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Synthesis and biological evaluation of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles as transforming growth factor-β type 1 receptor kinase inhibitors

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ABSTRACT

A series of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles **14a–ae**, **16a**, **16b**, and **21a–c** has been prepared and evaluated for their ALK5 inhibitory activity in an enzyme assay and in a cell-based luciferase reporter assay. The 4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-*N*-(4-methoxyphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrazole-1-carbothioamide (**14n**) inhibited ALK5 phosphorylation with IC_{50} value of 0.57 nM and showed 94% inhibition at 100 nM in a luciferase reporter assay using HaCaT cells permanently transfected with p3TP-luc reporter construct.

The transforming growth factor-β (TGF-β) is the most potent and ubiquitous profibrogenic cytokine. TGF-β transduces signals through two distinct serine/threonine kinase receptors, termed type I and type II.[1–3] Following the binding of ligand to the constitutively active type II receptor, the type I receptor, also called as activin receptor-like kinase 5 (ALK5), is phosphorylated, which further phosphorylates Smad2 or Smad3. Phosphorylated Smad2 and Smad3 form a heteromeric complex with Smad4, which translocates to the nucleus and binds to the promoters of TGF-β target genes involved in cell differentiation, proliferation, apoptosis, migration, and extracellular matrix production.[4] TGF-β plays a pivotal role in the development of fibrosis in various organ systems such as kidney,[5] heart,[6] lung,[7] and liver.[8] Deregulation of TGF-β signaling has been also implicated in various human diseases including cancer,[9] pancreatic diseases,[10] and hematological malignancies.[11] Recent studies have shown that blocking the TGF-β signaling pathway with several small molecule ATP-competitive ALK5 inhibitors (Fig. 1) such as **1** (SB-505154),[12] **2** (SB-525334),[13] **3** (GW6604),[14] **4** (SD-208),[15,16] and **5** (LY-2157299)[17] inhibited autophosphorylation of ALK5 and TGF-β induced transcription of matrix genes in receptor assays at sub-micromolar concentrations. Among them, **2**, **3**, and **4** effectively retarded progressive fibrosis in kidney, liver and lung, respectively, and **4** and **5** also strongly inhibited growth and invasiveness of cancer cells in animal models. 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] One of our preclinical candidates, IN-1130 (**6**), demonstrated its remarkable activity as a suppressor of fibrogenic process of unilateral ureteral obstruction in rats,[27] ameliorated experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis,[28] and reduced tunical fibrosis in rats.[29] It also inhibited cancer metastasis in MMTV/c-Neu breast cancer mice and enhanced CTL response in cancer mice.[30] Another preclinical candidate, IN-1233 (**7**), effectively prevented development and progression of pulmonary arterial hypertension in monocrotaline rat model through inhibition of TGF-β signaling[31] and reduced granulation tissue formation after bare metallic stent placement in a rat urethral model.[32]

Recently, Tojo et al.[33] and we[23] have reported a novel class of ALK5 inhibitors possessing a thioamide linkage between a pyrazole ring and a phenyl ring, such as A-83-01 (**8**) and 3-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazol-1-carbothioamido)benzmide (**9**).

