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Isochromanone-based urotensin-II receptor agonists

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Abstract—A series of analogues of the selective non-peptide urotensin II (UII) receptor agonist 3-(4-chlorophenyl)-3-(2-dimethylaminoethyl)-isochroman-1-one (AC-7954, **1**) was synthesized and evaluated for UII agonist activity using a functional cell-based assay. The introduction of a methyl group in the 4-position resulted in a complete loss of activity, whereas substituents in the aromatic rings were beneficial. Sterically demanding amino groups were also detrimental to the activity. Several potent agonists were identified, six compounds being equally or more potent than **1**. The most potent compound in the series was the 6,7-dimethyl analogue of **1** (**16**, pEC_{50} 6.87). The racemate of **16** was resolved into the pure enantiomers using preparative straight phase HPLC. It was shown that the potency resides in the (+)-enantiomer (pEC_{50} 7.11). The synthesized compounds seem to be selective for the UII receptor as no activities were observed at the closely related SSTR3 and 5 receptors.

1. Introduction

The neuropeptide urotensin-II (UII) is a cyclic undecapeptide that provokes a potent cardiovascular response in humans.[1–3] UII has been identified as the endogenous ligand at the GPR14/urotensin-II receptor,[4–7] and the pathophysiological relevance of UII has recently been reviewed.[8,9]

The cyclic hexapeptide unit (CFWKYC) of UII is highly conserved between species, with the Trp-Lys-Tyr sequence being critical for receptor activation.[10] Several non-peptide[10] and peptide based UII receptor antagonists[11–13] have appeared in the literature. Also peptide-based agonists[14–17] are known, but it was only recently that the first *non-peptidic* agonist (3-(4-chlorophenyl)-3-(2-dimethylaminoethyl)-isochroman-1-one, AC-7954) (**1**, Fig. 1) was reported.[18] Although **1** is much less potent than the natural ligand, it is highly selective for the UII receptor[18] and therefore considered interesting as a lead compound for further studies and optimization.

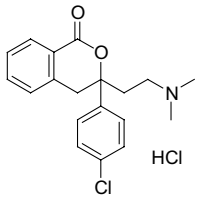

Figure 1. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)isochroman-1-one (**1**), the first reported non-peptidic UII-receptor agonist.

To study the structure–activity relationships around **1**, we have synthesized a series of analogues. In this initial study the isochromanone core has been kept intact and the effects from variation of ring substitutions have been investigated.

2. Results and discussion

2.1. Chemistry

A series of 3,4-dihydroisochromanone derivatives was synthesized according to Scheme 1. The *o*-tolubenzamides **3a–i** were dilitiated using BuLi followed by the

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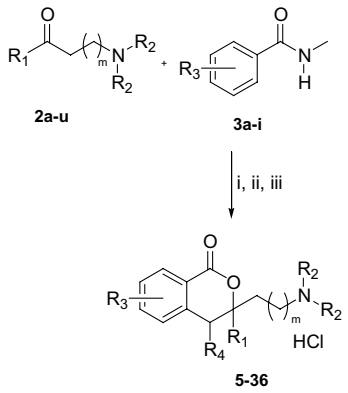


Scheme 1. Reagents and conditions: (i) *n*BuLi (2.2 equiv), THF, rt, (ii) 1,2-dichlorobenzene reflux, (iii) HCl_{ether}.

addition of the appropriate ketone (**2a**–**u**).[19] The resulting tertiary alcohols were not isolated, instead the crude product mixtures were heated in 1,2-dichlorobenzene (~105 °C) to afford the lactonization.[18] The yields in this two-step reaction were low (10–46% isolated yield), however the yields were in the same range as those reported for this synthetic sequence.[20] Other procedures to afford the desired isochromanone derivatives were also investigated, for example, dilithiation of *o*-methyl benzoic acids[21] or lithium–tellurium exchange on α-bromo-*o*-tolunitriles[22] or esters.[23] However, we were unable to obtain higher yields of the desired products and therefore settled for the *o*-tolubenzamide method. All compounds were isolated as their HCl salts (**5**–**36**).[24]

The β-aminoketones **2h**–**s** were synthesized by large scale microwave-enhanced Mannich reactions as reported elsewhere,[25] whereas **2c**–**g** and **2t** were synthesized by nucleophilic substitution of the corresponding alkyl chlorides at room temperature (Table 2). Compound **2u** was not possible to obtain by any of these methods as only starting material was detected even after long reaction times.[26] However, when subjecting a mixture of 3,4′-dichloropropiophenone and dimethylamine in THF to microwave irradiation (300 s, 180 °C), **2u** was obtained in 87% yield.

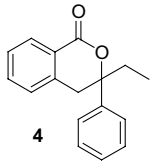
The benzamides **3b**–**i** were synthesized in high yields by reacting commercially available benzoic acids with thionyl chloride in the presence of triethylamine followed by the addition of methylamine in THF (Table 3).

2.2. Pharmacological testing

Compounds **5**–**36** were tested for their agonistic properties at human UII receptors using the functional R-SAT™ assay previously described.[18,27–30] The results are shown in Table 1. For control of the UII receptor selectivity all compounds were tested against the m3 receptor as a negative control. The activation of the closely related somatostatin 3 and 5 (SSTR3/5) receptors was also tested for some derivatives.[31] Several potent agonists were identified, six compounds being equally or more potent than **1**.

2.3. Structure–activity relationships

An amino function is essential for activation of the UII receptor as compounds lacking this functionality (e.g., **4**) were devoid of activity (results not shown). Interestingly, compounds containing amino functions larger than a dimethylamino group (**18**–**22**) showed a drastic drop or a complete loss of activity. The length of the aminoalkyl chain also seemed to be of importance for the activity as compound **35**, with a shorter chain than **1**, showed no activity, whereas **36**, having a longer chain, still retained some of its potency.

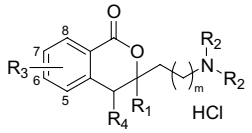


The results also showed that the substitution pattern of the phenyl ring on C-3 of the isochromanone scaffold (R_1, Table 1) influenced the activity. Generally substitution in the 3′- or 4′-position was favourable for the affinity and efficacy. In addition, the 4′-substituted compounds with electron-withdrawing substituents such as chloride (**1**), fluoride (**26**) or trifluoromethyl (**23**) groups showed higher efficacy than compounds substituted with electron-donating groups such as methyl (**25**), methoxy (**27**) or phenoxy (**24**). This effect was not observed for the 3′-substituted derivatives (compare **28**–**30**). The 3′- and 4′-methoxy substituted derivatives also showed higher affinities than the 2′-substituted derivative **31**.

Compounds containing larger substituents in the 3-position of the isochromanone system, such as 1- and 2-naphthyl groups (**32** and **33**, respectively), showed high efficacy, indicating that there is space available in this region of the receptor binding site. Interestingly, the smaller 2-thienyl substituted derivative **34** was of considerably lower activity than **1** and its non-chlorinated analogue **5**.

The synthesis of **12** was shown to be highly stereoselective as only one diastereomer of the product could be detected using either NMR spectroscopy or HPLC. The introduction of a methyl group in the 4-position of the isochromanone system resulted in a complete loss of activity, indicating that important ligand–receptor interactions have been disturbed. To determine which isomer that was preferentially formed in the lactonization both conformational analyses (MM3, MacroModel) of the two possible isomers and NOE experiments of **12** were performed. According to molecular mechanics calculations of **1** the dihydroisochromanone ring adopts an envelope conformation with the phenyl ring pseudoequatorially positioned and the aminoethyl chain extending in a pseudoaxial direction (Fig. 2). The conformational analyses of the *syn* and *anti* isomers of **12** indicate that the *syn* isomer is the most stable (6 kcal/mol more stable than the *anti* isomer). The results also showed that the

Table 1. Results from in vitro testing of urotensin-II agonist activity[a]



5 - 36

Compd	R_1	R_2	*m*	R_3	R_4	pEC_{50}UII	Efficacy[b]	*N*[c]
1	4′-Cl-Ph	Me	1	H	H	5.95 ± 0.12	133 ± 8	6
5	Ph	Me	1	H	H	4.84 ± 0.02	88 ± 3	2
6	Ph	Me	1	5-OMe	H	4.71 ± 0.0	70 ± 6	3
7	Ph	Me	1	5-F	H	4.74 ± 0.02	48 ± 4	4
8	Ph	Me	1	5-Me	H	4.74 ± 0.04	51 ± 15	3
9	Ph	Me	1	6-Me	H	4.94 ± 0.10	89 ± 12	3
10	Ph	Me	1	7-Me	H	4.98 ± 0.03	98 ± 15	3
11	4′-Cl-Ph	Me	1	5-OMe	H	5.87 ± 0.11	139 ± 11	5
12	4′-Cl-Ph	Me	1	H	Me	NA[d]		2
13	4′-Cl-Ph	Me	1	5-Me	H	5.65 ± 0.05	96 ± 8	5
14	4′-Cl-Ph	Me	1	6-Me	H	6.54 ± 0.11	114 ± 6	5
15	4′-Cl-Ph	Me	1	7-Me	H	6.64 ± 0.17	121 ± 9	5
16	4′-Cl-Ph	Me	1	6,7-Me	H	6.87 ± 0.03	146 ± 24	2
17	4′-Cl-Ph	Me	1	8-Me	H	5.23 ± 0.06	84 ± 17	2
18	4′-Cl-Ph	Et	1	H	H	5.44 ± 0.08	52 ± 24	2
19	4′-Cl-Ph	Pyrrolidino	1	H	H	5.31 ± 0.08	35 ± 3	3
20	4′-Cl-Ph	Piperidino	1	H	H	NA[d]		3
21	4′-Cl-Ph	Morpholino	1	H	H	NA[d]		3
22	4′-Cl-Ph	4-Me-Piperazino	1	H	H	NA[d]		3
23	4′-CF_3-Ph	Me	1	H	H	6.05 ± 0.07	109 ± 10	5
24	4′-OPh-Ph	Me	1	H	H	5.94 ± 0.26	54 ± 3	2
25	4′-Me-Ph	Me	1	H	H	5.19 ± 0.10	80 ± 11	5
26	4′-F-Ph	Me	1	H	H	5.60 ± 0.02	147 ± 40	2
27	4′-OMe-Ph	Me	1	H	H	5.01 ± 0.01	51 ± 1	3
28	3′-Cl-Ph	Me	1	H	H	5.59 ± 0.03	105 ± 18	2
29	3′-OMe-Ph	Me	1	H	H	5.33 ± 0.08	135 ± 51	2
30	3′-F-Ph	Me	1	H	H	5.32 ± 0.06	96 ± 52	2
31	2′-OMe-Ph	Me	1	H	H	4.97 ± 0.04	33 ± 4	3
32	1-Naphthyl	Me	1	H	H	5.33 ± 0.05	114 ± 7	2
33	2-Naphthyl	Me	1	H	H	6.20 ± 0.01	138 ± 21	2
34	2-Thienyl	Me	1	H	H	NA[d]		2
35	4′-Cl-Ph	Me	0	H	H	NA[d]		3
36	4′-Cl-Ph	Me	2	H	H	5.46 ± 0.12	62 ± 24	2

