Chapter 4

Part-A

Synthesis of D-ring annelated aryl substituted pyrido steroids from steroidal 1,5-dicarbonyl compounds

4A.1 Introduction

Pyridine is an important class of azaheterocycle found in many natural products, active pharmaceuticals, and functional materials.[1] This heterocyclic ring system is composed of five carbon atoms and one nitrogen atom. It is a cyclic aromatic imine and behaves as weak base as it can donate a lone pair of electrons of nitrogen. Pyridine ring is found in many natural products and this wide occurrence may be attributed to the stability of the ring and ease of its formation. Some of pyridine-based natural products are pyridoxine or vitamin $B_{6,}$ nicotinamide or niacinamide, nicotianamide adenine dinucleotide (NAD), and alkaloids like nicotine, anabasine, coniine, piperine, quinine, morphine, and ricinine. Diploclidine[2] and nakinadine A[3] are two examples of recently isolated and structurally diverse natural products containing the pyridine core (Figure 4A.1).

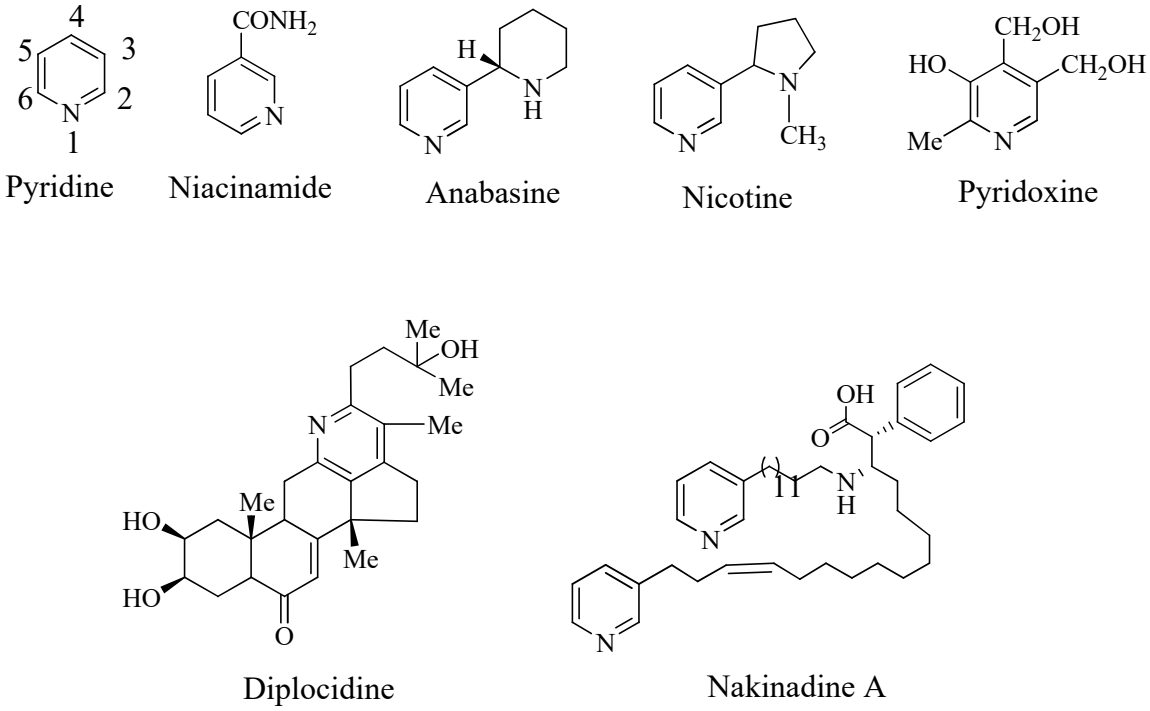
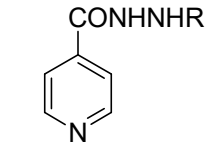
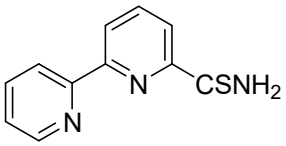


Figure 4A.1 The pyridine ring and some naturally occurring pyridine compounds

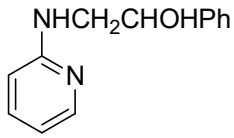
In addition to naturally occurring compounds, a large number of synthetic pyridine derivatives exist with enhanced biological properties. Pyridine-derived pharmaceuticals include atazanavir[4] (Reyataz) and imatinib mesylate[5] (Gleevec) (Figure 4A.2). These drugs are prescribed for human immunodeficiency virus (HIV) and chronic myelogenous leukemia, respectively. Pyridine derivatives are also incorporated into polymers such as polyvinyl pyridine (PVP).[6] Some other important pharmaceutical and veterinary applications of pyridine are as antihistaminic (doxylamine), antidepressant (iproniazid), anthelmintic (2-venylpyridine), analgesic and antirheumatic (phenyramidol), antifungal (2-mercaptopyridine-1-oxide), antituberculotic (isonicotinic hydrazide), and anticancer (2,2/-dipyridine-6-thiocarbamide).[7]



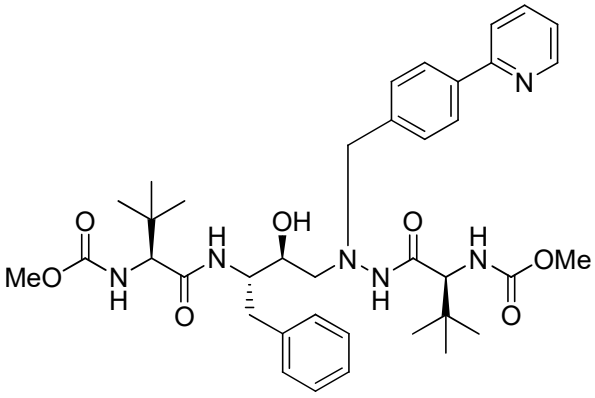
Isoniazid , R = H
Iproniazid, R = CO_2Me



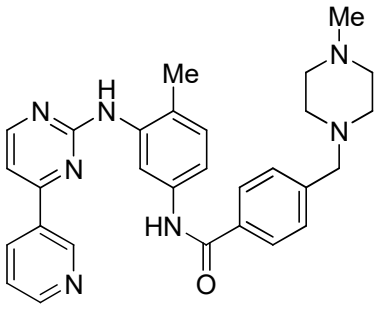
2,2/-Dipyridine-6-thiocarbamide



Phenyramidol



Atazanavir



Imatinib Mesylate

Figure 4A.2 Some biologically important synthetic pyridine derivatives

Pyridines fused to steroidal structure also exhibit interesting biological activities like other steroidal heterocycles. The importance of Abiraterone and Finasteride (**2**) as anticancer

drug is already discussed in Introduction and part B of chapter 3. Steroidal D-ring annelated pyridones and pyridines as **1** and **2** (Figure 4A.3) have shown excellent antiinflammatory activity.[8]

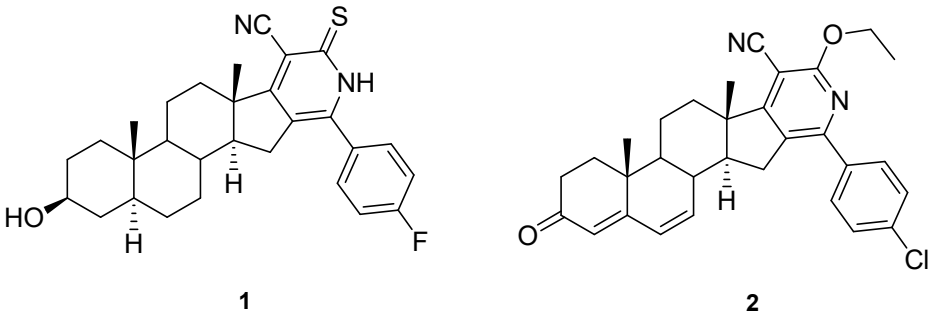
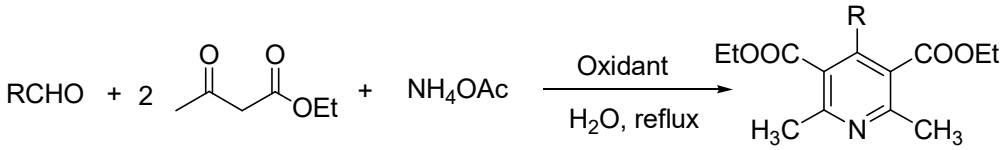


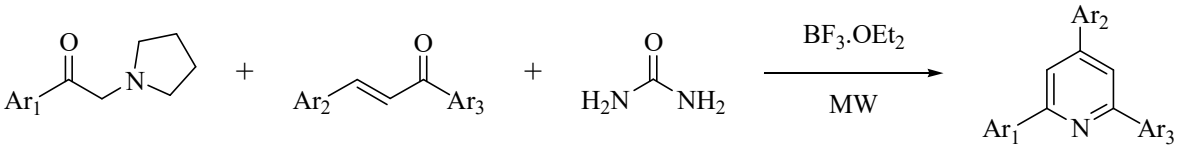
Figure 4A.3 Steroidal pyridines having ant-inflammatory properties

For well over a century, efforts are being made to develop methodologies for pyridine synthesis due to the continued importance of the pyridine core in both biological and chemical fields.

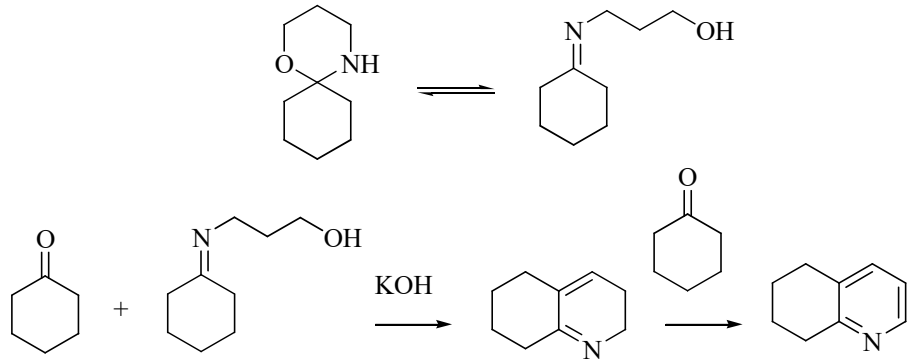


Hantzsch synthesis[9a] is one of the oldest methods for pyridine ring construction where ethyl acetoacetate, an aldehyde and ammonia (or other nitrogen donor) reacts to gave 1, 4-dihydro-3, 5-disubstituted pyridine. The dihydropyridine can easily be oxidized to pyridine. An improved Hantzsch pyridine synthesis was reported from aldehyde, ethylacetoacetate or acetylacetone and ammonium acetate using water as reaction medium.[9b] Presence of an oxidant in the reaction media led to *in situ* aromatization of dihydropyridines to corresponding pyridines.

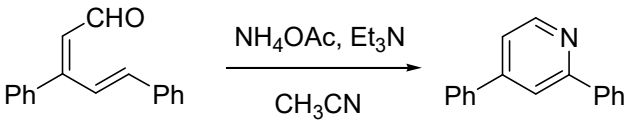
Boruah and co-workers successfully synthesized 2,4,6-triarylpyridine derivative via microwave-promoted and $BF_3.OEt_2$ catalysed one-pot reaction of ω-pyrrolidinoacetophenone, chalcone and urea.[10]



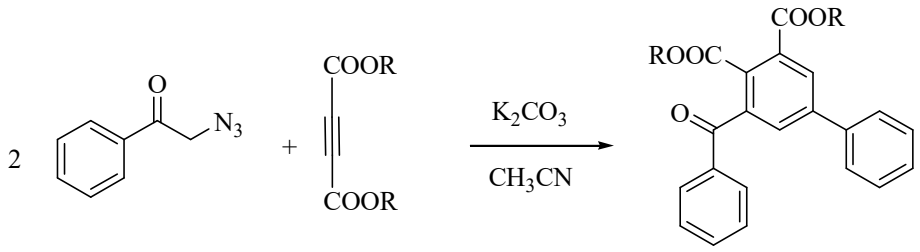
Pyridine derivatives were prepared by Kukharev and co-workers[11] by oxidation of perhydro-1,3-oxazines with cyclohexanone. The reaction proceeded through intramolecular condensation of imino alcohol, which is an open-chain tautomer of perhydro-1,3-oxazine, followed by oxidation with cyclohexanone.



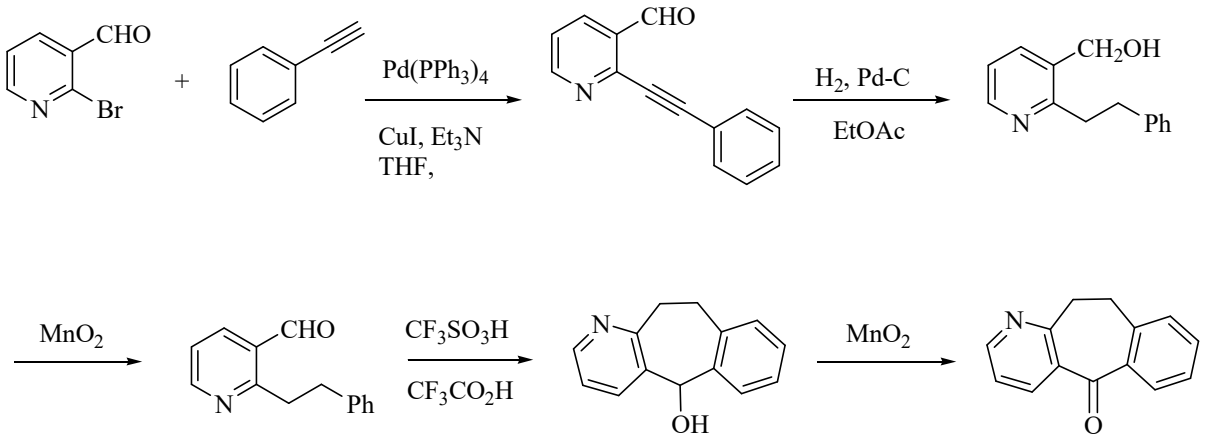
A number of 2,4-disubstituted pyridines were synthesized by Singha and co-workers[12] using *α,β,γ,δ*-unsaturated aldehydes and ammonium chloride in presence of triethylamine in acetonitrile solvent at 80 ^oC.



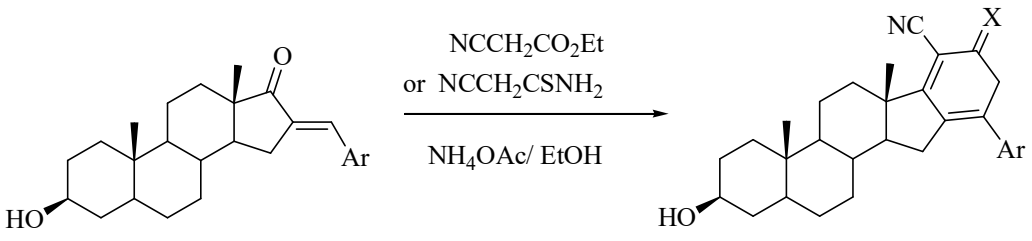
Chen and co-workers[13] reported a facile and efficient method for the synthesis of tetrasubstituted pyridines by the reaction of α-azidomethyl aryl ketones and dialkyl but-2-ynedioate in mild condition.



Naredla and co-workers[14] prepared some cycloheptabenzopyridine derivatives by cyclization reactions pyridinecarboxaldehydes in acidic media. These pyridinecarboxaldehydes were prepared from 2-bromo-3-pyridinecarboxaldehyde.

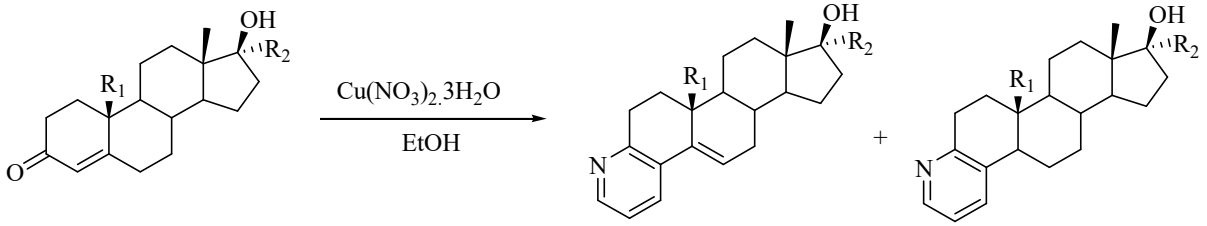


Amr and his co-workers[15] prepared a novel class of pyridines and pyridones fused to steroidal structure by the reaction of 16-arylmethylene-17-keto steroids with different reagents. Almost all of the prepared compounds were found to exhibit anti-inflammatory activities.



X = O or S

Pyridine rings fused to the 3, 4-positions of steroid nucleus were obtained by Yan and co-workers[16] in a reaction of propargylamine with 4-en-3-one steroids catalyzed by Cu(II).



R^1 = CH_3, H
R^2 = H, CH_3

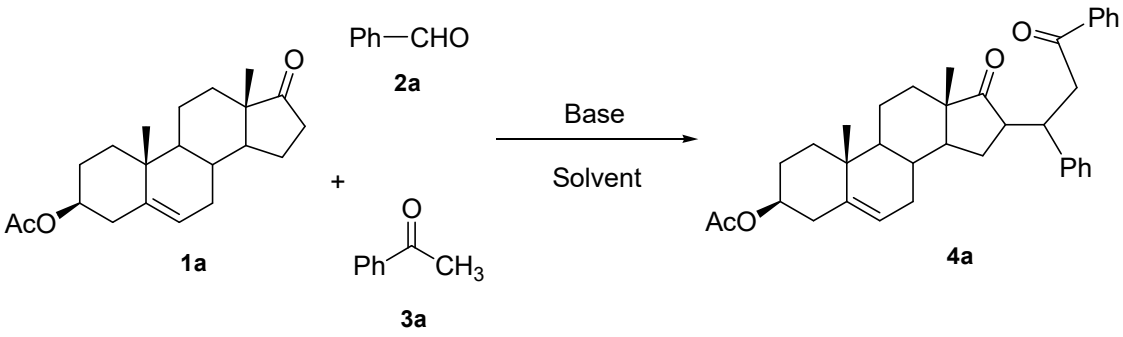
The above discussions clearly show that pyridine is an interesting class of aza-heterocyclic compound because of its presence in the core system of many biologically active compounds and other complex heterocycles. Therefore development of a new strategy for pyridine ring construction is considered to be important as they provide either a tool to easily inaccessible pyridine scaffolds or an improved procedure to replace existing synthesis.

The present study describes the synthesis of some D-ring annelated substituted pyridosteroids from steroidal 1,5-dicarbonyl compounds. The reaction proceeded through the formation of steroidal 1,5-dicarbonyl compounds by a one-pot multi-component reaction from 17-ketosteroid, an aldehyde and a ketone. The pyridosteroids were then obtained by the reaction of 1,5-dicarbonyl compounds with ammonium acetate in acetic acid under reflux condition.

4A.2 Results and discussion

Preparation of Steroidal 1,5 dicarbonyl compounds:

The initial effort was directed towards developing a suitable method for the synthesis of steroidal 1,5-dicarbonyl compound. Hence, 3*β*-Acetoxyandrost-17-one **1a**, benzaldehyde (**2a**) and acetophenone (**3a**) were selected as substrates for the synthesis of compound **4a** (Scheme 4A.1).



Scheme 4A.1

It was observed that the reaction was unsuccessful in most of the protic and aprotic organic solvents and poor yield was obtained in protic solvent (Entry 1-5, Table 4A.1). However, when the reactants were stirred in toluene at room temperature, a 4,5-diaryl-1,5-dicarbonyl steroidal derivative was obtained as the only product in excellent yield (Entry 6, Table 4A.1). Comparative study on different bases such as KO^{t}Bu, NaOMe, NaH and KOH showed that KOH was the most suitable base to perform the reaction to afford the 1,5-dicarbonyl derivative. When NaOMe, NaH and KO^{t}Bu were used in place of KOH, yield of **4a** was obtained 30%, 27% and 31%, respectively (Entry 7-9, Table 4A.1). It was observed that increasing the reaction time also could not result better yield under these conditions.

Table 4A.1 Optimization of reaction conditions for synthesis of compound

Entry	Solvent	Base	Reaction condition	Time (hour)	Yield (%)[a]
1	DMF	KOH	reflux	12	No reaction
2	THF	KOH	reflux	15	No reaction
3	CH_3CN	KOH	reflux	14	No reaction
4	EtOH	KOH	reflux	12	20
5	MeOH	KOH	reflux	12	26
6	Toluene	KOH	Stirring, rt	6	90
7	Toluene	NaOMe	Stirring, rt	12	30
8	Toluene	^{t}BuOK	Stirring, rt	12	31
9	Toluene	NaH	Stirring, rt	12	27

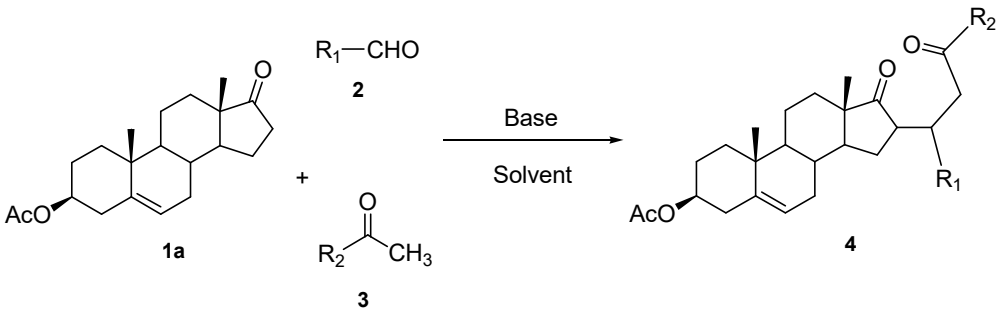
[a]Isolated yield

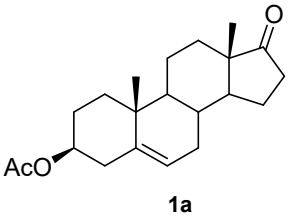
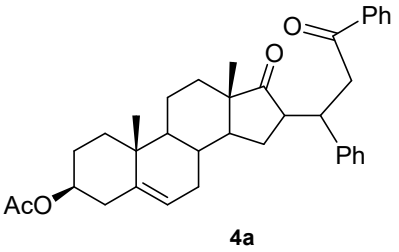
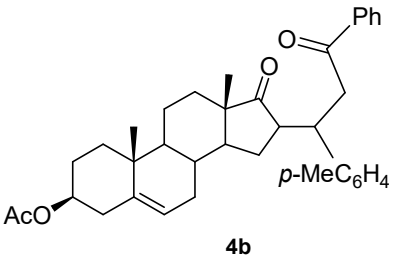
The structure of compound **4a** was confirmed by NMR, IR and mass spectrometric analysis. The IR spectrum of compound **4a** showed the presence of two sharp band at 1729 and 1629 cm^{-1} for two 1,5-dicarbonyl carbon. The ^1H NMR spectrum showed characteristic multiplet signal at 5.33-5.44 for olefinic proton and at 7.03-7.67 for aromatic protons. The ^{13}C NMR spectrum showed two peaks at 170.2 and 207.5 respectively for acyclic and cyclic carbonyl carbons. Finally structure of **4a** was confirmed by EI mass spectrum which showed strong molecular ion peak (M+) at m/z 478 $[M-60]^+$.

