Novel Potent and Efficacious Nonpeptidic Urotensin II Receptor Agonists

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Six different series of nonpeptidic urotensin II receptor agonists have been synthesized and evaluated for their agonistic activity in a cell-based assay (R-SAT). The compounds are ring-opened analogues of the isochromanone-based agonist AC-7954 with different functionalities constituting the linker between the two aromatic ring moieties. Several of the compounds are highly potent and efficacious, with *N*-[1-(4-chlorophenyl)-3-(dimethylamino)-propyl]-4-phenylbenzamide oxalate (**5d**) being the most potent. The pure enantiomers of **5d** were obtained from the corresponding diastereomeric amides. It was shown by a combination of X-ray crystallography and chemical correlation that the activity resides in the *S*-enantiomer of **5d** (pEC_{50} 7.49).

Introduction

Urotensin II (UII) has become the focus of many research studies in recent years.[1−8] This is mainly due to its proposed involvement in a range of body functions[1] and diseases such as cardiovascular disease,[7−10] atherosclerosis,[11] diabetic nephropathy,[12] and diabetes type II.[13] UII is a cyclic undecapeptide originally isolated from the long-jawed mud sucker.[3] The cyclic hexapeptide part (CFWKYC) is conserved between species and is considered essential for activity; Lys[8] and Tyr[9] are identified as particularly important.[14,15] Lavecchia et al. have recently examined the binding domain for both peptidic and nonpeptidic agonists using in silico methods.[16] However, to get a deeper understanding of the pharmacology of UII there is a need for nonpeptidergic agonists and antagonists.[2,17,18]

Recently we presented an initial structure−activity relationship (SAR) study on isochromanone-based UII receptor agonists[19] which were derived from AC-7954, the first reported nonpeptidic UII agonist (Figure 1).[20] The study showed that the introduction of substituents in either of the two aromatic rings was well tolerated, whereas sterically demanding amino functions, or substitution in the 4-position, were detrimental to the activity. (+)-6,7-Dimethyl-3-(4-chlorophenyl)-3-(2-dimethylaminoethyl)-isochromanone (FL68, Figure 1) was found to be the most potent compound in that study (pEC_{50} 7.11).

Although the isochromanone-based agonists are appealing in their druglikeness and their high selectivity for the UII receptor, the synthetic procedure to obtain these compounds is somewhat inefficient and has limited the availability of interesting compounds. We envisioned that breaking the C3−C4 bond (Figure 2) in the isochromanone scaffold would open up possibilities to chemical approaches that would enable the construction of series of structurally more diverse compounds for biological testing. This strategy proved to be successful, leading to six series of compounds (ether, ester, amide, sulfonamide, carbamate, and urea derivatives). Potent compounds were found in all series except ethers and sulfonamides, and the most potent agonists were found to be in the nanomolar range.

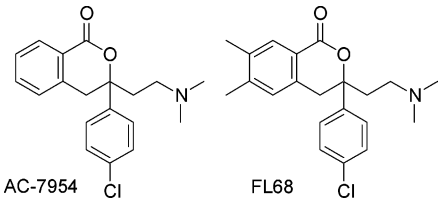

Figure 1. The first nonpeptidic UII receptor agonist AC-7954 (left) and FL68 (right), so far the most potent isochromanone-based UII agonist.

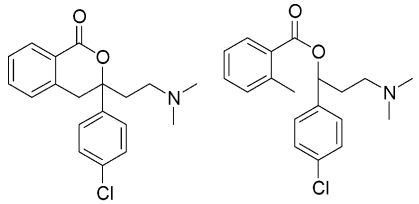

Figure 2. The similarity between the new lead compound **4a** and AC-7954.

Results and Discussion

Chemistry. Synthesis of Key Intermediates 1 and 2. To synthesize the series of ether, ester, and carbamate derivatives (**3**, **4**, **6**), respectively, their common intermediate, alcohol **1**, was prepared in 91% yield by reduction of the commercially available ketone 1-(4-chlorophenyl)-3-dimethylaminopropan-1-one with $LiAlH_4$ (Scheme 1). Alcohol **1** was also used to produce amine **2** used for the synthesis of the series of amide, urea and sulfonamide derivatives (**5**, **7**, **8**), respectively. Conversion of **1** to the corresponding acetamide via a Ritter reaction (Scheme 1),[21,22] using acetonitrile as the nitrogen source, and subsequent hydrolysis in refluxing 6 M HCl afforded the primary amine **2** in excellent yield (>99% over three steps).

Synthesis of Ether and Ester Derivatives. Compound **1** was used to prepare the ether derivatives **3v** and **3w** in acceptable yields (48 and 78%, respectively) by nucleophilic substitution

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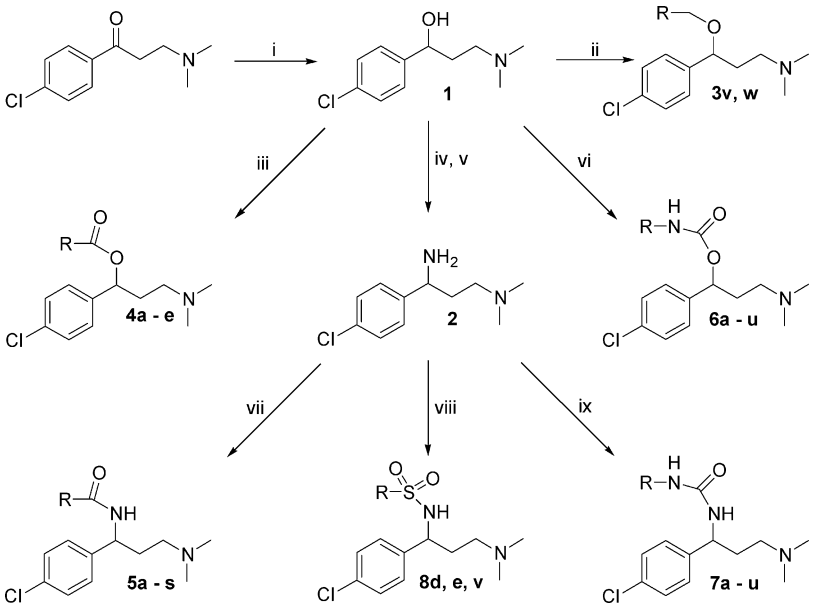
Scheme 1[a]



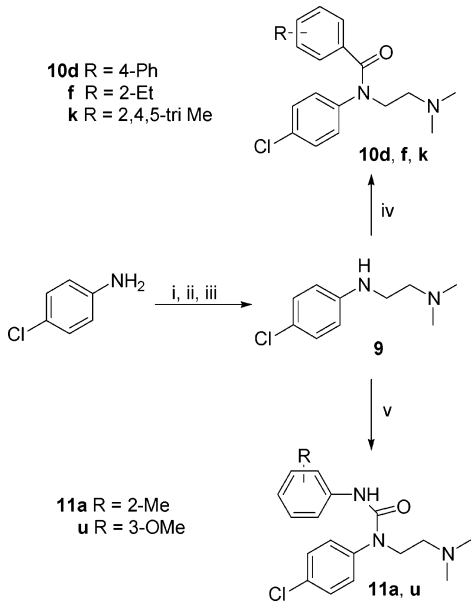
[a] (i) LAH, THF, 91%. (ii) R-CH_2-X, PS-DIPEA, CH_2Cl_2, 48 and 78%. (iii) R-COOH, EDC, DMAP, CH_2Cl_2, 43-98%. (iv) CH_3CN, H_2SO_4. (v) 6 M $HCl_{(aq)}$, >99%. (vi) R-NCO, NEt_3, THF, 29−91%. (vii) R-COOH, $SOCl_2$, NEt_3, THF, 42−98% or R-COOH, EDC, DMAP, CH_2Cl_2, 60−67%. (viii) R-SO_2-Cl, NEt_3, THF, quant. (ix) R-NCO, NEt_3, THF, 38−98%.

