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Discovery of *N*-Aryl-2-acylindole human glucagon receptor antagonists

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ABSTRACT

A novel class of *N*-aryl-2-acylindole human glucagon receptor (hGCGR) antagonists is reported. These compounds demonstrate good pharmacokinetic profiles in multiple preclinical species. One compound from this series, indole **33**, is orally active in a transgenic murine pharmacodynamic model. Furthermore, a 1 mg/kg oral dose of indole **33** lowers ambient glucose levels in an *ob*/*ob*/hGCGR transgenic murine diabetes model. This compound was deemed suitable for preclinical safety studies and was found to be well tolerated in an 8-day experimental rodent tolerability study. The combination of preclinical efficacy and safety observed with compound **33** highlights the potential of this class as a treatment for type 2 diabetes.

Glucagon and insulin are the primary counter-regulatory hormones responsible for maintaining glucose homeostasis.[1] In response to falling plasma glucose levels, glucagon is secreted from pancreatic α-cells. This hormone activates its receptor, a G-protein coupled receptor located predominately in the liver, leading to increased hepatic glucose production via glycogenolysis and gluconeogenesis. In patients with type 2 diabetes, inappropriately elevated glucagon levels result in excessive hepatic glucose output, a key contributor to hyperglycemia. This has stimulated efforts to develop various strategies targeting reduced glucagon action. Toward this end, both antisense oligonucleotides[2] and small molecule glucagon receptor antagonists[3,4] have been reported. Herein we report a novel class of acyl indole human glucagon receptor (hGCGR) antagonists which evolved from our earlier work on cyclic guanidine hGCGR antagonists.[4]

We recently disclosed a cyclic guanidine class of human glucagon receptor (hGCGR) antagonists, exemplified by compound **1** (Fig. 1).[4b] Compound **1** showed excellent efficacy in a murine glucagon challenge pharmacodynamic model, but displayed poor pharmacokinetic (PK) profiles across preclinical species. Many analogs also carried unacceptable off-target activities, often displaying potent binding of IKr, the ion channel derived from hERG. As we attempted to address these issues within the cyclic guanidine series, we initiated a parallel effort to identify a novel scaffold based on the cyclic guanidine design. We hypothesized that the suboptimal off-target profile could be attributed to Bronsted basicity of the core structure. We thus synthesized 2-acylindole **2**, a non-basic heterocycle designed to display the critical pharmacophores in a similar fashion as compound **1**. This compound class indeed showed improved selectivity over the hERG channel, but provided compounds with poor solubility. Varying the display of the hydrophobic groups on the acylindole scaffold and replacing the aminotetrazole amide moiety with a β-alanine amide led to indole **3**. Compounds of this type showed enhanced functional activity against the human glucagon receptor relative to indole **2**, and also generally displayed improved rat pharmacokinetic profiles relative to compounds typified by **1**. A further improvement in rat pharmacokinetic profile was realized upon conversion of the *N*-benzyl indole to an *N*-aryl indole, as in compound **4**. While this change led to a small loss in hGCGR binding potency, the promising rodent PK profile prompted further development of this novel series and ultimately led to the discovery of a highly potent, selective hGCGR antagonist with a profile suitable for evaluation in preclinical safety studies.

A synthetic route which allows for late stage introduction of a variety of *N*-aryl groups is depicted below (Scheme 1). Commercially available indole **5** was converted to the corresponding Weinreb amide. Exposure of this amide to an excess of an alkyllithium reagent such as *n*-butyllithium provided ketone **6**. A sequence involving protection of the indole nitrogen with a benzyl group to give indole **7**, ketone enolate alkylation and indole deprotection[5] gave the key intermediate **8**. From this intermediate, a wide variety of aryl and heteroaryl groups could be introduced by Buchwald's method,[6] giving rise to *N*-arylindoles exemplified by **9**. Saponification followed by EDC-mediated amide bond formation with a

