Bioorganic & Medicinal Chemistry 17 (2009) 4657–4665

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Novel and potent small-molecule urotensin II receptor agonists

Fredrik Lehmann [a], Erika A. Currier [d], Bryan Clemons [d], Lars K. Hansen [b], Roger Olsson [c], Uli Hacksell [d], Kristina Luthman [a,*]

[a] Department of Chemistry, Medicinal Chemistry, University of Gothenburg, SE-412 96 Göteborg, Sweden
[b] Department of Chemistry, University of Tromsø, 9037 Tromsø, Norway
[c] ACADIA Pharmaceuticals AB, Medeon Science Park, SE-205 12 Malmö, Sweden
[d] ACADIA Pharmaceuticals Inc., 3911 Sorrento Valley Boulevard, San Diego, CA 92121, USA

ARTICLE INFO

Article history:
Received 15 December 2008
Revised 24 April 2009
Accepted 28 April 2009
Available online 3 May 2009

Keywords:
Urotensin II
Agonists
SAR
R-SAT
Parallel synthesis

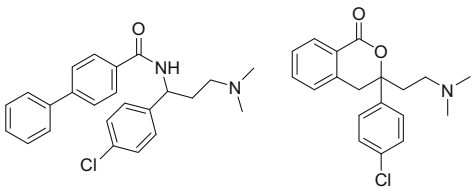
ABSTRACT

A series of analogs of the non-peptidic urotensin II receptor agonist *N*-[1-(4-chlorophenyl)-3-(dimethylamino)propyl]-4-phenylbenzamide (FL104) has been synthesized and evaluated pharmacologically. The enantiomers of the two most potent racemic analogues were obtained from the corresponding diastereomeric mandelic amides. In agreement with previously observed SAR, most of the agonist potency resided in the (*S*) enantiomers. The most potent UII receptor agonist in the new series was (*S*)-*N*-[3-dimethylamino-1-(2-naphthyl)propyl]-4-(4-chlorophenyl)benzamide (EC_{50} = 23 nM at the urotensin II receptor).

1. Introduction

The discovery of FL104, a potent urotensin II (UII) receptor[1] agonist was recently reported (Fig. 1).[2] This compound is more potent than isochromanone derivative AC-7954, the first non-peptide UII-receptor agonist (Fig. 1).[3] Herein, we describe the synthesis and pharmacological testing of a series of analogues of FL104. One of these novel compounds, (*S*)-{**C6**}, is the most potent non-peptide UII receptor agonist described in the literature.

In our previous study of benzamide derivatives, we observed that large substituents such as phenyl or phenoxy in the 4-position of the benzamide moiety were beneficial to agonist potency. In the present study, we synthesized a series of amides in which electron withdrawing (4-chlorophenyl), donating (4-methoxyphenyl) or sterically demanding (2-naphthyl) groups were introduced in either the 3- or 4-positions on the benzamide ring to further explore the requirements for potent UII receptor-agonist activity. In addition, we synthesized analogues in which the 4-chlorophenyl group of FL104 was replaced by electron donating (4-methylphenyl) or bulky (2-naphthyl) aromatic ring systems. To enable further comparisons between SAR in the isochromanone[4] and benzamide series of UII receptor agonists, we synthesized analogues in which (i) the distance between the aromatic rings and the dimethylamino group was varied and (ii) the dimethylamino group was replaced by a piperidine moiety.



{A5} FL104, pEC_{50} 7.11 AC-7954, pEC_{50} 5.95

Figure 1. FL104 (left) and AC-7954 (right) are potent UT receptor agonists.

2. Results and discussion

2.1. Chemistry

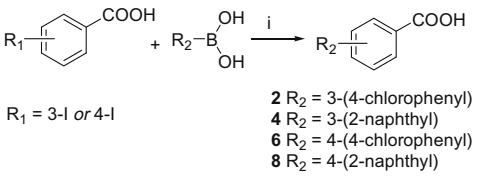
The target benzamide derivatives were synthesized in a library format from benzoyl chlorides (formed in situ) and the appropriate amines.

2.1.1. Synthesis of benzoic acids

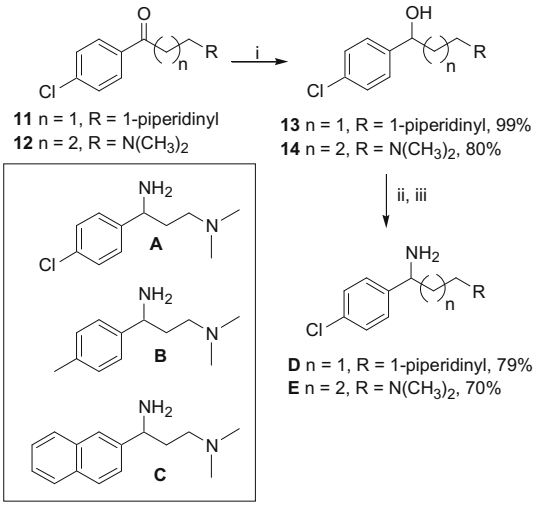
The benzoic acids **2**, **4**, **6** and **8** were synthesized (Scheme 1) from the corresponding 3- or 4-iodobenzoic acids in a Suzuki coupling reaction,[5] with boronic acids and palladium on charcoal using microwave heating at 180 °C for 15 min. After workup (filtration,

* Corresponding author. Tel.: +46 31 772 2894; fax: +46 31 772 3840.
E-mail address: luthman@chem.gu.se (K. Luthman).

0968-0896/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2009.04.062



Scheme 1. Reagents and conditions: (i) Pd/C (10%), H_2O, ethanol, 180 °C, 15 min (microwave).



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF; (ii) CH_3CN, H_2SO_4, −15 °C; (iii) 6 M HCl reflux.

extraction and recrystallization) the corresponding acids were obtained in moderate to excellent yields (65% for **8**, 99% for the others).

2.1.2. Synthesis of amines

The amines **A**–**E** were synthesized from their corresponding alcohols using a Ritter reaction as previously described[6] (Scheme 2), (for the synthesis of **A**–**C** see Ref. 6).

2.1.3. Synthesis of amides

The amides {**A1–C8**} (Table 1) and {**D5**, **E5**, **D10**, **E10**} (Table 2) were synthesized using a procedure previously reported (Scheme 3).[2]

The benzoic acids were dissolved in THF and triethylamine and thionyl chloride were added sequentially. The resulting benzoyl chlorides were not isolated, instead the amines **A**–**E** were added directly to the mixture. Basic workup and filtration through an ion-exchange resin afforded the amides in moderate to excellent yields (41–99%).

2.1.4. Resolution of racemates

To prepare the enantiomers of amines **A** and **C**, the corresponding racemates were reacted with (*R*)-2-methoxy-2-phenylacetic acid (**9**) in the presence of EDC and DMAP to produce {**A9**} and {**C9**}, respectively (Scheme 4).

The diastereomeric amides were separated by flash chromatography to yield (+)- and (−)-{**A9**} and {**C9**} which were subsequently hydrolyzed using refluxing 6 M HCl. The amines (+)- and (−)-**A** and **C** were reacted with 4-phenylbenzoic acid and 4-(4-chlorophenyl)benzoic acid to afford amides (+)- and (−)-{**A5**} and {**C6**}, respectively, in good yields using the same method as described above.

3. Pharmacological testing

3.1. Pharmacological testing

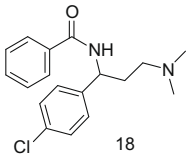
Compounds {**A1–E10**} were tested for their ability to stimulate the human UT-receptor using a functional R-SAT™ assay previously described.[7] The results are shown in Tables 1–4.

3.2. Structure–activity relationships

As is apparent from Table 1 and illustrated in Figure 2, the positioning of the biphenyl is of vital importance for potency, as all 4-biaryl derivatives ({**A5–C8**}) are significantly more potent than their corresponding 3-biaryl analogues ({**A1–C4**}) independent on other structural differences.

Within the 3-biaryl series it seems that the substitution pattern in the two rings plays only a minor role for the potency as all but two derivatives ({**B4**} and {**C4**}) exhibit EC_{50}-values within 0.5 log units (pEC_{50} 5.96–6.44) (Table 1 and Fig. 2). Another trend, especially in the 4-biaryl series, is that the 4-(2-naphthyl) substituent is least favoured of the substituents evaluated ({**A4–C4**} and {**A8–C8**}). Throughout, all 4-substituted biaryl derivatives showed higher or much higher efficacies than the corresponding 3-substituted analogues (Table 1).

