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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-

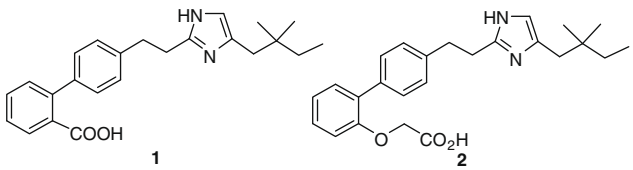

Figure 1.

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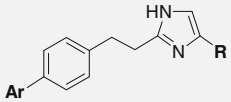
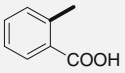
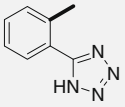
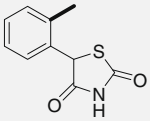
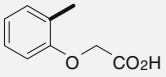
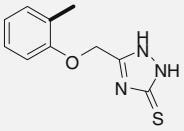
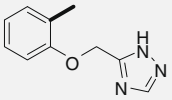
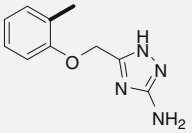
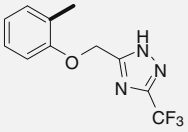
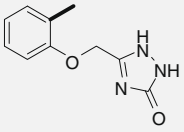
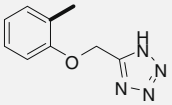
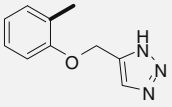
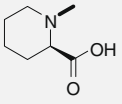
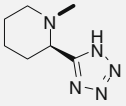
Table 1
The potency of BRS-3 agonists in human and mice BRS-3 receptors

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*)