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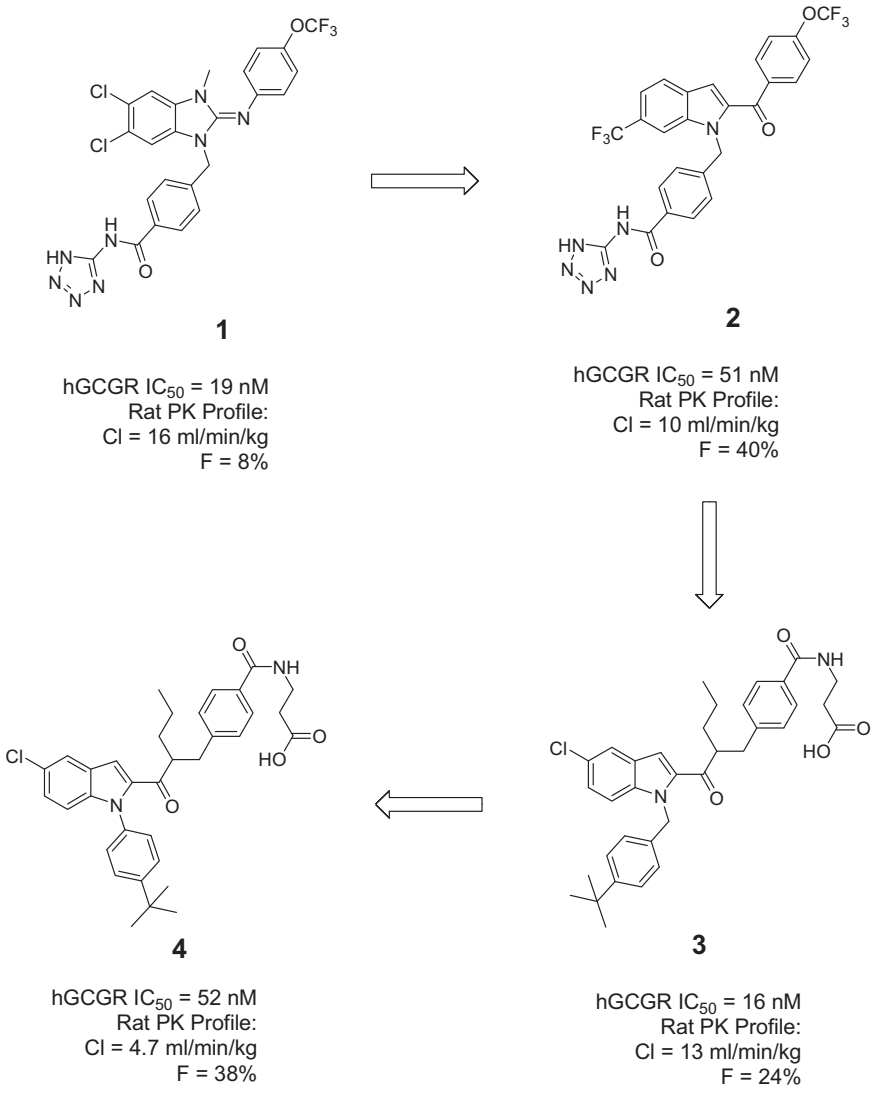


Figure 1. Evolution of *N*-aryl acylindole glucagon receptor antagonists.

protected β-alanine gave amides such as **10**. At this point, enantiopure compounds could be obtained via chiral HPLC.[7] Finally, TFA-mediated ester deprotection provided the target compounds such as **4**.

