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Design, synthesis, structure–activity relationships, and docking studies of pyrazole-containing derivatives as a novel series of potent glucagon receptor antagonists

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ABSTRACT

Glucagon receptor antagonists possess a great potential for treatment of type 2 diabetes mellitus. A series of pyrazole-containing derivatives were designed, synthesized and evaluated by biological assays as glucagon receptor antagonists. Most of the compounds exhibited good in vitro efficacy. Two of them, compounds **17f** and **17k**, displayed relatively potent antagonist effects on glucagon receptors with IC_{50} values of 3.9 and 3.6 μM, respectively. The possible binding modes of **17f** and **17k** with the cognate receptor were explored by molecular docking simulation.

1. Introduction

Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder characterized by fasting hyperglycemia consequential to dysfunction of pancreatic β-cells coupled with elevated insulin resistance and reduced insulin secretion, is affecting approximately 415 million people in 2015.[1] According to International Diabetes Federation (IDF), the estimated number of people suffering from diabetes will rise to 642 million in less than 25 years.[2] Despite many potential drug targets are continuously pursued and multiple therapeutic strategies exist for the treatment of T2DM, there is still a significant need for additional anti-diabetic agents to improve safety and efficacy.[3–6] In recent years, activation of glucagon-like peptide-1 receptor (GLP-1R) and inhibition of dipeptidyl peptidase-4 (DPP-4) to stimulate insulin secretion[7] and inhibition of sodium-glucose cotransporter-2 (SGLT-2) to regulate glucose reabsorption[8] have gained prominence in the management of T2DM, while glucagon receptor as drug target appeared to be less attractive.

Glucagon is a polypeptide hormone consisting of 29 amino acids that counteracts the action of insulin[9–13] and binds to glucagon receptor (GCGR) to trigger two transduction cascade signals resulting in stimulation of hepatic glucose production.[14–18] In patients with T2DM, inappropriately elevated glucagon levels lead to excessive hepatic glucose output, which is the main contributing factor to hyperglycemia. Therefore, blockage of glucagon-induced hyperglycemia by means of GCGR antagonism is theoretically prudent to treat T2DM.[19–25] Previous studies have validated this approach using glucagon-specific antibodies as well as peptidic and non-peptidic GCGR antagonists in animal models of diabetes.[22,25] Recently, a number of publications have claimed several chemical scaffolds as GCGR antagonists.[26–32] The biaryl containing compound **BAY-27-9955**[21] (Fig. 1) was the first active agent shown to decrease glucose output upon the administration of exogenous glucagon. Compounds **MK-3577**[33] and **MK-0893**[34,35] (Fig. 1) with β-alanine acid motif were discontinued in phase II clinical trials for treating T2DM.

In this paper, we adopted bioisosteric and conformational restraint strategies to synthesize a series of novel pyrazole-containing derivatives based on the structure of **MK-0893**. These compounds exhibited sound GCGR binding affinities and cAMP responses. Follow-up design, synthesis, structure–activity relationship (SAR) and docking studies report our efforts toward a novel series of GCGR antagonists.

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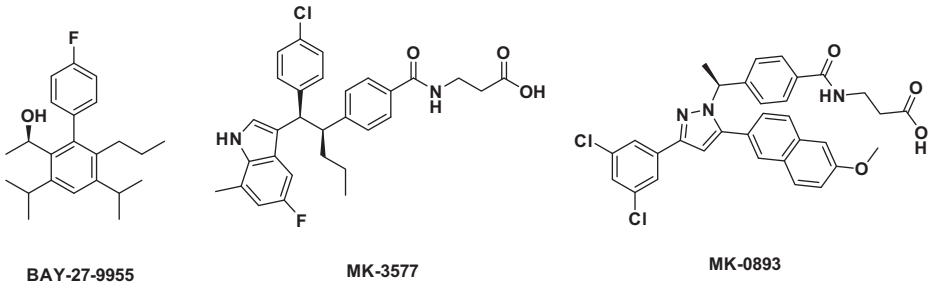


Figure 1. Structures of **BAY-27-9955**, **MK-3577** and **MK-0893**.

2. Materials and methods

2.1. Molecular design

In 2013, Fai *et al.* reported the crystal structure of the seven-transmembrane helical domain of human GCGR.[36] Comparison of the ligand-binding pocket of GCGR with that of class A GPCRs shows that GCGR has a larger binding cavity, and glucagon is capable of inducing this domain to the active state.[37] The crystal structure of GCGR (PDB ID: 4l6r) and Glide program were used for docking to study the interactions between GCGR and **MK-0893**.[38] The modeling results indicated that **MK-0893** occupied the S1 and S2 pockets and formed two hydrogen bonds in hydrogen binding districts (HB) with GCGR (Fig. 2A). In the well-defined hydrophobic S1 pocket, the 6-methoxy-2-naphthalenyl ring of **MK-0893** formed extensive hydrophobic interactions with residues Tyr149, Asp195, Ile194, Met231 and Gln232. In the S2 pocket, the 3,4-dichloro-phenyl ring formed hydrophobic interactions with residues Leu307, Val311, Tyr239, Ile235, Glu362 and Gln392. The 6-methoxy-2-naphthalenyl ring and two phenyl rings in the **MK-0893** are stacked against the side chain of Trp295 and Phe365. Moreover, 6-methoxyl and β-alanine carboxylic acid of **MK-0893** appear to form hydrogen bonds with Tyr149 and Lys381, respectively, which may account for the excellent antagonistic activity. However, the cavity formed by residues Gln232, Leu307 and Arg308 is a large pocket suggesting that introduction of steric hindrance on **MK-0893** may gain better antagonistic activity (Fig. 2B). To verify this hypothesis, we replaced β-alanine acid as substituted and cyclic β-alanine acid to obtain compound **9** (Fig. 3). Since conformational restraint is an established strategy to improve binding potency to GCGR,[39] we introduced an indane motif to obtain compound **17** (Fig. 3). A series of pyrazole-containing derivatives were subsequently synthesized and evaluated.

2.2. Chemical synthesis

The synthetic route of compound **9** was shown in Scheme 1. Briefly, esterification of commercially available compound **1** easily afforded **2**, which was subsequently transformed to compound **3** by reaction with *tert*-butyl carbazate and then reduced by sodium cyanoborohydride. Deprotection of compound **3** provided hydrazine **4**, which was smoothly reacted with ethyl 3-(3,5-dichlorophenyl)-3-oxopropanoate **5** to afford compound **6**. Triflate **7** was generated using trifluoromethanesulfonic anhydride (Tf_2O) and experienced a classical Suzuki coupling reaction with different boric acid (Z-$B(OH)_2$) to provide compound **8**. Compound **9** was then generated by hydrolysis of compound **8**, condensation with substituted 3-aminopropanoate and hydrolysis of ester.

The synthesis of compound **17** was shown in Scheme 2. Esterification of commercially available compound **10** easily afforded compound **11**, which was subsequently transformed to compound **12** by reaction with *tert*-butyl carbazate and then reduced by sodium cyanoborohydride. Deprotection of compound **12** provided hydrazine **13**, which was smoothly reacted with ethyl 3-(3,5-dichlorophenyl)-3-oxopropanoate **5** to afford compound **14**. Triflate **15** was generated using trifluoromethanesulfonic anhydride (Tf_2O) and experienced a classical Suzuki coupling reaction with boric acid (R_2-$B(OH)_2$) to provide pyrazoles **16**. Compound **17** was then generated by hydrolysis of **16**, condensation with β-alanine *tert*-butyl ester and removing of *tert*-butyl ester.

3. Results and discussion

All the synthesized compounds were evaluated for antagonism of human GCGR and the cAMP response in vitro. Antagonistic potency was measured by a competitive binding assay with *rac*-**MK-0893** as the positive control, and the results are reported as

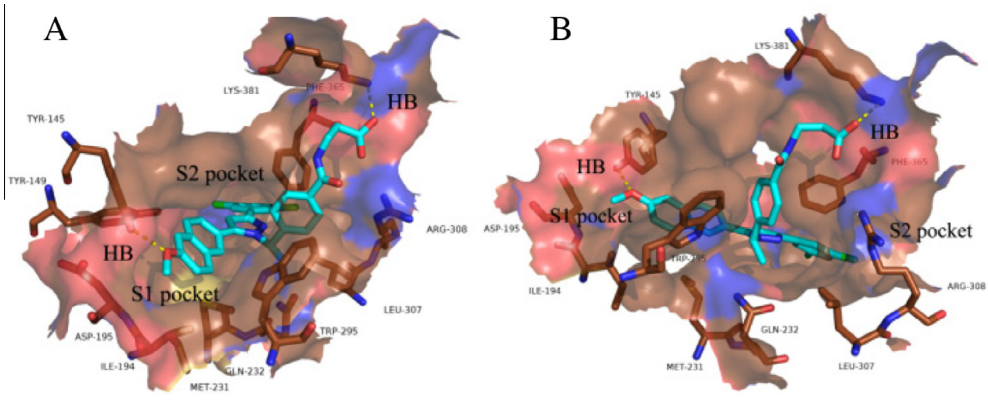


Figure 2. Docking study of **MK-0893**. All figures were prepared using PyMol (http://www.pymol.org).

