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Original Article

Synthesis, characterization and pharmacological evaluation of different 1,3,4-oxadiazole and acetamide derivatives of ethyl nipecotate

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ABSTRACT

A new series of *N*-substituted derivatives of 2-[(5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (**6a-w**) has been designed and synthesized with multifunctional moieties. The synthesized compounds were evaluated for their antibacterial and anti-enzymatic potential supported by % hemolytic activity. The synthesized compound 5-(1-(4-chlorophenylsulfonyl)-3-piperidinyl)-1,3,4-oxadiazole-2-thiol (**3**) was stirred with synthesized electrophiles as *N*-aryl/alkyl/aralkyl-2-bromoacetamide (**5a-w**) in an aprotic solvent under basic conditions to acquire the target molecules, **6a-w**. The spectral analytical techniques of IR, EI-MS, ^{1}H NMR and ^{13}C-NMR were utilized for structural elucidation of synthesized molecules. The antibacterial screening against certain bacterial strains of gram-negative and gram-positive bacteria rendered compound **6i** as good inhibitor of gram-negative bacterial strains. The enzyme inhibition revealed low potential against lipoxygenase (LOX) enzyme. The hemolytic study provided valuable information about cytotoxic behavior of synthesized molecules.

1. Introduction

Pharmacists and synthetic chemists have shown keen interest for search of novel potent drug candidates to compete the escalating resistant microbes more effectively and efficiently [1]. Research from decades has emphasized the importance of heterocyclic compounds like 1,3,4-oxadiazole derivatives possessing diverse therapeutic and antimicrobial applications [2,3]. The different biological activities relating to these heterocyclic compounds are anti-malarial, antimicrobial, anticancer, anti-tumor, anti-inflammatory, anti-HIV, anticonvulsant, anti-mycobacterial, anti-tuberculosis, antidepressant and anti-analgesic ones [4–11]. Another heterocyclic core of piperidine has also been found to constitute a number of natural and synthetic bioactive compounds [12]. Furthermore, it has been employed as intermediate for inorganic synthesis, curing agent for rubber, solvent and food additive [13,14].

The antibacterial activity was assessed against Gram-negative (*Salmonella typhi*, *Echerichia coli* and *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacteria. *S. aureus* is known to adhere to extracellular matrix and plasma proteins [15]. *B. subtilis* generates subtilisin responsible for hypersensitivity reactions on long exposure or dermal allergic [16]. *P. aeruginosa*, *S. typhi* and *E. coli* are associated with chronic infection [17], enteric fever [18] and food poisoning [19] respectively. Also enzyme inhibition activity was assessed against lipoxygenase enzyme. Lipoxygenases (EC 1.13.11.12) are implied in arachidonic acid metabolism. Furthermore these generate different bioactive lipids causing inflammation. Lipoxygenase inhibitors might be employed for the treatment of disorders like bronchial asthma, inflammation etc [20,21].

Presented research work was an effort to contribute to the pharmaceutical sector by synthesizing new bioactive compounds that may help to protect and conserve human health. The literature review for bioactivities of considered functionalities and the results of previous work by our group [9–11,22–25] prompted us to synthesize new some molecules. A series of synthesized *N*-substituted derivatives of 2-[(5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (**6a-w**) were

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screened for antibacterial, LOX inhibition and hemolytic activities. The most active enzyme inhibitors might be used as anti-inflammatory agents and the most active antibacterial agents as antibiotics.

2. Materials and methods

2.1. General

The analytical grade chemical reagents and solvents were purchased from Sigma Aldrich and Alfa Aesar (Germany) *via* local suppliers. The stereochemistry of ethyl nipecotate is (R)-(-)-ethyl nipecotate. Melting points of all synthesized compounds were determined by open capillary tube method using Griffin-George melting point apparatus and were uncorrected. Purity of all the synthesized derivatives was assured by TLC using ethyl acetate and *n*-hexane (30:70) as mobile phase and detected under UV lamp at 254 nm. Jasco-320-A spectrophotometer was used to record IR spectra by KBr pellet method. Bruker spectrometers working at 300 & 400 MHz were used to record ^{1}H-NMR and that working at 100 MHz for ^{13}C-NMR signals having chemical shift values in ppm unit. $CDCl_3$ was employed as solvent for NMR analysis. JMS-HX-110 spectrometer was utilized to record EIMS signals.

