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Original Article

Design, synthesis and pharmacological activity of substituted 1,2,3,6-tetrahydropyrimidine-5-carbonitrile

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ABSTRACT

Aim: The benzothiazole, pyrimidine and piperazine nucleuses having outstanding biological activates which prompted us to synthesis of substituted derivatives of *N*-(1,3-benzothiazol-2-yl)-2-[4-(5-cyano-6-imino-2-oxo1,2,3,4-tetrahydropyrimidin-4-yl)piperazin-1-yl]acetamide and to evaluate for anticancer and anti-inflammatory activity.

Method: Benzothiazole linked by acetamido bridge to 4-Imino-2 oxo-6-(piperazin-1-yl) 1,2,3,4-tetrahydropyrimidine -5-carbonitrile to afforded a series of substituted *N*-(1,3-benzothiazol-2-yl)-2-[4-(5-cyano-6-imino-2-oxo1,2,3,4-tetrahydropyrimidin 4-yl)piperazin-1-yl]acetamide in good yield.

Results and discussion: The structures of compounds were in agreement with IR, ^{1}H NMR, and MASS spectral data. Three compounds were screened for in-vitro anticancer activity at the national cancer institute for anticancer activity against a panel of 60 different human tumor cell lines derived from nine neoplastic cancer types at NCI, and for in vitro anti-inflammatory activity by albumin denaturation technique. The compound (**4b**) with 6-chloro substitution was showed selective influence on cancer cell lines and compounds (**4h**), (**4i**), (**4j**) exhibited excellent anti-inflammatory activity.

Conclusion: New derivatives having significant *in-vitro* anti-inflammatory activity showed remarkable inhibitory effects against cancer. This observation may promote a further development of this novel series that may lead to compounds with better anticancer and anti-inflammatory profile.

1. Introduction

The search for anti-inflammatory and anticancer compounds with a more selective activity and lower side effects continues to be an area of investigation in medicinal chemistry. Inflammation is the initial trigger of several different diseases such as cancer, alzheimer disease, asthma, atherosclerosis, colitis, rheumatoid arthritis. Development of new anti-inflammatory drugs having a significant antineoplastic effect, which is currently viewed in the context of the recently appreciated role of inflammation in cancer.[1] By using molecular hybridization techniques multiple-ligand drugs that can

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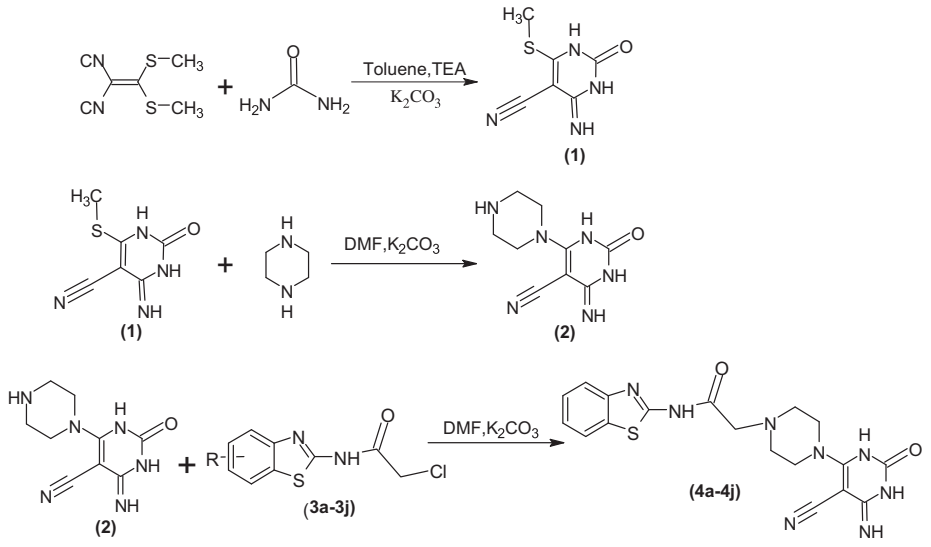
act at one or multiple targets showing synergic action and minimizing toxicity can be developed,[2] Takashi Morisaki et al collectively suggest that celecoxib enhances sorafenib-mediated antitumor effects. The role of celecoxib when administered in combination with other drugs in cancer therapy is modulatory rather than therapeutic, and the efficacy of this approach has been reported for various types of cancers.[3] The nonsteroidal anti-inflammatory drugs (NSAID) are promising chemopreventive agents having the correlated mechanism through binding and inhibit the COX-1 and COX-2 enzymes, which catalyze the conversion of arachidonic acid to prostaglandins. NSAIDs act to reduce carcinogenesis by inhibiting the activity of cyclooxygenase-2 (COX-2), an enzyme that is overexpressed in various cancer tissues.[4,5] Overexpression of COX-2 increases cell proliferation and inhibits apoptosis, Overviews of these studies have been presented by Tegeder et al[6] and by Soh and Weinstein.[7] COX-1 is expressed constitutively and is required for physiological processes such as maintenance of gastro intestinal mucosa and platelet aggregation, where as COX 2 is induced by cytokines, growth factors, and mutagens. Clinical studies suggest that NSAIDs, particularly the highly selective cyclooxygenase (COX)-2 inhibitors, are promising anticancer agents. Pyrimidinyl-piperazine fused with heterocyclic benzothiazole derivatives have shown an array of biological activities *viz.* antimicrobial anticancer and anti-inflammatory.[8] Piperazines attached to benzimidazole and indole were found to have potent anti-inflammatory activity.[9] With this concept of acetamide bridge, N. M. Raghavendra et al, reported the pharmacological activity of N-(benzo[d]thiazol-2-yl)-2-(piperazin-1-yl) acetamide analogs for their anti-inflammatory activity.[10,11]

