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Synthesis and activity of a new class of dual acting norepinephrine and serotonin reuptake inhibitors: 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines

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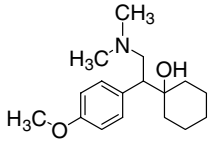
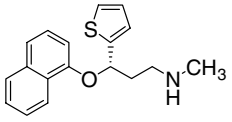
Abstract—Compounds with a combination of norepinephrine and serotonin reuptake inhibition have been approved in the US and Europe for a number of indications, including major depressive disorder and pain disorders such as diabetic neuropathy and fibromyalgia. Efforts to design selective norepinephrine reuptake inhibitors based on SAR from the aryloxypropanamine series of monoamine reuptake inhibitors have led to the identification of a potent new class of dual acting norepinephrine and serotonin reuptake inhibitors, namely the 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines.

1. Introduction

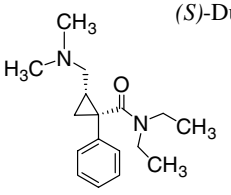
Drugs that selectively inhibit norepinephrine reuptake, including reboxetine (**7**), nisoxetine (**5**), and atomoxetine (**6**), are marketed for the treatment of major depressive disorder (MDD) and, more recently, attention deficit hyperactivity disorder (ADHD). In addition, these compounds have been reported to show efficacy for chronic pain disorders such as fibromyalgia[1,2] and low back pain.[1] Compounds that possess a combination of norepinephrine and serotonin reuptake inhibition, such as venlafaxine (**1**), duloxetine (**2**), and milnacipran (**3**), have been approved in the US and Europe for a number of indications including MDD and pain disorders such as diabetic neuropathy and fibromyalgia. Furthermore, these compounds have been reported to show efficacy for other ailments such as stress urinary incontinence (SUI)[3–6] and ADHD.[7,8]



Venlafaxine (**1**)



(S)-Duloxetine (**2**)



Milnacipran (**3**)

Compounds containing an aryloxypropanamine moiety have long been recognized as monoamine reuptake inhibitors. Their selectivity profile for the norepinephrine and serotonin transporters depends upon the substitution pattern of the aryloxy ring (see Table 1). Compounds that contain a substituent in the 2′-position of the aryloxy ring [e.g., nisoxetine (**5**), atomoxetine (**6**), and reboxetine (**7**)] are generally selective norepinephrine reuptake inhibitors (NRIs) while compounds that have a substituent in the 4′-position [e.g., fluoxetine (**4**) and paroxetine (**8**)] are selective serotonin reuptake

Keywords: Monoamine reuptake inhibitors; Norepinephrine reuptake inhibitors; Serotonin reuptake inhibitors; Aryloxypropanamines.
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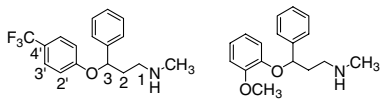
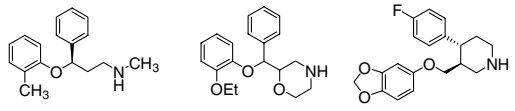
Table 1. Inhibitory activity at the human norepinephrine and serotonin transporters of compounds within the aryloxypropanamine class



Fluoxetine (**4**) Nisoxetine (**5**)



Atomoxetine (**6**) Reboxetine (**7**) Paroxetine (**8**)

Compound	Name	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hSERT IC_{50}/hNET IC_{50}[c]
2	(*S*)-Duloxetine	4	3	0.75
4	Fluoxetine	563	10	0.02
5	Nisoxetine	6	277	46
6	Atomoxetine	3	48	16
7	Reboxetine	3	242	81
8	Paroxetine	100	2	0.02

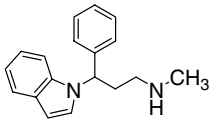
[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET.

[b] Inhibition of serotonin uptake in JAR cells, stably transfected with human SERT.

[c] Unitless value as a ratio in which higher numbers represent relatively greater NET selectivity. A value of 1 represents no selectivity.

inhibitors (SRIs). Duloxetine (**2**), which contains a phenyl group fused at the 2′- and 3′-positions, has similar potencies for the two transporters.

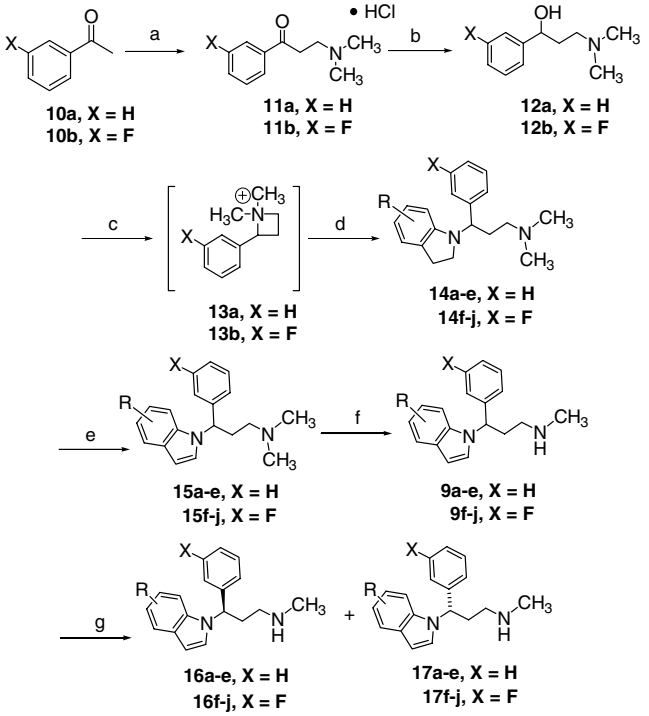
A drug discovery project was initiated to identify novel and selective norepinephrine reuptake inhibitors for screening in a panel of predictive animal models. Thus, a series of 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines **9**, which contained an indole ring as a replacement for the aryloxy group in the aryloxypropanamine scaffold, was designed. This scaffold was anticipated to be a selective NRI, because it incorporated the 2′-substituent, found to provide selectivity in the aryloxypropanamine series, into a fused, pyrrole ring. Compounds were screened in vitro in MDCK-Net6 cells that were stably transfected with the human norepinephrine transporter (hNET). These cells were then treated with the test compound followed by [^{3}H]NE to initiate norepinephrine (NE) uptake. Once the cells were washed and lysed, uptake of [^{3}H]NE was measured by collection of counts per minute (cpm) data. Uptake into JAR cells that were stably transfected with the human serotonin transporter (hSERT) was similarly measured. Target in vitro profiles for drug candidates included an $IC_{50} < 50$ nM and selectivity over hSERT. As expected, compound **9a** and its fluorinated analogs were potent NRIs, however, surprisingly, they were also potent SRIs. Herein, we report the synthesis and activity of a new series of potent NRIs that also exhibit potent inhibition of serotonin reuptake, namely the 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines **9**.



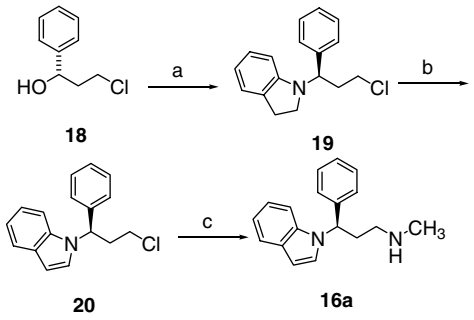
9a

2. Chemistry

The synthesis of the 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines **9**, depicted in Scheme 1, was designed to provide significant insight into the structure–activity relationship (SAR) within the series. This synthesis not only enabled an examination of the effect of chirality within the series (racemate **9** versus *R*-enantiomer **16** and *S*-enantiomer **17**), but it also provided information about the relative potencies of tertiary amines **15** versus secondary amines **9** and indolines **14** versus indoles **15**. Starting with an appropriately substituted acetophenone **10**, a Mannich reaction using paraformaldehyde and dimethylamine hydrochloride afforded the 3-dimethylamino-1-phenyl-1-propanone hydrochlorides (**11a–b**)[9] which were readily reduced to form alcohols **12a–b**[10] using aqueous sodium borohydride. Formation of the mesylate with methanesulfonyl chloride and triethylamine followed by treatment with the appropriately substituted indoline[11] and potassium carbonate yielded the desired indoline adduct **14** using a two-step, one-pot procedure. For similar systems, it has been reported that this process occurs by in situ generation of an azetidinium ion followed by regio-



Scheme 1. Synthesis of 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines. Reagents and conditions: (a) paraformaldehyde, dimethylamine hydrochloride, EtOH, reflux, 80–88% yield; (b) sodium borohydride, H_2O, 90–93% yield; (c) MsCl, Et_3N, CH_3CN; (d) indoline, K_2CO_3; 47–81% yield depending on indoline substitution; (e) MnO_2, CH_2Cl_2, reflux, 71–98% yield; (f) ACE-Cl, DIEA, CH_2Cl_2, then MeOH, reflux, 68–91% yield; (g) chiral SFC.