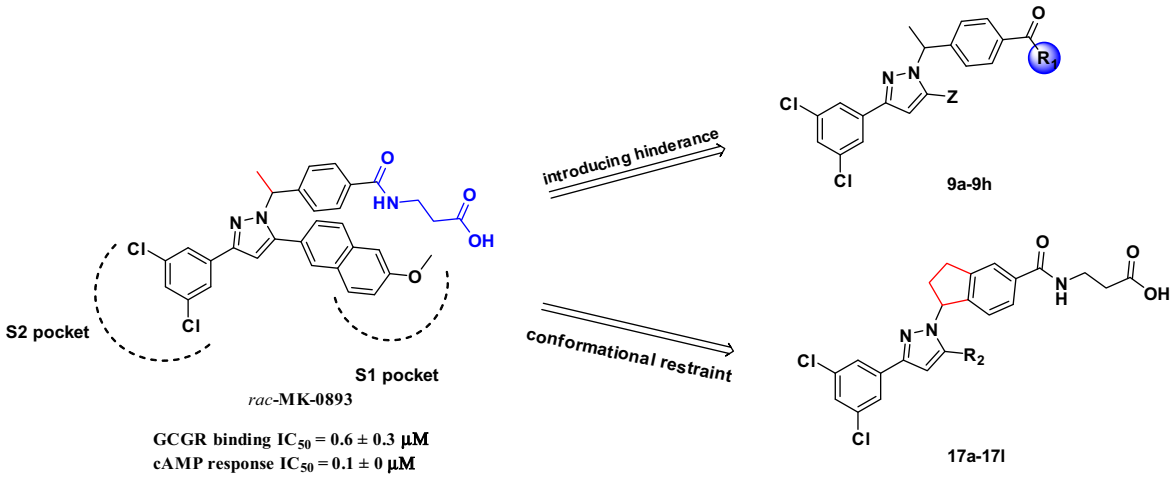
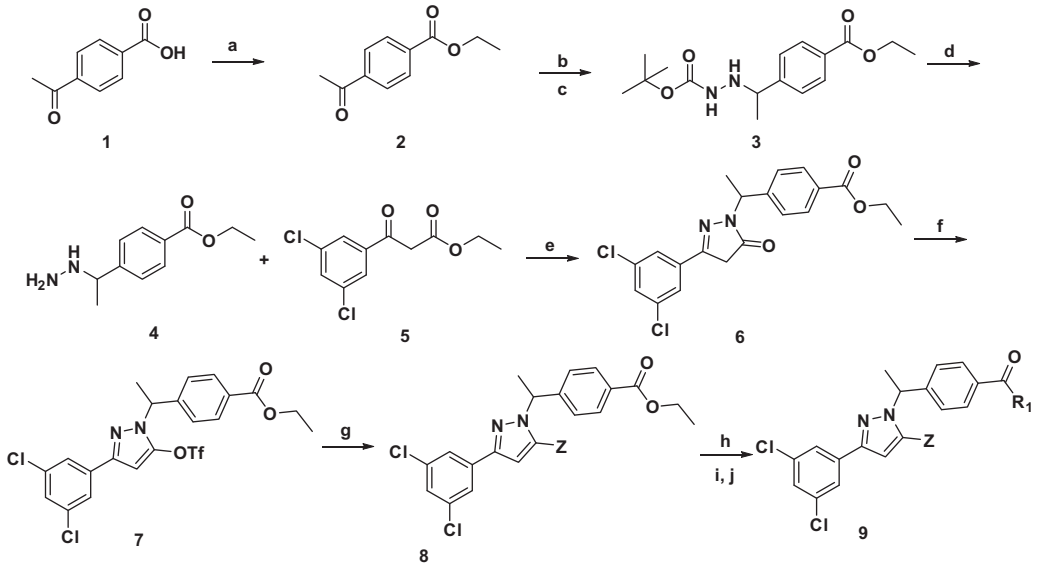


Figure 3. Design of novel GCGR antagonists **9** and **17**.

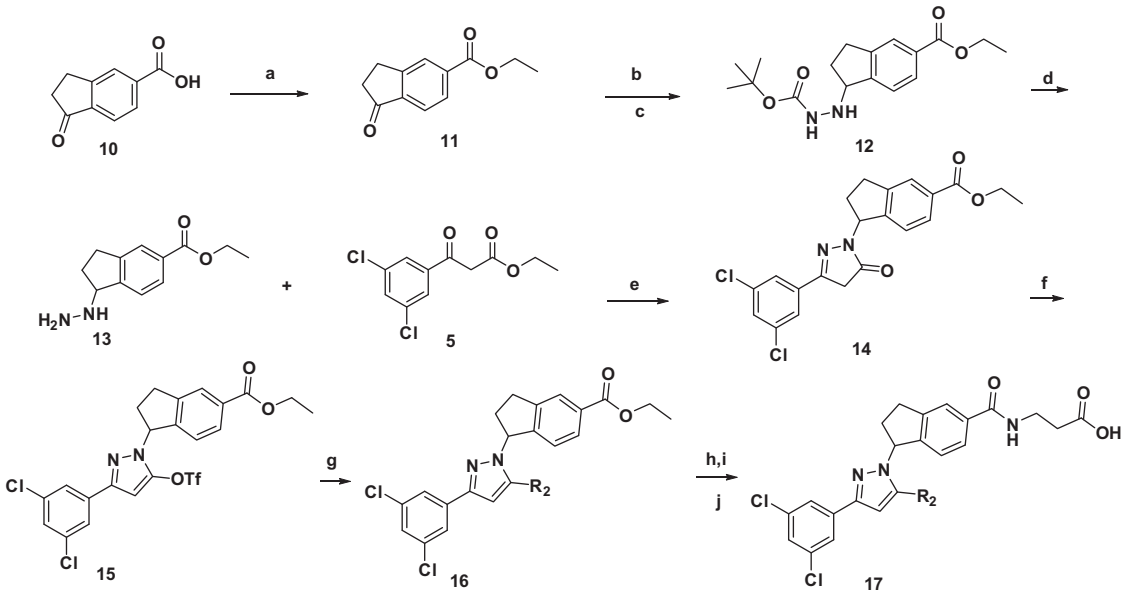


Scheme 1. Reagents and conditions: (a) EtOH, H_2SO_4, reflux, 3 h; (b) *cat.* HOAc, toluene, 80 °C, overnight; (c) $NaBH_3CN$, *p*-toluene sulfonic acid, THF, rt, 3 h; (d) TFA, DCM, rt, 1 h; (e) HOAc, reflux, 4 h; (f) Tf_2O, TEA, THF, −78 °C, 3 h; (g) Z-$B(OH)_2$, $Pd(PPh_3)_4$, TEA, DME, 85 °C, 2 h; (h) NaOH, MeOH, 1,4-dioxane, 60 °C, 1 h; (i) substituted 3-aminopropanoate, PyBOP, DIEA, DMF, rt, overnight; (j) NaOH, MeOH, 1,4-dioxane, 60 °C, 1 h.

concentration for 50% inhibition (IC_{50}). SAR for these compounds is summarized in Tables 1 and 2.

Firstly, we focus on the important pharmacophore Z with 3-aminobutanoic acid (Table 1). Compound **9c** containing 6-methoxynaphthalen-2-yl was able to bind GCGR (IC_{50} = 20.2 μM) and elicit cAMP responses (IC_{50} = 1.9 μM). Compared with 6-methoxynaphthalen-2-yl (**9c**), the 4-*tert*-butylphenyl (**9a**) and 2,3-dihydrobenzofuran-5-yl (**9b**) groups were not preferred for Z in the pyrazole series. Substituent of methyl at the α-position of β-amino acid (**9e**) exhibited better binding (IC_{50} = 8.4 μM) and cAMP activities (IC_{50} = 1.6 μM) than that of methyl (**9c**) and phenyl (**9d**) at the β-position. Cyclic amino acid substitution was also investigated and the six-membered heterocyclic amino acid substitution (**9g** and **9h**) showed better binding affinity than the five-membered heterocyclic amino acid (**9f**). In addition, the cAMP response of **9h** (IC_{50} = 4.5 μM) was better than that of **9f** and **9g** (IC_{50} = 6.9 μM and 26.5 μM, respectively). The compounds containing methyl substitution on β-amino acid induced better cAMP responses than those substituted by phenyl and heterocyclic amino acids. Compound **9e** thus appeared to be a potent GCGR antagonist. However, the activities of all the compounds in this series were poorer than *rac*-**MK-0893**, implying that the steric effect of β-alanine acid might have significantly reduced their antagonistic activity on GCGR.

Next, multiple substituents were introduced to understand the effect of conformational restraint (Table 2). By introducing large alkoxyl groups, compounds **17a** and **17b** were synthesized first and showed lower potencies as compared with *rac*-**MK-0893**. Compound **17a** showed better GCGR binding activity (IC_{50} = 5.7 μM) and cAMP response (IC_{50} = 1.2 μM) than compound **17b**. According to the results of **17a** and **17b**, we investigated the substitutions on phenyl ring by non-substitution and introduction of methyl group to make compounds **17c** and **17d** but both displayed low potency. However, **17c** exhibited a better cAMP response (IC_{50} = 3.5 μM) than **17d** (IC_{50} = 6.9 μM). Compound **17f** containing chloro-substituted at the *meta*-position of the phenyl ring demonstrated good GCGR binding (IC_{50} = 3.9 μM) and cAMP (IC_{50} = 1.4 μM) activities, while a fluoro-substituted (**17e**) was less active for GCGR binding



Scheme 2. Reagents and conditions: (a) EtOH, H_2SO_4, reflux, 4 h; (b) *cat.* HOAc, toluene, 80 °C, overnight; (c) $NaBH_3CN$, *p*-toluene sulfonic acid, THF, rt, 3 h; (d) TFA, DCM, rt, 2 h; (e) HOAc, reflux, 4 h; (f) Tf_2O, TEA, THF, −78 °C to rt, 1.5 h; (g) R_2-$B(OH)_2$, $Pd(PPh_3)_4$, TEA, DME, microwave, 100 °C, 25 min; (h) NaOH, MeOH, 1,4-dioxane, 60 °C, 1 h; (i) β-alanine *tert*-butyl ester, PyBOP, DIEA, rt, overnight; (j) TFA, DCM, rt, 1 h.

(IC_{50} = 8.9 μM) and displayed an equivalent cAMP response (IC_{50} = 1.4 μM) as **17f**. In addition, heterocyclic ring substituted compounds **17g** and **17h** were also studied and showed poor binding activity (IC_{50} = 71.8 μM and 14.5 μM, respectively). Meanwhile, it was observed that (1) thiophene-substitution (**17h**) was somewhat more favored than furan-substitution (**17g**) in the pyrazole scaffold; (2) naphthyl ring especially naphthyl-2-yl ring (**17k**) possessed good binding (IC_{50} = 3.6 μM) and cAMP (IC_{50} = 1.2 μM) activities, while 6-methoxy-substitution (**17l**) on the naphthyl ring modestly reduced the activity (Table 2). Like **9a**–**9h**, this series of compounds did not improve the bioactivity beyond that of *rac*-**MK-0893**, suggesting that the conformational restraint had a negative impact on GCGR antagonism.

