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Article

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Design, Synthesis and Biological Evaluation of Indoline and Indole Derivatives as Potent and Selective α_{1A}-Adrenoceptor Antagonists

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Abstract: A series of indoline and indole derivatives were designed, synthesized and evaluated as selective α_{1A}-adrenergic receptor (α_{1A}-AR) antagonists for the treatment of benign prostatic hyperplasia (BPH). In this study, two highly selective and potent α_{1A}-AR antagonists, compounds (*R*)-**14r** (IC_{50} = 2.7 nM, α_{1B}/α_{1A} = 640.1, α_{1D}/α_{1A} = 408.2) and (*R*)-**23l** (IC_{50} = 1.9 nM, α_{1B}/α_{1A} = 1506, α_{1D}/α_{1A} = 249.6), which exhibited similar activities and better selectivities in cell-based calcium assays as compared with the marketed drug silodosin (IC_{50} = 1.9 nM, α_{1B}/α_{1A} = 285.9, α_{1D}/α_{1A} = 14.4), were identified. In the functional assays with isolated rat tissues, compounds (*R*)-**14r** and (*R*)-**23l** also showed high potency

and uroselectivity. Most importantly, (*R*)-**14r** and (*R*)-**23l** can significantly decrease the micturition frequency and increase the mean voided volume of the BPH rats in a dose-dependent manner, making them worthy of further investigation for the development of anti-BPH agents.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases of middle and old aged men.[1-3] It is also the main cause of lower urinary tract symptoms (LUTS) in males.[4] LUTS can be categorized into filling or irritative symptoms (increased frequency of urination, increased urgency of urination, painful urination, and excessive passage of urine at night) and voiding or obstructive symptoms (poor stream, hesitancy, terminal dribbling, incomplete voiding, and overflow incontinence).[5] The irritative and obstructive symptoms seriously affect the health and quality of life of patients.[6-8] Medical therapy and surgery are two common treatments for LUTS associated with BPH, and medical therapy is the first line treatment for most patients.[9-15] Among the available medical therapies, α-adrenergic receptor (α-AR) antagonists are an important class of drugs that can relieve the obstructive symptoms of BPH via relaxing the smooth muscle tone of the lower urinary tract.[16-20]

The α-ARs are members of the G protein-coupled receptor (GPCR) superfamily, α_1 and α_2 are the two subtypes of α-ARs. In particular, three distinct α_1-AR subtypes, namely α_{1A}, α_{1B} and α_{1D}, have been characterized by molecular cloning and functional studies,[21-24] and they are different in tissue distribution and biological functions.[25-27] The α_{1A}-AR is predominantly expressed in the bladder neck, prostate and prostatic urethra,[28-29] and blockade of this subtype

can alleviate BPH symptoms by relaxation of the lower urinary tract.[30-31] The α_{1B} subtype is extensively expressed in vascular smooth muscle, and antagonism of this receptor can lead to cardiovascular side effects such as orthostatic hypotension, tachycardia, arrhythmia and dizziness.[32-34] The α_{1D}-AR is widely found in the bladder detrusor and epicardial coronary arteries, thus α_{1D}-AR blockers can relieve voiding symptoms but at the risk of causing coronary vasodilation.[35-37] Collectively, antagonists with better selectivities for α_{1A}-AR over α_{1B}-AR and α_{1D}-AR may alleviate the symptoms associated with BPH efficiently without causing significant cardiovascular side effects.

To date, three generations of α-AR antagonists have been developed, and seven α-AR antagonists have been approved by US Food and Drug Administration for the treatment of BPH. The first generation is nonselective α-AR antagonists such as phenoxybenzamine;[38] the second generation is nonselective α_1-AR antagonists such as prazosin,[39] terazosin,[40] doxazosin[41] and alfuzosin;[42] the third generation is selective α_{1A}-AR antagonists such as tamsulosin[43-45] and silodosin.[46-52] Compared with the first and second generation antagonists, the third generation antagonists improve the BPH symptoms with minimal cardiovascular side effects, due to their selective blockade of the α_{1A}-AR present in the lower urinary tract but avoiding the antagonism of the receptors in vascular smooth muscle. It is worth noting that silodosin exhibits unprecedented selectivities for α_{1A}-AR over both α_{1B}-AR and α_{1D}-AR among the currently marketed drugs.

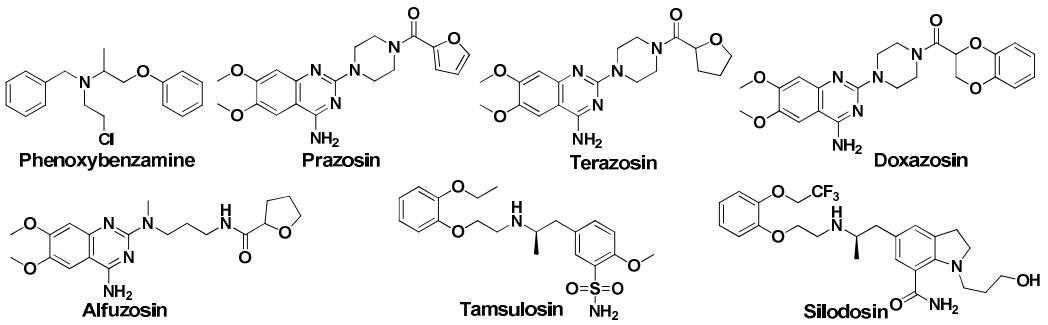


Figure 1. Marketed α-AR antagonists.

Results and Discussion

Design of the target compounds. Although silodosin is a marketed drug used for the treatment of BPH, there is very limited report on the structure-activity relationship of silodosin. Besides, silodosin is still associated with cardiovascular side effects such as orthostatic hypotension and dizziness. Therefore, structural modification of silodosin was carried out in this paper to improve its selectivity to reduce cardiovascular side effects. We hypothesized that the R substituents on the benzene ring might modulate the antagonist activities and subtype selectivities of the compounds (Figure 2). Therefore, we designed indoline derivatives (**14**) of silodosin to evaluate the influence of the R substituents on the antagonist activities and subtype selectivities. We also designed indole derivatives (**23**) using a scaffold hopping strategy based on the structure of silodosin in order to identify more potent and selective α_{1A}-AR antagonists. In this paper, we report the design, synthesis and biological evaluation of indoline and indole derivatives as potent and selective α_{1A}-AR antagonists.

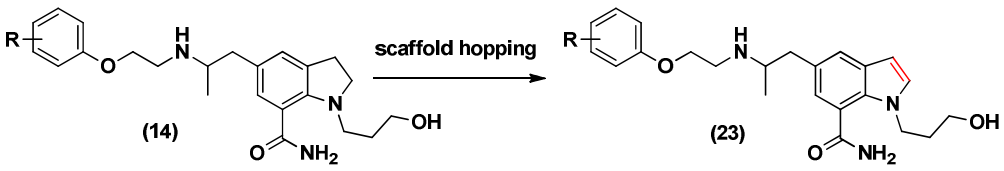
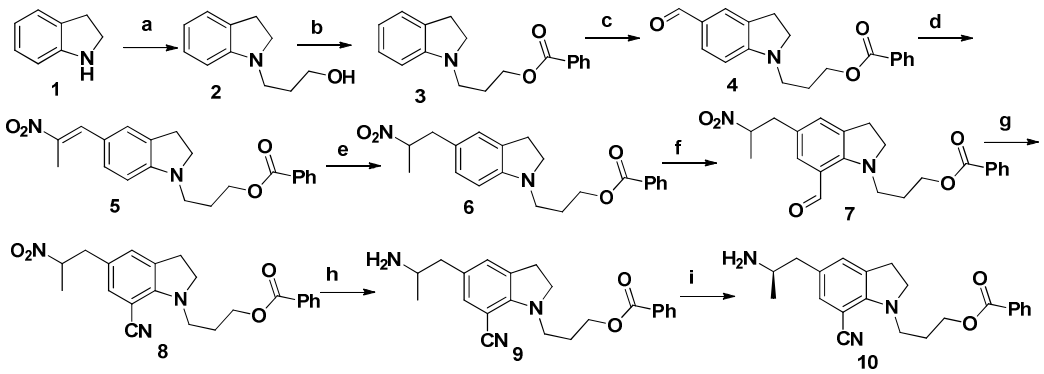


Figure 2. Design and modification strategies of the target compounds.

Synthesis procedures of the target compounds. The synthetic approach for the preparation of the key intermediates **9** and **10** is outlined in Scheme 1. Nucleophilic substitution of indoline with 3-bromo-1-propanol in the presence of K_2CO_3 provided compound **2** in 85% yield, which was acylated with benzoyl chloride to give intermediate **3**. Intermediate **3** was subjected to Vilsmeier-Haack reaction to yield the aldehyde **4**, which was condensed with $CH_3CH_2NO_2$ to form compound **5**. Reduction of **5** with sodium borohydride produced compound **6** in high yield, and subsequent formylation of **6** in the presence of DMF and $POCl_3$ produced the aldehyde **7**. Condensation of **7** with hydroxylamine hydrochloride gave intermediate **8**. Hydrogenation of **8** provided the key intermediate **9** in 93% yield, and the resolution of **9** using L-(+)-tartaric acid produced the key intermediate **10**.

Scheme 1. Synthesis of the key intermediates **9** and **10**[a]

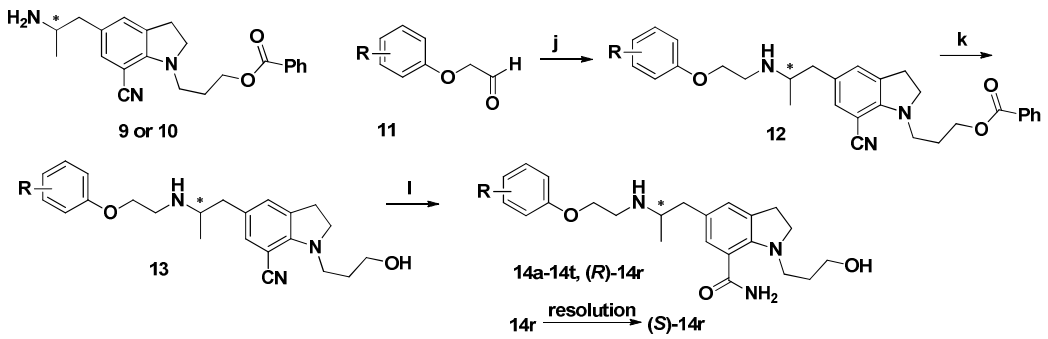


[a]Reagents and conditions: (a) 3-bromo-1-propanol, K_2CO_3, CH_3CN, 90 °C, 12 h; (b) benzoyl chloride, NEt_3, DCM, 0 °C-25 °C, 8 h; (c) DMF, $POCl_3$, DCE, 0 °C-80 °C, 2 h; (d)

$CH_3CH_2NO_2$, CH_3COONH_4, CH_3COOH, 80 ^oC, 4 h; (e) $NaBH_4$, MeOH, 0 ^oC-25 ^oC, 1 h; (f) DMF, $POCl_3$, 0 ^oC-80 ^oC, 2 h; (g) hydroxylamine hydrochloride, Py, Ac_2O, THF, 70 ^oC, 36 h; (h) Pd/C, H_2, MeOH:THF = 1:1, 40 ^oC, 48 h; (i) L-(+)-tartaric acid, Acetone:H_2O = 1:1, 48 h.

The desired products **14a**-**14t** and (*R*)-**14r** were synthesized according to the pathway shown in Scheme 2. Reductive amination of key intermediates **9** or **10** with compound **11** produced compound **12**, which was hydrolyzed by NaOH to give compound **13**. A further hydrolysis of the cyano group of **13** afforded the desired products **14a**-**14t** and (*R*)-**14r**. In particular, compound (*S*)-**14r** was prepared by the resolution of racemic **14r**.

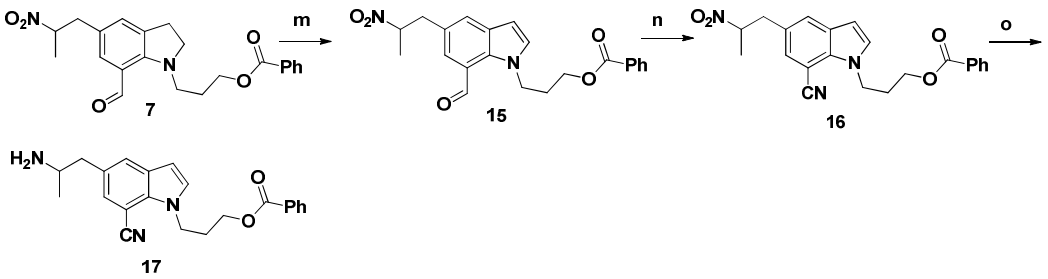
Scheme 2. Synthesis of the target compounds **14a**-**14t**, (*R*)-**14r** and (*S*)-**14r**[a]



[a]Reagents and conditions: (j) $NaBH(OAc)_3$, DCE, rt, 12 h; (k) 1 mol/L NaOH, MeOH, rt, 2 h; (l) 5 mol/L NaOH, 30% H_2O_2, DMSO, 48 h.

The synthetic method of the key intermediate **17** is shown in Scheme 3. Oxidation of **7** with 2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) gave compound **15** in 90% yield, which was condensed with hydroxylamine hydrochloride to produce compound **16**. Hydrogenation of **16** provided the key intermediate **17**.

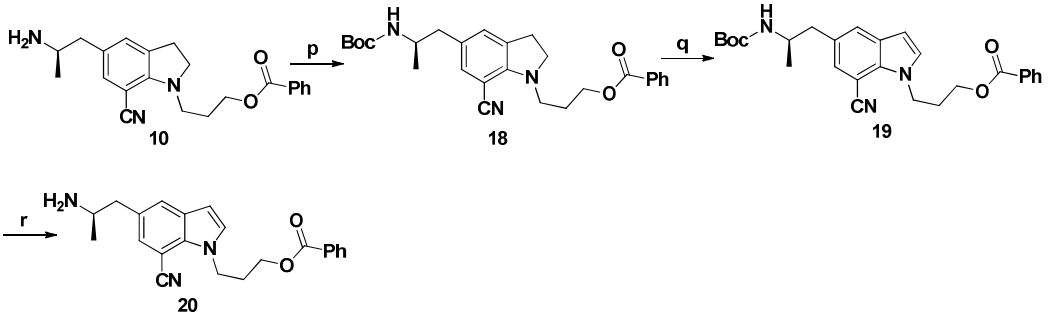
Scheme 3. Synthesis of the key intermediate **17**[a]



[a]Reagents and conditions: (m) DDQ, EA, 25 ^{o}C, 2 h; (n) hydroxylamine hydrochloride, Py, Ac_2O, THF, 70 ^{o}C, 36 h; (o) Pd/C, H_2, MeOH:THF = 1:1, 40 ^{o}C, 48 h.

