Arabian Journal of Chemistry (2014) 7, 986–993

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Novel pyrimidine and its triazole fused derivatives: Synthesis and investigation of antioxidant and anti-inflammatory activity

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Received 9 October 2010; accepted 23 December 2010
Available online 30 December 2010

KEYWORDS

Dihydropyrimidinecarbonitrile;
Triazole fused pyrimidine;
Antioxidant;
Anti-inflammatory activity

Abstract In the present study, we have carried out the synthesis of novel dihydropyrimidinecarbonitrile (**1a–c**), its dimethylated adduct (**2a–c**), and hydrazine derivative (**3a–c**) of **2a–c** and its triazole fused derivatives (**4a–c, 5a–c** and **6a–c**). The structure of newly synthesized compounds was confirmed by IR, ^{1}H NMR, mass spectral data and elemental analysis. Further the novel derivatives were investigated for their in vitro antioxidant and anti-inflammatory activity. The results revealed that some of the tested compounds showed potent antioxidant and anti-inflammatory activity. The mass spectral pattern of **6a** has been investigated in order to elucidate the structure.

1. Introduction

Pyrimidine, being an integral part of DNA and RNA, imparts to diverse pharmacological properties as effective bactericide and fungicide (Williams and Cline, 1936; Reidlinger and Dworczak, 1994; Hardtman and Otto, 1972). Certain pyrimidine derivatives were also known to exhibit antimalarial (Brown and Evans, 1985), antifilarial (Brown and Rees, 1984), antioxidant (Vanessa et al., 2010; Prasenjit et al., 2010) and anti-HIV activities (Okabe et al., 1991). Some of the 3,4-dihydropyrimidines (DHPM) have emerged as integral backbones of several calcium channel blockers, antihypertensive agents, adrenergic and neuropeptide antagonist (Pasha et al., 2005). Several alkaloids containing 3,4-dihydropyrimidine have been isolated from marine sources and among them the *batzelladine* alkaloids are found to be potent HIV-gp-120-CD_4 inhibitors (Kappe, 2000; Kappe et al., 2005; Patil et al., 1995).

Along with the varied biological activities of pyrimidine, other heterocycles fused with pyrimidines play an essential role in several biological processes and have a considerable chemical and pharmacological importance. Triazole in association

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.arabjc.2010.12.021
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with the pyrimidine has shown good antifungal (Singh et al., 2004) and hypoglycemic action (Agarwal, 1991). [1,2,4]Triazole fused pyrimidine exhibit good antimicrobial activity (Fathy et al., 2004), antitumour activity (Swelam, 1998), analgesic, anti-inflammatory and ulcerogenic activities (Hend et al., 2008).

In the view of the facts mentioned above and as part of our initial efforts to discover potentially active new agents. Hence, we have synthesized some new dihydropyrimidinecarbonitrile and its triazole fused derivatives. The novel derivatives were characterized by spectral data and elemental analysis and these compounds were used for their antioxidant and anti-inflammatory screening. Compound **6a** is one of the final triazole derivatives of pyrimidine and its intermediates **1a** and **3a** have shown good antioxidant activity so we have described the electron spray ionization mass spectral fragmentation of **6a**.

2. Materials and methods

2.1. Materials and reagents

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting point was determined by Micro control based melting point instrument and is uncorrected. All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel (60GF-254) plates, by using ethyl acetate: butanol: chloroform in the ratio of [1:2:1] as mobile phase and visualized with UV light. Column chromatography was performed on silica gel (200–300 mesh). Infra red (IR) spectra was recorded by using KBr disk on a Thermo Nicolate IR-400 FTIR spectrophotometer, ^{1}H NMR spectra was recorded on Bruker Avance-300F spectrometer (300 MHz) using tetramethylsilane as internal standard (chemical shift in δ ppm). Mass spectra were recorded on a Triple Quadrupole LC–MS–MS (Sciex with ESI source) spectrometer. The elemental analysis was carried out by using Heraus CHN rapid analyzer. All the compounds gave C, H and N analysis within $\pm 1.2\%$ of the theoretical values. Spectra facilities and elemental analysis were carried out by Department of University scientific instrument centre, Karnatak University, Dharwad, India and Suven Life Sciences, Hyderabad India.

