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Optimization of isochromanone based urotensin II receptor agonists

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ABSTRACT

A series of novel isochromanone based urotensin II receptor agonists have been synthesized and evaluated for their activity using a functional cell based assay (R-SAT). Several potent and efficacious derivatives were identified with 3-(3,4-dichlorophenyl)-6,7-dimethyl-3-(2-dimethylaminoethyl)isochroman-1-one (**28**) being the most potent compound showing an EC_{50}-value of 51 nM, thereby being the most potent compound so far within the isochromanone series. In addition, two other heterocyclic systems (isochromanes and tetrahydroisoquinolinones) were investigated and these derivatives were found to be both potent and efficacious. The activity of the isochromane derivatives implies that the carbonyl group of the isochromanone is not necessary for activity. Furthermore it was found that the geometry of the heterocycles was more important for receptor interaction than the composition of the heteroatoms present.

1. Introduction

The urotensin II receptor (UT, previously GRP14)[1] and its natural peptide ligand urotensin II (UII) have over the last years emerged as a potential therapeutic target.[2,3] The UT/UII system has been proposed to be involved in a variety of diseases, for example, type 2 diabetes,[4,5] cardiovascular diseases,[3,6] and eclampsia.[7] There are reports of non-peptidic UT modulators showing activity in vivo, for example, SB-611812 which attenuates cardiac dysfunction in rats.[8] Although there are examples of both peptide based and non-peptidergic agonists[9,10] and antagonists[11,12] there is still an urgent need for novel potent and selective non-peptidergic UT modulators to thoroughly investigate the potential of UT as a drug target.[13]

In an earlier study[9c] we reported the initial structure–activity relationships (SARs) around the isochromanone derivative AC-7954 (**1**),[9a] the first non-peptidic UT receptor agonist reported (Fig. 1). We found that the introduction of lipophilic substituents in the aromatic ring denoted A, or large substituents in the 3-position (replacements of ring B) of the isochromanone system was beneficial for activity. The activity dropped, however when the alkyl substituents on the basic nitrogen became larger than methyl.[9c] The most active compound in that study was the 6,7-dimethyl derivative FL68 (**2**) (Fig. 1).

We have also investigated a series of similar but non-heterocyclic derivatives and found that open chain amides were highly active,[9b,d,e] and that it was advantageous to introduce substituted phenyl groups in the 4-position on the benzamide moiety and allowing sterically demanding substituents replacing the B-ring. The most active compound in that series identified so far is the biphenylcarboxamide *N*-[3-(dimethylamino)-1-(2-naphthyl)propyl]-4-(4-chlorophenyl)benzamide (pEC_{50} 7.36).[9d] In the present study we have continued to explore the SAR around isochromanone based UT-receptor ligands. This has been done by expanding the series of

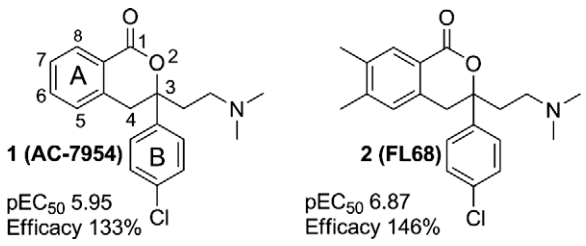

Figure 1. Compounds **1** (AC-7954) and **2** (FL68), examples of isochromanone based urotensin II receptor agonists.

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isochromanones to comprise derivatives with amino, methoxy and phenyl substituents in the A-ring and larger biphenyl substituents instead of the B-ring. We have also explored the effects of replacing the isochromanone by other heterocyclic ring systems such as isochromane or tetrahydroisoquinolinone, and of further modifying the size of the substituents around the basic amino function.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of isochromanones

The isochromanone derivatives were synthesized via the dilithiation of a 2,*N*-dimethyl-benzamide followed by the addition of a ketone and subsequent thermal ring closure (Scheme 1).[9c,14] The appropriate benzamides and β-aminoketones were synthesized according to methods described below.

2.1.2. Synthesis of benzamides

Benzoic acids **3a**–**c** were prepared by lithiation of the corresponding aromatic bromides followed by the addition of solid carbon dioxide. This procedure proceeded smoothly producing the desired acids in excellent yields (>99%) (Scheme 2). In case of the 4-bis-allylamino derivative **3a**, 4-bromo-3-methyl-aniline was first diallylated with allyl bromide in THF. After carboxylation, the product was not isolated due to its zwitterionic character. Instead, the crude product was directly converted to the corresponding benzamide using standard amide coupling reagents (EDC, DMAP), affording **4a** in 14% yield over two steps.

The other benzoic acids were converted to their corresponding methyl amides (Scheme 3) via reaction of the corresponding benzoyl chlorides with methyl amine[9c] generating amides **4b**–**e** in moderate (49%)[†] to good yields (72–99%).

The 4-phenyl derivative **4f** was obtained via a Suzuki arylation of **4e** in 76% yield (Scheme 4).

2.1.3. Synthesis of β-amino ketones

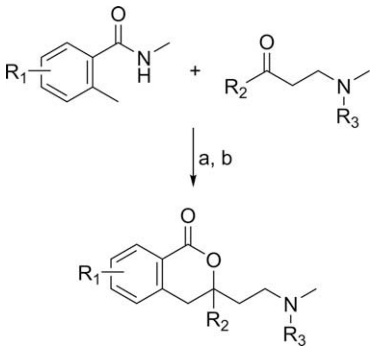
The β-amino ketones **5a**–**h** were produced via a microwave assisted Mannich reaction (Scheme 5).[15] In case of the bis-allylamino derivatives **5f** and **5g**, they were synthesized by diallylation of the corresponding 4- or 3-amino-acetophenone using allyl bromide in THF prior to the Mannich reaction. The allyl-methylamine derivative **5i** was obtained in excellent yield (94%) by dissolving 3,4′-dichloropropiophenone in THF and adding allyl-methylamine (Scheme 5).

2.1.4. Synthesis of isochromanones

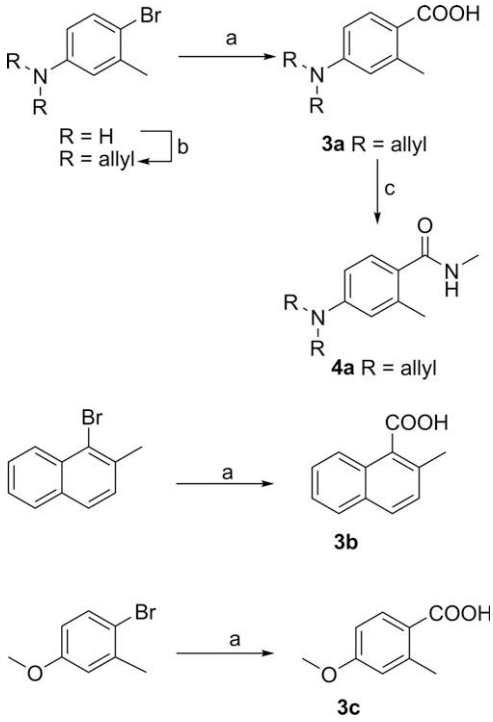
A series of 3,4-dihydroisochromanone derivatives (**6**, **11–28**) was synthesized as previously described (Scheme 1).[9c] The 2-methylbenzamides **4a–d** and **4f** were dilithiated using *n*-BuLi followed by addition of the appropriate ketone (**5a–i**). The resulting tertiary alcohols were not isolated, instead the crude product mixtures were heated in 1,2-dichlorobenzene (~105 °C) to afford the lactonization.[14] The isolated yields of isochromanone derivatives in this two-step reaction ranged between 15–79%, which were similar to results previously reported for this type of reactions.[9a,c,14] All compounds were converted to their HCl or oxalate salts for analysis and storage.

To study if smaller amino groups resulted in more active compounds the *N*-allyl group of **6** was removed using a literature procedure[16] involving $Pd(PPh_3)_4$ to afford a π-allyl complex which was reduced by 1,3-dimethylbarbituric acid to afford **7** (Scheme 6).

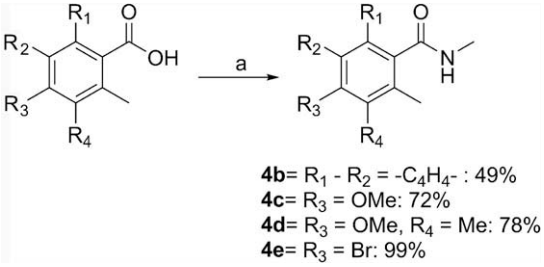
[†] For 2-methyl-1-naphthoic acid (to obtain **4b**) other protocols were examined (e.g., EDC, DMAP) but these failed to give better results and also required more elaborate purification.



Scheme 1. Reagents and conditions: (a) *n*-BuLi 2.2 equiv, THF; (b) 1,2-dichlorobenzene, Δ. 15–79% yield (20 examples).



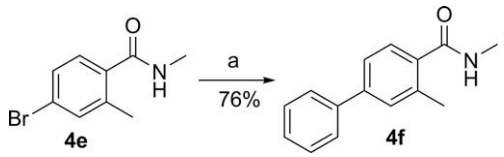
Scheme 2. Reagents and conditions: (a) *n*-BuLi CO_2(s), THF, −78 °C; (b) allyl bromide, K_2CO_3, THF, reflux, 24 h; (c) EDC, DMAP, CH_3NH_2·HCl, THF, rt, 24 h.



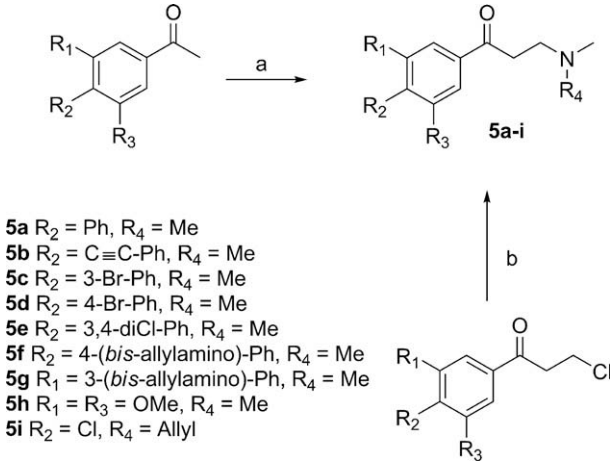
Scheme 3. Reagents and conditions: (a) $SOCl_2$, NEt_3, $MeNH_2$, THF rt, 2 h.

2.1.5. Synthesis of isochromane derivatives

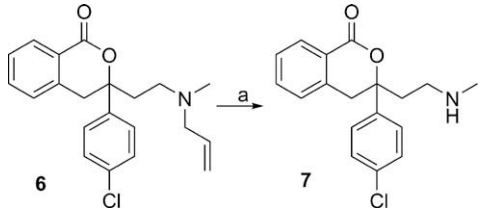
To investigate whether the carbonyl group in the isochromanone derivatives was necessary for activity it was desirable to reduce the lactone to acquire the corresponding isochromanes (Scheme 7). This was accomplished by boron trifluoride etherate



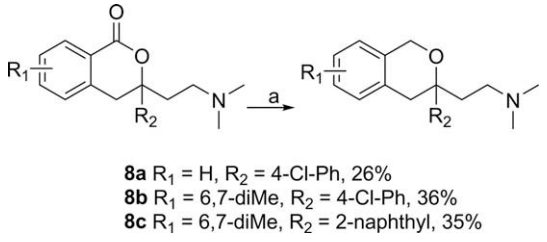
Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$ (5%), Cs_2CO_3, THF, 150 °C, 30 min.



Scheme 5. Reagents and conditions: (a) CH_2O, $HNMe_2$·HCl, dioxane, 200 °C, 10 min; (b) allyl-methylamine, THF, rt, 24 h.



Scheme 6. Reagents and conditions: (a) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, CH_2Cl_2, rt, 16 h, 49%.

