Synthesis and characterization of 2-aminothiophene derivatives by Gewald reaction

Project report submitted to the Central University of Punjab

For the award of

Master of Science

Chemical Science (Medicinal Chemistry)

In

Department of Pharmaceutical Sciences & Natural Products

BY

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May 2018

DECLARATION

I declare that the project report entitled "**Synthesis and characterization of 2-aminothiophen derivatives by Gewald reaction**'' has been prepared by me under the guidance of Dr. Kaki Venkata Rao, Assistant professor, Department of pharmaceutical sciences and natural products, School of basic and applied sciences. No part of this project has been formed the basis for the award of any degree of fellowship previously.

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CERTIFICATE

I certify that, **Pratibha Agarwala** has been prepared her project report entitled "**Synthesis and characterization of 2-aminothiophen derivatives by Gewald reaction**'' for the award of M.Sc Degree in Chemical science (Medicinal Chemistry) under my guidance. She has carried out this work at Department of Pharmaceutical Sciences and Natural Products, School of Basic and Applied Sciences, Central University of Punjab.

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ABSTRACT

"Synthesis and characterization of 2-aminothiophene derivatives by Gewald reaction''

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Substituted thiophene derivatives are very important heterocycles found in many biologically active and natural compounds. The Gewald multicomponent reaction was a remarkable discovery for the synthesis of wide variety of thiophene derivatives.

Also the synthesis of the thieno pyrimidine derivatives as potential surrogates for this quinazoline core structure has, therefore, became a routine strategy in modern drug design and development.

So we want do some multistep reaction to prepare thienopyrimidine derivative from thiophene which are very important core intermediates with various biological applications like anti-tumor, anti-bacterial, anti-microbial, anti-cancer agents.

Pratibha Agarwala Dr. Kaki Venkata Rao

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Pratibha Agarwala

TABLE OF CONTENT

LIST OF FIGURES

LIST OF SCHEMES

LIST OF APPENDICES

LIST OF ABBREVATION

Sr. No.	Full form	Abbreviation
1	Room temperature	rt
2	Gewald three component reaction	G-3CR
3	Celsius	C
4	Milligram	mg
5	Ultraviolet	UV
6	Structure activity relationship	SAR
7	Dimethyl sulphoxide	DMSO
8	Thin layer chromatography	TLC
9	Fourier transform Infrared	FTIR
10	Nanoclinoptilolite	NCP
11	Polyacrylonitrile Fiber	PANF
12	Deep eutectic solvents	DESs

CHAPTER 1

INTRODUCTION

1. Introduction:

Substituted thiophene derivatives are very important heterocycles found in many biologically active and natural compounds. Many methods for the synthesis of 2-aminothiophenes have been published in the last 50 years. The various existing preparative methods are as follows e.g. reduction of the nitro group (Steinkopf, 1914), nucleophilic displacement of hydroxy group(Pedersen & Lawesson, 1974), mercapto (Hartmann & Scheithauer, 1969), halo (Prim, Kirsch, & Nicoud, 1998), methoxy (Spinelli, Consiglio, & Noto, 1977), p-nitrophenoxy (Spinelli et al., 1977), and the benzenesulfonyl (Meth-Cohn & Narine, 1980) groups. But the difficulties is that all the above synthetic routes involve problematic preparation also do not always produce a good yields and high purity. But In 1966, the German chemist Karl Gewald discovered that a carbonyl compound like aliphatic ketones, aldehydes, or 1,3- dicarbonyl compounds reacts with the activated nitriles and sulfur in presence of a secondary amine at room temperature to give 2-aminothiophenes which is a multicomponent reactions (MCRs). This reaction was a remarkable discovery since elemental sulfur is rather inert and by these reaction a wide variety of thiophene derivative produce in a good yield. The application of G-3CR offers an untapped synthetic route for the construction of diverse thiophene scaffolds for drug discovery.

These thiophene scaffolds derive from the Gewald reaction have been found to exhibit a variety of pharmacological activities. Further by using these thiophen we prepared its derivatives basically substituted thienopyrimidines.

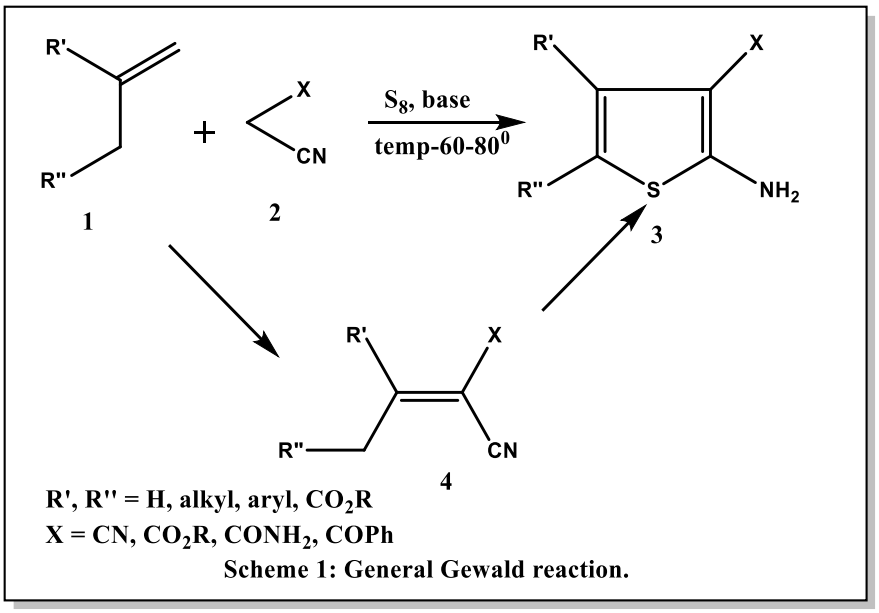
Thieno pyrimidine moiety is a bicyclic heterocyclic compound which consists a five-membered thiophene ring which is fused to a six-membered heterocyclic ring with two nitrogen atoms. The fusion may occur by three different orientations which give three important types of thieno pyrimidines, namely, thieno[2,3-*d*]pyrimidine, thieno[3,2-*d*]pyrimidine, and thieno[3,4-*d*]pyrimidine moiety. These thieno pyrimidine is among those fused pyrimidines which have a wide variety of pharmacological and biological applications, such as antimicrobial, anti-inflammatory, bronchodilator activity, and the vascular endothelial growth factor receptor kinase.

CHAPTER 2

REVIEW OF LITERATURE

2. Literature review:

Gewald multicomponent reaction (G-3CR) is an organic reaction which involves the condensation of a ketone (or aldehyde when R2 = H) and a α-cyanoester in the presence of elemental sulfur and a base to give poly-substituted 2-amino-thiophenes. (Scheme 1)

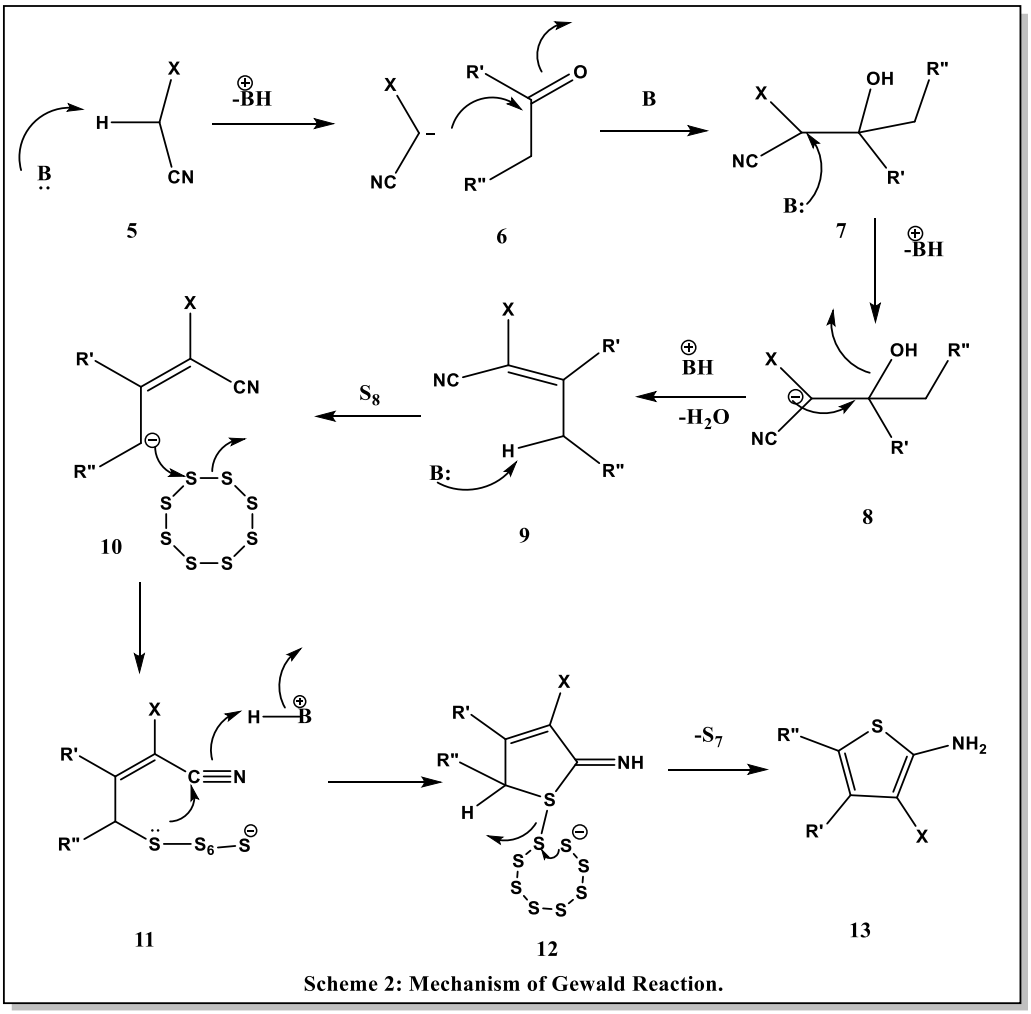


Scheme 1: General Gewald reaction.

Actually Multicomponent Reaction (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In 1966, the German chemist Karl Gewald discovered that a carbonyl compound (aliphatic ketones, aldehydes, or 1, 3-Di carbonyl compounds) reacts with activated nitriles and elemental sulfur in the presence of a secondary amine (base) at room temperature to give 2-aminothiophens This was an extraordinary finding since sulfur is rather inert and only very few organic reactions were known to involve elementary sulfur under mild conditions. Many reactive carbonyl compounds with an active methylene (The methylene group located between two strong electron withdrawing groups (such as nitro, carbonyl or nitrile groups are sometimes called active methylene compounds.) moiety can be used in the Gewald three component reaction. The most Significant nitrile components are malonodinitrile, cyanoacetic ester, primary cyanoacetamide, and ω-cyanoacetophenone.

2.1. Mechanism of Gewald reaction:

The reaction mechanism of the G-3CR is generally believed to proceed as shown in scheme 2 (Huang & Dömling, 2011). The first step of the Gewald reaction is a Knoevenagel condensation of an activated nitrile with an oxo component (ketone or aldehyde) to produce an acrylonitrile **9**, which is then thiolated at the *γ* -methylene group with elemental sulfur according to a SN_x mechanism. The sulfurated compound **11** undergoes ring closure via nucleophilic mercaptide attack at the cyano carbon to provide intermediate **12**. Finally, a prototropic rearrangement affords the 2-aminothiophen **3**.(Peet, Sunder, Barbuch, & Vinogradoff, 1986)



Scheme 2: Mechanism of Gewald Reaction.

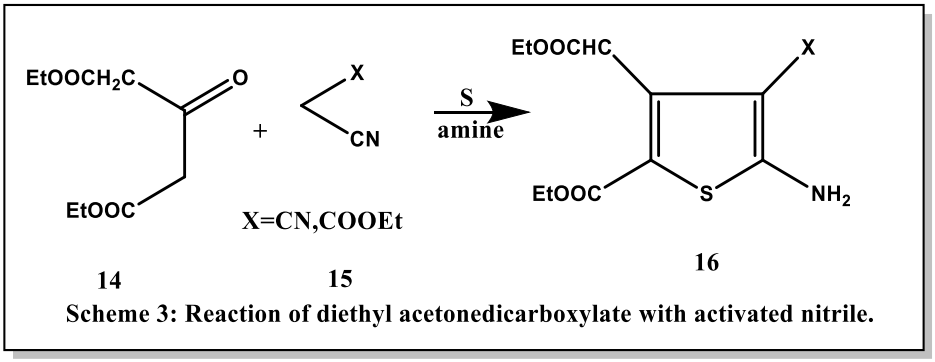
2.2. Scope:

Large number of methods for the synthesis of 2-aminothiophen derivatives has been developed using the G-3CR (R. Sabnis, Rangnekar, & Sonawane, 1999). In recent years, many new synthetic routes have been investigated to expand the scope of G-3CR. This reaction goes more readily with cyclic ketones, e. g. cyclohexanones and cycloalkylidene derivatives of methylene active nitriles and with cyclopentanones. More complex cyclic ketones and steroids such as androstane-3,17-dione, azepinones, 3-cholestanone, indanone , tropinones, quinuclidinones, pyranones, piperidones, thiacyclopentanones, undergo the Gewald reaction.(R. W. Sabnis, 1994) Yield of this reaction is very high, time is short. This method generates very active species such as 2-amino-3-substitued-thiophens which have not only has enormous applications in organic reactions but also in several applied fields such as dyes, pharmaceuticals. This data establishes that the Gewald reaction is the most convenient and promising route for the synthesis of 2-aminothiophens. This method will definitely remain a very stimulating field of research for the organic chemist in the years to come.

2.3. Variation: There are several variation made to Gewald reaction like variation in substrate, variation in base, variation in reaction condition

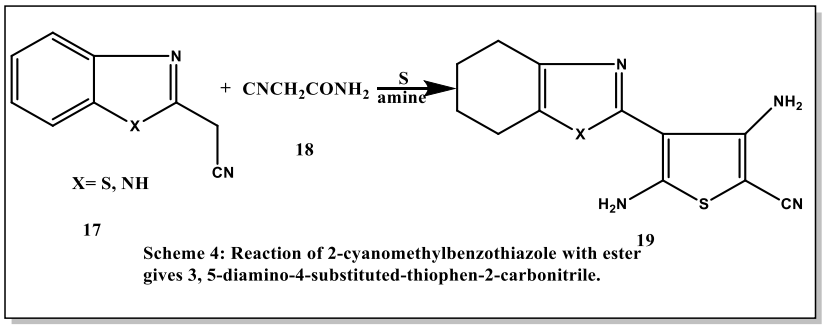
Some variation in substrate are as follows:

Sabnis and Rangnekar developed the most versatile compounds in more than 90% yields by condensing diethyl acetonedicarboxylate **14** with sulfur and an activated nitrile **15** (scheme 3).



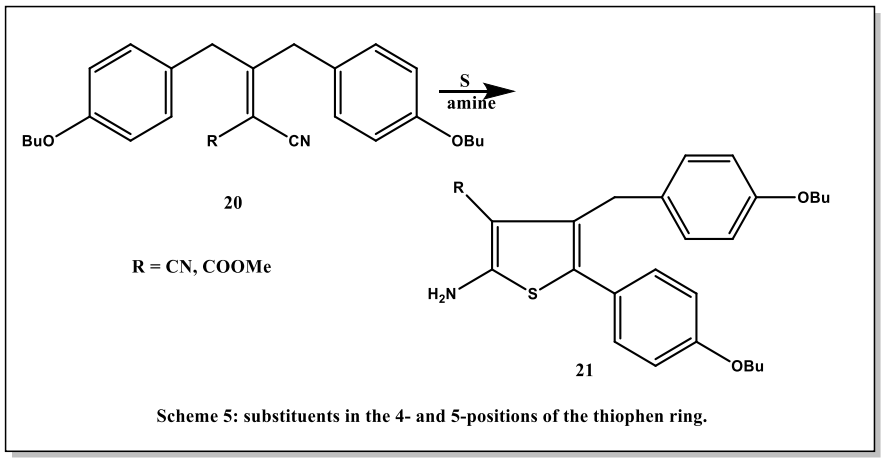
Scheme 3: Reaction of diethyl acetonedicarboxylate with activated nitrile.

These compounds have remarkable applications in synthesizing novel dyes and biologically active compounds. The scope of the Gewald reaction can further increased by introducing heterocyclic moieties into the thiophen nucleus. It has been found that by heating equimolar amounts of 2-cyanomethylbenzothiazole **17** with sulfur and cyanoacetamide **18** gives 3, 5-diamino-4-substituted-thiophen-2-carbonitrile **19** in excellent yield (scheme 4) (S. Sherif, 1996).



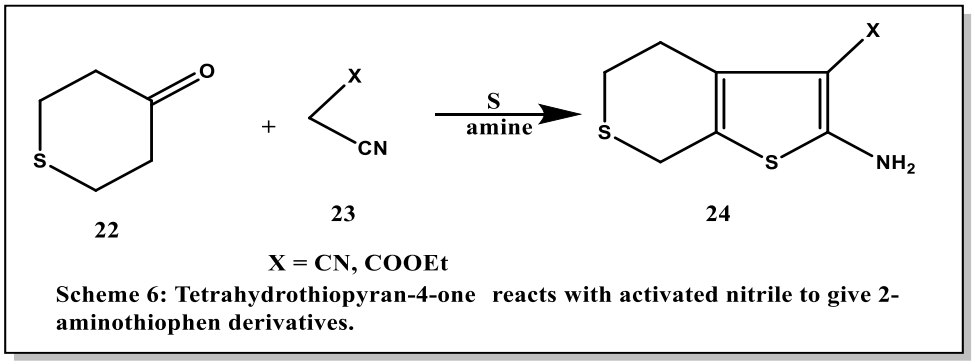
Scheme 4: Reaction of 2-cyanomethylbenzothiazole with ester gives 3, 5-diamino-4-substituted-thiophen-2-carbonitrile.

The usefulness of the Gewald reaction can not only obtain by different substituents in the 4- and 5-positions of the thiophen ring, but also by using different electrophilic substituents in the 3-position (Scheme 5). This approach helps to design many new drugs (M. Zhang & Harper, 1997)



Scheme 5: substituents in the 4- and 5-positions of the thiophen ring.

Tetrahydrothiopyran-4-one **22** reacts with activated nitrile **23** and sulfur giving the 2-aminothiophen derivatives **24** (scheme 6).



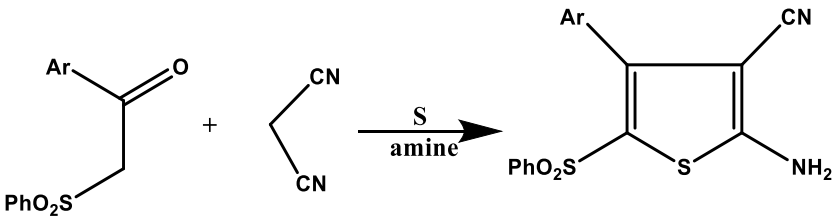
22 23 24

X = CN, COOEt

Scheme 6: Tetrahydrothiopyran-4-one reacts with activated nitrile to give 2-aminothiophen derivatives.

