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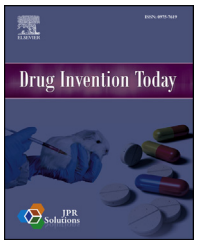

Original Article

Synthesis and biological activity of some pyrimidine derivatives

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ARTICLE INFO

Article history:
Received 15 July 2013
Accepted 14 August 2013

Keywords:
5-Bromo-2,4-dichloropyrimidine
MES
Rotorod
Anticonvulsant
Antioxidant

ABSTRACT

Objectives: To synthesize a variety of pyrimidine analogs, **3**, **4**, **5**, **6(a–d)**, **7(a–d)** and their anticonvulsant and antioxidant activity was determined.
Methods: Using 5-bromo-2,4-dichloropyrimidine and hydrazine hydrate, new compounds were synthesized. The structures of all the new compounds are established on the basis of FT-IR, ^{1}H NMR and mass spectral data. Anticonvulsant study was done by MES seizure model and rotorod method was employed to determine the neurotoxicity. Antioxidant activity was done by DPPH method.
Results: All the compounds were synthesized in good yield. Among the new compounds, **6c** and **7c** are found to be most potent and showed no neurotoxicity. All the compounds showed DPPH radical scavenging activity, where compounds **7b**, **7a** and **6b** were the best radical scavengers.
Conclusions: The results obtained justify the usage of these compounds from their promising anticonvulsant and antioxidant activity. Therefore, the nature of groups is very important for anticonvulsant activity in MES model.

1. Introduction

The word epilepsy usually describes a group of common chronic neurological disorders characterized by recurrent unprovoked seizures due to synchronous neuronal activity in the brain.[1] Several new drugs such as vigabatrin, lamotrigine, gabapentin, tiagabine, felbamate, topiramate, fosphenytoin and levetiracetam have appeared on the market, the development of novel agents, particularly compounds effective against complex partial seizures remains a major focus of antiepileptic drug research.[2] A review on new structural entities having anticonvulsant activity has recently appeared.[3] In recent years, there has been an increased interest in the application of antioxidants to medical treatment as information is constantly gathered linking the development of human diseases to oxidative stress. Schiff bases are characterized by the imine group which is important in elucidating the mechanism of transamination and racemization reactions in biological systems.

Fused pyrimidines continue to attract considerable attention because of their great practical usefulness,

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0975-7619/$ – see front matter
http://dx.doi.org/10.1016/j.dit.2013.08.004

primarily due to very wide spectrum of biological activities. This is evident in particular from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles such as purines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyralopyrimidines. Triazolopyrimidines represent an important class of heterocyclic compounds having wide range of pharmaceutical and biological activities.[4,5] Therefore, versatile and widely applicable methods for the synthesis of triazolopyrimidines are of considerable interest. The existing methods for the preparation of triazolopyrimidines are based on heterocyclic hydrazones or hydrazine precursors. Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals. A large number of pyrimidine derivatives are reported to exhibit antimycobacterial,[6] antitumor,[7] antiviral,[8] anticancer,[9] anti-inflammatory[10] and antimicrobial[11] activities. In the present study, a series of new pyrimidine analogs, **3, 4, 5, 6(a–d)** and **7(a–d)** have been synthesized and their biological effects are determined.

2. Materials and methods

2.1. *Chemistry*

Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar. The FT-IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Bruker DRX-500 spectrometer at 400/300 MHz using d_6-DMSO/$CDCl_3$ as a solvent and TMS as an internal standard. The mass spectra of the samples were recorded using the instrument LC-MSD-Trap-XCT. All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt Ltd.

2.1.1. *Synthesis of 1-(5-bromo-2-chloropyrimidin-4-yl) hydrazine (2)*

A mixture of 5-bromo-2,4-dichloropyrimidine (**1**) (0.01 mol) in methanol was taken and cooled to 0–5 °C in an ice bath. Trietheylamine (0.01 mol) was added to the cold reaction mixture and then hydrazine hydrate (0.012 mol) was added slowly at 5–10 °C. The reaction mass was allowed to stir at room temperature for 1 h. The solid thus obtained was filtered, washed with chilled water and dried to afford compound **2** (Pale yellow solid). Yield – 82%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.06 (s, 1H, NH), 7.85 (s, 1H, py-H), 4.34 (s, 2H, NH_2).

2.1.2. *Synthesis of 8-bromo-5-chloro-3-methyl[1,2,4]triazolo [4,3-c]pyrimidine (3)*

A mixture of compound **2** (0.01 mol) and acetic anhydride (10 ml) was heated under reflux for 4 h. The reaction mixture was concentrated under reduced pressure. The solid obtained was filtered off, washed with water, dried and crystallized from methanol to give the compound **3** (White solid). Yield: 71%. M.p.: 190–194 °C. FT-IR (KBr, cm^{-1}): 2937 (C–H), 1635 (C=N), 1463 (C=C), 1372 (C–N), 722 (C–Cl), 522 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.40 (s, 1H, Py-H), 2.48 (s, 3H OCH_3). MS (ESI) *m/z*: 248.2. Anal. Calcd. for $C_6H_4BrClN_4$ (in %): C, 29.12; H, 1.63; N, 22.64. Found: C, 29.0; H, 1.58; N, 22.54.

