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Design, synthesis, and pharmacological evaluation of benzamide derivatives as glucokinase activators

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ABSTRACT

A series of benzamide derivatives were assembled by using the privileged-fragment-merging (PFM) strategy and their SAR studies as glucokinase activators were described. Compounds **5** and **16b** were identified having a suitable balance of potency and activation profile. They showed EC_{50} values of 28.3 and 44.8 nM, and activation folds of 2.4 and 2.2, respectively. However, both compounds displayed a minor reduction in plasma glucose levels on imprinting control region (ICR) mice. Unfavorable pharmacokinetic profiles (PK) were also observed on these two compounds.

1. Introduction

Over the past decades, incidence rate of type 1 diabetes (T1D) has remained fairly stable, but the number of people diagnosed with type 2 diabetes (T2D) has been steadily growing. T2D currently comprises about 90% of all diabetes cases.[1] It is characterized by insulin resistance, excessive hepatic glucose production, and reduced glucose-triggered insulin secretion from the pancreatic β-cells.[2–7] The discovery of safe and effective drugs for the long term treatment of T2D patients remains the greatest challenge in diabetes research, predominantly owing to the continuous lack of understanding of the complex molecular pathogenesis and genetic basis of this disease.[8] Glucokinase (GK), a unique isoform of the hexokinase enzymes to phosphorylate D-glucose and other hexoses, was identified during the past three to four decades as a promising T2D drug target.[9,10] GK serves as a glucose sensor of the insulin-producing pancreatic islet β-cells, controlling the conversion of glucose to glycogen in the liver and regulating hepatic glucose production as well.[11–13] Guided by this fundamental knowledge, hundreds of small molecule compounds have been designed in the past few years with the hypothesis that compounds targeting this enzyme would activate the allosteric pocket of this protein and achieve anti-hyperglycemic effects by enhancing glucose usage in the liver, and by potentiating insulin secretion from pancreatic β-cells.[14–25] However, compounds with significant GK enzyme potency were very limited, and only a few of them have shown the capability of lowering blood glucose in animal models of type 2 diabetes.[8,19–21] Among the reported small molecule GK activators (GKAs), benzamides and phenylacetamides represent the two classes of major structural scaffolds. The former scaffold was represented by the clinical candidate compound **1** (GKA50, Fig. 1)[26–28] which was developed by AstraZeneca possessing good in vitro and in vivo glucose-lowering potency. Unfortunately, this compound was halted in clinical trials because of its epididymal and testicular toxicity observed in both rats and dogs. Further study showed that the pyridine-5-carboxylic acid moiety embedded in compound **1** was likely responsible for the toxic liability.[29] The latter chemotype was exemplified by compound **3** (PSN-GK1),[22,30] which was a back-up of compound **2** and currently in phase I clinical trial.

With the aim to identify new lead compounds possessing more efficacy and better pharmacokinetic properties, we recently initiated a privileged-fragment-merging (PFM) strategy and designed a series of new benzamides. Since the cyclopropylsulfonyl and aminothiazolyl moieties are the key elements responsible for the high GK potency in arylacetamides **2** and **3** where the former substituent provides the optimum potency-pharmacokinetic profile and the aminothiazolyl function affords a pair of H-bond donor-acceptors necessary to access the backbone hydrogen and carbonyl oxygen of Arg63 in GK binding pockets.[31] Therefore, these two

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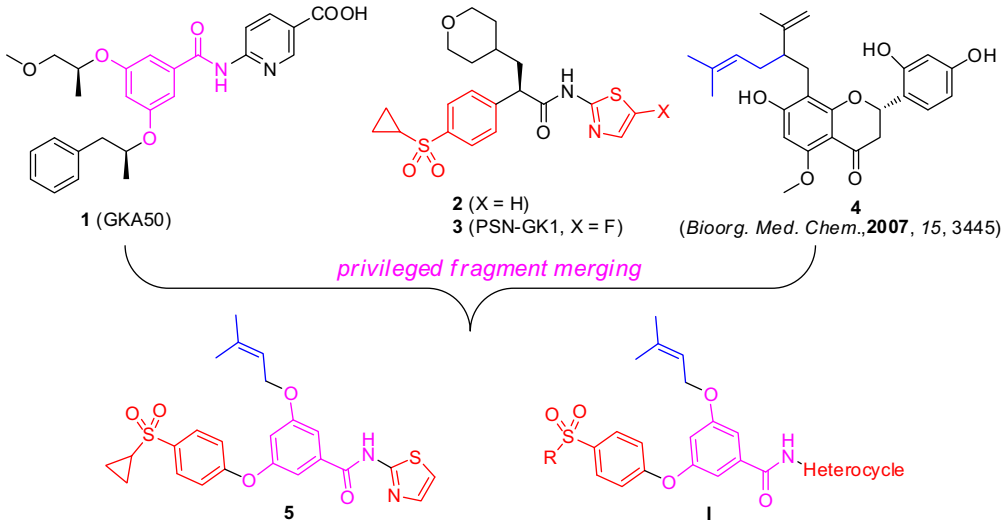


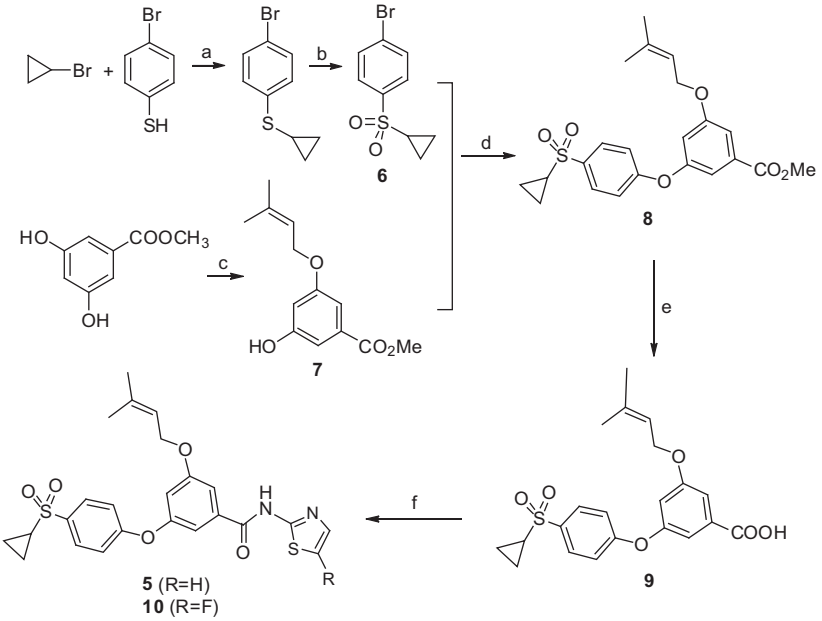
Figure 1. Known GKAs **1**–**3** and proposed new benzamides **5** and **I**.

privileged fragments were incorporated to the benzamide skeleton of compound **1**. Meanwhile, the 2-methylpenten-2-yl moiety, a lipophilic fragment often found in many natural anti-diabetic products (e.g., **4**[32]) was used to replace the 1-methoxypropan-2-yl substituent in compound **1**. With this PFM strategy, new benzamide **5** was designed followed by further tuning on the sulfonyl function as the *para*-substituent of the side-chain phenyl ring, and on the heterocyclic moiety in the amide portion (Fig. 1). Herein, we described our synthesis of these benzamide analogues **I**, and their GK potency and pharmacokinetic properties.