These compounds are useful intermediates for synthesizing pharmacologically active moieties such as thiazolo-, thiazino-, pyrido-, in a one-pot reaction (Sauter, Fröhlich, & Ahmed, 1996).

A modification of the Gewald reaction which reduces 4n-alkyl substituted-2-aminothiophen derivatives which bear no substituent at position 5.The Gewald reaction of 4-methyl-2-pentanone with alkyl cyanoacetate was examined(Guetschow, Schroeter, Kuhnle, & Eger, 1996). 2-Aminothiophens with a 5-sulfonyl group can be synthesized by the Gewald reaction. Phenylsulfonylacetophenones 25 react with the elemental sulfur and activated nitrile 26 to give 2-amino-5-phenylsulfonylthiophen 27 (S. M. Sherif & Hussein, 1997).(Scheme-7).

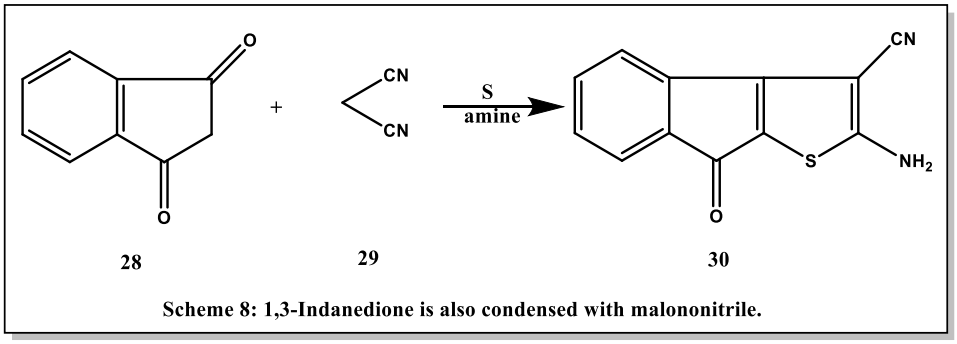


25 26 27

Ar = C_6H_5, 4-Br-C_6H_4

Scheme 7: Phenylsulfonylacetophenones activated nitrile to give 2-amino-5-phenylsulfonylthiophen.

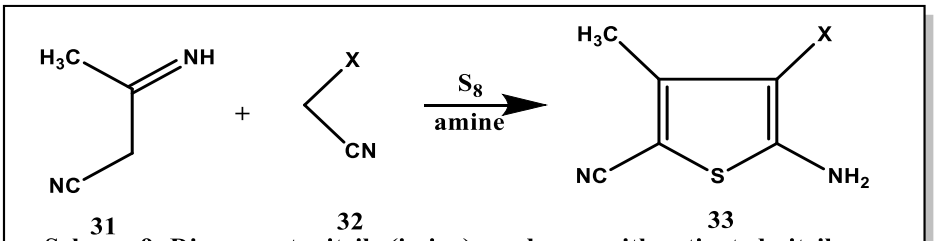
1,3-Indanedione **28** is also condensed with malononitrile **29** to yield the key precursor **30** for dyes (Rangnekar, Kamat, Ramamurthy, & Malanker, 1998) (Scheme 8).



28 29 30

Scheme 8: 1,3-Indanedione is also condensed with malononitrile.

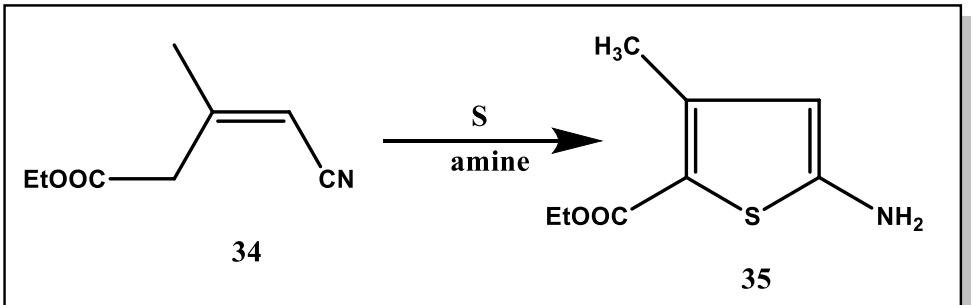
The dimer acetonitrile (imine) **31** was condenses with an activated nitrile **32** to produce 2-aminothiophen **33** in 80% yield. (Scheme 9)



31 32 33

Scheme 9: Dimer acetonitrile (imine) condenses with activated nitrile produce 2-aminothiophen.

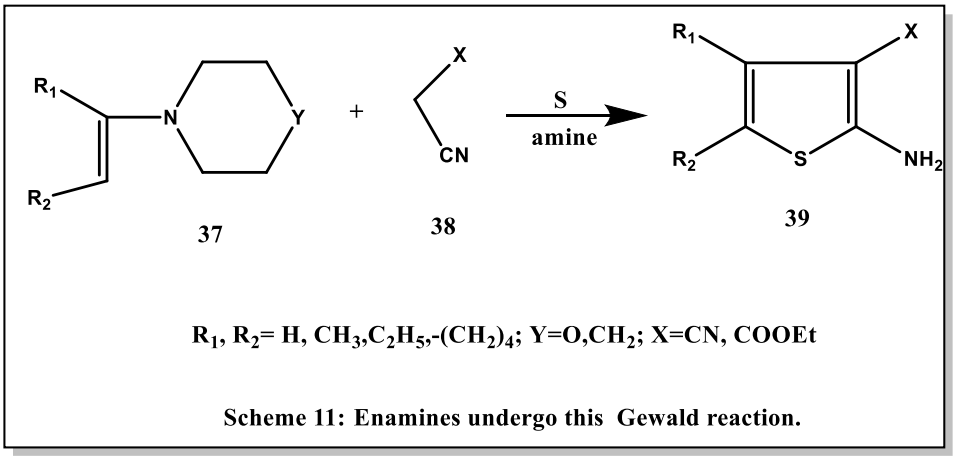
The Ethyl cyanoacetate reacts with cyanoacetic acid to yield a,ß-unsaturated nitrile **34**, which then undergoes the Gewald reaction generating 2-aminothiophen **35** (Gewald, Hentschel, & Heikel, 1973). (Scheme 10).



34 35

Scheme: 10-Ethyl cyanoacetate gives 2-aminothiophen without any electron-withdrawing groups in the 3-position.

Enamines **36** was undergo this reaction with activated nitriles **37** which give 2-aminothiophens **38** (Litvinov, Sharanin, & Babichev, 1986) (Scheme 11).

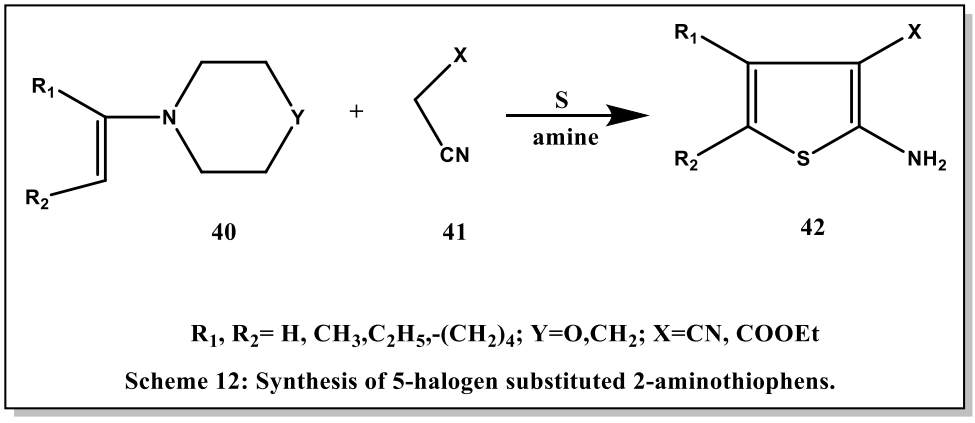


37 38 39

R_1, R_2= H, CH_3,C_2H_5,-$(CH_2)_4$; Y=O,CH_2; X=CN, COOEt

Scheme 11: Enamines undergo this Gewald reaction.

It is very inconvenient but none of the researcher was focused on the direct synthesis of 5-halogen substituted 2-aminothiophens. Finally, in 2003 Scammells and co-workers(Lütjens et al., 2003) have report the synthetic pathway for the preparation of 5-bromo substituted 2-aminothiophens **42**. Synthesized 5-bromo substituted 2-aminothiophens **42** were considered as a precursors in the development of new synthetic adenosine A_1 receptor agonists with similar activity to those which are already acting as successful therapeutics.

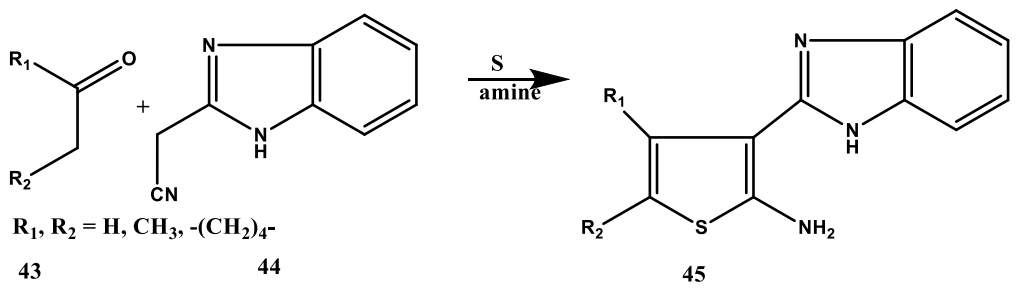


40 41 42

R_1, R_2= H, CH_3,C_2H_5,-$(CH_2)_4$; Y=O,CH_2; X=CN, COOEt

Scheme 12: Synthesis of 5-halogen substituted 2-aminothiophens.

Variation in base: 3-(Benzimidazol-2-yl)-2-aminothiophens **45** can be directly synthesized from the ketomethylene **23**, 2-cyanomethylbenzimidazole **44** and sulfur using the Gewald reaction (Elnagdi et al., 1995). (Scheme 13).



R_1, R_2 = H, CH_3, -$(CH_2)_4$-

43 44 45

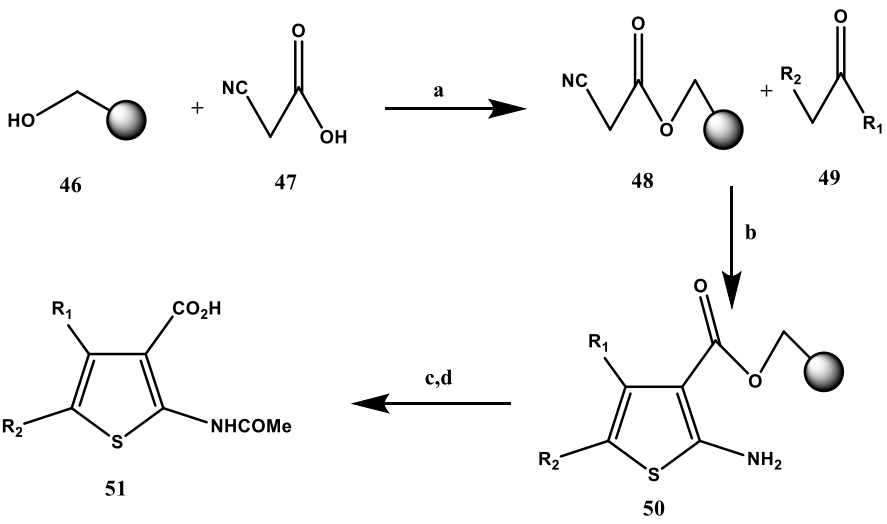
Scheme 13: 3-(Benzimidazol-2-yl)-2-aminothiophens synthesized from ketomethylene 28, 2-cyanomethylbenzimidazole.

2.4. Modification of Gewald reaction:

Because of the significant utility of the substituted 2-aminothiophens not only in organic synthesis but also in other several applied fields, Gewald's method have been modified in various way. Take benefit of the reaction conditions with starting substrates containing a wide range of functional groups and alkyl, aryl and heteroaryl substituents a broad range of modification have been found. Ionic liquids are also used as solvents in combination with ethylenediammonium diacetate which shown to be very effective in the case of the Gewald synthesis with aliphatic and alicyclic ketones with possibility of restoration of used liquids (Hu, Chen, Le, & Zheng, 2004). Here we discuss some modification:

Solid supported Gewald reaction: Heterogeneous organic reactions using reagents immobilized on porous solid supports have been often proved advantageous over conventional solution phase reactions because of good dispersion of active reagent sites, better selectivity and easier work-up. One of them is commercially available Agro Gel Wang resin, the grafted (polyethylene glycol) polystyrene -PEG-PS. The benefits of the reagent PEG-PS Wang linker during the Gewald synthesis have been highlight (Castanedo & Sutherlin, 2001) in synthesis of substituted 2- aminothiophens with carboxylic acid in the neighboring β-position. The acylation of this Agro Gel Wang resin **46** with cyanoacetic acid **47** under standard DIC/DMAP coupling conditions gave the resin-bound cyanoacetic ester **48**. After the dispersion of the reagent **48** in ethanol Gewald reaction was performed in QuestTM 210 synthesizer by mixing with the starting compound - α-methylene carbonyl compounds **49** and substrates - sulfur and

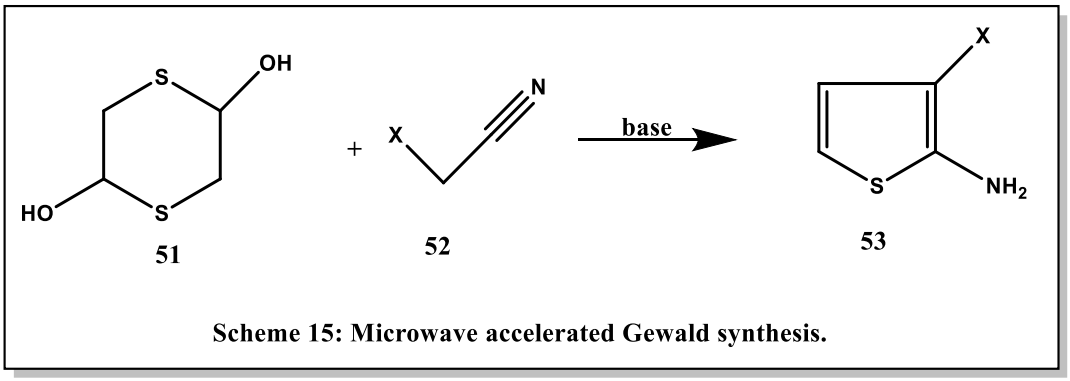
morpholine. Finally 2- aminothiophen carboxylic acids was isolated as *N*-acetyl protected derivatives **51** upon the cleavage of the resin with trifluoroacetic acid (Scheme 14).



a: DIC, DMAP, CH_2Cl_2; b: morpholine, S_8, EtOH, 75°C; c: AcCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, RT; d: TFA, H_2O, CH_2Cl_2. R_1,R_2-Any alkyl or aryl grp

Scheme 14: Solid supported Gewald reaction.

Microwave accelerated Gewald synthesis: Most of the reported Gewald synthesis required long reaction time in between 4 and 48 hours. Microwave heating is an area of which came on interest in both academic and industrial laboratories because it can enhance the rate of reaction and in many cases it also improve the product yields (Tierney & Lidström, 2009). The Gewald reaction under the microwave irradiation was applied for the preparation of 2-aminothiophens without the substituents in position C-4 and C-5 of thiophen ring. the following Reaction starting from 1,4-dithiane-2,5-diol **51** which react with α-activated acetonitrile **52** was completed after 2 min. in methanol where triethylamine used as a base (Scheme 17) (Hesse, Perspicace, & Kirsch, 2007) as Compared to classical reaction conditions the appropriate monosubstituted 2-aminothiophens **53** were obtained in higher yields with considerably shorter reaction time (Scheme-15)



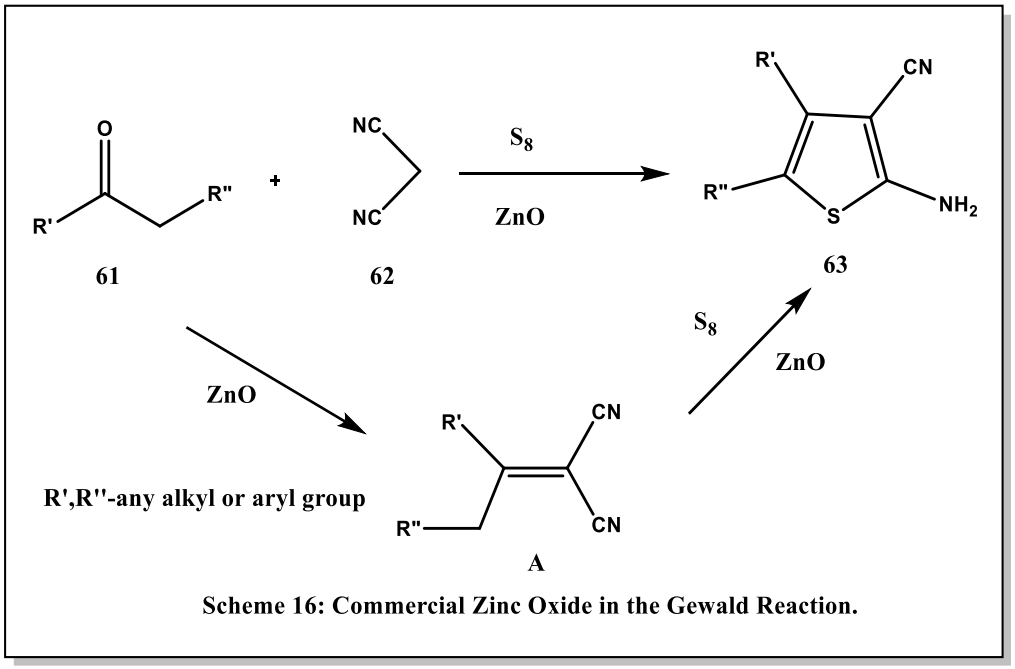
Scheme 15: Microwave accelerated Gewald synthesis.