The synthetic route of the key intermediate **20** is described in Scheme 4. Protection of the amino group of **10** with Boc_2O gave compound **18** in quantitative yield, and subsequent oxidation of **18** with DDQ provided compound **19**. Deprotection of **19** using CF_3COOH yielded the key intermediate **20**.

Scheme 4. Synthesis of the key intermediate **20**[a]

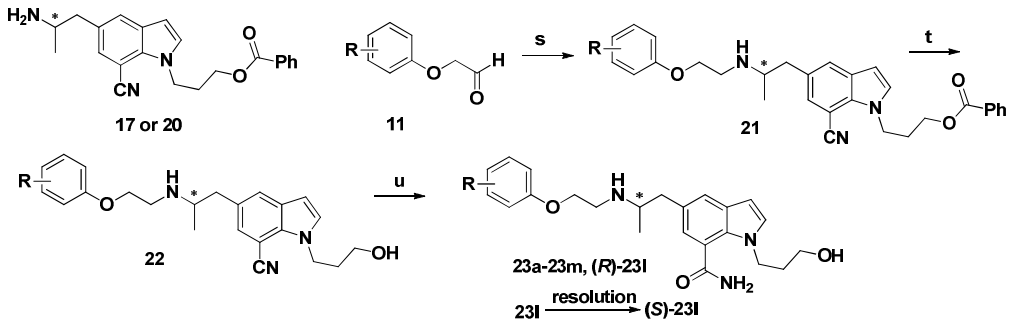


[a]Reagents and conditions: (p) $(Boc)_2O$, NEt_3, DCM, 25 ^{o}C, 10 h; (q) DDQ, EA, 25 ^{o}C, 2 h; (r) CF_3COOH, DCM, 25 ^{o}C, 10 h.

The desired products **23a**-**23m** and (*R*)-**23l** were synthesized according to the pathway shown in Scheme 5. Reductive amination of the key intermediate **17** or **20** with compound **11** produced intermediate **21**, which was hydrolyzed by NaOH to give intermediate **22**. A further hydrolysis of the cyano group of **22** afforded the desired products **23a**-**23m** and (*R*)-**23l**. In

particular, compound (*S*)-**23l** was prepared by the resolution of racemic **23l**.

Scheme 5. Synthesis of the target compounds **23a**-**23m**, (*R*)-**23l** and (*S*)-**23l**[a]



[a]Reagents and conditions: (s) $NaBH(OAc)_3$, DCE, rt, 12 h; (t) 1 mol/L NaOH, MeOH, rt, 2 h; (u) 5 mol/L NaOH, 30% H_2O_2, DMSO, 48 h.

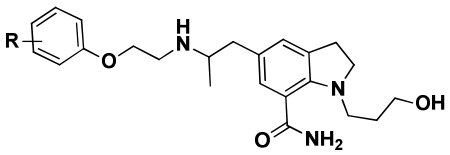
Biological evaluation

Calcium assays. The antagonist activities of the indoline compounds were evaluated using calcium mobilization assays in HEK293 cells expressing α_{1A}, α_{1B} or α_{1D}-AR, the marketed drug silodosin was used as the positive control (Table 1). Compared with silodosin (IC_{50} = 1.9 nM, α_{1B}/α_{1A} = 285.9, α_{1D}/α_{1A} = 14.4), compounds **14a-14c** with two substituents such as 2-Br-4-F, 3, 4-OCH_2O and 2, 6-di-Me and compounds **14d-14e** with three substituents such as 2, 3, 6-tri-Me and 2, 4, 6-tri-Me on the benzene ring showed moderate potency for α_{1A} (IC_{50} >20 nM) and moderate subtype selectivities over α_{1B} ($14<\alpha_{1B}/\alpha_{1A}<150$). We were pleased to find that compounds **14f-14j** possessing hydrophobic groups such as Me, Et, OMe, OCH_2CF_3, and OBn at the C2 position exhibited improved activities (3.2 nM<IC_{50}<25.6 nM) and selectivities ($74<\alpha_{1B}/\alpha_{1A}<417$) on the whole. Among them, compounds **14h** and **14i** displayed the most potent activities with IC_{50} values of 4.8 nM and 3.2 nM, respectively. Although compounds **14h** and **14i** showed almost equal activities as compared with silodosin,

the subtype selectivities of compounds **14h** (α_{1B}/α_{1A} = 126) and **14i** (α_{1B}/α_{1A} = 83.4) were unsatisfactory. Therefore, further optimization was carried out to improve the selectivities while maintaining the activities of compounds **14h** and **14i**. Various substituents were introduced on the benzene ring of **14h** to produce compounds **14k**-**14p**. Compound **14k** with a 5-F group and compound **14o** with a 4-Me group both showed a substantial loss of the selectivities for α_{1A}-AR over α_{1B}, while compounds **14l** (4-F), **14m** (4-Cl), **14n** (4-Br) exhibited more than 2-fold increase in selectivity, and the introduction of the bulky ethyl group (**14p**) at the C4 position of **14h** led to a sharp reduction in both activity and selectivity. Among the compounds obtained by the structural optimization of **14h**, compound **14n** (IC_{50} = 2.9 nM, α_{1B}/α_{1A} = 294.5) turned out to be the most potent molecule which displayed slightly higher selectivity but slightly weaker activity than silodosin. Subsequently, the structure optimization of **14i** was conducted and different groups were introduced on the benzene ring of **14i** to produce compounds **14q**-**14t**. Compound **14q** possessing a 4-F group and compound **14s** processing a 5-Br group both suffered a significant decrease in subtype selectivity for α_{1A}-AR over α_{1B}, compound **14t** bearing a 5-Et group showed a sharp reduction in potency. To our delight, compound **14r** with a 5-Cl group exhibited a considerable improvement in selectivity for α_{1A}-AR over both α_{1B}-AR and α_{1D}-AR while maintaining antagonist activity. It is worth noting that compound **14r** (IC_{50} = 3.2 nM, α_{1B}/α_{1A} = 371.4, α_{1D}/α_{1A} = 126.3) displayed higher selectivities for α_{1A}-AR over α_{1B}-AR and α_{1D}-AR than silodosin. Furthermore, (*R*)-**14r** and (*S*)-**14r** were synthesized to evaluate the effect of the enantiomers on the activities and selectivities. As a result, (*R*)-**14r** showed much better activities and selectivities than (*S*)-**14r**. This indicates that *R* configuration was preferred for receptor

function. (*R*)-**14r** (IC_{50} = 2.7 nM, α_{1B}/α_{1A} = 640.1, α_{1D}/α_{1A} = 408.2) was regarded as the most potent and selective α_{1A}-AR antagonist among all the indoline compounds.

Table 1. Antagonist activities and subtype selectivities of indoline compounds



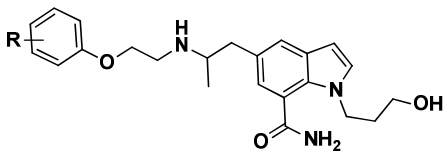
Compound	R	IC_{50} on calcium assays nM (Mean±SEM)			Selectivity	
		α_{1A}	α_{1B}	α_{1D}	α_{1B}/α_{1A}	α_{1D}/α_{1A}
14a	**2-Br, 4-F**	70.8±15.6	1361±323.2	436.2±59.6	19.2	7.3
14b	**3, 4-OCH_2O**	27.8±5.0	2768±535.2	5208±1649	99.5	187.1
14c	**2, 6-di-Me**	21.8±4.0	3266±1090	1621±356.4	149.5	74.2
14d	**2, 3, 6-tri-Me**	324.2±71.1	4807±265.0	996.1±258.3	14.8	3.1
14e	**2, 4, 6-tri-Me**	58.0±3.7	3139±118.5	1554±357.2	54.1	26.8
14f	**2-Me**	14.4±7.6	5992±1246	37.4±18.7	416.1	2.6
14g	**2-Et**	25.6±12.4	5320±1398	457.5±268.7	207.8	17.9
14h	**2-OMe**	4.8±0.9	610.2±167.8	15.8±2.4	126.0	3.3
14i	**2-OCH_2CF_3**	3.2±0.4	263.9±9.1	13.4±3.8	83.4	4.2
14j	**2-OBn**	8.6±0.1	640.6±165.6	1.7±0.3	74.7	0.2
14k	**2-OMe, 5-F**	2.9±0.5	168.9±5.5	0.4±0.1	57.5	0.1
14l	**2-OMe, 4-F**	4.6±0.7	1284±261.7	49.6±8.7	280.0	10.8
14m	**2-OMe, 4-Cl**	8.1±0.1	2162±297.6	196.8±13.2	265.4	24.2

14n	**2-OMe, 4-Br**	2.9±0.2	866.1±65.0	274.0±51.2	294.5	93.2
14o	**2-OMe, 4-Me**	7.6±1.7	617.6±53.6	60.6±9.1	81.3	8.0
14p	**2-OMe, 4-Et**	57.0±8.6	2248±157.9	883.2±85.6	39.5	15.5
14q	**2-OCH_2CF_3, 4-F**	4.0±0.7	158.5±19.0	143.9±25.4	40.0	36.3
14r	**2-OCH_2CF_3, 5-Cl**	3.2±0.6	1206±177.4	410.2±116.1	371.4	126.3
14s	**2-OCH_2CF_3, 5-Br**	2.7±0.5	32.7±1.7	0.3±0.07	12.2	0.1
14t	**2-OCH_2CF_3, 5-Et**	38.20±13.16	8488±6532	3464±1267	222.2	90.70
(*R*)-**14r**	-	2.7±1.4	1736±189.3	1107±5.3	640.1	408.2
(*S*)-**14r**	-	63.1±12.8	2959±341.5	457.1±60.8	46.9	7.2
Silodosin	-	1.9±0.3	541.4±242.8	27.3±26.2	285.9	14.4

The activities and selectivities of indole compounds were also evaluated. As shown in Table 2, compound **23a** with a 2-Br-4-F group on the benzene ring exhibited similar high α_{1A}-AR potency (IC_{50} = 2.7 nM) and moderate selectivity for α_{1A}-AR over α_{1B}-AR (α_{1B}/α_{1A} = 160.6). Compound **23b** with a 2-Et group displayed good selectivity (α_{1B}/α_{1A} = 208.9), but low potency (IC_{50} = 20.7 nM). Compounds **23c-23f** bearing hydrophobic groups such as OMe, OEt, OBn, OCH_2CF_3 at the C2 position showed promising potency (1.9 nM<IC_{50}<4.4 nM) but low selectivities (α_{1B}/α_{1A}<100). Among them, Compounds **23c** and **23f** were found to be the most potent molecules in terms of activity and selectivity. Subsequently, various groups were introduced on the benzene ring of **23c** and **23f** in order to improve their selectivities for α_{1A}-AR over α_{1B}-AR. The introduction of a 4-Cl (**23i**) or 4-Br (**23j**) group on the benzene ring of **23c** caused a slight reduction in selectivity, while the introduction of a 5-F (**23g**) or 4-F (**23h**) group leaded to a significant increase in selectivity. However, the selectivities of

23g and **23h** were still lower than silodosin. To identify highly selective α_{1A}-AR antagonists, the structural modification of **23f** was carried out. The introduction of a 5-Cl (**23k**) or 5-Me (**23l**) group on the benzene ring of **23f** resulted in a great improvement in selectivity while maintaining the potency, and the introduction of the bulky 5-Et group (**23m**) on the benzene ring of **23f** led to a sharp reduction in potency. Remarkably, compound **23l** (IC_{50} = 2.2 nM, α_{1B}/α_{1A} = 998.6, α_{1D}/α_{1A} = 611.4) displayed comparable potency and higher selectivity than silodosin. Further research revealed that (*R*)-**23l** showed much better activities and selectivities than (*S*)-**23l**. (*R*)-**23l** (IC_{50} = 1.9 nM, α_{1B}/α_{1A} = 1506, α_{1D}/α_{1A} = 249.6) was regarded as the most potent and selective α_{1A}-AR antagonist among all the indole compounds. Compared with silodosin, (*R*)-**23l** exhibited equal potency for α_{1A}-AR, while the selectivity for α_{1A}-AR over α_{1B}-AR is 5 times that of silodosin.

Table 2. Antagonist activities and subtype selectivities of indole compounds



Compound	R	IC_{50} on calcium assays nM (Mean±SEM)			Selectivity	
		α_{1A}	α_{1B}	α_{1D}	α_{1B}/α_{1A}	α_{1D}/α_{1A}
23a	**2-Br, 4-F**	2.7±0.5	980.5±182.5	21.7±1.3	160.6	8.1
23b	**2-Et**	20.7±1.8	4320±567.9	0.4±0.1	208.9	0.02
23c	**2-OMe**	4.4±0.5	262.9±33.4	0.4±0.1	59.2	0.09
23d	**2-OEt**	1.9±0.3	35.6±5.1	2.6±0.6	18.7	1.4

23e	**2-OBn**	2.7±0.04	130.6±29.4	0.1±0.001	47.7	0.04
23f	**2-OCH_2CF_3**	1.9±0.4	180.1±17.3	15.9±4.0	92.7	8.2
23g	**2-OMe, 5-F**	0.3±0.1	70.9±7.3	0.4±0.08	221.4	1.3
23h	**2-OMe, 4-F**	8.0±1.5	936.6±213.8	10.6±2.6	117.7	1.3
23i	**2-OMe, 4-Cl**	15.4±0.4	835.9±76.4	31.6±4.5	54.2	2.0
23j	**2-OMe, 4-Br**	3.7±0.6	169.6±30.2	162.2±18.8	46.0	44.0
23k	**2-OCH_2CF_3, 5-Cl**	1.3±1.0	287.1±39.6	94.0±30.8	227.7	74.1
23l	**2-OCH_2CF_3, 5-Me**	2.2±0.6	2197±463.9	1345±213.7	998.6	611.4
23m	**2-OCH_2CF_3, 5-Et**	17.1±3.3	7583±587.8	3794±641.8	443.5	221.9
(*R*)-23l	-	1.9±0.4	2862±846.7	474.3±156.4	1506	249.6
(*S*)-23l	-	453.9±106.1	>10000	3717±210.8	>22.0	8.2
Silodosin	-	1.9±0.3	541.4±242.8	27.3±26.2	285.9	14.4

Functional assays with isolated rat tissues. The effects of compounds (*R*)-**14r** and (*R*)-**23l**, which displayed optimal potency and selectivities on α_{1A}-AR, on the noradrenaline-induced contraction of isolated rat urethras and aortas were tested. The results of three separate experiments are summarized in Table 3. Compounds (*R*)-**14r** and (*R*)-**23l** inhibited the contraction of urethra smooth muscle with IC_{50} values of 30.1 nM and 76.8 nM, respectively. Compared with silodosin, compound (*R*)-**14r** showed a similar potency while compound (*R*)-**23l** exhibited slightly weaker potency on isolated urethra tissue. In addition, compounds (*R*)-**14r** and (*R*)-**23l** displayed 8.8-fold and 3.9-fold tissue selectivities, respectively. Both of them displayed higher uroselectivity than silodosin, which is very promising for the reduction of cardiovascular side effects.