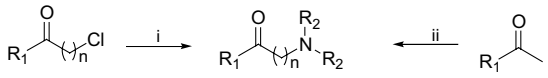
[a] Results were determined in R-SAT assays and are expressed as pEC_{50}, the negative of the log EC_{50} in molarity. Results are the average ± standard deviation of 2–6 determinations of the EC_{50} where each compound was tested in eight doses in triplicate.
[b] The % efficacy values are normalized to UII at 100%.
[c] Number of experiments.
[d] NA = Not active. Compounds showing <30% efficacy are not considered active.

only difference between the most stable conformation of *syn*-**12** and the 3D structure of **1** is the pseudoaxially positioned methyl group (Fig. 3). These results were corroborated by those obtained from NOE experiments (500 MHz, $CDCl_3$). Strong NOE interactions were observed between H-4 and H-5 and H-4 and the first CH_2 group in the aminoethyl chain, which is in agreement with a *syn* relationship between the methyl group and the 3-phenyl substituent. As **12** is devoid of activity the results indicate that the 4-methyl group is directed towards a region occupied by the receptor.

Derivatives containing a methyl substituent in the 5-, 6-, 7- or 8-position (**13**, **14**, **15** and **17**, respectively) all showed similar or slightly enhanced affinities compared to **1**. The favourable effects appeared to be additive as the 6,7-dimethylated derivative **16** showed the highest affinity of all synthesized compounds in this study. A 5-methoxy substituent, as in **11**, also resulted in a highly efficacious compound. Interestingly, analogous derivatives lacking the 4′-chloro substituent in the 3-phenyl ring (**6**–**10**) were of lower affinity indicating the importance of correct mapping of the different binding pockets of the receptor site.

The activity of **1** was earlier shown to reside in the (+)-enantiomer.[18] To investigate whether this was true also for **16** the racemate was resolved into the pure enantiomers using preparative HPLC. It was found also here that the activity mainly emanated from the (+)-enantiomer [(+)-**16** pEC_{50} = 7.11, (−)-**16** pEC_{50} = 5.78] (Fig. 4). The similarities observed between the CD spectra of (+)-**1** and (+)-(**16**) indicated that the compounds have the same absolute configuration (Fig. 5).

Table 2.

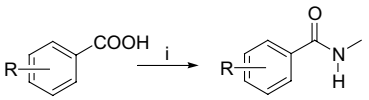


2a - u

Compd	R_1	R_2	Method	*n*
2a	Ph	Me	[a]	2
2b	4-Cl-Ph	Me	[a]	2
2c	4-Cl-Ph	Pyrrolidino	i	2
2d	4-Cl-Ph	Piperidino	i	2
2e	4-Cl-Ph	Morpholino	i	2
2f	4-Cl-Ph	4-Me-Piperazino	i	2
2g	4-Cl-Ph	Et	i	2
2h	4-CF_3-Ph	Me	ii	2
2i	4-OPh-Ph	Me	ii	2
2j	4-Me-Ph	Me	ii	2
2k	4-F-Ph	Me	ii	2
2l	4-OMe-Ph	Me	ii	2
2m	3-Cl-Ph	Me	ii	2
2n	3-OMe-Ph	Me	ii	2
2o	3-F-Ph	Me	ii	2
2p	2-OMe-Ph	Me	ii	2
2q	1-Naphthyl	Me	ii	2
2r	2-Naphthyl	Me	ii	2
2s	2-Thienyl	Me	ii	2
2t	4-Cl-Ph	Me	i	1
2u	4-Cl-Ph	Me	iii	3

Method (i): $HN(R_2)_2$ (2 equiv), THF, rt, 16 h.
Method (ii): paraformaldehyde, $HNMe_2$ HCl, dioxane, microwave heating 200 °C, 300 s (Ref. 25).
Method (iii): $HN(R_2)_2$ (2 equiv), THF, microwave heating 180 °C, 300 s.
[a] Commercially available.

Table 3.



3a - i

Compd	R
3a	2-Me[a]
3b	2,3-Di-Me
3c	2,4-Di-Me
3d	2,5-Di-Me
3e	2,6-Di-Me
3f	2-Me, 3-OMe
3g	2-Me, 3-F
3h	2-Et
3i	2,4,5-Tri-Me

(i) $SOCl_2$, H_2NMe, Et_3N, THF.
[a] Commercially available.

The tested derivatives showed a high selectivity for the UII receptor as no significant affinities were observed at the SSTR3/5 receptors (data not shown).

3. Conclusion

We have synthesized a series of novel 3,4-dihydroisochromanone derivatives as analogues of the potent and selective UII-receptor agonist **1**. Structural modifications such as the introduction of ring substituents and various basic amino moieties led to both increased and decreased activities. Favourable effects were observed when substituents were introduced in the aromatic part of the isochromanone ring system, whereas more sterically demanding amino groups were detrimental to the activity.

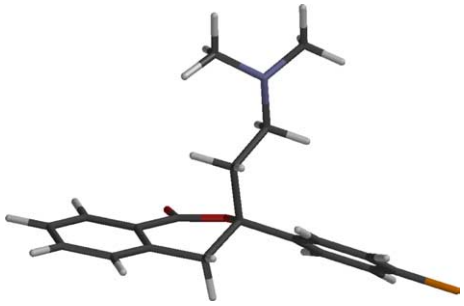


Figure 2. Global minimum conformation of **1** identified by conformational analysis using molecular mechanics calculations (MM3, MacroModel).

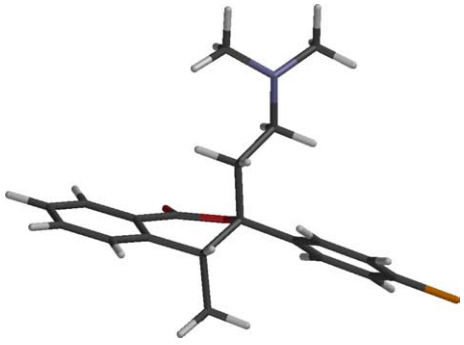


Figure 3. Global minimum structure of **12** identified by conformational analysis using molecular mechanics calculations (MM3, MacroModel).

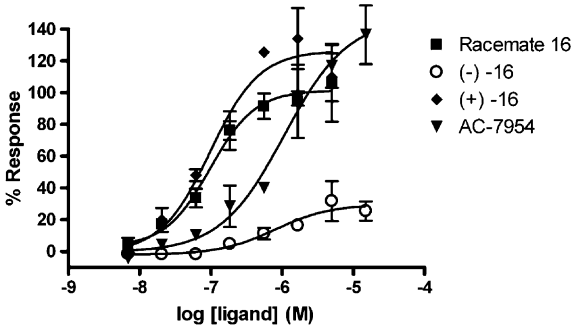


Figure 4. UII receptor activation of the racemate and the individual enantiomers of **16**. Compound **16** and **1** (AC-7954) were tested for agonist activity at the UII receptor in the functional cell based R-SAT assay.

4. Experimental section

4.1. Chemistry

4.1.1. General. ^1H and ^{13}C spectra were recorded in $CDCl_3$ unless otherwise stated using Varian Unity 400

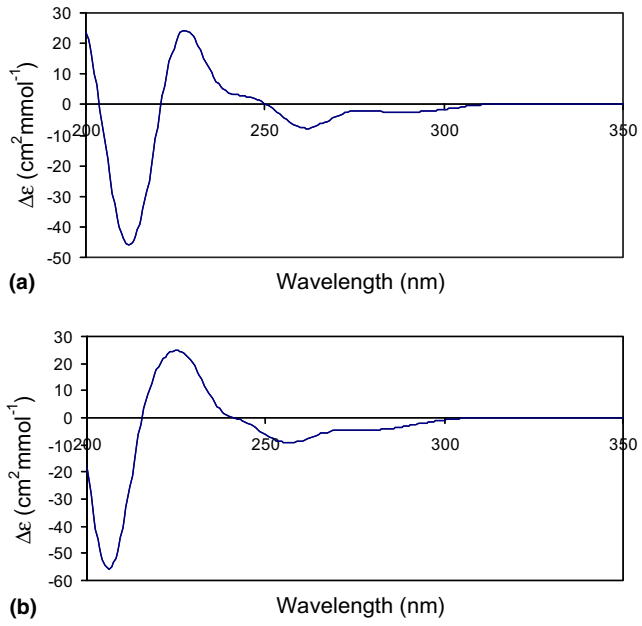


Figure 5. CD spectra of (a) (+)-**16** (HCl salt in MeOH, $c = 0.29$ mM) and (b) (+)-**1** (HCl salt in MeOH, $c = 0.32$ mM).