2.5. A green chemistry approach to Gewald reaction:

Synthesis of 2-aminothiophens via Gewald reaction induced by solar thermal energy: Recently (Sridhar, Rao, Baba, & Kumbhare, 2007), a new synthesis of substituted 2- aminothiophens has been reported by replacing the organic base with KF-alumina under microwave irradiation as well as the heating conditions.. This includes conventional, microwave and ultrasonic heating either in solvent or neat samples (Chowdhury, Mohan, & Scott, 2007). And also many other environmentally friendly techniques such as grind stone, the use of water or PEG as solvents and soluble polymer support were also used (Chen, Spear, Huddleston, & Rogers, 2005). But many of these techniques require a prolonged heating time by the use of harmful catalysts and the energy expenses. Currently researcher was done an efficient multicomponent synthesis of 2-aminothiophens via Gewald reaction induced by free solar thermal energy. In this case a variety of ketones were reacted with ethyl cyanoacetate (or malononitrile) and elemental Sulphur in ethanol and few drops of piperidine as a catalyst under the effect of solar thermal energy. The reaction proceed smoothly to produce 2- aminothiophen derivatives in moderate to good yield (Mekheimer, Ameen, & Sadek, 2008). At the same time, they performed the same reaction at a low temperature under the effect of artificial visible light and the reactants were recovered, unchanged even when exposure was performed for a longer reaction time. This rules out the possibility of a photochemical reaction. The procedure proved to be efficient, simple either in conducting the reaction or isolation of the products of

good yield and applicable to a variety of ketones. It is also economic since solar thermal energy is a free energy.

Use of Commercial Zinc Oxide in the Gewald Reaction: An eco-friendly, simple, and effective process was developed for the synthesis of various multi substituted 2-aminothiophens. In the presence of a catalytic amount of ZnO (5 mole %), ketones or aldehydes, malononitrile and elemental sulfur were produced corresponding 2-aminothiophen derivatives in moderate to high yields (27%−70%) under solvent free conditions at 100 °C (Scheme-16). Zinc oxide is an efficient, readily available, and reusable catalyst which showed very good catalytic activity. The experimental procedure is very simple, rapid, high yielding, and requires no toxic organic solvent or inert atmosphere(Bahrami, Khodaei, & Nejati, 2011).

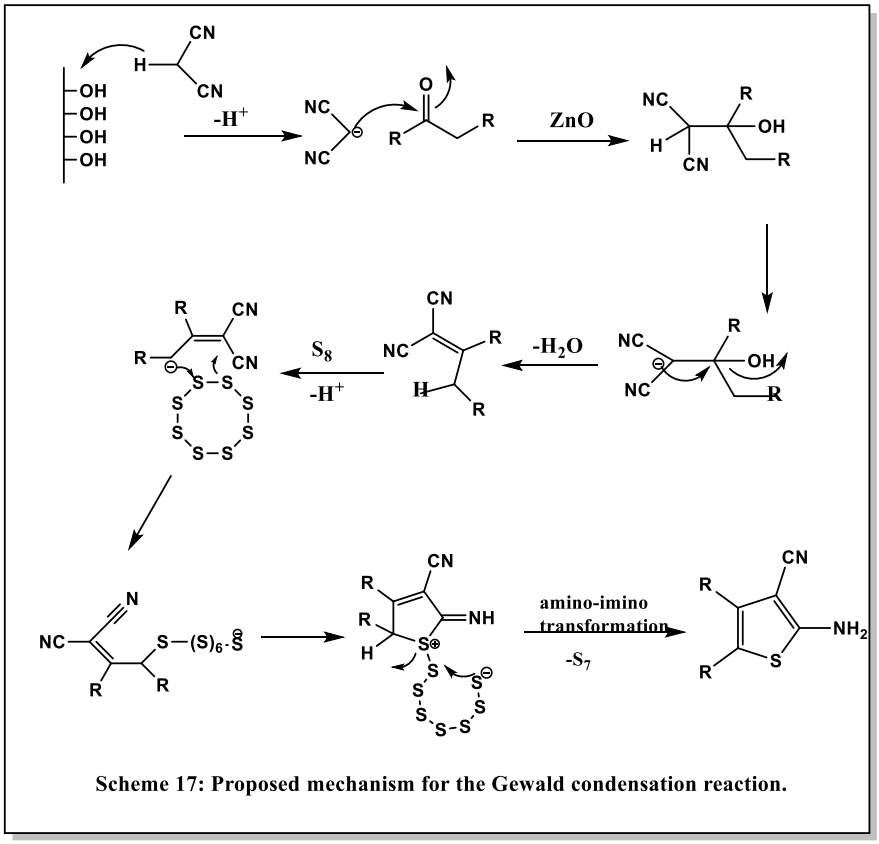


Scheme 16: Commercial Zinc Oxide in the Gewald Reaction.

It was observed that the same reaction did not afford an appreciable amount of the desired product in the absence of catalyst and only 12% it was shown that product was obtained after 6 hours. Whereas, the same reaction was successful in the presence of 2.5 mole % ZnO and obtained 50% of conversion after the same time. This observation was explained by considering the fact that the increase in the number of active sites

with enhancing catalyst amount, resulted in a decreasing concentration of reactants at the active sites.

Mechanism, the most crucial step in this mechanism is focused on the final ring-closure step, which is suggested to be an intramolecular nucleophilic attack of the sulfur atom to the triple bond of the cyano group (Scheme 17) (Tayebee et al., 2012).

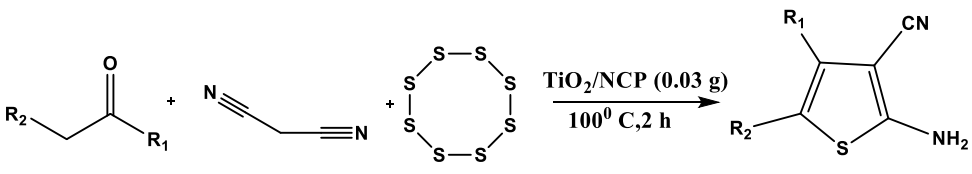


Scheme 17: Proposed mechanism for the Gewald condensation reaction.

Furthermore the catalyst was found to be reusable for at least seven cycles without its loss of activity.

Use of TiO_2/nanoclinoptilolite, act as an efficient Nano catalyst:

The efficiency of the newly prepared TiO_2/NCP Nano composite is act as a useful, low-cost and recyclable Nano catalyst for the synthesis of substituted 2-aminothiophens under solvent-free conditions at 100 °C (Scheme 18).

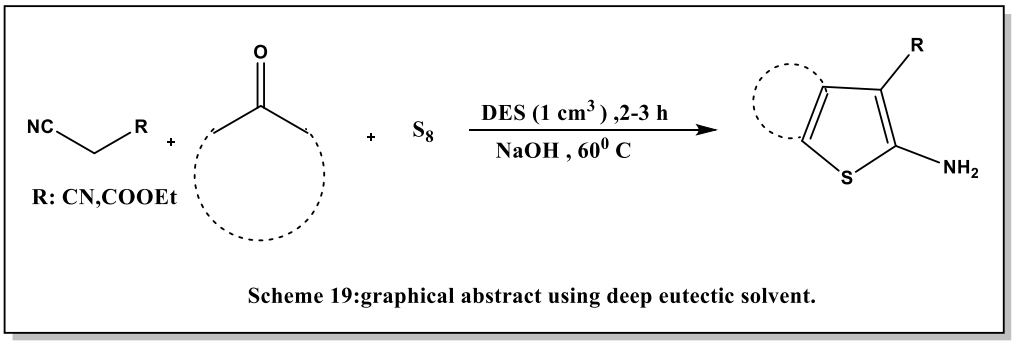


Scheme 18: General formulation for the synthesis of 2 aminothiophene derivatives using TiO_2.

The catalytic activity of TiO_2(32%)/NCP and TiO_2 (27%)/NCP for the synthesis of 2-amino-4,5,6,7- tetrahydro-1-benzothiophen-3-carbonitrile was compared by using the multi component condensation of cyclohexanone, malononitrile and S_8 under solvent-free conditions at 100°C. The results indicate a higher yield (90%) with TiO_2(32%)/NCP than with TiO_2(27%)/NCP (60%) under similar conditions.(Javadi, Tayebee, & Bahramian, 2017). Some data show that only a trace amount of the desired product is obtained in the catalyst-free condition after 2 h; but in the presence of 0.01 g of the Nano catalyst, the yield is increased from 2 to 50%. The higher quantity of the Nano catalyst improves the yield due to the fact by increase in the number of active sites, and besides, the improved contact opportunity between the Nano composite surfaces with the molecules of the starting material. This result was explained by considering agglomeration of the Nano catalyst active sites with increasing catalyst dosage, resulting in a decrease in concentration of the starting material molecules at the active sites and a decrease in yield. Therefore it was considered that 0.03 g of the catalyst is sufficient to achieve maximum yield (Ren, Zhang, Hua, Yue, & Gao, 2009). Clearly, the present procedure give a various economical approach such as short reaction time, easy workup, eco-friendly nature, low cost of the Nano catalyst and economic protocol over the other reported methods. Again the Nano catalyst is reusable for at least four cycles without considerable loss of activity. This method suggestions the benefits of high yield, easy work-up, short reaction time, recoverability of catalyst, inexpensive catalyst, low E-factor and green reaction conditions without formation of any other by-products.

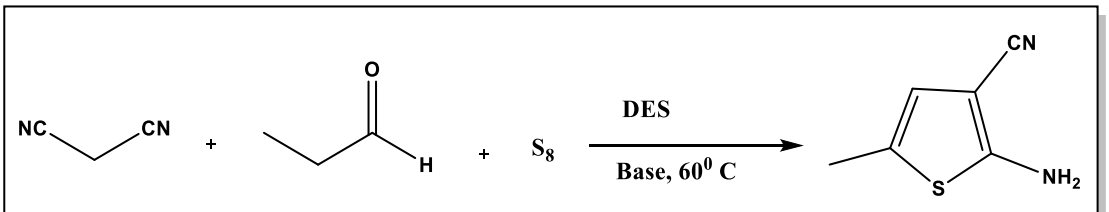
A straightforward one-pot synthesis of 2-aminothiophen derivatives via Gewald reaction in deep eutectic solvents: Deep eutectic solvents (DESs) have been

recognized as a superior green, bio renewable, and biodegradable solvents. (Q. Zhang, Vigier, Royer, & Jérôme, 2012). DESs have a similar characteristics to ionic liquids (ILs), but they have few more advantages relative to ionic liquids. For example DESs are non-toxic, can be sourced from feed stocks, and have a cheaper production procedure and lower cost of the raw materials (Abbott et al., 2011). The effect of choline chloride/urea as a deep eutectic solvent has been investigated in the synthesis of 2-aminothiophen derivatives via a three-component cyclocondensation of a ketone or an aldehyde with activated nitriles and elemental sulfur catalyzed by NaOH as cheap and highly used base. (Scheme 19)



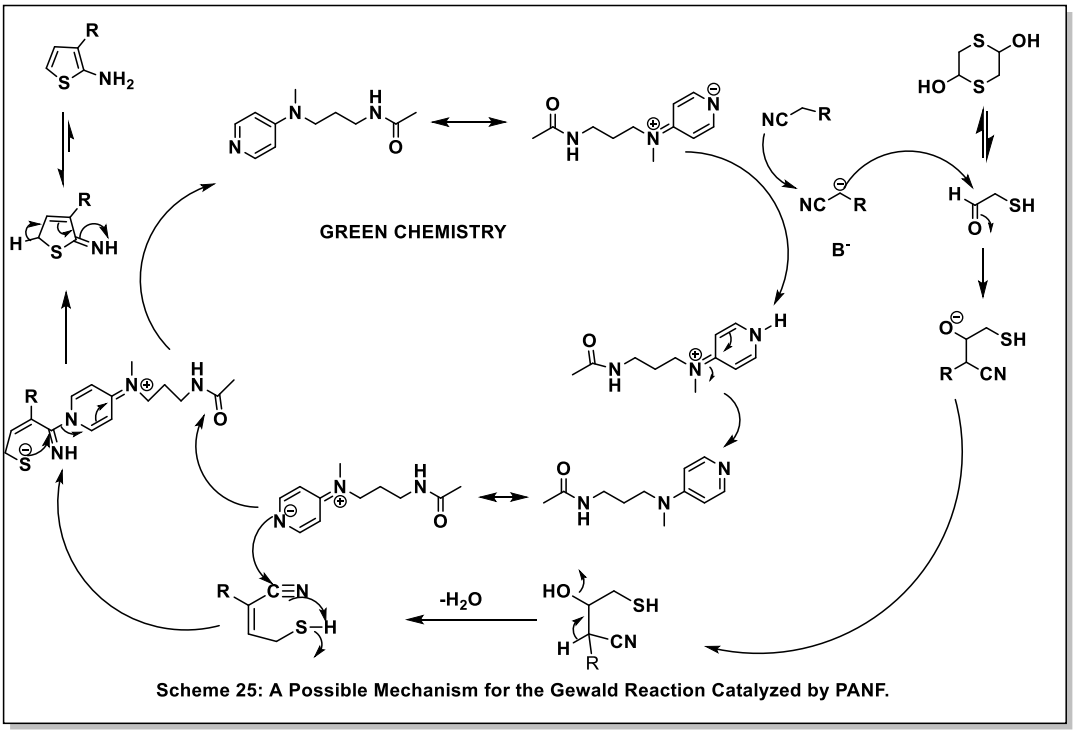
Scheme 19:graphical abstract using deep eutectic solvent.

The advantages of this are eco-friendly, easy to set up, reusability, and a simple separation and purification of products without using chromatography in high yields at short times. Choline chloride/urea may play a dual role in this reaction that is they can act as a solvent and as a cocatalyst which was activated carbonyl and cyano groups via hydrogen bonding. (Shaabani, Hooshmand, & Afaridoun, 2017). The choline chloride/urea can also be recovered and reused for second and third consecutive cycles without any important loss in catalytic activity.



Scheme 20:straightforward one-pot synthesis of 2-aminothiophen derivatives via Gewald reaction in deep eutectic solvents.

Highly efficient polyacrylonitrile fiber catalysts functionalized by aminopyridines for the synthesis of 3-Substituted 2-aminothiophens in water: Polyacrylonitrile fiber (PANF), a very common material in our daily life, has an excellent mechanical strength and contains an abundance of cyano groups which can be easily transformed into carboxyl, amide, amidoxime, etc.(R. Liu, Zhang, & Tang, 1999) Therefore the PANF is a suitable starting material to prepare heterogeneous catalysts. By this method various aminopyridines with different carbon chain lengths and positions functionalized by polyacrylonitrile fiber (PANAPF) catalysts were prepared. It can complete the reaction for 5 to 30 min in good to high yield. Among all the solvents, water gives the best result (92%).(Moroi, Bilba, & Bilba, 2004) Here a possible mechanism has been proposed, in which the nucleophilicity of AP was play an important role in the Gewald reaction.



Scheme 25: A Possible Mechanism for the Gewald Reaction Catalyzed by PANF.

A series of active nitriles proceed under the catalysis of PANF to give moderate to excellent yields from 76% to 93%. After completion of the reaction, the catalyst can separated easily from the reaction system and conveniently reused at least four times. It shown that the catalyst has many advantages, such as highly efficient activity, broad substrate scope, an environmentally friendly solvent, and good recyclability. It is believed that more, new applications of PANAPFs will be developed in the future.

2.6. Biological Activities of thiophenes and thieno-pyrimidines:

Thieno pyrimidine is among those fused pyrimidines rings which found to have a wide variety of pharmacological and biological applications which exhibit a variety of biological activities such as antimicrobial, anti-inflammatory, bronchodilator activity. It is evident that purine as an endogenous scaffold was played an important biochemical role in variety of regular physiological functions such as respiration, inflammation, cell proliferation, and so on. As a bioisoster to purines, thieno[2,3-*d*]pyrimidines were also found to exhibit several biological activities probably due to the interaction with various physiological elements. As a logical consequence of thiophene the phenyl isosterism, similarly thieno pyrimidines can be considered as bioisosteres of quinazolines, which are extensively used in scientific and patent literature as displaying a superfluity of biological activities.

The synthesis of the thieno pyrimidine derivatives as potential surrogates for this quinazoline core structure has, therefore, became a routine strategy in modern drug design and development.

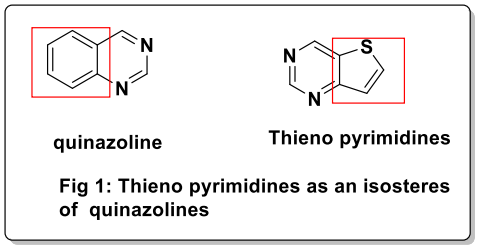


Fig 1: Thieno pyrimidines as an isosteres of quinazolines

Antimicrobial activity: The research study reports the successful synthesis of the antimicrobial, as well as antibacterial and antifungal compound using thieno[2,3-*d*]pyrimidine as a core unit. Furan rings also responsible for good antimicrobial activity and hence compounds **a**, **b**, **c** and **d** exhibited more potent in anti-microbial activity of all tested pathogenic strains. These novel thieno[2,3-*d*]pyrimidine derivatives have proved to be promising agent for further efficacy evaluation (Prabhakar, Kondra Sudhakar Babu, & Latha, 2017).