Table 3. Functional studies of compounds (*R*)-**14r** and (*R*)-**23l** on isolated rat tissues

Compound	IC_{50} (nM)		Uroselectivity
	Urethra	Aorta	Urethra/Aorta
(*R*)-**14r**	30.1±9.3	263.6±22.4	8.8
(*R*)-**23l**	76.8±24.7	297.8±46.0	3.9
Silodosin	17.3±4.6	26.6±3.0	1.5

Micturition behavior in BPH model rats. Similar to BPH patients, the BPH model rats have significantly increased micturition frequency (Fig.1A) and significantly reduced mean voided volume (Fig.1B) as compared with the sham rats. Silodosin significantly reduced the urinary frequency and increased the mean voided volume in a dose-dependent manner, with a minimal effective dose of 3 mg/kg (Fig.1A) and 1 mg/kg (Fig.1B), respectively. Both (*R*)-**14r** and (*R*)-**23l** showed beneficial effects in the micturition behavior of BPH rats, with the minimal effective dose of 10 mg/kg and 3 mg/kg (Fig.1A), respectively, in reducing micturition frequency; and minimal effective dose of 3 mg/kg and 10 mg/kg (Fig.1B), respectively, in increasing the mean voided volume. Although compounds (*R*)-**14r** and (*R*)-**23l** showed slightly weaker potency in BPH rats as compared with slodosin, they can significantly alleviate voiding symptoms of BPH rats, which makes them worthy of further investigation for the development of anti-BPH agents.

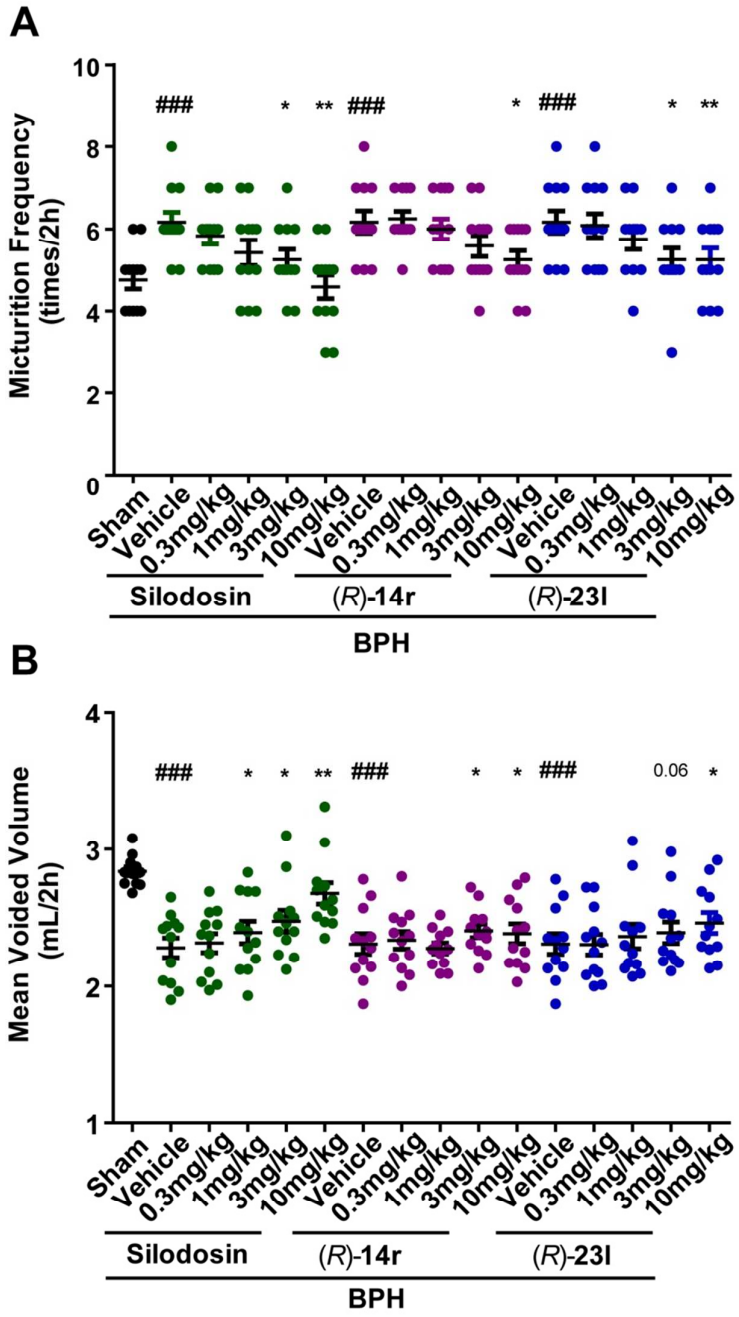


Figure 3. Effects of (*R*)-**14r** and (*R*)-**23l** on the micturition parameters in BPH rats. Micturition frequency (A) and mean voided volume (B) were measured in a metabolic cage. $^{###}P < 0.001$, versus sham control. $^{*}P < 0.05$, $^{**}P < 0.01$ versus vehicle control.

Preliminary pharmacokinetic evaluation of compounds (*R*)-14r and (*R*)-23l. The pharmacokinetic properties of (*R*)-**14r** and (*R*)-**23l** were evaluated in rats after intravenous

(10 mg/kg) and oral administration (20 mg/kg) (Table 4). Compound (*R*)-**14r** given orally at 20 mg/kg dosage displayed a T_{max} of 4 h, a C_{max} of 152.3 ng/mL, an $AUC_{0-\infty}$ of 1702.7 ng/mL*h, a mean retention time (MRT) of 6.22 h, and a $t_{1/2}$ of 4.67 h. Compound (*R*)-**14r** showed good exposure and oral bioavailability (F = 24.3%). Compound (*R*)-**23l** given orally at 20 mg/kg dosage exhibited a T_{max} of 0.5 h, a C_{max} of 108.6 ng/mL, an $AUC_{0-\infty}$ of 613.2 ng/mL*h, a MRT of 3.54 h, and a $t_{1/2}$ of 1.22 h, indicating the relatively low exposure and oral bioavailability (F = 7.0%) of compound (*R*)-**23l**.

Table 4. Pharmacokinetic parameters of compounds (*R*)-**14r** and (*R*)-**23l** (po and iv) in rats.

Compound		Dose	T_{max}	C_{max}	$AUC_{0-\infty}$	MRT	$t_{1/2}$	CLz	F
		mg/kg	h	ng/mL	ng/mL*h	h	h	L/h/kg	%
(*R*)-**14r**	po	20	4	152.3	1702.7	6.22	4.67	/	24.3
	iv	10	0.083	3004.7	3506.4	2.34	1.63	2.85	/
(*R*)-**23l**	po	20	0.5	108.6	613.2	3.54	1.22	/	7.0
	iv	10	0.083	2425.1	4396.0	2.94	1.10	2.275	/

Rat plasma protein binding assays of compounds (*R*)-14r and (*R*)-23l. The rat plasma protein binding (PPB) rate of the tested compounds was evaluated at the concentration of 2 μM using equilibrium dialysis. As shown in Table 5, compounds (*R*)-**14r** and (*R*)-**23l** displayed PPB rate of 83.52% and 62.25%, respectively. They both showed much higher PPB rate than silodosin (38.73%), this may led to their lower effective concentration in target tissue and weaker potency in BPH rats. We speculate the high PPB rate as well as unsatisfactory pharmacokinetic profiles of (*R*)-**14r** and (*R*)-**23l** are responsible for their

slightly weaker potency in BPH rats as compared with silodosin, further optimization of (***R***)-**14r** and (***R***)-**23l** aiming to improve their pharmacokinetic profiles and lower their PPB rate to improve their potency in vivo is undergoing in our laboratory.

Table 5. Rat plasma protein binding rate of compounds (*R*)-**14r** and (*R*)-**23l**.

Compound	Rat plasma protein binding rate (%)
(*R*)-**14r**	83.52±0.38
(*R*)-**23l**	62.25±0.97
Silodosin	38.73±1.90
Warfarin (positive control)	98.48±0.01

Conclusion

In this paper, we have described the design, synthesis, and biological evaluation of indoline and indole derivatives as selective α_{1A}-AR antagonists for the treatment of BPH. Structure-activity relationship (SAR) exploration led to the identification of two highly selective and potent α_{1A}-AR antagonists (*R*)-**14r** (IC_{50} = 2.7 nM, α_{1B}/α_{1A} = 640.1, α_{1D}/α_{1A} = 408.2) and (*R*)-**23l** (IC_{50} = 1.9 nM, α_{1B}/α_{1A} = 1506, α_{1D}/α_{1A} = 249.6). Compared with silodosin (IC_{50} = 1.9 nM, α_{1B}/α_{1A} = 285.9, α_{1D}/α_{1A} = 14.4), both compounds displayed similar activities and better selectivities in calcium assays. In addition, compounds (*R*)-**14r** and (*R*)-**23l** showed high potency and uroselectivity in the isolated rat tissues. More importantly, both compounds can significantly decrease the micturition frequency and increase the mean voided volume of the BPH rats in a dose-dependent manner. These results indicate that

compounds (*R*)-**14r** and (*R*)-**23l** are worthy of further investigation for the development of anti-BPH agents.

Experimental section

Chemistry. Chemicals and solvents were purchased from commercial sources (Alfa, Acros, Sigma-aldrich and Shanghai Chemical Reagent Company), and used without further purification. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness, YantaiHuiyou Company, China). Column chromatography was performed with CombiFlash® Companion system (Teledyne Isco, Inc.). Nuclear magnetic resonance spectra were recorded on a Brucker AMX-400 or 500 MHz instrument (TMS as IS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low and high-resolution mass spectra (LRMS and HRMS) were measured on Finnigan MAT 95 spectrometer. All target compounds were confirmed with over 95% purity which were determined by Agilent-1100 HPLC with binary pump, photodiode array detector (DAD), using Agilent Extend-C18 column (150×4.6 mm, 5 μm), CH_3OH/H_2O (0.1% diethylamine was added in H_2O) = 70/30 (v/v) at 0.6 mL/min, and calculated the peak areas at 254 nM. The enantiomeric excess (ee) of compound **10** was identified by Agilent-1100 HPLC, and CHIRALPAK AD-RH column (0.46 cm × 15 cm, 5 μm) was used with elution phase H_2O/CH_3CN (0.1% diethylamine was added in CH_3CN), 20/80 (v/v) at 1.0 mL/min. The enantiomeric excess (ee) of compounds **20**, (*R*)-**14r**, (*S*)-**14r**, (*R*)-**23l** and (*S*)-**23l** were identified by SHIMADZU LC-20AD with photodiode array detector

(DAD), and CHIRALPAK AD-H column (0.46 cm × 25 cm, 5 μm) was used with elution phase ethanol/hexane (0.1% diethylamine was added in hexane), 20/80 (v/v) at 1.0 mL/min. The ee (%) values were calculated by peak areas at 254 nM.

3-(indolin-1-yl)propan-1-ol (2). To a solution of indoline (10.0 g, 83.92 mmol) and 3-bromo-1-propanol (9.5 ml, 105.05 mmol) in CH_3CN (300 ml) was added K_2CO_3 (23.3 g, 168.58 mmol), the resulting mixture was heated to reflux for 12 h. Then the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated, and the residue obtained was purified by flash chromatography to give **2** (12.7 g, 85.4%) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.09 (m, 2H), 6.77-6.70 (m,1H), 6.61 (d, J = 7.7 Hz, 1H), 3.81 (t, J = 6.0 Hz, 2H), 3.37 (t, J = 8.2 Hz, 2H), 3.22 (t, J = 6.7 Hz, 2H), 2.99 (t, J = 8.2 Hz, 2H), 1.93-1.86 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.53, 130.25, 127.30, 124.47, 118.22, 107.70,61.66, 53.67, 47.79, 29.87, 28.57; ESI-MS m/z: 178 $[M+H]^+$.

3-(indolin-1-yl)propyl benzoate (3). Benzoyl chloride (9.15 ml, 78.82 mmol) was added dropwise to a solution of **2** (12.7 g, 71.65 mmol) and NEt_3 (19.92 ml, 143.31 mmol) in anhydrous DCM (250 ml) at 0 ^{o}C under nitrogen, the mixture was stirred for 8 h at room temperature. Then the resulting mixture was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give **3** (19.0 g, 94.3%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.12 (m, 2H), 7.66-7.60 (m,1H), 7.55-7.49 (m, 2H), 7.19-7.10 (m,2H), 6.79-6.69 (m, 1H), 6.59 (d, J = 6.5 Hz, 1H), 4.53 (t, J = 5.6 Hz, 2H), 3.44 (t, J = 8.3 Hz, 2H), 3.31 (t, J = 7.0 Hz, 2H), 3.04 (t, J = 8.2 Hz, 2H), 2.19-2.10 (m,2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.45, 152.28, 132.91, 130.24, 129.94, 129.49, 128.36, 127.28, 124.41, 117.71, 106.93, 62.83, 53.23, 46.10, 28.53, 26.78; ESI-MS m/z: 282 $[M+H]^+$.