Structures of all synthesized pyrazole-derivatives were docked against the binding domain of human GCGR to investigate the binding modes and gain insights into the interactions between these compounds and the receptor.

Docking results of compounds **17f** and **17k** indicated that these two compounds occupied the S1 and S2 pockets and showed binding modes similar to **MK-0893** (Fig. 4). They also formed extensive hydrophobic interactions in S1 pocket with residues Tyr145, Ile194, Met231 and Gln232. In S2 pocket, they both formed hydrophobic interactions with residues Leu307, Glu362 and Gln392.

The observable differences in the binding site originate from the interactions between different residues and moieties. Compared to the methyl group in **MK-0893**, the indane ring of compounds **17f** (Fig. 4A) and **17k** (Fig. 4B) is a relatively big group which may result in change of the direction of β-alanine carboxylic acid group and finally form a hydrogen bond with residue Arg308 leading to dramatic decrease of potential hydrophobic interactions. In addition, the three aryl rings heading for three directions in the **MK-0893** are all stacked against the side chain of Trp295 and Phe365, however, only one π–π stacking interaction remained with residue Trp295 was observed in compounds **17f** and **17k**. This may be the main reason why all the compounds of this series were not as potent as **MK-0893**. Therefore, we propose that the modification of **MK-0893** should take flexibility of introducing group at benzyl position into consideration. Furthermore, for other GCGR modulators, the hydrogen binding district is a promising pocket for in-depth investigation.

4. Conclusions

In conclusion, we designed, synthesized and evaluated a series of pyrazole derivatives as novel GCGR antagonists. SAR studies have identified compounds **17f**, **17k** and **17l** as potential candidates for further development. Among these, compound **17k** was found to display comparatively better GCGR antagonistic binding activity with an IC_{50} value of 3.6 μM. Molecular modeling demonstrated that this series of compounds occupied the large binding cavity of GCGR in three directions.

5. Experimental section

5.1. Biological evaluation

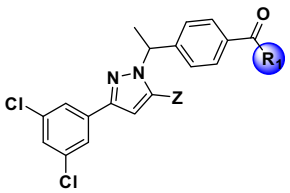
5.1.1. Construction of GCGR vector

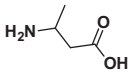
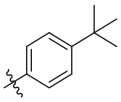
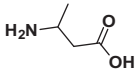
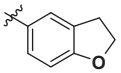
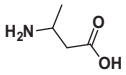
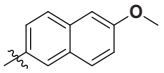
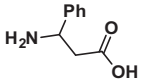
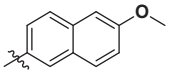
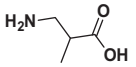
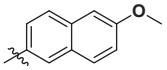
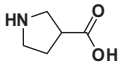
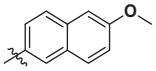
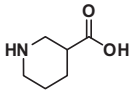
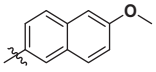
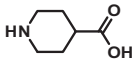
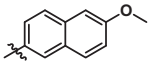
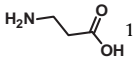
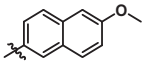
The wild-type human GCGR was cloned into the EcoRI and HindIII sites of the pcDNA3.1/V5-His-TOPO vector (Invitrogen, Carlsbad, CA, USA). Sequences of receptor clones were confirmed by sequencing with ABI 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA).

5.1.2. Binding assay

The whole cell binding was conducted according to previously reported method.[36] Briefly, cells were harvested 24 h after transfections with GCGR and incubated with blocking buffer (F12 supplemented with 33 mM HEPES and 0.1% bovine serum albumin (BSA), pH 7.4) for 2 h. Then the binding assay were performed by incubating the cells with constant concentration of [^{125}I]-glucagon (40 pM, PerkinElmer, Boston, MA, USA) and different concentrations of unlabeled compounds (1.28 nM–100 μM) at room temperature for 3 h. After washing cells with ice-cold PBS for three times, the cells were subsequently lysed and counted for radioactivity (counts per minute, CPM) in a scintillation counter (MicroBeta^2 Plate Counter, PerkinElmer) using a scintillation cocktail (OptiPhase SuperMix, PerkinElmer).

Table 1
In vitro GCGR binding and functional cAMP activities of compounds **9a**–**9h**



Compd	R_1	Z	GCGR binding[a] IC_{50} (μM)	cAMP response[a] IC_{50} (μM)
9a			41.0 ± 6.3	6.3 ± 0.9
9b			18.1 ± 4.7	13.0 ± 1.9
9c			20.2 ± 5.1	1.9 ± 0.4
9d			NA[c]	20.8 ± 3.8
9e			8.4 ± 1.5	1.6 ± 0.4
9f			131.1 ± 49.9	6.9 ± 1.2
9g			112.2 ± 55.1	26.5 ± 1.5
9h			41.7 ± 2.1	4.5 ± 1.1
rac-**MK-0893**	 1		0.6 ± 0.3	0.1 ± 0[b]

[a] Activities are reported as means ± SEM ($N \geqslant 3$).
[b] SEM < 0.05.
[c] NA: not active.

5.1.3. cAMP assays

cAMP accumulation was measured using HTRF-cAMP dynamic kit (Cisbio International, Gif sur Yvette Cedex, France) according to manufacturer's instructions and previous literature.[40] Briefly, HEK293T cells were transfected with GCGR. Cells were then transferred to 384-well plates at a density of 3000 cells per well and incubated for a further 24 h at 37 °C. After incubation for 30 min in assay buffer (DMEM, 1 mM 3-isobutyl-1-methylxanthine) with 1 nM glucagon and different concentration of compounds at 37 °C, the reactions were stopped by addition of lysis buffer containing HTRF reagents. Plates were then incubated for 60 min at room temperature, and time-resolved FRET signals were measured after excitation at 620 nm and 650 nm by EnVision (PerkinElmer).

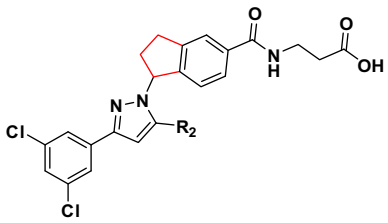
5.2. Molecular docking

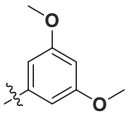
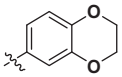
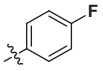
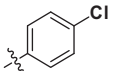
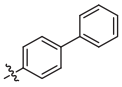
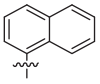
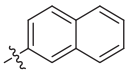
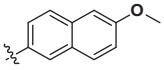
The Glide program from Schrödinger Suite[41] was employed for the docking simulation. The receptor protein was selected and downloaded from worldwide Data Bank (PDB ID: 4l6r), which was then imported, optimized and minimized to add hydrogen and to delete unwanted molecules using protein preparation wizard.[42] The receptor grid was sized to 15 Å in each direction and centered using Centroid of selected residues (Specify Met231 as center residue). All compounds were minimized by OPLS2001 force field to generate low energy 3D structure using LigPrep under its default parameters. Docking studies were carried out using Glide in standard precision mode, with up to 40 conformers saved per molecule. Glide score was obtained to assess the most favorable ligand and its conformer, which was then exported to a Maestro-formatted output file.

5.3. Synthesis

All commercially available compounds and solvents were used without further purification. All target products were characterized by their NMR and MS spectra. ^{1}H spectra were recorded in deuterochloroform ($CDCl_3$) and dimethylsulfoxid-d6 (DMSO-d_6) on 400 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on a spectrometer. All compounds (exclude compound **17f**) were confirmed with over 95% purity which were determined by Agilent-1100 HPLC with binary pump, photodiode array detector (DAD), using Agilent Extend-C18 column (150 × 4.6 mm, 5 μm). Compound **17f** was

Table 2
In vitro GCGR binding and functional cAMP activities of compounds **17a–17l**



Compd	R_2	GCGR binding[a] IC_{50} (μM)	cAMP response[a] IC_{50} (μM)
17a		5.7 ± 1.2	1.2 ± 0.2
17b		31.9 ± 7.7	6.3 ± 0.7
17c		11.1 ± 1.3	3.5 ± 0.5
17d		14.5 ± 2.3	6.9 ± 1.3
17e		8.9 ± 1.1	1.4 ± 0.3
17f		3.9 ± 0.3	1.4 ± 0.5
17g		71.8 ± 16.5	10.8 ± 0.9
17h		14.5 ± 0.3	5.3 ± 1.7
17i		12.7 ± 3.9	2.6 ± 0.6
17j		5.9 ± 1.4	2.1 ± 0.8
17k		3.6 ± 0.5	1.2 ± 0.3
17l		4.7 ± 0.7	1.5 ± 0.5
rac-**MK-0893**		0.6 ± 0.3	0.1 ± 0[b]

[a] Activities are reported as means ± SEM ($N \geqslant 3$).
[b] SEM < 0.05.

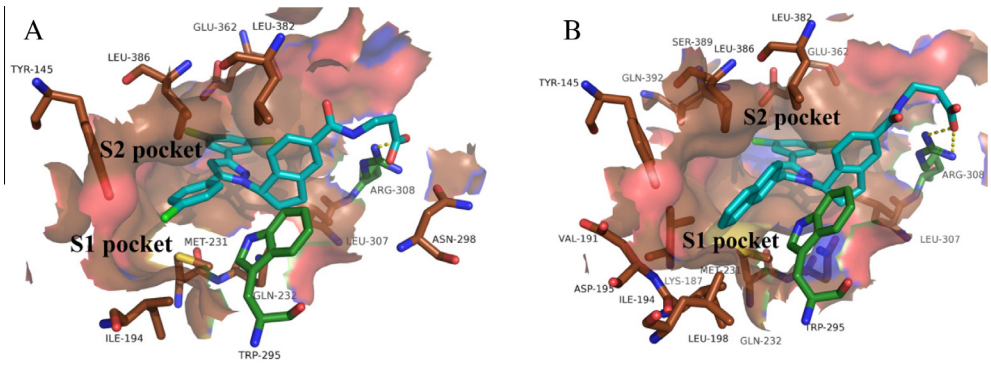


Figure 4. Docking structures of compounds **17f** (A) and **17k** (B).

analyzed by Agilent Eclipse XDB-C18 column (150 × 4.6 mm, 5 μm), using CH_3CN/H_2O = 70:30 (v/v) (7 min, 1 mL/min), then CH_3CN/H_2O = 85:15 (v/v) (5 min, 1 mL/min) and calculated the peak areas at 254 nM. Compounds **9a**–**9h** were analyzed using CH_3CN/H_2O = 85:15 (v/v) at 1 mL/min and calculated the peak areas at 254 nM. Compounds **17a**–**e**, **17g**–**l** were analyzed using CH_3CN/H_2O = 65:35 (v/v) at 1 mL/min and calculated the peak areas at 254 nM.

