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1-(Indolin-1-yl)-1-phenyl-3-propan-2-olamines as Potent and Selective Norepinephrine Reuptake Inhibitors

An T. Vu,*[,†] Stephen T. Cohn,[†] Puwen Zhang,[†] Callain Y. Kim,[†] Paige E. Mahaney,[†] Jenifer A. Bray,[‡] Grace H. Johnston,[‡] Elizabeth J. Koury,[‡] Scott A. Cosmi,[‡] Darlene C. Deecher,[‡] Valerie A. Smith,[§] James E. Harrison,[§] Liza Leventhal,[§] Garth T. Whiteside,[§] Jeffrey D. Kennedy,[§] and Eugene J. Trybulski[†]

[†]*Chemical Sciences, and* [‡]*Musculoskeletal Biology, Wyeth Research, 500 Arcola Road, Collegeville, Pennsylvania 19426, and* [§]*Neuroscience, Wyeth Research, CN 8000, Princeton, New Jersey 08543*

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Efforts to identify new selective and potent norepinephrine reuptake inhibitors (NRIs) for multiple indications by structural modification of the previous 3-(arylamino)-3-phenylpropan-2-olamine scaffold led to the discovery of a novel series of 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines (**9**). Investigation of the structure−activity relationships revealed that small alkyl substitution at the C3 position of the indoline ring enhanced selectivity for the norepinephrine transporter (NET) over the serotonin transporter (SERT). Several compounds bearing a 3,3-dimethyl group on the indoline ring, **9k**, **9o**,**p**, and **9s**,**t**, exhibited potent inhibition of NET ($IC_{50} = 2.7-6.5$ nM) and excellent selectivity over both serotonin and dopamine transporters. The best example from this series, **9p**, a potent and highly selective NRI, displayed oral efficacy in a telemetric rat model of ovariectomized-induced thermoregulatory dysfunction, a mouse *p*-phenylquinone (PPQ) model of acute visceral pain, and a rat spinal nerve ligation (SNL) model of neuropathic pain.

Introduction

Biogenic monoamine neurotransmitters such as serotonin (5-HT[a]), norepinephrine (NE), and dopamine (DA) play a crucial role in various central nervous system (CNS) functions, and deficiency in the levels of these neurotransmitters in the brain has been implicated in the pathophysiology of a variety of neuropsychiatric disorders.[1] A strategy to enhance monoaminergic neurotransmission is to inhibit reuptake after release into the synaptic cleft by blocking presynaptic transporters.[2] Inhibition of monoamine reuptake has been an effective pharmacological treatment for various CNS disorders.[3] Selective serotonin reuptake inhibitors (SSRI) such as fluoxetine (**1**) and sertraline (**2**) have been widely prescribed for depression (Figure 1). In recent years increasing efforts have focused on norepinephrine reuptake inhibition, and to date, two selective norepinephrine reuptake inhibitors (NRI) have been in clinical use.[4] Atomoxetine (**3**), a moderately selective NRI, was approved for attention deficit hyperactivity disorder (ADHD),[5] and racemic reboxetine (**4**), a selective NRI, is marketed in Europe for the treatment of major depressive disorder (MDD).[6] In addition, recent studies suggest other clinical implications for these two drugs in treating chronic pain disorders such as fibromyalgia and low back pain.[7] Furthermore, dual acting serotonin and norepinephrine reuptake inhibitors (SNRI) such as venlafaxine (**5**) and duloxetine (**6**) have emerged as another class of inhibitors with improved antidepressant efficacy and/or faster onset of action relative to SSRIs.[8] Duloxetine has also demonstrated efficacy in other therapeutic indications including neuropathic pain[7a,9] and stress urinary incontinence (SUI).[10] Accordingly, considerable research efforts continue to focus on the development of novel therapeutics that inhibit reuptake of norepinephrine.[11,12]

As part of our continuing interest to identify novel NRIs[11] for multiple therapeutic utilities, we recently reported a series of 3-(arylamino)-3-phenylpropan-2-olamines as a new class of SNRIs.[11c] Two compounds in this series, **7** with an ortho methyl group on the phenylamino moiety and **8** with a meta fluoro group on the phenyl ring, exhibited preferential affinity for the norepinephrine transporter (NET) over the serotonin transporter (SERT). Forming a ring between the ortho methyl group and the *N*-methyl group of the phenylamino moiety generated a novel series of 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines **9** as potentially selective NRIs (Figure 2). Exploration of this new scaffold led to a number of compounds that were potent and highly selective NRIs. Herein, we describe the synthesis, structure−activity relationships (SAR) of the 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines **9** and reveal several lead compounds that displayed oral efficacy in various

*To whom correspondence should be addressed. Phone: 484-865-8432. Fax: 484-865-9399. E-mail: vua@wyeth.com.

[a] Abbreviations: 5-HT, serotonin; ADHD, attention deficit hyperactivity disorder; ANOVA, analysis of variance; CHO, Chinese hamster ovary; cLogP, calculated octanol−water log *P*; CNS, central nervous system; DA, dopamine; hDAT, human dopamine transporter; hNET, human norepinephrine transporter; hSERT, human serotonin transporter; ip, intraperitoneal; JAR, human placental choriocarcinoma cell; MDCK, Madin−Darby canine kidney; MDD, major depressive disorder; NE, norepinephrine; NET, norephinephrine transporter; NRI, norepinephrine reuptake inhibitor; OVX, ovariectomized; po, oral; PPQ, *p*-phenylquinone; SAR, structure−activity relationship; SEM, standard error of the mean; SERT, serotonin transporter; SNL, spinal nerve ligation; SNRI, serotonin and norepinephrine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SUI, stress urinary incontinence; TST, tail-skin temperature; VMS, vasomotor symptoms.

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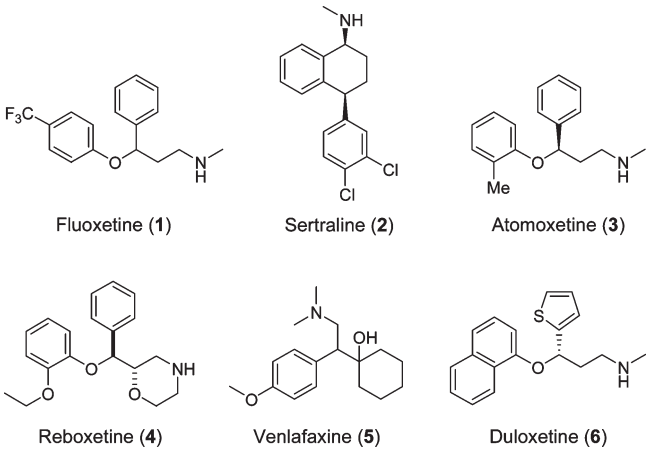


Figure 1. Chemical structures of known monoamine reuptake inhibitor drugs.

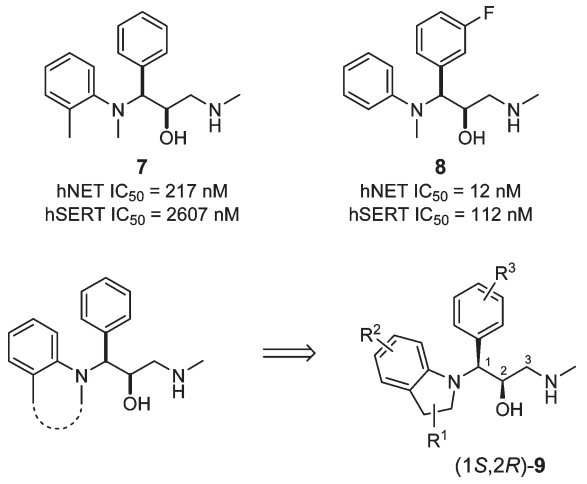


Figure 2. Designing novel 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamine series **9**.

predictive animal models of noradrenergic-related CNS disorders.

Chemistry

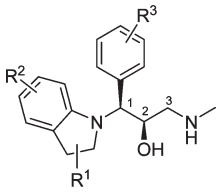
All 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines **9** in Table 1 were prepared as single (1*S*,2*R*)-enantiomers according to Scheme 1. The synthesis features a regioselective and stereospecific epoxide ring-opening reaction of optically pure (*R*,*R*)-3-phenylglycidols **17** by indolines **13** as the key synthetic step. The 3,3-disubstituted indolines were prepared by double C3-alkylation of oxindoles **10**[13] followed by reduction of the resulted 3,3-disubstituted oxindoles **11** using sodium bis(2-methoxyethoxy)aluminum hydride.[14] All other substituted indolines either were commercially available or were prepared by reduction of the corresponding indoles **12** using sodium cyanoborohydride.[15] The unsubstituted (*R*,*R*)-3-phenylglycidol was commercially available, whereas fluorine-substituted (*R*,*R*)-3-phenylglycidols were prepared from fluorine-substituted *trans*-cinnamic acids **14**. Thus, O-methylation of the carboxylic acid group of **14** (R^3 = 3-F and 3,5-di-F) followed by reduction of the resulted methyl *trans*-cinnamate esters **15** using diisobutylaluminium hydride provided *trans*-cinnamyl alcohols **16**. Subsequent Sharpless asymmetric expoxidation reaction[16] of **16** furnished fluorine-substituted (*R*,*R*)-3-phenylglycidols with excellent enantioselectivity (> 96% ee). The thermal[17] or titanium tetraisopropoxide[18] induced epoxide ring-opening reaction of **17** by **13** occurred stereospecifically and regioselectively at the C3 position of **17** to provide (2*S*,3*S*)-diols **18**.[19] Selective tosylation of the primary hydroxyl group followed by displacement of the tosylate with excess methylamine furnished (1*S*,2*R*)-amines **9**.[19] Finally, amines **9** were converted to their hydrochloride salts prior to biological evaluation.

Results and Discussion

As mentioned, the new 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamine series (**9**) was investigated as single (1*S*,2*R*)-enantiomers. The 1*S*,2*R* stereochemistry was chosen on the basis of the stereochemical preference that was established in a closely related 1-amino-3-(1*H*-indol-1-yl)-3-phenylpropan-2-ol series.[11b] In addition, the secondary *N*-methylamine group was selected as the side chain amino moiety of **9**, since it provided the optimal norepinephrine reuptake inhibition in the related 3-(arylamino)-3-phenylpropan-2-olamine and 1-amino-3-(1*H*-indol-1-yl)-3-phenylpropan-2-ol series.[11b,c] The 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines **9** were initially evaluated in vitro for their ability to inhibit the uptake of norepinephrine in MDCK-Net6 cells stably transfected with human norepinephrine transporter (hNET), and serotonin in JAR cells natively expressing the human serotonin transporter (hSERT). A small selected group of compounds were also tested for their inhibition of [^{3}H]nisoxetine binding to MDCK-Net6 cells stably transfected with hNET. Compounds were further evaluated for their inhibition of [^{3}H]WIN-35428 radioligand binding to the human dopamine transporter (hDAT). Detailed experimental protocols for these inhibitory assays were reported previously.[11f] Results of the in vitro screening are presented in Table 1.

