



## Aminomethylpiperazines as selective urotensin antagonists

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### ABSTRACT

Aminomethylpiperazines, reported previously as being  $\kappa$ -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  $\kappa$ -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 urophys*.<sup>1</sup> It was hypothesized to be involved primarily in osmoregulation in fish.<sup>2</sup> Human urotensin-II (hU-II) was subsequently identified and cloned.<sup>3</sup> 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.<sup>4</sup> 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.<sup>4</sup> More recently, vasoconstrictor activity was realized with administration of hU-II in both cat<sup>5</sup> and man.<sup>6,7</sup> In addition to regulating cardiac contractility,<sup>7</sup> hU-II is a natriuretic factor<sup>8</sup> and is implicated in the (dys)regulation of cardiorenal function.<sup>9</sup> As a result, an hUT antagonist has been identified as a therapeutic target for the treatment of numerous cardiorenal and metabolic diseases including hypertension<sup>10</sup>, heart failure<sup>7,11</sup>, atherosclerosis<sup>12</sup>, renal failure<sup>13</sup>, and diabetes.<sup>14</sup> To this end, several non-peptidic UT ligands have recently been reported.<sup>15</sup>

High-throughput screening for compounds with hUT antagonist activity identified compound **1** (Fig. 1) as a chemical lead with a

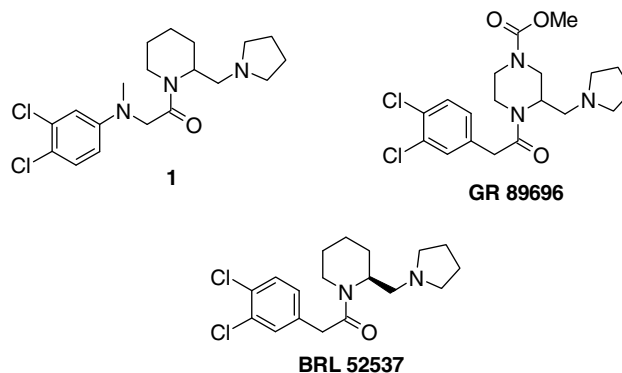
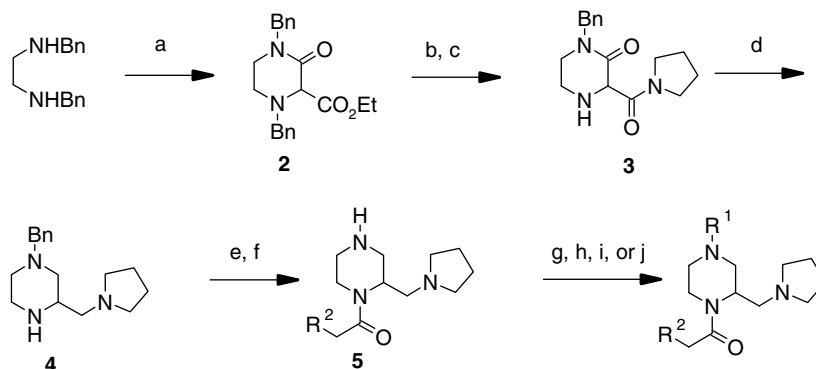


Figure 1. HTS hit **1** and literature  $\kappa$ -opioid agonists.

binding affinity ( $K_i$ ) of 500 nM.<sup>16</sup> Selectivity screening of **1** identified potent agonist activity at the  $\kappa$ -opioid receptor ( $EC_{50}$  3 nM).<sup>17</sup> Due to the pharmacological effects attributed to  $\kappa$ -opioid agonism (analgesia, sedation, diuresis, and dysphoria) it was desirable to design hUT antagonists devoid of this activity.<sup>18</sup> Indeed, subsequent analysis of the literature revealed that aminomethylpiperidines have been identified as  $\kappa$ -opioid agonists.<sup>19</sup> In addition, compounds in which the piperidine was modified to a N-substi-

