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Laboratory note

Design, parallel synthesis and SAR of novel urotensin II receptor agonists

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Abstract

A 30-membered library of amides based on the potent urotensin II (UII) receptor agonist FL104, has been synthesized from ten different carboxylic acids and three amines. A synthetic protocol producing the amides in 47–98% yield has been developed in which the purification involved only extractions and in a few cases filtration through an ion-exchange resin. It was found that 5 mg of starting material was enough to obtain reproducible results and excellent purities. Thus, the procedure is estimated to be transferable to fully automated systems. The synthesized compounds were evaluated for their UII receptor agonistic activities using a cell-based assay (R-SAT). The most active compounds were the 4-trifluoromethylcinnamic amides of 1-(4-chlorophenyl)-3-dimethylamino-propylamine and 1-(2-naphthyl)-3-dimethylamino-propylamine, both showed EC_{50} values of 130 nM.

Keywords: Urotensin II; Library synthesis; Solid supported reagents; Amidation; Structure–activity relationships

1. Introduction

We have recently reported on the structure–activity relationships (SAR) in a series of nonpeptidic urotensin II (UII) receptor agonists leading to the discovery of FL104 (Fig. 1), the most potent UII agonist reported to date [1].

We then also reported the facile and convenient synthesis of series of benzamide derivatives from benzoic acids and amine **A** (Scheme 1) using thionyl chloride to initially produce the acid chloride to which **A** was added.

However, when using the same protocol in the synthesis of the corresponding 2-phenylacetamide derivative, the workup procedure became more complicated and involved flash chromatography [1]. This limited the usefulness of this procedure when synthesizing larger series of non-aromatic amides. In this study we have therefore set out to find an efficient synthetic protocol to produce such compounds, ideally without the need for tedious workup. Thus, solid-supported coupling reagents (PS–DCC and PS–DMAP) have been used in combination with excess of the carboxylic acids to drive the reactions to completion, enabling the synthesis of a 30-membered library in moderate to excellent yields (47–98%) of the individual compounds using an easy purification protocol.

Our interest in UII receptor agonists is based on the potential role of UII in numerous diseases including hypertension [2], heart failure [3], atherosclerosis [4], renal failure [5], and diabetes [6,7]. Although there are some examples of non-peptidergic antagonists [8a–c] and agonists [1,9] in the literature there is a strong need for potent and selective low molecular weight ligands to further examine the biology/pharmacology of the UII system [10]. Therefore, the identification, design, and development of such compounds represent a rapidly emerging research field.

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2. Chemistry

2.1. Synthesis of amines

The starting amines **A**–**C** were synthesized according to Scheme 2. The Mannich bases **1a**–**c** and amine **A** were produced as reported earlier [11]. These amines were chosen to produce derivatives with electron withdrawing (*p*-Cl), electron donating (*p*-Me) and sterically demanding (naphthyl) substituents, respectively.

The conversion of the ketones to the primary amines was accomplished according to our previously published procedure [1]. First the ketones were reduced to alcohols (**2a**–**c**) using $LiAlH_4$ in THF in good yields (>90%). Conversion of the alcohols to their corresponding acetamide derivatives via a Ritter reaction [12] using acetonitrile as the nitrogen source, and subsequent hydrolysis in refluxing 6 M HCl afforded the primary amines (**B**–**C**) in moderate to good yields (47–76% over two steps). Interestingly, the Ritter reaction only worked for liquid nitriles. Any attempt to perform this reaction directly on a solid nitrile (e.g. 4-phenyl-benzonitrile) or by first dissolving the nitrile in an inert solvent such as toluene only resulted in the conversion of the nitrile to its corresponding primary amide.

2.2. Synthesis of amides

In order to examine both the SAR of the aromatic rings and also the reactivity in the amidation reaction, the carboxylic acids were chosen to include electron withdrawing (4-CF_3) and electron donating (4-OMe) substituents. We also wanted to examine both aliphatic acids (2-phenylacetic acids **1**–**3** and 3-phenylpropionic acids **4**–**6**) as well as conjugated acids (cinnamic acids **7**–**9** and propiolic acid **10**) to investigate if any differences in reactivity were observed.

The amines were dissolved in dichloromethane and 5 equiv of carboxylic acid,[1] 2 equiv of PS–DCC and 0.2 equiv of PS–DMAP were added. The reaction mixtures were shaken for four days at room temperature (Scheme 3).[2]

Dichloromethane was selected as solvent due to its higher density compared to water, thus making small-scale parallel extractions easier. After completion of the reaction, the resins were filtered off and the organic phase was washed twice with 1 M sodium hydroxide and once each with water and brine. This purification procedure was sufficient to provide pure amides (>99% purity according to ^{1}H NMR spectroscopy) from the non-conjugated acids (Table 1). However, for the cinnamic and propiolic acid derivatives an additional purification step involving filtration through an ion-exchange resin was sometimes needed.

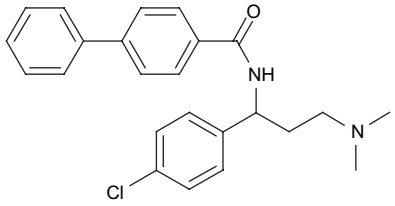


Fig. 1. FL104, the most potent UII-agonist reported to date.

2.3. Miniaturizing

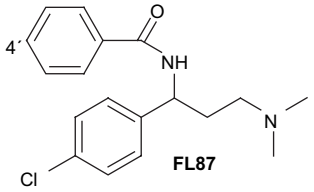
To check the robustness of the method and to enable the production of larger libraries we also scaled down linearly from 50 mg to 25 mg and to 5 mg of the starting amine . As seen in Table 2, this was accomplished without problems as both the yields and purities were in the same range as for the 50 mg reactions.

3. Pharmacological testing

Compounds **A1**–**C10** were tested for their agonistic properties at human UII receptors using the functional R-SAT™ assay as previously described [14–18].[3] The results are shown in Table 3. For control of the UII receptor selectivity all compounds were tested against the m3 receptor as a negative control.

4. Structure–activity relationships

We have previously reported the SAR around benzamide derivatives involving amine **A** [1]. We then found that the introduction of a phenyl ring in the 4′-position of FL87 remarkably enhanced the activity as compared to smaller substituents.

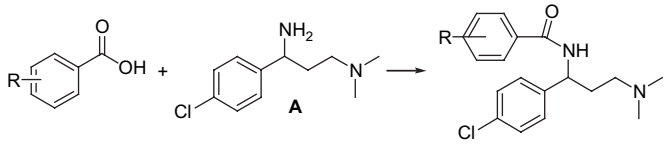


To investigate if substituents other than a 4′-phenyl group were acceptable for UII receptor interaction we used computer based conformational analysis (Macromodel, MM3) to identify derivatives that stretched longer in space than a benzamide, but shorter than a biphenyl derivative. As seen in Fig. 2, the

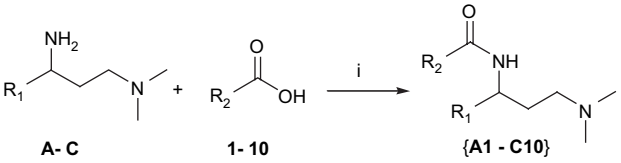
[1] In an optimization study different ratios of acid to amine were investigated. When using 1 or 2 equiv the reaction did not go to completion even after one week, making the purification troublesome. It was found that 5 equiv of acid was enough to drive the reaction to completion within four days.

