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Discovery of novel 2-(4-aryl-2-methylpiperazin-1-yl)-pyrimidin-4-ones as glycogen synthase kinase-3β inhibitors

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ABSTRACT

We herein describe the results of further evolution of glycogen synthase kinase (GSK)-3β inhibitors from our promising compounds containing a 3-methylmorpholine moiety. Transformation of the morpholine moiety into a piperazine moiety resulted in potent GSK-3β inhibitors. SAR studies focused on the nitrogen atom of the piperazine moiety revealed that a phenyl group afforded potent inhibitory activity toward GSK-3β. Docking studies indicated that the phenyl group on the piperazine nitrogen atom and the methyl group on the piperazine make cation-π and CH-π interactions with GSK-3β respectively. 4-Methoxyphenyl analogue **29** showed most potent inhibitory activity toward GSK-3β with good in vitro and in vivo pharmacokinetic profiles, and **29** demonstrated a significant decrease in tau phosphorylation after oral administration in mice.

In a previous paper, we described the transformation of the morpholine moiety of previously reported GSK-3β inhibitors with a 2-(2-phenylmorpholin-4-yl)-pyrimidin-4-one skeleton such as UDA-680 into the corresponding piperazine analogues. A docking study indicated that potent inhibitory activity of phenylpiperazine analogues toward GSK-3β was attributed to hydrogen bonding between the nitrogen atom of the piperazine moiety and the oxygen atom of the main chain of Gln185 which was not observed for the phenylmorpholine analogues.[1] We also reported that the alkylmorpholine analogues generally showed potent GSK-3β inhibitory activity together with a certain level of CYP inhibition probably due to the 3-fluoropyridin-4-yl group at the 6-position of the pyrimidone moiety. Based on the information about hydrogen bonding of the piperazine moiety, we hypothesize that transformation of the alkylmorpholine moiety into the corresponding piperazine moiety would introduce new hydrogen bonding toward the enzyme indicated by the docking study of the phenylpiperazine, and that a potential increase in activity by this interaction would enable a transformation of the 3-fluoropyridin-4-yl moiety into a pyridine-4-yl or a pyrimidin-4-yl moiety which would lead to evolution of a new chemical series with decreased CYP inhibition. Namely, we designed 2-methylpiperazine analogues by transforming the morpholine moiety of 3-methylmorpholine analogues such as **1** shown in Fig. 1.[2] In this paper we describe results of the transformation and successive optimization of alkylpiperazine derivatives **2**.

Preliminary results of the transformation of the 3-methylmorpholine moiety into a 2-methylpiperazine moiety are shown in Table 1.[3] Simple transformation of the oxygen atom of the (*R*)-3-methylmorpholine into a nitrogen atom was well tolerated and **3** and **5** showed good inhibitory activity, nearly 2-fold more active for a 4-pyrimidinyl analogue than for a 4-pyridyl analogue. Introduction of a methyl group on the nitrogen atom of the piperazine showed a 2- to 3-fold decrease in activity (**3** vs **4**, **5** vs **6**). The effect of the (*R*)-2-methyl group was clearly observed by comparing it with that of des-methyl piperazine analogue **11**, indicating that

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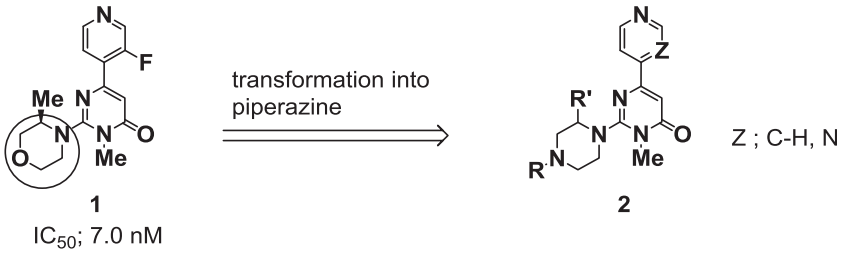
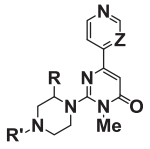


Fig. 1. Transformation of morpholine moiety.

