CHAPTER 2

A convenient synthesis of novel 5-aryl-pyrido[2,3-*d*]pyrimidines and screening of their preliminary antibacterial properties

2.1 Introduction

Among the various annulated pyrimidine derivatives, pyrido[2,3-*d*]pyrimidines bear special importance due to their rich pharmacological value [1]. The need for new and novel antibiotics to combat bacterial drug resistance has led the researchers to give enormous efforts in antibiotic research. In 2009, a report [2] in Nature Reviews Drug Discovery highlighted the work [3] of Stover et al. where screening of 1.6 million compounds from Pfizer compound library was carried out for antibacterial activity. The screening resulted the discovery of three pyrido[2,3-*d*]pyrimidine derivatives as potent synthetic antibacterials that targeted the bacterial biotin carboxylase selectively. Due to their immense potency against bacteria apart from other medicinal importance, there has been a flurry of synthetic and biological activities [1, 4-5] centered on pyrido[2,3-*d*]pyrimidine that attract considerable attentions from chemists and biologists. Exploiting the diene character of 6-[(dimethylamino)methylene-amino]-1,3-dimethyluracil (**1**, **Fig. 1**), a plethora of methods [5-8] have been reported for the synthesis of pyrido[2,3-*d*]pyrimidines and related compounds via [4+2] cycloaddition reaction with various electron deficient dienophiles. However, the simple acetamidine counterpart of **1**, that is 6-[1-aza-2-(dimethylamino)prop-l-enyl]-1,3-dimethyluracil (**2**, **Fig. 1**) and its diene behaviour are not well explored. To the best of our knowledge, no report of cycloaddition reaction using **2** has been published so far and only a single report [9] of coupling reaction using the 5-iodinated **2** in the presence of palladium catalyst has been found in literature.

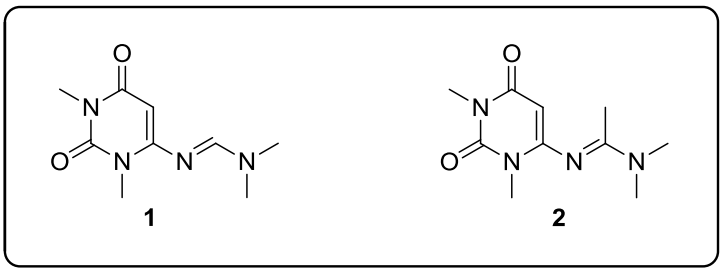
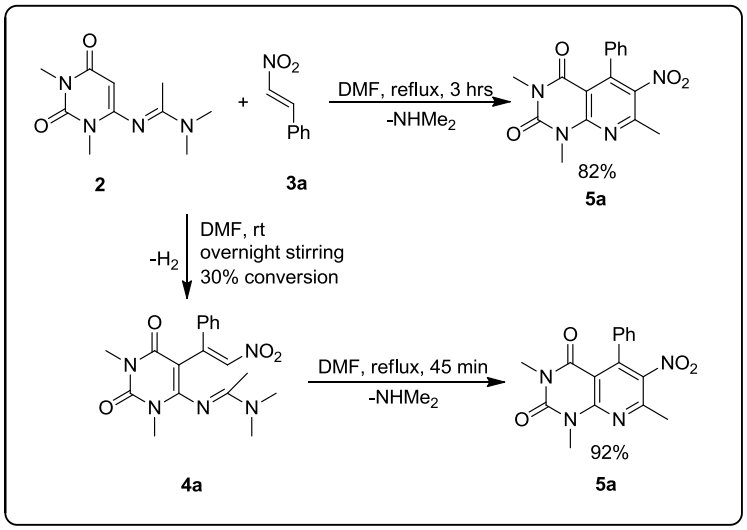


Fig. 1: Methylated (**2**) and non-methylated amidine (**1**)

In this chapter, we have described a study towards the convenient synthesis of 5-aryl-7-methylpyrido[2,3-*d*]pyrimidines by exploiting the diene behaviour of **2** and the in vitro antibacterial activity of the synthesized products. Formation of 5-aryl-7-methylpyrido[2,3-*d*]pyrimidines was not quite expected as **1** is reported to furnish 5-aryl-5,8-dihydropyrido[2,3-*d*]pyrimidines with nitrostyrenes under similar condition as reported very recently [8].

2.2 Results and discussion

To investigate the interesting diene behavior of the methylated amidine (**2**) in [4+2] cycloaddition reaction, we started by treating **2** with β-nitrostyrene (**3a**). A lower reactivity of the diene towards the electron deficient system was observed in case of **2** compared to **1** under similar reaction condition. The percentage conversion of **2** in chloroform was found to be only 35% (stirring at room temperature for 12 h, Entry 5, **Table 1**) whereas **1** underwent complete conversion within 5 minutes (stirring at 0 ^{0}C) as demonstrated in an earlier report [6]. This lower reactivity of **2** towards β-nitrostyrene, in spite of having one extra electron releasing methyl group is contradictory to the general rule of Diels-Alder reaction which suggests enhanced reactivity of **2** than **1**. This might be due to the reason that the presence of this extra methyl group hinders the extent of



2 3a 5a 4a 5a

Scheme 1: Synthesis of pyrido[2,3-*d*]pyrimidine **5a**

delocalization starting from the dimethylamino group and hinders the planarity. However, the reaction occurs smoothly in refluxing DMF with complete conversion of **2** within 3 h furnishing 1,3,7-trimethyl-6-nitro-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**5a**) in 82% yield (**Scheme 1**). The structure of **5a** has been established using FTIR, ^{1}H & ^{13}C NMR spectroscopy, MS (ESI), and elemental analysis. A comparison between the ^{1}H NMR spectra of the substrates and the product is shown in **Fig. 2**. To gain some insight into the mechanism of the reaction, the reaction was monitored at different time intervals using TLC. As the

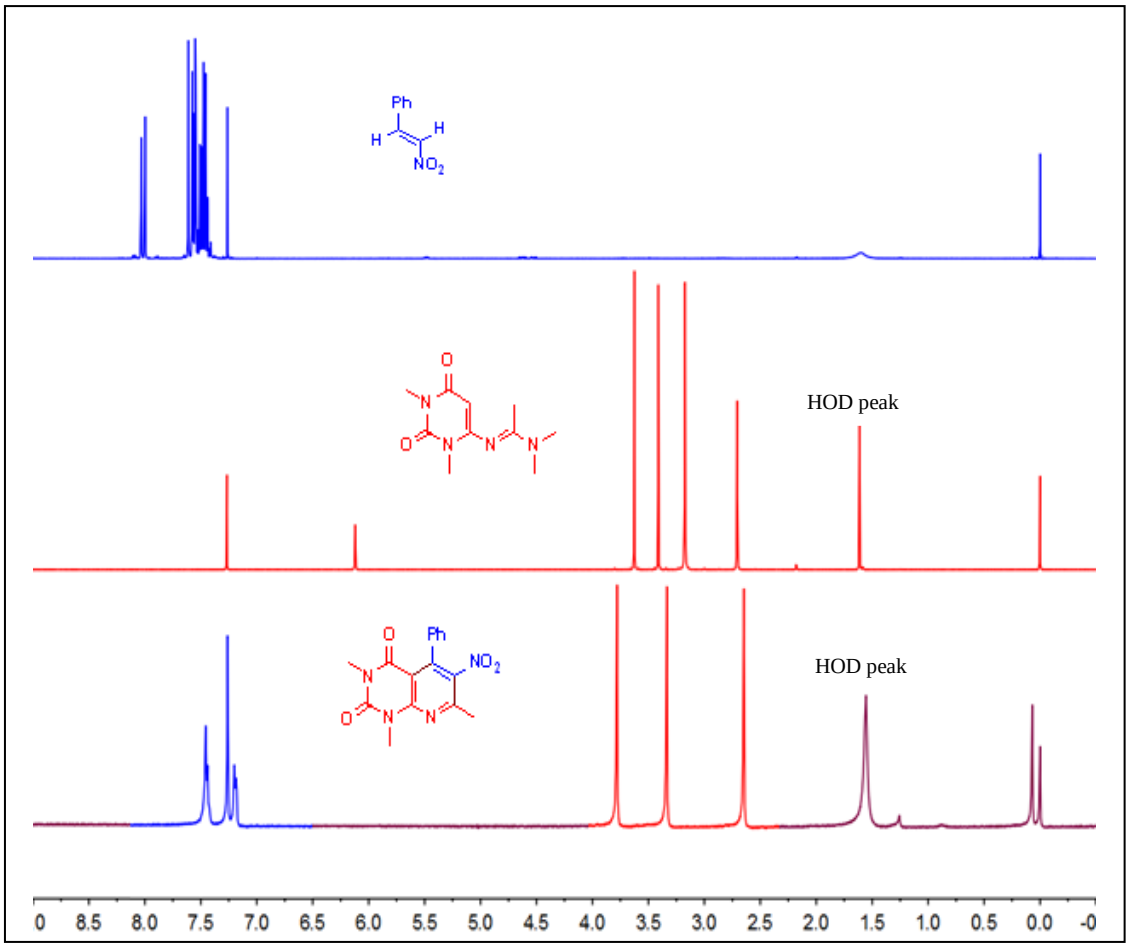


Fig. 2: Comparison of ^{1}H NMR spectra of substrates and product

reaction progressed, we noticed an extra spot in TLC with distinctly lower R_f value than that of **5a**, whose intensity decreased gradually with time. The same spot was observed in TLC as the single spot other than the starting compounds when we carried out the reaction at room temperature for 12 h (**Scheme 1**), although only

30% conversion of the starting materials was observed here. To check whether the compound responsible for this new spot was involved as an intermediate in the formation of the final product **5a**, it was isolated using column chromatography and a similar condition was imposed (i.e. refluxed in DMF) to it. As expected, **5a** was formed within shorter period of time supporting the involvement of the compound as intermediate. The structure of the intermediate was established as **4a** by single crystal X-ray analysis (**Fig. 3**).

