Journal of Saudi Chemical Society (2016) **20**, S426–S432

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Discovery of some novel imines of 2-amino, 5-thio, 1,3,4-thiadiazole as mucomembranous protector. Synthesis, anti-oxidant activity and *in silico* PASS approach

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Received 16 November 2012; accepted 14 January 2013
Available online 26 January 2013

KEYWORDS

Benzimidazole chalcones;
PASS;
DPPH;
Thiadiazole

Abstract A series of some novel imines (6a–f) of 2-amino, 5-thio 1,3,4-thiadiazole connected to benzimidazole chalcones were prepared. The structures of the final imines were ascertained by IR, ^{1}HNMR, mass and elemental analyses. Predicted activity spectra of all the final derivatives were determined in the category of mucomembranous protector nature with a Pa value more than 0.7. All the newly synthesized compounds were screened for their antiulcer activity in the pylorus-ligated rats. Free radical scavenging activity of all final derivatives was determined by DPPH method. Compounds 6e, 6a and 6b showed a percentage protection of (73.47, 72.17 and 70.43 at a dose of 10 mg/kg b.w.) when compared to standard omeprazole (77.37%, 2 mg/kg b.w.). Compounds 6e, 6a and 6b showed free radical scavenging activity with an IC_{50} of 0.32, 0.39 and 0.49 mM respectively. Scanning of stomach specimens using electron microscope revealed that the mice treated with standard and synthetic derivatives had no injury observed in stomach mucosa, which is identical to that of the control animal. It has been concluded that ulcer healing properties of the imines are probably due to their antioxidant action.

1. Introduction

Free radicals and reactive oxygen species have been involved in the aetiology and pathophysiology of gastric ulcers. The collapse of mucosal defence mechanism ultimately leads to gastric inflammation and ulceration (Onasanwo et al., 2010). Antioxidants have a significant role in the protection against the ulceration of gastric mucosa. It has been demonstrated that many

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2013.01.002

synthetic agents that possess potent antioxidant actions are an effective choice in healing experimentally induced gastric ulcers (Subudhi and Shaoo, 2011; Kim, 2005). Benzimidazoles were commonly used as proton pump inhibitors, which can control the hyperacidity in the stomach. The mechanism of the antiulcer effect of benzimidazole containing omeprazole was studied placing emphasis on its role to block oxidative damage and apoptosis during ulceration (Biswas et al., 2003).The recent literature suggested that 1,3,4-thiadiazole derivatives have received remarkable attention in antioxidant activity (Khan et al., 2010; Zhivotova et al., 2008; Vinay Kumar et al., 2012;Azam et al.,2008). In view of above reports, it was thought worthwhile to design a novel framework, by which the benzimidazole derivatives were linked with 1,3,4-thiadiazole to exhibit potent antioxidant action which can be effective in treating experimentally induced peptic ulcers.

The chalcones 4a–f were prepared by reacting 2-acetyl benzimidazole with appropriate aldehydes in the presence of a base by Claisen–Schmidt condensation (Mathew et al.,2012).The heteroaryl chalcones that undergo nucleophilic addition followed by dehydration with 5-amino-1,3,4-thiadiazole-2-thiol 5a gave the titled compounds 6a–f. In benzimidazole chalcone carbonyl carbon is less susceptible for the nucleophilic attack due to the conjugation of pi electrons from the adjacent olefinic system. So the nucleophilic attack can be facilitated by the protonation of carbonyl oxygen by a mineral acid. Thus the electron deficient carbonyl carbon can fairly attack on the amino group of 1,3,4-thiadiazole ring and forms an imine linkage between the two heterocyclic systems (Ahmed et al., 2008).

2. Materials and methods

2.1. Chemistry

All the solvents and chemicals were purchased from MERCK, Nice chemicals and SD Fine Chemicals. Melting points were determined by using an open capillary tube method and the values were uncorrected. IR spectra were recorded on JASCO FT/IR-140 spectrophotometer by using KBr pellet technique. PMR spectra were recorded using BRUCKER FT-NMR-500 MHz spectrophotometer by using DMSO as a solvent and TMS as an internal standard. The chemical shift was expressed in δ ppm. Mass spectra were recorded on a JEOL GCmate mass spectrometer.

2.1.1. Synthesis of benzimidazole chalcones (4a–f): general procedure

2-Acetyl benzimidazole (0.01 mol) and appropriately substituted aromatic aldehydes (0.012 mol) were mixed in ethanol (20 ml) containing 10% aq. KOH (8 ml) and magnetically stirred the solution constantly at room temperature for 10 h. The whole mixture was transferred into 100 ml ice cold water and acidified with dil. HCl. The solid formed was washed, filtered, dried and recrystallized from absolute ethanol.

