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Synthesis of pyrrolo[1,2-*a*]pyrazines and pyrazino[1,2-*a*]indoles by Curtius reaction in Morita–Baylis–Hillman derivatives☆

Maloy Nayak, Garima Pandey, Sanjay Batra *

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, PO Box 173, Lucknow 226001, India

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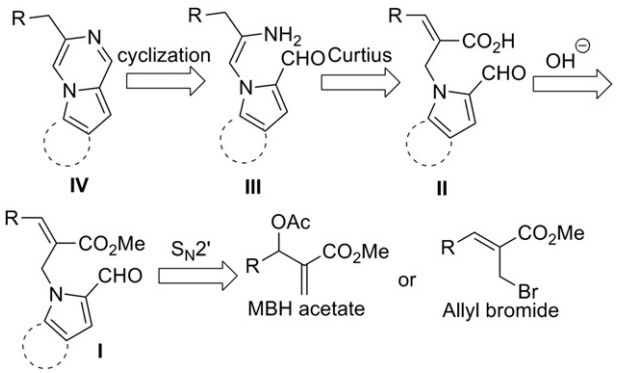
ABSTRACT

Synthesis of substituted pyrrolo[1,2-*a*]pyrazines and pyrazino[1,2-*a*]indoles from the Morita–Baylis–Hillman derivatives of acrylates via saponification followed by Curtius reaction is described.

1. Introduction

Pyrrolo[1,2-*a*]pyrazines and pyrazino[1,2-*a*]indoles are important templates from medicinal perspective. Compounds representing the pyrrolo[1,2-*a*]pyrazine core are known to act as Vasopressin$_{1b}$ antagonist,[1] 5HT$_{2C}$ agonist,[2] selective non-competitive mGluR5 antagonists,[3] HIV-1 integrase inhibitors[4] and neuroleptics.[5] Likewise pyrazino indole also forms sub-structural unit of several compounds, which display diverse pharmacological activities including serotoninergic,[6] anti-inflammatory,[7] antibacterial[8] and anti-obesity.[9] Although several synthetic methodologies for their preparation are available in the literature,[10] their significance in medicinal chemistry demands development of newer approaches for accessing them.

For many years, we have been interested in development of general protocols for the synthesis of heterocycles of biological significance using Morita–Baylis–Hillman derivatives as the key intermediates.[11] The substituted allylamines afforded from the aza-MBH reaction or MBH acetates are precursors to a variety of aza-heterocycles.[11c,12,13] As part of our ongoing interest, we envisaged the synthesis of pyrrolo[1,2-*a*]pyrazines and pyrazino[1,2-*a*]indoles from substituted allylamines afforded from the S_N2'-reaction between the MBH acetate of acrylate and pyrrole-2-carboxaldehyde or 3-methyl-indole-2-carbox-aldehyde, respectively. It is worthwhile to mention that these allylamines have been prepared by Raghunathan et al.[14a,b] and Kim et al.[14c] previously for different objectives. The retrosynthetic analysis illustrated in Scheme 1 explains our strategy. Cleavage of the pyrazine ring of the product **IV** gives **III**, which in turn can be synthesized from the acid **II** via Curtius reaction. The acid **II** can be easily obtained by saponification of the ester **I**. Working on the envisaged strategy we discovered that the synthesis of the title compounds can be readily achieved in high yields without any elaborate synthetic requirements. We report herein the results of our efforts to develop the envisaged protocol for achieving the synthesis of these scaffolds.



Scheme 1. Retrosynthetic analysis for the synthesis of pyrrolo[1,2-*a*]pyrazine and pyrazino[1,2-*a*]indole using MBH derivatives.

2. Results and discussion

The study commenced with preparation of **2a** from MBH acetate **1a** by reacting it with pyrrole-2-carboxaldehyde in DMF at rt for 3 h (Scheme 2). Saponification of **2a** with LiOH in aq THF at rt afforded the acrylic acid **3a**. The next objective was transforming of the acid group of **3a** to amine via Curtius reaction. Gratifyingly, after performing a series of reactions we were able to optimize the conditions as follows. Reacting **3a** with ethyl chloroformate followed by sodium azide in THF at −10 °C to rt for 30 min resulted in acrolyl azide. The formation of the azide derivative was confirmed by characteristic peak at 2135 cm^{-1} for the azido group in the IR

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* Corresponding author. Tel.: +91 522 2612411 18x4234, 4368; fax: +91 522 2623405, 2623938; e-mail addresses: batra_san@yahoo.co.uk, s_batra@cdri.res.in (S. Batra).

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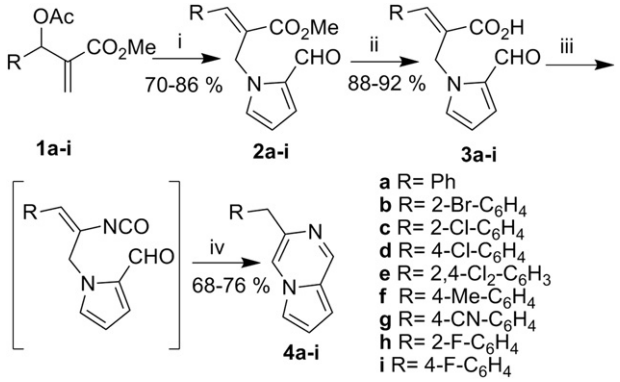
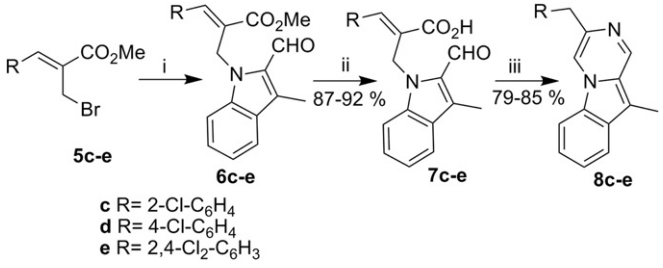
spectrum. Without any purification, the azide was transformed to isocyanate by heating it in toluene at 65 °C. The formation of isocyanate was established by the IR spectrum, which displayed the peak for isocyanate functionality at 2223 cm^{-1}. Treating the isocyanate with 90% formic acid and catalytic amount of DMAP in methylene chloride at rt for 4 h afforded a single product, which was isolated via column chromatography in 76% yields. Spectroscopic analysis of the product led us to assign its structure as **4a**. The formation of pyrrolo[1,2-*a*]pyrazine **4a** implied that expectedly the generated amino group participate in intramolecular cyclization with the formyl moiety of the pyrrole ring. The success of the protocol inspired us to investigate its general applicability. Hence several MBH acetates **2b**–**i** were treated with pyrrole-2-carboxaldehyde to afford corresponding products **3b**–**i**. It was a delight to observe that a similar set of reactions with **3b**–**i** under the optimized protocol resulted in the formation of respective substituted pyrrolo[1,2-*a*]pyrazines **4b**–**i** in 68–76% yields. Importantly purification was performed only at the final step wherein passing the crude material through a small band of silica gel furnished the products as solids or oils.



