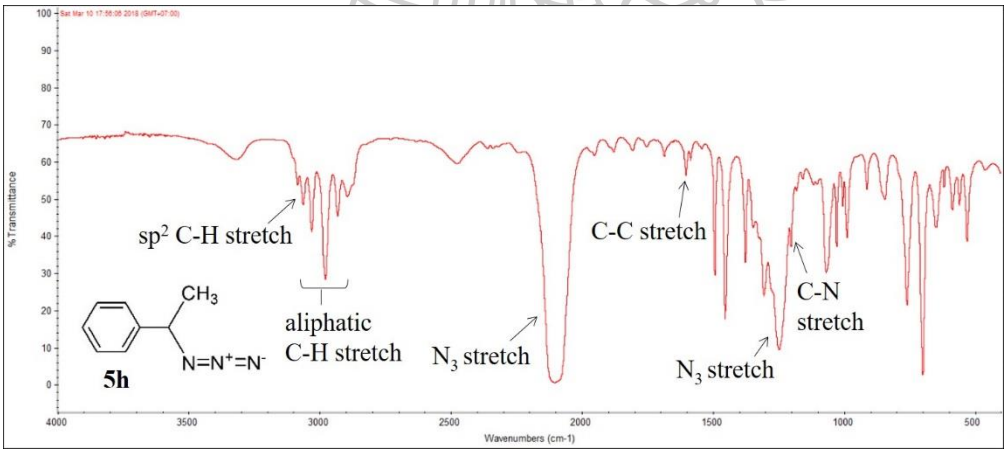
Benzyl azide 5g

IR spectrum



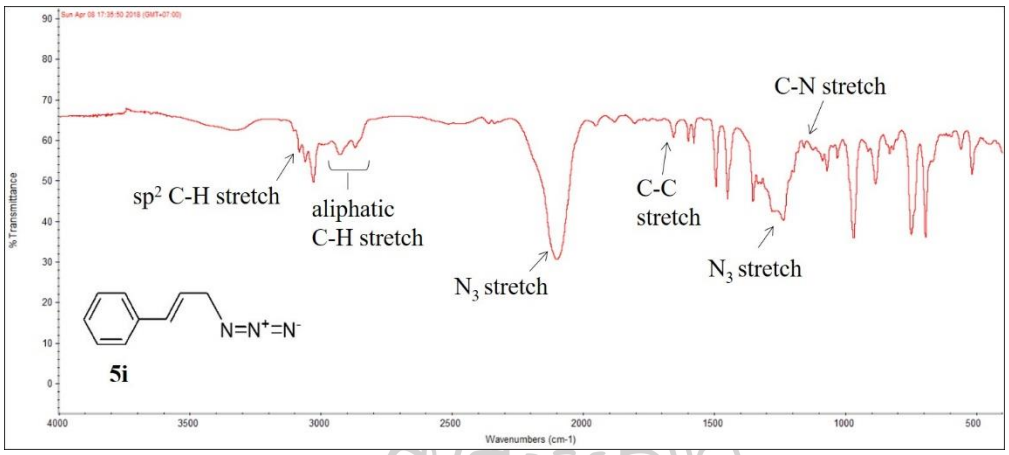
(1-Azidoethyl)benzene 5h

IR spectrum



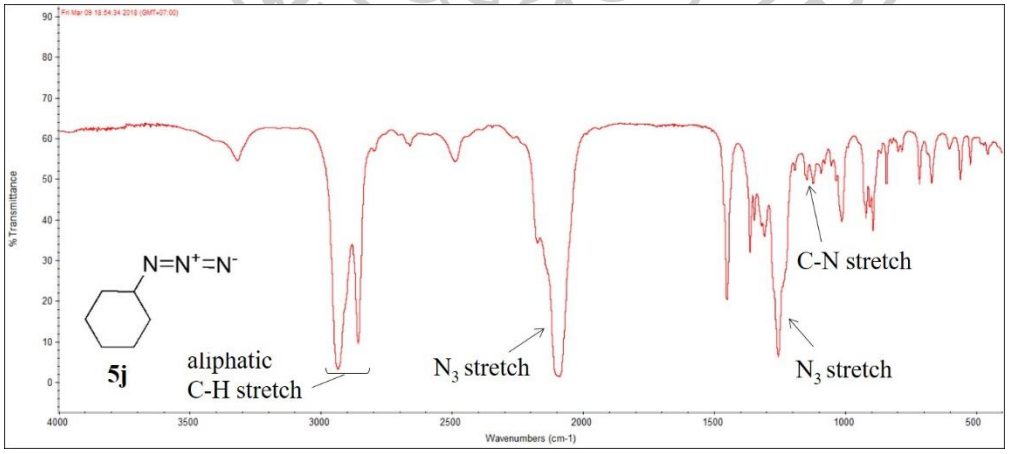
Cinnamyl azide 5i

IR spectrum



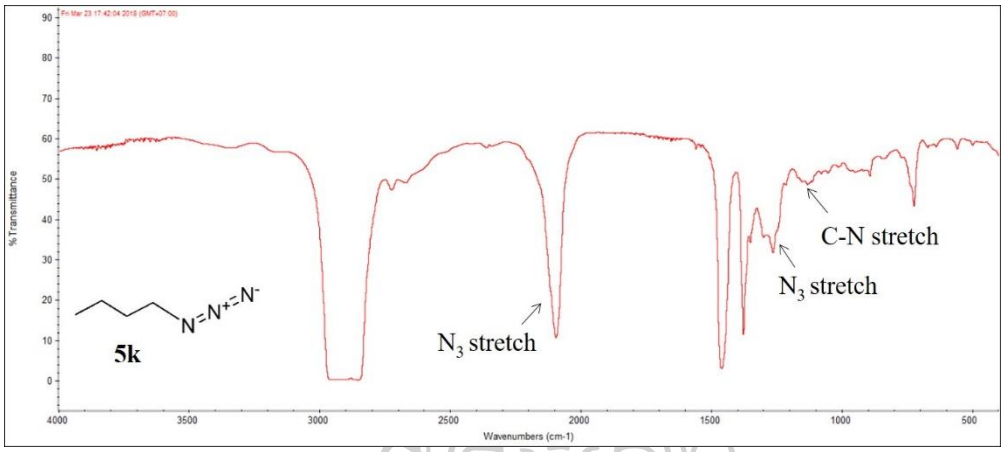
Cyclohexyl azide 5j

IR spectrum



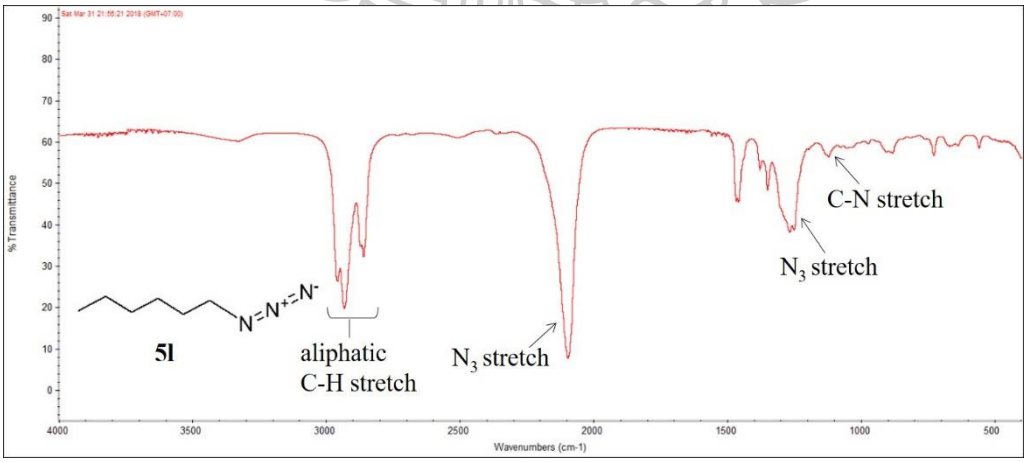
Butyl azide 5k

IR spectrum



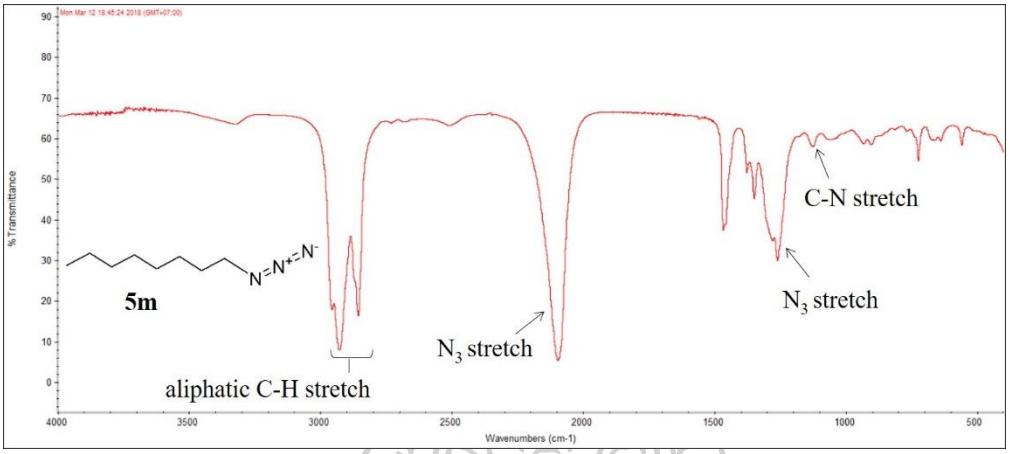
Hexyl azide 5l

IR spectrum



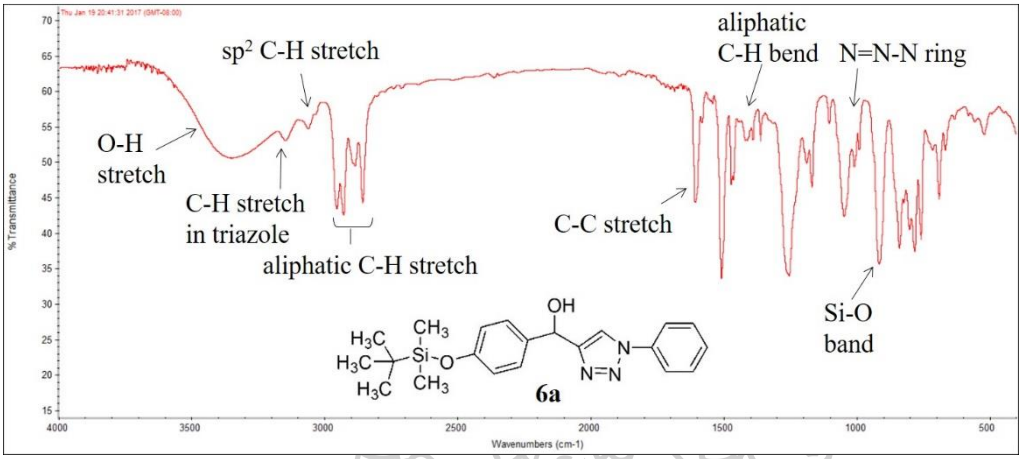
Octyl azide 5m

IR spectrum



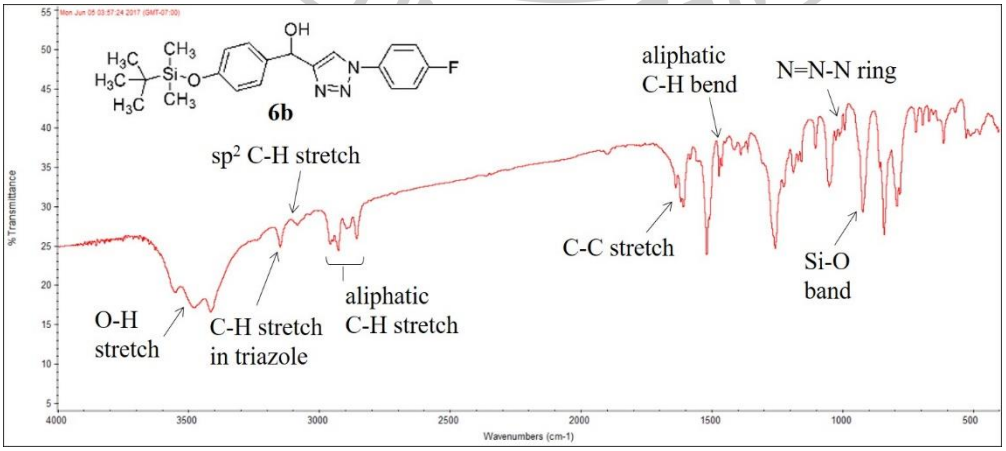
(1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl)methanol (6a)

IR spectrum



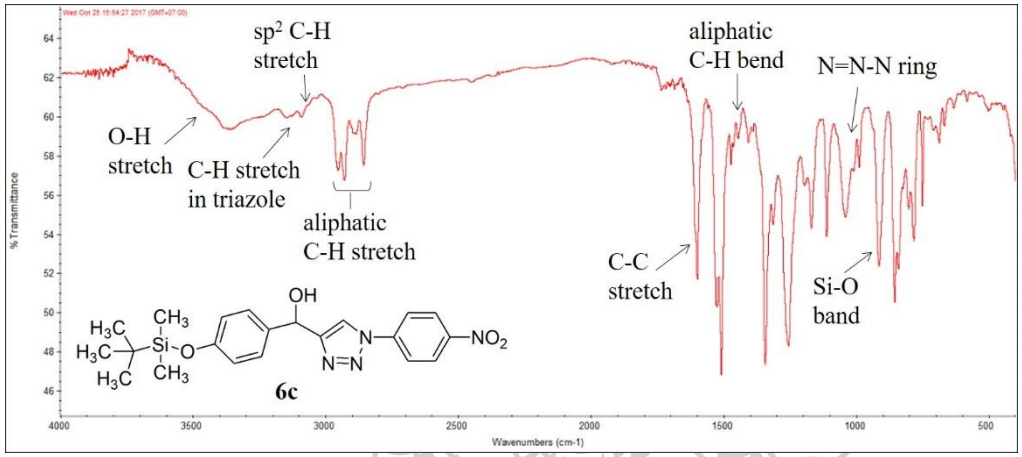
(1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6b)

IR spectrum



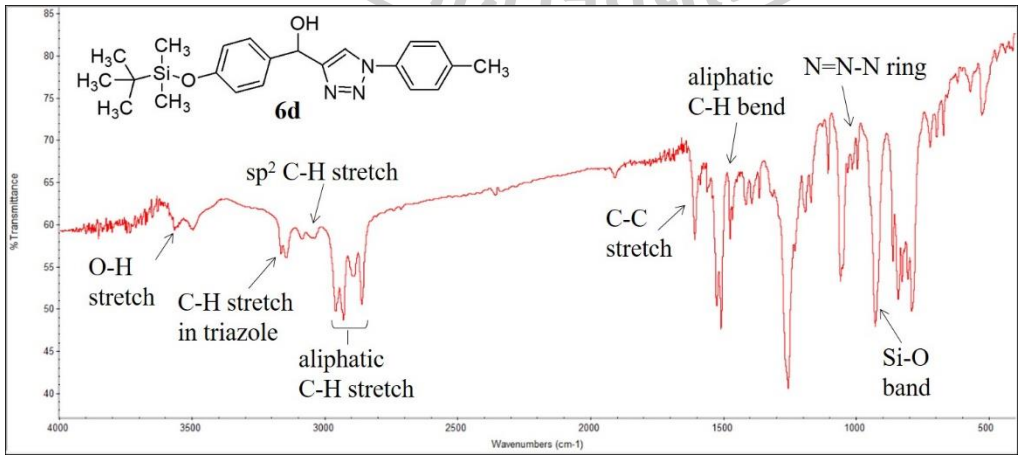
(1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6c)

IR spectrum



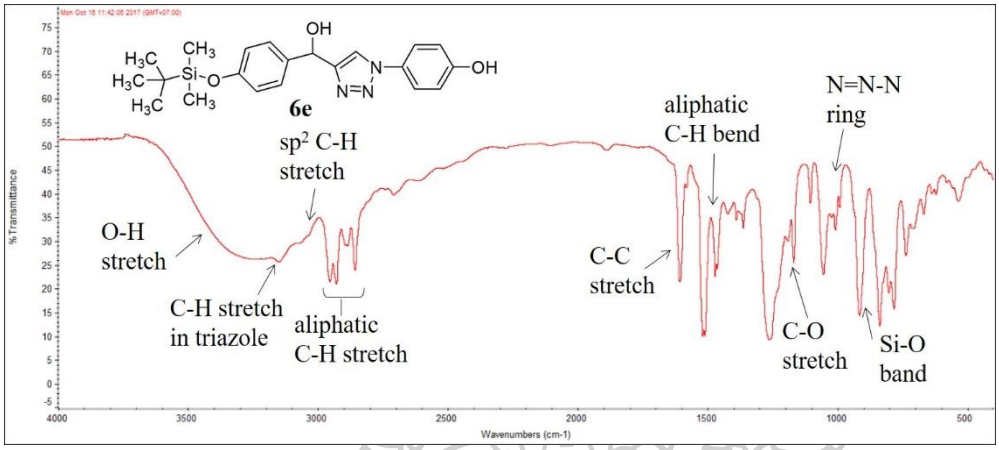
(1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6d)

IR spectrum



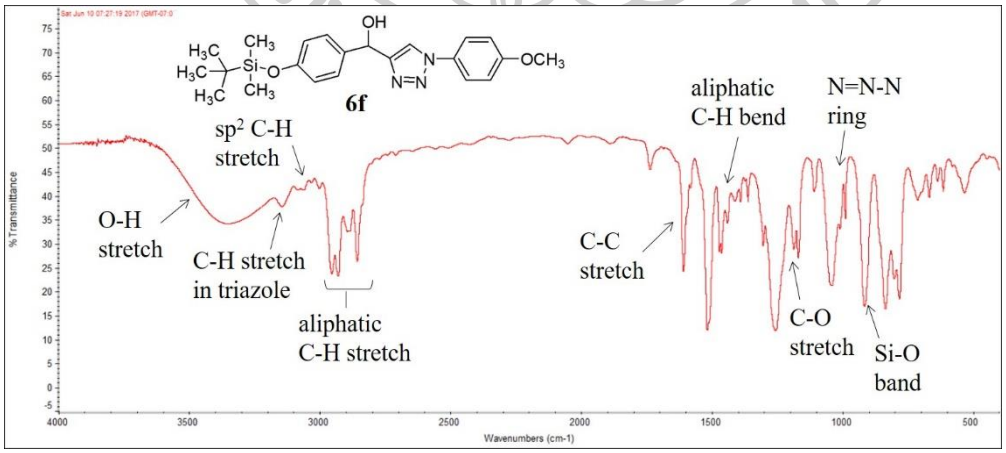
(1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6e)

IR spectrum



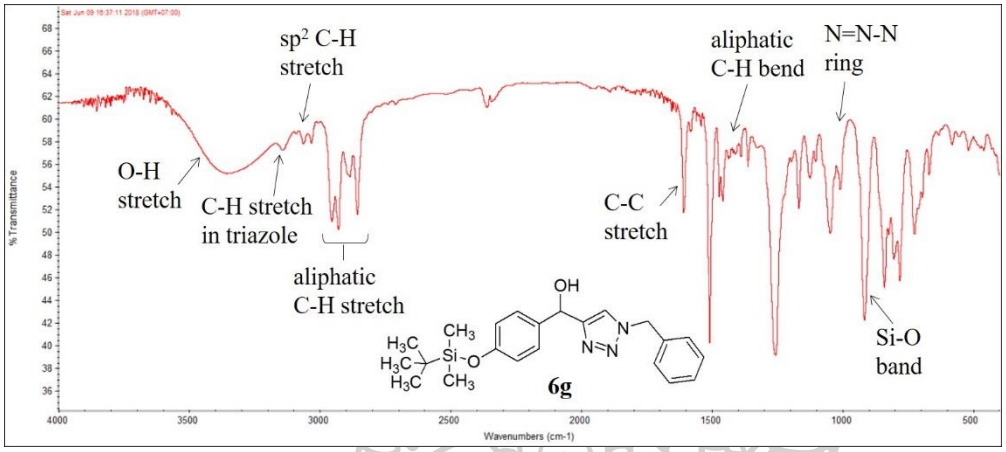
(1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6f)

IR spectrum



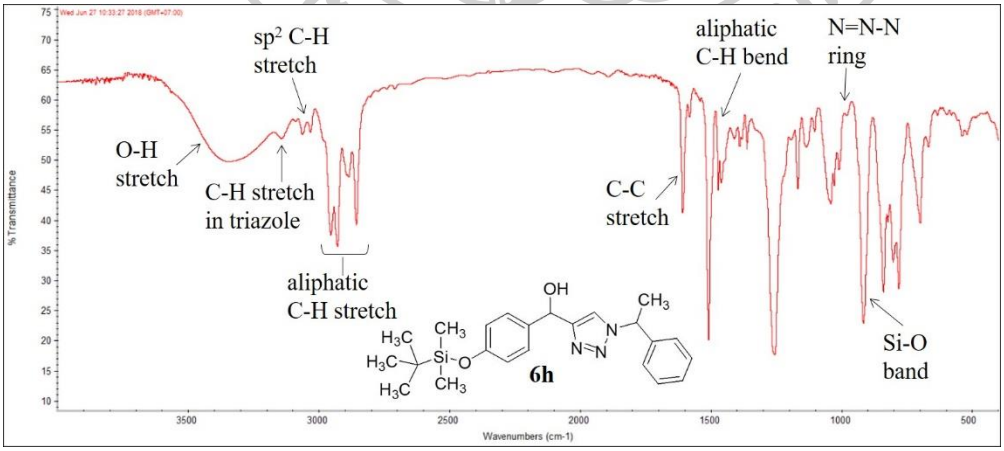
(1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl)methanol (6g)

IR spectrum



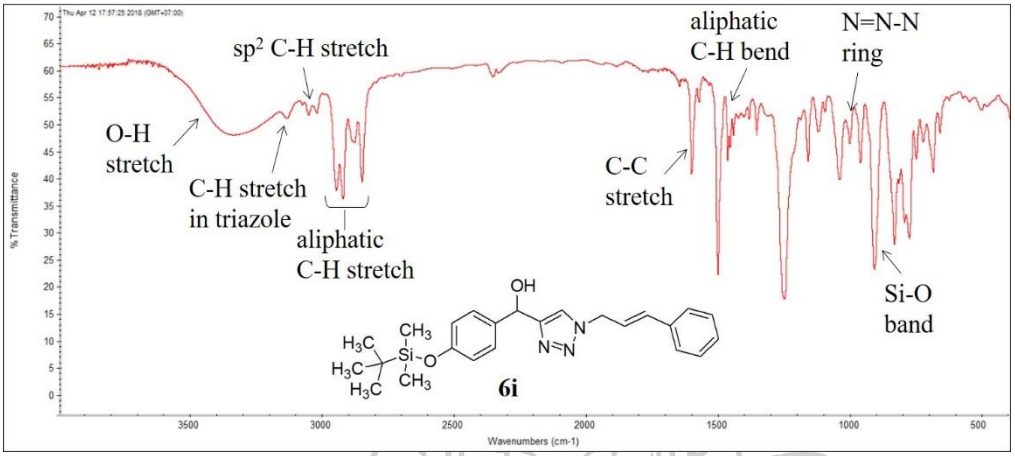
(1-(Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6h)

IR spectrum



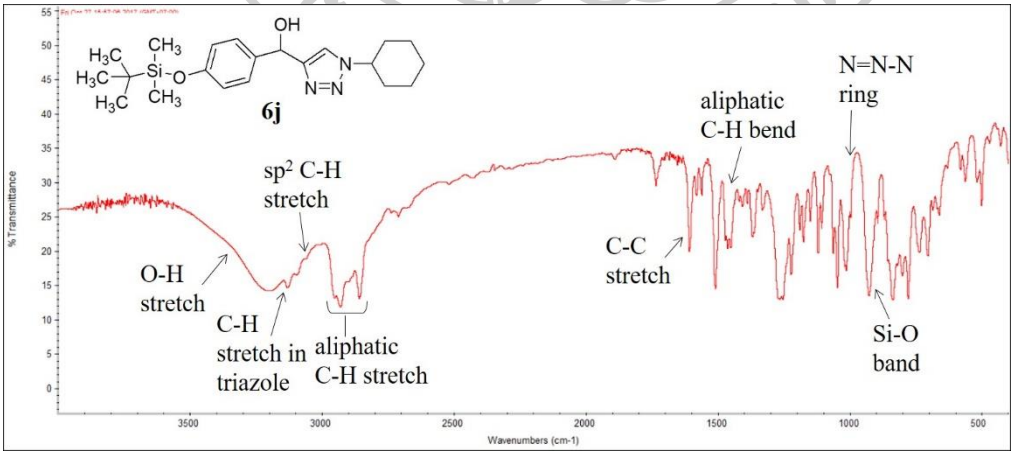
(1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6i)

IR spectrum



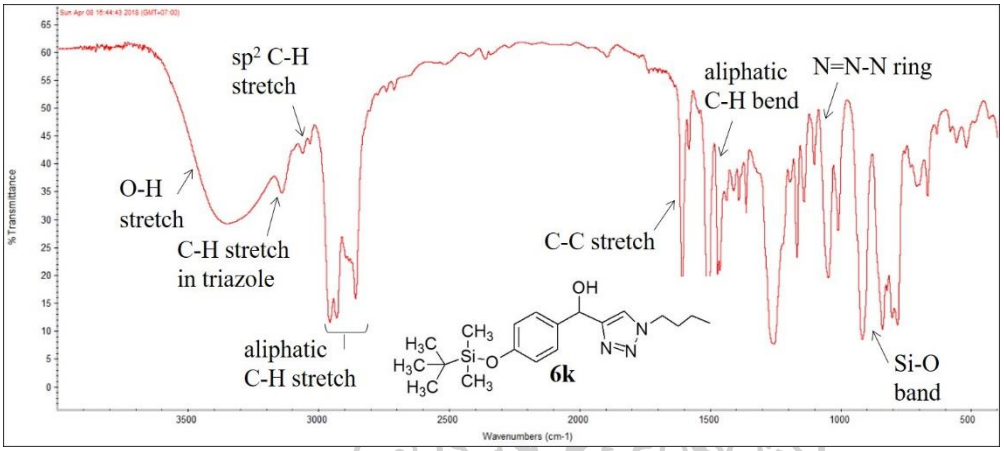
(1-(Cyclohexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl) methanol (6j)

IR spectrum



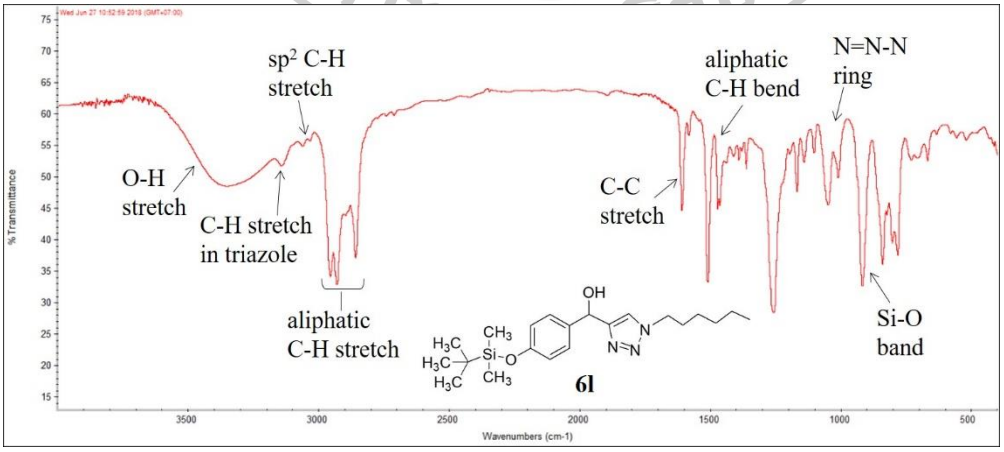
(1-(Butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl)methanol (6k)