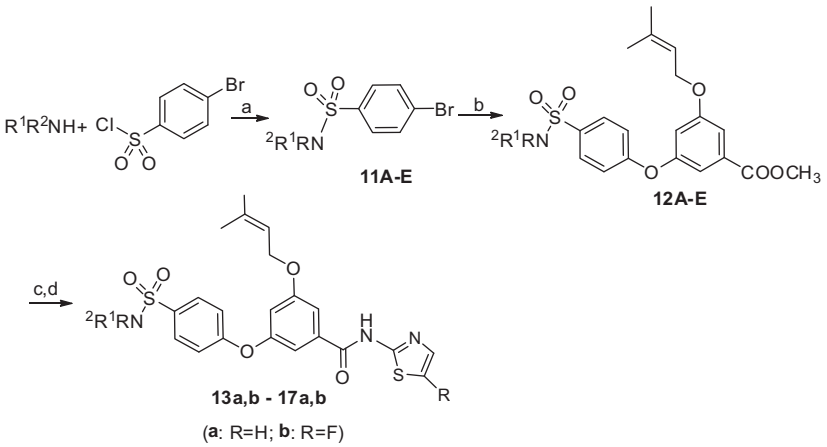
2. Results

2.1. Chemistry

The synthesis of compounds **5** and **10** was shown in Scheme 1. Intermediate **6**[33] was synthesized in two steps in 69% overall yield, including alkylation of 4-bromobenzenethiol with cyclopropyl bromide in the presence of potassium *tert*-butoxide as base to afford (4-bromophenyl)(cyclopropyl)sulfane, which was subsequently oxidized using *m*-chloroperbenzoic acid (*m*CPBA). Methyl 3-hydroxy-5-(3-methylbut-2-enyloxy) benzoate (**7**)[34] was prepared from methyl 3,5-dihydroxybenzoate through Williamson ether synthesis. Ullmann condensation[35] of compounds **6** and **7** with assistance of $CuBr/Cs_2CO_3$ resulted in ether **8**, but in poor yield (<8%). Optimization of the reaction conditions disclosed that ether **8** could be prepared in 80% yield by using 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) as ligand and *N*-methyl-2-pyrrolidone (NMP) as the solvent under 110 °C. Hydrolysis of benzoate **8** with LiOH afforded benzoic acid **2** in quantitative yield. Condensation[36] of **9** with 2-aminothiazole in the presence of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluo-rophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAt) under microwave (40 W, 60 °C) afforded target compound **5** in 87% yield. However,



Scheme 1. Reagents and conditions: (a) *t*-BuOK, DMSO, rt, 24 h, 82%; (b) *m*-CPBA (85%), $CHCl_3$, 2 h, 85%; (c) K_2CO_3, DMF, 60 °C, 24 h, 67%; (d) TMHD, CuBr, Cs_2CO_3, NMP, 110 °C, 80%; (e) LiOH, THF:H_2O = 3:1, reflux, 2 h, 100%; (f) compound **5**: 2-aminothiazole, HATU, HOAt, DMF, microwave, 40 W, 60 °C, 30 min, 87%; compound **10**: (i) $SOCl_2$, CH_2Cl_2, Cat. DMF, reflux 2 h; (ii) 5-fluorothiazol-2-amine, pyridine, THF, rt, 2 h, 82%.



Scheme 2. Reagents and conditions: (a) pyridine, CH_2Cl_2, 4 h, 80–90%; (b) compound **7**, TMHD, CuBr, Cs_2CO_3, NMP, 110 °C, 70–80%; (c) LiOH, THF:H_2O = 3:1, reflux, 2 h, 100%; (d) R = F: (i)$SOCl_2$, CH_2Cl_2, cat. DMF, reflux 2 h; (ii) pyridine, THF, rt, 2 h, 70–82%; R = H: HATU, HOAt, DMF, microwave, 40 W, 60 °C, 30 min, 72–85%.

when 5-fluorothiazol-2-amine was used, subsequent condensation with acid **9** proceeded dramatically sluggish. In this regard, acid **9** was treated firstly with refluxed $SOCl_2$ followed by coupling with 5-fluorothiazol-2-amine and compound **10** was obtained in 82% yield.

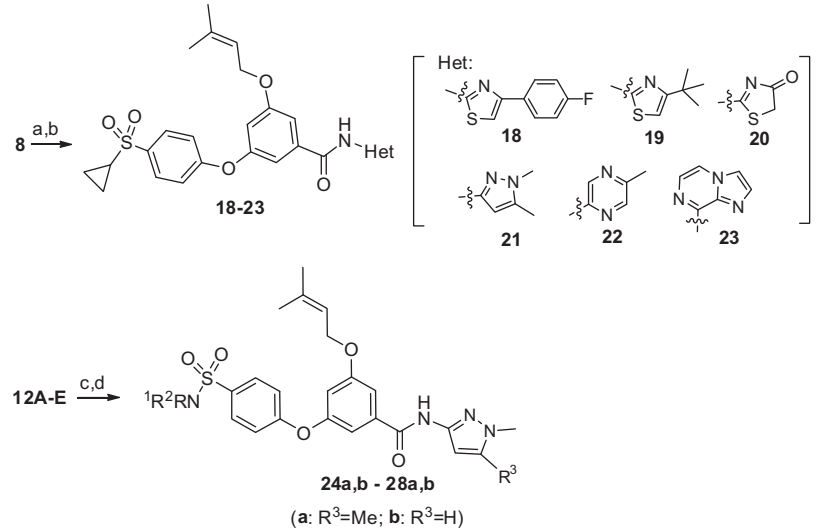
As indicated in Scheme 2, compounds **13a**,**b**–**17a**,**b** were synthesized in four steps. First, reaction of commercially available amines R^1R^2NH with 4-bromobenzene-1-sulfonyl chloride provided sulfonylamides **11A**–**E**, which were then condensed with benzoate **7** affording esters **12A**–**E**, respectively. Hydrolysis of esters **12A**–**E** with LiOH followed by amidation with aminothiazoles yielded final compounds **13a**,**b**–**17a**,**b** using a similar procedure[36] as described in Scheme 1.

Similarly, heterocyclic amides **18–23** and **24a**,**b**–**28a**,**b** were prepared as shown in Scheme 3. Hydrolysis of benzoate **8** followed by condensation with a series of heterocyclic amines provided the expected amides **18**–**23** in moderate yields. Whereas compounds **24a**,**b**–**28a**,**b** were prepared by hydrolysis of **12A–E** followed by condensation[36] with 1-methyl-1*H*-pyrazol-3-amine or 1,5-dimethyl-1*H*-pyrazol-3-amine using HATU and HOAt as the coupling agents.

2.2. In vitro pharmacological evaluation of benzamide derivatives

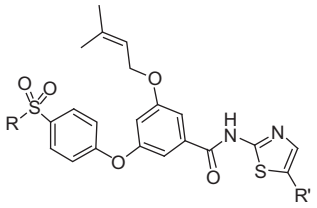
All newly synthetic compounds were evaluated in an enzymatic glucokinase (GK) assay using purified recombinant human islet GK following a similar procedure as we reported earlier.[33,36] Known compound **1** (GK50)[27] was also synthesized and evaluated in our assays for comparison (EC_{50} of 240 nM and activation fold 1.5).

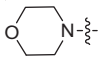
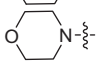
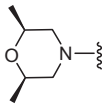
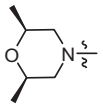
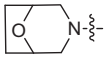
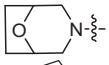
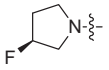
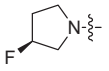
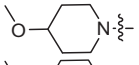
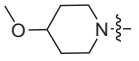
To our delight, compound **5** bearing the aminothiazolyl and 2-methylpenten-2-yl fragments displayed an EC_{50} value of 28.3 nM and maximum activation fold of 2.4. It was eightfold more potent than reference compound **1** in our assay (Table 1). Introducing a 5-fluoro atom to the aminothiazole component led to compound **10** possessing a statistically similar EC_{50} value (47 nM). Encouraged by the results, a sub-series of diversified aminosulfonyl moieties were introduced to replace the cyclopropylsulfonyl fragment in **5** and **10**. It was found that all the aminosulfonyl analogs **13a**,**b–17a**,**b** retained good GK potency with EC_{50} ranging between 48–100 nM. Comparing the non-substituted morpholinosulfonyl analogs **13a**,**b** with substituted morpholinosulfonyl analogs **14a**,**b** and **15a**,**b**, the bulky substituent on the morpholine ring slightly



Scheme 3. Reagents and conditions: (a) LiOH, THF:H_2O = 3:1, reflux, 2 h, 100%; (b) compounds **20** and **22**: (i) $SOCl_2$, CH_2Cl_2, cat. DMF, reflux 2 h; (ii) pyridine, THF, rt, 2 h, 70–82%; compounds **18**–**19**, **21**, **23**: HATU, HOAt, DMF, microwave, 40 W, 60 °C, 40 min, 72–76%; (c) LiOH, THF:H_2O = 3:1, reflux, 2 h, 100%; (d) HATU, HOAt, DMF, microwave, 40 W, 60 °C, 40 min, 72–85%.

