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Urotensin-II receptor antagonists: Synthesis and SAR of N-cyclic azaalkyl benzamides

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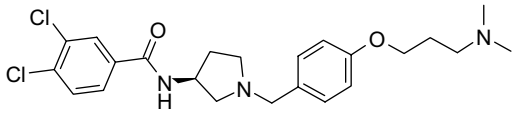
ABSTRACT

SAR exploration of the central diamine, benzyl, and terminal aminoalkoxy regions of the N-cyclic azaalkyl benzamide series led to the identification of very potent human urotensin-II receptor antagonists such as **1a** with a K_i of 4 nM. The synthesis and structure–activity relationships (SAR) of N-cyclic azaalkyl benzamides are described.

Urotensin-II (U-II), first isolated as a fish neuropeptide in the 1960's,[1] is the most potent vasoconstrictor known to date.[2] Human urotensin-II (hU-II) and its cognate receptor hUT (formerly known as the GPR-14 receptor) are proposed to be involved in the (dys) regulation of cardiorenal function,[3] and have been implicated in the etiology of numerous cardiorenal and metabolic diseases including hypertension[4] and heart failure.[5,6] The impressive in vitro and in vivo pharmacological activities of U-II has stimulated a great deal of interest in developing small molecule UT modulators.[7,8] We previously reported that initial SAR exploration of a novel aminoalkoxybenzyl pyrrolidine series resulted in the discovery of a truncated sub-series exemplified by **2a**.[7d] Herein, we describe the synthesis, SAR, and optimization of this N-cyclic azaalkyl benzamide series that led to the identification of very potent human urotensin-II receptor antagonists such as **1a**.

Compound **2a** showed good hUT receptor binding affinity with a K_i of 200 nM (Fig. 1) in a [^{125}I]hU-II radioligand binding assay using HEK293 cell membranes stably expressing human recombinant UT receptors[9,10] and was an antagonist in a fluorometric imaging plate reader (FLIPR) assay (measuring inhibition of hU-II-induced $[Ca^{2+}]_i$-mobilization in HEK293 cells expressing human recombinant UT receptor)[9] with an IC_{50} of 170 nM. With the left-hand side (LHS) phenyl moiety optimized previously,[7d] we focused our attention on investigating and optimizing the central diamine, benzyl, and terminal aminoalkoxy regions.



2a, hUT binding: K_i = 200 nM
hUT FLIPR: IC_{50} = 170 nM

Figure 1. In vitro profile of compound **2a**.

We first explored the 3-amino pyrrolidine region, also referred to as the central diamine region. Commercially available achiral or optically pure Boc-protected diamines **3** were converted to the corresponding triamines **4** via reductive amination, deprotection, and treatment with base (Scheme 1). Subsequent acid coupling of triamines **4** with benzoic acids afforded the desired benzamides **2**. Compared to 3(*S*)-amino pyrrolidine (**2a**), 4-amino piperidine (**2b**) had slightly lower affinity while piperazine (**2c**) and acyclic analog **2d** lost hUT binding affinity completely (Table 1). The preferred stereochemistry for 3-amino pyrrolidines was also studied. It was found that the *S* and *R* enantiomers had very similar binding affinity (**2e** vs **2f**).

To efficiently explore the right-hand side (RHS) amino alkoxy moiety and substituent(s) on the RHS phenyl ring, we developed a robust solid-phase synthetic route outlined in Scheme 2. Resin-bound pyrrolidine **5** was prepared from commercially available optically pure Boc-protected 3(*S*)-amino pyrrolidine following