The unsubstituted 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamine **9a** displayed high norepinephrine reuptake inhibition (hNET IC_{50} = 9.7 nM), demonstrating the potential of this new series as potent NRIs. Surprisingly, **9a** also exhibited significant serotonin reuptake inhibition, thus engendering a low selectivity for hNET over hSERT. Introduction of a *m*-fluoro group on phenyl ring (**9b**) led to a subtle increase in both the hNET potency and selectivity. A similar enhancement effect has been observed in other closely related series.[11a,c] Consequently the SAR of the indoline ring was investigated while maintaining the *m*-fluorophenyl group constant. Incorporating a small substituent such as methyl, ethyl, isopropyl, chloro, or benzyloxy group at various positions of the indoline ring (**9c**−**j**) offered essentially no further improvement on the hNET potency relative to their unsubstituted congener **9b**. A few analogues, **9d** and **9g**,**h**, however showed comparable norepinephrine reuptake inhibition to that of **9b**. In contrast, indoline ring substitution exerted marked effects on the hSERT potency. For example, the 5-chloro group substantially increased the hSERT potency (versus **9b**) while maintaining NE reuptake inhibition, thus rendering compound **9h** a potent SNRI exhibiting single-digit nanomolar IC_{50} values at both hNET and hSERT. Conversely, methyl substitution at the C3 position (**9d**) caused a significant decrease in the inhibitory activity for serotonin but not for norepinephrine, thus resulting in greater than 50-fold selectivity for hNET over hSERT. This selectivity enhancement was consistent with that observed in the closely related 1-amino-3-(1*H*-indol-1-yl)-3-phenylpropan-2-ol series.[11a] Separating **9d** into its enantiomers, **9d** isomers 1 and 2, or elongating the C3 alkyl substituent from methyl to ethyl (**9e**)

Table 1. Inhibitory Activity of the 1-(Indolin-1-yl)-1-phenyl-3-propan-2-olamines **9** at the Human Monoamine Transporters

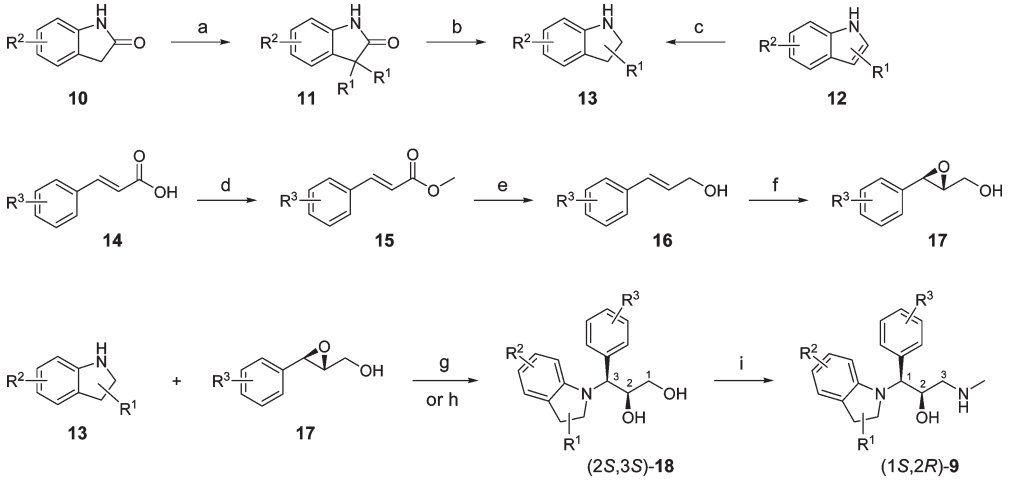


(1*S*,2*R*)-**9**

compd	R^1	R^2	R^3	hNET uptake IC_{50} (nM)[a]	hNET binding IC_{50} (nM)[b]	hSERT uptake IC_{50} (nM)[c]	(hSERT IC_{50})/(hNET IC_{50})[d]	hDAT binding % inh at 1 μM[e] (IC_{50} nM)	cLogP[f]
reboxetine (**4**)				3.2 ± 1.0		242 ± 39	76		
9a	H	H	H	9.7 ± 0.9		29 ± 4.2	3.0	8	2.8
9b	H	H	3-F	4.6 ± 0.4		21 ± 2.5	4.5	14	2.9
9c	2-Me	H	3-F	72 ± 42		84 ± 75	1.2	33	3.5
9d	3-Me	H	3-F	6.2 ± 0.9		329 ± 10	53	0	3.5
9d-isomer 1	3-Me	H	3-F	8.5 ± 6.4		154 ± 88	18	23	3.5
9d-isomer 2	3-Me	H	3-F	3.7 ± 0.1		194 ± 40	51	10	3.5
9e	3-Et	H	3-F	14 ± 1.9		499 ± 62	35	20	4.0
9f	3-*i*-Pr	H	3-F	23 ± 16		1123 ± 1006	49	31	4.4
9g	H	5-Me	3-F	2.3 ± 2.4		5.5 ± 7.2	2.4	2	3.4
9h	H	5-Cl	3-F	7.6 ± 10		2.8 ± 3.9	0.4	4	3.8
9i	H	5-OBn	3-F	15 ± 3.6		813 ± 606	54	45	4.7
9j	H	7-Me	3-F	170 ± 114		280 ± 78	1.6	2	3.4
9k	3,3-di-Me	H	3-F	6.3 ± 2.1	2.6 ± 0.6	4519 ± 565	717	0	4.0
9l	3,3-di-Et	H	3-F	150 ± 16		8971 ± 990	60	3	5.0
9m	3,3-cyclopentyl	H	3-F	21 ± 2.4		1969 ± 642	92	2	4.4
9n	3,3-cyclohexyl	H	3-F	39 ± 50		4917 ± 4095	136	39	4.9
9o	3,3-di-Me	H	H	5.7 ± 1.0		2871 ± 408	504	18	3.8
9p	3,3-di-Me	H	3,5-di-F	6.5 ± 2.4	4.1 ± 0.9	5293 ± 498	814	4	4.1
9q	3,3-di-Me	5-F	3-F	19 ± 13		364 ± 281	19	14	4.3
9r	3,3-di-Me	6-F	3-F	17 ± 3.5		4992 ± 5723	294	22	4.3
9s	3,3-di-Me	7-F	H	2.7 ± 1.0	1.6 ± 0.03	1099 ± 350	407	7 (20927)	4.1
9t	3,3-di-Me	7-F	3-F	5.5 ± 1.8	1.4 ± 1.7	1614 ± 348	293	2 (22834)	4.3

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells stably transfected with hNET. Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard. [b] Inhibition of [^{3}H]nisoxetine binding to MDCK-Net6 cells stably transfected with hNET. Desipramine (IC_{50} = 3.3 ± 1.1 nM) was used as a standard. [c] Inhibition of serotonin uptake in JAR cells natively expressing hSERT. Fluoxetine (IC_{50} = 9.4 ± 3.1 nM) was used as a standard. [d] Unitless value as a ratio of (hSERT uptake IC_{50})/(hNET uptake IC_{50}) in which higher values represent greater NET selectivity, a value of 1 represents no selectivity, and values approaching 0 represent SERT selectivity. [e] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant hDAT. Mazindol (IC_{50} = 22 ± 6.5 nM) was used as a standard. Values in the parentheses are IC_{50} (nM). [f] Calculated log *P* by Daylight engine, version 4.81.

Scheme 1. Synthesis of (1*S*,2*R*)-1-(Indolin-1-yl)-1-phenyl-3-propan-2-olamines **9**[a]



[a] Reagents and conditions: (a) *n*-BuLi, LiCl, THF, 0 °C, then R^1-I, room temp, 16 h, 41−50%; (b) Red-Al, toluene, 80 °C, 1 h, 79−93%; (c) $NaBH_3CN$, AcOH, 71−96%; (d) MeI, Cs_2CO_3, acetone, 65 °C, 1.5 h, 97−99%; (e) DIBAL-H, CH_2Cl_2, −78 to −30 °C, 1 h, 90−95%; (f) *t*-BuOOH, (−)-DIPT, Ti(O-*i*-Pr)$_4$, 4 Å molecular sieves, CH_2Cl_2, −25 °C, 70−90%, >96% ee; (g) 110 °C, neat, 5 h, 55−93%; (h) Ti(O-*i*-Pr)$_4$, CH_2Cl_2, 0 °C to room temp, 12 h, 74−82%; (i) *p*-TsCl, TEA, CH_2Cl_2, 0 °C to room temp, 5 h, then CH_3NH_2, EtOH, sealed tube, room temp, 12 h, 17−73%.

or isopropyl (**9f**) group showed no improvement on the hNET selectivity versus **9d**. However, a geminal dimethyl group at the C3 position caused a drastic reduction in the 5-HT reuptake inhibition while preserving the hNET potency, thus

engendering compound **9k** a potent and highly selective NRI (hNET $IC_{50} = 6$ nM with greater than 700-fold selective over hSERT). The remarkable selectivity enhancement of **9k** prompted us to focus on the C3 dialkyl substitution. However, larger geminal dialkyl groups such as diethyl (**9l**), cyclopentyl (**9m**), and cyclohexyl (**9n**) lowered both hNET potency and selectivity relative to **9k**. Exploring other 3,3-dimethyl analogues (**9o**−**t**) by fluorine modification of the phenyl ring and/or the indoline ring led to several other analogues (**9o**,**p** and **9s**,**t**) with similar inhibitory activities as that of **9k**. Compounds **9k**, **9o**,**p**, and **9s**,**t** exhibited potent inhibition of hNET ($IC_{50} = 2.7-6.5$ nM) and greater than 290-fold selective over hSERT, with **9s** being the most potent (hNET $IC_{50} = 2.7$ nM) and **9p** the most selective (814-fold).

A small selected group of compounds were also evaluated for their ability to bind to hNET, and generally their binding affinities were in good agreement with their hNET functional potencies. The 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines were further evaluated for their dopamine transporter binding affinity. Overall, the compounds were found to be weak ligands for hDAT (≤45% inhibition at 1 μM), indicating high selectivity over the dopamine transporter. Compounds **9s**,**t** displayed 1.4−1.6 nM hNET binding IC_{50} versus greater than 20 μM hDAT binding IC_{50}, demonstrating complete hNET selectivity against hDAT. The most selective compounds, **9k**, **9o**,**p**, and **9s**,**t**, were also found to be weak ligands for the 5-HT_{2B}, dopamine D_2, α_1-adrenergic (< 40% inhibition at 10 μM), and 5-HT_6 (< 40% inhibition at 5 μM) receptors.

Compounds **9k**, **9o**,**p**, and **9s**,**t** exhibit desirable druglike properties that are favorable for CNS penetration.[20] These include moderate lipophilicity (cLogP = 3.8−4.3), low molecular weights (310−346), and low polar surface area (TPSA = 36 Å^2). Consequently, they were selected for further in vivo characterization.

Neurotransmitters NE and 5-HT are thought to play an important role in the maintenance of temperature homeostasis in the hypothalamus, and alterations or reductions in the levels of these neurotransmitters have been implicated in thermoregulatory dysfunction that causes vasomotor symptoms (VMS) such as hot flushes.[21] Clinical studies have demonstrated the efficacy of paroxetine[22] (an SSRI), venlafaxine,[23] and desvenlafaxine succinate[24] (SNRIs) in alleviating hot flushes, suggesting that these drugs may provide effective nonhormonal therapies for the treatment of VMS.[25] Furthermore, we recently reported a selective NRI, WAY-256805 (**19**), from a series of cyclohexanol ethylpiperazines that alleviated thermoregulatory dysfunction in a preclinical rodent model of temperature regulation.[11f] The ability of a compound to restore the lowering of the tail-skin temperature (TST) during the dark phase in the rat model of ovariectomized (OVX) induced thermoregulatory dysfunction suggests efficacy toward alleviating vasomotor symptoms.[21b] Accordingly, potent and highly selective NRIs **9k**, **9o**, **p**, and **9s**,**t** were evaluated in this model[26,11f] for their effects on temperature homeostasis. An oral dose of 10 mg/kg (compared to 30 mg/kg po dose for **19**) was selected because these compounds were more potent at hNET ($IC_{50} = 2.7-6.5$ nM) than **19** ($IC_{50} = 82$ nM). As shown in Table 2, all five compounds were orally efficacious and significantly reduced TST with maximum temperature reduction between −2 to −4 °C. Note that compound **9p**, a potent (hNET $IC_{50} = 6.5$ nM) and the most selective NRI among the 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines, displayed the highest maximum temperature reduction of −4.0 °C. Despite their similar hNET potencies ($IC_{50} = 2.7-6.5$ nM), analogues **9k**, **9p**, and **9s**,**t** bearing fluorine substitution on the indoline ring and/or phenyl ring achieved considerably greater maximum TST reduction and longer duration of action than their des-fluoro congener **9o**. Furthermore, compounds **9p** and **9s** at 10 mg/kg po were substantially more efficacious in both TST reduction and duration than the previously reported cyclohexanol ethylpiperazine derivative **19**, at 30 mg/kg po.[11f]

Table 2. Effects of **9k**, **9o**,**p**, and **9s**,**t** in the Telemetric Rat Model of Ovariectomized-Induced Thermoregulatory Dysfunction[a]

compd	oral dose (mg/kg)	onset of activity (h)	duration of action (h)	mean reduction in TST (°C)	maximun reduction in TST (°C)
9o	10	1	2.5	−1.84	−2.01
9k	10	0.5	6.5	−2.14	−2.75
9p	10	0.5	8.5	−2.69	−4.04
9s	10	1	7	−2.52	−3.77
9t	10	1	> 11.5	−2.08	−3.27
19	30	1	3	−2.16	−3.15

[a] Compounds were dosed orally in 2% Tween−0.5% methylcellulose (vehicle). The onset of an effect was defined as the first half-hour interval of two consecutive significant ($p < 0.05$) half-hour intervals following any number of nonsignificant half-hour intervals. The treatment effect will be considered to have ended when two consecutive nonsignificant half-hour intervals follow any number of significant half-hour intervals. Mean temperature change is calculated from half-hour TST averages obtained over the treatment duration.

