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Small molecule *ago*-allosteric modulators of the human glucagon-like peptide-1 (hGLP-1) receptor

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Abstract—Following our previous publication describing the biological profiles, we herein describe the structure–activity relationships of a core set of quinoxalines as the hGLP-1 receptor agonists. The most potent and efficacious compounds are 6,7-dichloroquinoxalines bearing an alkyl sulfonyl group at the C-2 position and a secondary alkyl amino group at the C-3 position. These findings serve as a valuable starting point for the discovery of more drug-like small molecule agonists for the hGLP-1 receptor.

The β-cell insulin response to an oral glucose load is greater than the insulin response from glucose administered intravenously. This effect, known as the incretin effect, is due to the secretion of gut hormones during nutrient absorption, which potentiates glucose-dependent insulin secretion. One of the hormones believed to make the greatest contribution to normal glucose homeostasis is glucagon-like peptide 1 (GLP-1).[1] GLP-1 is a 30-amino acid peptide derived from the proglucagon gene.[2] It is secreted from the L-cells of the small intestine in response to nutrient intake. GLP-1 exerts its effect by binding to the G protein-coupled receptor (GPCR) on pancreatic β-cells. The resultant increase in intracellular cAMP initiates cell depolarization and raises the cytosolic Ca^{2+} concentration, ultimately resulting in an augmentation of insulin secretion.[3]

GLP-1 has demonstrated a number of pharmacological effects beneficial in the treatment of type 2 diabetes.[4] For example, GLP-1 has been shown to inhibit glucagon secretion, gastric acid secretion, and gastric emptying, resulting in reduced food intake and loss of body weight. Furthermore, it has been demonstrated that GLP-1

Abbreviations: cAMP, cyclic adenosine 3′,5′-monophosphate; GPCR, G protein-coupled receptor; hGLP-1, human glucagon-like peptide-1; hGIP, human gastric inhibitory polypeptide; DTT, 1,4-dithiothreitol.
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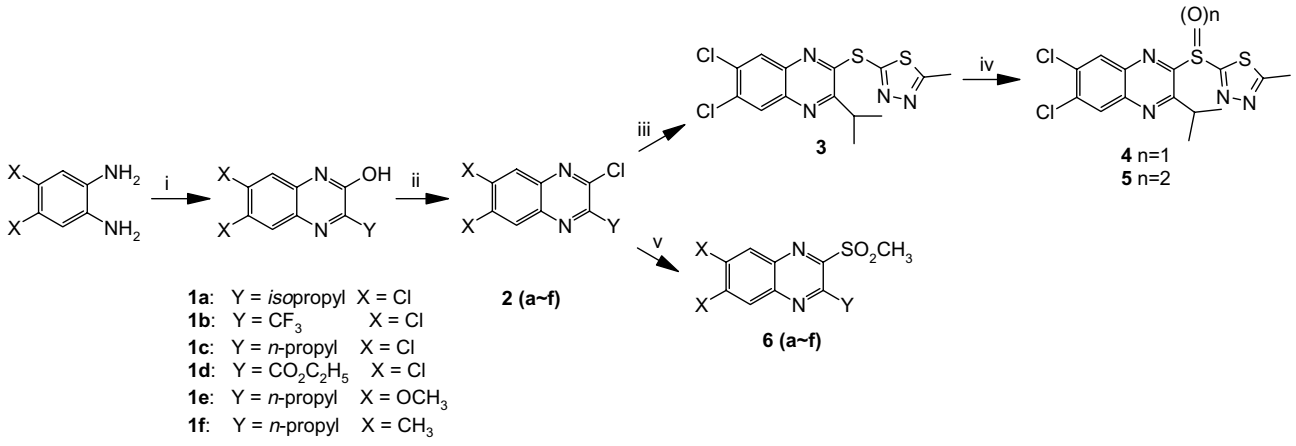
receptor ligands increase pancreatic β-cell mass by inducing neogenesis, proliferation, and anti-apoptosis of the β-cells.[5] GLP-1 is also known to stimulate insulin secretion in a glucose-dependent manner resulting in little risk of hypoglycemia. Because type 2 diabetes is characterized by a progressive decline in insulin secretion, reduced β-cell mass and/or function, increased glucagon secretion, and is often accompanied by obesity, GLP-1 has attracted enormous attention as a therapeutic target for the potential treatment of this disease.[6]