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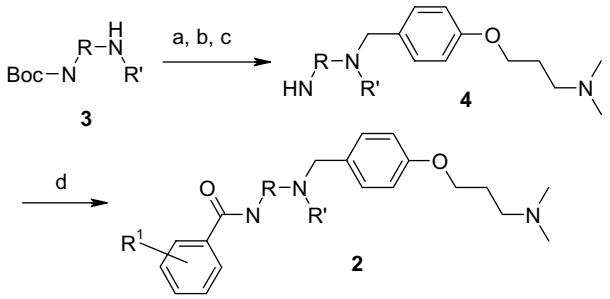
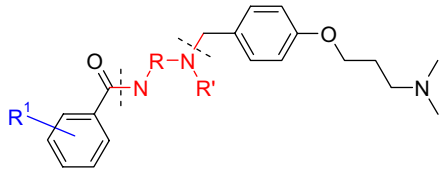
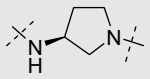
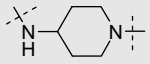
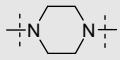
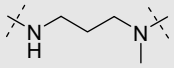
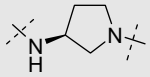
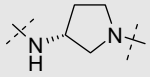


Scheme 1. Reagents and conditions: (a) 4-(3-dimethylaminopropoxy) benzaldehyde, PS-BH_4^-, NH_4Cl, EtOH, rt; (b) 4 M HCl in 1,4-dioxane, MeOH, rt; (c) PS-carbonate, MeOH, rt; (d) benzoic acids, PS-EDC, DCM, rt.

Table 1
SAR of the central diamine moiety

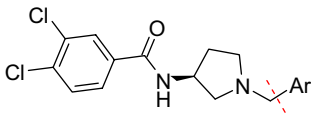


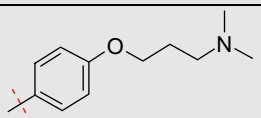
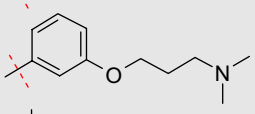
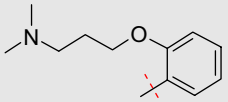
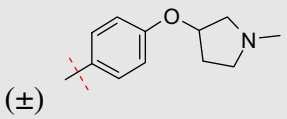
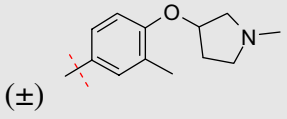
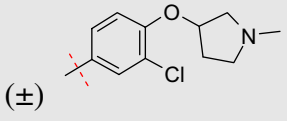
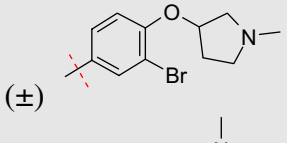
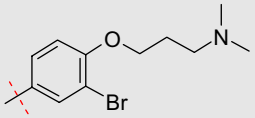
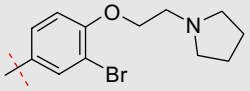
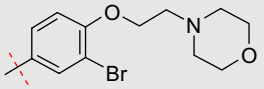
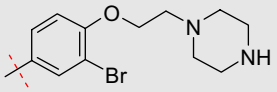
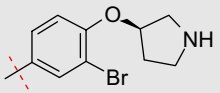
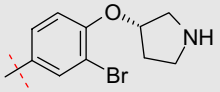
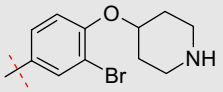
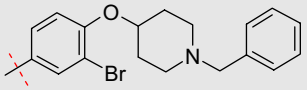
Compound	R^1		hUT binding K_i[a] (nM)
2a	3,4-Dichloro		200
2b	3,4-Dichloro		500
2c	3,4-Dichloro		>10,000
2d	3,4-Dichloro		>10,000
2e	4-Bromo		320
2f	4-Bromo		350

[a] Mean of at least two determinations.