In our previous study of isochromanone analogues,[4] we observed that a longer linker chain between the aromatic rings and the amino moiety decreased the activity by around 0.5 log units. We also established that larger amino groups than dimethylamino decreased the agonist potency.[4] In the current series of benzamides, {**E5**} and {**E10**}, that have a three-carbon linker chain showed a similar decrease (0.5 log units) in potency (Table 2) when compared with the corresponding compounds with a two-carbon linker ({**A5**} and **18**, respectively (**18**: pEC_{50}: 5.85, Efficacy 158%).[2]



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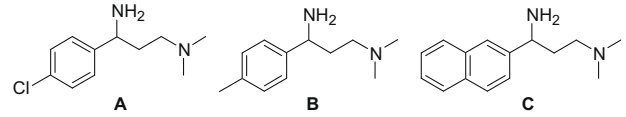
In addition, the piperidinyl analogues {**D5**} and {**D10**} are less potent that the corresponding dimethylamino derivatives (Table 2). Taken together, these results indicate that the isochromane and benzamide series bind to and activate the UII receptor in a similar fashion. Further support for this hypothesis comes from computational studies.[2]

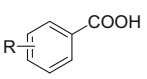
We have earlier shown that the more potent enantiomers in the benzamide series of UT-agonists have the *S*-configuration.[2] In order to study the stereoselectivity of the most potent analogs synthesized herein, the diastereomeric amides {**A9**} and {**C9**} were synthesized (Table 3). The absolute configuration of (−)-{**C9**} was determined using X-ray crystallography and was found to have the (*R*,*S*)-configuration (Fig. 3).

In separate experiments (−)- and (+)-{**C9**} were hydrolyzed and both enantiomers of amine **C** were reacted with acid **6** to yield (+)-{**C6**} and (−)-{**C6**}, respectively. Similarly, the separated diastereomers of {**A9**} were hydrolyzed and converted into benzamides (+) and (−)-{**A9**} (presumably (*S*) and (*R*)-{**A5**}, respectively). The (*S*) enantiomers were the more potent antipodes (Table 4) and (+)-(*S*)-{**C6**} is the most potent non-peptidic UT-receptor agonist identified so far.

Based on the results presented and previously[2,6] reported studies the SAR findings for these series of compounds could be summarized as defined in Figure 4.

Table 1
Yields, activity and efficacy of amides {**A1**–**C8**} at the UT-receptor[a,b]





1 R = 3-phenyl
2 R = 3-(4-chlorophenyl)
3 R = 3-(4-methoxyphenyl)
4 R = 3-(2-naphthyl)
5 R = 4-phenyl
6 R = 4-(4-chlorophenyl)
7 R = 4-(4-methoxyphenyl)
8 R = 4-(2-naphthyl)

Acids	Amines		
	A	**B**	**C**
1	{**A1**} Yield 65% pEC_{50} 6.24 ± 0.23 Efficacy 92 ± 26	{**B1**} Yield 65% pEC_{50} 6.09 ± 0.07 Efficacy 45 ± 4	{**C1**} Yield 95% pEC_{50} 6.27 ± 0.17 Efficacy 67 ± 5
2	{**A2**} Yield 60% pEC_{50} 6.36 ± 0.21 Efficacy 63 ± 13	{**B2**} Yield 74% pEC_{50} 6.19 ± 0.21 Efficacy 39 ± 4	{**C2**} Yield 92% pEC_{50} 5.96 ± 0.12 Efficacy 45 ± 6
3	{**A3**} Yield 60% pEC_{50} 6.24 ± 0.03 Efficacy 78 ± 18	{**B3**} Yield 70% pEC_{50} 5.97 ± 0.11 Efficacy 69 ± 10	{**C3**} Yield 67% pEC_{50} 6.19 ± 0.10 Efficacy 50 ± 16
4	{**A4**} Yield 72% pEC_{50} 6.44 ± 0.09 Efficacy 41 ± 14	{**B4**} Yield 85% pEC_{50} NA[c] Efficacy NA[c]	{**C4**} Yield 99% pEC_{50} 5.46 ± 0.13 Efficacy 38 ± 9
5	{**A5**} (FL104) Yield 50%[d] pEC_{50} 7.11 ± 0.01 Efficacy 116 ± 11	{**B5**} Yield 75% pEC_{50} 6.70 ± 0.17 Efficacy 114 ± 17	{**C5**} Yield 95% pEC_{50} 6.92 ± 0.18 Efficacy 111 ± 3
6	{**A6**} Yield 65% pEC_{50} 7.12 ± 0.04 Efficacy 137 ± 2	{**B6**} Yield 84% pEC_{50} 6.90 ± 0.13 Efficacy 108 ± 8	{**C6**} Yield 72% pEC_{50} 7.36 ± 0.11 Efficacy 129 ± 5
7	{**A7**} Yield 60% pEC_{50} 7.13 ± 0.31 Efficacy 143 ± 24	{**B7**} Yield 70% pEC_{50} 6.46 ± 0.21 Efficacy 119 ± 11	{**C7**} Yield 83% pEC_{50} 6.98 ± 0.07 Efficacy 111 ± 0
8	{**A8**} Yield 72% pEC_{50} 6.51 ± 0.02 Efficacy 131 ± 8	{**B8**} Yield 62% pEC_{50} 6.09 ± 0.03 Efficacy 83 ± 4	{**C8**} Yield 55% pEC_{50} 6.28 ± 0.05 Efficacy 77 ± 3

[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] NA = No detectable activity.
[d] For experimental details, see Ref. 2.

4. Conclusion

The optimization of FL104 lead to the discovery of (+)-(*S*)-{**C6**} with an EC_{50}-value of 23 nM which is the most active non-peptidergic UT-receptor agonist reported today. In addition several other low nanomolar agonists at the UT-receptor were identified, which allowed an extended SAR to be established.

5. Experimental

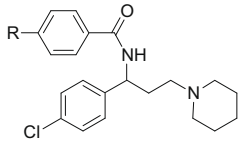
5.1. General

All chemicals were purchased from Aldrich, Acros, Lancaster or Maybridge and were used without prior purification. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in CD_3OD 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). Melting points were recorded on a Büchi melting point B-545 apparatus and are uncorrected. HRMS were recorded at Inovacia (Stockholm Sweden) using an Agilent MSD-TOF (G1969A) connected to an Agilent 1100 HPLC system. Elemental analyses were performed at Kolbe Analytishe Laboratorium, (Mülheim an der Ruhr, Germany). The carboxylic acids **2**, **4**, **6**, **8** are commercially available. The synthesis of {**A5**} (FL104) is described in Ref. 2. For experimental and analysis data see Supplementary data.

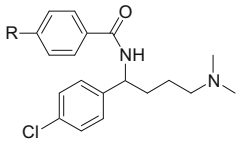
5.1.1. 1-(4-Chlorophenyl)-3-(1-piperidinyl)propan-1-ol (13)

Ketone **11**[2] (3.7 g, 14.7 mmol) was dissolved in THF (250 mL). LAH (0.57 g, 15.0 mmol) was added slowly and the mixture was

Table 2
Activity and efficacy of amides {**D5**–**E10**} in the R-SAT™ assay



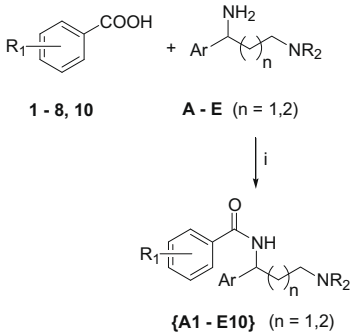
{**D5**}: R = Ph
{**D10**}: R = H



{**E5**}: R = Ph
{**E10**}: R = H

Compd	pEC$_{50}$[a]	Efficacy[b]
{**A5**} (FL104)[c]	7.11 ± 0.01	116 ± 11
{**D5**}	6.18 ± 0.09	57 ± 8
{**D10**}	5.19 ± 0.07	55 ± 0
{**E5**}	6.50 ± 0.21	91 ± 12
{**E10**}	5.42 ± 0.01	77 ± 23

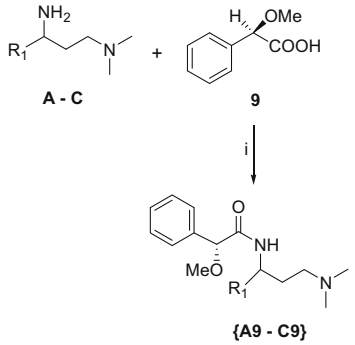
[a] Results were determined in R-SAT assays and are expressed as pEC$_{50}$-values, the negative of the log EC$_{50}$ in molarity. Results are the average ± standard deviations of 2–5 determinations of the EC$_{50}$ where each compound was tested in eight doses in triplicate.
[b] The % efficacy values are normalized to UII at 100%.
[c] For experimental details, see Ref. 2.



