Tricyclic Pyrazoles: An Efficient Approach to Cannabinoid Analogues with a Tricyclic Framework Incorporating the Pyrrole and Pyrazole Moieties

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Abstract: In this paper we report the synthesis of some new cannabinoid analogues that share with rimonabant, a potent and selective CB_1 antagonist, the 2,4-dichlorophenyl and piperidin-1-yl substituents on the pyrazole and amide nitrogens, respectively. The general synthesis involves the preparation of a cyclic ketone condensed with a pyrrole, followed by Claisen condensation with diethyl oxalate; from here, an aza-annulation reaction with a substituted hydrazine followed by an amidation step complete the synthesis.

Key words: cannabinoids, tricyclic pyrazoles, Friedel–Crafts acylation, Claisen condensation, aza-annulation

The endogenous cannabinoid system (ECS) in mammals incorporates a variety of cellular elements as potential recognition sites at which a broad group of compounds, termed cannabinoids, interact. At present, a number of cannabinoid binders have been identified, which can be roughly classified into a variety of chemical families (exocannabinoids), including tricyclic cannabinols,[1] bicyclic cannabinols,[2,3] indoles, pyrroles, and indenes,[4] anandamide analogues,[5] and diarylpyrazoles.[6] A prototypical example of a diarylpyrazole with a potent and selective CB_1 antagonist property is rimonabant, which, however, has been withdrawn from the market due to various psychiatric side effects (Figure 1).[7]

The 4-alkyl-5-arylpyrazole skeleton of rimonabant has been modified by us, giving rise to 1,4-dihydrobenzo[4,5]cyclopenta[1,2-*c*]pyrazole **Aa**,[8] 1,4,5-trihydrobenzo[5,6]cyclohexa[1,2-*c*]pyrazole **Ab**,[9] and 1,4,5,6-tetrahydrobenzo[6,7]cycloheptа[1,2-*c*]pyrazole-based ligands **Ac**[10] (Figure 1). These compounds displayed interesting cannabinoid-binding affinity and subtype selectivity. Interestingly, changes to the size and shape of the tricyclic unit in ligands **Aa–c** revealed intriguing effects on the biological activity. Thus, increasing the length of the carbon bridge between C4 of the pyrazole and the 4-chlorophenyl group from one to three methylene units led to a marked increase in the CB_1 binding affinity and selectivity. Moreover, the presence of a substituent, such as F, Cl, Br, or Me, on the phenyl ring of the tricyclic system generally gave an increase in the affinity and selectivity for CB_2 receptors.[8]

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Continuing our interest in this field, we have undertaken a study to prepare new cannabinoid binders related to both rimonabant and its derivatives **Aa–c** (Figure 1). Thus, we are developing practical and extendable methods to build compounds with a tricyclic framework incorporating the biologically interesting pyrrole and pyrazole moieties, and with a central ring that can be modulate in size, namely compounds of general formula **B** (Figure 1). In this paper we wish to report the results obtained in the synthesis of some representatives of this family **B′**, which share with rimonabant the 2,4-dichlorophenyl and piperidin-1-yl substituents on the pyrazole and amide nitrogens, respectively (Figure 1).

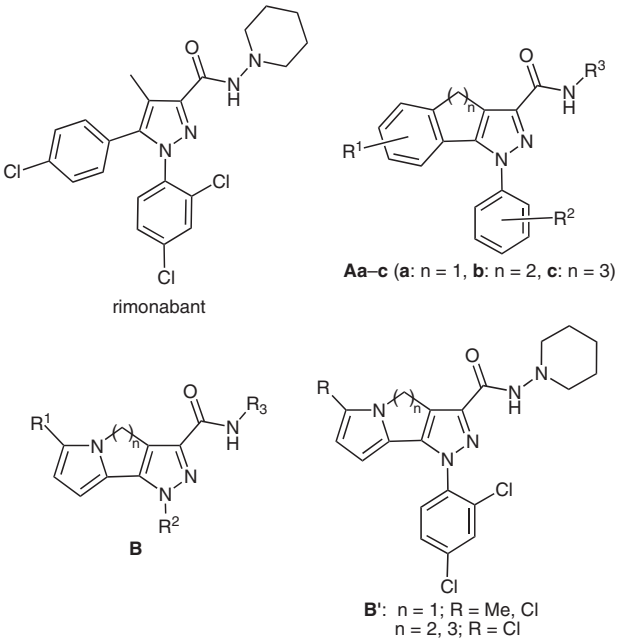
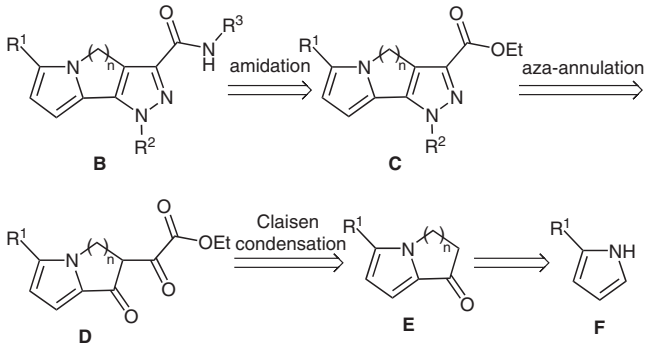


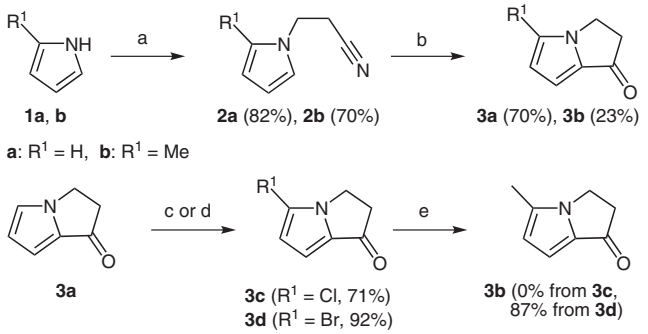
Figure 1

The planned retrosynthesis of the derivatives of general formula **B** is showed in Scheme 1. In this approach, the final amidation step is preceded by the aza-annulation of a 2,4-dioxobutanoic acid esters **D** with a substituted hydrazine. The polyoxo compounds **D** can be made through Claisen condensation between the appropriate substituted cyclic ketone **E** and diethyl oxalate. Finally, substituted cyclic ketone **E** can be built from 2-substituted pyrroles **F** by an N-alkylation/acylation sequence.

