Application of primary allyl amines afforded by the Baylis-Hillman adducts for heterocyclic synthesis: Generation of 5-benzyl-4(3*H*)-pyrimidinones and 2-benzylidene-2,3-dihydro-pyrrolizin-1-ones

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Abstract: The applications of the primary allyl amines afforded by the acetyl derivative of Baylis-Hillman adducts of acrylate for the synthesis of heterocycles using robust reactions are described. In the first strategy a one-pot synthesis of 5-benzyl-4(3*H*)-pyrimidinones have been achieved via N-formylation of the amines in the presence of neat formamide followed by ammonium formate-mediated cyclization. These pyrimidinones have been demonstrated to be excellent precursor to the 4-pyridinamine derivatives. In the second strategy the synthesis of 2-benzylidene-2,3-dihydro-pyrrolizin-1-ones have been accomplished via treatment of allyl amine with dimethoxyfuran followed by saponification and PPA-mediated intramolecular cyclization.

Key words: Baylis-Hillman, Formamide, N-formylation, primary allyl amine, 4(3*H*)-pyrimidinone, 4-pyridinamine, 2,3-dihydro-1*H*-pyrrolizin-1-one

The primary allyl amines[1-3] serves as important synthetic intermediate in organic chemistry. They have been shown to be viable precursors for preparation of a spectrum of compounds including α- and β-amino acids,[4] alkaloids,[5] carbohydrates,[6] heterocycles[7] and others.[8] In our objective aimed at generation of heterocycles from derivatives of the Baylis-Hillman chemistry,[9] we have effectively utilized the primary allyl amines[10] afforded from the Baylis-Hillman acetate for synthesis of cyclic ureides[9d] and 3,4,6,7,8,9-hexahydro-pyrimido[1,2-a]pyrimidin-2-ones.[9l]

Formamide in the presence of acetic acid has been described to be a formylating agent for aromatic amines,[11] but with the discovery of other efficient formylating agents,[12] formamide is generally employed as a one carbon source for the synthesis of a pyrimidone subunit from compounds bearing amino and ester group at adjacent carbon atoms in an aromatic system.[13] Based on these reports, it was reasoned that the primary allyl amine afforded via the Baylis-Hillman adduct of acrylate on treatment with formamide might furnish the 4(3*H*)-pyrimidinones. Unlike, similar reaction of the primary allyl amine obtained from the Baylis-Hillman adduct of acrylonitrile would lead to 4-aminopyrimidine. Substituted-4-pyrimdinone and 4-pyrimidinamine derivatives have been ascribed with a variety of biological activities. These includes antidiabetic,[14] antiplatelet,[15] antidepressants,[16] kinase inhibitors,[17] and non-nucleoside reverse transcriptase inhibitors.[18] Intriguingly, the literature survey revealed that the synthesis of 5-benzyl-4(3*H*)-pyrimidinones remain unreported.

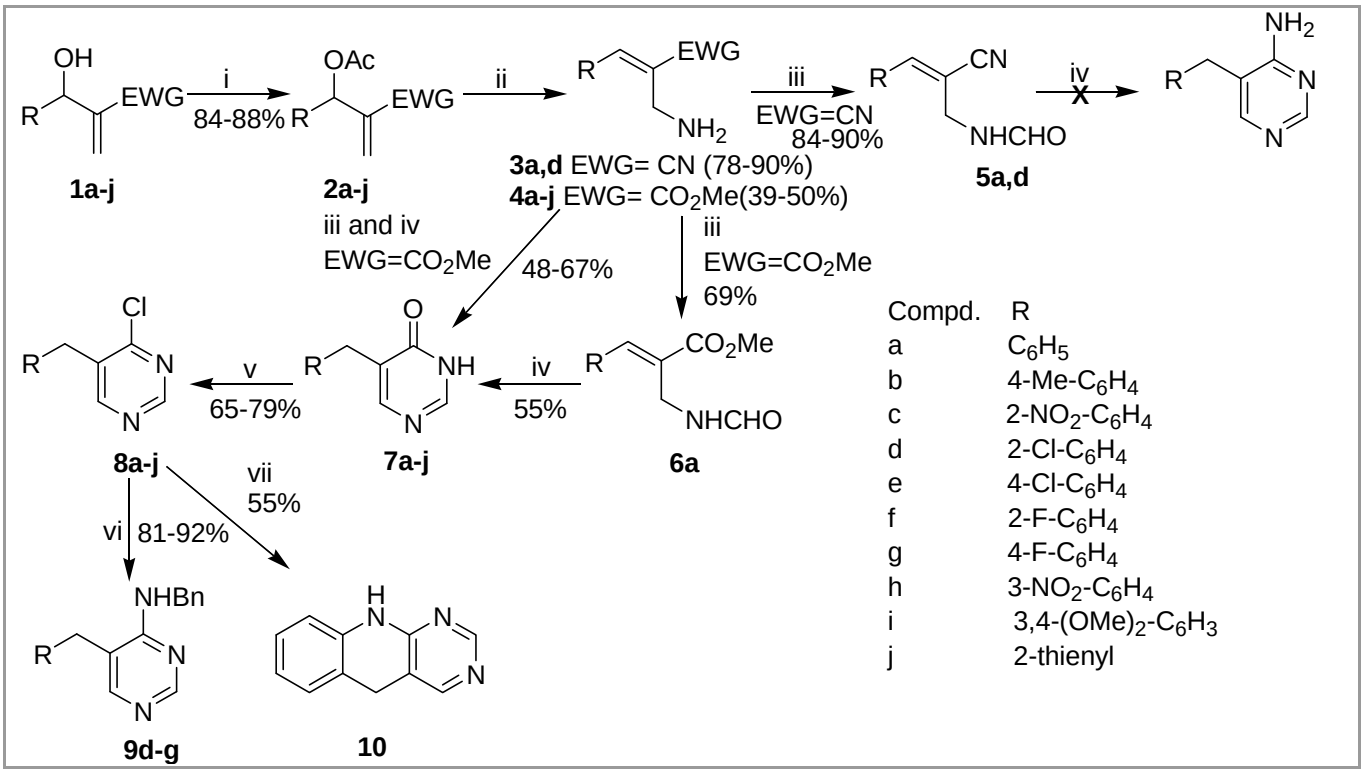
On the other hand substituted pyrrolizine derivatives have been reported to possess aromatase and platelet aggregation inhibitory activity.[19] The methodology described by Braunholtz et al.[20] for the synthesis of 2-benzylidene-pyrrolizin-1-one involve sequential alkylation of potassium salt of pyrrole with acrylonitrile, hydrolysis of the nitrile group to acid, intramolecular cyclization in the presence of $AlCl_3$ and addition of aldehyde to incorporate benzylidene group. They reported that the cyclization step in the reaction sequence required highly critical experimental conditions and was unsuccessful with PPA. Subsequently Dallemagne and co-workers obtained 3-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one starting from 3-amino-3-phenylpropionic acid and finally treating it with benzaldehyde.[19a] They accomplished the Vilsmeier type cyclization of the ester group onto the pyrrole via boron tribromide in dichloromethane. More recently, Michael et al. realized the formation of 6,7-dihydroindolizin-8(5*H*)-one from 4-(pyrrol-1-yl)butanoic acid via PPA-mediated cyclization in good yields.[21] Taking a cue from this report it was envisaged that 2-benzylidene-2,3-dihydro-pyrrolizin-1-ones could be readily generated from the Baylis-Hillman acetates via S_N2' addition of pyrrole followed by intramolecular cyclization. However our attempts to add pyrrole to the acetyl derivative of Baylis-Hillman adduct of acrylate resulted in low yield of the desired compound. In view of this outcome we developed an alternative route to 2-benzylidene-2,3-dihydro-pyrrolizin-1-one via the primary allyl amines. These results invoked us to present details of both the synthetic achievements in this paper.