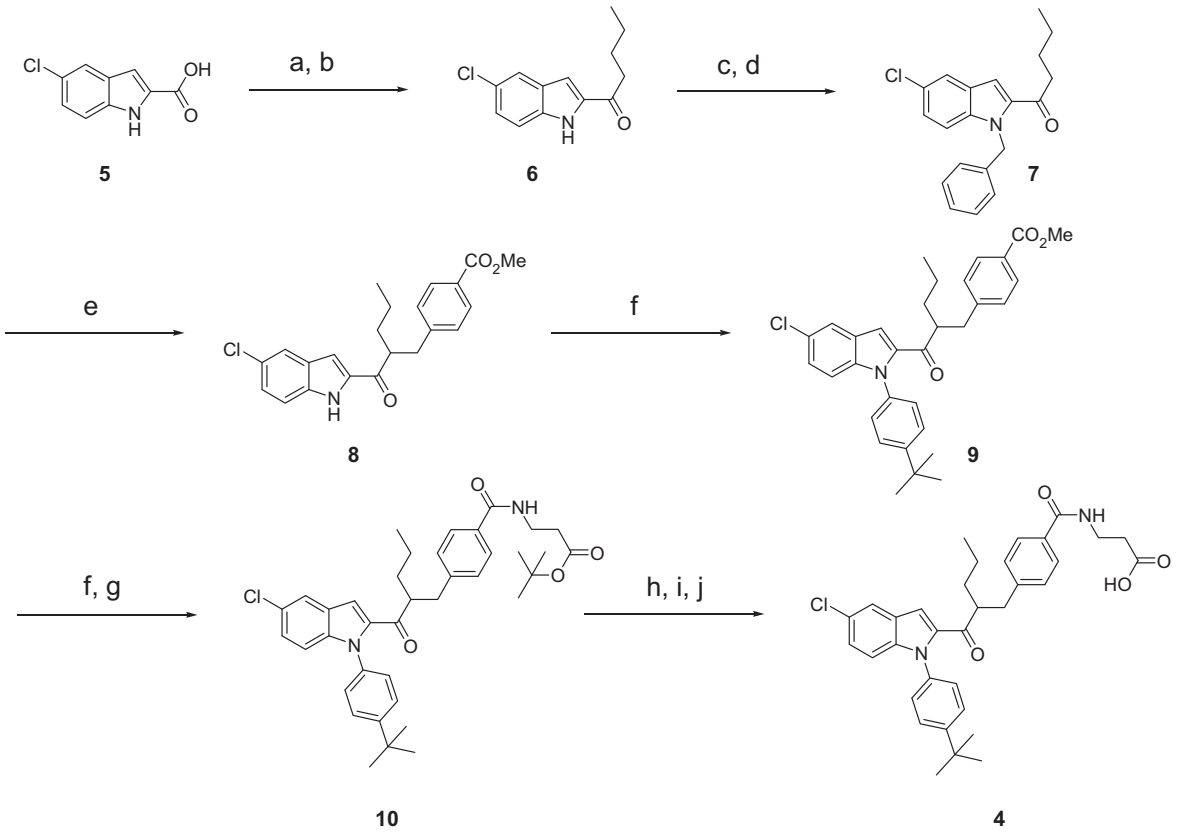
For certain α-keto groups either incompatible with the Lewis acid promoted indole deprotection (Scheme 1, step e) or not amenable to alkyllithium formation (Scheme 1, step b), an alternative approach was employed (Scheme 2). In one example, Claisen condensation of *t*-butyl acetate with indole **11** followed by C-alkylation with bromomethyl cyclopropane provided β-keto ester **12**. Acidic cleavage of the *t*-butyl ester and thermal decarboxylation gave ketone **13**, which could be processed to the target hGCGR antagonist as described in Scheme 1.

The in vitro biological activities of these compounds were evaluated in both binding and functional assays. Binding affinity was determined by a scintillation proximity assay measuring the inhibition of I^{125}-labelled glucagon binding to the hGCGR expressed on CHO cell membranes (hGCGR BND IC_{50}).[8] Compounds demonstrating good affinity (IC_{50} <100 nM) were tested for functional inhibition of glucagon-induced cAMP production in hGCGR-transfected CHO cells (hGCGR cAMP IC_{50}).[8]

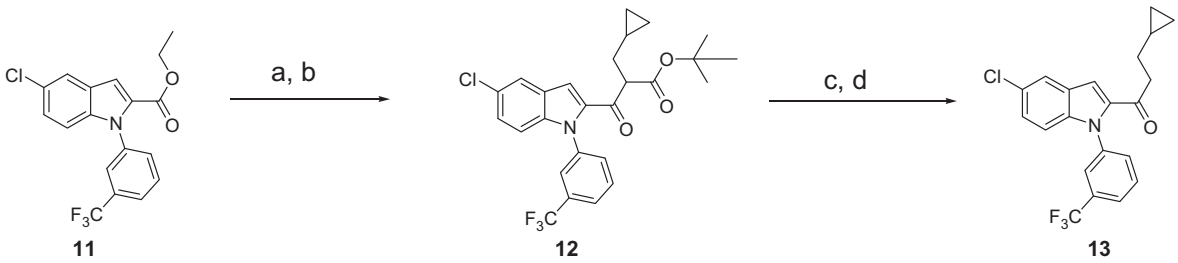
Table 1 summarizes hGCGR binding and functional data for a series of compounds displaying a range of *N*-aryl substituents, with the α-carbonyl substituent held constant. Compound **4**, which bears a sterically bulky *t*-butyl group at the 4-position of the aromatic ring, showed moderate activity in both the binding and functional assays. Replacing the *t*-butyl substituent with a 4-chloro substituent, as in **14**, led to an improvement in binding affinity but a concomitant decrease in functional activity. Modest increases in both binding affinity and functional activity were realized upon introduction of sterically bulky, electron withdrawing trifluoromethoxy and trifluoromethyl groups as in **15** and **16**. Shifting these substituents to the 3-position of the aromatic ring (compounds **17** and **18**) provided compounds of comparable activity.

