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Synthesis and SAR of heterocyclic carboxylic acid isosteres based on 2-biarylethylimidazole as bombesin receptor subtype-3 (BRS-3) agonists for the treatment of obesity

Mark Hadden [a,*], Allan Goodman [a], Cheng Guo [a], Peter R. Guzzo [a], Alan J. Henderson [a], Kevin Pattamana [a], Megan Ruenz [a], Bruce J. Sargent [a], Brian Swenson [a], Larry Yet [a], Jian Liu [b], Shuwen He [b], Iyassu K. Sebhat [b], Linus S. Lin [b], Constantin Tamvakopoulos [e], Qianping Peng [e], Yanqing Kan [c], Oksana Palyha [c], Theresa M. Kelly [c], Xiao-Ming Guan [c], Joseph M. Metzger [d], Marc L. Reitman [c], Ravi P. Nargund [b]

[a] AMRI, 26 Corporate Circle, Albany, NY 12212, USA
[b] Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[c] Department of Metabolic Disorders, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[d] Department of Pharmacology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[e] Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

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ABSTRACT

SAR around non-peptidic potent bombesin receptor subtype-3 (BRS-3) agonist lead **2** is presented. Attempts to replace the carboxylic acid with heterocyclic isosteres to improve oral bioavailability and brain penetration are described.

According to the CDC's Behavioral Risk Factor Surveillance System, over the past 20 years there has been a dramatic increase in obesity in young adults in the United States, with only one state having an obesity prevalence of less than 20%.[1,2] This high rate of occurrence combined with obesity being a risk factor in a wide range of diseases[3] such as type 2 diabetes, cardiovascular diseases and cancer make it an important indication for pharmaceutical intervention. Moreover, currently marketed drugs such as sibutramine[4] and orilstat[5] have unsatisfactory efficacy and undesirable side effects that limit their prescription amongst the general population.

Bombesin receptor subtype-3 (BRS-3 or BB3), is an orphan G-protein coupled receptor (GPCR) with high sequence identity to BB1 and BB2 (~50%) and is located primarily in the hypothalamus and testes.[6] Preclinical validation of BRS-3's role in energy homeostasis has been demonstrated with genetically altered mice lacking the BRS-3 receptor, causing induction of obesity, hypertension and diabetes.[7]

Through a combination of high-throughput screening and SAR development, a potent small molecule BRS-3 agonist **1**[8] was discovered (Fig. 1).

The carboxylic acid was mapped around the biphenyl ring (structures not shown); however, all of these compounds lost potency compared to **1**. Interestingly, extending the acid moiety away from the ring maintained good potency in compound **2** (Table 1).

Further SAR studies were pursued to improve oral bioavailability and brain penetration whilst retaining binding and functional agonism at the human BRS-3 receptor. Replacement of the carboxylic acid group in compound **1** with traditional acid isosteres such as tetrazole **1a** and phenol **1b** provided good binding and func-

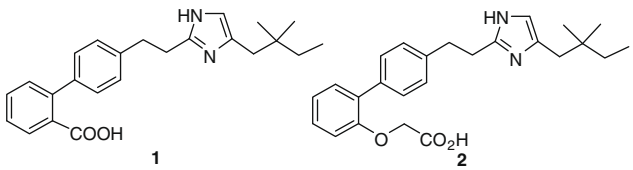

Figure 1.

* Corresponding author. Tel.: +1 518 512 2835; fax: +1 518 512 2079.
E-mail address: mark.hadden@amriglobal.com (M. Hadden).

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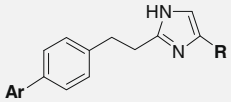
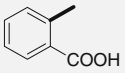
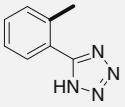
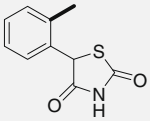
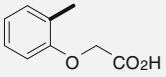
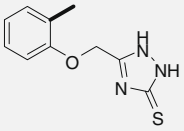
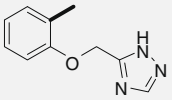
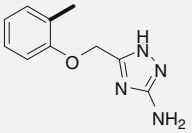
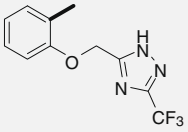
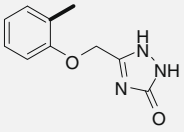
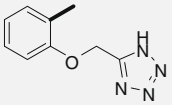
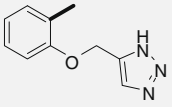
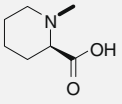
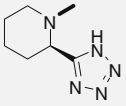
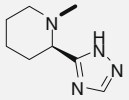
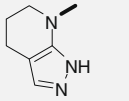
Table 1
The potency of BRS-3 agonists in human and mice BRS-3 receptors

