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Synthesis and biological evaluation of *N*-cyclopropylbenzamide-benzophenone hybrids as novel and selective p38 mitogen activated protein kinase (MAPK) inhibitors

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ABSTRACT

A series of hybrid molecules consisting of benzophenones and *N*-cyclopropyl-3-methylbenzamides were synthesized and biologically evaluated as novel p38 mitogen activated protein kinase (MAPK) inhibitors. In particular, we found that compound **10g** displayed potent p38α MAPK inhibitory activity (IC_{50} = 0.027 μM), high kinase selectivity, and significant anti-inflammatory activity in THP-1 monocyte cells.

As a class of mitogen-activated protein kinases (MAPKs) that can be activated by various stress stimuli, p38 MAPK plays a crucial role in the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) which are primarily involved in the progression of chronic inflammatory diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis, psoriasis and neuropathic pain.[1] Driven by the huge success of monoclonal antibodies which can directly neutralize TNF-α or IL-1β for the treatment of chronic inflammation, several small molecule inhibitors of p38 MAPK have been developed over the past several decades.[2] However, until now, none has been put on the clinical market for therapeutic purpose because safety issues related to liver toxicity, neurological side effects and low efficacy in preclinical/clinical test have been reported. These issues are partly due to the lack of kinase selectivity, which leads to off-target effects.[2a,d,3] Consequently, the discovery of a potent and selective p38 MAPK inhibitor based on novel scaffolds, which might be safe and efficacious in further development stages, remains necessary.

In 2003, a series of 4-aminobenzophenone derivatives such as compound **1** were identified as potent p38α MAPK inhibitors with high anti-inflammatory activities.[4] Further investigation into the binding mode of 4-aminobenzophenones within p38α MAPK active site by Laufer and his co-workers[5] disclosed that oxygen of carbonyl moiety in these derivatives makes a tight interaction with a hinge region of the kinase by forming strong double hydrogen bondings with the NH-group of Met109 and another NH-group of Gly110 instead of amide oxygen *via* glycine flip (PDB ID: 3QUD).[2a,6] This interaction provides high selectivity to the inhibitor toward p38α MAPK because it is only possible when the kinase has a hinge region composed of glycine and adjacent linker residue such as methionine, which exists in 9.2% of all kinases.[2a] Thus, it is assumed that the benzophenone scaffold can be a suitable backbone for tight and selective binding to p38α MAPK.

Recently, several biphenyl amides with good anti-inflammatory activities were developed as novel p38α MAPK inhibitors by GSK researchers.[7] Among them, *N*-cyclopropyl linked biphenyl amide **2** is one of the most promising p38α MAPK inhibitors. X-ray crystallography of **2** complexed with p38α revealed that the carbonyl group of *N*-cyclopropylmethyl amide forms a hydrogen bonding with Met109 in the hinge region, with no glycine flip, which is distinct from benzophenone **1** (PDB ID: 3D7Z). In particular, *N*-cyclopropyl amide, which is the opposite fragment of *N*-cyclopropylmethyl amide in compound **2**, makes hydrogen bondings