1 - 8, 10 **A - E** (n = 1,2)

{A1 - E10} (n = 1,2)

Scheme 3. Reagents and conditions: (i) NEt_3, $SOCl_2$, rt, 41–99%. For details on structures see Tables 1 and 2.



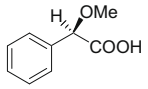
A - C **9**

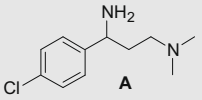
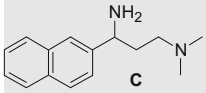
{A9 - C9}

Scheme 4. Reagents and conditions: (i) EDC, DMAP rt, 44–49%.

stirred for 18 h. NaOH (1 M) (100 mL) was added dropwise until pH 14. The resulting mixture was extracted twice with EtOAc (150 mL + 100 mL). The organic phases were combined, washed with water (200 mL) and brine (200 mL) and concentrated to afford **13** as a yellow oil (3.7 g, 99%). ^{1}H NMR ($CDCl_3$) δ 1.43–1.50 (m, 2H), 1.60–1.68 (m, 4H), 1.77–1.81 (m, 2H), 2.45–2.67 (m, 6H), 4.91 (dd, 1H, J = 3.6, 7.2 Hz), 7.29 (s, 4H). ^{13}C NMR ($CDCl_3$) δ 24.4, 26.3 (2 C:s), 33.8, 54.8, 57.9 (2 C:s), 75.3, 127.2 (2 C:s), 128.5 (2 C:s), 132.5, 143.9.

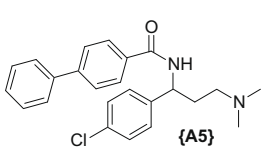
Table 3
Activity and efficacy of enantiomerically pure amides ({**A9**} and {**C9**}) in the R-SAT™ at the UT-receptor[a,b]



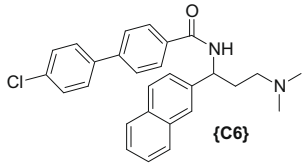
	(+)-(*R*,*R*)-{**A9**}[c]	(−)-(*R*,*S*)-{**A9**}[c]
 **A**	pEC$_{50}$ 5.30 ± 0.07 Efficacy 112 ± 22	pEC$_{50}$ 6.06 ± 0.03 Efficacy 165 ± 10
	(+)-(*R*,*R*)-{**C9**}	(−)-(*R*,*S*)-{**C9**}
 **C**	pEC$_{50}$ 5.56 ± 0.01 Efficacy 53 ± 5	pEC$_{50}$ 6.13 ± 0.12 Efficacy 140 ± 11

[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] For experimental details, see Ref. 2.

Table 4
Activity and efficacy of (*R*)- and (*S*)-{**A5**} and {**C6**} at the UT-receptor



{**A5**}



{**C6**}

Compd	pEC$_{50}$[a]	Efficacy[b]
(+)-(*S*)-{**A5**}[c]	7.49 ± 0.33	116 ± 18
(−)-(*R*)-{**A5**}[c]	5.84 ± 0.10	96 ± 16
(+)-(*S*)-{**C6**}	7.64 ± 0.23	129 ± 4
(−)-(*R*)-{**C6**}	6.34 ± 0.15	53 ± 5

[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] For experimental details, see Ref. 2.

5.1.2. 1-(4-Chlorophenyl)-3-(1-piperidinyl)propan-1-amine (D)

Compound **13** (3.0 g, 11.8 mmol) was dissolved in acetonitrile (5 mL) and stirred on an ice-salt bath. H_2SO_4 (15 mL) was added slowly. After 18 h NaOH pellets were added until pH 14. The mixture was extracted with EtOAc (2 × 150 mL). The organic phases were combined and washed with water (200 mL) and brine (200 mL) and concentrated to obtain the corresponding acetamide as a yellow oil. HCl (6 M) (40 mL) was then added and the solution was refluxed for 3 days. H_2O (100 mL) and NaOH pellets were added slowly to the mixture until pH 14. The mixture was extracted with EtOAc (2 × 100 mL) and the organic phases were combined and washed with water (100 mL) and brine (100 mL) and concentrated to afford **D** as a yellow oil (2.35 g, 79%). ^{1}H NMR ($CDCl_3$) δ 1.35–1.42 (m, 2H), 1.51–1.59 (m, 4H), 1.70–1.81 (m, 3H), 2.19–2.40 (m, 5H), 3.96 (t, 1H, J = 6.6 Hz), 7.26 (s, 4H). ^{13}C NMR ($CDCl_3$) δ 24.6, 26.1 (2 C:s), 36.4, 54.8 (2 C:s), 54.9, 56.8, 127.8 (2 C:s), 128.6 (2 C:s), 132.5, 145.2.

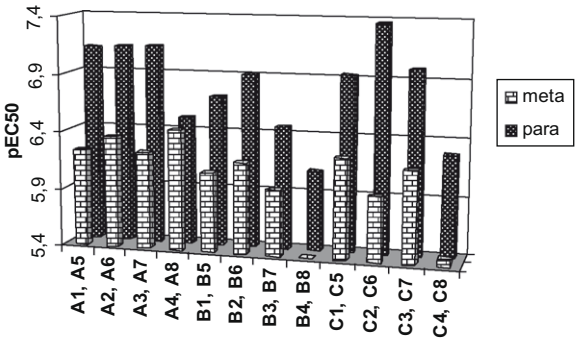


Figure 2. Comparison of pEC_{50} values with respect to the position of the biphenyl in amides {**A1**–**C8**}.

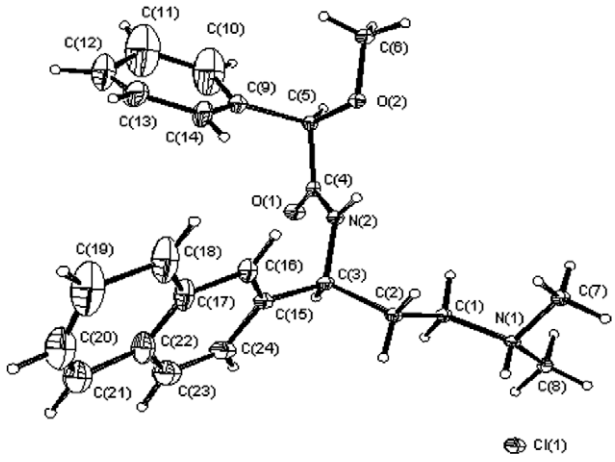


Figure 3. The crystal structure of (−)-{**C9**} as determined by X-ray diffraction. ORTEPIII view showing the atom-labelling scheme with thermal ellipsoids drawn at 20% probability.

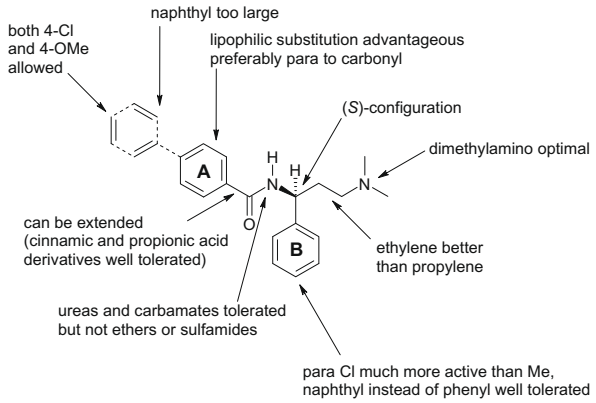


Figure 4. Summary of SAR results from this study and those in Refs. 2 and 6.

5.1.3. 1-(4-Chlorophenyl)-4-dimethylamino-butan-1-ol (14)

Ketone **12**[2] (1.5 g, 6.6 mmol) was reacted according to the same procedure as described for **13** to afford **14** as a yellow oil (1.2 g, 80%). ^{1}H NMR ($CDCl_3$) δ 1.65–1.78 (m, 3H), 1.89–1.99 (m, 1H), 2.29 (s, 6H), 2.32–2.40 (m, 2H), 4.61 (d, 1H, J = 8.8 Hz), 7.22–7.31 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 24.7, 39.7, 44.9 (2 C:s), 59.8, 72.8, 127.2 (2 C:s), 128.2 (2 C:s), 132.2, 144.6.

