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Azabicyclic Indole Esters as Potent 5-HT$_4$ Receptor Antagonists

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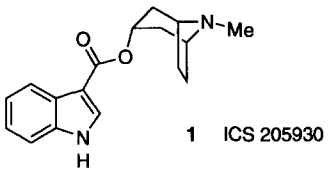
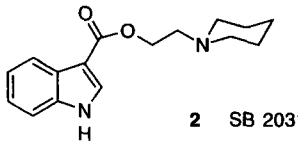
Abstract—The synthesis of a series of azabicyclic indole esters is described and their potency reported as 5-HT$_4$ receptor antagonists. Optimization of the most potent compound (**19**) by preparing the corresponding oxazino[3,2-*a*]indole ester afforded **34**, which had a pIC$_{50}$ of 9.5 in the guinea pig distal colon longitudinal muscle myenteric plexus preparation.

Introduction

The presence of functional 5-HT$_4$ receptors has been established in gut, heart and brain[1] and the initial characterization of the receptor was carried out using the mixed 5-HT$_3$/5-HT$_4$ receptor antagonist ICS 205930 (**1**, tropisetron).[2] Interest has continued in basic indole esters and recently more potent and selective 5-HT$_4$ receptor antagonists have been reported.[3,4] Among these was the piperidine ester SB 203186 (**2**).



1 ICS 205930



2 SB 203186

Previous work from our group has described the effect of conformational constraint of the side chain of substituted benzamides in the design of 5-HT$_4$ partial agonists.[5] We now describe the effect on 5-HT$_4$ receptor antagonist activity of introducing constraint and steric bulk into the basic side chain of a series of indole esters by using an azabicyclic ring system. The size of the azabicyclic ring system, the position of substitution on the ring, the two isomers possible at each substitution position, and the length of the linker chain to the ester have been studied. The investigation of the substitution position and linker chain length was undertaken in the quinolizidine series and the analogues of the most interesting compounds were prepared in two other azabicyclic series. We have also established in recently published work[6] that 5-HT$_4$ receptor antagonist potency is increased in a series of 4-*n*-butylpiperidinylmethyl indole esters by replacing the indole nucleus with an oxazino[3,2-*a*]indole analogue. We have therefore investigated conformational constraint of the side chain in the synthetically more accessible indole series and optimized potency by preparing the oxazino[3,2-*a*]indole analogue of the most potent indole.

Chemistry

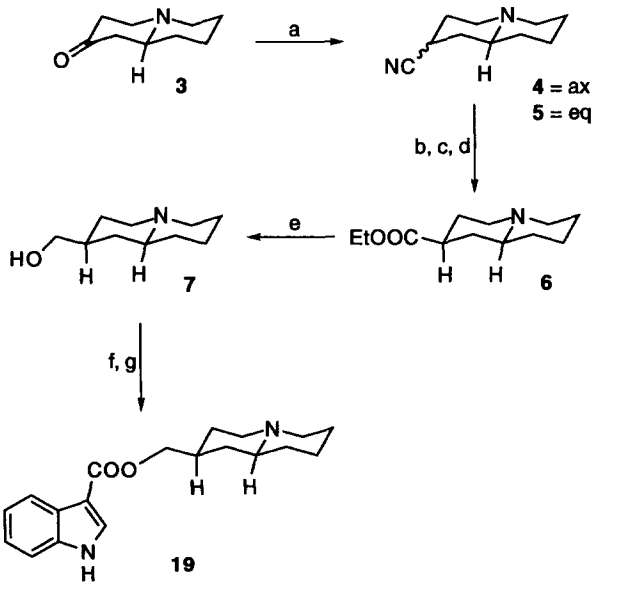
The ketones of the azabicyclic ring systems were common intermediates for building in the required functionality. For the indolizidines[7] and quinolizidines[8] these ketones were known compounds, but for the azabicyclo[5.4.0]undecane ring system, only the 1-azabicyclo[5.4.0]undecan-5-one had been previously prepared.[9] By use of a continuous extraction procedure to ensure high dilution conditions in a Dieckmann cyclization we obtained this ketone and the previously unreported 1-azabicyclo[5.4.0]undecan-4-one in 70% yield. For compounds **11–16**, the appropriate quinolizidinone was reduced to the corresponding quinolizidinol isomers following the methods of Aaron et al.[10] The examples with a methylene linker (**17–22** and **26–33**) were prepared by a common route, which is illustrated for the *equatorial* isomer of the 2-quinolizidine ring system (Scheme 1). Treatment of the appropriate ketone **3** with 4-toluenesulfonylmethyl isocyanide (TosMIC)[11] gave a mixture of the two nitrile isomers **4** and **5**, which were easily separated by chromatography. The two nitrile isomers of the other quinolizidines and indolizidines also proved separable by chromatography. Hydrolysis and esterification of the nitrile **5** gave the ester **6**, which was reduced with lithium aluminium hydride to afford the alcohol **7**. In the case of the azabicyclo[5.4.0]undecane ring system, the nitrile isomers could not be separated and were

converted to a mixture of the isomeric *cis* and *trans* alcohols. The preparation of the three examples with an ethylene linker (**23–25**) is illustrated for the *equatorial* isomer of the 2-quinolizidine in Scheme 2. The azabicyclic ketone **3** was converted to the unsaturated ester **8** using the Wadsworth–Emmons modification of the Wittig reaction. Reduction of the double bond by catalytic hydrogenation afforded the saturated ester **9**, which was reduced to the alcohol **10**. All the target esters were prepared by conversion of the appropriate alcohol to its alkoxide using an alkyllithium followed by reaction with indole-3-carboxylic acid chloride. Where mixtures of alcohol isomers had been used, the final esters were separable by chromatography.

