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Design and synthesis of calindol derivatives as potent and selective calcium sensing receptor agonists

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ABSTRACT

We report the first comprehensive structure–activity study of calindol (**4**, (*R*)-*N*-[(1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine), a positive allosteric modulator, or calcimimetic, of the calcium sensing receptor (CaSR). While replacement of the naphthyl moiety of calindol by other aromatic groups (phenyl, biphenyl) was largely detrimental to calcimimetic activity, incorporation of substituents on the 4, 5 or 7 position of the indole portion of calindol was found to provide either equipotent derivatives compared to calindol (e.g., 4-phenyl, 4-hydroxy, 5-hydroxycalindol **44**, **52**, **53**) or, in the case of 7-nitrocalindol (**51**), a 6-fold more active calcimimetic displaying an EC_{50} of 20 nM. Unlike calindol, the more active CaSR calcimimetics were shown not to act as antagonists of the closely related GPRC6A receptor, suggesting a more selective profile for these new analogues.

1. Introduction

G protein-coupled receptors (GPCRs), present exclusively in eukaryotes, are involved in a myriad of diseases and are the target of around half of all modern medicinal drugs.[1] Also referred to as seven transmembrane (7TM) domain receptors, GPCRs are able to sense molecules present outside the cell going from small molecules and peptides to large proteins. These then activate complex signal transduction pathways inside the cell resulting in a variety of cellular responses. Among this GPCR superfamily, the extracellular calcium sensing receptor (CaSR) has come under considerable focus for the discovery of new allosteric modulators with high therapeutic potential.[2]

The CaSR belongs to class C of GPCRs, which includes its close analogue GPRC6A, receptors for pheromones, odorants, taste, the excitatory amino acid glutamate, and the neurotransmitter γ-aminobutyric acid (GABA).[3] This receptor class shares an exceptionally large extra-cellular domain analogous to the bilobed 'Venus flytrap' domain (VFT) of bacterial periplasmic binding proteins.[4] The human CaSR is the unique cation-sensing GPCR and its localization in the parathyroid,[5] kidney[6] and brain[7] has received the most attention.[8] By detecting small changes in extracellular Ca^{2+} levels, the CaSR regulates calcium by controlling parathyroid hormone secretion (PTH) in a feedback process and thus plays a major role in maintaining calcium homeostasis.[9] Although Ca^{2+} is the endogenous ligand, the CaSR is also sensitive to several di- and trivalent cations (Mg^{2+}, Gd^{3+}) and organic cationic compounds such as spermine, polyamine, poly-L-arginine[10] and amyloid β-peptide.[8]

In the parathyroid gland, positive allosteric modulators of the CaSR, or calcimimetics, diminish PTH secretion.[11] While such modulators do not directly activate the receptor, they potentiate its action by increasing both the potency and efficacy of the endogenous agonists. In this context, primary hyperparathyroidism (1HPT) is an endocrine disorder characterized by excessive secretion of PTH by the parathyroid glands[12] while secondary hyperparathyroidism (2HPT), associated with chronic kidney disease, is associated with an increase in PTH as a compensatory response to reduced calcium levels. Calcimimetics are able to increase the sensitivity of the CaSR to circulating serum calcium and to consequently reduce both PTH and calcium levels.[13] Proof-of-concept was provided by one of the first-described calcimimetics NPS R-568 (**1**)[14] but the poor bioavailability of this compound precluded its clinical use. The structurally analogous derivative cinacalcet (**2**) (Sensipar®), however, provided clear clinical data demonstrating the ability of calcimimetic compounds to lower

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the circulating levels of PTH in patients with 1HPT or 2HPT and was the first calcimimetic to be approved for treatment of 2HPT in patients on dialysis and of hypercalcemia in patients with parathyroid cancer.[15]

The success of cinacalcet provided a powerful stimulus to the development of calcimimetics as therapeutic agents for the treatment of conditions characterized by high circulating PTH levels.[15–17] We ourselves have described several new families of calcimimetics including the acyclic arylsulfonamide derivatives exemplified by compound **3**[18] and conformationally restricted analogues of this family represented by calindol (**4**)[19] and the cyclic arylsulfonamide **5** (Fig. 1).[20] As with calcimimetics **1**–**5**, the α-methylarylamine group is a common structural feature of most of the calcimimetics described to date.[17] However, calcimimetics devoid of such a motif, for example, in which the branched α-methylarylamine is replaced by a linear urea functionality, have also been reported.[17,21,22]

Of these, calindol has proven to be a valuable tool for the study of the localization and mode of action of the CaSR. Thus, calindol was shown to stabilize a conformation of the CaSR's 7TM domain that in turn facilitates the active closed state of the VFT domain thereby increasing the receptor's affinity for Ca^{2+}.[23] Calindol has also been used to characterize the CaSR in endothelial cells in both porcine coronary and rat mesenteric arteries.[24] Calindol induced hyperpolarization of the vascular myocytes pointing to a role of CaSR in regulating blood pressure.[25] Calindol was employed to show that compromising the CaSR pathway may contribute to the vascular complications associated with type II diabetes via CaSR-mediated vasodilation.[26] Recently, it was found that coupling calindol with lanthanum chloride inhibited the calcification of vascular smooth muscle cells.[27] Finally, calindol allowed investigation of the function of the closely related GPRC6A receptors.[28,29] The latter are activated by calcium ions but also by basic amino acids such as L-ornithine.[30] While GPRC6A has been linked to inflammation and endocrine functions,[31] little is known concerning its physiological role.[32] We have previously shown, however, that calindol acts as a GPRC6A antagonist, inhibiting L-ornithine-mediated activation of this receptor.[29] These important findings encouraged us to undertake a more thorough structure–activity relationship study of calindol in an effort to optimize its calcimimetic activity and to eventually obtain more selective CaSR ligands with respect to GPRC6A (Fig. 2).

We now report the synthesis and calcimimetic activities of a series of structural analogues of calindol differing in the types and position of substituents incorporated on the indole moiety as well as replacement of the naphthalene unit by various aryl groups leading to the development of a calcimimetic having a 6-fold superior activity compared to calindol and displaying no significant activity with respect to GPRC6A.

2. Chemistry

Pharmacomodulation of the indole portion of calindol was first undertaken using a short and efficient methodology. Thus, appropriately substituted indole-2-carboxylic acids (**6**–**18**) (obtained from commercial sources or prepared as described in the Section 5) were coupled to (*R*)-1-(1-naphthyl)ethylamine (**19**)[33] using EDCI/HOBt in the presence of triethylamine (Scheme 1).[34] The resulting amides (**20**–**32**) were then reduced to the corresponding secondary amines (**33**–**45**) by the action of a mixture of lithium aluminium chloride and aluminium trichloride in refluxing THF. The structures and yields of the amides and amines so-prepared are reported in Table 1.

The strong amide reducing conditions could not be applied to preparation of nitrocalindol derivatives without concomitant reduction of the nitro group. Ethyl 5-nitroindole-2-carboxylate **46** and its 7-nitro analogue **47** were thus first reduced to the alcohols **48** and **49** using diisobutylaluminium hydride in THF and dichloromethane at −50 °C (Scheme 2). The alcohols were then coupled to (*R*)-naphthylethylamine (**19**) under standard Mitsunobu conditions to afford the desired 5-nitrocalindol (**50**) and 7-nitrocalindol (**51**).[35]

Some of the calindol analogues so-prepared then served as starting material for the synthesis of additional derivatives. Thus, 4-hydroxy- and 5-hydroxycalindol **52** and **53** were prepared by BBr_3-promoted demethylation of 4-methoxycalindol **33** and palladium/carbon catalyzed hydrogenolysis of 5-benzyloxycalindol **39**, respectively (Scheme 3).[36,37]

Calindol (**4**) was originally conceived as a structurally more rigid analogue of the acyclic arylsulfonamide **3**.[19] The gain in potency observed as a result encouraged us to study an alternative rigid calindol derivative, the 1-naphthylethylaminocarbazole **56**, which was easily prepared as shown in Scheme 4. Thus, indole-3-butanoic acid (**54**) was cyclized to give the carbazole-2-one derivative **55** using PPA in toluene[38] and the latter was subjected to reductive amination with (*R*)-1-(1-naphthyl)ethylamine (**19**) in the presence of sodium triacetoxyborohydride[39] providing compound **56** as a diastereomeric mixture with an overall yield of 68%.

Replacement of the naphthyl moiety of calindol by substituted aryl groups was also implemented. Thus, as shown in Scheme 5 and Table 2, the 1-arylethanamines **57**–**66** (obtained from commercial sources or prepared as described in the Section 5) were coupled to 1*H*-indole-2-carboxylic acid using EDCI/HOBt and the resulting amides **67**–**76** were reduced as before by the combined action of $LiAlH_4$ and $AlCl_3$ to provide calindol analogues **77**–**86**. Yields were generally moderate to good for the reduction step except in the case of bromo compounds **83** and **84** (in which partial debromination was observed) and the biphenyl derivative **85**, none of which exceeded 30%.

3. Results and discussion

The new calindol analogues synthesized were then evaluated for their calcimimetic activity in Chinese hamster ovarian (CHO) cells stably expressing cloned CaSR from rat brain (CHO(CaSR)) as previously described.[10] In these cells, Ca^{2+} as well as positive allosteric modulators (calcimimetics) stimulate phospholipase C (PLC) activity resulting in accumulation of inositol phosphates (IP). In order to rapidly identify the most active compounds, the IP accumulation produced by first 10 μM and/or 3 μM of each new derivative was measured in the presence of 3 mM $[Ca^{2+}]_e$ and compared to the effect produced by calindol.

The effects of structural variations on the indole portion of calindol were first studied. Thus, as shown in Table 3, while all the indole-modified analogues displayed calcimimetic activity, both the nature and the position of the substituents introduced had significant effects on the level of this activity with respect to calindol. Compared to calindol, which inhibited 83% of IP accumulation at 3 μM, it was immediately apparent that introduction of one or more alkoxy substituents (i.e., methoxy derivatives **33**–**36**, 5-benzyloxy derivative **39**), a 5-methyl (**38**), a 3- or 5-halogen (**41**, **37**) led in all cases to reduced calcimimetic activity as did a 7-hydroxy function (**42**), the electron-withdrawing 5-methylsulfonyl (**40**) and 5-nitro (**50**) groups, IP accumulation inhibition being in the 0–60% range. Interestingly, introduction of a hydroxy function at the 4- or 5-positions (**52**, **53**) instead of the 7-position (**42**) had essentially no effect on the calcimimetic activity of calindol. Concerning the phenyl substituted analogues **43**–**45**, no significant gain or loss in calcimimetic activity was observed for the 5- and 7-phenyl derivatives (**44** and **45**) compared to calindol

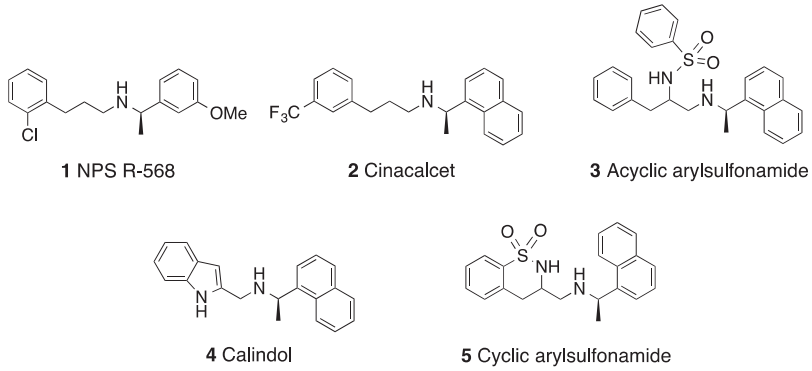


Figure 1. Examples of synthetic α-methylarylamine-type CaSR ligands acting as calcimimetics.

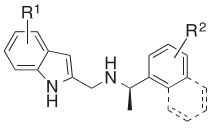


Figure 2. General structural modifications of calindol studied in this report.

while 3-phenylcalindol (**43**) was, on the other hand, considerably less active, displaying only about half the activity of calindol at 10 μM. Finally, from this series, only the 7-nitro derivative **51** could be considered as a potentially more potent calcimimetic than calindol itself. This was confirmed by comparison of their EC_{50}'s (*vide infra*).

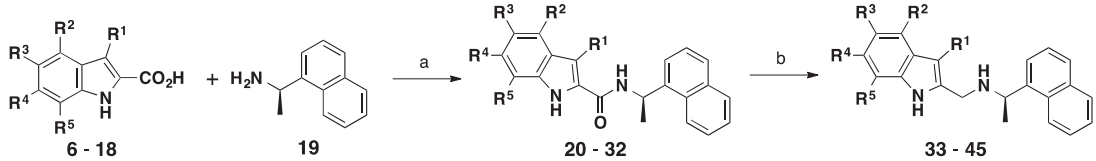
Effects of structural modifications of the naphthyl moiety of calindol on calcimimetic activity were next investigated. As shown in Table 4, replacement of the naphthyl ring by a phenyl (**77**) resulted in significant loss of activity (only 34% IP accumulation at 10 μM compared to 100% for calindol at the same concentration) and introduction of different types of substituents (alkyl (**78**), alkoxy (**79**, **80**), hydroxy (**81**), halogen (**82**–**84**), phenyl (**85**)) at various positions (*o*, *m*, *p*) on the phenyl ring led to no substantial increase in activity or even to complete loss of activity (**81**, **85**). The 4-fluoronaphthyl analogue **86** was the only compound of this series that, at 3 μM, displayed calcimimetic activity comparable to calindol.

