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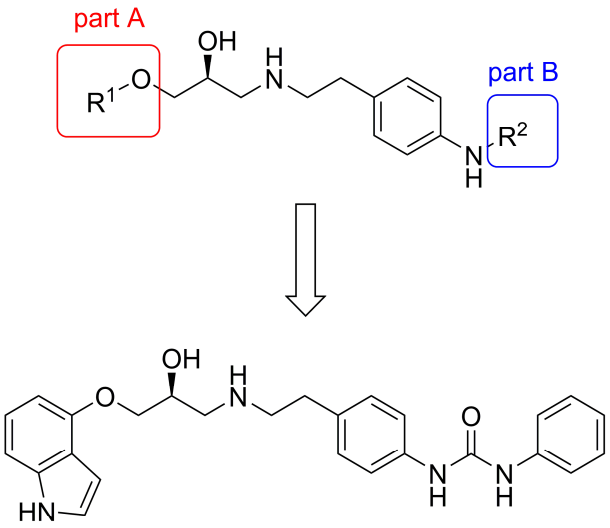

compound **23d**

In vitro, compound **23d** was found to display 23-fold more potent Beta3-AR antagonist activity (EC_{50} = 0.5117 nM) than L-748,337 (EC_{50} = 11.91 nM).

In vivo, compound **23d** could alleviate weight loss and inhibit tumor growth in C26 tumor cachexia animal model.

Design and Synthesis of aryloxypropanolamine as β_3-adrenergic receptor antagonist in cancer and lipolysis

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Abstract

β-adrenergic receptors (β-ARs) are broadly distributed in various tissues and regulate a panel of important physiological functions and disease states including cancer. Above all, β_3-adrenergic receptor (β_3-AR) plays a significant role in regulating lipolysis and thermogenesis in adipose tissue. In this study, we designed and synthesized a series of novel L-748,337 derivatives as selective human β_3-AR antagonists. Among all the tested L-748,337 analogs, compound **23d** was found to display 23-fold more potent β_3-AR antagonist activity (EC_{50} = 0.5117 nM) than L-748,337 (EC_{50} = 11.91 nM). *In vivo*, compound **23d** could alleviate weight loss and inhibit tumor growth in C26 tumor cachexia animal model.

Keywords: *β-adrenergic receptor, antagonist, cancer, lipolysis and cachexia*

1. Introduction

β-Adrenergic receptors (β-ARs) belong to the superfamily of membrane proteins termed G protein-coupled receptors. β-ARs are distributed in the effector cells of most of the sympathetic nerve fibers, and the receptors are of three types, the β_1 receptor, the β_2 receptor and the β_3 receptor.

In mouse models of breast and prostate carcinomas, [1, 2] as well as malignant melanoma and leukemia, [3, 4] β-ARs antagonists have been found to block stress-induced enhancement of tumor progression and/or metastasis without influencing primary tumor growth *in vivo* or tumor cell proliferation *in vitro*. β-ARs antagonists alone or in combination with nonsteroidal anti-inflammatory agents (NSAID) have also been found to inhibit surgery-induced metastasis in animal model. [3, 5, 6] Preclinical laboratory models and human pharmaco-epidemiologic studies both indicate that β-antagonists are likely to be the most effective drugs in inhibiting the micrometastatic spread of early-stage tumors. [7]

It has been found that β_3-AR plays a significant role in regulating lipolysis and thermogenesis in both rodent and human adipose tissue. In rodent white adipose tissue, β_3-AR accounts for 90% of the β-ARs on the cell surface. [8] Data show that chronic inflammation together with β-adrenergic activation functionally cooperate in the pathogenesis of increased adipose tissue thermogenesis in cachexia. [9] β-adrenergic blockers can reduce white blood cell adipose tissue (WAT) browning, decrease the severity of cachexia. β_3-AR blockade may protect against cachexia by means of decreased lipolysis. [10]

A few antagonists of β_3-AR have been identified. At present, there are two typical β_3-AR inhibitors: aryloxy propanolamine tetrahydrate β_3-AR inhibitor (SR59230A) [11] and aryloxypropanolamine β_3-AR inhibitor (L-748,337), and their structures are shown in Figure 1. SR59230A displays high affinity at human cloned β_1-AR and β_2-AR. Therefore, SR59230A is a potent and nonselective β-AR antagonist. [12] In contrast, L-748,337 displays more than 90-fold selectivity for human β_3-AR over β_1-AR, 45-fold selectivity for human β_3-AR over β_2-AR, respectively. [12] In this study, we clarified the process of exploring and developing potent and selective β_3-AR antagonists. Meanwhile, we discussed the structure-relationship (SAR) data that deviated from that of the aryloxypropanolamine chemotype.

Our design concept is outlined in Figure 2. We planned to introduce 2-ethylphenyl group or 1*H*-indole group into the left-wing (part A) and to introduce urea group into the right-wing (part B) to attempt to improve β_3-AR antagonist activity. We design compounds I based on an aryloxypropanolamine scaffold to facilitate rapid synthesis and SAR evaluation. This paper describes these efforts and the discovery of a novel, potent and selective human β_3-AR antagonist. These compounds would maintain favorable activities *in vitro* and *in vivo* with decreasing the severity of cancer cachexia and inhibiting the growth of cancer cells.

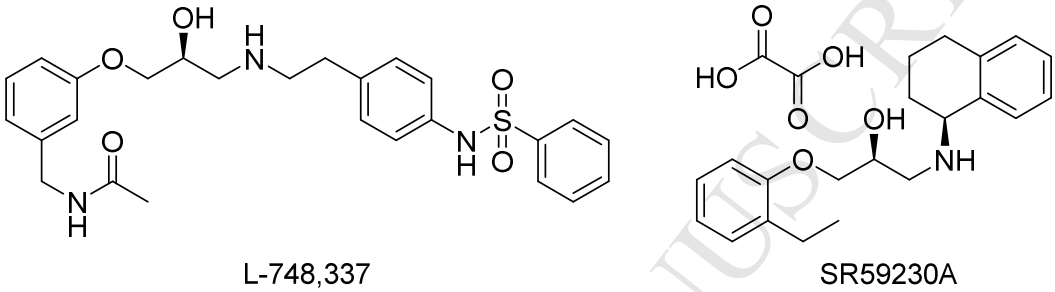


Figure 1. Chemical structure of early β_3-AR antagonist.

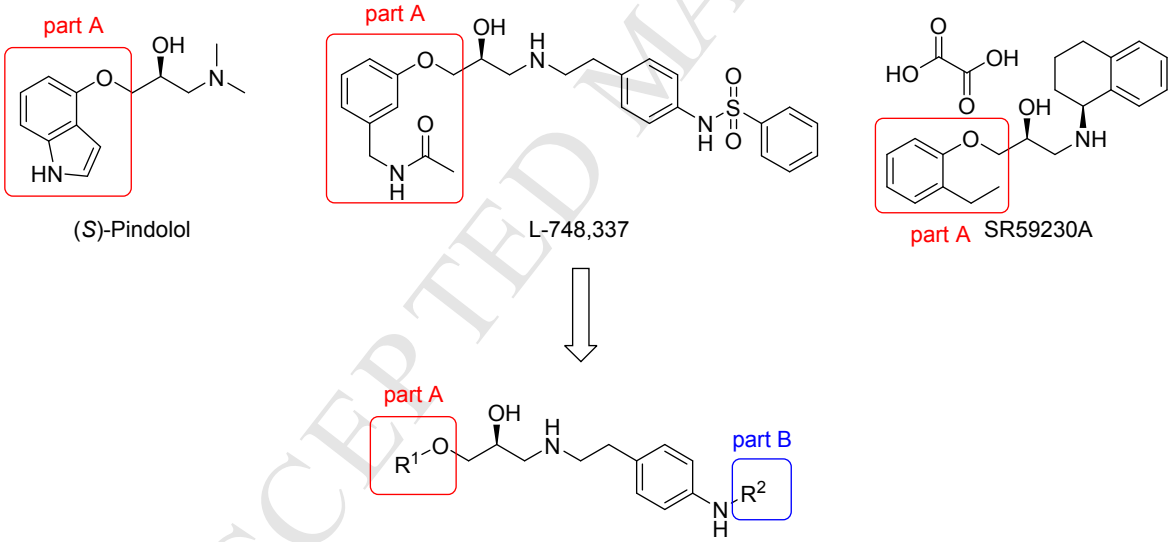


Figure 2. Design of compound based on (*S*)-pindolol, L-748,337 and SR59230A.

2. Results and discussion

2.1. Chemistry

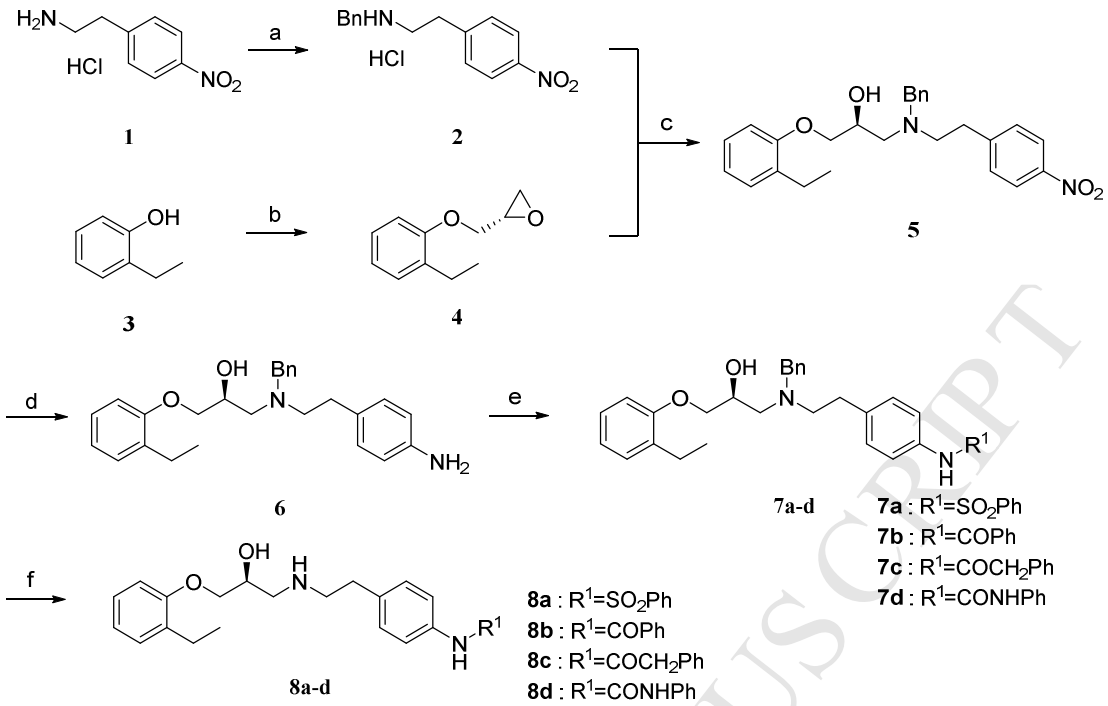
SR59230A derivatives **8a-d** were prepared as illustrated in Scheme 1. A commercially available *p*-nitrophenylethylamine hydrochloride salt (**1**) reacted with paraformaldehyde to form the Schiffs base. Without purification, the Schiffs base was reduced with $NaBH_4$ directly to produce intermediate **2**. 2-ethylphenol (**3**) was treated with sodium hydroxide in

water and dioxane, and the resultant sodium salt was alkylated with commercially available (*R*)-(-)-epichlorohydrin to provide epoxide **4**. Aniline intermediate **6** was synthesized by the reduction of the nitro group in the intermediate **5**, which in turn was made from the coupling of intermediate **2** and compound **4**. The coupling of **6** with the appropriate arylacetic acid derivatives, followed by deprotection of the benzyl group by hydrogenolysis afforded the desired products **8a-d**.

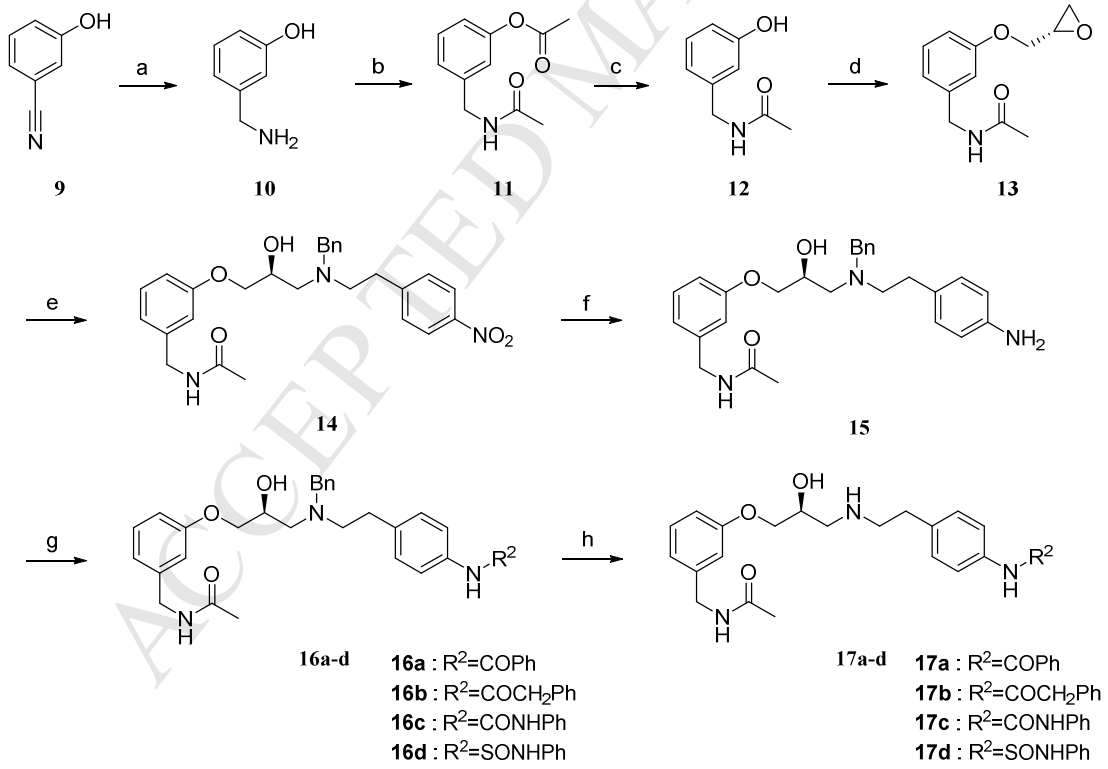
L-748,337 derivatives **17a-d** were prepared from compound 1**3** in the same manner as the synthesis of **8a-d** as illustrated in Scheme 2. Compound **13** was synthesized by 4 reactions from the starting material 3-hydroxybenzonitrile (**9**) *via* reduction, acylation, hydrolyzation and alkylation.

Scheme 3 shows the synthesis of Indole derivatives **23a-m** by the starting material 1*H*-indol-4-ol (**18**) in the same synthesis route of **8a-d**. 1*H*-indol-4-ol (**18**) was alkylated with (*R*)-(-)-epichlorohydrin using sodium hydroxide as a base to produce epoxide **19**. After the coupling of epoxide **19** and intermediate **2**, following by reduction of the nitro group with Tin(II) chloride, the desired product compound **21** was given. The coupling of compound **21** with the appropriate arylacetic acid derivatives, followed by de-protection of the benzyl group by hydrogenolysis afforded the desired products **23a-m**.

