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Original article

Design, synthesis and molecular modeling of pyrazole–quinoline–pyridine hybrids as a new class of antimicrobial and anticancer agents

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ABSTRACT

A new series of pyrazole–quinoline–pyridine hybrids were designed based on molecular hybridization technique and synthesized by a base-catalyzed cyclocondensation reaction through one-pot multicomponent reaction. All compounds were tested for *in vitro* antibacterial and anticancer activities. Enzyme inhibitory activities of all compounds were carried out against FabH and EGFR. Of the compounds studied, majority of the compounds showed effective antibacterial as well as anticancer activity against used strains and cancer cell lines respectively. Compound **7k** ($IC_{50} = 0.51 \pm 0.05$ μM) against EGFR and **7b** displayed the most potent inhibitory activity with IC_{50} of 3.1 μM against FabH as compared to other member of the series. In the molecular modeling study, compound **7k** was bound in to the active pocket of EGFR with three hydrogen bond and one π–cation interaction with minimum binding energy $\Delta G_b = -54.6913$ kcal/mol, as well as compound **7b** was bound in to the active site of FabH with hydrogen bond and π–sigma interactions with minimum binding energy $\Delta G_b = -45.9125$ kcal/mol.

1. Introduction

Along with the living habits and environment changes, cancer has become the major cause of death in both developing and developed countries [1]. Until now one significant way to induce the occurrence of cancers is still by mutation or mis-regulation of cell cycle regulatory genes and proteins to guide an abnormal control of cell proliferation [2]. Epidermal growth factor receptor (EGFR) is a kind of tyrosine kinase firstly reported in the literature [3,4]. It has become one of the targets of anticancer drug research and development because of it's widely distribution in the cell and important role in cell life. EGFRs are distributed in mammalian epithelial cell membranes and have relationships with cell proliferation, death, and differentiation. They are junctions to deliver extracellular growth signals intracellular. EGFR family comprise four members, including: EGFR (HER1/ErbB-1), ErbB-2 (HER2/neu), ErbB-3 (HER3), and ErbB-4 (HER4) [5]. EGFR tyrosine kinase-mediated cell growth signaling pathway plays an important role in the formation and development of many types of solid tumors, such as nonsmall cell lung cancer [6], head and neck cancer [7] and glioblastomas [8]. Overexpression of EGFR family receptors have always been observed in these tumors, approximately in 60% of all tumors [6]. EGFR and ErbB-2 are the hottest targets in current research and their over expression or abnormal activation often cause cell malignant transformation. Also they have relationship with postoperative adverse, radiotherapy and chemotherapy resistance and tumor angiogenesis [9].

Besides, bacteria resistant to known therapies are a growing threat across the globe. An increasing fraction of bacterial isolates shows reduced susceptibility to our most trusted antibiotics. In order to prevent this serious medical problem, the discovery of new types of antibacterial agents or the expansion of bioactivity of the previous drugs is a very important task [10]. Therefore, in recent years, the research has been focused on the development of new antibacterial agents, which may act through structure design and novel targets, overcoming the problem of acquired resistance. One of the most attractive biochemical pathways that could be targeted for new antibacterial agents is the fatty acid biosynthesis (FAS). This pathway has been demonstrated to be essential for the bacteria cell survival [11] and differs considerably from human FAS pathway. While in humans fatty acid synthesis occurs in a homodimeric multifunctional enzyme [12,13] in bacteria the pathway is composed of various discrete enzymes and each one can be considered a putative molecular target. Those features make the type II FAS pathway a potential target for new antimicrobial agents.