[2] To shorten the reaction times, we also tried to run this reaction using microwave heating. After filtration of the resins, however, only the starting carboxylic acid was detected. An explanation for this could be that under these conditions the amine reacts preferentially with the resin, e.g. with PS–DCC, to form a guanidine, which has been observed earlier [13].

[3] The EC_{50} value for UII in the R-SAT assay was found to be 1.1×10^{-11} M. This could be compared to values obtained from a rat aorta bioassay and FLIPR experiments on cells expressing the recombinant UT receptor [19–20].



Scheme 1.



Scheme 3.

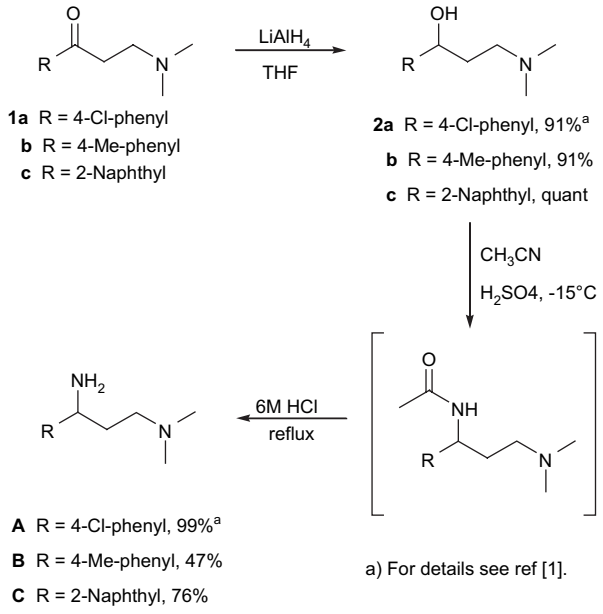
cinnamic (white) and the propiolic (yellow) amide derivatives fitted these criteria perfectly. On the other hand, to further examine the most favourable direction of the aromatic ring, we also envisioned that the 2-phenylacetic and 3-phenylpropionic amide derivatives would be considerably more flexible, thus being able to pick up binding interactions not accessible for the conjugated systems.

In contrast to our previous study where the aromatic ring of the amine moiety was kept constant (4-Cl-phenyl) we choose here to include both an electron donating (4-Me) as well as a sterically demanding (2-naphthyl) aromatic system to explore the SAR also in this part of the molecule.

As is apparent from Fig. 3, the **A** and **C** series showed higher potencies than the corresponding **B** derivatives in all examples except when using acid **3** (2-(4-methoxyphenyl)acetic acid). These results indicate that an electron deficient 4-Cl-phenyl or a sterically demanding 2-naphthyl system is more beneficial than an electron rich 4-Me-phenyl system. Another trend visible in Fig. 3 is that the 4-CF_3-phenyl substituent (in **2**, **5** and **8**) is more favourable for potency than phenyl (**1**, **4** and **7**) or 4-OMe-phenyl (**3**, **6** and **9**) substitution in the different series (**A**–**C**).

When comparing the amides in the series **A1**, **A4**, **A7**, and **A10**, as seen in Fig. 4, the trend is that the potency increases in the order 2-phenylacetic (**A1**) ≈ 3-phenylpropanoic (**A4**) < cinnamic (**A7**) ≈ 2-propiolic acid (**A10**). This could also be expressed as in Fig. 5, where it is shown that the conjugated amides have both higher potencies and efficacies as compared to the aliphatic derivatives.

In contrast to our previous study [1] the two most potent compounds in this series (**A8** and **C8**) were also among the most efficacious ones.



Scheme 2.

5. Conclusion

We have developed a highly efficient protocol for the production of large libraries of aliphatic and conjugated amides. The aliphatic amides required only one extraction to provide pure products, whereas the conjugated amides sometimes needed a filtration through an ion-exchange resin. The purification procedures used are easily transferable to fully automated systems. A thirty-membered test library revealed novel information regarding the SAR around FL104 and resulted in potent and efficacious compounds. It was shown that 13 compounds had EC_{50} values between 130–870 nM, but none was more active than FL104. It was also concluded that conjugated amides in general were better than aliphatic amides for activity.

6. Experimental procedures

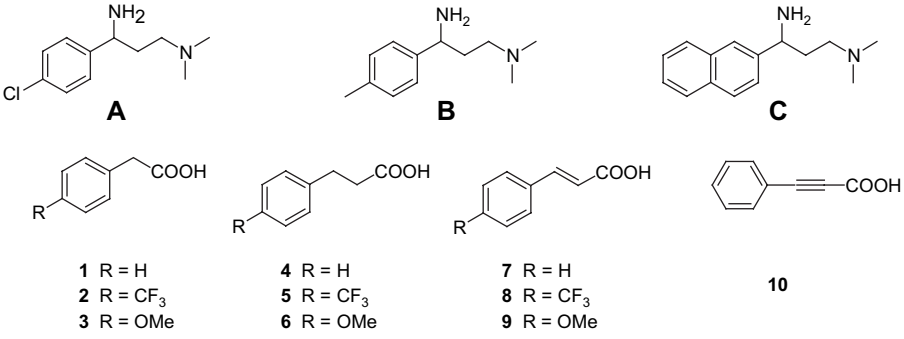
6.1. Chemistry

All commercial chemicals were used without purification, the solid supported reagents were purchased from Agronaut Technologies (Hengoed UK) and had loadings from 1.2 to 1.6 mmol/g depending on batch used. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) 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). Elemental analyses were performed at Kolbe Analytishe Laboratorium, Mülheim an der Ruhr, Germany. Accurate masses were measured at Biovitrum using an Agilent MSD-TOF (G1969A) connected to an Agilent 1100 HPLC system (G1312A, G4061AA, G1367A, G1316A) with a diode array detector (G1315B). The instrument is calibrated by Agilent ES–TOF tuning mix and spectra are acquired in positive electrospray mode.

6.1.1. 3-Dimethylamino-1-(4-methylphenyl)propanol *2b*

Ketone **1b** (3.6 g, 18.8 mmol) was dissolved in THF (250 ml). LAH (0.72 g, 18.8 mmol) was added slowly and

Table 1
Results from the synthesis of a thirty-membered amide library



Acid	Amine											
	A				**B**				**C**			
	Extraction		Ion exchange		Extraction		Ion exchange		Extraction		Ion exchange	
	Yield %	Purity %	Yield %	Purity %	Yield %	Purity %	Yield %	Purity %	Yield %	Purity %	Yield %	Purity %
1	92	100	–	–	93	100	–	–	67	100	–	–
2	96	100	–	–	98	100	–	–	88	100	–	–
3	96	100	–	–	93	100	–	–	79	100	–	–
4	92	100	–	–	96	100	–	–	66	100	–	–
5	83	100	–	–	78	100	–	–	84	100	–	–
6	91	100	–	–	98	100	–	–	94	100	–	–
7	87	85	62	100	132	93	86	100	76	100	–	–
8	97	100	–	–	56	100	–	–	200	51	59	100
9	83	97	68	100	87	100	–	–	118	88	47	100
10	147	88	46	100	120	75	60	100	102	76	64	100

Key: all reactions were run to 100% conversion according to ^{1}H NMR spectroscopy.
Purities were determined by ^{1}H NMR spectroscopy. All yields > 100% are mainly due to remaining carboxylic acid in the sample.

the mixture was stirred for 18 h. NaOH (1 M) (100 ml) was added dropwise until pH 14. The resulting mixture was extracted with EtOAc (150 ml + 100 ml). The organic phases were combined and washed with water (200 ml) and brine (200 ml) and concentrated to yield the title product as a yellow oil (3.3 g, 91%). ^{1}H NMR ($CDCl_3$) δ 1.78–1.82 (m, 2H), 2.30 (s, 3H), 2.35 (s, 6H), 2.44–2.50 (m, 1H), 2.62–2.69 (m, 1H), 4.90 (dd, 1H, $J = 7.2$, 12.0 Hz), 7.15 (d, 2H, $J = 7.6$ Hz), 7.27 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$) δ 21.4, 34.8, 45.6 (2 C:s), 58.7, 75.9, 125.7 (2 C:s), 129.1 (2 C:s), 136.6, 142.4.

