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Synthesis of Triazolo- and Oxadiazolopiperazines by Gold(I)-Catalyzed Domino Cyclization: Application to the Design of a Mitogen Activated Protein (MAP) Kinase Inhibitor

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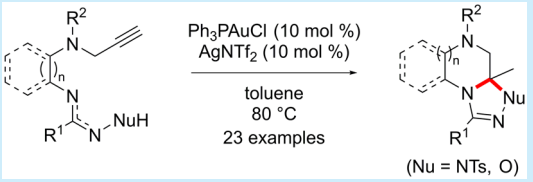
Supporting Information

ABSTRACT: An efficient method for the synthesis of [1,2,4]triazolo-[4,3-*a*]piperazine derivatives was established based on a gold(I)-catalyzed domino cyclization of an amidrazone substrate with a terminal alkyne. The amidoxime congeners were converted into [1,2,4]oxadiazolo[4,5-*a*]piperazine derivatives in the presence of a gold catalyst. The oxadiazolopiperazine is a promising scaffold for the design of novel inhibitors against p38 mitogen activated protein kinase (MAP kinase).



Fused piperazines are versatile building blocks for the development of bioactive substances. One representative example is the dipeptidyl peptidase IV inhibitor, sitagliptin, which is currently used in clinics for treatment of diabetes (Figure 1).[1] Fezolinetant is a neurokinin-3 (NK3) receptor

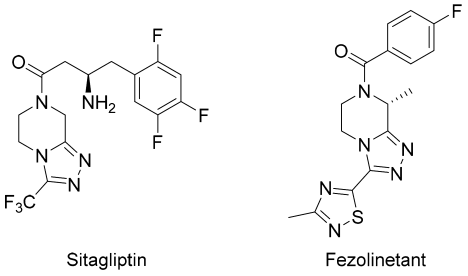
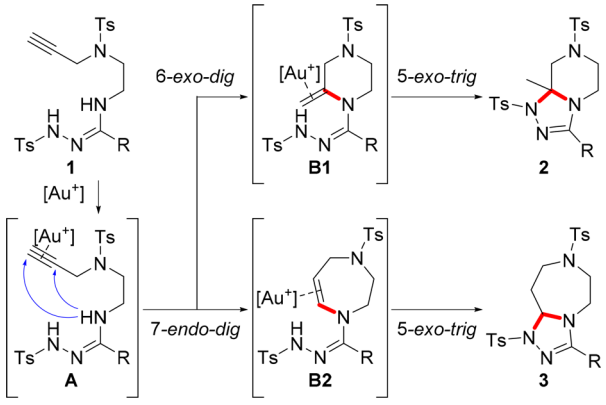


Figure 1. Structures of bioactive [1,2,4]triazolo[4,3-*a*]piperazine derivatives.

antagonist, which is expected to be a therapeutic agent candidate in clinical trials for hot flashes in menopausal women.[2] These agents share a characteristic [1,2,4]triazolo-[4,3-*a*]piperazine scaffold. There have also been a number of applications of fused piperazine scaffolds[3] as enzyme inhibitors and receptor ligands including a p38α kinase inhibitor,[4] poly(ADP-ribose) polymerase (PARP) inhibitors,[5] and histone deacetylase (HDAC) inhibitors.[6] For these medicinal chemistry investigations, a variety of synthetic approaches for obtaining fused piperazine scaffolds have been developed.[7]

During the past decade, gold(I) catalysts have attracted considerable attention as effective π-acids for the activation of alkynes.[8] The gold-catalyzed hydroalkoxylation and hydroamination of alkynes and alkenes have been used extensively to synthesize a broad range of heterocycles.[9−11] We envisaged that [1,2,4]triazolo[4,3-*a*]piperazine or related heterocycles would be provided by a gold-catalyzed intramolecular cascade reaction of open-chain precursors bearing an alkyne moiety. That is, the gold-catalyzed reaction of amidrazone **1** would lead to the formation of piperazine **B1** and tetrahydro-1,4-diazepine **B2** through a 6-*exo*-*dig* type and 7-*endo*-*dig* type hydroamination of **A**, respectively (Scheme 1). The piperazine

Scheme 1. Possible Reaction Pathways for Gold(I)-Catalyzed Domino Cyclization of Hydrazonamide