Scheme 2. Enantiospecific synthesis of (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine. Reagents and conditions: (a) i—MsCl, TEA, Et_2O, 0 °C, ii—indoline, 44% yield; (b) MnO_2, $ClCH_2CH_2Cl$, 70 °C, 98% yield; (c) $MeNH_2$, EtOH, 90 °C, 75% yield.

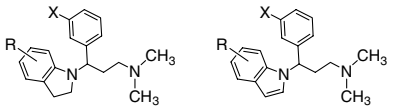
selective ring-opening.[12] The indoline adduct **14** was readily oxidized with manganese (IV) oxide to form the corresponding indole **15**. This product was then *N*-demethylated with 1-chloroethyl chloroformate[13] to afford the corresponding 3-(1*H*-indol-1-yl)-3-arylpropan-1-methylamine **9**. Inclusion of diisopropylethylamine to this reaction resulted in a significant increase in isolated yields. Separation of the enantiomers of racemic **9** by chiral supercritical fluid chromatography afforded both the *R*-enantiomer **16** and the *S*-enantiomer **17** in high optical purity.

Assignment of the configuration of enantiomers **16** and **17** was accomplished by unequivocally establishing the configuration of (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (**16a**) through independent synthesis using an enantiospecific route (Scheme 2). Assignment of the stereochemistry of subsequent compounds within the series was based upon analogy. Therefore, the mesylate of (*S*)-(−)-3-chloro-1-phenyl-1-propanol (**18**) was generated, in situ, using methanesulfonyl chloride and triethylamine, and subsequently displaced with indoline to form chloride **19**. Oxidation to the indole followed by amination with methylamine in ethanol afforded (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (**16a**) in 32% overall chemical yield and 91% enantiomeric purity as measured by chiral supercritical fluid chromatography.

3. Results and discussion

Data for a series of fluoro-substituted 3-(2,3-dihydro-1*H*-indol-1-yl)- *N*,*N*-dimethyl-3-arylpropan-1-amines **14** and 3-(1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-arylpropan-1-amines **15** are depicted in Table 2. Both structural classes were found to possess norepinephrine reuptake inhibitory activity. Furthermore, a comparison of these two compound classes revealed that they possessed similar NRI potencies. When the effect of fluorine substitution on the indole and indoline rings was examined, a similar SAR trend was found between the two scaffolds. In general, fluorine substitution on the 7-position of either the indole or indoline ring provided the most potent NRIs (**14e**, **14j**, **15e**, and **15j**), while substitution at the 4-, 5-, and 6-positions afforded compounds with similar but weaker potencies. Compounds with no substitution on the indole or indoline rings (**14a**, **14f**, **15a**, and **15f**) were less potent NRIs than the 7-fluoro analogs, but were generally more potent than the 4-, 5-, and 6-fluoro compounds. Finally, fluorine substitution on the *meta* position of the 3-phenyl ring had no significant effect on the NRI potency in either series.

Table 2. Inhibitory activity at the human norepinephrine and serotonin transporters of compounds within the *N*,*N*-dimethyl-3-arylpropan-1-amine series



Compound	X	R	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hSERT IC_{50}/hNET IC_{50}[c]
14a	H	H	495		
14b	H	4-F	984		
14c	H	5-F	1289	103	0.08
14d	H	6-F	1067		
14e	H	7-F	79		
14f	F	H	430		
14g	F	4-F	1144	172	0.15
14h	F	5-F	1395	108	0.08
14i	F	6-F	322		
14j	F	7-F	32	157	4.9
15a	H	H	603	191	0.32
15b	H	4-F	1374	48	0.03
15c	H	5-F	>5000		
15d	H	6-F	2492	467	0.19
15e	H	7-F	344	92	0.28
15f	F	H	759		
15g	F	4-F	270		
15h	F	5-F	1275	399	0.31
15i	F	6-F	1383		
15j	F	7-F	158		

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET. Desipramine (IC_{50} = 11.5 ± 1.3 nM) was used as a standard.

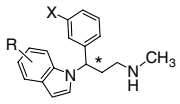
[b] Inhibition of serotonin uptake in JAR cells, stably transfected with human SERT. Fluoxetine (IC_{50} = 17.7 ± 1.2 nM) was used as a standard.

[c] Unitless value as a ratio in which higher numbers represent relatively greater NET selectivity. A value of 1 represents no selectivity.

When a select group of compounds within scaffolds **14** and **15** was tested for serotonin reuptake inhibitory activity, both structural classes were found to be potent SRIs. In fact, as a whole, both scaffolds exhibited selectivity for the serotonin transporter over the norepinephrine transporter, with the exception of compound **14j** which showed a modest, 5-fold NRI selectivity.

Data for the corresponding series of 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines **9** are depicted in Table 3. In general, for NRI potency, there is a preference for the secondary amines (**9a**–**9j**) when compared to the tertiary amines (**15a**–**15j**, Table 2). For example, the unsubstituted indole analog containing an *N*,*N*-dimethylamine (**15a**) exhibited an IC_{50} value in the NRI functional assay of 603 nM; the corresponding secondary amine (**9a**) was nearly 13 times more potent with an IC_{50} value of 47 nM. Similarly, the more potent 3-(7-fluoro-1*H*-

Table 3. Inhibitory activity at the human norepinephrine, serotonin, and dopamine transporters of compounds within the (3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine series



Compound	Stereochemistry	X	R	hNET IC_{50}[a] (nM)	hNET K_i[b] (nM)	hSERT IC_{50}[c] (nM)	hSERT IC_{50}/ hNET IC_{50}[d]	hDAT IC_{50}[e] (nM)	hDAT % inhibition at 1 μM[e]
9a	Racemic	H	H	47	32	327	7.0	1243	
9b	Racemic	H	4-F	154	132	38	0.3		
9c	Racemic	H	5-F	55	57				
9d	Racemic	H	6-F	87	25				
9e	Racemic	H	7-F	99	46				
9f	Racemic	F	H	86	25			1163	
9g	Racemic	F	4-F	24	57				
9h	Racemic	F	5-F	335	69				
9i	Racemic	F	6-F	68	23				
9j	Racemic	F	7-F	22	24				
16a	R	H	H	34	35	491	14.4	3200	
16b	R	H	4-F	115	59	21	5.5	563	
16c	R	H	5-F	82	37	30	0.4		22%[g]
16d	R	H	6-F	96	39	111	1.2		15%[g]
16e	R	H	7-F	44	23	62	1.4		12%[g]
16f	R	F	H	91	80	14	0.2	4100	
16g	R	F	4-F	22	11	160	7.3	1950	
16h	R	F	5-F	284	118	23%[f]	>21		
16i	R	F	6-F	69	19	236	3.4		20%[g]
16j	R	F	7-F	10	29	56	5.6		26%[g]
17a	S	H	H	33	41	276	8.4	>10,000	
17b	S	H	4-F	12	12	9	0.8	680	
17c	S	H	5-F	313	81	105	0.3		19%[g]
17d	S	H	6-F	11	28	196	17.8		20%[g]
17e	S	H	7-F	18	24	34	1.9		16%[g]
17f	S	F	H	86	47	12	0.1	>10,000	
17g	S	F	4-F	28	27	23	0.8	550	
17h	S	F	5-F	91	74	89	1.0		
17i	S	F	6-F	84	37	248	3.0		14%[g]
17j	S	F	7-F	35	26	117	3.3		35%[g]

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET. Desipramine (IC_{50} = 11.5± 1.3 nM) was used as a standard.

[b] Inhibition of [^{3}H] nisoxetine binding to membranes from MDCK-Net6 cells, stably transfected with human NET. Desipramine (K_i = 2.3 ± 0.13 nM) was used as a standard.

[c] Inhibition of serotonin uptake in JAR cells, stably transfected with human SERT. Fluoxetine (IC_{50} = 17.7± 1.2 nM) was used as a standard.

[d] Unitless value as a ratio in which higher numbers represent relatively greater NET selectivity. A value of 1 represents no selectivity.

[e] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant hDAT. Mazindol (IC_{50} = 22.6 ± 1.6 nM) was used as a standard.

[f] Percent inhibition measured at a concentration of 6000 nM.

