CHAPTER-5

Efficient one-pot synthesis of substituted diphenyl 1, 3-thiazole through multicomponent reaction by using green and efficient Iron-catalyst *via* cross dehydrogenative coupling (CDC)

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5.1 Introduction

The improvement of new strategies for the catalytic activation of organic molecules is among the fundamental aims in the field of organic synthesis. Catalyst, one of the most important parts in organic synthesis and an overarching principle of sustainable chemistry, and it is capable of producing substantial material in the organic synthesis and time as well as cast of whole reaction, also a very important in the green chemistry strategies [1-7]. In this work iron, catalyst has recently received much attention in organic synthesis outstanding to ready availability, sustainability, non-toxicity, and ease of handling of reaction condition. Herein, we report the formation C-C double bonds from two C(sp^3)-H bonds *via* cross-dehydrogenative coupling reaction by the use of iron catalyst [8-13]. The use of iron catalysts in organic synthesis is attractive for many of reasons. Iron is the second most abundant metal in the earth's crust after aluminum and therefore is much cheaper than the other precious metals. On the other hand, various iron compounds are unified in biological systems. During the evolutionary process, iron metal has become a vital part of many metabolic activities. A relatively low toxicity of many iron salts played an important role as catalyst in food, cosmetics and pharmaceutical industry. Thus, iron salt is very crucial catalyst for organic synthesis.

Herein iron salt oxidized (Fe^{+2} to Fe^{+3}) by oxygen (air) instead of other chemical oxidants. This is also a green strategy for this reaction wherein air being used as oxidizing agent due to easily available, eco-friendly nature and economical profits [13-16]. In this work, the multi-component reactions (MCRs) have emerged as powerful strategy in synthetic chemistry for the design of novel organic molecule [17-19]. This work one-pot reaction proceeds as MCRs which have three easily available starting materials to design of eco-friendly and cost-effective methodologies [20-21]. Thiazole is a five-membered heterocycle moiety containing nitrogen and sulfur in a heterocycle ring. Thiazole heterocycle show various types of biological activity and this moiety found in many natural products and pharmaceuticals [22–26]. Many drugs contain thiazole core in their structure, such as fentiazac (**a**) is a non-steroidal anti-inflammatory agent [27] which use in our daily life, such as, developed for the treatment of joint and muscular pain, febuxostat (**b**) is used for urate lowering drug [28]. Similarly, Sodelglitazar (GW677954) (**c**), also known as is an inhibitor of peroxisome proliferator activated receptor delta (PPARδ) [29].

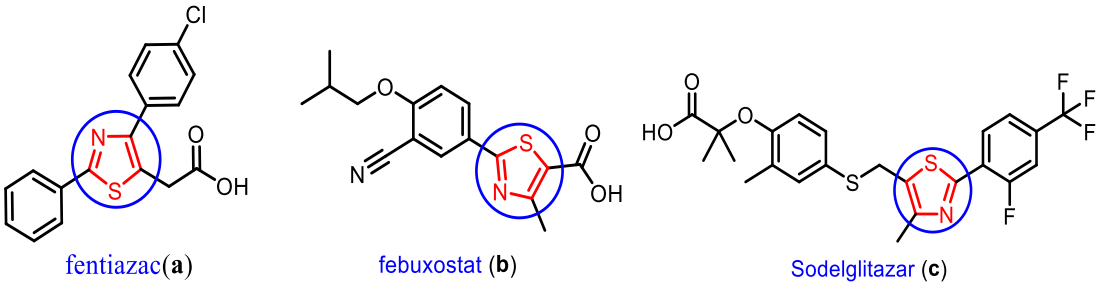


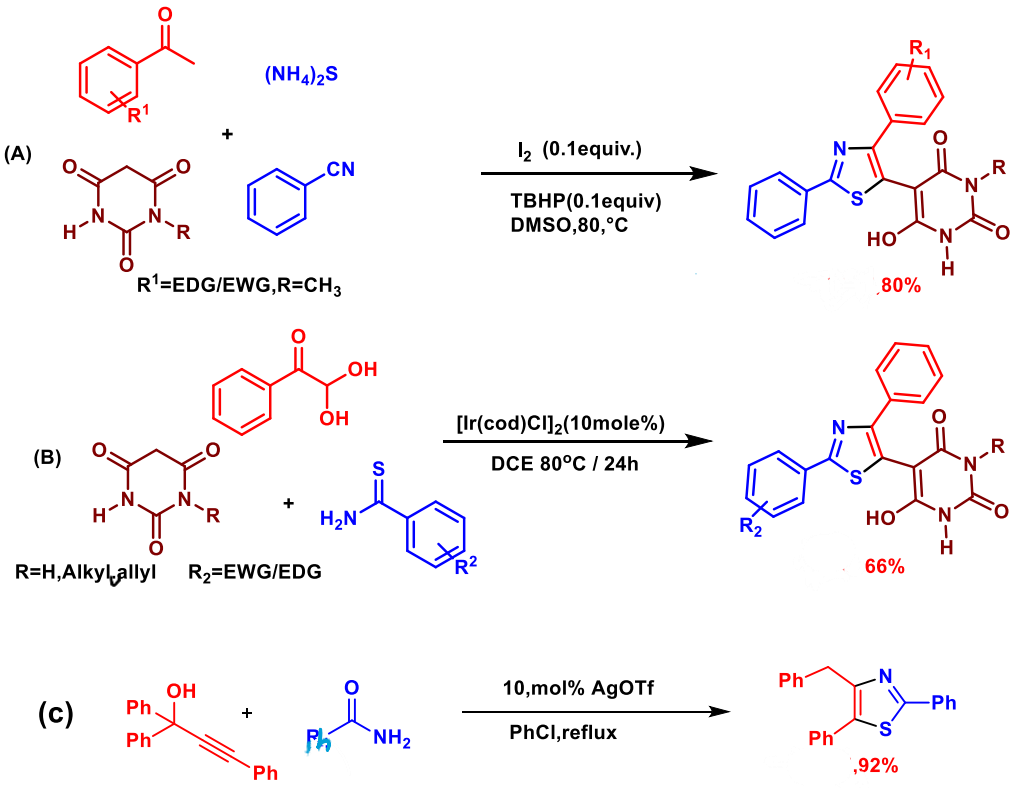
Figure 5.1 Some pharmacologically active thiazole compounds

Many chemists are interested in developing a new method for the synthesis of trisubstituted thiazole. One such method involves a two-component reaction of thioamides with propargylic alcohol, catalyzed by AgOTf, in a chlorobenzene medium under reflux conditions. This recent report by Zhan *et al* **[**30]. The synthesis of trisubstituted thiazoles was reported by Kshirsagar *et al*., wherein they conducted a two-component reaction involving a thioamide and styrene system. This reaction was carried out using NBS-water under heating conditions [31]. Murakami *et al*. used a multicomponent strategy to synthesized 2,5-disubstituted thiazoles by reacting terminal alkynes, sulfonyl azides, and thioesters with Cu(I) and Rh (II) catalysts [32]. Yan *et al*. described a two-component reaction of elemental sulphur and enaminone in the presence of ferric chloride as a catalyst in DMSO medium at high temperature (140 °C) to produce thiazole derivatives [33]. Another interesting three-component reaction using elemental Sulphur, primary amines and aldehydes was reported by Jiao *et al.* in the presence of a Cu (II) catalyst, DBU base and molecular oxygen [34]. Similarly, Deng *et a*l. synthesised trisubstituted thiazoles by combining ketones, aldehydes, ammonium halides, and elemental Sulphur (S_8) in a four-component reaction with pyridine and water at a high temperature (150 °C) and a long reaction time (20 hours) [35]. Apart from these reactions, recently, synthesis of trisubstituted thiazoles has been reported by aryl glyoxal-based multicomponent reactions in the presence of acetic acid [36], Et_3N [37] as well as under catalyst free conditions [38]. This synthesis approach involves cyclization and condensation of haloketones with thioamide, and it is considered the most widely popular process for the synthesis of thiazole moiety. Also, Cook-Heilbron used versatile methods for

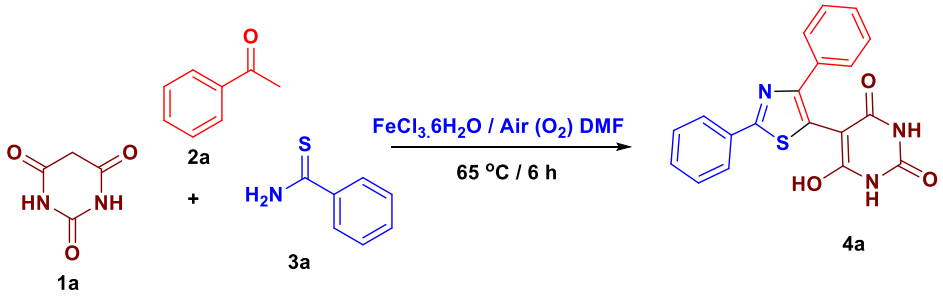
the synthesis of substituted aminothiazoles involving the reaction of α-aminonitriles with dithioacids or esters, carbon disulfide, carbonyl sulfide, and isothiocyanates under mild conditions [39-40]. Although all these methods can be considered useful for the synthesis of diverse thiazole derivatives, it must be noted that they are not exactly the greenest options out there. Metal catalysts tend to get involved, high temperatures are required along with a lengthy reaction time, and chlorinated solvents make an appearance, among other not-so-eco-friendly aspects. To the best of our knowledge, there is no available reported method in the literature for the synthesis of substituted thiazoles linked with aryl and barbituric acid moieties. In view of above points and in continuation of our interest was to develop more convenient and eco-friendly protocol for the construction of biologically potent heterocycles. We aimed to develop a new protocol for the synthesis of trisubstituted thiazole derivatives by the reaction of barbituric acid, acetophenone and aryl thioamides in the presence $FeCl_3.6H_2O$ and O_2(Air) in DMF solvent.

