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Synthesis and biological evaluation of novel pyrazolopyrimidines derivatives as anticancer and anti-5-lipoxygenase agents

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ABSTRACT

A novel series of 6-aryl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(*5H*)-ones **3a-h** were synthesized in a single step *via* condensation of carboxamide **2** with some aromatic aldehydes (presence of iodine). Treatment of aminopyrazole **1a** with acetic anhydride afforded pyrazolopyrimidines **4** which on treatment with ethyl chloroacetate in refluxing dry DMF furnished a single product identified as ethyl 2-(3,6-dimethyl-4-oxo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-5(*4H*)-yl) acetate **5**. On the other hand, esterification of compound **6** with different alcohol, led to the formation of new esters linked pyrazolo [3,4-*d*]pyrimidinones hybrids **7a-f**. The reaction of compound **2** with 3-propargyl bromide gave the compound **8** used as a dipolarophile to access to triazoles (4- and 5-regioisomers (**9a-e**) and (**10a-e**), respectively) *via* the 1,3-dipoar cycloaddition reaction. Finally, condensation reaction of aminopyrazole **1b** with α-cyanocinnamonitiles gave the new pyrazolo[1,5-*a*]pyrimidine-3,6-dicarbonitriles **11a-e**. Structures of compounds were established on the basis of $^{1}H/^{13}C$ NMR and ESI-HRMS. Compounds were screened for their cytotoxic (HCT-116 and MCF-7) and 5-lipoxygenase inhibition activities. The structure-activity relationship (SAR) was discussed.

1. Introduction

The pyrazole scaffold is a highly versatile drug-like template that is being used extensively in the design of cancer therapies and cellular apoptosis [1–3]. These compounds are capable to exert remarkable anticancer effects by the inhibition of different types of enzymes, proteins and receptors which play critical roles in cell division [4]. On the other hand, the synthesis and study of pyrazolo-fused compounds have been also emerged as an important heterocyclic system due to their wide range of biological activities [5–7], as well as synthetic applications in medicinal chemistry [8]. In particular, pyrazolo[3,4-*d*]pyrimidine has been a fruitful source of inspiration for medicinal chemists for many years and attracted their attention due to their numerous activities [9]. Pyrazolo[3,4-*d*]pyrimidines were identified as a general class of adenosine receptors [10]. There is no big difference in the basic structures of pyrazolopyrimidines and purines [11]. In the last several decades, these compounds are reported to encompass pharmacological potentials as antiinflammatory, antitumor antituberculostatic, antimicrobial, antifungal, herbicidal and antiviral [12–18].

Recently, it was reported that many pyrazolo[3,4-*d*] pyrimidine and their derivatives exhibit anticancer activity *via* the interaction with different enzymes and receptors [19,20]. For example, Abd El Hamid and collaborators reported that pyrazolo[3,4-*d*]pyrimidines were identified as potential anti-breast cancer agents (Fig. 1I) [21].

In 2011, Kumar et al. noted that pyrazolo[3,4-*d*]pyrimidines possessed cytotoxic activity towards Src kinase and human ovarian adenocarcinoma (SK-Ov-3), breast carcinoma (MDA-MB-361), and colon adenocarcinoma (HT-29) (Fig. 1II) [22].

In addition, in 2012, Kim et al. described the SAR and synthesis of pyrazolopyrimidines as potent and selective p70S6K inhibitors (Fig. 1III) [23].

Also a careful literature survey reveals that pyrazolo[1,5-*a*] pyrimidine derivatives were reported to exhibit a broad spectrum of biological activities including antitumor, antimicrobial, antiinflammatory and cytotoxic [24–27]. Furthermore, numerous synthetic strategies have been outlined for the synthesis of pyrazolo

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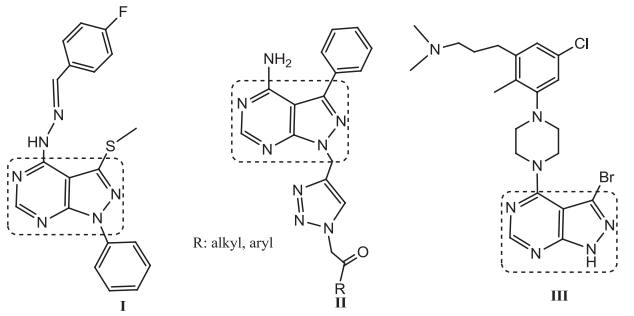


Fig. 1. Example of pyrazolo[3,4-*d*]pyrimidines as anticancer agents.

[1,5-*a*]pyrimidines, some of the synthetic methods are the condensation of arylhydrazone derivatives with 3-aminopyrazoleand the one-pot reaction of ketones, aromatic aldehydes and 3-aminopyrazoles [28,29].

Taking all the above findings into consideration and by continuing researches for new biaocative hybride molecules [30], we report herein the synthesis of new series of pyrazolo[3,4-*d*]pyrimidinones, new esters and triazoles linked to pyrazolo[3,4-*d*]pyrimidinones as well as the synthesis of new series of pyrazolo[1,5-*a*] pyrimidine derivatives. Most of the prepared compounds were evaluated for their cytotoxic and anti-5-lipoxygenase activities and the structure-activity relationship (SAR) were discussed.

