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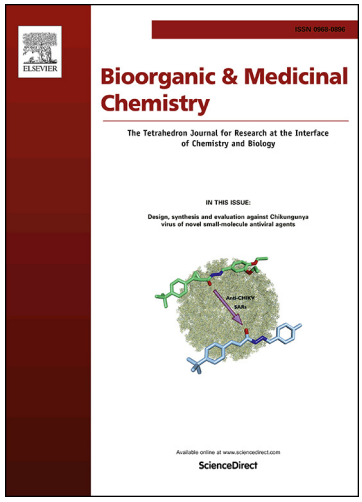

A novel series of 4-methyl substituted pyrazole derivatives as potent glucagon receptor antagonists: Design, synthesis and evaluation of biological activities

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A novel series of 4-methyl substituted pyrazole derivatives as potent glucagon receptor antagonists: Design, synthesis and evaluation of biological activities

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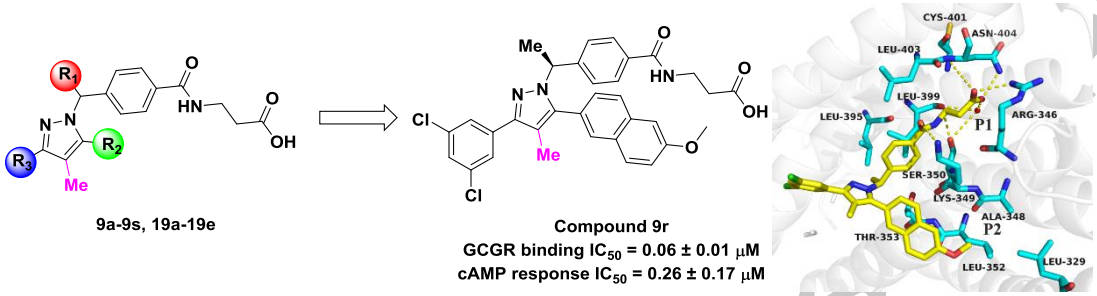
Graphical Abstract



Abstract

A novel series of 4-methyl substituted pyrazole derivatives were designed, synthesized and biologically evaluated as potent glucagon receptor (GCGR) antagonists. In this study, compounds **9q**, **9r**, **19d** and **19e** showed high GCGR binding (IC_{50} = 0.09 μM, 0.06 μM, 0.07 μM and 0.08 μM, respectively) and cyclic-adenosine monophosphate (cAMP) activities (IC_{50} = 0.22 μM, 0.26 μM, 0.44 μM and 0.46 μM, respectively) in cell-based assays. Most importantly, the docking experiment demonstrated that compound **9r** formed extensive hydrophobic interactions with the receptor binding pocket, making it justifiable to further investigate the potential of becoming a GCGR antagonist.

Keywords: pyrazole derivatives; glucagon receptor antagonist; docking study; binding pocket

1. Introduction

Glucagon, a 29-amino acid peptide hormone, secreted by α-cells of the pancreatic islets, was discovered by Kimball and Murlin in 1923.[1-3] As a main hormone to elevate the hepatic glucose production (HGP) by stimulating gluconeogenesis[4] and glycogenolysis,[5] glucagon along with insulin maintains blood glucose homeostasis.[6-8] It was reported that exogenous insulin may suppress the secretion of glucagon and immunoneutralization of insulin increased glucagon release. [9-12] Thus, in type 1 and type 2 diabetics, elevated levels of glucagon, insufficient glucagon suppression and decreased insulin secretion all contribute to hyperglycemia.[13,14]

Type 2 diabetes mellitus (T2DM) is a chronic disorder accompanied by polydipsia, polyphagia, polyuria and characterized by hyperglycemia. To reduce the risk of late-stage complications and drug resistance, new therapies for diabetes are still in need. Recently, several sodium-glucose cotransporter-2 (SGLT-2) inhibitors such as canagliflozin, dapagliflozin and embagliflozin have been approved, but they may lead to ketoacidosis.[15] Given the importance of suppressing glucagon action in treating T2DM, antagonism of glucagon receptor (GCGR) appears to be a promising approach to glycemic control.[16,17] GCGR is one of the 15 members of class B family of G-protein coupled receptors (GPCRs). In 2013, the high resolution crystal structure of seven-transmembrane (7-TM) helical domain of human GCGR was determined by research groups led by Wang and Stevens, which is conducive to understanding the molecular binding mode of the receptor.[18] 7-TM domain is the main part of GPCRs that share similar signal transduction mechanisms.[19] Compared with class A family of

GPCRs, GCGR has a large ligand binding pocket. The conformational states of the full-length GCGR were revealed suggesting that glucagon binds to GCGR by a conformational selection mechanism.[20] A full-length GCGR structure was revealed recently demonstrating how the extracellular domain interacts with the stalk to form a compact β-sheet structure.[21]

To date, several GCGR antagonists with different chemical scaffolds were reported to display efficacies in various bioassays.[22-30] The biaryl containing compound **BAY 27-9955** (Fig. 1) was the first GCGR antagonist to blunt elevation of HGP and plasma glucose induced by exogenous glucagon.[31] Clinical trial data of compounds **MK-3577** [32] and **MK-0893** [33,34] (Figure 1) exhibits that they are potent GCGR antagonists capable of modulating glucose homeostasis.

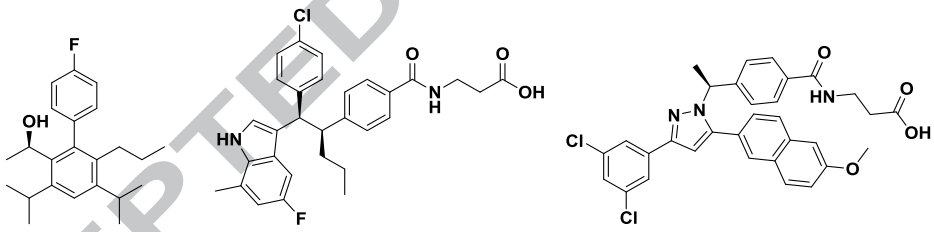


Figure 1. Structures of **BAY 27-9955**, **MK-3577** and **MK-0893**.

In this paper, a novel series of 4-methyl substituted pyrazole-containing derivatives as GCGR antagonists was designed and synthesized. Most of compounds exhibited good GCGR binding affinities and cyclic-adenosine monophosphate (cAMP) responses. Our structural optimization was dedicated to improve both GCGR binding and cAMP activities aiming at discovery of potent compounds for further development.

2. Results and discussion

2.1. Design of the target compounds

Although the structure-activity relationship (SAR) of **MK-0893** was explicit, it is very limited to understand the binding mode of this compound with GCGR. Therefore, structural modification of **MK-0893** and docking studies were carried out to make the binding information clearer. In 2016, the extra-helical binding site of **MK-0893** for GCGR was identified by a crystal complex structure.[35] Unlike glucagon binding in the 7-TM, **MK-0893** interacted with residues outside the 7-TM domain and formed interactions in two binding pockets (Figure 2A) at allosteric sites. The β-alanine moiety formed polar interactions with residues Lys349, Ser350, Arg346, Asn404 and Lys405 including a water-mediated hydrogen bond with residues Ser350 and Leu399 between transmembrane 6 and transmembrane 7 (Figure 2B). The hydrophobic moiety formed hydrophobic interactions with Leu329, Phe345, Leu352, Thr353 and Lys349 between transmembrane 5 and transmembrane 6. As an important strategy of lead compound optimization, introducing methyl group can modulate the physicochemical, pharmacodynamic and pharmacokinetic properties. We hypothesized that introducing methyl group on the pyrazole core may form potential hydrophobic interactions with the binding pockets (Figure 3). Thus, a series of 4-methyl substituted pyrazole derivatives (**9** and **19**) was designed to evaluate the influence of R_1, R_2 and R_3 substituents on antagonistic activities.

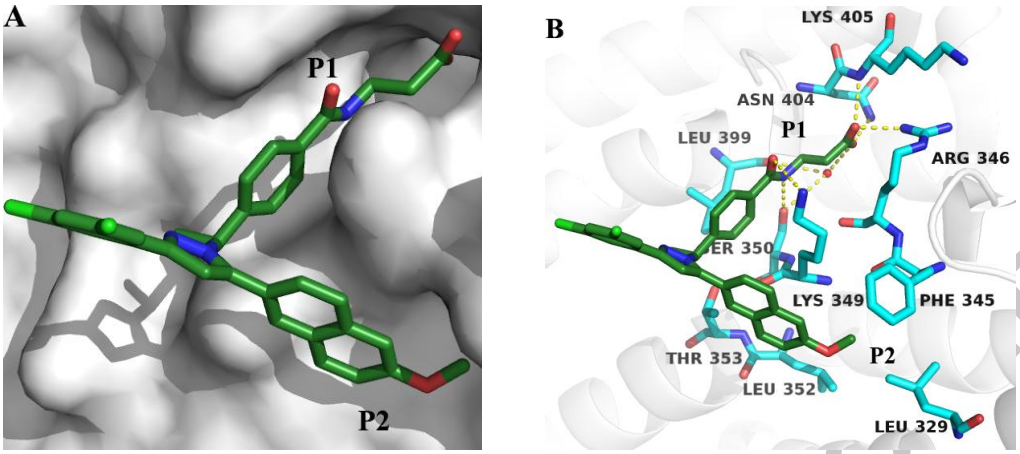


Figure 2. MK-0893 allosteric binding sites of GCGR. (A) surface of interactions. (B) interactions of **MK-0893** with GCGR. All figures were prepared using PyMol (http://www.pymol.org).

