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Substituted azaquinazolinones as modulators of GHSr-1a for the treatment of type II diabetes and obesity

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ABSTRACT

Substituted azaquinazolinones were identified as antagonists of the GHSr-1A receptor for the treatment of type II diabetes and obesity. Optimisation for potency and Log*D* lead to the identification of orally bioavailable, potent antagonists with improved selectivity over hERG.

According to the American Diabetes Association,[1] the direct costs in 2007, of treating the estimated 23.6 million type 2 diabetes mellitus (T2DM) patients and the estimated 57 million pre-diabetic patients[2] in the United States was approximately $116 billion with an additional $58 billion dollars in indirect costs. Wild et al.[3] have predicted that the number of patients worldwide, suffering from T2DM will rise to over 360 million by 2030. Many of the current therapies for T2DM suffer from the fact that they are prone to causing an increase in body weight.[4] Ghrelin has previously been shown to affect both appetite and body weight. Short term fasting has been demonstrated to cause an increase in systemic ghrelin levels, whereas infusion of ghrelin has been shown to stimulate appetite and promote spontaneous food in-take. Ghrelin has also been shown to have long term effects upon body weight. Ghrelin not only stimulates feeding but it also shown to affect energy homeostasis.[5] It has also been demonstrated that ghrelin impedes the ability of insulin to suppress endogenous glucose production. Acute administration of ghrelin to humans causes an increase in plasma glucose levels. This effect may not solely result from direct effects on hepatocytes; where ghrelin has been shown to modulate glycogen synthesis and gluconeogenesis; but also by stimulation of hepatic glucose production.[6] The reduction of food intake, with subsequent weight loss and the growing body of evidence suggesting increased insulin secretion and improved glucose tolerance in vivo make small molecule antagonists of the Growth hormone secretagogue receptor (GHS-R1a) receptor of great interest as drugs for the treatment of diabetes coupled with meaningful body-weight loss.

Several examples of structurally diverse small molecule GHS-R1a antagonists had previously been reported in the literature (Fig. 1).[7–9]

Compounds **1** and **3** were profiled further in-house to examine for any potential liabilities in each structural class. Once this profiling was complete, YIL-781 (**1**) was selected as a starting point for a fast follow-on approach to run in parallel to a program using in-house chemical matter. Compound 1 represented an attractive point, low molecular weight (410 Da) with good LipE (6.54). Whilst potent against GHS-R1a; in our hands compound 1 carried a significant potassium ion channel (hERG) liability (IC_{50} 1.6 μM) and showed >50% activity at 10 μM at several targets, for example the muscarinic receptors, M1 and M2, and the serotonin receptor, $5HT_{2b}$ in a Cerep metabolic screen. This presented an interesting challenge to the drug discovery team, designing molecules that maintained (or improved) the activity at the GHS-R1a receptor, whilst reducing the liability at hERG and other targets. Rudolph

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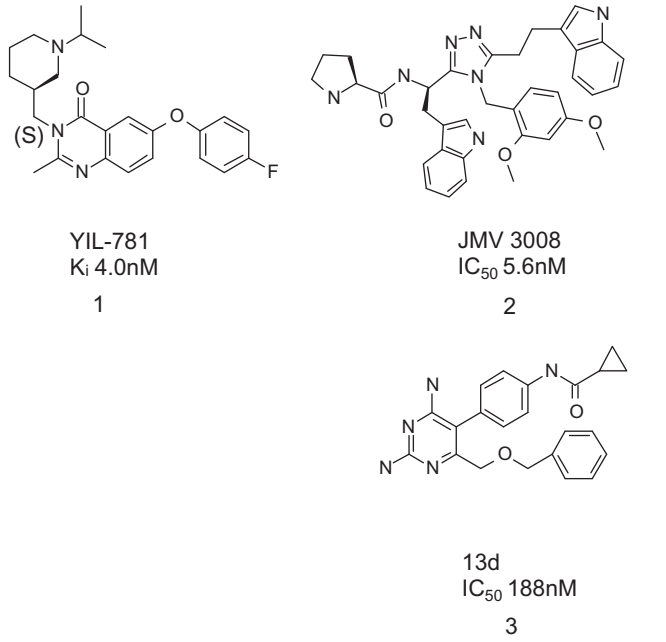