To begin to fulfill the strategy for the target derivatives **B** (Scheme 1), we devoted our attention to a reliable synthesis of substituted pyrrole-fused cyclopentanones **E** (n = 1). Thus, pyrrole and 2-methylpyrrole were treated with acrylonitrile in the presence of Triton B to give the N-alkylated derivatives **2a**,**b** in 82% and 70% yields, respectively. The intramolecular Friedel–Crafts acylation of **2a**,**b** gave the pyrrolizin-1-ones **3a**,**b** (Scheme 2). However, while the unsubstituted compound **3a** was obtained in 70% yield, the methyl counterpart **3b** was unexpectedly formed in only 23% yield. Therefore, an alternative synthesis of **3b** was also investigated (*vide infra*). To obtain 5-chloro-2,3-dihydro-1*H*-pyrrolizin-1-one (**3c**) the direct halogenation of **3a** was preferred to the synthesis from 2-chloropyrrole. Thus, treatment of **3a** with *N*-chlorosuccinimide in tetrahydrofuran at 60 °C gave **3c** in good yield (71%). With this compound in hand, the substitution of the chlorine atom with a methyl group was explored. Unfortunately, Suzuki cross-coupling of **3c** with methylboronic acid in the presence of palladium(II) acetate/tricyclohexylphosphine failed to give **3b**. In order to obtain the target compound **3b**, 5-bromo-2,3-dihydro-1*H*-pyrrolizin-1-one (**3d**) was synthesized by bromination of **3a** with *N*-bromosuccinimide in tetrahydrofuran at low temperature (92% yield). As expected, Suzuki cross-coupling of **3d** with methylboronic acid in the presence of palladium(II) acetate/tricyclohexylphosphine was in this case successful affording **3b** in 80% yield. Next, the yield of this coupling reaction could be improved to 87% when palladium(II) acetate/2-(dicyclohexylphosphino)-2′,6′-diisopropoxybiphenyl (RuPhos) was used as the catalyst.

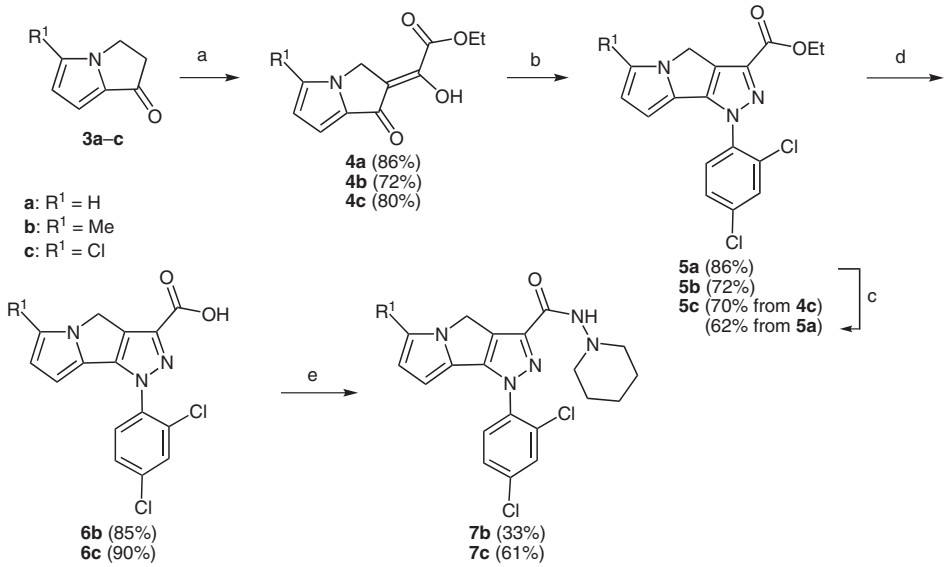


Scheme 1



Scheme 2 *Reagents and conditions*: (a) CH_2=CHCN, Triton B, 8–12 °C to r.t.; (b) (i) $AlCl_3$, KCl, NaCl, 120 °C, (ii) H_2O, 40 °C, 1 h then 90 °C, 1 h; (c) NCS, THF, 60 °C, 5 h; (d) NBS, THF, –50 to –10 °C, 2 h; (e) $MeB(OH)_2$, $Pd(OAc)_2$/RuPhos, Cs_2CO_3, toluene–H_2O, 130 °C, 30 min.

With multigram quantities of 5-substituted 2,3-dihydro-1*H*-pyrrolizin-1-ones **3** in hand, their conversion into the desired derivatives **B** was pursued according to the planned retrosynthesis. The treatment of ketones **3a**–**c** with diethyl oxalate in the presence of sodium ethoxide at room temperature afforded the expected 1,3-diketo esters, which were in all cases detected only as the enol form **4a**–**c** (72–86% yields) (Scheme 3). Compounds **4a**–**c** and 2,4-dichlorophenylhydrazine hydrochloride were heated in ethanol to afford the pyrazole derivatives **5a**–**c** in good yields (70–86%). An alternative access to the chlorine derivative **5c** was obtained by treating **5a** with *N*-chlorosuccinimide in tetrahydrofuran at 60 °C (62% yield). The



Scheme 3 *Reagents and conditions:* (a) Na, EtOH, diethyl oxalate, r.t., 1 h; (b) 2,4-$Cl_2C_6H_3NHNH_2$·HCl, EtOH, 80 °C, 48 h; (c) NCS, THF, 60 °C, 5 h; (d) LiOH, THF, 60 °C, 3 h; (e) EDC, BtOH, CH_2Cl_2, then 1-aminopiperidine, r.t., 12 h.

