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Identification of 3,4-dihydro-2*H*-thiochromene 1,1-dioxide derivatives with a phenoxyethylamine group as highly potent and selective α_{1D} adrenoceptor antagonists

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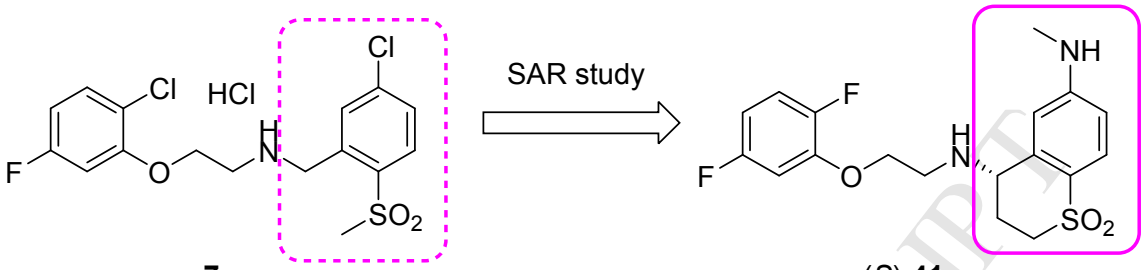
Graphical abstract



7

α_{1D} *K*i = 17 nM

α_{1A} *K*i = 1800 nM, α_{1B} *K*i = 1100 nM

(*S*)-**41**

α_{1D} *K*i = 0.3 nM

α_{1A} *K*i = 130 nM, α_{1B} *K*i = 150 nM

Identification of 3,4-dihydro-2*H*-thiochromene 1,1-dioxide derivatives with a phenoxyethylamine group as highly potent and selective α_{1D} adrenoceptor antagonists

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[1] AR, Adrenoceptor; BH_3, borane; Boc_2O, di-tert-butyl bicarbonate; *t*-BuXphos, 2-di-tert-butylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl; BOO, bladder outlet obstruction; BPH, benign prostatic hyperplasia; $(COCl)_2$, oxalyl chloride; *m*CPBA, *m*-chloroperoxybenzoic acid; DME, 1,2-dimethoxyethane; dppf, 1,1'-bis(diphenylphophino)ferrocene; Et_3N, triethylamine; HCl, hydrochloric acid; HOBt, 1-hydroxybenzotriazole monohydrate; H_2SO_4, sulfuric acid; K_2CO_3, potassium carbonate; $MeONH_2$, methoxyamine; NaOMe, sodium methoxide; NaSMe, sodium thiomethoxide; NMP, *N*-methyl-2-pyrrolidone; Pd/C, palladium on carbon; Pd_2dba_3, tris(dibenzylideneacetone)dipalladium(0); $Pd(OAc)_2$, palladium(II) acetate; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); *i*-Pr_2NEt, *N*,*N*-diisopropylethylamine; WSC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; Xphos, 2-(dicyclohexylphosphino)-2',4',6'-tri-isopropyl-1,1'-biphenyl, $Zn(CN)_2$, zinc cyanide.

Abstract

A series of phenoxyethylamine derivatives was designed and synthesized to discover potent and selective human α_{1D} adrenoceptor (α_{1D} adrenergic receptor; α_{1D}–AR) antagonists. Compound **7** was taken from our internal compound collection as an attractive starting point and exhibited moderate binding affinity for α_{1D}–AR and high selectivity against α_{1A}– and α_{1B}–ARs. We focused on modifying the 2-methylsulfonylbenzyl group of **7** to discover novel compounds structurally distinct from other reported α_1–AR antagonists containing the phenoxyethylamine motif. Study of structure activity relationship guided by a targeted ligand-lipophilicity efficiency score led to the discovery of a novel scaffold of 3,4-dihydro-2*H*-thiochromene 1,1-dioxide for selective α_{1D}–AR antagonists. Further optimization studies resulted in the identification of (4*S*)-N^4-[2-(2,5-difluorophenoxy)ethyl]-N^6-methyl-3,4-dihydro-2*H*-thiochromene-4,6-diamine 1,1-dioxide, (*S*)–**41**, as a novel, highly potent and selective α_{1D}–AR antagonist. Herein, we provide details of the structure activity relationship of the phenoxyethylamine analog for the potency and selectivity.

Keywords: phenoxyethylamine derivatives, selective human α_{1D} adrenoceptor antagonist, 3,4-dihydro-2*H*-thiochromene 1,1-dioxide, ligand–lipophilicity efficiency (LLE)

1. Introduction

The α_1 adrenergic receptors (α_1 adrenoceptors, α_1–ARs) are a part of the G protein-coupled receptor (GPCR) superfamily and are classified into three receptor subtypes, α_{1A}, α_{1B} and α_{1D}-ARs [1−4]. The functions and tissue distribution of each receptor subtype are known to be different. It has been demonstrated that α_{1A}-ARs mediate smooth muscle contractions in the human prostate and are predominantly expressed in the bladder neck, prostate, and prostatic urethra [5−8]. Some literature reports suggest that α_{1B}-ARs regulate vasoconstriction of large human arteries, and are extensively expressed in the vascular smooth muscle [9,10]. The α_{1D}-ARs are widely found in the human bladder detrusor muscle and epicardial coronary arteries [11−13].

Several non-subtype-selective α_1-AR antagonists, such as doxazosin and alfuzosin, are used in the treatment of hypertension and lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH), a urologic disorder prevalent in elderly men [14,15].

Subtype-selective α_1-AR ligands help understand the functional role of each receptor subtype and avoid unfavorable side effects in therapy. Increasing evidence for the involvement of α_{1A}-AR in bladder outlet obstruction (BOO) in patients with BPH has encouraged the use of α_{1A}-AR selective antagonists in symptomatic therapy of BPH [5,7]. Presently, a α_{1A}- and α_{1D}-AR dual antagonist **1** (tamsulosin) and a highly selective α_{1A}-AR antagonist **2** (silodosin) are available on the market for the treatment of BPH [16]. However, the effort to develop α_{1B}–AR or α_{1D}-AR selective ligands has been less fruitful than the search for α_{1A}- and α_{1D}-AR dual or α_{1A}-AR selective ligands. For example, cyclazosin and L–765,314 have been reported as selective α_{1B}-AR antagonists [17]. Antagonism of α_{1B}-AR may cause cardiovascular side effects such as orthostatic hypotension, tachycardia, arrhythmia, and dizziness [18−20]. Regarding α_{1D}-AR antagonists, we recently reported the discovery and optimization of iminopyridine derivatives yielding compound **3** (TAK–259), as a

potent, orally available, and selective α_{1D} antagonist with antiurinary frequency effects [21]. In addition, **4** (BMY7378) is well known as an α_{1D}-AR ligand that also binds the serotonergic 5-HT_{1A} receptor [22]. Furthermore, compound **5** (SNAP 8719) shows improved selectivity against the serotonergic 5-HT_{1A} receptor compared to **4**, and a phenoxyethylamine derivative **6** has been reported as a selective α_{1D}-AR antagonist [23].

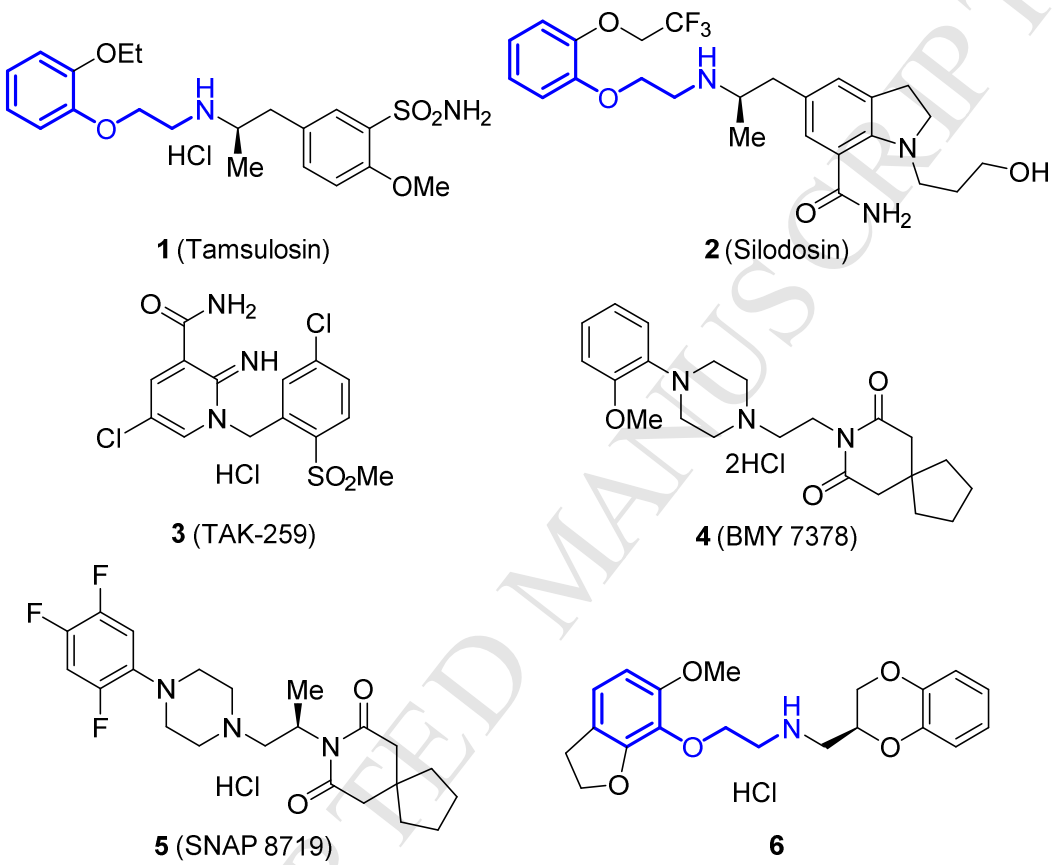
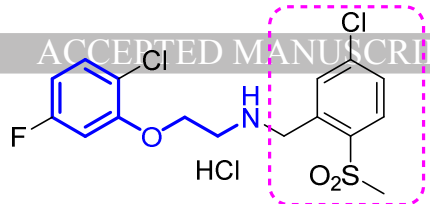


Figure 1. Structures of reported α_1-ARs antagonists. Blue lines indicate phenoxyethylamine analog.

Table 1. In vitro data and clog P of **6**, TAK-259 and **7**.



7

comp	*Ki* (nM)[a] α_{1D}	LLE[b]	selectivity 1A/1D	selectivity 1B/1D	phenylephrine-induced contraction[c], IC_{30} (nM)
6	2.2[d]	6.0	1.1[d]	10[d]	—
TAK-259	1.1	8.7	200	800	12
7	17	4.3	110	65	250

[a]*Ki* value for α_{1D} was obtained by displacement of 7-methoxy-[^{3}H]-prazosin from cloned human receptor.

[b]LLE = −log(*Ki*)−clog P.

[c]Effects on the phenylephrine-induced contractions of the bladder strips taken from the rats with BOO (n = 2−11).

[d]The data were taken from the literature [23].

In the course of discovering the selective α_{1D}-AR antagonist **3**, we were interested in expanding the range of α_{1D}-AR antagonists and sought a new series of compounds structurally different from **3**. The phenoxyethylamine derivative **7** was obtained from our internal compound collection with the phenoxyethylamine scaffold (Table 1). Compound **7**, containing a 5-chloro-2-methylsulfonylbenzyl group, showed higher subtype selectivity for α_{1A}- and α_{1B}-ARs than **6** did [23]. Compound **6** was also reported as a selective α_{1D}–AR antagonist with the phenoxyethylamine motif. However, a structure activity relationship (SAR) study of **6** using a human α_{1D}-AR binding assay showed room for improvement in subtype selectivity, while the functional assay of this compound using rat tissue showed a more than 100-fold α_{1D}-AR antagonistic selectivity over α_{1A}-AR. Therefore, we considered **7** to be an attractive starting point for further modification. In comparison with the clinical compound TAK-259, compound **7** exhibited lower binding affinity and effects on phenylephrine–induced bladder contraction in isolated bladder strips taken from rats with BOO, which were used for the in vitro evaluation of non-voiding contraction treatment in our previous

report [21]. Hence, we started the SAR study of **7** to increase its potency by introducing various amine functionalities on the phenoxyethylamine analog along with an adjustment of LLE score, as shown in Figure 2. Herein, we describe the identification of 3,4-dihydro-2*H*-thiochromene 1,1-dioxide derivative (*S*)-**41** as a highly potent and selective α_{1D}-AR antagonist.