Figure 1. Literature examples of small molecule GHS-R1a antagonists.

et al. had previously demonstrated that modification of the basicity (pK_a) of the piperidine nitrogen resulted in no significant reduction in activity at GHS-R1a, but also had no significant effect on plasma exposure levels.[7] Our aim was to investigate reduction of the Log*D* of the molecules in an attempt to improve selectivity levels and also to move away from lipophilic amino compounds, often associated with having hERG liabilities.[10] This account will highlight our main strategy; modification of the lipophilicity of the central core, moving from a quinazolinone type structure (as exemplified by **1**) to the azaquinazolinone type structures as exemplified in Figure 2: leading to the discovery of potent, selective GHS-R1a antagonists with improved activity against hERG.

The commercially available anthranilic acids **4**, 10 and **12** were coupled to C-((*R*)-1-isopropylpiperidine-3-yl)methylamine[11] using HOBt and EDCI. Compound **8** was synthesised in moderate yield from the commercially available nitrile–nitro compound [**7**]. The

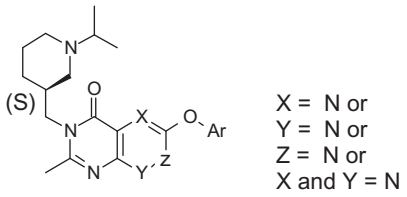
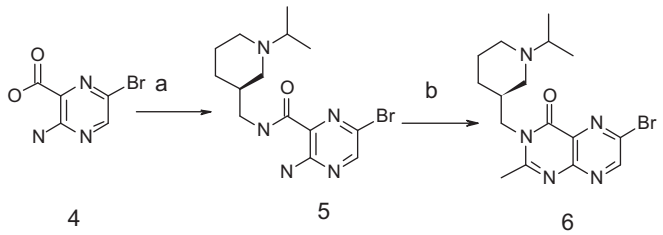
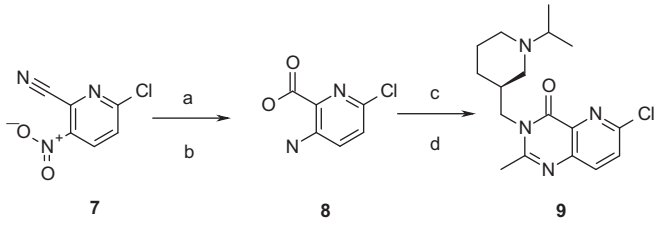


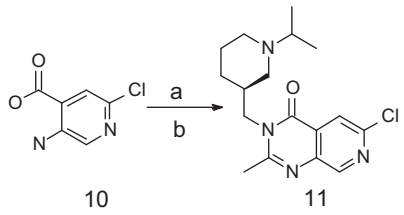
Figure 2. Azaquinazolinone cores.



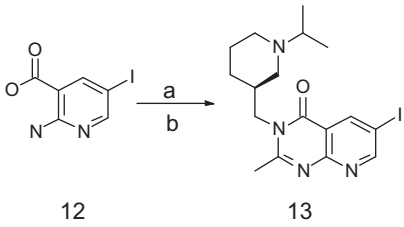
Scheme 1. Reagents and conditions: (a) C-((*R*)-1-isopropylpiperidine-3-yl)methylamine, HOBt, EDCI, NEt_3, DMF, 18 h, 45 °C, 90%; (b) 1,1,1-triethoxy ethane, AcOH, reflux, 3 h, 70%.