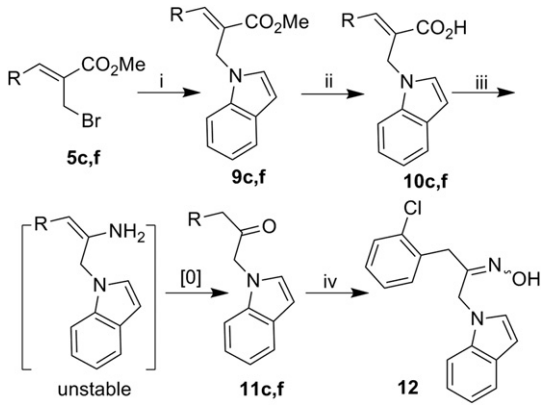
Scheme 2. Reagents and conditions. (i) Pyrrole-2-carboxaldehyde, K_2CO_3, DMF, rt, 3–4 h; (ii) LiOH, THF/H_2O (1:1, v/v), rt, 6–8 h; (iii) (a) $ClCO_2Et$, NMM, THF, 0 °C, 10 min; (b) NaN_3, 30 min; (c) PhMe, 65 °C, 30 min; (iv) Formic acid, DMAP, CH_2Cl_2, rt, 4–5 h.

Given the success of the strategy we considered to expand the scope by employing the indole-2-carboxaldehyde in place of pyrrole-2-carboxaldehyde. The required substrate **6c**–**e** were prepared following the literature procedure.[14b] Treating **6c**–**e** with aq LiOH produced the corresponding acid **7c**–**e** (Scheme 3). Similar set of reactions as described earlier with **7c**–**e** afforded the required pyrazino[1,2-*a*]indoles (**8c**–**e**) in 79–85% yields.



Scheme 3. Reagents and conditions. (i) Ref. 14b. (ii) LiOH, THF/H_2O (1:1, v/v), rt, 6–8 h; (iii) (a) $ClCO_2Et$, NMM, THF, 0 °C, 10 min; (b) NaN_3, 30 min; (c) PhMe, 65 °C, 30 min; (d) Formic acid, DMAP, CH_2Cl_2, rt, 2 h.

Mechanistic considerations generated interest to study the fate of the Curtius reaction in the absence of the formyl group in the system. For this objective compounds **9c**,**f** were prepared by reacting the allyl bromide **5c**,**f** with indole. Hydrolysis of **5c**,**f** gave corresponding acid **10c**,**f**, which upon similar series of reactions afforded products, which were identified as ketones **11c**,**f** (Scheme 4). The formation of the ketone can be rationalized on the basis that the generated enamine is unstable under the reaction conditions and is readily oxidized to furnish the ketone. The formation of ketone was chemically ascertained by reacting **11c** with hydroxylamine to produce the oxime **12** as diastereomeric mixture.



Scheme 4. Reagents and conditions: (i) Indole, TBAB, 50% aq NaOH, PhMe, rt, 3–4 h; (ii) LiOH, THF/H_2O (1:1, v/v), rt, 6 h; (iii) (a) $ClCO_2Et$, NMM, THF, 0 °C, 10 min; (b) NaN_3, 30 min; (c) PhMe, 65 °C, 30 min; (iv) Formic acid, DMAP, CH_2Cl_2, rt, 2 h; (iv) $NH_2OH.HCl$, NaOAc, MeOH, reflux, 2 h.

3. Conclusions

In summary we have developed a new protocol for the synthesis of pyrrolo[1,2-*a*]pyrazines and pyrazino[1,2-*a*]indoles via saponification followed by Curtius reaction in the MBH derivatives. This work further showcase the significance of the MBH derivatives in the realm of heterocyclic chemistry. Additionally, this route can also be employed for installing substitution containing β-keto group in the azoles.

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 a Perkin–Elmer's 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 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS were recorded on MICROMASS Quadro-II LCMS system. The HRMS were recorded as ESI or DART on a suitable mass spectrometer. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL *III* microanalyzer. All yields described herein are the isolated yields after column chromatography. Intermediate azides and isocyanates were used without purification and therefore no corresponding spectroscopic data exist. Spectroscopic data for previously reported derivatives in Ref. 14 are not included.

4.2. General procedure for the preparation of compound 2a–i as exemplified for 2a

To a stirred solution of compound **1b** (1.0 g, 3.2 mmol) in DMF (10 mL), pyrrole-2-carboxaldehyde (0.34 g, 3.5 mmol) and K_2CO_3 (0.67 g, 4.8 mmol) were added and reaction was continued at rt for 3.0 h. After completion, EtOAc (20 mL) and water (50 mL) were added and the mixture was partitioned in separating funnel. The organic layers were collected and the aq layer was extracted with

EtOAc (3×20 mL). The organic layers were combined and washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Purification by column chromatography on silica gel (hexanes/EtOAc, 19:1) led to furnish 1.07 g of pure **2b** as a white solid (86%).

*4.2.1. Methyl (E)-3-(2-bromophenyl)-2-[(2-formyl-1H-pyrrol-1-yl) methyl]prop-2-enoate (**2b**).* Mp 184–185 °C; R_f=0.48 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1661 (CHO), 1701 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.79 (s, 3H, OCH_3), 5.37 (s, 2H, CH_2), 6.17 (dd, 1H, J_1=2.6 Hz, J_2=3.9 Hz, ArH), 6.87–6.91 (m, 2H, ArH), 7.08–7.10 (m, 1H, ArH), 7. 18–7.29 (m, 2H, ArH), 7.61 (dd, 1H, J_1=0.9 Hz, J_2=7.6 Hz, ArH), 8.00 (s, 1H, =CH), 9.49 (d, 1H, J=0.7 Hz, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=44.5, 52.6, 110.1, 123.9, 124.7, 127.6, 129.3, 129.7, 129.8, 130.6, 131.8, 133.0, 134.9, 143.7, 166.8, 179.6; mass (ES^+) m/z=347.9 (M^++1); Anal. Calcd for: $C_{16}H_{14}BrNO_3$ (Exact mass: 347.0157); C, 55.19; H, 4.05; N, 4.02. Found C, 55.01; H, 3.88; N, 4.22.

*4.2.2. Methyl (E)-3-(2-chlorophenyl)-2-[(2-formyl-1H-pyrrol-1-yl) methyl]prop-2-enoate (**2c**).* Yield 79% as a yellow solid (0.45 g from 0.5 g); mp 78–80 °C R_f=0.46 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1662 (CHO), 1713 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.79 (s, 3H, OCH_3), 5.38 (s, 2H, CH_2), 6.17 (t, 1H, J=3.1 Hz, ArH), 6.88–6.91 (m, 2H, ArH), 7.10 (d, 1H, J=7.2 Hz, ArH), 7. 20–7.32 (m, 2H, ArH), 7.43 (d, 1H, J=7.7 Hz, ArH), 8.07 (s, 1H, =CH), 9.49 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ=44.8, 52.6, 110.2, 124.8, 127.0, 129.1, 129.6, 129.8, 129.9, 130.6, 131.9, 133.0, 134.1, 141.7, 166.9, 179.6; mass (ES^+) m/z=304.1 (M^++1); Anal. Calcd for: $C_{16}H_{14}ClNO_3$ (Exact mass: 303.0662); C, 63.27; H, 4.65; N, 4.61. Found C, 63.41; H, 4.49; N, 4.75.

