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Research paper

Synthesis, biological evaluation and molecular modeling of a novel series of 7-azaindole based tri-heterocyclic compounds as potent CDK2/Cyclin E inhibitors

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ABSTRACT

From four molecules, inspired by the structural features of fascaplysin, with an interesting potential to inhibit cyclin-dependent kinases (CDKs), we designed a new series of tri-heterocyclic derivatives based on 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) and triazole heterocycles. Using a Huisgen type [3 + 2] cycloaddition as the convergent key step, 24 derivatives were synthesized and their biological activities were evaluated. Comparative molecular field analysis (CoMFA), based on three-dimensional quantitative structure–activity relationship (3D-QSAR) studies, was conducted on a series of 30 compounds from the literature with high to low known inhibitory activity towards CDK2/cyclin E and was validated by a test set of 5 compounds giving satisfactory predictive r^2 value of 0.92. Remarkably, it also gave a good prediction of pIC_{50} for our tri-heterocyclic series which reinforce the validation of this model for the pIC_{50} prediction of external set compounds. The most promising compound, **43**, showed a micro-molar range inhibitory activity against CDK2/cyclin E and also an antiproliferative and proapoptotic activity against a panel of cancer cell lines.

1. Introduction

Cyclin-dependent protein kinases (CDKs) are universal eukaryotic cell cycle regulators that promote the passage through the restriction point, initiation of DNA replication, and mitosis [1]. Given the fact that CDKs have oncogenic potential and are amenable to pharmacological inhibition, their inhibitors have therefore attracted great interest as potential anticancer agents [2,3].

As a part of our research on medicinal chemistry, we are interested in developing new CDK inhibitors (CKIs), in particular towards CDK4/cyclin D and CDK2/cyclin E, since they both participate in the phosphorylation of the retinoblastoma protein (pRb). Each member of the pRb pathway (such as CDK4(6)/cyclin D, p16 and CDK2/cyclin E), which activates the transcription factors at the G1-S transition phase, which in its turn regulates the expression of several genes involved in DNA replication, can be deregulated in cancers. In some human cancers (such as lung cancer or leukemia), cyclin E (E1/E2) is over-expressed and CDK2 is hyper-activated [4]. Therefore, many CKIs have been developed and some of them are undergoing clinical trials [5]. Most inhibitors that entered clinical trials belong to the group of pan-selective CDK inhibitors [6], but some highly selective CDK inhibitors like THZ1 [7] or PD-0332991 [8] were also described (Fig. 1). However, simultaneous targeting of multiple CDKs (particularly CDK1 and 2) seems to be more

Abbreviation: CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5.

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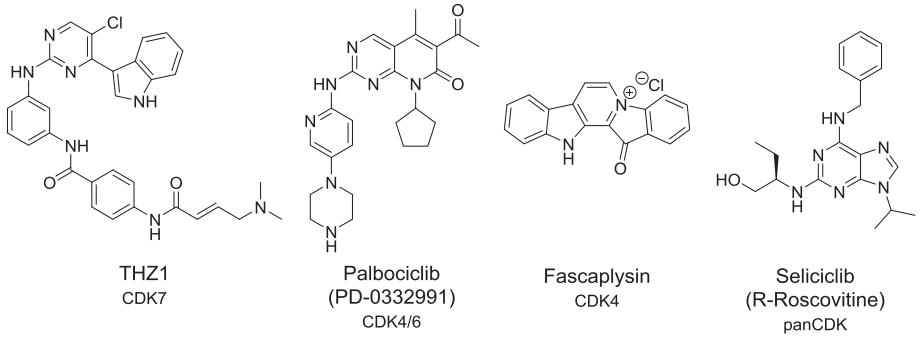

Fig. 1. Selected CDK inhibitors and their main CDK target.

advantageous in terms of anticancer activity, because many CDKs can compensate for the lack of others in cancer cells [9,10]. In addition, the knowledge about CDKs is growing constantly and it is still unclear whether observed effects are due to the activity of any single CDK or combinations of CDKs.