IR spectrum



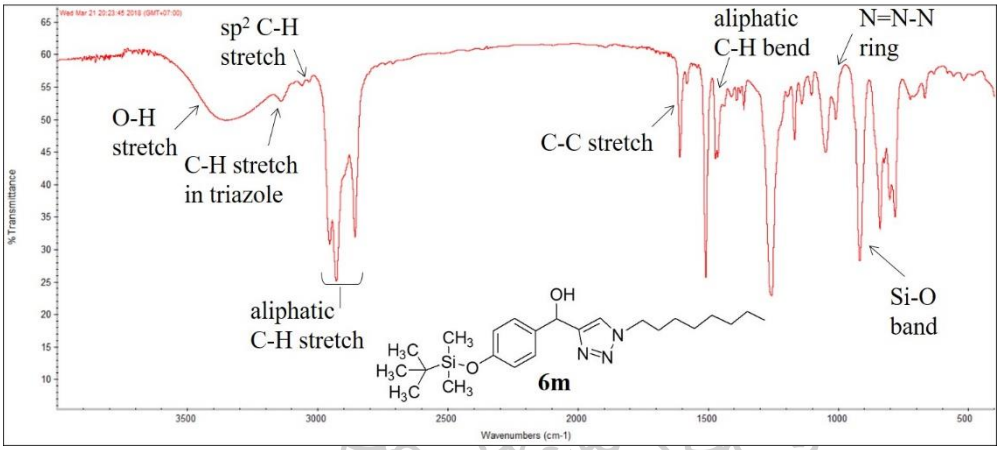
(1-(Hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl)methanol (6l)

IR spectrum

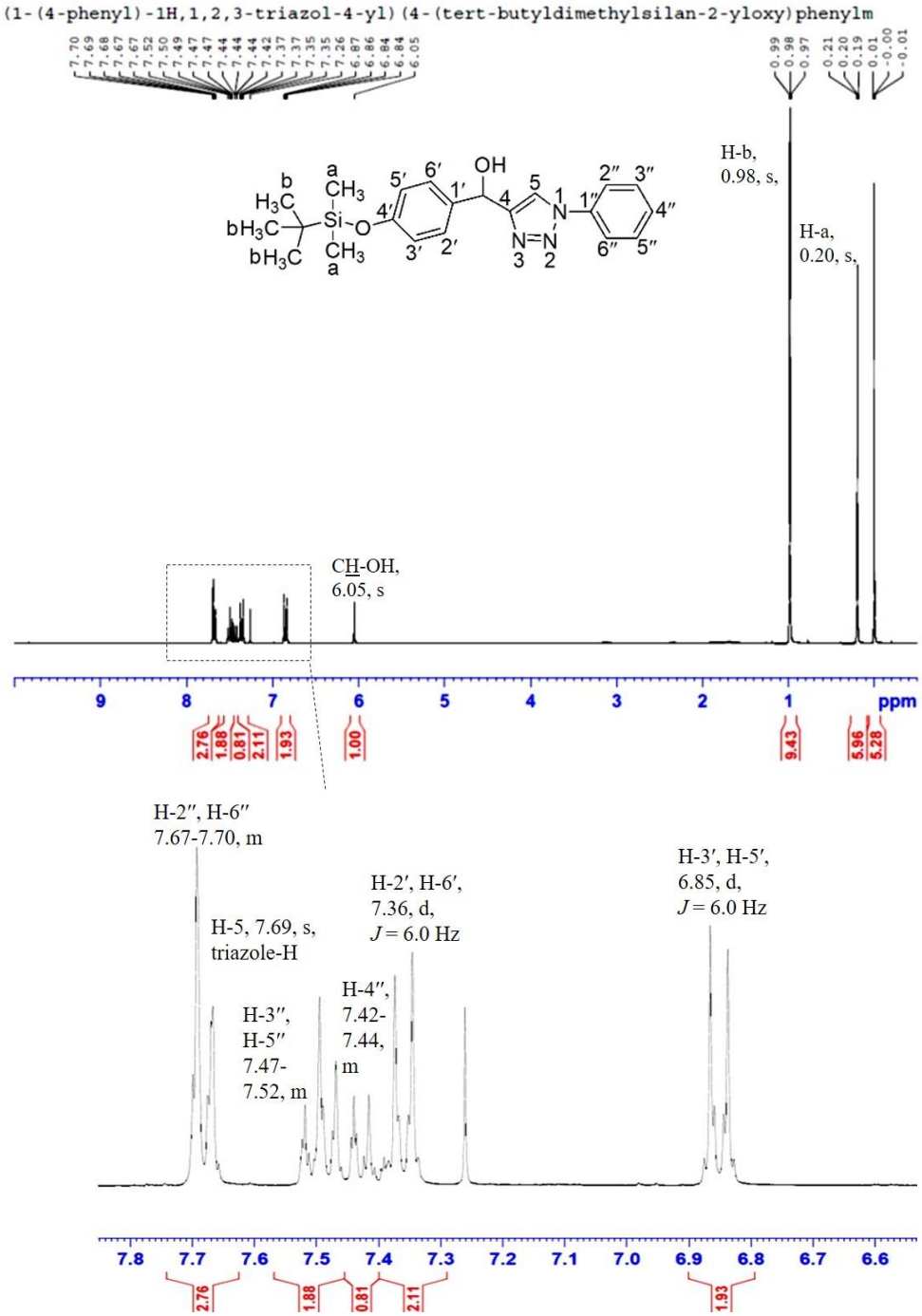


(1-(Octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethylsilyloxy)phenyl)methanol (6m)

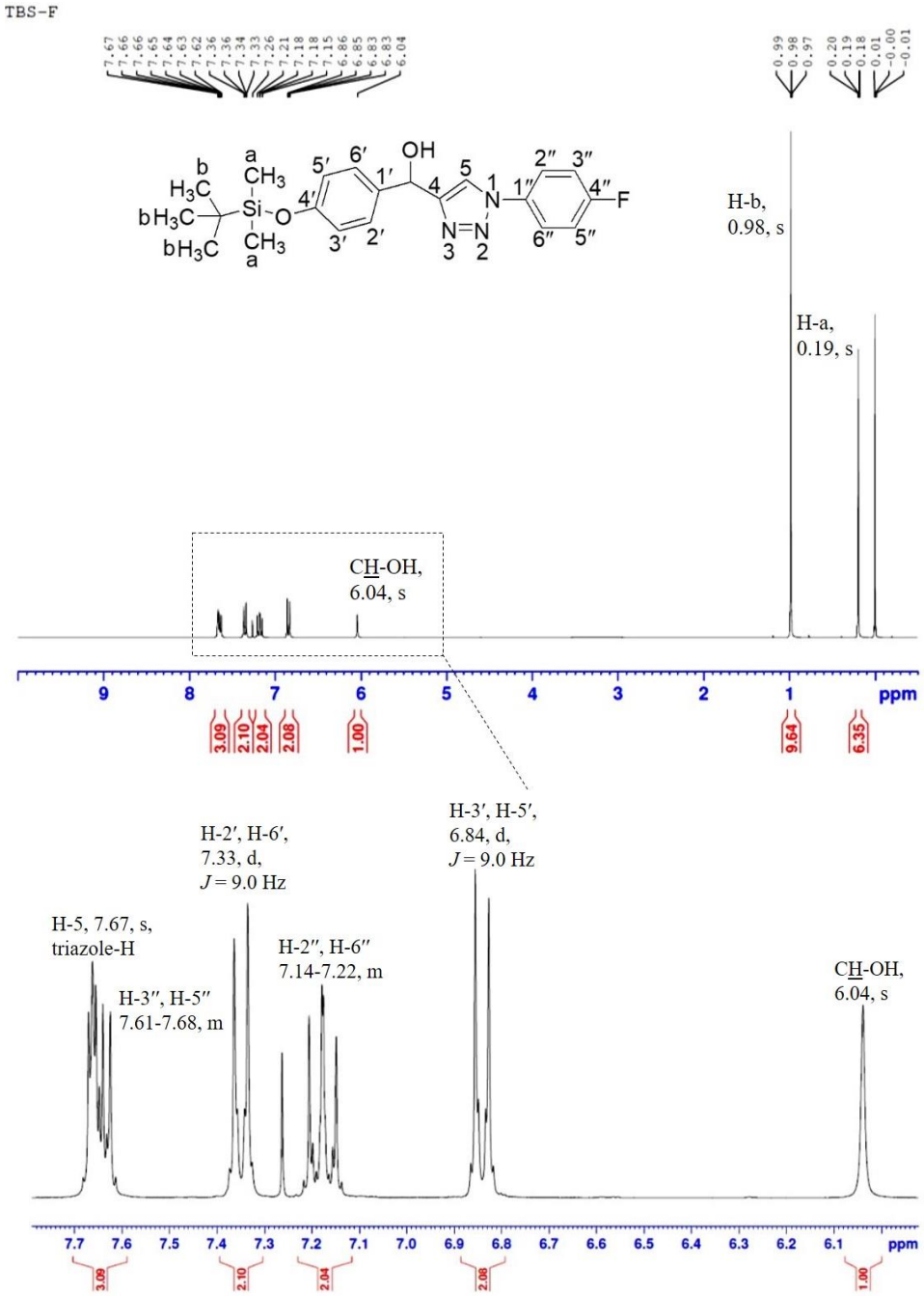
IR spectrum



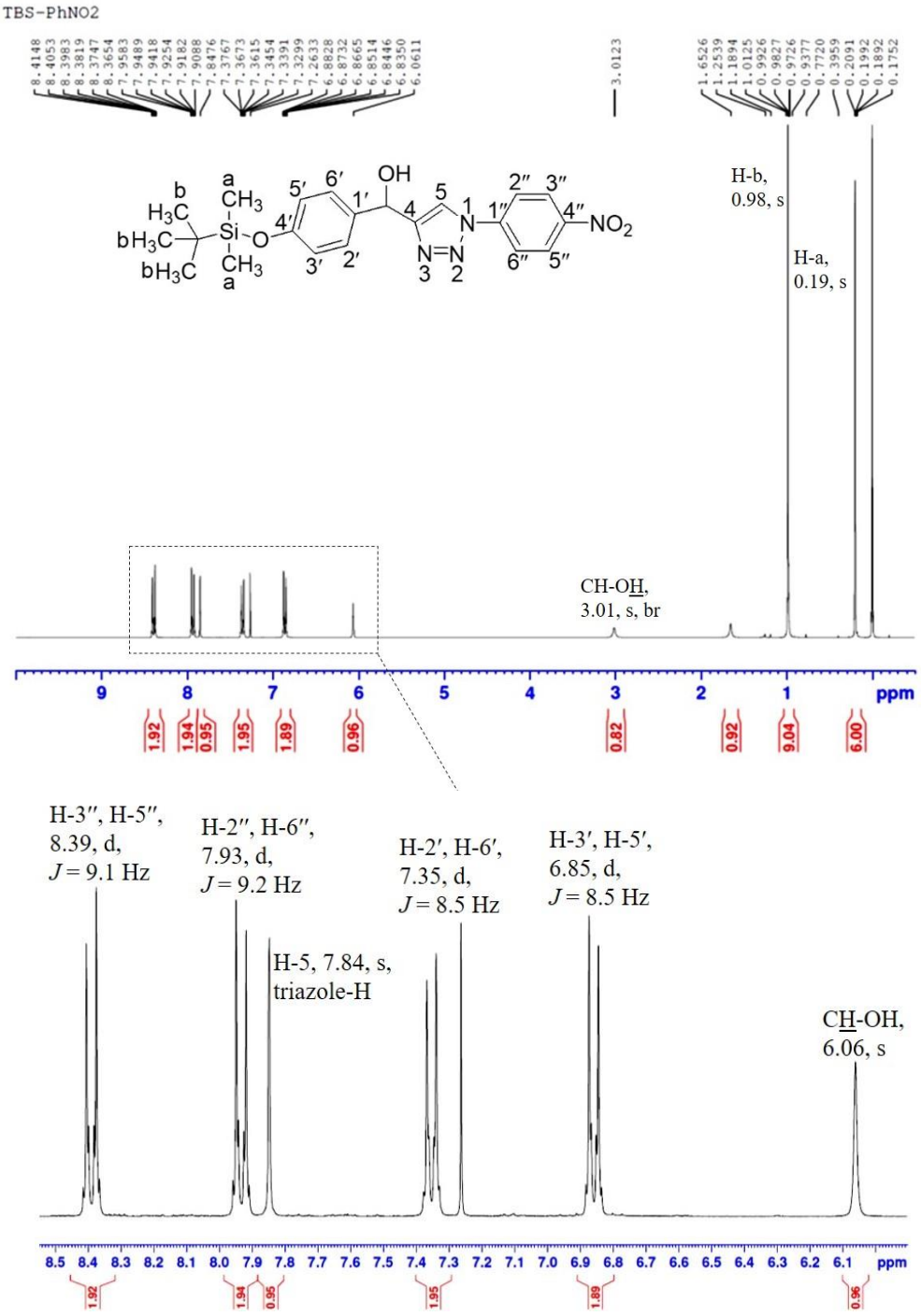
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol (6a)



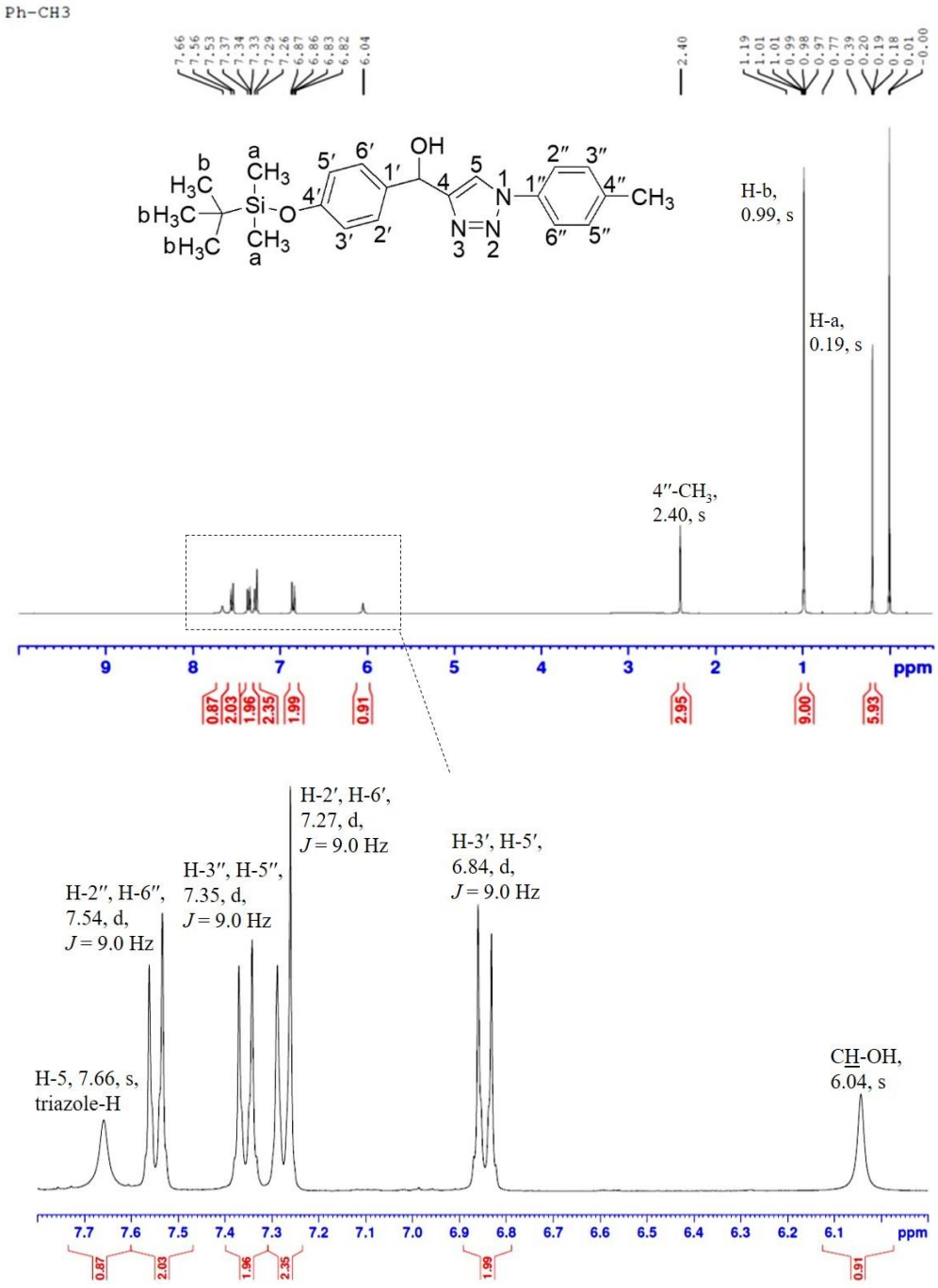
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6b)



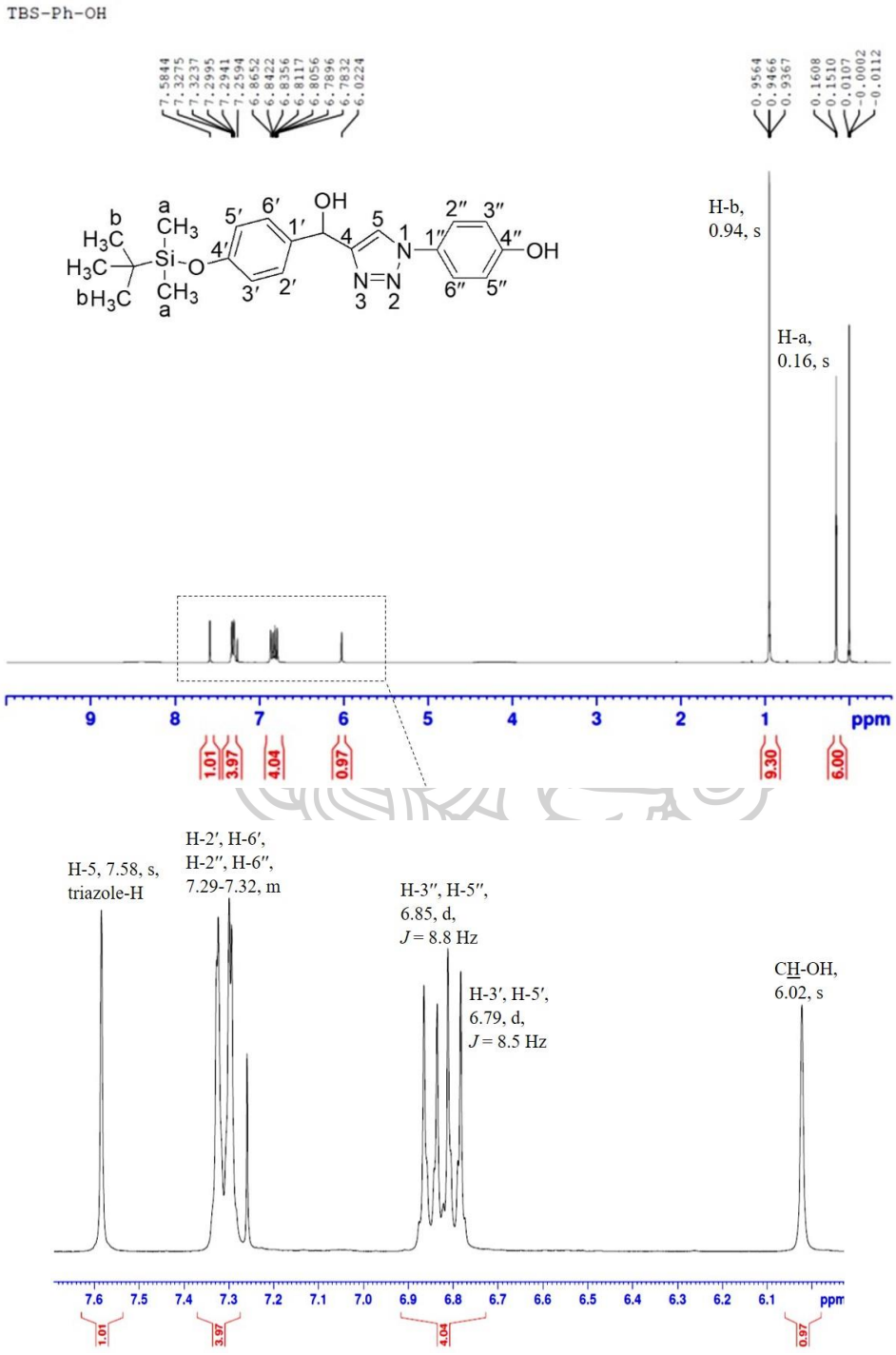
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6c)



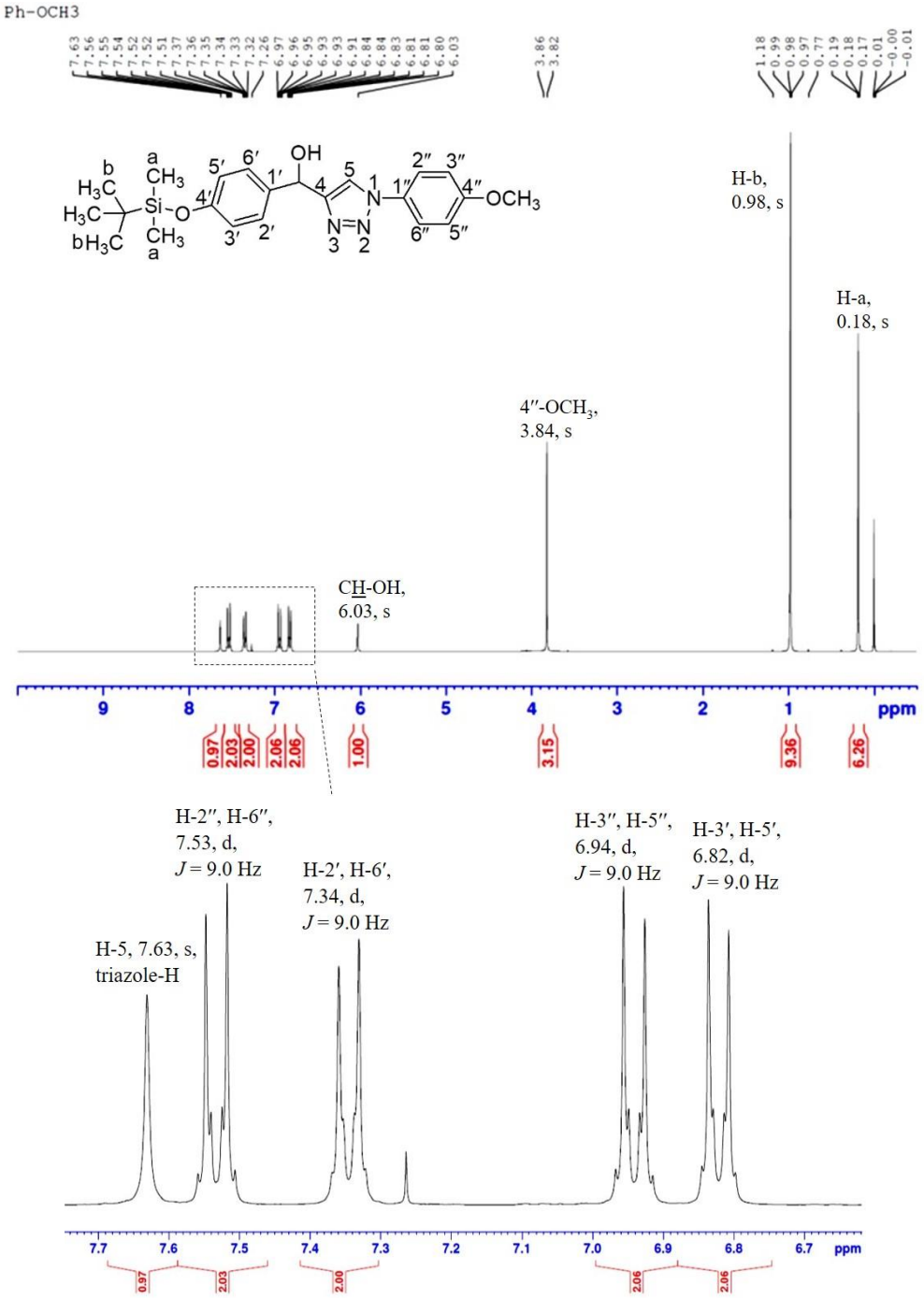
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6d)



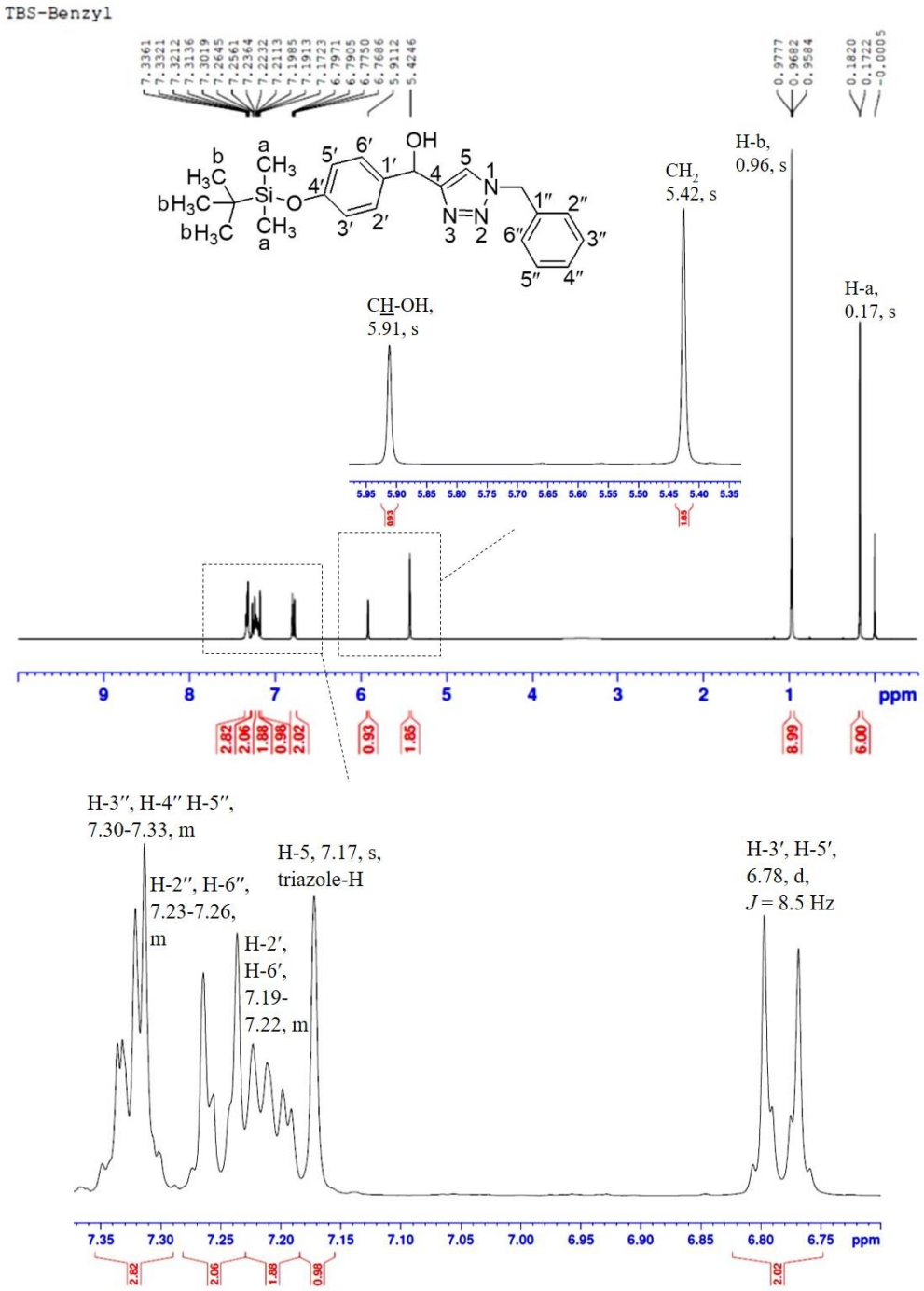
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6e)