[g] Percent inhibition measured at a concentration of 2000 nM.

indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (**15j**) had an IC_{50} value of 158 nM while the corresponding secondary amine (**9j**) exhibited a 7-fold increase in potency with an IC_{50} value of 22 nM.

When the purified enantiomers, **16** and **17**, were compared to their corresponding racemates in the 3-(1*H*-indol-1-yl)-3-arylpropan-1-amine series, no significant difference in NRI potency for a majority of the series (see Table 3) was observed. For example, the unsubstituted, racemic compound **9a** exhibited an IC_{50} value in the functional NRI assay of 47 nM while the *R*-enantiomer **16a** exhibited an IC_{50} value of 34 nM and the *S*-enantiomer was 33 nM. The same is true for racemates **9c**, **9e**, **9f**, **9g**, **9i**, and **9j** and their enantiomers. Surprisingly, it was found that the *S*-enantiomers of the 4-, and 6-fluoroindole analogs containing no substitution on the 3-phenyl group (**17b** and **17d**, respectively) were nearly 10-fold more potent than their corresponding *R*-enantiomers (**16b** and **16d**) and racemates (**9b** and **9d**). For example, the racemate of the 6-fluoroindole analog **9d** exhibited an NRI IC_{50} value of 87 nM while the *R*-enantiomer **16d** showed a similar potency (IC_{50} value of 96 nM). The corresponding *S*-enantiomer **17d**, however, was significantly more potent, with an IC_{50} value of 11 nM. It should be noted that the K_i values for this series, determined in a membrane-binding assay using nisoxetine as the competitive radioligand, showed good agreement with the IC_{50} values determined in the NRI functional assay.

The 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines were then tested for hNET selectivity over both hSERT and the

dopamine transporter (hDAT) (Table 3), and, while the compounds exhibited only weak affinity for hDAT, as a series, the 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines were found to be potent SRIs. When the potencies of the pure enantiomers in the serotonin reuptake assay were compared to their corresponding racemates, no significant difference was observed (**9a** vs **16a** and **17a**, and **9b** vs **16b** and **17b**). When selectivities for hNET over hSERT were compared, there was generally no difference between the *R*- and *S*-enantiomers; however, exceptions exist. Both the (3*R*)-3-(4-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (**16g**) and the (3*R*)-3-(5-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (**16h**) were significantly more selective NRIs than SRIs compared to their corresponding *S*-enantiomer (**17g** and **17h**) (7.3-fold vs 0.82 and >20-fold vs 0.98, respectively). In addition, (3*S*)-3-(6-fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (**17d**) was nearly 18-fold selective for hNET compared to hSERT while the corresponding *R*-enantiomer (**16d**) exhibited nearly equal potencies for both transporters. It is interesting that by altering only the position of a fluorine group within the molecule, selectivity ratios from 0.14 to >20 (a range of 150) could be achieved.

4. Conclusions

Efforts to design selective NRIs based on SAR from the aryloxypropanamine series of monoamine reuptake inhibitors have led to the identification of the 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines, a potent new class of dual acting norepinephrine and serotonin reuptake inhibitors. The selectivity profile for hNET and hSERT of this series of compounds spans a wide range, with selectivity ratios from 0.14 to >20, differing only by minor changes in substitution. Furthermore, these compounds exhibit good selectivity over the dopamine transporter.

5. Experimental

5.1. General methods: chemistry

Solvents were purchased as anhydrous grade and were used without further purification. Melting points were measured on a Mel-Temp II (Laboratory Device, Inc.) melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA 400 instrument, and chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard tetramethylsilane in $CDCl_3$ or DMSO-d_6. In all cases, NMR spectra of enantiomers were essentially identical to their corresponding racemates. Electrospray (ESI) mass spectra were recorded using a Waters Alliance-ZMD mass spectrometer. Electron impact ionization (EI, EE = 70 eV) mass spectra were recorded on a Finnigan Trace mass spectrometer. Combustion analyses were performed by Robertson Microlit. Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel, 60 F-254) and were visualized using UV light and/or staining with a phosphomolybdic acid solution in ethanol. In general, compound purity was assessed by ^{1}H NMR and an LC/UV/MS method.[14] Biological results were obtained on compounds of >97% chemical purity as determined by the above methods.

5.2. 3-(Dimethylamino)-1-(3-fluorophenyl)propan-1-ol (12b)

A solution of 3-(dimethylamino)-1-(3-fluorophenyl)-1-propanone (**11b**) (11.99 g, 51.75 mmol) in water (110 mL) at 0 °C was treated with sodium borohydride (2.49 g, 65.72 mmol) in small portions. The reaction mixture was allowed to warm to room temperature, where it was stirred for 2 h. After which time, acetone (5 mL) followed by concentrated HCl (14 mL) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then extracted with methylene chloride (50 mL) and the aqueous layer was basified to pH 10 by the addition of a 2 N aqueous solution of sodium hydroxide. The product was then extracted with methylene chloride (3× 50 mL), dried over $MgSO_4$, and concentrated to yield pure **12b** (9.39 g, 92%) as a colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.69 (q, J = 6.7 Hz, 2H), 2.12 (s, 6H), 2.25–2.31 (m, 2H), 4.64 (t, J = 6.4, 1H), 5.57 (br s, 1H), 7.03 (dddd, J = 0.9, 2.7, 9.0, 9.0, 1H), 7.11–7.16 (m, 2H), 7.35 (dd, J = 7.9, 13.9, 1H); HRMS: calcd for $C_{11}H_{16}FNO + H^+$, 198.1288. Found (ESI, $[M+H]^+$), 198.1281.

5.3. General procedure 1: 3-(2,3-dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amines (14a–14j)

A solution of the appropriately substituted 3-(dimethylamino)-1-arylpropan-1-ol (2.72 mmol) in acetonitrile (20 mL) was treated with triethylamine (0.45 mL, 3.26 mmol) followed by the dropwise addition of methanesulfonyl chloride (0.23 mL, 2.99 mmol). The reaction mixture was stirred at room temperature for 3 h, after which time indoline (0.92 mL, 8.16 mmol, 3 equiv) followed by potassium carbonate (752 mg, 5.44 mmol) was added. The reaction mixture was stirred at room temperature for 14 h then the reaction mixture was filtered and the filtrate was concentrated at reduced pressure. The product was purified via Biotage Horizon® [25 M, silica, gradient from 0% (20% methanol/methylene chloride)/methylene chloride to 55% (20% methanol/methylene chloride)/methylene chloride].

5.3.1. 3-(2,3-Dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (14a). Yield: 72% of a light pale yellow oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.06–2.25 (m, 2H), 2.25 (s, 6H), 2.33–2.49 (m, 2H), 2.81–2.87 (m, 2H), 3.12–3.20 (m, 1H), 3.50 (ddd, J = 6.4, 9.0, 9.0 Hz, 1H), 4.76 (t, J = 7.8 Hz, 1H), 6.46 (t, J = 7.2 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 6.91–6.95 (m, 2H), 7.22–7.26 (m, 1H), 7.30–7.37 (m, 4H); MS (ES) m/z 281.1; HRMS: calcd for $C_{19}H_{24}N_2 + H^+$, 281.20122. Found (ESI, $[M+H]^+$), 281.2003.

5.3.2. 3-(4-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (14b). Yield: 51% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99–2.15 (m, 2H), 2.15 (s, 6H), 2.24–2.27 (m, 2H), 2.89 (t, J= 9.4 Hz, 2H), 3.26 (q, J = 9.6 Hz, 1H), 3.60

(q, J = 7.6 Hz, 1H), 4.78 (t, J = 7.9 Hz, 1H), 6.25 (t, J = 8.6 Hz, 1H), 6.41 (d, J = 7.9 Hz, 1H), 6.95 (dd, J = 6.2, 8.1 Hz, 1H), 7.25–7.27 (m, 1H), 7.30–7.37 (m, 4H); MS (ES) m/z 299.1; HRMS: calcd for $C_{19}H_{23}FN_2 + H^+$, 299.19180. Found (ESI, $[M+H]^+$), 299.1793.

5.3.3. 3-(5-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (14c). Yield: 49% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.95–2.14 (m, 2H), 2.14 (s, 6H), 2.17–2.30 (m, 2H), 2.80–2.90 (m, 2H), 3.16–3.23 (m, 1H), 3.47–3.53 (m, 1H), 4.68 (t, J = 7.7 Hz, 1H), 6.48–6.52 (m, 1H), 6.70–6.77 (m, 1H), 6.80–6.85 (m, 1H), 7.16–7.26 (m, 2H), 7.30–7.39 (m, 3H); MS (ES) m/z 299.1; HRMS: calcd for $C_{19}H_{23}FN_2 + H^+$, 299.1918. Found (ESI, $[M+H]^+$), 299.1993.

