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Original Article

Synthesis, characterization and pharmacological studies of sulphur containing 1,2,4-triazole derivatives

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الملخص

أهدف البحث: تم تصميم طريقة مكونة من ٥ خطوات لتحضير سبعة مركبات من مشتقات ١,٢,٤-الترايازول تحتوي على الكبريت كمركبات ابتدائية والكشف عن نشاطهم الدوائي.

طرق البحث: تم توصيف هذه المركبات عن طريق تحليل العناصر والبيانات الطيفية الجماعية. وتم تقييم جميع هذه المركبات لنشاطها المضاد للميكروبات تجاه عينات مختارة من البكتيريا والفطريات حسب الطرق المذكورة في الأبحاث السابقة. وتم تقييم الخصائص شبه الدوائية من خلال دراسات سيليكو.

النتائج: المركبات ٨أ، ٨ب، ٨ج أظهرت نشاطا متوسطا لمضادات الميكروبات. أما مركبات ٨د، ٨هـ، ٨و، ٨ز والمسمية مشتقات نيترو، كلورو، برومو، والفلورو على التوالي، أظهرت نشاطا أفضل كمضادات للميكروبات مقارنة بالمركبات الأخرى. أوضحت دراسات السيليكو أن مركب ٨ هـ مع الكلورو يمتلك خصائص شبه دوائية ممتازة مقارنة بالمركبات الأخرى قيد الدراسة.

الاستنتاجات: أظهرت جميع المركبات نشاطا جيدا مضادا للبكتيريا والفطريات. كما كشفت دراسات الفحص الظاهري أن المركبات قيد الدراسة تمتلك خصائص شبه دوائية ممتازة.

الكلمات المفتاحية: تصنيع; مشتقات ١,٢,٤-الترايازول; التحليل الطيفي; نشاط مضادات الميكروبات; خصائص شبه دوائية

Abstract

Objectives: To design a five step procedure for the synthesis of seven novel sulphur containing 1,2,4-triazole derivatives namely 4-[(3-(4-Chloro-phenoxymethyl)-5-(4-substituted-benzylsulfonyl)-1,2,4-triazol-4-yl)methyl]-morpholine from 4-Chloro-phenol and Ethyl-bromoacetate as starting compounds and to screen for their pharmacological activity.

Methods: The compounds were characterised by elemental analysis, IR, ^{1}H NMR and mass spectral data. All compounds were evaluated for antimicrobial activity against selected bacteria and fungi by the methods reported in the literature. The drug-like characteristics were assessed by *in silico* studies.

Results: The compounds 8a, b and c showed moderate antimicrobial activity. Compounds 8d, e, f and g namely nitro, chloro, bromo and fluoro derivatives respectively, showed better antimicrobial activity than the other compounds. *In silico* studies indicated that the compound 8e with chloro substituent possesses excellent drug-like characteristics among the compounds under study.

Conclusion: All the title compounds showed good antibacterial and antifungal activities. Virtual screening studies reveal that the compounds under study possess excellent drug-like characteristics.

Keywords: Synthesis; 1,2,4-triazole derivatives; Spectral analysis; Antimicrobial activity; Drug-like characteristics

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Introduction

In the last few years, 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their medicinal significance. Several drugs containing 1,2,4-triazole group i.e. Etizolam,[1] Alprazolam,[2] Furacylin[3] etc are well known. Particularly, diverse biological activities, such as antibacterial,[4] antifungal,[5] anti-inflammatory,[6] antituberculosis,[7] anticancer,[8] antioxidant[9] and InhA inhibitory activity[10] etc. have been associated with 1,2,4-triazole derivatives. Keeping in view the above mentioned facts and the medicinal importance of sulphur containing 1,2,4-triazole ring systems,[11–14] the authors have made an attempt to synthesize, characterize and evaluate the biological activity of some sulphur containing 1,2,4-triazoles. A number of pharmacologically active compounds have been reported[15–17] from these laboratories.