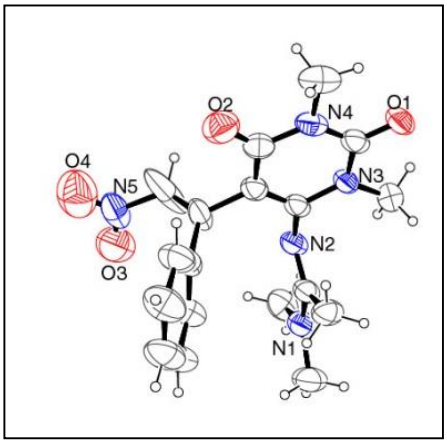


Fig. 3: ORTEP diagram of **4a**

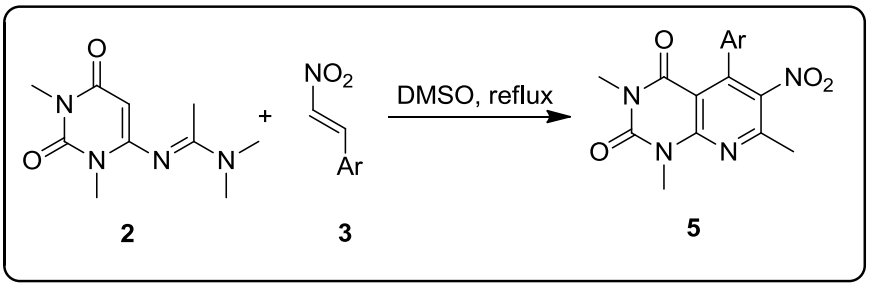
To study the effect of solvents in the formation of **4a** as well as **5a**, the reaction was carried out in various solvents (both polar and non-polar) by stirring the reaction mixture at room temperature for 12 h followed by refluxing it for 3 h. The results are summarized in **Table 1**. It is revealed from **Table 1** that high boiling aprotic polar solvents like DMF and DMSO (Entries 1 & 2, **Table 1**) are suitable for the formation of the final product **5a**, but the rate of conversion towards the intermediate **4a** is quite low. In contrast, H_2O is found to be the best solvent for the formation of the intermediate **4a**, but not so satisfactory for furnishing the final product **5a**. To examine the effect of H_2O, the reaction was then carried out in a 1:1 mixture of DMF & H_2O, but the result was not found satisfactory for the formation of **5a** in good yield (Entry 4, **Table 1**). On the basis of all these observations, it can be concluded that H_2O favours the formation of **4a** whereas it disfavours the conversion of **4a** to the final product (**5a**). Other solvents like $CHCl_3$, CH_3CN, C_6H_6 and CH_3OH were not found to be suitable at all. Among all these solvents checked,

DMSO was found to be the best solvent for the synthesis of pyrido[2,3-*d*]pyrimidine (**5a**) in a single step process. Generalization of the reaction was carried out using various β-nitrostyrenes (**3a-h**) as shown in **Scheme 2** and summarized in **Table 2**. The reaction did not proceed with aliphatic nitroalkenes. It is clearly reflected from **Table 2** that only one regioisomer was formed in all the cases. An attempt to extend the protocol for other comparatively less electron deficient dienophiles such as acryl amide, acrylic acid, cinnamaldehyde, cinnamic acid, cinnamamide, and benzylidene acetophenone went in vain.

Table 1: Screening of solvents for **Scheme 1**

Entry	Solvent	Reaction condition					
		Stirred at r.t. for overnight [12 h]			Refluxed for 3 h[a]		
		Conversion of **2** [%]	Yield of **4a** [%]	Yield of **5a** [%]	Conversion of **2** [%]	Yield of **4a** [%]	Yield of **5a** [%]
1	DMF	30	100	--[b]	100	<10	82
2	DMSO	32	100	**--**	100	<10	85
3	**H_2O**	**100**	**100**	--	**100**	**8**	**22**[c]
4	**DMF-H_2O (1:1)**	**100**	**100**	--	**100**	**12**	**28**[c]
5	$CHCl_3$	35	100	**--**	50	100	--
7	CH_3CN	38	100	**--**	68	>90	<10
8	C_6H_6	15	100	**--**	60	45	18[c]
9	CH_3OH	75	100	**--**	92	65	<10[c]

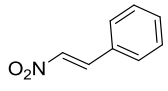
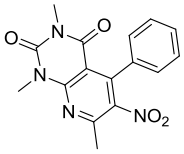
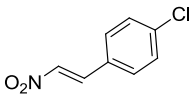
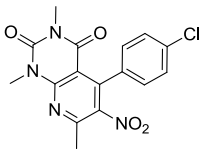
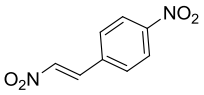
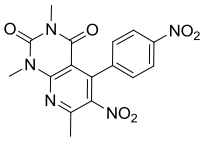
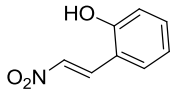
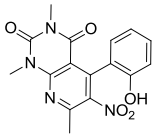
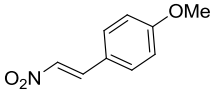
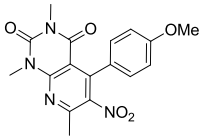
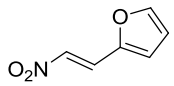
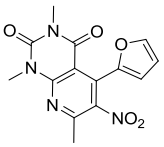
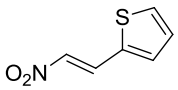
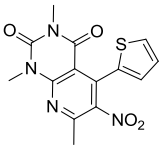
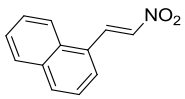
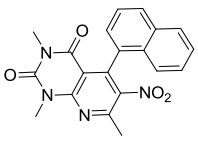
[a] Reaction mixture was stirred at room temperature for 12 h followed by reflux for 3 h
[b] No formation of **5a**
[c] Some other unidentified products were formed



Scheme 2: Synthesis of pyrido[2,3-*d*]pyrimidines (**5a-h**) in one step

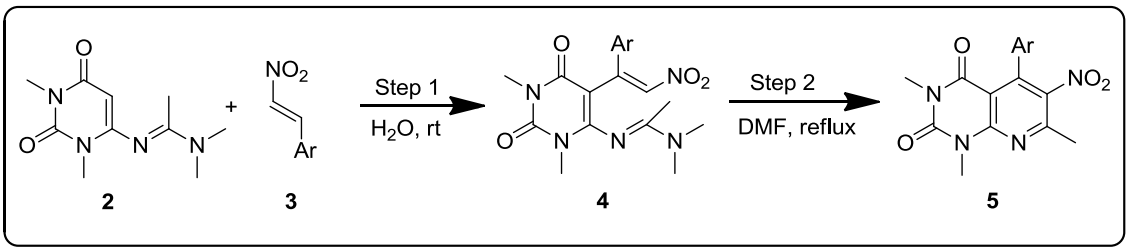
The synthesis of **5** was also attempted via a two-step route (**Scheme 3**) considering the observation that H_2O was the best solvent for the intermediate (**4**) formation step whereas DMF and DMSO were the excellent solvents for the

Table 2: Synthesis of pyrido[2,3-*d*] pyrimidines (**5a-h**)via **Scheme 2**

Entry	Substrate (3)	Product (5)	Time (h)	Yield of 5 [%][a]	mp of 5[^{0}C]
a			3	85	180
b			3	82	200
c			3.5	72	240
d			3.5	75	218
e			2.5	92	215
f			2.5	87	179
g			2.5	90	212
h			2.5	85	182

[a] Isolated yield

transformation of intermediate(**4**) to final product(**5**). It was found that this route was slightly more beneficial than the single step route when the overall isolated yields of **5** were considered. The 2nd step was carried out in refluxing DMF, although both DMF & DMSO were found to give almost comparable yield. However, DMF is preferred over DMSO, as DMSO has an extremely unpleasant smell when refluxed. Chloro, nitro, hydroxyl, methoxy and heterocyclic moieties (thiophene and furan) remained undisturbed during the reaction. The results are summarized in **Table 3**. All the intermediates (**4a-h**) were obtained by simple filtration and used for the 2nd step without any further purification.



