CHAPTER 5

Regioselective iodination at the C-5 position of activated pyrimidinediones using KI-$VO(acac)_2$-H_2O_2-AcOH as iodinating system

5.1 Introduction

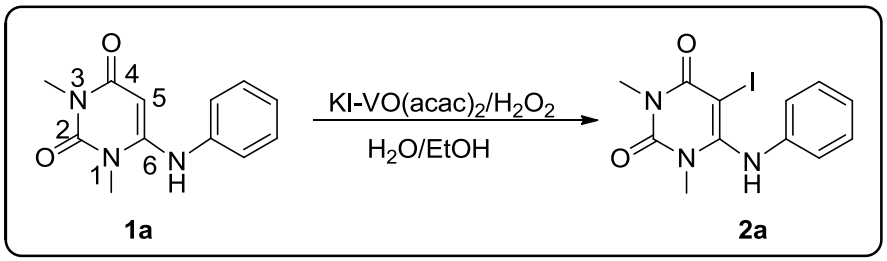
The halogenation reaction has been getting special attention as the halogenated species are very useful in preparation of organometallic compounds, metal-catalyzed cross coupling, and C-C and/or C-N bond forming reactions. However, halogenation reactions are associated with environmental hazards with respect to transport, handling, and storage [1]. Replacement of halogens with halide salts is considered as one of the various ways to minimize hazards as well as risks associated with it, as the later are comparatively safer commodities and can be oxidized to the corresponding positive halogen/hypohalous acids easily. Among the halogenation reactions, iodination is somewhat difficult because of the poor electrophilic nature of iodine compared to that of molecular bromine or chlorine and requires an oxidizing agent in order to produce electrophilic I^+ species. Among various oxidizing agents, H_2O_2 is considered to be the most preferable one due to its strong oxidizing ability and environment friendly nature [2]. A plethora of reports have been found describing iodination using H_2O_2 [3] as well as other oxidizing agents via in situ generation of I^+ [4]. Iodination of pyrimidines bears additional importance as some of the iodinated species are found to possess anticancer and antiviral properties [5]. Moreover, iodinated pyrimidines are excellent precursors for radical reactions as they easily generate radicals under suitable condition. Although, reports are well available for iodination of organic substrates like proteins, aldehydes, ketones, alkenes, aromatic amines, arenes, heteroarenes and even deactivated aromatics; iodination of pyrimidines are not so common and only a few reports have been found [6]. Nevertheless, these methods have one or more drawbacks like requirement of toxic and costly reagents, severe reaction condition, longer reaction time and formation of multiple products etc. Additionally, these reports are found to be substrate specific and failed to work in a general way.

Meanwhile, the excellent oxidative property of peroxo complexes of vanadium, molybdenum, and tungsten have been established [7] and the *in situ* generated peroxo complexes have been used for bromination of organic compounds [8]. In this chapter, KI-$VO(acac)_2$-H_2O_2-AcOH system is described as a novel iodinating

system for iodination of a series of pyrimidinedione. The developed protocol is found to be quite general covering a wide variety of pyrimidinediones and results 5-iodinated product regioselectively.

5.2 Results and discussion

To start with, we carried out a model reaction by taking 1,3-dimethyl-6-(phenylamino)pyrimidine-2,4(1*H*,3*H*)-dione(**1a**) as substrate (**Scheme 1**), which possessed multiple sites for iodination (both in phenyl and pyrimidine ring). For this, 0.1 mmol of $VO(acac)_2$ was dissolved in an ice-cooled solution of 30% H_2O_2 (10 mmol) and to it, a solution of KI (1mmol in 2 mL of H_2O) was added followed by **1a** (1 mmol) in 2 mL of EtOH. The reaction was found successful resulting the iodinated product (**2a**) in 50% yield within 4.5 h. While the formation of **2a** as single product was indicated by thin-layer chromatography, the iodination at C-5 position was confirmed by ^1H NMR spectrum. A comparison between ^1H NMR spectra of the substrate (**1a**) and the product (**2a**) is shown in **Fig. 1**, which cleanly reflects the absence of =C-H (in pyrimidine ring) proton in **2a** and thereby the iodination at C-5 position of the pyrimidine ring. We were delighted by the regioselectivity of the methodology as no iodination had taken place on the aromatic part of the substrate. A controlled experiment in absence of $VO(acac)_2$ resulted no product formation implying the importance of the catalyst. In an attempt to improve the percentage conversion of **1a** and the yield of **2a**, the reaction was tested with various catalyst loading. However, the results were not found encouraging as only a slight increase in yield was observed even after the catalyst loading was raised to 30 mol%. In a final attempt, a small amount of AcOH was added to the reaction mixture and to our delight, it worked exceptionally well



Scheme 1: Iodination of 1,3-dimethyl-6-(phenylamino)pyrimidine-2,4(1*H*,3*H*)-dione (**1a**)