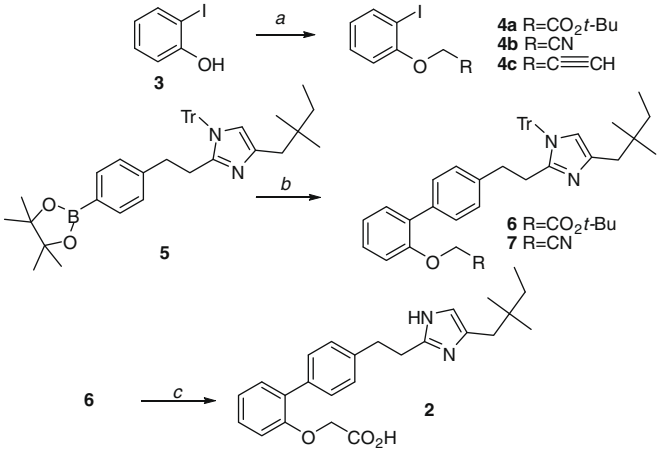
Compound 	Ar	R	hBRS-3 binding IC_{50}, nM[a]	hBRS-3 function EC_{50}, nM[a] (Activation%)[b]	mBRS-3 function EC_{50}, nM[a] (Activation%)[b]
1			11	25 (101)	9.6 (94)
1a			15	56 (112)	16 (85)
1b			31	133 (97)	34 (113)
1c			287	1767 (94)	ND[c]
2			103	54 (97)	ND[c]
10a			6.1	41 (114)	5.8 (120)
10b			22	172 (113)	ND[c]
10c			27	78 (98)	4.6 (115)
10d			127	129 (89)	12 (122)
10e			31	336 (107)	ND[c]
11			5.3	30 (111)	2.9 (109)
12			83	399 (97)	ND[c]
14a	See Scheme 3		10	29 (98)	11 (118)
14b	See Scheme 3		20	56 (96)	27 (119)
17			5.3	24 (100)	12 (111)
19a			6.2	15 (100)	16 (119)

(*continued on next page*)

Table 1 (*continued*)

Compound	Ar	R	hBRS-3 binding IC_{50}, nM[a]	hBRS-3 function EC_{50}, nM[a] (Activation%)[b]	mBRS-3 function EC_{50}, nM[a] (Activation%)[b]
19b			26	42 (96)	13 (117)
24			18	42 (101)	13 (120)

[a] The reported data are the average of at least three repeated experiments.
[b] The percentages of activation are the maxim activation of tested compounds relative to that of [D-Tyr^6,β-Ala^{11},Phe^{13},Nle^{14}]-Bombesin (6–14).
[c] Not determined.



Scheme 1. Reagents and conditions: (a) $BrCH_2CO_2t$-Bu or $BrCH_2CN$ or propargyl bromide, K_2CO_3, acetone, 91% (**4a**), 68% (**4b**), 99% (**4c**); (b) **4a** or **4b**, $PdCl_2$(dppf), Na_2CO_3, H_2O, DMF, 80 °C, 16 h, 59% (**6**), 72% (**7**); (c) TFA, CH_2Cl_2, 91%.