While 3,5-disubstituted *N*-aryl groups led to decreased activity (e.g., compounds **20** and **21**), certain 3,4-disubstituted *N*-aryl groups such as in compound **23** provided enhanced potency. Replacing the *N*-phenyl groups with substituted naphthyl rings or other [6.6]-systems as in compounds **24** and **25**, failed to provide an increase in activity. While the quinolyl group of **26** was poorly tolerated, the less basic 3-trifluoromethyl-2-pyridyl group present in compound **27** led to significantly enhanced binding affinity.

These chiral hGCGR antagonists showed considerable differences in activity as a function of absolute configuration. For example, while compound **27** was a highly potent antagonist (hGCGR



Scheme 1. Reagents and conditions: (a) MeONHOMe·HCl, EDC, HOBt, DIEA, DMF, 40 °C; (b) *n*-BuLi, THF, −78 °C to 0 °C; (c) NaH, BnBr, DMF, rt; (d) KHMDS, methyl 4-bromomethylbenzoate, −78 °C to rt; (e) $AlCl_3$, benzene, 0 °C to rt; (f) 4-^{t}Bu-iodobenzene, CuI, K_3PO_4, *trans*,*N*,*N*-dimethyl-1,2-cyclohexanediamine, toluene, 110 °C; (g) LiOH, dioxane/water; (h) β-alanine-O^{t}Bu·HCl, EDC, HOBt, DIEA; (i) chiral separation; for further details, see Ref. 7; (j) TFA, CH_2Cl_2.

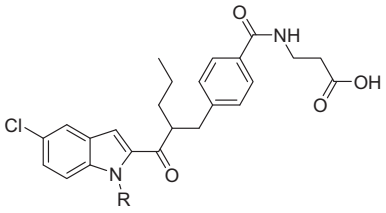


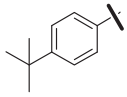
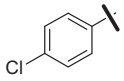
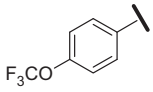
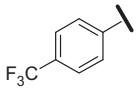
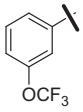
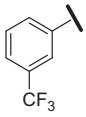
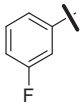
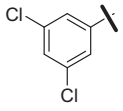
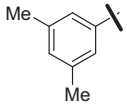
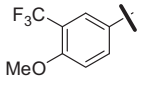
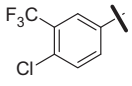
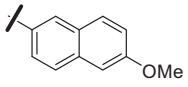
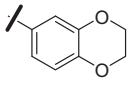
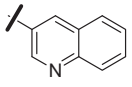
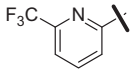
Scheme 2. Reagents and conditions: (a) ^{t}BuOAc, LHMDS, THF, −78 °C to 0 °C; (b) NaH, bromomethylcyclopropane, DMF, rt; (c) TFA, CH_2Cl_2, rt; (d) benzene, 90 °C.