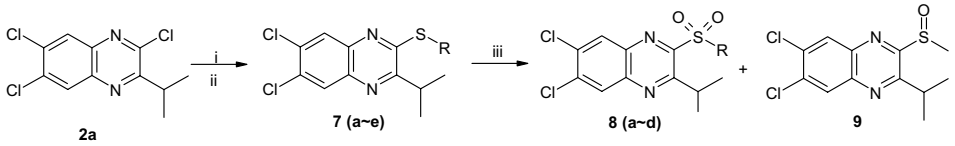
As a large peptide, GLP-1 is rapidly degraded in plasma by dipeptidyl peptidase-IV (DPP-IV).[7] Efforts to identify GLP-1 analogs with longer plasma half-lives have resulted in the clinical development of liraglutide for once daily subcutaneous administration.[8] Exenatide, another GLP-1 analog originally isolated from the saliva of the Gila monster, was approved by the FDA in 2005 as a twice daily subcutaneous administration for the treatment of type 2 diabetes.[9] However, as a peptide, GLP-1 and analogs thereof have to be administered through intravenous or subcutaneous route. Therefore, orally active, small molecule agonists of the hGLP-1 receptor are highly desirable.

Chen et al. recently described nonpeptidic-specific hGLP-1 receptor agonists.[10] At the same time, we reported the discovery of small molecule agonists of the hGLP-1 receptor.[11] Screening of 250,000 wells from our small molecule libraries against the hGLP-1 receptor, followed by structural modifications, led to the discovery of 6,7-dichloro-2-sulfonylquinoxalines, which acted as the hGLP-1 receptor agonists in several biochemical and cellular assays. These quinoxalines were able to stimulate cAMP in a dose-dependent manner in membranes expressing the hGLP-1 receptor but not other related GPCRs, such as the glucagon and GIP receptors. Interestingly, these compounds were unable to displace ^{125}I-GLP-1 in a competitive binding assay, but were able to potentiate binding of GLP-1. We have proposed they be called *ago*-allosteric modulators. Compound **16f** caused the release of insulin from normal mouse islets and from a perfused rat pancreas. The preliminary studies of the quinoxaline series demonstrated the feasibility of discovering small molecule agonists for the hGLP-1 receptor that may lead to a new therapy for diabetes. We herein describe the synthesis and structure–activity relationships of a core set of 2-sulfonylquinoxalines.

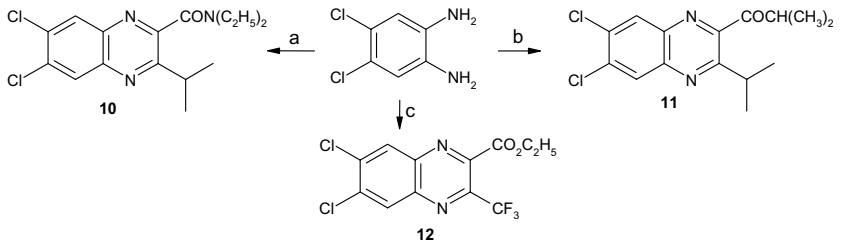
The synthesis of all quinoxalines is outlined in Schemes 1–8. Condensation of disubstituted (X = Cl, OCH_3 or CH_3) 1,2-phenylenediamines with an α-ketoester in DMF/AcOH yielded the corresponding 2-hydroxyquinoxalines **1** (**a**–**f**, Scheme 1), which were then chlorinated with $POCl_3$ under refluxing conditions to afford 2-chloroquinoxalines **2**(**a**–**f**). Displacement of the chloride in **2a** by 2-mercapto-5-methyl-1,3,4-thiadiazole in the presence of 40% KF on alumina in DMF led to **3**. Controlled oxidation of **3** by *m*CPBA afforded **4** and **5**. Compounds **6**(**a**–**f**) were synthesized by treating 2-chloroquinoxalines **2**(**a**–**f**) with sodium methanesulfinic acid in DMF at 100 °C for 12 h. Synthesis of **8**(**a**–**d**) and **9** is shown in Scheme 2. The synthesis of 3-*iso*propyl-6,7-dichloroquinoxaline-2-thiol was carried out by treating 2,6,7-trichloro-3-*iso*propylquinoxaline **(2a)** with $NaSH2H_2O$ in DMF. Subsequent treatment of the thiol with a variety of alkyl halides in DMF yielded the