of 4-methylbenzyl bromide and 2-methoxybenzyl chloride, respectively, in the presence of polymer-bound diisopropylbenzylamine.[23] Reaction of **1** with commercially available benzoic acids in the presence of EDC and DMAP in CH_2Cl_2 provided the desired esters **4a**−**e** in moderate to good yields (43−98%).[24]

Synthesis of Amide Derivatives. To produce amide **5s**, a solution of **1** in benzonitrile was treated with concentrated sulfuric acid. However, the Ritter reaction worked only with the liquid benzonitrile and acetonitrile. Attempts to perform the Ritter reaction of **1** with a solid aromatic nitrile such as 2-methylbenzonitrile or 4-phenylbenzonitrile dissolved in acid or in an inert solvent such as toluene did not succeed. The reactions only resulted in the conversion of the benzonitriles to the corresponding benzamides. Therefore, amides **5a**−**k**,**m** and **5o**−**r** were synthesized as outlined in Scheme 1 using amine **2** and the appropriate acid chlorides. The acid chlorides were produced in situ from commercially available benzoic acids and thionyl chloride, and subsequently **2** was added. This procedure afforded the desired amides in moderate to good yields (42−98%). 2-Phenylacetyl chloride failed to give good result with this method, and therefore 2-phenylacetic acid was reacted with amine **2** in the presence of EDC and DMAP to produce **5n** in an acceptable yield (60%). This coupling method was also employed in the synthesis of the diastereomeric amides (+)- and (−)-**5l**, which were subsequently separated by flash chromatography to yield the pure diastereomers.

Synthesis of Carbamate and Urea Derivatives. Carbamate and urea derivatives (**6a**−**u**, **7a**−**u**) were synthesized by reacting alcohol **1** or amine **2** with an isocyanate in methanol as outlined in Scheme 1. Evaporation of the solvent followed by flash chromatography afforded the desired compounds in varying yields (19−91%). For the synthesis of **6b**−**e** and **7b**−**e**, the isocyanates were first prepared in situ before addition of the alcohol or amine as described in a literature procedure.[25] The isocyanates were prepared from the corresponding benzoic acids and diphenylphosphoryl azide in toluene. In the synthesis of the carbamates an excess of isocyanate was needed to drive the reaction to completion as the products were difficult to separate from alcohol **1**.

Scheme 2[a]



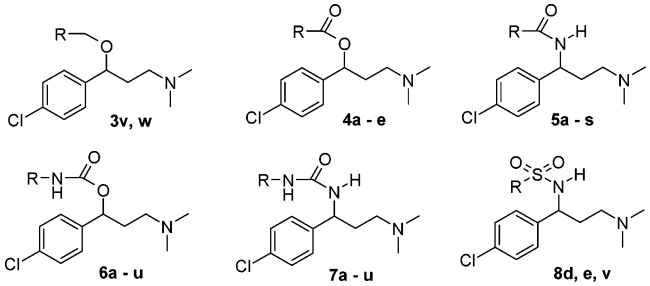
[a] (i) Chloroacetyl chloride, NEt_3, (ii) Me_2NH, NEt_3, (iii) $LiAlH_4$, 67% over three steps. (iv) RCOOH, $SOCl_2$, NEt_3, 73−90 %, (v) aryl isocyanate, NEt_3, 73−97%.

Synthesis of Sulfonamides. The pure sulfonamides **8d**,**e**,**v** were produced in almost quantitative yield by addition of the appropriate sulfonyl chloride to amine **2** in THF.

Synthesis of Achiral Amides and Ureas. For synthesis of the achiral amides **10d**,**f**,**k** and ureas **11a**,**u**, intermediate **9** was used (Scheme 2). Compound **9** was prepared from 4-chloroaniline in an overall yield of 67% over the three synthetic steps.

Pharmacological Testing. Compounds **3v**−**8v** and **10d**−**11u** were tested for their agonistic properties at human UII receptors using the functional R-SAT assay previously described.[26−29] The results are shown in Table 1. Several potent agonists were identified, four compounds being equally or more potent than FL68. In addition, 17 compounds showed higher or much higher efficacies.

Table 1. Results from in Vitro Testing of Urotensin-II Receptor Affinity



compd	R	pEC$_{50}$[a]	efficacy[b]	*N*[c]
AC7954		5.95 ± 0.12	133 ± 8	6
FL68		6.87 ± 0.03	146 ± 24	2
3v	4-MePh	NA[c]		2
3w	2-OMe-Ph	NA[c]		2
4a	2-MePh	5.77 ± 0.01	126 ± 34	2
4b	4-OMe-Ph	5.66 ± 0.2	84 ± 28	3
4c	4-CF_3-Ph	5.76 ± 0.15	47 ± 18	3
4d	4-Ph-Ph	6.28 ± 0.14	53 ± 27	2
4e	2-naphthyl	5.68 ± 0.04	49 ± 28	3
5a	2-MePh	5.45 ± 0.04	175 ± 15	2
5b	4-OMe-Ph	5.87 ± 0.2	162 ± 38	5
5c	4-CF_3−Ph	7.11 ± 0.1	115 ± 14	3
5d	4-Ph-Ph	7.11 ± 0.01	116 ± 11	2
(−)-5d	4-Ph-Ph	5.84 ± 0.1	96 ± 16	5
(+)-5d	4-Ph-Ph	7.49 ± 0.33	116 ± 18	5
5e	2-naphthyl	6.39 ± 0.19	109 ± 18	2
5f	2-EtPh	5.99 ± 0.01	140 ± 14	2
5g	2,3-diMePh	5.44 ± 0.08	159 ± 1	2
5h	2-Me-3-OMe-Ph	5.37 ± 0.14	179 ± 11	2
5i	3-Cl-2-Me-Ph	5.76 ± 0.13	142 ± 14	3
5j	2,5-diMePh	5.54 ± 0.04	164 ± 20	2
5k	2,4,5-triMePh	5.75 ± 0.22	159 ± 23	5
(+)-5l	(*R*)-Ph-CH(OMe)	5.30 ± 0.07	112 ± 22	2
(−)-5l	(*R*)-Ph-CH(OMe)	6.06 ± 0.03	165 ± 10	2
5m	4-OPh-Ph	7.18 ± 0.2	89 ± 13	4
5n	Ph-CH_2-	5.71 ± 0.16	155 ± 42	4
5o	4-(Me_2N)-Ph	5.87 ± 0.17	150 ± 22	5
5p	3,4-(OCH_2O)-Ph	5.67 ± 0.17	154 ± 31	5
5q	2,4-diMePh	5.81 ± 0.06	147 ± 29	2
5r	6-Cl-2-MePh	5.29 ± 0.09	105 ± 4	2
5s	Ph	5.85 ± 0.01	158 ± 39	2
6a	2-MePh	5.41 ± 0.07	176 ± 28	4
6b	4-OMe-Ph	5.78 ± 0.21	170 ± 48	3
6c	4-CF_3-Ph	6.60 ± 0.13	94 ± 22	3
6d	4-Ph-Ph	6.57 ± 0.12	58 ± 16	3
6e	2-naphthyl	6.28 ± 0.26	89 ± 19	3
6m	4-OPh-Ph	6.72 ± 0.25	107 ± 16	2
6n	Ph-CH_2	5.67 ± 0.15	180 ± 11	2
6t	4-t-BuPh	5.74 ± 0.8	105 ± 12	2
6u	3-OMe-Ph	5.95 ± 0.09	136 ± 37	4
7a	2-MePh	5.64 ± 0.15	175 ± 23	4
7b	4-OMe-Ph	5.70 ± 0.06	195 ± 31	3
7c	4-CF_3-Ph	6.93 ± 0.11	105 ± 14	3
7d	4-Ph-Ph	6.84 ± 0.11	91 ± 18	3
7e	2-naphthyl	6.54 ± 0.1	106 ± 21	3
7m	4-OPh-Ph	6.96 ± 0.2	108 ± 10	3
7n	Ph-CH_2	5.70 ± 0.08	179 ± 19	2
7t	4-tBuPh	6.56 ± 0.44	103 ± 36	3
7u	3-OMe-Ph	5.87 ± 0.17	146 ± 25	5
8d	4-Ph-Ph	NA		3
8e	2-naphthyl	NA		3
8v	4-MePh	5.19 ± 0.09	74 ± 10	4

