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Pyridinesulfonylureas and pyridinesulfonamides as selective bombesin receptor subtype-3 (BRS-3) agonists

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ABSTRACT

Bombesin receptor subtype-3 (BRS-3) is an orphan G-protein coupled receptor belonging to the subfamily of bombesin-like receptors. BRS-3 is implicated in the development of obesity and diabetes. We report here small-molecule agonists that are based on a 4-(alkylamino)pyridine-3-sulfonamide core. We describe the discovery of **2a**, which has mid-nanomolar potency, selectivity for human BRS-3 versus the other bombesin-like receptors, and good bioavailability.

Bombesin is a tetradecapeptide originally isolated from the skin of the European frog *Bombina bombina*.[1] Two mammalian bombesin-like peptides, gastrin-releasing peptide (GRP)[2] and neuromedin-B (NMB),[3] have been identified so far, and they modulate smooth muscle contraction, exocrine and endocrine processes, metabolism, and behavior.[4] Three mammalian bombesin-like receptors have been described: NMBR for NMB, GRPR for GRP, and BRS-3.[5] BRS-3 is an orphan G-protein coupled receptor, with relatively low affinities for bombesin, GRP, and NMB, and with no known high-affinity natural ligands. It is expressed primarily in the central nervous system, particularly in the hypothalamus, a brain region that regulates food intake, metabolic rate, and body weight.[6] Indeed, rodent genetics has implicated BRS-3 in the development of obesity and diabetes. Mice lacking BRS-3 have a reduced metabolic rate and become obese and insulin-resistant as they age. They are also hyperphagic, particularly with a high fat diet.[7] The dual effects on food intake and energy expenditure implicate BRS-3 agonists as candidate anti-obesity drugs. In addition, BRS-3 is found in developing lungs and certain carcinoma cells, suggesting that the receptor may play a role in cell growth and proliferation.[8] Thus, the development of a BRS-3-selective agonist will be useful for elucidating the physiologic and pharmacologic functions of the receptor. Several such agonists have been disclosed, including peptides[9] and peptidomimetics.[10] Recently, small-molecule BRS-3-selective agonists have been developed,[11,12] including a series we report here based on a 4-(alkylamino)pyridine-3-sulfonamide core. These compounds have allowed exploration of the physiology resulting from agonism of BRS-3.[13]

Since the endogenous ligand for BRS-3 remains unidentified, we relied on high-throughput screening for our initial lead. Compound **1** has a binding IC_{50} of 600 nM[14] and is an agonist with an EC_{50} of 220 nM[15] for human BRS-3. Its structure bears strong resemblance to the diuretic torsemide (Fig. 1),[16] suggesting that this class of compounds should have desirable pharmacokinetic properties. Another attractive feature of compound **1** is its modular nature, which enables the straightforward synthesis of analogs.

All the sulfonylureas reported here were synthesized from 4-chloropyridine-3-sulfonamide (Figs. 2 and 3). Nucleophilic aromatic substitution with amines or alcohols afforded the corresponding 4-(alkylamino) or 4-(alkyloxy)pyridine-3-sulfonamides.

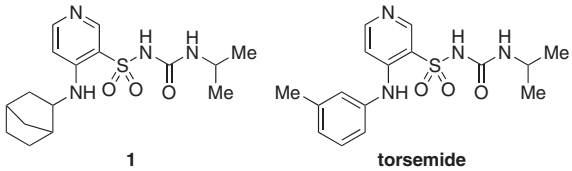

Figure 1. Initial lead from high-throughput screening.

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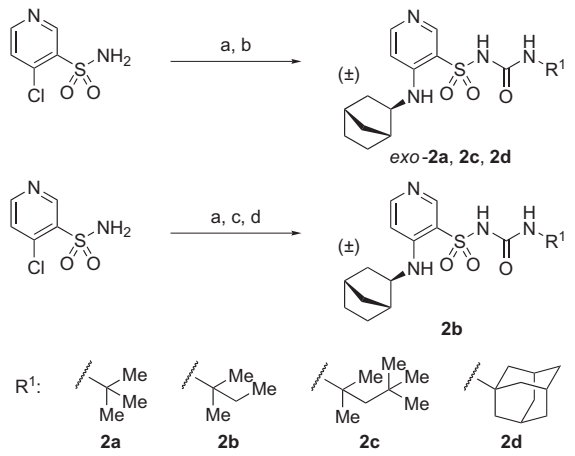

Figure 2. Synthesis of pyridinesulfonylureas—variation of the terminal amino group. Reagents and conditions: (a) (±)-*exo*-2-aminonorborane, Et_3N, *i*-PrOH, 100 °C; (b) R^1NCO, Et_3N, CH_2Cl_2; (c) ethyl chloroformate, pyridine; (d) *tert*-amylamine, toluene.

