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Synthesis and biological evaluation of 1-substituted-3(5)-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)pyrazoles as transforming growth factor-β type 1 receptor kinase inhibitors

Cheng Hua Jin, Maddeboina Krishnaiah, Domalapally Sreenu, Kota Sudhakar Rao, Vura Bala Subrahmanyam, Chul-Yong Park, Jee-Yeon Son, Yhun Yhong Sheen, Dae-Kee Kim *

College of Pharmacy, Ewha Womans University, 11-1 Daehyun-dong, Seodaemun-gu, Seoul 120-750, Republic of Korea

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ABSTRACT

A series of 1-substituted-3(5)-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)pyrazoles **14a–e**, **15a–e**, **17a–c**, and **18a–d** have been synthesized and evaluated for their ALK5 inhibitory activity in an enzyme assay and in a cell-based luciferase reporter assay. The 6-quinolinyl pyrazole analogue **14b** inhibited ALK5 phosphorylation with IC_{50} value of 0.022 μM and showed 84% inhibition at 0.1 μM in a luciferase reporter assay using HaCaT cells permanently transfected with p3TP-luc reporter construct.

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1. Introduction

The transforming growth factor-β (TGF-β) family members, which include TGF-βs, activins, and bone morphogenetic proteins (BMPs) are structurally related secreted cytokines found in species ranging from worms and insects to mammals. A wide spectrum of cellular functions such as proliferation, differentiation, adhesion, migration, and apoptosis are regulated by TGF-β family members. The three major TGF-β isoforms, TGF-β1, TGF-β2, and TGF-β3, are expressed in mammals, and each is encoded by unique gene and expressed in a tissue-specific manner. TGF-β1 is the prototype and major isoform of this family of cytokines. TGF-β transduces signals through two distinct serine/threonine kinase receptors, termed type I and type II.[1–3] The signaling cascade is promoted by the binding of ligand to the constitutively active type II receptor. Subsequently, the type I receptor, also called as activin receptor-like kinase 5 (ALK5), is phosphorylated in the juxtamembrane GS domain stimulating its kinase activity. The activated ALK5 propagates the signals through phosphorylation of receptor-regulated Smads such as Smad2 and Smad3 that in turn form complexes with the common-mediator Smad, Smad4. These Smad complexes, when delivered to the nucleus regulate the expression of several hundred genes involved in cell differentiation, proliferation, apoptosis, migration, and extracellular matrix production (Fig. 1).[4] TGF-β plays a critical role in the initiation and progression of fibrosis in various organ systems such as kidney,[5] heart,[6] lung,[7] and liver.[8] Deregulation of TGF-β signaling has been implicated in various human diseases including cancer,[9] pancreatic diseases,[10] and hematological malignancies.[11]

The extensive comprehension regarding TGF-β-mediated ALK5-dependent signaling pathway has suggested the therapeutic potential of TGF-β signaling antagonist. One of the strategies used to inhibit TGF-β signaling is to block the catalytic activity of ALK5. Small molecule ALK5 inhibitors bind to the ATP binding pocket located next to the Smad2 and Smad3 binding site in a competitive manner, thus, preventing phosphorylation of these proteins. Several small molecule ALK5 inhibitors such as **1** (SB-431542),[12] **2** (SB-505124),[13] **3** (GW6604),[14] **4** (SD-208),[15,16] and **5** (LY-2157299)[17] are in various stages of clinical development (Fig. 2).

We have prepared a number of the 2-pyridyl-substituted five-membered heterocycles as ALK5 inhibitors and found that insertion of a methylene, a methyleneamino, or an aminomethylene linkage between a central five-membered heterocyclic ring and a phenyl ring significantly increased ALK5 inhibitory activity and selectivity.[18–26] IN-1130 (**6**), one of our preclinical candidates, demonstrated its remarkable activity as a suppressor of fibrogenic process of unilateral ureteral obstruction in rats underscoring the

* Corresponding author. Tel.: +82 2 3277 3025; fax: +82 2 3277 2467.
E-mail addresses: dkkim@ewha.ac.kr, dkkim@in2gen.com (D.-K. Kim).

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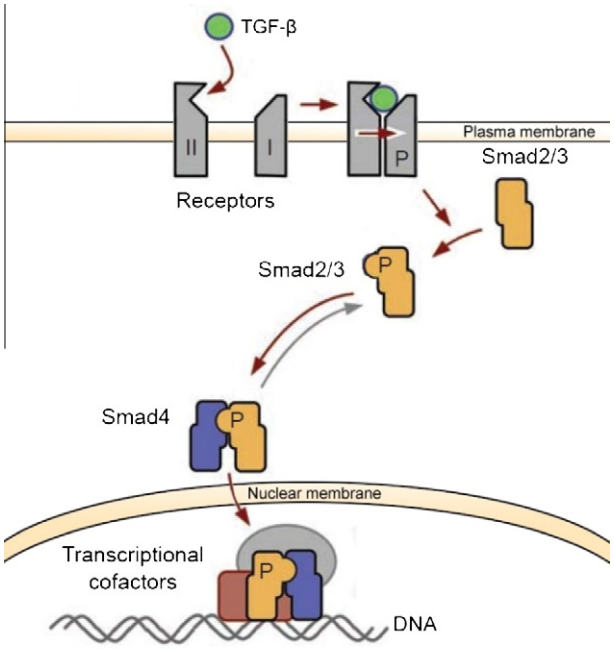


Figure 1. TGF-β signaling pathway.

potential clinical benefits in the treatment of renal fibrosis[27] and ameliorated experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis, by inhibition of TGF-β signaling.[28] It also lessened tunical fibrosis and corrected penile curvature in rats,[29] inhibited cancer metastasis in MMTV/c-Neu breast cancer mice, and enhanced CTL response in cancer mice.[30] IN-1233 (**7**), another preclinical candidate, effectively prevented development and progression of pulmonary arterial hypertension in monocrotaline rat model through inhibition of TGF-β signaling[31] and prevented granulation tissue formation after bare metallic stent placement in a rat urethral model.[32]

Tojo et al. reported a novel class of ALK5 inhibitors that possess a thioamide linkage between a pyrazole ring and a phenyl ring.[33] Among them, A-83-01 (**8**) exhibited significant inhibition of the transcriptional activity induced by ALK5. We recently reported a new class of 2-pyridyl-substituted pyrazoles possessing a thioamide linkage, and one of the compounds in this series, 3-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazole-1-carbothioamido)benzamide (**9**), showed more than 90% inhibition at 0.1 μM in luciferase reporter assay using HaCaT cells transiently transfected with p3TP-luc reporter construct and ARE-luc reporter construct.[23] Although insertion of a thioamide linkage between a pyrazole ring and a phenyl ring markedly increased ALK5 inhibitory activity as shown in previous reports,[23,33] it was found that this thioamide linkage was rather unstable and slowly cleaved to generate a pyrazole ring on long-term storage.

On the basis of this observation, we attempted to replace the thioamide linkage with a chemically stable thioamidomethylene or thioamidoethylene linkage, thus, prepared the compounds **18a**–**d** as target molecules. To compare the influence of the thioamidomethylene or thioamidoethylene linkage of **18a–d**, their counterpart derivatives **14a–e** and **17a–c** possessing the amidomethylene or amidoethylene linkage were also prepared. All target molecules in this report have a 6-quinolinyl moiety at the 4-position of the pyrazole ring rather than a 4-quinolinyl moiety of **8** since the former has been proved to be a better moiety in ALK5 inhibition than the latter in our previous work.[23] A docking model of ALK5:**7** complex showed that the nitrogen atom of the 6-quinolinyl moiety formed a H-bond with backbone amide NH of His283 in the hinge region of the kinase, originally a binding pocket for the adenine ring of ATP.[24] To examine whether the capability of the nitrogen atom of the 6-quinolinyl moiety as a H-bond acceptor could be increased by aromatic substitution, we introduced an electron-donating methoxy group at the 4-position of the 6-quinolinyl moiety (compounds **14c**, **14d**, and **17c**).

