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Design and Optimization of 3'-(imidazo[1,2-*a*]pyrazin-3-yl)-[1,1'-biphenyl]-3-carboxamides as Selective DDR1 Inhibitors

Cheng Mo[†, ‡, #], Zhang Zhang[†, #], Yupeng Li[‡, ξ, #], Minhao Huang[‡], Jian Zou[†], Jinfeng Luo[‡], Zheng-Chao Tu[‡], Yong Xu [‡], Xiaomei Ren[†,*], Ke Ding[†,*], Xiaoyun Lu[†,*]

[†]International Cooperative Laboratory of Traditional Chinese Medicine Modernization and Innovative Drug Development, Ministry of Education (MOE) of PR China, College of Pharmacy, Jinan University, 601 Huangpu Avenue West, Guangzhou 510632, China

[‡]Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530, China

[ξ]Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota 55455, United States

KEYWORDS: DDR1, Selective inhibitor, NSCLC, Drug discovery, SAR.

ABSTRACT: DDR1 is considered as a promising target for cancer therapy and selective inhibitors against DDR1 over other kinases may be considered as promising therapeutic agents. Herein, we have identified a series of 3'-(imidazo[1,2-*a*]pyrazin-3-yl)-[1,1'-biphenyl]-3-carboxamides as novel selective DDR1 inhibitors. Among these, compound **8v** potently inhibited DDR1 with an IC_{50} of 23.8 nM, while showed less inhibitory activity against DDR2 (IC_{50} = 1740 nM) and negligible activities against Bcr-Abl (IC_{50} > 10 μM) and c-Kit (IC_{50} > 10 μM). **8v** also exhibited excellent selectivity in a KINOMEscan screening platform with 468 kinases. This compound dose-dependently suppressed NSCLC cell tumorigenicity, migration and invasion. Collectively, these studies support its potential application for treatment of NSCLC.

Discoidin domain receptors (DDR1 and DDR2), discovered by homology cloning in 1990s, are transmembrane receptor tyrosine kinases (RTKs). [1,2] Unlike other RTKs, the endogenous ligands of DDRs are collagens.[3,4] DDRs can undergo autophosphorylation to actively regulate basic cellular processes by collagen binding, e.g. differentiation, adhesion, proliferation, survival and matrix remodeling. [5-7] Earlier studies have indicated that DDRs may serve as potential targets of treating some diseases, such as fibrotic disorders, osteoarthritis, and cancers.[8,9] For example, DDR1 was widely implicated in cell survival and invasiveness in a range of cancers, including lung cancer, hepatocellular carcinoma and prostate cancer, etc.[10,11] Overexpression or mutation of DDRs have also been detected in many cancer cell lines such as non-small cell lung cancer (NSCLC), breast cancer and ovarian cancer.[12-14] Experimental therapeutics targeting DDR1 by siRNA have indicated its potential to suppress tumorigenicity, inhibit lung cancer bone metastasis, and enhance cancer cell chemosensitivity.[15-17] Consequently, DDR1 inhibitors could serve as new potential therapeutic agents for cancer treatment.[9]

Numerous multi-kinase inhibitors have been reported to show good inhibitory activities against DDR1 and DDR2 functionality.[9] However, few of them were developed primarily by targeting DDRs. During recent five years, several selective DDR1 inhibitors were reported with various selectivity profiles (Figure 1).[18-23] Compound **1** was the first reported by our laboratory as a promising DDR1-selective inhibitor for cancer therapy. However, its selectivity against DDR1 over DDR2 (14 fold) and Abl (52 fold) is still relatively inadequate.[18] To further improve its selectivity profile, a series of 3'-(imidazo[1,2-*a*]pyrazin-3-yl)-[1,1'-biphenyl]-3-carboxamides were designed by featuring a novel substituted phenyl linker instead of the alkyne group in compound **1** and the nitrogen of imidazo[1,2-*a*]pyrazine forming a critical hydrogen bond with Met704 of DDR1 (Figure 2).