*4.2.3. Methyl (E)-3-(2,4-dichlorophenyl)-2-[(2-formyl-1H-pyrrol-1-yl)methyl]prop-2-enoate (**2e**).* Yield 76% as a yellow solid (0.42 g from 0.5 g); mp 82–84 °C; R_f=0.47 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1659 (CHO), 1715 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.81 (s, 3H, OCH_3), 5.24 (s, 2H, CH_2), 6.04 (t, 1H, J=6.1 Hz, ArH), 6.78 (d, 1H, J=2.4 Hz, ArH), 6.86 (s, 1H, ArH), 7.20 (t, 1H, J=7.9 Hz, ArH), 7. 30–7.33 (m, 2H, ArH), 7.65 (s, 1H, =CH), 9.41 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ=45.3, 52.6, 109. 9, 124.4, 128.1, 130.2, 130.9, 131.6, 132.4, 133.2, 134.3, 137.1, 166.3, 179.3; mass (ES^+) m/z=338.1 (M^++1); Anal. Calcd for: $C_{16}H_{13}Cl_2NO_3$ (Exact mass: 337.0272); C, 56.82; H, 3.87; N, 4.14. Found C, 56.80; H, 4.11; N, 3.89.

*4.2.4. Methyl (E)-2-[(2-formyl-1H-pyrrol-1-yl)methyl]-3-(4-methylphenyl)prop-2-enoate (**2f**).* Yield 82% as a white solid (0.47 g from 0.5 g); mp 79–80 °C; R_f=0.45 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1655 (CHO), 1710 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.35 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.47 (s, 2H, CH_2), 6.20 (dd, 1H, J_1=2.6 Hz, J_2=3.8 Hz, ArH), 6.95–6.97 (m, 2H, ArH), 7.16 (s, 4H, ArH), 8.05 (s, 1H, =CH), 9.59 (d, 1H, J=0.7 Hz, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.5, 45.4, 52.5, 110.0, 124.9, 125.5, 129.1, 129.5, 129.7, 131.2, 132.0, 140.0, 145.5, 167.7, 179.7; mass (ES^+) m/z=283.9 (M^++1); Anal. Calcd for: $C_{17}H_{17}NO_3$ (Exact mass: 283.1208); C, 72.07; H, 6.05; N, 4.94. Found C, 72.25; H, 6.16; N, 4.78.

*4.2.5. Methyl (E)-3-(4-cyanophenyl)-2-[(2-formyl-1H-pyrrol-1-yl) methyl]prop-2-enoate (**2g**).* Yield 70% as a yellow solid (0.4 g from 0.5 g); mp 65–66 °C R_f=0.49 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1665 (CHO), 1720 (CO_2Me), 2226 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.80 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2), 6.20 (s, 1H, ArH), 6.90–6.93 (m, 2H, ArH), 7.33 (d, 2H, J=7.0 Hz, ArH), 7.65 (d, 2H, J=6.4 Hz, ArH), 7.98 (s, 1H, =CH), 9.52 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=44.9, 52.8, 110.3, 113.0, 118.3, 125.2, 129.6, 129.7, 130.0, 131.8, 131.9, 132.5, 138.7, 142.3, 166.8, 179.7; mass (ES^+) m/z=294.9 (M^++1); Anal. Calcd for: $C_{17}H_{14}N_2O_3$ (Exact mass: 294.1004); C, 69.38; H, 4.79; N, 9.52. Found C, 69.46; H, 4.66; N, 9.67.

*4.2.6. Methyl (E)-3-(2-fluorophenyl)-2-[(2-formyl-1H-pyrrol-1-yl) methyl]prop-2-enoate (**2h**).* Yield 75% as oil (0.43 g from 0.5 g); R_f=0.47 (hexanes/EtOAc, 80:20, v/v); ν_{max} (Neat) 1659 (CHO), 1720 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.77 (s, 3H, OCH_3), 5.41 (s, 2H, CH_2), 6.18 (dd, 1H, J_1=2.7 Hz, J_2=3.8 Hz, ArH), 6.91–6.93 (m, 2H, ArH), 7.11–7.14 (m, 3H, ArH), 7.32–7.39 (m, 1H, ArH), 8.02 (s, 1H, =CH), 9.52 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ=45.3, 52.6, 110.1, 115.9, 116.2, 124.46, 124.51, 124.9, 129.6, 129.8, 129.9, 130.0, 131.5, 131.6, 131.9, 137.46, 137.51, 158.8, 166.9, 179.6; mass (ES^+) m/z=288.2 (M^++1). Anal. Calcd for: $C_{16}H_{14}FNO_3$ (Exact mass: 287.0958); C, 66.89; H, 4.91; N, 4.88. Found C, 67.02; H, 4.94; N, 4.71.

*4.2.7. Methyl (E)-3-(4-fluorophenyl)-2-((2-formyl-1H-pyrrol-1-yl) methyl) prop-2-enoate (**2i**).* Yield 73% as a yellow oil (0.66 g from 0.8 g); R_f=0.49 (hexanes/EtOAc, 80:20, v/v); ν_{max} (Neat) 1656 (CHO), 1712 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.79 (s, 3H, OCH_3), 5.45 (s, 2H, CH_2), 6.20–6.23 (m, 1H, ArH), 6.93–6.98 (m, 2H, ArH), 7.02–7.08 (m, 2H, ArH), 7.22–7.26 (m, 2H, ArH), 8.02 (s, 1H, =CH), 9.58 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=45.2, 52.6, 110.1, 111.4, 116.1, 116.3, 125.1, 126.5, 129.2, 130.2, 130.3, 131.4, 131.5, 131.9, 144.1, 161.9, 165.2, 167.5, 179.8; mass (ES^+) m/z=288.1 (M^++1); Anal. Calcd for: $C_{16}H_{14}FNO_3$ (Exact mass: 287.0958); C, 66.89; H, 4.91; N, 4.88. Found C, 67.10; H, 5.11; N, 4.67.

4.3. General procedure for the preparation of compounds 3a–i, 7c–e and 10c,f as exemplified by 3a

To a stirred solution of compound **2a** (0.5 g, 1.7 mmol) in THF/H_2O(1:1, v/v) (20 mL), LiOH (0.2 g, 8.3 mmol) was added and stirred at rt for 8 h. After completion of the reaction, reaction mixture was acidified with 50% HCl and EtOAc (20 mL) was added and layers were separated. The aq layer was again extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product on recrystallization with hexanes/EtOAc yielded 0.43 g of pure **3a** as a white solid (90%).

*4.3.1. (E)-2-[(2-Formyl-1H-pyrrol-1-yl)methyl]-3-phenylprop-2-enoic acid (**3a**).* Mp 136–137 °C; R_f=0.23 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1663 (CHO and CO_2H), 3413 (OH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=5.28 (s, 2H, CH_2), 6.23 (dd, 1H, J_1=2.6 Hz, J_2=3.9 Hz, ArH), 7.06–7.09 (m, 2H, ArH), 7.31–7.42 (m, 5H, ArH), 8.00 (s, 1H, =CH), 9.54 (d, 1H, J=0.8 Hz, CHO), 12.97 (br s, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6) δ=44.8, 109.9, 124.2, 127.2, 128.9, 129.1, 129.3, 129.6, 131.6, 134.1, 143.8, 167.9, 179.7; mass (ES^+) m/z=256.1 (M^++1); Anal. Calcd for: $C_{15}H_{13}NO_3$ (Exact mass: 255.0895); C, 70.58; H, 5.13; N, 5.49. Found C, 70.74; H, 5.20; N, 5.66.

