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Expeditious synthesis of 5,6,7,8-tetrahydro-imidazo-[1,2-*a*]pyrimidin-2-ones and 3,4,6,7,8,9-hexahydro-pyrimido-[1,2-*a*]pyrimidin-2-ones☆

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Abstract—A convenient synthesis of new 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-ones and 3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones from the Baylis–Hillman adducts of acrylonitrile and their derivatives is described. A common strategy employed to achieve the syntheses of title compounds involved generation of diamines from different Baylis–Hillman derivatives followed by treatment with cyanogen bromide at reflux temperature to trigger a double intramolecular cyclization.

1. Introduction

The versatility of Baylis–Hillman derivatives for the construction of diverse heterocyclic frameworks is stupendous. This is apparent by a recent surge in the number of publications describing synthetic methodologies toward this objective.[1] One of our interests in this area concerns achieving practical synthesis of heterocyclic systems from Baylis–Hillman derivatives containing a nitrile group.[2] We have been especially interested in the synthesis of ring systems incorporating guanidine functionality. In this context, recently, we have reported the solid-phase synthesis of annulated pyrimidinones from the Baylis–Hillman adducts via Michael addition of alkanediamines followed by cyanogen bromide-mediated cyclization of the diamine and finally base-promoted cyclative cleavage.[3] The adoption of this strategy on the solid-phase chemistry was a direct outcome of our unsuccessful attempt to carry out the Michael addition of alkanediamines onto the Baylis–Hillman acetates in solution-phase as it invariably led to the formation of the polymeric products. Intriguingly, imidazo-pyrimidinone system is not very well represented in the literature though some of the derivatives bearing this moiety have been reported to display significant bioactivities.[4] With the aim to diversify the synthesis of annulated [1,2-*a*]pyrimidin-2-ones in solution-phase, we decided to utilize the derivatives of Baylis–Hillman adduct of acrylonitrile. Conceptually, the Michael addition of an amino alkyl ester on the Baylis–Hillman adduct of acrylonitrile followed by reduction of the nitrile function would lead to a diamino system, which may be cyclized with cyanogen bromide to yield the annulated [1,2-*a*]pyrimidine-2-ones. On the other hand, the alkylation of a primary allyl amine,[5] generated from the acetyl derivative of Baylis–Hillman adducts, with alkyl haloacetate should lead to an allyl amino alkyl ester. Subsequently, reducing the nitrile to amine would also furnish a diamino framework, which should undergo a double intramolecular cyclization by reaction with cyanogen bromide to afford an annulated [1,2-*a*]pyrimidin-2-one system. Alternatively, acetates can be subjected to Michael addition with amino alkyl ester followed by reduction of nitrile group and successive cascade cyclizations with cyanogen bromide. It was reasoned that this strategy might be extended to the synthesis of pyrimido[1,2-*a*]pyrimidin-2-ones. In principle, primary allyl amine afforded from the acetyl derivative of Baylis–Hillman adducts of acrylonitrile would undergo S_N2 reaction with the acetyl derivative of Baylis–Hillman adduct of acrylate to yield a product, which may serve as substrate for the synthesis of the desired heterocyclic system. Herein, we describe the details of our successful attempts toward expeditious synthesis of a variety of annulated [1,2-*a*]pyrimidin-2-ones involving these approaches.

2. Results and discussion

2.1. Synthesis of 6-(hydroxy-substituted phenyl-methyl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-ones

We initiated our studies from the Baylis–Hillman adduct of acrylonitrile **1a**, which was easily obtained by following standard procedure.[2a] Subsequent reaction of glycine ester

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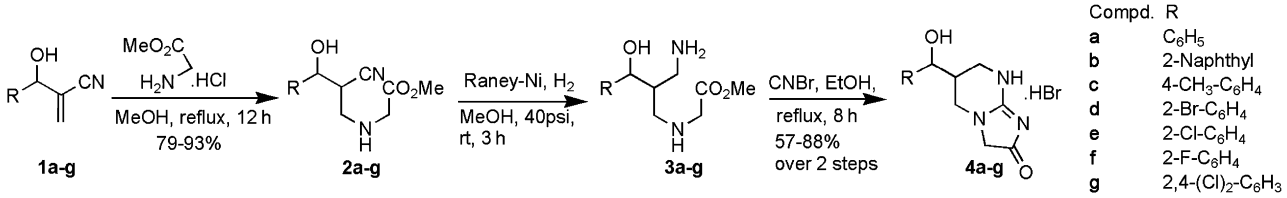
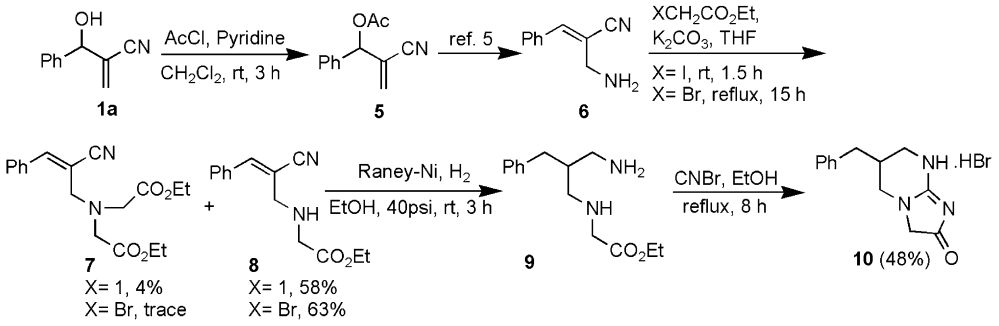
with **1a** at reflux temperature for 12 h gave the corresponding product **2a** as diastereoisomeric mixture (1:1) in excellent yield (Scheme 1). Hydrogenating **2a** in the presence of Raney-Ni for 3 h afforded the desired diamine **3a**. The diamine **3a** being unstable in nature was immediately subjected to reaction with cyanogen bromide in absolute ethanol at reflux temperature to yield the substituted imidazo[1,2-*a*]pyrimidine-2-one **4a** as hydrobromide salt in good yield (Scheme 1). The generality of this reaction protocol was evident from the synthesis of several analogs **4b–g**. The spectroscopic data especially the UV spectra of compounds **4a–g** supported the assigned structure to be the 5,6,7,8-tetrahydro-imidazo[1,2-*a*] pyrimidine-2-ones.[4a]

