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One-pot three-component synthesis of biologically important 3,4-Dihydropyrimidine-2 (1*H*)-thiones under Ultrasonic condition

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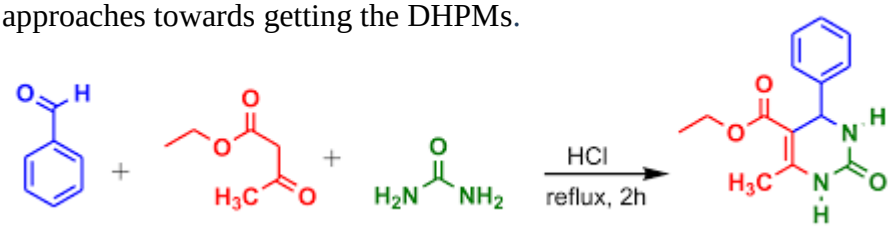
A B S T R A C T

Italian chemist Pietro Biginelli, in the year 1893, first reported a one-pot three-component synthesis of 3,4-dihydropyrimidin-2-(1H)-ones (DHMPs) using HCl as a catalyst via the cyclocondensation of ethyl acetoacetate, benzaldehyde and urea.[1] The reported protocol has drawbacks such as: prolonged reaction duration, low yield of products and tolerance of different functional groups throughout the reaction; which led to the growth of single-pot multi-component approaches towards getting the DHPMs.



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Project Report entitled

One-pot three-component synthesis of biologically important 3,4-Dihydropyrimidine-2-(1*H*)-thiones under Ultrasonic condition

Submitted to

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(Affiliated to Kannur University)

In partial fulfilment required for the award of
Master of Science Degree in Chemistry
By

FATHIMATHU NASRIYYA
C1PSCH1108

Under the guidance of

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And

Dr. Anjana George
Internal Guide

March 2023

CERTIFICATE

This is to certify that, the Project Report entitled: "**One-pot three-component synthesis of biologically important 3,4-Dihydropyrimidine-2-(1*H*)-thiones under Ultrasonic condition"** submitted by **Ms. Fathimathu Nasriyya** (C1PSCH1108) PG student, Department of Chemistry, **Government College, Kasaragod** [Affiliated to Kannur University] is based on the research work carried out by her under the guidance of **Dr. Mohamed Afzal Pasha,** UGC-BSR Faculty Fellow, Department of Chemistry, Jnanabharathi Campus, Bangalore University, Bangalore-560056 during 1st January-18th March,2023. This Project Report has not been submitted earlier to any university or institution for the award of any other degree or diploma.

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DECLARATION

I hereby declare that, the Project Report entitled: "**One-pot three-component synthesis of biologically important 3,4-Dihydropyrimidine-2-(1*H*)-thiones under Ultrasonic condition"** is the result of the research work carried out by me under the guidance of **Dr. Mohamed Afzal Pasha**, UGC-BSR Faculty Fellow, Department of Chemistry, Jnanabharathi Campus, Bangalore University, Bangalore-560056, and **Dr. Anjana George**, Internal Guide, during 1st January–16th March, 2023. I have not submitted this Project Report to any other Institute or University for the award of any Degree or Diploma.

Fathimathu Nasriyya
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Fathimathu Nasriyya

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Chapter-I

One-pot multicomponent reactions, Sonochemistry and Bioactive 3,4-Dihydropyrimidin-2-(1*H*)-thiones: An Overview

1. Introduction

1.1 One-Pot Multicomponent Reactions

Multicomponent reactions (MCRs) are the one-pot processes that combine two or more substrates in one synthetic operation either in a tandem or domino process or through a sequential addition of substrates to yield various organic compounds.[1] MCR in chemical processes is the combination of reactive inputs and sequential chemical transformation which allows the design and synthesis of novel organic compounds. In an MCR, the challenging task is assembling the reactive inputs in the formation of the desired product by avoiding the by-products. The solvent, temperature, catalyst and concentration; and the starting materials and functional groups present in them direct the formation of the products in MCRs. Hence, MCRs are highly dependent on the nature of reactants and reaction conditions.[2]

Green chemistry has clearly dictated the fascinating developments in the synthesis of large libraries of simple and complex organic compounds by one-pot multicomponent reactions (MCRs). These green protocols in synthetic chemistry have received considerable attention in chemical research.[3,4] The outcome of these efforts avail several advantages such as: simple and energy efficient methodology, molecular diversity, selective structural modifications, functionalization and ease in accessibility of a vast library of compounds.

In recent years, the ease in synthesis of functionalized heterocyclic compounds is *via* the one-pot multicomponent synthesis. MCRs have outlined the advancements in modern organic synthesis to offer constitutively complex, fused and highly functionalized heterocyclic moieties.[5] MCRs have emerged as a revolutionary concept in providing alternative focus in the *green synthesis*. A large number of one-pot MCRs have been developed and documented in the literature; a few of them have been highlighted in the **Fig. 1.1**.

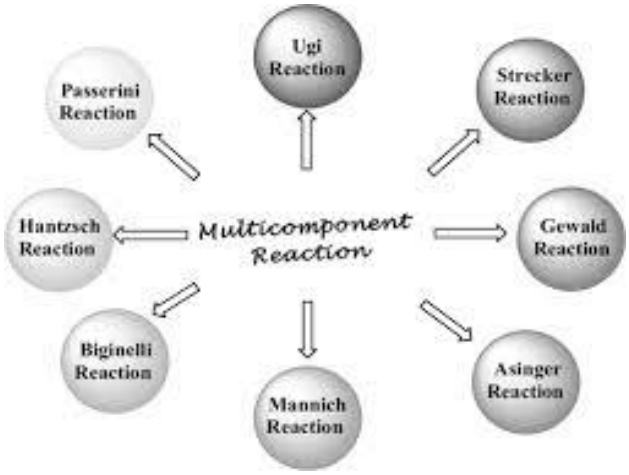


Fig. 1.1: Names of some important MCRs

Some of the *green* methods which have been used for the synthesis of heterocyclic compounds using one-pot multicomponent reactions are:
a). Solvent-free reactions
b). Solid state reactions
c). Microwave assisted reactions.
d). Ultrasound assisted reactions: Sonochemistry
e). Use of environment friendly catalysts, ionic liquids etc.
f). Reactions in water as medium
g). Catalyst-free reactions

1.2. Sonochemistry

Sonochemistry is a branch of chemistry which deals with the use and application of ultrasound in the study of chemical reactions and in chemical synthesis. Sound waves with frequencies above 20 KHz that lie beyond the upper limit of human hearing are used for this purpose. The ultrasonic spectrum includes ultrasonic waves with frequency ranging from 20 KHz to 1 MHz and can be generally divided into three regions: (i). High power ultrasound, low frequency (20–100 KHz); (ii). medium power ultrasound, high frequency (100 KHz–1 MHz) and (iii). low power ultrasound, high frequency (1–10 MHz) as shown in the **Fig. 1.2**.[6]

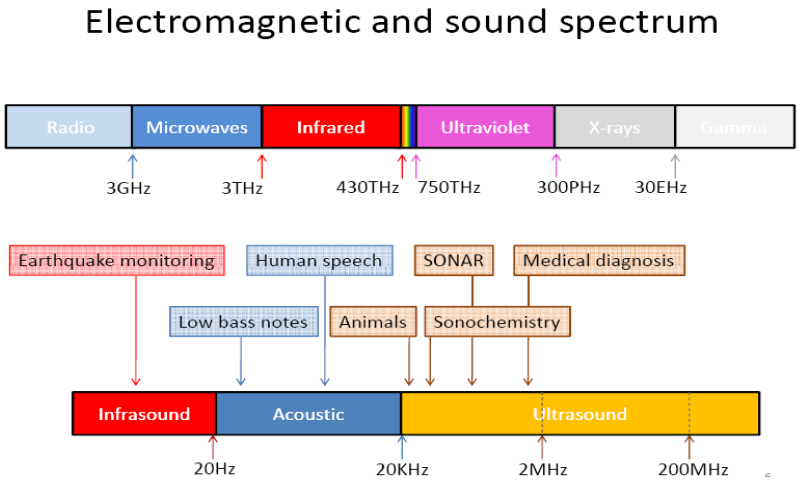
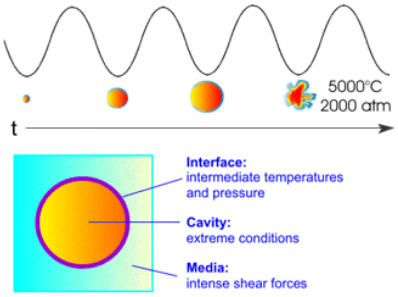


Fig. 1.2: Electromagnetic and sound spectra

1.2.1 The phenomenon of acoustic cavitation

Use of ultrasound in solution phase chemical reaction provides specific activation based on a physical phenomenon called acoustic cavitation. Cavitation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. On applying ultrasound, compression followed by rarefaction (expansion) of the liquid takes place, and a sudden pressure drop forms small oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size; they can then collide and/or violently collapse to produce enormous amounts of energy in the form of heat and pressure (**Fig. 1.3**) which can indirectly help the reactions to go to completion.[7]



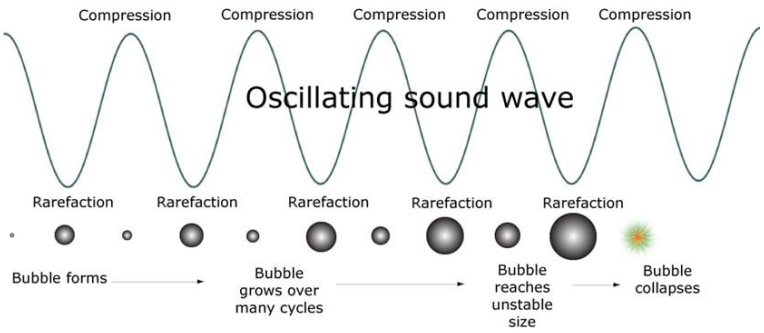


Fig. 1.3. Acoustic cavitation and bubble collapse

1.2.2 Sonochemistry in homogeneous and heterogeneous systems

1.2.2.1 Homogeneous systems

Ultrasonic reactions in homogeneous media commonly take place either inside the collapsing bubble where intense conditions are formed or at the interface between the cavity and the liquid, where the conditions are far less extreme or in bulk liquid immediately surrounding the bubble through 'shock waves' (**Fig. 1.4**).[8-10]

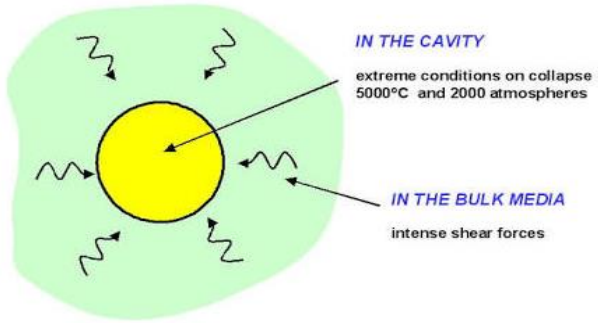


Fig. 1.4: Shock waves in homogeneous medium

1.2.2.2 Heterogeneous systems

There are two types of effects mediated by ultrasound: chemical and physical. When the quantity of bubbles is low as in case of standard laboratory sonic bath, it is mainly the physical rate acceleration that plays a role. A specific effect under ultrasonication is the asymmetric collapse of bubbles near a solid surface to produce high energy *micro-jets* which can be very effective in cleaning, and also responsible for the acceleration of the rate in the multiphasic or heterogeneous reactions, under these conditions the surface cleaning and erosion of the surface of the catalyst leads to improved mass transport (**Fig. 1.5**).[11]