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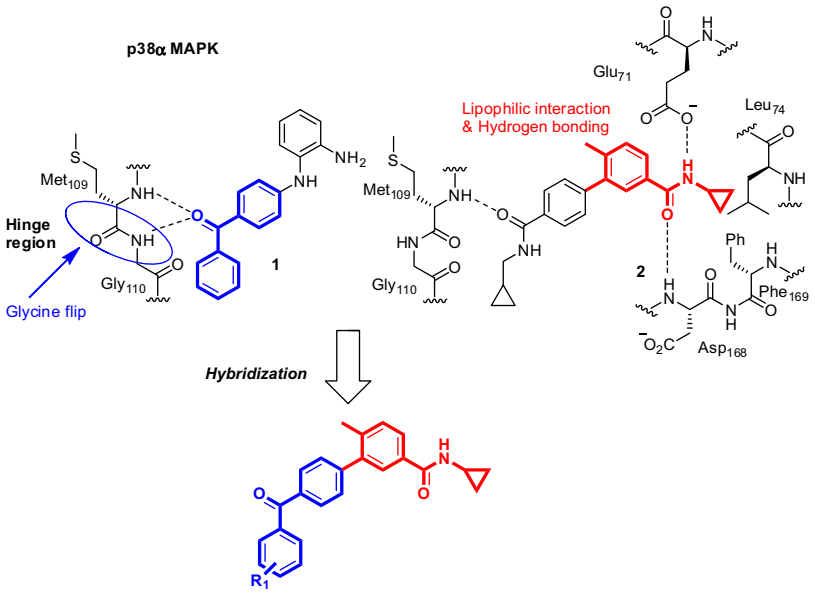
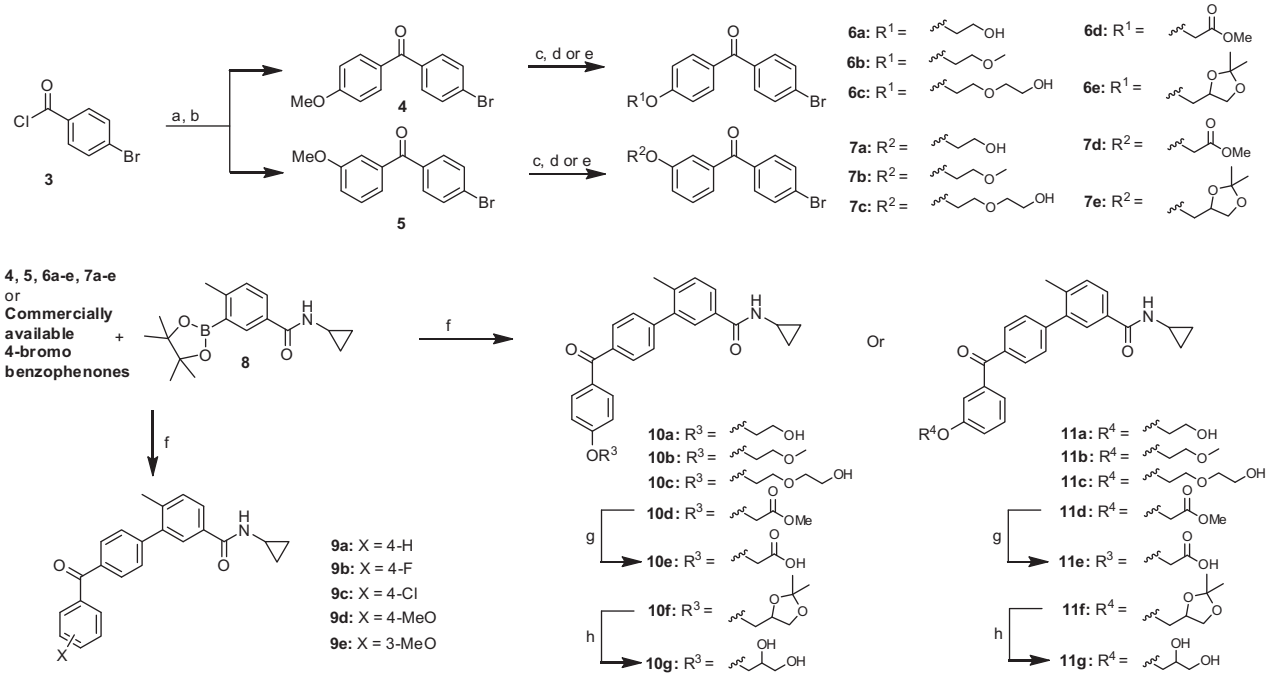


Figure 1. Design strategy for novel *N*-cyclopropylbenzamide-benzophenone hybrids.