A number of neurotransmitters, peptides, and ion channel modulators have been implicated in the modulation of nociceptive processing. NE and 5-HT are major components of the endogenous descending pain inhibitory system from the rostral ventral medulla to the spinal cord.[27] It has been suggested that altered or decreased activity of endogenous NE and 5-HT at both the spine and supraspine may in part lead to chronic pain.[28] Consequentially, it is presumed that NRIs and SRIs can attenuate pain by blocking reuptake of NE/5-HT leading to increased postsynaptic NE/5-HT levels and sustained activation of the descending pain inhibitory pathway.[29] However, clinical evidence suggests that compounds with greater NRI versus SRI activity would be more effective for the treatment of pain than those with only SRI activity.[30] This observation was also supported by preclinical data.[31] In addition to small molecules, the conopeptide Xen2174, a structural analogue of Mr1A and a highly selective NRI, reversed tactile allodynia following intrathecal administration to neuropathic rats.[32] Accordingly, the most hNET selective 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamine **9p** was selected to be evaluated in models of acute visceral and neuropathic pain to examine its antinociceptive effects. Detailed experimental protocols for these two pain models were reported previously.[33]

In the mouse *p*-phenylquinone (PPQ) model of acute visceral (abdominal) pain,[34] PPQ administered via intraperitoneal (ip) injection acts as a localized irritant resulting in an abdominal constriction response (i.e., writhing) that can be quantified. The ability of a compound to reduce the number of abdominal constrictions suggests efficacy toward attenuating visceral pain. As shown in Figure 3, compound **9p** was orally efficacious at 30 mg/kg and significantly reduced the number of PPQ-induced abdominal constrictions relative to vehicle ($p < 0.05$, ANOVA), with peak effects observed

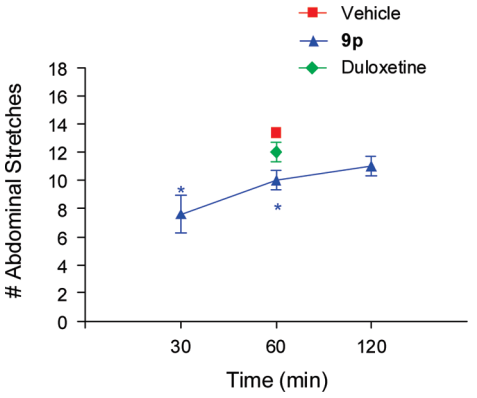


Figure 3. Effect of **9p** in the mouse PPQ model of acute visceral pain. Male CD-1 mice (weight 25−30 g, 10/group) were used. Compound **9p** and *S*-duloxetine (**6**) were administered orally at 30 mg/kg as a suspension in 2% Tween−0.5% methylcellulose (vehicle). Data shown are the mean ± SEM for each dose (N = 10 per group). The asterisk (∗) indicates a p value of ≤0.05 vs vehicle-treated mice (ANOVA).

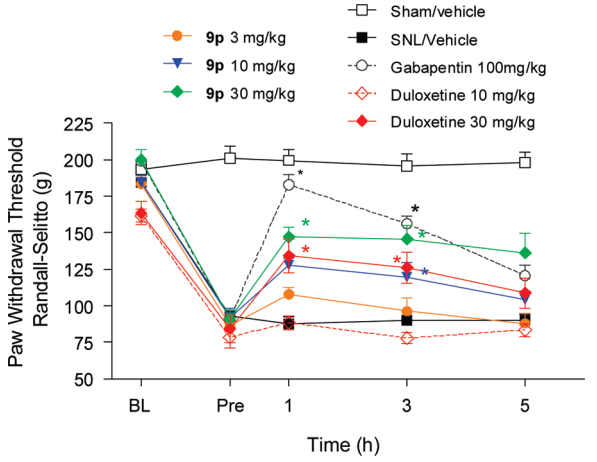


Figure 4. Effect of **9p** in the SNL-induced mechanical hyperalgesia. Male Sprague−Dawley rats (weight 235−300 g, 8−9/group) were used 3 weeks postsurgery. Threshold to paw withdrawal was measured. Compound **9p** and *S*-duloxetine (**6**) were administered orally as a solution in 2% Tween−0.5% methylcellulose (vehicle). Gabapentin was used as a positive control and administered (ip) as a solution in 0.9% saline. Data shown are the mean ± SEM. The asterisk (∗) indicates a p value of ≤0.05 vs SNL/vehicle (ANOVA).

following a 30 min pretreatment. The magnitude of effect was greater for **9p** compared to the clinical comparator *S*-duloxetine (**6**) when administered at the same dose with a 60 min pretreatment.

Compound **9p** was also evaluated in a rat spinal nerve ligation (SNL) model of neuropathic pain. Briefly in this model,[35] nerve injury was produced by tight ligation of the left L_5 spinal nerve. Assessment of mechanical thresholds was measured as the hind paw withdrawal threshold to a noxious mechanical stimulus as determined using the paw pressure technique (Randall−Selitto). The cutoff was set at 250 g and the end point taken as complete paw withdrawal. Thresholds were evaluated prior to surgery and reassessed 3−4 weeks after SNL surgery. The ability of a compound to reverse SNL-induced mechanical hyperalgesia predicts efficacy toward attenuating neuropathic pain. As shown in Figure 4, compound **9p** significantly and dose-dependently reversed mechanical hyperalgesia at doses of 10 and 30 mg/kg po. In contrast, *S*-duloxetine provided a statistically significant reversal of pain behavior at only 30 mg/kg, the highest dose tested.

Conclusion

Ring constraint of the previous 3-(arylamino)-3-phenylpropan-2-olamine scaffold led to a novel series of 1-(indolin-1-yl)-1-phenyl-3-propan-2-olamines **9**. The compounds in this class ranged from potent SNRI (**9h**) to potent and selective NRIs (**9k**, **9o**,**p**, and **9s**,**t**) depending on the indoline ring substitution. Moreover, the weak dopamine binding affinity of this series indicated high selectivity over the dopamine transporter. Compounds **9k**, **9o**,**p**, and **9s**,**t**, bearing a 3,3-dimethyl group on the indoline ring, exhibited low nanomolar hNET potency (hNET IC_{50} = 2.7−6.5 nM) and excellent selectivity over hSERT (superior to that of reboxetine **4**) and hDAT. The best analogue from this series, **9p**, a potent (hNET IC_{50}=6.5 nM) and highly selective NRI, was orally efficacious in a rat thermoregulatory dysfunction model, a mouse PPQ model of acute visceral pain, and a rat SNL model of neuropathic pain. These preclinical data suggest the potential efficacy of **9p** in alleviating vasomotor symptoms as well as attenuating acute and neuropathic pain.

Experimental Section

Indoline, 2-methylindoline, 5-methylindoline, 5-chloroindoline, 5-benzyloxyindoline, 7-methylindoline, and (2*R*,3*R*)-3-phenylglycidol were purchased from commercial sources. 3,3-Dimethylindoline, 3,3-diethylindoline, 1′,2′-dihydrospiro[cyclopentane-1,3′-indole], and 1′,2′-dihydrospiro[cyclohexane-1,3′-indole] were prepared according to literature procedure.[14] All reaction reagents and solvents (anhydrous grade) were purchased and were used without further purification. ^{1}H NMR spectra were recorded on a Varian INOVA 400 or a Varian INOVA 500 instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Electrospray (ESI) mass spectra were recorded using a Hewlett-Packard 5989B MS engine or Waters Alliance-ZMD mass spectrometer. Electron impact ionization (EI, EE=70 eV) mass spectra were recorded on a Finnigan Trace mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light or staining with a solution of phosphomolybdic acid in ethanol or potassium permanganate in water. Preparative HPLC purifications were performed on a preparative Gilson HPLC system using a CombiPrep Pro C18 column with acetonitrile (0.1% TFA) and water (0.1% TFA) as solvents at a flow rate of 20 mL/min. Compound purity was determined by analytical HPLC method, which was performed on an Agilent 1100 HPLC instrument using photodiode array detection (210−370 nm), a Waters Xterra RP18 HPLC column (150 mm length × 4.6 mm i.d., 3.5 μm), 40 °C column oven temperature, 1.2 mL/min flow rate, linear mobile phase gradient of 15% to 95% B over 10 min, holding 5 min at 95% B (mobile phase A is10 nM ammonium formate in water, pH 3.5; mobile phase B is 1:1 methanol/acetonitrile). Biological results were obtained on compounds of >95% chemical purity as determined by the above HPLC method.

General Methods for the Synthesis of 1-(Indolin-1-yl)-1-phenyl-3-propan-2-olamines (9). Method a: Double C3-Alkylation of Oxindoles 10.[13] To a mixture of 5-fluorooxindole (2.000 g, 13.23 mmol) and lithium chloride (1.39 g, 33.0 mmol) in tetrahydrofuran (40 mL) at 0 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 10.6 mL, 26.5 mmol, 2 equiv), and the mixture was stirred for 20 min. Iodomethane (1.65 mL, 26.5 mmol, 2 equiv) was added slowly, and the mixture was stirred at 0 °C for 2 h, then at ambient temperature for 16 h. The reaction was quenched with a saturated aqueous solution of ammonium

chloride, diluted with ethyl ether, and washed with water and brine. The organic layer was dried (anhydrous magnesium sulfate), filtered, and concentrated. The residue was purified by Isco silica gel chromatography (0−50% ethyl acetate/hexane) to give 3,3-dimethyl-5-fluorooxindole (**11a**) as white crystals. Yield: 1.18 g (50%).

Method b: Red-Al Reduction of 3,3-Disubstituted Oxindoles 11.[14] A mixture of 3,3-dimethyl-7-fluorooxindole (**11c**, 23.30 g 130 mmol) in toluene (250 mL) under nitrogen was heated at 80 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 65 wt % in toluene, 63 mL, 202 mmol) in toluene (75 mL) was added dropwise via an addition funnel. The resulting solution, which turned from light-yellow to dark-brown, was stirred at 80 °C for an additional 1 h, then cooled in an ice bath. Aqueous sodium hydroxide solution (1 N, 80 mL) was added slowly to quench the reaction. The reaction mixture was diluted with toluene (100 mL) and then washed with water (200 mL), brine, dried (anhydrous sodium sulfate), filtered through a pad of Celite, and concentrated under reduced pressure to give 7-fluoro-3,3-dimethylindoline (**13f**) as a brown solid. Yield 19.89 g (93%).