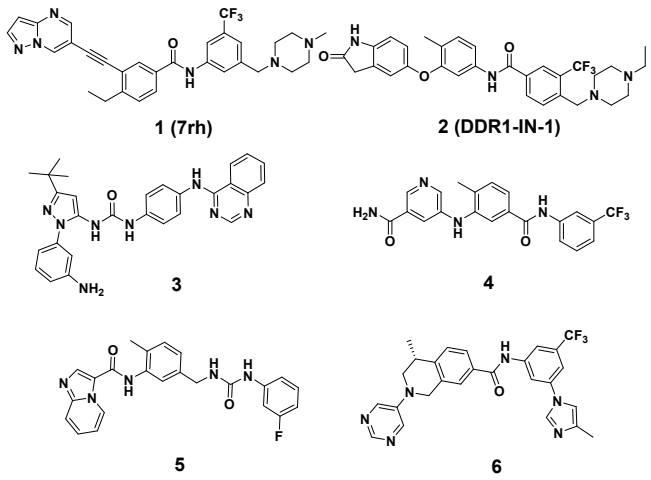


Figure 1. Structures of reported selective DDR1 inhibitors.

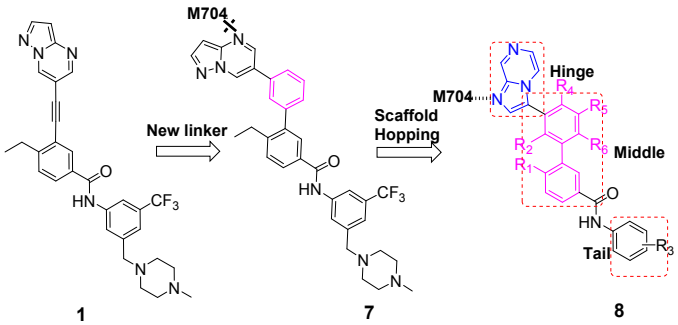
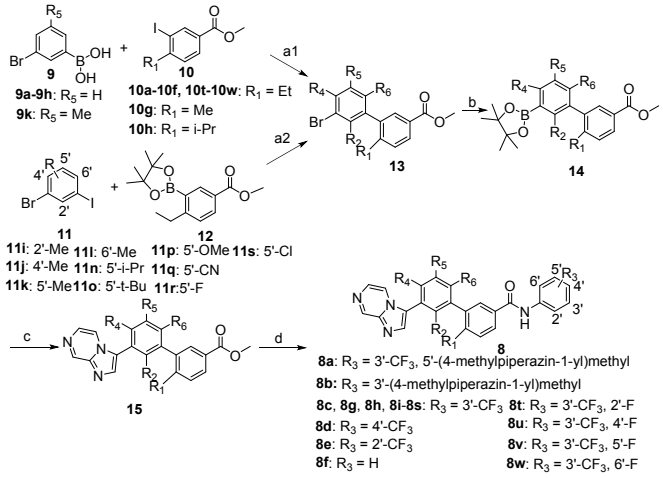


Figure 2. Designing of new DDR1 inhibitors based on compound **1**.

The title compounds were readily synthesized as described in Scheme 1. Substituted methyl 3'-bromo-[(1,1'-biphenyl)]-3-carboxyl-ates **13** were prepared by coupling a substituted 3-bromophenylboronic acid **9** with substituted methyl 3-iodobenzoates **10** or by coupling

substituted 1-bromo-3-iodobenzenes **11** with methyl 4-ethyl-3-(4,4,5,5-tetra-methyl-1,3,2-dioxaborolan-2-yl)benzoate (**12**). Compound **13** reacted with bis(pinacolato)diboron to give the intermediate **14**, which underwent the classical Suzuki coupling reaction to yield the key substituted methyl 3'-(imidazo[1,2-*a*]pyrazin-3-yl)-[1,1'-biphenyl]-3-carboxylates **15**. The title compounds **8** were obtained through the amidation of the intermediate **15** with different anilines under basic conditions.