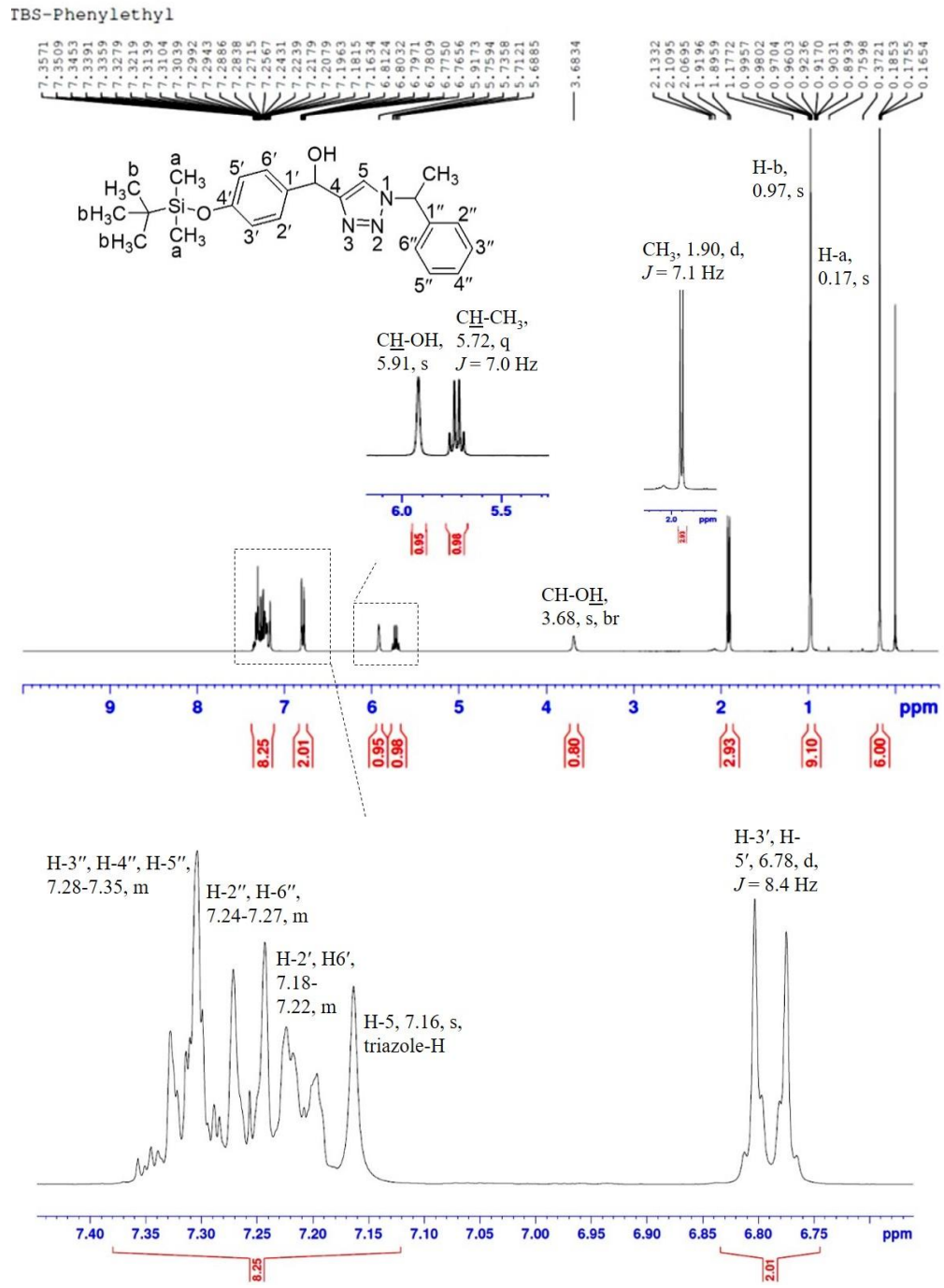
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6f)



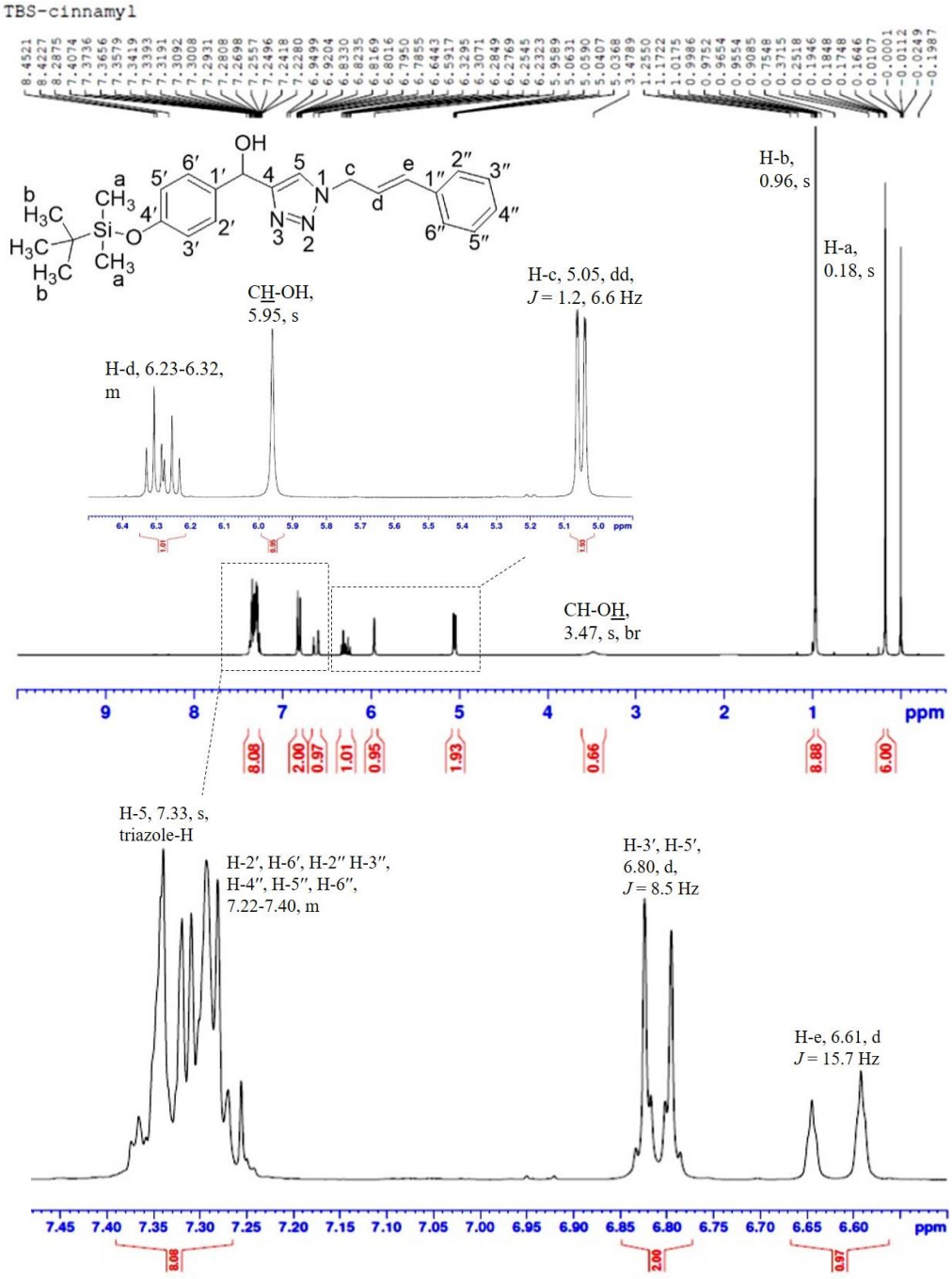
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6g)



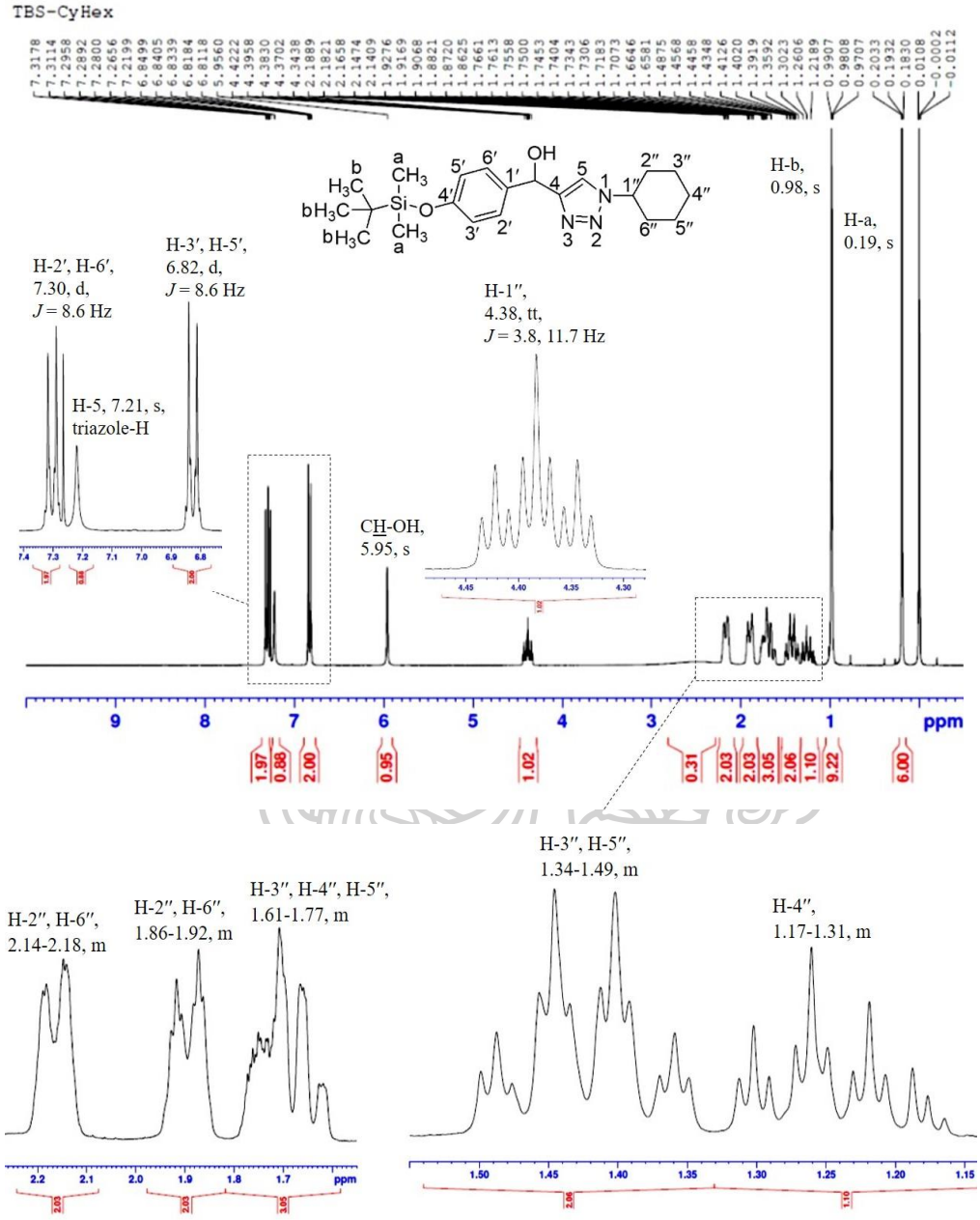
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6h)



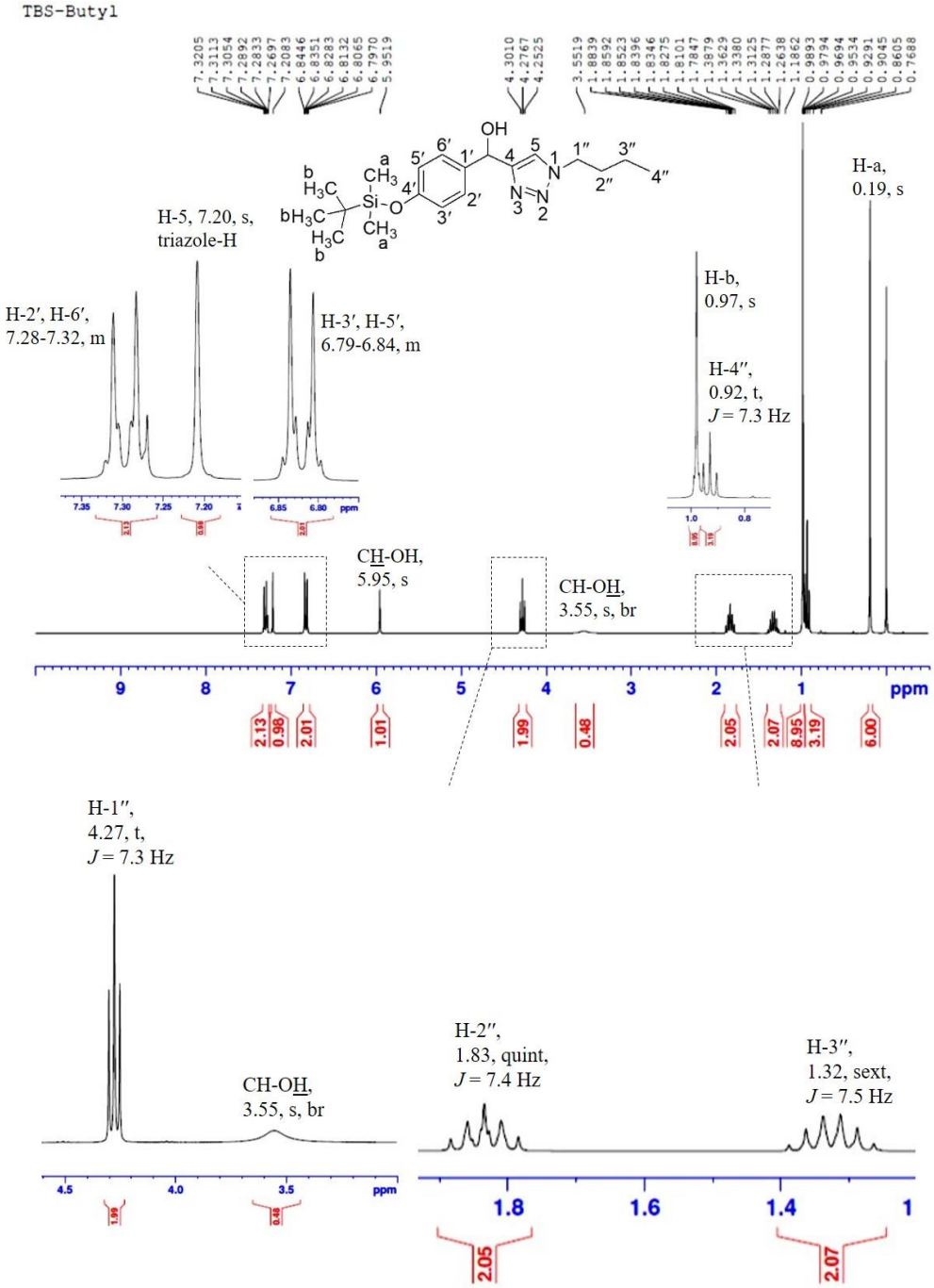
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(Cinnamyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6i)



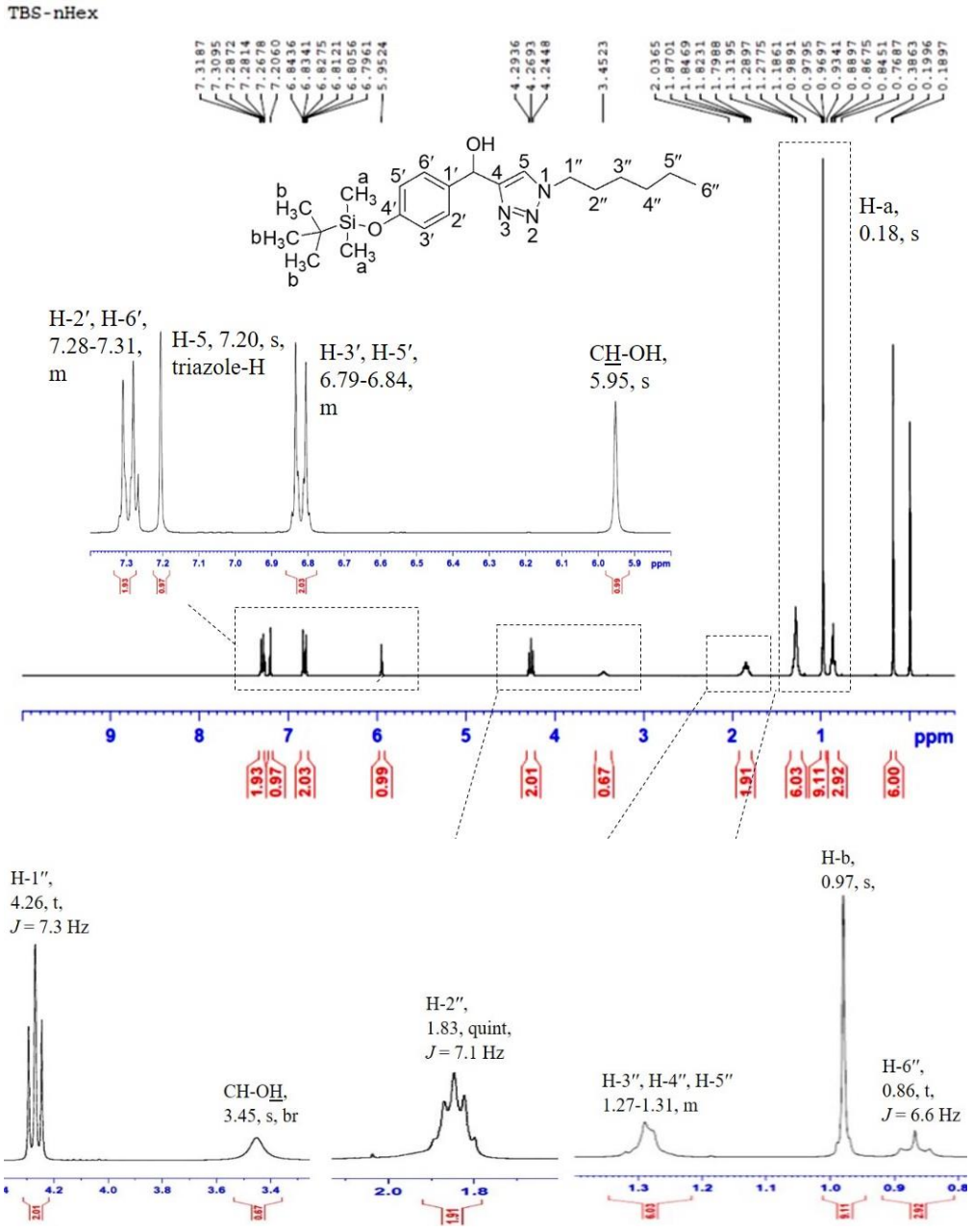
^{1}H NMR (300 MHz, $CDCl_3$) of 1-(Cyclohexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyl dimethylsilyloxy)phenyl)methanol (6j)



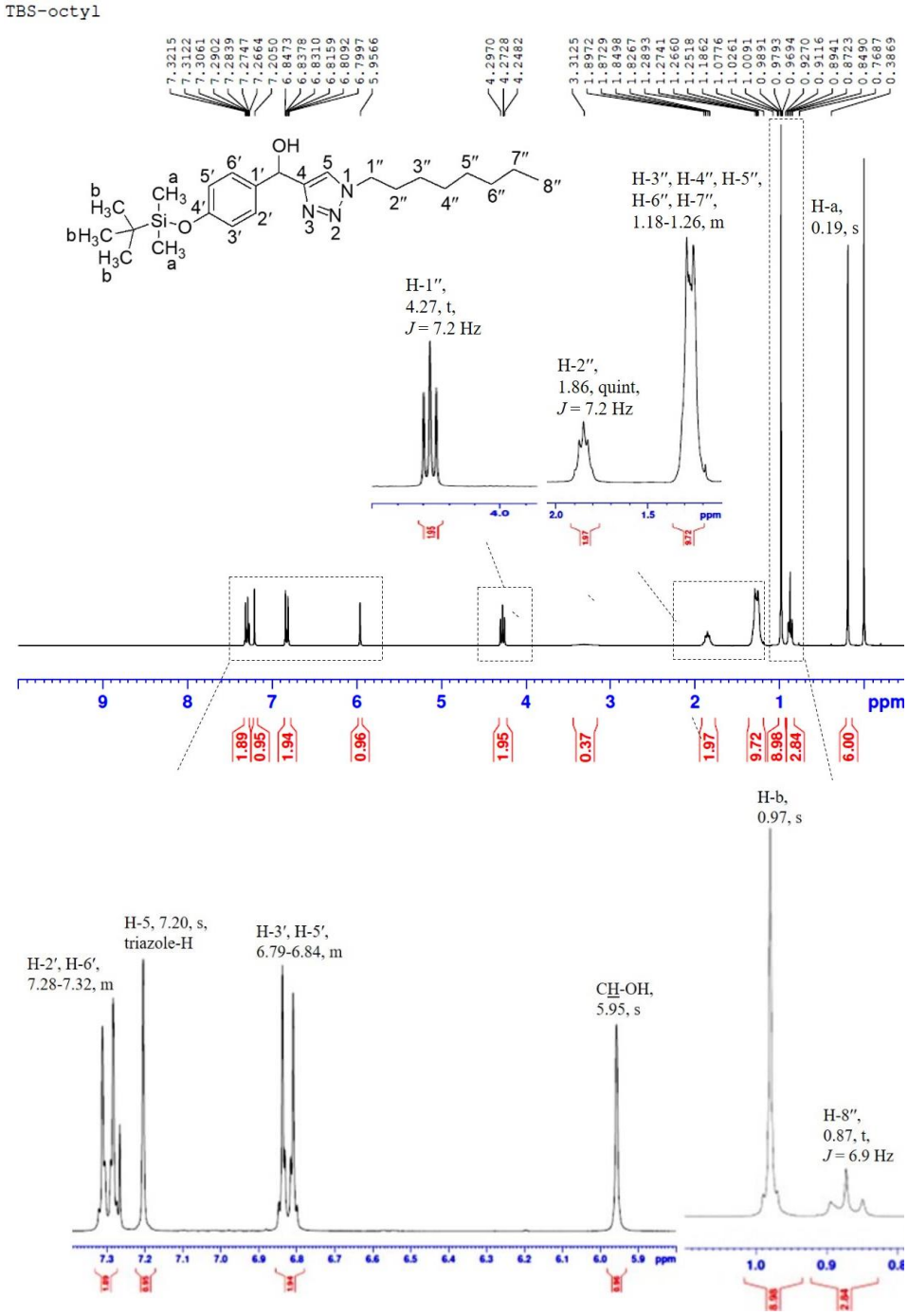
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(Butyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol (6k)



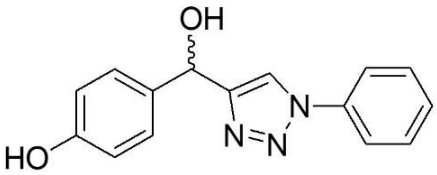
H NMR (300 MHz, $CDCl_3$) of (1-(Hexyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol (6l)



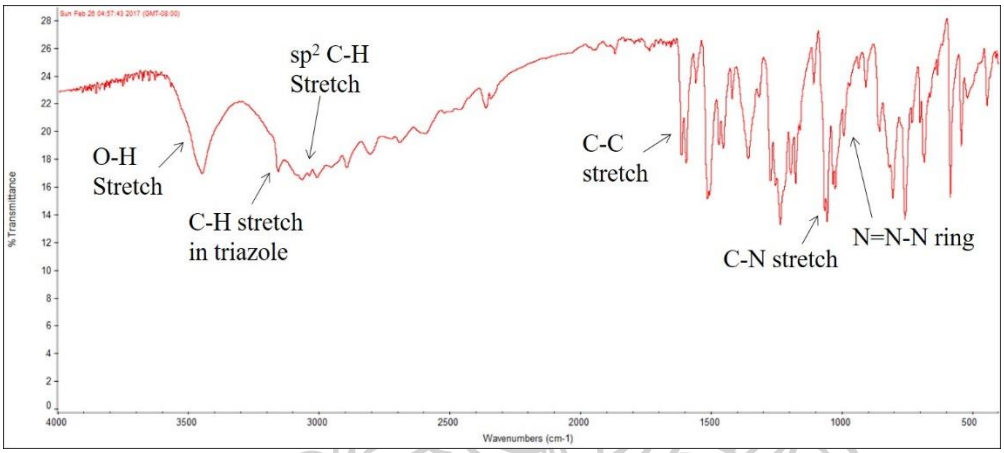
^{1}H NMR (300 MHz, $CDCl_3$) of (1-(Octyl)-1*H*-1,2,3-triazol-4-yl)(4-(*tert*-butyldimethyl silyloxy)phenyl)methanol (6m)



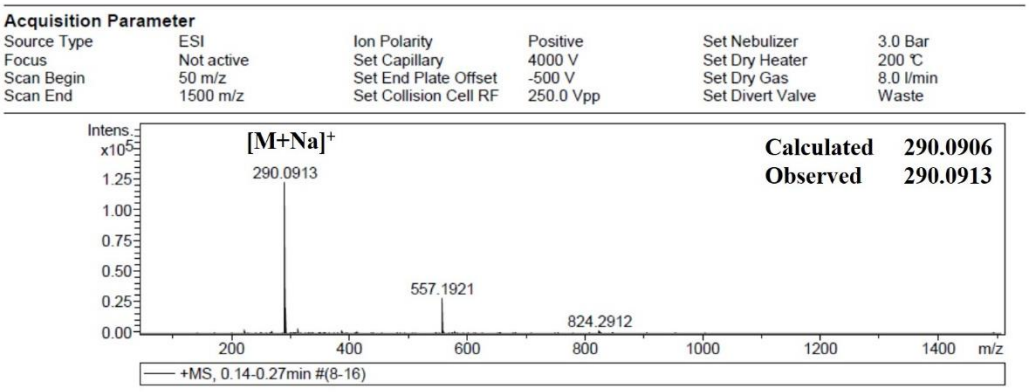
4-(Hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7a)



