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Original article

Synthesis and antitumor activity of some new pyrazolo[1,5-*a*] pyrimidines

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ABSTRACT

New series of pyrazolo[1,5-*a*]pyrimidine derivatives **7a–i**, **11a–c** and Schiff bases **13a–c** were synthesized and screened for their *in vitro* antitumor activity against three human carcinoma cell lines, namely colorectal carcinoma (HCT116), prostate adenocarcinoma (PC-3) and liver carcinoma (HepG-2) using MTT cytotoxicity assay at 100 μg/mL. Some of the tested compounds displayed good anticancer activities against HCT-116 and PC-3 cells. Whereas, compounds **7d** and **11a** showed better antitumor activity than the rest of the compounds against both cell lines. A structure-activity relationship (SAR) has been discussed and structures of the newly synthesized compounds were confirmed by different spectral data (MS, IR, ^{1}H NMR and ^{13}C NMR) and elemental analysis.

1. Introduction

Recently, there is an urgent need to give much attention for design, synthesis and production of more potent and effective human therapeutic agents to treat cancer diseases, which is responsible for major deaths worldwide [1]. On the other hand, pyrazolo[1,5-*a*]pyrimidines are purine analogue [2] of particular significance in medicinal chemistry due to their broad scope of remarkable antitumor [3] and antibacterial [4] activities. In addition, certain substituted pyrazolo[1,5-*a*]pyrimidines appeared as promising antitumor agents. For example, compound **A**, isopropyl pyrazolo[1,5-*a*]pyrimidine carbamate, showed good potency in the colon (HCT116) and p21 deficient cell line [5] and compound **B**, 5-(naphthalen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, is effective against HCT116 (colon) and HeLa (cervix) cell lines [6]. Furthermore, we have reported the synthesis of compound **C**, *N*-(phenyl)-7-hydroxy-5-methylpyrazolo[1,5-*a*] pyrimidine-3-carboxamide, as a potent antitumor agent against liver HepG2 cell lines [7] (Fig. 1).

During the last two decades, there is a growing interest in the synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives as promising drugs for treatment of cancer diseases. For example, Dinaciclib (SCH 727965) **D** (Fig. 1) was synthesized by *Paruch* et al., as a potent and selective cyclin-dependent kinase (CDK) inhibitor that is currently undergoing clinical evaluation [8]. Also, compound **E** (Fig. 1) is a potent and selective CDK2 inhibitor with IC_{50} of 0.013 μmol/L and showed efficacy in a mouse A2780 xenograft model [9].

From the previous findings of biological effectiveness of pyrazolo[1,5-*a*]pyrimidine derivatives and in continuation of our research program on the synthesis of new compounds exhibiting biological activities [10–16], we have herein synthesized a new series of pyrazolo[1,5-*a*]pyrimidine derivatives **7a–i** and **11a–c** (Fig. 1) for evaluation of their anticancer properties against three human carcinoma cell lines (HCT-116 “colon”, PC-3 “prostate” and HepG-2 “liver”) using MTT assay.

2. Results and discussion

2.1. Chemistry

The synthesized target compounds, pyrazolo[1,5-*a*]pyrimidine derivatives, are shown in Schemes 2–4. The starting materials, 5-amino-3-(4-methoxyphenylamino)-*N*-aryl-1*H*-pyrazole-4-carboxamides **2a–c** were prepared by reacting *N*-(aryl)-2-cyano-3-[(4-methoxyphenyl)amino]-3-(methylsulfanyl)acrylamides **1a–c** with hydrazine hydrate in boiling absolute ethanol as described in the literature [17] (Scheme 1).

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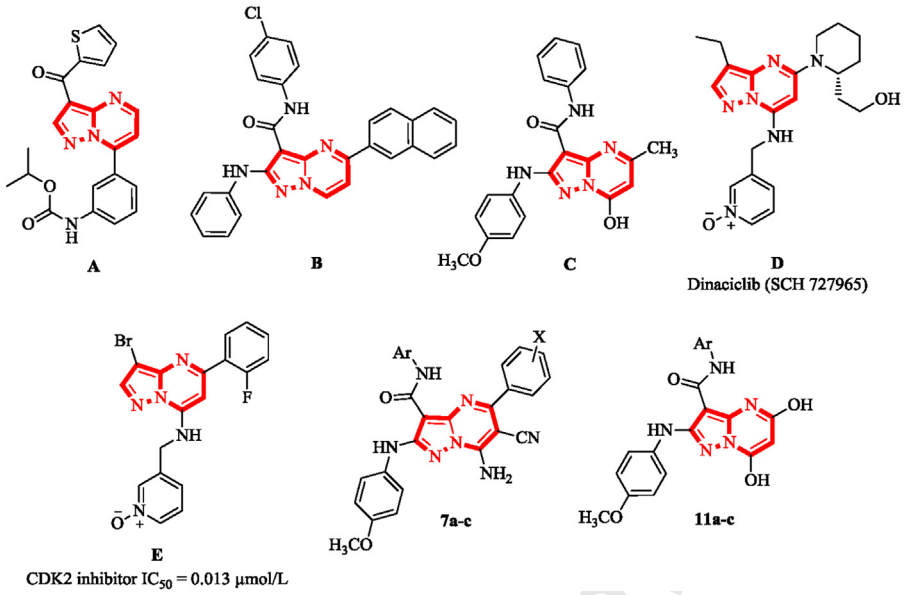
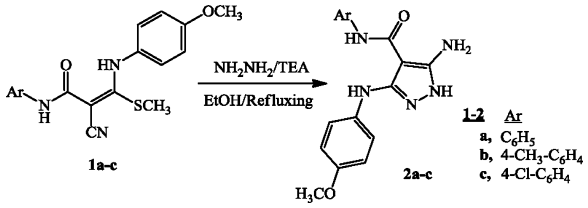


