CHAPTER 4

Development of green methodologies for the synthesis of 5-aryl/spiro-[1,2,4]-triazolidine-3-thiones

4.1 INTRODUCTION

First coined by Bladin in 1885, triazole was the name given to three- nitrogen containing- five membered aromatic heterocycles [1]. The basic skeleton of this class of molecule comprises of a two carbon and three nitrogen atoms containing heterocyclic ring, with the molecular formula $C_2H_3N_3$. With the nitrogen atoms assuming two different positional arrangements, there are two possible positional isomers, namely 1,2,3-triazole and the 1,2,4-triazole. Furthermore, each of these isomers also show two tautomeric forms on the basis of the nitrogen to which the hydrogen is bonded (**Figure 4.1**). The hybridization of each atom in the triazole ring is sp^2 and the structure is planar. The six π-electrons are available for delocalization around the ring and this gives rise to the aromatic character of the molecule. Additionally, the presence of three nitrogen atoms makes the molecule an energy-rich heterocycle [2].

1,2,3-triazole, the more popular isomer of the two, are generally prepared from azides and have been an integral part of the click chemistry for a very long time. However, when it comes to the 1,2,4-triazoles, reports are not as extensive. In this chapter we will be discussing about the 1,2,4-triazole derivatives and therefore, shall limit our discussion to it alone.

1,2,4-triazole is a white solid (mp 120–121 °C, bp 260 °C) having high solubility in water as well as in other organic solvents. Despite the two tautomers, shown in **Figure 4.1**, maintain a rapid equilibrium amongst them, the 1*H* variant is more stable than the 4-*H* tautomer [3]. Chemically, 1,2,4-triazoles are susceptible to both electrophilic and nucleophillic substitution reactions. However, electrophilic

substitution reactions are observed only at the nitrogen atoms. This can be attributed to the high electron density over the nitrogen atoms in the ring. The nucleophillic substitution reactions are observed at the ring carbon atoms due to the electron deficiency nature of the two, while being attached to the highly electronegative nitrogen atoms.

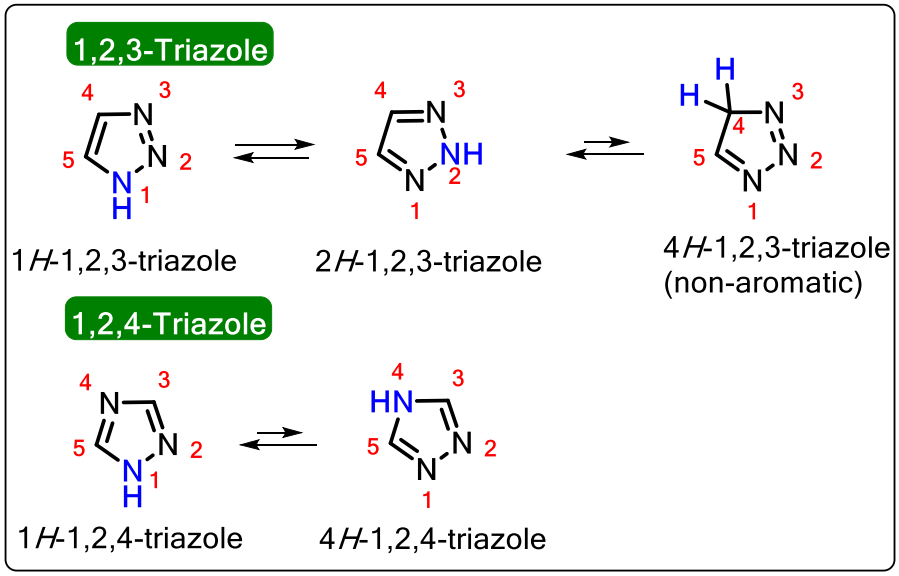


Figure 4.1: Structures of the isomers of triazole

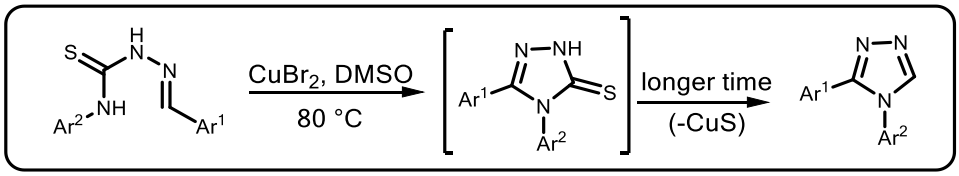
4.2 SYNTHESIS OF 1,2,4-TRIAZOLE ANALOGUES

1,2,4-Triazole has been a skeletal part of many biologically active molecules and has thereby drawn the interests of many synthetic chemists. There are several reports, exclusively dedicated to the design of the triazole scaffold alone and its functionalization. Some of the recent reports are highlighted in this section.

A. Copper catalysed synthesis

A Cu(II) catalysed oxidative-heterocyclisation was reported by Gogoi *et al.*, in 2015, which proceeded through the cyclisation of arylidene-aryl

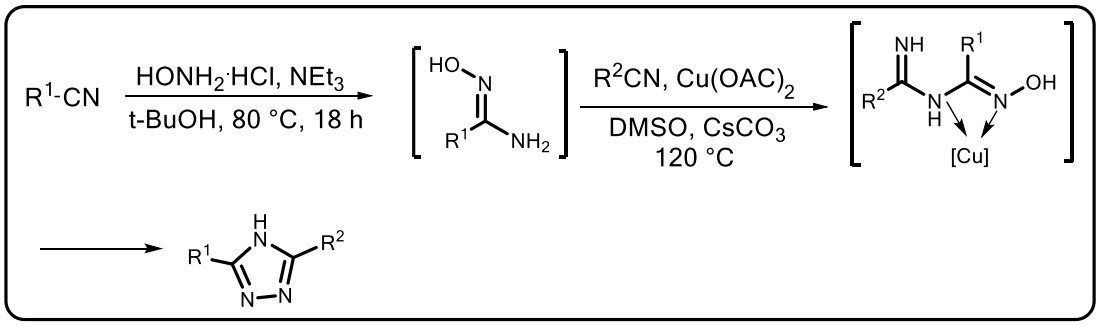
thiosemicarbazides to yield 4,5-disubstituted-1,2,4-triazole-3-thiones [4]. This product was shown to have undergone desulfonation, when the reaction time was extended to generate 4,5-diaryl-1,2,4-triazoles (**Scheme 4.1**). Xu *et al.* in 2015 reported an efficient one pot strategy for the synthesis of 1,2,4-triazoles, substituted symmetrically and unsymmetrically, from hydroxylamine and nitriles [5]. The strategy began with the formation of the amidoxime via intermolecular



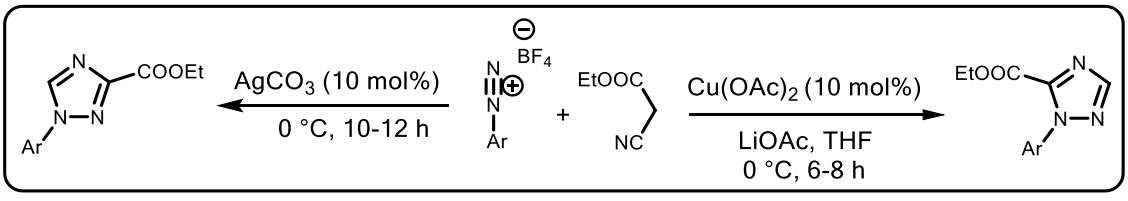
Scheme 4.1 Copper catalysed oxidative-heterocyclisation for the synthesis of 4,5 disubstituted 1,2,4-triazole thiones and corresponding desulfonated product (Gogoi *et al.*)

addition of hydroxylamine and nitriles, followed by the reaction of a second nitrile molecule to undergo an intramolecular cyclisation in the presence of copper catalyst and yield the disubstituted triazoles in moderate amounts (**Scheme 4.2**). During the cyclisation step, a sequential N-C and N-N bond formation takes place after dehydration. Synthesis of N^1-aryl-1,2,4-triazoles was reported by Liu *et al.*, in 2018, wherein a [3+2] cycloaddition reaction was carried out between aryl diazonium salts and ethyl cyanoacetate to yield catalyst dependent highly regioselective products [6]. When the reaction was carried out in the presence of Cu(II) catalyst, then 1,5-disubstituted-1,2,4-triazoles was formed and the same reaction yielded 1,3-disubstituted-1,2,4-triazoles in the presence of Ag(I) catalyst (**Scheme 4.3**).

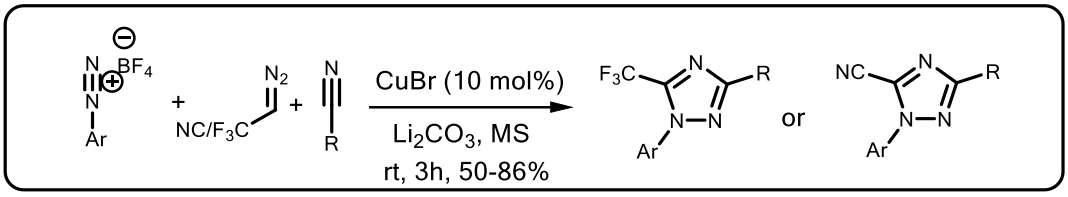
Similarly, another report by Peng *et al.*, in 2020, fluorinated diazo compounds and nitriles were reacted to generate a nitrile ylide and it underwent a reaction between the diazonium salt present to form an [1+2+2] annulated product [7]. This paved a way for the synthesis of diverge trifluoromethylated N^1-aryl-1,2,4-triazoles. Later, Zhou *et al.* in 2019, extended this protocol towards the synthesis of 1-aryl-5-cyano-1,2,4-triazoles (**Scheme 4.4**) [8]. Very recently, Zhang *et al.* in 2022, developed a copper catalysed decarbonylative cyclisation methodology for the synthesis of fluorinated and triply substituted 1,2,4-triazoles from trifluoroacetimidohydrazides and isatins [9]. This was an example of cascade condensation which was followed by hydrolysis, decarboxylation and intermolecular C-N bond formation (**Scheme 4.5**).



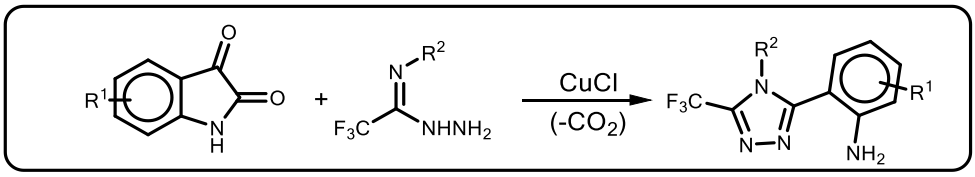
Scheme 4.2 Copper catalysed synthesis of 3,5-disubstituted symmetrical and unsymmetrical 1,2,4-triazole (Xu *et al.*)



Scheme 4.3 Catalyst dependent highly regioselective synthesis of 1,3- and 1,5-disubstituted 1,2,4-triazoles (Liu *et al.*)



Scheme 4.4 Copper catalysed [1+2+2] annulation reaction for the synthesis of fluoroalkyl/cyano-substituted *N*[1]-aryl-1,2,4-triazoles (Zhou *et al.*)



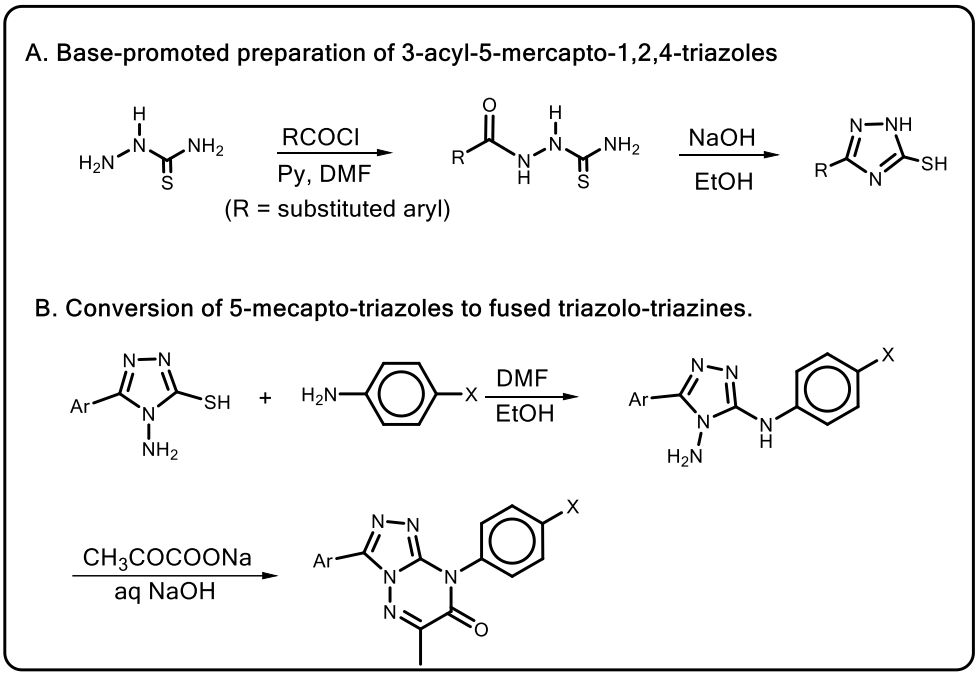
Scheme 4.5 Copper catalysed two component annulation reaction for the synthesis of fluoroalkyl-substituted *N*[1]-aryl-1,2,4-triazoles (Zhang *et al.*)

B. Base promoted synthesis

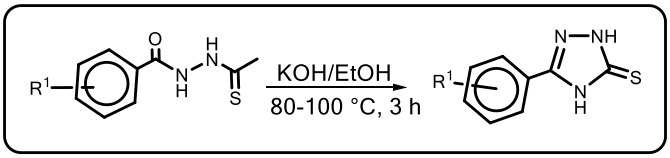
Mioc *et al.* in 2017, reported a facile synthesis of 3-aryl-5-mercapto-1,2,4-triazoles by refluxing acylthiosemicarbazides in the presence of base- ethanolic KOH/NaOH/$NaHCO_3$ (**Scheme 4.6 A**) [10]. The mercapto derivative was furthered with S-substitution. Similarly, 5-mercapto-1,2,4-triazole with 4-amino skeleton was treated with arylamines towards the synthesis of fused triazolo triazines (**Scheme 4.6 B**) [11]. These compounds showed excellent anticarcinogenic, antiproliferative, antimicrobial and anti-inflammatory activities. Sonawane *et al.* in 2017, also showed the preparation of 1,2,4-triazole-3-thiones *via* a base catalysed cyclisation of aroyldithiocarbazates (**Scheme 4.7**) [12]. Similar base catalysed cyclisation was reported by Aly *et al.* in 2019, wherein the regioselective synthesis of 1,3,5-trisubstituted-1,2,4-triazoles was accomplished from amidrazones and ethylazodicarboxylate (**Scheme 4.8**) [13].

C. Microwave assisted method

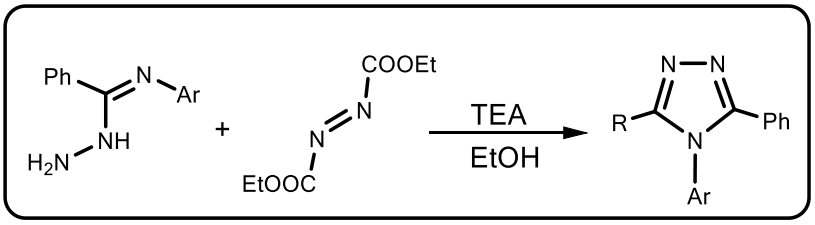
The number of microwave assisted methods for the synthesis of functionalised 1,2,4-triazoles are very few in number. Shelke *et al.* in 2015 reported the formation of 1,2,4-triazoles *via* microwave irradiated reaction between hydrazine and fromaides (**Scheme 4.9**) [14]. Similarly, Vaithiyalingam *et al.*, 2021 reported the utilisation of microwave heating to carry out a base free condensation reaction between *t*-butyl-1-cyanopiperazine carboxylate and 2-fluorobenzohydrazide for the formation of 3,5-disubstituted-1,2,4-triazole-based piperazine, with high yields (**Scheme 4.10**) [15].



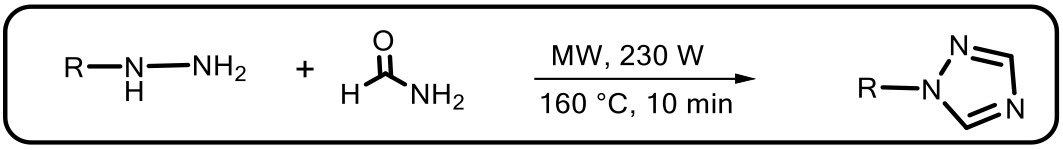
Scheme 4.6 Base promoted synthesis of 3,5-disubstituted-triazoles (Mioc *et al.*)



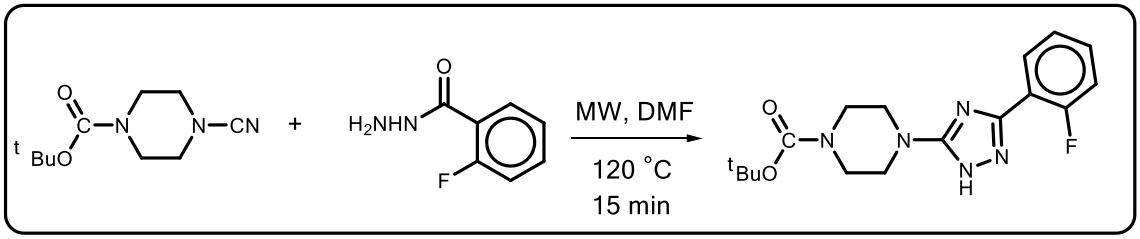
Scheme 4.7 Synthesis of 1,2,4-triazole-3-thiones *via* cyclization of aroyldithiocarbazate (Sonawane *et al.*)



Scheme 4.8 Triethylamine catalysed regioselective synthesis of 1,3,5-trisubstituted-1,2,4-triazoles (Aly *et al.*)



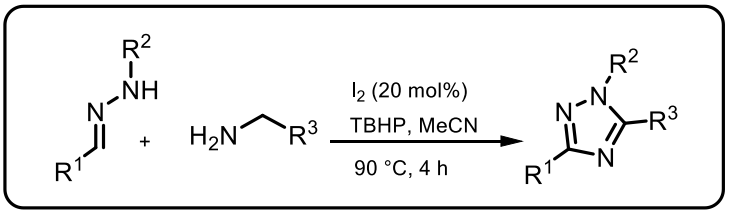
Scheme 4.9 Microwave assisted synthesis of 1,2,4-triazole (Shelke *et al.*)



Scheme 4.10 Microwave assisted synthesis of 3,5-disubstituted-1,2,4-triazole-based piperazine (Vaithiyalingam *et al.*)

D. Miscellaneous methods

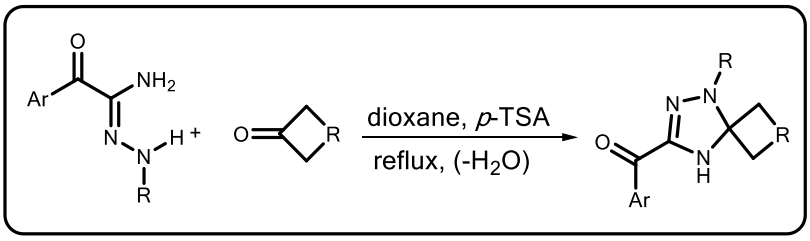
In addition to the above methodologies, there are several other methods for the synthesis of 1,2,4-triazoles. The methods progressively moved towards greener synthesis by introducing metal free conditions by using the oxidative conditions generated in the presence of molecular iodine and *t*-butylhydroperoxide (TBHP) (**Scheme 4.11**) [16].



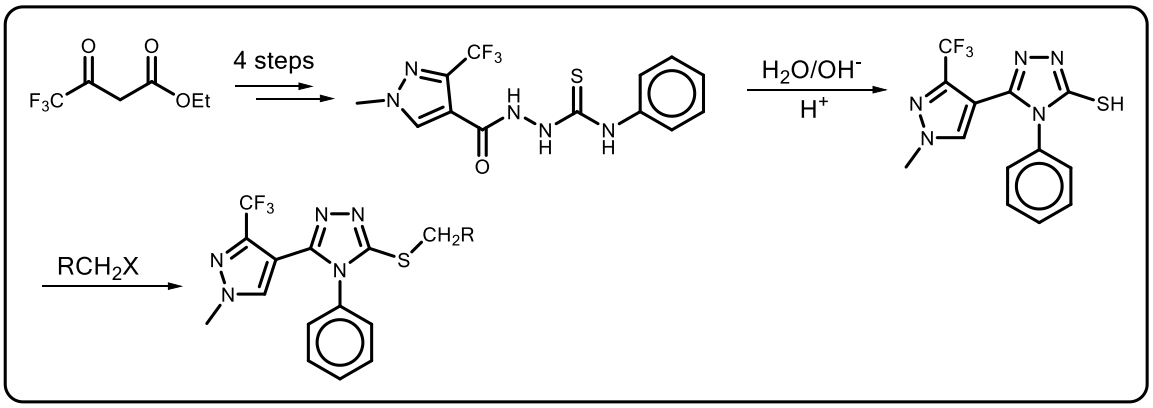
Scheme 4.11 I_2-catalysed synthesis of 1,2,4-triazoles

Amidrazones were also reacted with cyclic ketones in the presence of *p*-toluene sulphonic acid (*p*-TSA) catalyst, to yield spiro-1,2,4-triazoles, which exhibited antimicrobial properties (**Scheme 4.12**) [17].

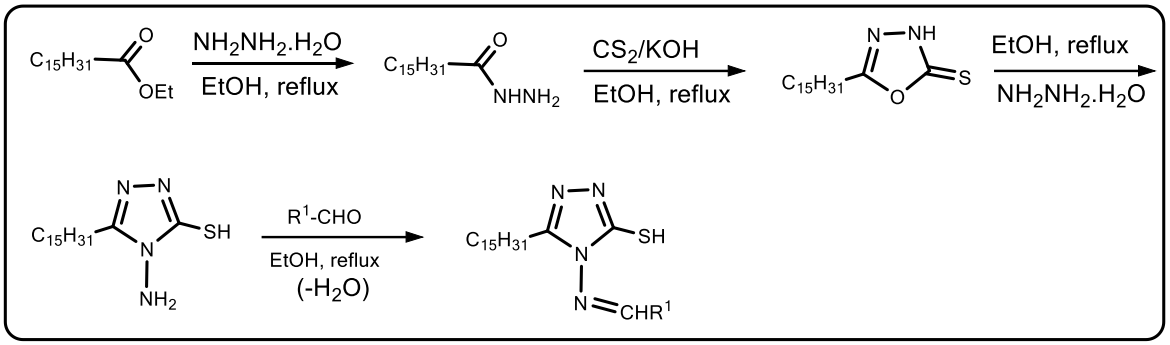
Zhai *et al.*, 2017, also reported a multistep synthesis of antifungal and herbicidal 1,2,4-triazoles functionalised with imidazole and thioether moieties, signifying the applications of the scaffold (**Scheme 4.13**) [18]. 1,2,4- triazoles functionalised at the 3,4,5 positions was reported by Kumari *et al.* in 2021, where replacement of the oxadiazole ring oxygen, to from a triazole ring, was carried out with hydrazine [19]. The resultant N-amino-1,2,4-triazoles showed promising antimicrobial and anticarcinogenic activities. The compounds were further modified into new kind of Schiff's bases by Abdulghani et. al., in 2022 (**Scheme 4.14**) [20].