5.3.1. General procedure for the preparation of compound 9

5.3.1.1. Ethyl 4-acetylbenzoate (2). A solution of 4-acetylbenzoic acid (10 g, 60.9 mmol) in ethanol (100 mL) was stirred in ice bath. After H_2SO_4 was slowly added, the mixture was refluxed at 80 °C for 3 h. The mixture was extracted with EtOAc, washed with saturated brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography to afford ethyl 4-acetylbenzoate as a white solid (10 g, 85.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.09 (m, 2H), 7.99 (dt, J = 6.7, 1.0 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). MS (ESI, m/z): 193.1 $[M+H]^+$.

5.3.1.2. *tert*-Butyl 2-{1-[4-(ethoxycarbonyl)-phenyl]ethyl} hydrazine carboxylate (3). A solution of *tert*-butyl carbazate (5.5 g, 41.6 mmol) and ethyl 4-acetylbenzoate (10 g, 52.0 mmol) in toluene (60 mL) with catalytic HOAc was stirred at 80 °C overnight. *tert*-Butyl-2-{1-[4-(ethoxycarbonyl)phenyl]-ethylidene}hydrazine carboxylate separated as a crystalline solid (10 g, 65.7%) and was collected by filtration. $NaBH_3CN$ (2.4 g, 38.2 mmol) and *tert*-butyl 2-{1-[4-(ethoxycarbonyl)phenyl]ethylidene}-hydrazinecarboxylate (10 g, 32.6 mmol) were dissolved in THF (100 mL). A solution of *p*-toluene sulfonic acid (4.3 g, 22.6 mmol) in THF (25 mL) was slowly added. After stirring the reaction for 3 h, the mixture was extracted with EtOAc and washed with brine, dried (Na_2SO_4), and concentrated to give a white solid. The solid was separated and washed with 1 N HCl twice and brine twice, dried (Na_2SO_4), and concentrated. Product precipitated as white solid and was washed with petroleum ether/ethyl acetate (4:1) to yield 5.6 g (55.6%) of *tert*-butyl 2-{1-[4-(ethoxycarbonyl)-phenyl]ethyl}hydrazine carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.22 (d, J = 6.4 Hz, 1H), 1.41 (d, J = 2.7 Hz, 9H), 1.38 (d, J = 7.1 Hz, 3H), 1.35 (d, J = 6.6 Hz, 3H). MS (ESI, m/z): 307.1 $[M-H]^-$.

5.3.1.3. {1-[4-(Ethoxycarbonyl)phenyl]ethyl}hydrazinium-trifluoroacetate (4). A solution of *tert*-butyl 2-{1-[4-(ethoxycarbonyl)-phenyl]ethyl}hydrazine carboxylate in DCM (10 mL) was treated with TFA (10 mL) at room temperature for 1 h. The mixture was concentrated under reduced pressure without further purification. MS (ESI, m/z): 209.0 $[M+H]^+$.

5.3.1.4. 3-(3,5-Dichlorophenyl)-3-oxopropanoate (5). Ethyl 3,5-dichlorobenzoate (5 g, 22.8 mmol) and sodium hydride (1.10 g, 27.4 mmol) were dissolved in 35 mL THF under N_2. Then the solution was added 7.8 mL ethyl acetate slowly at room temperature and refluxed overnight. The solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Flash column chromatography gave 5.5 g (92%) of 3-(3,5-dichlorophenyl)-3-oxopropanoate **5** as orange oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98–7.91 (m, 3H), 4.27 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). MS (ESI, m/z): 262.0 $[M+H]^+$.

5.3.1.5. Ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]ethyl}benzoate (6). A solution of compound **5** (3.0 g, 11.6 mmol) and {1-[4-(ethoxycarbonyl)phenyl]ethyl} hydrazinium trifluoroacetate (2.2 g, 10.6 mmol) was refluxed in HOAc (80 mL) for 4 h. The solvent was removed under reduced pressure and the residue taken up with ethyl acetate, washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Flash column chromatography gave 2.6 g (60.7%) of ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]ethyl}benzoate as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 2H), 7.51 (dd, J = 10.4, 5.0 Hz, 4H), 7.38 (dd, J = 4.8, 3.0 Hz, 1H), 5.56 (q, J = 7.1 Hz, 1H), 4.40–4.32 (m, 2H), 3.66–3.50 (m, 2H), 1.78 (d, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H). MS (ESI, m/z): 404.8 $[M+H]^+$.

5.3.1.6. Ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-{[(trifluoromethyl)-sulfonyl]oxy}-1*H*-pyrazol-1-yl]ethyl}benzoate (7). Ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl] ethyl}benzoate (2.6 g, 6.4 mmol) and TEA (1.9 g, 19.2 mmol) were dissolved in THF (100 mL) at −78 °C. Triflic anhydride (2.7 g, 9.6 mmol) was added. The reaction mixture was stirred for 3 h. The reaction was quenched by adding ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrazol-1-yl]ethyl}benzoate (2.5 g, 72.5%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 2H), 7.70–7.66 (m, 2H), 7.40–7.33 (m, 3H), 6.43 (s, 1H), 5.55 (q, J = 7.1 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.98 (d, J = 7.0 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H). MS (ESI, m/z): 536.3 $[M-H]^-$.

5.3.1.7. 4-{1-[3-(3,5-Dichlorophenyl)-5-[4-(*tert*-butyl)phenyl]-1*H*-pyrazol-1-yl]ethyl}benzoate (8). Ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrazol-1-yl]ethyl}benzoate (1.0 g, 1.9 mmol), 4-(*tert*-butyl)phenyl boronic acid (430.9 mg, 2.4 mmol), and TEA (1.0 g, 10.2 mmol) were dissolved in dimethoxyethane. The catalyst $Pd(PPh_3)_4$ (129.2 mg, 0.1 mmol) was added, and the mixture was deoxygenated before refluxed in 85 °C for 2 h. The mixture was extracted with EtOAc, washed with saturated brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography to afford ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-[4-(*tert*-butyl)phenyl]-1*H*-pyrazol-1-yl] ethyl}benzoate as a colorless oil (632.8 mg, 65.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.77 (t, J = 3.0 Hz, 2H), 7.48–7.40 (m, 2H), 7.31–7.24 (m, 3H), 7.22–7.16 (m, 2H), 6.56 (d, J = 4.1 Hz, 1H), 5.58 (q, J = 6.9 Hz, 1H), 4.41–4.32 (m, 2H), 1.95 (d, J = 7.0 Hz, 3H), 1.41–1.34 (m, 12H). MS (ESI, m/z): 518.8 $[M-H]^-$.

5.3.1.8. 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-[4-(*tert*-butyl)phenyl]-1*H*-pyrazol-1-yl]ethyl}-benzamido]butanoic acid (9a). Ethyl 4-{1-[3-(3,5-dichlorophenyl)-5-[4-(*tert*-butyl)phenyl]-1*H*-pyrazol-1-yl]ethyl}benzoate (632.8 mg, 1.2 mmol) was dissolved in MeOH–dioxane (1:1). A solution of NaOH (0.7 g/15 mL) was added. The mixture was heated to 60 °C for 1 h. This was acidified with 1 N HCl, extracted with EtOAc, washed with saturated brine, dried (Na_2SO_4), and concentrated to give a yellow solid. This solid was suspended in DMF, followed with addition of DIEA (2.4 mL), methyl 3-aminobutanoate (569.6 mg, 4.9 mmol). A solution of benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP) (760.0 mg, 1.5 mmol) in DMF was then added. After stirring at room temperature for 3 h, more PyBOP (380.0 mg, 0.75 mmol) was added, and the reaction mixture was stirred overnight. After addition of water (5 mL), the mixture was heated to 60 °C for 30 min. Ethyl acetate was added, and the organic layer was washed with 0.5 N HCl twice, 5% K_2CO_3 twice, and brine twice. Evaporation of solvent gave an oily residue. The oily residue was dissolved in MeOH–dioxane (1:1). A solution of NaOH (0.7 g/15 mL) was added. The mixture was heated to 60 °C for 1 h. This was acidified with 1 N HCl, extracted with EtOAc, washed with saturated brine, dried (Na_2SO_4), and concentrated to give a yellow solid, which after flash column

chromatography afforded 526.5 mg (75.0%) of 3-[4-{1-[3-(3,5-dichlorophenyl)-5-[4-(*tert*-butyl)phenyl]-1*H*-pyrazol-1-yl]ethyl}-benzamido]butanoic acid as a white solid. Mp 112–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 17.5, 4.9 Hz, 4H), 7.43 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 1.9 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 5.56 (d, J = 7.0 Hz, 1H), 4.55 (s, 1H), 2.68 (s, 2H), 1.92 (d, J = 6.9 Hz, 3H), 1.35 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 151.7, 147.7, 145.9, 145.2, 136.2, 134.6, 132.9, 128.3, 126.9, 126.8, 126.6, 126.1, 125.2, 123.5, 103.2, 57.1, 41.9, 39.2, 34.3, 30.8, 21.8, 19.5. LRMS (ESI, m/z): 578.0 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{32}H_{34}O_3N_3Cl_2$, 578.1972 $[M+H]^+$; found 578.1961, purity: 97.3%.