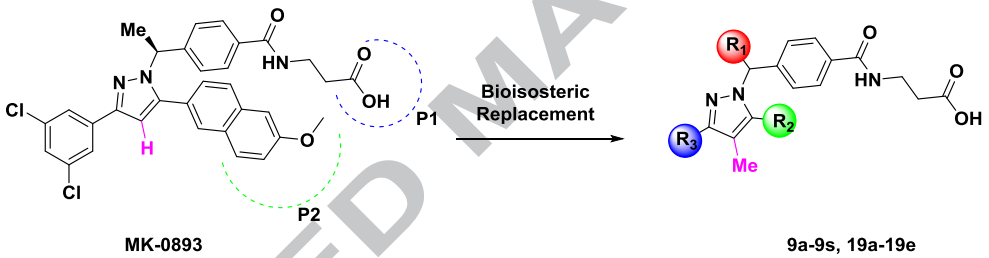


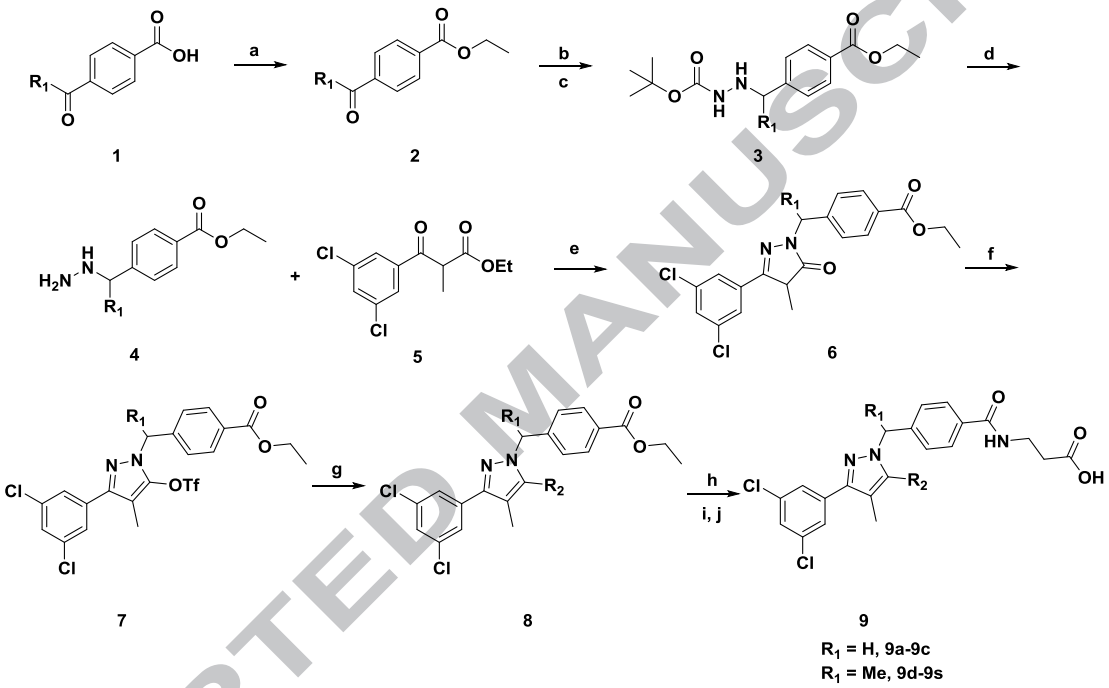
Figure 3. Design of 4-methyl substituted pyrazole derivatives **9** and **19**.

2.2. Synthetic procedure of the target compounds

The desired compound **9** was synthesized according to the synthetic route shown in Scheme 1. Esterification of compound **1** produced compound **2**, which reacted with *tert*-butyl carbazate and then reduced by sodium cyanoborohydride to give compound **3**. Deprotection of compound **3** in the presence of trifluoroacetic acid afforded hydrazine **4**, which reacted with ethyl 3-(3,5-dichlorophenyl)-2-methyl-3-oxopropanoate **5** to provide compound **6**. Triflation of compound **6** with triflic anhydride generated compound **7**, which was

subjected to a classic Suzuki coupling reaction to yield compound **8**. Hydrolysis of compound **8**, condensation with β-alanine *tert*-butyl ester hydrochloride and deprotection of *tert*-butyl ester obtained desired compound **9**.

Scheme 1. Synthesis of the target compounds 9a-9s[a]

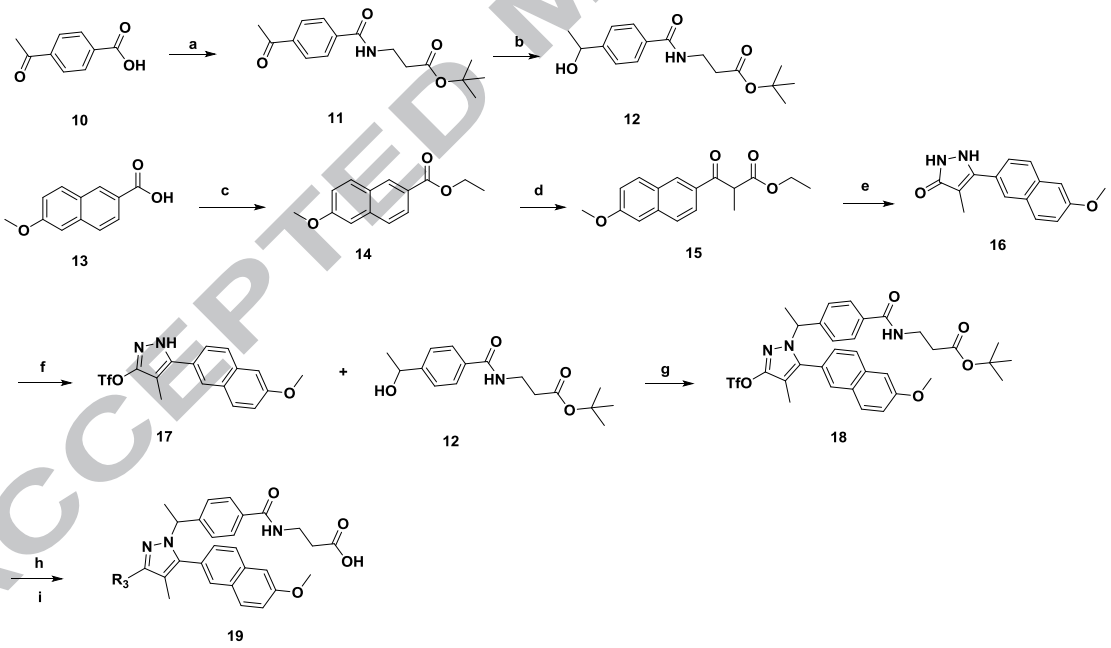


[a]Reagents and conditions: (a) EtOH, H_2SO_4, reflux, 4 h; (b) *cat.* HOAc, toluene, 80 ^oC, overnight; (c) $NaBH_3CN$, *p*-toluenesulfonic acid, THF, rt, 3 h; (d) TFA, DCM, rt, 1 h; (e) HOAc, reflux, 4 h; (f) triflic anhydride (Tf_2O), TEA, THF, -78 ^oC to 0 ^oC, 1.5 h; (g) R_2-$B(OH)_2$, $Pd(PPh_3)_4$, TEA, DME, 100 ^oC, MW, 25 min; (h) NaOH, MeOH, 1,4-dioxane, 60 ^oC, 1 h; (i) β-alanine *tert*-butyl ester hydrochloride, PyBOP, DIEA, DMF, rt, overnight; (j) TFA, DCM, rt, 1 h.

The intermediate **12** and desired compound **19** were synthesized according to the synthetic route shown in Scheme 2. Condensation of compound **10** with β-alanine

tert-butyl ester hydrochloride afforded compound **11**, which was reduced by sodium borohydride to provide intermediate **12**. Esterification of compound **13** produced compound **14**, which reacted with ethyl propionate to give compound **15**. Cyclization of compound **15** and hydrazine hydrate in glacial acetic acid produced compound **16**. Nucleophilic reaction of compound **16** in the presence of TEA generated compound **17**, which was subjected to Mitsunobu reaction with compound **12** to yield the main product **18**, the minor isomer is separated by chromatography. The desired compound **19** was generated by coupling reaction and deprotection of *tert*-butyl ester. [36]

Scheme 2. Synthesis of key intermediate 12 and target compounds 19a-19d[a]

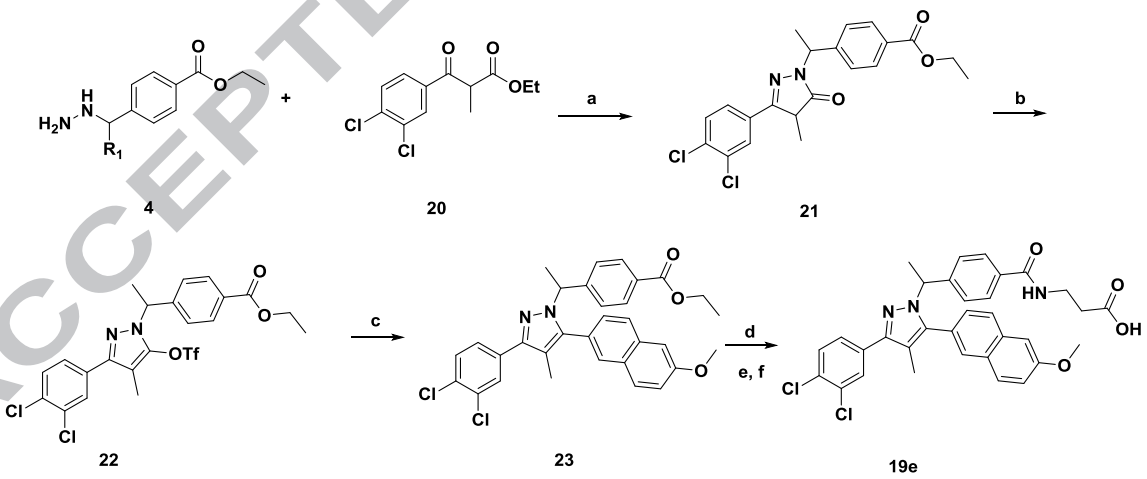


[a]Reagents and conditions: (a) β-alanine *tert*-butyl ester hydrochloride, PyBOP, DIEA, DMF, rt, overnight; (b) $NaBH_4$, DCM, rt, overnight; (c) EtOH, H_2SO_4, reflux, overnight; (d) NaH, ethyl propionate, THF, 80 ^oC, 24 h; (e) hydrazine hydrate (85%), HOAc, 80 ^oC, overnight; (f) pyridine, Tf_2O, THF, -78 ^oC to 0 ^oC, 2 h; (g) PPh_3, DIAD,

DCM, rt, 2 h; (h) XPhos aminobiphenyl palladium chloride precatalyst, R_3-$B(OH)_2$, XPhos, K_2CO_3, 17 h; (i) TFA, DCM, rt, 1 h.

The desired compound **19e** was synthesized according to the synthetic route shown in Scheme 3. Cyclization of hydrazine **4** with ethyl 3-(3,4-dichlorophenyl)-2-methyl-3-oxopropanoate **20** gave compound **21**. Nucleophilic reaction of compound **21** in the presence of TEA generated compound **22**, which was subjected to a classic Suzuki coupling reaction to yield compound **23**. Hydrolysis of compound **23**, condensation with β-alanine *tert*-butyl ester hydrochloride and deprotection of *tert*-butyl ester obtained desired compound **19e**.