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

Structure−Activity Relationships. In our previous study of isochromanone-based agonists it was found that substituents such as methyl, halogen, and/or methoxy groups in different positions of the two aromatic rings of AC-7954 generally improved the potency and efficacy.[19] This trend was most apparent in the aromatic part of the isochromanone scaffold. Substituents in the phenyl ring in the 3-position resulted in only limited improvements in affinity and efficacy. In the present study we have therefore kept one of the aromatic rings intact (4-chlorophenyl) and instead focused our attention on the use of different linkers between the two rings, as well as different substituent patterns in the other aromatic ring.

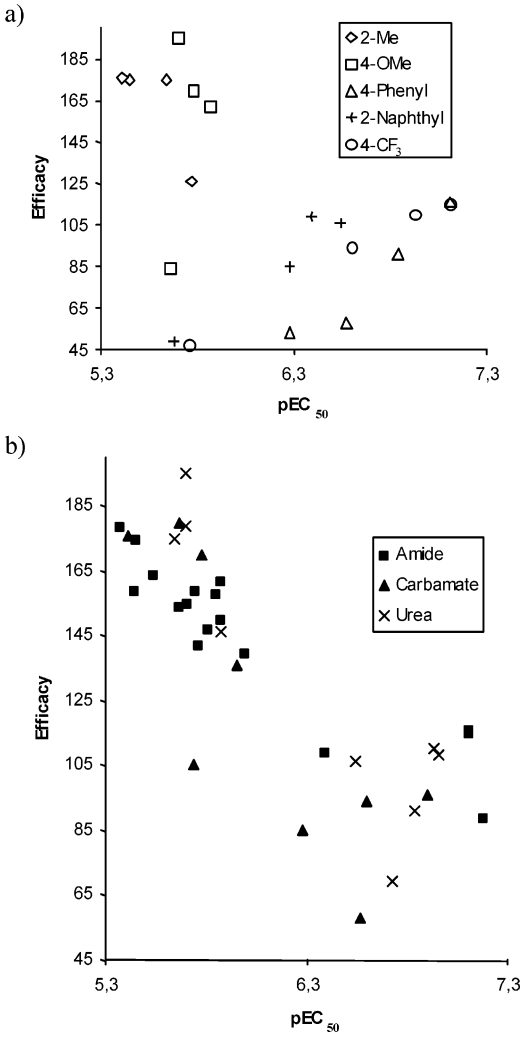
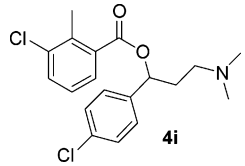


Figure 3. Scatter plots of the correlation between efficacy and pEC$_{50}$ values for (a) 2-methyl-substituted derivatives **4a**−**7a**, 4-methoxy-substituted derivatives **4b**−**7b**, 4-trifluoromethyl-substituted derivatives **4c**−**7c**, 4-phenyl-substituted derivatives **4d**-**7d**, and 2-naphthyl derivatives **4e**−**7e**. Small electron-donating substituents (methyl and methoxy) improve the efficacy whereas large and/or lipophilic substituents (4-phenyl, 4-trifluoromethyl, or the 2-naphthyl) contribute more to potency, (b) amides **5a**−**s**, carbamates **6a**-**u**, and urea derivatives **7a**-**u**.

As illustrated in Figure 2, we started our studies by synthesizing ester **4a**. This compound retained most of the activity and efficacy compared to AC-7954 (Table 1). To study the effect of different linkers between the aromatic rings the corresponding amide (**5a**), carbamate (**6a**), and urea (**7a**) derivatives were synthesized. These three compounds have comparable or slightly lower potency compared to **4a** but similar or enhanced efficacy. Four additional derivatives were synthesized in each series, the 4-OMe-phenyl (**4b**−**7b**), 4-CF_3-phenyl (**4c**−**7c**), 4-phenyl-phenyl (**4d**−**7d**), and 2-naphthyl (**4e**−**7e**) derivatives, respectively. As apparent from Table 1 and Figure 3, two trends can be observed: First, the ester derivatives **4a**−**e** seem to have

lower efficacy than the corresponding derivatives in the other series. Second, the larger and/or more lipophilic substituents 4-CF_3, 4-phenyl, and the 2-naphthyl generate compounds that are considerably more potent than the smaller substituents 2-methyl and 4-methoxy. This result could possibly also correlate to the electronic properties, since 2-methyl and 4-methoxy groups are electron-donating, whereas 4-CF_3 and 4-phenyl groups are electron withdrawing. To further examine these trends additional compounds were synthesized within each series. The compounds were selected based on differences in physicochemical properties such as size, lipophilicity, and polarity.



4i

The risk of chemical or enzyme catalyzed hydrolysis of esters in the test assay is apparent. We therefore used compound **4i** (see Supporting Information) to assess whether any of the hydrolysis products contributed to the activity observed. However, neither alcohol **1** nor 3-chloro-2-methylbenzoic acid were able to activate the UII receptor (data not shown). Thus the activity of **4i** (pEC_{50} 5.95 ± 0.05) was considered to originate from the ester itself. The observed activities of the ester derivatives (Table 1, Supporting Information) are therefore dependent on the degree of ester hydrolysis, i.e., on the amount of ester not being hydrolyzed. Test results obtained from esters **4a**−**d** differ from the derivatives carrying the same substituents but different linkers. Whether this result is due to a significant degree of hydrolysis during the assay is not known, and the ester derivatives were not considered any further.[30]

Increased lipophilicity tends to increase potency among the amides, where the large, more lipophilic compounds (**5c**, **5d**, **5e**, and **5m)** are approximately 1 order of magnitude more potent than the other amides. Similar trends are seen in the urea and carbamate series; substituents such as 4-phenyl-phenyl (**6d**, **7d**), 4-phenoxy-phenyl (**6m**, **7m**), 2-naphthyl (**6e**, **7e**), and 4-CF_3-phenyl (**6c**, **7c**) contribute more to the activity than the smaller substituents.