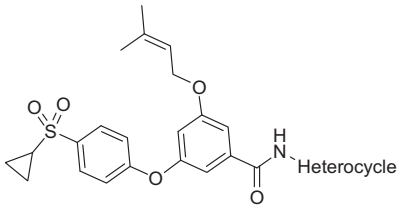
Table 1
In vitro activation of GK by benzamide-thiazole analogs

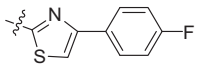
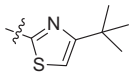
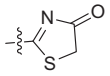
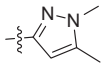
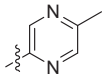
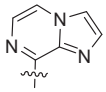


Compd[a]	R	R′	EC_{50} (nM)	Activation fold[b]
1(GK50)	—	—	240(30[c])	—
5		H	28.3	2.4
10		F	47.7	1.8
13a		H	48.0	2.1
13b		F	52.0	1.8
14a		H	62.6	1.5
14b		F	65.4	1.7
15a		H	101	1.7
15b		F	78.0	1.9
16a		H	52.3	1.9
16b		F	44.8	2.2
17a		H	90.4	1.7
17b		F	64.6	1.7

[a] Six different concentrations of compounds were tested in the assay, data were mean of three independent experiments.
[b] Maximum fold activation of GK over control level.
[c] Data from Ref.[30].

Table 2
In vitro activation of GK by benzamide-heterocycle analogs



Compd[a]	Heterocycle	EC_{50} (nM)	Activation fold[b]
18		250	0.9
19		890	0.7
20		120	1.5
21		90.1	1.5
22		165	1.6
23		>1000	—

[a] Six different concentrations of compounds were tested in the assay, data were mean of three independent experiments.
[b] Maximum fold activation of GK over control level.

reduced the GK potency. High GK activation potency was observed on the 3- fluoropyrrolidinylsulfonyl analogs **16a**,**b** showing EC_{50} values of 52 and 44 nM, respectively. The 4-methoxy piperidinylsulfonyl analogs **17a**,**b** displayed slightly lower potency and were twofold less potent than the five-membered congeners **16a**,**b**. However, in comparison to the good GK potency, the maximum activation fold was not improved. It was noteworthy that in all cases, the addition of a 5-fluoro to the thiazole component did not affect GK potency significantly.

On the basis of the results in Table 1, the cyclopropylsulfonyl analogue **5** remains the most potent GK activator, although variant aminosulfonyl moieties were well tolerated. Accordingly, with the cyclopropylsulfonyl fragment intact, a small series of heterocycles were screened as bioisosteres of the thiazole fragment, and the results were summarized in Table 2.

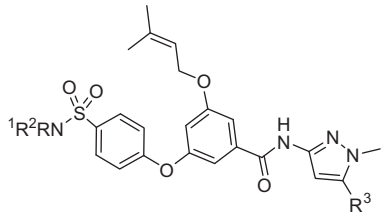
Aminothiazoles **18** and **19** bearing a bulky 4-substituent showed much lower potency. However, reasonable potency was observed on the 4-oxo-4,5-dihydrothiazolyl (**20**) and 1,5-dimethyl-1*H*-pyrazolyl (**21**) analogs. Replacing the thiazole fragment in GK activator **5** with 5-methylpyrazin-2-yl moiety led to analogue **22** having sixfold reduced potency (165 nM). The imidazo[1,2-*a*]pyrazin-8-yl analogue **23** completely lost GK activation potency. Although all the bioisosteres of thiazole analogs **18**–**23** displayed reduced potency in comparison to the parent **5**, the pyrazolyl analogue **21** caught our attention. In general, the pyrazolyl moiety has better chemical stability than the thiazole fragment and may raise less metabolic concerns in vivo,[24] although compound **21** was threefold less potent than thiazole **5**. In this regard, we used the pyrazolyl moiety (with or without 5-methyl substituent) as an additional privileged fragment, and counter-screened the sulfonyl fragment with the aim to find more potent GK activators.

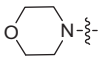
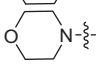
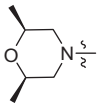
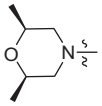
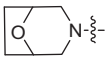
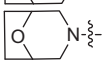
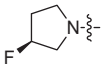
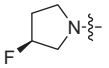
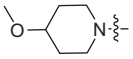
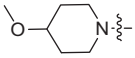
From the results in Table 3, a much wider range of potency was observed than that in Table 1. Morpholinylsulfonyl analogue **24a** gave a similar EC_{50} value (95 nM) as compound **21**, whereas the di-methyl substituted morpholinylsulfonyl analogue **25a** showed twofold increase in GK potency. Bridged morpholinyl analogue **26a** showed reduced potency indicating that much bulkier substituent was not tolerant at this position. 3-Fluoropyrrolidinyl analogue **27a** also showed improved potency with an EC_{50} value of 63 nM. Piperidinyl analogue **28a** had much lower potency. Interestingly, all the pyrazolyl analogs **24b**–**28b** lacking the 5-methyl substituent showed reduced GK potency, indicating that a small binding pocket in the GK enzyme may exist for the 5-methyl substituent. Overall, the thiazolyl series in Table 1 are more potent than the pyrazolyl series in Table 3.

2.3. In vivo pharmacological evaluation

On the basis of the structure–activity relationship (SAR) described above, compounds **5** and **16b** were identified as the most potent GK activators in current studies possessing optimum

Table 3
In vitro activation of GK by benzamide-pyrazol analogs



Compd[a]	NR^1R^2	R^3	EC_{50} (nM)	Activation fold[b]
24a		Me	95.1	1.5
24b		H	297	3.0
25a		Me	44.8	1.6
25b		H	265	1.8
26a		Me	144	1.5
26b		H	242	1.7
27a		Me	63.1	1.9
27b		H	83.5	2.1
28a		Me	460	1.8
28b		H	491	1.7

[a] Six different concentrations of compounds were tested in the assay, data were mean of three independent experiments.
[b] Maximum fold activation of GK over control level.

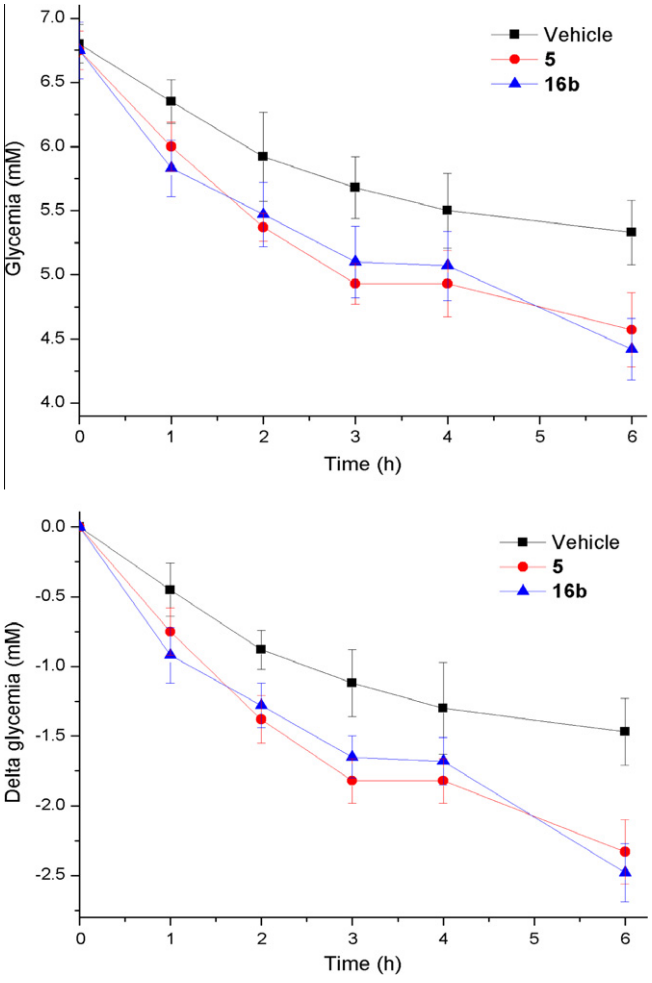


Figure 2. Effects of **5** and **16b** on blood glucose level in ICR mice. Upper panel: Blood glucose profiles. Lower panel: Delta blood glucose (ΔBG) profiles. ΔBG reflects the change in blood glucose concentrations from 0 min within each experimental group. Data were shown as mean ± SEM (n = 6).

combinations of GK potency (28 vs 45 nM) and maximum activation fold (>2). Therefore, they were carried forward for further evaluation. The hypoglycemic effect of **5** and **16b** was evaluated on imprinting control region (ICR) mice, a non-diabetic animal model.[33] It was found that administration of an oral dose of 10 mg/kg of compounds **5** and **16b** resulted in 5.5% and 8.1% blood glucose reduction of vehicle control within 1 h, respectively (Fig. 2). Therefore, no significant hypoglycemic effects of **5** and **16b** were achieved after single oral dosing at the dose of 10 mg/kg. The low glucose reduction of these two compounds is not in parallel with their GK enzymatic potency, which may be due to the relatively low intrinsic activity (maximum activation fold), and the pharmacokinetic properties (PK). Accordingly, as shown in Table 4, the PK profiles of compounds **5** and **16b** were evaluated in mice after single iv (10 mg/kg) and po (20 mg/kg) administration.[37] The cyclopropylsulfonyl analogue **5** displayed reasonable half-life time (2.3 h), and moderate oral bioavailability (38%). However, poor plasma clearance (0.20 L/h/kg, iv) was observed. The 3-fluoropyrrolidinylsulfonyl analogue **16b** showed longer half-life (~6.0 h), and improved plasma clearance (1.07 L/h/kg, iv), however poor bioavailability (less than 10%) was observed. The unfavorable PK profiles of compounds **5** and **16b** may partially explain the poor in vivo glucose-lowering properties. Therefore, further structural optimization will be focused on tuning the PK parameters.