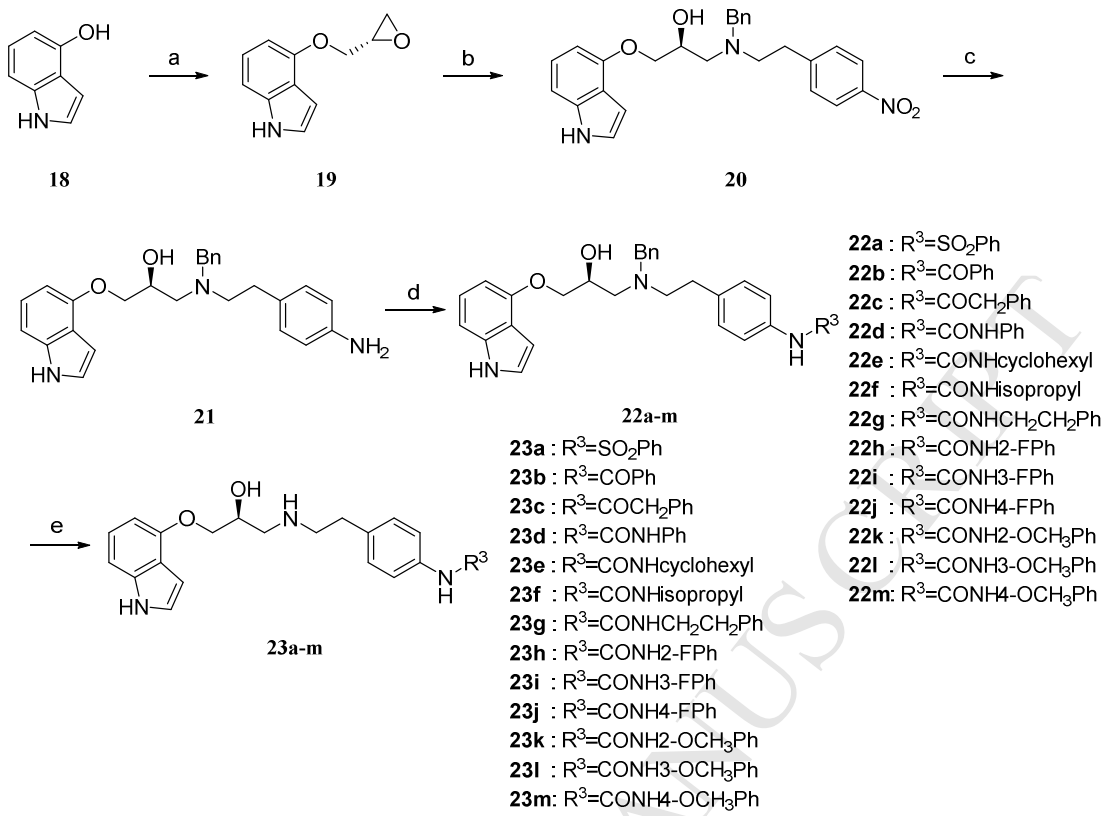
Compounds **27a-f** were prepared from aniline intermediate **21** as illustrated in Scheme 4. The coupling of aniline intermediate **21** with the appropriate arylacetic acid derivatives, followed by reduction of the nitro group with $Fe(OH)_3$ and hydrazine hydrate afforded the desired products **25a-c**. The acylation of **25a-c** with the appropriate arylacetic acid derivatives, followed by deprotection of the benzyl group by hydrogenolysis afforded the desired products **27a-f**.



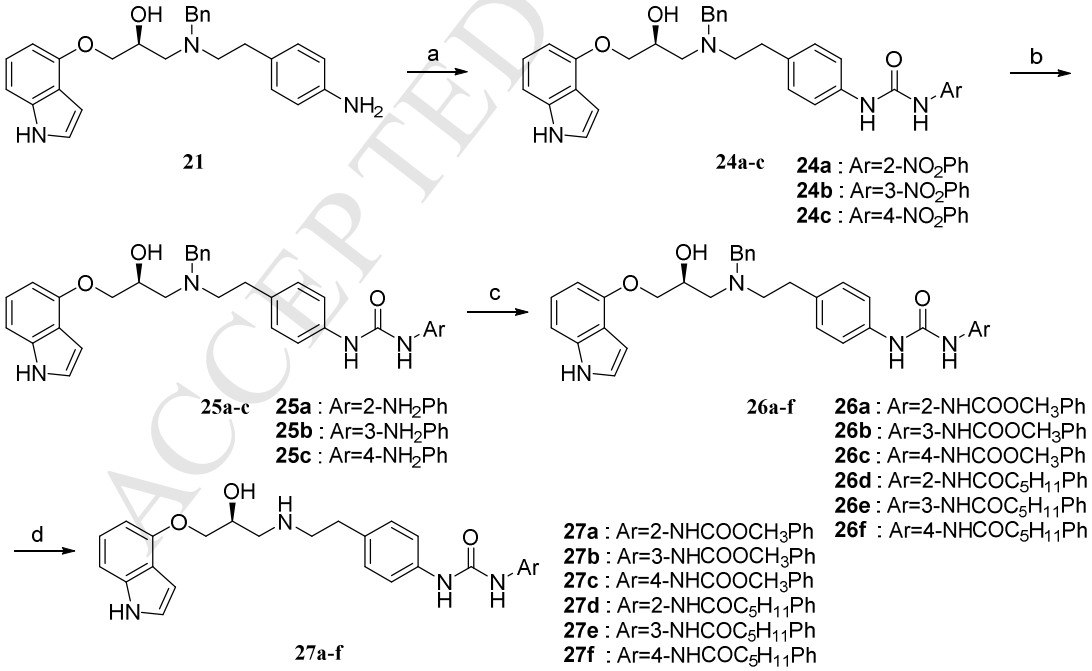
Scheme 1. Synthesis of SR59230A derivatives **8a-d**. Reagent and conditions: (a) Paraformaldehyde EtOH reflux, then $NaBH_4$, EtOH, rt; (b) (*R*)-(-)-Epichlorohydrin, NaOH, warer/Dioxane, rt; (c) NaOH, IPA, relfux; (d) $SnCl_2$, EtOH, reflux; (e) R^1Cl, Pyridine, DCM, rt; (f) Raney-Ni, H_2, MeOH, rt.



Scheme 2. Synthesis of L-748,337 derivatives **17a-d**. Reagent and conditions: (a) Raney-Ni, H_2, MeOH, rt; (b) Acetyl chloride, Pyridine, DCM, rt; (c) 15% NaOH(aq), MeOH, rt; (d) (*R*)-(-)-Epichlorohydrin, NaOH, warer/Dioxane, rt; (e) NaOH, IPA, relfux; (f) $SnCl_2$, EtOH, reflux; (g) R^2Cl, Pyridine, DCM, rt; (h) Raney-Ni, H_2, MeOH, rt.



Scheme 3. Synthesis of Indole derivatives **23a-m**. Reagent and conditions: (a) (*R*)-(-)-Epichlorohydrin, NaOH, warer/Dioxane, rt; (b) NaOH, IPA, relfux; (c) $SnCl_2$, EtOH, reflux; (d) R^3Cl, Pyridine, DCM, rt; (e) Raney-Ni, H_2, MeOH, rt.



Scheme 4. Synthesis of Indole derivatives **27a-f**. Reagent and conditions: (a) ArCNO, Pyridine, DCM, rt; (b) $Fe(OH)_3$, $N_2H_4H_2O$, EtOH, reflux; (c) Pyridine, DCM, rt; (d) Raney-Ni, H_2, MeOH, rt.

2.2. β_3-AR antagonist activity in vitro

All compounds listed in Table1, 2 and 3 were evaluated *in vitro* for their antagonist activities by using calcium mobilization assay with HEK293 cells expressing human β_3-, β_2- or β_1-ARs. The results of reference compounds (L-748,337) are also shown for comparison in Table 1.

The L-748,337 of our lead compound was found to be a modestly potent β_3-AR antagonist (EC_{50} = 11.91 nM) with a lower potency for the β_2-AR (EC_{50} = 23490 nM) and β_1-AR (EC_{50} = 889.0 nM). In order to improve β_3-AR antagonist activity and selectivity over β_2- and β_1-ARs, modification of the sulfonamido moiety in L-748,337 with the other functional moieties was investigated Table 1.

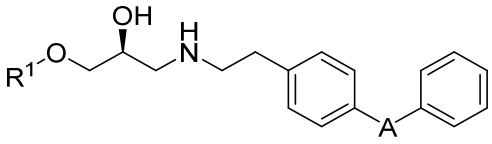
Replacement of the sulfonamido moiety of L-748,337 with the formamide moiety (**17a**) and the acetamide moiety (**17b**) resulted in slightly increased potency at the β_3-AR (EC_{50} = 7.805 nM and 4.584 nM, respectively). Next, replacement of the sulfonamido moiety in L-748,337 with the ureido moiety (**17c**) and the thiourea moiety (**17d**) resulted in a 3-fold increase in potency at the β_3-AR with antagonist activity (EC_{50} = 4.699 nM and 3.412 nM, respectively) relative to L-748,337. The thiourea moiety is well-known to produce toxic effects and unsuitable for drug designing, so we chose urea group for the next study. These results indicated that the urea group played an important role in β_3-AR antagonist activity (EC_{50} = 4.699 nM) and selectivity over β_2-AR (EC_{50} = 9842 nM) and β_1-AR (EC_{50} = 12700 nM). Then, using 2-ethylphenyl and 1*H*-indole as representatives, the phenoxymethyl compound **23d** displayed high potent β_3-AR antagonist activity (EC_{50} = 0.5117 nM) as compared to L-748,337 (EC_{50} = 11.91 nM) and high selectivity over β_2-AR (100-fold) and β1-AR (6-fold).

In order to improve β_3-AR antagonist activity, modification of the substituent on the thiourea moiety in **23d** was examined as shown in Table 2. For β_3-AR activity, while a bulky group such as cyclohexyl group and the alkyl substituted derivatives, **23e**, **23f** and **23g**, were less potent than compound **23d**. These results revealed that replacement of the phenyl ring with a cyclohexyl ring and isopropyl group and the insertion of an ethylene group between the phenyl ring and ureido moiety in **23d** may not have been efficacious for improving antagonist activity at the β_3-AR.

We then examined the effects of the substituents on the phenyl ring in **23d** in Table 2.

The introduction of the fluorine group as an electron-withdrawing group on the phenyl ring of the phenylthiourea moiety (**23h-j**) resulted in slightly decreased antagonist activity at the β_3-AR relative to **23d**, and the rank of order of potency seemed to be *para*-fluorine (EC_{50}= 2.491 nM) > *meta*-fluorine (EC_{50}= 2.927 nM) > *ortho*-fluorine (EC_{50}= 3.575 nM). The methoxy and methyl carbamate group as an electron-donating group was also introduced on the phenyl ring of the phenylthiourea moiety (**23k-m**, **27a-c**), which yielded results better than those of the fluorinephenyl derivatives. The pentanamide group as a huge group was also introduced on the phenyl ring of the phenylthiourea moiety (**27d-f**) resulted decreased antagonist activity at the β_3-AR relative to **23d**, especially *para*- pentanamide. These results revealed that the introduction of a substituent on the phenyl ring of the phenylthiourea moiety in **23d** allowed the potency of β_3-AR to be maintained, but no one can be stronger than that of **23d**.

Table 1. β_3-AR antagonist activity of aryloxypropanolamine derivatives.



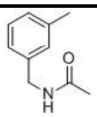
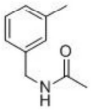
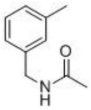
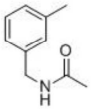
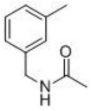
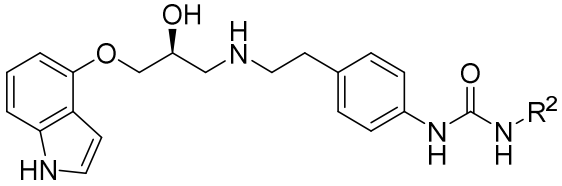
Compound	R^1	A	EC_{50}(nM)		
			β_3-AR	β_2-AR	β_1-AR
L-748,337		$NHSO_2$	11.91	23490	889.0
8a		$NHSO_2$	11.14	954.3	298.8
8b		NHCO	7.699	294.5	123.7
8c		$NHCOCH_2$	8.683	280.8	36.81
8d		NHCONH	55.45	1419	426.2
17a		NHCO	7.805	6058	~100000
17b		$NHCOCH_2$	4.584	15930	6204
17c		NHCONH	4.699	9842	12700
17d		NHCSNH	3.412	8433	223.6
23a		$NHSO_2$	2.086	353.1	14.79
23b		NHCO	1.424	117.8	35.98
23c		$NHCOCH_2$	1.089	83.14	7.643
23d		NHCOCNH	0.5117	52.21	2.884

Table 2. β_3-AR antagonist activity of urea derivatives.



Compound	R^2	EC_{50}(M)
		β_3-AR
23d	Ph	0.5117
23e	*c*-Hex	2.894
23f	*i*-Pr	1.029
23g	CH_2CH_2Ph	2.153
23h	2-F-Ph	3.575
23i	3-F-Ph	2.927
23j	4-F-Ph	2.491
23k	2-OMe-Ph	8.435
23l	3-OMe-Ph	4.623
23m	4-OMe-Ph	1.493
27a	2-NHCOOMe-Ph	2.616
27b	3-NHCOOMe-Ph	1.653
27c	4-NHCOOMe-Ph	1.422
27d	2-$NHCOC_5H_{11}$-Ph	2.082
27e	3-$NHCOC_5H_{11}$-Ph	1.782
27f	4-$NHCOC_5H_{11}$-Ph	10.45

2.3. Inhibitory effect of β_3-AR antagonists on lipolysis in vitro

In order to identify the ability of some β_3-AR antagonists to inhibit lipolysis, we used ISO to induce lipolysis of mature 3T3-L1 adipocytes *in vitro* (Figure 3). Results showed that the β_3-AR antagonists of urea derivatives inhibited lipolysis to different degrees compared with the inhibitory activity of SR59230A and L-748,337 *in vitro* (Figure 3). In detail, the compounds **23d**, **23e** and **23g** displayed a similar inhibitory activity compared with that of L-748,337. The *para*-substituent on the phenylthiourea moiety (**23j**, **23m** and **27c**) and **23f** exhibited a more potent inhibitory activity on lipolysis than L-748,337 did.