Scheme 3: Synthesis of pyrido[2,3-*d*]pyrimidines (**5a-h**) in two steps

Table 3: Synthesis of pyrido[2,3-*d*]pyrimidines **5a-h** via **Scheme 3** in two steps

Entry	Ar in 3	Step 1		mp of 4 [°C]	Step 2		Overall yield of 5 [%][a]
		Reaction time (h)	Yield of **4** [%][a]		Reaction time	Yield of 5[%][a]	
a	C_6H_5-	8	100	145	45 min	92	92
b	*p*-ClC_6H_4-	8	100	140	50 min	90	90
c	*p*-$NO_2C_6H_4$-	12	96	172	1.5 h	85	82
d	*o*-HOC_6H_4-	12	98	118	1.5 h	85	83
e	*p*-$MeOC_6H_4$-	7	100	139	40 min	95	95
f		7.5	100	157	45 min	92	92
g		7.5	100	152	45 min	90	90
h		8.5	100	161	1 h	88	88

[a]Isolated yield

The structure of all the final products were confirmed by FT-IR, ^{1}H and ^{13}C NMR spectroscopy, elemental analyses and mass spectral data. The structure of **5g** was confirmed by single crystal X-ray analysis (**Fig. 4**).

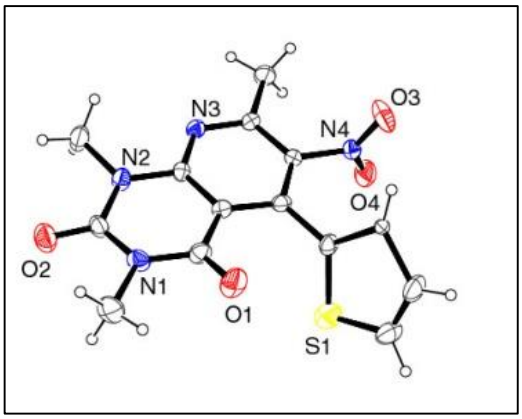
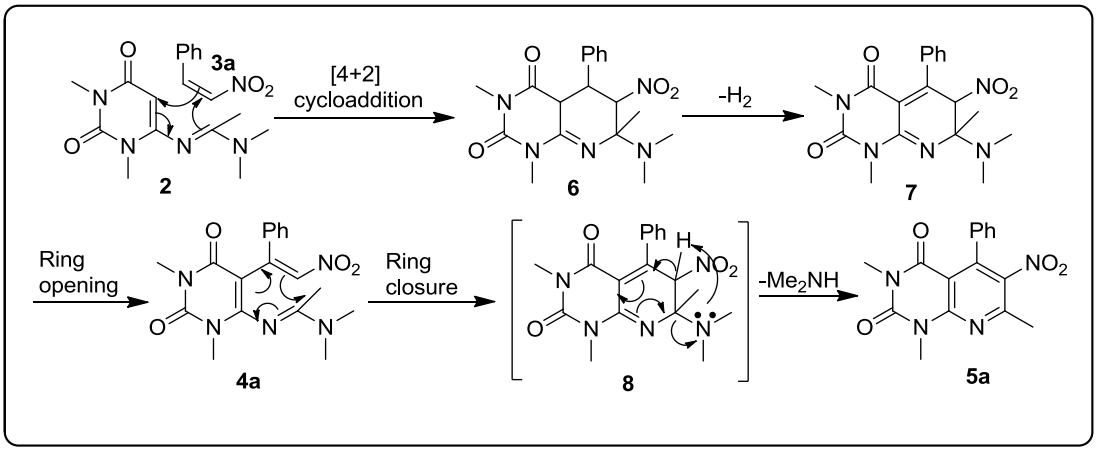


Fig. 4: ORTEP diagram of **5g**

Although the detailed mechanistic studies were not performed, a plausible mechanism has been suggested based on the involvement of **4a** as intermediate. The mechanism (**Scheme 4**) can rationalize the formation of the product **5** via aza-Diels-Alder pathway followed by elimination of hydrogen molecule, rearrangement and loss of dimethylamine.



Scheme 4: Plausible mechanism for the formation of **5a**

The synthesized pyrido[2,3-*d*]pyrimidines (**5a-h**) were screened for their in vitro antibacterial property against both the Gram positive (*Bacillus subtilis* and

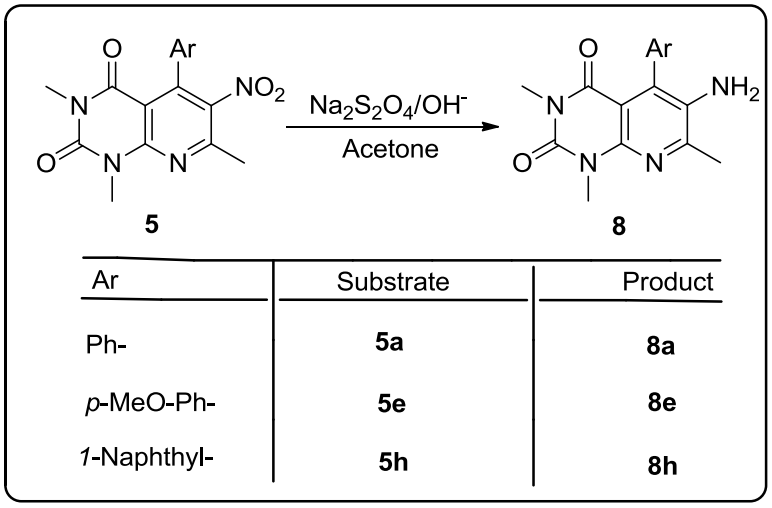
Staphylococcus aureus) and Gram negative (*Klebsilla pneumoniae* and *Escherichia coli*) bacterial strains. The minimum inhibitory concentrations (MIC) of the synthesized compounds were determined by the micro dilution method (**Table 4**) taking streptomycin sulfate (1 mg/mL) as positive control while sterilized DMSO as negative control. Among the compounds, **5a** exhibited maximum activity against all the tested (both Gram positive & Gram negative) microorganisms while compound **5h** showed identical activity against *S. aureus* (Gram positive). The results indicate that introduction of both electron withdrawing and releasing groups to the aryl ring at position 5 of the pyrido[2,3-*d*]pyrimidine decreases the activity of the compounds although the effect of electron releasing groups is much higher. Replacement of aryl rings by heteroaryl rings (Entry 6 & 7, **Table 4**) also

Table 4: MIC (in mg ml^{-1}) values of novel 5-Aryl-pyrido[2,3-*d*]pyrimidines

Entry	Compounds	Microorganisms			
		Gram positive		Gram negative	
		B. subtilis	*S. aureus*	*K. pneumoniae*	*E. coli*
1	**5a**	**0.375**	**0.375**	**0.75**	**0.75**
2	**5b**	1.8	0.9	1.8	0.9
3	**5c**	2	4	4	4
4	**5d**	3.75	7.5	7.5	7.5
5	**5e**	27	27	27	27
6	**5f**	2.5	1.25	2.5	2.5
7	**5g**	4.75	4.75	4.75	4.75
8	**5h**	**1.5**	**0.375**	**3**	**1.5**
9	**8a**	0.375	0.375	0.375	0.375
10	**8e**	**1.25**	**2.5**	**1.25**	**1.25**
11	**8h**	0.75	0.375	1.75	0.75

increase in MIC values. To examine the scope of the reduced products of **5** towards antibacterial activity, -NO_2 group of **5e** (compound with the highest MIC value) was reduced to -NH_2 functionality (**Scheme 5**) and the resulting amine (**8e**) was screened for possible antibacterial activity and to our delight, it showed excellent activity as compared to **5e** (Entry 10, **Table 4**). This result suggested that

reduction of -NO_2 to -NH_2 increases the activity of the compound enormously. Functionally transformed products (**8a** & **8h**) of the most active compounds (**5a** & **5h**) were also screened against bacterial strains and an increase in activity was observed (Entries 9 & 11, **Table 4**). However, the magnitude of increase in activity upon functional transformation here is very less in comparison to that observed in the functional transformation of the least active compound.



5 **8**

Ar	Substrate	Product
Ph-	**5a**	**8a**
p-MeO-Ph-	**5e**	**8e**
1-Naphthyl-	**5h**	**8h**

Scheme 5: Reduction of -NO_2 to -NH_2

2.3 Conclusion

In conclusion, a convenient catalyst-free regioselective synthesis of 5-aryl-pyrido[2,3-*d*]pyrimidines has been accomplished via hetero annulation, exploiting the diene nature of 6-[1-aza-2-(dimethylamino)prop-l-enyl]-1,3-dimethyluracil (**2**) for the first time. The reactivity of **2** towards nitrostyrenes is found to be somewhat lower than its non-methylated counterpart i.e. **1**. Unlike **1**; which was reported to result 5-aryl-5,8-dihydropyrido[2,3-*d*]pyrimidines [8] with nitrostyrenes, **2** is found to furnish a triene system (**4**) in H_2O, that can be cyclized to completely aromatic 5-aryl-pyrido[2,3-*d*]pyrimidines in refluxing DMF or DMSO. The generality of the protocol has been demonstrated by the successful conversion of eight substrates into pyrido[2,3-*d*]pyrimidines **5a**-**h**. This method allows the introduction of a high degree of chemical and structural diversity onto the pyrimidine scaffold with tolerability to several groups. Easy access of the starting

materials, good yields of the products and the simplicity of the experimental procedure make it a useful one. Synthesized compounds possess modest activity against gram positive and gram negative bacteria. Noticeably, functional conversion of the -NO_2 group to -NH_2 leads to enhanced antibacterial activity.