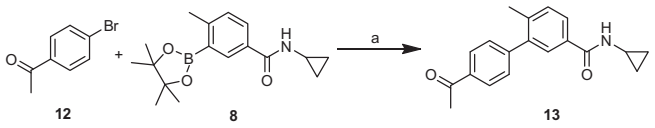


Scheme 1. Synthesis of compound **9a–e**, **10a–c**, **10e**, **10g**, **11a–c**, **11e**, and **11g**. Reagents and conditions: (a) *N*,*O*-dimethylhydroxylamine hydrochloride, Et_3N, CH_2Cl_2, rt, 97%; (b) 3-or 4-methoxyphenylmagnesiumbromide, DMF, rt, 96–98%; (c) pyridinium hydrochloride, 130 °C, 70–90%; (d) alkyl halides or 2,2-dimethyl-1,3-dioxolan-4-ylmethyl *p*-toluenesulfonate, K_2CO_3, KI, acetone, 60–85 °C, 80–100%; (e) 2-bromoethylmethylether, NaH, THF, rt, 90%; (f) $Pd(PPh_3)_4$, K_2CO_3, DMF, 120 °C, 25–74%; (g) LiOH, THF/MeOH/H_2O, 71-82%; (h) *p*-TsOH, H_2O/MeOH, 50 °C, 47–53%.

with Asp168 and Glu71 and tightly fits in a lipophilic pocket whose bases are Leu74, and Phe169, which leads to good and selective binding with p38α MAPK.[7c,7d] In addition, compound **2** significantly decreases the production of inflammatory cytokines such as TNF-α.

In an effort to identify a novel p38 MAPK inhibitor with high kinase selectivity and significant anti-inflammatory activity, we considered it worthwhile to exploit the pharmacological core moieties of compound **1** and **2** which are potent and selective kinase inhibitors. Based on the insights gained from those reports, we envisaged that the combination of the benzophenone group to induce glycine flip and *N*-cyclopropylbenzamide group to tightly and selectively fit in the enzyme[7d] could be the way to provide the novel scaffold for a potent and selective p38 MAPK inhibitor (Fig. 1). Herein, we report the synthesis and biological evaluation of *N*-cyclopropylbenzamide-benzophenone hybrids as novel p38 MAPK inhibitors.

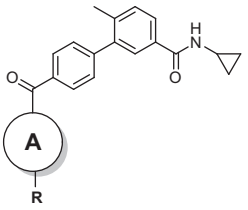
A variety of hybrids equipped with benzophenones and *N*-cyclopropylbenzamides were efficiently synthesized using a concise synthetic strategy, as outlined in Scheme 1. First, 4-alkoxy-4′-bromobenzophenones were prepared from the commercially available 4-bromobenzoyl chloride **3**, which was transformed into *meta*- or

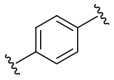
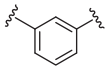
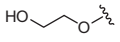
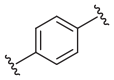
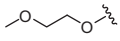
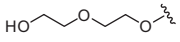
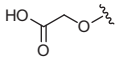
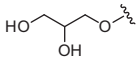
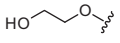
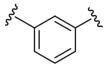
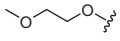
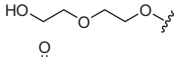
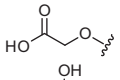
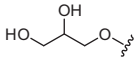


Scheme 2. Synthesis of compound **13**. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, DMF, 120 °C, 67%.

para-methoxybenzophenones by Weinreb amide formation and Grignard addition using methoxybenzene MgBrs in turn.[8] The sequential demethylation of the intermediates **4** and **5** in the presence of pyridine HCl, followed by alkylation afforded **6a–e** and **7a–e**.[9] Using the synthesized 4-alkoxy-4′-bromo benzophenones and commercially available other 4-bromobenzophenones, we synthesized most of the desired derivatives such as **9a–e**, **10a–d**, **10f**, **11a–d** and **11f** *via* a unified Suzuki–Miyaura coupling of them with the known compound **8**, which has *N*-cyclopropyl amide.[7] The hydrolysis of **10d** and **11d** provided **10e** and **11e**, respectively. Compounds such as **10g** and **11g** were prepared through an additional acetal deprotection of **10f** and **11f**.