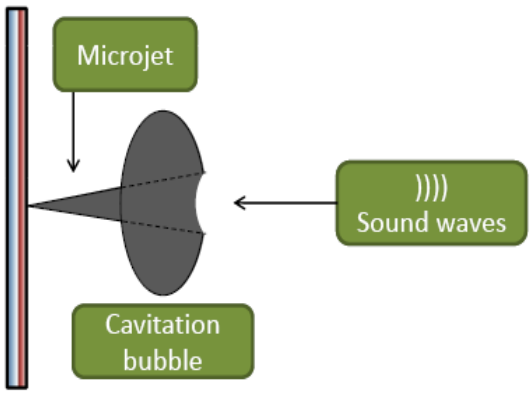


Fig. 1.5: Asymmetric collapse of the bubble in heterogeneous systems**.**

1.2.3 Benefits of Ultrasound assisted reactions:

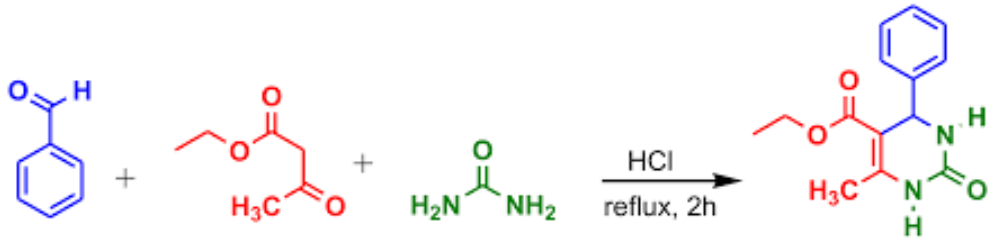
• Increased rate of reactions.
• Efficient source of Heating.
• Higher yields and shorter preparation time.
• Uniform heating.
• Greater reproducibility of Chemical reactions applied in Chemical synthesis.
• Environment-friendly Chemistry.
• Lower processing cost.
• High purity over the other conventional approaches.
• Maximize atom economy.

1.3 3,4-Dihydropyrimidin-2 (1*H*)-thiones

Heterocyclic motifs are the most important units of the biological and pharmaceutical studies. Basically, the wide spread applicability of varied heterocycles and structural similarity with the natural products have drawn the consensus of the Organic chemists throughout the world. Therefore, the efficient protocols for the synthesis of functionalized heterocyclic compounds are in demand.

The chemistry of heterocyclic compounds is a fascinating area in the organic synthesis owing to their broad spectrum of beneficial applications in medicinal chemistry. Heterocyclic compounds play a vital role in industrial applications such as: Pharmaceutical, agrochemical industries and serve as additives, modifiers and find application as photodiodes. Many drugs possess heterocyclic moieties hence, a brief introduction to the application of heterocycles has been discussed in this chapter. In view of their diverse and unusual pharmacological profiles when compared with their oxo-counter-parts: 3,4-dihydropyrimidin-2 (1*H*)-ones, we were provoked to start working on the synthesis of 3,4-dihydropyrimidin-2 (1*H*)-thiones by adopting simple, efficient and environmentally benevolent method.

In 1893, Biginelli synthesized 3,4-dihydropyrimidine-2 (1*H*)-ones *via* an acid catalyzed single-pot three-component reaction of an α,β-ketoester, aldehyde and urea.



1.3.1 Biological Applications of DHMPs

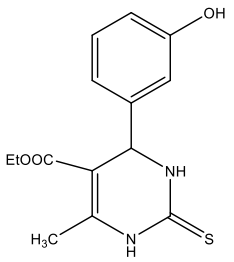
1). One of the significant, vital and biologically essential nitrogen containing heterocyclic scaffold is pyrimidine, and many natural products possess this motif including 3,4-dihydropyrimidin-2 (1*H*)-thiones. Molecules which are having pyrimidine skeleton exhibit unique therapeutic properties.

2). Pyrimidines have occupied a characteristic place in organic and medicinal chemistry and in designing pharmaceutical products since decades as they exhibit a wide-range of bio activity such as: calcium channel blocking property.

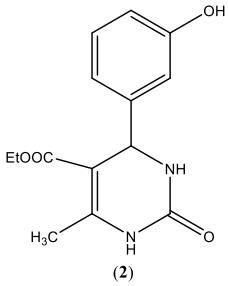
3). Pyrimidines are also known to be anticancer, antifungals, antimalarials, antibacterials, antihypertensive, anti-inflammatory agents and exhibit anti-microbical activity.

1.3.1.1 Anticancer agents

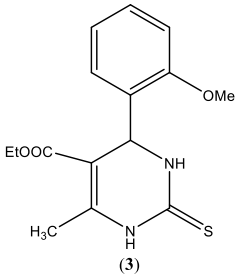
The synthesis and differential antiproliferative activity of monastrol (**1**), oxo-monastrol (**2**) and other derivatives on seven human cancer cell lines were screened by Russowsky D *et al*.[12] For all the evaluated cell lines, monastrol was shown to be more active than its oxo-analogue, except for HT-29 cell line, suggesting the importance of the sulfur atom for the antiproliferative activity. Monastrol and the thio-derivatives **3**, **4** and **5** displayed relevant antiproliferative properties with 3,4-methylenedioxy derivative **5** being approximately more than 30 times more potent than monastrol against colon cancer (HT-29) cell line.



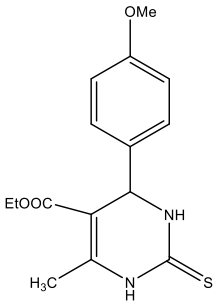
(**1**) Monastrol



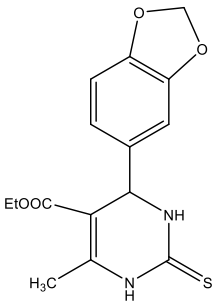
(**2**)



(**3**)



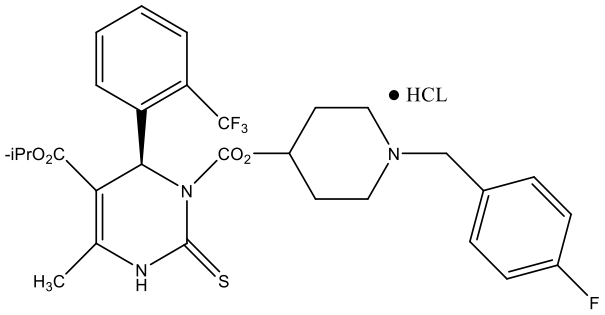
(**4**)



(**5**)

1.3.1.2 Vasorelaxant agents

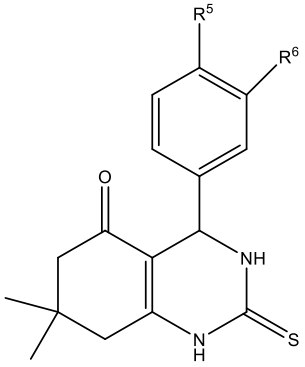
A series of dihydropyrimidine calcium channel blockers which contain a basic group attached to either C5 or N3 of the heterocyclic ring. Structure-activity studies show that a l-(phenylmethyl)-4-piperidinyl carbamate moiety at N3 and sulphur at C2 are optimal for vasorelaxant activity *in vitro* and impart potent and long-acting antihypertensive activity *in vivo*. Chirality was demonstrated to be a significant determinant of biological activity, with the dihydropyridine receptor recognizing the enamino ester moiety (**6**) but not the carbamate moiety (**7**). Dihydropyrimidine **6** is equipotent to nifedipine and amlodipine *in vitro*.[13]



(**6**) R-configuration
(**7**) S- configuration

1.3.1.3 Relaxant agents

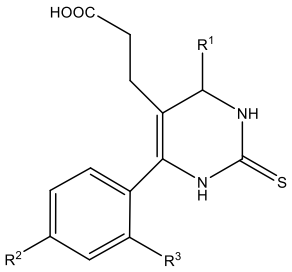
The *thio*-Biginelli adducts **8** and **9** were found to be relaxant agents as effective as the reference drug *nicardipine* having inhibition of stimulus by 35.5 ± 4.16%, on KCl-stimulated lamb carotid artery when used at 10^{-4} mol/l.[14]



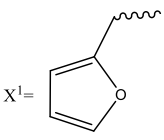
R^5= H and R^6= Cl (**8**)
R^5= Cl and R^6= H (**9**)

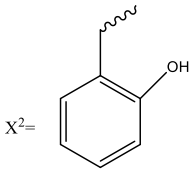
1.3.1.4 Anti-inflammatory agents

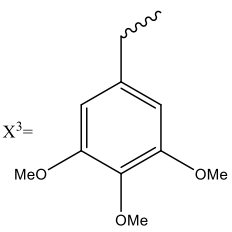
1. Biginelli-*thio* adducts have also received great attention with respect to their potential anti-inflammatory activity. Based on the duration of action and percentage of inflammation inhibition on Albino rats paw edema, the propanoic acid derivatives *thio*-adducts (**10**–**14**) were found to be the most promising anti-inflammatory compounds when compared to diclofenac, a reference drug.[15]



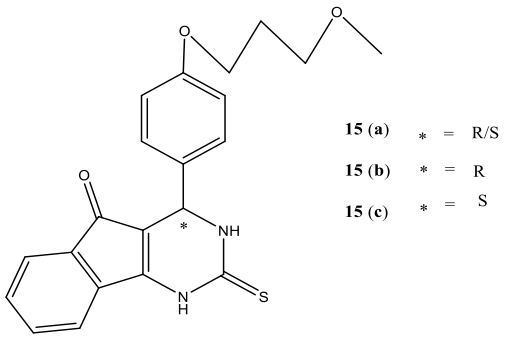
10 : $R^1 = X^1$, $R^2 = CH_3$ and R^3 = H
11 : $R^1 = X^1$ and $R^2 = R^3$ = H
12 : $R^1 = X^2$ and $R^2 = R^3$ = H
13: $R^1 = X^2$, R^2 = H and $R^3 = OCH_3$
14: $R^1 = X^3$, $R^2 = CH_3$ and R^3 = H

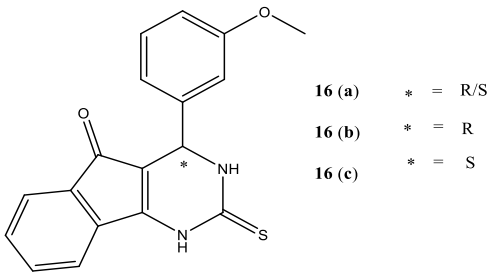




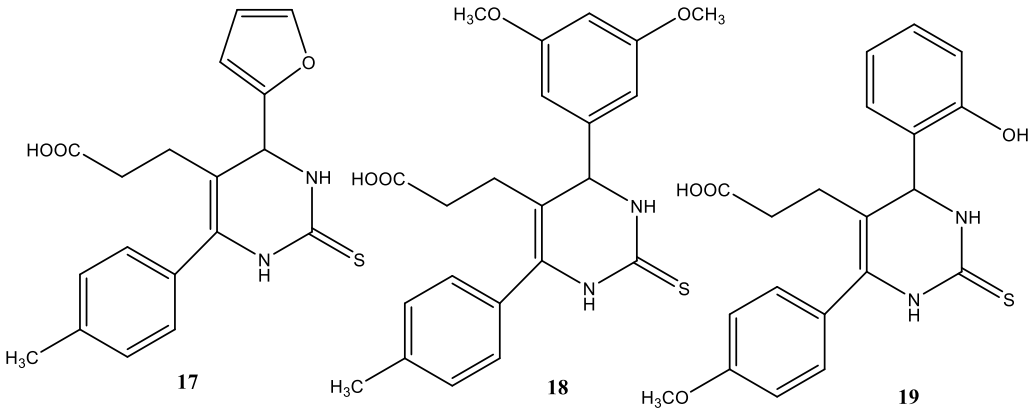


2) Biginelli adducts bearing *meta*-substituents have been described as very promising anti-inflammatory agents in human embryonic kidney 293 cell lines(HEK293) overexpressing the transient receptor potential A1(TRPA1) either from human or rat. The compounds **15a**, **15b** and **16a**, **16b** were able to inhibit both human and rat TRPA1 at concentrations ranging from 4 to 75 nM. The ***R*** isomers, were identified as the most potent inhibitors acting on rat TRPA1 at IC_{50} values as low as 4 and 12 nM, respectively, while the IC_{50} for the corresponding *S* isomers **15c** and **16c** were found to be higher than10,000 nM.[16]