2.4 Experimental section

2.4.1 General information

One of the substrate (**2**) was prepared by the procedure described in the following section. Nitrostyrenes were prepared by using already available standard procedures [10]. 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 hertz. X-ray intensity data were collected with a Bruker SMART APEX CCD area-detector diffractometer with Mo-*K*α radiation (λ = 0.71073 Å). The structures were solved by SHELX97 and refined by full-matrix least-squares on F^2(SHELX97) (Sheldrick, G. M. *Acta Crystallogr., Sect. A* 2008, *64*, 112-122). 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.

2.4.2 Screening of 5-aryl-pyrido[2,3-*d*]pyrimidines towards antibacterial activity

The microbroth dilution method was performed to determine the minimum inhibitory concentration (MIC). The dissolved solution of the synthesized pyrido[2,3-*d*]pyrimidine derivative was diluted to a series of tenfold in Luria

Bertani (LB) broth, seeded in a 96-well culture plate, and then inoculated with a fresh bacterial inoculum. Inoculated microplates were incubated at 37 °C for 24 h. Each pyrido[2,3-*d*]pyrimidine concentration was tested in duplicates for each organism. Two wells containing suspension test organism with no test compound (growth control) and 2 wells containing only media (background control) were included in the microtitre plate. The viability of the treated cells was determined by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium) assay and the absorbance was measured at 570 nm using a microtitre plate reader (Bio-Rad Model 680; Hercules, California). The MIC was determined as the lowest concentration of the synthesized compound required to inhibit the growth of each organism. The mean and standard deviation of triplicates for each treatment were calculated.

2.4.3 Procedure for the synthesis of 6-[1-aza-2-(dimethylamino)prop-l-enyl]-1,3-dimethyluracil (2)

A mixture of 6-amino-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione(1.55 g, 0.01 mol) and N,N-Dimethylacetamide dimethyl acetal (1.33 g, 0.01 mol) were refluxed in a round bottomed flask for 1 h and then the reaction mixture was allowed to cool at room temperature. The solid mass thus obtained was recrystallized from ethanol to get **2** as pure product. Yield (2.03 g, 90.62%).

2.4.4 General procedure for the synthesis of 5 via Scheme 2

6-[1-aza-2-(dimethylamino)prop-l-enyl]-1,3-dimethyl-uracil (**2**, 0.5 mmol) and nitrostyrene derivative (**3**, 0.5 mmol) were taken in DMSO (5 mL) and refluxed. After the completion of the reaction (monitored by TLC), DMSO was removed by vacuum distillation. The crude residue was purified to get the pure products (**5**) by column chromatography using silica gel (100-200 mesh) as adsorbent and Ethyl acetate-Hexane as eluent.

2.4.5 General procedure for the synthesis of 5 via Scheme 3

Step 1 (Synthesis of **4**): 6-[1-aza-2-(dimethylamino) prop-l-enyl]-1,3-dimethyluracil (**2**, 0.5 mmol) and the nitrostyrene (**3**, 0.5 mmol) were taken in H_2O (10 mL) and allowed to stir at room temperature. The reaction was monitored using TLC. After the completion of the reaction, the solid products (**4**) were collected by filtration. The crude products were used for the 2ndstep without further purification.

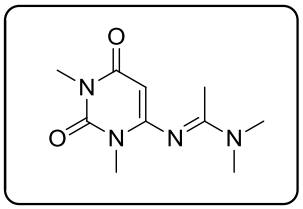
Step 2 (Synthesis of **5**): The crude product of the 1ststep (**4**, 0.5 mmol) was refluxed in DMF (5 mL). After the completion of the reaction (monitored by TLC), DMF was evaporated out under vacuum. The crude residue was purified by column chromatography using silica gel (100-200 mesh) as adsorbent and Ethyl acetate-Hexane as eluent.

2.4.6 General procedure for the reduction of -NO_2 to -NH_2 via Scheme 5

The nitro compound was dissolved in acetone (3 mL/mmol) and aqueous NaOH (0.5 N, 5 equiv). Excess sodium hydrosulfite (5 equiv) was added and the reaction was refluxed for 1.5 h. Acetone was evaporated, residue was taken up in ethyl acetate and washed with water, brine and dried over Na_2SO_4. Ethyl acetate was evaporated under vacuum and the residue was purified by column chromatography using silica gel (100-200 mesh) as adsorbent and Ethyl acetate-Hexane as eluent.

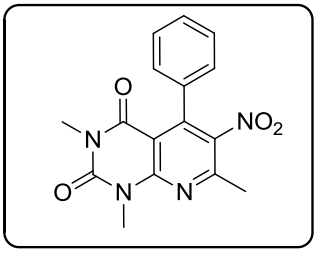
2.4.7 Spectral data

[1-aza-2-(dimethylamino)prop-l-enyl]-1,3-dimethyluracil (2)



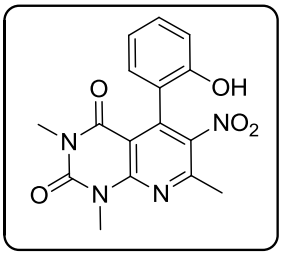
FT-IR (KBr): ν_{max}= 3025, 2926, 1716, 1673, 1662, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 6.12 (s, 1H), 3.62 (s, 3H), 3.41 (s, 3H), 3.17 (s, 6H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 159.5, 156.6, 150.2, 149.6, 96.2, 35.3, 27.1, 25.4, 20.6 ppm; MS(ESI): m/z= 224 [M^+]; Anal. Calcd (%) for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.57; H, 7.23; N, 24.95.

1,3,7-trimethyl-6-nitro-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5a)



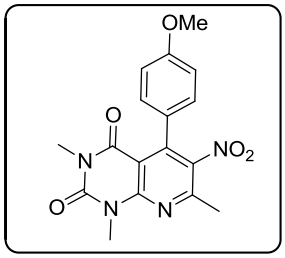
FT-IR (KBr): ν_{max}= 3455, 2926, 2370, 1716, 1673, 1561, 1483, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.45-7.33 (m, 3H), 7.18 (d, *J*=8 Hz, 2H), 3.78 (s, 3H), 3.33 (s, 3H), 2.64 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 158.5, 153.5, 149.8, 145.2, 131.1, 128.1, 127.1, 126.2, 105.1, 98.9, 29.3, 27.6, 20.3 ppm; MS(ESI): m/z= 326 [M^+]; Anal. Calcd (%) for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.91; H, 4.37; N, 17.19.

5-(2-hydroxyphenyl)-1,3,7-trimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5d)



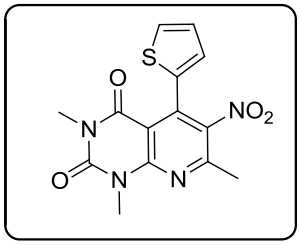
FT-IR (KBr): ν_{max}= 3405, 2926, 2857, 2377, 1720, 1661, 1585, 1452, 1364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 9.33 (t, *J*= 8.4 Hz, 1H), 7.66 (m, 2H), 7.45 (t, *J*= 6.4 Hz, 1H), 3.79 (s, 3H), 3.57 (s, 3H), 2.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.9, 161.7, 158.3, 151.4, 148.1, 147.9, 146.6, 131.1, 130.7, 129.1, 123.5, 122.1, 111.8, 103.5, 30.6, 28.5, 19.5 ppm; MS(ESI): m/z= 342 [M^+]; Anal. Calcd (%) for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.16; H, 4.17; N, 16.39.

5-(4-methoxyphenyl)-1,3,7-trimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5e)



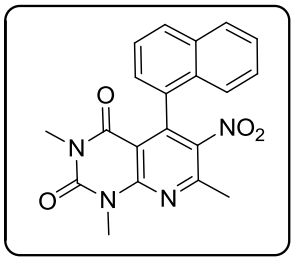
FT-IR (KBr): ν_{max}= 3425, 2923, 2362, 1713, 1671, 1565, 1487, 1342.cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.13 (d, *J*= 8 Hz, 2H), 6.95 (d, *J*= 8 Hz, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.34 (s, 3H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 160.2, 159.5, 154.4, 150.9, 146.3, 128.7, 124.0, 113.8,106.3, 55.2, 30.4, 28.7, 21.3 ppm; MS(ESI): m/z= 356 [M^+]; Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.29; H, 4.55; N, 15.75.