Another common trend in the three series is the positive effect of electron-donating groups for efficacy, whether weak (see e.g. **5a**, **5g**, **6a**, **6n**, **7a**, and **7n**) or strong (see e.g. **5b**, **5h**, **6b**, **6u**, **7b**, and **7u**). In contrast, the powerfully electron-withdrawing trifluoromethyl substituent (see e.g. **4c**, **5c**, **6c**, and **7c)** provides some of the least efficacious compounds in their respective series (Figure 3a).

Interestingly, the ether (**3v**,**w)** and sulfonamide (**8d**,**e**,**v**) derivatives were devoid of measurable activity. The inactivity might be due to the absence of the carbonyl group itself as an important pharmacophoric feature, or to the absence of conformational effects induced by the carbonyl group in the esters, amides, ureas, or carbamates, directing the aromatic moiety into a favorable position for receptor interaction. This suggestion is corroborated by a computer-based conformational analysis (Macromodel, MM3) which showed that conformational energies corresponding to 1.3 and 1.9 kcal/mol are required to align the ether or sulfonamide derivatives, respectively, with the active series (Figure 4).

Interestingly, the achiral compounds **10d**, **10f**, **10k**, **11a**, and **11u** were devoid of activity although these compounds have some resemblance to the active amide and urea derivatives.

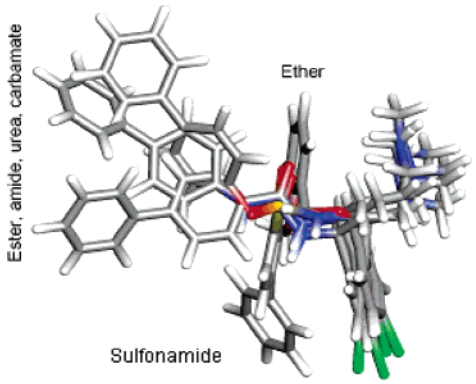


Figure 4. Alignment of the global minimum conformations of **3w**, **4d**, **5d**, **6d**, **7d**, and **8d** identified by conformational analysis using molecular mechanics calculations (MM3, MacroModel v.7.0).

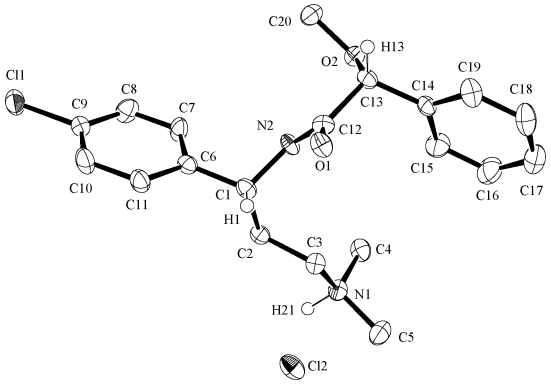


Figure 5. ORTEP plot of (+)-**5l** HCl showing the crystallographic numbering, with displacement ellipsoids drawn at the 50% probability level. All hydrogen atoms except H1, H13, and H21 have been omitted for clarity.

Previous work has shown that the activity of the chiral isochromanone derivatives resides mainly in one enantiomer.[19,20] This was shown to be true also among these more flexible compounds where (+)-**5d** was considerably more active than (−)-**5d**. To determine the absolute configuration of (+)-**5d** a combination of X-ray crystallography and chemical correlation was used. The hydrochloride salt of the (*R*)-2-methoxy-2-phenylacetamide derivative (+)-**5l** was shown by X-ray crystallographic analysis to have the *R*,*R*-configuration (Figure 5).[31] In separate experiments the diastereomeric amides (+)- and (−)-**5l** were hydrolyzed using strong acid (6 M HCl, reflux) to obtain the pure enantiomers of amine **2**. The amine isolated from (+)-**5l** gave (−)-**5d** after reaction with 4-phenylbenzoic acid. Thus, the most active enantiomer of **5d** has the *S*-configuration.

Pharmacophore Modeling. To evaluate if UII agonists from the isochromanone series and the new, open analogues reported herein might be able to interact similarly with the UII receptor, we studied if agonists from the two series could present the same pharmacophore. To generate a conceptual three-point pharmacophore model we assumed that the centers of the two aromatic rings and the basic nitrogen would be the three pharmacophore elements. We then generated low-energy conformations (having steric energies lower than 3 kcal/mol from the computationally identified global minimum) of (*S*)- and (*R*)-AC-7954 and (*S*)-**5d**, being potent representatives of the two series. A manual search of fits (MOE v. 2005.06) between these conformations revealed an excellent fit (RMS distances between pharmacophoric points = 0.22 Å) between the pharmacophore points of the lowest energy conformation of (*S*)-**5d** and a low-energy conformation of (*R*)-AC-7954 (ΔE = 0.8 kcal/mol),

Figure 6. Stereoscopic view of the alignment of the global minimum conformation of (*S*)-**5d** and a low energy conformation of (*R*)-AC-7954 (ΔE = 0.8 kcal/mol) using the centers of the aromatic rings and the amine nitrogen as the pharmacophoric points (RMS 0.22 Å) (MOE v. 2005.06). The distance between the centers of the aromatic rings is 6.8 Å, and the distance between each center of the aromatic rings to the amine nitrogen is 4.8 Å.

respectively (Figure 6). While the pharmacophore fit is excellent using the centers of the aromatic rings, the planes of the aromatic rings of the fitted conformations are oriented differently. Hence, SAR defined on the basis of aromatic ring substituent-induced potency changes may differ in the two series.

In contrast to (*R*)-AC-7954, the pharmacophore elements of the (*S*)-enantiomer do not provide good superpositions with low-energy conformations of (*S*)-**5d**: The best fit was obtained between a conformation of AC-7954 with an axial 4-chlorophenyl group (ΔE = 0.82 kcal/mol) and a high-energy *cis*-amide conformation of (*S*)-**5d** (ΔE = 6.7 kcal/mol). It is unlikely that an energetically disfavored conformation of (*S*)-**5d** would be responsible for the prominent potency observed (Table 1), and therefore these results demonstrate that whereas (*R*)-AC-7954 and (*S*)-**5d** readily can present the same pharmacophore to the UII receptor, (*S*)-AC-7954 and (*R*)-**5d** cannot. In this context, it should be noted that the absolute configuration of the active enantiomer of AC-7954 has not yet been determined. Docking experiments reported by Lavecchia et al.[16] indicated that (*R*)-AC-7954 would provide the most favorable ligand−receptor interactions, which is in agreement with the above pharmacophore comparisons.

Conclusion

We have synthesized six different series of compounds, four of which contain highly potent and efficacious UII receptor agonists. It was found that amide, carbamate and urea derivatives were most active with activities in the low nanomolar range. The introduction of lipophilic substituents in the variable aromatic part of the molecule was shown to improve potency. For efficacy, it seems that the introduction of electron-donating groups contributes positively.