*6.1.2. 3-Dimethylamino-1-(4-methylphenyl)propanamine **B***

Compound **2b** (3.3 g, 17.1 mmol) was dissolved in acetonitrile (6 ml) and stirred on an ice-salt bath and 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) (50 ml) was then added to the intermediate and the solution was refluxed for three 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 yield the title product as a yellow oil (1.55 g, 47%). ^{1}H NMR ($CDCl_3$) δ 1.81–1.87 (m, 2H), 2.23 (s, 6H), 2.28–2.36 (m, 2H), 2.32 (s, 3H), 3.96 (dd, 1H, $J = 6.8$, 7.2 Hz), 7.14 (d, 2H, $J = 8.4$ Hz), 7.22 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 21.3, 36.9, 45.7 (2 C:s), 54.8, 57.4, 126.4 (2 C:s), 129.4 (2 C:s), 136.8, 143.4.

*6.1.3. 3-Dimethylamino-1-(2-naphthyl)propanol **2c***

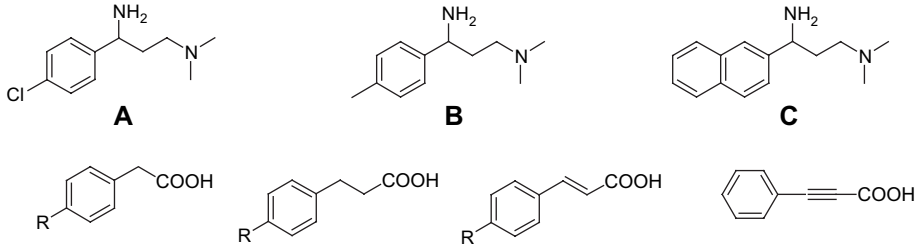
Ketone **1c** (4.0 g, 17.6 mmol) was dissolved in THF (250 ml). LAH (0.67 g, 17.6 mmol) was added slowly and the mixture was stirred for 18 h. NaOH (1 M) (100 ml) was then added dropwise until pH 14. The resulting mixture was extracted with EtOAc (150 ml + 100 ml). The organic phases were combined and washed with water (200 ml) and brine (100 ml) and concentrated to yield the title product as a yellow oil (4.1 g, quant). ^{1}H NMR ($CDCl_3$) δ 1.86–2.02 (m, 2H), 2.32–2.42 (m, 1H) 2.38 (s, 6H), 2.54–2.63 (m, 1H), 5.11 (dd, 1H, $J = 4.0$, 6.1 Hz), 7.40–7.52 (m, 3H), 7.76–7.90 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 34.5, 45.4 (2 C:s), 58.4, 75.8, 124.1, 124.3, 125.6, 126.0, 127.7, 128.0, 128.1, 132.8, 133.5, 142.6.

Table 2
Results from miniaturizing experiments

Compound	Scale (mg)	Yield %	Purity %	Scale (mg)	Yield %	Purity %
{**A1**}	25	94	100	5	92	100
{**A7**}	25	83	100	5	97	100

Key: all reactions were run to 100% conversion according to ^{1}H NMR spectroscopy. Purities were determined by ^{1}H NMR spectroscopy after base extraction.

Table 3
Results from in vitro testing of urotensin-II receptor activity



Acid	Amine					
	A		**B**		**C**	
	pEC_{50}[a]	Efficacy[b]	pEC_{50}[a]	Efficacy[b]	pEC_{50}[a]	Efficacy[b]
1	5.73 ± 0.47	76 ± 5	5.38 ± 0.07	83 ± 11	5.76 ± 0.17	121 ± 31
2	6.06 ± 0.23	53 ± 7	5.95 ± 0.03	25 ± 4	6.24 ± 0.06	40 ± 3
3	5.82 ± 0.21	65 ± 18	5.23 ± 0.05	62 ± 5	NA[c]	NA[c]
4	5.78 ± 0.10	139 ± 5	5.34 ± 0.14	73 ± 9	6.22 ± 0.20	107 ± 22
5	5.95 ± 0.31	73 ± 10	5.64 ± 0.09	60 ± 6	6.43 ± 0.07	75 ± 1
6	5.53 ± 0.03	101 ± 12	5.27 ± 0.02	67 ± 14	5.85 ± 0.11	113 ± 9
7	6.37 ± 0.12	128 ± 10	5.81 ± 0.07	97 ± 6	6.23 ± 0.18	116 ± 3
8	6.89 ± 0.06	133 ± 3	6.36 ± 0.08	96 ± 1	6.87 ± 0	117 ± 1
9	6.29 ± 0.04	99 ± 4	5.70 ± 0.08	79 ± 14	6.42 ± 0.06	106 ± 16
10	6.40 ± 0.04	124 ± 6	5.51 ± 0.07	131 ± 0	6.34 ± 0.05	115 ± 14

[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 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.

*6.1.4. 3-Dimethylamino-1-(2-naphthyl)propanamine **C***

Compound **2c** (4.1 g, 17.6 mmol) was dissolved in acetonitrile (6 ml) and stirred on an ice-salt bath and 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 yellow oil. HCl (6 M) (50 ml) was then added to the intermediate and the solution was refluxed for three 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 yield the title product as a yellow oil (3.05 g, 76%). ^{1}H NMR ($CDCl_3$) δ 1.88–1.95 (m, 2H), 2.15 (s, 6H), 2.24–2.39 (m, 2H), 4.15 (dd, 1H, J = 6.6, 13.6 Hz), 7.41–7.50 (m, 3H), 7.74–7.77 (m, 1H), 7.79–7.86 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 37.1, 45.7 (2 C:s), 55.1, 57.2, 124.8 (2 C:s), 126.1 (2 C:s), 127.7, 127.9, 128.3, 132.8, 133.4, 143.9.

6.1.5. General procedure for the synthesis of amides

The amine (1 equiv, 50 mg), PS–DCC (2 equiv), PS–DMAP (0.2 equiv), carboxylic acid (5 equiv) and DCM (15 ml) were added to a vial and shaken at room temperature for four days.

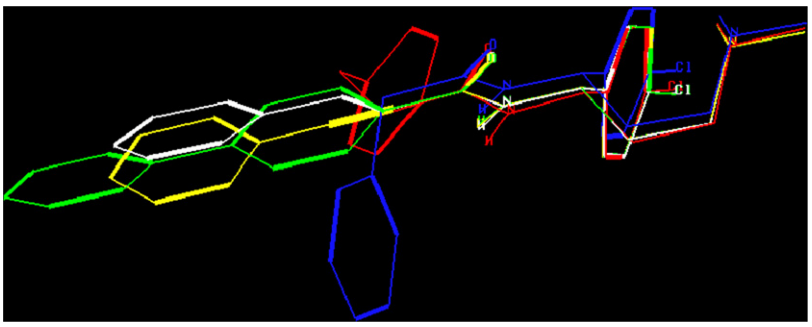


Fig. 2. Alignment of the global minimum conformations of **A1** (blue), **A4** (red), **A7** (white), **A10** (yellow) and FL104 (green) identified by conformational analysis using molecular mechanics calculations (MM3, MacroModel v. 7.0).