or Varian Unity 500 instruments. All reactions were followed by TLC (Merck silica gel 60 F_{254}) and analyzed under UV (254 nm). In case of flash chromatography, Merck silica gel 60 (230–400 mesh) was used. Melting points were recorded on a Büchi melting point B-545 and are uncorrected. Gas chromatographic analyses were performed on a Varian 3900 gas chromatograph equipped with a flame ionization detector (FID). For the separation a fused silica column (CP5860) was used with hydrogen as carrier gas. Elemental analyses were performed at MikroKemi AB, Uppsala, Sweden. HPLC analyses were performed on a ACE-122-0546 column using water/acetonitrile/TFA as the eluent (flow 1 mL/min, gradient from 95/4.9/0.1 up to 5/94.9/0.1 over 5 min) detection was carried out at $\lambda = 254$ nm. HPLC separation of the enantiomers of **16** was performed by the use of a Chiralpak AD 20 × 250 mm column (Daicel Chemical CO., Tokyo, Japan) and a mobile phase consisting of hexane/2-propanol/triethylamine/acetic acid (94.8/5.0/0.1/0.1) at a flow rate of 20 mL/min. Detection was carried out at 225 nm. A 800 μL volume of a 10 mg/mL solution of the racemate in the mobile phase was injected. This yielded a baseline separation of the enantiomers with $k' = 2.3$ and $\alpha = 1.5$. Both enantiomers were enantiomerically pure (>99.5% ee) according to analytical chiral LC.

FAB MS spectra were obtained from Stenhagen Analyslab AB using a VG 7070E magnetic sector instrument (VG Analytical/Micromass, Manchester UK). Conditions for FAB (fast atom bombardment): Xe gun at 8 kV, matrix glycerol or 3-nitrobenzylalcohol with PEG 600 as mass reference. A signal from a coil in the magnet field was used for mass calibration. Acceleration voltage 5 kV. Magnet scan from 150 to 700 in 4s (typical).

4.2. General procedure for the synthesis of aminoketones 2c–g and 2t

3,4′-Dichloropropiophenone was dissolved in THF and the appropriate secondary amine (2 equiv) was added. After stirring at room temperature for 16 h, the mixture was poured into saturated aqueous NH_4Cl and extracted twice with EtOAc. The combined organic phases were washed (H_2O and brine) and concentrated. The crude oil was dissolved in diethyl ether and an HCl saturated ether solution (HCl_{ether}) was added. The resulting solid was recrystallized from CH_2Cl_2/diethyl ether to afford the title compounds. All products were >99% pure according to HPLC.

4.2.1. 1-(4-Chlorophenyl)–3-(pyrrolidin-1-yl)propane-1-one HCl (2c).[32] 3,4′-Dichloropropiophenone (8.0 g, 39.4 mmol) and pyrrolidine (5.6 g, 78.8 mmol) yielded 3.0 g (32%) of the title compound as white crystals. Mp 184.2–184.8 °C. ^{1}H NMR (500 MHz) δ 2.09–2.13 (m, 2H), 2.22–2.26 (m, 2H), 2.83–2.88 (m, 2H), 3.51–3.55 (m, 2H), 3.71–3.78 (m, 4H), 7.45 (d, 2H, $J = 8.5$ Hz), 7.93 (d, 2H, $J = 8.5$ Hz), 12.75 (s, 1H). ^{13}C NMR (125 MHz) δ 23.4, 23.7, 34.9, 50.1, 54.1, 54.2, 129.5, 130.1 (2 C:s), 134.0 (2 C:s), 141.0, 194.1.

4.2.2. 1-(4-Chlorophenyl)–3-(piperidin-1-yl)propane-1-one HCl (2d). 3,4′-Dichloropropiophenone (6.0 g, 30 mmol) and piperidine (4.9 g, 60 mmol) yielded 6.7 g (80%) of the title compound as white crystals. Mp 194.2–194.8 °C. ^{1}H NMR (400 MHz) δ 1.38–1.45 (m, 1H), 1.78–1.82 (m, 3H), 2.16–2.26 (m, 2H), 2.65–2.74 (m, 2H), 3.37–3.40 (m, 2H), 3.48–3.51 (m, 2H), 3.78 (t, 2H, $J = 6.8$ Hz), 7.40 (d, 2H, $J = 8.4$ Hz), 7.90 (d, 2H, $J = 8.4$ Hz), 12.10 (s, 1H). ^{13}C NMR (100 MHz) δ 21.9, 22.6 (2 C:s), 33.3, 51.9, 53.8 (2 C:s), 129.1, 129.7 (2 C:s), 133.8 (2 C:s), 140.5, 195.0.

4.2.3. 1-(4-Chlorophenyl)–3-(morpholin-1-yl)propane-1-one HCl (2e). 3,4′-Dichloropropiophenone (6.0 g, 30 mmol) and morpholine (5.2 g, 60 mmol) yielded 7.5 g (99%) of the title compound as white crystals. Mp 85.8–86.2 °C. ^{1}H NMR (400 MHz) δ 2.49 (t, 4H, $J = 4.4$ Hz), 2.80 (t, 2H, $J = 7.6$ Hz), 3.14 (t, 2H, $J = 7.6$ Hz), 3.69 (t, 4H, $J = 4.4$ Hz), 7.42 (d, 2H, $J = 6.8$ Hz), 7.88 (d, 2H, $J = 6.8$ Hz), 12.10 (s, 1H). ^{13}C NMR (100 MHz) δ 35.9 (2 C:s), 53.4, 53.6, 66.8 (2 C:s), 128.9, 129.4 (2 C:s), 135.0 (2 C:s), 139.5, 197.6.

4.2.4. 1-(4-Chlorophenyl)–3-(4-methylpiperazin-1-yl)propane-1-one HCl (2f).[33] 3,4′-Dichloropropiophenone (6.0 g, 30 mmol) and 1-methyl-piperazine (6.0 g, 60 mmol) yielded 8.5 g (98%) of the title compound as white crystals. Mp 69.2–69.7 °C. ^{1}H NMR (400 MHz) δ 2.27 (s, 3H), 2.31–2.61 (m, 8H), 2.82 (t, 2H, $J = 7.1$ Hz), 3.12 (t, 2H, $J = 7.1$ Hz), 7.41 (d, 2H, $J = 8.0$ Hz), 7.88 (d, 2H, $J = 8.0$ Hz) 11.95 (br s, 1H). ^{13}C NMR (100 MHz) δ 36.2, 45.9 (2 C:s), 52.9, 53.2 (2 C:s), 55.0, 128.8 (2 C:s), 129.4 (2 C:s), 135.1, 139.5, 197.8.

4.2.5. 1-(4-Chlorophenyl)-3-diethylamino-propane-1-one HCl (2g).[34] 3,4′-Dichloropropiophenone (3.0 g, 15 mmol) and diethylamine (2.2 g, 30 mmol) yielded

3.1 g (75%) of the title compound as white crystals. Mp 137.2–137.9 °C. ^{1}H NMR (500 MHz) δ 1.41 (t, 6H, J = 7.5 Hz), 3.01–3.13 (m, 2H), 3.18–3.21 (m, 2H), 3.41–3.45 (m, 2H), 3.76–3.79 (m, 2H), 7.43 (d, 2H, J = 8.5 Hz), 7.93 (d, 2H, J = 8.5 Hz), 12.30 (s, 1H). ^{13}C NMR (125 MHz) δ 8.3 (2 C:s), 33.5, 46.7 (2 C:s), 47.1, 129.1 (2 C:s), 129.7 (2 C:s), 133.8, 140.6, 194.9.

4.2.6. 1-(4-Chlorophenyl)-2-dimethylamino-ethanone HCl (2t). 2,4′-Dichloroacetophenone (10.0 g, 50 mmol) and dimethylamine (2 M in THF) (50 mL, 100 mmol) yielded 6.0 g (61%) of the title compound as white crystals. Mp 190.2–190.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.86 (s, 6H), 5.01 (s, 2H), 7.68 (d, J = 8.0 Hz), 7.96 (d, J = 8.0 Hz), 10.50 (br s, 1H). ^{13}C NMR (125 MHz) δ 44.2, 62.3, 129.9 (2 C:s), 130.7 (2 C:s), 133.2, 140.2, 191.4.

4.2.7. 1-(4-Chlorophenyl)-4-dimethylamino-butane-1-one (2u).[35] 4,4′-Dichlorobutyrophenone (0.5 g, 2.3 mmol), dimethylamine (2 M solution in THF) (1.5 mL, 3 mmol) and THF (2.5 mL) were added to a capped vial and heated under microwave irradiation (Emry Synthesizer, Personal Chemistry) (180 °C, 300 s). EtOAc and saturated aqueous $NaHCO_3$ were added to the solution. The organic phase was separated, washed with water and brine and concentrated to afford the title compound as a dark yellow oil (0.45 g, 87%) that was used in the next step without further purification or characterization. ^{1}H NMR (400 MHz) δ 1.96–1.99 (m, 2H), 2.52–2.55 (m, 6H), 2.80–2.85 (m, 2H), 2.95–2.97 (m, 2H), 7.35 (d, 2H, J = 8.0 Hz), 7.90 (d, 2H, J = 8.0 Hz). ^{13}C NMR (100 MHz) δ 18.5, 35.2, 42.3 (2 C:s), 57.2, 129.1 (2 C:s), 129.5 (2 C:s), 134.4, 140.1, 197.0.