The EC_{50}'s of the more active analogues were then determined. As shown in Figure 3 and Table 5, the 7-nitro derivative **51** displayed an EC_{50} of 20 nM, representing an almost 6-fold superior calcimimetic activity compared to calindol (132 nM). The EC_{50}'s of 4- and 5-hydroxycalindols **52** and **53** (102 nM and 112 nM, respectively) were of the same order as that of calindol and 4-phenylcalindol (**44**), the latter presenting an EC_{50} of 136 nM. Nevertheless, the ease of incorporation of variously substituted phenyl groups at the C4 position via Suzuki coupling reactions opens the path to further optimization of this activity. Finally, the 4-fluoronaphthyl analogue **86**, tested as a racemic mixture, was equipotent with calindol in terms of EC_{50} (131 nM vs 132 nM, respectively).

We have previously shown that calindol is a negative modulator of mouse GPRC6A (mGPRC6A) response to L-ornithine (L-Orn).[29] We thus evaluated the ability of several of the chemically diverse active calindol analogues synthesized in this study to modify this same response. As shown in Figure 4, neither compounds **44**, **51** or **86**, tested at a concentration of 10 μM, had any significant inhibitory effect on L-Orn-promoted stimulation of IP production in HEK293 cells expressing mGPRC6A. In contrast, calindol produced an approximately 35% reduction in IP production under the same conditions. None of the compounds had any effect on IP production in the absence of L-Orn. These results suggest that, compared to calindol, these new analogues present a more selective profile with respect to the CaSR versus mGPRC6A which could be an eventual advantage in vivo in terms of reduction of possible side-effects.

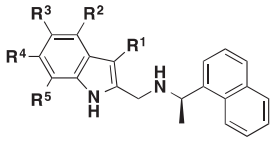
4. Conclusion

We present herein the first comprehensive study concerning the structure–activity relationships of the calcimimetic calindol. Our results lead to a first conclusion that, while incorporation of a variety of types of substituents at different positions of the indole portion of calindol can in many instances lead to equipotent or more potent compounds, the various attempts at replacing the naphthyl moiety by other aromatic groups (substituted phenyl, biphenyl) led to substantial decrease and even total loss of calcimimetic activity. Only the 4-fluoronaphthyl derivative **86** demonstrated equipotency with calindol. The naphthalene unit thus appears to be indispensable to ensure high activity. However, in view of the paucity of appropriate commercial derivatives of the naphthalene family together with the synthetic difficulties in accessing these, further exploration of this part of calindol does not appear at this point to be a promising pursuit. On the other hand, depending on the nature of the substituent incorporated, no particular position on the benzo portion of the indole nucleus seems adverse to maintaining or improving calcimimetic activity with respect to calindol. Thus, the 4-phenyl-, 4-hydroxy and 5-hydroxycalindol analogues (**44**, **52**, **53**, respectively) were as active as calindol while the 7-nitro derivative **51** was 6-fold more active. Interestingly, in contrast to calindol, these compounds had no effect on the closely related GPRC6A receptor suggesting a more favourable selectivity profile. Our present data argue that **51** should be a valuable tool for studying the CaSR without affecting



Scheme 1. Reagents and conditions: (a) EDCI, HOBt, NEt_3, CH_2Cl_2, 0 °C to rt, 16 h; (b) $LiAlH_4$, $AlCl_3$, THF, reflux, 16 h.

Table 1
Structural variation of the indole moiety of calindol



33 - 45

Starting indole	R^1	R^2	R^3	R^4	R^5	Amide (% yield)[a]	Calindol analogue (% yield)[a]
6	–H	–OMe	–H	–H	–H	**20** (91)	**33** (80)
7	–H	–OMe	–H	–OMe	–H	**21** (80)	**34** (54)
8	–H	–H	–H	–OMe	–H	**22** (95)	**35** (58)
9	–H	–H	–OMe	–OMe	–OMe	**23** (80)	**36** (53)
10	–H	–H	–F	–H	–H	**24** (98)	**37** (87)
11	–H	–H	–Me	–H	–H	**25** (97)	**38** (65)
12	–H	–H	–OBn	–H	–H	**26** (100)	**39** (63)
13	–H	–H	$–SO_2Me$	–H	–H	**27** (90)	**40** (60)
14	–Br	–H	–H	–H	–H	**28** (76)	**41** (61)[b]
15	–H	–H	–H	–H	–OH	**29** (54)	**42** (38)
16[c]	–Ph	–H	–H	–H	–H	**30** (75)	**43** (86)
17[c]	–H	–Ph	–H	–H	–H	**31** (90)	**44** (78)
18[c]	–H	–H	–H	–H	–Ph	**32** (83)	**45** (62)

[a] Yields are not optimized.
[b] 19% of debrominated product was isolated.
[c] See Section 5 for the preparation of the phenyl-substituted indoles.

the GPRC6A. Further work is needed to delineate whether antagonizing both the CaSR and the GPRC6A would be of therapeutic interest. But it is interesting to note that a family of 3-substituted-2-phenylindole derivatives has recently been described as the first selective allosteric antagonists of the GPRC6A including with respect to the CaSR. The availability now of selective and potent ligands for these two GPCRs should thus be highly useful for functional studies of both receptors.[41] The phenyl, hydroxyl and nitro groups introduced on the calindol scaffold provide 'handles' for further structural modification and optimization of these CaSR ligands. This will be the object of forthcoming investigations together with in vivo evaluation of the active calindol derivatives presented in this study.

5. Experimental section

5.1. Biological assays

5.1.1. IP-one assay in CHO(CaSR)

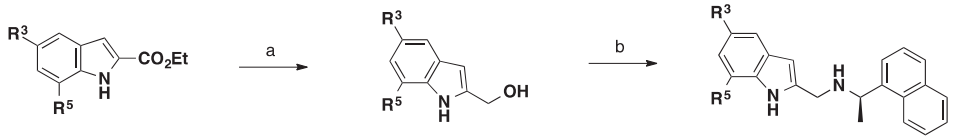
Chinese hamster ovarian (CHO) cells stably expressing cloned calcium sensing receptor from rat brain (CHO(CaSR)) were cultivated as described[10] and used to evaluate inositol phosphate (IP) production using the IP-one kit (Cisbio International) as previously described.[20] The compounds were dissolved in ethanol at 10 mM and tested in presence of 3 mM of $[Ca^{2+}]_e$ unless otherwise stated. The IP accumulation produced by the test compounds was measured and compared to the effect produced by calindol and by 10 mM $[Ca^{2+}]_e$ in the same experiment. Results are expressed as % of the maximal stimulation produced by 10 mM Ca^{2+} and are the mean of 2–6 experiments ± SEM. Concentration–response experiments were performed in triplicate. Curve fitting, determination of pEC_{50} and EC_{50} were performed using the non-linear regression curve fitting program Prism 4.03 (GraphPad software, San Diego, CA, USA).

5.1.2. [^{3}H]Inositol phosphate formation in HEK293 cells co-expressing mGPRC6A and GαqG66D

HEK293 cells were plated at $1.2 \cdot 10^5$ cells per well in a 24-well plate coated with poly-D-lysine (0.05 mg/ml, Sigma) and co-transfected the day after with 0.2 μg of plasmid containing WT mGPRC6A, and GαqG66D. Measurement of tritiated inositol phosphate ([^{3}H]IP) was performed as previously described.[29] Briefly, cells were labelled 24 h after transfection with 2 μCi/well of myo-[^{3}H]inositol (Perkin–Elmer) for 20 h in their growth medium, washed and pre-incubated 2 × 2 h at 37 °C in HBSS buffer (pH 7.4). The activity of mGPRC6A was then determined in response to L-ornithine alone or in the presence of indicated compounds and 2 mM $[Ca^{2+}]_e$ by measuring [^{3}H]IP production.

5.2. Chemistry

Melting points, measured in capillary tubes on a Büchi B-540 apparatus, are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. Optical rotations were determined with a JASCO P-1010 polarimeter at 23 °C. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP—C13, P31, F19—probe or Dual C13 probe) and Avance 500 MHz (BB0—ATM probe or BBI—ATM

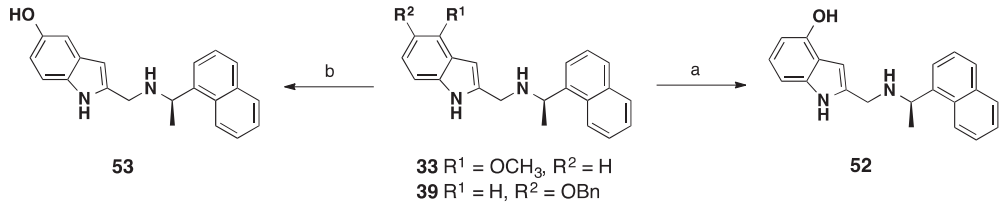


46 : $R^3 = NO_2$; $R^5 = H$
47 : $R^3 = H$; $R^5 = NO_2$

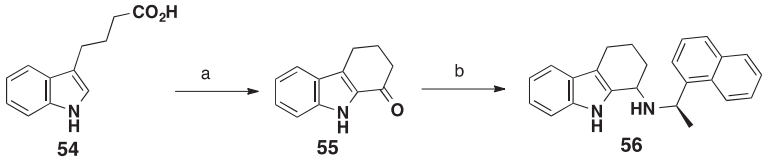
48 : $R^3 = NO_2$; $R^5 = H$ (98%)
49 : $R^3 = H$; $R^5 = NO_2$ (98%)

50 : $R^3 = NO_2$; $R^5 = H$ (60%)
51 : $R^3 = H$; $R^5 = NO_2$ (74%)

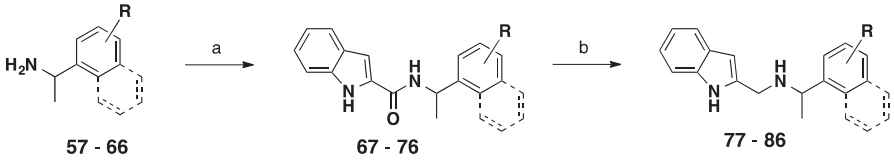
Scheme 2. Reagents and conditions: (a) DIBAH, THF/CH_2Cl_2, −50 °C, 2 h; (b) DIAD, PPh_3, **19**, THF, 0 °C to rt, 16 h.



Scheme 3. Reagents and conditions: (a) **33**, BBr_3, CH_2Cl_2, −78 °C, 4 h (87%); (b) **39**, Pd/C, H_2, MeOH, rt, 4 h (95%).

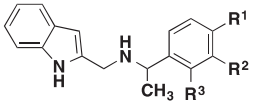


Scheme 4. Reagents and conditions: (a) PPA, toluene, reflux (91%); (b) $NaBH(OAc)_3$, AcOH, **19**, THF, rt, 24 h (75%).



Scheme 5. Reagents and conditions: (a) Indole-2-carboxylic acid, EDCI, HOBt, NEt_3, CH_2Cl_2, 0 °C to rt, 4 h; (b) $LiAlH_4$, $AlCl_3$, THF, reflux, 20 h.

Table 2
Structural variation of the naphthalene moiety of calindol



Starting amine[b]	R^1	R^2	R^3	Amide (% yield)[a]	Calindol analogue (% yield)[a]
(*R*)-**57**	–H	–H	–H	(*R*)-**67** (76)	(*R*)-**77** (90)
(*R*)-**58**	–Me	–H	–H	(*R*)-**68** (78)	(*R*)-**78** (55)
(*R*)-**59**	–OMe	–H	–H	(*R*)-**69** (62)	(*R*)-**79** (52)
(*R*)-**60**	–H	–OMe	–H	(*R*)-**70** (65)	(*R*)-**80** (60)
(*R,S*)-**61**	–H	–H	–OH	(*R,S*)-**71** (95)	(*R,S*)-**81** (41)
(*R*)-**62**	–F	–H	–H	(*R*)-**72** (70)	(*R*)-**82** (78)
(*R*)-**63**	–Br	–H	–H	(*R*)-**73** (77)	(*R*)-**83** (28)[c]
(*R,S*)-**64**	–H	–Br	–H	(*R,S*)-**74** (89)	(*R,S*)-**84** (27)[c]
(*R,S*)-**65**	$-C_6H_5$	–H	–H	(*R,S*)-**75** (89)	(*R,S*)-**85** (25)
(*R,S*)-**66**	–F	$-(CH_2)_4-$		(*R,S*)-**76** (97)	(*R,S*)-**86** (48)

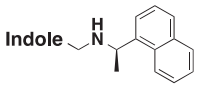
[a] Yields are not optimized.
[b] The optically pure (*R*)-amines were obtained commercially; the racemic amines were obtained by Leuckart amination (Ref. 40) of the corresponding commercial ketones (see Section 5 for details).
[c] A small percentage of debrominated product was also obtained.