2.2. Procedure for synthesis of ethyl 1-[(4-chlorophenyl)sulfonyl] piperidin-3-carboxylate (**1**)

Synthesis of Ethyl 1-[(4-chlorophenyl)sulfonyl]piperidin-3-car boxylate (**1**) was afforded by stirring 4-chlorobenzenesulfonyl chloride (**a**; 0.033 mol, 7.0 g) with ethyl piperidin-3-carboxylate (**b**; 0.033 mol, 5.2 g) for 4 h in 250 mL round bottom flask using water (100 mL) as solvent. During reaction pH was maintained at 8–10 by 5% aqueous Na_2CO_3 solution. Reaction proceeding was monitored by TLC. On completion, excess cold distilled water (150 mL) was added to reaction contents to get the precipitates of product. The precipitates were filtered and washed with distilled water.

2.3. Procedure for synthesis of 1-[(4-chlorophenyl)sulfonyl]piperidin-3-carbohydrazide (**2**)

1-[(4-Chlorophenyl)sulfonyl]piperidin-3-carbohydrazide (**2**) was synthesized by refluxing ethyl 1-[(4-chlorophenyl)sulfonyl]pi peridin-3-carboxylate (**1**; 6.4 mL, 0.02 mol) with hydrazine hydrate (13.0 mL, 0.03 mol) in methanol (100 mL) for 3 h in a RB flask (250 mL). The reaction completion was monitored by TLC. Product was obtained as precipitates on addition of distilled water which were separated through filtration and washing. Finally product was re-crystallized by using methanol.

2.4. Procedure for synthesis of 5-(1-(4-chlorophenylsulfonyl)-3-piperidinyl)-1,3,4-oxadiazol-2-thiol (**3**)

5-(1-(4-Chlorophenylsulfonyl)-3-piperidin)-1,3,4-oxadiazol-2-t hiol (**3**) was synthesized by refluxing compound **2** (9.5 g, 0.03 mol) with potassium hydroxide (3.36 g, 0.06 mol) and carbon disulphide (1.8 mL, 0.03 mol) in ethanol (80 mL) for 6 h in RB flask (250 mL). Reaction progress was monitored by TLC. On reaction completion, cold distilled water was added to the reaction contents and acidified up to pH of 2–3 to quench the precipitates. Precipitates were filtered and washed with distilled water and finally recrystallized by methanol. White amorphous solid; Yield: 85%; M.P. 145–146 °C; Molecular formula: $C_{13}H_{14}ClN_3O_3S_2$; Molecular Mass: 359 gmol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3033 (Ar-H), 2252 (S-H stretching), 1591 (C=N stretching), 1524 (Ar C=C stretching), 1327 (-SO_2 stretching), 1175 (C-O-C stretching); ^{1}H-NMR ($CDCl_3$, 300 MHz, δ/ppm): 7.70 (d, J = 8.4 Hz, 2H, H-2″ & H-6″), 7.52 (d, J = 8.7 Hz, 2H, H-3″ & H-5″), 3.90 (dd, J = 11.7, 3.6 Hz, 1H, H_e-2′), 3.65 (br.d, J = 11.7 Hz, 1H, H_a-2′), 3.10–3.02 (m, 1H, H-3′), 2.65 (br.t, J = 9.9 Hz, 1H, H_e-6′), 2.49 (td, J = 11.4, 3.0 Hz, 1H, H_a-6′), 2.10–2.06 (m, 1H, H_e-5′), 1.90–1.82 (m, 1H, H_e-4′), 1.81–1.70 (m, 1H, H_a-5′), 1.69–1.58 (m, 1H, H_a-4′); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ/ppm): 178.4 (C-2), 163.6 (C-5), 139.7 (C-1″), 134.6 (C-4″), 129.5 (C-2″ & C-6″), 128.9 (C-3″ & C-5″), 47.5 (C-2′), 46.1 (C-6′), 33.7 (C-3′), 26.5 (C-4′), 23.5 (C-5′); EIMS (m/z): 359 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\cdot+}$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\cdot+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$; Anal. Calcd for $C_{13}H_{14}ClN_3O_3S_2$: C 43.39, H 3.92, Cl 9.85, N 11.68, O 13.34, S 17.82; found C 43.31, H 3.79, Cl 9.77, N 11.61, O 13.22, S 17.73.