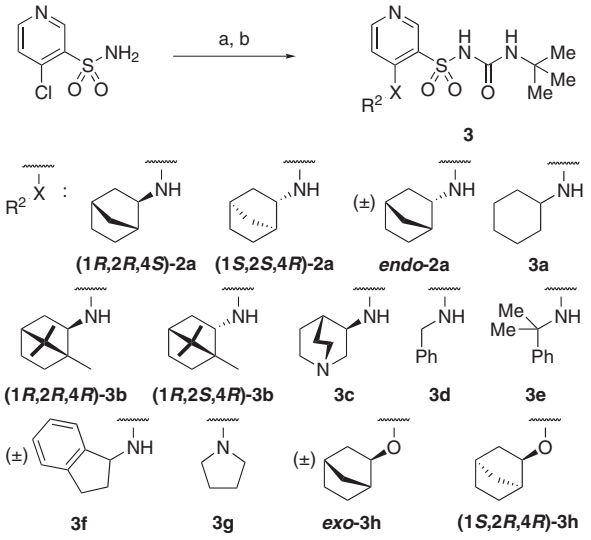

Figure 3. Synthesis of pyridinesulfonylureas—variation of the 4-substituent of pyridine. Reagents and conditions: (a) R^2-XH (X = NH, O), Et_3N, *tert*-amyl alcohol, 120 °C; (b) *t*-BuNCO, Et_3N, CH_2Cl_2.

Reaction of these sulfonamides with alkyl isocyanates under basic conditions gave most of the desired sulfonylureas.[17] The sulfonylurea **2b** was obtained by first acylating the sulfonamide with ethyl chloroformate, followed by displacement of the resultant sulfonylcarbamate with *tert*-amylamine.

Table 1 summarizes the binding and functional activity of various sulfonylureas for human and mouse BRS-3. No stereochemical information was known about the initial HTS lead **1**. Resynthesis of compound **1** with diastereomerically pure 2-aminonorbornane yielded racemic *endo*-**1** and *exo*-**1**. Binding and functional data indicate that the exo stereochemistry yields a slightly better ligand. Increasing the size of R^1 from isopropyl (*exo*-**1**) to *tert*-butyl (*exo*-**2a**) lowers the human EC_{50} value below 100 nM, and adding a methyl group to the *tert*-butyl group enhances the activity (**2b**). Further increase in the size of R^1 to 1,1,3,3-tetramethylbutyl (**2c**) or adamantyl (**2d**), however, leads to a loss in potency. Compound **2a** is selective for BRS-3 in the human bombesin-like receptor family. Its EC_{50} values in cell-based human NMBR and GRPR assays exceed 10 μM.

In view of the better pharmacokinetic profile of **2a** over **2b** (vide infra), *tert*-butyl was selected as the optimal substituent. Examination of various *tert*-butyl derivatives **3** reveals that the SAR of R^2 is quite stringent. A primary amine (R^2NH-) with a secondary cyclic R^2 is required for activity. The best substituent identified to date is (1*R*,2*R*,4*S*)-bicyclo[2.2.1]-hept-2-ylamine,[18] and even minor changes to the bicyclic core (**3a**, **3b**) significantly decrease the human BRS-3 potency. Linear primary amines (**3d**, **3e**) and cyclic secondary amines (**3g**) give compounds that are largely inactive. Introduction of a tertiary nitrogen (**3c**) or a fused aromatic ring (**3f**) also dramatically reduces the activity. Bicyclic alcohols that are isosteric with the optimal amines lower the activity at human BRS-3 by approximately 10- to 15-fold (**3h**).