Our study began with the preparation of primary allyl amines **3-4** generated from **1** using the reported procedure (scheme 1).[10] Treatment of the primary allyl amines **3a** and **4a** with formamide at 110 ^oC led to completion of reaction in approximately 1.5 h. The work up and subsequent column chromatography led to isolation of compounds which were identified as **5a** and **6a**, respectively. This made evident that contrary to earlier report[19] acetic acid was not required during formamide-mediated N-formylation. However this was not considered to be an unusual observation. Bhaskaran et al. too have proposed that formamide generated from the ammonium formate is responsible for the isolation of N-formanilide directly from aryl azides by reaction with Pd-C in the presence of ammonium formate.[12c] Earlier they have reported that although reaction of ammonium formate with aryl amine and sec-amine yield N-formamides, primary amine failed to react and only the alkyl ammonium formate salts were isolated.[12d] However, Kotha et al. reported the N-formylation of the primary amine of amino acid esters

in the presence of ammonium formate in dry acetonitrile.[12g] Notably the formamides **5a** and **6a** were obtained as mixture of rotamers in accordance to the literature.[22]

Once we had the N-formylated derivatives **5a** and **6a** in hand we decided to utilize them for the generation of desired heterocyclic system. In principle, compound **5** upon treatment with ammonium formate in situ should lead to 5-benzyl-4-pyrimidinamine while similar reaction of **6** should afford 5-benzyl-4(3*H*)-pyrimidinone. Therefore, the reaction of N-formamide **5a** and **6a** with ammonium formate were performed. The N-formamide **5a** failed to react with ammonium formate even after prolonged reaction time at elevated temperature. In comparison the N-formamide **6a** reacted with ammonium formate to yield the desired 5-benzyl-4(3*H*)-pyrimidinone **7a** in 54% yields. At this point, it occurred to us that the formamide formation and the subsequent cyclization with ammonium formate could be accomplished in one-pot. Consequently compound **4a** was treated with formamide for 1 h followed by addition of ammonium formate in the same flask. The work-up and isolation of the product furnished the desired pyrimidinone **7a** in 59% yield. Thus the yield of the final product was found to be better in the one-pot process as compared to two individual steps. With the objective to evaluate the generality of the methodology, several allyl amines **4b-j** were subjected to similar protocol to afford the 5-benzyl-4(3*H*)-pyrimidinones **7b-j** as shown in scheme 1.

In our efforts to overcome the shortcoming of our strategy wherein we failed to generate the 5-benzyl-4-pyrimidinamine directly from the primary allyl amines, we decided to employ an alternative route adopting robust strategies. Hence the pyrimidinones **7a-j** were transformed to corresponding 5-benzyl-4-chloro-pyrimidines

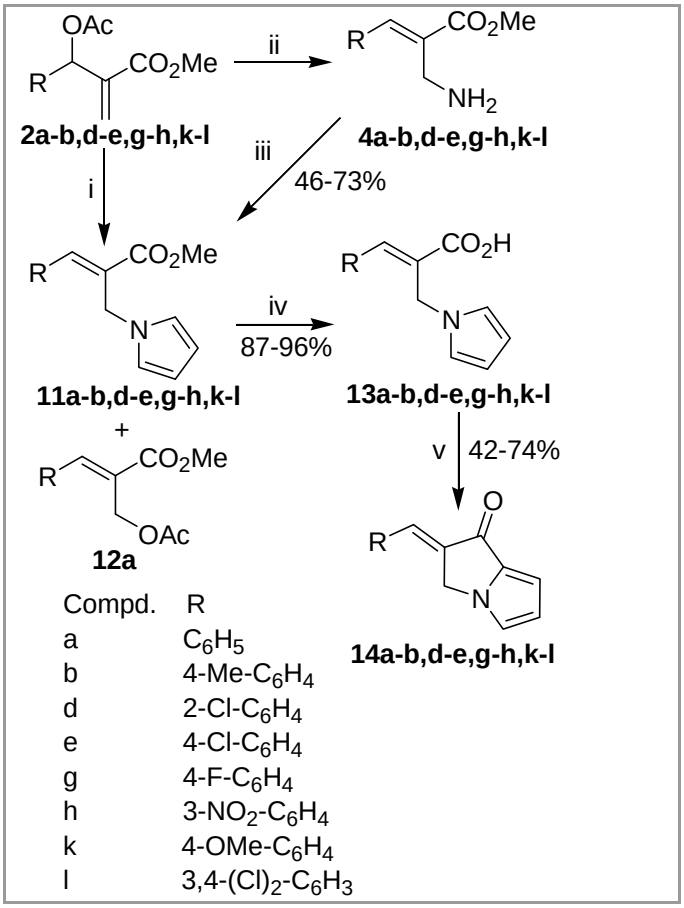


Scheme 1 *Reagents and conditions*. (i) AcCl, Pyridine, CH_2Cl_2, rt, 3 h. (ii) Methanolic-NH_3, rt, 30 min-1 h. (iii) Formamide, 110-120 ^oC, 1.0 h. iv) NH_4CO_2H, 140 ^oC, 3.0 h. v) $POCl_3$, 110 ^oC, 2.5 h. vi) $BnNH_2$, iPrOH, reflux, 3 h. vii) In, NH_4Cl, MeOH, reflux, 6 h.

8a-j via reaction with phosphorous oxychloride. This reaction takes place readily and the yields are usually excellent. Treatment of chloro-derivatives **8d-g** with benzyl amine furnished the desired 4-pyrimidinames **9d-g** in good yields. Although we have demonstrated the usefulness of the strategy by carrying out reactions with benzyl amine only, we believe the reaction should be successful with other amines too. Prompted by the facile reaction between the 4-chloro-pyrimidine and amine, we decided to investigate the synthesis of pyrimido quinoline from **8c**. In principle, reduction of the nitro group in **8c** to amino group should trigger an intra-molecular cyclization with the 4-chloro substitution of the pyrimidine ring to furnish the envisaged product. Gratifyingly the In-NH_4Cl-promoted reduction of nitro-group in compound **8c** initiated the intramolecular cyclization to furnish **10** in 55% yields. Similar reaction was successful with Fe-AcOH also albeit the product was isolated in 49% yields.

For the synthesis of pyrrolizin-1-ones, initially it was envisaged that they could be readily generated from the Baylis-Hillman acetates via S_N2' nucleophilic reaction of pyrrole on the Baylis-Hillman acetate followed by intramolecular cyclization. To investigate the feasibility of our approach in a representative reaction, compound **2a** was treated with pyrrole in the presence of K_2CO_3 or

DBU. However under both conditions 1,3-migration of the acetyl unit to yield **12a** occurred. Thereafter **2a** was reacted with sodium salt of pyrrole prepared via treatment of pyrrole with NaH. This reaction furnished the desired pyrrole derivative **11a** in 20% yield along with **12a** as the major product.



Scheme 2 *Reagents and conditions*. (i) NaH, pyrrole, rt, 5 min. (ii) Methanolic-NH_3, rt, 1 h. (iii) 2,5-Dimethoxyfuran, AcOH-water60 ^oC, 2.0 h. iv) NaOH, rt, 3.0 h. v) PPA, 100-110 ^oC, 2.0 h.

Inspired by the work of Michael et al. we decided to investigate an alternative route via primary allyl amines afforded from the Baylis-Hillman acetates of acrylate to achieve our goal. Treatment of **4a** with dimethoxyfuran in the presence of acetic acid yielded the substituted pyrrole derivative **11a** in 56% yield (scheme 2). Saponification with aqueous sodium hydroxide afforded the acid **13a**, which in the presence of PPA at 110 ^oC underwent the intramolecular cyclization to furnish the desired pyrrolizinone **14a** in 50% yield (Scheme 2). The generality of the reaction sequence was evaluated by preparing different pyrrolizinones **14b,d-e,g-h,k-l**.

In summary, we have demonstrated highly practical and general methods for the syntheses of 5-benzyl-4(3*H*)-pyrimidinones and 2-benzylidene-2,3-dihydro-pyrrolizin-1-ones from the primary allyl amines afforded by Baylis-Hillman chemistry using some robust reactions. The 4(3*H*)-pyrimidinones have been shown to be viable precursors for the synthesis of 5-benzyl-4(3*H*)-pyrimidinames and 3,4-dihydro-pyrimido(4,3-b)quinolines.

General

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometers, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The ESMS were recorded on MICROMASS LCMS system. Elemental analyses were performed on Carlo Erba's 108 or Elementar's Vario EL *III* microanalyzer. The solvent system described in each data corresponds to the one used for column chromatography. The data for the for the known N-formamide derivatives is not provided. The melting points of the pyrrolizinone derivatives (**14a-b,d-e,k-l**) synthesized herein were similar to the ones reported in ref. 19b.