(**B1**) and 1,4-diazepine (**B2**) intermediates could be converted into 1,2,4-triazole scaffolds (**2** and **3**, respectively) by the subsequent 5-*exo*-*trig* type hydroamination (aminal formation).[12] Herein, we report a novel synthetic approach for [1,2,4]triazolo[4,3-*a*]piperazine derivatives **2** and their 1,2,4-oxadiazole congeners by a gold-catalyzed intramolecular cascade reaction. The applications of the [1,2,4]oxadiazolo-

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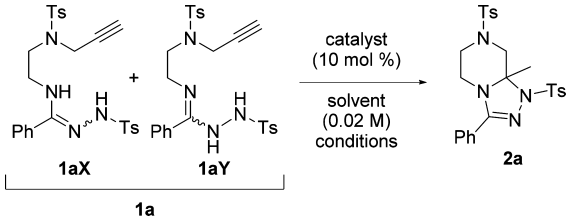
[4,5-*a*]piperazine scaffold to medicinal chemistry approaches are also presented.

For our initial experiments, we investigated the optimization of the reaction conditions for the cascade cyclization of amidrazone **1a** (Table 1). The substrate amidrazone **1a** was obtained by the reaction of the corresponding benzamide with trifluoromethanesulfonic anhydride (Tf_2O) followed by conjugation with *N*-tosylhyrdazine[13] as an inseparable mixture of hydrazonamide form **1aX** and imidohydrazine form **1aY** (see the Supporting Information). The reaction of **1a** with 10 mol % of IPrAuCl/$AgNTf_2$ in 1,2-dichloroethane (DCE) at 50 °C gave [1,2,4]triazolo[4,3-*a*]piperazine **2a** as the isolable isomer, albeit in a low yield of 19% (entry 1). After screening several other phosphine ligands [JohnPhos, BrettPhos, Ph_3P, $(t\text{-Bu})_3P$, and tris(4-trifluoromethylphenyl)phosphine (**L**); entries 2–6], we found that use of Ph_3PAuCl and **L**AuCl provided **2a** in 64% and 73% yields, respectively (entries 4 and 6). No transformation was observed by treatment with Tf_2NH or $(Ph_3C)B(C_6F_5)_4$ (entries 7 and 8).[14] The higher temperature (80 °C) in the presence of Ph_3PAuCl improved the reaction efficiency (entries 9). Among three silver salts ($AgNTf_2$, AgOTf, and $AgSbF_6$) tested for the reactions (entries 9, 11, and 12), use of AgOTf led to a decrease in the yield (38%, entry 11). Screening of the reaction solvent (entries 13–16) revealed that toluene afforded the best result in terms of the reaction time and yield (entry 16). Decreasing the loading of catalyst to 5 mol % led to a decrease in the yield of **2a** even after a prolonged reaction time (entry 17). The optimal reaction conditions were obtained in the presence of **L**AuCl/$AgNTf_2$ as a catalyst in toluene (entry 18).

Next, we examined the substituent effect at the phenyl group of amidrazone **1** on the intramolecular cyclizations (Table 2).

Table 1. Optimization of Reaction Conditions



entry	catalyst	solvent[a]	conditions	yield (%)[b]
1	IPrAuCl/$AgNTf_2$	DCE	50 °C, 21 h	19
2	JohnPhosAuCl/$AgNTf_2$	DCE	50 °C, 21 h	45
3	BrettPhosAuCl/$AgNTf_2$	DCE	50 °C, 21 h	38
4	$Ph_3PAuCl/AgNTf_2$	DCE	50 °C, 21 h	64
5	$(t\text{-Bu})_3PAuCl/AgNTf_2$	DCE	50 °C, 21 h	21
6	LAuCl/$AgNTf_2$	DCE	50 °C, 21 h	73
7	Tf_2NH	DCE	50 °C, 21 h	0
8	$(Ph_3C)B(C_6F_5)_4$	DCE	50 °C, 21 h	0
9	$Ph_3PAuCl/AgNTf_2$	DCE	80 °C, 3 h	74
10	$Ph_3PAuCl/AgNTf_2$	TCE	100 °C, 2 h	57
11	Ph_3PAuCl/AgOTf	DCE	80 °C, 98 h	38
12	$Ph_3PAuCl/AgSbF_6$	DCE	80 °C, 9.5 h	72
13	$Ph_3PAuCl/AgNTf_2$	CH_3CN	80 °C, 2 h	53
14	$Ph_3PAuCl/AgNTf_2$	*i*-PrOH	80 °C, 5 h	63
15	$Ph_3PAuCl/AgNTf_2$	1,4-dioxane	80 °C, 5 h	72
16	$Ph_3PAuCl/AgNTf_2$	toluene	80 °C, 2.5 h	73
17	$Ph_3PAuCl/AgNTf_2$[c]	toluene	80 °C, 9 h	60
18	LAuCl/$AgNTf_2$	toluene	80 °C, 2.5 h	78