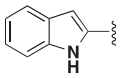
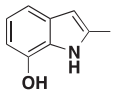
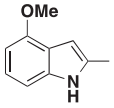
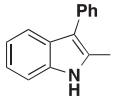
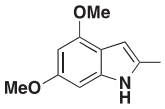
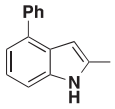
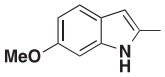
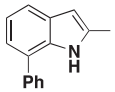
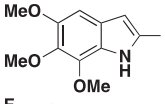
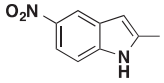
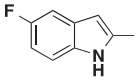
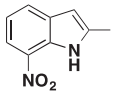
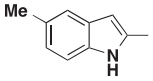
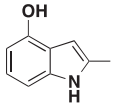
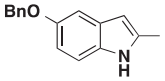
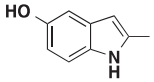
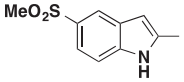
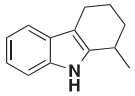
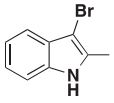
probe). Chemical shifts (δ) are reported in parts per million (ppm) with reference to $CDCl_3$ (^{1}H: 7.27; ^{13}C: 77.00), CD_3OD (^{1}H: 3.31; ^{13}C: 49.00), or DMSO-d_6 (^{1}H: 2.50; ^{13}C: 39.51). The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, qu: quintuplet, m: multiplet, br: broad. Coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained with a LCT (Micromass) instrument using electrospray ionization and Time of Flight analyzer (ESI-MS) for high resolution mass spectra (HRMS). Thin-layer chromatography was performed on silica gel 60 F_{254} on aluminium plates (Merck) and visualized under a UVP Mineralight UVLS-28 lamp (254 nm) and with *p*-anisaldehyde/H_2SO_4 in ethanol. Flash chromatography was performed using silica gel 60 (Merck, 40–63 μm) at medium pressure (300 mbar) or on CombiFlash (Serlabo Technologies). All solvents were freshly distilled when required. All reagents were obtained from commercial suppliers unless otherwise stated. Organic extracts were, in general, dried over magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4). Elemental analyses (Perkin Elmer CHN 2400 analyzer with a detection by catharometry) were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

5.2.1. (*R*)-4-Methoxy-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (20)

To a suspension of 4-methoxyindole-2-carboxylic acid (**6**, 93.7 mg, 0.49 mmol) in anhydrous dichloromethane (2 mL) was added at room temperature (*R*)-1-(1-naphthyl)ethylamine (**19**,

Table 3
IP accumulation produced by the calindol analogues in CHO cells expressing rat CaSR: effect of modification of the indole moiety



Compound	Indole	% IP accumulation[a]		Compound	Indole	% IP accumulation[a]	
		10 μM	3 μM			10 μM	3 μM
4 (calindol)		100 ± 10 103 ± 11[b]	83 ± 4 73 ± 6[b]	**42**		83 ± 11	55 ± 4
33		95 ± 6[b]	63 ± 3[b]	**43**		55 ± 15	
34		94 ± 12[b]	53 ± 2[b]	**44**		102 ± 6	85 ± 6
35		76 ± 16[b]	33 ± 4[b]	**45**			79 ± 6
36			40 ± 3	**50**			30 ± 4
37		74 ± 9[b]	30 ± 4[b]	**51**			102 ± 9 70 ± 8[c]
38		69 ± 22[b]	1 ± 4[b]	**52**			88 ± 7
39			23 ± 4	**53**			92 ± 5
40			54 ± 3	**56**		67 ± 11	
41			21 ± 4				

[a] The IP accumulation produced by the test compounds in the presence of 3 mM $[Ca^{2+}]_e$ was measured and compared to the effect produced by 10 mM $[Ca^{2+}]_e$ (a concentration producing maximal CaSR activation) and by calindol. Results are expressed as % of stimulation by 10 mM Ca^{2+} taken as 100%. See Ref. 10 for experimental details.

[b] In the presence of 2 mM $[Ca^{2+}]_e$.

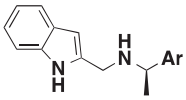
[c] % IP accumulation produced by 0.1 μM of test compound.

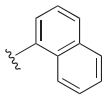
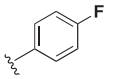
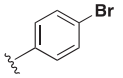
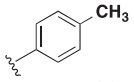
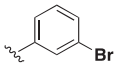
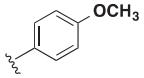
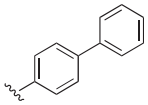
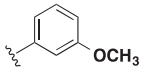
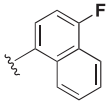
88 mg, 0.52 mmol). The mixture was cooled to 0 °C and *N*-hydroxybenzotriazole (HOBt, 70.3 mg, 0.52 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI, 80.7 mg, 0.52 mmol) and triethylamine (52.6 mg, 0.52 mmol) were added. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 5 h. Water was added, the mixture was extracted with dichloromethane, the organic extract was dried over sodium sulfate and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (ethyl acetate/heptane 1:4 then 2:3), providing compound **20** as a white powder (153 mg, 91%); mp 120–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.91 (br s, 1H), 8.20 (dd, J_1 = 7.3 Hz, J_2 = 2.1 Hz, 1H), 7.90 (dd, J_1 = 7.3 Hz, J_2 = 2.1 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.57–7.46 (m, 3H), 7.09 (t, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.48 (d, J = 8.1 Hz, 1H), 6.47 (d, J = 6.8 Hz, 1H), 6.17 (dq, J = 6.8 Hz, 1H), 3.91 (s, 3H), 1.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.8, 154.0, 138.2, 137.9, 134.0, 131.0, 129.2, 128.8, 128.5, 126.6, 125.9, 125.3, 123.2, 122.4, 118.8, 105.2, 99.7, 99.5, 55.2, 45.2, 21.1; HRESMS Calcd for $C_{22}H_{20}N_2NaO_2$ $[M+Na]^+$: 367.1422. Found: 367.1470.

5.2.2. (*R*)-4,6-Dimethoxy-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (21)

Compound **21** was prepared by the same method described for the synthesis of **20** starting from 4,6-dimethoxyindole-2-carboxylic acid (**7**) (80% yield, white powder); mp 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.53 (br s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.56–7.46 (m, 3H), 6.83 (d, J = 1.9 Hz, 1H), 6.47 (d, J = 1.9 Hz, 1H), 6.36 (br d, J = 7.7 Hz, 1H), 6.17 (d, J = 1.9 Hz, 1H), 6.14 (dq, J_1 = 7.7 Hz, J_2 = 6.8 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H),

Table 4
IP accumulation produced by the calindol analogues in CHO cells expressing rat CaSR: effect of modification of the naphthyl moiety



Compound	Ar	% IP accumulation[a]		Compound	Ar	% IP accumulation[a]	
		10 μM	3 μM			10 μM	3 μM
4 (calindol)		100 ± 10 103 ± 11[b]	83 ± 4 73 ± 6[b]	**82**			30 ± 9
77		34 ± 1[b]		**83**			26 ± 1
78		29 ± 15[b]		**84**[c]			49 ± 1
79		27 ± 15[b]		**85**[c]		1 ± 7	2 ± 3
80		54 ± 3[b]		**86**[c]			89 ± 5
81[c]		1 ± 5	1 ± 4				

[a] The IP accumulation produced by the test compounds in the presence of 3 mM $[Ca^{2+}]_e$ was measured and compared to the effect produced by 10 mM $[Ca^{2+}]_e$ and by calindol. Results are expressed as % of stimulation by 10 mM Ca^{2+}.
[b] In the presence of 2 mM $[Ca^{2+}]_e$.
[c] Compound tested as racemic mixture.

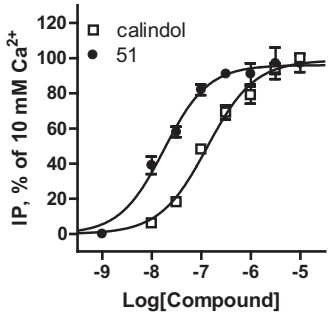


Figure 3. Potency of **51** and calindol in stimulating accumulation of IP in CHO (CaSR) stably expressing the rat CaSR. Cells were incubated with increasing concentrations of calindol or compound **51** for 30 min in the presence of 3 mM Ca^{2+}. The IP accumulation was measured as described in the Section 5. Results are expressed as % of 10 mM Ca^{2+} and are means ± SEM of triplicates. A representative experiment out of four is shown. Compound **51** and calindol displayed EC_{50}'s of 18 nM and 130 nM, respectively, and produced a similar maximum stimulation.

1.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7, 159.5, 154.5, 138.1, 138.0, 134.0, 131.0, 128.8, 128.5, 128.0, 126.6, 125.9, 125.2, 123.3, 122.5, 113.5, 100.1, 92.5, 86.4, 55.5, 55.3, 45.0, 21.0; HRESMS Calcd for $C_{23}H_{23}N_2O_3$ $[M+H]^+$: 375.1709. Found: 375.1158.

5.2.3. (*R*)-6-Methoxy-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (22)

Compound **22** was prepared by the same method described for the synthesis of **20** starting from 6-methoxyindole-2-carboxylic acid (**8**) (95% yield, white powder); mp 190–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.26 (br s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.55–7.48 (m, 3H), 7.44 (d, J = 8.8 Hz, 1H), 6.86 (br s, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.72 (s, 1H), 6.39 (d, J = 7.3 Hz, 1H), 6.16 (dq, J_1 = 7.3, J_2 = 6.7 Hz, 1H), 3.80 (s, 3H), 1.82 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7, 158.2, 138.0, 137.4, 134.0, 131.1, 129.4, 128.8, 128.5, 126.7, 125.9, 125.2, 123.3, 122.6, 121.8, 112.0, 102.4, 93.9, 55.4, 45.0, 20.9; HRESMS Calcd for $C_{22}H_{20}N_2NaO_2$ $[M+Na]^+$: 367.1422. Found: 367.1436.

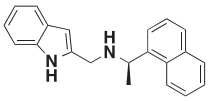
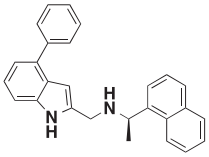
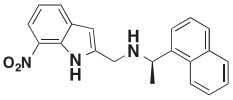
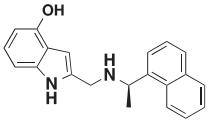
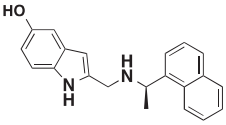
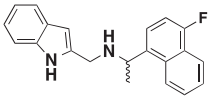
5.2.4. (*R*)-5,6,7-Trimethoxy-*N*-[(1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (23)

Compound **23** was prepared by the same method described for the synthesis of **20** starting from 5,6,7-trimethoxyindole-2-carboxylic acid (**9**) (80% yield, off-white powder); mp 114–119 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.14 (br s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.56–7.48 (m, 3H), 6.72 (s, 1H), 6.62 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 7.9 Hz, 1H), 6.13 (dq, J_1 = 7.9, J_2 = 6.6 Hz, 1H), 4.06 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 1.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.3, 150.1, 140.0, 139.0, 138.0, 134.0, 131.2, 130.2, 128.8, 128.6, 126.7, 125.9, 125.7, 125.2, 123.4, 123.2, 122.7, 102.2, 97.4, 61.4, 61.1, 56.3, 44.9, 20.8; HRESMS Calcd for $C_{24}H_{24}N_2NaO_4$ $[M+Na]^+$: 427.1634. Found: 427.1665.

5.2.5. (*R*)-5-Fluoro-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (24)

Compound **24** was prepared by the same method described for the synthesis of **20** starting from 5-fluoroindole-2-carboxylic acid (**10**) (98% yield, white powder); mp 195–197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 10.30 (br s, 1H), 8.19 (d, J = 7.3 Hz,

Table 5
EC_{50}'s of the most active calindol analogues in CHO cells expressing rat CaSR

Compound N°	Structure	EC_{50} (nM)	$pEC_{50} \pm SD$	*n*
4 (calindol)		132	6.88 ± 0.12	6
44		136	6.87 ± 0.03	4
51		20	7.69 ± 0.08	4
52		102	6.99 ± 0.11	2
53		112	6.95 ± 0.05	2
86		131	6.88 ± 0.09	2

The IP accumulation produced by the test compounds in the presence of 3 mM $[Ca^{2+}]_e$ was measured in CHO(CaSR) and compared to the effect produced by 10 mM $[Ca^{2+}]_e$. Concentration–response experiments were performed in triplicate. The number of experiments (*n*) and determination of pEC_{50}'s and EC_{50}'s are indicated. See Section 5 for curve fitting.

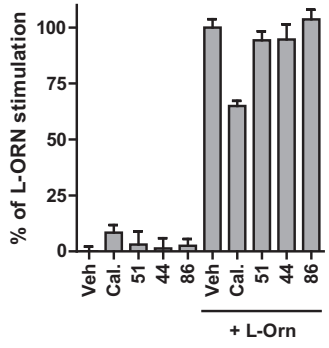


Figure 4. Effect of calindol analogues on L-Orn-stimulated increase of $[^3H]IP$ production in HEK293 cells co-expressing mGPRC6A and GαqG66D. Cells were incubated with vehicle (Veh), 10 μM of calindol (Cal.) or compounds **51**, **44** and **86** for 30 min in presence or not of 10 mM L-ornithine (+L-Orn) and the $[^3H]IP$ measured as described in the Section 5. Data are expressed as % of IP response observed with 10 mM L-Orn and are average ± SEM of points from 2 independent experiments in triplicate.

1H), 7.92 (d, J = 7.3 Hz, 1H), 7.85 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.57–7.52 (m, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.19 (dd, J_1 = 9.2, J_2 = 2.4 Hz, 1H), 7.05 (dd, J_1 = 9.2, J_2 = 4.6 Hz, 1H), 6.83 (dd, J_1 = 9.2, J_2 = 2.4 Hz, 1H), 6.76 (s, 1H), 6.52 (d, J = 7.0 Hz, 1H), 6.18 (dq, J = 7.0 Hz, 1H), 1.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7, 159.6–156.5 (d, J_{CF} = 236.0 Hz), 138.1, 134.0, 133.2, 131.9, 130.9, 129.0, 128.5, 127.6–127.4 (d, J_{CF} = 12.1 Hz), 126.7, 126.0, 125.3, 123.1, 122.4, 113.5–113.1 (d, J_{CF} = 26.3 Hz), 113.1–113.0 (d, J_{CF} = 9.3 Hz), 106.0–105.7 (d, J_{CF} = 23.6 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 45.4, 21.1; HRESMS Calcd for $C_{21}H_{17}FN_2NaO$ $[M+Na]^+$: 355.1223. Found: 355.1206.