Method c: $NaBH_3CN$ Reduction of Substituted Indoles 12.[15] To a solution of 3-methylindole (5.25 g, 40.0 mmol) in glacial acetic acid (15 mL) at 0 °C was added portionwise sodium cyanoborohydride (5.03 g, 80.0 mmol, 2 equiv), and the mixture was stirred for 2 h at room temperature. After cooling in an ice bath, the reaction mixture was diluted with water (100 mL) and basified with 40% aqueous NaOH, then extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried (anhydrous sodium sulfate), filtered through a pad of silica gel, and concentrated to give 3-methylindoline (**13a**) as a colorless liquid which was used in subsequent reactions without further purification. Yield: 5.12 g (96%).

Method d: Esterification of *trans*-Cinnamic Acids 14. To a mixture of *trans*-3-fluorocinnamic acid (62.69 g, 377 mmol) and iodomethane (100 mL) in acetone (600 mL) was added portionwise cesium carbonate (150 g, 460 mmol, 1.2 equiv), and the mixture was heated at 65 °C for 1.5 h in a sealed reaction vessel. Upon cooling to room temperature, the reaction mixture was filtered through a pad of silica gel, rinsed with ethyl acetate, and concentrated to give *trans*-3-fluorocinnamic acid methyl ester (**15a**) as a colorless oil. Yield: 66.17 g (97%).

Method e: DIBAL-H Reduction of *trans*-Cinnamate Esters 15. To a solution of *trans*-3-fluorocinnamic acid methyl ester (**15a**, 69.61 g, 386 mmol) in dry dichloromethane (1 L) at −78 °C under nitrogen was added dropwise diisobutylaluminum hydride (neat, 172 mL, 965 mmol, 2.5 equiv) via an addition funnel. After the addition was complete, the reaction mixture was allowed to warm to −30 °C and stirred for an additional 1 h, then quenched with methanol (150 mL). Upon warming to room temperature, the reaction mixture was treated with a saturated aqueous solution of sodium/potassium tartrate (300 mL) and stirred for 30 min. The organic layer was washed sequentially with 1 N aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, brine, then dried (anhydrous sodium sulfate), filtered, and concentrated. The crude oil was purified by silica gel chromatography (0−50% ethyl acetate/hexane) to give *trans*-3-fluorocinnamyl alcohol (**16a**) as a colorless oil. Yield: 53.07 g (90%).

Method f: Sharpless Asymmetric Expoxidation of *trans*-Cinnamyl Alcohols 16.[16] An oven-dried, three-neck, 2 L round-bottom flask fitted with two oven-dried addition funnels and a rubber septum was charged with diisoproyl D-tartrate (11.55 g, 49.3 mmol, 0.30 equiv), 4 Å activated molecular sieves powder (40 g), and dry diclorometane (800 mL) under nitrogen. After the mixture was cooled to −25 °C, titanium isopropoxide (9.6 mL, 33 mmol, 0.20 equiv) was added slowly via a hypodermic syringe. After the mixture was stirred for 10 min, anhydrous *tert*-butyl hydroperoxide (5.5 M in decane, 75.0 mL, 413 mmol, 2.5 equiv) was added at a moderate rate via an addition funnel. The resulting mixture was stirred at −25 °C for 30 min. *trans*-3-Fluorocinnamyl alcohol (**16a**, 25.0 g, 164 mmol) in dry dichloromethane (50 mL) was added dropwise via an addition funnel while maintaining the temperature at −25 °C. After the addition, the reaction mixture was stirred at −25 °C for another 3 h. After the reaction was complete, cooled 30% aqueous sodium hydroxide solution (20 mL) saturated with sodium chloride was added slowly at −25 °C. Diethyl ether (150 mL) was added. The cold bath was removed, and the mixture was allowed to warm to ∼5 °C and stirred for 1 h. Magnesium sulfate (anhydrous, 50 g) was added and the mixture stirred for 20 min, then filtered through a pad of silica gel and rinsed with diethyl ether. The filtrate was concentrated, and toluene was used to azeotropically remove excess *tert*-butyl hydroperoxide. The residual oil was purified on silica gel (0−30% ethyl acetate/hexane) to give (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) as a viscous, colorless oil. Yield: 24.40 g (90%, 96.5% ee).

Method g: Thermally Induced Epoxide Ring-Opening of (*R*,*R*)-3-Phenylglycidols 17. A mixture of 3,3-dimethylindoline[14] (5.89 g, 40.0 mmol) and (2*R*,3*R*)-3-phenylglycidol (6.00 g, 40.0 mmol) was heated neat at 110 °C for 5 h in a sealed reaction vessel. When the mixture was cooled, the crude product was dissolved in ethyl acetate, absorbed on Fluorocil, and purified by Isco column chromatography (silica, 0−60% ethyl acetate/hexane) to give (2*S*,3*S*)-3-(3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (**18o**) as a viscous amber liquid. Yield: 11.02 g (93%). Chiral purity: 99.9% (99.8% ee).

Method h: Ti(O-*i*-Pr)$_4$-Induced Epoxide Ring-Opening of (*R*,*R*)-3-Phenylglycidols 17. To a solution of (2*R*,3*R*)-3-phenylglycidol (9.01 g, 60 mmol) in dichloromethane (80 mL) under nitrogen was added titanium(IV) isopropoxide (19.3 mL, 66 mmol, 1.1 equiv) slowly via a syringe, and the mixture was stirred for 15 min at room temperature. After the mixture was cooled to 0 °C in an ice bath, 7-fluoro-3,3-dimethylindoline (**13f**, 9.91 g, 60 mmol) was added small-portionwise and the mixture was stirred overnight while warming to room temperature. The reaction mixture was poured into aqueous hydrochloric acid solution (2 N, 400 mL) and then extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with water, brine, then dried (anhydrous sodium sulfate), filtered, and concentrated. The crude brown liquid was purified by silica gel chromatography (10−70% ethyl acetate/hexane) to give pure (2*S*,3*S*)-3-(7-fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (**18s**) as an ivory foam. Yield: 15.55 g (82%).

Method i: Tosylation and Amination of Diols 18. To a solution of (2*S*,3*S*)-3-(7-fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (**18s**, 13.63 g, 43.22 mmol) in dichloromethane (150 mL) under nitrogen was added triethylamine (15.2 mL, 109 mmol), and the mixture was cooled to 0 °C in an ice bath. *p*-Toluenesulfonyl chloride (11.13 g, 58.35 mmol) was added small-portionwise, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 5 h. Methylamine (33 wt % in ethanol, 200 mL) was added, and the mixture was stirred at room temperature overnight. All volatiles were removed, and the resulting liquid residue was dissolved in ethyl acetate (300 mL). This solution was washed with aqueous potassium carbonate solution, water, brine, then dried (anhydrous sodium sulfate), filtered, and concentrated. The crude liquid was purified by Isco silica gel chromatography (0−20% methanol/dichloromethane with added 1% triethylamine) to give a viscous, colorless liquid. To a solution of this free base in ethanol (50 mL) was added a solution of hydrochloric acid (1.0 M in ethyl ether, 30 mL) slowly with stirring. Isopropyl ether was added until the mixture became slightly cloudy and then cooled to −25 °C overnight. The white precipitate formed was collected by decatation, washed with isopropyl ether, and dried in vacuo to give (1*S*,2*R*)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride (**9s**). Yield: 8.44 g (54%).

3,3-Dimethyl-5-fluorooxindole (11a). This compound was prepared as described in method a. White crystals. Yield: 1.18 g (50%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (s, 6H), 6.82 (dd, J = 8.5, 4.4 Hz, 1H), 6.98 (ddd, J = 9.7, 8.5, 2.7 Hz, 1H), 7.24 (dd, J = 8.6, 2.7 Hz, 1H), 10.32 (s, 1H). HRMS (ESI): m/z calcd for $[C_{10}H_{10}FNO + H]^+$, 180.0825; found, 180.0832.

3,3-Dimethyl-6-fluorooxindole (11b). This compound was prepared from 6-fluorooxindole according to method a. Yellowish solid. Yield: 41%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (s, 6H), 6.65 (dd, J = 9.4, 2.4 Hz, 1H), 6.75 (m, 1H), 7.29 (dd, J = 8.2, 5.6 Hz, 1H), 10.45 (s, 1H). HRMS (EI): m/z calcd for $[C_{10}H_{10}FNO]^+$, 179.0746; found, 179.0742.

3,3-Dimethyl-7-fluorooxindole (11c). This compound was prepared from 7-fluorooxindole according to method a. White solid. Yield: 48%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (s, 6H), 6.97 (m, 1H), 7.07 (ddd, J = 10.4, 8.4, 0.9 Hz, 1H), 7.14 (dd, J = 7.3, 0.9 Hz, 1H), 10.81 (s, 1H). HRMS (ESI): m/z calcd for $[C_{10}H_{10}FNO + H]^+$, 180.0825; found, 180.0831.

3-Methylindoline (13a). This compound was prepared as described in method c. Colorless liquid. Yield: 5.12 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, J = 6.9 Hz, 3H), 3.11 (t, J = 8.6 Hz, 1H), 3.37 (m, 1H), 3.70 (t, J = 8.6 Hz, 1H), 3.68−3.71 (br, 1H), 6.64 (d, J = 7.7 Hz, 1H), 6.73 (dt, J = 7.4, 0.9 Hz, 1H), 7.02 (dt, J = 7.7, 0.8 Hz, 1H), 7.08 (d, J = 7.3 Hz, 1H). HRMS (ESI): m/z calcd for $[C_9H_{11}N + H]^+$, 134.0964; found, 134.0964.

3-Ethylindoline (13b). This compound was prepared from 3-ethylindole[36] according to method c. Colorless liquid. Yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (t, J = 7.4 Hz, 3H), 1.44 (m, 1H), 1.75 (m, 1H), 3.07 (m, 2H), 3.52 (m, 1H), 5.37 (br s, 1H), 6.46 (d, J = 7.7 Hz, 1H), 6.51 (dt, J = 7.4, 1.0 Hz, 1H), 6.89 (dt, J = 7.5, 0.9 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H). HRMS (EI): m/z calcd for $[C_{10}H_{13}N]^+$, 147.1048; found, 147.1043.

3-Isopropylindoline (13c). This compound was prepared from 3-isopropylindole[36] according to method c. Colorless liquid. Yield: 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.95 (m, 1H), 3.10 (m, 1H), 3.21 (ddd, J = 11.4, 6.3, 2.1 Hz, 1H), 3.40 (dt, J = 9.4, 2.3 Hz, 1H), 5.33 (br s, 1H), 6.45 (d, J = 7.8 Hz, 1H), 6.50 (dt, J = 7.3, 1.0 Hz, 1H), 6.89 (m, 1H), 6.99 (d, J = 7.3 Hz, 1H). MS (ES) m/z 162.2 $[M + H]^+$.

5-Fluoro-3,3-dimethylindoline (13d). This compound was prepared from 3,3-dimethyl-5-fluorooxindole (**11a**) according to method b. Amber liquid. Yield: 86%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (s, 6H), 3.17 (d, J = 2.2 Hz, 2H), 5.32 (br s, 1H), 6.43 (dd, J = 8.4, 4.5 Hz, 1H), 6.70 (m, 1H), 6.84 (dd, J = 8.8, 2.7 Hz, 1H). HRMS (ESI): m/z calcd for $[C_{10}H_{12}FN + H]^+$, 166.1032; found, 166.1024.