Table 4
Pharmacokinetic parameters of compounds **5** and **16b**

	iv (10 mg/kg)[a]			
Compd	CL(L/h/Kg)	V_{ss}(L/kg)	$T_{1/2}$(h)	
5	0.20 ± 0.02	0.28 ± 1.2	2.3 ± 0.3	
16b	1.07 ± 0.15	1.20 ± 0.32	5.9 ± 0.56	
	po (20 mg/kg)[a]			
Compd	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\infty}$ (ng th/ml)	F (%)
5	15800 ± 2900	1.0 ± 0.0	39800 ± 5800	38.6
16b	1086 ± 751	1.0 ± 0.0	1790 ± 101	9.5

[a] Values are the average of three runs; vehicle: DMSO, tween-80, normal saline. CL, clearance; V_{ss}, volume of distribution; $T_{1/2}$, half-life; C_{max}, maximum concentration; T_{max}, time of maximum concentration; $AUC_{0-\infty}$, area under the plasma concentration time curve; F, oral bioavailability.

3. Conclusion

In summary, a series of benzamide derivatives were synthesized and evaluated as glucokinase activators (GKs) by using the privileged-fragment-merging (PFM) strategy. A variety of amino groups were introduced to the sulfonyl-terminal of benzamide derivatives to explore the electronic and spacial effects, and different types of heterocyclic fragments were evaluated as well. Compounds **5** and **16b** were identified as the most potent GK

activators having a suitable balance of potency and activation profile, with EC_{50} values of 28.3 and 44.8 nM, and activation fold of 2.4 and 2.2, respectively. However, these two compounds only showed a minor reduction in plasma glucose levels on imprinting control region (ICR) mice. Unfavorable pharmacokinetic profiles (PK) were also observed on these two compounds. Further structural optimization will be focused on tuning the PK parameters.

4. Experimental section

4.1. Preparation of recombinant glucokinase protein[33,36]

cDNA of human glucokinase (MGC: 1742, purchased from OriGene Technologies, USA) was subcloned into the pET28a (+) expression vector, and expressed in *Escherichia coli* strain BL21 (DE3). The NH_2 terminal end of (His)6-tag glucokinase fusion protein was purified by Ni-NTA metal chelate affinity chromatography and stored at −80 °C in 50 mM Tris–HCl pH 7.4, 1 mM dithiothreitol (DTT), 50 mM NaCl, and 10% glycerol.

4.2. Glucokinase enzymatic assay

The GK activity was assessed spectrometrically by a coupled reaction with glucose-6-phosphate dehydrogenase (G6PDH).[33,36] Briefly, GK catalyzes glucose phosphorylation to generate glucose-6-P, which was oxidized by the G6PDH with the concomitant reduction of NADPH. The product NADPH was then monitored by the increase rate of absorbance at 340 nm in a plate reader (Spectra-Max 190; Molecular Devices, USA). All compounds were prepared in DMSO. The assay was performed in 96-well plates in a final volume of 100 μL containing 50 mM HEPES pH 7.4, 5 mM glucose, 25 mM KCl, 2 mM $MgCl_2$, 1 mM DTT, 1 mM ATP, 1 mM NADP, 2.5 U/mL G6PDH, 0.5 μg (His)6-glucokinase, and test compounds. The velocities of the enzyme reaction were expressed as mOD/min, and the fold activation of the enzyme was achieved by comparing with control (GK activation with only DMSO was considered as 100%). For EC_{50} determination, six different concentrations of compounds were tested in the assay, and the fold changes in activity versus controls were fitted to sigmoidal curve using a four parameter logistic model in GraphPad Prism 4.

4.3. Animal studies[33]

Male ICR mice (8 weeks old), housed with free access to diet and reversed light cycles, were used. Before the studies, food was deprived for 2 h in ICR mice, while free access to water was provided. The ICR mice were assigned to different groups based on the body weight. Mice were then orally dosed with test compounds or vehicle (0.5% carboxymethylcellulose). Blood glucose levels were measured via blood sample from tail vein by using an ACCU-CHEK Advantage (Roche) at the indicated time after dosing.

4.4. Chemistry

^1H NMR spectral data were recorded in $CDCl_3$ on Varian Mercury 300 NMR spectrometer and ^{13}C NMR data were recorded in $CDCl_3$ on Varian Mercury 400 NMR spectrometer. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer. Column chromatography was carried out on silica gel (200–300 mesh). Reactions using microwave irradiation was conducted on CZM (DC-5415, CEM) instrument. All reactions were monitored using thin-layer chromatography (TLC) on silica gel plates.

4.4.1. General procedure for the synthesis of compounds 8 and 12A–E

Methyl 3-hydroxy-5-((3-methylbut-2-en-1-yl)oxy) benzo-ate **7**[34] (1.6 g, 6.8 mmol, 1 equiv), aryl bromide **6**[36] or **11A–E** (7.5 mmol, 1.1 equiv), copper (I) bromide (0.34 mmol, 0.5 equiv) and cesium carbonate (3.32 g, 10.2 mmol, 1.5 equiv) were added to a pear-shaped Schlenk flask. Degased NMP (9 mL) was added via needle, then TMHD (0.13 mmol, 0.1 equiv) was dropped. The reaction mixture was heated at 110 °C under nitrogen, and then cooled to the room temperature. The reaction mixture was filtered through a pad of celite and washed with EtOAc. Combined filtrates were washed subsequently with 2 N HCl, 2 M NaOH, and 10% NaCl. The resulting organic layer was dried over anhydrous $NaSO_4$ and concentrated. The crude product was then purified by flash column chromatography to give the title intermediate in 70–80% yield (**8** and **12A–E**).

4.4.2. Methyl 3-(4-(cyclopropylsulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)benzoate (8)

Yield 80% (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.85 (d, J = 8.5 Hz, 2H), 7.42 (s, 1H), 7.30 (s, 1H),7.09 (d, J = 8.5 Hz, 2H), 6.81 (s, 1H), 5.46 (t, J = 6.4 Hz, 1H), 4.54 (d, J = 6.8 Hz, 2H), 3.90 (s, 3H), 2.70–2.31 (td, J = 7.7, 4.0 Hz, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1.07–1.01 (m, 2H), 0.89–0.82 (m, 2H); EI-MS m/z 416 (M^+).

4.4.3. Methyl 3-(4-(cyclopropylsulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)benzoate (12A)

Yield 80% (white solid);^1H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.6 Hz, 2H), 7.44 (s, 1H), 7.31 (s, 1H), 7.09 (d, J = 8.6 Hz, 2H), 6.82 (s, 1H), 5.47 (t, J = 6.5 Hz, 1H), 4.55 (d, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.81–3.68 (m, 4H), 3.14–2.87 (m, 4H), 1.80 (s, 3H), 1.75 (s, 3H); EI-MS m/z 461 (M^+).

4.4.4. Methyl 3-(4-(((2*S*,6*R*)-2,6-dimethylmorpholino)sulfonyl) phe-noxy)-5-((3-methylbut-2-en-1-yl)oxy)benzoate (12B)

Yield 78% (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.7 Hz, 2H), 7.44 (s, 1H), 7.32 (s, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 1.9 Hz, 1H), 5.47 (t, J = 6.6 Hz, 1H), 4.55 (d, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.72 (dd, J = 8.4, 5.6 Hz, 2H), 3.55 (d, J = 11.0 Hz, 2H), 2.00 (t, J = 10.8 Hz, 2H), 1.80 (s, 3H), 1.75 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H); EI-MS m/z 489 (M^+).