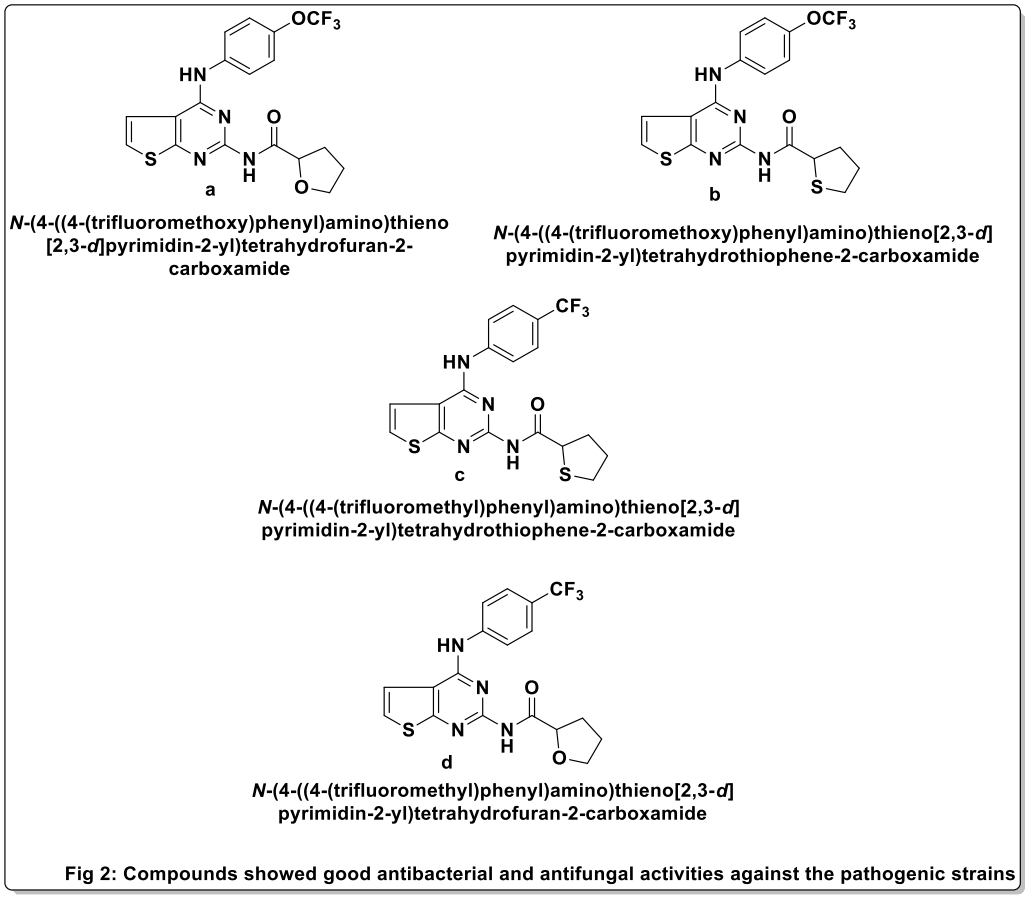


Fig 2: Compounds showed good antibacterial and antifungal activities against the pathogenic strains

Thieno[2, 3-*d*] pyrimidine-amides as Potential Anticancer Agents: The anticancer activity of the thienopyrimidines, through inhibition of various protein kinase enzymes has also been investigated (Sutherlin et al., 2010). A number of drug candidates which is a potent and orally bioavailable currently undergo Phase II clinical trials,GNE-490 and GNE-493 also possess this thieno[2, 3-d]pyrimidine scaffold.(Fig 6) (Folkes et al., 2008)

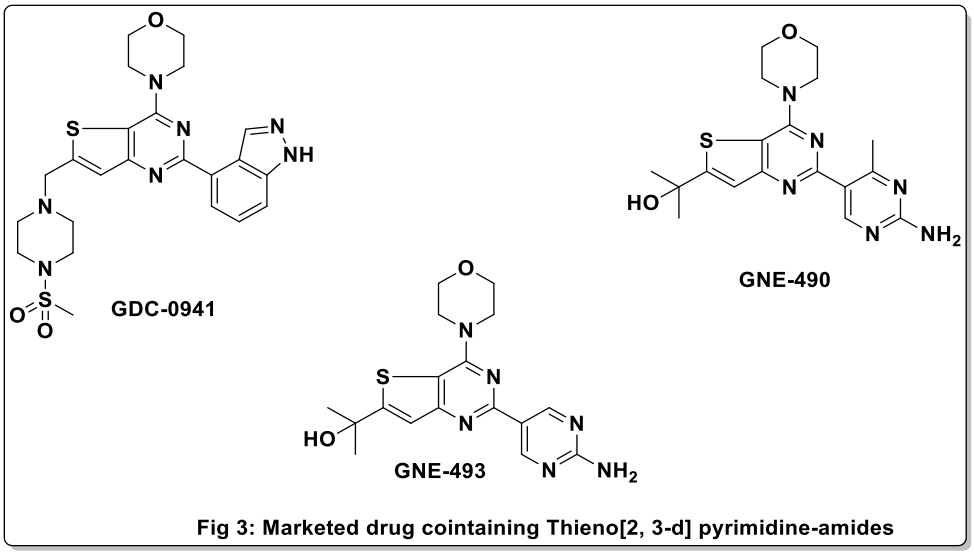


Fig 3: Marketed drug cointaining Thieno[2, 3-d] pyrimidine-amides

Thienopyrimidinedione Derivatives as Potential Antihypertensive Agent: The use of antihypertensive drugs such as diuretics, α-agonists, α-and β-antagonist, calcium channel blockers, and the ACE inhibitors has been very effective. Unfortunately, these antihypertensive drugs because of their various side-effect e.g. hyperuricemia, sedation, tachycardia or postural hypertension (MacCoss, Ryu, & Matsushita, 1978). The novel thieno[3,4-d]-, thieno[3,2-d]-, and thieno[2,3-d]pyrimidine ring isosteres of **b** were prepared and shows good to excellent antihypertensive activity. Placement of the various substituents at the 2-, 3-, or 4-position of the phenyl ring affected the SAR activity with these compounds like the 2-substituted phenylpiperazine group showing the greatest activity. The most potent compounds were those in which the 2-methoxy substituent on the phenyl piperazine moiety and hydrogen at the N-1 position **(c-e)** (Russell et al., 1988).The literature shows that the utility of replacing the quinazoline ring of **b** with a thienopyrimidine moiety produce two compounds **c** and **d** which are more potent as α-antagonists than prazosin and equipotent to the quinazoline-2,4-dione **b.** (fig-4).

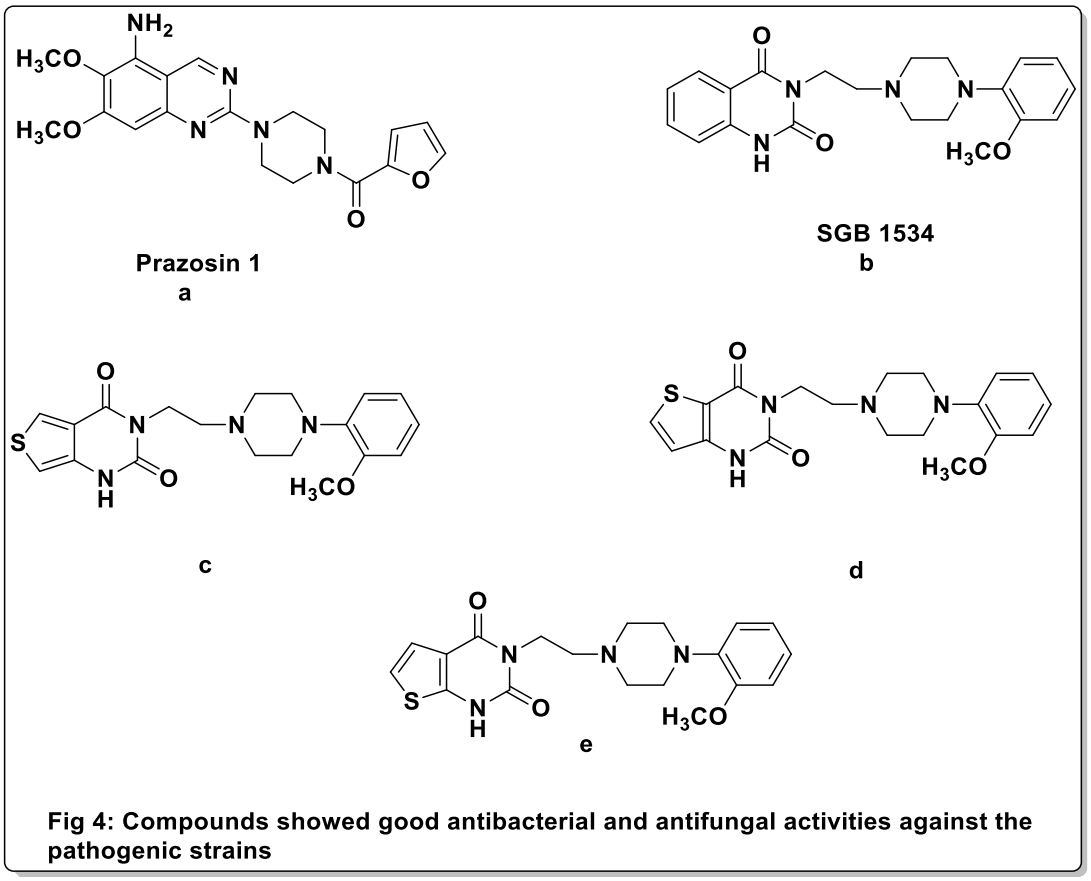


Fig 4: Compounds showed good antibacterial and antifungal activities against the pathogenic strains

Thieno[2,3-d]-pyrimidines as New Anti-inflammatory and Analgesic Agents: Rheumatic diseases are the most predominant causes of disability in Western countries, and the non-steroidal anti-inflammatory drugs (NSAIDs) are still the most commonly used remedies(Wolfe, Lichtenstein, & Singh, 1999), (El-Gazzar, Hussein, & Hafez, 2007). However, they synthesized thioglycosides of thieno[2,3-d]- pyrimidine the literature the derivatives of **1a,b**, which did not carry the S-glycosides moiety on the second position, are weaker than that bearing S-glycosides residue on this position. When substituents is considered, it was determined that the substituted 3-aminothieno[2,3-d]pyrimidines bearing S-glycosides (**4a,b and5a–d**) had a stronger inhibitory effect on analgesic, anti-inflammatory activity than that of the acetylated-S-glycosides derivatives (**2a,b and 3a–d**). According to this phenomenon they suggest that the S-glycoside with free hydroxyl groups was an important structural characteristic of the analgesic-anti-inflammatory action(Hafez, El-Gazzar, & Nawwar, 2010)(fig-5).

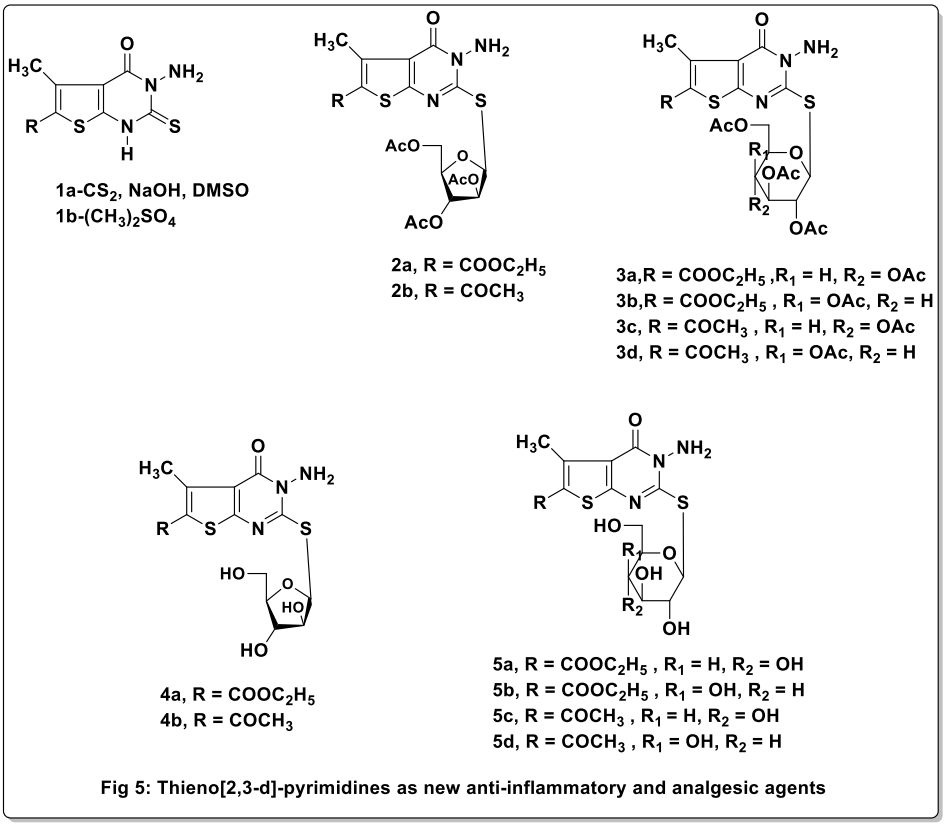


Fig 5: Thieno[2,3-d]-pyrimidines as new anti-inflammatory and analgesic agents

Thieno[2,3-d]pyrimidine Derivatives as Anti-Inflammatory Agents: In addition, this is a bioisostere of quinazoline, so thieno[2,3-*d*]pyrimidine has been used widely for a pharmacophore and synthesis of compounds with various biological activities including anti-tumor(Ji et al., 2014), anti-microbial(Abdelaziz, El-Sehrawi, & Mohareb, 2015), anti-viral(Hafez, Hussein, & El-Gazzar, 2010), anti-diabetic(Deng et al., 2011). The inflammatory activity of the compound **B1**,tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine compound has been reported so now scientist attempted to change the amino group into carbonyl to obtain the compound **A1**, which contain hydrogen bond receptor to improve the binding between compounds and inflammatory cytokine. It was found that the anti-inflammation activity, **A1** is superior to **B1.** These literature suggest that the **A2**, **A3** and **B2** may work as an effective anti-inflammatory agent Moreover, further experiments showed that these compounds possess an anti-inflammatory activity in vivo, with compound **A3** possesses similar activities to the drug Indomethacin (Y. Zhang et al., 2017)(fig-6)

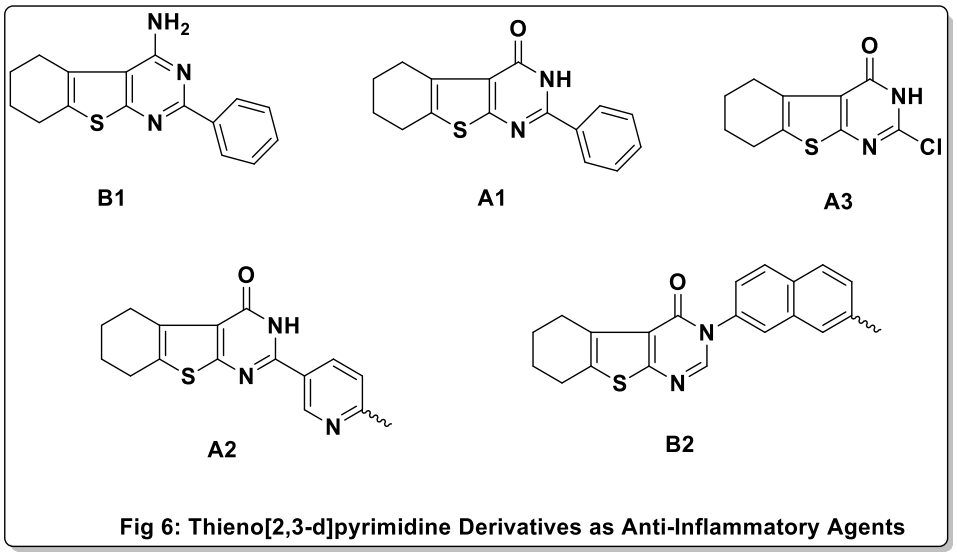


Fig 6: Thieno[2,3-d]pyrimidine Derivatives as Anti-Inflammatory Agents

4-Substituted Thieno[2,3-*d*] pyrimidines as Potent Antibacterial Agents: For discover a new class of antibacterial agents with an improved efficiency and to overcome the problem of drug-resistant, some novel 4-substituted thieno[2,3-*d*] pyrimidines have been synthesized and evaluated for their antibacterial activity. Also they reported the similar compounds for antiproliferative activity(Rupinder Kaur Gill et al., 2016). The antibacterial activity of the 4-substituted anilino-thieno[2,3-*d*] pyrimidines ***4a–l***, it was shown that the compounds **4***e*, **4*f***, **4*g***, **4*h*** and **4*l*** showed moderate inhibitory potential against the *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli*. On the other hand if the anilino group is replaced by the with azacyclic ring like morpholine or piperidine in **2*a–f***, significantly improved the antibacterial activity against all pathogenic strains, with the only exception of from these activity is the compound **2*a***. Furthermore it was deceptive that the 4-carboxyanilino substituted derivatives **3*a–c*** displayed pronounced effect against *S. aureus* and *B. subtilis*, while compound **3*b*** and **3*c*** also showed significant activity against *P. aeruginosa* and *E. coli*. The increased activity of the compound **3*b*** compared to **3*c*** and **3*a*** suggests the importance of 5,6-dimethyl substitution on thieno[2,3-*d*] pyrimidine than the cyclopentane fused tricyclic derivative. Particularly, the *N*-4-chlorophenylbenzamide derivatives **1*a***, **1*c*** and **1*e*** exhibited better activity than the *N*-4methoxyphenylbenzamide derivatives of **1*b***, **1*d*** and **1*f*** (Rupinder K Gill et al., 2017) (fig-7)

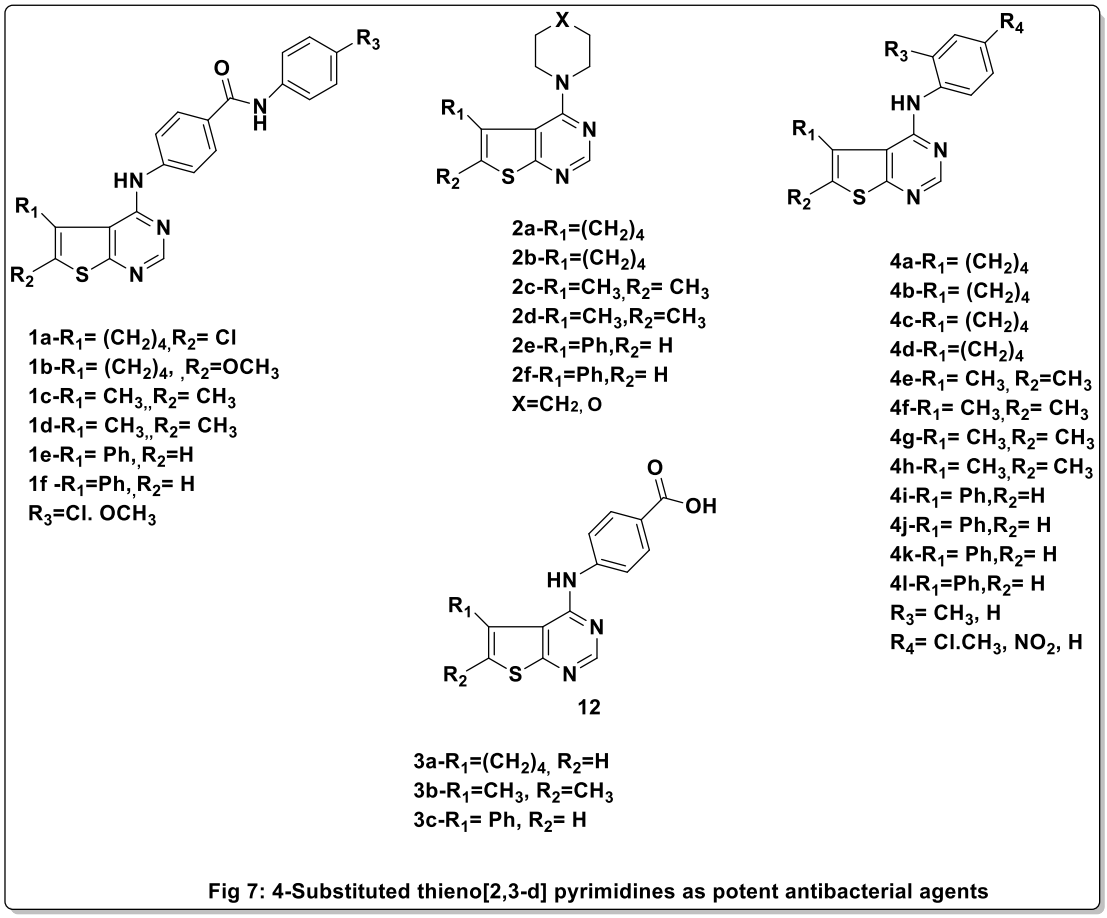


Fig 7: 4-Substituted thieno[2,3-d] pyrimidines as potent antibacterial agents

***N*-substituted thieno[3,2-*d*] pyrimidine Derivatives as Potent Antitumor Agent :** Thiophene derivatives are among the most important chemotherapeutic agents and are widely used as antitumor(Ni et al., 2011), antimetabolite(Tan, Zhang, Hui, Zhao, & Zhu, 2014), antiviral, anti-HIV-1(Kim et al., 2014), antiproliferative(Temburnikar et al., 2014), antimicrobial(Hafez, Hussein, et al., 2010), analgesic and anti-inflammatory(Hafez, El-Gazzar, et al., 2010)agents. Among these active compounds, thieno[3,2-*d*]pyrimidines have generated wide-spread interest due to their remarkable antitumor activities(Z. Liu et al., 2014). So they work on the synthesis and evaluation of novel thiophenes bearing biologically active sulfonamide, pyrole, pyrrolopyrimidine derivatives, and thieno[3,2-*d*]pyrimidine derivatives containing 1,2,4-triazole moiety, as antitumor and antibacterial agents.. Activities of these compounds were strongly dependent on the basic skeleton of the molecules and the nature of the heterocyclic

ring attached to the thiophene unit as well as on the nature of the substituent at the thiophene unit.(Hafez, Alsalamah, & El-Gazzar, 2017)(fig-12)