A comparison of the previous and present methodologies is illustrated in **scheme 5.1Aand 5.1B**.

Previous methods: 5.1 (A)



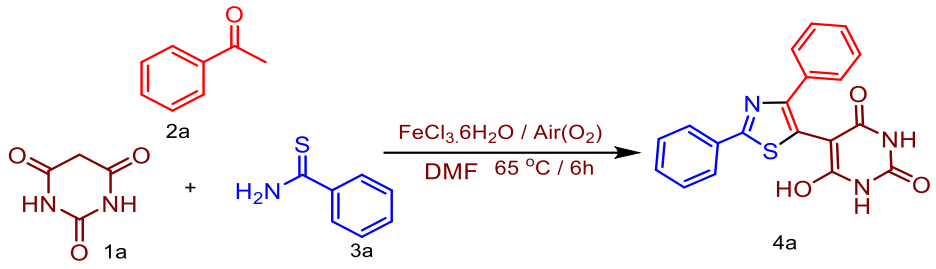
Present Approach:5.1(B)



Scheme 5.1: Previous (5.1A) & present (5.1B) method for the synthesis of trisubstituted thiazole.

5.2 Result Discussion

5.2.1 Optimization of Reaction Conditions: We have started our experiments by taking barbituric acid **(1)**, acetophenone **(2)** and aryl thioamides **(3)** as the model substrates for the synthesis of trisubstituted thiazole using iron salt as a catalyst in the presence air (O_2) and DMF as reaction medium **(scheme 2).**



Scheme 5.2. Model reaction for the synthesis of trisubstituted thiazole

Further, we have used different types of catalyst with solvents to improve the result of our experiment. Initially we have used EtOH as solvent without catalyst at RT and observed no yield of the product (**Table 5.1, Entry 1**). Next the experiment was held with AcOH and no yield was obtained (**Table 5.1, Entry 2**) but with MeOH trace of the reaction (**Table 5.1, Entry 3**) was obtained. Next, we used $Fe(OAc)_2$ as a catalyst with DMF yield increase and obtained 38 % but that is not good yields of this reaction (**Table 5.1, Entry 5**). In our efforts to increase the yield of the product, we performed the reaction using $FeBr_3$ / Air (O_2) in DMF at 65 ^oC, which led to a conspicuous increase in yield 69% within 6 h (**Table 5.1, Entry 6**),

but when experiment was held **$FeCl_3.6H_2O$ / Air(O_2)** in DMF at 65 ^oC to get excellent yield (84 %) of the products of this reaction (**Table 5.1, Entry 7).** Finally, we observed that $FeCl_3.6H_2O$ / Air(O_2) in DMF at 65 ^oC was the most effective promoter for the formation of the corresponding product in terms of both the reaction time and yield (**Table 5.1, Entry 8-9**).

Table 5.1. Screening of the reaction conditions for the synthesis of compound.[a]

Entry	catalyst system	Solvent	Temp. (^OC)	Time (hour)	Yields (%)[b]
1	------	EtOH	RT	10	NA
2	------	AcOH	RT	10	NA
3	------	MeOH	RT	10	Trace
4	------	DMF	RT	10	28
5	$Fe(OAc)_2$	DMF	65	6h	38
6	$FeBr_3$ / Air (O_2)	DMF	65	6	69
7	**$FeCl_3.6H_2O$ / Air(O_2)**	**DMF**	**65**	**6**	**84**
8	$FeCl_3.6H_2O$ / Air(O_2)	DMSO	65	6	62
9	$FeCl_3.6H_2O$ /Air(O_2)	DMF	65	8	84

[a]**Reaction conditions:** barbituric acid **1a** (1.0 mmol), acetophenone **2a** (1.0 mmol) and aryl thioamides **3a** (1.0 mmol). [b]Yields of isolated pure product.

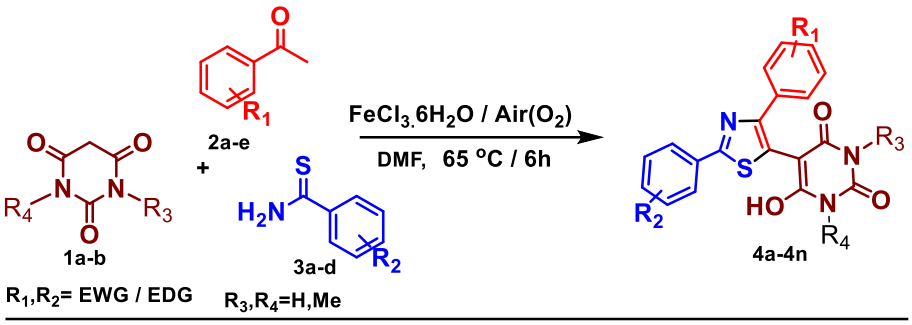
After the optimization of catalyst, we investigate the amount of catalyst. Using 5 mole% of iron salt resulted in a lower product yield (**Table 5.2, entry 1**). The amount of catalyst for the model reaction was then increased to 10% iron salt $FeCl_3.6H_2O$., and we found extraordinary yield which is 84%. (**Entry 2 in Table 5.2**). Subsequently, the product yield was not significantly increased by the catalyst loading of 12 to 15 moles (**Table 5.2, entries 3 & 4**).

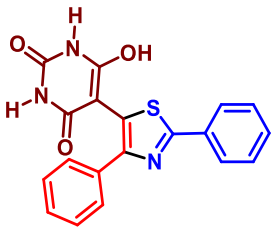
Table 5.2: Screening of the amount of catalyst system for the synthesis of compound.

Entry	Catalyst System (Mole %)	Yield of product[b] (%)
1	$FeCl_3.6H_2O$ (5)	76
2	**$FeCl_3.6H_2O$ (10)**	84
3	$FeCl_3.6H_2O$ (12)	84
4	$FeCl_3.6H_2O$ (15)	84
[a]**Reaction conditions:** barbituric acid **1a** (1.0 mmol), acetophenone **2a** (1.0 mmol) and aryl thioamides **3a** (1.0 mmol). [b]Yields of isolated pure product.		

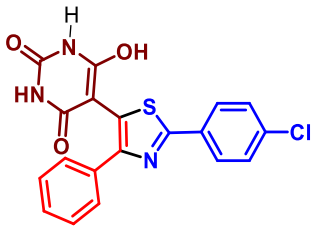
After screening of the reaction conditions, to delineate this approach, to develop substrate scope for the synthesis of trisubstituted thiazole derivatives in (**Table 5.3**). There are total of fourteen derivatives of trisubstituted thiazole were synthesized. The above one-pot sequential protocol was synthesized by using different acetophenone derivatives, aryl thioamides derivatives and barbituric acid derivatives were chosen for library validation.