3-(5-formylindolin-1-yl)propyl benzoate (4). Phosphorus oxychloride (18.55 ml, 202.60 mmol) was added dropwise to a solution of DMF (15.62 ml, 202.60 mmol) in anhydrous 1, 2-dichloroethane (50 ml) at 0 ^{o}C under nitrogen. The reaction mixture was stirred for 1 h, then a solution of **3** (19.0 g, 67.53 mmol) in 1, 2-dichloroethane (200 ml) was added dropwise. After addition, the mixture was heated to 80 ^{o}C for 2 h. Then the reaction mixture was allowed to cool and poured into a vigorously stirred and ice-cold saturated aqueous $NaHCO_3$ solution (400 ml). The organic layer was separated, dried and concentrated, and the residue was purified by flash chromatography to give **4** (16.8 g, 80.4%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.57-7.52 (m, 1H), 7.51-7.47 (m, 2H), 7.45-7.39 (m,2H), 6.36 (d, *J* = 8.5 Hz, 1H), 4.38 (t, *J* = 6.2 Hz, 2H), 3.59 (t, *J* = 8.6 Hz, 2H), 3.37 (t, *J* = 6.9 Hz, 2H), 3.00 (t, *J* = 8.6 Hz, 2H), 2.13-1.95 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.79, 166.37, 157.12, 134.18, 133.08, 130.18, 129.96, 129.44, 128.41, 126.68, 124.51, 104.22, 62.38, 52.24, 43.94, 27.16, 26.39; ESI-MS m/z: 310 $[M+H]^+$.

3-(5-(2-nitroprop-1-en-1-yl)indolin-1-yl)propyl benzoate (5). CH_3COONH_4 (10.47 g, 135.76 mmol) and CH_3COOH (100 ml, 1.75 mol) were added to a solution of **4** (16.8 g, 54.31 mmol) in $CH_3CH_2NO_2$ (200 ml, 2.78 mol), the resulting mixture was heated to reflux for 4 h and then concentrated. The residue was dissolved in EA, the resulting mixture was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. Then the residue was suspended in isopropanol, and the mixture was stirred overnight at room temperature. The red solids of **5** (13.9 g, 69.9%) which had precipitated out were obtained by filtration. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.00 (m, 3H), 7.61-7.54 (m,1H), 7.49-7.42 (m, 2H), 7.24-7.17 (m, 2H), 6.44 (d, *J* = 8.1 Hz, 1H), 4.43 (t, *J* = 6.2 Hz, 2H), 3.58 (t, *J* = 8.5 Hz,

2H), 3.37 (t, *J* = 6.9 Hz, 2H), 3.05 (t, *J* = 8.5 Hz, 2H), 2.47 (s, 3H), 2.15-2.05 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.56,154.25, 142.40, 135.55, 133.18, 132.98, 130.58, 130.14, 129.58, 128.52, 126.75, 120.90, 105.73, 62.58, 52.55, 44.57, 27.88, 26.65, 14.53; ESI-MS m/z: 367 $[M+H]^+$.

3-(5-(2-nitropropyl)indolin-1-yl)propyl benzoate (6). To a solution of **5** (13.9 g, 37.94 mmol) in DCM (50 ml) and MeOH (200 ml) in ice bath was added $NaBH_4$ (14.35 g, 379.36 mmol) by portion. After addition, the mixture was allowed to stir at room temperature for 1 h, then concentrated. EA and saturated solution of NH_4Cl was added to the residue obtained, the organic layer was separated and washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to afford **6** (12.85 g, 91.9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08-8.02 (m, 2H), 7.61-7.55 (m, 1H), 7.49-7.43 (m, 2H), 6.86 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 4.76-4.64 (m, 1H), 4.45 (t, *J* = 6.3 Hz, 2H), 3.38 (t, *J* = 8.3 Hz, 2H), 3.25-3.15 (m, 3H), 2.94 (t, *J* = 8.3 Hz, 2H), 2.88 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.12-2.03 (m, 2H), 1.51 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.68, 151.94, 133.11, 130.75, 130.37, 129.65, 128.53, 128.17, 125.27, 124.51, 106.83, 85.08, 62.94, 53.47, 46.20, 41.00, 28.55, 26.98, 18.73; ESI-MS m/z: 369 $[M+H]^+$.

3-(7-formyl-5-(2-nitropropyl)indolin-1-yl)propyl benzoate (7). Phosphorus oxychloride (9.58 ml, 104.63 mmol) was added dropwise to anhydrous DMF (50 ml, 648.48 mmol) at 0 ^{o}C under nitrogen. The resulting mixture was stirred for 1 h, then a solution of **6** (12.85 g, 34.88 mmol) in DMF (50 ml, 648.48 mmol) was added dropwise. After addition, the mixture was heated to 80 ^{o}C for 2 h. Then the reaction mixture was allowed to cool and poured into a vigorously stirred and ice-cold saturated aqueous $NaHCO_3$ solution (400 ml). The mixture

was extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give **7** (12.0 g, 86.8%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.08-8.01 (m, 2H), 7.59-7.52 (m, 1H), 7.48-7.40 (m, 2H), 7.21 (s, 1H), 6.92 (d, *J* = 1.7 Hz, 1H), 4.78-4.64 (m, 1H), 4.40 (t, *J* = 6.3 Hz, 2H), 3.71-3.57 (m,4H), 3.17 (dd, *J* = 14.2, 7.7 Hz, 1H), 3.02 (t, *J* = 8.8 Hz, 2H), 2.90 (dd, *J* = 14.2, 6.4 Hz, 1H), 2.15-2.04 (m, 2H), 1.53 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.41, 166.62, 152.37, 134.24, 133.11, 131.48, 130.14, 129.86, 129.66, 128.50, 123.88, 118.00, 84.60, 62.76, 54.70, 49.95, 40.29, 27.78, 26.86, 18.82; ESI-MS m/z: 397 $[M+H]^+$.

3-(7-cyano-5-(2-nitropropyl)indolin-1-yl)propyl benzoate (8). Hydroxylamine hydrochloride (4.21 g, 60.54 mmol) and pyridine (9.74 ml, 121.08 mmol) were added to a solution of **7** (12.0 g, 30.27 mmol) in anhydrous THF (150 ml), the mixture was stirred for 12 h under reflux. Then acetic anhydride (14.21 ml, 151.35 mmol) was added slowly and the resulting mixture was stirred for 24 h under reflux. Water was added and the mixture was extracted with EA, the organic layer was washed sequentially with 1 mol/L HCl, saturated aqueous $NaHCO_3$ solution and brine, and dried with Na_2SO_4. The solid obtained by concentration was wash with MeOH to give **8** (10.5 g, 88.2%) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.00 (m, 2H), 7.58-7.52 (m, 1H), 7.46-7.39 (m, 2H), 6.92 (s, 1H), 6.88 (d, *J* = 0.9 Hz, 1H), 4.7-4.62 (m, 1H), 4.46 (t, *J* = 6.3 Hz, 2H), 3.75 (t, *J* = 7.2 Hz,2H), 3.60 (t, *J* = 8.7 Hz, 2H), 3.10 (dd, *J* = 14.3, 7.9 Hz, 1H), 2.95 (t, *J* = 8.7 Hz, 2H), 2.84 (dd, *J* = 14.3, 6.2 Hz, 1H), 2.20-2.10 (m, 2H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.68, 152.33, 133.28, 133.10, 131.87, 130.16, 129.73, 129.01, 128.45, 123.92, 119.15,

87.94, 84.47, 62.59, 53.37, 45.11, 40.03, 27.30, 27.20, 18.84; ESI-MS m/z: 394 $[M+H]^+$.

3-(5-(2-aminopropyl)-7-cyanoindolin-1-yl)propyl benzoate (9). A solution of **8** (10.5 g, 26.69 mmol) in MeOH (100 ml) and THF (100 ml) was treated with 10% Pd/C catalyst (1.0 g), the mixture was stirred for 48 h at 40 ^oC under hydrogen. After the removal of the catalyst by filtration, the filtrate was concentrated to afford **9** (9.0 g, 92.8%) as pale yellow oil. ^1H NMR (400 MHz, MeOD) δ 8.06-8.00 (m, 2H), 7.63-7.56 (m, 1H), 7.49-7.42 (m, 2H), 7.02 (d, *J* = 1.5 Hz, 1H), 6.95 (s, 1H), 4.45 (t, *J* = 6.2 Hz, 2H), 3.76 (t, *J* = 7.1 Hz,2H), 3.61 (t, *J* = 8.7 Hz, 2H), 3.06-2.90 (m, 3H), 2.54-2.38 (m, 2H), 2.21-2.08 (m, 2H), 1.06 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 168.02, 153.13, 134.60, 134.20, 132.32, 131.32, 130.95, 130.63, 129.50, 120.56, 88.48, 63.97, 54.14, 49.27, 46.36, 45.34, 28.16, 27.86, 22.45; ESI-MS m/z: 364 $[M+H]^+$.

(*R*)-3-(5-(2-aminopropyl)-7-cyanoindolin-1-yl)propyl benzoate (10). An aqueous solution of L-(+)-tartaric acid (1.15 g, 7.66 mmol) in water (30 ml) was added dropwise to a solution of **9** (5 g, 13.76 mmol) in acetone (30 ml) over 1 h. The resulting mixture was stirred for 48 h, the white solids which had precipitated out were obtained by filtration. The white solids were further recrystallized with a solvent mixture of acetone and water (acetone/water = 1/1) to give pure L-(+)-tartaric acid salt of **10** (2.05 g). ^1H NMR (400 MHz, DMSO + D2O) δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.66-7.58 (m,1H), 7.51-7.42 (m, 2H), 7.07 (s, 1H), 7.00 (s, 1H), 4.35 (t, *J* = 6.0 Hz, 2H), 4.07 (s, 2H), 3.66 (t, *J* = 7.1 Hz, 2H), 3.56 (t, *J* = 8.7 Hz, 2H), 3.32-3.20 (m, 1H), 2.91 (t, *J* = 8.6 Hz, 2H), 2.80 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.52 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.09-1.99 (m, 2H), 1.08 (d, *J* = 6.5 Hz, 3H); ESI-MS m/z: 364 $[M+H]^+$. The L-(+)-tartaric acid salt of **10** (2.05 g) was dissolved in water (50 ml), and saturated aqueous

Na_2CO_3 solution was added to adjust the pH to 10. Then the mixture was extracted with DCM, the organic extracts were dried and concentrated to yield **10** (1.25 g, 25%) as pale yellow oil. ee > 99.9%. ^{1}H NMR (400 MHz, MeOD) δ 8.08-8.01 (m, 2H), 7.65-7.56 (m, 1H), 7.51-7.43 (m, 2H), 7.05 (s, 1H), 6.97 (s, 1H), 4.48 (t, *J* = 6.1 Hz, 2H), 3.80 (t, *J* = 7.1 Hz,2H), 3.64 (t, *J* = 8.7 Hz, 2H), 3.07-2.92 (m, 3H), 2.55-2.40 (m, 2H), 2.22-2.08 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 167.99, 153.11, 134.58, 134.18, 132.32, 131.34, 130.95, 130.63, 129.53, 129.50, 120.57, 88.51, 63.97, 54.15, 49.26, 46.38, 45.41, 28.17, 27.88, 22.53; ESI-MS m/z: 364 $[M+H]^+$.

3-(7-formyl-5-(2-nitropropyl)-*1H*-indol-1-yl)propyl benzoate (15). To a solution of **7** (6.0 g, 15.13 mmol) in EA (200 ml) was added DDQ (5.2 g, 22.91 mmol). After addition, the mixture was stirred at room temperature for 2 h. Then the reaction mixture was washed with saturated aqueous Na_2CO_3 solution. The organic layer was dried and concentrated, the residue was purified by flash chromatography to afford **15** (5.4 g, 90%) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.06-7.96 (m,2H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.60-7.53 (m,1H), 7.48-7.38 (m, 3H), 7.16 (d, *J* = 3.2 Hz, 1H), 6.55 (d, *J* = 3.2 Hz, 1H), 4.89-4.71 (m, 3H), 4.24 (t, *J* = 6.1 Hz, 2H), 3.45 (dd, *J* = 14.2, 7.7 Hz, 1H), 3.16 (dd, *J* = 14.2, 6.5 Hz, 1H), 2.24-2.13 (m, 2H), 1.58 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.53, 166.50, 133.12, 133.05, 132.58, 132.53, 131.66, 130.10, 129.66, 128.74, 128.48, 126.17, 122.88, 102.97, 84.77, 62.10, 48.11, 40.63, 30.48, 18.95; ESI-MS m/z: 395 $[M+H]^+$.

3-(7-cyano-5-(2-nitropropyl)-*1H*-indol-1-yl)propyl benzoate (16). Compound **16** (4.7 g, 87%) was obtained as yellow solid following the similar procedure carried out for compound **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.62 (s, 1H), 7.61-7.55 (m, 1H),

7.49-7.41 (m,2H), 7.35 (s, 1H), 7.18 (d, *J* = 3.1 Hz, 1H), 6.52 (d, *J* = 3.1 Hz, 1H), 4.87-4.76 (m,1H), 4.66 (t, *J* = 6.8 Hz, 2H), 4.36 (t, *J* = 6.0 Hz, 2H), 3.39 (dd, *J* = 14.2, 7.9 Hz, 1H), 3.11 (dd, *J* = 14.2, 6.2 Hz, 1H), 2.46-2.34 (m, 2H), 1.58 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.54, 133.34, 133.27, 131.69, 131.13, 129.98, 129.76, 129.09, 128.55, 127.05, 126.76, 118.30, 102.74, 94.06, 84.73, 61.84, 44.65, 40.62, 30.57, 19.03; ESI-MS m/z: 392 $[M+H]^+$.

3-(5-(2-aminopropyl)-7-cyano-*1H*-indol-1-yl)propyl benzoate (**17**). Compound **17** (4.0 g, 92%) was obtained as yellow oil following the similar procedure carried out for compound **9**. ^{1}H NMR (400 MHz, MeOD) δ 7.92-7.87 (m, 2H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.59-7.54 (m, 1H), 7.44-7.39 (m, 2H), 7.38 (d, *J* = 1.5 Hz, 1H), 7.35 (d, *J* = 3.2 Hz, 1H), 6.54 (d, *J* = 3.2 Hz, 1H), 4.66 (t, *J* = 6.9 Hz, 2H), 4.33 (t, *J* = 5.9 Hz, 2H), 3.11 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.77-2.63 (m, 2H), 2.39-2.29 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 167.83, 134.19, 132.63, 132.47, 131.75, 131.07, 130.57, 130.38, 129.43, 128.23, 119.70, 103.31, 94.14, 63.50, 49.66, 45.91, 45.53, 31.41, 22.52; ESI-MS m/z: 362 $[M+H]^+$.