5.2.6. (*R*)-5-Methyl-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (25)

Compound **25** was prepared by the same method described for the synthesis of **20** starting from 5-methylindole-2-carboxylic acid (**11**) (97% yield, white powder); mp 214–216 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.57 (br s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.56–7.48 (m, 3H), 7.35 (s, 1H), 7.24 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.69 (s, 1H), 6.43 (br d, J = 7.6 Hz, 1H), 6.17 (dq, J_1 = 7.6, J_2 = 6.7 Hz, 1H), 2.42 (s, 3H), 1.81 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.8, 138.0, 134.8, 134.0, 131.1, 130.5, 129.9, 128.8, 128.5, 127.8, 126.7, 126.4, 125.9, 125.2, 123.3, 122.6, 121.1, 111.6, 101.6, 45.1, 21.4, 21.0; HRESMS Calcd for $C_{22}H_{20}N_2NaO$ $[M+Na]^+$: 351.1473. Found: 351.1440.

5.2.7. (*R*)-5-(Benzyloxy)-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (26)

Compound **26** was prepared by the same method described for the synthesis of **20** starting from 5-benzyloxyindole-2-carboxylic acid (**12**) (100% yield, orange powder); mp 185–187 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.77 (br s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.56–7.31 (m, 8H), 7.18 (d, J = 9.2 Hz, 1H), 7.04 (s, 1H), 6.93 (d, J = 9.2 Hz, 1H), 6.69 (s, 1H), 6.44 (d, J = 7.3 Hz, 1H), 6.16 (dq, J_1 = 7.3, J_2 = 6.4 Hz, 1H), 5.06 (s, 2H), 1.81 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7, 153.7, 138.1, 137.4, 134.0, 132.0, 131.0, 130.9, 128.8, 128.5, 127.8, 127.5, 126.7, 125.9, 125.2, 123.2, 122.5, 115.6, 112.9, 103.8, 101.7, 70.7, 45.2, 21.0; HRESMS Calcd for $C_{28}H_{24}N_2NaO_2$ $[M+Na]^+$: 443.1735. Found: 443.1755.

5.2.8. (*R*)-5-(Methylsulfonyl)-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (27)

Compound **27** was prepared by the same method described for the synthesis of **20** starting from 5-(methylsulfonyl)indole-2-carboxylic acid (**13**) (90% yield, white powder); mp 210–213.5 °C; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 12.15 (br s, 1H), 9.27 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 1.8 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.70 (dd, J_1 = 8.8, J_2 = 1.8 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.58–7.49 (m, 4H), 6.00 (dq, J_1 = 8.0, J_2 = 6.9 Hz, 1H), 3.17 (s, 3H), 1.66 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 159.5, 159.4, 140.0, 133.4, 132.2, 130.4, 128.7, 127.4, 126.3, 126.2, 125.6, 125.5, 123.1, 122.7, 122.2, 121.2, 112.9, 104.5, 44.5, 44.3, 21.4 (13); HRESMS (negative mode) Calcd for $C_{22}H_{19}N_2O_3S$ $[M-H]^-$: 391.1116. Found: 391.1141.

5.2.9. (*R*)-3-Bromo-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (28)

Compound **28** was prepared by the same method described for the synthesis of **20** starting from 3-bromoindole-2-carboxylic acid (**14**) (76% yield, light brown powder); mp 222–223.5 °C (decomposition); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.96 (br s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.59–7.49 (m, 4H), 7.24–7.18 (m, 3H), 6.21 (dq, J_1 = 7.3, J_2 = 6.7 Hz, 1H), 1.83 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 157.4, 138.5, 134.7, 130.7, 129.8, 128.9, 128.3, 126.8, 126.5, 125.8, 125.6, 125.4, 123.1, 122.4, 121.3, 120.3, 112.2, 94.0, 45.9, 22.0; HRESMS Calcd for $C_{21}H_{17}{}^{79}BrN_2NaO$ $[M+Na]^+$: 415.0422. Found: 415.0427; Calcd for $C_{21}H_{17}{}^{81}BrN_2NaO$ $[M+Na]^+$: 417.0401. Found: 417.0423.

5.2.10. (*R*)-7-Hydroxy-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (29)

Compound **29** was prepared by the same method described for the synthesis of **20** starting from 7-hydroxyindole-2-carboxylic acid (54% yield, yellowish amorphous solid). Because of its sensitive nature, it was used directly without purification to prepare compound **42** (vide infra).

5.2.11. (*R*)-3-Phenyl-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (30)

Ethyl 3-iodo-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (105 mg, 0.23 mmol)[42] was dissolved in degassed dioxane (2 mL). Palladium diacetate (1.5 mg, 0.007 mmol, 3 mol %), 1,1′-bis (diphenylphosphino)ferrocene (dppf, 5.8 mg, 0.01 mmol, 4.5 mol %), phenylboronic acid (56 mg, 0.46 mmol), and cesium fluoride (140 mg, 0.92 mmol) were then added to the solution at room temperature. The mixture was stirred at 90 °C for 4 h. Upon completion of the reaction, the solution was diluted with a saturated aqueous solution of NH_4Cl, extracted with ethyl acetate, dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/heptane 30:70 then 40:60) affording ethyl 3-phenyl-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (84%, white amorphous solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.6 Hz, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.49–7.40 (m, 7H), 7.27 (t, J = 7.6 Hz, 2H), 4.36 (d, J = 7.0 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.6, 137.6, 136.0, 134.0, 131.1, 129.4, 129.3, 129.0, 128.5, 128.2, 128.0, 127.4, 126.8, 126.6, 124.3, 121.2, 114.9, 62.3, 13.8; HRESMS Calcd for $C_{23}H_{19}NNaO_4S$ $[M+Na]^+$: 428.0932. Found: 428.0918.

This compound (50 mg, 0.12 mmol) was then dissolved in THF (1 mL) and an aqueous 1 N solution of LiOH (0.5 mL, 0.5 mmol) was added at room temperature. The reaction mixture was stirred at 60 °C until TLC showed complete consumption of starting material. The solution was cooled to room temperature, an aqueous 1 N solution of HCl (0.6 mL, 0.6 mmol) was added and the mixture was extracted with ethyl acetate. The organic extract was dried over sodium sulfate and the solvents were removed under vacuum. The residue, corresponding to 3-phenylindole-2-carboxylic acid (**16**), was then transformed directly without further purification into compound **30** using the same method described for the synthesis of **20** (75% yield, yellow powder); mp 171–171.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.83 (br s, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.37–7.34 (m, 3H), 7.30 (t, J = 7.6 Hz, 1H), 7.23 (m, 3H), 7.10 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 6.29 (d, J = 7.6 Hz, 1H), 6.04 (dq, J_1 = 7.6, J_2 = 6.7 Hz, 1H), 1.53 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.7, 138.1, 135.0, 133.9, 133.4, 130.7, 130.5, 128.9, 128.8, 128.2, 129.1, 127.9, 126.6, 126.5, 125.8, 125.2, 124.8, 123.2, 122.1, 120.7, 120.6, 118.3, 111.8, 45.1, 21.3; HRESMS Calcd for $C_{27}H_{22}N_2NaO$ $[M+Na]^+$: 413.1630. Found: 413.1618.

5.2.12. (*R*)-4-Phenyl-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (31)

Methyl 4-hydroxyindole-2-carboxylate (745 mg, 3.90 mmol) was dissolved in dry dichloromethane (13 ml) and freshly distilled lutidine (590 µL, 5.07 mmol) was added. The solution was cooled to −78 °C and triflic anhydride (760 µL, 4.48 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h and warmed to room temperature. A saturated aqueous solution of NH_4Cl was added, the mixture was extracted with dichloromethane, the organic extract was dried over sodium sulfate and the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel (ethyl acetate/heptane 20:80) affording methyl (trifluoromethylsulfonyloxy)-1*H*-indole-2-carboxylate (84% yield, white powder); mp 127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.30 (br s, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.12 (d, J = 7.9 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.8, 143.2, 138.4, 128.6, 125.4, 121.0, 112.9, 112.3, 104.7, 52.4; HRESMS (negative mode) Calcd for $C_{11}H_7F_3NO_5S$ $[M-H]^-$: 321.9970. Found: 322.0000.

In a sealing tube under argon, the indole triflate (100 mg, 0.31 mmol) was dissolved in degassed THF (1 mL) and Pd(dppf) Cl_2-CH_2Cl_2 (13 mg, 0.015 mmol, 5 mol %) was added at room temperature followed by phenylboronic acid (75.6 mg, 0.62 mmol), and K_3PO_4 (197 mg, 0.93 mmol). The reaction mixture was stirred at 70 °C for 5 h and, after cooling to room temperature, a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with ethyl acetate, the organic extract was dried over sodium sulfate and the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel (ethyl acetate/heptane 20:80), affording methyl 4-phenyl-1*H*-indole-2-carboxylate (88% yield, off-white powder); mp 189–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.05 (br s, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.44–7.40 (m, 4H), 7.24 (dd, J_1 = 5.8, J_2 = 2.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.3, 140.3, 137.3, 136.5, 128.7, 128.6, 127.4, 126.0, 125.7, 120.5, 110.9, 108.5, 52.1; HRESMS (negative mode) Calcd for $C_{16}H_{12}NO_2$ $[M-H]^-$: 250.0868. Found: 250.0861.

As described above for the preparation of **16**, LiOH-promoted hydrolysis of this methyl ester then afforded 4-phenylindole-2-carboxylic acid (**17**, 100% yield, white amorphous solid) which was coupled directly with amine **19** using the same procedure as for the synthesis of **20** to afford carboxamide **31** (90% yield, amorphous off-white powder). The latter was then used without further purification to prepare compound **44** (vide infra).

5.2.13. (*R*)-7-Phenyl-*N*-[1-(1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (32)

Using the same method described for the synthesis of **17**, the 7-*O*-triflate of ethyl 7-hydroxyindole-2-carboxylate was first prepared followed by Suzuki coupling with phenylboronic acid thereby providing ethyl 7-phenylindole-2-carboxylate (83% overall yield, white powder); mp 83–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR 9.01 (br s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.63 (dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 2H), 7.54 (t, J = 7.7 Hz, 2H), 7.44 (tt, J_1 = 7.7 Hz, J_2 = 1 .4 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 1621, 138.6, 135.1, 129.5, 128.4, 128.2, 128.0, 126.7, 125.2, 122.0, 121.5, 109.2, 61.3, 14.6; HRESMS Calcd for $C_{17}H_{14}NO_2$ $[M]^+$: 264.1025. Found: 264.1025.

Then, as described above for the preparation of **16**, LiOH-promoted hydrolysis of the ethyl ester group afforded 7-phenylindole-2-carboxylic acid **18** (100% yield, white solid) which was coupled directly with amine **19** using the same procedure as for the synthesis of **20** to provide carboxamide **32** (91% yield, amorphous off-white powder). The latter was used without further purification to prepare compound **45** (vide infra).

5.2.14. (*R*)-*N*-[(4-Methoxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (33)

To a suspension of $LiAlH_4$ (22 mg, 0.6 mmol) in anhydrous THF (3 mL) was added $AlCl_3$ (40 mg, 0.3 mmol) portionwise at room temperature. The mixture was stirred 30 min and a solution of compound **20** (100 mg, 0.29 mmol) in THF (3 mL) was slowly added. The reaction mixture was refluxed until complete disappearance of starting material as indicated by TLC. The mixture was cooled to room temperature, methanol was added followed

by a saturated aqueous solution of sodium potassium tartrate. After 30 min, the mixture was extracted with ethyl acetate (3×), the combined organic extracts were dried over sodium sulfate and the solvents were removed under vacuum. The residue was purified by flash chromatography (silica gel, AcOEt/heptane/MeOH 46:50:4), affording compound **33** (80% yield, orange oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR 8.42 (br s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.54–7.49 (m, 3H), 7.08 (t, J = 7.9 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 6.52 (d, J = 7.9 Hz, 1H), 6.42 (s, 1H), 4.73 (q, J = 6.7 Hz, 1H), 3.95 (s, 3H), 3.92 (d, J_{gem} = 14.0 Hz, 1H), 3.87 (d, J_{gem} = 14.0 Hz, 1H), 1.55 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 152.9, 140.6, 137.2, 136.4, 134.0, 131.3, 129.0, 127.4, 125.9, 125.6, 125.4, 123.0, 122.6, 122.2, 119.0, 104.2, 99.6, 97.2, 55.3, 53.0, 44.8, 23.4; HRESMS Calcd for $C_{22}H_{23}N_2O$ $[M+H]^+$: 331.1810. Found: 331.1824.

For biological evaluation, the hydrochloride salt of **33** was prepared by dissolving it in methanol, adding methanolic HCl until the solution was acidic, adding pentane and collecting the solid precipitate formed by filtration; mp 213.5–215 °C (decomposition); $[\alpha]_D$ = −22.2 (c 1.0, MeOH); Anal. Calcd for $C_{22}H_{23}ClN_2O{\cdot}0.1H_2O$: C, 71.67; H, 6.34; N, 7.60. Found: C, 71.55; H, 6.42; N, 7.42.

5.2.15. (*R*)-*N*-[(4,6-Dimethoxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (34)

Compound **34** was prepared by the same method described for the synthesis of **33** starting from **21** (54% yield, dark orange oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.33 (br s, 1H), 8.16 (dd, J_1 = 6.4, J_2 = 3.2 Hz, 1H), 7.89 (dd, J_1 = 6.4, J_2 = 3.2 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.54–7.49 (m, 3H), 6.45 (d, J = 1.7 Hz, 1H), 6.32 (d, J = 1.7 Hz, 1H), 6.22 (d, J = 1.7 Hz, 1H), 4.72 (q, J = 6.6 Hz, 1H), 3.91 (s, 3H), 3.84 (m, 5H), 1.54 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.2, 153.3, 140.6, 137.2, 134.8, 134.0, 131.3, 129.0, 127.4, 125.9, 125.6, 125.4, 123.0, 122.6, 113.3, 97.2, 91.5, 86.9, 55.7, 55.3, 53.0, 44.8, 23.4; HRESMS Calcd for $C_{23}H_{24}N_2NaO_2$ $[M+Na]^+$: 383.1735. Found: 383.1747.

