Egyptian Journal of Basic and Applied Sciences xxx (2017) xxx–xxx

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Contents lists available at ScienceDirect

Egyptian Journal of Basic and Applied Sciences

journal homepage: www.elsevier.com/locate/ejbas

Full Length Article

Synthesis, antibacterial and molecular docking studies of new benzimidazole derivatives

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ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form 17 September 2017
Accepted 17 September 2017
Available online xxxx

Keywords:
Benzimidazole
Triazinane & oxadiazinane 4-thiones
Antibacterial activity
Molecular docking

ABSTRACT

The new analogs of benzimidazole fused heterocyclic compounds such as triazinane and oxadiazinanes were synthesised by classical amino methylation with different aryl-*N*,*N*′ unsymmetrical thioureas. The antibacterial activity of triazinane and oxadiazinane compounds have been assessed with zone of inhibition by well diffusion method using a panel of selected gram positive and gram negative bacterial strains and which have showed good activity. The synthesised molecules were subjected to molecular docking studies with two proteins, namely *topoisomerase II* (*PDB ID*: 1JIJ) and *DNA gyrase subunit b* (*PDB ID*: 1KZN). The molecular docking studies are supporting the antibacterial activity exhibiting high inhibition constant and binding energy.

1. Introduction

The organic compounds specifically with N-heterocyclic ring systems exhibit a wide range of biological activities through effective binding to enzyme receptor site. As per the present global scenario, thousands of new heterocyclic compounds either isolated from natural sources or synthesized in the laboratories are added to the literature every year. Many of these compounds have drawn the attention of researchers based on their biological, therapeutic and industrial potential.

Benzimidazoles are found to be useful intermediates for the development of new molecules of biological or pharmaceutical interest. Substituted benzimidazole derivatives have been found to possess Biological activities such as antitumor [1], antimicrobial [2], anthelmintic [3], antibacterial [4], analgesic [5], anti inflammatory [6] etc. In recent times, new techniques have been adopted for the efficient synthesis of novel heterocycles by using heterogeneous, nano-catalysts and photocatalysis that are highly effective and ecofriendly [7–13]. Triazinane derivatives belonging to nitrogen heterocycles have greatest importance due to their potential applications. These have been identified as commercial products which are used as H_2S scavengers in the areas with relatively low concentrations of H_2S and it is inexpensive to use. The products of the scavenging reactions are believed to be biodegradable and water soluble [14]. Little work has been published in the area of 1,3,5-triazinane-4-thiones and 1,3,5-triazinane-2-ones showing antimicrobial activity [15]. These are also promising intermediates in the synthesis of tyrosine derivatives, which are well-known compounds used as Biocidal [16] and enantio-differentiating coupling reagents [17]. Heterocyclic structural unit has a significant place among pharmaceutically important synthetic and natural materials [18], showing powerful antiproliferative action [19]. For these reasons, 1,3,5-triazinane derivatives incorporating thiourea unit may be important in many fields [20].

2. Experimental section

2.1. Materials and methods

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. Reaction Progress was observed by TLC plates, Bruker 300 MHz instrument was used to record ^{1}H NMR spectra in DMSO/$CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Perkin Elmer BX series FT-IR was to record IR spectra, Elemental analysis were performed on a PerkinElmer 240 CHN analyzer (Scheme 1).