(*R*)-3-(5-(2-((tert-butoxycarbonyl)amino)propyl)-7-cyanoindolin-1-yl)propyl benzoate (18). To a solution of **10** (1.0 g, 2.75 mmol) and NEt_3 (0.8 ml, 5.76 mmol) in DCM (30 ml) was added di-tert-butyl dicarbonate (0.72 g, 3.30 mmol), and the mixture was stirred at room temperature for 10 h. Then the reaction mixture was washed with water, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give **18** (1.26 g, 99%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$ + D2O) δ 8.06 (d, *J* = 7.7 Hz, 2H), 7.58-7.51 (m, 1H), 7.47-7.39 (m, 2H), 6.98 (s, 1H), 6.92 (s, 1H), 4.47 (t, *J* = 6.3 Hz, 2H), 3.80-3.71 (m, 3H), 3.58 (t, *J* = 8.7 Hz, 2H), 2.95 (t, *J* = 8.7 Hz, 2H), 2.72-2.60 (m, 1H), 2.47 (dd, *J* = 13.6,

7.3 Hz, 1H), 2.22-2.11 (m, 2H), 1.42 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H); ESI-MS m/z: 464$[M+H]^+$.

(*R*)-3-(5-(2-((tert-butoxycarbonyl)amino)propyl)-7-cyano-*1H*-indol-1-yl)propyl benzoate (19). Compound **19** (0.92 g, 73%) was obtained as pale yellow oil following the similar procedure carried out for compound **15**. ^{1}H NMR (400 MHz, $CDCl_3$ + D2O) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.64 (s, 1H), 7.61-7.52 (m, 1H), 7.48-7.41 (m, 2H), 7.37 (s, 1H), 7.15 (d, *J* = 2.9 Hz, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 4.66 (t, *J* = 6.6 Hz, 2H), 4.45-4.30 (m, 3H), 2.96-2.87 (m, 1H), 2.75 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.47-2.32 (m, 2H), 1.42 (s, 9H), 1.09 (d, *J* = 6.6 Hz, 3H); ESI-MS m/z: 462$[M+H]^+$.

(*R*)-3-(5-(2-aminopropyl)-7-cyano-*1H*-indol-1-yl)propyl benzoate (20). To a solution of **19** (0.92 g, 1.99 mmol) in DCM (20 ml) was added CF_3COOH (2.0 ml, 26.93 mmol), the mixture was stirred at room temperature for 10 h. The reaction mixture was extracted with water, the organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and rine, dried with Na_2SO_4, and concentrated to give **20** (0.68 g, 94%). ^{1}H NMR (400 MHz, MeOD) δ 7.94-7.89 (m, 2H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.63-7.56 (m, 1H), 7.47-7.40 (m, 3H), 7.39 (d, *J* = 3.2 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 4.72 (t, *J* = 6.9 Hz, 2H), 4.37 (t, *J* = 5.9 Hz, 2H), 3.21-3.03 (m, 1H), 2.81-2.63 (m, 2H), 2.45-2.31 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 167.82, 134.17, 132.62, 132.48, 131.76, 131.10, 130.57, 130.38, 129.42, 128.22, 119.70, 103.31, 94.16, 63.48, 49.65, 45.94, 45.53, 31.42, 22.55; ESI-MS m/z: 362$[M+H]^+$.

5-(2-((2-(2-bromo-4-fluorophenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14a). To a solution of **9** (200 mg, 550 μmol) and

2-(2-bromo-4-fluorophenoxy)acetaldehyde (205 mg, 880 μmol) in 1,2-dichloroethane (6.0 ml) was added $NaBH(OAc)_3$ (187 mg, 880 μmol), the resulting mixture was stirred at room temperature for 12 h. Then the reaction mixture was purified by flash chromatography to give **12a** (R = 2-Br, 4-F) (271.5 mg, 85%). ESI-MS m/z: 580:582 = 1:1 $[M+H]^+$. A solution of **12a** (R = 2-Br, 4-F) (271.5 mg, 468 μmol) in MeOH (5.0 ml) was treated with 1 mol/L NaOH (1.0 ml). Two hours later, the reaction mixture was extracted with EA, the organic extracts were dried and concentrated to give **13a** (R = 2-Br, 4-F) (220.6 mg, 99%). ESI-MS m/z: 476:478 = 1:1 $[M+H]^+$. To a solution of **13a** (R = 2-Br, 4-F) (220.6 mg, 463 μmol) in DMSO (5.0 ml) in ice bath was added 5 mol/L NaOH (280 μl) and 30% H_2O_2 (200 μl), the mixture was warmed to room temperature and stirred for 24 h. Then water was added and resulting mixture was extracted with EA, the organic extracts were washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography to afford **14a** (217.0 mg, 95%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.17 (s, 1H), 7.00 (s, 1H), 6.99-6.88 (m, 2H), 6.80-6.76 (m, 2H), 4.12-3.93 (m, 2H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.40-3.32 (m, 2H), 3.18-3.10 (m, 2H), 2.98-2.90 (m, 5H), 2.66-2.51 (m, 2H), 1.81-1.71 (m, 2H), 1.07 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 494:496 = 1:1 $[M+H]^+$. ESI-HRMS calcd for $C_{23}H_{30}BrFN_3O_3$ $[M+H]^+$ 494.1455, found 494.1450. Purity: 96.8%.

Compounds **14b-14t** were prepared following the similar procedure carried out for **14a**.

5-(2-((2-(benzo[*d*][1,3]dioxol-5-yloxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14b). Pale yellow oil (194.2 mg, yield 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.56 (s, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 6.23 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.88 (s, 2H), 4.01-3.89 (m, 2H), 3.71 (t, *J* = 5.6

Hz, 2H), 3.40 (t, *J* = 8.5 Hz, 2H), 3.17 (t, *J* = 6.8 Hz, 2H), 3.00-2.85 (m, 5H), 2.64 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.55 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.83-1.73 (m, 2H), 1.07 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 442 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{32}N_3O_5$ $[M+H]^+$ 442.2342, found 442.2344. Purity: 97.1%.

5-(2-((2-(2,6-dimethylphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14c). Pale yellow oil (177.3 mg, yield 90%). ^{1}H NMR (400 MHz, CDCl3) δ 7.27 (s, 1H), 7.16 (s, 1H), 6.96 (s, 1H), 6.95-6.87 (m, 3H), 6.87-6.80 (m, 1H), 3.93-3.82 (m, 2H), 3.65-3.53 (m, 2H), 3.29 (t, J = 8.4 Hz, 2H), 3.15-2.97 (m, 5H), 2.87 (t, J = 7.9 Hz, 2H), 2.83-2.70 (m, 1H), 2.64-2.53 (m, 1H), 2.15 (s, 6H), 1.69-1.66 (m, 2H), 1.11 (d, J = 6.0 Hz, 3H); ESI-MS m/z: 426 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{36}N_3O_3$ $[M+H]^+$ 426.2757, found 426.2750. Purity: 96.3%.

1-(3-hydroxypropyl)-5-(2-((2-(2,3,6-trimethylphenoxy)ethyl)amino)propyl)indoline-7-carboxamide (14d). Pale yellow oil (187.2 mg, yield 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.02 (s, 1H), 6.97 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 3.88-3.76 (m, 2H), 3.68 (t, *J* = 5.6 Hz, 2H), 3.37 (t, *J* = 8.5 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 3.07-3.02 (m, 1H), 3.00-2.91 (m, 4H), 2.69 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.58 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 1.79-1.70 (m, 2H), 1.09 (d, *J* = 6.3 Hz, 3H); ESI-MS m/z: 440 $[M+H]^+$. ESI-HRMS calcd for $C_{26}H_{38}N_3O_3$ $[M+H]^+$ 440.2913, found 440.2906. Purity: 96.8%.

1-(3-hydroxypropyl)-5-(2-((2-(2,4,6-trimethylphenoxy)ethyl)amino)propyl)indoline-7-carboxamide (14e). Pale yellow solid (189.3 mg, yield 93%), mp 105-106 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.02 (s, 1H), 7.01-6.98 (m, 1H), 6.78 (s, 2H), 6.70 (s, 1H),

3.90-3.80 (m, 2H), 3.68 (t, *J* = 5.6 Hz, 2H), 3.37 (t, *J* = 8.5 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 3.07-3.02 (m, 1H), 3.01-2.93 (m, 4H), 2.71 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.63-2.56 (m, 1H), 2.20 (s, 3H), 2.16 (s, 6H), 1.79-1.69 (m, 2H), 1.10 (d, *J* = 6.3 Hz, 3H); ESI-MS m/z: 440 $[M+H]^+$. ESI-HRMS calcd for $C_{26}H_{38}N_3O_3$ $[M+H]^+$ 440.2913, found 440.2909. Purity: 96.3%.

1-(3-hydroxypropyl)-5-(2-((2-(o-tolyloxy)ethyl)amino)propyl)indoline-7-carboxamide (14f). Pale yellow oil (167.7 mg, yield 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.13-7.01 (m, 3H), 6.98 (s, 1H), 6.90 (s, 1H), 6.84-6.79 (m, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.09-3.97 (m, 2H), 3.68 (t, *J* = 5.6 Hz, 2H), 3.39-3.31 (m, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 3.11-3.04 (m, 1H), 3.03-2.94 (m, 2H), 2.90 (t, *J* = 8.8 Hz, 2H), 2.70-2.55 (m, 2H), 2.03 (s, 3H), 1.82-1.69 (m, 2H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.58, 156.73, 149.99, 133.97, 130.61, 130.22, 128.25, 127.94, 126.82, 126.62, 120.51, 118.42, 110.98, 67.03, 59.44, 54.20, 53.62, 50.94, 46.26, 42.75, 31.05, 28.28, 20.05, 16.15; ESI-MS m/z: 412 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{34}N_3O_3$ $[M+H]^+$ 412.2600, found 412.2609. Purity: 95.1%.

5-(2-((2-(2-ethylphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14g). Pale yellow oil (187.2 mg, yield 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.15-7.07 (m, 2H), 7.06-6.97 (m, 2H), 6.90 (s, 1H), 6.89-6.83 (m, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 4.07-3.95 (m, 2H), 3.68 (t, *J* = 5.6 Hz, 2H), 3.36 (t, *J* = 8.6 Hz, 2H), 3.14 (t, *J* = 6.7 Hz, 2H), 3.08-3.01 (m, 1H), 2.99-2.89 (m, 4H), 2.63 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.55 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.47 (q, *J* = 7.5 Hz, 2H), 1.82-1.69 (m, 2H), 1.12-1.04 (m, *J* = 10.0, 5.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.68, 156.36, 149.94, 133.93, 132.55, 130.16, 128.97,

128.28, 127.95, 126.84, 120.69, 118.36, 111.14, 67.01, 59.43, 54.23, 53.62, 50.94, 46.27, 42.71, 30.99, 28.29, 23.31, 19.95, 14.23; ESI-MS m/z: 426 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{36}N_3O_3$ $[M+H]^+$ 426.2757, found 426.2746. Purity: 96.6%.

1-(3-hydroxypropyl)-5-(2-((2-(2-methoxyphenoxy)ethyl)amino)propyl)indoline-7-carboxamide (14h). Pale yellow oil (166.3 mg, yield 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.99 (s, 2H), 6.93-6.83 (m, 4H), 6.63 (s, 1H), 4.12-4.04 (m, 2H), 3.78 (s, 3H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.36 (t, *J* = 8.5 Hz, 2H), 3.16 (t, *J* = 6.7 Hz, 2H), 3.08-3.00 (m, 1H), 3.00-2.87 (m, 4H), 2.69 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.53 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.80-1.71 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.76, 149.93, 149.74, 148.24, 133.85, 129.91, 128.26, 128.17, 121.83, 121.11, 118.12, 114.60, 112.17, 68.98, 59.49, 55.97, 54.54, 53.73, 50.67, 46.11, 42.34, 31.04, 28.33, 19.83; ESI-MS m/z: 428 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{34}N_3O_4$ $[M+H]^+$ 428.2549, found 428.2551. Purity: 96.8%.

1-(3-hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxamide (14i). Pale yellow oil (199.6 mg, yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.04-6.92 (m, 4H), 6.90-6.86 (m, 2H), 6.66 (s, 1H), 4.34-4.23 (m, 2H), 4.13-3.99 (m, 2H), 3.68 (t, *J* = 5.7 Hz, 2H), 3.39-3.33 (m, 2H), 3.14 (t, *J* = 7.0 Hz, 2H), 3.08-3.01 (m, 1H), 2.97-2.88 (m, 4H), 2.66 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.50 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.82-1.70 (m, 2H), 1.05 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 496 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{33}F_3N_3O_4$ $[M+H]^+$ 496.2423, found 496.2419. Purity: 97.8%.

5-(2-((2-(2-(benzyloxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14j). Pale yellow oil (212.2 mg, yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H), 7.36-7.28 (m, 3H), 7.13 (s, 1H), 6.99-6.95 (m, 2H), 6.91-6.86 (m, 4H),

6.70 (s, 1H), 5.04 (s, 2H), 4.13-4.04 (m, 2H), 3.69 (t, *J* = 5.3 Hz, 2H), 3.33 (t, *J* = 8.5 Hz, 2H), 3.12 (t, *J* = 6.7 Hz, 2H), 3.05-3.00 (m, 1H), 2.96-2.87 (m, 4H), 2.65 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.46 (dd, *J* = 13.5, 6.9 Hz, 1H), 1.79-1.71 (m, 2H), 1.02 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.75, 149.86, 148.96, 148.87, 137.21, 133.78, 130.06, 128.53, 128.46, 128.18, 128.12, 127.88, 127.31, 121.81, 121.76, 118.13, 115.01, 71.18, 69.07, 59.39, 54.41, 53.63, 50.66, 46.18, 42.39, 31.02, 28.26, 19.86; ESI-MS m/z: 504 $[M+H]^+$. ESI-HRMS calcd for $C_{30}H_{38}N_3O_4$ $[M+H]^+$ 504.2862, found 504.2860. Purity: 97.9%.

5-(2-((2-(5-fluoro-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14k). Pale yellow oil (183.6 mg, yield 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.00 (s, 1H), 6.98 (s, 1H), 6.78-6.72 (m, 1H), 6.62 (s, 1H), 6.61-6.54 (m, 2H), 4.07-3.95 (m, 2H), 3.74 (s, 3H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.37 (t, *J* = 8.6 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 3.06-2.89 (m, 5H), 2.65 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.52 (dd, *J* = 13.6, 6.6 Hz, 1H), 1.81-1.71 (m, 2H), 1.05 (d, *J* = 6.3 Hz, 3H); ESI-MS m/z: 446 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{33}FN_3O_4$ $[M+H]^+$ 446.2455, found 446.2448. Purity: 97.3%.