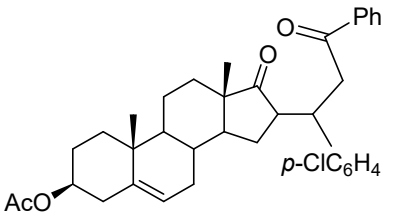
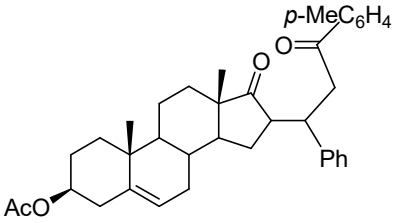
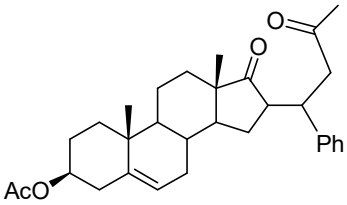
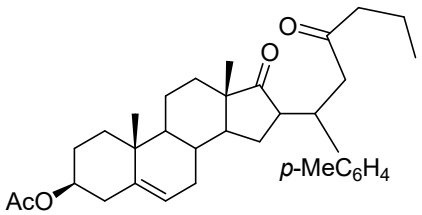
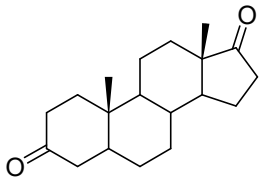
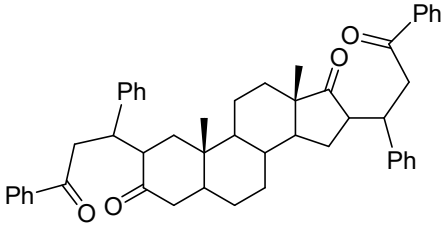
The scope of the reaction was then investigated by employing a variety of aldehydes and arylketones including both electron-deficient and electron-rich groups. The results of this

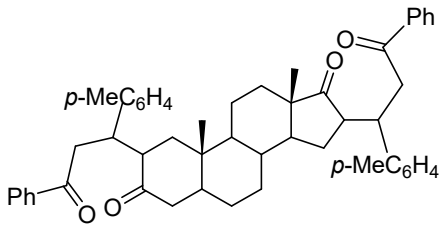
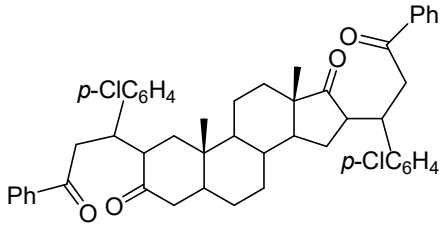
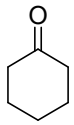
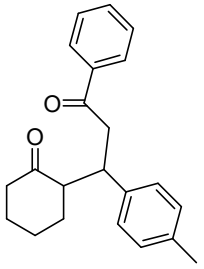
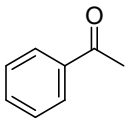
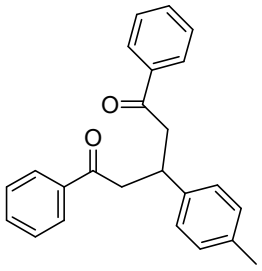
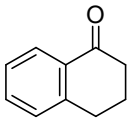
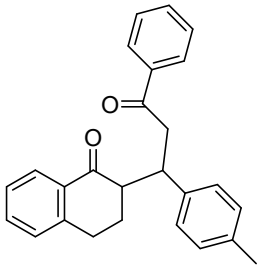
study are summarised in Table 4A.2. Interestingly, the 1,5-dicarbonyl compound was obtained in excellent yield in all cases with little variation of reaction time depending on the nature of the substituent present. Further the reaction was extended to non-steroidal monocyclic and bicyclic ketones (**1c-e**) and in all the cases the corresponding 1,5-dicarbonyl compounds (**4j-l**) were isolated in good yields. All the results are summarized in Table 4A.2. Thus, the products obtained were characterized by various spectroscopic means such as NMR, IR and mass spectrometric analysis.

Table 4A.2 Synthesis of various substituted 1,5-dicarbonyl compounds **4a-l**



Entry	Ketone	R_1	R_2	1,5-dicarbonyl Compound	Yield (%)[a]
1	 **1a**	Ph	Ph	 **4a**	96
2	**1a**	4-Me-Ph	Ph	 **4b**	93

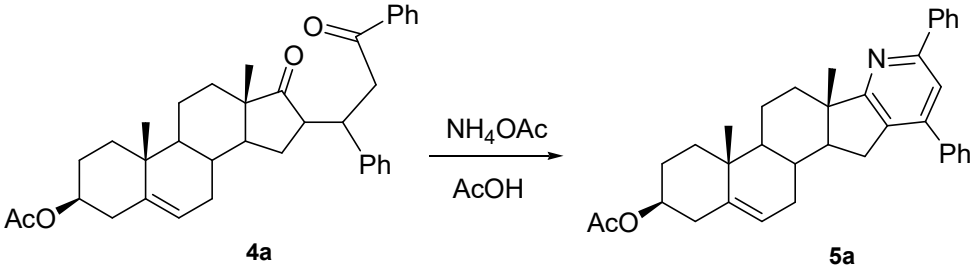
3	**1a**	4-Cl-Ph	Ph	 **4c**	93
4	**1a**	Ph	4-Me-Ph	 **4d**	93
5	**1a**	Ph	Me	 **4e**	90
6	**1a**	4-Me-Ph	C_3H_7	 **4f**	96
7	 **1b**	Ph	Ph	 **4g**	91

8	**1b**	4-Me-Ph	Ph	 **4h**	92
9	**1b**	4-Cl-Ph	Ph	 **4i**	86
10	 **1c**	4-Me-Ph	Ph	 **4j**	95
11	 **1d**	4-Me-Ph	Ph	 **4k**	92
12	 **1e**	4-Me-Ph	Ph	 **4l**	91

[a]Yield of the isolated product.

Preparation of D-ring annelated pyridosteroids from steroidal 1,5-dicarbonyl compounds:

The D-ring annelated pyridosteroids have been prepared using steroidal 1,5-dicarbonyl compounds as starting material. The reaction of 1,5-dicarbonyl compound **4a** with ammonium acetate was explored as the first example. Accordingly, compound **4a** (1 mmol) was refluxed with ammonium acetate (1 mmol) using acetic acid as solvent and product **5a** was obtained as pale yellow solid (Scheme 4A.2).



Scheme 4A.2

The compound **5a** has R_f value of 0.7 (10% EtOAc in hexane). The IR spectrum also showed the absence of absorptions at 1729 and 1629 cm^{-1} due to two carbonyl groups. The ^1H NMR spectrum showed a characteristic signal at 7.72 for pyridine proton. The ^{13}C NMR spectrum showed the absence of carbonyl carbons at δ 207.9. Finally, the the compound **5a** was confirmed by EI mass spectrum which showed the molecular ion peak at 518.3.

The reaction of 1,5-dicarbonyl compound **4a** was also studied with different solvent and ammonia sources to determine the ideal reaction condition. However, the yields of all the reactions in polar protic and aprotic solvents were found to be unsatisfactory. When the reaction of **4a** was carried out under reflux condition in methanol and ethanol for 5 hours, the product **5a** was obtained in 20 and 25% respectively. However, when acetic acid was used as solvent, the pyridine compound **5a** was formed in excellent yield (90%). Thus acetic acid was

found to be the most effective solvent to perform this reaction. The results obtained are summarized in Table 4A.3.

Table 4A.3 Solvent effect for the synthesis of various pyridine derivatives

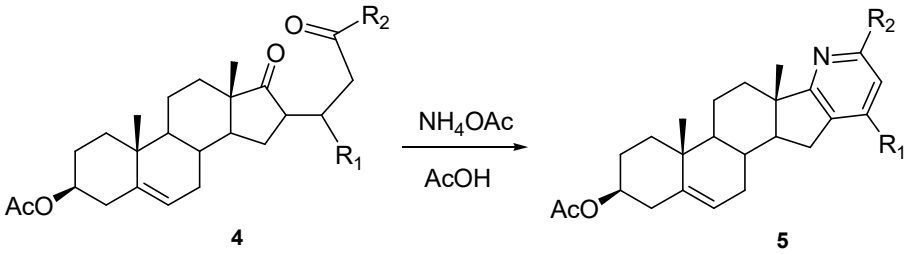
Entry	Solvent	Time (hrs)	Yield (%)[a]
1	Methanol	5	20
2	Ethanol	5	25
3	Toluene	8	No reaction
4	Acetonitrile	8	No reaction
5	Tetrahydrofuran	8	No reaction
6	Acetic acid	2	90

[a]Yield of the isolated product.

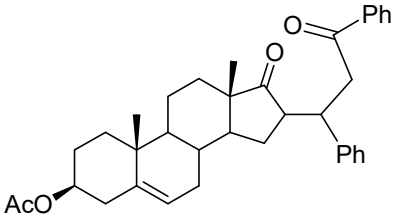
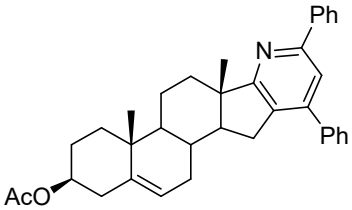
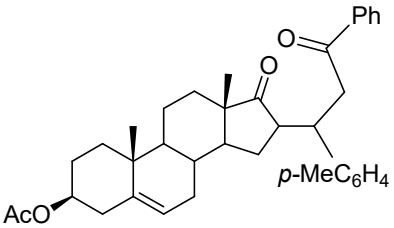
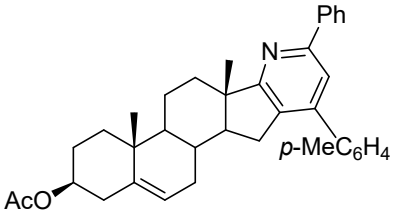
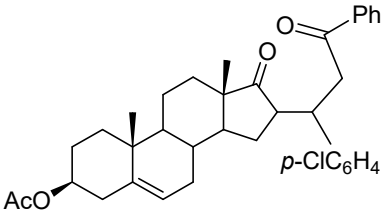
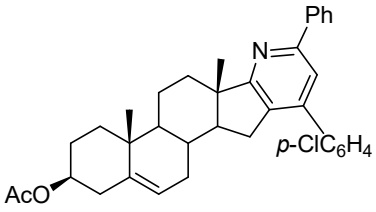
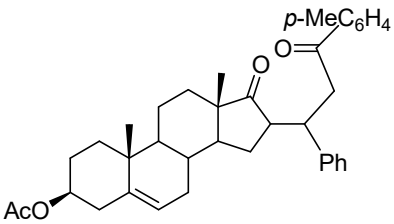
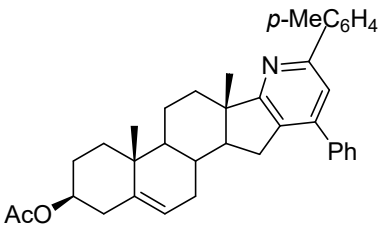
Further, it was observed that when aqueous (19.5%) ammonia was directly employed as source to carry out the reaction in acetic acid, the product **5a** was formed only in 50% yield. As urea is environmentally benign and safe source of ammonia, the reaction was tried with urea also. When 1,5-dicarbonyl compound **4a** was reacted with urea in acetic acid under reflux condition, the steroidal pyridine **5a** was obtained in poor yield (20%). When the reaction of 1,5-dicarbonyl compound with ammonium acetate was performed in neat condition using MW and the yield was obtained 85%. Consequently, it was observed that thermal heating in acetic acid was a superior strategy than neat microwave mediated reaction.

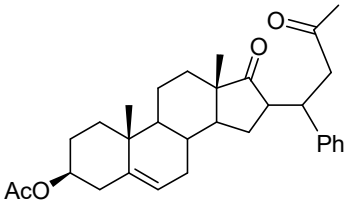
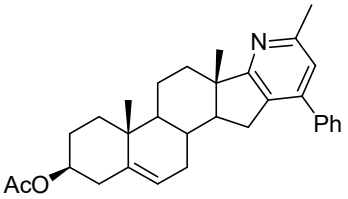
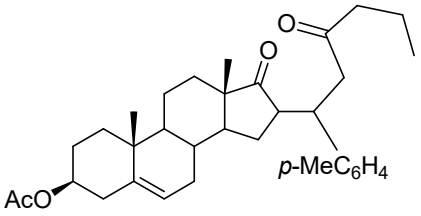
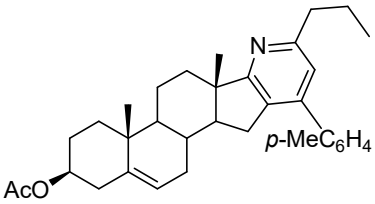
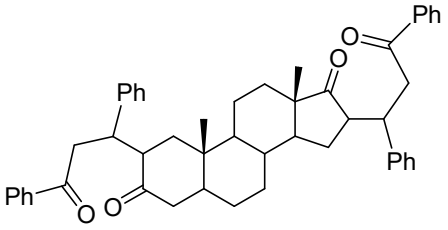
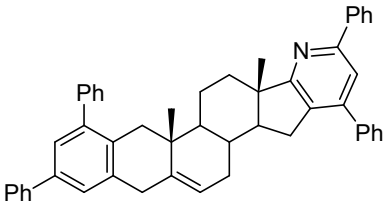
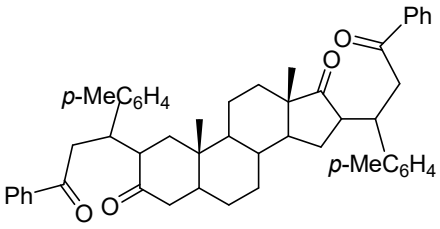
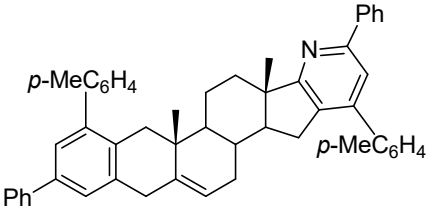
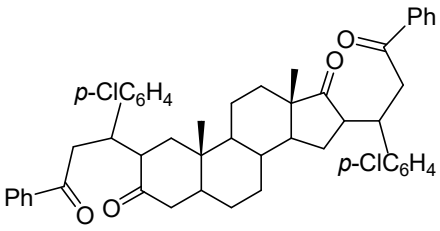
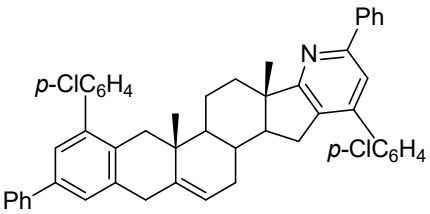
Under the optimised condition (Entry 6, Table 4A.3), the reaction was studied with variety of steroidal as well as non-steroidal 1,5-dicarbonyl compounds. The results are summarised in Table 4A.4. All the compounds were characterised and confirmed by NMR, IR and mass spectrometric analysis.

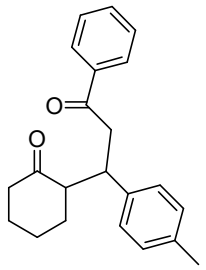
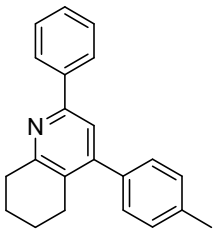
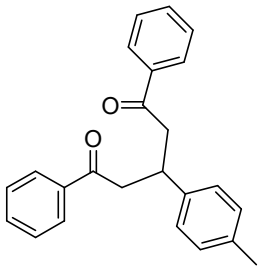
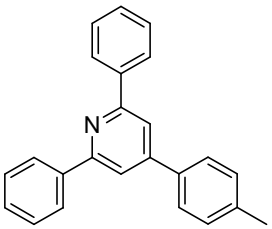
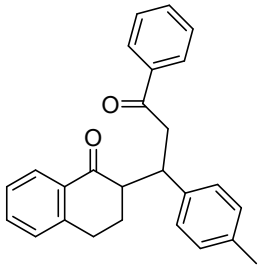
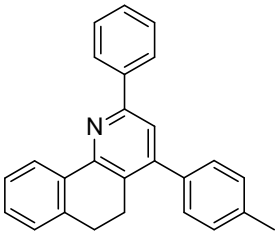
Table 4A.4 Synthesis of various substituted pyridine derivatives **5a-l**



4 **5**

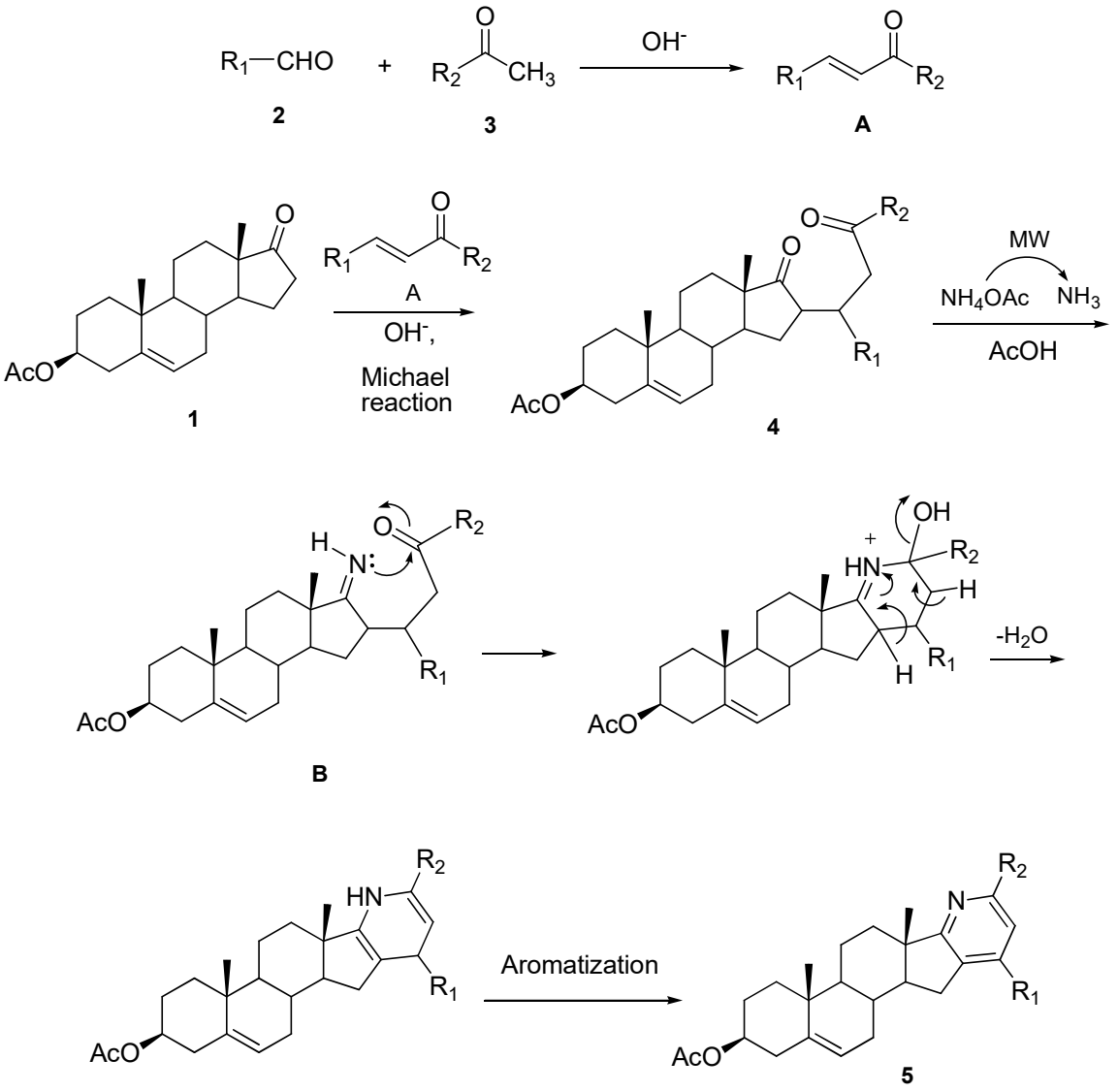
Entry	1,5 di-carbonyl Compound	Pyridine derivative	Yield (%)[a]
1	 **4a**	 **5a**	94
2	 **4b**	 **5b**	95
3	 **4c**	 **5c**	96
4	 **4d**	 **5d**	93

5	 **4e**	 **5e**	90
6	 **4f**	 **5f**	96
7	 **4g**	 **5g**	83
8	 **4h**	 **5h**	84
9	 **4i**	 **5i**	80

10	 **4j**	 **5j**	95
11	 **4k**	 **5k**	90
12	 **4l**	 **5l**	90

[a]Yield of the isolated product.

The probable mechanism for the formation of the observed product may be rationalized as shown in Scheme 4A.3. Under the influence of base, steroidal ketone (**1**) undergoes Michael addition reaction to chalcones **(A)**, formed *in situ* from **2** and **3**, to afford the 1,5-dicarbonyl intermediate **(4)**. The ammonia released by ammonium acetate formed an imine intermediate **(B)** with steroidal 1,5-dicarbonyl compound **(4)**. The nucleophilic attack of the NH-group to electron deficient carbonyl functional group resulted aza cyclization reaction with subsequent loss of water to afford **5.**



Scheme 4A.3

4A.3 Conclusions

In conclusion, an efficient methodology for the synthesis of steroidal D-ring fused 4,6-diarylpyridines from steroidal 1,5-dicarbonyl compounds was developed. This methodology gave excellent yields when ammonium acetate is employed as the source of ammonia. The intermediate steroidal 1,5-diketo compounds were synthesized by Michael addition reaction of steroidal ketones with *in situ* generated chalcones from aromatic ketones

and aldehydes. The procedure involves several features such as high reaction yields, broad application scope, less catalyst loading and operation simplicity.

4A.4 Experimental

General experimental Procedure

Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR-2000 spectrometer using KBr pellets or on a thin film using chloroform. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (60-120 mesh, Merck Chemicals).

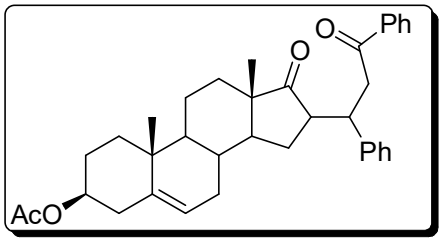
Chemical synthesis

(a) General procedure for synthesis of steroidal 1,5-dicarbonyl Compounds

To a stirring solution of steroidal ketone (1.0 mmol), aromatic aldehyde (1.0 mmol) and aryl ketone (1.0 mmol) in toluene (5.0 mL), KOH (2.0 mmol) was added at room temperature. The reaction mixture was stirred for 6 hours and after completion of the reaction, as indicated by TLC, solvent was removed under vacuum. The residue obtained was washed with water, extracted with DCM and dried over Na_2SO_4. The crude product obtained after removal of the solvent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to get pure steroidal 1,5-dicarbonyl compounds.