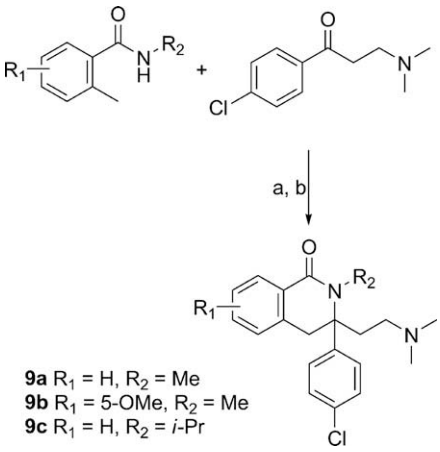


Scheme 7. Reagents and conditions: (a) BF_3OEt_2, 30 equiv, $NaBH_4$, THF, −78 °C, 16 h.

in THF followed by sodium borohydride reduction resulting in the desired products **8a–c** in modest yields (26–36%).

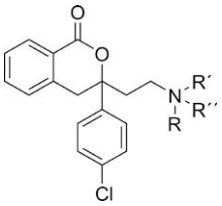
2.1.6. Synthesis of tetrahydroisoquinolinone derivatives

The tetrahydroisoquinolinone derivatives (**9a–c**) were synthesized via the same intermediary tertiary alcohol as the isochromanones,[17] but instead of heating to afford the lactonization, the resulting viscous oil was cooled and concd H_2SO_4 was added slowly under vigorous stirring. After 18 h at room temperature the solution was carefully basified using 1 M NaOH to obtain the tetrahydroisoquinolinones in low to moderate yields (29–68%) (Scheme 8).



Scheme 8. Reagents and conditions: (a) *n*-BuLi 2.2 equiv, THF; (b) H_2SO_4, 16 h, 29–68%.

Table 1
Results from in vitro testing of UII agonist activity of isochromanone derivatives with variations in the amine moiety



Compd	R	R′	R″	pEC_{50}[a]	Efficacy[b]
1 (AC-7954)	Methyl	Methyl	—	5.95 ± 0.12	133 ± 8
6	Methyl	Allyl	—	5.38 ± 0.19	77 ± 40
7	Methyl	H	—	5.71 ± 0.03	46 ± 9
10	Methyl	Methyl	Methyl	5.42 ± 0.13	118 ± 6

[a] Results were determined in R-SAT assays and are expressed as pEC_{50}-values, the negative of the log EC_{50} in molarity. Results are the average ± standard deviations of 2–5 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%.

3. Pharmacological testing

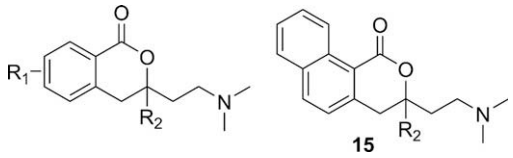
Compounds **6–28** were tested for their agonistic properties at human UII receptors using the functional R-SAT™ assay,[18] the results are shown in Tables 1–4.

4. Structure–activity relationships

4.1. The amine moiety

All natural UII peptide isoforms contain the amino acid triad Trp^7-Lys^8-Tyr^9 which is essential for activity. The amino function in the Lys side chain has been proposed to form an ionic interaction with Asp130 in the receptor, and using docking studies it was implicated that **1** is interacting similarly with the receptor.[12a] Guerrini et al. have shown that if the δ-amino group of Lys^8 in UII is dimethylated the activity drops by 0.6 log units.[12b] To investigate whether the activity of **1** would increase if the tertiary amine was converted to a secondary amine, compound **7** was synthesized. However the demethylated **7** did not show higher potency and was found to be considerably less efficacious than **1** (Table 1). In agreement with our previous findings the tertiary amine **6** with a larger allyl substituent also showed low activity (Table 1). Interestingly, the quaternary ammonium iodide salt **10** showed

Table 2
Results from in vitro testing of UII agonist activity of isochromanone derivatives with variations in the substitution pattern in the aromatic rings

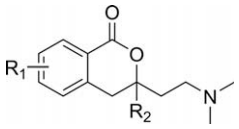


15

Compd	R_1	R_2	pEC_{50}[a]	Efficacy[b]
1 (AC-7954)	H	4-Cl-Ph	5.95 ± 0.12	133 ± 8
2[c]	6,7-Me	4-Cl-Ph	6.87 ± 0.03	146 ± 24
11	6-OMe	4-Cl-Ph	6.02 ± 0.15	165 ± 2
12	5-Me, 6-OMe	4-Cl-Ph	5.76 ± 0.02	118 ± 6
13	6-Bis-allylamino	4-Cl-Ph	6.14 ± 0.17	132 ± 7
14	6-Ph	4-Cl-Ph	NA[d]	NA[d]
15	7,8-$(CH)_4$	4-Cl-Ph	5.94 ± 0.11	124 ± 19
16	H	3-Bis-allylamino	5.62 ± 0.01	55 ± 13
17	H	4-Bis-allylamino	NA[d]	NA[d]
18	H	3,4-diCl-Ph	6.17 ± 0.01	172 ± 13
19	H	3-Br-Ph	5.53 ± 0.02	68 ± 8
20	H	4-Br-Ph	6.03 ± 0.04	127 ± 8
21	H	4-C≡C-Ph	NA[d]	NA[d]
22[c]	H	4-OPh-Ph	5.94 ± 0.26	54 ± 3
23	H	4-Ph-Ph	NA[d]	NA[d]
24	H	3-Ph-Ph	5.85 ± 0.07	50 ± 11

[a] Results were determined in R-SAT assays and are expressed as pEC_{50}-values, the negative of the log EC_{50} in molarity. Results are the average ± standard deviations of 2–5 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] Data taken from Ref. 9c.
[d] NA = No detectable activity.

Table 3
Results from in vitro testing of UII agonist activity of isochromanone derivatives with variations in the 3-position



Compd	R_1	R_2	pEC_{50}[a]	Efficacy[b]
2[c]	6,7-diMe	4-Cl-Ph	6.87 ± 0.03	146 ± 24
25	6,7-diMe	2-Naphthyl	6.83 ± 0.12	126 ± 0
26	6,7-diMe	3-OMe-Ph	5.54 ± 0.05	149 ± 7
27	6,7-diMe	3,5-diOMe-Ph	5.28 ± 0.01	156 ± 10
28	6,7-diMe	3,4-diCl-Ph	7.29 ± 0.36	98 ± 7

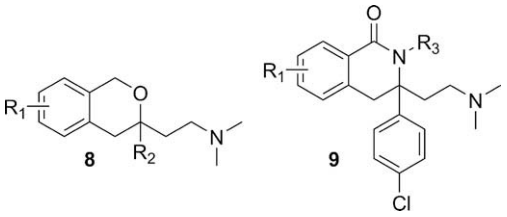
[a] Results were determined in R-SAT assays and are expressed as pEC_{50}-values, the negative of the log EC_{50} in molarity. Results are the average ± standard deviations of 2–5 determinations of the EC_{50} where each compound was tested in eight doses in triplicate.
[b] The % efficacy values are normalized to UII at 100%.
[c] Data taken from Ref. 9c.

the same potency as **6** but retained most of the efficacy of **1**. Taken together, these results suggest that the dimethylamino group is most advantageous for activity (Table 1).

4.2. Substitution in the aromatic rings

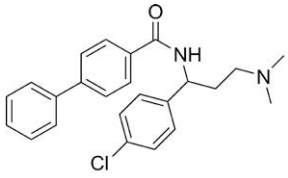
The 6-phenyl-isochromanone derivative **14** was interesting to synthesize for comparison with the corresponding highly active non-heterocyclic derivatives.[9b,d,e] Interestingly, this compound was totally devoid of activity (Table 2). This result might be rationalized by inspecting our previously suggested pharmacophore model[9b] which showed a difference in the tilting of the aromatic rings in **14** compared to that in the open chain amide FL104.

Table 4
Results from in vitro testing of UII agonist activity of isochromane and tetrahydroisoquinolinone derivatives



Compd	R_1	R_2	R_3	pEC_{50}	Efficacy
8a	H	4-Cl-Ph	—	6.30 ± 0.49	110 ± 24
8b	6,7-diMe	4-Cl-Ph	—	6.16 ± 0.06	47 ± 3
8c	6,7-diMe	2-Naphthyl	—	6.58 ± 0.39	49 ± 2
9a	H	—	Me	5.64 ± 0.06	152 ± 15
9b	5-OMe	—	Me	5.93 ± 0.05	151 ± 30
9c	H	—	*i*-Pr	5.65 ± 0.08	145 ± 17

[a]Results were determined in R-SAT assays and are expressed as pEC_{50}-values, the negative of the log EC_{50} in molarity. Results are the average ± standard deviations of 2–5 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%.



N-[1-(4-chlorophenyl)-3-(dimethylamino)propyl]-4-phenylbenzamide (FL104) pEC_{50} 7.11

As shown in FL68 (**2**, Fig. 1) introducing methyl substituents in the aromatic moiety of the isochromanone scaffold is beneficial for activity.[9c] To expand these findings and to gain more knowledge about the topology of the UT-receptor binding site some compounds containing larger and/or more flexible substituents in both aromatic rings were synthesized. As is apparent from Table 2 the 6-OMe (**11**), 5-Me,6-OMe (**12**) and the 6-bis-allylamino-(**13**) substituted compounds were approximately as potent as **1**. Thus, bulky substituents are tolerated as long as they are conformationally flexible. This means that the inactivity of **14** might be explained by the rigidity of the biphenyl system, suggesting that this compound stretches too far out in a direction occupied by the receptor. However, the naphthyl derivative **15** was equipotent with **1** indicating that there is space available in this direction of the binding pocket.

In the aromatic B-ring (Fig. 1) a derivative containing a 4-phenoxyphenyl group (as in **22**) was equipotent with a 4-chlorophenyl substituent (**1**) (Table 2).[10c] We therefore synthesized the corresponding 4-biphenyl and 4-(2-phenylethynyl)phenyl derivatives (**23** and **21**, respectively) to find that these were devoid of activity. Hence, also in this position bulky substituents are tolerated as long as they are flexible. However, the 3-substituted phenyl derivatives (3-bis-allylaminophenyl (**16**) and 3-biphenyl (**24**)) were found to be approximately equipotent in spite of the lack of flexibility in **24**. The most beneficial substitution pattern turned out to be the 3,4-dichlorophenyl group as in derivative **18**.

4.3. Additivity

When combining the best features from our previous study[9c] (e.g., 6,7-dimethyl substitution in ring A for potency and a 3-methoxy group in ring B for efficacy, or substitution of the 4-Cl-phenyl group for 2-naphthyl) (Table 3) it becomes clear that the effects are not additive. For example, the methoxy analogue **26** is substan-

tially less potent but shows similar efficacy as the parent compound **2**. This trend is even more pronounced when considering the 3′,5′-dimethoxy analogue **27** which again is less potent but as efficacious as the parent compound. This lack of additivity is also seen in the naphthyl derivative **25**, which showed no improvements over the 4-Cl-phenyl moiety. However, compound **28** with 6,7-dimethyl groups combined with the 3,4-dichlorophenyl system in the 3-position was found to be the most potent compound in this series so far, indicating that the substitution pattern in both rings is important, but that it is difficult to predict which combinations that are most advantageous.

Compound **28** was also tested using the R-SAT assay for its selectivity towards the related somatostatin subreceptors sst-1 and sst-4. The results showed that **28** was selective for UII receptors as it was inactive at sst-1 and acted as a significantly less potent partial agonist at sst-4 (**28:** maximum effect of 31% at a top concentration of 3 μM).

4.4. Other heterocycles

On similar, but non-heterocyclic derivatives it has been found that open chain amides, esters, ureas and carbamates were active, but not ether or sulfonamide derivatives.[9b] In the present study we therefore wanted to examine if the carbonyl group per se is important for receptor activation. To do this, the lactone moiety of isochromanones **1**, **2** and **25** was reduced to the corresponding isochromane derivatives (**8a–c**).