5-(2-((2-(4-fluoro-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14l). Pale yellow oil (193.9 mg, yield 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.04 (s, 1H), 6.98 (s, 1H), 6.78-6.65 (m, 2H), 6.62-6.46 (m, 2H), 4.09-3.96 (m, 2H), 3.76 (s, 3H), 3.67 (t, *J* = 5.6 Hz,2H), 3.36 (t, *J* = 8.5 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 3.03-2.98 (m, 1H), 2.99-2.88 (m, 4H), 2.66 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.51 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.81-1.68 (m, 2H), 1.05 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 446 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{33}FN_3O_4$ $[M+H]^+$ 446.2455, found 446.2450. Purity: 98.0%.

5-(2-((2-(4-chloro-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoli

ne-7-carboxamide (14m). Pale yellow oil (184.0 mg, yield 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.05 (s, 1H), 6.96 (s, 1H), 6.84-6.79 (m, 2H), 6.77-6.70 (m, 2H), 4.07-3.96 (m, 2H), 3.76 (s, 3H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.36 (t, *J* = 8.5 Hz, 2H), 3.14 (t, *J* = 6.9 Hz, 2H), 3.02-2.98 (m, 1H), 2.96-2.88 (m, 4H), 2.64 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.50 (dd, *J* = 13.5, 6.6 Hz, 1H), 1.80-1.71 (m, 2H), 1.04 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 462:464 = 3:1 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{33}ClN_3O_4$ $[M+H]^+$ 462.2160, found 462.2157. Purity: 97.9%.

5-(2-((2-(4-bromo-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoli ne-7-carboxamide (14n). Pale yellow oil (194.6 mg, yield 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.01-6.91 (m, 4H), 6.72 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.07-3.96 (m, 2H), 3.76 (s, 3H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.36 (t, *J* = 8.5 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 3.04-2.88 (m, 5H), 2.65 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.50 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.79-1.71 (m, 2H), 1.04 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 506:508 = 1:1 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{33}BrN_3O_4$ $[M+H]^+$ 506.1654, found 506.1659. Purity: 99.1%.

1-(3-hydroxypropyl)-5-(2-((2-(2-methoxy-4-methylphenoxy)ethyl)amino)propyl)indoli ne-7-carboxamide (14o). Pale yellow oil (184.0 mg, yield 90%). ^{1}H NMR (400 MHz, MeOD) δ 7.09 (d, *J* = 6.5 Hz, 2H), 6.90-6.83 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.25-4.10 (m, 2H), 3.84 (s, 3H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.46 (t, *J* = 8.5 Hz,2H), 3.42-3.36 (m, 1H), 3.33-3.28 (m, 2H), 3.25 (t, *J* = 7.4 Hz,2H), 3.04-2.93 (m, 3H), 2.65 (dd, *J* = 13.3, 8.5 Hz, 1H), 2.31 (s, 3H), 1.86-1.76 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H); ESI-MS m/z: 442 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{36}N_3O_4$ $[M+H]^+$ 442.2706, found 442.2706. Purity: 96.9%.

5-(2-((2-(4-ethyl-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indolin

e-7-carboxamide (14p). Pale yellow oil (179.3 mg, yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.07 (d, *J* = 5.6 Hz, 1H), 6.98 (s, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.71-6.65 (m, 2H), 6.57-6.53 (m, 1H), 4.14-4.00 (m, 2H), 3.76 (s, 3H), 3.69 (t, *J* = 4.6 Hz, 2H), 3.36 (t, *J* = 8.5 Hz, 2H), 3.15 (t, *J* = 6.7 Hz, 2H), 3.10-2.88 (m, 5H), 2.70 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.62-2.50 (m, 3H), 1.81-1.70 (m, 2H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H); ESI-MS m/z: 456 $[M+H]^+$. ESI-HRMS calcd for $C_{26}H_{38}N_3O_4$ $[M+H]^+$ 456.2862, found 456.2866. Purity: 96.1%.

5-(2-((2-(4-fluoro-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxy propyl)indoline-7-carboxamide (14q). Pale yellow oil (216.4 mg, yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.02-6.85 (m, 2H), 6.85-6.76 (m, 1H), 6.73-6.62 (m, 3H), 4.35-4.26 (m, 2H), 4.10-3.97 (m, 2H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.37 (t, *J* = 8.8 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 3.04-3.00 (m, 1H), 2.97-2.91 (m, 4H), 2.67 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.52 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.80-1.71 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 514 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{32}F_4N_3O_4$ $[M+H]^+$ 514.2329, found 514.2321. Purity: 96.6%.

5-(2-((2-(5-chloro-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxy propyl)indoline-7-carboxamide (14r). Pale yellow oil (211.0 mg, yield 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.99 (s, 1H), 6.91-6.82 (m, 4H), 6.56 (s, 1H), 4.30-4.20 (m, 2H), 4.11-3.99 (m, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.42-3.35 (m, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 3.08-3.02 (m, 1H), 3.00-2.88 (m, 4H), 2.65 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.51 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.82-1.71 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.63, 150.14, 150.02, 146.06, 134.10, 129.14, 128.41, 128.13, 124.61, 123.50 (q, J_{C-F} = 278.9 Hz),

121.42, 118.67, 118.01, 115.02, 68.29, 68.20 (q, J_{C-F} = 35.1 Hz), 59.66, 54.99, 53.72, 50.62, 45.48, 41.90, 31.04, 28.32, 19.16; ESI-MS m/z: 530:532 = 3:1 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{32}ClF_3N_3O_4$ $[M+H]^+$ 530.2033, found 530.2030. Purity: 99.2%.

5-(2-((2-(5-bromo-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14s). Pale yellow oil (215.4 mg, yield 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.03-6.96 (m, 3H), 6.93 (s, 1H), 6.84-6.80 (m, 1H), 6.66 (s, 1H), 4.3-4.21 (m, 2H), 4.09-3.98 (m, 2H), 3.69 (t, *J* = 5.6 Hz, 2H), 3.41-3.32 (m, 2H), 3.14 (t, *J* = 7.0 Hz, 2H), 3.08-2.89 (m, 5H), 2.65 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.50 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.81-1.71 (m, 2H), 1.05 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 574:576 = 1:1 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{32}BrF_3N_3O_4$ $[M+H]^+$ 574.1528, found 574.1525. Purity: 96.4%.

5-(2-((2-(5-ethyl-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (14t). Pale yellow oil (206.1 mg, yield 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.98 (s, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.73-6.68 (m, 2H), 6.62 (s, 1H), 4.31-4.18 (m, 2H), 4.10 (t, *J* = 7.5 Hz, 2H), 3.68 (t, *J* = 5.5 Hz, 2H), 3.37 (t, *J* = 9.0Hz,2H), 3.16-3.10 (m, 2H), 3.08-2.87 (m, 5H), 2.69 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.62-2.46 (m, 3H), 1.82-1.67 (m, 2H), 1.17 (t, *J* = 7.7 Hz,3H), 1.07 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 524 $[M+H]^+$. ESI-HRMS calcd for $C_{27}H_{37}F_3N_3O_4$ $[M+H]^+$ 524.2736, found 524.2733. Purity: 97.0%.

(*R*)-5-(2-((2-(5-chloro-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide [(*R*)-14r]. (*R*)-**14r** was prepared using intermediate **10** as material and following the similar procedure carried out for **14r**. (215.9 mg, yield 88%), ee: 97.4%, Purity: 99.1%.

(*S*)-5-(2-((2-(5-chloro-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide [(*S*)-14r]. Racemate **14r** was resolved by CHIRALPAK AD-H colum to provide (***S*)-14r**, ee: 98.1%, Purity: 99.3%.

Compounds **23a-23m** were also prepared following the similar procedure carried out for **14a**.

5-(2-((2-(2-bromo-4-fluorophenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-indole-7-carboxamide (23a). White solid (182.4 mg, yield 80%), mp 134-135 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.28-7.23 (m, 2H), 7.21 (s, 1H), 7.07-7.00 (m, 1H), 7.00-6.93 (m,1H), 6.46 (d, J = 3.1 Hz, 1H), 4.43 (t, J = 6.9 Hz, 2H), 4.19-3.96 (m, 2H), 3.47 (t, J = 6.2 Hz, 2H), 3.19-3.02 (m, 2H), 3.00-2.75 (m, 3H), 2.00-1.88 (m, 2H), 1.19 (d, J = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 175.05, 158.15 (d, J_{C-F} = 241.8 Hz), 153.03, 133.03, 132.39, 131.66, 129.83, 124.65, 124.02, 122.38, 120.96 (d, J_{C-F} = 26.1 Hz), 115.79 (d, J_{C-F} = 22.8 Hz), 115.43 (d, J_{C-F} = 8.5 Hz), 113.37 (d, J_{C-F} = 9.8 Hz), 102.35, 70.02, 59.83, 55.68, 46.80, 46.08, 44.05, 34.59, 19.94; ESI-MS m/z: 492:494 = 1:1 $[M+H]^+$. ESI-HRMS calcd for $C_{23}H_{28}BrFN_3O_3$ $[M+H]^+$ 492.1298, found 492.1296. Purity: 96.0%.

5-(2-((2-(2-ethylphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-indole-7-carboxamide (23b). White solid (160.8 mg, yield 82%), mp 108-109 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 1.4 Hz, 1H), 7.13-7.09 (m, 2H), 7.09-7.05 (m, 2H), 6.88-6.83 (m, 1H), 6.78-6.71 (m, 2H), 6.52 (s, 1H), 6.46 (d, J = 3.2 Hz, 1H), 4.31 (t, J = 7.1 Hz, 2H), 4.06-3.92 (m, 2H), 3.46 (t, J = 5.8 Hz, 2H), 3.07-3.00 (m, 2H), 2.98-2.91 (m, 1H), 2.82-2.68 (m, 2H), 2.32 (q, J = 7.5 Hz, 2H), 2.00-1.85 (m, 2H), 1.11 (d, J = 6.2 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.75, 156.33, 132.63, 131.26, 130.57, 128.95, 126.82,

123.91, 123.11, 120.74, 120.22, 111.15, 101.84, 67.05, 58.98, 54.36, 46.25, 45.09, 43.19, 33.70, 23.09, 20.08, 14.01; ESI-MS m/z: 424 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{34}N_3O_3$ $[M+H]^+$ 424.2600, found 424.2591 Purity: 95.5%.

1-(3-hydroxypropyl)-5-(2-((2-(2-methoxyphenoxy)ethyl)amino)propyl)-*1H*-indole-7-carboxamide (23c). Pale yellow solid (169.4 mg, yield 86%), mp 133-134 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.1 Hz, 1H), 7.14 (s, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.91-6.84 (m, 2H), 6.83-6.76 (m, 3H), 6.57 (s, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 4.31 (t, *J* = 7.1 Hz, 2H), 4.09-4.01 (m, 2H), 3.64 (s, 3H), 3.45 (t, *J* = 5.7 Hz, 2H), 3.04-2.99 (m, 2H), 2.96-2.92 (m, 1H), 2.80 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.72 (dd, *J* = 13.6, 6.3 Hz, 1H), 1.98-1.88 (m, 2H), 1.08 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.70, 149.59, 148.14, 131.25, 130.65, 130.55, 128.93, 124.08, 123.30, 121.79, 121.14, 120.23, 114.41, 112.19, 101.85, 68.87, 59.04, 55.82, 54.59, 46.07, 45.07, 42.83, 33.79, 19.91; ESI-MS m/z: 426 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{32}N_3O_4$ $[M+H]^+$ 426.2393, found 426.2390. Purity: 95.4%.

5-(2-((2-(2-ethoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-indole-7-carboxamide (23d). Pale yellow oil (183.2 mg, yield 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.14 (s, 1H), 7.06 (d, *J* = 3.1 Hz, 1H), 6.89-6.86 (m, 1H), 6.85-6.80 (m, 2H), 6.79-6.71 (m, 2H), 6.58 (s, 1H), 6.45 (d, *J* = 3.1 Hz, 1H), 4.31 (t, *J* = 7.0 Hz, 2H), 4.10-4.00 (m, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.44 (t, *J* = 5.7 Hz, 2H), 3.07-2.96 (m, 3H), 2.81 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.71 (dd, *J* = 13.6, 6.3 Hz, 1H), 1.97-1.88 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.67, 149.03, 148.50, 131.22, 130.59, 130.55, 128.98, 124.05, 123.21, 121.92, 121.24, 120.24, 115.13, 114.00, 101.78, 69.15, 64.58, 58.96, 54.52, 46.10, 45.01, 42.83, 33.77, 20.00, 14.82; ESI-MS m/z: 440

$[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{34}N_3O_4$ $[M+H]^+$ 440.2549, found 440.2552. Purity: 99.4%.

5-(2-((2-(2-(benzyloxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-indole-7-carboxamide (23e). White solid (195.1 mg, yield 84%), mp 98-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.3 Hz, 1H), 7.34-7.22 (m,5H), 7.11 (d, *J* = 1.4 Hz, 1H), 7.05 (d, *J* = 3.2 Hz, 1H), 6.91-6.84 (m, 3H), 6.83-6.78 (m, 1H), 6.59 (s, 1H), 6.45 (d, *J* = 3.1 Hz, 1H), 6.39 (s, 1H), 4.94 (s, 2H), 4.27 (t, *J* = 7.0 Hz, 2H), 4.14-4.02 (m, 2H), 3.44 (t, *J* = 5.6 Hz, 2H), 3.07-2.94 (m, 3H), 2.78 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.68 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.97-1.90 (m, 2H), 1.05 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.59, 148.95, 148.83, 137.13, 131.21, 130.63, 130.48, 129.06, 128.52, 127.90, 127.33, 124.14, 123.19, 121.91, 121.82, 120.11, 115.17, 115.08, 101.84, 71.26, 69.19, 58.99, 54.50, 46.21, 44.92, 42.89, 33.78, 20.07; ESI-MS m/z: 502 $[M+H]^+$. ESI-HRMS calcd for $C_{30}H_{36}N_3O_4$ $[M+H]^+$ 502.2706, found 502.2701. Purity: 96.6%.