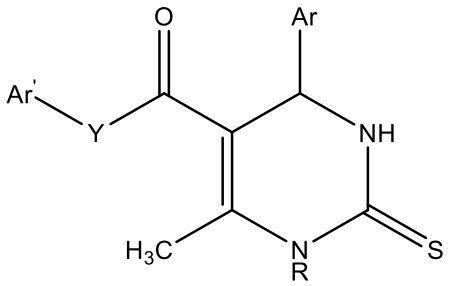


3) A series of compounds 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives **17–19** were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant anti-inflammatory activity.[17]



1.3.1.5 Antiviral agents

A series of derivatives of Biginelli-thio pyrimidines were evaluated as potential anti-HSV-1 compounds by the plaque reduction method. The cellular toxicity was assessed by XTT proliferation assay. The time course of anti-HSV activity of the most active compound was studied to show the anti-viral effect of the following compounds **20**.[18]

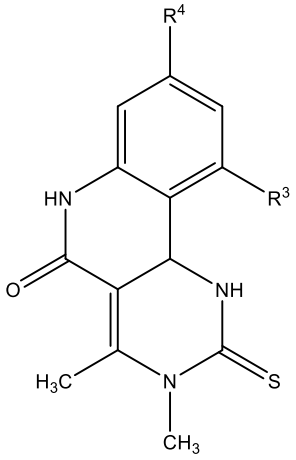


Ar' = methyl, ethyl, *iso*-butyl
Ar = Thienyl

20

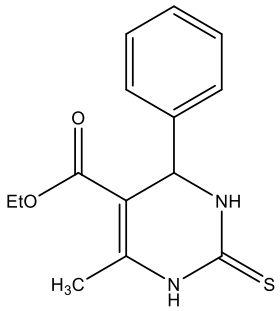
1.3.1.6 Antioxidant agents

1. New 2-thioxohexahydropyrimido[5,4-*c*]quinoline-5-ones were prepared from 4-phenyl-6-methyl-2-thioxotetrahydropyrimidine-5-carboxylates (**21** and **22**), previously prepared by Biginelli reaction using appropriate aldehyde, urea derivatives and ethyl acetoacetate. Their antioxidant properties were evaluated by two methods: i). Scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and ii). Scavenging effect on hydroxyl radicals. The results showed that, the compounds containing thiourea moiety have better activity than their oxo analogues.[19]



R^3 = Cl and R^4 = H (**21**)
R^3 = H and R^4 = Cl (**22**)

2. The antioxidant capacity of the compounds synthesized by the 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay and the thiobarbituric acid-reactive species test. Two compounds (**23** and **24**) presented antioxidant activity and also reduced lipid peroxidation at concentrations of 200 and 300 μM. In summary, an environmentally friendly procedure for the preparation of DHPMs and demonstrate the antioxidant capacity of some of the compounds.[20]



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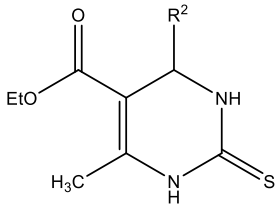
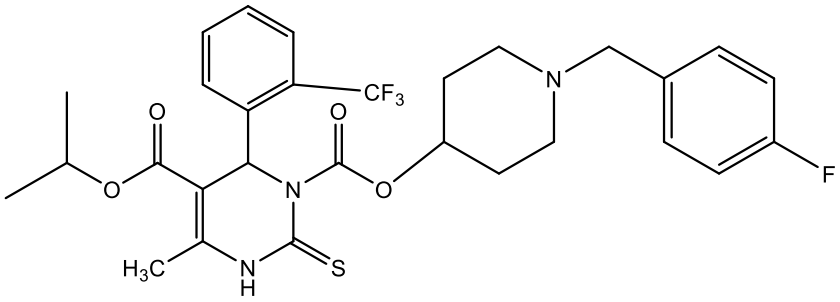


R^2 = 4-$CH_3OC_6H_4$- (**24**)

1.3.1.7 Antihypertensive Agent

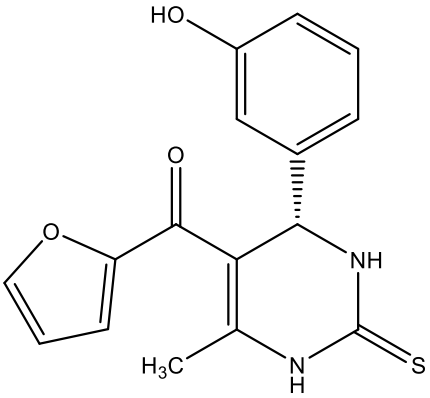
Biologists have found that, Biginelli products resemble Hantzsch 1,4-dihydropyridines; the Biginelli compound **25** which is an effective oral active anti-hypertensive agent is found to be a promising target for bringing it to actual use. The thio-substituted DHPM (**25**) with a branched ester (e.g. *iso*-propyl) was found to be a potent mimic of dihydropyridine calcium channel blockers.[21]



(**25**)

1.3.1.8 Antitumor Agent

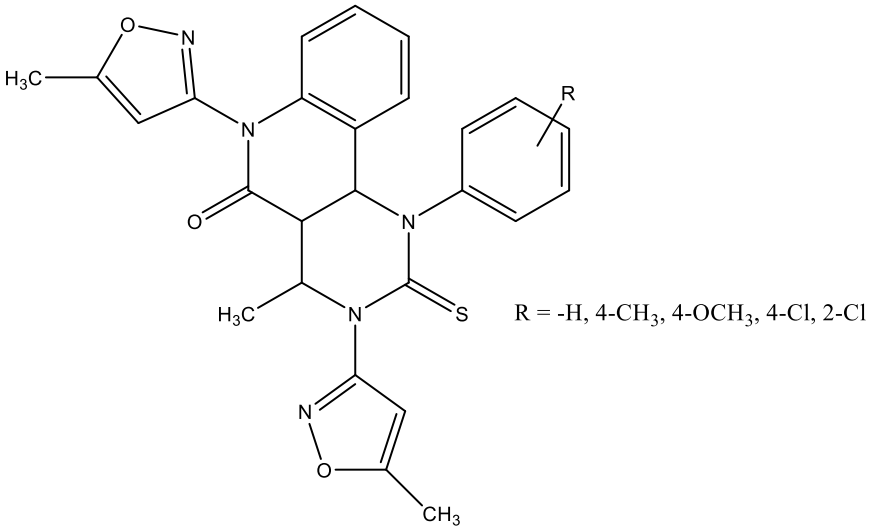
Human kinesin Eg5 is an interesting drug target for the development of cancer chemo therapeutics. Monastrol is the first Biginelli compound which has excellent anticancer activity, further a series of compounds for their ability to inhibit Eg5 activity has been investigated using two *in vitro* steady-state ATPase assays (basal and microtubule-stimulated) as well as a cell-based assay. In an attempt, another dihydropyrimidine *i.e.*, furyl derivative **26** appeared to be more potent than monastrol by a five-fold factor.[22]



(**26**)

1.3.1.9 Anti-microbial agents

Thio-Biginelli compounds multi-functionalized with isoxazole moieties such: 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10*b*-tetrahydro-1*H*-pyrimido[5,4-*c*]quinolin-5-thiones **(27)** showed antimicrobial, antibacterial, antifungal and antimalarial activities.[23]



(**27**)

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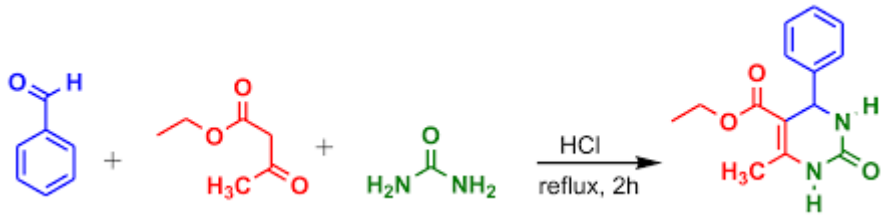
Chapter-II

SiO_2-I catalyzed, one-pot three-component synthesis of Biologically active 3,4-Dihydropyrimidin-2 (1*H*)-thiones under Ultrasonic condition

1. Introduction

Italian chemist Pietro Biginelli, in the year 1893, first reported a one-pot three-component synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones (DHMPs) using HCl as a catalyst via the cyclocondensation of ethyl acetoacetate, benzaldehyde and urea.[1] The reported protocol has drawbacks such as: prolonged reaction duration, low yield of products and tolerance of different functional groups throughout the reaction; which led to the growth of single-pot multi-component approaches towards getting the DHPMs.



Scheme 1: Biginelli's synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones

The growing interest in this reaction is mainly due to the therapeutic and pharmacological properties of Biginelli products, namely DHPMs. DHPMs based natural marine polycyclic alkaloids, such as batzelladine A and B are known to inhibit the binding of HIV gp-120 to CD4 cells in AIDS therapy.[2] Furthermore, several DHPMs have been found to exhibit a broad spectrum of biological activities such as: antiviral, antitumour, antibacterial, anti-inflammatory, antimalarial, antitubercular, antidiabetic, antiepileptic, antileishmanial, antiproliferative activities. A number of functionalized DHPMs have been found to be potent calcium channel blockers, antihypertensive agents, a1a-adrenergic antagonists, mPGES-1 inhibitors, and A2B receptor antagonists. Exhibit novel optical properties and DHPMs have also been exploited as design elements in the development of functional materials such as polymers, adhesive and dyes.[3,4]

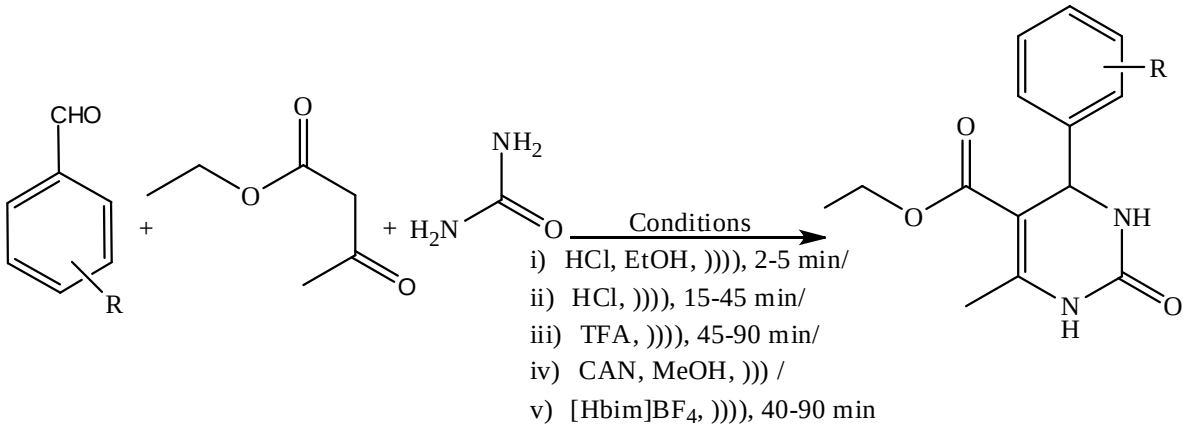
The diverse applications of the Biginelli structural variations have driven much attention to explore the synthetic ideas in the field of modern organic synthesis. Beginning of 1980s to till date, MCRs have proved that the Biginelli reaction is considered as one of the important reaction in heterocyclic synthesis, and a large number of catalysts have been developed for the synthesis of these biologically important compounds.[3,5]

2. Literature survey on the synthesis of 3,4-dihydropyrimidine-2 (1*H*)-ones/thiones using silica based catalyst; and under untrasonic conditions.