[a]DCE: 1,2-dichloroethane. TCE: 1,1,2,2-tetrachloroethane. [b]Isolated yield. [c]5 mol % of the catalyst was used.

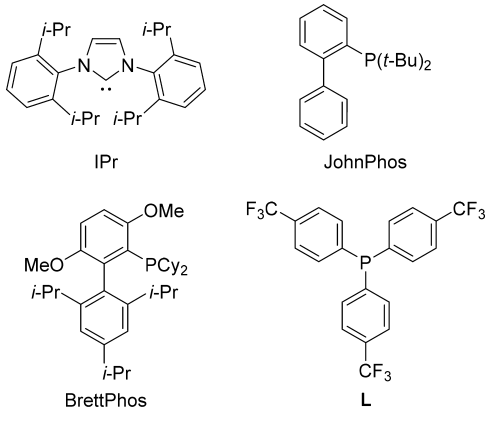
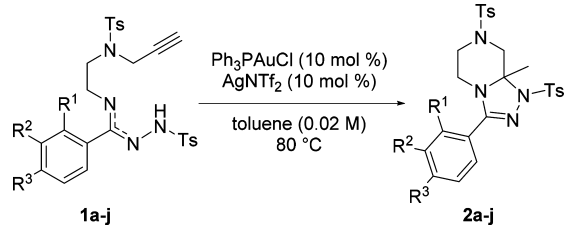


Table 2. Investigation of the Substituent Effect at the Substrate Phenyl Group



entry	substrate	R^1	R^2	R^3	yield (%)[a]
1	**1a**	H	H	H	74 (78[b])
2	**1b**	Me	H	H	69
3	**1c**	OMe	H	H	62 (86[b])
4	**1d**	NO_2	H	H	69
5	**1e**	F	H	H	63 (71[b])
6	**1f**	Cl	H	H	58
7	**1g**	Br	H	H	58
8	**1h**	I	H	H	52
9	**1i**	H	Me	H	78
10	**1j**	H	H	Me	83

[a]Isolated yield. [b]LAuCl was used instead of Ph_3PAuCl.

$Ph_3PAuCl/AgNTf_2$-mediated reaction of amidrazones **1b** and **1c** bearing an electron-donating methyl and methoxy group at the *ortho* position (R^1) proceeded smoothly to give the desired products **2b** and **2c** in 69% and 62% yields, respectively (entries 2 and 3). Amidrazones **1d–h** bearing an electron-withdrawing nitro and halogen group at the same position were well tolerated (entries 4–8). Use of **L**AuCl instead of Ph_3PAuCl led to improvement in the product yields (entries 1, 3, and 5). The positions of the substituent in the reaction were investigated by using amidrazones **1i** and **1j** bearing a methyl group at the *meta* position (R^2) or *para* position (R^3). Both substrates reacted more efficiently to give the corresponding triazolopiperazines **2i** and **2j** in 78% and 83% yields, respectively (entries 9 and 10). These results implied that the substituents at the phenyl group were unlikely to significantly affect the cyclization mode and yield.