Table 5. 3: Screening of the substrate scope.[a-b]

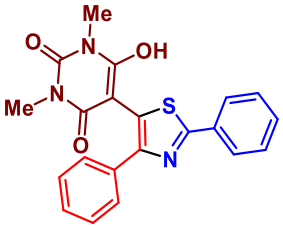




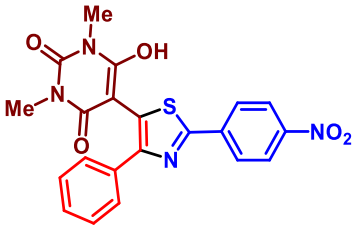
4a, 84%



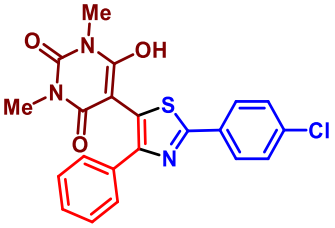
4b, 82%



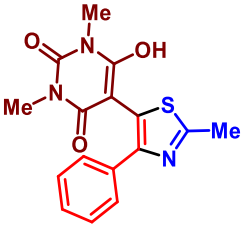
4c, 80%



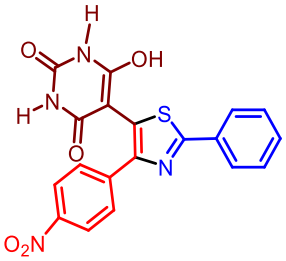
4d, 74%



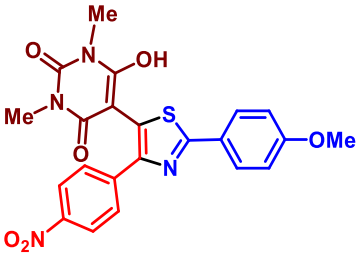
4e, 82%



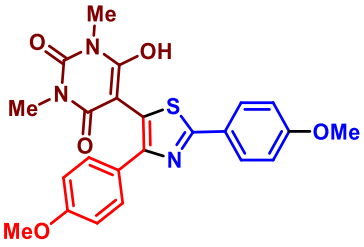
4f, 68%



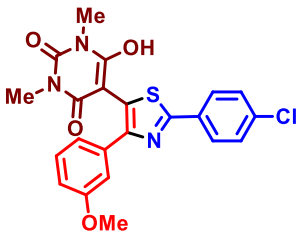
4g, 77%



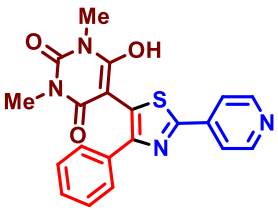
4h, 85%



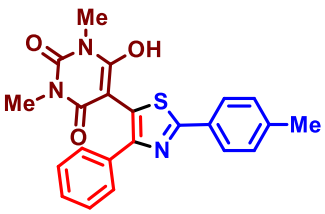
4i, 78%



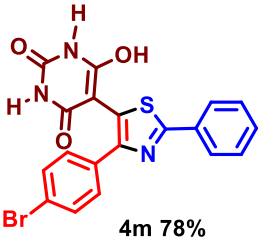
4j, 71%



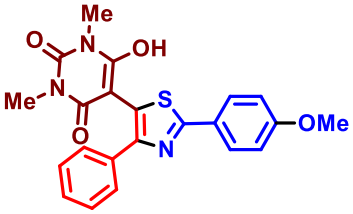
4k, 73%



4l, 80%



4m 78%



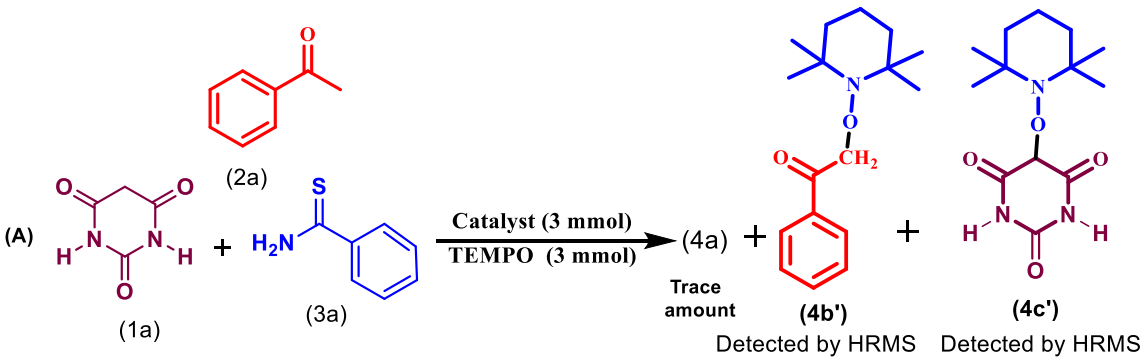
4n, 78%

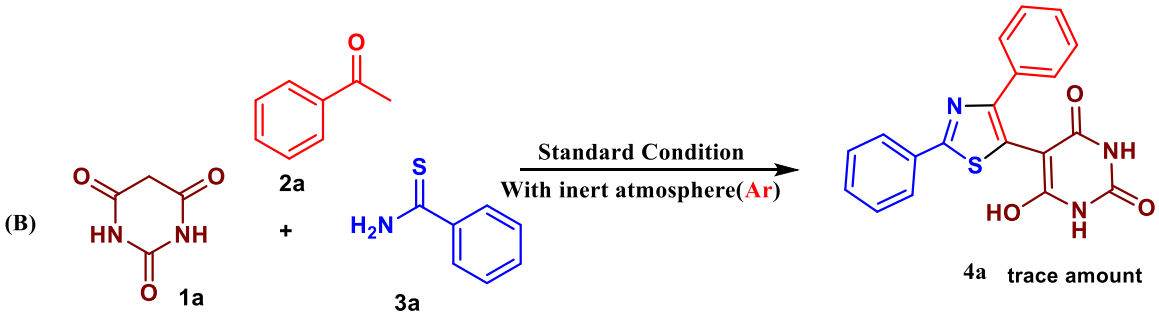
[a] **Reaction conditions**: barbituric acid 1a (1.0 mmol), acetophenone 2a (1.0 mmol) and aryl thioamides 3a (1.0 mmol). [b]Yields of isolated pure product.

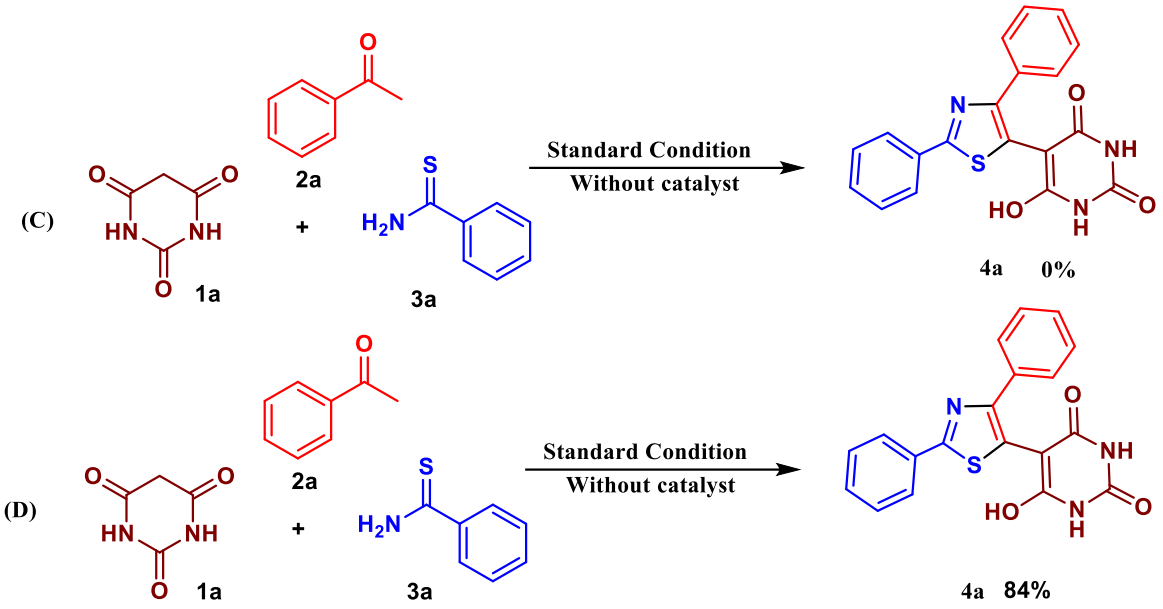
5.2.2 Controlled Experiments and Mechanistic studies

A control experiment was performed between barbituric acid 1a (1.0 mmol), acetophenone 2a (1.0 mmol) and thioamides 3a (1.0 mmol), using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as radical trapping agent and it was observed that TEMPO quench the reaction. This shows that reaction proceed via radical intermediate and this observation was confirmed by the **HRMS** spectra (**scheme 5.3A**). Next control reaction was performed under the inert atmosphere (argon) to give only trace amount of **4a** was obtained (**scheme 5.3B**). This result signifies the importance of air (molecular oxygen). Air can be considering as diluted oxygen, thus help the oxidation of Fe(II) to Fe(III), Further next control reaction was performed

without catalyst which failed to give the product (**scheme 5.3 C**). This indicates that acetophenone is not converted into acetophenone radical intermediate without iron salt as a catalyst in the presence **air** and **DMF** as promoting medium. when the same reaction was carried out in the presence of iron salt as catalyst to give desired product was obtained in 84% yield (**scheme 5.3 D**). These results indicate that catalyst not only take part in the oxidation of acetophenone but also converts later to alpha β-unsaturated carbonyl compound through Michael addition reaction.