Hydrochloride of **34**: mp 154–156.5 °C (decomposition); $[\alpha]_D$ = −12.8 (c 0.6, MeOH); Anal. Calcd for $C_{23}H_{25}ClN_2O_2{\cdot}0.6H_2O$: C, 67.75; H, 6.48; N, 6.87. Found: C, 67.48; H, 6.17; N, 6.75.

5.2.16. (*R*)-*N*-[(6-Methoxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (35)

Compound **35** was prepared by the same method described for the synthesis of **33** starting from **22** (58% yield, orange oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.35 (br s, 1H), 8.17 (dd, J_1 = 6.4, J_2 = 3.4 Hz, 1H), 7.93 (dd, J_1 = 6.4, J_2 = 3.4 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.57–7.50 (m, 3H), 7.44 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 1.9 Hz, 1H), 6.80 (dd, J_1 = 8.3, J_2 = 1.9 Hz, 1H), 6.24 (s, 1H), 4.73 (q, J = 6.6 Hz, 1H), 3.87 (m, 5H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.0, 140.6, 136.7, 136.6, 134.0, 131.3, 129.0, 127.4, 125.8, 125.6, 125.4, 122.9, 122.7, 122.6, 120.6, 109.3, 99.9, 94.5, 55.6, 52.9, 44.8, 23.4; HRESMS Calcd for $C_{22}H_{22}N_2NaO$ $[M+Na]^+$: 353.1630. Found: 353.1643.

Hydrochloride of **35**: mp 163.5–166 °C (decomposition); $[\alpha]_D$ = −25.5 (c 1.1, MeOH); Anal. Calcd for $C_{22}H_{23}ClN_2O{\cdot}0.6H_2O$: C, 70.30; H, 6.44; N, 7.45. Found: C, 70.33; H, 6.77; N, 7.05.

5.2.17. (*R*)-*N*-[(5,6,7-Trimethoxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (36)

Compound **36** was prepared by the same method described for the synthesis of **33** starting from **23** (53% yield, orange oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.50 (br s, 1H), 8.16 (dd, J_1 = 6.2, J_2 = 3.3 Hz, 1H), 7.90 (dd, J_1 = 6.2, J_2 = 3.3 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55–7.49 (m, 3H), 6.78 (s, 1H), 6.20 (d, J = 2.2 Hz, 1H), 4.71 (q, J = 6.6 Hz, 1H), 4.06 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.91 (d, J_{gem} = 14.2 Hz, 1H), 3.84 (d, J_{gem} = 14.2 Hz, 1H), 1.55 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 149.0, 140.5, 138.6, 137.7, 137.5, 134.0, 131.3, 129.0, 127.4, 125.8, 125.6, 125.4, 124.2, 124.1, 122.9, 122.6, 100.3, 97.1, 61.4, 61.0, 56.4, 53.0, 44.8, 23.4; HRESMS Calcd for $C_{24}H_{27}N_2O_3$ $[M+H]^+$: 391.2022. Found: 391.2028.

Hydrochloride of **36**: mp 147–151 °C (decomposition); $[\alpha]_D$ = −14.5 (c 0.7, MeOH); Anal. Calcd for $C_{24}H_{27}ClN_2O_3{\cdot}0.6\ H_2O$: C, 64.53; H, 6.23; N, 6.27. Found: C, 64.16; H, 6.39; N, 5.97.

5.2.18. (*R*)-*N*-[(5-Fluoro-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (37)

Compound **37** was prepared by the same method described for the synthesis of **33** starting from **24** (87% yield, yellow oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.16 (dd, J_1 = 6.0, J_2 = 3.0 Hz, 1H), 7.93 (dd, J_1 = 6.0, J_2 = 3.0 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.57–7.51 (m, 3H), 7.23 (d, J = 2.5 Hz, 1H), 7.21 (dd, J_1 = 9.1, J_2 = 1.5 Hz, 1H), 6.92 (dt, J_1 = 9.1, J_2 = 2.5 Hz, 1H), 6.27 (d, J = 1.2 Hz, 1H), 4.73 (q, J = 6.6 Hz, 1H), 3.92 (d, J_{gem} = 14.4 Hz, 1H), 3.86 (d, J_{gem} = 14.4 Hz, 1H), 1.97 (br s, 1H), 1.58 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.4–156.3 (d, $^1J_{CF}$ = 233.3 Hz), 140.5, 139.9, 134.0, 132.3, 131.3, 129.0, 128.8 (d, $^3J_{CF}$ = 10.4 Hz), 127.5, 125.9, 125.6, 125.4, 122.8, 122.6, 111.1 (d, $^3J_{CF}$ = 9.9 Hz), 109.6–109.3 (d, $^2J_{CF}$ = 26.3 Hz), 105.0–104.7 (d, $^2J_{CF}$ = 23.3 Hz), 100.0 (d, $^4J_{CF}$ = 4.9 Hz), 53.1, 44.7, 23.4; HRESMS Calcd for $C_{21}H_{20}FN_2$ $[M+H]^+$: 319.1611. Found: 319.1614.

Hydrochloride of **37**: mp 193–196 °C (decomposition); $[\alpha]_D$ = −5.2 (c 0.8, MeOH); Anal. Calcd for $C_{21}H_{20}ClFN_2{\cdot}0.1H_2O$: C, 70.72; H, 5.71; N, 7.85. Found: C, 70.53; H, 5.85; N, 7.75.

5.2.19. (*R*)-*N*-[(5-Methyl-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (38)

Compound **38** was prepared by the same method described for the synthesis of **33** starting from **25** (65% yield, dark orange oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.35 (br s, 1H), 8.17 (dd, J_1 = 6.3, J_2 = 3.1 Hz, 1H), 7.93 (dd, J_1 = 6.3, J_2 = 3.1 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.58–7.52 (m, 3H), 7.38 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.02 (dd, J_1 = 8.1, J_2 = 1.8 Hz, 1H), 6.25 (s, 1H), 4.74 (q, J = 6.6 Hz, 1H), 3.93 (d, J_{gem} = 14.1 Hz, 1H), 3.85 (d, J_{gem} = 14.1 Hz, 1H), 2.49 (s, 3H), 1.98 (br s, 1H), 1.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.6, 138.0, 134.2, 134.0, 131.3, 129.0, 128.8, 128.7, 127.4, 125.9, 125.7, 125.4, 122.9, 122.6, 119.8, 110.3, 99.6, 52.9, 44.8, 23.4, 21.4; HRESMS Calcd for $C_{22}H_{23}N_2$ $[M+H]^+$: 315.1861. Found: 315.1858.

Hydrochloride of **38**: mp 178–180 °C (decomposition); $[\alpha]_D$ = −16.2 (c 1.0, MeOH); Anal. Calcd for $C_{22}H_{23}ClN_2{\cdot}0.4\ H_2O$: C, 73.06; H, 6.74; N, 7.74. Found: C, 73.21; H, 6.89; N, 7.36.

5.2.20. (*R*)-*N*-[(5-Benzyloxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (39)

Compound **39** was prepared by the same method described for the synthesis of **33** starting from **26** (63% yield, orange oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.32 (br s, 1H), 8.16 (dd, J_1 = 6.4, J_2 = 3.2 Hz, 1H), 7.92 (dd, J_1 = 6.4, J_2 = 3.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.55–7.49 (m, 5H), 7.41 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.91 (dd, J_1 = 8.8, J_2 = 2.4 Hz, 1H), 6.23 (s, 1H), 5.12 (s, 2H), 4.72 (q, J = 6.7 Hz, 1H), 3.91 (d, J_{gem} = 14.3 Hz, 1H), 3.85 (d, J_{gem} = 14.3 Hz, 1H), 1.88 (br s, 1H), 1.56 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.3, 140.6, 138.8, 137.8, 134.0, 131.3, 131.1, 129.0, 128.9, 1284, 127.7, 127.5, 127.4, 125.9, 125.7, 125.4, 122.9, 122.6, 112.1, 111.3, 103.8, 99.9, 70.9, 53.0, 44.8, 23.5; HRESMS Calcd for $C_{28}H_{27}N_2O$ $[M+H]^+$: 407.2123. Found: 407.2119.

Hydrochloride of **39**: mp 245.5–248 °C (decomposition); $[\alpha]_D = -22.8$ (*c* 0.5, MeOH); Anal. Calcd for $C_{28}H_{27}ClN_2O{\cdot}0.3H_2O$: C, 74.26; H, 6.08; N, 6.19. Found: C, 74.11; H, 6.19; N, 6.24.

5.2.21. (*R*)-*N*-[(5-Methylsulfonyl-1*H*-indol-2-yl)methyl]-1-(1-naphthyl)ethanamine (40)

Compound **40** was prepared by the same method described for the synthesis of **33** starting from **27** (60% yield, off-white amorphous solid); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.90 (br s, 1H), 8.16 (s, 1H), 8.14 (d, J = 6.4 Hz, 1H), 7.91 (dd, J_1 = 6.4, J_2 = 3.3 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.54–7.49 (m, 3H), 7.42 (d, J = 8.6 Hz, 1H), 6.40 (s, 1H), 4.72 (q, J = 6.6 Hz, 1H), 3.94 (s, 2H), 3.07 (s, 3H), 1.85 (br s, 1H), 1.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.1, 140.3, 138.1, 134.0, 131.5, 131.3, 129.1, 128.2, 127.6, 126.0, 125.6, 125.5, 122.8, 122.6, 120.8, 119.9, 111.2, 101.1, 53.3, 45.2, 44.6, 23.4; HRESMS Calcd for $C_{22}H_{23}N_2O_2S$ $[M+H]^+$: 379.1480. Found: 379.1474.

Hydrochloride of **40**: mp 223–226 °C (decomposition); $[\alpha]_D = -49.9$ (*c* 0.5, MeOH); Anal. Calcd for $C_{22}H_{23}ClN_2O_2S{\cdot}0.5H_2O$: C, 61.24; H, 5.49; N, 6.49. Found: C, 61.01; H, 5.49; N, 6.29.

5.2.22. (*R*)-*N*-[(3-Bromo-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (41)

Compound **41** was prepared by the same method described for the synthesis of **33** starting from **28** (61% yield, yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.65 (br s, 1H), 8.16 (dd, J_1 = 6.4, J_2 = 3.4 Hz, 1H), 7.92 (dd, J_1 = 6.4, J_2 = 3.4 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.55–7.52 (m, 4H), 7.28 (d, J = 7.0 Hz, 1H), 7.22 (t, J = 7.0 Hz, 1H), 7.19 (t, J = 7.0 Hz, 1H), 4.73 (q, J = 6.4 Hz, 1H), 3.96 (s, 2H), 1.99 (br s, 1H), 1.58 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.1, 134.7, 134.6, 134.1, 131.2, 129.0, 127.6, 126.0, 125.6, 125.5, 122.9, 122.7, 122.5, 120.3, 118.6, 111.0, 89.4, 53.3, 43.2, 23.2; HRESMS Calcd for $C_{21}H_{20}^{79}BrN_2$ $[M+H]^+$: 379.0810. Found: 379.0793; Calcd for $C_{21}H_{20}{}^{81}BrN_2$ $[M+H]^+$: 381.0789. Found: 381.0775.

Hydrochloride of **41**: mp 206.5–209.5 °C (decomposition); $[\alpha]_D = -23.4$ (*c* 0.5, MeOH); Anal. Calcd for $C_{21}H_{20}BrClN_2$: C, 60.67; H, 4.85; N, 6.74. Found: C, 60.59; H, 4.71; N, 6.51

5.2.23. (*R*)-*N*-[(7-Hydroxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (42)

Compound **42** was prepared by the same method used for the synthesis of **33** starting from crude **29** (38% yield, dark orange oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 114 (br s, 1H), 7.99 (m, 1H), 7.89 (m, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.55–7.45 (m, 3H), 7.10 (d, J = 7.8 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H), 6.50 (d, J = 7.8 Hz, 1H), 6.19 (br s, 1H), 4.83 (q, J = 6.7 Hz, 1H), 4.63 (br s, 2H), 4.02 (d, J_{gem} = 13.5 Hz, 1H), 3.91 (d, J_{gem} = 13.5 Hz, 1H), 1.65 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 1419, 139.1, 135.2, 134.3, 131.4, 130.2, 129.3, 128.3, 127.8, 126.5, 126.0, 125.9, 122.7, 120.2, 113.1, 107.3, 102.6, 52.7, 45.0, 23.1; HRESMS Calcd for $C_{21}H_{21}N_2O$ $[M+H]^+$: 317.1654. Found: 317.1657.

Hydrochloride of **42**: mp 182–185 °C (decomposition); Anal. Calcd for $C_{21}H_{21}ClN_2O{\cdot}0.7H_2O$: C, 69.01; H, 6.18; N, 7.66. Found: C, 68.96; H, 6.52; N, 7.26.

5.2.24. (*R*)-*N*-[(3-Phenyl-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (43)

Compound **43** was prepared by the same method described for the synthesis of **33** starting from **30** (86% yield, yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.77 (br s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.52–7.48 (m, 3H), 7.40–7.36 (m, 5H), 7.27 (m, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 4.71 (q, J = 6.7 Hz, 1H), 4.08 (d, J_{gem} = 14.6 Hz, 1H), 4.02 (d, J_{gem} = 14.6 Hz, 1H), 1.87 (br s, 1H), 1.54 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.2, 135.1, 134.8, 134.1, 133.9, 131.2, 129.3, 129.0, 128.4, 127.7, 127.5, 125.9, 125.8, 125.6, 125.4, 122.9, 122.7, 121.9, 119.9, 119.1, 114.6, 110.8, 53.6, 43.3, 23.3; HRESMS (negative mode) Calcd for $C_{27}H_{23}N_2$ $[M-H]^-$: 375.1861. Found: 375.1853.