5.3.4. 3-(6-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (14d). Yield: 64% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.24–2.34 (m, 1H), 2.40–2.51 (m, 1H), 2.49 (s, 6H), 2.74–2.85 (m, 3H), 3.00–3.20 (m, 2H), 3.56–3.64 (m, 1H), 4.87 (dd, J = 5.8, 9.2 Hz, 1H), 6.23 (ddd, J = 2.3, 8.0, 10.0 Hz, 1H), 6.59 (dd, J = 2.3, 11.1 Hz, 1H), 6.91 (dd, J = 6.1, 7.7 Hz, 1H), 7.28–7.41 (m, 5H); MS (ES) m/z 299.1; HRMS: calcd for $C_{19}H_{23}FN_2 + H^+$, 299.19180. Found (ESI, $[M+H]^+$), 299.1950.

5.3.5. 3-(7-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (14e). Yield: 47% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05–2.17 (m, 2H), 2.17 (s, 6H), 2.30–2.36 (m, 2H), 2.83–2.89 (m, 2H), 3.11 (q, J = 9.4 Hz, 1H), 3.51 (ddd, J = 6.2, 9.5, 9.5 Hz, 1H), 5.06 (t, J = 7.6 Hz, 1H), 6.49–6.54 (m, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.84 (dd, J = 8.8, 13.2 Hz, 1H), 7.23–7.27 (m, 1H), 7.30–7.35 (m, 4H); MS (ES) m/z 299.1; HRMS: calcd for $C_{19}H_{23}FN_2 + H^+$, 299.19180. Found (ESI, $[M+H]^+$), 299.1900.

5.3.6. 3-(2,3-Dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (14f). Yield: 81% of a pale purple oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.90–2.10 (m, 2H), 2.07 (s, 6H), 2.22–2.30 (m, 2H), 2.77–2.83 (m, 2H), 3.13 (q, J = 9.0 Hz, 1H), 3.50 (ddd, J = 6.8, 9.0, 9.0 Hz, 1H), 4.76 (t, J = 7.4 Hz, 1H), 6.41 (t, J = 7.5 Hz, 1H), 6.50 (d, J = 7.8 Hz, 1H), 6.85–6.90 (m, 2H), 7.01 (ddd, J = 1.9, 7.8, 7.8 Hz, 1H), 7.11–7.15 (m, 2H), 7.31 (ddd, J = 6.0, 7.9, 7.9 Hz, 1H); MS (ES) m/z 299.1; HRMS: calcd for $C_{19}H_{23}FN_2 + H^+$, 299.19180. Found (ESI, $[M+H]^+$), 299.1906.

5.3.7. 3-(4-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (14g). Yield: 64% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.92–2.10 (m, 2H), 2.07 (s, 6H), 2.15–2.21 (m, 2H), 2.85 (t, J= 8.7 Hz, 2H), 3.23 (q, J = 9.1 Hz, 1H), 3.55 (q, J = 8.2 Hz, 1H), 4.74 (t, J = 7.1 Hz, 1H), 6.20 (t, J = 8.5 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.90 (ddd, J = 6.2, 7.9, 7.9 Hz, 1H), 7.03 (dddd, J = 1.8, 1.8, 9.1, 11.7 Hz, 1H), 7.10–7.15 (m, 2H), 7.31 (ddd, J = 5.9, 7.8, 7.8 Hz, 1H); MS (ES) m/z 317.1; HRMS: calcd for $C_{19}H_{22}F_2N_2 + H^+$, 317.1824. Found (ESI, $[M+H]^+$), 317.1835.

5.3.8. 3-(5-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (14h). Yield: 51% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.94–2.13 (m, 2H), 2.13 (s, 6H), 2.14–2.29 (m, 2H), 2.84–2.86 (m, 2H), 3.21 (q, J = 9.4 Hz, 1H), 3.51 (q, J = 8.8 Hz, 1H), 4.70 (t, J = 6.8 Hz, 1H), 6.50 (dd, J = 4.4, 8.6 Hz, 1H), 6.73 (ddd, J = 2.0, 8.6, 8.6 Hz, 1H), 6.83 (dd, J = 2.7, 8.6 Hz, 1H) 7.06–7.08 (m, 1H), 7.18–7.24 (m, 2H), 7.36 (dd, J = 7.9, 14.1 Hz, 1H); MS (ES) m/z 317.1; HRMS: calcd for $C_{19}H_{22}F_2N_2 + H^+$, 317.1824. Found (ESI, $[M+H]^+$), 317.1842.

5.3.9. 3-(6-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,N-dimethylpropan-1-amine (14i). Yield: 75% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.22–2.34 (m, 1H), 2.38–2.48 (m, 1H), 2.49 (s, 6H), 2.75–2.88 (m, 3H), 2.89–3.20 (m, 2H), 3.56–3.62 (m, 1H), 4.89 (dd, J = 6.0, 9.4 Hz, 1H), 6.25 (ddd, J = 2.3, 7.9, 10.0 Hz, 1H), 6.61 (dd, J = 2.3, 11.2 Hz, 1H), 6.92 (dd, J = 6.2, 8.0 Hz, 1H), 7.14 (ddd, J = 2.6, 8.3, 8.3 Hz, 1H), 7.22–7.27 (m, 2H), 7.42 (ddd, J = 6.2, 7.9, 7.9 Hz, 1H); MS (ES) m/z 317.1; HRMS: calcd for $C_{19}H_{22}F_2N_2 + H^+$, 317.1824. Found (ESI, $[M+H]^+$), 317.1826.

5.3.10. 3-(7-Fluoro-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (14j). Yield: 47% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.06–2.15 (m, 2H), 2.15 (s, 6H), 2.27-2.31 (m, 2H), 2.86-2.91 (m, 2H), 3.13 (q, J = 9.7 Hz, 1H), 3.53 (ddd, J = 6.9, 9.1, 9.1 Hz, 1H), 5.07 (t, J = 6.9 Hz, 1H), 6.54 (dd, J = 4.4, 7.8 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.85 (dd, J = 8.2, 13.3 Hz, 1H) 7.08–7.16 (m, 3H), 7.37 (dd, J = 7.8, 13.3 Hz, 1H); MS (ES) m/z 317.1; HRMS: calcd for $C_{19}H_{22}F_2N_2 + H^+$, 317.1824. Found (ESI, $[M+H]^+$), 317.1811.

5.4. General procedure 2: 3-(1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amines (15a–15j)

A solution of the appropriate 3-(2,3-dihydro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (1.95 mmol) in methylene chloride (10 mL) was treated with manganese (IV) oxide (19.5 mmol, 1.70 g). The reaction mixture was heated at reflux for 30 min after which time the reaction was filtered through a pad of Celite which was washed several times with methylene chloride. The filtrate was then concentrated under reduced pressure, and the product was purified via Biotage Horizon® [25 M, silica, gradient from 0% (20% methanol/methylene chloride)/methylene chloride to 40% (20% methanol/methylene chloride)/methylene chloride].

5.4.1. 3-(1*H*-Indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (15a). Yield: 98% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05–2.19 (m, 2H), 2.10 (s, 6H), 2.30–2.40 (m, 1H), 2.48–2.53 (m, 1H), 5.70 (dd, J = 6.4, 9.0 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 3H), 7.35–7.37 (m, 2H), 7.50 (dd, J = 7.8, 14.1 Hz, 1H), 7.72 (d, J = 3.2 Hz, 1H); MS (ES) m/z 279.1; HRMS: calcd for $C_{19}H_{22}N_2 + H^+$, 279.18557. Found (ESI, $[M+H]^+$), 279.1845.

5.4.2. 3-(4-Fluoro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (15b). Yield: 74% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.03–2.17 (m, 2H), 2.09 (s, 6H), 2.31–2.41 (m, 1H), 2.49–2.56 (m, 1H), 5.72 (dd, J = 6.4, 9.0 Hz, 1H), 6.58 (d, J = 3.2 Hz, 1H), 6.77 (dd, J = 7.8, 10.6 Hz, 1H), 7.06 (ddd, J = 5.4, 8.1, 8.1 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.1 Hz, 2H), 7.37 (t, J = 6.9 Hz, 3H), 7.79 (d, J = 3.2 Hz, 1H); MS (ES) m/z 297.2; HRMS: calcd for $C_{19}H_{21}FN_2 + H^+$, 297.17615. Found (ESI, $[M+H]^+$), 297.1659.