5.1.4. 1-(4-Chlorophenyl)-4-dimethylamino-butan-1-amine (E)

Compound **14** (1.25 g, 5.5 mmol) was reacted according to the same procedure as described for **13** to afford **E** as a yellow oil (0.87 g, 70%). ^{1}H NMR ($CDCl_3$) δ 1.29–1.67 (m, 4H), 2.16 (s, 6H), 2.21 (t, 2H, J = 7.3 Hz), 3.88 (t, 1H, J = 6.9 Hz), 7.27 (s, 4H). ^{13}C NMR ($CDCl_3$) δ 24.7, 37.4, 45.6 (2 C:s), 55.7, 59.7, 127.8 (2 C:s), 128.6 (2 C:s), 132.5, 145.0.

5.2. General procedure for the synthesis of amide derivatives {A1}–{E10}

The benzoic acid (0.5 mmol) was dissolved in THF (75 mL/g) and triethylamine (0.14 mL, 1 mmol) was added. Under vigorous stirring $SOCl_2$ (0.05 mL, 0.6 mmol) was added dropwise and the mixture was stirred at rt for 10 min. A 25 mg/mL solution of the amine (100 mg, 0.44–0.50 mmol) in THF was added slowly and the reaction mixture was stirred for another 2 h. The mixture was poured into NaOH (1 M) and extracted twice with EtOAc. The combined organic phases were washed (water, brine) and concentrated. The crude oil was dissolved in CH_2Cl_2 and applied to a SAX-2 ion-exchange column, washed with CH_2Cl_2 and MeOH. The product was eluted using methanolic NH_3 (2 M), and concentrated. The pure products were converted to the corresponding hydrochloride salts for analysis, storage and biological testing. The salts were hygroscopic and turned into slight yellow oils immediately after isolation.

5.2.1. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-phenylbenzamide HCl {A1}

Reaction of 3-phenylbenzoic acid with **A** yielded 120 mg (65%) {**A1**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.29–2.48 (m, 2H), 2.91 (s, 6H), 3.16–3.32 (m, 2H), 5.26 (dd, 1H, J = 5.9, 9.9 Hz), 7.34–7.49 (m, 7H), 7.55 (t, 1H, J = 7.7 Hz), 7.67 (d, 2H, J = 7.3 Hz), 7.80 (d, 1H, J = 8.8 Hz), 7.85 (d, 1H, J = 7.0 Hz), 8.11 (s, 1H). ^{13}C NMR δ 30.3, 42.2, 42.6, 51.1, 55.3, 125.8, 126.2, 126.8 (2 C:s), 127.6, 128.3 (2 C:s), 128.6 (2 C:s), 128.7 (2 C:s), 128.9, 130.2, 133.3, 134.4, 140.1, 140.2, 141.6, 168.6. HRTofMS calcd for $C_{24}H_{25}ClN_2O$ (M+) m/z 392.1655, found 392.1663.

5.2.2. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-chlorophenyl)benzamide HCl {A2}

Reaction of 3-(4-chlorophenyl)benzoic acid with **A** yielded 120 mg (60%) of {**A2**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.29–2.38 (m, 1H), 2.43–2.53 (m, 1H), 2.90 (s, 6H), 3.16–3.34 (m, 2H), 5.24 (dd, 1H, J = 5.5, 9.5 Hz), 7.37 (d, 2H, J = 8.1 Hz), 7.43 (d, 2H, J = 8.1 Hz), 7.49 (d, 2H, J = 8.1 Hz), 7.52 (dd, 1H, J = 7.7, 7.9 Hz), 7.66 (d, 2H, J = 8.1 Hz), 7.77 (d, 1H, J = 7.7 Hz), 7.87 (d, 1H, J = 7.9 Hz), 8.11 (s, 1H). ^{13}C NMR δ 30.3, 42.2, 42.5, 51.1, 55.3, 125.7, 126.6, 128.3 (2 C:s), 128.4 (2 C:s), 128.6 (2 C:s), 128.8 (2 C:s), 129.0, 130.0, 133.3, 133.6, 134.5, 138.7, 140.1, 140.2, 168.4. HRTofMS calcd for $C_{24}H_{24}Cl_2N_2O$ (M+) m/z 426.1266, found 426.1273.

5.2.3. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-methoxyphenyl)benzamide HCl {A3}

Reaction of 3-(4-methoxyphenyl)benzoic acid with **A** yielded 120 mg (60%) of {**A3**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.28–2.49 (m, 2H), 2.90 (s, 6H), 3.16–3.29 (m, 2H), 3.82 (s, 3H), 5.26 (dd, 1H, J = 5.9, 9.5 Hz), 7.00 (d, 2H, J = 8.8 Hz), 7.39 (d, 2H, J = 8.1 Hz), 7.47–7.53 (m, 3H), 7.61 (d, 2H, J = 8.8 Hz), 7.74–7.80 (m, 2H), 8.06 (d, 1H, J = 1.8 Hz). ^{13}C NMR δ 30.3, 42.2, 42.5, 51.1, 54.5, 55.3, 114.1 (2 C:s), 125.3, 125.5, 127.9 (2 C:s), 128.3 (2 C:s), 128.6 (2 C:s), 128.8, 129.7, 132.4, 133.2, 134.3, 140.2, 141.2, 159.8, 168.7. HRTofMS calcd for $C_{25}H_{27}ClN_2O_2$ (M+) m/z 422.1761, found 422.1765.

5.2.4. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(2-naphthyl)benzamide HCl {A4}

Reaction of 3-(2-naphthyl)benzoic acid with **A** yielded 150 mg (72%) of {**A4**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.28–2.38 (m, 1H), 2.43–2.53 (m, 1H), 2.87 (s, 6H), 3.14–3.33 (m, 2H), 5.26 (dd, 1H, J = 8.1, 13.6 Hz), 7.36 (d, 2H, J = 8.8 Hz), 7.47–7.58 (m, 5H), 7.77–7.90 (m, 6H), 8.14 (s, 1H), 8.27 (s, 1H). ^{13}C NMR δ 30.2, 42.1, 42.5, 51.1, 55.4, 124.9, 125.6, 126.0, 126.1, 126.2, 126.4, 127.3, 128.0, 128.3 (2 C:s), 128.4, 128.6 (2 C:s), 129.0, 130.4, 133.0, 133.3, 133.8, 134.4, 137.3, 140.2, 141.3, 168.6. HRTofMS calcd for $C_{28}H_{27}ClN_2O$ (M+) m/z 442.1812, found 442.1816.

5.2.5. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-(4-chlorophenyl)benzamide HCl {A6}

Reaction of 4-(4-chlorophenyl)benzoic acid with **A** yielded 130 mg (65%) of {**A6**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.29–2.37 (m, 1H), 2.41–2.50 (m, 1H), 2.91 (s, 6H), 3.17–3.33 (m, 2H), 5.23 (dd, 1H, J = 5.5, 9.9 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.96 (d, 2H, J = 8.4 Hz). ^{13}C NMR δ 30.3, 42.2, 42.6, 51.0, 55.3, 126.6 (2 C:s), 128.0 (2 C:s), 128.2 (2 C:s), 128.3 (2 C:s), 128.6 (2 C:s), 128.8 (2 C:s), 132.7, 133.3, 133.9, 138.4, 140.1, 143.2, 168.3. HRTofMS calcd for $C_{24}H_{24}Cl_2N_2O$ (M+) m/z 426.1266, found 426.1267.

5.2.6. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-(4-methoxyphenyl)benzamide HCl {A7}

Reaction of 4-(4-methoxyphenyl)benzoic acid with **A** yielded 120 mg (60%) of {**A7**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.29–2.37 (m, 1H), 2.41–2.51 (m, 1H), 2.90 (s, 6H), 3.17–3.33 (m, 2H), 3.78 (s, 3H), 5.24 (dd, 1H, J = 5.5, 9.5 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.48 (d, 2H, J = 8.4 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.64 (d, 2H, J = 8.0 Hz), 7.93 (d, 2H, J = 8.0 Hz). ^{13}C NMR δ 30.4, 42.1, 42.6, 51.0, 54.5, 55.3, 114.1 (2 C:s), 126.1 (2 C:s), 127.9 (2 C:s), 128.0 (2 C:s), 128.3 (2 C:s), 128.6 (2 C:s), 131.6, 131.9, 133.2, 140.3, 144.2, 160.0, 168.4. HRTofMS calcd for $C_{25}H_{27}ClN_2O_2$ (M+) m/z 422.1761, found 422.1777.