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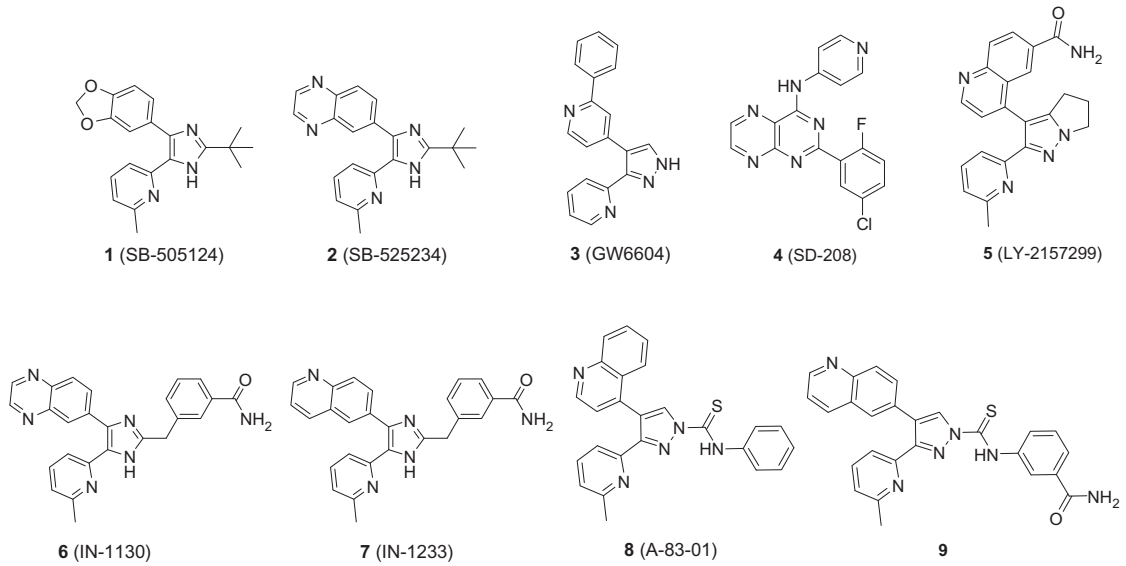
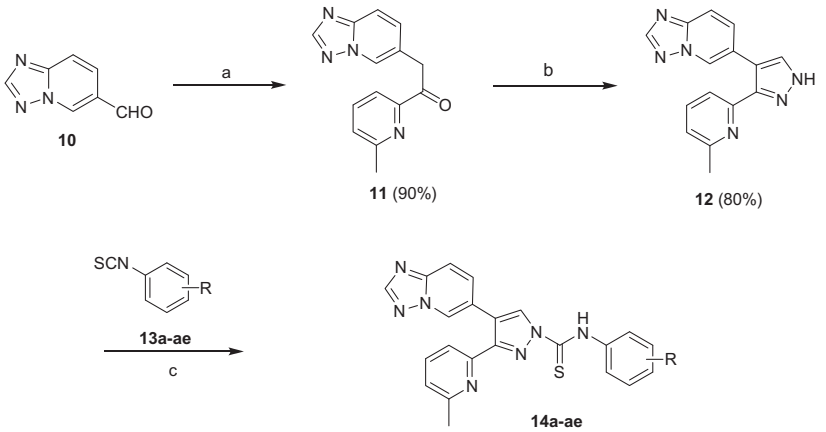


Figure 1. ALK5 inhibitors under development.

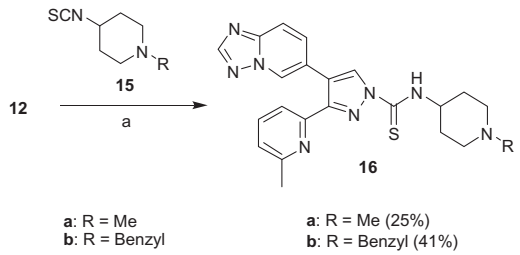
Insertion of a thioamide linkage between a pyrazole ring and a phenyl ring markedly increased ALK5 inhibitory activity, thus, **8** exhibited significant inhibition of the transcriptional activity induced by ALK5,[33] and **9** showed more than 90% inhibition at 100 nM in luciferase reporter assays using HaCaT cells transiently transfected with p3TP-luc reporter construct and ARE-luc reporter construct.[23] As part of our continuing efforts to develop more potent and selective ALK5 inhibitors, in this Letter, we have prepared a series of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles **14a–ae**, **16a**, **16b**, and **21a–c** possessing a thioamide linkage between a pyrazole ring and a phenyl ring or a piperidinyl ring. The target molecules **14a–ae** have a [1,2,4]triazolo[1,5-*a*]pyridin-6-yl moiety rather than a quinoxalin-6-yl moiety of **2** and **6** or a quinolin-6-yl moiety of **7** and **9** at the 4-position of the pyrazole and have various substituents such as F, Cl, Me, CF_3, OMe, OCF_3, CN, and $CONH_2$ in the phenyl ring. In



a: R = H
b: R = *m*-F
c: R = *m*-Cl
d: R = *m*-Me
e: R = *m*-CF_3
f: R = *m*-OMe
g: R = *m*-OCF_3
h: R = *m*-CN
i: R = *m*-$CONH_2$
j: R = *p*-F
k: R = *p*-Cl
l: R = *p*-Me
m: R = *p*-CF_3
n: R = *p*-OMe
o: R = *p*-OCF_3
p: R = *p*-CN
q: R = *p*-$CONH_2$
r: R = *o*-F
s: R = *o*-Cl
t: R = *o*-Me
u: R = *o*-OMe
v: R = *o*-OCF_3
w: R = 3,4-F_2
x: R = 3,5-F_2
y: R = 3,4-Cl_2
z: R = 3,5-Cl_2
aa: R = 3,4-Me_2
ab: R = 3,5-Me_2
ac: R = 3,5-$(CF_3)_2$
ad: R = 3,4-$(OMe)_2$
ae: R = 3,5-$(OMe)_2$

