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Full Length Article

6-(2-Morpholinoethyl)-thiazolo[3,2-*a*]pyrimidin-5-one: A novel scaffold for the synthesis of potential PI3kα inhibitors

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ABSTRACT

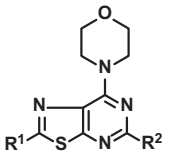
The present study involves the development of certain thiazolo[3,2-*a*]pyrimidin-5-ones linked through an ethylene bridge to various amines. The newly synthesized compounds **4–6(a–c)** were subjected to *in vitro* anticancer evaluation using NCI antitumor screening. The target compounds showed observed activity against *Renal UO-31* cancer cell line with cell growth promotion 52.72–64.52%. COMPARE analyses revealed compounds **4a** and **4b** exhibiting high correlation levels with rapamycin (mTOR inhibitor). Kinase assays were performed for compounds **4a** and **4b** on mTOR and structurally-related PI3Kα. They displayed moderate activity against PI3Kα with IC_{50} values of 120 and 151 μM, respectively. Compounds **4a** and **4b** could thus be considered as a promising leading scaffold for further development of potential PI3Kα inhibitors.

1. Introduction

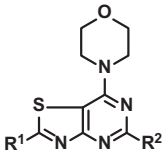
Fused thiazoles are an important class of compounds which have attracted much attention to make use of their remarkable biological and pharmacological properties. Several publications have pointed to the antitumor activity of fused thiazole compounds e.g. thiazolo[5,4-*c*]pyridin-4(5*H*)-one [1], and thiazolo[3,2-*a*] pyrimidine derivatives [2–5].

Based on these findings, and in continuation to our efforts to synthesize biologically active compounds against cancer [6,7], we became interested in the evaluation of a series of thiazolo[3,2-*a*] pyrimidin-5-one derivatives with various substituents at the 3-, 6- and 7-positions, aiming at identifying potent anticancer agents.

The phosphoinositide 3-kinase (PI3K) pathway is an intracellular signaling pathway that has regulatory roles in cell survival, proliferation, and differentiation, and a critical role in tumorigenesis [8,9]. In cancer, multiple studies have investigated the therapeutic targeting of the PI3K pathway, and multiple inhibitors targeting PI3K and its isoforms, protein kinase B/AKT, and mammalian target of rapamycin (mTOR), have been developed [8]. A US patent reported thiazolopyrimidine compounds, substituted with a morpholine ring, of formulae I and II, with anticancer activity, and more specifically with PI3 kinase inhibitory activity. The compounds may inhibit tumor growth in mammals and may be useful for treating human cancer patients [10].

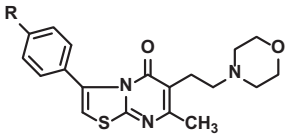


(I)



(II)

Taking the above mentioned compounds as a lead, a part of the research undertaken here involved the combination of a morpholinoalkyl moiety with the thiazolo[3,2-*a*]pyrimidin-5-one series in a single molecular frame of the general structure (**A**) with the hope of finding interesting antitumor activity through inhibiting PI3K. A morpholine ring is often introduced to enhance water solubility. The group is attached through alkyl chain in order to protrude from the binding site and be exposed to the surrounding aqueous environment [11].



(A)

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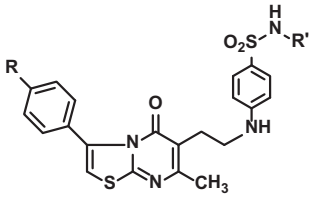
Moreover, it is well documented that aryl/heteroaryl sulfonamides, where the nitrogen of -SO_2NH_2 group is either free or substituted, exhibited substantial antitumor activity *in vitro* and/or *in vivo* [12–13]. The discovery of E-7010 [14] and vemurafenib (PLX4032) [15], fused heterocyclic compounds incorporating sulfonamide moiety, emphasized the role of sulfonamides as an important class of anticancer agents which interact with a wide range of different cellular targets. In addition, series of novel compounds containing benzenesulfonamide moiety and incorporating benzoquinones [16], quinazolin-2-ones [17] or coumarins [18] have revealed promising anticancer activities.

In view of the preceding information, it was envisaged to construct a system which combines both thiazolo[3,2-a]pyrimidin-5-ones and sulfonamides in a single molecular frame (**B**), in order to explore the additive effects towards their anticancer activities.



R'=$COCH_3$, C(NH)NH_2

(B)

2. Results and discussion

2.1. Chemistry

A general approach to synthesize the designed compounds **4–6 (a–c)** is shown in Scheme 1. 2-Amino-4-arylthiazoles **2a–c** were prepared utilizing either phenacyl chloride or bromide according to a reported procedure [19] which is considered to be an easy, rapid and purification-free procedure. Thiourea was allowed to react with phenacyl halide at room temperature for 2–3 min to yield the corresponding arylthiazole. The reaction of **2a–c** with α -acetyl-γ-butyrolactone in phosphorus oxychloride afforded 6-(2-chloroethyl)-7-methyl-3-(un)substituted phenyl-5*H*-thiazolo [3,2-*a*]pyrimidin-5-ones **3a–c** without isolating the intermediates [20,21] in quantitative yields.