Somewhat surprisingly, it seems that the carbonyl group of **1** is not necessary for activity as **8a** is equipotent and as efficacious as its parent compound. Compounds **8b** and **8c** showed somewhat lower activity than their respective isochromanone derivatives, but are still among the most potent compounds identified in this study. Three tetrahydroisoquinolinone derivatives (**9a–c**) were also evaluated for their agonistic effect at the UT-receptor (Table 4). From the results it can be concluded that there is space left in the binding pocket for substituents in the 2-position of the central heterocyclic scaffold as **9a–c** were about as active as **1** and even somewhat more efficacious. We therefore conclude that the geometry of the bicyclic systems is more important for activity than the heteroatoms present in the ring system.

Based on the results presented above and those obtained in our earlier studies[9] the SAR of isochromanone and related compounds so far can be summarized as shown in Figure 2.

The results show that various heterocyclic scaffolds were tolerated and more importantly that the carbonyl function of the isochromanones is not necessary for activity. It can also be concluded that the dimethylamino group is superior to either larger or smaller steric bulk around the amino group. Finally it was also shown that the substitution pattern in both aromatic rings was of vital importance, although the best combination of substituents was difficult to predict.

5. Experimental procedures

5.1. General

All chemicals were purchased from Aldrich, Acros, Lancaster or Maybridge and were used without purification. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ unless otherwise stated using a JEOL JMN-ECP400 instrument. All reactions were monitored 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 apparatus and are uncorrected. Elemental analyses were performed at Kolbe Analytishe Laboratorium, Mülheim an der Ruhr, Germany. Accurate masses were measured at Biovitrum using an Agilent MSD-TOF (G1969A) connected to an Agilent 1100 HPLC system (G1312A, G4061AA, G1367A, G1316A) with a diode array detector (G1315B). The instrument is calibrated by Agilent ES-TOF tuning mix and spectra are acquired in positive electrospray mode.

5.2. Allylation of 4-bromo-3-methyl-aniline to obtain *N,N*-diallyl-4-bromo-3-methyl-aniline

Cs_2CO_3 (25.8 g, 79 mmol) and allyl bromide (6.8 mL, 79 mmol) were added to a solution of 4-bromo-3-methyl-aniline (6.7 g, 36 mmol) in THF (250 mL) and the mixture was heated to reflux for 48 h. NaOH (1 M) (250 mL) was added and the resulting solution was extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated. The resulting yellow oil was purified using flash chromatography (20% EtOAc in hexane) to afford 8.8 g (97%) of the title product as a slightly yellow oil. ^{1}H NMR δ 2.31 (s, 3H), 3.87 (d, 4H, J = 4.8 Hz), 5.12–5.17 (m, 4H), 5.77–5.87 (m, 2H), 6.39 (dd, 1H, J = 4.5, 9.9 Hz), 6.54 (d, 1H, J = 4.5 Hz), 7.26 (d, 1H, J = 9.9 Hz). ^{13}C NMR δ 23.0, 52.9 (2 C:s), 110.9, 111.7, 114.6, 116.2 (2 C:s), 132.5, 133.7 (2 C:s), 138.0, 148.0.

5.3. General procedure for the synthesis of benzoic acids 3b and c

The aryl bromide was dissolved in THF, cooled to −78 °C and *n*-BuLi (1.2 equiv) was added dropwise. To the resulting solution was added a large excess of solid carbon dioxide and the solution was slowly heated to rt. The solution was acidified using 1 M HCl and extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated to afford the desired product.

5.3.1. 2-Methyl-1-naphthoic acid (3b)

1-Bromo-2-methyl-naphthalene (2.2 g, 10 mmol) yielded 1.85 g (quant) of the title compound as white crystals. Mp 110.1–111.5 °C. ^{1}H NMR (CD_3OD) δ 2.51 (s, 3H), 7.74 (d, 1H, J = 8.4 Hz), 7.41–7.51 (m, 2H), 7.78 (d, 1H, J = 8.4 Hz), 7.82 (dd, 1H, J = 1.1,

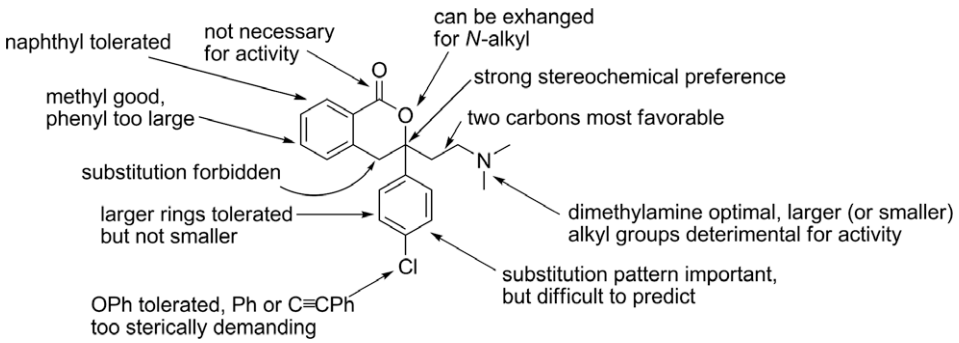


Figure 2. Summary of the SAR of isochromanone and related compounds.

8.1 Hz), 7.88 (d, 1H, J = 8.4 Hz). ^{13}C NMR (CD_3OD) δ 18.8, 124.4, 125.1, 126.4, 127.7, 128.0, 128.6, 129.6, 131.6, 131.8, 132.6, 173.3.

5.3.2. 4-Methoxy-2-methyl-benzoic acid (3c)

4-Bromo-3-methyl-anisole (5.0 g, 25 mmol) yielded 4.6 g (quant) of the title compound as white crystals. Mp 179.9–181.2 °C. ^{1}H NMR (CD_3OD) δ 2.56 (s, 3H), 3.82 (s, 3H), 6.77–6.81 (m, 2H), 7.92 (dd, 1H, J = 2.9, 7.3 Hz). ^{13}C NMR (CD_3OD) δ 21.1, 54.4, 110.6, 116.6, 121.8, 132.9, 142.9, 162.6, 169.3.

5.3.3. 4-Diallylamino-(2,*N*-dimethyl)benzamide (4a)

4-Bromo-*N*,*N*-diallyl-3-methyl-aniline (8.7 g, 33 mmol) was dissolved in THF and cooled to −78 °C and *n*-BuLi (1.2 equiv) was added dropwise. To the resulting solution was added a large excess solid carbon dioxide and the solution was slowly heated to rt. Aqueous saturated NH_4Cl was added to the solution and the mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated. The crude product (**3a**) was dissolved in THF and EDC (6.3 g, 33 mmol), DMAP (0.34 g, 3 mmol) and methylamine (2 M in THF) (20 mL, 40 mmol) were added and the mixture was stirred for 48 h. NaOH (1 M) was added and the mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated. The crude oil was purified using flash chromatography (CH_2Cl_2/MeOH/triethylamine; 94.9:5:0.1) to afford the title compound (1.1 g, 14%) as slightly brown oil that slowly solidified. ^{1}H NMR δ 2.43 (s, 3H), 2.96 (d, 3H, J = 5.2 Hz), 3.93 (d, 4H, J = 4.8 Hz), 5.12–5.18 (m, 4H), 5.71 (br s, 1H), 5.79–5.88 (m, 2H), 6.45–6.48 (m, 2H), 7.21 (d, 1H, J = 1.1 Hz). ^{13}C NMR δ 26.9, 30.4, 52.7 (2 C:s), 109.1, 114.4, 116.4 (2 C:s), 123.8, 128.7, 133.5 (2 C:s), 138.5, 149.9, 154.0.

5.4. General procedure for the synthesis of benzamides 4b–e

The benzoic acid was dissolved in THF (75 mL/g), triethylamine (4 equiv) and $SOCl_2$ (1.2 equiv) were added and the mixture was stirred for 10 min. Methylamine (1.5 equiv) was added and the mixture was stirred for an additional 15 min. Then NaOH (1 M) (twice the volume THF) was added and the resulting mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated to afford the desired product.

5.4.1. 2,*N*-Dimethyl-naphthalene-carboxamide (4b)

Compound **3b** (2.4 g, 13 mmol) yielded 1.3 g (49%) of the title compound as an off-white solid. Mp 177.7–178.6 °C. ^{1}H NMR δ 2.48 (s, 3H), 3.11 (d, 3H, J = 4.8 Hz), 5.83 (br s, 1H), 7.29 (d, 1H, J = 8.4 Hz), 7.40–7.49 (m, 2H), 7.76–7.80 (3H). ^{13}C NMR δ 19.7, 26.7, 124.6, 125.5, 126.9, 128.0, 128.4, 128.9, 130.2, 131.7, 132.2, 134.0, 170.7.

5.4.2. 4-Methoxy-2,*N*-dimethyl-benzamide (4c)

Compound **3c** (4.2 g, 25 mmol) yielded 3.2 g (72%) of the title compound as an off-white solid. Mp 96.1–97.2 °C. ^{1}H NMR δ 2.45 (s, 3H), 2.97 (d, 3H, J = 5.1 Hz), 3.80 (s, 3H), 5.70 (br s, 1H), 6.89 (dd, 1H, J = 2.6, 8.0 Hz), 6.73 (d, 1H, J = 2.6 Hz), 7.31 (d, 1H, J = 8.0 Hz). ^{13}C NMR δ 20.4, 26.7, 55.3, 110.8, 116.6, 128.6, 129.0, 138.6, 160.5, 170.5.

5.4.3. 4-Methoxy-2,3,*N*-trimethyl-benzamide (4d)

4-Methoxy-2,3-dimethyl-benzoic acid (3.6 g, 20 mmol) yielded 3.0 g (78%) of the title compound as white crystals. Mp 169.5–170.1 °C. ^{1}H NMR δ 2.14 (s, 3H), 2.32 (s, 3H), 2.97 (s, 3H), 3.82 (s, 3H), 5.68 (br s, 1H), 6.67 (d, 1H, J = 8.4 Hz), 7.16 (d, 1H, J = 8.4 Hz). ^{13}C NMR δ 11.7, 16.8, 26.8, 55.6, 107.1, 124.9, 126.2, 130.2, 135.9, 158.5, 171.6.

5.4.4. 4-Bromo-2,*N*-dimethyl-benzamide (4e)

4-Bromo-2-methyl-benzoic acid (2.5 g, 11.6 mmol) yielded 2.6 g (99%) of the title compound as light yellow crystals. Mp 113.1–113.6 °C. ^{1}H NMR δ 2.38 (s, 3H), 2.95 (d, 3H, J = 5.0 Hz), 5.99 (s, 1H), 7.15–7.18 (m, 1H), 7.27–7.31 (m, 1H), 7.35–7.37 (m, 1H). ^{13}C NMR δ 19.5, 26.6, 123.8, 128.2, 128.7, 133.8, 135.3, 138.4, 169.8.

5.4.5. 2,*N*-Dimethyl-4-phenyl-benzamide (4f)

Compound **4e** (0.1 g, 0.44 mmol), phenylboronic acid (0.07 g, 0.6 mmol), Cs_2CO_3 (0.33 g, 1 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.044 mmol) were dissolved in THF (4 mL) and heated to 150 °C for 30 min using microwave heating. The reaction mixture was filtered through Celite® and extracted using 1 M NaOH and EtOAc. The phases were separated and the water phase was extracted with EtOAc. The organic phases were combined, washed with water and brine and concentrated. The crude product was purified using flash chromatography (5% EtOAc in hexane) to yield 75 mg (76%) of the title compound as a viscous oil. ^{1}H NMR δ 2.52 (s, 3H), 3.02 (d, 3H, J = 4.8 Hz), 5.89 (br s, 1H), 7.35–7.47 (m, 5H), 7.57–7.68 (m, 3H). ^{13}C NMR δ 20.6, 27.3, 124.9, 127.7 (2 C:s), 127.8, 128.3, 129.3 (2 C:s), 130.3, 132.5, 135.7, 140.8, 143.2, 171.1.