Pyrimidine and fused benzothiazole heterocycles are reported to be effective pharmacophores, Ahmed Kamal et al synthesized pyrazolo[1,5a] pyrimidine linked 2-aminobenzothizole conjugate which were evaluated for their anticancer activity against five human cancer cell lines.[12] According to quantitative structure–activity relationship approach Papadopoulou C et al, reported that derivatives of 4-phenyl-piperazine were found to be potent anti-inflammatory agents.[13] Literature review showed that benzothiazole substituted at 4 or 5 positions with electron withdrawing groups have significant anti-inflammatory activity.[14] In the light of these overall observations, prompted us to synthesize a novel derivatives of substituted *N*-(1,3-benzothiazol-2-yl)-2-[4-(5-cyano-6-imino-2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl) piperazin-1-yl]acetamide, and to screen for *In-vitro* anti-inflammatory activity by inhibition of albumin denaturation technique and for anticancer activity at NCI.

1.1. *Chemistry*

In present work target compounds were obtained by reaction of starting material of bis (methylthio) methylene malononitrile with molar equivalent amount of urea in presence of toluene and triethylamine for five hrs to give compound 4-imino-6-(methylsulfanyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**1**). Compound (**1**) posses nucleophilic replaceable active methylthio group at the 6th position, which is activated by the ring 1st position nitrogen atom and the electron withdrawing cyano group at 5th position, which was substituted by piperazine ring by reacting equal molar quantities of compound (**1**) & piperazine to give 4-imino-2-oxo-6-(piperazin-1-yl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**2**). The formation of compound (**2**) was confirmed by spectral data. Substituted 2-amino benzothiazoles reacted independently with chloroacetyl chloride to give substituted 2-chloroacetylamino benzothiazole (**3a**–**3j**). Final compounds of Scheme 1 were obtained by reacting 4-imino-2-oxo-6-(piperazin-1-yl) 1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**2**) with substituted 2-chloroacetylamino benzothiazole (**3a**–**3j**) independently to give the substituted N-(1,3-benzothiazol-2-yl)-2-[4-(5-cyano-6-imino-2-oxo-1,2,3,6 tetrahydropyrimidin-4-yl) piperazin-1-yl]acetamide (**4a**–**4j**). The formations of all compounds were confirmed by FTIR, ^{1}H NMR and MASS spectral analysis.



Scheme 1