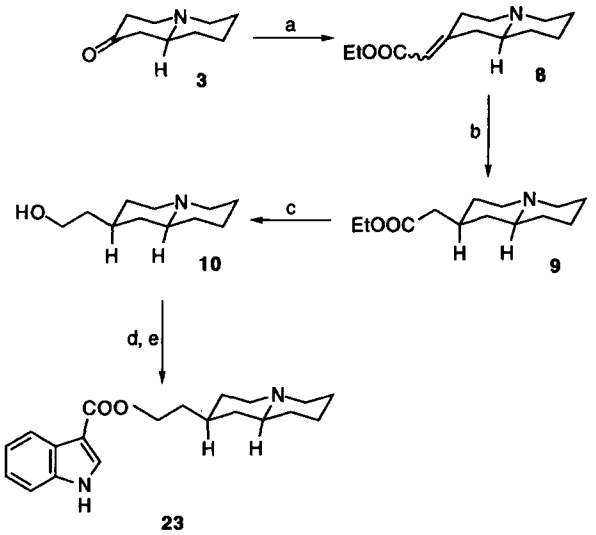
Results and Discussion

The structure–activity relationships within this series were obtained by operational pharmacology using the guinea pig isolated distal colon longitudinal muscle myenteric plexus (LMMP) preparation,[12] in which the ability of the test compound to block the 5-HT-evoked 5-HT_4 receptor mediated contraction was assessed. The results given in the Tables are expressed as pIC_{50} values.[13]

Table 1 gives results for variation in the length of the linker group and position of ring substitution within the quinolizidine series. With a one methylene linker length ($p = 1$) and substitution at the 1-position, both the *equatorial* and *axial* isomers (**17** and **18**) had low activity. With substitution at the 2-position, approximately a 1000-fold increase in potency was gained with each isomer (**19** and **20**). At the 3-position, the *equatorial* isomer **21** was more potent than the *axial* isomer **22**, the activity of the former approaching that of the 2-substituted compounds. The length of the linker chain was investigated at various ring positions. The removal of the methylene linker ($p = 0$) resulted in low potency for each isomer at all three ring positions (**11–16**). An increase in chain length to ethylene ($p = 2$) also resulted in low potency when investigated at the 2- and 3-positions (**23–25**). In view of these results, we concluded that only compounds with a one methylene linker should be investigated in other ring systems.

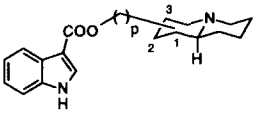


Scheme 1. Preparation of *eq*-quinolizidin-2-ylmethyl indole-3-carboxylate. Reagents and conditions: (a) TosMIC/KO'Bu/DME; (b) chromatography/SiO_2/Et_2O; (c) 8 M HCl; (d) EtOH/HCl; (e) $LiAlH_4$/THF; (f) BuLi/THF; (g) indole-3-carboxylic acid chloride.



Scheme 2. Preparation of *eq*-quinolizidin-2-ylethyl indole-3-carboxylate. Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$/KO'Bu/DMF; (b) H_2/Pd-C/EtOH; (c) $LiAlH_4$/THF; (d) BuLi/THF; (e) indole-3-carboxylic acid chloride.

Table 1. pIC_{50}s for substitution position on quinolizidines

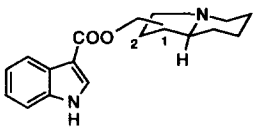


Compound	p	Isomer	Position	pIC_{50} (n)
ICS 205930				5.5±0.1 (5)
SB 203186				7.2±0.2 (4)
11	0	*eq*	1	5.8±0.2 (3)
12	0	*ax*	1	5.9±0.1 (3)
13	0	*eq*	2	5.8±0.5 (2)
14	0	*ax*	2	5.8±0.2 (3)
15	0	*eq*	3	6.1±0.1 (2)
16	0	*ax*	3	5.7±0.2 (2)
17	1	*eq*	1	5.6±0.2 (2)
18	1	*ax*	1	5.7±0.1 (2)
19	1	*eq*	2	8.5±0.2 (3)
20	1	*ax*	2	8.2±0.2 (2)
21	1	*eq*	3	7.8±0.3 (2)
22	1	*ax*	3	6.2±0.1 (2)
23	2	*eq*	2	5.6±0.1 (2)
24	2	*eq*	3	5.8±0.2 (2)
25	2	*ax*	3	6.6±0.1 (2)

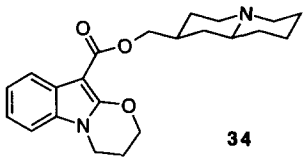
Within the indolizidine ring system (Table 2), the *trans* isomer[14] (**26**), with a methylene linker and substitution at the 1-position, was 10-fold more potent than the *cis* isomer[14] (**27**). As with the quinolizidines, a further increase in potency was observed when substitution was moved to the 2-position, with the activity of **28** and **29** similar to that of the best quinolizidines (**19** and **20**). In the azabicyclo[5.4.0]undecane ring system, examples were restricted to substitution at the 4- and 5-positions with a one methylene linker. At the 4-position both *trans* and *cis* isomers[14] (**30** and **31**) were approximately equipotent and were comparable to the best of the quinolizidines. When substitution was moved to the 5-position (**32** and **33**), activity fell by 50- to 100-fold.