2. Results and discussion

2.1. Chemistry

The 3-(6-methylpyridin-2-yl)-1-(phenylcarboxamidomethyl)-4-(quinolin-6-yl)pyrazoles **14a–e** were synthesized as shown in Scheme 1. The 6-chloroquinoline (**10a)** and 6-chloro-4-methoxyquinoline (**10b)** were coupled with 2-acetyl-6-methylpyridine in

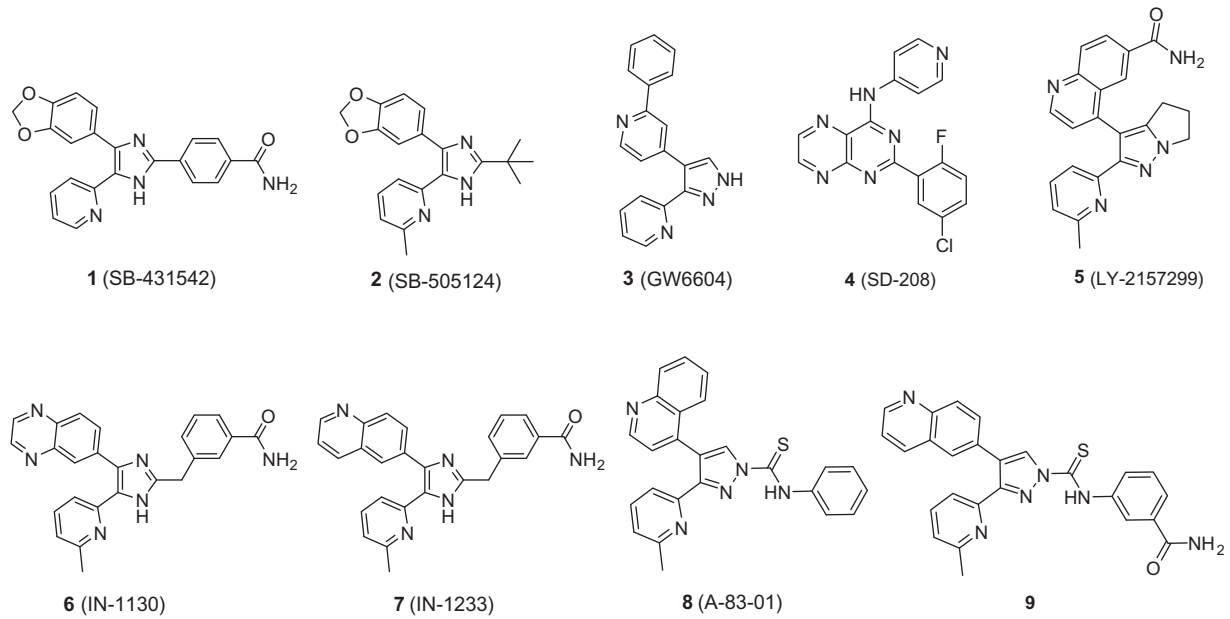
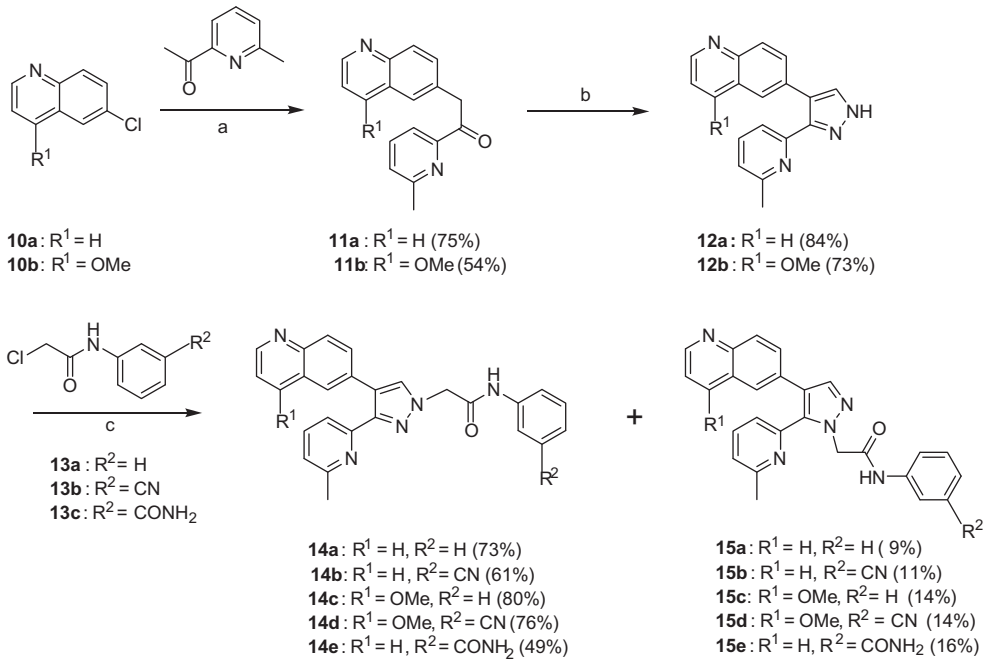


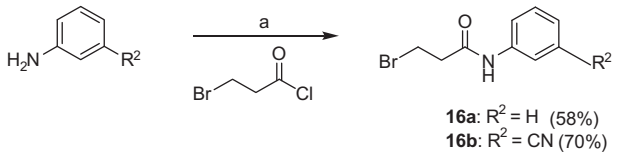
Figure 2. ALK5 inhibitors under development.



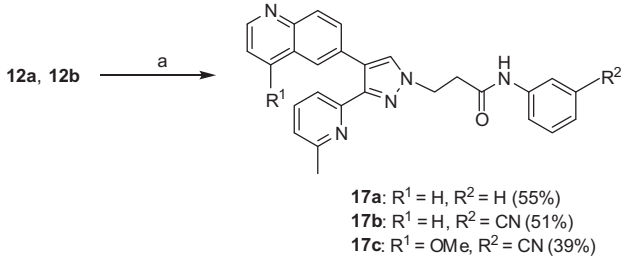
Scheme 1. Reagents and conditions: (a) palladium(II) acetate, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, potassium *tert*-butoxide, anhydrous THF, 75 °C, 14 h; (b) (i) DMF·DMA, 90 °C, 4 h; (ii) $N_2H_4·H_2O$, EtOH, reflux, 4 h; (c) NaH, NaI (cat.), DMF, rt, 30 min (for **13a** and **13b**) or Cs_2CO_3, DMF, 120 °C, 1 h (for **13c**).

the presence of potassium *tert*-butoxide, palladium(II) acetate, and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl in anhydrous THF to afford the ketones **11a**[23] and **11b**[34] in 75% and 54% yields, respectively. Treatment of **11a** and **11b** with *N*,*N*-dimethylformamide dimethyl acetal and followed by reaction with hydrazine monohydrate in absolute EtOH gave the pyrazoles **12a**[23] and **12b**[34] in 84% and 73% yields, respectively. The pyrazoles **12a** and **12b** were alkylated with 2-chloro-*N*-phenylacetamide (**13a**)[35] or 2-chloro-*N*-(3-cyanophenyl)acetamide (**13b**)[36] in the presence of NaH in anhydrous DMF to yield the target compounds 14a–**d** and their positional isomers **15a**–**d** in 61–80% and 9–14% yields, respectively. The positional isomers were separated by MPLC, and their structures were confirmed by NOE experiments. In NOE experiments, irradiation of the methylene protons of the **14a** at δ 5.14 gave an enhancement of the proton *H*-5 in pyrazole ring at δ 7.81, while irradiation of the methylene protons of the **15a** at δ 5.06 gave no enhancement of the proton *H*-5 in pyrazole ring at δ 7.90, confirming the respective positions of alkylation. Alkylation of **12a** with 3-(2-chloroacetamido)benzamide (**13c**)[37] in the presence of Cs_2CO_3 in DMF at 120 °C gave the positional isomers **14e** and **15e** in 49% and 16% yields, respectively.