2.2. Synthesis of 6-benzyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-ones and 6-Methyl-5-phenyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-ones

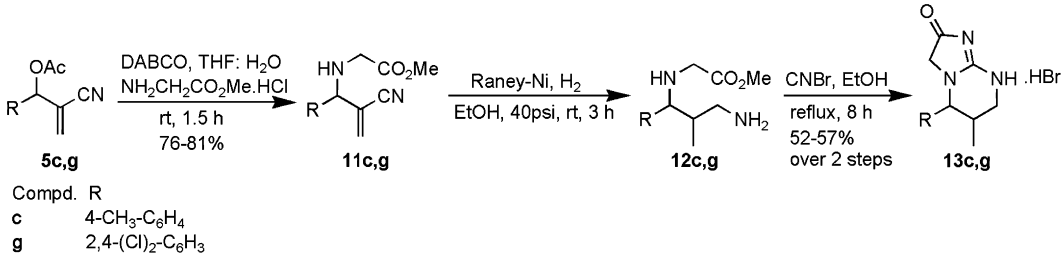
In order to increase the scope of this strategy, it was decided to carry out similar reactions with the acetyl derivative of the Baylis–Hillman adducts of acrylonitrile. In view of our earlier observation that during the reaction of the acetyl derivatives of the Baylis–Hillman adducts large excess of primary amine has to be used,[5] we decided to avoid the reaction of glycine ester directly with **5**. Therefore, the allyl amine **6**, generated via a reported procedure,[5] was treated with ethyl iodoacetate in THF in the presence of K_2CO_3 for 1.5 h to yield a mixture of two products (Scheme 2). These products were isolated in 4 and 58% yields and were established to be **7** and **8**, respectively (Scheme 2). Alternatively, the treatment of amine **6** with ethyl bromoacetate yielded the desired secondary amine **8** in 63% yield with only traces of **7**, though the reaction was completed in 15 h. Hydrogenating the allyl amine **8** with Raney-Ni gave the diamino derivative **9** in good yield. The product **9** was immediately treated with cyanogen bromide in absolute alcohol at reflux temperature to furnish the product **10** (Scheme 2). Encouraged with these results, we decided to extend the utility of this method to the synthesis of substituted imidazo[1,2-*a*]pyrimidin-2-ones from the substrate afforded by the S_N2 reaction of glycine ester and the acetyl derivative of Baylis–Hillman adduct. Therefore, the acetates **5c**,**g** were treated with glycine ester in the presence of DABCO in a THF/water system (1:1, v/v) to furnish corresponding products **11c**,**g** (Scheme 3). Reduction of the nitrile group with Raney-Ni in **11c**,**g** led to the isolation of diamines **12c**,**g**, respectively. Treatment of diamines **12c**,**g** with cyanogen bromide in absolute ethanol at reflux temperature afforded the desired 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidine-2-one **13c**,**g** as diastereoisomeric mixture in 1:1 ratio.



Scheme 1.



Scheme 2.



Scheme 3.

2.3. Synthesis of 7-substituted phenyl-methyl-3-methyl-4-substituted phenyl-3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones

Buoyed by the success of our strategy for the generation of a variety of imidazo[1,2-*a*]pyrimidinone system, we decided to investigate the synthesis of pyrimido[1,2-*a*]pyrimidin-2-ones. In principle, S_N2 reaction between the primary allyl amine **6** and the acetyl derivative of Baylis–Hillman adduct of acrylate would yield a suitable starting substrate for the desired motif. Hence, treatment of compounds **6a–c** with **14** and **15** in the presence DABCO in a THF/water system (1:1, v/v) furnished the products **16–19** in excellent yields (Scheme 4). Hydrogenation of **16–19** with Raney-Ni and subsequent treatment of the diamine **20–23** with cyanogen bromide in absolute ethanol gave the desired 3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones **24–27** in moderate yields as diastereoisomeric mixture in 1:1 ratio.

3. Conclusions

In summary, we have demonstrated convenient and practical strategies for the synthesis of differently substituted new annulated 5,6,7,8-tetrahydro-imidazo[1,2-*a*] pyrimidine-2-ones and 3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones from the derivatives of Baylis–Hillman adducts of acrylonitrile.

4. Experimental

4.1. General

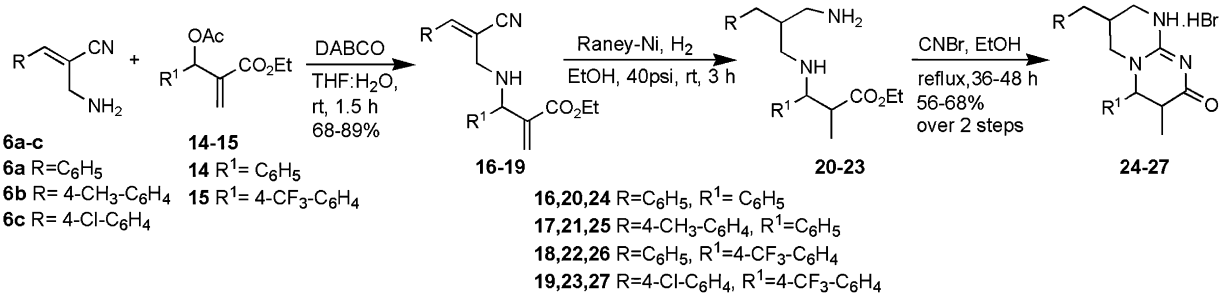
Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using Perkin–Elmer Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometers, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The ESMS were recorded on MICROMASS LC–MS system and FABMS were recorded on JEOL/SX-102 spectrometer. Elemental analyses were performed on Carlo Erba 108 or Elementar Vario EL *III* microanalyzer. The HRMS spectra were recorded as EI-HRMS. The HPLCs were performed on RP C-18 column (250×4.5 mm, 5μm) using a gradient of 10–100% methanol containing 0.1% TFA and water in 25 min at a flow rate of 1 mL/min on Agilent 1100. The silica gel used for column chromatography of compounds **4a–g**, **10**, **13c**,**g**, and **24–27** was deactivated prior to use by adding 12 mL of water per 100 g of silica gel. Compounds **2a–g**, **4a–g**, **13c**,**g**, and **24–27** were obtained as diastereoisomeric mixture in 1:1 ratio as evident from the ^{1}H NMR of the crude products.