These results indicate that there is an optimum distance required between the ester and the basic nitrogen for 5-HT_4 receptor antagonist potency, which is evident from our work within the quinolizidine ring system. The two compounds of highest potency (**19** and **20**) have a one methylene spacer between the ester and azabicyclic ring system. When this spacer group is removed as in the corresponding 2-substituted analogues **13** and **14**, potency drops by over 200-fold. Equally, when the distance is increased between ester and azabicyclic ring system as in **23**, the corresponding analogue of **19**, then almost a 1000-fold decrease in potency is observed. However, distance between the ester and basic nitrogen cannot be the only factor affecting potency, as **24** and **25** have the same apparent distance as **19** and **20**. The difference between these sets of compounds is the substitution position on the azabicylic ring, which suggests that the significantly lower potency of the latter two compounds is the result of an unfavourable steric interaction with the receptor. This optimum ester–nitrogen distance is again observed in the 1-azabicyclo[5.4.0]undecanes, with **30** and **31** showing high potency. The lower potency of positional isomers **32** and **33** may again be due to adverse steric interactions. In the indolizidine system, the smaller difference between the potencies may reflect the smaller ring size and a decreased demand of the restricted steric volume at the receptor.

Table 2. pIC_{50}s for variation in ring size of azabicycles



Compound	Isomer	Position	pIC_{50} (n)
26	*trans*	1	7.4±0.3 (2)
27	*cis*	1	6.3±0.4 (2)
28	*trans*	2	8.1±0.3 (2)
29	*cis*	2	7.7±0.3 (2)
30	*trans*	4	8.4±0.4 (2)
31	*cis*	4	8.1±0.1 (2)
32	*trans*	5	7.0±0.3 (4)
33	*cis*	5	6.5±0.2 (3)



34

Recently reported work from our group[6] has described the synthesis of an oxazino[3,2-*a*]indole ring system and established that this nucleus is superior to a 3-substituted indole regarding binding affinity in a series of 5-HT_4 receptor antagonists. Therefore, the quinolizidinylmethyl side chain of one of the best compounds reported here (**19**) was incorporated with the oxazino[3,2-a]indole nucleus to give compound **34**, which showed a 10-fold increase in potency with a pIC_{50} of 9.5±0.1 ($n = 5$). This compound was also evaluated for its ability to inhibit the binding of the 5-HT_4 receptor radioligand [^{125}I] SB 207710[15] to piglet hippocampal membranes giving a pK_i value of 10.00±0.05 ($n = 3$).

Experimental

General

Starting materials were purchased from Lancaster Synthesis or Aldrich Chemical Co. and were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone prior to use. Silica gel used for column chromatography was Kieselgel 60 (70–230 mesh) purchased from Merck. ^{1}H NMR spectra were recorded at 250 MHz on a Brucker AC 250, or at 200 MHz on a Bruker AC 200 spectrometer using tetramethylsilane (TMS) as internal standard. Melting points were recorded on a Reichert hot-plate apparatus and are uncorrected. Mass spectra were recorded on a Fisons VG 302 single quadrapole mass spectrometer. Concentration of solutions was carried out under vacuum. Stereochemical assignments were determined using data from previous literature studies.[9,16–21]

1-Azabicyclo[5.4.0]undecan-4-one. A stirred solution of ethyl piperidinyl-2-propionate[22] (22.2 g, 0.12 mol) in EtOH (350 mL) was treated with ethyl acrylate (26 mL, 0.24 mol) and heated under reflux for 4 h. The solution was concentrated and the residue was chromatographed on silica gel eluting with Et_2O to give diethyl piperidinyl-1,2-dipropionate (9.6 g, 28%) as a yellow oil. In a continuous extraction apparatus, a solution of this diester (13.7 g, 0.047 mol) in xylene

(100 mL) was added dropwise over 4 h via the condenser to a 250 mL upper flask containing xylene. This upper flask was being continuously extracted into a heated lower flask containing a stirred mixture of NaH (4.2 g of 80% oil dispersion, 0.14 mol) in xylene (100 mL) and EtOH (0.5 mL) under N_2. Vigorous reflux was maintained for a total of 40 h to ensure complete extraction of the diester from the upper flask. The lower flask was then cooled in an ice bath and treated with 5 M HCl (250 mL). The aqueous layer was separated, treated with concentrated HCl (30 mL) and heated under reflux for 18 h. The solution was cooled, basified with K_2CO_3, and extracted with Et_2O (3×100 mL). The combined extracts were dried, concentrated and the residue distilled in a Kugelrohr apparatus to give a colourless oil (4.6 g, 84%): bp ca. 110 °C at 0.25 mm Hg; ^{1}H NMR ($CDCl_3$) δ 2.75–3.05 (m, 4H), 2.44–2.70 (m, 4H), 2.15–2.30 (m, 1H), 2.00–2.15 (m, 1H), 1.15–1.90 (m, 7H).