*4.3.2. (E)-3-(2-Bromophenyl)-2-[(2-formyl-1H-pyrrol-1-yl)methyl] prop-2-enoic acid (**3b**).* Yield 90% as a white solid (0.52 g from 0.6 g); mp 73–74 °C; R_f=0.19 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1654 (CHO), 1689 (CO_2H), 3412 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=5.38 (s, 2H, CH_2), 6.17–6.19 (m, 1H, ArH), 6.89–6.90 (m, 1H, ArH), 6.94 (s, 1H, ArH), 7.09–7.11 (m, 1H, ArH), 7.20–7.30 (m, 2H, ArH), 7.61–7.65 (m, 1H, ArH), 8.13 (s, 1H, =CH), 9.48 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=44.5, 110.4, 124.0, 125.2, 127.7, 128.6, 129.8, 130.1, 130.9, 131.8, 133.1,

134.7, 145.7, 171.1, 179.9; mass (ES^+) m/z=334.1 (M^++1); DART-HRMS calcd for $C_{15}H_{13}BrNO_3$ $[MH]^+$: 334.0079. Found: 334.0076.

*4.3.3. (E)-3-(2-Chlorophenyl)-2-[(2-formyl-1H-pyrrol-1-yl)methyl] prop-2-enoic acid (**3c**).* Yield 92% as a yellow solid (0.44 g from 0.5 g); mp 84–85 °C; R_f=0.18 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1659 (CHO), 1676 (CO_2H), 3414 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=5.38 (s, 2H, CH_2), 6.19 (dd, 1H, J_1=2.6 Hz, J_2=4.0 Hz, ArH), 6.91 (dd, 1H, J_1=1.7 Hz, J_2=4.0 Hz, ArH), 6.95 (s, 1H, ArH), 7.10 (d, 1H, J=7.5 Hz, ArH), 7.22 (dt, 1H, J_1=1.1 Hz, J_2=7.5 Hz, ArH), 7.31 (dt, 1H, J_1=1.4 Hz, J_2=7.6 Hz, ArH), 7.43 (dd, 1H, J_1=1.1 Hz, J_2=8.0 Hz, ArH), 8.21 (s, 1H, =CH), 9.49 (d, 1H, J=0.9 Hz, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=44.7, 110.3, 125.2, 127.1, 129.8, 130.0, 130.1, 130.8, 131.1, 131.8, 132.9, 134.2, 143.5, 163.9, 179.9; mass (ES^+) m/z=290.1 (M^++1); Anal. Calcd for: $C_{15}H_{12}ClNO_3$ (Exact mass: 289.0506); C, 62.19; H, 4.17; N, 4.83. Found C, 62.20; H, 4.32; N, 4.65.

*4.3.4. (E)-3-(4-Chlorophenyl)-2-[(2-formyl-1H-pyrrol-1-yl)methyl] prop-2-enoic acid (**3d**).* Yield 89% as a white solid (0.42 g from 0.5 g); mp 184–185 °C; R_f=0.19 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1661 (CHO), 1685 (CO_2H), 3412 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=5.45 (s, 2H, CH_2), 6.24 (dd, 1H, J_1=2.6 Hz, J_2=3.8 Hz, ArH), 6.97–7.00 (m, 2H, ArH), 7.21 (d, 2H, J=8.4 Hz, ArH), 7.36 (d, 2H, J=8.4 Hz, ArH), 8.12 (s, 1H, =CH), 9.58 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ=45.2, 109.9, 125.0, 127.4, 128.7, 129.0, 129.3, 130.5, 131.0, 131.6, 132.6, 135.6, 143.7, 168.8, 179.6; mass (ES^+) m/z=290.1 (M^++1); Anal. Calcd for: $C_{15}H_{12}ClNO_3$ (Exact mass: 289.0506); C, 62.19; H, 4.17; N, 4.83. Found C, 62.26; H, 3.96; N, 4.97.

*4.3.5. (E)-3-(2,4-Dichlorophenyl)-2-((2-formyl-1H-pyrrol-1-yl) methyl)acrylic acid (**3e**).* Yield 92% as a white solid (0.44 g from 0.5 g); mp 185–186 °C; R_f=0.18 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1665 (CHO and CO_2H), 3422 (OH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=5.21 (s, 2H, CH_2), 6.13 (dd, 1H, J_1=2.5 Hz, J_2=3.9 Hz, ArH), 6.92–6.93 (m, 1H, ArH), 7.03 (s, 1H, ArH), 7.22 (d, 1H, J=8.1 Hz, ArH), 7.40–7.43 (m, 1H, ArH), 7.68 (d, 1H, J=1.8 Hz, ArH), 7.75 (s, 1H, =CH), 9.40 (s, 1H, CHO), 12.97 (br s, 1H, COOH); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6) δ=44.0, 109.3, 123.8, 126.5, 128.7, 129.2, 129.8, 130.0, 130.8, 131.0, 133.8, 134.6, 138.8, 167.0, 178.5; mass (ES^+) m/z=323.8 (M^++1); Anal. Calcd for: $C_{15}H_{11}Cl_2NO_3$ (Exact mass: 323.0116); C, 55.58; H, 3.42; N, 4.32. Found C, 55.67; H, 3.50; N, 4.51.

*4.3.6. (E)-2-[(2-Formyl-1H-pyrrol-1-yl)methyl]-3-(4-methylphenyl) prop-2-enoic acid (**3f**).* Yield 89% as a white solid (0.42 g from 0.5 g); mp 159–160 °C; R_f=0.19 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1661 (CHO and CO_2H), 3435 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.36 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 6.23 (t, 1H, J=3.2 Hz, ArH), 7.00 (d, 2H, J=3.2 Hz, ArH), 7.18 (s, 4H, ArH), 8.17 (s, 1H, =CH), 9.60 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.6, 45.3, 110.2, 124.6, 125.3, 129.3, 129.8, 129.9, 131.0, 131.9, 140.9, 147.7, 172.3, 179.9; mass (ES^+) m/z=270.1 (M^++1); DART-HRMS calcd for $C_{16}H_{16}NO_3$ $[MH]^+$: 270.1130. Found: 270.1143.

*4.3.7. (E)-3-(4-Cyanophenyl)-2-[(2-formyl-1H-pyrrol-1-yl)methyl] prop-2-enoic acid (**3g**).* Yield 88% as a yellow solid (0.42 g from 0.5 g); mp 175–176 °C; R_f=0.20 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1660 (CHO and CO_2H), 2230 (CN), 3432 (OH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=5.27 (s, 2H, CH_2), 6.19 (d, 1H, J=2.7 Hz, ArH), 7.00 (d, 1H, J=2.5 Hz, ArH), 7.09 (s, 1H, ArH), 7.50 (d, 2H, J=8.0 Hz, ArH), 7.84 (d, 2H, J=8.0 Hz, ArH), 7.92 (s, 1H, =CH), 9.45 (s, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6) δ=44.6, 109.9, 111.5, 118.7, 124.3, 129.8, 130.4, 130.5, 131.5, 132.5, 139.1, 141.0, 167.5, 179.6; mass (ES^+) m/z=281.1 (M^++1); Anal. Calcd for: $C_{16}H_{12}N_2O_3$ (Exact mass: 280.0848); C, 68.56; H, 4.32; N, 9.99. Found C, 68.39; H, 4.45; N, 10.20.