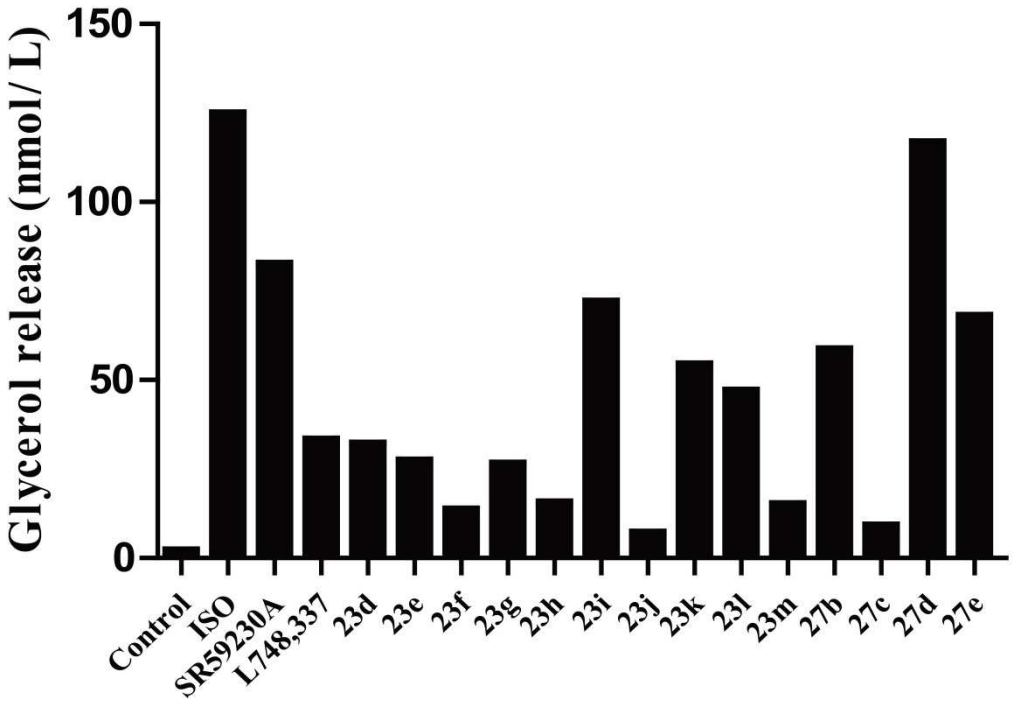


Figure 3. Antagonist of β_3-adrenergic receptor inhibits lipolysis of 3T3-L1 mature adipocyte *in vitro*. The lipolysis of 3T3-L1 adipocyte in cancer cachexia model *in vitro* was induced 1 μM ISO for 2 hr. Data presented are the mean ± SE of three independent experiments. * versus control group. # versus ISO group. #$p < 0.05$, ###$p < 0.001$. *$p < 0.05$, **$p < 0.01$.

*2.4. Inhibitory effect of β_3-AR antagonist **23d** on C26 tumor-bearing mice*

Finally, we tested the potent capacity of β_3-AR antagonist (**23d**) attenuating lipolysis with the C26 tumor bearing mice *in vivo*. At the end of the treatment (day 13), to avoid the influence of tumor weight on body weight, we analyzed the tumor-free body weight. The tumor-free body weight of mice treated with **23d** (2.5 mg/kg) was higher than that of C26 model group. The changes of tumor-free body weight increased by 18.5% in healthy mice, decreased by 8.3% and 4.6% in C26 model group and in **23d** treatment group(2.5 mg/kg) respectively (Figure. 4A). Interesting, compound **23d** also influenced C26 tumor growth in mice. C26 tumor volume of **23d** (2.5 mg/kg) treated mice was significantly less than that of C26 model mice (Figure. 4B). What's more, **23d** PDTC also effectively inhibited the lipolysis of body fat. The glycerol content in mice serum further confirmed the protection of **23d** on lipolysis (Figure. 4C). It demonstrated that β3-adrenergic receptor antagonists (**23d**) have a certain inhibitory effect on lipolysis in C26 tumor bearing mice.

The experimental results show that β_3-adrenergic receptor antagonists (**23d**) can reduce

the weight loss of cancer cachexia and also reduce tumor volume in animal models of tumor cachexia.

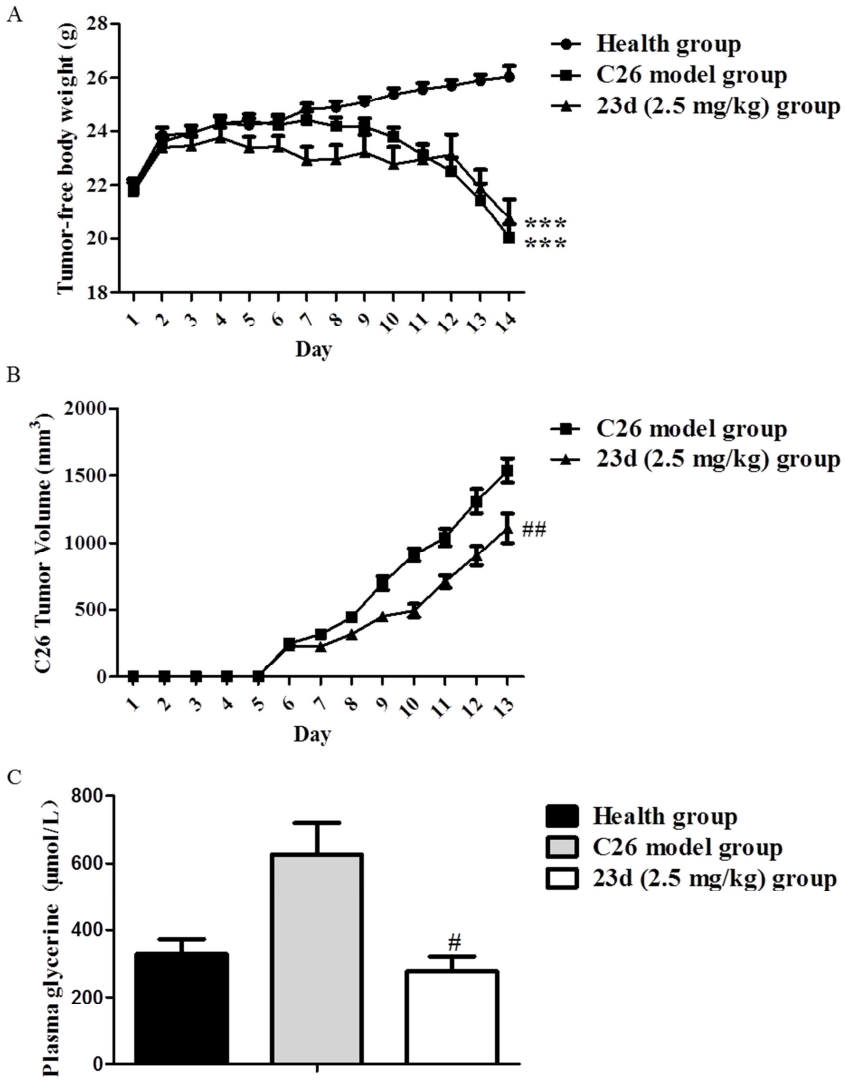


Figure 4. 23d attenuates C26 tumor-induced body weight loss *in vivo*. Compound **23d** (2.5 mg/kg) was injected in tail vein daily (n=7). A) Tumor-free body weight of mice. B) C26 tumor volume of mice. C) Content of glycerol in serum. Data presented are the mean ± SE of three independent experiments. * versus health group mice. # versus C26 tumor bearing group mice. ###p<0.001. **p<0.01, ***p<0.001.

3. Conclusion

In summary, a series of novel L-748,337 derivatives as selective human β_3-AR antagonists were designed and synthesized to explore their biological activity and SAR with the lead compound, L-748,337. SAR analysis indicated that 1*H*-indole moiety derivatives showed higher β_3-AR antagonist activity than that of 3-(acetamidomethyl)phenyl and 2-ethylphenyl moiety in part A, and the rank of order of potency seemed to be 1*H*-indole >

3-(acetamidomethyl)phenyl > 2-ethylphenyl. In the part B position, the connection moiety was crucial for the β_3-AR antagonist activity, and the preferred group was ureido moiety. For the 1*H*-indole moiety antagonists of the human β_3-AR described herein demonstrates in this receptor of binding interaction that can accommodate small (**23d**) to larger and bulkier substituents.

Among all the compounds, the novel L-748,337 derivative (**23d**) showed the potent human β_3-AR antagonist activity and high lipolysis inhibitory activity *in vitro*. The compound **23d** displayed 23-fold more potent β_3-AR antagonist activity (EC_{50} = 0.5117 nM) than that of L-748,337 (EC_{50} = 11.91 nM) and high selectivity over β_2-AR (100-fold) and β_1-AR (6-fold). *In vivo*, compound **23d** could alleviate weight loss and inhibit tumor growth in C26 tumor cachexia animal model.

In conclusion, in this study, we investigated potent and selective human β_3-AR antagonist and demonstrated **23d** as a useful *in vitro* and *in vivo* pharmacological tool for decreasing the severity of cancer cachexia and inhibiting the growth of cancer cells.

4. Experimental sections

4.1. Materials and methods

All reagents are commercially available and were used without further purification. The solvents used were of analytical grade. Melting points were taken on a FishereJohns melting point apparatus, uncorrected and reported in degrees Centigrade. ^{1}H NMR and ^{13}C NMR spectra were scanned on a Bruker DRX-400 (400 MHz) using tetramethylsilane (TMS) as internal standard and using one or two of the following solvents, DMSO-*d6* and $CDCl_3$. Chemical shifts are given in δ, ppm. Splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet. The mass spectra (MS) were recorded on a Finnigan MAT-95 mass spectrometer. The purity of all tested compounds was established by HPLC to be >95.0%. HPLC analysis was performed at room temperature using an Agilent Eclipse XDBC18 (250 mm × 4.6 mm) and as a mobile phase gradient from 5% MeCN/H_2O (1‰ TFA) for 1 min, 5% MeCN/H_2O (1‰ TFA) to 95% MeCN/H_2O (1‰ TFA) for 9 min and 95% MeCN/H_2O (1‰ TFA) for 5 min more, a flow rate of 1.0 mL/min and plotted at 254 nm.

4.2. General synthesis

*4.2.1. N-benzyl-2-(4-nitrophenyl)ethan-1-amine hydrochloride (**2**)*

In a 250 mL round-bottomed flask was added 2-(4-nitrophenyl)ethan-1-amine hydrochloride (**1**) (14.3 g, 70.6 mmol, 1.0 eq) in water (45 mL) and EA (75 mL) to give a colorless solution. NaOH (3.10 g, 78 mmol, 1.1 eq) was added. The reaction mixture was held at rt with stirring on for 30 min. The aqueous layer was backextracted with EA. The organic was dried Na_2SO_4, filt and conc to give residue 11.7 g. In a 250 mL round-bottomed flask was added residue and benzaldehyde (8.20 ml, 81 mmol, 1.15 eq) in EtOH (100 mL) to give a yellow suspension. The reaction vessel was purged with nitrogen. The reaction was heated to 80°C with stirring on for 16 hr to give a yellow solution. The reaction mixture was cooled to rt with stirring on to give yellow suspension. $NaBH_4$ (2.94 g, 78 mmol, 1.1 eq) was added slowly. The reaction mixture was held at rt with stirring on for 1.5 hr. 1M HCl (75 mL) was added to adjust pH to 4. The reaction mixture was filtered through sintered glass funnel and washed with EtOH and E_2O to give *N*-benzyl-2-(4-nitrophenyl)ethan-1-amine hydrochloride (**2**) (20.5 g, 99 % yield) as white solid. m.p. 255–257 °C; ^{1}H NMR (400 MHz, DMSO) δ: 9.74 (s, 2H), 8.20 (d, J = 8.7 Hz, 2H), 7.58 (dd, J = 17.9, 7.1 Hz, 4H), 7.42 (d, J = 6.0 Hz, 3H), 4.17 (s, 2H), 3.20 (s, 4H). ^{13}C NMR (101 MHz, DMSO) δ 146.38, 145.66, 132.04, 130.13, 130.01, 128.74, 128.51, 123.66, 49.77, 46.65, 31.01.

*4.2.2. General procedure for the synthesis of **4**, **13** and **19***

In a 100 mL round-bottomed flask was added 2-ethylphenol (5 g, 40.9 mmol, 1.1 eq) and sodium hydroxide (1.964 g, 49.1 mmol, 1.2 eq) in water (5 mL) and dioxane (20 mL) to give a colorless solution. The reaction mixture was held at rt with stirring on for 5 hr. (*R*)-2-(chloromethyl)oxirane (4.81 ml, 61.4 mmol, 1.5 eq) was added. The reaction mixture was held at rt with stirring on for 5 days. The mixture was concentrated by rotovap. Water (10 mL) was added. The aqueous layer was backextracted with EA. Combined the organic layers and wash with water. The organic was dried Na_2SO_4, filt and conc. The crude product was purified by column chromatography to give ***4***, ***13*** *and* ***19***.

*4.2.2.1. (S)-2-((2-ethylphenoxy)methyl)oxirane (**4**)*

Clear oil (5.58 g, 76% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.15 (t, J = 8.0 Hz, 2H), 6.91 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.23 (dd, J = 11.0, 2.6 Hz, 1H), 3.98 (dd, J = 11.0,

5.4 Hz, 1H), 3.37 (s, 1H), 2.90 (t, J = 4.5 Hz, 1H), 2.81-2.75 (m, 1H), 2.67 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.34, 133.02, 129.20, 126.86, 121.16, 111.50, 68.69, 50.39, 44.57, 23.38, 14.28.

*4.2.2.2. (S)-N-(3-(oxiran-2-ylmethoxy)benzyl)acetamide (**13**)*

Light-yellow solid (3.3 g, 50% yield). m.p. 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 11.2 Hz, 2H), 5.95 (s, 1H), 4.38 (d, J = 5.8 Hz, 2H), 4.23 (dd, J = 11.1, 2.9 Hz, 1H), 3.92 (dd, J = 11.0, 5.8 Hz, 1H), 3.34 (td, J = 6.2, 3.1 Hz, 1H), 2.90 (t, J = 4.5 Hz, 1H), 2.75 (dd, J = 4.9, 2.6 Hz, 1H), 2.01 (s, 3H).

*4.2.2.3. (S)-4-(oxiran-2-ylmethoxy)-1H-indole (**19**)*

White solid (3.6 g, 42% yield). m.p. 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.12 – 7.05 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.67 (t, *J* = 2.3 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 4.34 (dd, *J* = 11.2, 3.3 Hz, 1H), 4.12 (dd, *J* = 11.1, 5.5 Hz, 1H), 3.44 (dt, *J* = 5.9, 3.2 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.80 (dd, *J* = 5.0, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.22, 137.47, 123.13, 122.62, 118.82, 105.24, 100.91, 99.73, 68.87, 50.52, 44.89.

*4.2.3. General procedure for the synthesis of **5**, **14** and **20***

In a 250 mL round-bottomed flask was added *N*-benzyl-2-(4-nitrophenyl)ethan-1-amine hydrochloride (**2**) (1.15 eq) in water (3 mL) and EA (5 mL) to give a white suspension. NaOH (1.15 eq) was added. The reaction mixture was held at RT with stirring on for 1 hr. The aqueous layer was backextracted with EA. The organic was dried Na_2SO_4, filt and conc to give residue. In a 100 mL round-bottomed flask was added residue and ***4***, ***13*** *or* ***19*** (1.0 eq) in 2-Propanol (50 ml) to give a yellow solution. The reaction vessel was purged with nitrogen. The reaction was heated to 85 °C with stirring on for 16 hr. The mixture was concentrated by rotovap. The crude product was purified by column chromatography to give ***5***, ***14*** *and* ***20***.