1,3,7-trimethyl-6-nitro-5-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5g)



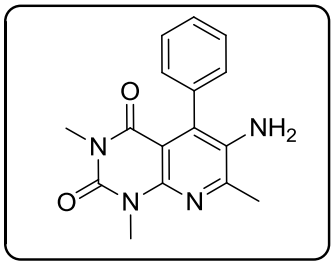
FT-IR (KBr): ν_{max}=3434, 2929, 2377, 1715, 1672, 1560, 1488, 1353 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.56 (d, *J*= 6 Hz, 1H), 7.10 (t, *J*= 4 Hz, 1H), 6.97 (d, *J*= 6 Hz, 1H), 3.77 (s, 3H), 3.37 (s, 3H), 2.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 159.0, 154.6, 150.8, 139.8, 130.9, 130.7, 128.5, 128.2, 127.0, 107.1, 30.5, 28.8, 21.4 ppm; MS(ESI): m/z= 332 [M^+]; Anal. Calcd for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.61; H, 3.67; N, 16.82.

1,3,7-trimethyl-5-(naphthalen-1-yl)-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5h)



FT-IR(KBr): ν_{max}= 3442, 2929, 2376, 1713, 1671, l1567, 1488, 1342 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.93 (dd, *J*= 8.8 , 17.2 Hz, 2H), 7.51 (q, *J*= 8 Hz, 2H), 7.38 (t, *J*= 8 Hz, 1H), 7.27 (dd, *J*= 8.8, 17.2 Hz, 2H), 3.82 (s, 3H), 3.22 (s, 3H), 2.69 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 158.7, 155.1, 150.8, 145.1, 132.9, 131.1, 130.1, 129.6, 128.7, 126.7, 126.2, 124.9, 124.7, 124.2, 107.2, 30.4, 28.6, 21.5 ppm; MS(ESI): m/z= 376 [M^+]; Anal. Calcd for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.84; H, 4.25; N, 14.91.

6-Amino-1,3,7-trimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8a)



FT-IR (KBr): ν_{max}= 3467, 3369, 2928, 2374, 1702,1647, 1570, 1455, 1314 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ= 7.43-7.35 (m, 3H), 7.10 (d, *J*= 8 Hz, 2H), 4.19 (bs, 2H), 3.53 (s, 3H), 3.08 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C (100 MHz, DMSO-d_6): δ= 160.2, 150.5, 149.0, 142.2, 136.4, 133.2, 128.7, 128.0, 127.4, 106.0, 29.3, 27.9, 22.1 ppm; MS (ESI): m/z =296 [M^+]; Anal. Calcd (%) for $C_{16}H_{14}N_4O_4$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.93; H, 5.52; N, 18.83.