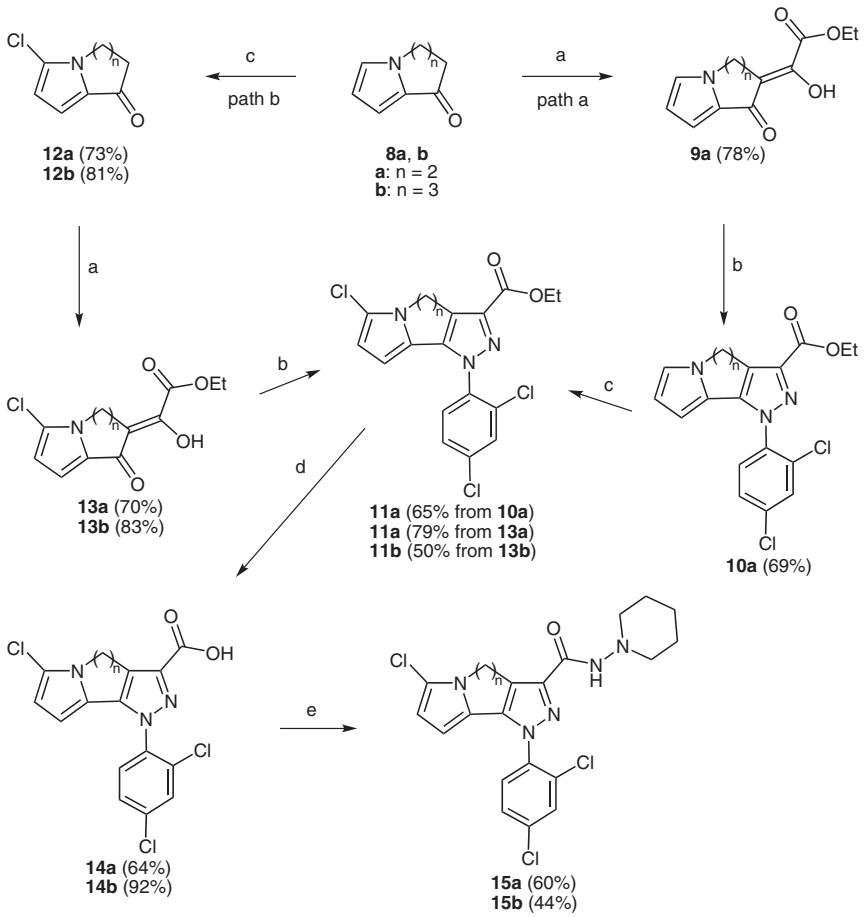
ethyl ester groups in **5b**,**c** were converted with lithium hydroxide in tetrahydrofuran at 60 °C into the related acids **6b**,**c** (85–90% yields), which were reacted in sequence with *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide and 1-hydroxybenzotriazole, and then with piperidin-1-amine to give the target compounds **7b** and **7c** in 33% and 61% yields, respectively.

For the synthesis of the analogue of **A**, where the central ring in the tricyclic unit of **A** is a six- or seven-membered ring and the R^1 substituent is a chlorine atom, two convergent paths were pursued (Scheme 4). These routes follow the reliable methodologies employed to obtain compounds **7b**,**c** by using as starting materials the known cyclic ketones 6,7-dihydroindolizin-8(5*H*)-one (**8a**) and 5,6,7,8-tetrahydro-9*H*-pyrrolo[1,2-*a*]azepin-9-one (**8b**). Initially, the ketone **8a** was converted into the pyrazole derivative **9a** by Claisen condensation with ethyl oxalate, followed by aza-cyclization with 2,4-dichlorophenylhydrazine (54% yield in two steps) (path a). Chlorination of **10a** with *N*-chlorosuccinimide in tetrahydrofuran at 60 °C gave **11a** in 65% isolated yield; the the overall yield for the three steps was 35%. In the alternative route (path b), the ketone **8a** was reacted with *N*-chlorosuccinimide in tetrahydrofuran at 60 °C to give **12a** (73% yield), which was converted into **11a** in the usual way. This three-step protocol gave an overall yield of 40%, slightly higher than that obtained with path a, making it the preferred route when taking into account that it gave cleaner products.

Following path b compound **8b** was converted into the 1,3-diketo ester **13b** in 67% yield. In the next step the treatment of **13b** with 2,4-dichlorophenylhydrazine hydrochloride gave a mixture of products from which the expected pyrazole derivative **11b** was isolated in moderate 50% yield. Finally, compounds **11a**,**b** were converted in very similar yields over two steps (~40%) into **15a**,**b** by hydrolysis followed by amidation under the usual reaction conditions.

In conclusion, we report a practical synthesis of compounds of structure **B′** (Figure 1), which share with rimonabant the 2,4-dichlorophenyl and piperidin-1-yl substituents on the pyrazole and amide nitrogens, respectively. The CB binding affinity and selectivity of these new compounds will be determined, thus indicating which further structural modifications will be pursued to modulate advantageously their biological activity.

All reagents and solvents were purchased from Aldrich and used as received. Low boiling petroleum ether (PE) was the fraction bp 40–60 °C. THF was distilled from Na/benzophenone ketyl and degassed thoroughly with dry N_2 directly before use. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. NMR spectra were obtained with a Varian VXR-300 spec-



Scheme 4 *Reagents and conditions:* (a) Na, EtOH, diethyl oxalate, r.t., 1 h; (b) 2,4-$Cl_2C_6H_3NHNH_2$·HCl, EtOH, 80 °C, 8 h; (c) NCS, THF, 60 °C, 5 h; (d) LiOH, THF, 60 °C, 3 h; (e) EDC, BtOH, CH_2Cl_2, then 1-aminopiperidine, r t, 12 h.

trometer at 300 for ^{1}H and 75.4 MHz for ^{13}C; reference: internal TMS in $CDCl_3$. IR spectra were recorded on a Jasco FT/IR-460 plus spectrophotometer. Microwave experiments were carried out by a Biotage Iniziator-8-microwave system (max pressure 20 bar, IR temperature sensor). Elemental analyses were performed on a Perkin-Elmer 240 B analyzer. TLC was performed on Merck silica gel 60 TLC plates F254 and visualized using UV or phosphomolybdic acid. Flash chromatography was carried out on 230–400 mesh silica gel.

3-(1*H*-Pyrrol-1-yl)propanenitrile (**2a**),[11] 2,3-dihydro-1*H*-pyrrolizin-1-one (**3a**),[11] ethyl 2-hydroxy-2-(1-oxo-2,3-dihydro-1*H*-pyrrolizin-2-ylidene)acetate (**4a**),[12] 6,7-dihydroindolizin-8(5*H*)-one (**8a**),[13] 5,6,7,8-tetrahydro-9*H*-pyrrolo[1,2-*a*]azepin-9-one (**8b**)[14] were obtained according to reported procedures.

3-(2-Methyl-1*H*-pyrrol-1-yl)propanenitrile (2b)

Acrylonitrile (7.75 g, 0.147 mol) was slowly added, keeping the temperature at 8–12 °C, to a soln of 2-methylpyrrole (7.50 g, 92.5 mmol) in 40% aq Triton B soln (0.77 mL). When the addition was complete, the mixture was stirred at 12 °C for 30 min and then at r.t. for an additional 1 h. The obtained red/brown oil was bulb-to-bulb distilled (oven temperature 90 °C/67 mbar) to give **2b** (8.69 g, 70%) as a colorless oil.

IR (Nujol): 2248 cm^{-1}.

^{1}H NMR: δ = 6.62 (t, *J* = 2.8 Hz, 1.8 Hz, 1 H), 6.09 (t, *J* = 2.8 Hz, 1 H), 6.00–5.95 (m, 1 H), 4.12 (t, *J* = 7.0 Hz, 2 H), 2.69 (t, *J* = 7.0 Hz, 2 H), 2.26 (s, 3 H).