6-Fluoro-3,3-dimethylindoline (13e). This compound was prepared from 3,3-dimethyl-6-fluorooxindole (**11b**) according to method b. Colorless liquid. Yield: 79%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (s, 6H), 3.21 (d, J = 1.8 Hz, 2H), 5.72 (br s, 1H), 6.23 (m, 2H), 6.91 (dd, J = 7.9, 6.0 Hz, 1H). HRMS (ESI): m/z calcd for $[C_{10}H_{12}FN + H]^+$, 166.1032; found, 166.1048.

7-Fluoro-3,3-dimethylindoline (13f). This compound was prepared as described in method b. Brown solid. Yield: 93%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (s, 6H), 3.22 (s, 2H), 5.59 (br s, 1H), 6.55 (m, 1H), 6.82 (m, 2H). HRMS (ESI): m/z calcd for $[C_{10}H_{12}FN + H]^+$, 166.1032; found, 166.1040.

***trans*-3-Fluorocinnamic Acid Methyl Ester (15a).** This compound was prepared as described in method d. Colorless oil. Yield: 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.43 (d, J = 16.1 Hz, 1H), 7.08 (m, 1H), 7.29 (m, 3H), 7.64 (d, J = 16.0 Hz, 1H). MS (ES) m/z 180.0 (M^+).

***trans*-3,5-Difluorocinnamic Acid Methyl Ester (15b).** This compound was prepared from *trans*-3,5-difluorocinnamic acid according to method d. White solid. Yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.42 (d, J = 16.0 Hz, 1H), 6.84 (m, 1H), 7.03 (m, 2H), 7.58 (d, J = 16.0 Hz, 1H). HRMS (EI): m/z calcd for $[C_{10}H_8F_2O_2]^+$, 198.0492; found, 198.0489.

***trans*-3-Fluorocinnamyl Alcohol (16a).** This compound was prepared as described in method e. Colorless oil. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, J = 5.6 Hz, 1H), 4.34 (t, J = 4.5 Hz, 2H), 6.37 (td, J = 15.9, 5.5 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.93 (ddt, J = 8.7, 2.6, 0.7 Hz, 1H), 7.08 (ddd, J = 10.1, 2.2, 1.7 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.27 (td, J = 7.9, 6.0 Hz, 1H). MS (ES) m/z 152.0 (M^+).

***trans*-3,5-Difluorocinnamyl Alcohol (16b).** This compound was prepared from *trans*-3,5-difluorocinnamic acid methyl ester (**15b**) according to method e. Colorless oil. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (t, J = 5.7 Hz, 1H), 4.35 (t, J = 5.2 Hz, 2H), 6.37 (td, J = 15.9, 5.2 Hz, 1H), 6.56 (d, J = 15.9 Hz, 1H), 6.68 (tt, J = 8.9, 2.2 Hz, 1H), 6.88 (dd, J = 8.6, 2.0 Hz, 2H). MS (ES) m/z 153.1 $[M + H - H_2O]^+$).

(2*R*,3*R*)-3-(3-Fluorophenyl)glycidol (17a). This compound was prepared as described in method f. Colorless liquid. Yield: 90%. Percent ee: 96.5%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 (dd, J = 7.9, 5.2 Hz, 1H), 3.18 (m, 1H), 3.81 (ddd, J = 13.8, 7.9, 3.7 Hz, 1H), 3.93 (d, J = 2.0 Hz, 1H), 4.05 (ddd, J = 12.8, 5.1, 2.3 Hz, 1H), 6.98 (m, 2H), 7.10 (m, 1H), 7.31 (m, 1H). MS (ESI) m/z 169.1 ($[M + H]^+$).

(2*R*,3*R*)-3-(3,5-Difluorophenyl)glycidol (17b). This compound was prepared from *trans*-3,5-difluorocinnamyl alcohol (**16b**) according to method f. Viscous, colorless liquid. Yield: 70%. Percent ee: 97.9%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 (dd, J = 7.9, 5.1 Hz, 1H), 3.15 (m, 1H), 3.83 (ddd, J = 12.6, 8.1, 3.5 Hz, 1H), 3.93 (d, J = 1.4 Hz, 1H), 4.06 (ddd, J = 12.9, 4.9, 2.3 Hz, 1H), 6.74 (m, 1H), 6.84 (m, 2H). HRMS (EI): m/z calcd for $[C_9H_8F_2O_2]^+$, 186.0492; found, 186.0501.

(2*S*,3*S*)-3-(2,3-Dihydro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (18a). This compound was prepared from indoline and (2*R*,3*R*)-3-phenylglycidol according to method g. Viscous colorless liquid. Yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.80 (m, 2H), 3.21 (q, J = 9.2 Hz, 1H), 3.40 (p, J = 5.6 Hz, 1H), 3.52 (m, 2H), 4.22 (m, 1H), 4.58 (q, J = 5.6 Hz, 2H), 4.71 (d, J = 5.6 Hz, 1H), 6.43 (dt, J = 7.3, 0.9 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 6.90 (m, 2H), 7.20 (m, 1H), 7.28 (m, 2H), 7.38 (m, 2H). HRMS (ESI): m/z calcd for $[C_{17}H_{19}NO_2 + H]^+$, 270.1489; found, 270.1493.

(2*S*,3*S*)-3-(2,3-Dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol (18b). This compound was prepared from indoline and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, colorless liquid. Yield: 75%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.81 (m, 2H), 3.25 (q, J = 9.4 Hz, 1H), 3.40 (p, J = 5.6 Hz, 1H), 3.52 (m, 2H), 4.21 (m, 1H), 4.63 (m, 2H), 4.82 (d, J = 5.6 Hz, 1H), 6.46 (t, J = 7.4 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 6.92 (m, 2H), 7.04 (m, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.32 (q, J = 7.7 Hz, 1H). MS (ESI) m/z 288.1 ($[M + H]^+$).

(2*S*,3*S*)-3-(3-Fluorophenyl)-3-(2-methyl-2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (18c). This compound was prepared from 2-methylindoline and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, amber liquid. Yield: 63%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (d, J = 5.8 Hz, 1.5H), 1.21 (d, J = 6.5 Hz, 1.5H), 2.44 (m, 1H), 3.01 (dd, J = 15.5, 9.1 Hz, 0.5H), 3.11 (dd, J = 15.8, 9.1 Hz, 0.5H), 3.39 (p, J = 5.5 Hz, 0.5H), 3.48 (p, J = 5.5 Hz, 0.5H), 3.58 (m, 1.5H), 3.89 (m, 0.5H), 4.29 (m, 0.5H), 4.37 (m, 0.5H), 4.44 (m, 0.5H), 4.62 (m, 1.5H), 4.82 (d, J = 5.9 Hz, 0.5H), 4.90 (d, J = 5.1 Hz, 0.5H), 6.47 (m, 1.5H), 6.62 (d, J = 7.6 Hz, 0.5H), 6.90 (m, 2H), 7.05 (m, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.29 (m, 2H). HRMS (ESI): m/z calcd for $[C_{18}H_{20}FNO_2 + H]^+$, 302.1551; found, 302.1556.

(2*S*,3*S*)-3-(3-Fluorophenyl)-3-(3-methyl-2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (18d). This compound was prepared from 3-methylindoline (**13a**) and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, amber liquid. Yield: 75%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, J = 6.8 Hz, 1.5H), 1.17 (d, J = 6.5 Hz, 1.5H), 2.74 (t, J = 9.1 Hz, 0.5H), 3.13 (m, 2H), 3.34−3.56 (m, 4H), 3.69 (t, J = 8.8 Hz, 0.5H), 4.20 (m, 1H), 4.58 (d, J = 7.3 Hz, 0.5H), 4.65 (d, J = 7.9 Hz, 0.5H), 6.47 (m, 1.5H), 6.58 (d, J = 7.8 Hz, 0.5H), 6.92 (m, 2H), 7.04 (m, 1H), 7.20 (m,

2H), 7.31 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{20}FNO_2 + H]^+$, 302.1551; found, 302.1539.

(2*S*,3*S*)-3-(3-Ethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18e). This compound was prepared from 3-ethylindoline (**13b**) and (2*R*,3*R*)-3-(3-fluorophenyl)-glycidol (**17a**) according to method g. Viscous, colorless liquid. Yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.81 (t, J = 7.4 Hz, 1.5H), 0.90 (t, J = 7.4 Hz, 1.5H), 1.27 (m, 0.5 H), 1.45 (m, 0.5 H), 1.61 (m, 0.5 H), 1.71 (m, 0.5 H), 2.91 (t, J = 8.8 Hz, 0.5H), 2.96 (m, 0.5H), 3.06 (m, 0.5 H), 2.23 (dd, J = 7.5, 5.1 Hz, 0.5H), 3.38 (m, 1.5H), 3.48 (m, 1H), 3.68 (t, J = 7.4 Hz, 0.5H), 4.22 (m, 1H), 4.63 (m, 2H), 4.81 (t, J = 5.5 Hz, 1H), 6.48 (m, 2H), 6.93 (m, 2H), 7.04 (m, 1H), 7.20 (m, 2H), 7.32 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{22}FNO_2 + H]^+$, 316.1707; found, 316.1699.

(2*S*,3S)-3-(3-Fluorophenyl)-3-(3-isopropyl-2,3-dihydro-1*H*-indol-1-yl)propane-1,2- diol (18f). This compound was prepared from 3-isopropylindoline (**13c**) and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, colorless liquid. Yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.55 (d, J = 6.8 Hz, 1.5H), 0.80 (d, J = 6.8 Hz, 1.5H), 0.83 (d, J = 6.8 Hz, 1.5H), 0.89 (d, J = 6.8 Hz, 1.5H), 1.86 (m, 1H), 2.95 (m, 0.5H), 3.08 (m, 0.5H), 3.17 (t, J = 9.1 Hz, 0.5H), 3.24 (t, J = 9.7 Hz, 0.5H), 3.37 (m, 1.5H), 3.46 (m, 0.5H), 3.52 (m, 1H), 4.22 (m, 1H), 4.62 (m, 2H), 4.78 (d, J = 5.6 Hz, 0.5H), 4.84 (d, J = 5.6 Hz, 0.5H), 6.46 (m, 1.5H), 6.54 (d, J = 7.9 Hz, 0.5H), 6.92 (m, 2H), 7.03 (m, 1H), 7.18 (m, 2H), 7.31 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{24}FNO_2 + H]^+$, 330.1864; found, 330.1855.

(2*S*,3*S*)-3-(3-Fluorophenyl)-3-(5-methyl-2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (18g). This compound was prepared from 5-methylindoline and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, amber liquid. Yield: 68%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.77 (m, 2H), 3.20 (q, J = 9.2 Hz, 1H), 3.39 (p, J = 5.6 Hz, 1H), 3.49 (m, 2H), 4.19 (m, 1H), 4.56 (d, J = 7.4 Hz, 1H), 4.60 (t, J = 5.5 Hz, 1H), 4.79 (d, J = 5.6 Hz, 1H), 6.40 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.76 (s, 1H), 7.02 (m, 1H), 7.18 (m, 2H), 7.30 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{20}FNO_2 + H]^+$, 302.1551; found, 302.1551.

(2*S*,3*S*)-3-(5-Chloro-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18h). This compound was prepared from 5-chloroindoline and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, amber liquid. Yield: 61%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.85 (m, 2H), 3.30 (q, J = 9.1 Hz, 1H), 3.38 (p, J = 5.6 Hz, 1H), 3.46 (m, 1H), 3.60 (q, J = 8.7 Hz, 1H), 4.18 (m, 1H), 4.60 (d, J = 7.4 Hz, 1H), 4.64 (t, J = 5.5 Hz, 1H), 4.86 (d, J = 5.6 Hz, 1H), 6.48 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 8.3, 2.2 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 7.06 (m, 1H), 7.19 (m, 2H), 7.34 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{17}ClFNO_2 + H]^+$, 322.1005; found, 322.1005.

