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Synthesis and biological evaluation of trisubstituted imidazole derivatives as inhibitors of p38α mitogen-activated protein kinase

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ABSTRACT

A series of trisubstituted imidazole derivatives containing a 4-fluorophenyl group, a pyrimidine ring, and a CN- or $CONH_2$-substituted benzyl moiety have been synthesized and evaluated for p38α MAP kinase inhibitory activity. Among them, compounds **22c**, **27b**, and **28b** inhibited p38α MAP kinase with IC_{50} values 27.6, 28, and 31 nM, respectively.

The mitogen-activated protein kinase (MAPK) p38α is a serine/threonine kinase originally identified as an enzyme that was phosphorylated and activated by lipopolysaccharide (LPS) stimulation of monocytes. Subsequently, p38α MAP kinase has been shown to be involved in the biosynthesis of TNF-α and IL-1β at the translational and transcriptional level.[1–5] Activation of p38α MAP kinase is accomplished by double phosphorylation on both threonine-180 and tyrosine-182 by specific kinases (mainly MKK3, MKK6) which are themselves activated by other kinases (MKKK).[6–8] Among the downstream substrates in the p38α MAP kinase signaling pathways, some transcription factors and MAP kinase-activated protein kinases (MAPKAP) have been identified, which transduce signals to specific genes as well as to other cellular elements.[9] The transduction cascades mediated by activated p38α MAP kinase lead to the production of proinflammatory cytokines, mainly TNF-α and IL-1β.[10] TNF-α and IL-1β play key roles in the pathogenesis of rheumatoid arthritis and other autoimmune inflammatory diseases.[2,3,11] TNF-α and IL-1β are produced by synovial macrophages and are present in rheumatoid synovial fluid. Both of these cytokines have similar effects on cell proliferation, collagenase production, adhesion molecule expression, and chemokine production.[4,5,11,12]

The inhibition of cytokine production through transcriptional inhibition is an alternative strategy for therapeutic intervention. In the expectation of providing a safer treatment for chronic inflammation, many pharmaceutical companies are pursuing p38α MAP kinase inhibitors to intervene in cytokine production[6,11,13] As a result of these efforts, several p38α MAP kinase inhibitors (Fig. 1) such as Compound-006,[14] VX-702,[15] TAK-715,[16] SCIO-469,[17] BIRB-796,[18] SB-242235,[19] and 1-(2,6-dichloro-

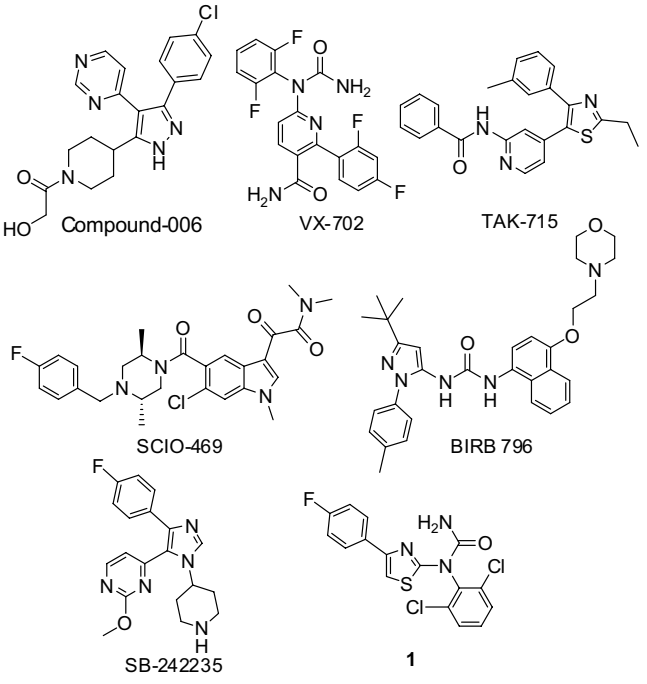

Figure 1. Structures of p38α MAP kinase inhibitors under development.

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phenyl)-1-(4-(4-fluorophenyl)thiazol-2-yl)urea (**1**) [20] have entered into clinical trials or are under preclinical development.

