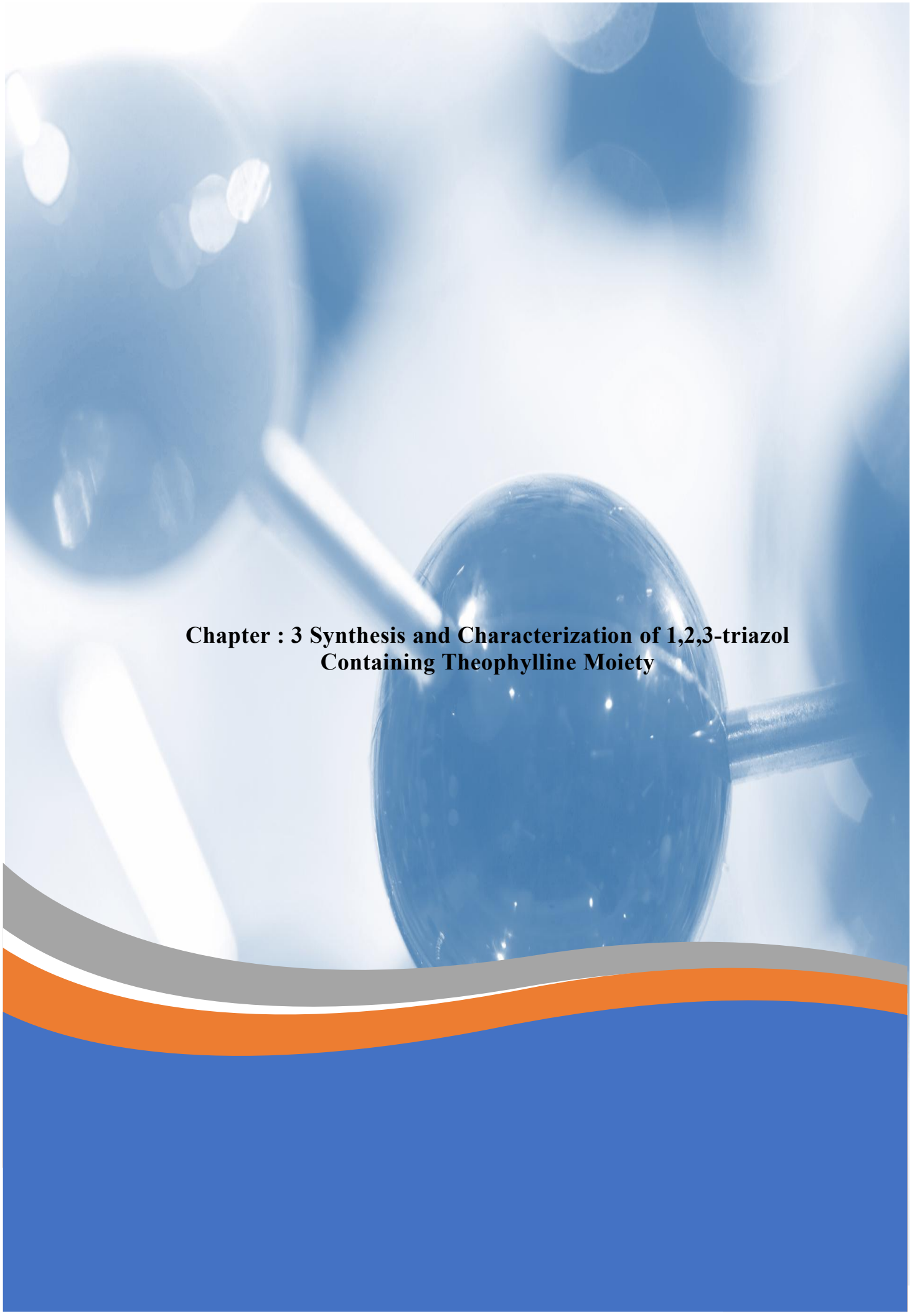


Chapter : 3 Synthesis and Characterization of 1,2,3-triazol Containing Theophylline Moiety

3. Click Synthesis of disubstituted 1,2,3-triazoles:

3.1 Introduction:

1,2,3-Triazole is a five-membered heterocyclic compound containing three nitrogen atoms and two carbon atoms in its ring structure. This class of organic compounds is characterized by its versatile nature and widespread applications in various fields. [124] The triazole ring system is composed of three adjacent nitrogen atoms and a carbon atom, resulting in a unique structure that imparts distinctive properties to the molecule. One of the notable features of 1,2,3-triazole is its significance in medicinal chemistry, where it serves as a fundamental scaffold for the development of pharmaceutical compounds. Many biologically active substances, including some antifungal, antibacterial, and antiviral agents, incorporate the 1,2,3-triazole moiety into their structures. The presence of nitrogen atoms in the triazole ring contributes to the compound's ability to form coordination complexes with metal ions, further expanding its applications in catalysis and materials science.[125]

Additionally, 1,2,3-triazole derivatives exhibit interesting properties in the field of agriculture, where they are utilized as fungicides to control various plant diseases. The effectiveness of these derivatives arises from their ability to inhibit crucial enzymes in fungal cells, disrupting their metabolic pathways and leading to the prevention of fungal growth.[126]

In summary, 1,2,3-triazole is a chemically significant and versatile compound with diverse applications in medicinal chemistry, materials science, and agriculture. Its unique molecular structure, characterized by a five-membered ring containing three nitrogen atoms, underlies its various biological and chemical activities, making it a valuable building block in the synthesis of functional molecules across different disciplines.[127]

Triazole, an essential member of the azole family, is a five-membered heterocyclic compound with the molecular formula $C_2H_3N_3$. This compound exists as an isomeric mixture, comprising both 1,2,3-triazole and 1,2,4-triazole [128] . The distinctive structure of triazole, characterized by a five-membered ring containing three nitrogen atoms, classifies it as a key component within the azole family. Its isomeric nature

contributes to its diverse chemical properties, making it a versatile compound with applications in various fields.

1,2,3-triazole **1,2,4-triazole**

Fig.3.1: Isomeric mixture of triazole

Within this group, 1,2,3-triazole stands out as a fundamental aromatic heterocycle that exhibits notable stability when compared to other organic compounds. This stability is attributed to the distinctive feature of having three closely positioned nitrogen atoms within its structure.

Within 1,2,3-triazole, there are three closely positioned nitrogen atoms, each offering three potential substitution positions. The classification of 1,2,3-triazoles into distinct sub-categories is determined by the specific location of substituents along the ring structure. The potential for substitution at different positions within the ring adds to the structural diversity and versatility of 1,2,3-triazoles.

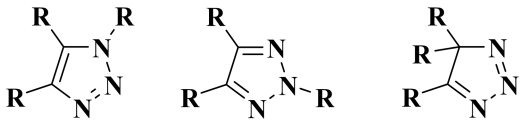
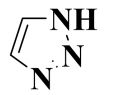
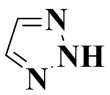


Fig.3.2: Structure of different forms of 1,2,3-triazole

The classification of 1,2,3-triazoles encompasses three primary categories: Monocyclic 1,2,3-triazoles, Benzotriazoles, and 1,2,3-triazolium salts. In the case of Monocyclic 1,2,3-triazoles, the position of the substituent on the nitrogen atom leads to the existence of three isomers—namely, 1*H*-1,2,3-triazole, 2*H*-1,2,3-triazole, and 4*H*-1,2,3-triazole. On the other hand, both benzotriazoles and 1,2,3-triazolium salts manifest in two tautomeric forms, showcasing the structural diversity within this class of compounds.

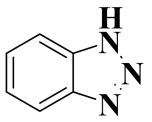


1H-1,2,3-triazole

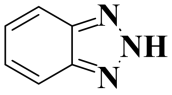


2H-1,2,3-triazole

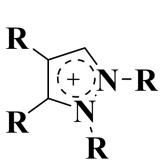
4H-1,2,3-triazole

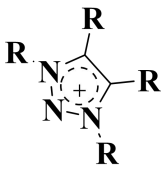


1H-Benzotriazole



2H-Benzotriazole





1,2,3-triazolium salts

Fig.3.3: Classification of 1,2,3-triazoles

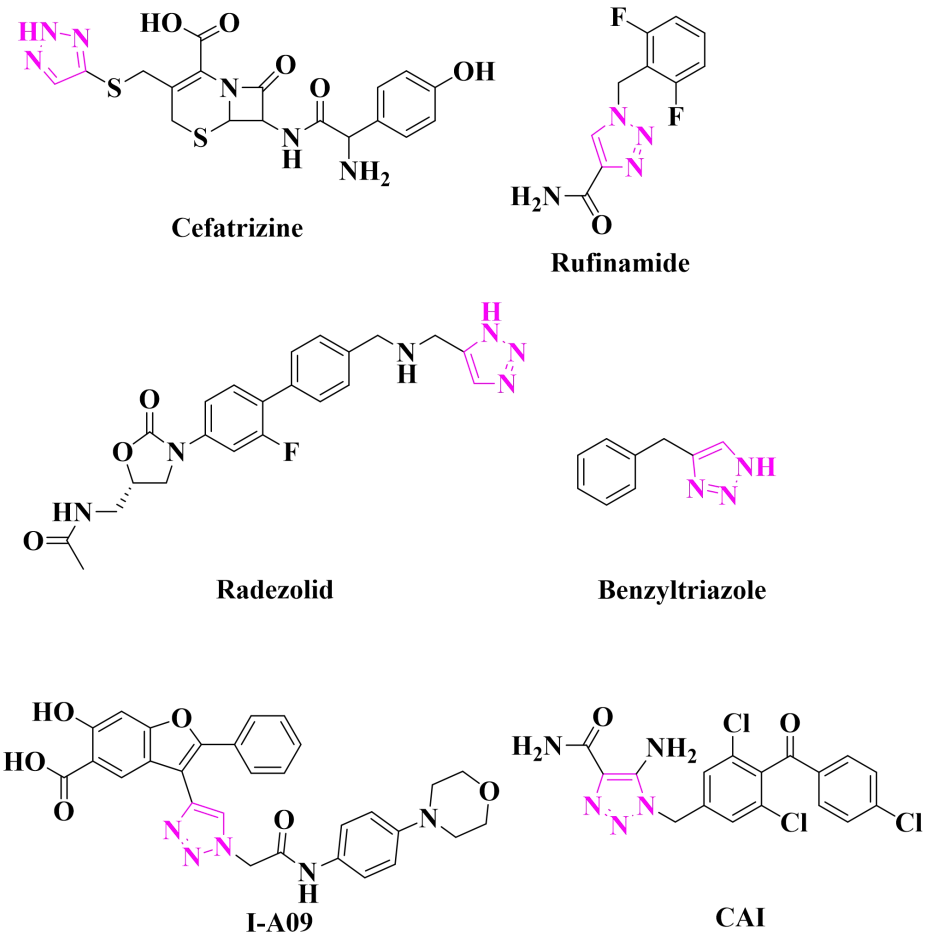


Fig.3.4: 1,2,3-triazole nucleus are currently available in the market

The 1,2,3-triazole moiety plays a crucial role as a significant component in several pharmaceutical drugs, including Rufinamide, Cefatrizine, Radezolid and Benzyltriazole. Rufinamide, specifically, is an antiepileptic drug derived from the amide of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid. It is utilized in the treatment of Lennox-Gastaut syndrome.

Monocyclic 1,2,3-triazoles exhibit notable stability when exposed to hydrolysis, oxidative/reductive conditions, and enzymatic degradation. The ability of triazoles to form hydrogen bonds, engage in dipole-dipole interactions, and participate in π stacking interactions has heightened their importance in medicinal chemistry. [129] This is attributed to their effective binding with various biological targets. In diverse industrial sectors such as agrochemicals, corrosion inhibitors, additives, dyes, polymers, pharmaceuticals, and material sciences, 1,2,3-triazole plays a crucial role as

a synthetic intermediate. Currently, there is a significant focus on 1,4-disubstituted 1,2,3-triazoles and their derivatives due to their wide-ranging biological activities. These compounds exhibit diverse functions, including anticancer [130] , antimicrobial [131] [132] , antioxidant [133] , antitubercular [134] [135] , antimalarial[136], antibacterial[137], anti-inflammatory[138], anticholinesterase[139], antileishmanial [140] , O-GlcNAcase (OGA) inhibition [141] , and antiepileptic properties[142].

The dominance of triazoles as a prominent class of synthetic heterocyclic compounds stems from their structural diversity and the presence of heteroatoms. This assertion is firmly supported by the abundant triazole derivatives documented in the literature, showcasing a myriad of pharmacological activities. A selection of these derivatives is summarized here.

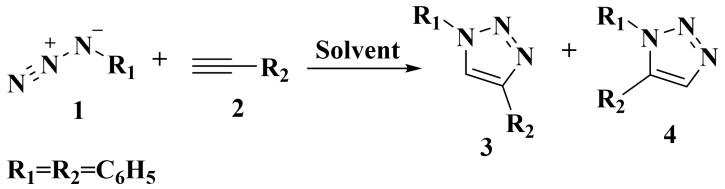
3.2 Common Procedures for 1,2,3-triazole:

In 2001, Karl Barry Sharpless[143] coined the term "Click Chemistry" to describe a set of reactions that possess broad applicability, high efficiency, produce benign byproducts removable without chromatography, exhibit stereospecificity, are simple to execute, and can be carried out in environmentally friendly solvents. This concept emerged concurrently with the growing interest across pharmaceutical, materials, and related industries in generating extensive compound libraries for screening in discovery research. Various reaction types have been identified to meet these criteria, including thermodynamically favored reactions leading to a single product, such as nucleophilic ring openings of epoxides and aziridines, non-aldol type carbonyl reactions like hydrazone and heterocycle formation, additions to carbon-carbon multiple bonds such as oxidative epoxide formation and Michael additions, as well as cycloaddition reactions.

Cycloaddition of azides and alkynes:

In 1893, Michael reported [144], [145], [146] the initial synthesis of 1,2,3-triazoles through the azide-alkyne cycloaddition, utilizing diethyl acetylene dicarboxylate **2** and phenyl azide **1**. During the 1960s, Huisgen conducted a scientific investigation into 1,3-dipolar cycloaddition reactions involving 1,3-dipoles like azides, diazo

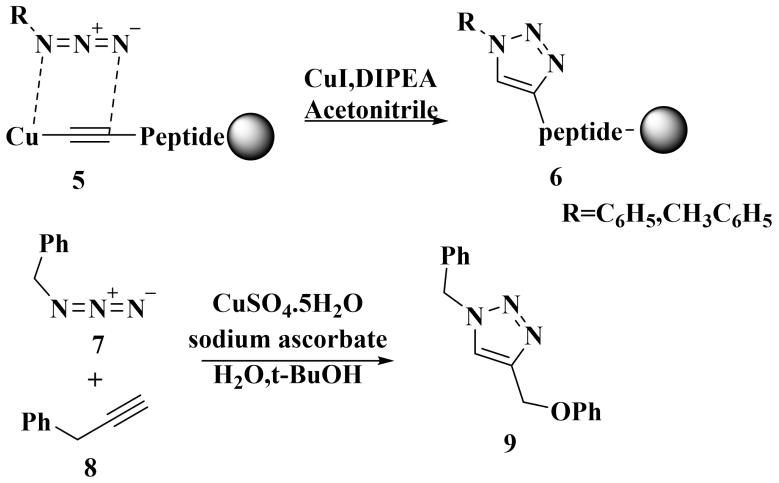
compounds, nitrones, and nitrile oxides, along with various dipolarophiles. Moreover, Huisgen identified that the mechanism of 1,3-dipolar cycloadditions occurs in a step-wise manner rather than through a concerted process. Yet, the non-catalysed reaction between azide and alkyne resulted in a blend of 1,4-disubstituted-1,2,3-triazoles **3** and 1,5-disubstituted-1,2,3-triazoles **4**. Moreover, this reaction takes place under elevated temperatures and requires prolonged reaction times. **(Scheme3.1)**



Scheme3.1

Azidea-alkyne cycloaddition catalysed by Copper(I):

In 2002, researchers Meldal[147] and Sharpless[148] independently documented the synthetic versatility of azide-alkyne cycloaddition employing copper(I) salts as a catalyst, commonly referred to as CuAAC. This method exclusively yielded 1,4-disubstituted-1,2,3-triazole **6** and **9** under mild conditions. The reaction exhibited high yields, eliminating the need for chromatographic purification, showcasing a broad applicability, and producing stereospecific products. **(Scheme3.2)**



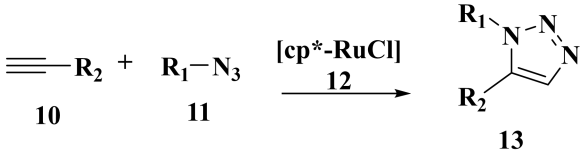
Scheme3.2

Sharpless introduced a highly convenient and practical procedure involving the use of copper(II) sulphate pentahydrate or copper(II) acetate, along with sodium ascorbate as

a mild reductant in an H_2O/t-Butanol mixture at room temperature. This method resulted in high yields without the need for additives.