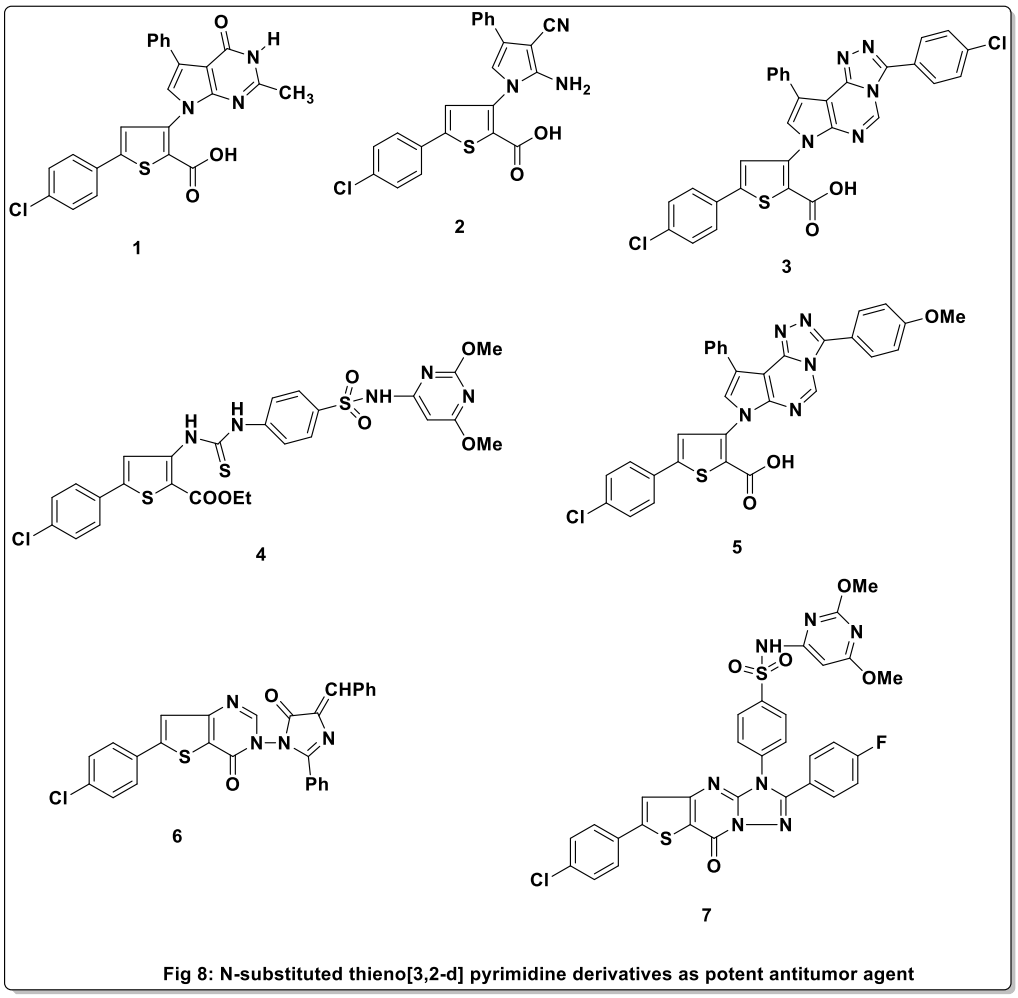


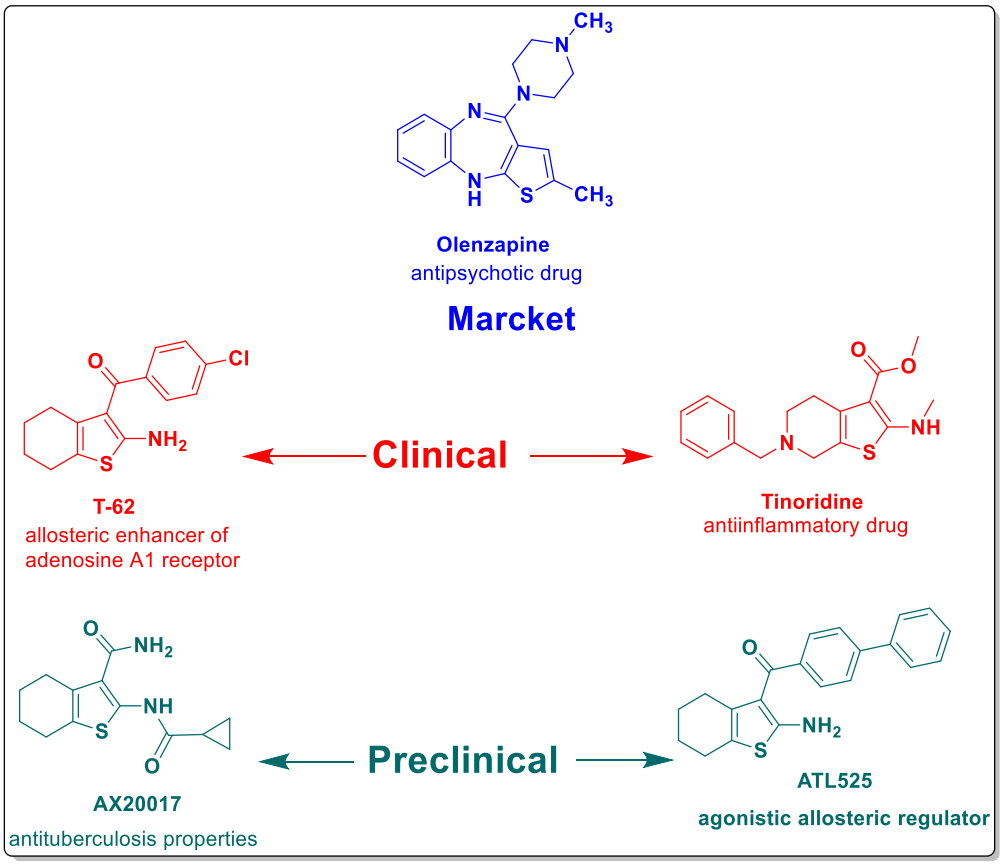
Fig 8: N-substituted thieno[3,2-d] pyrimidine derivatives as potent antitumor agent

CHAPTER 3

RATIONALE & OBJECTIVES

3.1 Rationale

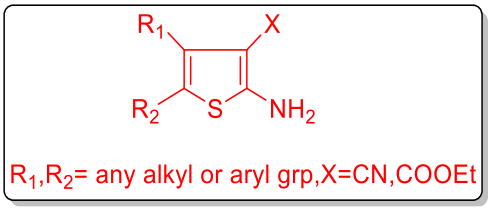
The synthesized thiophene derivatives are useful precursor to synthesize many active New Chemical Entities (NCE's).



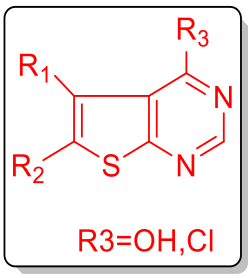
3.2. Objective:

Based on the literature search we set the following objective:

- To synthesize the following 2-amino thiophene under Gewald reaction condition.



- To synthesize thieno[2,3-*d*]pyrimidines from the above synthesized 2-aminothiophenen derivatives.



CHAPTER 4

MATERIALS AND METHOD

Materials and method:

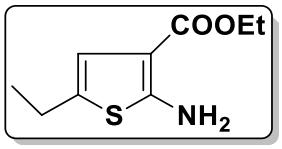
4.1 Synthesis:

4.1.1 General-

1. All the reagent were purchased from Sigma-Aldrich, Loba-Chemic Pt. Ltd., and Avra, Spectrochem synthesis Ltd, which were used without any additional purification.
2. For weighing purposes Analytical balance was used. Rotary evaporator, heating mantle, spinot, digital hot top, oven and vacuum filtration was used for workup of reaction procedure.
3. The progress of a reaction can be monitored by TLC, petroleum ether/ ethyl acetate used as a mobile phase on pre-coated TLC plate (Merck) in UV/ fluorescent cabinet.
4. Melting point were recorded on melting point apparatus (SMP-30) with open glass capillary tubes and were uncorrected.
5. Infrared spectra (IR) of compound was recorded with KBr/neat on a Bruker FT-IR spectrophotometer.
6. ^{1}H and ^{13}C NUCLEAR MAGNETIC RESONENCE (NMR) spectra was recorded at IIT Bhubaneswar in $CDCl_3$/ d^6- DMSO and $CDCl_3$ on a Bruker Advance II 400 MHz using TMS(δ= 0) as an internal standard.
7. Mass spectra were recorded on Shimadzu CGMS-QP2010 with EI Mode available at Central University of Punjab.

4.2 General procedure for synthesized compound:

4.2.1 Synthesis of ethyl 2-amino-4-ethylthiophene-3-carboxylate (PRA-1):



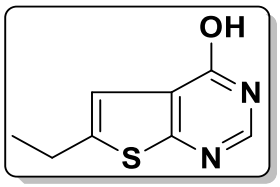
Into a mixture of butaraldehyde (12ml, 0.055mol, 1.0eq), ethyl 2-cyanoacetate (11.85 ml, 0.055mol, 1.0 eq), and Sulphur (3.4 g, 0.055mol, 1.0 eq) in 80mL of ethanol was added diethylamine (13ml, 0.055mol, 1.0 eq) dropwise. The mixture was stirred for 6 hour at temperature 60℃.

Yield: 72%; color: Orange; m.p:72℃.

FTIR(in KBr): 3438 cm^{-1} (NH_2 stretching), 1673 cm^{-1} (NH_2 bending), 1759 cm^{-1} (ester COOEt).

MS(EI): m/z: 199[M^+], 83 (base peak).

4.2.2 Synthesis of 6-ethylthieno[2,3-*d*]pyrimidin-4-ol (PRA-2):



The mixture of ethyl 2-amino-4-ethylthiophene-3-carboxylate (PRA-1) (10g, 0.15 mol) in 35 ml of formamide was heated at reflux 180°C for 12h and cooled down. The mixture was poured into ice-water and filtered using vacuum filtration.
Yield: 89%; Colour: brown; m.p:196 ^0C

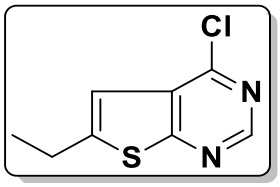
FTIR (in KBr): 3396 cm^{-1} (alcoholic OH)

^1H NMR (400MHz, $CDCl_3$, TMS=0) δ: 12.79 (1H, s), 8.05 (1H, s), 7.18 (1H, s), 2.9 (2H, q, J-7.2), 1.3(3H, t, J-7.6).

$^{13}CNMR$ (100MHz, $CDCl_3$,TMS=0) δ: 164, 159, 146, 142, 124, 116, 24, 15.

MS (EI): m/z: 180[M^+], 61(base peak).

4.2.3. Synthesis of compound 4-chloro-6-ethylthieno[2,3-*d*]pyrimidin (PRA-3):

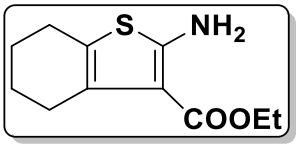


A Suspension of compound (PRA-2)(8g, 0.11 mol)in 20 mL of $POCl_3$ was heated at reflux for 6 h. then the mixture was poured onto ice and filtered using vacuum filtration.

Yield: 92%; Color: grey; m.p: 55 ^{0}C.

MS(EI): m/z: 198[M^+], 91(base peak).

4.2.4. Synthesis of compound ethyl 2-amino-,5,6,7-tetrahydrobenzo-[*b*]-thiophene-3-carboxylate (PRA-4):



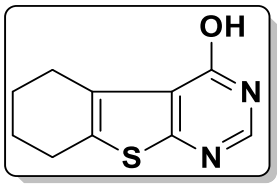
Into a mixture of cyclohexanone (25ml, 0.24mol, 1.0 eq), ethyl 2-cyanoacetate (26ml., 0.24 mol, 1.0 eq), and Sulphur (7gm., 0.24 mol, 1.0 eq) in 100ml of ethanol was added dietylamine(24ml, 0.24 mol, 1.0 eq)added dropwise. The mixture was stirred for 4h at temperature 55°. The reaction mixture was diluted with ice-water and the precipitate was collected by vacuum filtration

Yield: 73%; color-yellow; m.p-117 ^{0}C .

FTIR (in KBr): 3445 cm^{-1} (NH_2 stretching), 1543 cm^{-1} (NH_2 bending), 1734 cm^{-1} (ester COOEt).

MS(EI): m/z: 225[M^+], 179(base peak).

4.2.5: Synthesis of 5,6,7,8-tetrahydrobenzo-[4,5]thieno-[2,3-*d*]pyrimidin-4-ol (PRA-5):



The mixture of compound (PRA-4) (15g, 0.16 mol) in 35 ml of formamide was heated at 180°C at reflux for 14h and cooled down. The mixture was poured into ice-water and filtered using vacuum filtration.

Yield: 85%; Color- Brown; m.p.-248^0 .

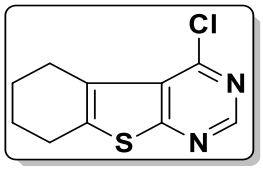
FTIR(in KBr): 3469 cm^{-1} (alcoholic -OH) .

MS(EI): m/z: 206[M$^+$], 178(base peak) .

^{1}H NMR (400MHz, DMSO-d$_6$, TMS=0) δ: 12.29 (1H, s), 7.97 (1H, s), 2.7 (2H, t,J-3.2), 2.8 (2H, t,J-6), 1.7(4H, m).

^{13}CNMR (100MHz, DMSO-d$_6$, TMS=0) δ: 162, 158, 145, 132, 131, 123, 25, 24, 22.9, 22.2.

4.2.6: Synthesis of compound 4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin (PRA-6):



A Suspension of compound PRA-5(10 g, 0.12 mol) in 20 mL of $POCl_3$ was heated at reflux for 4h.and the residue was poured into ice and filtered.

Yield: 92%; Color- White; m.p-178 ^{0}C

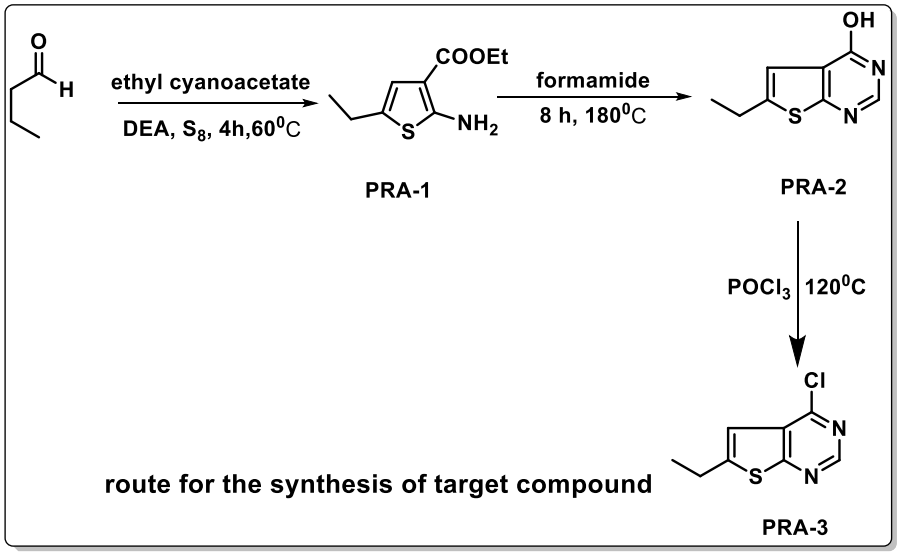
MS(EI): m/z: 226[M$^+$], 198(base peak).

CHAPTER 5

RESULTS AND DISCUSSION

5.1 Result and Discussion:

For the synthesis of targeted compound we follow the route (scheme-26).



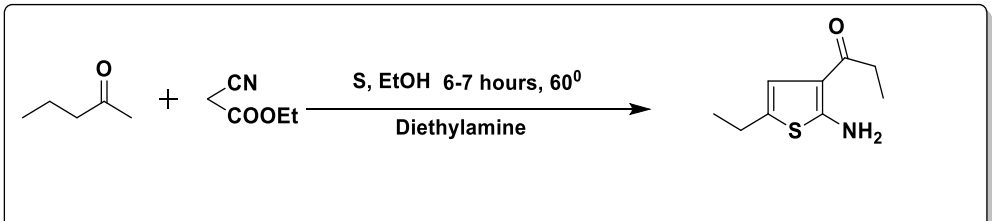
5.1.1. Synthesis of ethyl 2amino-4ethylthiophene-3-carboxylate (PRA-1):

In the step I the mixture of butaraldehyde, ethyl 2-cyanoacetate, and sulpher in ethanol was stirred and the base diethylamine added dropwise to maintain the temp. 60̊. The progress of the reaction was monitored by the TLC. The compound was used for the next step without further purification. (Scheme-27).

Formation of these compound was confirmed by IR and Mass Spectroscopy.

FTIR(in KBr): 3438 cm^{-1} (stretching), 1673 cm^{-1} (bending) IR spectrum shows the characteristic peaks of primary amine (stretching-3438 cm^{-1}), (bending 1673 cm^{-1}) and ester at 1759 cm^{-1}.