5.3.1.9. 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(2,3-dihydrobenzofuran-5-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]butanoic acid (9b). 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(2,3-dihydrobenzofuran-5-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]butanoic acid (**9b**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 21.0, 5.1 Hz, 4H), 7.27 (t, J = 1.9 Hz, 1H), 7.24 (s, 1H), 7.04 (s, 1H), 7.00–6.93 (m, 1H), 6.82–6.74 (m, 2H), 6.51 (s, 1H), 5.51 (q, J = 6.9 Hz, 1H), 4.63 (t, J = 8.7 Hz, 2H), 4.54 (d, J = 6.8 Hz, 1H), 3.20 (dd, J = 20.7, 12.1 Hz, 2H), 2.70–2.64 (m, 2H), 1.91 (d, J = 7.0 Hz, 3H), 1.34 (dd, J = 6.8, 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.0, 160.4, 147.5, 145.8, 145.4, 136.1, 134.6, 132.9, 128.8, 127.3, 126.8, 126.1, 125.4, 123.5, 121.6, 109.0, 103.3, 71.1, 57.1, 41.8, 39.0, 29.0, 21.7, 19.6. LRMS (ESI, m/z): 564.1 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{30}H_{28}O_4N_3Cl_2$, 564.1451 $[M+H]^+$; found 564.1455, purity: 98.0%.

5.3.1.10. 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]butanoic acid (9c). 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]butanoic acid (**9c**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.58 (m, 7H), 7.30 (s, 1H), 7.25–7.12 (m, 4H), 6.84–6.54 (m, 2H), 5.58 (s, 1H), 4.55 (s, 1H), 3.95 (d, J = 8.9 Hz, 3H), 2.65 (s, 2H), 2.03–1.79 (m, 3H), 1.41–1.28 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 166.1, 158.1, 147.7, 145.8, 145.4, 136.1, 134.7, 134.0, 133.0, 129.2, 127.9, 126.9, 126.8, 126.4, 126.1, 124.5, 123.6, 119.4, 105.2, 103.6, 57.5, 54.9, 41.8, 39.0, 21.8, 19.5. LRMS (ESI, m/z): 602.1 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{33}H_{30}O_4N_3Cl_2$, 602.1608 $[M+H]^+$; found 602.1600, purity: 97.5%.

5.3.1.11. 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]-3-phenylpropanoic acid (9d). 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}benzamido]-3-phenylpropanoic acid (**9d**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.60 (m, 8H), 7.30 (d, J = 15.7 Hz, 7H), 7.21–7.13 (m, 3H), 6.63 (s, 1H), 5.60 (dd, J = 14.3, 7.3 Hz, 2H), 3.94 (s, 3H), 3.13–2.88 (m, 2H), 1.93 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 166.5, 158.6, 148.2, 146.5, 145.9, 140.1, 136.5, 135.2, 134.5, 133.2, 129.7, 128.9, 128.4, 127.9, 127.5, 127.4, 127.3, 126.9, 126.7, 126.3, 125.0, 124.1, 119.9, 105.7, 104.1, 58.0, 55.5, 49.8, 39.3, 22.3. LRMS (ESI, m/z): 664.0 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{38}H_{32}O_4N_3Cl_2$, 664.1764 $[M+H]^+$; found 664.1758, purity: 98.4%.

5.3.1.12. 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]-2-methylpropanoic acid (9e). 3-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzamido]-2-methylpropanoic acid (**9e**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 131–133 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 7.96–7.78 (m, 4H), 7.72 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 1.8 Hz, 1H), 7.46–7.34 (m, 2H), 7.25–7.13 (m, 4H), 5.83–5.67 (m, 1H), 3.88 (s, 3H), 3.43–3.37 (m, 1H), 3.23 (dd, J = 13.7, 6.7 Hz, 1H), 2.56 (d, J = 7.0 Hz, 1H), 1.90 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 158.5, 148.2, 146.4, 145.8, 136.7, 135.2, 134.5, 129.7, 128.4, 128.4, 127.4, 127.3, 126.9, 126.6, 125.1, 124.0, 119.9, 105.7, 104.0, 57.8, 55.4, 31.6, 22.4, 14.2. LRMS (ESI, m/z): 602.0 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{33}H_{30}O_4N_3Cl_2$, 602.1608 $[M+H]^+$; found 602.1599, purity: 98.2%.

5.3.1.13. 1-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzoyl]pyrrolidine-3-carboxylic acid (9f). 1-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzoyl]pyrrolidine-3-carboxylic acid (**9f**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 12.0, 5.1 Hz, 3H), 7.70–7.63 (m, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.33–7.28 (m, 2H), 7.26–7.15 (m, 4H), 6.65 (s, 1H), 5.58 (q, J = 6.9 Hz, 1H), 3.95 (s, 3H), 3.81–3.43 (m, 3H), 3.14 (d, J = 40.7 Hz, 1H), 2.22 (dd, J = 24.7, 16.8 Hz, 2H), 1.94 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 158.1, 147.5, 145.6, 144.1, 135.7, 134.9, 134.7, 134.1, 129.2, 128.0, 127.9, 127.2, 127.1, 126.9, 126.4, 126.0, 124.4, 123.7, 119.4, 105.2, 103.8, 57.7, 55.0, 29.2, 21.8. LRMS (ESI, m/z): 614.0 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{34}H_{29}O_4N_3Cl_2Na$, 636.1427 $[M+Na]^+$; found 636.1428, purity: 99.7%.

5.3.1.14. 1-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzoyl]piperidine-3-carboxylic acid (9g). 1-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzoyl]piperidine-3-carboxylic acid (**9g**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 128–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 11.9, 5.1 Hz, 3H), 7.73–7.63 (m, 2H), 7.32 (dd, J = 17.1, 7.2 Hz, 4H), 7.25 (d, J = 3.7 Hz, 2H), 7.22–7.15 (m, 2H), 6.65 (s, 1H), 5.58 (q, J = 6.9 Hz, 1H), 4.77–4.06 (m, 1H), 3.95 (s, 3H), 3.64 (s, 1H), 3.21 (s, 1H), 3.05 (s, 1H), 2.61 (s, 1H), 2.13 (d, J = 9.1 Hz, 1H), 1.94 (d, J = 7.0 Hz, 3H), 1.75 (dd, J = 21.7, 10.6 Hz, 2H), 1.49 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 169.7, 158.1, 147.6, 145.4, 143.9, 136.2, 134.68, 134.4, 134.0, 129.2, 127.9, 126.8, 126.8, 126.4, 126.1, 124.6, 123.6, 119.3, 105.2, 103.5, 57.5, 54.9, 40.0, 22.0. LRMS (ESI, m/z): 628.1 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{35}H_{31}O_4N_3Cl_2Na$, 650.1584 $[M+Na]^+$; found 650.1589, purity: 97.5%.

5.3.1.15. 1-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzoyl]piperidine-4-carboxylic acid (9h). 1-[4-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}-benzoyl]piperidine-4-carboxylic acid (**9h**) was prepared as **9a** according to the general procedure for the preparation of compounds **9**. Mp 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 11.5, 5.2 Hz, 3H), 7.72–7.65 (m, 2H), 7.36–7.28 (m, 4H), 7.27 (s, 1H), 7.25 (s, 2H), 7.22–7.16 (m, 2H), 6.65 (s, 1H), 5.59 (q, J = 6.8 Hz, 1H), 3.95 (s, 3H), 3.77 (s, 1H), 3.06 (s, 2H), 2.68–2.56 (m, 1H), 2.04 (s, 1H), 1.94 (d, J = 7.0 Hz, 3H), 1.73 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 170.0, 158.0, 147.6, 145.4, 144.0, 136.1, 134.7, 134.3, 134.0, 129.2, 127.9, 127.0, 126.9, 126.8, 126.5, 126.0, 124.6, 123.6, 119.3, 105.2, 103.6, 57.5, 54.9, 29.2, 26.9, 22.0. LRMS (ESI, m/z): 628.0 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{35}H_{32}O_4N_3Cl_2$, 628.1764 $[M+H]^+$; found 628.1760, purity: 97.0%.

5.3.2. General procedure for the preparation of compounds 17

5.3.2.1. Ethyl 1-indanone-5-carboxylate (11). A solution of 1-indanone-5-carboxylic acid **10** (5.0 g, 28.4 mmol) in 30 mL anhydrous ethanol was added 3.00 mL sulfuric acid slowly at 0 °C. After stirring at 80 °C for 4 h, the mixture was extracted with ethyl acetate and washed sequentially with water and saturated sodium bicarbonate and brine, dried over sodium sulfate, and concentrated as white solid (5.3 g, 90%). The crude product ethyl 1-indanone-5-carboxylate **11** was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.73 (dd, J = 7.9, 2.5 Hz, 1H), 4.35 (qd, J = 7.1, 1.4 Hz, 2H), 3.22–3.09 (m, 3H), 2.75–2.63 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H). MS (ESI, m/z) 205.1 $[M+H]^+$.

5.3.2.2. *tert*-Butyl 2-[5-(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-1-yl]-hydrazin-1-carboxylate (12). A solution of compound **11** (5.0 g, 24.5 mmol) and *tert*-butyl carbazate (4.9 g, 36.7 mmol) in 40 mL toluene was added catalytic acetic acid and was stirred at 80 °C overnight. The *tert*-butyl-2-[5-(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-1-ylidene]hydrazine-1-carboxylate separated as a crystalline solid and was collected by filtration (5.5 g, 17.3 mmol, 70%). Then the crude product and sodium cyanoborohydride (1.2 g, 19.0 mmol) were dissolved in 30 mL THF under N_2 atmosphere. A solution of *p*-toluene sulfonic acid (3.6 g, 20.7 mmol) in 10 mL THF was added dropwise. After stirring at room temperature for 3 h, the mixture was diluted with ethyl acetate and washed by saturated sodium bicarbonate, brine and dried over sodium sulfate, concentrated under reduced pressure to afford *tert*-butyl 2-[5-(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-1-yl]-hydrazine-1-carboxylate **12** as white solid (5.1 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.87 (m, 2H), 7.41 (d, J = 7.7 Hz, 1H), 6.08 (s, 1H), 4.54 (d, J = 6.0 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.13–3.01 (m, 1H), 2.91–2.80 (m, 1H), 2.29 (dd, J = 14.4, 7.5 Hz, 1H), 2.06–1.95 (m, 1H), 1.54 (s, 1H), 1.46 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H). MS (ESI, m/z) 319.2 $[M-H]^-$.