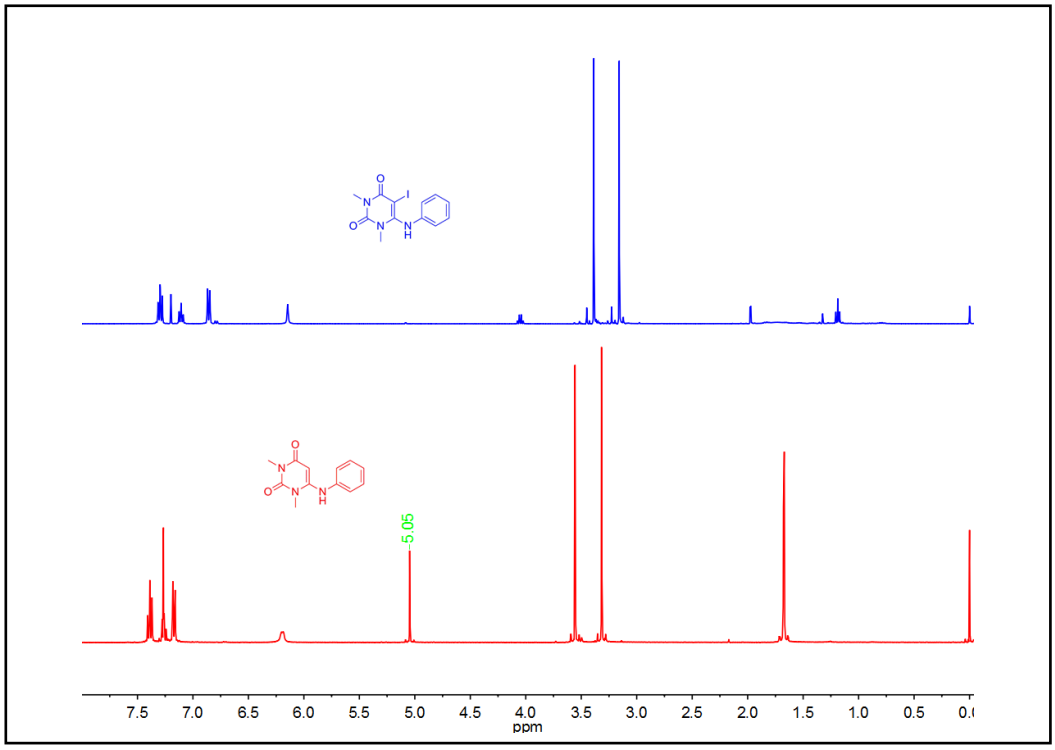
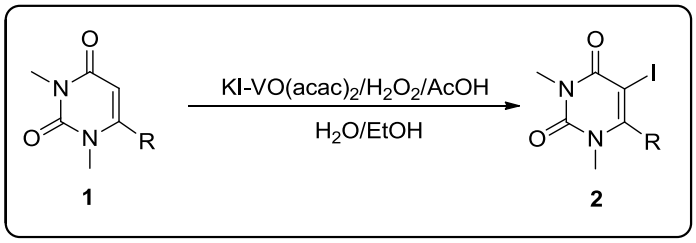


Fig. 1: ^{1}H NMR spectra of **1a** (red) and **2a** (blue)

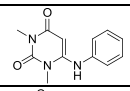
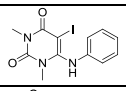
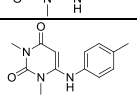
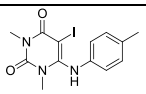
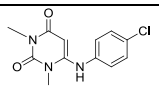
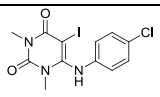
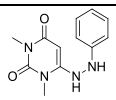
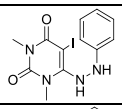
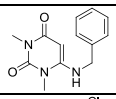
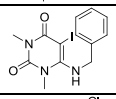
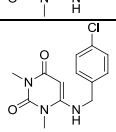
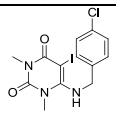
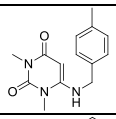
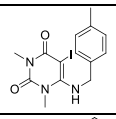
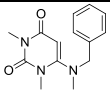
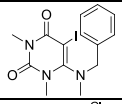
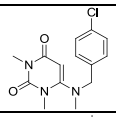
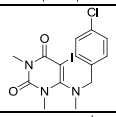
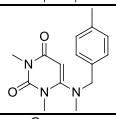
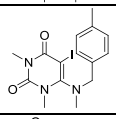
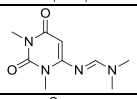
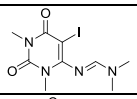
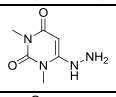
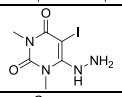
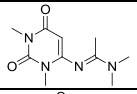
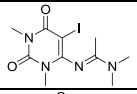
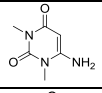
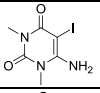
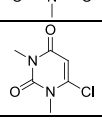
to improve the yield of **2a** within a very short period of time.

To optimize the stoichiometry of substrate, catalyst, oxidant and promoter, a set of reactions were carried out which concluded with 1:0.05:1.2:5:0.5 as optimal stoichiometry for **1a**, $VO(acac)_2$, KI, H_2O_2 and AcOH. Notably, an increase in the amount of KI did not effect the regioselectivity of the reaction under an otherwise identical reaction condition. However, use of mineral acids like HCl, H_2SO_4 was not found suitable due to formation of multiple products as indicated by TLC monitoring. To access the generality and regioselectivity, the methodology was applied to a series of pyrimidinedione as shown in **Scheme 2**and the results are



Scheme 2: Iodination of pyrimidinediones

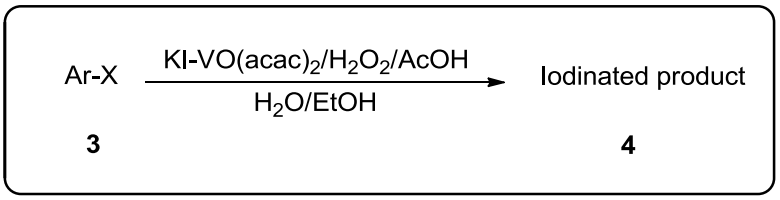
Table 1: Iodination of pyrimidinediones via **Scheme 2**

Entry	Substrate (**1**)	Product (**2**)	Time	Yield (%)[a]
a			35 min	93
b			32 min	94
c			40 min	92
d			15 min	90
e			30 min	92
f			35 min	88
g			30 min	89
h			25 min	92
i			25 min	90
j			25 min	92
k			20 min	94
l			10 min	95
m			15 min	96
n			10 min	98
o			6 hr	23
p		--	6 hr	--[b]