(2*S*,3*S*)-3-[5-(Benzyloxy)-2,3-dihydro-1*H*-indol-1-yl]-3-(3-fluorophenyl)propane-1,2-diol (18i). This compound was prepared from 5-benzyloxyindoline and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, amber liquid. Yield: 61%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.78 (m, 2H), 3.20 (q, J = 9.1 Hz, 1H), 3.39 (p, J = 5.6 Hz, 1H), 3.48 (m, 2H), 4.18 (m, 1H), 4.51 (d, J = 7.3 Hz, 1H), 4.59 (t, J = 5.5 Hz, 1H), 4.77 (d, J = 5.5 Hz, 1H), 4.93 (s, 2H), 6.40 (d, J = 8.8 Hz, 1H), 6.58 (dd, J = 8.3, 2.2 Hz, 1H), 6.70 (s, 1H), 7.02 (m, 1H), 7.19 (d, J = 7.7 Hz, 2H), 7.26−7.40 (m, 6H). HRMS (ESI): *m*/*z* calcd for $[C_{24}H_{24}FNO_3 + H]^+$, 394.1813; found, 394.1808.

(2*S*,3*S*)-3-(3-Fluorophenyl)-3-(7-methyl-2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (18j). This compound was prepared from 7-methylindoline and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. White solid. Yield: 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (m, 1H), 2.40 (s, 3H), 2.53 (m, 1H), 3.35 (m, 2H), 3.62 (p, J = 5.6 Hz, 1H), 3.73 (m, 1H), 4.21 (m, 1H), 4.42 (t, J = 5.5 Hz, 1H), 4.70 (d, J = 8.6 Hz, 1H), 4.78 (d, J = 6.2 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 7.4 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 7.01 (m, 2H), 7.22 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{20}FNO_2 + H]^+$, 302.1551; found, 302.1551.

(2*S*,3*S*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18k). This compound was prepared from 3,3-dimethylindoline[14] and (2*R*,3*R*)-3-(3-fluorophenyl)-glycidol (**17a**) according to method g. Viscous, colorless liquid. Yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (s, 3H), 1.17 (s, 3H), 3.01 (d, J = 8.7 Hz, 1H), 3.29 (d, J = 8.7 Hz, 1H), 3.41 (dd, J = 10.9, 5.9 Hz, 1H), 3.51 (dd, J = 10.9, 4.2 Hz, 1H), 4.20 (m, 1H), 4.63 (br s, 1H), 4.64 (d, J = 7.8 Hz, 1H), 4.79 (br s, 1H), 6.46 (dt, J = 7.4, 0.9 Hz, 1H), 6.53 (d, J = 7.9 Hz, 1H), 6.92 (m, 2H), 7.04 (m, 1H), 7.20 (m, 2H), 7.33 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{22}FNO_2 + H]^+$, 316.1713; found, 316.1713.

(2*S*,3*S*)-3-(3,3-Diethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18l). This compound was prepared from 3,3-diethylindoline[14] and (2*R*,3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, colorless liquid. Yield: 55%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.48 (t, J = 7.4 Hz, 3H), 0.72 (t, J = 7.4 Hz, 3H), 1.35−1.57 (m, 4H), 3.09 (d, J = 9.4 Hz, 1H), 3.28 (d, J = 9.4 Hz, 1H), 3.40 (p, J = 5.5 Hz, 1H), 3.51 (m, 1H), 4.21 (m, 1H), 4.63 (m, 2H), 4.80 (d, J = 5.8 Hz, 1H), 6.47 (t, J = 7.4 Hz, 1H), 6.51 (d, J = 7.9 Hz, 1H), 6.81 (dd, J = 7.2, 1.0 Hz, 1H), 6.91 (dt, J = 7.8, 1.3 Hz, 1H), 7.04 (m, 1H), 7.17 (m, 2H), 7.32 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{21}H_{26}FNO_2 + H]^+$, 344.2020; found, 344.2019.

(2*S*,3*S*)-3-(3-Fluorophenyl)-3-spiro[cyclopentane-1,3′-indol]-1′(2′*H*)-ylpropane-1,2-diol (18m). This compound was prepared from 1′,2′-dihydrospiro[cyclopentane-1,3′-indole][14] and (2*R*, 3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Amber gum. Yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43−1.82 (m, 8H), 3.03 (d, J = 8.9 Hz, 1H), 3.35 (d, J = 8.9 Hz, 1H), 3.39 (m, 1H), 3.50 (m, 1H), 4.20 (m, 1H), 4.63 (d, J = 7.7 Hz, 2H), 4.79 (d, J = 5.4 Hz, 1H), 6.50 (m, 2H), 6.91 (m, 2H), 7.04 (m, 1H), 7.19 (m, 2H), 7.32 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{21}H_{24}FNO_2 + H]^+$, 342.1864; found, 342.1862.

(2*S*,3*S*)-3-(3-Fluorophenyl)-3-spiro[cyclohexane-1,3′-indol]-1′(2′H)-ylpropane-1,2-diol (18n). This compound was prepared from 1′,2′-dihydrospiro[cyclohexane-1,3′-indole][14] and (2*R*, 3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. White solid. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13−1.74 (m, 10H), 2.19 (br, 2H), 2.98 (d, J = 8.9 Hz, 1H), 3.33 (d, J = 8.9 Hz, 1H), 3.76 (dd, J = 11.2, 5.9 Hz, 1H), 3.91 (dd, J = 11.2, 3.5 Hz, 1H), 4.45 (m, 1H), 4.72 (d, J = 9.2 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.98 (m, 2H), 7.03−7.18 (m, 3H), 7.32 (m, 1H). HRMS (ESI): *m*/*z* calcd for $[C_{22}H_{26}FNO_2 + H]^+$, 356.2020; found, 356.2031.

(2*S*,3*S*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (18o). This compound was prepared as described in method g. Viscous amber liquid. Yield: 93%. Chiral purity: 99.9% (99.8% ee). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (s, 3H), 1.16 (s, 3H), 2.99 (d, J = 8.7 Hz, 1H), 3.27 (d, J = 8.7 Hz, 1H), 3.41 (p, J = 5.9 Hz, 1H), 3.54 (m, 1H), 4.21 (m, 1H), 4.58 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 8.5 Hz, 1H), 4.68 (d, J = 5.6 Hz, 1H), 6.47 (dt, J = 7.4, 0.9 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.90 (m, 2H), 7.20 (m, 1H), 7.29 (m, 2H), 7.38 (m, 2H). HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{23}NO_2 + H]^+$, 298.1807; found, 298.1807.

(2*S*,3*S*)-3-(3,5-Difluorophenyl)-3-(3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (18p). This compound was prepared from 3,3-dimethylindoline[14] and (2*R*,3*R*)-3-(3,5-difluorophenyl)glycidol (**17b**) according to method g. Viscous, amber liquid. Yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (s, 3H), 1.18 (s, 3H), 3.04 (d, J = 8.7 Hz, 1H), 3.31 (d, J = 8.7 Hz, 1H), 3.41 (p, J = 5.6 Hz, 1H), 3.49 (m, 1H), 3.18 (m, 1H), 4.66 (m, 2H), 4.88 (d, J = 5.6 Hz, 1H), 6.53 (m, 2H), 6.92 (m, 2H), 7.08 (m, 3H). HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{21}F_2NO_2 + H]^+$, 334.1613; found, 334.1619.

(2*S*,3*S*)-3-(5-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18q). This compound was prepared from 5-fluoro-3,3-dimethylindoline (**13d**) and (2*R*, 3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g.

Viscous, colorless liquid. Yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (s, 3H), 1.18 (s, 3H), 3.04 (d, J = 8.8 Hz, 1H), 3.30 (d, J = 8.8 Hz, 1H), 3.40 (p, J = 5.6 Hz, 1H), 3.49 (m, 1H), 4.17 (m, 1H), 4.58 (d, J = 7.5 Hz, 1H), 4.63 (t, J = 5.6 Hz, 1H), 4.79 (d, J = 5.6 Hz, 1H), 6.46 (dd, J = 8.6, 4.2 Hz, 1H), 6.72 (ddd, J = 11.3, 8.6, 2.7 Hz, 1H), 6.82 (dd, J = 8.6, 2.7 Hz, 1H), 7.04 (m, 1H), 7.20 (m, 2H), 7.32 (m, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{21}F_2NO_2 + H]^+$, 334.1613; found, 334.1606.

(2*S*,3*S*)-3-(6-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18r). This compound was prepared from 6-fluoro-3,3-dimethylindoline (**13e**) and (2*R*, 3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method g. Viscous, amber liquid. Yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (s, 3H), 1.17 (s, 3H), 3.06 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 3.39 (m, 1H), 3.48 (m, 1H), 4.18 (m, 1H), 4.62 (d, J = 7.7 Hz, 1H), 4.66 (t, J = 5.5 Hz, 1H), 4.83 (d, J = 5.6 Hz, 1H), 6.21 (ddd, J = 11.9, 8.0, 2.3 Hz, 1H), 6.35 (dd, J = 11.2, 2.2 Hz, 1H), 6.86 (dd, J = 7.9, 5.9 Hz, 1H), 7.07 (m, 1H), 7.24 (m, 2H), 7.34 (m, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{21}F_2NO_2 + H]^+$, 334.1613; found, 334.1597.

(2*S*,3*S*)-3-(7-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (18s). This compound was prepared as described in method h. Ivory foam. Yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 3H), 1.14 (s, 3H), 2.91 (d, J = 9.2 Hz, 1H), 3.24 (d, J = 9.2 Hz, 1H), 3.37 (br, 1H), 3.51 (dd, J = 10.9, 6.1 Hz, 1H), 3.69 (dd, J = 10.9, 3.4 Hz, 1H), 4.22 (m, 1H), 4.63 (br, 1H), 4.99 (dd, J = 9.1, 1.7 Hz, 1H), 6.53 (ddd, J = 8.1, 7.3, 4.3 Hz, 1H), 6.75 (dd, J = 7.3, 1.0 Hz, 1H), 6.85 (ddd, J = 13.4, 8.2, 1.0 Hz, 1H), 7.22 (m, 1H), 7.31 (m, 4H). HRMS (ESI): m/z calcd for $[C_{19}H_{22}FNO_2 + H]^+$, 316.1707; found, 316.1690.

(2*S*,3*S*)-3-(7-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (18t). This compound was prepared from 7-fluoro-3,3-dimethylindoline (**13f**) and (2*R*, 3*R*)-3-(3-fluorophenyl)glycidol (**17a**) according to method h. Viscous, amber liquid. Yield: 74%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 3H), 1.15 (s, 3H), 2.92 (d, J = 9.4 Hz, 1H), 3.28 (d, J = 9.4 Hz, 1H), 3.51 (p, J = 5.6 Hz, 1H), 3.64 (m, 1H), 4.20 (m, 1H), 4.61 (t, J = 5.6 Hz, 1H), 4.80 (d, J = 6.2 Hz, 1H), 5.02 (dd, J = 8.8, 1.5 Hz, 1H), 6.55 (ddd, J = 8.1, 7.3, 4.2 Hz, 1H), 6.78 (dd, J = 7.3, 1.0 Hz, 1H), 6.86 (ddd, J = 13.3, 8.2, 1.0 Hz, 1H), 7.06 (m, 1H), 7.14 (m, 2H), 7.35 (m, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{21}F_2NO_2 + H]^+$, 334.1613; found, 334.1616.

(1*S*,2*R*)-1-(2,3-Dihydro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol Hydrochloride (9a). This compound was prepared from **18a** according to method i. White powder. Yield: 28%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (t, J = 5.4 Hz, 3H), 2.76−2.96 (m, 3H), 3.03 (dd, J = 18.8, 10.1 Hz, 1H), 3.32 (m, 1H), 3.51 (dt, J = 8.7, 4.4 Hz, 1H), 4.60 (dt, J = 9.4, 2.2 Hz, 1H), 4.65 (d, J = 9.4 Hz, 1H), 5.82 (br, 1H), 6.50 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 7.26 (m, 1H), 7.33 (m, 4H), 8.62 (br, 1H), 8.77 (br, 1H). HRMS (ESI): m/z calcd for $[C_{18}H_{22}N_2O + H]^+$, 283.1805; found, 283.1810.