The design of target compounds was based on the known inhibitor SB-242235[19] and our potent inhibitors of transforming growth factor-β type1 receptor kinase (ALK5) (Fig. 2). It was previously demonstrated that incorporation of a methoxypyrimidine or an aminopyrimidine moiety in place of an unsubstituted 4-pyridine moiety improved selectivity profile and decreased p450 inhibition[19,21] During the development of ALK5 inhibitors in our laboratory, we realized that a cyano- or carboxamide-substituted phenyl substitution on a central five-membered heterocyclic ring leads to dramatic increase in activity and selectivity[22–28] The use of this strategy for ALK5 inhibitors has resulted in the discovery of highly potent and selective preclinical candidates IN-1166 (IC_{50} = 11.7 nM)[24] and IN-1130 (IC_{50} = 36 nM)[23,25,26] The selectivity profiles of IN-1166 and IN-1130 on a panel of tyrosine and serine/threonine kinases showed that the most sensitive kinase except ALK5 was p38α MAP kinase (IN-1166; IC_{50} = 1.03 μM, IN-1130; IC_{50} = 4.3 μM). This is not surprising that the kinase domain of ALK5 is known to be the most homologous to that of p38α MAP kinase[29] Therefore, we envisioned that incorporation of a 4-fluorophenyl group and a pyrimidine ring moiety of SB-242235 into our imidazole ALK5 scaffold may result in highly potent and selective inhibitors of p38α MAP kinase. To our delight this approach was successful to provide several potent inhibitors that possess activity in micromolar or submicromolar range against p38α MAP kinase.

N-Substituted imidazole derivatives **14–17** and **20–23** were prepared as shown in Scheme 1. The commercially available 2-mercapto-4-methylpyrimidine hydrochloride (**2**) was reacted with NaOH and MeI in EtOH to give 4-methyl-2-thiomethylpyrimidine[30] in 94% yield. Coupling of this thiomethyl compound with methyl 4-fluorobenzoate in anhydrous THF using NaHMDS as a base gave the monoketone **3**[30] in 94% yield. Oxidation of **3** with HBr (48 wt.% in water) in DMSO gave the diketone **4**[30] in 62% yield, which was subsequently cyclized with HCHO/NH_4OAc in AcOH to afford the imidazole **5** in 91% yield. Alkylation of **5** with α-bromo-*m*-tolunitrile (**6**) using Cs_2CO_3 in anhydrous DMF produced the trisubstituted imidazoles **8** and **10** in 54% and 22% yields, respectively. These two positional isomers were separated by MPLC, and each isomer was identified through the NOE study. Irradiation of the methylene group for compound **10** at δ 5.62 gave an enhancement of the methyl protons at δ 2.49, while irradiation of the methylene group for compound **8** at δ 5.02 gave no enhancement of the methyl protons at δ 1.85. Oxidation[21] of the methyl sulfides **8** and **10** with Oxone® in H_2O/MeOH gave the sulfones **12** and **18** in 94% and 95% yields, respectively. Nucleophilic aromatic substitution[21] of **12** with 4-methoxybenzylamine, (*S*)-(−)-α-methylbenzylamine, cyclopropylamine, and NaOMe yielded **14a** and **14c–e** in 89%, 90%, 51%, and 94% yields, respectively. Removal of 4-methoxybenzyl group of **14a** was affected in 3 M HCl to give **14b** in 59% yield. Conversion of the nitrile functionality of **14b–e** to carboxamide was accomplished by treatment of 28% H_2O_2 and 1 N NaOH in 95% EtOH to give **16a–d** in 43%, 57%, 68%, and 39% yields, respectively. The target compounds **20a–e** and **22a–d**, the positional isomers of **14a–e** and **16a–d**, were prepared by the same procedures for **14a–e** and **16a–d**. To compare the inhibitory activity of *m*-cyano- or *m*-carboxamide-substituted derivatives with *p*-cyano- or *p*-carboxamide-substituted ones, the trisubstituted imidazole analogs, **15a**, **15b**, **17a**, **17b**, **21a**, **21b**, **23a**, and **23b**, were prepared by alkylating **5** with α-bromo-*p*-tolunitrile (**7**) and following similar sequence as for the counterpart *m*-cyano and *m*-carboxamide derivatives, **14c**, **14e**, **16b**, **16d**, **20c**, **20e**, **22b**, and **22d**. Also, the related series, in which imidazole carries substitution at 2-position, was prepared as outlined in Scheme 2. Synthesis of the (imidazol-2-yl)methylbenzonitriles **27a–e** and (imidazol-2-yl)methylbenzamides **28a–c** was initiated using diketone **4**. Cyclization of **4** with 3-cyanophenylacetaldehyde (**24**) in *t*-BuOMe/MeOH in the presence of NH_4OAc at 0 °C produced 3-((4-(4-fluorophenyl)-5-(2-(methylthio)-pyrimidin-4-yl)-1*H*-imidazol-2-yl)methyl)benzonitrile (**25**) in 13% yield. Oxidation of the methylsulfide **25** and followed by nucleophilic aromatic substitutions as described for Scheme 1 yielded **27a** and **27c–e** in 98%, 96%, 69%, and 99% yields, respectively. Amino derivative **27b** was obtained from **27a** in 76% yield by acidic cleavage of 4-methoxybenzyl group. The nitrile functionality of **27c–e** was converted as mentioned for Scheme 1 to carboxamide analogs **28a–c** in 60%, 64%, and 52% yields, respectively. Compound **1** specifically claimed in a patent filed by Vertex Pharmaceuticals was synthesized according to a published procedure for comparison of biological activity.[20]