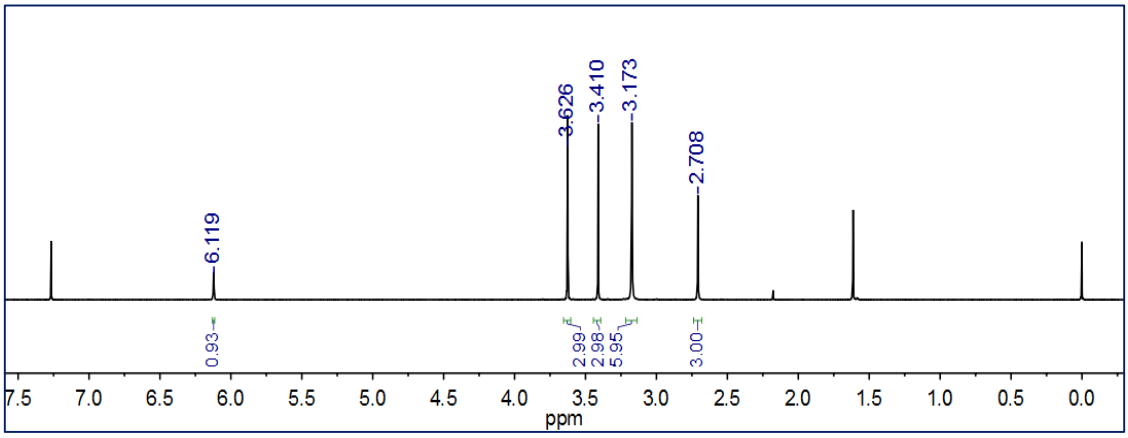


Fig. 5: ^{1}H NMR spectrum of compound **2**

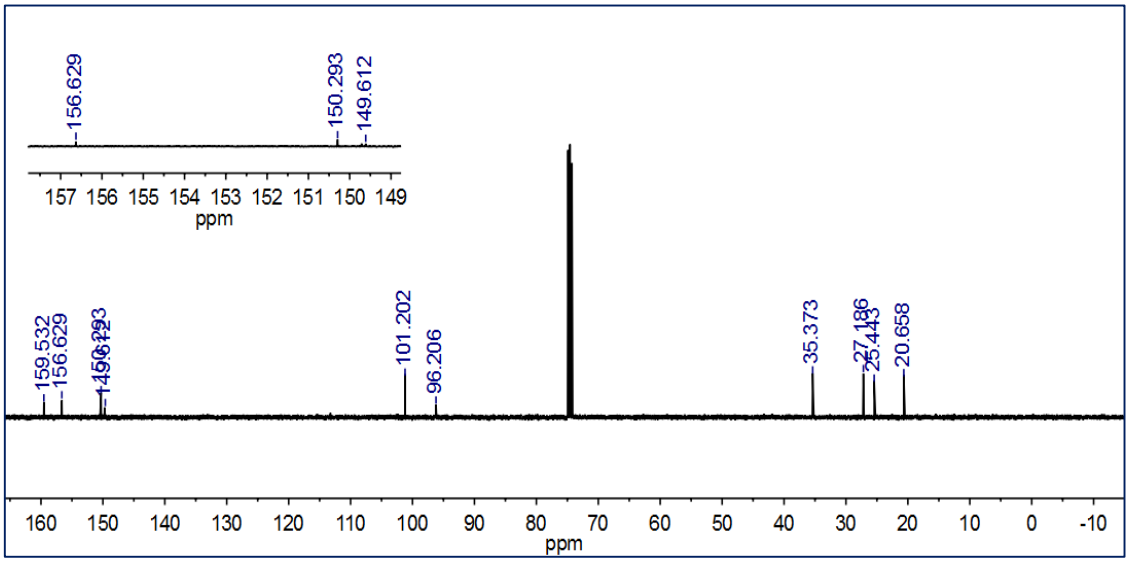


Fig. 6: ^{13}C NMR spectrum of compound **2**

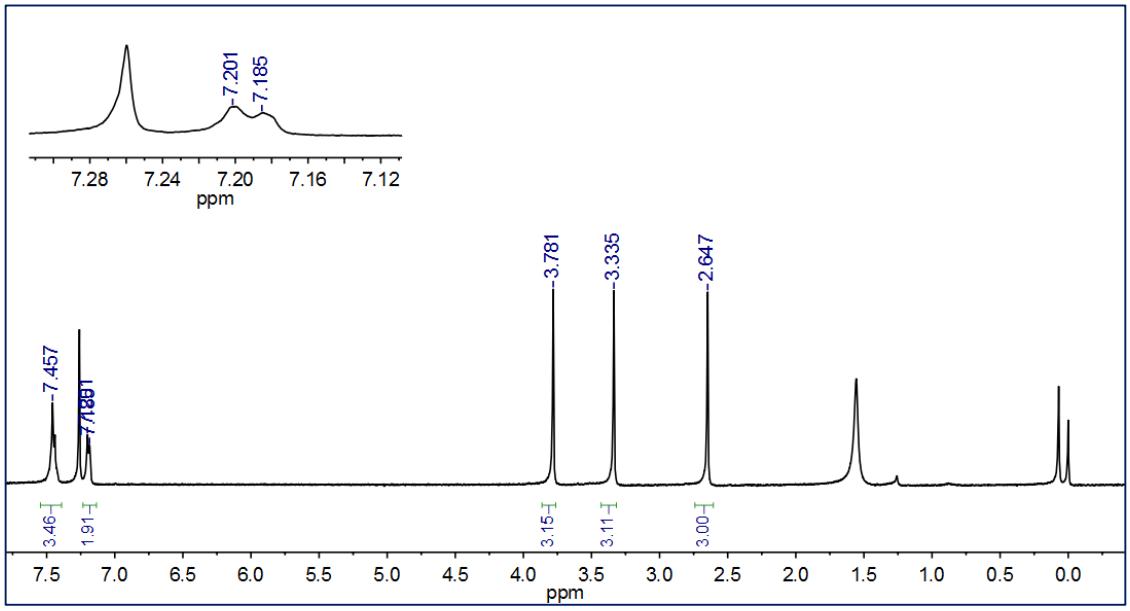


Fig. 7: ^{1}H NMR spectrum of compound **5a**

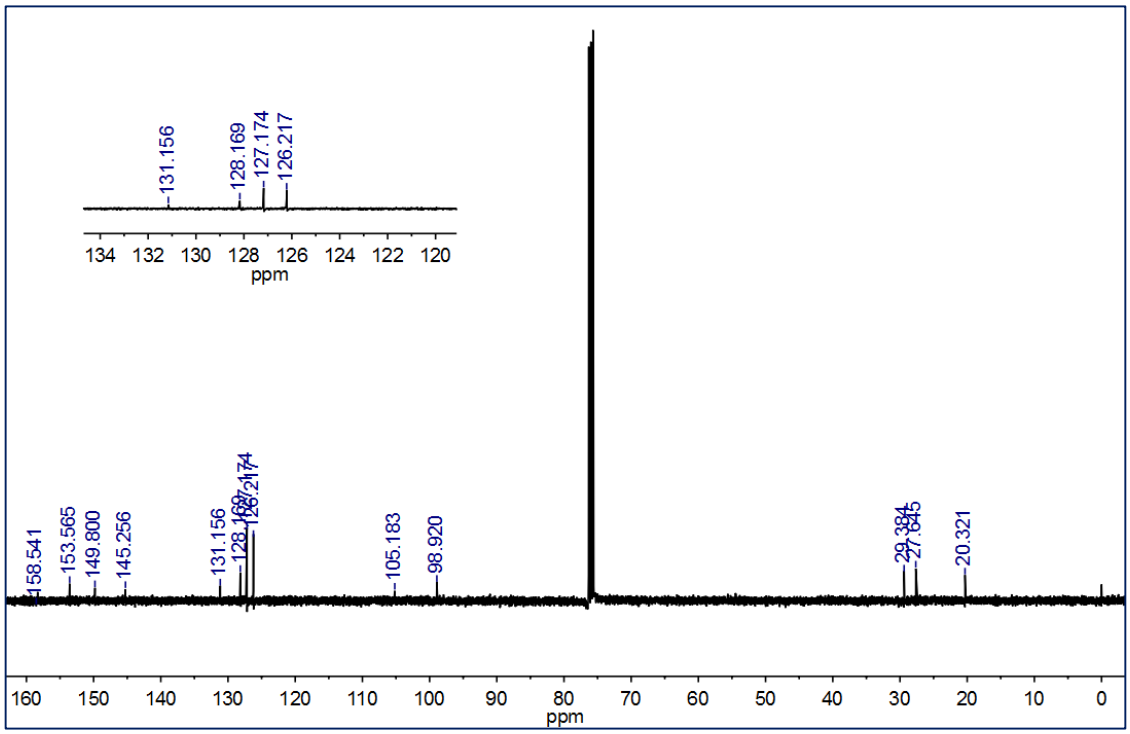


Fig. 8: ^{13}C NMR spectrum of compound **5a**

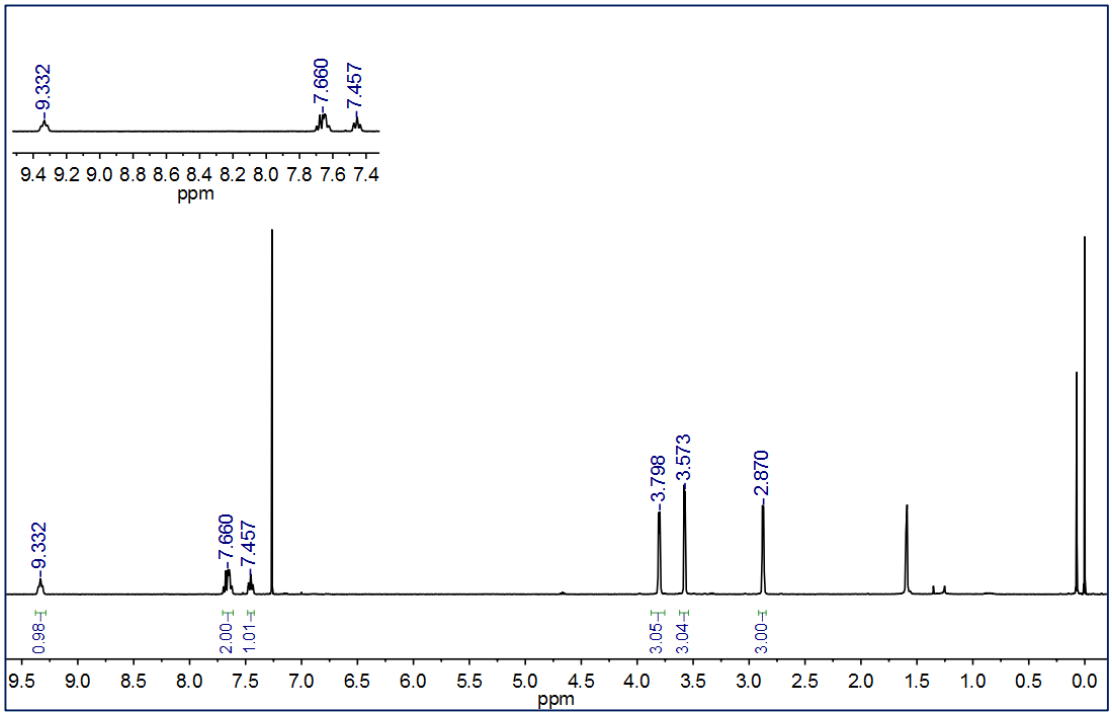


Fig. 9: ^{1}H NMR spectrum of compound **5d**