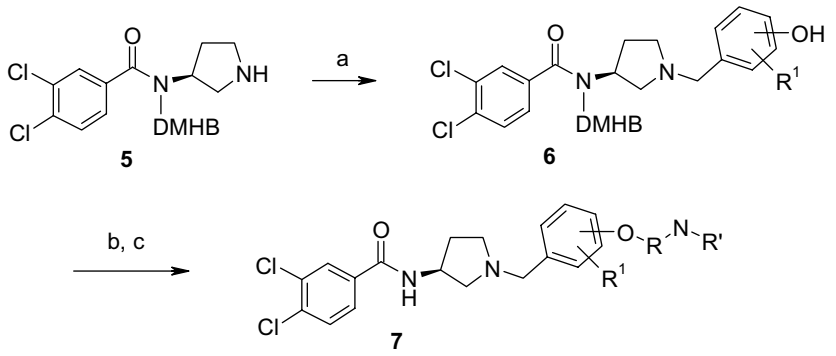
literature procedures.[7d,11] Reductive amination of **5** with hydroxyl benzaldehydes afforded resin-bound phenols **6**. Mitsunobu reaction of **6** with various amino alcohols and subsequent resin cleavage produced the desired compounds **7**.[11] Moving the 3-dimethylaminopropoxy from the *para*-position (**2a**) to the *meta*-(**7a**) or *ortho*-(**7b**) position resulted in significant affinity loss (Table 2). *N*-Methylpyrrolidin-3-yloxy compound **7c**, a mixture of two diastereoisomers, was slightly more potent than the 3-dimethylaminopropoxy analog **2a**. A halo group such as bromo and chloro at the 3-position modestly enhanced binding affinity (**7e–f** vs **7c**, **7g** vs **2a**) while a 3-methyl substituent did not provide affinity enhancement (**7d** vs **7c**). The aminoalkoxy moiety was further optimized via holding the 3-bromo group constant. While 2-(pyrrolidin-1-yl)ethoxy (**7h**), 2-(morpholin-4-yl)ethoxy (**7i**) and 2-(piperizin-4-yl)ethoxy (**7j**) had significantly lower affinity compared to *N*-methylpyrrolidin-3-yloxy (**7c**) and 3-dimethylaminopropoxy (**2a**), cyclic secondary amines such as piperidin-4-yloxy (**1a**) and

Table 2
SAR of the aminoalkoxyphenyl moiety



Compound	Ar	hUT binding K_i[a] (nM)
2a		200
7a		>3000
7b		>10,000
7c	 (±)	97
7d	 (±)	108
7e	 (±)	47
7f	 (±)	41
7g		61
7h		1000
7i		3500
7j		1500
7k		5.5
7m		44
1a		4
7n		230

[a] Mean of at least two determinations.



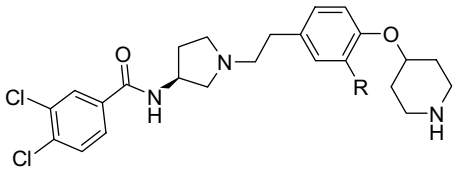
Scheme 2. Reagents and conditions: (a) various hydroxybenzaldehydes, $Na(OAc)_3BH$, 10% of HOAc in NMP, rt; (b) various amino alcohols, DIAD, PPh_3, THF, −78 °C—rt; (c) 50% of TFA in DCE, rt.

pyrrolidin-3(*R*)-yloxy (**7k**) were preferred. Pyrrolidin-3(*R*)-yloxy (**7k**) was 8-fold more potent than pyrrolidin-3(*S*)-yloxy (**7m**). Adding a large alkyl group such as benzyl to the piperidine significantly reduced binding affinity (**7n** vs **1a**).

Having identified the optimal amino alkoxy phenyl moiety, we then investigated alternative linkers at the benzylic position. We first prepared a series of phenethyl analogs (Scheme 3).[11] Bis-nosylates **9** were synthesized from commercially available 4-hydroxyethyl phenols **8** via a one-pot procedure. Alkylation of resin-bound amine **5** with bis-nosylates **9** and subsequent hydrolysis afforded phenethyl amines **10**, which were then converted to the desired products **11** via Mitsunobu reaction, resin cleavage and simultaneous Boc group removal. Similar to benzyl amine **1a**, phenethyl amine **11a** had high hUT binding affinity (Table 3). We also studied the 3-substituent on the RHS phenyl ring for the phenethyl sub-series and found that 3-bromo (**11a**) and 3-chloro (**11b**) were preferred, and 3-fluoro, 3-methoxy and 3-nitro did not enhance affinity (**11c**–**e** vs **11f**). The SAR in this region followed the same trend as the benzyl series.