^{13}C NMR: δ = 127.8, 119.5, 117.1, 107.9, 107.5, 41.7, 20.0, 11.5.

Anal. Calcd for $C_8H_{10}N$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.54; H, 7.59; N, 20.95.

5-Methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (3b) from 2b

A mixture of $AlCl_3$ (18.35 g, 0.138 mol), KCl (3.77 g, 64.45 mmol), and NaCl (3.83 g, 51.45 mmol) was heated at 130 °C until complete formation of a brown oily soln. The propanenitrile **2b** (5.38 g, 40.84 mmol) was rapidly added and the mixture was vigorous stirred at this temperature for 10 min. After this time, the hot soln was poured into ice-H_2O (~250 mL) and then the resulting mixture was heated at 40 °C for 1 h and then at 90 °C for an additional 1 h. The soln was cooled and extracted with CH_2Cl_2 (3 × 70 mL). The organic phase was dried (anhyd Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (PE–EtOAc, 7:3) to give **3b** (1.27 g, 23%) as a brown solid; mp 55–57 °C; R_f = 0.20 (PE–EtOAc, 85:15).

IR (Nujol): 1680 cm^{-1}.

^{1}H NMR: δ = 6.69 (d, *J* = 4.0 Hz, 1 H), 6.26 (d, *J* = 4.0 Hz, 1 H), 4.14 (t, *J* = 6.0 Hz, 2 H), 3.07 (t, *J* = 6.0 Hz, 2 H), 2.30 (s, 3 H).

^{13}C NMR: δ = 182.9, 149.5, 134.7, 116.7, 110.7, 45.1, 14.1, 11.7.

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.16; H, 6.78; N, 10.41.

5-Bromo-2,3-dihydro-1*H*-pyrrolizin-1-one (3d)

NBS (4.57 g, 25.67 mmol) was added portionwise to a soln of **3a** (2.39 g, 19.74 mmol) in THF (79 mL) at –50 °C. After 5 min at –50 °C, the temperature was raised to –10 °C and then the mixture was stirred at this temperature for 2 h. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (100 mL) and the organic phase was washed with H_2O (3 × 50 mL) The organic phase was dried (anhyd Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (PE–EtOAc, 7:3) giving **3d** (3.95 g, 92%) as a brownish solid; mp 52–53 °C; R_f = 0.25 (PE–EtOAc, 7:3).

IR (Nujol): 1687 cm^{-1}.

^{1}H NMR: δ = 6.77 (d, *J* = 4.2 Hz, 1 H), 6.48 (d, *J* = 4.2 Hz, 1 H), 4.19 (t, *J* = 6.2 Hz, 2 H), 3.11 (t, *J* = 6.2 Hz, 2 H).

^{13}C NMR: δ = 187.7, 133.4, 118.2, 108.9, 105.2, 41.7, 39.1.

Anal. Calcd for C_7H_6BrNO: C, 42.03; H, 3.02; N, 7.00. Found: C, 43.01; H, 3.08; N, 6.92.

5-Methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (3b) from 3d

In a glass tube fitted with a Teflon screw seal, $Pd(OAc)_2$ (0.03 g, 0.13 mmol), RuPhos (0.12 g, 0.25 mmol), Cs_2CO_3 (2.43 g, 7.47 mmol), and methylboronic acid (0.43 g, 4.99 mmol) were added to a soln of **3d** (0.50 g, 2.50 mmol), in a degassed mixture of toluene–H_2O (19:1, 2.5 mL). The reactor was flushed with argon and the mixture was heated in microwave apparatus at 130 °C for 30 min. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc, (3 × 10 mL) The combined organic layers were dried (anhyd Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by plug chromatography (PE–EtOAc, 7:3) giving **3b** (0.294 g, 87%).

Chlorination with *N*-Chlorosuccinimide of 3a, 5a, 8a,b, 10a; General Procedure 1

NCS (0.15 g, 1.09 mmol) was added to a soln of the substrate (0.91 mmol) in THF (4 mL). After stirring at r.t. for few min, the mixture was heated at 60 °C for 5 h. After cooling, the organic soln was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and the organic soln was washed with 5% aq $NaHCO_3$ (3 × 10 mL). The organic phase was dried (anhyd Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (PE–EtOAc, 7:3).

5-Chloro-2,3-dihydro-1*H*-pyrrolizin-1-one (3c)

Following general procedure 1 using **3a** gave **3c** (0.101 g, 0.65 mmol, 71%) as a yellow solid; mp 76–77 °C; R_f = 0.64 (PE–EtOAc, 1:1).

IR (Nujol): 1691 cm^{-1}.

^{1}H NMR: δ = 6.72 (d, *J* = 4.2 Hz, 1 H), 6.38 (d, *J* = 4.2 Hz, 1 H), 4.22 (t, *J* = 6.2 Hz, 2 H), 3.10 (t, *J* = 6.2 Hz, 2 H).

^{13}C NMR: δ = 188.2, 131.4, 119.5, 114.6, 108.3, 40.6, 39.0.

Anal. Calcd for C_7H_6ClNO: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.96; H, 3.95; N, 9.04.

3-Chloro-6,7-dihydroindolizin-8(5*H*)-one (12a)

Following general procedure 1 using **8a** gave **12a** (0.111 g, 0.66 mmol, 73%) as a yellow oil; R_f = 0.52 (PE–EtOAc, 7:3).

IR (film): 1653 cm^{-1}.

^{1}H NMR: δ = 7.01 (d, *J* = 4.2 Hz, 1 H), 6.21 (d, *J* = 4.2 Hz, 1 H), 4.06 (t, *J* = 6.2 Hz, 2 H), 2.60 (t, *J* = 6.2 Hz, 2 H), 2.36–2.22 (m, 2 H).

^{13}C NMR: δ = 187.5, 133.5, 119.0, 115.2, 109.0, 105.2, 42.8, 37.9.

Anal. Calcd for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.74; H, 4.83; N, 8.20.

3-Chloro-5,6,7,8-tetrahydro-9*H*-pyrrole[1,2-*a*]azepin-9-one (12b)

Following general procedure 1 using **8b** gave **12b** (0.136 g, 0.74 mmol, 81%) as a yellow oil; R_f = 0.54 (PE–EtOAc, 7:3).

IR (film): 1690 cm^{-1}.

^{1}H NMR: δ = 6.98 (d, *J* = 4.2 Hz, 1 H), 6.16 (d, *J* = 4.2 Hz, 1 H), 4.27 (t, *J* = 6.4 Hz, 2 H), 2.75 (t, *J* = 6.4 Hz, 2 H), 2.20–1.80 (m, 4 H).