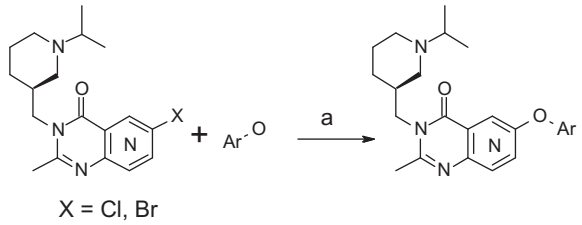
Scheme 2. Reagents and conditions: (a) $SnCl_2{\cdot}2H_2O$, EtOH, reflux, 2 h, 59%; (b) concd HCl, 90 °C, 5 h, quant; (c) C-((*R*)-1-isopropylpiperidine-3-yl)methylamine, HOBt, EDCI, NEt_3, DMF, 18 h, 45 °C, 50%; (d) 1,1,1-triethoxy ethane, AcOH, reflux, 3 h, 70%.



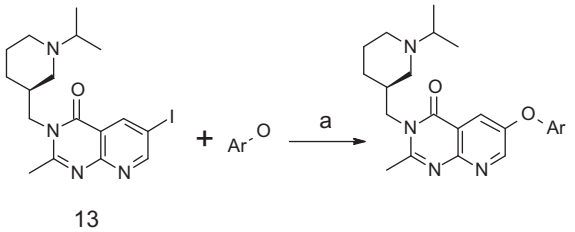
Scheme 3. Reagents and conditions: (a) C-((*R*)-1-isopropylpiperidine-3-yl)methylamine, HOBt, EDCI, NEt_3, DMF, 45%; (b) 1,1,1-triethoxy ethane, AcOH, reflux, 3 h, 94%.



Scheme 4. Reagents and conditions: (a) C-((*R*)-1-isopropylpiperidine-3-yl)methylamine, HOBt, EDCI, NEt_3, DMF, 57%; (b) 1,1,1-triethoxy ethane, AcOH, reflux, 3 h, 90%.

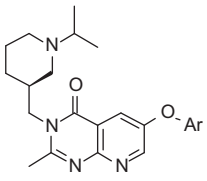


Scheme 5. Reagents and conditions: (a) Cs_2CO_3, DMF, 120 °C, μW, 30 min: 40–80%.



Scheme 6. Reagents and conditions: (a) Cs_2CO_3, NMP, CuCl, TMHD, 125–150 °C, 7–35%

Table 1
8-Azaquinazolinone SAR



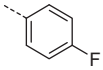
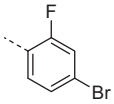
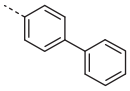
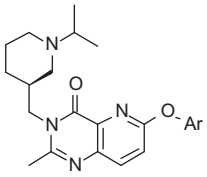
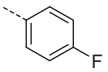
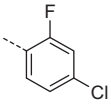
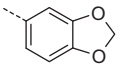
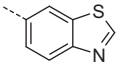
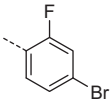
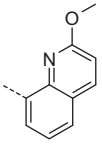
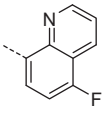
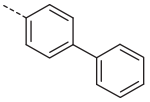
No.	Ar	GHS-R1a K_i (nM)	GHS-R1a IC_{50} (nM)	LipE	ACD Log*D*
14		6.7	357	6.86	1.32
15		0.16	26	7.82	1.98
16		1.7	131	6.23	2.53

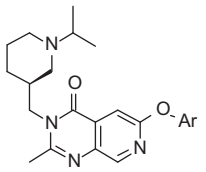
Table 2
5-azaquinazolinone SAR

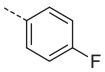
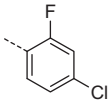
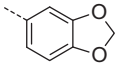
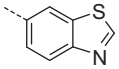
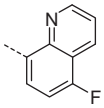
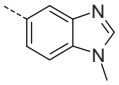