Scheme 1. Synthesis of the designed new DDR1 inhibitors.



Reagents and conditions: (a1) $Pd(PPh_3)_4$, Na_2CO_3, PhMe/H_2O (3:1), Ar, 90 °C, overnight,58-98%; (a2) $Pd(PPh_3)_4$, K_3PO_4, dioxane, Ar, 90 °C, overnight,55-91%; (b) $Pd(dffp)Cl_2$, AcOK, Bis(pinacolato)diboron, dioxane, Ar, 90 °C, overnight,64-92%; (c) $Pd(PPh_3)_4$, Na_2CO_3, PhMe/H_2O (3:1), Ar, 90 °C, overnight, 42-82%; (d) *t*-BuOK, anilines, dry THF, -20 °C, 4-79%.

Our previous study indicated that **1** bound to the active pocket of DDR1 with a type II binding mode, and the alkynyl moiety served as a linking group for the pyrazolo[3,4-b]pyridine and the ethylbenzene.[24] In our continuous efforts to improve its selectivity, the conformationally restricted bioisostere phenyl group of the alkynyl was first explored (Figure 2), similar to that of bioisostere triazol. [25]

Starting with the simplest modification, compound **7** indeed improved the selectivity against Bcr-Abl and c-Kit, although it had about 50-fold decreased inhibitory activities against DDR1 and DDR2 (Table 1). In an investigation of the reason for the loss of activity, modeling studies suggested that compound **7** did not fit nicely into the DDR1 ATP binding pocket and could not achieve the essential hydrogen bond (HB) with Met704 in DDR1 (Figure 2). In view of the importance of the HB interactions in the hinge region of kinases, imidazo[1,2-*a*]pyrazine was used as a privileged moiety to restore the key HB formed with Met704 of DDR1.[26] Compound **8a** exhibited 37-fold increased potency against DDR1 (IC_{50} = 8.7 nM), although its selectivity against other homologous kinases was unexpectedly decreased (Table 1).

As a new scaffold for DDR1 inhibitor, compound **8a** exhibited digital nM inhibitory activity against DDR1, and served as a promising lead molecule for further optimization. Further computational docking studies suggested that **8a** bound to DDR1 with a classical type II bind mode (Figure 3A). The imidazo[1,2-*a*]pyrazine moiety of **8a** formed a critical HB with the Met704 of DDR1. The phenyl linker participated in an additional π-π interaction with Phe785, and this contributes greatly to its improved selectivity against Bcr-Abl and c-Kit. The amide of **8a** also formed two HBs with Glu672 and Asp784 of DDR1, respectively. The modeling results suggested that the trifluoromethyl group of **8a** was deeply bound in a DFG-out hydrophobic pocket and the 1-(4-methyl)piperazinyl moiety was extended to solvent region of protein. So, these two parts were firstly eliminated to investigate the contribution to DDR1 inhibitory activity, respectively.

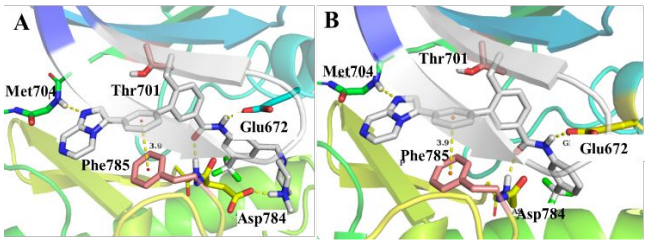
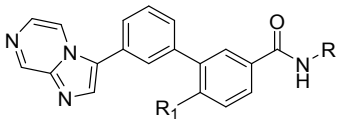
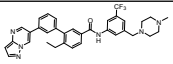
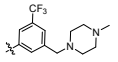
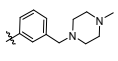
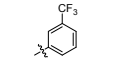
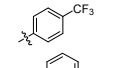
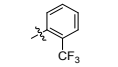
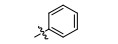
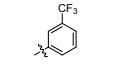
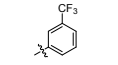


Figure 3. Binding modes of compounds **8a** (A) and **8c** (B) to DDR1 Kinase (PDB: 4bkj). HBs and π-π interactions with key amino acids are indicated by yellow dotted lines .