^{13}C NMR: δ = 190.7, 134.1, 119.2, 116.0, 109.5, 44.2, 40.1, 39.3, 25.7.

Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.93; H, 5.40; N, 7.68.

Claisen Condensation of 3a–c, 8a, 12a,b with Ethyl Oxalate; General Procedure 2

Na metal (0.09 g, 3.70 mmol) was cautiously added portionwise to dry EtOH (4.4 mL) under stirring until all the Na had reacted. Ethyl oxalate (0.60 g, 4.07 mmol) and then the ketone (3.70 mmol) were added sequentially. The soln was stirred at r.t. for 1 h and then slowly poured into ice. To this cold mixture 2 M HCl soln was added and the resulting suspension was filtered, and the collected solid was dried in air.

Ethyl 2-Hydroxy-2-[1-oxo-1*H*-pyrrolizin-2(3*H*)-ylidene]acetate (4a)

Following general procedure 2 using **3a** gave **4a** (0.703 g, 3.18 mmol, 86%) as a yellow solid; mp 70–71 °C; R_f = 0.56 (PE–EtOAc, 7:3).

IR (Nujol): 1718, 1668, 1631 cm^{-1}.

^1H NMR: 12.98 (br s, 1 H), 7.16 (m, 1 H), 6.86 (d, J = 4.2 Hz, 1 H), 6.60–6.55 (m, 1 H), 5.09 (s, 2 H), 4.40 (q, J = 7.0 Hz, 2 H), 1.42 (t, J = 7.0 Hz, 3 H).

^{13}C NMR: δ = 184.0, 162.5, 149.8, 133.4, 123.8, 118.1, 117.5, 109.7, 62.4, 47.0, 14.1.

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.79; H, 5.09; N, 6.29.

Ethyl 2-Hydroxy-2-[5-methyl-1-oxo-1*H*-pyrrolizin-2(3*H*)-ylidene]acetate (4b)

Following general procedure 2 using **3b** gave **4b** (0.625 g, 2.66 mmol, 72%) as a yellow solid; mp 66–68 °C; R_f = 0.14 (PE–EtOAc, 8:2).

IR (Nujol): 1718, 1664, 1631 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 13.03 (br s, 1 H), 6.82 (d, J = 4.0 Hz, 1 H), 6.31 (d, J = 4.0 Hz, 1 H), 4.91 (s, 2 H), 4.41 (q, J = 7.0 Hz, 2 H), 2.34 (s, 3 H), 1.42 (t, J = 7.0 Hz, 3 H).

^{13}C NMR: δ = 182.9, 162.7, 149.5, 134.7, 132.2, 117.8, 116.7, 110.6, 62.3, 45.1, 14.1, 11.7.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.20; H, 5.61; N, 6.00.

Ethyl 2-[5-Chloro-1-oxo-1*H*-pyrrolizin-2(3*H*)-ylidene]-2-hydroxyacetate (4c)

Following general procedure 2 using **3c** gave **4c** (0.756 g, 2.96 mmol, 80%) as a yellow solid; mp 76–77 °C; R_f = 0.28 (PE–EtOAc, 7:3).

IR (Nujol): 1718 1672, 1644 cm^{-1}.

^1H NMR: δ = 12.00–13.00 (br s, 1 H), 6.84 (d, J = 3.8 Hz, 1 H), 6.42 (d, J = 3.8 Hz, 1 H), 4.99 (s, 2 H), 4.41 (q, J = 7.0 Hz, 2 H), 1.42 (t, J = 6.8 Hz, 3 H).

^{13}C NMR: δ = 183.2, 162.3, 150.6, 132.2, 121.1, 118.0, 116.5, 115.4, 110.6, 62.7, 45.8.

Anal. Calcd for $C_{11}H_{10}ClNO_4$: C, 51.68; H, 3.94; N, 5.48. Found: C, 51.61; H, 3.87; N, 5.53.

Ethyl 2-Hydroxy-2-[8-oxo-5,6-dihydroindolizin-7(8*H*)-ylidene]acetate (9a)

Following general procedure 2 using **8a** gave **9a** (0.680 g, 2.89 mmol, 78%) as a yellow solid; mp 72–73 °C; R_f = 0.52 (PE–EtOAc, 7:3).

IR (Nujol): 1718, 1606 cm^{-1}.

^1H NMR: δ = 15.97 (s, 1 H), 7.11 (d, J = 3.9 Hz, 1 H), 6.95 (d, J = 3.9 Hz, 1 H), 6.34 (dd, J = 1.8, 3.9 Hz, 1 H), 4.37 (q, J = 6.9 Hz, 2 H), 4.09 (t, J = 6.9 Hz, 2 H), 3.27 (t, J = 6.9 Hz, 2 H), 1.41 (t, J = 6.9 Hz, 3 H).

^{13}C NMR: δ = 181.0, 162.9, 162.1, 128.7, 118.0, 116.0, 111.7, 106.8, 62.0, 44.1, 23.9, 14.1.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.34; H, 5.50; N, 5.91.

Ethyl 2-[3-Chloro-8-oxo-5,6-dihydroindolizin-7(8*H*)-ylidene]-2-hydroxyacetate (13a)

Following general procedure 2 using **12a** gave **13a** (0.698 g, 2.59 mmol, 70%) as a yellow solid; mp 77–78 °C; R_f = 0.60 (PE–EtOAc, 7:3).

IR (Nujol): 1728, 1608 cm^{-1}.

^1H NMR: δ = 15.81 (s, 1 H), 7.09 (d, J = 4.2 Hz, 1 H), 6.28 (d, J = 4.2 Hz, 1 H), 4.37 (q, J = 7.0 Hz, 2 H), 4.04 (t, J = 6.6 Hz, 2 H), 3.28 (t, J = 6.6 Hz, 2 H), 1.41 (t, J = 7.0 Hz, 3 H).

^{13}C NMR: δ = 179.8, 162.5, 162.4, 127.8, 123.8, 115.7, 110.5, 106.0, 61.9, 41.1, 23.1, 13.8.

Anal. Calcd for $C_{12}H_{12}ClNO_4$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.40; H, 4.52; N, 5.16.

Ethyl 2-[3-Chloro-9-oxo-6,7-dihydro-5*H*-pyrrole[1,2-*a*]azepin-8(9*H*)-ylidene]-2-hydroxyacetate (13b)

Following general procedure 2 using **12b** gave **13b** (0.807 g, 3.07 mmol, 83%) as a yellow solid; mp 80–82 °C; R_f = 0.64 (PE–EtOAc, 7:3).