We have examined the pharmacokinetic profiles of **2a** and **2b** in male Sprague–Dawley rats (Table 2).[19] As anticipated, both sulfonylureas exhibit moderate clearance rates and good oral exposures. A comparison of pharmacokinetic parameters shows that **2a** exhibits a more desirable profile in terms of higher oral exposure and longer half-life.[20]

Based on **2a**, we designed **4a**–**4f** to probe the importance of each hydrogen-bond donor and acceptor to the overall potency of the molecule (Fig. 4). Compound **4a** was synthesized in a similar fashion as **2a**, with 4-chloropyridine-3-sulfonamide replaced by 2-fluorobenzenesulfonamide. Compounds **4b** and **4c** were obtained by acylation of 4-(*exo*-bicyclo[2.2.1]hept-2-ylamino)pyridine-3-

Table 1
Binding and functional activity of compounds **1**, **2a**–**2d**, **3a**–**3h** at human and mouse BRS-3

Compound	Human BRS-3 binding IC_{50}[a] (nM)	Human BRS-3 agonism EC_{50}, nM[a] (activity%)	Mouse BRS-3 agonism EC_{50}, nM[a] (activity%)
exo-**1**	510 ± 40	440 ± 80 (86)	86 ± 11 (88)
endo-**1**	820 ± 150	940 ± 80 (78)	98 ± 14 (86)
exo-**2a**	100 ± 20	81 ± 12 (96)	28 ± 4 (101)
endo-**2a**	230 ± 50	160 ± 20 (95)	49 ± 5 (91)
(1*R*,2*R*,4*S*)-**2a**	68 ± 7	55 ± 4 (100)	21 ± 1 (100)
(1*S*,2*S*,4*R*)-**2a**	630 ± 50	720 ± 110 (89)	110 ± 20 (93)
2b	75 ± 5	51 ± 11 (105)	13 ± 2 (108)
2c	530 ± 100	350 ± 30 (91)	100 ± 10 (102)
2d	310 ± 50	220 ± 20 (44)	39 ± 8 (55)
3a	400 ± 70	450 ± 40 (93)	260 ± 50 (90)
(1*R*,2*R*,4*R*)-**3b**	660 ± 90	1700 ± 400 (73)	90 ± 24 (88)
(1*R*,2*S*,4*R*)-**3b**	300 ± 70	450 ± 30 (86)	33 ± 6 (82)
3c	>10,000	>10,000 (0)	>10,000 (0)
3d	>10,000	7500 (24)	6900 (20)
3e	3000	8100 (19)	4300 (43)
3f	3800	6800 (39)	1300 ± 300 (63)
3g	>10,000	>10,000 (2)	>10,000 (5)
exo-**3h**	990, 1200	1200 ± 300 (90)	320 ± 90 (92)
(1*S*,2*R*,4*R*)-**3h**	880, 1600	1600 ± 300 (80)	320 ± 70 (77)

[a] Values under 2 μM with reported standard errors are means of at least three experiments. Data under 2 μM from duplicate experiments are reported individually.