Hydrochloride of **43**: mp 202–204.5 °C (decomposition); $[\alpha]_D$ = +27.9 (*c* 0.5, MeOH); Anal. Calcd for $C_{27}H_{25}ClN_2{\cdot}0.1H_2O$: C, 77.91; H, 6.08; N, 6.73. Found: C, 77.91; H, 6.49; N, 6.52.

5.2.25. (*R*)-*N*-[(4-Phenyl-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (44)

Compound **44** was prepared by the same method used for the synthesis of **33** starting from crude carboxamide **31** (78% yield, dark orange oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.55 (br s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.3 Hz, 2H), 7.54–7.50 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.47 (s, 1H), 4.74 (q, J = 6.4 Hz, 1H), 3.96 (d, J_{gem} = 14.3 Hz, 1H), 3.88 (d, J_{gem} = 14.3 Hz, 1H), 1.96 (br s, 1H), 1.56 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.3, 140.4, 138.1, 136.3, 134.0, 133.8, 131.3, 129.0, 128.7, 128.4, 127.5, 126.8, 126.7, 125.9, 125.7, 125.5, 122.9, 122.6, 121.8, 229.5, 109.9, 99.7, 52.9, 44.8, 23.5; HRESMS (negative mode) Calcd for $C_{27}H_{23}N_2$ $[M-H]^-$: 375.1861. Found: 375.1855.

Hydrochloride of **44**: mp 164.5–167 °C (decomposition); $[\alpha]_D = -61.7$ (*c* 0.5, MeOH); Anal. Calcd for $C_{27}H_{25}ClN_2{\cdot}0.6H_2O$: C, 76.53; H, 6.23; N, 6.61. Found: C, 76.44; H, 6.25; N, 6.24.

5.2.26. (*R*)-*N*-[(7-Phenyl-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (45)

Compound **45** was prepared by the same method used for the synthesis of **33** starting from crude carboxamide **32** (62% yield, off-white oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.64 (br s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.66–7.61 (m, 3H), 7.56–7.39 (m, 7H), 7.19–7.17 (m, 2H), 6.38 (d, J = 1.8 Hz, 1H), 4.70 (q, J = 6.6 Hz, 1H), 3.93 (d, J_{gem} = 14.3 - Hz, 1H), 3.87 (d, J_{gem} = 14.3 Hz, 1H), 1.85 (br s, 1H), 1.53 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147, 1396, 1384, 1343, 133.9, 131.5, 129.3, 129.2, 128.4, 127.7, 127.5, 126.1, 125.8, 125.4, 123.2, 123.0, 121.7, 120.4, 119.7, 101.0, 53.7, 45.0, 23.6; HRESMS Calcd for $C_{27}H_{25}N_2$ $[M+H]^+$: 377.2018. Found: 377.2020.

Hydrochloride of **45**: mp 198–203 °C (decomposition); $[\alpha]_D = -149.0$ (*c* 0.5, acetone); Anal. Calcd for $C_{27}H_{25}ClN_2{\cdot}0.5H_2O$: C, 76.85; H, 6.21; N, 6.64. Found: C, 76.67; H, 6.59; N, 6.25.

5.2.27. (5-Nitro-1*H*-indol-2-yl)methanol (48)

To a solution of ethyl 5-nitroindole-2-carboxylate (**46**, 100 mg, 0.43 mmol) in anhydrous THF (4 mL) held at −50 °C was added dropwise a 1 M solution of diisobutylaluminium hydride (DIBAH) in dichloromethane (1.3 mL, 1.3 mmol). The reaction mixture was stirred 2 h at −50 °C and then allowed to come to rt before being quenched by slow addition of methanol followed by a saturated aqueous solution of sodium potassium tartrate. The mixture was then extracted with ethyl acetate (3×), the combined organic extracts were dried over sodium sulfate and the solvents were removed under vacuum. The residue was purified by flash chromatography (silica gel, AcOEt/heptane 1:4), affording compound **48** (98% yield, yellow powder); mp 163.5–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.75 (br s, 1H), 8.55 (s, 1H), 8.11 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 6.57 (s, 1H), 4.91 (s, 2H), 1.91 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.5, 139.3, 139.2, 127.3, 118.3, 116.5, 111.6, 104.5, 59.7; HRESMS Calcd for $C_9H_8N_2O_3Na$ $[M+Na]^+$:215.0433. Found: 215.0431.

5.2.28. (7-Nitro-1*H*-indol-2-yl)methanol (49)

Compound **49** was prepared by the same method described for the synthesis of **48** starting from ethyl 7-nitroindole-2-carboxylate (**47**) (98% yield, yellow powder); mp 155–158 °C; ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.08 (dd, J_1 = 7.9, J_2 = 0.8 Hz, 1H), 7.92 (dd, J_1 = 7.9, J_2 = 0.8 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 6.60 (s, 1H), 4.80 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 143.7, 134.1, 133.9, 130.7, 129.3, 119.7, 119.3, 102.0, 58.2; HRESMS (negative mode) Calcd for $C_9H_7N_2O_3$ $[M-H]^-$:191.0457. Found: 191.045

5.2.29. (*R*)-*N*-[(5-Nitro-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (50)

To a solution of PPh_3 (57 mg, 0.22 mmol) in anhydrous THF (0.5 mL) kept at 0 °C was added dropwise diisopropyl azodicarboxylate (DIAD, 45 μL, 0.22 mmol). (*R*)-1-(1-Naphthyl)ethylamine (**19**) (35 μL, 0.22 mmol) was then added, followed by compound **48** (30 mg, 0.16 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at rt for 18 h. A 5% aqueous solution of NaOH (1 mL) was added, the mixture was extracted with EtOAc (3×), the combined organic extracts were dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by preparative chromatography (silica gel, AcOEt/CH_2Cl_2/MeOH 50:47:3 + 5% NEt_3) affording compound **50** as an orange oil (60% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.94 (br s, 1H), 8.47 (d, J = 2.3 Hz, 1H), 8.17 (dd, J_1 = 6.4, J_2 = 3.4 Hz, 1H), 8.06 (dd, J_1 = 6.4, J_2 = 3.4 Hz, 1H), 7.91 (dd, J_1 = 8.9 J_2 = 2.3 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.54–7.49 (m, 3H), 7.32 (d, J = 8.9 Hz, 1H), 6.42 (s, 1H), 4.72 (q, J = 6.7 Hz, 1H), 3.93 (s, 2H), 1.92 (br s, 1H), 1.58 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.8, 141.6, 140.2, 138.8, 134.1, 131.3, 129.1, 127.9, 127.7, 126.0, 125.6, 125.5, 122.8, 122.6, 117.2, 117.1, 110.4, 101.9, 53.4, 44.5, 23.4; HRESMS Calcd for $C_{21}H_{20}N_3O_2$ $[M+H]^+$: 346.1556. Found: 346.1540.

Hydrochloride of **50**: mp 192.5–194.5 °C (decomposition); $[\alpha]_D$ = −23.2 (*c* 0.3, MeOH); Anal. Calcd for $C_{21}H_{20}ClN_3O_2{\cdot}0.3H_2O$: C, 64.38; H, 5.22; N, 10.73. Found: C, 64.66; H, 5.45; N, 10.25.

5.2.30. (*R*)-*N*-[(7-Nitro-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (51)

Compound **51** was prepared by the same method described for the synthesis of **50** starting from **49** (74% yield, yellow oil); mp 155–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 10.09 (br s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.55–7.50 (m, 3H), 7.15 (t, J = 7.8 Hz, 1H), 6.40 (s, 1H), 4.74 (q, J = 6.6 Hz, 1H), 3.95 (s, 2H), 2.52 (br s, 1H), 1.59 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.8, 140.1, 134.0, 132.6, 132.3, 131.3, 129.3, 129.0, 128.0, 127.6, 126.0, 125.6, 125.5, 122.8, 119.0, 118.5, 101.3, 53.5, 44.4, 23.5; HRESMS Calcd for $C_{21}H_{20}N_3O_2$ $[M+H]^+$: 346.1556. Found: 346.1569.

Hydrochloride of **51**: mp 171.5–174 °C (decomposition); $[\alpha]_D$ = −29.8 (*c* 0.6, MeOH); Anal. Calcd for $C_{21}H_{20}ClN_3O_2{\cdot}0.3H_2O$: C, 65.25; H, 5.26; N, 10.65. Found: C, 65.13; H, 5.36; N, 10.85.

5.2.31. (*R*)-*N*-[(4-Hydroxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (52)

To a solution of compound **33** (65 mg, 0.20 mmol) in anhydrous DCM (2 mL) held at −78 °C was added dropwise BBr_3 (0.8 mL, 0.80 mmol). The reaction mixture was stirred at −78 °C for 1 h and the solution was allowed to warm to rt. After complete reaction as monitored by TLC, aqueous KOH (10%) was added and stirring was continued for 30 min at rt. The mixture was acidified by addition of aqueous HCl (1 N), extracted with DCM (3×), the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by preparative chromatography (silica gel, AcOEt/Hept/MeOH 47:50:3 + 5% NEt_3) affording compound **52** (87% yield, unstable grey oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.59 (br s, 1H), 8.11 (d, J = 7.0 Hz, 1H), 7.90 (d, J = 7.0 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.53–7.49 (m, 3H), 6.99 (t, J = 7.9 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 6.32 (s, 1H), 4.74 (q, J = 6.7 Hz, 1H), 3.90 (d, J_{gem} = 14.2 Hz, 1H), 3.85 (d, J_{gem} = 14.2 Hz, 1H), 1.55 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 148.7, 140.2, 137.9, 136.2, 134.0, 131.3, 129.0, 127.5, 126.0, 125.6, 125.5, 122.8, 122.6, 122.4, 118.1, 104.3, 103.9, 96.8, 52.8, 44.6, 23.2; HRESMS Calcd for $C_{21}H_{21}N_2O$ $[M+H]^+$:317.1654. Found: 317.1645.

Hydrochloride of **52**: mp 182–186.5 °C (decomposition); $[\alpha]_D$ = −25.4 (*c* 0.5, MeOH); Anal. Calcd for $C_{21}H_{21}ClN_2O{\cdot}1.5H_2O$: C, 66.40; H, 6.37; N, 7.37. Found: C, 66.63; H, 6.33; N, 6.99.

5.2.32. (*R*)-*N*-[(5-Hydroxy-1*H*-indol-2-yl)methyl]-1-(1-naphthyl) ethanamine (53)

A solution of compound **39** (60 mg, 0.16 mmol) in MeOH (1 mL) was hydrogenated at rt and at atmospheric pressure for 4 h in the presence of 10% palladium on charcoal (17 mg). An equivalent quantity of catalyst was then added and hydrogenation was continued for another 4 h. The reaction mixture was then filtered through a small pad of celite, the latter was washed with MeOH and the combined filtrates were evaporated under vacuum. The residue was purified by preparative chromatography (silica gel, AcOEt/Hept/MeOH 42:50:8 + 5% NEt_3), affording compound **53** (95% yield, unstable grey oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.44 (br s, 1H), 8.11 (d, J = 6.5 Hz, 1H), 7.90 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.55–7.49 (m, 3H), 7.13 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.72 (dd, J_1 = 8.6, J_2 = 2.4 Hz, 1H), 6.14 (s, 1H), 4.74 (q, J = 6.7 Hz, 1H), 3.90 (d, J_{gem} = 14.2 Hz, 1H), 3.84 (d, J_{gem} = 14.2 Hz, 1H), 1.57 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 149.5, 140.3, 138.6, 134.0, 131.3, 131.2, 129.1, 129.0, 127.5, 125.9, 125.6, 125.5, 122.8, 122.6, 111.3, 104.9, 99.9, 52.8, 44.8, 23.9; HRESMS Calcd for $C_{21}H_{21}N_2O$ $[M+H]^+$: 317.1654. Found: 317.1635.

Hydrochloride of **53**: mp 195.5–199 °C (decomposition); $[\alpha]_D$ = −21.6 (*c* 0.6, MeOH); Anal. Calcd for $C_{21}H_{21}ClN_2O{\cdot}1.5H_2O$: C, 66.40; H, 6.37; N, 7.37. Found: C, 66.63; H, 6.33; N, 6.99.

5.2.33. 2,3,4,9-Tetrahydro-1*H*-carbazol-1-one (55)

To a solution of polyphosphoric acid (PPA, 15 equiv, 36.9 mmol, 3.61 g) in toluene (12 mL) was added 4-(3-indolyl)butyric acid (**54**, 500 mg, 2.46 mmol). The solution was stirred at 110 °C for 4 h and then ice-water (25 mL) was slowly added. The mixture was extracted with DCM (3×) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduce pressure. The residue was purified by flash chromatography (silica gel, AcOEt/heptane 20:80 to 30:70) affording compound **55** (91% yield, yellow powder); mp 169–171 °C (lit. 37 mp 168–171 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.26 (br s, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 8.3 Hz, 1H), 7.17 (t, J = 8.2 Hz, 1H), 3.03 (t, J = 6.4 Hz, 2H), 2.69 (t, J = 6.4 Hz, 2H), 2.29 (q, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 191.5, 137.9, 131.2, 129.5, 127.0, 125.8, 121.3, 120.3, 112.6, 38.2, 25.0, 21.4.