5.3.2.3. Ethyl 1-hydrazinyl-2,3-dihydro-1*H*-indene-5-carboxylate (13). Compound **12** (5.1 g, 15.9 mmol) was treated with 40 mL of TFA/DCM (1:1) at room temperature for 2 h. The mixture was concentrated under reduced pressure to provide crude product hydrazine **13** (2.6 g, 75%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.88 (m, 2H), 7.56 (d, J = 8.1 Hz, 1H), 4.95–4.84 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.16 (dt, J = 25.6, 8.4 Hz, 1H), 3.09–2.84 (m, 1H), 2.56 (dd, J = 15.4, 7.8 Hz, 1H), 2.50–2.33 (m, 1H), 1.40 (t, J = 6.7 Hz, 3H). MS (ESI, m/z) 221.2 $[M+H]^+$.

5.3.2.4. Ethyl 1-[3-(3,5-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxylate (14). Without further purification, hydrazine **13** (2.6 g, 11.9 mmol) and ethyl 3-(3,5-dichlorophenyl)-3-oxopropanoate **5** (3.4 g, 13.1 mmol) were refluxed in 80 mL acetic acid for 4 h. The solvent was removed under reduced pressure, then redissolved in ethyl acetate, washed sequentially by saturated sodium carbonate, brine and dried over sodium sulfate. The flash chromatography (SiO_2, 10% to 20% ethyl acetate in petroleum ether) gave 2.5 g (50%) of ethyl 1-[3-(3,5-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxylate **14** as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 1.9 Hz, 2H), 7.33 (t, J = 1.9 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 5.89 (t, J = 7.6 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.65 (d, J = 2.2 Hz, 2H), 3.26 (ddd, J = 16.0, 8.9, 4.5 Hz, 1H), 3.00 (dt, J = 15.9, 7.9 Hz, 1H), 2.66–2.50 (m, 1H), 2.41 (ddt, J = 13.1, 8.9, 7.2 Hz, 1H), 1.38 (t, J = 7.1 Hz, 3H). MS (ESI, m/z) 415.1 $[M-H]^-$.

5.3.2.5. Ethyl 1-{3-(3,5-dichlorophenyl)-5-{[(trifluoromethyl)-sulfonyl]oxy}-1*H*-pyrazol-1-yl}-2,3-dihydro-1*H*-indene-5-carboxylate (15). Compound **14** (2.5 g, 6.0 mmol) and TEA (2.5 mL, 17.9 mmol) were stirred in 50 mL anhydrous THF at −78 °C. The trifluoromethanesulfonic anhydride (1.5 mL, 9.1 mmol) was added over half an hour. Then the temperature was slowly rose to room temperature and the mixture was stirred for 1 h. The reaction was quenched by adding ethyl acetate and water. The organic layer was washed by 0.5 N HCl and brine, dried over sodium sulfate. The flash chromatography (SiO_2, 10% ethyl acetate in petroleum ether) gave 2.3 g (70%) of ethyl 1-{3-(3,5-dichlorophenyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrazol-1-yl}-2,3-dihydro-1*H*-indene-5-carboxylate **15** as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 1.9 Hz, 2H), 7.28 (t, J = 1.9 Hz, 1H), 7.11 (d, J = 7.9 Hz, 1H), 6.46 (s, 1H), 5.88 (t, J = 7.5 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.37 (ddd, J = 16.1, 8.8, 4.4 Hz, 1H), 3.07 (dt, J = 16.0, 7.9 Hz, 1H), 2.85–2.55 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H). MS (EI, m/z) 572.1 $[M+Na]^+$.

5.3.2.6. Ethyl 1-[3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxylate (16). Compound **15** (181.3 mg, 0.3 mmol), TEA (233.3 μL, 1.7 mmol), and 6-methoxy-2-naphthylboronic acid (84.7 mg, 0.4 mmol) were dissolved in 6 mL dimethoxyethane and deoxygenated by vacuum-N2 fill cycles. Tetrakis(triphenylphosphine) palladium $[Pd(PPh_3)_4]$ (38.1 mg, 10% mmol) was add quickly as catalyst and deoxygenated again before heated in microwave reactor at 100 °C for 25 min. The mixture was quenched by saturated ammonium chloride, extracted by ethyl acetate, and washed by brine, dried over sodium sulfate. The flash chromatography (SiO_2, 10% ethyl acetate in petroleum ether) gave 166 mg (90%) of ethyl 1-[3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxylate **16** as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.98 (dd, J = 19.0, 8.8 Hz, 2H), 7.89 (s, 1H), 7.79 (d, J = 1.9 Hz, 2H), 7.75 (d, J = 7.9 Hz, 1H), 7.68 (dd, J = 8.5, 1.6 Hz, 1H), 7.52 (t, J = 1.9 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.26 (dd, J = 9.0, 2.5 Hz, 1H), 7.19 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.06 (t, J = 7.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.23 (dt, J = 16.1, 6.3 Hz, 1H), 2.98 (dt, J = 16.1, 8.3 Hz, 1H), 2.76–2.64 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). MS (ESI, m/z) 558.8 $[M+H]^+$.

5.3.2.7. 3-{1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido} propanoic acid (17l). Compound **16** (166 mg, 0.3 mmol) was dissolved in MeOH–dioxane (1:1, 3 mL). A solution of NaOH (0.7 g/15 mL) was added at room temperature. After stirring at 60 °C for 1 h, the mixture was acidified by 2 N HCl and extracted by DCM, dried over sodium sulfate and concentrated under reduced pressure to give 150 mg (95%) of 1-[3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxylic acid as pale yellow solid. The solid was directly dissolved in DMF (3 mL), followed by addition of DIEA (0.2 mL, 1.3 mmol), β-alanine *tert*-butyl ester hydrochloride (154.4 mg, 0.9 mmol) and a solution of PyBOP (165.1 mg, 0.3 mmol) in 2 mL DMF. After stirring at room temperature for 3 h, 53 mg PyBOP was added directly. The mixture was stirred at room temperature overnight and quenched by water before heated to 60 °C for 30 min. Ethyl acetate was added, the organic layer was washed sequentially by 0.5 N HCl, 5% potassium carbonate, brine and then dried over sodium sulfate. The flash chromatography (SiO_2, 25% ethyl acetate in petroleum ether) gave 149 mg (80%) of *tert*-butyl 3-{1-[3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoate as white solid.

The solid was then treated with TFA–DCM (1:2, 3 mL) for 1 h. The solvent was removed under reduced pressure. The flash chromatography (SiO_2, 5% MeOH in DCM) gave 130 mg (95%) of 3-{1-[3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid **17l** as white solid. Mp 129–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.48 (t, J = 5.5 Hz, 1H), 8.11 (s, 1H), 7.98 (dd, J = 18.8, 8.8 Hz, 2H), 7.79 (d, J = 1.9 Hz, 2H), 7.76 (s, 1H), 7.68 (dd, J = 8.4, 1.9 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 1.9 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.26 (dd, J = 9.0, 2.5 Hz, 1H), 7.19 (s, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.04 (t, J = 7.7 Hz, 1H), 3.91 (s, 3H), 3.43 (q, J = 6.7 Hz, 2H), 3.24–3.10 (m, 1H), 2.97 (d, J = 8.0 Hz, 1H), 2.74–2.60 (m, 2H), 2.47 (t, J = 7.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.3, 166.7, 158.6, 147.9, 146.6, 145.9, 143.9, 137.1, 135.0, 134.9, 134.7, 130.4, 128.7, 128.6, 128.0, 127.4, 127.3, 126.4, 125.2, 124.1, 123.9, 123.8, 120.0, 106.4, 105.0, 63.3, 56.5, 55.8, 36.0, 34.2, 33.3, 30.4, 19.0. LRMS (ESI, m/z): 602.2 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{33}H_{26}N_3O_4Cl_2$, 598.1300 [M+H]$^+$; found 598.1312, purity: 95.4%.

5.3.2.8. 3-{1-[3-(3,5-Dichlorophenyl)-5-(3,5-dimethoxyphenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17a). 3-{1-[3-(3,5-Dichlorophenyl)-5-(3,5-dimethoxyphenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17a**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 118–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.48 (t, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.75 (d, J = 2.0 Hz, 2H), 7.66–7.54 (m, 1H), 7.50 (t, J = 1.9 Hz, 1H), 7.11 (s, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 2.3 Hz, 2H), 6.65 (t, J = 2.2 Hz, 1H), 6.01 (t, J = 7.7 Hz, 1H), 3.81 (s, 6H), 3.44 (q, J = 6.8 Hz, 2H), 3.19 (m, 1H), 2.98 (m, 1H), 2.65 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.2, 160.8, 147.4, 145.8, 145.4, 143.5, 136.5, 134.5, 134.5, 131.5, 126.9, 126.0, 123.7, 123.4, 123.3, 107.1, 104.4, 100.8, 62.9, 55.4, 35.60, 33.8, 32.8, 30.0. LRMS (ESI, m/z): 582.2 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{30}H_{26}N_3O_5Cl_2$, 578.1250 [M+H]$^+$; found 578.1234, purity: 99.3%.

5.3.2.9. 3-{1-[3-(3,5-Dichlorophenyl)-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17b). 3-{1-[3-(3,5-Dichlorophenyl)-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17b**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 118–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.48 (t, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.74 (d, J = 1.9 Hz, 2H), 7.60 (dd, J = 7.8, 1.6 Hz, 1H), 7.49 (t, J = 1.9 Hz, 1H), 7.12–6.99 (m, 4H), 6.92 (d, J = 7.9 Hz, 1H), 5.93 (t, J = 7.8 Hz, 1H), 4.30 (s, 4H), 3.44 (q, J = 7.0 Hz, 2H), 3.24–3.13 (m, 1H), 2.97 (dt, J = 16.0, 8.2 Hz, 1H), 2.70–2.58 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.2, 147.3, 145.6, 145.4, 144.2, 143.6, 143.4, 136.6, 134.5, 126.8, 126.0, 123.7, 123.4, 123.2, 122.7, 122.0, 117.7, 104.1, 64.2, 64.1, 62.6, 35.6, 33.8, 32.8, 29.9. LRMS (ESI, m/z): 579.0 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{30}H_{24}N_3O_5Cl_2$, 576.1093 [M+H]$^+$; found 576.1078, purity: 99.4%.