To investigate whether these compounds could inhibit p38α MAP kinase, IC_{50} values of these were measured. As shown in Table 1, compounds having a CN- or $CONH_2$-substituted benzyl group at the nitrogen adjacent to the 4-fluorophenyl ring in the central imidazole ring did not show potent p38α MAP kinase inhibition (IC_{50} > 1.0 μM). However, all the compounds having that group at the nitrogen which is next to the pyrimidine ring or at 2-position on the central imidazole ring showed significant p38α MAP kinase inhibition. Among the *m*-CN-substituted benzyl derivatives (**20a–e**) that possess substitution at the nitrogen which is next to the pyrimidine moiety on the central imidazole ring, amine derivatives (**20a–d**) are more inhibitory than OMe derivative (**20e**). Introduction of larger functionalities such as (*S*)-(−)-α-methylbenzyl (**20c**) and 4-methoxybenzyl (**20a**) on primary amine of compound **20b** did not lead to the improvement of activity. However, a smaller cyclopropyl group seemed to be accommodated favorably leading to increase in activity, and the resulted cyclopropylamino compound (**20d**) is the most potent with an IC_{50} value of 27.6 nM among the amine derivatives (**20a–d**). The *m*-CN-substituted derivatives **20c** and **20e** were compared with the corresponding *p*-CN-substituted ones **21a** and **21b**. In the case of compounds that contain (*S*)-(−)-α-methylbenzylamino group, *m*-CN derivative **20c** was slightly less potent than the corresponding *p*-CN derivative **21a**. But methoxy derivatives (**20e** and **21b**) showed significant variation in inhibitory activity. The *m*-CN derivative **20e** was 3.3-fold more inhibitory than the *p*-CN analog **21b**. The SAR of *m*-CN (**20b–e**) and *m*-$CONH_2$ (**22a–d**) derivatives reveals the contribution of CN

