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Design and synthesis of novel imidazo[4,5-*b*]pyridine based compounds as potent anticancer agents with CDK9 inhibitory activity

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ABSTRACT

New imidazo[4,5-*b*]pyridine derivatives were designed, synthesized and screened for their anticancer activity against breast (MCF-7) and colon (HCT116) cancer cell lines. Nine compounds (**I, II, IIIa, IIIb, IV, VI, VIIa, VIII, IX**) showed significant activity against MCF-7, while six compounds (**I, VIIc, VIIe, VIIf, VIII, IX**) elicited a remarkable activity against HCT116. Compounds showing significant anticancer activity revealed remarkable CDK9 inhibitory potential (IC_{50} = 0.63–1.32 μM) relative to sorafenib (IC_{50} = 0.76 μM). Moreover, a molecular docking study was performed to illustrate the binding mode of the most active compounds in the active site of CDK9 where it revealed superior binding affinity relative to the natural ligand (T3C).

1. Introduction

Cancer is considered as the second leading cause of death after cardiovascular diseases [1]. Targeted chemotherapeutic agents have advantages over the traditional ones due to their selectivity towards cancer cells and their lower side effects [1].

Cyclin Dependent Kinases (CDKs) are a group of serine/threonine kinases. They are instrumental regulatory enzymes involved in cell cycle progression and cell proliferation. Their hyperactivity in breast, lung as well as colorectal tumors contributes to cancer cell proliferation, accordingly their inhibition is a valid targeted anticancer approach [2,3]. Nevertheless, cells lacking CDK 2, 4 and 6 can proliferate normally [4]. Thus in many cancer cases specifically targeting those CDKs may not result in optimum activity. This may be due to cell compensation mechanisms and functional substitution. This drew the attention to target the CDKs affecting transcription, namely CDK9/7 [5].

CDK9 regulates the RNA transcription of short-lived anti-apoptotic proteins [6]. Literature review revealed that the scaffolds showing CDK9 inhibitory action include chromones, thiazole [7], pyrimidines [5,8,9], macrolides [10], imidazoles, purines, and aminopyrazole [7,11].

It is worth pointing out that, the imidazoline derivative **A** is a potent CDK9 inhibitor with promising anticancer activity against HCT116 colon cancer cell line [12]. Furthermore, the imidazo[4,5-*b*]pyridine **B** was reported to have a potent anti-proliferative activity against MCF-7 (IC_{50}: 0.58–78.66 μM) and HCT116 (IC_{50}: 0.49–87.33 μM) cancer cell lines via selective inhibition of CDK9 [12,13] (Fig. 1). Accordingly, the present study deals with the design and synthesis of new imidazo[4,5-*b*] pyridines as potential anticancer agents targeting CDK9 enzyme with improved activity.

The synthetic route adopted to prepare the new imidazo[4,5-*b*] pyridine derivatives was based on reaction of the key intermediate 4((1*H*)-imidazo[4,5-*b*]pyridine-2-yl)aniline **I** with either diethyl ethoxymethylenemalonate to obtain **II** followed by cyclization to the appropriate pyrazolidine **IIIa,b** and **IV,** pyrimidine **Va,b**, triazepine **VI** or via diazotization of the amino functionality of **I** followed by coupling with phenol, aniline or active methylene derivatives to afford **VIIa-f**, **VIII** and **IX,** respectively. The biological evaluation of the synthesized compounds was performed in terms of anti-proliferative activity against MCF-7 and HCT 116 cancer cell lines and CDK9 enzyme inhibitory assay. Furthermore, a docking study of the synthesized imidazo[4,5-*b*] pyridine compounds and the native ligand T3C was carried out in the CDK9 active site in order to explore and compare their binding mode and validate their mechanism of action.

2. Results and discussion

2.1. Chemistry

The novel imidazo[4,5-*b*]pyridine derivatives were synthesized according to Schemes 1 and 2. 4-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)aniline **I**