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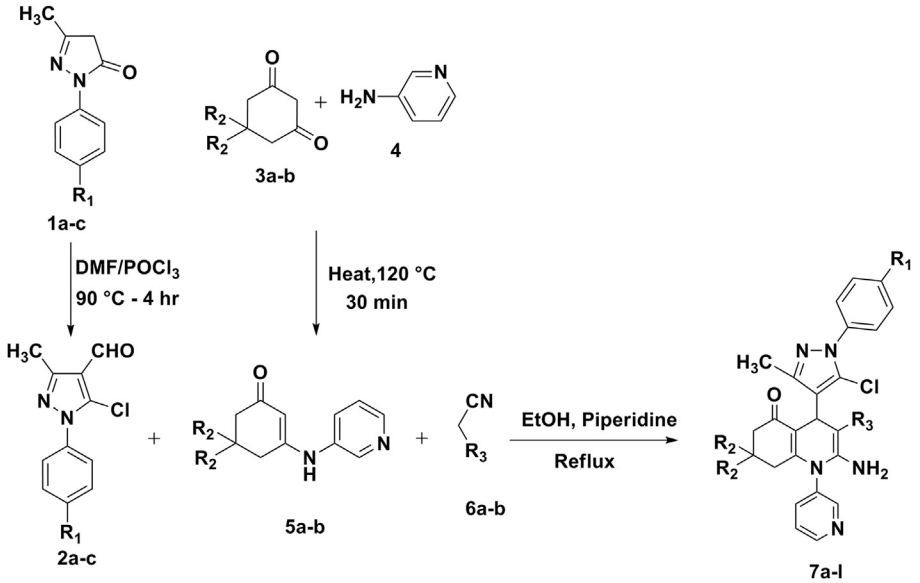
A key enzyme in this pathway is the β-ketoacyacyl carrier protein synthase III (FabH), which is the responsible enzyme of the first pathway reaction and play an important regulatory role. FabH has also been demonstrated to be essential for organism survival and it is presented in a wide number of important human pathogens. Furthermore, some chemical compounds have shown to inhibit FabH from diverse microl-organisms, including multi-drug resistant strains [14,15] These facts support the idea that FabH can be used as an effective molecular target for the development of new antimicrobial agents. Over the past few years, we have been principally engrossed in the synthesis of pyrazole incorporating structures for biological evaluations [16–21] on the premise that the several 4-functionally substituted *N*-arylpyrazole derivatives identified as antimicrobial [22–24], anti-inflammatory (COX-2 inhibitor and ulcerogenic activity) [23], antitubercular [24], antitumor [25,26], anticancer [27–30] as well as inhibitory activity against FabH [31]. Furthermore, quinoline moiety is found in a large variety of naturally occurring compounds and also chemically useful synthons bearing diverse bioactivities [32–42] including EGFR inhibitory activity [43]. Also, no one can ignore the role of pyridine as an appreciable pharmacophore for antimicrobial and anticancer activity [44,45] including EGFR inhibitory activity [46]. Moreover, multicomponent reactions were employed as a powerful tool to synthesize diverse and complex heterocyclic compounds due to their advantages of the intrinsic atom economy, simpler procedures, structural diversity, energy savings, and reduced waste [47–49]. In view of biological significance of pyrazole, quinoline and pyridine a modification on the 1 and 4-position on 4*H*-quinoline by pyridine and 1*H*-pyrazole-4-carbaldehydes respectively may bring significant changes in pharmacological activities and may provide new classes of therapeutically active compounds, with this hope and as a part of our current studies in developing new therapeutically active agents *via* combination of two therapeutically active moieties [16–21], we report herein the preparation of *N*-pyridinyl-4-pyrazolyl-4*H*-quinoline **7a–l** derivatives *via* MCR approach i.e. one pot base-catalyzed cyclocondensation reaction of 1*H*-pyrazole-4-carbaldehydes, malononitrile/ethylcyanoacetate and β-pyridinyle naminone.

2. Chemistry

The synthetic approach adopted to obtain the target compounds is depicted in Scheme 1. The starting material 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehydes **2a–c** was prepared according to literature procedure [16] by Vilsmeier–Haack reaction of 1-aryl-3-methyl-1*H*-pyrazol-5(4*H*)-one **1a–c**. The required 3-(pyridin-3-*yl*amino)cyclohex-2-enones **5a**, **b** were synthesized by nucleophilic addition reaction of 1,3-cyclohexanedione/dimedone **3a**, **b** and 3-aminopyridine **4** at 120 °C for 30 min under solvent free condition [32]. The title compounds **7a–l** were prepared *via* one-pot three component cyclocondensation reaction between **2a–c**, **5a**, **b** and malononitrile/ethylcyanoacetate **6a**, **b** in ethanol containing a catalytic amount of piperidine in good to excellent yields.



Comp	R_1	R_2	R_3	Comp	R_1	R_2	R_3
7a	H	H	CN	**7g**	H	H	COOEt
7b	CH_3	H	CN	**7h**	CH_3	H	COOEt
7c	Cl	H	CN	**7i**	Cl	H	COOEt
7d	H	CH_3	CN	**7j**	H	CH_3	COOEt
7e	CH_3	CH_3	CN	**7k**	CH_3	CH_3	COOEt
7f	Cl	CH_3	CN	**7l**	Cl	CH_3	COOEt

Scheme 1. Synthetic pathway for the synthesis of title derivatives **7a–l**.