2.1 Undersonic condition:[6]

Some of the ultrasound assisted methods towards the synthesis of DHPMs involve use of a variety of reagents such as: HCl in EtOH, HCl, TFA, CAN in MeOH and $[Hbim]BF_4$. The rates

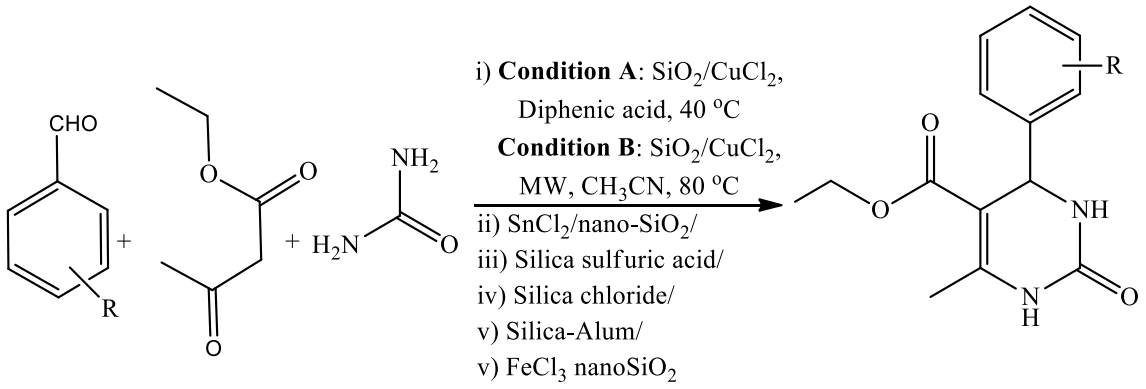
of all the reactions are shown to get accelerated under the influence of ultrasound as shown in the **Scheme 2**.



Scheme 2: Different methods of synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones/thiones under sonic condition

2.2 Use of silica based catalysts:[7-12]

The application of different silica based catalysts in the one-pot multicomponent Biginelli reaction are documented under reflux and microwave reaction conditions. SiO_2-$CuCl_2$ (Diphenic acid/solvent-free, 40 ºC and MW, CH_3CN, 80 ºC), $SnCl_2$/nanosilica in ethanol; $KAl(SO_4)_2 \cdot 12H_2O$ supported on silica, SiO_2-OSO_3H and SiO_2-Cl under reflux condition, and $FeCl_3$-supported nanopore silica under microwave irradiation have resulted in high yields of the 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones as shown in the **Scheme 3**.



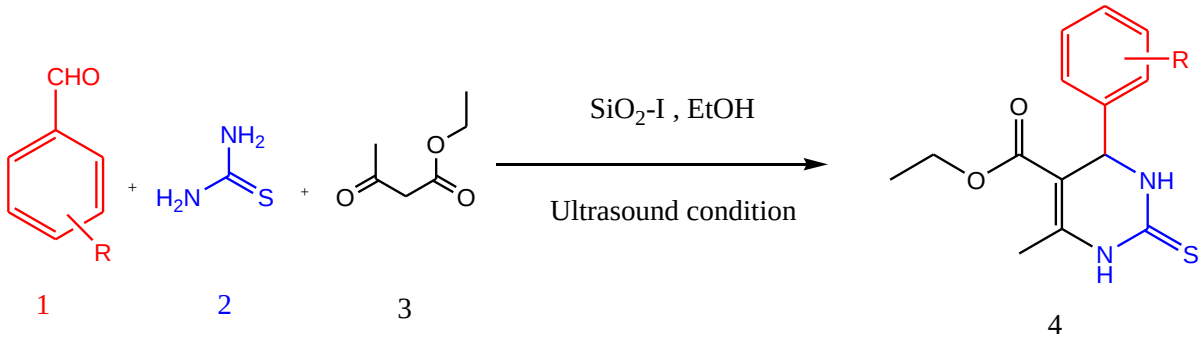
Scheme 3: Different methods of synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones using silica based catalysts

Many of the reported protocols involve harsh conditions, tedious work-up and require long time, use of expensive reagents, non-recoverability of catalysts, strong acidic or basic conditions, environmental contamination, undesirable yields and non-tolerance of certain functional groups and moieties. Hence, the progress of devising mild and eco-friendly methods which can overcome these drawbacks is of great significance towards the preparation of DHPMs.

3. Present work

In organic synthesis, ultrasonication offers copious advantages like: better yield of the target molecules, superior reaction rates, works under mild and energy efficient reaction conditions, and minimization of waste takes place when compared with conventional methods. Combination of these two *viz.*, use of a suitable catalyst and ultrasonication can provide a best and energy efficient way to prepare the 3,4-dihydropyrimidin-2-(1*H*)-thiones.

The viability of single-pot multicomponent reactions (MCRs) under ultrasonication using the heterogeneous silica iodide (SiO_2-I) as a catalyst has shown considerable progress in their efficiency from implementation and environmental points of view in recent years. We, herein, report an ultrasound assisted SiO_2-I catalysed one-pot three-component condensation of aldehydes, thiourea and ethyl acetoacetate for the synthesis of a series of 3,4-dihydropyrimidin-2-(1*H*)-thiones as shown in the **Scheme 4**.



Scheme 4: SiO_2-I catalyzed, ultrasound assisted synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones

3.1 Objectives of the study

- To develop sustainable and novel synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones.
- Application of new SiO_2-I heterogeneous catalyst in the synthesis of the desired products.
- Characterization of the synthesized compounds by m.p comparison; and by the ^{1}H NMR, ^{13}C NMR and LC-Mass spectral analysis.
- To publish the work in a reputed journal.

3.2 Results and discussion

The model reaction, 3-methoxybenzaldehyde (**1**), thiourea (**2**) and ethyl acetoacetate (**3**) was selected in the presence of SiO_2-I (0.1 g). Initially, a solvent-free reaction under sonic condition was carried out, the product was not obtained. The effect of various solvents such as, DCM, toluene, acetonitrile, methanol, tetrahydrofuran, water and ethanol was then, studied on the model reaction. DCM, toluene and acetonitrile did not facilitate the one-pot three-component reaction; but the reaction in tetrahydrofuran, methanol and water afforded low to moderate yields in 360 min as shown in the **Table 1**(entries 1–7). Among all the solvents, ethanol was found to be the most suitable solvent to accelerate the reaction time (30 min) and afford 96% yield of **4a** (entry 8).

Table1: Effect of solvents in the SiO_2-I assisted synthesis of ethyl-4-(4'-chlorophenyl)-6-methyl-2-thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**)

Entry	**Solvent**[a]	**Time (min)**	**Yield**[c]**(%)**
1	No solvent	360	ND[d]
2	CH_2Cl_2[b]	360	25
3	Toluene[b]	360	27
4	CH_3CN[b]	360	37
5	THF[b]	360	39
6	MeOH[b]	360	48
7	H_2O[b]	360	46
8	**EtOH** [b]	**30**	**96**

[a]5 mL; [b]SiO_2-I (0.1g); [c]Isolated yield; [d]ND-Not Detected.

To select the best catalyst, we carried out the reaction between 4-chlorobenzaldehyde (**1**), thiourea (**2**) and ethyl acetoacetate (**3**) in the presence of 10 mol% of different catalysts such as: NaI, SiO_2, TiO_2, $CeCl_3$, $ZnCl_2$, K_2CO_3 and nano ZnO in EtOH, the results of this study are presented in the **Table 2** (entry 1–8). In the model reaction, the use of 10 mol% of TiO_2, $CeCl_3$, $ZnCl_2$ and K_2CO_3 (entries 4−7), offered moderate to good yields. Nano ZnO in EtOH (5 mL) afforded 87% yield of the corresponding product (entry 8). In addition, among all the catalysts used, 0.1g of SiO_2-I in EtOH (5 mL) offered 96% yield in 30 min and it was again found to be the best catalyst (entry 9) for the synthesis of **4a**.

Table 2: Effect of various catalysts on the synthesis of ethyl-4-(4'-chlorophenyl)-6-methyl-2-thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**)

Entry	**Catalyst**	**Time (min)**	**Yield (%)**[c,d]
1	No catalyst	360	20
2	NaI[a]	90	27
3	SiO_2[a]	90	24
4	TiO_2[a]	90	48
5	$CeCl_3$[a]	90	59
6	$ZnCl_2$[a]	90	62
7	K_2CO_3[a]	90	76
8	Nano ZnO[a]	90	87
9	**SiO_2-I**[b]	**30**	**96**

[a]10 mol% catalyst in EtOH (5 mL); [b]0.1 g in EtOH (5 mL);
[c]Compared on TLC with the standard; and characterized by ^{1}H NMR, ^{13}C NMR and LC-MS techniques; [d]Isolated yield.

For optimizing the amount of SiO_2-I, we worked with different amounts (0.05, 0.06, 0.07, 0.08, 0.09 and 0.10 g) of the catalyst for the reaction and the results of this study are given in **Table 3**. From this Table, it is clear that, sonication of the model substrates using 0.1 g of SiO_2–I is essential for the present reaction to afford excellent yield of the corresponding product **4a** (**Table 3**, entry 6).

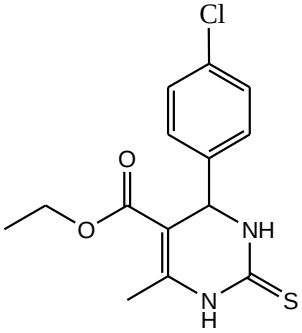
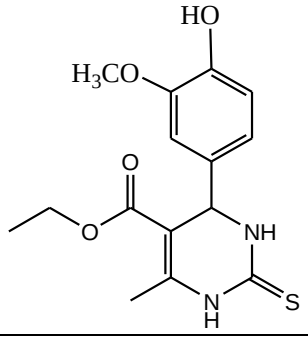
Table 3: Effect of catalyst loading on the synthesis of ethyl-4-(4′-chlorophenyl)-6-methyl-2-thioxo-3,4-dihydropyrimidin-(1*H*)-5-carboxylate (**4a**) in ethanol

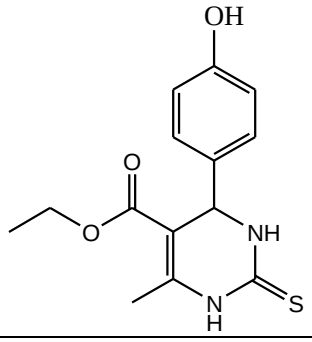
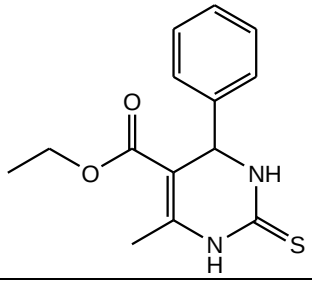
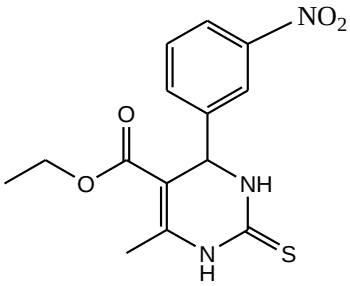
Entry	**Catalyst loading (g)**	**Yield (%)**[a]
1	0.05	57
2	0.06	62
3	0.07	67
4	0.08	75
5	0.09	84
6	**0.10**	**96**

[a]Isolated yield.

