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Discovery of potent, orally active benzimidazole glucagon receptor antagonists

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ABSTRACT

The discovery and optimization of potent and selective aminobenzimidazole glucagon receptor antagonists are described. One compound possessing moderate pharmacokinetic properties in multiple preclinical species was orally efficacious at inhibiting glucagon-mediated glucose excursion in transgenic mice expressing the human glucagon receptor, and in rhesus monkeys. The compound also significantly lowered glucose levels in a murine model of diabetes.

Type 2 diabetes is characterized by chronically elevated plasma glucose levels. A major contributor to this condition is excessive hepatic glucose production resulting from inappropriately high levels of the hormone glucagon, which signals via the glucagon receptor to promote hepatic gluconeogenesis and glycogenolysis.[1] Disruption of glucagon signaling may therefore provide a means to alleviate hyperglycemia in type 2 diabetic patients.[2] Indeed, biological agents that do so, including glucagon-neutralizing antibodies,[3] antisense oligonucleotides,[4] and peptide glucagon receptor antagonists[5] have been shown to reduce glucose levels in animal models of diabetes. Several small molecule glucagon receptor antagonists have also been reported to block glucagon-induced glucose production in animals[6] and in man,[7] and more recently, to decrease glucose levels in animal models of diabetes.[8,9e] Continuing our efforts to develop small molecule glucagon receptor antagonists,[9] we describe the discovery and development of potent and selective 2-aminobenzimidazoles that are orally efficacious in blocking glucagon-mediated glucose excursion in vivo, and lower glucose levels in a diabetic animal model.

Screening efforts against the human glucagon receptor (hGCGR) led to the identification of moderately active acylurea antagonists including **1** (Fig. 1). Poor physical properties of the compounds, however, led us to replace the acylurea moiety with aminoheterocycles, providing analogs such as **2a**. While the aminoheterocycle derivatives showed significantly decreased activity against the glucagon receptor, molecular modeling comparisons with cyclic urea **3**[9d] and other previously reported glucagon receptor antagonists[8] prompted us to append benzyl-linked acidic groups to the amino moiety to provide compounds such as **2b**. Indeed, **2b** showed improved in vitro potency, and was orally efficacious in inhibiting glucagon-induced glucose excursion in transgenic mice expressing the human glucagon receptor (hGCGR mice) at 30 mg/kg (data not shown).

Further evaluation of the aminoheterocycle platform led to the preparation of aminobenzimidazole glucagon receptor antagonist **4**. Listed in Table 1, the compound showed high receptor affinity as measured by inhibition of ^{125}I-glucagon binding to hGCGR expressed in CHO cell membranes (Bnd IC_{50}), though functional antagonism of glucagon-induced cAMP accumulation in hGCGR-transfected CHO cells (cAMP IC_{50}) was weak.[10] Replacement of the diaryl ether moiety with a *tert*-butylcyclohexyl group provided compound **5**, which showed similar binding affinity to **4**, and also poor functional activity. N-Methylation of the benzimidazole ring of **5** provided compound **6**, which maintained high receptor affinity, and now showed significantly improved functional activity.

Benzimidazole **6** was synthesized as depicted in Scheme 1, which typifies the methodology used to obtain the majority of analogs. A one-pot reaction involving reaction of methyl-4-(4-*trans*-*tert*-butylcyclohexylaminomethyl) benzoate[10] with one equivalent of thiophosgene, followed by addition of phenylenediamine **13**,

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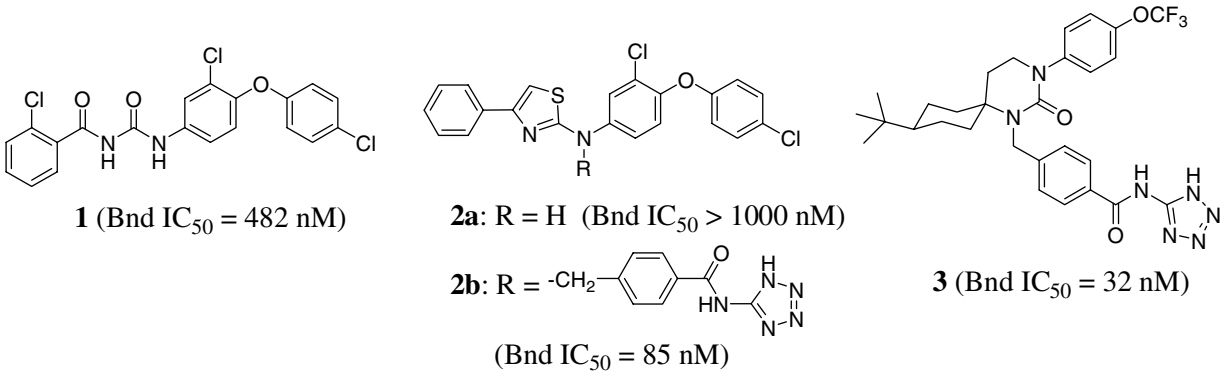
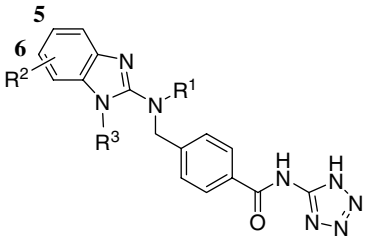
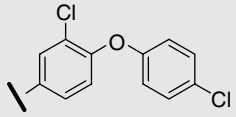
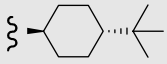
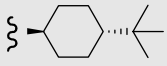
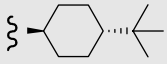
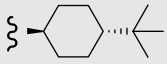
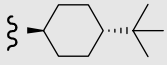
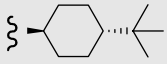
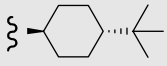
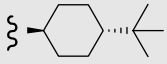


Figure 1. Small molecule glucagon receptor antagonists.

Table 1
Binding and functional activity of benzimidazole glucagon receptor antagonists



Entry	R^1	R^2	R^3	Bnd IC_{50} (nM)	cAMP IC_{50} (nM)
4		5-Me	H	13	>1000
5		5-Me	H	10	>1000
6		5-Me	Me	15	71
7		H	Me	4	55
8		H	Et	16	ND[a]
9		H	Pr	24	ND[a]
10		H	cPent	120	ND[a]
11		H	Ph	950	ND[a]
12		H	Bn	16	ND[a]

[a] ND, not determined.

then cyclization with mercuric trifluoroacetate, provided the aminobenzimidazole **14a**. Saponification of the ester and coupling of the aminotetrazole provided the desired product **6**. Outlined in Scheme 2, compounds could also be prepared by an alternative route, involving one-pot reaction of phenylenediamine **15** with the desired isothiocyanate, followed by mercury-mediated cyclization to afford the aminobenzimidazole **16**. Benzylation in the presence of sodium hydride strongly favored alkylation of the 2-amino group to provide ester **14b**, which could then be processed to the tetrazole product, as described in Scheme 1.