Scheme 4.12 Synthesis of spiro-1,2,4-triazoles



Scheme 4.13 Synthesis of imidazole and thioether containing 1,2,4-triazoles (Zhai *et al.*)



Scheme 4.14 Synthesis of 3,4,5- trisubstituted triazoles and the corresponding Schiff's base (Abdulghani et al.)

4.3 APPLICATIONS OF 1,2,4-TRIAZOLES

Ever since the incorporation of the 1,2,4-triazole ring, it has introduced an array of therapeutically important molecules, showing efficient bioactivities such as antimicrobial, antianxiety, antimigraine, antimycotic, anti-inflammatory, sedatives and CNS stimulants [21, 22]. Commercially available drugs such as Triazolam, Rizatriptan (antimigraine), Estazolam (anticonvulsant) and Ribavirin (antiviral) also contains the 1,2,4-triazole nucleus [23]. This class of triazole is also the precursor to heteroatomic organic compounds like Mannich bases, thioethers and thioureas, triazolothia-diazoles, diazines, azines and azepines and Schiff bases [24]. Furthermore, it is a well-known fact that heterocycles containing Sulphur have proven their efficacy in different arenas of practical applications. In combination with 1,2,4-triazoles, the mercapto and thione derivatives have been exclusively studied for their biological activities [25]. More specifically, the 5-aryl-1,2,4-triazolidine-3-thione derivatives have outperformed a number of over-the-counter anticonvulsant, antioxidant, anti-inflammatory, analgesic, antibacterial, antifungal, antiparasitic, antiurease and anticancer drugs (**Figure 4.2**) [26].

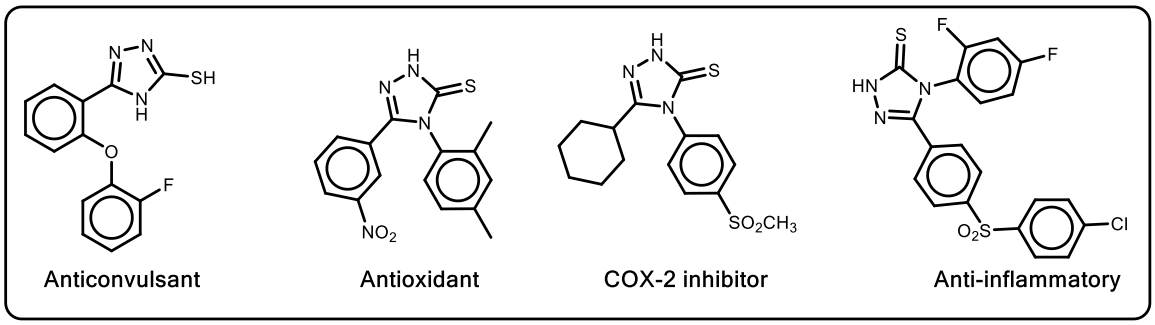


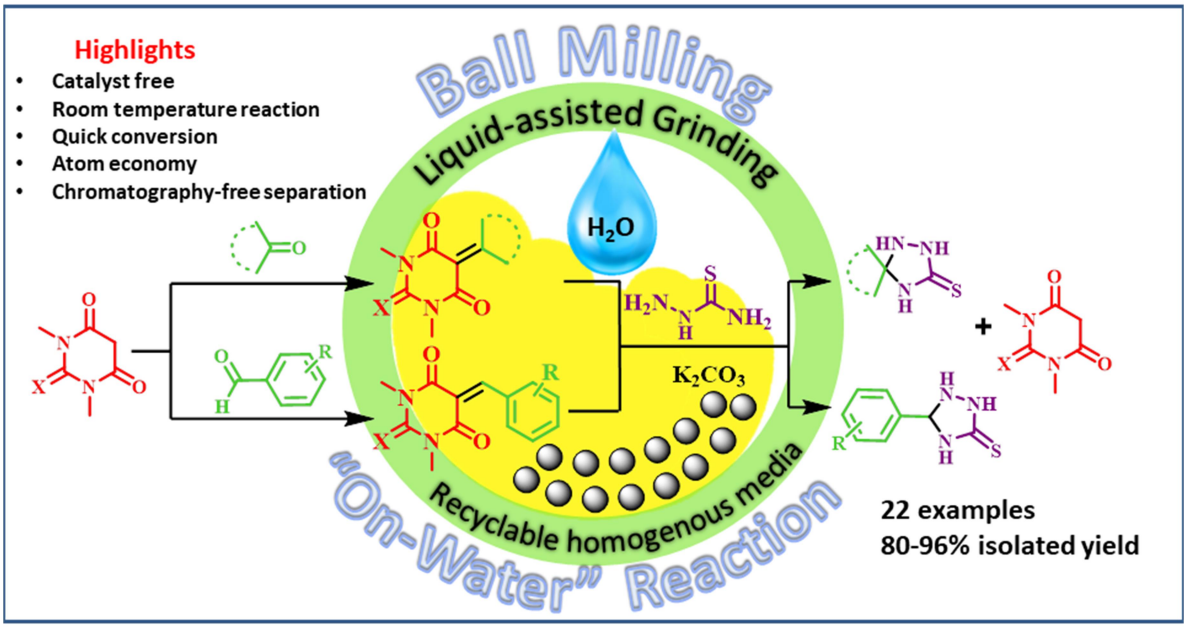
Figure 4.2 Examples of pharmaceutically active 5-aryl-1,2,4-triazolidine-3-thiones

Owing to the wide range of importance, popularity and applications of 1,2,4-triazole, we embarked upon designing greener protocols for the synthesis of this scaffold. In this chapter, development of two protocols for the synthesis of 5-aryl-1,2,4-triazole-thiones and spiro-1,2,4-triazole-thiones have been discussed. The objectives of both the works being:

- Synthesis of 5-substituted-1,2,4-triazole-3-thiones.
- To promote economical and environmentally friendly experimental procedures- Liquid assisted grinding and sonochemistry.
- To study the chemoselectivity and regioselectivity of the reactions.
- To study the scope and limitations of the cyclisation methodologies.

Section 4.1

Liquid assisted mechanochemical synthesis of 5-aryl/spiro-[1,2,4]-triazolidine-3-thiones



4.1.1 INTRODUCTION

The growth of interests in discovering greener methodologies for organic transformation saw a considerable surge in the applicability of mechanochemical methods to serve the purpose [27]. A plethora of reactions that involved carbon-carbon [28] and carbon-heteroatom bond formation [29], have been extensively explored. It has led to the application of mechanochemistry in multicomponent reactions and has been furthered by heterocycle synthesis [30], which includes C-H Allylation and C-2 selective arylation of Indoles [31, 32], alkenylating and heteroarylating *N*1-protected 1*H*-Indazoles [33], multicomponent synthesis of polysubstituted pyrroles and trans-2,3-*D*ihydropyrroles [34] and the preparation of hydantoins [35]. Another aspect of mechanochemical transformation includes Liquid-assisted grinding (LAG). As, on one hand, the solvent free processes enlist their own advantages, LAG, at many a times, have come up with its own set of advantages in promoting chemo selectivity and improvement of yield [36]. The relationship was exemplified by Mack et al. showing dependence of the selectivity of diyne or enyne on the polarity of solvents [16] and by Halasz *et al*. showing the correlation of the rate of reaction with the donor number of solvents [37]. Although, ambiguity regarding the participation of solvent molecules, in the mechanism of both the reactions, is prominent, the mentioned effect cannot be disregarded.

Falling in trend towards developing newer methodologies, particularly bearing greener prospects, the synthesis of 1,2,4-triazoles caught our attention, more specifically 5-aryl-1,2,4-triazolidine-3-thiones. Despite the wide range applications

of this class of triazole, reports on their synthesis are quite limited. Among those available, the usage of catalysts such as Sm_2O_3/Fap [38], Fe-FAp/glutamic acid [39], $[C_{16}MPy]AlCl_3Br$ [40], $[2\text{-HMPyBSA}]HSO_4$ [41], $[(Py)_2SO][HSO_4]_2$ [42], rice husk biomass derived activated carbon [43], brings about additional, tedious steps of catalyst preparation and others come with their own set of short-comings. Mane and Pore reported sulfamic acid catalysed synthesis using aldehyde, hydrazine hydrate, and the not-so-easily available trimethylsilyl isothiocyanate [44]. Recently, Pore and his group also reported multicomponent synthesis of this class of compound with the aid of a Lewis acid-surfactant ($AlCl_3$-benzethonium chloride), by using phenyl isothiocyanate, hydrazine hydrate and aromatic aldehydes/cyclic ketones/isatins [45]. Mali and Telvekar used aldehydes and thiosemicarbazides, in the presence of DMAP, to synthesize 5-aryl-1,2,4-triazolidine-3-thiones, in aqueous media [46]. This method also showed the reusability of the homogeneous DMAP-water system but lacked the prolonged reusability factor of DMAP and did not have chromatography free isolation of product. Ramesh and Lalitha reported two highly efficient chromatography free and greener methods of obtaining 5-aryl-1,2,4-triazolidine-3-thiones from aldehydes and thiosemicarbazides in PEG-400 and in the presence of malononitrile respectively but the reactions had to be carried out under thermal conditions, the reaction media i.e. PEG-400 was not reported to be reusable and malononitrile, utilized in stoichiometric amounts, was not reused, thereby reducing atom-economy [47,48].

Here, we introduce a new application of mechanochemical process while also developing a route towards the synthesis of 5-aryl-1,2,4-triazolidine-3-thiones.

The focus of the work is also shared by discussing the mechanism of the reaction at room temperature and how the active methylene compound, here 1,3-Dimethylbarbituric acid, plays a crucial role in aiding the formation of the five membered ring. The protocol also paves a way towards recovering the active methylene compound and thereby reuses it over and over again without loss of activity.

4.1.2. RESULTS AND DISCUSSION

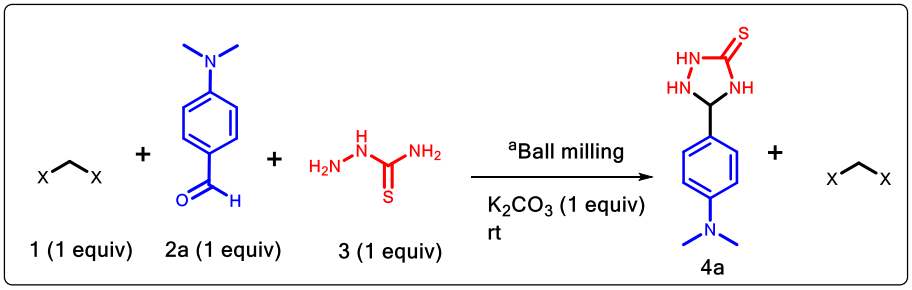
We initiated our experimentation with the reaction of 4-Dimethylamino benzaldehyde with various active methylene groups (**Table 4.1.1**), in addition to equal volumes of the other components, viz. thiosemicarbazide and a base, in a planetary ball mill under LAG conditions, for 10 minutes, at room temperature (rt) i.e. 25 ºC. We preferred going with a mild and easily available base, Potassium carbonate (K_2CO_3) and used water as the solvent. This multicomponent reaction has never been tried out mechanochemically, but deriving the concept from similar reported reactions [47, 48]. We expected the formation of 5-(4-(dimethylamino)phenyl)-1,2,4-triazolidine-3-thione, and the non-incorporation of the active methylene group. Our hypothesis was proven correct after analyzing the product and the spectral data were in fine agreement with those reported in literature [44-47]. The product obtained with all other active methylene compounds was same. It is also noteworthy that the best results were obtained with 1,3-Dimethylbarbituric acid and therefore, the subsequent experiments were conducted using it. We checked the feasibility and enhancement of the reaction by altering various factors (**Table 4.1.2**), such as, solvent (**entries 1-12 of Table 4.1.2**), base (**entries 13-18 of Table 4.1.2**), and time (**entries 9-21 of Table**

4.1.2) and were able to deduce the optimized scheme (**entry 20 of Table 4.1.2**) for the reaction, which is shown in **Scheme 4.1.1**. The instrument used for ball milling was an indigenously built planetary ball mill which had monitoring segment for measuring the rotations per minute. It had a fixed rotation per minute of 300 rpm and hence further optimization of this parameter was not done. It can be seen that the reaction proceeded well in the presence of polar solvents as well as water-ethanol binary solvent mixture (of varying ratios) (**entries 4-6 of Table 4.1.2**). However, owing to the simplicity of the solvent and keeping up with the greenness factor, we kept our solvent of choice as water. Again, performance of the reaction in the presence of K_2CO_3, a mild base, was at par with its stronger counterparts, such as, NaOH and KOH. As a matter of fact, isolation of the product was less efficient in the presence of strong bases. This can be attributed to the partial solubility of the product in the presence of strong bases. Moreover, increasing the amount of base did not affect the yield but decreasing it definitely lowered the conversion. The reaction did not proceed in the absence of a base. Isolation of the solid product was simply dilution of the reaction mixture with water, followed by filtration. Now, as it was clear that the 1,3-Dimethylbarbituric acid, in fact, all the active methylene group containing moieties, was not introduced into the skeleton of the product, so, we thought of the possibilities of reusing it. But, before proceeding we examined the utility of 1,3-Dimethylbarbituric acid, in catalytic amount. This attempt was not at all satisfactory and got only traces of the desired product along with the thiosemicarbazone of 4-Dimethylamino benzaldehyde (**entry 7 of Table 4.1.1**). Continuing with our quest for a homogeneous recyclable reaction media, we

analyzed the filtrate from our model reaction. As a part of the post synthesis workup, water was added to the slurry after LAG was completed. The product precipitate out and the eliminated starting material, 1,3-Dimethylbarbituric acid, goes into the solution, which also contains the base. No other starting materials were found to be present in the precipitate as well as the supernatant liquid. Therefore, we also came upon a proposition to use this basic supernatant liquid, containing 1,3-Dimethylbarbituric acid, as a reusable homogeneous reaction media, after collecting it as a filtrate.

To check the validity of our proposition, we carried out a reaction by adding equimolar amounts (with respect to the amount of 1,3-Dimethylbarbituric acid taken during the previous LAG method) of 4-Dimethylamino benzaldehyde and

Table 4.1.1: Screening of active methylene compounds

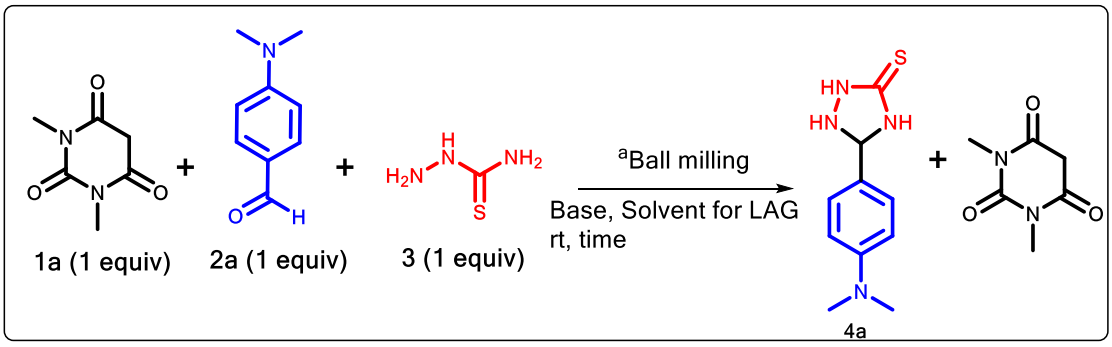


Sl. no	Active methylene compound 1	Isolated Yield % of 4a
1	1,3-Dimethylbarbituric acid (1a)	94
2	Barbituric acid (1b)	92
3	4-hydroxycoumarin (1c)	88
4	Meldrum's acid (1d)	85
5	1,3-cyclohexanedione (1e)	75
6	Dimedone (1f)	82
7	1,3-Dimethylbarbituric acid (1a) (0.1mmol)-catalytic	Traces

[a]Reaction conditions: Active methylene compound 1 (1 mmol), 4-Dimethylaminobenzaldehyde 2a (1 mmol), Thiosemicarbazide 3 (1 mmol), 1 mL H_2O for LAG, Planetary ball mill 300 rpm, 10 stainless steel balls (2 mm diameter), 10mins, room temperature (rt, 25 ˚C)

thiosemicarbazide to the filtrate obtained after separation of the 5-aryl-1,2,4-triazolidine-3-thione product and allowing it to stir at room temperature for 30 minutes. Upon completion of the reaction, as monitored by thin layer chromatography, the product was again isolated *via* simple filtration. We were glad to observe that this reaction too yielded 5-(4-(dimethylamino)phenyl)-1,2,4-triazolidine-3-thione in excellent amount (92%) and the filtrate, obviously, still contained 1,3-Dimethylbarbituric acid and was still basic. This also paved a way to develop an "on-water" methodology for the synthesis of 5-aryl-[1,2,4]-triazolidine-3-thiones, using 1,3-Dimethylbarbituric acid-H_2O as a homogeneous recyclable media.

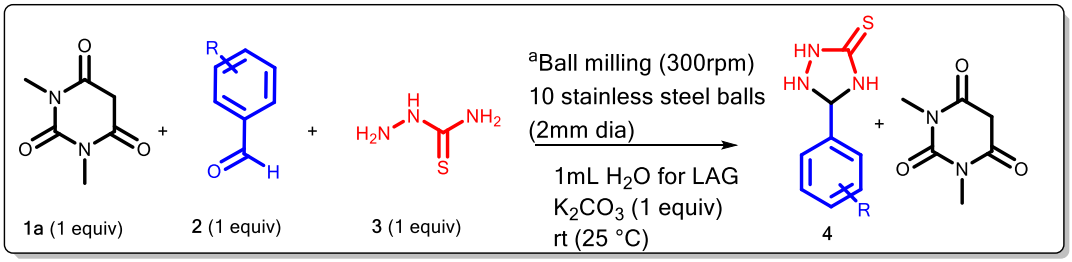
Table 4.1.2: Optimization of reaction



Sl. no	Solvent (1 mL)	Base (Amount)	Time (min)	Isolated Yield% of 4a
1	No solvent	K_2CO_3 (1mmol)	30	50
2	Water	K_2CO_3 (1mmol)	10	94
3	Ethanol	K_2CO_3 (1mmol)	10	80
4	Water:Ethanol (1:1)	K_2CO_3 (1mmol)	10	94
5	Water:Ethanol (2:1)	K_2CO_3 (1 mmol)	10	90

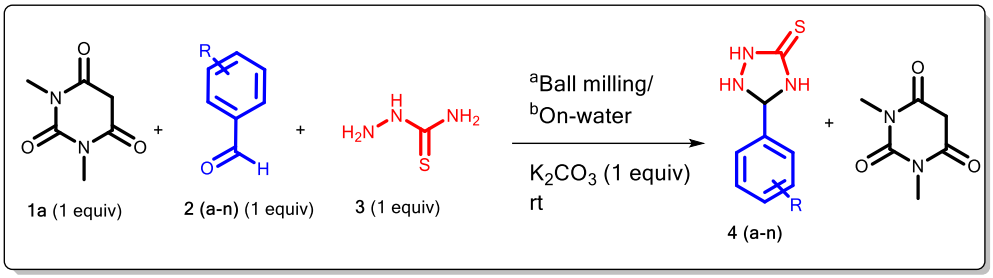
6	Water:Ethanol (4:1)	K_2CO_3 (1 mmol)	10	96
7	Methanol	K_2CO_3 (1 mmol)	10	75
8	Dimethyl formamide	K_2CO_3 (1 mmol)	30	40
9	Dimethyl sulphoxide	K_2CO_3 (1 mmol)	30	60
10	Tetrahydrofuran	K_2CO_3 (1 mmol)	30	trace
11	Acetonitrile	K_2CO_3 (1 mmol)	30	20
12	Toluene	K_2CO_3 (1 mmol)	30	trace
13	Water	No base	60	trace
14	Water	K_2CO_3 (0.1 mmol-catalytic)	30	10
15	Water	K_3PO_4 (1 mmol)	10	90
16	Water	NaOH (1 mmol)	10	92
17	Water	Et_3N (1 mmol)	10	65
18	Water	DMAP (1 mmol)	10	80
19	Water	K_2CO_3 (1 mmol)	05	94
20[b]	Water	**K_2CO_3 (1 mmol)**	02	94
21	Water	K_2CO_3 (1 mmol)	01	75

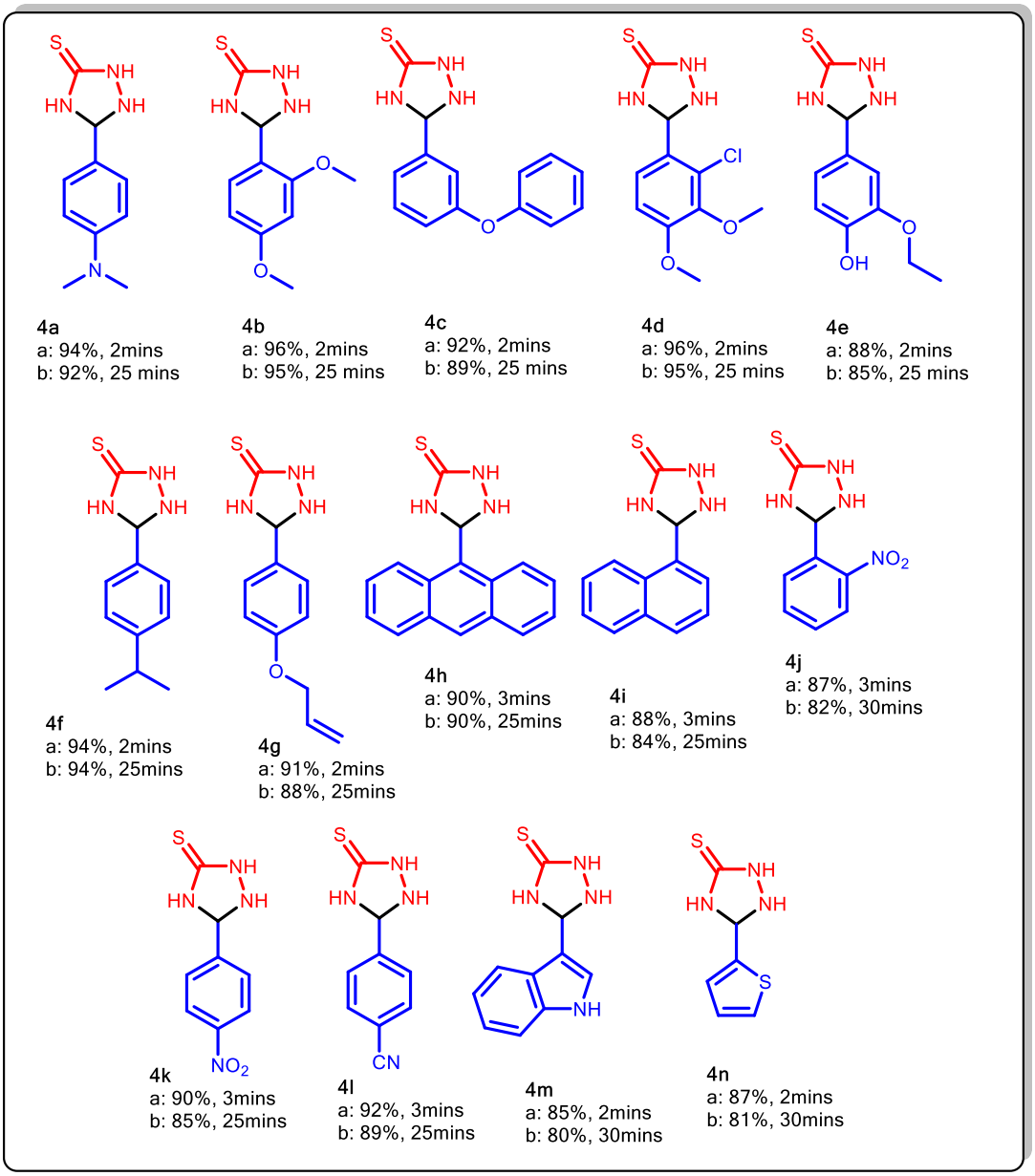
[a]Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), Aromatic aldehyde 2a (1 mmol), Thiosemicarbazide 3 (1 mmol), Planetary ball mill 300 rpm, 10 stainless steel balls (2 mm diameter). [b]Best reaction condition