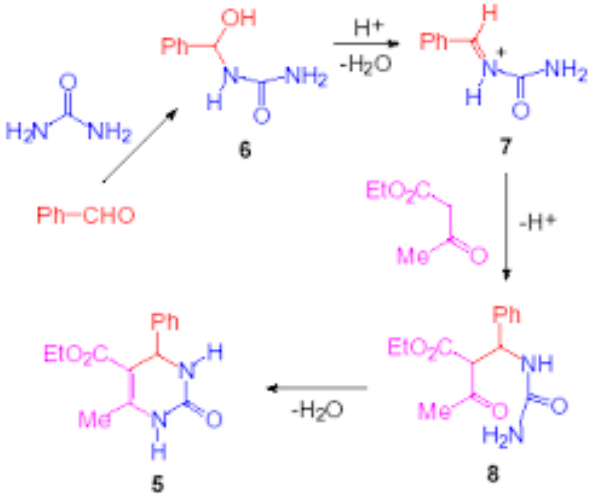
Encouraged by this result, the reaction of various substituted aryl aldehydes was attempted and the results are presented in the **Table 4**. To our fortune, SiO_2–I worked as a best catalyst irrespective of the presence of electron donating or electron withdrawing groups in the aromatic aldehydes, and the reaction proceeded in short reaction time and afforded differentially substituted 3,4-dihydropyrimidin-2-(1*H*)-thiones in excellent yield as shown in the **Table4**.

Table 4: Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones

Sl. No.	Aldehyde	Product	M.p (Ob) (°C)	M.p (Rep) (°C)	Yield (%)
4a	4-Chlorobenzaldehyde		193	(192–194)[13]	95
4b	4-Hydroxy-3-methoxybenzaldehyde		145	(147–149)[14]	95

4c	4-Hydroxybenzaldehyde		202	(202–203)[14]	70
4d	Benzaldehyde		183	(184)[15]	75
4e	3-Nitrobenzaldehyde		208	(206–207)[15]	96

From the above results, it is evident that, SiO_2-I may activate the carbonyl group of the aldehyde as an acid and ease the attack of thiourea to form an acyl imine intermediate. The active methylene present in ethyl acetoacetate may then attack the intermediate imine to produce an open chain ureide. Which on subsequent cyclization may lead to the corresponding dihydropyrimidin-thiones; as shown in the acid catalyzed Biginelli reaction mechanism (**Scheme 5**).



Scheme 5: Mechanism of acid catalyzed Biginelli Reaction

4. Experimental

4.1 Materials and methods

All reagents were commercially available and were used without further purification. Melting points were determined on a Raaga, INDIAN make melting point apparatus. The progress of the reactions was monitored on TLC analytical silica gel plates (Merck 60 F250) and observed under the UV light. ^{1}H NMR spectra were recorded on a Varian Mercury spectrometer at 500 MHz and ^{13}C NMR spectra were recorded on 100 MHz instruments respectively in DMSO-d_6 with TMS as an internal standard. LC-MS were recorded on an Agilent Technologies 1200 series instrument. Sonication was performed using a SIDILU Indian make sonic bath operating at 35 kHz (constant frequency, 80 W).

4.2 Preparation of Silica iodide (SiO_2-I):[16]

Silica gel (20 g) was suspended in CH_2Cl_2 (50 mL), and $SOCl_2$ (20 mL) was added drop wise with continuous stirring at 26 C. Evolution of HCl and SO_2 occurred instantaneously; after stirring for 1 h, the solvent was removed by distillation; and the residual solvent was removed under reduced pressure to get a dry solid of silica chloride (26.2 g). The solid SiO_2–Cl was washes with cold water and dried under vacuum. NaI (3 g) was first dissolved in a mixture of EtOH–H_2O (8:2, 10 mL), to this silica chloride (6 g) was added, mixed well and filtered after 15 min, washed with cold water and dried under vacuum to get SiO_2–I (7.5 g).

4.3 Detection of the iodide in SiO_2-I: Qualitative analysis:

Test: 1.

To detect the presence of iodide in the catalyst, 0.25 mg of silica iodide was transferred to a dry test tube; 0.25 mg of sodium metal was then introduced and heated till the test tube turned red-hot. After cooling the test tube, water (3 mL) was introduced and filtered
to get the Sodium Fusion Extract (SFE). SFE (1.5 mL) was then acidified with dil. HNO_3 and treated with $AgNO_3$ solution to get a pale yellow precipitate which was insoluble in aqueous ammonia to confirm the presence of iodide in the heterogeneous catalyst.24

Test: 2. SFE (1.5 mL) was acidified with dil. HCl, carbon tetrachloride (0.3 mL) was then added and treated with chlorine water (1 mL) to get a violet globule which confirmed the presence of iodide in the heterogeneous catalyst.

4.4 SEM-EDX of (a) silica; (b) silica chloride and (c) SiO_2-I.[16]

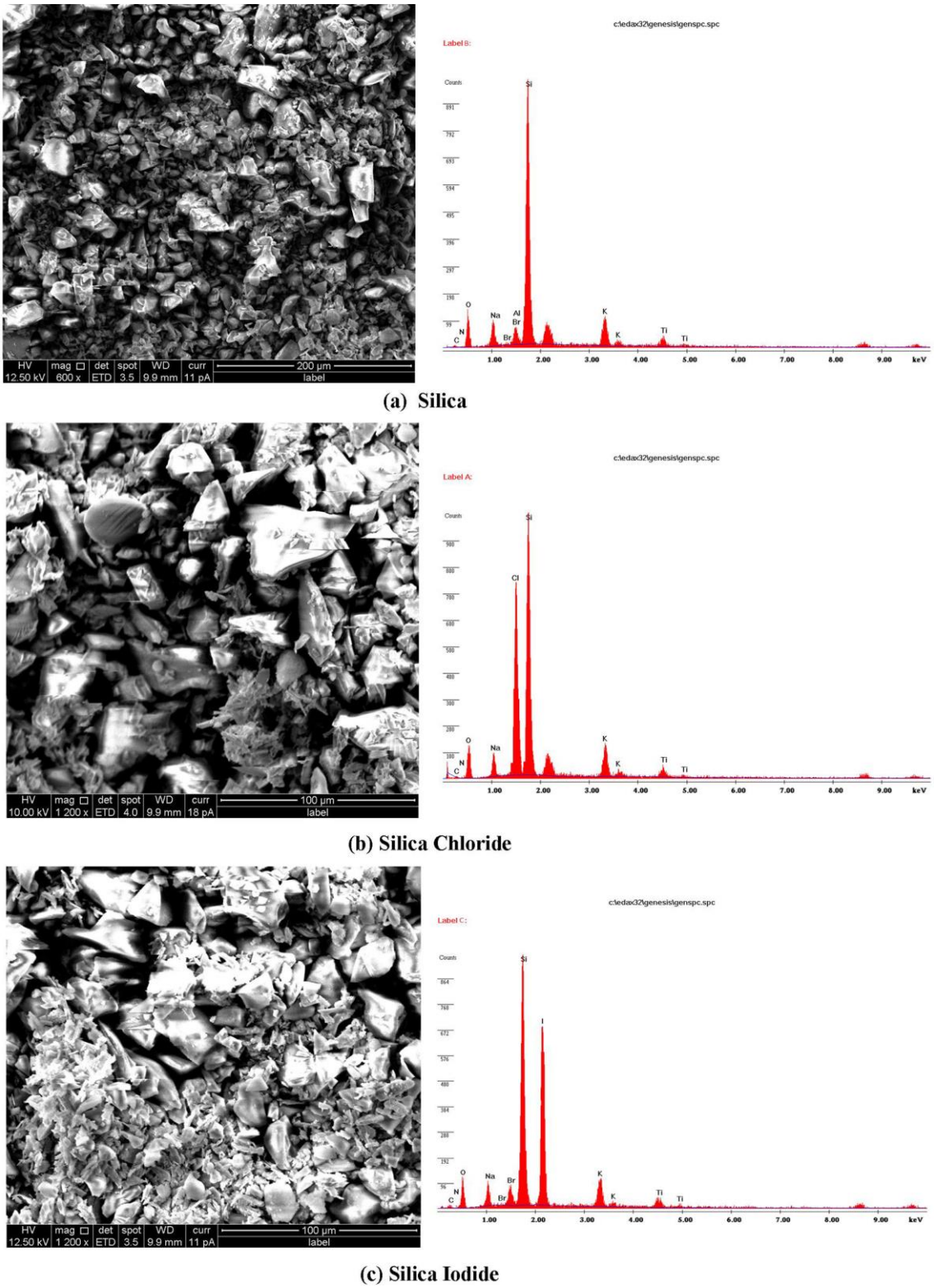
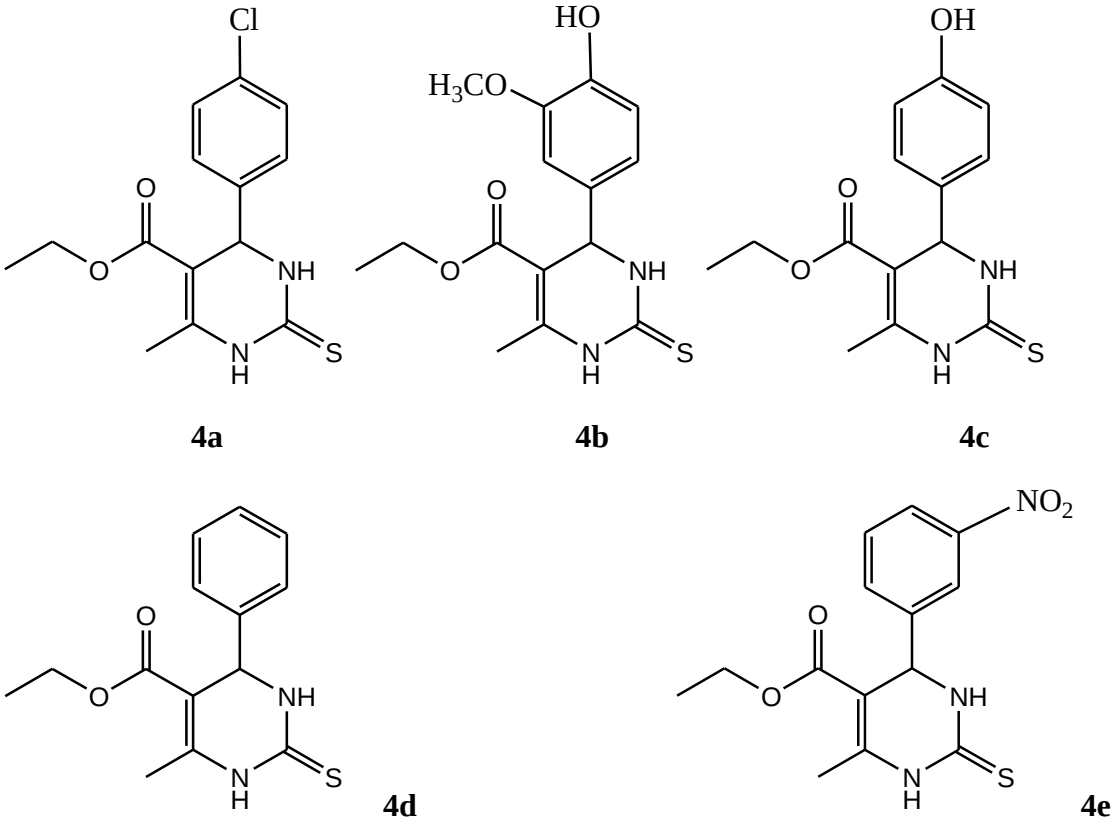


Fig 1. SEM-EDX of (**a**) silica; (**b**) silica chloride and (**c**) SiO_2-I.