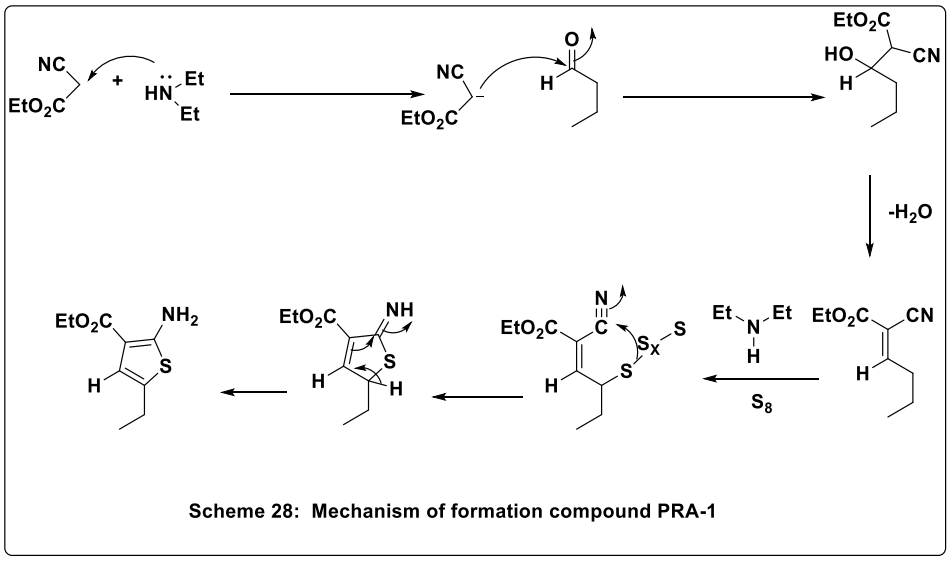
Mass spectroscopy shows that the m/z: 199[M^{+}], 83 (base peak).



Scheme 27: Ethyl 2amino-4ethylthiophene-3-carboxylate (PRA-1).

Mechanistically:

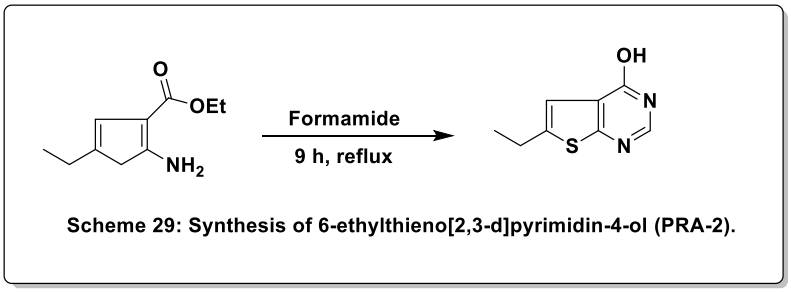
The formation of the above reaction can be predicted as the nucleophilic attack of one of the nitrogen's lone pair of ethyl cyanoacetate attach on electrophilic carbon of butaraldehyde via intermediate with loss of one molecule of water as shown below.



Scheme 28: Mechanism of formation compound PRA-1

5.1.2. Synthesis of 6-ethylthieno[2,3-d]pyrimidin-4-ol (PRA-2):

The compound PRA-1 was reflux with formamide180°C for 12h and cooled down. The progress of the reaction was monitored by the TLC. The mixture was poured into ice-water and filtered using vacuum filtration. The compound was used for the next step without further purification (scheme-29).



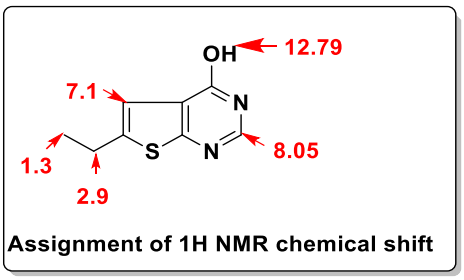
Scheme 29: Synthesis of 6-ethylthieno[2,3-d]pyrimidin-4-ol (PRA-2).

The formation of the compound was confirmed by IR, Mass, and NMR spectroscopy. FTIR (in KBr): 3396 cm^{-1} (alcoholic -OH).

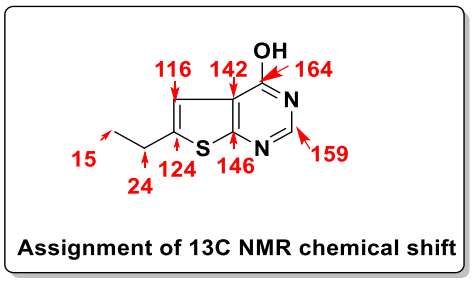
IR spectrum shows the characteristic peaks of Alcoholic group at 3396 cm^{-1} (alcoholic -OH) this confirm the presence of –OH group.

Mass spectroscopy shows that the m/z: 180[M^+], 61(base peak).

NMR spectroscopy shows that the H-1 is appeared at 12.79(s) due to the –OH grp, the H-2 is more de-shielded due to electron- withdrawing nature of N and appeared as 8.0(s). The H-3 appeared as 7.1(s) due to aromatic ring and the H-4, H-5 appeared as respectively 2.9 (q), 1.3 (t).



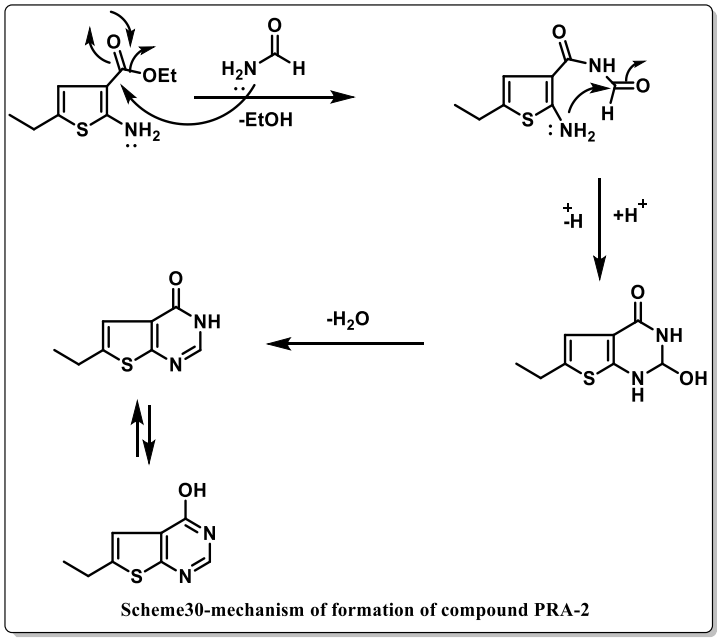
Assignment of 1H NMR chemical shift



Assignment of 13C NMR chemical shift

The C-1 appeared as 164 due to the more de-shielding effect of -OH group. Now the C-2 is more de-shielded due to the two N grp which is electron withdrawing in nature and appeared at 159. The C-3 is also de-shielded and appeared at 146 higher than 4 because in 4 there is a ethyl grp attached which shielded the C. The C-5 is also more de-shielded than 6 due to the presence of neighboring keto grp which is electron withdrawing in nature and appeared as 142 whereas C-6 appeared as 116. And the C-7 and C-8 appeared at respectively 24 and 15.

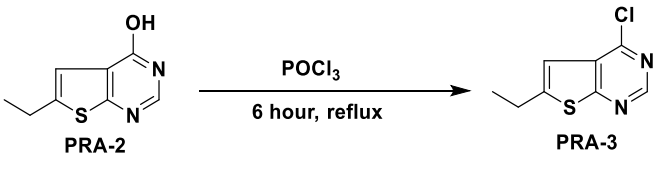
Mechanistically: The formation of PRA-2 can be predicted as the nucleophilic attack of one of the nitrogen's lone pair of formamide of carbon of compound PRA-1 via intermediate with loss of one molecule of water and EtOH as shown below.



Scheme30-mechanism of formation of compound PRA-2

5.1.3: Synthesis of compound 4-chloro-6-ethylthieno[2,3-*d*]pyrimidin (PRA-3):

Further reflux of compound PRA-2 with $POCl_3$ was heated for 6 h. to afford compound PRA-3(scheme-31). The progress of the reaction was monitored by the TLC.

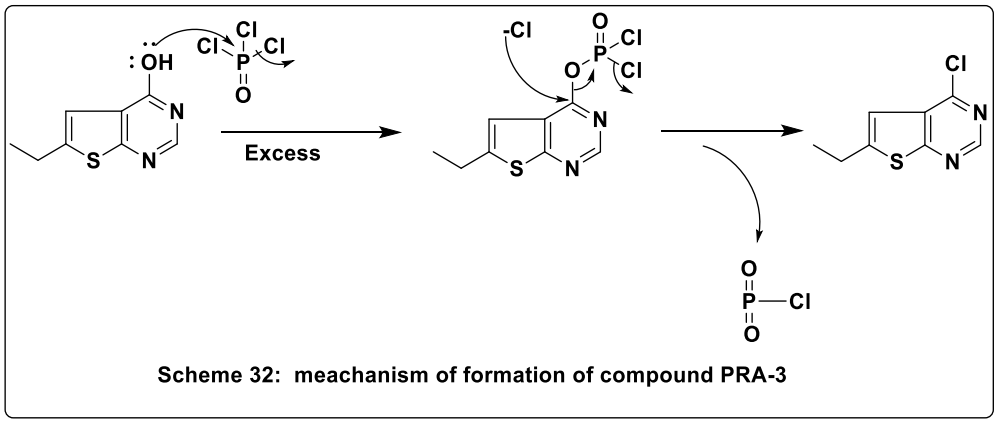


Scheme 31: Synthesis of compound 4-chloro-6-ethylthieno[2,3-d]pyrimidin (PRA-3).

The formation of the compound is confirmed by mass spectroscopy. From mass spectroscopy we also confirmed the formation of these compound.

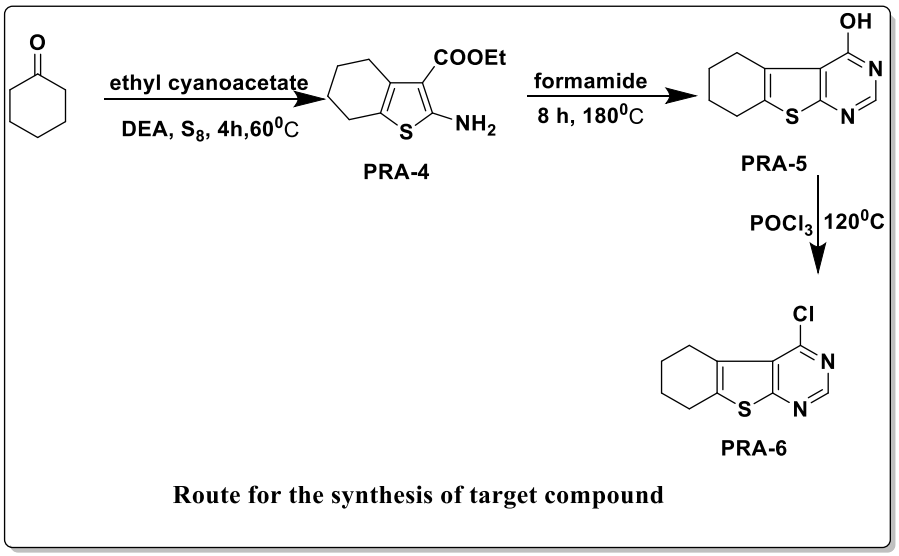
MS(EI): m/z: 198[M^+], 91(base peak).

Mechanistically: The formation of PRA-3 can be predicted as the nucleophilic attack of oxygen's lone pair of compound PRA-2 on electrophilic phosphorus of $POCl_3$ via intermediate with loss of $POCl_2$ as shown below.



Scheme 32: meachanism of formation of compound PRA-3

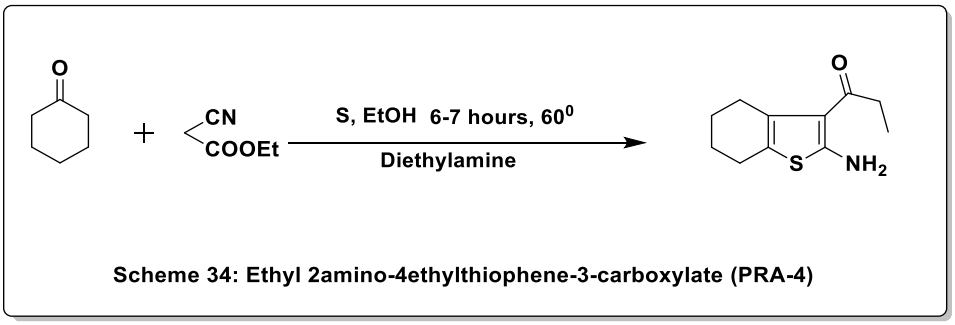
For the synthesis of targeted compound we follow the route (scheme-33):



Route for the synthesis of target compound

5.1.4. Synthesis of compound ethyl-2-amino-,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate(PRA-4):

Into a mixture of cyclohexanone, ethyl 2-cyanoacetate, and sulphur in ethanol diethylamine was added dropwise to maintain the temp 60˚. The progress of the reaction was monitored by the TLC. The compound was used for the next step without further purification (scheme 34).



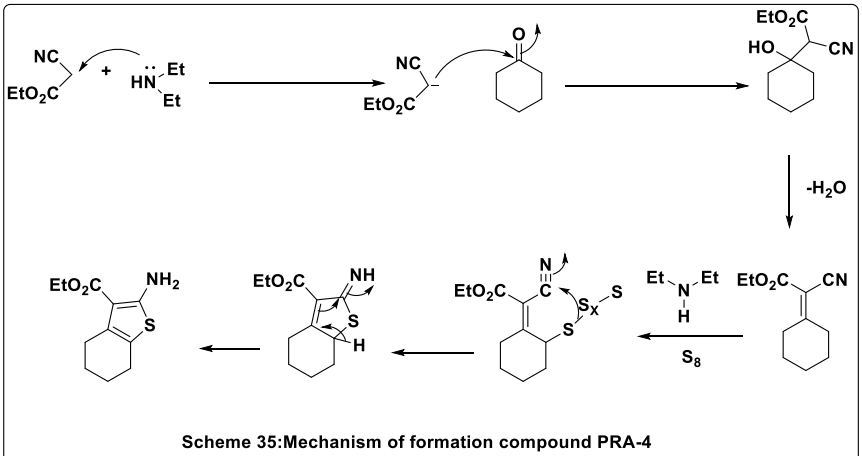
Scheme 34: Ethyl 2amino-4ethylthiophene-3-carboxylate (PRA-4)

Formation of these compound was confirmed by IR and Mass Spectroscopy.

FTIR(in KBr): 3445 cm^{-1} (NH_2 stretching), 1543 cm^{-1} (NH_2 bending) .IR spectrum shows the characteristic peaks of primary amine (stretching-3445 cm^{-1}), (bending 1543 cm^{-1}) and ester at 1734 cm^{-1}.

Mass spectroscopy shows that the m/z: 225[M^+], 179(base peak).

Mechanistically: The formation of the above reaction can be predicted as the nucleophilic attack of one of the nitrogen's lone pair of ethyl cyanoacetate attach on electrophilic carbon of cyclohexanone via intermediate with loss of one molecule of water as shown below.

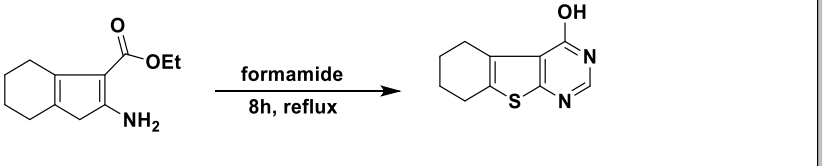


Scheme 35:Mechanism of formation compound PRA-4

5.1.5. Synthesis of 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-ol (PRA-5):

The compound (PRA-4) was reflux with formamide 180° C for 14h. The progress of the reaction was monitored by the TLC. The mixture was poured into ice-water and filtered

using vacuum filtration. The compound was used for the next step without further purification (scheme-36).

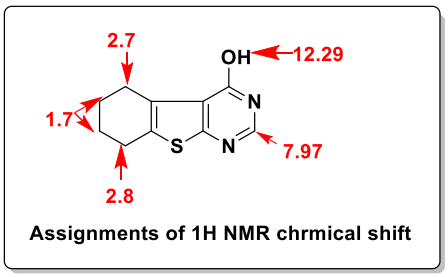


Scheme 36: Synthesisof 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-ol (PRA-5)

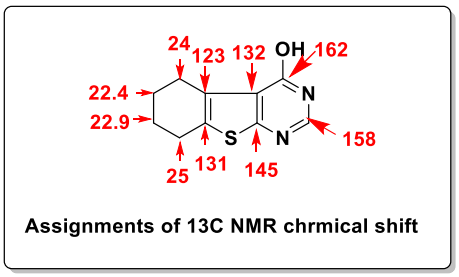
The formation of the compound was confirmed by IR, Mass, and NMR spectroscopy. FTIR(in KBr): 3396 cm^{-1} (alcoholic OH) .FTIR spectrum shows the characteristic peaks of Alcoholic group at 3469 cm^{-1} (alcoholic OH) this confirm the presence of –OH group.

Mass spectroscopy shows that the m/z: 206[M^{+}], 178(base peak)

NMR spectroscopy shows that the H-1 is appeared at 12.29(s) due to the –OH grp, the H-2 is more deshielded due to electron-withdrawing nature of N and appeared as 7.9 (s). The H-4 appeared as 1.7 (m) due to neighbouring H it shows multiplet.



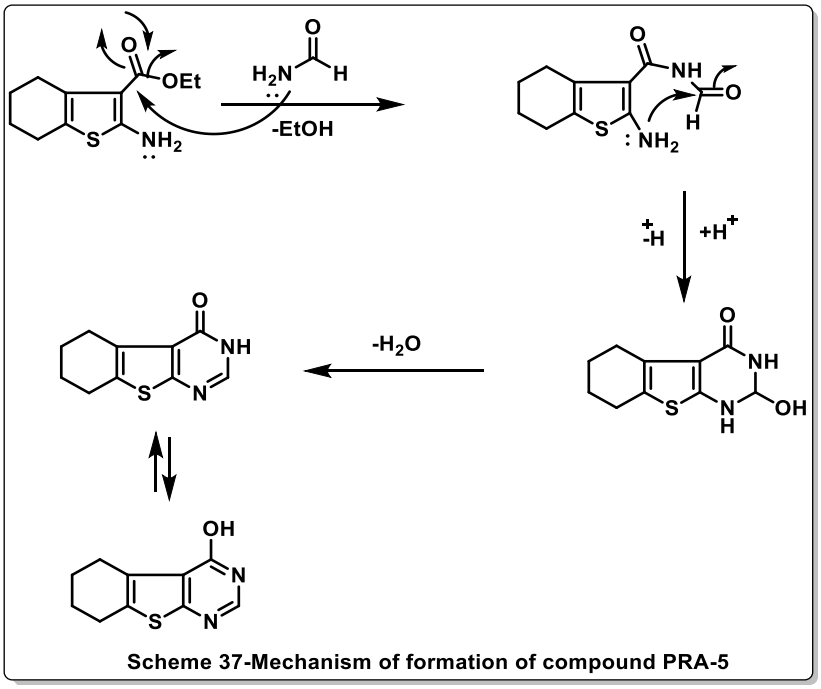
Assignments of 1H NMR chrmical shift



Assignments of 13C NMR chrmical shift

The C-1 appeared as 162 due to the presence of –OH grp. Now the C-2 is more deshielded due to the two N grp which is electron withdrawing in nature and appeared at 158. The C-3 is also deshielded and appeared at 145 higher than 4 because in 4 there is a cyclohexane ring attached which shielded the C-4 and appeared at 132. The C-7 and C-10 are more deshielded because of the presence of neighboring aromatic ring.