Table 1
Preliminary structure-activity relationship of 2 and/or 4-substituted piperazine derivatives.



Piperazine	Compound	Z	R'	GSK-3β inhibition (IC_{50}, nM)
	**3**	C—H	H	29
	4	C—H	Me	80
	5	N	H	13
	6	N	Me	22
	**7**	C—H	H	920
	8	C—H	Me	>1000
	9	N	H	76
	10	N	Me	>1000
	**11**	N	Me	630

introduction of a (*R*)-methyl group afforded a nearly 30-fold increase in activity. The methyl group with (*S*)-configuration generally showed a large decrease in activity. For example, **7** and **9** showed a 6 to 30-fold decrease in activity compared with the corresponding (*R*)-isomers, **3** and **5**, respectively, and *N*-methyl analogues **8** and **10** lost the activity. The (*S*)-2-methyl group seemed detrimental to the inhibitory activity compared with des-methyl analogue **11** which still had weak inhibitory activity.

In order to analyze the effects of the piperazine moiety, an induced fit docking simulation of **1** and **5** with GSK-3β was performed.[4] Fig. 2 shows that the pyrimidone moiety of both compounds makes interactions which are common to our pyrimidine-type GSK-3β inhibitors. The nitrogen atom at the 1-position of the pyrimidin-4-yl group makes hydrogen bonding with the main chain of Val135 in the hinge region, and the carbonyl oxygen atom of the pyrimidone moiety forms hydrogen bond with the side chain of Lys85.[2,5] The methyl group of 3-(*R*)-methylmorpholine of **1** was buried in a hydrophobic pocket of the active site in the enzyme.[2] The amino moiety of the piperazine of **5** makes hydrogen bonding with the oxygen atom of the main chain of Gln185. This hydrogen bonding is the same interaction as that of phenylpiperazine.[1] And the methyl group with (*R*)-configuration on the piperazine makes a CH-π interaction with Phe67. We consider that the interaction between the piperazine and Gln185 would rotate the piperazine moiety, which would result in making a CH-π interaction between the methyl group of the piperazine and Phe67.

The effect of the configuration of the methyl group was also analyzed using docking simulation (Fig. 3). The (*R*)-enantiomer, **5** makes a CH-π interaction with Phe67 and hydrogen bonding with

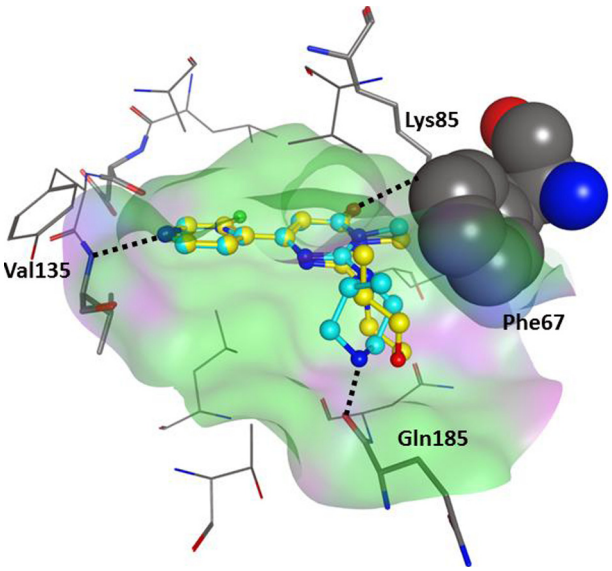


Fig. 2. Docking model of **1** (yellow) and **5** (cyan) with GSK-3β.

Gln185. The docking study suggests that there are no effective interactions between the enzyme and the piperazine moiety of **9** which have (*S*)-configuration at the methyl group. We think lack of effective interactions between the piperazine moiety of **9** and the enzyme leads to decreased inhibitory activity of **9**.

Preliminary in vitro pharmacokinetic studies indicated that **5** had no CYP450 inhibition (>50 μM, recombinant human CYP1A2,