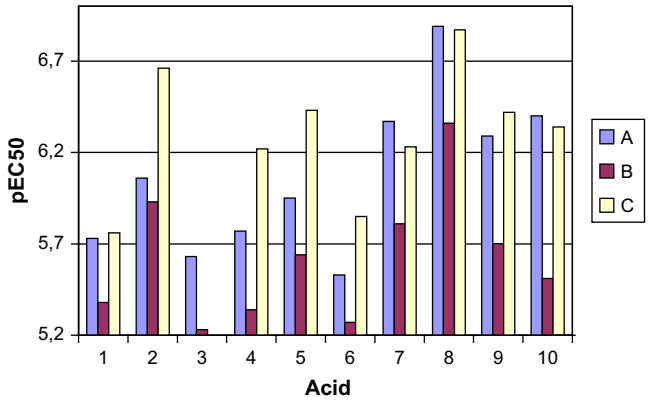


Fig. 3. Comparisons of the UII-receptor agonist potencies of the synthesized amides divided into families. The potencies were determined in the cell based R-SAT assay.

The mixture was then filtered and the solute was concentrated. ^{1}H NMR spectra were run to control that the reactions had gone to completion. The crude product was then dissolved in CH_2Cl_2 (20 ml) and washed with 1 M NaOH (2 × 15 ml). The CH_2Cl_2-phase was then concentrated. ^{1}H NMR spectra were run to control the purity. If the product was not pure (>98% purity) ion exchange chromatography (SCX-2) was used for the final purification. The pure product was then converted to the corresponding HCl salt using HCl saturated ether.

*6.1.6. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-2-phenylacetamide HCl {**A1**}*

2-Phenylacetic acid (161 mg, 1.18 mmol) yielded 72 mg {**A1**} (92%). ^{1}H NMR δ 2.83–2.92 (m, 2H), 3.29 (s, 6H), 3.72–3.80 (m, 2H), 4.26 (s, 2H), 5.63 (dd, 1H, $J = 6.6$, 14.6 Hz), 7.97–8.12 (m, 5H), 8.13–8.23 (m, 4H). ^{13}C NMR δ 30.5, 42.2, 42.5 (2 C:s), 50.4, 55.2, 126.7, 128.1 (2 C:s), 128.3 (2 C:s), 128.5 (2 C:s), 128.8 (2 C:s), 133.2, 135.6, 139.8, 172.5. HRTofMS calcd for $C_{19}H_{23}ClN_2O$ (M+) *m/z* 330.1499, found 330.1504.

*6.1.7. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-2-(4-trifluoromethylphenyl)acetamide HCl {**A2**}*

2-(4-Trifluoromethylphenyl)acetic acid (250 mg, 1.18 mmol) yielded 90 mg {**A2**} (96%). ^{1}H NMR δ 2.16–2.30 (m, 1H), 2.79–2.90 (m, 1H), 2.86 (s, 6H), 3.00–3.20 (m, 2H), 3.67 (s, 2H), 4.96 (dd, 1H, $J = 6.2$, 8.8 Hz), 7.35 (app. s, 4H), 7.48 (d, 2H, $J = 8.3$ Hz), 7.60 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR δ 30.5, 41.6, 42.1, 42.4, 51.6, 55.2, 124.4 (q, $^1J_{CF} = 269.1$ Hz), 125.0 (q, 2 C:s, $^3J_{CF} = 3.8$ Hz), 128.2 (2 C:s), 128.6 (2 C:s), 128.8 (q, $^2J_{CF} = 32.1$ Hz), 129.6 (2 C:s), 133.3, 139.8, 140.2, 171.5. HRTofMS calcd for $C_{20}H_{22}ClF_3N_2O$ (M+) *m/z* 398.1373, found 398.1378.

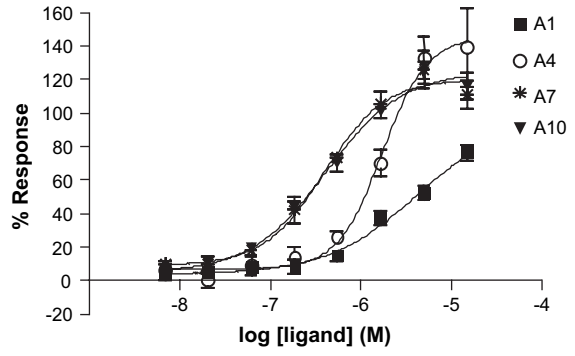


Fig. 4. UII receptor activity of **A1**, **A4**, **A7** and **A10** in the functional cell based R-SAT assay.

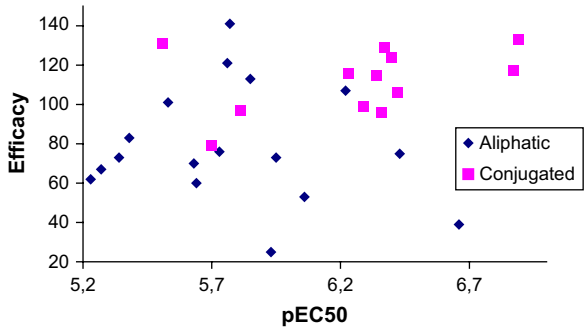


Fig. 5. Scatter plot of the correlation between efficacy and pEC_{50} values for aliphatic [**A1**–**C6**] (diamonds) and conjugated derivatives [**A7**–**C10**] (squares).

*6.1.8. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-2-(4-methoxyphenyl)acetamide HCl {**A3**}*

2-(4-Methoxyphenyl)acetic acid (196 mg, 1.18 mmol) yielded 82 mg {**A3**} (96%). ^{1}H NMR δ 2.18–2.26 (m, 2H), 2.83 (app d, 6H, $J = 7.3$ Hz), 2.99–3.12 (m, 2H), 3.49 (s, 2H), 3.75 (s, 3H), 4.95 (t, 1H, $J = 7.3$ Hz), 6.85 (d, 2H, $J = 8.4$ Hz), 7.20 (d, 2H, $J = 8.4$ Hz), 7.35 (app. s, 4H). ^{13}C NMR δ 30.4, 41.6, 42.0, 42.6, 50.2, 54.4, 55.1, 113.7 (2 C:s), 127.5, 128.2 (2 C:s), 128.6 (2 C:s), 129.8 (2 C:s), 133.4, 139.5, 158.9, 173.1. HRTofMS calcd for $C_{20}H_{25}ClN_2O_2$ (M+) *m/z* 360.1605, found 360.1611.

*6.1.9. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-3-phenylpropionamide HCl {**A4**}*

3-Phenylpropionic acid (179 mg, 1.18 mmol) yielded 75 mg {**A4**} (92%). ^{1}H NMR δ 2.06–2.20 (m, 2H), 2.50–2.64 (m, 2H), 2.82 (s, 6H), 2.89–2.94 (m, 2H), 2.94–3.00 (m, 2H), 4.90 (dd, 1H, $J = 6.6$, 15.0 Hz), 7.16–7.20 (m, 3H), 7.21–7.27 (m, 4H), 7.29–7.34 (m, 2H). ^{13}C NMR δ 14.1, 30.3, 31.3, 37.2, 41.9, 42.7, 65.6, 126.0, 128.1 (2 C:s), 128.2 (2 C:s), 128.3 (2 C:s), 128.5 (2 C:s), 133.2, 139.6, 140.6, 173.6. HRTofMS calcd for $C_{20}H_{25}ClN_2O$ (M+) *m/z* 344.1655, found 344.1659.