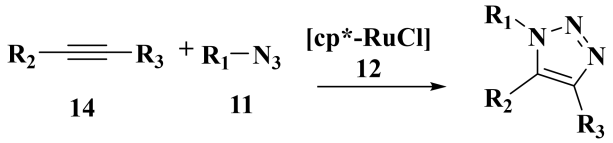
Azide-alkyne cycloaddition catalysed by ruthenium:

Huisgen's 1,3-dipolar cycloaddition [149] resulted in a mixture of 1,4-disubstituted-1,2,3-triazoles and 1,5-disubstituted-1,2,3-triazoles in the absence of a catalyst, whereas CuAAC selectively produced the 1,4-isomer. To address the limited methods for exclusively forming 1,5-disubstituted-1,2,3-triazoles, azide-alkyne cycloaddition was conducted using a ruthenium(II) catalyst (RuAAC) **12**. High regioselectivity and excellent yields of fully substituted 1,2,3-triazoles were achieved using pentamethylcyclopentadienyl ruthenium chloride ([Cp*RuCl]) as the catalyst.**(Scheme3.3)**



10 11 13

$R_1=R_2=CH_3C_6H_5,OCH_3C_6H_5,ClC_6H_5$



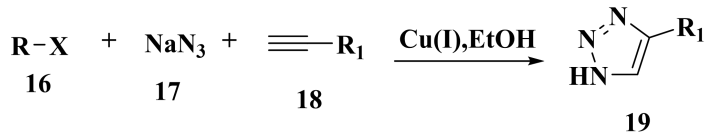
14 11 15

$R_1=R_2=R_3=CH_3C_6H_5,OCH_3C_6H_5,ClC_6H_5$

Scheme3.3

Synthesis of 1,2,3-triazole through azide-alkyne cycloaddition:

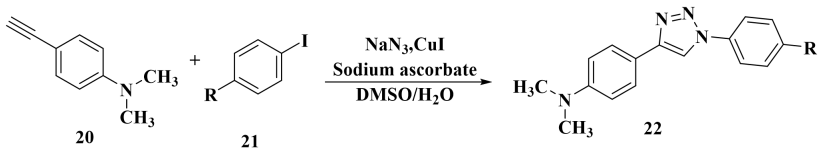
Lee et al., [150] documented the synthesis process, terminal alkynes undergo a reaction with a combination of benzyl or alkyl halides **16** in the presence of sodium azide **17** within ethanol, resulting in the formation of 1,4-disubstituted 1,2,3-triazoles **19** with favorable yields. Copper, immobilized on silica gel functionalized with 3-aminopropyl groups, serves as the catalyst for this reaction. **(Scheme3.4)**



R=CH_3,CH_2CH_3;X=Cl;R_1=$CH_3C_6H_5$,$OCH_3C_6H_5$,ClC_6H_5

Scheme3.4

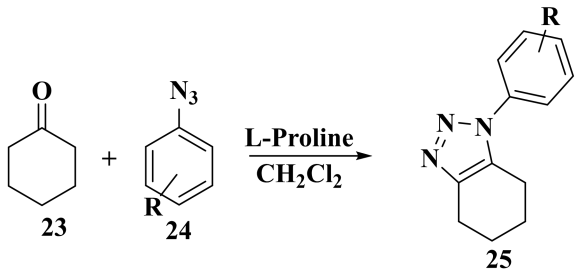
Watzke et al., [151] reported the in-situ generation of phenyl azide via 1-iodo-4-substituted benzene **21**, followed by its reaction with a 4-ethynyl-*N*,*N*-dimethylaniline **20** in the presence of cuprous iodide and sodium ascorbate, results in the formation of *N*,*N*-dimethyl-4-(1-(substituted)-1*H*-1,2,3-triazol-4-yl)aniline derivative **22** with excellent yields.**(Scheme3.5)**



R=CH_3,CH_2CH_3,C_6H_5

Scheme3.5

Belkheira et al.,[152] reported synthesis initiated from Cyclohexanone **23** and various ketones undergo a reaction with 1-azido-4-substituted benzene **24** to produce 1-(4-substituted phenyl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole derivatives **25** in the presence of L-proline, utilizing dichloromethane as the solvent. **(Scheme3.6)**

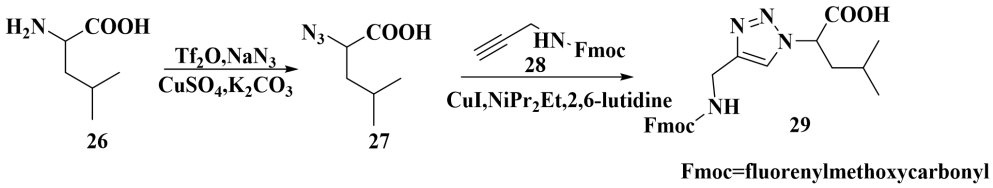


R=H,OCH_3,Br

Scheme3.6

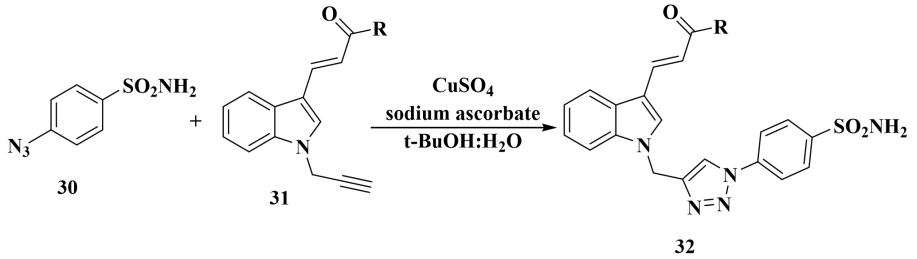
Ingale et al.,[153] reported Leucine **26** reacts with trifluoromethanesulfonic anhydride, sodium azide, and copper sulfate in a basic medium to produce 2-azido-4-methylpentanoic acid **27**. This intermediate **27** reacted with (9*H*-fluoren-9-yl)methyl

prop-2-yn-1-ylcarbamate **28** in the presence of copper(I) iodide, 2,6-lutidine, and *N*,*N*-diisopropylethylamine (Hünig's base), resulting in the formation of 2-(4-(((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)-4-methylpentanoic acid **29**. **(Scheme3.7)**



Scheme3.7

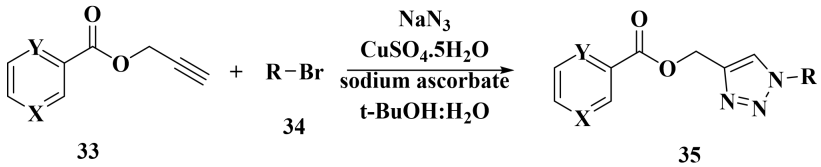
Singh et al., [154] have detailed a collection of novel indolyl chalcone and benzene sulfonamide linked 1,2,3-triazole hybrids, alongside additional derivatives. These compounds were synthesized via a copper-catalyzed 1,3-dipolar cycloaddition reaction. The process involved reacting substituted 3-(1-(prop-2-yn-1-yl)-1*H*-indol-3-yl)prop-2-en-1-one **31** with 4-azidobenzenesulfonamide **30**, yielding 4-(4-((3-(3-oxo-3-(substituted)prop-1-en-1-yl)-1*H*-indol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide derivatives **32**. This synthesis effectively utilized the principles of click chemistry. **(Scheme3.8)**



Scheme3.8

Reddyrajula et al., [155] synthesized a range of pyrazine-linked 1,4-disubstituted 1,2,3-triazole **35** compounds via a copper-catalyzed cycloaddition reaction. 1-Bromo-4-substituted benzene **34** reacts with sodium azide in a BuOH:H_2O solvent mixture at room temperature to form various substituted azides. These azides are then reacted with substituted prop-2-yn-1-yl derivatives **33** in the presence of sodium ascorbate and copper sulfate, resulting in the formation of (1-substituted-1*H*-1,2,3-triazol-4-yl)methyl benzoate derivatives **35**. This process includes substituting the pyrazine

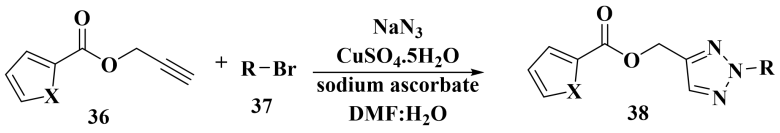
moiety with pyridine and benzene rings, respectively. **(Scheme3.9)**



X=N,CH;Y=N,CH;R=4-CNC$_6$H$_5$,4-FC$_6$H$_5$,4-NO$_2$C$_6$H$_5$,4-NO$_2$C$_6$H$_5$

Scheme3.9

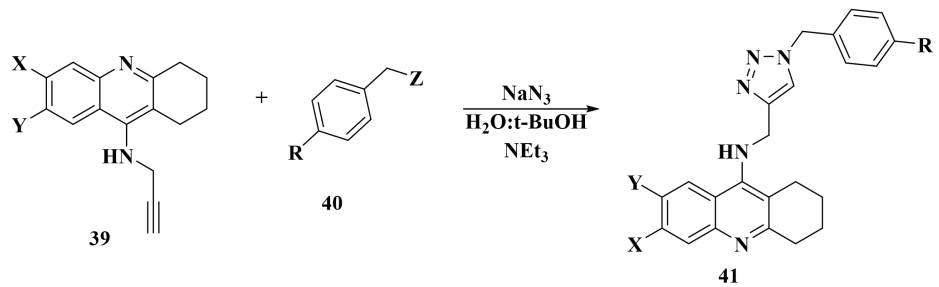
Kaushik et al., [156] conducted the synthesis of ester-linked 1,4-disubstituted 1,2,3-triazoles containing a furyl/thienyl moiety. They achieved this through a one-pot click reaction involving prop-2-yn-1-yl (furan/thiophene)-2-carboxylate **36**, (bromo substituted)benzene **37** and sodium azide to give (2-substituted-2*H*-1,2,3-triazol-4-yl)methyl (furan/thiophene)-2-carboxylate **38**. **(Scheme3.10)**



X=O,S;R=C$_6$H$_5$CH$_2$,C$_6$H$_5$CH$_2$CH$_2$,C$_6$H$_5$CH$_2$CH$_2$CH$_2$

Scheme3.10

Najafi et al.,[157] carried out the synthesis of a series of tacrine 1,2,3-triazole hybrids. The synthesis involved reacting 6 or 7-substituted *N*-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroacridin-9-amine **39** with 1-((chloro/bromo)methyl)-4-substituted benzene **40**. Using Cu(I) as the catalyst, this reaction produced 6 or 7-substituted *N*-((1-(4-ethylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroacridin-9-amine derivatives **41**. **(Scheme3.11)**

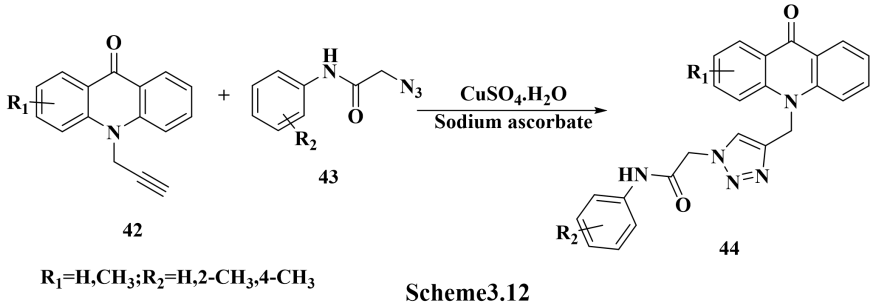


X=Y=H,Cl;Z=Cl,Br;R=Cl,CH$_3$

Scheme3.11

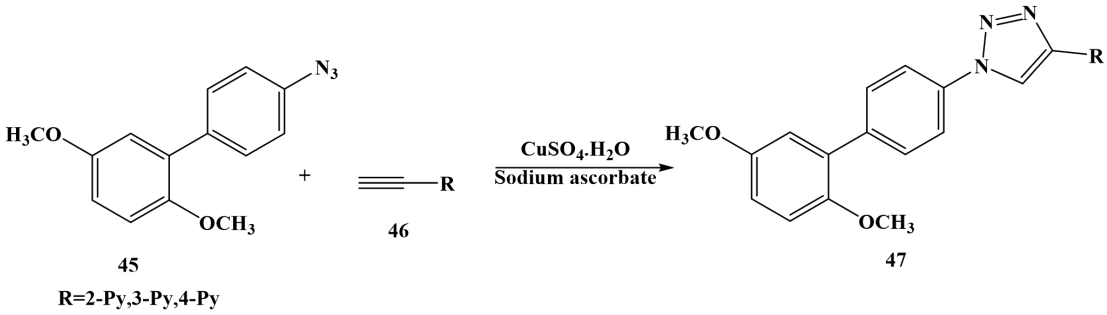
Aarjane et al.,[158] presented a novel approach for synthesizing a series of acridone-

bearing 1,2,3-triazole derivatives. This involved utilizing substituted 10-(prop-2-yn-1-yl)acridin-9(10*H*)-one **42** and 2-azido-*N*-phenylacetamide derivatives **43** in a copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction produced 2-(4-((9-oxoacridin-10(9*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide derivatives **44**, which was carried out using both conventional and microwave-assisted synthetic methods. **(Scheme3.12)**



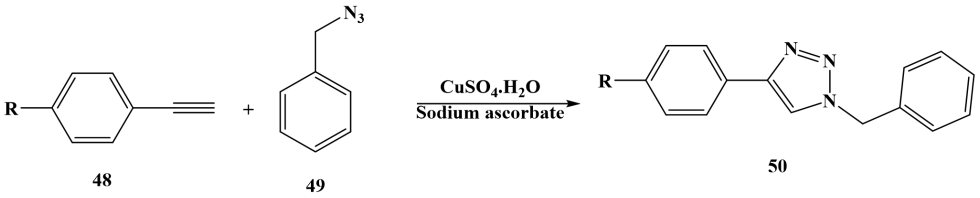
Scheme3.12

Serafini et al., [159] described the synthesis of a group of biphenyl triazoles. This synthesis involved the reaction between 4'-azido-2,5-dimethoxy-1,1'-biphenyl **45** and 4-ethynyl substituted pyridine **46** via a copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction, employing copper sulfate pentahydrate as the catalyst to produced 4-(1-(2',5'-Dimethoxy-[1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazol-4-yl)-substituted pyridine **47**. **(Scheme3.13)**



Scheme3.13

Shin et al., [160] conducted a copper(I)-catalysed azide-alkyne 1,3-cycloaddition (CuAAC) reaction using 1-ethynyl-4-substituted benzene **48** and (azidomethyl)benzene **49**. This reaction was facilitated by the presence of copper sulfate pentahydrate and sodium ascorbate, resulting in the formation of 1-benzyl-4-(substituted)-1*H*-1,2,3-triazole derivatives **50** in an aqueous environment. **(Scheme3.14)**

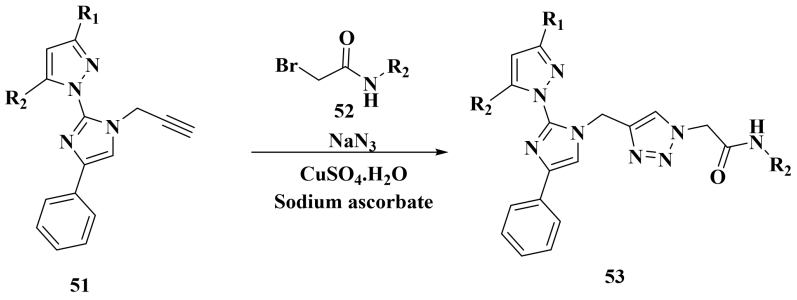


48 49 50

R=H,F,CH_3,OCH_3

Scheme3.14

Punia et al., [161] orchestrated the synthesis of a range of 2-(4-((2-(3-methyl-5-(substituted)-1*H*-pyrazol-1-yl)-4-phenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(substituted)acetamide derivatives **53** through a Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction. This reaction involved 2-bromo-*N*-substituted acetamides **52**, sodium azide, and terminal alkynes containing pyrazole-imidazole moieties 3-methyl-1-(4-phenyl-1-(prop-2-yn-1-yl)-1*H*-imidazol-2-yl)-5-(substituted)-1*H*-pyrazole **51**, in the presence of copper sulfate pentahydrate and sodium ascorbate. **(Scheme3.15)**

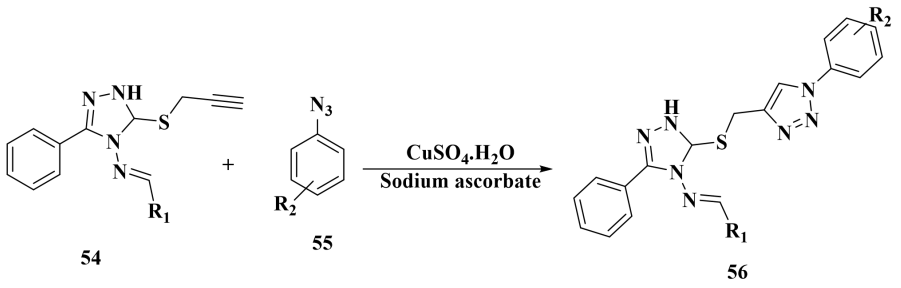


51 53

R_1=H,CH_3;R_2=4-$CH_3C_6H_5$,4-ClC_6H_5,4-$OCH_3C_6H_5$

Scheme3.15

Ashry et al., [162] developed a method for synthesizing hybrids of 1,2,4-triazole containing 1,2,3-triazoles **56**. This involved reacting 1-azido nitrobenzene derivatives **55** with *N*-(3-phenyl-5-(prop-2-yn-1-ylthio)-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)-1-(substituted)methanimine **54** through a 1,3-dipolar cycloaddition reaction, employing copper sulfate as the catalyst and produced *N*-(5-(((1-(nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-3-phenyl-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)-1-(substituted)methanimine **56**. **(Scheme3.16)**

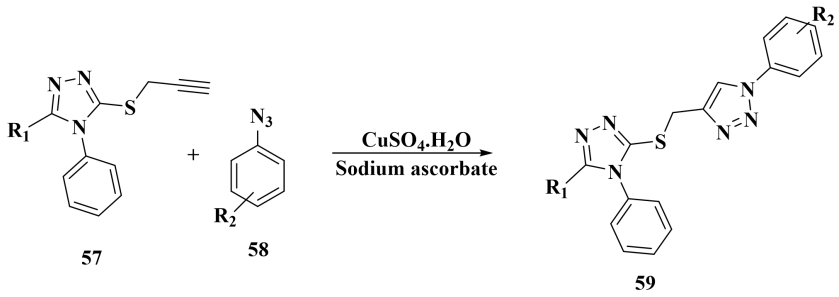


54 55 56

R_1=C_6H_5,4-$CH_3C_6H_5$,4-$OCH_3C_6H_5$,4-$NO_2C_6H_5$,R_2=3-NO_2,4-NO_2

Scheme3.16

sundaramoorthy et al., [163] conducted a Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction involving 1,2,4-triazole-based terminal alkynes 4-phenyl-3-(prop-2-yn-1-ylthio)-5-(substituted)-4*H*-1,2,4-triazole **57** and 1-azido-4-substituted benzene **58**. This reaction yielded 1-(4-substituted)-4-(((4-phenyl-5-(substituted)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazole **59**. **(Scheme3.17)**

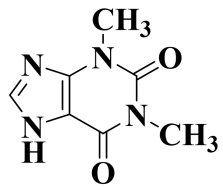


57 58 59

R_1=C_6H_5,4-$CH_3C_6H_5$,4-$OCH_3C_6H_5$,4-$NO_2C_6H_5$,R_2=4-CH_3,4-F,4-Br

Scheme3.17

3.3 Study on Theophylline

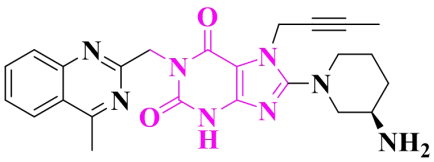


3.4 Introduction:

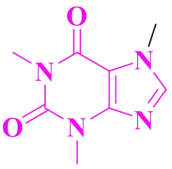
Theophylline is derived from xanthine, a naturally occurring compound found in tea leaves, coffee beans, and cocoa beans. It is available in different formulations, including oral tablets, extended-release capsules, and intravenous (IV)

preparations. [164], [165], [166], [167] Theophylline, a xanthine derivative, holds significant medical importance owing to its versatile properties in the realm of respiratory and cardiovascular health. Primarily employed in the management of chronic respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD), theophylline acts as a bronchodilator, easing airflow by relaxing the smooth muscles in the airways. Its role in treating apnoea of prematurity in premature infants underscores its value in neonatal care, stimulating respiratory centers and reducing episodes of apnoea. Beyond respiratory ailments, theophylline finds application in certain cardiac arrhythmias, specifically atrial fibrillation, where it enhances heart contractions, thus augmenting cardiac output. Additionally, it is employed in cases where COPD leads to pulmonary hypertension, mitigating vascular resistance in the lungs and reducing strain on the heart. Despite its efficacy, theophylline requires careful administration due to its narrow therapeutic window and potential interactions with other medications, necessitating vigilant monitoring and medical supervision. While newer treatments have emerged, theophylline remains a vital option in specific clinical scenarios, offering relief and improving the quality of life for individuals grappling with diverse respiratory and cardiac challenges. Theophylline works by relaxing the smooth muscles in the airways, which helps to improve breathing and relieve symptoms such as wheezing, coughing, and shortness of breath. [168] Theophylline has a complex mechanism of action, which involves blocking certain enzymes called phosphodiesterases and inhibiting the release of inflammatory substances such as histamine and leukotrienes. Additionally, it can also stimulate the respiratory centers in the brain and improve the contractility of the diaphragm, further aiding in the relaxation of the airway muscles. [169] The bronchospasmolytic, [170], [171] anticancer, [172], [173] and circulatory blood system activities of theophylline derivatives at positions 7 and 8 have been studied. The fused systems produced from theophylline have been the subject of extensive research, including structural analysis and synthetic methods but small number of the synthesized heterocyclic compounds demonstrated anti-inflammatory [174], [175],anti-P-388-leukemia[176] and vascular relaxing properties in pharmacological testing.[177], [178], [179]

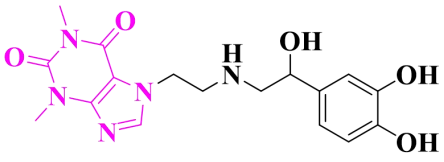
Every day, there is greater difficulty in the discovery and/or improvement of innovative antimicrobial medications due to the persistent threat of bacterial and fungal-caused infectious diseases to global health. It has been observed recently that several harmful bacteria and fungi have become resistant to popular pharmaceuticals used in clinical settings; as a result, it is necessary to enhance the chemo- and/or physiological qualities of medications. [180] Several studies have examined the antibacterial properties of xanthine and their derivatives on a range of microbes, demonstrating the noteworthy efficacy of certain molecules. [181] Theophylline derivatives have been reported to be associated with diverse biological activities. Drug having theophylline nucleus with good activity are shown as below figure.