General Procedure for N-formylation of amines with formamide as exemplified for 5a. A mixture of **3a** (2.0 mmol, 0.32 g) and formamide (6.3 mmol, 0.25 mL) was heated at a temperature between 110-120 ^oC for 1.5 h. The reaction mixture was cooled and partitioned between EtOAc (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated on rotavapor. The residue was purified via silica-gel column chromatography with hexane: EtOAc (1:2, v/v) as eluant to yield **5a**. The product **5a** was recrystallized with EtOAc-hexane mixture to yield 0.316 g (84%) analytically pure **5a** as a white solid.

(*Z*)-2-Cyano-3-phenylprop-2-enylformamide (5a)

Hexane: EtOAc, 1:2 (v/v); a white solid, mp 70-72 ^oC

ν_{max} (KBr) 1657 (NHCHO), 2219 (CN), 3309 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 4.13 (d, 2H, *J*= 6.8 Hz, CH_2), 4.19 (d, 2H, *J*= 6.2 Hz, CH_2), 6.52 (brs, 1H, NH), 6.68 (brs, 1H, NH), 7.11 (s, 1H, =CH), 7.18 (s, 1H, =CH), 7.36-7.45 (m, 6H, 2 x 3ArH), 7.70-7.75 (m, 4H, 2 x 2ArH), 8.17 (d, 1H, *J*= 11.7 Hz, CHO), 8.29 (s, 1H, CHO)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 41.9, 45.7, 107.1, 108.0, 117.8, 128.8, 128.9, 129.0, 130.7, 131.0, 132.7, 144.8, 145.7, 161.5, 164.6

Mass (ES+) *m/z*= 209.0 (M^++23)

Anal. Calcd. for $C_{11}H_{10}N_2O$ (Exact Mass: 186.0793); C, 70.95; H, 5.41; N, 15.04; Found C, 70.79; H, 5.64; N, 15.21

(*Z*)-3-(2-chlorophenyl)-2-cyanoprop-2-enylformamide (5d)

Hexane: EtOAc, 1:2 (v/v); 90% as a white solid, mp 96-98 °C

ν_{max} (KBr) 1674 (NHCHO), 2214 (CN), 3266 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 4.21 (d, 2H, *J*= 6.9 Hz, CH_2), 4.28 (d, 2H, *J*= 6.3 Hz, CH_2), 6.17 (brs, 1H, NH), 7.31-7.54 (m, 8H, 2 x 3ArH and 2 x =CH), 7.92-7.97 (m, 2H, 2 x ArH), 8.21 (d, 1H, *J*= 11.7 Hz, CHO), 8.34 (s, 1H, CHO)

^1H NMR ($CDCl_3$+D_2O, 200 MHz) δ= 4.20 (s, 2H, CH_2), 4.27 (s, 2H, CH_2), 7.33-7.54 (m, 8H, 2 x 3ArH and 2 x =CH), 7.92-7.96 (m, 2H, 2 x ArH), 8.20 (s, 1H, CHO), 8.33 (s, 1H, CHO)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 41.5, 45.4, 110.7, 116.9, 127.1, 129.1, 129.8, 131.2, 131.5, 131.8, 134.2, 141.4, 141.9, 161.4, 164.5

Mass (ES+) *m/z*= 243.0 (M^++23)

Anal. Calcd. for $C_{11}H_9ClN_2O$ (Exact Mass: 220.0403); C, 59.88; H, 4.11; N, 12.70; Found C, 60.11; H, 4.26; N, 12.63

Methyl (*E*)-2-[(formylamino)methyl]-3-phenylprop-2-enoate (6a)

Hexane: EtOAc, 2:3 (v/v); 69% as a white solid, mp 64-65 °C

ν_{max} (KBr) 1648 (NHCHO), 1717 (CO_2Me), 3248 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 3.85 (s, 6H, 2 x CH_3), 4.22 (d, 2H, *J*= 6.3 Hz, CH_2), 4.39 (d, 2H, *J*= 5.7 Hz, CH_2), 6.32 (brs, 1H, NH), 7.40-7.52 (m, 10H, 2 x 5ArH), 7.83 (s, 1H, =CH), 7.87 (s, 1H, =CH), 8.05 (d, 1H, *J*= 12.0 Hz, CHO), 8.18 (s, 1H, CHO)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 35.7, 38.8, 52.7, 127.7, 129.2, 129.8, 130.0, 134.4, 143.3, 161.1, 165.0, 168.6

Mass (ES+) *m/z*= 220.0 (M^++1)

Anal. Calcd. for $C_{12}H_{13}NO_3$ (Exact Mass: 219.0895); C, 65.74; H, 5.98; N, 6.39; Found C, 65.59; H, 5.76; N, 6.65

General procedure for one-pot synthesis of 5-benzyl-4-pyrimidinones 7a-j as exemplified for 7a. A mixture of **4a** (8.0 mmol, 1.53 g) and formamide (24.0 mmol, 0.96 mL) was heated at 110 °C for 1 h followed by addition of ammonium acetate (40.0 mmol, 2.52 g). This mixture was further heated at 140 °C for 3 h. Thereafter the reaction mixture was cooled and neutralized with saturated bicarbonate solution. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (40 mL), dried (Na_2SO_4) and evaporated on rotavapor to yield the crude product which was purified via silica-gel chromatography. Elution with hexane-EtOAc (3:2, v/v) gave 0.88 g (59%) of pure **7a** as a white solid.

5-Benzylpyrimidin-4(3*H*)-one (7a)

Hexane: EtOAc, 3:2 (v/v); 59% as a white solid, mp 125-128 °C

ν_{max} (KBr) 1674 (NHCO), 3430 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ= 3.81 (s, 2H, CH_2), 7.20-7.34 (m, 5H, ArH), 7.79 (s, 1H, =CH), 8.03 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 33.3, 126.6, 128.6, 128.4, 128.9, 138.0, 147.1, 152.7, 168.7

Mass (ES+) *m/z* =187.2 (M^++1)

Anal. Calcd. for $C_{11}H_{10}N_2O$ (Exact Mass: 186.0793); C, 70.95; H, 5.41; N, 15.04; Found C, 71.16; H, 5.73; N, 15.12

5-(4-Methylbenzyl)pyrimidin-4(3*H*)-one (7b)

Hexane: EtOAc, 3:2 (v/v); 57% as a white solid, mp 149-152 °C

ν_{max} (KBr) 1676 (NHCO), 3446 (NH), cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 2.33 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 7.11-7.17 (m, 4H, ArH), 7.78 (s, 1H, =CH), 8.04 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 21.4, 33.3, 129.2, 129.5, 129.7, 135.3, 136.6, 147.6, 152.9, 164.0, 164.3

Mass (ES+) m/z= 201.2 (M^++1)

Anal. Calcd. for $C_{12}H_{12}N_2O$ (Exact Mass: 200.0950); C, 71.98; H, 6.04; N, 13.99; Found C, 72.31; H, 6.13; N, 14.06

5-(2-Nitrobenzyl)pyrimidin-4(3*H*)-one (7c)

Hexane: EtOAc, 3:2 (v/v); 48% as a white solid, mp 176-178 °C

ν_{max} (KBr) 1655 (NHCO), 3425 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 4.14 (s, 2H, CH_2), 7.39-7.46 (m, 2H, ArH), 7.53-7.57 (m, 1H, ArH), 7.75 (s, 1H, =CH), 7.96-8.01 (m, 1H, ArH), 8.08 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ= 29.5, 123.8, 125.8, 126.9, 131.6, 132.2, 132.3, 147.3, 148.3, 150.8, 160.8, 162.7

Mass (ES+) m/z= 232.2 (M^++1)

Anal. Calcd. for $C_{11}H_9N_3O_3$ (Exact Mass: 231.0644); C, 57.14; H, 3.92; N, 18.17; Found C, 57.31; H, 4.16; N, 18.38

5-(2-Chlorobenzyl)pyrimidin-4(3*H*)-one (7d)