*6.1.10. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-3-(4-trifluoromethylphenyl)propionamide HCl {**A5**}*

3-(4-Trifluoromethylphenyl)propanoic acid (256 mg, 1.18 mmol) yielded 81 mg {**A5**} (83%). ^{1}H NMR δ 2.10–2.18 (m, 2H), 2.52–2.67 (m, 2H), 2.84 (s, 6H), 2.96–3.30 (m, 2H), 3.32–3.40 (m, 2H), 4.92 (dd, 1H, $J = 4.8$, 7.3 Hz), 7.20–7.26 (m, 2H), 7.32–7.38 (m, 4H), 7.48–7.54 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR δ 30.0, 31.3, 32.0, 37.5, 43.1, 43.5, 64.8, 126.3 (2 C:s), 128.5 (q, $^1J_{CF} = 271.4$ Hz), 128.8 (q,

$^2J_{CF}$ = 29.8 Hz), 129.5 (2 C:s), 129.6 (2 C:s), 130.4 (2 C:s), 132.9, 142.8, 147.4, 172.2. HRTofMS calcd for $C_{21}H_{24}ClF_3N_2O$ (M+) *m/z* 412.1529, found 412.1529.

*6.1.11. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-3-(4-methoxyphenyl)propionamide HCl {**A6**}*

3-(4-Methoxyphenyl)propionic acid (218 mg, 1.21 mmol) yielded 80 mg {**A6**} (91%). ^{1}H NMR δ 2.06–2.16 (m, 2H), 2.47–2.60 (m, 2H), 2.76–2.84 (m, 2H), 2.82 (s, 6H), 2.91–3.02 (m, 2H), 3.70 (s, 3H), 4.88 (dd, 1H, *J* = 6.2, 8.8 Hz), 6.78 (d, 2H, *J* = 8.4 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR δ 30.4, 30.5, 37.5, 42.0 (2 C:s), 54.3, 55.1, 65.6, 113.6 (2 C:s), 128.0 (2 C:s), 128.5 (2 C:s), 129.3 (2 C:s), 132.5, 133.1, 139.6, 158.3, 173.7. HRTofMS calcd for $C_{21}H_{27}ClN_2O_2$ (M+) *m/z* 374.1761, found 360.1770.

*6.1.12. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-3-cinnamamide HCl {**A7**}*

Cinnamic acid (179 mg, 1.18 mmol) yielded 50 mg {**A7**} (62%). ^{1}H NMR δ 2.20–2.38 (m, 2H), 2.80–2.94 (m, 1H), 2.89 (s, 6H), 3.12–3.27 (m, 1H), 5.12 (dd, 1H, *J* = 5.5, 9.2 Hz), 6.75 (d, 1H, *J* = 15.8 Hz), 7.30–7.50 (m, 6H), 7.50–7.60 (m, 4H). ^{13}C NMR δ 14.1, 30.7, 42.1, 42.5, 65.6, 120.1, 127.6 (2 C:s), 128.2 (2 C:s), 128.7 (4 C:s), 129.7, 133.3, 134.8, 139.8, 141.3, 170.0. HRTofMS calcd for $C_{20}H_{23}ClN_2O$ (M+) *m/z* 342.1499, found 342.1510.

*6.1.13. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-4-trifluoromethyl-cinnamamide HCl {**A8**}*

4-Trifluoromethyl-cinnamic acid (259 mg, 1.18 mmol) yielded 70 mg {**A8**} (97%). ^{1}H NMR δ 2.20–2.40 (m, 2H), 2.84–2.96 (m, 1H), 2.90 (s, 6H), 3.12–3.28 (m, 1H), 5.11 (dd, 1H, *J* = 5.2, 13.9 Hz), 6.85 (d, 1H, *J* = 15.8 Hz), 7.30–7.47 (m, 4H), 7.60 (d, 1H, *J* = 15.8 Hz), 7.65–7.71 (m, 2H), 7.72–7.80 (m, 2H). HRTofMS calcd for $C_{21}H_{22}ClF_3N_2O$ (M+) *m/z* 410.1373, found 410.1382.

*6.1.14. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-4-methoxy-cinnamamide HCl {**A9**}*

4-Methoxycinnamic acid (234 mg, 1.31 mmol) yielded 60 mg {**A9**} (68%). ^{1}H NMR δ 2.20–2.38 (m, 2H), 2.80–2.98 (m, 1H), 2.90 (s, 6H), 3.10–3.32 (m, 1H), 3.80 (s, 3H), 5.11 (dd, 1H, *J* = 5.5, 9,2 Hz), 6.60 (d, 1H, *J* = 15.8 Hz), 6.93 (d, 2H, *J* = 8.4 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 7.47–7.58 (m, 3H). ^{13}C NMR δ 30.8, 42.1, 42.6, 50.5, 54.6, 55.2, 114.1 (2 C:s), 117.5, 127.4, 128.2 (2 C:s), 128.7 (2 C:s), 129.3 (2 C:s), 133.3, 140.0, 141.1, 161.5, 167.4. HRTofMS calcd for $C_{21}H_{25}ClN_2O_2$ (M+) *m/z* 372.1605, found 372.1609.

*6.1.15. N-[1-(4-Chlorophenyl)-3-dimethylamino-propyl]-3-phenylpropiolamide HCl {**A10**}*

3-Phenylpropiolic acid (172 mg, 1.19 mmol) yielded 40 mg {**A10**} (50%). ^{1}H NMR δ 2.20–2.36 (m, 2H), 2.84–2.94 (m, 2H), 2.90 (s, 6H), 5.07 (dd, 1H, *J* = 5.5, 8.8 Hz), 7.36–7.44 (m, 6H), 7.45–7.50 (m, 1H), 7.54–7.60 (m, 2H). ^{13}C NMR δ 30.3, 42.3 (2 C:s), 51.0, 55.1, 82.1, 85.5, 119.9, 128.2 (2 C:s), 128.5 (2 C:s), 128.7 (2 C:s), 130.3, 132.2 (2 C:s), 133.5, 139.2, 153.9. HRTofMS calcd for $C_{20}H_{21}ClN_2O$ (M+) *m/z* 340.1342, found 340.1346.

*6.1.16. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-2-phenylacetamide HCl {**B1**}*

2-Phenylacetic acid (187 mg, 1.32 mmol) yielded 75 mg {**B1**} (93%). ^{1}H NMR δ 2.00–2.10 (m, 2H), 2.15 (s, 3H), 2.65 (s, 6H), 2.80–3.00 (m, 2H), 3.41 (s, 2H), 4.80 (dd, 1H, *J* = 6.8, 9.2 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.15–7.19 (m, 5H). ^{13}C NMR δ 23.9, 34.8, 46.1, 46.6 (2 C:s), 54.7, 59.3, 130.5 (2 C:s), 130.7, 132.4 (2 C:s), 132.9 (2 C:s), 133.2 (2 C:s), 139.8, 141.5, 141.8, 176.6. HRTofMS calcd for $C_{20}H_{26}N_2O$ (M+) *m/z* 310.2045, found 310.2045.