No.	Ar	GHS-R1a K_i (nM)	GHS-R1a IC_{50} (nM)	LipE	ACD Log*D*
17		2.0	185	8.13	0.57
18		0.2	2.0	9.20	0.49
19		0.9	19.2	8.86	0.18
20		0.01	2.7	10.75	0.11
21		0.01	2.3	9.87	0.33
22		3.1	118	8.00	0.50
23		2.6	131	8.12	0.46
24		0.4	37.7	7.57	1.78

nitrile was converted to the primary amide and the nitro group was simultaneously reduced to the primary amine using $SnCl_2$, followed by acid catalysed hydrolysis to the acid as in moderate overall yield, as shown in Scheme 1. Compound **8** was coupled to

Table 3
7-Azaquinazolinone SAR



No.	Ar	GHS-R1a K_i (nM)	GHS-R1a IC_{50} (nM)	LipE	ACD Log*D*
25		3.4	399	7.83	0.63
26		0.2	146	9.08	0.56
27		0.3	86.5	9.23	0.25
28		0.10	29.2	9.78	0.19
29		6.6	1440	7.57	0.61
30		0.5	137	9.65	−0.38

C-((*R*)-1-isopropylpiperidine-3-yl)methylamine using HOBt and EDCI, giving the resulting amide intermediate in moderate yield. The amide intermediates were heated to reflux in a 1:1 mixture of AcOH and 1,1,1-triethoxy ethane to give the azaquinazolinone intermediates **6**, **9**, 11 and **13** in excellent yields. (Scheme 1–4).

S_NAr reactions of intermediates [**6**, 9 and **11**] with selected aryl alcohols, using Cs_2CO_3 in DMF under microwave conditions, gave the desired biaryl ethers in moderate to excellent yield as outlined in Scheme 5.

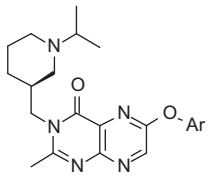
Attempts to synthesis biaryl ethers from compound **13** and other halo analogues using the same S_NAr conditions were unsuccessful. Similarly conversion of the iodo compound **13** to a boronic acid intermediate followed by Chan–Lam couplings[12] also proved to be unsuccessful (due to the difficulty in isolating the boronic acid intermediate), whilst attempts to apply Buchwald–Hartwig[13] methodology met with very limited success. Modified Ullmann coupling conditions, using a stoichiometric amount of CuCl and 2,2,6,6-tetramethyl-3,5-heptanedione(THMD) ligand, as outlined in Scheme 6 proved to be more successful. The yields of recovered material however remained poor, with <35% being recorded for all analogues synthesised.

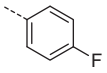
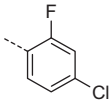
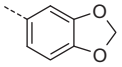
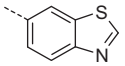
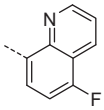
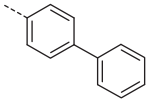
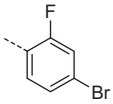
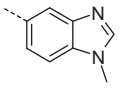
The in vitro SAR studies were carried out as follows: Binding affinities (K_i) for GHS-R1a were determined using an ^{125}I-ghrelin displacement assay (saturation binding assay, Millipore human GHS-R1a membranes) and the functional activities (IC_{50}) were determined using a FLIPR Ca^{2+} mobilisation assay. A more detailed description of the assays is given by Bloxham et al.[11] and in the Supplementary data. hERG assays were performed at Essen Biosciences (mini-patch clamp).[14] LipE, also known as ligand-lipophilicity efficiency (LLE) was calculated using the formula [pK_i − ACD Log*D*].