4.4.5. Methyl 3-(4-(8-oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl) ph -enoxy)-5-((3-methylbut-2-en-1-yl)oxy)benzoate (12C)

Yield 78% (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, J = 6.1 Hz, 2H), 7.44 (d, J = 1.1 Hz, 1H), 7.31 (s, 1H), 7.06 (d, J = 5.7 Hz, 2H), 6.82 (d, J = 1.3 Hz, 1H), 5.47 (t, J = 6.7 Hz, 1H), 4.55 (d, J = 6.7 Hz, 2H), 4.38 (s, 2H), 3.90 (s, 3H), 3.38 (d, J = 11.0 Hz, 2H), 2.64 (d, J = 11.0 Hz, 2H), 2.01–1.87 (m, 2H), 1.96-1.91 (m, 1H), 1.80 (s, 3H), 1.75 (s, 3H); EI-MS m/z 487 (M^+).

4.4.6. (*S*)-Methyl 3-(4-((3-fluoropyrrolidin-1-yl)sulfonyl) phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)benzoate (12D)

Yield 70% (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.81 (t, J = 5.8 Hz, 2H), 7.43 (d, J = 1.0 Hz, 1H), 7.30 (s, 1H), 7.09 (t, J = 5.8 Hz, 2H), 6.81 (t, J = 2.1 Hz, 1H), 5.47 (t, J = 6.7 Hz, 1H), 5.17 (d, J = 51.7 Hz, 1H), 4.55 (d, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.66–3.47 (m, 3H), 3.34–3.26 (m, 1H), 2.29–1.88 (m, 3H), 1.81 (s, 3H), 1.75 (s, 3H); EI-MS m/z 463 (M^+).

4.4.7. Methyl 3-(4-((4-methoxypiperidin-1-yl)sulfonyl) phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)benzoate (12E)

Yield 76% (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.7 Hz, 2H), 7.43 (s, 1H), 7.31 (s, 1H), 7.06 (d, J = 8.7 Hz, 2H), 6.82 (t, J = 2.2 Hz, 1H), 5.47 (t, J = 6.5 Hz, 1H), 4.55 (d, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.38–3.26 (m, 4H), 3.26–3.10 (m, 2H), 2.98 (ddd,

J = 11.3, 7.1, 3.8 Hz, 2H), 1.90 (ddd, *J* = 11.8, 8.2, 3.8 Hz, 2H), 1.80 (s, 3H), 1.79–1.66 (m, 5H); EI-MS *m*/*z* 489 (M^+).

4.4.8. General procedure for the synthesis of compounds 5, 13a–17a, 18–19, 21, 23 and 24a,b–28a,b

Method A To a solution of benzoic acid which was obtained by hydrolysis of methyl esters **8** or **12A**–**E** (0.22 mmol, 1.0 equiv), aminothiazole or imidazo[1,2-*a*]pyrazin-8-amine or aminopyrazole (0.33 mmol, 1.5 equiv), HATU (0.33 mmol, 1.5 equiv) and HOAt (0.33 mmol, 1.5 equiv) in DMF (2 mL) was added dropwise di(isopropyl)ethylamine (DIPEA) (0.12 mL, 0.67 mmol, 3 equiv). The reaction was run under microwave at 60 °C (40 W) for 30 min, and then cooled to room temperature and poured into brine. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $NaSO_4$ and concentrated. The residue was purified by chromatography (SiO_2, petroleum ether/EtOAc = 4:1–1:1) to yield corresponding amides as white or yellow powder.

Method B for compounds **10**,**13b**–**17b**, **20** and **22**. A mixture of benzoic acid **9** (0.22 mmol, 1 equiv), anhydrous CH_2Cl_2 (4 mL) and DMF (15 μL) was cooled to 0 °C, $SOCl_2$ (0.66 mmol, 3 equiv) was added dropwise. The mixture was warmed to room temperature, and then refluxed for 2 h. After cooling to room temperature, CH_2Cl_2 was evacuated by vacuum under nitrogen atmosphere. Anhydrous THF (4 mL) was added slowly, followed by addition of a catalytic amount of pyridine, and 5-fluoroaminothiazole or 2-aminothiazol-4(5*H*)-one or 5-methylpyr-azin-2-amine (0.26 mmol, 1.2 equiv). The reaction was stirred for 2 h at room temperature, quenched with water, and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $NaSO_4$ and concentrated. The residue was purified by chromatography (SiO_2, petroleum ether/EtOAc = 4:1 to 1:1) to yield corresponding amides as white or yellow powder.

4.4.9. 3-(4-(Cyclopropylsulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(thiazol-2-yl)benzamide (5)

Yield 87% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91–7.77 (m, 2H), 7.36 (s, 1H), 7.24 (s, 1H), 7.21 (d, *J* = 3.5 Hz, 1H), 7.15–7.08 (m, 2H), 6.98 (d, *J* = 3.5 Hz, 1H), 6.85 (t, *J* = 2.0 Hz, 1H), 5.45 (t, *J* = 7.3 Hz, 1H), 4.53 (d, *J* = 6.7 Hz, 2H), 2.76–1.88 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.49–1.30 (m, 2H), 1.19–0.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9, 160.9, 160.6, 160.0, 156.8, 139.3, 137.0, 135.4, 135.3, 129.9, 118.6, 118.5, 113.7, 111.3, 111.1, 110.0, 65.4, 33.1, 25.8, 18.2, 6.0 ppm; HRMS (EI) calcd for $C_{24}H_{24}N_2O_5S_2$: 484.1127, found 484.1124.

4.4.10. 3-(4-(Cyclopropylsulfonyl)phenoxy)-*N*-(5-fluorothiazol-2-yl)-5-((3-methylbut-2-en-1-yl)oxy)benzamide (10)

Yield 82% (yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 8.6 Hz, 2H), 7.31 (s, 1H), 7.18 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 6.7 Hz, 2H), 5.46 (t, *J* = 6.9 Hz, 1H), 4.55 (d, *J* = 7.1 Hz, 2H), 2.47 (dd, *J* = 10.8, 6.3 Hz, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.49–1.27 (m, 2H), 1.18–0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.5, 160.8, 160.7, 156.9, 139.5, 135.5, 134.6, 130.0, 118.6, 118.4, 117.5, 117.4, 111, 110.9, 110.1, 65.5, 33.1, 25.8, 18.2, 6.0 ppm; HRMS (EI) calcd for $C_{24}H_{23}FN_2O_5S_2$: 502.1032, found 502.1030.

4.4.11. 3-((3-Methylbut-2-en-1-yl)oxy)-5-(4-(morpholinosulfo nyl)phe -noxy)-*N*-(thiazol-2-yl)benzamide (13a)

Yield 82% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.6 Hz, 2H), 7.38 (s, 1H), 7.27 (s, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 3.6 Hz, 1H), 6.85 (s, 1H), 5.45 (t, *J* = 6.5 Hz, 1H), 4.53 (d, *J* = 6.8 Hz, 2H), 3.83–3.58 (m, 4H), 3.09–2.77 (m, 4H), 1.80 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.0, 160.8, 160.6, 160.1, 156.5, 139.4, 137.1, 135.5, 130.2, 129.6, 118.5, 118.2, 113.8, 111.6, 111.1, 110.2, 66.0, 65.4, 46.0, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{25}H_{27}N_3O_6S_2$: 529.1341, found 529.1339.

4.4.12. *N*-(5-Fluorothiazol-2-yl)-3-((3-methylbut-2-en-1-yl)oxy)-5-(4-(morpholinosulfonyl)phenoxy)benzamide (13b)

Yield 74% (yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 1.6 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 7.13 (d, *J* = 1.7 Hz, 2H), 7.11 (d, *J* = 1.8 Hz, 1H), 6.96–6.90 (m, 1H), 6.85 (t, *J* = 1.8 Hz, 1H), 5.47 (t, *J* = 5.9 Hz, 1H), 4.56 (d, *J* = 6.2 Hz, 2H), 3.85–3.70 (m, 4H), 3.16–2.84 (m, 4H), 1.81 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 160.7, 160.6, 156.7, 139.5, 134.7, 130.2, 129.8, 118.4, 118.2, 117.6, 117.5, 111.1, 110.2, 66.0, 65.5, 45.9, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{25}H_{26}FN_3O_6S_2$: 547.1247, found 547.1245

4.4.13. 3-(4-(((*2S*,*6R*)-2,6-Dimethylmorpholino)sulfonyl) phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(thiazol-2-yl) benzamide (14a)

Yield 78% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.5 Hz, 2H), 7.37 (s, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.85 (s, 1H), 5.45 (t, *J* = 6.5 Hz, 1H), 4.53 (d, *J* = 6.7 Hz, 2H), 3.83–3.64 (m, 2H), 3.56 (d, *J* = 11.1 Hz, 2H), 1.99 (t, *J* = 10.8 Hz, 2H), 1.80 (s, 3H), 1.72 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9, 160.7, 160.6, 160.1, 156.6, 139.3, 136.9, 135.4, 130.0, 129.9, 118.5, 118.2, 113.7, 111.7, 111.1, 110.1, 71.3, 65.4, 50.7, 25.8, 18.6, 18.2 ppm; HRMS (EI) calcd for $C_{27}H_{31}N_3O_6S_2$: 557.1654, found 557.1656.