a: R = H (55%)
b: R = *m*-F (50%)
c: R = *m*-Cl (40%)
d: R = *m*-Me (64%)
e: R = *m*-CF_3 (48%)
f: R = *m*-OMe (50%)
g: R = *m*-OCF_3 (4%)
h: R = *m*-CN (34%)
i: R = *m*-$CONH_2$ (52%)
j: R = *p*-F (45%)
k: R = *p*-Cl (52%)
l: R = *p*-Me (70%)
m: R = *p*-CF_3 (46%)
n: R = *p*-OMe (59%)
o: R = *p*-OCF_3 (39%)
p: R = *p*-CN (75%)
q: R = *p*-$CONH_2$ (46%)
r: R = *o*-F (24%)
s: R = *o*-Cl (53%)
t: R = *o*-Me (47%)
u: R = *o*-OMe (69%)
v: R = *o*-OCF_3 (31%)
w: R = 3,4-F_2 (38%)
x: R = 3,5-F_2 (38%)
y: R = 3,4-Cl_2 (45%)
z: R = 3,5-Cl_2 (22%)
aa: R = 3,4-Me_2 (29%)
ab: R = 3,5-Me_2 (47%)
ac: R = 3,5-$(CF_3)_2$ (41%)
ad: R = 3,4-$(OMe)_2$ (51%)
ae: R = 3,5-$(OMe)_2$ (26%)

Scheme 1. Reagents and conditions: (a) (i) diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate, Cs_2CO_3, THF/i-PrOH (4:1), rt, 16 h; (ii) 3 N HCl, rt, 1 h; (b) (i) DMF·DMA, 90 °C, 4 h; (ii) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 3 h; (c) NaH, anhydrous THF, 0 °C to rt, 1 h.



Scheme 2. Reagents and conditions: (a) NaH, anhydrous THF, 0 °C to rt, 1 h.

pharmacokinetic studies, the bioavailability of orally administered **6** was 84.9%, 34.4%, 11.4%, and 8.95% in dogs, monkeys, rats, and mice, respectively.[25] The major metabolite of **6** was detected in the systemic circulation of rat and mouse and was identified as 3-((4-(2-hydroxyquinoxalin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzamide or 3-((4-(3-hydroxyquinoxalin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzamide.[25] To overcome metabolic oxidation of 2- or 3-position of quinoxalin-6-yl moiety of **6**, we adopted a [1,2,4]triazolo[1,5-*a*]pyridin-6-yl moiety since metabolic oxidation of 2-position of this moiety is assumed to be difficult due to the presence of two adjacent nitrogen atoms.

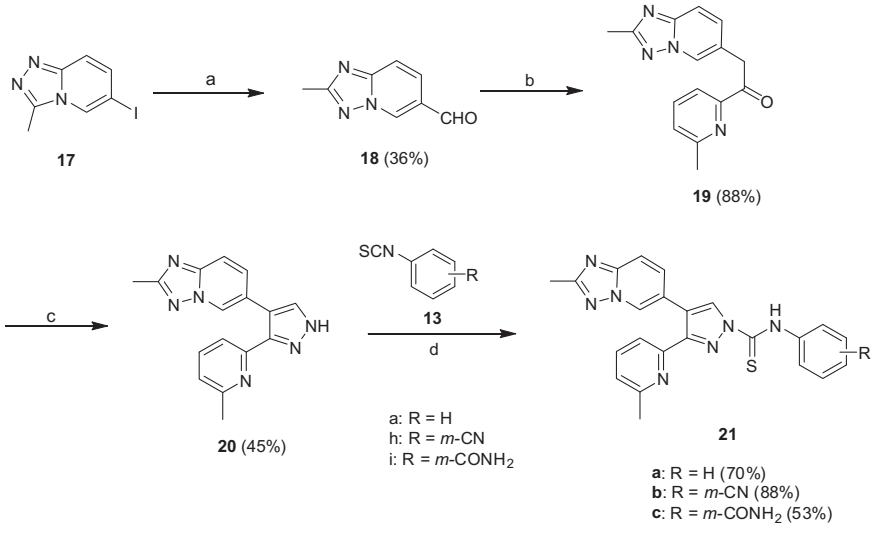
The target molecules **16a** and **16b** have been prepared to compare the role of a phenyl ring of **14a–ae** with a piperidinyl ring. To examine the influence of a methyl substituent at the 2-position of the [1,2,4]triazolo[1,5-*a*]pyridin-6-yl moiety on ALK5 inhibition, we have also prepared the target molecules **21a–c**.