Scheme 4.1.1: Optimised scheme of the reaction

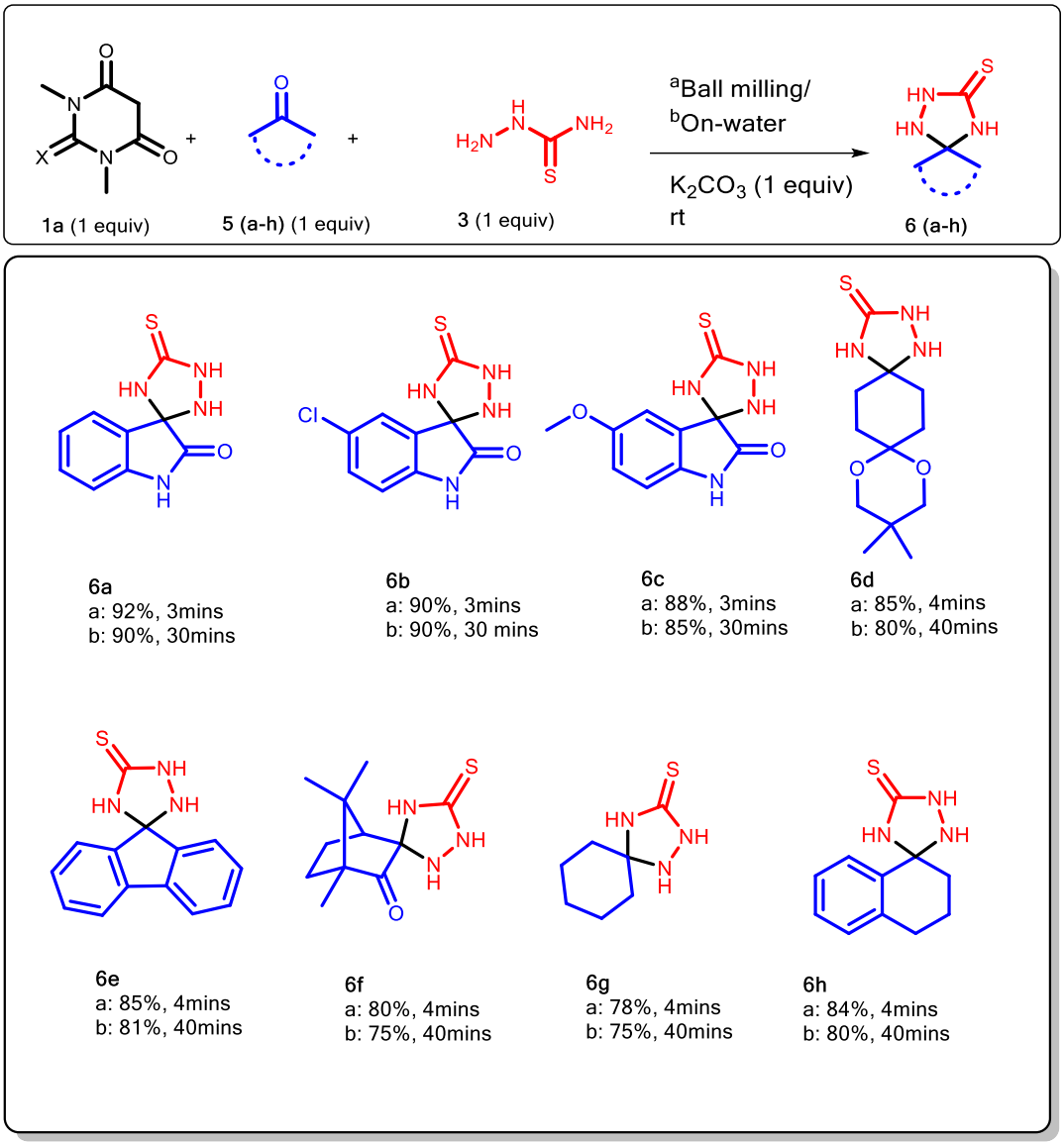
Scheme 4.1.2 Substrate scope with aromatic aldehydes





[a]Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), cyclic ketone 5 a-h (1 mmol), Thiosemicarbazide 3 (1 mmol), 1 mL H_2O for liquid assisted grinding (LAG), Planetary ball mill, 10 stainless steel balls (2 mm diameter) [b]Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), cyclic ketone 5 a-h (1mmol), Thiosemicarbazide 3 (1 mmol), 5 mL H_2O. Stir at room temperature (rt, 25 ˚C)

Scheme 4.1.3: Substrate scope with cyclic ketones

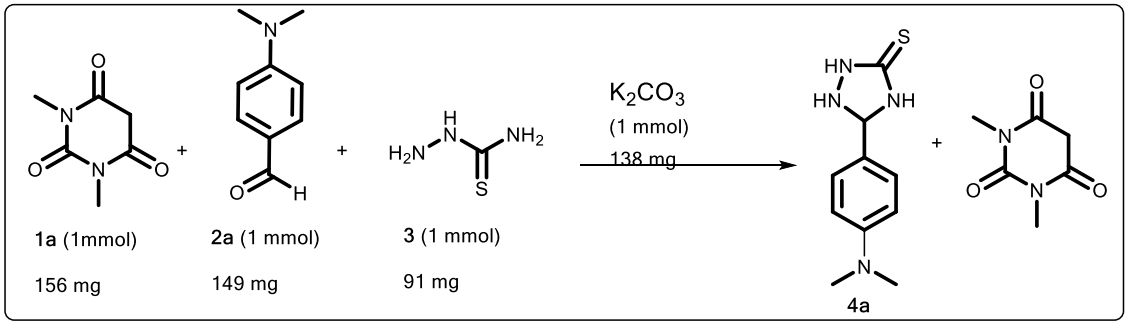


[a]Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), cyclic ketone 5 a-h (1 mmol), Thiosemicarbazide 3 (1 mmol), 1 mL H_2O for liquid assisted grinding (LAG), Planetary ball mill, 10 stainless steel balls (2 mm diameter) [b]Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), cyclic ketone 5 a-h (1 mmol), Thiosemicarbazide 3 (1 mmol), 5 mL H_2O. Stir at room temperature (rt, 25 ˚C)

The consideration of this reaction as a Liquid assisted grinding protocol can be done on the basis of the empirical definition given by Friščić et al. in 2009, [48] wherein an empirical parameter η, that represented the ratio of the volume of liquid (in μL) to the total amount of reactants/sample (in mg), was calculated. An

η value of 0-2 μL/mg was considered to be a LAG reaction [49-52]. In our case, if we consider the model reaction (**Table 4.1.2**, **entry 20**), we have four reactants, each of 1 mmol amount (making a total of 4 mmol sample) and the amount of water taken as the liquid assistant is 1000μL (1mL). The calculated value of η for the model reaction is 1.8726 μL/mg and it is within the range of being considered as a LAG. Similarly, the η values for all other reactions considered under substrate study falls within this range. Although, another report by Friščić and Do, in 2017 [43] stated that for a reaction to be considered as LAG, the value of η must lie in the range of $0-1$ μL/mg, yet we can state that our protocol can be considered as a borderline LAG, if not purely a LAG. However, the amount of sample and thereby, the volume of solid components in comparison to the liquid, should also be taken into consideration.

Calculation of η for the model reaction



Net sample weight: (156+149+91+138) mg = 534 mg

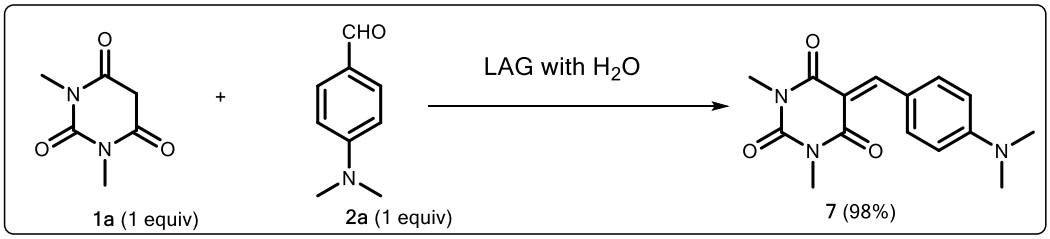
Amount of solvent taken = 1000 μL

$$\eta = \frac{\text{amount of solvent}}{\text{Total amount of sample}} = \frac{1000\ \mu l}{534\ mg} = 1.8726\ \mu L/mg$$

It was also observed that the solvent played a prominent role in the reaction, and we can hypothesise that water, with a high static permittivity (eT= 78.4) could

have activated the substrates [44]. The hydrogen bonding between the carbonyl oxygen atoms of the aromatic aldehyde/cyclic ketones and the hydrogen of water molecule increases the electrophilicity of the carbonyl carbon.

Also, there can be efficient hydrogen bonding between the water molecule and the acidic hydrogen of the active methylene group. This would lead to enhanced nucleophilicity. The simultaneous activation of the substrates in water would lead to Knoevenagel reaction, even in the absence of a base (**Scheme 4.1.4**).

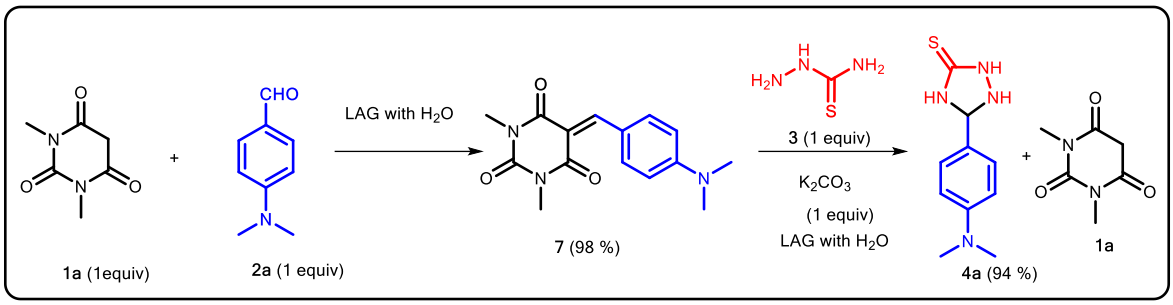


Scheme 4.1.4: Formation of the benzylidene barbiturate (Knoevenagel reaction) in absence of base

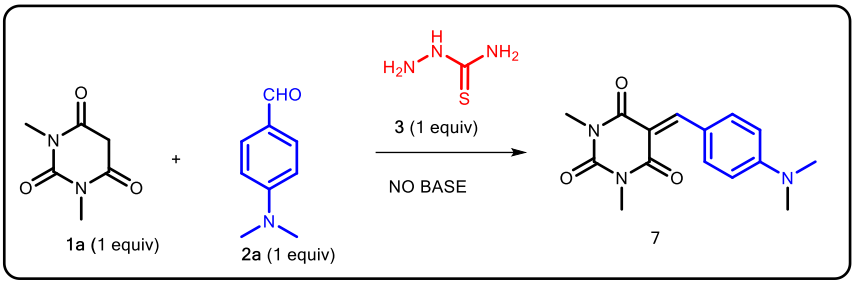
The benzylidene product of this reaction is highly susceptible to a nucleophilic attack from thiosemicarbazide, which results in a Michael addition reaction. This Michael addition product undergoes cyclisation to form a seven membered intermediate, the pyrimido[4,5-*e*][1,2,4]triazepine. The presence of strong electron withdrawing groups in Carbon-6 of the pyrimidine ring and the additional ring strain due to their repulsive behavior results in the adduct being unstable. Hence, it undergoes a rearrangement and form the 5-membered heterocycles, 5-aryl-1,2,4-triazolidine-3-thione (**Scheme 4.1.5**).

The reaction does not proceed beyond the Knoevenagel reaction, in the absence of a base (**Scheme 4.1.6**).

The reported protocols for the synthesis of this class of compounds shows the formation of a thiosemicarbazone intermediate *via* elimination of the active

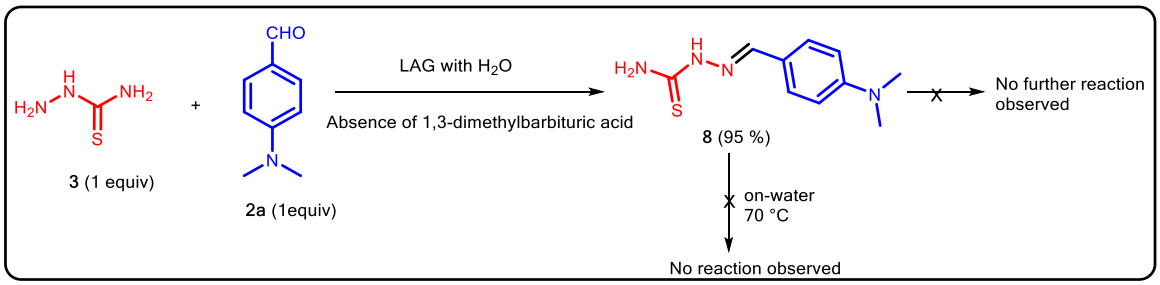


Scheme 4.1.5: Stepwise reaction



Scheme 4.1.6: Reaction in absence of base

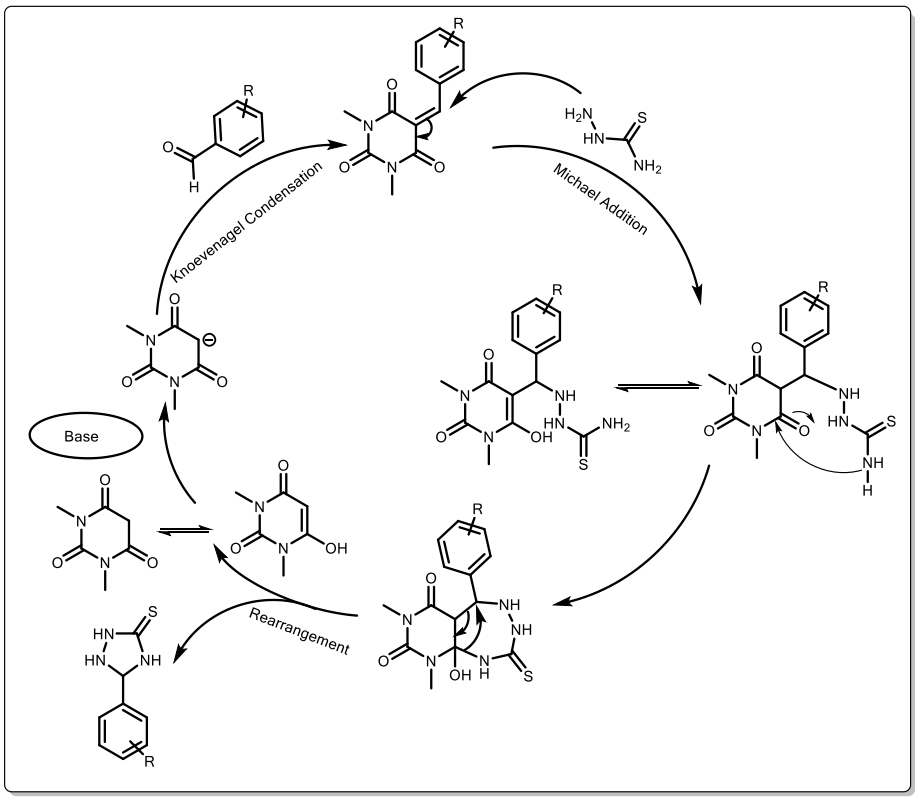
methylene compound, and then undergoes cyclisation to give the desired product. However, in our case, when we subjected the thiosemicarbazone adduct of the aromatic aldehyde 3a, to LAG in the presence of base, but absence of 1,3-Dimethyl barbituric acid, we did not observe the formation of the desired product (**Scheme 4.1.7**).



Scheme 4.1.7: Reaction in absence of 1,3-Dimethylbarbituric acid

As a matter of fact, the “on water” methodology also failed to give us the desired product in the absence of 1,3-Dimethylbarbituric acid, despite elevated temperature (70 ºC). This shows that the active methylene group plays a

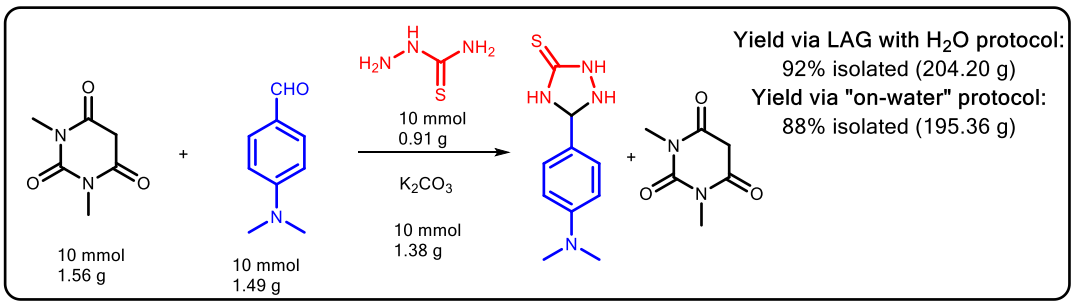
significant role until the end of the reaction. Hence we propose a new mechanism for the synthesis of 5-aryl/spiro-[1,2,4]-triazolidine-3-thiones (**Scheme 4.1.8**).



Scheme 4.1.8: Plausible Mechanism of the reaction at room temperature

However, the protocol could not be applied to aromatic ketones. This can be attributed to the reluctance of aromatic ketones towards Knoevenagel reaction at room temperature and “on-water”.

We have successfully performed a gram scale synthesis (**Scheme 4.1.9**) *via* both the methodologies and have isolated the desired product with near to 90% yield.



Scheme 4.1.9: Gram Scale synthesis **4a**

It is worth noting that our protocol requires only simple filtration for the isolation of highly pure compounds, the formation of which were confirmed by ^{1}H and ^{13}C NMR spectroscopic analyses and mass spectrometry.

4.1.3. EXPERIMENTAL SECTION

General Information

All reagents were purchased from commercial sources and used as received, without any purification. Commercially available solvents were distilled before the reactions and water used for reaction as well as during work up was double distilled prior to use. ^{1}H and ^{13}C NMR spectra of the products were recorded with a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using deuterated dimethyl sulphoxide (DMSO-D_6, δ= 2.46ppm, quintet, for ^{1}H and 40.0 ppm, septet, for ^{13}C) as the solvent as well as the internal standard. However, due to solubility issue in DMSO-D_6, the ^{1}H and ^{13}C NMR spectra of product 6e was recorded, in the same instrument, using deuterated chloroform ($CDCl_3$) as the solvent and Tetramethylsilane (TMS) as the internal standard. Additional signal at 3.30 ppm, in ^{1}H NMR spectra, is seen because of the presence of HOD in DMSO-D_6. Similarly, due to the presence of HOD in $CDCl_3$ an additional signal at 1.59 ppm is observed in the ^{1}H spectrum. Chemical shift values are expressed in ppm. Coupling constants (*J*) are expressed in Hertz (Hz). The signals are reported as “s”= singlet, “d”= doublet, “t”= triplet, “dd”= doublet of doublet and “m”= multiplet. HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer. Reactions were monitored by thin-layer chromatography using

aluminium sheets with silica gel $60F_{254}$ (Merck). UV light and Iodine vapors were used as visualizer.

General Procedure for the synthesis of 5-aryl-[1,2,4]-triazolidine-3-thiones (4a-4n), 5-spiro-[1,2,4]-triazolidine-3-thiones (6a-6h)

METHOD A (Liquid assisted mechanochemical method): A mixture of 1 mmol of the aromatic aldehyde or cyclic ketone, 0.156 g of 1,3-Dimethylbarbituric acid (1 mmol), 0.091 g of thiosemicarbazide K_2CO_3 (0.138 g, 1 mmol) along with 1 mL of distilled water was ball-milled in a 5 mL stainless steel closed container with 10 stainless steel balls (diameter= 2 mm) at 300 rpm, for the requisite period of time, in a planetary ball mill. The reaction was monitored with the help of thin layer chromatography and upon completion the reaction mixture was treated with 5 mL distilled water. The precipitate was collected *via* normal filtration and the filtrate was collected for further recovery of barbituric acid and/usage as homogeneous recyclable media. The resulting product, in the form of precipitate, was further washed with 25% ethanolic solution and dried under vacuum. It was then characterized without further purification.

METHOD B ("On-water" method): A mixture of 1 mmol of the aromatic aldehyde or cyclic ketone and 0.156 mg of 1,3-Dimethylbarbituric acid (1 mmol) in 5 mL distilled water was stirred at room temperature until thick curdy precipitates of benzylidene/alkylidene barbiturates formed. To this, 0.091 mg of thiosemicarbazide and K_2CO_3 (0.138 mg=1 mmol) was added and stirring was continued for the requisite period of time. The progress of the reaction is evident from the colorimetric change of the reaction mixture (precipitates) **Figure 4.1.2**. However, the completion of the same was ascertained with the help of thin layer

chromatography. The product, in the form of precipitate, was separated *via* simple filtration and the filtrate, which primarily comprised of the base and 1,3-Dimethylbarbituric acid, was collected, for further usage as a homogenous recyclable media or for isolation of 1,3-Dimethylbarbituric acid. Further purification process of the product included washing with 10 mL of 25% ethanolic solution and drying under vacuum.

Procedure for regeneration of 1,3-Dimethylbarbituric acid from the filtrate, post workup.

The filtrate was neutralized *via* drop wise addition of 1N HCl solution. Any precipitate formed now was discarded and the clear solution was kept at a low temperature (5-10 ^{o}C) for about 3 hrs. Crystals of 1,3-Dimethylbarbituric acid separated out and they were collected after drying. This could be used again for the reaction.