***eq*- and *ax*-Quinolizidin-2-ylcarbonitrile (4 and 5).** A stirred solution of quinolizidin-2-one[16] (2.5 g, 0.016 mol), 4-toluenesulphonylmethyl isocyanide (3.89 g, 0.020 mol) and EtOH (1.9 mL, 0.032 mol) in dimethoxyethane (60 mL) at 5 °C under N_2 was treated portionwise over 0.25 h with potassium *tert*-butoxide (3.8 g, 0.032 mol) keeping the temperature below 15 °C. The mixture was allowed to warm to room temperature (rt) over 2 h, heated at 40 °C for 0.5 h, then concentrated. The residue was treated with a concentrated K_2CO_3 solution and extracted with EtOAc. The extract was dried, concentrated and the residue was chromatographed on silica gel eluting initially with Et_2O, then with EtOAc to give 1.1 g (42%) of *eq* isomer (**4**): ^{1}H NMR ($CDCl_3$) δ 2.91–2.73 (m, 2H), 2.56–2.38 (m, 1H), 2.10–1.45 (m, 11H), 1.38–1.15 (m, 2H) and 0.75 g (29%) of *ax* isomer (**5**): ^{1}H NMR ($CDCl_3$) δ 3.05–2.95 (m, 1H), 2.87–2.70 (m, 2H), 2.52–2.28 (m, 1H), 2.20–2.00 (m, 2H), 1.98–1.45 (m, 8H), 1.40–1.10 (m, 2H).

***eq*-Ethyl quinolizidin-2-ylcarboxylate (6).** A solution of **4** (1.1 g, 0.0068 mol) in concentrated HCl (40 mL) was heated under reflux for 7 h, then concentrated to leave a brown solid. This was treated with EtOH (60 mL) and concentrated HCl (2 mL) and heated under reflux for 3 h. The solution was concentrated and the residue basified with concentrated K_2CO_3 solution and extracted with EtOAc. The extract was dried and concentrated to leave **6** as a brown oil (1.23 g, 86%): ^{1}H NMR ($CDCl_3$) δ 4.12 (q, 2H), 2.92–2.77 (m, 2H), 2.40–2.25 (m, 1H), 2.10–1.54 (m, 10H), 1.50–1.20 (m, 3H), 1.25 (t, 3H).

***eq*-Quinolizidin-2-ylmethanol (7).** A solution of **6** (1.22 g, 0.0058 mol) in THF (10 mL) was added to a stirred suspension of lithium aluminium hydride (0.23 g, 0.0060 mol) in THF (15 mL) under N_2, and then stirred at rt for 1 h. The reaction mixture was cooled and treated cautiously with water (0.25 mL), followed by 10% NaOH solution (0.25 mL), followed by water (0.75 mL), then filtered through kieselguhr and the filtrate concentrated. The residue was distilled in a Kugelrohr apparatus to give **7** as a colourless oil (0.86 g, 88%), which solidified on standing: ^{1}H NMR ($CDCl_3$) δ 3.46 (d, 2H), 2.92–2.78 (m, 2H), 2.30–1.50 (m, 11H), 1.42–1.20 (m, 3H), 0.98 (q, 1H).

2-Ethoxycarbonylmethylenequinolizidine (8). A stirred solution of triethyl phosphonoacetate (23.1 g, 0.10 mol) in dimethoxyethane (80 mL) under N_2 was treated portionwise with potassium *tert*-butoxide (10.5 g, 0.094 mol). After 20 min at rt the mixture was cooled in an ice bath and treated dropwise with a solution of quinolizidin-2-one (8.0 g, 0.052 mol) in dimethoxyethane (25 mL). The reaction mixture was allowed to warm to rt and stirred for 20 h, before adding 5 M HCl (200 mL). The mixture was washed with EtOAc (3×100 mL), then basified by addition of K_2CO_3 and extracted with Et_2O. The extract was dried and concentrated to afford **8** as a yellow oil (9.4 g, 81%): ^{1}H NMR ($CDCl_3$) δ 5.59 (s, 1H), 4.12 (q, 2H), 3.83–3.68 (m, 1H), 2.98–2.78 (m, 2H), 2.60–2.45 (m, 1H), 2.32–1.55 (m, 9H), 1.40–1.13 (m, 2H), 1.25 (t, 3H).