*4.3.8. (E)-3-(2-Fluorophenyl)-2-[(2-formyl-1H-pyrrol-1-yl)methyl] prop-2-enoic acid (**3h**).* Yield 91% as a white solid (0.43 g from 0.5 g); mp 129–130 °C; R_f=0.19 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1659 (CHO and CO_2H), 3432 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=5.41 (s, 2H, CH_2), 6.20 (dd, 1H, J_1=3.0 Hz, J_2=3.7 Hz, ArH), 6.93–6.97 (m, 2H, ArH), 7.09–7.14 (m, 3H, ArH), 7. 34–7.40 (m, 1H, ArH), 8.15 (s, 1H, =CH), 9.51 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ=45.2, 110.2, 116.0, 116.3, 122.0, 122.2, 124.6, 125.3, 128.7, 130.0, 130.1, 131.9, 132.0, 139.6, 159.3, 161.8, 171.4, 179.9; mass (ES^+) m/z=274.1 (M^++1); Anal. Calcd for: $C_{15}H_{12}FNO_3$ (Exact mass: 273.0801); C, 65.93; H, 4.43; N, 5.13. Found C, 66.11; H, 4.60; N, 5.19.

*4.3.9. (E)-3-(4-Fluorophenyl)-2-((2-formyl-1H-pyrrol-1-yl)methyl) acrylic acid (**3i**).* Yield 90% as a white solid (0.43 g from 0.5 g); R_f=0.18 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1660 (CHO and CO_2H), 3434 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=5.48 (s, 2H, CH_2), 6.23 (t, 1H, J=3.2 Hz, ArH), 6.99 (d, 2H, J=3.3 Hz, ArH), 7.26–7.30 (m, 2H, ArH), 7.34–7.39 (m, 3H, ArH), 8.19 (s, 1H, =CH), 9.58 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=44.3, 109.5, 115.3, 115.8, 124.7, 128.6, 129.1, 129.2, 130.8, 131.0, 160.5, 165.5, 171.3, 179.2; mass (ES^+) m/z=274.1 (M^++1); Anal. Calcd for: $C_{15}H_{12}FNO_3$ (Exact mass: 273.0801); C, 65.93; H, 4.43; N, 5.13. Found C, 66.19; H, 4.66; N, 5.31.

*4.3.10. (E)-3-(2-Chlorophenyl)-2-[(2-formyl-3-methyl-1H-indol-1-yl)methyl]prop-2-enoic acid (**7c**).* Yield 92% as a yellow solid (0.35 g from 0.4 g); mp 184–185 °C; R_f=0.20 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1661 (CHO), 1696 (CO_2H), 3426 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.49 (s, 3H, CH_3), 5.69 (s, 2H, CH_2), 6.99–7.09 (m, 4H, ArH), 7.12–7.17 (m, 1H, ArH), 7.28–7.30 (m, 2H, ArH), 7.52 (d, 1H, J=8.0 Hz, ArH), 7.93 (s, 1H, =CH), 10.00 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ=8.3, 41.5, 111.1, 120.0, 120.8, 125.9, 126.2, 126.8, 126.9, 128.9, 129.2, 129.9, 131.0, 131.6, 132.9, 133.1, 138.1, 138.9, 168.1, 181.5; mass (ES^+) m/z=354.1 (M^++1); DART-HRMS calcd for $C_{20}H_{17}ClNO_3$ $[MH]^+$: 354.0897. Found: 354.0908.

*4.3.11. (E)-3-(4-Chlorophenyl)-2-[(2-formyl-3-methyl-1H-indol-1-yl)methyl]prop-2-enoic acid (**7d**).* Yield 90% as a yellow solid (0.43 g from 0.5 g); mp 181–182 °C; R_f=0.21(hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1664 (CHO), 1691 (CO_2H), 3423 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=2.52 (s, 3H, CH_3), 5.76 (s, 2H, CH_2), 6.89 (d, 1H, J=8.4 Hz, ArH), 7.07–7.10 (m, 3H, ArH), 7.23–7.28 (m, 3H, ArH), 7.58 (d, 1H, J=8.0 Hz, ArH), 7.87 (s, 1H, =CH), 10.01 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.6, 41.3, 111.0, 120.5, 121.5, 127.5, 128.6, 129.4, 130.0, 131.3, 132.7, 135.0, 139.3, 142.2, 170.7, 181.8; mass (ES^+) m/z=354.1 (M^++1); DART-HRMS calcd for $C_{20}H_{17}ClNO_3$ $[MH]^+$: 354.0897. Found: 354.0905.

*4.3.12. (E)-3-(2,4-Dichlorophenyl)-2-[(2-formyl-3-methyl-1H-indol-1-yl)methyl]prop-2-enoic acid (**7e**).* Yield 87% as a yellow solid (0.42 g from 0.5 g); mp 152–153 °C; R_f=0.18 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1659 (CHO), 1693 (CO_2H), 3447 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ=2.47 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 6.80–6.87 (m, 2H, ArH), 7.04–7.16 (m, 3H, ArH), 7.26–7.31 (m, 1H, ArH), 7.50 (d, 1H, J=7.8 Hz, ArH), 7.64 (s, 1H, = CH), 9.97 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ=7.6, 41.1, 110.2, 119.5, 120.1, 125.3, 125.5, 126.0, 126.3, 127.5, 129.6 130.0, 130.8, 132.0, 132.5, 133.3, 135.4, 138.1, 167.0, 180.5; mass (ES^+) m/z=388.0 (M^++1); Anal. Calcd for: $C_{20}H_{15}Cl_2NO_3$ (Exact

mass: 387.0429); C, 61.87; H, 3.89; N, 3.61. Found C, 62.03; H, 4.11; N, 3.43.

*4.3.13. (E)-3-(2-Chlorophenyl)-2-(1H-indol-1-ylmethyl)prop-2-enoic acid (**10c**).* Yield 92% as a white solid (0.44 g from 0.5 g); mp 119–120 °C; R_f=0.17 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1691 (CO_2H), 3426 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=5.04 (s, 2H, CH_2), 6.46 (d, 1H, J=4.8 Hz, CH_2), 6.98–7.17 (m, 4H, ArH), 7.20–7.28 (m, 2H, ArH), 7.31–7.40 (m, 1H, ArH), 7.49–7.60 (m, 2H, ArH), 8.20 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=42.2, 101.9, 109.7, 119.7, 121.0, 121.7, 127.2, 127.5, 128.8, 129.1, 130.19, 130.22, 131.0, 132.9, 134.4, 136.2, 143.2, 172.2; mass (ES^+) m/z=312.1 (M^++1); Anal. Calcd for: $C_{18}H_{14}ClNO_2$ (Exact mass: 311.0713); C, 69.35; H, 4.53; N, 4.49. Found: C, 69.42; H, 4.67; N, 4.71.

*4.3.14. (E)-2-(1H-Indol-1-ylmethyl)-3-(4-methylphenyl)prop-2-enoic acid (**10f**).* Yield 91% as a white solid (0.43 g from 0.5 g); mp 160–161 °C; R_f=0.16 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1669 (CO_2H), 3430 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=2.38 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 6.47 (d, 1H, J=3.1 Hz, CH_2), 7.08–7.15 (m, 4H, ArH), 7.20 (d, 2H, J=8.0 Hz, ArH), 7.27 (d, 2H, J=8.4 Hz, ArH), 7.62 (m, 2H, J=7.6 Hz, ArH), 8.16 (s, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.6, 42.3, 101.6, 109.8, 119.7, 121.1, 121.7, 125.6, 127.1, 129.0, 129.88, 129.92, 131.4, 136.3, 140.7, 146.8, 172.3; mass (ES^+) m/z=292.0 (M^++1); DART-HRMS calcd for $C_{19}H_{18}NO_2$ $[MH]^+$: 292.1338. Found: 292.1345.