*6.1.17. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-2-(4-trifluoromethylphenyl)acetamide HCl {**B2**}*

2-(4-Trifluoromethylphenyl)acetic acid (270 mg, mmol) yielded 95 mg {**B2**} (98%). ^{1}H NMR δ 2.00–2.10 (m, 2H), 2.15 (s, 3H), 2.55 (s, 6H), 2.65–2.90 (m, 2H), 3.15 (s, 2H), 4.75 (t, 1H, *J* = 5.2 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.43 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR δ 19.8, 31.2, 42.1, 42.6 (2 C:s), 51.1, 55.4, 124.5 (q, $^1J_{CF}$ = 270.0 Hz), 125.0 (q, 2 C:s, $^3J_{CF}$ = 3.8 Hz), 126.4 (2 C:s), 128.8 (q, $^2J_{CF}$ = 32.1 Hz), 129.1 (2 C:s), 129.6 (2 C:s), 137.4, 136.0, 140.3, 171.3. HRTofMS calcd for $C_{21}H_{25}F_3N_2O$ (M+) *m/z* 378.1919, found 378.1921.

*6.1.18. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-2-(4-methoxyphenyl)acetamide HCl {**B3**}*

2-(4-Methoxyphenyl)acetic acid (229 mg, 1.38 mmol) yielded 82 mg {**B3**} (93%). ^{1}H NMR δ 2.03–2.08 (m, 2H), 2.13 (s, 3H), 2.65 (app. d, 6H), 2.58–3.00 (m, 2H), 3.35 (app d, 2H, *J* = 2.4 Hz), 3.75 (s, 3H), 4.80 (dd, 1H, *J* = 6.4, 6.4 Hz), 6.71 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 7.06–7.14 (m, 4H). ^{13}C NMR δ 23.9, 34.8, 45.7, 46.1, 46.6, 54.7, 58.5, 59.3, 117.7 (2 C:s), 130.4 (2 C:s), 131.7, 133.2 (2 C:s), 133.9 (2 C:s), 141.5, 141.8, 162.9, 177.0. HRTofMS calcd for $C_{21}H_{28}N_2O_2$ (M+) *m/z* 340.2151, found 340.2159.

*6.1.19. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-phenylpropionamide HCl {**B4**}*

3-Phenylpropionic acid (207 mg, 1.37 mmol) yielded 81 mg {**B4**} (96%). ^{1}H NMR δ 1.80–2.17 (m, 2H), 2.30 (s, 3H), 2.50–2.64 (m, 2H), 2.80 (s, 6H), 2.85–2.98 (m, 4H), 4.84 (dd, 1H, *J* = 8.08, 8.08 Hz), 7.10–7.26 (m, 9H). ^{13}C NMR δ 19.8, 30.6, 31.4, 37.2, 42.6, 47.1, 51.0, 55.2, 126.0, 126.3 (2 C:s), 128.2 (2 C:s), 128.3 (2 C:s), 129.1 (2 C:s), 137.3, 137.8, 140.7, 173.5. HRTofMS calcd for $C_{21}H_{28}N_2O$ (M+) *m/z* 324.2202, found 324.2214.

*6.1.20. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-(4-trifluoromethylphenyl)propionamide HCl {**B5**}*

3-(4-Trifluoromethylphenyl)propionic acid (284 mg, 1.32 mmol) yielded 80 mg {**B5**} (78%). ^{1}H NMR δ 1.88–1.96 (m, 2H), 2.30 (s, 3H), 2.50–2.66 (m, 4H), 2.82 (s, 6H), 2.94–3.02 (m, 2H), 4.80 (t, 1H, $J = 5.3$ Hz),7.04 (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz), 7.44–7.50 (m, 4H). ^{13}C NMR δ 19.8, 30.6, 31.1, 36.9 (2 C:s), 42.1, 42.6, 52.5, 125.0 (2 C:s), 126.3 (q, 2 C:s, $^3J_{CF} = 9.2$ Hz), 127.0 (q, $^1J_{CF} = 280$ Hz), 128.4 (q, $^2J_{CF} = 33.1$ Hz), 128.9 (2 C:s), 129.1 (2 C:s), 137.3, 137.9, 145.4, 173.0. HRTofMS calcd for $C_{22}H_{27}F_3N_2O$ (M+) *m/z* 392.4685, found 392.4683.

*6.1.21. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-(4-methoxyphenyl)propionamide HCl {**B6**}*

3-(4-Methoxyphenyl)propionic acid (236 mg, 1.31 mmol) yielded 90 mg {**B6**} (98%). ^{1}H NMR δ 1.95–2.05 (m, 2H), 2.08 (s, 3H), 2.32–2.48 (m, 2H), 2.67 (s, 6H), 2.68–2.86 (m, 4H), 3.60 (s, 3H), 4.75 (t, 1H, $J = 9.6$ Hz), 6.65 (d, 2H, $J = 8.8$ Hz), 6.97 (d, 2H, $J = 8.8$ Hz), 6.98–7.40 (m, 4H). ^{13}C NMR δ 23.9, 34.7 (2 C:s), 41.6, 46.0, 46.7, 54.4, 58.4, 59.3, 117.6 (2 C:s), 130.4 (2 C:s), 133.1 (2 C:s), 133.3 (2 C:s), 136.6, 141.3, 141.8, 162.3, 177.7. HRTofMS calcd for $C_{22}H_{30}N_2O_2$ (M+) *m/z* 354.2307, found 354.2306.

*6.1.22. N-[3-Dimethylamino-1-(4-methylphenyl)propyl] cinnamamide {**B7**}*

Cinnamic acid (198 mg, 1.34 mmol) yielded 72 mg {**B7**} (86%). ^{1}H NMR δ 2.20–2.38 (m, 2H) 2.30 (s, 3H), 2.78–2.94 (m, 1H) 2.86 (s, 6H), 3.28–3.32 (m, 1H), 5.07 (dd, 1H, $J = 8.8$, 14.6 Hz), 6.73 (d, 1H, $J = 16.8$ Hz), 7.14 (d, 2H, $J = 7.7$ Hz), 7.23–7.42 (m, 5H), 7.46–7.60 (m, 3H). ^{13}C NMR δ 19.8, 30.9, 42.1 (2 C:s), 50.9, 55.3, 120.3, 126.5 (2 C:s), 127.6 (2 C:s), 128.7 (2 C:s), 129.2 (2 C:s), 129.7, 134.9, 137.6, 137.8, 141.1, 166.9. HRTofMS calcd for $C_{21}H_{26}N_2O$ (M+) *m/z* 322.2045, found 322.2055.

*6.1.23. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-4-trifluoromethyl-cinnamamide HCl {**B8**}*

4-Trifluoromethyl-cinnamic acid (286 mg, mmol) yielded 60 mg {**B8**} (56%). ^{1}H NMR δ 1.90–2.08 (m, 2H), 2.20 (s, 6H), 2.30 (s, 3H), 3.28–3.34 (m, 2H), 4.96–5.02 (dd, 1H, $J = 7.3$, 15.0 Hz), 6.78 (d, 1H, $J = 15.8$ Hz), 7.14 (d, 2H, $J = 8.0$ Hz), 7.22 (d, 2H, $J = 8.0$ Hz), 7.54 (d, 1H, $J = 15.8$ Hz), 7.65 (d, 2H, $J = 8.0$ Hz), 7.72 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR δ 19.8, 33.6, 44.2 (2 C:s), 52.0, 56.4, 123.5, 125.5 (q, 2 C:s, $^3J_{CF} = 8.8$ Hz), 126.3 (2 C:s), 126.5 (q, $^1J_{CF} = 240$ Hz), 128.0 (2 C:s), 128.6 (q, $^2J_{CF} = 30.0$ Hz), 128.9 (2 C:s), 136.9, 138.7, 138.9, 139.2, 165.7. HRTofMS calcd for $C_{22}H_{25}F_3N_2O$ (M+) *m/z* 390.4526, found 390.4528.