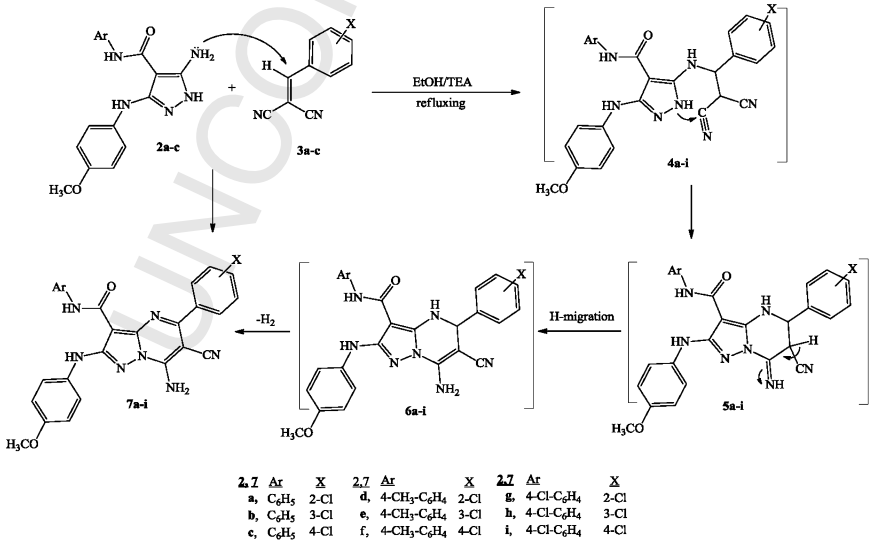
Fig. 1. Structures of the anticancer pyrazolo[1,5-*a*]pyrimidine derivatives **A–C**, Dinaciclib **D,** enzyme inhibitor **E** and the target pyrazolo[1,5-*a*]pyrimidines **7a–i** and **11a–c**.



Scheme 1. Synthesis of the starting compounds **2a–c**.

Base-catalyzed condensation of 5-amino-3-(4-methoxyphenylamino)-*N*-aryl-1*H*-pyrazole-4-carboxamides **2a–c** with 2-(*o*-, *m*- or *p*-chlorobenzylidene)malononitriles **3a–c** in absolute ethanol afforded 7-amino-6-cyano-5-aryl-2-(4-methoxyphenylamino)-*N*-aryl-pyrazolo[1,5-*a*]pyrimidine-3-carboxamides **7a–i** (Scheme 2).

The structure of compounds **7a–i** was confirmed and established by different spectral data (MS, IR, ^{1}H NMR and ^{13}C NMR) and elemental analysis. For example, the mass spectrum of compound **7c** confirmed the molecular formula $C_{27}H_{20}ClN_7O_2$ (509.95) {MS (*m/z*, %): 511 (M^++2, 2.20), 509 (M^+, 6.97)}. The IR spectrum of **7c** reveals the presence of absorption bands due to the NH, NH_2, C≡N and C=O groups at 3434, 3290, 2217 and 1665 cm^{-1}, respectively. Its ^{1}H NMR (400 MHz, DMSO-d_6, δ) spectrum showed protons of the OCH_3 group as a singlet at 3.76. Protons of the *N*-phenyl ring (5H) appeared as a doublet (2H, J_{HH} = 9.0 Hz) at 6.91, a triplet (1H, J_{HH} = 7.4 Hz) at 7.10 and a triplet (2H, J_{HH} = 7.6 Hz) at 7.37. Protons of the *p*-substituted benzene rings (AB-system) (8H) appeared as a four doublets at 7.60 (d, 2H, J_{HH} = 7.6 Hz), 7.72 (d, 2H, J_{HH} = 8.6 Hz), 7.85 (d, 2H, J_{HH} = 9.0 Hz) and at 8.02 (d, 2H, J_{HH} = 8.6 Hz). The spectrum also revealed three signals at 9.12, 9.26, 10.03 referred to the protons of NH_2 (2H), NH (1H), NH (1H), respectively. The ^{13}C NMR (100 MHz, DMSO-d_6, δ) spectrum was characterized by four signals at 55.6, 116.4, 133.7 and 160.3 due to the —OCH_3, —C≡N, C_{3a} (pyrazolopyrimidine) and —C=O groups, respectively. Additionally, we investigated the structure of **7a–i** from previous studies for similar analog by the single crystal X-ray structure analysis [18,19].



Scheme 2. Synthesis of 7-amino-6-cyano-5-aryl-2-(4-methoxyphenylamino)-*N*-aryl-pyrazolo[1,5-*a*]pyrimidine-3-carboxamides **7a–i**.