4.3. General procedure for the preparation of 2,*N*-dimethylbenzamides 3b–i

The benzoic acid was dissolved in THF (75 mL/g)[36] and triethylamine (5 equiv) was added. Under vigorous stirring $SOCl_2$ (1.3 equiv) was added dropwise and the mixture was stirred at rt for 20 min. Methylamine (2 M in THF) (2 equiv) was added slowly and the reaction mixture was stirred for another 2 h. The mixture was poured into water and extracted twice with EtOAc. After concentration of the combined organic phases the crude oil was dissolved in CH_2Cl_2 and filtered through a plug of silica/$MgSO_4$ (5:1). Evaporation of the solvent yielded the pure amides. All products were >99% pure according to GC.

4.3.1. 2,3,*N*-Trimethylbenzamide (3b).[37] 2,3-Dimethylbenzoic acid (3 g, 20 mmol), triethylamine (10.1 g, 100 mmol), $SOCl_2$ (3.1 g, 26 mmol) and methylamine (2 M in THF) (20 mL, 40 mmol) yielded 2.0 g (63%) of the title compound as light yellow crystals. Mp 99.0–99.1 °C. ^{1}H NMR (400 MHz) δ 2.20 (s, 3H), 2.22 (s, 3H), 2.90 (d, 3H, J = 4.8 Hz), 5.70 (br s, 1H), 7.00–7.11 (m, 2H), 7.18 (d, 1H, J = 3.6 Hz). ^{13}C NMR (100 MHz) δ 16.1, 20.1, 26.4, 124.1, 125.2, 130.8, 133.8, 137.2, 137.5, 171.5. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.4; H, 8.0; N, 8.4.

4.3.2. 2,4,*N*-Trimethylbenzamide (3c).[37] 2,4-Dimethylbenzoic acid (3 g, 20 mmol), triethylamine (10.1 g, 100 mmol), $SOCl_2$ (3.1 g, 26 mmol) and methylamine (2 M in THF) (20 mL, 40 mmol) yielded 3.0 g (92%) of the title compound as light yellow crystals. Mp 95.9–96.1 °C. ^{1}H NMR (400 MHz) δ 2.42 (s, 3H), 2.48 (s, 3H), 2.97 (d, 3H, J = 7.5 Hz), 5.80 (br s, 1H), 6.98 (d, 1H, J = 7.7 Hz), 7.01 (s, 1H), 7.24 (d, 1H, J = 7.7 Hz). ^{13}C NMR (100 MHz) δ 19.8, 21.2, 26.6, 126.2, 126.7, 131.7, 133.5, 136.1, 139.8, 170.8.

4.3.3. 2,5,*N*-Trimethylbenzamide (3d).[37] 2,5-Dimethylbenzoic acid (3 g, 20 mmol), triethylamine (10.1 g, 100 mmol), $SOCl_2$ (3.1 g, 26 mmol) and methylamine (2 M in THF) (20 mL, 40 mmol) yielded 2.9 g (89%) of the title compound as light yellow crystals. Mp 119.0–119.7 °C. ^{1}H NMR (400 MHz) δ 2.29 (s, 3H), 2.37 (s, 3H), 2.96 (d, 3H, J = 7.6 Hz), 5.80 (br s, 1H), 7.08–7.11 (m, 2H), 7.14 (s, 1H). ^{13}C NMR (100 MHz) δ 19.2, 20.7, 26.5, 127.2, 130.3, 130.7, 132.6, 135.1, 136.2, 171.0.

4.3.4. 2,6,*N*-Trimethylbenzamide (3e).[37] 2,6-Dimethylbenzoic acid (2.5 g, 16 mmol) triethylamine (8.1 g, 80 mmol), $SOCl_2$ (2.5 g, 21 mmol) and methylamine (2 M in THF) (16 mL, 32 mmol) yielded 1.5 g (71%) of the title compound as light yellow crystals. Mp 145.0–145.5 °C. ^{1}H NMR (400 MHz) δ 2.28 (s, 6H), 2.98 (s, 3H), 5.85 (s, 1H), 6.99 (d, 2H, J = 7.6 Hz), 7.13 (t, 1H, J = 7.6 Hz). ^{13}C NMR (100 MHz) δ 19.4 (2 C:s), 26.6, 127.6, 128.9 (2 C:s), 134.4 (2 C:s), 137.9, 171.3.

4.3.5. 3-Methoxy-2,*N*-dimethylbenzamide (3f).[38] 3-Methoxy-2-methylbenzoic acid (3.5 g, 21.0 mmol), triethylamine (10.6 g, 105 mmol), $SOCl_2$ (3.2 g, 26 mmol) and methylamine (2 M in THF) (21 mL, 42 mmol) yielded 3.7 g (99%) of the title compound as light yellow crystals. Mp 107.1–107.6 °C. ^{1}H NMR (500 MHz) δ 2.32 (s, 3H), 2.99 (d, 3H, J = 5.0 Hz), 3.85 (s, 3H), 5,89 (br s, 1H), 6.80–6.95 (m, 2H), 7.10–7.16 (m, 1H). ^{13}C NMR (125 MHz) δ 12.5, 26.5, 55.6, 111.2, 118.6, 124.5, 126.5, 138.2, 157.9, 170.7.

4.3.6. 3-Fluoro-2,*N*-dimethylbenzamide (3g). 3-Fluoro-2-methylbenzoic acid (3.0 g, 19.4 mmol), triethylamine (9.8 g, 97 mmol), $SOCl_2$ (3.0 g, 25 mmol) and methylamine (2 M in THF) (20 mL, 40 mmol) yielded 3.1 g (96%) of the title compound as light yellow crystals. Mp 91.5–92.4 °C. ^{1}H NMR (500 MHz) δ 2.26 (s, 3H), 2.92 (d, 3H, J = 4.5 Hz), 6.08 (br s, 1H), 7.00–7.13 (m, 3H). ^{13}C NMR (125 MHz) δ 11.2 (d, $^3J_{CF}$ = 4.6 Hz), 26.5, 116.4 (d, $^2J_{CF}$ = 23 Hz), 122.1, 123.3 (d, $^2J_{CF}$ = 18 Hz), 126.9 (d, $^3J_{CF}$ = 8.9 Hz), 138.8 (d, $^3J_{CF}$ = 4.1 Hz), 161.3 (d, $^1J_{CF}$ = 244 Hz), 169.5. HRFABMS calcd for $C_9H_{10}FNO$ (M+H) m/z 168.0825, found 168.0820.

4.3.7. 2-Ethyl-*N*-methylbenzamide (3h). 2-Ethylbenzoic acid (3.5 g, 23.3 mmol), triethylamine (11.8 g, 117 mmol), $SOCl_2$ (3.6 g, 30 mmol) and methylamine (2 M in THF) (24 mL, 48 mmol) yielded 1.9 g (50%) of the title compound as a light yellow oil. ^{1}H NMR (400 MHz) δ 2.22 (t, 3H, J = 8.2 Hz), 2.77 (q, 2H,

J = 8.2 Hz), 2.97 (d, 3H, J = 4.5 Hz), 5.78 (br s, 1H), 7.15–7.13 (m, 4H). ^{13}C NMR (100 MHz) δ 15.9, 26.4, 26.8, 125.7, 126.7, 129.4, 130.0, 136.3, 142.3, 171.0. HRFABMS calcd for $C_{10}H_{13}NO$ (M+H) m/z 164.1075, found 164.1040.

4.3.8. 2,4,5,*N*-Tetramethylbenzamide (3i). 2,4,5-Trimethylbenzoic acid (3.0 g, 18.3 mmol), triethylamine (9.2 g, 92 mmol), $SOCl_2$ (2.8 g, 24 mmol) and methylamine (2 M in THF) (19 mL, 38 mmol) yielded 3.1 g (94%) of the title compound as light yellow crystals. Mp 140.0–141.2 °C. ^{1}H NMR (400 MHz) δ 2.20 (s, 3H), 2.22 (s, 3H), 2.38 (s, 3H), 2.97 (d, 3H, J = 4.5 Hz), 6.97 (s, 1H), 7.12 (s, 1H). ^{13}C NMR (100 MHz) δ 19.2, 19.4, 19.6, 26.7, 128.1, 132.4, 133.4, 133.8, 133.9, 138.5, 170.1. HRFABMS calcd for $C_{11}H_{15}NO$ (M+H) m/z 178.1232, found 178.1280.

4.3.9. 3-Ethyl-3-phenyl-isochromane-1-one (4).[39] 2,*N*-Dimethylbenzamide (0.5 g, 3.4 mmol) was dissolved in THF (10 mL) and *n*-BuLi (1.6 M in hexanes) (4.6 mL, 7.4 mmol) was added slowly at rt. After 1 h, propiophenone (0.45 g, 3.4 mmol) was added to the intense red solution and the mixture was stirred over night. The reaction mixture was poured into a saturated aqueous NH_4Cl solution (twice the THF volume) and extracted twice with EtOAc. The combined organic phases were washed with brine and concentrated. The crude oil was dissolved in 1,2-dichlorobenzene and heated to 105 °C for 48 h. After cooling, the mixture was diluted with EtOAc/hexane (5:95) and applied directly to a flash column. After flash chromatography using EtOAc/hexane (5:95) as eluent, the fractions containing the product were concentrated to afford the title compound (0.35 g, 42%) as a light yellow oil. ^{1}H NMR (500 MHz) δ 0.85 (t, 3H, J = 7.6 Hz), 2.01–2.07 (m, 2H), 3.44 (s, 2H), 7.13–7.26 (m, 5H), 7.31–7.34 (m, 2H), 7.40–7.44 (m, 1H), 7.96 (dd, 1H, J = 0.8, 7.6 Hz). ^{13}C NMR (125 MHz) δ 7.9, 35.7, 37.1, 86.4, 125.3 (2 C:s), 127.3, 127.4, 127.6, 128.3 (2 C:s), 128.4, 129.9, 133.8, 137.8, 141.8, 164.1.