Compound **8b** in which R was replaced by 1-benzyl-4-methylpiperazine, showed a substantial potency loss towards DDR1 (IC50 = 357.1 nM), while compound **8c** without the 1-(4-methyl)piperazinyl group was almost equal potent with **8a** and had significantly improved selectivity over DDR2, Bcr-Abl and c-Kit (Table 1). The results suggested the CF_3 group is essential for the compounds to maintain DDR1 inhibitory activity and improve the selectivity over the aforementioned kinases. Moving the CF_3 group to the *ortho*- (**8d**) or *para*- (**8e**) positions, or simply eliminating it (**8f**) totally negated the inhibitory activity against DDR1 kinase. The contribution of R_1 substituents to the DDR1 potency and selectivity was also investigated. The methyl-substituted compound (**8g**) totally abolished the selectivity over DDR2, Bcr-Abl and c-Kit (Table 1), although the inhibitory activity was maintained. The isopropyl-substituted compound (**8h**) also totally abolished the activity. These results clearly suggested that R1 group, directed towards the gatekeeper Thr701 (Figure 3), played a crucial role in regulating kinase selectivity and activity.

Table 1. Kinase inhibition of compounds **7** and **8a**-**8h** against DDR1, DRR2, Bcl-Abl, and c-Kit.



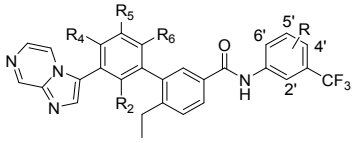
Cpds	R1	R	Kinase inhibition (IC_{50}, nM) DDR1 [a]	DDR2 [a]	Bcr-Abl [b]	c-Kit [b]
7			359.5	196.7	>10μM	>10μM
8a	Et		9.6	66.1	437	619.7
8b	Et		357.1	>10μM	989.3	4934
8c	Et		10.4	725	2220	2917
8d	Et		1296	>10μM	4992	3984
8e	Et		4879	>10μM	>10μM	>10μM
8f	Et		4850	>10μM	5120	8990
8g	Me		9.2	135	237	72.4
8h	*i*-Pr		1260	>10μM	>10μM	1686
1		-	6.8	101.4	355	>10μM

[a]DDR1 and DDR2 inhibition were performed with the LanthaScreen Eu kinase assay. [b] Bcr-Abl and c-Kit inhibition were performed with the FRET-based Z′-Lyte assay. *Data means of three independent experiments, and the variations are <20%.

Our previous study suggested that the π-π interaction between the phenyl linker of **8c** with Phe785 contributed significantly to the selectivity against Bcr-Abl and c-Kit,[23] and a detailed SAR study focusing on phenyl linker was undertaken. When a methyl group was added at the R_2, R_4, R_5 or R_6 position of **8c**, the resulting compounds **8i-8l** showed reduced inhibitory activity against DDR1 with IC_{50} values of 30.1, 107.8, 22.5 and 63.7 nM, respectively. Although **8k** in which R_5 as methyl, was about 2-fold less potent than **8c**, it displayed superior selectivity over other three kinases (DDR2, Bcr-Abl and c-Kit). Next, we examined the contribution of R5 substituent to the DDR1 inhibitory potency and selectivity. Obviously, as the bulk of the substituents increased, the potency against DDR1 decreased accordingly. For example, replacement of the R_5-methyl with ethyl (**8m**), isopropyl (**8n**), or *tert*-butyl (**8o**) led to compounds with IC_{50} values of 42.3, 66.9 and 92 nM, respectively. Further study showed that this position was generally tolerant to both medium sized electron-donating and -withdrawing groups. For example, compounds with methoxy (**8p**), cyano (**8q**), fluorine (**8r**), and chlorine (**8s**) groups at this position exhibited IC_{50} values of 16.5, 15.6, 30.3 and 21.3 nM, respectively, against the DDR1 kinase, but the selectivity over DDR2, Bcr-Abl and c-Kit was obviously decreased.