5.2.34. (*R,S*)-*N*-[(*R*)-1-(1-Naphthyl)ethyl]-1,2,3,4-tetrahydro-1-amino-1*H*-carbazole (56)

To a solution of compound **55** (80 mg, 0.43 mmol) in anhydrous THF (2.2 mL) was added at rt $NaBH(OAc)_3$ (128 mg, 0.60 mmol) followed by (*R*)-naphthylethylamine (**19**, 76 μL, 0.47 mmol) and acetic acid (25 μL, 0.43 mmol). The reaction mixture was stirred at rt for 24 h, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (3×). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by preparative chromatography (silica gel, AcOEt/

heptane 30:70), affording compound **56** (75% yield, off-white amorphous solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.9 Hz, 1H), 8.01 (br s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.53 (t, J = 7.9 Hz, 2H), 7.48 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 4.99 (q, J = 6.4 Hz, 1H), 4.11 (t, J = 5.5 Hz, 1H), 2.73 (m, 2H), 2.28 (m, 1H), 2.07 (m, 1H), 1.87 (m, 1H), 1.75 (m, 1H), 1.60 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.3, 136.3, 135.6, 134.0, 130.8, 129.2, 127.5, 127.4, 126.1, 125.8, 125.5, 123.4, 122.7, 121.5, 119.0, 118.2, 110.9, 110.7, 50.1, 49.2, 31.0, 22.9, 21.1, 20.9; HRESMS (negative mode) Calcd for $C_{24}H_{23}N_2$ $[M-H]^-$: 339.1861. Found: 339.1863.

Hydrochloride of **56**: mp 105.5–154 °C (decomposition); $[\alpha]_D$ = −26.3 (c 0.6, MeOH); Anal. Calcd for $C_{24}H_{25}ClN_2.0.8\ CHCl_3$: C, 71.65; H, 6.26; N, 6.74. Found: C, 71.65; H, 6.39; N, 6.85.

5.2.35. (*R,S*)-1-(2-Methoxyphenyl)ethanamine (61)

To a solution of 2′-methoxyacetophenone (2.00 g, 13.3 mmol) in formamide (11 mL) was added formic acid (50 mL) and the mixture was heated at 190 °C for 6 h with addition at 1 h intervals of additional formic acid (1.5 mL for each addition). At the end of the reaction period, the mixture was cooled to rt, water was added followed by EtOAc. The mixture was washed with saturated aqueous NaCl solution (3×), the organic fraction was dried over $MgSO_4$ and the solvents were removed under vacuum. The residue was then dissolved in a mixture of ethanol (50 mL), water (75 mL) and HCl (25 mL) and the solution was refluxed for 12 h. After cooling to rt, the reaction mixture was concentrated under vacuum and an aqueous solution of ammonia was added until a pH of 9–10 was attained. The mixture was extracted with diethyl ether (2×) and the combined organic extracts were washed successively with water and saturated aqueous NaCl and dried over $MgSO_4$. The solvent was then removed under vacuum and the residue was purified by column chromatography on silica gel (DCM/EtOH/NH_4OH 10:2:0.2) affording compound **61** (56% yield, yellow oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35–7.32 (m, 1H), 7.25–7.20 (m, 1H), 6.98–6.93 (m, 1H), 6.88 (d, J = 8.1 Hz, 1H), 4.37 (q, J = 6.8 Hz, 1H), 3.86 (s, 3H), 1.87 (br s, 2H), 1.41 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.8, 135.5, 127.6, 125.7, 120.6, 10.4, 55.2, 46.1, 23.1; ESIMS $C_9H_{14}NO$ m/z 152 $[M+H]^+$.

5.2.36. (*R,S*)-1-(3-Bromophenyl)ethanamine (64)

Compound **64** was prepared by the same method described for the synthesis of **61** starting from 3′-bromoacetophenone (76% yield, orange oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45–7.43 (m, 1H), 7.31–7.27 (m, 1H), 7.22–7.18 (m, 1H), 7.18–7.09 (m, 1H), 4.03 (q, J = 6.6 Hz, 1H), 1.53 (br s, 2H), 1.30 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 150.1, 130.1, 129.9, 128.9, 124.4, 122.6, 51.0, 25.6; ESIMS $C_8H_{11}BrN$ m/z 200 (^{79}Br), 202 (^{81}Br) $[M+H]^+$.

5.2.37. (*R,S*)-1-Biphenyl-4-ylethanamide (65)

Compound **65** was prepared by the same method described for the synthesis of **61** starting from 4-acetyl-biphenyl (79%, brown oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.62–7.57 (m, 4H), 7.48–7.43 (m, 4H), 7.38–7.32 (m, 1H), 4.19 (q, J = 6.6 Hz, 1H), 1.80 (br s, 2H), 1.46 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.7, 140.2, 138.2, 128.8 (×2), 127.1, 126.5 (×2), 126.4 (×4), 50.3, 25.9; ESIMS $C_{14}H_{15}N$ m/z 198 $[M+H]^+$.

5.2.38. (*R,S*)-1-(4-Fluoronaphthalen-1-yl)ethanamine (66)

Compound **66** was prepared by the same method described for the synthesis of **61** starting from 4′-fluoro-1′-acetonaphthone (90% yield, yellow oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.17–8.13 (m, 2H), 7.61–7.51 (m, 3H), 7.13 (dd, J = 8.1 Hz, 1H), 4.91 (q, J = 6.6 Hz, 1H), 1.63 (br s, 2H), 1.53 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7–156.4 (J = 250.8 Hz), 139.3–139.2 (J = 3.8 Hz), 132.2–132.1 (J = 3.8 Hz), 127.7, 125.9, 124.3–124.1 (J = 15.9 Hz), 123.2 (J = 2.7 Hz), 121.6, 121.6–121.5 (J = 4.9 Hz), 109.2–108.9 (J = 19.2 Hz), 46.6, 25.2; HRESMS Calcd for $C_{12}H_{13}FN$ $[M+H]^+$: 190.1032. Found: 190.1025.

5.2.39. (*R*)-*N*-(1-Phenylethyl)-1*H*-indole-2-carboxamide (67)

Compound **67** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 620 μmol) and (*R*)-1-phenylethanamine (**57**, 75 mg, 620 μmol) (76% yield, yellow powder); mp 163–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 10.15 (br s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.46–7.24 (m, 7H), 7.16–7.13 (m, 1H), 6.91 (s, 1H), 6.56 (d, J = 7.3 Hz, 1H), 5.44 (q, J = 7.0 Hz, 1H), 1.67 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.9, 143.0, 136.4, 130.6, 128.8, 127.6, 127.5, 126.2, 124.5, 121.8, 120.6, 112.0, 101.9, 49.1, 21.9; ESIMS $C_{17}H_{16}N_2ONa$ m/z 287.1 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.21; H, 5.93; N, 10.54.

5.2.40. (*R*)-*N*-[1-(4-Methylphenyl)ethyl]-1*H*-indole-2-carboxamide (68)

Compound **68** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 620 μmol) and (*R*)-1-*p*-tolylethanamine (**58**, 84 mg, 620 μmol) (78% yield, yellow powder); mp 177–178 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm) 10.70 (br s, 1H), 8.00 (br s, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.23–7.14 (m, 4H), 7.07 (br t, J = 7.3 Hz, 1H), 5.31 (q, J = 7.3 Hz, 1H), 2.30 (s, 3H), 1.56 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 161.7, 161.2, 142.8, 137.0, 129.8, 128.8, 128.4, 127.1, 124.4, 122.4, 120.8, 118.9, 113.0, 103.0, 49.1, 21.0; ESIMS $C_{18}H_{18}N_2ONa$ m/z 301.1 $[M+Na]^+$.

5.2.41. (*R*)-*N*-[1-(4-Methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide (69)

Compound **69** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 620 μmol) and (*R*)-1-(4-methoxyphenyl)ethanamine (**59**, 124 mg, 620 μmol) (62% yield, yellow powder); mp 164–165 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm) 10.67 (br s, 1H), 7.96 (br s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.22–7.15 (m, 2H), 7.05 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 8.2 Hz, 2H), 5.30 (q, J = 7.0 Hz, 1H), 3.77 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 160.7, 158.8, 136.9, 136.6, 131.8, 127.8, 127.3, 123.6, 121.5, 119.9, 113.7, 112.3, 102.3, 54.6, 48.1, 21.6; ESIMS $C_{18}H_{18}N_2O_2Na$ m/z 317.1 $[M+Na]^+$.

5.2.42. (*R*)-*N*-[1-(3-Methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide (70)

Compound **70** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 620 μmol) and (*R*)-1-(3-methoxyphenyl)ethanamine (**60**, 124 mg, 620 μmol) (65% yield, yellow powder); mp 216–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.10 (br s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.22–7.10 (m, 3H), 7.01 (br t, J = 7.9 Hz, 1H), 6.93–6.87 (m, 2H), 6.79 (d, J = 1.5 Hz, 1H), 6.74 (dd, J = 8.0 Hz, J = 1.9 Hz, 1H), 6.50 (d, J = 7.9 Hz, 1H), 5.28 (q, J = 7.0 Hz, 1H), 3.69 (s, 3H), 1.53 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.2, 160.0, 144.8, 136.7, 130.6, 129.9, 127.5, 124.4, 121.8, 120.5, 118.4, 112.7, 112.3, 112.2, 102.2, 55.2, 49.2, 22.0; ESIMS $C_{18}H_{19}N_2O_2$ m/z 295.1 $[M+H]^+$.

5.2.43. (*R*,*S*)-*N*-[1-(2-Methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide (71)

Compound **71** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (200 mg, 1.24 mmol) and 1-(2-methoxyphenyl)ethanamine (**61**, 188 mg, 1.24 mmol) (95% yield, yellow powder); mp 161–162 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 10.57 (br s, 1H), 7.84 (br s, 1H), 7.48 (br d, J = 8.3 Hz, 1H), 7.39 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H), 7.28 (dd, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.13–7.05 (m, 3H), 6.92 (dt, J = 7.9 Hz, J = 0.9 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.78 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 5.46 (q, J = 7.0 Hz, 1H), 3.79 (s, 3H), 1.37 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 160.1, 156.4, 136.6, 136.4, 132.3, 127.7, 127.6, 126.0, 123.3, 121.3, 120.2, 119.6, 111.9, 110.6, 101.8, 54.7, 44.4, 20.6; ESIMS $C_{18}H_{19}N_2O_2$ m/z 295.2 [M+H]$^+$.

5.2.44. (*R*)-*N*-[1-(4-Fluorophenyl)ethyl]-1*H*-indole-2-carboxamide (72)

Compound **72** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 620 μmol) and (*R*)-1-(4-fluorophenyl)ethanamine (**62**, 87 mg, 620 μmol) (70% yield, yellow powder); mp 179–180 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm) 10.73 (br s, 1H), 8.10 (br s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.54–7.50 (m, 3H), 7.24–7.17 (m, 2H), 7.12–7.05 (m, 3H), 5.34 (q, J = 7.0 Hz, 1H), 1.58 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 164.2–161.0 ($^1J_{C\text{-}F}$ = 243.2 Hz), 161.5, 141.7, 137.7, 132.6, 129.0, 128.9, 128.7, 124.5, 122.4, 120.8, 115.9, 115.6, 113.0, 103.2, 48.9, 22.4; ESIMS $C_{17}H_{16}FN_2O$ m/z 282.1 [M+H]$^+$.

5.2.45. (*R*)-*N*-[1-(4-Bromophenyl)ethyl]-1*H*-indole-2-carboxamide (73)

Compound **73** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 620 μmol) and (*R*)-1-(4-bromophenyl)ethanamine (**63**, 124 mg, 620 μmol) (77% yield, white powder); mp 203–204 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm) 10.61 (br s, 1H), 8.98 (br s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.37–7.33 (m, 3H), 7.29–7.27 (m, 2H), 7.07–7.03 (m, 2H), 6.91 (d, J = 7.3 Hz, 1H), 5.16 (q, J = 7.0 Hz, 1H), 1.42 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 160.7, 144.3, 136.9, 131.7, 131.3, 128.4, 127.9, 123.7, 121.7, 120.1, 120.0, 112.2, 102.5, 48.3, 21.5; ESIMS $C_{17}H_{16}{}^{79}BrN_2O$ m/z 343.0 [M+H]$^+$.

5.2.46. (*R*,*S*)-*N*-[1-(3-Bromophenyl)ethyl]-1*H*-indole-2-carboxamide (74)

Compound **74** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (200 mg, 1.24 mmol) and 1-(3-bromophenyl)ethanamine (**64**, 250 mg, 1.25 mmol) (89% yield, yellow powder); mp 208–209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.76 (br s, 1H), 8.18 (br s, 1H), 7.67–7.61 (m, 2H), 7.54–7.41 (m, 3H), 7.33–7.28 (m, 1H), 7.25–7.20 (m, 2H), 7.10–7.04 (m, 1H), 5.33 (q, J = 7.0 Hz, 1H), 1.59 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.5, 152.5, 141.7, 136.3, 135.2, 134.6, 134.0, 132.7, 130.1, 128.5, 126.8, 126.5, 124.8, 117.0, 107.3, 53.2, 26.3; ESIMS $C_{17}H_{15}BrN_2ONa$ m/z 365.0 [M+Na]$^+$.

5.2.47. (*R*,*S*)-*N*-(1-Biphenyl-4-ylethyl)-1*H*-indole-2-carboxamide (75)

Compound **75** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (200 mg, 1.24 mmol) and amine **65** (245 mg, 1.24 mmol) (89% yield, yellow powder); mp 196–197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.36 (br s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.63–7.59 (m, 4H), 7.51–7.42 (m, 5H), 7.38 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 6.90 (s, 1H), 6.44 (d, J = 7.3 Hz, 1H), 5.43 (q, J = 7.0 Hz, 1H), 1.70 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.8, 140.7, 140.6, 140.0, 136.3, 130.7, 128.8, 127.7, 127.6, 127.4, 127.1, 126.7, 124.6, 121.9, 120.7, 112.0, 102.0, 48.8, 21.9; ESIMS $C_{23}H_{20}N_2ONa$ m/z 363.2 [M+Na]$^+$.