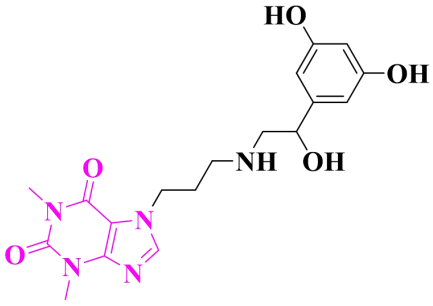
Linagaliptin(anti-diabetic)



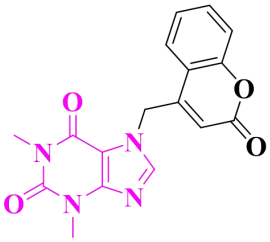
Caffeine(CNS stimulant)



Theodrenaline(cardiac stimulant)



Reproterol(anti-asthma)



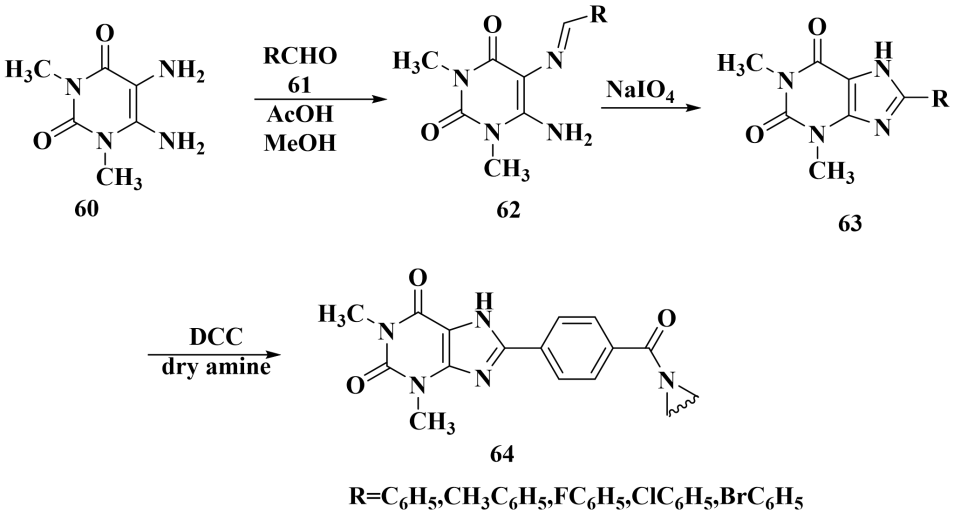
9-[(5,7-dimethyl-2-oxo-2Hchromen-4-yl)methyl]-1,3-dimethyl-3,9-dihydro-1H-purine-2,6-dione (anti-TB)

Fig.3.5: Drugs containing theophylline nucleus

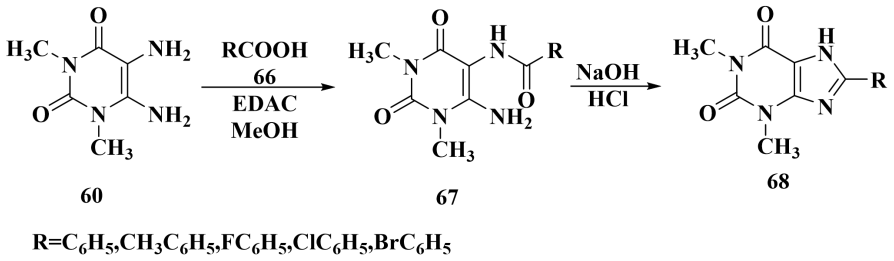
3.5 Common Procedures of Theophylline:

Berk et al.,[182] reported series of 8-(substituted)-1,3-dimethyl-3,7-dihydropurin-2,6-dione **64** and 8-[4-(substitutedcarbamoyl)phenyl]-1,3-dimethyl-3,7-dihydropurin-2,6-dione **68** were synthesized through a two-stage process. In the initial step, commercially available 5,6-diamino-1,3-dimethyl uracil **60** was reacted with substituted aldehydes **61** or substituted carboxylic acids **66** to yield products: 6-amino-5-[substituted methylenamino]-1,3-dimethyl-1*H*-pyrimidine-2,4-dione **62** and

6-amino-5-(substitutedcarbonylamino)-1,3-dimethyl-1*H*-pyrimidine-2,4-dione **67**, respectively. **(Scheme3.18) (Scheme3.19)**

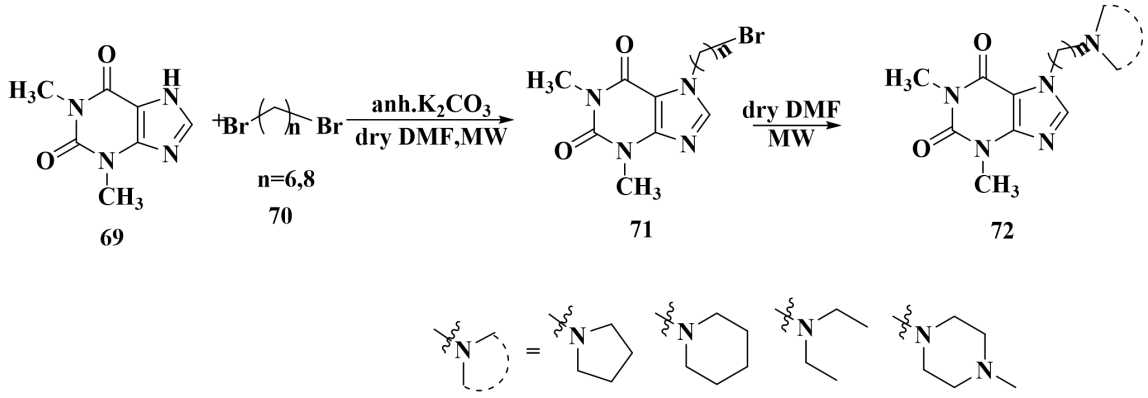


Scheme3.18



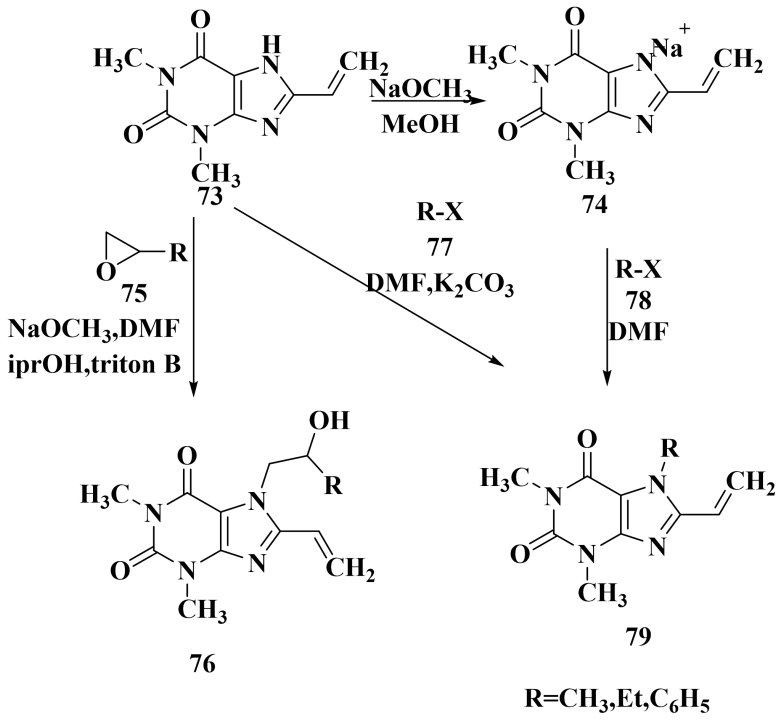
Scheme3.19

Biscussi et al., [183] reported the natural alkaloid 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **69** was reacted with the corresponding dibromo alkane **70** and subsequently with a secondary amine (pyrrolidine, piperidine, diethylamine and 1-methylpiperazine) **72**. All derivatives were obtained in very short reaction times using the microwave reactor and with good to very good yields.**(Scheme3.20)**



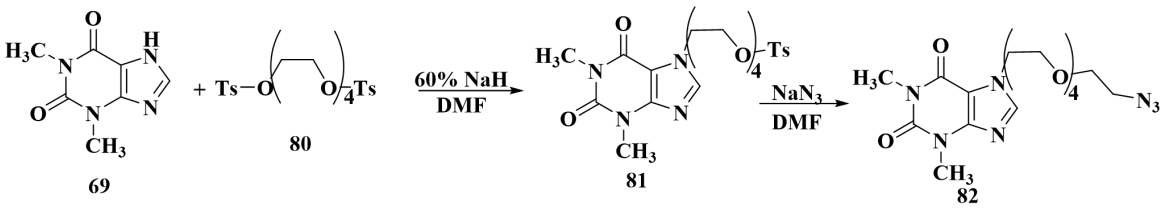
Scheme3.20

Nemekov T et al., [184] reported the alkylation process involved the reaction of 8-vinyl-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **73** with substituted halides in DMF, utilizing potassium carbonate as a catalyst. Alternatively, the sodium salt of the compound underwent alkylation with substituted iodide or hydroxyalkyl iodide, resulting in the formation of 7-alkyl- or 7-(co-hydroxyalkyl)-8-vinyl-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-diones **79**. Furthermore, 2-substituted oxiranes **75** were subjected to reaction with Triton B, leading to the production of 7-(2-hydroxyalkyl)-8-vinyl-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-diones **76**. The broncholytic activity of these compounds was evaluated. **(Scheme3.21)**



Scheme3.21

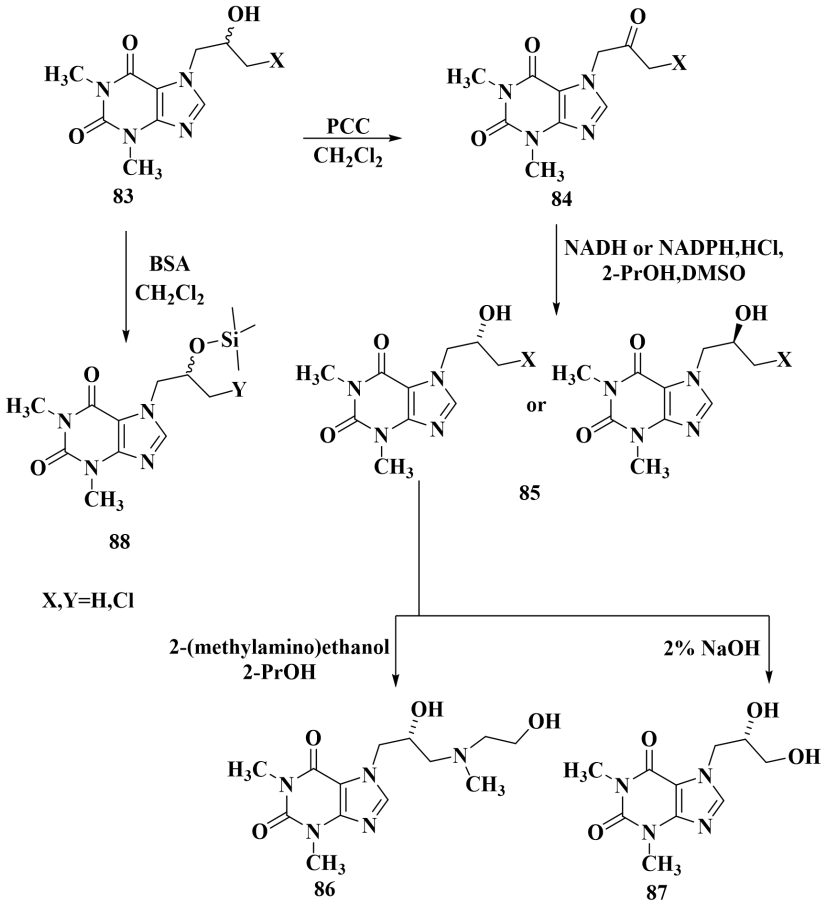
Hierrezuelo et al., [185] reported a series in certain (theophylline) 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione derivatives **69**, the alkenyl substituent facilitates their covalent bonding onto hydrogen-terminated silicon substrate surfaces through hydrosilylation **81**. Another approach involved integrating an azido group into an oligo(ethylene glycol)theophylline derivative **82** to serve as an anchor for tethering the molecules onto ethynyl-presenting surfaces via click reaction. **(Scheme3.22)**



Scheme3.22

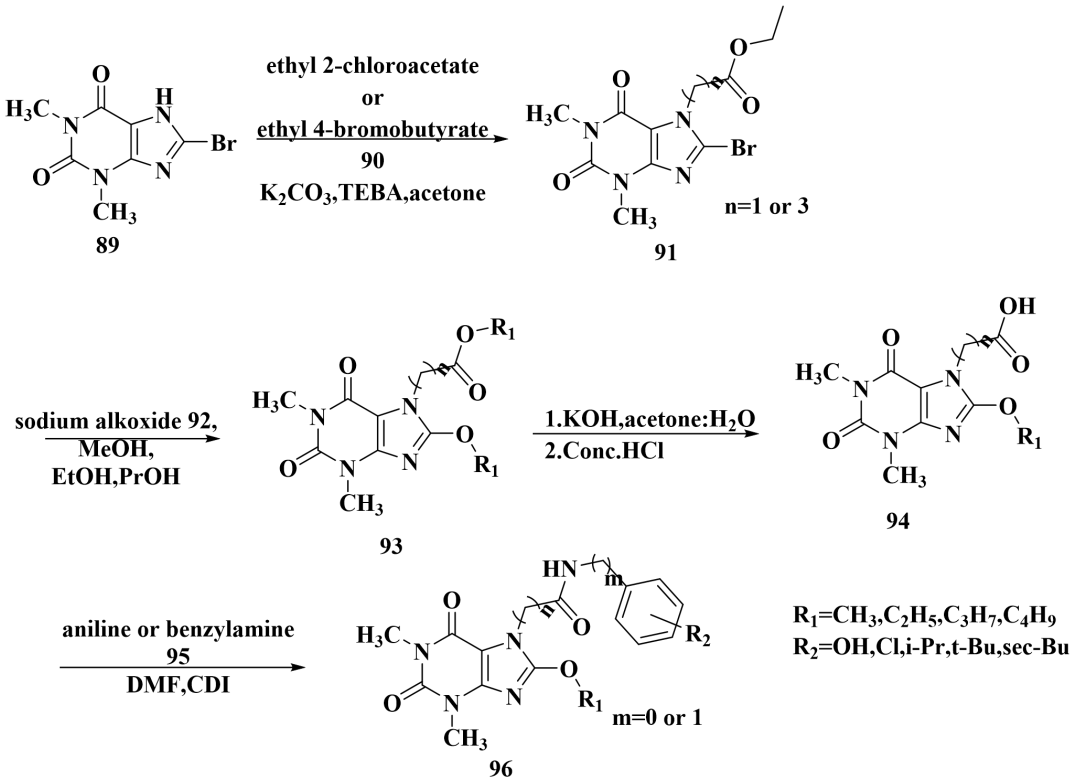
Borowiecki et al., [186] documented Alcohol dehydrogenases have found extensive application in reversible redox reactions involving carbonyl compounds and primary or secondary alcohols, leading to the production of optically pure hydroxyl products with significant added value. Initially The compound 7-(3-chloro-2-hydroxypropyl)-

1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **83** is oxidized using PCC to yield 7-(3-chloro-2-oxopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **84**. This intermediate **84** is then reacted with β-nicotinamide adenine dinucleotide 2′-phosphate reduced tetrasodium salt (NADPH), 2-PrOH, and DMSO in presence of acidic media to produce a racemic mixture of 7-(3-chloro-2-hydroxypropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **85**. Subsequently, compound **85** reacting this mixture with 2-(methylamino)ethanol and 2-PrOH results in (R)-7-(2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **86**. Compound **85** treatment with 2% NaOH yields (S)-7-(2,3-dihydroxypropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **87**. And further 7-(3-chloro-2-hydroxypropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **83** with BSA to give 7-(3-chloro-2-((trimethylsilyl)oxy)propyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **88**.**(Scheme3.23)**