Procedure for reusing the filtrate as a homogeneous recyclable media

To the collected filtrate from Method A and B, 1mmol of aromatic aldehyde/cyclic ketone and thiosemicarbazide was added and stirred for the appropriate amount of time that corresponds to the aromatic aldehyde/cyclic ketone taken. The next steps are same as those done for Method B. It must be kept in mind that the filtrate must be reused for one type of aldehydes/cyclic ketones only. Using different substrates may result in the presence of impurity traces in the product. Since we have tried to avoid chromatographic means of separation, therefore this precaution was a necessary.

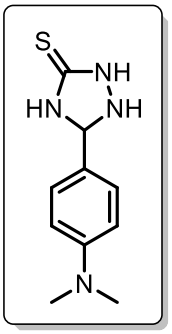
4.1.4. CONCLUSION

The liquid assisted grinding methodology for the one-pot synthesis of 5-aryl/spiro-1,2,4-triazolidie-3-thiones is a fast and environmentally benign methodology, where there is near to zero waste of chemicals, and which also holds the prospect of expanding the domains of homogeneous recyclable reaction media. In addition to this, we have also developed the protocol for the “on-water” synthesis of the mentioned class of compounds, which is equally potent, despite taking comparatively more time. Moreover, there has been a revisit to the mechanism of the reaction, which we have tried to explain in accordance with experimental observations. The mechanism proposed is based on our observation alone and the experiments have been conducted according to our reaction protocol alone. We have also successfully demonstrated a protocol for gram scale synthesis.

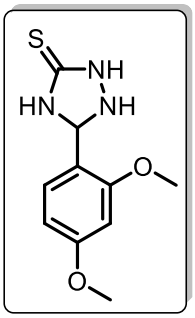
Figure 4.1.1: Visual observations to show the progress of the reaction “on-water”

4.1.5. CHARACTERISATION DATA OF THE PRODUCTS

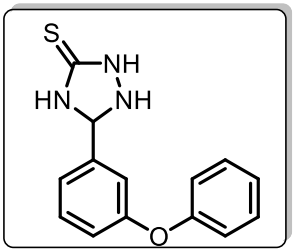
The following are the details of the compounds synthesised *via* the above mentioned methods. [a] denotes the amount of product obtained *via* method A and [b] denotes the amount of product obtained *via* method B.



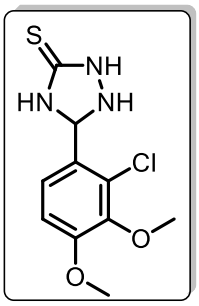
5-(4-(dimethylamino)phenyl)-1,2,4-triazolidine-3-thione (4a) Yellow solid (Method A: 208.52 mg, Method B: 204.28 mg**)** ^{1}H NMR (400 MHz, DMSO-D_6) δ 11.13 (s, 1H), 7.95 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.54 (d, *J*= 8.9 Hz, 2H), 6.66 (d, *J*= 8.8 Hz, 2H), 2.92 (s, 6H**)** **^{13}C NMR** (100 MHz, DMSO-D_6) δ 177.5, 151.9, 143.8, 129.1, 122.1, 112.2, 40.3 **HRMS (+ESI)** calcd for $C_{10}H_{14}N_4S$ $(M+H)^+$: 223.0963 found: 223.0975



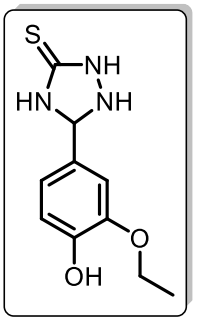
5-(2,4-*D*imethoxyphenyl)-1,2,4-triazolidine-3-thione (4b) Yellow solid (Method A: 229.51 mg, Method B: 227.10 mg**)** **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.23 (s, 1H), 8.27 (s, 1H), 8.01–7.93 (m, 2H), 7.78 (s, 1H), 6.55 (s, 1H), 6.51 (d, *J*= 8.2 Hz, 1H), 3.78 (d, *J*= 6.9 Hz, 6H) **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.0, 162.8, 159.7, 138.6, 127.8, 115.5, 106.9, 98.5, 56.3, 56.0 **HRMS (+ESI)** calcd for $C_{10}H_{13}N_3O_2S$ $(M+H)^+$: 239.0744 found: 239.0768



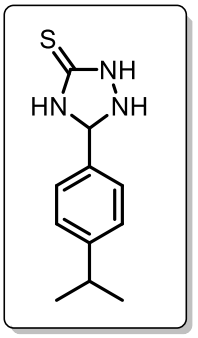
5-(3-phenoxyphenyl)-1,2,4-triazolidine-3-thione (4c) White solid (Method A: 249.51 mg, Method B: 241.25 mg**)** **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.41 (s, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.99 (s, 1H), 7.57 (s, 1H), 7.49 (d, *J*= 7.8 Hz, 1H), 7.42–7.29 (m, 3H), 7.09 (t, *J*= 7.4 Hz, 1H), 7.00–6.92 (m, 3H) **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.6, 157.3, 142.0, 136.9, 130.8, 130.6, 123.9, 123.7, 120.7, 118.8, 117.8 **HRMS (+ESI)** calcd for $C_{14}H_{13}N_3OS$ $(M+H)^+$: 271.0786 found: 271.0798



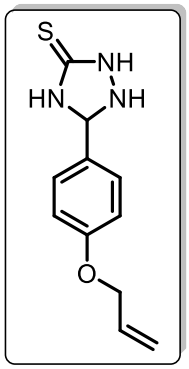
5-(2-chloro-3,4-*D*imethoxyphenyl)-1,2,4-triazolidine-3-thione (4d) Pale yellow solid (Method A: 262.10 mg, Method B: 259.40 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.45 (s, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 8.01-7.93 (m, 2H), 7.04 (d, *J*= 9.0 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 155.1, 145.1, 139.1, 128.2, 125.0, 123.3, 112.3, 60.7, 56.8 **HRMS (+ESI)** calcd for $C_{10}H_{12}ClN_3O_2S$ $(M+H)^+$: 273.0337 found: 273.0392



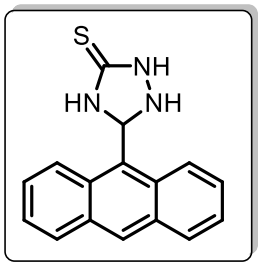
5-(3-ethoxy-4-hydroxyphenyl)-1,2,4-triazolidine-3-thione (4e) White solid (Method A: 210.37 mg, Method B: 203.20 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.19 (s, 1H), 9.31 (s, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.88 (s, 1H), 7.41 (s, 1H), 6.98 (d, *J*= 10.1 Hz, 1H), 6.74 (d, *J*= 8.1 Hz, 1H), 4.04 (q, *J*= 7.0 Hz, 2H), 1.30 (t, *J*= 7.0 Hz, 3H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 177.9, 149.6, 147.8, 143.5, 126.1, 122.8, 115.8, 111.0, 64.4, 15.5 **HRMS (+ESI)** calcd for $C_{10}H_{13}N_3O_2S$ $(M+H)^+$: 239.0781 found: 239.0788



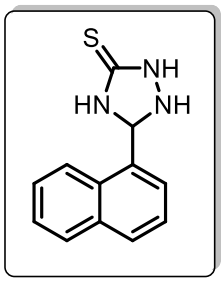
5-(4-isopropylphenyl)-1,2,4-triazolidine-3-thione (4f) White solid (Method A: 207.83 mg, Method B: 207.80 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.33 (s, 1H), 8.11 (s, 1H), 7.99 (s, 1H), 7.88 (s, 1H), 7.66 (d, *J*= 8.1 Hz, 2H), 7.23 (d, *J*= 7.8 Hz, 2H), 2.94–2.77 (m, 1H), 1.16 (d, *J*= 6.9 Hz, 6H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 151.0, 142.9, 132.4, 127.9, 127.1, 33.9, 24.2 **HRMS (+ESI)** calcd for $C_{11}H_{15}N_3S$ $(M+H)^+$: 221.1002 found: 221.1019



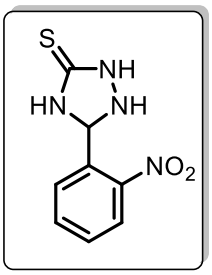
5-(4-(allyloxy)phenyl)-1,2,4-triazolidine-3-thione (4g) Pinkish white solid (Method A: 213.90 mg, Method B: 206.87 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.28 (s, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.69 (d, *J*= 8.7 Hz, 2H), 6.93 (d, *J*= 8.7 Hz, 2H), 6.07-5.84 (m, 1H), 5.35 (d, *J*= 17.28 Hz, 1H), 5.22 (d, *J*= 11.84 Hz, 1H) 4.56 (d, *J*= 5.2 Hz, 2H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.1, 160.0, 142.7, 134.0, 129.4, 127.4, 118.4, 115.4, 68.9 **HRMS (+ESI)** calcd for $C_{11}H_{13}N_3OS$ $(M+H)^+$: 235.0921found: 235.0955



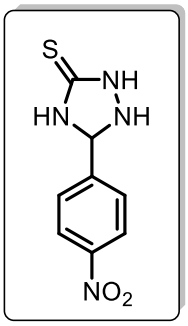
5-(anthracen-9-yl)-1,2,4-triazolidine-3-thione (4h) Dark yellow solid (Method A: 251.20 mg, Method B: 251.18 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.60 (s, 1H), 9.29 (s, 1H), 8.67 (s, 1H), 8.53 (d, *J*= 8.9 Hz, 2H), 8.27 (s, 1H), 8.11 (d, *J*= 8.2 Hz, 2H), 7.73–7.50 (m, 5H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.6, 142.7, 131.4, 130.2, 130.0, 129.5, 127.8, 126.1, 125.5, 125.3 **HRMS (+ESI)** calcd for $C_{16}H_{13}N_3S$ $(M+H)^+$: 279.3721 found: 279.3744



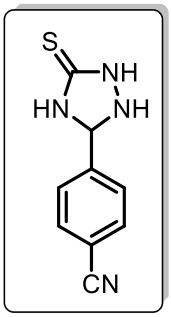
5-(naphthalen-1-yl)-1,2,4-triazolidine-3-thione (4i) Off white solid (Method A: 01.60 mg, Method B: 192.41 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ: 11.42 (s, 1H), 8.88 (s, 1H), 8.32 (d, *J*= 8.4 Hz, 1H), 8.25 (s, 1H), 8.18 (d, *J*= 8.2 Hz, 1H), 7.96 (d, *J*= 9.7 Hz, 3H), 7.63-7.51 (m, 3H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 141.5, 133.9, 131.0, 130.7, 129.8, 129.4, 127.8, 126.7, 126.3, 126.1, 123.4 **HRMS (+ESI)** calcd for $C_{12}H_{11}N_3S$ $(M+H)^+$: 229.0701 found: 229.0715



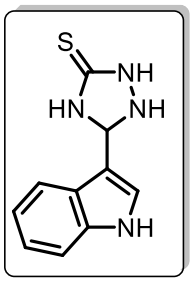
5-(2-nitrophenyl)-1,2,4-triazolidine-3-thione (4j) Light yellow solid (Method A: 194.90 mg, Method B: 183.71 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.59 (s, 1H), 8.51 (d, *J*= 4.9 Hz, 1H), 8.30 (s, 1H), 8.23 (d, *J*= 7.1 Hz, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.77 (t, *J*= 7.8 Hz, 1H), 7.32 (t, *J*= 7.8 Hz, 1H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.8, 153.9, 153.8, 150.0, 143.0, 137.1, 124.6, 120.7 **HRMS (+ESI)** calcd for $C_8H_8N_4O_2S$ $(M+H)^+$: 224.0512 found: 224.0526



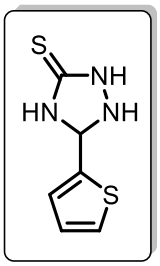
5-(4-nitrophenyl)-1,2,4-triazolidine-3-thione (4k) Light yellow solid (Method A: 201.62 mg, Method B: 190.43 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.29–8.14 (m, 3H), 8.13–8.01 (m, 3H) **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.0, 148.1, 141.2, 140.1, 128.7, 124.3 **HRMS (+ESI)** calcd for $C_8H_8N_4O_2S$ $(M+H)^+$: 224.0512 found: 224.0555



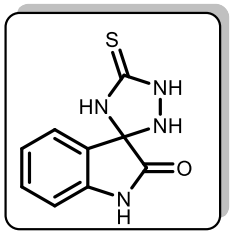
4-(5-thioxo-1,2,4-triazolidin-3-yl)benzonitrile (4l) Light yellow solid (Method A: 201.62 mg, Method B: 190.43 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.29–8.14 (m, 3H), 8.13–8.01 (m, 3H) **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.0, 148.1, 141.2, 140.1, 128.7, 124.3 **HRMS (+ESI)** calcd for $C_8H_8N_4O_2S$ $(M+H)^+$: 204.0512 found: 204.0541



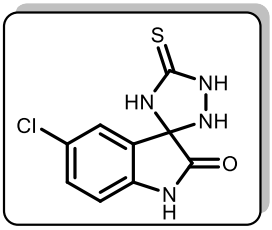
5-(1*H*-indol-3-yl)-1,2,4-triazolidine-3-thione (4m) Pale yellow solid (Method A: 185.35 mg, Method B: 174.50 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.55 (s, 1H), 11.12 (s, 1H), 8.26 (s, 1H), 8.17 (d, *J*= 7.8 Hz, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.38 (d, *J*= 8.2 Hz, 1H), 7.36 (s, 1H), 7.15 (t, *J*= 7.11 Hz, 1H), 7.08 (t, *J*= 7.98 Hz, 1H. **^{13}C NMR** (100 MHz, DMSO-D_6) δ 177.0, 141.3, 137.6, 131.5, 124.5, 123.2, 122.7, 121.1, 112.3, 111.6 **HRMS (+ESI)** calcd for $C_{10}H_{10}N_4S$ $(M+H)^+$: 218.0671 found: 218.0693



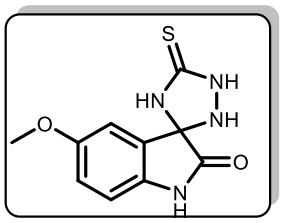
5-(thiophen-2-yl)-1,2,4-triazolidine-3-thione (4n) Off white solid (Method A: 161.00 mg, Method B: 149.90 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.40 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 7.61 (d, *J*= 5.0 Hz, 1H), 7.51 (s, 1H), 7.41 (d, *J*= 4.2 Hz, 1H), 7.07 (dd, *J*= 5.0, 3.6 Hz, 1H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.1, 139.1, 138.1, 131.1, 129.4, 128.5 **HRMS (+ESI)** calcd for $C_6H_7N_3S_2$ $(M+H)^+$: 185.0119 found: 185.0131



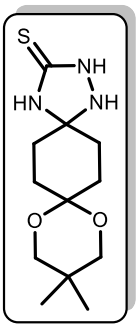
5$^{/}$-thioxospiro[indoline-3,3$^{/}$-[1,2,4]triazolidin]-2-one (6a) Dark yellow solid (Method A: 202.44 mg, Method B: 198.04 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 12.43 (s, 1H), 11.16 (s, 1H), 9.00 (s, 1H), 8.64 (s, 1H), 7.61 (d, *J*= 7.4 Hz, 1H), 7.31 (t, *J*= 7.7 Hz, 1H), 7.04 (t, *J*= 7.6 Hz, 1H), 6.88 (d, *J*= 7.8 Hz, 1H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.2, 163.2, 142.9, 132.6, 131.8, 122.9, 121.5, 120.5, 111.6 **HRMS (+ESI)** calcd for $C_9H_8N_4OS$ $(M+H)^+$: 220.0439 found: 220.0451



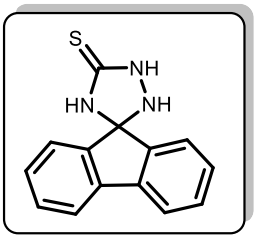
5-chloro-5^{l}-thioxospiro[indoline-3,3^{l}-[1,2,4]triazolidin]-2-one (6b) Dark yellow solid (Method A: 228.60 mg, Method B: 228.58 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 12.25 (s, 1H), 11.27 (s, 1H), 9.10 (s, 1H), 8.79 (s, 1H), 7.71 (d, *J*= 2.2 Hz, 1H), 7.34 (dd, *J*= 8.3, 2.2 Hz, 1H), 6.89 (d, *J*= 8.5 Hz, 1H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.2, 162.8, 141.5, 131.4, 131.0, 127.1, 122.4, 121.2, 113.0 **HRMS (+ESI)** calcd for $C_9H_7ClN_4OS$ $(M+H)^+$: 254.0082 found: 254.0122



5-methoxy-5^{l}-thioxospiro[indoline-3,3^{l}-[1,2,4]triazolidin]-2-one (6c) Orange solid (Method A: 220.05 mg, Method B: 212.52 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 12.38 (s, 1H), 10.97 (s, 1H), 9.04 (s, 1H), 8.71 (s, 1H), 7.28 (d, *J*= 2.6 Hz, 1H), 6.88 (dd, *J*= 8.5, 2.6 Hz, 1H), 6.79 (d, *J*= 8.5 Hz, 1H), 3.71 (s, 3H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.2, 163.3, 155.8, 136.5, 132.8, 121.4, 117.9, 112.3, 106.6, 56.0 **HRMS (+ESI)** calcd for $C_{10}H_{10}N_4O_2S$ $(M+H)^+$: 250.0574 found: 250.0599

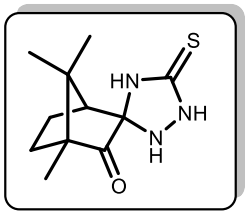


11,11-Dimethyl-9,13-*D*ioxa-1,2,4triazadispiro[4.2.5^{8}.2^{5}]pentadecane-3-thione (6d) White solid (Method A: 230.48 mg, Method B: 216.90 mg**) ^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.17 (s, 1H), 7.99 (s, 1H), 7.53 (s, 1H), 3.43 (s, 4H), 2.36 (t, *J*= 6.5 Hz, 2H), 2.23 (t, *J*= 6.36 Hz, 2H), 1.86–1.78 (m, 4H), 0.87 (s, 6H**) ^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.1, 155.6, 96.9, 69.7, 31.0, 30.3, 23.4, 22.8, 22.7 **HRMS (+ESI)** calcd for $C_{12}H_{21}N_3O_2S$ $(M+H)^+$: 271.1377 found: 271.1385

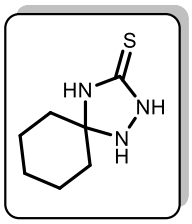


Spiro[fluorene-9,3^{l}-[1,2,4]triazolidine]-5^{l}-thione (6e) Pale yellow solid (Method A: 215.12 mg, Method B: 205.00 mg**) ^{1}H NMR** (400 MHz, CHLOROFORM-*D*) δ 9.72 (s, 1H), 7.87 (d, *J*= 7.7 Hz, 1H), 7.71 (t, *J*= 8.1 Hz, 2H), 7.60 (d, *J*= 8.4 Hz, 1H), 7.57 (s, 1H), 7.48 (t, *J*= 8.0 Hz, 1H), 7.38 (td, *J*= 14.2, 7.0 Hz, 2H), 7.29 (t, *J*= 7.5 Hz, 1H), 6.54 (s, 1H), 3.72, 2.15, 1.23= residual ethanol impurity. **^{13}C NMR** (100 MHz, CHLOROFORM-*D*) δ 179.2, 145.3, 142.7, 140.0, 136.4, 131.9, 130.7, 129.7, 128.5, 128.4, 125.9, 121.8, 121.2, 120.1

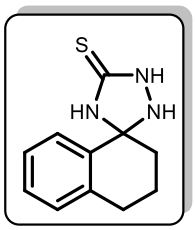
HRMS (+ESI) calcd for $C_{14}H_{11}N_3S$ $(M+H)^+$: 253.0701 found:253.0719



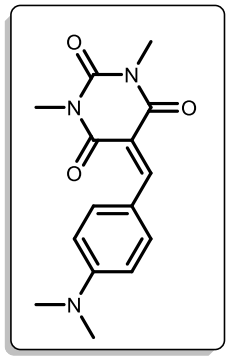
(1*S*,2*S*,4*S*)-4,7,7-trimethyl-5′-thioxospiro[bicyclo[2.2.1]heptane -2,3′-[1,2,4]triazolidin]-3-one (6f) White solid (Method A: 191.30 mg, Method B: 179.33 mg**) ^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 10.84 (s, 1H), 8.45 (s, 1H), 7.66 (s, 1H), 3.44 (d, *J*= 4.4 Hz, 1H), 2.01–1.88 (m, 1H), 1.71 (dd, *J*= 19.0, 10.5 Hz, 1H), 1.40–1.26 (m, 2H), 0.91 (s,3H), 0.88 (s, 3H), 0.72 (s, 3H**) ^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 205.1, 180.9, 151.9, 58.4, 48.0, 45.1, 30.6, 24.3, 20.9, 18.0, 9.5 **HRMS (+ESI)** calcd for $C_{11}H_{17}N_3OS$ $(M+H)^+$: 239.1113 found: 239.1141



1,2,4-triazaspiro[4.5]decane-3-thione (6g). Pale yellow solid (Method A: 133.48 mg, Method B: 128.29 mg**) ^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 10.11 (s, 1H), 7.93 (s, 1H), 7.47 (s, 1H), 2.33-2.36 (m, 2H), 2.25–2.11 (m, 2H), 1.64–1.42 (m, 6H) **^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 179.1, 157.4, 35.4, 27.7, 27.4, 26.2, 25.6 **HRMS (+ESI)** calcd for $C_7H_{13}N_3S$ $(M+H)^+$: 171.0845 found: 171.0863



3,4-Dihydro-2H-spiro[naphthalene-1,3′-[1,2,4]triazolidine]-5′-thione (6h) Pinkish white solid (Method A: 184.03 mg, Method B: 175.30 mg**) ^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 10.10 (s, 1H), 8.25 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.23 (t, *J*= 6.7 Hz, 1H), 7.18–7.10 (m, 2H), 2.70–2.63 (m, 4H), 1.82–1.70 (m, 2H**) ^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 179.1, 148.2, 140.6, 132.5, 129.6, 129.0, 126.7, 125.8, 29.4, 26.3, 21.9 **HRMS (+ESI)** calcd for $C_{11}H_{13}N_3S$ $(M+H)^+$: 219.0861 found: 219.0893



5-(4-(dimethylamino)benzylidene)-1,3-Dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (7) [74] Reddish orange solid (281.2 mg) **^{1}H NMR** (400 MHz, CHLOROFORM-*D*) δ 8.41 (d,*J*= 7.8 Hz, 2H), 8.38 (s,1H), 6.69 (d,*J*= 7.3 Hz, 2H), 3.39 (s,6H), 3.13 (s,6H) **^{13}C NMR** (100 MHz, CHLOROFORM-*D*) δ 164.1, 158.9, 154.5, 151.9, 139.6, 121.5, 111.1, 109.7, 40.2, 29.0, 28.3 **HRMS (+ESI)** calcd for $C_{15}H_{17}O_3$ $(M+H)^+$: 287.1270 found: 287.1193