5.3.2.10. 3-{1-[3-(3,5-Dichlorophenyl)-5-phenyl-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17c). 3-{1-[3-(3,5-Dichlorophenyl)-5-phenyl-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17c**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 205–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.49 (t, J = 5.3 Hz, 1H), 7.77 (s, 2H), 7.76 (s, 1H), 7.66–7.49 (m, 7H), 7.12 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 5.94 (t, J = 7.7 Hz, 1H), 3.43 (q, J = 7.0 Hz, 2H), 3.20 (m, 1H), 3.03–2.97 (m, 1H), 2.73–2.60 (m, 2H), 2.47 (t, J = 7.1 Hz, 2H), 1.78–1.68 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.2, 147.4, 146.0, 145.3, 143.4, 136.5, 134.5, 130.0, 129.1, 129.0, 126.9, 126.0, 123.7, 123.4, 123.3, 104.4, 62.7, 45.9, 35.6, 33.8, 32.7, 30.0, 25.9. LRMS (ESI, m/z): 519.1 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{28}H_{22}N_3O_3Cl_2$, 518.1038 [M+H]$^+$; found 518.1047, purity: 98.2%.

5.3.2.11. 3-{1-[3-(3,5-Dichlorophenyl)-5-(*o*-tolyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17d). 3-{1-[3-(3,5-Dichlorophenyl)-5-(*o*-tolyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17d**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 124–126 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.47 (t, J = 5.5 Hz, 1H), 7.81–7.71 (m, 3H), 7.63–7.55 (m, 1H), 7.50 (t, J = 1.9 Hz, 1H), 7.48–7.41 (m, 3H), 7.40–7.31 (m, 1H), 7.02 (s, 1H), 6.92 (d, J = 7.9 Hz, 1H), 5.51 (t, J = 7.7 Hz, 1H), 3.43 (q, J = 7.0 Hz, 2H), 3.18 (dt, J = 15.7, 6.6 Hz, 1H), 2.93 (dt, J = 16.0, 8.1 Hz, 1H), 2.65–2.54 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.3, 147.5, 145.2, 144.5, 143.5, 137.3, 136.7, 134.6, 130.5, 129.6, 129.5, 126.9, 126.2, 126.0, 123.7, 123.4, 123.4, 104.5, 62.7, 35.6, 33.8, 32.7, 30.0, 19.8. LRMS (ESI, m/z): 535.2 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{29}H_{24}N_3O_3Cl_2$, 532.1195 [M+H]$^+$; found 532.1188, purity: 97.6%.

5.3.2.12. 3-{1-[3-(3,5-Dichlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17e). 3-{1-[3-(3,5-Dichlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17e**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 154–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.49 (t, J = 5.5 Hz, 1H), 7.78 (s, 1H), 7.76 (d, J = 1.9 Hz, 2H), 7.73–7.65 (m, 2H), 7.63–7.58 (m, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.47–7.36 (m, 2H), 7.12 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 5.91 (t, J = 7.7 Hz, 1H), 3.44 (q, J = 7.0 Hz, 2H), 3.20 (m, 1H), 2.97 (dt, J = 16.0, 8.1 Hz, 1H), 2.71–2.59 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.3, 163.5, 161.6, 147.5, 145.3, 145.0, 143.5, 136.5, 134.6, 134.6, 131.5, 131.4, 127.0, 126.3, 126.2, 126.0, 123.7, 123.5, 123.4, 116.2, 116.1, 104.6, 62.8, 35.6, 33.8, 32.9, 30.0. LRMS (ESI, m/z): 540.0 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{28}H_{21}N_3O_3FCl_2$, 536.0944 [M+Na]$^+$; found 536.0956, purity: 97.5%.

5.3.2.13. 3-{1-[5-(4-Chlorophenyl)-3-(3,5-dichlorophenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17f). 3-{1-[5-(4-Chlorophenyl)-3-(3,5-dichlorophenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17f**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.60 (d, J = 1.8 Hz, 2H), 7.53 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 23.3, 8.5 Hz, 4H), 7.22 (t, J = 1.8 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.81 (t, J = 6.1 Hz, 1H), 6.59 (s, 1H), 5.84 (t, J = 7.9 Hz, 1H), 3.74–3.65 (m, 2H), 3.32–3.20 (m, 1H), 3.01–2.88 (m, 1H), 2.83–2.74 (m, 1H), 2.67 (t, J = 5.7 Hz, 2H), 2.64–2.51 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 167.8, 149.0, 145.9, 145.1, 144.1, 136.3, 135.5, 135.2, 134.6, 130.5, 129.5, 128.8, 127.6, 126.0, 124.2, 124.0, 123.9, 104.1, 63.5, 35.4, 33.64, 33.4, 30.6. LRMS (ESI, m/z): 555.8 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{28}H_{21}N_3O_3Cl_3$, 552.0648 [M+H]$^+$; found 556.0754, purity: 94.5%.

5.3.2.14. 3-{1-[3-(3,5-Dichlorophenyl)-5-(furan-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17g). 3-{1-[3-(3,5-Dichlorophenyl)-5-(furan-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17g**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 128–130 °C. ^{1}H NMR

(400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.49 (t, J = 5.1 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.80 (s, 1H), 7.76 (d, J = 1.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.29 (s, 1H), 7.06–6.90 (m, 2H), 6.73 (dd, J = 3.4, 1.8 Hz, 1H), 6.30 (t, J = 7.3 Hz, 1H), 3.44 (d, J = 6.6 Hz, 2H), 3.26 (dt, J = 8.3, 3.7 Hz, 1H), 3.03 (dt, J = 15.6, 7.6 Hz, 1H), 2.75–2.60 (m, 2H), 2.47 (t, J = 7.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 147.5, 145.0, 144.2, 143.7, 143.2, 136.1, 135.8, 134.6, 134.6, 127.0, 126.0, 123.8, 123.6, 123.5, 112.0, 110.3, 103.5, 63.9, 35.6, 33.8, 32.4, 30.2. LRMS (ESI, m/z): 511.1 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{26}H_{20}N_3O_4Cl_2$, 508.0831 [M+H]$^+$; found 508.0816, purity: 97.4%.

5.3.2.15. 3-{1-[3-(3,5-Dichlorophenyl)-5-(thiophen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17h). 3-{1-[3-(3,5-Dichlorophenyl)-5-(thiophen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17h**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 203–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.50 (t, J = 5.5 Hz, 1H), 7.84–7.74 (m, 4H), 7.65–7.59 (m, 1H), 7.51 (t, J = 1.9 Hz, 1H), 7.47 (dd, J = 3.6, 1.2 Hz, 1H), 7.27 (dd, J = 5.1, 3.6 Hz, 1H), 7.22 (s, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.15 (t, J = 7.6 Hz, 1H), 3.44 (q, J = 6.7 Hz, 2H), 3.23 (ddd, J = 15.9, 8.0, 4.7 Hz, 1H), 3.07–2.92 (m, 2H), 2.66 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.3, 147.5, 145.1, 143.6, 138.6, 136.2, 134.6, 134.6, 129.6, 128.5, 128.4, 128.4, 127.1, 126.0, 123.8, 123.5, 123.5, 105.3, 63.0, 45.9, 35.6, 33.8, 32.7, 30.1, 25.9. LRMS (ESI, m/z): 525.0 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{26}H_{20}N_3O_3Cl_2S$, 524.0602 [M+H]$^+$; found 524.0605, purity: 97.2%.

5.3.2.16. 3-{1-[5-([1,1′-Biphenyl]-4-yl)-3-(3,5-dichlorophenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17i). 3-{1-[5-([1,1′-Biphenyl]-4-yl)-3-(3,5-dichlorophenyl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17i**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 142–144 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (t, J = 5.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.83–7.68 (m, 7H), 7.62 (d, J = 8.0 Hz, 1H), 7.57–7.46 (m, 3H), 7.42 (d, J = 7.4 Hz, 1H), 7.16 (s, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.02 (t, J = 7.8 Hz, 1H), 3.44 (q, J = 6.9 Hz, 3H), 3.25–3.16 (m, 1H), 2.98 (dt, J = 15.6, 8.0 Hz, 1H), 2.68 (q, J = 7.4 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.2, 147.5, 145.7, 145.4, 143.4, 140.7, 139.2, 136.5, 134.5, 129.6, 129.1, 128.7, 127.9, 127.3, 126.9, 126.8, 126.0, 123.7, 123.4, 123.3, 104.4, 62.9, 35.6, 33.8, 32.9, 29.9. LRMS (ESI, m/z): 597.1 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{34}H_{26}N_3O_3Cl_2$, 594.1351 [M+H]$^+$; found 594.1352, purity: 97.4%.

5.3.2.17. 3-{1-[3-(3,5-Dichlorophenyl)-5-(naphthalen-1-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17j). 3-{1-[3-(3,5-Dichlorophenyl)-5-(naphthalen-1-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17j**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 146–148 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.45 (s, 1H), 8.11 (m, 2H), 7.83 (d, J = 1.9 Hz, 3H), 7.75–7.45 (m, 7H), 7.20 (s, 1H), 7.12–6.77 (m, 1H), 5.64–5.32 (t, 1H), 3.42 (q, J = 6.7 Hz, 2H), 3.16 (m, J = 14.5, 9.3 Hz, 1H), 2.82 (m, 1H), 2.57 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 166.2, 136.6, 134.6, 131.8, 128.6, 127.4, 126.9, 126.6, 125.6, 123.6, 123.5, 123.4, 62.9, 35.5, 33.7, 31.0, 29.9. LRMS (ESI, m/z): 571.2 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{32}H_{24}N_3O_3Cl_2$, 568.1195 [M+H]$^+$; found 568.1199, purity: 94.5%.