[a] Isolated yield

[b] No product formation

summarized in **Table 1**. It is revealed from **Table 1** that the developed protocol is suitable for a wide variety of pyrimidinediones (Entries a-p)and iodination takes place at C-5 position selectively (Entries a-k) when the substrate possesses multiple sites for reaction. Presence of electron releasing group at C-6 position of pyrimidine ring facilitates the reaction by activating the C-5 position (Entries a-n, **Table 1**) while electron withdrawing groups exert opposite effect to retard the reaction (Entries o & p, **Table 1**). An attempt was made to extend the protocol for aromatic system via **Scheme 3** and the results are found as in **Table 2**. While aromatic amide and acid (Entries a-c, **Table 2**) did not respond to the protocol, aromatic amines (Entries d-h, **Table 2**) were observed to suit it very well. Iodination takes place preferably at *para* position, although *ortho* attack is observed when para position is blocked by some other group. It is reflected from **Table 2** that activated amines (Entries e & h) undergo iodination more easily than their non-activated and deactivated counterparts (Entries f & g). However, 4-nitroaniline and diphenylamine (Entries i & j) are found to be inert to the reaction condition.



Scheme 3: Iodination of aromatics

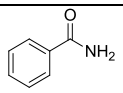
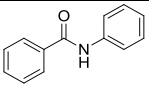
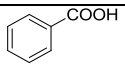
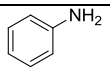
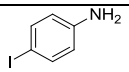
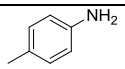
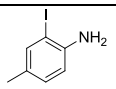
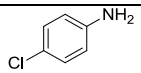
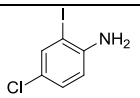
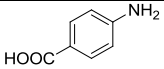
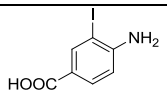
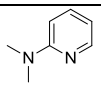
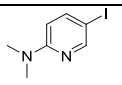
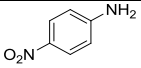
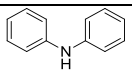
Although mechanistic study has not been carried out, a plausible mechanism has been proposed (**Scheme 4**) based on literature findings. It involves the formation of peroxo-vanadium complex with H_2O_2 which convert I^- of KI to I^+ in acidic medium. I^+ thus generated is attacked by the most nucleophilic centre of the substrate to result the iodinated product.

5.3 Conclusion

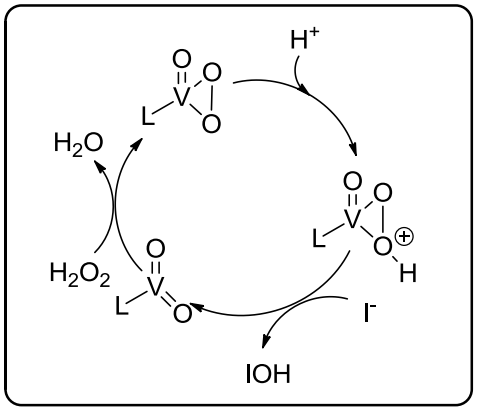
In conclusion, a convenient method for iodination using KI-$VO(acac)_2$-H_2O_2-AcOH has been developed. The method is suitable for regioselective iodination of pyrimidinediones at C-5 position and is equally effective for iodination of aromatic

amines also. This simple and mild methodology is found to cover a wide spectrum of pyrimidinediones and aromatic amines resulting the iodinated product in moderate to excellent yield.

Table 2: Iodination of aromatics via **Scheme 3**

Entry	Substrate (**3**)	Product (**4**)	Time (h)	Yield (%)[a]
a		--	12	--
b		--	12	--
c		--	--	--
d			2	92
e			1.5	96
f			2.5	92
g			3	91
h			2	96
i		--	12	--
j		--	12	--

[a]Isolated yield



Scheme 4: Plausible mechanism for iodination

5.4 Experimental section

5.4.1 General information

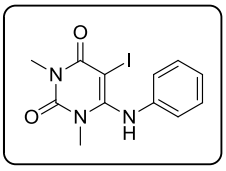
Substrates (**1**) were synthesized as per literature procedure [9]. All other chemicals were of reagent grade (AR grade) and were used as purchased without further purification. Melting points were determined with a Büchi 504 apparatus and are uncorrected. IR spectra were recorded as KBr pallets with a Nicolet (Impact 410) FT-IR spectrophotometer with frequencies expressed in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded with a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using tetramethylsilane (TMS) as the internal standard. Chemical shift values are expressed in ppm. Coupling constants are expressed in Hz. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel $60F_{254}$ (Merck). UV light and Iodine vapour were used as visualizer. Elemental analyses were carried out with a Perkin-Elmer CHN analyzer (2400 series II). Mass spectrometric analysis were performed using a Waters Q-TOF Premier & Aquity UPLC spectrometer.

5.4.2 General procedure for iodination via Scheme 2 & Scheme 3

Vanadyl acetylacetonate (0.05 mmol) was added to an ice cooled solution of 30% hydrogen peroxide (5 mmol). The solution became light green coloured due to formation of per-oxovanadium complex. Acetic acid (0.5 mmol) was added dropwise to the solution. A solution of potassium iodide (1.2 mmol) in 2 mL of water was added to the cooled solution followed by the substrate (1 mmol) in 2 mL of ethanol. Then the reaction mixture was allowed to stir at r.t. for the required period of time. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was treated with $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and finally performed column chromatography to afford the pure product.