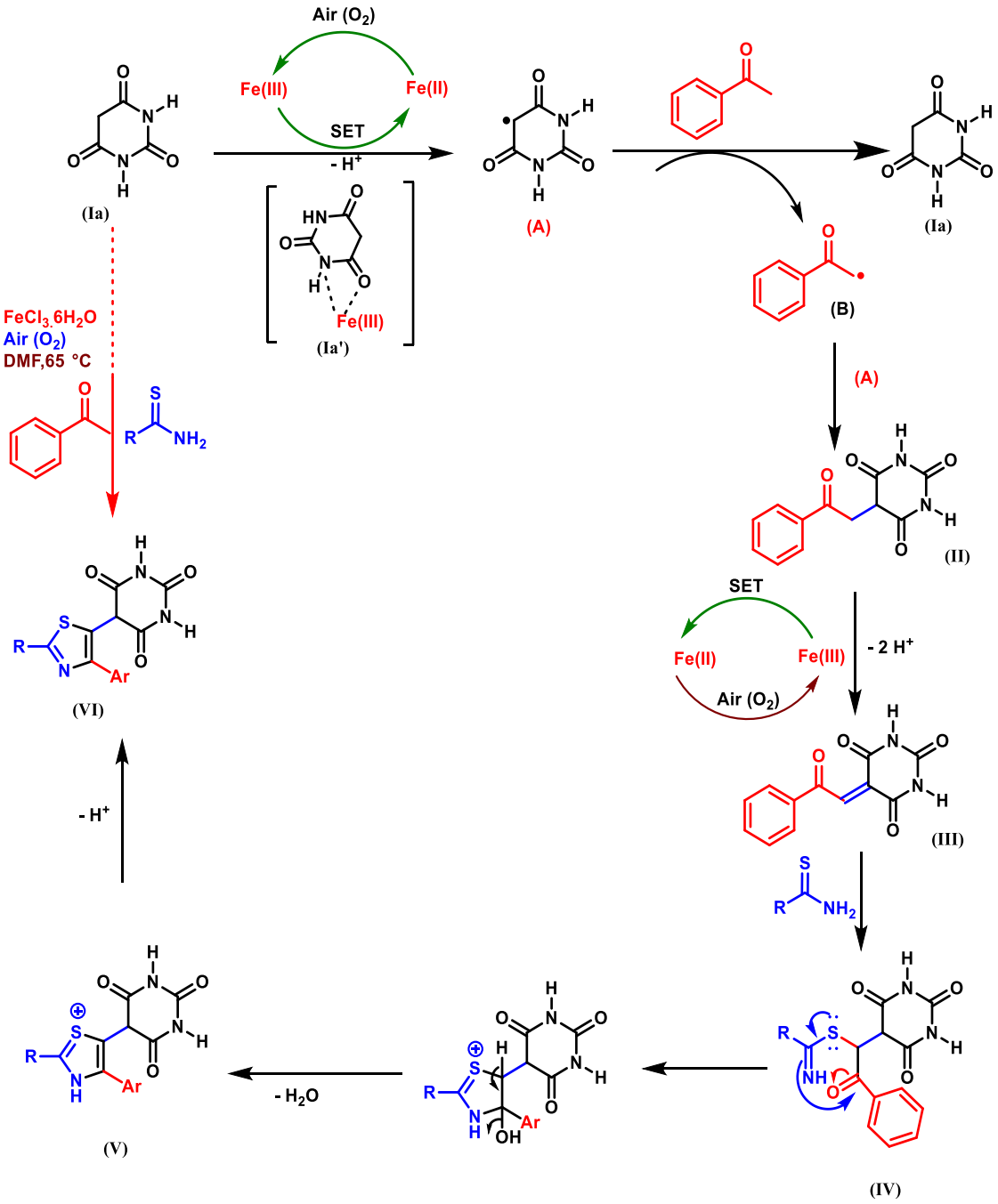


Scheme 5.3 Control experiment using TEMPO as radical trapping agents

5.2.3 Plausible Reaction Mechanism

Based on the above-mentioned control experiment and in accordance with the literature survey [41-43], a plausible reaction mechanism was proposed as shown in **Scheme 5.4**. The reaction proceeds with the formation of an intermediate **(A)** from the sp^3 carbon of barbituric acid (**I a**) when reacted with an iron catalyst system **($FeCl_3.6H_2O$)** in presence of air **(O_2) via SET** (single electron transfer) to give the radical intermediate **(A)** and loss of H^+ while at the same time Fe (II) is formed[**42b**]. In this step substrate (**Ia**) act as auxiliary ligand with **Fe (III)** leading to a chelate **Fe** complex (**Ia'**) which may play a key role in the oxidation step of (**Ia**) to **A** (Tan, Zhi-Yu, et al.). Intermediate **(A)** reacts with acetophenone to form the carbon radical intermediate **(B)**. Intermediate **(B)** coupled with **'A'** to form **(II)** and molecule

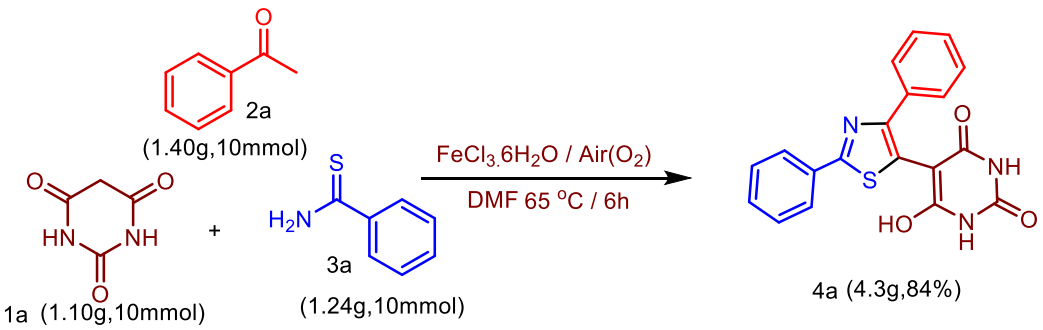
(II) was oxidized to provide the moiety **(III)** via two single-electron transfers **(SET)** and removal of two H^+ moiety **(III)** reacts with aryl thioamides undergo Michael addition to form **(IV)** then it undergoes hetero cyclization followed by removal of the water molecule to form **(V)** and fallowed by aromatization to give **thiazole (VI)**



Scheme 5.4 Plausible mechanism for the formation of trisubstituted thiazole.

5.3 Gram-scale synthesis of trisubstituted thiazole derivatives.

To establish the potential synthetic application of this methodology the synthesis of substituted diphenyl 1, 3-thiazole (**4a**) was carried out on gram scale with barbituric acid (**1a**) (**1.10** g, 10 mmol), acetophenone (**2a**) (**1.40** g, 10 mmol) and thioamide **(3a) (1.24** g,**10** mmol) using iron salt (**5** mg,10 mmol) under optimized reaction conditions gave desired products (**4a**) in **84%** yield (**4.3** g). at **55** °C using iron salt as a catalyst in the presence air and DMF as promoting medium. A model reaction is documented herein (**Scheme 5.5)**.



Scheme 5.5 Gram-scale synthesis of trisubstituted thiazole.

5.4 Experimental Section

5.4.1 General Procedure for the synthesis of trisubstituted thiazole derivative (3a-3l)

All chemicals were purchased from Aldrich and Alfa Assar and were used without purification. IR spectra were recorded on a Perkin Elmer Spectrum RX-IFTIR spectrometer. NMR spectra were recorded on a BRUKER AVANCE II-400FT spectrometer (400 for ^{1}HNMR,) using DMSO-*d6* as solvent and TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Elemental analyses were

carried out in a coleman automatic carbon, hydrogen, and nitrogen analyzer. All the reactions were monitored by TLC using pre-coated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254). Melting points were determined by the open glass capillary method and were uncorrected.

5.4.2 Procedure for the synthesis of 1,3-trisubstituted thiazole derivative (4a-4s)

Preparation of Compound 4a: Typically, we have started our experiments by taking barbituric acid (1.0 mmol) and acetophenone (1.0 mmol) which were stirred in a 50 ml round bottom flask at 65 ^{o}C using $FeCl_3.6H_2O$ (10 mmol) as a catalyst in DMF. After 4.5 hours, aryl thioamides (1.0 mmol) were then successively added. Subsequently, the reaction was completed in the next 1.5 hours. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. The crude products were purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent.

5.5. Analytical data

5.5.1 Analytical data of 1,3-trisubstituted thiazole derivative

6-hydroxy-5-(2,4-diphenylthiazol-5-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (4a):

Yield (84%); m.p. 324-326 ^{o}C. **IR** (KBr, *v* cm^{-1}) 3164, 3029, 1686, 1662, 1574, 1495, 1447, 1426, 1362, 1208, 922, 817, 762, 687 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 11.02 (s, 2H, NH), 7.98 (d, *J* = 8.0 Hz, 2H, ArH), 7.74 (d, *J* = 4.0 Hz, 2H, ArH), 7.54 – 7.47 (m, 3H, ArH), 7.42 (t, *J* = 8.0 Hz, 2H, ArH), 7.31 (t, *J* = 8.0 Hz, 1H, ArH), 4.22 (1H, OH). **^{13}C NMR** (100

MHz, DMSO-*d6*) δ 164.8, 162.8, 154.2, 149.1, 136.0, 134.32, 131.1, 130.2, 127.4, 126.6, 128.3, 126.7, 124.1, 81.0 ppm. **HRMS** (ESI): m/z [M+H$^+$] Calc. for $C_{19}H_{14}N_3O_3S$, 364.0750; Obser.: 364.0744.