Scheme 3. Synthesis of the target compounds 19e[a]



[a]Reagents and conditions: (a) HOAc, reflux, 4 h; (b) Tf_2O, TEA, THF, -78 °C to 0 °C, 1.5 h; (c) 6-Methoxy-2-naphthaleneboronic acid, $Pd(PPh_3)_4$, TEA, DME, 100 °C, MW, 25 min; (c) NaOH, MeOH, 1,4-dioxane, 60 °C, 1 h; (e) β-alanine *tert*-butyl ester hydrochloride, PyBOP, DIEA, DMF, rt, overnight; (f) TFA, DCM, rt, 1 h.

2.3. Biological evaluation

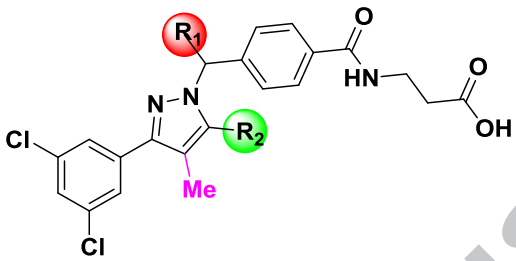
The antagonistic activities of all pyrazole derivatives were evaluated by a competitive binding assay with *rac*-**MK-0893** and **MK-0893** as the positive control using stably transfected CHO-K1 cells expressing human GCGR. The results are reported as concentration for 50% inhibition (IC_{50}) shown in Tables 1 and 2. SAR analysis for these compounds is summarized below.

After introduction of methyl group on the pyrazole, we investigated R_1 and R_2 substitutions (Table 1). Compounds **9a**, **9b** and **9c** with R_1 as hydrogen at benzyl position showed decreased activities compared with *rac*-**MK-0893**, while compound **9b** with 2-naphthyl ring led to high binding activity (IC_{50} = 2.79 μM) among these compounds. Compound **9d** with methyl group at benzyl position substituted by phenyl ring provided moderate binding activity (IC_{50} = 0.20 μM) and cAMP response (IC_{50} = 0.80 μM). When compared with non-substitution on phenyl ring, compounds **9e** and **9f** with a methyl group on the phenyl ring exhibited high potencies. Between them, methyl substitution at *meta*-position (**9e**) on the phenyl ring provided better GCGR binding activity (IC_{50} = 0.1 μM). Sterically hindered moiety such as biphenyl was subsequently introduced and showed good GCGR binding activities and cAMP responses. Compound **9g** with 2-biphenyl group showed moderate GCGR binding activity (IC_{50} = 0.31 μM) and cAMP response (IC_{50} = 1.49 μM). Compound **9h** with 3-biphenyl group showed equivalent GCGR binding activity (IC_{50} = 0.37 μM) and cAMP response (IC_{50} = 0.45 μM). Various aryl rings were introduced to improve the

antagonistic activity. Thiophene substituted compound **9i** displayed low binding affinity (IC_{50} = 0.55 μM) and cAMP response (IC_{50} = 0.88 μM). Compounds with fused rings such as quinoline (**9j**), benzofuran (**9k**), indole (**9l**) and 1-Me-indole (**9m**) were subsequently synthesized. It was observed that (1) quinoline-substitution presented decreased binding activity (IC_{50} = 0.50 μM) and cAMP response (IC_{50} = 2.03 μM); (2) benzofuran-substitution was more favorable than indole-substitution; and (3) methyl group substituted on indole elevated the binding activity (IC_{50} = 0.28 μM) and cAMP response (IC_{50} = 2.31 μM) in comparison with compound **9l**. In addition, compared with these heterocyclic rings, naphthyl ring (compounds **9n** and **9o**) especially 2-naphthyl ring possessed good binding activity (IC_{50} = 0.11 μM) and cAMP response (IC_{50} = 0.33 μM), while compound **9p** with 6-ethoxy-substitution on 2-naphthyl ring showed good activities (GCGR biding activity, IC_{50} = 0.18 μM; cAMP response, IC_{50} = 0.37 μM) as well. Compound **9q** with a methoxy group showed better GCGR binding activity (IC_{50} = 0.09 μM) and cAMP response (IC_{50} = 0.22 μM) compared with compound **9p**. Furthermore, the resolution of compound **9q** yielded compounds **9r** and **9s**. Compound **9r** bearing (*S*)-configured methyl group showed equivalent GCGR binding activity (IC_{50} = 0.06 μM) and cAMP response (IC_{50} = 0.26 μM) compared with (*rac*)-**9q**. The GCGR binding activity and cAMP response of compound **9r** were increased by approximately 10-fold and 5-fold, respectively, compared with (*R*)-configuration (**9s**) (GCGR binding activity, IC_{50} = 0.63 μM; cAMP response, IC_{50} = 1.19 μM). This round of optimization indicated that compounds with R_1 as methyl at benzyl position gained equivalent activities.

Compounds with R_2 as 6-methoxy-substitution on 2-naphthyl ring were more capable of binding to GCGR and inducing better cAMP response activity.

Table 1. *In vitro* GCGR binding and functional cAMP activities of compounds **9a-9s.**



Compound	R_1	R_2	GCGR binding[a]	cAMP response[a]
			IC_{50} (μM)	IC_{50} (μM)
9a	H	4-Cl-Ph	4.92 ± 1.65	27.34 ± 7.30
9b	H	naph-1-yl	2.79 ± 1.78	2.38 ± 0.49
9c	H	6-MeO-naph-2-yl	3.23 ± 1.79	7.53 ± 0.50
9d	Me	Ph	0.20 ± 0.04	0.80 ± 0.17
9e	Me	3-Me-Ph	0.10 ± 0.01	0.45 ± 0.11
9f	Me	4-Me-Ph	0.39 ± 0.15	0.83 ± 0.20
9g	Me	biph-2-yl	0.31 ± 0.14	1.49 ± 0.45
9h	Me	biph-3-yl	0.37 ± 0.20	0.45 ± 0.04
9i	Me	thioph-2-yl	0.55 ± 0.22	0.88 ± 0.21
9j	Me	quinoline-6-yl	0.50 ± 0.10	2.03 ± 0.36
9k	Me	benzofuran-5-yl	0.30 ± 0.07	1.29 ± 0.82

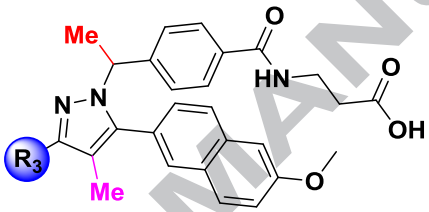
9l	Me	indole-5-yl	3.90 ± 1.69	5.52 ± 1.23
9m	Me	1-Me-indole-5-yl	0.28 ± 0.02	2.31 ± 0.60
9n	Me	naph-1-yl	0.57 ± 0.35	17.06 ± 5.04
9o	Me	naph-2-yl	0.11 ± 0.01	0.33 ± 0.15
9p	Me	6-EtO-naph-2-yl	0.18 ± 0.06	0.37 ± 0.01
9q	Me	6-MeO-naph-2-yl	0.09 ± 0.04	0.22 ± 0.05
9r	(*S*)-Me	6-MeO-naph-2-yl	0.06 ± 0.01	0.26 ± 0.17
9s	(*R*)-Me	6-MeO-naph-2-yl	0.63 ± 0.37	1.19 ± 0.29
rac-**MK-0893**			0.05 ± 0.01	0.10 ± 0.01
MK-0893			0.02 ± 0.01	0.08 ± 0.001

[a]Activities are reported as means ± SEM (N ≥ 3).

To fully understand the SAR of R_3 group after making compounds with R_1 as methyl and with R_2 as 6-MeO-naphthalene, multiple substituents were explored (Table 2). All compounds in Table 2 are racemic, which is much better to explore the SAR with racemic compounds **9a-9q** in Table 1. Compound **19a** with phenyl substitution showed low binding activity (IC_{50} = 1.92 μM) and cAMP response (IC_{50} = 2.69 μM). Compound **19b** (3-Me-Ph) exhibited better cAMP response (IC_{50} = 0.74 μM). According to the results of compounds **19a** and **19b**, we investigated the electron-withdrawing substituent such as trifluoromethyl group on the phenyl ring at

the *othor*- and *meta*-positions. Compound **19c** displayed low binding activity (IC_{50} = 0.23 μM) and cAMP response (IC_{50} = 1.70 μM). While compound **19d** exhibited a better binding activity (IC_{50} = 0.07 μM) than compound **19c**. Furthermore, compound **19e** containing 3,4-dichloro-substitution on the phenyl ring demonstrated good GCGR binding activity (IC_{50} = 0.08 μM) and cAMP response (IC_{50} = 0.46 μM).

Table 2. *In vitro* GCGR binding and functional cAMP activities of compounds **19a-19e**.



Compound	R_3	GCGR binding[a]	cAMP response[a]
		IC_{50} (μM)	IC_{50} (μM)
19a	Ph	1.92 ± 0.94	2.69 ± 1.33
19b	3-Me-Ph	2.75 ± 0.80	0.74 ± 0.16
19c	2-CF_3-Ph	0.23 ± 0.07	1.70 ± 0.71
19d	3-CF_3-Ph	0.07 ± 0.01	0.44 ± 0.26
19e	3,4-Cl_2-Ph	0.08 ± 0.01	0.46 ± 0.05
rac-**MK-0893**		0.05 ± 0.01	0.10 ± 0.01
MK-0893		0.02 ± 0.01	0.08 ± 0.001

[a]Activities are reported as means ± SEM (N ≥ 3).

2.4. Docking studies

As compound **9r** ((*S*)-isomer of compound **9q**) exhibited both good GCGR binding activity and cAMP response, it was docked into the GCGR binding domain to investigate the binding modes and the interactions (Fig. 4). It was observed that compound **9r** occupied the P1 and P2 pockets and shown similar binding modes as **MK-0893** (Fig. 4A). The β-alanine moiety was in the P1 pocket forming hydrogen bonds with residues Ser350, Arg346, Asn404, Lys349, Lys405 and a water-mediated hydrogen bond with residues Ser350 and Leu399. Docking results showed that 6-MeO-naphthalene occupied P2 pocket and formed extensive hydrophobic interactions with residues Leu329, Leu352 and Ala348 (Fig. 4B). Inspired by the docking results, we proposed that addition of appropriate hindrance on the pyrazole may modestly improve the antagonistic activity.