5.4.3. 3-(5-Fluoro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (15c). Yield: 72% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.02–2.16 (m, 2H), 2.09 (s, 6H), 2.30–2.40 (m, 1H), 2.45–2.53 (m, 1H), 5.65 (dd, J = 6.4, 9.0 Hz, 1H), 6.50 (d, J = 3.2 Hz, 1H), 6.92 (ddd, J = 2.6, 9.2, 9.2 Hz, 1H), 7.20–7.24 (m, 1H), 7.26–7.37 (m, 5H), 7.50 (dd, J = 4.5, 9.0 Hz, 2H), 7.80 (d, J = 3.2 Hz, 1H); MS (ES) m/z 297.2; HRMS: calcd for $C_{19}H_{21}FN_2 + H^+$, 297.17615. Found (ESI, $[M+H]^+$), 297.1750.

5.4.4. 3-(6-Fluoro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (15d). Yield: 75% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.03–2.18 (m, 2H), 2.10 (s, 6H), 2.30–2.39 (m, 1H), 2.45–2.53 (m, 1H), 5.65 (dd, J = 6.4, 9.0 Hz, 1H), 6.52 (d, J = 3.2 Hz, 1H), 6.85 (ddd, J = 1.3, 7.4, 7.4 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.3 Hz, 2H), 7.36–7.40 (m, 3H), 7.51 (dd, J = 5.3, 8.7 Hz, 1H), 7.73 (d, J = 3.2 Hz, 1H) ; MS (ES) m/z 297.2; HRMS: calcd for $C_{19}H_{21}FN_2 + H^+$, 297.17615. Found (ESI, $[M+H]^+$), 297.1750.

5.4.5. 3-(7-Fluoro-1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (15e). Yield: 89% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.09–2.21 (m, 2H), 2.11 (s, 6H), 2.30–2.39 (m, 1H), 2.49–2.58 (m, 1H), 5.91 (dd, J = 6.8, 8.6 Hz, 1H), 6.60 (t, J = 2.4 Hz, 1H), 6.82–6.98 (m, 2H), 7.20–7.36 (m, 6H), 7.81 (d, J = 3.2 Hz, 1H); MS (ES) m/z 297.1; HRMS: calcd for $C_{19}H_{21}FN_2 + H^+$, 297.17615. Found (ESI, $[M+H]^+$), 297.1772.

5.4.6. 3-(3-Fluorophenyl)-3-(1*H*-indol-1-yl)-*N*,*N*-dimethylpropan-1-amine (15f). Yield: 88% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99–2.12 (m, 2H), 2.04 (s, 6H), 2.26–2.48 (m, 1H), 2.49–2.50 (m, 1H), 5.68 (dd, J = 6.4, 9.2 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 6.94 (t, J = 7.1 Hz, 1H), 6.96–7.05 (m, 2H), 7.13–7.17 (m, 2H), 7.27 (ddd, J = 6.7, 8.3, 8.3 Hz, 1H), 7.46 (t, J = 8.0, 2H), 7.70 (d, J = 3.2 Hz, 1H); MS (ES) m/z 297.1; HRMS: calcd for $C_{19}H_{21}FN_2 + H^+$, 297.17615. Found (ESI, $[M+H]^+$), 297.1761.

5.4.7. 3-(4-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (15g). Yield: 74% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.02–2.17 (m, 2H), 2.09 (s, 6H), 2.31–2.42 (m, 1H), 2.49–2.59 (m, 1H), 5.75 (dd, J = 6.4, 9.1 Hz, 1H), 6.60 (d, J = 3.3 Hz, 1H), 6.79 (dd, J = 7.6, 10.6 Hz, 1H), 7.02–7.10 (m, 2H), 7.20–7.28 (m, 2H), 7.31–7.41 (m, 2H), 7.82 (d, J = 3.3 Hz, 1H); MS (ES) m/z 315.2; HRMS: calcd for $C_{19}H_{20}F_2N_2 + H^+$, 315.16673. Found (ESI, $[M+H]^+$), 315.1649.

5.4.8. 3-(5-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (15h). Yield: 71% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.03–2.15 (m, 2H), 2.09 (s, 6H), 2.30–2.40 (m, 1H), 2.47–2.54 (m, 1H), 5.72 (dd, J = 6.4, 9.1 Hz, 1H), 6.52 (d, J = 3.1 Hz, 1H), 6.93 (ddd, J = 2.4, 9.2, 9.2 Hz, 1H), 7.07 (ddd, J = 1.8, 7.8, 7.8 Hz, 1H), 7.19–7.23 (m, 2H), 7.29 (dd, J = 2.6, 9.9 Hz, 1H), 7.34 (q, J = 6.3 Hz, 1H), 7.53 (dd, J = 4.6, 9.1 Hz, 1H), 7.84 (d, J = 3.2 Hz, 1H); MS (ES) m/z 315.2; HRMS: calcd for $C_{19}H_{20}F_2N_2 + H^+$, 315.16673. Found (ESI, $[M+H]^+$), 315.1652.

5.4.9. 3-(6-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (15i). Yield: 83% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.02–2.17 (m, 2H), 2.09 (s, 6H), 2.31–2.39 (m, 1H), 2.49–2.54 (m, 1H), 5.68 (dd, J = 6.3, 9.2 Hz, 1H), 6.54 (d, J = 3.2 Hz, 1H), 6.86 (ddd, J = 6.4, 9.7, 9.7 Hz, 1H), 7.07 (ddd, J = 2.1, 7.4, 7.4 Hz, 1H), 7.23–7.28 (m, 2H), 7.32–7.38 (m, 1H), 7.43 (dd, J = 2.3, 10.6 Hz, 1H), 7.52 (dd, J = 5.5, 8.6 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H); MS (ES) m/z 315.3; HRMS: calcd for $C_{19}H_{20}F_2N_2 + H^+$, 315.1667. Found (ESI, $[M+H]^+$), 315.1623.

5.4.10. 3-(7-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpropan-1-amine (15j). Yield: 78% of a colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.10–2.20 (m, 2H), 2.11 (s, 6H), 2.31–2.40 (m, 1H), 2.49–2.58 (m, 1H), 5.93 (dd, J = 6.8, 8.8 Hz, 1H), 6.62 (dd, J = 2.4, 3.1 Hz, 1H), 6.85–6.98 (m, 2H), 7.04–7.10 (m, 3H), 7.31–7.39 (m, 2H), 7.84 (d, J = 3.2 Hz, 1H); MS (ES) m/z 315.1; HRMS: calcd for $C_{19}H_{20}F_2N_2 + H^+$, 315.1667. Found (ESI, $[M+H]^+$), 315.1623.

5.5. General procedure 3: 3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amines (9a–9j)

A solution of 3-(1*H*-indol-1-yl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (1.38 mmol) in methylene chloride (2 mL) and diisopropylethylamine (0.42 mL, 2.42 mmol) was treated with 1-chloroethyl chloroformate (0.26 mL, 2.42 mmol). The reaction mixture was stirred at room temperature for 2 h (until the starting material had disappeared as analyzed by TLC) after which time the methylene chloride was evaporated at reduced pressure and the resulting residue was dissolved in methanol (2 mL) and heated at reflux for 3 h. The methanol was then evaporated at reduced pressure and the product was purified via Biotage Horizon® [25 M, silica, gradient from 0% (20% methanol/methylene chloride)/methylene chloride to 60% (20% methanol/methylene chloride)/methylene chloride]. The purified product was converted to the hydrochloride salt by dissolving the free base in methylene chloride (2 mL) and adding a 4 N HCl solution in dioxane (1.2 equiv). The solvents were then evaporated at reduced pressure and the resulting residue was dissolved in water (2 mL) and lyophilized to afford the hydrochloride salt as a white powder.

5.5.1. 3-(1*H*-Indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine hydrochloride (9a). Yield: 72%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.24 (s, 3H), 2.31–2.43 (m, 3H), 2.47–2.52 (m, 1H), 5.76 (dd, J = 6.2, 8.5 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 8.2 Hz, 1H), 7.22 (t, J = 7.1 Hz, 1H), 7.27–7.35 (m, 5H), 7.51 (dd, J = 7.7, 12.4 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 8.74 (br s, 2H); MS (ES) m/z 265.1; HRMS: calcd for $C_{18}H_{20}N_2 + H^+$, 265.16992. Found (ESI, $[M+H]^+$), 265.1682.

5.5.2. 3-(4-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine hydrochloride (9b). Yield: 71%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.53 (s, 3H), 2.59–2.66 (m, 1H), 2.72–2.82 (m, 2H), 2.87–2.91 (m, 1H), 5.95 (dd, J = 6.0, 8.3 Hz, 1H), 6.63 (d, J = 3.2 Hz, 1H), 6.80 (dd, J = 7.7, 10.5 Hz, 1H), 7.09 (ddd, J = 5.4, 8.1, 8.1 Hz, 1H), 7.25–7.29 (m, 1H), 7.32–7.38 (m, 4H), 7.42 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 3.2 Hz, 1H), 9.10 (br s, 2H); MS (ES) m/z 283.0; HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.16050. Found (ESI, $[M+H]^+$), 283.1597.