Experimental Section

General. All chemicals were purchased from Aldrich, Acros, 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. The NMR-spectral data are provided in the Supporting Information. All reactions were followed by TLC (Merck silica gel 60 F_{254}) and analyzed under UV (254 nm). In case of flash chromatography, Merck silica gel 60 (230−400 mesh) was used. Melting points were recorded on a Büchi melting point B-545 apparatus and are uncorrected. Elemental analyses were performed at Kolbe Analytishe Laboratorium, Mülheim an der Ruhr, Germany. FAB MS spectra were obtained from Stenhagen Analyslab AB, Mölndal, Sweden, using a VG 7070E magnetic sector instrument (VG Analytical/Micromass, Manchester UK). Conditions for FAB (fast atom bombardment): Xe gun at 8 kV, matrix glycerol or 3-nitrobenzyl alcohol with PEG 600 as mass reference. A signal from a coil in the magnet field was used for mass calibration. Acceleration voltage 5 kV. Magnet scan from 150 to 700 in 4 s (typical).

1-(4-Chlorophenyl)-3-dimethylaminopropan-1-ol (1). 1-(4-Chlorophenyl)-3-dimethylaminopropan-1-one (3.0 g, 14.2 mmol) was dissolved in THF (250 mL), and $LiAlH_4$ (0.68 g, 18 mmol) was added. The solution was stirred at room temperature for 2 h. A saturated aqueous $NaHCO_3$ solution was slowly added, and the mixture was extracted twice with EtOAc. The combined organic phases were washed (water, brine) and concentrated to afford the title compound (2.75 g, 91%) as a pale yellow oil which solidified slowly upon standing.

1-(4-Chlorophenyl)-3-dimethylaminopropan-1-amine (2). A solution of alcohol **1** (3.0 g, 14 mmol) in CH_3CN (6 mL) was cooled to −15 °C. Concentrated H_2SO_4 (15 mL) was added, and the solution was stirred for 18 h. Water (45 mL) was slowly added to the reaction, and the mixture was basified to pH 14 using NaOH pellets and extracted twice with EtOAc. The combined organic phases were washed (water, brine) and concentrated. The resulting yellowish oil was refluxed for 18 h in 6 M HCl (50 mL). The reaction mixture was again basified to pH 14 using NaOH pellets and extracted twice with EtOAc. The combined organic phases were washed (water, brine) and concentrated to yield 3.10 g (quant) of the title compound as a yellow oil which was used without further purification.

[3-(4-Chlorophenyl)-3-(4-methylbenzyloxy)propyl]-*N,N*-dimethylamine (3v). Alcohol **1** (0.15 g, 0.7 mmol) was dissolved in CH_2Cl_2. PS-DIPEA (1 g, 3 mmol amine/g) and 4-methylbenzyl bromide (0.13 g, 0.7 mmol) were added, and the solution was shaken for 48 h. The solution was filtered, concentrated, and purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient up to 50% MeOH). The fractions containing product were pooled and concentrated. The residue was dissolved in diethyl ether and $HCl_{(ether)}$ was added. Evaporation of the solvent afforded the title product as a white hygroscopic solid (120 mg, 48%). HRFABMS 317.164 ($C_{19}H_{24}ClNO$ requires 317.155)

[3-(4-Chlorophenyl)-3-(2-metoxybenzyloxy)propyl]-*N,N*-dimethylamine (3w). Alcohol **1** (0.2 g, 1 mmol) was dissolved in CH_2Cl_2. PS-DIPEA (1 g, 3 mmol amine/g) and 2-methoxybenzyl chloride (0.15 g, 1 mmol) were added, and the solution was shaken for 48 h. The solution was filtered, concentrated, and purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient up to 50% MeOH). The fractions containing product were pooled and concentrated. The residue was dissolved in diethyl ether and $HCl_{(ether)}$ was added. Evaporation of the solvent afforded the title product as a white hygroscopic solid (290 mg, 78%). Anal. ($C_{19}H_{25}ClN_2O \cdot 1.5\ H_2O$) C, H, N.

General Procedure for the Synthesis of Ester Derivatives. EDC (96 mg, 0.5 mmol), DMAP (12 mg, 0.01 mmol), and the appropriate carboxylic acid (0.47 mmol) were added to a solution of alcohol **1** (0.1 g, 0.47 mmol) in CH_2Cl_2 (15 mL), and the solution was stirred at room temperature overnight. NaOH (1 M, 15 mL) was added to the mixture, which was stirred for 15 min and then extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated. The crude product was purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient up to 50% MeOH). The pure products were either converted to the corresponding hydrochloride salts or oxalate salts, for analysis, storage, and biological testing.

1-(4-Chlorophenyl)-3-dimethylaminopropyl 2-Methylbenzoate HCl (4a). Reaction of 2-methylbenzoic acid with **1** yielded 90 mg of free amine (58%) which was converted to the hydrochloride salt. HRFABMS 332.147 ($C_{19}H_{22}ClNO_2$ requires 332.142).

1-(4-Chlorophenyl)-3-dimethylaminopropyl 4-methoxybenzoate Oxalate (4b). Reaction of 4-methoxybenzoic acid with **1** yielded 75 mg of free amine (46%) which was converted to the oxalate salt isolated as a yellow oil. Anal. ($C_{21}H_{24}ClNO_7 \cdot 1.5H_2O$) C, H, N.

1-(4-Chlorophenyl)-3-dimethylaminopropyl 4-trifluoromethylbenzoate Oxalate (4c). Reaction of 4-trifluoromethylbenzoic acid with **1** yielded 110 mg of free amine (61%) which was converted to the oxalate salt. Mp 186.5−188.0 °C. Anal. ($C_{21}H_{21}ClF_3NO_6$) C, H, N.

1-(4-Chlorophenyl)-3-dimethylaminopropyl 4-Phenylbenzoate HCl (4d). Reaction of 4-phenylbenzoic acid with **1** yielded 80 mg of free amine (43%) which was converted to the hydrochloride salt. HRFABMS 394.156 ($C_{24}H_{24}ClNO_2$ requires 394.157)

1-(4-Chlorophenyl)-3-dimethylaminopropyl Naphthalene-2-carboxylate HCl (4e). Reaction of naphthalene-2-carboxylic acid with **1** yielded 170 mg of free amine (98%) which was converted to the hydrochloride salt. HRFABMS 368.138 ($C_{22}H_{22}ClNO_2$ requires 368.142)

General Procedure for the Synthesis of Amide Derivatives 5a−5k, 5m, and 5o−5r. The benzoic acid was dissolved in THF (75 mL/g) and triethylamine (2 equiv) was added. Under vigorous stirring $SOCl_2$ (1.1 eqv) was added dropwise, and the mixture was stirred at room temperature for 20 min. A solution of **2** (0.6 eqv) 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, applied to a SAX-2 ion exhange column, and 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 oxalate salts for analysis, storage, and biological testing.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2-methylbenzamide Oxalate (5a).** Reaction of 2-methylbenzoic acid (70 mg, 0.47 mmol) with **2** yielded 110 mg of pure product (79%) which was converted to the oxalate salt obtained as a yellow oil. Anal. ($C_{21}H_{25}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-methoxybenzamide Oxalate (5b).** Reaction of 4-methoxybenzoic acid (71 mg, 0.47 mmol) with **2** yielded 150 mg of pure product (92%), which was converted to the oxalate salt. Mp 172.6−172.9 °C. Anal. ($C_{21}H_{25}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-trifluoromethylbenzamide Oxalate (5c).** Reaction of 4-trifluoromethylbenzoic acid (150 mg, 0.78 mmol) with **2** yielded 120 mg of pure product (66%) which was converted to the oxalate salt obtained as an yellow oil. Anal. ($C_{21}H_{22}ClF_3N_2O_5 \cdot H_2O$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-phenylbenzamide Oxalate (5d).** Reaction of 4-phenylbenzoic acid (310 mg, 1.56 mmol) with **2** yielded 152 mg of pure product (50%) which was converted to the oxalate salt. Mp 203.9−205.7 °C. Anal. ($C_{26}H_{27}ClN_2O_5$) C, H, N.