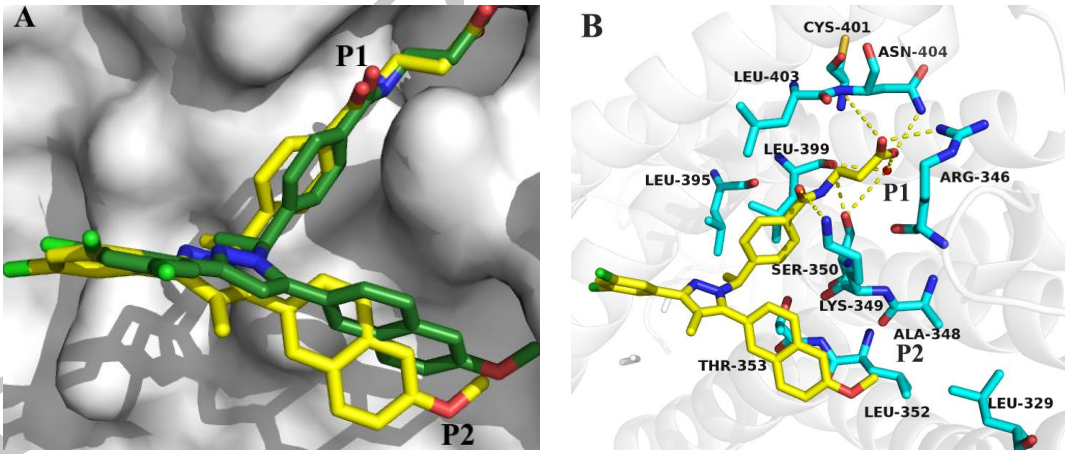


Fig. 4. Superposition of compounds **9r** (yellow) with **MK-0893** (green) (A). Docking structures of compounds **9r** (B). Some hydrogen atoms were omitted for clarity. All figures were prepared using PyMol (http://www.pymol.org).

3. Conclusion

In this paper, we described the design, synthesis and biological evaluation of a

novel series of 4-methyl substituted pyrazole derivatives as potent GCGR antagonists. SAR was summarized and the binding mode was studied. Among the derivatives, compounds **9q**, **9r**, **19d** and **19e** showed high GCGR binding activities (IC_{50} = 0.09 μM, 0.06 μM, 0.07 μM and 0.08 μM, respectively) and cAMP responses (IC_{50} = 0.22 μM, 0.26 μM, 0.44 μM and 0.46 μM, respectively). These results indicate that compounds **9q**, **9r**, **19d** and **19e** are useful leads for further investigations.

4. Experimental

4.1. Chemistry

All commercially available compounds and solvents were used without further purification. The target products were characterized by their NMR and MS spectra. Nuclear magnetic resonance spectra were recorded in deuterochloroform ($CDCl_3$), dimethylsulfoxid-d_6 (DMSO-d_6) or methonal-d_4 (CD_3OD) on a Brucker AMX-400 or 500 MHz instrument (TMS as IS). 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 Finnigan MAT 95 spectrometer. All of the microwave-assistant reactions were performed in an Initiator^{TM} EXP microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation. All target compounds 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 (4.6 × 150 mm, 5 μm),

CH_3CN/H_2O at 1 mL/min and calculated the peak areas at 254 nm. The enantiomeric excess (ee) of compounds **9r** and **9s** were identified by Agilent-1100 HPLC with photodiode array detector (DAD), and CHIRALPAK IE column (0.46 cm × 15 cm, 5 μm) was used with elution phase PE/EtOH/HAOc = 85/15/0.1 (v/v) at 1.0 mL/min. The ee (%) values were calculated by peak areas at 254 nm.

Ethyl 4-acetyl benzoate (2). A solution of 4-acetylbenzoic acid (13.0 g, 79.2 mmol) in ethanol (100 mL) was stirred in ice bath. Concentrated H_2SO_4 was slowly added and the mixture was refluxed at 80 ^oC for 3 h. Extracted with EtOAc, washed with saturated brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography to afford ethyl 4-acetylbenzoate as a white solid (13.6 g, 89.4%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (m, 4H), 4.35 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). MS (ESI, m/z): 191.1 $[M-H]^-$.

***tert*-Butyl 2-{1-[4-(ethoxycarbonyl)-phenyl]ethyl}hydrazine carboxylate (3).** A solution of *tert*-butyl carbazate (14.0 g, 106.1 mmol) and compound **2** (13.6 g, 70.8 mmol) in toluene (120 mL) with catalytic HOAc was stirred at 80 ^oC overnight. *tert*-Butyl-2-{1-[4-(ethoxycarbonyl)phenyl]-ethylidene}hydrazine carboxylate was collected by filtration as a crystalline solid (14.8 g, 68.3%). Without further purification, $NaBH_3CN$ (3.3 g, 53.1 mmol) and *tert*-butyl 2-{1-[4-(ethoxycarbonyl)phenyl]ethylidene}-hydrazinecarboxylate (14.8 g, 48.3 mmol) were dissolved in THF (120 mL). A solution of *p*-toluenesulfonic acid (9.7 g, 56.5 mmol) in THF (50 mL) was slowly added for 3 h and the reaction was detected by TLC. The mixture was extracted with EtOAc and washed with brine, dried over

anhydrous Na_2SO_4 and concentrated to give a white solid. The solid was redissolved in DCM and washed with 1 N NaOH and the organic layer was washed with 1 N HCl and brine, dried over Na_2SO_4 and concentrated to yield white solid. Flash column chromatography petroleum ether/ethyl acetate = 4/1 to yield 13.6 g (91%) *tert*-butyl 2-{1-[4-(ethoxycarbonyl)-phenyl]ethyl}hydrazine carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 4.73 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 1H), 1.33 (d, *J* = 6.2 Hz, 9H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H). MS (ESI, *m/z*): 307.1 $[M-H]^-$.

{1-[4-(Ethoxycarbonyl)phenyl]ethyl}hydrazinium-trifluoroacetate (4). The *tert*-butyl 2-{1-[4-(ethoxycarbonyl)-phenyl]ethyl}hydrazine carboxylate (13.6 g, 44.1 mmol) was dissolved in DCM (50 mL) and treated with TFA (50 mL) at room temperature for 1 h. The mixture was concentrated under reduced pressure without further purification. MS (ESI, *m/z*): 209.1 $[M+H]^+$.

Ethyl 3-(3,5-dichlorophenyl)-2-methyl-3-oxopropanoate (5). Ethyl 3,5-dichlorobenzoate (8.4 g, 38.3 mmol) and sodium hydride (1.1 g, 46.0 mmol) were dissolved in 100 mL THF under N_2. To the mixture was added 13.2 mL ethyl propionate 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 9.7 g (92%) ethyl 3-(3,5-dichlorophenyl)-2-methyl-3-oxopropanoate **5** as orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (t, *J* = 3.3 Hz, 3H), 4.80 (q, *J* = 6.9 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). MS

(ESI, *m/z*): 274.0 $[M-H]^-$.

Ethyl 4-(1-(3-(3,5-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)ethyl)benzoate (6). A solution of compound **4** and compound **5** (19.8 g, 72.0 mmol) was refluxed in 300 mL HOAc for 4 h. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate, washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. Flash column chromatography gave 8.1 g (30%) ethyl 4-(1-(3-(3,5-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)ethyl)benz oate as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 7.95 – 7.86 (m, 2H), 7.62 (d, *J* = 1.8 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 5.64 (q, *J* = 6.9 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 2.05 (s, 3H), 1.78 (d, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). MS (ESI, *m/z*): 420.0 $[M+H]^+$.

Ethyl 4-(1-(3-(3,5-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzoate (7). The solution of compound **6** (6.5 g, 15.5 mmol) in THF (120 mL) at −78 ^{o}C was added TEA (6.5 mL, 46.5 mmol). Triflic anhydride (4.0 mL, 23.7 mmol) was added over half an hour. The reaction mixture was stirred for 1 h at −78 ^{o}C and moved to room temperature and detected by TLC. 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 provide ethyl 4-(1-(3-(3,5-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzoate (6.0 g, 70.2%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 0.9 Hz, 2H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 5.66 (q, *J* = 6.6 Hz,

1H), 4.28 (q, *J* = 7.0 Hz, 2H), 2.15 (s, 3H), 1.86 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H). MS (ESI, *m/z*): 574.1 $[M+Na]^+$.

Ethyl 4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzoate (8). Compound **7** (221.0 mg, 0.4 mmol), (6-methoxynaphthalen-2-yl)boronic acid (101.2 mg, 0.5 mmol), and TEA (306 μL, 2.2 mmol) were dissolved in dimethoxyethane. $Pd(PPh_3)_4$ (46.3 mg, 40 μmol) was added, and the mixture was deoxygenated before heated in microwave at 100 ^oC for 25 min. The mixture was added EtOAc and saturated ammonium chloride, washed with saturated brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to give ethyl 4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzoate a colorless oil (175.0 mg, 78.0%). ^1H NMR (400 MHz, CD_3OD) δ 7.94 – 7.77 (m, 4H), 7.72 (s, 3H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.38 (s, 1H), 7.21 (ddd, *J* = 18.0, 10.7, 5.0 Hz, 4H), 5.53 (d, *J* = 4.1 Hz, 1H), 4.25 (dd, *J* = 5.6, 3.9 Hz, 2H), 3.88 (s, 3H), 2.09 (d, *J* = 2.0 Hz, 3H), 1.84 (d, *J* = 3.5 Hz, 3H), 1.26 (t, *J* = 8.0 Hz, 3H). MS (ESI, *m/z*): 557.1 $[M-H]^-$.

3-(4-(1-(3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9r). Compound **8** (175.0 mg, 0.3 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 ^oC for 1 h. This was acidified with 2 N HCl, extracted with EtOAc, washed with saturated brine, dried over Na_2SO_4 and concentrated to produce a white solid (145 mg, 87.2%). This solid was suspended in 2 mL DMF, followed by addition of DIEA (216 μL, 1.3 mmol), β-alanine *tert*-butyl ester

hydrochloride (148.7 mg, 0.8 mmol). A solution of benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP) (159.0 mg, 0.3 mmol) in DMF was added. After stirring at room temperature for 3 h, 46.4 mg PyBOP was added, and the reaction mixture was stirred overnight. After addition of water (1 mL), the mixture was heated to 60 ^{o}C for 30 min. Ethyl acetate was added, and the organic layer was washed with 0.5 N HCl, 5% K_2CO_3 and brine. The flash chromatography (SiO_2, 25 % ethyl acetate in petroleum ether) gave 130 mg (72.3%) of *tert*-butyl 3-(4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoate as white solid. The solid was then treated with TFA-DCM (1:2, 3 mL) for 1 hour. The solvent was removed under reduced pressure. The flash chromatography (SiO_2, 5% MeOH in DCM) gave 95.0 mg (80%) 3-(4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid **9r** as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.45 (t, *J* = 5.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.78 – 7.66 (m, 5H), 7.62 (t, *J* = 1.8 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.53 (q, *J* = 6.8 Hz, 1H), 3.91 (s, 3H), 3.43 – 3.38 (m, 2H), 2.47 (d, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.86 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.9, 165.9, 158.1, 145.5, 145.4, 143.1, 137.6, 134.4, 134.2, 133.5, 129.8, 129.2, 128.1, 127.5, 127.4, 126.7, 126.0, 125.3, 124.1, 119.4, 112.7, 105.9, 57.2, 55.4, 35.6, 33.8, 21.6, 9.8. LRMS (ESI, *m/z*): 600.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{33}H_{29}Cl_2N_3O_4$, 600.1457 $[M-H]^-$; found 600.1459, purity: 98.4%; $[\alpha]^{20}_D$ = 1.18 (c = 1,

CH_3OH).