IR (Nujol): 1812, 1707, 1599 cm^{-1}.

^1H NMR: δ = 15.08 (br s, 1 H), 6.96 (d, J = 4.2 Hz, 1 H), 6.22 (d, J = 4.2 Hz, 1 H), 4.35 (q, J = 7.0 Hz, 2 H), 4.30–4.10 (m, 2 H), 2.80–2.40 (m, 2 H), 2.20–1.95 (m, 2 H), 1.41 (t, J = 7.0 Hz, 3 H).

^{13}C NMR: δ = 178.7, 160.9, 158.2, 128.8, 118.0, 115.9, 100.6, 57.1, 45.4, 29.7, 25.3, 14.1.

Anal. Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; N, 4.94. Found: C, 55.09; H, 4.91; N, 4.97.

Aza-annulation of 4a–c, 9a, 13a,b with 2,4-Dichlorophenylhydrazine; General Procedure 3

A mixture of keto-enol ester (2.26 mmol) and 2,4-dichlorophenylhydrazine hydrochloride (0.57 g, 2.71 mmol) in abs EtOH (14.90 mL) was heated under reflux for 8–48 h. The mixture was allowed to cool to r.t. and poured into ice-water (100 mL). The precipitate was filtered and the collected solid was dried. Plug chromatography of this crude solid (PE–EtOAc, 9:1) gave the pure product as a yellow/white solid.

Ethyl 1-(2,4-Dichlorophenyl)-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxylate (5a)

Following general procedure 3 using **4a** gave **5a** (0.703 g, 1.94 mmol, 86%) as a yellow solid; mp 130–131 °C; R_f = 0.41 (PE–EtOAc, 8:2).

IR (Nujol): 1720 cm^{-1}.

^1H NMR: δ = 7.60 (d, J = 2.2 Hz, 1 H), 7.55 (s, 1 H), 7.41 (dd, J = 8.4, 2.2 Hz, 1 H), 7.02 (s, 1 H), 6.24 (dd, J = 3.4, 2.8 Hz, 1 H), 5.93 (d, J = 3.4 Hz, 1 H), 4.98 (s, 2 H), 4.45 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 6.9 Hz, 3 H).

^{13}C NMR: δ = 161.7, 144.8, 135.7, 135.6, 130.8, 130.7, 130.3, 129.2, 127.9, 126.8, 126.5, 119.4, 112.1, 99.6, 61.4, 46.3, 14.3.

Anal. Calcd for $C_{17}H_{13}Cl_2N_3O_2$: C, 56.37; H, 3.62; N, 11.60. Found: C, 56.46; H, 3.64; N, 11.58.

Ethyl 1-(2,4-Dichlorophenyl)-6-methyl-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxylate (5b)

Following general procedure 3 using **4b** gave **5b** (0.613 g, 1.63 mmol, 72%) as a yellow solid; mp 160–162 °C; R_f = 0.17 (PE–EtOAc, 9:1).

IR (Nujol): 1713 cm^{-1}.

^1H NMR: δ = 7.59 (s, 1 H), 7.56 (d, J = 8.6 Hz, 1 H), 7.40 (d, J = 8.6 Hz, 1 H), 5.94 (d, J = 3.6 Hz, 1 H), 5.89 (d, J = 3.6 Hz, 1 H),

4.80 (s, 2 H), 4.46 (q, *J* = 7.0 Hz, 2 H), 2.29 (s, 3 H), 1.44 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR: δ = 161.7, 145.1, 138.6, 135.7, 135.6, 130.6, 130.2, 129.2, 129.0, 127.9, 126.0, 124.9, 109.6, 99.8, 61.3, 44.3, 14.3, 11.8.

Anal. Calcd for $C_{18}H_{15}Cl_2N_3O_2$: C, 57.46; H, 4.02; N, 11.17. Found: C, 57.50; H, 4.00; N, 11.15.

Ethyl 6-Chloro-1-(2,4-dichlorophenyl)-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxylate (5c)

From **5a** using general procedure 1 **5c** (0.222 g, 0.56 mmol, 62%); from **4c** using general procedure 3 gave **5c** (0.626 g, 1.58 mmol, 70%) as a yellow solid; mp 170–171 °C; R_f = 0.26 (PE–EtOAc, 85:15).

IR (Nujol): 1718 cm^{-1}.

^{1}H NMR: δ = 7.60 (d, *J* = 2.2 Hz, 1 H), 7.57 (d, *J* = 8.6 Hz, 1 H), 7.40 (dd, *J* = 8.6, 2.2 Hz, 1 H), 6.10 (d, *J* = 4.0 Hz, 3 H), 5.94 (d, *J* = 4.0 Hz, 1 H), 4.89 (s, 2 H), 4.46 (q, *J* = 7.0 Hz, 2 H), 1.44 (t, *J* = 7.0 Hz, 1 H).

^{13}C NMR: δ = 161.7, 144.9, 138.7, 135.8, 135.6, 130.8, 130.4, 129.2, 128.0, 126.8, 126.5, 119.3, 112.1, 99.6, 61.4, 46.3, 14.4.

Anal. Calcd for $C_{17}H_{12}Cl_3N_3O_2$: C, 51.48; H, 3.05; N, 10.59. Found: C, 51.55; H, 2.99; N, 10.54.

Ethyl 1-(2,4-Dichlorophenyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*g*]indolizine-3-carboxylate (10a)

Following general procedure 3 using **9a** gave **10a** (0.587 g, 1.56 mmol, 69%) as a yellow solid; mp 186–187 °C; R_f = 0.44 (PE–EtOAc, 85:15).

IR (Nujol): 1708 cm^{-1}.

^{1}H NMR: δ = 7.60 (s, 1 H), 7.48–7.34 (m, 2 H), 6.76 (m, 1 H), 6.05 (d, *J* = 4.0 Hz, 1 H), 5.48 (d, *J* = 4.0 Hz, 1 H), 4.44 (q, *J* = 6.9 Hz, 2 H), 4.16 (t, *J* = 6.9 Hz, 2 H), 3.31 (t, *J* = 6.9 Hz, 2 H), 1.43 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR: δ = 162.5, 140.8, 137.1, 136.5, 135.8, 133.6, 130.4, 130.2, 127.9, 122.5, 120.4, 113.8, 108.5, 104.6, 61.0, 44.8, 21.4, 14.4.

Anal. Calcd for $C_{18}H_{15}Cl_2N_3O_2$: C, 57.46; H, 4.02; N, 11.17. Found: C, 57.55; H, 4.06; N, 11.14.