***eq*-Ethyl quinolizidin-2-ylacetate (9).** A solution of **8** (7.0 g, 0.031 mol) in EtOH (100 mL) and AcOH (10 mL) was treated with 10% Pd-C (1 g) and hydrogenated at 200 psi pressure and rt for 14 h. The catalyst was removed by filtration through kieselguhr and the filtrate was concentrated. The residue was treated with excess K_2CO_3 solution and extracted with EtOAc. The extract was dried and concentrated to afford **9** as a yellow oil (6.7 g, 95%): ^{1}H NMR ($CDCl_3$) δ 4.12 (q, 2H), 2.90–2.78 (m, 2H), 2.21 (d, 2H), 2.15–1.50 (m, 10H), 1.48–1.19 (m, 3H), 1.26 (t, 3H), 1.02 (q, 1H).

2-(*eq*-Quinolizidin-2-yl)ethanol (10). A solution of **9** in THF was reduced with lithium aluminium hydride using the method described for **7** (90%): bp (Kugelrohr apparatus) ca. 120 °C at 0.15 mm Hg: ^{1}H NMR ($CDCl_3$) δ 3.75–3.63 (m, 2H), 2.84 (dt, 2H), 2.13–1.90 (m, 2H), 1.80–1.15 (m, 14H), 1.10–0.90 (m, 1H).

***eq*-Quinolizidin-2-ylmethyl indole-3-carboxylate (19).** A suspension of indole-3-carboxylic acid (0.40 g, 0.0025 mol) in dichloromethane (25 mL) at rt under N_2 was treated with oxalyl chloride (0.24 mL, 0.0028 mol) followed by DMF (1 drop) and stirred for 2 h. The solution was then concentrated to leave the acid chloride as a yellow solid. A stirred solution of **7** (0.44 g, 0.0025 mol) in dry THF (10 mL) at 5 °C under N_2 was treated with 1.6 M *n*-butyllithium in hexanes (1.56 mL, 0.0025 mol) and stirred for 10 min. A solution of the above acid chloride (0.0025 mol) in dry THF (5 mL) was added to the alkoxide solution, which was then allowed to warm to rt and stirred for 2 h. The reaction mixture was treated with 10% Na_2CO_3 solution and extracted with EtOAc. The extract was dried and concentrated to leave a yellow oil, which crystallized from Et_2O to afford **19** as a beige solid (0.15 g, 20%): mp 154–157 °C: ^{1}H NMR ($CDCl_3$) δ

9.40 (br s, 1H), 8.20–8.10 (m, 1H), 7.87 (d, 1H), 7.45–7.35 (m, 1H), 7.30–7.20 (m, 2H), 4.20 (d, 2H), 2.97–2.80 (m, 2H), 2.20–1.43 (m, 11H), 1.40–1.10 (m, 3H); calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97%. Found: C, 72.65; H, 7.49; N, 8.87%.

The following compounds were prepared using analogous methods.

***eq*-Quinolizidin-1-yl indole-3-carboxylate (11).** Mp 230–232 °C (from Et_2O); ^1H NMR ($CDCl_3$) δ 8.88 (br s, 1H), 8.20–8.11 (m, 1H), 7.93 (d, 1H), 7.46–7.38 (m, 1H), 7.32–7.22 (m, 2H), 4.94–4.80 (m, 1H), 2.98–2.75 (m, 2H), 2.32–1.92 (m, 5H), 1.88–1.38 (m, 6H), 1.35–1.15 (m, 2H); calcd for $C_{18}H_{22}N_2O_2.0.25H_2O$: C, 71.40; H, 7.44; N, 9.26%. Found; C, 71.78; H, 7.29; N, 9.57%.

***ax*-Quinolizidin-1-yl indole-3-carboxylate (12).** Mp 80–85 °C (from Et_2O); ^1H NMR ($CDCl_3$) δ 9.75 (br s, 1H), 8.36–8.27 (m, 1H), 7.83 (d, 1H), 7.45–7.17 (m, 3H), 5.20 (s, 1H), 3.05–2.90 (m, 2H), 2.30–1.15 (m, 13H); calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.44; N, 9.26%. Found: C, 72.08; H, 7.38; N, 9.39%.

***eq*-Quinolizidin-2-yl indole-3-carboxylate (13).** Mp 215–216 °C (from EtOAc/60–80 petrol); ^1H NMR (DMSO-d_6) δ 12.0 (br s, 1H), 8.15 (s, 1H), 8.10–8.04 (m, 1H), 7.60–7.53 (m, 1H), 7.35–7.22 (m, 2H), 5.00–4.84 (m, 1H), 2.95–2.80 (m, 2H), 2.23–1.18 (m, 13H); calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%. Found: C, 72.22; H, 7.32; N, 9.33%.

***ax*-Quinolizidin-2-yl indole-3-carboxylate (14).** Mp 67–72 °C (from EtOAc); ^1H NMR ($CDCl_3$) δ 8.97 (br s, 1H), 8.27–8.18 (m, 1H), 7.96 (d, 1H), 7.48–7.39 (m, 1H), 7.37–7.23 (m, 2H), 5.43–5.35 (m, 1H), 2.98–2.87 (m, 1H), 2.83–2.71 (m, 1H), 2.67–2.52 (m, 1H), 2.40–1.90 (m, 5H), 1.85–1.48 (m, 5H), 1.43–1.20 (m, 2H); calcd for $C_{18}H_{22}N_2O_2 \cdot H_2O$: C, 68.35; H, 7.59; N, 8.86%. Found: C, 68.23; H, 7.43, N, 8.72%.