5.2.7. *N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-(2-naphthyl)benzamide HCl {A8}

Reaction of 4-(2-naphthyl)benzoic acid with **A** yielded 150 mg (72%) of {**A8**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.29–2.38 (m, 1H), 2.44–2.53 (m, 1H), 2.89 (s, 6H), 3.16–3.24 (m, 2H), 5.25 (dd, 1H, J = 4.8, 9.2 Hz), 7.36 (d, 2H, J = 9.9 Hz), 7.43–7.51 (m, 4H), 7.72 (d, 1H, J = 8.8 Hz), 7.79–7.89 (m, 5H), 8.01 (d, 2H, J = 8.1 Hz), 8.08 (s, 1H). ^{13}C NMR δ 30.3, 42.3, 42.6, 51.2, 55.4, 124.7, 125.7, 126.1, 126.3, 126.9 (2 C:s), 127.4, 128.1 (2 C:s), 128.2, 128.3 (2 C:s), 128.4, 128.6 (2 C:s), 132.4, 133.1, 133.2, 133.7, 137.0, 140.3, 144.3, 168.4. HRTofMS calcd for $C_{28}H_{27}ClN_2O$ (M+) m/z 442.1812, found 442.1822.

5.2.8. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-phenylbenzamide HCl {B1}

Reaction of 3-phenylbenzoic acid with **B** yielded 120 mg (65%) of {**B1**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.19 (s, 3H), 2.20–2.28 (m, 1H), 2.34–2.42 (m, 1H), 2.77 (s, 3H), 2.78 (s, 3H), 3.05–3.10 (m, 1H), 3.15–3.19 (m, 1H), 5.14 (dd, 1H, J = 5.6, 9.6 Hz), 7.07 (d, 2H, J = 8.0 Hz), 7.22–7.35 (m, 5H), 7.42 (t, 1H, J = 7.6 Hz), 7.56 (d, 2H, J = 7.2 Hz), 7.66 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 7.6 Hz), 8.04 (s, 1H). ^{13}C NMR δ 24.0, 34.6, 46.2, 46.6, 55.5, 59.5, 129.9, 130.3, 130.6 (2 C:s), 130.9 (2 C:s), 131.6, 132.8 (2 C:s), 133.0, 133.3 (2 C:s), 134.1, 138.6, 141.4, 142.5, 144.2, 145.5, 172.6. HRTofMS calcd for $C_{25}H_{28}N_2O$ (M+) m/z 372.2202, found 372.2204.

5.2.9. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-(4-chlorophenyl)benzamide HCl {B2}

Reaction of 3-(4-chlorophenyl)benzoic acid with **B** yielded 150 mg (74%) of {**B2**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.20 (s, 3H), 2.21–2.28 (m, 1H), 2.31–2.42 (m, 1H), 2.80 (s, 6H), 3.05–3.10 (m, 1H), 3.17–3.26 (m, 1H), 5.14 (dd, 1H, J = 5.6, 9.2 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.42 (dd, 1H, J = 7.6, 7.8 Hz), 7.54 (d, 2H, J = 8.0 Hz), 7.64 (d, 1H, J = 7.6 Hz), 7.78 (d, 1H, J = 7.8 Hz), 8.01 (s, 1H). ^{13}C NMR δ 24.0, 34.6, 46.2, 46.6, 55.5, 59.6, 129.9, 130.6 (2 C:s), 132.4 (2 C:s), 132.9 (2 C:s), 133.1, 133.3 (2 C:s), 134.0, 137.7, 138.7, 138.8, 141.5, 142.3, 142.8, 144.1, 172.4. HRTofMS calcd for $C_{25}H_{27}ClN_2O$ (M+) m/z 406.1812, found 406.1814.

5.2.10. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-(4-methoxyphenyl)benzamide HCl {B3}

Reaction of 3-(4-methoxyphenyl)benzoic acid with **B** yielded 140 mg (70%) of {**B3**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.20 (s, 3H), 2.21–2.27 (m, 1H), 2.30–2.38 (m, 1H), 2.79 (s, 6H), 3.03–3.10 (m, 1H), 3.15–3.21 (m, 1H), 3.74 (s, 3H), 5.13 (dd, 1H, J = 5.6, 9.4 Hz), 6.89 (d, 2H, J = 8.4 Hz), 7.09 (d, 2H, J = 7.6 Hz), 7.28 (d, 2H, J = 7.6 Hz), 7.39 (dd, 1H, J = 7.6, 8.0 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 7.6 Hz), 7.98 (s, 1H). ^{13}C NMR δ 23.9, 34.6, 46.2, 46.7, 55.4, 58.6, 59.6, 118.2 (2 C:s), 129.4, 129.5, 130.6 (2 C:s), 131.9 (2 C:s), 132.9, 133.3 (2 C:s), 133.6, 136.5, 138.6, 141.5, 142.3, 145.2, 163.8, 172.5. HRTofMS calcd for $C_{26}H_{30}N_2O_2$ (M+) m/z 402.2307, found 402.2324.

5.2.11. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-(2-naphthyl)benzamide HCl {B4}

Reaction of 3-(2-naphthyl)benzoic acid with **B** yielded 180 mg (85%) of {**B4**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.19 (s, 3H), 2.20–2.26 (m, 1H), 2.35–2.44 (m, 1H), 2.79 (s, 6H), 3.01–3.09 (m, 1H), 3.12–3.20 (m, 1H), 5.16 (dd, 1H, J = 6.0, 9.6 Hz), 7.07 (d, 2H, J = 8.0 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.36–7.46 (m, 3H), 7.69 (dd, 1H, J = 2.0, 8.4 Hz), 7.73–7.82 (m, 5H), 8.05 (s, 1H), 8.18 (s, 1H). ^{13}C NMR δ 24.0, 34.6, 46.2, 46.6, 55.5, 59.5, 129.0, 129.7, 130.0, 130.1, 130.2, 130.4, 130.6 (2 C:s), 131.4, 132.1, 132.5, 133.0, 133.3 (2 C:s), 134.4, 137.0, 137.9, 138.7, 141.4, 141.5, 142.4, 145.3, 172.6. HRTofMS calcd for $C_{29}H_{30}N_2O$ (M+) m/z 422.2358, found 422.2358.

5.2.12. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-4-phenylbenzamide HCl {B5}

Reaction of 4-phenylbenzoic acid with **B** yielded 140 mg (75%) of {**B5**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.23 (s, 3H), 2.27–2.34 (m, 2H), 2.81 (s, 6H), 3.08–3.12 (m, 1H), 3.16–3.22 (m, 1H), 5.15 (dd, 1H, J = 5.6, 9.4 Hz), 7.12 (d, 2H, J = 8.0 Hz), 7.26–7.31 (m, 4H), 7.36 (tt, 1H, J = 1.6, 6.8 Hz), 7.70 (d, 2H, J = 8.0 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.4 Hz). ^{13}C NMR δ 23.9, 34.6, 46.2, 46.7, 55.4, 59.6, 130.6 (2 C:s), 130.7 (2 C:s), 130.9 (2 C:s), 131.9, 132.0 (2 C:s), 132.8 (2 C:s), 133.3 (2 C:s), 136.7, 141.5, 142.2, 143.9, 148.6, 172.5. HRTofMS calcd for $C_{25}H_{28}N_2O$ (M+) m/z 372.2202, found 372.2218.

5.2.13. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-4-(4-chlorophenyl)benzamide HCl {B6}

Reaction of 4-(4-chlorophenyl)benzoic acid with **B** yielded 170 mg (84%) of {**B6**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.23 (s, 3H), 2.24–2.38 (m, 2H), 2.82 (s, 6H), 3.05–3.13 (m, 1H), 3.16–3.22 (m, 1H), 5.13 (dd, 1H, J = 5.6, 9.2 Hz), 7.11 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.55 (d, 2H, J = 8.4 Hz), 7.62 (d, 2H, J = 8.0 Hz), 7.87 (d, 2H, J = 8.0 Hz). ^{13}C NMR δ 23.9, 34.6, 46.2, 46.7, 55.4, 59.6, 130.6 (2 C:s), 130.7 (2 C:s), 132.1 (2 C:s), 132.4 (2 C:s), 132.9 (2 C:s),

133.3 (2 C:s), 137.0, 138.0, 141.5, 142.2, 142.6, 147.1, 172.3. HRTofMS calcd for $C_{25}H_{27}ClN_2O$ (M+) *m/z* 406.1812, found 406.1816.

