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Short communication

Synthesis of potential Rho-kinase inhibitors based on the chemistry of an original heterocycle: 4,4-Dimethyl-3,4-dihydro-1*H*-quinolin-2-one

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Abstract

A new series of substituted 4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one have been prepared via condensation of 3,3-dimethylacryloyl chloride with aniline. Details of synthetic procedures are shown. Our aim was to investigate the potency of our original heterocycle in the inhibition of the Rho-kinase enzyme, known to be of major importance in the cascade reactions leading to arterial hypertension. Biological activity for the seven compounds has been investigated and is presented.
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1. Introduction

Hypertension, commonly referred to as ‘‘high blood pressure’’, is a medical condition where the blood pressure is chronically elevated. It is one of the most important cardiovascular risk factors (as diabetes mellitus, dyslipidemia and tobacco) all over the world. Twenty percentage of the industrial population is concerned according to the World Health Organization.

This disease is defined by a rise in the blood pressure in the arteries due to the abnormal contraction of the smooth muscle. The contraction being regulated by the cytosolic calcium concentration to which the Rho/Rho-kinase intracellular pathway is associated, designing compounds that inhibit the enzyme seem to be of great interest [1–5]. Different kinds of molecules have already been studied. Two of most effective inhibitors of Rho-kinase are now considered as the research leaders: Y-27632, a pyridine derivative which selectively inhibits smooth-muscle contraction by inhibiting Ca^{2+} sensitization [6–8], and HA-1077, an isoquinolinesulfonamide derivative which has an antispatic effect on the cerebral artery [9–11] (Fig. 1).

Considering these two molecules Takami et al. [12] studied Rho-kinase ligand-binding site. They described it as a three region (A, F and D) pocket. The A region, composing the bottom of the cavity, is flat and possesses an amine function (NH of Met 167) allowing the formation of a hydrogen bond with any heteroatom correctly oriented. The F region is spherical and relatively spacious. Docking simulation indicated that several chemical fragments could occupy this space especially planar linkers such as amide or urea moieties. The third region (D region) being also hydrophobic and cleft-like in shape, substituents should preferably be aromatic (Fig. 2).

Inspired by Takami et al.’s work [13,14], we elaborated new potential Rho-kinase inhibitors investigating the synthesis of 4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one [15]. This 6–6 ring system should enable the substrate to settle Rho-kinase’s active site twice by the presence of its two hydrogen acceptors. Hopefully thinking of imitating the HA-1077 sequence we

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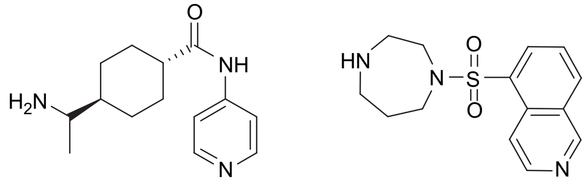


Y-27632 **HA-1077**

Fig. 1. Two most effective inhibitors of Rho-kinase.

also wished to evaluate the relevance of the same sulfonamide linker.

2. Chemistry

The sulfonyl chloride key intermediate was synthesized in three steps starting from the commercially available aniline. Condensation of 3,3-dimethylacryloyl chloride in pyridine yielded the desired amide **1** [16] which was further cyclized by a Friedel and Crafts reaction [17]. Chlorosulfonylation of the quinolinone **2** was then carried out under rather drastic conditions: direct introduction into pure chlorosulfonic acid (Scheme 1).

The last step to afford the desired sulfonamide derivatives was carried out either in dichloromethane with triethylamine or by using pyridine as the solvent as well as the required base.

It is noteworthy we investigated among others the insertion of 2-methylpiperazine described by Hidaka [18,19] as a more rigid configuration of the homopiperazine moiety of HA-1077 (Scheme 2).

In order to investigate the relevance of the linker's sequence, the synthesis of a molecule containing a switched linker was also elaborated as shown in Scheme 3. Classical methylation reaction provided the expected product starting from the amide **2**. Several attempts were necessary to find the right conditions in order to afford the correctly substituted nitro-intermediate **11**. First cyclization of 3-methyl-*N*-(4-nitrophenyl)but-2-enamide was investigated but never we were able to achieve the reaction within the conditions previously elaborated. Nitration of the intermediate **10** was therefore carried out in an inert solvent where the nitronium ion NO_2^+ is directly generated by concentrated nitric acid (Scheme 3).

