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Aminomethylpiperazines as selective urotensin antagonists

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ABSTRACT

Aminomethylpiperazines, reported previously as being κ-opioid receptor agonists, were identified as lead compounds in the development of selective urotensin receptor antagonists. Optimized substitution of the piperazine moiety has provided high affinity urotensin receptor antagonists with greater than 100-fold selectivity over the κ-opioid receptor. Select compounds were found to inhibit urotensin-induced vasoconstriction in isolated rat aortic rings consistent with the hypothesis that an urotensin antagonist may be useful for the treatment of hypertension.

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Urotensin-II (U-II) is a cyclic undecapeptide originally isolated from the *goby urophysis*.[1] It was hypothesized to be involved primarily in osmoregulation in fish.[2] Human urotensin-II (hU-II) was subsequently identified and cloned.[3] In 1999, hU-II was identified as a ligand of human GPR-14 (hUT), an "orphan" G-protein-coupled receptor predominantly expressed in cardiovascular tissue.[4] In non-human primates, urotensin-II acts effectively to constrict isolated blood vessels with vasoconstrictor activity 10 times greater than that of endothelin-1, making hU-II the most potent mammalian vasoconstrictor identified to date.[4] More recently, vasoconstrictor activity was realized with administration of hU-II in both cat[5] and man.[6,7] In addition to regulating cardiac contractility,[7] hU-II is a natriuretic factor[8] and is implicated in the (dys)regulation of cardiorenal function.[9] As a result, an hUT antagonist has been identified as a therapeutic target for the treatment of numerous cardiorenal and metabolic diseases including hypertension[10], heart failure[7,11], atherosclerosis[12], renal failure[13], and diabetes.[14] To this end, several non-peptidic UT ligands have recently been reported.[15]

High-throughput screening for compounds with hUT antagonist activity identified compound **1** (Fig. 1) as a chemical lead with a binding affinity (K_i) of 500 nM.[16] Selectivity screening of **1** identified potent agonist activity at the κ-opioid receptor (EC_{50} 3 nM).[17] Due to the pharmacological effects attributed to κ-opioid agonism (analgesia, sedation, diuresis, and dysphoria) it was desirable to design hUT antagonists devoid of this activity.[18] Indeed, subsequent analysis of the literature revealed that aminomethylpiperidines have been identified as κ-opioid agonists.[19] In addition, compounds in which the piperidine was modified to a N-substi-

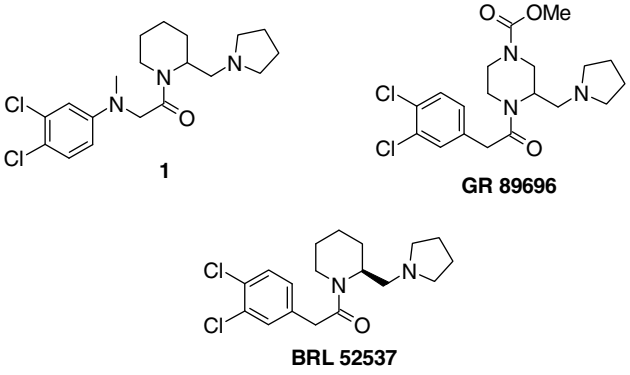

Figure 1. HTS hit **1** and literature κ-opioid agonists.

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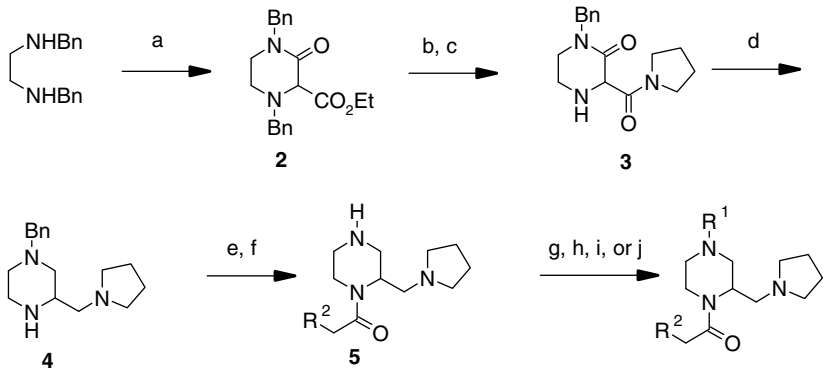