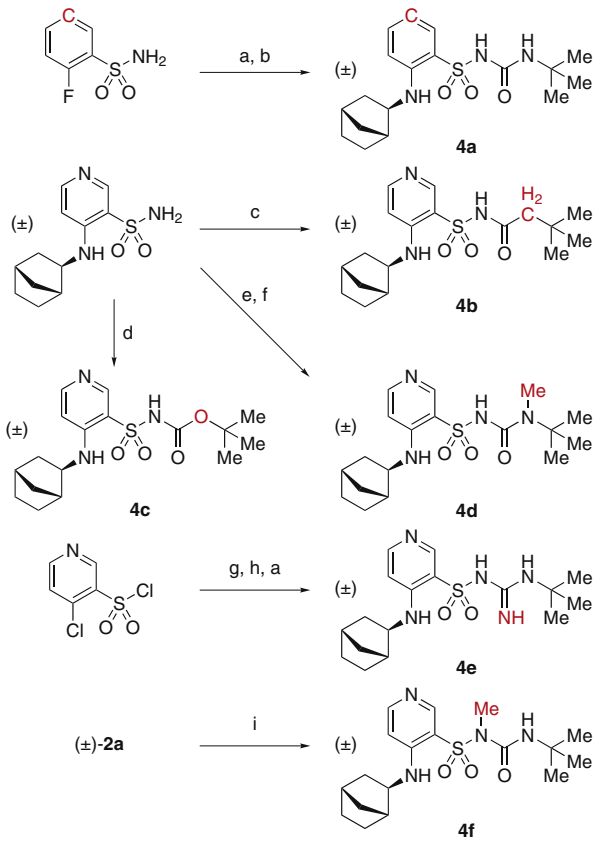

Figure 4. Analogs of sulfonylurea **2a**, with replacements of hydrogen-bond donor/acceptor highlighted in red. Reagents and conditions: (a) (±)-*exo*-2-aminonorbornane, Et_3N, *tert*-amyl alcohol, microwave (160–180 °C); (b) *t*-BuNCO, Et_3N, CH_2Cl_2; (c) *tert*-butylacetyl chloride, Et_3N, CH_2Cl_2; (d) di-*tert*-butyl dicarbonate, Et_3N, CH_2Cl_2; (e) ethyl chloroformate, toluene; (f) *N*-methyl-*tert*-butylamine, toluene; (g) 1*H*-pyrazole-1-carboxamidine hydrochloride, Et_3N, CH_2Cl_2; (h) *tert*-butylamine, CH_2Cl_2, 50 °C; (i) 2.0 M $TMSCHN_2$, MeOH.

sulfonamide with *tert*-butylacetyl chloride and di-*tert*-butyl dicarbonate respectively. Displacement of the corresponding ethyl sulfonylcarbamate by *N*-methyl-*tert*-butylamine afforded **4d**. The synthesis of **4e** was achieved in three steps from 4-chlorosulfonyl chloride: (a) sulfonylation of 1*H*-pyrazole-1-carboxamidine; (b) displacement with *tert*-butylamine; (c) nucleophilic aromatic substitution by *exo*-2-aminonorbornane. Finally, **4f** was obtained by methylating racemic **2a** with trimethylsilyldiazomethane.

The binding and activity data for compounds **4a**–**4f** (Table 3) suggest that each hydrogen-bond donor and acceptor in **2a** is essential for activity at mouse and particularly human BRS-3, with the possible exception of the less acidic sulfonylurea N–H. Given these findings, we next explored heterocyclic replacements of the amide group (Fig. 5). Heterocyclic amines were first sulfonylated with 4-chlorosulfonyl chloride. The resultant products were displaced with racemic *exo*-2-aminonorborane to afford sulfonamides **5a**–**5e**.

The phenyl, thiazole, pyrazole, and triazole rings are viable but mediocre replacements of the amide functionality (Table 3). Compounds **5a**–**5e** are active compounds with EC_{50} values for human BRS-3 increased to 1–4 μM. Their potencies at the mouse BRS-3, however, are considerably better, with EC_{50} values in the range of 150–400 nM and close to full activity. A sterically demanding alkyl substituent at the 3-position is essential for potency.[21] To understand the intrinsic activity of the compound, racemic **5e** was separated by chiral HPLC,[22] and the faster eluting enantiomer was determined to be a partial agonist of human BRS-3 with an

Table 2
Pharmacokinetic properties in rats (1/4 mg kg^{-1} iv/po) for racemic **2a** and **2b**

Parameters	(±)-**2a**	(±)-**2b**
Cl_p (mL min^{-1} kg^{-1})	14	26
Vd_{ss} (L kg^{-1})	0.57	0.30
MRT (h)	0.66	0.19
$t_{1/2}$ (h)	4.8	0.25
PO AUC_{Norm} (μM h kg mg^{-1})	3.5	0.68
C_{max} (μM)	7.0	2.0
F%	100	41

Table 3
Binding and functional activity of compounds **4a–4f**, **5a–5e** at human and mouse BRS-3

Compound	Human BRS-3 binding IC_{50}, nM[a]	Human BRS-3 agonism EC_{50}, nM (activity%)[a]	Mouse BRS-3 agonism EC_{50}, nM (activity%)[a]
4a	6200	6400 (50)	340 ± 40 (91)
4b	>10,000	8300 (11)	4900 (61)
4c	>10,000	8200 (44)	590 ± 60 (89)
4d	650 ± 90	640 ± 20 (99)	180 ± 20 (96)
4e	9700	>10,000 (6)	7000 (13)
4f	6700	8300 (22)	6500 (49)
5a	520, 1400	2600 (57)	160 ± 50 (102)
5b	2500	2100 (81)	200 ± 30 (81)
5c	250 ± 60	4000 (96)	270 ± 30 (113)
5d	770 ± 320	4000 (20)	410 ± 110 (72)
5e	290 ± 120	1200 ± 500 (55)	170 ± 60 (84)
(+ or −)-**5e**	68 ± 7	380 ± 110 (62)	51 ± 15 (87)
(− or +)-**5e**	310 ± 40	1700 ± 300 (57)	190 ± 20 (88)

[a] Values under 2 μM with reported standard errors are means of at least three experiments. Data under 2 μM from duplicate experiments are reported individually.