4.2. General procedure for the preparation of 2a–g

To a stirred solution of appropriate compound from **1a–g** (3.16 mmol) in MeOH (5 mL) were added Et_3N (6.3 mmol, 0.65 mL) and glycine methyl ester hydrochloride (4.74 mmol, 0.6 g). The reaction mixture was heated at reflux temperature till the completion of reaction (monitored by TLC, ca. 12 h). Thereafter, methanol was removed in vacuo and the residue was extracted with EtOAc (3×25 mL) and water (40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to afford crude products, which were purified via silica gel column chromatography using hexane/EtOAc (60:40, v/v) to yield the pure products.

4.2.1. (2-Cyano-3-hydroxy-3-phenyl-propylamino)-acetic acid methyl ester (2a). Yield: 92% as colorless oil; R_f=0.4 (hexane/EtOAc, 60:40); ν_{max} (neat) 1739 (CO_2Me), 2245 (CN), 3331 (NH, OH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.71 (br s, 2H, 2×NH), 2.92–3.10 (m, 4H, 2×C*H*$_2$NH), 3.19–3.25 (m, 2H, 2×CH), 3.50 (s, 2H, CH_2CO), 3.53 (s, 2H, CH_2CO), 3.75 (s, 6H, 2×OCH_3), 5.07 (d, 1H, J=3.0 Hz, C*H*OH), 5.08 (d, 1H, J=3.0 Hz, C*H*OH), 7.33–7.47 (m, 10H, 2×5ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.5, 49.5, 50.3, 52.1, 53.1, 53.6, 71.9, 73.3, 74.1, 120.1, 121.1, 121.4, 127.7, 127.8, 128.0, 128.2, 129.8, 129.4, 130.1, 142.6, 142.8, 143.1, 166.0, 174.1; mass (FAB+) m/z=249 (M^++1); Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.13; H, 6.28; N, 11.35.

4.2.2. (2-Cyano-3-hydroxy-3-naphthalen-2-propylamino)-acetic acid methyl ester (2b). Yield: 83% as colorless oil; R_f=0.6 (hexane/EtOAc, 60:40); ν_{max} (neat) 1739 (CO_2Me), 2244 (CN), 3451 (NH, OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92–3.06 (m, 4H, 2×C*H*$_2$NH), 3.16–3.23 (m, 2H, 2×CH), 3.42–3.50 (m, 4H, 2×CH_2CO), 3.78 (s, 6H, 2×OCH_3), 5.23 (d, 1H, J=2.8 Hz, C*H*OH), 5.29 (d, 1H, J=2.8 Hz, C*H*OH), 7.49–7.52 (m, 6H, 2×3ArH), 7.81–7.93 (m, 8H, 2×4ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.3, 14.6, 40.1, 41.3, 48.5, 49.7, 50.5, 50.7, 52.5, 60.9, 61.6, 73.7, 74.3, 76.9, 77.5, 78.2, 119.1, 119.6, 124.0, 124.2, 125.6, 126.7, 126.8, 128.6, 128.9, 133.6, 133.7, 138.3, 172.6; mass (ES+) m/z=299 (M^++1);



Scheme 4.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.29; H, 5.90; N, 9.57.

4.2.3. (2-Cyano-2-hydroxy-3-*p*-tolyl-propylamino)-acetic acid methyl ester (2c). Yield: 92% as colorless oil; R_f=0.5 (hexane/EtOAc, 60:40); ν_{max} (neat) 1739 (CO_2Me), 2245 (CN), 3322 (NH, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 6H, 2×CH_3), 2.56 (br s, 2H, 2×NH), 2.91–3.06 (m, 6H, 2×CH and 2×CH_2NH), 3.48–3.50 (m, 4H, 2×CH_2CO), 3.75 (s, 6H, 2×OCH_3), 5.00 (d, 1H, J=4.7 Hz, C*H*OH), 5.03 (d, 1H, J=4.6 Hz, C*H*OH), 7.20 (d, 4H, J=8.0 Hz, 2×ArH), 7.33 (d, 4H, J=8.0 Hz, 2×4ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 19.9, 38.6, 39.7, 47.0, 48.0, 48.8, 49.0, 50.8, 59.2, 72.1, 72.5, 117.4, 117.8, 124.5, 124.9, 128.0, 136.1, 136.9, 137.1, 170.9, 171.0; mass (ES+) m/z=263 (M^++1); Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.82; H, 7.05; N, 10.51.

4.2.4. [3-(2-Bromo-phenyl)-2-cyano-3-hydroxy-propylamino]-acetic acid methyl ester (2d). Yield: 93% as colorless oil; R_f=0.5 (hexane/EtOAc, 60:40); ν_{max} (neat) 1717 (CO_2Me), 2200 (CN), 3463 (NH, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.93–3.22 (m, 4H, 2×CH_2NH), 3.23–3.32 (m, 2H, 2×CH), 3.41 (s, 2H, CH_2CO), 3.60 (d, 2H, J=0.5 Hz, CH_2CO), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.37 (d, 1H, J=1.4 Hz, C*H*OH), 5.48 (d, 1H, J=3.0 Hz, C*H*OH), 7.20–7.25 (m, 2H, ArH), 7.39–7.60 (m, 4H, ArH), 7.82–7.89 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5, 37.0, 45.9, 48.8, 49.0, 50.9, 71.3, 71.9, 116.6, 117.9, 119.8, 120.7, 126.6, 126.8, 127.1, 127.2, 128.5, 128.7, 131.2, 131.8, 137.8, 138.0, 170.7, 170.8; mass (ES+) m/z=328 (M^+), 330 (M^++2); Anal. Calcd for $C_{13}H_{15}BrN_2O_3$: C, 47.72; H, 4.62; N, 8.56. Found: C, 47.97; H, 4.78; N, 8.22.