A series of 3-(6-methylpyridin-2-yl)-1-(phenylcarbothioamido)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles **14a–ae** was prepared as shown in Scheme 1. The [1,2,4]triazolo[1,5-*a*]pyridine-6-carbaldehyde (**10**)[34] was coupled with diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate[35] in a mixture of THF and *i*-PrOH (4:1) in the presence of Cs_2CO_3 at room temperature and subsequently treated with 3 N HCl to afford the monoketone **11**[36] in 90% yield. Treatment of **11** with *N,N*-dimethylformamide dimethyl acetal at 90 °C and followed by reaction with hydrazine monohydrate in absolute EtOH produced the pyrazole **12**[37] in 80% yield. The pyrazole **12** was alkylated with appropriately substituted phenyl isothiocyanates (**13a–ae**) in the presence of NaH in anhydrous THF to afford the target compounds **14a–ae** in various yields (4–75%). Compound **14g** was obtained only in 4% yield due to the low reactivity of 3-(trifluoromethoxy)phenyl isothiocyanate (**13g**).

The 4-([1,2,4]tria zolo[1,5-*a*]pyridin-6-yl)-*N*-(1-methylpiperidin-4-yl)-3-(6-methylpyridin-2-yl)-1*H*-pyrazole-1-carbothioamide (**16a**) and 4-([1,2,4] triazolo[1,5-*a*]pyridin-6-yl)-*N*-(1-benzylpiperidin-4-yl)-3-(6-met hylpyridin-2-yl)-1*H*-pyrazole-1-carbothioamide (**16b**) were prepared as shown in Scheme 2. The pyrazole **12** was alkylated with 4-isothiocyanato-1-methylpiperidine (**15a**)[38] or 1-benzyl-4-isothiocyanatopiperidine (**15b**)[39] in the same reaction condition as described in Scheme 1 to afford the **16a** or **16b** in 25% or 41% yields, respectively.

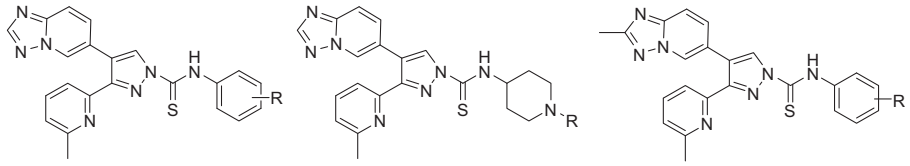
The 3-(6-methylpyridin-2-yl)-4-(2-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-1-(phenylcarbothioamido)pyrazoles **21a–c** were prepared as shown in Scheme 3. Formylation of 6-iodo-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine (**17**)[40] with *i*-PrMgCl and *N,N*-dimethylformamide in anhydrous THF followed by quenching with 1 N HCl gave the Dimroth-like rearranged aldehyde **18** in 36% yield. The aldehyde **18** was coupled with diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate to afford the monoketone **19** in 88% yield. The monoketone **19** was converted to the pyrazole **20** in 45% yield in the same reaction condition as described in Scheme 1. The pyrazole **20** was further alkylated with phenyl isothiocyanates (**13a**, **13h**, and **13i**) in the presence of NaH in anhydrous THF to afford the target compounds **21a–c** in 53–88% yields.

To investigate whether these compounds **14a–ae**, **16a**, **16b**, and **21a–c** could inhibit ALK5, a kinase assay was performed using the purified human ALK5 kinase domain produced in Sf9 insect cells (Table 1). The ALK5 inhibitory activity of the pyrazoles **14b–14ae** having various substituents such as F, Cl, Me, CF_3, OMe, OCF_3, CN, and $CONH_2$ in the phenyl ring was compared with that of the unsubstituted pyrazole **14a**. All the pyrazoles **14a–ae** inhibited ALK5 at concentrations (IC_{50} = 0.57–15.60 nM) as shown in Table 1. Among the *meta*-substituted compounds **14b–i**, the *m*-Cl substituted compound **14c** (IC_{50} = 2.37 nM) and *m*-OMe substituted compound **14f** (IC_{50} = 2.26 nM) displayed slightly more potent ALK5 inhibition than the unsubstituted compound **14a** (IC_{50} = 2.82 nM). Among the *para*-substituted compounds **14j–q**, the *p*-OMe substituted compound **14n** (IC_{50} = 0.57 nM) was highly potent and was five-fold more potent than the compound **14a**. The *p*-CN substituted compound **14p** (IC_{50} = 2.95 nM) showed the similar level of potency to that of the compound **14a**. Introduction of a substituent at the *ortho*-positon was proved to be not beneficial, thus, the *o*-Cl substituted compound **14s** (IC_{50} = 2.83 nM) only displayed the comparable ALK5 inhibitory activity to that of the **14a**. Among the di-substituted compounds **14w–ae**, the 3,4-F_2 substi-