1-(3-hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-*1H*-indole-7-carboxamide (23f). Pale yellow oil (207.9 mg, yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.3 Hz, 1H), 7.13 (d, *J* = 1.3 Hz, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 7.01-6.84 (m, 3H), 6.81 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.67-6.54 (m, 2H), 6.45 (d, *J* = 3.2 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 4.23-4.11 (m, 2H), 4.11-3.97 (m, 2H), 3.46 (t, *J* = 5.8 Hz, 2H), 3.06-2.91 (m, 3H), 2.80-2.71 (m,2H), 1.99-1.88 (m, 2H), 1.09 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 494 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{31}F_3N_3O_4$ $[M+H]^+$ 494.2267, found 494.2260. Purity: 97.1%.

5-(2-((2-(5-fluoro-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-in

dole-7-carboxamide (23g). Pale yellow solid (191.0 mg, yield 93%), mp 116-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.4 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.79-6.66 (m, 2H), 6.63-6.51 (m, 3H), 6.45 (d, *J* = 3.2 Hz, 1H), 4.38-4.25 (m, 2H), 4.05-3.90 (m, 2H), 3.60 (s, 3H), 3.47 (t, *J* = 5.8 Hz, 2H), 3.05-2.94 (m, 3H), 2.79-2.70 (m, 2H), 2.00-1.86 (m, 2H), 1.08 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 444 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{31}FN_3O_4$ $[M+H]^+$ 444.2299, found 444.2305. Purity: 98.4%.

5-(2-((2-(4-fluoro-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-in dole-7-carboxamide (23h). White solid (186.9 mg, yield 91%), mp 141-142 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.96 (s, 1H), 7.53 (s, 1H), 7.42 (d, *J* = 1.2 Hz, 1H), 7.30 (d, *J* = 3.1 Hz, 1H), 7.03 (d, *J* = 1.2 Hz, 1H), 6.93-6.82 (m, 2H), 6.69-6.59 (m, 1H), 6.40 (dd, *J* = 7.8, 3.1 Hz, 1H), 4.32 (t, *J* = 6.9 Hz, 2H), 4.00-3.91 (m, 2H), 3.70 (s, 3H), 3.25 (t, *J* = 6.2 Hz, 2H), 2.99-2.89 (m, 3H), 2.88-2.81 (m, 1H), 2.53 (dd, *J* = 11.3, 5.6 Hz, 1H), 1.83-1.71 (m,2H), 0.98 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 444 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{31}FN_3O_4$ $[M+H]^+$ 444.2299, found 444.2289. Purity: 95.9%.

5-(2-((2-(4-chloro-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-in dole-7-carboxamide (23i). Pale yellow solid (185.3 mg, yield 87%), mp 131-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 6.84 (s, 1H), 6.79-6.71 (m, 3H), 6.63 (d, *J* = 9.1 Hz, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 4.29 (t, *J* = 7.1 Hz, 2H), 4.05-3.89 (m, 2H), 3.61 (s, 3H), 3.43 (t, *J* = 5.8 Hz, 2H), 3.03-2.87 (m, 3H), 2.80-2.63 (m,2H), 1.96-1.82 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 460:462 = 3:1 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{31}ClN_3O_4$ $[M+H]^+$ 460.2003, found 460.2000. Purity: 98.1%.

5-(2-((2-(4-bromo-2-methoxyphenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-i

ndole-7-carboxamide (23j). Pale yellow oil (200.8 mg, yield 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.3 Hz, 1H), 7.13 (d, *J* = 1.3 Hz, 1H), 7.09 (d, *J* = 3.2 Hz, 1H), 6.95-6.89 (m, 2H), 6.65 (s, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.49 (s, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 4.33 (t, *J* = 7.1 Hz, 2H), 4.06-3.90 (m, 2H), 3.63 (s, 3H), 3.48 (t, *J* = 5.7 Hz, 2H), 3.06-2.88 (m, 3H), 2.81-2.70 (m, 2H), 2.01-1.88 (m, 2H), 1.08 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 504:506 = 1:1 $[M+H]^+$. ESI-HRMS calcd for $C_{24}H_{31}BrN_3O_4$ $[M+H]^+$ 504.1498, found 504.1493. Purity: 96.3%.

5-(2-((2-(5-chloro-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxy propyl)-*1H*-indole-7-carboxamide (23k). Pale yellow solid (215.1 mg, yield 88%), mp 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.2 Hz, 1H), 7.11 (d, *J* = 1.3 Hz, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.87-6.80 (m, 3H), 6.65 (s, 1H), 6.60 (s, 1H), 6.45 (d, *J* = 3.1 Hz, 1H), 4.31 (t, *J* = 6.9 Hz, 2H), 4.20-4.06 (m, 2H), 4.06-3.90 (m, 2H), 3.47 (t, *J* = 5.7 Hz, 2H), 3.03-2.92 (m, 3H), 2.79 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.69 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.99-1.86 (m, 2H), 1.08 (d, *J* = 6.2 Hz, 3H); ESI-MS m/z: 528:530 = 3:1 $[M+H]^+$. ESI-HRMS calcd for $C_{25}H_{30}ClF_3N_3O_4$ $[M+H]^+$ 528.1877, found 528.1874. Purity: 97.2%.

1-(3-hydroxypropyl)-5-(2-((2-(5-methyl-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-*1H*-indole-7-carboxamide (23l). White solid (202.1 mg, yield 86%), mp 105-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.3 Hz, 1H), 7.12 (d, *J* = 1.3 Hz, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.68-6.64 (m, 2H), 6.61 (s, 1H), 6.56 (s, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 4.34-4.28 (m, 2H), 4.18-3.98 (m, 4H), 3.47 (t, *J* = 5.7 Hz, 2H), 3.06-2.99 (m, 2H), 2.98-2.91 (m, 1H), 2.80 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.71 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.25 (s, 3H), 1.99-1.87 (m, 2H), 1.08 (t, *J* = 8.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

172.57, 149.33, 145.21, 134.47, 131.31, 130.73, 130.64, 128.93, 124.12, 123.65 (q, J_{C-F} = 279.2 Hz), 123.18, 121.98, 120.12, 118.39, 115.66, 101.95, 68.63, 68.36 (q, J_{C-F} = 34.6 Hz), 59.15, 54.83, 46.12, 44.97, 42.94, 33.87, 21.18, 19.92; ESI-MS m/z: 508 $[M+H]^+$. ESI-HRMS calcd for $C_{26}H_{33}F_3N_3O_4$ $[M+H]^+$ 508.2423, found 508.2418. Purity: 99.0%.

5-(2-((2-(5-ethyl-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)-*1H*-indole-7-carboxamide (23m). White solid (217.3 mg, yield 90%), mp 107-108 ^oC. ^1H NMR (500 MHz, MeOD) δ 7.52 (s, 1H), 7.25 (d, J = 3.0 Hz, 1H), 7.17 (d, J = 1.1 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.83 (s, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 3.1 Hz, 1H), 4.41 (t, J = 7.0 Hz, 2H), 4.38-4.30 (m, 2H), 4.19-4.05 (m, 2H), 3.45 (t, J = 6.2 Hz, 2H), 3.15-2.97 (m, 3H), 2.93 (dd, J = 13.4, 6.3 Hz, 1H), 2.71 (dd, J = 13.4, 7.3 Hz, 1H), 2.58 (q, J = 7.6 Hz, 2H), 1.99-1.82 (m, 2H), 1.21 (t, J = 7.6 Hz, 3H), 1.11 (t, J = 11.0 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 175.17, 150.48, 146.98, 141.72, 132.90, 132.34, 131.53, 130.12, 125.33 (q, J_{C-F} = 277.9 Hz), 124.51, 124.03, 122.22, 121.85, 118.53, 115.97, 102.27, 69.58, 68.77 (q, J_{C-F} = 34.3 Hz), 59.80, 55.89, 46.92, 46.05, 43.73, 34.58, 29.43, 19.65, 16.28; ESI-MS m/z: 522 $[M+H]^+$. ESI-HRMS calcd for $C_{27}H_{35}F_3N_3O_4$ $[M+H]^+$ 522.2580, found 522.2575. Purity: 98.3%.

(*R*)-1-(3-hydroxypropyl)-5-(2-((2-(5-methyl-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-*1H*-indole-7-carboxamide [(*R*)-23l]. (*R*)-**23l** was prepared using intermediate **20** as material and following the similar procedure carried out for **23l**. (209.1 mg, yield 89%), ee: 96.7%, Purity: 99.4%.

(*S*)-1-(3-hydroxypropyl)-5-(2-((2-(5-methyl-2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-*1H*-indole-7-carboxamide [(*S*)-23l]. Racemate **23l** was resolved by

CHIRALPAK AD-H column to provide (***S***)-**23l**, ee: 97.5%, Purity: 99.8%.

Bioassay.

Chemicals and reagents. Silodosin was purchased from Longsheng chemical (Shanghai, China). Phenylephrine was purchased from Tokoyokasei (Tokoy, Japan), and noradrenaline was purchased from Matrix Scientific (Columbia, USA). Mammalian expression vectors encoding Gα16, α_{1A}-AR, α_{1B}-AR and α_{1D}-AR were purchased from the UMR cDNA Resource Center.

Cells culture and transfection. HEK293 cells obtained from American Type Culture Collection were maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 mg/L penicillin, and 100 mg/L streptomycin at 37 ^{o}C in a humidified atmosphere of 5% CO_2. HEK293 cells were cotransfected with plasmids encoding various α_1-ARs and Gα16 by electroporation. To generate stable cell lines, transfected cells were seeded onto 10-cm dishes and 1 mg/mL G418 and 40 μg/mL blasticidin were added to the culture medium 24 h later. The selection medium was changed every 3 days until colonies formed. A single colony was isolated, expanded, and tested with a calcium mobilization assay to confirm the expression and proper function of the transfected genes.

Calcium mobilization assay. Cells were seeded onto 96-well plates at a density of 3×10^4 cells/well and cultured overnight. Cells were then incubated with 2 μM Fluo-4 AM in HBSS (5.4 mM KCl, 0.3 mM Na_2HPO_4, 0.4 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 1.3 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.6 mM $MgSO_4$, 137 mM NaCl, 5.6 mM D-glucose and 250 μM sulfinpyrazone,

pH 7.4) at 37 ^{o}C for 45 min. After a thorough washing, 50 μL of HBSS containing either antagonists or 1% DMSO (negative control) were added. After incubation at room temperature for 10 min, 25 μL of agonist were dispensed into the well using a FlexStation microplate reader (Molecular Devices), and intracellular calcium change was recorded at an excitation wavelength of 485 nm and an emission wavelength of 525 nm.

Functional assays with isolated rat tissues. Freshly isolated male SD rat urethra and aorta were cleaned of adherent connective tissue and cut helically, and the endothelium was removed by gentle rubbing. The tissue strips were then mounted vertically inan organ bath containing 20 ml of Krebs-Henseleit solution of the following composition (mM): NaCl, 118; KCl 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; $NaHCO_3$, 25; KH_2PO_4, 1.2, glucose 11.1. These tissues were then mounted in the buffer maintained at 37 ^{o}C and aerated with carbogen (95% oxygen and 5% carbon dioxide) during the entire length of experiment. Resting tension applied was 1 g for rat urethra or aorta, and the responses were recorded isometrically through force-displacement transducers. The tissue strips noradrenaline cumulative concentration response curve was obtained in the absence or presence of compounds with different concentrations incubated for 20 min.

The BPH animal model. Male SD rats (200-250 g) were randomly assigned to one of two groups- either castrated or subjected to a sham surgery. After a 7-day recovery, the castrated animals (BPH group, n = 48) were subcutaneously injected with olive oil mixed with testosterone (20 mg/kg per day) for 4 weeks, and sham operated animals (sham group, n = 12) were subcutaneously injected with olive oil.

Micturition recording. Micturition behavior was measured 4 weeks after the induction of

BPH. We divided the rats into 5 groups: sham (n = 12), vehicle (n = 12), silodosin (n = 12), (*R*)-**14r** (n = 12) and (*R*)-**23l** (n = 12). Four doses of each compound were tested (0.3, 1, 3, and 10 mg/kg). One day after a lower-dose administration, rats switch to the next higher-dose administration. Rats were weighed and underwent an oral administration of compounds, and 0.5% carboxymethylcellulose sodium was given as a vehicle control. Twenty minutes after compound administration, rats received distilled water (30 mL/kg) orally. Each rat was placed in a metabolic cage in which urine was directed into collectors on an electronic balance (YP2002, Yueping Co, Ltd, Shanghai, China) immediately after water loading. Micturition frequency and mean voided volume was monitored for 2 hours.

Data analysis. Data were analyzed with GraphPad Prism software (GraphPad). Nonlinear regression analysis was performed to generate dose-response curves and calculate concentrations for 50% inhibition (IC_{50}) values. Means ± SEM were calculated using this software. The analyses were assessed by a Student *t* test. A p value < 0.05 was considered statistically significant.

Plasma protein binding assays. The plasma protein binding (PPB) assays in rat plasma were evaluated using equilibrium dialysis. During the experiment, the tested compounds were spiked into plasma to achieve the concentration of 2 μM. The compounds spiked plasma was kept in donor side, blank PBS buffer was kept in receiver side. This assembly was kept in CO_2 incubator and maintained at 37 ^{o}C for 16 h to achieve equilibrium between plasma and PBS buffer. The donor and receiver sides were collected after the incubation. The concentration in both sides was determined by UPLC-MS/MS analysis. PPB rate was calculated using the following equation.

$$\text{PPB}\ (\%) = \frac{\text{Concentration}_{\text{donor}}}{\text{Concentration}_{\text{donor}} + \text{Concentration}_{\text{receiver}}} \times 100$$

Sample pretreatment. The donor side (20 μL) was mixed with PBS (pH = 7.4, 60 μL). The receiver side (60 μL) was mixed with plasma (20 μL). Then the mixture was precipitated with 200 μl ice cold acetonitrile. Samples were vortexed and centrifuged at 11000 g for 5 min. The supernatant was then injected into LC-MS/MS for analysis.