Heating compounds **3a–c** with morpholine, sulfacetamide, and sulfaguanidine in dry DMF in the presence of triethylamine gave the corresponding target compounds **4–6(a–c)** in moderate yields.

The structures of the synthesized compounds **4–6(a–c)** were confirmed by microanalyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and EI-MS) which showed full agreement with their structures. In the ^{1}H NMR spectra of compounds **4a–c**, the triplet signals of the morpholine ring protons resonated at the expected regions integrating for eight protons. In the ^{13}C NMR spectra of compound **4a**, new bands appeared at 53.16 and 66.15 ppm, attributed to ((CH_2)$_2$N-morpholine) and ((CH_2)$_2$O-morpholine), respectively. For compounds **5a–c**, the aromatic protons (—NH-**C6H4**-SO_2NH—) in the ^{1}H NMR spectra and the ^{13}C signals of CO**CH3** and **CO**CH_3 in compound **5a** were observed at the expected regions. The ^{13}C signal for guanidine moiety in compound **6a** was observed at 159.23 ppm. The mass spectral data of the synthesized compounds **4–6(a–c)** displayed molecular ion peaks which confirmed their molecular weights.

2.2. Biological evaluation

2.2.1. In vitro anticancer screening

The target compounds **4–6(a–c)** were submitted to the National Cancer Institute (NCI) [22], Bethesda, Maryland, USA, under the Developmental Therapeutic Program (DTP). The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. Structures are generally selected for screening based on their ability to add diversity to the NCI small molecule compound collection. Compounds with drug-like properties based on computer-aided design are to be prioritized in the NCI screening service. All compounds submitted to the NCI 60 cell screen were tested initially at a single high dose (10^{-5} M) in the full NCI 60 cell panel. The compounds were added at a single concentration (10^{-5} M) and the culture was incubated for 48 h. End point determinations were made with a protein binding dye, Sulforhodamine B [23–25].

The mean percentage growth percentages and the growth percentage with the most sensitive cell lines of all of the tested compounds over the full panel of cell lines are illustrated in Table 1.

In light of the NCI results, the following could be considered:

- Regarding the sensitivity against individual cell lines in Table 1, all target compounds **4–6(a–c)** showed observed low cell growth promotion against *Renal UO-31*cancer cell line with cell growth promotion varying from 52.72% to 64.52%.
- By comparing the results from different series, it was found that the introduction of sulfacetamide in compounds **5a–c** or sulfaguanidine in compounds **6a–c** instead of morpholine moiety in compounds **4a–c** proved to enhance the potency towards *Renal UO-31*cancer cell line and reduce potency towards *Leukemia SR* cancer cell line.
- It is worth mentioning that compounds **4–6(a)** exhibited increased potency towards *Leukemia SR* cancer cell line and reduced the potency towards *Non-Small Cell Lung HOP-92* cancer.

2.2.2. COMPARE analyses

We performed COMPARE [26] analyses for compounds **4–6(a–c)** in order to investigate the similarity of their cytotoxicity pattern (mean graph fingerprints) with those of known anticancer standard agents, NCI active synthetic compounds and natural extracts, which are present in public available databases. If the data pattern correlates well with that of compounds belonging to a standard agent database (Pearson's correlation coefficient (PCC > 0.6), the compound of interest may have the same mechanism of action [27,28]. On the other hand, if the activity pattern does not correlate with any standard agent, it is possible that the compound has a novel mechanism of action. Standard COMPARE analyses were performed at the GI_{50} level.

It was established that compounds **4a** and **4b** demonstrated high correlation levels with rapamycin (NSC S226080) with PCC values of 0.607 and 0.629, respectively. Considerable correlations between compounds **4c**, **5a**, **5b**, **5c**, **6a**, **6b,** and **6c**, and rapamycin were noted with PCC values of 0.523, 0.507, 0.496, 0.53, 0.448, 0.453, and 0.538, respectively. Such similarity in COMPARE results could indicate the resemblance in mechanisms of action with rapamycin. Rapamycin is reported to be mTOR inhibitor which is considered to be a key enzyme in regulation of cellular metabolism, growth, and proliferation [29,30].

2.2.3. Enzymatic screening

Compounds **4a** and **4b**, exhibiting the highest correlation levels with rapamycin (mTOR inhibitor), were selected to explore their biological targets at the molecular level. They were subjected to *in vitro* enzymatic screening against mTOR and structurally-related phosphatidylinositol 3-kinase-alpha (PI3Kα) to determine their potential affinity as inhibitors for those enzymes. A literature survey was conducted to search for similar compounds with previously reported mTOR or PI3Kα activities [31]. It was found that our

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