4.4. General procedure for the synthesis of 3,4-dihydroisochromanones 5–36

The benzamide was dissolved in THF (15 mL/g) and *n*-BuLi (2.2 equiv) was added slowly at room temperature. After 1 h, the ketone (0.5 equiv) was added to the intense red solution and the mixture was stirred over night. The reaction mixture was poured into a saturated aqueous NH_4Cl solution (twice the THF volume) and extracted twice with EtOAc. The combined organic phases were washed with brine and concentrated. The crude oil was dissolved in 1,2-dichlorobenzene and heated to 105 °C for 48 h. After cooling, the 1,2-dichlorobenzene was either distilled off, or the solution was diluted with CH_2Cl_2 and applied directly to a flash column. After flash chromatography (CH_2Cl_2/MeOH/triethylamine; 94:5:1) the fractions containing product were pooled and concentrated and the resulting oil was dissolved in diethyl ether. After filtration HCl_{ether} was added to the filtrate. The resulting crystals were recrystallized from CH_2Cl_2/diethyl ether to afford the title compounds as white solids. All products were >99% pure according to HPLC.

4.4.1. 3-(2-Dimethylaminoethyl)-3-phenyl-isochroman-1-one HCl (5).[22] Compound **3a** (1 g, 6.7 mmol) and **2a** (0.55 g, 3 mmol) yielded 100 mg (10%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.63–2.81 (m, 9H), 3.18–3.26 (m, 1H), 3.50 (s, 2H), 7.14, (d, 1H, J = 7.6 Hz), 7.19–7.22 (m, 1H), 7.26–7.35 (m, 5H), 7.44 (dd, 1H, J = 1.2, 7.6 Hz), 7.97 (d, 1H, J = 7.6 Hz), 12.30 (br s, 1H). ^{13}C NMR (100 MHz) δ 36.5 (2 C:s), 39.1, 42.3, 53.3, 83.9, 124.4, 124.7 (2 C:s), 127.8, 127.9, 128.2, 129.1 (2 C:s), 129.9, 134.4, 136.5, 139.6, 164.3. Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.4; H, 8.0; N, 8.4.

4.4.2. 3-(2-Dimethylaminoethyl)-5-methoxy-3-phenyl-isochroman-1-one HCl (6). Compound **3f** (1 g, 5.6 mmol) and **2a** (0.55 g, 3 mmol) yielded 175 mg (19%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.62–2.80 (m, 9H), 3.14–3.19 (m, 1H), 3.28 (d, 1H, ^2J = 17 Hz), 3.64 (d, 1H, ^2J = 17 Hz), 3.83 (s, 3H), 7.01 (d, 1H, J = 8.0 Hz), 7.23–7.39 (m, 6H), 7.61 (d, 1H, J = 8.0 Hz), 12.35 (br s, 1H). ^{13}C NMR (125 MHz) δ 32.6, 36.4, 42.5, 43.8, 53.4, 55.8, 83.7, 115.5, 121.4, 124.7 (2 C:s), 125.3, 125.5, 128.1, 128.2, 129.1 (2 C:s), 140.2, 155.9, 164.4. HRTofMS calcd for $C_{20}H_{24}NO_3$ (M+H) m/z 326.1756, found 326.1760.

4.4.3. 3-(2-Dimethylaminoethyl)-5-fluoro-3-phenyl-isochroman-1-one HCl (7). Compound **3g** (0.5 g, 3.0 mmol) and **2a** (0.3 g, 1.5 mmol) yielded 245 mg (46%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.66–2.81 (m, 9H), 3.20–3.25 (m, 1H), 3.37 (d, 1H, ^2J = 16.5 Hz), 3.70 (d, 1H, ^2J = 16.5 Hz), 7.20–7.33 (m, 7H), 7.80 (d, 1H, J = 8.0 Hz), 12.60 (br s, 1H). ^{13}C NMR (125 MHz) δ 31.9, 36.7, 42.7, 43.7, 53.2, 83.9, 120.9, 121.1, 123.8 (d, $^2J_{CF}$ = 25.5 Hz), 124.7 (2 C:s), 125.7, 126.2, 128.6 (d, $^2J_{CF}$ = 25.5 Hz), 129.3 (2 C:s), 139.4, 158.9 (d, $^1J_{CF}$ = 246.6 Hz), 163.3. Anal. Calcd for $C_{19}H_{21}ClFNO_2$: C, 65.2; H, 6.1; N, 4.0. Found: C, 65.0; H, 6.1; N, 4.2.

4.4.4. 3-(2-Dimethylaminoethyl)-5-methyl-3-phenyl-isochroman-1-one HCl (8). Compound **3b** (1 g, 6.1 mmol) and **2a** (0.55 g, 3 mmol) yielded 250 mg (24%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.27 (s, 3H), 2.65–2.83 (m, 9H), 3.18–3.22 (m, 1H), 3.31 (d, 1H, ^2J = 16.4 Hz), 3.52 (d, 1H, ^2J = 16.4 Hz), 7.16–7.36 (m, 7H), 7.86 (d, 1H, J = 7.6 Hz), 12.30 (br s, 1H). ^{13}C NMR (100 MHz) δ 18.9, 36.2, 36.6, 42.5, 44.0, 53.4, 83.3, 124.4 (2 C:s), 124.6, 127.3, 127.8, 128.3, 129.2 (2 C:s), 135.1, 135.5, 135.8, 140.0, 164.8. HRTofMS calcd for $C_{20}H_{24}NO_2$ (M+H) m/z 310.1807, found 310.1811.

4.4.5. 3-(2-Dimethylaminoethyl)-6-methyl-3-phenyl-isochroman-1-one HCl (9). Compound **3c** (1 g, 6.1 mmol) and **2a** (0.55 g, 3 mmol) yielded 200 mg (19%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.31 (s, 3H), 2.63–2.80 (m, 9H), 3.15–3.22 (m, 1H), 3.40–3.48 (m, 2H), 6.94 (s, 1H), 7.08 (d, 1H, J = 8.0 Hz), 7.21–7.35 (m, 5H), 7.86 (d, 1H,

J = 8.0 Hz), 12.40 (br s, 1H). ^{13}C NMR (125 MHz) δ 21.7, 36.4, 39.2, 42.5, 43.8, 53.4, 83.8, 121.7, 124.8 (2 C:s), 128.2, 128.4, 128.8 (2 C:s), 129.1, 130.0, 136.6, 139.9, 145.6, 164.5. Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.5; H, 7.0; N, 4.0. Found: C, 69.4; H, 7.1; N, 4.0.

4.4.6. 3-(2-Dimethylaminoethyl)-7-methyl-3-phenyl-isochroman-1-one HCl (10). Compound **3d** (1 g, 6.1 mmol) and **2a** (0.55 g, 3 mmol) yielded 250 mg (24%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.30 (s, 3H), 2.64–2.81 (m, 9H), 3.16–3.22 (m, 1H), 3.46 (s, 2H), 7.04 (d, 1H, J = 7.6 Hz), 7.20–7.36 (m, 6H), 7.80 (s, 1H), 12.25 (br s, 1H). ^{13}C NMR (100 MHz) δ 20.9, 36.5, 38.8, 42.6, 43.9, 53.4, 84.0, 124.1, 124.7 (2 C:s), 127.7, 128.3, 129.1 (2 C:s), 130.2, 133.5, 135.4, 137.8, 139.8, 164.7. HRTofMS calcd for $C_{20}H_{24}NO_2$ (M+H) m/z 310.1807, found 310.1826.

4.4.7. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-5-methoxy-isochroman-1-one HCl (11). Compound **3f** (1 g, 5.6 mmol) and **2b** (0.59 g, 2.8 mmol) yielded 130 mg (13%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.58–2.76 (m, 9H), 3.01–3.12 (m, 1H), 3.21 (d, 1H, ^2J = 17.2 Hz), 3.53 (d, 1H, ^2J = 17.2 Hz), 3.77 (s, 3H), 6.96 (dd, 1H, J = 8.4, 1.2 Hz), 7.20–7.28 (m, 5H), 7.54 (dd, 1H, J = 8.0, 0.8 Hz), 12.50 (br s, 1H). ^{13}C NMR (100 MHz) δ 32.5, 36.2, 42.4, 43.9, 53.3, 55.8, 83.4, 115.6, 121.4, 125.0, 125.1, 126.2 (2 C:s), 128.3, 129.3 (2 C:s), 134.2, 138.8, 155.8, 164.1. Anal. Calcd for $C_{20}H_{23}Cl_2NO_3 \times 0.5\ H_2O$: C, 59.3; H, 6.0; N, 3.5. Found: C, 59.6; H, 5.8; N, 3.6.

4.4.8. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-4-methyl-isochroman-1-one HCl (12). Compound **3h** (1.0 g, 6.1 mmol) and **2b** (0.62 g, 3.1 mmol) yielded 120 mg (18%) of the title compd. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 0.86 (d, 3H, J = 7.0 Hz), 2.41–2.53 (m, 7H), 2.55–2.61 (m, 1H), 2.76–2.89 (m, 2H), 3.11–3.14 (q, 1H, J = 7.0 Hz), 7.30–7.35 (m, 1H), 7.42–7.53 (m, 5H), 7.64–7.66 (m, 1H), 8.12 (d, 1H, J = 7.4 Hz), 12.80 (br s, 1H). ^{13}C NMR (100 MHz) δ 19.2, 34.0, 41.5, 42.3, 44.6, 53.7, 86.0, 122.5, 126.5 (2 C:s), 128.2, 128.3, 129.6 (2 C:s), 130.5, 134.4, 135.4, 136.9, 144.1, 163.4. Anal. Calcd for $C_{20}H_{23}Cl_2NO_2 \times H_2O$: C, 60.3; H, 6.3; N, 3.5. Found: C, 60.3; H, 5.9; N, 3.5.