Compound **1** in our hands had K_i of 1.0 nM in the competition binging assay, an IC_{50} of 141 nM in the FLIPR assay, a calculated Log*D* of 2.34 and a LipE value of 6.54. Addition of hetero atoms into the central core was seen as a strategy to reduce the Log*D* of the molecules and maintain activity and functionality. As shown in Table 1, whilst the binding affinity of **14** remained at a single digit nanomolar level, it showed a twofold drop-off in functional activity in the FLIPR assay; importantly **14** maintained full antagonist activity at GHS-R1a. There was however no significant improvement in LipE when compared to compound **1**. Synthetic challenges, as already mentioned, meant that only a limited number of 8-azaquinazolinone were ever synthesised. Compound **15** represented the most potent compound synthesised in this series, with sub-nanomolar binding affinity, excellent functional activity and an improvement in LipE compared to compound **1**.

It was envisaged that moving the nitrogen to the 5 position would improve the ease of synthesis of the molecules. It was hoped to improve ACD Log*D* and retain activity at GHS-R1a, thus improving LipE. Compound **17** displayed both binding affinity and functional activity comparable to that of compound **1**, but the calculated Log*D* value was much improved, 0.57. The LipE of **17** was significantly improved as a result. Ease of synthesis lead to greater exploration of the right side of the biaryl ether linkage, leading to the identification of compounds (Table 2) with subnanomolar affinity and single digit functional activity at GHS-R1a. The molecules also maintained antagonist activity at the receptor and had much improved LipE compared to **1**. We were able to show that a wide variety of aryl alcohols were tolerated on the right hand side of the molecule. Compounds **19** and **20** for example, showed that significant improvements in binding, functional activity and LipE could be made using 6,5 ring systems, with compound **20** representing the best overall combination of binding, activity and physicochemical properties for this series. Compounds **22** and **23** displayed comparable binding and functional activity to compound **1** but with a much improved LipE, demonstrating that 6,6 ring systems were also well tolerated.

Table 4
Pteridinone SAR

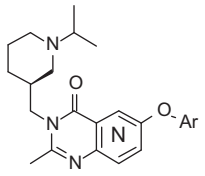


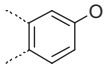
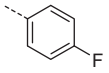
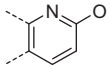
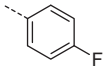
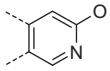
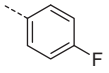
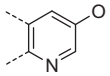
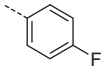
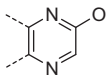
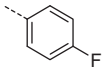
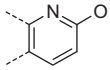
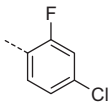
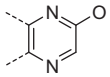
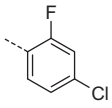
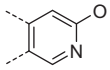
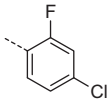
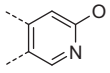
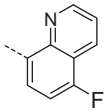
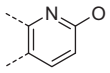
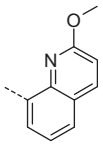
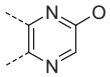
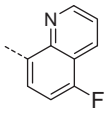
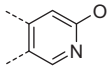
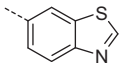
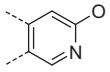
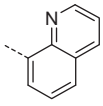
No.	Ar	GHS-R1a K_i (nM)	GHS-R1a IC_{50} (nM)	LipE	ACD Log*D*
31		3.1	587	8.30	0.20
32		0.6	102	9.10	0.13
33		1.5	16.5	9.00	−0.18
34		0.26	5.7	9.83	−0.25
35		1.9	142	8.63	0.10
36		0.27	80	8.15	1.41
37		0.05	1.17	9.46	0.86
38		5.0	51.8	9.12	−0.82

Following on from the 5-azaquinazolinones, the nitrogen was again moved around the ring to the 7 position. Compound **25**, as with compound **17**, showed excellent affinity for the GHS-R1a receptor; however it suffered a twofold drop off with respect to functional activity when compared to compound **1**. This effect was noted across the series. Applying some the SAR knowledge derived from the 5-aza series we were able to identify compounds with subnanomolar binding affinity, as seen in Table 3. However comparing the functional activities of the compounds to **1** or the isomeric nitrogen match pair for example, comparing compounds **18** and **26** or compounds **23** and **29**, there was at least a twofold drop in functional activity and in some cases the drop off was >10-fold. Whilst the LipE values of the molecules were improved with respect to compound **1**, the functional activities of the 7-aza molecules were disappointing.