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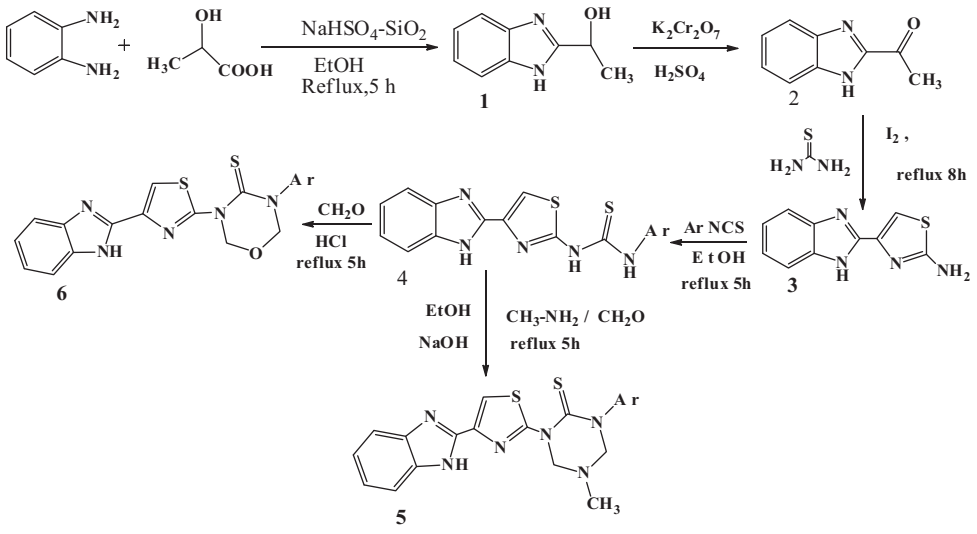
https://doi.org/10.1016/j.ejbas.2017.09.002
2314-808X/



Scheme 1. Synthesis of 1-(4-(1*H*-benzo[*d*]imidazol-2-yl)thiazol-2-yl)-5-methyl-3-phenyl-1,3,5-triazinane-2-thiones/oxadiazinane-2-thiones.

*2.1.1. Synthesis of 4-(1H-Benz[d]imidazol-2yl)-1,3-thiazol-2-amine (**3**)*

A solution of 2-acetyl benzimidazole (0.01 mmol) in isopropanol (20 ml) was added to the mixture of thio urea (0.01 mmol) and iodine (0.12 mmol) taken in isopropanol (20 ml). The reaction mixture was heated under reflux for 3 h. After completion of the reaction, (monitored by TLC) the solvent was removed *in vacuo*. The solid separated was washed with aq. Sodium bicarbonate solution, dried and recrystallized from ethanol to give the product (**3**) in a pure state (Figs. 1 and 2).

*2.1.2. Synthesis of 4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-3-phenyl thiourea (**4**)*

A mixture of compound (**3**) (0.01 mmol) and sodium hydride (0.5 g, 20 mmol) in Ethanol (80 ml) was heated under reflux for 30 min and cooled. Phenylisothiocynate (0.01 mmol) was added and refluxing continued for a further 4 h. The solvent was evaporated off and the residue dissolved in DCM (50 ml) was washed with dilute HCl. The organic phase was dried ($MgSO_4$) and the solvent was evaporated off to give the desired compound (**4**). The progress of the reaction was monitored by TLC and recrystallized from ethanol. Compounds **4**(**b**–**e**) were prepared by similar procedure with minor changes in reaction conditions. The structures of the compounds (**4**) have been confirmed on the basis of analytical and spectral IR, ^{1}H NMR and Mass data.

*2.1.2.1. 4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-3-phenyl thiourea (**4a**).* Yield 72%, m.p 162–164 °C. IR (KBr) λ_{max} in (cm^{-1}) 3368 (NH), 1590 (C═N), 1231 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm) 8.28–8.40 (m, 4H, Ar H), 7.49–7.68 (m, 2H, Ar H), 6.87–7.13 (m, 3H, Ar H), 11.28 (s, 1H, NH), 6.52 (S, 1H, CH Ar); MS, *m*/*z* (%), 352 (M^+) Anal. Calcd. For $C_{17}H_{13}N_5S_2$: C, 58.10; H, 3.73; N, 19.93%; Found: C, 57.78; H, 3.58; N, 19.85%.