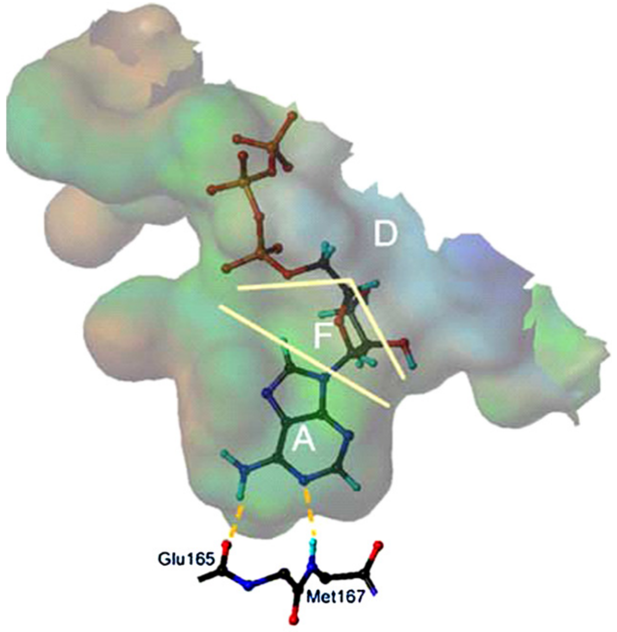
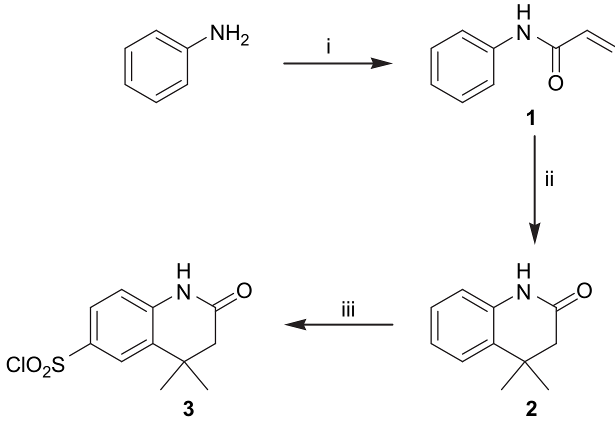


Fig. 2. Ligand-binding pocket of Rho-kinase homology model. A docking model of ATP is shown. Hydrogen bonds between N1 of ATP and HN of Met167, and the amino group at the 6-position and C═O of Glu165 are indicated as dashed lines [12].



Scheme 1. Synthesis of 4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonyl chloride. *Reagents*: (i) 3,3-dimethylacryloyl chloride, pyridine; (ii) $AlCl_3$, DCM; (iii) $ClSO_3H$.

The best conditions were identified as being the addition of nitric acid at 0 °C in dichloromethane. The reduction was next carried out under rather mild conditions with tin(II) chloride dihydrate to afford the amine derivative **12** in a good yield. Treatment with a pretty bulky and flat sulfonyl chloride led to the desired sulfonamide **13** (Scheme 4).

3. Biological activity

The seven synthesized compounds have been studied for possible future biological functions.

3.1. Purification of the recombinant Rho-kinase

The plasmid encoding for human Rho-kinase as a fusion protein with glutathione-*S*-transferase was a generous gift from Prof. Pierre Pacaud (Nantes). The protein was expressed by baculovirus infection of the Tn5 insect cell line. Fifty milliliters of Tn5 cells (1 L of culture) was solubilized in 150 mL of extraction buffer (20 mM Tris–HCl, pH 7.2, 10 mM glycerophosphate, 10 mM $MgCl_2$, 100 μM EGTA, 1 mM DTT, including complete Roche® protease inhibitor cocktail). The suspension was sonicated three times for 15 s in cold. The extract was then centrifuged (10,000*g*, 15 min, 4 °C) and the pellet thereof was re-suspended in the same buffer, sonicated and centrifuged as above. Both supernatants were saved and used as material for the purification of the enzyme. In brief, affinity chromatography was achieved on a glutathione–sepharose column equilibrated in the extraction buffer. Four hundred

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