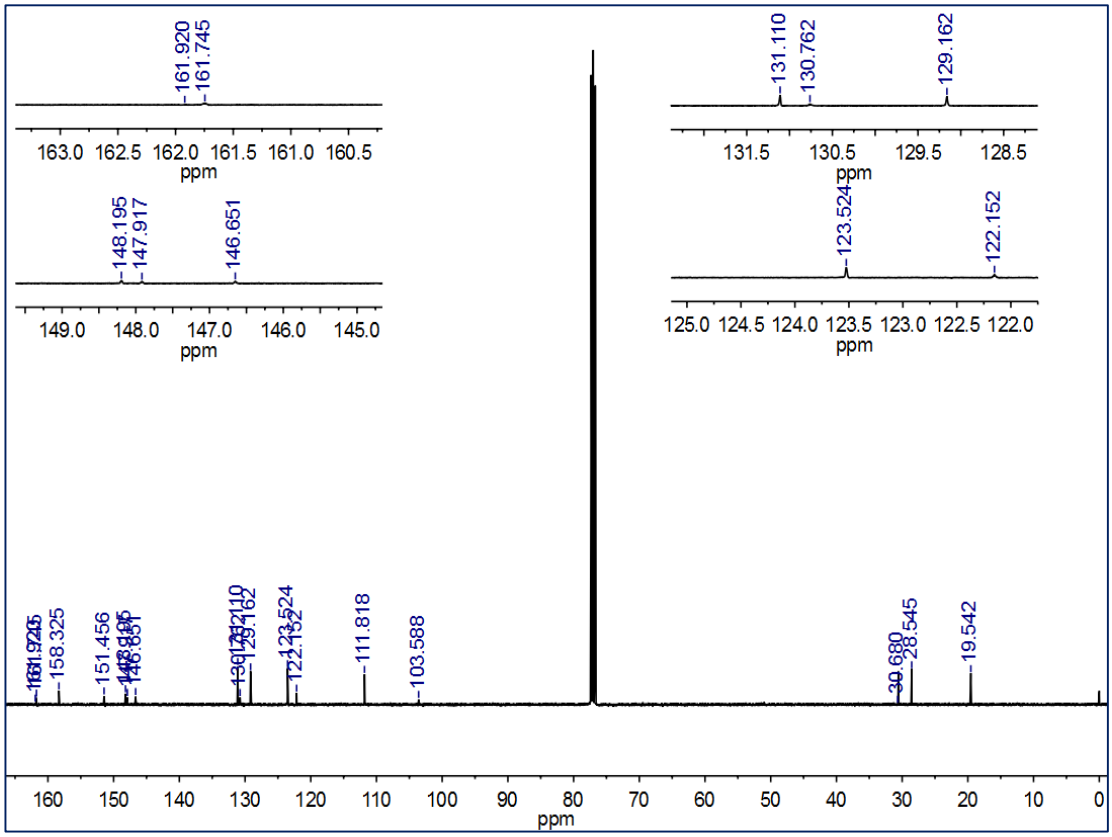


Fig. 10: ^{13}C NMR spectrum of compound **5d**

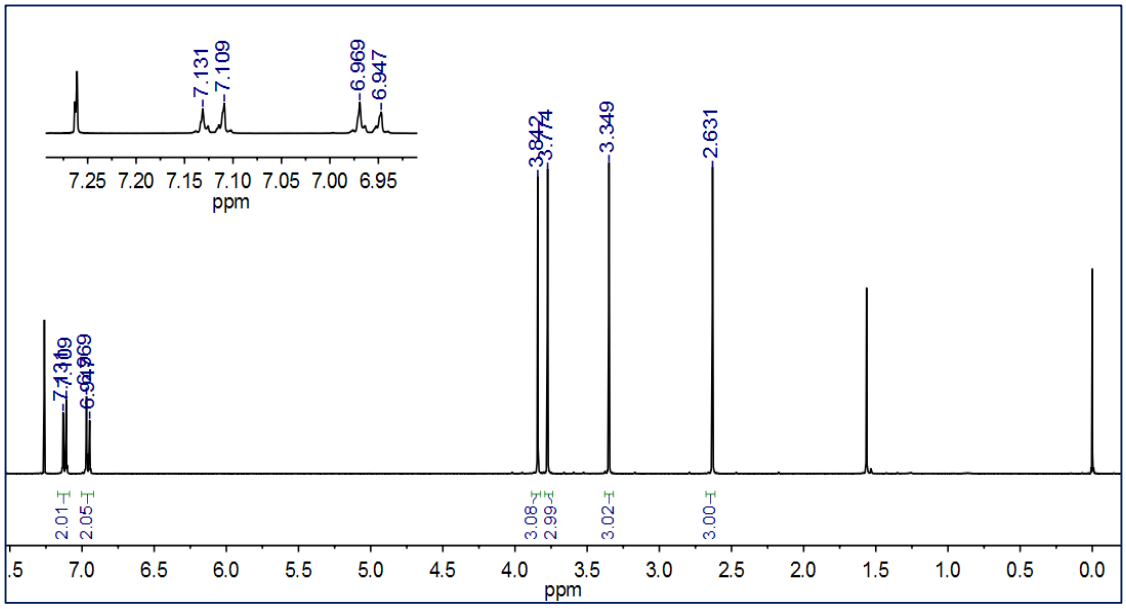


Fig. 11: ^{1}H NMR spectrum of compound **5e**

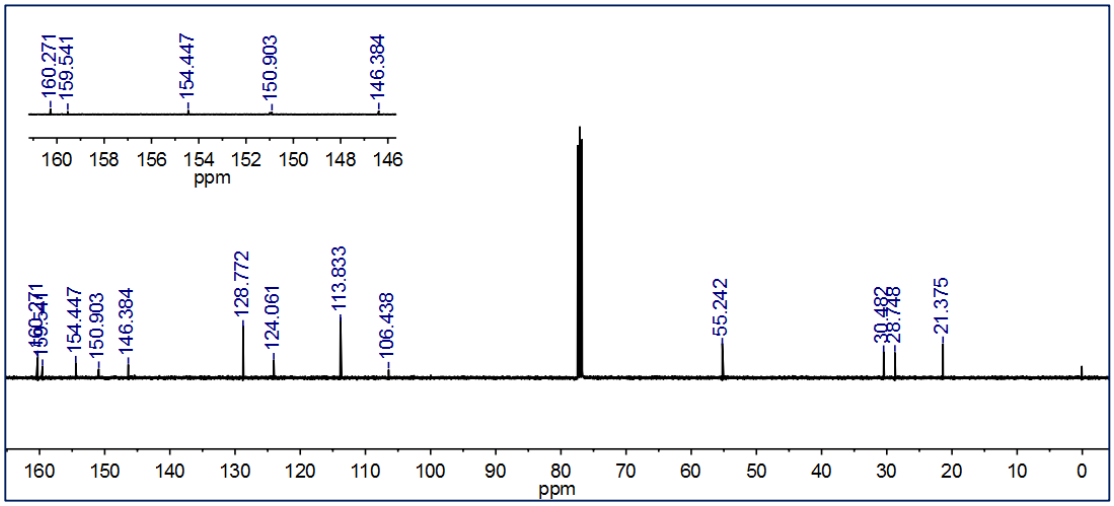


Fig. 12: ^{13}C NMR spectrum of compound **5e**

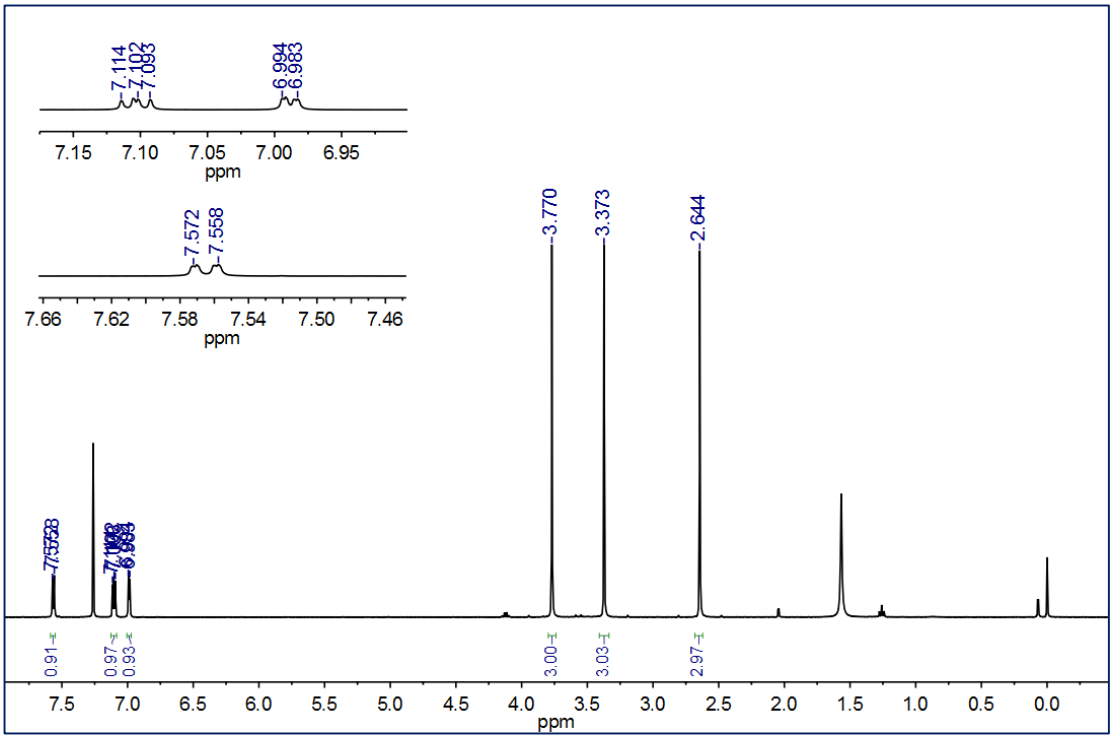


Fig. 13: ^{1}H NMR spectrum of compound **5g**

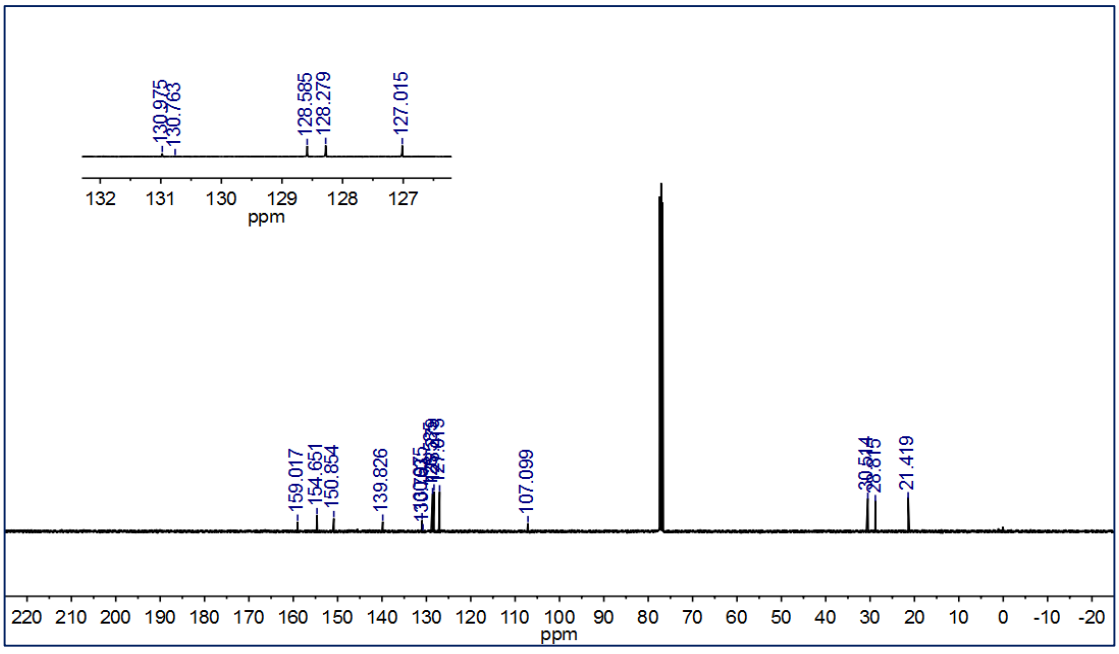


Fig. 14: ^{13}C NMR spectrum of compound **5g**