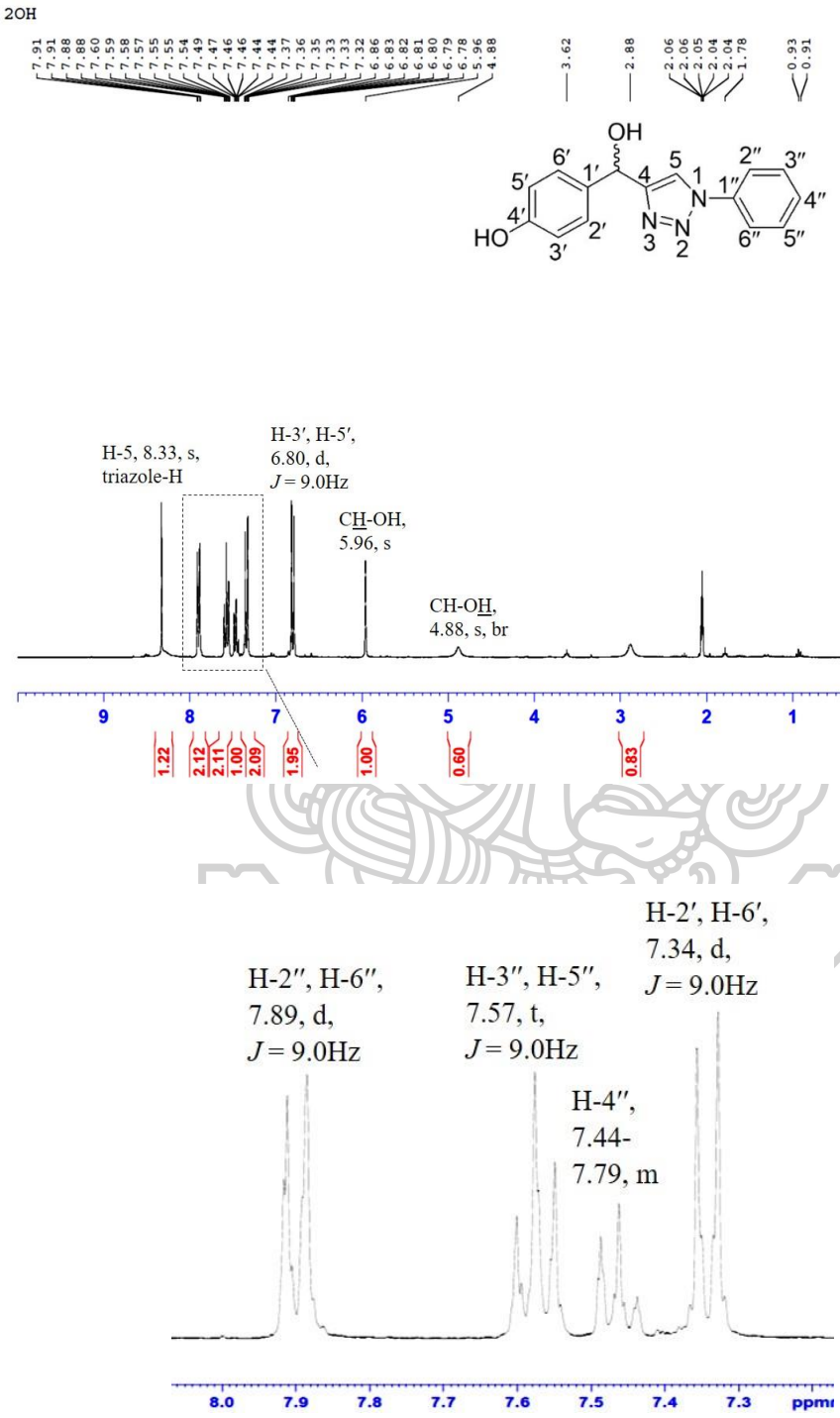
IR spectrum



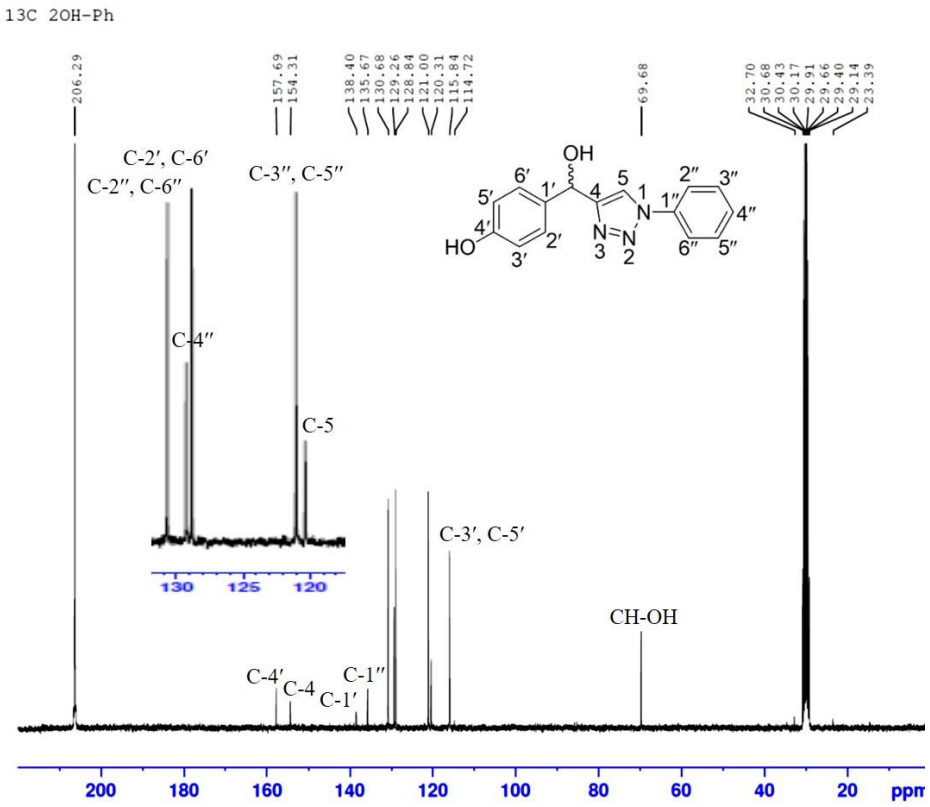
High resolution mass spectrum



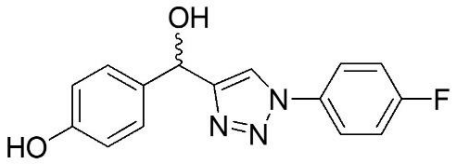
^{1}H NMR (300 MHz, acetone-d_6) of 4-(hydroxyl- (1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7a)



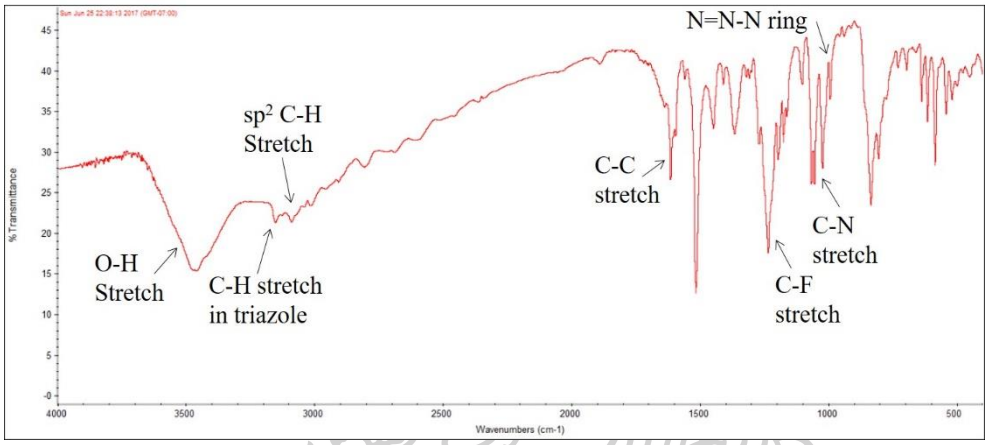
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7a)



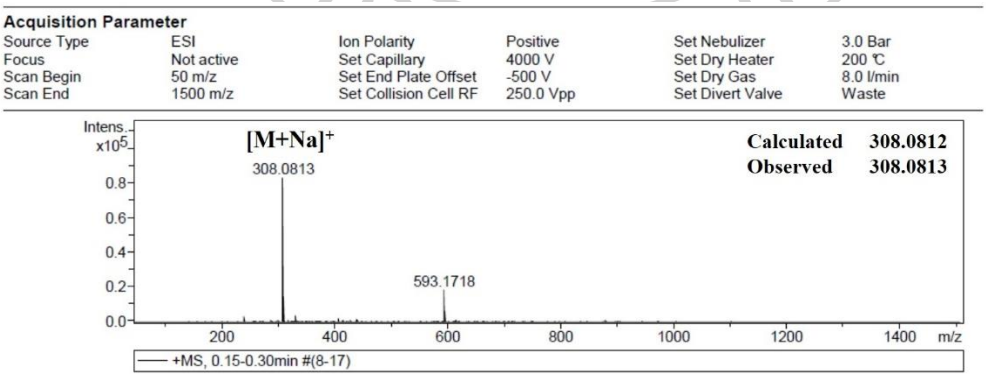
4-(Hydroxyl-(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7b)



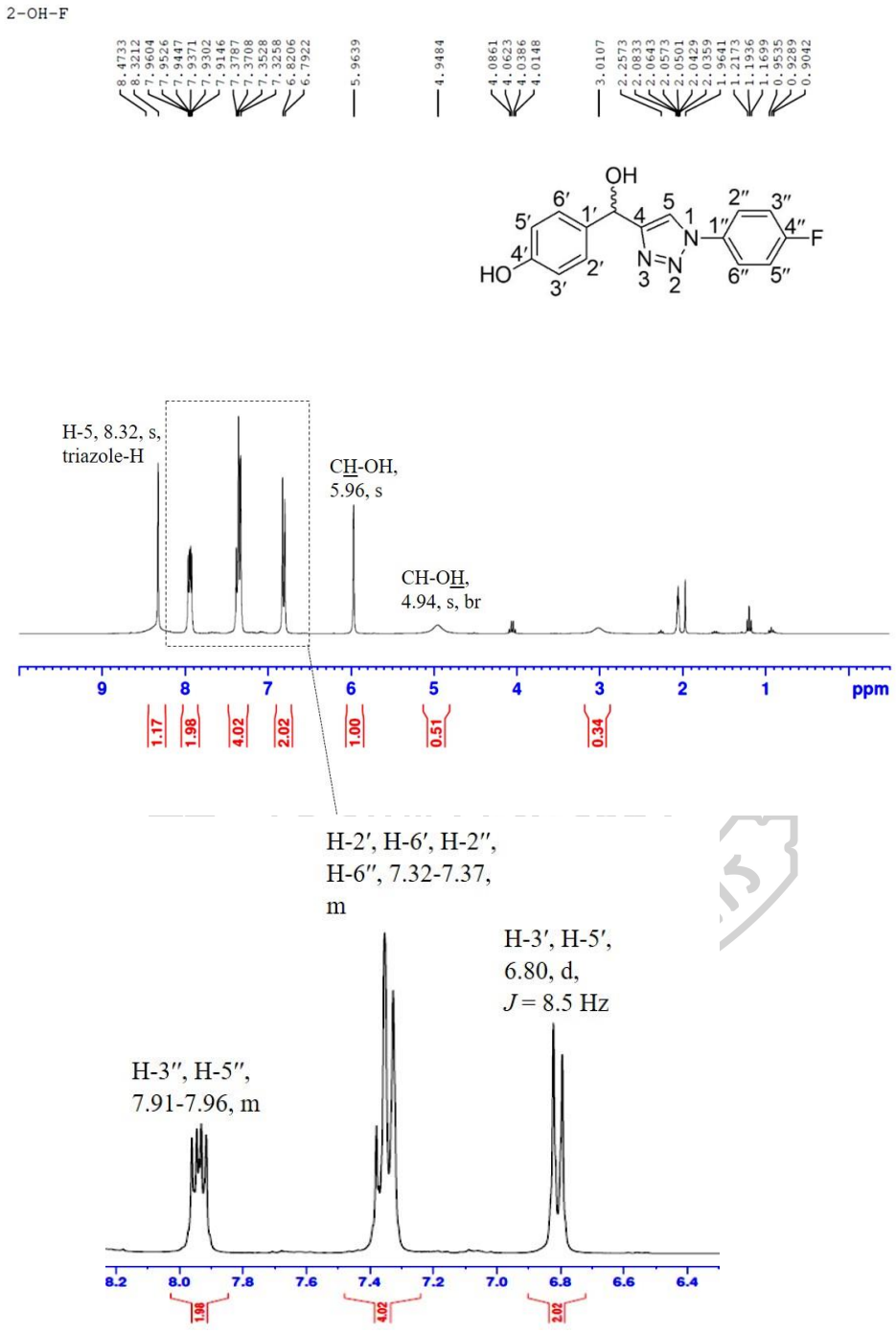
IR spectrum



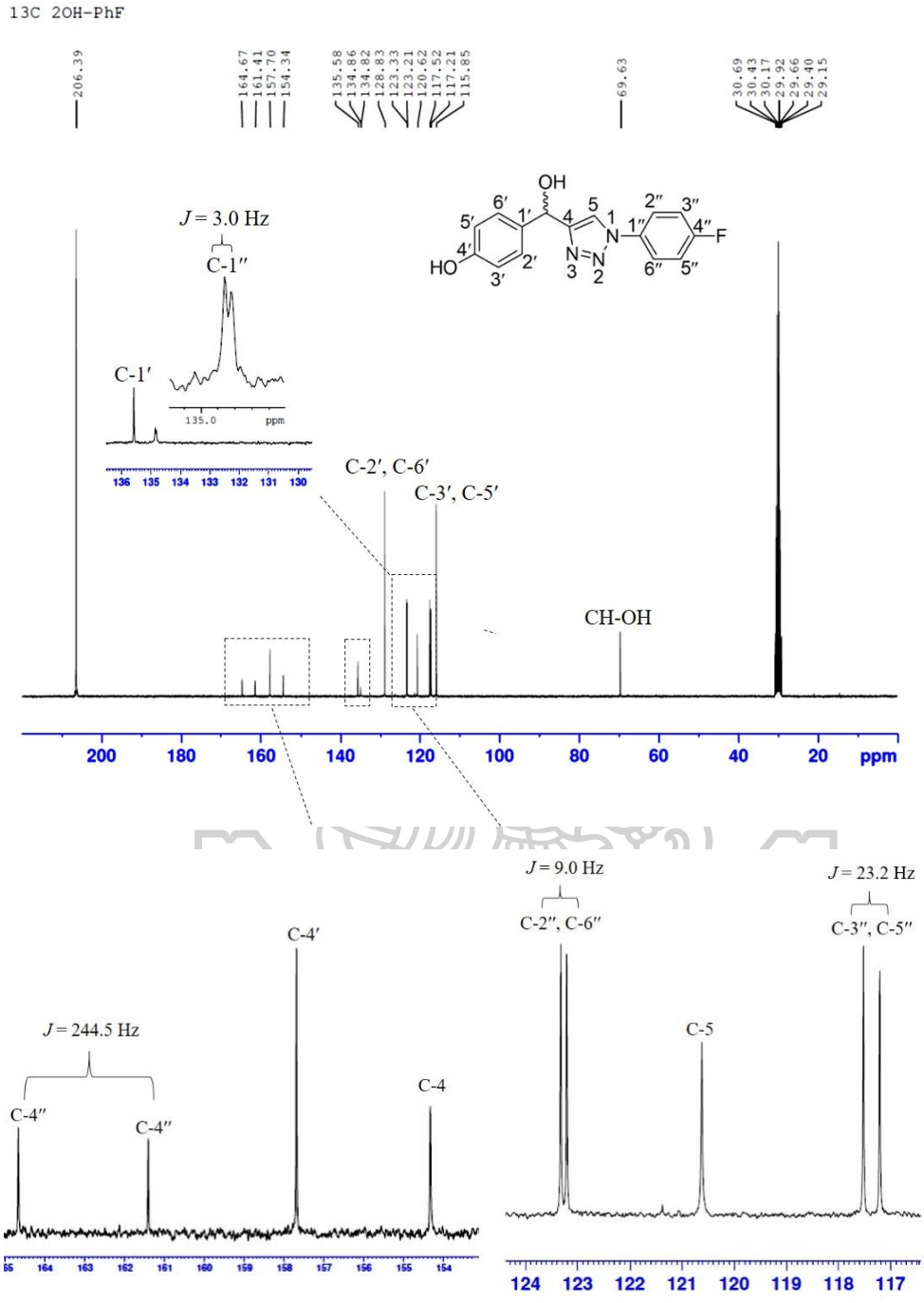
High resolution mass spectrum



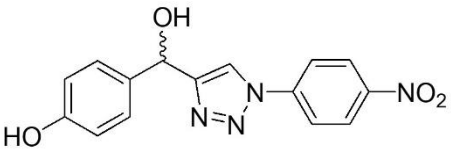
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7b)



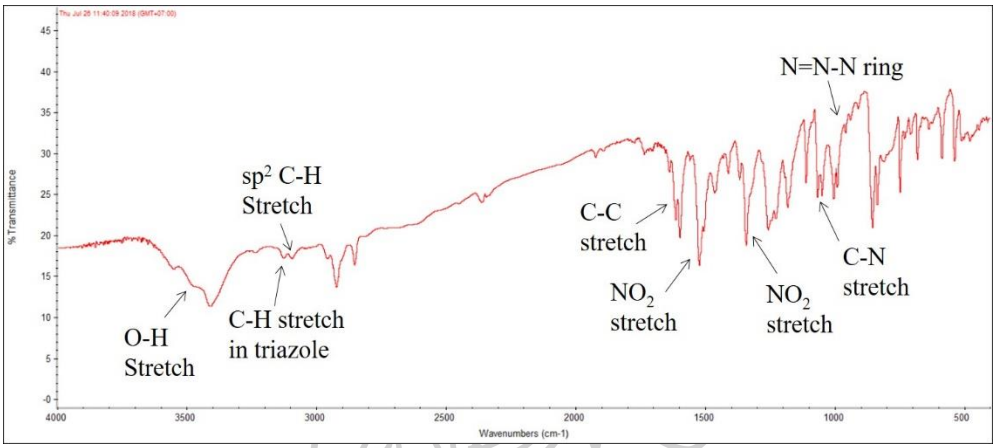
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7b)



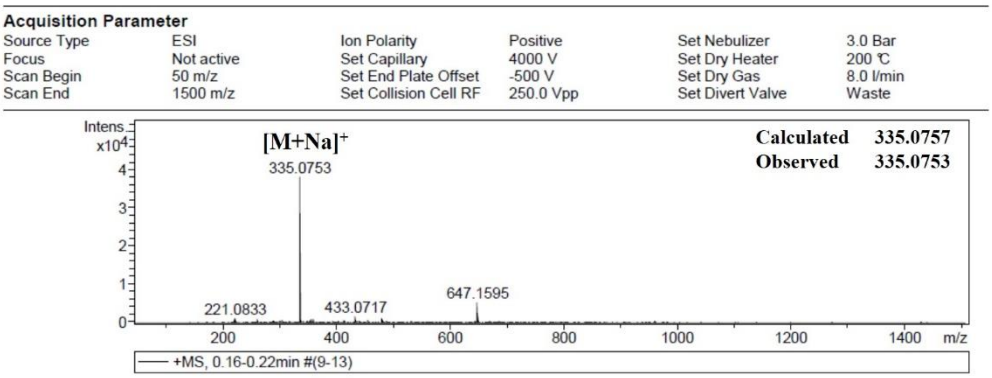
4- (Hydroxyl-(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7c)



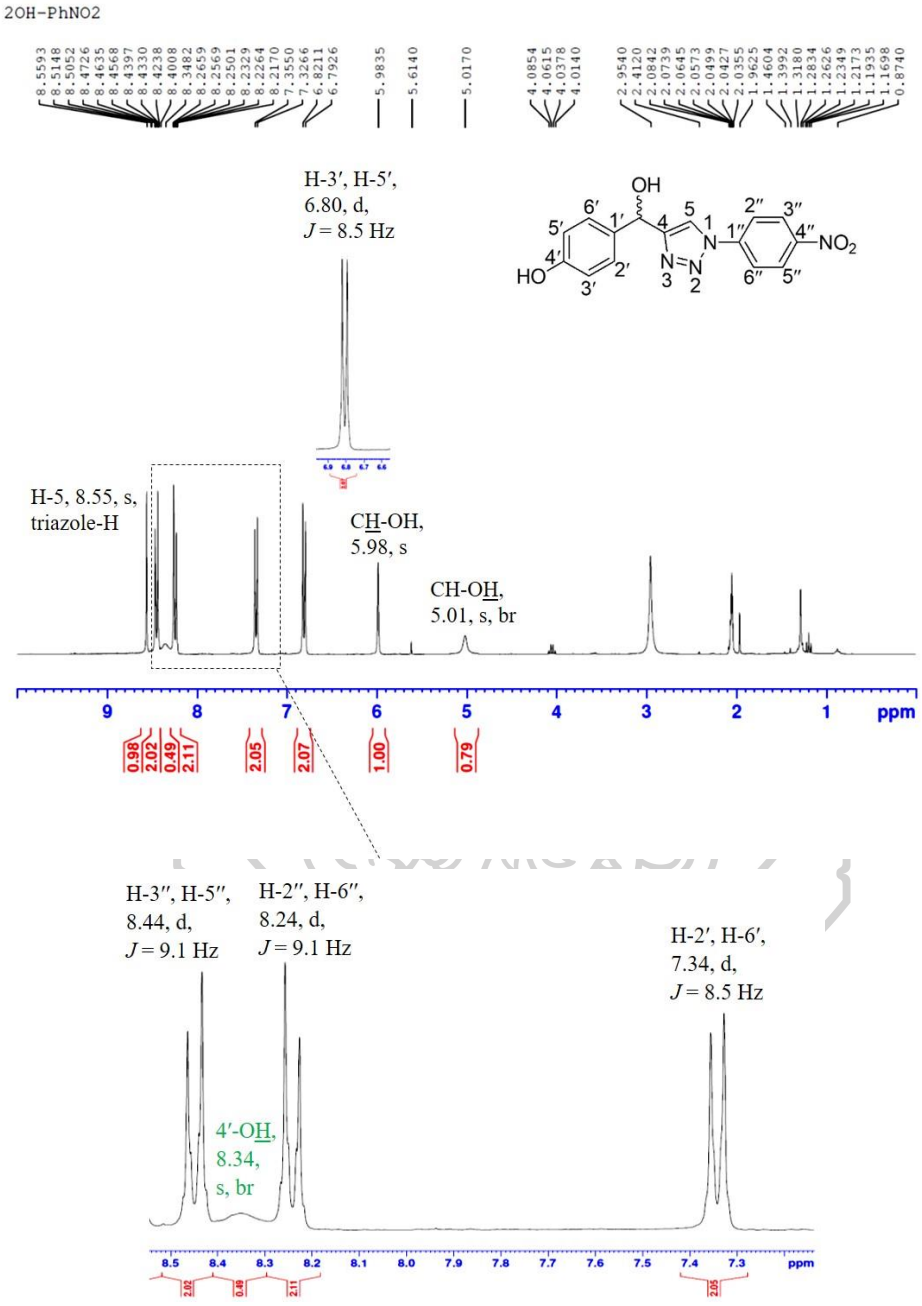
IR spectrum



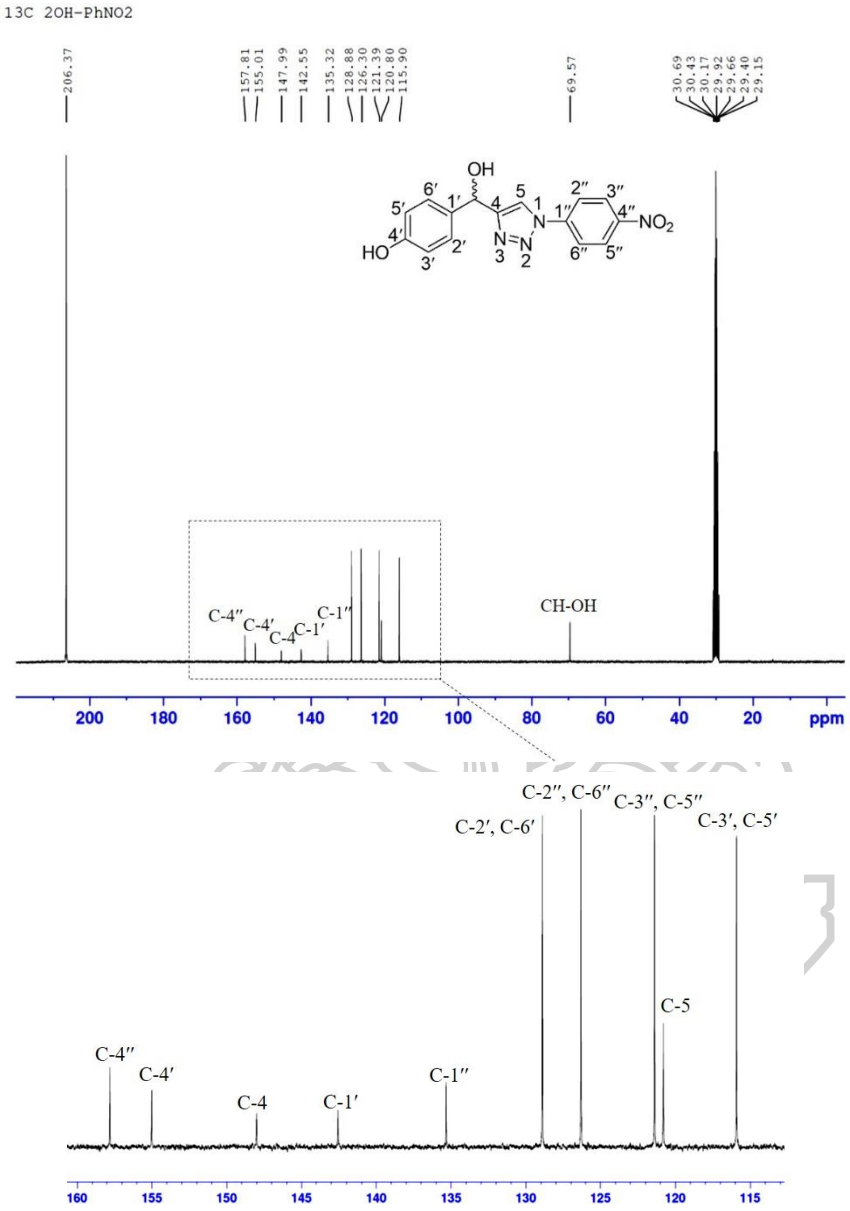
High resolution mass spectrum



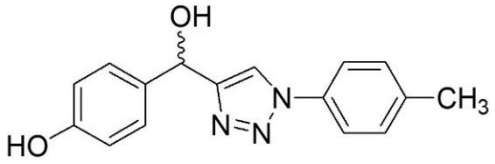
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7c)