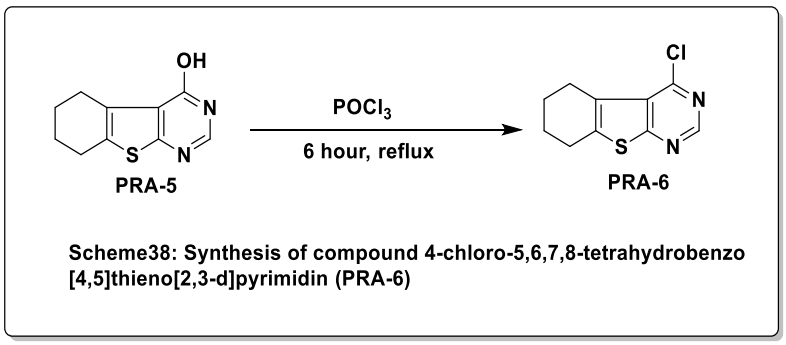
Mechanistically: The formation of PRA-5 can be predicted as the nucleophilic attack of one of the nitrogen's lone pair of formamide to the carbon of PRA 4via intermediate with loss of one molecule of water and EtOH as shown below.



Scheme 37-Mechanism of formation of compound PRA-5

5.1.6: Synthesis of compound 4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin (PRA-6):

Further reflux of compound PRA-5 with $POCl_3$ was heated for 6 h. to afford compound PRA-6(scheme-38). The progress of the reaction was monitored by the TLC.



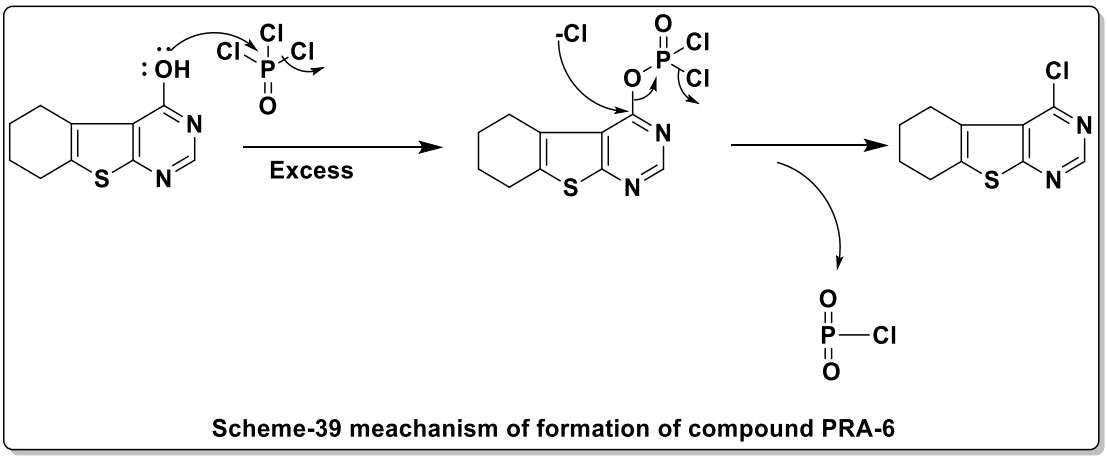
Scheme38: Synthesis of compound 4-chloro-5,6,7,8-tetrahydrobenzo [4,5]thieno[2,3-d]pyrimidin (PRA-6)

The formation of the compound is confirmed by mass spectroscopy.

Further from mass spectroscopy we also confirmed the formation of these compound.

MS(EI): m/z: 226[M^+], 198(base peak)

Mechanistically: The formation of PRA-6 can be predicted as the nucleophilic attack of oxygen's lone pair of compound PRA-5 on electrophilic phosphorus of $POCl_3$ via intermediate with loss of $POCl_2$ as shown below.



Scheme-39 meachanism of formation of compound PRA-6

CHAPTER 6

CONCLUSION

6.1 Conclusion:

Several synthetic approaches for the synthesis of 2-aminothiophenes have been reported. But the application of Gewald three-component reaction has already been rewarding for the pharmaceutical industry. From a medicinal chemistry perspective, a discovery by design or logic based approach utilizing G-3CR could be also advantageous.

Then we do some multistep reaction to prepare thienopyrimidine derivative which are very important core intermediate with various biological application like anti-tumor, anti-bacterial, anti-microbial, anti-cancer etc.

In our current work we synthesized thienopyrimidine based derivatives PRA-2, PRA-3, PRA-5 PRA-6. The synthesized compounds may be further explored for generation new compounds introducing some ligand which have good biological application in medicinal chemistry field.

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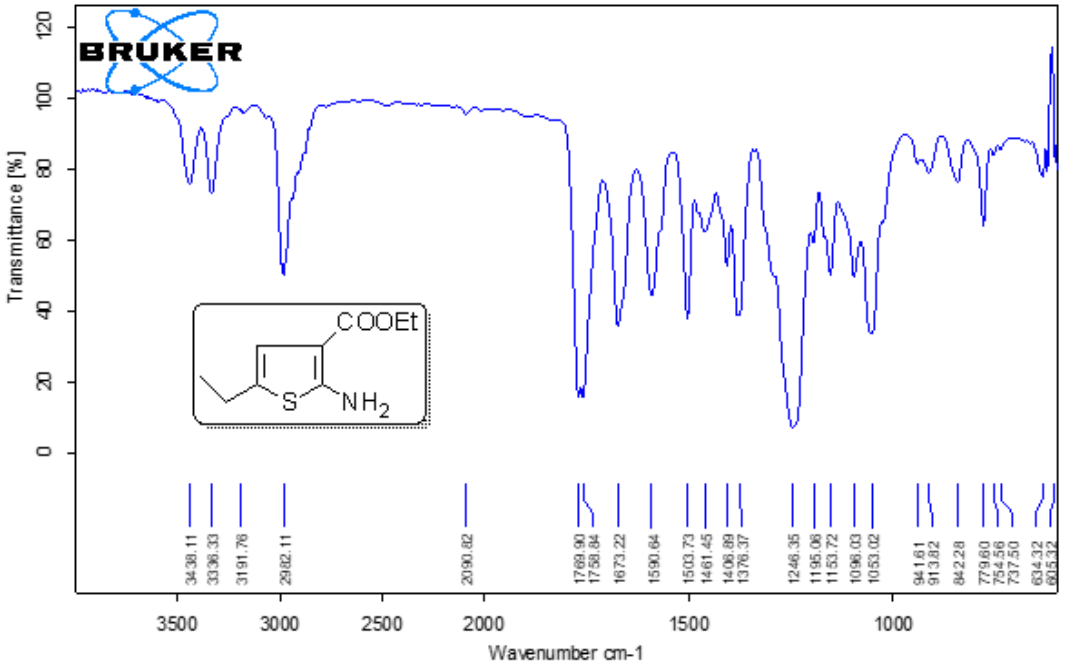
APPENDIX

Spectral data of synthesized Compound:



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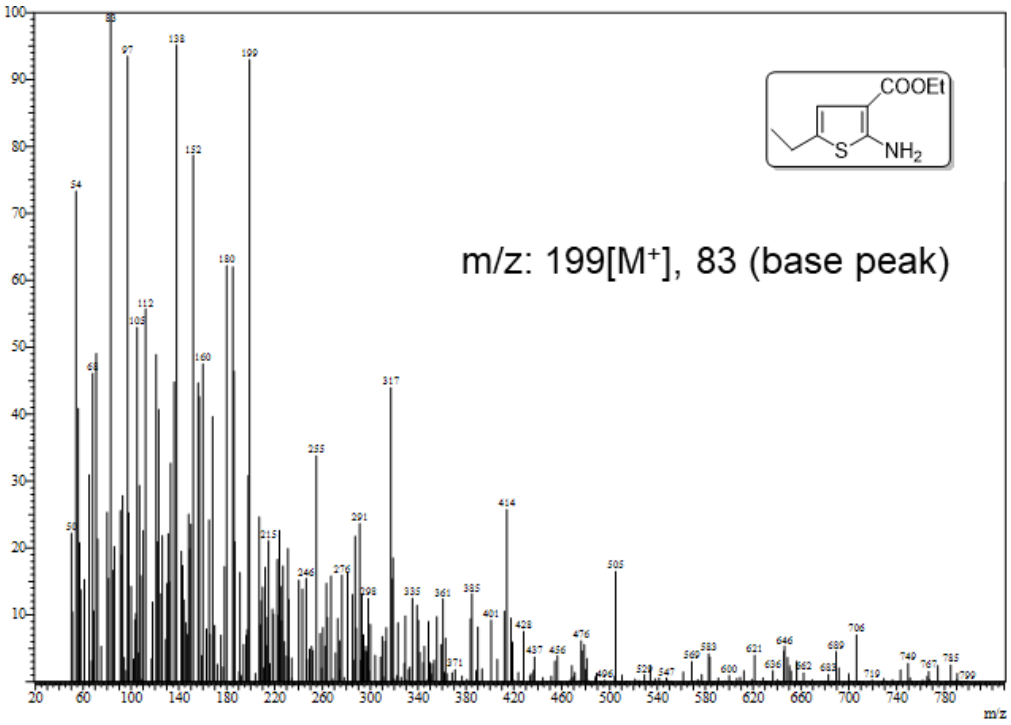
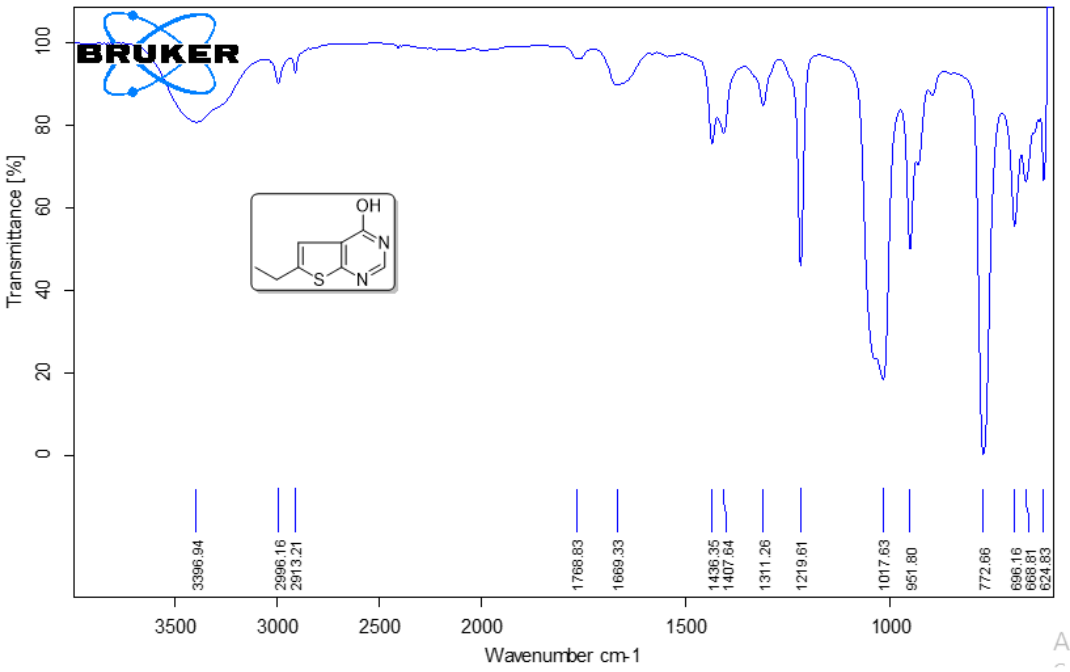


MASS of COMPOUND PRA-1



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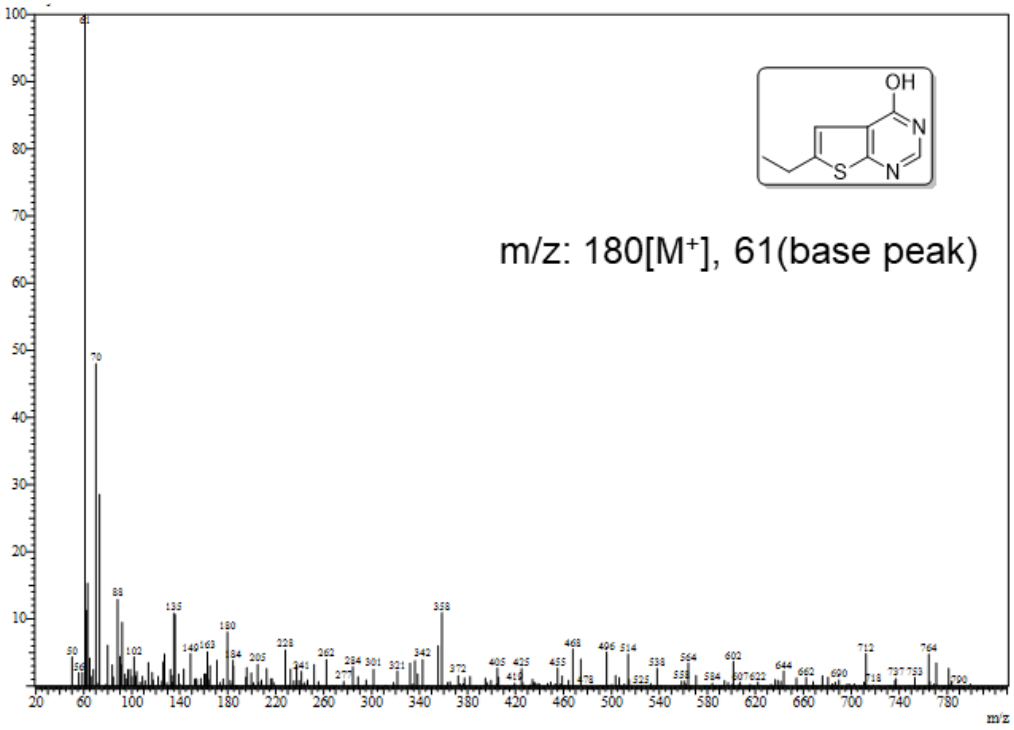

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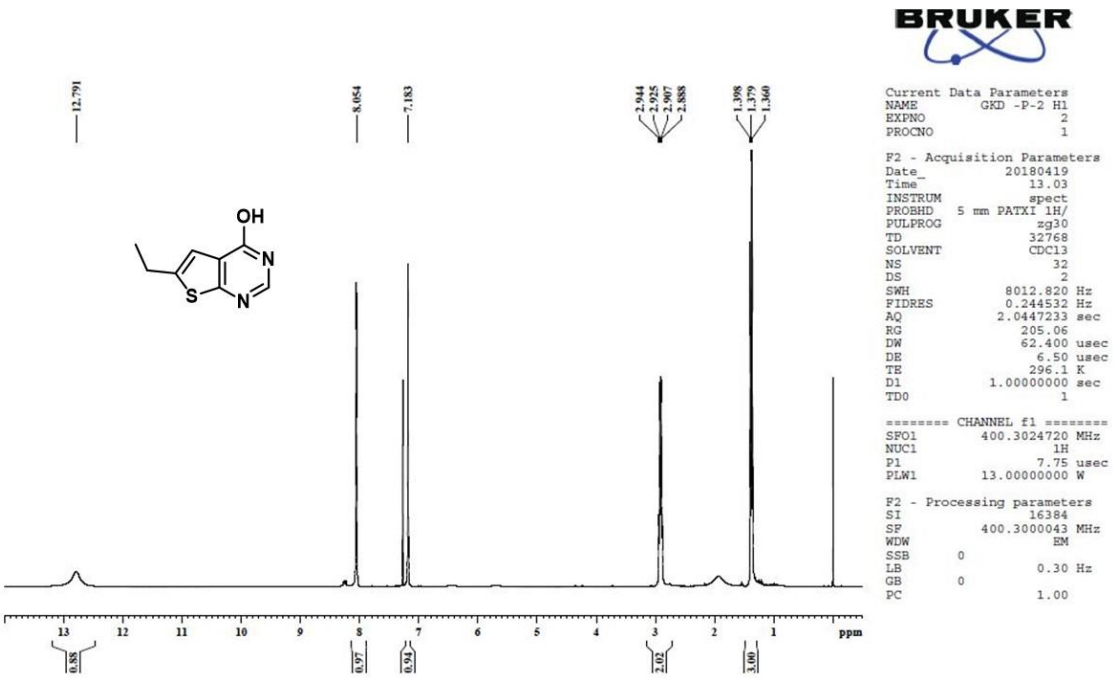

BRUKER

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PROCNO                  1

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DS                    2
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FIDRES            0.244532 Hz
AQ             2.0447233 sec
RG                205.06
DW                62.400 usec
DE                 6.50 usec
TE                296.1 K
D1             1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
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P1                 7.75 usec
PLW1          13.00000000 W

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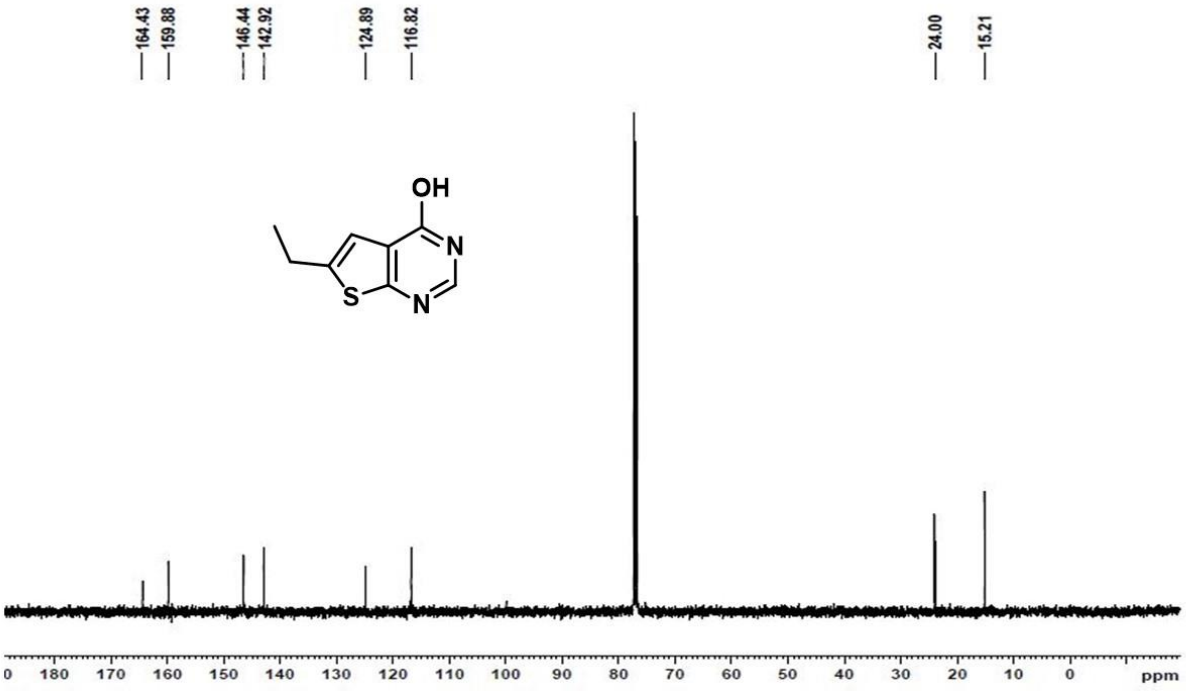
^{1}H NMR of Compound PRA-2 in $CDCl_3$