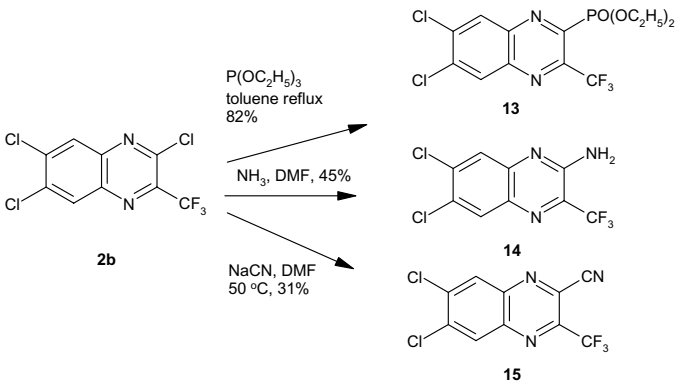
Scheme 1. Preparation of quinoxaline derivatives. Reagents and conditions: (i) α-ketoester, DMF, HOAc; (ii) $POCl_3$, reflux; (iii) 2-mercapto-5-methyl-1,3,4-thiadiazole, KF 40% wt on alumina, DMF, rt, overnight; (iv) *m*CPBA/DCM, DCM; (v) $NaSO_2CH_3$, DMF, 100 °C.



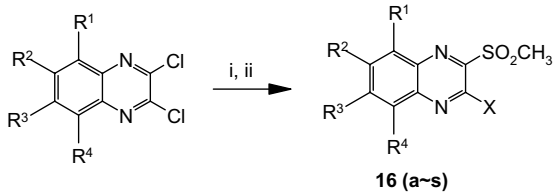
Scheme 2. Preparation of quinoxalines **8**(**a**–**d**), **9**. Reagents and conditions: (i) $NaSH{\cdot}2H_2O$, DMF, rt, 2 h; (ii) Na_2CO_3, alkyl halide, DMF; (iii) *m*CPBA, DCM.



Scheme 3. Reagents and conditions: (a) i—4-Methyl-2,3-dioxo-pentanoic acid ethyl ester, HOAc, DMF; ii—KOH, EtOH; iii—EDCI, DMAP, diethylamine, DCM, 48% (three steps); (b) 2,6-Dimethyl-heptane-3,4,5-trione, HOAc, DMF, 27%; (c) 2-Chloro-4,4,4-trifluoro-3-*oxo*-butyric acid ethyl ester, EtOH, reflux.

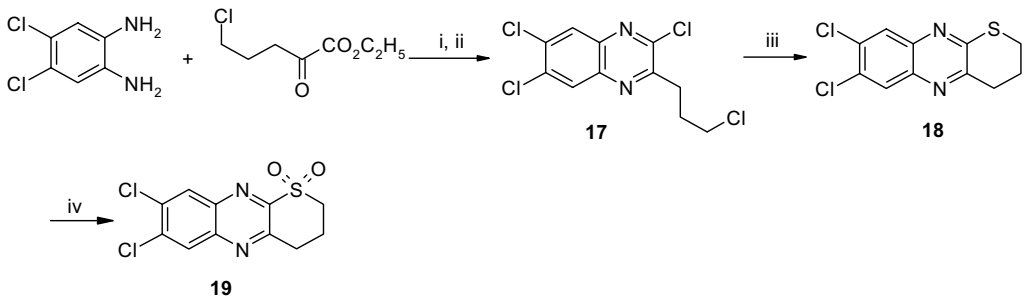


Scheme 4.

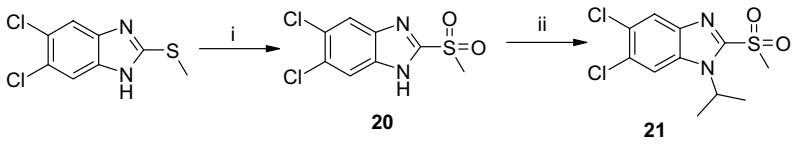


Scheme 5. Preparation of quinoxalines **16(a–s)**. Reagents and conditions: (i) nucleophile, Cs_2CO_3, DMF, 0 °C; (ii) $NaSO_2CH_3$, DMF, 100 °C.