Materials and Methods

All Chemicals and reagents were procured from Ranbaxy Laboratories Ltd, Chemical Division, India. The standard bacterial and fungal strains were procured from National Centre for Cell Sciences, Pune, India. Nutrient broth, nutrient agar and 5 mm diameter antibiotic assay discs were obtained from Hi-Media Laboratories Limited, India. Melting points were determined by Scientific melting point apparatus, India and uncorrected. Synthesized compounds were recrystallized using suitable solvent. Digital electronics balance (Shankar Scientific Supplies, India), horizontal laminar air flow bench (Yorco Sales Pvt. Ltd, New Delhi, India), incubator (Yorco Sales Pvt. Ltd, New Delhi, India), zone reader (Cintex Industrial Corporation, India), hot air oven, autoclave and UV-Visible spectrophotometer (Shimadzu Corporation, Japan) were used for respective investigations. Elemental analysis was carried out on CHNS/O Elemental Analyser manufactured by PerkinElmer. The amount of halogens present in the compound was determined by the procedure reported in the literature.[18] Infrared spectra of the compounds were recorded in KBr discs on Perkin-Elmer FT-IR spectrometer (υ_{max} in cm^{-1}). ^1H NMR spectra were recorded on a JOEL (300 MHz) spectrometer using TMS as an internal standard (chemical shifts in δ). The mass spectra were recorded on a mass spectrometer JOEL sx-102.

Experimental section

Synthesis of ethyl-2-(4-chlorophenoxy)acetate (2)

4-Chloro-phenol (5 g, 29 mmol, 1.0 eq.) was added to a stirred suspension of Sodium hydride (1.12 g, 46.8 mmol, 1.2 eq) in DMF (25 mL) and the reaction mixture was stirred for 30 min. Ethylbromoacetate (9.8 g, 58 mmol, 1.5 eq) was added drop wise and was stirred for 3 h. The reaction mixture was poured in cold water, extracted with Ethyl acetate, organic layer was washed with water, brine solution, dried over anhydrous Sodium sulphate and the solvent was removed under reduced pressure to get crude compound. The crude solid was purified by silica gel (100−200 mesh) column chromatography, eluted with 2% Ethylacetate/Petroleum ether to get pure Ethyl-2-(4-chlorophenoxy)acetate (Yield:76%).

Synthesis of 2-(4-Chlorophenoxy)acetohydrazide (3)

A mixture of Hydrazine hydrate (0.980 g, 19.6 mmol, 4 eq.), Ethyl-2-(4-chlorophenoxy)acetate (2) (2.1 g, 9.8 mmol,1 eq.) in Ethanol (20 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature, filtered, so obtained solid was washed with Ethanol and dried under vacuum to get pure 2-(4-Chlorophenoxy)acetohydrazide (Yield:71%).

Synthesis of 1-(2-(4-Chlorophenoxy)acetyl) thiosemicarbazide (4)

Potassium thio cyanate (10.7 g, 110 mmol, 3.5 eq.) was added to a stirred solution of 2-(4-Chlorophenoxy)acetohydrazide (3) (6.2 g, 31 mmol,1 eq) in H_2O (31 mL) and HCl (7.75 mL) and the reaction mixture was heated to 90 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with water and filtered. The solid so obtained was dried under vacuum to get crude 1-(2-(4-Chlorophenoxy) acetyl) thiosemicarbazide (Yield:79%).

Synthesis of 5-(4-Chlorophenoxymethyl)-2,4-dihydro-1,2,4-triazole-3-thione (5)

1-(2-(4-Chlorophenoxy)acetyl) thiosemicarbazide (4) (0.500 g, 1.92 mmol) was dissolved in saturated K_2CO_3 (70.0 mL) solution and stirred at room temperature for 2 days. The reaction mixture was filtered and the filtrate was acidified with 2N HCl. The reaction mixture was filtered and solid so obtained was dried under vacuum to get pure 5-(4-Chlorophenoxymethyl)-2,4-dihydro-1,2,4-triazole-3-thione (Yield:69%).

Synthesis of 3-Benzylsulfanyl-5-(4-chloro-phenoxymethyl)-4H-1,2,4-triazole (6a)

To a stirred solution of Potassium hydroxide in Ethanol (0.300 g in 15 mL), 5-(4-Chlorophenoxymethyl)-2,4-dihydro-1,2,4-triazole-3-thione (5) (0.483 g, 2 mmol) and Benzyl chloride (12 mL) were added. The reaction mixture was heated to reflux temperature for 4 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with Ethylacetate. The organic layer was washed with water, brine solution, dried over anhydrous Sodium sulphate and the solvent was removed under reduced pressure to obtain 3-Benzylsulfanyl-5-(4-chloro-phenoxymethyl)-4*H*-1,2,4-triazole (6a). The product was isolated by recrystallization from a mixture of Ethylacetate-petroleum ether (1:1) (Yield:70%).