5.4.3 Spectral data

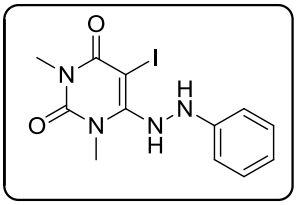
5-iodo-1,3-dimethyl-6-(phenylamino)pyrimidine-2,4(1*H*,3*H*)-dione (2a)



FT-IR (KBr): ν_{max} =3464, 3300, 2926, 2376, 2279, 1701, 1633, 1538, 1458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.23 (s, 3H),

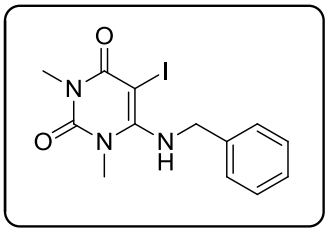
3.45 (s, 3H), 6.21 (bs, 1H), 6.91-7.38 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 31.3, 35.1, 61.2, 119.0, 120.0, 124.9, 129.5, 130.0, 139.9, 151.1, 152.1, 160.2 ppm; MS(ESI): m/z= 357[M^+]; Anal. Calcd. (%) for $C_{12}H_{12}IN_3O_2$: C, 40.36; H, 3.39; N, 11.77. Found: C, 40.38; H, 3.37; N, 11.78.

6-(2-phenylhydrazinyl)-5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2d)



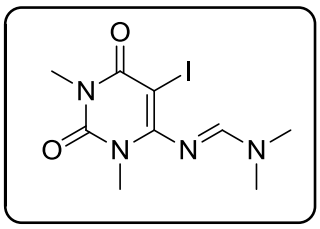
FT-IR (KBr): ν_{max} =3419, 3371, 3037, 2957, 1672, 1618, 1532, 1431 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.24 (bs, 1H), 3.48 (s, 3H), 3.64 (s, 3H), 6.9-7.5 (m, 5H), 8.24 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.6, 30.7, 55.2, 111.2, 119.5, 121.9, 122.4, 123.9, 134.7, 145.0, 151.5, 159.1 ppm; MS(ESI): m/z= 372 [M^+]; Anal. Calcd. (%) for $C_{12}H_{13}IN_4O_2$: C, 38.73; H, 3.52; N, 15.05. Found: C, 38.75; H, 3.50; N, 15.03.

6-(Benzylamino)-5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2e)



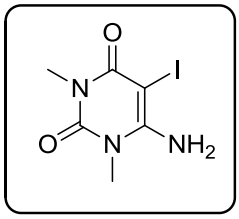
FT-IR (KBr): ν_{max} =3421, 3389, 3112, 2987, 1682, 1650, 1557, 1442 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.23 (s, 3H), 3.45 (s, 3H), 4.13 (s, 2H), 4.73 (bs, 1H), 6.91-7.38 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.8, 28.7, 47.4 127.6, 128.3, 129.1, 136.0, 151.9, 152.9, 163.1 ppm; MS(ESI): m/z= 371 [M^+]; Anal. Calcd. (%) for $C_{13}H_{14}IN_3O_2$: C, 42.07; H, 3.80; N, 11.32. Found: C, 42.05; H, 3.82; N, 11.35.

(*E*)-N'-(5-iodo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-N,N-dimethylformimidamide (2k)



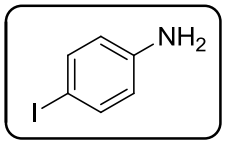
FT-IR (KBr): ν_{max} =3105, 2952, 1682, 1650, 1557, 1442 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.08 (s, 3H), 3.15 (s, 3H), 3.48 (s, 6H), 7.75 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 31.8, 34.1, 39.8, 54.8, 151.8, 155.6, 157.8, 160.8 ppm; MS(ESI): m/z= 336 [M^+];Anal. Calcd. (%) for $C_9H_{13}IN_4O_2$: C, 32.16; H, 3.90; N, 16.67. Found: C, 32.15; H, 3.91; N, 16. 64.

6-amino-5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2n)



FT-IR (KBr): ν_{max} = 3421, 3102, 1694, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 3.3 (s, 3H), 3.5 (s, 3H), 5.1 (bs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 160.2, 157.6, 151.6, 91.6, 28.9, 27.3 ppm; MS(ESI): m/z= 281 [M^+]; Anal. Calcd. (%) for $C_6H_8IN_3O_2$: C, 25.64; H, 2.87; N, 14.95. Found: C, 25.61; H, 2.90; N, 15.02.

4-iodoaniline (4d)



^1H NMR (400 MHz, $CDCl_3$): δ= 3.6 (bs, 2H), 6.4 (d, *J*=8.8 Hz, 2H), 7.4 (d, J=8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 79.6, 117.8, 138.5, 146.5 ppm; MS(ESI): m/z= 219 [M^+]; Anal. Calcd. (%) for C_6H_6IN: C, 32.90; H, 2.76; N, 6.40. Found: C, 32.85; H, 2.79; N, 6.51.