4.2.5. [3-(2-Chloro-phenyl)-2-cyano-2-hydroxy-3-propylamino]-acetic acid methyl ester (2e). Yield: 89% as colorless oil; R_f=0.6 (hexane/EtOAc, 60:40); ν_{max} (neat) 1740 (CO_2Me), 3430 (NH, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.93–3.20 (m, 4H, 2×CH_2NH), 3.37–3.44 (m, 2H, 2×CH), 3.50 (s, 2H, CH_2CO), 3.60 (s, 2H, CH_2CO), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.45 (d, 1H, J=4.2 Hz, C*H*OH), 5.53 (d, 2H, J=4.3 Hz, C*H*OH), 7.32–7.42 (m, 5H, ArH), 7.62–7.66 (m, 1H, ArH), 7.83–7.87 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 37.3, 38.6, 38.9, 45.9, 48.6, 49.0, 50.9, 68.5, 69.2, 116.8, 118.1, 126.0, 126.1, 126.9, 127.9, 128.1, 128.3, 128.5, 129.6, 130.6, 136.7, 170.9; mass (ES+) m/z=283 (M^++1), 285 (M^++3); Anal. Calcd for $C_{13}H_{15}ClN_2O_3$: C, 55.23; H, 5.35; N, 9.91. Found: C, 55.01; H, 5.54; N, 10.11.

4.2.6. [2-Cyano-3-(2-fluoro-phenyl)-3-hydroxy-propylamino]-acetic acid methyl ester (2f). Yield: 79% as colorless oil; R_f=0.5 (hexane/EtOAc, 60:40); ν_{max} (neat) 1734 (CO_2Me), 2233 (CN), 3437 (NH, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (br s, 2H, 2×NH), 2.95–3.14 (m, 6H, 2×CH_2NH and CH), 3.49 (s, 2H, CH_2CO), 3.57 (s, 2H, CH_2CO), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.37 (d, 1H, J=2.6 Hz, C*H*OH), 5.38 (d, 1H, J=2.6 Hz, C*H*OH), 7.01–7.11 (m, 2H, ArH), 7.21–7.32 (m, 4H, ArH), 7.58–7.59 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 37.1, 45.8, 48.7, 48.9, 50.8, 50.9, 71.1, 71.8, 116.7, 118.0, 119.8, 120.7, 126.6, 126.8, 127.1, 127.2, 128.5, 127.7, 131.2, 131.8, 137.9, 138.0, 170.7, 170.9; mass (ES+) m/z=267 (M^++1); Anal. Calcd for $C_{13}H_{15}FN_2O_3 \cdot H_2O$: C, 54.92; H, 6.03; N, 9.85. Found, C, 55.12; H, 5.88; N, 10.05.

4.2.7. [2-Cyano-3-(2,4-dichloro-phenyl)-3-hydroxy-3-propylamino]-acetic acid methyl ester (2g). Yield: 81% as colorless oil; R_f=0.7 (hexane/EtOAc, 60:40); ν_{max} (neat) 1740 (CO_2Me), 3430 (NH, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.08–3.20 (m, 4H, 2×CH_2NH), 3.37–3.50 (m, 6H, 2×CH and CH_2CO), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.42 (d, 1H, J=4.6 Hz, C*H*OH), 5.50 (d, 2H, J=4.6 Hz, C*H*OH), 7.36–7.40 (m, 4H, ArH), 7.56–7.61 (m, 1H, ArH), 7.78–7.82 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 36.9, 46.2, 48.9, 51.0, 60.1, 69.3, 70.0, 116.6, 126.2, 126.9, 127.9, 128.1, 128.3, 128.6, 129.6, 136.3, 170.7, 170.9; mass (ES^+) m/z=317 (M^++1), 319 (M^++3); Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_3$: C, 49.23; H, 4.45; N, 8.83. Found: C, 49.28; H, 4.20; N, 8.86.

4.3. General procedure for the preparation of 3a–g, 9, 12c,g, and 20–23

A mixture of appropriate compound from **2a–g**, **8** or **11c**,**g**, **16–19** (2.0 mmol) and Raney-Ni (0.1 g wet) in methanol (10 mL) was subjected to hydrogenation at 40 psi in the Parr assembly for 3 h. The catalyst was filtered through a pad of Celite and the filtrate was concentrated. The residue was used directly for further reactions.

4.4. General procedure for the preparation of 4a–g, 10, 13c,g, and 24–27

To a stirred solution of appropriate diamines from **3a–g**, **9**, **12c**,**g** or **20–23** (1.98 mmol) in absolute EtOH (15 mL) was added CNBr (2.97 mmol, 0.315 g) and the reaction mixture was heated at reflux temperature for 8 h (36–48 h for **20–23**). Ethanol was removed from the mixture and the residue was subjected to silica gel column chromatography using ($CHCl_3$/MeOH, 90:10, v/v) as the eluant to furnish the pure products as hydrobromide salts.

4.4.1. 6-(Hydroxy-phenyl-methyl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4a). Yield: 57% as a brown oil; R_f=0.3 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1658 (CONH), 3370 (NH, OH) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.32–2.49 (m, 2H, 2×CH), 2.76–2.89 (m, 4H, 2×CH_2N), 3.11–3.23 (m, 4H, 2×CH_2NH), 3.56 (s, 4H, 2×CH_2CO), 5.03 (d, 1H, J=3.6 Hz, C*H*OH), 5.11 (d, 1H, J=3.5 Hz, C*H*OH), 7.48–7.61 (m, 4H, ArH), 7.88–7.93 (m, 6H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 37.1, 37.5, 42.9, 43.5, 49.9, 51.6, 69.6, 72.6, 125.3, 126.7, 126.9, 127.3, 127.8, 128.4, 128.6, 143.5, 144.2, 158.5, 158.7, 172.2, 172.5; mass (ES+) m/z=246 (M^++1); λ_{max}=226 nm; HR-EIMS Calcd for $C_{13}H_{15}N_3O_2$: 245.1164, found: 245.1166.

4.4.2. 6-(Hydroxy-naphthalen-2-yl-methyl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4b). Yield: 62% as a brown oil; R_f=0.5 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1661 (CONH), 3427 (NH, OH) cm^{-1}; ^1H NMR (200 MHz,

DMSO-d_6) δ 2.26–2.28 (m, 2H, 2×CH), 3.05–3.19 (m, 4H, 2×CH_2N), 3.46–3.74 (m, 4H, 2×CH_2NH), 3.75 (s, 4H, 2×CH_2CO), 4.87 (d, 1H, J=4.2 Hz, C*H*OH), 4.92 (d, 1H, J=4.2 Hz, C*H*OH), 7.42–7.52 (m, 6H, ArH), 7.75–7.86 (m, 8H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 37.3, 37.8, 41.4, 41.9, 42.5, 43.0, 51.6, 52.0, 73.3, 73.9, 126.4, 127.2, 129.1, 129.7, 130.1, 130.7, 131.5, 131.8, 132.0, 133.2, 133.4, 138.3, 138.9, 146.7, 147.1, 158.0, 158.7, 177.6, 178.3; mass (ES+) m/z=296 (M^++1); λ_{max}=224 nm; HR-EIMS Calcd for $C_{17}H_{17}N_3O_2$: 295.1321, found: 295.1325.