4.5 General experimental procedure for the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-thiones

A mixture of aromatic aldehyde (1 mmol), thiourea (1 mmol), ethyl acetoacetate (1 mmol) and SiO_2-I (0.1 g) in ethanol (5 mL) were taken in a 50 mL conical flask and placed in a sonic bath working at 35 kHz (constant frequency, maintained at 25 °C by circulating water) for 30 min. The course of the reaction was monitored by TLC (3:7; EtOAc/hexane). After the completion of the reaction, the mixture was quenched with crushed ice and the precipitated product was filtered along with the catalyst. The residue containing the catalyst was washed with diethyl ether then the solid SiO_2–I was collected, dried at 100 °C for 2 h and kept aside for reuse. The product was recovered by removing the solvent from the filtrate under vacuum and recrystallized from hot ethanol to get the pure product. The structures of the prepared products **4a** to **4e** (**Chart 1**) were confirmed either by ^{1}H NMR, ^{13}C NMR and Mass spectral analysis, or by the comparison of melting points and on TLC with the standard samples.



4a **4b** **4c**

4d **4e**

Chart 1: The prepared 3,4-dihydropyrimidine-2 (1*H*)-thiones

4.6 Study on the reusability of SiO_2–I:

The results of the study of reusability of the catalyst are presented in the form of a graph as shown in the **Fig. 2**. From the results, it is clear that, SiO_2–I can be used successively for at least five runs after which the yield of the product dropped from 96 % in the first fresh run to 80 % in the fifth run. The yield of **4a** was found to be 96 %, 95 %, 90 %, 85 % and 80 %, respectively, for cycles 1–5. The decrease in the yield of **4a** from first to fifth time reuse of the catalyst may be due to the loss of the catalyst during the recovery.

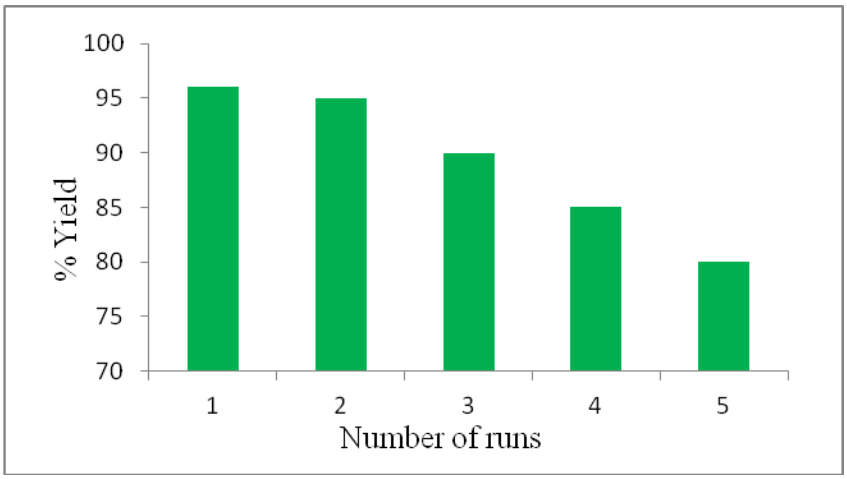


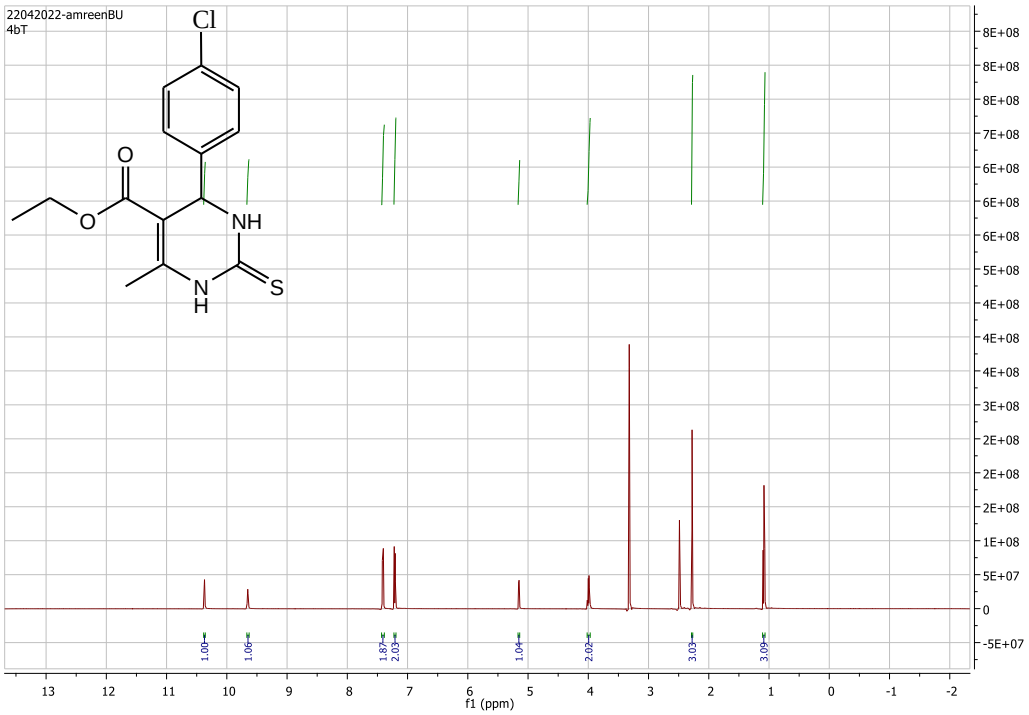
Fig. 2: Reusability of the catalyst

5. SPECTRAL DATA

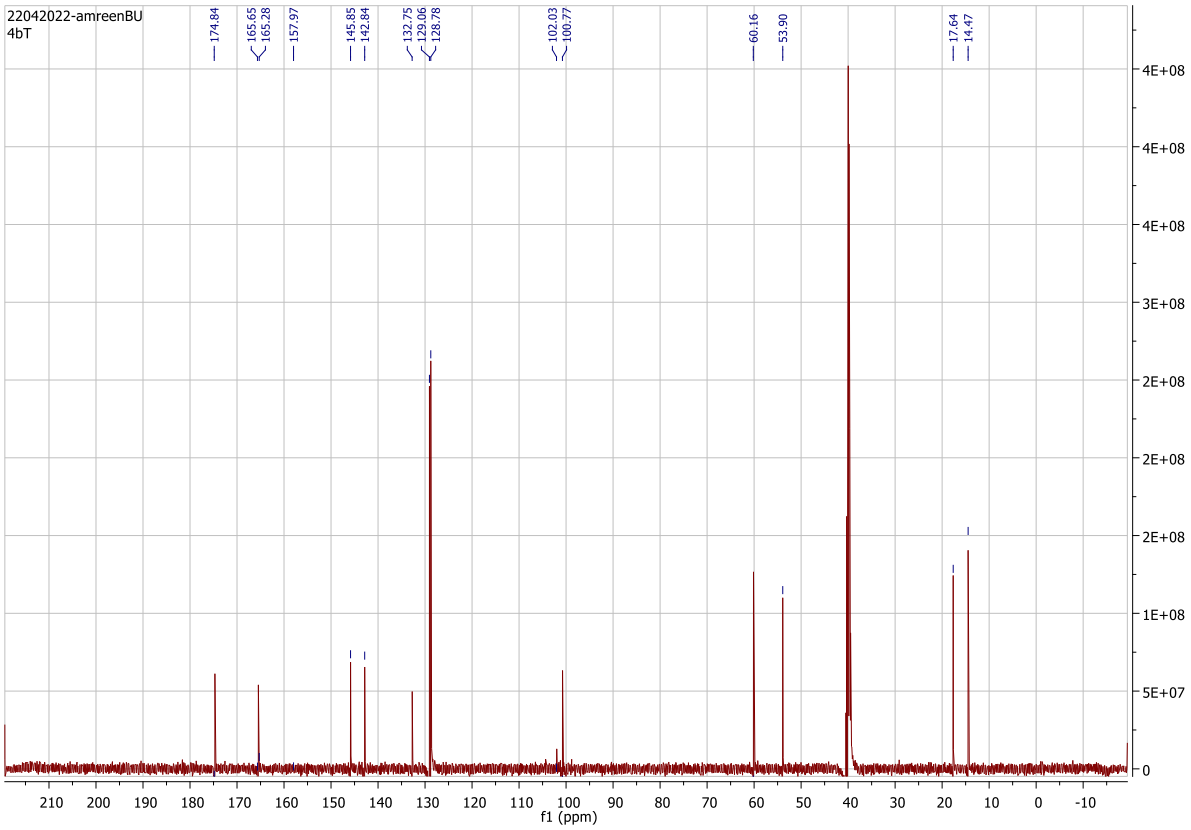
4-(4′-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidine-2 (1*H*)-thione (4a):

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.37 (s, 1H), 9.65 (d, *J* 1/4 1.7 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.2 Hz, 2H), 7.22 (t, *J* = 5.5 Hz, 2H), 5.15 (d, *J* = 3.7 Hz, 1H), 4.06–3.92 (m, 2H), 2.28 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm;
^{13}C NMR (100 MHz, DMSO-d_6): δ 174.69, 165.44, 145.83, 142.83, 132.71, 129.05, 128.91, 100.96, 60.11, 53.90, 40.68–39.40, 17.63, 14.45 ppm;
MS: e/m: Observed Mass: (M+H) 311.0621, Calculated Mass: (M+H) 311.0621.

