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Discovery of furan-2-carbohydrazides as orally active glucagon receptor antagonists

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ABSTRACT

Furan-2-carbohydrazides were found as orally active glucagon receptor antagonists. Starting from the hit compound **5**, we successfully determined the structure activity relationships of a series of derivatives obtained by modifying the acidity of the phenol. We identified the *ortho*-nitrophenol as a good scaffold for glucagon receptor inhibitory activity. Our efforts have led to the discovery of compound **7l** as a potent glucagon receptor antagonist with good bioavailability and satisfactory long half-life.

Type 2 diabetes is characterized not only by insulin resistance and β-cell dysfunction but also by hyperglucagonemia in the fasting state and lack of glucagon suppression following meal ingestion.[1,2] It is therefore necessary for a complete treatment of type 2 diabetes to include agents that reverse hyperglucagonemia.

Glucagon, a peptide hormone consisting of 29 amino acid residues and produced in the α-cells of the pancreas, acts in the liver where it binds to the glucagon receptor (GCGR) to initiate gluconeogenesis and glycogenolysis.[3] It has been reported that plasma glucagon levels are abnormally high throughout the day in type 2 diabetic patients.[2] This led to the idea that GCGR antagonists may reduce hepatic glucose output and lower abnormal plasma glucose levels.[3b,4] In fact, Bayer reported that the GCGR antagonist, Bay 27-9955 (**1**, Fig. 1), suppresses excess glucagon-induced high plasma glucose levels in humans.[5] These findings indicate that GCGR antagonists may be useful in the treatment of type 2 diabetes.

To date, a number of non-peptidic GCGR antagonists with various acidic moieties including, β-alanine (NNC 25-0926[6] and MK-0893, **2**[7]), tetrazole (**3**[8]), or *ortho*-cyanophenol (**4**[9]) have been reported (Fig. 1). Although some of these compounds proceeded to clinical trials,[7,10] none is clinically available. In our search for new chemotypes of GCGR antagonists, we screened our chemical library and found compound **5**, 3,4-diphenylfuran-2-carbohydrazide derivative (Fig. 1), as a hit compound with moderate binding affinity for GCGR (50% inhibition at 10 μM in rat hepatocyte).[11] Our strategy for hit to lead generation focused on introducing the acidic moiety (Fig. 2).

Initially we replaced the furyl group in **5** with various groups as shown in Table 1. Since the phenyl compound **6a** exhibited a GCGR binding affinity similar to that of **5**, we next introduced a hydroxy group, as acidic moiety, at the phenyl group of **6a**. The obtained *para*-hydroxyphenyl compound **6b** showed a slight improvement in GCGR affinity, whereas the *meta*-hydroxyphenyl compound **6c** gave a loss in GCGR affinity. When the *para*-hydroxy group was masked with a methyl group, the resulting compound **6d** showed a complete loss of GCGR affinity. Regarding the other acidic group, benzoic acid **6e** showed a slight loss in GCGR affinity compared to the phenol **6b**. Introduction of two hydroxy groups (**6f**) resulted in no improvement in GCGR affinity. Remarkably, further improvement was seen with the hydroxypyridine **6g**, which showed a 10-fold IC_{50} value improvement compared to the hit compound **5**. Based on these results, it became clear that the pK_a values and GCGR affinity of compounds **6b**,**c**,**f**,**g** had similar variation. These findings suggested that an acidic proton at the *para*-position is needed for high GCGR affinity and that the acidity of the phenol group relates to GCGR affinity. However, a too strong acid such as benzoic acid **6e** would not exceptionally be well tolerated.

To confirm the relationship between the pK_a values and the affinity for GCGR, we screened substituents at the *meta*-position of the phenol shown as R^2 in Table 2 and calculated the pK_a values

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0960-894X/

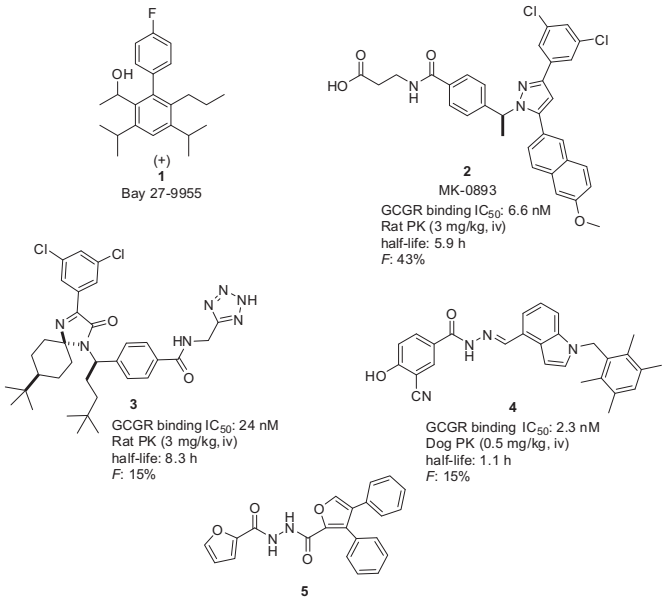


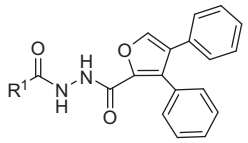
Figure 1. Representative chemotypes of GCGR antagonists and hit compound **5**.