5.5. General procedure for the synthesis of aminoketones 5a–h

The acetophenone, paraformaldehyde and dimethylamine hydrochloride (1:1:1 counting on the monomer of paraformaldehyde) were dissolved in dioxane (10 mL/3 mmol acetophenone) and heated under microwave irradiation (200 °C for 10 min). The mixture was poured into saturated aqueous $NaHCO_3$ and extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated. The residue was purified using flash chromatography (CH_2Cl_2/MeOH/triethylamine; 94.9:5:0.1) to afford to desired product.

5.5.1. 3-Dimethylamino-1-(4-biphenyl)propan-1-one (5a)

4-Phenylacetophenone (1.2 g, 6 mmol), paraformaldehyde (0.18 g, 6 mmol) and dimethylamine hydrochloride (0.49 g, 6 mmol) yielded 0.63 g (41%) of the title compound as a colorless oil. ^{1}H NMR δ 2.32 (s, 6H), 2.80 (t, 2H, J = 7.2 Hz), 3.20 (t, 2H, J = 7.2 Hz), 7.38–7.48 (m, 3H), 7.62 (d, 2H, J = 7.2 Hz), 7.69 (d, 2H, J = 8.8 Hz), 8.04 (d, 2H, J = 8.8 Hz). ^{13}C NMR δ 37.2, 45.8 (2 C:s), 54.6, 127.5 (3 C:s), 128.4 (2 C:s), 128.9 (2 C:s), 129.2 (2 C:s), 135.8, 140.0, 145.9, 198.9.

5.5.2. 3-Dimethylamino-1-(4-(2-phenylethynyl)phenyl)propan-1-one (5b)

4-(2-Phenylethynyl)acetophenone (1.2 g, 6 mmol), paraformaldehyde (0.18 g, 6 mmol) and dimethylamine hydrochloride (0.49 g, 6 mmol) afforded 0.42 g (24%) of the title compound as a light brown oil. ^{1}H NMR δ 2.35 (s, 6H), 2.83 (t, 2H, J = 6.8 Hz), 3.21 (t, 2H, J = 6.8 Hz), 7.36–7.40 (m, 2H), 7.54–7.57 (m, 3H), 7.62 (d, 2H, J = 8.8 Hz), 7.96 (d, 2H, J = 8.8 Hz). ^{13}C NMR δ 36.9, 45.6 (2 C:s), 54.4, 88.8, 93.0, 122.8, 128.3 (2 C:s), 128.5, 128.7 (2 C:s), 129.1, 132.0 (4 C:s), 136.0, 198.3.

5.5.3. 1-(3-Bromophenyl)-3-dimethylamino-propan-1-one (5c)

3-Bromoacetophenone (1.2 g, 6 mmol), paraformaldehyde (0.18 g, 6 mmol) and dimethylamine hydrochloride (0.49 g, 6 mmol) afforded 0.55 g (34%) of the title compound as a yellow oil. ^{1}H NMR δ 2.28 (s, 6H), 2.74 (t, 2H, J = 7.0 Hz), 3.11 (t, 2H, J = 7.0 Hz), 7.35 (dd, 1H, J = 6.2, 8.0 Hz), 7.68 (dd, 1H, J = 0.7, 8.0 Hz), 7.87 (d, 1H, J = 6.2 Hz), 8.08 (d, 1H, J = 0.7 Hz). ^{13}C NMR δ 37.0, 45.6 (2 C:s), 54.3, 123.1, 126.7, 130.2, 131.2, 136.0, 138.6, 197.8.

5.5.4. 1-(4-Bromophenyl)-3-dimethylamino-propan-1-one (5d)

4-Bromoacetophenone (1.2 g, 6 mmol), paraformaldehyde (0.18 g, 6 mmol) and dimethylamine hydrochloride (0.49 g, 6 mmol) yielded 0.50 g (31%) of the title compound as a yellow oil. ^{1}H NMR δ 2.31 (s, 6H), 2.78 (t, 2H, J = 7.4 Hz), 3.14 (t, 2H, J = 7.4 Hz), 7.60 (d, 2H, J = 8.1 Hz), 7.82 (d, 2H, J = 8.1 Hz). ^{13}C NMR δ 36.8, 45.5 (2 C:s), 54.2, 128.4, 129.6 (2 C:s), 132.0 (2 C:s), 135.6, 198.3.

5.5.5. 1-(3,4-Dichlorophenyl)-3-dimethylamino-propan-1-one (5e)

3,4-Dichloroacetophenone (3 g, 16 mmol), paraformaldehyde (0.48 g, 16 mmol) and dimethylamine hydrochloride (1.3 g, 16 mmol) afforded 1.4 g (36%) of the title compound as a yellow oil. ^{1}H NMR δ 2.27 (s, 6H), 2.73 (t, 2H, J = 7.0 Hz), 3.09 (t, 2H, J = 7.0 Hz), 7.53 (d, 1H, J = 8.2 Hz), 7.76 (dd, 1H, J = 1.8, 8.2 Hz), 8.02 (d, 1H, J = 1.8 Hz). ^{13}C NMR δ 36.9, 45.6 (2 C:s), 54.1, 127.2, 130.2, 130.8, 133.4, 136.5, 137.7, 196.8.

5.5.6. 1-(4-Bis-allylaminophenyl)-3-dimethylamino-propan-1-one (5f)

4-Bis-allylamino-acetophenone (1.3 g, 6 mmol), paraformaldehyde (0.18 g, 6 mmol) and dimethylamine hydrochloride (0.49 g, 6 mmol) yielded 0.30 g (18%) of the title compound as a yellow oil. ^{1}H NMR δ 2.54 (s, 6H), 3.13 (t, 2H, J = 7.0 Hz), 3.29 (t, 2H, J = 7.0 Hz), 3.92 (s, 4H), 5.05–5.14 (m, 4H), 5.74–5.81 (m, 2H), 6.58 (d, 2H, J = 8.8 Hz), 7.78 (d, 2H, J = 8.8 Hz). ^{13}C NMR δ 34.2, 44.2 (2 C:s), 52.6 (2 C:s), 53.8, 111.1 (2 C:s), 116.6 (2 C:s), 124.4, 130.6 (2 C:s), 132.4 (2 C:s), 152.6, 194.8.

5.5.7. 1-(3-Bis-allylaminophenyl)-3-dimethylamino-propan-1-one (5g)

Cs_2CO_3 (33 g, 100 mmol) and allyl bromide (7 mL, 80 mmol) were added to a solution of 3-acetylaniline (5 g, 37 mmol) in 100 mL DMF and the mixture was heated to 100 °C for 16 h. Brine (twice the volume of DMF) was added and the resulting mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated to afford 3-acetyl-*N*,*N*-diallylaniline as a yellow oil (6.7 g, 84%). ^{1}H NMR (CD_3OD) δ 2.56 (s, 3H), 3.96 (d, 4H, J = 4.4 Hz), 5.14–5.19 (m, 4H), 5.80–5.90 (m, 2H), 6.85–6.89 (m, 1H), 7.22–7.28 (m, 2H). The product (1.3 g, 6 mmol) was then reacted with paraformaldehyde (0.18 g, 6 mmol) and dimethylamine hydrochloride (0.49 g, 6 mmol) according to the general procedure to afford 0.25 g (15%) of the title compound as a yellow oil. ^{1}H NMR δ 2.39 (s, 6H), 2.89 (t, 2H, J = 6.6 Hz), 3.23 (t, 2H, J = 6.6 Hz), 3.96 (d, 4H, J = 4.8 Hz), 5.12–5.19 (m, 4H), 5.80–5.89 (m, 1H), 6.85–6.89 (m, 1H), 7.23–7.28 (m, 3H). ^{13}C NMR δ 36.4, 45.1 (2 C:s), 52.9 (2 C:s), 54.2, 111.1, 116.4 (3 C:s), 117.4, 129.3, 133.5 (2 C:s), 137.5, 148.8, 199.1.

5.5.8. 1-(3,5-Dimethoxyphenyl)-3-dimethylamino-propan-1-one (5h)

3,5-Dimethoxyacetophenone (2.5 g, 14 mmol), paraformaldehyde (0.45 g, 14 mmol) and dimethylamine hydrochloride (1.2 g, 14 mmol) afforded 0.7 g (21%) of the title compound as a yellow oil. ^{1}H NMR δ 2.32 (s, 6H), 2.79 (t, 2H, J = 7.3 Hz), 3.14 (t, 2H, J = 7.3 Hz), 3.82 (s, 6H), 6.64 (d, 1H, J = 2.2 Hz), 7.08 (d, 2H, J = 2.2 Hz). ^{13}C NMR δ 36.8, 45.4 (2 C:s), 54.3, 55.6 (2 C:s), 105.5, 105.9 (2 C:s), 138.8, 161.0 (2 C:s), 198.6.

5.5.9. 3-(Allylmethylamino)-1-(4-chlorophenyl)propan-1-one (5i)

To a solution of 3,4′-dichloro-propiophenone (10 g, 50 mmol) in THF (250 mL) was added triethylamine (8.6 mL, 60 mmol) and allyl-methylamine (5 mL, 50 mmol) and the solution was stirred 18 h. The reaction was then poured into 1 M NaOH (300 mL) and extracted twice with EtOAc. The combined organic phases were washed with water and brine and concentrated to afford the title compound as a colorless oil (11.1 g, 94%). ^{1}H NMR δ 2.29 (s, 3H), 2.84 (t, 2H, J = 7.2 Hz), 3.06 (d, 2H, J = 6.4 Hz), 3.14 (t, 2H, J = 7.2 Hz), 5.14–5.22 (m, 2H), 5.80–5.89 (m, 1H), 7.44 (d, 2H, J = 8.6 Hz), 7.90 (d, 2H, J = 8.6 Hz). ^{13}C NMR δ 37.0, 42.4, 52.1, 61.3, 118.1, 129.2 (2 C:s), 129.7 (2 C:s), 135.4, 135.6, 139.7, 198.3.

5.5.10. 3-(4-Chlorophenyl)-3-(2-trimethylammoniumethyl) isochroman-1-one iodide (10)

Compound **1** (AC-7954) (0.13 g, 0.4 mmol) was dissolved in THF and MeI (0.03 mL, 0.5 mmol) was added. After 3 h, the solvent was concentrated and the residue crystallized from MeOH/diethyl ether to yield 0.07 g (37%) of the title compound as a hygroscopic solid. ^{1}H NMR (CD_3OD) δ 2.75–2.82 (m, 1H), 3.02–3.09 (m, 1H), 3.17–3.24 (m, 1H), 3.39 (s, 9H), 3.68–3.78 (m, 3H), 7.23–7.31 (m, 4H), 7.45–7.48 (m, 3H), 7.94 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD) δ 36.3, 38.6, 54.3 (3 C:s), 63.4, 84.1, 124.3, 126.8 (2 C:s), 128.0, 128.3, 129.5 (2 C:s), 130.0, 134.6, 134.9, 136.8, 138.5, 164.4. Anal. Calcd for ($C_{20}H_{23}ClINO_2$): C, 50.9; H, 4.9; N, 3.0. Found: C, 50.6; H, 5.2; N, 2.9.

5.6. General procedure for the synthesis of isochromanones 6, 11–21 and 23–28

The benzamide was dissolved in THF (15 mL/g) and *n*-BuLi (2.2 equiv) was added slowly at room temperature. The ketone was dissolved in THF (15 mL/g) and added to the intense red solution and the mixture was stirred for 30 min. The reaction was poured into saturated aqueous NH_4Cl (twice the THF volume) and extracted twice with EtOAc. The combined organic phases were washed with water and brine and concentrated. The crude oil was dissolved in 1,2-dichlorobenzene and heated to 105 °C for 48 h. After cooling, the solution was diluted with CH_2Cl_2 and applied directly to a flash column. After flash chromatography (CH_2Cl_2/MeOH/triethylamine; 94.9:5:0.1) the fractions containing product were pooled and concentrated and the resulting oil was dissolved in methanol. After filtration, HCl_{ether} or 1 equiv of oxalic acid was added to the filtrate. The resulting solid was recrystallized from MeOH/diethyl ether to afford the desired compound.