IC_{50} = 9.2 nM), the corresponding enantiomer **28** was nearly fifty-fold less potent (Scheme 3). This prompted us to elucidate the absolute configuration of the more potent enantioseries. Toward this end, hydrolysis of ester **8**, EDC coupling with β-alanine *t*-butyl ester and chiral separation gave rise to compound **29**, a single enantiomer of unknown configuration (Scheme 3). Buchwald arylation[6] with 2-bromo-6-trifluoromethylpyridine followed by deprotection of the β-alanine *t*-butyl ester gave compound **27**, indicating that indole **29** belongs to the more potent enantioseries. Treatment of **29** with excess *m*CPBA gave rise to Baeyer–Villiger type oxidation[9] with in situ hydrolysis, providing a carboxylic acid which could be coupled with (*R*,*R*)-pseudoephedrine to give amide **30**. Intermediate **30** made possible the elucidation of stereochemistry by chemical correlation, as this compound could be synthesized by a well precedented route (Scheme 4). Thus, Myers alkylation[10] of (*R*,*R*)-pseudoephedrine valeramide (**31**) with methyl 4-bromomethylbenzoate, saponification and amide bond formation with β-alanine *t*-butyl ester gave compound **30**, thereby establishing the (*S*)-configuration for the more potent enantioseries.[11]

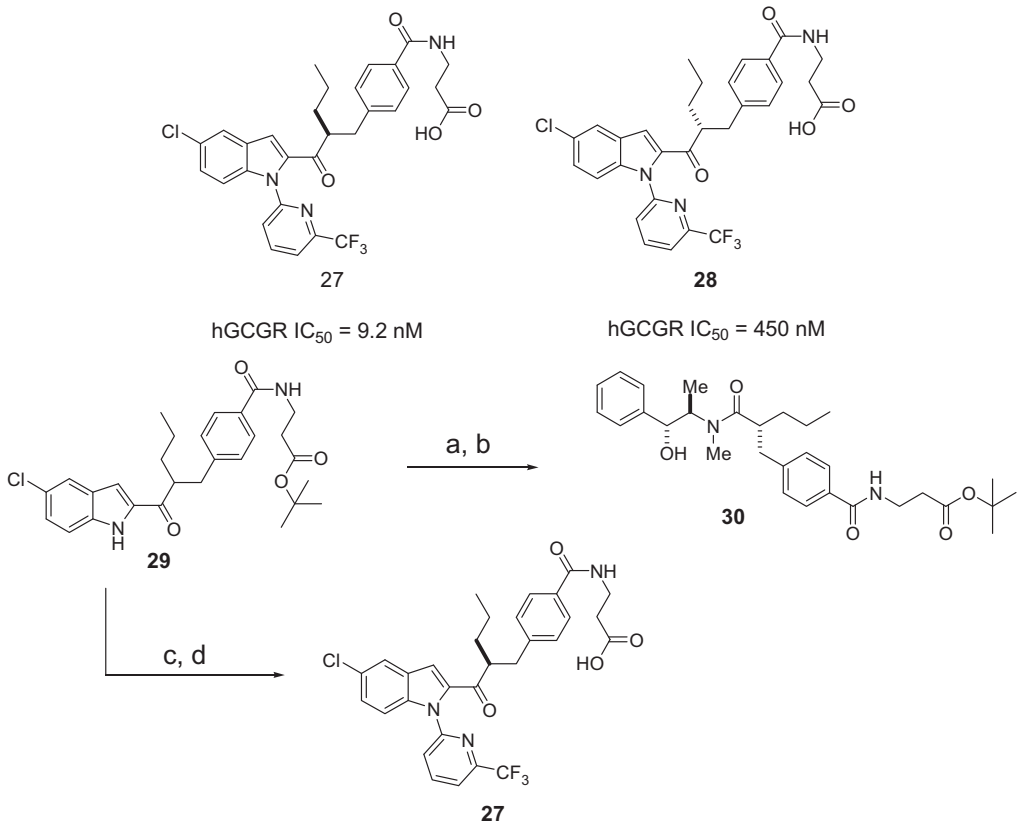
Since installation of an *N*-3-trifluoromethylphenyl group led to potent compounds with favorable pharmacokinetic profiles (vide infra), this substituent was held constant in a survey of α-carbonyl alkyl groups (Table 2). While increasing the alkyl chain length from *n*-propyl to *n*-butyl had no discernible effect (cf., compounds **18** and **32**), the *n*-pentyl homologue **33** showed improved binding and functional activity. Replacing the *n*-pentyl group with its isopentyl isomer as in **34** led to a three-fold reduction in functional activity. Likewise, introduction of the cyclopropylmethyl group in compound **35** resulted in decreased activity. Thus, the combination of *N*-3-trifluoromethylphenyl and α-keto *n*-pentyl moieties in compound **33** appeared optimal. Efforts to further optimize in vitro activity by varying substitution at the 5-position of the indole served to confirm the 5-chloroindole fragment as providing the optimal combination of binding and functional activity (Table 3).