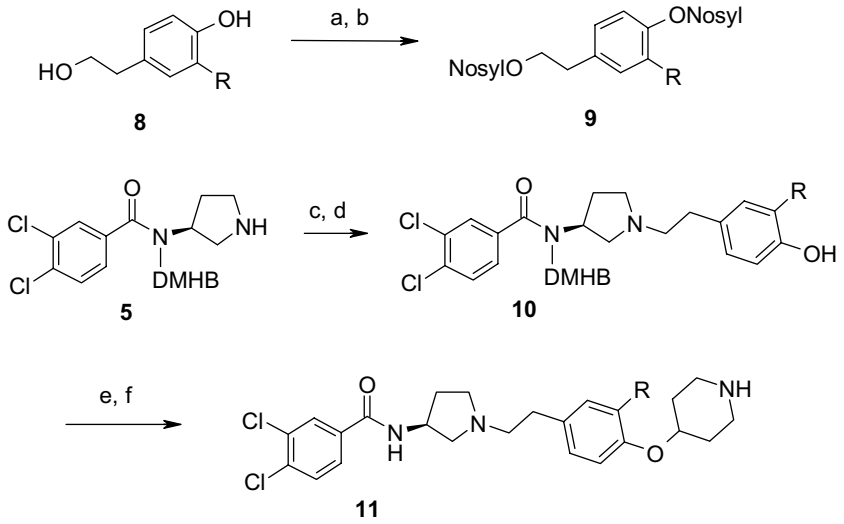
We next explored whether the basicity of the central pyrrolidine was necessary for hUT binding affinity via replacing the methylene or ethylene linker with a sulfonyl linker. A solid-phase synthesis of sulfonamides **15** is outlined in Scheme 4.[12] Resin-bound nosyl-protected diamines **13** were prepared from diamines **3** via nosylation, de-Boc, loading onto 2,6-dimethoxy-4-polystyrene benzyloxybenzaldehyde (DMHB-resin)[13] and acid coupling. Deprotection of **13**, followed by sulfonylation of the resulting secondary amines with 3-bromo-4-hydroxy benzenesulfonyl chloride (**12**), which was prepared from 2-bromophenol, and hydrolysis of sulfonate byproducts formed during the sulfonylation step, pro-

Table 3
SAR of the phenethyl sub-series

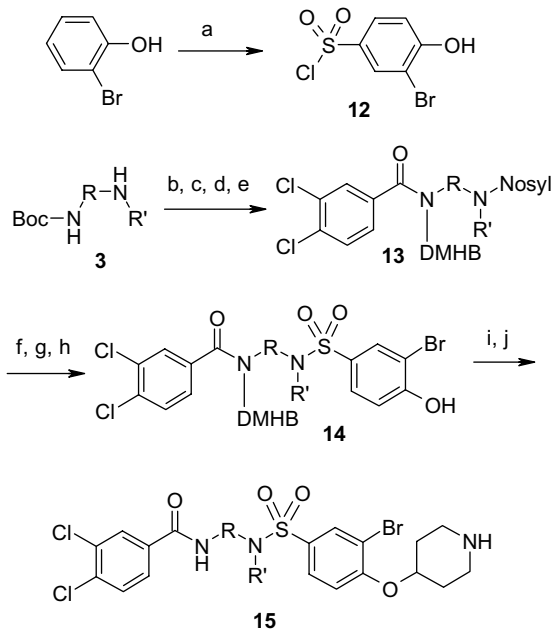


Compound	R	hUT binding K_i[a] (nM)
11a	3-Bromo	10
11b	3-Chloro	15
11c	3-Fluoro	62
11d	3-Methoxy	36
11e	3-Nitro	69
11f	Hydrogen	42

[a] Mean of at least two determinations.