2.1.3. *Synthesis of 8-bromo-5-chloro-[1,2,4]triazolo[4,3-c] pyrimidine-3-amine (4)*

Compound **2** (0.01 mol) was dissolved in dioxane (10 ml) and the solution was treated with Na_2CO_3 (0.02 mol) in H_2O (5 ml). Then 5 ml dioxane (0.2 mol) was added to the mixture under ice-bath and kept the reaction below 10 °C, after stirring for 2 h. The solvent was removed under reduced pressure and crystallized from ethanol to give the compound **4** (Brown solid). Yield: 36%. M.p.: 206–208 °C. FT-IR (KBr, cm^{-1}): 2937 (C–H), 1635 (C=N), 1463 (C=C), 1375 (C–N), 722 (C–Cl), 522 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.47 (s, 1H, Py-H), 6.64 (s, 2H, $-NH_2$). MS (ESI) *m/z*: 249.42. Anal. Calcd. for $C_5H_3BrClN_5$ (in %): C, 24.17; H, 1.22; N, 28.19. Found: C, 24.29; H, 1.32; N, 28.30.

2.1.4. *Synthesis of 5-bromo-2-chloro-4-(3,5-dimethyl-1H-pyrazol-1-yl)-pyrimidine (5)*

To a mixture of compound **2** (0.01 mol) in methanol (50 ml), acetylacetone (0.01 mol) was added. The reaction mixture was refluxed for 5 h, and then the obtained solid was filtered off, dried and crystallized from ethanol to give compound **5** (Brown solid). Yield: 71%. M.p.: 214–215 °C. FT-IR (KBr, cm^{-1}): 2940 (C–H), 1655 (C=N), 1510 (C=C), 728 (C–Cl), 530 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.67 (s, 1H, Py-H), 6.10 (s, 1H), 2.30 (s, 3H, OCH_3), 2.16 (s, 3H, OCH_3). MS (ESI) *m/z*: 288.50. Anal. Calcd. for $C_9H_8BrClN_4$ (in %): C, 37.59; H, 2.80; N, 19.48. Found: C, 37.79; H, 2.86; N, 19.40.

2.1.5. *General procedures for the synthesis 8-bromo-5-chloro-3-aryl-[1,2,4]triazolo[4,3-c]pyrimidine 6(a–d)*

Compound **2** (0.01 mol) and substituted benzoic acid (0.012 mol) were taken in $POCl_3$ (5 ml) and heated to reflux for 6 h. The reaction mass was concentrated under reduced pressure and then quenched in ice. The solid obtained was filtered off, washed with water, dried and crystallized from methanol solvent.

2.1.5.1. 8-Bromo-5-chloro-3-(4-ethylphenyl)[1,2,4]triazolo[4,3-c]pyrimidine (6a). The product obtained from compound **2** (0.01 mol) and 4-ethyl benzoic acid (0.01 mol). White solid. Yield: 83%. M.p.: 102–104 °C. FT-IR (KBr, cm^{-1}): 2937 (C–H), 1645 (C=N), 1453 (C=C), 1375 (C–N), 720 (C–Cl), 522 (C–Br). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (s, 1H, Py-H), 7.63 (d, 2H, J = 8.13 Hz, Ar-H), 7.35 (d, 2H, J = 8.34 Hz, Ar-H), 2.73-2.68 (m, 2H, CH_2), 0.99 (t, 3H, J = 7.50 Hz, OCH_3). MS (ESI) *m/z*: 338.2. Anal. Calcd. for $C_{13}H_{10}BrClN_4$ (in %): C, 46.25; H, 2.99; N, 16.60. Found: C, 46.15; H, 2.79; N, 16.67.

2.1.5.2. 8-Bromo-5-chloro-3-(4-methoxyphenyl)[1,2,4]triazolo [4,3-c]pyrimidine (6b). The product obtained from compound **2** (0.01 mol) and 4-methoxy benzoic acid (0.01 mol). Off white solid. Yield: 79%. M.p.: 165–168 °C. FT-IR (KBr, cm^{-1}): 2940 (C–H), 1639 (C=N), 1460 (C=C), 1371 (C–N), 726 (C–Cl), 520 (C–Br). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (s, 1H, Py-H), 7.71 (d, 2H, J = 6.40 Hz, Ar-H), 7.54 (d, 2H, J = 6.21 Hz, Ar-H), 3.90 (s, 3H, OCH_3). MS (ESI) *m/z*: 340.0. Anal. Calcd. for $C_{12}H_8BrClN_4O$(in %): C, 42.44; H, 2.37; N, 16.50. Found: C, 42.58; H, 2.32; N, 16.50.