When we examined the data from the other series it was clear that we had been successful in lowering the Log*D* of the molecule and had succeeded in improving in binding and activity, thus improving LipE compared to **1**. We decided to explore whether we could further lower the Log*D* of our compound by the introduction of an additional heteroatom into the central core, and could the improvements seen in binding and functional activity seen in the 5 and 8-aza compounds be maintained. This led to the discovery of compound **31**, a compound with excellent binding affinity for the GHS-R1a receptor but which suffered a fourfold drop in functional activity at the receptor. Applying the knowledge gained from the 5 and 8-aza compounds, we were able to identify compounds with excellent binding affinities, comparable or better functional activities when compared to **1** (Table 4). As with the 5-aza series, a wide variety of aryl substituents were tolerated on the right hand side of the molecule. By analogy to compound **17**, compound **34** with the benzothiazol-6-ol right hand side, gave a molecule with the best combination of binding, functional activity and physicochemical properties.The main driver behind reducing the Log*D* of our molecules was to reduce the potential hERG liability we identified during the initial profiling of compound **1**. With compounds **14** and **17** we were able to show moderate improvement in the hERG IC_{50}, as shown in Table 5. In the case of compound **25**, there was no improvement in hERG with respect to compound **1**. However with compound **31**, we were able to achieve a 10-fold improvement in hERG IC_{50}. With compound **18**, when the lipophilicity of the right hand side of the biaryl ether was increased we lost the improvement in hERG IC_{50} observed with compound **14** and in the case of compound **26**, we observed a 10-fold increase in activity at hERG. Compound **32** maintained the improvement at hERG shown by **31**, with an $IC_{50} > 33$ μM. Although the design of our molecules was driven by improvements in bulk Log*D*, we retrospectively believe we have observed local Log*D* and/or shape/configuration components to the hERG SAR. Researchers at Vertex[10] previously reported observing a connection between shape/conformation and the potential for hERG channel blockade. As expected, there is a clear trend towards increased activity at hERG