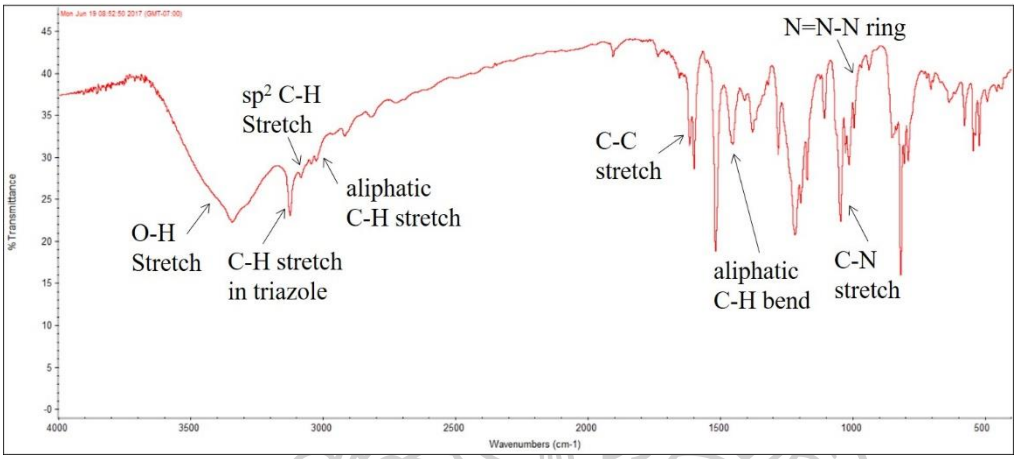
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7c)



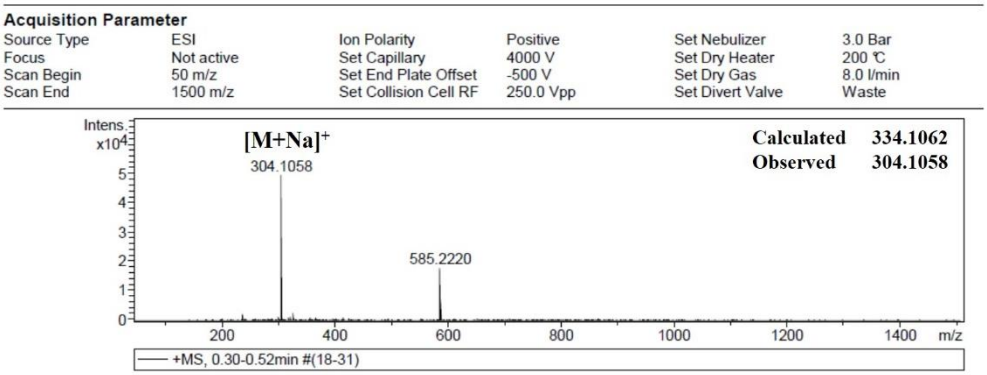
4-(Hydroxyl-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7d)



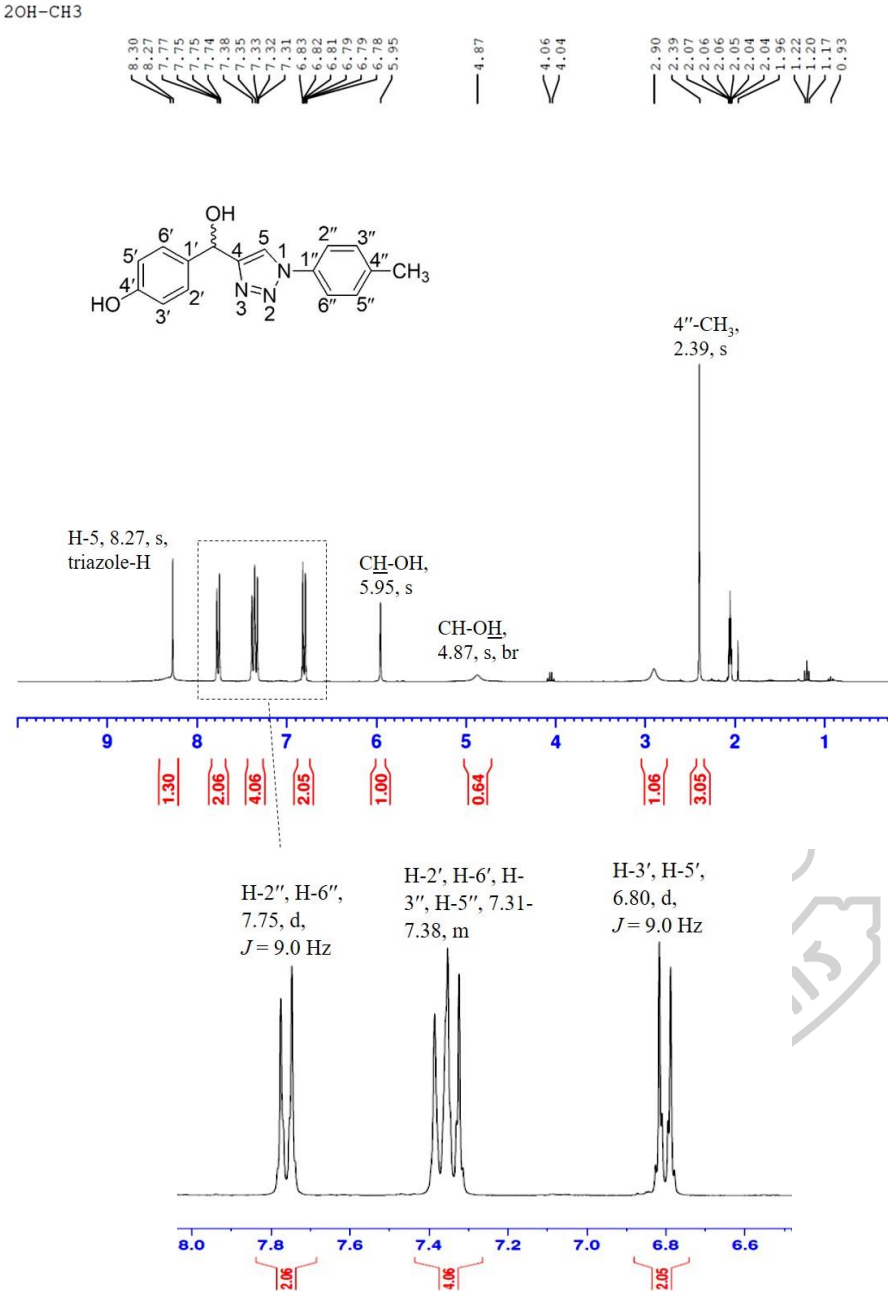
IR spectrum



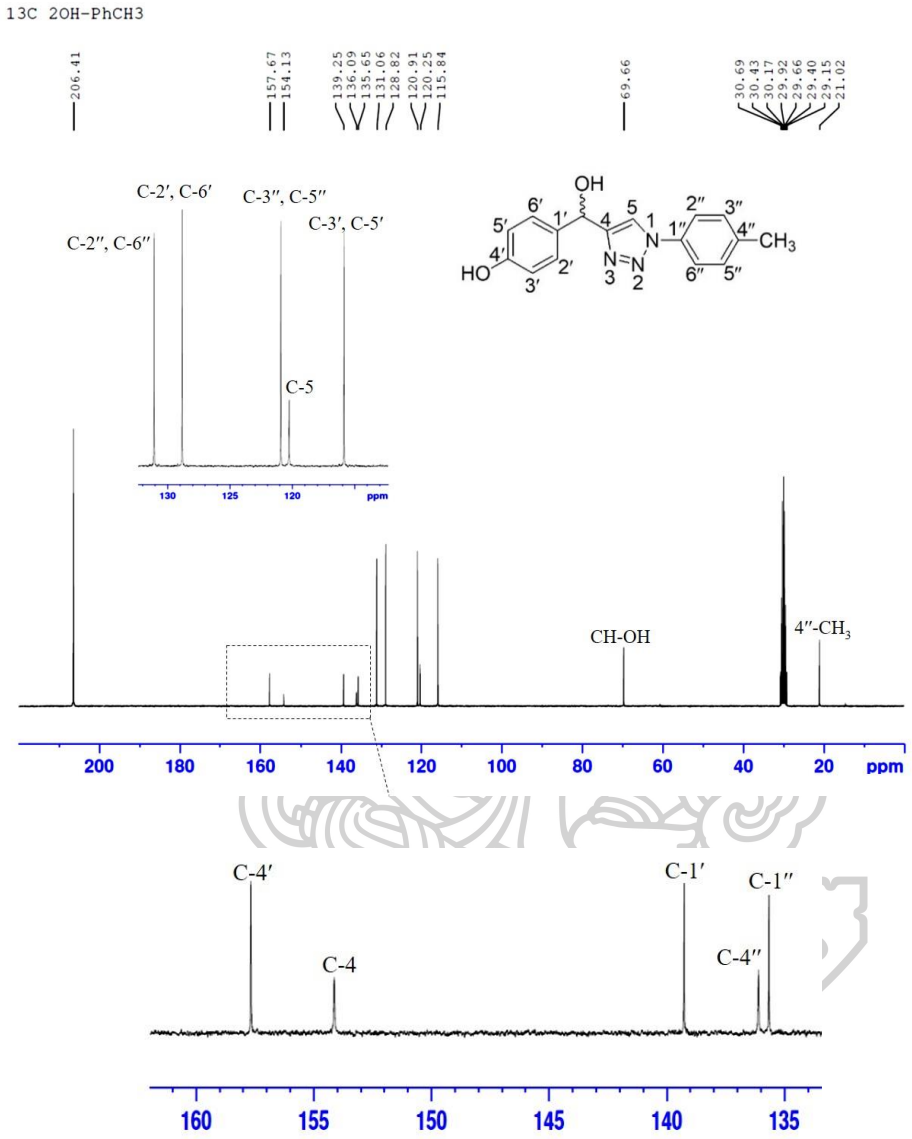
High resolution mass spectrum



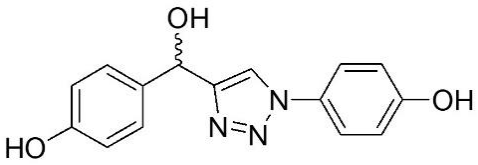
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7d)



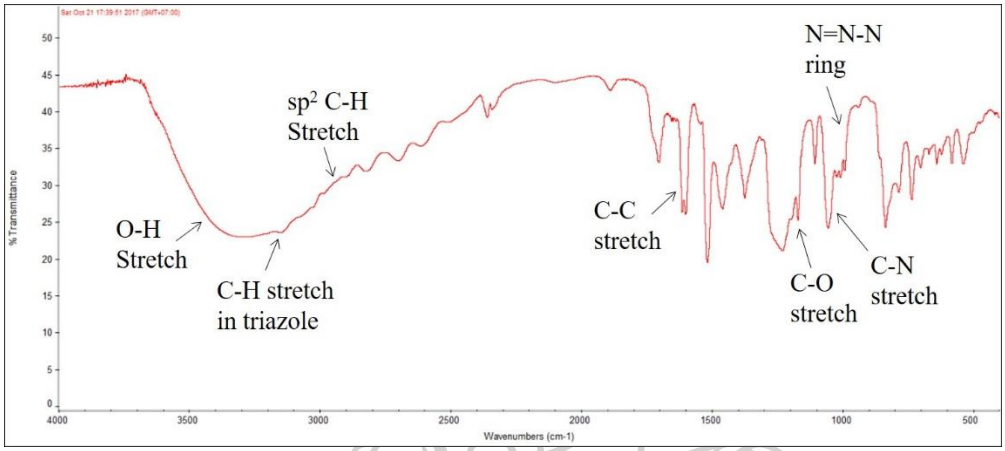
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7d)



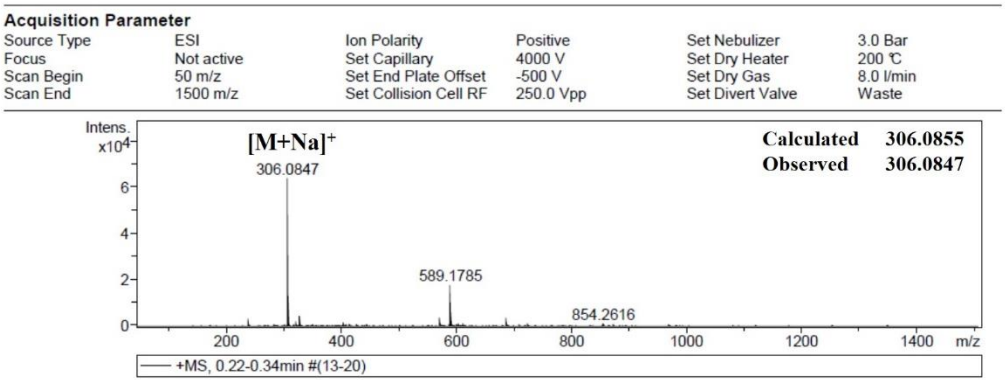
4-(Hydroxyl-(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7e)



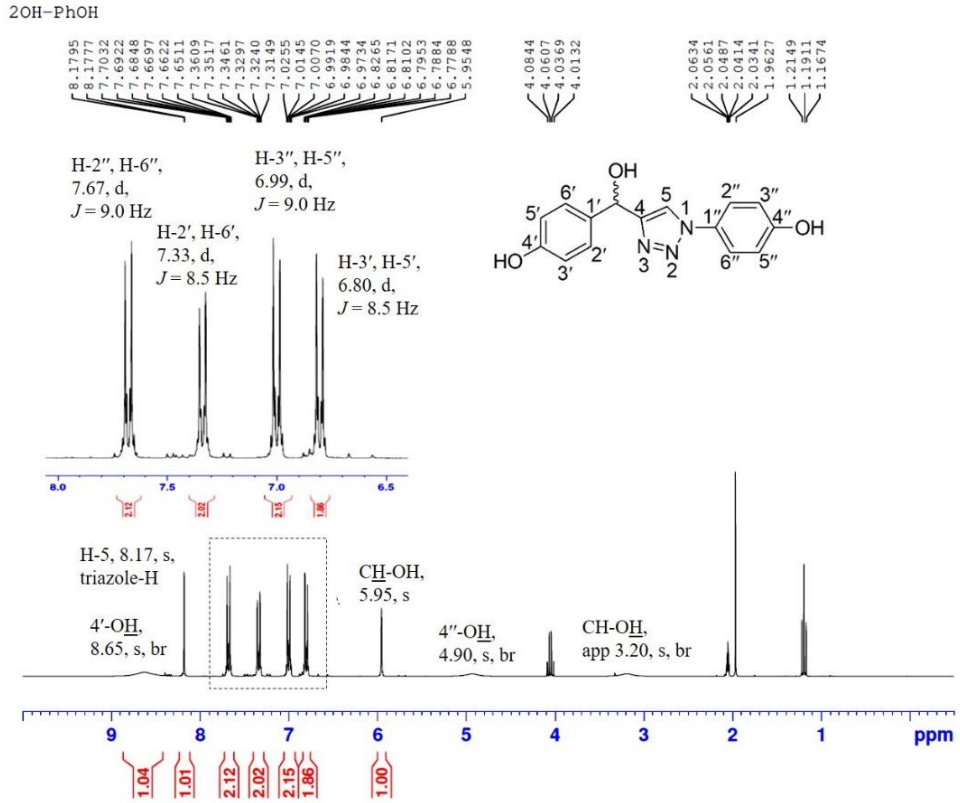
IR spectrum



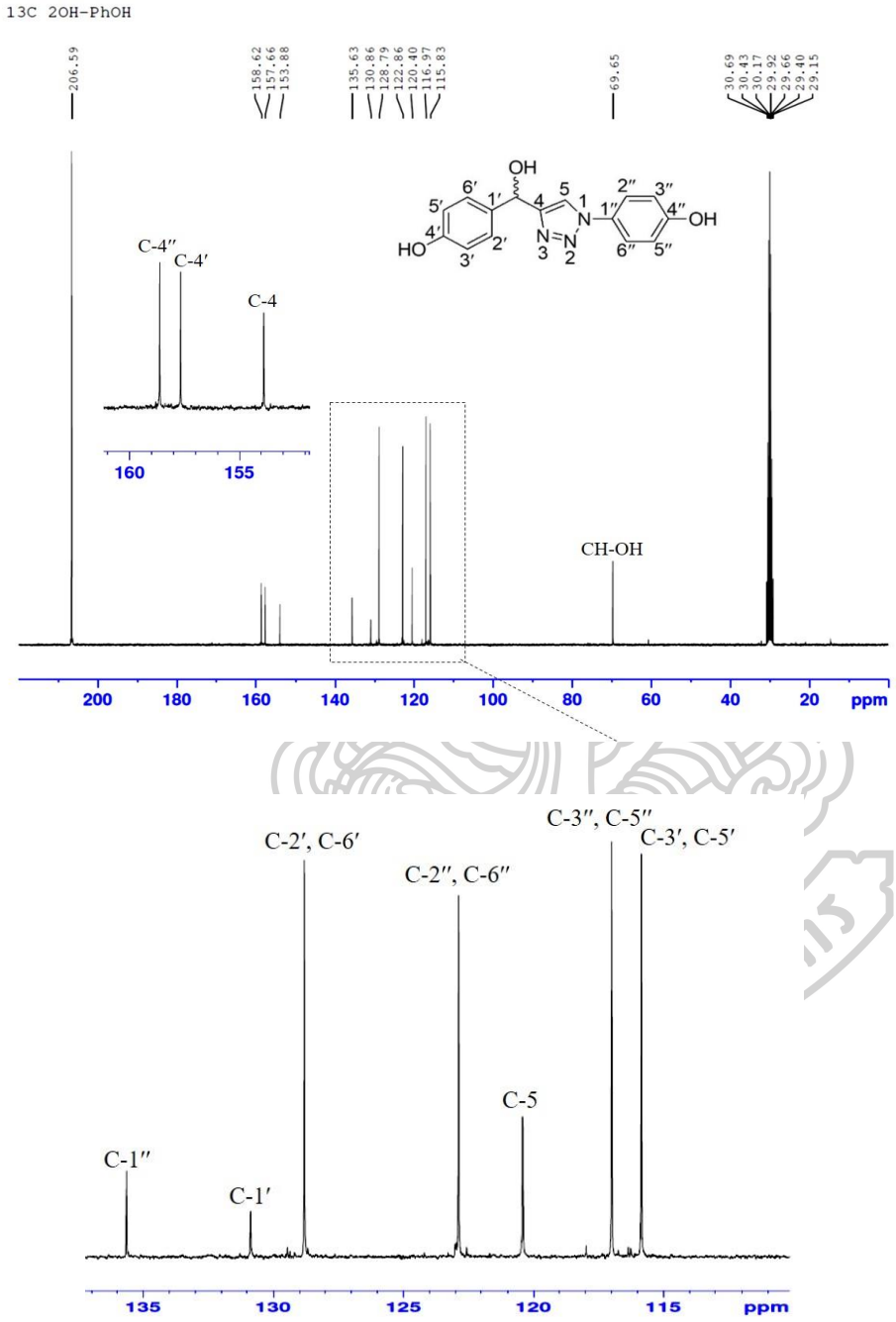
High resolution mass spectrum



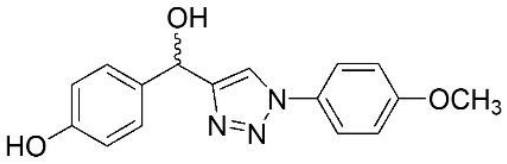
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7e)



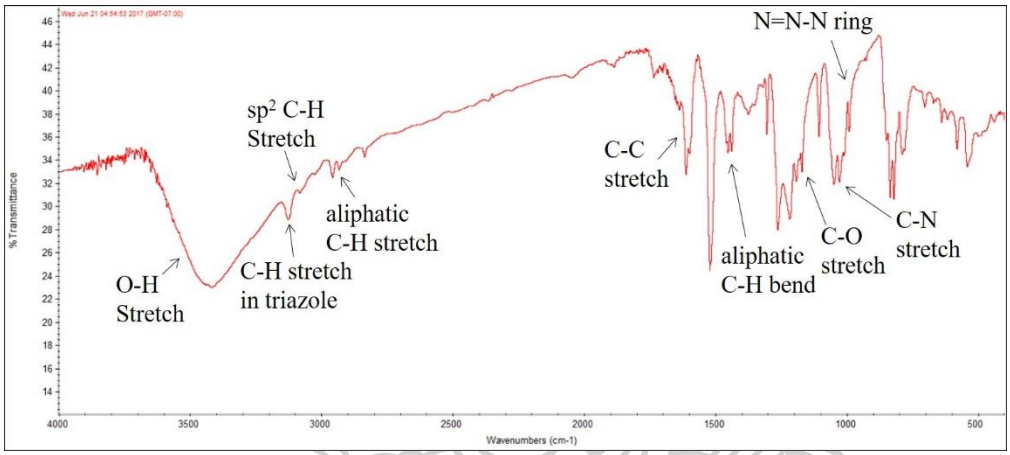
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7e)



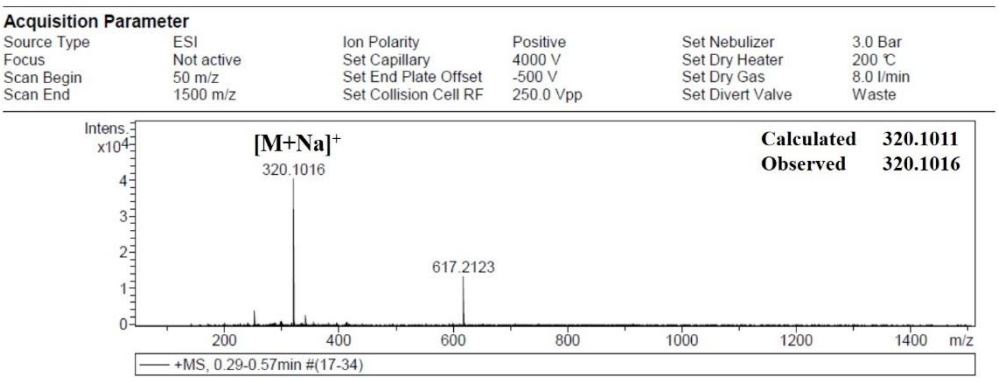
4-(Hydroxyl-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7f)



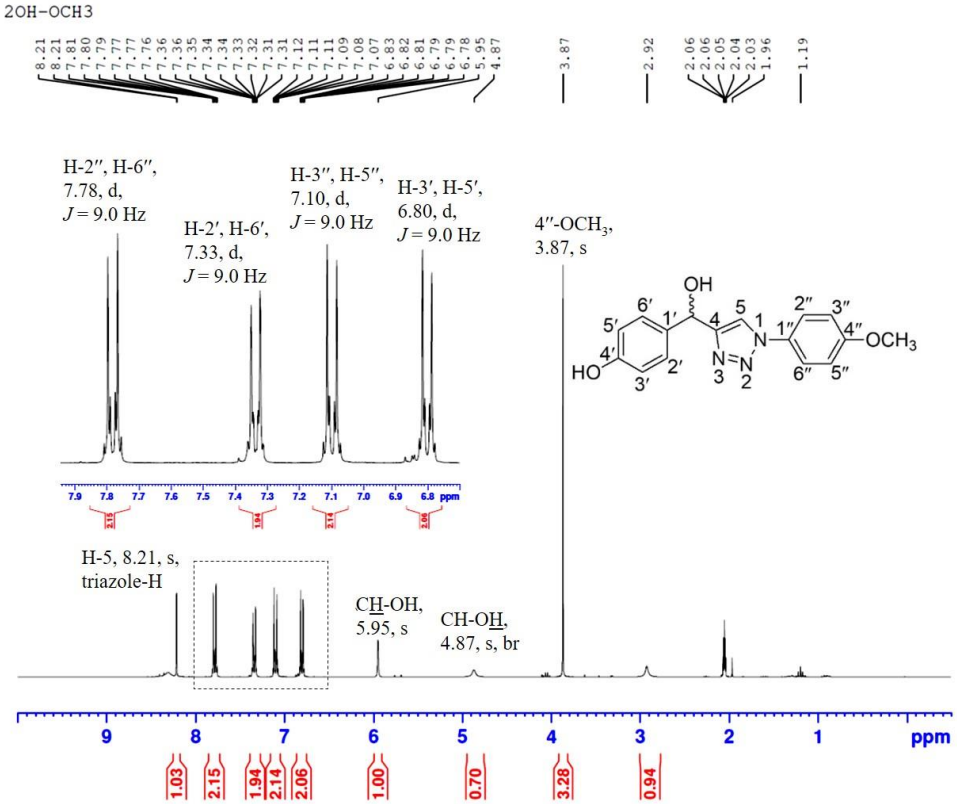
IR spectrum



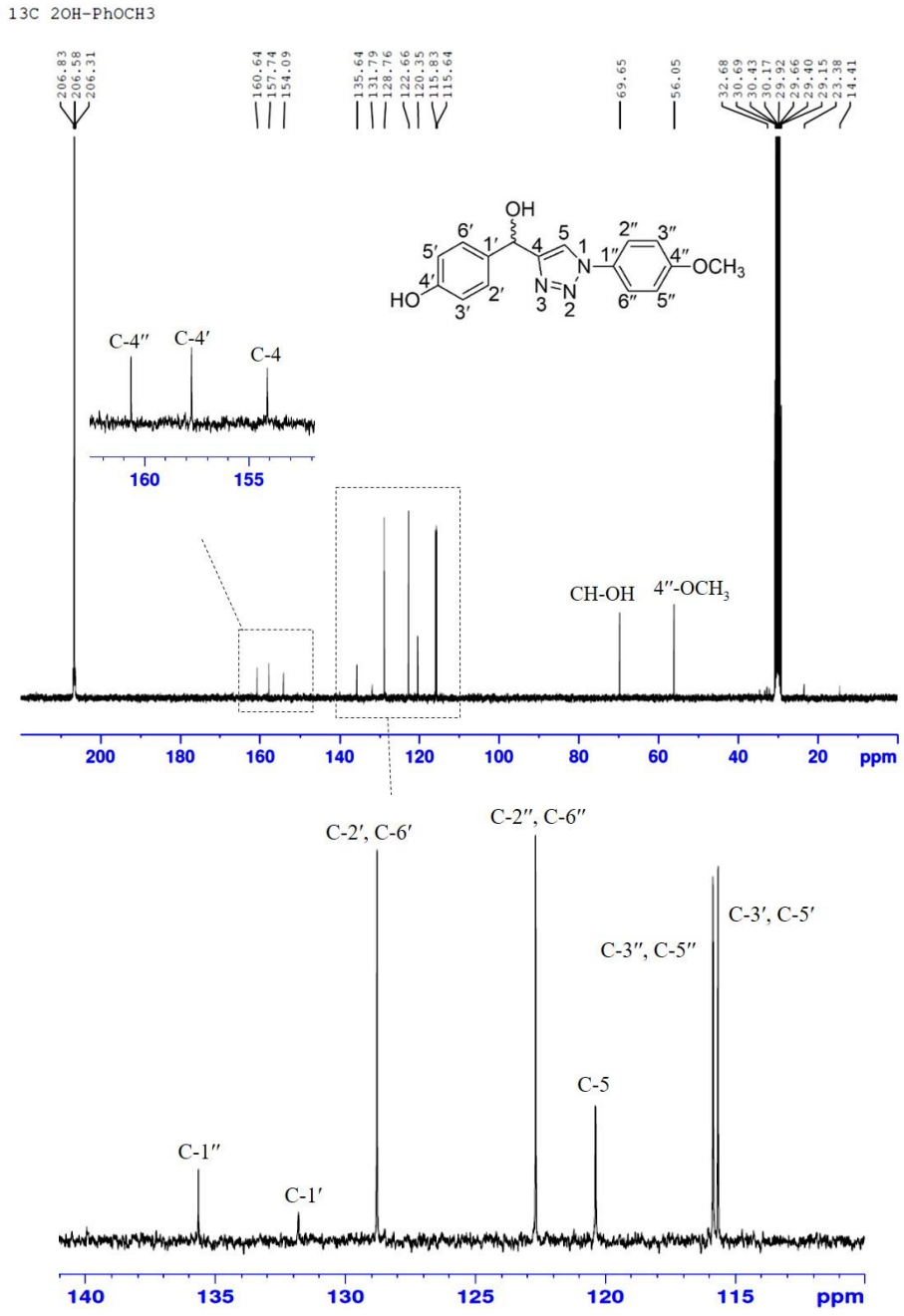
High resolution mass spectrum



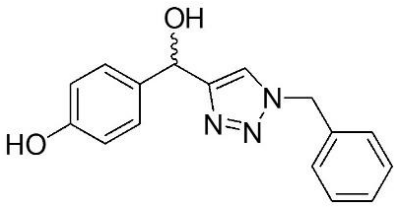
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7f)