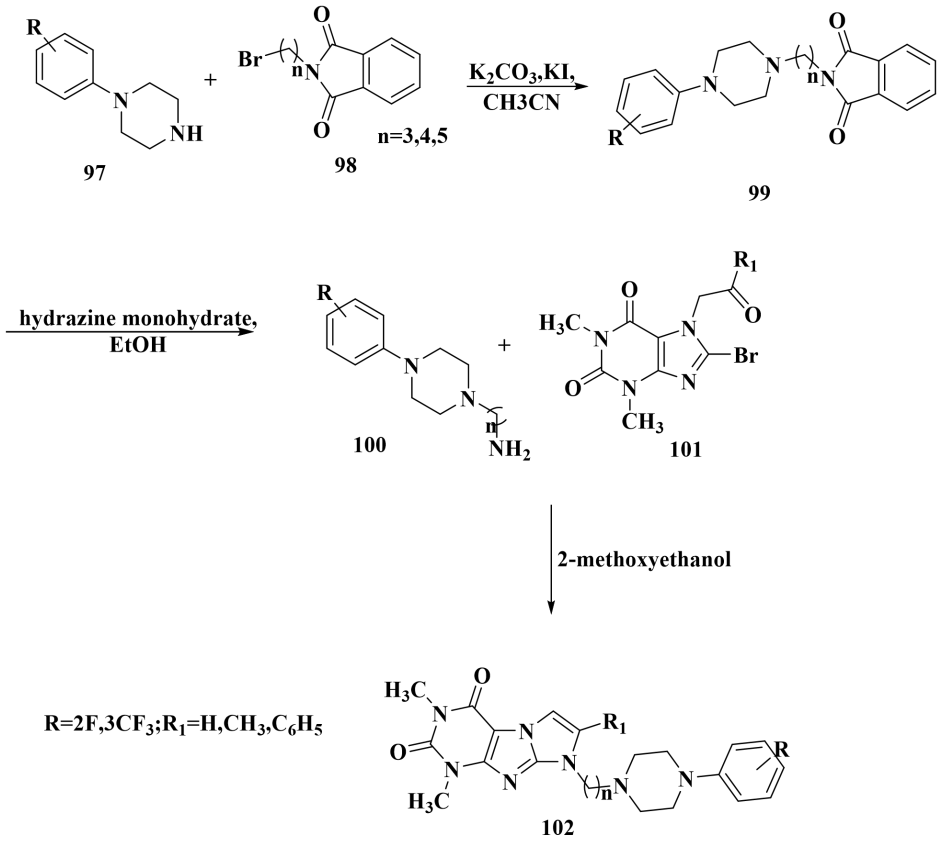
Scheme3.23

Chlon Rzepa et al., [187] reported analgesic and anti-inflammatory activity The designed compound 4-(1,3-dimethyl-2,6-dioxo-8-(1-phenylpropan-2-yl)-1,2,3,6-tetrahydro-7*H*-purin-7-yl)-*N*'-(2,3,4 trihydroxybenzylidene)butanehydrazide **96** were synthesized according to multistep procedure. The synthesis of ethyl 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)acetate **91** was carried out by reacting 8-bromo-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione **89** with ethyl 2-chloroacetate or ethyl 4-bromobutyrate **90**, using K_2CO_3 and TEBA in acetone. The resulting compound **91** was then treated with sodium alkoxide **92** in the presence of the corresponding alcohol to yield butyl 4-(8-butoxy-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)butanoate **93**. This intermediate **93** was further reacted with KOH in an acetone/water mixture to obtain 2-(8-methoxy-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)acetic acid **94**. The acid derivative **94** was then combined with DMF and CDI, followed by the addition of the respective aniline derivative or 2-chlorobenzylamine **95**, resulting in the formation of substituted 4-[8-alkoxy-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl]-*N*-phenylbutanamides **96**. **(Scheme3.24)**



Scheme3.24

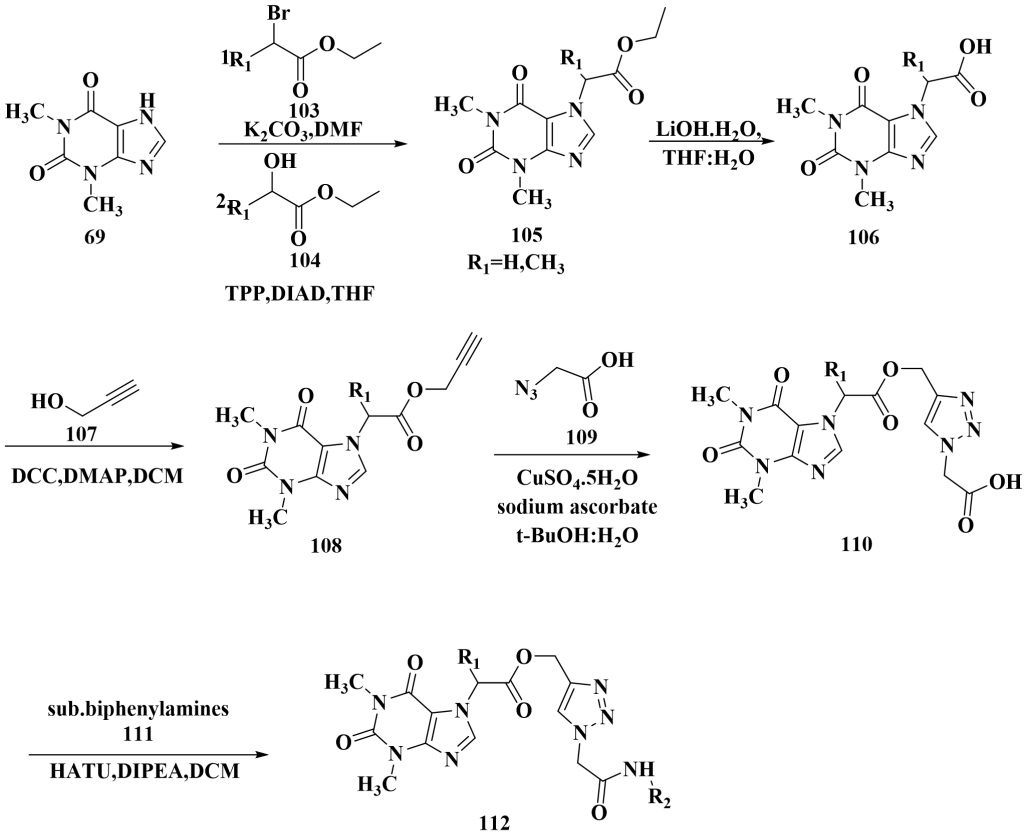
Zagorska et al., [188] reported derivatives of 1,3-dimethyl-(1*H*,8*H*)-imidazo[2,1-f]purine-2,4-dione **102** were synthesized through a multistep process. Initially, 1-(3-trifluoromethyl)phenyl)piperazine **97** was alkylated in a biphasic system using a catalytic amount of potassium iodide and the appropriate 2-(bromoalkyl)-1*H*-isoindoline-1,3(2*H*)-dione **98** in the presence of potassium carbonate in acetonitrile, yielding the corresponding 2-(2-(4-phenylpiperazin-1-yl)substituted)isoindoline-1,3-dione derivatives **99**. These derivatives **99** were then hydrolyzed with hydrazine monohydrate to produce *N*-(amino-substituted)piperazines **100**. Finally, these piperazines **100** were reacted with an 8-bromotheophylline derivative **101** in the presence of ethoxyethanol to form 1,3-dimethyl-(1*H*,8*H*)-imidazo[2,1-f]purine-2,4-dione **102**. Compounds **102** evaluated for serotonin receptor affinity and phosphodiesterase inhibitor activity. **(Scheme3.25)**



Scheme3.25

Ruddarraju et al., [189] worked on the novel set of theophylline derivatives incorporating 1,2,3-triazoles with diverse amide groups has been formulated and synthesized, followed by an assessment of their biological properties as prospective anticancer agents. Theophylline **69** was initially alkylated with ethyl 2-bromoacetate **103** and K_2CO_3 in DMF. Subsequently, theophylline was reacted with ethyl 2-hydroxypropanoate **104** using triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD) in a Mitsunobu reaction to produce ethyl 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propanoate derivatives **105**. These ester **105** compounds were hydrolyzed with $LiOH{\cdot}H_2O$ in a THF and water mixture to yield 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propanoic acid **106**. The acid derivatives **106** were then coupled with propargyl alcohol **107** using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to form prop-2-yn-1-yl 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-

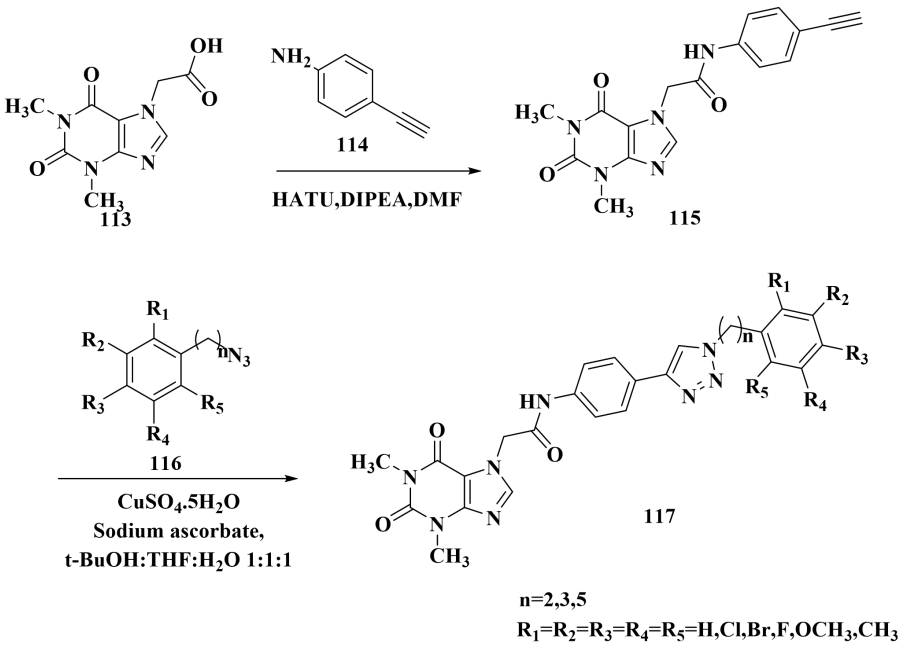
yl)propanoate **108**. These propanoate derivatives **108** were further reacted with 3-azidopropanoic acid **109** in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in t-BuOH and water to produce 2-(4-(((2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propanoyl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetic acid derivatives **110**. Finally, these derivatives **110** were coupled with various aliphatic cyclic amines or biphenyl amines **111** using the reagent 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate (HATU) and base *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane to obtain the desired final compounds, specifically (1-(2-(cyclohexylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propanoate derivatives **112**. **(Scheme3.26)**



Scheme3.26

R_1=H, CH_3; R_2= cyclohexyl, cyclopropyl, cyclobutyl, morpholine

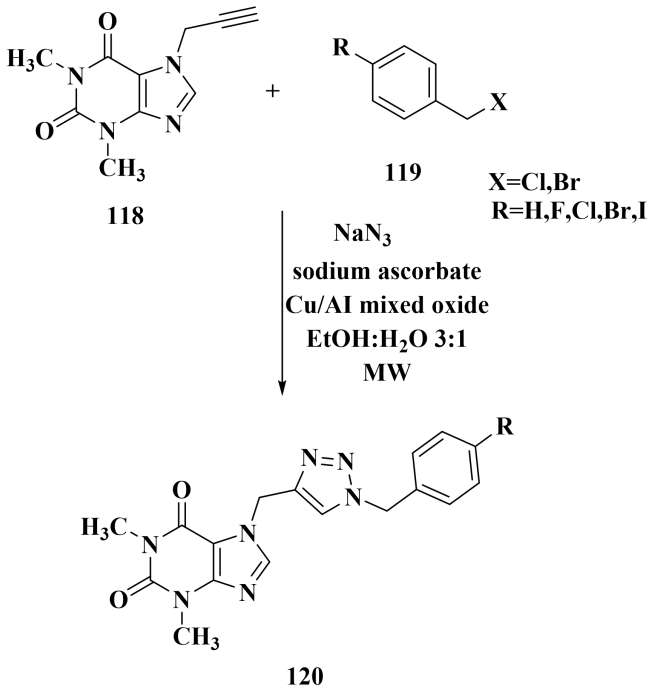
Ye et al., [190] documented a series of theophylline derivatives featuring the 1,2,3-triazole ring were meticulously designed and synthesized, followed by an assessment of their antiproliferative effects on different types of cancer cells. 2-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)acetic acid **113** was reacted with 4-ethynylaniline **114** using HATU (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate) and *N*,*N*-diisopropylethylamine (DIPEA) in DMF to form 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)-*N*-(4-ethynylphenyl)acetamide **115**. This acetamide derivative **115** was then reacted with (azidomethyl)substituted benzene **116** in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in a solvent mixture of t-BuOH, THF, and H2O (1:1:1) to yield *N*-(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)acetamide derivatives **117**. **(Scheme3.27)**



Scheme3.27

Espinoza-Vazquez et al., [191] presents the design and synthesis of a range of theophylline derivatives incorporating 1,2,3-triazole functionalities. The corrosion inhibition properties of these novel triazole-theophylline compounds were investigated by examining the corrosion of API 5 L X52 steel in a 1M HCl environment. 1,3-Dimethyl-7-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione **118**

was initially reacted with (azidomethyl)substituted benzene to from (chloromethyl)substituted benzene **119**. This intermediate was then subjected to a reaction in the presence of sodium ascorbate and a Cu/AI mixed oxide catalyst in an EtOH:H_2O (3:1) mixture under microwave conditions. This procedure yielded 7-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione derivatives **120**. **(Scheme3.28)**



Scheme3.28

Theophylline, a xanthine derivative, has garnered considerable interest in recent literature, particularly regarding its conjugation with 1,2,3-triazole derivatives. This class of compounds exhibits diverse pharmacological activities, ranging from antimicrobial to anticancer properties, thus enhancing the therapeutic potential of theophylline. Studies have shown that the incorporation of 1,2,3-triazole moieties into theophylline molecules can impart improved pharmacokinetic profiles, increased solubility, and enhanced target specificity. Additionally, the conjugation of theophylline with 1,2,3-triazole derivatives has been explored as a strategy to overcome drug resistance mechanisms and to minimize adverse effects associated with traditional theophylline formulations. These findings underscore the significance of theophylline-1,2,3-triazole conjugates as promising candidates for the development of novel therapeutic agents with broader applications across various medical domains.

3.6 Result and Discussion:

A series of novel substituted 2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamides (7a–7o) were successfully synthesized via a multistep route beginning from commercially available theophylline. The key intermediate, 1,3-dimethyl-7-(prop-2-yn-1-yl)-3,7-dihydro-1H-purine-2,6-dione (3), was obtained by N-propargylation of theophylline using propargyl bromide in the presence of anhydrous potassium carbonate in DMF at room temperature. In parallel, substituted 2-azido-N-phenylacetamides (6a–6o) were synthesized through a two-step procedure involving acetylation of substituted anilines followed by azidation with sodium azide. A copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) was employed to couple compound (3) with azides (6a–6o), affording the final triazole-linked purine derivatives (7a–7o) in excellent yields ranging from 86% to 95%.

The structural integrity of the synthesized compounds was confirmed through a combination of spectroscopic techniques, including IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. IR spectra consistently displayed characteristic absorptions for N–H (around 3310–3495 cm^{-1}), aromatic C–H stretching (3000–3100 cm^{-1}), carbonyl groups (amide and purine C=O stretching at 1640–1700 cm^{-1}), and triazole/aromatic

C=C vibrations (around 1470–1550 cm^{-1}).

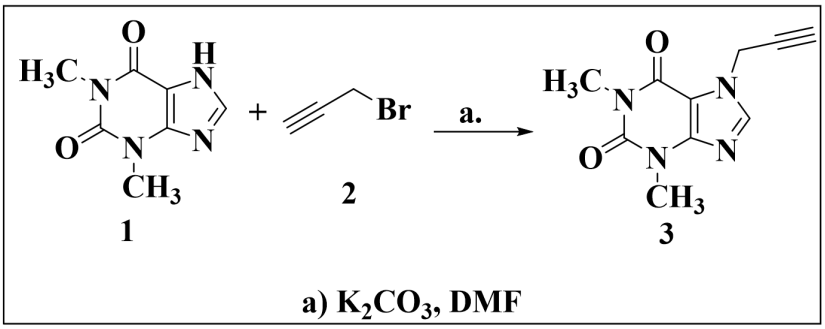
In the ^{1}H NMR spectra, all compounds showed two prominent singlets around δ 3.20–3.45 ppm corresponding to the N-methyl groups of the theophylline moiety. The methylene protons bridging the purine and triazole rings appeared consistently as singlets near δ 5.28–5.61 ppm. The singlets at δ 8.14–8.21 ppm were attributed to the triazole proton, while the N–H proton of the acetamide group was observed as a downfield singlet in the range δ 10.31–10.58 ppm. Aromatic protons exhibited multiplet or doublet signals between δ 6.87–7.58 ppm depending on the substitution pattern.

^{13}C NMR spectra confirmed the expected carbon environments, with resonances for methyl (δ ~27–30 ppm), methylene (δ ~41–52 ppm), and aromatic and triazole carbons distributed in the δ 105–165 ppm range. These assignments supported the incorporation of all key functional groups and molecular frameworks.

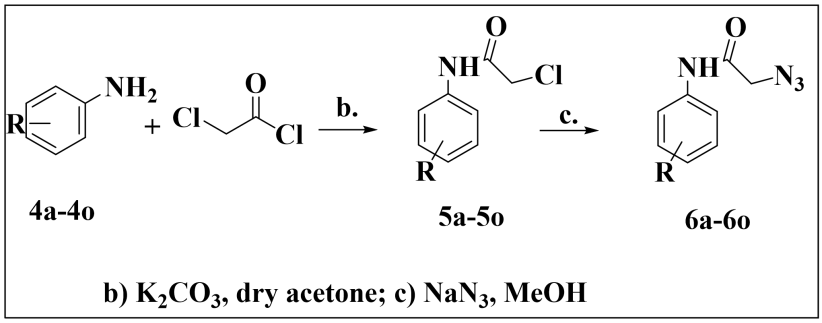
Mass spectrometry further confirmed the molecular weights of all final compounds, with molecular ion peaks [M^{+}] matching the calculated values. Elemental analysis results were also in close agreement with theoretical values, substantiating the high purity of the synthesized compounds.