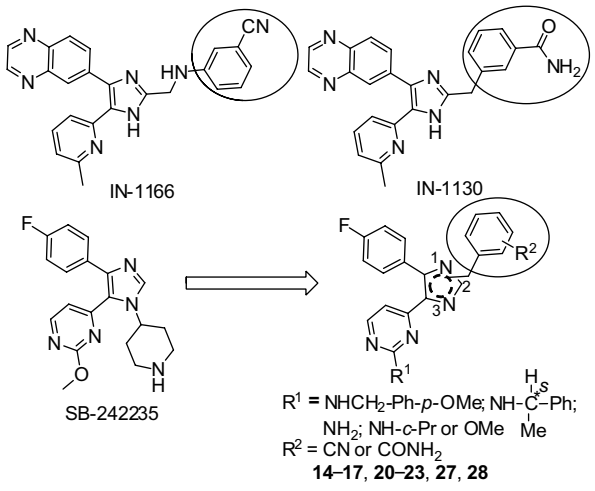
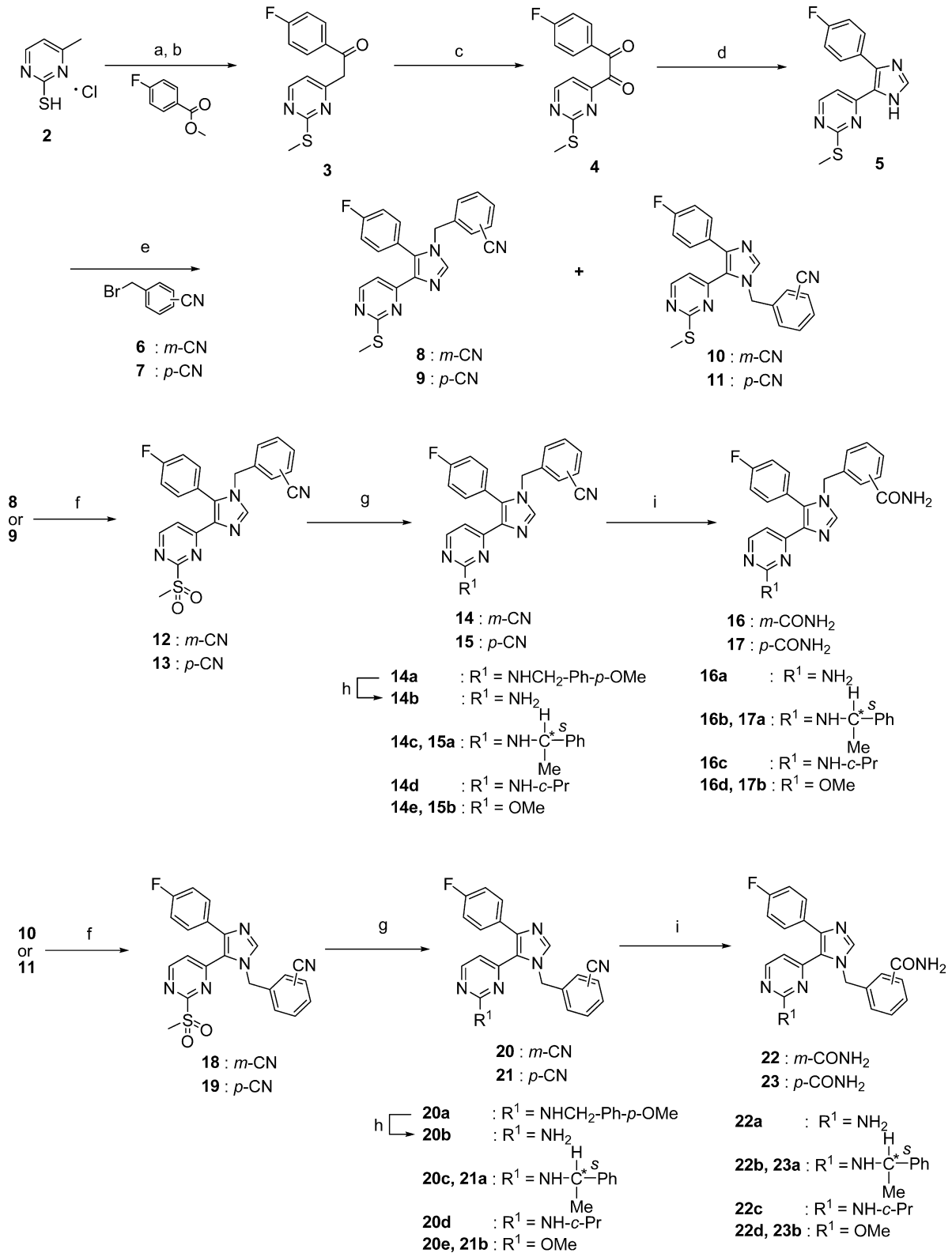
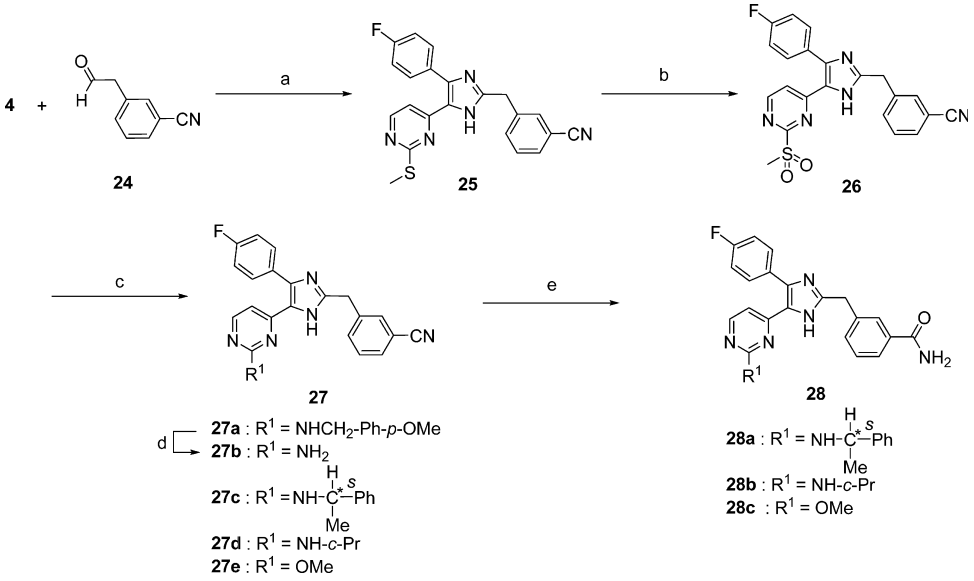


Figure 2. Rationale behind the design of target compounds.