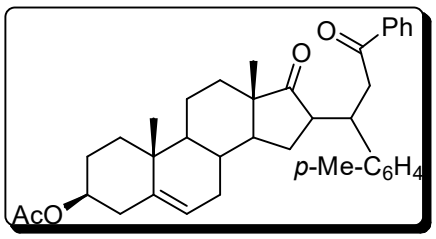
Chracterization of 1,5-dicarbonyl compounds:

3*β*-Acetoxy-16-(1′,3′-diphenyl-propyl-3′-one)-5-en-androst-17-one (4a)



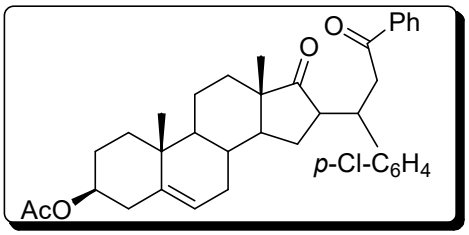
Gum, Yield 96%; IR ($CHCl_3$, cm^{-1}) 2947, 1729, 1715, 1629, 1256, 1030, 754; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-2.47 (m, 23H), 0.90 (s, 3H), 1.07 (s, 3H), 2.84-2.68 (m, 1H), 4.65-4.50 (m, 1H), 5.44-5.33 (m, 1H), 7.67-7.03 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 14.3, 19.4, 20.3, 21.3, 27.6, 29.5, 30.9, 31.0, 31.3, 31.5, 36.6, 36.8, 38.0, 47.4, 49.7, 50.0, 50.4, 73.8, 121.7, 128.1, 128.5, 129.1, 129.5, 130.2, 132.4, 133.2, 134.0, 139.1, 139.5, 140.2, 170.2, 207.5, 209.6; MS (EI, m/z) 478 $[M-60]^+$.

3*β*-Acetoxy-16-[1′-(p-methylphenyl)-3′-phenyl-propyl-3′-one]-5-en-androst-17-one (4b)



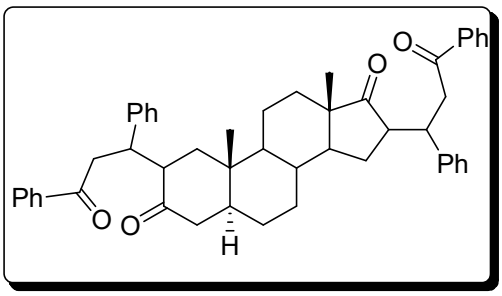
Gum, Yield 93%; IR ($CHCl_3$, cm^{-1}) 2946, 1729, 1713, 1628, 1255, 1032, 755; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88-2.45 (m, 20H), 0.89 (s, 3H), 1.09 (s, 3H), 2.04 (s, 3H), 2.44 (s, 3H), 2.68-2.85 (m, 1H), 4.51-4.60 (m, 1H), 5.34-5.42 (m, 1H), 7.00-7.64 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 14.3, 19.4, 20.4, 21.4, 21.5, 27.7, 29.4, 30.9, 31.1, 31.4, 31.46, 31.5, 36.8, 36.9, 38.1, 47.3, 49.8, 50.1, 50.2, 73.7, 121.8, 128.2, 128.6, 129.0, 129.5, 130.4, 132.8, 133.2, 134.9, 139.6, 139.9, 140.0, 170.5, 207.0, 209.8; MS (EI, m/z) 492 $[M-60]^+$.

3*β*-Acetoxy-16-[1′-(*p*-chlorophenyl)-3′-phenyl-propyl-3′-one]-5-en-androst-17-one (4c)



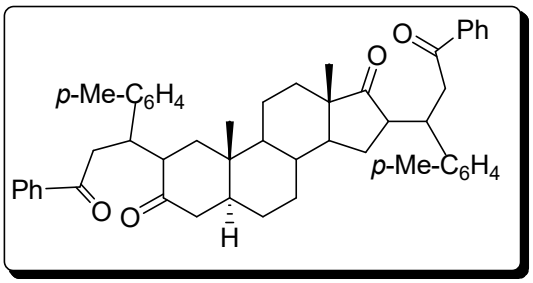
Gum, Yield 93%; IR ($CHCl_3$, cm^{-1}) 2948, 1726, 1715, 1626, 1259, 1036; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-2.43 (m, 20H), 0.91 (s, 3H), 1.08 (s, 3H), 2.03 (s, 3H), 2.68-2.84 (m, 1H), 4.53-4.62 (m, 1H), 5.34-5.42 (m, 1H), 7.05-7.63 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 14.4, 19.4, 20.4, 21.4, 27.5, 29.4, 30.9, 31.2, 31.4, 31.46, 31.5, 36.8, 36.9, 38.1, 47.2, 49.8, 50.1, 50.2, 73.5, 121.8, 128.2, 128.6, 129.0, 129.5, 130.4, 132.8, 133.1, 134.7, 139.6, 139.7, 140.1, 170.4, 207.2, 209.5; MS (EI, m/z) 512 $[M-60]^+$, 514 $[(M+2)-60]^+$.

2,16-Bis[1′-phenyl-3′-phenyl-propyl-3′-one]-5*α*-androst-3,17-dione (4g)



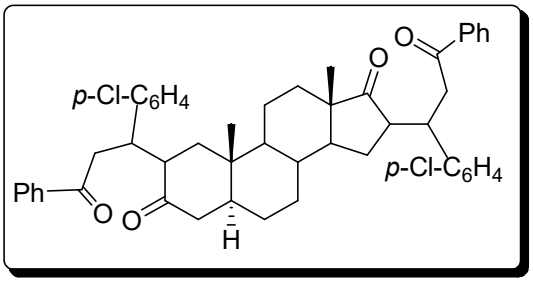
Gum, Yield 91%; IR ($CHCl_3$, cm^{-1}) 2924, 1709, 1686, 1448, 756; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-2.49 (m, 20H), 0.90 (s, 3H), 1.08 (s, 3H), 2.80-3.75 (m, 6H), 7.17-7.89 (m, 20H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 21.0, 21.4, 21.7, 22.6, 24.6, 26.3, 29.5, 31.6, 35.0, 35.2, 35.7, 36.6, 37.1, 40.9, 42.0, 44.1, 47.4, 47.8, 51.2, 53.0, 124.8, 125.5, 128.0, 128.1, 128.3, 128.4, 128.5, 128.9, 129.2, 129.5, 130.5, 132.7, 132.9, 133.1, 137.2, 139.2, 139.4, 198.6, 198.8, 212.2, 220.6; MS (ESI, m/z) 705.4 $[M+1]^+$.

2,16-Bis[1′-(*p*-methylphenyl)-3′-phenyl-propyl-3′-one]-5*α*-antrost-3,17-dione (4h)



Gum, Yield 92%; IR ($CHCl_3$, cm^{-1}) 2948, 1727, 1715, 1625, 1260, 1036, 751; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-2.46 (m, 20H), 0.91 (s, 3H), 1.07 (s, 3H), 2.18 (s, 6H), 2.80-3.75 (m, 6H), 7.17-7.89 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 26.3, 29.7, 31.6, 35.0, 35.1, 35.7, 36.9, 37.1, 40.9, 42.2, 44.1, 47.7, 47.8, 51.3, 53.8, 125.3, 128.0, 128.1, 128.3, 128.4, 128.5, 128.9, 129.0, 129.5, 130.9, 132.7, 132.9, 133.0, 137.0, 139.1, 139.6, 198.5, 199.1, 213.0, 220.9; MS (ESI, m/z) 733.4 $[M+1]^+$, 755.9 $[M+23]^+$.

2,16-Bis[1′-(*p*-chlorophenyl)-3′-phenyl-propyl-3′-one]-5α-antrost-3,17-dione (4i)



Gum, Yield 86%; IR ($CHCl_3$, cm^{-1}) 2950, 1729, 1713, 1624, 1260, 1036, 750; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-2.46 (m, 20H), 0.88 (s, 3H), 1.09 (s, 3H), 2.79-3.73 (m, 6H), 7.18-7.90 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 21.1, 21.5, 21.7, 22.7, 24.7, 26.3, 29.8, 31.6, 35.0, 35.7, 36.9, 37.1, 40.9, 42.0, 44.1, 47.4, 47.8, 51.1, 53.8, 125.0, 127.5, 127.7, 127.8, 128.0, 128.1, 128.2, 128.5, 128.7, 129.3, 130.7, 132.6, 132.66, 132.7, 137.1, 139.0, 139.4, 198.2, 198.6, 213.1, 220.5; MS (ESI, m/z) 773.3 $[M+1]^+$.

(b) Synthesis of steroidal 4′,6′-diphenyl-pyridines

(i) Thermal reaction with ammonium acetate in acetic acid

To a mixture of 3*β*-Acetoxy-16-(1′,3′-diphenyl-propyl-3′-one)-5-en-androst-17-one **(4a)** (1 mmol) and ammonium acetate (1.5 mmol), acetic acid was added as solvent and the reaction mixture was refluxed for 2 hours. After completion of the reaction, the reaction mixture was treated with water (50 ml), added $NaHCO_3$ and extracted with dichloromethane. The organic portion was washed with water, dried over anhydrous sodium sulfate and the solvent was removed to obtain a crude product which on silica gel column chromatographic purification using EtOAc/hexane as eluent afforded the pyridine derivative **5a** in 90% yield.

(ii) Thermal reaction with aqueous ammonia in acetic acid

To a solution of steroidal 1,5-dicarbonyl compound **4a** (0.42 mmol) in acetic acid 0.42 mmol of aqueous ammonia (19.5%) was added dropwise and the reaction mixture was refluxed for 8 hours. The residue obtained after removal of the solvent was treated with water (50 ml), added $NaHCO_3$ and extracted with dichloromethane. The organic portion was washed with water and dried over anhydrous sodium sulfate. The crude product obtained after removal of the solvent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent. The product **5a** was isolated as white solid in 50% yield.

(iii) Thermal reaction with urea in acetic acid

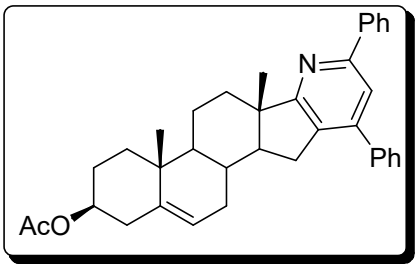
3*β*-Acetoxy-16-(1′,3′-diphenyl-propyl-3′-one)-5-en-androst-17-one (**4a**) (1 mmol) and urea (1.5 mmol) were refluxed for 8 hours using acetic acid as solvent. The reaction mixture was treated with water (50 ml), extracted with dichloromethane. The organic portion was washed with water, dried over anhydrous sodium sulfate and the solvent removed to obtain a crude product. Silica gel column chromatography separation using EtOAc/hexane as eluant over silica gel afforded the purified product **5a** in 20% yield.

(iv) Microwave reaction with ammonium acetate

3*β*-Acetoxy-16-(1′,3′-diphenyl-propyl-3′-one)-5-en-androst-17-one (**4a**) (1 mmol) and ammonium acetate (1.5 mmol) were irradiated in a closed vessel in a Synthos 3000 microwave reactor at 720 Watt, 130 ^{0}C and 21 bar for 5 minutes. The reaction mixture was treated with water (50 ml), extracted with dichloromethane. The organic portion was washed with water and dried over anhydrous sodium sulphate. The crude product obtained after removal of the solvent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent. The product **5a** was isolated as white solid in 85% yield.

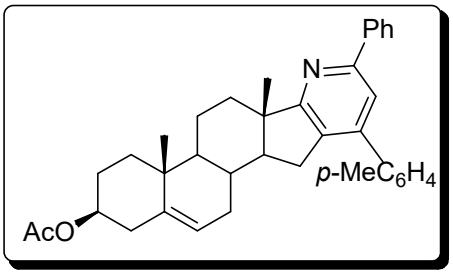
Chracterization of 4′,6′-diphenyl-pyridines (5)

3*β*-Acetoxy-5-en-4′,6′-bisphenyl-androst[17,16-*b*]pyridine (5a)



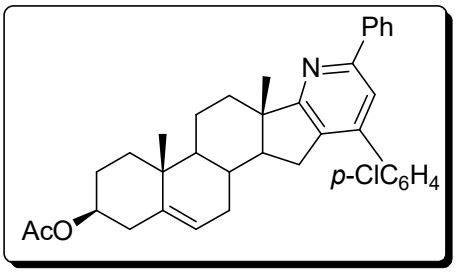
White solid, Yield 94%; m.p. 174-176 ^{o}C; IR ($CHCl_3$, cm^{-1}) 2934, 1733, 1561, 1457, 1371, 1245, 762; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 3H), 1.06 (s, 3H), 2.04 (s, 3H), 0.89-2.84 (m, 17H), 4.49-4.63 (m, 1H), 5.35-5.42 (m, 1H), 7.19-7.56 (m, 8H), 7.72 (s, 1H), 8.02 (d, J = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.2, 19.2, 20.6, 21.3, 21.5, 27.6, 30.4, 30.6, 31.4, 33.8, 36.5, 38.1, 45.2, 56.7, 73.2, 117.3, 122.4, 127.1, 127.4, 128.1, 128.9, 132.1, 135.6, 138.0, 140.0, 140.2, 145.7, 154.8, 170.5; MS (ESI, *m/z*) 518.3 $[M+1]^+$. Anal. calcd. for $C_{36}H_{39}NO_2$: C, 83.52; H, 7.59; N, 2.71; Found: C, 83.56; H, 7.47; N, 2.59.

3*β*-Acetoxy-5-en-[4′-(*p*-methylphenyl)-6′-phenyl]-androst[17,16-*b*]pyridine (5b)



White solid, Yield 95%; m.p. 177-179 ^{o}C; IR ($CHCl_3$, cm^{-1}) 2934, 1733, 1590, 1494, 1371, 1245, 771; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87-2.44 (m, 16H), 0.90 (s, 3H), 1.07 (s, 3H), 2.04 (s, 3H), 2.43 (s, 3H), 2.69-2.84 (m, 1H), 4.50-4.63 (m, 1H), 5.37-5.42 (m, 1H), 7.21-7.57 (m, 8H), 8.01 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 19.4, 20.6, 21.3, 21.5, 27.8, 30.4, 30.9, 31.4, 33.8, 36.9, 38.2, 45.8, 50.7, 56.2, 73.9, 117.8, 122.1, 127.1, 128.2, 128.3, 128.6, 129.4, 132.2, 136.1, 138.2, 140.1, 140.3, 145.9, 155.9, 170.6; MS (ESI, *m/z*) 532.7 $[M+1]^{+}$. Anal. calcd. for $C_{37}H_{41}NO_2$: C, 83.58; H, 7.77; N, 2.63; Found: C, 83.66; H, 7.64; N, 2.79.

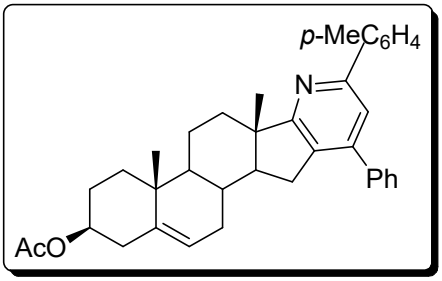
3*β*-Acetoxy-5-en-[4′-(*p*-chlorophenyl)-6′-phenyl]-androst[17,16-*b*]pyridine (5c)



White solid, Yield 96%; m.p. 185-187 ^{o}C; IR ($CHCl_3$, cm^{-1}) 2930, 1733, 1572, 1246, 772; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86-2.34 (m, 16H), 1.12 (s, 3H), 1.18 (s, 3H), 2.04 (s, 3H), 2.65-2.80 (m, 1H), 4.50-4.60 (m, 1H), 5.37-5.41 (m, 1H), 7.11-7.57 (m, 8H), 7.95 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 19.8, 20.6, 21.3, 21.8, 27.9, 30.4, 30.9, 31.2, 33.8, 36.8, 38.2, 45.8, 50.9, 56.3, 73.7, 118.5, 122.2, 127.6, 128.3, 128.4, 128.7, 129.1, 132.4,

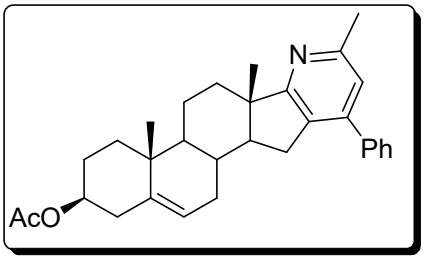
136.4, 138.6, 140.4, 140.8, 146.3, 156.5, 170.9; MS (ESI, *m/z*) 552.3 $[M+1]^+$. Anal. calcd. for $C_{36}H_{38}ClNO_2$: C, 78.31; H, 6.94; N, 2.54; Found: C, 78.60; H, 6.68; N, 2.62.

3*β*-Acetoxy-5-en-[4′-phenyl-6′-(*p*-methylphenyl)]-androst[17,16-*b*]pyridine (5d)



White solid, Yield 93%; m.p. 174-177 ^oC; IR ($CHCl_3$, cm^{-1}) 2929, 1630, 1449, 1730, 1373, 1245; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85-2.40 (m, 19H), 1.06 (s, 3H), 1.25 (s, 3H), 4.58-4.63 (m, 1H), 5.37-5.42 (m, 1H), 7.21-7.55 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 20.6, 21.3, 21.5, 24.6, 28.5, 29.4, 29.7, 30.9, 36.9, 38.2, 45.8, 50.7, 56.2, 73.9, 117.8, 122.1, 127.1, 128.2, 128.3, 128.6, 129.4, 132.2, 133.1, 137.1, 138.2, 140.1, 145.9, 155.9, 170.6; MS (EI, *m/z*) 531.7$[M]^+$. Anal. calcd. for $C_{37}H_{41}NO_2$: C, 83.58; H, 7.77; N, 2.63; Found: C, 83.76; H, 7.49; N, 2.32.

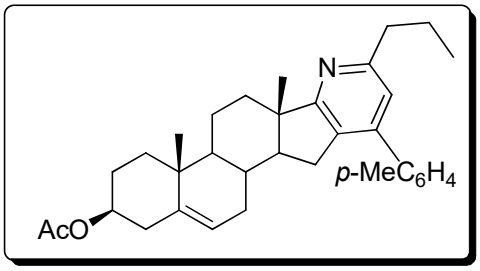
3*β*-Acetoxy-5-en-[4′-phenyl-6′-methyl]-androst[17,16-*b*]pyridine (5e)



White solid, Yield 90%; m.p. 175-179 ^oC; IR ($CHCl_3$, cm^{-1}) 2929, 1732, 1453, 1368, 1219, 772; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86-2.86 (m, 20H), 1.05 (s, 3H), 1.25 (s, 3H), 2.04 (s, 3H), 4.55-4.66 (m, 1H), 5.39-5.41 (m, 1H), 7.21-7.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 22.1, 23.3, 24.8, 28.5, 28.9, 29.6, 30.1, 34.1, 36.5, 37.6, 38.7, 46.1, 50.2, 56.1, 73.5,

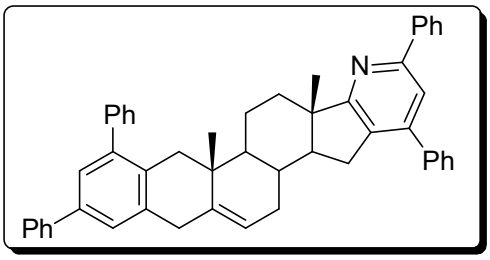
109.2, 121.2, 126.9, 127.2, 129.4, 132.3, 138.1, 140.7, 150.2, 156.1, 169.8; MS (EI, *m/z*) 455.6 $[M]^+$. Anal. calcd. for $C_{31}H_{37}NO_2$: C, 81.72; H, 8.19; N, 3.07; Found: C, 81.65; H, 8.35; N, 3.22.

3*β*-Acetoxy-5-en-[4′-(*p*-tolyl)-6′-propyl]-androst[17,16-*b*] pyridine (5f)



White solid, Yield 96%; m.p. 180-185 ^oC; IR ($CHCl_3$, cm^{-1}) 2938, 1732, 1637, 1513, 1373, 1244, 814; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.66-2.86 (m, 31H), 1.08 (s, 3H), 1.25 (s, 3H), 4.55-4.63 (m, 1H), 5.35-5.43 (m, 1H), 7.02-7.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 19.4, 20.4, 21.4, 27.7, 30.9, 31.2, 31.5, 36.8, 38.1, 47.3, 49.8, 50.3, 73.7, 121.8, 128.8, 129.5, 130.4, 132.8, 133.2, 134.9, 139.6, 140.1, 170.5; MS (EI, *m/z*) 499.7 $[M]^+$. Anal. calcd. for $C_{34}H_{45}NO_2$: C, 81.72; H, 9.08; N, 2.80; Found: C, 81.86; H, 9.31; N, 2.65.

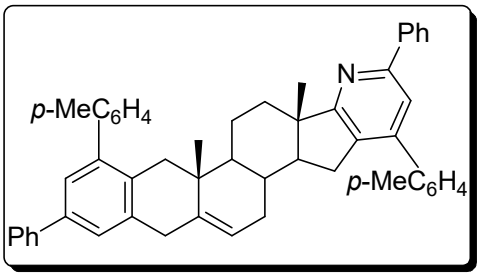
4′,6′,4″,6″-Tetraphenyl-5*α*-Androst[3,2-*b*][17,16-*b*]bispyridine (5g)



Gum, Yield 83%; IR ($CHCl_3$, cm^{-1}) 2924, 1598, 1546, 775; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-2.39 (m, 18H), 2.67-3.00 (m, 6H), 7.19-8.08 (m, 22H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 17.2, 19.3, 20.7, 21.1, 21.2, 21.3, 27.4, 30.4, 30.7, 31.4, 33.8, 36.6, 39.3, 46.4, 51.7,

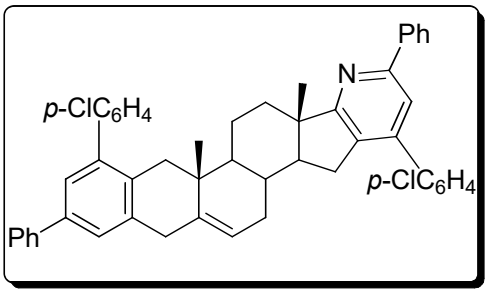
56.4, 74.0, 117.7, 122.6, 126.7, 127.4, 128.2, 128.5, 128.7, 129.8, 132.3, 135.4, 137.4, 138.6, 140.1, 140.2, 141.0, 146.2, 155.7, 173.3; MS (ESI, *m/z*) 662.4 $[M+1]^+$.

4′,4″-Bis-(*p*-tolyl)-6′,6″-bisphenyl-5*α*-Androst[3,2-*b*][17,16-*b*]bispyridine (5h)



White solid, Yield 84%; m.p. 187-188 ^oC; IR ($CHCl_3$, cm^{-1}) 2924, 1597, 1547, 775; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81-2.36 (m, 18H), 2.37 (s, 3H), 2.38 (s, 3H), 2.65-3.02 (m, 6H), 7.17-7.99 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 17.2, 19.2, 20.7, 21.1, 21.3, 27.4, 30.4, 30.5, 31.4, 33.8, 36.7, 39.5, 46.6, 51.7, 56.4, 73.8, 117.4, 122.4, 126.6, 127.6, 128.5, 128.8, 128.9, 129.8, 132.3, 135.4, 137.6, 138.8, 140.0, 140.1, 140.6, 145.4, 156.9, 174.6; MS (ESI, *m/z*) 691.3 $[M+1]^+$. Anal. calcd. for $C_{51}H_{50}N_2$: C, 88.65; H, 7.29; N, 4.05; Found: C, 88.57; H, 7.35; N, 4.21.