Reaction of aniline and 3-aminobenzonitrile with 3-bromopropanoyl chloride in the presence of K_2CO_3 in CH_2Cl_2 gave 3-bromo-*N*-phenylpropanamide (**16a**)[38] and 3-bromo-*N*-(3-cyanophenyl)propanamide (**16b**) in 58% and 70% yields, respectively (Scheme 2). The 3-(6-methylpyridin-2-yl)-1-(phenylcarboxamidoethyl)-4-(quinolin-6-yl)pyrazoles **17a–c** were synthesized as shown in Scheme 3. Alkylation of the pyrazoles **12a** and **12b** with **16a** or **16b** in the presence of Cs_2CO_3 in anhydrous DMF at 120 °C afforded the



Scheme 2. Reagents and conditions: (a) K_2CO_3, CH_2Cl_2, reflux, 4 h.



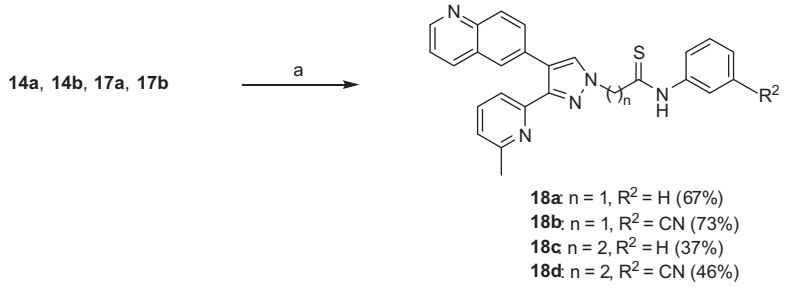
Scheme 3. Reagents and conditions: (a) **16a** or **16b**, Cs_2CO_3, DMF, 120 °C, 1–3 h.

target compounds **17a**–**c** in 39–55% yields. In this case, the positional isomers of the **17a–c** were not isolated after column chromatography.

Thionation of the **14a**, **14b**, **17a**, and **17b** with Lawesson's reagent in anhydrous DME at 85 °C produced the thioamides **18a**–**d** in 37–67% yields (Scheme 4). As expected, all prepared target compounds were quite stable at room temperature on long-term storage.

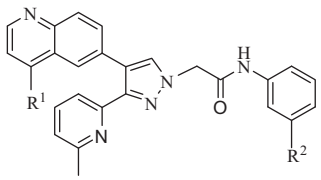
2.2. Biological evaluation

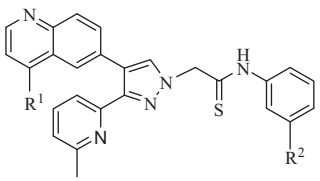
To investigate whether these compounds **14a–e**, **17a–c**, and **18a–d** could inhibit ALK5, a kinase assay was performed using the purified human ALK5 kinase domain produced in Sf9 insect cells. The compounds **15a–e**, the positional isomers of **14a–e**, displayed no significant ALK5 inhibitory activity up to a concentration of 1 μM (Table 1). It has been also observed that all the compounds having a methoxy substituent at the 4-position of the 6-quinolinyl moiety (**14c**, **14d**, **15c**, **15d**, and **17c**) displayed no significant ALK5 inhibitory activity up to a concentration of 1 μM. We envisioned that introduction of an electron-donating group in the 6-quinolinyl moiety may increase the capability of the nitrogen atom in that moiety as a H-bond acceptor, thus, potentiating ALK5 inhibitory activity. But, the result showed that a 4-methoxy group in the 6-quinolinyl moiety seemed to be not accommodated favorably into

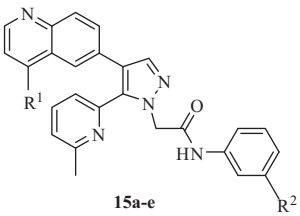


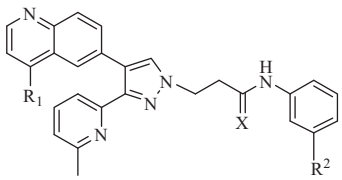
Scheme 4. Reagents and conditions: (a) Lawesson's reagent, DME, 85 °C, 12 h.

Table 1
Inhibitory activity of 1-substituted-3(5)-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)pyrazoles **14a–e**, **15a–e**, **17a–c**, and **18a–d** on ALK5









Compd	R^1	R^2	X	IC_{50} (μM)		Selectivity index[c]	p3TP-luciferase activity[d,e] (% control)
				ALK5[a]	p38α[b]		
Mock							9 ± 1
TGF-β							100 ± 4
14a	H	H		0.207	>1.0	>5	51 ± 3
14b	H	CN		0.022	>1.0	>45	16 ± 1
14c	OMe	H		>1.0	>1.0		108 ± 2
14d	OMe	CN		>1.0	>1.0		108 ± 9
14e	H	$CONH_2$		0.075	>1.0	>13	58 ± 4
15a	H	H		>1.0	>1.0		102 ± 8
15b	H	CN		>1.0	>1.0		110 ± 2
15c	OMe	H		>1.0	>1.0		104 ± 7
15d	OMe	CN		>1.0	>1.0		107 ± 7
15e	H	$CONH_2$		>1.0	>1.0		104 ± 2
17a	H	H	O	0.025	>1.0	>40	34 ± 5
17b	H	CN	O	0.101	>1.0	>10	61 ± 5
17c	OMe	CN	O	>1.0	>1.0		119 ± 13
18a	H	H		0.094	>1.0	>11	44 ± 4
18b	H	CN		0.051	>1.0	>20	31 ± 5
18c	H	H	S	0.088	>1.0	>11	64 ± 6
18d	H	CN	S	0.232	0.63	>3	77 ± 3
2				0.054	0.594	11	34 ± 0
6				0.017	0.480	28	20 ± 3

[a] ALK5 was expressed in Sf9 insect cells as human recombinant GST-fusion protein by means of the vaculovirus expression system. A Proprietary radioisotopic protein kinase assay (33PanQinase® Activity Assay) was performed at ProQinase GmbH (Freiburg, Germany) using casein as a substrate.

[b] p38α MAP kinase was expressed as untagged human recombinant protein in *E. coli*. The enzyme was purified by Ni-NTH-agarose (Qiagen). A Proprietary radioisotopic protein kinase assay (^{33}PanQinase® Activity Assay) was performed at ProQinase GmbH (Freiburg, Germany) using ATF2 as a substrate.

[c] IC_{50} of p38α/IC_{50} of ALK5.

[d] Luciferase activity was determined at a concentration of 0.1 μM of inhibitor.

[e] Activity is given as the mean ± SD of three independent experiments run in triplicate relative to control incubations with DMSO vehicle.

the ATP binding pocket of ALK5. As we expected, among the pyrazoles possessing an amidomethylene or a thioamidomethylene linkage, introduction of a carbonitrile- or a carboxamide-substituent at the *meta*-position on the phenyl ring increased ALK5 inhibitory activity, thus, **14b** (IC_{50} = 0.022 μM) and **14e** (IC_{50} = 0.075 μM) were 9.4-fold and 2.8-fold more inhibitory than the unsubstituted **14a** (IC_{50} = 0.207 μM), respectively, and **18b** (IC_{50} = 0.051 μM) was 1.8-fold more inhibitory than the unsubstituted **18a** (IC_{50} = 0.094 μM). However, in the pyrazoles possessing an amidoethylene or a thioamidoethylene linkage, introduction of a carbonitrile-substituent at the *meta*-position on the phenyl ring decreased ALK5 inhibitory activity. The pyrazoles **17b** (IC_{50} = 0.101 μM) and **18d** (IC_{50} = 0.232 μM) were 4.0-fold and 2.6-fold less inhibitory than the unsubstituted **17a** (IC_{50} = 0.025 μM) and **18c** (IC_{50} = 0.088 μM), respectively, suggesting that the combination of a longer linkage and an aromatic substituent in the phenyl ring makes the inhibitors difficult to bind into the ATP binding pocket of ALK5. Although it was previously demonstrated by Tojo et al.[33] and us (unpublished work) that the pyrazoles possessing a thioamido linkage between a pyrazole ring and a phenyl ring were much more potent in ALK5 inhibition than those possessing a respective carboxamido linkage, it is not the case in this series of compounds. The pyrazole **18a** possessing a thioamidomethylene linkage was 2.2-fold more potent than the corresponding **14a** possessing an amidomethylene linkage, whereas **18b**, **18c**, and **18d** possessing a thioamidomethylene or a thioamidoethylene linkage were 2.3-fold, 3.5-fold, and 2.3-fold less potent than the corresponding **14b**, **17a**, and **17b** possessing an amidomethylene or an