*4.2.3.1. (S)-1-(benzyl(4-nitrophenethyl)amino)-3-(2-ethylphenoxy)propan-2-ol (**5**)*

Light-yellow oil (2.6 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.28 (t, *J* = 6.3 Hz, 3H), 7.22 (dd, *J* = 10.3, 6.4 Hz, 4H), 7.18 – 7.10 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.07 – 3.99 (m, 1H), 3.97 – 3.88 (m, 2H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.02 (s, 1H), 2.93 – 2.83 (m, 3H), 2.83 – 2.72 (m, 3H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.24, 147.94, 146.50, 138.11, 132.57, 129.52, 129.02, 128.97, 128.53, 127.50, 126.85, 123.65,

120.89, 111.04, 69.76, 66.66, 58.96, 56.79, 55.05, 33.47, 23.29, 14.20.

*4.2.3.2. (S)-N-(3-(3-(benzyl(4-nitrophenethyl)amino)-2-hydroxypropoxy)benzyl)acetamide (**14**)*

Yellow oil (8.5 g, 98 % yield). ^{1}H NMR (400 MHz, DMSO) δ 8.30 (t, J = 5.7 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.30 - 7.20 (m, 5H), 7.18 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.71 (s, 1H), 6.65 (dd, J = 8.2, 2.0 Hz, 1H), 4.83 (d, J = 4.9 Hz, 1H), 4.21 (d, J = 5.9 Hz, 2H), 3.87 (dd, J = 9.3, 5.0 Hz, 1H), 3.82 - 3.73 (m, 2H), 3.71 - 3.55 (m, 2H), 2.89 (t, J = 7.0 Hz, 2H), 2.83 - 2.69 (m, 2H), 2.65 (dd, J = 13.2, 6.7 Hz, 1H), 2.54 (d, J = 5.8 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.06, 158.66, 149.30, 145.69, 141.12, 139.19, 129.91, 129.16, 128.71, 128.02, 126.75, 123.12, 119.28, 113.46, 112.24, 70.49, 67.22, 58.41, 56.28, 55.10, 41.99, 32.38, 22.53.

*4.2.3.3. (S)-1-((1H-indol-4-yl)oxy)-3-(benzyl(4-nitrophenethyl)amino)propan-2-ol (**20**)*

Yellow oil (4.9 g, 99% yield). ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.28 – 7.15 (m, 6H), 7.01 – 6.89 (m, 2H), 6.39 (s, 1H), 6.33 (d, J = 7.2 Hz, 1H), 4.86 (d, J = 4.8 Hz, 1H), 3.97 (ddd, J = 19.0, 9.8, 4.4 Hz, 2H), 3.84 (dd, J = 9.6, 5.8 Hz, 1H), 3.77 (d, J = 13.8 Hz, 1H), 3.65 (d, J = 13.7 Hz, 1H), 2.88 (t, J = 7.0 Hz, 2H), 2.77 (hept, J = 6.2 Hz, 3H), 2.60 (dd, J = 13.2, 5.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 152.03, 149.24, 145.67, 139.23, 137.27, 129.87, 128.68, 128.00, 126.72, 123.30, 123.06, 121.60, 118.32, 104.70, 99.67, 98.42, 70.37, 67.46, 58.48, 56.44, 55.03, 54.87, 32.38.

*4.2.4. General procedure for the synthesis of **6**, **15** and **21***

In a 50 mL round-bottomed flask was added ***5***, ***14*** *and* ***20*** (1.0 eq) and Tin(II) chloride dihydrate (3.0 eq) in EtOH (200 ml) to give a white suspension. The reaction was heated to 85°C with stirring on for 2 hr. 3M NaOH was added to adjust pH to 9. The reaction mixture was filtered through sintered glass funnel with EtOH. The mixture was concentrated by rotovap. Water (5 mL) was added. The aqueou layer was backextracted with EA. The organic was dried Na_2SO_4, filt and conc to give ***6***, ***15*** and ***21***. The crude product was used to next step without further purification.

*4.2.4.1. (S)-1-((4-aminophenethyl)(benzyl)amino)-3-(2-ethylphenoxy)propan-2-ol (**6**)*

Yellow oil (1.7 g, 73 % yield). ^{1}H NMR (400 MHz, DMSO) δ 7.33 – 7.18 (m, 5H), 7.14 (ddd, *J* = 9.9, 8.5, 3.8 Hz, 2H), 6.89 – 6.82 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 8.3 Hz,

2H), 4.80 (s, 2H), 4.74 (d, *J* = 4.3 Hz, 1H), 4.00 – 3.89 (m, 2H), 3.84 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.74 (d, *J* = 13.8 Hz, 1H), 3.66 (d, *J* = 13.8 Hz, 1H), 2.75 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.68 – 2.55 (m, 5H), 2.55 – 2.50 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.31, 146.41, 139.58, 131.78, 128.89, 128.57, 127.97, 127.24, 126.84, 126.62, 120.12, 113.96, 111.20, 70.33, 67.46, 58.67, 56.58, 56.47, 31.87, 22.70, 14.18.

*4.2.4.2. (S)-N-(3-(3-((4-aminophenethyl)(benzyl)amino)-2-hydroxypropoxy)benzyl)acetamide (**15**)*

light-yellow oil (5.4 g, 96 % yield). ^{1}H NMR (400 MHz, DMSO) δ 8.31 (t, J = 5.7 Hz, 1H), 7.28 (d, J = 4.5 Hz, 4H), 7.21 (dd, J = 10.4, 5.3 Hz, 2H), 6.86 – 6.68 (m, 5H), 6.44 (d, J = 8.2 Hz, 2H), 4.85 – 4.69 (m, 3H), 4.21 (d, J = 6.0 Hz, 2H), 3.95 – 3.84 (m, 2H), 3.73 (dd, J = 11.3, 6.7 Hz, 2H), 3.61 (d, J = 13.8 Hz, 1H), 2.69 – 2.51 (m, 6H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.06, 158.77, 146.41, 141.10, 139.53, 129.24, 128.89, 128.62, 128.00, 127.17, 126.66, 119.25, 113.89, 113.49, 112.46, 70.61, 67.26, 58.58, 56.49, 42.01, 40.12, 39.92, 39.70, 39.50, 39.29, 39.08, 38.87, 31.84, 22.53.

*4.2.4.3. (S)-1-((1H-indol-4-yl)oxy)-3-((4-aminophenethyl)(benzyl)amino)propan-2-ol (**21**)*

Yellow oil (11.3 g, 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.35 – 7.18 (m, 5H), 7.03 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.56 (s, 1H), 6.53 (d, *J* = 8.3 Hz, 2H), 6.43 (d, *J* = 7.7 Hz, 1H), 4.12 – 3.98 (m, 3H), 3.82 (d, *J* = 13.6 Hz, 1H), 3.56 (d, *J* = 13.6 Hz, 1H), 3.33 (d, *J* = 48.6 Hz, 3H), 2.89 – 2.57 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.49, 144.58, 138.74, 137.44, 129.98, 129.58, 129.12, 128.48, 127.27, 122.93, 122.61, 118.81, 115.47, 104.90, 100.74, 99.72, 70.41, 66.60, 58.80, 56.71, 56.10, 32.69.

*4.2.5. General procedure for the synthesis of **7a-d**, **16a-d**, **22a-m** and **24a-c***

In a 250 mL round-bottomed flask was added ***6***, ***15*** *and* ***21*** (1.0 eq), benzoyl chloride (1.2 eq), and pyridine (1.5 eq) in DCM (100 ml) to give a yellow solution. The reaction mixture was held at rt with stirring on for 1 hr. The mixture was concentrated by rotovap. The crude product was purified by column chromatography to give ***7a-d***, ***16a-d***, ***22a-m*** *and* ***24a-c***.

4.2.5.1.

*(S)-N-(4-(2-(benzyl(3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzenesulfonamide (**7a**)*

White solid (200 mg, 74% yield). m.p. 86-88 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.74 (d, *J* = 57.8 Hz, 1H), 10.37 (s, 1H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.69 (s, 2H), 7.62 – 7.57 (m, 1H), 7.57 – 7.51 (m, 2H), 7.44 (s, 3H), 7.09 (d, *J* = 7.8 Hz, 6H), 6.88 (d, *J* = 6.9 Hz, 2H), 6.05 (d, *J* = 9.1 Hz, 1H), 4.49 (t, *J* = 38.2 Hz, 3H), 3.94 (s, 1H), 3.86 (s, 1H), 3.37 (s, 3H), 3.07 (s, 2H), 2.42 (d, *J* = 6.1 Hz, 2H), 1.04 (dd, *J* = 12.4, 5.6 Hz, 3H).

4.2.5.2.

*(S)-N-(4-(2-(benzyl(3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzamide (**7b**)*

White solid (160 mg, 64% yield). m.p. 57-59 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.81 – 7.70 (m, 4H), 7.51 (dd, *J* = 19.7, 10.5 Hz, 6H), 7.29 – 7.21 (m, 2H), 7.17 – 7.09 (m, 2H), 6.89 (dd, *J* = 12.1, 7.4 Hz, 2H), 6.10 (s, 1H), 4.72 – 4.36 (m, 3H), 4.05 – 3.85 (m, 2H), 3.35 (dd, *J* = 40.0, 12.4 Hz, 4H), 3.23 – 3.06 (m, 2H), 2.49 – 2.41 (m, 2H), 1.06 (dd, *J* = 17.9, 7.5 Hz, 3H).

4.2.5.3.

*(S)-N-(4-(2-(benzyl(3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)-2-phenylaceta mide (**7c**)*

White solid (200 mg, 77% yield). m.p. 76-78 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.66 (d, *J* = 46.7 Hz, 1H), 10.41 (s, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 5.4 Hz, 2H), 7.45 (s, 2H), 7.33 (d, *J* = 12.5 Hz, 3H), 7.14 (d, *J* = 8.9 Hz, 4H), 6.88 (d, *J* = 6.7 Hz, 2H), 6.06 (s, 1H), 4.52 (t, *J* = 41.0 Hz, 3H), 4.03 – 3.79 (m, 2H), 3.66 (s, 2H), 3.38 (s, 4H), 3.11 (s, 2H), 2.44 (s, 2H), 1.06 (s, 3H).

4.2.5.4.

*(S)-1-(4-(2-(benzyl(3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-phenylurea (**7d**)*

White solid (190 mg, 73% yield). m.p. 94-96 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.40 (d, *J* = 35.4 Hz, 1H), 9.31 (s, 2H), 7.70 (s, 2H), 7.46 (t, *J* = 10.1 Hz, 7H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.09 (m, 4H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.88 (t, *J* = 8.4 Hz, 2H), 6.06 (d, *J* = 13.7 Hz, 1H), 4.55 (dd, *J* = 71.7, 36.2 Hz, 3H), 4.07 – 3.83 (m, 2H), 3.39 (s, 4H), 3.10 (s, 2H), 2.47 (d, *J* = 7.6 Hz, 2H), 1.13 – 0.97 (m, 3H).

4.2.5.5.

(S)-N-(4-(2-((3-(3-(acetamidomethyl)phenoxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)

*benzamide (**16a**)*

White solid (195 mg, 90% yield). m.p. 97-99 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.17 (s, 1H), 8.32 (t, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 7.1 Hz, 2H), 7.75 – 7.44 (m, 6H), 7.44 – 7.01 (m, 8H), 6.84 – 6.66 (m, 3H), 4.21 (d, *J* = 5.9 Hz, 2H), 4.04 – 3.47 (m, 5H), 3.33 (s, 1H), 2.73 (s, 5H), 1.87 (s, 3H).

4.2.5.6.

*(S)-N-(4-(2-((3-(3-(acetamidomethyl)phenoxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-2-phenylacetamide (**16b**)*

White solid (2.3 g, 91% yield). m.p. 65-67 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 8.35 (s, 1H), 7.72 – 7.43 (m, 6H), 7.37 – 7.00 (m, 9H), 6.92 – 6.66 (m, 3H), 6.04 (s, 1H), 4.45 (t, *J* = 42.0 Hz, 4H), 4.21 (d, *J* = 5.7 Hz, 2H), 3.90 (s, 2H), 3.63 (s, 2H), 3.39 (s, 3H), 3.17 (s, 1H), 1.87 (s, 3H).

4.2.5.7.

*(S)-N-(3-(3-(benzyl(4-(3-phenylureido)phenethyl)amino)-2-hydroxypropoxy)benzyl)acetamide (**16c**)*

White solid (1.9 g, 75% yield). m.p. 70-72 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.52 (s, 1H), 8.30 (t, *J* = 5.8 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.33 – 7.17 (m, 10H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.76 (s, 1H), 6.72 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.78 (d, *J* = 4.5 Hz, 1H), 4.22 (d, *J* = 5.9 Hz, 2H), 3.90 (d, *J* = 8.3 Hz, 2H), 3.79 – 3.69 (m, 2H), 3.63 (d, *J* = 13.8 Hz, 1H), 2.68 (dd, *J* = 13.0, 9.4 Hz, 5H), 2.54 (dd, *J* = 13.1, 5.6 Hz, 1H), 1.87 (s, 3H).

4.2.5.8.

*(S)-N-(3-(3-(benzyl(4-(3-phenylthioureido)phenethyl)amino)-2-hydroxypropoxy)benzyl)acetamide (**16d**)*

White solid (120 mg, 46% yield). m.p. 61-63 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.69 (s, 2H), 8.34 (t, *J* = 5.6 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.37 – 7.26 (m, 8H), 7.22 (dd, *J* = 10.4, 5.3 Hz, 2H), 7.11 (dd, *J* = 15.4, 7.8 Hz, 3H), 6.84 – 6.70 (m, 3H), 4.85 (d, *J* = 3.9 Hz, 1H), 4.23 (d, *J* = 5.9 Hz, 2H), 3.93 (d, *J* = 7.3 Hz, 2H), 3.83 – 3.73 (m, 2H), 3.65 (d, *J* = 13.7 Hz, 1H), 2.80 – 2.63 (m, 5H), 2.57 (dd, *J* = 13.1, 5.4 Hz, 1H), 1.88 (s, 3H).

4.2.5.9.

*(S)-N-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)benzenesulfonamide (**22a**)*

White solid (120 mg, 45% yield). m.p. 104-106 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.13 (s, 1H), 10.56 (d, *J* = 41.4 Hz, 1H), 10.35 (s, 1H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.65 (d, *J* = 29.2 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.45 (s, 3H), 7.20 (s, 1H), 7.10 – 6.93 (m, 6H), 6.44 (d, *J* = 7.2 Hz, 1H), 6.33 (s, 1H), 6.07 (d, *J* = 10.3 Hz, 1H), 4.50 (t, *J* = 23.4 Hz, 3H), 4.00 (d, *J* = 30.2 Hz, 2H), 3.30 (s, 4H), 3.05 (s, 2H).

4.2.5.10.

*(S)-N-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)benzamide (**22b**)*

White solid (180 mg, 72% yield). m.p. 57-59 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 10.16 (s, 1H), 7.95 (d, *J* = 6.9 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.55 (dd, *J* = 16.4, 6.7 Hz, 3H), 7.41 – 7.16 (m, 7H), 7.08 (d, *J* = 7.4 Hz, 2H), 6.98 (s, 2H), 6.43 (s, 2H), 4.83 (s, 1H), 4.04 (s, 2H), 3.92 (s, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.69 (d, *J* = 13.9 Hz, 1H), 2.85 – 2.59 (m, 6H).

4.2.5.11.

*(S)-N-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-2-phenylacetamide (**22c**)*

White solid (165 mg, 64% yield). m.p. 58-60 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 10.08 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.14 (m, 12H), 7.08 – 6.94 (m, 4H), 6.53 – 6.35 (m, 2H), 4.83 (s, 1H), 4.04 (s, 2H), 3.92 (s, 1H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.68 (d, *J* = 14.8 Hz, 1H), 3.64 (s, 2H), 2.86 – 2.59 (m, 6H).