2.1.2. Synthesis of 5-{[(1E, 2E)-1-(1H-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] amino}-1,3,4-thiadiazole-2-thiol (6a–f)

(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (0.02 mol) (4a–f) was suspended in 20 ml of absolute ethanol in the presence of 1–2 drops of conc. HCl. The resulting solution was stirred for 45 min and added (0.03 mol) 5-amino-1,3,4-thiadiazole-2-thiol.The whole mixture was refluxed for 5–6 h with a continuous shaking under the bottom of RBF in order to prevent the adherence of reaction mixture to the wall of flask. The progress of the reaction was monitored by TLC. After the complete disappearance of the starting material (TLC), the reaction mixture was cooled and poured crushed ice into it. The solid obtained was filtered and thoroughly washed with water until it is free from acids. The crude product was dried and recrystallized with methanol:water (9:1).

2.1.3. 5-{[(1E, 2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ylidene] amino}-1,3,4-thiadiazole-2-thiol (6a)

Pale orange solid, mp 165–167 °C, yield 67%. IR: ν_{max}/cm^{-1} 3150 (–NH), 1595 (C═N), 742 (C–S). ^{1}HNMR (DMSO-d_6/TMS):11.9 (s, 1H, SH), 8.9 (s, 1H, NH), 7.5–8.7 (m, 9H, aryl protons), 7.1–7.3 (d, 2H, ene-H). MS:$m/z(M+1)^+$364. (Anal. Calcd. for $C_{18}H_{13}N_5S_2$:C, 59.48; H, 3.61; N, 19.27. Found: C, 59.79; H, 2.85; N, 19.15.)

2.1.4. 5-{[(1E, 2E)-1-(1H-benzimidazol-2-yl)-3-(4-chlorophenyl)prop-2-en-1-ylidene]amino}-1,3,4-thiadiazole-2-thiol (6b)

Pale red solid, mp 190–191 °C, yield 81%.IR: ν_{max}/cm^{-1} 3061(–NH), 1589 (C═N), 744 (C–S). ^{1}HNMR (DMSO-d_6/TMS):11.7 (s, 1H, SH), 9.2 (s, 1H, NH), 7.5–8.8 (m, 8H, aryl protons), 7.2–7.4 (d, 2H, ene-H). MS:$m/z(M+2)^+$400. (Anal. Calcd. for $C_{18}H_{12}ClN_5S_2$:C, 54.33; H, 3.04; N, 17.60. Found: C, 54.31; H, 2.84; N, 17.83.)

2.1.5. 5-{[(1E, 2E)-1-(1H-benzimidazol-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-ylidene]amino}-1,3,4-thiadiazole-2-thiol (6c)

Yellow solid, mp 178–180 °C, yield 71%.IR: ν_{max}/cm^{-1} 3064(–NH), 1529 (C═N), 754 (C–S). ^{1}HNMR (DMSO-d_6/TMS):11.6 (s, 1H, SH), 8.7 (s, 1H, NH), 7.4–8.2 (m, 8H, aryl protons), 6.8–7.2 (d, 2H, ene-H). 3.9 (s, 3H, OCH_3) MS:$m/z(M+)^+$394. (Anal. Calcd. for $C_{19}H_{15}N_5S_2O$:C, 58.00; H, 3.84; N, 17.80. Found: C, 58.26; H, 3.08; N, 17.13.)

2.1.6. 5-({(1E,2E)-1-(1H-benzimidazol-2-yl)-3-[4-(dimethyl amino) phenyl]prop-2-en-1-ylidene}amino)-1,3,4-thiadiazole-2-thiol(6d)

Brick red solid: mp 170–171 °C, yield 78%. IR: ν_{max}/cm^{-1} 3058(–NH), 1532 (C═N) 761 (C–S).1HNMR (DMSO-d_6/TMS):11.3 (s, 1H, SH), 8.8 (s, 1H, NH), 7.3–8.1 (m, 8H, arylprotons), 6.8–7.1 (d, 2H, ene-H), 3.8 (s, 3H, $N(CH_3)_2$). MS:$m/z(M+1)^+$407. (Anal. Calcd. for $C_{20}H_{18}N_6S_2$:C, 59.09; H, 4.46; N, 20.67. Found: C, 58.38; H, 4.32; N, 20.20.)

2.1.7. 5-{[(1E,2E)-1-(1H-benzimidazol-2-yl)-3-(3-nitro phenyl)prop-2-en-1-ylidene]amino}-1,3,4-thiadiazole-2-thiol (6e)

Pale rose solid, mp 181–182 °C, yield 79%. IR: ν_{max}/cm^{-1} 3082(-NH), 1543 (C═N), 746 (C–S), 1350 (N═O); ^{1}HNMR (DMSO-d_6/TMS):12.3 (s, 1H, SH), 9.1 (s, 1H, NH), 7.9–8.9 (m, 8H, arylprotons),6.9–7.1 (d, 2H, ene-H). MS:$m/z(M+1)^+$:409. (Anal. Calcd. for $C_{18}H_{12}N_6S_2O_2$:C, 59.93; H, 2.96; N, 20.58. Found: C, 52.75; H, 2.64; N, 19.70.)