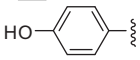
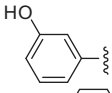
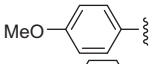
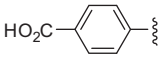
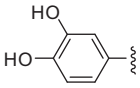
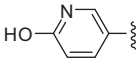
of the obtained compounds **6h–n**. The use of a fluoride (**6h**) resulted in a remarkable improvement in GCGR affinity with a pK_a value much lower than that of compound **6b**. Similarly, a chloride (**6i**) or a bromide (**6j**) led to improved GCGR affinity. Compounds possessing a strong electron withdrawing group, such as a trifluoromethyl group (**6k**) or a nitro group (**6l**) showed dramatically improved GCGR affinity, especially compound **6l** exhibited more than 100-fold improved affinity compared to the hit compound **5**. On the other hand, compounds with electron-donating groups, a methoxy (**6m**) or a phenyl group (**6n**) showed no improvement in GCGR affinity compared to **6b**. These findings confirmed our hypothesis as good correlation was observed between IC_{50} values and pK_a values (correlation coefficient: $r = 0.96$, from **6b** to **6n** in Table 2).

Next, the effects of a phenyl group at the 3- and 4-positions of the furan on GCGR affinity were investigated (Fig. 3). Surprisingly, despite the lack of a 4-phenyl group at the furan, compound **7a** exhibited almost the same GCGR affinity as compound **6l**. On the other hand, when the phenyl group at the 3-position of the furan was removed, GCGR affinity diminished (**8**, and **9**). Therefore, only the phenyl group at the 4-position of furan was removed from **6l** to decrease its molecular weight and lipophilicity.

Finally, we optimized the substituents at the *ortho*-, *meta*- or *para*-position of the phenyl ring (shown as R^3, R^4, R^5 in Table 3). The *para*-methyl compound **7d** exhibited high affinity compared to the *ortho*-isomer **7b** or the *meta*-isomer **7c**. As the *para*-substituent was critical for good affinity, we fixed a mono substituent at the *para*-position of the phenyl ring. The *para*-methoxy compound **7e** had weak GCGR affinity compared to the methyl compound **7d**.

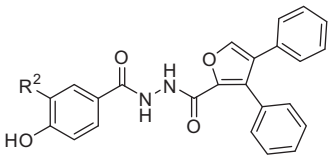
Table 1
SARs following modification of the furyl ring in **5**



Compound no.	R^1	GCGR binding[a,b] (%)	pK_a[c]
5		50	
6a		42	
6b		65	8.04
6c		21	8.52
6d		No inhibition	
6e		61	3.14
6f		57	7.96
6g		IC_{50} = 0.97 μM	7.83

[a] Activities are shown as the percent inhibition at 10 μM in rat hepatocytes.
[b] The assay was performed in duplicate ($n = 2$).
[c] Predicted using ADMET Predictor (SimulationsPlus, Lancaster, CA, USA).

Table 2
SARs following *meta*-substitution at the phenyl ring



Compound no.	R^2	GCGR binding IC_{50}[a] (μM)	pK_a[b]
6b	H	9.5	8.04
6h	F	1.4	6.41
6i	Cl	0.43	6.71
6j	Br	0.27	6.78
6k	CF_3	0.16	6.11
6l	NO_2	0.087	6.21
6m	MeO	9.5	8.02
6n	Ph	>10	8.08

[a] The assay was performed in duplicate using rat hepatocytes ($n = 2$).
[b] Predicted using ADMET Predictor (SimulationsPlus, Lancaster, CA, USA).

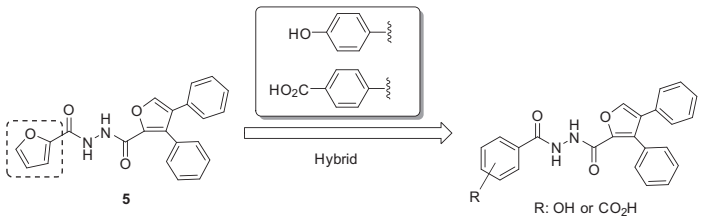


Figure 2. Strategy for hit to lead generation.