2. Results and discussion

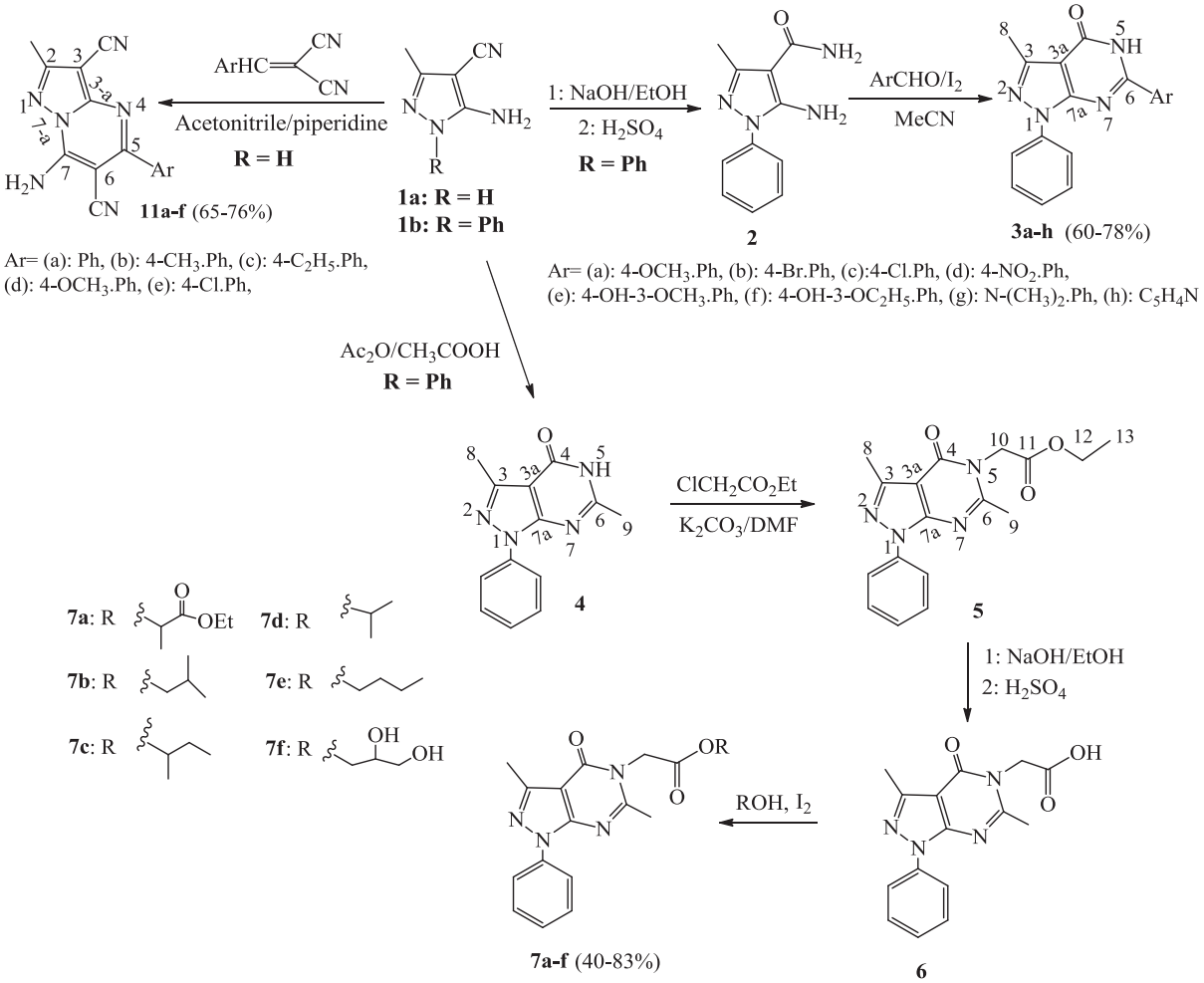
2.1. Chemistry

According to the previously reported method [31] the starting materials 5-aminopyrazole-4-carbonitriles **1a**,**b** were prepared. The treatment of compound **1b** in ethanol by a solution of sodium hydroxide affords the 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamide **2**. Thus, the latter readily underwent cyclization when heated in acetonitrile with various substituted aromatic aldehydes in the presence of equimolar molecular iodine used as a mild Lewis acid, to give a new series of pyrazolo[3,4-*d*]pyrimidinones derivatives **3a-h** in good yields (60–78%) (Scheme 1).

The structures of these compounds were confirmed according to their spectral data. In fact, the ^{1}H NMR spectrum of compound **3c**, as an example, showed a singlet for NH proton at δ_H 12.4. Furthermore, the same spectrum showed in addition of the signals corresponding to the protons introduced by the pyrazole moiety, an AB quartet peak at the aromatic region, confirming the presence of the *para*-substituted aromatic ring and the occurrence of heterocyclization.

FTIR and High Resolution Mass Spectrometry (HRMS) data of all the formed derivatives were also in agreement with the proposed structures.

Refluxing of compound **1b** in acetic anhydride in the presence of acetic acid afforded a white product identified as 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5H)-one **4**



Scheme 1. Synthetic route of compounds **2–7** and **11a-e**.