4.4. General procedure for the preparation of compound 4a–i, 8c–e and 11c,f

A stirred solution of compound **3a** (0.25 g, 0.83 mmol) in THF (10 mL) was cool to −10 °C and then ethyl chloroformate (0.09 mL, 0.92 mmol) and NMM (0.10 mL, 0.92 mmol) were added. After 5 min NaN_3 (80 mg, 1.25 mmol) dissolved in 0.1 mL of water was added to it and stirred for 30 min. After completion of the reaction water (20 mL) and EtOAc (10 mL) were added, layers were separated and aq layer was further extracted with EtOAc (2×10 mL). The organic layer were pooled and washed with brine solution (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was dissolved in toluene (10 mL) and heated at 65 °C for 30 min. Thereafter toluene was removed under reduced pressure and the crude reaction mixture was dissolved in CH_2Cl_2 (10 mL) and 98% formic acid (0.08 mL, 1.70 mmol) and DMAP (0.003 g, 0.25 mmol) were added and the mixture stirred for 4 h. The reaction mixture was quenched with water (20 mL) and layers were separated. The aq layer was further extracted with CH_2Cl_2 (2×15 mL). The organic layers were combined, washed with brine solution (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude product. Purification by column chromatography on silica gel (hexanes/EtOAc, 9:1) led to 0.12 g of pure **4a** as dark brown oil (75%).

*4.4.1. 3-Benzylpyrrolo[1,2-a]pyrazine (**4a**).* R_f=0.47 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=4.03 (s, 2H, CH_2), 6.73 (d, 1H, J=4.0 Hz, ArH), 6.81 (t, 1H, J=3.2 Hz, ArH), 7.26–7.33 (m, 6H, ArH), 7.52 (s, 1H, ArH), 8.76 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=41.1, 103.5, 115.0, 116.0, 126.7, 128.8, 129.3, 138.8, 139.1, 144.8; mass (ES^+) m/z=209.1 (M^++1); ESI-HRMS calcd for $C_{14}H_{13}N_2$ $[MH]^+$: 209.1079. Found: 209.1066.

*4.4.2. 3-(2-Bromobenzyl)pyrrolo[1,2-a]pyrazine (**4b**).* Yield 76% as a brown solid (0.13 g from 0.2 g); mp 71–72 °C; R_f=0.49 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=4.17 (s, 2H, CH_2), 6.74 (d, 1H, J=3.8 Hz, ArH), 6.81–6.82 (m, 1H, ArH), 7.13 (t, 1H, J=6.9 Hz, ArH), 7.28–7.36 (m, 3H, ArH), 7.52 (s, 1H, ArH), 7.59 (d, 1H, J=7.9 Hz, ArH), 8.77 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=41.3, 103.4, 115.0, 116.3, 125.1, 127.6, 127.8, 128.5, 131.6, 133.1, 137.1, 138.5, 144.5; mass (ES^+) m/z=287.5 (M^++1); DART-HRMS calcd for $C_{14}H_{12}BrN_2$ $[MH]^+$: 287.0184. Found: 287.0198.

*4.4.3. 3-(2-Chlorobenzyl)pyrrolo[1,2-a]pyrazine (**4c**).* Yield 72% as brown oil (0.12 g from 0.2 g); R_f=0.50 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=4.16 (s, 2H, CH_2), 6.74 (s, 1H, ArH), 6.82 (s, 1H, ArH), 7.22–7.41 (m, 5H, ArH), 7.53 (s, 1H, ArH), 8.77 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=38.7, 103.3, 114.86, 114.95, 116.2, 127.1, 127.6, 128.2, 129.8, 131.5, 134.5, 136.8, 137.1, 144.9; mass (ES^+) m/z=243.2 (M^++1); ESI-HRMS calcd for $C_{14}H_{12}ClN_2$ $[MH]^+$: 243.0689. Found: 243.0700.

*4.4.4. 3-(4-Chlorobenzyl)pyrrolo[1,2-a]pyrazine (**4d**).* Yield 71% as dark brown oil (0.15 g from 0.25 g); R_f=0.48 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=3.99 (s, 2H, CH_2), 6.75 (d, 1H, J=3.6 Hz, ArH), 6.83 (s, 1H, ArH), 7.19–7.33 (m, 5H, ArH), 7.55 (s, 1H, ArH), 8.75 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=40.5, 103.6, 115.0, 115.1, 115.9, 128.9, 129.1, 130.6, 131.2, 132.5, 137.8, 138.3, 144.9; mass (ES^+) m/z=243.1 (M^++1); ESI-HRMS calcd for $C_{14}H_{12}Cl_1N_2$ $[MH]^+$: 243.0689. Found: 243.0685.

*4.4.5. 3-(2,4-Dichlorobenzyl)pyrrolo[1,2-a]pyrazine (**4e**).* Yield 78% as brown oil (0.13 g from 0.2 g); R_f=0.47 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=4.10 (s, 2H, CH_2), 6.76 (d, 1H, J=4.0 Hz, ArH), 6.84 (dd, 1H, J_1=2.5 Hz, J_2=4.0 Hz, ArH), 7.22 (dd, 1H, J_1=2.0 Hz, J_2=8.3 Hz, ArH), 7.26–7.30 (m, 1H, ArH), 7.34 (s, 1H, ArH), 7.41 (d, 1H, J=2.0 Hz, ArH), 7.56 (s, 1H, ArH), 8.76 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=36.5, 103.4, 114.9, 115.1, 128.6, 128.8, 134.7, 136.0, 136.6, 144.7; mass (ES^+) m/z=277.0 (M^++1); DART-HRMS calcd for $C_{14}H_{11}Cl_2N_2$ $[MH]^+$: 277.0299. Found: 277.0292.

*4.4.6. 3-(4-Methylbenzyl)pyrrolo[1,2-a]pyrazine (**4f**).* Yield 73% as brown oil (0.12 g from 0.2 g); R_f=0.49 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=2.33 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 6.72 (d, 1H, J=4.1 Hz, ArH), 6.80 (dd, 1H, J_1=2.5 Hz, J_2=4.0 Hz, ArH), 7.13 (d, 2H, J=7.9 Hz, ArH), 7.20 (d, 2H, J=8.0 Hz, ArH), 7.29 (s, 1H, ArH), 7.51 (s, 1H, ArH), 8.75 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.2, 39.6, 102.6, 114.0, 114.9, 126.5, 128.2, 128.4, 128.6, 128.7, 134.9, 135.2, 137.9, 143.6; mass (ES^+) m/z=223.2 (M^++1); ESI-HRMS calcd for $C_{15}H_{15}N_2$ $[MH]^+$: 223.1235. Found: 223.1253.