Hexane: EtOAc, 3:2 (v/v); 59% as a white solid, mp 164-165 °C

ν_{max} (KBr) 1651 (NHCO), 3445 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ= 3.94 (s, 2H, CH_2), 7.20-7.25 (m, 2H, ArH), 7.30-7.33 (m, 1H, ArH), 7.38-7.41 (m, 1H, ArH), 7.73 (s, 1H, =CH), 8.10 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 31.0, 126.9, 128.3, 129.7, 131.2, 134.3, 135.3, 147.1, 153.0, 163.9

Mass (ES+) m/z= 221.2 (M^++1)

Anal. Calcd. for $C_{11}H_9ClN_2O$ (Exact Mass: 220.0403); C, 59.88; H, 4.11; N, 12.70; Found C, 59.76; H, 4.02; N, 12.95

5-(4-Chlorobenzyl)pyrimidin-4(3*H*)-one (7e)

Hexane: EtOAc, 3:2 (v/v); 67% as a white solid, mp 94-96 °C

ν_{max} (KBr) 1687 (NHCO), 3429 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.76 (s, 2H, CH_2), 7.19 (d, 2H, *J*= 8.4 Hz, ArH), 7.23-7.28 (m, 2H, ArH), 7.79 (s, 1H, =CH), 8.06 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 32.8, 128.4, 128.7, 130.2, 132.4, 136.6, 147.4, 152.5, 163.3, 163.6

Mass (ES+) *m/z*= 221.2 (M^++1

Anal. Calcd. for $C_{11}H_9ClN_2O$ (Exact Mass: 220.0403); C, 59.88; H, 4.11**;** N, 12.70; Found C, 59.56; H, 3.86; N, 12.83

5-(2-Fluorobenzyl)pyrimidin-4(3*H*)-one (7f)

Hexane: EtOAc, 3:2 (v/v); 53% as a white solid, mp 86-88 ^oC

ν_{max} (KBr) 1653 (NHCO), 3424 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.86 (s, 2H, CH_2), 7.04-7.13 (m, 2H, ArH), 7.22-7.33 (m, 2H, ArH), 7.81 (s, 1H, =CH), 8.08 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 27.0, 115.7, 116.1, 124.5, 124.6, 125.1, 125.4, 127.8, 129.0, 129.1, 131.6, 131.7, 147.7, 153.1, 159.1, 164.0, 164.3

Mass (ES+) m/z= 205.2 (M^++1)

Anal. Calcd. for $C_{11}H_9FN_2O$ (Exact Mass: 204.0699); C, 64.70; H, 4.44; N, 13.72; Found C, 64.73; H, 4.25; N, 13.53

5-(4-Fluorobenzyl)pyrimidin-4(3*H*)-one (7g)

Hexane: EtOAc, 3:2 (v/v); 58% as a white solid, mp 110-113 ^oC

ν_{max} (KBr) 1689 (NHCO), 3417 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.77 (s, 2H, CH_2), 6.96-7.02 (m, 2H, ArH), 7.20-7.25 (m, 2H, ArH), 7.78 (s, 1H, =CH), 8.06 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 32.6, 115.2, 115.5, 128.7, 130.3, 130.4, 133.7, 147.2, 152.5, 160.0, 163.5

Mass (ES+) m/z= 205.2 (M^++1)

Anal. Calcd. for $C_{11}H_9FN_2O$ (Exact Mass: 204.0699); C, 64.70; H, 4.44; N, 13.72; Found C, 64.92; H, 4.21; N, 13.59

5-(3-Nitrobenzyl)pyrimidin-4(3*H*)-one (7h)

Hexane: EtOAc, 1:1 (v/v); 66% as a white solid, mp 175-178 ^oC

ν_{max} (KBr) 1663 (NHCO), 3461 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.91 (s, 2H, CH_2), 7.45-7.51 (m, 1H, ArH), 7.62 (d, 1H, *J*= 7.5 Hz, ArH), 7.93 (s, 1H, =CH), 8.09-8.11 (m, 2H, ArH), 8.17 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ= 32.8, 121.0, 123.0, 126.9, 128.8, 134.7, 140.4, 147.8, 151.4, 161.5

Mass (ES+) m/z= 232.2 (M^++1)

Anal. Calcd. for $C_{11}H_9N_3O_3$ (Exact Mass: 231.0644); C, 57.14; H, 3.92; N, 18.17; Found C, 57.05; H, 4.21; N, 18.35

5-(3,4-Dimethoxybenzyl)pyrimidin-4(3*H*)-one (7i)

Hexane: EtOAc, 3:2 (v/v); 49% as a white solid, mp 141-148 ^oC

ν_{max} (KBr) 1657 (NHCO), 3431 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.77 (s, 2H, CH_2), 3.86 (s, 6H, 2 x OCH_3), 6.78-6.84 (m, 3H, ArH), 7.80 (s, 1H, =CH), 8.09 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 32.8, 55.8, 111.2, 112.1, 120.9, 129.0, 130.3, 147.0, 147.7, 148.9, 152.6, 163.8

Mass (ES+) m/z= 247.0 (M^++1)

Anal. Calcd. for $C_{13}H_{14}N_2O_3$ (Exact Mass: 246.1004); C, 63.40; H, 5.73; N, 11.38; Found C, 63.28; H, 5.97; N, 11.46

5-(2-Thienylmethyl)pyrimidin-4(3*H*)-one (7j)

Hexane: EtOAc, 3:2 (v/v); 53% as a white solid, mp 122-124 ^oC

ν_{max} (KBr) 1662 (NHCO), 3449 (NH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 4.02 (s, 2H, CH_2), 6.90-6.96 (m, 2H, ArH), 7.16-7.18 (s, 1H, ArH), 7.90 (s, 1H, =CH), 8.09 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 27.4, 124.3, 125.9, 127.0, 128.1, 140.2, 147.4, 152.8, 163.5

Mass (ES+) m/z= 193.2 (M^++1)

Anal. Calcd. for $C_9H_8N_2OS$ (Exact Mass: 192.0357); C, 56.23; H, 4.19; N, 14.57; Found C, 56.39; H, 4.06; N, 14.85

General procedure for the synthesis of 5-benzyl-4-chloro-pyrimidines 8a-j as exemplified for 8a. A mixture of **7a** (4.0 mmol, 0.74 g) and $POCl_3$ (18.0 mmol, 1.7 mL) was refluxed at 110 ^oC for 2.5 h. After completion of the reaction as monitored by TLC, the reaction mixture was poured onto crushed ice and neutralized with solid $NaHCO_3$. This mixture was then extracted with EtOAc (3 x 25 mL). The combined organic layer was processed as usual and the residue so obtained was column chromatographed over silica gel using hexane-EtOAc (11:1, v/v) to yield 0.64 g (79%) of pure **8a** as yellow oil.

5-Benzyl-4-chloropyrimidine (8a)

Hexane: EtOAc, 11:1 (v/v); 79% as yellow oil

^1H NMR ($CDCl_3$, 300 MHz) δ= 4.01 (s, 2H, CH_2), 7.18-7.21 (m, 2H, ArH), 7.27-7.37 (m, 3H, ArH), 8.44 (s, 1H, ArH), 8.87 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 36.2, 127.1, 128.9, 129.0, 133.4, 136.6, 156.9, 158.4, 161.0

Mass (ES+) *m/z*= 205.3 (M^++1)

Anal. Calcd. for $C_{11}H_9ClN_2$ (Exact Mass: 204.0454); C, 64.56; H, 4.43; N, 13.69; Found C, 64.83; H, 4.42; N, 13.72

4-Chloro-5-(4-methylbenzyl)pyrimidine (8b)

Hexane: EtOAc, 10:1 (v/v); 70% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 2.33 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 7.08 (d, 2H, *J*= 8.1 Hz, ArH), 7.14 (d, 2H, *J*= 8.1 Hz, ArH), 8.43 (s, 1H, ArH), 8.85 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 21.0, 35.8, 128.7, 129.6, 133.5, 133.6, 136.8, 156.8, 158.3, 161.0

Mass (ES+) m/z= 219.2 (M^++1)

Anal. Calcd. for $C_{12}H_{11}ClN_2$ (Exact Mass: 218.0611); C, 65.91; H, 5.07; N, 12.81; Found C, 66.19; H, 5.21; N, 12.57

4-Chloro-5-(4-nitrobenzyl)pyrimidine (8c)