5.2.48. (*R*,*S*)-*N*-[1-(4-Fluoro-1-naphthyl)ethyl]-1*H*-indole-2-carboxamide (76)

Compound **76** was prepared by the same method described for the synthesis of **20** starting from 1*H*-indole-2-carboxylic acid (100 mg, 622 μmol) and amine **66** (118 mg, 622 μmol) (97% yield, off-white powder); mp 223–224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.21 (br s, 1H), 8.18 (d, J = 8.2 Hz, 2H), 7.64–7.54 (m, 5H), 7.44 (d, J = 8.5 Hz, 1H), 7.19–7.12 (m, 2H), 6.77 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.11 (q, J = 7.0 Hz, 1H), 1.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7–158.3 (J = 234.4 Hz), 159.6, 151.9, 135.3, 134.4, 132.8, 129.3, 126.6, 126.5, 125.2 (J = 2.2 Hz), 123.6, 122.3 (J = 2.7 Hz), 121.5 (J = 8.8 Hz), 120.9, 120.2 (J = 6.0 Hz), 119.7, 110.9, 107.4 (J = 19.8 Hz), 101.1, 43.8, 19.9; ESIMS $C_{21}H_{17}FN_2ONa$ m/z 355.2 [M+Na]$^+$.

5.2.49. (*R*)-*N*-(1*H*-Indol-2-ylmethyl)-1-phenylethanamine (77)

Compound **77** was prepared by the same method described for the synthesis of **33** starting from carboxamide **67** (90% yield, white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.46 (br s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.39–7.26 (m, 7H), 7.14 (td, J = 7.7 Hz, J = 1.1 Hz, 1H), 7.06 (td, J = 7.3 Hz, J = 1.1 Hz, 1H), 6.28 (m, 1H), 3.86–3.79 (m, 3H), 1.40 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 143.9, 136.7, 134.9, 127.6, 127.4, 126.1, 125.6, 120.3, 119.1, 118.5, 109.7, 99.1, 56.5, 43.6, 23.0; HRESMS Calcd for $C_{17}H_{19}N_2$ [M+H]$^+$: 251.1548. Found: 251.1548.

Hydrochloride of **77**: mp 193–195 °C; $[\alpha]_D$ = +26.0 (*c* 1.20, acetone).

5.2.50. (*R*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(4-methylphenyl) ethanamine (78)

Compound **78** was prepared by the same method described for the synthesis of **33** starting from carboxamide **68** (55% yield, yellow oil); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 9.90 (br s, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 6.89 (td, J = 7.2 Hz, J = 1.1 Hz, 1H), 6.81 (td, J = 7.2 Hz, J = 1.1 Hz, 1H), 6.09 (br s, 1H), 3.64 (q, J = 6.6 Hz, 1H), 3.65 (d, J_{gem} = 14.2 Hz, 1H), 3.57 (d, J_{gem} = 14.2 Hz, 1H), 2.40 (br s, 1H), 2.16 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 142.3, 138.3, 136.0, 135.4, 128.3, 128.1, 126.0, 120.0, 119.0, 118.3, 110.2, 98.7, 56.3, 43.8, 23.4, 19.6; HRESMS Calcd for $C_{18}H_{21}N_2$ [M+H]$^+$: 265.1705. Found: 265.1705.

Hydrochloride of **78**: mp 187–189 °C; $[\alpha]_D$ = +4.9 (*c* 0.23, acetone).

5.2.51. (*R*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(4-methoxyphenyl) ethanamine (79)

Compound **79** was prepared by the same method described for the synthesis of **33** starting from carboxamide **69** (52% yield, pink oil); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 9.88 (br s, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.20 (br d, J = 7.9 Hz, 1H), 7.16 (br d, J = 8.7 Hz, 2H), 6.88 (td, J = 7.9, Hz, J = 1.3 Hz, 1H), 6.81 (td, J = 7.7 Hz, J = 1.1 Hz, 1H), 6.74 (br d, J = 8.7 Hz, 2H), 6.09 (br s, 1H), 3.63 (s, 3H), 3.62 (q, J = 6.6 Hz, 1H), 3.64 (d, J_{gem} = 14.1 Hz, 1H), 3.57 (d, J_{gem} = 14.1 Hz, 1H), 2.29 (br s, 1H), 1.16 (d, J = 6.6 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 159.6, 139.8, 138.7, 137.5, 129.6, 128.5, 121.4, 120.4, 119.7, 114.5, 111.7, 100.2, 57.4, 55.5, 45.2, 24.9; HRESMS Calcd for $C_{18}H_{20}N_2$ [M+H]$^+$: 281.1654. Found: 281.1641.

Hydrochloride of **79**: mp 148–149 °C; $[\alpha]_D$ = +40.0 (*c* 0.10, acetone).

5.2.52. (*R*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(3-methoxyphenyl) ethanamine (80)

Compound **80** was prepared by the same method described for the synthesis of **33** starting from carboxamide **70** (60% yield, yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.44 (br s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.24–7.15 (m, 2H), 7.05 (td, *J* = 7.0 Hz, *J* = 1.3 Hz, 1H), 6.98 (td, *J* = 7.7 Hz, *J* = 1.3 Hz, 1H), 6.85–6.80 (m, 2H), 6.73 (ddd, *J* = 8.1 Hz, *J* = 2.6 Hz, *J* = 1.1 Hz, 1H), 6.19 (d, *J* = 1.1 Hz, 1H), 3.75–3.65 (m, 6H), 1.80 (br s, 1H), 1.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.9, 145.7, 136.8, 134.9, 128.6, 127.4, 120.4, 119.1, 118.6, 117.9, 111.4, 111.2, 109.7, 99.1, 56.6, 54.2, 43.7, 23.0; HRESMS Calcd for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1654. Found: 281.1649.

Hydrochloride of **80**: mp 134–136 °C; $[\alpha]_D$ = +35.0 (*c* 0.25, acetone).

5.2.53. (*R,S*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(2-hydroxyphenyl) ethanamine (81)

Compound **81** was prepared by the same method described for the synthesis of **33** starting from carboxamide **71** (41% yield, yellow oil); ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm) 10.12 (br s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.13 (td, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H), 7.10 (td, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H), 7.04–7.00 (m, 2H), 6.78 (td, *J* = 7.3 Hz, *J* = 1.3 Hz, 1H), 6.75 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H), 6.38 (s, 1H), 4.08 (q, *J* = 6.6 Hz, 1H), 3.99 (d, J_{gem} = 14.5 Hz, 1H), 3.90 (d, J_{gem} = 14.5 Hz, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 157.7, 136.7, 136.6, 128.6, 128.4, 128.0, 126.9, 121.1, 119.8, 119.1, 118.8, 116.3, 110.9, 100.5, 57.7, 44.0, 21.6; HRESMS Calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$: 267.1497. Found: 267.1499.

5.2.54. (*R*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(4-fluorophenyl) ethanamine (82)

Compound **82** was prepared by the same method described for the synthesis of **33** starting from carboxamide **72** (78% yield, pink powder); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 10.08 (br s, 1H), 7.48–7.43 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.14–7.07 (m, 2H), 7.05 (td, *J* = 8.1 Hz, *J* = 1.1 Hz, 1H), 6.97 (td, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 6.25 (d, *J* = 1.1 Hz, 1H), 3.85 (q, *J* = 6.6 Hz, 1H), 3.80 (d, J_{gem} = 14.1 Hz, 1H), 3.73 (d, J_{gem} = 14.1 Hz, 1H), 2.52 (br s, 1H), 1.33 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 164.2–161.0 ($J_{C\text{-}F}$ = 242.6 Hz), 142.0, 138.7, 136.6, 128.7, 128.5, 128.4, 120.6, 119.6, 118.9, 115.0, 114.7, 110.8, 99.4, 56.4, 44.3, 24.0; HRESMS Calcd for $C_{17}H_{18}FN_2$ $[M+H]^+$: 269.1454. Found: 269.1477.

Hydrochloride of **82**: mp 62–63 °C; $[\alpha]_D$ = +44.4 (*c* 0.21, acetone).

5.2.55. (*R*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(4-bromophenyl) ethanamine (83)

Compound **83** was prepared by the same method described for the synthesis of **33** starting from carboxamide **73** (28% yield, orange powder); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 9.91 (br s, 1H), 7.38–7.30 (m, 3H), 7.25–7.19 (m, 3H), 6.89 (td, *J* = 7.0 Hz, *J* = 1.3 Hz, 1H), 6.82 (td, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 6.09 (d, *J* = 1.1 Hz, 1H), 3.68 (q, *J* = 6.6 Hz, 1H), 3.65 (d, J_{gem} = 14.3 Hz, 1H), 3.58 (d, J_{gem} = 14.3 Hz, 1H), 2.48 (br s, 1H), 1.17 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 145.4, 138.5, 136.5, 131.2, 128.7, 128.6, 120.5, 119.7, 119.5, 118.8, 110.7, 99.3, 56.4, 44.2, 23.7; HRESMS Calcd for $C_{17}H_{18}{}^{79}BrN_2$ $[M+H]^+$: 329.0653. Found: 329.0655; Calcd for $C_{17}H_{18}{}^{81}BrN_2$ $[M+H]^+$: 331.0633. Found: 331.0642.

Hydrochloride of **83**: mp 198–199 °C; $[\alpha]_D$ = +38.7 (*c* 0.26, acetone).

5.2.56. (*R,S*)-*N*-(1*H*-Indol-2-ylmethyl)-1-(3-bromophenyl) ethanamine (84)

Compound **84** was prepared by the same method described for the synthesis of **33** starting from carboxamide **74** (27% yield, orange oil); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 9.92 (br s, 1H), 7.46 (t, *J* = 1.9 Hz, 1H), 7.30 (br d, *J* = 7.2 Hz, 1H), 7.27–7.22 (m, 2H), 7.21–7.18 (m, 1H), 7.14–7.09 (m, 1H), 6.88 (td, *J* = 7.2 Hz, *J* = 1.3 Hz, 1H), 6.80 (td, *J* = 7.2 Hz, *J* = 1.3 Hz, 1H), 6.09 (d, *J* = 1.3 Hz, 1H), 3.67 (q, *J* = 6.6 Hz, 1H), 3.65 (d, J_{gem} = 14.1 Hz, 1H), 3.58 (d, J_{gem} = 14.1 Hz, 1H), 2.31 (br s, 1H), 1.17 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 148.8, 138.4, 134.3, 130.1, 129.5, 129.3, 128.5, 125.6, 121.9, 120.4, 119.4, 118.7, 110.6, 99.2, 56.6, 44.2, 23.7; HRESMS Calcd for $C_{17}H_{18}{}^{79}BrN_2$ $[M+H]^+$: 329.0653. Found: 329.0664; Calcd for $C_{17}H_{18}{}^{81}BrN_2$ $[M+H]^+$: 331.0633. Found: 331.0663.

5.2.57. (*R,S*)-1-Biphenyl-4-yl-*N*-(1*H*-indol-2-ylmethyl) ethanamine (85)

Compound **85** was prepared by the same method described for the synthesis of **33** starting from carboxamide **75** (25% yield, pink powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.04 (br s, 1H), 7.57–7.53 (m, 5H), 7.46–7.32 (m, 6H), 7.13 (td, *J* = 7.2 Hz, *J* = 1.3 Hz, 1H), 7.07 (td, *J* = 7.2 Hz, *J* = 1.1 Hz, 1H), 6.28 (s, 1H), 3.98–3.83 (m, 3H), 3.12 (br s, 1H), 1.46 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.7, 140.6, 140.5, 136.3, 136.2, 128.8, 128.3, 127.4, 127.3, 127.2, 127.0, 121.7, 120.2, 119.7, 110.9, 101.2, 57.0, 44.2, 23.3; HRESMS Calcd for $C_{23}H_{23}N_2$ $[M+H]^+$: 327.1861. Found: 327.1865.

Hydrochloride of **85**: mp 228–229 °C (decomposition).

5.2.58. (*R,S*)-1-(4-Fluoro-1-naphthyl)-*N*-(1*H*-indol-2-ylmethyl) ethanamine (86)

Compound **86** was prepared by the same method described for the synthesis of **33** starting from carboxamide **76** (48% yield, pink powder); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.49 (br s, 1H), 8.20–8.10 (m, 2H), 7.66–7.59 (m, 1H), 7.59–7.51 (m, 3H), 7.35–7.32 (m, 1H), 7.20–7.13 (m, 2H), 7.08 (td, *J* = 7.7 Hz, *J* = 1.3 Hz, 1H), 6.28 (s, 1H), 4.66 (q, *J* = 6.6 Hz, 1H), 3.93 (d, J_{gem} = 14.1 Hz, 1H), 3.69 (d, J_{gem} = 14.1 Hz, 1H), 2.06 (br s, 1H), 1.54 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7–156.4 (*J* = 251.4 Hz), 137.8, 136.0 (*J* = 4.4 Hz), 135.9, 132.5 (*J* = 4.4 Hz), 128.4, 126.9, 125.8 (*J* = 2.2 Hz), 124.2–124.0 (*J* = 15.9 Hz), 122.9 (*J* = 2.7 Hz), 122.8–122.7 (*J* = 8.2 Hz), 121.5, 121.4 (*J* = 6.0 Hz), 120.2, 119.7, 110.7, 109.2–108.9 (*J* = 19.8 Hz), 100.4, 52.8, 44.7, 23.4; HRESMS Calcd for $C_{21}H_{19}FN_2$ $[M+H]^+$: 319.1611. Found: 319.1615.

Hydrochloride of **86**: mp 196–197 °C.

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