***eq*-Quinolizidin-3-yl indole-3-carboxylate (15).** Mp 199–202 °C (from EtOAc/60–80 petrol); ^1H NMR ($CDCl_3$) δ 8.95 (br s, 1H), 8.18–8.10 (m, 1H), 7.93 (d, 1H), 7.46–7.38 (m, 1H), 7.30–7.20 (m, 2H), 5.24–5.10 (m, 1H), 3.27–3.16 (m, 1H), 2.93–2.82 (m, 1H), 2.33–1.40 (m, 11H), 1.40–1.19 (m, 2H); calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%. Found: C, 71.96; H, 7.27; N, 9.46%.

***ax*-Quinolizidin-3-yl indole-3-carboxylate (16).** Mp 202–204 °C (from Et_2O); ^1H NMR ($CDCl_3$) δ 11.35 (br s, 1H), 7.90–7.82 (m, 1H), 7,52 (d, 1H), 7.25–7.16 (m, 1H), 7.10–6.94 (m, 2H), 5.21 (br s, 1H), 3.45–3.33 (m, 1H), 3.00–2.86 (m, 1H), 2.60–1.20 (m, 13H); calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%. Found: C, 72.25; H, 7.45; N, 9.38%.

***eq*-Quinolizidin-1-ylmethyl indole-3-carboxylate (17).** Mp 55–60 °C; ^1H NMR ($CDCl_3$) δ 10.35 (br s, 1H), 8.25–8.15 (m, 1H), 7.94 (d, 1H), 7.47–7.37 (m, 1H), 7.32–7.22 (m, 2H), 4.43–4.22 (m, 2H), 2.97–2.83 (m, 2H), 2.20–1.50 (m, 11H), 1.46–1.20 (m, 3H); calcd for $C_{19}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 72.05; H, 7.74; N, 8.85%. Found: C, 72.24; H, 7.60; N, 8.90%.

***ax*-Quinolizidin-1-ylmethyl indole-3-carboxylate (18).** Mp 173–177 °C; ^1H NMR ($CDCl_3$) δ 9.75 (br s, 1H), 8.23–8.12 (m, 1H), 7.92 (s, 1H), 7.47–7.36 (m, 1H), 7.32–7.20 (m, 2H), 4.72–4.60 (m, 1H), 4.53–4.40 (m, 1H), 2.95–2.80 (m, 2H), 2.25–1.15 (m, 14H); calcd for $C_{19}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 72.05; H, 7.74; N, 8.85%. Found: C, 71.96; H, 7.54; N, 8.93%.

***ax*-Quinolizidin-2-ylmethyl indole-3-carboxylate (20).** Mp 156–157 °C (from Et_2O/pentane); ^1H NMR ($CDCl_3$) δ 9.40 (br s, 1H), 8.20–8.10 (m, 1H), 7.93 (d, 1H), 7.45–7.37 (m, 1H), 7.33–7.22 (m, 2H), 4.50–4.35 (m, 2H), 2.93–2.77 (m, 1H), 2.75–2.63 (m, 1H), 2.43–2.23 (m, 2H), 2.20–1.43 (m, 10H), 1.40–1.17 (m, 2H); calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74, N, 8.97%. Found: C, 72.86; H, 7.69; N, 8.86%.

***eq*-Quinolizidin-3-ylmethyl indole-3-carboxylate (21).** Mp 187–188 °C; ^1H NMR ($CDCl_3$) δ 9.65 (br s, 1H), 8.23–8.15 (m, 1H), 7.90 (d, 1H), 7.50–7.40 (m, 1H), 7.30–7.22 (m, 2H), 4.18 (d, 2H), 3.17–3.07 (m, 1H), 2.93–2.82 (m, 1H), 2.37–2.15 (m, 1H), 2.15–1.53 (m, 9H), 1.50–1.07 (m, 4H); calcd for $C_{19}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 72.05; H, 7.74; N, 8.85%. Found: C, 72.12; H, 7.56; N, 8.80%.

***ax*-Quinolizidin-3-ylmethyl indole-3-carboxylate (22).** Mp 157–158 °C; ^1H NMR ($CDCl_3$) δ 9.40 (br s, 1H), 8.20–8.13 (m, 1H), 7.91 (d, 1H), 7.45–7.37 (m, 1H), 7.30–7.21 (m, 2H), 4.60–4.45 (m, 2H), 2.96–2.85 (m, 1H), 2.79–2.68 (m, 1H), 2.28–1.20 (m, 14H); calcd for $C_{19}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 72.05; H, 7.74; N, 8.85%. Found: C, 72.37; H, 7.57; N, 8.70%.

***eq*-Quinolizidin-2-ylethyl indole-3-carboxylate (23).** Mp 170–172 °C (from EtOAc/60–80 petrol); ^1H NMR ($CDCl_3$) δ 9.15 (br s, 1H), 8.22–8.12 (m, 1H), 7.91 (d, 1H), 7.45–7.36 (m, 1H), 7.30–7.20 (m, 2H), 4.38 (t, 2H), 2.92–2.80 (m, 2H), 2.17–1.93 (m, 3H), 1.83–1.20 (m, 12H), 1.18–1.00 (m, 1H); calcd for $C_{20}H_{26}N_2O_2 \cdot 0.25H_2O$: C, 72.61; H, 8.02; N, 8.47%. Found: C, 72.65; H, 7.80; N, 8.46%.