Table 1
P38α MAPK inhibitory activities of synthesized compounds



Compound	R	A	IC_{50}[a] (μM)
9a	H		0.109
9b	F		0.287
9c	Cl		0.271
9d	MeO		0.135
9e	MeO		0.129
10a			0.053
10b			0.076
10c			0.056
10e			0.085
10g			0.027
11a			0.069
11b			0.056
11c			0.046
11e			0.098
11g			0.044
13		CH_3	0.350
SB203580			0.062

[a] IC_{50}s of the compounds were determined in 10 point titration.

Acetophenone **13**, where the benzene group was not incorporated was prepared *via* Suzuki–Miyaura coupling of the commercially available **12** and the known intermediate **8** (Scheme 2).

The in vitro activities of the synthesized compounds were evaluated through SelectScreen™ Kinase Profiling Services (Life technologies).The assay result of the synthesized compounds is summarized in Table 1.

As shown in Table 1, most of the compounds showed potent p38α MAPK inhibitory activities, with IC_{50} values in the sub-micromolar range. Interestingly, compound **9a**, an initially designed hybrid of the benzophenone and *N*-cyclopropylamide, was active (IC_{50} = 0.109 μM). However, compound **13**, where the simple methyl group was introduced at A position, showed less activity than **9a** (IC_{50} = 0.350 μM). Thus, the lipophilic moiety such as benzene is beneficial for the desired activity. Compounds such as **9b** and **9c** that have electron-withdrawing halogens at the *para* position of the benzophenone moiety were also less potent than **9a** (IC_{50} = 0.287 and 0.271 μM, respectively), whereas **9d** which have a methoxy group at the *para* position of the benzophenone moiety, was more potent than **9b** and **9c**. The *meta*-methoxy substituted compound also displayed good potency, similar to **9d**.

With the results, we moved our attention to fine-tuning of the hybrid compounds. Inspired by our result, and previous reports that incorporation of the hydrophilic substituents on R group, directing toward the solvent exposable region, might increase p38 MAPK inhibitory activities of the compounds, due to enhancement of their water solubility and possibilities for additional interactions[3a,5,6,10], we focused on the synthesis of analogs with various ether moieties and investigated their biological activities. In the case of incorporating hydrophilic moieties at the *para* position, compounds such as **10a** and **10c**, which contain ethers linked with a terminal hydroxyl group, exhibited more potent activity (IC_{50} = 0.053 and 0.056 μM, respectively) than compound **10b** with no terminal hydroxyl group (IC_{50} = 0.076 μM). The carboxylalkoxy substituent which is more hydrophilic than the hydroxyalkyl ether group makes the inhibitors less active. It is noteworthy that compound **10g** with dihydroxypropoxy residue showed the greatest activity with an IC_{50} of 0.027 μM, which indicates that it is significantly more potent than SB203580, the representative p38α MAPK inhibitor (IC_{50} = 0.062 μM). Thus, compounds **10a**, **10c** and **10g** with ethylene glycol or its repeated moiety showed more potent activities than more hydrophilic carboxylate (**10e**) and less hydrophilic methoxy ether (**10b**), but similar in size to them. These

Table 2
Selectivity profiling of compound **10g** against a panel of kinases[a]

Kinase	% Activity remaining[b]	Kinase	% Activity remaining[b]
ABL1	101	MAPK8 (JNK1)	105
BTK	105	MAPK9 (JNK2)	112
BRAF	89	MAPK10 (JNK3)	96
CDK1	100	MAPK11 (p38β)	**3**
EGFR (ErbB1)	94	MAPK12 (p38γ)	103
ERBB2 (HER2)	94	MAPK13 (p38δ)	93
FLT3	94	MAPK14 (p38α)	**1**
GSK3β	102	MAPK15 (ERK7)	98
IKK β	98	MAPKAPK2	98
JAK1	111	MEK1	97
JAK2	96	SRC	92
JAK2	99	TYK2	105
LCK	84	cRAF	94
MAPK1 (ERK2)	107	ROCK2	93
MAPK3 (ERK1)	108	VEGFR1	88

[a] Kinase selectivities of synthesized compounds (1 μM) were profiled through SelectScreen™ Kinase Profiling Services (Life technologies).