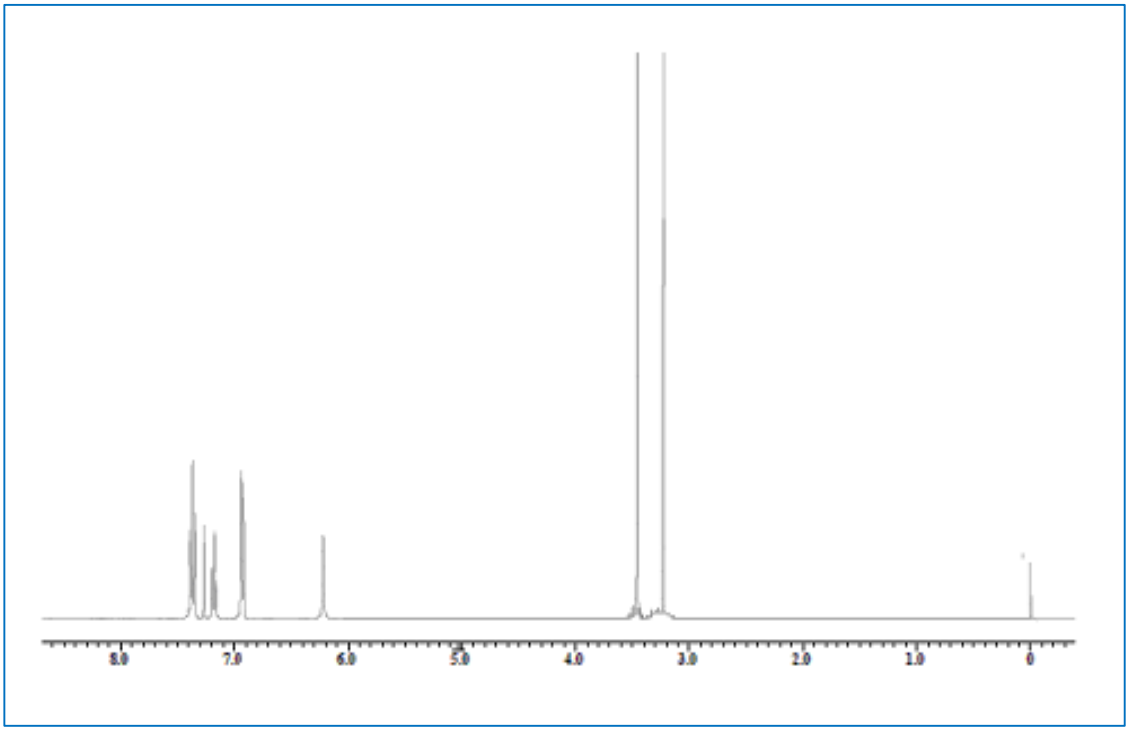


Fig. 2: ^1H NMR spectrum of compound **2a**

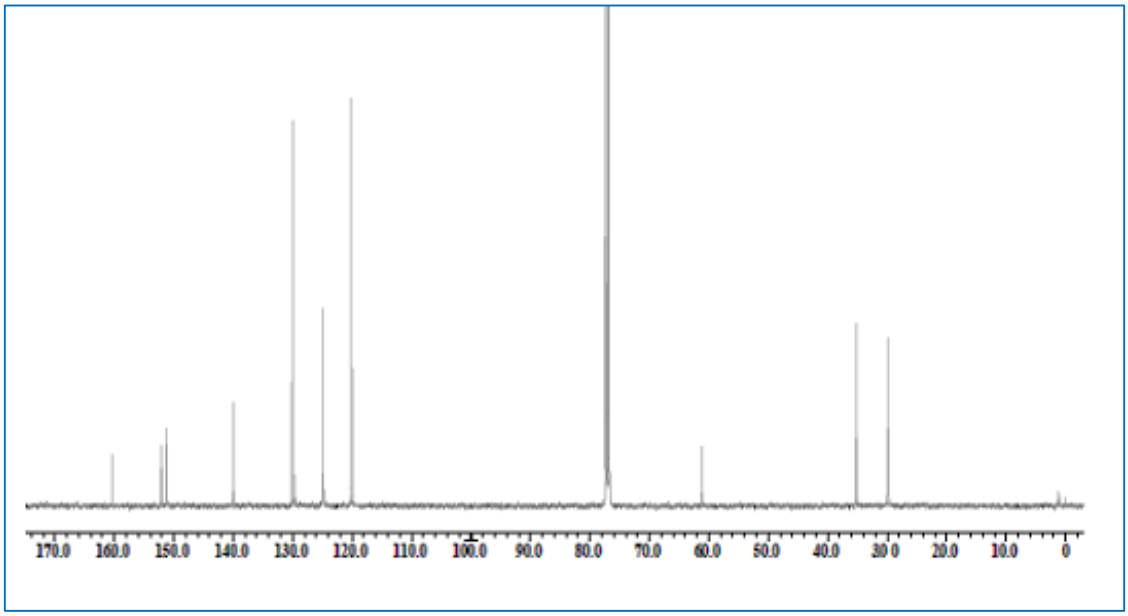


Fig. 3: ^{13}C NMR spectrum of compound **2a**

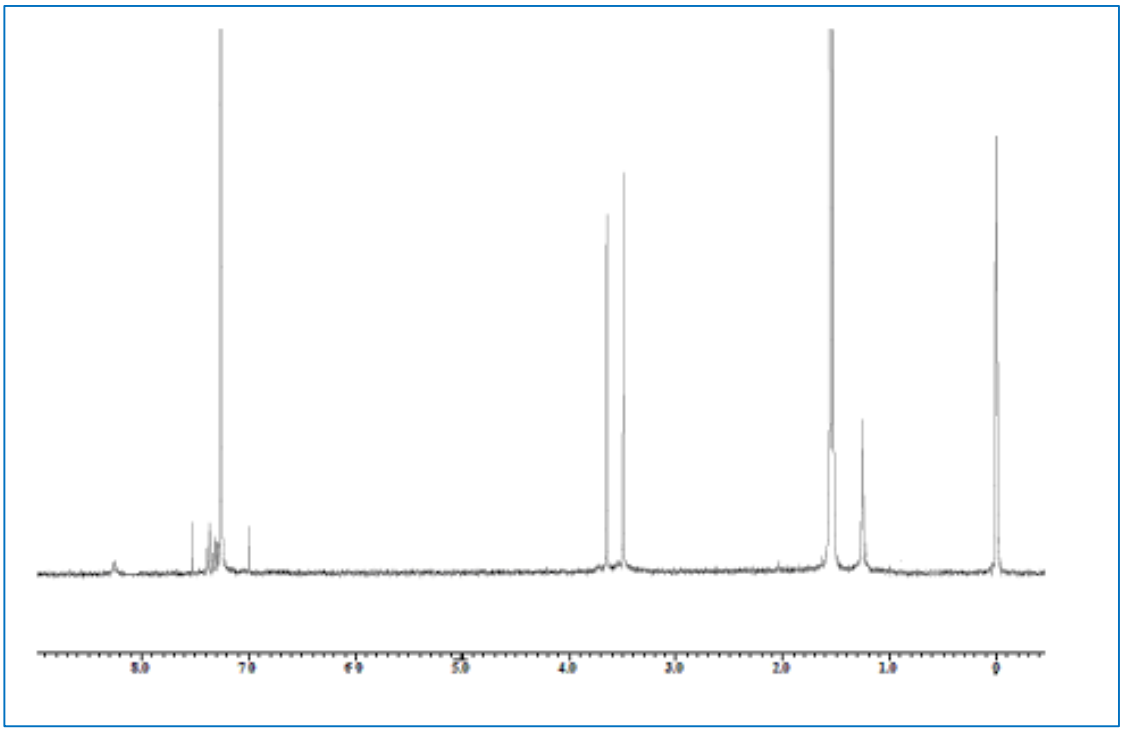