We further investigated the scope of the reaction using a variety of substrates (Table 3). Amidrazone **1k** bearing a cyclohexyl group at the R^1 position reacted less efficiently to give the corresponding triazole **2k** in 48% yield (entry 1). In contrast, amidrazone **1l** bearing a *n*-propyl group was well

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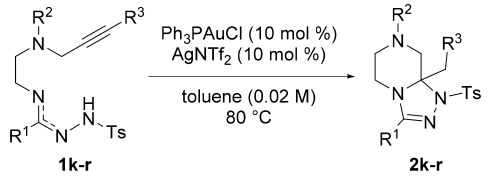
Table 3. Substrate Scopes



1k-r 2k-r

entry	substrate	R^1	R^2	R^3	yield (%)[a]
1	**1k**	cyclohexyl	Ts	H	48
2	**1l**	*n*-Pr	Ts	H	68
3	**1m**	2-thienyl	Ts	H	81
4	**1n**	2-pyridyl	Ts	H	75
5	**1o**	Ph	Ns	H	65 (68[b])
6	**1p**	Ph	Ts	Br	30
7	**1q**	Ph	Ts	Me	0
8	**1r**	Ph	Ts	Ph	0

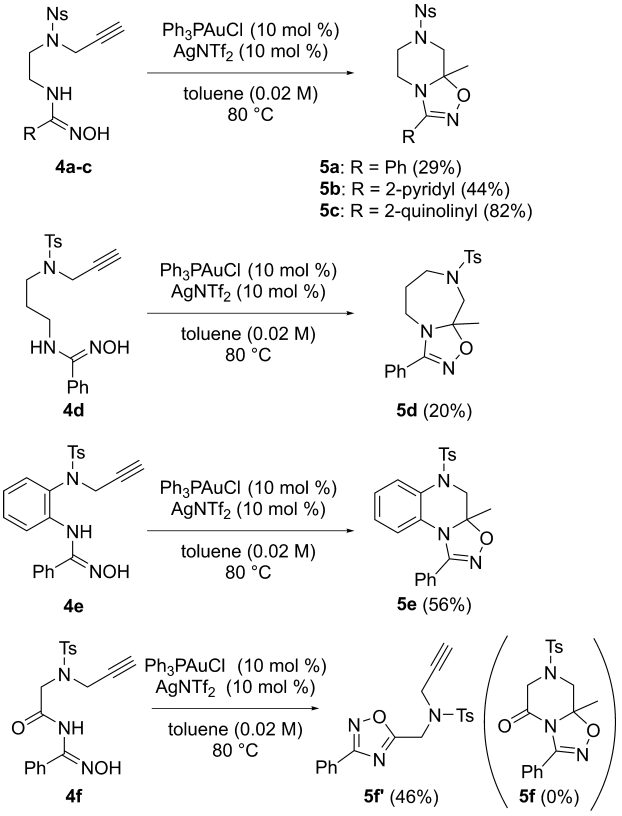
[a]Isolated yield. [b]LAuCl was used instead of Ph_3PAuCl.

tolerated and gave 3-propyltriazole **2l** in 68% yield (entry 2). Thiophene **1m** and pyridine **1n** also reacted smoothly to provide the triazoles **2m** and **2n**, respectively (entries 3 and 4). The reaction of the substrate having an easily removable nosyl (Ns) group at the R^2 position also afforded an *N*-Ns protected piperazine derivative **2o** (entry 5). Amidrazone **1p** incorporating a bromoalkynyl group was also converted to the desired product **2p**, but in a lower yield (entry 6). Unfortunately, the reactions of amidrazone derivatives **1q** and **1r** bearing a methyl and phenyl group at the alkynyl terminus (R^3 position) did not proceed at all probably as a result of the lower reactivity of the internal alkyne for the first step or instability of the possible product(s) via 7-*endo-dig* cyclization (entries 7 and 8).