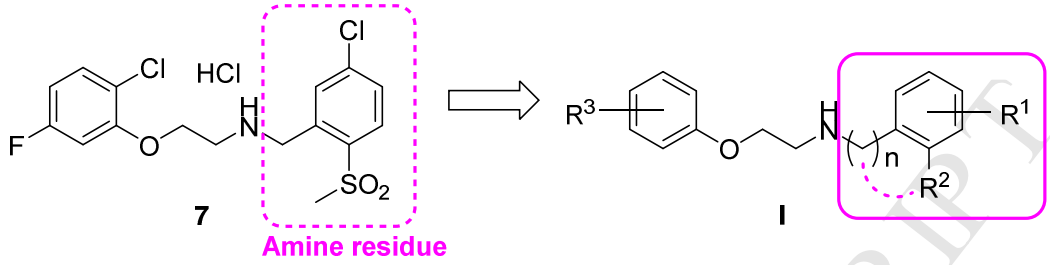
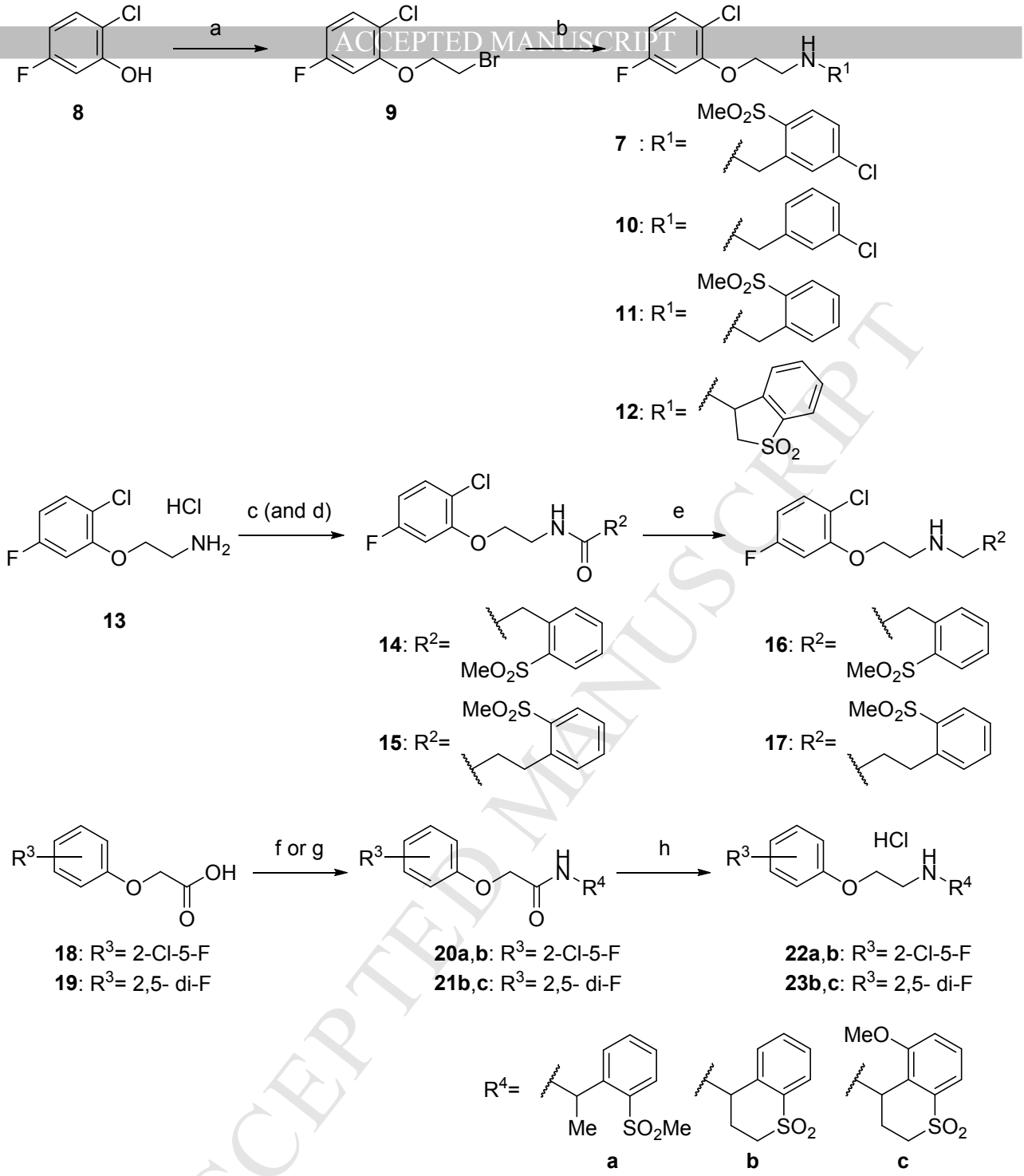


Figure 2. Design strategy.

2. Chemistry

The synthesis of target compounds is depicted in Scheme 1–3. Scheme 1 outlines the synthesis of **7**, **10**–**12**, **16**, **17**, **22** and **23**. Phenol **8** was treated with 1,2-bromoethane in the presence of aqueous sodium hydroxide (NaOH) to afford phenoxyethylbromide **9**, followed by treatment of corresponding benzylamines to provide 2-chloro-5-fluorophenyloxyethylamine derivatives **7**, **10**, **11** and **12**, respectively. Condensation of phenoxyethylamine **13** with an appropriate carboxylic acid yielded phenoxyethylamides **14** and **15**, followed by reduction using borane-tetrahydrofuran complex (BH_3·THF) to provide phenoxyethylamines **16** and **17**, respectively. Condensation of phenoxyacetic acids **18** and **19** with appropriate amines afforded phenoxyacetamides **20** and **21**, respectively, followed by reduction using BH_3·THF to obtain phenoxyethylamines **22** and **23**, respectively.

Scheme 1. Synthesis of **7**, **10**–**12**, **16**, **17**, **22** and **23**[a]

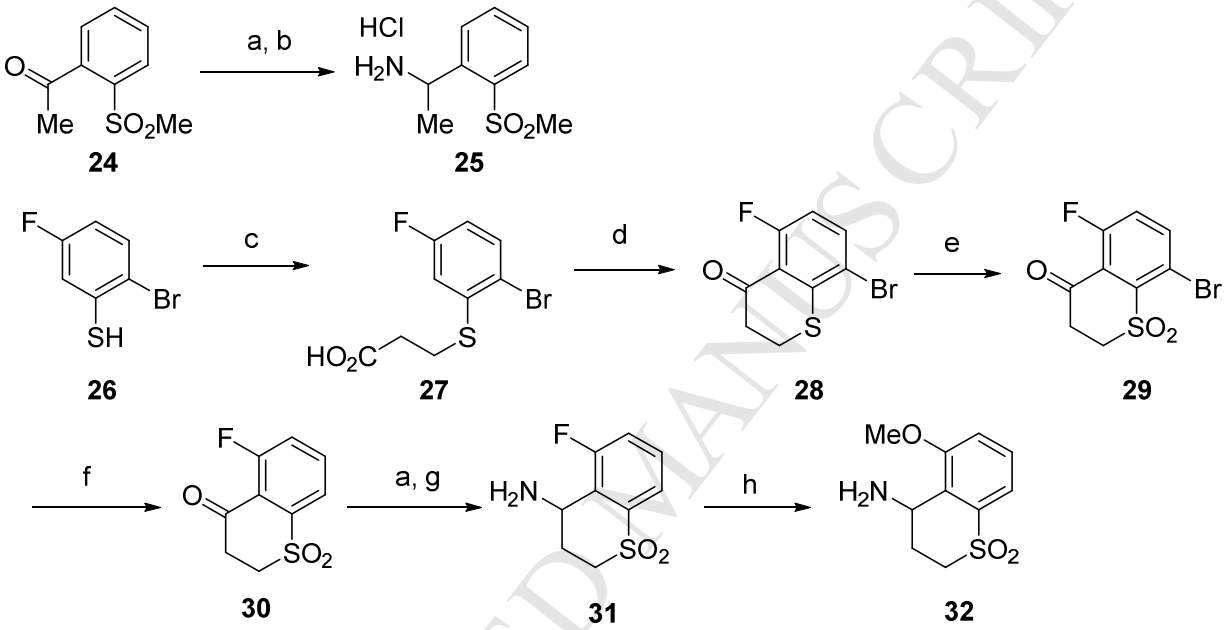


[a]Reagents and conditions: (a) 1,2-dibromoethane, 1 M NaOH, 90 °C; (b) benzylamines, K_2CO_3, EtOH, 90 °C; (c) carboxylic acids, WSC, HOBt, Et_3N, DMF; (d) *m*CPBA, AcOEt; (e) BH_3·THF, THF, 0 to 80 °C; (f) amines, WSC, HOBt, Et_3N, CH_3CN or DMF; (g) $(COCl)_2$, cat. DMF, THF, then amines, Et_3N, THF; (h) BH_3·THF, THF, 0 to 80 °C then 4 M HCl in AcOEt.

Phenethylamine **25** and thiochroman-4-amine **32** for the synthesis of **22a** and **23c** were prepared as shown in Scheme 2. Acetophenone **24** was converted into **25** via oxime formation and

reduction. Alkylation of benzenethiol **26** with 3-bromopropionic acid followed by cyclization with concentrated sulfuric acid and oxidation of the sulfanyl group with *m*-chloroperoxybenzoic acid (*m*CPBA) yielded thiochromanone derivative **29**. Thiochroman-4-amine **31** was obtained by reduction of the bromo group in **29** and amination of the ketone group. Finally, substitution of the fluoro group in **31** with sodium methoxide afforded amine **32**.

Scheme 2. Synthesis of intermediates **25** and **32**[a]

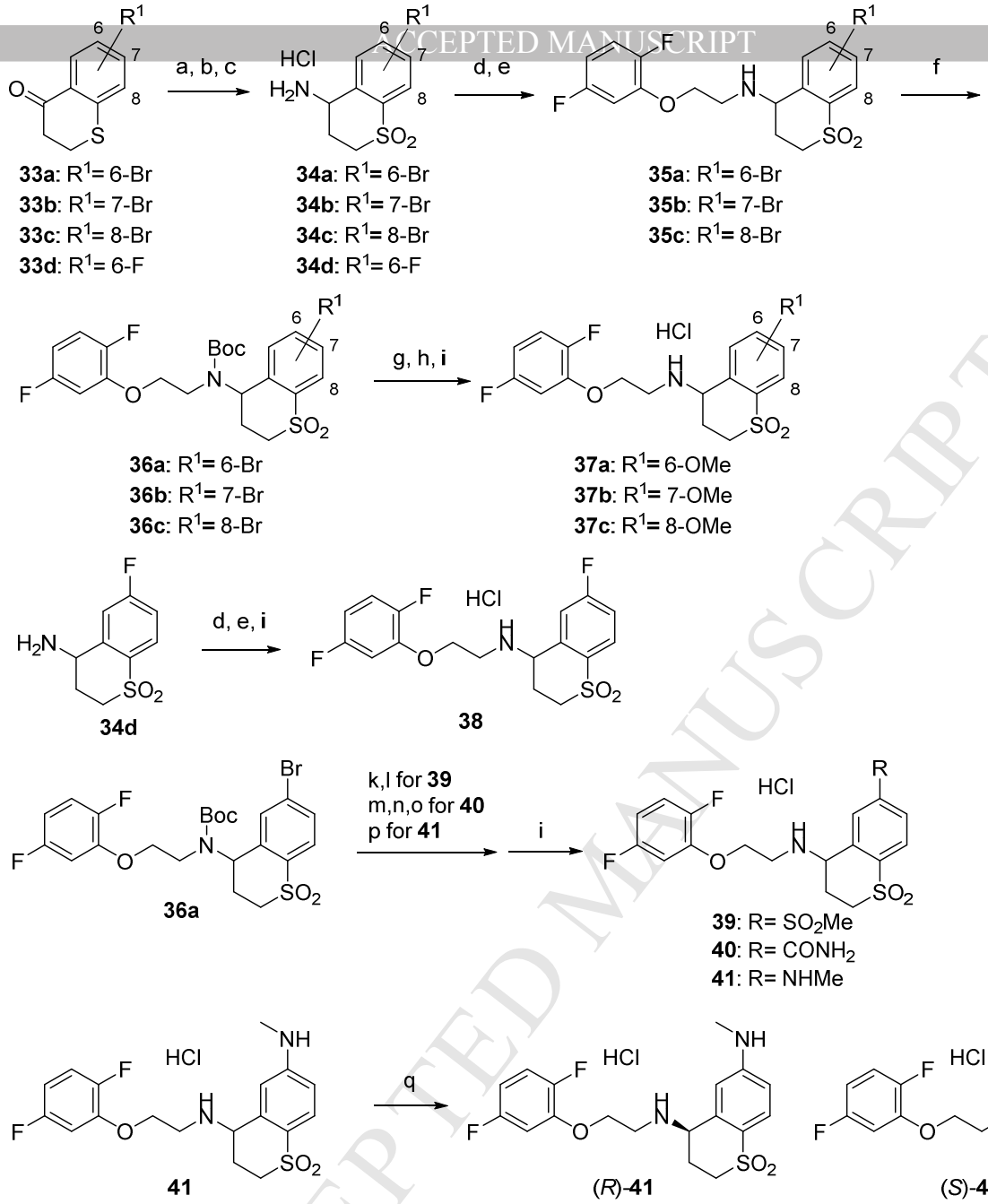


[a]Reagents and conditions: (a) $MeONH_2 \cdot HCl$, pyridine; (b) $BH_3 \cdot THF$, THF, 0 to 80 °C then 4 M HCl in AcOEt; (c) 8 M NaOH, H_2O, then 3-bromopropionic acid, K_2CO_3, H_2O; (d) conc. H_2SO_4; (e) *m*CPBA, AcOEt, 0 °C; (f) Pd/C, H_2, EtOH; (g) $BH_3 \cdot THF$, THF, 0 to 80 °C; (h) NaOMe, MeOH, rt to 95 °C.