Table 1
SAR of *N*-aryl substituent[a]

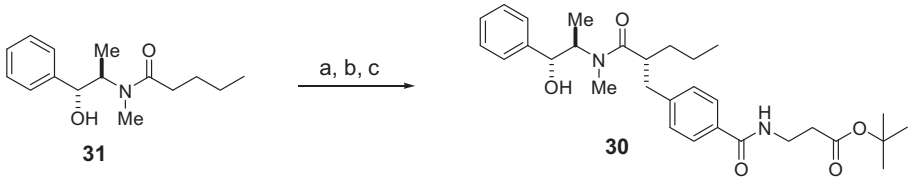


Compound	R	hGCGR BND[b] IC_{50} (nM) (*n*)	hGCGR cAMP[b] IC_{50} (nM) (*n*)
4		58	52 ± 11 (2)
14		32	100 ± 11 (2)
15		28 ± 4.7 (2)	45 ± 6.5 (2)
16		31 ± 3.7 (2)	30 ± 13 (2)
17		24 ± 3.5 (2)	35
18		17 ± 6.4 (2)	55 ± 7.0 (2)
19		47	150 ± 32 (2)
20		110	n/d
21		120	n/d
22		23 ± 8.5 (2)	39 ± 4.5 (2)
23		12 ± 5.4 (2)	17 ± 1.1 (2)
24		34	95 ± 55 (2)
25		28 ± 9.2 (2)	49 ± 5.7 (2)
26		58 ± 19 (3)	718
27		9.2 ± 0.8 (2)	34 ± 5.4 (5)

[a] All compounds are single enantiomers which were resolved via chiral HPLC (see footnote 7 for details); data shown are for the enantiomer which is the more potent hGCGR antagonist.
[b] Each IC_{50} in this Letter is reported as an average rounded to two significant figures ± standard error of the mean when more than one measurement was made.



Scheme 3. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, rt; (b) (*R*,*R*)-pseudoephedrine·HCl, EDC, HOBt, DIEA, DMF; (c) 2-bromo-6-trifluoromethylpyridine, CuI, K_3PO_4, *trans*,*N*,*N*-dimethyl-1,2-cyclohexanediamine, toluene, 110 °C; (d) TFA, CH_2Cl_2, rt.



Scheme 4. Reagents and conditions: (a) *n*-BuLi, LiCl, methyl 4-bromomethyl benzoate, THF; (b) LiOH, dioxane/water; (c) β-alanine-O^{t}Bu, EDC, HOBt, DIEA, DMF.

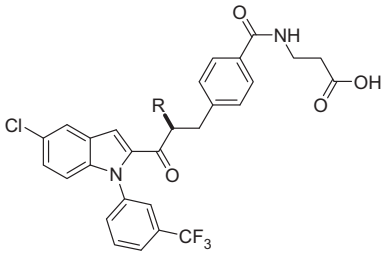
A number of compounds were selected for determination of their PK profiles in the rat (Table 4). These analogs, though structurally similar, showed diverse PK profiles. Compound **18** showed moderate plasma clearance, a moderate half-life, and good bioavailability (F = 42%). Compound **23**, which differs from **18** by the presence of an additional 4-chloro group on the *N*-aryl ring, showed lower plasma clearance, but decreased oral bioavailability. Pyridine analog **27** showed relatively high plasma clearance and low bioavailability. While increased lipophilicity on the *N*-aryl ring had a detrimental effect on rat PK (cf., compounds **18** and **23**) increasing the α-carbonyl chain length as in compound **33** gave rise to an improved pharmacokinetic profile relative to compound **18**, with lower plasma clearance, increased oral exposure, and moderate oral bioavailability. Compound **33** also displayed a favorable PK profile in the dog ($t_{1/2}$ = 2.7 h, F = 60%).