(−)-*N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-phenylbenzamide Oxalate. $[\alpha]_D$ −19.0 (*c* 0.36, MeOH).

(+)-*N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-phenylbenzamide Oxalate. $[\alpha]_D$ +20.8 (*c* 0.21, MeOH).

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]naphthyl-2-carboxamide Oxalate (5e).** Reaction of naphthalene-2-carboxylic acid (270 mg, 1.56 mmol) with **2** yielded 170 mg of pure product (47%) which was converted to the oxalate salt. Mp 206.0−206.9 °C. Anal. ($C_{24}H_{25}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2-ethylbenzamide Oxalate (5f).** Reaction of 2-ethylbenzoic acid (230 mg, 1.56 mmol) with **2** yielded 135 mg of pure product (44%) which was converted to the oxalate salt. Mp 96.4−97.2 °C. Anal. ($C_{22}H_{27}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2,3-dimethylbenzamide Oxalate (5g).** Reaction of 2,3-dimethylbenzoic acid (210 mg, 1.40 mmol) with **2** yielded 150 mg of pure product (51%) which was converted to the oxalate salt. Mp 176.0−176.4 °C. Anal. ($C_{21}H_{24}Cl_2N_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-methoxy-2-methylbenzamide Oxalate (5h).** Reaction of 3-methoxy-2-methylbenzoic acid (230 mg, 1.40 mmol) with **2** yielded 230 mg of pure product (75%) which was converted to the oxalate salt. Mp 198.2−198.6 °C. Anal. ($C_{22}H_{27}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-chloro-2-methylbenzamide Oxalate (5i).** Reaction of 3-chloro-2-methylbenzoic acid (510 mg, 3.0 mmol) with **2** yielded 500 mg of pure product (76%) which was converted to the oxalate salt. Mp 133.8−134.5 °C. Anal. ($C_{21}H_{24}Cl_2N_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2,5-dimethylbenzamide Oxalate (5j).** Reaction of 2,5-dimethylbenzoic acid (230 mg, 1.56 mmol) with **2** yielded 162 mg of pure product (44%), which was converted to the oxalate salt. Mp 189.8−190.4 °C. Anal. ($C_{22}H_{27}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2,4,5-trimethylbenzamide Oxalate (5k).** Reaction of 2,4,5-trimethylbenzoic acid (160 mg, 1.0 mmol) with **2** yielded 300 mg of pure product (98%) which was converted to the oxalate salt. Mp 183.4−184.5 °C. Anal. ($C_{23}H_{29}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-phenoxybenzamide Oxalate (5m).** Reaction of 4-phenoxybenzoic acid (100 mg, 0.47 mmol) with **2** yielded 150 mg of pure product (78%) which was converted to the oxalate salt. Mp 112.5−113.6 °C. Anal. ($C_{26}H_{27}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-dimethylaminobenzamide Oxalate (5o).** Reaction of 4-dimethylaminobenzoic acid (77 mg, 0.47 mmol) with **2** yielded 90 mg of pure product (59%) which was converted to the oxalate salt obtained as a yellow oil. Anal. ($C_{22}H_{28}ClN_3O_5$) C, H, N.

Benzo[1,3]dioxole-{*N*-[1-(4-chlorophenyl)-3-dimethylaminopropyl]}-5-carboxamide Oxalate (5p). Reaction of benzo[1,3]-dioxole-5-carboxylic acid (78 mg, 0.47 mmol) with **2** yielded 150 mg of pure product (88%) which was converted to the oxalate salt. Mp 93.3−94.6 °C. Anal. ($C_{21}H_{23}ClN_2O_7$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2,4-dimethylbenzamide Oxalate (5q).** Reaction of 2,4-dimethylbenzoic acid (210 mg, 1.40 mmol) with **2** yielded 180 mg of pure product (62%) which was converted to the oxalate salt. Mp 161.8−162.5 °C. Anal. ($C_{22}H_{27}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-6-chloro-2-methylbenzamide Oxalate (5r).** Reaction of 6-chloro-2-methylbenzoic acid (240 mg, 1.4 mmol) with **2** yielded 130 mg of pure product (42%) which was converted to the oxalate salt obtained as a yellow oil. Anal. ($C_{21}H_{24}Cl_2N_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-(*R*)-2-methoxy-2-phenylacetamide Oxalate (5l).** Compound **2** (0.9 g, 4.2 mmol) was dissolved in THF (100 mL). (*R*)-2-Methoxy-2-phenylacetic acid (0.7 g, 4.2 mmol), EDC (0.9 g, 4.5 mmol), and DMAP (0.12 g, 0.9 mmol) were added, and the mixture was stirred for 3 days. Saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (100 mL) were added. The phases were separated, and the water phase was extracted with EtOAc. The combined organic phases were washed (water, brine) and evaporated. The resulting mixture was purified with flash chromatography using $MeOH/CH_2Cl_2/NEt_3$ (5/94.9/0.1) to give 1.1 g (67%) 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 (>99.7%).

(+)-*N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-(*R*)-2-methoxy-2-phenylacetamide Oxalate ((+)-5l). Mp 179.2−181.0 °C. $[\alpha]_D$ +50.0 (*c* 0.034, MeOH). Anal. ($C_{22}H_{27}ClN_2O_6$) C, H, N.

(−)-*N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-(*R*)-2-methoxy-2-phenylacetamide Oxalate ((−)-5l). Mp 163.0−163.8 °C. $[\alpha]_D$ −111.4 (*c* 0.044, MeOH). Anal. ($C_{22}H_{27}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2-phenylacetamide Oxalate (5n).** Compound **2** (0.1 g, 0.47 mmol) was dissolved in THF (20 mL). 2-Phenylacetic acid (0.07 g, 0.5 mmol),

EDC (0.1 g, 0.5 mmol), and DMAP (6 mg, 0.05 mmol) were added, and the mixture was stirred for 3 days. Saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (20 mL) were added. The phases were separated, and the water phase was extracted with EtOAc. The combined organic phases were washed (water, brine) and evaporated. The resulting mixture was purified with flash chromatography using MeOH/CH_2Cl_2/NEt_3 (5/94.9/0.1) to give 0.1 g (60%) of the title compound which was converted to the oxalate salt. Mp 140.3−141.2 °C. Anal. ($C_{21}H_{25}ClN_2O_5$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]benzamide HCl (5s).** A solution of alcohol 1 (0.1 g, 0.47 mmol) in benzonitrile (0.05 mL, 0.5 mmol) was cooled to −15 °C. Conc H_2SO_4 (15 mL) was added, and the solution was stirred for 18 h. Water (45 mL) was slowly added, and the mixture was basified to pH 14 using NaOH pellets and extracted twice with EtOAc. The combined organic phases were washed (water, brine) and concentrated. Flash chromatography using CH_2Cl_2/MeOH/NEt_3 (89.9/10/0.1) as eluent afforded the pure compound that was converted to the corresponding HCl salt obtained as a yellow oil (48 mg, 27%). Anal. ($C_{18}H_{21}ClN_2O$) C, H, N.