Scheme 3. Reagents and conditions: (a) i-PrMgCl, anhydrous THF, anhydrous DMF, 1 N HCl, 0 °C to rt, 4 h; (b) (i) diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate, Cs_2CO_3, THF/i-PrOH (4:1), rt, 16 h; (ii) 3 N HCl, rt, 1 h; (c) (i) DMF·DMA, 90 °C, 4 h; (ii) $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 h; (d) NaH, anhydrous THF, 0 °C to rt, 1 h.

Table 1
Inhibitory activity of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles **14a–ae**, **16a**, **16b**, and **21a–c** on ALK5



14a-ae **16a, 16b** **21a-c**

Compd	R	IC_{50} (nM)		Selectivity index[c]	p3TP-luciferase activity (% control)[d,e]
		ALK5[a]	p38α[b]		
Mock	—	—	—	—	6 ± 1.9
TGF-β	—	—	—	—	100 ± 2.6
14a	H	2.82	2800	993	10 ± 1.4
14b	*m*-F	4.43	5680	1282	8 ± 0.1
14c	*m*-Cl	2.37	5440	2295	8 ± 0.6
14d	*m*-Me	3.98	3680	925	8 ± 0.4
14e	*m*-CF_3	3.01	1980	658	5 ± 0.1
14f	*m*-OMe	2.26	>10000	>4425	8 ± 0.5
14g	*m*-OCF_3	10.00	>10000	>1000	7 ± 0.4
14h	*m*-CN	4.50	6430	1429	5 ± 0.4
14i	*m*-$CONH_2$	3.45	4280	1241	8 ± 0.4
14j	*p*-F	4.09	6670	1631	6 ± 0.1
14k	*p*-Cl	3.87	5530	1429	7 ± 0.7
14l	*p*-Me	6.61	2960	448	6 ± 0.1
14m	*p*-CF_3	3.04	4120	1355	6 ± 0.2
14n	*p*-OMe	0.57	6360	11158	6 ± 0.2
14o	*p*-OCF_3	3.30	5220	1582	7 ± 0.8
14p	*p*-CN	2.95	5230	1773	5 ± 0.1
14q	*p*-$CONH_2$	15.60	4950	317	9 ± 0.4
14r	*o*-F	5.39	3000	557	4 ± 0.3
14s	*o*-Cl	2.83	3220	1138	5 ± 0.3
14t	*o*-Me	4.00	3680	920	21 ± 0.7
14u	*o*-OMe	5.69	7560	1329	11 ± 1.3
14v	*o*-OCF_3	3.98	3830	962	5 ± 0.1
14w	3,4-F_2	2.12	1450	684	7 ± 1.0
14x	3,5-F_2	3.20	3810	1191	6 ± 0.2
14y	3,4-Cl_2	3.78	1690	447	6 ± 0.3
14z	3,5-Cl_2	5.08	2850	561	7 ± 0.4
14aa	3,4-Me_2	3.54	5810	1641	7 ± 0.5
14ab	3,5-Me_2	3.97	5390	1358	9 ± 0.2
14ac	3,5-$(CF_3)_2$	4.12	5040	1223	8 ± 1.4
14ad	3,4-$(OMe)_2$	4.37	3840	879	10 ± 1.1
14ae	3,5-$(OMe)_2$	2.49	2460	988	8 ± 0.4
16a	Me	39.47	496	13	81 ± 0.8
16b	Benzyl	95.70	598	6	90 ± 4.5
21a	H	102.00	7260	71	64 ± 3.2
21b	*m*-CN	85.30	3200	38	53 ± 2.1
21c	*m*-$CONH_2$	66.80	6580	99	63 ± 1.5
1 (SB-505124)	—	54.40	594	11	34 ± 2.7
6 (IN-1130)	—	17.20	480	28	20 ± 0.7

[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 (^{33}PanQinase® 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 100 nM of inhibitor.
[e] Activity is given as the mean ± SD of three independent experiments run in triplicate relative to control incubations with DMSO vehicle.

tuted compound **14w** (IC_{50} = 2.12 nM) and 3,5-$(OMe)_2$ substituted compound **14ae** (IC_{50} = 2.49 nM) displayed slightly more potent ALK5 inhibition than the **14a**.