Scheme 3 demonstrates the synthesis of compounds **37**–**41**. Intermediates **35** and **36** were prepared by using a method similar to that described in Scheme 1. Compound **35** was obtained by amination of **33a**–**c**, followed by oxidation, and subsequent condensation and reduction with $BH_3 \cdot THF$. Boc-protection of the amine group yielded **36**. The phenoxyethylamine derivatives **37a**–**c**, which contained methoxy groups on the thiochromene ring, were afforded by substitution of the bromo group with potassium hydroxide followed by methylation of hydroxy group and removal of

the protecting group. Intermediate **34d**, which was obtained by amination and oxidation of **33d**, was converted to **38** through condensation and reduction with $BH_3 \cdot THF$ followed by salt formation with 4 M HCl in AcOEt. Intermediate **36a** was used as a starting material for the synthesis of **39**–**41**. The methylsulfonyl derivative **39** was prepared by introduction of a methylsulfanyl group into **36a**, followed by oxidation and removal of the protecting group, and salt formation. The carboxamide derivative **40** was obtained by methoxycarbonylation of **36a**, followed by hydrolysis, amidation, and removal of the protecting group and salt formation. Finally, the methylamine derivative **41** was obtained by introduction of a methylamino group into **36a**, followed by removal of the protecting group and salt formation. The optically active compounds (*R*)-**41** and (*S*)-**41** were prepared by chiral supercritical fluid chromatography (SFC) of **41**. The stereochemistry was determined by single X-ray crystal structure analysis as shown in Figure 3.

Scheme 3. Synthesis of **37**–**41**[a]



[a]Reagents and conditions: (a) $MeONH_2 \cdot HCl$, pyridine; (b) $BH_3 \cdot THF$, THF, 0 to 80 °C then Boc_2O, AcOEt; (c) *m*CPBA, AcOEt then 4 M HCl in AcOEt; (d) **19**, WSC, HOBt, Et_3N, DMF; (e) $BH_3 \cdot THF$, THF, 0 to 80 °C; (f) Boc_2O, AcOEt, (g) KOH, Pd_2dba_3, *t*-BuXphos, DME, H_2O, 100 °C; (h) Iodomethane, K_2CO_3, DMF, (i) 4 M HCl in AcOEt; (j) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C; (k) NaSMe, Pd_2dba_3, Xantphos, xylene, 140 °C; (l) *m*CPBA, AcOEt; (m) CO, $Pd(OAc)_2$, dppf, Et_3N, MeOH, THF; (n) 1N NaOH, THF; (o) $HOBt \cdot NH_3$, WSC, *i*-Pr_2NEt, DMF; (p) Methylamine, Pd_2dba_3, X-Phos, NaO-*t*-Bu, toluene, 100 °C; (q) optical resolution by chiral supercritical fluid chromatography (SFC).

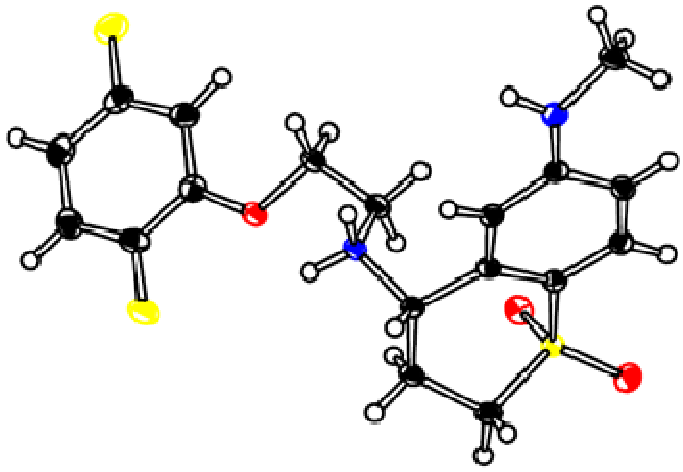


Figure 3. ORTEP diagram of (*S*)-**41**, thermal ellipsoids are drawn at 50% probability.

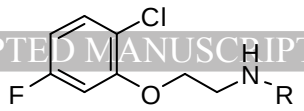
3. Results and Discussion

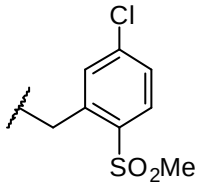
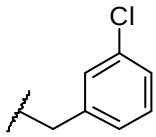
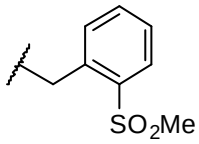
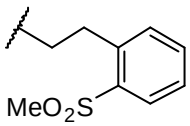
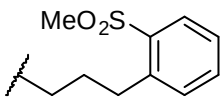
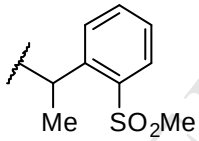
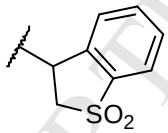
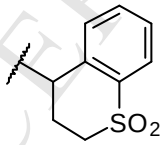
All compounds were evaluated for their affinities toward cloned human α_1–ARs in binding assays, and the results were expressed as *K*i values. Clog P values were determined by ACD labs ver. 12.0 [24].

First, we investigated the substituent effect at the amine residue as shown in Figure 2, to determine the most important substituents of **7** to drive its potency and selectivity (Table 2). The 3-chlorobenzyl derivative **10** and 2-methylsulfonylbenzyl derivative **11** were synthesized in order to confirm the essential moiety for α_1–AR binding affinity. The removal of chloro group led to an increase in the binding affinity for α_{1D}-AR. Therefore, **11** was selected for further investigation. Next, the influence of linker length between the core scaffold amine and the *N*-terminal phenyl ring was investigated. Compounds **16** (phenethyl) and **17** (3-phenylpropyl) showed binding affinities equipotent to that of **11**; however, the LLE score decreased with increasing clog P values. As for the subtype selectivity, a longer linker length worsened the selectivity (**11** vs **16** and **17**). This indicated that a methylene linker is essential for selective α_{1D}-AR binding, while linker lengths of more than two atoms are needed to exhibit binding affinity for both α_{1A}- and α_{1B}-ARs. These observations are consistent with the known structures and biological activities of tamsulosin, silodosin, and **6**, which had linkers of two or three atoms and showed binding affinity for α_{1A}- and α_{1B}-ARs (Figure 4). We then decided to determine if the binding affinity would be affected by the introduction of a methyl

group at the benzylic position. Thus, the 2-methylsulfonylphenethyl derivative **22a** was synthesized and found to have a significantly reduced α_{1D}-AR binding affinity, presumably due to an unfavorable conformation of the 2-methylsulfonyl group caused by the introduction of the methyl group. We therefore postulated that immobilization of the methylsulfonyl moiety into a favorable conformation around the ortho-position could be used to favor strong binding affinity. Indeed, the thiochromene derivative **22b** exhibited binding affinity equipotent to that of **11**, while the dihydrobenzothiophene derivative **12** showed a decreased binding affinity due to an undesired position of sulfonyl moiety. This suggested that the orientation of the sulfonyl group must be quite restricted to demonstrate both strong binding affinity and high subtype selectivity for α_{1D}-AR.

Table 2. Affinity towards cloned human α_{1A}-, α_{1B}- and α_{1D}-ARs and physicochemical properties of 2-chloro-5-fluorophenoxyethylamine derivatives.



compd	R	*K*i (nM)[a]			LLE[b]	clog P
		α_{1A}	α_{1B}	α_{1D}		
7		1800	1100	17	4.3	3.49
10		>270	>120	65	2.2	5.00
11		>270	>120	4.3	5.7	2.65
16		150	30	8.6	5.2	2.84
17		50	44	9.1	4.8	3.22
22a		>270	>120	>94	—	2.96
12		>270	>120	>94	—	2.92
22b		>270	>120	3.9	5.2	3.17

[a]*K*i value for α_{1D} was obtained by displacement of 7-methoxy-[^{3}H]-prazosin from cloned human receptor.

[b]LLE = −log(*K*i)−clog P.

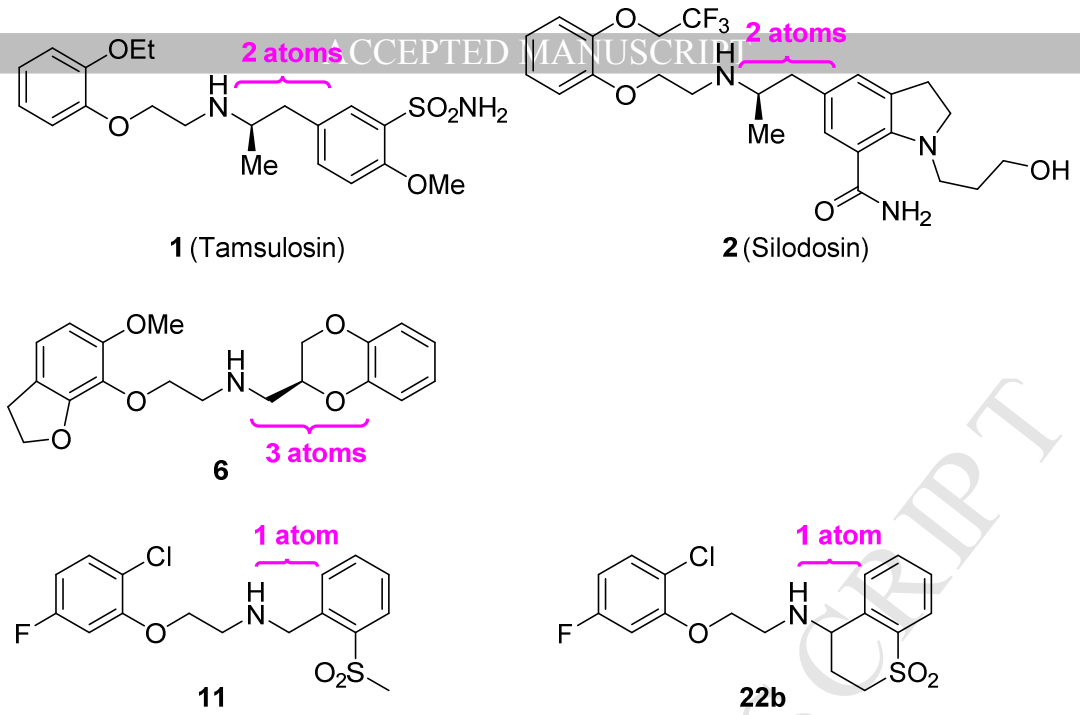


Figure 4. Linker length at the amine residue of **1**, **2**, **6**, **11** and **22b**.

On the basis of the results shown in Table 2, it was determined that linker length was crucial for subtype selectivity for α_{1A}- and α_{1B}-AR, and immobilization by cyclization was an acceptable approach to retain the potency for α_{1D}-AR. Thus, we selected the 2-methylsulfonylbenzyl derivative **11** and thiochromene derivative **22b**, which showed higher binding activities and LLE scores than compound **7** did, to evaluate their effects on phenylephrine–induced bladder contractions in isolated bladder strips taken from rats with BOO (Table 3). Both compounds showed better bladder contraction-inhibitory potency than **7** did. In particular, **22b** showed a 4.6-fold higher potency than **11** did. This indicated that rigidification of the structure was an effective method of inhibiting α_{1D}-AR-mediated bladder contractions.