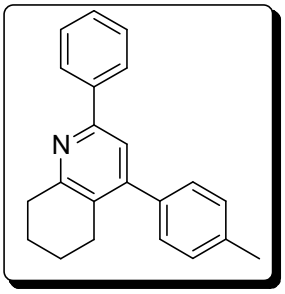
4′,4″-Bis-(*p*-chlorophenyl)-6′,6″-bisphenyl- 5*α*-Androst[3,2-*b*][17,16-*b*]bispyridine (5i)



Gum, Yield 80%; IR ($CHCl_3$, cm^{-1}) 2926, 1598, 1547, 775; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82-2.35 (m, 18H), 2.69-3.02 (m, 6H), 7.15-8.04 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.4, 17.2, 19.4, 20.9, 21.1, 21.3, 27.4, 30.6, 31.1, 31.4, 33.9, 36.6, 39.3, 46.6, 51.7, 56.4,

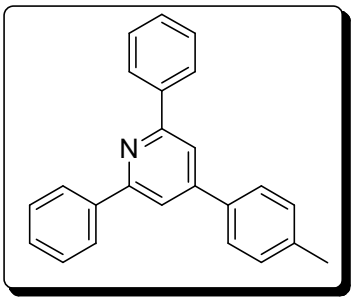
74.2, 117.7, 122.6, 126.8, 127.4, 128.2, 128.5, 128.6, 129.7, 132.3, 135.5, 137.8, 138.9, 140.5, 140.8, 141.3, 146.8, 156.6, 173.5, ; MS (ESI, *m/z*) 731.3 $[M+1]^+$.

5,6,7,8-Tetrahydro-2-phenyl-4-*p*-tolylquinoline (5j)



Liquid, Yield 95%; IR ($CHCl_3$, cm^{-1}) 2932, 1589, 1442, 772; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65-1.78 (m, 2H), 1.72-1.97 (m, 2H), 2.40 (s, 3H), 2.41-2.67 (m, 2H), 3.06-3.10 (m, 2H), 7.04-7.50 (m, 8H), 7.95 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 23.2, 27.4, 33.4, 119.2, 126.9, 128.5, 128.6, 129.1, 136.9, 137.6, 139.9, 150.3, 154.3, 157.6; MS (EI, *m/z*) 299.4 $[M]^+$. Anal. calcd. for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68; Found: C, 88.45; H, 7.32; N, 4.44.

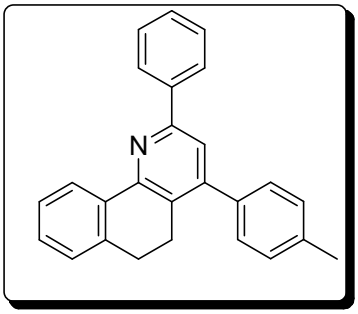
2,6-Diphenyl-4-*p*-tolylpyridine (5k)



White solid, Yield 90%; m.p. 122-124 ^oC; (literature[17]:123-24^oC) IR ($CHCl_3$, cm^{-1}) 2924, 1650, 1598, 1536, 775; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 3H), 7.09-7.22 (m, 12H), 7.36 (d, 2H, J=7.5Hz), 7.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 116.9, 127.2, 128.7,

129.0, 129.9, 136.1, 139.1, 139.7, 150.1, 157.5; MS (EI, *m/z*) 321.4 $[M]^+$. Anal. calcd. for $C_{24}H_{19}N$: C, 89.68; H, 5.96; N, 4.36; Found: C, 89.35; H, 5.68; N, 4.21.

5,6-Dihydro-2-phenyl-4-*p*-tolylbenzo[h]quinoline (5l)



Yellow solid, Yield 90%; m.p. 155-157 ^oC; IR ($CHCl_3$, cm^{-1}) 2940, 1591, 1542, 750; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45(s, 3H), 2.85-2.88 (t, *J* = 5.7 Hz, 2H), 2.93-2.97 (t, *J* = 5.5 Hz, 2H), 7.09-7.52 (m, 9H), 7.59 (s, 1H), 8.17 (d, *J* = 7.5 Hz, 2H), 8.57 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 25.3, 28.2, 120.0, 125.8, 126.8, 127.1, 127.5, 128.0, 128.6, 128.7, 128.8, 129.0, 129.2, 135.3, 136.4, 137.9, 138.2, 139.6, 149.3, 152.6, 154.4; IR ($CHCl_3$, cm^{-1}) 2926, 1598, 1547, 775; MS (EI, *m/z*) 347.4 $[M]^+$. Anal. calcd. for $C_{26}H_{21}N$: C, 89.88; H, 6.09; N, 4.03; Found: C, 89.76; H, 6.31; N, 4.21.

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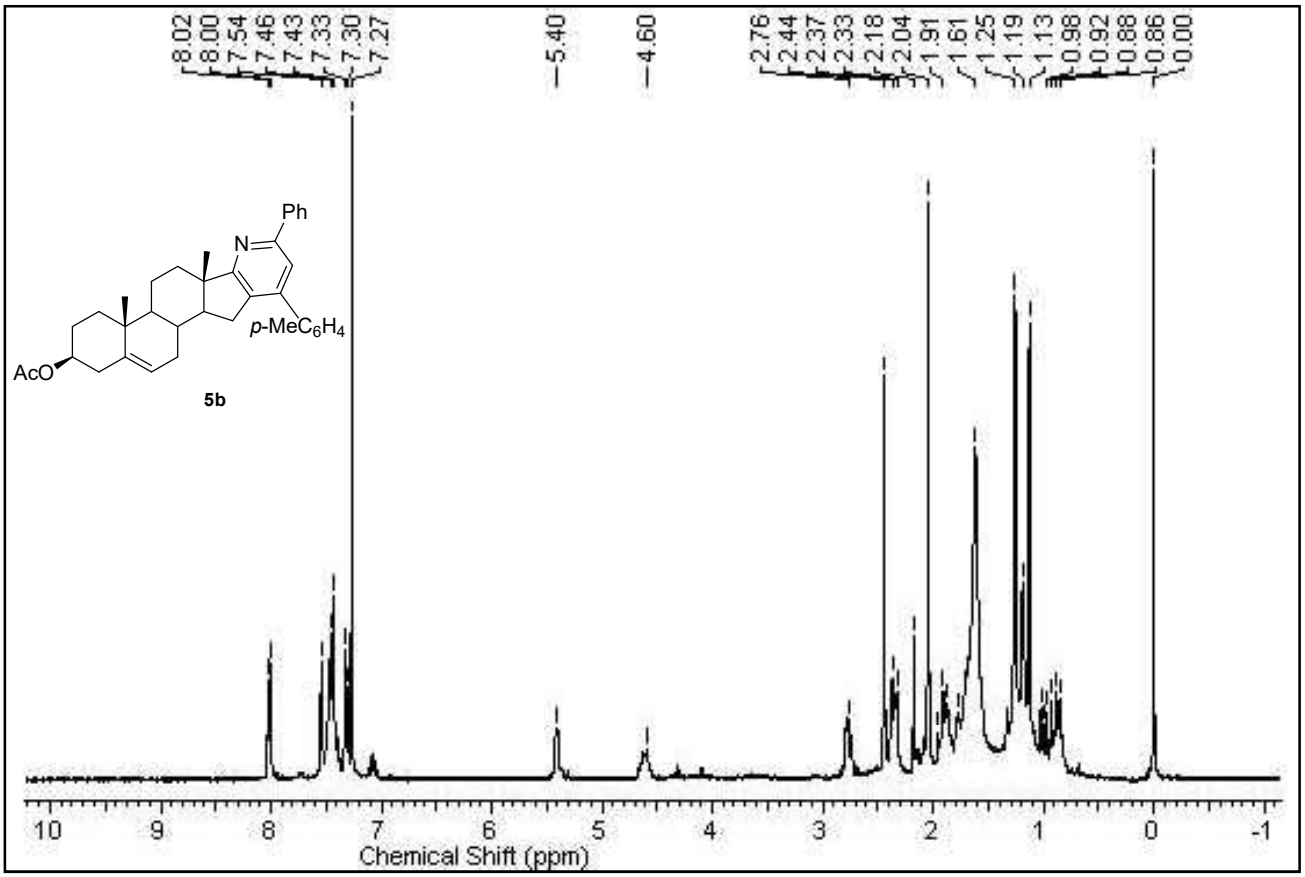
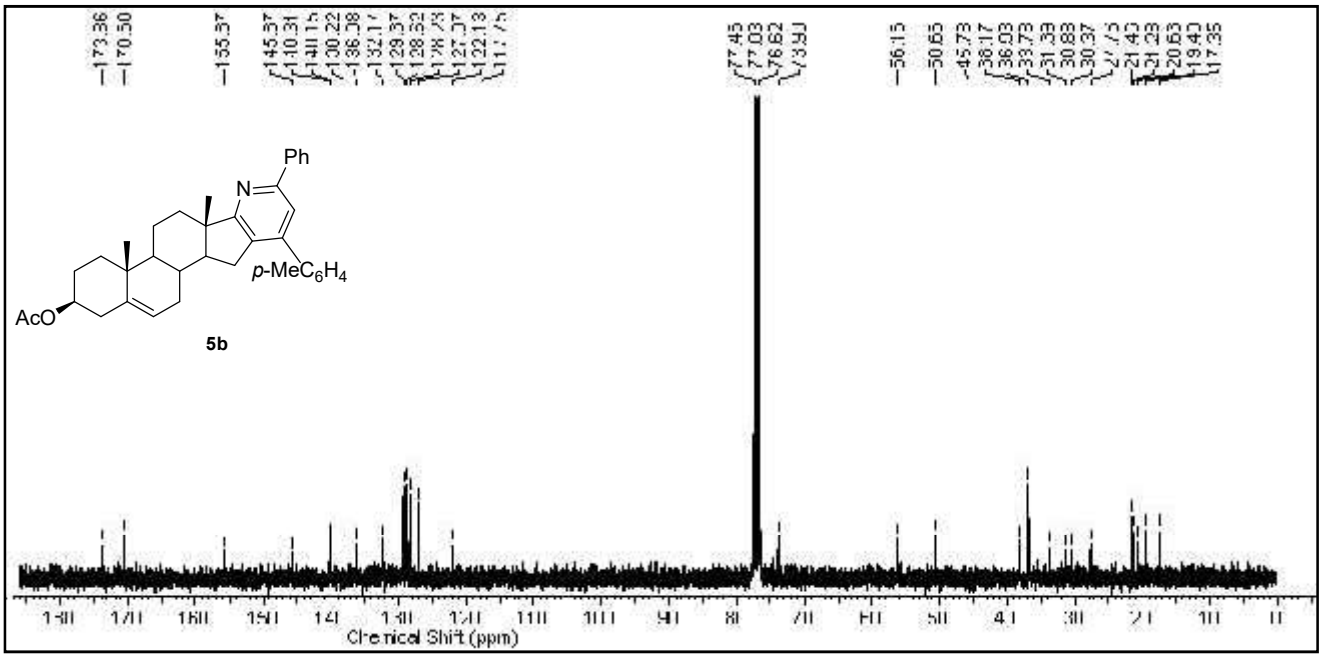
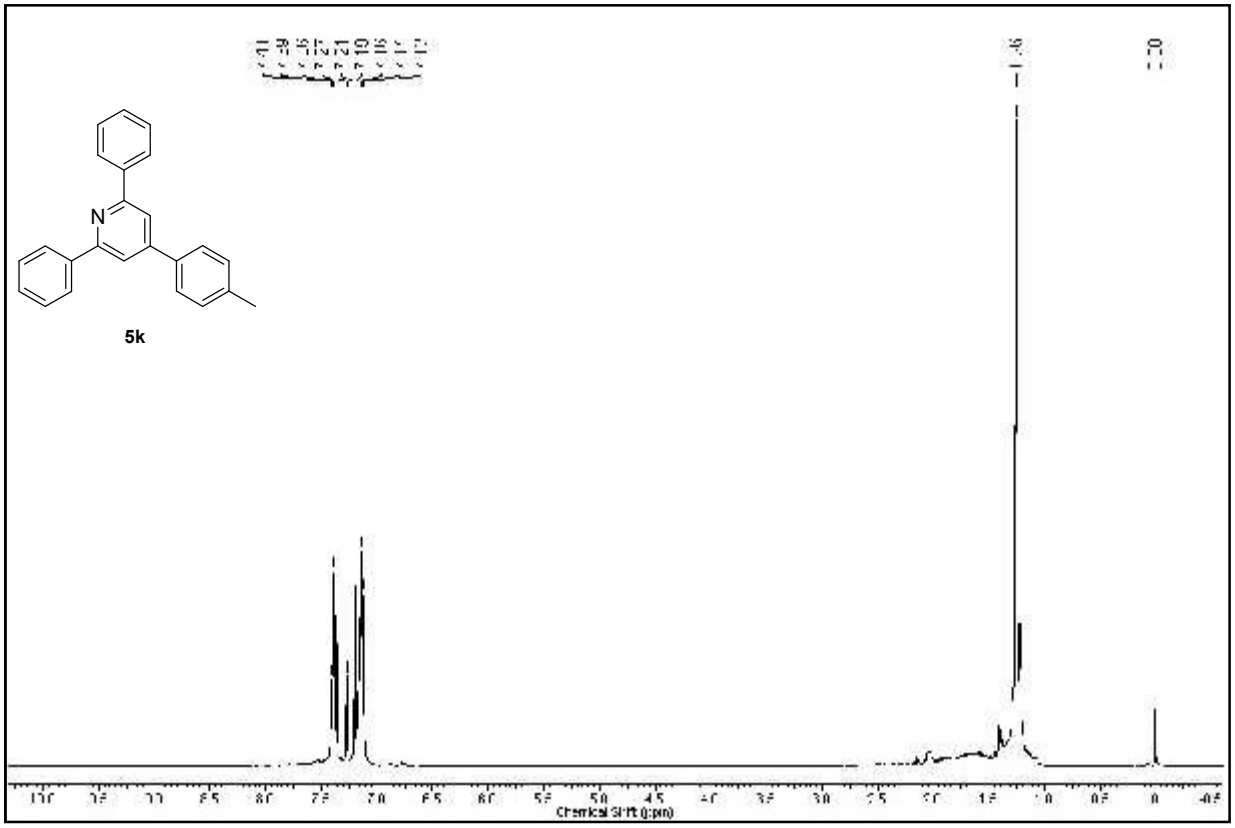
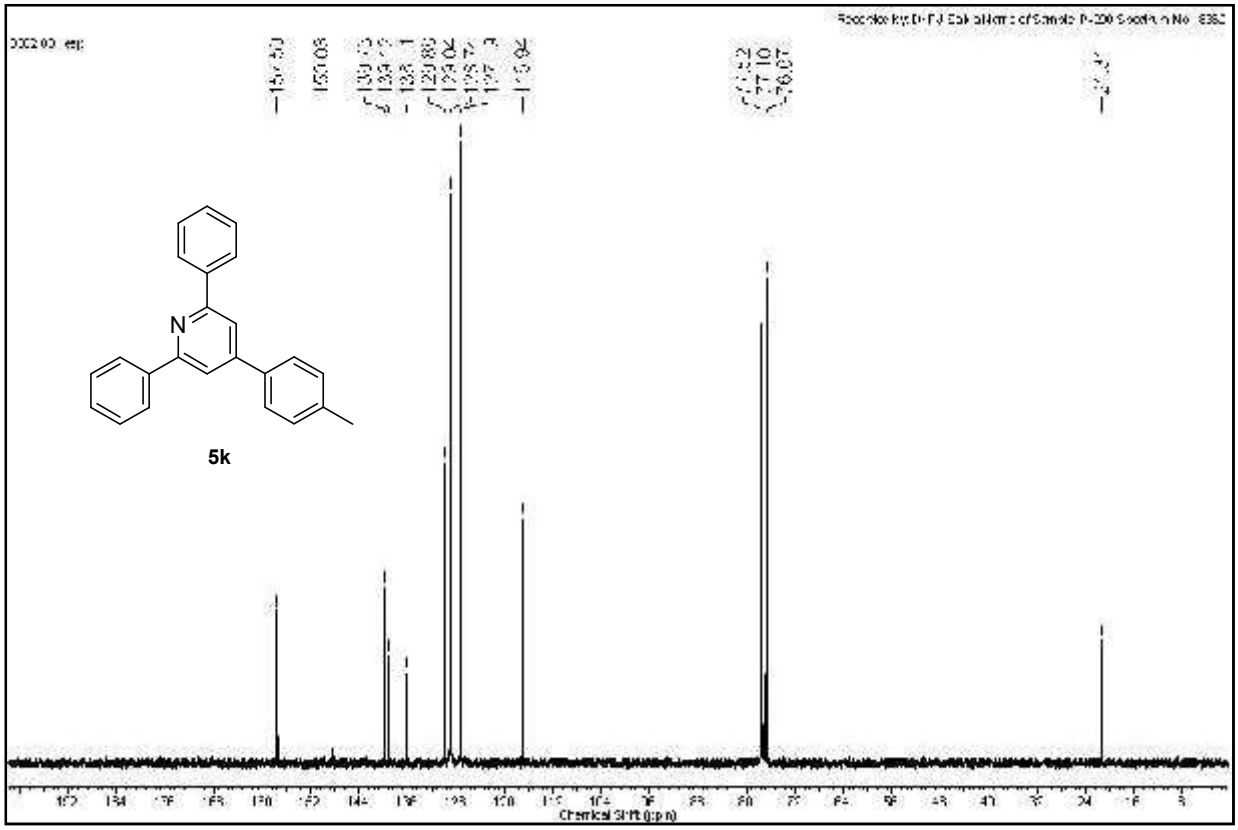
^{1}H NMR and ^{13}C NMR of some selected pyridine derivatives






N
5k
Chemical Shift (ppm)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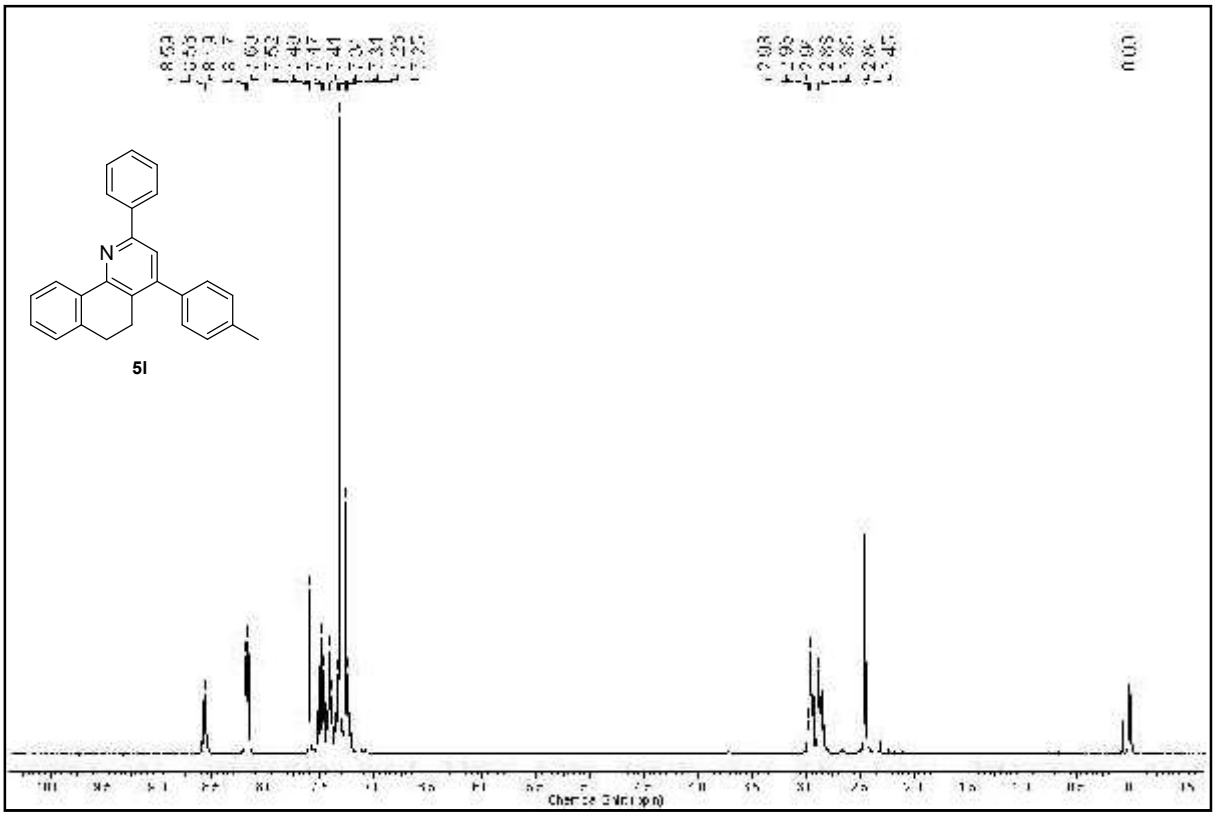
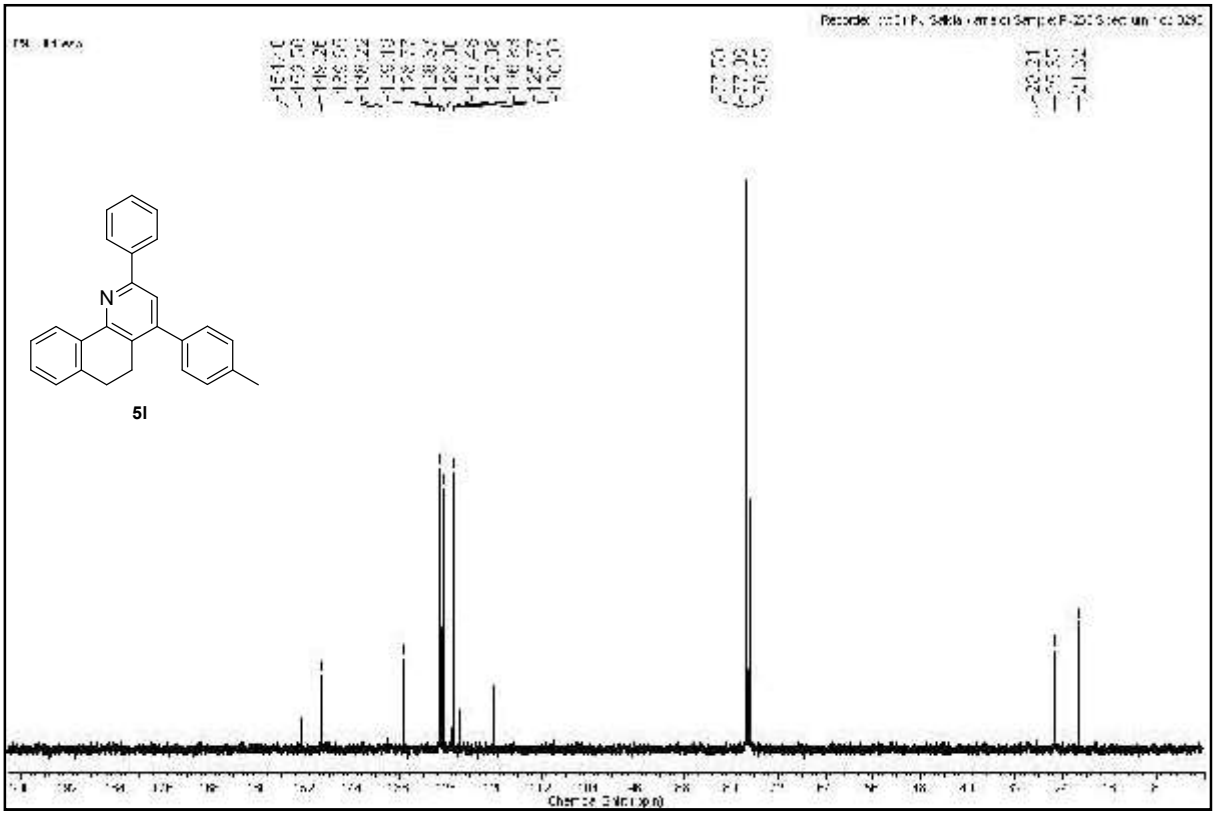


5l



5l

Chapter 4

Part-B

Pd-catalyzed synthesis of steroidal and non-steroidal pyrido[2,3-d]pyrimidine derivatives from β-halo-α,β-unsaturated aldehydes

4B.1 Introduction

Pyrido[2,3-*d*]pyrimidine represents a nitrogen containing heterocyclic ring system of considerable interests because of several biological activities associated with this scaffold. This ring system is associated with diverse immunopharmacological activities such as anti-inflammatory, analgesic, antihypertensive, antiviral, antimicrobial, antiasthmatics and anticancer activities.[1] Some analogues have been found to act as antitumor agents inhibiting dihydrofolate reductases or tyrosine kinases,[2] while others are known as antiviral agents.[3] Pyridopyrimidines have been described as potent inhibitors of tyrosine kinase [4], dihydrofolate reductase[5], adenosine kinase[6] and also specific inhibitors of cyclin-dependent kinase[7]and cholecystokinin receptor subtype-1 (CCK1R)[8]. Some of the biologically active pyrido[2,3-*d*]pyrimidine derivatives are shown in figure 4B.1.