5.2.14. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-4-(4-methoxyphenyl)benzamide HCl {B7}

Reaction of 4-(4-methoxyphenyl)benzoic acid with **B** yielded 140 mg (70%) of {**B7**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.20 (s, 3H), 2.21–2.28 (m, 1H), 2.30–2.41 (m, 1H), 2.79 (s, 3H), 2.80 (s, 3H), 3.05–3.11 (m, 1H), 3.16–3.22 (m, 1H), 3.71 (s, 3H), 5.13 (dd, 1H, *J* = 5.6, 9.6 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 8.8 Hz), 7.55 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR δ 23.9, 34.7, 46.2, 46.6, 55.4, 58.6, 59.6, 118.2 (2 C:s), 130.1 (2 C:s), 130.5 (2 C:s), 131.9 (2 C:s), 132.0 (2 C:s), 133.2 (2 C:s), 135.9, 136.1, 141.4, 142.5, 148.2, 164.1, 172.4. HRTofMS calcd for $C_{26}H_{30}N_2O_2$ (M+) *m/z* 402.2307, found 402.2314.

5.2.15. *N*-[3-Dimethylamino-1-(4-methylphenyl)propyl]-4-(2-naphthyl)benzamide HCl {B8}

Reaction of 4-(2-naphthyl)benzoic acid with **B** yielded 130 mg (62%) of {**B8**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.17 (s, 3H), 2.19–2.27 (m, 1H), 2.30–2.38 (m, 1H), 2.76 (s, 6H), 3.00–3.09 (m, 1H), 3.11–3.17 (m, 1H), 5.10 (dd, 1H, *J* = 5.2, 8.4 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.32–7.38 (m, 2H), 7.61 (dd, 1H, *J* = 1.2, 8.4 Hz), 7.66–7.77 (m, 5H), 7.87 (d, 2H, *J* = 6.8 Hz), 7.96 (s, 1H). ^{13}C NMR δ 24.0, 34.7, 46.2, 46.7, 55.5, 59.6, 128.8, 129.8, 130.2, 130.3, 130.6 (2 C:s), 131.0 (2 C:s), 131.4, 132.1 (2 C:s), 132.2, 132.5, 133.3 (2 C:s), 136.7, 137.2, 137.8, 141.1, 141.4, 142.5, 148.3, 172.4. HRTofMS calcd for $C_{29}H_{30}N_2O$ (M+) *m/z* 422.2358, found 422.2362.

5.2.16. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-phenylbenzamide HCl {C1}

Reaction of 3-phenylbenzoic acid with **C** yielded 170 mg (95%) of {**C1**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.40–2.43 (m, 1H), 2.50–2.53 (m, 1H), 2.82 (s, 6H), 3.13–3.17 (m, 1H), 3.23–3.28 (m, 1H), 5.37 (dd, 1H, *J* = 4.8, 7.6 Hz), 7.26–7.29 (m, 1H), 7.34–7.40 (m, 4H), 7.46 (t, 1H, *J* = 6.0 Hz), 7.57–7.60 (m, 3H), 7.70 (d, 1H, *J* = 6.0 Hz), 7.75–7.84 (m, 4H), 7.90 (s, 1H), 8.08 (s, 1H). ^{13}C NMR δ 34.4, 46.3, 46.6, 55.9, 59.6, 128.6, 129.5, 129.9, 130.0, 130.2, 130.3, 130.8 (2 C:s), 131.4, 131.6, 131.8, 132.5, 132.8 (2 C:s), 132.9, 134.1, 137.2, 137.6, 138.6, 142.5, 144.2, 145.6, 172.8. HRTofMS calcd for $C_{28}H_{28}N_2O$ (M+) *m/z* 408.2202, found 408.2206.

5.2.17. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-(4-chlorophenyl)benzamide HCl {C2}

Reaction of 3-(4-chlorophenyl)benzoic acid with **C** yielded 180 mg (92%) of {**C2**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.36–2.51 (m, 2H), 2.81 (s, 6H), 3.10–3. 20 (m, 2H), 5.34 (dd, 1H, *J* = 5.6, 10.4 Hz), 7.33–7.41 (m, 4H), 7.43–7.47 (m, 1H), 7.55–7.59 (m, 3H), 7.67–7.83 (m, 5H), 7.88 (s, 1H), 8.05 (s, 1H). ^{13}C NMR δ 34.4, 46.2, 46.6, 55.8, 59.5, 128.6, 129.5, 129.8, 130.0, 130.2, 130.6, 131.4, 131.8, 132.4 (2 C:s), 132.6, 132.8 (2 C:s), 133.0, 134.0, 137.2, 137.6, 137.7, 138.7, 142.5, 142.8, 144.2, 172.6. HRTofMS calcd for $C_{28}H_{27}ClN_2O$ (M+) *m/z* 442.1812, found 442.1816.

5.2.18. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-(4-methoxyphenyl)benzamide HCl {C3}

Reaction of 3-(4-methoxyphenyl)benzoic acid with **C** yielded 130 mg (67%) of {**C3**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.32–2.51 (m, 2H), 2.80 (s, 6H), 3.08–3.11 (m, 1H), 3.21–3.31 (m, 1H), 3.66 (s, 3H), 5.34 (dd, 1H, *J* = 4.2, 7.2 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 7.32–7.37 (m, 3H), 7.45–7.49 (m, 2H), 7.52–7.60 (m, 2H), 7.68–7.78 (m, 4H), 7.87 (s, 1H), 8.02 (s, 1H). ^{13}C NMR δ 34.5, 46.3, 46.6, 55.9, 58.6, 59.5, 118.1 (2 C:s), 128.6, 129.4, 129.5, 129.6, 130.0, 130.2, 131.5, 131.8, 132.0 (2 C:s), 132.6, 132.9, 133.7, 136.4, 137.1, 137.5, 138.5, 142.8, 145.1, 163.8, 172.8. HRTofMS calcd for $C_{29}H_{30}N_2O_2$ (M+) *m/z* 438.2307, found 438.2324.

5.2.19. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-(2naphthyl)benzamide HCl {C4}

Reaction of 3-(2-naphthyl)benzoic acid with **C** yielded 200 mg (99%) of {**C4**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.34–2.40 (m, 1H), 2.47–2.52 (m, 1H), 2.75 (s, 3H), 2.77 (s, 3H), 3.06–3.13 (m, 1H), 3.20–3.32 (m, 1H), 5.36 (dd, 1H, *J* = 5.6, 9.6 Hz), 7.32–7.39 (m, 4H), 7.41–7.45 (m, 1H), 7.56 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.65–7.78 (m, 7H), 7.80–7.84 (m, 2H), 7.88 (s, 1H), 8.02 (s, 1H), 8.20 (s, 1H). ^{13}C NMR δ 34.5, 46.2, 46.6, 55.9, 59.5, 128.6, 129.0, 129.5, 129.7, 129.9, 130.0, 130.1, 130.2 (2 C:s), 130.4, 131.4, 131.5, 131.8, 132.1, 132.4, 132.6, 133.0, 134.4, 137.0, 137.1, 137.6, 137.9, 138.6, 141.4, 142.7, 145.3, 172.6. HRTofMS calcd for $C_{32}H_{30}N_2O$ (M+) *m/z* 458.2358, found 458.2363.

5.2.20. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-4-phenylbenzamide HCl {C5}

Reaction of 4-phenylbenzoic acid with **C** yielded 170 mg (95%) of {**C5**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.33–2.40 (m, 1H), 2.47–2.52 (m, 1H), 2.77 (s, 3H), 2.79 (s, 3H), 3.09–3.16 (m, 2H), 5.34 (dd, 1H, *J* = 5.6, 9.6 Hz), 7.28 (d, 2H, *J* = 8.8 Hz), 7.32–7.36 (m, 3H), 7.44 (d, 2H, *J* = 8.8 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.56 (dd, 1H, *J* = 1.2, 8.4 Hz), 7.68–7.77 (m, 3H), 7.88–7.92 (m, 3H). ^{13}C NMR δ 34.5, 46.2, 46.6, 55.9, 59.5, 128.6, 129.4, 130.0, 130.2, 130.8 (2 C:s), 130.9 (2 C:s), 131.5, 131.8, 131.9, 132.1 (2 C:s), 132.6, 132.8 (2 C:s), 136.6, 137.1, 137.6, 142.8, 143.8, 148.6, 172.5. HRTofMS calcd for $C_{28}H_{28}N_2O$ (M+) *m/z* 408.2202, found 408.2204.