Scheme 1. Reagents and conditions: (a) $BrCH(CO_2Et)_2$, MeCN, reflux, 18 h, 81%; (b) H_2, Pd/C, EtOH, 25 °C, 24 h, 88%; (c) pyrrolidine, NMP, 200 °C, 0.5 h, 66%; (d) $LiAlH_4$, THF, 25 °C, 4 h, 62%; (e) acid chloride, Et_3N, DCM, 25 °C; (f) H_2 (1 atm), Pd/C, THF, H_2O, HCl, 25 °C, 80%; (g) R^1 = aryl; $ArB(OH)_2$, $Cu(OAc)_2$, Et_3N, DCM, 25 °C, 20–50%; (h) R^1 = amide; acid chloride, Et_3N, DCM, 25 °C, 43–50%; (i) R^1 = sulfonamide; aryl or alkyl sulfonylchloride, Et_3N, DCM, 25 °C, 39–60%; (j) R^1 = phenylurea; PhNCO, DIEA, DCM, 25 °C, 61%.

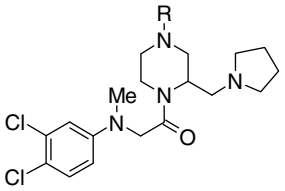
tuted piperazine (GR 89696 for example) are also reported to have κ-agonist activity.[20] In general, the arylacetamide group and the basic amine are conserved in these known κ-agonists. While the basic amine is required for attaining hUT affinity in this series, we hypothesized that modification of the arylacetamide group may provide an opportunity to design selective hUT antagonists. In addition, the piperazine core scaffold contains an added ring nitrogen which serves as an alternative point of diversity and could provide an additional opportunity for achieving high hUT affinity and selectivity over the κ-receptor.

Synthesis of the racemic pyrrolidinylmethylpiperazine core was accomplished as shown in Scheme 1 starting with the previously described synthesis of oxopiperazine **2** prepared by the condensation of *N*,*N*′-dibenzylethylenediamine with diethylbromomalonate.[20f] Selective debenzylation of the more basic nitrogen by catalytic hydrogenolysis followed by amidation with pyrrolidine provided pyrrolidine amide **3**. Double amide reduction using $LiAlH_4$ provided 1-benzyl-3-(pyrrolidinylmethyl)piperazine **4**. Selective functionalization of the piperazine nitrogens was accomplished by acylation of the unprotected amine followed by debenzylation and subsequent functionalization of piperazine **5**. *N*-Arylpiperazines were prepared by copper-catalyzed coupling of arylboronic acids and piperazine **5**.[21] Piperazine sulfonamides, amides, and ureas were synthesized via standard reaction of **5** with sulfonylchlorides, acid chlorides, and isocyanates.

Initial SAR efforts focused on piperazine substitution conserving the *N*-arylsarcosine moiety (Table 1). Arylpiperazines (**6**–**9**) are substantially more active at kappa than hUT displaying low nanomolar potency at kappa. Incorporation of amides, ureas, and sulfonamides on the piperazine effectively reversed this selectivity in favor of hUT antagonism. Arylamides and sulfonamides in particular showed significant improvement in binding affinity relative to HTS hit **1** and achieved greater than 10-fold selectivity over kappa. Interestingly, the methanesulfonyl analog **21** was very potent and selective for the κ-receptor much like the arylpiperazines (**6**–**9**). This result would indicate that the larger arylsulfonamide substituents (**16**–**20**) engage in negative steric or conformational interactions at the κ-receptor which are more easily accommodated in the UT binding pocket.

After surveying piperazine substitution the nature of the amide group was explored (Table 2). The insertion of an amino group within the standard arylacetamide moiety, as exemplified by HTS hit **1**, provided an attachment point for incorporating additional polar groups within this region of the molecule. Within the *N*-phenylpiperazine series (**22**–**25**) benzoxazolone **25** demonstrated the most potential for achieving improved hUT affinity and κ-selectivity while other heterocyclic acetamides retained high levels of selectivity favoring kappa agonism. Translation of this group to piperazinesulfonamide **26** resulted in decreased hUT affinity and similar levels of selectivity, but the incorporation of chlorine substitution in compound **27** restored the hUT affinity and selectivity.

Table 1
SAR analysis of piperazine substitution

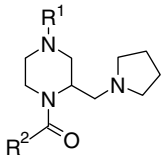


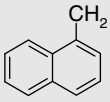
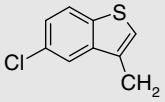
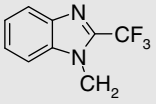
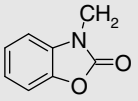
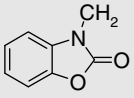
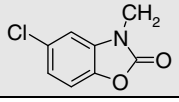
Compound	R	hUT K_i[a] (nM)	Kappa EC_{50}[b] (nM)
6	Ph	250	1.3
7	3,4-Di-F-Ph	100	6.3
8	3-MeO-Ph	50	3.2
9	3-Cl-Ph	63	4.0
10	Ph-NH(CO)	790	4000
11	PhCO	200	7900
12	(3,4-Di-MeO-Ph)CO	400	>10,000
13	(4-CN-Ph)CO	1300	3200
14	(Pyridine-4-yl)CO	100	630
15	(3-Cl-Ph)CO	130	>10,000
16	Ph-SO_2	20	250
17	3-Cl-Ph-SO_2	160	200
18	4-Cl-Ph-SO_2	100	790
19	3-MeO-Ph-SO_2	79	79
20	3,4-Di-F-Ph-SO_2	130	400
21	$MeSO_2$	100	3.0

