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ROCK inhibitors 3: Design, synthesis and structure-activity relationships of 7-azaindole-based Rho kinase (ROCK) inhibitors

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ABSTRACT

Rho kinase (ROCK) inhibitors are potential therapeutic agents for the treatment of a variety of disorders including hypertension, glaucoma and erectile dysfunction. Here we disclose a series of potent and selective ROCK inhibitors based on a substituted 7-azaindole scaffold. Substitution of the 3-position of 7-azaindole led to compounds such as **37**, which possess excellent ROCK inhibitory potency and high selectivity against the closely related kinase PKA.

The Rho kinases (ROCK) are Ser/Thr kinases of the AGC-family involved in the regulation of vital cellular processes such as motility, morphology, division, differentiation and contraction [1]. Two kinase isoforms, ROCK-1 and ROCK-2, have been identified that share 65% overall sequence homology and 92% sequence identity in their ATP-binding domain [2]. Activation of ROCK by GTP-bound Rho leads to phosphorylation of various protein substrates, including most notably myosin light chain (MLC) and myosin phosphatase-both regulators of smooth muscle contraction [3]. Thus, ROCK inhibitors may have clinical potential as treatments for a variety of disorders such as hypertension [4], glaucoma [5] and erectile dysfunction [6]. To date, three ROCK inhibitors have been approved for clinical use: fasudil (**1**), approved for the treatment of cerebral vasospasm [7] in Japan and China; ripasudil (**2**) approved in Japan for the treatment of glaucoma [8]; and more recently, a third ROCK inhibitor, netarsudil (**3**), has been approved for the treatment of elevated intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension [9].

In addition to these compounds, many classes of ROCK inhibitor have been reported [10], including some containing a 7-azaindole moiety (Fig. 1: compounds **4**–**7**). LoGrasso et al. reported azaindole-based inhibitors of ROCK such as **4**, however in these inhibitors the kinase hinge-binding element is the pyrazole group [11,12]. Uehata et al. reported the first valuable ROCK inhibitor tool molecules, including the 7-azaindole derivatives **5** (Y-30141) and **6** (Y-39983) in the original [13] and subsequent reports [14]. Shirock et al. reported a series of 3-methyl-4-substituted 7-azaindole inhibitors of ROCK, represented by compound **7** [15,16]. Notable among these latter, hinge-binding 7-azaindoles, is the common 4-substitution. Herein, we report SAR evolution of our previously reported 4-pyridyl ROCK inhibitors to 3-substituted 7-azaindoles: this non-obvious substitution was guided by structure-based design.

We previously reported compound **8** in the development of a series of 4-pyridyl-based ROCK inhibitors [17]. To further improve our ROCK inhibitors we focused on optimizing physicochemical properties and reducing the CYP inhibition liability observed within this series. Although the 2-aminopyridine **8** showed good ROCK inhibition (K_i = 165 nM), and 11-fold selectivity against PKA (a closely homologous AGC-family kinase) this compound was less potent and selective relative to other 2-substituted pyridines [17]. The X-ray crystal structure of compound **8** bound to ROCK-1 shows a similar binding conformation as previously reported for the 2-unsubstituted system [17]. Notably, hydrogen bonds exist between the pyridine ring nitrogen 2-amino group and the backbone NH and CO of Met156 respectively, between the amide carbonyl and the side chain of Lys105, and between the methoxy group and the NH of both Ala86 and Phe87 of the Gly-rich loop (Fig. 2). It should also be noted that the pyridine and thiazole rings are in a co-planar arrangement.

To further develop this series of ROCK inhibitors, we were interested in evaluating analogous compounds, in which the 2-amino substituent of **8** is connected to the pyridine ring through a two-carbon (vinyl) spacer forming a 4-substituted 7-azaindole ring system, as illustrated in Fig. 3.

However, conformational analysis of this 2-dimensional design showed that the desired coplanarity of the azaindole and thiazole rings

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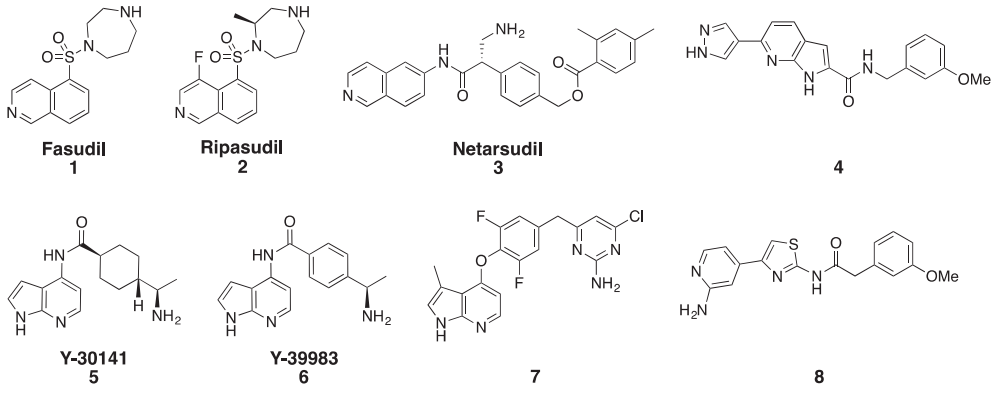

Fig. 1. ROCK inhibitors.