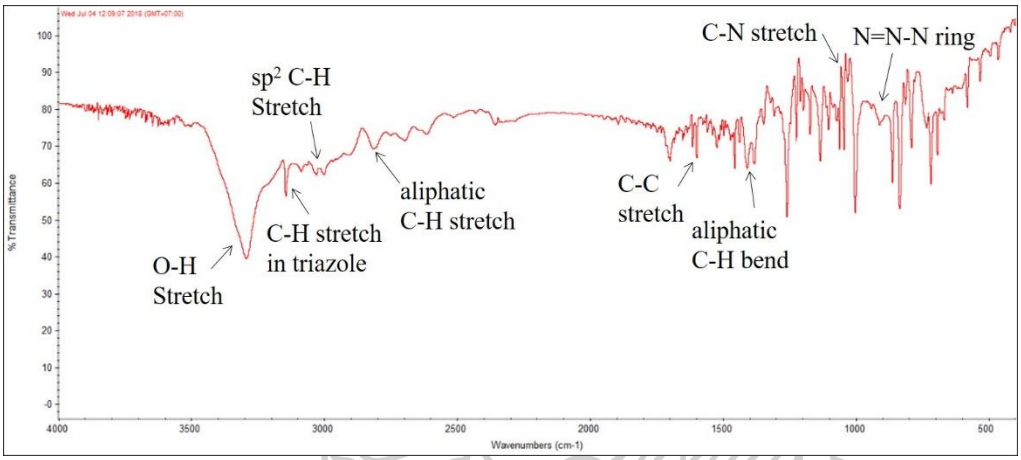
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7f)



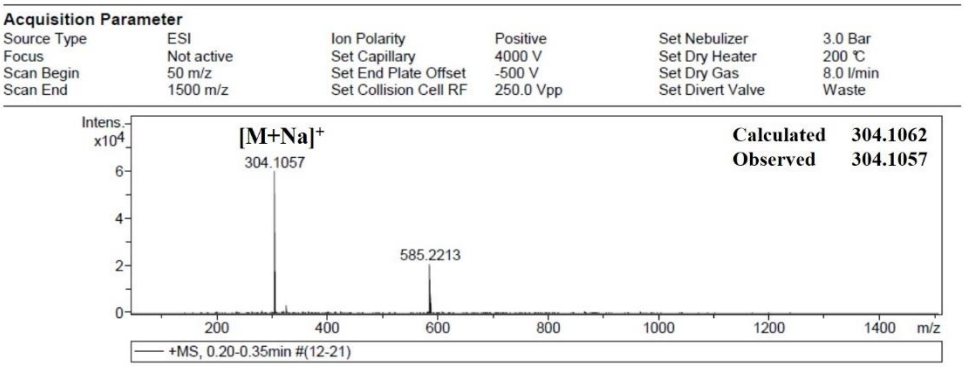
4-(Hydroxyl-(1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7g)



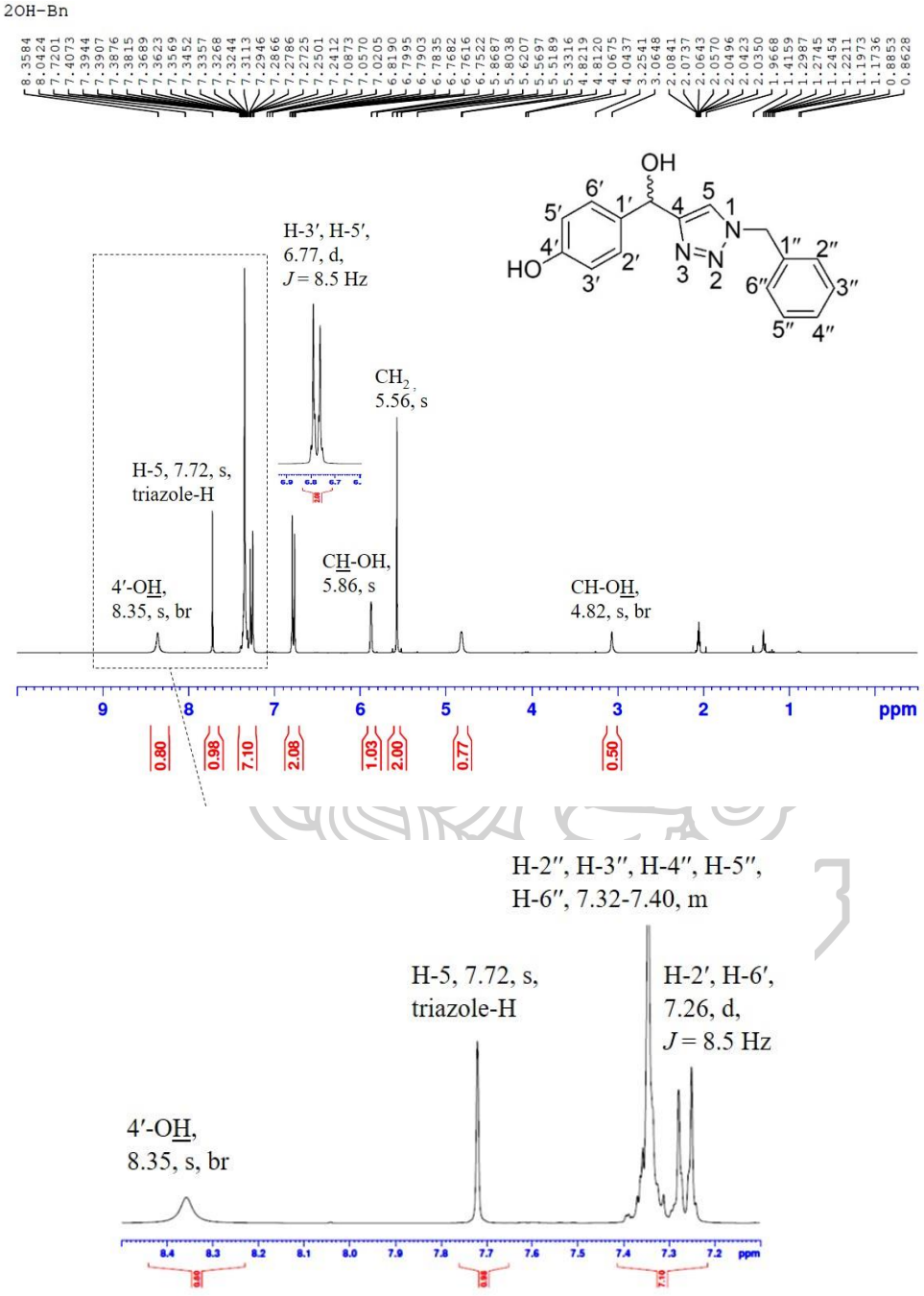
IR spectrum



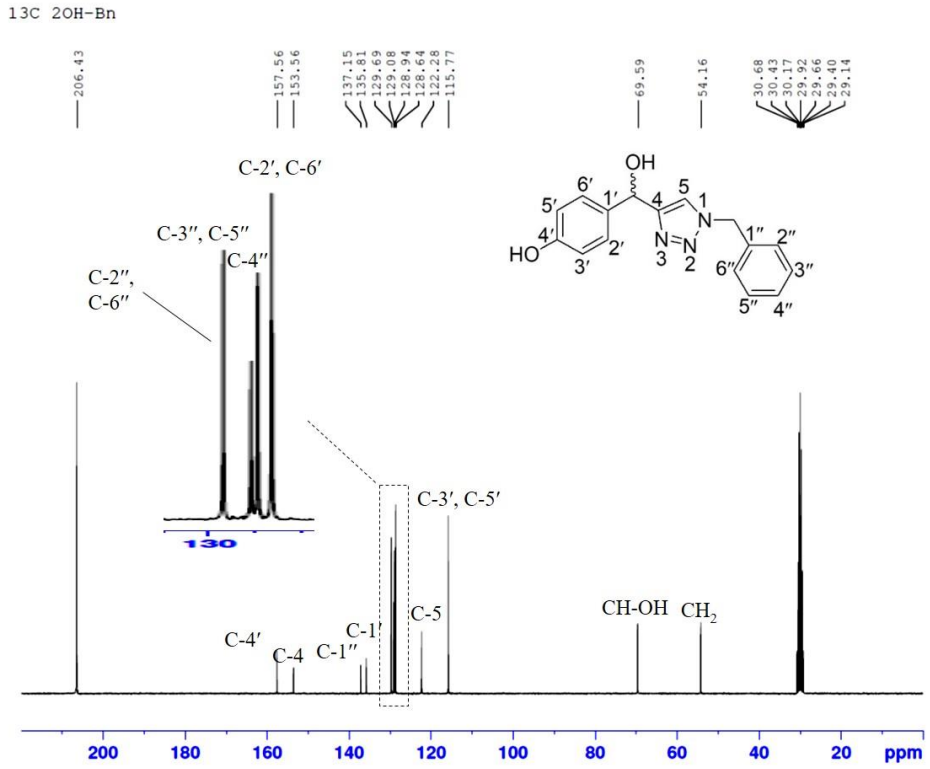
High resolution mass spectrum



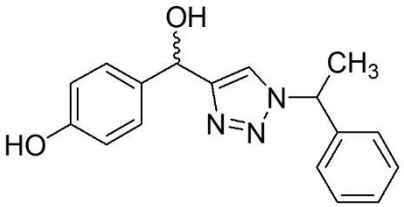
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7g)



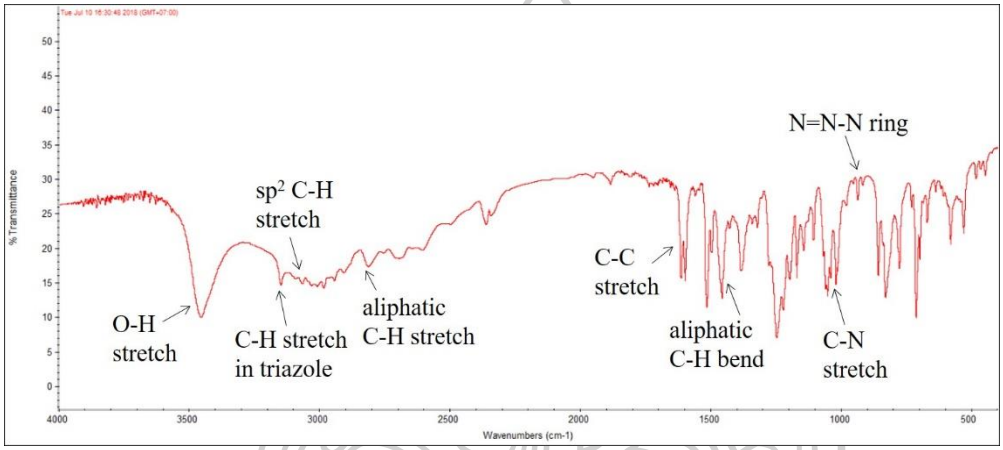
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7g)



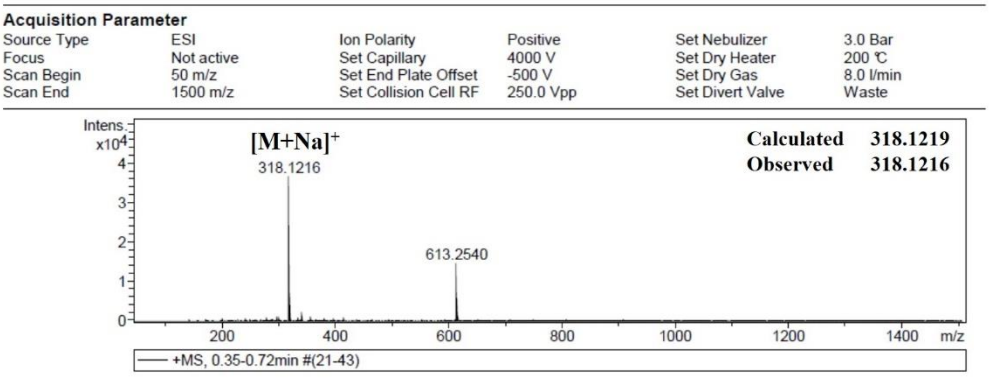
4-(Hydroxyl-(1-(ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7h)



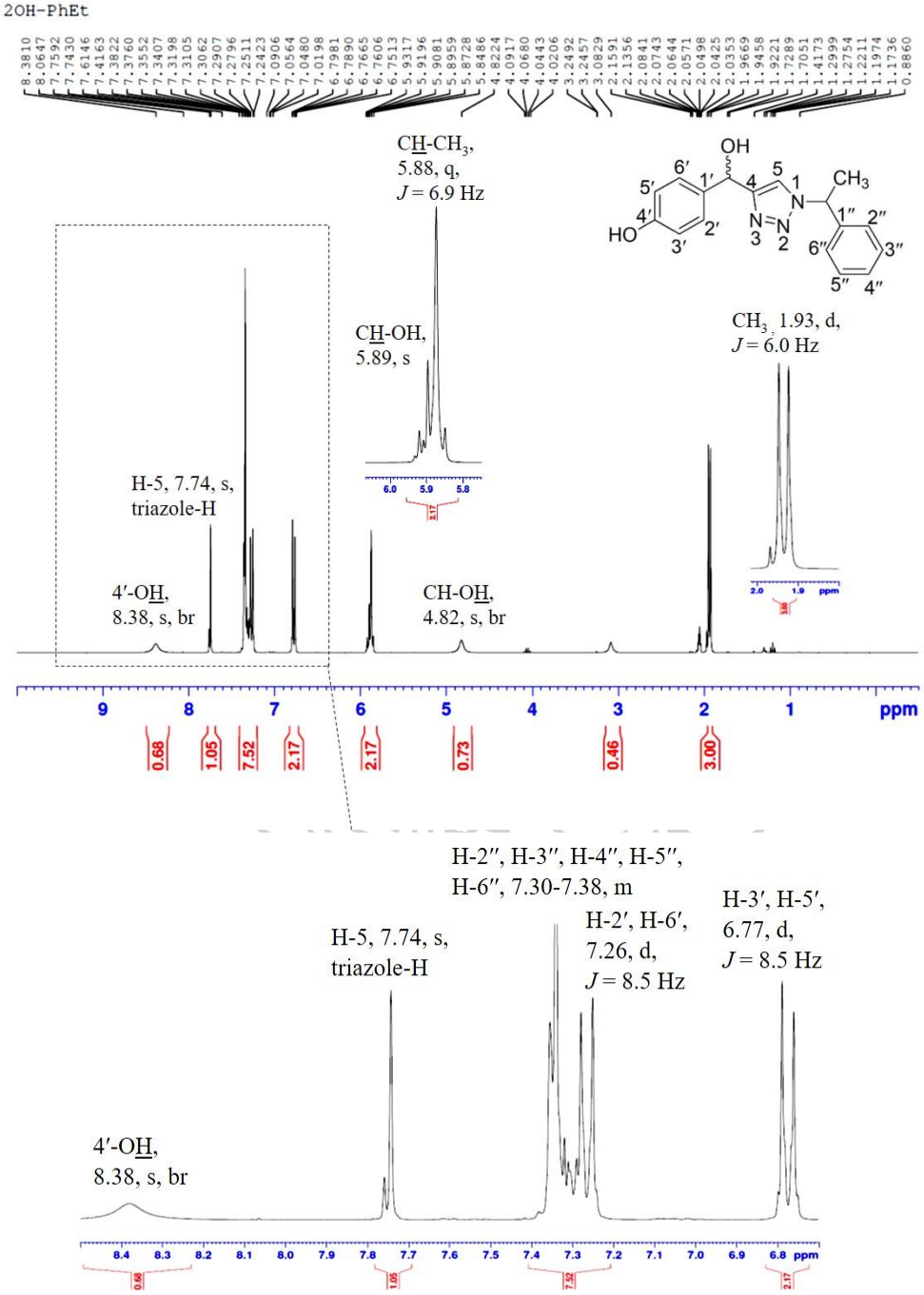
IR spectrum



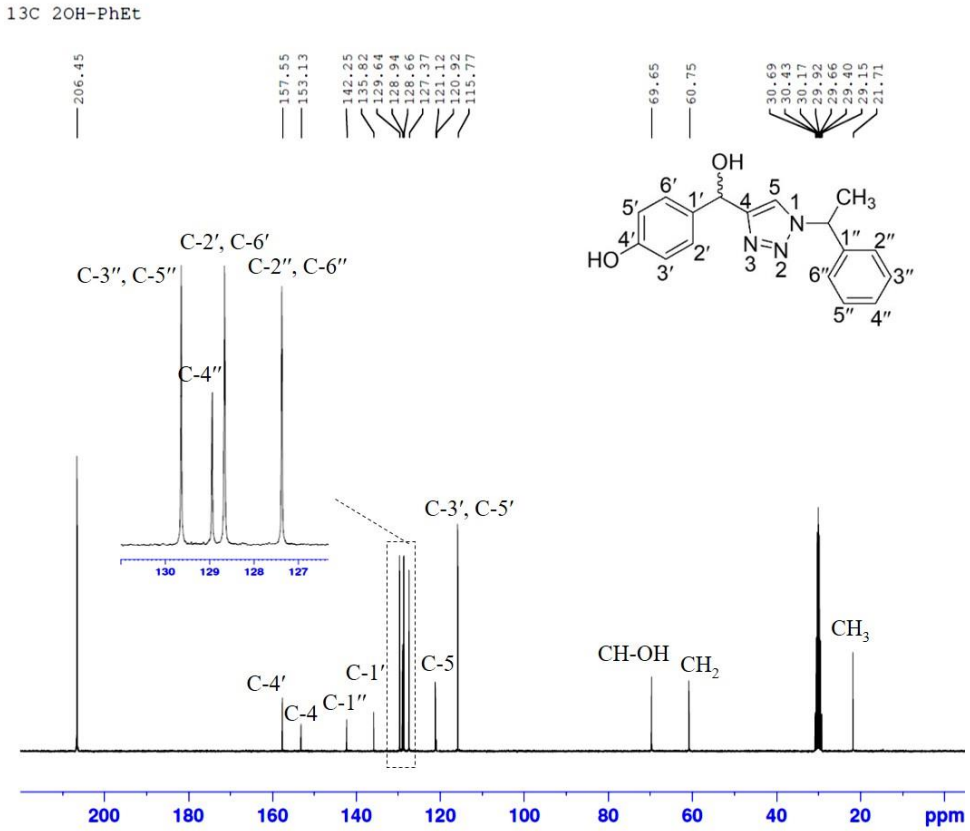
High resolution mass spectrum



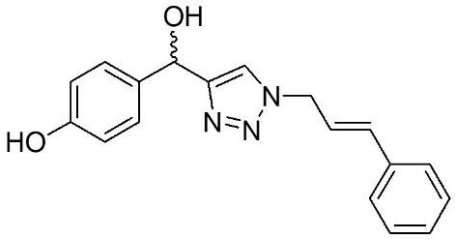
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7h)



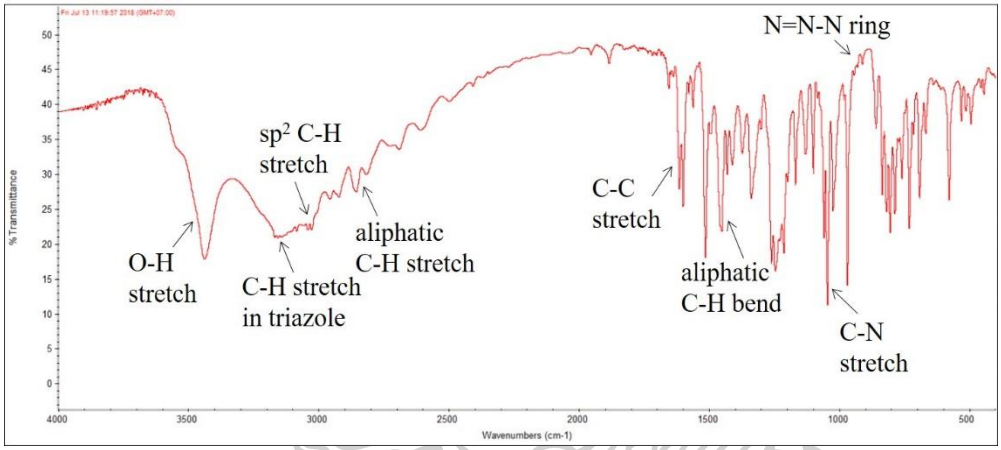
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7h)



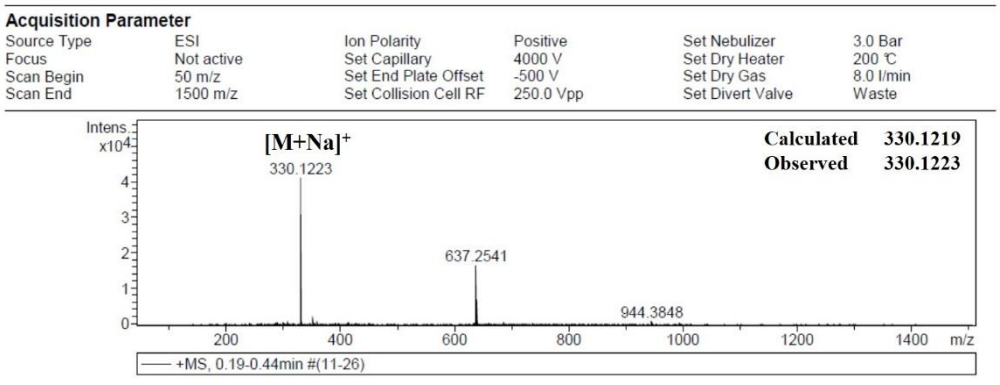
4-(Hydroxyl-(1-(cinnamyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7i)



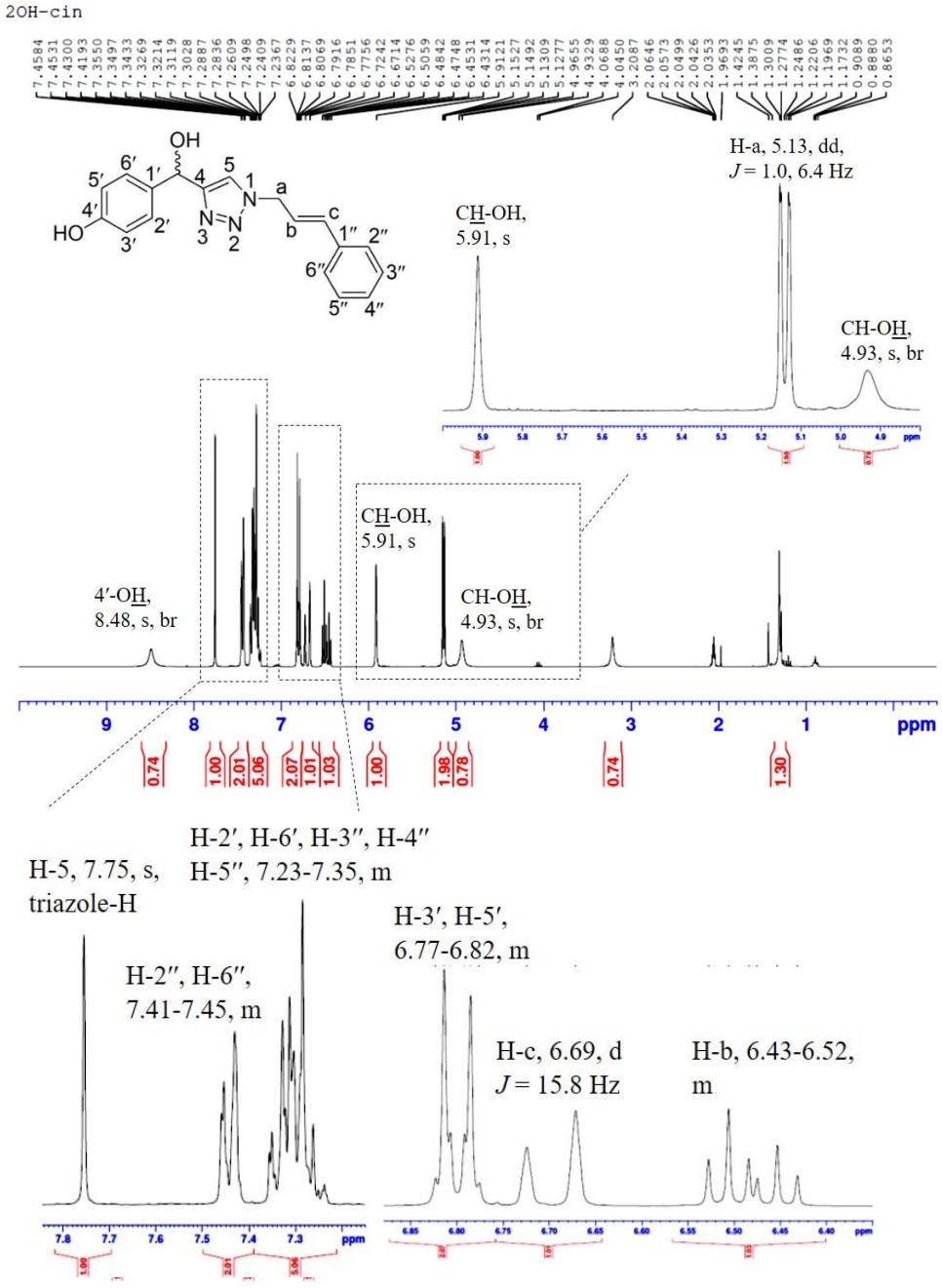
IR spectrum



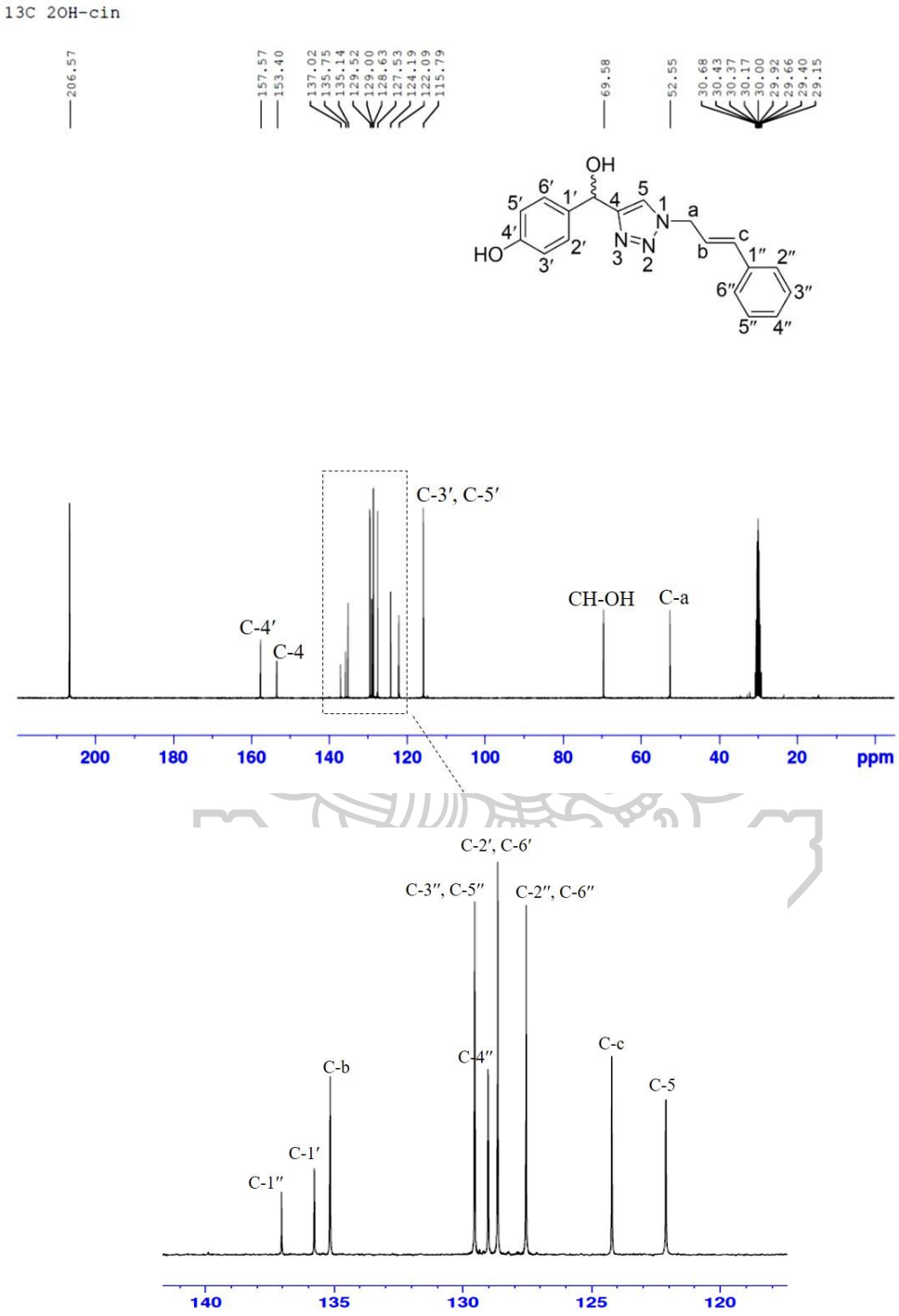
High resolution mass spectrum



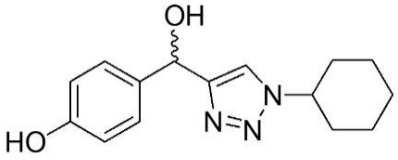
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(cinnamyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7i)