Scheme 3. Reagents and conditions: (a) 2-nitrobenzenesulfonyl chloride, NaH, THF, rt; (b) ether, water, 0 °C; (c) bis-nosylates **9**, tetrabutylammonium iodide, NMP, rt to 65 °C; (d) potassium trimethylsilanolate, THF, rt; (e) 4-hydroxy-*N*-Bocpiperidine, DIAD, PPh_3, THF, −78 °C—rt; (f) 50% of TFA in DCE, rt.



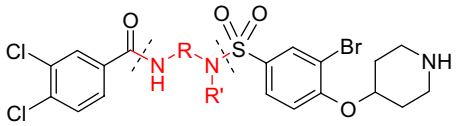
Scheme 4. Reagents and conditions: (a) $ClSO_3H$, DCM, −3 °C—rt; (b) 2-nitrobenzenesulfonyl chloride, pyridine, DCM, 0 °C—rt; (c) 4 M HCl in 1,4-dioxane, MeOH, rt; (d) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB-resin), $Na(OAc)_3BH$, DIEA, 1% of HOAc in NMP, rt; (e) 3,4-dichlorobenzoic acid, DIC, HOAt, NMP, rt; (f) K_2CO_3 PhSH, NMP, rt; (g) **12**, DCE, NMP, rt; (h) potassium trimethylsilanolate, THF, rt; (i) 4-hydroxy-*N*-Bocpiperidine, DIAD, PPh_3, THF, −78 °C—rt; (j) 50% of TFA in DCE, rt.

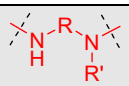
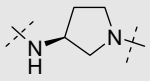
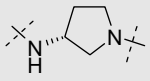
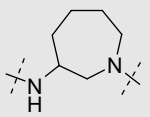
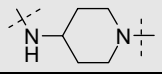
duced resin-bound phenols **14** cleanly. **14** were then converted to the desired products **15** via Mitsunobu reaction, resin cleavage, and Boc deprotection. Although sulfonamide **15a** was 10- to 30-fold less potent than benzyl amine **1a** and phenethyl amine **11a**, **15a** still possessed good binding affinity (K_i 120 nM)—indicating the basicity of the central pyrrolidine was not necessary for hUT binding (Table 4). Furthermore, similar effects (K_i 12–140 nM) were seen with the sulfonamides derived from azepine (**15c**),[14] piperidine (**15d**) and benzothiophene-leucine amide **16d** (vide infra). The stereochemistry of the 3-amino pyrrolidine was also examined. Similar to the benzyl sub-series, 3(*R*)-amino pyrrolidine (**15b**) also showed good affinity, only slightly less potent than the *S*-enantiomer **15a**.

We next incorporated these newly identified affinity-enhancing structural features into the previously reported benzothiophene-leucine amide sub-series exemplified by **16a**.[7d] As shown in Table 5, 3-bromo-4-(piperidin-4-yloxy)benzyl compound **16b**, 3-bromo-4-(pyrrolidin-3(*R*)-yloxy)phenethyl compound **16c**, and 3-bromo-4-(piperidin-4-yloxy)benzene sulfonyl compound **16d** had excellent binding affinity to the hUT receptor.[15] The SAR in these regions for the benzothiophene-leucine amide sub-series was similar to that of the truncated benzamide series (vide supra).