5.5.3. 3-(5-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine hydrochloride (9c). Yield: 71%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.52 (s, 3H), 2.52–2.63 (m, 1H), 2.71–2.79 (m, 2H), 2.85–2.90 (m, 1H), 5.92 (dd, J = 6.3, 8.8 Hz, 1H), 6.55 (d, J = 3.2 Hz, 1H), 6.95 (ddd, J = 2.6, 9.4, 9.4 Hz, 1H), 7.24–7.35 (m, 6H), 7.42 (dd, J = 4.5, 9.0 Hz, 1H), 7.82 (d, J = 3.2 Hz, 1H), 9.03 (br s, 2H); MS (ES) m/z 283.0; HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1602.

5.5.4. 3-(6-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine hydrochloride (9d). Yield: 69%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.53 (s, 3H), 2.53–2.63 (m, 1H), 2.72–2.80 (m, 2H), 2.86–2.91 (m, 1H), 5.88 (dd, J = 6.2, 8.6 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 6.88 (dddd, J = 2.4, 2.4, 9.7, 11.0 Hz, 1H), 7.25–7.29 (m, 1H), 7.32–7.39 (m, 4H), 7.45 (dd, J = 2.2, 10.6 Hz, 1H), 7.54 (dd, J = 5.5, 8.6 Hz, 1H), 7.72 (d, J = 3.3 Hz, 1H), 9.04 (br s, 2H); MS (ES) m/z 283.0; HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1602.

5.5.5. 3-(7-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine hydrochloride (9e). Yield: 91%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.49–2.60 (m, 1H), 2.56 (s, 3H), 2.67–2.90 (m, 2H), 2.92–3.00 (m, 1H), 5.92 (dd, J = 5.8, 9.6 Hz, 1H), 6.66 (t, J = 3.1 Hz, 1H), 6.90 (dd, J = 7.2, 13.2 Hz, 1H), 6.98 (ddd, J = 4.6, 7.8, 7.8 Hz, 1H), 7.21–7.38 (m, 6H), 7.80 (d, J = 3.3 Hz, 1H), 8.68 (br s, 2H); MS (ES) m/z 283.0; HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1624.

5.5.6. 3-(3-Fluorophenyl)-3-(1*H*-indol-1-yl)-*N*-methylpropan-1-amine hydrochloride (9f). Yield: 84%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.53 (s, 3H), 2.55–2.68 (m, 1H), 2.70–2.79 (m, 2H), 2.85–2.92 (m, 1H), 5.93 (dd, J = 6.4, 8.6 Hz, 1H), 6.58 (t, J = 3.2 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 7.08–7.13 (m, 2H), 7.17–7.20 (m, 2H), 7.38 (ddd, J = 5.9, 8.2, 8.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 3.2 Hz, 1H), 8.83 (br s, 2H); MS (ES) m/z 283.1; HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1570.

5.5.7. 3-(4-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine hydrochloride (9g). Yield: 91%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.52 (s, 3H), 2.60–2.69 (m, 1H), 2.71–2.82 (m, 2H), 2.86–2.92 (m, 1H), 6.00 (br s, 1H), 6.65 (d, J = 3.3 Hz, 1H), 6.82 (dd, J = 7.8, 10.5 Hz, 1H), 7.07–7.13 (m, 2H), 7.20 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 2.3, 9.73 Hz, 1H), 7.25 (q, J = 6.2 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 3.3 Hz, 1H), 9.23 (br s, 2H); MS (ES) m/z 301.0; HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1510. Found (ESI, $[M+H]^+$), 301.1503.

5.5.8. 3-(5-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine hydrochloride (9h). Yield: 68%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.45–2.58 (m, 1H), 2.50 (s, 3H), 2.60–2.78 (m, 2H), 2.79–2.90 (m, 1H), 5.87 (dd, J = 6.8, 8.7 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 6.93 (ddd, J = 2.6, 9.2, 9.2 Hz, 1H), 7.07 (dddd, J = 1.8, 1.8, 8.3, 8.3 Hz, 1H), 7.11–7.17 (m, 2H), 7.28 (dd, J = 2.4, 9.7 Hz, 1H), 7.34 (ddd, J = 6.3, 8.1, 8.1 Hz, 1H), 7.50 (dd, J = 4.4, 9.0 Hz, 1H), 7.78 (d, J = 3.2 Hz, 1H), 8.78 (br s, 2H); MS (ES) m/z 301.0; HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1510. Found (ESI, $[M+H]^+$), 301.1530.

5.5.9. 3-(6-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine hydrochloride (9i). Yield: 78%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.52–2.62 (m, 1H), 2.55 (s, 3H), 2.66–2.79 (m, 2H), 2.83–2.93 (m, 1H), 5.88 (t, J = 8.1 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 6.90 (dddd, J = 2.3, 8.7, 8.7, 10.9 Hz, 1H), 7.13 (ddd, J = 1.9, 8.3, 8.3 Hz, 1H), 7.20–7.25 (m, 2H), 7.40 (ddd, J = 6.2, 7.9 Hz, 1H), 7.46 (dd, J = 1.9, 8.7 Hz, 1H), 7.55 (dd, J = 5.5, 7.9 Hz, 1H), 7.74 (d, J = 3.2 Hz, 1H), 8.81 (br s, 2H); MS (ES) m/z 301.0; HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1510. Found (ESI, $[M+H]^+$), 301.1477.

5.5.10. 3-(7-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine hydrochloride (9j). Yield: 89%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.54 (s, 3H), 2.54–2.64 (m, 1H), 2.71–2.89 (m, 2H), 2.92–3.01 (m, 1H), 5.97 (dd, J = 5.6, 9.7 Hz, 1H), 6.68 (t, J = 2.7 Hz, 1H), 6.90 (dd, J = 7.7, 13.2 Hz, 1H), 6.96–7.06 (m, 3H), 7.11 (ddd, J = 2.2, 8.8, 8.8 Hz, 1H), 7.35–7.41 (m, 2H), 7.86 (d, J = 3.3 Hz, 1H), 9.00 (br s, 2H); MS (ES) m/z 301.0; HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1510. Found (ESI, $[M+H]^+$), 301.1528.

5.6. General procedure 4: chiral supercritical fluid chromatography resolution of 3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amines (16a–16j and 17a–17j)

The racemic material was dissolved in methanol at a concentration of approximately 40 mg/mL, and the resulting solution was injected onto the Supercritical Fluid Chromatography (SFC) instrument with a volume of 1.0 mL per injection. The baseline resolved enantiomers were collected using a Berger MultiGram Prep

SFC (Berger Instruments, Inc. Newark, DE) under the following conditions: Chiralcel OD-H SFC column (5μ, 250 mm L × 20 mm ID, Chiral Technologies, Inc, Exton, PA), 35 °C column temperature, 20% MeOH with 0.2% DEA as CO_2 modifier, 50 mL/min flow rate, 100 bar outlet pressure, 220 nm UV detection. The chiral purity of each enantiomer was determined under the same SFC conditions using a Chiralcel OD column (10 μ, 250 mm L × 4.6 mm ID) at 2.0 mL/min flow rate on a Berger Analytical SFC instrument. Each enantiomer was converted to the hydrochloride salt by dissolving the free base in methylene chloride (2 mL) and adding a 4 N HCl solution in dioxane (1.2 equiv). The solvents were then evaporated at reduced pressure and the resulting residue was dissolved in water (2 mL) and lyophilized to afford the hydrochloride salt as a white powder.

5.6.1. (3*R*)-3-(1*H*-Indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (16a). The enantiomeric purity was determined to be 99.5% (with 0.5% of the undesired enantiomer) isolated as peak 2; t_R: 11.28 min; $[\alpha]_D^{25}$ 79.2 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{20}N_2 + H^+$, 265.1699. Found (ESI, $[M+H]^+$), 265.1703.

5.6.2. (3*S*)-3-(1*H*-Indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (17a). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 1; t_R: 6.39 min; $[\alpha]_D^{25}$ −80.2 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{20}N_2 + H^+$, 265.1699. Found (ESI, $[M+H]^+$), 265.1690.

5.6.3. (3*R*)-3-(4-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (16b). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 2; t_R: 7.80 min; $[\alpha]_D^{25}$ 79.9 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1613.

5.6.4. (3*S*)-3-(4-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (17b). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 1; t_R: 4.25 min; $[\alpha]_D^{25}$ −90.2 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1622.