Fig. 4: ^{1}H NMR spectrum of compound **2d**

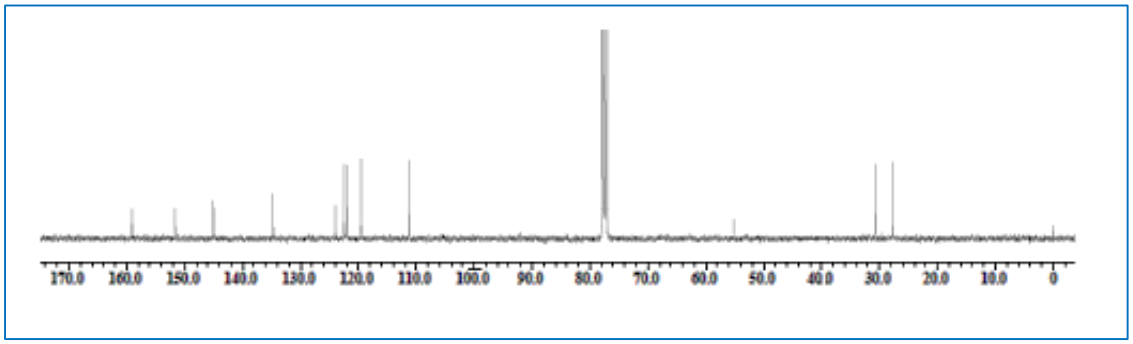


Fig. 5: ^{13}C NMR spectrum of compound **2d**

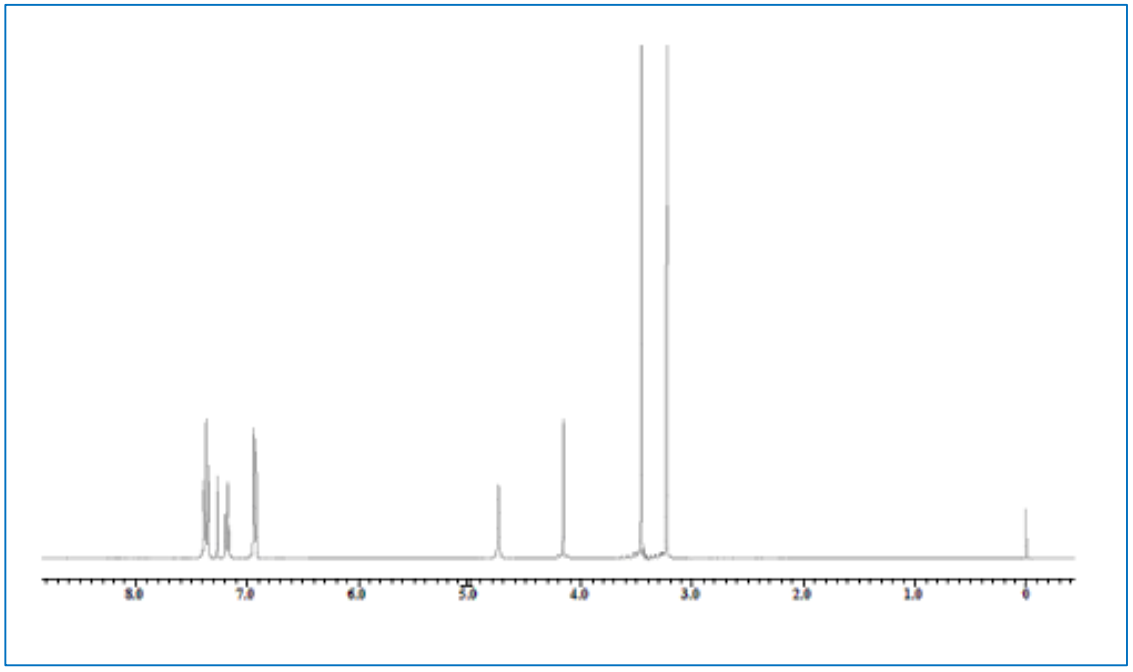


Fig. 6: ^{1}H NMR spectrum of compound **2e**

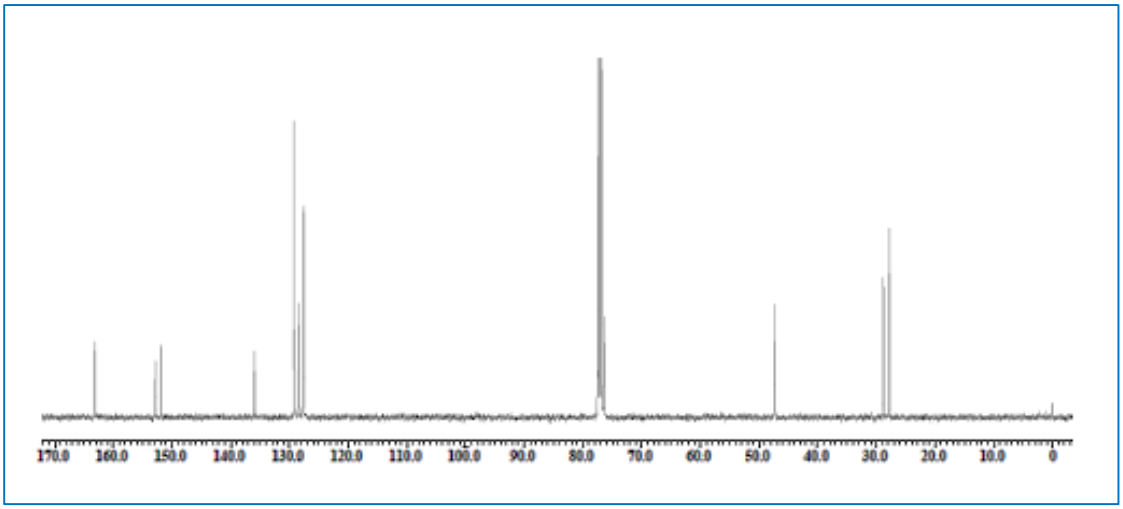