*4.4.7. 4-(Pyrrolo[1,2-a]pyrazin-3-ylmethyl)benzonitrile (**4g**).* Yield 69% as brown oil (0.12 g from 0.2 mg); R_f=0.48 (hexanes/EtOAc, 80:20, v/v); ν_{max} (Neat) 2229 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=4.05 (s, 2H, CH_2), 6.77 (d, 1H, J=3.8 Hz, ArH), 6.84–6.86 (m, 1H, ArH), 7.36 (m, 1H, ArH), 7.41 (d, 2H, J=8.0 Hz, ArH), 7.60 (d, 2H, J=8.1 Hz, ArH), 7.64 (s, 1H, ArH), 8.75 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=40.1, 103.7, 110.4, 110.5, 115.1, 115.2, 116.1, 119.0, 124.9, 127.4, 129.9, 130.7, 132.4, 137.0, 145.0; mass (ES^+) m/z=234.2 (M^++1); ESI-HRMS calcd for $C_{15}H_{12}N_3$ $[MH]^+$: 234.1031. Found: 234.1037.

*4.4.8. 3-(2-Fluorobenzyl)pyrrolo[1,2-a]pyrazine (**4h**).* Yield 72% as a brown solid (0.12 g from 0.2 g); mp 59–60 °C; R_f=0.53 (hexanes/EtOAc, 80:20, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=4.05 (s, 2H, CH_2), 6.73 (d, 1H, J=2.4 Hz, ArH), 6.80–6.82 (m, 1H, ArH), 7.02–7.12 (m, 2H, ArH), 7.20–7.24 (m, 1H, ArH), 7.32–7.35 (m, 2H, ArH), 7.58 (s, 1H, ArH), 8.75 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=34.17 (d, J=3.2 Hz), 103.3, 114.8, 114.9, 115.2, 115.7, 115.8, 124.2, 124.3, 126.1, 126.4, 127.5, 128.4, 128.5, 131.4, 131.5, 137.3, 144.7, 158.8, 163.6; mass (ES^+) m/z=227.1 (M^++1); DART-HRMS calcd for $C_{14}H_{12}F_1N_2$ $[MH]^+$: 227.0985. Found: 227.0952.

*4.4.9. 3-(4-Fluorobenzyl)pyrrolo[1,2-a]pyrazine (**4i**).* Yield 68% as dark brown oil (0.11 g from 0.2 g); R_f=0.51 (hexanes/EtOAc, 80:20,

v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.99 (s, 2H, CH_2), 6.74 (d, 1H, J=4.0 Hz, ArH), 6.82 (dd, 1H, J_1=2.5 Hz, J_2=4.0 Hz, ArH), 7.01 (t, 2H, J=8.7 Hz, ArH), 7.24–7.28 (m, 2H, ArH), 7.32 (s, 1H, ArH), 7.54 (s, 1H, ArH), 8.75 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=40.2, 103.8, 115.1, 115.2, 115.4, 115.7, 115.9, 127.5, 130.6, 130.7, 134.8, 138.5, 144.8, 160.2, 163.4; mass (ES^+) m/z=227.1 (M^++1); ESI-HRMS calcd for $C_{14}H_{12}F_1N_2$ $[MH]^+$: 227.0985. Found: 227.0991.

*4.4.10. 3-(2-Chloro-benzyl)-10-methyl-pyrazino[1,2-a]indole (**8c**).* Yield 79% as a yellow solid (0.15 g from 0.22 g); mp 110–112 °C; R_f=0.43 (hexanes/EtOAc, 80:20, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.63 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.21–7.26 (m, 2H, ArH), 7.36–7.42 (m, 4H, ArH), 7.78–7.85 (m, 3H, ArH), 8.98 (d, 1H, J=1.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=8.1, 38.6, 104.2, 110.8, 114.6, 120.4, 122.2, 122.9, 126.6, 127.1, 128.2, 128.5, 128.6, 129.7, 131.4, 133.1, 134.4, 137.1, 145.7; mass (ES^+) m/z=307.2 (M^++1). ESI-HRMS calcd for $C_{19}H_{16}ClN_2$ $[MH]^+$: 307.1002. Found: 307.1004.

*4.4.11. 3-(4-Chloro-benzyl)-10-methyl-pyrazino[1,2-a]indole (**8d**).* Yield 81% as a yellow solid (0.21 g from 0.3 g); mp 122–124 °C; R_f=0.45 (hexanes/EtOAc, 80:20, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.64 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 7.26–7.32 (m, 4H, ArH), 7.36–7.44 (m, 2H, ArH), 7.80–7.87 (m, 3H, ArH), 8.97 (d, 1H, J=1.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=8.2, 40.5, 104.4, 110.8, 114.2, 120.5, 122.4, 123.0, 126.6, 128.6, 128.7, 128.9, 130.5, 132.5, 134.5, 138.1, 145.9; mass (ES^+) m/z=307.2 (M^++1). ESI-HRMS calcd for $C_{19}H_{16}ClN_2$ $[MH]^+$: 307.1002. Found: 307.1006.

*4.4.12. 3-(2,4-Dichloro-benzyl)-10-methyl-pyrazino[1,2-a]indole (**8e**).* Yield 85% as a yellow solid (0.19 g from 0.25 mg); mp 162–163 °C; R_f=0.44 (hexanes/EtOAc, 80:20, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.64 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 7.22 (dd, 1H, J_1=2.0 Hz, J_2=8.3 Hz, ArH), 7.31 (d, 1H, J=8.2 Hz, ArH), 7.36–7.44 (m, 3H, ArH), 7.81–7.87 (m, 3H, ArH), 8.98 (d, 1H, J=1.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=8.2, 38.1, 104.5, 110.9, 114.8, 120.5, 122.4, 122.1, 126.6, 127.4, 128.6, 128.7, 129.5, 132.1, 132.7, 133.2, 135.1, 135.8, 145.9; mass (ES^+) m/z=341.2 (M^++1); ESI-HRMS calcd for $C_{19}H_{15}Cl_2N_2$ $[MH]^+$: 341.0612. Found: 341.0608.

*4.4.13. 1-(2-Chlorophenyl)-3-(1H-indol-1-yl)acetone (**11c**).* Yield 75% as a white solid (0.14 g from 0.2 g); mp 126–127 °C; R_f=0.48 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1725 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.71 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 6.60 (d, 1H, J=3.1 Hz, ArH), 7.05–7.14 (m, 2H, ArH), 7.16–7.25 (m, 5H, ArH), 7.36–7.39 (m, 1H, ArH), 7.65 (d, 1H, J=7.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=44.5, 55.4, 103.0, 109.0, 120.2, 121.4, 122.4, 127.2, 128.5, 128.9, 129.1, 129.7, 131.9, 134.4, 136.6, 202.6; mass (ES^+) m/z=284.1 (M^++1); ESI-HRMS calcd for $C_{17}H_{15}ClNO$ $[MH]^+$: 284.0842. Found: 284.0774.

*4.4.14. 1-(1H-Indol-1-yl)-3-(4-methylphenyl)acetone (**11f**).* Yield 76% as a white solid (0.14 g from 0.2 g); mp 89–90 °C; R_f=0.46 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1725 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.34 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 4.84 (s, 2H, CH_2), 6.58 (d, 1H, J=3.0 Hz, ArH), 6.97–7.05 (m, 4H, ArH), 7.11–7.21 (m, 4H, ArH), 7.65 (d, 1H, J=7.3 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.2, 46.4, 54.7, 102.9, 109.0, 120.1, 121.4, 122.3, 128.6, 128.8, 129.4, 129.7, 129.9, 136.5, 137.2, 203.9; mass (ES^+) m/z=264.1 (M^++1); ESI-HRMS calcd for $C_{18}H_{18}NO$ $[MH]^+$: 264.1388. Found: 264.1345.