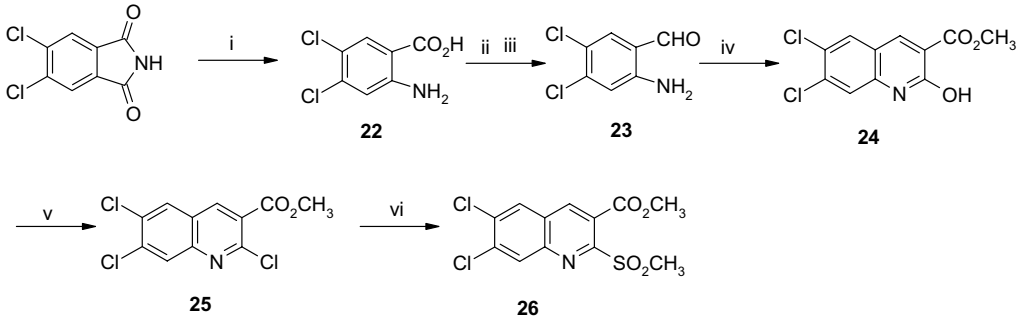
corresponding thioethers **7(a–e)**. Without further purification, the thioethers were oxidized with *m*CPBA in DCM to give sulfones **8(a–d)** and sulfoxide **9**. The synthesis of quinoxalines **10–15** is described in Schemes 3 and 4. 4-Methyl-3-*oxo*-pentanoic acid ethyl ester was oxidized by selenium dioxide in refluxing dioxane to afford 4-methyl-2,3-dioxo-pentanoic acid ethyl ester, which was subsequently treated with 4,5-dichlorophenylenediamine in HOAc/DMF to give 2-ethoxycarbonylquinoxaline. Saponification followed by coupling with diethylamine led to **10** (Scheme 3). Similarly, 2,6-dimethyl-3,5-heptadione was oxidized by selenium dioxide to yield 2,6-dimethyl-heptane-3,4,5-trione. Without isolation, this trione was reacted with 4,5-dichlorophenylenediamine to afford **11**. Compound **12** was obtained by reacting 4,5-dichlorophenylenediamine with ethyl 2-chloro-3-keto-4,4,4-trifluorobutyrate in refluxing ethyl alcohol. Treatment of 2,6,7-trichloro-3-trifluoroquinoxaline **(2b)** with triethylphosphite in refluxing toluene for 12 h afforded **13** (Scheme 4). Compounds **14** and **15** were synthesized by treating **2b** with ammonia and NaCN, respectively. Compounds **16(a–s)** were synthesized by treating the 2,3-dichloroquinoxalines with either 2-propanethiol or a variety of alkylamines in the presence of cesium carbonate in DMF, followed by treatment with sodium methanesulfinic acid in DMF



Scheme 6. Preparation of Compound **19**. Reagents and conditions: (i) HOAc/DMF, rt, 3 days; (ii) $POCl_3$, 0.5 h, reflux, 21% (two steps); (iii) sodium hydrosulfide, K_2CO_3, DMF, rt, 4 days, quant; (iv) *m*CPBA, DCM, 31%.



Scheme 7. Reagents: (i) *m*CPBA, DCM; (ii) *iso*propyl bromide, K_2CO_3, DMF, 22% (two steps).



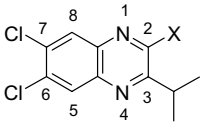
Scheme 8. Reagents and conditions: (i) NaOBr, NaOH aq 0 °C, 5 min, then 80 °C, 2 min, 72%; (ii) LAH, THF; (iii) MnO2, DCM, 46%; (iv) dimethyl malonate, NaOMe, MeOH, then 1 N HCl, 87%; (v) $POCl_3$, reflux, 73%; (vi) sodium methanesulfinate, DMF, 100 °C, 1 h, 36%.