The fluorine atom is a bioisostere of hydrogen and can reduce the electrical properties of the phenyl group. We investigated the potential influence of the "tail phenyl" region of **8k** by introducing a fluorine atom to the R position. The resulting 2'-F (**8t**), 4'-F (**8u**), and 6'-F (**8w**) compounds displayed decreased inhibitory activity against DDR1, while 5'-F (**8v**) exhibited a similar DDR1 inhibitory activity and selectivity to those of **8k**. Compound **8v** potently exhibited DDR1 inhibitory activity (IC50 = 23.8 nM) and also targeted selectivity over aforementioned kinases DDR2, Bcr-Abl and c-Kit of 73-, 420-, and 420-fold, respectively.

Table 2. Kinase inhibition of compounds **8i–8y** against DDR1, DRR2, Bcr-Abl, and c-Kit.

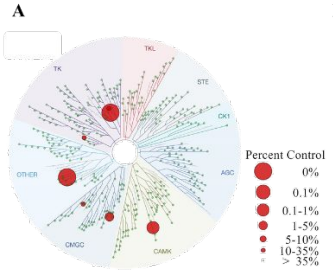


Cpds	R2	R4	R5	R6	R	Kinase inhibition (IC_{50}, nM) DDR1[a]	DDR2[a]	Abl[b]	c-Kit[b]
8i	Me	H	H	H	H	30.1	663.5	1813	5978
8j	H	Me	H	H	H	107.8	>10μM	>10μM	>10μM
8k	H	H	Me	H	H	22.5	1728	>10μM	>10μM
8l	H	H	H	Me	H	63.7	610	1452	>10μM
8m	H	H	Et	H	H	42.3	3227	>10μM	>10μM
8n	H	H	i-Pr	H	H	66.9	2631	>10μM	>10μM
8o	H	H	t-Bu	H	H	92	>10μM	>10μM	>10μM
8p	H	H	OMe	H	H	16.5	1018	3696	4994
8q	H	H	CN	H	H	15.6	947	5637	3721
8r	H	H	F	H	H	30.3	1326	5345	6591

8s	H	H	Cl	H	H	21.3	1080	>10μM	8414
8t	H	H	Me	H	2'-F	73.8	>5μM	>10μM	>10μM
8u	H	H	Me	H	4'-F	55.6	>5μM	>10μM	>10μM
8v	H	H	Me	H	5'-F	23.8	1740	>10μM	>10μM
8w	H	H	Me	H	6'-F	36.5	>5μM	>10μM	>10μM
1			-			6.8	101.4	355	>10μM

[a]DDR1 and DDR2 inhibition were performed with the LanthaScreen Eu kinase assay. [b] Bcr-Abl and c-Kit inhibition were performed with the FRET-based Z'-Lyte assay. *Data means of three independent experiments, and the variations are <20%.