*6.1.24. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-4-methoxy-cinnamamide HCl {**B9**}*

4-Methoxy-cinnamic acid (232 mg, 1.30 mmol) yielded {**B9**} (87%). ^{1}H NMR δ 2.18–2.39 (m, 2H), 2.30 (s, 3H), 2.85 (s, 6H), 3.08–3.24 (m, 2H), 3.34 (s, 3H), 5.07 (dd, 1H, $J = 6.2$, 8.8 Hz), 6.58 (d, 1H, $J = 15.8$ Hz), 6.92 (d, 2H, $J = 8.8$ Hz), 7.19 (d, 2H, $J = 8.0$ Hz), 7.30 (d, 2H, $J = 8.0$ Hz), 7.46–7.49 (m, 3H). ^{13}C NMR δ 19.8, 31.0, 42.0, 42.6, 50.7, 54.6, 55.3, 114.0 (2 C:s), 117.6, 126.4 (2 C:s), 127.4, 129.2 (2 C:s), 129.3 (2 C:s), 130.0, 137.5, 140.9, 161.4, 167.2. HRTofMS calcd for $C_{22}H_{28}N_2O_2$ (M+) *m/z* 352.2151, found 352.2152.

*6.1.25. N-[3-Dimethylamino-1-(4-methylphenyl)propyl]-3-phenylpropiolamide {**B10**}*

3-Phenylpropiolic acid (193 mg, 1.32 mmol) yielded 50 mg {**B10**} (60%). ^{1}H NMR δ 2.10–2.40 (m, 2H), 2.25 (s, 3H), 2.80 (s, 6H), 3.00–3.20 (m, 2H), 5.00 (dd, 1H, $J = 6.2$, 8.1 Hz), 7.17 (d, 2H, $J = 8.0$ Hz), 7.27 (d, 2H, $J = 8.0$ Hz), 7.32–7.50 (m, 3H), 7.50–7.60 (m, 2H). ^{13}C NMR δ 19.8, 30.5, 41.0 (2 C:s), 51.2, 55.2, 81.0, 82.5, 120.0, 126.4 (2 C:s), 128.5 (2 C:s), 129.2 (2 C:s), 130.2, 132.2 (2 C:s), 137.0, 137.5, 154.0. HRTofMS calcd for $C_{21}H_{24}N_2O$ (M+) *m/z* 320.1889, found 320.1887.

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

2-Phenylacetic acid (148 mg, 1.18 mmol) yielded 51 mg {**C1**} (67%). ^{1}H NMR δ 2.26–2.40 (m, 2H), 2.82 (s, 6H), 3.00–3.20 (m, 2H), 3.59 (s, 2H), 5.14 (dd, 1H, $J = 6.2$, 8.8 Hz), 7.20–7.36 (m, 5H), 7.43–7.53 (m, 3H), 7.78–7.91 (m, 4H). ^{13}C NMR δ 30.5, 42.1, 42.5 (2 C:s), 51.0, 54.9, 124.4, 125.2, 125.9, 126.2, 126.7, 127.3, 127.6, 128.3 (2 C:s), 128.5, 128.8 (2 C:s), 132.8, 133.2, 135.4, 137.8, 172.6. Anal. Calcd. for $C_{23}H_{27}ClN_2O \times H_2O$: C, 68.9; H, 7.3; N, 7.0. Found: C, 68.8; H, 7.3; N, 6.7.

*6.1.27. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-2-(4-trifluoromethylphenyl)acetamide HCl {**C2**}*

2(4-Trifluoromethylphenyl)acetic acid (223 mg, 1.18 mmol) yielded 80 mg {**C2**} (88%). ^{1}H NMR δ 2.30–2.40 (m, 2H), 2.85 (s, 6H), 3.02–3.22 (m, 2H), 3.70 (s, 2H), 5.14 (dd, 1H, $J = 7.3$, 15.0 Hz), 7.42–7.54 (m, 5H), 7.56–7.64 (d, 2H, $J = 8.0$ Hz), 7.76–7.92 (m, 4H). ^{13}C NMR δ 30.5, 41.8, 42.1, 42.5, 51.2, 55.0, 124.2 (q, $^1J_{CF} = 269.1$ Hz), 124.4, 125 (q, 2 C:s, $^3J_{CF} = 3.8$ Hz), 125.2, 126.0, 126.2, 127.4, 127.6, 128.5, 128.8 (q, $^2J_{CF} = 32.1$ Hz), 129.6 (2 C:s), 133.1, 133.4, 137.9, 140.2, 171.6. Anal. Calcd. for $C_{24}H_{26}ClF_3N_2O \times H_2O$: C, 61.5; H, 6.0; N, 6.0. Found: C, 61.7; H, 6.0; N, 5.6.

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

2-(4-Methoxyphenyl)acetic acid (182 mg, 1.10 mmol) yielded 65 mg {**C3**} (79%). ^{1}H NMR δ 2.05–2.23 (m, 2H), 2.43 (s, 6H), 2.58–2.60 (m, 2H), 3.49 (s, 2H), 3.75 (s, 3H), 5.09 (dd, 1H, $J = 6.24$, 8.44 Hz), 6.85 (d, 2H, $J = 8.8$ Hz), 7.22 (d, 2H, $J = 8.8$ Hz), 7.40–7.49 (m, 3H), 7.77–7.84 (m, 4H). ^{13}C NMR δ 32.0, 41.8, 43.3 (2 C:s), 54.4, 55.8, 65.6, 113.7 (2 C:s), 124.4, 124.9, 125.7, 126.0, 127.3, 127.6, 127.7, 128.2, 129.8 (2 C:s), 132.9, 133.5, 138.9, 158.9, 172.8. HRTofMS calcd for $C_{24}H_{28}N_2O_2$ (M+) *m/z* 376.2151, found 376.2165.

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

3-Phenylpropionic acid (164 mg, 1.20 mmol) yielded 52 mg {**C4**} (66%). ^{1}H NMR δ 2.10–2.30 (m, 2H), 2.52–2.68 (m, 2H), 2.83 (s, 6H), 2.93 (t, 2H, $J = 7.7$ Hz), 2.99 (t, 2H, $J = 7.7$ Hz), 5.10 (dd, 1H, $J = 5.9$, 9.5 Hz), 7.10–7.23 (m, 6H), 7.38 (dd, 1H, $J = 1.8$, 8.8 Hz), 7.45–7.53 (m, 2H), 7.80–7.90 (m, 3H). ^{13}C NMR δ 30.4, 31.4, 37.2, 41.9, 42.6, 50.7, 55.4, 124.4, 125.2, 125.9, 126.0, 126.1, 127.3, 127.7, 128.2 (2 C:s), 128.3 (2 C:s), 128.4, 133.0, 133.4, 138.0, 140.7, 173.9. HRTofMS calcd for $C_{24}H_{28}N_2O$ (M+) *m/z* 360.2202, found 360.2210.

*6.1.30. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-2-(4-trifluoromethylphenyl)propionamide HCl {**C5**}*

3-(4-Trifluoromethylphenyl)propionic acid (239 mg, 1.17 mmol) yielded 79 mg {**C5**} (84%). ^{1}H NMR δ 2.20–2.35 (m, 2H), 2.56–2.60 (m, 2H), 2.79–2.80 (m, 1H), 2.84 (s, 6H), 2.96–3.02 (m, 2H), 3.03–3.20 (m, 1H), 5.11 (dd, 1H, $J = 7.3$, 14.3 Hz), 7.29–7.40 (m, 2H), 7.41–7.54 (m, 4H), 7.74–7.93 (m, 5H). ^{13}C NMR δ 30.4, 31.1, 36.7, 42.1, 42.3, 50.9, 55.3, 124.3, 124.9 (q, 2 C:s, $^3J_{CF} = 3.8$ Hz), 125.3, 125.9, 126.2, 126.8 (q, $^1J_{CF} = 241.5$ Hz), 127.4, 127.7, 128.5 (q, $^2J_{CF} = 35.3$ Hz), 128.9 (2 C:s), 133.0, 133.4, 138.1, 145.4, 173.2. Anal. Calcd. for $C_{25}H_{28}ClF_3N_2O \cdot HCl \times H_2O$: C, 62.2; H, 6.3; N, 5.8. Found: C, 62.3; H, 6.2; N, 5.6.