General Method for the Synthesis of Carbamates 6a, 6m−u, and Ureas 7a, 7m−u. NEt_3 (0.15 mL, 1 mmol) and the appropriate isocyanate (0.5 mmol) were added to a solution of **1** or **2** (100 mg, 0.47 mmol) in THF (25 mL), and the reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated and purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient up to 50% MeOH). The fractions containing product were pooled and evaporated, and the residue was converted to the corresponding oxalate salt.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-2-methylphenylamine (6a).** 2-Methylphenyl isocyanate (62 mg) and **1** yielded 160 mg (98%) of the title compound, which was converted to the oxalate salt. Mp 134.0−135.7 °C. Anal. ($C_{21}H_{25}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-4-phenoxyphenylamine (6m).** 4-Phenoxyphenyl isocyanate (100 mg) and **1** yielded 130 mg (64%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{26}H_{27}ClN_2O_7$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-benzylamine (6n).** Benzyl isocyanate (66 mg) and **1** yielded 81 mg (50%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{21}H_{25}ClN_2O_6 \cdot 1/3H_2O$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-4-*tert*-butylphenylamine (6t).** 4-*tert*-Butylphenyl isocyanate (88 mg) and **1** yielded 180 mg (99%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{24}H_{31}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-3-methoxyphenylamine (6u).** 3-Methoxyphenyl isocyanate (70 mg) and **1** yielded 100 mg (57%) of the title compound, which was converted to the oxalate salt. Mp 191.9−193.2 °C. Anal. ($C_{21}H_{25}ClN_2O_7$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(2-methylphenyl)carbamide Oxalate (7a). 2-Methylphenyl isocyanate (67 mg) and **2** yielded 70 mg (43%) of the title compound, which was converted to the oxalate salt obtained as a yellow oil. Anal. ($C_{21}H_{26}ClN_3O_5$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-phenoxyphenyl)carbamide Oxalate (7m). 4-Phenoxyphenyl isocyanate (100 mg) and **2** yielded 150 mg (75%) of the title compound, which was converted to the oxalate salt isolated as a yellowish oil. Anal. ($C_{26}H_{28}ClN_3O_6$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-benzylcarbamide Oxalate (7n). Benzyl isocyanate (66 mg) and **2** yielded 93 mg (57%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{21}H_{26}ClN_3O_5$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-*tert*-butylphenyl)carbamide Oxalate (7t). 4-*tert*-Butylphenyl isocyanate (88 mg) and **2** yielded 150 mg (82%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{24}H_{32}ClN_3O_5$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(3-methoxyphenyl)carbamide Oxalate (7u). 3-Methoxyphenyl isocyanate (74 mg) and **2** yielded 120 mg (71%) of the title compound, which was converted to the oxalate salt obtained as a yellow oil. Anal. ($C_{21}H_{26}ClN_3O_6$) C, H, N.

General Method for the Synthesis of Carbamates 6b−e. The carboxylic acid (2.7 mmol) and NEt_3 (0.42 mL, 3 mmol) were dissolved in toluene (10 mL). Diphenylphosphoryl azide (0.6 mL, 3 mmol) was added, and the solution was heated to reflux for 1 h. A solution of **1** (200 mg, 0.94 mmol) in THF (5 mL) was added, and the reaction was stirred at room temperature for 18 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, applied to a SAX-2 ion exchange column, and 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 oxalate salts for analysis, storage, and biological testing.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-4-methoxyphenylamine Oxalate (6b).** 4-Methoxybenzoic acid (429 mg) and **1** yielded 140 mg (41%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{21}H_{25}ClN_2O_7$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-4-trifluoromethylphenylamine Oxalate (6c).** 4-Trifluoromethylbenzoic acid (510 mg) and **1** yielded 110 mg (29%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{21}H_{22}ClF_3N_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-4-phenylamine (6d).** 4-Phenylbenzoic acid (594 mg) and **1** yielded 280 mg (91%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{26}H_{27}ClN_2O_6$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyloxycarbonyl]-2-naphthylamine (6e).** Naphthalene-2-carboxylic acid (486 mg) and **1** yielded 180 mg (50%) of the title compound, which was converted to the oxalate salt isolated as a yellow oil. Anal. ($C_{24}H_{25}ClN_2O_6$) C, H, N.

General Method for the Synthesis of Ureas 7b−e. The carboxylic acid (0.94 mmol) and NEt_3 (0.14 mL, 1 mmol) were dissolved in toluene (10 mL). Diphenylphosphoryl azide (0.2 mL, 1 mmol) was added, and the solution was heated to reflux for 1 h. A solution of **2** (200 mg, 0.94 mmol) in THF (5 mL) was added, and the reaction was stirred at room temperature for 18 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 oxalate salts for analysis, storage, and biological testing.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-methoxyphenyl)carbamide Oxalate (7b). 4-Methoxybenzoic acid (143 mg) and **2** yielded 110 mg (32%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{21}H_{26}ClN_3O_6 \cdot 1.5H_2O$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-trifluoromethylphenyl)carbamide Oxalate (7c). 4-Trifluoromethylbenzoic acid (180 mg) and 2 yielded 150 mg (38%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{21}H_{23}ClF_3N_3O_5$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(4-phenylphen-yl)carbamide Oxalate (7d). 4-Phenylbenzoic acid (186 mg) and **2** yielded 230 mg (60%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{26}H_{28}ClN_3O_5 \cdot 2\ H_2O$) C, H, N.

1-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-3-(2-naphthyl)carbamide Oxalate (7e). Naphthalene-2-carboxylic acid (162 mg) and **2** yielded 190 mg (53%) of the title compound, which was converted to the oxalate salt isolated as a colorless oil. Anal. ($C_{24}H_{26}ClN_3O_5$) C, H, N.

General Method for the Synthesis of Sulfonamides 8d, 8e, and 8v. NEt_3 (0.15 mL, 1 mmol) and the sulfonyl chloride were added to a solution of **2** (100 mg, 0.47 mmol) in THF (25 mL), and the reaction was stirred at room temperature for 18 h. Saturated aqueous $NaHCO_3$ (25 mL) was added, and the mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated to afford the title compounds, which were converted to the corresponding oxalate salt.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-phenylbenzenesulfonamide Oxalate (8d).** 4-Phenylbenzenesulfonyl chloride (119 mg, 0.47 mmol) and **2** yielded 200 mg (quant) of pure product, which was converted to the oxalate salt. Mp 198.0−198.6 °C. Anal. ($C_{25}H_{27}ClN_2O_6S \cdot 1.5\ H_2O$) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-2-naphthylsulfonamide Oxalate (8e).** 2-Naphthylsulfonyl chloride (106 mg, 0.47 mmol) and **2** yielded 190 mg (quant) pure product, which was converted to the oxalate salt. Mp 246.5−248.1 °C. Anal. ($C_{23}H_{25}ClN_2O_6S$ x 2 H_2O) C, H, N.