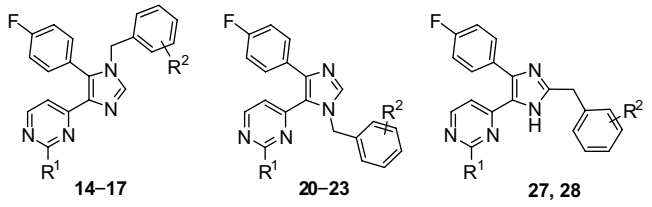
Scheme 1. Reagents and conditions: (a) NaOH, MeI, EtOH, rt, 16 h; (b) NaHMDS, anhydrous THF, rt, 0.5 h then methyl 4-fluorobenzoate, rt, 3 h; (c) 48% HBr, DMSO, 55 °C, 1 h; (d) HCHO, NH_4OAc, AcOH, reflux, 2 h; (e) Cs_2CO_3, anhydrous DMF, rt, 1 h; (f) Oxone®, H_2O/MeOH, rt, 1 h (for **12**, **13** and **19**) or 40 °C, 1.5 h (for **18**); (g) RNH_2, 140 °C, 2 h (for **14a**, **14c**, **15a**, **20a**, **20c**, and **21a**), cyclopropylamine, anhydrous DMF, 100 °C, 3 h (for **14d** and **20d**), or NaOMe, MeOH, rt, 1 h (for **14e**, **15b**, **20e**, and **21b**); (h) 3 M HCl, reflux, 30 h; (i) 28% H_2O_2, 1 N NaOH, EtOH, 60 °C (40–50 °C for **16c** and **22c**), 1 h.

and $CONH_2$ group to the inhibitory activity. The *m*-CN derivative **20b** was 3.4-fold more inhibitory than the *m*-$CONH_2$ derivative **22a**. However, in other cases, the *m*-$CONH_2$ derivatives **22b** and **22c** were 2.5- and 2.3-fold more potent inhibitors of p38α MAP



Scheme 2. Reagents and conditions: (a) NH_4OAc, *t*-BuOMe, MeOH, 0 °C, 1 h; (b) Oxone®, H_2O/MeOH, 40 °C, 1.5 h; (c) 4-methoxybenzylamine, 140 °C, 1 h (for **27a**), (*S*)-(−)-α-methylbenzylamine, 140 °C, 1 h (for **27c**), cyclopropylamine, DMF, 100 °C, 1 h (for **27d**), or NaOMe, MeOH, rt, 1 h (for **27e**); (d) 3 M HCl, 110 °C, 1 h; (e) 28% H_2O_2, 1 N NaOH, EtOH, 40–50 °C, 1 h.

Table 1
Inhibitory activity of trisubstituted imidazoles, **14–17**, **20–23**, **27**, and **28**, on p38α MAP kinase