*2.1.2.2. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-3-P-tolyl thiourea (**4b**).* Yield 70%, m.p 165–167 °C. IR (KBr) λ_{max} in (cm^{-1}) 3371 (NH), 1586 (C═N), 1248 (C═S), ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm), 8.25–8.38 (m, 4H, Ar H), 7.46–7.65 (m, 2H, Ar H), 6.85–7.11 (m, 2H, Ar H), 10.45 (s, 1H, NH), 6.60 (s, 1H, CH, Ar), 2.27 (s, 3H, CH_3); MS, *m*/*z* (%), 365 (M^+) Anal. Calcd. For $C_{18}H_{15}N_5S_2$: C, 59.15; H, 4.14; N, 19.16%; Found: C, 58.78; H, 4.02; N, 18.78%.

*2.1.2.3. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-3-(4-methoxy phenyl)thiourea (**4c**).* Yield 68%, m.p 166–168 °C. IR (KBr) λ_{max} in (cm^{-1}) 3365 (NH), 1565 (C═N), 1252 (C═S), 1085 (OCH_3), ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm), 10.48 (s, 1H, NH), 6.66 (S, 1H, CH Ar), 3.52 (s, 3H, CH_3), 8.22–8.35 (m, 4H, Ar H), 7.43–7.60 (m, 2H, Ar H), 6.85–7.18 (m, 2H, Ar H), MS, *m*/*z* (%), 381 (M^+); Anal. Calcd. For $C_{18}H_{15}N_5OS_2$: C, 56.67; H, 3.96; N, 18.36 (%); Found: C, 56.12; H, 3.45; N, 18.22 (%).

*2.1.2.4. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-3-(4-nitrophenyl) thio urea (**4d**).* Yield 64% m.p 164–166 °C. IR (KBr) λ_{max} in (cm^{-1}) 3373 (NH), 1565 (C═N), 1520 (NO_2); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm), 8.26–8.36 (m, 4H, Ar H), 7.45–7.60 (m, 2H, Ar H), 6.857.23 (m, 2H, Ar H), 10.92 (s, 1H, NH), 6.62 (s, 1H, CH Ar), MS, *m*/*z* (%), 396 (M^+); Anal. Calcd. For $C_{17}H_{12}N_6O_2S_2$: C, 51.50; H, 3.06; N, 21.20%; Found: C, 50.88; H, 2.82; N, 20.75%.

*2.1.2.5. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-3-(4-chloro phenyl)thio urea (**4e**).* Yield 65% m.p 168–169 °C. IR (KBr) λ_{max} in (cm^{-1}) 3366 (NH), 1562 (C═N), 780 (C—Cl); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm), 8.22–8.33 (m, 4H, Ar H), 7.42–7.63 (m, 2H, Ar H), 6.80–7.25 (m, 2H, Ar H), 11.17 (s, 1H, NH), 6.62 (s, 1H, CH Ar); MS, *m*/*z* (%), 387 (M^+); Anal. Calcd. For $C_{17}H_{12}ClN_5S_2$: C, 52.91; H, 3.13; N, 18.15%; Found: C, 52.21; H, 2.78; N, 17.84%.

*2.1.3. Synthesis of 4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl-5-methyl-3-phenyl-1,3,5-triazinane-2-thione (**5**)*

A mixture of compound (**4**) in (1 mmol), 30% formaldehyde (2 mmol) methyl amine (1 mmol) and (0.01 mol) NaOH was taken in ethanol (30 ml) and refluxed for about 5–6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, it was cooled and the product was filtered. The crude product was passed through silica gel by column and the product was eluted from 60% ethyl acetate and hexane. These compounds were purified by crystallization from suitable solvents. The structures of the compounds (**5**) have been confirmed on the basis of analytical and spectral IR, ^{1}H NMR and Mass data. Compounds **5**(**b**–**e**) were prepared by similar procedure with minor changes in reaction conditions.

*2.1.3.1. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-methyl-3-phenyl-1,3,5-triazinane-2-thione (**5a**).* Yield 74% m.p 175–178 °C. IR (KBr) λ_{max} in (cm^{-1}) 3355 (NH), 1563 (C═N), 1263 (C═S); ^{1}