(1*S*,2*R*)-1-(2,3-Dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9b). This compound was prepared from **18b** according to method i. White powder. Yield: 41%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (t, J = 5.4 Hz, 3H), 2.75−2.97 (m, 3H), 3.03 (dd, J = 18.7, 10.0 Hz, 1H), 3.30 (m, 1H), 3.54 (dt, J = 8.6, 4.6 Hz, 1H), 4.60 (dt, J = 9.4, 2.2 Hz, 1H), 4.69 (d, J = 9.2 Hz, 1H), 6.18 (br, 1H), 6.52 (dt, J = 7.3, 0.7 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 7.10 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 8.68 (br, 1H), 8.84 (br, 1H). HRMS (ESI): m/z calcd for $[C_{18}H_{21}FN_2O + H]^+$, 301.1711; found, 301.1716.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1*H*-indol-1-yl)propan-2-ol Hydrochloride (9c). This compound was prepared from **18c** according to method i. White powder. Yield: 57%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (d, J = 6.1 Hz, 1.5H), 1.25 (d, J = 6.1 Hz, 1.5H), 2.45 (m, 1H), 2.60 (t, J = 5.6 Hz, 1.5H), 2.62 (t, J = 5.6 Hz, 1.5H), 2.88−3.05 (m, 1H), 2.96 (dd, J = 15.7, 8.8 Hz, 0.5H), 3.11 (dd, J = 15.9, 9.2 Hz, 0.5H), 3.15 (m, 0.5H), 3.27 (m, 0.5H), 3.38 (m, 0.5H), 3.80 (m, 0.5H), 4.32 (d, J = 9.4 Hz, 0.5H), 4.64 (dt, J = 9.4, 2.1 Hz, 0.5H), 4.76 (d, J = 9.9 Hz, 0.5H), 4.88 (dt, J = 9.4, 2.1 Hz, 0.5H), 5.43 (br, 1H), 6.54 (t, J = 7.3 Hz, 0.5H), 6.58 (t, J = 7.3 Hz, 0.5H), 6.70 (d, J = 8.1 Hz, 0.5H), 6.74 (d, J = 7.9 Hz, 0.5H), 6.94 (m, 1H), 7.03 (t, J = 7.8 Hz, 0.5H), 7.06−7.14 (m, 2.5H), 7.28 (m, 1H), 7.36 (m, 1H), 8.57 (br, 0.5H), 8.63 (br, 0.5H), 8.79 (br, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{23}FN_2O + H]^+$, 315.1867; found, 315.1850.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1*H*-indol-1-yl)propan-2-ol Hydrochloride (9d). This compound was prepared from **18d** according to method i. White powder. Yield: 33%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, J = 6.6 Hz, 1.5H), 1.16 (d, J = 6.8 Hz, 1.5H), 2.53 (m, 0.5H), 2.59 (t, J = 5.3 Hz, 1.5H), 2.60 (t, J = 5.3 Hz, 1.5H), 2.90 (m, 1H), 3.05−3.21 (m, 2H), 3.27 (t, J = 8.8 Hz, 0.5H), 3.30 (m, 0.5H), 3.67 (t, J = 8.6 Hz, 0.5H), 4.61 (m, 1H), 4.69 (m, 1H), 6.08 (br, 1H), 6.54 (t, J = 7.4 Hz, 0.5H), 6.56 (t, J = 7.4 Hz, 0.5H), 6.71 (d, J = 7.8 Hz, 0.5H), 6.82 (d, J = 7.9 Hz, 0.5H), 6.94−7.02 (m, 2H), 7.10 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 8.73 (br, 1H), 8.97 (br, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{23}FN_2O + H]^+$, 315.1867; found, 315.1881.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-[(3*S*)-3-methyl-2,3-dihydro-1*H*-indol-1-yl]propan-2-ol Hydrochloride (9d-Isomer 1). Diastereomeric mixture of (1*S*,2*R*)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1*H*-indol-1-yl)propan-2-ol hydrochloride (**9d**) was dissolved in methanol, and the resulting solution was injected onto the supercritical fluid chromatography (SFC) instrument with a volume of 1.0 mL per injection. The baseline resolved diastereomers were collected using a Berger MultiGram Prep SFC (Berger Instruments, Inc., Newark, DE) under the following conditions: Chiralpak AD-H SFC column (5 μm, 250 mm length × 20 mm i.d., Chiral Technologies, Inc., Exton, PA), 35 °C column temperature, 10% MeOH with 0.2% DEA as CO_2 modifier, 50 mL/min flow rate, 100 bar outlet pressure, 254 nm UV detection. The chiral purity of each diastereomer was determined under the same SFC conditions using a Chiralcel OD column (10 μm, 250 mm length × 4.6 mm i.d.) at 2.0 mL/min flow rate on a Berger Analytical SFC instrument. (1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-[(3*S*)-3-methyl-2,3-dihydro-1*H*-indol-1-yl]propan-2-ol was isolated as peak 1 with >99.8% diastereomeric purity and was subjected to hydrochloride salt formation in an analogous manner described in method i to give **9d**-isomer 1 as a white powder. The stereochemistry at the C3 position of the indoline ring was arbitrarily assigned. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, J = 6.8 Hz, 3H), 2.53 (m, 1H), 2.61 (t, J = 5.3 Hz, 3H), 2.92 (m, 1H), 3.18 (m, 1H), 3.31 (m, 1H), 3.66 (t, J = 8.6 Hz, 1H), 3.81 (br, 1H), 4.61 (t, J = 7.8 Hz, 1H), 4.71 (d, J = 9.4 Hz, 1H), 6.56 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.10 (dt, J = 8.6, 1.9 Hz, 1H), 7.20 (m, 2H), 7.38 (m, 1H), 8.73 (br, 1H), 8.92 (br, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{23}FN_2O + H]^+$, 315.1867; found, 315.1869.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-[(3*R*)-3-methyl-2,3-dihydro-1*H*-indol-1-yl]propan-2-ol Hydrochloride (9d-Isomer 2). (1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-[(3*R*)-3-methyl-2,3-dihydro-1*H*-indol-1-yl]propan-2-ol was isolated as peak 2 from the above HPLC separation of diastereomers with >99.8% diastereomeric purity and was subjected to hydrochloride salt formation in an analogous manner described in method i to give **9d**-isomer 2 as a white powder. The stereochemistry at the C3 position of the indoline ring was arbitrarily assigned. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (d, J = 6.5 Hz, 3H), 2.60 (t, J = 5.3 Hz, 3H), 2.90 (m, 1H), 3.11−3.17 (m, 3H), 3.27 (t, J = 8.6 Hz, 1H), 3.80 (br, 1H), 4.61 (t, J = 7.6 Hz, 1H), 4.67 (d, J = 8.8 Hz, 1H), 6.54 (t, J = 7.3 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.96 (d, J = 7.4 Hz, 1H), 6.99 (t, J = 8.2 Hz, 1H), 7.10 (m, 1H), 7.22 (m, 2H), 7.37 (m, 1H), 8.69 (br, 1H), 8.93 (br, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{23}FN_2O + H]^+$, 315.1867; found, 315.1867.

(1*S*,2*R*)-1-(3-Ethyl-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9e). This compound was prepared from **18e** according to method i. White powder. Yield: 61%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.74 (t, J = 7.4 Hz, 1.5H), 0.85 (t, J = 7.4 Hz, 1.5H), 1.18 (m, 1H), 1.43 (m, 1H), 2.54 (t, J = 5.4 Hz, 1.5H), 2.56 (t, J = 5.4 Hz, 1.5H), 2.85 (m, 2H), 2.99−3.28 (m, 2.5H), 3.58 (t, J = 8.8 Hz, 0.5H), 4.55 (m, 1H), 4.63 (m, 1H), 5.70 (br, 1H), 6.47 (t, J = 6.8 Hz, 0.5H), 6.49 (t, J = 6.9 Hz, 0.5H), 6.69 (d, J = 7.8 Hz, 0.5H), 6.73 (d, J = 7.9 Hz, 0.5H), 6.89−6.96 (m, 2H), 7.03 (m, 1H), 7.13 (m, 2H), 7.32 (m, 1H), 8.58 (br, 1H), 8.68 (br, 0.5H), 8.79 (br, 0.5H). HRMS (ESI): m/z calcd for $[C_{20}H_{25}FN_2O + H]^+$, 329.2024; found, 329.2023.

(1*S*,2*R*)-1-(3-Fluorophenyl)-1-(3-isopropyl-2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)propan-2-ol Hydrochloride (9f). This compound was prepared from **18f** according to method i. White powder. Yield: 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.37 (d, J = 6.9 Hz, 1.5H), 0.75 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 1.5H), 1.75 (m, 0.5H), 1.86 (m, 0.5H), 2.53 (t, J = 5.6 Hz, 1.5H), 2.55 (t, J = 5.5 Hz, 1.5H), 2.80−2.93 (m, 2H), 3.03 (t, J = 9.6 Hz, 0.5H), 3.06 (m, 1H), 3.19 (m, 0.5H), 3.31 (m, 0.5H), 3.42 (t, J = 9.6 Hz, 0.5H), 4.52−4.67 (m, 2H), 5.73 (br, 1H), 6.47 (t, J = 7.3 Hz, 1H), 6.69 (d, J = 8.0 Hz, 0.5H), 6.72 (d, J = 8.0 Hz, 0.5H), 6.89 (d, J = 7.3 Hz, 1H), 6.94 (m, 1H), 7.03 (m, 1H), 7.14 (m, 2H), 7.31 (m, 1H), 8.63 (br, 1H), 8.74 (br, 0.5H), 8.94 (br, 0.5H). HRMS (ESI): m/z calcd for $[C_{21}H_{27}FN_2O + H]^+$, 343.2180; found, 343.2191.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1*H*-indol-1-yl)propan-2-ol Hydrochloride (9g). This compound was prepared from **18g** according to method i. White powder. Yield: 57%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H), 2.61 (t, J = 5.4 Hz, 3H), 2.73−2.82 (m, 2H), 2.91 (m 1H), 2.98 (dd, J = 18.7, 10.1 Hz, 1H), 3.30 (m, 1H), 3.48 (dt, J = 8.6, 4.6 Hz, 1H), 4.57 (dt, J = 9.2, 2.1 Hz, 1H), 4.63 (d, J = 9.2 Hz, 1H), 5.61 (br, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.79 (m, 2H), 7.09 (m, 1H), 7.18 (m, 2H), 7.36 (m, 1H), 8.63 (br, 1H), 8.77 (br, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{23}FN_2O + H]^+$, 315.1867; found, 315.1869.

(1*S*,2*R*)-1-(5-Chloro-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9h). This compound was prepared from **18h** according to method i. White powder. Yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (t, J = 5.4 Hz, 3H), 2.81−2.94 (m, 3H), 3.08 (dd, J = 19.0, 10.0 Hz, 1H), 3.27 (m, 1H), 3.56 (m, 1H), 4.57 (dt, J = 9.4, 2.2 Hz, 1H), 4.67 (d, J = 9.1 Hz, 1H), 4.92 (br, 1H), 6.76 (d, J = 8.2 Hz, 1H), 7.00 (m, 2H), 7.12 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 8.63 (br, 1H), 8.72 (br, 1H). HRMS (ESI): m/z calcd for $[C_{18}H_{20}ClFN_2O + H]^+$, 335.1321; found, 335.1325.