4.1.6 REPRESENTATIVE NMR SPECTRA

Figure 4.1.2 ^{1}H NMR Spectrum of 4a in DMSO-D_6

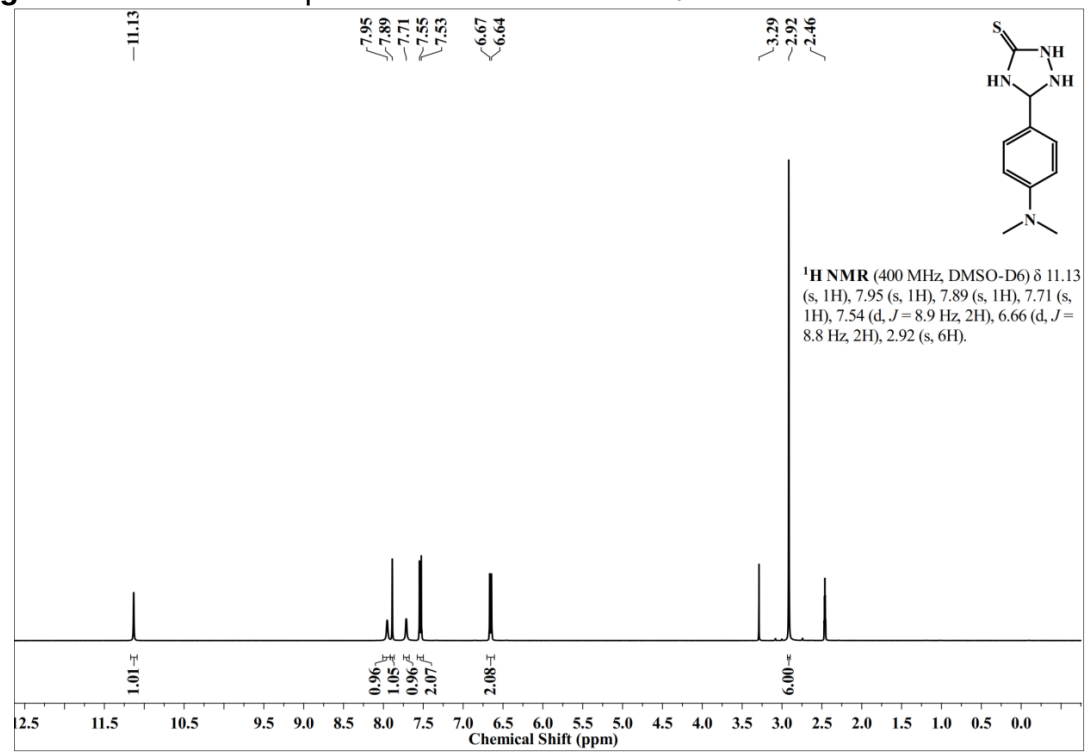


Figure 4.1.3 ^{13}C NMR Spectrum of 4a in DMSO-D_6

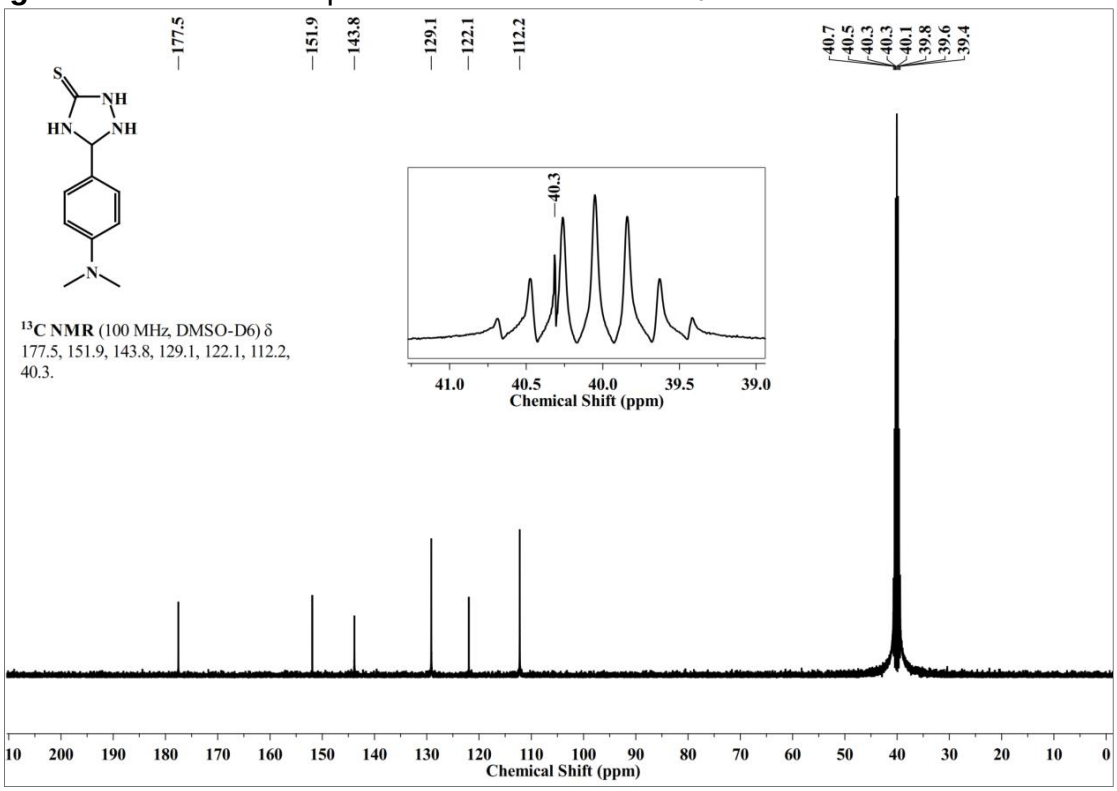


Figure 4.1.4 ^{1}H NMR Spectrum of 4j in DMSO-D_6

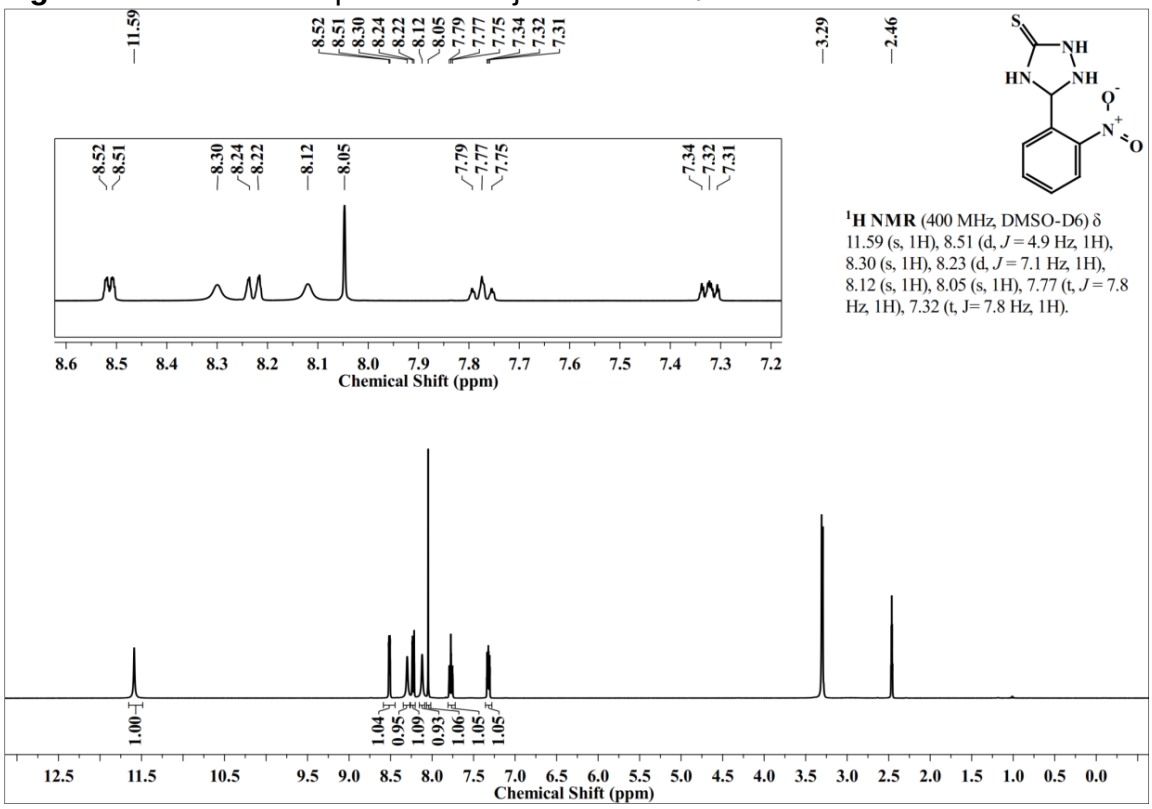


Figure 4.1.5 ^{13}C NMR Spectrum of 4j in DMSO-D_6

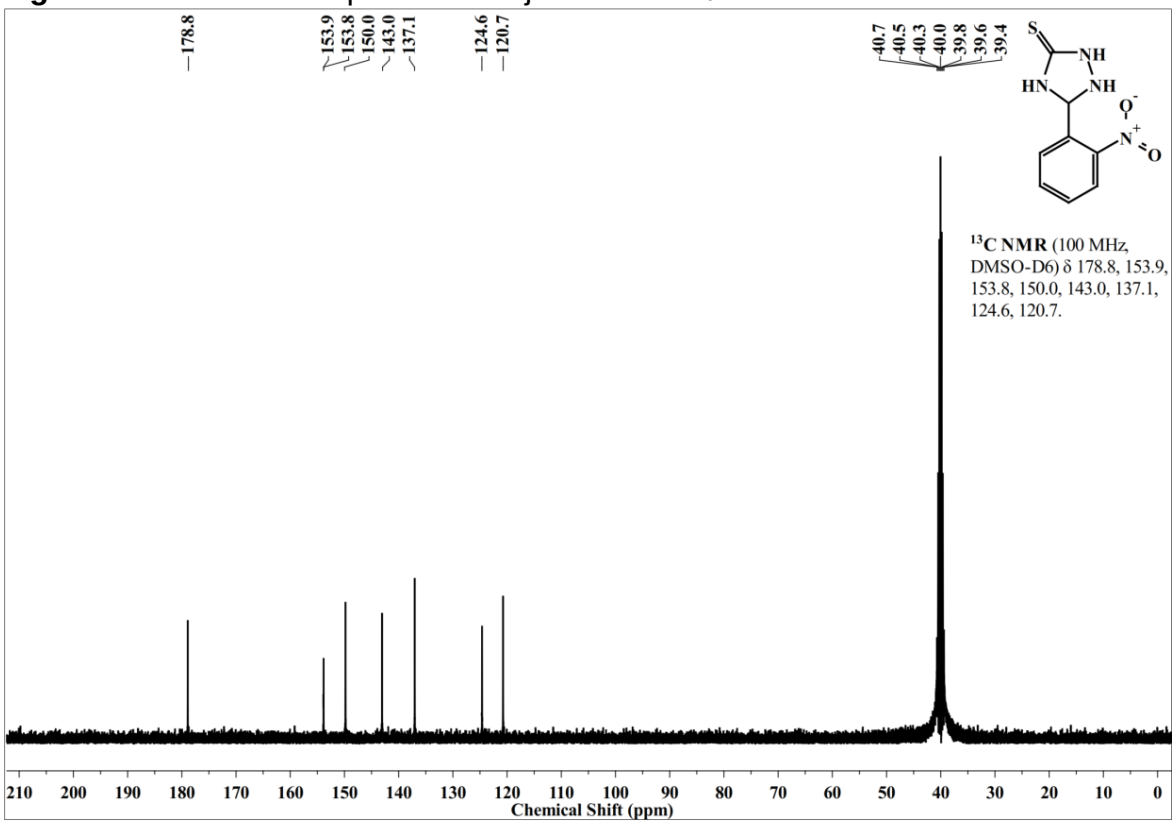


Figure 4.1.6 ^{1}H NMR Spectrum of 4m in DMSO-D_6

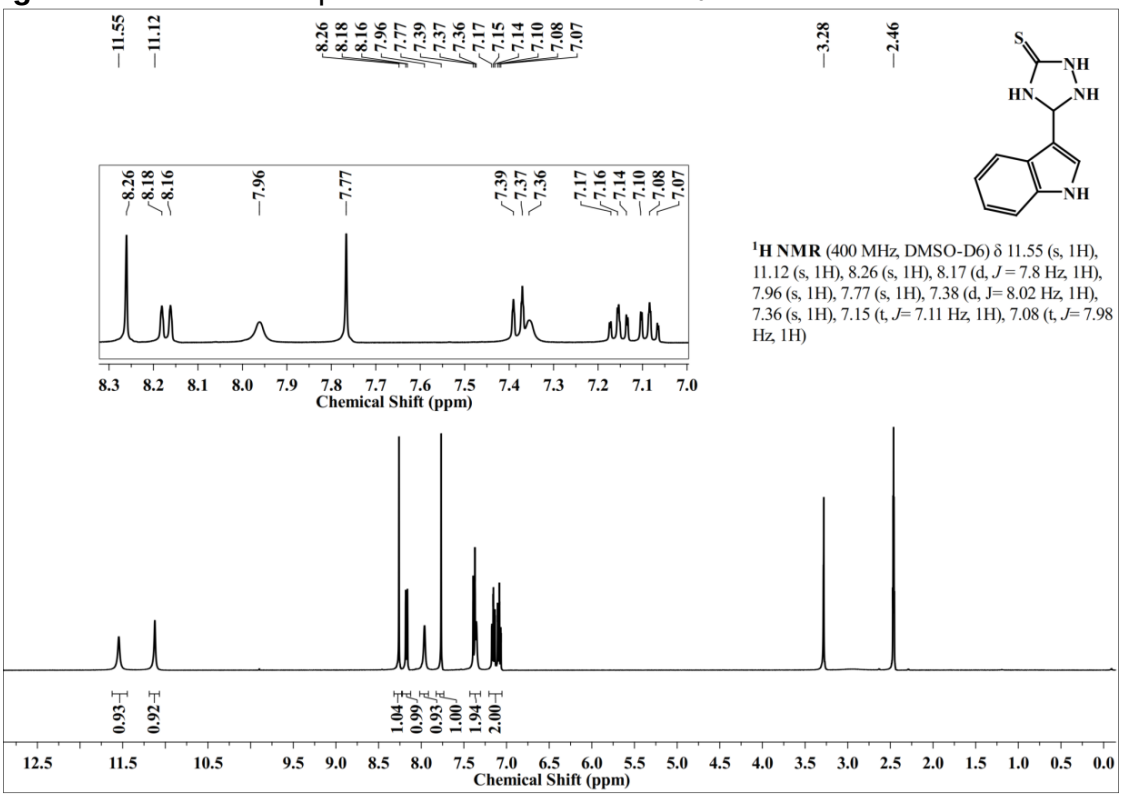


Figure 4.1.7 ^{13}C NMR Spectrum of 4m in DMSO-D_6

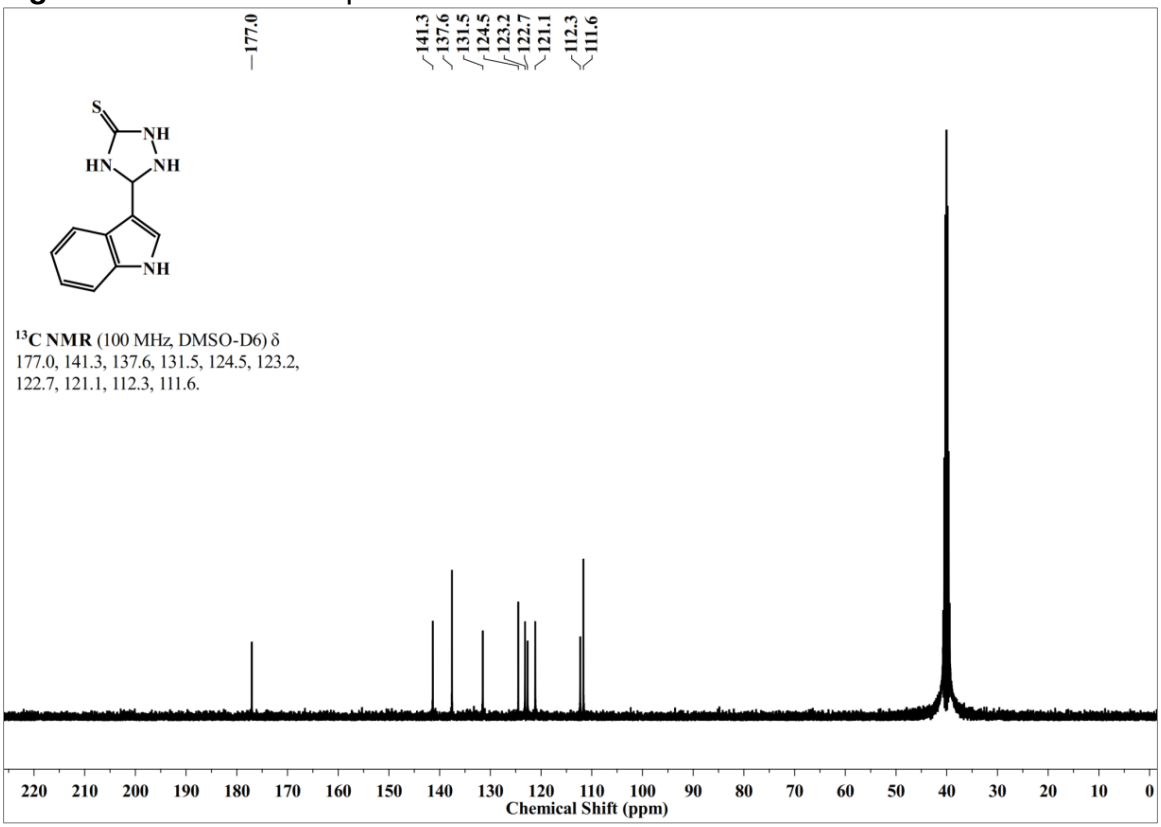


Figure 4.1.8 ^{1}H NMR Spectrum of 6a in DMSO-D_6

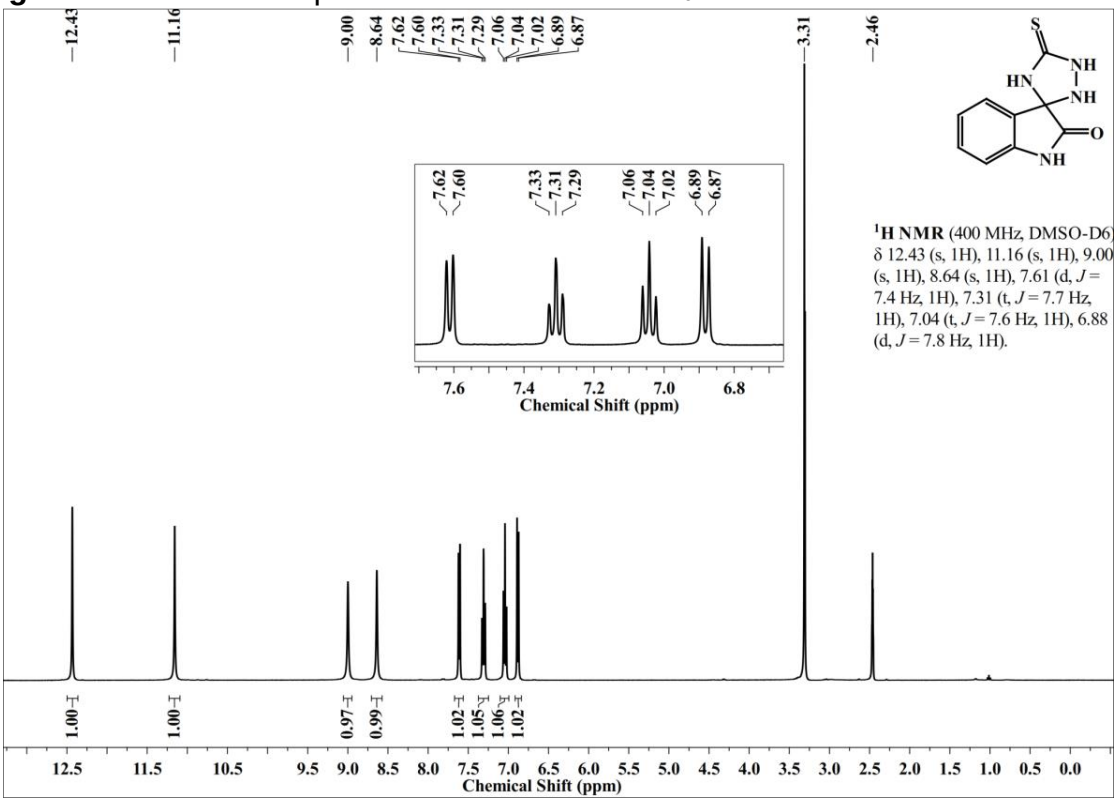


Figure 4.1.9 ^{13}C NMR Spectrum of 6a in DMSO-D_6

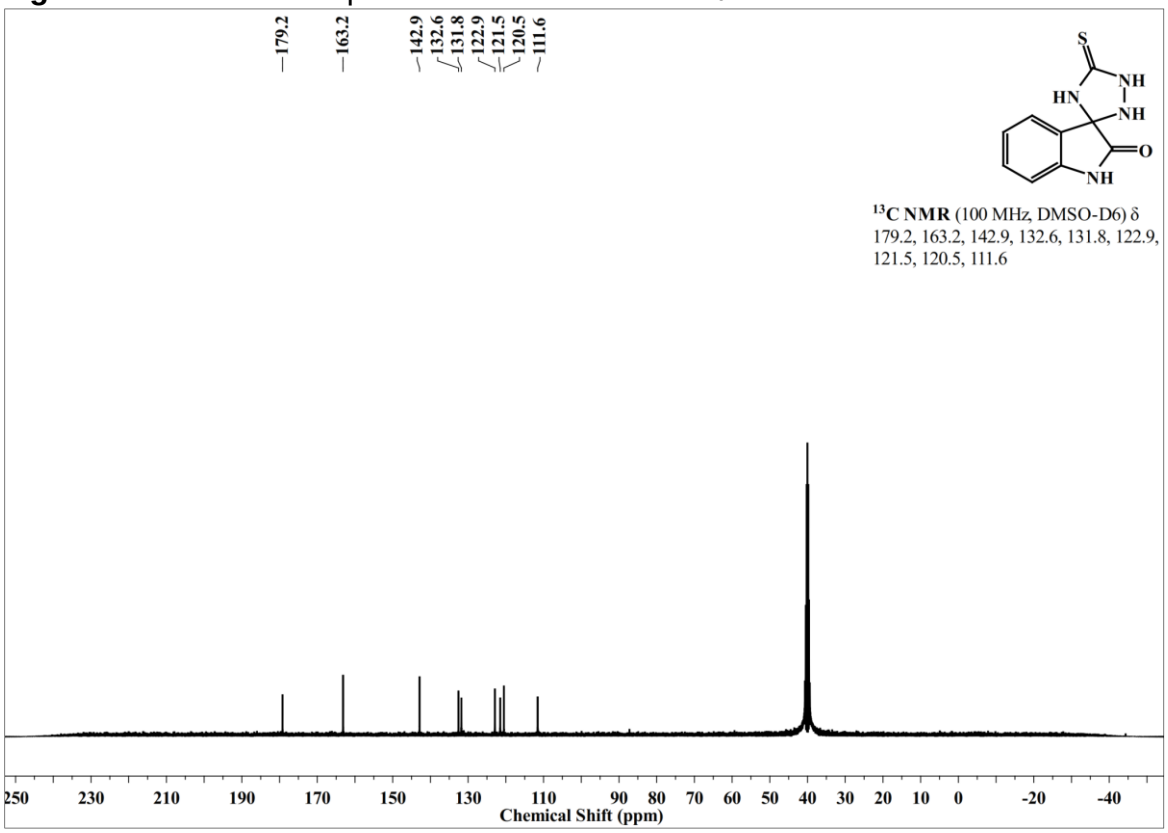


Figure 4.1.10 ^{1}H NMR Spectrum of 6f in DMSO-D_6

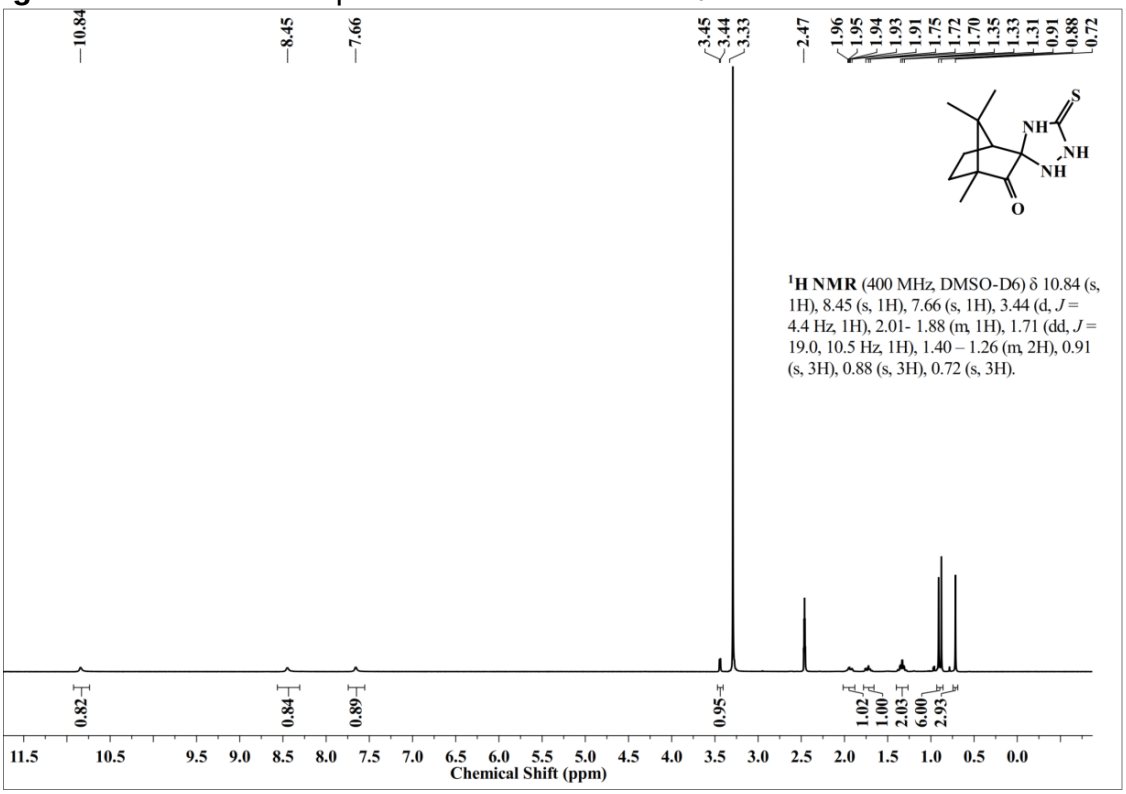
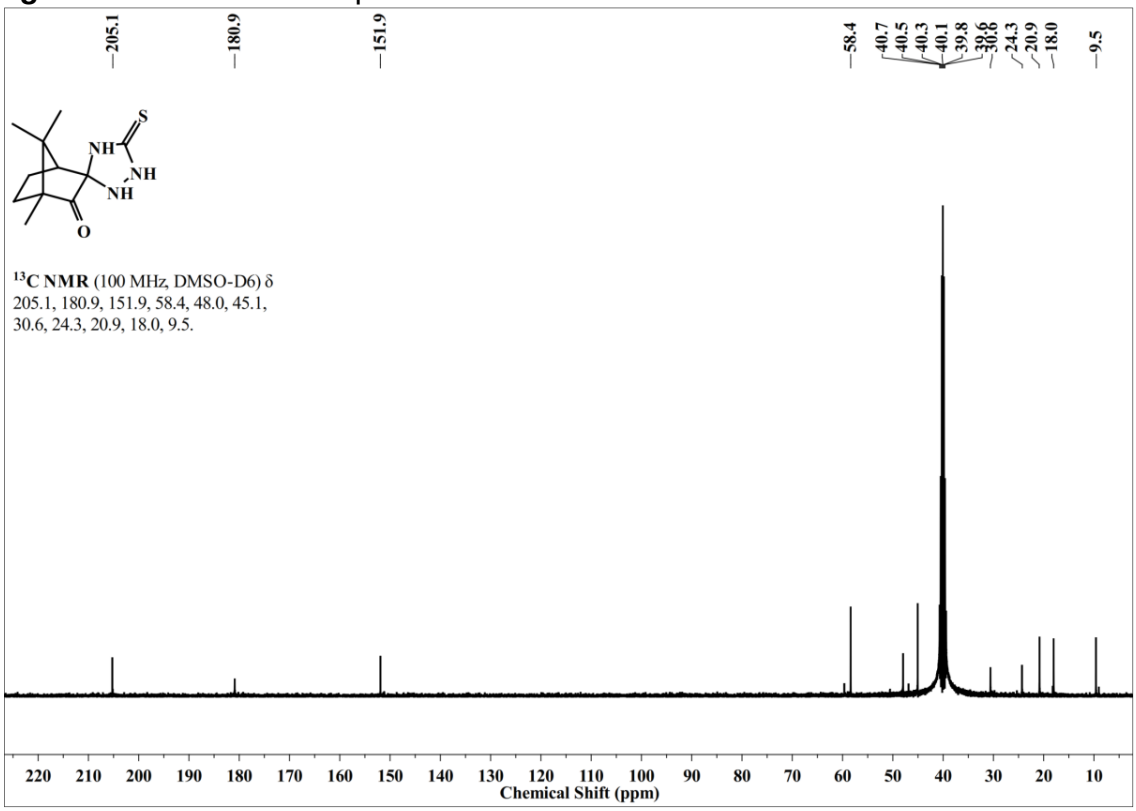
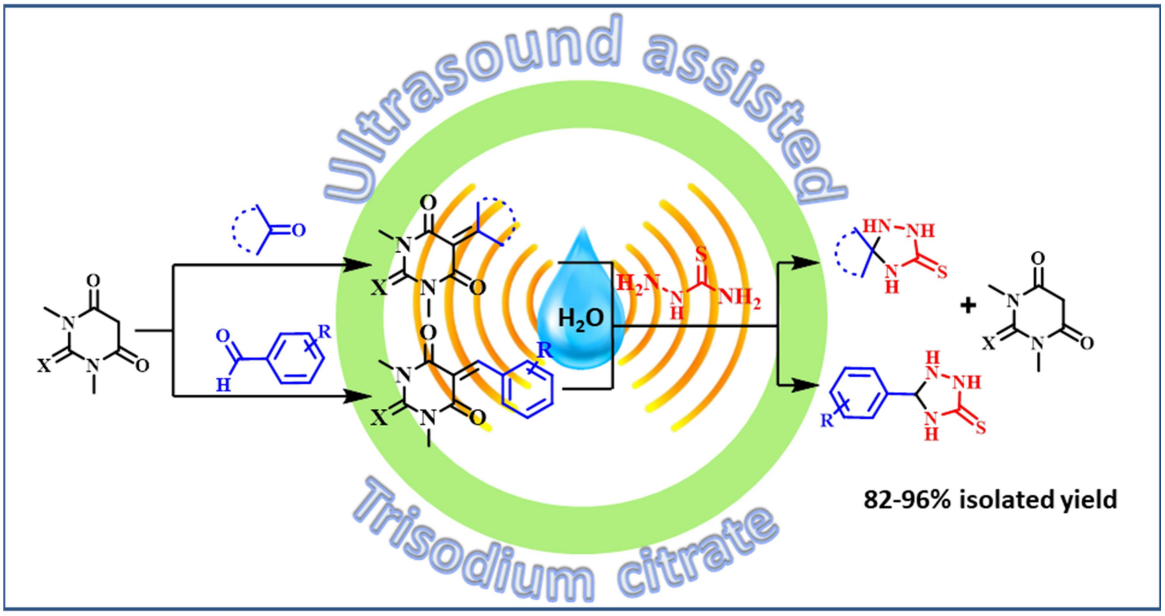


Figure 4.1.11 ^{13}C NMR Spectrum of 6f in DMSO-D_6



Section 4.2

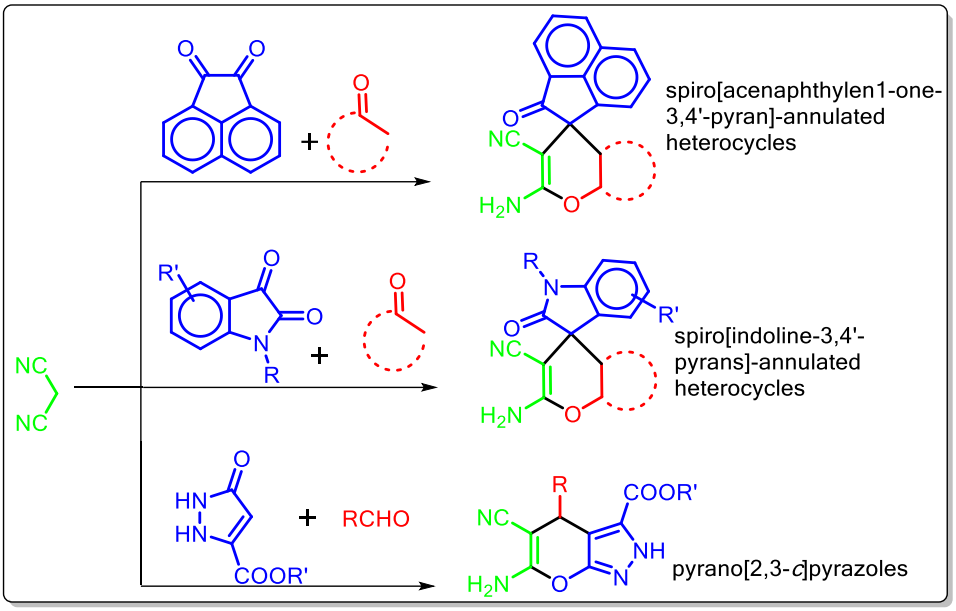
Trisodium citrate dihydrate catalysed “on-water” sonochemical synthesis of 5-aryl/spiro triazolidone-3-thiones



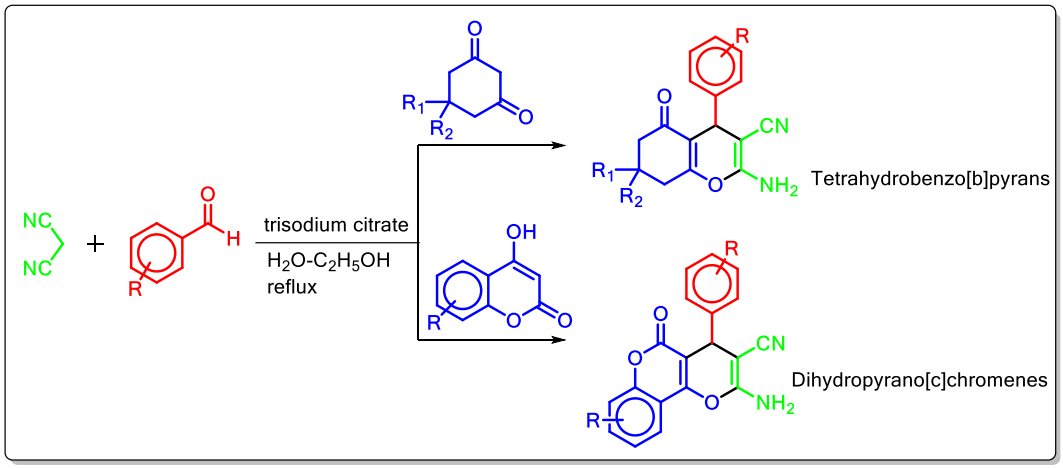
4.2.1 INTRODUCTION

Trisodium 2-hydroxypropane1,2,3-tricarboxylate dihydrate, better known as trisodium citrate dihydrate with a chemical formula $C_6H_5Na_3O_7 \cdot 2H_2O$ is a popular food additive and has been used in the food and beverage industry for quite a long time, as an acidity regulator and as a buffering agent [61]. It is added to soft drinks, wines, soups, jams, desserts and many confectionaries because it is cheap, commercially available and above all chemically benign; which also makes it a go to chemical for various medical applications such as an anticoagulant for blood or as a component of the oral rehydration solution [61]. Overall, it can be said that trisodium citrate dihydrate is chemically safe and non-toxic in nature. Owing to this, it has also entered into the domains of synthetic chemistry, where researchers have explored its catalytic proficiency in one-pot multicomponent reactions towards the synthesis of a plethora of biologically potent *O*- and *N*-heterocycles, under ambient conditions [61,62] (**Scheme 4.2.1** and **Scheme 4.2.2**). Despite the wide range prospects of utilising trisodium citrate in organic synthesis, it is underutilised.

When it comes to the development of greener methods of synthesis, Sonochemistry has made great contributions into the development of efficient protocols and has attracted the attention of the scientific community towards its utilization in the field of organic synthesis. Ultrasound-assisted organic synthesis has been declared to be eco-friendly and its usage in the development of accelerated synthetic strategies for the synthesis of organic scaffolds, especially heterocycles, is noteworthy [63-66].



Scheme 4.2.1 Synthesis of diverse *O*- and *N*-heterocyclic functionalities *via* one-pot, room-temperature trisodium citrate dihydrate catalysis



Scheme 4.2.2 One-pot, trisodium citrate catalysed synthesis of diverse *O*-heterocyclic functionalities

Ultrasound accelerated synthesis has been efficiently employed for the synthesis of benzoxazole, isoxazole, 1,2,4-oxadiazole, pyrazole, thiazole, triazole, imidazoline, pyrimidine, thiazolidine, and thiazinanone skeletons. This strategy adheres to the goals of green chemistry and allows achieving efficacy in reducing the requirements for energy driven methods, with high conversion rates, milder reaction conditions, shorter reaction time and yields with high purity. While

discussing the technical attributes of sonochemistry, we can safely sit upon the acoustic cavitation theory to explain the mechanism of these reactions. The process involves the formation of a bubble, where a localized high pressure and temperature condition is developed within a matter of seconds to create a turbulence, which provides enough energy for the transportation of mass and solubilizing or diffusing it, to accelerate the formation of product within less reaction time. In due course the bubble grows and collapses in an ultrasound irradiated liquid [67-73].