5.6.1. 3-(2-(Allylmethylamino)ethyl)-3-(4-chlorophenyl) isochroman-1-one oxalate (6)

2,*N*-Dimethyl-benzamide (3.3 g, 22 mmol) and **5i** (5.0 g, 21 mmol) yielded 2.4 g (32%) of the title compound as a yellow oil which was converted to the corresponding oxalate salt, isolated as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.51–2.66 (m, 2H), 2.77 (s, 3H), 2.88–2.96 (m, 1H), 3.29–3.35 (m, 1H), 3.60 (d, 1H, J = 16.5 Hz), 3.66 (d, 1H, J = 16.5 Hz), 3.73 (d, 2H, J = 7.3 Hz), 5.46–5.52 (m, 2H), 5.83–5.94 (m, 1H), 7.25–7.30 (m, 4H), 7.38 (d, 2H, J = 8.8 Hz), 7.48–7.52 (m, 1H), 7.88 (dd, 1H, J = 1.1, 8.0 Hz). ^{13}C NMR (CD_3OD) δ 35.8, 37.2, 38.9, 50.3, 57.9, 84.2, 124.6, 125.2, 126.6, 126.8 (2 C:s), 127.6, 128.0, 128.7 (2 C:s), 129.3, 133.8, 134.4, 137.6, 139.5, 164.8, 165.9. Anal. Calcd for ($C_{23}H_{24}ClNO_6 \cdot H_2O$): C, 59.6; H, 5.7; N, 3.0. Found: C, 59.5; H, 5.9; N, 2.9.

5.6.2. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-6-methoxy-isochroman-1-one oxalate (11)

Benzamide **4c** (0.80 g, 4.4 mmol) and 1-(4-chlorophenyl)-3-dimethylamino-propan-1-one (0.46 g, 2.2 mmol) yielded 0.86 g (54%) of the title compound as a yellow oil, which was converted to the corresponding oxalate salt. Mp 93.5–94.8 °C. ^{1}H NMR (CD_3OD) δ 2.43–2.58 (m, 3H), 2.84 (s, 6H), 2.89–2.96 (m, 1H), 3.56 (d, 1H, J = 16.8 Hz), 3.61 (d, 1H, J = 16.8 Hz), 3.82 (s, 3H), 6.82 (d, 1H, J = 1.1 Hz), 6.85 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H,

J = 9.0 Hz), 7.39 (d, 2H, J = 9.0 Hz), 7.85 (dd, 1H, J = 1.1, 8.8 Hz). ^{13}C NMR (CD_3OD) δ 36.3, 37.3, 42.3 (2 C:s), 52.7, 54.8, 83.8, 112.4, 113.5, 116.7, 126.6 (2 C:s), 128.7 (2 C:s), 131.8, 133.9, 139.4, 140.1, 164.9, 165.2. Anal. Calcd for ($C_{22}H_{24}ClNO_3$): C, 58.7; H, 5.4; N, 3.1. Found: C, 58.6; H, 5.3; N, 3.0.

5.6.3. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-6-methoxy-5-methyl-isochroman-1-one oxalate (12)

Benzamide **4d** (0.80 g, 4.1 mmol) and 1-(4-chlorophenyl)-3-dimethylamino-propan-1-one (0.43 g, 2.1 mmol) yielded 0.61 g (79%) of the title compound as a yellow oil, which was converted to the corresponding oxalate salt. Mp 198.1–199.0 °C. ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H), 2.38–2.44 (m, 2H), 2.67 (s, 6H), 2.72–2.79 (m, 1H), 3.08–3.15 (m, 1H), 3.37 (d, 1H, J = 16.9 Hz), 3.75 (d, 1H, J = 16.9 Hz), 3.81 (s, 3H), 6.93 (d, 1H, J = 8.8 Hz), 7.39 (s, 4H), 7.73 (d, 1H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6) δ 11.5, 34.5, 37.0, 42.9 (2 C:s), 52.4, 56.4, 83.6, 109.9, 117.4, 123.5, 127.5 (2 C:s), 129.3 (2 C:s), 129.8, 133.0, 138.0, 141.2, 162.1, 164.6, 164.9. Anal. Calcd for ($C_{23}H_{26}ClNO_7$): C, 59.6; H, 5.6; N, 3.0. Found: C, 59.4; H, 5.7; N, 3.0.

5.6.4. 6-(Bis-allylamino)-3-(4-chlorophenyl)-3-(2-dimethylamino ethyl)isochroman-1-one HCl (13)

Benzamide **4a** (1.1 g, 4.5 mmol) and 1-(4-chlorophenyl)-3-dimethylamino-propan-1-one (0.95 g, 4.5 mmol) yielded 0.44 g (23%) of the title compound which was converted to the corresponding oxalate salt, obtained as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.45–2.55 (m, 2H), 2.81 (s, 6H), 2.87–2.94 (m, 1H), 3.24–3.28 (m, 1H), 3.46 (d, 2H, J = 8.5 Hz), 3.49 (d, 2H, J = 8.5 Hz), 3.98 (d, 4H, J = 4.4 Hz), 5.06–5.15 (m, 4H), 5.79–5.87 (m, 2H), 6.48 (d, 1H, J = 2.2 Hz), 6.56 (dd, 1H, J = 2.2, 9.2 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.66 (d, 1H, J = 9.2 Hz). ^{13}C NMR (CD_3OD) δ 36.3, 37.8, 42.3 (2 C:s), 52.3 (2 C:s), 52.8, 83.4, 109.4, 110.8, 110.9, 115.5 (2 C:s), 126.7 (2 C:s), 128.6 (2 C:s), 131.4, 132.5 (2 C:s), 133.6, 139.4, 139.8, 153.4, 165.4, 165.9. Anal. Calcd for ($C_{27}H_{31}ClN_2O_6\cdot1.5H_2O$): C, 59.8; H, 6.3; N, 5.2. Found: C, 60.0; H, 6.2; N, 5.0.

5.6.5. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-6-phenyl-isochroman-1-one oxalate (14)

Benzamide **4f** (0.12 g, 0.5 mmol) and 1-(4-chlorophenyl)-3-dimethylaminopropan-1-one (0.11 g, 0.5 mmol) yielded 0.05 g (23%) of the title compound which was converted to the corresponding oxalate salt isolated as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.49–2.59 (m, 2H), 2.84 (s, 6H), 2.86–2.96 (m, 2H), 3.67 (d, 1H, J = 16.1 Hz), 3.71 (d, 1H, J = 16.1 Hz), 7.32–7.45 (m, 7H), 7.57–7.65 (m, 4H), 7.97 (d, 1H, J = 8.0 Hz). ^{13}C NMR (CD_3OD) δ 36.4, 37.3, 42.2 (2 C:s), 57.8, 84.1, 123.2, 126.1, 126.3, 126.8 (2 C:s), 127.0 (2 C:s), 128.4, 128.8 (2 C:s), 128.9 (2 C:s), 130.0, 133.9, 138.2, 139.2, 139.4, 147.4, 164.7, 165.1. Anal. Calcd for ($C_{27}H_{26}ClNO_6$): C, 65.4; H, 5.3; N, 2.8. Found: C, 65.3; H, 5.2; N, 2.9.

5.6.6. 2-(4-Chlorophenyl)-2-(2-dimethylaminoethyl)-1,2-dihydro-3-oxa-phenanthren-4-one oxalate (15)

Benzamide **4b** (0.5 g, 2.5 mmol) and 1-(4-chlorophenyl)-3-dimethylaminopropan-1-one (0.52 g, 2.5 mmol) yielded 0.35 g (37%) of the title compound which was converted to the corresponding oxalate salt isolated as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 2.40–2.49 (m, 2H), 2.68 (s, 6H), 2.73–2.80 (m, 1H), 3.11–3.15 (m, 1H), 3.82 (d, 1H, J = 16.9 Hz), 3.88 (d, 2H, J = 16.9 Hz), 7.35 (d, 2H, J = 8.8 Hz), 7.42–7.48 (m, 3H), 7.53–7.57 (m, 1H), 7.63–7.69 (m, 1H), 7.94 (d, 1H, J = 8.1 Hz), 8.14 (d, 1H, J = 8.4 Hz), 9.02 (d, 1H, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6) δ 36.8, 38.3, 43.0 (2 C:s), 52.5, 83.3, 119.5, 125.6, 126.4, 126.8, 127.6 (2 C:s), 129.2 (2 C:s), 129.4, 129.5, 131.2, 133.0, 133.2, 135.8, 140.6, 140.7, 164.8. Anal. Calcd for ($C_{25}H_{24}ClNO_6$): C, 63.9; H, 5.1; N, 3.0. Found: C, 64.0; H, 5.1; N, 2.9.

5.6.7. 3-(3-Bis-allylaminophenyl)-3-(2-dimethylaminoethyl) isochroman-1-one HCl (16)

2,*N*-Dimethyl-benzamide (0.40 g, 2.7 mmol) and **5g** (0.70 g, 2.7 mmol) yielded 0.3 g (28%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. Mp 190.1–191.8 °C. ^{1}H NMR (CD_3OD) δ 2.60–2.66 (m, 2H), 2.88 (s, 3H), 2.91 (s, 3H), 3.00–3.07 (m, 1H), 3.34–3.41 (m, 1H), 3.69 (d, 1H, J = 16.5 Hz), 3.81 (d, 1H, J = 16.5 Hz), 4.23 (d, 4H, J = 7.0 Hz), 5.24–5.32 (m, 4H), 5.60–5.70 (m, 2H), 7.31–7.35 (m, 1H), 7.38–7.40 (m, 2H), 7.49–7.57 (m, 4H), 7.65 (s, 1H), 7.89 (d, 1H, J = 7.4 Hz). ^{13}C NMR (CD_3OD) δ 36.4, 36.7, 42.3, 42.4, 52.8, 59.3 (2 C:s), 84.0, 119.0 (2 C:s), 121.6 (2 C:s), 124.4, 124.7, 126.0, 127.0, 127.6, 128.1, 129.4, 130.8, 134.5, 137.5, 139.4, 143.6, 164.6. Anal. ($C_{25}H_{30}N_2O_2\cdot2HCl\cdot2H_2O$): C, 60.1; H, 7.3; N, 5.6. Found: C, 60.2; H, 7.3; N, 5.8.

5.6.8. 3-(4-Bis-allylaminophenyl)-3-(2-dimethylaminoethyl) isochroman-1-one HCl (17)

2,*N*-Dimethyl-benzamide (0.11 g, 0.7 mmol) and **5f** (0.17 g, 0.6 mmol) yielded 0.16 g (65%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. Mp 178.0–179.3 °C. ^{1}H NMR (CD_3OD) δ 2.53–2.62 (m, 2H), 2.86 (s, 3H), 2.88 (s, 3H), 2.98–3.06 (m, 1H), 3.33–3.40 (m, 1H), 3.66 (d, 1H, J = 16.8 Hz), 3.72 (d, 1H, J = 16.8 Hz), 4.14 (d, 4H, J = 6.6 Hz), 5.26–5.30 (m, 4H), 5.67–5.77 (m, 2H), 7.30–7.33 (m, 2H), 7.42–7.44 (d, 2H, J = 8.4 Hz), 7.51–7.55 (m, 1H), 7.59 (d, 2H, J = 8.4 Hz), 7.88 (dd, 1H, J = 0.7, 8.3 Hz). ^{13}C NMR (CD_3OD) δ 36.4, 36.8, 42.3, 42.4, 52.8, 58.6 (2 C:s), 84.1, 121.5 (2 C:s), 126.8, 127.1 (3 C:s), 127.3, 127.4, 127.5 (2 C:s), 128.0 (2 C:s), 128.3, 129.3, 134.4, 137.5, 164.7. Anal. Calcd for ($C_{25}H_{30}N_2O_2\cdot2HCl\cdot1.5H_2O$): C, 61.2; H, 7.2; N, 5.7. Found: C, 60.9; H, 6.8; N, 5.7.