4.4.9. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-5-methyl-isochroman-1-one HCl (13). Compound **3b** (1 g, 6.1 mmol) and **2b** (0.65 g, 3.1 mmol) yielded 260 mg (23%) of the title compound. Mp 243.6–244.3 °C. ^{1}H NMR (400 MHz) δ 2.28 (s, 3H), 2.65–2.90 (m, 9H), 3.18–3.22 (m, 1H), 3.32 (d, 1H, ^2J = 16.5 Hz), 3.48 (d, 1H, ^2J = 16.5 Hz), 7.21–7.37 (m, 6H), 7.88 (d, 1H, 6.5 Hz), 12.70 (br s, 1H). ^{13}C NMR (100 MHz) δ 19.2, 36.1, 36.6, 42.8, 44.3, 53.4, 81.3, 124.5 (2 C:s), 126.4, 128.0 (2 C:s), 128.2, 129.6, 134.6, 135.1, 135.8, 136.3, 138.9, 164.8. Anal. Calcd for $C_{20}H_{23}Cl_2NO_2$: C, 60.2; H, 6.1; N, 3.7. Found: C, 60.2; H, 6.3; N, 4.0.

4.4.10. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-6-methyl-isochroman-1-one HCl (14). Compound **3c** (1 g, 6.1 mmol) and **2b** (0.65 g, 3.1 mmol) yielded 180 mg (20%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.31 (s, 3H), 2.65–2.82 (m, 9H), 3.13–3.20 (m, 1H), 3.32–3.46 (m, 2H), 7.04 (d, 1H, J = 8.0 Hz), 7.26–7.31 (m, 5H), 7.80 (br s, 1H), 12.30 (br s, 1H). ^{13}C NMR (100 MHz) δ 21.1, 36.3, 39.8, 42.5, 44.0, 53.3, 83.6, 123.9, 124.3 (2 C:s), 126.7, 129.3 (2 C:s), 130.3, 133.3, 134.3, 135.4, 138.0, 139.4, 164.4. Anal. Calcd for $C_{20}H_{23}Cl_2NO_2 \times 0.25\ H_2O$: C, 62.4; H, 6.2; N, 3.6. Found: C, 62.6; H, 6.0; N, 3.7.

4.4.11. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-7-methyl-isochroman-1-one HCl (15). Compound **3d** (1 g, 6.1 mmol) and **2b** (0.65 g, 3.1 mmol) yielded 150 mg (13%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.33 (s, 3H), 2.63–2.84 (m, 9H), 3.17–3.21 (m, 1H), 3.38–3.49 (m, 2H), 7.05 (d, 1H, J = 7.8 Hz), 7.29–7.32 (m, 5H), 7.82 (d, 1H, J = 2.0 Hz), 12.70 (br s, 1H). ^{13}C NMR (100 MHz) δ 21.8, 35.4, 38.9, 41.5, 44.9, 53.3, 83.7, 122.9, 126.3 (2 C:s), 127.9, 129.3 (2 C:s), 130.3, 133.3, 134.3, 135.6, 137.1, 138.5, 164.4. Anal. Calcd for $C_{20}H_{23}Cl_2NO_2$: C, 63.2; H, 6.1; N, 3.7. Found: C, 63.1; H, 6.2; N, 3.9.

4.4.12. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-6,7-dimethyl-isochroman-1-one HCl (16). Compound **3i** (0.5 g, 2.8 mmol) and **2b** (0.30 g, 1.4 mmol) yielded 200 mg (40%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.21 (s, 3H), 2.23 (s, 3H), 2.58–2.82 (m, 9H), 3.13–3.20 (m, 1H), 3.31–3.43 (m, 2H), 6.89 (s, 1H), 7.28–7.30 (m, 4H), 7.78 (s, 1H), 12.75 (br s, 1H). ^{13}C NMR (100 MHz) δ 19.4, 38.9, 36.3, 38.9, 42.5, 44.2, 53.5, 83.7, 121.7, 126.4 (2 C:s), 129.1, 129.4 (2 C:s), 130.9, 133.8, 134.3, 136.9, 138.7, 144.9, 164.5.

(−)-**16**: preparative HPLC t_R 19.6 min. $[\alpha]_D$ −51.18 (c 0.21, MeOH). Anal. Calcd for $C_{21}H_{25}Cl_2NO_2 \times 1/4\ H_2O$: C, 63.2; H, 6.4; N, 3.5. Found: C, 63.2; H, 6.7; N, 3.3.

(+)-**16**: preparative HPLC t_R 26.5 min. $[\alpha]_D$ +50.84 (c 0.12, MeOH). Anal. Calcd for $C_{21}H_{25}Cl_2NO_2 \times 1/2\ H_2O$: C, 62.5; H, 6.5; N, 3.5. Found: C, 62.3; H, 6.5; N, 3.5.

4.4.13. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-8-methyl-isochroman-1-one HCl (17). Compound **3e** (0.42 g, 2.6 mmol) and **2b** (0.27 g, 1.3 mmol) yielded 100 mg (22%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.59–2.80 (m, 12H), 3.16–3.25 (m, 1H), 3.38–3.51 (m, 2H), 6.95 (d, 1H, J = 8.8 Hz), 7.09 (d, 1H, J = 8.4 Hz), 7.21–7.47 (m, 5H), 12.38 (br s, 1H). ^{13}C NMR (100 MHz) δ 22.1, 29.4, 36.2, 39.7, 42.6, 43.9, 82.7, 122.7, 125.8, 126.2 (2 C:s), 129.4 (2 C:s), 131.5, 133.5, 134.3, 137.2, 138.4, 143.1, 163.6. HRFABMS calcd for $C_{20}H_{22}ClNO_2$ (M+H) m/z 344.1417, found 344.1420.

4.4.14. 3-(4-Chlorophenyl)-3-(2-diethylaminoethyl)isochroman-1-one HCl (18). Compound **3a** (1.0 g, 6.7 mmol) and **2g** (0.79 g, 3.3 mmol) yielded 500 mg (16%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 1.24 (t, 3H, J = 7.2 Hz), 1.36 (t, 3H,

J = 7.6 Hz), 2.66–3.19 (m, 8 H), 3.42–3.55 (m, 2H), 7.16 (d, 1H, J = 7.6 Hz), 7.29–7.35 (m, 5H), 7.47–7.51 (m, 1H), 8.01 (dd, 1H, J = 1.2, 8.0 Hz), 12.10 (br s, 1H). ^{13}C NMR (100 MHz) 8.1, 8.4, 35.8, 39.3, 45.9, 47.3, 47.4, 84.0, 124.3, 126.5 (2 C:s), 128.0, 128.1, 129.4 (2 C:s), 130.2, 134.4, 134.8, 136.5, 138.6, 164.1. HRTofMS calcd for $C_{21}H_{24}ClNO_2$ (M+H) m/z 358.1574, found 358.1577.

4.4.15. 3-(4-Chlorophenyl)-3-[2-(pyrrolidin-1-yl)ethyl]isochroman-1-one HCl (19). Compound **3a** (1 g, 6.7 mmol) and **2c** (0.78 g, 3.3 mmol) yielded 340 mg (24%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 1.66–1.77 (m, 4H), 2.10–2.18 (m, 3H), 2.30–2.38 (m, 4H), 2.44–2.47 (m, 1H), 3.40–3.46 (m, 2H), 7.11–7.30 (m, 6H), 7.40–7.45 (m, 1H), 7.96 (d, 1H, J = 8.0 Hz), 12.10 (br s, 1H). ^{13}C NMR (100 MHz) 23.3 (2 C:s), 38.0, 41.2, 50.5, 54.1 (2 C:s), 84.8, 125.0, 126.6 (2 C:s), 127.6, 127.7, 128.6 (2 C:s), 129.9, 133.3, 134.0, 137.3, 140.4, 164.7. HRTofMS calcd for $C_{21}H_{23}ClNO_2$ (M+H) m/z 356.1417, found 356.1421.

4.4.16. 3-(4-Chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]isochroman-1-one HCl (20). Compound **3a** (1 g, 6.7 mmol) and **2d** (0.83 g, 3.3 mmol) yielded 480 mg (38%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 1.29–1.32 (m, 1H), 1.67–1.82 (m, 3H), 2.13–2.20 (m, 2H), 2.40–2.53 (m, 2H), 2.63–2.69 (m, 2H), 2.88–2.93 (m, 1H), 3.01–3.08 (m, 1H), 3.23–3.26 (m, 1H), 3.35–3.50 (m, 3H), 7.09 (d, 1H, J = 7.2 Hz), 7.20–7.29 (m, 5H), 7.41–7.45 (m, 1H), 7.95 (dd, 1H, J = 0.8, 8.0 Hz), 12.10 (br s, 1H).^{13}C NMR (100 MHz) δ 22.0, 22.4, 22.5, 35.2, 39.2, 52.7, 52.9, 54.6, 83.9, 124.2, 126.4 (2 C:s), 127.9, 128.0, 129.3 (2 C:s), 130.0, 134.2, 134.6, 136.4, 138.5, 164.2. HRTofMS calcd for $C_{22}H_{25}ClNO_2$ (M+H) m/z 370.1574, found 370.1576.

4.4.17. 3-(4-Chlorophenyl)-3-[2-(morpholin-1-yl)ethyl]-isochroman-1-one HCl (21).[22] Compound **3a** (1 g, 6.7 mmol) and **2e** (0.85 g, 3.3 mmol) yielded 230 mg (19%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.69–2.84 (m, 4H), 2.93–2.97 (m, 1H), 3.12–3.21 (m, 2H), 3.44–3.49 (m, 3H), 3.89–3.99 (m, 2H), 4.12–4.26 (m, 2H), 7.17 (d, 1H, J = 7.5 Hz), 7.30–7.36 (m, 5H), 7.51 (dd, 1H, J = 7.5, 8.0 Hz), 8.02 (d, 1H, J = 8.0 Hz), 13.20 (br s, 1H). ^{13}C NMR (125 MHz) δ 34.9, 39.3, 51.6, 53.0, 53.2, 63.5 (2 C:s), 83.7, 124.2, 126.4 (2 C:s), 127.9, 128.1, 129.4 (2 C:s), 130.1, 134.4, 134.7, 136.2, 138.3, 164.1. Anal. Calcd for $C_{21}H_{23}Cl_2NO_3 \times H_2O$: C, 59.2; H, 5.9; N, 3.3. Found: C, 59.1; H, 5.7; N, 3.5.