Fig. 7: ^{13}C NMR spectrum of compound **2e**

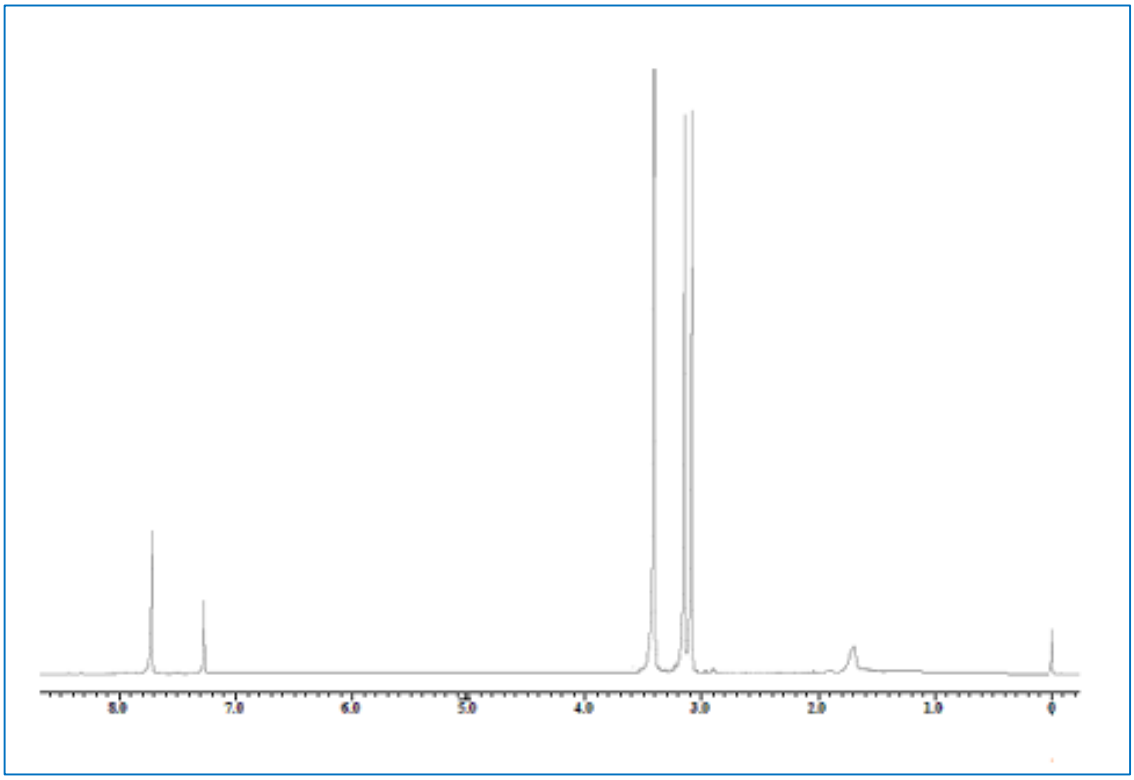


Fig. 8: ^{1}H NMR spectrum of compound **2k**

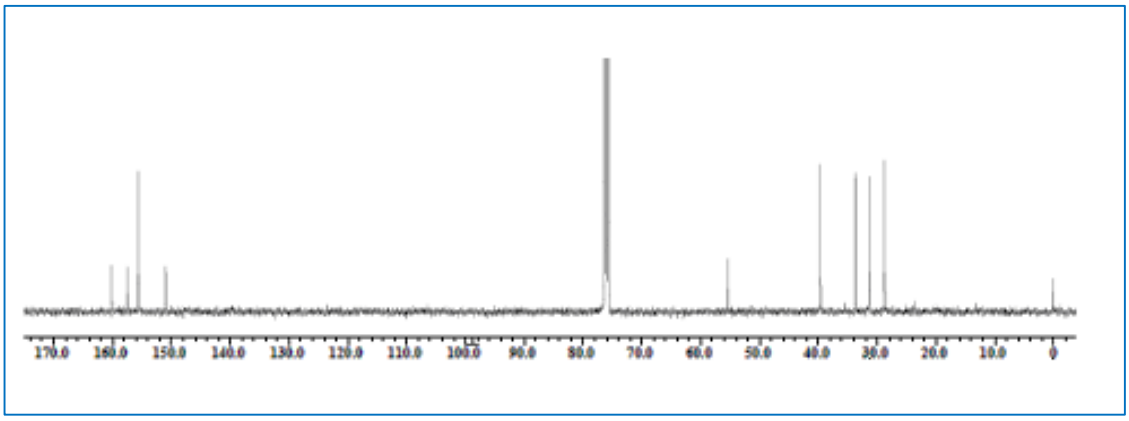


Fig. 9: ^{13}C NMR spectrum of compound **2k**