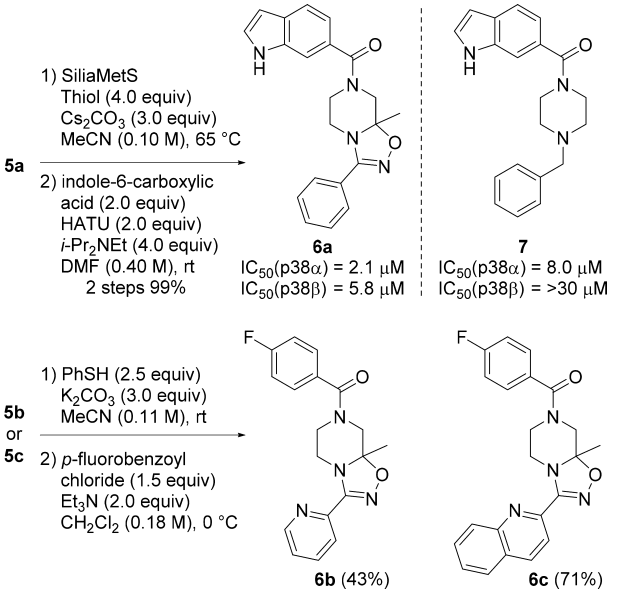
To expand the substrate scope, we then moved on to investigate the reactions of amidoxime derivatives **4**, in which the oxime OH group was expected to work as the second nucleophilic group of the domino cyclization (Scheme 2). The reaction under the same conditions using $Ph_3PAuCl/AgNTf_2$ for amidoxime **4a** provided a [1,2,4]oxadiazolo[4,5-*a*]-piperazine **5a** in 29% yield. Similarly pyridyl and quinolyl derivatives (**4b** and **4c**) were converted to the oxadiazolo-piperazines **5b** and **5c**, respectively. Amidoxime **4d** with a propylene diamine tether was also subjected to the cyclization conditions to provide the [1,2,4]oxadiazolo[4,5-*a*][1,4]-diazepine **5d** via 7-*exo-dig*/5-*exo-trig* cyclizations, although in a lower yield (20%). The *o*-phenylenediamine derivative **4e** reacted smoothly to produce a unique oxadiazole-fused quinoxaline derivative **5e** in 56% yield. These observations imply that this reaction would be applicable to the synthesis of a wide variety of fused triazole and oxadiazole derivatives including piperidines, diazepines, and quinoxalines. As an exception, the reaction of imide-derived amidoxime **4f** provided a monocyclic 1,2,4-oxadiazole **5f′** (46%), likely through the nucleophilic addition of the oxime OH group onto the intramolecular amide carbonyl group in **4f** followed by dehydration.

The resulting [1,2,4]oxadiazolo[4,5-*a*]piperazine scaffold was applied to the development of novel bioactive substances (Scheme 3). Initially, we designed an oxadiazolopiperazine derivative **6a**, which is a ring-constrained analogue of the p38α mitogen activated protein kinase (MAP kinase) inhibitor **7**.[15] It was expected that the 1,2,4-oxadiazole substructure of **6a** could restrict the spatial disposition of the key phenyl group in **7**. We assessed the inhibitory activities against p38 kinase-

Scheme 2. Reaction Scope of Amidoximes



Scheme 3. Synthesis of Oxadiazolopiperazine Derivatives and Their Biological Activities



mediated phosphorylation of a modified erktide by mobility shift assay. Compound **6a** showed more potent inhibition against p38α kinase compared with the simple piperazine derivative **7** [IC_{50}(**6a**) = 2.1 μM; IC_{50}(**7**) = 8.0 μM]. Interestingly, oxadiazolopiperazine **6a** also exhibited potent p38β inhibition [IC_{50}(**6a**) = 5.8 μM], although no inhibition of piperazine **7** was observed at 30 μM. Of note, no inhibitory activities of **6a** and **7** were observed against p38γ and p38δ kinases. Alternatively, we designed and synthesized two

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oxadiazolopiperazine derivatives **6b,c** of an NK3 receptor antagonist, fezolinetant. After removal of the *N*-Ns group of **5b,c**, a fluorobenzoyl group was appended on the piperizine to provide the expected derivatives **6b,c**, respectively. However, no inhibition of **6b,c** against activation of the NK3 receptor was observed by monitoring intracellular Ca^{2+} flux (data not shown).[16]

To identify the contributing isomer of oxadiazolopiperazine **6a** to the bioactivity, two enantiomers (*R*)-**6a** and (*S*)-**6a** possessing a quaternary carbon stereocenter were synthesized via chiral separation using camphorsulfonic acid (see the Supporting Information). When these two isomers were independently evaluated for their inhibitory activity against p38α kinase, the *S*-isomer (*S*)-**6a** exhibited 18-fold more potent bioactivity compared with the *R*-isomer [IC_{50}((*S*)-**6a**) = 1.6 μM; IC_{50}((*R*)-**6a**) = 29.2 μM]. Similarly, (*S*)-**6a** showed more potent inhibition against p38β kinase [IC_{50}((*S*)-**6a**) = 3.6 μM; IC_{50}((*R*)-**6a**) = 163 μM].