Table 3. Evaluation of the selected compounds.

comp	α_{1D} *Ki* (nM)[a]	LLE[b]	phenylephrine-induced contraction[c], IC_{30} (nM)[d]
7	17	4.3	250 [43–1400]
11	4.3	5.7	140 [34–550]
22b	3.9	5.2	54 [18–170]

[a]*K*i value for α_{1D} was obtained by displacement of 7-methoxy-[^{3}H]-prazosin from cloned human receptor.

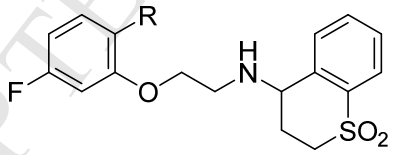
[b]LLE = −log(*K*i)−clog P.

[c]Effects on the phenylephrine-induced contractions of the bladder strips taken from the rats with BOO (n = 2−11).

[d]Numbers in brackets represent 95% confidence interval.

Next, we evaluated in vitro pharmacokinetic properties (absorption, distribution, metabolism, elimination [ADME]) of **22b**. This compound exhibited improved human metabolic stability and less ability to inhibit cytochrome P-450 3A4 inhibition (CYP3A4) as shown in Table 4. Thus, we investigated the substituent effect at the phenoxy residue on the terminal phenyl ring. In comparison with **22b**, **23b** with a 2,5-difluorophenoxy substituent demonstrated better in vitro ADME properties and similar LLE, but showed a lower *K*i value. Accordingly, further optimization was carried out with the 2,5-difluorophenoxy substituent pattern.

Table 4. Profiles of **22b** and **23b**.



comp.	R	α_{1D} *K*i (nM)[a]	LLE[b]	clog P	Cl_{int} (human) (μL/min/mg)	CYP3A4 (%inh. at 10 μM)
22b	Cl	3.9	5.2	3.17	78	52.3
23b	F	17	5.1	2.63	44	26.5

[a]*K*i value for α_{1D} was obtained by displacement of 7-methoxy-[^{3}H]-prazosin from cloned human receptor.

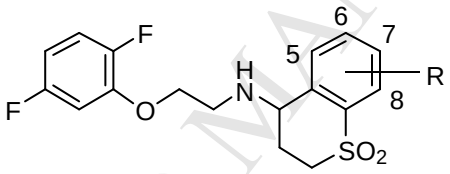
[b]LLE = −log(*K*i)−clog P.

First, we examined the SAR of the thiochromene ring by introducing methoxy groups onto 4 positions. Stronger binding affinity was observed when methoxy was substituted onto the 5- or 6-

position, although a lower binding affinity was confirmed when methoxy was substituted onto the 7-

or 8-position. It is notable that the 6-methoxy derivative **37a** demonstrated a more than 10-fold higher binding affinity than **23b** did. This result implied that introduction of the substituent onto the 6-position of the thiochromene ring provides the highest affinity. Next, we explored various substituents at the 6-position to determine which showed the strongest potency. Compounds **38** (R = fluoro), **39** (R = methylsulfonyl), and **40** (R = aminocarbonyl) showed weaker potency than **37a** did. Interestingly, compound **41** (R= methylamino) showed 2-fold higher binding affinity to α_{1D}-AR and a better LLE score than **37a** without loss of ADME properties. These results indicated that 6-methylamino group of **41** is the optimal substituent.

Table 5. Affinity for cloned human α_1-AR and physicochemical properties for (2,5-di-fluorophenoxyethyl)thiochroman-4-amine 1,1-dioxide derivatives.



compd	R	α_{1D} *Ki*[a] (nM)	LLE[b]	clog P	Clint (human) (µL/min/mg)	CYP3A4 (%inh. at 10 µM)
23b	H	17	5.1	2.63	44	26.5
23c	5-OMe	9.5	5.0	2.98	87	28.6
37a	6-OMe	1.5	5.8	2.98	53	22.7
37b	7-OMe	38	4.4	2.98	71	34.3
37c	8-OMe	170	3.8	2.98	34	17.1
38	6-F	12	5.0	2.90	39	23.1
39	6-SO_2Me	310	4.9	1.62	11	5.2
40	6-$CONH_2$	86	5.4	1.71	19	12.5
41	6-NHMe	0.85	6.2	2.89	45	26.1

[a]*K*i value for α_{1D} was obtained by displacement of 7-methoxy-[^{3}H]-prazosin from cloned human receptor.

[b]LLE = −log(*K*i)−clog P.

From the results shown in Table 5, we selected **41** for further evaluation. The biochemical data from in vitro studies of **41** are shown in Table 6. This analog exhibited more than 400-fold AR-subtype selectivity for α_{1D}-AR over α_{1A}- and α_{1B}-ARs, and dose-dependently inhibited bladder contractions with an IC_{30} value of 80 nM. We then evaluated the difference between the two enantiomers of **41**. The eutomer, (*S*)-**41**, showed better a IC_{30} value than the racemate, with high subtype selectivity. The other optically resolved chiral derivatives tended to yield similar results (data not shown). Additionally, the α_{1D}-AR binding affinity, subtype selectivity over α_{1A}- and α_{1B}-ARs, and inhibitory activity on the phenylephrine-induced contractions of bladder strips of (*S*)-**41** were equivalent to those for TAK–259.

Table 6. In vitro biochemical activity profile of **41**.

compd	*K*i (nM)[a]			LLE[b]	Selectivity		phenylephrine-induced contraction[c], IC_{30} (nM)[d]	Clint (human) (μL/min/mg)	CYP3A4 (%inh. at 10 μM)
	α_{1A}	α_{1B}	α_{1D}		1A/1D	1B/1D			
41	350	430	0.85	6.2	410	510	80 [6.7–970]	45	26.1
(*R*)-**41**	1200	>1200	62	4.3	19	>20	–	59	26.7
(*S*)-**41**	130	150	0.30	6.6	430	500	5.5 [3.0–10]	45	20.7
TAK-259	220	880	1.1	8.7	200	800	12 [5.6–19]	1	-1.9

[a]*K*i value for α_{1D} was obtained by displacement of 7-methoxy-[^{3}H]-prazosin from cloned human receptor.

[b]LLE = −log(*K*i)−clog P.

[c]Effects on the phenylephrine-induced bladder contractions in rats with BOO (n = 7 − 8).

[d]Numbers in brackets represent 95% confidence interval.

4. Conclusion

In this report, we describe the discovery of (4*S*)-N^4-[2-(2,5-difluorophenoxy)ethyl]-N^6-methyl-3,4-dihydro-2*H*-thiochromene-4,6-diamine 1,1-dioxide, (*S*)-**41**, as a novel and selective human α_{1D}-AR antagonist containing a phenoxyethylamine based scaffold. Our modification activities using LLE score as an evaluation index led to the identification of an important structural

motif contributing to selective α_{1D}-AR antagonist activity. First, retaining subtype selectivity was indispensable to choose the proper linker length between the amine and phenyl ring. Next, thiochromene analog by conformational constraint approach of the sulfonyl group was found as more suitable substituent for inhibition of the bladder contractions. Further SAR exploration resulted in the identification of the highly selective and potent α_{1D}-AR antagonist (*S*)-**41** equivalent to our clinical compound TAK–259. These results indicated that (*S*)-**41** is worthy of further investigation for the development of drugs for the treatment of overactive bladder symptoms.

5. Experimental Section

5.1 Chemistry

Reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a BÜCHI B-545 melting point apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker Ultra Shield-300 (300 MHz), 400 (400 MHz) or Bruker Avance II 600 (600 MHz) instruments. Chemical shifts are given in δ values (ppm) with tetramethylsilane as an internal standard. Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, tt = triplet of triplets, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, br = broad, quin = quintet. Coupling constants (*J* values) are given in hertz (Hz). Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and were within ±0.4% of the theoretical values unless otherwise noted. Low-resolution mass spectra (MS) were determined on a Shimadzu UFLC/MS (Prominence UFLC high pressure gradient system/LCMS-2020) with an L-column 2 ODS (3.0 × 50 mm I.D., CERI, Japan), and Waters Liquid Chromatography–Mass Spectrometer System (MS), using a CAPCELL PAK UG-120 ODS (Shiseido Co., Ltd.) column (2.0 mm i.d. × 50 mm) with aqueous CH_3CN (10–95%) containing 0.05% trifluoroacetic acid (TFA), or an HP-1100 (Agilent Technologies) apparatus for monitoring at 220 nm. All MS experiments were performed using electrospray ionization (ESI) in positive ion mode. HPLC separation was carried out using a Gilson system employing the following conditions; Column: Shiseido Capcelpak C18 UG-120, S-5 μM, 20 x 50 mm or YMC CombiPrep Hydrosphere

C18 HS-340-CC, S-5 μM, 20 x 50 mm; Mobile phase: A: 0.1% trifluoroacetic acid in water, B: 0.1% trifluoroacetic acid in acetonitrile; gradient cycle: 0.00 min (A/B＝95/5), 1.10 min (A/B＝95/5), 5.00 min (A/B＝0/100), 6.40 min (A/B＝0/100), 6.50 min (A/B＝95/5); flow rate; 20 ml/min; detection UV 200 nm. After purification by preparative HPLC, the solutions were neutralized by PL-HCO_3 MP tube (200 mg cartridge, Polymer Laboratories Ltd.). Reaction progress was determined by thin layer chromatography (TLC) analysis on Merck Kieselgel 60 F254 plates or Fuji Silysia NH plates. Chromatographic purification was carried out on silica gel columns (Merck Kieselgel 60, 70–230 mesh; Merck, 230–400 mesh; or Chromatorex NH-DM 1020, 100–200 mesh) or on Purif-Pack (SI ϕ 60 μm or NH ϕ 60 μm, Fuji Silysia Chemical, Ltd.). Yields are not optimized.

5.1.1. General procedure for the preparation of compounds 7, 10–12

A mixture of **9** (0.54 g, 2.15 mmol), benzylamine (1.95 mmol) and K_2CO_3 (4.88 mmol) in EtOH (20 mL) was stirred for 24 h at 90 °C, poured into water and extracted with AcOEt. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (AcOEt/ hexane) to give **7** and **10**–**12** as free bases. The free bases of **7** and **10**–**12** were then dissolved in EtOH (1 mL) and 4 M HCl in AcOEt (1 mL) was added. The resulting precipitate was collected by filtration and recrystallized from EtOH and Et_2O to give **7**, **10**–**12**.

5.1.2. 2-(2-Chloro-5-fluorophenoxy)-N-[5-chloro-2-(methylsulfonyl)benzyl]ethanamine hydrochloride (7)

Yield 8%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.33 (s, 3H), 3.52 (br. s. 2H), 4.45 (t, 2H, *J* = 4.7 Hz), 4.67 (br. s., 2H), 6.90 (td, 1H, *J* = 8.4, 2.8 Hz), 7.22 (dd, 1H, *J* = 10.6, 2.7 Hz), 7.51 (dd, 1H, J = 8.7, 6.1 Hz), 7.76–7.90 (m, 1H), 7.96–8.11 (m, 2H), 9.45 (br. s., 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.0, 46.6, 47.6, 65.6, 103.0, 109.2, 117.5, 130.5, 131.3, 132., 133.0, 133.9, 138.9, 139.2, 154.6,

160.4. Mp 180–182 °C. Anal. Calcd for $C_{16}H_{17}Cl_3FNO_3S$: C, 44.82; H, 4.00; N, 3.27. Found: C, 44.85; H, 4.16; N, 3.23. LC–MS (ESI) *m*/*z*: 393.1 [M+H$^+$−(HCl)].

5.1.3. 2-(2-Bromoethoxy)-1-chloro-4-fluorobenzene (9)

A mixture of **8** (25.0 g, 0.171 mol) and 1,2-dibromoethane (64.1 g, 0.341 mol) in 1 M NaOH (171 mL) was stirred for 16 h at 90 °C and extracted with AcOEt. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:10) to give the title compound (16.7 g, 39%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59–3.76 (m, 2H), 4.32 (t, 2H, *J* = 6.4 Hz), 6.59–6.75 (m, 2H), 7.32 (dd, 1H, *J* = 5.9 Hz).