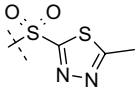
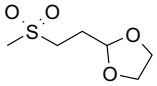
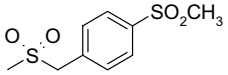
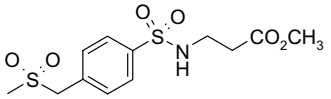
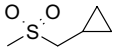
(Scheme 5). The synthesis of **19** started with the condensation of 5-chloro-2-*oxo*-pentanoic acid ethyl ester with 4,5-dichlorophenylenediamine to yield 2-hydroxyquinoxaline, which was then converted into **17** by refluxing in $POCl_3$. The subsequent sluggish cyclization to **18** was achieved by using sodium hydrosulfide and K_2CO_3 in DMF. Finally, oxidation of **18** by *m*CPBA produced the desired sulfone **19** (Scheme 6). Compounds **21**[12] and **26**[13] were synthesized according to literature procedures as outlined in Schemes 7 and 8.

To systematically explore the structure–activity relationships of 2-sulfonylquinoxalines as agonists for the hGLP-1 receptor, our initial efforts included mapping out the space requirement for the C-2 sulfonyl group. This was approached through both singleton executions and parallel synthesis, using intermediate thiols with a well-established chemistry route shown in Scheme 2. Data for representative compounds are shown in Table 1. Test results from the membrane cAMP assay indicated that the C-2 region tolerated a variety of substituted sulfones, some of which were relatively bulky. All sulfones were partial agonists with similar efficacy and potency at the hGLP-1 receptor. Interestingly, compound **19** had no measurable activity, which appeared due to the locked conformation of the sulfone moiety to the quinoxaline ring (Fig. 1).

Keeping the C-3 position as an *iso*propyl or CF_3, we explored the C-2 position using non-sulfonic substituents possessing either electron-donating or electron-withdrawing features (Table 2). With the exception of sulfoxides **4** and **9**, all the non-sulfonic compounds (**10**–**15**) failed to produce measurable cAMP when tested at concentrations of up to 10 μM in the membrane assay. These results indicated that compounds with a sulfone or sulfoxide group at the C-2 position have a unique way of binding. We speculated that unlike cyano, ester, amide, keto or phosphonate, sulfone and sulfoxide moieties possess the proper polarization effect on the quinoxaline ring to elicit the observed GLP-1 agonistic activity.

Table 1. The effect of the C-2 sulfonyl group on the agonistic activity at hGLP-1



Compound	X	EC_{50} (μM)	E_{max} (%)
5		1.0	47
6a	SO_2CH_3	5	35
8a		3	71
8b		1.2	63
8c		4.9	65
8d		3.3	64

Data is from the membrane cAMP assay. Efficacy for the test compounds is expressed as percentage activity normalized to that of GLP-1 activity. EC_{50} is the concentration at which a test compound produces 50% of cAMP response produced by GLP-1. Extrapolation of the curve is applied when E_{max} is below 50%. Data is the mean of triplicates with a SD of ±10%.

To explore the C-3 position, we kept the C-2 position as a methylsulfone (Table 3). Both EC_{50} and E_{max} data

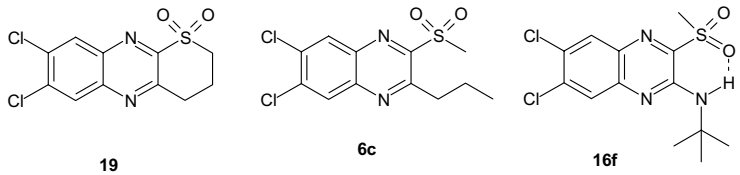
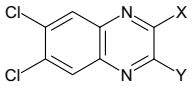
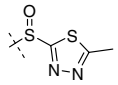


Figure 1. Agonistic activities vary with the conformation of the C-2 sulfonyl group.

Table 2. Comparison of potency and efficacy of sulfonic and non-sulfonic quinoxalines



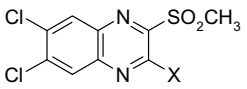
Compound	X	Y	EC_{50} (μM)	E_{max} (%)
6a	SO_2CH_3	*i*-Pr	5	35
1a	OH	*i*-Pr	—	—
4		*i*-Pr	5.1	19
9	$SOCH_3$	*i*-Pr	30	29
10	$CON(C_2H_5)_2$	*i*-Pr	—	—
11	$COCH(CH_3)_2$	*i*-Pr	—	—
6b	SO_2CH_3	CF_3	2.6	40
12	$CO_2C_2H_5$	CF_3	—	—
13	$PO(OC_2H_5)_2$	CF_3	—	—
14	NH_2	CF_3	—	—
15	CN	CF_3	—	—