4.4.3. 6-(Hydroxy-*p*-tolyl-methyl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4c). Yield: 89% as a colorless oil; R_f=0.4 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1662 (CONH), 3409 (NH, OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 6H, 2×CH_3), 2.80–2.83 (m, 2H, 2×CH), 3.06–3.11 (m, 4H, 2×CH_2N), 3.27–3.43 (m, 4H, 2×CH_2NH), 3.83 (s, 4H, 2×CH_2CO), 4.64 (d, 1H, J=4.4 Hz, C*H*OH), 4.69 (d, 1H, J=4.4 Hz, C*H*OH), 7.18 (d, 4H, J=8.0 Hz, ArH), 7.27 (d, 4H, J=8.0 Hz, ArH), 7.78 (br s, 2H, 2×NH), 10.78 (s, 2H, 2×OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.2, 24.6, 24.7, 43.5, 43.9, 45.3, 45.8, 47.0, 47.8, 55.2, 56.3, 63.7, 76.5, 77.1, 130.3, 131.4, 132.7, 132.9, 140.5, 142.1, 144.0, 161.7, 161.9, 173.9, 175.8; mass (ES+) m/z=260 (M^++1); λ_{max}=220 nm; HR-EIMS Calcd for $C_{14}H_{17}N_3O_2$: 259.1321, found: 259.1349.

4.4.4. 6-[(2-Bromo-phenyl)-hydroxy-methyl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4d). Yield: 66% as colorless oil; R_f=0.4 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1658 (CONH), 3370 (NH, OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30–2.36 (m, 2H, 2×CH), 3.02–3.29 (m, 8H, 2×CH_2N and 2×CH_2NH), 3.67 (s, 4H, 2×CH_2CO), 4.87 (d, 1H, J=4.4 Hz, C*H*OH), 4.89 (d, 1H, J=4.4 Hz, C*H*OH), 7.22–7.27 (m, 2H, ArH), 7.42–7.46 (m, 2H, ArH), 7.54–7.58 (m, 4H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 37.6, 37.9, 39.5, 40.7, 41.8, 42.1, 52.0, 52.6, 71.2, 71.9, 121.6, 125.4, 126.8, 127.6, 128.2, 129.0, 129.8, 133.0, 142.2, 158.0, 172.1, 172.6; mass (ES+) m/z=324 (M^++1); λ_{max}=226 nm; HR-EIMS Calcd for $C_{13}H_{14}BrN_3O_2$: 323.0269, found: 323.0265.

4.4.5. 6-[(2-Chloro-phenyl)-hydroxy-methyl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4e). Yield: 83% as white solid; mp 272–274 °C; R_f=0.5 ($CHCl_3$/MeOH, 90:10); ν_{max} (KBr) 1648 (CONH), 3415 (NH, OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32–2.34 (m, 2H, 2×CH), 2.83–2.97 (m, 4H, 2×CH_2N), 3.25–3.32 (m, 4H, 2×CH_2NH), 4.01 (s, 4H, 2×CH_2CO), 5.05 (d, 1H, J=4.5 Hz, C*H*OH), 5.09 (d, 1H, J=4.5 Hz, C*H*OH), 7.16–7.31 (m, 6H, ArH), 7.58–7.60 (m, 2H, ArH), 7.87 (br s, 2H, 2×NH), 10.89 (br s, 2H, 2×OH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 37.6, 38.2, 40.2, 40.9, 41.7, 42.5, 51.4, 51.9, 69.0, 69.8, 127.7, 128.7, 129.0, 129.4, 129.7, 130.1, 131.2, 133.9, 140.8, 158.0, 158.6, 172.1, 172.9; mass (ES+) m/z=280 (M^++1); λ_{max}=222 nm; HR-EIMS Calcd for $C_{13}H_{14}ClN_3O_2$: 279.0775, found: 279.0778.

4.4.6. 6-[(2-Fluoro-phenyl)-hydroxy-methyl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4f). Yield: 74% as colorless oil; R_f=0.5 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat): 1676 (CONH), 3436 (NH, OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98–3.16 (m, 6H, 2×CH and 2×CH_2N), 3.51–3.62 (m, 4H, 2×CH_2NH), 3.77 (s, 4H, 2×CH_2CO), 5.42 (d, 1H, J=4.5 Hz, C*H*OH), 5.45 (d, 1H, J=4.5 Hz, C*H*OH), 7.05–7.12 (m, 2H, ArH), 7.23–7.36 (m, 4H, ArH), 7.58–7.59 (m, 2H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 38.5, 38.8, 41.7, 41.9, 42.3, 43.0, 51.6, 52.1, 73.0, 73.5, 126.7, 127.0, 127.3, 128.6, 129.1, 129.4, 130.0, 136.9, 140.4, 158.1, 158.7, 172.2, 173.1; mass (ES+) m/z=264 (M^++1); λ_{max}=226 nm; HR-EIMS Calcd for $C_{13}H_{14}FN_3O_2$: 263.1070, found: 263.1074.

4.4.7. 6-[(2,4-Dichloro-phenyl)-hydroxy-methyl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (4g). Yield: 88% as a white solid; mp 248–250 °C; R_f=0.6 ($CHCl_3$/MeOH, 90:10); ν_{max} (KBr) 1662 (CONH), 3367 (NH, OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24–2.26 (m, 2H, 2×CH), 2.76–2.79 (m, 4H, 2×CH_2N), 3.35–3.42 (m, 4H, 2×CH_2NH), 3.88 (s, 4H, 2×CH_2CO), 4.99 (d, 1H, J=3.9 Hz, C*H*OH), 5.01 (d, 1H, J=3.9 Hz, C*H*OH), 6.10 (s, 2H, 2×NH), 7.50–7.53 (m, 2H, ArH), 7.60–7.69 (m, 4H, ArH), 10.86 (s, 2H, 2×OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.5, 36.8, 40.6, 41.9, 42.6, 50.7, 51.4, 67.6, 69.1, 126.7, 127.6, 128.0, 128.7, 129.0, 129.8, 131.0, 138.9, 156.8, 158.0, 170.9, 172.1; mass (ES+) m/z=314 (M^++1); λ_{max}=230 nm; HR-EIMS Calcd for $C_{13}H_{12}Cl_2N_3O_2$: 313.0385, found: 313.0389.