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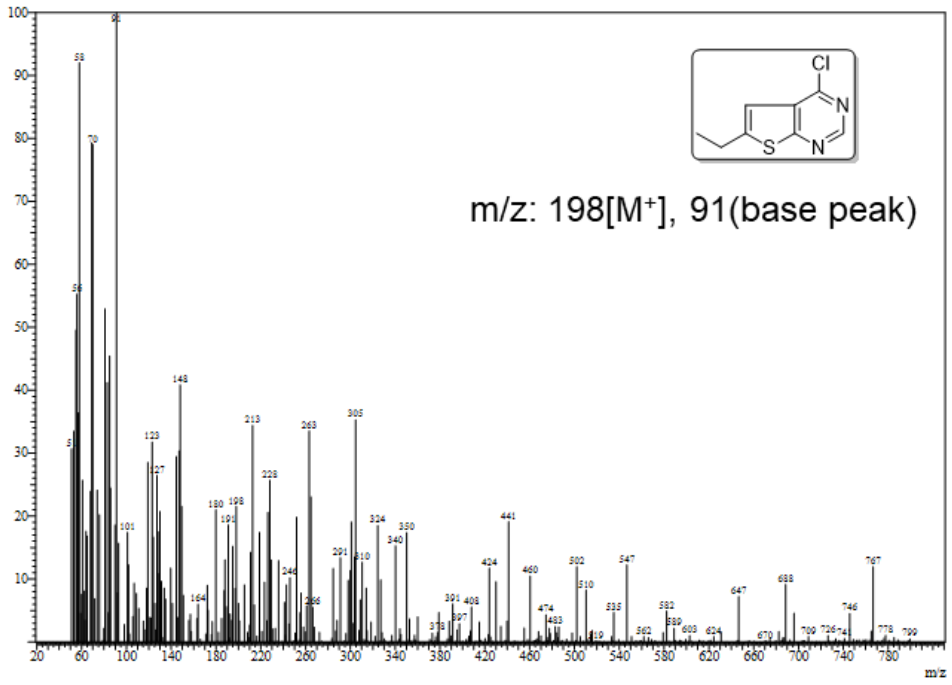
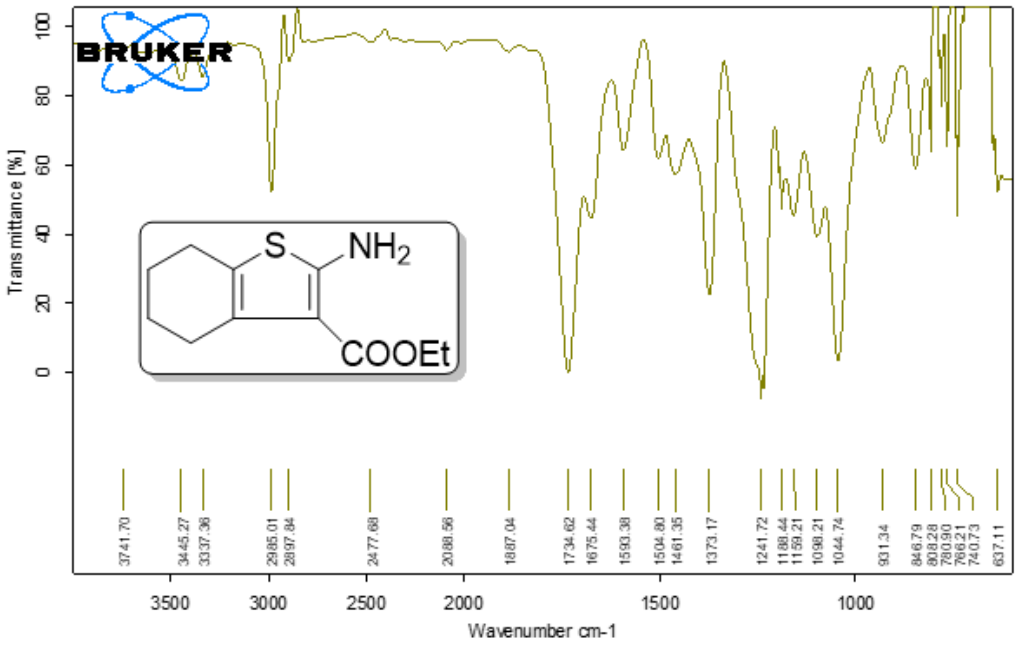


MASS of COMPOUND PRA-3



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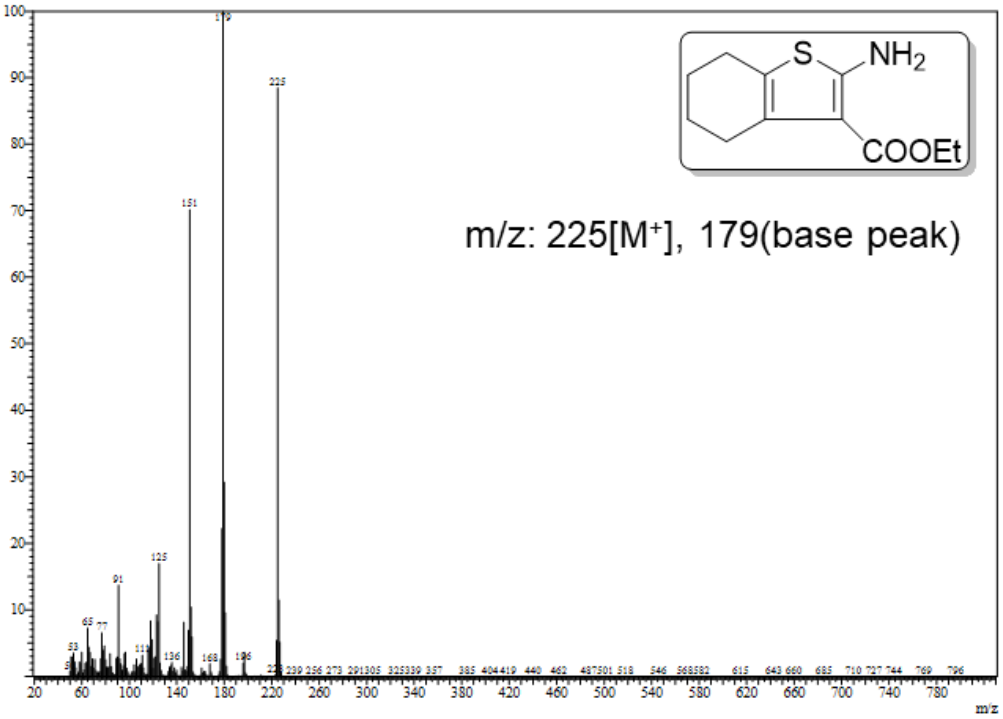
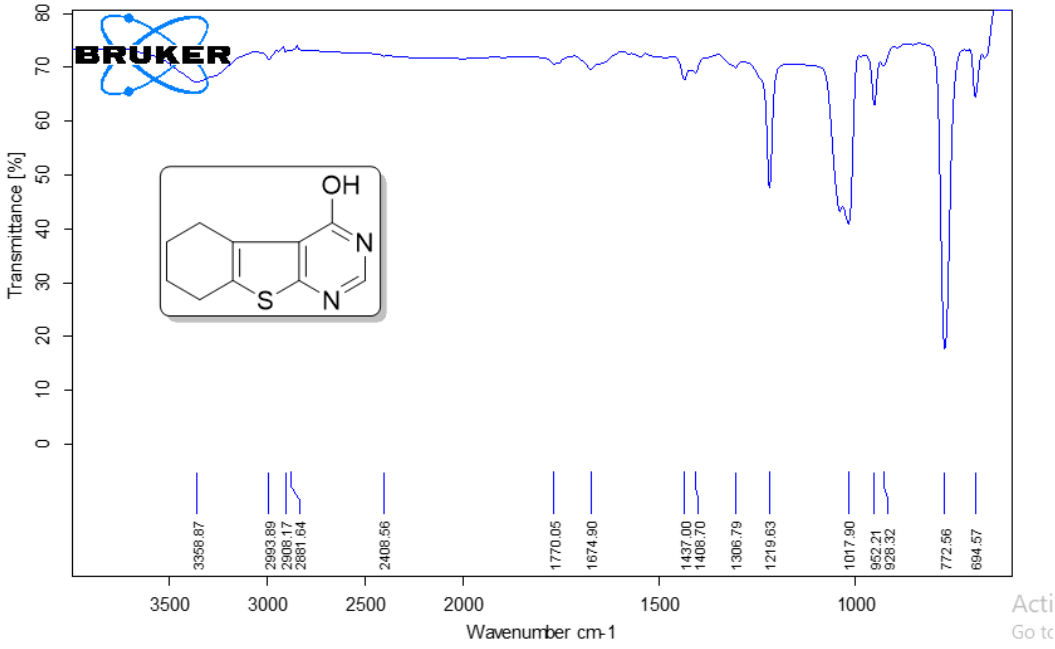


MASS of COMPOUND PRA-4



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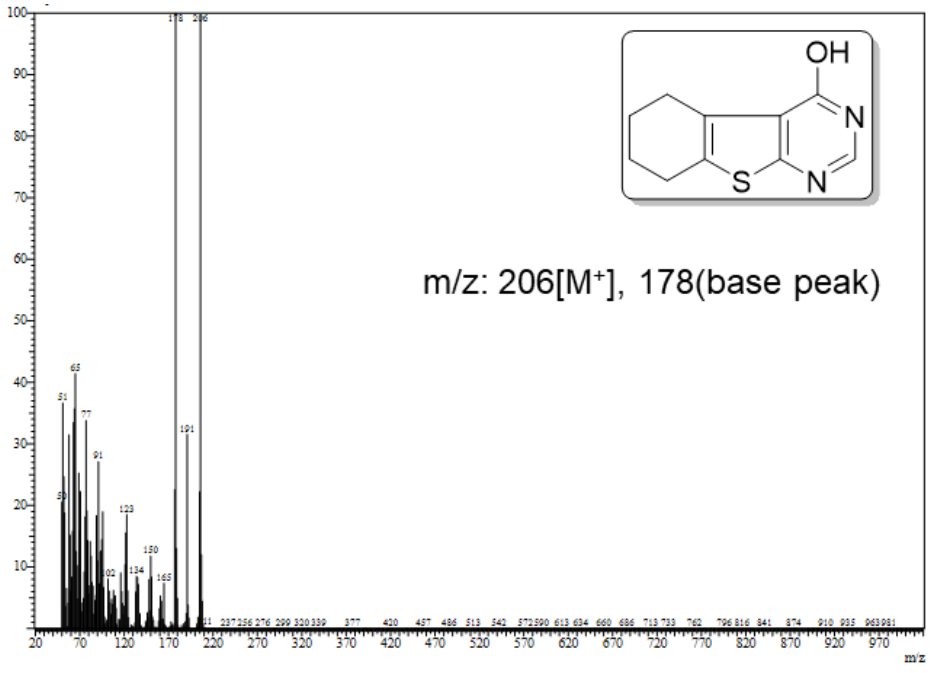

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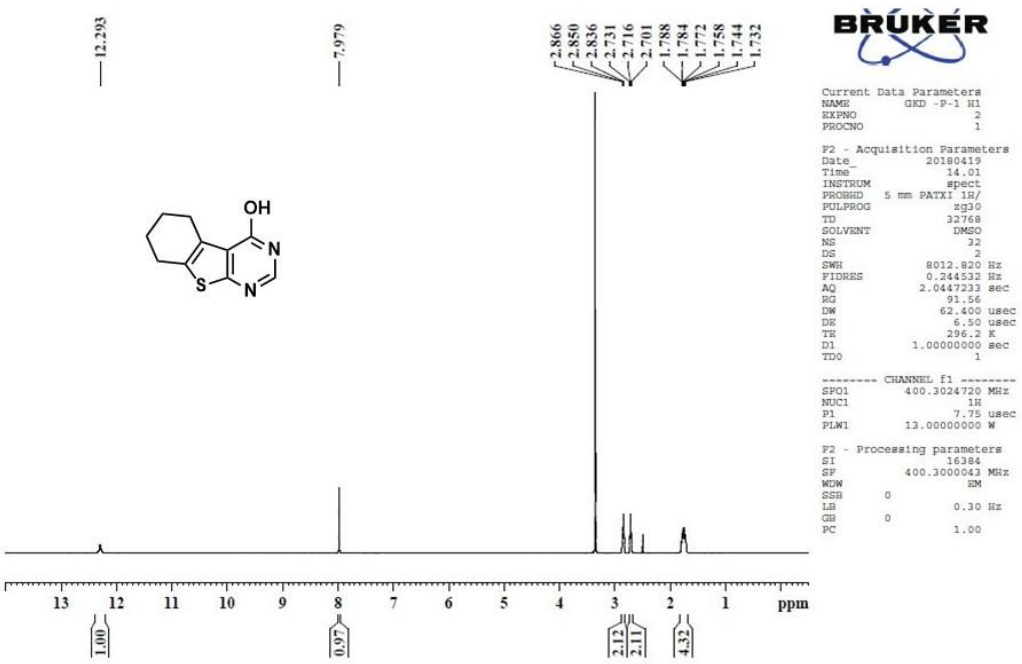
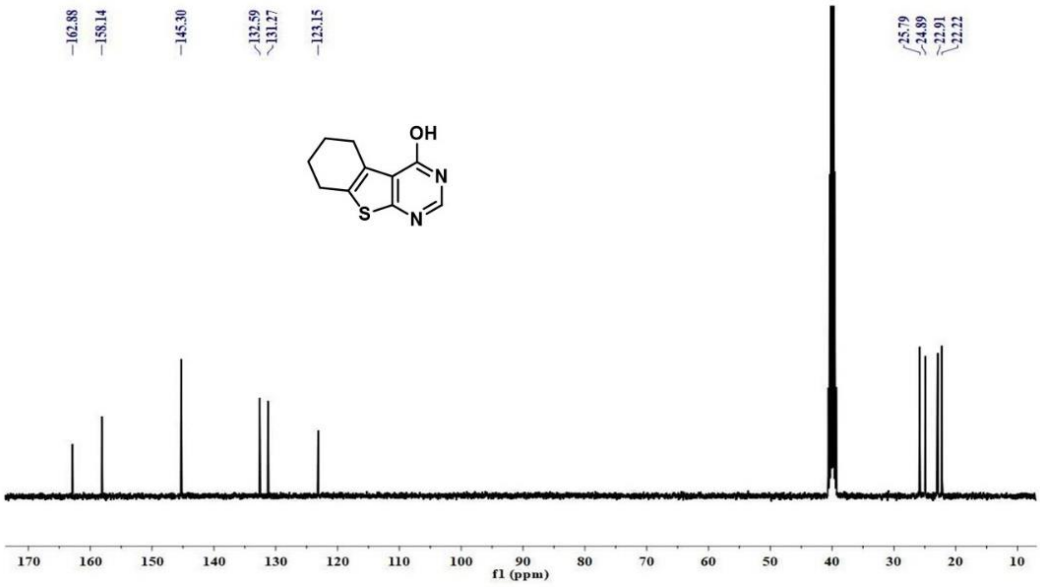
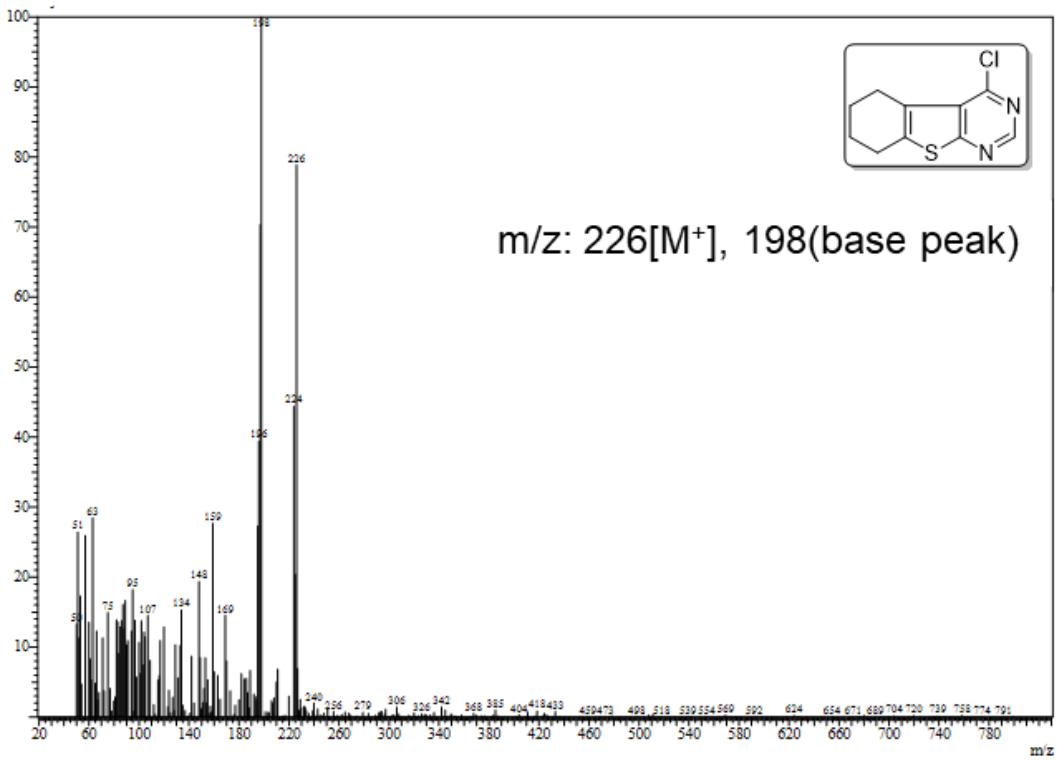


^{1}H NMR of Compound PRA-5 in d^{6}-DMSO



13C NMR of Compound PRA-5 in d^{6}-DMSO



MASS of COMPOUND PRA 6