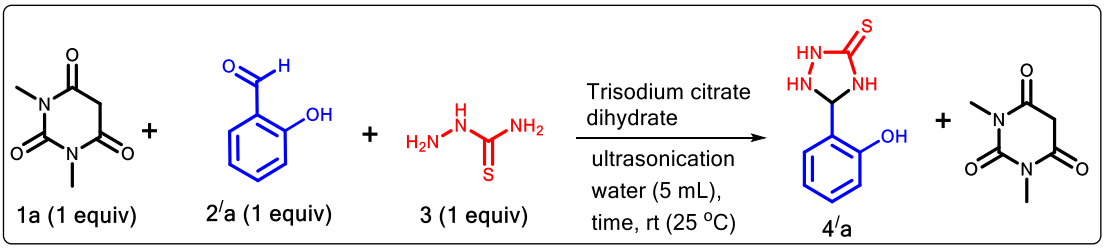
In the previous section (**Section 4.1**), we have discussed the design of a novel route for the synthesis of 5-substituted 1,2,4-triazolidine-thiones. However, there were a few shortcomings of the method. Firstly, the usage of stoichiometric amounts of base still kept the door open for a catalytic approach. Secondly, the usage of 2-hydroxy aromatic aldehydes was not discussed. Both of these issues were taken care of by the development of a novel sonochemical route for the synthesis of 5-substituted-1,2,4-triazolidine thiones which is catalyzed by trisodium citrate dihydrate, obviously used as a base, and by the inclusion of the study on 2-hydroxy aromatic aldehydes.

4.2.2. RESULTS AND DISCUSSION

In continuation of our efforts to discover novel greener methods for the synthesis of the multi-utilitarian 5-aryl/spiro-1,2,4-triazolidine thiones, we derived inspirations from our previous study. For example, while selecting the best active methylene group containing entity, we directly went for 1,3-dimethylbarbituric acid

and used water as the solvent. To begin with the initial experimentation based on our hypothesis that trisodium citrate dihydrate would be an efficient basic catalyst for the reaction, under sonochemical conditions, we began by studying the one-pot reaction between 1,3-dimethylbarbituric acid (**1**), salicyladehyde (**2′a**), and thiosemicarbazide (**3**) in the presence of trisodium citrate dihydrate (10 mol% with respect to salicylaldehyde) and 5 mL water. The reaction mixture was subjected to ultrasonic irradiation (150 W/30 KHz) for a period of 30 minutes. A white colour precipitate was formed at the end of the reaction. It was filtered and washed with aqueous ethanol and upon analyzing it with the help of ^{1}H NMR and ^{13}C NMR studies; it was found that the desired product 5-(2-hydroxyphenyl)-1,2,4-triazolidine-3-thione (**4′a**) was formed. This paved a way for us to optimize the reaction protocol and continue our study to establish a catalytic route for the synthesis of the mentioned class of compounds. The optimization of the reaction conditions is presented in **Table 4.2.1**.

Table 4.2.1 Optimisation of the reaction



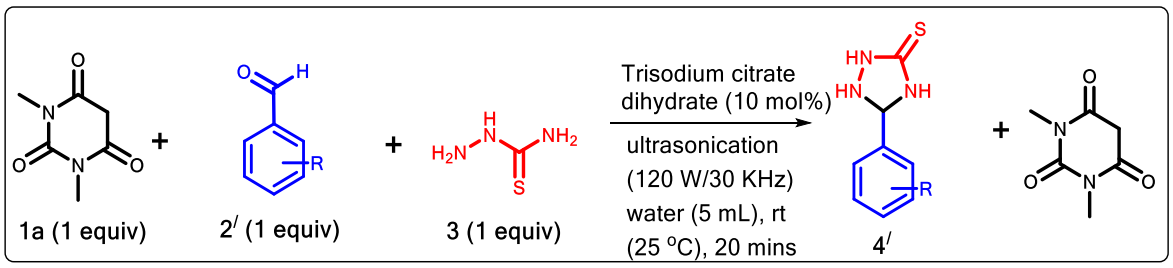
Optimisation parameter	Entry	Catalyst	Power (W)	Time (min)	[a]Isolated Yield %
Amount of catalyst	1	No catalyst	150	30	N.R
	2	Trisodium citrate dihydrate (5 mol%)	150	30	78
	3	Trisodium citrate dihydrate (10 mol%)	150	30	90

	4	Trisodium citrate dihydrate (20 mol%)	150	30	92
Power of ultra-sonication	5	Trisodium citrate dihydrate (10 mol%)	130	30	90
	6	Trisodium citrate dihydrate (10 mol%)	120	30	90
	7	Trisodium citrate dihydrate (10 mol%)	110	30	86
	8	Trisodium citrate dihydrate (10 mol%)	100	30	82
Time required	**9[b]**	**Trisodium citrate dihydrate (10 mol%)**	**120**	**20**	**90**
	10	Trisodium citrate dihydrate (10 mol%)	120	10	76
	11	Trisodium citrate dihydrate (10 mol%)	120	50	90
	12	Trisodium citrate dihydrate (10 mol%)	120	60	90
Other basic Catalysts	13	CH_3COONa (10 mol%)	120	60	40
	14	Disodium Oxalate (10 mol%)	120	30	54
	15	Sodium metasilicate (10 mol%)	120	20	75
	16	Sodium Stearate (10 mol%)	120	45	30
	17	CH_3COONH_4 (10 mol%)	120	60	36
	18	Triammonium citrate (10 mol%)	120	30	55
	19	$NaHCO_3$ (10 mol%)	120	20	60
	20	NaOH (10 mol%)	120	20	80
	21	KOH (10 mol%)	120	20	82
	22	Na_2CO_3 (10 mol%)	120	20	76
Blank	23	No catalyst	No sonication	180	N.R

Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), Aromatic aldehyde 2/a (1 mmol), Thiosemicarbazide 3 (1 mmol), Ultra-sonication, Water (5 mL), catalyst, rt (room temperature: 25 °C. [a]Isolated Yield. [b]Best reaction conditions.

From the observations made during the optimization of the reaction protocol, we deduced the optimized reaction condition for the trisodium citrate dihydrate catalysed synthesis of 5-aryl-1,2,4-triazolidine-3-thiones (**Scheme 4.2.3**).