4.4.8. 6-Benzyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (10). Yield: 48% as a brown oil; R_f=0.4 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1660 (CONH), 3362 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20–2.41 (m, 1H, CH), 2.67–2.71 (m, 2H, CH_2N), 3.12–3.45 (m, 4H, ArCH_2 and CH_2NH), 3.88 (s, 2H, CH_2CO), 6.52 (br s, 1H, NH), 7.16–7.38 (m, 5H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 45.9, 57.1, 73.9, 75.9, 76.3, 133.1, 134.3, 135.4, 137.3, 138.2, 145.3, 163.2, 177.4; mass (ES+) m/z=230 (M^++1); λ_{max}=222 nm; HR-EIMS Calcd for $C_{13}H_{14}N_3O$: 229.1215, found: 229.1218.

4.4.9. 6-Methyl-5-*p*-tolyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (13c). Yield: 52% as a brown oil; R_f=0.5 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1668 (CONH), 3357 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, 3H, J=6.6 Hz, CH_3), 0.88 (d, 3H, J=6.6 Hz, CH_3), 2.36 (s, 6H, 2×ArCH_3), 2.53–2.56 (m, 2H, 2×C*H*CH_2), 3.03–3.15 (m, 4H, 2×CH_2NH), 3.76 (s, 2H, CH_2CO), 3.77 (s, 2H, CH_2CO), 4.44 (d, 2H, J=5.2 Hz, 2×C*H*Ph), 6.98 (d, 4H, J=8.0 Hz, 2×2ArH), 7.23 (d, 4H, J=8.0 Hz, 2×2ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 14.6, 19.8, 29.6, 33.1, 39.5, 42.0, 51.6, 58.5, 61.5, 125.7, 126.1, 127.7, 128.2, 128.5, 132.0, 133.9, 137.0, 165.7, 182.9; mass (ES+) m/z=244 (M^++1); λ_{max}=225 nm; HR-EIMS Calcd for $C_{14}H_{17}N_3O$: 243.1372, found: 243.1365.

4.4.10. 5-(2,4-Dichloro-phenyl)-6-methyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-one (13g). Yield: 57% as a brown oil; R_f=0.7 ($CHCl_3$/MeOH, 90:10); ν_{max} (neat) 1660 (CONH), 3350 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, 3H, J=6.4 Hz, CH_3), 0.88 (d, 3H, J=6.4 Hz, CH_3), 2.23–2.40 (m, 2H, 2×C*H*–CH_2), 2.49–2.71 (m, 4H, 2×CH_2NH), 3.67 (s, 2H, CH_2CO), 3.73 (s, 2H, CH_2CO), 4.07 (d, 1H, J=1.4 Hz, C*H*Ph), 4.13 (d, 1H, J=1.4 Hz, C*H*Ph), 7.03–7.09 (m, 2H, 2×ArH), 7.30–7.47

(m, 2H, 2×ArH), 7.53 (s, 1H, ArH), 7.55 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 13.2, 14.2, 15.1, 28.4, 29.3, 32.9, 34.7, 39.7, 42.5, 44.5, 51.5, 58.2, 61.1, 126.8, 127.0, 127.4, 127.6, 127.8, 128.2, 128.3, 133.6, 133.8, 134.6, 170.4, 180.7; mass (ES+) m/z=298 (M^++1); λ_{max}=223 nm; HR-EIMS Calcd for $C_{13}H_{13}Cl_2N_3O$: 297.0436, found: 297.0438.

4.4.11. 7-Benzyl-3-methyl-4-phenyl-3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-one (24). Yield: 63% as colorless oil; t_R=19.3 min; ν_{max} (neat) 1688 (CONH), 3412 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84–0.97 (m, 3H, CH_3), 1.05–1.33 (m, 3H, CH_3), 2.19–2.42 (m, 2H, 2×CH), 2.49–2.75 (m, 4H, 2×CH_2), 2.96–3.35 (m, 10H, 2×2CH_2 and CH), 3.43–3.67 (m, 2H, 2×CH), 3.92–4.09 (m, 1H, CH), 4.11–4.29 (m, 1H, CH) 7.05–7.36 (m, 20H, ArH), 10.61 (br s, 2H, 2×NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 33.3, 37.4, 43.5, 50.06, 51.38, 60.8, 66.3, 67.2, 68.7, 76.9, 77.6, 78.2, 127.0, 127.3, 128.5, 129.4, 138.5, 139.5, 157.6, 177.8; λ_{max}=215 nm; mass (ES+) m/z=334 (M^++1); HR-EIMS Calcd for $C_{21}H_{23}N_3O$: 333.1841, found: 333.1840.

4.4.12. 3-Methyl-7-(4-methyl-benzyl)-4-phenyl-3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-one (25). Yield: 56% as colorless oil; t_R=18.1 min; ν_{max} (neat) 1690 (CONH), 3431 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87–0.93 (m, 3H, CH_3), 1.24–1.29 (m, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.60–2.74 (m, 2H, 2×CH), 2.85–3.37 (m, 12H, 2×3CH_2), 3.59–3.78 (m, 2H, 2×CH), 3.92–4.01 (m, 1H, CH), 4.05–4.13 (m, 1H, CH), 6.89–7.22 (m, 18H, 2×9ArH), 10.50 (br s, 2H, 2×NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 17.3, 17.7, 21.5, 33.4, 37.6, 39.4, 43.7, 50.2, 127.0, 128.2, 128.4, 129.2, 130.1, 133.9, 134.4, 136.4, 138.8, 157.8, 178.3; λ_{max}=224 nm; mass (ES+) m/z=348 (M^++1); HR-EIMS Calcd for $C_{22}H_{25}N_3O$: 347.1998, found: 347.1999.