In conclusion, the synthetic methodology proved efficient and reproducible, yielding structurally well-characterized target molecules. The spectral analyses strongly support the successful construction of the desired purine-triazole-acetamide hybrids, which may hold promise for further evaluation in pharmaceutical or biological studies.

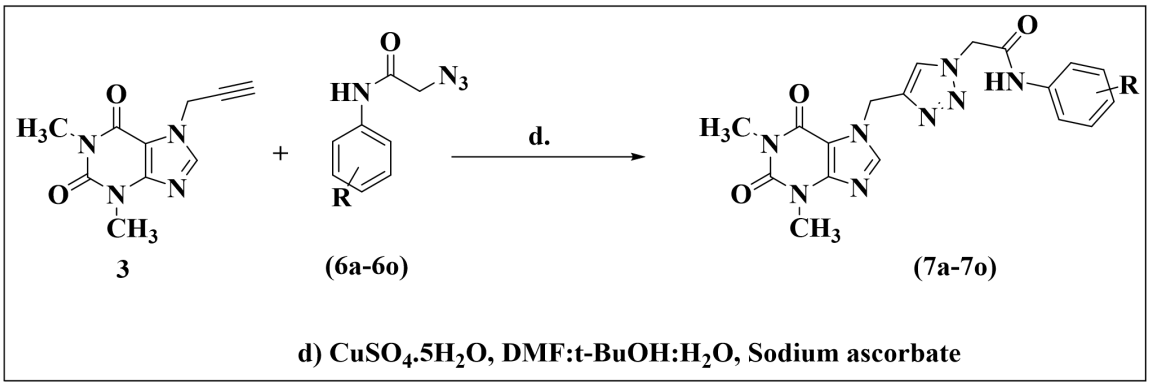
3.7 Reaction Scheme:



Scheme 1 : Synthesis of 1,3-dimethyl-7-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



Scheme 2: Synthesis of Substituted 2-azido-*N*-phenylacetamide



Scheme 3: Synthesis of Substituted 2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide

3.8 Physical Characteristics:

Table:3.1 physical characteristics of synthesized compound

Entry	Compound code	R	Molecular formula	Molecular weight	M.P. in ^{o}C	Yield (%)
1	7a	H	$C_{18}H_{18}O_3N_8$	394.40	238-240	95
2	7b	4-Me	$C_{19}H_{20}O_3N_8$	408.42	231-233	90
3	7c	4-OMe	$C_{19}H_{20}O_4N_8$	424.42	239-241	86
4	7d	4-Cl	$C_{18}H_{17}O_3ClN_8$	428.84	241-243	89
5	7e	4-F	$C_{18}H_{17}O_3FN_8$	412.39	243-245	91
6	7f	4-Br	$C_{18}H_{17}O_3BrN_8$	473.29	261-263	87

7	7g	2,4-Me	$C_{20}H_{22}O_3N_8$	422.45	249-251	80
8	7h	3-Cl	$C_{18}H_{17}O_3ClN_8$	428.84	256-258	81
9	7i	2-OMe	$C_{19}H_{20}O_4N_8$	424.42	251-253	80
10	7j	2-Me	$C_{19}H_{20}O_3N_8$	408.42	253-255	82
11	7k	3-Me	$C_{19}H_{20}O_3N_8$	408.42	229-231	81
12	7l	3-Ome	$C_{19}H_{20}O_4N_8$	424.42	223-225	83
13	7m	3-Cl,4-F	$C_{18}H_{16}O_3FClN_8$	446.83	253-255	82
14	7n	2,4-F	$C_{18}H_{16}O_3F_2N_8$	430.38	256-258	84
15	7o	3,4-Cl	$C_{18}H_{16}O_3ClN_8$	463.28	253-255	82

All compounds are pale yellow solid.

3.9 Conclusion:

In this study, we successfully synthesized and characterized a series of 1,2,3-triazole derivatives containing the theophylline moiety using click chemistry. The synthetic approach employed, leveraging the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, proved to be highly efficient and reliable, yielding high amounts of the target compounds with excellent regioselectivity. Thorough spectral analysis, including ^{1}H NMR, ^{13}C NMR, and mass spectrometry, confirmed the structural integrity and composition of the synthesized compounds. The successful attachment of the 1,2,3-triazole ring to the theophylline core was validated, ensuring the desired chemical structures were achieved. The use of click chemistry facilitated a straightforward and modular synthesis, demonstrating the versatility of this approach in constructing complex molecules with potential pharmacological significance. The introduction of the triazole ring onto the theophylline scaffold enhances the structural diversity and potentially the biological activity of these derivatives.

Overall, the successful synthesis and detailed characterization of these 1,2,3-triazole-theophylline derivatives underscore the effectiveness of click chemistry in medicinal chemistry applications. These novel compounds hold promise for further investigation

in drug discovery and development, warranting additional studies to explore their biological activities and therapeutic potential.

3.10 Experimental Section:

3.10.1 Materials and methods

The experiment utilized reagents procured from reputable suppliers such as Sigma-Aldrich and Spectrochem chemicals, which were directly employed without any purification steps. Thin-layer chromatography (TLC) on silica gel-G plates (G60 F254, E-Merck Co.) was employed to monitor the reaction progress, with visualization under UV light. The melting points of synthesized compounds were determined using open capillaries and remained uncorrected. Infrared (IR) spectra were recorded using an FT-IR-8400 instrument, with wavenumbers expressed in cm^{-1} and potassium bromide (KBr) as the matrix. Nuclear magnetic resonance (NMR) spectra, including ^{1}H NMR at 400 MHz and ^{13}C NMR at 101 MHz, were acquired on a Bruker Avance 400MHz spectrometer. Chemical shifts were reported in δ ppm relative to the solvent DMSO-d^6, with tetramethylsilane (TMS) used as the internal reference. Mass spectra were obtained using ultraperformance liquid chromatography coupled with mass spectrometry (LC/MS) employing electrospray ionization in positive ion mode, covering a mass range from 100 to 1500 Da with a cone voltage set at 30 V.

3.10.2 General Procedures:

General procedure for 1,3-dimethyl-7-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione(3):

A mixture of 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione(1) (theophylline) (10 mmol) and Potassium carbonate (K_2CO_3) (10 mmol) were dissolved in 10 mL of dimethylformamide (DMF). After stirring the mixture for 15 minute at room temperature, to the solution of propargyl bromide(2) (10 mmol) was added dropwise. The reaction mixture was then refluxed at 80°C for 2h, Once the reaction was complete, the mixture was cooled to room temperature and poured into ice slowly.

The resulting solid product was isolated by filtration, washed with water, and subsequently dried in a refrigerator overnight to give solid 1,3-dimethyl-7-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione(3) as product **(Scheme1)**. [192]Yield: 93%

General procedure for substituted 2-chloro-*N*-phenylacetamide derivatives(5a-5o):

A mixture of substituted anilines(4a-4o) (10 mmol) and Potassium carbonate (K_2CO_3) (1 mmol) were dissolved in dry acetone. The reaction mixture was stirred for 10 minute at 0°C. Chloroacetylchloride (10 mmol) was then added dropwise while maintaining 0°C temperature. The reaction mixture was stirred at room temperature for 2 hours. The reaction progress was observed through TLC until it was complete, and the purity of the products was evaluated using TLC with a mobile phase consisting of a mixture of ethyl acetate and hexane. the mixture was slowly poured into ice-cold water. The resulting solid product was collected by filtration and washed successively with water and n-hexane. The collected solid product was dried in a refrigerator overnight to give substituted 2-chloro-*N*-phenylacetamide (5a-5o)**(Scheme2)**.[193] Yield:96%

Note: Anhydrous magnesium sulphate ($MgSO_4$) is effective in absorbing water and used as a drying agent for acetone.

General procedure for derivatives of substituted 2-azido-*N*-phenylacetamide(6a-6o):

substituted 2-chloro-*N*-phenylacetamide derivative(5a-5o) (10 mmol) was dissolved in 10 mL of DMF. Sodium azide (NaN_3) (10 mmol) was added portion-wise to the solution. The reaction mixture was stirred at room temperature 3h. Upon completion, the reaction mixture was slowly poured into ice-cold water. The resulting solid product was collected via filtration and washed with water followed by n-hexane. The collected solid product was then dried in a refrigerator overnight, avoiding the use of an oven to give substituted 2-azido-*N*-phenylacetamide derivatives(6a-6o)**(Scheme2)**.[194] Yield:92%

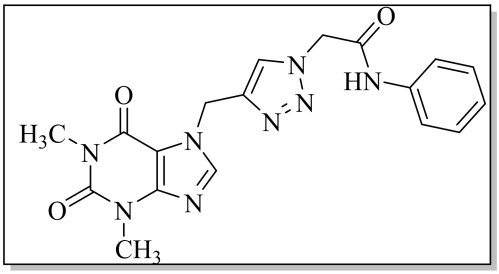
General procedure for novel substituted 2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-

tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide(7a-7o):

An equimolar amount (0.005 mol) of substituted 2-azido-*N*-phenylacetamide(6a-6o) (1 gm) and 1,3-dimethyl-7-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3) (1.23 gm) were combined. A solvent mixture of DMF:t-BuOH:H_2O (2:2:1) was added to the flask. Catalytic amounts of sodium ascorbate and $CuSO_4{\cdot}5H_2O$ solution were added into the reaction mixture. (Wang et al., 2010) Following addition, the reaction mixture was agitated for 3 hours at ambient temperature with using thin-layer chromatography(TLC) for monitoring using Ethyl acetate : hexane (1:4, v/v) as the phase of mobility. The reaction was permitted to proceed until completion. Upon completion, The mixture used for the reaction was put into ice-cold water, and The solid material that resulted was gathered via filtration. To remove $CuSO_4{\cdot}5H_2O$ from the product, it was washed with an ammonium chloride solution. Further purification involved vacuum filtration, followed by washing with water and cold methanol. Finally, the solid product was dried in a refrigerator. The procedure for R=H remains consistent, and the same method is employed for preparing the remaining derivatives(7a-7o).**(Scheme3)** Yield:80-95%. The physical constants pertaining to the product are documented in **Table-1**.

3.10.3 Spectral Characterization:

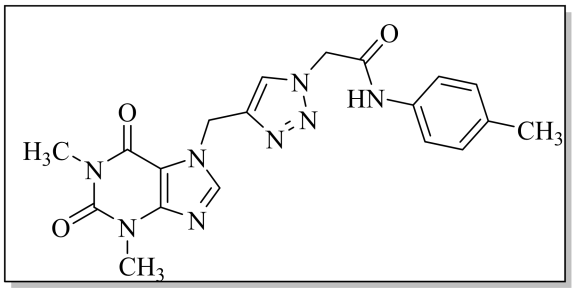
2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide(7a):



Pale yellow; Yield: 95%; M.P.: 238-240 °C; IR(KBr,υ_{max},cm^{-1}): 3456, 3101, 2951,

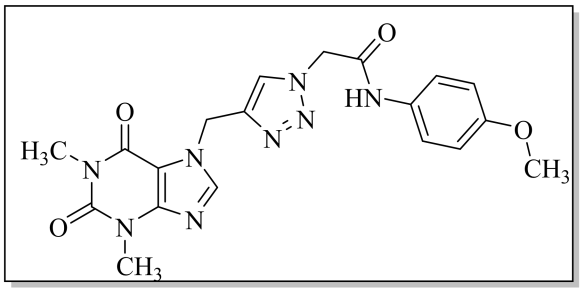
1697, 1550,1608 & 1650, 1473, 756, 698; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ 3.40 (s, 6H), 5.33 (s, 2H), 5.61 (s, 2H), 7.07 (s, 1H), 7.31 (s, 2H), 7.55 (s, 2H), 8.17 (s, 1H), 8.21 (s, 2H), 10.45 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d^{6}) δ 27.58, 29.46, 41.13, 52.32, 105.83, 119.17, 123.79, 125.58, 128.91, 138.38, 142.28, 142.49, 148.31, 151.00, 154.44, 164.09.; Mass (*m*\z): 395.5(M^{+}).; Anal. Calcd. For $C_{18}H_{18}N_8O_3$: C, 54.82; H, 4.60; N, 28.41; found: C, 54.80; H, 4.60; N, 28.40.

2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(p-tolyl)acetamide(7b):



Pale yellow; Yield: 90%; M.P.: 231-233 °C; IR(KBr,υ_{max},cm^{-1}): 3495, 3093, 2958, 1701, 1550,1600 & 1658, 1458, 864; ^{1}H NMR (400 MHz, DMSO- d^{6}) δ ^{1}H NMR (400 MHz, DMSO) δ 2.23 (s, 3H), 3.37 – 3.43 (m, 6H), 5.29 (s, 2H), 5.60 (s, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 3H), 8.14 (s, 1H), 8.20 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (101 MHz, DMSO- d^{6}) δ 20.44, 27.57, 29.44, 41.13, 52.24, 105.83, 119.17, 125.43, 129.26, 132.77, 135.87, 142.25, 142.49, 148.34, 151.00, 154.44, 163.85; Mass (*m*\z): 409.5(M^{+}); Anal. Calcd. For $C_{19}H_{20}N_8O_3$: C, 55.88; H, 4.94; N, 27.44; found: C, 55.85; H, 4.92; N, 27.42.

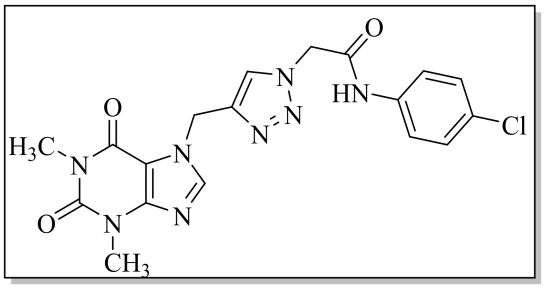
2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-(methoxymethyl)phenyl)acetamide(7c):



Pale yellow; Yield: 86%; M.P.: 239-241°C; IR(KBr,υ_{max},cm^{-1}): 3321, 3105, 3009,

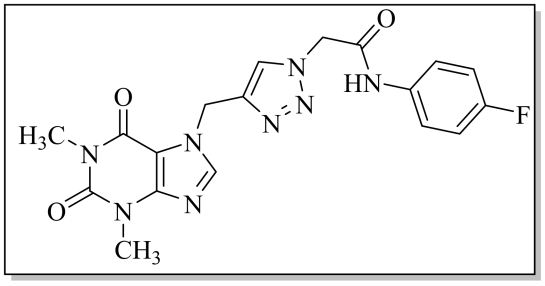
1878, 1550,1643 & 1693, 1469, 837; ^{1}H NMR (400 MHz, DMSO- d^{6}) δ 3.40 (s, 6H), 3.70 (s, 3H), 5.28 (s, 2H), 5.60 (s, 2H), 6.87 (d, J = 8.3 Hz, 3H), 7.46 (d, J = 8.3 Hz, 3H), 8.14 (s, 1H), 8.20 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (101 MHz, DMSO- d^{6}) δ 27.54, 29.41, 41.12, 52.18, 55.13, 105.81, 113.95, 120.70, 125.43, 131.46, 142.46, 148.33, 150.98, 154.41, 155.52, 163.55; Mass (m\z): 425.5(M^{+}).; Anal. Calcd. For $C_{19}H_{20}N_{8}O_{4}$: C, 53.77; H, 4.75; N, 26.40; found: C, 53.72; H, 4.71; N, 26.38.

(4-chlorophenyl)-2-(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide(7d):



Pale yellow; Yield: 89%; M.P.: 241-243°C; IR(KBr,υ_{max},cm^{-1}): 3313, 3117, 3005, 1890, 1546,1643 & 1693, 1481, 833; ^{1}H NMR (400 MHz, DMSO- d^{6}) δ 3.21 (s, 3H), 3.41 (s, 3H), 5.32 (s, 2H), 5.60 (s, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 8.14 (s, 1H), 8.20 (s, 1H), 10.58 (s, 1H); ^{13}C NMR (101 MHz, DMSO- d^{6}) δ 28.02, 29.90, 41.59, 52.68, 106.28, 121.20, 125.89, 127.82, 129.28, 137.79, 142.73, 142.96, 148.81, 151.46, 154.89, 164.79.; Mass (m\z): 429.4(M^{+}); Anal. Calcd. For $C_{18}H_{17}ClN_{8}O_{3}$: C, 50.41; H, 4.00; Cl, 8.27; N, 26.13; found: C, 50.37; H, 4.00; N, 26.10.

(4-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl)acetamide(7e):



Pale yellow; Yield: 91%; M.P.: 243-245°C; IR(KBr,υ_{max},cm^{-1}): 3317, 3101, 3005,

1882, 1554,1643 & 1693, 1473, 837; ^{1}H NMR (400 MHz, DMSO- d^{6}) δ 3.21 (s, 3H), 3.40 (s, 3H), 5.31 (s, 2H), 5.60 (s, 2H), 7.15 (t, J = 8.0, 8.0 Hz, 2H), 7.57 (s, 2H), 8.14 (s, 1H), 8.20 (s, 1H), 10.50 (s, 1H); ^{13}C NMR (101 MHz, DMSO- d^{6}) δ 27.54, 29.42, 41.12, 52.17, 105.81, 115.37, 115.59, 120.94, 121.01, 125.45, 134.77, 142.48, 148.33, 150.99, 154.42, 157.04, 159.43, 164.06..; Mass ($m\backslash z$): 413.5(M^{+}).; Anal. Calcd. For $C_{18}H_{17}FN_{8}O_{3}$: C, 52.43; H, 4.16; N, 27.17; found: C, 52.40; H, 4.14; N, 27.14.