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**Scheme 1.** Reagents and conditions: (a)  $\text{BrCH}(\text{CO}_2\text{Et})_2$ , MeCN, reflux, 18 h, 81%; (b)  $\text{H}_2$ , Pd/C, EtOH, 25 °C, 24 h, 88%; (c) pyrrolidine, NMP, 200 °C, 0.5 h, 66%; (d)  $\text{LiAlH}_4$ , THF, 25 °C, 4 h, 62%; (e) acid chloride,  $\text{Et}_3\text{N}$ , DCM, 25 °C; (f)  $\text{H}_2$  (1 atm), Pd/C, THF,  $\text{H}_2\text{O}$ , HCl, 25 °C, 80%; (g)  $\text{R}^1$  = aryl;  $\text{ArB}(\text{OH})_2$ ,  $\text{Cu}(\text{OAc})_2$ ,  $\text{Et}_3\text{N}$ , DCM, 25 °C, 20–50%; (h)  $\text{R}^1$  = amide; acid chloride,  $\text{Et}_3\text{N}$ , DCM, 25 °C, 43–50%; (i)  $\text{R}^1$  = sulfonamide; aryl or alkyl sulfonylchloride,  $\text{Et}_3\text{N}$ , DCM, 25 °C, 39–60%; (j)  $\text{R}^1$  = phenylurea;  $\text{PhNCO}$ , DIEA, DCM, 25 °C, 61%.

tuted piperazine (GR 89696 for example) are also reported to have  $\kappa$ -agonist activity.<sup>20</sup> In general, the arylacetamide group and the basic amine are conserved in these known  $\kappa$ -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  $\kappa$ -receptor.

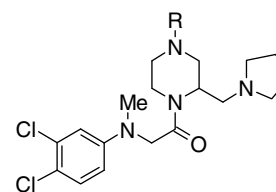
Synthesis of the racemic pyrrolidinylmethylpiperazine core was accomplished as shown in Scheme 1 starting with the previously described synthesis of oxopiperazine **2** prepared by the condensation of *N,N'*-dibenzylethylenediamine with diethylbromomalonate.<sup>20f</sup> Selective debenzoylation of the more basic nitrogen by catalytic hydrogenolysis followed by amidation with pyrrolidine provided pyrrolidine amide **3**. Double amide reduction using  $\text{LiAlH}_4$  provided 1-benzyl-3-(pyrrolidinylmethyl)piperazine **4**. Selective functionalization of the piperazine nitrogens was accomplished by acylation of the unprotected amine followed by debenzoylation and subsequent functionalization of piperazine **5**. *N*-Arylpiperazines were prepared by copper-catalyzed coupling of arylboronic acids and piperazine **5**.<sup>21</sup> 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  $\kappa$ -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  $\kappa$ -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  $\kappa$ -selectivity while other heterocyclic acetamides retained high levels of

**Table 1**

SAR analysis of piperazine substitution



Compound	R	hUT $K_i^a$ (nM)	Kappa $\text{EC}_{50}^b$ (nM)
<b>6</b>	Ph	250	1.3
<b>7</b>	3,4-Di-F-Ph	100	6.3
<b>8</b>	3-MeO-Ph	50	3.2
<b>9</b>	3-Cl-Ph	63	4.0
<b>10</b>	Ph-NH(CO)	790	4000
<b>11</b>	PhCO	200	7900
<b>12</b>	(3,4-Di-MeO-Ph)CO	400	>10,000
<b>13</b>	(4-CN-Ph)CO	1300	3200
<b>14</b>	(Pyridine-4-yl)CO	100	630
<b>15</b>	(3-Cl-Ph)CO	130	>10,000
<b>16</b>	Ph-SO <sub>2</sub>	20	250
<b>17</b>	3-Cl-Ph-SO <sub>2</sub>	160	200
<b>18</b>	4-Cl-Ph-SO <sub>2</sub>	100	790
<b>19</b>	3-MeO-Ph-SO <sub>2</sub>	79	79
<b>20</b>	3,4-Di-F-Ph-SO <sub>2</sub>	130	400
<b>21</b>	MeSO <sub>2</sub>	100	3.0

<sup>a</sup> Mean of at least two determinations with a standard deviation of  $<\pm 0.3$  log units.

<sup>b</sup> Single determination or a mean of two determinations with a standard deviation of  $<\pm 0.3$  log units.

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.

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.

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