***N*-[1-(4-Chlorophenyl)-3-dimethylaminopropyl]-4-methylbenzenesulfonamide Oxalate (8v).** *p*-Tosyl chloride (94 mg, 0.47 mmol) and **2** yielded 190 mg (quant) pure product, which was converted to the oxalate salt. Mp 191.1−192.0 °C. Anal. ($C_{20}H_{25}ClN_2O_6S$) C, H, N.

***N*-(4-Chlorophenyl)-2-dimethylaminoetylamine (9).** NEt_3 (7.2 mL, 50 mmol) and 2-chloroacetyl chloride (4.4 g, 39 mmol) were added sequentially to a solution of 4-chloroaniline (5 g, 39 mmol) in THF (250 mL). After 2 h, saturated aqueous NH_4Cl (250 mL) was added and the mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine), concentrated, and redissolved in THF. Dimethylamine (2 M in THF) (40 mL, 80 mmol) was added, and the mixture was stirred for 18 h. Saturated aqueous $NaHCO_3$ (250 mL) was added, and the mixture was extracted twice with EtOAc. The combined organic phases were washed (water and brine), concentrated, and redissolved in THF. $LiAlH_4$ (1.9 g, 50 mmol) was added carefully, and the mixture was stirred for 18 h. NaOH (1 M, 150 mL) was slowly added to the mixture, which was stirred for 15 min and then extracted twice with EtOAc. The combined organic phases were washed (water and brine) and concentrated. The crude product was purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient to 50% MeOH) to afford the title compound (5.17 g, 67%) as a slightly reddish oil.

General Procedure for Synthesis of Amides 10d,f,k. The benzoic acid was dissolved in THF (75 mL/g), and NEt_3 (2 equiv) was added. Under vigorous stirring $SOCl_2$ (1.1 equiv) was added dropwise, and the mixture was stirred at room temperature for 20 min. Amine **9** (100 mg, 0.5 mmol) was dissolved in THF and added slowly to the reaction mixture, which 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, applied to a SAX-2 ion exchange column, and 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 oxalate salts for analysis, storage and biological testing.

***N*-(4-Chlorophenyl)-*N*-(2-dimethylaminoethyl)-4-phenylbenzamide Oxalate (10d).** Reaction of 4-phenylbenzoic acid (100 mg, 0.5 mmol) with **9** yielded 170 mg of pure product (90%) which was converted to the oxalate salt. Mp 157.1−159.0 °C. Anal. ($C_{25}H_{25}ClN_2O_5$) C, H, N.

***N*-(4-Chlorophenyl)-*N*-(2-dimethylaminoethyl)-2-ethylbenzamide Oxalate (10f).** Reaction of 2-ethylbenzoic acid (75 mg, 0.5 mmol) with **9** yielded 120 mg of pure product (73%), which was converted to the oxalate salt. Mp 198.2−199.6 °C. Anal. ($C_{21}H_{25}ClN_2O_5$) C, H, N.

***N*-(4-Chlorophenyl)-*N*-(2-dimethylaminoethyl)-2,4,5-trimethylbenzamide Oxalate (10k).** Reaction of 2,4,5-trimethylbenzoic acid (82 mg, 0.5 mmol) with **9** yielded 140 mg of pure product (81%), which was converted to the oxalate salt. Mp 179.0−180.2 °C. Anal. ($C_{22}H_{27}ClN_2O_5$) C, H, N.

1-(4-Chlorophenyl)-1-(2-dimethylaminoethyl)-3-(2-methylphenyl)carbamide Oxalate (11a). NEt_3 (0.15 mL, 1 mmol) and 2-methylphenyl isocyanate (130 mg, 1.0 mmol) were added to a solution of **9** (200 mg, 1.0 mmol) in THF (25 mL), and the reaction was stirred for 18 h. The reaction mixture was concentrated and purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient to 50% MeOH). The fractions containing product were pooled and concentrated to yield 320 mg (97%) of the title compound, which was converted to the oxalate salt. Mp 169.7−170.4 °C. Anal. ($C_{20}H_{24}ClN_3O_5$) C, H, N.

1-(4-Chlorophenyl)-1-(2-dimethylaminoethyl)-3-(3-methoxyphenyl)carbamide Oxalate (11u). NEt_3 (0.15 mL, 1 mmol) and 3-methoxyphenyl isocyanate (160 mg, 1.1 mmol) were added to a solution of **9** (210 mg, 1.1 mmol) in THF (25 mL), and the reaction was stirred for 18 h. The reaction mixture was concentrated and purified using flash chromatography (first CH_2Cl_2 100%, thereafter a gradient to 50% MeOH). The fractions containing product were pooled and concentrated to yield 270 mg (73%) of the title compound which was converted to the oxalate salt. Mp 147.9−148.3 °C. Anal. ($C_{20}H_{24}ClN_3O_6$) C, H, N.

X-ray Structure Determination. Crystal and experimental data are summarized in Table 2 in Supporting Information. Crystals of **(+)-5l** were selected and mounted under nitrogen in a glass capillary at low temperature and transferred in liquid nitrogen to the Rigaku R-AXIS IIc image plate system.[32] Diffracted intensities were measured using graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation from a RU-H3R rotating anode operated at 50 kV and 90 mA. With the R-AXIS IIc detector, 90 oscillation photos with a rotation angle of 2° were collected and processed using the CrystalClear software package.[33] An empirical absorption correction was applied using the REQAB program under CrystalClear. The structure was solved by direct methods, SIR-92,[34] and refined using full-matrix least-squares calculations on F^2, SHELXL-97,[35] operating in the WinGX program package.[36] Anisotropic thermal displacement parameters were refined for all the non-hydrogen atoms. All hydrogen atoms except H21 and H22 were included in calculated positions and refined using a riding model. H21 and H22 were located in a difference map and allowed to refine without constraints. Structural illustrations have been drawn with ORTEP-III[37] under WinGX.

Biological Activity. R-SAT Testing. R-SAT assays for pharmacological testing were performed as previously described,[26−29] 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 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.

Molecular Modeling. For conformational analysis of the six different series of compounds Monte Carlo conformational analysis were performed using the MM3 force field as implemented in hte MacroModel program v.7.1. For the pharmacophore modeling of **5d** and AC-7954, molecular conformations were generated using the stochastic conformational search protocol and the MMFF94x

force field as implemented in MOE, version 2005.06.[38] Conformations with energies above 3 kcal/mol from the global minimum were discarded, and the remaining ones were manually superimposed. Each overlap was refined using the flexible alignment module in MOE and ranked by the values of conformational energy.

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Supporting Information Available: Elemental analysis and ^{1}H and ^{13}C NMR spectral data for all synthesized compounds. Synthetic procedures, compound characterizations, and results from in vitro testing of UII receptor affinity of the ester derivatives **4f**−**4bb**. A table of crystal data and structure refinement for compound (+)-**5l** HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Crystallographic data (excluding structure factors) for (+)-**5l** HCl has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 272185. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Rd., Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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