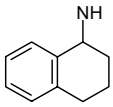
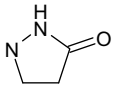
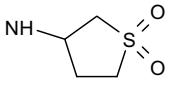
— indicates E_{max} (%) <2%.

suggested that, unlike the C-2 position, the C-3 position tolerated a variety of functional groups with secondary amino groups being optimal. Quinoxalines **16(d–f)** are the most potent and efficacious compounds identified in this study. Potency (EC_{50}) declined with primary and tertiary amines as seen in **16(b, h–k)**. Furthermore, the C-3 region had a poor tolerance for polar functional groups, as evidenced by the dramatic drop in potency and efficacy in **16(l–o)**. We postulated that the enhanced activity displayed by quinoxalines with a secondary amino group at the C-3 position is the result of an intramolecular H-bond between the NH of the amine and the S=O of the sulfone (Fig. 1). It seems plausible that this conformation is necessary for a favorable interaction, perhaps through crucial H-bond with the hGLP-1 protein. By contrast, compound **19** has a sulfone moiety locked within a ring in an unfavorable conformation. Not surprisingly, this compound showed no activity.

Next, we examined the quinoxaline ring. We deliberately chose substituents which would have differing electronic effects on the benzo ring (Table 4). When the C-3 position was an *isop*ropyl group, **6c** was the only compound that showed measurable activity. In compounds with the C-3 position fixed as a *sec*-butyl group, replacement of C-7 chloride with a nitro group **(16p)** significantly decreased both potency and efficacy. Introducing a nitro group at the C-5 position **(16q)** also decreased the activity compared to **16d**. A few asymmetric substituted quinoxalines were examined. Compounds **16(r, s)** showed weaker activity compared to the corresponding 6,7-dichloroquinoxalines. These data suggested that chloride substituents at the C-6,7 are required for the best activity. Generally speaking, electron-donating substituents at the C-6,7 positions appeared detrimental to the agonistic activity. A nitro group on the quinoxaline ring, though strongly electron withdrawing, decreased the agonistic activity as well.

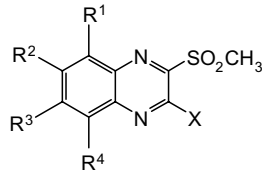
Table 3. Substitution effects at the C-3 position



Compound	X	EC_{50} (μM)	E_{max} (%)
6b	CF_3	2.6	40
6c	$(CH_2)_2CH_3$	1.2	68
6d	$CO_2C_2H_5$	>10	24
16a	$SCH(CH_3)_2$	0.661	46
16b	NH_2	6.3	24
16c	NHC_2H_5	0.725	46
16d	$NHCH(CH_3)_2$	0.214	82
16e	$NHCH(CH_3)C_2H_5$	0.175	94
16f	$NHC(CH_3)_3$	0.155	85
16g		0.433	69
16h	$N(CH_3)_2$	2.2	47
16i	$N(CH_3)i$Pr	1.8	75
16j	$N(CH_3)OCH_3$	2.6	52
16k		2.2	72
16l	$NHNHCOCH_3$	14	32
16m	$NH(CH_2)_2NHCOCH_3$	7.1	22
16n		14	38
16o		1.4	43

Examination of other heterocyclic systems revealed that agonistic activity at the hGLP-1 receptor appeared more pronounced for quinoxalines. As shown in Figure 2, quinoxalines **6(a, d)** exhibited agonistic activity while the corresponding benzimidazole **21** and quinoline **26** showed no measurable activity when tested at concentrations of up to 10 μM.