5.1.4. *N*-(3-Chlorobenzyl)-2-(2-chloro-5-fluorophenoxy)ethanamine hydrochloride (10)

Yield 10%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.38 (t, 2H, *J* = 5.1 Hz), 4.31 (s, 2H), 4.44 (t, 2H, *J* = 5.1 Hz), 6.89 (td, 1H, *J* = 8.5, 3.0 Hz), 7.21 (dd, 1H, *J* = 10.6, 2.7 Hz), 7.40–7.59 (m, 4H), 7.71 (s, 1H), 9.59 (br. s., 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 44.9, 49.7, 65.1, 102.5, 108.7, 116.9, 128.9, 130.0, 130.5, 130.8, 133.1, 134.4, 154.1, 160.3, 162.7. Mp 165–166 °C. Anal. Calcd for $C_{15}H_{15}Cl_3FNO$: C, 51.38; H, 4.31; N, 3.99. Found: C, 51.37; H, 4.28; N, 3.84. LC–MS (ESI) *m*/*z*: 314.0 [M+H$^+$−(HCl)].

5.1.5. 2-(2-Chloro-5-fluorophenoxy)-*N*-[2-(methylsulfonyl)benzyl]ethanamine (11).

Yield 21%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14 (t, 2H, *J* = 5.1 Hz), 3.29 (s, 3H), 4.06–4.18 (m, 2H), 4.31 (s, 2H), 6.59–6.71 (m, 2H), 7.29 (dd, 1H, *J* = 8.5, 5.9 Hz), 7.43–7.52 (m, 1H), 7.54–7.66 (m, 2H), 8.09 (d, 1H, *J* = 7.6 Hz). NH proton was not observed. ^{13}C NMR (76 MHz, DMSO-d_6) δ 44.53,

47.30, 49.61, 68.90, 102.08, 107.81, 116.70, 127.80, 129.03, 130.48, 131.40, 133.56, 138.95, 154.90, 159.90, 163.12. LC–MS (ESI) *m*/*z*: 358.0 [M+H$^+$].

5.1.6. *N*-[2-(2-Chloro-5-fluorophenoxy)ethyl]-2,3-dihydro-1-benzothiophen-3-amine 1,1-dioxide hydrochloride (12)

Yield 4%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.29–3.45 (m, 1H), 3.46–3.62 (m, 1H), 3.89–4.10 (m, 1H), 4.17–4.34 (m, 1H), 4.47 (br. s., 2H), 5.33–5.62 (m, 1H), 6.89 (dt, 1H, *J* = 2.6, 8.5 Hz), 7.22 (dd, 1H, *J* = 10.9, 2.6 Hz), 7.50 (dd, 1H, J = 8.7, 6.0 Hz), 7.69–8.05 (m, 3H), 8.09–8.32 (m, 1H), 9.60–11.17 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 43.7, 52.1, 53.5, 64.9, 102.4, 108.6, 116.7, 121.2, 127.7, 130.7, 131.5, 134.2, 139.6, 154.0, 160.2, 162.6. Mp 219–222 °C. LC–MS (ESI) *m*/*z*: 356.1 [M+H$^+$−(HCl)].

5.1.7. *N*-[2-(2-Chloro-5-fluorophenoxy)ethyl]-2-[2-(methylsulfonyl)phenyl]acetamide (14)

A mixture of **13** (1.24 g, 5.49 mmol), 2-[2-(methylsulfanyl)phenyl]acetic acid (1.00 g, 5.49 mmol), WSC (1.26 g, 6.59 mmol), HOBt (1.01 g, 6.59 mmol) and Et_3N (0.83 g, 8.23 mmol) in DMF (20 mL) was stirred for 14 h at 60 °C, poured into water and extracted with AcOEt. The extract was washed with 1 M HCl, aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. To a solution of the residue in AcOEt (50 mL) was added 70 % *m*CPBA (2.91 g, 11.8 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature and poured into aq. sodium thiosulfate. The separated organic layer was washed with aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo to give the title compound (1.28 g, 62%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.67 (q, 2H, *J* = 5.3 Hz), 4.00–4.07 (m, 4H), 6.58–6.75 (m, 3H), 7.27–7.33 (m, 1H), 7.43–7.63 (m, 3H), 8.05 (d, 1H, *J* = 7.9 Hz). Mp 165–167 °C. LC–MS (ESI) *m*/*z*: 386.0 [M+H$^+$].

5.1.8. *N*-[2-(2-Chloro-5-fluorophenoxy)ethyl]-3-[2-(methylsulfonyl)phenyl]propanamide (15)

A mixture of **13** (0.99 g, 4.38 mmol), 3-[2-(methylsulfanyl)phenyl]propanoic acid (1.00 g, 4.38 mmol), WSC (1.09 g, 5.69 mmol), HOBt (0.87 g, 5.69 mmol), and Et_3N (0.89 g, 8.76 mmol) in DMF (20 mL) was stirred for 3 days at 50 °C, poured into 1 M HCl and extracted with AcOEt. The extract was washed with aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo to give the title compound (1.35 g, 77%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59–2.68 (m, 2H), 3.10 (s, 3H), 3.26–3.36 (m, 2H), 3.69 (q, 2H, J = 5.3 Hz), 4.03 (t, 2H, *J* = 5.1 Hz), 6.19 (br. s., 1H), 6.60–6.70 (m, 2H), 7.27–7.43 (m, 3H), 7.47–7.55 (m, 1H), 8.00 (d, 1H, *J* = 7.9 Hz). Mp 96–97 °C. Anal. Calcd for $C_{18}H_{19}ClFNO_4S$: C, 54.07; H, 4.79; N, 3.50. Found C, 54.04; H, 4.73; N, 3.37. LC–MS (ESI) *m*/*z*: 400.1 [$M+H^+$].

5.1.9. 2-(2-Chloro-5-fluorophenoxy)-*N*-{2-[2-(methylsulfonyl)phenyl]ethyl}ethanamine (16)

To a solution of **14** (1.00 g, 2.59 mmol) in THF (50 mL) was added 1 M BH_3 in THF (9.0 mL) at 0 °C. After stirring at 80 °C for 4 h, the reaction was quenched with ice. The whole was added to 1 M HCl and stirred at 80 °C for 14 h. The mixture was cooled to room temperature and diluted with AcOEt. The aqueous layer was basified by 8 M NaOH and extracted with AcOEt and THF. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo to give the title compound (80.0 mg, 8%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03–3.16 (m, 7H), 3.21–3.30 (m, 2H), 4.10 (t, 2H, *J* = 5.1 Hz), 6.58–6.71 (m, 2H), 7.24–7.32 (m, 1H), 7.36–7.47 (m, 2H), 7.53–7.63 (m, 1H), 8.05 (d, 1H, *J* = 7.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 33.3, 44.8, 48.0, 51.2, 69.8, 102.7, 108.3, 117.3, 127.3, 129.1, 131.0, 132.5, 134.0, 139.5, 140.5, 155.5, 162.0. LC–MS (ESI) *m*/*z*: 372.1 [$M+H^+$].

5.1.10. *N*-[2-(2-chloro-5-fluorophenoxy)ethyl]-3-[2-(methylsulfonyl)phenyl]propan-1-amine (17)

The title compound was prepared in a manner similar to that described for the synthesis of **16**.

Yield 5%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–2.02 (m, 2H), 2.82 (t, 2H, *J* = 6.8 Hz), 3.03–3.16 (m, 7H), 4.11 (t, 2H, *J* = 5.1 Hz), 6.57–6.73 (m, 2H), 7.27–7.32 (m, 1H), 7.34–7.45 (m, 2H), 7.51–7.60 (m, 1H), 7.99–8.08 (m, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 29.8, 31.7, 44.2, 47.7, 48.7, 69.3, 102.2, 107.8, 116.7, 126.6, 128.6, 130.5, 131.7, 133.5, 138.7, 142.0, 155.0, 161.5. LC–MS (ESI) *m*/*z*: 386.1 [M+H$^+$].

5.1.11. General procedure for the preparation of compounds 20 and 21

A mixture of amine (1.30 mmol), **18** or **19** (1.30 mmol), WSC (1.95 mmol), HOBt (1.95 mmol) and Et_3N (2.60 mmol) in CH_3CN (5 mL) was stirred for 2 h at room temperature, poured into water and extracted with AcOEt. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/ hexane) to afford **20** and **21**, respectively.

5.1.12. 2-(2-Chloro-5-fluorophenoxy)-*N*-{1-[2-(methylsulfonyl)phenyl]ethyl}acetamide (20a)

Yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (d, 3H, *J* = 6.6 Hz), 3.44 (s, 3H), 4.35–4.60 (m, 2H), 5.75–5.88 (m, 1H), 6.65 (dd, 1H, *J* = 9.6, 2.8 Hz), 6.73–6.82 (m, 1H), 7.37–7.49 (m, 4H), 7.56–7.65 (m, 1H), 8.01–8.08 (m, 1H). LC–MS (ESI) *m*/*z*: 386.0 [M+H$^+$].

5.1.12. 2-(2-Chloro-5-fluorophenoxy)-*N*-(1,1-dioxido-3,4-dihydro-2*H*-thiochromen-4-yl)acetamide (20b)

Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59–2.87 (m, 2H), 3.39–3.57 (m, 2H), 4.61 (s, 2H), 5.49 (td, 1H, *J* = 8.4, 5.1 Hz), 6.65–6.80 (m, 2H), 7.18 (d, 1H, *J* = 8.3 Hz), 7.34 (dd, 1H, *J* = 8.9, 5.8 Hz), 7.39–7.46 (m, 1H), 7.51–7.62 (m, 2H), 7.90–8.02 (m, 1H). Mp 120–121 °C. Anal. Calcd for

$C_{17}H_{15}ClFNO_4S$: C, 53.20; H, 3.94; N, 3.65. Found: C, 53.31; H, 4.03; N, 3.65. LC–MS (ESI) *m*/*z*: 382.0 [M−H$^+$].

5.1.13. 2-(2,5-Difluorophenoxy)-*N*-(1,1-dioxido-3,4-dihydro-2*H*-thiochromen-4-yl)acetamide (21b)

Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57–2.84 (m, 2H), 3.36–3.57 (m, 2H), 4.54–4.68 (m, 2H), 5.50 (td, 1H, *J* = 8.3, 5.3 Hz), 6.65–6.78 (m, 2H), 7.00–7.14 (m, 2H), 7.34–7.43 (m, 1H), 7.48–7.64 (m, 2H), 7.91–8.01 (m, 1H). LC–MS (ESI) *m*/*z*: 368.0 [M+H$^+$].

5.1.14. 2-(2,5-Difluorophenoxy)-*N*-(5-methoxy-1,1-dioxido-3,4-dihydro-2*H*-thiochromen-4-yl)acetamide (21c)

Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70–2.80 (m, 2H), 3.25–3.35 (m, 1H), 3.45–3.60 (m, 1H), 3.83 (s, 3H), 4.50 (d, 1H, *J* = 14.7 Hz), 4.58 (d, 1H, *J* = 14.7 Hz), 5.54 (quin, 1H, *J* = 3.5 Hz), 6.64–6.76 (m, 3H), 6.96–7.10 (m, 2H), 7.49–7.56 (m, 2H). LC–MS (ESI) *m*/*z*: 396.0 [M−H$^+$].

5.1.15. General procedure for the preparation of compounds 22 and 23

To a solution of **20** or **21** (1.14 mmol) in THF (5 mL) was added 1 M BH_3 in THF (3.4 mL) at 0 °C. After stirring at 70 °C for 2 h, the reaction was quenched with ice. The whole was added to 1 M HCl and stirred at 70 °C for 2 h. The mixture was cooled to room temperature and diluted with AcOEt. The aqueous layer was basified by 8 M NaOH and extracted with AcOEt. The extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. To the residue was added 4 M HCl in AcOEt at room temperature. The resulting precipitate was filtered off and washed with diisopropyl ether to give **22** or **23**.

5.1.16. *N*-[2-(2-Chloro-5-fluorophenoxy)ethyl]-1-[2-(methylsulfonyl)phenyl]ethanamine hydrochloride (22a)

Yield Quant. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (d, 3H, *J* = 6.8 Hz), 3.12–3.20 (m, 3H), 3.25–3.60 (m, 2H), 4.32–4.62 (m, 2H), 5.52–5.70 (m, 1H), 6.58–6.76 (m, 2H), 7.22–7.36 (m, 1H), 7.54–7.67 (m, 1H), 7.75–7.89 (m, 1H), 8.00–8.17 (m, 1H), 8.33–8.47 (m, 1H), 9.67–9.94 (m, 1H), 10.80–11.05 (m, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 19.9, 44.7, 53.0, 59.7, 64.9, 102.5, 108.6, 116.9, 128.6, 129.5, 130.7, 134.7, 137.0, 139.0, 154.1, 159.8, 163.0. LC–MS (ESI) *m*/*z*: 372.1 [$M+H^+$−(HCl)].