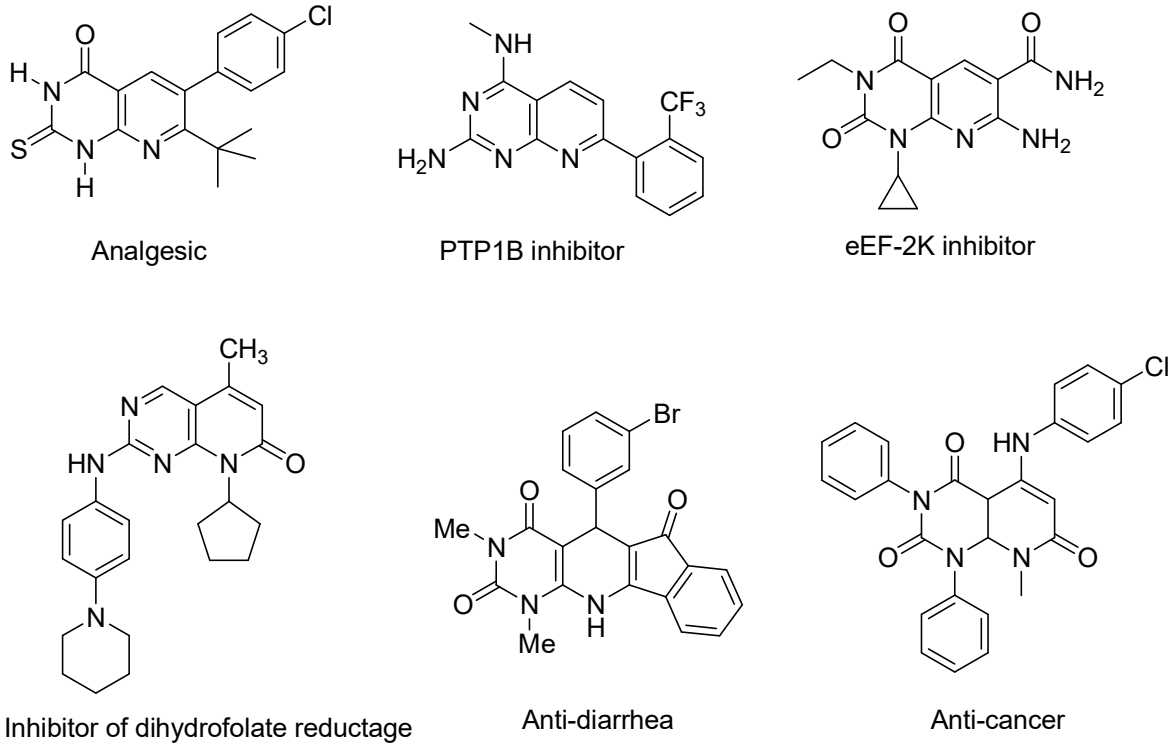


Figure 4B.1 Examples of bioactive pyrido[2,3-*d*]pyrimidines

Besides non-steroidal pyridopyrimidine compounds, steroidal derivatives are also found to have important biological activities such as antioxidant and anti-inflammatory activities (Figure 4B.2).[9]

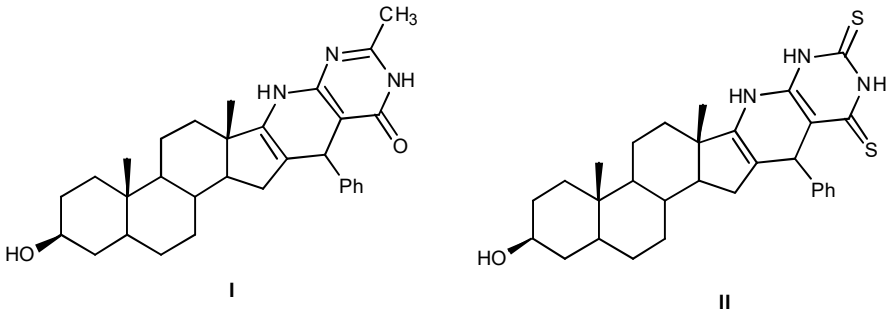
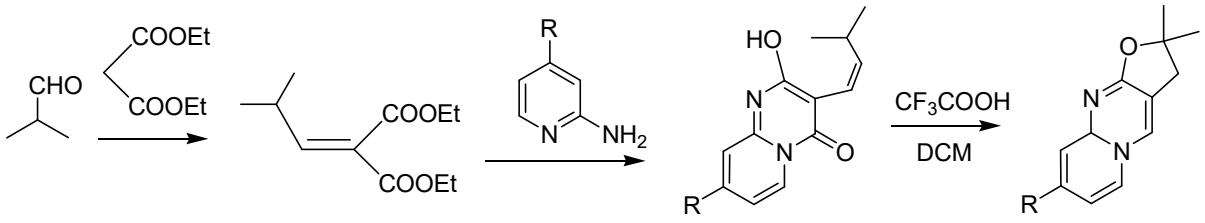


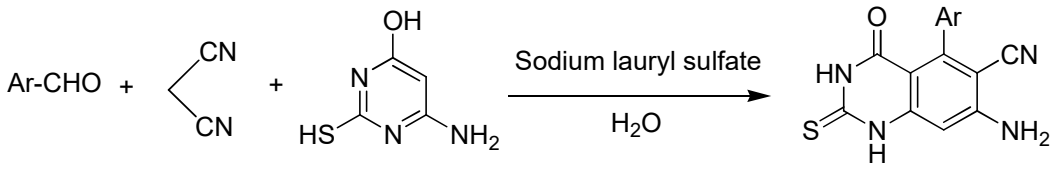
Figure 4B.2 Steroidal pyridopyrimidine having antioxidant and anti-inflammatory

In view of their very high biological and pharmaceutical importances, synthesis of these pyrido[2,3-*d*]pyrimidine derivatives have received considerable attentions in the literature as shown below.

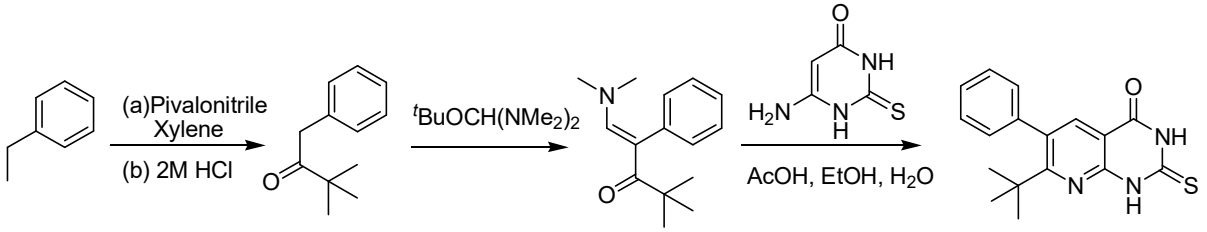
Furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine was synthesized by Gullu and co-workers[10] by condensation reaction of 2-aminopyridine and 1,3-dicarbonyl compound in acidic medium.



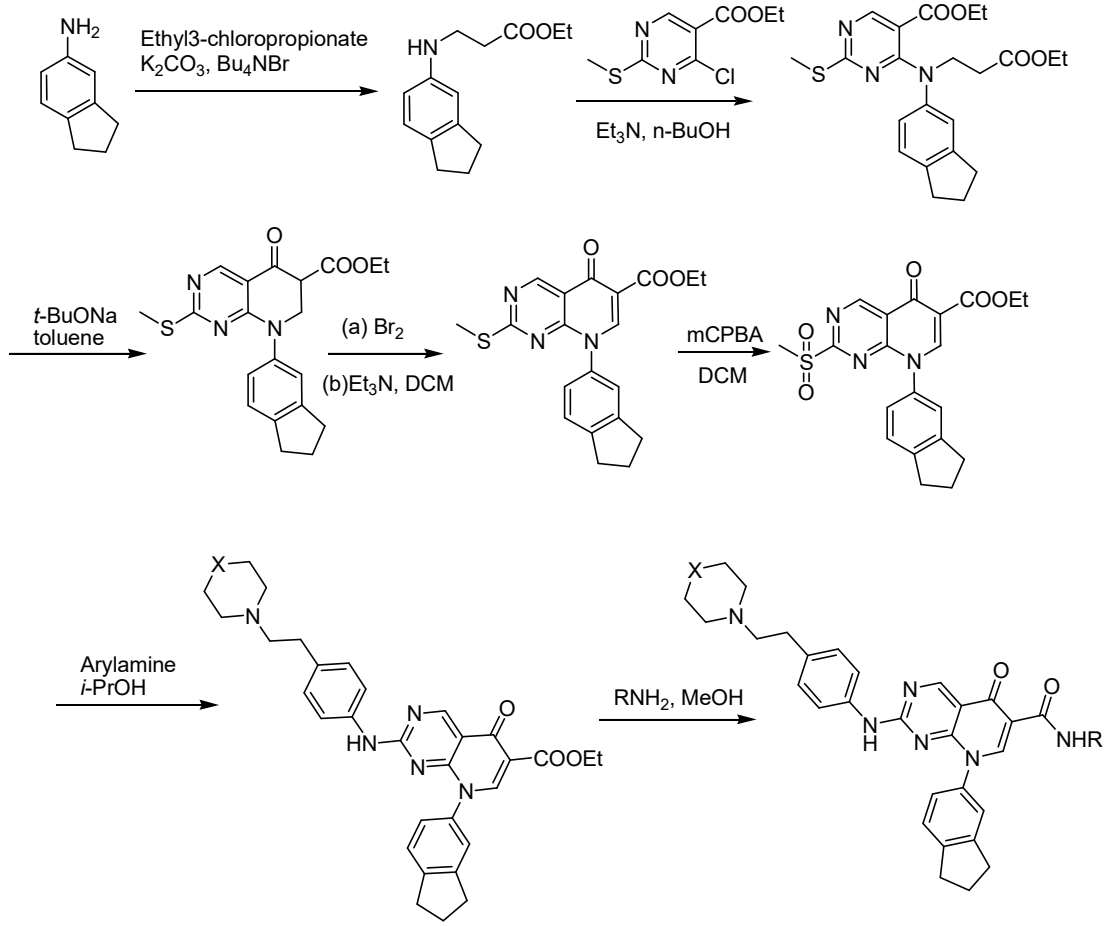
Li and co-workers[11] synthesized a series of pyrido[2,3-*d*]pyrimidine derivatives by the three-component reaction of aromatic aldehyde, malononitrile and 6-amino-4-hydroxy-2-mercaptopyrimidine catalyzed by sodium lauryl sulfate (SDS) in aqueous media.



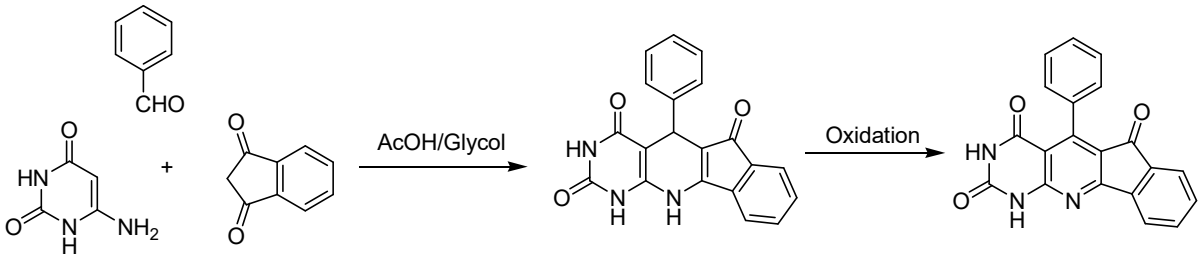
6-Aryl-7-isopropylpyridopyrimidine derivatives were synthesized by a multistep reaction of benzylmagnesium bromide with pivalonitrile, Bredereck's reagent and 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidin- 4-one in moderate to good yield.[12] These compounds were found to be TRPV1 antagonists effective in chronic pain.



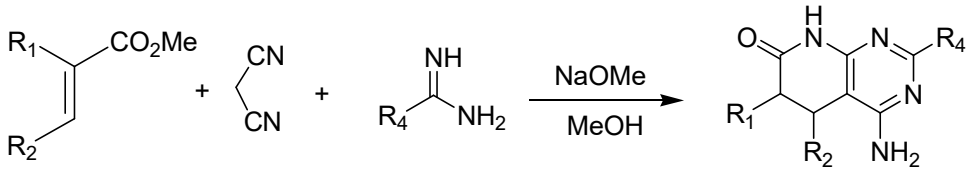
Huang and co-worker[13] synthesized a series of pyrido[2,3-*d*]pyrimidin-5-ones treating 5-aminoindan with ethyl-3-chloropropionate and ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate followed by Dieckmann reaction.



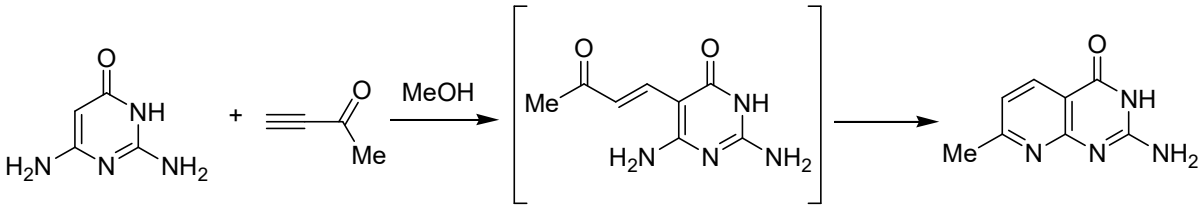
Evdokimov and co-workers[14] synthesized a series of dihydropyrido[2,3-*d*]pyrimidine reacting aldehydes, indane-1,3-dione, and 6-aminouracil. These compounds are found to have interesting antiproliferative potencies toward human cancer cell lines.



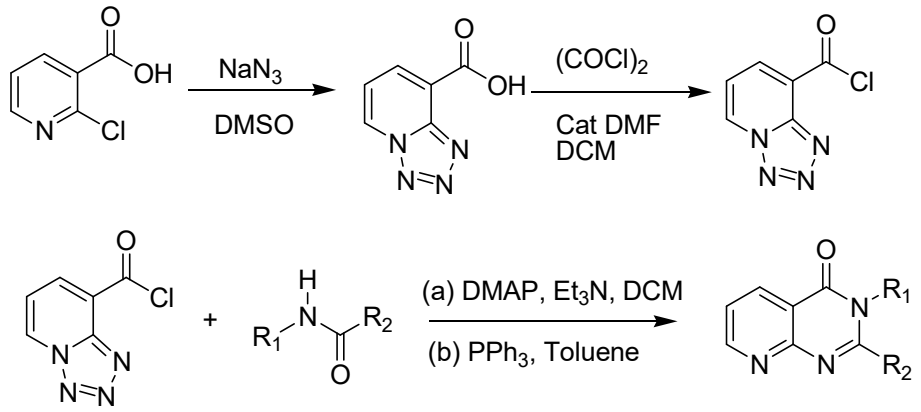
An efficient method for the synthesis of pyridopyrimidine by one-pot cyclocondensation of α,β-unsaturated esters, amidine systems and malononitrile under microwave irradiation was reported by Mont *et al*.[15]



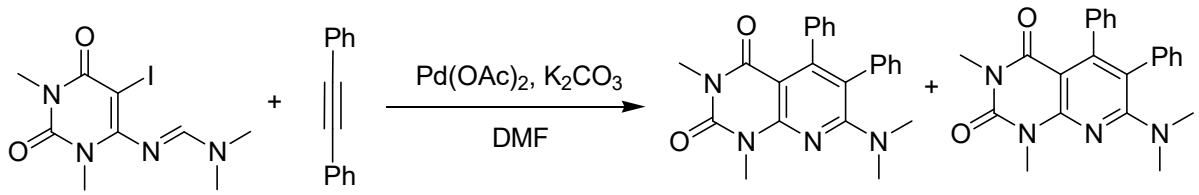
Pyrido[2,3-*d*]pyrimidines was synthesized by Bagley and co-workers[16] in excellent yield without a need for further purification, by the Michael addition of 2,6-diaminopyrimidin-4-one with but-3-yn-2-one followed by subsequent cyclodehydration.



Application of the intramolecular aza-Wittig reaction of amides and tetrazolo[1,5-*a*]pyridine-8-carbonylchloride resulted variety of substituted pyrido[2,3-*d*]pyrimidines in good to moderate yields.[17] The intermediate tetrazolo[1,5-*a*]pyridine-8-carbonylchloride was first prepared by reacting 2-chloronicotinic acid with sodium azide and oxalyl chloride.



The reactions of iodouracils having a formamidine or acetamidine moiety with various acetylenes in DMF resulted pyrido[2,3-*d*]pyrimidine derivatives in good to high yields. Here potassium carbonate and palladium acetate were used as base and catalyst respectively.[18]

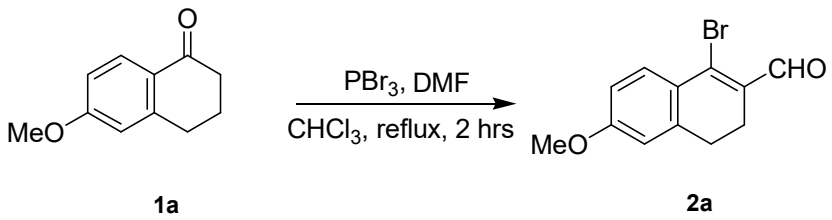


In spite of the presence of various methods for the synthesis of pyrido[2,3-*d*]pyrimidines, however, an environmentally benign general method for the synthesis of this heterocyclic ring system is scarce in the literature. The present study describes an efficient Pd catalyzed synthesis of the pyrido[2,3-*d*]pyrimidines using *β*-halovinyl/aryl aldehydes and 6-amino-1,3-dialkyluracils as the starting materials under microwave irradiation in solvent-free conditions.

4B.2 Results and discussion

Preparation of *β*-bromo-*α,β*-unsaturated aldehydes:

The initial effort was directed towards developing a library of the key intermediate *β*-bromo-*α,β*-unsaturated aldehydes from corresponding carbonyl compounds. The study began with the preparation of 1-bromo-3,4-dihydro-6-methoxynaphthalene-2-carbaldehyde **2a** from 6-methoxytetralone **1a** (Scheme-4B.1). Vilsmeier Reaction of 6-methoxytetralone **1a** with PBr_3 and DMF in presence of base afforded compound **2a** in 90 % yield and after purification by column chromatography the product was obtained as pale yellow solid .



1a **2a**

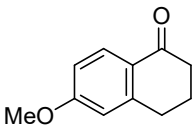
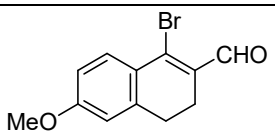
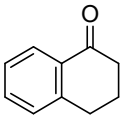
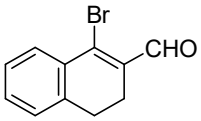
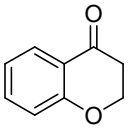
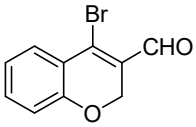
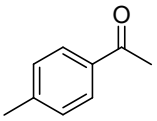
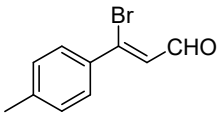
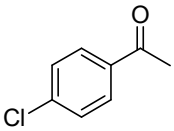
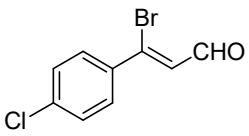
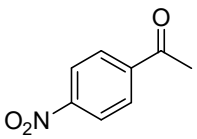
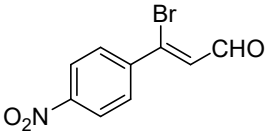
Scheme-4B.1

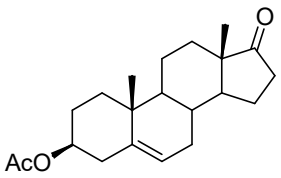
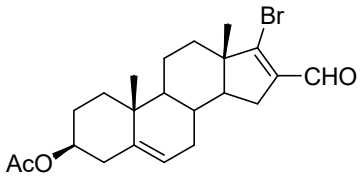
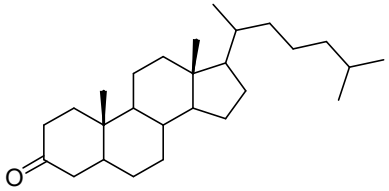
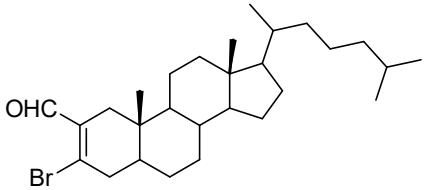
The structure of the compound was ascertained from the IR, NMR and mass spectroscopic analysis. The IR spectrum showed presence of a sharp band at 1662 cm^{-1} for C=O stretching of aldehyde group. The ^1H NMR spectrum of compound **2a** showed a characteristic signal at 10.2 for aldehyde proton and one signal at 3.85 as singlet for -OMe protons respectively. The ^{13}C NMR spectrum showed a characteristic peak at 192.9 for the aldehyde carbonyl carbon. Finally structure of **2a** was confirmed by EI mass spectrum which showed the molecular ion peak (M+) at m/z 267.

The reaction was then extended to variety of carbonyl compounds of non-steroidal derivatives. Similarly α,β-unsaturated ketones in A ring and D ring of the steroid were prepared. The results of this study are summarised in Table 4B.1. In all cases, the product

obtained was characterized by various spectroscopic means such as NMR, IR and mass spectrometric analysis.

Table-4B.1 Synthesis *β*-bromo-*α,β*-unsaturated aldehyde

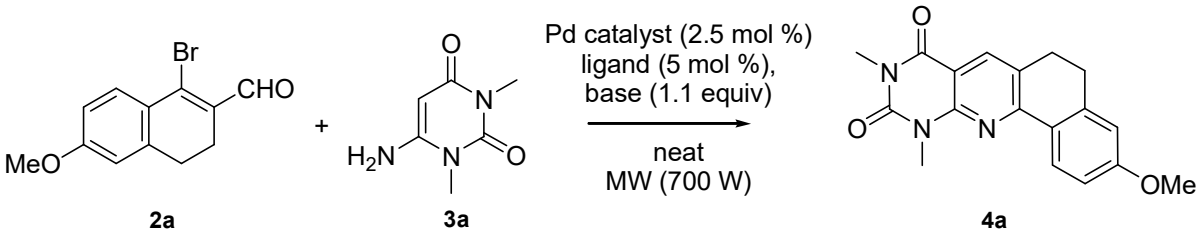
Entry	Carbonyl Compound	*β*-chloro-*α,β*-unsaturated aldehydes	Yield(%)[a]
1	 **1a**	 **2a**	90
2	 **1b**	 **2b**	85
3	 **1c**	 **2c**	82
4	 **1d**	 **2d**	90
5	 **1e**	 **2e**	85
6	 **1f**	 **2f**	90

7	 **1g**	 **2g**	75
8	 **1h**	 **2h**	80

[a]Isolated yield

Preparation of steroidal and non-steroidal pyrido[2,3-*d*]pyrimidines from *β*-bromo-*α*,*β*-unsaturated aldehydes:

The pyrido[2,3-*d*]pyrimidine compounds have been prepared by using *β*-bromo-*α*,*β*-unsaturated aldehyde as starting material. Accordingly, the reaction of *β*-bromovinyl aldehyde **2a** (1.0 mmol) with 6-amino-1,3-dimethyluracil (**3a**, 1.0 mmol) was explored as the first example (Scheme 4B.2).