3-(4-((5-(4-Chlorophenyl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)methyl)benzamido)propanoic acid (9a). 3-(4-((5-(4-Chlorophenyl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)methyl)benzamido)propanoic acid (**9a**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.49 (t, *J* = 5.4 Hz, 1H), 7.73 (s, 1H), 7.72 – 7.68 (m, 3H), 7.63 (t, *J* = 1.9 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.35 (s, 2H), 3.46 – 3.40 (m, 2H), 2.48 (d, *J* = 7.1 Hz, 2H), 2.11 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.3, 164.9, 145.9, 141.8, 134.0, 137.1, 134.4, 131.6, 129.1, 127.1, 126.8, 126.6, 125.3, 113.1, 52.7, 37.4, 37.3, 9.8. LRMS (ESI, *m/z*): 540.0 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{27}H_{22}Cl_3N_3O_3$, 540.0648 $[M-H]^-$; found 540.0651, purity: 95.2%.

3-(4-((3-(3,5-Dichlorophenyl)-4-methyl-5-(naphthalen-1-yl)-1*H*-pyrazol-1-yl)methyl)benzamido)propanoic acid (9b). 3-(4-((3-(3,5-Dichlorophenyl)-4-methyl-5-(naphthalen-1-yl)-1*H*-pyrazol-1-yl)methyl)benzamido)propanoic acid (**9b**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.43 (s, 1H), 8.07 (dd, *J* = 21.2, 8.2 Hz, 2H), 7.78 (d, *J* = 1.8 Hz, 2H), 7.67 – 7.54 (m, 5H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 5.28 (d, *J* = 16.0 Hz, 1H), 5.01 (d, *J* = 15.9 Hz, 1H), 3.40 (d, *J* = 5.8 Hz, 2H), 2.46 (d, *J* = 7.0 Hz, 2H), 1.97 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.7, 145.8, 141.1, 140.1, 137.3, 134.4, 133.4, 133.2, 131.5, 129.9, 129.2, 128.6, 127.2, 127.2, 126.7, 126.5, 126.3, 125.5, 125.3, 124.7, 69.7, 52.7,

35.5, 33.7, 9.9. LRMS (ESI, *m/z*): 556.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{31}H_{25}Cl_2N_3O_3$, 556.1195 $[M-H]^-$; found 556.1189, purity: 95.6%.

3-(4-((3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)methyl)benzamido)propanoic acid (**9c**). 3-(4-((3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)methyl)benzamido)propanoic acid (**9c**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.45 (t, *J* = 5.5 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 9.1 Hz, 2H), 7.73 (d, *J* = 1.9 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.62 (t, *J* = 1.9 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.23 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.39 (s, 2H), 3.90 (s, 3H), 3.41 (dd, *J* = 12.6, 7.0 Hz, 2H), 2.46 (d, *J* = 7.1 Hz, 2H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 165.0, 158.2, 145.9, 143.2, 140.2, 137.4, 134.4, 134.1, 129.8, 129.1, 128.2, 127.4, 127.1, 126.8, 126.7, 125.3, 124.1, 119.5, 112.9, 106.0, 55.4, 52.8, 37.5, 37.3, 10.0. LRMS (ESI, *m/z*): 586.0 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{32}H_{27}Cl_2N_3O_4$, 586.1300 $[M-H]^-$; found 586.1315, purity: 96.2%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-phenyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9d). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-phenyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9d**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.17 – 10.49 (m, 1H), 8.44 (s, 1H), 7.77 – 7.66 (m, 5H), 7.61 (s, 1H), 7.50 (s, 5H), 7.31 – 7.20 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 3H), 5.47 (d, *J* = 6.8 Hz, 1H), 3.42 (dd, *J* = 12.5, 6.6 Hz, 3H), 2.47 (d, *J* = 7.1 Hz, 3H), 2.08 (s, 4H), 1.84 (d, *J* = 6.9 Hz, 4H). ^{13}C NMR

(125 MHz, DMSO-d_6) δ 172.9, 165.9, 145.4, 145.3, 142.9, 137.5, 134.3, 133.5, 129.9, 129.2, 129.0, 128.9, 127.4, 126.7, 125.9, 125.3, 112.5, 57.1, 35.5, 33.8, 21.5, 9.7. LRMS (ESI, *m/z*): 520.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{28}H_{25}Cl_2N_3O_3$, 520.1196 $[M-H]^-$; found 520.1188 purity: 95.5%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(*m*-tolyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9e). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(*m*-tolyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9e**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, CD_3OD) δ 12.15 (s, 1H), 8.44 (s, 1H), 7.72 (t, *J* = 5.6 Hz, 3H), 7.59 (s, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.45 (q, *J* = 6.8 Hz, 1H), 3.43 (dd, *J* = 12.7, 6.8 Hz, 2H), 2.47 (d, *J* = 7.1 Hz, 2H), 2.33 (s, 2H), 2.09 (d, *J* = 16.0 Hz, 2H), 1.83 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.9, 145.5, 145.4, 143.0, 138.2, 137.6, 134.4, 133.5, 130.4, 129.6, 129.1, 128.8, 127.4, 127.0, 126.7, 125.9, 125.3, 112.4, 57.1, 35.6, 33.8, 21.6, 21.0, 9.7. LRMS (ESI, *m/z*): 534.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{29}H_{28}Cl_2N_3O_3$, 536.1502 $[M+H]^+$; found 536.1510 purity: 94.9%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(*p*-tolyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9f). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(*p*-tolyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9f**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 7.80 – 7.66 (m, 4H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.14 (dd, *J* = 8.0, 2.7 Hz, 4H), 5.46 (q, *J* = 6.7 Hz, 1H), 3.42 (dd, *J* = 12.5, 6.7 Hz, 3H),

2.46 (d, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 2.12 – 1.99 (m, 3H), 1.81 (t, *J* = 13.7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 165.9, 145.4, 145.4, 142.9, 138.5, 137.5, 134.3, 133.4, 129.7, 129.5, 127.4, 126.6, 126.2, 125.9, 125.2, 112.4, 57.0, 35.5, 33.8, 21.5, 20.9, 9.7. LRMS (ESI, *m/z*): 534.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{29}H_{27}Cl_2N_3O_3$, 534.1351 $[M-H]^-$; found 534.1358, purity: 95.5%.

3-(4-(1-(5-([1,1'-Biphenyl]-2-yl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9g). 3-(4-(1-(5-([1,1'-Biphenyl]-2-yl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9g**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.43 (t, *J* = 5.6 Hz, 1H), 7.68 – 7.55 (m, 9H), 7.35 (d, *J* = 7.3 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 2H), 4.90 (q, *J* = 7.1 Hz, 1H), 3.42 – 3.37 (m, 2H), 2.45 (t, *J* = 7.1 Hz, 2H), 2.08 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.4, 166.3, 145.6, 145.4, 142.5, 142.3, 140.3, 138.0, 134.8, 134.0, 132.2, 130.7, 130.5, 130.4, 129.1, 128.9, 128.8, 128.4, 128.3, 127.8, 127.7, 127.5, 127.1, 127.0, 126.2, 125.5, 125.3, 113.7, 57.4, 36.0, 34.3, 20.2, 10.2. LRMS (ESI, *m/z*): 596.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{34}H_{29}Cl_2N_3O_3$, 596.1513 $[M-H]^-$; found 596.1514, purity: 99.2%.

3-(4-(1-(5-([1,1'-Biphenyl]-3-yl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9h). 3-(4-(1-(5-([1,1'-Biphenyl]-3-yl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9h**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.48 (t, *J* = 5.4 Hz, 1H), 7.81 – 7.71 (m, 5H), 7.65 –

7.52 (m, 4H), 7.41 (dq, *J* = 14.3, 7.2 Hz, 4H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.54 (q, *J* = 7.0 Hz, 1H), 3.43 (dd, *J* = 12.8, 6.6 Hz, 2H), 2.47 (m, 2H), 2.12 (s, 3H), 1.86 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.4, 166.3, 146.2, 145.9, 143.2, 141.1, 139.7, 138.0, 134.8, 133.9, 130.3, 130.0, 129.4, 129.3, 128.5, 128.3, 127.9, 127.7, 127.2, 127.2, 126.3, 125.8, 113.3, 57.9, 36.0, 34.3, 22.2, 10.2. LRMS (ESI, *m/z*): 596.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{34}H_{29}Cl_2N_3O_3$, 596.1513 $[M-H]^-$; found 596.1515, purity: 99.5%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(thiophen-2-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9i). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(thiophen-2-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9i**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.45 (s, 1H), 7.81 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.78 – 7.68 (m, 4H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.11 (dd, *J* = 3.5, 1.1 Hz, 1H), 5.63 (q, *J* = 6.9 Hz, 1H), 3.43 (dd, *J* = 12.7, 7.0 Hz, 2H), 2.47 (d, *J* = 7.1 Hz, 2H), 2.15 (d, *J* = 13.3 Hz, 3H), 1.84 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 165.8, 145.6, 145.3, 137.2, 135.6, 134.3, 133.5, 130.1, 129.3, 128.3, 127.9, 127.4, 126.8, 125.8, 125.4, 114.5, 57.3, 35.5, 33.8, 21.6, 9.8. LRMS (ESI, *m/z*): 526 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{26}H_{23}Cl_2N_3O_3S$, 528.4480 $[M+H]^+$; found 528.0745, purity: > 99.9%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(quinolin-6-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9j). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(quinolin-6-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9j**) was prepared as

white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 9.00 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.46 (t, *J* = 5.7 Hz, 1H), 8.40 (d, *J* = 7.5 Hz, 1H), 8.16 – 8.06 (m, 1H), 7.94 (d, *J* = 1.3 Hz, 1H), 7.75 (d, *J* = 1.9 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.57 (q, *J* = 6.9 Hz, 1H), 3.41 (dd, *J* = 12.6, 7.0 Hz, 2H), 2.47 (m, 2H), 2.13 (s, 3H), 1.87 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.9, 151.6, 147.3, 145.6, 145.3, 142.2, 137.4, 136.4, 134.4, 133.5, 130.7, 129.9, 129.6, 127.8, 127.4, 127.3, 126.7, 125.9, 125.3, 122.2, 113.1, 57.4, 35.6, 33.8, 21.6, 9.7. LRMS (ESI, *m/z*): 571.0 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{31}H_{26}Cl_2N_4O_3$, 571.1309 $[M-H]^-$; found 573.0453, purity: 95.7%.