4.4.14. 3-(4-(((*2S*,*6R*)-2,6-Dimethylmorpholino)sulfonyl) phenoxy)-*N*-(5-fluorothiazol-2-yl)-5-((3-methylbut-2-en-1-yl)oxy)benzami-de (14b)

Yield 79% (yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.7 Hz, 2H), 7.31 (s, 1H), 7.20 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.97 (s, 1H), 6.85 (s, 1H), 5.47 (t, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.7 Hz, 2H), 3.83–3.66 (m, 2H), 3.57 (d, *J* = 11.2 Hz, 2H), 2.00 (t, *J* = 10.7 Hz, 2H), 1.81 (s, 3H), 1.75 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 160.8, 160.6, 156.7, 139.5, 134.4, 130.1, 118.3, 118.2, 117.7, 111.3, 111.0, 109.8, 71.3, 65.5, 50.7, 43.1, 29.6, 25.8, 18.6, 18.2 ppm; HRMS (EI) calcd for $C_{27}H_{30}FN_3O_6S_2$: 575.1560, found 575.1558.

4.4.15. 3-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl) phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(thiazol-2-yl) benzamide (15a)

Yield 84% (off white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.6 Hz, 2H), 7.37 (s, 1H), 7.27 (s, 1H), 7.20 (d, *J* = 3.2 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 3.3 Hz, 1H), 6.84 (s, 1H), 5.45 (t, *J* = 7.0 Hz, 1H), 4.53 (d, *J* = 6.7 Hz, 2H), 4.37 (s, 2H), 3.38 (d, *J* = 10.9 Hz, 2H), 2.65 (d, *J* = 10.6 Hz, 2H), 2.06–1.90 (m, 4H), 1.80 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9, 160.6, 160.1, 156.5, 139.3, 136.9, 135.5, 130.1, 129.8, 118.5, 118.1, 113.7, 111.6, 111.0, 110.2, 73.6, 65.4, 50.9, 27.7, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{27}H_{29}N_3O_6S_2$: 555.1498, found 555.1500.

4.4.16. 3-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl) phenoxy)-*N*-(5-fluorothiazol-2-yl)-5-((3-methylbut-2-en-1-yl) oxy)benza-mide (15b)

Yield 74% (yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.7 Hz, 2H), 7.31 (s, 1H), 7.18 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.97 (s, 1H), 6.84 (s, 1H), 5.46 (t, *J* = 7.0 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 2H), 4.38 (s, 2H), 3.39 (d, *J* = 10.7 Hz, 2H), 2.66 (d, *J* = 11.3 Hz, 2H), 2.14–1.90 (m, 4H), 1.81 (s, 3H), 1.75 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ = 163.8, 160.8, 160.5, 156.8, 139.4, 134.4, 130.3, 129.9, 118.4, 118.2, 111.2, 110.9, 109.9, 73.6, 65.5, 51.0, 27.7, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{27}H_{28}FN_3O_6S_2$: 573.1404, found 573.1402.

4.4.17. (*S*)-3-(4-((3-Fluoropyrrolidin-1-yl)sulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(thiazol-2-yl)benzamide (16a)

Yield 78% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.7 Hz, 1H), 7.37 (s, 2H), 7.22 (s, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.98 (s, 1H), 6.84 (s, 1H), 5.45 (t, *J* = 6.4 Hz, 1H), 5.16 (d, *J* = 53.1 Hz, 1H), 4.53 (d, *J* = 6.7 Hz, 2H), 3.58 (d, *J* = 1.3 Hz, 1H), 3.56–3.41 (m, 2H), 3.30 (td, *J* = 10.2, 6.6 Hz, 1H), 2.31–1.86 (m, 2H), 1.80 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9, 160.5, 160.5, 160.2, 156.6, 139.2, 136.9, 135.4, 131.2, 129.8, 118.5, 118.3, 113.7, 111.4, 111.0, 110.1, 93.0, 91.3, 65.4, 54.4, 54.2, 45.8, 32.6, 32.4, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{25}H_{26}FN_3O_5S_2$: 531.1298, found 531.1299.

4.4.18. (*S*)-3-(4-((3-Fluoropyrrolidin-1-yl)sulfonyl)phenoxy)-*N*-(5-fluorothiazol-2-yl)-5-((3-methylbut-2-en-1-yl)oxy) benzamide (16b)

Yield 78% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.7 Hz, 2H), 7.30 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 3H), 6.91 (s, 1H), 6.84 (s, 1H), 5.46 (t, *J* = 6.1 Hz, 1H), 5.18 (d, *J* = 53.2 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 2H), 3.63–3.58 (m, 1H), 3.58–3.42 (m, 2H), 3.30 (td, *J* = 10.2, 6.6 Hz, 1H), 2.23 - 2.04 (m, 1H), 1.81 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0, 160.7, 160.3, 157.0, 139.5, 134.5, 131.4, 129.8, 118.4, 118.4, 110.9, 110.6, 109.9, 93.1, 91.3, 65.5, 54.4, 54.2, 45.9, 32.6, 32.4, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{25}H_{25}F_2N_3O_5S_2$: 549.1204, found 549.1202

4.4.19. 3-(4-((4-Methoxypiperidin-1-yl)sulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(thiazol-2-yl)benzamide (17a)

Yield 84% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.55 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.36 (s, 1H), 7.24 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 3.6 Hz, 1H), 6.85 (t, *J* = 1.9 Hz, 1H), 5.46 (t, *J* = 6.9 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 2H), 3.37–3.29 (m, 1H), 3.27 (s, 3H), 3.24–3.13 (m, 2H), 2.97 (ddd, *J* = 8.7, 5.3, 1.9 Hz, 2H), 1.91 (ddd, *J* = 11.4, 7.1, 3.5 Hz, 2H), 1.80 (s, 3H), 1.76 (dd, *J* = 7.0, 3.3 Hz, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9, 160.6, 160.4, 156.6, 139.3, 136.9, 135.4, 130.9, 129.9, 118.5, 118.1, 113.7, 111.5, 111.1, 110.0, 73.9, 65.4, 55.7, 43.0, 29.7, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{27}H_{31}N_3O_6S_2$: 557.1654, found 557.1657

4.4.20. *N*-(5-Fluorothiazol-2-yl)-3-(4-((4-methoxypiperidin-1-yl)sulfo-nyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy) benzamide (17b)

Yield 84% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8.8 Hz, 2H), 7.29 (s, 1H), 7.18 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.94 (s, 1H), 6.84 (s, 1H), 5.46 (t, *J* = 6.4 Hz, 1H), 4.56 (d, *J* = 6.5 Hz, 2H), 3.40–3.29 (m, 1H), 3.28 (s, 3H), 3.25–3.13 (m, 2H), 3.05–2.93 (m, 2H), 1.98–1.85 (m, 2H), 1.80 (s, 3H), 1.78–1.69 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1, 160.7, 160.2, 156.9, 139.5, 134.5, 131.1, 129.9, 118.3, 118.2, 111.0, 111.0, 109.9, 73.8, 65.5, 55.7, 43.0, 29.7, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{27}H_{30}FN_3O_6S_2$: 575.1560, found 575.1564.