*6.1.31. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-(4-methoxyphenyl)propionamide HCl {**C6**}*

3-(4-Methoxyphenyl)propionic acid (220 mg, 1.22 mmol) yielded 80 mg {**C6**} (93%). ^{1}H NMR δ 2.10–2.22 (m, 2H), 2.48–2.61 (m, 2H), 2.61–2.70 (m, 1H), 2.65 (s, 6H), 2.76–2.89 (m, 3H), 3.66 (s, 3H), 5.07 (dd, 1H, $J = 6.2$, 8.4 Hz), 6.71 (d, 2H, $J = 8.4$ Hz), 7.06 (d, 2H, $J = 8.4$ Hz), 7.34–7.39 (dd, 1H, $J = 1.8$, 8.4 Hz), 7.42–7.50 (m, 2H), 7.71 (s, 1H), 7.78–7.86 (m, 3H). ^{13}C NMR δ 30.6, 31.2, 37.6, 42.7 (2 C:s), 50.9, 54.3, 55.5, 113.5 (2 C:s), 124.5, 125.0, 125.8, 126.0, 127.3, 127.7, 128.3, 129.2 (2 C:s), 132.5, 133.0, 133.5, 138.5, 158.2, 173.7. HRTofMS calcd for $C_{25}H_{30}N_2O_2$ (M+) *m/z* 390.2307, found 390.2316.

*6.1.32. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-cinnamamide HCl {**C7**}*

Cinnamic acid (162 mg, 1.17 mmol) yielded 60 mg {**C7**} (76%). ^{1}H NMR δ 2.37–2.45 (m, 2H), 2.88–2.95 (m, 1H), 2.91 (s, 6H), 3.13–3.29 (m, 1H), 5.30 (t, 1H, $J = 7.0$ Hz), 6.75 (d, 1H, $J = 15.8$ Hz), 7.34–7.42 (m, 3H), 7.45–7.52 (m, 2H), 7.53–7.59 (m, 4H), 7.82–7.95 (m, 4H). ^{13}C NMR δ 30.7, 42.1 (2 C:s), 55.4, 65.6, 120.0, 124.4, 125.3, 126.0, 126.2, 127.4, 127.6 (2 C:s), 127.7, 128.6, 128.7 (2 C:s), 129.7, 133.0, 133.4, 134.8, 138.0, 141.4, 167.0. HRTofMS calcd for $C_{24}H_{26}N_2O$ (M+) *m/z* 358.2045, found 358.2045.

*6.1.33. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-4-trifluoromethyl-cinnamamide HCl {**C8**}*

4-Trifluoromethylcinnamic acid (237 mg, 1.20 mmol) yielded 55 mg {**C8**} (59%). ^{1}H NMR δ 2.37–2.50 (m, 2H), 2.84–2.96 (m, 1H), 2.90 (s, 6H), 3.14–3.22 (m, 1H), 5.30 (dd, 1H, $J = 6.6$, 14.7 Hz), 6.90 (d, 1H, $J = 15.8$ Hz), 7.44–7.53 (m, 2H), 7.54–7.62 (m, 1H), 7.63–7.71 (m, 2H), 7.72–7.79 (m, 3H), 7.82–7.96 (m, 4H). ^{13}C NMR δ 30.7, 42.4 (2 C:s), 51.2, 55.1, 123.1, 124.2 (q, $^1J_{CF} = 279.1$ Hz), 124.4, 125.4, 125.5 (q, 2 C:s, $^3J_{CF} = 3.8$ Hz), 126.0, 126.2, 127.4, 127.7, 128.1 (2 C:s), 128.6, 130.9 (q, $^2J_{CF} = 34.3$ Hz), 133.1, 133.5, 138.0, 138.7, 139.3, 166.4. HRTofMS calcd for $C_{25}H_{25}F_3N_2O$ (M+) *m/z* 426.1919, found 426.1922.

*6.1.34. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-4-methoxy-cinnamamide HCl {**C9**}*

4-Methoxycinnamic acid (220 mg, 1.23 mmol) yielded 40 mg {**C9**} (47%). ^{1}H NMR δ 2.36–2.45 (m, 2H), 2.85–2.94 (m, 1H), 2.91 (s, 6H), 3.10–3.30 (m, 1H), 3.80 (s, 3H), 5.29 (dd, 1H, $J = 7.32$, 15.0 Hz), 6.60 (d, 1H, $J = 7.0$ Hz), 6.88–6.98 (m, 2H), 7.44–7.60 (m, 6H), 7.80–7.96 (m, 4H). ^{13}C NMR δ 30.8, 42.0, 42.5, 54.5, 55.3, 88.0, 114.1 (2 C:s), 117.1, 124.1, 125.0, 125.8, 126.0, 127.4 (2 C:s), 127.7, 128.0, 129.3 (2 C:s), 133.0, 133.2, 138.0, 141.0, 161.1, 167.0. HRTofMS calcd for $C_{25}H_{28}N_2O_2$ (M+) *m/z* 388.2151, found 388.2162.

*6.1.35. N-[3-Dimethylamino-1-(2-naphthyl)propyl]-3-phenylpropiolamide HCl {**C10**}*

3-Phenylpropiolic acid (161 mg, 1.19 mmol) yielded 50 mg {**C10**} (64%). ^{1}H NMR δ 2.32–2.48 (m, 2H), 2.80–2.94 (m, 1H), 2.88 (s, 6H), 3.12–3.22 (m, 1H), 5.25 (t, 1H, $J = 8.4$ Hz), 7.36–7.43 (m, 2H), 7.44–7.51 (m, 2H), 7.53–7.60 (m, 3H), 7.81–7.95 (m, 5H). ^{13}C NMR δ 30.0, 42.0, 52.0, 54.5, 65.0, 82.0, 85.0, 120.0, 124.0, 125.0, 126.0, 126.1, 127.0, 127.1, 129.0 (2 C:s), 130.0, 131.5 (2 C:s), 133.0, 133.1, 137.5, 152.4, 154.0. HRTofMS calcd for $C_{24}H_{24}N_2O$ (M+) *m/z* 356.1889, found 356.1887.

6.2. Biological activity

R-SAT-testing: R-SAT™ assays for pharmacological testing were performed as previously described, 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 roller bottles for 18 h with the human urotensin II receptor and the β-galactosidase marker. After the 18 h transfection, cells were trypsinized, harvested, and frozen. Aliquots of frozen cell batches were thawed and tested for response to control compound to perform quality control before initiation of pharmacological testing, ensuring the correct pharmacological response and sufficient sensitivity. To initiate the pharmacological assay, cells were thawed rapidly and prepared in DMEM media containing 0.4% calf serum (Hyclone), 30% UltraCulture (Biowhittaker), and 1%

penicillin/streptomycin/glutamine (Invitrogen), and then added to half-area 96-well microtiter plates containing either test compounds or reference ligands. After a five-day incubation of drug with cells in 5% ambient CO_2, media was removed and reporter enzyme activity was measured at 420 nm.

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