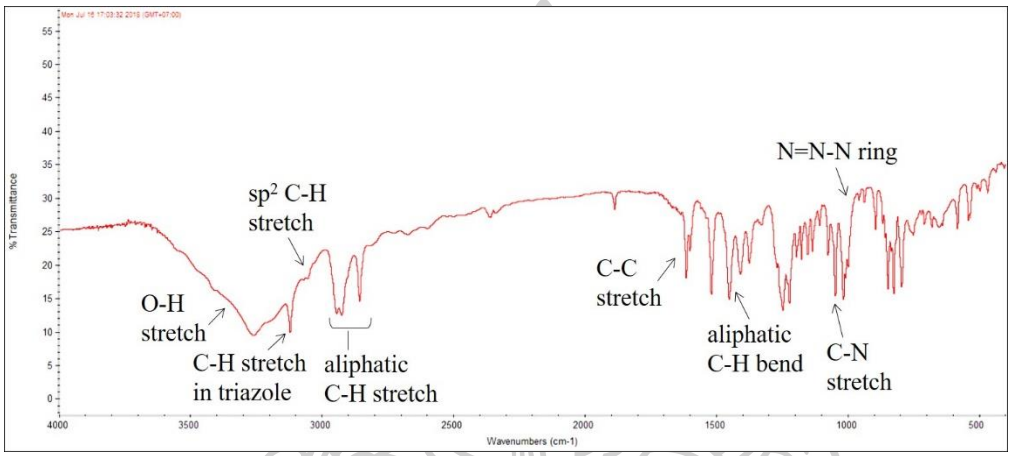
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(cinnamyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7i)



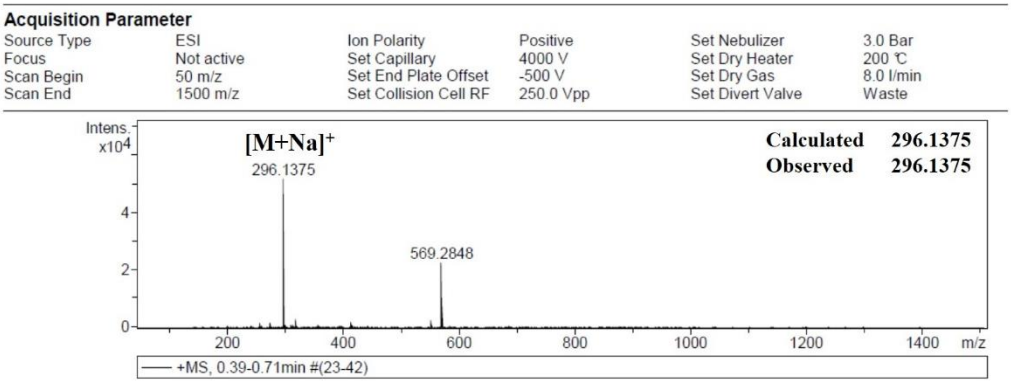
4-(Hydroxyl-(1-(cyclohexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7j)



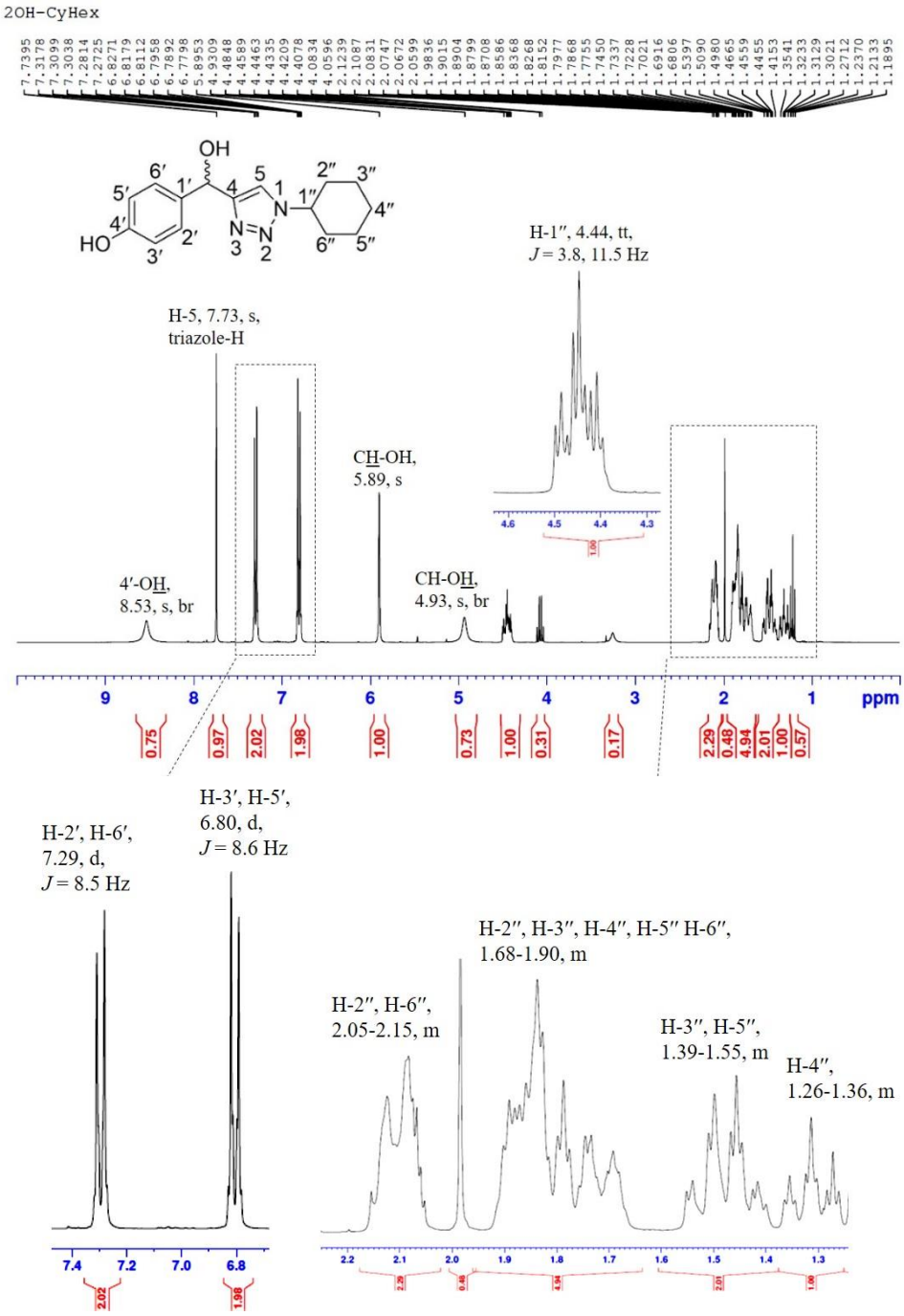
IR spectrum



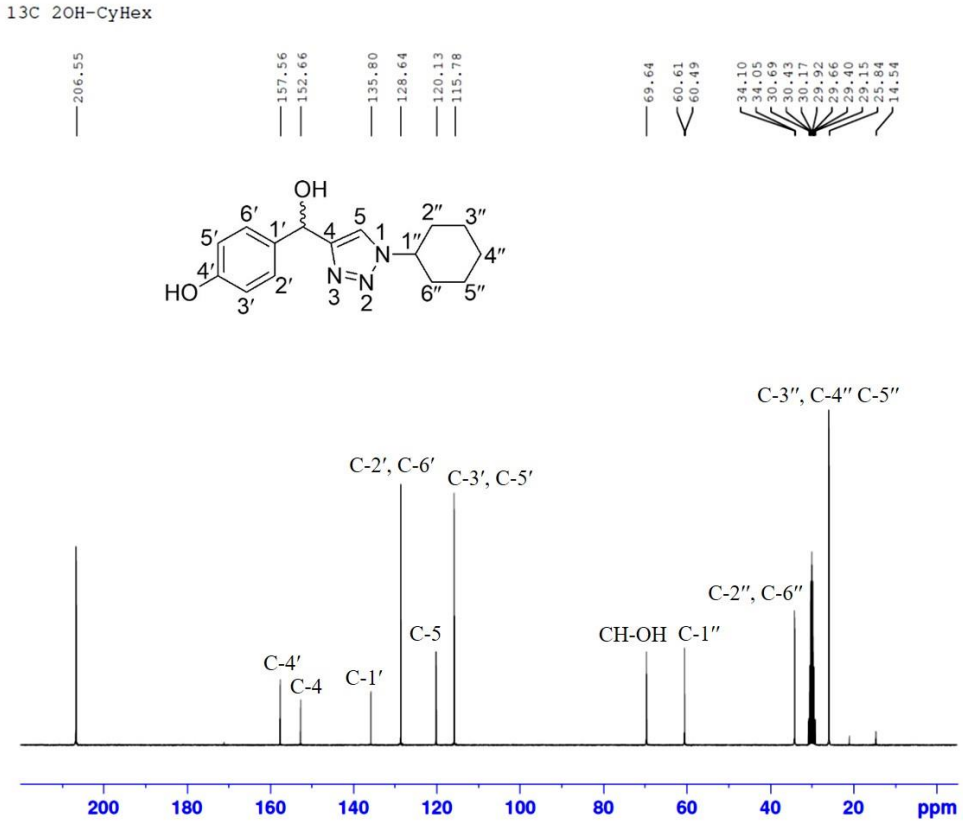
High resolution mass spectrum



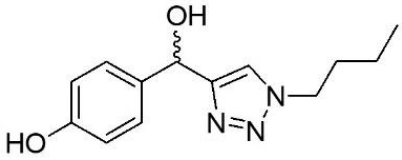
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(cyclohexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7j)



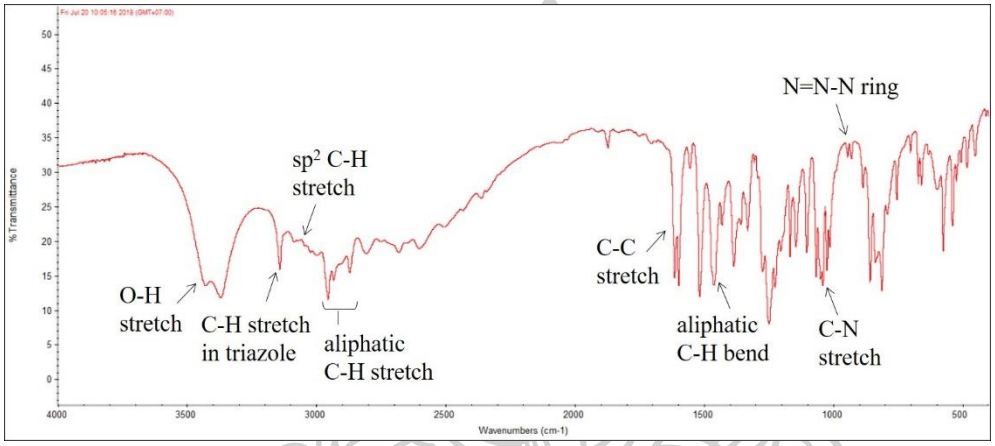
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(cyclohexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7j)



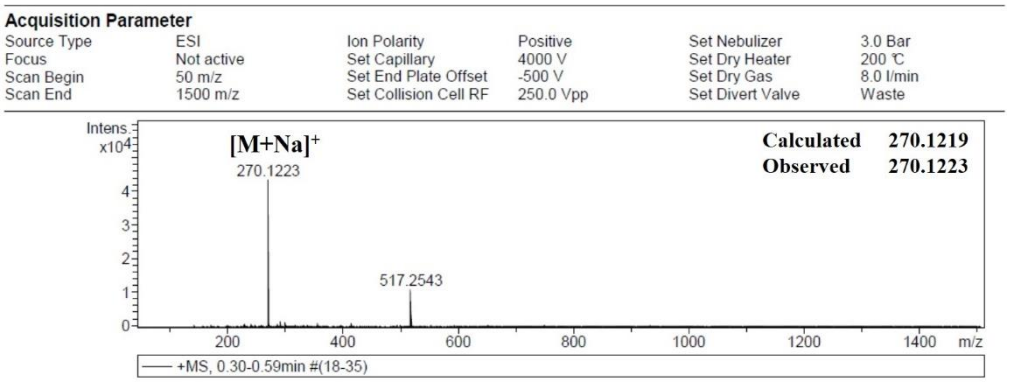
4-(Hydroxyl-(1-(butyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7k)



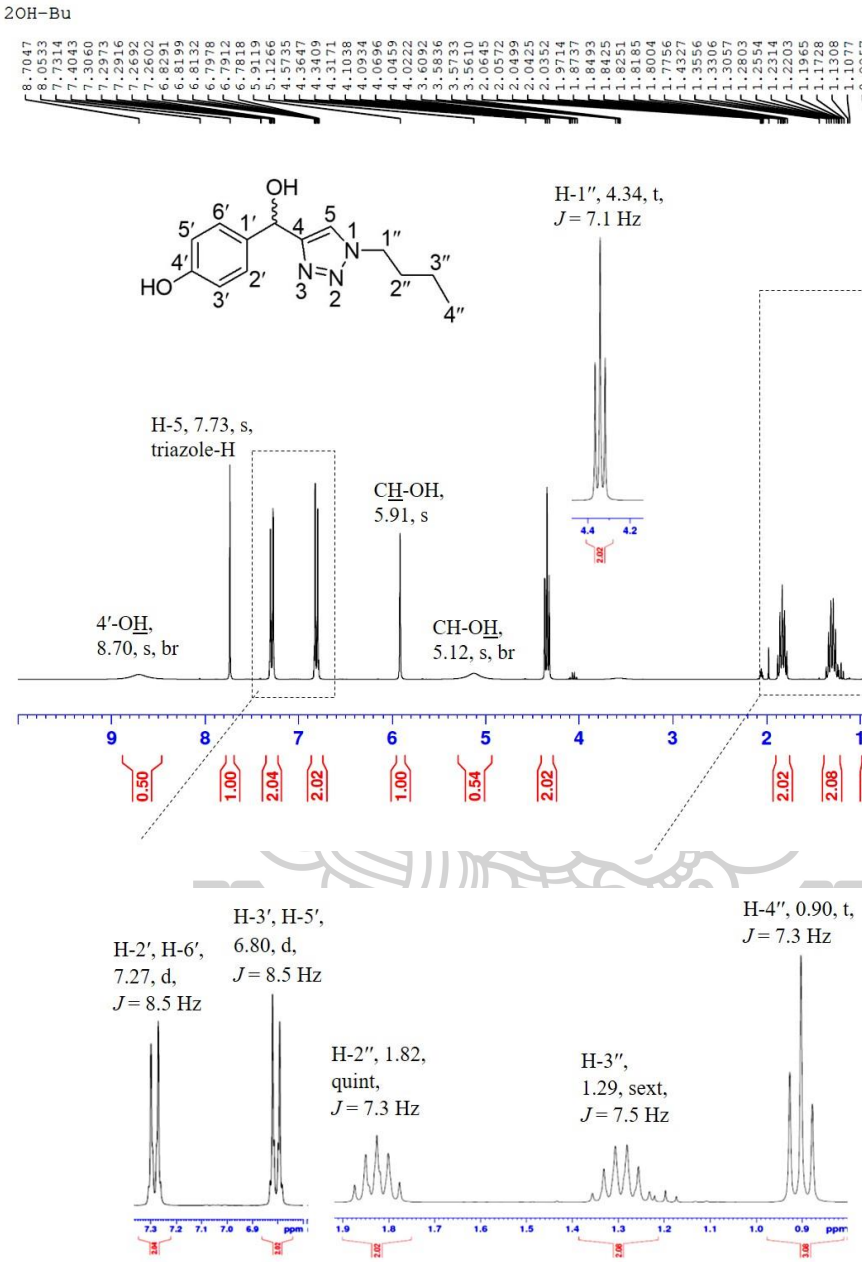
IR spectrum



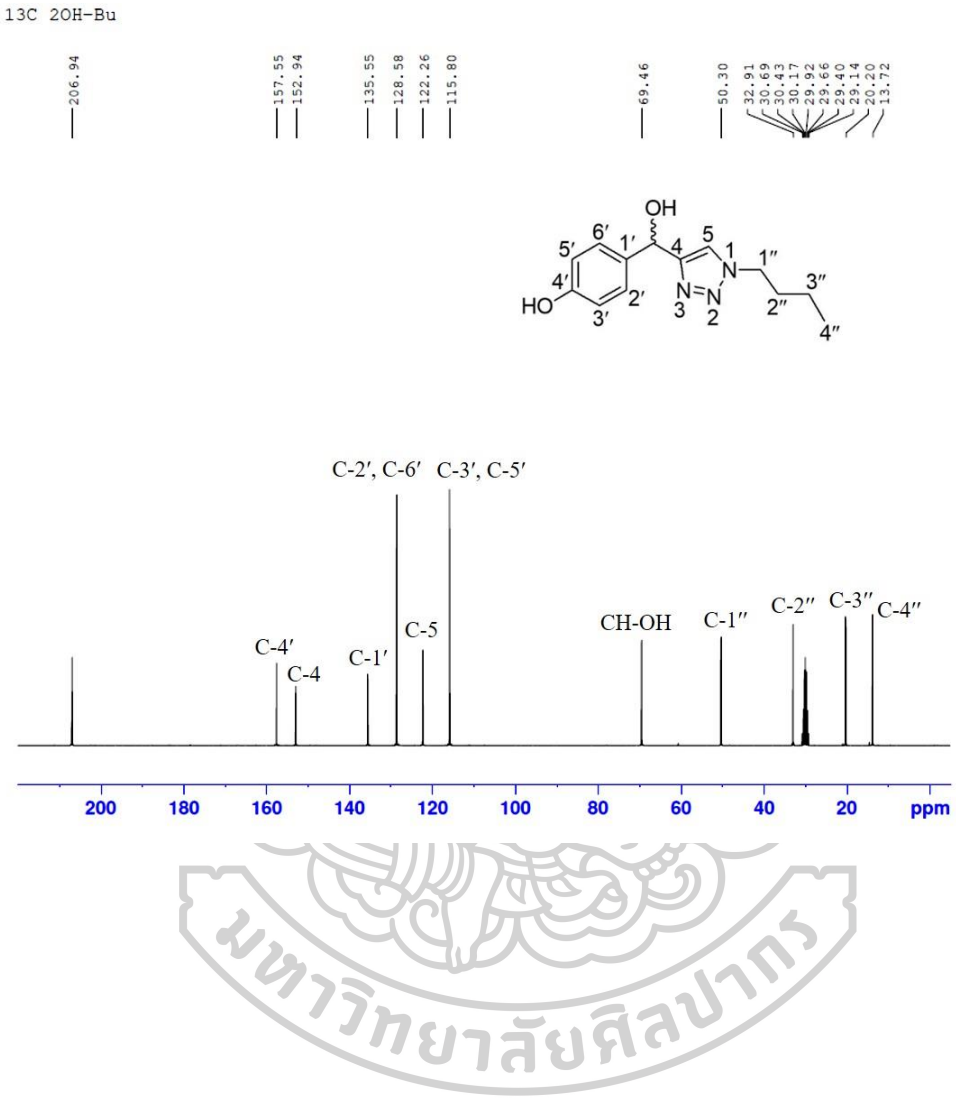
High resolution mass spectrum



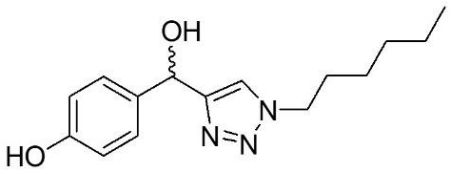
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(butyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7k)



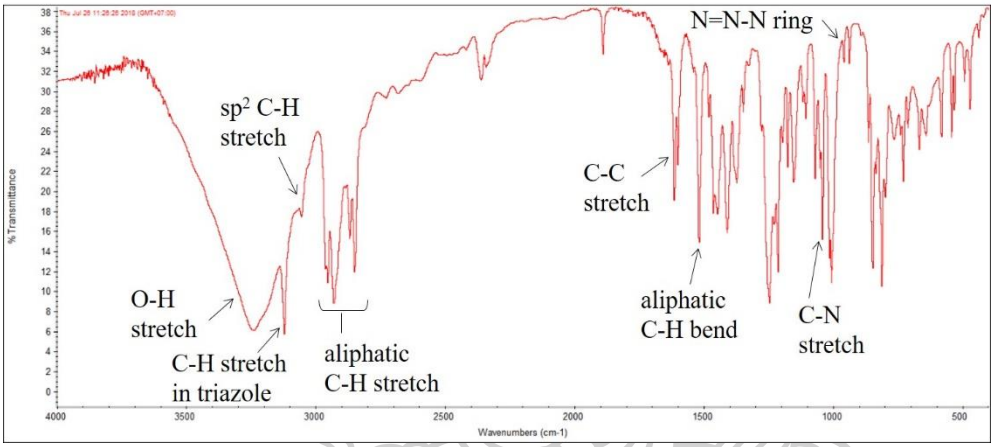
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(butyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7k)



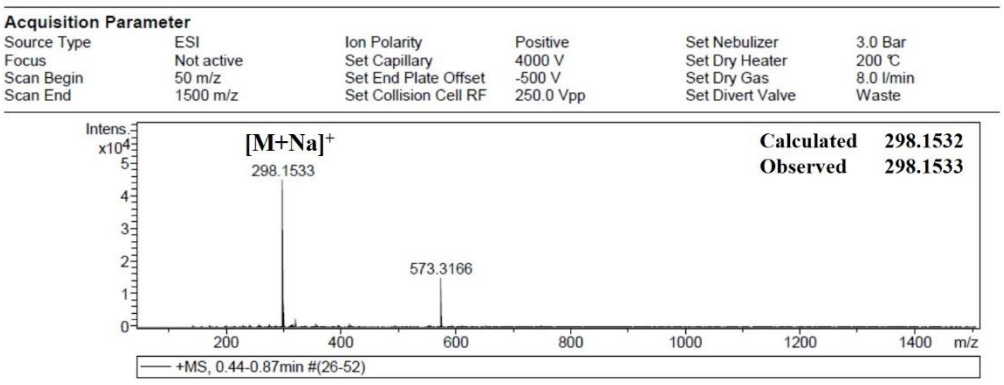
4-(Hydroxyl-(1-(hexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7l)