4.2.5.12.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-phenylurea (**22d**)*

White solid (2.0 g, 78% yield). m.p. 74-76 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 8.59 (s, 1H), 8.53 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.24 (ddd, *J* = 20.5, 14.1, 4.6 Hz, 10H), 7.05 – 6.90 (m, 5H), 6.42 (s, 2H), 4.81 (d, *J* = 2.8 Hz, 1H), 4.04 (d, *J* = 7.5 Hz, 2H), 3.91 (s, 1H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 2.82 – 2.58 (m, 6H).

4.2.5.13.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-cyclohexylurea (**22e**)*

White solid (188 mg, 72% yield). m.p. 75-77 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.14 (s, 1H), 7.28 (t, *J* = 6.8 Hz, 4H), 7.25 – 7.19 (m, 3H), 7.19 – 7.15 (m, 1H), 7.00 – 6.95 (m, 2H), 6.93 (d, *J* = 8.5 Hz, 4H), 6.40 (t, *J* = 4.1 Hz, 2H), 5.98 (d, *J* = 7.9 Hz, 1H), 4.78 (d, *J* = 4.6 Hz, 1H), 4.03 (dd, *J* = 12.9, 5.5 Hz, 2H), 3.94 – 3.85 (m, 1H), 3.71 (dd, *J* = 36.9, 13.8 Hz, 2H), 3.49 – 3.39 (m, 1H), 2.77 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.69 – 2.57 (m, 5H), 1.79 (dd, *J* = 12.1, 3.2 Hz, 2H), 1.65 (dd, *J* = 8.8, 3.8 Hz, 2H), 1.53 (dd, *J* = 8.0, 4.3 Hz, 1H), 1.30 (dd, *J* = 23.3, 12.1 Hz, 2H), 1.22 – 1.09 (m, 3H).

4.2.5.14.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-isopropylurea (**22f**)*

White solid (170 mg, 70% yield). m.p. 68-70 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.13 (s, 1H), 7.28 (q, *J* = 7.5 Hz, 4H), 7.21 (d, *J* = 8.5 Hz, 3H), 7.19 – 7.16 (m, 1H), 7.00 – 6.95 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.40 (t, *J* = 3.5 Hz, 2H), 5.90 (d, *J* = 7.5 Hz, 1H), 4.79 (d, *J* = 4.6 Hz, 1H), 4.03 (dd, *J* = 13.2, 5.6 Hz, 2H), 3.94 – 3.84 (m, 1H), 3.79 – 3.62 (m, 3H), 2.77 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.69 – 2.56 (m, 5H), 1.07 (s, 6H).

4.2.5.15.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-phenethylurea (**22g**)*

White solid (227 mg, 84% yield). m.p. 63-65 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.33 (s, 1H), 7.33 – 7.20 (m, 12H), 7.19 – 7.16 (m, 1H), 6.96 (dt, *J* = 15.2, 6.7 Hz, 4H), 6.40 (dd, *J* = 5.1, 2.9 Hz, 2H), 6.03 (t, *J* = 5.6 Hz, 1H), 4.79 (d, *J* = 4.6 Hz, 1H), 4.03 (dd, *J* = 13.4, 5.8 Hz, 2H), 3.94 – 3.84 (m, 1H), 3.71 (dd, *J* = 36.6, 13.9 Hz, 2H), 3.32 (s, 2H), 2.80 – 2.71 (m, 3H), 2.70 – 2.56 (m, 5H).

4.2.5.16.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(2-fluorophenyl)urea (**22h**)*

White solid (243 mg, 91% yield). m.p. 76-78 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.95 (s, 1H), 8.48 (d, *J* = 2.6 Hz, 1H), 8.15 (td, *J* = 8.2, 1.6 Hz, 1H), 7.33 – 7.19 (m, 8H),

7.19 – 7.17 (m, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.04 – 6.95 (m, 5H), 6.45 – 6.37 (m, 2H), 4.80 (d, *J* = 4.3 Hz, 1H), 4.06 – 3.98 (m, 2H), 3.95 – 3.85 (m, 1H), 3.72 (dd, *J* = 36.8, 13.8 Hz, 2H), 2.79 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.74 – 2.56 (m, 5H).

4.2.5.17.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(3-fluor ophenyl)urea (**22i**)*

White solid (245 mg, 91% yield). m.p. 75-77 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 8.82 (s, 1H), 8.58 (s, 1H), 7.48 (d, *J* = 11.9 Hz, 1H), 7.35 – 7.04 (m, 10H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.99 – 6.94 (m, 2H), 6.76 (td, *J* = 8.6, 2.4 Hz, 1H), 6.42 (dd, *J* = 8.8, 4.0 Hz, 2H), 4.80 (d, *J* = 4.1 Hz, 1H), 4.04 (d, *J* = 8.3 Hz, 2H), 3.96 – 3.85 (m, 1H), 3.72 (dd, *J* = 36.5, 13.9 Hz, 2H), 2.79 (dd, *J* = 13.1, 5.9 Hz, 1H), 2.74 – 2.56 (m, 5H).

4.2.5.18.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(4-fluor ophenyl)urea (**22j**)*

White solid (213 mg, 80% yield). m.p. 78-80 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 8.63 (s, 1H), 8.52 (s, 1H), 7.49 – 7.42 (m, 2H), 7.25 (dt, *J* = 17.6, 9.3 Hz, 8H), 7.11 (t, *J* = 8.5 Hz, 2H), 7.03 – 6.95 (m, 4H), 6.42 (s, 2H), 4.81 (s, 1H), 4.04 (s, 2H), 3.91 (s, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.68 (d, *J* = 13.7 Hz, 1H), 2.86 – 2.60 (m, 6H).

4.2.5.19.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(2-meth oxyphenyl)urea (**22k**)*

White solid (245 mg, 90% yield). m.p. 79-81 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.18 (s, 1H), 8.16 (s, 1H), 8.12 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 6H), 7.22 (d, *J* = 6.5 Hz, 1H), 7.18 (t, *J* = 2.6 Hz, 1H), 7.03 – 6.85 (m, 7H), 6.41 (t, *J* = 4.2 Hz, 2H), 4.80 (s, 1H), 4.03 (dd, *J* = 7.3, 4.0 Hz, 2H), 3.91 (d, *J* = 9.7 Hz, 1H), 3.87 (s, 3H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 2.79 (dd, *J* = 13.2, 5.8 Hz, 1H), 2.72 – 2.59 (m, 6H).

4.2.5.20.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(3-meth oxyphenyl)urea (**22l**)*

White solid (250 mg, 92% yield). m.p. 75-77 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s,

1H), 8.61 (s, 1H), 8.52 (s, 1H), 7.29 (dd, *J* = 15.2, 7.9 Hz, 6H), 7.23 – 7.13 (m, 4H), 6.99 (dd, *J* = 11.3, 6.0 Hz, 4H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.42 (s, 2H), 4.82 (s, 1H), 4.05 (d, *J* = 7.6 Hz, 2H), 3.92 (d, *J* = 5.4 Hz, 1H), 3.79 – 3.65 (m, 5H), 2.82 – 2.60 (m, 6H).

4.2.5.21.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(4-methoxyphenyl)urea (**22m**)*

White solid (220 mg, 81% yield). m.p. 81-83 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 8.44 (s, 1H), 8.40 (s, 1H), 7.36 – 7.17 (m, 11H), 6.99 (d, *J* = 8.4 Hz, 4H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.42 (s, 2H), 4.81 (s, 1H), 4.05 (d, *J* = 7.7 Hz, 2H), 3.91 (d, *J* = 3.1 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.71 (s, 3H), 3.64 (d, *J* = 10.8 Hz, 1H), 2.81 – 2.60 (m, 6H).

4.2.5.22.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(2-nitrophenyl)urea (**24a**)*

White solid (1.03 g, 74% yield). m.p. 71-73 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 9.74 (s, 1H), 9.56 (s, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.16 (m, 9H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 4.0 Hz, 2H), 6.42 (d, *J* = 8.2 Hz, 2H), 4.82 (d, *J* = 3.9 Hz, 1H), 4.04 (d, *J* = 7.3 Hz, 2H), 3.98 – 3.87 (m, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 2.86 – 2.58 (m, 6H).

4.2.5.23.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(3-nitrophenyl)urea (**24b**)*

White solid (540 mg, 77% yield). m.p. 84-86 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 9.15 (s, 1H), 8.70 (s, 1H), 8.57 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.27 (ddd, *J* = 29.2, 19.5, 10.2 Hz, 8H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 4.0 Hz, 2H), 6.42 (s, 2H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.04 (t, *J* = 6.9 Hz, 2H), 3.97 – 3.87 (m, 1H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 2.86 – 2.59 (m, 6H).

4.2.5.24.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(4-nitrophenyl)urea (**24c**)*

White solid (500 mg, 72% yield). m.p. 91-93 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.37 (s, 1H), 8.79 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 2H), 7.36 – 7.24 (m, 6H), 7.24 – 7.13 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 3.8 Hz, 2H), 6.42 (s, 2H), 4.81 (d, *J* = 4.1 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.94 – 3.88 (m, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 2.79 (dd, *J* = 13.0, 5.6 Hz, 1H), 2.75 – 2.57 (m, 5H).

4.2.6. General procedure for the synthesis of ***8a-d***, ***17a-d***, ***23a-m*** *and* ***27a-f***

In a 50 mL round-bottomed flask was added ***7a-d***, ***16a-d***, ***22a-m*** *and* ***24a-c*** (1.0 eq) and Raney-Ni (0.1 eq) in MeOH (10 mL) to give a colorless solution. The reaction vessel was purged with nitrogen. The reaction vessel was purged with hydrogen (100 eq). The reaction mixture was held at rt with stirring on for 2 hr. The reaction mixture was filtered through celite with MeOH (5 mL). The mixture was concentrated by rotovap. The crude product was purified by column chromatography to give ***8a-d***, ***17a-d***, ***23a-m*** *and* ***27a-f***.

4.2.6.1.

(S)-N-(4-(2-((3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzenesulfonamide ***(8a)***

White solid (50 mg, 45% yield). m.p. 101-103 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.37 (s, 1H), 9.34 (s, 1H), 9.03 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.20 – 7.09 (m, 4H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 5.89 (d, *J* = 4.9 Hz, 1H), 4.26 (s, 1H), 3.96 (qd, *J* = 10.0, 5.2 Hz, 2H), 3.21 – 2.99 (m, 4H), 2.97 – 2.85 (m, 2H), 2.58 (q, *J* = 7.5 Hz, 2H), 1.12 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.87, 139.55, 136.27, 133.04, 132.77, 131.77, 129.16, 128.67, 126.88, 126.63, 120.56, 120.49, 111.44, 69.69, 64.94, 49.70, 47.99, 30.49, 22.59, 14.23. HPLC: room temperature; t_R=7.075 min, UV_{254}=97.9%; HRMS(ESI)*m/z* calcd for $C_{25}H_{30}N_2O_4S$ $[M+H]^+$: 455.1999, Found: 455.1997.

4.2.6.2. (S)-N-(4-(2-((3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzamide ***(8b)***

White solid (60 mg, 34% yield). m.p. 166-168 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 9.16 (s, 1H), 8.93 (s, 1H), 7.97 (d, *J* = 7.0 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 7.4 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 5.90 (s, 1H), 4.28 (d, *J* = 5.1 Hz, 1H), 3.99 (qd, *J*

= 10.0, 5.2 Hz, 2H), 3.21 (dt, *J* = 14.6, 8.6 Hz, 3H), 3.13 – 3.05 (m, 1H), 2.99 (ddd, *J* = 13.2, 7.8, 4.2 Hz, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.41, 155.89, 137.88, 134.83, 132.41, 131.80, 131.50, 128.70, 128.30, 127.67, 126.90, 120.60, 111.44, 69.70, 65.00, 49.72, 48.24, 30.84, 22.62, 14.25. HPLC: room temperature; t_R=8.314 min, UV_{254}=97.9%; HRMS(ESI)*m/z* calcd for $C_{26}H_{30}N_2O_3$ $[M+H]^+$: 419.2329, Found: 419.2330.

4.2.6.3.

(S)-N-(4-(2-((3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)-2-phenylacetamide ***(8c)***

White solid (68 mg, 54% yield). m.p. 173-175 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.30 (s, 1H), 9.05 (s, 1H), 8.86 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 5.88 (s, 1H), 4.25 (d, *J* = 5.4 Hz, 1H), 3.97 (ddd, *J* = 21.0, 10.0, 5.2 Hz, 2H), 3.64 (s, 2H), 3.25 – 3.13 (m, 3H), 3.06 (dd, *J* = 19.2, 10.3 Hz, 1H), 3.00 – 2.86 (m, 2H), 2.59 (q, *J* = 7.3 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.07, 155.87, 138.02, 136.13, 131.80, 129.09, 128.77, 128.70, 128.20, 126.90, 126.42, 120.62, 119.31, 111.42, 69.68, 64.98, 49.67, 48.23, 43.21, 30.79, 22.61, 14.24. HPLC: room temperature; t_R=8.976 min, UV_{254}=96.7%; HRMS(ESI)*m/z* calcd for $C_{27}H_{32}N_2O_3$ $[M+H]^+$: 433.2486, Found: 433.2484.

4.2.6.4. (S)-1-(4-(2-((3-(2-ethylphenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-phenylurea ***(8d)***

White solid (77 mg, 60% yield). m.p. 290-292 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.70 (s, 2H), 9.44 (s, 1H), 9.14 (s, 1H), 7.44 (dd, *J* = 13.0, 8.1 Hz, 4H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.15 (dd, *J* = 7.7, 5.8 Hz, 4H), 6.93 (t, *J* = 7.4 Hz, 2H), 6.88 (t, *J* = 7.4 Hz, 1H), 5.93 (d, *J* = 4.9 Hz, 1H), 4.36 – 4.24 (m, 1H), 4.04 – 3.93 (m, 2H), 3.24 – 3.12 (m, 3H), 3.10 – 2.93 (m, 3H), 2.60 (dd, *J* = 15.0, 7.5 Hz, 2H), 1.14 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.89, 152.86, 140.02, 138.62, 131.75, 130.18, 128.80, 128.68, 126.88, 121.36, 120.53, 117.78, 117.55, 111.47, 69.73, 64.99, 49.76, 48.33, 30.60, 22.60, 14.25. HPLC: room temperature; t_R=9.023 min, UV_{254}=99.4%; HRMS(ESI)*m/z* calcd for $C_{26}H_{31}N_3O_3$ $[M+H]^+$: 434.2438, Found: 434.2433.

4.2.6.5.