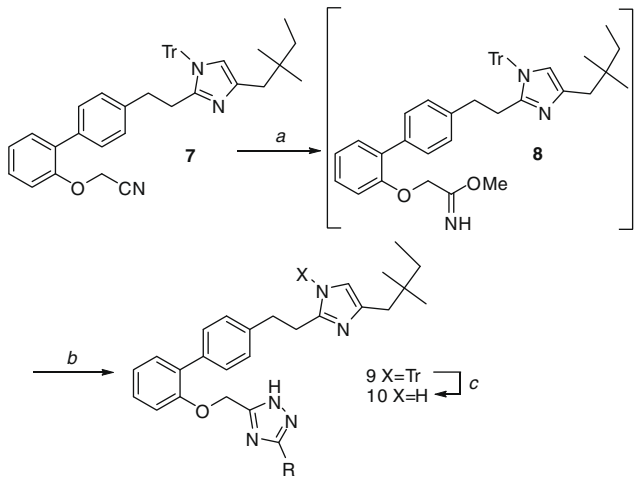
tional responses at the human receptor and these results further encouraged us to prepare a range of heterocyclic isosteres based on compounds **1** and **2**.

A convergent synthesis was adopted using key intermediate, boronate ester **5**[9] (Scheme 1). Alkylation of 2-iodophenol provided the precursors **4a**–**c**. Suzuki coupling of **4a** and **4b** with **5** yielded intermediates **6** and **7**. Double deprotection of **6** under acidic conditions provided **2**.

Electrophilic nitrile **7** was easily transformed into the corresponding methylimidate **8** via reaction with alkoxide anion in methanol.[10] Reaction of this intermediate with an appropriately substituted hydrazine, followed by removal of the trityl group with TFA, provided rapid access to a range of heterocycles **10** (Scheme 2).

Alternatively, tetrazole **11** could be prepared via 1,3-dipolar cycloaddition of nitrile **7** with sodium azide and ammonium chloride in DMF.[11] 1,2,3-Triazole **12** was prepared via addition of benzylazide to **4c** using Click chemistry[12] followed by Suzuki coupling with **5** and double deprotection (syntheses not shown).

Of the range of heterocycles prepared, triazolothione **10a** and tetrazole **11** showed some of the best activity (hEC_{50} = 41, 30 nM, respectively), indicating that isosteric replacement of the carboxylic acid in **2** (hEC_{50} = 54 nM) was feasible. But unfortunately these analogs failed to provide significant brain levels following intravenous administration (Table 2). It was hoped that switching to the less acidic aminotriazole **10c** (pK_a = 12.13)[13] would help improve brain penetration compared with **10a** (pK_a = 8.92) and **11**

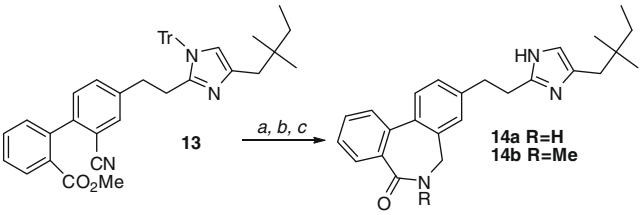


Scheme 2. Reagents and conditions: (a) KO*t*-Bu, MeOH, 65 °C, 15 min, 100%; (b) $NH_2NHC(S)NH_2$, 39% (R = SH, **9a**); $NH_2NHC(O)H$, 71%, (R = H, **9b**); $NH_2NHC(NH)NH_2$, 19%, (R = NH_2, **9c**); NH_2NH_2, TFAA, pyridine, 59%, (R = CF_3, **9d**); NH_2NHCO_2Et, 69%, (R = OH, **9e**); (c) TFA, CH_2Cl_2.

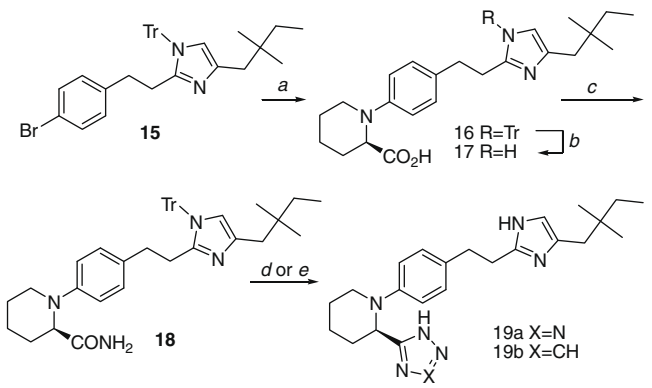
Table 2
Total plasma and brain levels[a] of BRS-3 agonists 1 h following IV dose in rats