5-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-6-hydroxypyrimidine-2,4(1*H*,3*H*)-dione (4b): Yield 82%; m.p. 329-331 ºC; **IR** (KBr, *v*,cm^{-1}) : 3054, 1694, 1565, 1512, 1454, 1396, 1094, 827, 777, 765, 689 cm-^{1}; **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 11.01 (s, 2H, NH), 8.02 (d, *J* = 8.0 Hz, 2H, ArH), 7.74 (d, *J* = 8.0 Hz, 2H, ArH), 7.58 (d, *J* = 8.0 Hz, 2H, ArH), 7.41 (d, *J* = 4.0 Hz, 2H, ArH), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 4.01 (bs, OH), 3.18 (s, ^{1}H, CH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.2, 162.7, 154.3, 151.0, 135.7, 136.6, 134.2, 130.2, 127.2, 128.7, 126.7, 128.2, 124.7, 82.7, ppm. **HRMS** (ESI): m/z [M+H$^+$] Calc. for $C_{19}H_{13}ClO_3N_3S$, 398.0361; Obser.: 398.0355.

6-hydroxy-1,3-dimethyl-5-(2,4-diphenylthiazol-5-yl)-pyrimidine-2,4(1*H*,3*H*)-dione(4c): Yield 80%; m.p. 264-266 ºC; IR (KBr, *v*, cm^{-1}): 3482, 3051, 1688, 1677, 1564, 1485, 1418, 1381, 1247, 1139, 1018, 780 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-*d6*) δ = 7.96 (d, *J* = 8.0 Hz, 2H, ArH), 7.75 (d, *J* = 8.0 Hz, 2H, ArH), 7.55 -7.47 (m, 3H, ArH), 7.36 (t, *J* = 8.0 Hz, 2H, ArH), 7.29 (t, *J* = 8.0 Hz, 1H, ArH), 4.67 (bs, OH), 4.37 (bs, CH), 3.16 (s, 6H, NCH_3), **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 166.0, 161.4, 151.0, 152.2, 134.1, 134.2, 131.2, 128.4, 129.2, 129.1, 128.4, 126.7, 82.4, 29.1 ppm. **HRMS** (ESI) Calc. for $C_{21}H_{18}N_3O_3S$ [M+H$^+$] 392.1063, Obser.: 392.1044.

6-hydroxy-1,3-dimethyl-5-(2-(4-nitrophenyl)-4-phenylthiazol-5-yl) pyrimidine2,4(1H,3H) dione (4d):

Yield 74%; m.p. 233-235 ºC; IR (KBr, *v*, cm^{-1}): 2952,1705, 1597, 1555, 1524, 1505, 1458, 1359, 1312, 1275, 1253, 1182, 1138, 1085, 1031, 995,947, 854, 803, 764 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-*d6*) δ = 8.35 (d, *J* = 10.0 Hz, 2H, ArH),8.22 (d, *J* = 10.1 Hz, 2H, ArH), 7.76 (d, *J* = 10.0Hz, 2H, ArH), 7.39-7.34 (m, 2H, ArH), 7.28(d, *J* = 10.0 Hz, 1H, ArH), 4.01 (bs, OH), 3.12 (s, 6H, NCH_3); **^{13}C NMR** (100 MHz, DMSOd_6) δ = 162.4, 161.3, 153.8, 152.5, 146.8, 140.0, 136.3, 128.8, 129.0, 128.4, 126.5, 127.6, 125.6, 82.1, 29.0 ppm. **HRMS** (ESI) Calc. for $C_{21}H_{17}N_4O_5S$ [M+H^+] 437.0914, Obser.: 437.0921.

5-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4e): Yield 82%; m.p. 261-263 ºC; **IR** (KBr, *v*,cm^{-1}): 3102, 1704,1602, 1501, 1187, 1088, 997, 835,764,701 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 7.98 (d, *J*= 8.0 Hz, 2H, ArH), 7.73 (d, *J* = 8.0 Hz, 2H, ArH), 7.52 (d, *J* = 8.0 Hz, 2H, ArH), 7.35 (t, *J* =8.0 Hz, 2H, ArH), 7.27 (t, *J* = 8.0 Hz, 1H, ArH), 4.02 (1H, OH), 3.14 (s, 6H, NCH_3); **^{13}C NMR**(100 MHz, DMSO-*d6*) δ 162.4, 161.3, 151.5, 150.3, 136.0, 133.5, 133.0, 130.1, 129.0, 126.6, 126.5, 125.4, 82.3, 29.0 ppm. **HRMS** (ESI): m/z [M+H^+] Calc. for $C_{21}H_{17}ClO_3N_3S$, 426.0674; Obser.: 426.0688.

6-hydroxy-1,3-dimethyl-5-(2-methyl-4-phenylthiazol-5-yl)-pyrimidine-2,4(1*H*,3*H*)-dione(4f): Yield 68%; m.p. 315-318 ºC; **IR** (KBr, *v*,cm^{-1}): 2941, 1742, 1675, 1621, 1559, 1438, 1421, 1382, 1243, 1136, 981, 842 cm^{-1}.**^{1}H NMR** (400 MHz, DMSO-*d*6) δ = 7.51 (d, *J* = 8.0 Hz, 2H, ArH), 7.34 (t, *J* = 8.0 Hz, 2H, ArH), 7.29 (t, *J* = 8.0 Hz, 1H, ArH), 3.08 (s, 6H,

NCH_3), 2.81 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, DMSO-*d*6) δ = 165.6, 161.1, 160.6, 152.4, 133.4, 127.4, 127.0, 126.5, 81.0, 25.6, 14.9 ppm. **HRMS** (ESI) Calc. for $C_{16}H_{16}N_3O_3S$ [M+H$^+$] 330.0907, Obser.: 330.0932.

6-hydroxy-5-(4-(4-nitrophenyl)-2-phenylthiazol-5-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (4g): Yield 78%; m.p. 301-303 ºC; **IR** (KBr, *v*,cm^{-1}): 3425, 2946, 2786, 1736, 1655, 1572, 1515, 1483, 1386, 1335, 1217, 1107, 1066, 852 cm^{-1}.**^{1}H NMR** (400 MHz, DMSO-d_6) δ =10.91 (s, 2H, NH), 8.27 (d, *J* = 8.0Hz, 2H, ArH), 8.02 (t, *J* = 8.0Hz, 4H, ArH), 7.53 (d, *J* = 8.1 Hz, 3H, ArH), 4.82 (bs, OH),; **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 165.6, 162.7, 151.13, 151.06, 145.1, 142.7, 134.0, 131.3, 125.3, 127.2, 126.8, 124.2, 124.5, 82.6 ppm. **HRMS** (ESI) Calc. for $C_{19}H_{13}N_4O_5S$ [M+H$^+$] 409.0601, Obser.: 409.0578.

6-hydroxy-5-(2-(4-methoxyphenyl)-4-(4-nitrophenyl)thiazol-5-yl)-1,3dimethylpyrimidine-2,4(1*H*,3*H)* dione (4h): Yield 85%; m.p. 308-310 ºC; **IR** (KBr, *v*, cm^{-1}): 2975, 1738, 1664, 1595, 1572, 1518, 1504, 1423, 1344, 1265, 1191, 1015, 842 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.21 (d, *J* = 8.0 Hz, 2H, ArH), 8.02 (d, *J* = 8.0 Hz, *2*H, ArH), 7.92 (d, *J* = 8.1 Hz, 2H, ArH), 7.07 (d, *J* = 8.0, 2H, ArH), 4.91 (bs, OH), 3.83 (s, 3H, OCH_3), 3.14 (s, 6H, NCH_3); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 165.7, 161.8, 159.4, 152.2, 147.2, 144.8, 143.2, 128.7, 127.3, 126.5, 125.0, 122.3, 115.7, 82.5, 56.3, 29.0 ppm. **HRMS** (ESI) Calc. for $C_{22}H_{19}N_4O_6S$ [M+H$^+$] 467.1020, Obser.: 467.1025.