5.6.5. (3*R*)-3-(5-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (16c). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 2; retention time: 7.94 min; $[\alpha]_D^{25}$ 70.4 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1589.

5.6.6. (3*S*)-3-(5-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (17c). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 1; t_R: 5.10 min; $[\alpha]_D^{25}$ −76.0 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1596.

5.6.7. (3*R*)-3-(6-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (16d). The enantiomeric purity was determined to be 99.6% (with 0.4% of the undesired enantiomer) isolated as peak 2; t_R: 15.31 min; $[\alpha]_D^{25}$ 86.9 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1617.

5.6.8. (3*S*)-3-(6-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (17d). The enantiomeric purity was determined to be 98.3% (with 1.7% of the undesired enantiomer) isolated as peak 1; t_R: 13.91 min; $[\alpha]_D^{25}$ −92.0 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1628.

5.6.9. (3*R*)-3-(7-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (16e). The enantiomeric purity was determined to be 99.3% (with 0.7% of the undesired enantiomer) isolated as peak 2; t_R: 6.98 min; $[\alpha]_D^{25}$ 138.2 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1577.

5.6.10. (3*S*)-3-(7-Fluoro-1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (17e). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 1; t_R: 5.60 min; $[\alpha]_D^{25}$ −144.8 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1585.

5.6.11. (3*R*)-3-(3-Fluorophenyl)-3-(1*H*-indol-1-yl)-*N*-methylpropan-1-amine (16f). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 2; retention time: 11.28 min; $[\alpha]_D^{25}$ 67.9 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1581.

5.6.12. (3*S*)-3-(3-Fluorophenyl)-3-(1*H*-indol-1-yl)-*N*-methylpropan-1-amine (17f). The enantiomeric purity was determined to be >99.9% (with <0.1% of the undesired enantiomer) isolated as peak 1; t_R: 5.18 min; $[\alpha]_D^{25}$ −68.9 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{19}FN_2 + H^+$, 283.1605. Found (ESI, $[M+H]^+$), 283.1599.

5.6.13. (3*R*)-3-(4-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (16g). The enantiomeric purity was determined to be 99.3% (with 0.7% of the undesired enantiomer) isolated as peak 2; t_R: 5.83 min; $[\alpha]_D^{25}$ 70.1 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1493.

5.6.14. (3*S*)-3-(4-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (17g). The enantiomeric purity was determined to be 99.8% (with 0.2% of the undesired enantiomer) isolated as peak 1; t_R: 4.95 min; $[\alpha]_D^{25}$ −67.8 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1506.

5.6.15. (3*R*)-3-(5-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (16h). The enantiomeric purity was determined to be 99.1% (with 0.9% of the undesired enantiomer) isolated as peak 2; t_R: 10.15 min; $[\alpha]_D^{25}$ 71.0 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1510.

5.6.16. (3*S*)-3-(5-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (17h). The enantiomeric purity was determined to be 99.7% (with 0.3% of the undesired enantiomer) isolated as peak 1; t_R: 8.30 min; $[\alpha]_D^{25}$ −73.1 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1514.

5.6.17. (3*R*)-3-(6-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (16i). The enantiomeric purity was determined to be 99.8% (with 0.2% of the undesired enantiomer) isolated as peak 2; t_R: 10.15 min; $[\alpha]_D^{25}$ 73.5 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1507.

5.6.18. (3*S*)-3-(6-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (17i). The enantiomeric purity was determined to be 98.9% (with 1.1% of the undesired enantiomer) isolated as peak 1; t_R: 10.24 min; $[\alpha]_D^{25}$ −89.2 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1525.

5.6.19. (3*R*)-3-(7-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (16j). The enantiomeric purity was determined to be 99.8% (with 0.2% of the undesired enantiomer) isolated as peak 2; t_R: 4.91 min; $[\alpha]_D^{25}$ 111.9 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1490.

5.6.20. (3*S*)-3-(7-Fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-*N*-methylpropan-1-amine (17j). The enantiomeric purity was determined to be 99.1% (with 0.9% of the undesired enantiomer) isolated as peak 1; t_R: 4.78 min; $[\alpha]_D^{25}$ −95.9 ° (*c* 10 mg/mL, MeOH); HRMS: calcd for $C_{18}H_{18}F_2N_2 + H^+$, 301.1511. Found (ESI, $[M+H]^+$), 301.1527.

5.7. 1-[(1*R*)-3-Chloro-1-phenylpropyl]indoline (18)

To a solution of (*S*)-(−)-3-chloro-1-phenyl-1-propanol, purchased from Aldrich, 99% ee, $[\alpha]_D^{25}$ −25 ° (*c* 10 mg/mL, $CDCl_3$) (342 mg, 2.00 mmol) in dry diethyl ether (8 mL) was added triethylamine (0.84 mL, 6.00 mmol) and the solution was cooled to 0 °C in an ice bath. Methanesulfonyl chloride (0.187 mL, 2.40 mmol) was added dropwise via a syringe. After stirring at 0 °C for 30 min, additional triethylamine (0.56 mL, 4.00 mmol) was added, followed by slow addition of indoline (0.28 mL) and the resulting mixture was stirred for 48 h while warming to room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with aqueous sodium bicarbonate, water, and brine. The organic layer was dried (anhydrous sodium sulfate) and concentrated. The crude oil was purified by Isco flash column chromatography (silica, 0–15% EtOAc/hexane) to give 237 mg (44%) of pure product as a viscous, colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (m, 1H), 2.52 (m, 1H), 2.90 (m, 2H), 3.20 (dd, J = 17.9, 8.6 Hz, 1H), 3.41 (dd, J = 15.8, 8.8 Hz, 1H), 3.58 (m, 1H), 3.68 (m, 1H), 4.94 (dd, J = 8.3, 6.8 Hz, 1H), 6.61 (m, 2H), 7.03 (m, 2H), 7.26–7.35 (m, 5H); MS (ESI) *m*/*z* 272.0 ($[M+H]^+$).

5.8. 1-[(1*R*)-3-Chloro-1-phenylpropyl]-1*H*-indole (19)

A mixture of 1-[(1*R*)-3-chloro-1-phenylpropyl]indoline**18** (160 mg, 0.589 mmol) and activated manganese dioxide (512 mg, 5.89 mmol) in anhydrous 1,2-dichloroethane (5 mL) was heated at 70 °C with stirring for 30 min. The reaction mixture was diluted with ethyl acetate (5 mL), filtered through a pad of silica gel, and concentrated to give 156 mg (98%) of pure product as a viscous, colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.69 (m, 1H), 2.78 (m, 1H), 3.35 (m, 1H), 3.50 (dt, J = 11.1, 5.6 Hz, 1H), 5.80 (dd, J = 9.4, 5.9 Hz, 1H), 6.55 (d, J = 3.3 Hz, 1H), 7.05–7.35 (m, 9H), 7.60 (d, J = 7.7 Hz, 1H); MS (ESI) *m*/*z* 270.0 ($[M+H]^+$).

5.9. (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine hydrochloride (16a)

A mixture of 1-[(1*R*)-3-chloro-1-phenylpropyl]-1*H*-indole **19** (150 mg, 0.556 mmol) and ethanolic methylamine (33% in EtOH, 5 mL) in a sealed reaction vessel was heated at 90 °C for 3 h. All volatiles were removed under reduced pressure. The oil residue was dissolved in methylene chloride (15 mL), washed with aqueous potassium carbonate (10 mL), dried (anhydrous sodium sulfate), concentrated, and purified by Isco flash column chromatography (silica, 0–15% MeOH/CH_2Cl_2) to give 110 mg (75%) of pure free base product as a viscous, colorless liquid. This was dissolved in dichloromethane (3 mL) and treated with an ethereal solution of hydrochloric acid (1 M, 0.5 mL, and 0.5 mmol) with swirling. To the resulting solution was added hexane until white precipitate formed, which was collected, washed with hexane, and dried in vacuo to yield 119 mg (71%) of pure hydrochloride salt as a white powder. The enantiomeric purity was determined to be 91% (with 9% of the undesired enantiomer); t_R: 11.22 min; $[\alpha]_D^{25}$ 79.3 ° (*c* 10 mg/mL, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.47 (s, 3H), 2.57 (m, 1H), 2.71 (m, 2H), 2.84 (m, 1H), 5.80 (dd, J = 8.8, 6.3 Hz, 1H), 6.50 (d, J = 3.2 Hz, 1H), 6.95 (t, J = 7.9 Hz, 1H), 7.04 (t, J = 8.2 Hz, 1H), 7.17–7.30 (m, 5H), 7.48 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 3.3 Hz, 1H), 9.02 (br s, 2H); HRMS: *m*/*z* calcd for $C_{18}H_{20}N_2 + H^+$, 265.1699. Found (ESI, $[M+H]^+$), 265.1685.