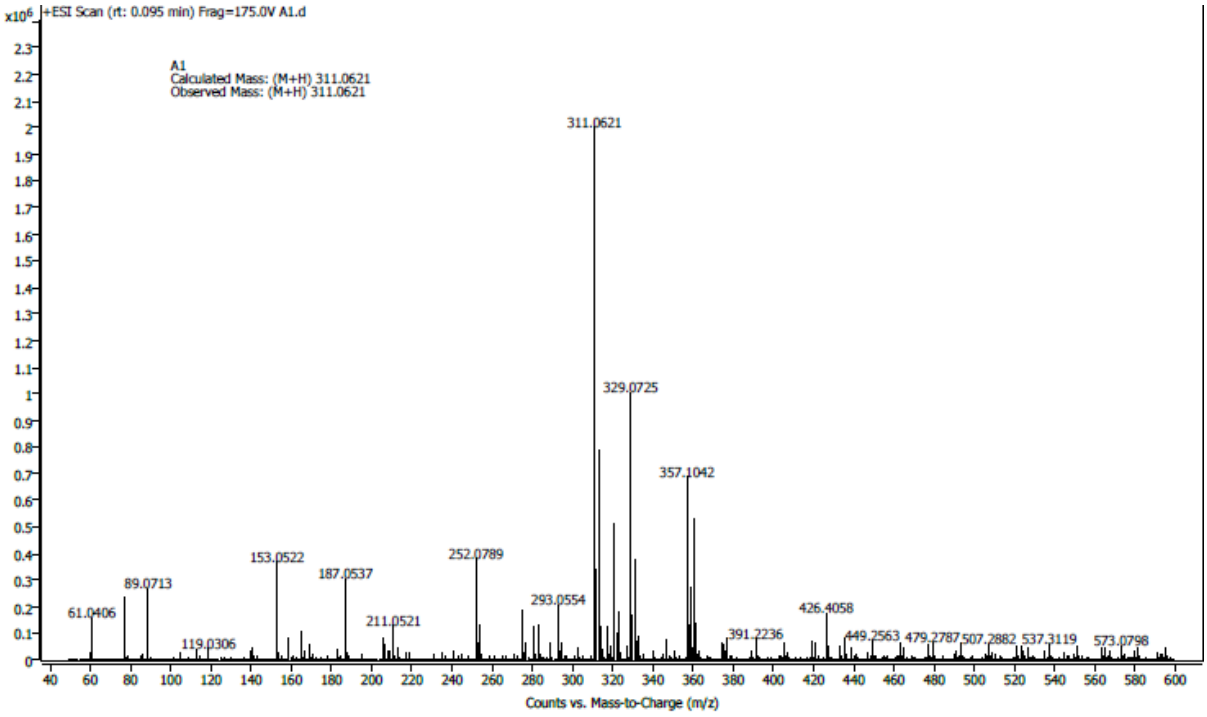
^{1}HNMR Spectrum



^{13}C NMR Spectrum

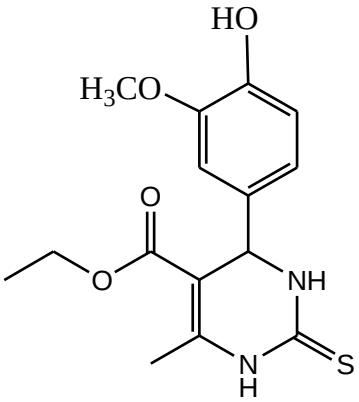


Mass Spectrum



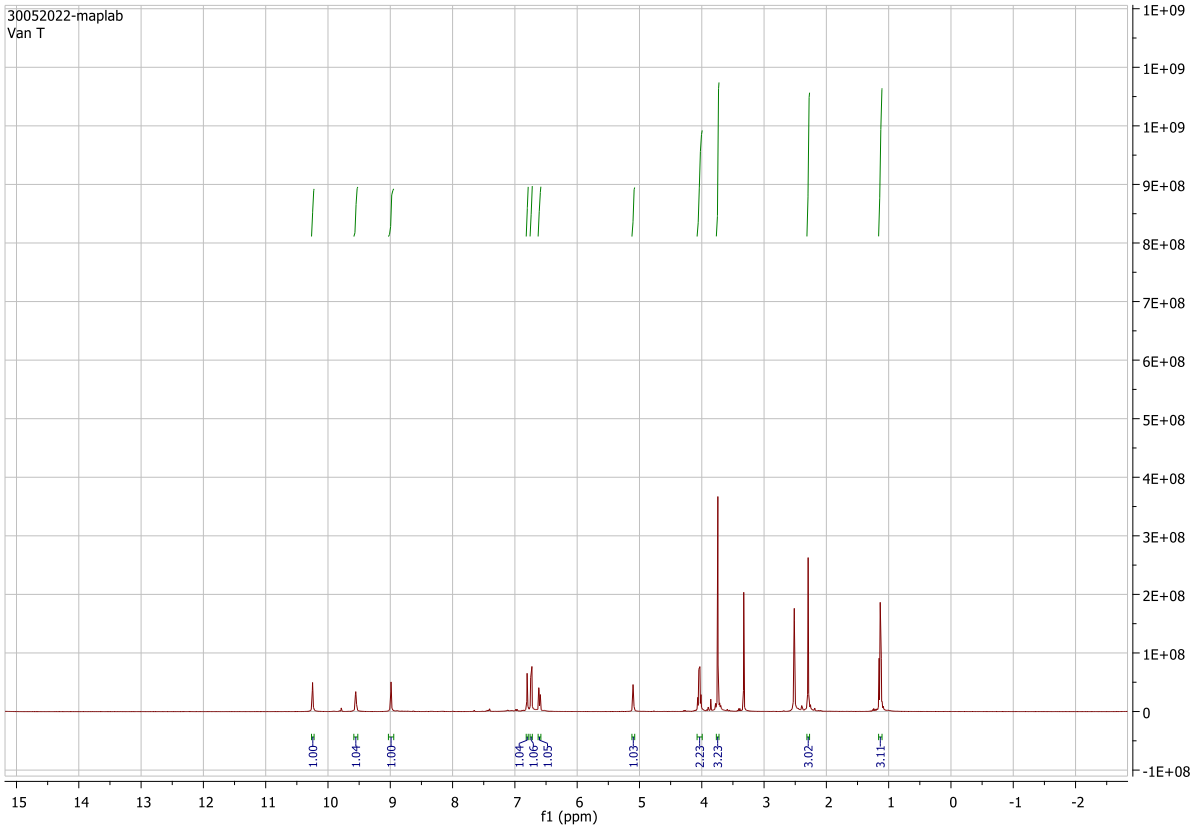
4-(4′-Hydroxy-3′-methoxyphenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidine-2 (1*H*)-thione (4b):

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 9.55 (d, *J* = 1.5 Hz, 1H), 8.99 (s, 1H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.10 (d, *J* = 3.6 Hz, 1H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 2.29 (s, 3H), 1.15 – 1.10 (m, 3H) ppm;
^{13}C NMR (101 MHz, DMSO-d_6): δ 174.68, 165.91, 147.83, 146.65, 145.11, 135.05, 119.03, 115.88, 111.55, 101.54, 59.83, 56.31, 54.34, 17.82, 14.73 ppm.

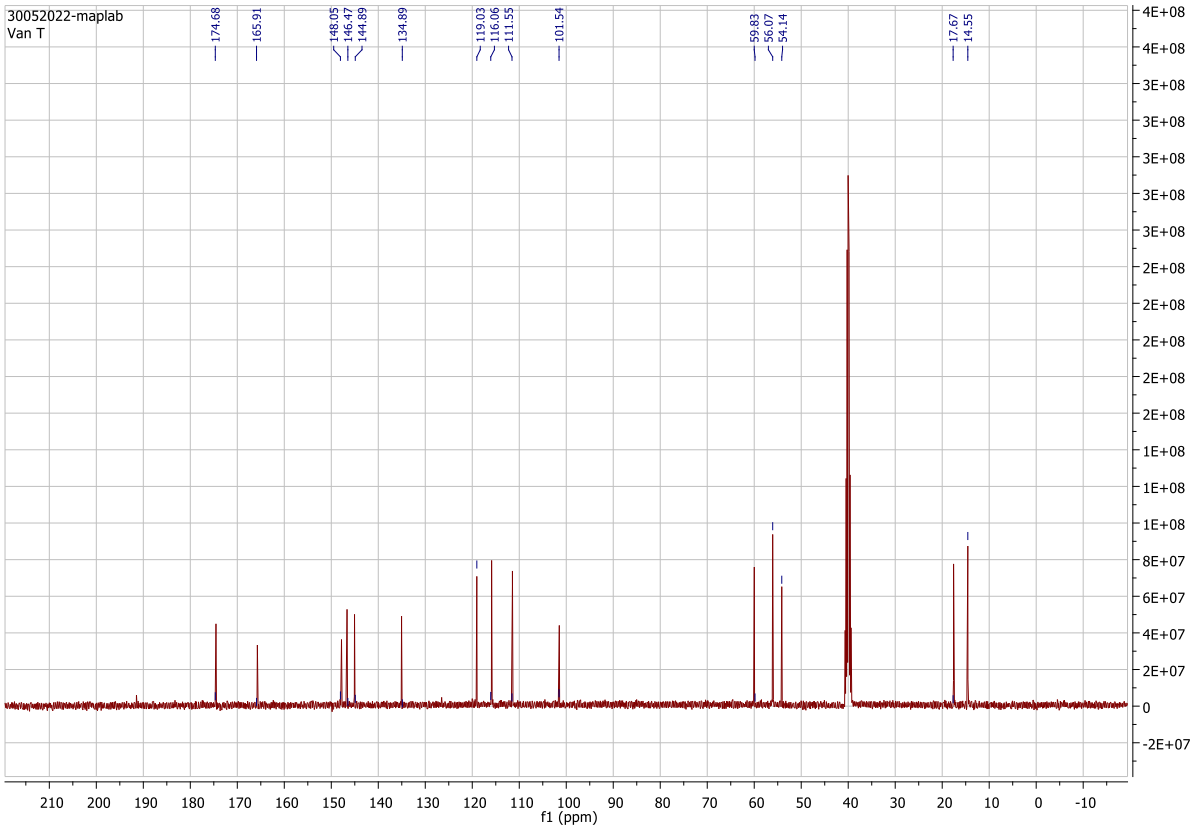


4b

^{1}H NMR Spectrum

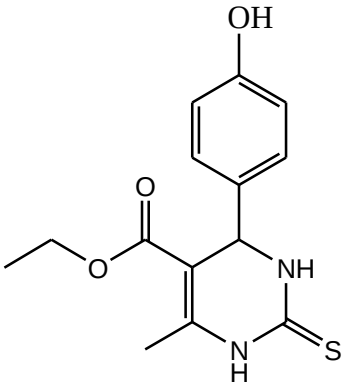


^{13}C NMR Spectrum



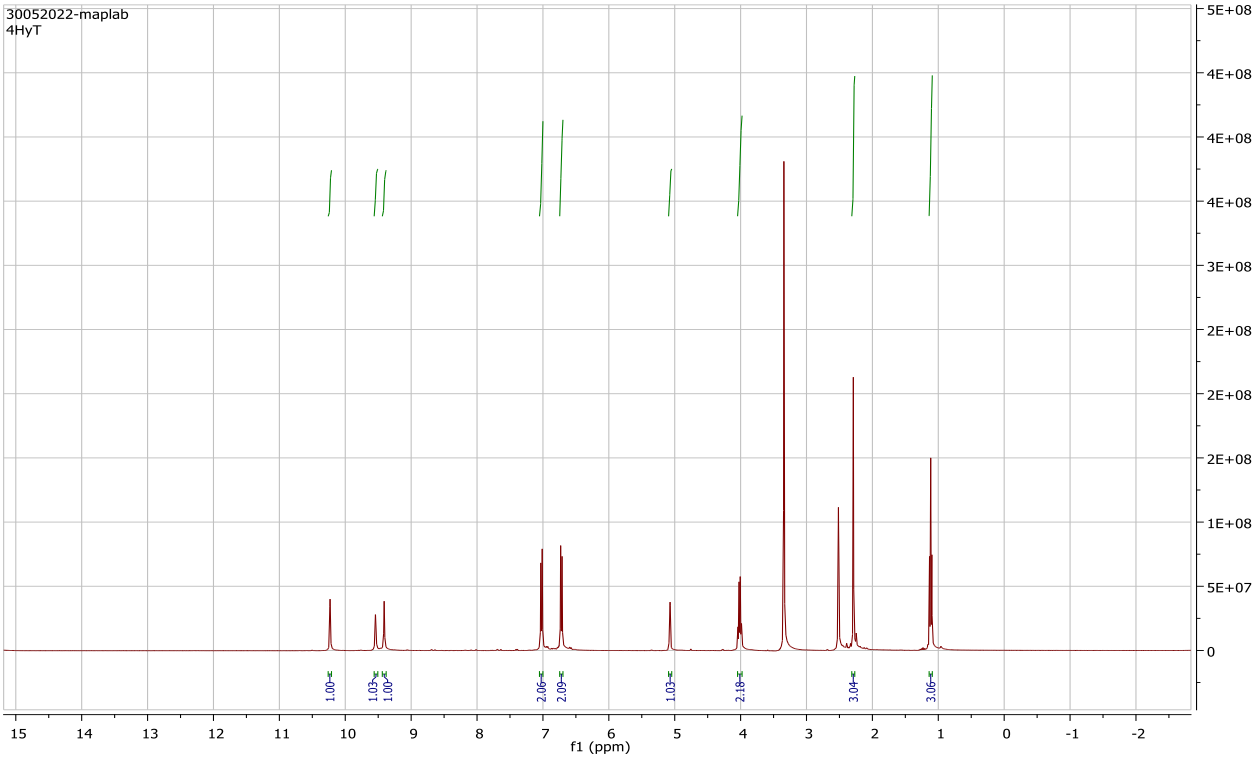
4-(4′-Hydroxyphenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (4c)

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 9.54 (d, J = 1.5 Hz, 1H), 9.41 (s, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.07 (d, J = 3.6 Hz, 1H), 4.07–3.98 (m, 2H), 2.29 (s, 3H), 1.15–1.09 (m, 3H) ppm;
^{13}C NMR (101 MHz, DMSO-d_6): δ 174.43, 165.75, 157.37, 144.96, 134.67, 128.11, 115.74, 101.70, 60.00, 54.04, 17.58, 14.50 ppm.