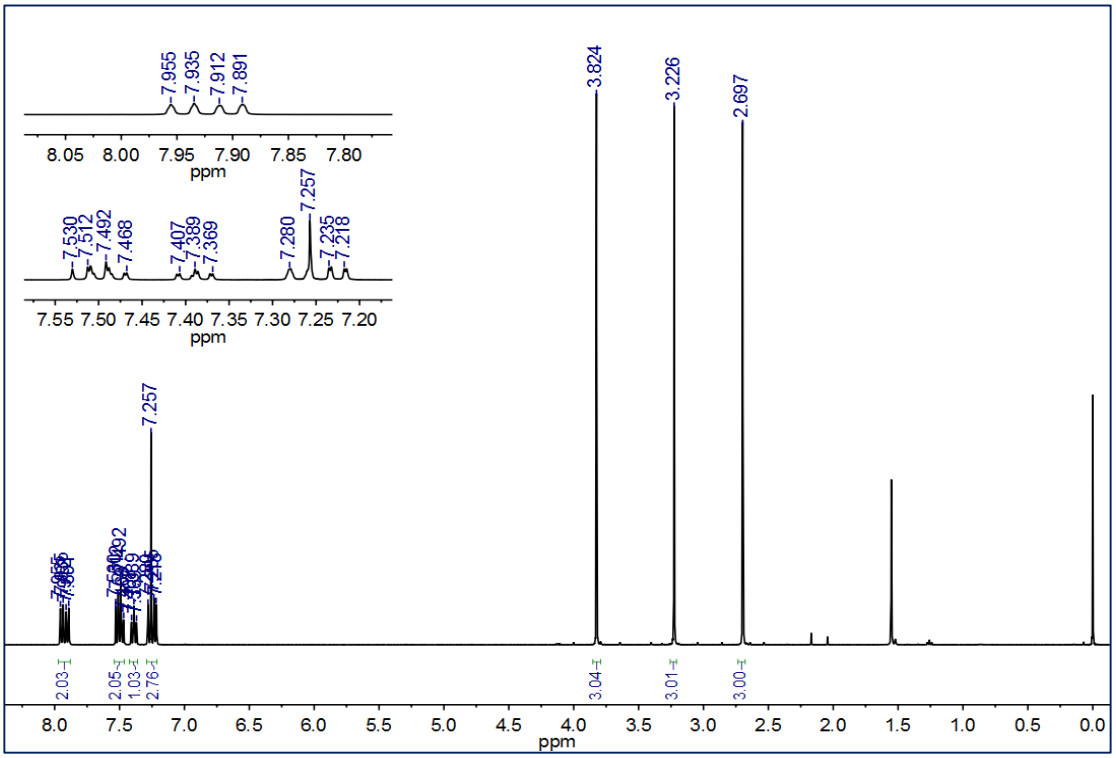


Fig. 15: ^{1}H NMR spectrum of compound **5h**

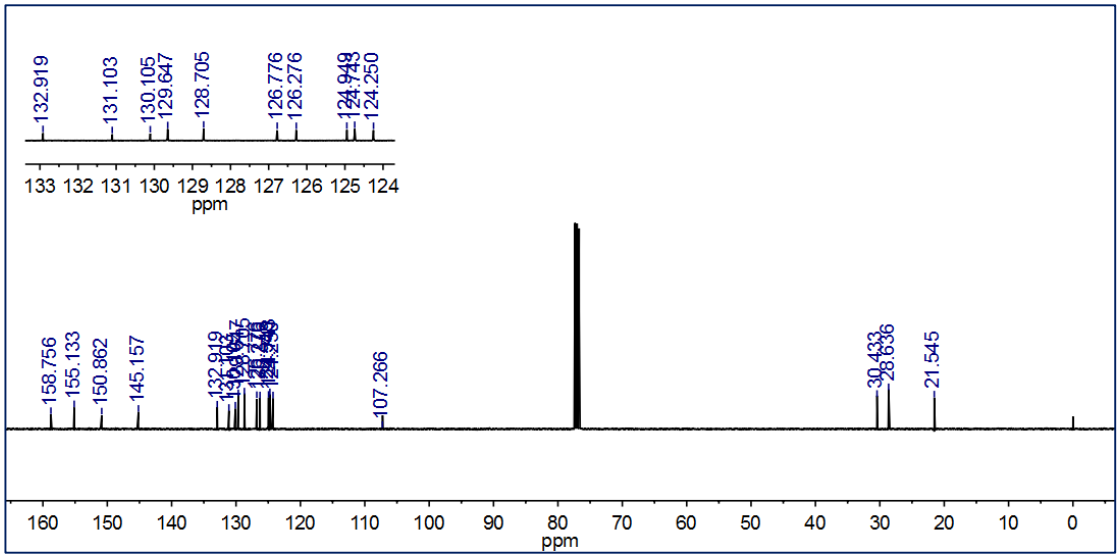


Fig. 16: ^{13}C NMR spectrum of compound **5h**

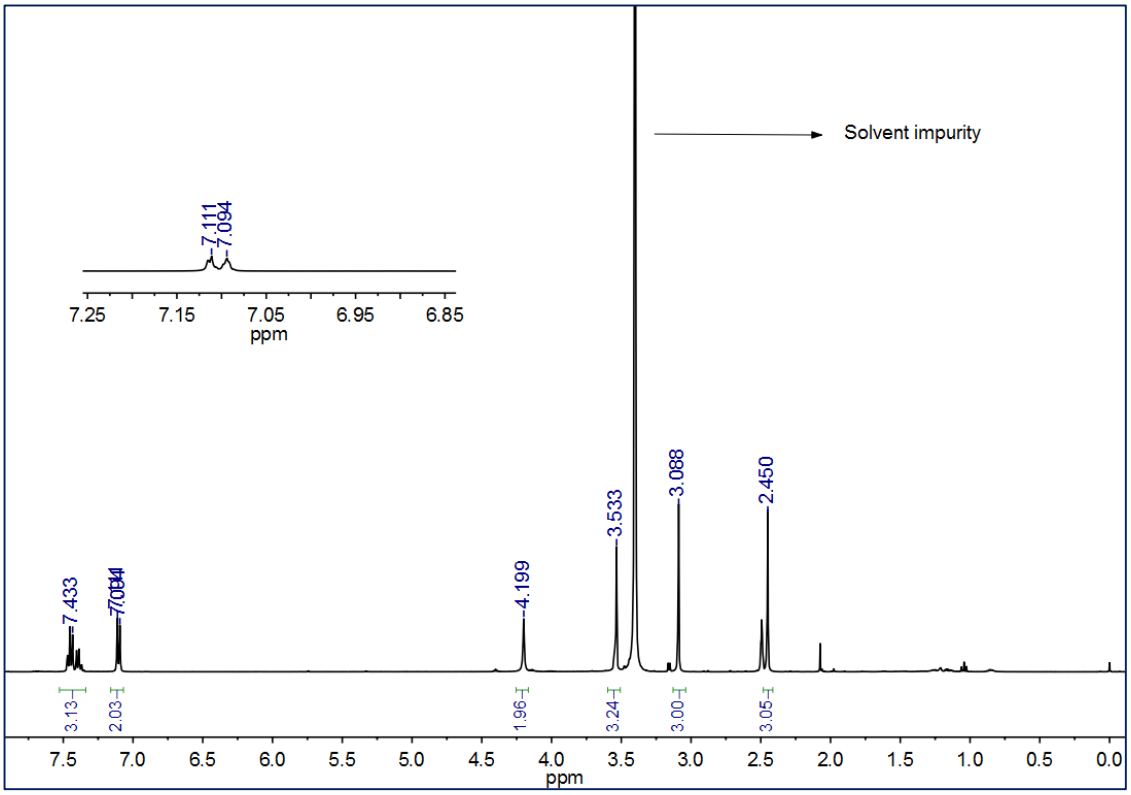


Fig. 17: ^{1}H NMR spectrum of compound **8a**

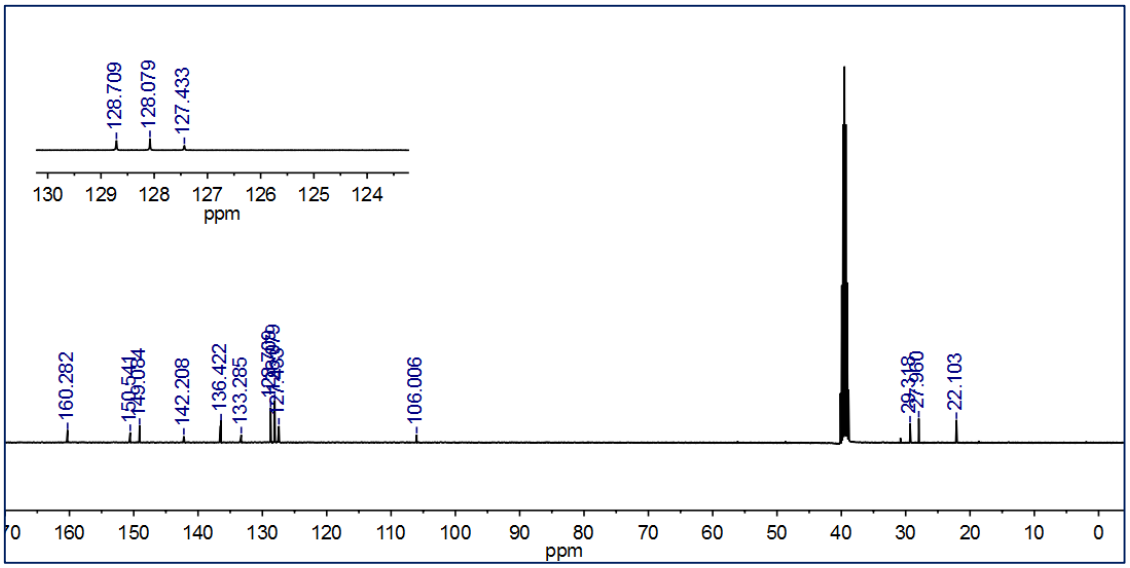


Fig. 18: ^{13}C NMR spectrum of compound **8a**

2.5 References

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