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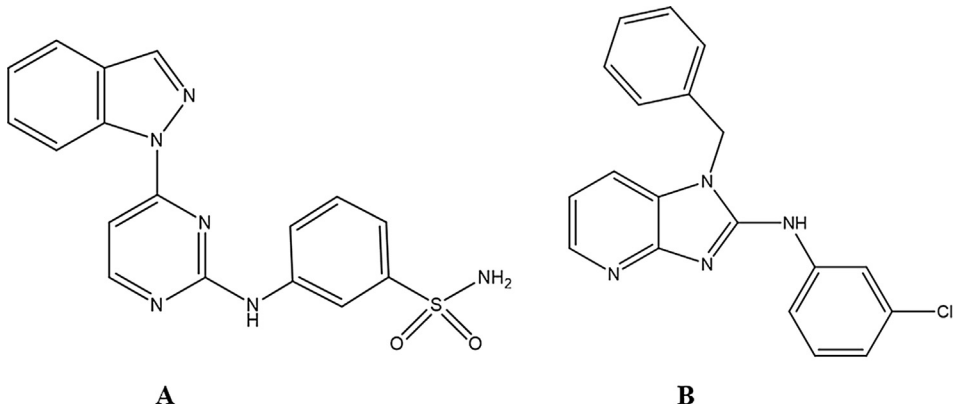
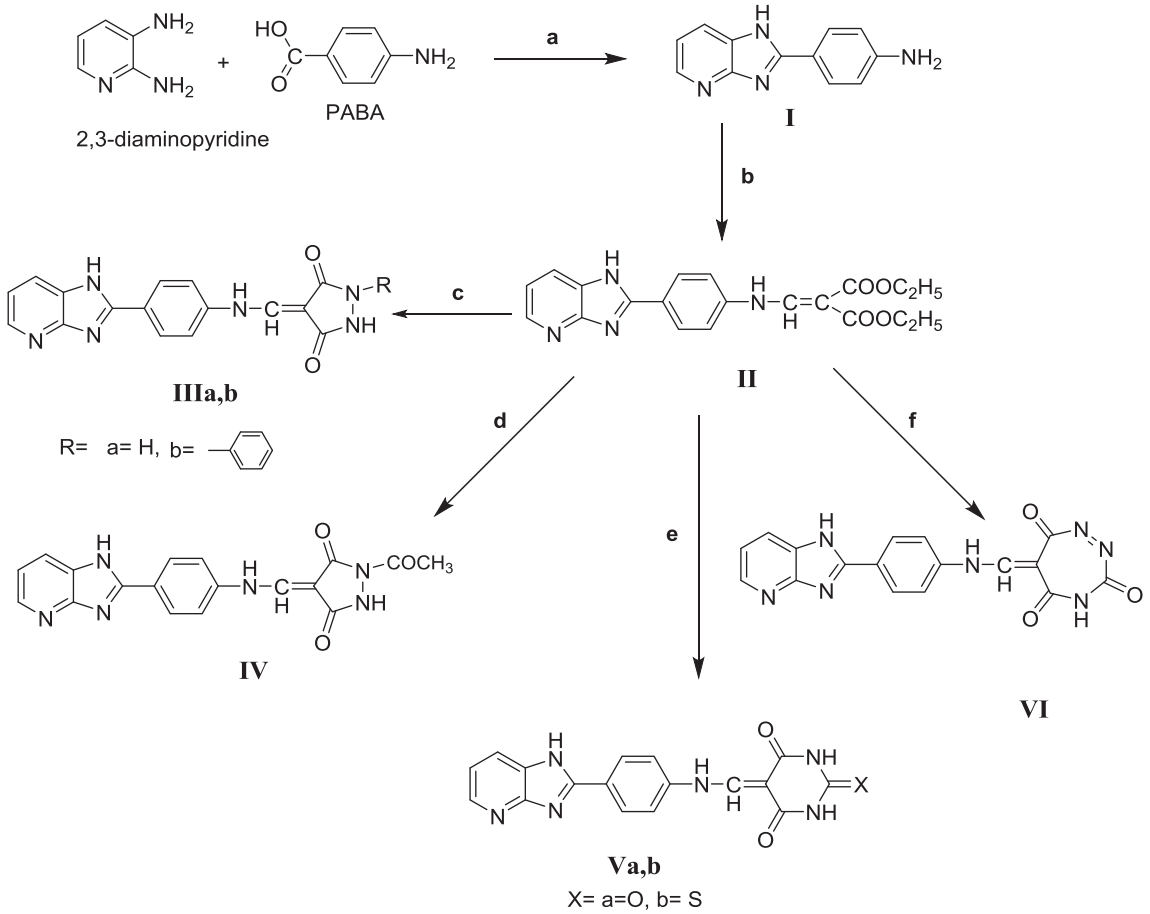


Fig. 1. Structures of potent anti-proliferative agents.

was prepared via condensation of 2,3-diaminopyridine with 4-aminobenzoic acid (PABA) in the presence of polyphosphoric acid (PPA). IR spectrum of **I** showed a forked band at 3344 and 3300 cm^{-1} assigned to NH_2 group, a broad band at 3128–3400 cm^{-1} attributed to NH group. ^1H NMR spectrum revealed two exchangeable singlet signals at 2.50 and 5.69 ppm attributed to NH and NH_2 protons respectively, in addition to doublet, doublet of doublet and doublet signals at 7.84, 7.90 and 8.20 ppm, respectively corresponding to pyridine protons. Reaction of **I** with diethyl ethoxymethylenemalonate in absolute ethanol resulted in the diethyl methylenemalonate derivative **II**. IR spectrum showed a strong band at 3402–3325 cm^{-1} attributed to NH groups in addition to a band at 1708–1689 cm^{-1} assigned to C=O of ester. ^1H NMR spectrum revealed the presence of the two geometrical isomers appearing as two adjacent singlet signals assigned to the olefinic proton at 5.92–5.94 ppm equal to 0.5 proton which does not disappear after D_2O, the triplet quartet pattern at 1.22 and 1.28 ppm and 4.11 and 4.22 ppm



Reagents and reaction conditions: a: PPA, 220 °C, 3h, **b:** diethylethoxymethylene malonate / ethanol, reflux 6 h, **c:** hydrazine hydrate/phenyl hydrazine, Na ethoxide in ethanol, reflux 6 h, **d:** hydrazine hydrate in glacial acetic acid, reflux 6 h, **e:** urea or thiourea / Na ethoxide in ethanol, reflux 6 h, **f:** semicarbazide / Na ethoxide in ethanol, reflux 6 h.

Scheme 1. Synthesis of 1*H*-imidazo[4,5-*b*]pyridine derivatives **I-VI**.