***eq*-Quinolizidin-3-ylethyl indole-3-carboxylate (24).** HCl salt mp 224–225 °C (from acetone); ^1H NMR ($CDCl_3$) δ 10.0 (br s, 1H), 8.18–8.10 (m, 1H), 7.68 (d, 1H), 7.42–7.32 (m, 1H), 7.25–7.15 (m, 2H), 4.35 (t, 2H), 2.98–2.78 (m, 2H), 2.12–1.45 (m, 11H), 1.45–0.90 (m, 5H); calcd for $C_{20}H_{26}N_2O_2 \cdot HCl \cdot 0.25H_2O$: C, 65.39; H, 7.49; N, 7.63%. Found; C, 65.55, H, 7.31; N, 7.72%.

***ax*-Quinolizidin-3-ylethyl indole-3-carboxylate (25).** HCl salt mp 207–209 °C (from acetone); ^1H NMR ($CDCl_3$) δ 9.30 (br s, 1H), 8.18–8.10 (m, 1H), 7.87 (d, 1H), 7.45–7.35 (m, 1H), 7.30–7.20 (m, 2H), 4.36 (t, 2H), 2.80–2.65 (m, 2H), 2.25–1.85 (m, 5H), 1.80–1.15

(m, 11H); calcd for $C_{20}H_{26}N_2O_2 \cdot 0.25H_2O$: C, 72.61; H, 8.02; N, 8.47%. Found: C, 72.84; H, 7.81; N, 8.50%.

***trans*-1,9-*H*-Indolizidin-1-ylmethyl indole-3-carboxylate (26).** Mp 116–118 °C (from Et_2O); ^1H NMR ($CDCl_3$) δ 9.30 (br s, 1H), 8.23–8.12 (m, 1H), 7.90 (d, 1H), 7.47–7.37 (m, 1H), 7.33–7.22 (m, 2H), 4.40–4.28 (m, 2H), 3.18–3.05 (m, 2H), 2.35–1.95 (m, 5H), 1.85–1.47 (m, 5H), 1.43–1.13 (m, 2H); calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%. Found: C, 72.31; H, 7.30; N, 9.54%.

***cis*-1,9-*H*-Indolizidin-1-ylmethyl indole-3-carboxylate (27).** Mp 140–141 °C (from Et_2O); ^1H NMR ($CDCl_3$) δ 9.00 (br s, 1H), 8.25–8.15 (m, 1H), 7.90 (d, 1H), 7.45–7.37 (m, 1H), 7.30–7.20 (m, 2H), 4.50–4.40 (dd, 1H), 4.20–4.08 (dd,1H), 3.20–3.00 (m, 2H), 2.68–2.50 (m, 1H), 2.15–1.35 (m, 10H), 1.30–1.10 (m, 1H); calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%. Found: C, 71.98; H, 7.36; N, 9.41%.

***trans*-2,9-*H*-Indolizidin-2-ylmethyl indole-3-carboxylate (28).** HCl salt mp 199–201 °C (from acetone); HCl salt ^1H NMR (DMSO-d_6) δ 12.15 (br s, 1H), 10.95 (br s, 1H), 8.14 (d, 1H), 7.99–7.92 (m, 1H), 7.54–7.47 (m, 1H), 7.24–7.17 (m, 2H), 4.37–4.18 (m, 2H), 3.70–3.60 (m, 1H), 3.54–3.45 (m, 1H), 3.27–3.10 (m, 1H), 2.95–2.75 (m, 2H), 2.15–1.55 (m, 8H), 1.50–1.32 (m, 1H); calcd for $C_{18}H_{22}N_2O_2 \cdot HCl \cdot 0.25H_2O$: C, 63.73; H, 6.93; N, 8.26%. Found: C, 63.77; H, 6.71; N, 8.17%.

***cis*-2,9-*H*-Indolizidin-2-ylmethyl indole-3-carboxylate (29).** HCl salt mp 191–194 °C (from acetone); HCl salt ^1H NMR (DMSO-d_6) δ 12.10 (br s, 1H), 10.95 (br s, 1H), 8.18 (d, 1H), 8.00–7.90 (m, 1H), 7.55–7.45 (m, 1H), 7.26–7.14 (m, 2H), 4.34 (d, 2H), 3.56–3.35 (m, 2H), 3.25–3.04 (m, 2H), 2.96–2.74 (m, 2H), 2.45–2.28 (m, 1H), 2.10–1.30 (m, 7H); calcd for $C_{18}H_{22}N_2O_2 \cdot HCl \cdot 0.5H_2O$: C, 62.88; H, 6.98; N, 8.15%. Found: C, 62.83; H, 6.63; N, 7.86%.