3-(4-(1-(5-(Benzofuran-5-yl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl) ethyl)benzamido)propanoic acid (9k). 3-(4-(1-(5-(Benzofuran-5-yl)-3-(3,5-dichlorophenyl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9k**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.47 (t, *J* = 5.5 Hz, 1H), 8.11 (d, *J* = 2.1 Hz, 1H), 7.80 – 7.67 (m, 5H), 7.60 (dd, *J* = 7.1, 5.4 Hz, 2H), 7.14 (t, *J* = 9.5 Hz, 3H), 7.03 (d, *J* = 2.2 Hz, 1H), 5.48 (q, *J* = 6.9 Hz, 1H), 3.42 (dd, *J* = 12.6, 7.0 Hz, 2H), 2.47 (m, 2H), 2.08 (s, 3H), 1.84 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 165.9, 154.3, 147.1, 145.3, 145.3, 143.1, 137.6, 134.3, 133.4, 127.7, 127.3, 126.6, 126.1, 125.9, 125.2, 123.9, 123.0, 112.6, 111.8, 106.9, 57.0, 35.5, 33.8, 21.5, 9.7. LRMS (ESI, *m/z*): 560.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{30}H_{25}Cl_2N_3O_4$, 560.1149 $[M-H]^-$; found 560.1159, purity: 95.9%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-5-(1*H*-indol-5-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9l). 3-(4-(1-(3-(3,5-Dichlorophenyl)-5-(1*H*-indol-5-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9l**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.48 (t, *J* = 5.3 Hz, 1H), 7.72 (t, *J* = 5.0 Hz, 4H), 7.60 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.49 (s, 1H), 5.51 (q, *J* = 6.5 Hz, 1H), 3.43 – 3.39 (m, 2H), 2.46 (m, 2H), 2.09 (s, 3H), 1.83 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.0, 165.9, 145.5, 145.2, 144.6, 137.8, 135.8, 134.3, 133.4, 127.7, 127.3, 126.5, 126.5, 126.0, 125.2, 122.6, 121.8, 119.5, 112.1, 111.8, 101.5, 56.7, 35.6, 334.0, 21.5, 9.9. LRMS (ESI, *m/z*): 559.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{30}H_{26}Cl_2N_4O_3$, 559.1309 $[M-H]^-$; found 559.1306, purity: 96.4%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(1-methyl-1*H*-indol-5-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9m). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(1-methyl-1*H*-indol-5-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9m**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.47 (t, *J* = 5.5 Hz, 1H), 7.73 (dt, *J* = 10.4, 5.2 Hz, 4H), 7.60 (t, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.46 (s, 1H), 7.44 (d, *J* = 3.1 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 5.49 (q, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 3.42 (dd, *J* = 12.4, 6.9 Hz, 2H), 2.47 (m, 2H), 2.08 (s, 3H), 1.84 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.9, 145.5, 145.2, 144.4, 137.8, 136.3, 134.3, 133.4, 130.8, 128.1, 127.3,

126.5, 126.0, 125.2, 122.6, 122.0, 119.6, 112.2, 110.2, 100.8, 56.8, 35.5, 33.8, 32.6, 21.5, 9.9. LRMS (ESI, *m/z*): 573.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{31}H_{28}Cl_2N_4O_3$, 573.1466 $[M-H]^-$; found 573.1479, purity: > 99.9%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(naphthalen-1-yl)-1*H*-pyrazol-1-yl) ethyl)benzamido)propanoic acid (9n). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(naphthalen-1-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9n**) was prepared as white solid according to the preparation of compound **9r**.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (t, *J* = 5.6 Hz, 1H), 8.34 (d, *J* = 5.8 Hz, 1H), 8.10 (t, *J* = 7.8 Hz, 3H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.72 (s, 1H), 7.70 (s, 1H), 7.67 – 7.60 (m, 4H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H), 7.52 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 6.7 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 5.28 (t, *J* = 7.0 Hz, 1H), 5.00 (q, *J* = 7.1 Hz, 1H), 3.49 – 3.24 (m, 4H), 2.48 – 2.41 (m, 2H), 1.96 (s, 3H), 1.92 (d, *J* = 6.8 Hz, 2H), 1.85 (d, *J* = 6.9 Hz, 2H), 1.78 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 165.1, 145.6, 145.0, 144.3, 141.0, 137.6, 134.5, 134.4, 134.1, 131.9, 131.5, 129.9, 129.9, 129.4, 128.8, 127.1, 126.7, 126.4, 126.2, 126.0, 125.3, 125.3, 124.4, 113.8, 57.6, 37.5, 37.3, 21.4, 9.7. LRMS (ESI, *m/z*): 570.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{32}H_{27}Cl_2N_3O_3$, 570.1351 $[M-H]^-$; found 570.1357, purity: 97.3%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(naphthalen-2-yl)-1*H*-pyrazol-1-yl) ethyl)benzamido)propanoic acid (9o). 3-(4-(1-(3-(3,5-Dichlorophenyl)-4-methyl-5-(naphthalen-2-yl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9o**) was prepared

as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, *J* = 5.4 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 6.7 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.75 (d, *J* = 1.8 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.67 – 7.55 (m, 3H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.55 (d, *J* = 6.9 Hz, 1H), 3.42 (dd, *J* = 12.5, 6.8 Hz, 2H), 2.47 (d, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.87 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 165.8, 145.5, 145.3, 142.8, 137.5, 134.3, 133.5, 132.7, 132.6, 129.4, 128.5, 128.1, 127.7, 127.4, 127.0, 126.8, 126.7, 126.6, 125.9, 125.3, 112.8, 57.3, 35.5, 33.7, 21.6, 9.7. LRMS (ESI, *m/z*): 570.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{32}H_{27}Cl_2N_3O_3$, 570.1351 $[M-H]^-$; found 570.1343, purity: 97.0%.

3-(4-(1-(3-(3,5-Dichlorophenyl)-5-(6-ethoxynaphthalen-2-yl)-4-methyl-*1H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9p). 3-(4-(1-(3-(3,5-Dichlorophenyl)-5-(6-ethoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9p**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.46 (t, *J* = 5.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.80 – 7.67 (m, 5H), 7.62 (t, *J* = 1.8 Hz, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.53 (q, *J* = 6.8 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 3.42 (dd, *J* = 12.6, 6.9 Hz, 2H), 2.48 (d, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.86 (d, *J* = 6.9 Hz, 3H), 1.41 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.9, 165.9, 157.3, 145.5, 145.4, 143.1, 137.6 134.4, 134.2, 133.5, 129.7, 129.2, 128.1, 127.5, 127.4, 127.3, 126.7, 126.0, 125.3, 124.0, 119.6, 112.7, 106.5, 63.3, 57.2, 54.9, 35.5, 33.8, 21.6, 14.6,

9.8. LRMS (ESI, *m/z*): 614.1 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{34}H_{31}Cl_2N_3O_4$, 614.1619 $[M-H]^-$; found 614.1628, purity: 99.6%.

(*S*)-3-(4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9q). (*S*)-3-(4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9q**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.46 (t, *J* = 5.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.79 – 7.67 (m, 5H), 7.63 (t, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.53 (q, *J* = 6.9 Hz, 1H), 3.91 (s, 3H), 3.42 (q, *J* = 7.1 Hz, 2H), 2.47 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 1.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.9, 158.1, 145.5, 145.4, 143.0, 137.6, 134.4, 134.1, 133.5, 129.7, 129.2, 128.1, 127.5, 127.4, 126.7, 125.9, 125.3, 124.1, 119.4, 112.7, 105.9, 57.2, 55.3, 35.5, 33.8, 29.0, 21.6, 9.7. LRMS (ESI, *m/z*): 600.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{33}H_{29}Cl_2N_3O_4$, 600.1457 $[M-H]^-$; found 600.1469, purity: 95.8%.

(*R*)-3-(4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (9s). (*R*)-3-(4-(1-(3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**9s**) was prepared as white solid according to the preparation of compound **9r**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.46 (t, *J* = 5.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.78 – 7.67 (m, 5H), 7.62 (t, *J*

= 1.9 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.53 (q, *J* = 7.4 Hz, 1H), 3.91 (s, 3H), 3.42 (q, *J* = 6.7 Hz, 2H), 2.47 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 1.86 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.9, 158.1, 145.5, 145.4, 143.0, 137.6, 134.4, 134.1, 133.5, 129.7, 129.2, 128.1, 127.5, 127.4, 126.7, 125.9, 125.3, 124.1, 119.4, 112.7, 105.9, 57.2, 55.4, 35.5, 33.8, 29.0, 21.6, 9.7. LRMS (ESI, *m/z*): 600.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{33}H_{29}Cl_2N_3O_4$, 600.1457 $[M-H]^-$; found 602.1458, purity: 96.9%; $[\alpha]^{20}_D$ = - 8.57 (c = 1, CH_3OH).

***tert*-Butyl 3-(4-acetylbenzamido)propanoate (11).** To a solution of 4-acetylbenzoic acid (13.6 g, 82.5 mmol) in DMF (300 mL) was added DIEA (68.4 mL, 412.7 mmol), β-alanine *tert*-butyl ester hydrochloride (30.0 g, 165.1 mmol) and PyBOP (51.6 g, 99.2 mmol) at room temperature. After stirring for 3 h, 15.0 g PyBOP was slowly added. The mixture was stirred overnight and extracted with EtOAc. After addition of water (60 mL), the mixture was heated to 60 ^oC for 30 min. Ethyl acetate was added and the organic layer was washed with 0.5 N HCl, 5% K_2CO_3 and brine. The flash chromatography (SiO_2, DCM/MeOH = 30/1) gave 20.0 g (83%) of *tert*-butyl 3-(4-acetylbenzamido)propanoate as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (t, *J* = 5.4 Hz, 1H), 7.98 (dd, *J* = 39.8, 8.3 Hz, 4H), 3.47 (dd, *J* = 12.6, 6.9 Hz, 2H), 2.62 (s, 3H), 2.48 (s, 2H), 1.39 (s, 9H). MS (ESI, *m/z*): 292.1 $[M+H]^+$.