5-(2,4-bis(4-methoxyphenyl)-thiazol-5-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1h,3h)-dione (4i): Yield 77%; m.p. 257-259 ºC; **IR** (KBr, *v*, cm^{-1}): 2946, 2840, 1684, 1620, 1566, 1507, 1441, 1247, 1184, 1028, 832 cm^{-1}. **^{1}H NMR** (400 MHz, **DMSO-d_6**) δ =

7.92 (d, *J* = 8.0 Hz, 2H, ArH), 7.68 (d, *J* = 8.0 Hz, *2*H, ArH), 7.08 (d, *J* = 8.0 Hz, 2H, ArH), 6.94 (d, *J* = 8.0, 2H, ArH), 5.05 (bs, OH), 3.83 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.15 (s, 6H, NCH_3); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 163.4, 161.7, 162.5, 157.5, 152.5, 153.6, 127.7, 127.8, 126.5, 126.4, 116.5, 114.5, 82.4, 56.5, 55.8, 26.8 ppm. **HRMS** (ESI) Calc. for $C_{23}H_{22}N_3O_5S$ [M+H$^+$] 452.1274, Obser.: 452.1270.

5-(2-(4-chlorophenyl)-4-(3-methoxyphenyl)thiazol-5-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4j): Yield 76%; m.p. 279-281 °C; **IR** (KBr, *v*,cm^{-1}): 2960, 1708, 1602, 1575, 1498, 1478, 1235, 1190, 1087, 1046, 1002, 764, cm-^{1}. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.97 (d, *J* = 8.0 Hz, 2H, ArH), 7.58 (d, *J* = 4.0 Hz, 2H, ArH), 7.32-7.24 (m, 3H, ArH), 6.85 (d, *J* = 8.0 Hz, 1H, ArH), 4.35 (bs, OH), 3.72 (s, 3H, OCH_3), 3.16 (s, 6H, NCH_3); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 164.1, 161.7, 160.1, 152.5, 135.6, 135.7, 131.2, 130.4, 129.0, 128.4, 127.5 121.2, 112.4, 111.9, 82.0, 55.7, 27.2 ppm. **HRMS** (ESI) Calc. for $C_{22}H_{19}N_3O_4SCl$ [M+H$^+$] 456.0779, Obser.: 456.0781.

6-hydroxy-1,3-dimethyl-5-(4-phenyl-2-(pyridin-4-yl)thiazol-5-yl)pyrimidine-2,4(1*H*,3*H*)-dione (4k). Yield 73%; m.p. 324-326 °C; IR (KBr, *v*, cm^{-1}): 3070, 3033, 1684, 1608, 1547, 1481, 1433, 1411, 1084, 972 cm-1. **^{1}H NMR** (400 MHz, DMSO-d6) δ = 8.79 (d, *J* = 4.0 Hz, 2H, ArH), 8.30 (d, *J* = 4.0, 2H, ArH), 7.75 (d, *J* = 8.0 Hz, 2H, ArH), 7.31 (t, *J* = 8.0 Hz, 2H, ArH), 7.22 (t, *J* = 8.0 Hz, 1H, ArH), 3.80 (bs, OH), 3.10 (s, 6H, NCH_3); **^{13}C NMR** (100 MHz, DMSO-d6) δ =160.5, 154.1, 152.3, 151.9, 147.3, 143.0, 139.5, 136.9, 127.6, 127.1, 126.8, 121.1, 81.6, 27.3 ppm. **HRMS** (ESI) Calc. for $C_{20}H_{17}N_4O_3S$ [M+H$^+$] 393.1015, Obser.: 393.1002.

6-hydroxy-1,3-dimethyl-5-(4-phenyl-2-(*p*-tolyl) thiazol-5-yl) pyrimidine-2,4(1*H*,3*H*)-dione(4l): Yield 82%; m.p. 271-273 °C; IR (KBr, *v* cm^{-1}): 2952, 1705, 1607, 1488, 1186, 1089, 998, 816 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-*d*6) δ = 7.87 (d, *J* = 8.0 Hz, 2H, ArH), 7.74 (d, *J* = 8.0 Hz, 2H, ArH), 7.39-7.28 (m, 5H, ArH), 3.17 (s, 6H, NCH_3), 2.38 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, DMSO-*d*6) δ = 165.2, 160.3, 151.6, 151.0, 140.1, 134.9, 130.3, 129.8, 128.1, 127.53, 127.46, 125.9, 125.0, 81.7, 28.2, 20.9 ppm. **HRMS** (ESI) Calc. for $C_{22}H_20N_3O_3S$ [M+H^+] 406.1219, Obser.: 406.1202

5-(4-(4-bromophenyl)-2-phenylthiazol-5-yl)-6-hydroxypyrimidine-2,4(1H,3H)-dione (4m): Yield 78%; m.p. 339-341 °C; **IR** (KBr, *v*,cm^{-1}): 3119, 2973, 2789, 1674, 1573, 1485, 1421, 1404, 1385, 1212, 1077, 756 cm^{-1}.**^{1}H NMR** (400 MHz, DMSO-*d6*) δ =10.97 (s, 2H, NH), 7.98 (d, *J* = 8.0 Hz, 2H, ArH), 7.69 (d, *J* = 12.0 Hz, 2H, ArH), 7.61 (d, *J* = 8.0 Hz, 2H, ArH), 7.55-7.50 (m, 3H, ArH), 4.14 (bs, OH),; **^{13}C NMR** (100 MHz, DMSO-*d*6) δ = 165.7, 161.8, 151.7, 150.0, 134.4, 133.1, 131.2, 130.2, 129.4, 129.3, 125.9, 124.3, 120.8, 81.7 ppm. **HRMS** (ESI) Calc. for $C_{19}H_{13}N_3O_3BrS$ [M+ H^+]441.9856, Obser.: 441.9844.

6-hydroxy-5-(2-(4-methoxyphenyl)-4-phenylthiazol-5-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4n): Yield 78%; m.p. 260-262 °C; **IR** (KBr, *v*, cm^{-1}): 2971, 1739, 1674, 1601, 1522, 1453, 1374, 1253, 1177, 1025, 914 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.93 (d, *J* = 8.0 Hz, 2H, ArH), 7.74 (d, *J* = 4.0 Hz, 2H, ArH), 7.35 (t, *J* = 8.0 Hz, 2H, ArH), 7.31 (d, *J* = 4.0 Hz, 1H, ArH), 7.01 (d, *J* = 8.0 Hz, 2H, ArH), 4.45 (bs, OH), 3.83 (s, 3H, OCH_3) 3.15 (s, 6H, NCH_3); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 162.7, 161.5, 160.5, 152.3, 151.6, 136.7,

127.5, 126.8, 126.8, 124.5, 124.5, 115.3, 82.5, 56.3, 27.2 ppm. **HRMS** (ESI) Calc. for $C_{22}H_{20}N_3O_4S$ [M+H$^+$] 422.1169, Obser.: 422.1176.