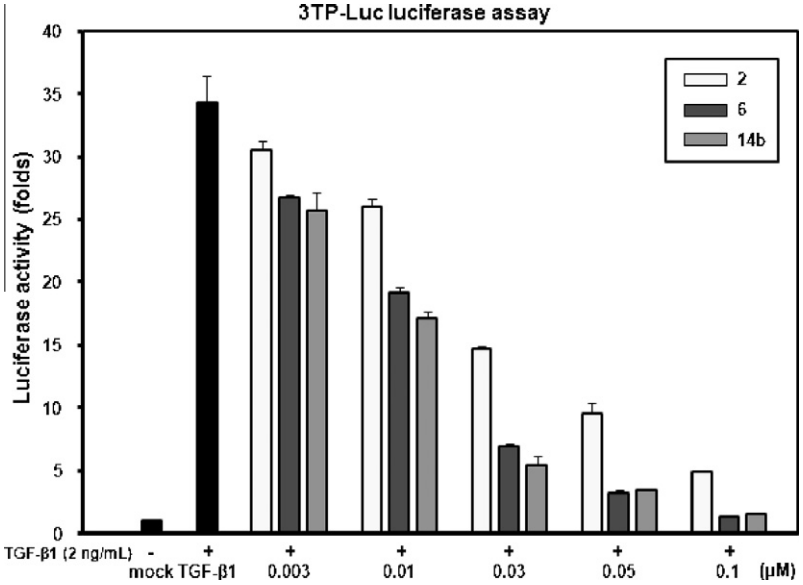


Figure 3. Effect of **14b** on the activity of TGF-β-induced ALK5. HaCaT cells were permanently transfected with p3TP-luciferase reporter gene. Luciferase activity was determined in the presence of different concentrations of each compound and is given as the mean ± SD of three independent experiments run in triplicate relative to control.

amidoethylene linkage, respectively. In this series, the most potent compound **14b** was equipotent to **6** (IC_{50} = 0.017 μM) and 2.5-fold more potent than **2** (IC_{50} = 0.054 μM).

To evaluate TGF-β-induced downstream transcriptional activation to ALK5 signaling, cell-based luciferase activity of all target molecules was measured using HaCaT cells permanently transfected with p3TP-luciferase reporter gene at a concentration of 0.1 μM (Table 1). The p3TP-luciferase reporter construct contains three AP-1 binding elements and the plasminogen-activator inhibitor-1 (PAI-1) promoter.[39] Similar to kinase assay, the compounds **15a–e**, **14c**, **14d**, and **17c** showed no ALK5 inhibitory activity, and inhibition of the luciferase activity by most compounds consisted with that of kinase assay. The pyrazole **14b** was the most inhibitory, showing 84% inhibition that is comparable to that of **6** (80%) and higher than that of **2** (66%).

The ALK5 inhibitory activity of **14b** was compared with those of **2** and **6** at five different concentrations (0.003, 0.01, 0.03, 0.05, and 0.1 μM) using HaCaT cells permanently transfected with p3TP-luciferase reporter gene. As shown in Figure 3, **14b** inhibited ALK5 in a dose-dependent manner and was equipotent to **6** and more potent than **2**.

The kinase domain of p38α MAP kinase is known to be one of the most homologous to that of ALK5,[40] therefore, it was chosen to examine the selectivity profile of this series of compounds. All the target molecules we prepared were devoid of p38α MAP kinase inhibitory activity up to the maximum concentration of 1 μM tested. The **14b** was found to be the most selective in this series, showing the selectivity index of >45, that is, higher than those of **6** (28) and **2**(11).

3. Conclusion

In this report, a series of 1-substituted-3(5)-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)pyrazoles have been synthesized and evaluated for their ALK5 inhibitory activity in an enzyme assay and in a cell-based luciferase reporter assay. The structure–activity relationships in this series of compounds have been established and discussed. The pyrazole analogue **14b** showed the most significant ALK5 inhibitory activity in the series of compounds that is much higher than that of **2** and is equipotent to **6**. This series of compounds didn't inhibit p38α MAP kinase up to the maximum concentration of 1 μM. The selectivity index of **14b** against p38α MAP kinase is >45, that is, higher than those of **2** (11) and **6** (28).

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded on a varian Unity 400 spectrophotometer. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane in $CDCl_3$, $CDCl_3$/CD_3OD, or DMSO-d_6. Infrared spectra were recorded on a FT-infrared spectrometer (Bio-Rad). High resolution mass spectra electro spray ionization (HRMS-ESI) was obtained on an Agilent technologies 6220 TOF LC/MS spectrometer. All melting points were taken in Pyrex capillaries using an electrothermal digital melting point apparatus (Buchi) and were not corrected. Analytical thin-layer chromatography (TLC) was performed on Merck Silica Gel 60F-254 glass plates. Medium pressure liquid chromatography (MPLC) was performed using Merck Silica Gel 60 (230–400 mesh) with an YFLC-540 ceramic pump (Yamagen). All chemicals and solvents were purchased from Aldrich or TCI Laboratory Chemicals.

4.2. General procedures

4.2.1. Synthesis of 1-(6-methylpyridin-2-yl)-2-(quinolin-6-yl)-ethanone (11a)

To a solution of 6-chloroquinoline (12.24 mmol) in tetrahydrofuran (50 mL), 1-(6-methylpyridin-2-yl)ethanone (12.24 mmol), palladium(II) acetate (0.24 mmol), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (0.49 mmol), and potassium *tert*-butoxide (26.92 mmol) were added. The resulting mixture was heated to 75 °C for 14 h. After cooled to room temperature, the reaction mixture was slowly quenched with acetic acid (3 mL). The mixture was filtered through a celite pad and washed with EtOAc (50 mL). The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by MPLC on silica gel using and EtOAc/hexane (1:1) as eluent to give the titled compound as an off-white solid. Yield 75%; ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H), 4.75 (s, 2H), 7.34 (dd, 1H, *J* = 7.6, 0.4 Hz), 7.40 (dd, 1H, *J* = 8.2, 4.2 Hz), 7.71

(t, 1H, J = 7.6 Hz), 7.76 (dd, 1H, J = 8.8, 2.0 Hz), 7.80 (d, 1H, J = 2.0 Hz), 7.87 (br d, 1H, J = 7.6 Hz), 8.11 (d, 1H, J = 8.8 Hz), 8.15 (br d, 1H, J = 8.2 Hz), 8.88 (dd, 1H, J = 4.2, 1.8 Hz).

4.2.2. 2-(4-Methoxyquinolin-6-yl)-(6-methylpyridin-2-yl)ethanone (11b)

This compound was prepared according to the same procedure for **11a** using **10b** as the starting material. Yield 54%; ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H), 3.70 (s, 3H), 4.67 (s, 2H), 6.14 (d, 1H, J = 7.6 Hz) 7.31 (br d, 1H, J = 7.6 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.39 (d, 1H, J = 7.6 Hz), 7.63 (dd, 1H, J = 8.8, 2.2 Hz), 7.67 (t, 1H, J = 7.8 Hz), 7.81 (br d, 1H, J = 8.0 Hz), 8.37 (dd, 1H, J = 2.2, 0.4 Hz).