Ethyl 7-Chloro-1-(2,4-dichlorophenyl)-4,5-dihydropyrazolo[4,3-*g*]indolizine-3-carboxylate (11a)

Using **10a** and general procedure 1 gave **11a** (0.378 g, 0.59 mmol, 65%); using **13a** and general procedure 3 gave **11a** (0.735 g, 1.79 mmol, 79%) as a yellow solid; mp 186–187 °C; R_f = 0.44 (PE–EtOAc, 85:15).

IR (Nujol): 1704 cm^{-1}.

^{1}H NMR: δ = 7.60 (s, 1 H), 7.44–7.33 (m, 2 H), 5.96 (d, *J* = 3.9 Hz, 1 H), 5.30 (d, *J* = 3.9 Hz, 1 H), 4.45 (q, *J* = 6.9 Hz, 2 H), 4.13 (t, *J* = 6.9 Hz, 2 H), 3.34 (t, *J* = 6.9 Hz, 2 H), 1.43 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.5, 140.3, 136.1, 136.0, 135.9, 133.6, 131.4, 130.2, 128.2, 122.6, 121.4, 114.8, 108.7, 104.6, 61.3, 44.3, 22.4, 14.4.

Anal. Calcd for $C_{18}H_{14}Cl_3N_3O_2$: C, 52.64; H, 3.44; N, 10.23. Found: C, 52.77; H, 3.46; N, 10.29.

Ethyl 8-Chloro-1-(2,4-dichlorophenyl)-1,4,5,6-tetrahydropyrazolo[3,4-*c*]pyrrolo[1,2-*a*]azepine-3-carboxylate (11b)

Following general procedure 3 using **13b** gave **11b** (0.479 g, 1.13 mmol, 50%) as a pink solid; mp 108–110 °C. R_f = 0.55 (PE–EtOAc, 8:2).

IR (Nujol): 1718 cm^{-1}.

^{1}H NMR: δ = 7.60–7.30 (m, 3 H), 5.90 (d, *J* = 4.2 Hz, 1 H), 5.36 (d, *J* = 4.2 Hz, 1 H), 4.44 (q, *J* = 7.0 Hz, 2 H), 4.20–4.00 (m, 2 H), 3.40–3.20 (m, 2 H), 2.27–2.00 (m, 2 H), 1.42 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR: δ = 162.9, 142.8, 137.2, 136.5, 136.1, 133.9, 131.0, 130.6, 128.3, 121.6, 119.7, 118.3, 108.9, 107.2, 61.3, 44.9, 27.3, 24.5, 14.7.

Anal. Calcd for $C_{19}H_{16}Cl_3N_3O_2$: C, 53.73; H, 3.80; N, 9.89. Found: C, 53.85; H, 3.83; N, 9.84.

Hydrolysis of 5b,c, 11a,b; General Procedure 4

A soln of 0.8 M LiOH (0.58 g, 13.82 mmol) was added dropwise to a soln of the tricyclic ester (6.91 mmol) in THF (32 mL). The resulting mixture was heated under reflux for 3 h and then the solvent was evaporated under reduce pressure. The residue was dissolved in H_2O (50 mL) and 2 M aq HCl was added until pH 1. The precipitate was filtered and the collected solid was dried in air.

1-(2,4-Dichlorophenyl)-6-methyl-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxylic Acid (6b)

Following general procedure 4 using **5b** gave **6b** (2.042 g, 5.87 mmol, 85%) as a yellow solid; mp 253–255 °C; R_f = 0.42 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 1701 cm^{-1}.

^{1}H NMR: δ = 13.00–12.50 (br s, 1 H), 7.62 (s, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 6.00–5.95 (m, 1 H), 5.93–5.90 (m, 1 H), 4.83 (s, 2 H), 2.29 (s, 3 H).

^{13}C NMR: δ = 162.8, 144.4, 138.7, 135.2, 134.8, 129.6, 128.6, 128.4, 127.4, 125.5, 124.3, 108.9, 99.2, 43.8, 11.3.

Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 55.19; H, 3.18; N, 12.07. Found: C, 55.11; H, 3.28; N, 12.08.

6-Chloro-1-(2,4-dichlorophenyl)-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxylic Acid (6c)

Following general procedure 4 using **5c** gave **6c** (2.292 g, 6.22 mmol, 90%) as a yellow solid; mp 262–264 °C; R_f = 0.24 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 1708 cm^{-1}.

^{1}H NMR ($CDCl_3$, DMSO-d_6): δ = 12.40–11.80 (br s, 1 H), 7.70–7.50 (m, 3 H), 6.08 (d, *J* = 3.2 Hz, 1 H), 5.95 (d, *J* = 3.2 Hz, 1 H), 4.89 (s, 2 H).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 162.4, 143.9, 139.0, 135.2, 134.9, 130.2, 129.6, 128.7, 126.6, 126.2, 120.1, 112.8, 111.6, 98.8, 46.2.

Anal. Calcd for $C_{15}H_8Cl_3N_3O_2$: C, 48.88; H, 2.19; N, 11.40. Found: C, 48.99; H, 2.15; N, 11.47.

7-Chloro-1-(2,4-dichlorophenyl)-4,5-dihydropyrazolo[4,3-*g*]indolizine-3-carboxylic Acid (14a)

Following general procedure 4 using **11a** gave **14a** (1.691 g, 4.42 mmol, 64%) as a brown solid; mp 239–240 °C; R_f = 0.44 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 1703 cm^{-1}.

^{1}H NMR ($CDCl_3$, DMSO-d_6): δ = 11.20–10.80 (br s, 1 H), 7.72 (s, 1 H). 7.55–7.50 (m, 2 H), 5.96 (d, *J* = 3.9 Hz, 1 H), 5.41 (d, *J* = 3.9 Hz, 1 H), 4.13 (t, *J* = 6.9 Hz, 2 H), 3.32 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 162.6, 143.2, 139.7, 135.7, 134.9, 130.2, 129.8, 127.5, 122.7, 121.4, 120.8, 110.8, 110.4, 107.3, 46.3, 16.9.

Anal. Calcd for $C_{16}H_{10}Cl_3N_3O_2$: C, 50.22; H, 2.63; N, 10.98. Found: C, 50.34; H, 2.67; N, 11.07.

8-Chloro-1-(2,4-dichlorophenyl)-1,4,5,6-tetrahydropyrazolo[3,4-*c*]pyrrolo[1,2-*a*]azepine-3-carboxylic Acid (14b)
Following general procedure 4 using **11b** gave **14b** (2.520 g, 6.36 mmol, 92%) as a orange solid; mp 112–113 °C; R_f = 0.50 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 1701 cm^{-1}.