***tert*-Butyl 3-(4-(1-hydroxyethyl)benzamido)propanoate (12).** A solution of *tert*-butyl 3-(4-acetylbenzamido)propanoate (20 g, 68.7 mmol) and $NaBH_3$ (3.9g，

103.0 mmol) in 100 mL DCM and 80 mL MeOH was stirred at room temperature overnight. The solvents were removed under reduced pressure. Ethyl acetate was added, and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. *tert*-Butyl 3-(4-(1-hydroxyethyl)benzamido)propanoate was produced as white solid (16.8 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (t, J = 5.5 Hz, 1H), 7.59 (dd, J = 142.7, 8.1 Hz, 4H), 4.76 (q, J = 6.3 Hz, 1H), 3.45 (q, J = 6.8 Hz, 2H), 3.35 (s, 1H), 2.47 (d, J = 7.0 Hz, 2H), 1.39 (s, 9H), 1.32 (d, J = 6.5 Hz, 3H). MS (ESI, *m/z*): 294.1 $[M+H]^+$.

Ethyl 6-methoxy-2-naphthoate (14). A solution of 6-methoxy-2-naphthyl carboxylic acid (20.0 g, 98.8 mmol) in ethanol (200 mL) was stirred in ice bath. After H_2SO_4 was slowly added, the mixture was refluxed at 80 ^{o}C for 3 h. The mixture was extracted with EtOAc, washed with saturated brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to afford ethyl 6-methoxy-2-naphthoate as white solid (20.0 g, 87.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.03 (dd, J = 8.6, 1.7 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.22 – 7.13 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 1.42 (d, J = 7.1 Hz, 3H). MS (ESI, *m/z*): 229.1 $[M-H]^-$.

Ethyl 3-(6-methoxynaphthalen-2-yl)-2-methyl-3-oxopropanoate (15). Ethyl 6-methoxy-2-naphthoate (20.0 g, 86.9 mmol) and sodium hydride (5.2 g, 217.1 mmol) were dissolved in 200 mL THF under N_2. Then the solution was added 40.0 mL ethyl propionate slowly at room temperature and refluxed 4 h. 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 11.6 g (47%) of ethyl 3-(6-methoxynaphthalen-2-yl)-2-methyl-3-oxopropanoate as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 7.15 (s, 1H), 4.52 (q, *J* = 7.0 Hz, 1H), 4.15 (dd, *J* = 14.0, 7.0 Hz, 2H), 3.94 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). MS (ESI, *m/z*): 287.1 $[M+H]^+$.

5-(6-Methoxynaphthalen-2-yl)-4-methyl-1,2-dihydro-3*H*-pyrazol-3-one (16). A solution of compound **15** (15.1 g, 52.6 mmol) and hydrazine hydrate (10.2 mL, 210.4 mmol) was refluxed in HOAc (200 mL) for 3 h. The solvent was removed under reduced pressure and the residue precipitated in DCM, and filtrated to gave 10.7 g (80%) of 5-(6-methoxynaphthalen-2-yl)-4-methyl-1,2-dihydro-3*H*-pyrazol-3-one as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 7.97 (s, 1H), 7.87 (dd, *J* = 8.7, 4.6 Hz, 2H), 7.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.19 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.89 (s, 3H), 3.35 (s, 1H), 2.06 (s, 3H). MS (ESI, *m/z*): 255.1 $[M+H]^+$.

5-(6-Methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-3-yl trifluoromethane sulfonate (17). 5-(6-methoxynaphthalen-2-yl)-4-methyl-1,2-dihydro-3*H*-pyrazol-3-one (10.0 g, 42.1 mmol) and pyridine (10.2 mmL, 126.2 mmol) were dissolved in THF (100 mL) at −78 °C. Triflic anhydride (10.6 mL, 63.1 mmol) was added in microwave at 100 °C for 25 min. The mixture was washed quenched with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to provide ethyl

5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-3-yl trifluoromethane sulfonate (4.3 g, 28.3%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.09 (s, 1H), 7.95 (dd, *J* = 11.1, 8.9 Hz, 2H), 7.68 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.90 (s, 3H), 2.19 (s, 3H). MS (ESI, *m/z*): 387.1 $[M+H]^+$.

***tert*-Butyl 3-(4-(1-(5-(6-methoxynaphthalen-2-yl)-4-methyl-3-(((trifluoro methyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoate (18).** *tert*-Butyl 3-(4-acetylbenzamido)propanoate **12** (8.6 g, 22.3 mmol) and ethyl 5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-3-yl trifluoromethanesulfonate (10.3 g, 26.6 mmol) and triphenylphosphine (8.0 g, 30.4 mmol) were dissolved in dimethoxyethane (150 mL). The diisopropyl azodicarboxylate (DIAD) (5.8 mL, 29.4 mmol) was slowly added, and the mixture was stirred for 2 h at room temperature. After concentrating to 20 mL, EtOAc was added. The mixture was washed with saturated brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to afford *t*ert-butyl 3-(4-(1-(5-(6-methoxynaphthalen-2-yl)-4-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzamido)propano ate as yellow oil (2.2 g, 11.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 3H), 7.53 (s, 1H), 7.21 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.16 (dd, *J* = 9.6, 5.3 Hz, 4H), 6.86 (t, *J* = 5.8 Hz, 1H), 5.35 (q, *J* = 6.9 Hz, 1H), 3.95 (s, 3H), 3.67 (dd, *J* = 11.8, 6.0 Hz, 2H), 2.55 (t, *J* = 5.9 Hz, 2H), 1.96 (s, 3H), 1.80 (d, *J* = 7.0 Hz, 3H), 1.46 (s, 9H). MS (ESI, *m/z*): 661.0 $[M-H]^-$.

3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-phenyl-1*H*-pyrazol-1-yl)eth

yl)benzamido)propanoic acid (19a). *tert*-Butyl 3-(4-(1-(5-(6-methoxynaphthalen-2-yl)-4-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzamido) propanoate (150 mg, 226.7 μmol), phenylboronic acid (37 mg, 272.1 μmol), chloro(2-dicyclohexylphosphino-2',4',6'-tri*iso*propyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium (8.3 mg, 10.6 μmol), 2-(dicyclohexylphosphino)-2',4',6'-tri*iso*propylbiphenyl (X-PHOS) (5.1 mg, 10.7 μmol) and potassium phosphate (64 mg，301.5 μmol) were dissolved in 1,4-dioxane and H_2O (4:1, 5 mL) under N_2. The mixture was stirred at 100 ^oC for 17 h and then filtrated, prepared by preparatory thin-layer chromatography and concentrated. A solution of DCM and TFA (2:1, 3 mL) was added. The mixture was stirred at room temperature for 1 h. The solvents were removed under reduced pressure. The residue was purified by chromatography (DCM:MeOH = 30:1) to give compound **19a** as white solid (85 mg, 71%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.45 (t, *J* = 5.5 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.24 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.51 (q, *J* = 6.9 Hz, 1H), 3.91 (s, 3H), 3.42 (dd, *J* = 12.7, 7.0 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.86 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.9, 165.9, 158.0, 148.3, 145.8, 142.5, 134.2, 134.0, 133.4, 129.7, 129.1, 128.5, 128.2, 127.6, 127.3, 127.3, 127.2, 126.0, 124.6, 119.4, 111.8, 105.9, 56.9, 55.4, 54.9, 35.6, 33.8, 21.7, 9.9. LRMS (ESI, *m/z*): 532.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{33}H_{31}O_4N_3$, 532.2242 $[M-H]^-$; found 532.2250, purity: 99.5%.

3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-(*m*-tolyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (19b). 3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-(*m*-tolyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**19b**) was prepared as white solid according to the preparation of compound **19a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.58 (s, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.25 – 7.05 (m, 6H), 5.43 (q, *J* = 6.9 Hz, 1H), 3.93 (s, 3H), 3.61 (dd, *J* = 11.2, 5.6 Hz, 2H), 2.56 (t, *J* = 5.5 Hz, 2H), 2.39 (s, 3H), 2.11 (s, 3H), 1.89 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 165.9, 158.0, 148.4, 145.8, 142.4, 137.5, 134.1, 134.0, 133.3, 129.7, 129.1, 128.3, 128.2, 127.9, 127.8, 127.6, 127.3, 127.2, 125.9, 124.7, 124.4, 119.3, 111.8, 105.9, 56.8, 55.3, 35.5, 33.8, 21.6, 21.2, 9.9. LRMS (ESI, *m/z*): 546.3 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{34}H_{33}O_4N_3$, 546.2398 $[M-H]^-$; found 546.2390, purity: 95.2%.

3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-(2-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (19c). 3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-(2-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**19c**) was prepared as white solid according to the preparation of compound **19a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.85 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.61 – 7.54 (m, 2H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.28 – 7.16 (m, 5H), 7.08 (d, *J* = 5.2 Hz, 1H), 5.47 (q, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 3.67 (d, *J* = 5.5 Hz, 2H), 2.66 (t, *J* = 5.4 Hz, 2H), 2.10 (s, 3H), 1.90 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9,

165.9, 158.0, 148.3, 145.8, 142.4, 136.4, 134.0, 133.3, 131.4, 129.7, 129.0, 128.2, 127.6, 127.3, 127.2, 127.1, 125.9, 124.7, 119.3, 111.6, 105.9, 56.8, 55.3, 35.5, 33.8, 21.6, 20.8, 9.9. LRMS (ESI, *m/z*): 600.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{34}H_{30}O_4N_3F_3$, 600.2116 $[M-H]^-$; found 600.2130, purity: 99.4%.

3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (19d). 3-(4-(1-(5-(6-Methoxynaphthalen-2-yl)-4-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid (**19d**) was prepared as white solid according to the preparation of compound **19a**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.46 (t, *J* = 5.4 Hz, 1H), 8.10 – 8.05 (m, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.79 (s, 1H), 7.72 (dd, *J* = 10.2, 7.1 Hz, 4H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.55 (q, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 3.42 (dd, *J* = 12.6, 6.8 Hz, 2H), 2.47 (d, *J* = 7.1 Hz, 2H), 2.13 (s, 3H), 1.87 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.9, 165.9, 158.1, 146.8, 145.6, 143.0, 135.2, 134.1, 133.4, 131.0, 129.8, 129.7, 129.2, 128.2, 127.6, 127.4, 125.9, 124.3, 123.2, 123.1, 119.4, 112.3, 105.9, 57.1, 55.4, 35.6, 33.8, 21.6, 9.8. LRMS (ESI, *m/z*): 600.2 $[M+H]^+$. $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{34}H_{30}O_4N_3F_3$, 600.2116 $[M-H]^-$; found 600.2115, purity: 96.3%.