4.4.13. 3-Methyl-4-phenyl-7-(4-trifluoromethyl-benzyl)-3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-one (26). Yield: 68% as colorless oil; t_R=21.1 min; ν_{max} (neat) 1683 (CONH), 3409 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86–0.96 (m, 3H, CH_3), 1.09–1.36 (m, 3H, CH_3), 2.03–2.19 (m, 2H, 2×CH), 2.58–2.79 (m, 4H, 2×CH_2), 3.13–3.42 (m, 4H, 2×CH_2), 3.72–4.21 (m, 6H, 2×CH_2 and 2×CH), 7.32–7.49 (m, 10H, ArH), 7.57–7.73 (m, 8H, ArH) 10.32 (br s, 2H, 2×NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 15.5, 43.8, 44.8, 47.2, 51.6, 56.5, 61.9, 64.3, 66.3, 104.4, 114.7, 117.3, 126.6, 128.5, 129.5, 130.8, 132.0, 144.4, 145.1, 148.5, 173.0; λ_{max}=222 nm; mass (ES+) m/z 402 (M^++1); HR-EIMS Calcd for $C_{22}H_{22}F_3N_3O$: 401.1715, found: 401.1718.

4.4.14. 7-(4-Chloro-benzyl)-3-methyl-4-(4-trifluoromethyl-phenyl)-3,4,6,7,8,9-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-one (27). Yield: 67% as colorless oil; t_R=21.8 min; ν_{max} (neat): 1686 (CONH), 3457 (NH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.97 (m, 3H, CH_3), 1.30–1.38 (m, 3H, CH_3), 2.21–2.46 (m, 2H, 2×CH), 2.53–2.80 (m, 6H, 2×CH_2 and 2×1H of CH_2), 2.83–3.29 (m, 6H, 2×CH_2 and 2×1H of CH_2), 3.60–3.72 (m, 2H, 2×CH), 4.01–4.10 (m, 1H, CH), 4.15–4.24 (m, 1H, CH), 6.84–7.03 (m, 4H, ArH), 7.19–7.40 (m, 8H, ArH), 7.58–7.65 (m, 4H, ArH), 10.54 (br s, 2H, 2×NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 51.9, 61.4, 61.5, 111.0, 118.4, 121.8, 125.8, 125.9, 127.0, 128.4, 129.6, 129.9, 130.5, 131.2, 131.9, 136.8, 141.4, 143.2, 145.3, 166.2; λ_{max}=221 nm; mass (ES+) m/z=436 (M^++1); HR-EIMS Calcd for $C_{22}H_{21}ClF_3N_3O$: 435.1325, found: 435.1321.

4.5. Typical procedure for the preparation of 8

To a stirred solution of **6** (6.33 mmol, 1.0 g) in THF (50 mL) was added K_2CO_3 (9.49 mmol, 1.31 g) followed by ethyl iodoacetate (7.59 mmol, 0.89 mL) and the reaction was allowed to continue for 1.5 h at room temperature. Thereafter, the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3×30 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated under vacuo to yield a residue. This crude product was purified via silica gel column chromatography using hexane/EtOAc (90:10, v/v) to afford **7** followed by hexane/EtOAc (80:20, v/v) to furnish **8**.

4.5.1. [(3-Cyano-4-phenyl-but-3-enyl)-ethoxycarbonyl-amino]-acetic acid ethyl ester (7). Yield: 4% as colorless oil; R_f=0.8 (hexane/EtOAc; 80:20); ν_{max} (neat) 1736 (2×CO_2Et), 2218 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, 6H, J=7.1 Hz, 2×$CH_2C\mathit{H}_3$), 3.65 (s, 4H, CH_2), 3.77 (s, 2H, CH_2), 4.20 (q, 4H, J=7.1 Hz, 2×$C\mathit{H}_2CH_3$), 7.23 (s, 1H, =CH), 7.42–7.44 (m, 3H, ArH), 7.78–7.80 (m, 2H, ArH); mass (ES+) m/z=331 (M^++1); Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.42; H, 6.59; N, 8.66.

4.5.2. (3-Cyano-4-phenyl-but-3-enyl)-carbamic acid ethyl ester (8). Yield: 58% as colorless oil; R_f=0.7 (hexane/EtOAc; 80:20); ν_{max} (neat) 1738 (CO_2Et), 2213 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.2 Hz, $CH_2C\mathit{H}_3$), 1.97 (br s, 1H, NH), 3.48 (s, 2H, CH_2), 3.63 (d, 2H, J=1.2 Hz, CH_2), 4.23 (q, 2H, J=7.2 Hz, $C\mathit{H}_2CH_3$), 7.13 (s, 1H, =CH), 7.42–7.46 (m, 3H, ArH), 7.76–7.78 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 53.5, 57.1, 57.2, 60.0, 106, 107.1, 117.1, 127.7, 129.4, 131.7, 144.0, 144.9, 169.0; mass (ES+) m/z=245 (M^++1); Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.17; H, 6.47; N, 11.66.

4.6. General procedure for the of preparation of 11c,g

To a solution of appropriate acetate[6] from **5c**,**g** (2.5 mmol) in a THF/H_2O system (10 mL, 1:1, v/v) was added DABCO (0.42 g, 3.76 mmol) at room temperature and the mixture was stirred for 10 min. Simultaneously, in another flask to the solution of glycine methyl ester hydrochloride (0.47 g, 3.75 mmol) in H_2O (5 mL) was added Et_3N (0.52 mL, 5.0 mmol) and the mixture was stirred for 10 min. This mixture was then added dropwise to the flask containing the acetate and the reaction was continued at room temperature for 1.5 h. The THF was removed from the reaction mixture and the residue was extracted with EtOAc (2×20 mL) and water (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford the crude product. Purification of the crude product via column chromatography over silica gel with hexane/EtOAc (85:15, v/v) furnished the pure products.

4.6.1. (2-Cyano-1-*p*-tolyl-allylamino)-acetic acid methyl ester (11c). Yield: 76% as colorless oil; R_f=0.6 (hexane/EtOAc; 85:15); ν_{max} (neat) 1737 (CO_2Me), 2226 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 (br s, 1H, NH), 2.35 (s, 3H, CH_3), 3.36 (d, 2H, J=2.5 Hz, CH_2CO), 3.71 (s, 3H, OCH_3), 4.41 (s, 1H, CH), 5.98 (s, 1H, =CH_2), 6.09 (s, 1H, =CH_2), 7.17 (d, 2H, J=8.0 Hz, ArH), 7.28 (d, 2H, J=8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 46.7, 50.7, 63.4, 116.2, 125.0, 126.0, 128.4, 128.8, 134.3, 137.2, 171.2; mass (ES+) m/z=245 (M^++1); Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.11; H, 6.66; N, 11.55.