3.10.4 Representative Spectra:

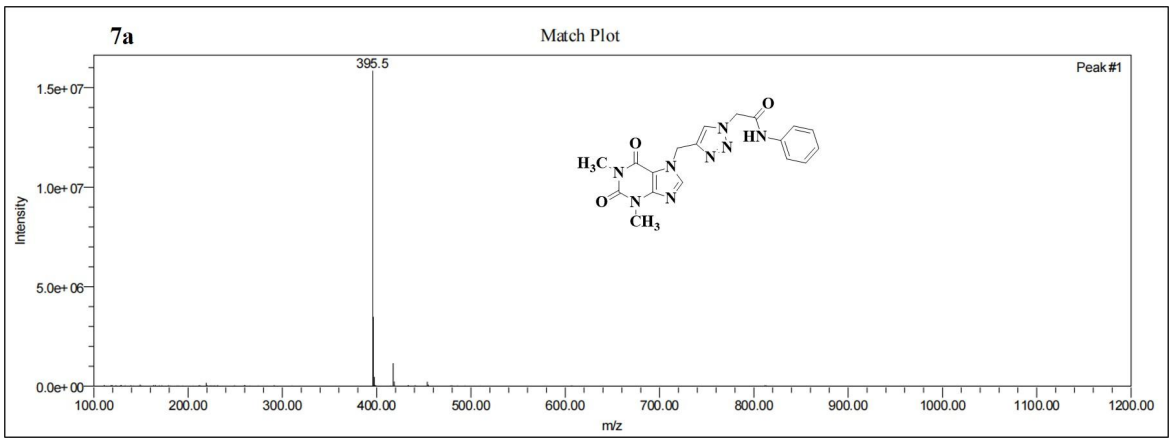


Fig.3.6: Representative mass spectrum of compound 7a

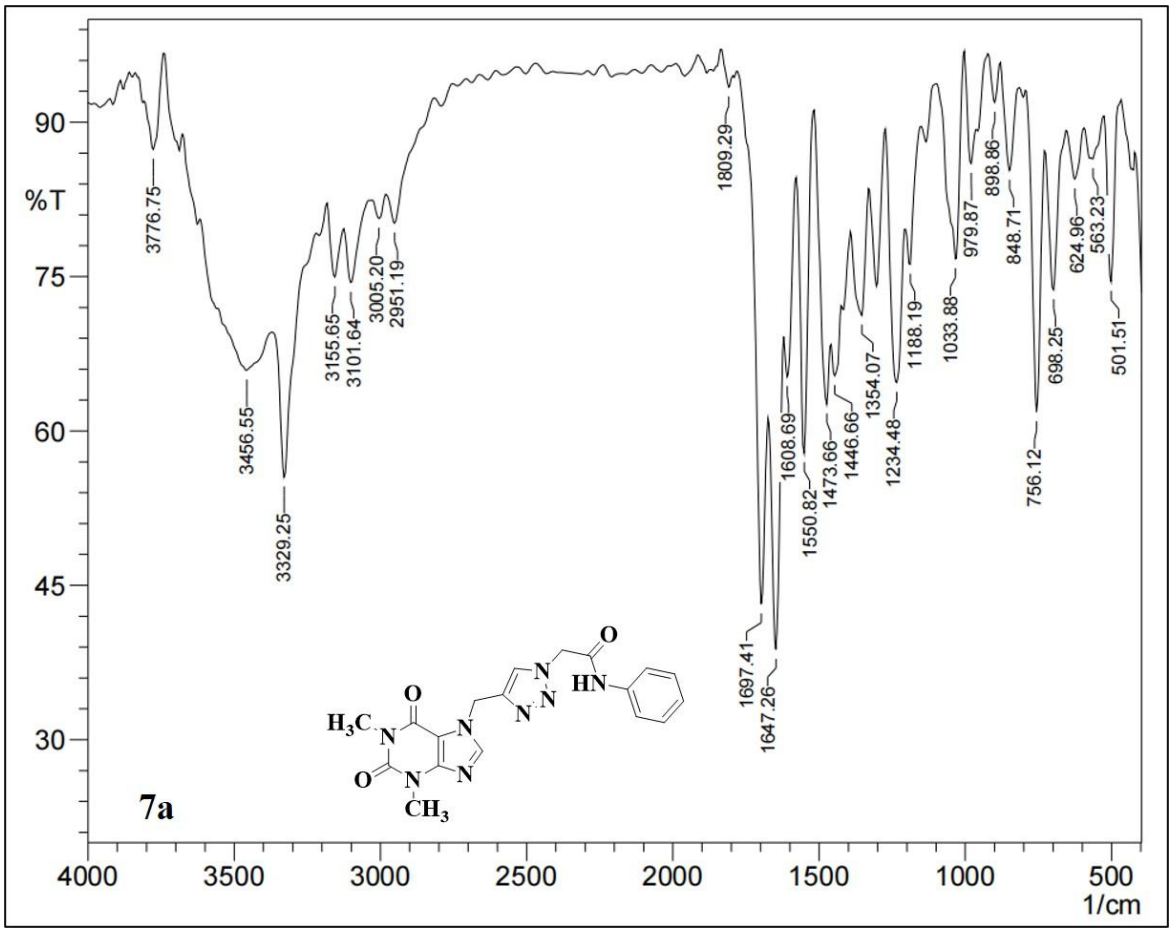


Fig.3.7: Representative IR spectrum of compound 7a

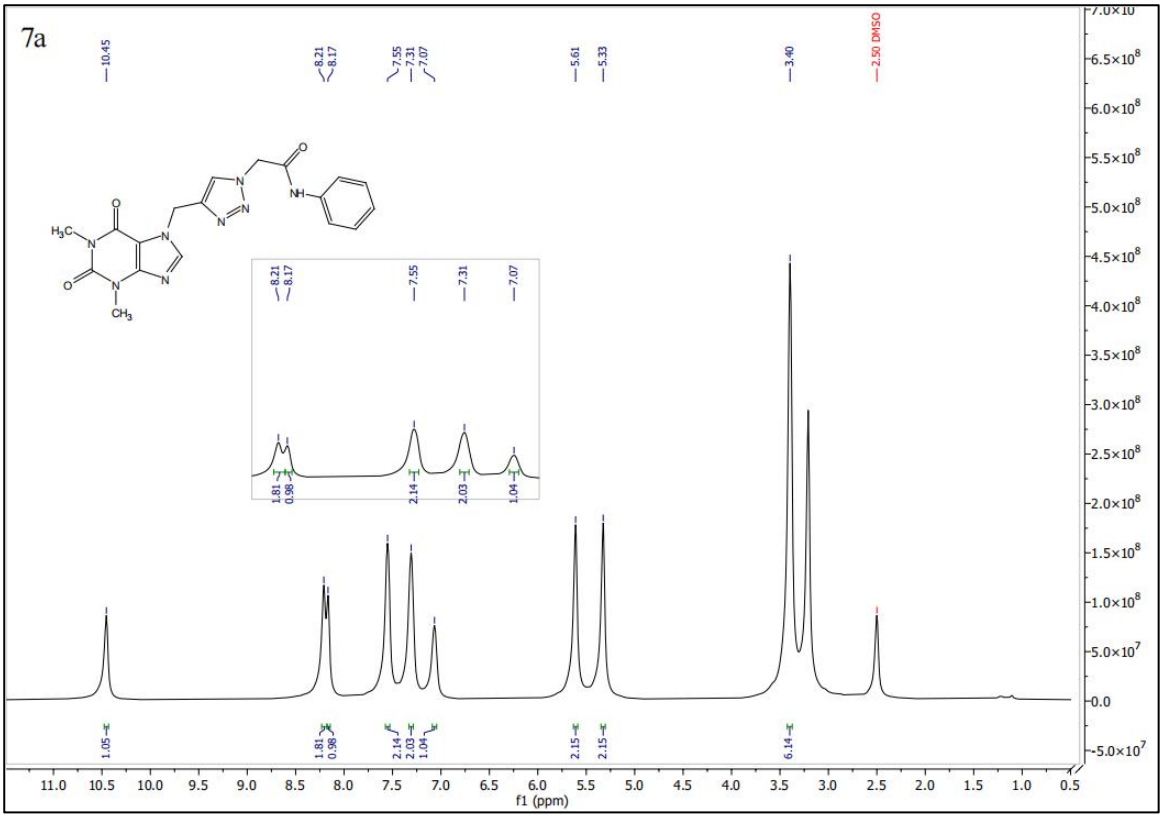


Fig.3.8: Representative ^{1}H NMR spectrum of compound 7a

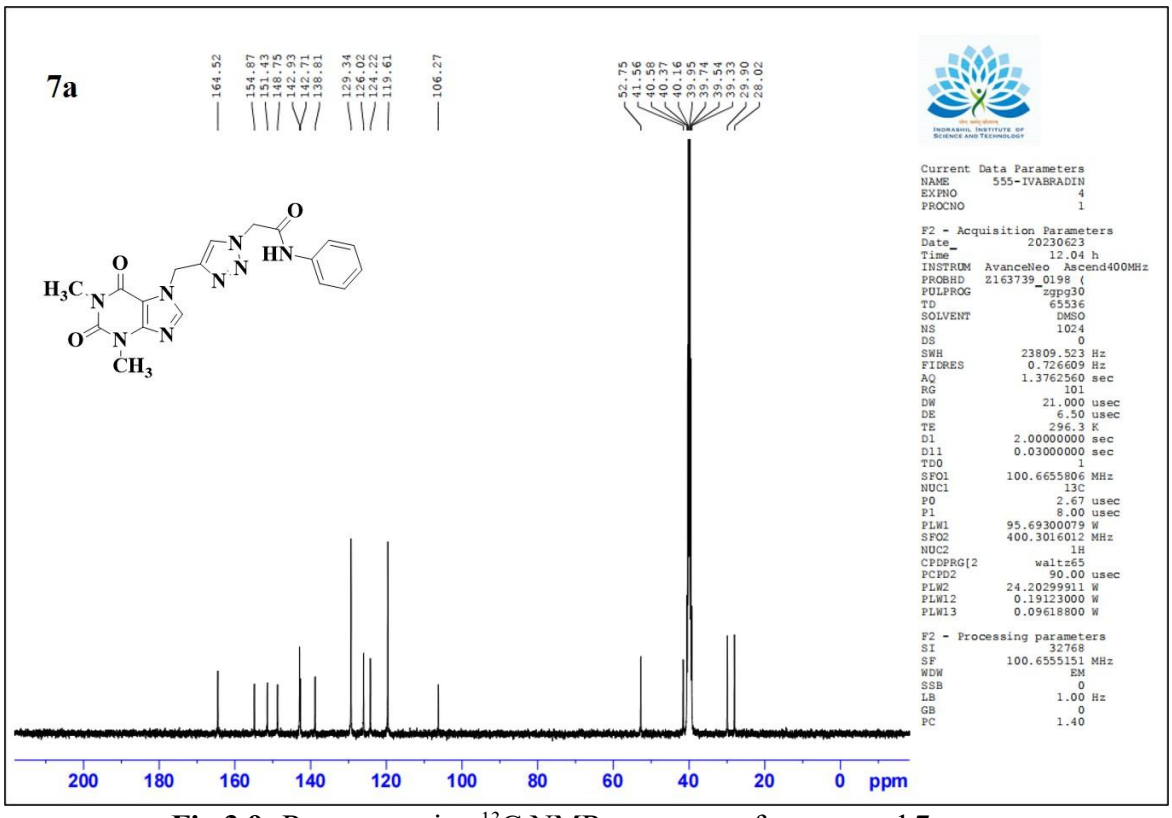


Fig.3.9: Representative ^{13}C NMR spectrum of compound 7a

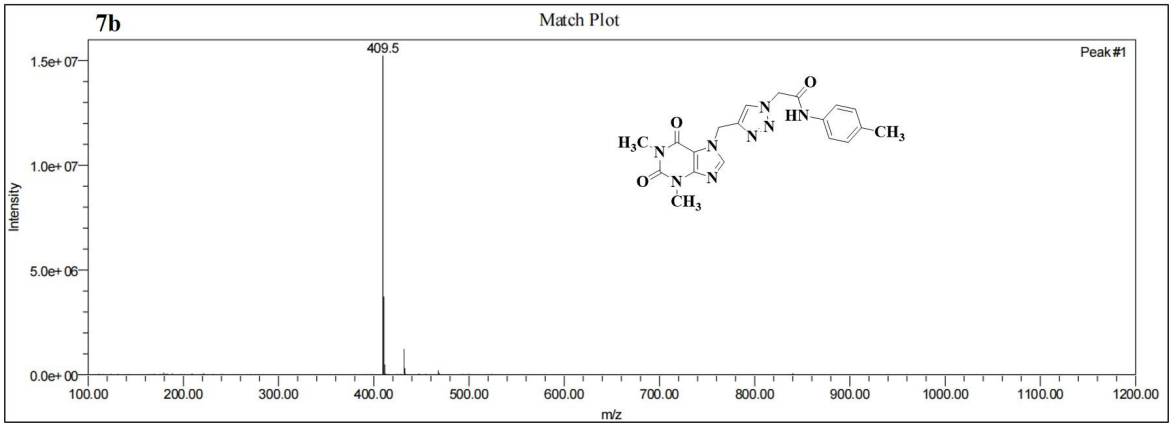


Fig.3.10: Representative mass spectrum of compound 7b

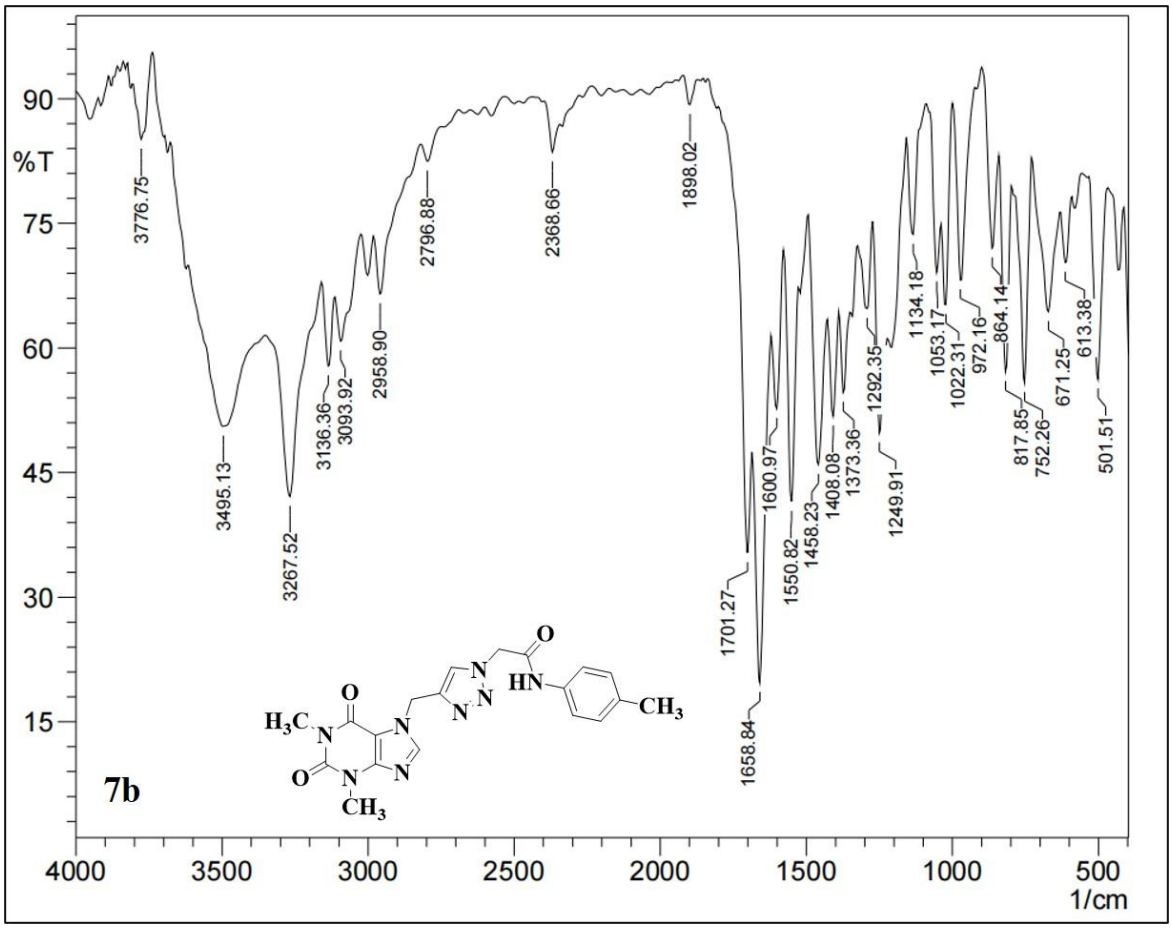


Fig.3.11: Representative IR spectrum of compound 7b

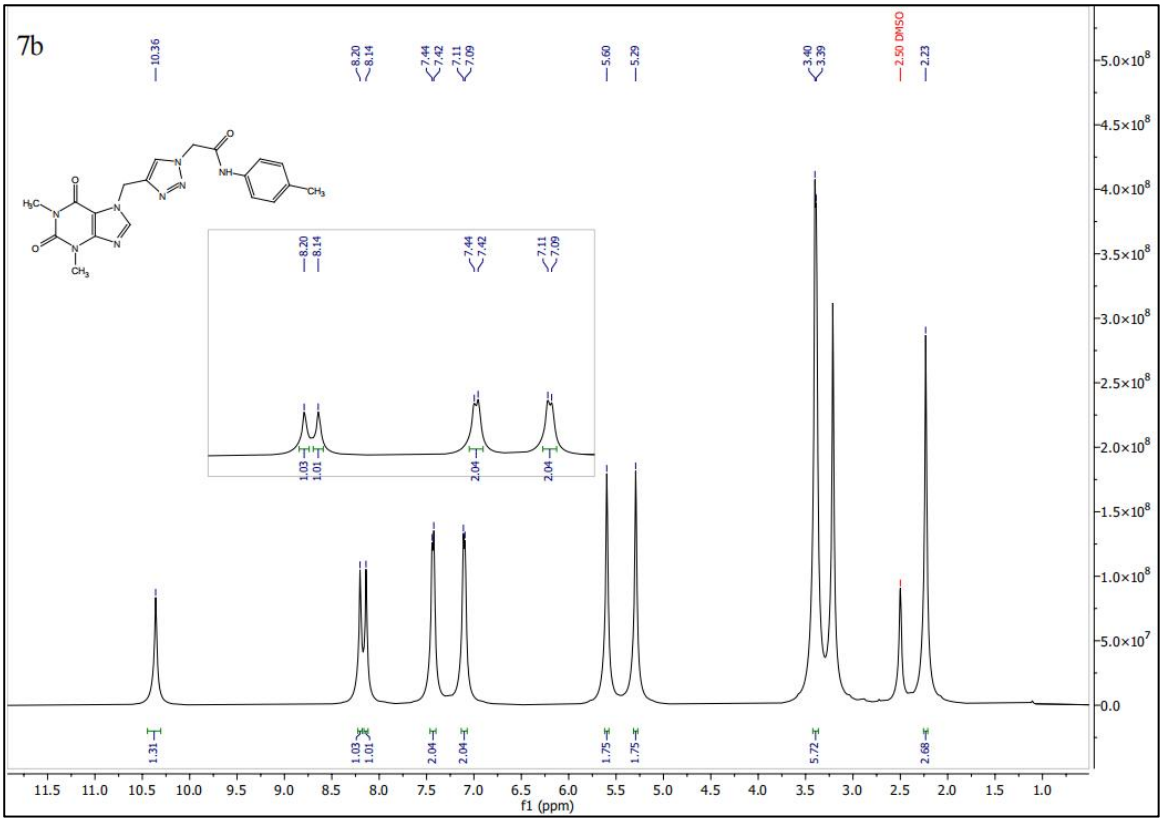