2.5. General procedure for synthesis of N-aryl/alkyl/aralkyl-2-bromoacetamides (**5a-w**)

N-aryl/alkyl/aralkyl amines (**4a-w**; 0.015 mol) were suspended in distilled water (15.0 mL) in 100 mL RB flask containing 5% Na_2CO_3 solution to maintain the pH 9.0 to 10.0. The reaction contents were set to stir at RT and after a few minutes 2-bromoacetyl bromide (**c**; 0.015 mol) was introduced to reaction flask drop wise and subjected to vigorous shaking till the emergence of precipitates. The reaction contents were stirred for 15 min. Purity of product was assured by TLC. At the end, the precipitates were filtered, washed with distilled water and dried to get the electrophiles, *N*-aryl/alkyl/aralkyl-2-bromoacetamides (**5a**-**w**).

2.6. General procedure for the synthesis of N-substituted 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-1,3,4-oxadiazol-2-yl-2-sulfanyl acetamide (**6a-w**)

Compound **3** (0.2 g, 0.55 mmol) was dissolved in 8–10 mL DMF in 100 mL round bottom flask, followed by 0.002 g NaH used as a weak base and set to stir at room temperature for half an hour. Equimolar *N*-aryl/alkyl/aralkyl-2-bromoacetamides (**5a-w**) were added to the reaction contents and left to stir at 50–60 °C till reaction completion. The time duration for completion of reaction varied from 3 to 5 h for different electrophiles. TLC was performed to check the reaction progress. Cold distilled water was added to the reaction mixture to separate the precipitates. Precipitates so obtained were filtered, washed and dried for pharmacological & structural analysis.

2.6.1. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-1,3,4-oxadiazol-2-yl)sulfanyl]-N-(2,3-dimethylphenyl)acetamide (**6a**)

Off white amorphous solid; Yield: 83%; M.P. 129–131 °C; Molecular formula: $C_{23}H_{25}ClN_4O_4S_2$; Molecular Mass: 521 gmol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3340 (N–H stretching), 3035 (Ar-H), 1660 (C=O stretching), 1593 (C=N stretching), 1521 (Ar C=C stretching), 1325 (–SO_2 stretching), 1170 (C-O-C stretching); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 8.65 (br. s, 1H, -NH), 7.69 (d, J = 8.4 Hz, 2H, H-2″ & H-6″), 7.55 (d, J = 8.0 Hz, 1H, H-6‴′), 7.51 (d, J = 8.8 Hz, 2H, H-3″ & H-5″), 7.06 (t, J = 8.0 Hz, 1H, H-5‴′), 6.98 (d, J = 7.6 Hz, 1H, H-4‴′), 3.97 (s, 2H, H-2‴), 3.89 (dd, J = 11.6, 3.6 Hz, 1H, H_e-2′), 3.64 (br.d, J = 11.6 Hz, 1H, H_a-2′), 3.11–3.03 (m, 1H, H-3′), 2.65 (br.t, J = 10.2 Hz, 1H, H_e-6′), 2.49 (td, J = 11.2, 3.0 Hz, 1H, H_a-6′), 2.26 (s, 3H, CH_3-3‴′), 2.11 (s, 3H, CH_3-2‴′), 2.09–2.04 (m, 1H, H_e-5′), 1.92–1.84 (m, 1H, H_e-4′), 1.83–1.72 (m, 1H, H_a-5′), 1.68–1.57 (m, 1H, H_a-4′); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ/ppm): 171.0 (C-1‴), 165.7 (C-2), 163.5 (C-5), 142.7 (C-1″), 140.1 (C-4″), 137.5 (C-3‴′), 136.1 (C-1‴′), 130.1 (C-2″ & C-6″), 129.6 (C-3″ & C-5″), 128.2 (C-2‴′), 127.5 (C-4‴′), 125.2 (C-5‴′), 121.6 (C-6‴′), 50.5 (C-2′), 47.5 (C-6′), 40.7 (C-3′), 33.2 (C-2‴), 28.3 (C-4′), 24.5 (C-5′), 19.9 (CH_3-3‴′), 14.8 (CH_3-2‴′); EIMS (m/z): 521 $[M]^+$, 359 $[C_{13}H_{13}ClN_3O_3S_2]^+$,

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