5.3.2.18. 3-{1-[3-(3,5-Dichlorophenyl)-5-(naphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (17k). 3-{1-[3-(3,5-Dichlorophenyl)-5-(naphthalen-2-yl)-1*H*-pyrazol-1-yl]-2,3-dihydro-1*H*-indene-5-carboxamido}propanoic acid (**17k**) was prepared as **17l** according to the general procedure for preparation of compounds **17**. Mp 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 8.48 (t, J = 5.4 Hz, 1H), 8.20 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.09–7.99 (m, 2H), 7.87–7.71 (m, 4H), 7.66–7.58 (m, 3H), 7.51 (t, J = 1.9 Hz, 1H), 7.23 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.06 (t, J = 7.7 Hz, 1H), 3.44 (q, J = 7.1 Hz, 2H), 3.21 (dt, J = 15.9, 6.3 Hz, 1H), 2.96 (dt, J = 16.0, 8.2 Hz, 1H), 2.78–2.67 (m, 2H), 2.49 (t, J = 6.4 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 166.2, 147.5, 146.0, 145.4, 143.4, 136.5, 134.6, 134.5, 132.8, 132.7, 128.7, 128.3, 127.7, 127.2, 127.1, 126.9, 126.5, 126.0, 123.7, 123.5, 123.4, 104.8, 62.9, 62.2, 35.6, 33.8, 32.8, 30.0. LRMS (ESI, m/z): 571.1 [M+H]$^+$. HRMS (ESI, m/z): calcd for $C_{32}H_{24}N_3O_3Cl_2$, 568.1195 [M+H]$^+$; found 568.1201, purity: 96.9%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2016.04.053.

References and notes

1. Saltiel, A. R. *Cell* **2001**, *104*, 517.
2. Cavan, D.; Fernandes, J.; da, R.; Makaroff, L.; Ogurtsova, K.; Webber, S. *IDF Diabetes Atlas*, 7th ed.; International Diabetes Federation: Brussels, Belgium, 2015.
3. DeMong, D. E.; Miller, M. W.; Lachowicz, J. E. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Elsevier Academic Press: San Diego, 2008; Vol. 4, pp 119–137.
4. Krentz, A. J.; Patel, M. B.; Bailey, C. J. *Drugs* **2008**, *68*, 2131.
5. Tahrani, A. A.; Bailey, C. J.; Del Prato, S.; Barnett, A. H. *Lancet* **2011**, *378*, 182.
6. Shen, D. M.; Lin, S.; Parmee, E. R. *Expert Opin. Ther. Pat.* **2011**, *21*, 1211.
7. Drucker, D. J.; Nauck, M. A. *Lancet* **2006**, *368*, 1696.
8. Chao, E. C.; Henry, R. R. *Nat. Rev. Drug Disc.* **2010**, *9*, 551.
9. Mojsov, S.; Heinrich, G.; Wilson, I. B.; Ravazzola, M.; Orci, L.; Habener, J. F. *J. Biol. Chem.* **1986**, *261*, 1880.
10. Ferner, H. *Am. J. Dig. Dis.* **1953**, *20*, 301.
11. Bromer, W. W.; Sinn, L. G.; Behrens, O. K. *J. Am. Chem. Soc.* **1957**, *79*, 2807.
12. Ørskov, C.; Holst, J. J.; Knuhtsen, S.; Baldissera, F. G. A.; Poulsen, S. S.; Nielsen, O. V. *Endochrinology* **1986**, *119*, 1467.
13. Kimball, C. P.; Murlin, J. R. *J. Biol. Chem.* **1923**, *58*, 337.
14. Burcelin, R.; Katz, E. B.; Charron, M. J. *Diabetes Metab.* **1996**, *22*, 373.
15. Jiang, G.; Zhang, B. B. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E671.
16. Johnson, D. G.; Goebel, C. U.; Hruby, V. J.; Bregman, M. D.; Trivedi, D. *Science* **1982**, *215*, 1115.
17. Unger, R. H.; Orci, L. *N. Eng. J. Med.* **1981**, *304*, 1575.
18. Zhang, B. B.; Moller, D. B. *Curr. Opin. Chem. Biol.* **2000**, *4*, 461.
19. Ali, S.; Drucker, D. J. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *296*, E415.
20. DeMong, D. E.; Miller, M. W. *RSC*; Drug Discovery: Rahway, 2012. Chapter 15.
21. Petersen, K. F.; Sullivan, J. T. *Diabetologia* **2001**, *44*, 2018.
22. Sloop, K. W.; Michael, M. D.; Moyers, J. S. *Expert Opin. Ther. Targets* **2005**, *9*, 593.
23. Bagger, J. I.; Knop, F. K.; Holst, J. J.; Vilsbøll, T. *Diabetes Obes. Metab.* **2011**, *13*, 965.
24. Ling, A. L.; Wasserman, J. I. *Expert Opin. Ther. Pat.* **2003**, *13*, 15.
25. Kurukulasuriya, R.; Link, J. T. *Expert Opin. Ther. Pat.* **2005**, *15*, 1739.
26. de Laszlo, S. E.; Hacker, C.; Li, B.; Kim, D.; MacCoss, M.; Mantlo, N.; Pivnichny, J. V.; Colwell, L.; Koch, G. E.; Cascieri, M. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 641.
27. Madsen, P.; Knudsen, L. B.; Wiberg, F. C.; Carr, R. D. *J. Med. Chem.* **1998**, *41*, 5150.
28. Ling, A.; Hong, Y. F.; Gonzalez, J.; Gregor, V.; Polinsky, A.; Kuki, A.; Shi, S. H.; Teston, K.; Murphy, D.; Porter, J.; Kiel, D.; Lakis, J.; Anderes, K.; May, J. *J. Med. Chem.* **2001**, *44*, 3141.
29. Duffy, J. L.; Kirk, B. A.; Konteatis, Z.; Campbell, E. L.; Liang, R.; Brady, E. J.; Candelore, M. R.; Ding, V. D. H.; Jiang, G. Q.; Liu, F.; Qureshi, S. A.; Saperstein, R.; Szalkowski, D.; Tong, S.; Tota, L. M.; Xie, D.; Yang, X. D.; Zafian, P.; Zheng, S.; Chapman, K. T.; Zhang, B. B.; Tata, J. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1401.

30. Shen, D. M.; Zhang, F.; Brady, E. J.; Candelore, M. R.; Dallas-Yang, Q.; Ding, V. D. H.; Dragovic, J.; Feeney, W. P.; Jiang, G. Q.; McCann, P. E.; Mock, S.; Qureshi, S. A.; Saperstein, R.; Shen, X. L.; Tamvakopoulos, C.; Tong, X. C.; Tota, L. M.; Wright, M. J.; Yang, X. D.; Zheng, S.; Chapman, K. T.; Zhang, B. B.; Tata, J. R.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4564.
31. Shen, D. M.; Brady, E. J.; Candelore, M. R.; Dallas-Yang, Q.; Ding, V. D. H.; Feeney, W. P.; Jiang, G. Q.; McCann, M. E.; Mock, S.; Qureshi, S. A.; Saperstein, R.; Shen, X. L.; Tong, X. C.; Tota, L. M.; Wright, M. J.; Yang, X. D.; Zheng, S.; Chapman, K. T.; Zhang, B. B.; Tata, J. R.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 76.
32. Lee, E. C.; Tu, M.; Stevens, B. D.; Bian, J.; Aspnes, G.; Perreault, C.; Sammons, M. F.; Wright, S. W.; Litchfield, J.; Kalgutkar, A. S.; Sharma, R.; Didiuk, M. T.; Ebner, D. C.; Filipski, K. J.; Brown, J.; Atkinson, K.; Pfefferkorn, J. A.; Guzman-Perez, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 839.
33. Filipski, K. J. *Expert Opin. Ther. Pat.* **2015**, *25*, 819.
34. Parmee, E. R. **2011**, *241*, 1.
35. Xiong, Y.; Guo, J.; Candelore, M. R.; Liang, R.; Miller, C.; Dallas-Yang, Q.; Jiang, G.; McCann, P. E.; Qureshi, S. A.; Tong, X.; Xu, S. S.; Shang, J.; Vincent, S. H.; Tota, L. M.; Wright, M. J.; Yang, X.; Zhang, B. B.; Tata, J. R.; Parmee, E. R. *J. Med. Chem.* **2012**, *55*, 6137.
36. Siu, F. Y.; He, M.; de Graaf, C.; Han, G. W.; Yang, D. H.; Zhang, Z.; Zhou, C.; Xu, Q.; Wacker, D.; Joseph, J. S.; Liu, W.; Lau, J.; Cherezov, V.; Katritch, V.; Wang, M. W.; Stevens, R. C. *Nature* **2013**, *499*, 444.
37. Yang, L.; Yang, D.; de Graaf, C.; Moeller, A.; West, G. M.; Dharmarajan, V.; Wang, C.; Siu, F. Y.; Song, G.; Reedtz-Runge, S.; Pascal, B. D.; Wu, B.; Potter, C. S.; Zhou, H.; Griffin, P. R.; Carragher, B.; Yang, H.; Wang, M. W.; Stevens, R. C.; Jiang, H. *Nat. Commun.* **2015**, *6*, 7859.
38. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Shaw, D. E.; Francis, P.; Shenkin, P. S. *J. Med. Chem.* **2004**, *47*, 1739.
39. Liang, R.; Abrardo, L.; Brady, E. J.; Candelore, M. R.; Ding, V.; Saperstein, R.; Tota, L. M.; Wright, M.; Mock, S.; Tamvakopolous, C.; Tong, S.; Zheng, S.; Zhang, B. B.; Tata, J. R.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 587.
40. Koole, C.; Wootten, D.; Simms, J.; Valant, C.; Sridhar, R.; Woodman, O. L.; Miller, L. J.; Summers, R. J.; Christopoulos, A.; Sexton, P. M. *Mol. Pharmacol.* **2010**, *78*, 456.
41. Glide, version 5.7, Schrödinger, LLC, New York, NY, 2011.
42. Schrödinger Suite 2011 Schrödinger Suite; Epik version 2.2, Schrödinger, LLC, New York, NY, 2011; Impact version 5.7, Schrödinger, LLC, New York, NY, 2011; Prime version 2.3, Schrödinger, LLC, New York, NY, 2011.