5.2.21. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-4-(4-chlorophenyl)benzamide HCl {C6}

Reaction of 4-(4-chlorophenyl)benzoic acid with **C** yielded 140 mg (72%) of {**C6**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.36–2.40 (m, 1H), 2.48–2.52 (m, 1H), 2.77 (s, 3H), 2.78 (s, 3H), 3.08–3.15 (m, 1H), 3.21–3.27 (m, 1H), 5.34 (dd, 1H, *J* = 5.6, 9.6 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.31–7.36 (m, 2H), 7.44 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.56 (dd, 1H, *J* = 1.2, 8.4 Hz), 7.69–7.77 (m, 3H), 7.88–7.92 (m, 3H). ^{13}C NMR δ 34.5, 46.2, 46.6, 55.9, 59.5, 128.6, 129.4, 130.0, 130.2, 130.7 (2 C:s), 131.5, 131.8, 132.2 (2 C:s), 132.4 (2 C:s), 132.6, 132.9 (2 C:s), 136.9, 137.1, 137.5, 137.9, 142.4, 142.9, 147.0, 172.3. HRTofMS calcd for $C_{28}H_{27}ClN_2O$ (M+) *m/z* 442.1812, found 442.1818.

5.2.22. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-4-(4-methoxyphenyl)benzamide HCl {C7}

Reaction of 4-(4-methoxyphenyl)benzoic acid with **C** yielded 160 mg (83%) of {**C7**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.35–2.39 (m, 1H), 2.45–2.48 (m, 1H), 2.76 (s, 3H), 2.77 (s, 3H), 3.09–3.12 (m, 1H), 3.18–3.22 (m, 1H), 3.68 (s, 3H), 5.33 (dd, 1H, *J* = 5.6, 9.4 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 7.33–7.38 (m, 2H), 7.43 (d, 2H, *J* = 8.8 Hz), 7.52–7.56 (m, 3H), 7.70–7.78 (m, 3H), 7.85–7.88 (m, 3H). ^{13}C NMR δ 34.5, 46.2, 46.6, 55.8, 58.6, 59.5, 118.2 (2 C:s), 128.6, 129.4, 130.0, 130.2 (2 C:s), 130.3, 131.5, 131.8, 131.9 (2 C:s), 132.1 (2 C:s), 132.6, 135.8, 136.0, 137.1, 137.6, 142.8, 148.2, 164.0, 172.5. HRTofMS calcd for $C_{29}H_{30}N_2O_2$ (M+) *m/z* 438.2307, found 438.2322.

5.2.23. *N*-[3-Dimethylamino-1-(2-naphthyl)propyl]-4-(2-naphthyl)benzamide HCl {C8}

Reaction of 4-(2-naphthyl)benzoic acid with **C** yielded 110 mg (55%) of {**C8**} which was converted to the hydrochloride salt. ^{1}H NMR δ 2.33–2.39 (m, 1H), 2.42–2.56 (m, 1H), 2.78 (s, 3H), 2.79 (s, 3H), 3.10–3.14 (m, 1H), 3.20–3.27 (m, 1H), 5.35 (dd, 1H, J = 5.6, 9.6 Hz), 7.34–7.39 (m, 4H), 7.56 (d, 1H, J = 8.4 Hz), 7.62 (dd, 1H, J = 1.6, 8.8 Hz), 7.70–7.79 (m, 8H), 7.88 (s, 1H), 7.94 (d, 2H, J = 8.4 Hz), 7.99 (s, 1H). ^{13}C NMR δ 34.5, 46.2, 46.6, 55.9, 59.6, 128.6, 128.8, 129.4, 129.8, 130.0, 130.2 (2 C:s), 130.3, 131.0 (2 C:s), 131.4, 131.5, 131.8, 132.2 (3 C:s), 132.5, 132.6, 136.6, 137.1, 137.2, 137.6, 137.8, 141.0, 142.8, 148.4, 172.5. HRTofMS calcd for $C_{32}H_{30}N_2O$ (M+) m/z 458.2358, found 458.2362.

5.2.24. *N*-[3-Dimethylaminopropyl-1-(4-methylphenyl)]-(*R*)-2-methoxy-2-phenylacetamide HCl {B9}

Compound **B** (0.55 g, 2.9 mmol) was dissolved in THF (100 mL). (*R*)-2-Methoxy-2-phenylacetic acid (0.48 g, 2.9 mmol), EDC (0.60 g, 3.2 mmol) and DMAP (35 mg, 0.29 mmol) were added and the mixture was stirred for three days. Saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (100 mL) were added. The phases were separated and the water phase extracted with EtOAc. The combined organic phases were washed (water, brine) and concentrated. The residue was purified with flash chromatography using MeOH/CH_2Cl_2/NEt_3 (5/94.9/0.1) to afford 0.42 g (44%) of the pure diastereomeric mixture which was separated by repeated flash chromatography using MeOH/CH_2Cl_2/NEt_3 (5/94.9/0.1) until the pure diastereomers were obtained (200 mg (+), 220 mg (−)) which were converted to their corresponding hydrochloride salt for analysis, storage and biological testing.

5.2.25. (+)-*N*-[3-Dimethylaminopropyl-1-(4-methylphenyl)]-(*R*)-2-methoxy-2-phenylacetamide HCl ((+)-B9)

$[\alpha]_D$ +9.1 (c 0.72, MeOH). ^{1}H NMR δ 2.13–2.19 (m, 5H), 2.62 (s, 3H), 2.65 (s, 3H), 2.83–2.87 (m, 2H), 3.21 (s, 3H), 4.60 (s, 1H), 4.85 (dd, 1H, J = 6.0, 9.2 Hz), 7.01 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 8.0 Hz), 7.20–7.27 (m, 3H), 7.36 (d, 2H, J = 7.2 Hz). ^{13}C NMR δ 24.0, 34.5, 46.1, 46.5, 54.3, 59.3, 60.3, 87.6, 130.4 (2 C:s), 131.1 (2 C:s), 132.5 (3 C:s), 133.2 (2 C:s), 141.5, 141.6, 141.8, 176.0.

5.2.26. (−)-*N*-[3-Dimethylaminopropyl-1-(4-methylphenyl)]-(*R*)-2-methoxy-2-phenylacetamide HCl ((−)-B9)

$[\alpha]_D$ −137.2 (c 0.27, MeOH). ^{1}H NMR δ 2.20–2.28 (m, 2H), 2.30 (s, 3H), 2.80 (s, 6H), 3.00–3.04 (m, 2H), 3.33 (s, 3H), 4.72 (s, 1H), 4.95 (dd, 1H, J = 5.9, 9.1 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.0 Hz), 7.31–7.39 (m, 5H). ^{13}C NMR δ 19.8, 30.3, 42.3 (2 C:s), 50.4, 55.3, 56.1, 83.4, 126.3 (2 C:s), 127.2 (2 C:s), 128.3 (2 C:s), 128.4, 129.1 (2 C:s), 137.4, 137.5, 137.7, 171.8.

5.2.27. *N*-[3-Dimethylaminopropyl-1-(2-naphthyl)]-(*R*)-2-methoxy-2-phenylacetamide HCl {C9}

Compound **C** (0.70 g, 3.0 mmol) was reacted according to the same procedure as described for **B** to afford 0.55 g (49%) of the pure diastereomeric mixture of **C9** which was separated by repeated flash chromatography using MeOH/CH_2Cl_2/NEt_3 (5/94.9/0.1) until the pure diastereomers were obtained (250 mg (+), 300 mg (−)). The amines were converted to their corresponding hydrochloride salt for analysis, storage and biological testing.

5.2.28. (+)-*N*-[3-Dimethylaminopropyl-1-(2-naphthyl)]-(*R*)-2-methoxy-2-phenylacetamide HCl ((+)-C9)

$[\alpha]_D$ +26.0 (c 1.5, MeOH). ^{1}H NMR δ 2.23–2.29 (m, 2H), 2.64 (s, 6H), 2.87–2.93 (m, 2H), 3.21 (s, 3H), 4.62 (s, 1H), 5.06 (t, 1H, J = 7.6 Hz), 7.21–7.27 (m, 3H), 7.32–7.39 (m, 5H), 7.65–7.72 (m, 4H). ^{13}C NMR δ 32.3, 46.4 (2 C:s), 54.6, 59.3, 60.3, 87.6, 128.4, 129.2, 130.0, 130.2, 131.0 (2 C:s), 131.1, 131.4, 131.7, 132.4 (2 C:s), 132.5, 137.1, 137.5, 141.6, 142.0, 176.2.