5.6 Some spectrum of intermediates and 1,3-trisubstituted thiazole derivatives of ^{1}H NMR,^{13}C NMR and HRMS.

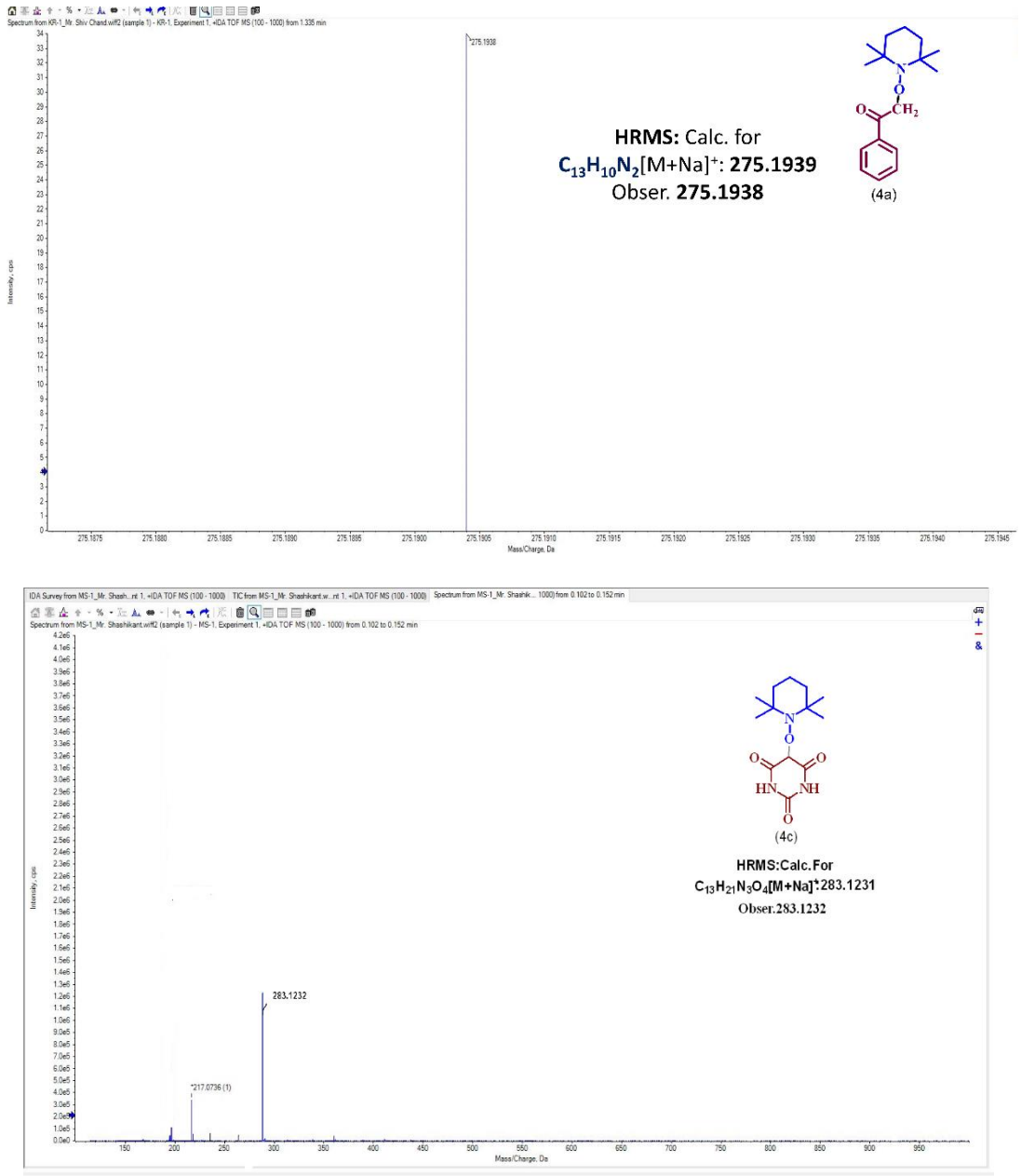


Figure 5.2 HRMS spectra of 4b' and 4c' compounds.

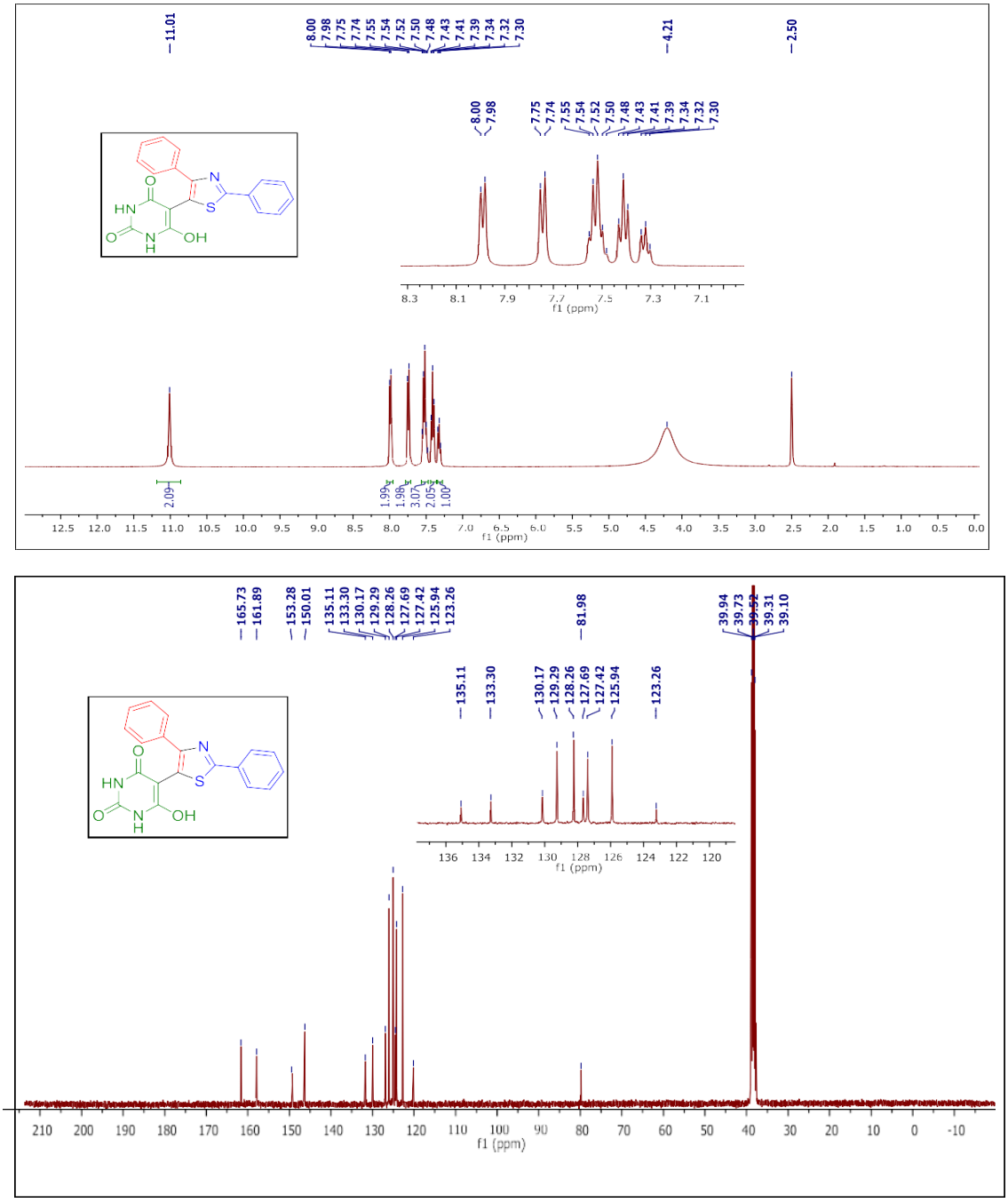


Figure 5.3 ^{1}H NMR and ^{13}C NMR of 1,3-trisubstituted thiazole **4a** in DMSO

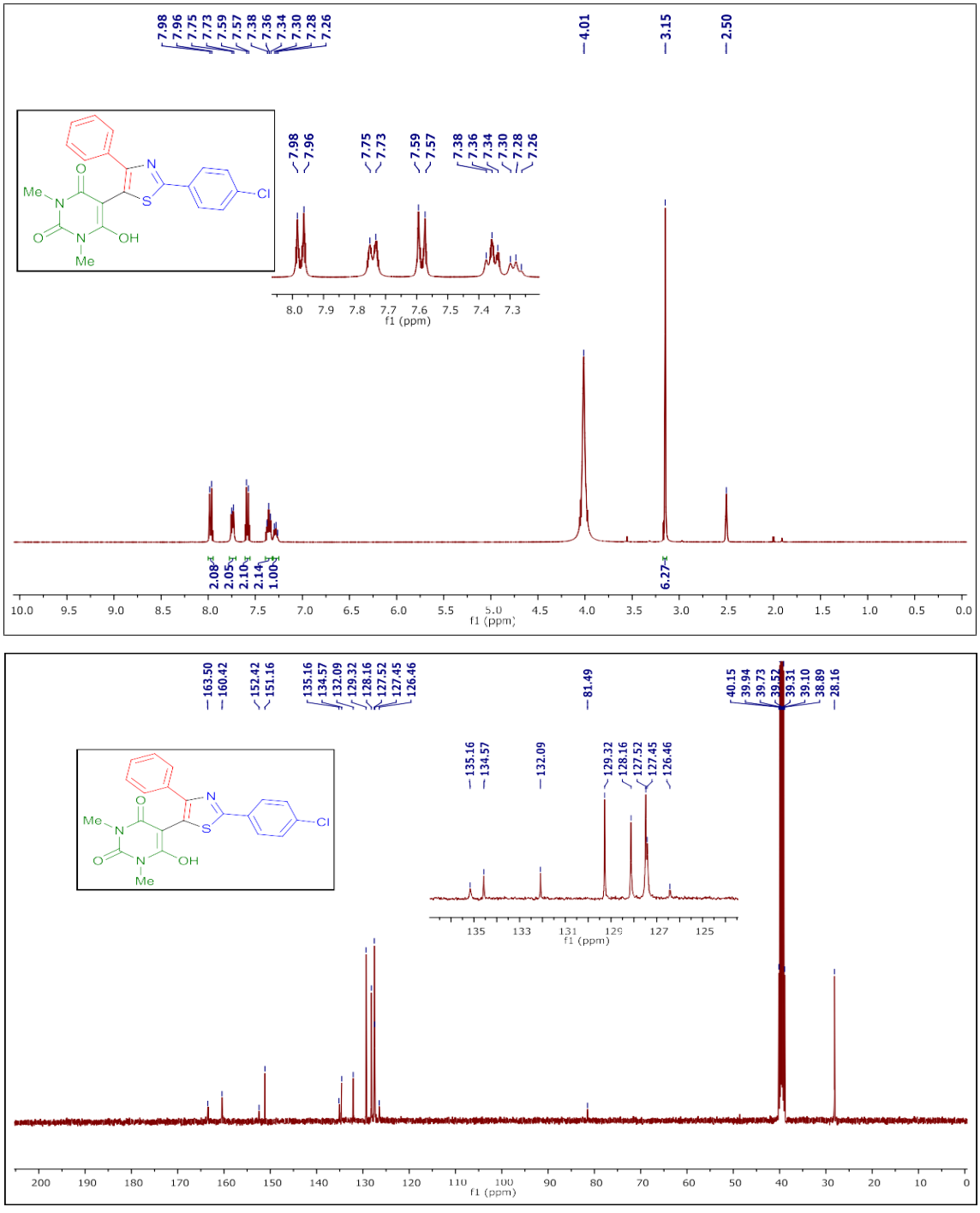


Figure 5.4 ^{1}H NMR and ^{13}C NMR of 1,3-trisubstituted thiazole **4e** in DMSO