To further evaluate the selectivity of **8v** over other kinases, a KINOMEscan screening platform with 468 kinases was conducted at DiscoveRx (San Diego, CA). [27] The results demonstrated that **8v** displayed extraordinary target selectivity (S core (10) = 0.01 and S core (1) = 0.007) (Figure 4A, Tables S1 and S2). The apparent "off-target" kinases included only DDR2, calcium dependent protein kinase ID (CAMK1D), CDC like kinase 4 (CLK4), and spindle assembly checkpoint kinase (TTK). The K_d values of **8v** against above "off targets" and DDR1 were further evaluated using DiscoveRx's platform. The results showed that **8v** tightly bound to DDR1 (K_d = 7.8 nM, Figure 4B), which was consistent with the *in vitro* kinase inhibitory activity. For potential "off-targets", compound **8v** had no detectable binding affinities to three apparent "off target" kinases (CAMK1D, CLK4, and TTK) at a >1 μM concentration except for DDR2 (Figure 4B). Although K_d value of **8v** to DDR2 appears to be as low as 86 nM, its IC_{50} value against DDR2 was 1739 nM in our kinase assay. In comparison, the IC_{50} value of compound **8v** against DDR1 was determined to be 23.8 nM (73-fold selective). Taken together, these results suggested the extraordinary target selectivity of compound **8v** against a panel of 468 kinases.



B

Kinases	%Ctrl@ 200 nM	Binding affinity (Kd, nM)
DDR1	0	7.8
DDR2	15	86
CAMK1D	0.9	>1000
CLK4	1.8	>1000
TTK	0	>1000

Figure 4. KINOMEscan profiles of compound **8v**. (A) KINOMEscan profiling of **8v** at a concentration of 200 nM (25-fold Kd value) against 468 kinases. (B) The K_d determination of compound **8v** against DDR1 and the potential off targets.

A previous study has shown that DDR1 inhibitors strongly suppress cancer tumorigenicity.[18] The effect of **8v** on the tumorigenicity of H1299 NSCLC cancer cells was firstly investigated by colony formation assay. The results demonstrated that compound **8v** dose-dependently suppressed colony formation in H1299 NSCLC cancer cells after 10 continuous day treatment of cells with **8v** (IC50 = 0.046 μM, Figures 5A and 5B). However, the direct anti-proliferation of **8v** against H1299 NSCLC cancer cells seemed to be moderate with an IC_{50} value of 6.6 μM (Figure 5C). It was suggested that compound **8v** significantly suppressed the number of colony formation (not the size).

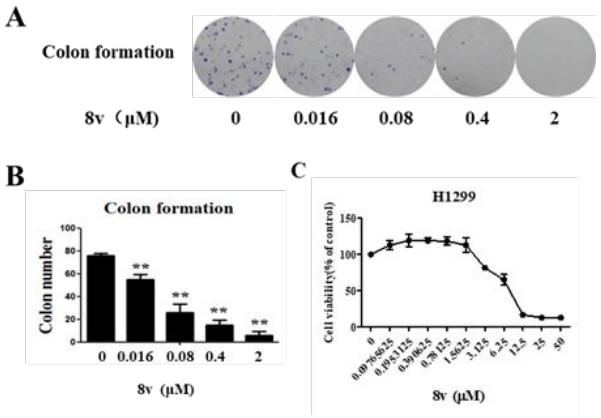


Figure 5. Compound **8v** suppresses H1299 NSCLC cell tumorigenicity and proliferation. (A) Compound **8v** effectively inhibits H1299 NSCLC cell colony formation. (B) The quantitative result of Figure 5A. (C) The proliferation result of **8v** evaluated with an CCK-8 assay. The data are means from three independent experiments.

It has been reported that DDR1 plays important roles in tumor migration and invasion.[18] The effect of **8v** on the migration and invasion of H1299 NSCLC cancer cells was investigated using the wound healing assay and the transwell assay. As shown in Figure 6A, compound **8v** suppressed wound closure in H1299 cells by 40%, 60% and 84% at concentrations of 1.25, 2.5 and 5.0 μM, respectively, compared with blank control groups. Further the study showed that **8v** dose-dependently inhibits the invasion of H1299 cancer cells by 17%, 50% and 71% at the 1.25, 2.5 and 5.0 μM concentrations for 24 h, respectively (Figures 6B). These results clearly indicated that compound **8v** can potentially suppress migration and invasion of H1299 NSCLC cancers.