Compound	R^1	R^2	IC_{50} (μM)	
			p38α[a]	ALK5[b]
14a	$NHCH_2$-Ph-*p*-OMe	*m*-CN	>1.0	>1.0
14b	NH_2	*m*-CN	>1.0	>1.0
14c	(*S*)-(−)-α-methylbenzylamino	*m*-CN	>1.0	>1.0
14d	NH-*c*-Pr	*m*-CN	>1.0	>1.0
14e	OMe	*m*-CN	>1.0	>1.0
15a	(*S*)-(−)-α-methylbenzylamino	*p*-CN	>1.0	>1.0
15b	OMe	*p*-CN	>1.0	>1.0
16a	NH_2	*m*-$CONH_2$	>1.0	>1.0
16b	(*S*)-(−)-α-methylbenzylamino	*m*-$CONH_2$	>1.0	>1.0
16c	NH-*c*-Pr	*m*-$CONH_2$	>1.0	>1.0
16d	OMe	*m*-$CONH_2$	>1.0	>1.0
17a	(*S*)-(−)-α-methylbenzylamino	*p*-$CONH_2$	>1.0	>1.0
17b	OMe	*p*-$CONH_2$	>1.0	>1.0
20a	$NHCH_2$-Ph-*p*-OMe	*m*-CN	0.191	>1.0
20b	NH_2	*m*-CN	0.101	>1.0
20c	(*S*)-(−)-α-methylbenzylamino	*m*-CN	0.140	>1.0
20d	NH-*c*-Pr	*m*-CN	0.0626	>1.0
20e	OMe	*m*-CN	0.260	>1.0
21a	(*S*)-(−)-α-methylbenzylamino	*p*-CN	0.0871	>1.0
21b	OMe	*p*-CN	0.859	>1.0
22a	NH_2	*m*-$CONH_2$	0.344	>1.0
22b	(*S*)-(−)-α-methylbenzylamino	*m*-$CONH_2$	0.0551	>1.0
22c	NH-*c*-Pr	*m*-$CONH_2$	0.0276	>1.0
22d	OMe	*m*-$CONH_2$	0.225	>1.0
23a	(*S*)-(−)-α-methylbenzylamino	*p*-$CONH_2$	0.0556	>1.0
23b	OMe	*p*-$CONH_2$	0.916	>1.0
27a	$NHCH_2$-Ph-*p*-OMe	*m*-CN	0.148	>1.0
27b	NH_2	*m*-CN	0.0280	>1.0
27c	(*S*)-(−)-α-methylbenzylamino	*m*-CN	0.0954	>1.0
27d	NH-*c*-Pr	*m*-CN	0.0544	>1.0
27e	OMe	*m*-CN	0.0628	>1.0
28a	(*S*)-(−)-α-methylbenzylamino	*m*-$CONH_2$	0.0780	>1.0
28b	NH-*c*-Pr	*m*-$CONH_2$	0.0310	>1.0
28c	OMe	*m*-$CONH_2$	0.0485	>1.0
1			0.822	

[a] p38α MAP kinase was expressed as untagged human recombinant protein in *Escherichia 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.

[b] 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.

kinase than the corresponding *m*-CN derivatives **20c** and **20d**, respectively. The inhibitory activity of *m*-$CONH_2$-substituted derivatives **22b** and **22d** were compared with that of the corresponding *p*-$CONH_2$-substituted ones **23a** and **23b**. Although compounds **22b** and **23a** showed the similar level of inhibitory activity, *m*-$CONH_2$ derivative **22d** was 4.1-fold more inhibitory than *p*-$CONH_2$ derivative **23b**. The derivatives (**27a–e**) that possess a *m*-CN-substituted benzyl group at 2-position of imidazole ring were found to be 1.3-, 3.6-, 1.5-, 1.2-, and 4.1-fold more potent than the corresponding derivatives (**20a–e**) that possess the same substitution at nitrogen which is next to the pyrimidine ring. Among the 2-substituted imidazole compounds, *m*-$CONH_2$ analogs (**28a–c**) were 1.2-, 1.8-, and 1.3-fold more inhibitory than the respective *m*-CN derivatives (**27c–e**). As expected, all the trisubstituted imidazole derivatives we prepared were devoid of ALK5 inhibitory activity up to the maximum concentration of 1 μM tested. Among all the compounds, **22c** (IC_{50} = 27.6 nM), **27b** (IC_{50} = 28 nM), and **28b** (IC_{50} = 31 nM) are the most active compounds, and these compounds are approximately 27- to 30-

fold more potent inhibitors of p38α MAP kinase than compound **1** (IC_{50} = 822 nM) of Vertex Pharmaceuticals.

In this report, a series of trisubstituted imidazole derivatives containing a 4-fluorophenyl group, a pyrimidine ring, and a CN- or $CONH_2$-substituted benzyl moiety have been synthesized and evaluated for p38α MAP kinase inhibitory activity. The structure–activity relationships in this series of compounds have been established and discussed. Compounds **22c**, **27b**, and **28b** showed the most significant p38α MAP kinase inhibitory activity in the series of compounds that is much higher than that of **1**. This report conclusively confirms the important role of a methoxypyrimidine or an aminopyrimidine moiety in the design of p38α MAP kinase inhibitors to obtain the selectivity over ALK5. Moreover, our strategy that was successfully used in the development of ALK5 inhibitors[22–28] has been found to be applicable to the design of p38α MAP kinase inhibitors. The introduction of a cyano- or carboxamide-substituted phenyl substitution on a central five-membered heterocyclic ring in p38α MAP kinase inhibitors has led to the significant increase in inhibitory activity.

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