[b] Data are given in percent remaining activity (i.e., 100% indicates no observed inhibition).

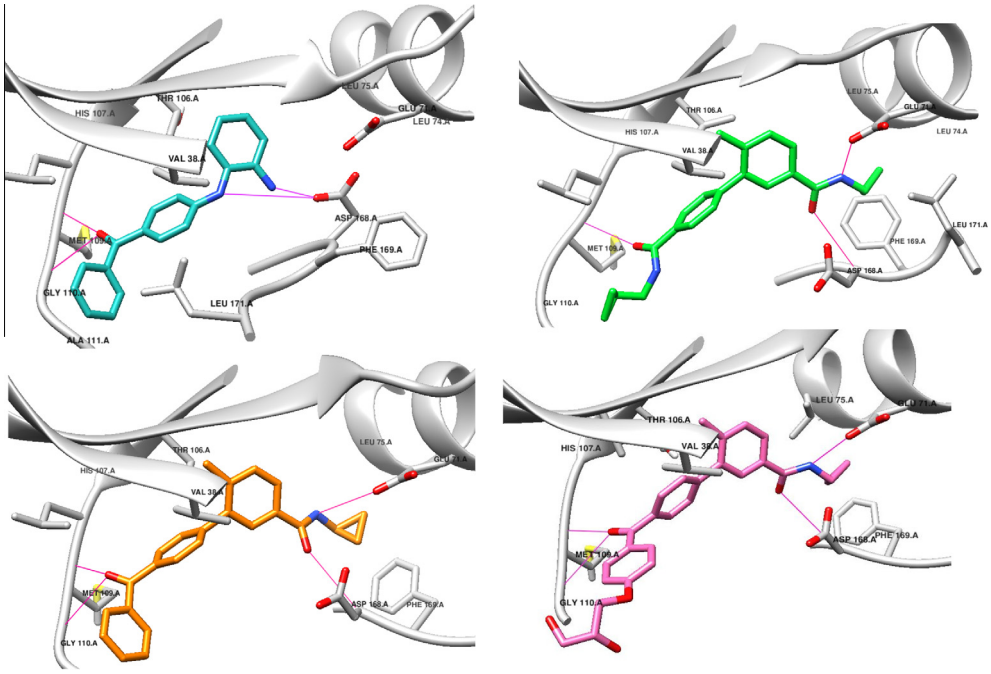


Figure 2. X-ray structures of **1** (Cyan, PDB Code: 3QUD) and **2** (green, PDB Code: 3D7Z), and molecular docking model of **9a** (yellow, PDB Code: 3ZYA), and **10g** (pink, PDB Code: 3ZYA) with p38α MAPK, which were visualized using Chimera 1.10 (UCSF Chimera).[13]

results implied that hydroxyl group-including ethers as *para* substituents might provide better activities with the analogs, partly due to their moderate hydrophilicity.

Next, we tried to synthesize the compounds with hydrophilic moieties at the *meta* position of the benzophenone moieties. Compound **11a** with hydroxyethoxy ether as a substituent also showed potent activity but it was slightly less than *para* isomer **10a** (IC_{50} = 0.069 μM). Unlike the case of *para*-substituted analogs, methoxyethyl analog **11b** was slightly more potent than **11a**. In addition, the lengthened glycol ether-including analog **11c** showed more potent activity than **11b**. Compound **11g** with a dihydroxypropoxy group showed similar activity to **11c**. The compound equipped with carboxylalkoxy group was less active than **11a**, which is similar to the case of *para*-substituted analogs. These results suggest that the compounds such as **11b**, **11c**, and **11g** with longer ether chains are marginal better in comparison to the shorter ether chain. But the diol **11g** was the most active compounds among compounds with hydrophilic *meta* substituents, which is consistent in the case of the analogs including *para* substituents on R group.