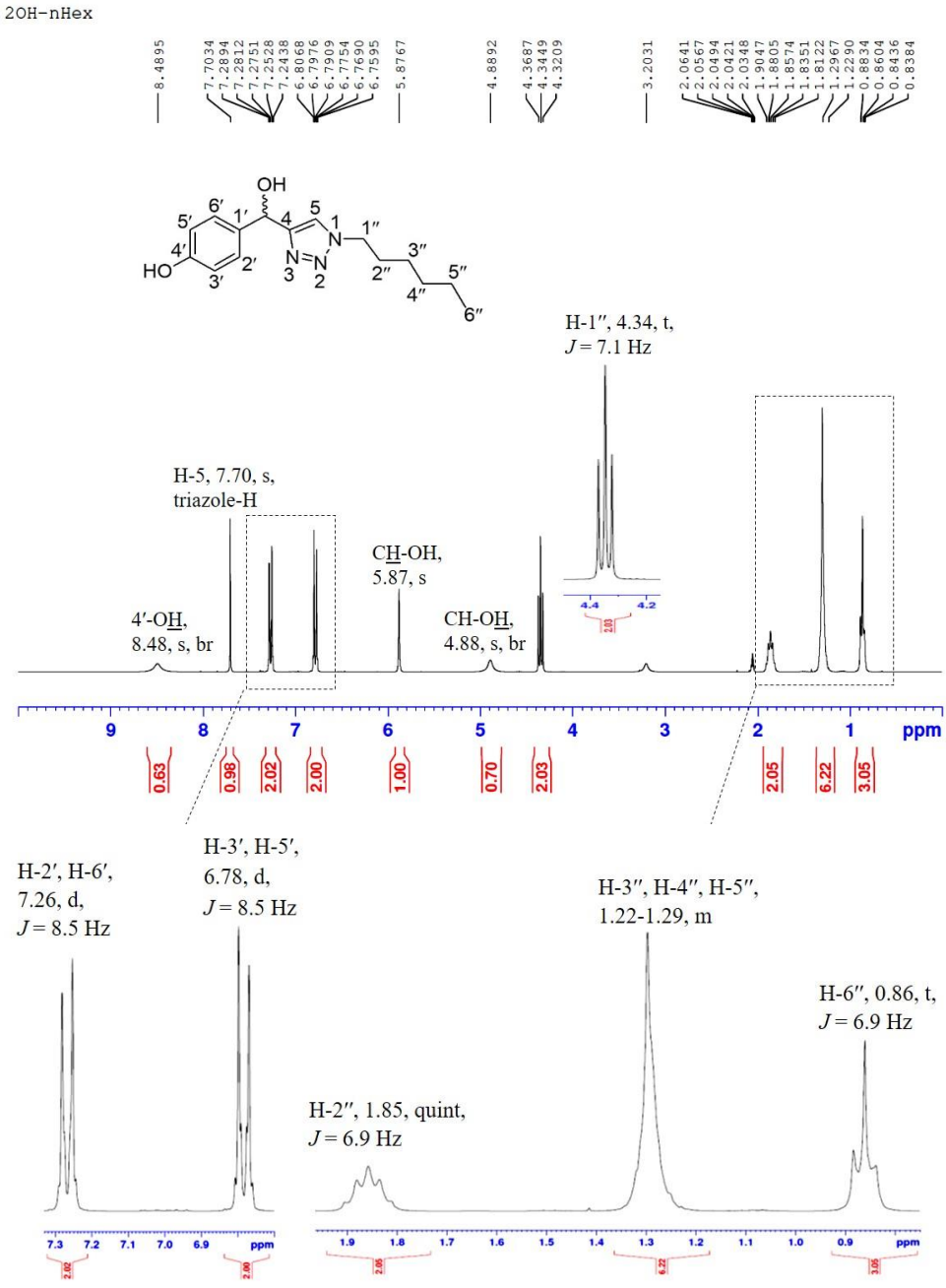
IR spectrum



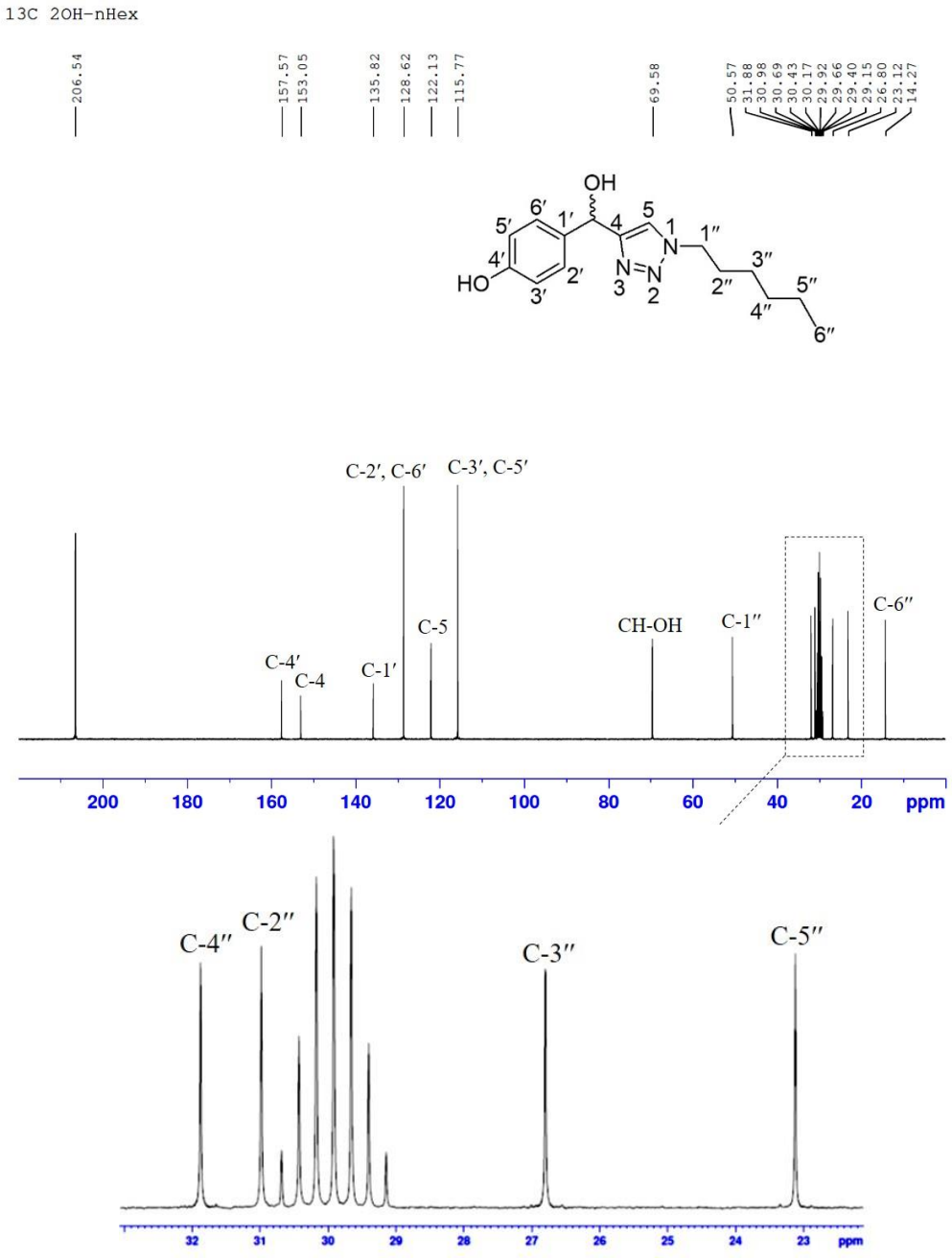
High resolution mass spectrum



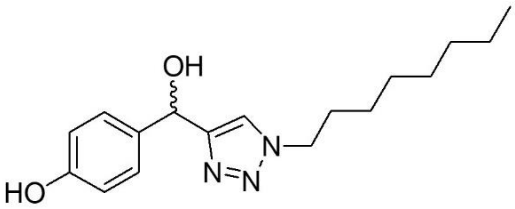
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(hexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7l)



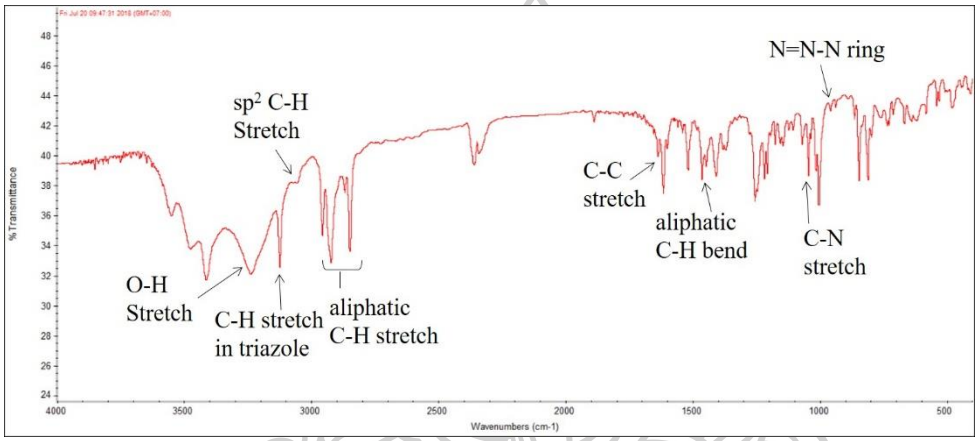
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(hexyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7l)



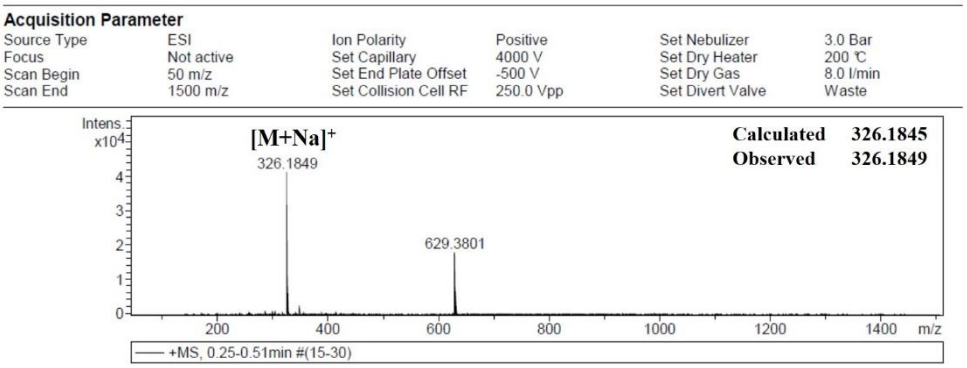
4-(Hydroxyl-(1-(octyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7m)



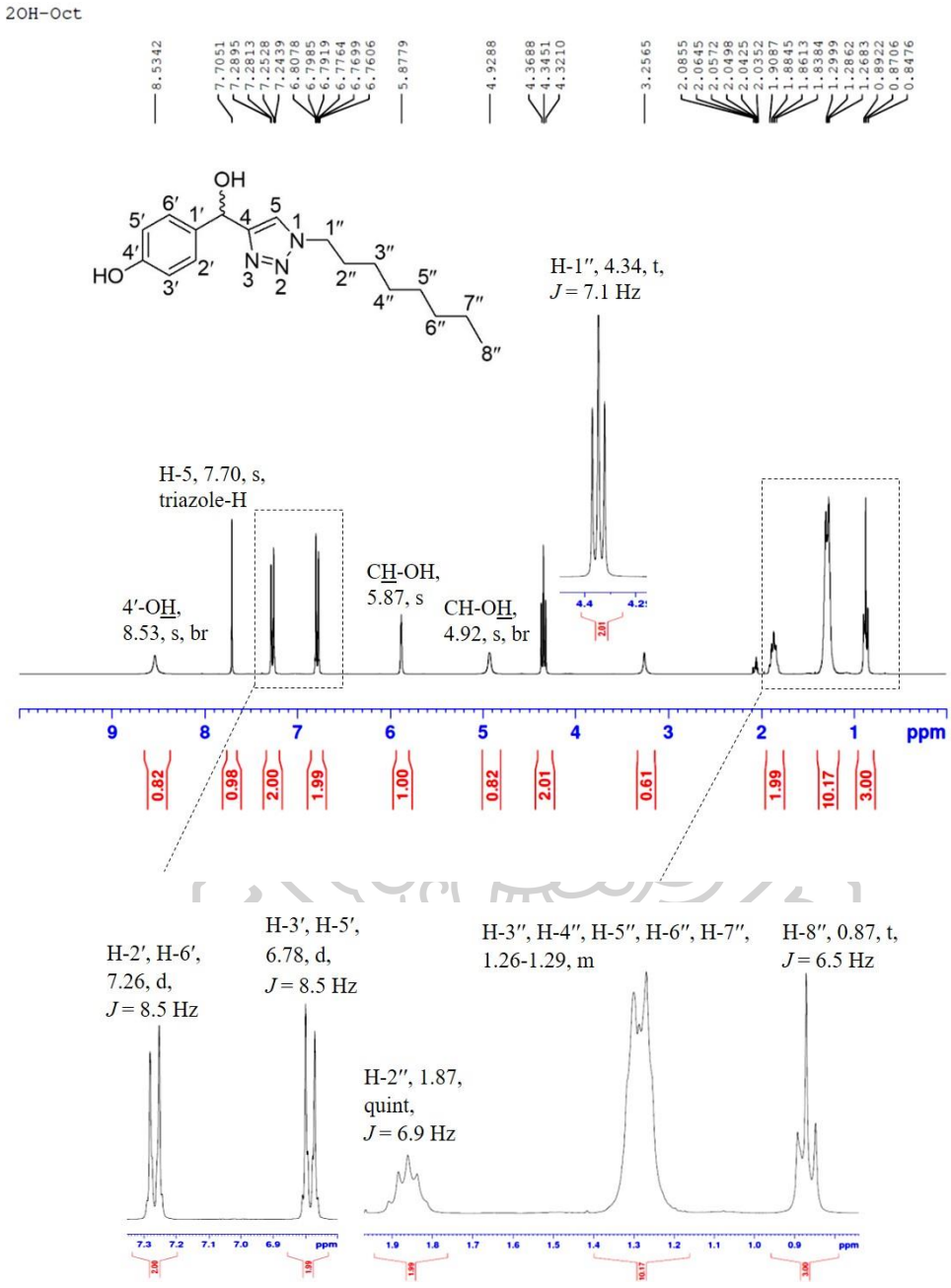
IR spectrum



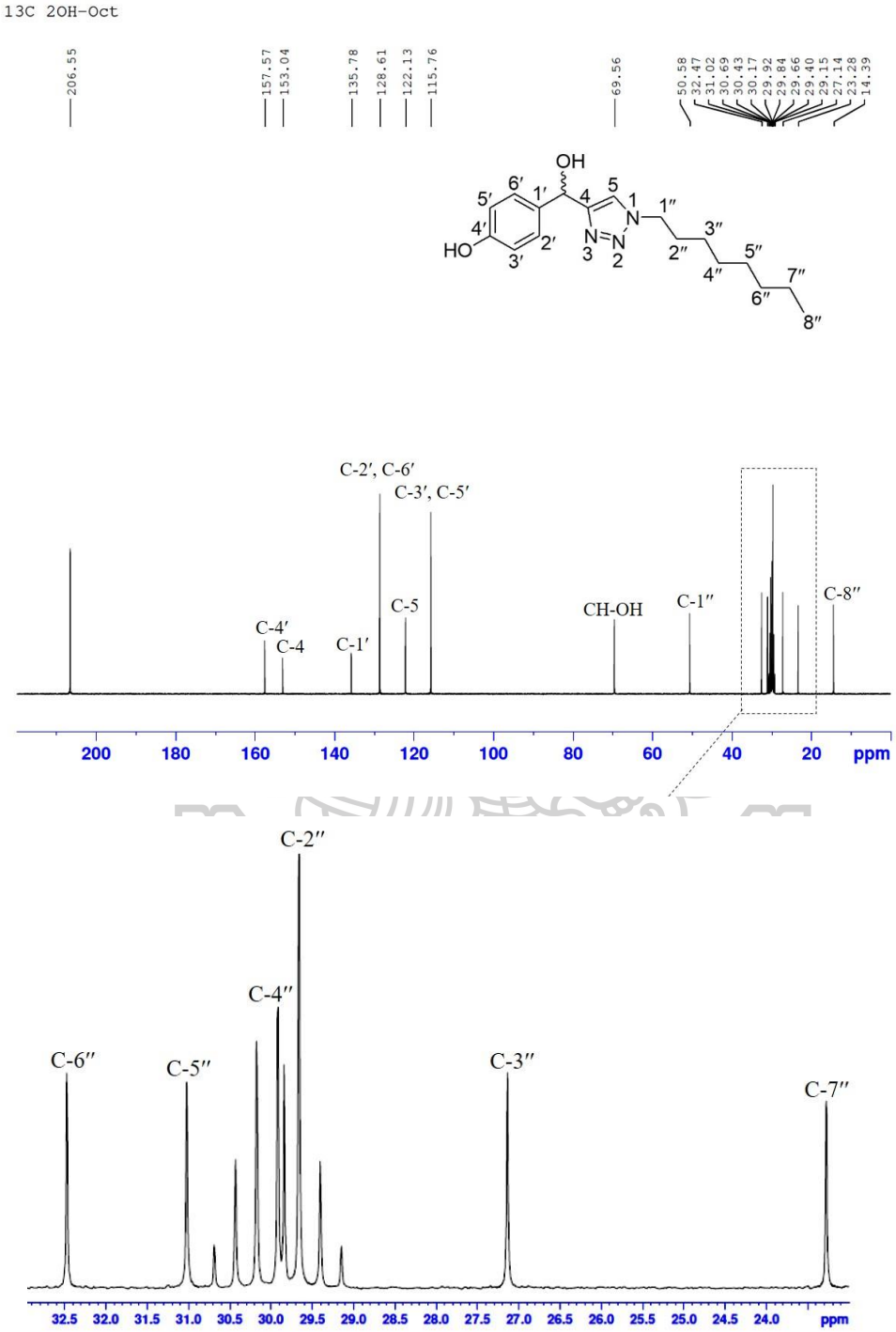
High resolution mass spectrum



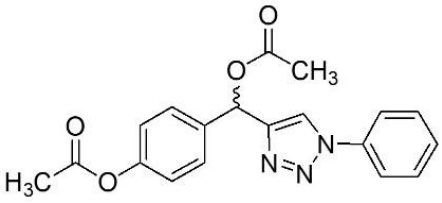
^{1}H NMR (300 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(octyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7m)



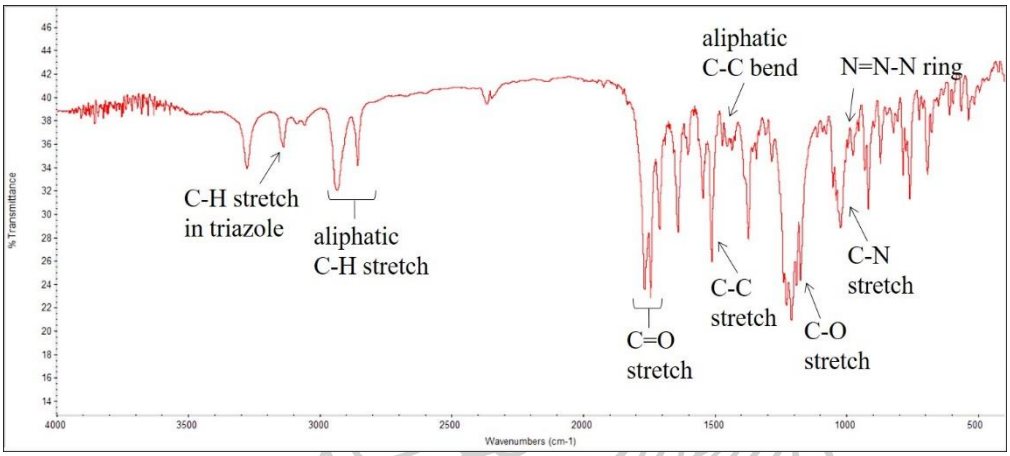
^{13}C NMR (75 MHz, acetone-d_6) of 4-(Hydroxyl-(1-(octyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenol (7m)



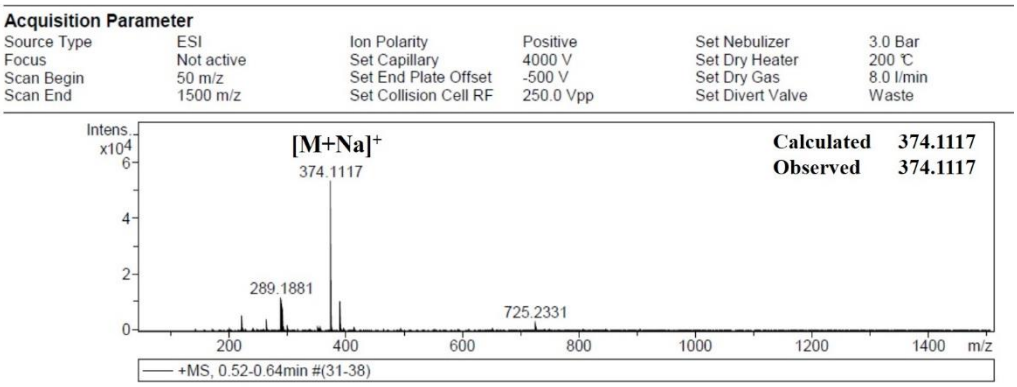
4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl acetate (8)



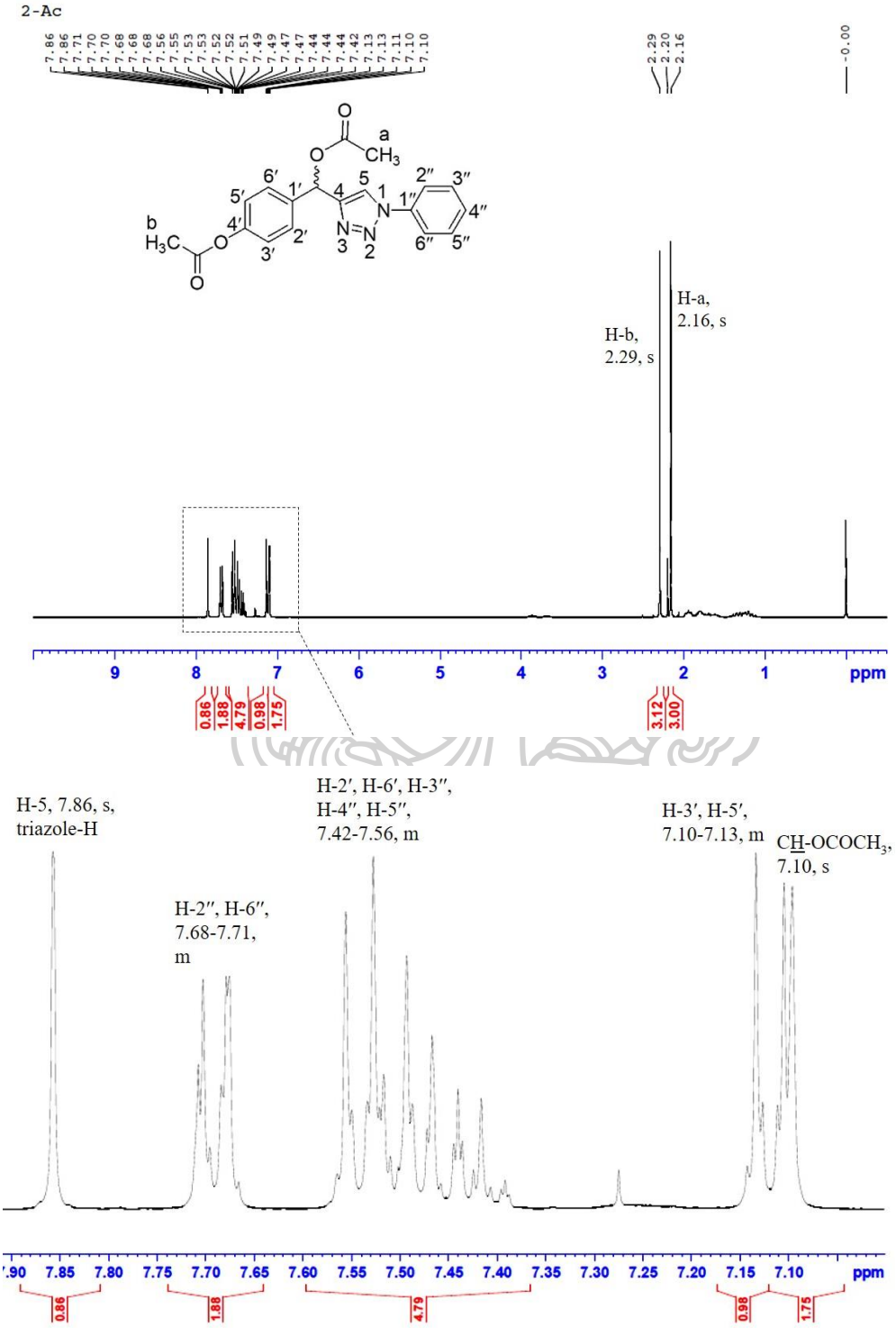
IR spectrum



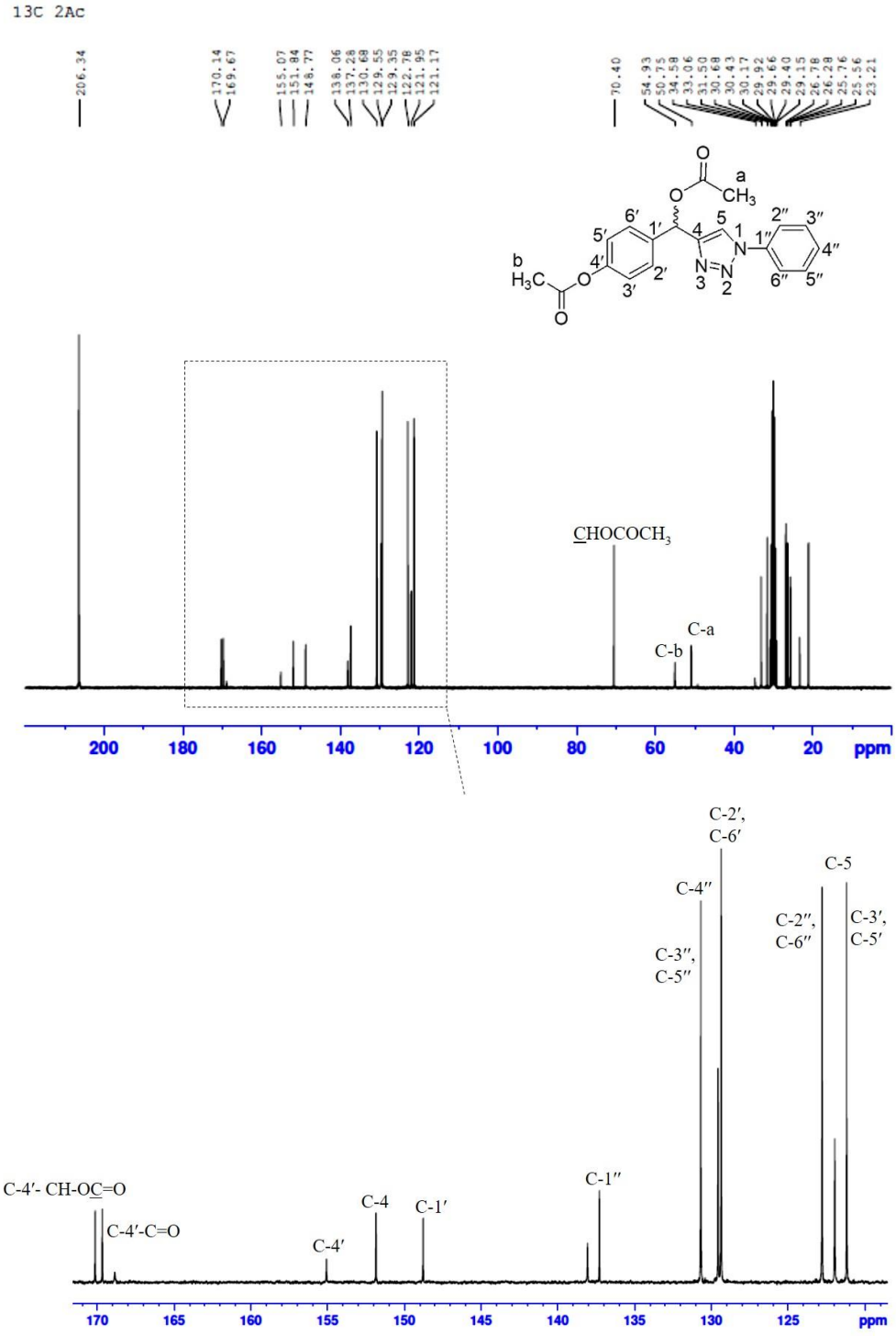
High resolution mass spectrum



^{1}H NMR (300 MHz, $CDCl_3$) of 4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl) phenyl acetate (8)



^{13}C NMR (75 MHz, acetone-d_6) of 4-(Acetyloxy-(1-(phenyl)-1*H*-1,2,3-triazol-4-yl)methyl) phenyl acetate (8)



VITA

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HOME ADDRESS	Yangon, Myanmar