5.6.9. 3-(3,4-Dichlorophenyl)-3-(2-dimethylaminoethyl) isochroman-1-one HCl (18)

2,*N*-Dimethyl-benzamide (0.84 g, 5.7 mmol) and **5e** (0.7 g, 2.8 mmol) yielded 0.17 g (17%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. ^{1}H NMR (CD_3OD) δ 2.60–2.85 (m, 9H), 3.13–3.22 (m, 1H), 3.41 (d, 1H, J = 16.5 Hz), 3.49 (d, 1H, J = 16.5 Hz), 7.18 (d, 1H, J = 7.7 Hz), 7.25–7.29 (m, 1H), 7.33–7.37 (m, 1H), 7.43 (d, 1H, J = 6.3 Hz), 7.48–7.53 (m, 2H), 8.02 (d, 1H, J = 7.3 Hz), 12.85 (br s, 1H). ^{13}C NMR (CD_3OD) δ 36.2, 36.7, 42.5, 42.6, 52.0, 84.0, 124.8, 126.2, 128.0, 128.3, 128.7, 129.8, 131.3, 131.5, 132.2, 135.2, 138.2, 142.8, 164.0. Anal. Calcd for ($C_{19}H_{20}Cl_3NO_2$): C, 57.0; H, 5.0; N, 3.5. Found: C, 57.1; H, 5.1; N, 3.6.

5.6.10. 3-(3-Bromophenyl)-3-(2-dimethylaminoethyl) isochroman-1-one HCl (19)

2,*N*-Dimethyl-benzamide (1.3 g, 8.5 mmol) and **5c** (2.1 g, 8.5 mmol) yielded 0.7 g (21%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt, isolated as a brown oil. ^{1}H NMR (CD_3OD) δ 2.53–2.61 (m, 2H), 2.85 (s, 3H), 2.88 (s, 3H), 2.94–3.01 (m, 1H), 3.32–3.39 (m, 1H), 3.64 (d, 1H, J = 16.5 Hz), 3.69 (d, 1H, J = 16.5 Hz), 7.22–7.27 (m, 1H), 7.32–7.35 (m, 2H), 7.40–7.42 (m, 2H), 7.52–7.56 (m, 1H), 7.61 (s, 1H), 7.92 (d, 1H, J = 8.1 Hz). ^{13}C NMR (CD_3OD) δ 36.5, 37.0, 42.1, 42.4, 52.7, 83.7, 122.8, 123.9, 124.4, 127.6, 127.9, 128.2, 129.4, 130.5, 131.2, 134.5, 137.5, 143.2, 164.7. Anal. Calcd for ($C_{19}H_{21}BrClNO_2\cdot2H_2O$): C, 51.0; H, 5.6; N, 3.1. Found: C, 49.6; H, 5.6; N, 2.8.

5.6.11. 3-(4-Bromophenyl)-3-(2-dimethylaminoethyl) isochroman-1-one HCl (20)

2,*N*-Dimethyl-benzamide (1.3 g, 8.5 mmol) and **5d** (2.1 g, 8.5 mmol) yielded 1.4 g (42%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt, isolated as a brown oil. ^{1}H NMR (CD_3OD) δ 2.47–2.61 (m, 2H), 2.86 (s, 6H), 2.91–2.99 (m, 1H), 3.30–3.37 (m, 1H), 3.63 (d, 1H, J = 16.5 Hz), 3.68 (d, 1H, J = 16.5 Hz), 7.30–7.35 (m, 4H), 7.48 (d, 2H, J = 8.8 Hz), 7.52–7.55 (m, 1H), 7.91 (d, 1H, J = 7.3 Hz). ^{13}C NMR (CD_3OD) δ 36.5, 37.1, 42.3, 52.8, 84.1, 122.0, 124.5, 127.0 (2 C:s), 127.6, 127.9, 129.3, 131.8 (2 C:s), 134.5, 137.5, 139.8, 164.8. Anal. ($C_{19}H_{21}BrClNO_2 \cdot H_2O$): C, 53.2; H, 5.4; N, 3.3. Found: C, 53.0; H, 5.0; N, 3.2.

5.6.12. 3-(2-Dimethylaminoethyl)-3-(4-(2-phenylethynyl) phenyl)isochroman-1-one HCl (21)

2,*N*-Dimethyl-benzamide (0.22 g, 1.5 mmol) and **5b** (0.41 g, 1.5 mmol) yielded 0.21 g (35%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt, isolated as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.54–2.62 (m, 2H), 2.83 (s, 3H), 2.88 (s, 3H), 2.94–3.02 (m, 1H), 3.29–3.33 (m, 1H), 3.62 (d, 1H, J = 16.5 Hz), 3.70 (d, 1H, J = 16.5 Hz), 7.25–7.32 (m, 5H), 7.43–7.51 (m, 7H), 7.89 (d, 1H, J = 7.0 Hz). ^{13}C NMR (CD_3OD) δ 36.5, 37.1, 42.2, 42.5, 52.8, 84.3, 87.9, 89.9, 122.8, 123.2, 124.6, 125.4 (2 C:s), 127.6, 128.0, 128.3 (2 C:s), 128.4, 129.4, 131.3 (2 C:s), 131.7 (2 C:s), 134.5, 137.6, 140.8, 164.9. HRTofMS 395.1884 ($C_{27}H_{25}NO_2$ requires 395.1885).

5.6.13. 3-(2-Dimethylaminoethyl)-3-(4-biphenyl)isochroman-1-one HCl (23)

2,*N*-Dimethyl-benzamide (0.30 g, 2.0 mmol) and **5a** (0.50 g, 2.0 mmol) yielded 0.38 g (51%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt, isolated as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.59–2.64 (m, 2H), 2.85 (s, 3H), 2.88 (s, 3H), 2.96–3.01 (m, 1H), 3.33–3.40 (m, 1H), 3.66 (d, 1H, J = 16.5 Hz), 3.75 (d, 1H, J = 16.5 Hz), 7.27–7.38 (m, 6H), 7.46–7.58 (m, 6H), 7.91 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD) δ 36.9, 37.3, 42.2, 42.5, 52.9, 84.5, 124.7, 125.7 (2 C:s), 126.6 (2 C:s), 127.2 (2 C:s), 127.5, 127.6, 128.1, 128.7 (2 C:s), 129.4, 134.5, 137.8, 139.4, 139.8, 140.8, 165.3. HRTofMS 371.1884 ($C_{25}H_{25}NO_2$ requires 371.1885).

5.6.14. 3-(2-Dimethylaminoethyl)-3-(3-biphenyl)isochroman-1-one HCl (24)

2,*N*-Dimethyl-benzamide (0.25 g, 1.0 mmol) and 1-(3-biphenyl)-3-dimethylamino-propan-1-one (0.15 g, 1.0 mmol) yielded 0.21 g (57%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt, isolated as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.61–2.65 (m, 2H), 2.85 (s, 3H), 2.87 (s, 3H), 2.99–3.02 (m, 1H), 3.32–3.41 (m, 1H), 3.68 (d, 1H, J = 16.5 Hz), 3.79 (d, 1H, J = 16.5 Hz), 7.29–7.35 (m, 3H), 7.39–7.44 (m, 4H), 7.48–7.54 (m, 4H), 7.63 (d, 1H, J = 0.8 Hz), 7.92 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD) δ 36.8, 37.3, 42.2, 42.5, 52.9, 84.6, 123.7, 124.0, 124.7, 126.6, 126.8 (2 C:s), 127.5, 128.0, 128.7, 129.3, 134.5, 137.9, 140.3, 141.2, 141.9, 165.3. HRTofMS 371.1890 ($C_{25}H_{25}NO_2$ requires 371.1885).

5.6.15. 3-(2-Dimethylaminoethyl)-6,7-dimethyl-3-(2-naphthyl)isochroman-1-one HCl (25)

2,4,5,*N*-Tetramethyl-benzamide (0.56 g, 3.2 mmol) and 3-dimethylamino-1-(2-naphthyl)propan-1-one (0.55 g, 2.4 mmol) yielded 0.18 g (20%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. ^{1}H NMR (CD_3OD) δ 2.14 (s, 3H), 2.20 (s, 3H), 2.61–2.65 (m, 2H), 2.83 (s, 6H), 2.88–2.94 (m, 1H), 3.32–3.40 (m, 1H), 3.62 (d, 1H, J = 16.5 Hz), 3.73 (d, 1H, J = 16.5 Hz), 7.07 (s, 1H), 7.43–7.48 (m, 2H), 7.52 (dd, 1H, J = 1.8, 8.4 Hz), 7.65 (s, 1H), 7.77–7.79 (m, 2H), 7.83–7.85 (m, 2H). ^{13}C NMR (CD_3OD) δ 17.9, 18.8, 36.5, 37.1, 42.3 (2 C:s), 53.0, 84.6, 122.1, 122.3, 124.5, 126.4, 126.5, 127.2, 127.8, 128.7, 128.8, 129.9, 132.8, 133.0, 135.1, 136.5, 137.8, 144.7, 165.7. Anal. Calcd for ($C_{25}H_{27}ClNO_2$): C, 73.2; H, 6.9; N, 3.4. Found: C, 73.3; H, 6.8; N, 3.5.

5.6.16. 3-(2-Dimethylaminoethyl)-3-(3-methoxyphenyl)-6,7-dimethyl-isochroman-1-one HCl (26)

2,4,5,*N*-Tetramethyl-benzamide (0.75 g, 4.3 mmol) and 3-dimethylamino-1-(3-methoxy-phenyl)propan-1-one (0.45 g, 2.1 mmol) yielded 0.22 g (15%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. ^{1}H NMR (CD_3OD) δ 2.20 (s, 3H), 2.22 (s, 3H), 2.57–2.83 (m, 9H), 3.14–3.22 (m, 1H), 3.33–3.42 (m, 2H), 3.77 (s, 3H), 6.74 (d, 1H, J = 6.2 Hz), 6.86–6.97 (m, 3H), 7.21 (dd, 1H, J = 8.0, 8.1 Hz), 7.73 (s, 1H), 12.60 (br s, 1H). ^{13}C NMR (CD_3OD) δ 19.4, 20.2, 36.5, 39.0, 42.6, 44.1, 53.5, 55.4, 83.8, 111.0, 113.5, 117.1, 121.9, 129.1, 130.3, 130.7, 134.1, 136.7, 141.8, 144.6, 160.1, 164.8. Anal. Calcd for ($C_{22}H_{27}ClNO_3$): C, 67.8; H, 7.2; N, 3.6. Found: C, 67.9; H, 7.2; N, 3.6.

5.6.17. 3-(3,5-Dimethoxyphenyl)-6,7-dimethyl-3-(2-dimethylaminoethyl)isochroman-1-one HCl (27)

2,4,5,*N*-Tetramethyl-benzamide (0.65 g, 3.6 mmol) and **5h** (0.45 g, 1.8 mmol) yielded 0.30 g (43%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. Mp 244.5–246.0 °C. ^{1}H NMR (CD_3OD) δ 2.22 (s, 3H), 2.24 (s, 3H), 2.61–2.80 (m, 9H), 3.12–3.21 (m, 1H), 3.35 (s, 2H), 3.76 (s, 6H), 6.30 (d, 1H, J = 2.2 Hz), 6.46 (d, 1H, J = 2.2 Hz), 6.90 (s, 1H), 7.75 (s, 1H), 12.65 (br s, 1H). ^{13}C NMR (CD_3OD) δ 19.4, 20.2, 36.4, 39.0, 42.5, 44.2, 53.5, 55.6 (2 C:s), 83.8, 99.7, 103.2 (2 C:s), 121.8, 129.0, 130.8, 134.0, 136.6, 142.6, 144.5, 161.4 (2 C:s), 164.8. Anal. Calcd for ($C_{23}H_{29}ClNO_4$): C, 65.8; H, 7.2; N, 3.3. Found: C, 65.7; H, 7.1; N, 3.4.