*(S)-N-(4-(2-((3-(3-(acetamidomethyl)phenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzamide (**17a**)*

White solid (150 mg, 89% yield). m.p. 223-225 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 9.39 (s, 1H), 9.07 (s, 1H), 8.45 (t, *J* = 5.8 Hz, 1H), 7.99 (d, *J* = 7.0 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 9.0 Hz, 3H), 6.90 – 6.81 (m, 3H), 6.67 (s, 2H), 4.34 – 4.25 (m, 1H), 4.23 (d, *J* = 5.8 Hz, 2H), 4.05 – 3.92 (m, 2H), 3.18 (dd, *J* = 12.8, 5.6 Hz, 3H), 3.12 – 2.91 (m, 3H), 1.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.14, 165.41, 158.29, 141.30, 137.85, 134.84, 132.42, 131.50, 129.31, 128.70, 128.31, 127.65, 120.60, 119.72, 113.60, 112.60, 69.66, 64.87, 49.60, 48.22, 41.95, 30.81, 22.54. HPLC: room temperature; t_R=6.813 min, UV_{254}=96.4%; HRMS(ESI)*m/z* calcd for $C_{27}H_{31}N_3O_4$ $[M+H]^+$: 462.2388, Found: 462.2386.

4.2.6.6.

*(S)-N-(4-(2-((3-(3-(acetamidomethyl)phenoxy)-2-hydroxypropyl)amino)ethyl)phenyl)-2-phenylacetamide (**17b**)*

White solid (95 mg, 80% yield). m.p. 221-223 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 9.28 (s, 1H), 8.99 (s, 1H), 8.43 (t, *J* = 5.8 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 6.9 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.88 – 6.79 (m, 3H), 4.27 (dd, *J* = 8.5, 5.3 Hz, 1H), 4.22 (d, *J* = 5.9 Hz, 2H), 4.05 – 3.89 (m, 2H), 3.66 (s, 2H), 3.25 – 3.10 (m, 3H), 3.08 – 2.88 (m, 3H), 1.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.14, 169.06, 158.27, 141.30, 137.98, 136.11, 131.85, 129.31, 129.08, 128.77, 128.21, 126.43, 119.72, 119.32, 113.57, 112.58, 69.64, 64.85, 49.55, 48.21, 43.20, 41.95, 30.76, 22.54. HPLC: room temperature; t_R=7.323 min, UV_{254}=98.2%; HRMS(ESI)*m/z* calcd for $C_{28}H_{33}N_3O_4$ $[M+H]^+$: 476.2544, Found: 476.2540.

4.2.6.7.

*(S)-N-(3-(2-hydroxy-3-((4-(3-phenylureido)phenethyl)amino)propoxy)benzyl)acetamide (**17c**)*

White solid (100 mg, 66 % yield). m.p. 203-205 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.45 (d, J = 3.6 Hz, 2H), 9.18 (s, 1H), 8.94 (s, 1H), 8.43 (s, 1H), 7.45 (dd, J = 11.4, 8.4 Hz, 4H), 7.25 (dd, J = 16.9, 8.2 Hz, 4H), 7.16 (d, J = 8.0 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 6.89 – 6.78 (m, 3H), 4.22 (d, J = 5.4 Hz, 3H), 3.97 (s, 2H), 3.28 – 3.11 (m, 3H), 3.09 – 2.87 (m, 3H), 1.88 (s,

3H). ^{13}C NMR (101 MHz, DMSO) δ 169.16, 158.27, 152.75, 141.28, 139.94, 138.62, 130.13, 129.32, 128.89, 128.69, 121.49, 119.73, 118.07, 117.80, 113.57, 112.59, 69.64, 64.86, 49.55, 48.33, 41.96, 30.72, 22.53. HPLC: room temperature; t_R=7.394 min, UV_{254}=98.9%; HRMS(ESI)*m/z* calcd for $C_{27}H_{32}N_4O_4$ $[M+H]^+$: 477.2497, Found: 477.2495.

4.2.6.8.

(S)-N-(3-(2-hydroxy-3-((4-(3-phenylthioureido)phenethyl)amino)propoxy)benzyl)acetamide ***(17d)***

White solid (123 mg, 81% yield). m.p. 145-147 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.31 (d, *J* = 5.3 Hz, 2H), 9.06 (s, 1H), 8.85 (s, 1H), 8.41 (t, *J* = 5.9 Hz, 1H), 7.44 (dd, *J* = 10.5, 8.2 Hz, 4H), 7.25 (dd, *J* = 16.4, 8.8 Hz, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.90 – 6.79 (m, 3H), 4.22 (d, *J* = 5.9 Hz, 3H), 4.04 – 3.89 (m, 2H), 3.23 – 3.11 (m, 3H), 3.09 – 2.89 (m, 3H), 1.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.27, 158.27, 141.22, 130.13, 129.89, 129.44, 129.30, 129.20, 126.10, 125.89, 125.51, 122.90, 122.30, 119.71, 113.59, 112.58, 69.64, 64.87, 49.53, 48.11, 41.95, 30.67, 22.51. HPLC: room temperature; t_R=8.164 min, UV_{254}=96.1%; HRMS(ESI)*m/z* calcd for $C_{27}H_{32}N_4O_3S$ $[M+H]^+$: 493.2268, Found: 493.2266.

4.2.6.9.

(S)-N-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzenesulfonamide ***(23a)***

White solid (145 mg, 91% yield). m.p. 76-78 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.60 – 7.49 (m, 3H), 7.19 (t, *J* = 2.6 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.02 – 6.92 (m, 4H), 6.48 – 6.38 (m, 2H), 4.95 (s, 1H), 4.07 – 3.82 (m, 3H), 3.32 (s, 2H), 2.79 – 2.65 (m, 3H), 2.65 – 2.55 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 152.03, 139.82, 137.30, 136.06, 135.71, 132.63, 129.21, 129.12, 126.58, 123.38, 121.72, 120.45, 118.37, 104.79, 99.87, 98.44, 70.49, 68.08, 52.33, 50.91, 35.02. HPLC: room temperature; t_R=7.995 min, UV_{254}=97.0%; HRMS(ESI)*m/z* calcd for $C_{25}H_{27}N_3O_4S$ $[M+H]^+$: 466.1795, Found: 466.1790.

4.2.6.10.

(S)-N-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)benzamide ***(23b)***

White solid (150 mg, 80% yield). m.p. 155-157 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s,

1H), 10.18 (s, 1H), 7.94 (d, *J* = 7.0 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.56 (dt, *J* = 24.5, 7.1 Hz, 3H), 7.19 (dd, *J* = 5.7, 2.6 Hz, 3H), 7.06 – 6.91 (m, 2H), 6.56 – 6.41 (m, 2H), 4.98 (d, *J* = 3.3 Hz, 1H), 4.00 (dt, *J* = 13.8, 6.6 Hz, 3H), 2.79 (dd, *J* = 7.1, 5.1 Hz, 3H), 2.73 – 2.63 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.33, 152.05, 137.29, 137.02, 135.72, 135.03, 131.41, 128.66, 128.30, 127.57, 123.36, 121.70, 120.34, 118.36, 104.75, 99.86, 98.44, 70.55, 68.22, 52.49, 51.22, 35.42. HPLC: room temperature; t_R=7.946 min, UV_{254}=98.1%; HRMS(ESI)*m/z* calcd for $C_{26}H_{27}N_3O_3$ $[M+H]^+$: 430.2125, Found: 430.2121.

4.2.6.11.

*(S)-N-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-2-phenylacetamide (**23c**)*

White solid (64 mg, 77% yield). m.p. 70-72 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 10.07 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 7.20 – 7.16 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.01 – 6.90 (m, 2H), 6.51 – 6.35 (m, 2H), 4.95 (s, 1H), 4.08 – 3.84 (m, 3H), 3.61 (s, 2H), 2.76 (dd, *J* = 13.9, 5.1 Hz, 3H), 2.69 – 2.60 (m, 3H), 1.87 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 168.86, 152.04, 137.31, 137.12, 136.08, 135.10, 129.05, 128.77, 128.25, 126.46, 123.37, 121.71, 119.13, 118.38, 104.78, 99.87, 98.44, 70.50, 68.07, 52.37, 51.07, 43.28, 35.15. HPLC: room temperature; t_R=8.164 min, UV_{254}=96.1%; HRMS(ESI)*m/z* calcd for $C_{27}H_{29}N_3O_3$ $[M+H]^+$: 444.2282, Found: 444.2278.

4.2.6.12.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-phenylurea (**23d**)*

White solid (1.3 g, 87% yield). m.p. 159-161 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 8.61 (s, 1H), 8.55 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.9 Hz, 2H), 7.21 – 7.17 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.89 (m, 3H), 6.46 (dd, *J* = 6.1, 2.3 Hz, 1H), 6.45 – 6.40 (m, 1H), 4.94 (s, 1H), 3.99 (dd, *J* = 13.4, 7.9 Hz, 3H), 2.77 (dd, *J* = 14.2, 5.3 Hz, 3H), 2.70 – 2.62 (m, 3H), 1.75 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 152.58, 152.00, 139.71, 137.45, 137.24, 133.74, 128.80, 128.75, 123.31, 121.67, 118.40, 118.22, 118.11, 104.73, 99.82, 98.41, 70.50, 68.17, 52.45, 51.32, 35.25. HPLC: room temperature; t_R=8.189 min, UV_{254}=97.7%; HRMS(ESI)*m/z* calcd for $C_{26}H_{28}N_4O_3$ $[M+H]^+$: 445.2234, Found: 445.2228.

4.2.6.13.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-cyclohexylurea (**23e**)*

White solid (60 mg, 48% yield). m.p. 156-158 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 8.18 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 6.5 Hz, 2H), 6.46 (dd, *J* = 9.8, 3.3 Hz, 2H), 6.00 (d, *J* = 7.9 Hz, 1H), 4.95 (s, 1H), 4.06 – 3.91 (m, 3H), 3.47 – 3.43 (m, 1H), 2.80 – 2.71 (m, 3H), 2.70 – 2.59 (m, 3H), 1.80 (dd, *J* = 12.0, 3.0 Hz, 2H), 1.66 (dd, *J* = 8.9, 4.0 Hz, 2H), 1.54 (s, 1H), 1.39 – 1.11 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 154.46, 152.02, 138.39, 137.27, 132.66, 128.67, 123.32, 121.67, 118.35, 117.54, 104.73, 99.83, 98.42, 70.51, 68.16, 52.45, 51.30, 47.50, 35.20, 32.97, 25.20, 24.30. HPLC: room temperature; t_R=8.441 min, UV_{254}=96.1%; HRMS(ESI)*m/z* calcd for $C_{26}H_{34}N_4O_3$ $[M+H]^+$: 451.2700, Found: 451.2700.

4.2.6.14.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-isopropylurea (**23f**)*

White solid (100 mg, 81% yield). m.p. 129-131 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.18 (s, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.19 (s, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.02 – 6.91 (m, 2H), 6.45 (d, *J* = 10.5 Hz, 2H), 5.93 (d, *J* = 7.5 Hz, 1H), 4.97 (s, 1H), 4.06 – 3.90 (m, 3H), 3.74 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.76 (dd, *J* = 20.8, 5.4 Hz, 3H), 2.69 – 2.57 (m, 3H), 1.98 (s, 1H), 1.08 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 154.57, 152.04, 138.41, 137.29, 132.69, 128.68, 123.36, 121.70, 118.36, 117.59, 104.74, 99.85, 98.42, 70.52, 68.16, 52.46, 51.31, 40.81, 35.19, 23.00. HPLC: room temperature; t_R=7.482 min, UV_{254}=98.7%; HRMS(ESI)*m/z* calcd for $C_{23}H_{30}N_4O_3$ $[M+H]^+$: 411.2391, Found: 411.2391.

4.2.6.15.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-phenethylurea (**23g**)*

White solid (125 mg, 74% yield). m.p. 127-129 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.34 (s, 1H), 7.34 – 7.17 (m, 8H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.00 – 6.90 (m, 2H), 6.52 – 6.38 (m, 2H), 6.04 (t, *J* = 5.6 Hz, 1H), 4.92 (d, *J* = 3.9 Hz, 1H), 4.05 – 3.88 (m, 3H), 3.35 – 3.31 (m, 2H), 2.80 – 2.71 (m, 5H), 2.67 – 2.60 (m, 3H), 1.68 (s, 1H). ^{13}C NMR (101 MHz,

DMSO) δ 155.19, 152.06, 139.55, 138.38, 137.30, 132.83, 128.70, 128.65, 128.32, 126.03, 123.37, 121.71, 118.38, 117.69, 104.76, 99.87, 98.44, 70.55, 68.20, 52.49, 51.35, 40.59, 35.87, 35.24. HPLC: room temperature; t_R=8.398 min, UV_{254}=97.7%; HRMS(ESI)*m/z* calcd for $C_{28}H_{32}N_4O_3$ $[M+H]^+$: 473.2547, Found: 473.2545.

4.2.6.16.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-(2-fluorophenyl) urea (**23h**)*

White solid (130 mg, 65% yield). m.p. 164-166 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 8.97 (s, 1H), 8.49 (d, *J* = 2.5 Hz, 1H), 8.15 (dd, *J* = 8.3, 6.7 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.17 (m, 2H), 7.13 (dd, *J* = 7.6, 6.0 Hz, 3H), 7.03 – 6.92 (m, 3H), 6.54 – 6.36 (m, 2H), 4.94 (d, *J* = 4.5 Hz, 1H), 4.09 – 3.88 (m, 3H), 2.77 (dd, *J* = 12.9, 5.3 Hz, 3H), 2.70 – 2.63 (m, 3H), 1.66 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.09, 152.18, 152.07, 150.70, 137.31, 137.25, 134.09, 128.95, 127.71, 127.60, 124.45, 123.36, 122.26, 122.19, 121.71, 120.41, 118.39, 118.18, 114.97, 114.78, 104.76, 99.87, 98.45, 70.55, 68.24, 52.52, 51.30, 35.31. HPLC: room temperature; t_R=8.577 min, UV_{254}=98.8%; HRMS(ESI)*m/z* calcd for $C_{26}H_{27}FN_4O_3$ $[M+H]^+$: 463.2140, Found: 463.2136.

4.2.6.17.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-(3-fluorophenyl) urea (**23i**)*

White solid (130 mg, 60% yield). m.p. 164-166 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.47 (s, 1H), 9.16 (s, 1H), 7.51 (d, *J* = 12.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.20 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.02 – 6.93 (m, 2H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.51 – 6.40 (m, 2H), 6.16 (dd, *J* = 10.8, 8.1 Hz, 1H), 4.99 (s, 1H), 4.04 – 3.97 (m, 3H), 3.85 (s, 1H), 2.83 – 2.75 (m, 4H), 2.68 – 2.65 (m, 2H), 1.70 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.21, 155.32, 152.59, 152.05, 141.95, 137.41, 133.86, 130.25, 130.15, 128.84, 123.36, 121.69, 118.37, 118.15, 114.85, 113.53, 107.83, 104.77, 104.30, 99.86, 98.42, 70.54, 68.21, 52.51, 51.31, 35.31. HPLC: room temperature; t_R=7.851 min, UV_{254}=98.5%; HRMS(ESI)*m/z* calcd for $C_{26}H_{27}FN_4O_3$ $[M+H]^+$: 463.2140, Found: 463.2136.

4.2.6.18.