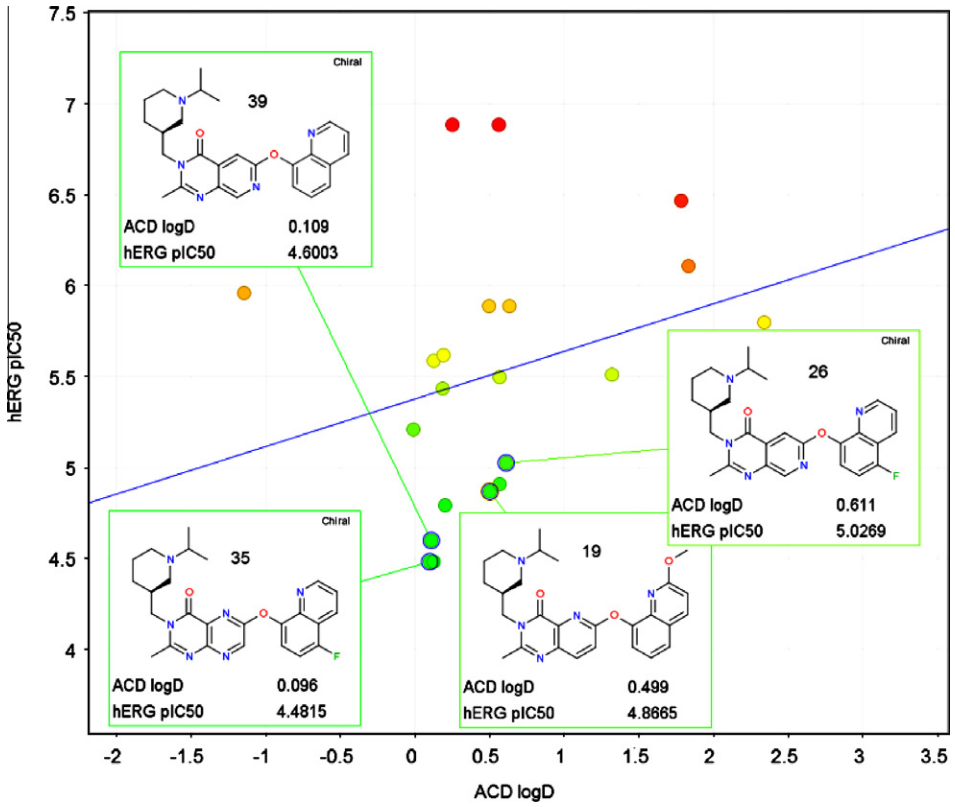
Table 5
hERG SAR



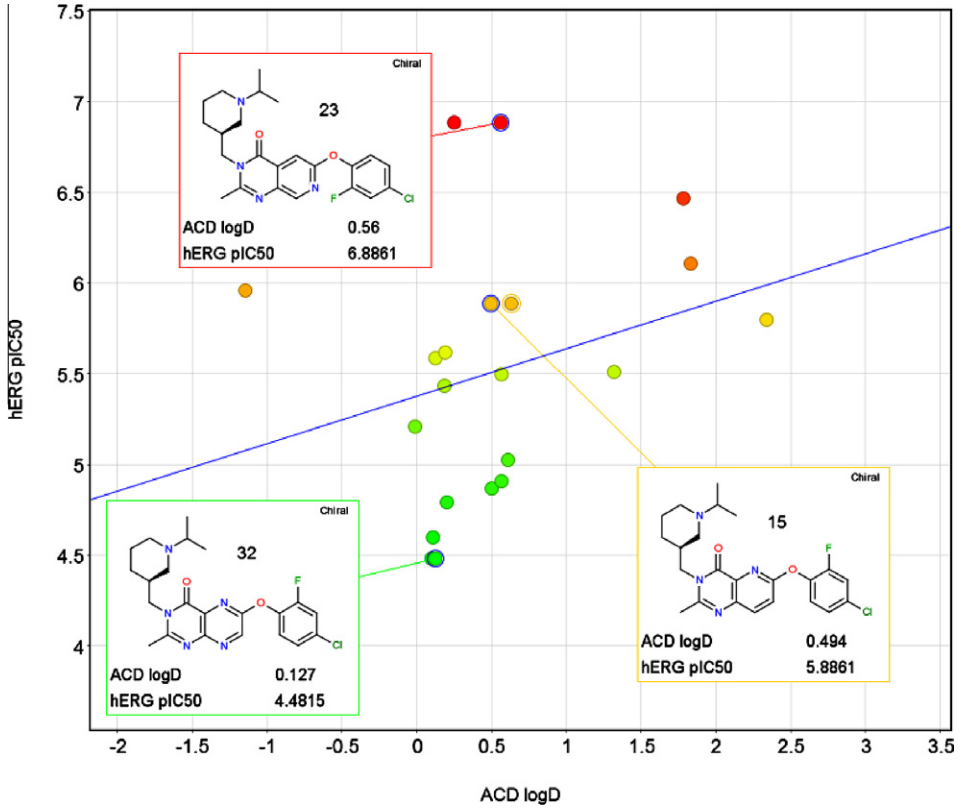
No.	Core	Ar	GHS-R1a IC_{50} (nM)	hERG IC_{50} (μM)	hERG pIC_{50}	ACD Log*D*
1			141	1.6	5.79	2.34
17			185	3.2	5.49	0.57
25			399	1.3	5.89	0.63
14			357	3.1	5.51	1.32
31			587	16.1	4.79	0.20
18			2.0	1.3	5.89	0.49
32			102	>33	4.48	0.13
26			146	0.13	6.89	0.56
29			1440	9.4	5.02	0.61
22			118	13.6	4.87	0.50
35			142	>33	4.48	0.10
28			29.2	2.4	5.62	0.19
39			2180	25.1	4.60	0.11

with increasing Log*D*. However, several outliers are quite apparent from the plots shown in Graph 1 and Graph 2.