Compd.	Dose (mg/kg)	Plasma (μM)	Brain (μM)	B/P ratio
10a	1	4.96	0.03	0.006
10c	1	0.86	0.01	0.016
11	2	1.25	0.01	0.010
14a	1	0.31	0.02	0.068
17	1	0.21	0.01	0.04

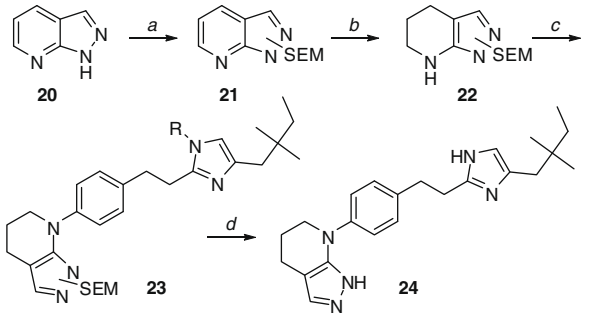
[a] Data are averages of three repeated experiments.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, $CoCl_2{\cdot}6H_2O$ MeOH, 0 °C to 65 °C, 58%; (c) TFA, CH_2Cl_2, 78% (**14a**); (a) $NaBH_4$, $CoCl_2{\cdot}6H_2O$ MeOH, 0 °C to 65 °C, 47%; (b) NaH, MeI, DMF, 71%; (c) TFA, CH_2Cl_2, 88% (**14b**).



Scheme 4. Reagents and conditions: (a) CuI, K_2CO_3, (*R*)-pipecolinic acid, DMSO, 90 °C, 55%; (b) TFA, CH_2Cl_2; (c) NH_3, EDC, HOBt, CH_2Cl_2, 66%; (d) (i) pyridine, TFAA, dioxane, 50%; (ii) NaN_3, NH_4Cl, DMF, 100 °C, 8% (**19a**); (e) (i) $Me_2NCH(OEt)_2$, reflux; (ii) AcOH, hydrazine, 90 °C, 24% (**19b**).



Scheme 5. Reagents and conditions: (a) NaH, SEM-Cl, DMF, 64%; (b) Pd/C, H_2, EtOH, 68%; (c) **15**, $Pd(OAc)_2$, KO*t*-Bu, dicyclohexylbiphenylphosphine, toluene, 150 °C, microwaves, 32%; (d) TFA, H_2O, 60 °C, 59%.

(pK_a = 4.58). Although functional activity was maintained (hEC_{50} = 78 nM, 98%) no in increase B/P ratio was seen.

In an effort to reduce rotatable bonds to help improve brain penetration verses unconstrained analogs, constrained lactams **14a** and **14b** were synthesized (Scheme 3). Good agonist functional potency was observed with **14a** (hEC_{50} = 29 nM, 98%). Surprisingly compound **14b**, in which the H-bond donor was replaced with a methyl group, also showed good activity (hEC_{50} = 56 nM, 96%). However no improvement in brain concentration was observed with these analogs.

In an attempt to use an active transport mechanism such as an amino acid transporter[14] to improve brain penetration, amino acid **17** was prepared via a copper mediated[15] coupling of bromide **15** with (*R*)-pipecolic acid[16] (Scheme 4). This compound exhibited equally good potency at both the mouse and the human receptor but failed to substantially increase brain levels. Heterocyclic analogs of compound **17** (tetrazole **19a** and triazole **19b**) showed good potency demonstrating the acid moiety in this series could also be replaced by isosteres, but these compounds were not pursued further due to low bioavailability in rat (*F* = 4.9% and 4.8%, respectively). Constraining the heterocyclic system to form pyrazolopiperidine analog **24** (Scheme 5) maintained good binding and functional potency and also significantly improved oral bioavailability to 29%. Unfortunately this did not translate into improved brain penetration. Further SAR studies which led to BRS-3 agonists with improved CNS penetrating properties are reported in the previous Letter.[9]

In summary, SAR studies were carried out around acids **1** and **2**. Replacement of the acid moiety with a range of isosteres maintained good in vitro potency. Despite improvements made in bioavailability, significant increases in brain levels were not realized.

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