[a] Mean of at least two determinations with a standard deviation of <±0.3 log units.
[b] Single determination or a mean of two determinations with a standard deviation of <±0.3 log units.

Having identified the 5-chlorobenzoxazolone acetamide as the optimal piperazine amide group, a survey of arylsulfonamide substitution based on **27** was explored (Table 3). In general, a variety of substitution patterns were well tolerated with *para*-substitution providing greater than 100-fold selectivity over kappa agonism in many cases. hUT affinity was significantly improved with *ortho*-bromine substitution as seen in **30** and **35**. In addition to simple ether substitution, polar functional groups such as the acetamide and carboxylic acid (**37**–**39**) were well tolerated giving high hUT affinity and good levels of selectivity. Compounds in this series were also found to have similar binding affinities at the rat UT receptor (Table 4) allowing for them to be studied in a functional rat tissue assay.

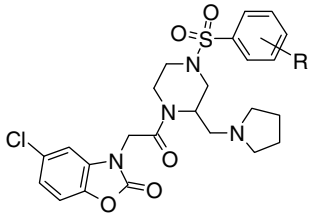
Table 2
Evaluation of acetamide group substitution



Compound	R1	R2	hUT K_i[a] (nM)	Kappa EC_{50}[b] (nM)
22	Ph		320	1.6
23	Ph		63	2.0
24	Ph		79	4.0
25	Ph		130	400
26	$PhSO_2$		500	1000
27	$PhSO_2$		20	790

[a] Mean of at least two determinations with a standard deviation of <±0.3 log units.
[b] Single determination or a mean of two determinations with a standard deviation of <±0.3 log units.

Table 3
Survey of arylsulfonamide substitution



Compound	R	hUT K_i[a] (nM)	Kappa EC_{50}[b] (nM)
28	3-CN	10	630
29	3-CF_3	50	2000
30	2-Br	8.0	2000
31	2-Cl-5-CF_3	13	1000
32	3-MeO	25	320
33	4-MeO	25	2000
34	3,4-Di-MeO	13	320
35	2-Br-3,4-di-MeO	1.6	1300
36	3-Br-6-MeO	130	790
37	4-NHAc	2.5	1300
38	4-CO_2H	25	2000
39	3-OH-4-CO_2H	13	7900

[a] Mean of at least two determinations with a standard deviation of <±0.3 log units.
[b] Single determination or a mean of two determinations with a standard deviation of <±0.3 log units.

Table 4
Inhibition of UT-induced contraction of isolated rat aortic rings

Compound	Rat UT K_i[a] (nM)	Rat aorta K_b[b] (nM)	K_b/rat K_i Ratio
30	ND	52.8 ± 13.0	
35	10.0	14.2 ± 13.7	1.4
37	4.0	13.1 ± 3.6	3.3
38	32.0	81.8 ± 38.2	2.6
39	8.0	10.0 ± 2.2	1.3

[a] ND, not determined; mean of at least two determinations with a standard deviation of <±0.3 log units.
[b] A mean of two determinations ± SEM.

In an effort to assess functional inhibition of UT on isolated rat blood vessels, a number of optimized inhibitors were evaluated in vitro for their ability to inhibit UT-mediated aortic ring contraction (Table 4).[22] All of the compounds studied demonstrated potent and competitive inhibition of UT-induced vasoconstriction with similar potencies (K_b) to their binding affinities (rat UT K_i).

In conclusion, a number of racemic pyrrolidinylmethyl piperazines have been synthesized. The dichlorophenylacetamide functionality common to many kappa agonists was modified to the 5-chlorobenzoxazolone resulting in compounds with high hUT affinity. Complementary arylsulfonamide substitution provided a diverse set of high affinity hUT inhibitors with greater than 100-fold selectivity over kappa. In vitro, results from the rat isolated aortic contraction bioassay show that this series demonstrates potent, competitive inhibition of the aortic contractile response to exogenous hU-II consistent with the hypothesis that UT antagonists have the potential to mediate the effects of hU-II on vascular tone.

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