Hexane: EtOAc, 4:1 (v/v); 72% as a white solid, mp 96-98 ^oC

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.41 (s, 2H, CH_2), 7.25-7.28 (m, 1H, ArH), 7.48-7.54 (m, 1H, ArH), 7.59-7.65 (m, 1H, ArH), 8.08-8.11 (dd, 1H, J_1= 1.4 Hz, J_2= 8.1 Hz, ArH), 8.28 (s, 1H, ArH), 8.90 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 33.7, 125.4, 128.7, 131.5, 131.6, 132.2, 133.7, 149.1, 157.1, 157.8, 161.0

Mass (ES+) m/z= 250.2 (M^++1)

Anal. Calcd. for $C_{11}H_8ClN_3O_2$ (Exact Mass: 249.0305); C, 52.92; H, 3.23; N, 16.83; Found C, 53.15; H, 3.46; N, 16.76

4-Chloro-5-(2-chlorobenzyl)pyrimidine (8d)

Hexane: EtOAc, 11:1 (v/v); 78% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.19 (s, 2H, CH_2), 7.16-7.19 (m, 1H, ArH), 7.25-7.28 (m, 2H, ArH), 7.42-7.45 (m, 1H, ArH), 8.31 (s, 1H, ArH), 8.88(s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 34.0, 127.3, 128.9, 130.0, 131.0, 131.8, 134.2, 134.4, 156.9, 158.1, 161.0

Mass (ES+) m/z= 239.2 (M^++1)

Anal. Calcd. for $C_{11}H_8Cl_2N_2$ (Exact Mass: 238.0065); C, 55.26; H, 3.37; N, 11.72; Found C, 55.01; H, 3.62; N, 11.98

4-Chloro-5-(4-chlorobenzyl)pyrimidine (8e)

Hexane: EtOAc, 11:1 (v/v); 65% as brown oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.05 (s, 2H, CH_2), 7.12-7.15 (m, 2H, ArH), 7.29-7.33 (m, 2H, ArH), 8.45 (s, 1H, ArH), 8.89 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 35.5, 129.1, 130.1, 132.8, 133.1, 135.1, 157.1, 158.2, 161.0

Mass (ES+) m/z= 239.5 (M^++1)

Anal. Calcd. for $C_{11}H_8Cl_2N_2$ (Exact Mass: 238.0065); C, 55.26; H, 3.37; N, 11.72; Found C, 55.53; H, 3.48; N, 11.91

4-Chloro-5-(2-fluorobenzyl)pyrimidine (8f)

Hexane: EtOAc, 11:1 (v/v); 70% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.11 (s, 2H, CH_2), 7.06-7.14 (m, 2H, ArH), 7.18-7.23 (m, 1H, ArH), 7.25-7.32 (m, 1H, ArH), 8.49 (s, 1H, ArH), 8.88 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 29.7, 29.8, 115.6, 115.8, 123.5, 123.7, 124.4, 124.5, 129.2, 129.3, 131.0, 131.1, 156.9, 158.2, 159.4, 160.9, 162.7

Mass (ES+) m/z= 223.3 (M^++1)

Anal. Calcd. for $C_{11}H_8ClFN_2$ (Exact Mass: 222.0360); C, 59.34; H, 3.62; N, 12.58; Found C, 59.06; H, 3.85; N, 12.64

4-Chloro-5-(4-fluorobenzyl)pyrimidine (8g)

Hexane: EtOAc, 11:1 (v/v); 67% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.05 (s, 2H, CH_2), 7.00-7.06 (m, 2H, ArH), 7.14-7.19 (m, 2H, ArH), 8.44 (s, 1H, ArH), 8.88 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 35.4, 115.7, 116.0, 130.3, 130.4, 132.2, 132.3, 133.2, 157.0, 158.2, 160.2, 161.0, 163.5

Mass (ES+) m/z= 223.2 (M^++1)

Anal calcd (Exact Mass: 222.0360) for $C_{11}H_8ClFN_2$; C, 59.34; H, 3.62; N, 12.58; Found C, 59.46; H, 3.81; N, 12.32

4-Chloro-5-(3-nitrobenzyl)pyrimidine (8h)

Hexane: EtOAc, 4:1 (v/v); 74% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.21 (s, 2H, CH_2), 7.53-7.55 (m, 2H, ArH), 8.09 (s, 1H, ArH), 8.16-8.17 (m, 1H, ArH), 8.55 (s, 1H, ArH), 8.93 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 35.8, 122.3, 123.7, 129.9, 131.8, 134.8, 138.7, 148.6, 157.5, 158.3, 161.2

Mass (ES+) m/z= 250.2 (M^++1)

Anal. Calcd. for $C_{11}H_8ClN_3O_2$ (Exact Mass: 249.0305); C, 52.92; H, 3.23; N, 16.83; Found C, 52.61; H, 3.41; N, 16.79

4-Chloro-5-(3,4-dimethoxybenzyl)pyrimidine (8i)

Hexane:EtOAc::11:1 (v/v); 77% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2), 6.72-6.74 (m, 2H, ArH), 6.84 (d, 1H, *J*= 8.7 Hz, ArH), 8.42 (s, 1H, ArH), 8.87 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 35.8, 55.9, 111.6, 112.1, 121.1, 129.0, 133.6, 148.2, 149.3, 156.8, 158.2, 160.9

Mass (ES+) *m/z*= 265.2 (M^++1)

Anal calcd (Exact Mass: 264.0666) for $C_{13}H_{13}ClN_2O_2$; C, 58.99; H, 4.95; N, 10.58; Found C, 58.73; H, 4.89, N, 10.69

4-Chloro-5-(2-thienylmethyl)pyrimidine (8j)

Hexane: EtOAc, 9:1 (v/v); 69% as yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.27 (s, 2H, CH_2), 6.87-6.88 (m, 1H, ArH), 6.96-6.98 (s, 1H, ArH), 7.21-7.23 (m, 1H, ArH), 8.52 (s, 1H, ArH), 8.89 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 30.4, 125.0, 126.5, 127.2, 132.7, 138.6, 157.1, 158.1, 160.6

Mass (ES+) m/z= 211.2 (M^++1)

Anal. Calcd. for $C_9H_7ClN_2S$ (Exact Mass: 210.0018); C, 51.31; H, 3.35; N, 13.30; Found C, 51.65; H, 3.16; N, 13.49

General procedure for the synthesis of 5-benzyl-4-pyridinamines 9d-g as exemplified for 9g. To a solution of **8g** (1.5 mmol, 0.33g) in isopropanol (5.0 mL) was added benzyl amine (3.0 mmol, 0.33 mL) and the mixture was refluxed for 3 h. Thereafter, the excess solvent was removed and diluted with water (25 mL). The mixture was then extracted with EtOAc (2 x 20 mL). The combined organic layer was processed as usual to furnish a residue which was purified via silica gel column chromatography. Elution with hexane-EtOAc (7:3, v/v) gave 0.375 g (86%) of pure **9g** as brown oil.

***N*-Benzyl-5-(2-chlorobenzyl)pyrimidin-4-amine (9d)**

Hexane: EtOAc, 7:3 (v/v); 81% as a white solid, mp 90-93 ^{o}C

ν_{max} (KBr) 3446 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 3.84 (s, 2H, CH_2), 4.65 (d, 2H, *J*= 5.4 Hz, CH_2), 5.00 (brs, 1H, NH), 7.03-7.06 (m, 1H, ArH), 7.12-7.14 (m, 1H, ArH), 7.15-7.31 (m, 7H, ArH), 7.96 (s, 1H, ArH), 8.57 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 31.7, 44.7, 115.0, 127.3, 127.4, 128.6, 129.8, 130.0, 134.0, 138.3, 154.3, 157.4, 160.0

Mass (ES+) m/z= 310.3 (M^++1)

Anal. Calcd. for $C_{18}H_{16}ClN_3$ (Exact Mass: 309.1033); C, 69.79; H, 5.21; N, 13.56; Found C, 69.95; H, 5.53; N, 13.68