4.5. Typical procedure for the synthesis of compound 12

To a stirred solution of compound **11c** (0.1 g, 0.35 mmol), in EtOH (15 mL) was added $NH_2OH{\cdot}HCl$ (0.03 g, 0.42 mmol) and NaOAc (0.035 g, 0.42 mmol) and stirred at reflux temperature for 2 h. Thereafter, EtOH was evaporated and residue was extracted with EtOAc (3×15 mL) and water (30 mL). The organic layers were combined, washed with brine solution (20 mL) and dried over Na_2SO_4 and concentrated under reduced pressure to afford 0.086 g of pure **12** as white solid (82%).

*4.5.1. 1-(2-Chlorophenyl)-3-(1H-indol-1-yl)acetone oxime (diastereomeric mixture 2:1) (**12**).* Mp 105–106 °C; R_f=0.41 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 3292 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.30 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.47 (d, 1H, J=3.0 Hz, ArH), 6.53 (d, 1H, J=3.2 Hz, ArH), 6.87 (d, 1H, J=3.2 Hz, ArH), 6.98–7.07 (m, 2H, ArH), 7.07–7.23 (m, 8H, ArH), 7.28–7.32 (m, 1H, ArH), 7.37 (d, 1H, J=7.9 Hz, ArH), 7.59 (d, 1H, J=7.2 Hz, ArH), 7.64 (d, 1H, J=7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=30.0, 34.9, 42.5, 48.6, 102.3, 102.5, 109.5, 109.8, 119.8, 120.0, 121.1, 121.2, 122.0, 122.3, 126.9, 127.2, 128.2, 128.5, 128.7, 128.8, 128.9, 129.71, 129.74, 131.1, 131.2, 133.3, 133.8, 134.3, 134.5, 136.5, 136.6, 154.9, 156.0; mass (ES^+) m/z=299.1 (M^++1); Anal. Calcd. For: $C_{17}H_{15}ClN_2O$ (Exact mass: 298.087); C, 68.34; H, 5.06; N, 9.38. Found: C, 68.52; H, 5.17; N, 9.16.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.07.074. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Arban, R.; Bianchi, F.; Buson, A.; Cremonesi, S.; Di Fabio, R.; Gentile, G.; Micheli, F.; Pasquarello, A.; Pozzan, A.; Tarsi, L.; Terreni, S.; Tonelli, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5044–5049.
2. Fong, C. J.; Addo, J.; Dukat, M.; Smith, C.; Mitchell, N. A.; Herrick-Davis, K.; Teitler, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 155–158.
3. Micheli, F.; Bertani, B.; Bozzoli, A.; Crippa, L.; Cavanni, P.; Di Fabio, R.; Donati, D.; Marzorati, P.; Merlo, G.; Paio, A.; Perugini, L.; Zarantonello, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1804–1809.
4. Fisher, T. E.; Kim, B.; Staas, D. D.; Lyle, T. A.; Young, S. D.; Vacca, J. P.; Zrada, M. M.; Hazuda, D. J.; Felock, P. J.; Schleif, W. A.; Gabryelski, L. J.; Anari, M. R.; Kochanskyd, C. J.; Wai, J. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6511–6515.
5. (a) Rault, S.; Lancelot, J. C.; Prunier, H.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D. H.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1996**, *39*, 2068–2080; (b) Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Valle, F. D.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362–4379.
6. Ruppelt, M.; Bartel, S.; Guarnieri, W.; Raddatz, S.; Rosentreter, U.; Wild, H.; Endermann, R.; Kroll, H. P. Ger. Offen. DE 19802235, 1999; *Chem. Abstr.* **1999**, *131*, 129985.
7. Goldberg, D. R.; Choi, Y.; Cogan, D.; Corson, M.; DeLeon, R.; Gao, A.; Gruenbaum, L.; Hao, M. H.; Joseph, D.; Kashem, M. A.; Miller, C.; Moss, N.; Netherton, M. R.; Pargellis, C. P.; Pelletier, J.; Sellati, R.; Skow, D.; Torcellini, C.; Tseng, Y.-C.; Wang, J.; Wasti, R.; Werneburg, B.; Wua, J. P.; Xiong, Z. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 938–941.
8. Tiwari, R. K.; Singh, D.; Singh, J.; Yadav, V.; Pathak, A. K.; Dabur, R.; Chhillar, A. K.; Singh, R.; Sharma, G. L.; Chandra, R.; Verma, A. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 413–416.
9. Rover, S.; Adams, D. R.; Bénardeau, A.; Bentley, J. M.; Bickerdike, M. J.; Bourson, A.; Cliffe, I. A.; Coassolo, P.; Davidson, J. E. P.; Dourish, C. T.; Hebeisen, P.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mattei, P.; Misra, A.; Mizrahi, J.; Muller, M.; Porter, R. H. P.; Richter, H.; Taylor, S.; Vickers, S. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3604–3608.
10. Only a few citations. (a) For pyrrolo[1,2-*a*]pyrazine see Chen, W.; Hu, M.; Wu, J.; Zou, H.; Yu, Y. *Org. Lett.* **2010**, *12*, 3863–3865; (b) Alfonsi, M.;

Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, *17*, 2852–2862; (c) Mınguez, J. M.; Castellote, M. I.; Vaquero, J. J.; García-Navio, J. L.; Alvarez-Builla, J.; Castano, O.; Andres, J. L. *J. Org. Chem.* **1996**, *61*, 4655–4664; (d) For indolo[1,2-*a*]pyrazine see Laliberte, S.; Dornan, P. K.; Chen, A. *Tetrahedron Lett.* **2010**, *51*, 363–366; (e) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola, S. *J. Org. Chem.* **2005**, *70*, 4088–4095.

11. (a) Basavaiah, D.; Reddy, B. S.; Singh, B. S. *Chem. Rev.* **2010**, *110*, 5447–5674 and references cited therein; (b) Gowrisankar, S.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2009**, *65*, 8769–8780; (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574 and references cited therein.
12. (a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48 and references cited therein; (b) Zhong, W.; Liu, Y.; Wang, G.; Hong, L.; Chen, Y.; Chen, X.; Zheng, Y.; Zhang, W.; Ma, W.; Shen, Y.; Yao, Y. *Org. Prep. Proced. Int.* **2011**, *43*, 1–66.
13. (a) Mishra, A.; Batra, S. *Eur. J. Org. Chem.* **2010**, 4832–4840; (b) Nag, S.; Bhowmik, S.; Gauniyal, H. M.; Batra, S. *Eur. J. Org. Chem.* **2010**, 4705–4712; (c) Mishra, A.; Batra, S. *Synthesis* **2009**, 3077–3088; (d) Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.* **2009**, 3454–3466; (e) Nag, S; Batra, S. *Tetrahedron* **2011**, doi: 10.1016/j.tet.2011.07.087 released on web on 3 August.
14. (a) Kathiravan, S.; Ramesh, E.; Raghunathan, R. *Tetrahedron Lett.* **2009**, *50*, 2389–2391; (b) Kathiravan, S.; Raghunathan, R. *Synlett* **2009**, 952–954; (c) Lee, H. S.; Kim, S. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1773–1776.