4.2.3. 6-(3-(6-Methylpyridin-2-yl)-1*H*-pyrazol-4-yl)quinoline (12a)

A mixture of **11a** (4.58 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (10 mL) was heated at 90 °C for 4 h. After cooled to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in EtOH (10 mL), and to it, hydrazine monohydrate (22.9 mmol) was added. The mixture was heated at reflux temperature for 4 h, then cooled to room temperature, and evaporated to dryness under reduced pressure. The residue was diluted with $CHCl_3$ (200 mL) and washed with water (50 mL) and brine (50 mL). The $CHCl_3$ solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:30) as eluent to give the titled compound as a white foam. Yield 84%; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H), 7.08 (dd, 1H, J = 7.6, 0.4 Hz), 7.14 (d, 1H, J = 8.0 Hz), 7.42 (t, 1H, J = 7.8 Hz), 7.47 (dd, 1H, J = 8.2, 4.2 Hz), 7.76 (s, 1H), 7.80 (dd, 1H, J = 8.8, 2.0 Hz), 7.92 (d, 1H, J = 2.0 Hz), 8.20 (d, 1H, overlapped, J = 8.8 Hz), 8.21 (dd, 1H, overlapped, J = 8.2, 1.8 Hz), 8.95 (dd, 1H, J = 4.2, 1.8 Hz).

4.2.4. 4-Methoxy-6-(3-(6-methylpyridin-2-yl)-1*H*-pyrazol-4-yl)-quinoline (12b)

This compound was prepared according to the same procedure for **12a** using **11b** as the starting material. Yield 73%; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 3.84 (s, 3H), 6.30 (d, 1H, J = 8.0 Hz) 7.05 (d, 1H, J = 7.6, Hz), 7.11 (d, 1H, J = 8.0 Hz), 7.40 (t, 1H, overlapped, J = 7.6 Hz), 7.42 (d, 1H, overlapped, J = 8.8 Hz), 7.53 (d, 1H, J = 7.6 Hz), 7.71 (s, 1H), 7.72 (dd, 1H, J = 8.8, 2.0 Hz), 8.57 (d, 1H, J = 2.0 Hz), 11.20 (br s, 1H).

4.2.5. 3-(2-Chloroacetamido)benzamide (13c)

To a stirred solution of 3-aminobenzamide (2.20 mmol) in $CHCl_3$ (22 mL), a saturated $NaHCO_3$ solution (22 mL) and chloroacetyl chloride (4.41 mmol) were added. The mixture was stirred at room temperature for 2 h and diluted with H_2O (40 mL). The mixture was extracted with $CHCl_3$ (2 × 50 mL), and the $CHCl_3$ solution was dried over anhydrous $NaSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was crystallized from Et_2O/hexane to give the titled compound as a white solid. Yield 91%; ^{1}H NMR (DMSO-d_6) δ 4.28 (s, 2H), 7.36 (br s, 1H), 7.40 (t, 1H, J = 7.6 Hz), 7.58 (dt, 1H, J = 7.6, 0.8 Hz), 7.76 (ddd, 1H, J = 8.0, 2.0, 0.8 Hz), 7.96 (br s, 1H), 8.05 (t, 1H, J = 1.8 Hz), 10.49 (br s, 1 H).

4.2.6. 2-(3-(6-Methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)-*N*-phenylacetamide (14a) and 2-(5-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)-*N*-phenylacetamide (15a)

To a solution of pyrazole **12a** (0.47 mmol) in anhydrous DMF (4 mL), a catalytic amount of sodium iodide, 2-chloro-*N*-phenylacetamide (**13a**) (0.56 mmol), and NaH (0.56 mmol) were added. The mixture was stirred at room temperature for 30 min and then evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:40) as eluent to give the two positional isomers **14a** and **15a** as white solids. Compound **14a**: yield 73%; mp 198.9 °C; IR (KBr) 3274, 2930, 1688, 1554 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.14 (s, 2H), 7.08 (t, 1H, J = 7.6 Hz), 7.12 (d, 1H, J = 7.6 Hz), 7.27 (t, 2H, J = 7.6 Hz), 7.30 (d, 1H, J = 7.6 Hz), 7.40 (dd, 1H, J = 8.2, 4.2 Hz), 7.48 (d, 2H, J = 8.0 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.65 (dd, 1H, J = 8.8, 1.6 Hz), 7.81 (s, 1H), 7.85 (d, 1H, J = 1.6 Hz), 8.03 (d, 1H, J = 8.8 Hz), 8.08 (d, 1H, J = 8.2 Hz), 8.90 (dd, 1H, J = 4.2, 1.6 Hz), 8.98 (br s, 1H); HRMS-ESI m/z [M+H]$^+$ calcd for $C_{26}H_{22}N_5O$: 420.1819, found 420.1834. Compound **15a**: yield 9%; mp 189.2 °C; IR (KBr) 3278, 2924, 1686, 1553 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 5.06 (s, 2H), 7.04 (d, 1H, J = 7.6 Hz), 7.11 (tt, 1H, J = 7.4, 1.2 Hz), 7.23 (dd, 1H, J = 8.0, 0.4 Hz), 7.30–7.35 (m, 2H), 7.40 (br d, 1H, overlapped, J = 8.4, 4.4 Hz), 7.51 (d, 1H, overlapped, J = 8.8 Hz), 7.53 (t, 1H, overlapped, J = 7.8 Hz), 7.61 (dd, 2H, J = 8.4, 0.8 Hz), 7.76 (d, 1H, J = 2.4 Hz), 7.90 (s, 1H), 8.01 (d, 1H, J = 8.8 Hz), 8.08 (br d, 1H, overlapped, J = 8.4 Hz), 8.89 (dd, 1H, J = 4.4, 1.8 Hz), 9.76 (br s, 1H); HRMS-ESI m/z [M+H]$^+$ calcd for $C_{26}H_{22}N_5O$: 420.1819, found 420.1832.

4.2.7. *N*-(3-Cyanophenyl)-2-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)acetamide (14b) and *N*-(3-cyanophenyl)-2-(5-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)acetamide (15b)

These compounds were prepared according to the same procedure for **14a** and **15a** using **12a** and **13b**, and the residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:40) as eluent to give the titled compounds as white solids. **14b**: yield 61%; mp 222.1 °C; IR (KBr) 3263, 2927, 2228, 1702, 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 5.23 (s, 2H), 7.17 (d, 1H, J = 7.6 Hz), 7.24 (d, 1H, J = 8.0 Hz), 7.31–7.36 (m, 2H), 7.43 (dd, 1H, J = 8.4, 4.4 Hz), 7.55 (t, 1H, J = 7.8 Hz), 7.63–7.67 (m, 2H), 7.82 (s, 1H), 7.85 (d, 1H, J = 2.0 Hz), 7.92 (br s, 1H), 8.07 (d, 1H, J = 8.8 Hz), 8.11 (br d, 1H, overlapped, J = 8.4 Hz), 8.93 (dd, 1H, J = 4.4, 1.6 Hz), 9.94 (br s, 1H); HRMS-ESI m/z [M+H]$^+$ calcd for $C_{27}H_{21}N_6O$: 445.1771, found 445.1790. Compound **15b**: yield 11%; mp 136.8 °C; IR (KBr) 3281, 2928, 2231, 1696, 1586 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 5.05 (s, 2H), 7.06 (d, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 7.6 Hz), 7.39 (dt, 1H, J = 7.6, 1.4 Hz), 7.41–7.47 (m, 2H), 7.54 (dd, 1H, overlapped, J = 8.8, 1.6 Hz), 7.57 (t, 1H, overlapped, J = 7.8 Hz), 7.78 (d, 1H, J = 2.0 Hz), 7.89 (ddd, 1H, J = 8.0, 2.4, 1.6 Hz), 7.91 (s, 1H), 7.99 (t, 1H, J = 1.6 Hz), 8.10 (br d, 1H, J = 8.8 Hz), 8.16 (br d, 1H, overlapped, J = 8.0 Hz), 8.91 (dd, 1H, J = 4.4, 2.0 Hz), 10.41 (br s, 1H); HRMS-ESI m/z [M+H]$^+$ calcd for $C_{27}H_{21}N_6O$: 445.1771, found 445.1791.