Fig.3.12: Representative ^{1}H NMR spectrum of compound 7b

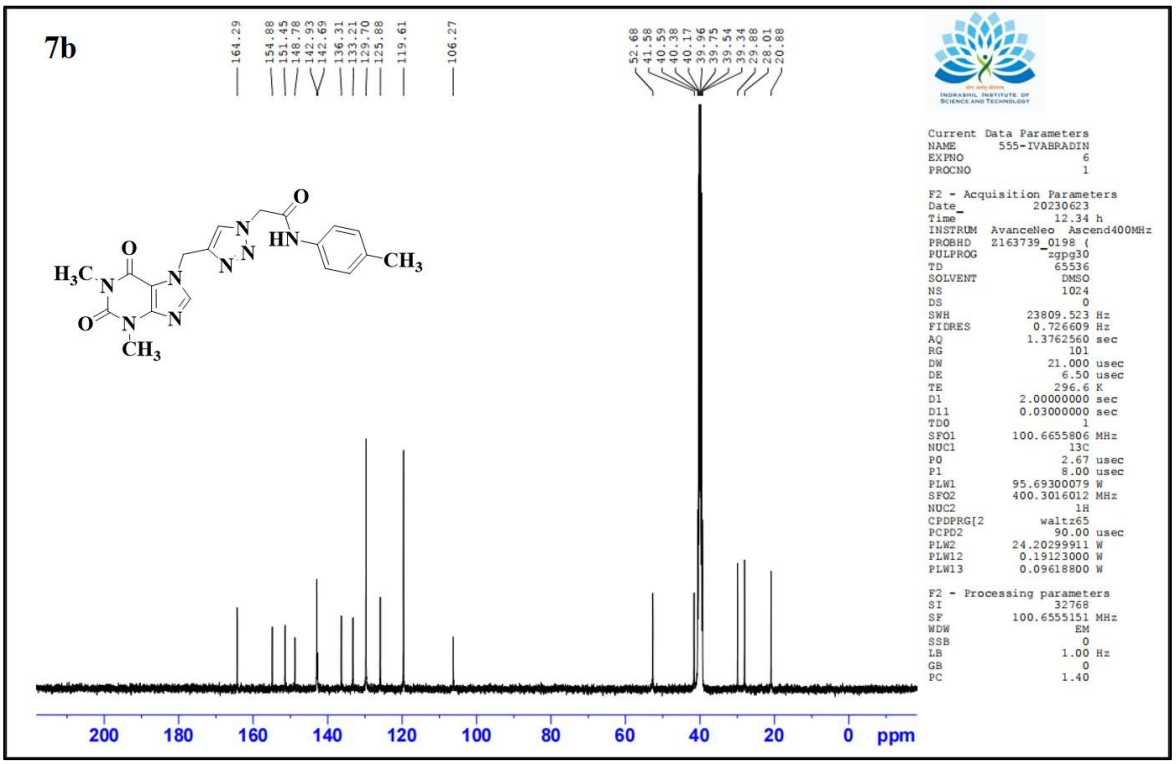


Fig.3.13: Representative ^{13}C NMR spectrum of compound 7b

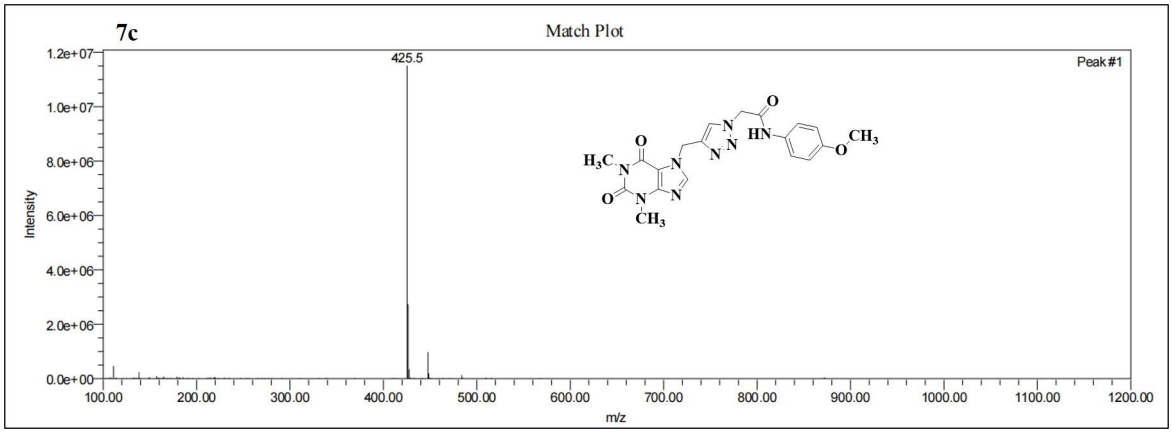


Fig.3.14: Representative mass spectrum of compound 7c

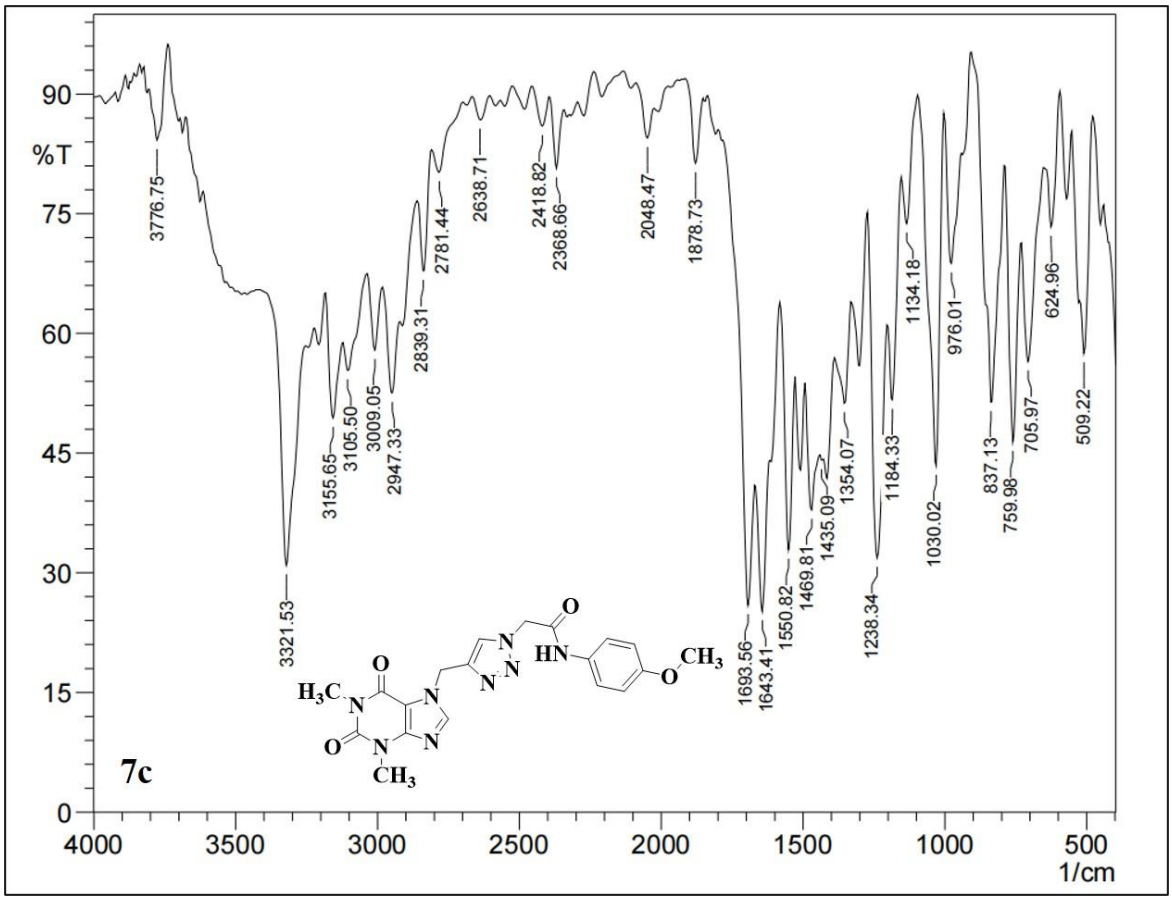


Fig.3.15: Representative IR spectrum of compound 7c

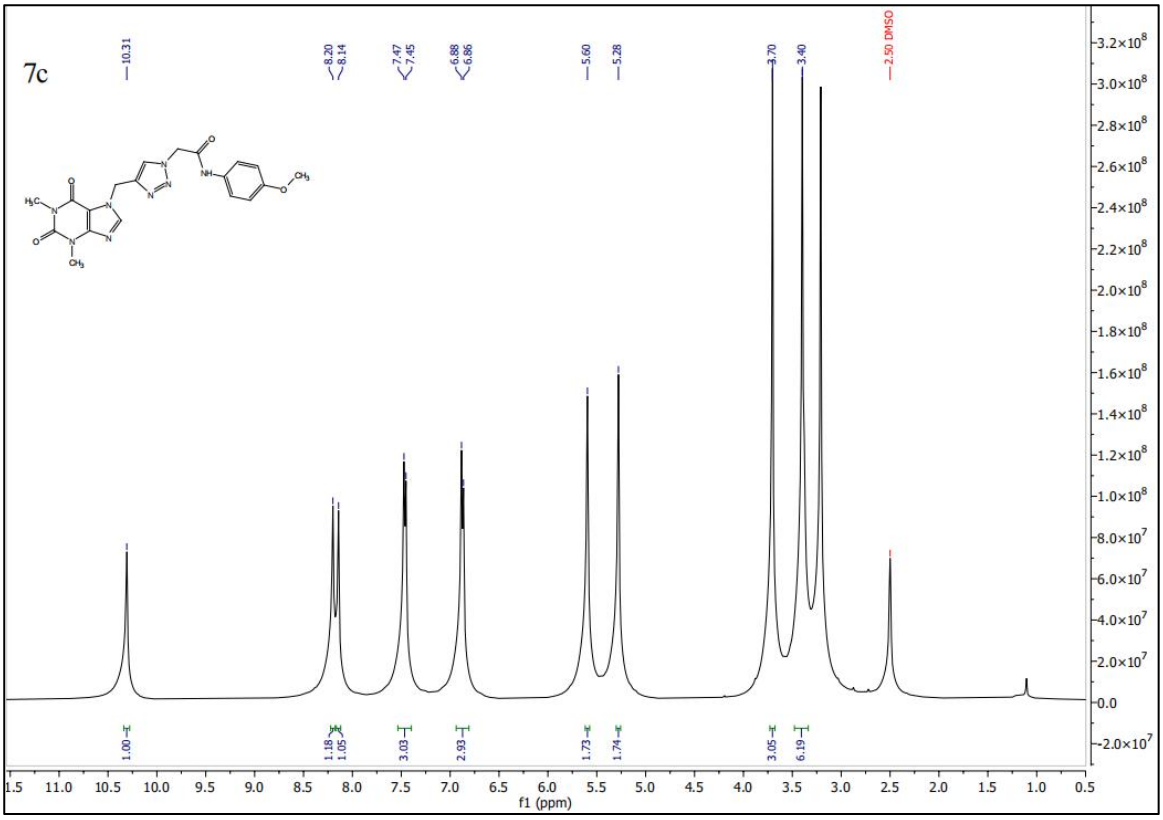


Fig.3.16: Representative ^{1}H NMR spectrum of compound 7c

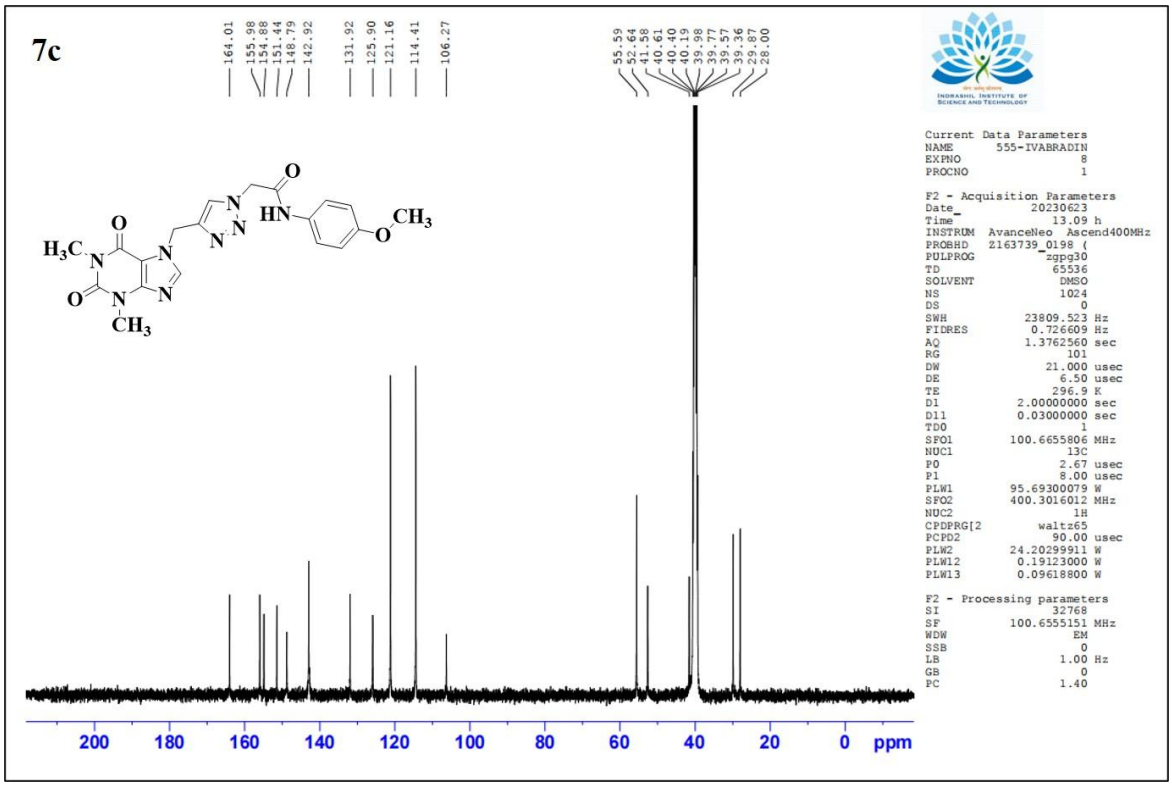


Fig.3.17: Representative ^{13}C NMR spectrum of compound 7c

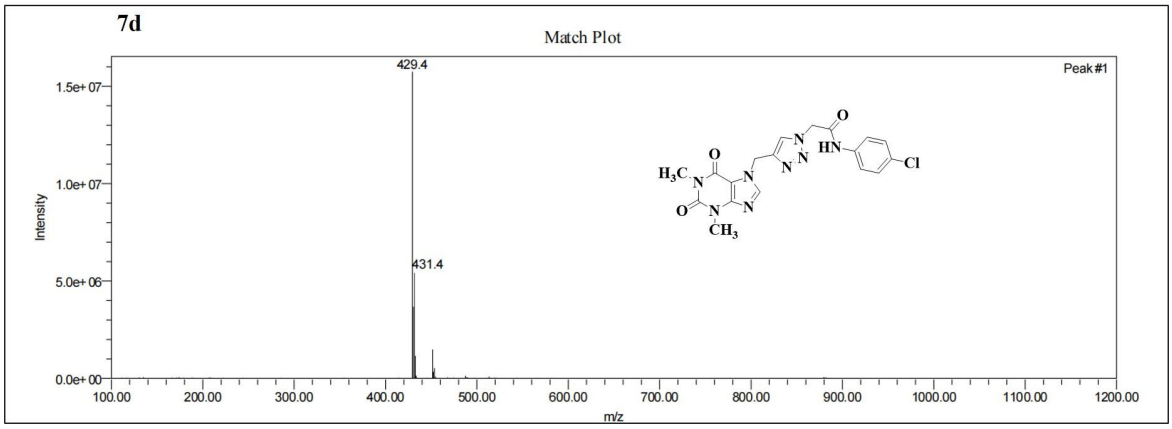


Fig.3.18: Representative mass spectrum of compound 7d

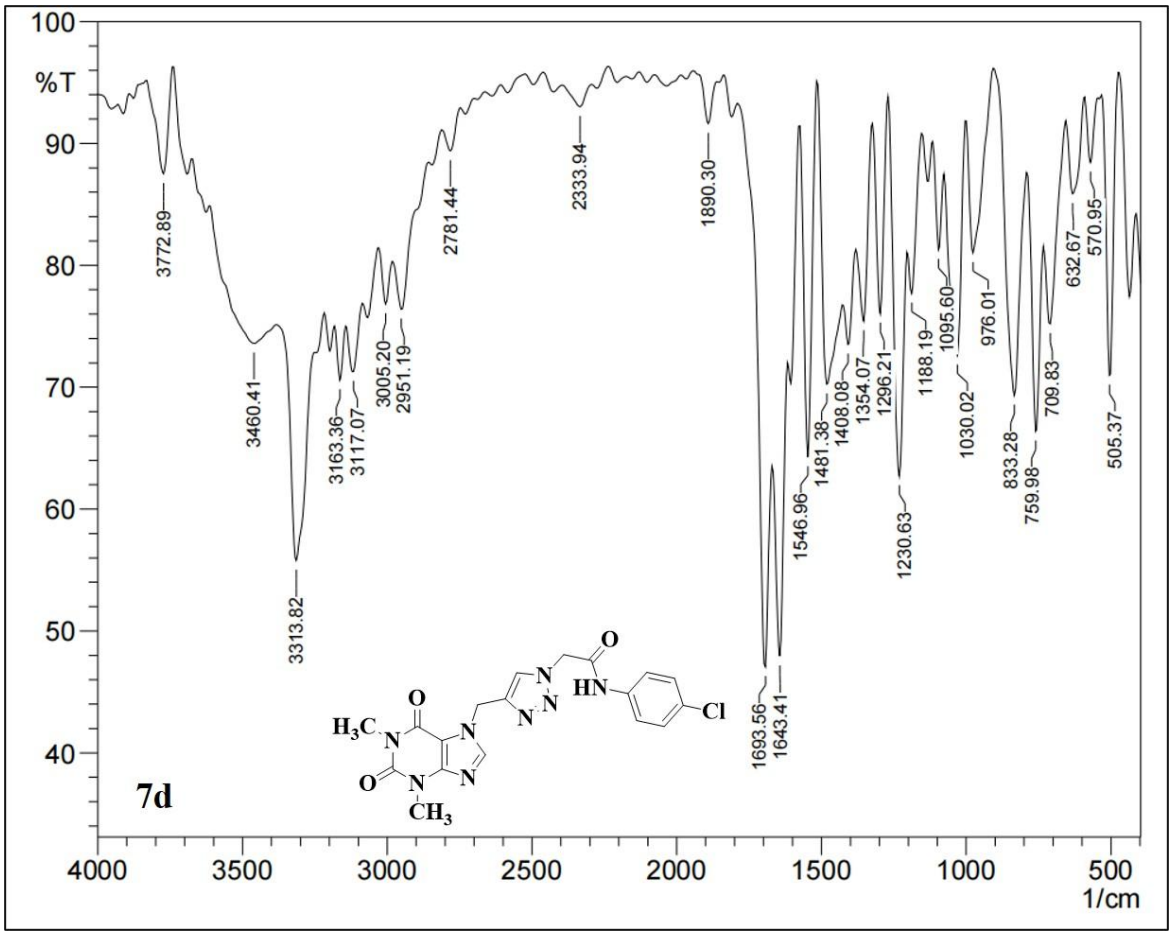