2.2. Synthesis

2.2.1. General procedure for the synthesis of 6-oxo-4-substituted aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitrile (*1a–c*)

Mixture equimolar quantities of ethyl cyanoacetate (5.7 g, 50 mmol), thiourea (3.8 g, 50 mmol), appropriate aromatic aldehyde (50 mmol) and potassium carbonate (6.9 g, 50 mmol) in absolute ethanol (50 ml) was gently refluxed till the completion of reaction. The reaction mixture was neutralized with glacial acetic acid to precipitate out the product. The product was isolated and recrystallized from ethanol as yellow crystals.

2.2.2. General procedure for the synthesis of 1-methyl-2-(methylsulfanyl)-6-oxo-4-substituted aryl-1,6-dihydropyrimidine-5-carbonitrile (*2a–c*)

To a solution of 6-oxo-4-substituted aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitrile (**1a–c**, 20 mmol) in *N*,*N*-dimethyl formamide (DMF, 30 ml), potassium carbonate (5.52 g, 40 mmol) and methyl iodide (5.68 g, 40 mmol) were added and stirred till the completion of reaction at room temperature. Then the reaction mixture was diluted with cold water and neutralized by glacial acetic acid. The product was filtered off and recrystallized from ethanol as creamy crystals.

2.2.3. General procedure for the synthesis of 2-hydrazinyl-1-methyl-6-oxo-4-substituted aryl-1,6-dihydropyrimidine-5-carbonitrile (*3a–c*)

A mixture of compound 1-methyl-2-(methylsulfanyl)-6-oxo-4-substituted aryl-1,6-dihydropyrimidine-5-carbonitrile (**2a–c**, 10 mmol) and hydrazine hydrate (80%, 1.90 g, 30 mmol) in absolute alcohol was refluxed till the completion of reaction. The reaction mixture was poured into crushed ice. Then the product was isolated and recrystallized from ethanol/DMF mixture as yellow crystals.

2.2.4. General procedure for the synthesis of 8-methyl-7-oxo-5-substituted aryl-7,8-dihydro[1,2,4]triazolo[4,3-α]pyrimidine-6-carbonitrile (*4a–c*)

A mixture of compound 2-hydrazinyl-1-methyl-6-oxo-4-substituted aryl-1,6-dihydropyrimidine-5-carbonitrile (**3a–c**, 5 mmol) in 20 ml formic acid was refluxed till the completion of reaction. The excess of formic acid was distilled. The reaction mixture after cooling was poured into crushed ice. Then the product was isolated and recrystallized from DMF as yellow crystals.

2.2.5. General procedure for the synthesis of 3,8-dimethyl-7-oxo-5-substituted aryl-7,8-dihydro[1,2,4]triazolo[4,3-α]pyrimidine-6-carbonitrile (*5a–c*)

A mixture of compound 2-hydrazinyl-1-methyl-6-oxo-4-substituted aryl-1,6-dihydropyrimidine-5-carbonitrile (**3a–c**, 5 mmol) in 20 ml acetic anhydride was refluxed till the completion of reaction. The excess of acetic anhydride was distilled. The reaction mixture after cooling was poured into crushed ice. Then the product was isolated and recrystallized from DMF as yellow crystals.

2.2.6. General procedure for the synthesis of 8-methyl-7-oxo-3-phenyl-5-substituted aryl-7,8-dihydro[1,2,4]triazolo[4,3-α]pyrimidine-6-carbonitrile (*6a–c*)

A mixture of compound 2-hydrazinyl-1-methyl-6-oxo-4-substituted aryl-1,6-dihydropyrimidine-5-carbonitrile (**3a–c**, 5 mmol) in 20 ml benzoyl chloride was refluxed till the completion of reaction. The excess of benzoyl chloride was distilled. The reaction mixture after cooling was poured into crushed ice. Then the product was obtained as semisolid.

The physical constants and spectral (IR, ^{1}H NMR, mass) characterization and elemental analysis supported the structure of various synthesized compounds (Tables 1 and 2).

3. Pharmacological screening

3.1. Antioxidant screening: (in vitro)

3.1.1. Hydrogen peroxide scavenging activity

A solution of hydrogen peroxide (20 mM) was prepared in phosphate buffer saline (pH 7.4). Various concentrations (12.5, 25, 50, 100 μg/ml) of 1 ml of the test samples or standard, ascorbic acid (Ismaili et al., 2008; Rang et al., 2003) in methanol were added to 2 ml of hydrogen peroxide solution