4.4.18. 3-(4-Chlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-ethyl]isochroman-1-one HCl (22).[22] Compound **3a** (1 g, 6.7 mmol) and **2f** (0.88 g, 3.3 mmol) yielded 300 mg (22%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.12–2.61 (m, 15H), 3.46–3.56 (m, 2H), 7.19–7.32 (m, 6H), 7.48 (t, 1H, J = 6.5 Hz), 7.99 (d, 1H, J = 6.5 Hz), 12.40 (s, 1H). ^{13}C NMR (125 MHz) δ 26.2, 37.9, 39.3, 45.8, 46.6, 52.5, 53.1, 54.9, 84.9, 126.5, 127.4 (2 C:s), 128.3 (2 C:s), 128.6, 128.7, 131.3, 132.4, 133.2, 138.4, 144.7, 170.5. HRTofMS calcd for $C_{22}H_{26}ClN_2O_2$ (M+H) m/z 385.1683, found 385.1694.

4.4.19. 3-(2-Dimethylaminoethyl)-3-(4-trifluoromethylphenyl)isochroman-1-one HCl (23). Compound **3a** (0.66 g, 4.4 mmol) and **2h** (0.54 g, 2.2 mmol) yielded 320 mg (40%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.69–2.86 (m, 9H), 3.21–3.28 (m, 1H), 3.48–3.58 (m, 2H), 7.16 (d, 1H, J = 7.0 Hz), 7.31 (t, 1H, J = 7.0 Hz), 7.46–7.58 (m, 5H), 7.98 (d, 1H, J = 7.2 Hz), 12.45 (br s, 1H). ^{13}C NMR (125 MHz) δ 36.2, 38.8, 42.6, 43.7, 53.2, 83.6, 123.5 (q, $^1J_{CF}$ = 270.0 Hz), 124.1 (2 C:s), 125.4, 126.1, 128.1 (2 C:s, q, $^3J_{CF}$ = 5.0 Hz), 130.2, 130.5 (q, $^2J_{CF}$ = 32.6 Hz), 134.7, 136.1 (2 C:s), 144.4, 163.9. Anal. Calcd for $C_{20}H_{21}ClF_3NO_2$: C, 60.1; H, 5.3; N, 3.5. Found: C, 60.5; H, 5.6; N, 3.6.

4.4.20. 3-(2-Dimethylaminoethyl)-3-(4-phenoxyphenyl)-isochroman-1-one HCl (24). Compound **3a** (1.2 g, 8.0 mmol) and **2i** (1.08 g, 4.0 mmol) yielded 650 mg (38%) of the title compound. Mp 245.2–246.3 °C. ^{1}H NMR (400 MHz) δ 2.60–2.84 (m, 8H), 3.06–3.25 (m, 2H), 3.43–3.52 (m, 2H), 6.89 (d, 2H, J = 5.6 Hz), 6.96 (d, 2H, J = 8.1 Hz), 7.11–7.18 (m, 2H), 7.24–7.35 (m, 5H), 7.47–7.51 (m, 1H), 8.00 (d, 1H, J = 8.0 Hz), 12.65 (br s, 1H). ^{13}C NMR (100 MHz) δ 36.6, 39.3, 42.6, 44.1, 53.5, 83.8, 118.4 (2 C:s), 119.7 (2 C:s), 119.9, 124.2, 124.5, 126.4 (2 C:s), 128.1, 129.9 (2 C:s), 130.2, 133.9, 134.6, 136.7, 155.9, 157.7, 164.4. Anal. Calcd for $C_{25}H_{26}ClNO_3 \times 1/3\ H_2O$: C, 69.8; H, 6.3; N, 3.3. Found: C, 70.0; H, 6.2; N, 3.3.

4.4.21. 3-(2-Dimethylaminoethyl)-3-(4-methylphenyl)-isochroman-1-one HCl (25). Compound **3a** (0.76 g, 5.1 mmol) and **2j** (0.49 g, 2.5 mmol) yielded 150 mg (17%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.25 (s, 3H), 2.64–2.76 (m, 9H), 3.15–3.21 (m, 1H), 3.47–3.48 (m, 2H), 7.01 (d, 2H, J = 8.1 Hz), 7.14 (d, 1H, J = 7.3 Hz), 7.19–7.31 (m, 3H), 7.43–7.47 (m, 1H), 7.99 (d, 1H, J = 7.7 Hz) 12.80 (br s, 1H). ^{13}C NMR (100 MHz) δ 20.1, 36.5, 39.3, 42.6, 43.9, 53.7, 84.1, 124.5, 124.8 (2 C:s), 128.0 (2 C:s), 129.9 (2 C:s), 130.1, 134.6, 136.7, 136.8, 138.3, 164.5. Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.5; H, 7.0; N, 4.1. Found: C, 69.4; H, 7.0; N, 4.3.

4.4.22. 3-(2-Dimethylaminoethyl)-3-(4-fluorophenyl)isochroman-1-one HCl (26).[22] Compound **3a** (0.24 g, 1.6 mmol) and **2k** (0.16 g, 0.82 mmol) yielded 100 mg (38%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.62–2.87 (m, 9H), 3.15–3.24 (m, 1H), 3.43–3.53 (m, 2H), 6.98–7.02 (m, 2H), 7.16 (d, 1H, J = 7.4 Hz), 7.30–7.37 (m, 3H), 7.46–7.51 (m, 1H), 8.00 (dd, 1H, J = 1.2, 8.0 Hz), 12.65 (br s, 1H). ^{13}C NMR (100 MHz) δ 36.5, 39.4, 42.6, 44.1, 53.5, 83.8, 116.1, 116.4, 117.8 (d, $^1J_{CF}$ = 316.5 Hz), 124.3, 126.8 (2 C:s) (d, $^3J_{CF}$ = 10.7 Hz), 128.0 (2 C:s) (d, $^2J_{CF}$ = 18.7 Hz), 130.2, 134.8, 135.7, 136.5, 164.2. HRTofMS calcd for $C_{19}H_{20}FNO_2$ (M+H) m/z 314.1556, found 314.1542.

4.4.23. 3-(2-Dimethylaminoethyl)-3-(4-methoxyphenyl)-isochroman-1-one HCl (27).[40] Compound **3a** (0.89 g, 6.0 mmol) and **2l** (0.62 g, 3.0 mmol) yielded 160 mg (16%) of the title compound. Mp > 250 °C (decomp).

^{1}H NMR (500 MHz) δ 2.62–2.80 (m, 9H), 3.16–3.22 (m, 1H), 3.44–3.52 (m, 2H), 3.76 (s, 3H), 6.83 (d, 2H, J = 8.2 Hz), 7.17 (d, 1H, J = 7.0 Hz), 7.25–7.29 (m, 2H), 7.30–7.34 (m, 1H), 7.47–7.50 (m, 1H), 8.01 (d, 1H, J = 8.1 Hz), 12.85 (br s, 1H). ^{13}C NMR (125 MHz) δ 36.8, 39.6, 42.7, 44.2, 53.7, 55.4, 84.1, 114.7, 124.7, 126.3 (2 C:s), 127.8, 128.1 (2 C:s), 130.2, 131.7, 134.7, 136.9, 159.5, 164.7.

4.4.24. 3-(3-Chlorophenyl)-3-(2-dimethylaminoethyl)-isochroman-1-one HCl (28). Compound **3a** (1.2 g, 8.0 mmol) and **2m** (0.83 g, 4.0 mmol) yielded 160 mg (11%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.66–2.83 (m, 9H), 3.16–3.23 (m, 1H), 3.44–3.54 (m, 2H), 7.19 (d, 1H, J = 7.2 Hz), 7.22–7.38 (m, 5H), 7.48–7.52 (m, 1H), 8.02 (d, 1H, J = 7.6 Hz), 12.70 (s, 1H). ^{13}C NMR (100 MHz) δ 36.0, 39.0, 42.2, 43.8, 53.2, 83.5, 122.9, 124.2, 125.1, 127.9, 128.2, 128.8, 130.4, 130.7, 134.8, 135.5, 136.3, 142.2, 164.1. Anal. Calcd for $C_{19}H_{21}Cl_2NO_2$: C, 62.3; H, 5.8; N, 3.8. Found: C, 62.1; H, 5.8; N, 3.8.

4.4.25. 3-(2-Dimethylaminoethyl)-(3-methoxyphenyl)-isochroman-1-one HCl (29). Compound **3a** (0.92 g, 6.1 mmol) and **2n** (0.63 g, 3.0 mmol) yielded 190 mg (20%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.66–2.82 (m, 9H), 3.13–3.23 (m, 1H), 3.44–3.52 (m, 2H), 3.76 (s, 3H), 6.74 (dd, 1H, J = 2.2, 8.4 Hz), 6.86 (s, 1H), 6.89 (d, 1H, J = 7.7 Hz), 7.15–7.32 (m, 3H), 7.45–7.48 (m, 1H), 8.00 (d, 1H, J = 8.8 Hz), 12.75 (br s, 1H). ^{13}C NMR (100 MHz) δ 36.3, 39.2, 42.4, 44.1, 53.3, 55.2, 83.8, 111.0, 113.5, 117.1, 124.5, 128.0, 128.1, 130.1, 130.4, 134.7, 136.7, 141.4, 160.1, 164.5. HRTofMS calcd for $C_{20}H_{24}NO_3$ (M+H) m/z 326.1772, found 326.1756.