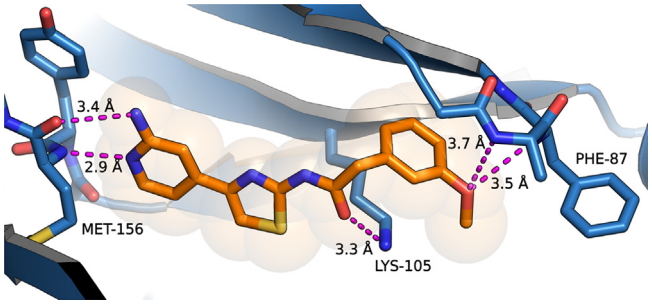

Fig. 2. Compound **8** bound to ROCK-1 (PDB ID: 5UZJ).

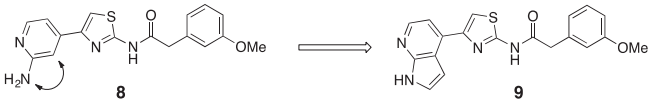

Fig. 3. Ring constraint to 4-substituted 7-azaindole system.

would likely be less energetically favorable. The torsional strain around the biaryl bond of this system is illustrated in Fig. 4A.

The lowest energy state for the 4-thiazol-4-yl-7-azaindoles occurs when the two ring systems are at approximately 45° – poorly aligned for optimal kinase active site binding. Conformations in which the azaindole and thiazole rings are co-planar (0° and 180°) are at high relative energies. However, when the biaryl connection is shifted to the 3-position of 7-azaindole, the lowest energy conformation occurs when the thiazole and azaindole rings are coplanar, with the azaindole pyridine ring adjacent to the thiazole nitrogen (Fig. 4B, 180°). The opposite coplanar conformation (0° as illustrated in Fig. 4B), is at a higher, though not maximal, energy which occurs when the ring systems are perpendicular. With the understanding that this structure possesses the important low-energy coplanarity of the two ring systems, the question remained whether a 3-substituted 7-azaindole compound would still form effective hydrogen bond interactions with the hinge region of ROCK, while maintaining the other important binding interactions between inhibitor and enzyme. Molecular modeling of the 3-substituted-7-azaindole system docked in the ROCK active site suggested that, despite the shift of substitution from the pyridyl ring (4 position substituted azaindole) to the pyrrole ring (3 position substituted azaindole), the relative location of the pyridine nitrogen would still support hydrogen bonding with Met156. Thus we hypothesized that the 7-azaindole system might provide an alternative hinge-binder to replace 2-aminopyridine and, counter intuitively, that the 7-azaindole 3-position might provide both a suitable vector to direct substituents, as well as an appropriate 3-dimensional configuration. Contacts with the enzyme that had previously been exploited were expected to be retained. To test this hypothesis, compounds were prepared bearing the 2-

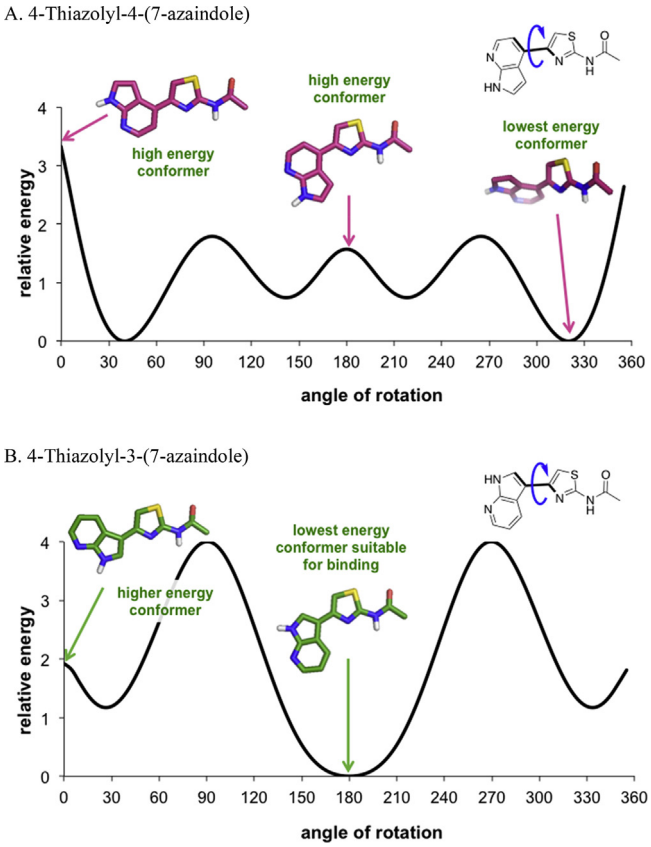

Fig. 4. Torsion drive of biaryl systems illustrating relative energy (kcal/mol) plotted against angle of rotation [18].

(phenylacetylamino)-thiazole substituent at both the 3- and 4-position on the 7-azaindole ring.

The synthesis of 4-substituted azaindole compounds **9** and **13** was achieved in six steps, as shown in Scheme 1. Benzenesulfonyl protection of 4-chloro-7-azaindole **10**, followed by reaction with 1-ethoxyvinyl tri-*n*-butyltin in the presence of $PdCl_2(PPh_3)_2$ yielded enol-ether **11** in moderate yield. Reaction of **11** with NBS afforded α-bromoketone **12**, which was reacted with thiourea, to afford the aminothiazole ring system. Subsequent acylation and followed by acidolytic removal of the benzenesulfonyl protecting group afforded compounds **9** and **13**.

3-Substituted-7-azaindoles (**17**–**32**) were prepared in three steps as shown in Scheme 2. Friedel-Crafts acylation of commercially available 7-azaindole **14** with bromoacetyl bromide in dichloromethane afforded 3-(2-bromoacetyl)-7-azaindole **15** in 64% yield. Hantzsch thiazole synthesis using thiourea in refluxing EtOH the thiazole **16** in 83% yield.