In addition to high affinity in the hUT binding assay, **1a** was a potent antagonist in the functional FLIPR assay with an IC_{50} of 4 nM (Fig. 2). The FLIPR potency of **1a** was commensurate with its receptor binding affinity consistent with the proposition that the observed inhibition of intracellular calcium mobilization in these cells was a result of hUT blockade. In mode of action studies using the FLIPR assay, **1a** was found to be an insurmountable antagonist that significantly suppressed the maximal response of hU-II. The observed kinetics of **1a** were similar to those of known UT antagonist palosuran,[7c] but distinct from those of SB-706375[7e] and aminomethyl piperidines,[7h] which behaved as competitive and reversible UT antagonists. In addition, key compounds in the series including **1a** were tested in a rat UT binding assay[16] and found to have poor rat UT binding affinity (e.g. **1a**, K_i = 4100 nM). Although it is not clear what contributes to the poor rat receptor affinity, the significant sequence differences between human and rodent receptors[8b] might be a reason for the observed receptor binding affinity difference. Known UT antagonists such as palosuran[7c] showed a similar binding affinity difference between human and rodent receptors. Compound **1a** was also evaluated

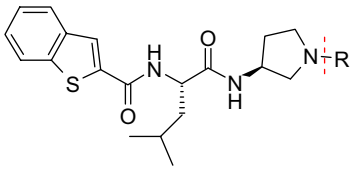
Table 4
SAR of the sulfonamide sub-series

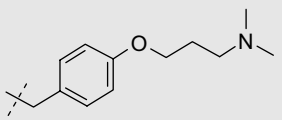
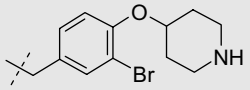
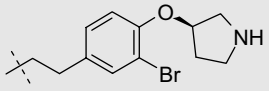
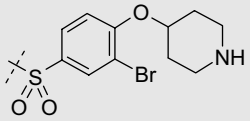


Compound		hUT binding K_i[a] (nM)
15a		120
15b		380
15c	 (±)	71
15d		140

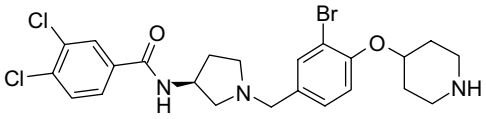
[a] Mean of at least two determinations.

Table 5
SAR of the benzothiophene-leucine amide sub-series



Compound	R	hUT binding K_i[a] (nM)
16a		110
16b		3
16c		18
16d		12

[a] Mean of at least two determinations.



1a, hUT binding K_i = 4 nM
hUT FLIPR IC_{50} = 4 nM
rUT binding K_i = 4,100 nM

Figure 2. In vitro profile of compound **1a**.

in cytochrome P450 (CYP450) and selectivity versus other 7TM receptors. **1a** had CYP450 3A4 (IC_{50} 1.9 μM) and 2D6 (IC_{50} 2.2 μM) liability, but was clean again 1A2, 2C9 and 2C19 isozymes. **1a** was 10- to 30-fold selective for hUT over 5HT1A (K_i = 38 nM), 5HT1D (K_i = 140 nM), 5HT2B (K_i = 140 nM), 5HT2C (K_i = 85 nM) and D2 (K_i = 100 nM), and greater than 1000-fold selective for hUT over 5HT1E (K_i > 10,000 nM), 5HT1F (K_i = 7200 nM), 5HT6 (K_i = 4100 nM) and β2 (K_i > 10,000 nM). In rat pharmacokinetic (PK) studies (dosed at 0.5 mg/kg (iv) and 2.6 mg/kg (po) in Sprague–Dawley rats), **1a** had low oral bioavailability and high in vivo clearance. Surprisingly, **1a** showed low to moderate intrinsic clearance (human: 4.3 mL/min/g liver; rat 4.8 mL/min/g liver) in the in vitro human and rat liver microsome stability studies.

In summary, SAR exploration of multiple regions of the N-cyclic azaalkyl benzamide series led to the identification of very potent human urotensin-II receptor antagonists such as **1a** and key structural motifs necessary for achieving high hUT binding affinity.

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