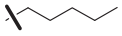
In addition to providing favorable PK profiles in the rat and the dog, compound **33** was found to have acceptable selectivity over related GPCRs and other ancillary targets. When tested for functional antagonism of the human GLP-1 and human GIP receptors, which play roles in glucose dependent insulin secretion, compound **33** was >100-fold selective for the human glucagon receptor (hGLP-1 cAMP IC_{50} >10000 nM; hGIP cAMP IC_{50} = 1400 nM). Compound **33** was a weak binder of the hERG gene product (IKr IC_{50} = 3700 nM),[12] and showed minimal inhibition of the major CYP isoforms (CYP3A4, 2C9, 2D6: IC_{50} >11000 nM).

The ketone moiety in compound **33** raised the theoretical potential for racemization of the α-chiral center and covalent trapping of nucleophiles. To address the first concern, compound **33** was incubated at 40 °C for 24 h in 1:1 mixtures of dioxane and buffered solutions from pH 2 to pH 10. In all cases, chiral HPLC analysis indicated no racemization. Furthermore, compound **33** demonstrated no racemization or irreversible covalent binding when incubated with human liver microsomes, or when administered orally in the rat.[13]

Indole **33**, a highly potent hGCGR antagonist (cAMP IC_{50} = 12 nM) with desirable PK profiles and a good off-target profile, was further evaluated for activity in vivo. When administered orally to mice expressing the human glucagon receptor, followed after 60 min by an IP injection of glucagon,[8] compound **33** effected a significant blockade of the glucagon-induced glucose excursion at all doses (3, 10, and 30 mg/kg, Fig. 2). Compound **33** was then tested for its ability to lower ambient glucose levels in *ob*/*ob* mice expressing only the human glucagon receptor. In this hyperglycemic rodent model (baseline glucose levels ~275 mg/dl), oral

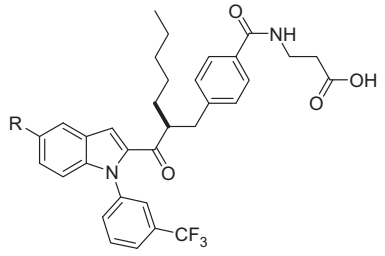
Table 2
Effect of α-keto substitution[a]



Compound	R	hGCGR BND[b] IC_{50} (nM) (*n*)	hGCGR cAMP[b] IC_{50} (nM) (*n*)
18		17	55
32		16 ± 0.6 (2)	42
33		10 ± 1.9 (4)	12 ± 1.6 (4)
34		17 ± 3.0 (2)	36
35		37	55

[a] All compounds are single enantiomers which were resolved via chiral HPLC (see footnote 7 for details); data shown are for the enantiomer which is the more potent hGCGR antagonist.
[b] Each IC_{50} in this Letter is reported as an average rounded to two significant figures ± standard error of the mean when more than one measurement was made.

Table 3
Optimization of indole 5-substituent[a]



Compound	R	hGCGR BND[b] IC_{50} (nM) (*n*)	hGCGR cAMP[b] IC_{50} (nM) (*n*)
33	Cl	10 ± 1.9 (4)	12 ± 1.7 (4)
36	F	10 ± 5.8 (3)	20
37	OMe	26 ± 3.7 (2)	35
38	OCF_3	5.7 ± 1.5 (2)	17 ± 0.8 (2)
39	CF_3	16 ± 6.9 (3)	44 ± 19 (2)
40	Me	12 ± 4.7 (3)	24

[a] All compounds are single enantiomers which were resolved via chiral HPLC (see footnote 7 for details); data shown are for the enantiomer which is the more potent hGCGR antagonist.
[b] Each IC_{50} in this Letter is reported as an average rounded to two significant figures ± standard error of the mean when more than one measurement was made.

administration of **33** at 1 mg/kg led to a significant reduction in ambient glucose levels over a 6 h period (Fig. 3).