Scheme 4B.2

Heating the reaction mixture at 120 ^{o}C for 12 hours in presence of $PdCl_2$ (2.5 mol %), K_2CO_3 (1.0 mmol) and PPh_3 (5.0 mol %), afforded pyrido[2,3-*d*]pyrimidine derivative **4a** in 54% yield (Table 4B.2, Entry 1). The product was characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The IR spectrum showed presence of two sharp bands at 1701 and 1657 cm^{-1} for C=O stretching keto group. The ^{1}H NMR of compound **3a** exhibited two

characteristic aromatic doublet signals at δ 6.92 (d, *J* = 6.0 Hz, 1H) and 8.30 (d, *J* = 8.5 Hz, 1H) and a singlet at δ 8.20 (s, 1H). The ^{1}H NMR also showed three signals at δ 3.50 (s, 3H), 3.81 (s, 3H) and 3.89 (s, 3H) for the six methyl protons and three methoxy protons. The ^{13}C NMR spectrum showed the presence of two carbonyl carbons at δ 161.6 and 161.9 and ten double bonded carbons at δ 108.1, 113.1, 126.2, 126.3, 128.1, 135.9, 141.6, 149.7, 151.7 and 156.8. The signal at δ 55.4 indicates the $–OCH_3$ carbon. The mass spectra showed a strong molecular ion peak at m/z 323 $[M]^+$.

Comaparative study of the palladium catalysts such as $PdCl_2(PPh_3)_2$, $Pd(dppf)Cl_2$, $Pd(OAc)_2$ and $Pd(TFA)_2$, revealed $Pd(OAc)_2$ as the most effective catalyst to synthesize **4a** (Table 4B.2, Entries 2-5). The effect of ligand on the reaction was further studied. The ligand xphos turned out to be the best ligand amongst the screened ligands (dppf, 1,10-phen) to carry out this reaction under thermal conditions (Table 4B.2, Entries 6-8). Use of base Cs_2CO_3 in place of K_2CO_3 in this reaction provided inferior result (Table 4B.2, Entry 9). To decrease the reaction time when the influence of microwave (MW) irradiation (700 W, 120 ^{o}C, 14 bar) was studied, it was observed a significant reduction in reaction time from 12 hours to 5 minutes to perform this reaction under microwave (MW) irradiation (Table 4B.2, Entry 10). Subsequently, when the reaction was performed under solvent free condition, there was a slight increase of **4a** to 91% in 5 minutes of reaction time under microwave irradiation (Table 4B.2, Entry 11). The attempt to perform the reaction without catalyst did not provide **4a** under the solvent free condition (Table 4B.2, Entry 12).

Table 4B.2 Optimization of the reaction conditions for the synthesis of **4a**[a]

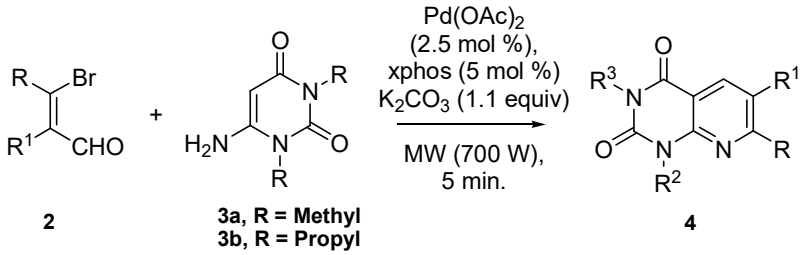
Entry	Pd catalyst	Solvent	Ligand	Thermal/ MW	Time	**3a** (%)[b]
1	$PdCl_2$	DMF	PPh_3	120 °C	12 h	54
2	$PdCl_2(PPh_3)_2$	DMF	PPh_3	120 °C	12 h	47
3	$Pd(dppf)Cl_2$	DMF	PPh_3	120 °C	12 h	50
4	$Pd(OAc)_2$	DMF	PPh_3	120 °C	12 h	72
5	$Pd(TFA)_2$	DMF	PPh_3	120 °C	12 h	61
6	$Pd(OAc)_2$	DMF	dppf	120 °C	12 h	64
7	$Pd(OAc)_2$	DMF	xphos	120 °C	12 h	84
8	$Pd(OAc)_2$	DMF	1,10-phen	120 °C	12 h	69
9[c]	$Pd(OAc)_2$	DMF	xphos	120 °C	12 h	72
10	$Pd(OAc)_2$	DMF	xphos	MW	5 min	87
11	$Pd(OAc)_2$	Neat	xphos	MW	5 min	91
12	-	Neat	-	MW	5 min	0

[a]All reactions were performed in presence of K_2CO_3 (1.1 equiv) unless otherwise mentioned; [b]Isolated yield. [c]Cs_2CO_3 (1.1 equiv) was used.

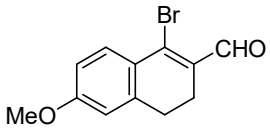
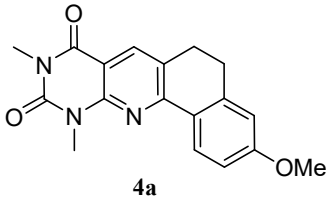
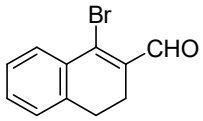
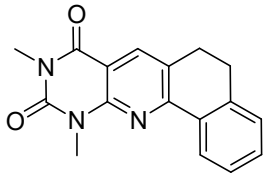
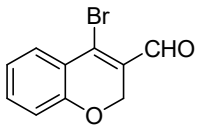
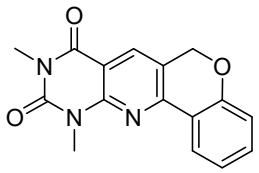
With the optimized reaction condition (Table 4B.2, entry 11), the feasibility of the reaction was explored by selecting some other *β*-halovinyl/aryl aldehydes **2b-m** and 6-amino-1,3-dialkyluracils **3a-b** (Table 4B.3). The other cyclic *β*-bromovinyl aldehydes **2b-c** reacted with **3a** under the optimized reaction conditions to afford pyrido[2,3-*d*]pyrimidines **4b-c** in 85-88% yield. The substituted *β*-bromovinyl aldehydes with electron donating and electron-withdrawing groups such as methyl, chloro and nitro present in the aromatic ring reacted

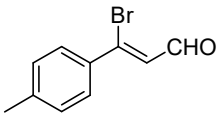
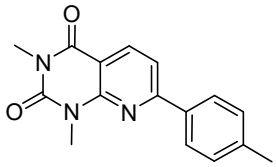
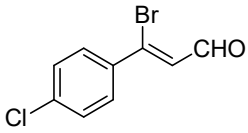
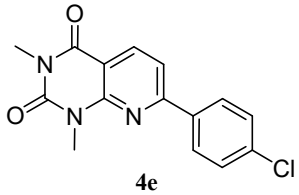
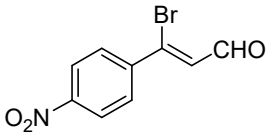
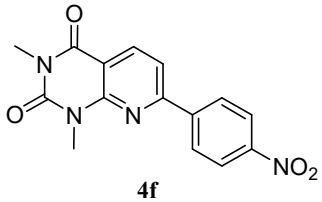
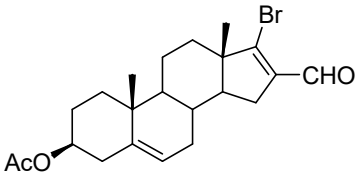
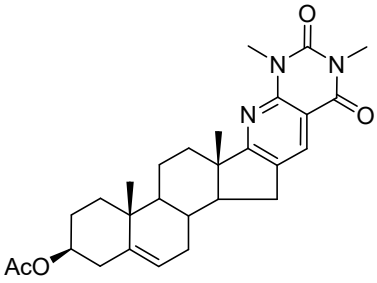
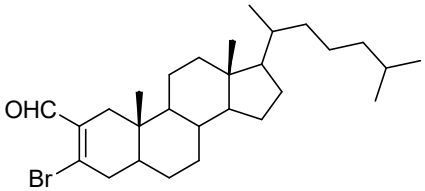
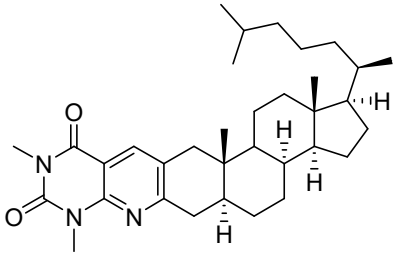
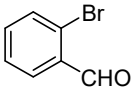
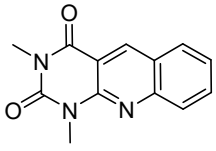
smoothly with 6-amino-1,3-dimethyluracil **3a** to afford pyrazolo[3,4-*b*]pyridines **4d-f** in 77-93% yields. The heterocycle sustituted *β*-bromovinyl aldehyde **2m** was also converted to 7-furyl substituted pyrido[2,3-*d*]pyrimidine **4m** in good yields (84%). The reactions of steroidal *β*-bromovinyl aldehydes **2g-h** with **2a** were performed under the above reaction conditions to afford corresponding steroidal pyrido[2,3-*d*]pyrimidines **4g-h** in 73-78% yields. In addition, the reaction of *β*-bromovinyl aldehyde **2l** and **2m** with 6-amino-1,3-dipropyluracil **2b** proceeded smoothly to provide pyrido[2,3-*d*]pyrimidine **4n** and **4o** in 86 and 74% yield respectively.

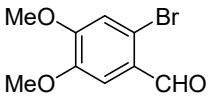
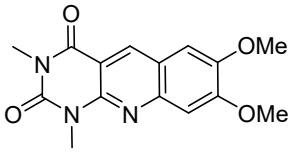
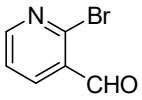
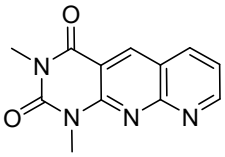
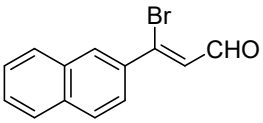
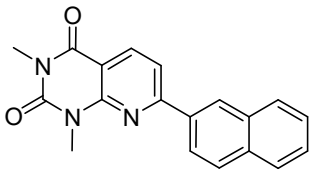
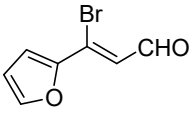
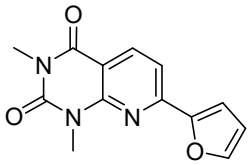
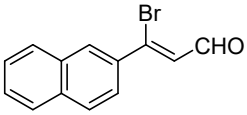
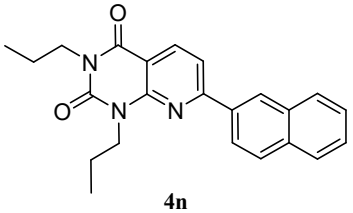
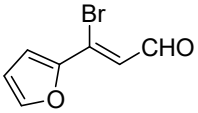
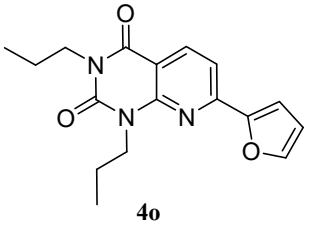
Table 4B.3 Synthesis of various substituted pyrido[2,3-*d*]pyrimidine **4a-o**



2 **3a, R = Methyl** **3b, R = Propyl** **4**

Entry	Carbonyl Compound	*β*-chloro-*α*,*β*-unsaturated aldehydes	Yield(%)[a]
1	 **2a**	 **4a**	90
2	 **2b**	 **4b**	88
3	 **2c**	 **4c**	85

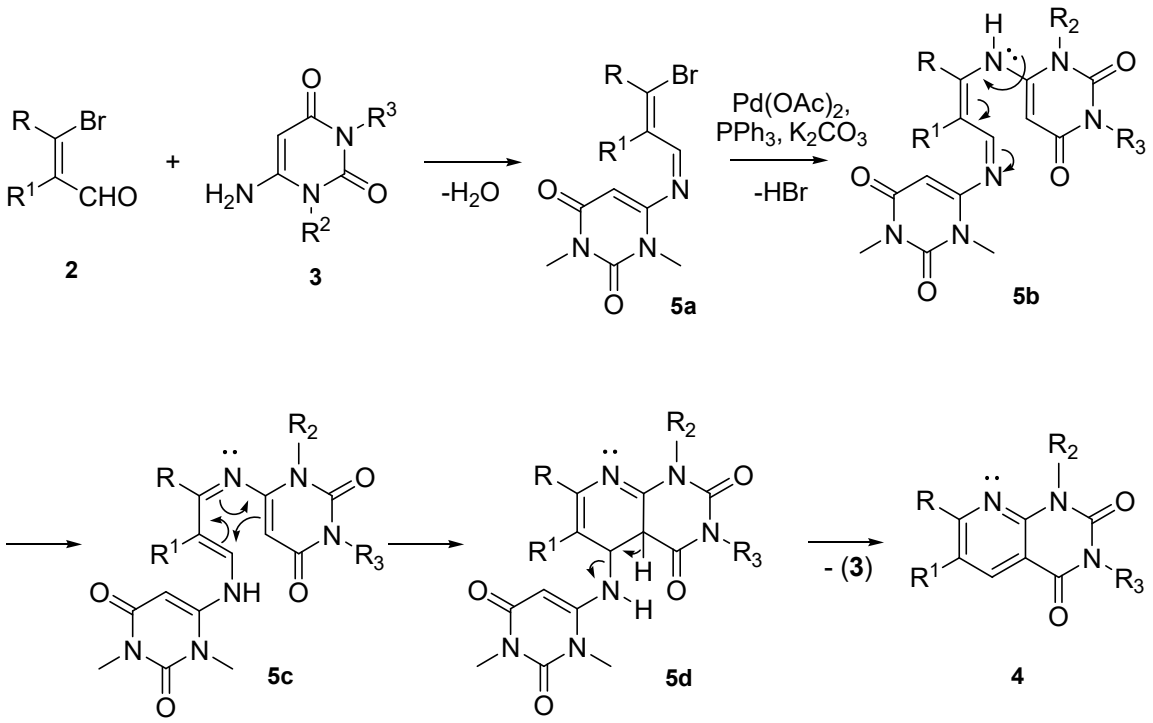
4	 **2d**	 **4d**	93
5	 **2e**	 **4e**	80
6	 **2f**	 **4f**	77
7	 **2g**	 **4g**	78
8	 **2h**	 **4h**	73
9	 **2i**	 **4i**	78

10	 **2j**	 **4j**	79
11	 **2k**	 **4k**	72
12	 **2l**	 **4l**	91
13	 **2m**	 **4m**	84
14	 **2l**	 **4n**	86
15	 **2m**	 **4o**	74

[a]Isolated yield

A probable mechanism for the formation of pyrido[2,3-*d*]pyrimidine **4** is shown in Scheme 4B.3. First the aldehyde **2** forms imine with 6-amino-1,3-dialkyluracil **3** to produce imine **5a**, which on subsequent coupling with uracil molecules affords intermediate **5b**. Then,

rearrangement of electron generates probably azadiene intermediate **5c** which on six-electron cyclization and subsequent elimination of one molecule of **3** affords the final compound **4**.



Scheme 4B.3

4B.3 Conclusion

In conclusion, an environmentally benign methodology for the efficient synthesis of biologically important pyrido[2,3-*d*]pyrimidines was developed. The reaction was studied with variety of *β*-halovinyl/aryl aldehydes in presence of palladium catalyst under microwave irradiation. Several features such as solvent-free synthesis, energy efficiency, less catalyst loading and operation simplicity make this procedure greener.

4B.4 Experimental

General experimental Procedure

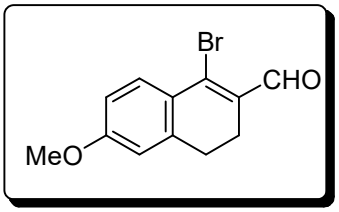
Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Elmer FT-IR-2000 spectrometer on a thin film using chloroform. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer or Bruker Avance III 500 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (100-200 mesh, Merck). All MW reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor.

(a) Preparation and characterization of *β*-halovinyl/aryl aldehydes 2:

In a two necked round bottom flask 2 equivalent of PBr_3 and 6 equivalent of DMF was taken and stirred about half and hour at 5 ^oC-0 ^oC in dry $CHCl_3$ under the inert condition of N_2 atm. After formation of bromomethyleneiminium salt, a solution of compound of **1** (2 gm in 5 ml dry $CHCl_3$) is poured slowly into the Vilsmeier reagent (prepared in a separate flask) and continued stirring for 6 hs at room temperature. After product formation, monitored by TLC, the reaction mixture is slowly poured into ice cold water and neutralized by $NaHCO_3$ solution, extracted in $CHCl_3$, dried over anhydrous Na_2SO_4. Removal of $CHCl_3$ in rotavapour and purification of the crude product by column chromatography using hexane and ethyl acetate as eluent afforded the final compound **2**.

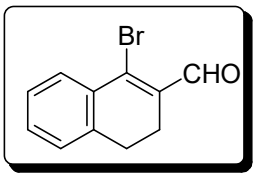
Characterization of *β*-halovinyl/aryl aldehydes 2

1-Bromo-3,4-dihydro-6-methoxynaphthalene-2-carbaldehyde (2a)



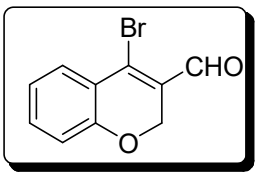
Yellow solid, Yield 90%; m.p. 60-62 °C; IR ($CHCl_3$, cm^{-1}): 2941, 2839, 1662, 1606, 1552, 1252, 1183, 1036, 956, 802, 705; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55-2.83 (m, 4H), 3.85 (s, 3H), 6.73 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 10.2 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 27.7, 55.5, 112.1, 113.4, 125.9, 130.8, 132.2, 139.2, 141.3, 162.1, 192.9; MS (EI, *m/z*): 267.1 $[M]^+$.

1-Bromo-3,4-dihydronaphthalene-2-carbaldehyde (2b)



Yellow solid, Yield 85%; m.p. 90-92 °C; IR ($CHCl_3$, cm^{-1}): 2941, 2837, 1660, 1601, 1550, 1035, 956, 709; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.52-2.82 (m, 4H), 6.88 (d, *J* = 6.9 Hz, 1H), 7.02-7.15 (m, 1H), 7.32- 7.35 (m, 1H), 7.65 (d, *J* = 6.7 Hz, 1H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 27.3, 112.4, 113.1, 125.6, 131.0, 132.2, 139.1, 141.2, 162.4, 191.9; MS (EI, *m/z*): 237.0 $[M]^+$.

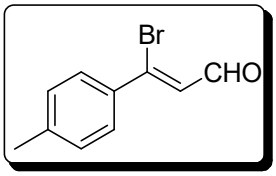
4-Bromo-2H-chromene-3-carbaldehyde (2c)



Yellow solid, Yield 82%; m.p. 72-75 °C; IR ($CHCl_3$, cm^{-1}): 2939, 2835, 1660, 1430, 1252, 951, 695; ^1H NMR ($CDCl_3$, 300 MHz) δ ^1H NMR ($CDCl_3$, 300 MHz) δ 4.97 (s, 2H), 6.89 (d,

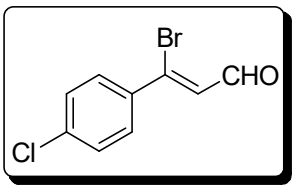
J = 7.6 Hz, 1H), 7.03-7.14 (m, 1H), 7.36 (t, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.1, 116.1, 121.4, 122.8, 127.3, 129.4, 134.2, 135.1, 156.3, 190.1; MS (EI, *m/z*): 239.0 $[M]^+$.

3-Bromo-3-*p*-tolylacrylaldehyde (2d)



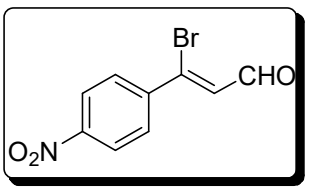
Yellow solid, Yield 90%; m.p. 92-95 °C; IR ($CHCl_3$, cm^{-1}): 2940, 2835, 1661, 1253, 955, 705; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 6.77 (s, 1H), 7.28 (d, *J* = 4.8 Hz, 2H), 7.60 (d, *J* = 5.1 Hz, 2H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 126.5, 127.9, 129.4, 134.4, 142.4, 145.2, 193.7; MS (EI, *m/z*): 225.0 $[M]^+$.

3-Bromo-3-(4-chlorophenyl)acrylaldehyde (2e)



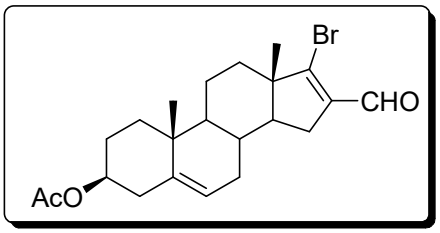
Yellow solid, Yield 85%; m.p. 100-105 °C; IR ($CHCl_3$, cm^{-1}): 2941, 2838, 1662, 1550, 950, 806, 703; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.76 (s, 1H), 7.44 (d, *J* = 4.9 Hz, 2H), 7.64 (d, *J* = 4.8 Hz, 2H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 127.7, 129.3, 135.8, 137.9, 143.3, 193.3; MS (EI, *m/z*): 245.5 $[M]^+$.

Bromo-3-(4-nitrophenyl)acrylaldehyde (2f)



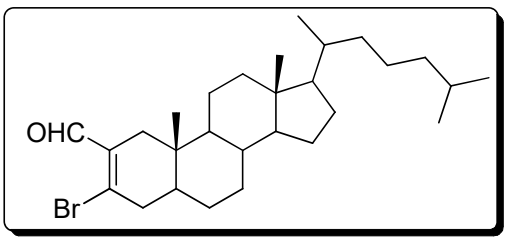
Yellow solid, Yield 90%; m.p. 90-92 °C; IR ($CHCl_3$, cm^{-1}): 2940, 2835, 1660, 1547, 945, 805, 701; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 1H), 7.87 (d, *J* = 5.9 Hz, 2H), 8.31 (d, *J* = 6.0 Hz, 2H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 127.7, 129.3, 135.8, 137.9, 143.3, 193.3; MS (EI, *m/z*): 256.0 $[M]^+$.

3*β*-Acetoxy-17-bromo-16-formyl-androst-5,16-diene (2g)



White solid, Yield 75%; m.p. 154-158 °C; IR ($CHCl_3$, cm^{-1}): 2927, 2853, 1733, 1673, 1581, 1373, 1241, 1032, 772; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.95 (s, 3H), 1.06 (s, 3H), 0.85-2.51 (m, 20H), 4.52-4.66 (m, 1H), 5.40 (s, 1H), 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 13.5, 15.1, 19.2, 20.3, 21.4, 21.8, 27.7, 30.7, 31.4, 35.8, 36.7, 38.1, 47.5, 50.1, 51.6, 53.8, 73.7, 121.8, 139.8, 155.1, 170.5, 189.7; MS (EI, *m/z*): 421.0 $[M]^+$.