Contrary to the pyrazoles **14a–ae** possessing a phenycarbothioamido moiety, the pyrazoles **16a** (IC_{50} = 39.47 nM) and **16b** (IC_{50} = 95.70 nM) possessing a 4-piperidinylcarbothioamido moiety were 14-fold and 34-fold less potent in ALK5 inhibition than the **14a**. This result may suggest us that the binding region for the phenyl ring of **14a–ae** or piperidinyl ring of **16a** and **16b** in ATP binding site of ALK5 is rather planar. The compounds **21a–c** having a methyl substituent at the 2-position of [1,2,4] triazolo[1,5-*a*]pyridin-6-yl moiety displayed much lower ALK5 activity compared to the unsubstituted ones, thus, **21a** (IC_{50} = 102.00 nM), **21b** (IC_{50} = 85.30 nM), and **21c** (IC_{50} = 66.80 nM) were 36-fold, 19-fold, and 19-fold less potent than the **14a**, **14h** (IC_{50} = 4.50 nM), and **14i** (IC_{50} = 3.45 nM), respectively. The pyrazole **14n** showed the most potent ALK5 inhibitory activity in this series of compounds, and was 95-fold and 30-fold more potent than **1** (IC_{50} = 54.40 nM) and **6** (IC_{50} = 17.20 nM), respectively.

To evaluate TGF-β-induced downstream transcriptional activation to ALK5 signaling, cell-based luciferase activity of **14a–ae**, **16a**, **16b**, and **21a–c** was measured using HaCaT cells permanently transfected with p3TP-luciferase reporter construct at a concentra tion of 100 nM (Table 1). The p3TP-luciferase reporter construct

contains three Ap-1 binding elements and the plasminogen-activator inhibitor-1 (PAI-1) promoter.[41] Similar to kinase assay, all the pyrazoles **14a–ae** significantly inhibited the luciferase activity, thus, showing 89–96% inhibition except the *o*-Me substituted compound **14t** (79% inhibition). But, the pyrazoles **16a** and **16b** showed no significant ALK5 inhibition (<20% inhibition), and **21a–c** showed only modest ALK5 inhibition (36–47% inhibition). The competitor compounds **1** and **6** showed 66% and 80% inhibition in this assay, respectively.

The kinase domain of p38α MAP kinase is known to be one of the most homologous to that of ALK5,[42] therefore, it was chosen to examine the selectivity profile of this series of compounds. The pyrazoles **14a–ae** and **21a–c** possessing a phenycarbothioamido moiety did not inhibit p38α MAP kinase efficiently, showing IC_{50} values of >1450 nM, whereas the pyrazoles **16a** (IC_{50} = 496 nM) and **16b** (IC_{50} = 598 nM) possessing a 4-piperidinylcarbothioamido moiety were more inhibitory than the **14a–ae** and **21a–c**. The *p*-OMe substituted compound **14n** was the most selective in this series of compounds, showing a selectivity index of 11158 that is much higher than those of **1** (11) and **6** (28). It is noteworthy that the compound **14n**[43] is the most potent and selective ALK5 inhibitor reported to date.

In this Letter, a series of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles having a thioamido linkage between a pyrazole ring and a phenyl ring or a piperidinyl ring has been prepared and evaluated for their ALK5 inhibitory activity in an enzyme assay and in a cell-based luciferase reporter assay. It has been proved that incorporation of the [1,2,4]triazolo[1,5-*a*]pyridin-6-yl moiety and phenycarbothioamido moiety at the 4- and 1-positions of the pyrazole ring, respectively, significantly increased both ALK5 inhibitory activity and selectivity. The most potent compound **14n** inhibited ALK5 phosphorylation with IC_{50} value of 0.57 nM and showed 94% inhibition at 100 nM in a luciferase reporter assay using HaCaT cells permanently transfected with p3TP-luc reporter construct. The selectivity index of **14n** against p38α MAP kinase is 11158 that is much higher than those of **1** (11) and **6** (28).

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