5.6.18. 3-(3,4-Dichlorophenyl)-6,7-dimethyl-3-(2-dimethyl aminoethyl)isochroman-1-one HCl (28)

2,4,5,*N*-Tetramethyl-benzamide (0.35 g, 2 mmol) and 1-(3,4-dichlorophenyl)-3-dimethyl-aminopropan-1-one (0.5 g, 2 mmol) yielded 0.2 g (26%) of the title compound as a yellow oil, which was converted to the corresponding HCl salt. ^{1}H NMR (CD_3OD) δ 2.23 (s, 3H), 2.27 (s, 3H), 2.49–2.55 (m, 2H), 2.86 (s, 6H), 2.96–2.99 (m, 1H), 3.29–3.31 (m, 1H), 3.56 (s, 2H), 7.09 (s, 1H), 7.34 (dd, 1H, J = 2.2, 8.4 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.59 (d, 1H, J = 2.2 Hz), 7.68 (s, 1H). ^{13}C NMR (CD_3OD) δ 18.0, 18.8, 36.3, 36.6, 42.5 (2 C:s), 52.6, 83.5, 121.8, 125.0, 127.3, 128.9, 130.0, 130.8, 132.8, 134.7, 136.1, 136.8, 141.7, 145.1, 164.9. Anal. Calcd for ($C_{21}H_{27}Cl_2NO \cdot 0.5H_2O$): C, 57.6; H, 5.8; N, 3.2. Found: C, 58.0; H, 5.4; N, 3.0.

5.6.19. 3-(4-Chlorophenyl)-3-(2-methylaminoethyl) isochroman-1-one HCl (7)

1,3-Dimethylbarbituric acid (0.62 g, 3.9 mmol) and $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol) were added to a solution of **6** (0.28 g, 0.78 mmol) in CH_2Cl_2, and the mixture was stirred at rt for 18 h. The mixture was filtered through Celite and concentrated. The crude product was dissolved in 1 M HCl and washed twice with EtOAc. The water phase was basified using solid NaOH (pH 14) and extracted twice with EtOAc. The combined organic phases were washed with water and brine and concentrated to yield 120 mg (49%) of the title compound which was converted to the corresponding HCl salt isolated as a yellow oil. ^{1}H NMR (CD_3OD) δ 2.41–2.54 (m, 2H), 2.66 (s, 3H), 2.84–2.89 (m, 1H) 3.11–3.16 (m, 1H), 3.62 (d, 1H, J = 16.5 Hz), 3.69 (d, 1H, J = 16.5 Hz), 7.29–7.34 (m, 4H), 7.41 (d, 2H, J = 6.8 Hz), 7.51–7.56 (m, 1H), 7.90 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD) δ 32.5, 37.0, 38.0, 44.1, 84.4, 124.5, 126.8 (2 C:s), 127.6, 128.0, 128.7 (2 C:s), 129.4, 133.9, 134.5, 137.6, 139.5, 164.9. Anal. Calcd for ($C_{18}H_{19}Cl_2NO_2 \cdot 0.5H_2O$): C, 59.8; H, 5.6; N, 3.9. Found: C, 59.4; H, 5.4; N, 3.7.

5.7. General procedure for reduction of isochromanones to isochromanes 8a–c

Sodium borohydride (4 equiv) was added to a solution of the isochromanone (1 equiv) and boron trifluoride etherate (30 equiv) in THF (3 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 6 h at rt., and then refluxed for 13 h. The reaction was carefully quenched by addition of aqueous saturated NH_4Cl (10 mL). Saturated aqueous $NaHCO_3$ was added and the mixture was extracted twice with EtOAc. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified using flash chromatography (CH_2Cl_2/MeOH/triethylamine; 94.9:5:0.1). The fractions containing product were pooled and concentrated to afford the desired product, which was converted to the corresponding HCl or oxalic acid salt.

5.7.1. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl) isochromane HCl (8a)

Compound **1** (AC-7954) (0.28 g, 0.9 mmol), sodium borohydride (0.13 g, 3.4 mmol) and boron trifluoride etherate (3.62 g, 25.5 mmol) yielded 78 mg (26%) of the title product as white crystals. Mp 58–60 °C. ^{1}H NMR δ 2.26–2.50 (m, 2H), 2.51–2.81 (m, 7H), 2.91–3.26 (m, 3H), 4.69 (d, 1H, J = 16.0 Hz), 4.85 (d, 1H, J = 16.0 Hz), 6.90–7.40 (m, 8H). ^{13}C NMR δ 35.1, 38.4, 43.0, 53.8, 63.9, 75.5, 124.2, 126.7, 127.1 (3 C:s), 128.6, 129.1 (2 C:s), 131.3, 133.6, 133.7, 141.1. Anal. Calcd for ($C_{19}H_{23}Cl_2NO{\cdot}2/3H_2O$): C, 62.6; H, 6.7; N, 3.8. Found: C, 62.6; H, 6.7; N, 3.8.

5.7.2. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-6,7-dimethyl-isochromane HCl (8b)

Compound **2** (0.55 g, 1.6 mmol), sodium borohydride (0.23 g, 6.1 mmol) and boron trifluoride etherate (6.0 g, 46.0 mmol) yielded 208 mg (36%) of the title product as a white hygroscopic solid. ^{1}H NMR (CD_3OD) δ 2.16 (s, 3H), 2.19 (s, 3H), 2.22–2.27 (m, 2H), 2.81 (s, 6H), 2.99–3.18 (m, 4H), 4.62 (d, 1H, J = 15.0 Hz), 4.79 (d, 1H, J = 15.0 Hz), 6.73 (s, 1H), 6.94 (s, 1H), 7.32 (d, 2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.8 Hz). ^{13}C NMR (CD_3OD) δ 18.0, 18.2, 35.9, 36.4, 42.3 (2 C:s), 53.8, 63.3, 76.2, 124.7, 127.5 (2 C:s), 128.4 (2 C:s), 128.9, 129.2, 131.0, 133.1, 134.5, 134.9, 141.3. Anal. ($C_{21}H_{27}Cl_2NO{\cdot}H_2O$): C, 63.3; H, 7.3; N, 3.5. Found: C, 63.7; H, 7.4; N, 3.2.

6.7.3. 3-(2-Dimethylaminoethyl)-6,7-dimethyl-3-(2-naphthyl)isochromane HCl (8c)

Compound **25** (0.16 g, 0.4 mmol), sodium borohydride (65 mg, 1.6 mmol) and boron trifluoride etherate (1.8 g, 12.9 mmol) yielded 60 mg (35%) of the title product as a white gum. ^{1}H NMR (DMSO-d_6) δ 2.10 (s, 3H), 2.16 (s, 3H), 2.24–2.44 (m, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 2.51–2.63 (m, 1H), 3.12 (d, 1H, J = 16.1 Hz), 3.23 (d, 1H, J = 16.1 Hz), 4.64 (d, 1H, J = 15.4 Hz), 4.84 (d, 1H, J = 15.4 Hz), 6.74 (s, 1H), 6.98 (s, 1H), 7.47–7.50 (m, 2H), 7.63 (dd, 1H, J = 1.5, 8.8 Hz), 7.83–7.93 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 19.6, 19.7, 34.3, 37.4, 51.1, 51.9, 59.6, 62.9, 76.4, 124.4, 124.9, 125.3, 126.5, 126.7, 127.9, 128.6, 128.7, 129.7, 130.1, 131.4, 132.6, 133.2, 134.3, 134.7, 141.3. Anal. Calcd for ($C_{25}H_{30}ClNO$): C, 75.8; H, 7.6; N, 3.5. Found: C, 76.1; H, 7.3; N, 3.4.

5.8. General procedure for the synthesis of tetrahydroisoquinolinones 9a–c

The benzamide was dissolved in THF (15 mL/g) and *n*-BuLi (2.2 equiv) was added slowly at room temperature. The ketone dissolved in THF (15 mL/g) was added dropwise and the solution was stirred for 30 min. The reaction mixture was poured into saturated aqueous ammonium chloride (twice the THF volume) and extracted twice with EtOAc. The combined organic phases were washed with water and brine and concentrated. The resulting viscous oil was cooled (−15 °C) and stirred vigorously. Conc. sulfuric acid (10 mL/g) was added slowly and the mixture was stirred over night. Aqueous NaOH (1 M) was carefully added until pH >12. Then EtOAc was added and the phases were separated. The water phase was extracted twice with EtOAc. The combined organic phases were washed with water and brine and concentrated. The residue was purified using flash chromatography (CH_2Cl_2/MeOH/triethylamine; 94.9:5:0.1) to afford the pure tetrahydroisoquinolinone, which was converted to the corresponding HCl salt.

5.8.1. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-3,4-dihydro-2-methyl-2*H*-isoquinolin-1-one HCl (9a)

2,*N*-Dimethyl-benzamide (1.0 g, 6.7 mmol) and 1-(4-chlorophenyl)-3-dimethylamino-propan-1-one (0.70 g, 3.3 mmol) yielded 0.57 g (50%) of the title compound, which was converted to the corresponding HCl salt. Mp 179.0–179.9 °C. ^{1}H NMR (CD_3OD) δ 2.76–2.81 (m, 2H), 2.87 (s, 3H), 2.90 (s, 3H), 3.01–3.13 (m, 1H), 3.34–3.42 (m, 1H), 3.49 (s, 3H), 3.83 (d, 1H, J = 16.8 Hz), 3.94 (d, 1H, J = 16.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.8 Hz), 7.48–7.55 (m, 2H), 7.73–7.77 (m, 1H), 8.01 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD) δ 29.0, 35.5, 36.4, 42.0, 42.4, 52.2, 89.2, 119.7, 126.8 (2 C:s), 127.5, 128.6, 129.2 (2 C:s), 129.4, 134.8, 136.4, 136.8, 136.9, 167.3. HRTofMS 342.1505 ($C_{20}H_{23}ClN_2O$ requires 342.1499).

5.8.2. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-3,4-dihydro-5-methoxy-2-methyl-2*H*-isoquinolin-1-one HCl (9b)

Benzamide **4c** (0.50 g, 2.8 mmol) and 1-(4-chlorophenyl)-3-dimethylamino-propan-1-one (0.29 g, 1.4 mmol) yielded 0.17 g (29%) of the title compound, which was converted to the corresponding HCl salt. Mp 136.5–137.7 °C. ^{1}H NMR (CD_3OD) δ 2.77–2.81 (m, 2H), 2.87 (s, 3H), 2.89 (s, 3H), 3.07–3.16 (m, 1H), 3.35–3.41 (m, 1H), 3.47 (s, 3H), 3.53 (d, 1H, J = 17.2 Hz), 3.94 (s, 3H), 4.04 (d, 1H, J = 17.2 Hz), 7.38–7.42 (m, 5H), 7.44–7.47 (m, 1H), 7.57 (d, 1H, J = 7.7 Hz). ^{13}C NMR (CD_3OD) δ 29.1, 29.9, 35.6, 42.0, 42.3, 52.2, 55.6, 89.0, 118.1, 118.6, 120.3, 125.1, 126.6, 129.2, 129.4, 134.8, 136.6, 156.7, 167.3. HRTofMS 372.1603 ($C_{21}H_{25}ClN_2O_2$ requires 372.1605).