3-Bromo-2-formyl-cholest-2-ene (2h)



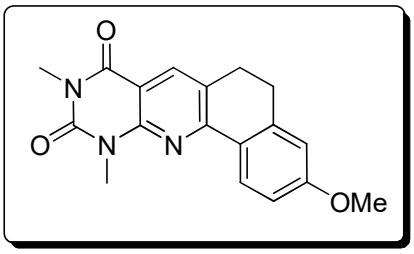
White solid, Yield 80%; m.p. 115-117 °C; IR ($CHCl_3$, cm^{-1}): 2934, 2867, 1663, 1609, 1255, 1019, 701; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 3H), 0.72 (s, 3H), 0.78-2.65 (m, 38H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ11.2, 18.3, 21.3, 22.8, 24.6, 35.5, 36.4, 42.1, 53.4, 56.9, 76.1, 77.2, 134.1, 142.3, 194.1; MS (EI, *m/z*): 477.5 $[M]^+$.

(b) Preparation and characterization of pyrido[2,3-*d*]pyrimidines 4

A mixture of *β*-bromovinyl/aryl aldehyde (**2,** 1.0 mmol), 6-amino-1,3-dialkyluracil (**3**, 1.0 mmol), $Pd(OAc)_2$ (2.5 mol %), xphos (5.0 mol %) and K_2CO_3 (1 mmol) was irradiated in a closed vessel in a Synthos 3000 microwave reactor at 700 Watt (120 ^oC and 14 bar) for 5 minutes. After completion of the reaction, the reaction mixture was treated with water (40 mL) and then extracted with ethylacetate (30 x 3 mL). The organic portion was washed with water, dried over anhydrous sodium sulfate and the solvent was removed in vacuo to obtain crude product which on silica gel column chromatographic purification using EtOAc/hexane as the eluent afforded compounds **4a-o**.

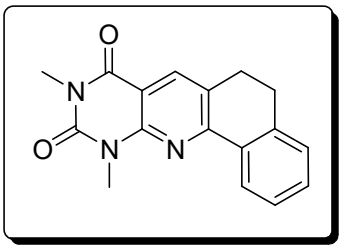
Characterization of pyrido[2,3-*d*]pyrimidines 4

3-Methoxy-9,11-dimethyl-5,6-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(9*H*,11*H*)-dione (4a)



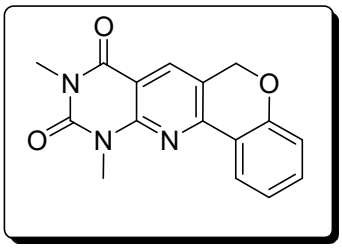
Yellow solid, Yield 90%; m.p. 216-219 °C; IR ($CHCl_3$, cm^{-1}): 2926, 1701, 1657, 1598, 1411, 1368, 1277, 1044, 790; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.92-3.03 (m, 4H), 3.50 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 6.79 (s, 1H), 6.92 (d, J = 6.0 Hz, 1H), 8.20 (s, 1H), 8.30 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 27.1, 28.3, 29.4, 29.7, 55.4, 108.1, 113.1, 126.2, 126.3, 128.1, 135.9, 141.6, 149.7, 151.7, 156.8, 161.6, 161.9; MS (EI, *m/z*): 323.3 $[M]^+$. Anal. calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.59; H, 5.48; N, 13.31.

9,11-Dimethyl-5,6-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(9*H*,11*H*)-dione (4b)



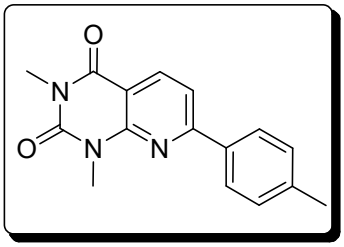
Yellow solid, Yield 88%; m.p. 253-255 °C; IR ($CHCl_3$, cm^{-1}): 2946, 1706, 1654, 1599, 1444, 1370, 1219, 1018, 773; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.01 (m, 4H), 3.51 (s, 3H), 3.83 (s, 3H), 7.39 (m, 2H), 8.26 (s, 1H), 8.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 27.1, 27.9, 28.4, 29.4, 108.9, 126.2, 127.2, 127.3, 128.2, 130.9, 133.3, 136.4, 139.5, 149.7, 151.7, 156.7, 161.5; MS (EI, *m/z*): 293.3 $[M]^+$. Anal. calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.78; H, 5.01; N, 14.15.

1,3-Dimethylpyrimido[4,5-*b*][1,8]naphthyridine-2,4(1*H*,3*H*)-dione (4c)



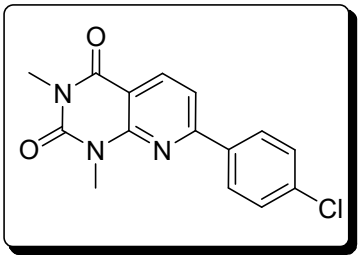
Yellow solid, Yield 85%; m.p. 189-191 °C; IR ($CHCl_3$, cm^{-1}): 2924, 1715, 1670, 1618, 1500, 1437, 1181, 1119, 721; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.50 (s, 3H), 3.81 (s, 3H), 5.28 (s, 2H), 6.92 (d, J = 7.5 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.20 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 28.7, 29.7, 112.1, 131.7, 133.1, 138.6, 141.6, 151.2, 160.6; MS (EI, *m/z*): 295.2 $[M]^+$. Anal. calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.36; H, 4.67; N, 14.41.

1,3-Dimethyl-7-*p*-tolylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4d)



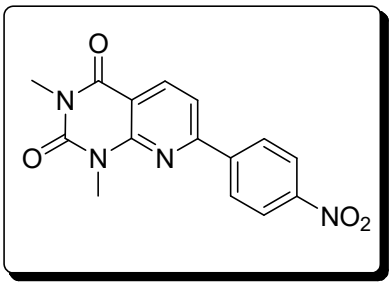
Yellow solid, Yield 93%; m.p. 180-182 °C; IR ($CHCl_3$, cm^{-1}): 2924, 1707, 1661, 1597, 1424, 1370, 1099, 789; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.44 (s, 3H), 3.51 (s, 3H), 3.83 (s, 3H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 1H), 8.47 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.4, 28.3, 29.3, 108.6, 114.7, 127.3, 129.6, 134.6, 138.1, 141.1, 150.6, 151.6, 161.1, 161.3; MS (EI, *m/z*): 281.3 $[M]^+$. Anal. calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.12; H, 5.46; N, 14.78.

7-(4-Chlorophenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e)



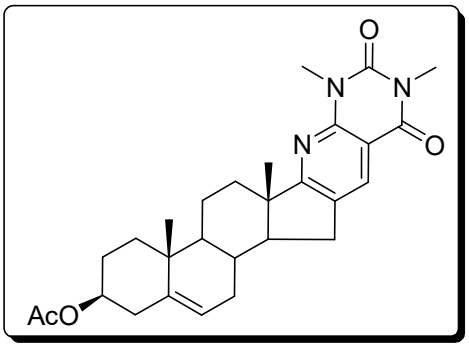
Yellow solid, Yield 80%; m.p. 142-145 °C; IR ($CHCl_3$, cm^{-1}): 2924, 1705, 1661, 1600, 1566, 1424, 1090, 750; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.51 (s, 3H), 3.82 (s, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.51 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 28.5, 29.5, 109.3, 114.9, 128.8, 129.2, 135.9, 136.9, 138.6, 159.9, 161.3. MS (EI, *m/z*): 301.7 $[M]^+$; Anal. calcd. for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.58; H, 3.92; N, 13.77.

1,3-Dimethyl-7-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4f)



Yellow solid, Yield 77%; m.p. 161-163 °C; IR ($CHCl_3$, cm^{-1}): 2918, 1710, 1662, 1562, 1466, 1345, 1219, 1018, 772; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.30 (s, 3H), 3.72 (s, 3H), 6.92 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.3 Hz, 2H), 8.61 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 28.5, 29.7, 121.0, 123.2, 128.7, 145.9, 147.6, 151.1, 151.8, 152.8, 160.5; MS (EI, *m/z*): 312.2 $[M]^+$. Anal. calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.81; H, 3.64; N, 18.09.

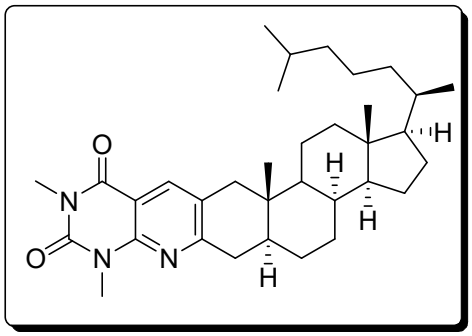
3*β*-Acetoxy-1′,3′-dimethyl-5-en-androst[16,17-*g*]pyrido[2′,3′-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4g)



White solid, Yield 78%; m.p. 146-148 °C; IR ($CHCl_3$, cm^{-1}): 2924, 2853, 1732, 1709, 1663, 1612, 1462, 1243, 1032, 771; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.78 (s, 3H), 0.93 (s, 3H), 0.75-2.47 (m, 20H), 3.41 (s, 3H), 3.67 (s, 3H), 4.54-4.59 (m, 1H), 5.36 (s, 1H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.2, 17.1, 21.4, 22.7, 27.7, 28.4, 29.4, 29.7, 30.8, 31.9, 33.2, 36.9, 38.1, 46.3, 50.5, 55.7, 73.7, 108.1, 121.9, 131.6, 132.7, 140.1, 148.6, 150.4, 161.9, 170.5,

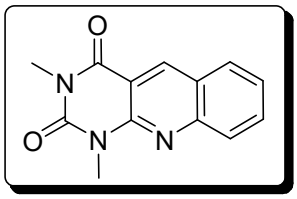
179.2; MS (EI, *m/z*): 477.6 $[M]^+$. Anal. calcd. for $C_{28}H_{35}N_3O_4$: C, 70.42; H, 7.39; N, 8.80. Found: C, 70.73; H, 7.48; N, 8.87.

1′,3′-Dimethyl-cholest[2,3-*g*]pyrido[2′,3′-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4h)



White solid, Yield 73%; m.p. 164-167 °C; IR ($CHCl_3$, cm^{-1}): 2929, 2867, 1709, 1663, 1612, 1467, 1382, 1019, 752; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.69 (s, 3H), 0.88 (s, 3H), 0.70-2.87 (m, 39H), 3.45 (s, 3H), 3.69 (s, 3H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 18.7, 22.6, 22.8, 23.8, 28.0, 28.2, 35.6, 35.8, 36.2, 39.5, 39.9, 42.5, 53.5, 56.3, 56.4, 107.7, 127.2, 128.3, 138.0, 153.7, 161.6, 162.3, 162.9; MS (EI, *m/z*): 533.7 $[M]^+$. Anal. calcd. for $C_{34}H_{51}N_3O_2$: C, 76.50; H, 9.63; N, 7.87. Found: C, 76.75; H, 9.59; N, 7.75.

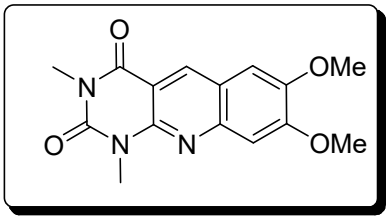
1,3-Dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (4i)



Yellow solid, Yield 78%; m.p. 210-212 °C; IR ($CHCl_3$, cm^{-1}): 2921, 1708, 1659, 1621, 1608, 1470, 1292, 1018, 790; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.54 (s, 3H), 3.84 (s, 3H), 7.50-7.55 (m, 1H), 7.80-7.85 (m, 1H), 7.93-7.99 (m, 2H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 28.5, 29.7, 110.9, 124.7, 125.8, 128.1, 129.3, 133.2, 140.1, 149.9, 161.4; MS (EI, *m/z*): 241.2

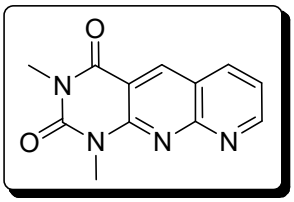
$[M]^+$. Anal. calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.44; H, 4.67; N, 17.71.

7,8-Dimethoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (4j)



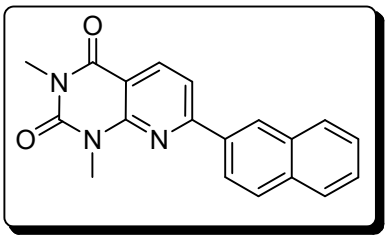
Yellow solid, Yield 79%; m.p. 248-250 °C; IR ($CHCl_3$, cm^{-1}): 2923, 1703, 1657, 1611, 1502, 1422, 1254, 1007, 747; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.52 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 7.14 (s, 1H), 7.31 (s, 1H), 8.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 29.5, 29.7, 56.2, 56.4, 105.9, 108.7, 113.7, 120.3, 136.1, 137.2, 147.8, 149.5, 153.2, 155.8, 161.7; MS (EI, *m/z*): 301.3 $[M]^+$. Anal. calcd. for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.46; H, 4.87; N, 13.74.

1,3-Dimethylpyrimido[4,5-*b*][1,8]naphthyridine-2,4(1*H*,3*H*)-dione (4k)



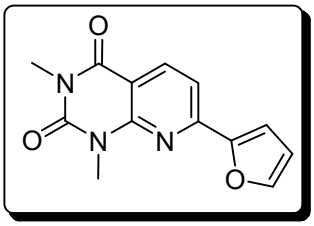
Yellow solid, Yield 72%; m.p. 183-186 °C; IR ($CHCl_3$, cm^{-1}): 2924, 1715, 1670, 1618, 1500, 1437, 1181, 1119, 721; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.55 (s, 3H), 3.90 (s, 3H), 8.33-8.36 (m, 3H), 9.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 28.7, 29.7, 112.1, 131.7, 133.1, 138.6, 141.6, 151.2, 160.6; MS (EI, *m/z*): 242.2 $[M]^+$. Anal. calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.38; H, 3.97; N, 22.91.

1,3-Dimethyl-7-(naphthalen-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4l)



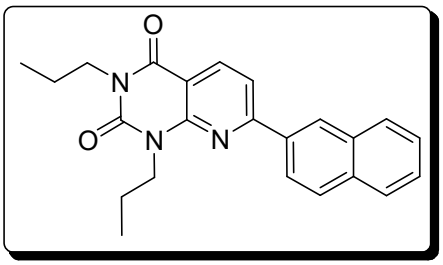
Yellow solid, Yield 91%; m.p. 208-209 °C; IR ($CHCl_3$, cm^{-1}): 2925, 1705, 1659, 1557, 1423, 1372, 1289, 1018, 791; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.51 (s, 3H), 3.88 (s, 3H), 7.56 (d, *J* = 5.4 Hz, 2H), 7.81 (d, *J* = 4.8 Hz, 1H), 7.89 (d, *J* = 6.5 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 8.24 (d, *J* = 7.1 Hz, 1H), 8.52 (d, *J* = 7.9 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 28.4, 29.4, 108.9, 115.3, 122.2, 124.3, 126.6, 127.4, 127.6, 127.7, 128.6, 128.9, 132.8, 133.1, 138.2, 150.6, 151.6, 161.0, 161.3; MS (EI, *m/z*): 317.3 $[M]^+$. Anal. calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.77; H, 4.61; N, 13.17.

7-(Furan-2-yl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4m)



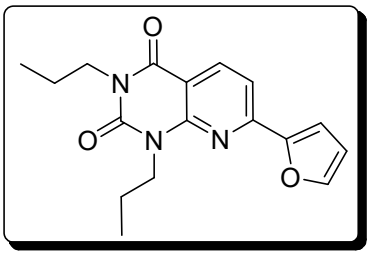
Brown solid, Yield 84%; m.p. 136-140 °C; IR ($CHCl_3$, cm^{-1}): 2921, 1706, 1658, 1602, 1476, 1366, 1295, 1018, 750; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.49 (s, 3H), 3.76 (s, 3H), 6.60 (d, *J* = 5.0 Hz, 1H), 7.26 (d, *J* = 3.5 Hz, 1H), 7.57 (d, *J* = 4.8 Hz, 1H), 7.62 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 28.3, 29.2, 108.5, 112.2, 112.6, 113.3, 138.2, 144.9, 150.7, 151.5, 152.6, 161.1; MS (EI, *m/z*): 257.2 $[M]^+$. Anal. calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.74; H, 4.62; N, 16.21.

7-(Naphthalen-3-yl)-1,3-dipropylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4n)



Yellow solid, Yield 86%; m.p. 142-145 °C; IR ($CHCl_3$, cm^{-1}): 2928, 1704, 1661, 1560, 1421, 1373, 1288, 1019, 789; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.00 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H), 1.69-1.79 (m, 2H), 1.85-1.94 (m, 2H), 4.04 (t, *J* = 7.5 Hz, 2H), 4.46 (t, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 5.9 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.51 (d, *J* = 6.9 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 11.3, 21.1, 43.3, 44.1, 109.0, 115.1, 124.2, 126.6, 127.5, 127.7, 128.6, 128.9, 133.1, 134.3, 134.8, 138.3, 150.5, 151.1, 160.9, 161.2; MS (EI, *m/z*): 373.4 $[M]^+$. Anal. calcd. for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.12; H, 6.24; N, 11.49.

7-(Furan-2-yl)-1,3-dipropylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4o)



Yellow solid, Yield 74%; m.p. 114-116 °C; IR ($CHCl_3$, cm^{-1}): 2927, 1705, 1659, 1599, 1473, 1369, 1299, 1017, 759; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H), 1.66-1.77 (m, 2H), 1.78-1.89 (m, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 4.35 (t, *J* = 6.0 Hz, 2H), 6.60 (d, *J* = 3.5 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 7.56 (d, *J* = 4.8 Hz, 1H), 7.61 (s, 1H), 8.45 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 11.3, 21.0, 43.2, 44.0, 108.7, 112.0, 112.5, 113.1, 138.3, 144.9, 150.5, 151.0, 152.4, 152.8, 160.9; MS (EI, *m/z*): 313.3

$[M]^+$. Anal. calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.34; H, 6.10; N, 13.50.

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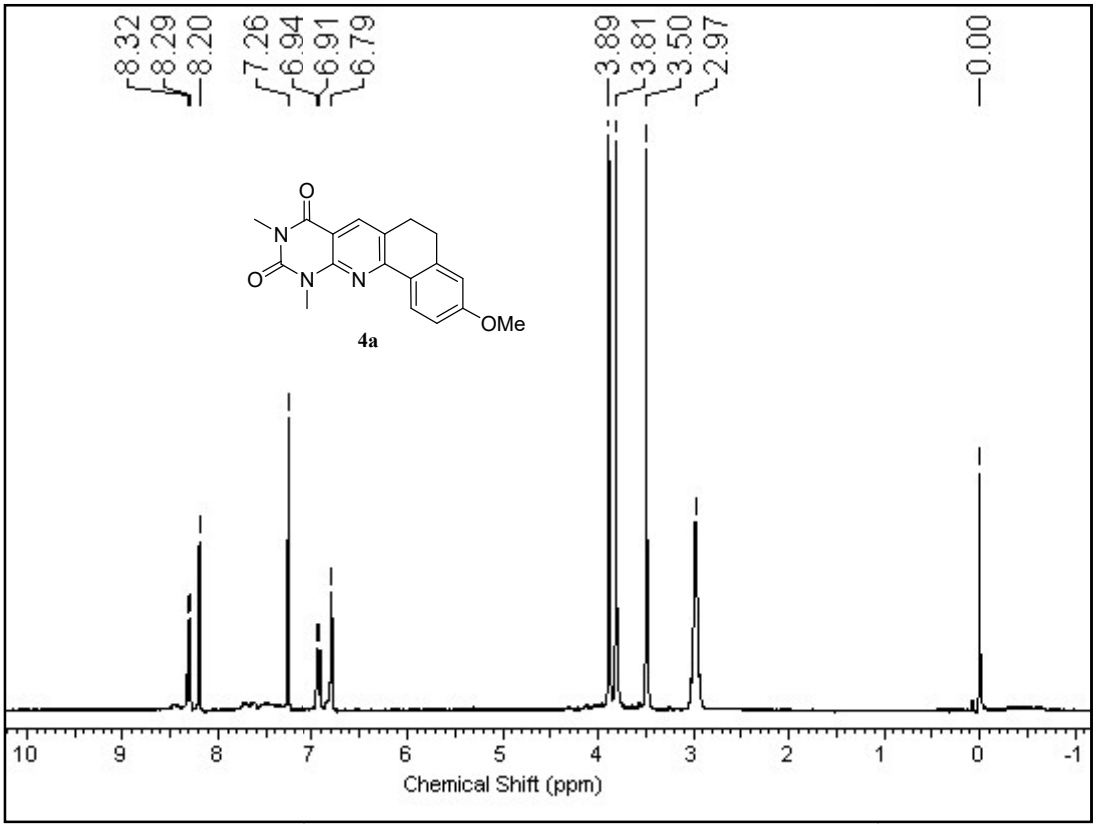
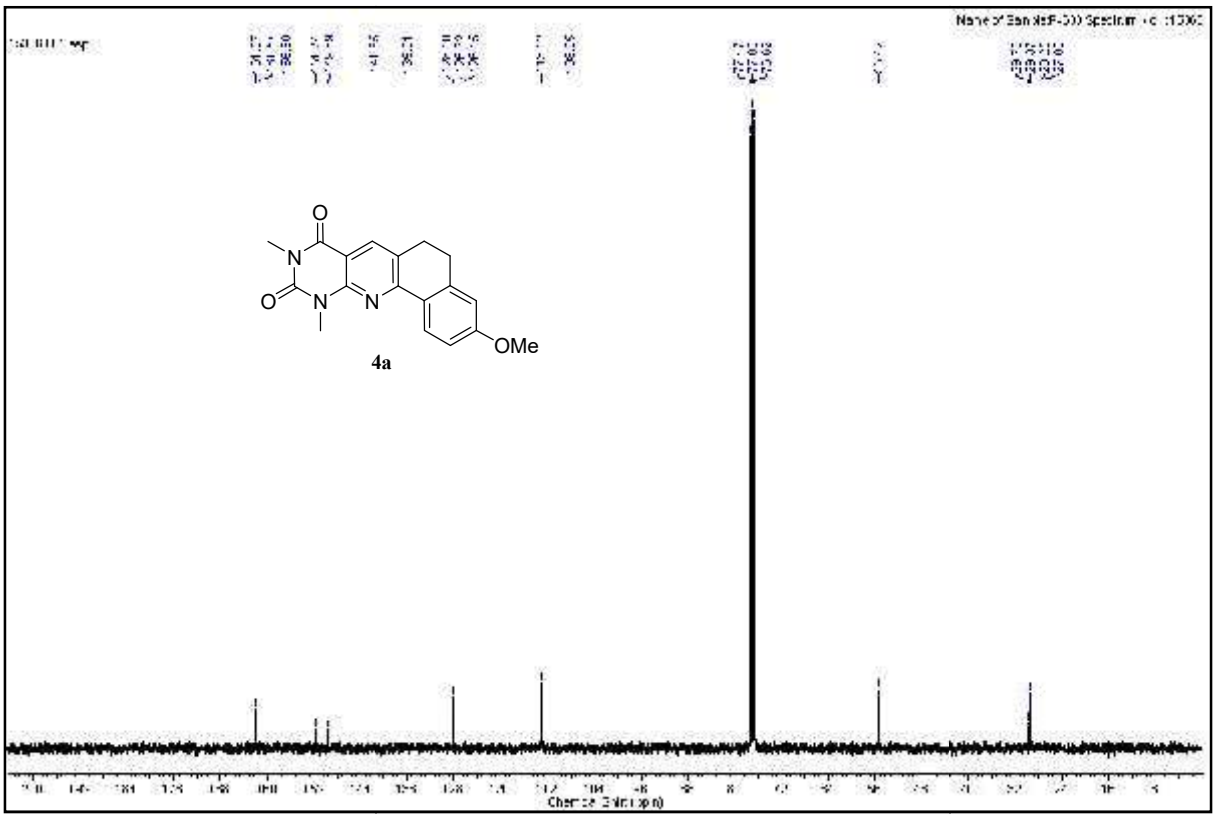
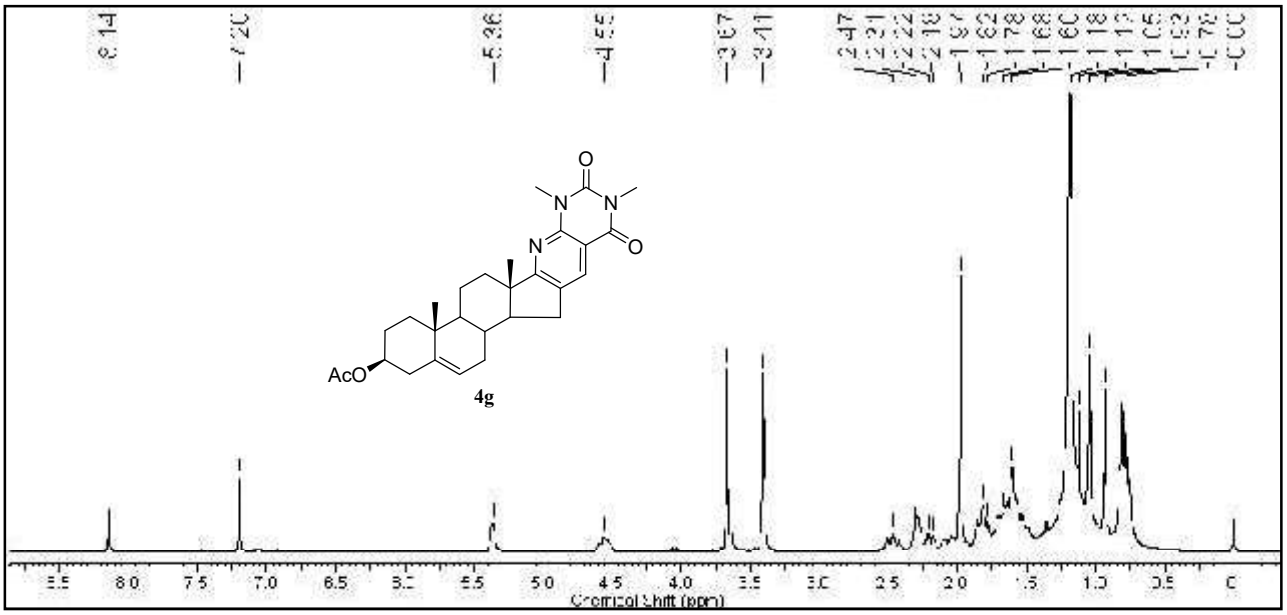
^{1}H NMR and ^{13}C NMR of some selected Pyrido[2,3-*d*]pyrimidine compounds