In the case of the 7-aza molecules, activity at hERG was in general at best similar to that of **1**. Compound **25**, the isomeric nitrogen match pair of **1**, whilst having a 2-Log unit difference in the calculated Log*D*, had an IC_{50} of 1.3 μM. Compound **26** has a similar calculated Log*D* value however the hERG IC_{50} was 0.13 μM. When we moved to quinolin-8-ol derived right hand sides similar to those as exemplified by **29** we saw a marked, and unexpected, improvement in hERG activity, beyond what we believe to be the contribution from lowering Log*D* alone. Compound **28** whilst having a calculated Log*D* of 0.19, has a hERG IC_{50} of 2.4 μM, a moderate improvement, but not statistically significant within the parameters of the assay. We hypothesised that



Graph 1. Log*D* versus pIC_{50}.



Graph 2. Log*D* versus pIC_{50}.

having the nitrogen in 7-position, allows the molecule to adopt a conformation favourable to blocking the hERG channel. With the larger, spatially demanding substituted quinolin-8-ol derivatives, we believe the conformation adopted is no longer favourable.

Table 6
Pharmacokinetic profile of compounds 17, 18 and 31

	Compound					
	17		**18**		**31**	
Route	iv	po	iv	po	iv	po
Dose (mg/kg)	1.0	3.0	1.0	3.0	1.0	3.0
AUC (mg h/L)	523	941	695	736	1172[a]	1171[a]
C_{max} (ng h/ml)	0.47	0.18	0.89	0.16	1.87	0.52
$T_{1/2}$ (h)	7.16		4.71		3.01	
Cl (ml min/kg)	32		24		13	
V_{ss} (L/kg)	11.95		6.64		2.87	
F (%)	60		35		33[a]	

[a] See note in text.

Similarly with the 5-aza compounds, in general the hERG IC_{50}'s recorded were around 3–4 μM, or twofold better when compared to **1**. Compound **22** however showed a marked improvement in hERG activity, 10-fold when compared to **1**. Due to the limited number of compounds synthesised in the 8-aza series we are unable to discern any useful information with any degree of certainty. The results from the Pteridinone series of compounds seem to be driven largely by Log*D*.

PK experiments were performed in male SD rats, using 20% trappsol_WFI as the vehicle. Compounds **17**, 18 and **31** were taken forward as representative examples for pharmacokinetic profiling. As a consequence of reducing lipophilicity, compounds can often become less bioavailable due to lower permeability. Compounds **17** and **31** were chosen as direct comparators for compound **1**. Compound **18** was selected for PK profiling to determine suitability to progress to OGTT. As can be seen from Table 6, all of the compounds were orally absorbed. We were unable to calculate a percentage bioavailability for **31** using the standard calculation due to difficulties extrapolating the concentration versus time plot to infinity with a high degree of confidence; the bioavailability was estimated using AUC_{0-last}.

In summary using **1** as a starting point, using LipE as a key measure of improvement, we have identified a number of orally bioavailable, potent, selective GHS-R1a antagonists, with an improved profile against the hERG potassium channel. We have been able to demonstrate that lowering of Log*D* has resulted in an initial drop in functional activity against GHS-R1a but that by careful selection of aryl substituents we have been able to recover this activity and maintain improved profiles against hERG.

Acknowledgments

Many thanks to Dr. Craig Johnstone, head of Medicinal Chemistry, for the tremendous amount of advice, discussion and time given during writing. A big thank you to Dr. Linda Hirons, Research Technologies, for her help in analysing the hERG data and finally thank you to Dr. Andreas Scheel, head of in vitro pharmacology for help and discussion with the assay protocols.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.078.

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