(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-(4-fluorophenyl)

*urea (**23j**)*

White solid (1400 mg, 64% yield). m.p. 163-165 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.71 (s, 1H), 8.61 (s, 1H), 7.47 (dd, *J* = 8.8, 5.0 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.20 (s, 1H), 7.11 (t, *J* = 8.7 Hz, 4H), 7.02 – 6.92 (m, 2H), 6.47 (d, *J* = 8.0 Hz, 2H), 4.99 (s, 1H), 4.00 (dd, *J* = 11.5, 6.9 Hz, 3H), 2.79 (dd, *J* = 16.3, 5.2 Hz, 3H), 2.70 (dd, *J* = 16.1, 8.8 Hz, 3H), 1.23 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 158.43, 156.06, 152.66, 152.04, 137.51, 137.30, 136.12, 133.74, 128.85, 123.37, 121.71, 119.86, 119.78, 118.38, 118.32, 115.32, 115.10, 104.77, 99.87, 98.44, 70.53, 68.16, 52.44, 51.25, 35.21. HPLC: room temperature; t_R=8.460 min, UV_{254}=98.9%; HRMS(ESI)*m/z* calcd for $C_{26}H_{27}FN_4O_3$ $[M+H]^+$: 463.2140, Found: 463.2137.

4.2.6.19.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-(2-methoxyphenyl)urea (**23k**)*

White solid (130 mg, 64% yield). m.p. 90-92 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 9.23 (s, 1H), 8.19 (s, 1H), 8.14 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.20 (s, 1H), 7.13 (d, *J* = 7.7 Hz, 2H), 7.07 – 6.82 (m, 5H), 6.46 (d, *J* = 8.8 Hz, 2H), 4.98 (s, 1H), 4.08 – 3.94 (m, 3H), 3.87 (s, 3H), 2.86 – 2.60 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 152.39, 152.04, 147.55, 137.66, 137.29, 133.68, 128.89, 128.75, 123.37, 121.70, 121.62, 120.51, 118.36, 118.19, 117.98, 110.65, 104.74, 99.85, 98.43, 70.53, 68.20, 55.71, 52.50, 51.30, 35.28. HPLC: room temperature; t_R=8.576 min, UV_{254}=98.3%; HRMS(ESI)*m/z* calcd for $C_{27}H_{30}N_4O_4$ $[M+H]^+$: 475.2340, Found: 475.2337.

4.2.6.20.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-(3-methoxyphenyl)urea (**23l**)*

White solid (85 mg, 40% yield). m.p. 89-90 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.72 (s, 1H), 8.64 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.08 (m, 5H), 6.99 (t, *J* = 6.6 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.54 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.47 (dd, *J* = 8.5, 1.9 Hz, 2H), 4.99 (s, 1H), 4.09 – 3.92 (m, 3H), 3.73 (s, 3H), 2.86 – 2.73 (m, 3H), 2.68 (dd, *J* = 15.3, 7.5 Hz, 3H), 1.23 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 159.66, 152.52, 152.04, 141.05, 137.53, 137.31, 133.65, 129.48, 128.86, 123.37, 121.72, 118.38, 118.30, 110.42, 107.06,

104.78, 103.86, 99.87, 98.45, 70.51, 68.08, 54.86, 52.38, 51.18, 35.10. HPLC: room temperature; t_R=8.343 min, UV_{254}=95.9%; HRMS(ESI)*m/z* calcd for $C_{27}H_{30}N_4O_4$ $[M+H]^+$: 475.2340, Found: 475.2335.

4.2.6.21.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-(4-methoxyphenyl)urea (**23m**)*

White solid (80 mg, 43% yield). m.p. 168-170 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 7.35 (dd, *J* = 8.5, 4.3 Hz, 4H), 7.20 (t, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.02 – 6.92 (m, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.46 (dd, *J* = 8.7, 1.9 Hz, 2H), 4.98 (s, 1H), 4.08 – 3.90 (m, 3H), 3.71 (s, 3H), 2.82 – 2.70 (m, 3H), 2.70 – 2.61 (m, 3H), 1.82 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 154.37, 152.77, 152.06, 137.72, 137.31, 133.55, 132.81, 128.82, 123.37, 121.72, 119.92, 118.38, 118.18, 113.95, 104.76, 99.87, 98.45, 70.55, 68.21, 55.12, 52.50, 51.32, 35.28. HPLC: room temperature; t_R=8.654 min, UV_{254}=99.1%; HRMS(ESI)*m/z* calcd for $C_{27}H_{30}N_4O_4$ $[M+H]^+$: 475.2340, Found: 475.2336.

*4.2.6.22. methyl (S)-(2-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)ureido)phenyl) carbamate (**27a**)*

White solid (50 mg, 40% yield). m.p. 112-114 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 9.19 (s, 1H), 8.85 (s, 1H), 8.15 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.20 (s, 1H), 7.14 (t, *J* = 8.1 Hz, 3H), 7.05 – 6.92 (m, 3H), 6.46 (d, *J* = 11.8 Hz, 2H), 5.06 (s, 1H), 4.01 (s, 3H), 3.66 (s, 3H), 2.82 (d, *J* = 8.5 Hz, 3H), 2.75 – 2.61 (m, 3H), 1.23 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 155.09, 152.78, 151.96, 137.74, 137.30, 133.83, 133.21, 128.92, 127.72, 125.97, 125.65, 123.40, 122.43, 121.69, 121.24, 118.36, 118.15, 104.83, 99.88, 98.42, 70.39, 67.69, 52.04, 51.86, 50.82, 34.56. HPLC: room temperature; t_R=8.016 min, UV_{254}=97.1%; HRMS(ESI)*m/z* calcd for $C_{28}H_{31}N_5O_5$ $[M+H]^+$: 518.2398, Found: 518.2396.

*4.2.6.23. methyl (S)-(3-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)ureido)phenyl) carbamate (**27b**)*

White solid (80 mg, 63% yield). m.p. 155-157 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.11 (s,

1H), 9.59 (s, 1H), 9.14 (s, 1H), 9.10 (s, 1H), 7.60 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.23 (s, 1H), 7.16 (dd, *J* = 8.5, 6.8 Hz, 4H), 7.00 (dd, *J* = 18.9, 8.0 Hz, 2H), 6.50 (d, *J* = 7.2 Hz, 2H), 5.91 (d, *J* = 4.5 Hz, 1H), 4.30 (s, 1H), 4.19 – 3.95 (m, 3H), 3.65 (s, 3H), 3.15 (dd, *J* = 31.9, 11.0 Hz, 4H), 2.96 (t, *J* = 11.4 Hz, 2H), 1.24 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 153.93, 152.62, 151.58, 140.25, 139.52, 138.61, 137.33, 130.16, 128.92, 128.85, 123.54, 121.63, 118.29, 118.04, 112.20, 111.85, 108.07, 105.17, 99.98, 98.40, 69.60, 65.04, 51.49, 49.74, 48.37, 30.79. HPLC: room temperature; t_R=7.962 min, UV_{254}=95.9%; HRMS(ESI)*m/z* calcd for $C_{28}H_{31}N_5O_5$ $[M+H]^+$: 518.2398, Found: 518.2396.

*4.2.6.24. methyl (S)-(4-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)ureido)phenyl) carbamate (**27c**)*

White solid (100 mg, 90% yield). m.p. 161-163 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 9.47 (s, 1H), 8.49 (s, 2H), 7.33 (d, *J* = 7.9 Hz, 6H), 7.19 (s, 1H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.00 – 6.93 (m, 2H), 6.45 (dd, *J* = 7.6, 5.9 Hz, 2H), 4.95 (s, 1H), 4.08 – 3.90 (m, 3H), 3.64 (s, 3H), 2.77 (dd, *J* = 14.5, 5.3 Hz, 3H), 2.66 (dd, *J* = 12.2, 5.7 Hz, 3H), 1.72 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.99, 152.56, 151.96, 137.67, 137.23, 134.56, 133.39, 128.78, 123.32, 121.65, 118.85, 118.69, 118.29, 118.09, 104.71, 99.80, 98.39, 70.42, 67.99, 52.30, 51.44, 51.11, 34.99. HPLC: room temperature; t_R=8.132 min, UV_{254}=98.8%; HRMS(ESI)*m/z* calcd for $C_{28}H_{31}N_5O_5$ $[M+H]^+$: 518.2398, Found: 518.2400.

*4.2.6.25. (S)-N-(2-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)ureido)phen yl)hexanamide (**27d**)*

White solid (100 mg, 77% yield). m.p. 119-121 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 9.52 (s, 1H), 9.11 (s, 1H), 7.81 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.22 – 7.07 (m, 4H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.46 (d, *J* = 12.7 Hz, 2H), 4.97 (s, 1H), 4.06 – 3.90 (m, 3H), 2.77 (t, *J* = 7.8 Hz, 3H), 2.72 – 2.61 (m, 3H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.72 – 1.57 (m, 2H), 1.32 (s, 4H), 1.09 (t, *J* = 7.0 Hz, 1H), 0.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.04, 152.83, 152.04, 137.73, 137.30, 133.60, 133.41, 128.84, 125.95, 125.58, 123.36, 122.94, 122.90, 121.70, 118.38, 118.26, 104.77, 99.87, 98.44, 70.52, 68.13, 52.43, 51.23, 35.81, 35.19, 30.90, 24.80, 21.91, 13.84.

HPLC: room temperature; t_R=8.718 min, UV_{254}=98.2%; HRMS(ESI)*m/z* calcd for $C_{32}H_{39}N_5O_4$ $[M+H]^+$: 558.3075, Found: 558.3073.

4.2.6.26.

*(S)-N-(3-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)ureido)phenyl)hexanamide (**27e**)*

White solid (65 mg, 38% yield). m.p. 145-147 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 9.83 (s, 1H), 8.68 (s, 1H), 8.53 (s, 1H), 7.78 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.17 (m, 2H), 7.14 (dd, *J* = 12.3, 7.9 Hz, 4H), 7.02 – 6.92 (m, 2H), 6.52 – 6.36 (m, 2H), 4.98 (s, 1H), 3.99 (dd, *J* = 12.6, 7.5 Hz, 3H), 2.78 (dd, *J* = 15.2, 5.3 Hz, 3H), 2.67 (dd, *J* = 12.2, 5.7 Hz, 3H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.99 (s, 1H), 1.65 – 1.53 (m, 2H), 1.30 (d, *J* = 3.4 Hz, 4H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.26, 152.41, 152.02, 140.01, 139.74, 137.52, 137.29, 133.69, 128.84, 123.34, 121.69, 118.35, 118.14, 112.70, 112.57, 108.78, 104.74, 99.85, 98.42, 70.52, 68.16, 52.46, 51.25, 36.39, 35.21, 30.87, 24.82, 21.86, 13.83. HPLC: room temperature; t_R=8.956 min, UV_{254}=95.6%; HRMS(ESI)*m/z* calcd for $C_{32}H_{39}N_5O_4$ $[M+H]^+$: 558.3075, Found: 558.3093.

4.2.6.27.

*(S)-N-(4-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)ureido)phenyl)hexanamide (**27f**)*

White solid (95 mg, 61% yield). m.p. 208-210 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.16 (s, 1H), 9.89 (s, 1H), 9.40 (s, 1H), 9.36 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.38 (dd, *J* = 13.2, 8.7 Hz, 4H), 7.23 – 7.20 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.03 – 6.95 (m, 2H), 6.48 (d, *J* = 7.7 Hz, 2H), 4.17 (s, 1H), 4.05 (s, 2H), 3.15 – 2.71 (m, 5H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.66 – 1.50 (m, 2H), 1.25 (dd, *J* = 33.0, 9.0 Hz, 5H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.86, 152.82, 151.77, 138.36, 137.30, 135.20, 133.55, 131.48, 128.82, 123.44, 121.63, 119.67, 118.30, 118.07, 117.91, 104.99, 99.90, 98.37, 70.01, 66.41, 50.95, 49.67, 36.21, 32.75, 30.88, 24.87, 21.88, 13.84. HPLC: room temperature; t_R=8.800 min, UV_{254}=97.8%; HRMS(ESI)*m/z* calcd for $C_{32}H_{39}N_5O_4$ $[M+H]^+$: 558.3075, Found: 558.3069.

*4.2.7. 3-(aminomethyl)phenol (**10**)*

In a 1 L round-bottomed flask was added 3-hydroxybenzonitrile (**9**) (10 g, 84 mmol, 1.0 eq) in MeOH (200 mL) to give a yellow solution. The reaction vessel was purged with nitrogen.

Rany-Ni (0.719 g, 8.39 mmol, 0.1 eq) was added. The reaction vessel was purged with hydrogen. The reaction was heated to rt with stirring on for 10 hr. The reaction mixture was filtered through celite with MeOH. The mixture was concentrated by rotovap. DCM (20 mL) was added. The reaction mixture was filtered through sintered glass funnel to give 3-(aminomethyl)phenol (**10**) (10 g, 97% yield) as white solid. m.p. 170–172 °C; ESI-MS m/z: 124.65, [M+H]+.

*4.2.8. 3-(acetamidomethyl)phenyl acetate (**11**)*

In a 250 mL round-bottomed flask was added 3-(aminomethyl)phenol (**10**) (8 g, 65.0 mmol, 1.0 eq) and pyridine (10.51 ml, 130 mmol, 2.0 eq) in anhydrous DCM (100 ml) to give a white suspension. Acetyl chloride (10.16 ml, 143 mmol, 2.2 eq) was added. The reaction mixture was held at rt with stirring on for 2 hr. The reaction mixture was washed with water and sat. NaCl. The organic was dried Na_2SO_4, filt and conc to give 3-(acetamidomethyl)phenyl acetate (**11**) (12 g, 89 % yield) as yellow oil. The product was used to next step without further purification.

*4.2.9. N-(3-hydroxybenzyl)acetamide (**12**)*

In a 25 mL round-bottomed flask was added 3-(acetamidomethyl)phenyl acetate (**11**) (13.4 g, 64.7 mmol, 1.0 eq) in MeOH (75 mL) to give a colorless solution. NaOH (12.93 g, 323 mmol, 5.0 eq) in water (75 ml) were added. The reaction mixture was held at rt with stirring on for 18 hr. The mixture was concentrated by rotovap. The aqueous layer was adjusted pH to 4 with 75 mL 4M HCl(aq). The aqueous layer was backextracted with EA. Combined the organic layers and washed with brine. The organic was dried Na_2SO_4, filt and conc. The crude product was purified by column chromatography to give *N*-(3-hydroxybenzyl)acetamide (**12**) (9.8 g, 92% yield) as light-yellow solid. m.p. 95-97 °C; ^{1}H-NMR (400 MHz, DMSO) δ: 9.31 (s, 1H), 8.28 (s, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.72-6.55 (m, 3H), 4.16 (d, J = 5.9 Hz, 2H), 1.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.03, 157.32, 140.95, 129.16, 117.79, 114.04, 113.63, 41.99, 22.51.

*4.2.10. General procedure for the synthesis of **25a-c***

In a 100 mL round-bottomed flask was added ***24a-c*** (1.0 eq), hydrazine hydrate (10 eq), and trihydroxyiron (0.1 eq) in EtOH (20 mL) to give a yellow suspension. The reaction was heated to 85°C with stirring on for 3 hr. The reaction mixture was filtered through celite with

EtOH (20 mL). The mixture was concentrated by rotovap. EA (30 mL) was added. The organic was washed with water and brine. The organic was dried Na_2SO_4, filt and conc to give ***25a-c***. The product was used to next step without further purification.

4.2.10.1.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(2-aminophenyl)urea (**25a**)*

White solid (650 mg, 98% yield). m.p. 70-72 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.62 (s, 1H), 7.66 (s, 1H), 7.39 – 7.23 (m, 7H), 7.20 (dd, *J* = 14.4, 4.5 Hz, 2H), 7.02 – 6.89 (m, 4H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.76 – 6.71 (m, 1H), 6.57 (t, *J* = 7.5 Hz, 1H), 6.44 – 6.40 (m, 2H), 4.79 (d, *J* = 4.0 Hz, 1H), 4.75 (s, 2H), 4.10 – 3.97 (m, 2H), 3.91 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.80 – 3.62 (m, 2H), 2.81 – 2.54 (m, 6H).