(1*S*,2*R*)-1-[5-(Benzyloxy)-2,3-dihydro-1*H*-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9i). This compound was prepared from **18i** according to method i. White powder. Yield: 73%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (t, J = 5.4 Hz, 3H), 2.77 (m, 2H), 2.89 (m, 1H), 2.98 (dd, J = 18.7, 9.9 Hz, 1H), 3.32 (m, 1H), 3.46 (m, 1H), 4.56 (m, 2H), 4.95 (m, 2H), 5.79 (br, 1H), 6.63−6.72 (m, 2H), 7.10 (m, 2H), 7.18 (m, 2H), 7.29 (m, 1H), 7.33−7.41 (m, 4H), 7.47 (d, J = 8.1 Hz, 1H), 8.61 (br, 1H), 8.73 (br, 1H). HRMS (ESI): m/z calcd for $[C_{25}H_{27}FN_2O_2 + H]^+$, 407.2129; found, 407.2131.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1*H*-indol-1-yl)propan-2-ol Hydrochloride (9j). This compound was prepared from **18j** according to method i. White powder. Yield: 64%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (m, 1H), 2.42 (s, 3H), 2.54 (m, 1H), 2.66 (t, J = 5.4 Hz, 3H), 3.07 (m, 1H), 3.37 (m, 2H), 3.53 (m, 1H), 4.61 (m, 2H), 6.69 (t, J = 7.0 Hz, 1H), 6.82 (d, J = 7.0 Hz, 1H), 6.92 (d, J = 7.2 Hz, 2H), 6.95 (br, 1H), 6.98 (d, J = 10.3 Hz, 1H), 7.08 (dt, J = 8.6, 2.2 Hz, 1H), 7.27 (m, 1H), 8.77 (br, 1H), 8.95 (br, 1H). HRMS (ESI): m/z calcd for $[C_{19}H_{23}FN_2O + H]^+$, 315.1867; found, 315.1862.

(1*S*,2*R*)-1-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9k). This compound was prepared from **18k** according to method i. White powder. Yield: 56%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (s, 3H), 1.17 (s, 3H), 2.60 (t, J = 5.4 Hz, 3H), 2.81 (d, J = 8.7 Hz, 1H), 2.95 (m, 1H), 3.18 (m, 1H), 3.28 (d, J = 8.7 Hz, 1H), 4.19 (br, 1H), 4.61 (dt, J = 9.4, 2.2 Hz, 1H), 4.72 (d, J = 9.2 Hz, 1H), 6.56 (dt, J = 7.4, 0.7 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.94 (dd, J = 7.3, 1.1 Hz, 1H), 6.99 (dt, J = 7.8, 1.2 Hz, 1H), 7.10 (m, 1H), 7.20 (m, 2H), 7.38 (m, 1H), 8.72 (br, 1H), 8.98 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{25}FN_2O + H]^+$, 329.2024; found, 329.2026.

(1*S*,2*R*)-1-(3,3-Diethyl-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9l). This compound was prepared from **18l** according to method i. White powder. Yield: 54%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.41 (t, J = 7.4 Hz, 3H), 0.72 (t, J = 7.4 Hz, 3H), 1.37 (m, 1H), 1.46 (m, 1H), 1.51 (q, J = 7.4 Hz, 2H), 2.61 (t, J = 5.4 Hz, 3H), 2.91 (d, J = 9.4 Hz, 1H), 2.97 (m, 1H), 3.12 (m, 1H), 3.21 (d, J = 9.2 Hz, 1H), 4.58 (t, J = 9.0 Hz, 1H), 4.71 (d, J = 9.4 Hz, 1H), 5.68 (br, 1H), 6.55 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.84 (dd, J = 7.2, 1.0 Hz, 1H), 7.00 (dt, J = 7.8, 1.2 Hz, 1H), 7.10 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 8.60 (br, 1H), 8.69 (br, 1H). HRMS (ESI): m/z calcd for $[C_{22}H_{29}FN_2O + H]^+$, 357.2337; found, 357.2340.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3′-indol]-1′(2′*H*)-ylpropan-2-ol Hydrochloride (9m). This compound was prepared from **18m** according to method i. White powder. Yield: 17%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.44 (m, 2H), 1.63 (m, 1H), 1.68−1.90 (m, 5H), 2.60 (t, J = 5.4 Hz, 3H), 2.81 (d, J = 8.7 Hz, 1H), 2.93 (m, 1H), 3.20 (m, 1H), 3.38 (d, J = 8.7 Hz, 1H), 4.22 (br, 1H), 4.62 (dt, J = 9.4, 2.0 Hz, 1H), 4.71 (d, J = 9.2 Hz, 1H), 6.56 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.94 (dd, J = 7.3, 0.9 Hz, 1H), 6.99 (dt, J = 7.8, 1.2 Hz, 1H), 7.11 (m, 1H), 7.20 (m, 2H), 7.36 (m, 1H), 8.72 (br, 1H), 9.06 (br, 1H). HRMS (ESI): m/z calcd for $[C_{22}H_{27}FN_2O + H]^+$, 355.2180; found, 355.2178.

(1*S*,2*R*)-1-(3-Fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3′-indol]-1′(2′*H*)-ylpropan-2-ol Hydrochloride (9n). This compound was prepared from **18n** according to method i. White powder. Yield: 46%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17−1.38 (m, 4H), 1.47−1.68 (m, 6H), 2.60 (t, J = 5.4 Hz, 3H), 2.86 (d, J = 9.2 Hz, 1H), 2.94 (m, 1H), 3.14 (m, 1H), 3.50 (d, J = 9.4 Hz, 1H), 4.68 (m, 2H), 5.59 (br, 1H), 6.54 (t, J = 7.3 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.93 (dd, J = 7.3, 0.9 Hz, 1H), 6.98 (dt, J = 7.8, 1.2 Hz, 1H), 7.10 (m, 1H), 7.22 (m, 2H), 7.38 (m, 1H), 8.73 (br, 1H), 9.01 (br, 1H). HRMS (ESI): m/z calcd for $[C_{23}H_{29}FN_2O + H]^+$, 369.2337; found, 369.2332.

(1*S*,2*R*)-1-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol Hydrochloride (9o). This compound was prepared from **18o** according to method i. White powder. Yield: 59%. Chiral purity: 99.3% (98.6%ee). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (s, 3H), 1.16 (s, 3H), 2.60 (t, J = 5.4 Hz, 3H), 2.80 (d, J = 8.7 Hz, 1H), 2.95 (m, 1H), 3.20 (m, 1H), 3.26 (d, J = 8.7 Hz, 1H), 4.61 (dt, J = 9.4, 2.2 Hz, 1H), 4.67 (d, J = 9.4 Hz, 1H), 5.42 (br, 1H), 6.54 (dt, J = 7.4, 0.6 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.92 (dd, J = 7.2, 1.0 Hz, 1H), 6.99 (dd, J = 7.8, 1.3 Hz, 1H), 7.26 (m, 1H), 7.34 (m, 4H), 8.70 (br, 1H), 8.98 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{26}N_2O + H]^+$, 311.2118; found, 311.2122.

(1*S*,2*R*)-1-(3,5-Difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)propan-2-ol Hydrochloride (9p). This compound was prepared from **18p** according to method i. White powder. Yield: 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (s, 3H), 1.17 (s, 3H), 2.60 (t, J = 5.4 Hz, 3H), 2.84 (d, J = 8.8 Hz, 1H), 2.94 (m, 1H), 3.17 (m, 1H), 3.28 (d, J = 8.7 Hz, 1H), 4.52 (br, 1H), 4.58 (dt, J = 9.5, 2.3 Hz, 1H), 4.72 (d, J = 9.2 Hz, 1H), 6.58 (t, J = 7.3 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.96 (dd, J = 7.3, 1.0 Hz, 1H), 7.00 (dt, J = 7.8, 1.2 Hz, 1H), 7.08−7.18 (m, 3H), 8.70 (br, 1H), 8.88 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{24}F_2N_2O + H]^+$, 347.1929; found, 347.1929.

(1*S*,2*R*)-1-(5-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9q). This compound was prepared from **18q** according to method i. White powder. Yield: 57%. ^{1}H NMR (400 MHz,

DMSO-d_6): δ 1.11 (s, 3H), 1.17 (s, 3H), 2.61 (t, J = 5.4 Hz, 3H), 2.83 (d, J = 8.8 Hz, 1H), 2.94 (m, 1H), 3.19 (m, 1H), 3.26 (d, J = 8.7 Hz, 1H), 3.96 (br, 1H), 4.55 (m, 1H), 4.65 (d, J = 9.1 Hz, 1H), 6.74 (dd, J = 8.6, 4.3 Hz, 1H), 6.79 (m, 1H), 6.84 (m, 1H), 7.11 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 8.61 (br, 1H), 8.71 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{24}F_2N_2O + H]^+$, 347.1929; found, 347.1940.

(1*S*,2*R*)-1-(6-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9r). This compound was prepared from **18r** according to method i. White powder. Yield: 24%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (s, 3H), 1.17 (s, 3H), 2.60 (t, J = 5.4 Hz, 3H), 2.87 (d, J = 9.0 Hz, 1H), 2.94 (m, 1H), 3.14 (m, 1H), 3.35 (d, J = 8.8 Hz, 1H), 4.58 (t, J = 9.1, 1H), 4.72 (d, J = 9.1 Hz, 1H), 5.75 (br, 1H), 6.28 (ddd, J = 10.1, 8.1, 2.3 Hz, 1H), 6.66 (dd, J = 11.2, 2.2 Hz, 1H), 6.90 (dd, J = 8.1, 6.0 Hz, 1H), 7.13 (dt, J = 9.1, 2.0 Hz, 1H), 7.24 (m, 2H), 7.39 (m, 1H), 8.68 (br, 1H), 8.86 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{24}F_2N_2O + H]^+$, 347.1929; found, 347.1914.

(1*S*,2*R*)-1-(7-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol Hydrochloride (9s). This compound was prepared as described in method i. White powder. Yield: 54%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 3H), 1.16 (s, 3H), 2.63 (t, J = 5.3 Hz, 3H), 2.81 (d, J = 9.4 Hz, 1H), 2.93 (m, 1H), 3.29 (d, J = 9.2 Hz, 1H), 3.30 (m, 1H), 4.55 (m, 1H), 4.92 (dd, J = 10.1, 2.0 Hz, 1H), 5.57 (br, 1H), 6.61 (dt, J = 8.1, 4.3 Hz, 1H), 6.79 (dd, J = 7.3, 0.9 Hz, 1H), 6.92 (ddd, J = 13.4, 8.2, 0.9 Hz, 1H), 7.22 (m, 3H), 7.30 (m, 2H), 8.65 (br, 1H), 9.04 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{25}FN_2O + H]^+$, 329.2024; found, 329.2021.

(1*S*,2*R*)-1-(7-Fluoro-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol Hydrochloride (9t). This compound was prepared from **18t** according to method i. White powder. Yield: 68%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 3H), 1.16 (s, 3H), 2.64 (t, J = 5.4 Hz, 3H), 2.82 (d, J = 9.2 Hz, 1H), 3.00 (m, 1H), 3.29 (d, J = 9.2 Hz, 1H), 3.34 (m, 1H), 4.57 (m, 1H), 4.92 (dd, J = 10.0, 2.0 Hz, 1H), 5.64 (d, J = 7.7 Hz, 1H), 6.64 (dt, J = 8.1, 4.3 Hz, 1H), 6.82 (dd, J = 7.4, 0.9 Hz, 1H), 6.93 (ddd, J = 13.3, 8.2, 0.9 Hz, 1H), 7.13 (m, 3H), 7.40 (m, 1H), 8.67 (br, 1H), 8.88 (br, 1H). HRMS (ESI): m/z calcd for $[C_{20}H_{24}F_2N_2O + H]^+$, 347.1929; found, 347.1935.

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