***N*-Benzyl-5-(4-chlorobenzyl)pyrimidin-4-amine (9e)**

Hexane: EtOAc, 7:3 (v/v); 92% as brown oil

ν_{max} (Neat) 3434 (NH)cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.74 (s, 2H, CH_2), 4.60 (d, 2H, *J*= 5.3 Hz, CH_2), 4.82 (brs, 1H, NH), 6.99-7.08 (m, 4H, ArH), 7.24-7.35 (m, 5H, ArH), 8.02 (s, 1H, ArH), 8.58 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 34.6, 45.1, 115.9, 127.7, 127.9, 128.4, 128.7, 129.1, 129.6, 130.1, 133.5, 135.7, 138.7, 154.7, 158.0, 160.5

Mass (ES+) m/z= 310.3 (M^++1, 100)

Anal. Calcd. for $C_{18}H_{16}ClN_3$ (Exact Mass: 309.1033); C, 69.79; H, 5.21; N, 13.56; Found C, 69.42; H, 5.42; N, 13.66

***N*-Benzyl-5-(2-fluorobenzyl)pyrimidin-4-amine (9f)**

Hexane: EtOAc, 7:3 (v/v); 87% as brown oil

ν_{max} (Neat) 3449 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 3.75 (s, 2H, CH_2), 4.66 (d, 2H, *J*= 5.4 Hz, CH_2), 5.11 (brs, 1H, NH), 7.01-7.08 (m, 3H, ArH), 7.13-7.16 (m, 2H, ArH), 7.23-7.30 (m, 4H, ArH), 8.02 (s, 1H, ArH), 8.55 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 27.1, 27.2, 44.7, 115.0, 115.4, 115.7, 123.5, 123.7, 124.5, 124.6, 127.3, 128.6, 128.8, 128.9, 130.2, 130.3, 138.3, 154.0, 157.3, 159.1, 159.9, 162.3

Mass (ES+) m/z= 294.3 (M^++1)

Anal. Calcd. for $C_{18}H_{16}FN_3$ (Exact Mass: 293.1328); C, 73.70; H, 5.50; N, 14.32; Found C, 73.81; H, 5.69; N, 14.09

***N*-Benzyl-5-(4-fluorobenzyl)pyrimidin-4-amine (9g)**

Hexane:EtOAc, 7:3 (v/v); as brown oil

ν_{max} (Neat) 3443 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 3.74 (s, 2H, CH_2), 4.60 (d, 2H, *J*= 5.4 Hz, CH_2), 4.76 (brs, 1H, NH), 6.95-7.12 (m, 6H, ArH), 7.24-7.31 (m, 3H, ArH), 8.02 (s, 1H, ArH), 8.58 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 34.0, 44.7, 115.7, 116.0, 127.2, 127.4, 128.6, 129.7, 129.8, 132.4, 138.3, 154.1, 157.5, 160.1

Mass (ES+) *m/z*= 294.3 (M^++1)

Anal. Calcd. for $C_{18}H_{16}FN_3$ (Exact Mass: 293.1328); C, 73.70; H, 5.50; N, 14.32; Found C, 73.56; H, 5.28; N, 14.64

Typical procedure for the synthesis of 10. To a solution of **8c** (1.0 mmol, 0.25 g) in MeOH (4.0 mL) was added a saturated aqueous solution of NH_4Cl (2.0 ml) followed by In powder (2.5 mmol, 0.285 g). The mixture was heated at reflux temperature under nitrogen for 6 h. The reaction was cooled and filtered through a celite-bed with water and washed with EtOAc (2 x 10 mL). The pH of the filtrate was adjusted to 9.0 with aqueous NaOH (4 N) and then it was extracted with EtOAc (2 x 25 mL). The combined organic layer was processed and the residue left after concentration was purified via column chromatography over silica gel using hexane-EtOAc (3:1, v/v) to yield pure **10** as yellow solid (0.1 g, 55%).

5,10-Dihydropyrimido[4,5-*b*]quinoline (10)

mp 185-187 ^{o}C

ν_{max} (KBr) 3247 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.49 (s, 2H, CH_2), 7.28-7.34 (m, 2H, ArH), 7.47-7.52 (m, 2H, ArH), 8.52 (s, 1H, ArH), 8.87 (s, 1H, ArH), 9.35 (s, 1H, NH)

^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ= 26.7, 111.1, 114.5, 118.2, 121.4, 126.6, 127.7, 136.9, 152.9, 155.8, 156.8

Mass (ES+) *m/z*= 184.4 (M^++1)

Anal. Calcd for $C_{11}H_9FN_3$ (Exact Mass: 183.0796); C, 72.11; H, 4.95; N, 22.94; Found C, 71.89; H, 4.76;N 23.12

General procedure for the synthesis of methyl (*E*)-3-(substituted phenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate 11a-b,d-e,g-h,k-l as exemplified for 11g. To a solution of **4g** (10.0 mmol, 2.1 g) in dichloroethane (25 mL), 2,5-dimethoxy tetrahydrofuran (12.4 mmol, 1.6 mL), glacial acetic acid (4.0 mL) and water (5.0 mL) were added simultaneously. The reaction mixture was heated at 60 ^{o}C for 2 h. Thereafter, water was added to the reaction mixture and the two layers were partitioned and separated. The aqueous layer was extracted with $CHCl_3$ (3 x 20 mL), the organic layers were combined

and dried over Na_2SO_4. Removal of solvent in vacuum followed by column chromatography over silica-gel using hexane-EtOAc as eluent furnished the pure **11g** as yellow oil (1.3 g, 48%).

Methyl (*E*)-3-phenyl-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11a)

Hexane: EtOAc, 19:1 (v/v); 56% as yellow oil

ν_{max} (Neat) 1717 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.80 (s, 3H, CO_2Me), 4.94 (s, 2H, CH_2), 6.13 (t, 2H, *J*= 2.1 Hz, ArH), 6.65 (t, 2H, *J*= 2.1 Hz, ArH), 7.34-7.42 (m, 5H, ArH), 8.00 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.6, 52.8, 108.6, 120.8, 128.5, 128.9, 129. 3, 129.5, 129.8, 134.8, 144.3, 167.9

mass (ES+) *m/z*= 242.0 (M^++1)

Anal. Calcd. for $C_{15}H_{15}NO_2$ (Exact Mass: 241.1103); C, 74.67; H, 6.27; N, 5.81; Found C, 74.82; H, 6.46; N, 5.72

Methyl (*E*)-3-(4-methylphenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11b)

Hexane: EtOAc, 24:1 (v/v), 54% as yellow oil

ν_{max} (Neat) 1715 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 2.38 (s, 3H, CH_3), 3.79 (s, 3H, CO_2Me), 4.95 (s, 2H, CH_2), 6.13 (t, 2H, *J*= 2.1 Hz, ArH), 6.66 (t, 2H, *J*= 2.0 Hz, ArH), 7.22-7.28 (m, 4H, ArH), 7.97 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 22.0, 45.9, 52.9, 108.9, 120.9, 127.7, 129.9, 130.2, 132.1, 140.4, 144.7, 168.3

mass (ES+) *m/z*= 256.1 (M^++1)

Anal. Calcd. for $C_{16}H_{17}NO_2$ (Exact Mass: 255.1259); C, 75.27; H, 6.71; N, 5.49; Found C, 75.23; H, 6.97; N, 5.32

Methyl (*E*)-3-(2-chlorophenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11d)

Hexane: EtOAc, 29:1 (v/v), 58% as yellow oil

ν_{max} (Neat) 1720 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.84 (s, 3H, CO_2Me), 4.83 (s, 2H, CH_2), 6.13 (t, 2H, *J*= 2.1 Hz, ArH), 6.62 (t, 2H, *J*= 2.0 Hz, ArH), 7.23-7.39 (m, 3H, ArH), 7.48-7.51 (dd, 1H, J_1= 1.5 Hz, J_2= 7.9 Hz, ArH), 8.02 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.7, 52.9, 108.7, 120.9, 127.3, 130.3, 130.4, 130.8, 133.6, 134.3, 141.1, 167.3

mass (ES+) *m/z*= 276.0 (M^++1)

Anal. Calcd. for $C_{15}H_{14}ClNO_2$ (Exact Mass: 275.0713); C, 65.34; H, 5.12; N, 5.08; Found C, 65.23; H, 5.26; N, 4.93

Methyl (*E*)-3-(4-chlorophenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11e)