***trans*-4,7-*H*-1-Azabicyclo[5.4.0]undecan-4-ylmethyl indole-3-carboxylate (30).** HCl salt mp 160–162 °C (from acetone); HCl salt ^1H NMR (DMSO-d_6) δ 12.05 (s, 1H), 10.30 (br s, 1H), 8.10 (d, 1H), 8.02–7.94 (m, 1H), 7.54–7.45 (m, 1H), 7.25–7.14 (m, 2H), 4.08 (d, 2H), 3.60–2.85 (m, 5H), 2.65–1.30 (m, 13H); LRMS (CI) 327 (M^+H, 43), 166 (100), 118 (98), HRMS calcd for $C_{20}H_{26}N_2O_2$: 326.1994; found: 326.1990.

***cis*-4,7-*H*-1-Azabicyclo[5.4.0]undecan-4-ylmethyl indole-3-carboxylate (31).** HCl salt mp 130–135 °C; HCl salt ^1H NMR ($CDCl_3$) δ 11.30 (br s, 1H), 10.10 (br s, 1H), 8.15–8.03 (m, 2H), 7.58–7.48 (m, 1H), 7.30–7.20 (m, 2H), 4.12 (d, 2H), 3.55–3.30 (m, 2H), 2.93–2.50 (m, 3H), 2.50–1.60 (m, 12H), 1.50–1.30 (m, 1H); LRMS (CI) 327 (M^+H, 88), 166 (100), 118 (94), HRMS calcd for $C_{20}H_{26}N_2O_2$: 326.1995; found: 326.2009.

***trans*-5,7-*H*-1-Azabicyclo[5.4.0]undecan-5-ylmethyl indole-3-carboxylate (32).** Mp 138–140 °C; ^1H NMR ($CDCl_3$) δ 9.30 (br s, 1H), 8.21–8.11 (m, 1H), 7.92 (s, 1H), 7.47–7.38 (m, 1H), 7.32–7.22 (m, 2H), 4.26–4.07 (m, 2H), 2.98–2.83 (m, 2H), 2.60–2.05 (m, 5H), 1.98–1.15 (m, 11H); calcd for $C_{20}H_{26}N_2O_2 \cdot 0.5H_2O$: C, 71.64; H, 8.06; N, 8.35%. Found: C, 71.94; H, 7.66; N, 8.60%.

***cis*-5,7-*H*-1-Azabicyclo[5.4.0]undecan-5-ylmethyl indole-3-carboxylate (33).** Mp 109–110 °C; ^1H NMR ($CDCl_3$) δ 9.05 (br s, 1H), 8.23–8.15 (m, 1H), 7.92 (d, 1H), 7.45–7.35 (m, 1H), 7.30–7.20 (m, 2H), 4.15 (d, 2H), 2.90–2.80 (m, 1H), 2.72–2.45 (m, 2H), 2.42–2.18 (m, 3H), 2.05–1.90 (m ,1H), 1.87–1.35 (m, 9H) 1.35–1.10 (m, 2H); LRMS (CI) 327(M^+H, 98), 166 (100), 118 (93), HRMS calcd for $C_{20}H_{26}N_2O_2$: 326.1995; found: 236.2005.

***eq*-Quinolizidin-2-ylmethyl 3,4-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxylate (34).** A stirred solution of *N*-chlorosuccinimide (175 mg, 0.0014 mol) in $CHCl_3$ (5 mL) was treated with a solution of **19** (300 mg, 0.96 mmol) in $CHCl_3$ (5 mL) and kept at rt for 2 h. The solution was treated with 3-bromopropan-1-ol (0.14 mL, 0.0015 mol), stirred at rt for 18 h, then treated with additional 3-bromopropan-1-ol (0.06 mL, 0.64 mmol). The solution was stirred at rt for a further 3 h, then treated with 10% Na_2CO_3 solution and extracted with $CHCl_3$. The extract was dried, concentrated and the residue treated with acetone (20 mL) and anhydrous K_2CO_3 (580 mg, 0.0042 mol) and stirred at rt for 18 h. The mixture was concentrated, the residue treated with 10% Na_2CO_3 solution and extracted with EtOAc. The extract was dried, concentrated and the residue was chromatographed on silica gel eluting with 3% MeOH/$CHCl_3$, then on basic alumina eluting with EtOAc to afford **34** as a colourless oil (180 mg, 51%); ^1H NMR ($CDCl_3$) δ 7.97 (d, 1H), 7.30–7.06 (m, 3H), 4.50 (t, 2H), 4.23–4.10 (m, 2H), 4.07 (t, 2H), 2.93–2.78 (m, 2H), 2.40–2.23 (m, 2H), 2.15–1.03 (m, 14H); HCl salt mp 164–167 °C (from acetone); LRMS (EI) 368 (M^+, 17), 168 (56), 151 (100); HRMS calcd for $C_{22}H_{28}N_2O_3$: 368.2100; found: 368.2107.

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13. pIC_{50} is the negative logarithm of the concentration of compound required to reduce by 50% the response evoked by the EC_{50} concentration of 5-HT.

14. *cis* refers to the isomer where the indole ester is on the same side of the reference plane as the bridgehead hydrogen atom and *trans* refers to the isomer where the indole ester is on the opposite side of the reference plane to the bridgehead hydrogen atom.

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