5.1.17. *N*-[2-(2-Chloro-5-fluorophenoxy)ethyl]-3,4-dihydro-2H-thiochromen-4-amine 1,1-dioxide hydrochloride (22b)

Yield 9%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.84 (br. s., 2H), 3.48–3.96 (m, 4H), 4.43 (br. s., 2H), 4.95 (br. s., 1H), 6.81–6.95 (m, 1H), 7.22 (dd, 1H, J = 10.4, 2.5 Hz), 7.52 (dd, 1H, J = 8.7, 6.1 Hz), 7.76 (br. s., 2H), 7.93 (br. s., 2H), 9.60 (br. s., 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 22.5, 43.1, 45.2, 52.5, 65.0, 102.4, 108.6, 116.8, 123.5, 130.6, 132.8, 139.5, 154.2, 158.7, 159.1, 159.8, 163.1. Mp 193–194 °C. Anal. Calcd for $C_{17}H_{18}Cl_2FNO_3S$: C, 50.25; H, 4.47; N, 3.45. Found: C, 50.01; H, 4.66; N, 3.45. LC–MS (ESI) *m*/*z*: 370.0 [$M+H^+$−(HCl)].

5.1.18. *N*-[2-(2,5-Difluorophenoxy)ethyl]-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (23b)

Yield 74%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.67–2.95 (m, 2H), 3.46–3.58 (m, 2H), 3.59–3.74 (m, 1H), 3.82–4.01 (m, 1H), 4.32–4.51 (m, 2H), 4.83–5.01 (m, 1H), 6.76–6.91 (m, 1H), 7.15–7.38 (m, 2H), 7.65–7.82 (m, 2H), 7.84–8.03 (m, 2H), 9.47–9.95 (m, 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 22.5, 43.2, 45.2, 52.6, 64.8, 103.2, 107.2, 116.6, 123.4, 130.7, 130.7, 132.7, 139.6, 146.4, 149.7, 156.6, 159.8. Mp 153–156 °C. Anal. Calcd for $C_{17}H_{18}ClF_2NO_3S$: C, 52.38; H, 4.65; N, 3.59. Found: C, 52.30; H, 4.75; N, 3.56. LC–MS (ESI) *m*/*z*: 354.1 [$M+H^+$−(HCl)].

5.1.19. *N*-[2-(2,5-Difluorophenoxy)ethyl]-5-methoxy-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (23c)

Yield 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.60–2.80 (m, 1H), 2.85–3.00 (m, 1H), 3.50–3.70 (m, 3H), 3.86 (s, 3H), 4.18–4.36 (m, 1H), 4.36–4.60 (m, 2H), 4.80–4.95 (m, 1H), 6.80–6.90 (m, 1H), 7.20–7.38 (m, 2H), 7.41 (d, 1H, *J* = 8.4 Hz), 7.49 (d, 1H, *J* = 8.4 Hz), 7.72 (t, 1H, *J* = 8.3 Hz), 8.64 (br. s., 1H), 9.92 (br. s. , 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.8, 44.4, 44.9, 48.5, 56.4, 64.8, 103.2, 107.2, 114.4, 115.1, 116.6, 118.5, 132.4, 140.0, 146.4, 148.1, 156.9, 158.3. Anal. Calcd for $C_{18}H_{20}ClF_2NO_4S$: C, 51.49; H, 4.80; N, 3.34. Found C, 51.60; H, 4.82; N, 3.37. LC–MS (ESI) *m*/*z*: 384.1 [M+H$^+$−(HCl)].

5.1.20. 1-[2-(Methylsulfonyl)phenyl]ethanamine hydrochloride (25)

A mixture of **24** (5.11 g, 25.8 mmol) and $MeONH_2$·HCl (2.80 g, 33.5 mmol) in pyridine (30 mL) was stirred overnight at room temperature, poured into water and extracted with AcOEt. The extract was washed with 1 M HCl and brine, dried with $MgSO_4$ and concentrated in vacuo. To a solution of the residue in THF (100 mL) was added 1 M BH_3 in THF (75 mL) at 0 °C. After stirring at 80 °C for 4 h, the mixture was cooled to room temperature and 1 M HCl (120 mL) was added. After stirring at 80 °C for 2 h, the mixture was cooled to room temperature and diluted with AcOEt. The separated aqueous layer was basified with 8 M NaOH and extracted with AcOEt and THF. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in MeOH and 4 M HCl in AcOEt (20 mL) was added. The resulting precipitate was filtered off and washed with AcOEt to give the title compound (1.35 g, 22%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55 (d, 3H, *J* = 6.8 Hz), 3.36 (s, 3H), 5.21 (br. s., 1H), 7.63–7.72 (m, 1H), 7.83–7.91 (m, 1H), 7.97–8.06 (m, 2H), 8.68 (br. s., 3H). Mp 238–240 °C. LC–MS (ESI) *m*/*z*: 200.0 [M+H$^+$−(HCl)].

5.1.21. 3-[(2-Bromo-5-fluorophenyl)sulfanyl]propionic acid (27)

A mixture of **26** (2.38 g, 11.5 mmol) and 8 M NaOH (1.8 mL) in H_2O (5.8 mL) was stirred at room temperature for 10 min. To the mixture was added a solution of 3-bromopropionic acid (1.76 g, 11.5 mmol) and K_2CO_3 (0.80 g, 5.79 mmol) in H_2O (5.3 mL) at room temperature, and the mixture was stirred at room temperature for 5 days. The reaction mixture was acidified by 1 M HCl, and extracted with AcOEt. The extract was washed with H_2O and brine, dried with $MgSO_4$ and concentrated to provide the title compound (3.18 g, 11.4 mmol, 99%) as a pale solid, which was collected with hexane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (t, 2H, *J* = 7.2 Hz), 3.20 (t, 2H, *J* = 7.2Hz), 6.74–6.81 (m, 1H), 6.98 (dd, 1H, *J* = 9.0, 2.7 Hz), 7.49 (dd, 1H, *J* = 8.4, 5.1 Hz), 7.62 (dd, 1H, *J* = 9.0, 5.4 Hz). Mp 124–126 °C.

5.1.22. 8-Bromo-5-fluoro-2,3-dihydro-4*H*-thiochromen-4-one (28)

A mixture of **27** (2.0 g, 7.17 mmol) in conc. H_2SO_4 (20 mL) was stirred at room temperature for 30 min and poured into ice and H_2O. The product was extracted with AcOEt and the extract was washed with H_2O and brine , dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 19:1–4:1) to provide the title compound (692 mg, 37%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95–3.00 (m, 2H), 3.23–3.28 (m, 2H), 6.78 (dd, 1H, *J* = 10.8, 8.7 Hz), 7.60 (dd, 1H, *J* = 9.0, 4.8 Hz). Mp 102–104 °C. LC–MS (ESI) *m*/*z*: 258.8 [M−H$^+$].

5.1.23. 8-Bromo-5-fluoro-2,3-dihydro-4*H*-thiochromen-4-one 1,1-dioxide (29)

To a solution of **28** (0.62 g, 2.38 mmol) in AcOEt (20 mL) was added *m*CPBA (1.17 g, 4.75 mmol) at 0 °C, and the mixture was stirred at room temperature for 14 h and poured into aq. $NaHCO_3$. The separated organic layer was washed with aq. $NaHCO_3$ and brine, dried with $MgSO_4$

and concentrated to provide the title compound (0.63 g, 91%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35–3.39 (m, 2H), 3.74–3.79 (m, 2H), 7.27 (dd, 1H, *J* = 10.2, 8.7 Hz), 7.94 (dd, 1H, *J* = 9.0, 4.5 Hz). Mp 162–165 °C.

5.1.24. 5-Fluoro-2,3-dihydro-4*H*-thiochromen-4-one 1,1-dioxide (30)

A mixture of **29** (1.00 g, 3.41 mmol) and Pd/C (0.50 g) in EtOH (100 mL) was stirred at room temperature for 14 h under H_2 atmosphere. The mixture was filtrated through Celite and concentrated in vacuo. The precipitate was collected by diisopropyl ether to provide the title compound (713 mg, 98%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37–3.42 (m, 2H), 3.67–3.71 (m, 2H), 7.44 (ddd, 1H, *J* = 9.6, 8.1, 1.8 Hz), 7.76–7.87 (m, 2H). Mp 140–141 °C.

5.1.25. 5-Fluoro-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide (31)

A mixture of **30** (577 mg, 2.69 mmol) and $MeONH_2$.HCl (292 mg, 3.50 mmol) in pyridine (5 mL) was stirred at room temperature for 14 h. The mixture was poured into 1 M HCl and extracted with ethyl acetate. The separated organic layer was washed with 1 M HCl and water, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:9–1:2) to provide a white powder. To a solution of the obtained powder in THF (5 mL) was added 1 M BH_3 in THF (13.4 mL) at 0 °C. The resulting mixture was stirred at 80 °C for 1.5 h, and then the reaction mixture was allowed to reach room temperature and 1 M HCl (27 mL) was added. The mixture was stirred at 80 °C for 1 h, cooled to room temperature, basified with 8 M NaOH (4 mL) and extracted with AcOEt. The extract was washed with water, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:1–7:3, then MeOH/AcOEt = 1:19) to provide the title compound (420 mg, 73%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35–2.42 (m, 1H), 2.74–2.88 (m, 1H), 3.24 (ddd, 1H, *J* = 8.7, 6.3, 2.4 Hz), 3.80–3.92 (m, 1H), 4.55 (t, 1H, *J* = 3.9 Hz), 7.23–7.30 (m, 1H),

7.48 (dt, 1H, *J* = 8.1, 5.1 Hz), 7.74 (d, 1H, *J* = 8.1 Hz). Mp 122–124 °C. LC–MS (ESI) *m*/*z*: 216.0 [M+H$^+$].

5.1.26. 5-Methoxy-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide (32)

To a mixture of **30** (500 mg, 2.32 mmol) in MeOH (15 mL) was slowly added sodium (533 mg, 23.2 mmol) at room temperature and then the mixture was stirred at 95 °C for 14 h and poured into aq. NH_4Cl and AcOEt. The separated organic layer was washed with aq. NH_4Cl and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (MeOH/AcOEt = 1:19–1:9) to provide the title compound (222 mg, 42%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30–2.40 (m, 1H), 2.70–2.85 (m, 1H), 3.21 (ddd, 1H, *J* = 8.7, 6.0, 2.7 Hz), 3.77 (dt, 1H, *J* = 13.5, 3.0 Hz), 3.91 (s, 3H), 4.47 (t, 1H, *J* = 4.1 Hz), 7.04 (dd, 1H, *J* = 7.8, 0.9 Hz), 7.44 (t, 1H, *J* = 8.1 Hz), 7.52 (dd, 1H, *J* = 8.1, 1.2 Hz).

5.1.27. 6-Bromo-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (34a)

A mixture of **33a** (150 mg, 0.62 mmol) and $MeONH_2 \cdot HCl$ (67.0 mg, 0.80 mmol) in pyridine (1.5 mL) was stirred at room temperature for 16 h. The mixture was concentrated in vacuo and poured into water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:99–1:9) to provide an oxime (140 mg, 83%). To a mixture of the oxime (140 mg, 0.52 mmol) in THF (1 mL) was slowly added 1 M BH_3 in THF (1.30 mL, 1.30 mmol) at 0 °C. The mixture was stirred at 60 °C for 4 h, and then the mixture was allowed to reach room temperature, and MeOH was added. The obtained solution was concentrated and cooled to 0 °C. To the residue was slowly added 6 M HCl, and the mixture was stirred at 70 °C for 2 h. The mixture was allowed to reach room temperature, and then 8 M NaOH was added. The mixture was extracted with AcOEt.

The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in AcOEt (1 mL) and Boc_2O (112 mg, 0.52 mmol) was added. The mixture was stirred for 2 h at room temperature and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 3:97–3:17) to provide an *N*-Boc protected product (82.5 mg, 47%). The product (76.1 mg, 0.22 mmol) was dissolved in AcOEt (1 mL), and 70% *m*CPBA (109 mg, 0.44 mmol) was added at 0°C. The mixture was stirred for 3 h at room temperature and aq. sodium thiosulfate was added. The mixture was extracted with AcOEt. The extract was washed with aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4–3:2) to provide a sulfonyl product. The product was treated with 4 M HCl in AcOEt (1 mL) and then concentrated in vacuo. The resulting precipitate was collected by filtration and washed with AcOEt to provide the title compound (55.9 mg, 81%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.53–2.82 (m, 2H), 3.65–3.77 (m, 1H), 3.78–3.91 (m, 1H), 4.80 (t, 1H, *J* = 5.5 Hz), 7.79–7.93 (m, 2H), 8.17 (d, 1H, *J* = 1.5 Hz), 8.96 (br. s., 3H). Mp 281–283 °C. LC–MS (ESI) *m*/*z*: 276.2 [M+H$^+$−(HCl)].