Hexane: EtOAc, 24:1 (v/v), 73% as yellow oil

ν_{max} (Neat) 1720 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 3.80 (s, 3H, CO_2CH_3), 4.90 (s, 2H, CH_2), 6.14 (t, 2H, *J*= 2.1 Hz, ArH), 6.63 (t, 2H, *J*= 2.1 Hz, ArH), 7.24-7.29 (m, 2H, ArH), 7.37-7.40 (dd, 2H, J_1= 2.1 Hz, J_2= 6.7 Hz, ArH), 7.93 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.5, 52.8, 108.8, 120.6, 128.8, 129.5, 130.3, 130.9, 131.7, 133.1, 136.0, 143.0, 167.7

mass (ES+) *m/z*= 276.1 (M^++1)

Anal. Calcd. for $C_{15}H_{14}ClNO_2$ (Exact Mass: 275.0713); C, 65.34; H, 5.12; N, 5.08; Found C, 65.21; H, 5.35; N, 5.19

Methyl (*E*)-3-(4-fluorophenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11g)

Hexane: EtOAc, 24:1 (v/v)

ν_{max} (Neat) 1718 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 3.80 (s, 3H, CO_2CH_3), 4.92 (s, 2H, CH_2), 6.14 (t, 2H, *J*= 2.0 Hz, ArH), 6.65 (t, 2H, *J*= 2.0 Hz, ArH), 7.05-7.13 (m, 2H, ArH), 7.29-7.36 (m, 2H, ArH), 7.96 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.2, 52.8, 108.8, 116.2, 116.7, 120.6, 128.3, 130.8, 131.5, 131.7, 143.3, 161.1, 166.1, 167.8

mass (ES+) *m/z*= 260.2 (M^++1)

Anal. Calcd. for $C_{15}H_{14}FNO_2$ (Exact Mass: 259.1009); C, 69.49; H, 5.44; N, 5.40; Found C, 69.62; H, 5.56; N, 5.32

Methyl (*E*)-3-(3-nitrophenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11h)

Hexane: EtOAc, 10:1 (v/v), 46% as yellow oil

ν_{max} (Neat) 1719 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 3.84 (s, 3H, CO_2Me), 4.91 (s, 2H, CH_2), 6.13 (t, 2H, *J*= 2.0 Hz, ArH), 6.61 (t, 2H, *J*= 2.1 Hz, ArH), 7.59-7.62 (m, 2H, ArH), 7.98 (s, 1H, =CH), 8.19-8.25 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.4, 53.1, 109.1, 120.7, 124.3, 129.4, 130.3, 131.4, 136.3, 137.2, 141.1, 148.9, 167.2

mass (ES+) *m/z*= 287.3 (M^++1)

Anal. Calcd. for $C_{15}H_{14}ClNO_2$ (Exact Mass: 286.0954); C, 62.93; H, 4.93; N, 9.79; Found C, 63.11; H, 5.20; N, 4.81

Methyl (*E*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11k)

Hexane: EtOAc, 19:1 (v/v), 59% as yellow oil

ν_{max} (Neat) 1710 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 4.97 (s, 2H, CH_2), 6.14 (t, 2H, *J*= 2.1 Hz, ArH), 6.69 (t, 2H, *J*= 2.1 Hz, ArH), 6.92 (d, 2H, *J*= 8.8 Hz, ArH), 7.33 (d, 2H, *J*= 8.7 Hz, ArH), 7.96 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.8, 52.7, 55.8, 106.5, 108.6, 114.8, 120.6, 125.8, 127.1, 131.7, 144.4, 161.2, 168.3

mass (ES+) *m/z*= 271.9 (M^++1)

Anal. Calcd. for $C_{16}H_{17}NO_3$ (Exact Mass: 271.1208); C, 70.83; H, 6.32; N, 5.16; Found C, 70.65; H, 6.59; N, 5.02

Methyl (*E*)-3-(3,4-dichlorophenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoate (11l)

Hexane: EtOAc, 29:1 (v/v), 60% as yellow oil

ν_{max} (Neat) 1720 (CO_2Me) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 3.81 (s, 3H, CO_2CH_3), 4.88 (s, 2H, CH_2), 6.14 (t, 2H, *J*= 2.1 Hz, ArH), 6.62 (t, 2H, *J*= 2.0 Hz, ArH), 7.13-7.16 (dd, 1H, J_1= 1.7 Hz, J_2= 8.3 Hz, ArH), 7.40 (d, 1H, *J*= 1.7 Hz, ArH), 7.47 (d, 1H, *J*= 8.3 Hz, ArH), 7.86 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 44.9, 52.5, 108.6, 120.2, 128.0, 129.8, 130.8, 130.9, 133.2, 134.2, 141.1, 166.9

mass (ES+) *m/z*= 310.0 (M^++1), 311.9 (M^++3)

Anal. Calcd. for $C_{15}H_{13}Cl_2NO_2$ (Exact Mass: 309.0323); C, 58.08; H, 4.22; N, 4.52; Found C, 58.23; H, 4.34; N, 4.39

General procedure for the synthesis of (*E*)-3-(substituted phenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid 13a-b,d-e,g-h,k-l as exemplified for 13g. To a solution of **11g** (4.2 mmol, 1.1 g) in MeOH (15 mL), 5% aq. NaOH (10 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with 10% aq. HCl followed by removal of MeOH under reduced pressure. Then residue was extracted with EtOAc (3 x 15 mL), the organic layers combined, dried and concentrated in vacuo. The crude product was purified via column chromatography on silica gel to afford 1.01g (97%) pure **13g** as a white solid.

(*E*)-3-phenyl-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoic acid (12a)

Hexane: EtOAc, 8:1 (v/v); 91% as a white solid, mp 90-92 ^oC

ν_{max} (KBr) 1672 (CO_2H), 2942 (OH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 4.95 (s, 2H, CH_2), 6.15 (t, 2H, *J*= 2.0 Hz, ArH), 6.68 (t, 2H, *J*= 2.0 Hz, ArH), 7.37-7.41 (m, 5H, ArH), 8.13 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.3, 108.8, 120.8, 127.6, 129.1, 129.4, 129.8, 130.3, 134.5, 146.7, 173.2

mass (ES+) *m/z*= 228.2 (M^++1)

Anal. Calcd. for $C_{14}H_{13}NO_2$ (Exact Mass: 227.0946); C, 73.99; H, 5.77; N, 6.16; Found C, 74.22; H, 5.92; N, 6.23

(*E*)-3-(4-methylphenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid (13b)

Hexane: EtOAc, 8:1 (v/v); 93% as a white solid, mp 184-186 ^oC

ν_{max} (KBr) 1673 (CO_2H), 3428 (OH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 2.39 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 6.15 (t, 2H, *J*= 2.1 Hz, ArH), 6.70 (t, 2H, *J*= 2.1 Hz, ArH), 7.22 (d, 1H, *J*= 8.1 Hz, ArH), 7.31 (d, 1H, *J*= 8.1 Hz, ArH), 8.10 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 23.3, 46.8, 110.2, 122.2, 128.0, 131.5, 131.6, 133.1, 142.3, 148.4, 174.8

mass (ES+) *m/z*= 242.2 (M^++1)

Anal. Calcd. for $C_{15}H_{15}NO_2$ (Exact Mass: 241.1103); C, 74.67; H, 6.27; N, 5.81; Found C, 74.49; H, 6.18; N, 5.93

(*E*)-3-(2-chlorophenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid (13d)

Hexane: EtOAc, 9:1 (v/v); 96% as a white solid, mp 153-155 ^oC

ν_{max} (KBr) 1679 (CO_2H), 2945 (OH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ= 4.81 (s, 2H, CH_2), 6.12 (t, 2H, *J*= 2.1 Hz, ArH), 6.61 (t, 2H, *J*= 2.0 Hz, ArH), 7.22-7.38 (m, 3H, ArH), 7.47-7.49 (dd, 1H, J_1= 1.3 Hz, J_2= 7.9 Hz, ArH), 8.15 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.3, 108.8, 120.9, 127.4, 130.0, 130.3, 131.1, 133.2, 134.5, 143.5, 172.4

mass (ES+) *m/z*= 262.2 (M^++1)

Anal. Calcd. for $C_{14}H_{12}ClNO_2$ (Exact Mass: 261.0557); C, 64.25; H, 4.62; N, 5.35; Found C, 64.06; H, 4.54; N, 5.51