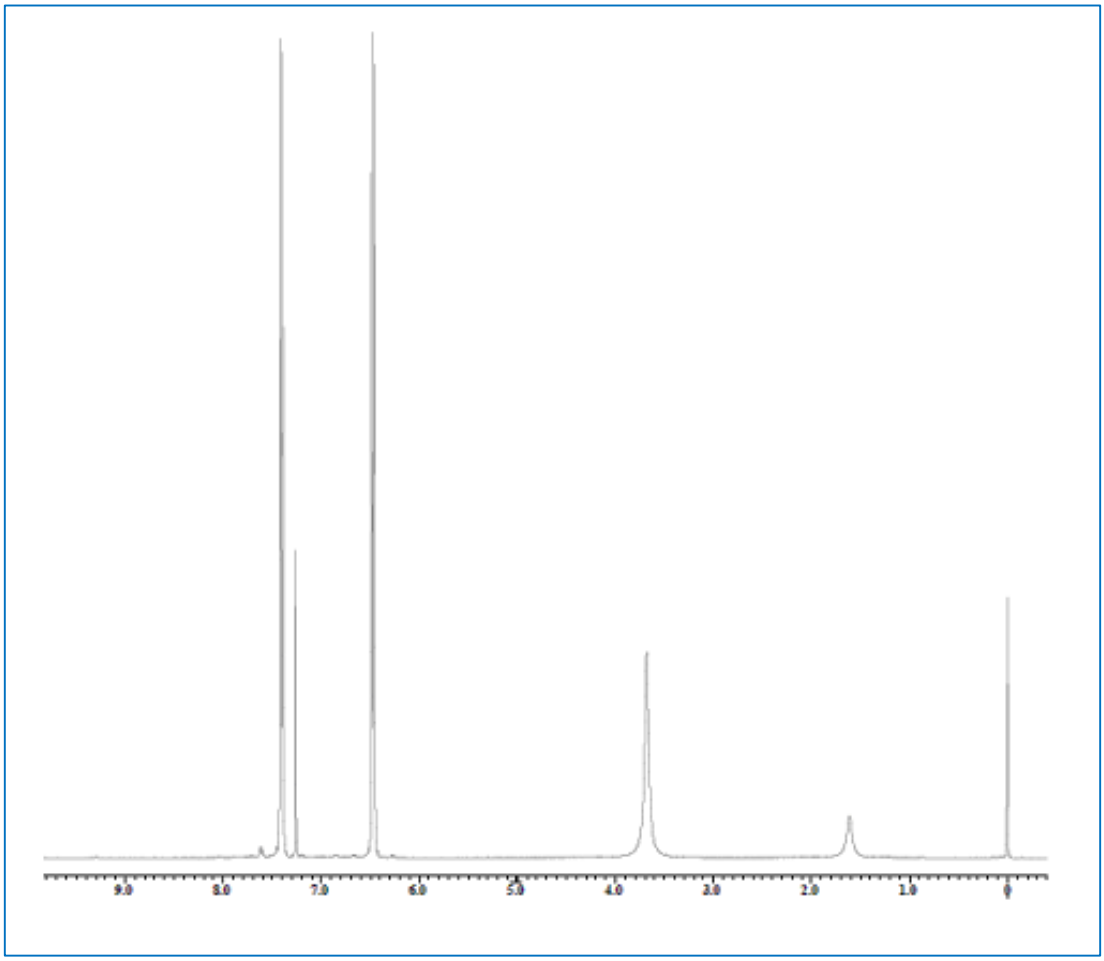


Fig. 10: ^{1}H NMR spectrum of compound **4d**

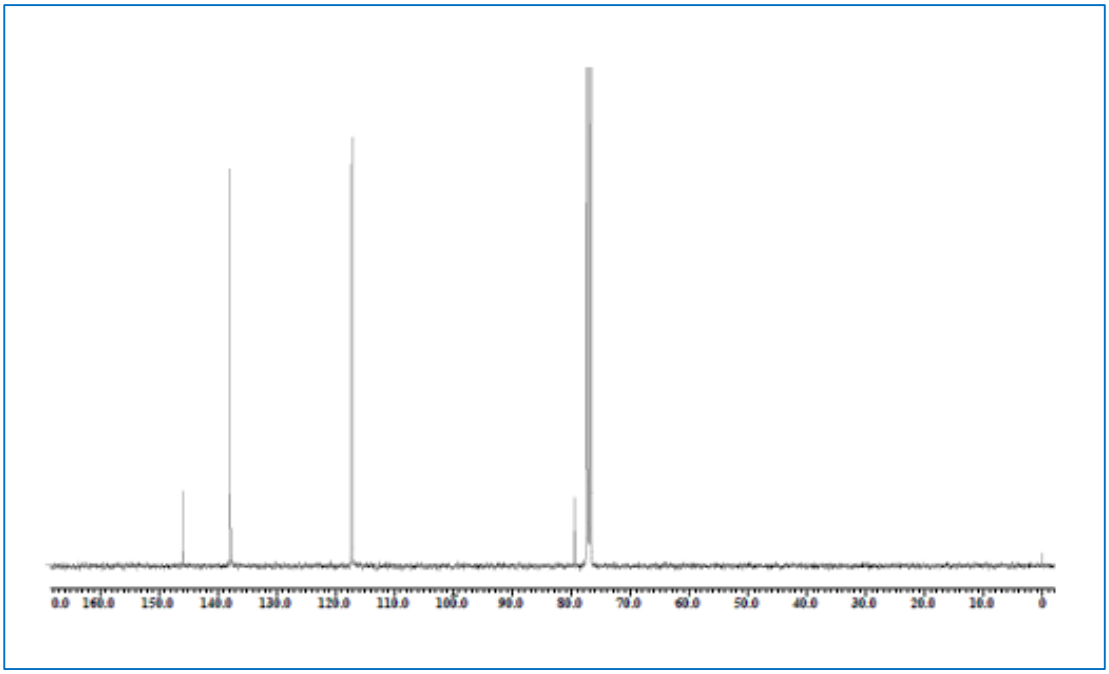


Fig. 11: ^{13}C NMR spectrum of compound **4d**

5.5 References

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