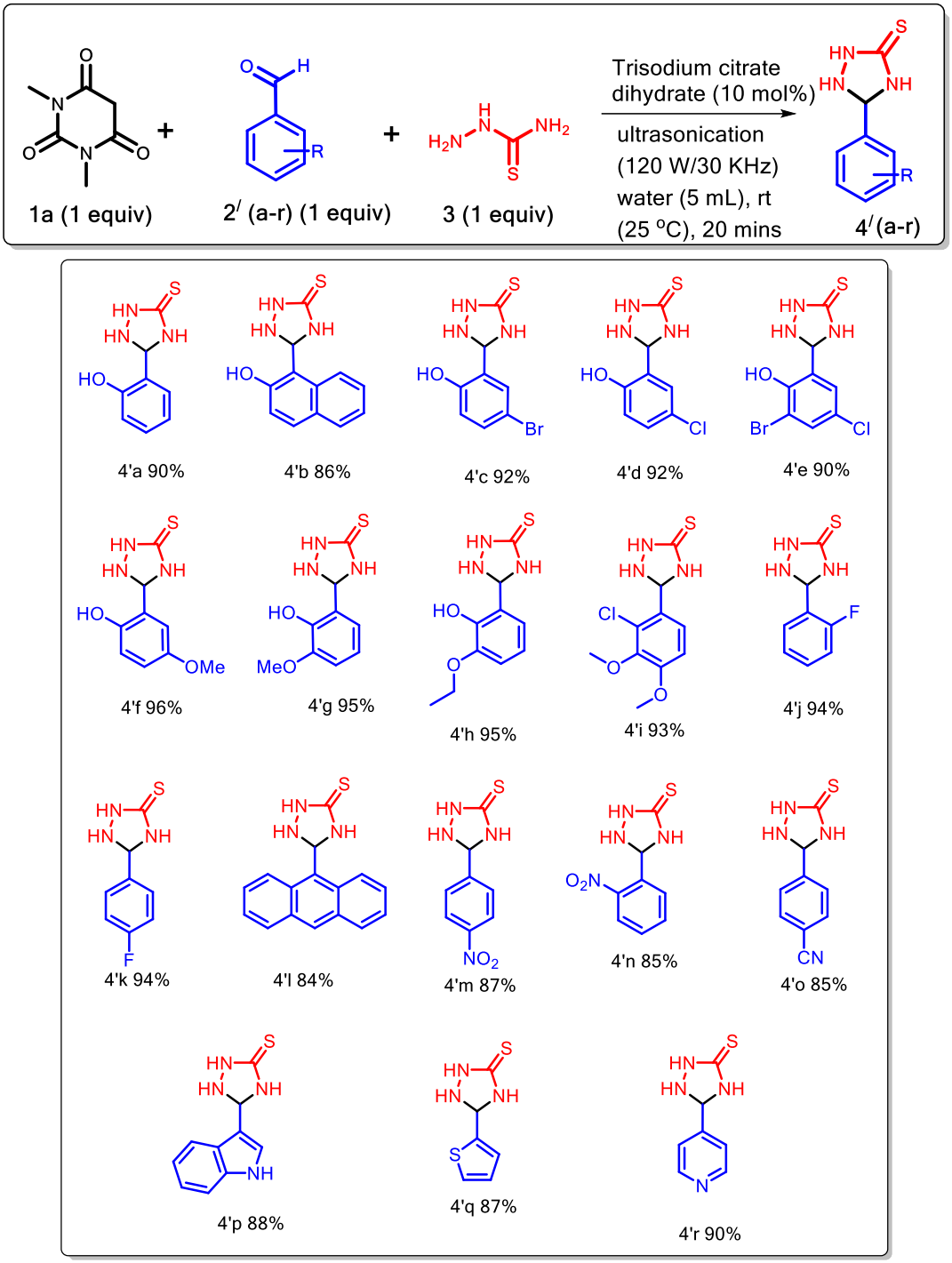
It is noteworthy that trisodium citrate dihydrate happens to be the best catalyst among those tested, from various perspectives. It is commercially available, low cost and a very mild basic catalyst. It helps in attaining the selectivity of the reaction and does not activate any other site/ group, as is seen in case of NaOH or KOH, where a number of side products appeared to have formed, as observed from the preliminary thin layer chromatography analysis. This is the reason for the comparative lower yields of the products despite being chemically more reactive than trisodium citrate dihydrate.



Scheme 4.2.3 Optimised reaction scheme

Following this we extended the method for the synthesis of diversified 5-aryl-1,2,4-triazolidine-3-thiones (**Scheme 4.2.4**). Diverse 5-aryl-1,2,4-triazolidine-3-thiones were synthesised with the help of the reaction protocol and as observed trisodium citrate dihydrate turned out to be an excellent catalyst for the methodology. It being water soluble remained in the reaction media and offered no difficulty in the isolation of the products. The protocol was also extended towards the synthesis of some spiro-1,2,4-triazolidine-3-thiones by replacing

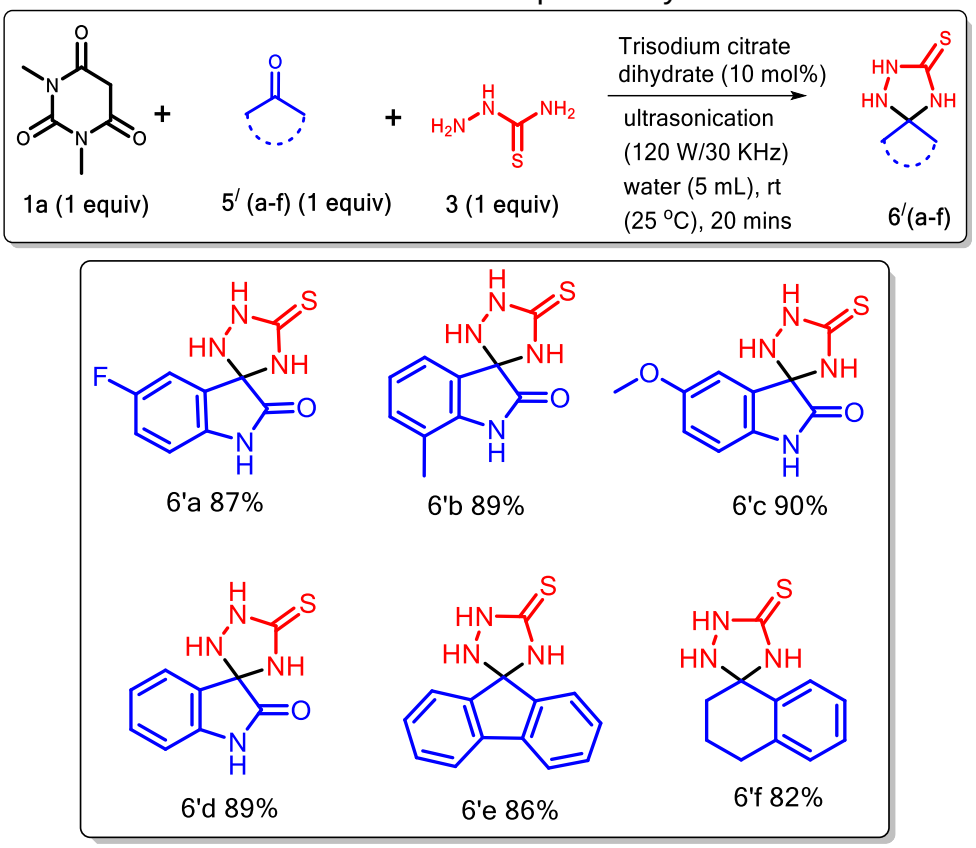
Scheme 4.2.4 Substrate scope with aromatic aldehydes



Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), Aromatic aldehyde 2/ (1 mmol), Thiosemicarbazide 3 (1 mmol), Ultra-sonication (120 W/30 KHz), Water (5 mL), trisodium citrate dihydrate (10 mol%), rt (room temperature: 25 °C).

aromatic aldehydes with cyclic ketones (**Scheme 4.2.5**). It was observed that the presence of electron withdrawing groups in the aromatic aldehydes or cyclic

Scheme 4.2.5 Substrate scope with cyclic ketones



Reaction conditions: 1,3-Dimethylbarbituric acid 1a (1 mmol), cyclic ketone 5/ (1 mmol), Thiosemicarbazide 3 (1 mmol), Ultra-sonication (120 W/30 KHz), Water (5 mL), trisodium citrate dihydrate (10 mol%), rt (room temperature: 25 °C).

resulted in a slight decrease in the yield of the desired product. This may be attributed to the initial step of formation of the arylidene/alkylidene barbiturate, which happens to be a bit lethargic in the presence of electron withdrawing groups. Also, rate of formation of alkylidene barbiturate is slower than the aromatic counterparts. Hence, the products formed thereof is lower in yield. The reaction protocol was also tested with aromatic ketones. However, the reluctance of aromatic ketones to form arylidene barbiturates at room temperatures led to the non-formation of the desired product. It is also worth noting that the products formed were isolated in pure form by simple filtration followed by washing with

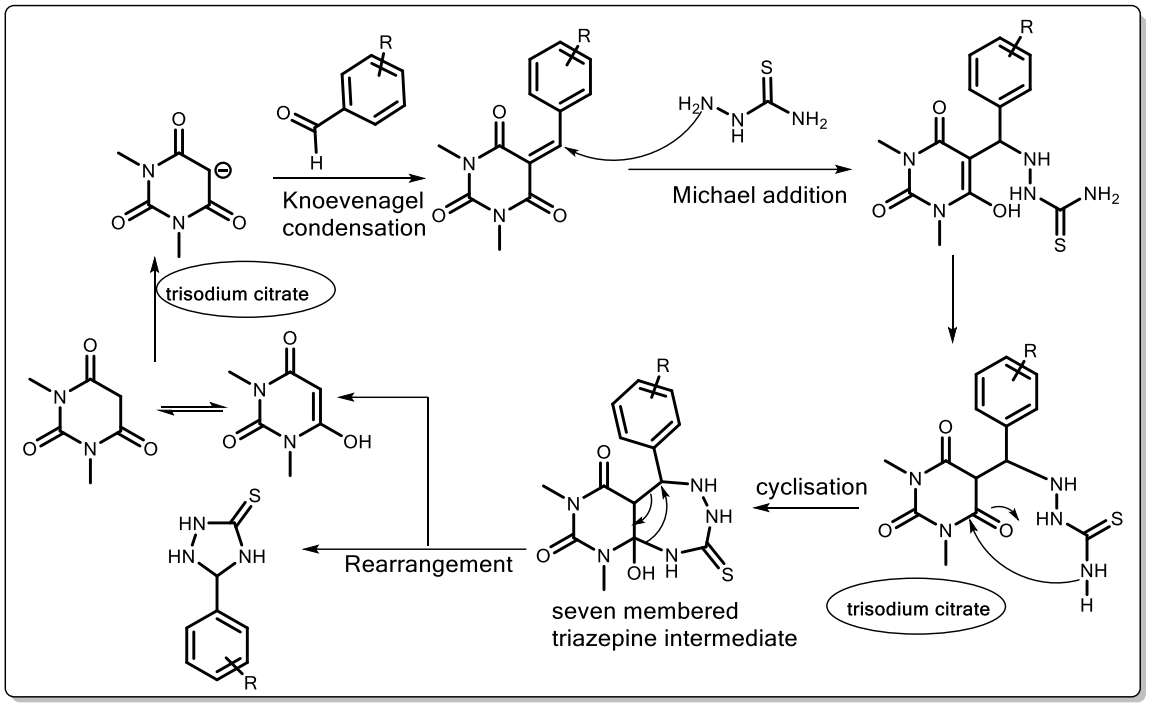
aqueous ethanolic solution. The isolation process is chromatography free as the solid products formed easily precipitated out from the reaction media.

As we have observed in all the above reactions and also during the initial trials, that the filtrate obtained after isolation of the product contained 1,3-dimethylbarbituric acid and the catalyst- trisodium citrate dehydrate, therefore we embarked upon studying the prospects of using this filtrate as a homogeneous recyclable media and checked the number of times it could be reused only by recharging with the requisite amount of aromatic aldehyde/cyclic ketone and thiosemicarbazide. The reusability is shown in **Table 4.2.2**. It can be noted that the decrease in the yield of product in the subsequent cycles is because of the loss of some amount of catalyst and barbituric acid in the filtration process. It is entirely a result of human error and limitations associated with conventional methods of filtration and not because of the loss of the catalytic potency.

Table 4.2.2 Reuse of reaction media containing residual solvent, catalyst, and substrates.

No. of cycles	Compound 4^{l}a		Compound 4^{l}n		Compound 6^{l}c	
	Time (min)	[a]Yield%	Time (min)	[a]Yield%	Time (min)	[a]Yield%
Fresh run	**20**	**90**	**20**	**85**	**20**	**90**
1st cycle	20	87	20	81	20	87
2nd cycle	20	82	20	76	20	82
3rd cycle[b]	30	75	30	70	30	78

[a]Isolated Yield %, [b]Additional 2 mL distilled water was added to the reaction media to compensate for the loss of solvent during workup of the previous cycles.



Scheme 4.2.6 Plausible mechanism of trisodium citrate dihydrate catalysed formation of 5-aryl-1,2,4-triazolidine-3-thiones.

Keeping in mind the usefulness of the triazolidine-3-thione scaffold, the methodology described here, offers a greener aspect to its synthesis along with high selectivity of product formation, tolerance of various functional groups, mild reaction conditions, reusability of the catalyst and operational simplicity. The catalyst used is highly efficient in ticking all the boxes for it to be considered as an ideal one for the job.

The plausible reaction mechanism of the reaction begins with trisodium citrate accelerating the formation of the arylidene/alkylidene barbiturate at room temperature, followed by the nucleophillic attack of the thiosemicarbazide on the electrophilic double bond. This is followed by another base driven cyclisation towards the formation of a seven membered 9a-hydroxy-5-aryl-2-thioxooctahydro-6*H*-pyrimido[4,5-*e*][1,2,4]triazepine-6,8(7*H*)-dione intermediate,

which undergoes rearrangement to form the comparatively stable five membered triazolidine adduct (**Scheme 4.2.6**). The mechanism is similar to the one described in **Scheme 4.1.8**, in the previous section (**Section 4.1**). The only change is the usage of trisodium citrate dihydrate as the base and in catalytic amount.

4.2.3 EXPERIMENTAL SECTION

General Information

All reagents were purchased from commercial sources and used as received, without any purification. Commercially available solvents were distilled before the reactions and water used for reaction as well as during work up was double distilled prior to use. The specifications of the ultra-sonictor and processing parameters used for the experiments are: Make: GT SONIC-QTD series ultrasonicator; Operating frequency: 30 KHz; Maximum outout power: 150 W; Inner tank dimensions: 300mm X 170mm X 150mm. ^{1}H and ^{13}C NMR spectra of the products were recorded with a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using deuterated dimethyl sulfoxide (DMSO-*D*6, δ= 2.46ppm, quintet, for ^{1}H and 40.0 ppm, septet, for ^{13}C) as the solvent as well as the internal standard. However, due to solubility issue in DMSO-D_6, the ^{1}H and ^{13}C NMR spectra of product 6′g was recorded, in the same instrument, using deuterated chloroform ($CDCl_3$) as the solvent and Tetramethylsilane (TMS) as the internal standard. Additional signal at 3.30 ppm, in ^{1}H NMR spectra, is seen because of the presence of HOD in DMSO-D_6. Similarly, due to the presence of HOD in $CDCl_3$ an additional signal at 1.59 ppm is observed in the ^{1}H spectrum. Chemical shift

values are expressed in ppm. Coupling constants (*J*) are expressed in Hertz (Hz). The signals are reported as “s”= singlet, “d”= doublet, “t”= triplet, “dd”= doublet of doublet, “td”= doublet of a triplet and “m”= multiplet. HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel $60F_{254}$ (Merck). UV light and Iodine vapors were used as visualizer.

General Procedure for the synthesis of 5-aryl-[1,2,4]-triazolidine-3-thiones (*4′*a-r), 5-spiro-[1,2,4]-triazolidine-3-thiones (*6′*a-f) *via* trisodium citrate dihydrate catalysis under ultra-sonication.

A mixture of 1 equiv of the aromatic aldehyde or cyclic ketone, 0.156 g of 1,3-Dimethylbarbituric acid (1 equiv), 0.091 g of thiosemicarbazide (1 equiv), trisodium citrate dihydrate (10 mol%) along with requisite amount of distilled water was taken in a glass vial and subjected to ultra-sonication of 120 W/30 KHz power, for the requisite period of time. The reaction was monitored with the help of thin layer chromatography. Upon completion, the reaction mixture was filtered and the first batch filtrate (without washing) was kept aside for reuse. The precipitate was separately washed with 25% ethanol: water mixture and dried under vacuum. It was then characterized without further purification.

Procedure for reusing the filtrate containing the catalyst and 1,3-dimethylbarbituric acid

The filtrate collected in the above procedure was charged with 1 equiv of the same aldehyde and thiosemicarbazide and was subjected to ultra-sonication of the same power and same period of time to yield the desired product. The

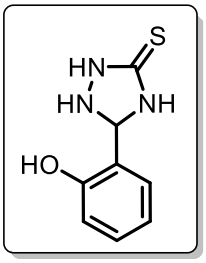
reaction mixture was again filtered and kept aside for reuse. The precipitate was washed with 25% aqueous ethanolic solution and dried under vacuum.

4.2.4 CONCLUSION

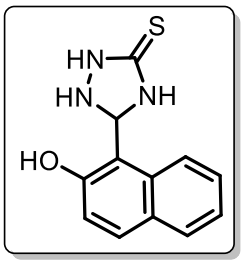
In conclusion, the reaction protocol developed is a simple, efficient and convenient route for the synthesis of 5-aryl/spiro-1,2,4-triazolidine-3-thione derivatives *via* "on-water" trisodium citrate dihydrate catalysed one-pot three component reaction between aromatic aldehydes/cyclic ketones, 1,3-dimethyl barbituric acid and thiosemicarbazide, under ultra-sonication. The use of commercially available, non-toxic, economically viable and reusable catalyst, excellent yields, short reaction time, easy post reaction work-up, column chromatography free isolation of products are some of the major advantages and salient features of the developed methodology.

4.2.5 CHARACTERISATION DATA OF THE PRODUCTS

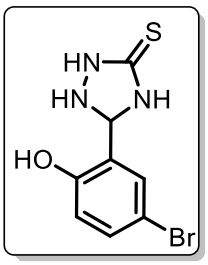
The following are the details of the compounds synthesised *via* the above mentioned method.



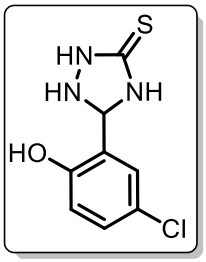
5-(2-hydroxyphenyl)-1,2,4-triazolidine-3-thione (4′a) White solid (175.60 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.34 (s, 1H), 9.84 (s, 1H), 8.32 (s, 1H), 8.07 (s, 1H), 7.87 (s, 2H), 7.16 (t, *J*= 8.4 Hz, 1H), 6.86 – 6.71 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.1, 156.9, 140.0, 131.6, 127.2, 120.9, 119.8, 116.5. **HRMS (+ESI)** calcd for $C_8H_9N_3OS$ $(M+H)^+$: 195.0521 found:195.0543



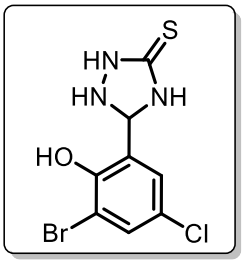
5-(2-hydroxynaphthalen-1-yl)-1,2,4-triazolidine-3-thione (4^{l}b) Off white solid (197.00 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ: 11.42 (s, 1H), 8.88 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.25 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 9.7 Hz, 3H), 7.63-7.51 (m, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 141.5, 133.9, 131.0, 130.7, 129.8, 129.4, 127.8, 126.7, 126.3, 126.1, 123.4 **HRMS (+ESI)** calcd for $C_{12}H_{11}N_3S$ $(M+H)^+$: 229.0708 found: 229.0718



5-(5-bromo-2-hydroxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}c) Pale yellow solid (251.10 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.38 (s, 1H), 10.18 (s, 1H), 8.24 (s, 1H), 8.18 – 8.09 (m, 3H), 7.28 (d, *J*= 7.8 Hz, 1H), 6.77 (d, *J*=7.8 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 156.1, 137.8, 133.7, 128.8, 123.4, 118.6, 111.6. **HRMS (+ESI)** calcd for $C_8H_8BrN_3OS$ $(M+H)^+$: 272.9631 found: 272.9645

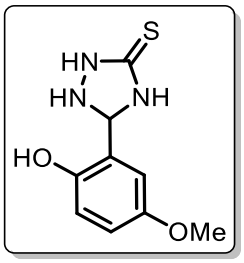


5-(5-chloro-2-hydroxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}d) White solid (210.70 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.39 (s, 1H), 10.17 (s, 1H), 8.25 (s, 1H), 8.15-80.3 (m, 3H), 7.16 (d, *J* = 11.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.3, 155.7, 137.8, 130.9, 126.0, 124.0, 122.9, 118.2. **HRMS (+ESI)** calcd for $C_8H_8ClN_3OS$ $(M+H)^+$: 229.0112 found: 229.0121

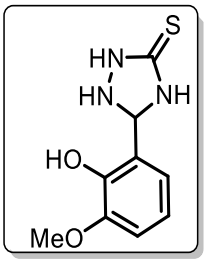


5-(3-bromo-5-chloro-2-hydroxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}e) White solid (276.24 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.50 (s, 1H), 9.91 (s, 1H), 8.26 (s, 1H), 8.23 (s, 2H), 8.01 (s, 1H), 7.61 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 177.9, 162.2, 158.4, 140.6, 128.8, 113.8, 106.8, 55.6. **HRMS (+ESI)** calcd for $C_8H_7BrClN_3OS$ $(M+H)^+$: 306.9281 found:

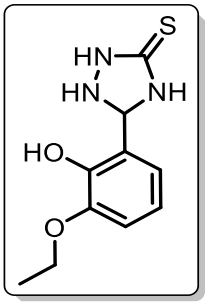
306.9305



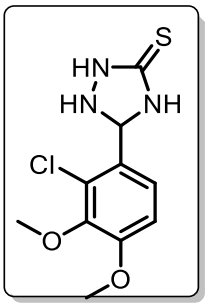
5-(2-hydroxy-5-methoxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}f) Pale yellow solid (216.06 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.31 (s, 1H), 9.40 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.97 (s, 1H), 7.44 (s, 1H), 6.79 – 6.71 (m, 2H), 3.67 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.2, 152.9, 151.2, 139.8, 121.2, 118.8, 117.6, 110.0, 55.8. **HRMS (+ESI)** calcd for $C_9H_{11}N_3O_2S(M+H)^+$: 225.0673 found: 225.0679



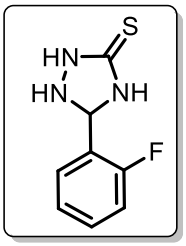
5-(2-hydroxy-3-methoxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}g) Pale yellow solid (213.82 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.34 (s, 1H), 9.12 (s, 1H), 8.36 (s, 1H), 8.05 (s, 1H), 7.83 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.72 (t, *J* = 8.0 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.1, 148.5, 146.5, 140.0, 121.3, 119.4, 113.3, 75.6, 56.4. **HRMS (+ESI)** calcd for $C_9H_{11}N_3O_2S$ $(M+H)^+$: 225.0673 found: 225.0685



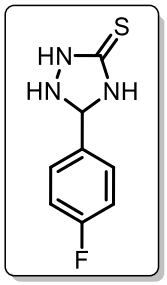
5-(3-ethoxy-2-hydroxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}h) Yellow solid (227.12 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.34 (s, 1H), 8.96 (s, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 6.6 Hz, 1H), 6.70 (t, *J* = 8.0 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.1, 147.5, 146.7, 140.1, 121.3, 119.6, 118.8, 114.5, 64.7, 15.2. **HRMS (+ESI)** calcd for $C_{10}H_{13}N_3O_2S$ $(M+H)^+$: 239.0702 found: 239.0711



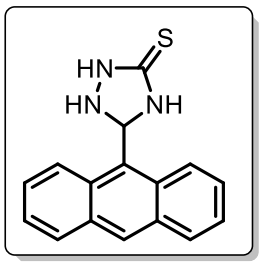
5-(2-chloro-3,4-dimethoxyphenyl)-1,2,4-triazolidine-3-thione (4^{l}i) Pale yellow solid (254.00 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.45 (s, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 8.01-7.93 (m, 2H), 7.04 (d, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 155.1, 145.1, 139.1, 128.2, 125.0, 123.3, 112.3, 60.7, 56.8 **HRMS (+ESI)** calcd for $C_{10}H_{12}ClN_3O_2S$ $(M+H)^+$: 273.0337 found: 273.0356