(*E*)-3-(4-chlorophenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid (13e)

Hexane: EtOAc, 8:1 (v/v); 93% as a white solid, mp 161-162 ^oC

ν_{max} (KBr) 1687 (CO_2H), 2926 (OH) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 4.92 (s, 2H, CH_2), 6.16 (t, 2H, *J*= 2.0 Hz, ArH), 6.66 (t, 2H, *J*= 1.9 Hz, ArH), 7.30 (d, 2H, *J*= 8.6 Hz, ArH), 7.40 (d, 2H, *J*= 8.5 Hz ArH), 8.07 (s, 1H, =CH), 8.24-8.29 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.2, 109.0, 120.7, 128.0, 129.7, 131.1, 132.8, 136.5, 145.4, 172.6

mass (ES+) *m/z*= 262.1 (M^++1)

Anal. Calcd. for $C_{14}H_{12}ClNO_2$ (Exact Mass: 261.0557); C, 64.25; H, 4.62; N, 5.35; Found C, 65.38; H, 4.87; N, 5.41

(*E*)-3-(4-Fluorophenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid (13g)

Hexane: EtOAc, 8:1 (v/v); mp 158-159 ^oC

ν_{max} (KBr) 1683 (CO_2H), 2850 (OH) cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ= 4.93 (s, 2H, CH_2), 6.16 (t, 2H, *J*= 2.0 Hz, ArH), 6.68 (t, 2H, *J*= 2.0 Hz, ArH), 7.06-7.15 (m, 2H, ArH), 7.34-7.40 (m, 2H, ArH), 8.09 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.2, 109.0, 116.4, 116.8, 120.6, 127.3, 130.4, 130.5, 131.9, 132.0, 145.7, 161.4, 166.4, 173.0

mass (ES+) *m/z*= 246.1 (M^++1)

Anal. Calcd. for $C_{14}H_{12}FNO_2$ (Exact Mass: 245.0852); C, 68.56; H, 4.93; N, 5.71; Found C, 68.72; H, 5.21; N, 5.78.

(*E*)-3-(3-Nitrophenyl)-2-(1*H*-pyrrol-1-ylmethyl)prop-2-enoic acid (13h)

Hexane: EtOAc, 8:1 (v/v); 87% as a white solid, mp 157-160 ^{o}C

ν_{max} (KBr) 1687 (CO_2H), 2927 (CO_2H) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 4.93 (s, 2H, CH_2), 6.16 (t, 2H, *J*= 2.0 Hz, ArH), 6.65 (t, 2H, *J*= 2.0 Hz, ArH), 7.58-7.65 (m, 2H, ArH), 8.12 (s, 1H, =CH), 8.24-8.29 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.0, 109.3, 120.7, 124.5, 124.7, 130.5, 135.1, 135.9, 143.4, 148.9, 171.8

mass (ES+) *m/z*= 273.4 (M^++1)

Anal. Calcd. for $C_{14}H_{12}N_2O_4$ (Exact Mass: 272.0797); C, 61.76; H, 4.44; N, 10.29; Found C, 61.62; H, 4.76; N, 10.31

(*E*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid (13k)

Hexane: EtOAc, 8:1 (v/v); 92% as a white solid, mp 172-175 ^{o}C

ν_{max} (KBr) 1669 (CO_2H), 2934 (OH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 3.84 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2), 6.17 (t, 2H, *J*= 2.1 Hz, ArH), 6.72 (t, 2H, *J*= 2.1 Hz, ArH), 6.92 (d, 1H, *J*= 8.8 Hz, ArH), 7.38 (d, 1H, *J*= 8.7 Hz, ArH), 8.09 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 45.5, 55.8, 108.8, 114.9, 120.6, 124.7, 126.9, 132.1, 146.7, 161.6, 173.2

mass (ES+) *m/z*= 258.1 (M^++1)

Anal. Calcd. for $C_{15}H_{15}NO_3$ (Exact Mass: 257.1052); C, 70.02; H, 5.88; N, 5.44; Found C, 70.16; H, 6.01; N, 5.53

(*E*)-3-(3,4-dichlorophenyl)-2-(1*H*-pyrrol-1-ylmethyl) prop-2-enoic acid (13l)

Hexane: EtOAc, 8:1 (v/v); 95% as a white solid, mp 146-148 ^{o}C

ν_{max} (KBr) 1685 (CO_2H), 2959 (OH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.89 (s, 2H, CH_2), 6.15 (t, 2H, *J*= 2.0 Hz, ArH), 6.64 (t, 2H, *J*= 2.0 Hz, ArH), 7.15-7.18 (dd, 1H, J_1= 1.9 Hz, J_2= 8.3 Hz, ArH), 7.42 (d, 1H, *J*= 1.8 Hz, ArH), 7.48 (d, 1H, *J*= 8.3 Hz, ArH), 7.98 (s, 1H, =CH)

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 44.6, 108.7, 120.2, 128.2, 129.0, 130.9, 131.1, 133.3, 133.8, 134.1, 143.3, 171.9

mass (ES+) *m/z*= 296.1 (M^++1)

Anal. Calcd. for $C_{14}H_{11}Cl_2NO_2$ (Exact Mass: 295.0167); C, 56.78; H, 3.74; N, 4.73; Found C, 56.62; H, 3.89; N, 4.81

General procedure for the synthesis of 2-[(*E*)-(substituted phenyl)methylidene]-2,3-dihydro-1*H*-pyrrolizin-1-one 14a-b,d-e,g-h,k-l as exemplified for 14g. A mixture of **13g** (2.0 mmol, 0.5 g) and PPA (2.0 mL) was heated at 110 ^{o}C for 1 h. To the cooled reaction mixture 50 mL ice-water was added, and the organic part was extracted with $CHCl_3$ (3 x 20 mL). The combined organic phase was dried over anhyd. Na_2SO_4, concentrated and purified on silica gel column using hexane-EtOAc as eluent to obtain pure **14g** (0.3g, 65%) as a white solid.

2-[(*E*)-(4-Fluorophenyl)methylidene]-2,3-dihydro-1*H*-pyrrolizin-1-one (14g)

Hexane: EtOAc, 8:1 (v/v); 64% as a white solid, mp 177-178 ^{o}C

ν_{max} (KBr) 1696 (CO) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 5.17 (d, 2H, *J*= 2.0 Hz, CH_2), 6.56-6.58 (m, 1H, ArH), 6.89-6.91 (m, 1H, ArH), 7.14-7.20 (m, 3H, ArH), 7.45-7.52 (m, 3H, ArH and =CH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 47.9, 109.4, 116.5, 116.9, 117.3, 122.7, 130.7, 131.1, 132.3, 132.5, 134.7, 134.8, 161.2, 166.2, 179.6

mass (ES+) *m/z*= 228.2 (M^++1)

Anal. Calcd. for $C_{14}H_{10}FNO$ (Exact Mass: 227.0746); C, 74.00; H, 4.44; N, 6.16; Found C, 74.18; H, 4.63; N, 6.04.

2-[(*E*)-(3-nitrophenyl)methylidene]-2,3-dihydro-1*H*-pyrrolizin-1-one (14h)

Hexane: EtOAc, 6:1 (v/v); 42% as a white solid, mp 213-215 ^{o}C

ν_{max} (KBr) 1693 (CO) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 5.26 (d, 2H, *J*= 1.7 Hz, CH_2), 6.58-6.60 (m, 1H, ArH), 6.92-6.93 (m, 1H, ArH), 7.19 (s, 1H, ArH), 7.56 (s, 1H, ArH), 7.63-7.68 (m, 1H, ArH), 7.78-7.80 (m, 1H, ArH), 8.24 (s, 1H, =CH), 8.27-8.29 (m, 1H, ArH)

^{13}C NMR ($CDCl_3$, 50 MHz) δ= 47.4, 109.8, 117.4, 122.7, 123.5, 123.9, 128.5, 130.2, 134.2, 136.0, 136.1, 137.7, 148.7, 178.2

mass (ES+) *m/z*= 255.3 (M^++1)

Anal. Calcd. for $C_{14}H_{10}N_2O_3$ (Exact Mass: 254.0691); C, 66.14; H, 3.96; N, 11.02; Found C, 66.02; H, 4.15; N, 10.86.

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