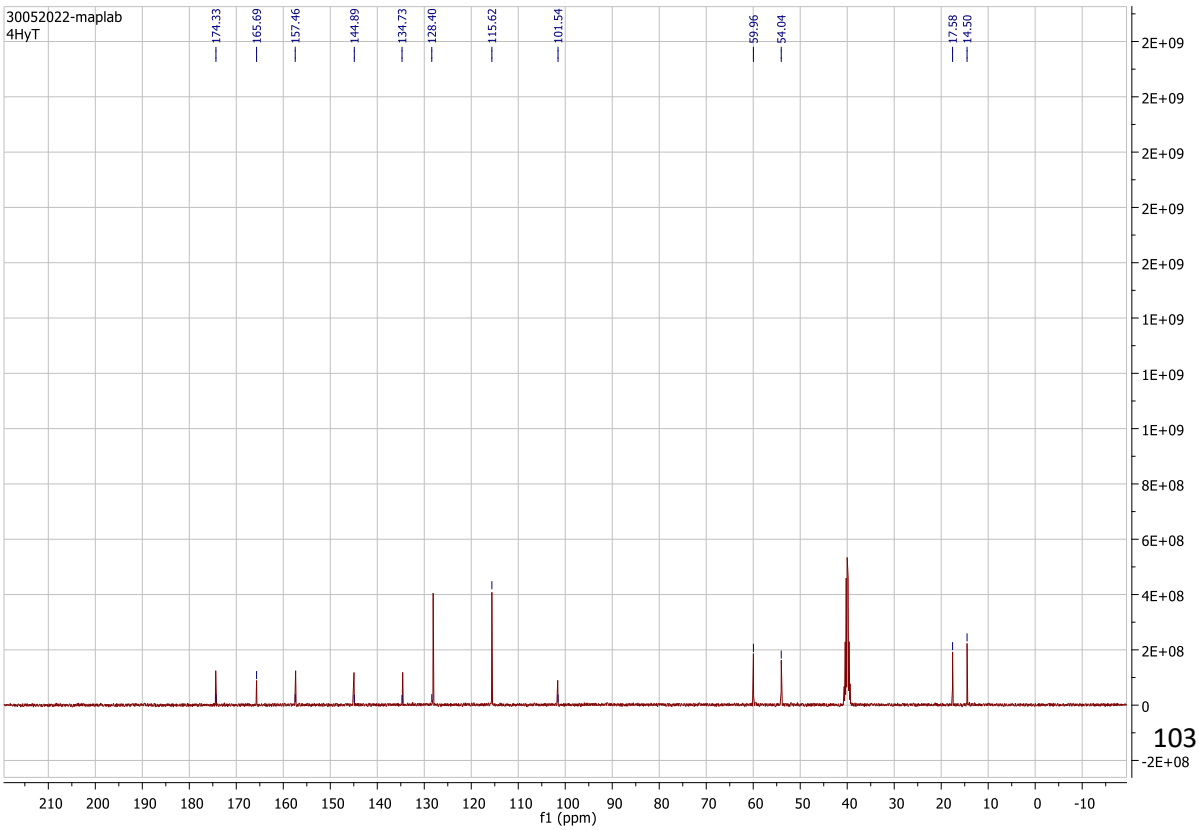


4c

^{1}H NMR Spectrum

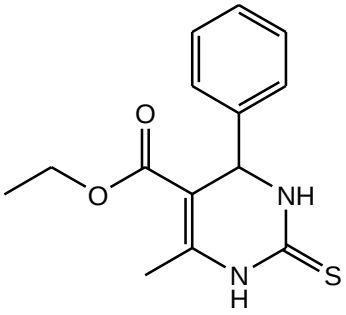


^{13}C NMR Spectrum



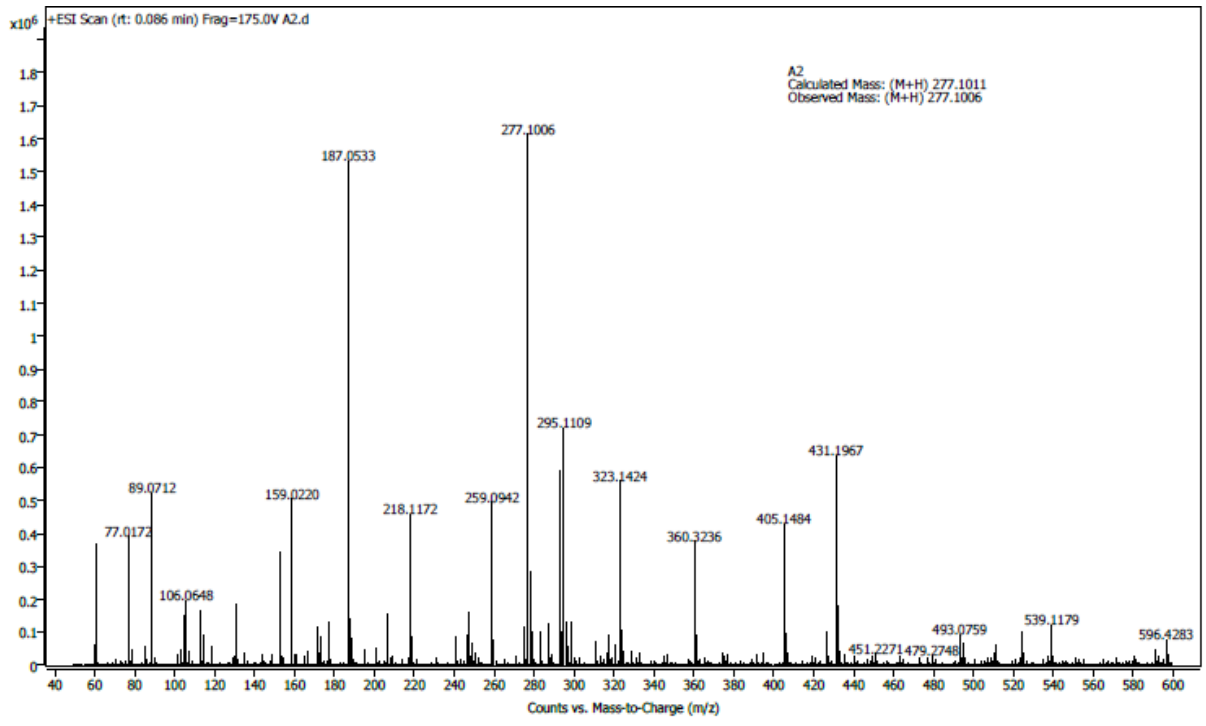
4-(Phenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidine-2 (1*H*)-thione (4d):

^{1}H NMR: δ 10.30 (s, 1H, NH), 9.63 (s, 1H, NH), 7.28 (m, 5H, Ar CH), 5.18 (s, 1H, CH), 4.00 (q, *J* = 7.0 Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.10 (t, *J* =7.06 Hz, 3H, OCH_2CH_3) ppm;
^{13}C NMR: δ 12.2, 15.5, 52.2, 57.8, 99.2, 124.7, 125.8, 126.6, 143.1, 163.4, 172.6 ppm;
MS: e/m: Observed Mass: (M+H) 277.1006, Calculated Mass: (M+H) 277.1011



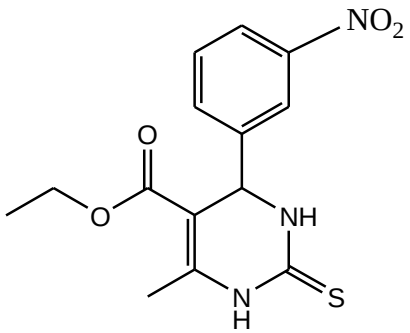
4d

Mass spectrum



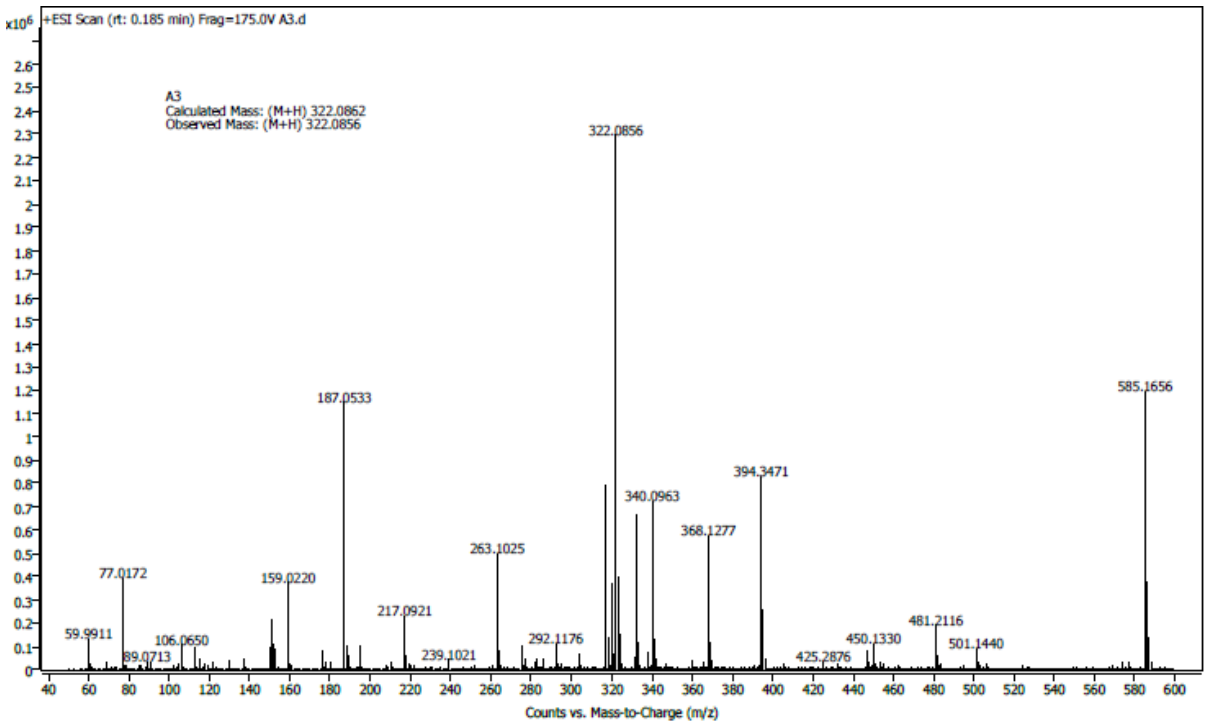
4-(3′-Nitrophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidine-2 (1*H*)-thione (4e):

^{1}H NMR: δ 10.56 (s, 1H, NH), 9.80 (s, 1H, NH), 8.08 (s, 1H, Ar CH), 7.65–7.73 (m, 2H, arom CH), 5.36 (s, 1H, CH), 4.04 (q, *J* = 7.6 Hz, 2H, OCH_2), 2.34 (s, 3H, CH_3), 1.11 (t, *J* = 7.5 Hz, 3H, CH_3) ppm;
MS: e/m: Observed Mass: (M+H) 322.0856, Calculated Mass: (M+H) 322.0862.



4e

Mass spectrum



6. Conclusions

An energy efficient and one-pot three-component reaction for a competent preparation of 3,4-dihydropyrimidine-2-(1*H*)-thiones using SiO_2-I (Silica Iodide) as a reliable and reusable heterogeneous catalyst has been developed. The reaction proceeds *via* condensation of aryl aldehydes, thiourea and ethyl acetoacetate in ethanol as a medium under ultrasonic condition to afford the target molecules in excellent yields. The reaction proceeds in 30 min; and the heterogeneous catalyst: SiO_2-I, has showed high proficiency in performing this one-pot multicomponent Biginelli reaction through recoverability, recyclability and minimization of the waste.

7. References

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