4.2.8. 2-(4-(4-Methoxyquinolin-6-yl)-3-(6-methylpyridin-2-yl)-1*H*-pyrazol-1-yl)-*N*-phenylacetamide (14c) and 2-(4-(4-methoxyquinolin-6-yl-)-5-(6-methylpyridin-2-yl-)-1*H*-pyrazol-1-yl)-*N*-phenylacetamide (15c)

These compounds were prepared according to the same procedure for **14a** and **15a** using **12b** and **13a**, and the residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1/30) as eluent to give the titled compounds as white solids. Compound **14c**: yield 80%; mp 268.9 °C; IR (KBr) 3409, 2925, 1691, 1563 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.80 (s, 3H), 5.05 (s, 2H), 6.27 (d, 1H, J = 7.6 Hz), 7.08–7.13 (m, 2H), 7.27–7.33 (m, 4H), 7.47–7.50 (m, 3H), 7.54 (t, 1H, J = 7.6 Hz), 7.69 (dd, 1H, J = 8.8, 2.0 Hz), 7.79 (s, 1H), 8.53 (d, 1H, J = 2.0 Hz), 8.59 (br s, 1H); HRMS-ESI m/z [M+H]$^+$ calcd for $C_{27}H_{24}N_5O_2$: 450.1925, found 450.1943. Compound **15c**: yield 14%; mp 193.2 °C; IR (KBr) 3264, 2931, 1692, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H), 3.81 (s, 3H), 5.04 (s, 2H), 6.34 (d, 1H, J = 7.6 Hz), 7.03 (d, 1H, J = 7.6 Hz), 7.09 (tt, 1H, J = 7.4, 1.2 Hz), 7.21 (d, 1H, J = 7.6 Hz), 7.29–7.36 (m, 3H), 7.49–7.53 (m, 2H), 7.55 (dd, 1H, J = 7.6, 2.0 Hz), 7.61 (dd, 2H, J = 8.4, 1.2 Hz), 7.87 (s, 1H), 8.42 (d, 1H, J = 1.6 Hz), 9.76 (br s, 1H); HRMS-ESI m/z [M+H]$^+$ calcd for $C_{27}H_{24}N_5O_2$: 450.1925, found 450.1921.

4.2.9. *N*-(3-Cyanophenyl)-2-(4-(4-methoxyquinolin-6-yl)-3-(6-methylpyridin-2-yl)-1*H*-pyrazol-1-yl)acetamide (14d) and *N*-(3-cyanophenyl)-2-(4-(4-methoxyquinolin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-pyrazol-1-yl)acetamide (15d)

These compounds were prepared according to the same procedure for **14a** and **15a** using **12b** and **13b**, and the residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:25) as eluent to give the titled compounds as white solids. Compound **14d**: yield 76%; mp 149.5 °C; IR (KBr) 3254, 2942, 2229, 1700, 1572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.79 (s, 3H), 5.21 (s, 2H), 6.26 (d, 1H, J = 7.6 Hz), 7.05 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.24–7.29 (m, 2H), 7.33 (d, , 1H, J = 8.8 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.53 (d, 1H, J = 7.6 Hz), 7.62 (dd, 1H, J = 8.8, 2.0 HZ), 7.64–767 (m, 1H), 7.76 (s, 1H), 7.84 (br d, 1H, J = 1.2 Hz), 8.46 (d, 1H, J = 2.4 Hz), 10.65 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{28}H_{23}N_6O_2$: 475.1877, found 475.1880. Compound **15d**: yield 14%; mp 245.9 °C; IR (KBr) 2955, 2231, 1700, 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H), 3.80 (s, 3H), 5.03 (s, 2H), 6.26 (d, 1H, J = 7.6 Hz), 7.05 (d, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 7.34 (d, 1H, J = 8.8 Hz), 7.38 (dt, 1H, J = 7.6, 1.2 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.50 (dd, 1H, overlapped, J = 8.8, 2.4 Hz), 7.51 (d, 1H, overlapped, J = 7.6 Hz), 7.55 (t, 1H, J = 7.8 Hz), 7.83 (ddd, 1H, J = 8.4, 2.4, 1.6 Hz), 7.86 (s, 1H), 8.04 (t, 1H, J = 1.4 Hz), 8.41 (d, 1H, J = 2.4 Hz), 10.40 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{28}H_{23}N_6O_2$: 475.1877, found 475.1878.

4.2.10. 3-(2-(3-(6-Methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-yl)-1*H*-pyrazol-acetamido)benzamide (14e) and 3-(2-(5-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)-acetamido)benzamide (15e)

To a stirred solution of 1**2a** (0.17 mmol) in anhydrous DMF (1.5 mL), **13c** (0.21 mmol) and Cs_2CO_3 (0.26 mmol) were added. The mixture was heated at 120 °C for 1 h and then cooled to room temperature. The mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using MeOH/CH_2Cl_2 (1:20) as eluent to give the titled compounds as yellow solids. Compound **14e**: yield 49%; mp 245.0 °C; IR (KBr) 3401, 3317, 3218, 1699, 1646, 1585 cm^{-1}; ^1H NMR ($CDCl_3$/CD_3OD) δ 2.50 (s, 3H), 5.11 (s, 2H), 7.17 (d, 1H, J = 7.6 Hz), 7.25 (d, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.44 (dd, 1H, J = 8.4, 4.4 Hz), 7.57 (t, 1H, J = 7.6 Hz), 7.58–7.61 (m, 1H, J = 8.0 Hz), 7.64 (dd, 1H, J = 8.8, 2.0 Hz), 7.76 (ddd, 1H, J = 8.0, 2.0, 1.2 Hz), 7.85 (d, 1H, J = 2.0 Hz), 7.93 (d, 1H, J = 8.8 Hz), 7.98 (s, 1H), 7.99 (t, 1H, J = 2.0 Hz), 8.15 (dd, 1H, J = 8.4, 1.2 Hz), 8.77 (dd, 1H, J = 4.4, 1.2 Hz); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{27}H_{23}N_6O_2$: 463.1877, found 463.1891. Compound **15e**: yield 16%; mp 207.8 °C; IR (KBr) 3286, 3202, 1669, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.69 (s, 3H), 5.08 (s, 2H), 5.87 (br s, 1H), 6.31 (br s, 1H), 7.05 (d, 1H, J = 7.6 Hz), 7.24 (d, 1H, J = 8.0 Hz), 7.38–7.42 (m, 2H), 7.51–7.55 (m, 3H), 7.76 (d, 1H, J = 2.0 Hz), 7.88 (s, 1H), 7.90 (dd, 1H, J = 8.0, 1.2 Hz), 8.03 (d, 1H, J = 8.8 Hz), 8.06 (t, 1H, J = 1.8 Hz), 8.10 (br d, 1H, J = 8.0 Hz), 8.89 (dd, 1H, J = 4.4, 1.6 Hz), 10.32 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{27}H_{23}N_6O_2$: 463.1877, found 463.1897.

4.2.11. 3-Bromo-*N*-(3-cyanophenyl)propanamide (16b)

3-Bromopropanoyl chloride (40.63 mmol) was added dropwise to a mixture of 3-aminobenzonitrile (33.86 mmol) and anhydrous K_2CO_3 (40.63 mmol) in CH_2Cl_2 at room temperature. The resulting mixture was heated at reflux temperature for 4 h, then cooled to room temperature, and slowly poured into cold water (120 mL). The aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL), and the CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give a white solid which was purified by crystallization from Et_2O/hexane to give the titled compound. Yield 70%; mp 98.4 °C; IR (KBr) 3222, 2233, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.99 (t, 2H, J = 6.4 Hz), 3.70 (t, 2H, J = 6.4 Hz), 7.39–7.45 (m, 2H), 7.75 (dt, 1H, J = 7.6, 2.0 Hz), 7.94 (br s, 1H), 7.97 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{10}H_{10}BrN_2O$: 252.9971, found 252.9980.