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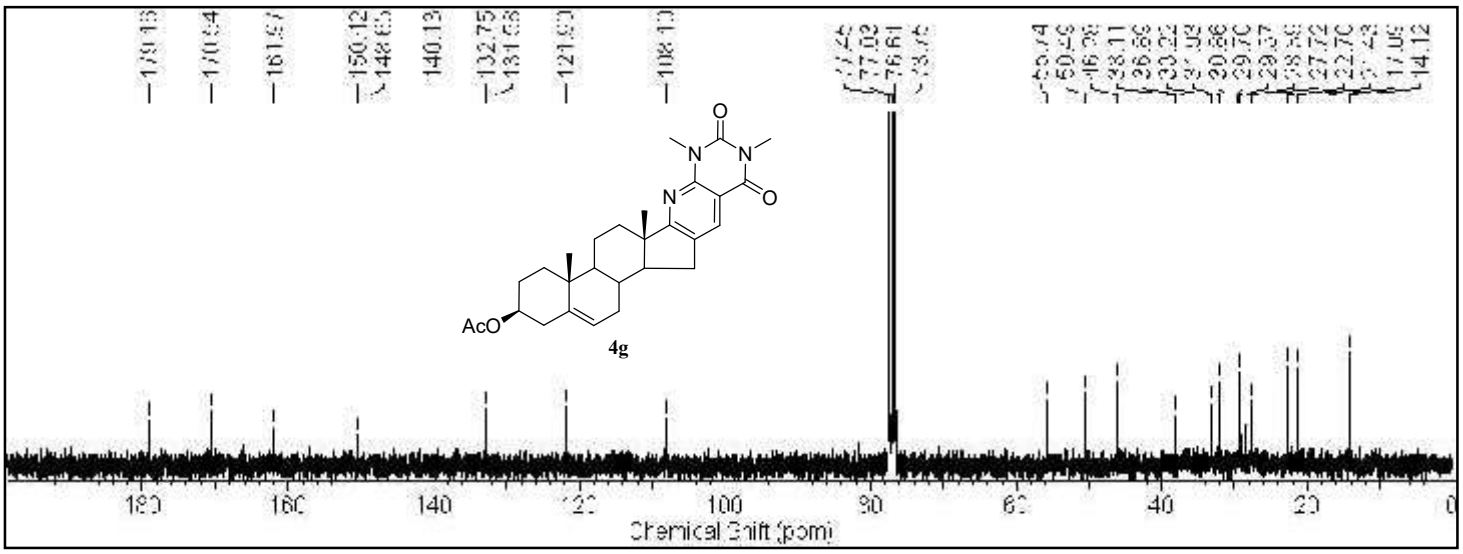
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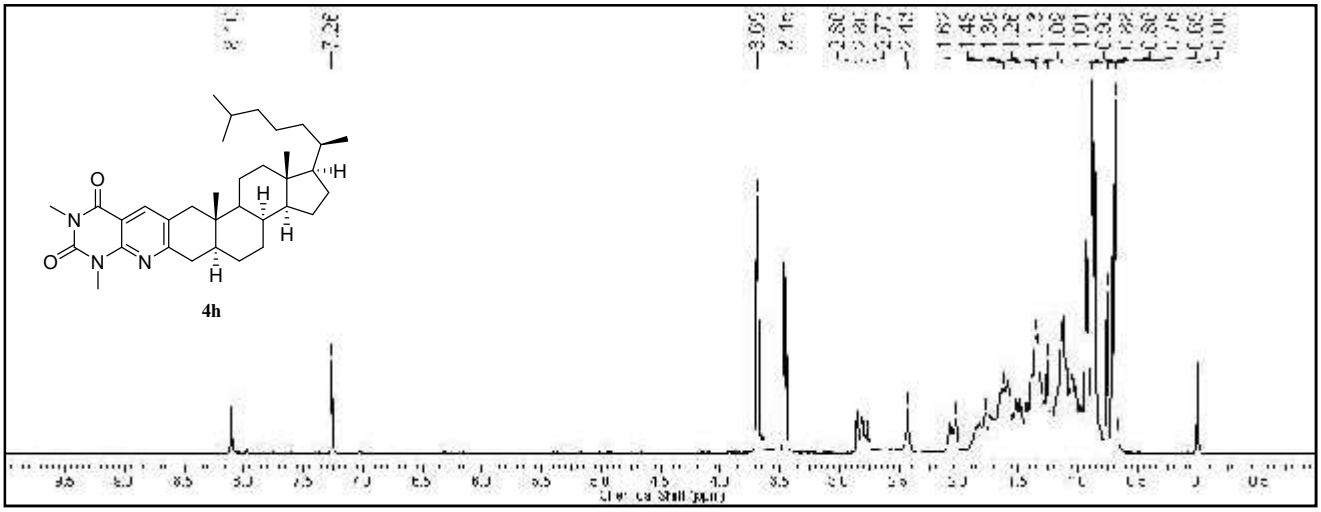
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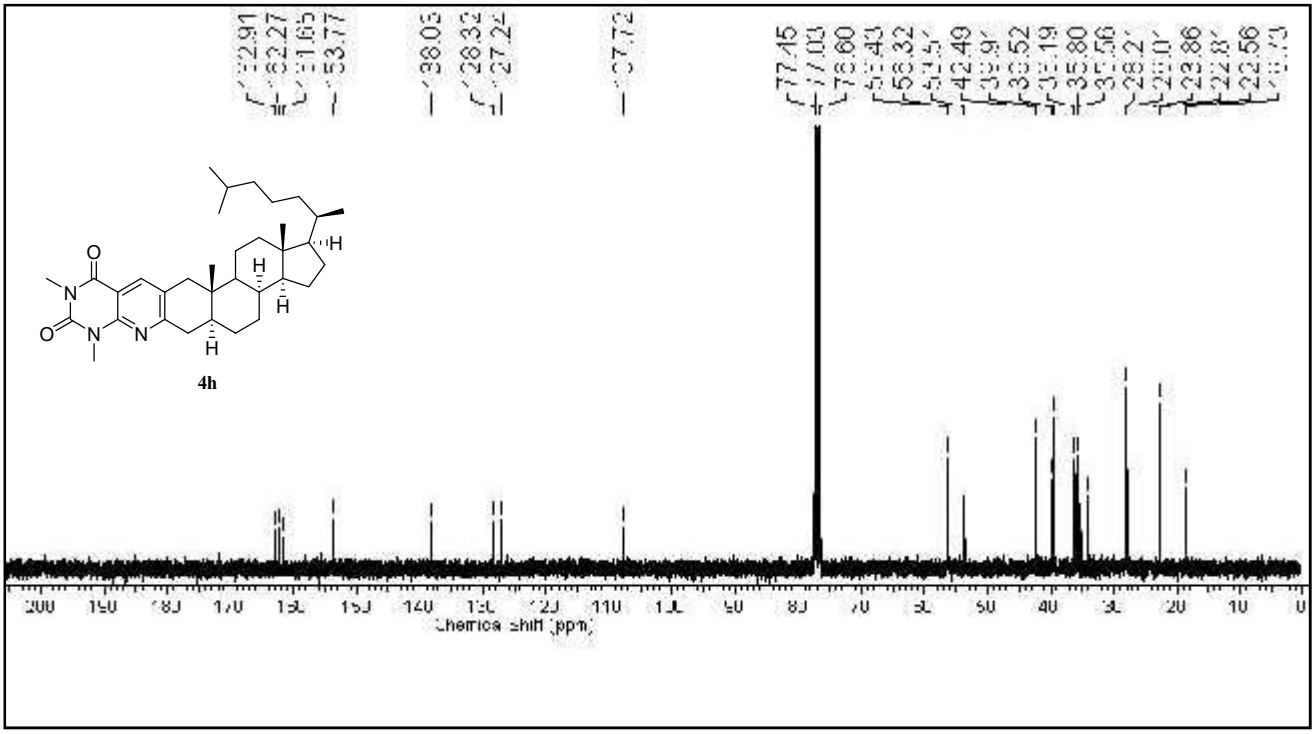
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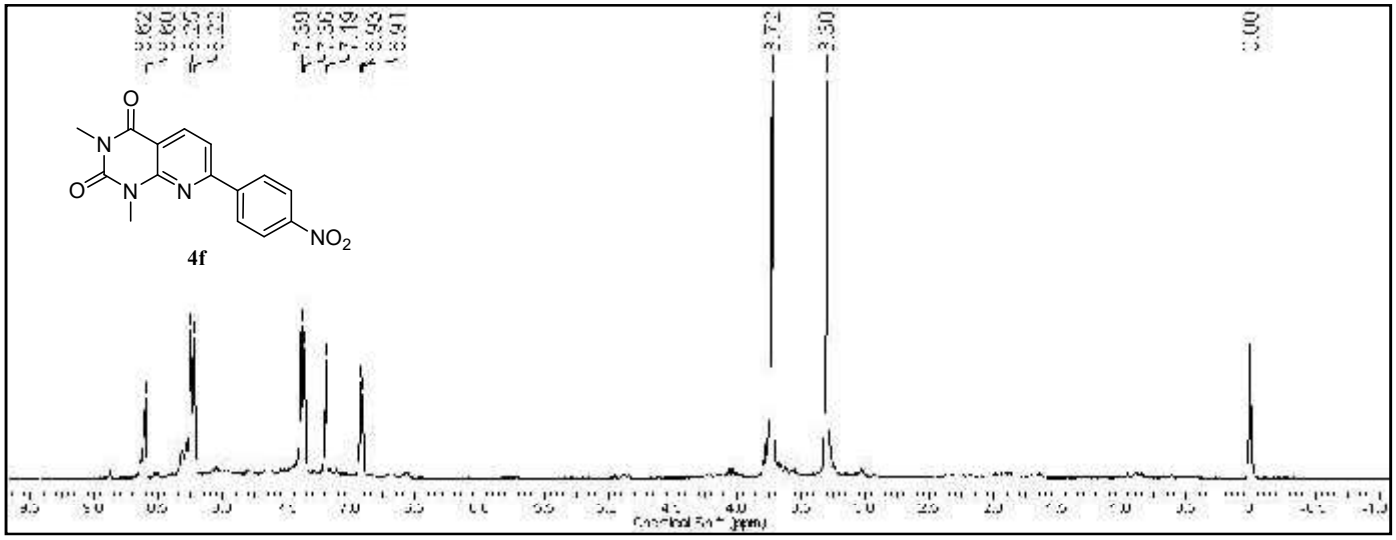

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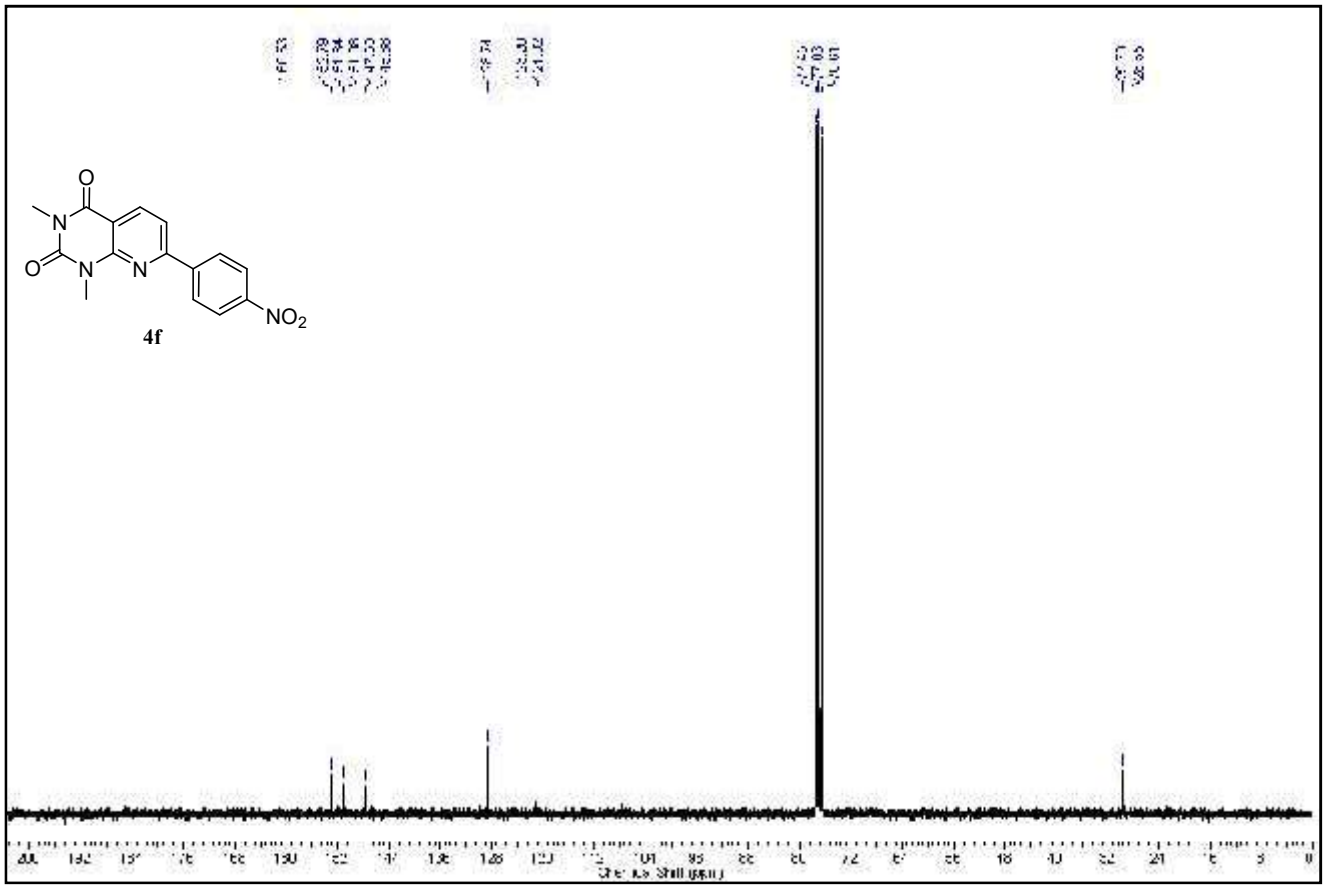

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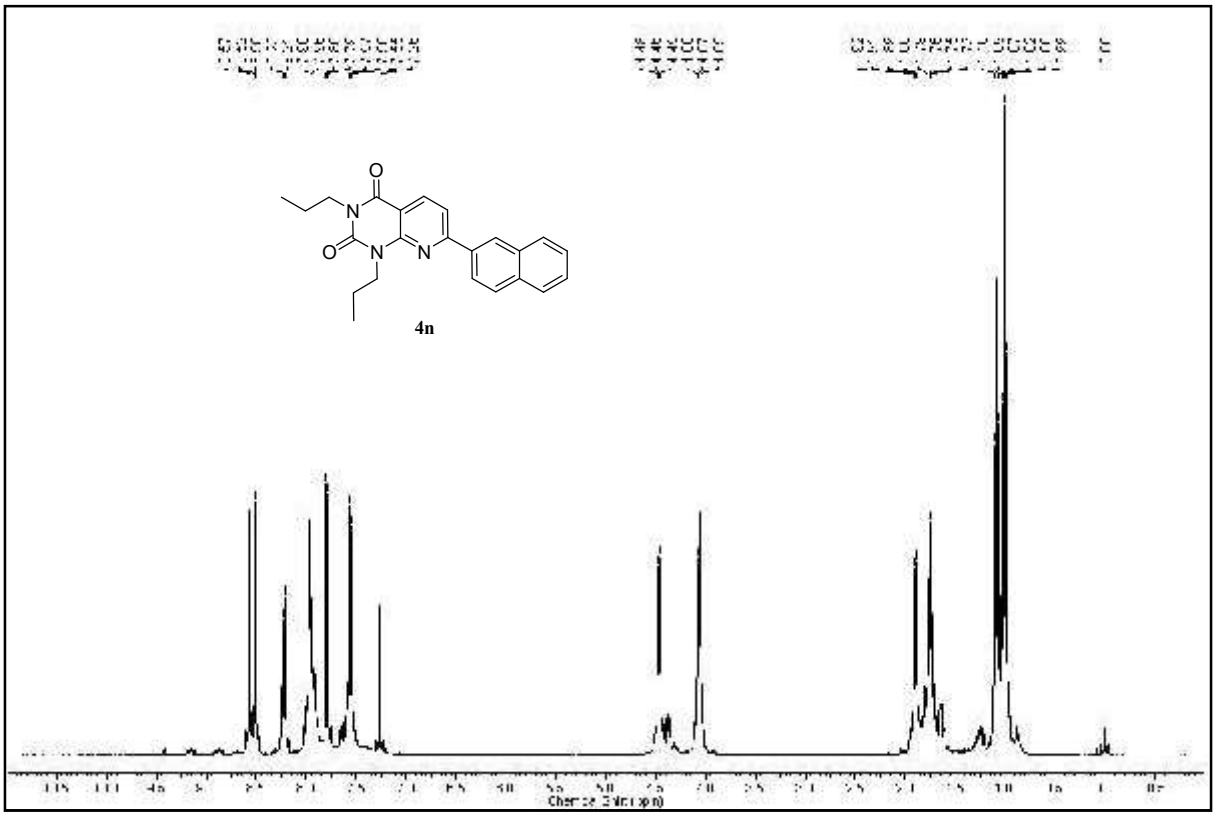

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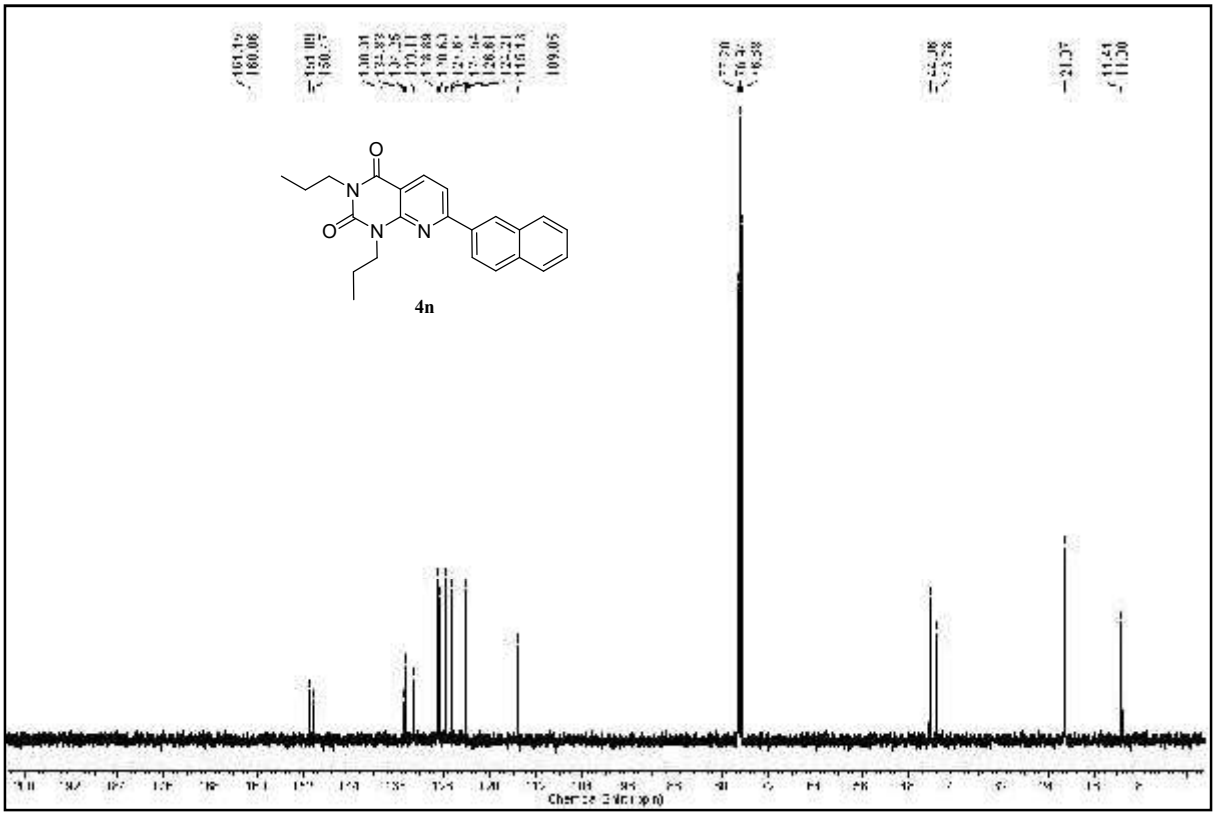

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