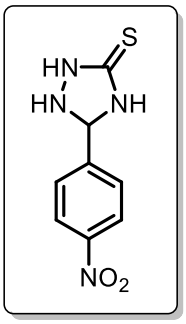
5-(2-fluorophenyl)-1,2,4-triazolidine-3-thione (4^{l}j) White solid (185.22 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.52 (s, 1H), 8.27 – 8.15 (m, 3H), 8.04 (s, 1H), 7.40 (dd, *J* = 14.1, 6.8 Hz, 1H), 7.19 (dd, *J* = 16.1, 8.5 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.7, 162.2, 160.0, 135.2, 127.4, 122.5, 122.3, 99.5. **HRMS (+ESI)** calcd for $C_8H_8FN_3S$ $(M+H)^+$: 197.0422 found: 197.0428



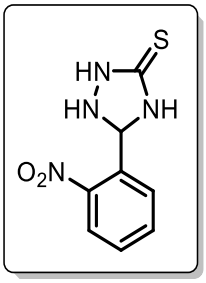
5-(4-fluorophenyl)-1,2,4-triazolidine-3-thione (4^{l}k) White solid (185.30 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.40 (s, 1H), 8.16 (s, 1H), 7.99 (s, 2H), 7.83 (t, *J*= 8.7 Hz, 2H), 7.18 (t, *J* = 8.7 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.5, 164.7, 162.3, 141.6, 131.3, 130.1, 116.0. **HRMS (+ESI)** calcd for $C_8H_8FN_3S$ $(M+H)^+$: 197.0422 found: 197.0436



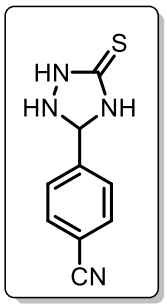
5-(anthracen-9-yl)-1,2,4-triazolidine-3-thione (4^{l}l) Dark yellow solid (234.70 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.60 (s, 1H), 9.29 (s, 1H), 8.67 (s, 1H), 8.53 (d, *J* = 8.9 Hz, 2H), 8.27 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 2H), 7.73–7.50 (m, 5H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.6, 142.7, 131.4, 130.2, 130.0, 129.5, 127.8, 126.1, 125.5, 125.3 **HRMS (+ESI)** calcd for $C_{16}H_{13}N_3S$ $(M+H)^+$: 279.3719 found: 279.3732



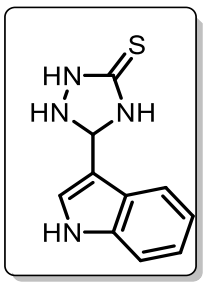
5-(4-nitrophenyl)-1,2,4-triazolidine-3-thione (4*l*m) Pale yellow solid (194.92 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.29–8.14 (m, 3H), 8.13–8.01 (m, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.0, 148.1, 141.2, 140.1, 128.7, 124.3 **HRMS (+ESI)** calcd for $C_8H_8N_4O_2S$ $(M+H)^+$: 224.0512 found: 224.0532



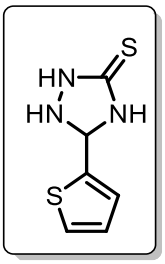
5-(2-nitrophenyl)-1,2,4-triazolidine-3-thione (4*l*n) Pale yellow solid (190.44 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.59 (s, 1H), 8.51 (d, *J* = 4.9 Hz, 1H), 8.30 (s, 1H), 8.23 (d, *J* = 7.1 Hz, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.32 (t, J= 7.8 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.8, 153.9, 153.8, 150.0, 143.0, 137.1, 124.6, 120.7 **HRMS (+ESI)** calcd for $C_8H_8N_4O_2S$ $(M+H)^+$: 224.0512 found: 224.0502



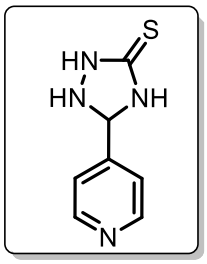
4-(5-thioxo-1,2,4-triazolidin-3-yl)benzonitrile (4*l*o) Pale yellow solid (173.44 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.29–8.14 (m, 3H), 8.13–8.01 (m, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.0, 148.1, 141.2, 140.1, 128.7, 124.3 **HRMS (+ESI)** calcd for $C_8H_8N_4O_2S$ $(M+H)^+$: 204.0512 found: 204.0528



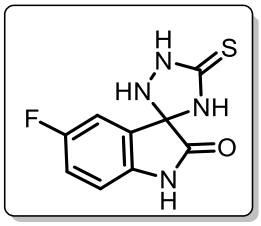
5-(1*H*-indol-3-yl)-1,2,4-triazolidine-3-thione (4*l*p) Pale yellow solid (191.88 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.55 (s, 1H), 11.12 (s, 1H), 8.26 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.38 (d, *J*= 8.02 Hz, 1H), 7.36 (s, 1H), 7.15 (t, *J*= 7.11 Hz, 1H), 7.08 (t, *J*= 7.98 Hz, 1H. **^{13}C NMR** (100 MHz, DMSO-D_6) δ 177.0, 141.3, 137.6, 131.5, 124.5, 123.2, 122.7, 121.1, 112.3, 111.6 **HRMS (+ESI)** calcd for $C_{10}H_{10}N_4S$ $(M+H)^+$: 218.0671 found: 218.0693



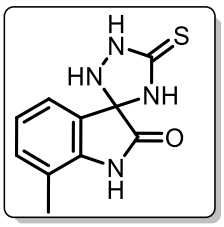
5-(thiophen-2-yl)-1,2,4-triazolidine-3-thione (4^{l}q) Off white solid (161.00 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.40 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 7.61 (d, J = 5.0 Hz, 1H), 7.51 (s, 1H), 7.41 (d, J = 4.2 Hz, 1H), 7.07 (dd, J = 5.0, 3.6 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.1, 139.1, 138.1, 131.1, 129.4, 128.5 **HRMS (+ESI)** calcd for $C_6H_7N_3S_2$ $(M+H)^+$: 185.0119 found: 185.0131



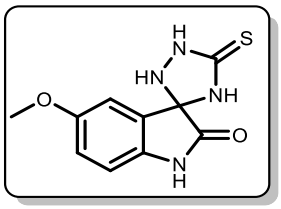
5-(pyridin-4-yl)-1,2,4-triazolidine-3-thione (4^{l}r) White solid (162.47 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.66 (s, 1H), 8.54 (dd, J = 4.5, 1.6 Hz, 2H), 8.37 (s, 1H), 8.18 (s, 1H), 7.95 (s, 1H), 7.73 (d, J = 6.1 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.0, 150.6, 142.0, 140.0, 121.7. **HRMS (+ESI)** calcd for $C_7H_8N_4S$ $(M+H)^+$: 180.0527 found: 180.0541



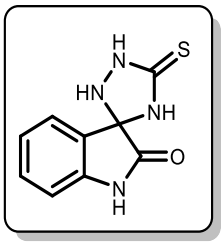
5-fluoro-5^{l}-thioxospiro[indoline-3,3^{l}-[1,2,4]triazolidin]-2-one (6^{l}a) Yellow solid (207.10 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 12.32 (s, 1H), 11.16 (s, 1H), 9.07 (s, 1H), 8.71 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.18 – 7.03 (m, 1H), 6.86 (dd, J = 8.4, 3.9 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.6, 163.3, 159.5, 159.1, 158.7, 158.3, 121.7, 117.0, 114.0. **HRMS (+ESI)** calcd for $C_9H_7FN_4OS$ $(M+H)^+$: 238.0337 found: 238.0349



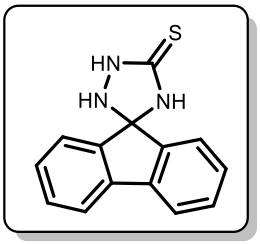
7-methyl-5^{l}-thioxospiro[indoline-3,3^{l}-[1,2,4]triazolidin]-2-one (6^{l}b) Yellow solid (208.30 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 12.47 (s, 1H), 11.22 (s, 2H), 8.98 (s, 1H), 8.64 (s, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.98 – 6.89 (m, 1H), 2.16 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 181.7, 159.1, 158.7, 147.8, 133.0, 121.3, 120.0, 99.5, 97.4, 56.1. **HRMS (+ESI)** calcd for $C_9H_7FN_4OS$ $(M+H)^+$: 234.0661 found: 234.0680



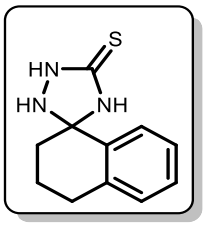
5-methoxy-5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-one (6′c) Orange solid (225.53 mg) **^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 12.38 (s, 1H), 10.97 (s, 1H), 9.04 (s, 1H), 8.71 (s, 1H), 7.28 (d, *J* = 2.6 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 3.71 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 179.2, 163.3, 155.8, 136.5, 132.8, 121.4, 117.9, 112.3, 106.6, 56.0 **HRMS (+ESI)** calcd for $C_{10}H_{10}N_4O_2S$ $(M+H)^+$: 250.0574 found: 250.0599



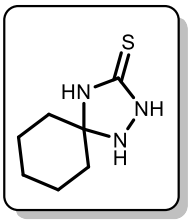
5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-one (6′d) Dark yellow solid (196.00 mg)**^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 12.43 (s, 1H), 11.16 (s, 1H), 9.00 (s, 1H), 8.64 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 179.2, 163.2, 142.9, 132.6, 131.8, 122.9, 121.5, 120.5, 111.6 **HRMS (+ESI)** calcd for $C_9H_8N_4OS$ $(M+H)^+$: 220.0439 found: 220.0451



Spiro[fluorene-9,3′-[1,2,4]triazolidine]-5′-thione (6′e) Pale yellow solid (217.66 mg) **^{1}H NMR** (400 MHz, CHLOROFORM-*D*) δ 9.72 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.38 (td, *J* = 14.2, 7.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.54 (s, 1H**)** 3.72, 2.15, 1.23= residual ethanol impurity. **^{13}C NMR** (100 MHz, CHLOROFORM-*D*) δ 179.2, 145.3, 142.7, 140.0, 136.4, 131.9, 130.7, 129.7, 128.5, 128.4, 125.9, 121.8, 121.2, 120.1 **HRMS (+ESI)** calcd for $C_{14}H_{11}N_3S$ $(M+H)^+$: 253.0701 found: 253.0719



3,4-dihydro-2H-spiro[naphthalene-1,3′-[1,2,4]triazolidine]-5′-thione (6′f) Pinkish white solid (179.67 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.10 (s, 1H), 8.25 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.23 (t, J = 6.7 Hz, 1H), 7.18–7.10 (m, 2H), 2.70–2.63 (m, 4H), 1.82–1.70 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.1, 148.2, 140.6, 132.5, 129.6, 129.0, 126.7, 125.8, 29.4, 26.3, 21.9 **HRMS (+ESI)** calcd for $C_{11}H_{13}N_3S$ $(M+H)^+$: 219.0861 found: 219.0893



1,2,4-triazaspiro[4.5]decane-3-thione (6′g) Pale yellow solid (133.48 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.11 (s, 1H), 7.93 (s, 1H), 7.47 (s, 1H), 2.34-2.37 (m, 2H), 2.25–2.11 (m, 2H), 1.64–1.42 (m, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.1, 157.4, 35.4, 27.7, 27.4, 26.2, 25.6 **HRMS (+ESI)** calcd for $C_7H_{13}N_3S$ $(M+H)^+$: 171.0845 found: 171.0863

4.2.6 REPRESENTATIVE NMR SPECTRA

Figure 4.2.1 ^{1}H NMR Spectrum of 4′f in DMSO-D_6

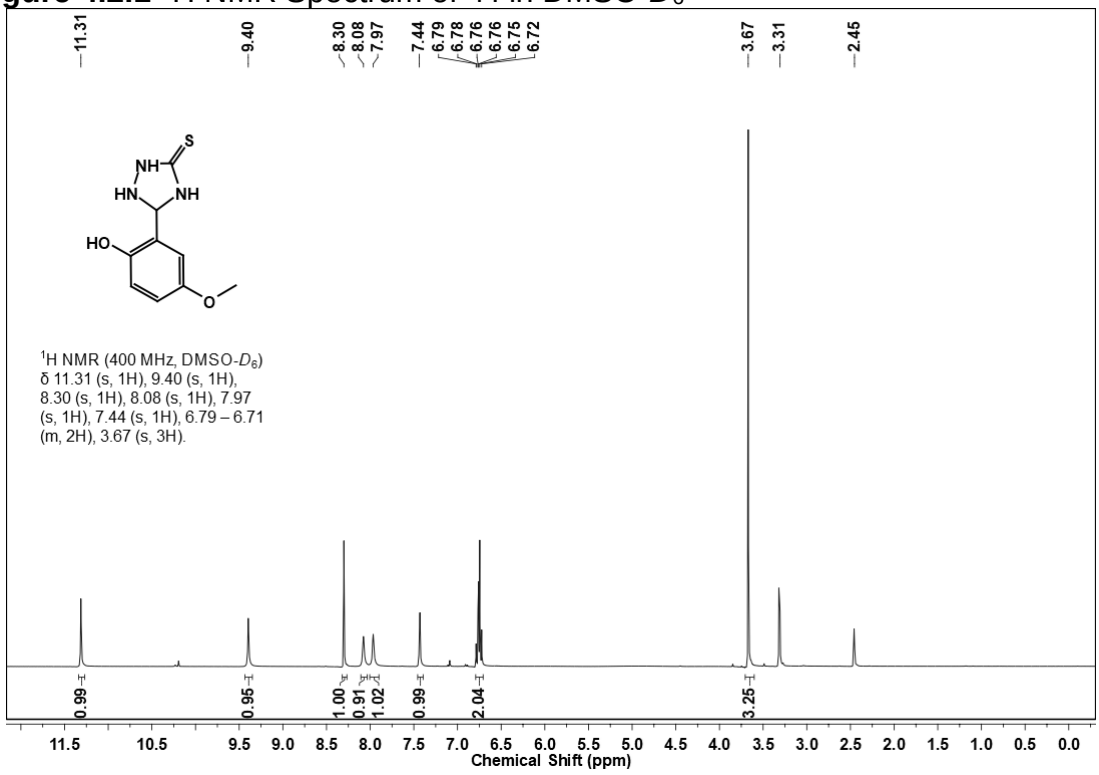


Figure 4.2.2 ^{13}C NMR Spectrum of 4′f in DMSO-D_6

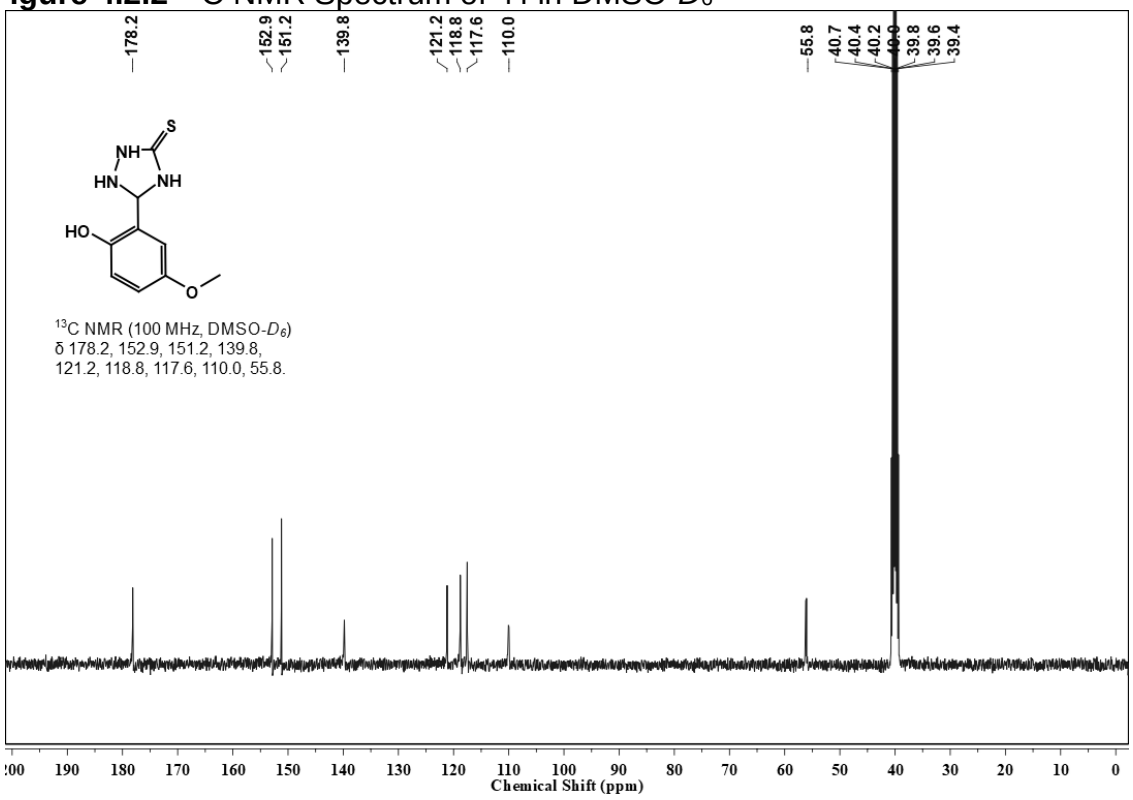


Figure 4.2.3 ^{1}H NMR Spectrum of 6′a in DMSO-D_6

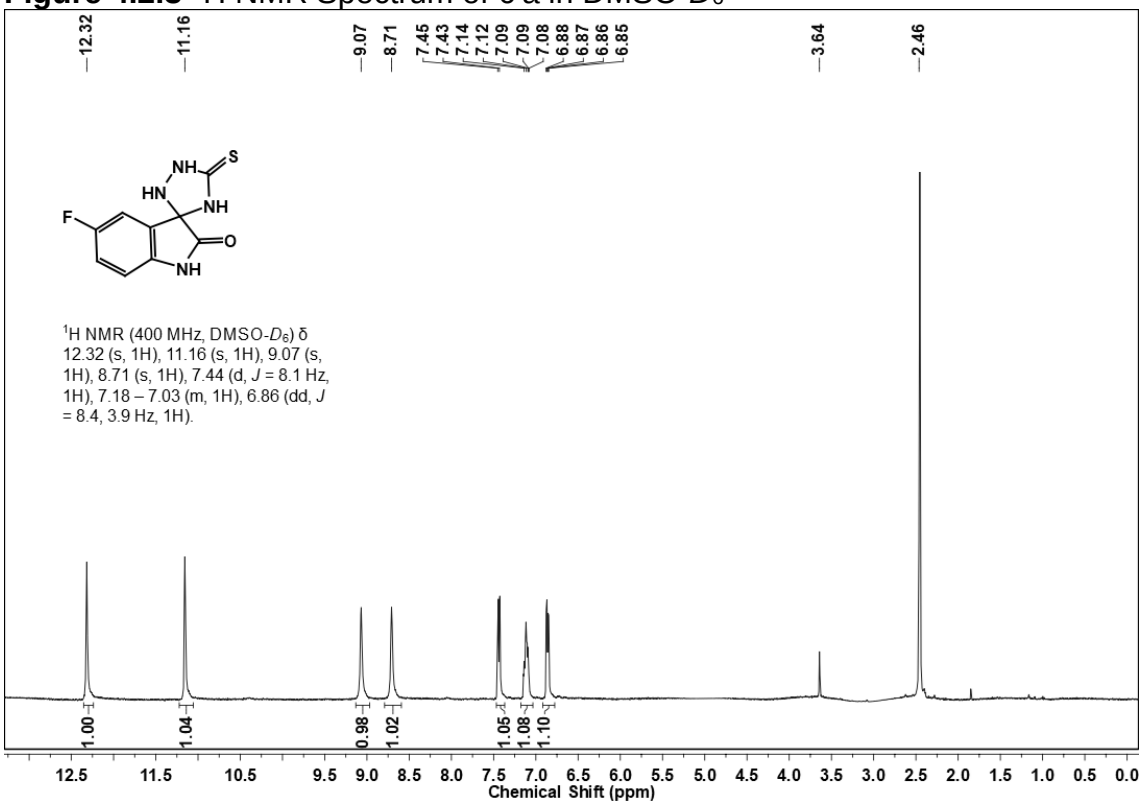
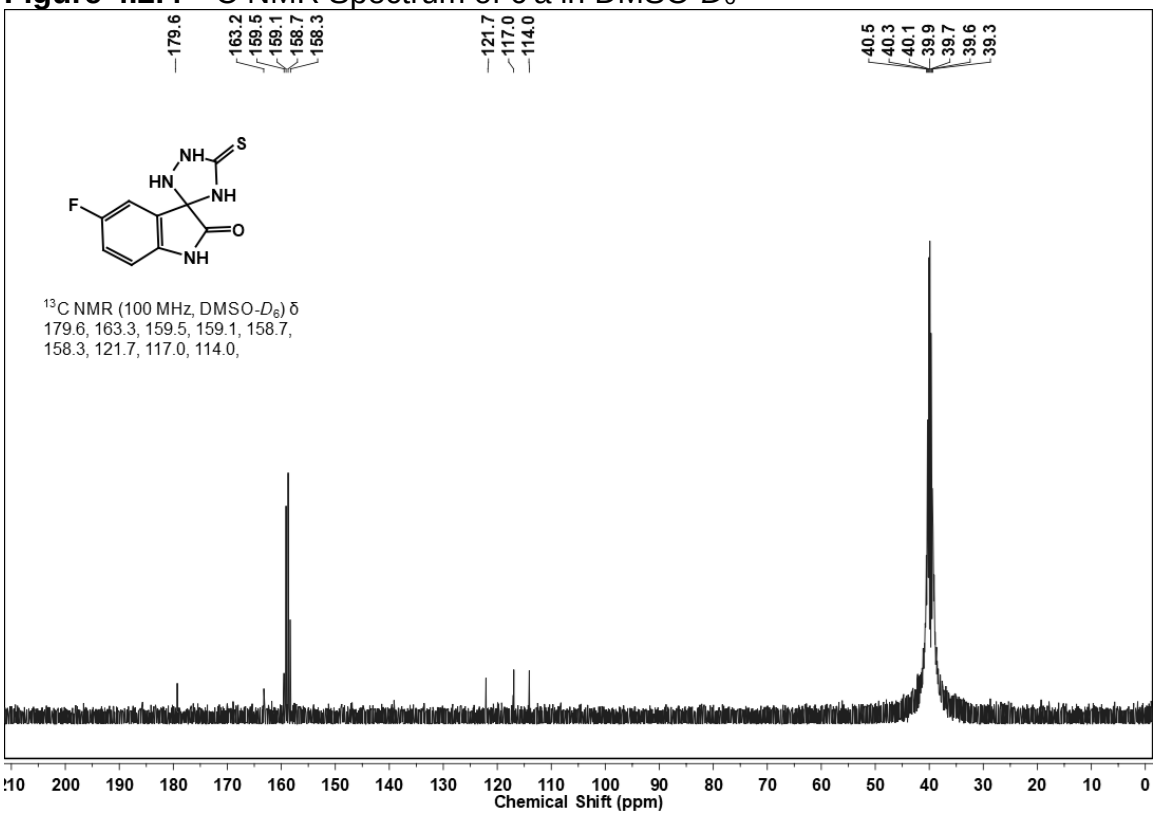


Figure 4.2.4 ^{13}C NMR Spectrum of 6′a in DMSO-D_6



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