4.4.26. 3-(2-Dimethylaminoethyl)-3-(3-fluorophenyl)-isochroman-1-one HCl (30). Compound **3a** (0.3 g, 2.0 mmol) and **2o** (0.2 g, 1.0 mmol) yielded 60 mg (17%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.60–2.84 (m, 9H), 3.16–3.22 (m, 1H), 3.44–3.53 (m, 2H), 6.90–7.47 (m, 7H), 7.97 (d, 1H, J = 8.7 Hz), 12.50 (br s, 1H). ^{13}C NMR (100 MHz) δ 36.4, 38.9, 42.7, 43.9, 53.3, 83.5, 112.5 (d, $^2J_{CF}$ = 36.7 Hz), 115.4 (d, $^2J_{CF}$ = 29.8 Hz), 120.6, 124.3, 127.9, 128.1, 130.2, 131.1 (d, $^3J_{CF}$ = 9.9 Hz), 134.7, 136.3, 142.7 (d, $^3J_{CF}$ = 9.9 Hz), 163.3 (d, $^3J_{CF}$ = 275 Hz), 164.1. HRTofMS calcd for $C_{19}H_{20}FNO_2$ (M+H) m/z 314.1556, found 314.1563.

4.4.27. 3-(2-Dimethylaminoethyl)-3-(2-methoxyphenyl)-isochroman-1-one HCl (31). Compound **3a** (0.6 g, 4.1 mmol) and **2p** (0.43 g, 2.0 mmol) yielded 100 mg (15%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.52–2.74 (m, 8H), 3.17–3.27 (m, 2H), 3.44–3.47 (m, 2H), 3.96 (s, 3H), 6.81–6.88 (m, 2H), 7.09–7.28 (m, 4H), 7.41–7.44 (m, 1H), 7.98 (d, 1H, J = 7.5 Hz), 12.45 (br s, 1H). ^{13}C NMR (125 MHz) 33.2, 36.7, 42.3, 43.9, 53.7, 55.8, 84.2, 111.8, 120.7, 124.4, 126.6, 127.3, 127.6, 127.8, 129.4, 129.9, 134.3, 137.4, 155.1, 164.7. Anal. Calcd for $C_{20}H_{24}ClNO_3 \times 0.5\ H_2O$: C, 64.8; H, 6.8; N, 3.8. Found: C, 64.9; H, 6.9; N, 3.9.

4.4.28. 3-(2-Dimethylaminoethyl)-3-(1-naphthyl)isochroman-1-one HCl (32). Compound **3a** (1.3 g, 8.8 mmol) and **2q** (1.0 g, 4.4 mmol) yielded 140 mg (18%) of the title compd. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.54–2.98 (m, 8H), 3.13–3.34 (m, 2H), 3.75 (d, 1H, ^2J = 16.5 Hz), 4.03 (d, 1H, ^2J = 16.5 Hz), 7.09–7.32 (m, 4H), 7.44–7.52 (m, 3H), 7.61–7.65 (m, 1H), 7.74 (d, 1H, J = 8.1 Hz), 7.84 (d, 1H, J = 8.4 Hz), 7.96 (d, 1H, J = 7.7 Hz), 12.85 (br s, 1H). ^{13}C NMR (100 MHz) δ 35.1, 37.9, 43.0, 43.3, 53.8, 85.7, 124.3, 124.5, 124.7, 125.7, 126.1, 127.2, 128.0, 130.0, 130.1, 130.4, 133.9, 134.0, 134.6, 135.0, 137.2, 137.6, 164.4. Anal. Calcd for $C_{23}H_{24}ClNO_2H_2O$: C, 69.1; H, 6.5; N, 3.5. Found: C, 69.0; H, 6.3; N, 3.9.

4.4.29. 3-(2-Dimethylaminoethyl)-3-(2-naphthyl)isochroman-1-one HCl (33). Compound **3a** (1.3 g, 8.8 mmol) and **2r** (1.0 g, 4.4 mmol) yielded 400 mg (24%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.61 (d, 3H, J = 4.8 Hz), 2.69–2.78 (m, 5H), 2.89–2.98 (m, 1H), 3.19–3.29 (m, 1H), 3.56 (s, 2H), 7.16 (d, 1H, J = 7.7 Hz), 7.26–7.30 (m, 1H), 7.42–7.51 (m, 4H), 7.77–7.85 (m, 4H), 8.02 (d, 1H, J = 7.7 Hz), 12.75 (s, 1H). ^{13}C NMR (100 MHz) δ 36.4, 39.4, 42.7, 44.1, 53.6, 84.0, 122.0, 124.5, 124.6, 126.9, 127.0, 127.7, 128.0, 128.1, 128.4, 129.7, 130.1, 132.7, 132.9, 134.7, 136.5, 137.0, 164.5. Anal. Calcd for $C_{23}H_{24}ClNO_2 \times 0.25\ H_2O$: C, 71.5; H, 6.4; N, 3.6. Found: C, 71.7; H, 6.4; N, 3.5.

4.4.30. 3-(2-Dimethylaminoethyl)-3-(2-thienyl)isochroman-1-one HCl (34). Compound **3a** (1.5 g, 9.8 mmol) and **2s** (0.9 g, 4.9 mmol) yielded 200 mg (12%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 2.71–2.82 (m, 8H), 2.89–2.97 (m, 1H), 3.25–3.34 (m, 1H), 3.43–3.59 (m, 2H), 6.86 (dd, 1H, J = 4.0, 8.8 Hz), 6.97 (dd, 1H, J = 1.0, 4.4 Hz), 7.17–7.22 (m, 2H), 7.31–7.34 (m, 1H), 7.48–7.52 (m, 1H), 8.00 (dd, 1H, J = 1.5, 8.0 Hz), 12.70 (s, 1H). ^{13}C NMR (100 MHz) δ 37.6, 40.3, 42.8, 43.8, 53.4, 82.7, 124.2, 125.4, 125.9, 127.5, 128.1, 128.2, 130.3, 134.6, 136.5, 143.8, 163.7. Anal. Calcd for $C_{17}H_{20}ClNO_2S$: C, 60.4; H, 6.0; N, 4.1. Found: C, 60.1; H, 6.0; N, 4.1.

4.4.31. 3-(4-Chlorophenyl)-3-(dimethylaminomethyl)-isochroman-1-one HCl (35). Compound **3a** (1 g, 6.7 mmol) and **2t** (0.66 g, 3.4 mmol) yielded 175 mg (16%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (500 MHz) δ 2.88 (s, 3H), 3.13 (s, 3H), 3.50 (d, 1H, J = 14.5 Hz), 3.74 (d, 1H, J = 14.5 Hz), 3.94 (d, 1H, J = 16.5 Hz), 4.30 (d, 1H, J = 16.5 Hz), 7.24–7.29 (m, 4H), 7.42–7.48 (m, 3H), 7.91 (d, 1H, J = 7.0 Hz), 12.4 (s, 1H). ^{13}C NMR (125 MHz) δ 35.1, 44.5, 46.7, 65.2, 83.2, 124.0, 127.1 (2 C:s), 128.0, 128.2, 129.5 (2 C:s), 130.1, 134.8, 135.2, 136.4, 137.1, 163.2. Anal. Calcd for $C_{18}H_{19}Cl_2NO_2$: C, 61.4; H, 5.5; N, 4.0. Found: C, 61.5; H, 5.5; N, 3.9.

4.4.32. 3-(4-Chlorophenyl)-3-(3-dimethylaminopropyl)-isochroman-1-one HCl (36). Compound **3a** (0.7 g, 4.7 mmol) and **2u** (0.53 g, 2.4 mmol) yielded 250 mg (27%) of the title compound. Mp > 250 °C (decomp). ^{1}H NMR (400 MHz) δ 1.76–1.83 (m, 1H), 1.90–1.99

(m, 1H), 2.16–2.34 (m, 2H), 2.62 (d, 3H, $J = 5.5$ Hz), 2.77 (d, 3H, $J = 6.2$ Hz), 2.92–2.99 (m, 2H), 3.42–3.56 (m, 2H), 7.17 (d, 1H, $J = 8.4$ Hz), 7.23–7.36 (m, 5H), 7.44–7.49 (m, 1H), 7.97 (d, 1H, $J = 9.2$ Hz), 12.45 (s, 1H). ^{13}C NMR (100 MHz) 18.7, 37.9, 39.1, 42.2, 43.4, 57.6, 84.9, 124.5, 126.5 (2 C:s), 127.9, 128.0 (2 C:s), 129.9, 130.0, 133.8, 134.5, 137.0, 139.8, 164.8. HRFABMS calcd for $C_{20}H_{22}ClNO_2$ (M+H) *m*/*z* 344.1417, found 344.1390.

4.5. Biological activity

4.5.1. R-SAT-testing. R-SAT™ assays for pharmacological testing were performed as previously described,[27–30] with the following modifications. NIH-3T3 cells were grown to 80% confluence in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% bovine calf serum (Hyclone) and 1% penicillin/streptomycin/glutamine (Invitrogen). Cells were transfected in rollerbottles for 18 h with the human urotensin II receptor and the β-galactosidase marker. After the 18 h transfection, cells were trypsinized, harvested, and frozen. Aliquots of frozen cell batches were thawed and tested for response to control compound to perform quality control before initiation of pharmacological testing, ensuring the correct pharmacological response and sufficient sensitivity. To initiate the pharmacological assay, cells were thawed rapidly and prepared in DMEM media containing 0.4% calf serum (Hyclone), 30% UltraCulture (Biowhittaker), and 1% penicillin/streptomycin/glutamine (Invitrogen), and then added to half-area 96-well microtiter plates containing either test compounds or reference ligands. After a five day incubation of drug with cells in 5% ambient CO_2, media was removed and reporter enzyme activity was measured at 420 nm.

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