5.8.3. 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-3,4-dihydro-2-isopropyl-2*H*-isoquinolin-1-one HCl (9c)

N-Isopropyl-2-methyl-benzamide (0.50 g, 2.8 mmol) and 1-(4-chlorophenyl)-3-dimethylamino-propan-1-one (0.29 g, 1.4 mmol) yielded 0.35 g (68%) of the title compound, which was converted to the corresponding HCl salt as a yellow oil. ^{1}H NMR (CD_3OD) δ 1.53–1.56 (m, 6H), 2.85–2.90 (m, 2H), 2.88 (s, 3H), 2.90 (s, 3H), 3.08–3.16 (m, 1H), 3.32–3.37 (m, 2H), 3.88 (d, 1H, J = 16.8 Hz), 3.99 (d, 1H, J = 16.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.8 Hz), 7.48–7.52 (m, 1H), 7.56 (d, 1H, J = 7.3 Hz), 7.73–7.77 (m, 1H), 8.09 (d, 1H, J = 8.1 Hz). ^{13}C NMR (CD_3OD) δ 20.4, 20.6, 35.6, 36.1, 42.1, 42.3, 47.3, 52.3, 89.3, 119.7, 127.0 (2 C:s), 128.1, 128.4, 129.2 (2 C:s), 129.3, 134.8, 136.4, 136.9, 137.2, 166.0. HRTofMS 370.9266 ($C_{22}H_{27}ClN_2O$ requires 370.9263).

6. Biological activity

6.1. R-SAT-testing

R-SAT™ assays for pharmacological testing were performed as previously described,[18] 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 cell factories (Nunc) with the human urotensin II, somatostatin 1, and somatostatin 4 receptors 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/gluatmine (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. For control of the UII receptor selectivity all compounds were tested against the m3 receptor as a negative control (data not shown). For the selectivity test of **28** on somatostatin receptors SST-14 was used as the reference compound.

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References and notes

1. Ames, R. S.; Sarau, H. M.; Chambers, J. K.; Willette, R. N.; Alyar, N. V.; Romanic, A. M.; Louden, C. S.; Foley, J. J.; Sauermelch, C. F.; Coatney, R. W.; Ao, Z. H.; Disa, J.; Holmes, S. D.; Stadel, J. M.; Martin, J. D.; Liu, W. S.; Glover, G. I.; Wilson, S.; McNulty, D. E.; Ellis, C. E.; Elshourbagy, N. A.; Shabon, U.; Trill, J. J.; Hay, D. W. P.; Ohlstein, E. H.; Bergsma, D. J.; Douglas, S. A. *Nature* **1999**, *402*, 282.
2. Douglas, S.; Dhanak, D.; Johns, D. G. *Trends Pharmacol. Sci.* **2004**, *25*, 76.
3. Douglas, S.; Aiyar, N. V.; Ohlstein, E. H.; Willette, R. N. *Eur. Heart J.* **2000**, *21*, 229.
4. Suzuki, S.; Zong, W. Y.; Hirai, M.; Hinokio, Y.; Suzuki, C.; Yamada, T.; Yoshizumi, S.; Suzuki, M.; Tanizawa, Y.; Matsutani, A.; Oka, Y. *Peptides* **2004**, *25*, 1803.
5. Russell, F. D. *Pharmacol. Ther.* **2004**, *103*, 223.
6. Balat, O.; Aksoy, F.; Kutlar, I.; Ugur, M. G.; Iyikosker, H.; Balat, A.; Anarat, R. *Eur. J. Obstet. Gynecol. Reproduct. Biol.* **2005**, *120*, 33.
7. (a) Sidharta, P. N.; Wagner, F. D.; Bohnemeier, H.; Jungnik, A.; Halabi, A.; Krahenbuhl, S.; Chadha-Boreham, H.; Dingemanse, J. *Clin. Pharmacol. Ther.* **2006**, *80*, 246; (b) Clozel, M.; Binkert, C.; Birker-Robaczewska, M.; Boukhadra, C.; Ding, S. S.; Fischli, W.; Hess, P.; Mathys, B.; Morrison, K.; Muller, C.; Muller, C.; Nayler, O.; Qiu, C. B.; Rey, M.; Scherz, M. W.; Velker, J.; Weller, T.; Xi, J. F.; Ziltener, P. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 204.
8. Bousette, N.; Hu, F.; Ohlstein, E. H.; Dhanak, D.; Douglas, S. A.; Giaid, A. *J. Mol. Cell. Cardiol.* **2006**, *41*, 285.
9. (a) Croston, G. E.; Olsson, R.; Currier, E. A.; Burstein, E. S.; Weiner, D.; Nash, N.; Severance, D.; Allenmark, S. G.; Thunberg, L.; Ma, J. N.; Mohell, N.; O'Dowd, B.; Brann, M. R.; Hacksell, U. *J. Med. Chem.* **2002**, *45*, 4950; (b) Lehmann, F.; Pettersen, A.; Currier, E. A.; Sherbukhin, V.; Olsson, R.; Hacksell, U.; Luthman, K. *J. Med. Chem.* **2006**, *49*, 2232; (c) Lehmann, F.; Currier, E. A.; Olsson, R.; Hacksell, U.; Luthman, K. *Bioorg. Med. Chem.* **2005**, *13*, 3057; (d) Lehmann, F.; Currier, E. A.; Clemmons, B.; Hansen, L. K.; Olsson, R.; Hacksell, U.; Luthman, K. *Bioorg. Med. Chem.* **2009**, *17*, 4657; (e) Lehmann, F.; Lake, L.; Currier, E. A.; Olsson, R.; Hacksell, U.; Luthman, K. *Eur. J. Med. Chem.* **2007**, *42*, 276.
10. (a) Carotenuto, A.; Grieco, P.; Novellino, E.; Rovero, P. *Med. Res. Rev.* **2004**, *24*, 577; (b) Foister, S.; Taylor, L. L.; Feng, J. J.; Chen, W. L.; Lin, A.; Cheng, F. C.; Smith, A. B. *Org. Lett.* **2006**, *8*, 1799; (c) Grieco, P.; Carotenuto, A.; Campiglia, P.; Zampelli, E.; Patacchini, R.; Maggi, C. A.; Novellino, E.; Rovero, P. *J. Med. Chem.* **2002**, *45*, 4391; (d) Odagami, T.; Tsuda, Y.; Kogami, Y.; Kouji, H.; Okada, Y. *Bioorg. Med. Chem.* **2009**, *17*, 6742; (e) Grieco, P.; Carotenuto, A.; Campiglia, P.; Gomez-Monterrey, I.; Auriemma, L.; Sala, M.; Marcozzi, C.; d'Emmanuele di Villa Bianca, R.; Brancaccio, D.; Rovero, P.; Santicioli, P.; Meini, S.; Maggi, C. A.; Novellino, E. *J. Med. Chem.* **2009**, *52*, 3927.
11. (a) Flohr, S.; Kurz, M.; Kostenis, E.; Brkovich, A.; Fournier, A.; Klabunde, T. *J. Med. Chem.* **2002**, *45*, 1799; (b) Jin, J.; Dhanak, D.; Knight, S. D.; Widdowson, K.; Aiyar, N.; Naselsky, D.; Sarau, H. M.; Foley, J. J.; Schmidt, D. B.; Bennett, C. D.; Wang, B.; Warren, G. L.; Moore, M. L.; Keenan, R. M.; Rivero, R. A.; Douglas, S. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3229; (c) Luci, D. K.; Ghosh, S.; Smith, C. E.; Qi, J.; Wang, Y.; Haertlein, B.; Parry, T. J.; Li, J.; Almond, H. R., Jr.; Minor, L. K.; Damiano, B. P.; Kinney, W. A.; Maryanoff, B. E.; Lawson, E. C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6489; (d) Jin, J.; Wang, Y.; Wang, F.; Shi, D.; Erhard, K. F.; Wu, Z.; Guida, B. F.; Lawrence, S. K.; Behm, D. J.; Disa, J.; Vaidya, K. S.; Evans, C.; McMillan, L. J.; Rivero, R. A.; Neeb, M. J.; Douglas, S. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2860; (e) McAtee, J. J.; Dodson, J. W.; Dowdell, S. E.; Girard, G. R.; Goodman, K. B.; Hilfiker, M. A.; Sehon, C. A.; Sha, D.; Wang, G. Z.; Wang, N.; Viet, A. Q.; Zhang, D.; Aiyar, N. V.; Behm, D. J.; Carballo, L. H.; Evans, C. A.; Fries, H. E.; Nagilla, R.; Roethke, T. J.; Xu, X.; Yuan, C. C. K.; Douglas, S. A.; Neeb, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3500; (f) McAtee, J. J.; Dodson, J. W.; Dowdell, S. E.; Erhard, K.; Girard, G. R.; Goodman, K. B.; Hilfiker, M. A.; Jin, J.; Sehon, C. A.; Sha, D.; Shi, D.; Wang, F.; Wang, G. Z.; Wang, N.; Wang, Y.; Viet, A. Q.; Yuan, C. C. K.; Zhang, D.; Aiyar, N. V.; Behm, D. J.; Carballo, L. H.; Evans, C. A.; Fries, H. E.; Nagilla, R.; Roethke, T. J.; Xu, X.; Douglas, S. A.; Neeb, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3716; (g) Jin, J.; An, M.; Sapienza, A.; Aiyar, N.; Naselsky, D.; Sarau, H. M.; Foley, J. J.; Salyers, K. L.; Knight, S. D.; Keenan, R. M.; Rivero, R. A.; Dhanak, D.; Douglas, S. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3950; (h) Hilfiker, M. A.; Zhang, D.; Dowdell, S. E.; Goodman, K. B.; McAtee, J. J.; Dodson, J. W.; Viet, A. Q.; Wang, G. Z.; Sehon, C. A.; Behm, D. J.; Wu, Z.; Carballo, L. H.; Douglas, S. A.; Neeb, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4470; (i) Wang, Y.; Wu, Z.; Guida, B. F.; Lawrence, S. K.; Neeb, M. J.; Rivero, R. A.; Douglas, S. A.; Jin, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4936.
12. (a) Grieco, P.; Rovero, P.; Novellino, E. *Curr. Med. Chem.* **2004**, *11*, 969; (b) Guerrini, R.; Camarda, V.; Marzola, E.; Arduin, M.; Calo, G.; Spagnol, M.; Rizzi, A.; Salvadori, S.; Regoli, D. *J. Peptide Sci.* **2005**, *11*, 85; (c) Labarrere, P.; Chatenet, D.; Leprince, J.; Marionneau, C.; Loirand, G.; Tonon, M. C.; Dubessy, C.; Scalbert, E.; Pfeiffer, B.; Renard, P.; Calas, B.; Pacaud, P.; Vaudry, H. *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 77.
13. (a) Herold, C. L.; Behm, D. J.; Buckley, P. T.; Foley, J. J.; Wixted, W. E.; Sarau, H. M.; Douglas, S. A. *Br. J. Pharmacol.* **2003**, *139*, 203; (b) Dogrell, S. A. *Expert Opin. Invest. Drug* **2004**, *13*, 479; (c) Maryanoff, B. E.; Kinney, W. A. *J. Med. Chem.* **2010**, *5*, 2695.
14. Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514.
15. Lehmann, F.; Pilotti, Å.; Luthman, K. *Mol. Div.* **2003**, *7*, 145.
16. (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797.
17. Kao, L. F.; Barfield, M. *J. Am. Chem. Soc.* **1985**, *107*, 2323.
18. (a) Spalding, T. A.; Burstein, E. S.; Jorgensen, H. B.; Hilleubanks, D.; Brann, M. R. *Life Sci.* **1995**, *56*, 1021; (b) Burstein, E. S.; Piu, F.; Ma, J. N.; Weissman, J. T.; Currier, E. A.; Nash, N. R.; Weiner, D. M.; Spalding, T. A.; Schiffer, H. H.; Del Tredici, A. L.; Brann, M. R. *Curr. Pharm. Des.* **2006**, *12*, 1717; (c) Burstein, E. S.; Spalding, T. A.; Brann, M. R. *Mol. Pharmacol.* **1997**, *51*, 312; (d) Bräuner-Osborne, H.; Brann, M. R. *Eur. J. Pharmacol.* **1996**, *295*, 93; (e) Burstein, E. S.; Bräuner-Osborne, H.; Spalding, T. A.; Conklin, B. R.; Brann, M. R. *J. Neurochem.* **1997**, *68*, 525.