4.2.12. 3-(3-(6-Methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)-*N*-phenylpropanamide (17a)

This compound was prepared according to the same procedure for **14e** using **12a** and 3-bromo-*N*-phenylpropanamide (**16a**), and the residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:30) as eluent to give the titled compound as a white solid. Yield 55%; mp 191.4 °C; IR (KBr) 3266, 2927, 1677, 1596, 1548 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.07 (t, 2H, J = 6.0 Hz), 4.65 (t, 2H, J = 6.0 Hz), 7.07 (t, 1H, J = 7.4 Hz), 7.11 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 8.0 Hz), 7.24–7.29 (m, 2H), 7.37 (dd, 1H, J = 8.4, 4.4 Hz), 7.46 (t, 1H, J = 7.8 Hz), 7.49 (d, 2H, J = 7.6 Hz), 7.56 (dd, 1H, J = 8.8, 2.0 Hz), 7.71 (br s, 2H), 7.97 (d, 1H, J = 8.8 Hz), 8.03 (d, 1H, J = 7.6 Hz), 8.28 (br s, 1H), 8.87 (dd, 1H, J = 4.4, 1.8 Hz); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{27}H_{24}N_5O$: 434.1975, found 434.1978.

4.2.13. *N*-(3-Cyanophenyl)-3-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)propanamide (17b)

This compound was prepared according to the same procedure for **14e** using **12a** and **16b**, and the residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:30) as eluent to give the titled compound as a white solid. Yield 51%; mp 74.9 °C; IR (KBr) 3258, 2934, 2230, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (s, 3H), 3.11 (t, 2H, J = 5.8 Hz), 4.62 (t, 2H, J = 5.8 Hz), 7.11 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.28–7.34 (m, 2H), 7.39 (dd, 1H, J = 8.2, 4.4 Hz), 7.48 (t, 1H, J = 7.6 Hz), 7.54 (dd, 1H, J = 8.8, 2.0 Hz), 7.68 (s, 1H), 7.70 (d, 1H , J = 2.0 Hz), 7.77–7.80 (m, 1H), 7.91 (br s, 1H), 7.98 (d, 1H, J = 8.8 Hz), 8.05 (br d, 1H, overlapped, J = 8.0 Hz), 8.88 (dd, 1H, J = 4.4, 1.8 Hz), 9.52 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{28}H_{23}N_6O$: 459.1928, found 459.1931.

4.2.14. *N*-(3-Cyanophenyl)-3-(4-(4-methoxyquionolin-6-yl)-3-(6-methylpyridin-2-yl)-1*H*-pyrazol-1-yl)propanamide (17c)

This compound was prepared according to the same procedure for **14e** using **12b** and **16b**, and the residue was purified by MPLC on silica gel using MeOH/CH_2Cl_2 (1:20) as eluent to give the titled compound as a white solid. Yield 39%; mp 140 °C; IR (KBr) 3066, 2230, 1689, 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.03 (t, 2H, J = 6.2 Hz), 3.78 (s, 3H), 4.56 (t, 2H, J = 6.2 Hz), 6.24 (d, 1H, J = 7.6 Hz), 7.09 (br d, 1H, J = 8.0 Hz), 7.14 (br d, 1H, J = 7.6 Hz), 7.26–7.35 (m, 3H), 7.46 (t, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.54 (dd, 1H, J = 8.8, 1.6 Hz), 7.66 (s, 1H), 7.87 (d, 1H, overlapped, J = 1.6 Hz), 7.88 (d, 1H, overlapped, J = 8.0 Hz), 8.41 (d, 1H, J = 2.4 Hz), 9.98 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{29}H_{25}N_6O_2$: 489.2034, found 489.2051.

4.2.15. 2-(3-(6-Methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)-*N*-phenylethanethioamide (18a)

A stirred mixture of **14a** (0.96 mmol), Lawesson's reagent (0.96 mmol), and anhydrous DME (3 mL) in a dry sealed tube was heated at 85 °C for 12 h. After cooled to room temperature, the solvent was evaporated to dryness under reduced pressure, and the residue was purified by MPLC on silica gel using MeOH/$CHCl_3$ (1:30) as eluent to give the titled compound as a light yellow solid. Yield 67%; mp 214.6 °C; IR (KBr) 3265, 2934, 1594, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 5.47 (s, 2H), 7.15 (d, 1H, J = 8.0 Hz), 7.23–7.27 (m, 1H), 7.32 (d, 1H, J = 7.6 Hz), 7.36–7.42 (m, 3H), 7.55 (t, 1H, J = 7.8 Hz), 7.66 (dd, 1H, J = 8.8, 2.0 Hz), 7.75 (dd, 2H, J = 7.6, 1.2 Hz), 7.83 (s, 1H), 7.86 (d, 1H, J = 2.0 Hz), 8.03 (d, 1H, J = 8.8 Hz), 8.10 (dd, 1H, J = 8.4, 0.8 Hz),

8.91 (dd, 1H, J = 4.4, 1.6 Hz), 10.53 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{26}H_{22}N_5S$: 436.1590, found 436.1611.

4.2.16. *N*-(3-Cyanophenyl)-2-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)ethanethioamide (18b)

This compound was prepared according to the same procedure for **18a** using **14b** as the starting material. Yield 73%; mp 230.8 °C; IR (KBr) 3282, 2926, 2233, 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 5.54 (s, 2H), 7.14 (d, 1H, J = 7.6 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.37–7.43 (m, 2H), 7.46–7.52 (m, 2H), 7.66 (d, 1H, J = 8.4 Hz), 7.85 (br s, 2H), 7.95 (d, 1H, J = 8.0 Hz), 8.06 (d, 1H, J = 8.8 Hz), 8.11 (d, 1H, J = 8.0 Hz), 8.23 (s, 1H), 8.92 (d, 1H, J = 4.0 Hz), 11.57 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{27}H_{21}N_6S$: 461.1543, found 461.1566.

4.2.17. 3-(3-(6-Methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)-*N*-phenylpropanethioamide (18c)

This compound was prepared according to the same procedure for **18a** using **17a** as the starting material. Yield 37%; mp 87.4 °C; IR (KBr) 3197, 2926, 1590, 1129 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.54 (t, 2H, J = 6.0 Hz), 4.77 (t, 2H, J = 6.0 Hz), 7.08 (d, 1H, J = 7.6 Hz), 7.11–7.16 (m, 2H), 7.23 (td, 2H, J = 7.6, 1.6 Hz), 7.39 (dd, 1H, J = 8.2, 4.2 Hz), 7.47 (t, 1H, J = 7.8 Hz), 7.49–7.55 (m, 2H), 7.67 (d, 1H, J = 2.0 Hz), 7.70 (s, 1H), 7.98 (d, 1H, J = 8.8 Hz), 8.03 (dd, 1H, J = 8.2, 1.2 Hz), 8.88 (dd, 1H, J = 4.2, 1.8 Hz), 10.64 (br s, 1H); HRMS-ESI m/z $[M+H]^+$ calcd for $C_{27}H_{24}N_5S$: 450.1747, found 450.1767.

4.2.18. *N*-(3-Cyanophenyl)-3-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-yl)propanethioamide (18d)

This compound was prepared according to the same procedure for **18a** using **17b** as the starting material. Yield 46%; mp 94.6 °C; IR (KBr) 3200, 2927, 2232, 1586, 1171 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (s, 3H), 3.58 (t, 2H, J = 5.8 Hz), 4.74 (t, 2H, J = 5.8 Hz), 7.04 (d, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 8.0 Hz), 7.31 (t, 1H, J = 8.0 Hz), 7.37–7.40 (m, 2H), 7.47 (t, 1H, J = 7.6 Hz), 7.50 (dd, 1H, J = 8.8, 2.0 Hz), 7.66 (s, 1H), 7.67 (d, 1H, J = 2.0 Hz), 7.90 (br s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 8.06 (br d, 1H, J = 8.4 Hz), 8.88 (dd, 1H, J = 4.4, 1.6 Hz), 11.27 (br s, 1H); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{28}H_{22}N_6NaS$: 497.1519, found 497.1537.