In order to rationalize the higher potency of the *S*-isomer (*S*)-**6a**, the possible binding modes of (*R*)-**6a** and (*S*)-**6a** with p38α kinase were estimated by docking simulation using Glide in Schrödinger Suite 2018-1.[17] The docking models were obtained by energy minimization of the complex of each inhibitor and p38α kinase using MacroModel[18] with an OPLS3 force field.[19] For simulation, the crystal structure of the p38α kinase complexed with an imidazo[1,5-*a*]piperazine-type inhibitor **8** was employed (PDB ID: 2QD9; for the structure of **8**, see the Supporting Information), because the 3-phenyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine substructure in **8** was similar to the 3-phenyl-5,6,8,8a-tetrahydro-7*H*-[1,2,4]-oxadiazolo[4,5-*a*]pyrazine part in **6a**. In the crystal structure, a nitrogen atom at the ring junction (position 4 of imidazo[1,5-*a*]piperazine) in **8** interacts with the backbone NH group of Ala34, and the side chains of Lys53 and Asp168 of p38α kinase interact through a water molecule. The binding mode of the less potent (*R*)-**6a** was similar to that of **8**, in which an oxadiazole nitrogen atom interacts with p38α kinase through a water-mediated interaction. The carbonyl oxygen makes hydrogen bonds with the NH groups of Met109 and Gly110 in the hinge region (see the Supporting Information). Interestingly, the more potent (*S*)-**6a** binds with p38α with an alternative binding mode (Figure 2). The indolylcarbonyl group of (*S*)-**6a** occupied the pocket where the phenyl-oxadiazole moiety of (*R*)-**6a** was bound while the phenyl-oxadiazole of (*S*)-**6a** formed an interaction with the hinge region of the p38α kinase. In this model, the oxadiazole nitrogen works as a hydrogen bond acceptor for the backbone NH groups of Met109 and Gly110. Thus, the more potent inhibition of (*S*)-**6a** is likely attributable to the favorable interaction between the [1,2,4]oxadiazolo[4,5-*a*]piperazine scaffold and p38α kinase.

In summary, we developed a facile synthetic process for triazolopiperazines via a gold-catalyzed cascade cyclization of amidrazones having a terminal alkyne moiety. We demonstrated that a variety of fused piperazine derivatives can be constructed by this reaction. Additionally, the resulting oxadiazolopiperazine derivative exhibited potent p38α and p38β kinase inhibition. These types of fused piperazines may be applicable as a promising scaffold to design novel kinase inhibitors.

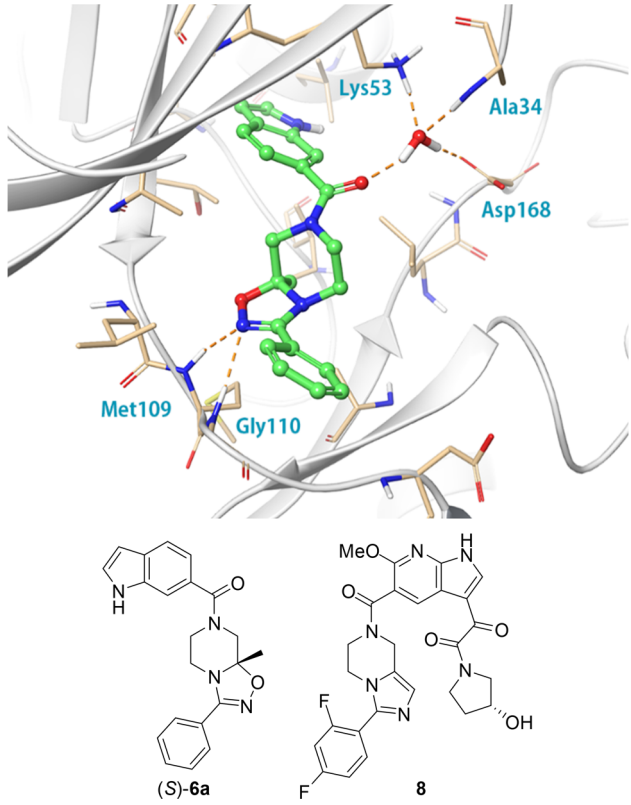

Figure 2. Structures of MAP kinase inhibitors and the binding mode of oxadiazolopiperazine (*S*)-**6a** with p38α kinase.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03500.

Experimental procedures, characterization data for all new compounds (PDF)

Accession Codes

CCDC 1872940 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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