UPLC-MS/MS conditions. Chromatography was performed on an Acquity UPLC BEH C18 column (1.7 μm, 2.1 x 50 mm, WatersCorp.Milford, MA, USA) in an Acquity UPLC system (Waters Corp). The mobile phase consisted 10 mM ammonium acetate with 0.1% formic acid in water (A) and acetonitrile (B). The gradient elution program was set up as follows: 0-1.0 min (20-95% B); 1.0-1.5 min (held at 95% B); 1.5-2.2 min (recondition column). The flow rate was 0.5 mL/min. The column temperature was set at 40 ^{o}C. Mass spectrometric detection was conducted on an AB6500 triple quadrupole mass spectrometer (Applied Biosystems, Con-cord, Ontario, Canada) equipped with an ESI source. The mass spectrometer was operated in the positive ion mode. The optimized tuning parameters were as follows: ionspray voltage, 5000 V; source temperature, 500 ^{o}C; nebulizer gas, 50 psi; heater gas, 60 psi; curtain gas, 20 psi and collision activated dissociation gas, 8 psi. The declustering potential was set at 130 V. The optimized multiple reaction monitoring (MRM) fragmentation transitions were m/z 530→m/z 261 and m/z 508→m/z 259 for (*R*)-**14r** and (*R*)-**23l**, respectively. The optimized multiple reaction monitoring (MRM) fragmentation transitions was m/z 496→m/z 479, 261, 244 for Silodosin. The dwell time for each transition was kept at 60 ms. Data were collected and processed using Analyst1.6.1 software (Applied Biosystems).

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; α-adrenergic receptor, α-AR; α_1-ARs, α_1-adrenergic receptors; GPCR, G protein-coupled receptor; AUC, area under the curve; MRT, mean retention time; SAR, structure-activity relationship

REFERENCES

(1) Mobley, D.; Feibus, A.; Baum, N. Benign prostatic hyperplasia and urinary symptoms: evaluation and treatment. *Postgrad. Med*. **2015**, *127*, 301-307.

(2) Thorpe, A.; Neal, D. Benign prostatic hyperplasia. *Lancet*. **2003**, *361*, 1359-1367.

(3) Pagano, E.; Laudato, M.; Griffo, M.; Capasso, R. Phytotherapy of benign prostatic hyperplasia. A minireview. *Phytother. Res*. **2014**, *28*, 949-955.

(4) Wasserman, N. F. Benign prostatic hyperplasia: A review and ultrasound classification. *Radiol. Clin. North. Am*. **2006**, *44*, 689-710.

(5) Chapple, C. R.; Roehrborn, C. G. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: Focus on the bladder. *Eur. Urol*. **2006**, *49*, 651-659.

(6) Kim, T. H.; Han, D. H.; Ryu, D. S.; Lee, K. S. The impact of lower urinary tract symptoms on quality of life, work productivity, depressive symptoms, and sexuality in Korean men aged 40 years and older: a population-based survey. *Int. Neurourol. J*. **2015**, *19*, 120-129.

(7) Sountoulides, P.; van Dijk, M. M.; Wijkstra, H.; de la Rosette, J. J.; Michel, M. C. Role of voiding and storage symptoms for the quality of life before and after treatment in men with voiding dysfunction. *World. J. Urol*. **2010**, *28*, 3-8.

(8) Abáigar-Pedraza, I.; Pelluch-Auladell, A. M.; Galiano-Baena, J. F.; Mira-Moreno, A.; Bravo-López, D. F.; Lobato-Encinas, J. J. Quality of life of patients with benign prostatic hyperplasia (BPH): endoscopic surgery versus laser therapy. *Arch. Esp. Urol*. **2014**, *67*, 823-830.

(9) Lebdai, S.; Descazeaud, A. Management of benign prostate hyperplasia. *Prog. Urol*. **2014**, *24*, 929-933.

(10) De-Nunzio, C.; Tubaro, A. Benign prostatic hyperplasia in 2014: innovations in medical and surgical treatment. *Nat. Rev. Urol*. **2015**, *12*, 76-78.

(11) Martov, A. G.; Ergakov, D. V.; Andronov, A. S.; Baĭkov, N. A. Transurethral electroenucleation of benign prostatic hyperplasia. *Urologiia*. **2014**, *5*, 95-101.

(12) Schauer, I.; Madersbacher, S. Medical treatment of lower urinary tract symptoms/benign prostatic hyperplasia: anything new in 2015. *Curr. Opin. Urol*. **2015**, *25*, 6-11.

(13) Filson, C. P.; Wei, J. T.; Hollingsworth, J. M. Trends in medical management of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Urology*. **2013**, *82*, 1386-1392.

(14) Gilling, P. TURP remains a safe and effective alternative for benign prostatic hyperplasia (BPH) surgery. *BJU. Int*. **2014**, *113*, 5-6.

(15) Russo, A.; La Croce, G.; Capogrosso, P.; Ventimiglia, E.; Colicchia, M.; Serino, A.; Mirone, V.; Damiano, R.; Montorsi, F.; Salonia, A. Latest pharmacotherapy options for benign prostatic hyperplasia. *Expert. Opin. Pharmacother*. **2014**, *15*, 2319-2328.

(16) Kaplan, S. A. Treatment patterns in alpha-blocker therapy for benign prostatic hyperplasia. *J. Urol*. **2015**, *193*, 1593-1594.

(17) Mathur, R. P.; Nayak, S.; Sivaramakrishnan, R.; Jain, V. Role of alpha blockers in hypertension with benign prostatic hyperplasia. *J. Assoc. Physicians. India*. **2014**, *62*, 40-44.

(18) Fonseca, J.; Martins da Silva, C. The diagnosis and treatment of lower urinary tract

symptoms due to benign prostatic hyperplasia with α-blockers: focus on silodosin. *Clin. Drug. Investig*. **2015**, *35*, 17-18.

(19) Schoenfeld, M. J.; Shortridge, E. F.; Gelwicks, S. C.; Cui, Z.; Wong, D. G. Treatment patterns in alpha-blocker therapy for benign prostatic hyperplasia. *Am. J. Mens. Health*. **2014**, *8*, 267-272.

(20) Park, S. G.; Chung, B. H.; Lee, S. W.; Park, J. K.; Park, K.; Cheon, J.; Lee, K. S.; Kim, H. J.; Seong, D. H.; Oh, S. J.; Kim, S. W.; Lee, J. Y.; Choo, S. H.; Choi, J. B. Alpha-blocker treatment response in men with lower urinary tract symptoms based on sympathetic activity: prospective, multicenter, open-labeled, observational study. *Int. Neurourol. J*. **2015**, *19*, 107-112.

(21) Schwinn, D. A.; Johnston, G. I.; Page, S. O.; Mosley, M. J.; Wilson, K. H.; Worman, N. P.; Campbell, S.; Fidock, M. D.; Furness, L. M.; Parrysmith, D. J.; Peter, B.; Bailey, D. S. Cloning and pharmacological characterization of human alpha-1-adrenergic receptors : sequence corrections and direct comparison with other specie homologs. *J. Pharmacol. Exp. Ther*. **1995**, *272*, 134-142.

(22) Weinberg, D. H.; Trivedi, P.; Tan, C. P.; Mitra, S.; Perkinsbarrow, A.; Borkowski, D.; Strader, C. D.; Bayne, M. Cloning, expression and characterization of human α adrenergic receptors α_{1A}, α_{1B} and α_{1D}. *Biochem. Biophys. Res. Comm*. **1994**, *201*, 1296-1304.

(23) Muramatsu, I.; Oshita, M.; Ohmura, T.; Kigoshi, S.; Akino, H.; Gobora, M.; Okada, K. Pharmacological characterization of alpha 1-adrenoceptor subtypes in the human prostate: functional and binding studies. *Br. J. Urol*. **1994**, *74*, 572-578.

(24) Hieble, J. P.; Bylund, D. B.; Clarke, D. E.; Eikenburg, D. C.; Langer, S. Z.;

Lefkowitz, R. J.; Minneman, K. P.; Ruffolo, RR Jr. International union of pharmacology. X. recommendation for nomenclature of alpha 1-adrenoceptors: consensus update. *Pharmacol Rev*. **1995**, *47*, 267-270.

(25) Zhong, H.; Minneman, P. α_1-Adrenoceptor subtypes. *Eur. J. Pharmacol*. **1999**, *375*, 261-276.

(26) Michelotti, G. A.; Price, D. T.; Schwinn, D. A. α_1-Adrenergic receptor regulation: basic science and clinical implications. *Pharmacol. Ther*. **2000**, *88*, 281-309.

(27) Docherty, J. R. Subtypes of functional α_1-adrenoceptor. *Cell. Mol. Life Sci*. **2010**, *67*, 405-417.

(28) Moriyama, N.; Kurimoto, S.; Horie, S.; Nasu, K.; Tanaka, T.; Yano, K.; Hirano, H.; Tsujimoto, G.; Kawabe, K. Detection of alpha 1-adrenoceptor subtypes in human hypertrophied prostate by in situ hybridization. *Histochem. J*. **1996**, *28*, 283-288.

(29) Nasu, K.; Moriyama, N.; Kawabe, K.; Tsujimoto, G.; Murai, M.; Tanaka, T.; Yano, J. Quantification and distribution of alpha 1-adrenoceptor subtype mRNAs in human prostate: comparison of benign hypertrophied tissue and non-hypertrophied tissue. *Br. J. Pharmacol*. **1996**, *119*, 797-803.

(30) Ruffolo, RR Jr.; Hieble, J. P. Adrenoceptor pharmacology: urogenital applications. *Eur. Urol*. **1999**, *36*, 17-22.

(31) Yamagishi, R.; Akiyama, K.; Nakamura, S.; Hora, M.; Masuda, N.; Matsuzawa, A.; Murata, S.; Ujiie, A.; Kurashina, Y.; Iizuka, K.; Kitazawa, M. Effect of KMD-3213, an alpha 1A-adrenoceptor-selective antagonist, on the contractions of rabbit prostate and rabbit and rat aorta. *Eur. J. Pharmacol*. **1996**, *315*, 73-79.

(32) Roehrborn, C. G.; Schwinn, D. A. Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. *J. Urol*. **2004**, *171*, 1029-1035.

(33) Lepor, H.; Auerbach, S.; Puras, B. A.; Narayan, P.; Soloway, M.; Lowe, F.; Moon, T.; Leifer, G.; Madsen, P. Randomized placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. *J. Urol*. **1992**, *148*, 1467-1474.

(34) Lepor, H.; Tang, R.; Meretyk, S.; Shapiro, E. Binding and functional properties of alpha1 adrenoceptors in different regions of the human prostate. *J. Urol*. **1993**, *150*, 252-256.

(35) Michelotti, G. A.; Price, D. T.; Schwinn, D. A. Alpha 1-adrenergic receptor regulation: basic science and clinical implications. *Pharmacol. Ther*. **2000**, *88*, 281-309.

(36) Malloy, B. J.; Price, D. T.; Price, R. R.; Bienstock, A. M.; Dole, M. K.; Funk, B. L.; Rudner, X. L.; Richardson, C. D.; Donatucci, C. F.; Schwinn, D. A. Alpha1-adrenergic receptor subtypes in human detrusor. *J. Urol*. **1998**, *160*, 937-943.

(37) Schwinn, D. A.; Roehrborn, C. G. Alpha1-adrenoceptor subtypes and lower urinary tract symptoms. *Int. J. Urol*. **2008**, *15*, 193-199.

(38) Te, A. E. A modern rationale for the use of phenoxybenzamine in urinary tract disorders and other conditions. *Clin. Ther*. **2002**, *24*, 851-861.

(39) Generali, J. A.; Cada, D. J. Prazosin: benign prostatic hyperplasia. *Hosp. Pharm*. **2013**, *48*, 196-197.

(40) Wilt, T. J.; Howe, W.; MacDonald, R. Terazosin for treating symptomatic benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU. Int*. **2002**, *89*,

214-225.

(41) Sun, G. H.; Tsui, K. H.; Wu, T. T.; Chang, C. H.; Cheng, C. L.; Schou, M. Efficacy and safety of the doxazosin gastrointestinal therapeutic system for the treatment of benign prostate hyperplasia. *Kaohsiung. J. Med. Sci*. **2010**, *26*, 532-539.

(42) Ben Rhouma, S.; H'sairi, M.; Adbi, H.; Binous, M. Y.; Nouira, Y.; Ben Raies, N.; Mosbah, A. T.; Horchani, A. Impact of alfuzosin 10 mg once daily on quality of life in tunisian patients with lower urinary symptoms suggestive of benign prostatic hyperplasia. *Tunis. Med*. **2015**, *93*, 164-167.

(43) Shelbaia, A.; Elsaied, W. M.; Elghamrawy, H.; Abdullah, A.; Salaheldin, M. Effect of selective alpha-blocker tamsulosin on erectile function in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. *Urology*. **2013**, *82*, 130-135.

(44) Gorgel, S. N.; Sefik, E.; Kose, O.; Olgunelma, V.; Sahin, E. The effect of combined therapy with tamsulosin hydrochloride and meloxicam in patients with benign prostatic hyperplasia symptoms and impact on nocturia and sleep quality. *Int Braz. J. Urol*. **2013**, *39*, 657-662.

(45) Shtein, R. M.; Hussain, M. T.; Cooney, T. M.; Elner, V. M.; Hood, C. T. Effect of tamsulosin on iris vasculature and morphology. *J. Cataract. Refract. Surg*. **2014**, *40*, 793-798.

(46) Pande, S.; Hazra, A.; Kundu, A. K. Evaluation of silodosin in comparison to tamsulosin in benign prostatic hyperplasia: a randomized controlled trial. *Indian. J. Pharmacol*. **2014** ,*46*, 601-607.

(47) Keating, G. M. Silodosin: a review of its use in the treatment of the signs and symptoms of benign prostatic hyperplasia. *Drugs*. **2015**, *75*, 207-217.

(48) Castro-Díaz, D.; Callejo, D.; Cortés, X.; Pérez, M. Study of quality of life in patients with benign prostatic hyperplasia under treatment with silodosin. *Actas. Urol. Esp*. **2014**, *38*, 361-366.

(49) Moriyama, N.; Akiyama, K.; Murata, S.; Taniguchi, J.; Ishida, N.; Yamazaki, S.; Kawabe, K. KMD-3213, a novel alpha1A-adrenoceptor antagonist, potently inhibits the functional alpha1-adrenoceptor in human prostate. *Eur. J. Pharmacol*. **1997**, *16*, 39-42.

(50) Akiyama, K.; Hora, M.; Tatemichi, S.; Masuda, N.; Nakamura, S.; Yamagishi, R.; Kitazawa, M. KMD-3213, a uroselective and long-acting alpha(1a)-adrenoceptor antagonist, tested in a novel rat model. *J. Pharmacol. Exp. Ther*. **1999**, *291*, 81-91.

(51) Rossi, M.; Roumeguère, T. Silodosin in the treatment of benign prostatic hyperplasia. *Drug. Des. Devel. Ther*. **2010**, *27*, 291-297.

(52) Huang, X. -H.; Aslanian, R. G. Case studies in modern drug discovery and development. *John Wiley & Sons, Inc*. 2012, pp. 360-391.

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