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References and notes

1. Heldin, C. H.; Miyazono, K.; Ten Dijke, P. *Nature* **1997**, *390*, 465.
2. Shi, J.; Massague, J. *Cell* **2003**, *113*, 685.
3. Massague, J. *Nat. Rev. Mol. Cell Biol.* **2000**, *1*, 169.
4. Derynck, R.; Zhang, Y. E. *Nature* **2003**, *425*, 577.
5. Wang, W.; Koka, V.; Lan, H. Y. *Nephrology* **2005**, *10*, 48.
6. Lim, H.; Zhu, Y. Z. *Cell. Mol. Life Sci.* **2006**, *63*, 2584.
7. Gu, L.; Zhu, Y.-J.; Yang, X.; Guo, Z.-J.; Xu, W.-B.; Tian, X.-L. *Acta Pharmacol. Sin.* **2007**, *28*, 382.
8. Shek, F. W.; Benyon, R. C. *Eur. J. Gastroenterol. Hepatol.* **2004**, *16*, 123.
9. Bierie, B.; Moses, H. L. *Nat. Rev. Cancer* **2006**, *6*, 506.
10. Rane, S. G.; Lee, J.-H.; Lin, H.-M. *Cytokine Growth Factor Rev.* **2006**, *17*, 107.
11. Dong, M.; Blobe, G. C. *Blood* **2006**, *107*, 4589.
12. Halder, S. K.; Beauchamp, R. D.; Datta, P. K. *Neoplasia* **2005**, *7*, 509.
13. Byfield, S. D.; Major, C.; Laping, N. J.; Roberts, A. B. *Mol. Pharmacol.* **2004**, *65*, 744.
14. De Gouville, A. C.; Boullay, V.; Krysa, G.; Pilot, J.; Brusq, J. M.; Loriolle, F.; Gauthier, J. M.; Papworth, S. A.; Laroze, A.; Gellibert, F.; Huet, S. *Br. J. Pharmacol.* **2005**, *145*, 166.
15. Ge, R.; Rajeev, V.; Ray, P.; Lattime, E.; Rittling, S.; Medicherla, S.; Protter, A.; Murphy, A.; Chakravarty, J.; Dugar, S.; Schreiner, G.; Barnard, N.; Reiss, M. *Clin. Cancer Res.* **2006**, *12*, 4315.
16. Kapoun, A. M.; Gaspar, N. J.; Wang, Y.; Damm, D.; Liu, Y.-W.; O'Young, G.; Quon, D.; Lam, A.; Munson, K.; Tran, T.-T.; Ma, J. Y.; Murphy, A.; Dugar, S.; Chakravarty, S.; Protter, A. A.; Wen, F.-Q.; Liu, X.; Rennard, S. I.; Higgins, L. S. *Mol. Pharmacol.* **2006**, *70*, 518.
17. Mundla, S. R. PCT Int. Appl. WO 2007018818 A1, 2007.
18. Kim, D.-K.; Kim, J.; Park, H.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401.
19. Kim, D.-K.; Kim, J.; Park, H.-J. *Bioorg. Med. Chem.* **2004**, *12*, 2013.
20. Kim, D.-K.; Jang, Y.; Lee, H. S.; Park, H.-J.; Yoo, J. *J. Med. Chem.* **2007**, *50*, 3143.
21. Kim, D.-K.; Choi, J. H.; An, Y. J.; Lee, H. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2122.
22. Kim, D.-K.; Jung, S. H.; Lee, H. S.; Dewang, P. M. *Eur. J. Med. Chem.* **2009**, *44*, 568.
23. Dewang, P. M.; Kim, D.-K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4228.
24. Kim, D.-K.; Lee, Y.-I.; Lee, Y. W.; Dewang, P. M.; Sheen, Y. Y.; Kim, Y. W.; Park, H.-J.; Yoo, J.; Lee, H. S.; Kim, Y.-K. *Bioorg. Med. Chem.* **2010**, *18*, 4459.
25. Kim, Y. W.; Kim, Y. K.; Lee, J. Y.; Chang, K. T.; Lee, H. J.; Kim, D.-K.; Sheen, Y. Y. *Xenobiotica* **2008**, *38*, 325.
26. Kim, Y. W.; Kim, Y. K.; Kim, D.-K.; Sheen, Y. Y. *Xenobiotica* **2008**, *38*, 451. 23.
27. Moon, J.-A.; Kim, H.-T.; Cho, I.-S.; Sheen, Y. Y.; Kim, D.-K. *Kidney Int.* **2006**, *70*, 1234.
28. Luo, J.; Ho, P. P.; Buckwalter, M. S.; Hsu, T.; Lee, L. Y.; Zhang, H.; Kim, D.-K.; Kim, S.-J.; Gambhir, S. S.; Steinman, L.; Wyss-Coray, T. *J. Clin. Invest.* **2007**, *117*, 3306.
29. Ryu, J.-K.; Piao, S.; Shin, H.-Y.; Choi, M. J.; Zhang, L. W.; Jin, H.-R.; Kim, W. J.; Han, J.-Y.; Hong, S. S.; Park, S. H.; Lee, S.-J.; Kim, I.-H.; Lee, C. R.; Kim, D.-K.; Mamura, M.; Kim, S.-J.; Suh, J.-K. *J. Sex. Med.* **2009**, *6*, 1284.
30. Lee, G. T.; Hong, J. H.; Mueller, T. J.; Watson, J. A.; Kwak, C.; Sheen, Y. Y.; Kim, D.-K.; Kim, S. J.; Kim, I. Y. *J. Urol.* **2008**, *180*, 2660.
31. Long, L.; Crosby, A.; Yang, X.; Southwood, M.; Upton, P. D.; Kim, D.-K.; Morrell, N. W. *Circulation* **2009**, *119*, 566.
32. Kim, J. H.; Song, H.-Y.; Park, J.-H.; Yoon, H.-J.; Park, H. G.; Kim, D.-K. *Radiology* **2010**, *255*, 75.
33. Tojo, M.; Hamashima, Y.; Hanyu, A.; Kajimoto, T.; Saitoh, M.; Miyazono, K.; Node, M.; Imamura, T. *Cancer Sci.* **2005**, *96*, 791.
34. Munchhof, M. J.; Blumberg, L. C. PCT Int. Appl. WO 2004/026306 A2, 2004.
35. Pier, G. B.; Delia, P.; Mojgan, A. T.; Francesca, F.; Giulia, S.; Stefania, B.; Romeo, R.; Allan, R. M.; Stefania, G.; Katia, V.; Pier, A. B. *Bioorg. Med. Chem.* **2007**, *15*, 2514.
36. Zhang, L.; Li, H.; Zhu, Q.; Liu, J.; Chen, L.; Leng, Y.; Jiang, H.; Liu, H. *Bioorg. Med. Chem.* **2009**, *17*, 7301.
37. Jacobs, W. A.; Heidelberger, M. *J. Am. Chem. Soc.* **1917**, *39*, 1439.
38. Rajavel, R.; Mahesh, U.; Shao, Q. Y. *Org. Lett.* **2006**, *8*, 713.
39. Wrana, J. L.; Attisano, L.; Carcamo, J.; Zentella, A.; Doody, J.; Laiho, M.; Wang, X. F.; Massague, J. *Cell* **1992**, *71*, 1003.
40. Eyers, P. A.; Craxton, M.; Morrice, N.; Cohen, P.; Goedert, M. *Chem. Biol.* **1998**, *5*, 321.