4.4.21. 3-(4-(Cyclopropylsulfonyl)phenoxy)-*N*-(4-(4-fluoro phenyl)thi -azol-2-yl)-5-((3-methylbut-2-en-1-yl)oxy) benzamide (18)

Yield 85% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.80–7.68 (m, 2H), 7.29 (s, 1H), 7.16 - 7.05 (m, 6H), 6.81 (t, *J* = 2.1 Hz, 1H), 5.47 (t, *J* = 6.4 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 2.53–2.44 (m, 1H), 1.82 (s, 3H), 1.75 (s, 3H), 1.56–1.18 (m, 2H), 1.25–0.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 163.7, 161.2, 160.8, 160.4, 158.9, 156.7, 149.1, 139.2, 135.2, 134.5, 130.1, 129.9, 127.7, 127.6, 118.5, 118.4, 115.6, 115.3, 110.9, 110.7, 109.4, 107.9, 65.2, 33.1, 25.8, 18.2, 6.0; HRMS (EI) calcd for $C_{30}H_{27}FN_2O_5S_2$: 578.1345, found 578.1355

4.4.22. *N*-(4-(*tert*-Butyl)thiazol-2-yl)-3-(4-(cyclopropylsulfonyl) phen -oxy)-5-((3-methylbut-2-en-1-yl)oxy)benzamide (19)

Yield 84% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.48 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.32 (s, 1H), 7.18 (s, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.83 (s, 1H), 6.59 (s, 1H), 5.47 (t, *J* = 6.1 Hz, 1H), 4.56 (d, *J* = 6.6 Hz, 2H), 2.68–2.38 (m, 1H), 1.81 (s, 3H), 1.75 (s, 3H), 1.45–1.34 (m, 2H), 1.30 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.3, 161.0, 160.7, 156.8, 139.4, 135.1, 134.8, 130.0, 118.5, 118.4, 111.2, 110.5, 109.3, 105.5, 65.4, 34.3, 33.1, 29.7, 25.8, 18.2, 6.0; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S_2$: 540.1753, found 540.1757.

4.4.23. 3-(4-(Cyclopropylsulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)benzamide (20)

Yield 82% (yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.7 Hz, 2H), 7.60 (s, 1H), 7.48 (s, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.85 (s, 1H), 5.48 (t, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 2H), 3.86 (s, 2H), 2.62–2.23 (m, 1H), 1.81 (s, 3H), 1.75 (s, 3H), 1.42–1.31 (m, 2H), 1.12–0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.1, 161.3, 160.5, 156.5, 139.2, 129.9, 118.7, 118.4, 113.2, 112.4, 111.2, 96.6, 65.4, 33.1, 25.8, 18.2, 6.0; HRMS (EI) calcd for $C_{24}H_{24}N_2O_6S_2$: 500.1076, found 500.1072

4.4.24. 3-(4-(Cyclopropylsulfonyl)phenoxy)-*N*-(1,5-dimethyl-1*H*-pyr-azol-3-yl)-5-((3-methylbut-2-en-1-yl)oxy)benzamide (21)

Yield 81% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.92 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.24 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 3H), 6.76 (s, 1H), 6.60 (s, 1H), 5.45 (t, *J* = 6.4 Hz, 1H), 4.52 (d, *J* = 6.7 Hz, 2H), 3.60 (s, 3H), 2.59–2.37 (m, 1H), 2.26 (s, 3H), 1.79 (s, 3H), 1.73 (s, 3H), 1.37–1.31 (m, 2H), 1.07–1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 161.2, 160.5, 156.5, 145.6, 139.7, 139.1, 137.1, 135.0, 129.9, 118.6, 118.3, 110.7, 110.3, 109.4, 97.4, 65.3, 35.5, 33.1, 25.8, 18.2, 11.3, 6.0 ppm; HRMS (EI) calcd for $C_{26}H_{29}N_3O_5S$: 495.1828, found 495.1825.

4.4.25. 3-(4-(Cyclopropylsulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy)-*N*-(5-methylpyrazin-2-yl)benzamide (22)

Yield 70% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.54 (s, 1H), 8.14 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.32 (s, 1H), 7.20 (s, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.83 (s, 1H), 5.47 (t, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 2.57 (s, 3H), 2.54–2.34 (m, 1H), 1.81 (s, 3H), 1.75 (s, 3H), 1.39–1.33 (m, 2H), 1.09–1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2, 161.0, 160.7, 156.8, 149.5, 145.5, 141.3, 139.3, 136.3, 135.8, 135.2, 129.9, 118.5, 118.4, 110.7, 110.6, 109.6, 65.4, 33.1, 25.8, 20.8, 18.2, 6.0; HRMS (EI) calcd for $C_{26}H_{27}N_3O_5S$ 493.1671, found 493.1677.

4.4.26. 3-(4-(Cyclopropylsulfonyl)phenoxy)-*N*-(imidazo[1,2-*a*]pyraz in-8-yl)-5-((3-methylbut-2-en-1-yl)oxy)benzamide (23)

Yield 74% (yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 3H), 7.71 (s, 1H), 7.64 (d, *J* = 14.2 Hz, 2H), 7.40 (s, 1H), 7.30 (s, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.78 (s, 1H), 5.44 (t, *J* = 6.7 Hz, 1H), 4.56 (d, *J* = 5.0 Hz, 2H), 2.48–2.45 (m, 1H), 1.79 (s, 3H), 1.73 (s, 3H), 1.38–1.32 (m, 2H), 1.08–1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.1, 160.5, 156.4, 139.264, 136.932, 134.878, 133.407, 129.804, 118.581, 118.2, 115.4, 111.1, 110.7, 110.2, 65.3, 33.1, 25.7, 18.1, 5.9; HRMS (EI) calcd for $C_{27}H_{26}N_4O_5S$:518.1624, found 518.1628.

4.4.27. *N*-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-((3-methylbut-2-en-1-yl) oxy)-5-(4-(morpholinosulfonyl)phenoxy)benzamide (24a)

Yield 82% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.80 (s, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.19–7.00 (m, 3H), 6.77 (s, 1H), 6.60 (s, 1H), 5.46 (t, J = 6.6 Hz, 1H), 4.53 (d, J = 6.7 Hz, 2H), 3.84–3.70 (m, 4H), 3.63 (s, 3H), 3.13–2.95 (m, 4H), 2.27 (s, 3H), 1.80 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 161.0, 160.5, 156.2, 145.7, 139.7, 139.1, 137.2, 130.1, 129.3, 118.6, 117.9, 111.0, 110.4, 109.6, 97.4, 66.0, 65.3, 45.9, 35.5, 25.8, 18.2, 11.3 ppm; HRMS (EI) calcd for $C_{27}H_{32}N_4O6S$: 540.2043, found 540.2045.

4.4.28. 3-(4-(Cyclopropylsulfonyl)phenoxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-((3-methylbut-2-en-1-yl)oxy)benzamide (24b)

Yield 79% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (s, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.30 (s, 2H), 7.18–7.04 (m, 3H), 6.80 (s, 2H), 5.47 (t, J = 6.9 Hz, 1H), 4.56 (d, J = 6.6 Hz, 2H), 2.58–2.29 (m, 2H), 1.81 (s, 3H), 1.74 (s, 3H), 1.40–1.32 (m, 3H), 1.06 (q, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 161.1, 160.5, 156.6, 146.9, 139.1, 137.0, 135.0, 131.1, 129.9, 118.6, 118.4, 110.6, 110.3, 109.4, 97.6, 65.3, 38.6, 33.1, 25.8, 18.2, 6.0 ppm; HRMS (EI) calcd for $C_{25}H_{27}N_3O_5S$: 481.1671, found 481.1673.

4.4.29. N-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-(4-(((2*S*,6*R*)-2,6-dimethyl morpholino)sulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy) benzamide(25a)

Yield 80% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.51 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.20–7.01 (m, 3H), 6.78 (s, 1H), 6.60 (s, 1H), 5.47 (t, J = 6.8 Hz, 1H), 4.55 (d, J = 6.3 Hz, 2H), 3.81–3.71 (m, 2H), 3.68 (s, 3H), 3.56 (d, J = 11.4 Hz, 2H), 2.29 (s, 3H), 2.01 (t, J = 8.5 Hz, 2H), 1.80 (s, 3H), 1.74 (s, 3H), 1.16 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 160.9, 160.4, 156.2, 145.6, 139.7, 139.0, 137.2, 129.9, 129.6, 118.6, 117.9, 111.0, 110.4, 109.5, 97.4, 71.2, 65.3, 50.7, 35.4, 25.7, 18.6, 18.1, 11.3 ppm; HRMS (EI) calcd for $C_{29}H_{36}N_4O_6S$: 568.2356, found 568.2353.

4.4.30. *N*-(1-Methyl-1*H*-pyrazol-3-yl)-3-((3-methylbut-2-en-1-yl)ox y)-5-(4-(morpholinosulfonyl)phenoxy)benzamide (25b)

Yield 75% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.84 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.29 (s, 1H), 7.17–7.03 (m, 3H), 6.79 (d, J = 7.5 Hz, 2H), 5.46 (t, J = 6.2 Hz, 1H), 4.53 (d, J = 6.6 Hz, 2H), 3.77 (m, 4H), 3.75 (s, 3H), 3.03–3.01 (m, 4H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 161.0, 160.5, 156.3, 146.9, 139.1, 137.1, 131.1, 130.1, 129.3, 118.6, 118.0, 110.8, 110.5, 109.6, 97.6, 66.0, 65.3, 45.9, 38.6, 25.8, 18.2 ppm; HRMS (EI) calcd for $C_{26}H_{30}N_4O_6S$: 526.1886, found 526.1884.