5.1.28. 7-Bromo-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (34b)

The title compound was prepared in a manner similar to that described for the synthesis of **34a**. Yield 70%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.56–2.69 (m, 1H), 2.69–2.83 (m, 1H), 3.67–3.80 (m, 1H), 3.83–3.96 (m, 1H), 4.77 (t, 1H, *J* = 5.5 Hz), 7.85–7.91 (m, 1H), 7.97–8.02 (m, 2H), 9.09 (br. s., 3H). LC–MS (ESI) *m*/*z*: 276.2 [M+H$^+$−(HCl)].

5.1.29. 8-Bromo-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (34c)

The title compound was prepared in a manner similar to that described for the synthesis of **34a**. Yield 62%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.53–2.64 (m, 1H), 2.65–2.78 (m, 1H), 3.68–3.79 (m,

1H), 3.81–3.93 (m, 1H), 4.81 (t, 1H, *J* = 5.5 Hz), 7.56–7.65 (m, 1H), 7.85–7.95 (m, 2H), 9.07 (br. s. , 2H). LC–MS (ESI) *m*/*z*: 276.2 [M+H$^+$−(HCl)].

5.1.30. 6-Fluoro-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (34d)

The title compound was prepared in a manner similar to that described for the synthesis of **34a**. Yield 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55–2.84 (m, 2H), 3.61–3.91 (m, 2H), 4.81 (s, 1H), 7.43–7.64 (m, 1H), 7.79 (s, 1H), 7.99 (dd, 1H, *J* =5.7, 8.9 Hz), 8.95 (3H, s). LC–MS (ESI) *m*/*z*: 216.1 [M+H$^+$−(HCl)].

5.1.31. *tert*-Butyl (6-bromo-1,1-dioxido-3,4-dihydro-2*H*-thiochromen-4-yl)[2-(2,5-difluorophenoxy)ethyl] carbamate (36a)

A mixture of **34a** (6.68 g, 21.4 mmol), **19** (4.42 g, 23.5 mmol), WSC (4.50 g, 23.5 mmol), HOBt (3.18 g, 23.5 mmol) and *N*,*N*-diisopropylethylamine (6.08 g, 47.0 mmol) in DMF (50 mL) was stirred for 3 h at room temperature, poured into water and extracted with AcOEt. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 7:13–1:1) to give the amide (8.19 g, 86%). To a solution of the product (8.19 g, 18.4 mmol) in THF (20 mL) was added dropwise 1 M BH_3 in THF (45.9 mL) at 0 °C. The mixture was stirred at 65 °C for 2 h, and then the reaction mixture was allowed to reach room temperature and 6 M HCl (25 mL) was slowly added. The mixture was stirred at 75 °C for 2 h, cooled to room temperature, basified with 8 M NaOH and extracted with AcOEt. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in AcOEt (36 mL), and Boc_2O (4.00 g, 18.4 mmol) was added. The mixture was stirred for 2 h at 50 °C, cooled to room temperature and concentrated in vacuo. The residue was crystallized from diisopropyl ether to provide the title compound (8.50 g, 87%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14–1.56 (m, 9H), 2.53–2.70 (m, 1H), 2.94–3.21 (m,

1H), 3.34–3.54 (m, 2H), 3.57–3.81 (m, 1H), 3.91–4.35 (m, 3H), 4.67–5.56 (m, 1H), 6.56–6.77 (m, 2H), 7.02 (ddd, 1H, *J* = 10.5, 9.0, 5.3 Hz), 7.32–7.51 (m, 1H), 7.59 (d, 1H, J = 8.3 Hz), 7.78 (d, 1H, *J* = 8.3 Hz). Mp 173–175 °C. LC–MS (ESI) *m*/*z*: 432.1 [M+H$^+$].

5.1.32. *tert*-Butyl (7-bromo-1,1-dioxido-3,4-dihydro-2*H*-thiochromen-4-yl)[2-(2,5-difluorophenoxy)ethyl] carbamate (36b)

The title compound was prepared from **34b** in a manner similar to that described for the synthesis of **36a**. Yield 40%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15–1.53 (m, 9H), 2.66 (br. s., 1H), 3.12 (br. s., 1H), 3.27–3.63 (m, 3H), 3.64–4.00 (m, 1H), 4.00–4.37 (m, 2H), 4.64-5.54 (m, 1H), 6.55–6.76 (m, 2H), 7.02 (td, 1H, *J* = 9.9, 5.1 Hz), 7.20 (br. s., 1H), 7.61 (d, 1H, *J* = 7.5 Hz), 8.05 (s, 1H). LC–MS (ESI) *m*/*z*: 530.0 [M−H$^+$].

5.1.33. *tert*-Butyl (8-bromo-1,1-dioxido-3,4-dihydro-2*H*-thiochromen-4-yl)[2-(2,5-difluorophenoxy)ethyl] carbamate (36c)

The title compound was prepared from **34c** in a manner similar to that described for the synthesis of **36a**. Yield 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07–1.56 (m, 9H), 2.58 (d, 1H, *J* = 13.6 Hz), 3.07 (br. s., 1H), 3.36–4.38 (m, 6H), 4.50–5.70 (m, 1H), 6.55–6.75 (m, 2H), 7.02 (ddd, 1H, *J* = 10.6, 9.1, 5.1 Hz), 7.13–7.39 (m, 2H), 7.66 (d, 1H, *J* = 8.7 Hz). LC–MS (ESI) *m*/*z*: 530.0 [M−H$^+$].

5.1.34. *N*-[2-(2,5-Difluorophenoxy)ethyl]-6-methoxy-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (37a)

A mixture of **36a** (1.00 g, 1.88 mmol), Pd_2dba_3 (86.0 mg, 93.9 μmol), potassium hydroxide (316 mg, 5.63 mmol), *t*-BuXPhos (160 mg, 0.38 mmol) in DME (5 mL) and water (2.5 mL) was stirred at 100 °C for 17 h, poured into water and extracted with AcOEt. The extract was washed with

brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography on silica gel (AcOEt/hexane = 3:17–1:1) to provide a coupling product (546 mg, 62%). A mixture of the product (235 mg, 0.5 mmol), iodomethane (46.7 μL, 0.75 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in DMF (2 mL) was stirred for 3 h at room temperature, poured into water and extracted with AcOEt. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 3:7–3:2) to provide a methoxy product (253 mg). The product and 4 M HCl in AcOEt (2 mL) was stirred for 1 h at room temperature and concentrated in vacuo. The resulting precipitate was filtered off and recrystallized from EtOH, diethyl ether and water to provide the title compound (152 mg, 73%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (br. s., 2H), 3.60 (d, 3H, J = 7.5 Hz), 3.76–3.86 (m, 1H), 3.89 (s, 3H), 4.45 (br. s., 2H), 4.89 (br. s., 1H), 6.83 (tt, 1H, J = 8.5, 3.2 Hz), 7.16–7.36 (m, 3H), 7.57 (br. s., 1H), 7.84 (d, 1H, J = 8.7 Hz), 9.86 (br. s., 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.5, 43.0, 45.4, 52.7, 56.1, 64.8, 103.2, 107.3, 115.1, 116.6, 116.9, 125.5, 131.5, 132.6, 146.4, 148.1, 158.3, 161.9. Mp 216–218 °C. Anal. Calcd for $C_{18}H_{20}F_2ClNO_4S$: C, 51.49; H, 4.80; N, 3.34. Found C, 51.54; H, 4.84; N, 3.31. LC–MS (ESI) m/z: 384.1 [M+H$^+$−(HCl)].

5.1.35. *N*-[2-(2,5-Difluorophenoxy)ethyl]-7-methoxy-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (37b)

The title compound was prepared from **36b** in a manner similar to that described for the synthesis of **37a**. Yield 66%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68–2.90 (m, 2H), 3.33–3.55 (m, 3H), 3.64 (br. s., 1H), 3.87 (s, 3H), 4.40 (br. s., 2H), 4.84 (br. s., 1H), 6.78–6.89 (m, 1H), 7.15–7.25 (m, 1H), 7.25–7.39 (m, 3H), 7.83 (br. s., 1H), 9.51 (br. s., 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.6, 43.1, 45.0, 52.2, 56.0, 64.8, 103.2, 107.3, 107.2, 116.6, 119.1, 122.1, 132.8, 140.8, 146.4, 148.1, 158.2, 160.3. Mp 219–221 °C. Anal. Calcd for $C_{18}H_{20}ClF_2NO_4S$: C, 51.49; H, 4.80; N, 3.34. Found C, 51.53; H, 4.93; N, 3.29. LC–MS (ESI) m/z: 384.0 [M+H$^+$−(HCl)].

5.1.36. *N*-[2-(2,5-Difluorophenoxy)ethyl]-8-methoxy-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (37c)

The title compound was prepared from **36c** in a manner similar to that described for the synthesis of **37a**. Yield 52%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57–2.82 (m, 2H), 3.33–3.70 (m, 3H), 3.74–3.87 (m, 1H), 3.90 (s, 3H), 4.44 (br. s., 2H), 4.85 (br. s., 1H), 6.83 (tt, 1H, *J* = 8.6, 3.1 Hz), 7.21 (ddd, 1H, *J* = 10.3, 7.1, 3.0 Hz), 7.26–7.38 (m, 2H), 7.48 (d, 1H, *J* = 7.5 Hz), 7.61–7.71 (m, 1H), 9.90 (br. s., 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.1, 43.2, 47.7, 53.2, 56.7, 64.8, 103.2, 107.3, 114.4, 116.6, 122.2, 127.6, 132.1, 133.5, 146.4, 148.1, 158.2, 157.4. Mp 211–212 °C. Anal. Calcd for $C_{18}H_{20}ClF_2NO_4S$: C, 51.49; H, 4.80; N, 3.34. Found C, 51.61; H, 4.99; N, 3.23. LC–MS (ESI) *m*/*z*: 384.1 [M+H$^+$−(HCl)].

5.1.37. *N*-[2-(2,5-Difluorophenoxy)ethyl]-6-fluoro-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (38)

The title compound was prepared from **34d** in a manner similar to that described for the synthesis of **20a** and **22a**. Yield 83%. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 2.80 (br. s., 2H), 3.50 (br. s., 2H), 3.61–3.75 (m, 1H), 3.85–4.00 (m, 1H), 4.45 (br. s., 2H), 4.93 (br. s., 1H), 6.75–6.93 (m, 1H), 7.14–7.39 (m, 2H), 7.49–7.67 (m, 1H), 7.86–8.12 (m, 2H, *J* = 8.9, 5.5 Hz), 10.03 (br. s., 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.0, 43.8, 45.9, 53.0, 65.4, 103.7, 107.8, 117.1, 118.4, 127.3, 136.7, 147.0, 150.2, 157.2, 160.3, 162.3, 165.7. Mp 233–235 °C. Anal. Calcd for $C_{17}H_{17}ClF_3NO_3S$: C, 50.06; H, 4.20; N, 3.43. Found C, 49.97; H, 4.06; N, 3.47. LC–MS (ESI) *m*/*z*: 372.1 [M+H$^+$−(HCl)].