4.2.10.2.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(3-aminophenyl)urea (**25b**)*

White solid (278 mg, 98% yield). m.p. 81-83 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 7.37 – 7.14 (m, 8H), 6.99 (d, *J* = 8.2 Hz, 4H), 6.88 (t, *J* = 7.9 Hz, 1H), 6.77 (s, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.42 (s, 2H), 6.18 (d, *J* = 7.9 Hz, 1H), 5.00 (s, 2H), 4.80 (d, *J* = 3.9 Hz, 1H), 4.03 (t, *J* = 9.4 Hz, 2H), 3.91 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 2.82 – 2.58 (m, 6H).

4.2.10.3.

*(S)-1-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)-3-(4-aminophenyl)urea (**25c**)*

White solid (380 mg, 99% yield). m.p. 83-85 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.34 (s, 1H), 8.06 (s, 1H), 7.30 – 7.15 (m, 8H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 5.0 Hz, 4H), 6.50 (d, *J* = 8.5 Hz, 2H), 6.42 (dd, *J* = 9.0, 4.0 Hz, 2H), 4.80 (s, 1H), 4.76 (s, 2H), 4.04 (d, *J* = 8.3 Hz, 2H), 3.96 – 3.86 (m, 1H), 3.76 (d, *J* = 13.7 Hz, 1H), 3.67 (d, *J* = 13.8 Hz, 1H), 2.78 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.72 – 2.59 (m, 5H).

*4.2.11. General procedure for the synthesis of **26a-f***

In a 100 mL round-bottomed flask was added ***25a-c*** (1.0 eq) and DIPEA (1.5 eq) in DCM (30 mL) to give a colorless solution. Methyl carbonochloridate or hexanoyl chloride (1.2 eq) was

added. The reaction mixture was held at rt with stirring on for 16 hr. The mixture was concentrated by rotovap. The crude product was purified by column chromatography to give ***26a-f***.

4.2.11.1. *methyl (S)-(2-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)ureido) phenyl)carbamate (**26a**)*

White solid (165 mg, 60% yield). m.p. 86-88 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.08 (s, 1H), 8.83 (s, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.27 (dt, *J* = 16.5, 7.1 Hz, 8H), 7.16 (dd, *J* = 14.8, 5.3 Hz, 2H), 6.99 (dd, *J* = 13.1, 5.8 Hz, 5H), 6.42 (s, 2H), 4.81 (d, *J* = 3.9 Hz, 1H), 4.05 (d, *J* = 8.0 Hz, 2H), 3.95 – 3.87 (m, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.68 (d, *J* = 15.4 Hz, 4H), 2.79 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.72 – 2.59 (m, 5H).

4.2.11.2. *methyl (S)-(3-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)ureido) phenyl)carbamate (**26b**)*

White solid (190 mg, 86% yield). m.p. 84-86 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.59 (s, 1H), 8.61 (s, 1H), 8.44 (s, 1H), 7.56 (s, 1H), 7.36 – 7.14 (m, 10H), 7.09 – 6.93 (m, 5H), 6.41 (s, 2H), 4.79 (d, *J* = 4.1 Hz, 1H), 4.04 (d, *J* = 8.0 Hz, 2H), 3.90 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.68 (d, *J* = 14.2 Hz, 4H), 2.83 – 2.58 (m, 6H).

4.2.11.3. *methyl (S)-(4-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)ureido) phenyl)carbamate (**26c**)*

White solid (130 mg, 74% yield). m.p. 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.30 (dd, *J* = 14.9, 8.7 Hz, 5H), 7.22 – 7.14 (m, 6H), 7.08 – 7.02 (m, 4H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 6.64 (s, 2H), 6.56 (s, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 4.01 (d, *J* = 9.2 Hz, 3H), 3.87 (d, *J* = 13.3 Hz, 1H), 3.75 (s, 3H), 3.62 (d, *J* = 13.6 Hz, 1H), 2.88 – 2.70 (m, 6H).

4.2.11.4.

*(S)-N-(2-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)urei do)phenyl)hexanamide (**26d**)*

White solid (210 mg, 71% yield). m.p. 91-93 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.50 (s, 1H), 9.07 (s, 1H), 7.78 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.26 (dt, *J* = 31.0, 16.3

Hz, 10H), 7.09 – 6.95 (m, 5H), 6.41 (s, 2H), 4.80 (s, 1H), 4.04 (d, *J* = 7.8 Hz, 2H), 3.91 (dd, *J* = 8.1, 5.1 Hz, 1H), 3.77 (d, *J* = 13.9 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 2.79 (dd, *J* = 12.7, 5.2 Hz, 1H), 2.72 – 2.59 (m, 5H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.69 – 1.55 (m, 2H), 1.31 (s, 4H), 0.86 (s, 3H).

4.2.11.5.

*(S)-N-(3-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)ureido)phenyl)hexanamide (**26e**)*

White solid (240 mg, 77% yield). m.p. 85-87 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.83 (s, 1H), 8.62 (s, 1H), 8.46 (s, 1H), 7.78 (s, 1H), 7.28 (dd, *J* = 13.9, 7.7 Hz, 6H), 7.24 – 7.12 (m, 6H), 6.99 (dd, *J* = 10.9, 6.1 Hz, 4H), 6.42 (s, 2H), 4.80 (d, *J* = 3.4 Hz, 1H), 4.04 (d, *J* = 7.9 Hz, 2H), 3.95 – 3.86 (m, 1H), 3.77 (d, *J* = 13.9 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 2.79 (dd, *J* = 12.9, 5.5 Hz, 1H), 2.73 – 2.54 (m, 5H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.58 (dd, *J* = 14.2, 7.1 Hz, 2H), 1.30 (d, *J* = 3.3 Hz, 4H), 0.88 (t, *J* = 6.7 Hz, 3H).

4.2.11.6.

*(S)-N-(4-(3-(4-(2-((3-((1H-indol-4-yl)oxy)-2-hydroxypropyl)(benzyl)amino)ethyl)phenyl)ureido)phenyl)hexanamide (**26f**)*

White solid (180 mg, 80% yield). m.p. 97-99 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.86 (s, 1H), 9.53 (s, 1H), 8.62 (s, 1H), 7.78 (s, 1H), 7.31 – 7.26 (m, 6H), 7.24 – 7.12 (m, 6H), 7.01 – 6.97 (m, 4H), 6.42 (s, 2H), 4.80 (s, 1H), 4.04 (d, *J* = 7.9 Hz, 2H), 3.95 – 3.86 (m, 1H), 3.77 (d, *J* = 13.9 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 2.79 (dd, *J* = 12.9, 5.5 Hz, 1H), 2.73 – 2.54 (m, 5H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.58 (dd, *J* = 14.2, 7.1 Hz, 2H), 1.30 (d, *J* = 3.3 Hz, 4H), 0.87 (t, *J* = 6.6 Hz, 3H).

4.3. Biological evaluation

4.3.1. β_3-AR antagonist activity in vitro （Calcium mobilization assay）

HEK293 cells stably expressing Gα16 with human β_3-, β_2- or β_1-ARs were seeded onto 96-well plates and incubated for 24 h. Cells were loaded with 2.00 μmol/L Fluo-4 AM in Hanks balanced salt solution (HBSS, containing KCl 5.40 mmol/L, Na_2HPO_4 0.30 mmol/L, KH_2PO_4 0.4 mmol/L, $NaHCO_3$ 4.20 mmol/L, $CaCl_2$ 1.30 mmol/L, $MgCl_2$ 0.50 mmol/L, Mg_2SO_4 0.60 mmol/L, NaCl 137.00 mmol/L, BSA 5.00 g/L, glucose 5.60 mmol/L,

sulfinpyrazone 250 μmol/L, pH 7.4) at 37℃ for 45 min. The excess dye was removed and 50 μL HBSS containing test compounds were added. After incubation at room temperature for 10 min, 25 μL isoproterenol was dispensed into the well using a FlexStation II microplate reader (Molecular Devices, Sunnyvale, CA, USA) and intracellular calcium change was recorded with an excitation wavelength of 485 nm and emission wavelength of 525 nm. The half maximal inhibitory concentrations (IC_{50}) of compounds were determined with GraphPad Prism software by constructing their dose-response curves.

4.3.2. Inhibitory effect of β_3-AR antagonists on lipolysis in vitro

3T3-L1 pre-adipocytes cells, obtained from Shanghai Institute of Materia Medica, Chinese Academy of sciences, were cultured in adipocytes medium (AM, high-glucose DMEM with 10% fetal bovine serum) at 37 °C with 5% CO2. During differentiation, the pre-adipocytes were planted on culture plates coated with 0.1% gelatin, with confluence reached 100% for 48 hr in AM. Then they were induced to differentiate by treatment with differentiation media (DM I and DM II) for 48 hr respectively, DM I containing 10 μg/ml insulin, 1 μM dexamethasone (DEX) and 0.5 mM 3-isobutyl-1-methylxanthine (IBMX) in AM and DM II (DEX- and IBMX-free DM I). Thereafter, the differentiated cells were maintained in AM changed in every 2 days until used. Cells were negative for mycoserum contamination before use.

For lipolysis experiments, glycerol accumulation in the media from 3T3-L1 mature adipocytes was measured using a Lipolysis Assay Kit following the manufacturer instructions. Briefly, 3T3-L1 mature adipocytes were washed three times with PBS and incubated with 100 μl phenol red-free DMEM supplemented with 2% fatty acid-free BSA containing 1 μM ISO with or without antagonist of β3-adrenergic receptor for 2 hr. After incubation, the 100 μl medium was collected and centrifuged at 12000 g for 10 min to remove cell debris. The 50 μl supernatant and glycerol assay reagent (150 μl) were plated in a clean 96 well plate for 10 min at 37 °C and optical density of each well was measured at 550 nm.

*4.3.3. Inhibitory effect of β_3-AR antagonist **23d** on C26 tumor bearing mice*

Male BALB/c mice (6–8 weeks old) were purchased from the SHANGHAI SLAC LABORATORY ANIMAL CO. LTD. Mice were maintained on a 12:12 light-dark cycle in a temperature-controlled (21~23°C) and specific pathogen-free (SPF) conditional room, and

were provided standard rodent chow and water *ad libitum*. All animals were acclimatized for a week before beginning the study. All experiment procedures with animals were in accordance with the guidelines of the Institutional Animal Care and Use Committee.

BALB/c mice with same initial body weight were randomly divided into three groups: health group (without tumor), Colon-26 (C26) tumor-bearing mice group (C26 model group) and C26 tumor-bearing mice treated with **23d** (2.5 mg/kg) group. On day 0, mice were implanted subcutaneously in the right flank with 100 μl (1.0×10^6) C26 adenocarcinoma cells. Starting from the next day, C26 model group mice received daily intraperitoneal injections of sterile saline, while **23d** treated mice received daily injection in tail vein of **23d** (2.5 mg/kg). Body weight and tumor volume were measured daily from inoculation to completion of the study. On day 6, tumors were first noticed. Record the shortest diameter (x) and longest diameter (y) of tumor using calipers. Tumor volume was calculated following the formula: V =x * x * y * 0.5. When the mice lost 10% of their body weight or when their tumor volumes reached 2,000 mm^3, serum was rapidly gathered and stored at -80°C until ready for further analyses. All treatment groups were sacrificed 6 hr after the last treatment.

Statistical analysis

Data are expressed as mean ± SEM. Two-tailed Student's t test was used for comparisons between two groups. One-way ANOVA test was performed to compare multiple groups followed by Bonferroni's post hoc test. All analyses were performed using GraphPad Prism 5.0. Values of p less than 0.05 were considered to be statistically significant and were presented as $*p< 0.05$, $**p < 0.01$, $***p< 0.001$ or $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$.

Supplementary data

Supplementary data related to this article can be found at.

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Figure 1. Chemical structure of early β_3-AR antagonist.

Figure 2. Design of compound based on (*S*)-pindolol, L-748,337 and SR59230A.

Figure 3. Antagonist of β_3-adrenergic receptor inhibits lipolysis of 3T3-L1 mature adipocyte *in vitro*. The lipolysis of 3T3-L1 adipocyte in cancer cachexia model *in vitro* was induced 1 μM ISO for 2 hr. Data presented are the mean ± SE of three independent experiments. * versus control group. # versus ISO group. #$p < 0.05$, ###$p < 0.001$. *$p < 0.05$, **$p < 0.01$.

Figure 4. 23d attenuates C26 tumor-induced body weight loss *in vivo*. Compound **23d** (2.5 mg/kg) was injected in tail vein daily (n=7). A) Tumor-free body weight of mice. B) C26 tumor volume of mice. C) Content of glycerol in serum. Data presented are the mean ± SE of three independent experiments. * versus health group mice. # versus C26 tumor bearing group mice. ###$p<0.001$. **$p<0.01$, ***$p<0.001$.

Scheme 1. Synthesis of SR59230A derivatives **8a-d**. Reagent and conditions: (a) Paraformaldehyde EtOH reflux, then $NaBH_4$, EtOH, rt; (b) (*R*)-(-)-Epichlorohydrin, NaOH, warer/Dioxane, rt; (c) NaOH, IPA, relfux; (d) $SnCl_2$, EtOH, reflux; (e) R^1Cl, Pyridine, DCM, rt; (f) Raney-Ni, H_2, MeOH, rt.

Scheme 2. Synthesis of L-748,337 derivatives **17a-d**. Reagent and conditions: (a) Raney-Ni, H_2, MeOH, rt;

(b) Acetyl chloride, Pyridine, DCM, rt; (c) 15% NaOH(aq), MeOH, rt; (d) (*R*)-(-)-Epichlorohydrin, NaOH, warer/Dioxane, rt; (e) NaOH, IPA, relfux; (f) $SnCl_2$, EtOH, reflux; (g) R^2Cl, Pyridine, DCM, rt; (h) Raney-Ni, H_2, MeOH, rt.

Scheme 3. Synthesis of Indole derivatives **23a-m**. Reagent and conditions: (a) (*R*)-(-)-Epichlorohydrin, NaOH, warer/Dioxane, rt; (b) NaOH, IPA, relfux; (c) $SnCl_2$, EtOH, reflux; (d) R^3Cl, Pyridine, DCM, rt; (e) Raney-Ni, H_2, MeOH, rt.

Scheme 4. Synthesis of Indole derivatives **27a-f**. Reagent and conditions: (a) ArCNO, Pyridine, DCM, rt; (b) $Fe(OH)_3$, $N_2H_4H_2O$, EtOH, reflux; (c) Pyridine, DCM, rt; (d) Raney-Ni, H_2, MeOH, rt.

Table 1. β_3-AR antagonist activity of aryloxypropanolamine derivatives.

Table 2. β_3-AR antagonist activity of urea derivatives.

Highlights

- In this study, we designed and synthesized a series of novel L-748,337 derivatives as selective human β_3-AR antagonists.
- Among all analogs, compound **23d** was found to display 23-fold more potent β_3-AR antagonist activity than L-748,337 *in vitro*.
- *In vivo*, compound **23d** could alleviate weight loss and inhibit tumor growth in C26 tumor cachexia animal model.