4.6.2. [2-Cyano-1-(2,4-dichloro-phenyl)-allylamino]-acetic acid methyl ester (11g). Yield: 81% as colorless oil; R_f=0.8 (hexane/EtOAc; 85:15); ν_{max} (neat) 1732 (CO_2Me), 2216 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.38 (d, J=5.6 Hz, 2H, CH_2CO), 3.74 (s, 3H, OCH_3), 4.94 (s, 1H, CH), 6.05 (s, 1H, =CH_2), 6.13 (s, 1H, =CH_2), 7.31–7.42 (m, 2H, ArH), 7.61–7.66 (d, 1H, J=8.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.6, 50.8, 62.9, 115.8, 124.4, 127.5, 127.9, 129.4, 133.2, 135.8, 171.1; mass (ES+) m/z=299 (M^++1), 301 (M^++3); Anal. Calcd for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.19; H, 4.04; N, 9.36. Found: C, 51.87; H, 3.95; N, 9.29.

4.7. General procedure for the preparation of 16–19

To a stirred solution of appropriate acetate from **14** and **15** (5.2 mmol) in THF/H_2O (5 mL, 1:1, v/v) system was added DABCO (7.8 mmol, 0.87 g,) at room temperature and the reaction mixture was allowed to stir for 5 min. This was followed by dropwise addition of a solution of appropriate allyl amine from **6a–c** (5.2 mmol) in THF (5 mL) and the reaction was allowed to proceed till completion (as analyzed by TLC, ca. 1 h). Thereafter excess THF was evaporated in vacuo and the residue was extracted with EtOAc (3×30 mL) and water 50 mL. The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo to obtain a residue, which was purified via silica gel column chromatography using hexane/EtOAc (85:15, v/v) to yield the pure product.

4.7.1. 2-[(2-Cyano-3-phenyl-allylamino)-phenyl-methyl]-acrylic acid ethyl ester (16). Yield: 68% as colorless oil; R_f=0.5 (hexane/EtOAc; 85:15); ν_{max} (neat) 1713 (CO_2Et), 2212 (CN), 3340 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.53 (s, 2H, CH_2NH), 4.17 (q, 2H, J=7.2 Hz, CH_2CH_3), 4.79 (s, 1H, CHNH), 6.01 (s, 1H, =CH_2), 6.41 (s, 1H, =CH_2), 7.05 (s, 1H, =CH), 7.27–7.46 (m, 8H, ArH), 7.74–7.77 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 13.1, 43.3, 50.3, 52.2, 59.8, 108.9, 117.2, 124.5, 126.5, 127.3, 127.4, 127.6, 128.3, 129.0, 132.0, 133.7, 139.4, 140.5, 142.8, 165.0, 166.7; mass (ES+) m/z=347 (M^++1). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.41; H, 6.20; N, 7.92.

4.7.2. 2-[(2-Cyano-3-*p*-tolyl-allylamino)-phenyl-methyl]-acrylic acid ethyl ester (17). Yield: 73% as colorless oil; R_f=0.6 (hexane/EtOAc; 85:15); ν_{max} (neat) 1712 (CO_2Et), 2217 (CN), 3399 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.38 (s, 3H, $ArCH_3$), 3.47 (s, 2H, CH_2NH), 4.14 (q, 2H, J=7.2 Hz, CH_2CH_3), 4.76 (s, 1H, CHNH), 6.01 (s, 1H, =CH_2), 6.39 (s, 1H, =CH_2), 6.97 (s, 1H, =CH), 7.19–7.42 (m, 7H, ArH), 7.64 (d, 2H, J=8.0 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.8, 13.0, 50.4, 59.8, 108.6, 117.0, 124.1, 124.2, 124.6, 125.3, 126.7, 127.5, 127.6, 127.9, 128.2, 128.5, 128.6, 129.1, 131.8, 139.8, 143.0, 143.7, 164.5; mass (ES+) m/z=361 (M^++1); Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.68; H, 6.50; N, 7.66.

4.7.3. 2-[(2-Cyano-3-phenyl-allylamino)-(4-trifluoromethyl-phenyl)-methyl]-acrylic acid ethyl ester (18). Yield: 89% as colorless oil; R_f=0.8 (hexane/EtOAc; 85:15); ν_{max} (neat) 1714 (CO_2Et), 2214 (CN), 3343 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.54 (s, 2H, CH_2NH), 4.16 (q, 2H, J=7.2 Hz, CH_2CH_3), 4.84 (s, 1H, CHNH), 6.04 (s, 1H, =CH_2), 6.46 (s, 1H, =CH_2), 7.04 (s, 1H, =CH), 7.41–7.51 (m, 3H, ArH), 7.56–7.63 (m, 4H, ArH), 7.72–7.77 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.8, 50.3, 59.8, 59.9, 109.3, 116.8, 124.3, 125.4, 126.7, 127.9, 128.8, 130.3, 135.1, 139.8, 141.6, 143.6, 164.6; mass (ES+) m/z=415 (M^++1); Anal. Calcd for $C_{23}H_{21}F_3N_2O_2$: C, 66.66; H, 5.11; N, 6.76. Found: C, 66.50; H, 4.88; N, 6.92.

4.7.4. 2-[[3-(4-Chloro-phenyl)-2-cyano-allylamino]-(4-trifluoromethyl-phenyl)-methyl]-acrylic acid ethyl ester (19). Yield: 78% as colorless oil; ν_{max} (neat) 1720 (CO_2Et), 2214 (CN), 3400 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.53 (d, 2H, J=2.1 Hz, CH_2NH), 4.20 (q, 2H, J=7.5 Hz, CH_2CH_3), 4.82 (s, 1H, CHNH), 6.01 (s, 1H, =CH_2), 6.45 (s, 1H, =CH_2), 7.00 (s, 1H, =CH), 7.37 (d, 2H, J=8.4 Hz, ArH), 7.47–7.70 (m, 4H, ArH), 7.68 (d, 2H, J=8.4 Hz, ArH); mass (ES+) m/z=449 (M^++1); Anal. Calcd for $C_{23}H_{20}ClF_3N_2O_2$: C, 61.54; H, 4.49; N, 6.24. Found: C, 61.68; H, 4.50; N, 6.56.

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