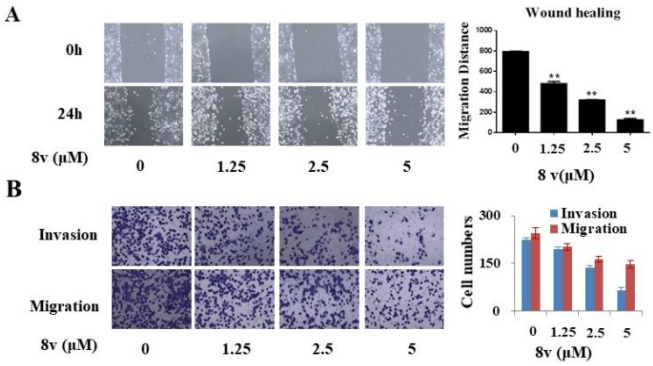


Figure 6. Compound **8v** suppresses H1299 NSCLC cell migration and invasion. (A) Compound **8v** inhibition of H1299 cell migration with wound healing assay. (B) Compound **8v** inhibition of H1299 cell migration and invasion with transwell assay. The data are means from three independent experiments.

In summary, a series of 3'-(imidazo[1,2-a]pyrazin-3-yl)-[1,1'-biphenyl]-3-carboxamides were synthesized and investigated as highly selective DDR1 inhibitors. The comprehensive SARs study reported here led to the most promising compound **8v**, which binds tightly to the DDR1 (K_d = 7.8 nM) and potently inhibits DDR1 kinase function (IC_{50} = 23.8 nM). Furthermore, **8v** exhibits ideal target selectivity in KINOMEscan screen against the 468 kinases. Compound **8v** also potently suppresses NSCLC cell tumorigenicity, invasion and adhesion. However, the pharmacokinetic parameters of compound **8v** is not ideal (t1/2 = 1.2 hr and F % = 3.9). Further pharmacokinetics-oriented optimization of **8v** is on-going and the results will be disclosed in due course. Collectively, compound **8v** may be as a promising lead compound for the future studies.

ASSOCIATED CONTENT

Supporting information

Synthetic procedures for compounds **8a-8w**, the results of the kinase selectivity profiling study of compound **8v**, procedures for Kinome*scan* screening, *in vitro* kinase assay, colony formation assay, in vitro cell proliferation by MTT assay, wound healing, transwell assay, computational study and the ^{1}H and ^{13}C NMR spectra of compounds **8a-8w** will be released upon article publication.

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*E-mail addresses: ren_xiaomei@jnu.edu.cn (X. R.), dingke @jnu.edu.cn (K. D.), luxy2016@jnu.edu.cn (X. L.).

Author Contributions

# These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DDR1, discoidin domain receptor 1; K_d, binding constant; RTKs, receptor tyrosine kinases; CF_3, trifluoromethylphenyl; CAMK1D, calcium/calmodulin dependent protein kinase ID; NSCLC, non-small cell lung cancer; CLK4, CDC like kinase 4; SAR, structure-activity relationship; TTK spindle assembly checkpoint kinase; DFG, Asp-Phe-Gly; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenytetrazolium bromide.

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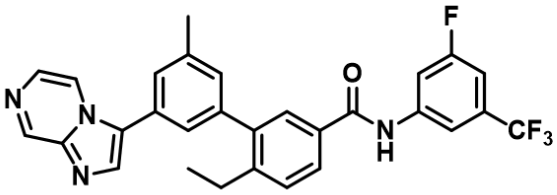

8v

DDR1 IC_{50} = 23.8 nM, K_d =7.8 nM
DDR2 IC_{50} = 1740 nM
Abl IC_{50} > 10 μM
c-Kit IC_{50} > 10 μM