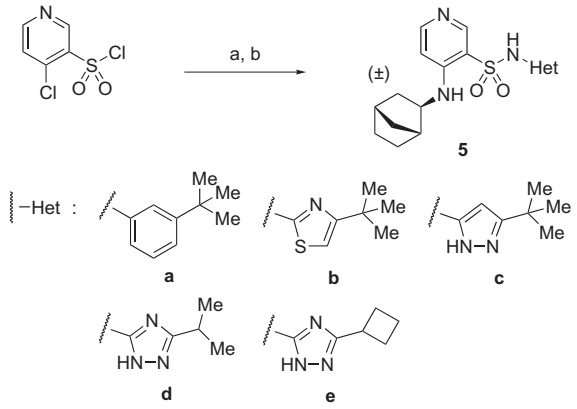

Figure 5. Synthesis of pyridinesulfonamides. Reagents and conditions: (a) Het–NH_2, Et_3N, CH_2Cl_2; (b) (±)-*exo*-2-aminonorbornane, Et_3N, *tert*-amyl alcohol, microwave (160–180 °C).

EC_{50} value of 380 nM and a full agonist of mouse BRS-3 with an EC_{50} value of 51 nM.

In conclusion, we have identified pyridinesulfonylureas and pyridinesulfonamides with a 4-(alkylamino)pyridine-3-sulfonamide core that are potent and selective agonists for human and mouse BRS-3. The SAR defined by the current study is summarized in Figure 6. In the sulfonylurea class, we have identified compound **2a** as a potent human BRS-3 agonist that also has good bioavailability and pharmacokinetic parameters in rats. Replacement of the hydrogen-bond donors/acceptors in the sulfonylureas led to a

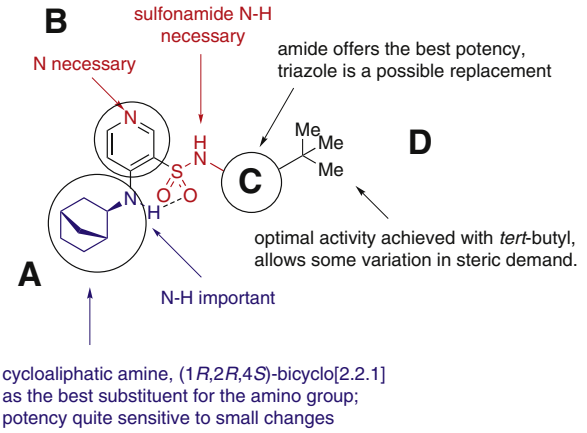

Figure 6. SAR summary of pyridinesulfonamides as BRS-3 agonists.

series of sulfonamides that are good mouse BRS-3 agonists, and one of the enantiomeric triazolyl sulfonamide **5e** shows moderate human BRS-3 activity.

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14. The binding affinity for human BRS-3 is determined in competitive binding assays with [^{125}I]-[D-Tyr^{6}, β-Ala^{11}, Phe^{13}, Nle^{14}]-Bombesin(6–14) '[^{125}I]-dY-peptide'.
15. The functional activities are determined with HEK293AEQ cell lines expressing human and mouse BRS-3. The EC_{50} value for activation is determined as the inflection point of the sigmoidal curve between the bioluminescence readings and the log molar concentration of the compound, normalized against the EC_{50} value determined with an internal standard. 100% activation is defined as the bioluminescence value obtained with 10 μM dY-peptide for human BRS-3 and 10 μM of a proprietary small-molecule standard for mouse BRS-3.
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17. All compounds reported in this letter were characterized by both ^{1}H NMR and LC–MS.
18. The absolute stereochemistry of the amine was determined by stereospecific synthesis from (+)-*endo*-2-norborneol.
19. The blood samples were collected at various time points into lithium heparin tubes and centrifuged. The plasma samples were kept at −70 °C until analysis. The plasma samples were extracted by protein precipitation and analyzed by LC/MS/MS.
20. We used a mouse PD model to determine target engagement in the CNS from our compounds (see Ref. 13b for details of the model). Compound **2a** was tested active at 10 mpk when dosed orally.
21. Sulfonamides with heterocycles lacking sterically demanding 3-substituents are inactive.
22. Chiralpak AD column, 12:88 ethanol/hexanes as eluent, t_R = 11.4, 12.6 min.