Based on the promising activity of the compound at the kinase assay, we chose compound **10g** as a lead compound for further study and checked its selectivity against a panel of 94 different kinases which are considered functionally or structurally similar to p38 MAPK based on the kinome analysis and the cross reactivity to other p38 MAPK inhibitors such as BIRB-796.[2d,7d,11] The selectivity profiles of the compound are summarized in Table 2 and full profiles using 94 different kinases are described in Supplementary information Table S1. Interestingly, **10g** showed significant inhibitory activity against p38 MAPKs but no or weak inhibitory activities against other kinases including JNKs and LCK, which implies that it has high selectivity against p38 MAPK over other kinases.

To investigate the binding mode of the *N*-cyclopropylamide-benzophenone hybrids that was identified as a novel p38 MAPK inhibitor, docking analysis of **9a** and **10g** within p38α MAPK active site was performed using Autodock 4.2 (Molecular Graphic Laboratory).[12] As illustrated in Figure 2, both compounds fitted well into the active site, which concurred with their potent activities. The estimated free binding energy of more potent compound **10g** (−10.06 kcal/mol) was lower compared to that of **9a** (−9.54 kcal/mol), indicating that **10g** might have energetically more favored conformation. It is plausible that the benzophenone moieties in **9a** and **10g** interact with the hinge region of a kinase through double hydrogen bondings, which is induced by glycine flip, whereas *N*-cyclopropylamide, which forms hydrogen bondings with Glu71 and Asp168, is oriented toward a lipophilic pocket surrounded by Leu74 and Phe169. Thus, the binding mode of our compound was postulated in accordance with our initial design strategy.

To further determine whether the newly identified p38 MAPK inhibitor **10g** can reduce inflammatory cytokines on a cellular level, THP-1 cells were treated with increasing concentrations of **10g** followed by LPS stimulation. Anti-inflammatory effect of **10g** was tested using enzyme-linked immunosorbent assay (ELISA)

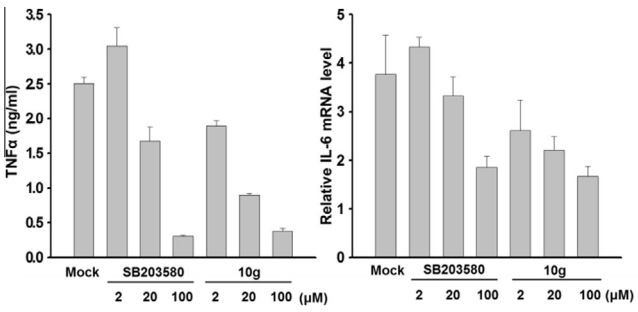


Figure 3. Anti-inflammatory effects of compound **10g** on THP-1 cells: (a) cells were treated with indicated concentrations of SB203580 or **10g** followed by LPS stimulation for 24 h. Production of TNFα was determined by ELISA. (b) Cells were treated with indicated concentrations of SB203580 or **10g** followed by LPS stimulation for 10 h. Synthesis of interleukin-6 (IL-6) mRNA was measured by RT-qPCR

and quantitative polymerase chain reaction (qPCR). As depicted in Figure 3, LPS-induced production of TNF-α and IL-6, which are known to be representative inflammatory procytokines were decreased by **10g** treatment in dose-dependent manners, further proving its p38 MAPK inhibitory biological role.

In summary, we identified a series of *N*-cyclopropylbenzamide-benzophenone hybrids as novel p38 MAPK inhibitors based on rational design and convenient synthetic approaches. In particular, the analog **10g** showed potent and selective p38α MAPK inhibition activity (IC_{50} = 0.027 μM) as well as significant anti-inflammatory properties in monocyte cells. Based on molecular modeling, it is postulated that the binding mode of **9a** and **10g** is demonstrated as combining the advantageous moieties of benzophenone and *N*-cyclopropyl benzamide group for being potent and selective p38 MAPK inhibitors. Further work for the development of therapeutically useful anti-inflammatory drugs based on our current study is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.06.036.

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