Fig.3.19: Representative IR spectrum of compound 7d

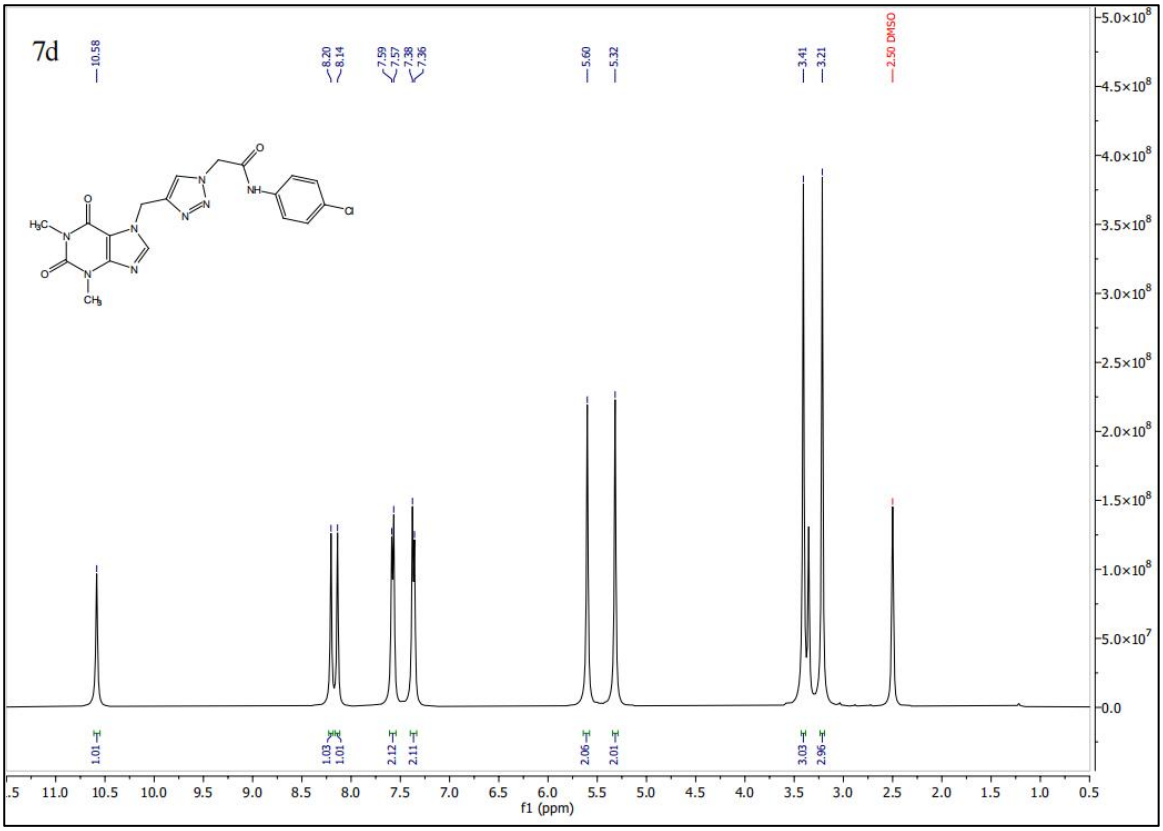


Fig.3.20: Representative ^{1}H NMR spectrum of compound 7d

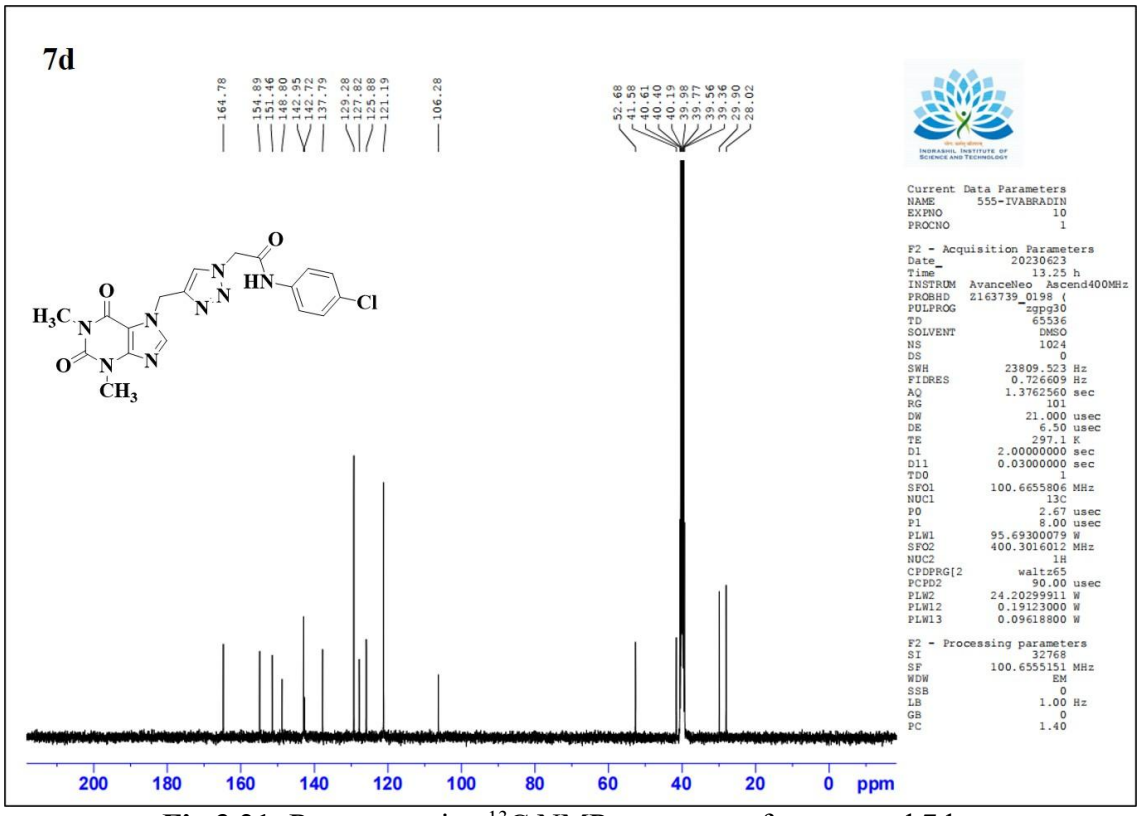


Fig.3.21: Representative ^{13}C NMR spectrum of compound 7d

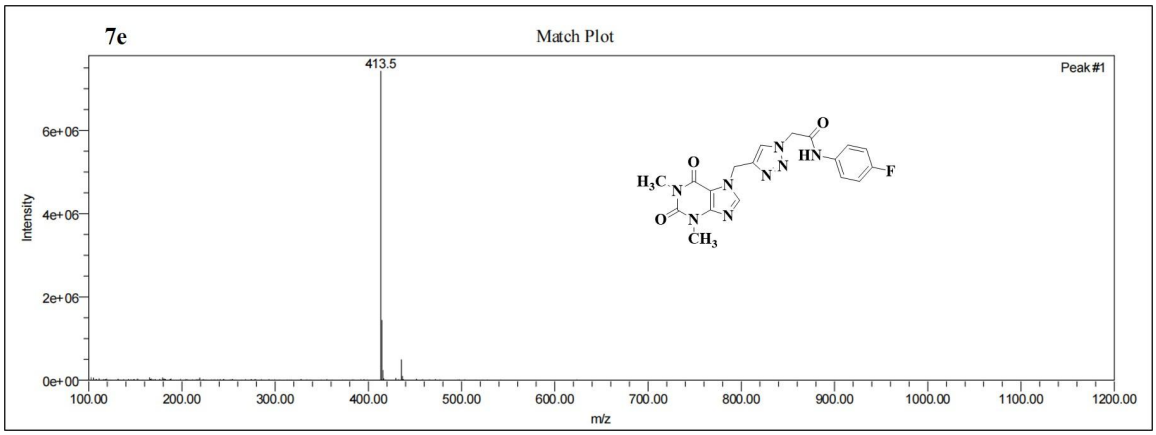


Fig.3.22: Representative mass spectrum of compound 7e

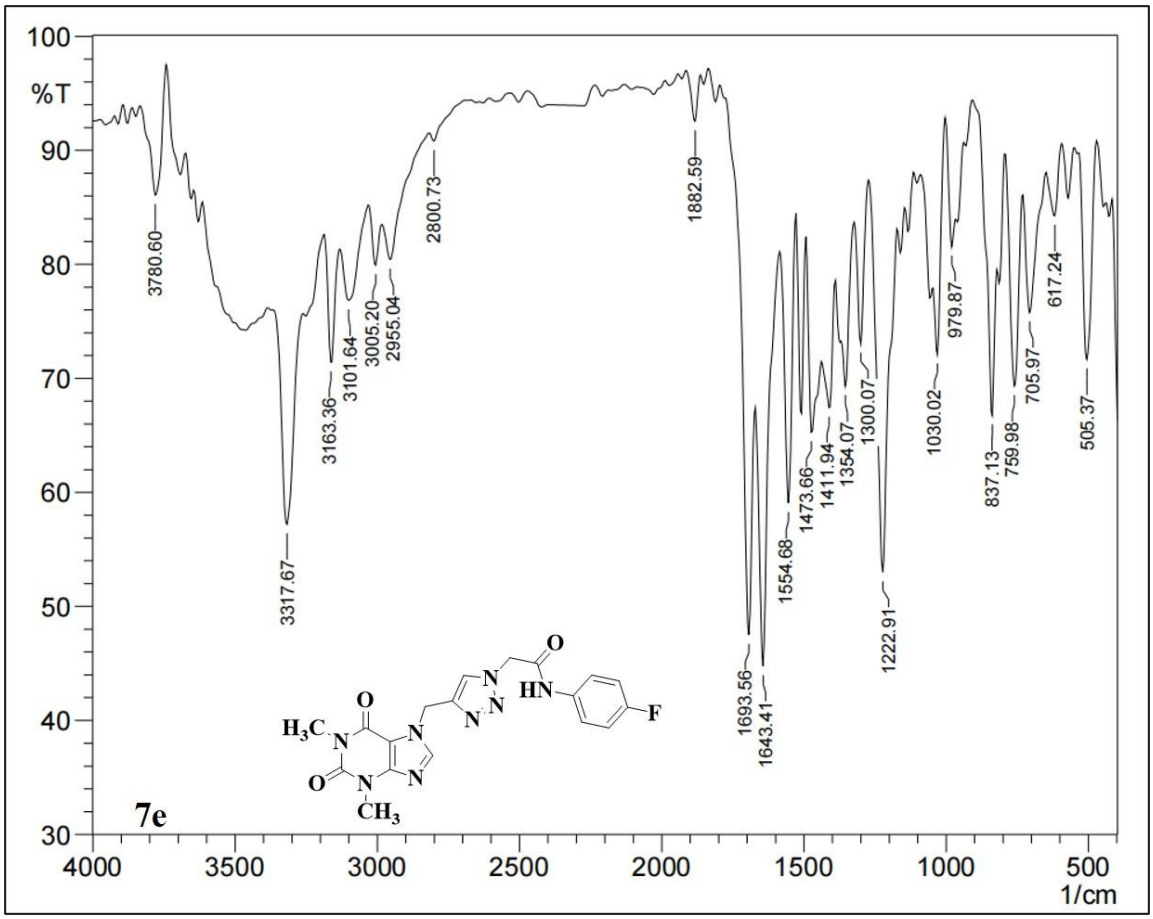


Fig.3.23: Representative IR spectrum of compound 7e

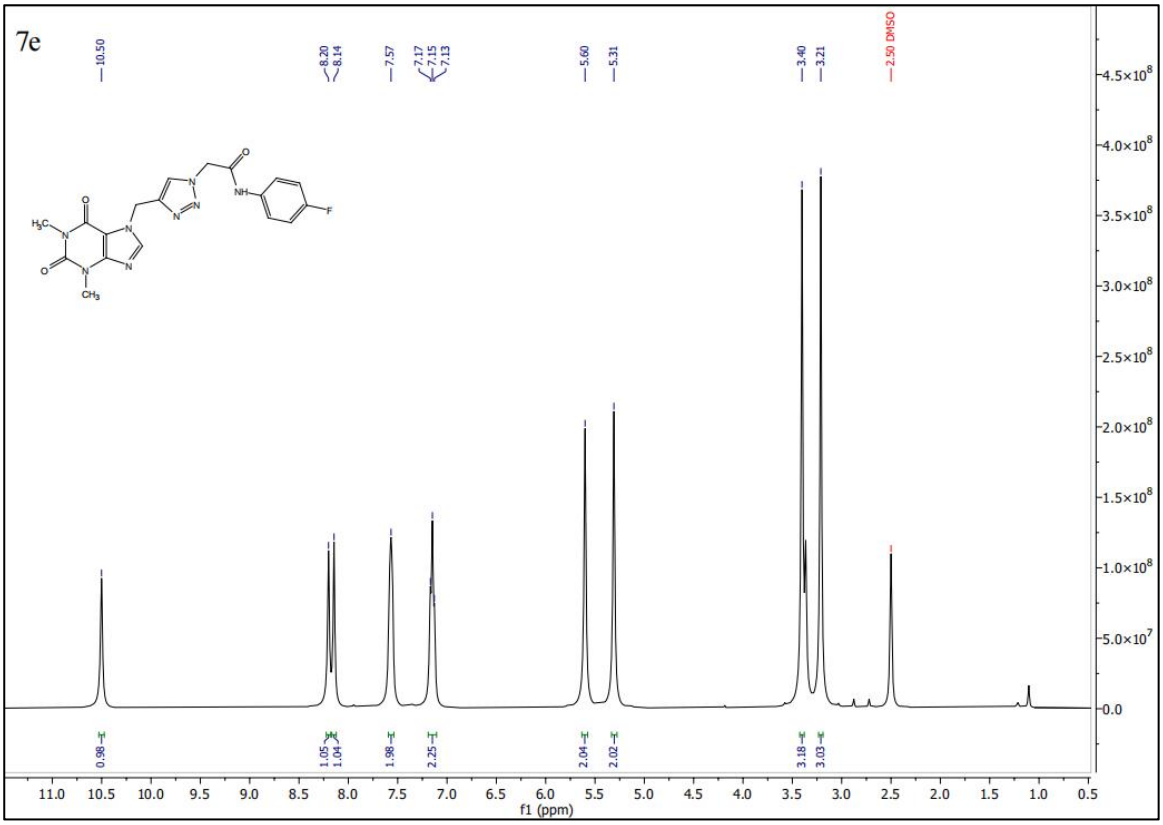


Fig.3.24: Representative ^{1}H NMR spectrum of compound 7e

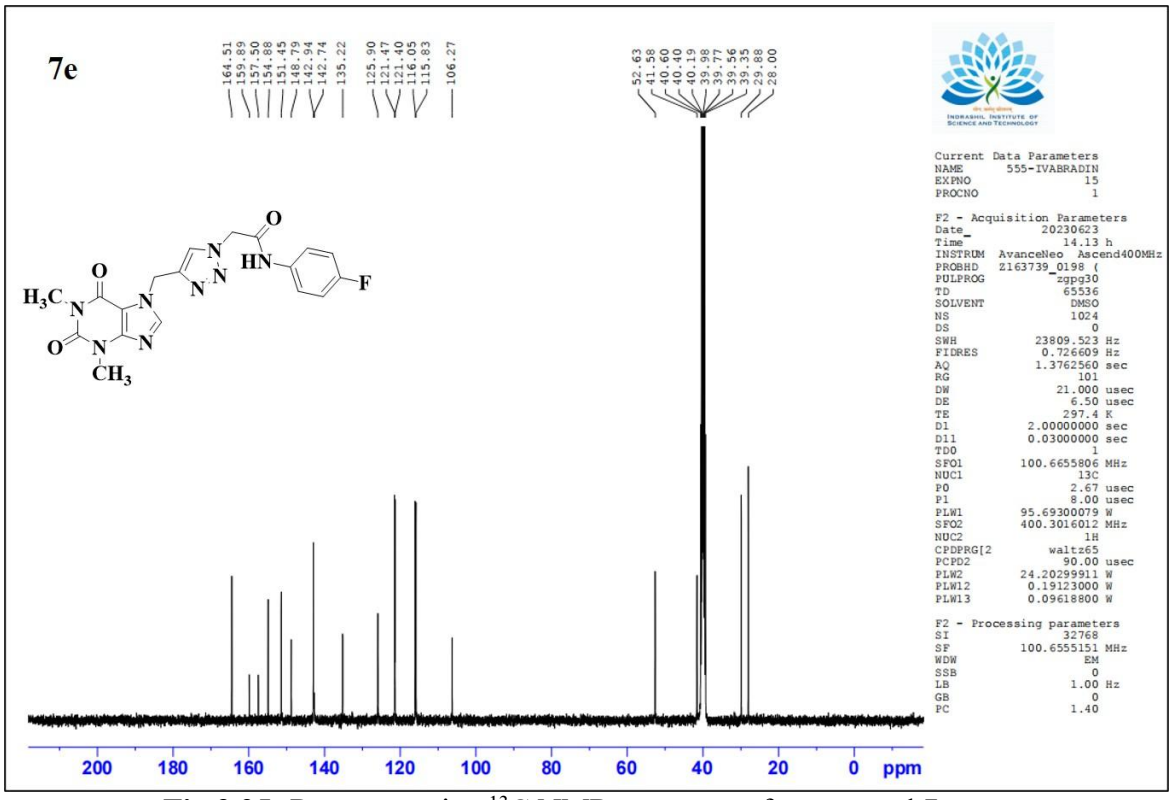


Fig.3.25: Representative ^{13}C NMR spectrum of compound 7e