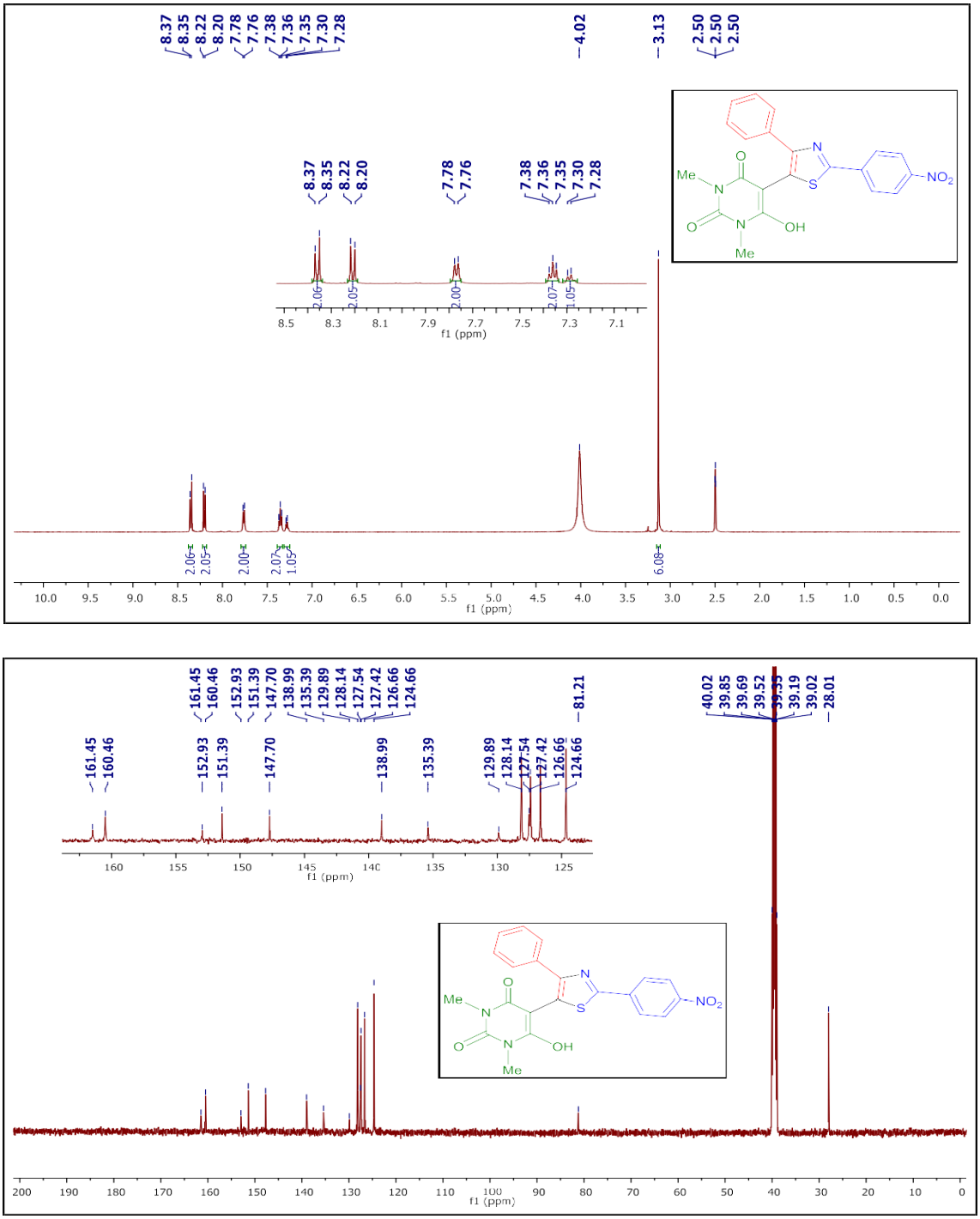


Figure 5.5 ^{1}H NMR and ^{13}C NMR of 1,3-trisubstituted thiazole **4d** in DMSO

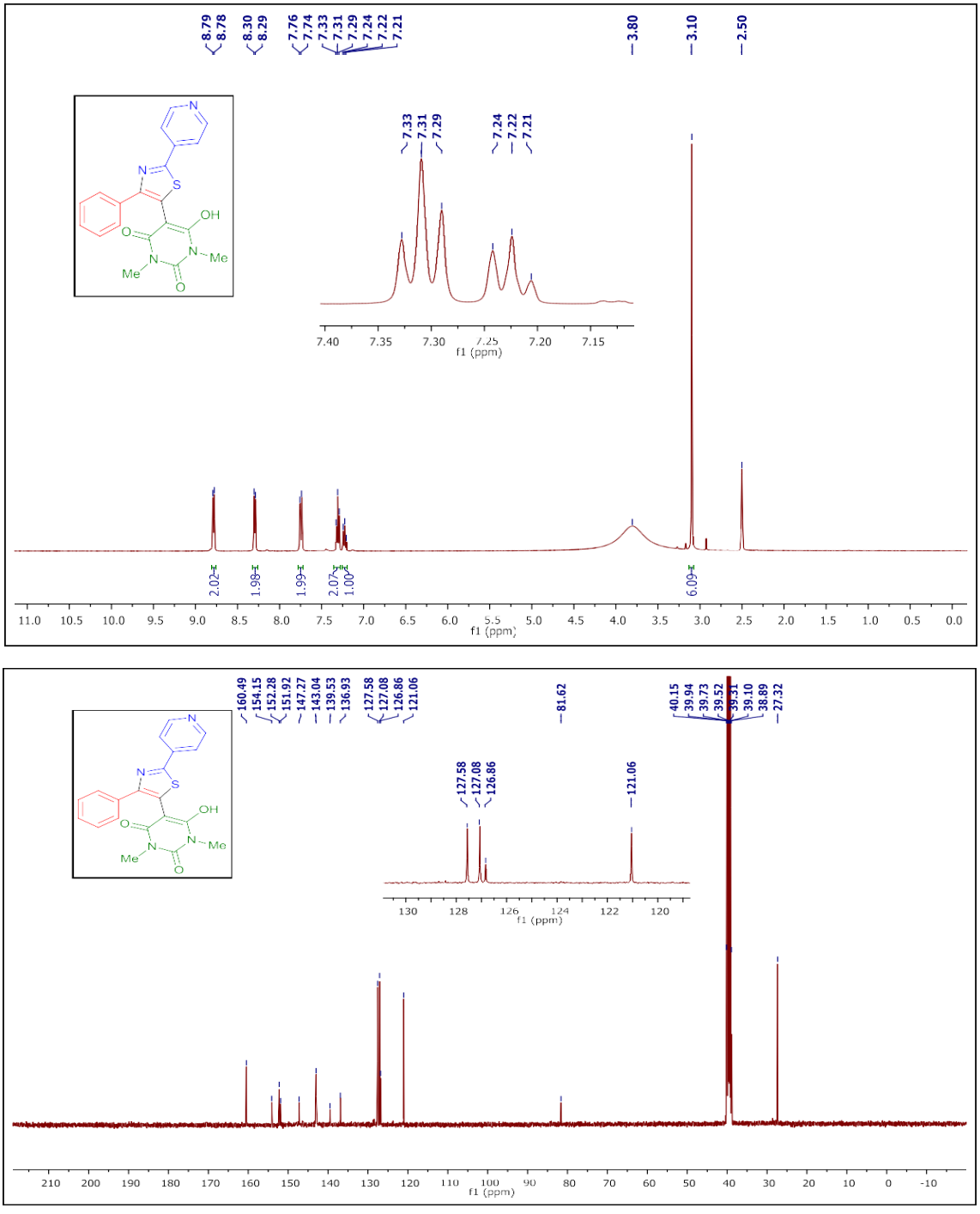


Figure 5.6 ^{1}H NMR and ^{13}C NMR of 1,3-trisubstituted thiazole **4k** in DMSO

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