Table 4. Substitution effects at the quinoxaline ring



Compound	R^1	R^2	R^3	R^4	X	EC_{50} (μM)	E_{max} (%)
6c	H	Cl	Cl	H	$(CH_2)_2CH_3$	1.2	68
6e	H	CH_3O	CH_3O	H	$(CH_2)_2CH_3$	—	—
6f	H	CH_3	CH_3	H	$(CH_2)_2CH_3$	—	—
16e	H	Cl	Cl	H	$NHCH(CH_3)C_2H_5$	0.175	94
16p	H	NO_2	Cl	H	$NHCH(CH_3)C_2H_5$	4.3	44
16d	H	Cl	Cl	H	$NHCH(CH_3)_2$	0.214	82
16q	H	Cl	Cl	NO_2	$NHCH(CH_3)_2$	1.5	38
16r	CF_3	NO_2	Cl	H	$NHCH(CH_3)_2$	5.0	31
16f	H	Cl	Cl	H	$NHC(CH_3)_3$	0.155	85
16s	H	CF_3	H	Cl	$NHC(CH_3)_3$	2.2	42

— indicates E_{max} (%) <2%.

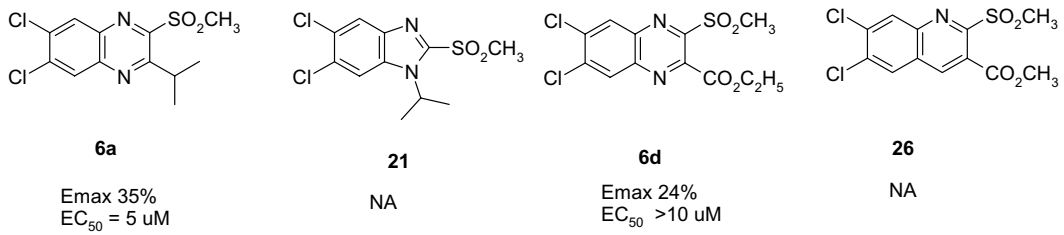


Figure 2. Quinoxalines appeared more potent GLP-1 agonists compared to the benzimidazole and quinoline analogs.

Table 5. Correlation between the potency in binding augmentation (IC_{50}) and the EC_{50}/E_{max}

Compound	EC_{50} (μM)	E_{max} (%)	IC_{50} (μM)
6a	5	35	0.253
6b	2.6	40	0.091
6c	1.2	68	0.404
6d	>10	24	3.1
8a	3	71	0.551
8b	1.2	63	0.459
9	30	29	1.1
16c	0.725	46	0.109
16d	0.214	82	0.107
16f	0.155	85	0.032
16h	2.2	47	0.53
16i	1.8	75	0.46
10	—	—	>10
11	—	—	>10

— indicates E_{max} (%) <2%.

As mentioned previously, active quinoxalines were able to activate hGLP-1 receptor in the competitive binding assay without competing with GLP-1 for the GLP-1 binding site. This suggested that the quinoxalines bind at an allosteric site on the hGLP-1 receptor. Moreover, the affinity of GLP-1 for the receptor increased in a dose-dependent manner upon incubation with the quinoxalines. An IC_{50} was measured and defined as the concentration of the quinoxalines at which 50% of the augmentation of GLP-1 to its receptor was reached by the quinoxaline. As Table 5 shows, there is generally a good correlation between the potency in binding augmentation (IC_{50}) and the EC_{50}/E_{max}.

The active quinoxalines showed good stability in simulated gastric fluid media at ambient temperature for at least 1 h, but they appeared chemically unstable when treated with strong nucleophiles or bases. For example, **6b** was hydrolyzed to 2-hydroxyquinoxaline **1b** when treated with potassium hydroxide in methanol. When treated with 1,4-dithiothreitol (DTT), the methylsulfone moiety was replaced by the nucleophile. The active quinoxalines had a high microsomal turnover rate when incubated with human liver microsomes without addition of co-factors, indicating non-enzymatic breakdown of the compounds. The stability issues hindered further in vivo characterization of these compounds, although some ex vivo experiments were conducted.[11]

In conclusion, we have identified a series of 2-sulfonylquinoxalines as small molecule agonists, so called *ago*-allosteric modulators, for the hGLP-1 receptor. The most potent and efficacious compounds are 6,7-dichloroquinoxalines bearing an alkyl sulfonyl group at the C-2 position and a secondary alkyl amino group at the C-3 position. It appeared that proper polarization of the quinoxaline ring and a suitable conformation of the C-2 sulfonyl group are required for the observed agonistic activities. The active quinoxalines appeared stable to gastric fluid conditions, however, improvement of chemical stability and pharmacokinetic properties is

clearly necessary. The binding mode of these small molecules is a subject for future investigation and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.06.086.

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