Ethyl 3-(3,4-dichlorophenyl)-2-methyl-3-oxopropanoate (20). Methyl 3,4-dichlorobenzoate (5 g, 24.4 mmol) and sodium hydride (2.44 g, 61.0 mmol) were dissolved in 35 mL anhydrous THF under N_2. To the solution was added 8.4 mL ethyl propionate slowly at room temperature and the mixture was 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 5.7 g (85%) of ethyl 3-(3,4-dichlorophenyl)-2-methyl-3-oxopropanoate **20** as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (t, J = 3.3 Hz, 3H), 4.78 (q, J = 6.9 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 1.31 (d, J = 6.9 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H). MS (ESI, *m/z*): 274.0 $[M-H]^-$.

Ethyl 4-(1-(3-(3,4-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)ethyl)benzoate (21). A solution of compound **20** (5.1 g, 18.5 mmol) and {1-[4-(ethoxycarbonyl)phenyl]ethyl}hydraziniumtrifluoro acetate (8.4 g, 25.9 mmol) were 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 3.2 g (41.5%) of ethyl 4-(1-(3-(3,4-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)ethyl)benzoate as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 1.7 Hz, 1H), 7.63 (dt, J = 8.4, 5.1 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 5.64 (q, J = 7.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.04 (s, 3H), 1.77 (d, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). MS (ESI, *m/z*): 420.0 $[M+H]^+$.

Ethyl 4-(1-(3-(3,4-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzoate (22). Ethyl 4-(1-(3-(3,4-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)ethyl)benzoate (3.1 g, 7.5 mmol) and TEA (3.1 mL, 22.4 mmol) were dissolved in anhydrous THF (30 mL) at −78 ^{o}C. Triflic

anhydride (1.6 mL, 11.4 mmol) was added. The reaction mixture was stirred for 1 h and warmed to room temperature for 30 min. 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 provide ethyl 4-(1-(3-(3,4-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulfonyl) oxy)-1*H*-pyrazol-1-yl)ethyl)benzoate (2.9 g, 70.6%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.90 (m, 3H), 7.71 (dt, *J* = 8.4, 5.2 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 5.66 (q, *J* = 6.7 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.16 (s, 3H), 1.87 (d, *J* = 6.9 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). MS (ESI, *m/z*): 574.1 $[M+Na]^+$.

Ethyl 4-(1-(3-(3,4-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzoate (23). Ethyl 4-(1-(3-(3,4-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-1-yl)ethyl)benzoate (0.5 g, 0.9 mmol), (6-methoxynaphthalen-2-yl)boronic acid (232.7 mg, 1.2 mmol), and TEA (0.7 mL, 4.9 mmol) were dissolved in dimethoxyethane. $Pd(PPh_3)_4$ (104.8 mg, 0.1 mmol) was added, and the mixture was deoxygenated before heating in microwave at 100 ^{o}C for 25 min. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to afford ethyl 4-(1-(3-(3,4-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzoate as colorless oil (471 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (dd, *J* = 12.8, 4.7 Hz, 2H), 7.85 (dd, *J* = 8.4, 6.4 Hz, 3H), 7.77 – 7.71 (m, 3H), 7.41 (d, *J* = 2.3 Hz, 1H), 7.31 – 7.16 (m, 4H), 5.55 (q, *J* = 6.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 2.10 (s, 3H), 1.86 (d, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 7.1 Hz,

3H). MS (ESI, *m/z*): 560.1 $[M+H]^+$.

3-(4-(1-(3-(3,4-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1H-pyrazol-1-yl)ethyl)benzamido)propanoic acid (19e). Ethyl 4-(1-(3-(3,4-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzoate (230.0 mg, 1.2 mmol) was dissolved in MeOH-1,4-dioxane (1:1, 6 mL). A solution of NaOH (0.7 g/15 mL) was added. The mixture was heated to 60 ^oC for 1 h. The mixture was acidified with 1 N HCl, extracted with EtOAc, washed with saturated brine, dried (Na_2SO_4), and concentrated to give 4-(1-(3-(3,4-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1H-pyrazol-1-yl)ethyl)benzoic acid as yellow solid (345.0 mg, 98%). Without further purification, this solid (0.3 g, 564.5 μmol) was suspended in DMF (3 mL), followed with addition of DIEA (436.0 μL, 2.6 mmol), β-alanine *tert*-butyl ester hydrochloride (308.0 mg, 1.7 mmol). A solution of PyBOP (329.0 mg, 0.6 mmol) in DMF was then added. After stirring for 3 h, more PyBOP (95.9 mg, 0.2 mmol) was added, and the reaction mixture was stirred overnight at room temperature. After addition of water (2 mL), the mixture was heated to 60 ^oC for 30 min. Ethyl acetate was added, and the organic layer was washed with 0.5 N HCl, 5% K_2CO_3, and brine. The compound *tert*-butyl 3-(4-(1-(3-(3,4-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1H-pyrazol-1-yl)ethyl)benzamido)propanoate was obtained by flash chromatography (petroleum ether : ethyl acetate = 2 : 1) and concentrated as white solid (297.0 mg, 80%). This compound (230.0 mg, 349.2 μmol) was dissolved in DCM-TFA (2:1, 9 mL). The mixture was stirred at room temperature for 1 h and then concentrated to give a

yellow solid, which flash column chromatography afforded 142 mg (67.5%) of 3-(4-(1-(3-(3,4-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-4-methyl-1*H*-pyrazol-1-yl)ethyl)benzamido)propanoic acid as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.46 (t, *J* = 5.4 Hz, 1H), 7.94 (d, *J* = 1.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.77 (s, 1H), 7.76 – 7.73 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.52 (q, *J* = 6.8 Hz, 1H), 3.91 (s, 3H), 3.42 (dd, *J* = 12.7, 6.9 Hz, 2H), 2.48 (d, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.86 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.9, 165.9, 158.1, 145.8, 145.5, 143.0, 134.8, 134.1, 133.4, 131.3, 130.9, 129.8, 129.7, 129.2, 128.4, 128.1, 127.5, 127.4, 127.3, 127.1, 126.0, 124.2, 119.4, 112.4, 105.9, 57.1, 55.4, 35.5, 33.8, 21.6, 9.8. LRMS (ESI, *m/z*): 600.2 $[M-H]^-$. HRMS (ESI, *m/z*): calcd for $C_{32}H_{29}O_4N_3Cl_2$, 600.1462 $[M-H]^-$; found 600.1464, purity: 97.7%.

4.2. Biological evaluation

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).

4.2.1. Binding assay

CHO-K1 cells were obtained from ATCC and confirmed as negative for mycoplasma contamination. HEK-293T cells were obtained from the Cell Bank at the

Chinese Academy of Science and confirmed as negative for mycoplasma contamination.

CHO-K1 cells were seeded onto 6-well cell culture plates and were transiently transfected with GCGR DNA using Lipofectamine 2000 transfection reagent (Invitrogen). Stably transfected cells were selected on 750 mg/ml G418 (Roche, Indianapolis, IN, USA). We screened the drug-resistant colonies and selected the clone with highest expression level and functional functional efficacy.

Based on the previously reported method [18], stable cells were seeded onto 96-well poly-D-lysine treated cell culture plates (PerkinElmer, Boston, MA, USA) for 24 h at a density of 3×10^4 cells per well. Cells were then harvested, washed twice and incubated with blocking buffer (F12 supplemented with 33 mM HEPES and 0.1% bovine serum albumin (BSA), pH 7.4) for 2 h. After incubating the cells with constant concentration of [^{125}I]-glucagon (40 pM, PerkinElmer) and different concentrations of unlabeled compounds (1.28 nM-100 μM) at room temperature, the assay was continued for 3 h. The cells were then washed with ice-cold PBS for three times and 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). ***rac*-MK-0893** and **MK-0893** were synthesized according to the literature.[34]

4.2.2. cAMP assay

According to the manufacturer's instructions and the literature [37] cAMP

accumulation was measured using HTRF-cAMP dynamic kit (Cisbio International, Gif sur Yvette Cedex, France). The HEK293T cells were transfected with GCGR and then transferred to 384-well plates (3,000 cells per well). The incubation was conducted at 37^{o}C for 24 h. Then cells were incubated in assay buffer (DMEM, 1 mM 3-isobutyl-1-methylxanthine) for 30 min with 1 nM glucagon and different concentration of compounds at 37 ^{o}C. After addition of lysis buffer containing HTRF reagents, the reactions were stopped. The incubation of plates took 60 min at room temperature with time-resolved FRET signals measured after excitation at 620 nm and 650 nm by EnVision (PerkinElmer). ***rac*-MK-0893** and **MK-0893** were synthesized according to the literature.[34]

4.2.3. Statistical analysis

Results are presented as means ± SEM with at least three independent experiments in duplicate. IC_{50} values in binding and cAMP assays were determined by nonlinear regression analysis using the Prism 7 software (GraphPad Software).

4.3. Molecular docking

Docking studies were carried out using Glide program from Schrödinger Suite.[38-40] The receptor protein was downloaded from RCSB Protein Data Bank (PDB ID: 5EE7), which was imported and optimized to remove all solvents (except for water 1313) and unwanted molecules using protein preparation wizard. The receptor grid was sized to 15 Å in each direction and centered using original molecule (**MK-0893**).

All compounds were minimized for docking using LigPrep under its default parameters. Docking was performed using Glide in standard precision mode, with up to 40 conformers saved per molecule. Glide score was obtained to assess the favorable compound and its conformer, which was then exported to a Maestro-formatted output file.

Supporting Information

Information is about elucidation and purity analysis including ^{1}H NMR and ^{13}C NMR spectra of target compounds, HPLC analysis of target compounds.

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Notes

The authors declare no competing financial interest.

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6. Abbreviation used

GCGR, glucagon receptor; cAMP, cyclic-adenosine monophosphate; T2DM, type 2 diabetes mellitus; SGLT-2, sodium-glucose cotransporter-2; HGP, hepatic glucose production; GPCRs, G-protein coupled receptors; SAR, structure-activity relationship; Ser, Serine; Arg, Arginine; Asn, Asparagine; Lys, Lysine; Leu, Leucine; Thr, Threonine; Phe, Phenylalanine; Ala, Alanine.

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