^1H NMR ($CDCl_3$, DMSO-d_6): δ = 11.80–11.40 (br s, 1 H), 7.81 (s, 1 H), 7.70–7.60 (m, 2 H), 5.97 (d, *J* = 4.0 Hz, 1 H), 5.29 (d, *J* = 4.0 Hz, 1 H), 3.80–3.20 (m, 4 H), 2.55–2.45 (m, 2 H).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 166.5, 141.3, 136.3, 135.7, 134.2, 130.5, 130.1, 128.1, 123.2, 118.2, 110.8, 110.2, 107.4, 43.4, 29.6, 19.3.

Anal. Calcd for $C_{17}H_{12}Cl_3N_3O_2$: C, 51.48; H, 3.05; N, 10.59. Found: C, 51.59; H, 3.01; N, 10.71.

Amidation of 6b,c, 14a,b; General Procedure 5
EDC (1.2 mmol) and BtOH (1.2 mmol) were added sequentially to a suspension of the tricyclic acid (1 mmol) in CH_2Cl_2 (15 mL). After 1 h the suspension became a soln and then 1-aminopiperidine (2 mmol) was added and stirring was continued at r.t. for 12 h. The organic phase was washed with H_2O (3 × 10 mL) and dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (PE–EtOAc, 7:3).

1-(2,4-Dichlorophenyl)-6-methyl-*N*-(piperidin-1-yl)-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxamide (7b)
Following general procedure 5 using **6b** gave **7b** (0.141 g, 0.33 mmol, 33%) as an orange solid; mp 157–158 °C; R_f = 0.21 (PE–EtOAc, 8:2).

IR (Nujol): 1645 cm^{-1}.

^1H NMR: δ = 7.65–7.60 (m, 2 H), 7.55 (d, *J* = 8.6 Hz, 1 H), 7.42 (d, *J* = 8.6 Hz, 1 H), 5.94 (d, *J* = 3.0 Hz, 1 H), 5.87 (d, *J* = 3.0 Hz, 1 H), 4.83 (s, 2 H), 2.88 (t, *J* = 5.0 Hz, 4 H), 2.27 (s, 3 H), 1.80–1.60 (m, 4 H), 1.50–1.35 (m, 2 H).

^{13}C NMR: δ = 158.5, 145.2, 135.7, 135.5, 130.6, 129.2, 128.8, 128.0, 125.2, 124.8, 118.1, 109.5, 99.7, 57.1, 44.4, 25.3, 23.2, 11.9.

Anal. Calcd for $C_{21}H_{21}Cl_2N_5O$: C, 58.61; H, 4.92; N, 16.27. Found: C, 58.78; H, 4.95; N, 16.38.

6-Chloro-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1,4-dihydropyrazolo[3,4-*a*]pyrrolizine-3-carboxamide (7c)
Following general procedure 5 using **6c** gave **7c** (0.275 g, 0.61 mmol, 61%) as an orange solid; mp 170–172 °C; R_f = 0.21 (PE–EtOAc, 8:2).

IR (Nujol): 1648 cm^{-1}.

^1H NMR: δ = 7.65–7.60 (m, 2 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.42 (d, *J* = 8.6 Hz, 1 H), 7.40–7.30 (m, 1 H), 6.08 (d, *J* = 3.8 Hz, 1 H), 5.92 (d, *J* = 3.8 Hz, 1 H), 4.91 (s, 2 H), 3.00–2.80 (m, 2 H), 1.80.1.60 (m, 4 H), 1.50–1.30 (m, 2 H).

^{13}C NMR: δ = 160.7, 142.9, 142.7, 135.4, 130.6, 130.3, 130.1, 129.8, 128.4, 128.3, 127.7, 125.8, 115.6, 109.2, 100.5, 47.7, 45.7, 43.8, 26.7, 24.6.

Anal. Calcd for $C_{20}H_{18}Cl_3N_5O$: C, 53.29; H, 4.03; N, 15.54. Found: C, 53.40; H, 4.00; N, 15.42.

7-Chloro-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-4,5-dihydropyrazolo[4,3-*g*]indolizine-3-carboxamide (15a)
Following general procedure 5 using **14a** gave **15a** (0.278 g, 0.60 mmol, 60%) as an orange solid; mp 165–166 °C; R_f = 0.23 (PE–EtOAc, 7:3).

IR (Nujol): 1639 cm^{-1}.

^1H NMR: δ = 7.60–7.30 (m, 4 H), 5.95 (d, *J* = 3.9 Hz, 1 H), 5.40 (d, *J* = 3.9 Hz, 1 H), 4.10 (t, *J* = 6.9 Hz, 2 H), 3.39 (t, *J* = 6.9 Hz, 2 H), 2.90–2.70 (m, 4 H), 1.80–1.60 (m, 4 H), 1.60–1.38 (m, 2 H).

^{13}C NMR: δ = 159.5, 142.3, 136.7, 135.7, 133.6, 130.6, 130.4, 128.2, 120.4, 118.9, 113.0, 107.4, 104.3, 57.1, 42.1, 25.4, 23.3, 20.6.

Anal. Calcd for $C_{21}H_{20}Cl_3N_5O$: C, 54.27; H, 4.34; N, 15.07. Found: C, 54.41; H, 4.31; N, 15.14.

8-Chloro-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydropyrazolo[3,4-*c*]pyrrolo[1,2-*a*]azepine-3-carboxamide (15b)
Following general procedure 5 using **14b** gave **15b** (0.211 g, 0.44 mmol, 44%) as an orange solid; mp 72–73 °C; R_f = 0.18 (PE–EtOAc, 7:3).

IR (Nujol): 1651 cm^{-1}.

^1H NMR: δ = 7.60–7.30 (m, 4 H), 5.89 (d, *J* = 4.2 Hz, 1 H), 5.34 (d, *J* = 4.2 Hz, 1 H), 4.30–4.05 (m, 2 H), 3.90–3.57 (m, 4 H), 3.02 (t, *J* = 7.2 Hz, 2 H), 2.20–2.00 (m, 2 H), 1.90–1.42 (m, 6 H).

^{13}C NMR: δ = 163.2, 146.5, 136.2, 135.9, 133.5, 133.6, 130.7, 130.4, 128.2, 121.8, 117.9, 116.4, 108.4, 106.9, 57.0, 48.4, 44.7, 43.0, 26.8, 22.9.

Anal. Calcd for $C_{22}H_{22}Cl_3N_5O$: C, 55.19; H, 4.63; N, 14.63. Found: C, 55.31; H, 4.61; N, 14.62.

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