5.2.29. (−)-*N*-[3-Dimethylaminopropyl-1-(2-naphthyl)]-(*R*)-2-methoxy-2-phenylacetamide HCl ((−)-C9)

$[\alpha]_D$ −133.5 (c 0.29, MeOH). ^{1}H NMR δ 2.31–2.42 (m, 2H), 2.81 (s, 6H), 3.00–3.11 (m, 2H), 3.36 (s, 3H), 4.76 (s, 1H), 5.16 (dd, 1H, J = 7.0, 8.1 Hz), 7.29–7.32 (m, 3H), 7.39–7.49 (m, 4H), 7.77–7.85 (m, 4H). ^{13}C NMR δ 30.1, 42.3 (2 C:s), 50.7, 55.3, 56.1, 83.5, 124.3, 125.1, 125.9, 126.1, 127.1 (2 C:s), 127.3, 127.6, 128.3 (2 C:s), 128.4, 128.5, 133.0, 133.4, 137.4, 137.9, 172.1.

5.2.30. *N*-[1-(4-Chlorophenyl)-3-(1-piperidinyl)-propyl]-4-phenylbenzamide oxalate {D5}

Reaction of 4-phenylbenzoic acid with **D** yielded 115 mg (67%) of {**D5**} which was converted to the hydrochloride salt. ^{1}H NMR δ 1.15–1.23 (m, 1H), 1.74–1.94 (m, 5H), 2.31–2.51 (m, 2H), 2.85–2.92 (m, 2H), 3.11–3.31 (m, 2H), 3.51–3.60 (m, 2H), 5.23 (dd, 1H, J = 5.5, 9.5 Hz), 7.35–7.40 (m, 3H), 7.43–7.49 (m, 4H), 7.64 (d, 2H, J = 7.3 Hz), 7.72 (d, 2H, J = 8.1 Hz), 7.95 (d, 2H, J = 8.1 Hz). ^{13}C NMR δ 21.3, 23.0, 23.1, 29.6, 29.7, 51.1, 53.0, 54.4, 54.6, 126.7 (2 C:s), 126.8 (2 C:s), 127.8, 127.9 (2 C:s), 128.3 (2 C:s), 128.6 (2 C:s), 128.8 (2 C:s), 132.4, 133.3, 139.8, 140.1, 144.7, 168.5. Anal. Calcd for $C_{27}H_{29}ClN_2O$·HCl: C, 69.1; H, 6.4; N, 6.0. Found: C, 69.5; H, 6.5; N, 6.4.

5.2.31. *N*-[1-(4-Chlorophenyl)-3-(1-piperidinyl)-propyl]benzamide oxalate {D10}

Reaction of benzoic acid with **D** yielded 95 mg (67%) of {**D10**} which was converted to the hydrochloride salt. ^{1}H NMR δ 1.12–1.20 (m, 1H), 1.61–1.80 (m, 5H), 2.10–2.22 (m, 2H), 2.85–2.93 (m, 2H), 3.00–3.23 (m, 4H), 5.14 (dd, 1H, J = 5.6, 9.6 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.33–7.45 (m, 5H), 7.81 (d, 2H, J = 8.4 Hz). ^{13}C NMR δ 25.4, 27.1, 38.9, 52.5, 55.4, 57.4, 58.7, 69.7, 131.5 (2 C:s), 132.3, 132.4 (2 C:s), 132.7 (2 C:s), 135.8 (2 C:s), 137.2, 137.9, 144.6, 170.0. Anal. Calcd for $C_{21}H_{25}ClN_2O$·HCl: C, 64.1; H, 6.7; N, 7.1. Found: C, 64.5; H, 6.5; N, 7.4.

5.2.32. *N*-[1-(4-Chlorophenyl)-4-dimethylaminobutyl]-4-phenylbenzamide oxalate {E5}

Reaction of 4-phenylbenzoic acid with **E** yielded 110 mg (61%) {**E5**} which was converted to the oxalate salt. ^{1}H NMR δ 1.72–2.06 (m, 4H), 2.87 (s, 6H), 3.16–3.21 (m, 2H), 5.18 (dd, 1H, J = 5.9, 9.2 Hz), 7.36–7.39 (m, 3H), 7.43–7.48 (m, 4H), 7.65 (d, 2H, J = 7.3 Hz), 7.72 (d, 2H, J = 8.1 Hz), 7.93 (d, 2H, J = 8.1 Hz). ^{13}C NMR δ 21.7, 32.2, 42.2 (2 C:s), 52.8, 57.2, 126.7 (2 C:s), 126.8 (2 C:s), 127.8, 127.9 (2 C:s), 128.2 (2 C:s), 128.4 (2 C:s), 128.7 (2 C:s), 132.8, 132.9, 139.8, 141.2, 144.5, 168.4. HRTofMS calcd for $C_{25}H_{27}ClN_2O$ (M+) m/z 406.9597, found 406.9600.

5.2.33. *N*-[1-(4-Chlorophenyl)-4-dimethylaminobutyl]benzamide oxalate {E10}

Reaction of benzoic acid with **E** yielded 60 mg (41%) of {**E10**} which was converted to the oxalate salt. ^{1}H NMR δ 1.71–2.01 (m, 4H), 2.86 (s, 6H), 3.14–3.22 (m, 2H), 5.13 (dd, 1H, J = 5.8, 9.5 Hz), 7.35 (d, 2H, J = 9.2 Hz), 7.42 (d, 2H, J = 9.2 Hz), 7.45–7.47 (m, 2H), 7.53 (tt, 1H, J = 1.4, 7.3 Hz), 7.84 (dd, 2H, J = 1.4, 7.3 Hz). ^{13}C NMR δ 21.7, 32.2, 42.1, 42.2, 52.8, 57.2, 127.2 (2 C:s), 128.1 (2 C:s), 128.3 (2 C:s), 128.4 (2 C:s), 131.5, 132.8, 134.1, 141.2, 168.7. HRTofMS calcd for $C_{19}H_{23}ClN_2O$ (M+) m/z 330.8610, found 330.8613.

6. Biological activity

6.1. R-SAT-testing

R-SAT™ assays for pharmacological testing were performed as previously described,[7] 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/gluatmine (Invitrogen), and then added to half-area 96-well microtitre 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 UT receptor selectivity all compounds were tested against the m3 receptor as a negative control (data not shown).

7. X-ray structure determination of (−)-{C9}

7.1. Data collection

A colourless block crystal of *N*-[3-dimethylaminopropyl-1-(2-naphthyl)]-1-methoxy-2-phenyl-acetamide HCl ($C_{24}H_{29}ClN_2O_2$) (−)-{**C9**} having approximate dimensions of $0.40 \times 0.30 \times 0.25\ mm^3$ was mounted with epoxy cement on the tip of a fine glass fibre. All measurements were made on a Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation.[8] Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

$a = 5.4068(11)$ Å $\quad \alpha = 90^\circ$

$b = 10.174(2)$ Å $\quad \beta = 93.02(2)^\circ$

$c = 20.701(6)$ Å $\quad \gamma = 90^\circ$

$V = 1137.1(5)$ Å^3

For $Z = 2$ and FW = 412.94, the calculated density is 1.206 mg/m^3. The space group was determined to be *P*21 (#4). The data were collected at a temperature of 298(2) K to a maximum 2θ value of 51.92°.

7.2. Data reduction

A total of 2492 reflections including Friedel equivalents were collected of which 2366 were unique and observed ($R_{int} = 0.0113$). The linear absorption coefficient, μ, for Mo Kα radiation is $0.189\ mm^{-1}$, and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.[9]

7.3. Structure solution and refinement

The structure was solved by direct methods and expanded using Fourier techniques.[10,11] The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were treated as idealized contributions. The final cycle of full-matrix least-squares refinement on *F* was based on 1428 observed reflections ($I > 2.00\sigma(I)$) and 265 variable parameters and converged with unweighted and weighted agreement factors of:

$$R = \sum \|F_o| - |F_c\| / \sum |F_o| = 0.0669;$$

$$R_w = \left\{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \right\}^{1/2} = 0.1840$$

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.641 and −0.570 e/Å^3 respectively. The absolute structure Flack parameter is 0.03(19).[12]

Acknowledgements

Financial support was obtained from The Knut and Alice Wallenberg Foundation and The Swedish Research Council.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.04.062.

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