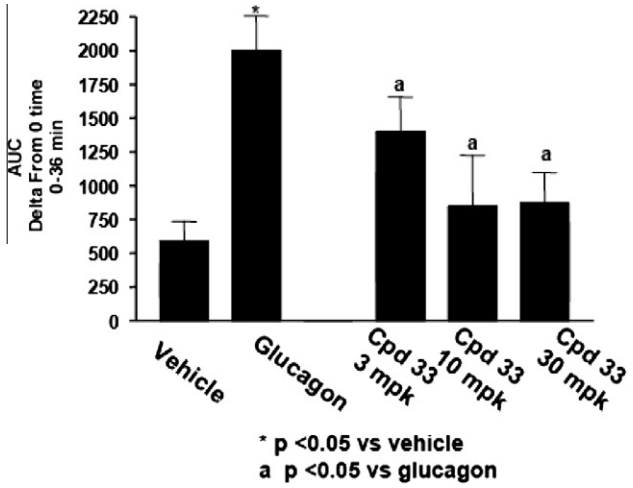


Figure 2. Effect of compound **33** on glucagon-induced glucose excursion in hGCGR mice. Compound was administered orally in 0.25% methylcellulose.

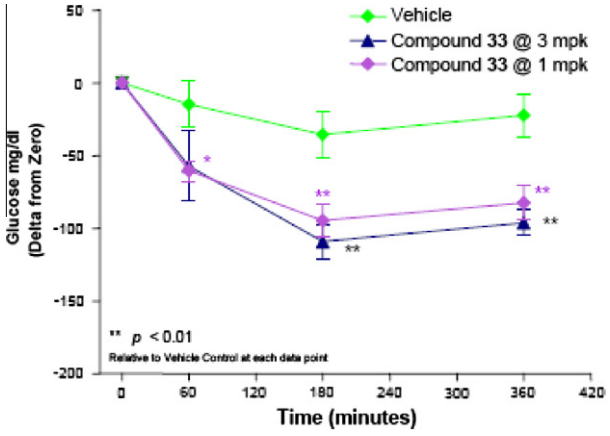


Figure 3. Acute lowering of ambient glucose levels by compound **33** in an hGCGR/*ob*/*ob* mouse model. Compound was administered orally in 0.5% methylcellulose.

N-Aryl-2-acylindoles are a novel class of potent human glucagon receptor antagonists. These chiral compounds displayed a considerable preference for a single enantiomer. Optimization of the indole C5-substituent, substitution on the *N*-aryl ring, and the α-carbonyl group led to the discovery of indole **33**. This compound displayed desirable PK profiles in the rat and the dog, as well as good activity in both an acute hGCGR murine pharmacodynamic assay and an acute *ob*/*ob*/hGCGR murine efficacy model. Based on this overall profile, compound **33** was selected for further evaluation in preclinical safety studies. Toward this end, compound **33** was found to be well tolerated at 100 mg/kg/day in an 8-day experimental rodent tolerability study, lending further support for the potential utility of *N*-aryl-2-acylindoles as a treatment for type 2 diabetes.

Table 4
Pharmacokinetic profiles of human glucagon receptor antagonists in rat[a] and dog[b]

Compound	Animal	Cl_p (ml/min/kg)	V_d (L/kg)	$t_{1/2}$ (h)	PO AUC_N (μM.h/dose)	C_{max}/dose (μM)	%*F*
18	Rat	14.2	1.5	1.7	0.85	0.25	42
23	Rat	9.2	0.84	1.3	0.52	0.15	17
27	Rat	24	0.90	1.1	0.15	0.07	9.1
33	Rat	6.8	0.98	1.9	1.46	0.33	33
33	Dog	3.8	0.32	2.7	4.2	0.84	60

[a] Compounds were dosed at 1 mg/kg IV, 2 mg/kg PO in a 15:35:55 mixture of DMSO, water, and PEG400.
[b] Compound was dosed at 0.5 mg/kg IV, 2 mg/kg PO in a 10:50:40 mixture of EtOH, PEG400, and water.

References and notes

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13. For in vitro experiments, a radiolabelled (^{3}H) analog of compound **33** (10 μM, 60 min, 37 °C) was incubated with human and rat liver microsomes and irreversible protein binding was measured. For in vivo covalent binding experiments, a radiolabelled analog of compound **33** was administered PO (20 mg/kg) to Sprague-Dawley rats and irreversible binding was measured to plasma and liver proteins 2, 6 and 24 h post dose; for analysis of racemization in vivo, radiolabelled **33** was administered IV (2 mg/kg) to bile duct cannulated rats, and the excreted parent compound was assayed via chiral HPLC.