Since our laboratory has an expertise in the heterocyclic chemistry domain and by analogy with the structural features of a known CKI, fascaplysin [11] (IC_{50} CDK4/D = 0.35 μM) (Fig. 1), as other groups did with indole analogues [12–14], we designed and synthesized four novel heterocyclic molecules (**21**, **22**, **24** and **37**) (Figs. 2 and 3). **21** and **37** are composed of two 7-azaindole heterocycles linked each other by a 1,4- or 1,5-triazole type linker. The

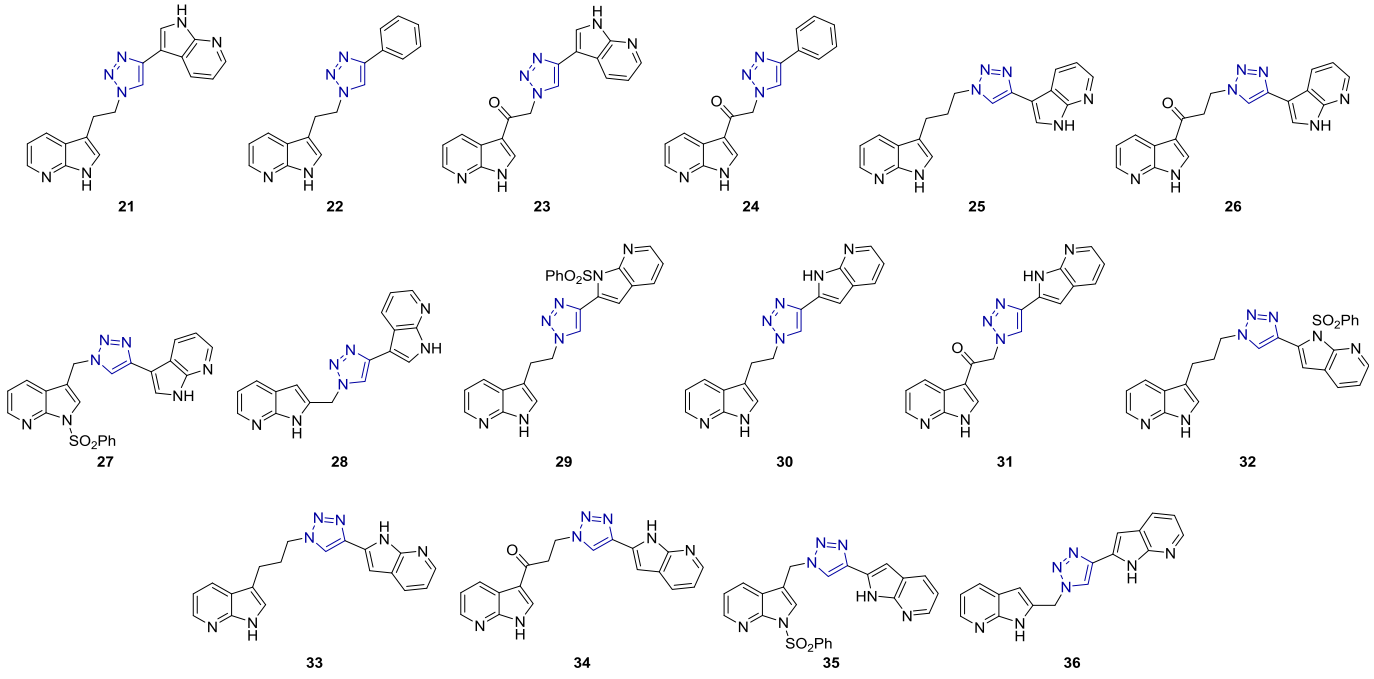

Fig. 2. 1,4-disubstituted triazole derivatives **21**–**36**.

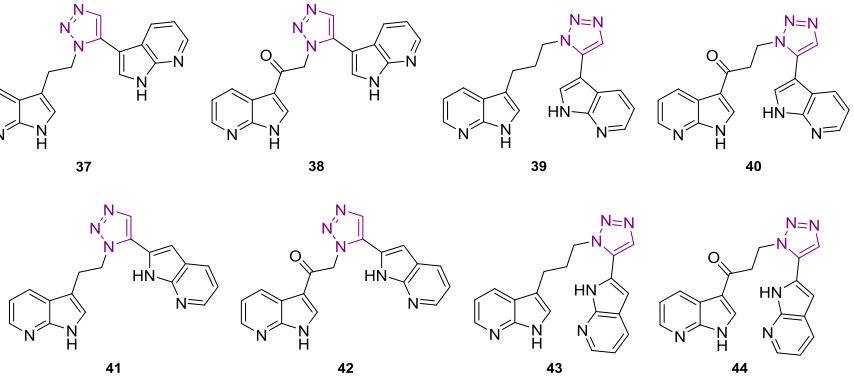

Fig. 3. 1,5-disubstituted triazoles derivatives **37**–**44**.