5.1.38. *N*-[2-(2,5-Difluorophenoxy)ethyl]-6-(methylsulfonyl)-3,4-dihydro-2*H*-thiochromen-4-amine 1,1-dioxide hydrochloride (39)

A mixture of **36a** (532 mg, 1.00 mmol), Pd_2dba_3 (91.6 mg, 0.10 mmol), NaSMe (105 mg, 1.50 mmol), and xantphos (63.6 mg, 0.11 mmol) in xylene (5 mL) was stirred for 20 h at 140 °C, poured into water and extracted with AcOEt. The extract was washed with brine, dried with$MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3–1:1) to provide a coupling product (419 mg, 84%) as an amorphous solid. To a solution of the product (400 mg, 0.80 mmol) in AcOEt (3 mL) was added *m*CPBA (394 mg, 1.60 mmol) at room temperature. The mixture was stirred for 3 h at room temperature, poured into aq. sodium thiosulfate, and extracted with AcOEt. The extract was washed with aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography on silica gel (AcOEt/hexane = 1:3–1:1) to provide a sulfonyl product (400 mg, 94%) as a colorless oil. The product and 4 M HCl in AcOEt (2 mL) was stirred for 1 h at room temperature. The mixture was concentrated in vacuo. The resulting precipitate was filtered off and recrystallized from MeOH and diethylether to provide the title compound (172 mg, 49%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68–3.01 (m, 2H), 3.37 (s, 3H), 3.59–3.84 (m, 3H), 4.03 (q, 1H, J = 7.2 Hz), 4.47 (br. s., 2H), 5.04 (br. s., 1H), 6.77–6.89 (m, 1H), 7.17–7.37 (m, 2H), 8.21 (s, 2H), 8.60 (br. s., 1H), 9.85 (, br. s., 1H), 10.10 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.8, 43.2, 43.8, 44.7, 52.3, 65.0, 103.3, 107.2, 116.6, 124.8, 129.1, 130.4, 132.1, 143.7, 144.0, 146.4, 148.1, 158.3. Mp 222 °C. LC–MS (ESI) *m*/*z*: 432.0 [M+H$^+$−(HCl)].

5.1.39. 4-{[2-(2,5-Difluorophenoxy)ethyl]amino}-3,4-dihydro-2*H*-thiochromene-6-carboxamide 1,1-dioxide hydrochloride (40)

A mixture of **36a** (1.50 g, 2.82 mmol), $Pd(OAc)_2$ (31.6 mg, 0.14 mmol), dppf (78.2 mg, 0.140 mmol), Et_3N (0.43 mL, 3.10 mmol) in MeOH (6 mL) and THF (6 mL) was stirred at 100 °C for 6 h under a carbon monoxide atmosphere, concentrated in vacuo, poured into water and extracted with AcOEt. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3–1:1) to provide a coupling product (1.43 g, 99%) as an amorphous solid. A mixture of the product (1.27 g, 2.48

mmol) and 1 M NaOH (5 mL) in THF (10 mL) was stirred for 3 h at 50 °C. The mixture was acidified with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was washed with diethylether to provide a carboxylic acid product (1.00 g, 81%) as a colorless solid. A mixture of the product (300 mg, 0.60 mmol), *N*,*N*-diisopropylethylamine (0.126 mL, 0.724 mmol), HOBt·NH_3 (110 mg, 0.724 mmol), and WSC (139 mg, 0.72 mmol) in DMF (2 mL) was stirred for 19 h at room temperature, poured into water and extracted with AcOEt. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 3:7–3:2) to provide an amide product (200 mg, 67%) as a colorless solid. A mixture of the product and 4 M HCl in AcOEt (2 mL) was stirred for 1 h at room temperature and concentrated in vacuo. The resulting precipitate was recrystallized from EtOH, diethyl ether, and water to provide the title compound (147 mg, 84%) as colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69–2.97 (m, 2H), 3.53–3.77 (m, 3H), 3.95 (br. s., 1H), 4.45 (br. s., 2H), 4.95 (br. s., 1H), 6.78–6.88 (m, 1H), 7.16–7.35 (m, 2H), 7.76 (br. s., 1H), 7.96–8.07 (m, 1H), 8.12 (d, 1H, *J* = 8.7 Hz), 8.24 (br. s., 1H), 8.45 (br. s., 1H), 9.71 (br. s., 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.1, 43.9, 44.8, 52.9, 64.9, 103.3, 107.3, 116.6, 123.6, 129.5, 130.5, 137.9, 141.4, 146.3, 146.9, 149.3, 158.2, 166.4. Mp 224–226 °C; Anal. Calcd for $C_{18}H_{19}ClF_2N_2O_4S\cdot 0.8H_2O$: C, 48.34; H, 4.64; N, 6.26. Found C, 48.37; H, 4.70; N, 6.22. LC–MS (ESI) *m*/*z*: 397.1 [M+H$^+$−(HCl)].

5.1.40. N^4-[2-(2,5-Difluorophenoxy)ethyl]-N^6-methyl-3,4-dihydro-2*H*-thiochromene-4,6-diamine 1,1-dioxide hydrochloride (41)

A mixture of **36a** (300 mg, 0.69 mmol), Pd_2dba_3 (10.3 mg, 11.3 μmol), XPhos (21.5 mg, 45.0 μmol), and 40% methyl amine in MeOH (161 mg, 2.08 mmol) in toluene (4 mL) was stirred for 17 h at 100 °C. The mixture was filtered through Celite and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane = 3:7–3:2) to provide a coupling product (114 mg). A mixture of the product and 4 M HCl in AcOEt (3 mL) was stirred for 1 h at

room temperature and concentrated in vacuo. The resulting precipitate was filtered off and recrystallized from EtOH, diethyl ether and water to provide the title compound (80.8 mg, 28%) as an amorphous solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.62–2.86 (m, 5H), 3.40–3.59 (m, 3H), 3.68–3.82 (m, 1H), 4.46 (t, 2H, *J* = 5.1 Hz), 4.77 (br. s., 1H), 6.73–6.88 (m, 2H), 6.91 (d, 1H, *J* = 2.3 Hz), 7.16–7.37 (m, 2H), 7.55 (d, 1H, *J* = 8.7 Hz), 9.82 (br. s., 2H). (A NH proton was not observed). ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.1, 29.8, 43.4, 46.0, 53.5, 65.3, 103.7, 107.8, 110.5, 114.6, 117.1, 125.1, 125.3, 132.5, 146.8, 148.7, 153.2, 158.7. LC–MS (ESI) *m*/*z*: 383.3 [M+H$^+$−(HCl)].

5.1.41. (4*R*)-*N*^{4}-[2-(2,5-Difluorophenoxy)ethyl]-*N*^{6}-methyl-3,4-dihydro-2*H*-thiochromene-4,6-diamine 1,1-dioxide hydrochloride ((*R*)-41).

Optical resolution of the coupling product (400 mg, 0.83 mmol) described in the synthesis of **41** was determined using HPLC (Chiralpak ASH (LA005), 20 mm i.d. × 250 mm length, solvent phase CO_2/MeOH = 700/300) after desalting. The desired fraction with smaller retention time was separated and concentrated in vacuo. To the residue (192 mg, >99.9% ee) was added 4 M HCl in AcOEt (2 mL) at room temperature. The resulting precipitate was collected by filtration and recrystallized from *i*-PrOH, diethyl ether, and water to give the title compound (83.2 mg, 50%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57–2.84 (m, 5H), 3.40–3.57 (m, 3H), 3.72 (br. s., 1H), 4.42 (br. s., 2H), 4.76 (br. s., 1H), 6.63–6.89 (m, 4H), 7.15–7.37 (m, 2H), 7.56 (d, 1H, *J* = 8.3 Hz), 9.35–9.79 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.7, 29.3, 43.0, 45.5, 53.0, 64.9, 103.3, 107.3, 109.9, 114.0, 116.6, 124.6, 124.7, 132.0, 146.4, 148.1, 152.7, 158.3. Mp 173–175 °C. Anal. Calcd for $C_{18}H_{21}ClF_2N_2O_3S$: C, 51.61; H, 5.05; N, 6.69. Found C, 51.67; H, 5.00; N, 6.63. LC–MS (ESI) *m*/*z*: 383.3 [M+H$^+$−(HCl)]. $[\alpha]^{25}_{D}$ −58.4 (c 0.229, MeOH).

5.1.42. (4*S*)-*N*^{4}-[2-(2,5-Difluorophenoxy)ethyl]-*N*^{6}-methyl-3,4-dihydro-2*H*-thiochromene-4,6-diamine 1,1-dioxide hydrochloride ((*S*)-41).

Optical resolution of the coupling product (400 mg, 0.83 mmol) described in the synthesis of **40** was determined using HPLC (Chiralpak ASH (LA005), 20 mm i.d. × 250 mm length, solvent phase CO_2/MeOH = 700/300) after desalting. The desired fraction with larger retention time was separated and concentrated in vacuo. To the residue (192 mg, >99.9% ee) was added 4 M HCl in AcOEt (2 mL) at room temperature. The resulting precipitate was collected by filtration and recrystallized from *i*-PrOH, diethylether, and water to give the title compound (102 mg, 61%) as a colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.67–2.82 (m, 5H) 3.40–3.56 (m, 3H) 3.74 (t, 1H, *J* = 11.6 Hz), 4.45 (br. s., 2H), 4.77 (br. s., 1H), 6.71 (br. s., 1H), 6.78 (d, 1H, *J* = 8.4 Hz), 6.80–6.86 (m, 1H), 6.88 (br. s., 1H), 7.22 (ddd, 1H, *J* = 10.0, 7.1, 2.8 Hz), 7.30 (ddd, 1H, *J* = 10.8, 9.2, 5.3 Hz), 7.55 (d, 1H, *J* = 8.8 Hz), 9.55–9.92 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 22.6, 29.2, 43.1, 45.3, 53.0, 64.8, 103.2, 107.2, 109.8, 113.9, 116.5, 124.6, 124.7, 131.9, 146.3, 148.1, 152.6, 158.2. Mp 173–175 °C. Anal. Calcd for $C_{18}H_{21}ClF_2N_2O_3S$: C, 51.61; H, 5.05; N, 6.69. Found C, 51.73; H, 5.07; N, 6.66. LC–MS (ESI) *m*/*z*: 383.3 [M+H$^+$−(HCl)]. $[\alpha]^{25}_D$ +57.4 (c 0.226, MeOH).

5.2 Biochemical evaluation

5.2.1 α_1-AR binding assay

Membranes of human α_{1A}-, α_{1B}-, and α_{1D}-ARs were prepared from CHO-K1 cells stably expressing each α_1-AR. A binding assay for α_1-AR was performed in 200 µL of α_1 binding assay buffer (50 mmol/L Tris-HCl pH7.5, 10 mmol/L $MgCl_2$, 5 mmol/L EDTA and 0.5% BSA) containing membrane protein (10 µg for each α_1 receptor) and 2.5 nmol/L 7-methoxy-[^{3}H]-prazosin in the presence of the trial compound at 12 different concentrations. Following incubation at room temperature for 60 min, the membranes were filtered through GF/C filter plates (Perkin Elmer Life and Analytical Sciences) and washed with 50 mmol/L Tris-HCl (pH 7.5). The membrane-associated radioactivity was determined using a TopCount liquid scintillation counter (Perkin Elmer Life and Analytical Sciences). Non-specific binding was defined as binding in the presence of 10 µmol/L phentolamine. IC_{50} values were calculated by logistic regression analysis. The *K*d values of α_1-AR

subtypes (α_{1A}, α_{1B} and α_{1D}) were 0.93, 0.35 and 0.26 nmol/L, respectively. *K*i values were calculated as *K*i= IC_{50}/{1+(^{3}H-ligand concentration)/ *K*d} [25].

5.2.2 In vitro metabolic clearance in human hepatic microsomes.

Human liver microsomes were purchased from Xenotech, LLC (Lenexa, KS). An incubation mixture consisted of microsomal protein in 50 mM KH_2PO_4−K_2HPO_4 phosphate buffer (pH 7.4) and 1 μM test compound. The concentration of microsomal protein was 0.2 mg/mL. An NADPH-generating system containing 5 mM $MgCl_2$, 5 mM glucose 6-phosphate, 0.5 mM β-$NADP^+$, and 1.5 units/mL glucose 6-phosphate dehydrogenase was added to the incubation mixture to initiate the enzyme reaction. The reaction was terminated 15 and 30 min after the initiation of the reaction by mixing the reaction mixture with acetonitrile, followed by centrifugation. The supernatant was subjected to LC/MS/MS analysis. The metabolic velocity was calculated as the slope of the concentration−time plot.

5.2.3 Evaluation of reversible inhibition of cytochrome P450 3A4.

Human liver microsomes were purchased from Xenotech, LLC (Lenexa, KS). Inhibition activity of a test compound of cytochrome P450 3A4 was evaluated by incubating midazolam with 0.1 mg/mL human microsomes in the presence of 10 μM test compound. The incubation mixture was allowed to stand for 10 min at 37 °C, and then the incubation was terminated by addition of acetonitrile/water. After centrifugation, the supernatant was subjected to LC/MS/MS analysis to measure the peak of 1'-hydroxymidazolam.

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Highlights

- Phenoxyethylamine derivative **7** was selected as an attractive starting point.
- Retaining α_{1D}–AR selectivity was indispensable to choose the proper linker length.
- Conformational constraint was effective to inhibit the bladder contractions.
- (*S*)-**41** was identified as a novel and selective human α_{1D}-AR antagonist.