5.10. General procedure 5: norepinephrine (NE) uptake assay in cells expressing human norepinephrine transporter (hNET)

5.10.1. Cell preparation. [^{3}H] NE uptake studies were performed using MDCK-Net6 cells stably expressing human norepinephrine transporter (hNET)[15] cultured in growth medium containing high glucose DMEM (Gibco, Cat. No. 11995), 10% FBS (dialyzed, heat-inactivated, US Bio-Technologies, Lot FBD1129HI) and 500 μg/ml G418 (Gibco, Cat. No. 10131). Cells were seeded at 300,000/T75 flask and split twice weekly.

5.10.2. Norepinephrine (NE) uptake assay. All uptake experiments were performed in 96-well plates (Falcon Optilux, cat #353947) in a total volume of 250 μl/well. MDCK-Net6 cells were plated at 6000 cells/well. At the time of the assay, the media were removed, and 200 μl assay buffer (25 mM Hepes, 120 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4{\cdot}7H_2O$, 2 mg/ml glucose, 0.2 mg/ml ascorbic acid, and 1 μM pargyline, pH 7.4) was added to each well. Twenty-five microliters of each test compound was subsequently added to plates in triplicate and incubated at 37 °C for 5 min. All test compounds were dissolved in 100% DMSO and diluted in 4% DMSO/H_2O, and assayed using a 7-point dose response curve (1 nM–10 μM). Next, 25 μl [^{3}H] NE (74.9 Ci/mmol, Perkin-Elmer, Boston, MA) was added to all wells and incubated at 37 °C for an additional 5 min. The final concentration of [^{3}H] NE was 16 nM. The reaction mixture was terminated by aspiration and washed with ice-cold 50 mM Tris (pH 7.4). The plates were left to air dry for roughly 30 min, and the MDCK-Net6 cells were lysed by the addition of 25 μl of 0.25 M NaOH. Hundred microliters of Microscint-20 was added to each well (Packard, Perkin-Elmer, Boston, MA), and the plates were counted using a TopCount (Perkin-Elmer, Downer's Grove, IL) liquid scintillation counter.

5.11. General procedure 6: radioligand binding assay in membranes containing the human norepinephrine transporter

Frozen membranes (Perkin-Elmer RBHNETM, 2.8 mg/ml), were suspended in binding buffer (50 mM Tris–HCl, 300 mM NaCl, and 5 mM KCl, pH 7.4) and prepared to approximately 2.8 μg protein per 20 μl aliquot. Test compounds were dissolved in 100% DMSO to 10 mM and further dilutions (0.1–10 μM) made in 4% DMSO/H_2O. Binding reactions were incubated in polypropylene 96-well format strip tubes (Denville Scientific; Cat. No. B1259). Binding buffer (100 μl) was added to each assay tube followed by the addition of 20 μl of 2× binding buffer to account for compounds diluted in 4% DMSO/H_2O. Compounds were added at a volume of 20 μl. Next, 40 μl of the radioligand, [^{3}H] nisoxetine, diluted in binding buffer, was dispensed to yield a final assay concentration of 4 nM. Non-specific binding was determined by a saturating concentration of desipramine (1 μM; prepared as the test compounds). The reactions were vortexed and incubated while shaking for 60 min at room temperature. The binding reaction mixture was terminated by vacuum filtration (Brandel) through Whatman glass fiber filters (GF/B paper), presoaked in 0.5% polyethylenimine/H_2O (PEI; Sigma Cat. No. P-3143) followed by six washes with 800 μl of ice-cold wash buffer (50 mM Tris–HCl, 0.9% NaCl, pH 7.4 at 4 °C). Filter circles were removed to 20 ml glass vials, mixed with 5 ml of scintillation cocktail (OptiFlour; Perkin-Elmer), and incubated at room temperature for 8 h. The vials were counted and DPMs were determined using a Perkin-Elmer liquid scintillation analyzer.

5.12. General procedure 7: serotonin (hSERT) uptake assay in cells expressing human serotonin transporter

5.12.1. Cell preparation. [^{3}H] 5-HT uptake studies were performed using JAR cells (human placental choriocarcinoma; ATCC Cat. No. HTB-144) natively expressing the human serotonin transporter (hSERT), and cultured in growth medium containing RPMI 1640 (Gibco, Cat. No. 72400), 10% FBS (Irvine, Cat. No. 3000), 1% sodium pyruvate (Gibco, Cat. No. 1136), and 0.25% glucose. Cells were seeded at 250,000 cells/T75 flask and split twice weekly. For the SERT uptake assay, JAR cells were incubated for 24 h with 40 nM staurosporine to enhance the expression of the hSERT. Following an additional 24 h the cells were assayed for the [^{3}H] 5-HT uptake.[16]

5.12.2. Serotonin (5-HT) uptake assay. All uptake experiments were performed in 96-well plates (Falcon Optilux, cat #353947) in a total volume of 250 μl/well. JAR cells were plated at 90,000 cells/well. At the time of the assay, the media was removed, and 200 μl assay buffer (25 mM Hepes, 120 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4{\cdot}7H_2O$, 2 mg/ml glucose, 0.2 mg/ml ascorbic acid, 1 μM pargyline, pH 7.4) was added to each well. Twenty-five microliters of each test compound was subsequently added to plates in triplicate and incubated at 37 °C for 5 min. All test compounds were dissolved in 100% DMSO and diluted in 4% DMSO/H_2O, and assayed using a 7-point dose–response curve (1 nM–10 μM). Next, 25 μl [^{3}H] 5-HT (30 Ci/mmol, Perkin-Elmer, Boston, MA) was added to all wells for the SERT assay and incubated at 37 °C for an additional 5 min. The final concentration of [^{3}H] 5-HT was 12 nM. The reaction mixture was terminated by aspiration and the mixture was washed with ice-cold 50 mM Tris (pH 7.4). The plates were centrifuged (3000 rpm for 5 min) prior to aspiration of the supernatant. The JAR cells underwent another wash step, centrifuged, and aspirated again. The plates were left to air dry for roughly 30 min, and the JAR cells were lysed by the addition of 25 μl of 0.25 M NaOH. Hundred microliters of Microscint-20 was added to each well (Packard, Perkin-Elmer, Boston, MA), and the plates were counted using a TopCount (Perkin-Elmer, Downer's Grove, IL) liquid scintillation counter.

5.13. General procedure 8: dopamine transporter (hDAT) membrane binding assay

Frozen membranes (Perkin-Elmer RBHDATM) were suspended in binding buffer (50 mM Tris–HCl, 100 mM

NaCl, pH 7.4) and prepared to approximately 9.8 μg protein/ml, and 160 μl of the homogenized suspended membranes was added to polypropylene 96-well format strip tubes (Denville Scientific; Cat. No. B1259). Test compounds were dissolved in 100% DMSO to 10 mM and further dilutions (0.1–10 μM) made in 4% DMSO/H_2O. Compounds were added at a volume of 20 μl and pre-incubated with the test compounds for 20 min at 4 °C on a Titer Plate Shaker at a speed setting of six. Next, 20 μl of the radioligand, [^{3}H] WIN-35,428, diluted in binding buffer, was dispensed to yield a final assay concentration of 32 nM, the Kd value estimated for [^{3}H] WIN-35,428 for hDAT membranes was 29.7 nM. Non-specific binding was determined by a saturating concentration of mazindol (10 μM; prepared as the test compounds). The reactions were vortexed and incubated while shaking for 2 h at 4 °C. The binding reaction mixture was terminated by vacuum filtration (Brandel) through Whatman glass fiber filters (GF/B paper), presoaked in 0.5% polyethylenimine/H_2O (PEI; Sigma Cat. No. P-3143) followed by six washes with 800 μl of ice cold wash buffer (50 mM Tris–HCl, 0.9% NaCl, pH 7.4 at 4 °C). Filter circles were removed to 7 ml glass vials, mixed with 5 ml of scintillation cocktail (OptiFlour; Perkin-Elmer), and incubated at room temperature for 8 h. The vials were counted and DPMs were determined using a Perkin-Elmer liquid scintillation analyzer.

5.14. General procedure 9: analysis of results

Positive controls were run on each plate for all assays. Calculations of IC_{50} were performed using a sigmoidal non-linear regression program (Prism Graphpad 3 Software, San Diego, CA). In this program, maximum uptake is represented by those wells supplemented with assay buffer, and non-specific uptake is determined by wells treated with positive controls.

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