4.4.31. 3-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl) phenoxy)-*N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-5-((3-methylbut-2-en-1-yl)oxy) benzamide (26a)

Yield 85% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 7.69 (d, J = 7.1 Hz, 2H), 7.17–6.98 (m, 3H), 6.77 (s, 1H), 6.59 (s, 1H), 5.47 (t, J = 6.1 Hz, 1H), 4.55 (d, J = 6.4 Hz, 2H), 4.37 (s, 2H), 3.66 (s, 3H), 3.38 (d, J = 10.8 Hz, 2H), 2.66 (d, J = 11.0 Hz, 2H), 2.28 (s, 3H), 2.13–1.87 (m, 4H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 160.8, 160.4, 156.2, 145.6, 139.6, 139.0, 137.2, 129.8, 118.6, 117.8, 110.9, 110.3, 109.5, 97.4, 73.6, 65.3, 50.9, 35.4, 27.6, 25.7, 18.2, 11.3 ppm; HRMS (EI) calcd for $C_{29}H_{34}N_4O_6S$: 566.2199, found 566.2197.

4.4.32. 3-(4-(((2*S*,6*R*)-2,6-Dimethylmorpholino)sulfonyl) phen oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-((3-methylbut-2-en-1-yl) oxy) benzamide (26b)

Yield 84% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 4.2 Hz, 2H), 7.18–7.05 (m, 3H), 6.79 (s, 2H), 5.47 (t, J = 6.7 Hz, 1H), 4.56 (d, J = 6.7 Hz, 2H), 3.80 (s, 3H), 3.76–3.66 (m, 2H), 3.56 (d, J = 11.1 Hz, 2H), 2.00 (t, J = 10.8 Hz, 2H), 1.80 (s, 3H), 1.74 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 160.9, 160.5, 156.3, 146.8, 139.1, 137.0, 131.1, 130.0, 129.6, 118.6, 118.0, 110.9, 110.5, 109.4, 97.6, 71.3, 65.3, 50.7, 38.7, 25.8, 18.6, 18.2 ppm; HRMS (EI) calcd for $C_{28}H_{34}N_4O_6S$: 554.2199, found 554.2202.

4.4.33. (*S*)-*N*-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-(4-((3-fluoro pyrrolidin-1-yl)sulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl) oxy) benz-amide (27a)

Yield 81% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 1.6 Hz, 1H), 7.09 (d, J = 8.8 Hz, 3H), 6.76 (t, J = 1.9 Hz, 1H), 6.59 (s, 1H), 5.46 (t, J = 6.8 Hz, 1H), 5.16 (d, J = 52.8 Hz, 1H), 4.54 (d, J = 6.7 Hz, 2H), 3.65 (s, 3H), 3.57 (d, J = 3.5 Hz, 1H), 3.56–3.39 (m, 2H), 3.31 (td, J = 10.1, 6.5 Hz, 1H), 2.27 (s, 3H), 2.09–1.97 (m, 2H), 1.80 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 160.7, 160.4, 156.4, 145.6, 139.7, 139.0, 137.1, 130.8, 129.7, 118.6, 118.0, 110.8, 110.3, 109.4, 97.4, 93.0, 91.2, 65.3, 54.4, 54.1, 45.8, 35.4, 32.5, 32.3, 25.7, 18.1, 11.3 ppm; HRMS (EI) calcd for $C_{27}H_{31}FN_4O_5S$: 542.1999, found 542.2001.

4.4.34. 3-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl) phenoxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-((3-methylbut-2-en-1-yl)oxy) benzamide (27b)

Yield 83% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (s, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.28 (s, 1H), 7.19–6.99 (m, 3H), 6.78 (d, J = 2.4 Hz, 2H), 5.47 (t, J = 6.5 Hz, 1H), 4.55 (d, J = 6.7 Hz, 2H), 4.37 (s, 2H), 3.80 (s, 3H), 3.38 (d, J = 11.0 Hz, 2H), 2.67 (d, J = 9.8 Hz, 2H), 2.21–1.87 (m, 4H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 160.8, 160.5, 156.3, 146.8, 139.0, 137.0, 131.1, 129.8, 118.6, 117.9, 110.8, 110.4, 109.5, 97.6, 73.6, 65.3, 50.9, 38.6, 27.6, 25.7, 18.2 ppm; HRMS (EI) calcd for $C_{28}H_{32}N_4O_6S$: 552.2043, found 552.2040.

4.4.35. *N*-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-(4-((4-methoxypi peridin-1-yl)sulfonyl)phenoxy)-5-((3-methylbut-2-en-1-yl)oxy) benza-mide (28a)

Yield 83% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.62 (s, 1H), 7.71 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 7.13 (s, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.77 (s, 1H), 6.60 (s, 1H), 5.46 (t, J = 6.5 Hz, 1H), 4.54 (d, J = 6.7 Hz, 2H), 3.65 (s, 3H), 3.34–3.29 (m, 1H), 3.28 (s, 3H), 3.25–3.18 (m, 2H), 2.93 (ddd, J = 11.5, 7.7, 3.7 Hz, 2H), 2.28 (s, 3H), 2.00–1.85 (m, 2H), 1.80 (s, 3H), 1.76 (d, J = 4.3 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 160.6, 160.4, 156.3, 145.6, 139.7, 139.0, 137.1, 130.5, 129.8, 118.6, 117.9, 110.9, 110.3, 109.4, 97.4, 74.0, 65.3, 55.6, 43.1, 35.4, 29.7, 25.7, 18.1, 11.3 ppm; HRMS (EI) calcd for $C_{29}H_{36}N_4O_6S$: 568.2356, found 568.2352.

4.4.36. (*S*)-3-(4-((3-Fluoropyrrolidin-1-yl)sulfonyl)phenoxy)-*N*-(1-me thyl-1*H*-pyrazol-3-yl)-5-((3-methylbut-2-en-1-yl)oxy) benzami-de (28b)

Yield 83% (white powder); H NMR (300 MHz, $CDCl_3$) δ = 8.76 (t, J = 6.9 Hz, 1H), 7.80 (d, J = 8.6 Hz, 2H), 7.27 (s, 2H), 7.09 (d, J = 8.9 Hz, 3H), 6.78 (d, J = 5.9 Hz, 2H), 5.46 (t, J = 6.6 Hz, 1H), 5.16 (d, J = 52.6 Hz, 1H), 4.54 (d, J = 6.7 Hz, 2H), 3.77 (s, 3H), 3.57 (d, J = 3.9 Hz, 1H), 3.55–3.39 (m, 2H), 3.31 (td, J = 10.1, 6.6 Hz, 1H), 2.35–1.86 (m, 2H), 1.80 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 160.7, 160.5, 156.4, 146.9, 139.0, 136.9, 131.1, 130.9, 129.7, 118.6, 118.1, 110.7, 110.4, 109.4, 97.6, 93.0, 91.2, 65.3, 54.4, 54.1, 45.8, 38.5, 32.5, 32.3, 25.7, 18.1 ppm; HRMS (EI) calcd for $C_{26}H_{29}FN_4O_5S$: 528.1843, found 528.1846.

4.4.37. 3-(4-((4-Methoxypiperidin-1-yl)sulfonyl)phenoxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-((3-methylbut-2-en-1-yl)oxy) benzamide (29b)

Yield 80% (white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 2.8 Hz, 2H), 7.14 (s, 1H), 7.08 (d, J = 8.3 Hz, 2H), 6.78 (s, 2H), 5.46 (t, J = 6.4 Hz, 1H), 4.55 (d, J = 6.7 Hz, 2H), 3.79 (s, 3H), 3.34–3.29 (m, 1H), 3.27 (s, 3H), 3.26–3.15 (m, 2H), 2.96–2.90 (m, 2H), 1.99–1.85 (m, 2H), 1.80 (s, 2H), 1.78–1.68 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 160.6, 160.5, 156.4, 146.8, 139.1, 137.0, 131.1, 130.5, 129.8, 118.6, 117.9, 110.8, 110.4, 109.3, 97.5, 74.0, 65.3, 55.6, 43.1, 38.6, 29.7, 25.7, 18.2 ppm; HRMS (EI) calcd for $C_{28}H_{34}N_4O_6S$: 554.2199, found 554.2197.

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