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ORIGINAL ARTICLE

Synthesis of some new 5-substituted-2-((6-chloro-3,4-methylenedioxyphenyl)methylthio)-1,3,4-oxadiazole derivatives as suitable antibacterial inhibitors

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Abstract Heterocyclic molecules belong to the most attractive group owing to their broad spectrum of antimicrobial activities. In the undertaken research, a number of new 5-substituted-2-((6-chloro-3,4-methylenedioxyphenyl)methylthio)-1,3,4-Oxadiazole derivatives (**6a–l**) were synthesized by converting various aryl/aralkyl carboxylic acids (**1a–l**) into corresponding esters (**2a–l**), carbohydrazides (3**a–l**) and 5-substituted-1,3,4-Oxadiazol-2-thiols (**4a–l**). The last step included the synthesis of target molecules, **6a–l**, by stirring **4a–l** and 6-chloro-3,4-methylenedioxybenzyl chloride (**5**) in a polar aprotic solvent. The structures of all the synthesized molecules were corroborated through spectral analysis. The screening of these molecules against antibacterial activity rendered them moderate inhibitors and most likely against *Escherichia coli*, relative to the reference standard, ciprofloxacin.

1. Introduction

Heterocyclic molecules such as Oxadiazoles have been synthesized and evaluated for medical and agricultural activities. The disubstituted Oxadiazoles have executed a range of pharmacologic activities. 1,3,4-Oxadiazole heterocycle has displayed many activities like antibacterial, antifungal, hypoglycemic and anti-inflammatory. It also possesses an important place in medicinal chemistry. Chemists are much interested in 2,5-disubstituted 1,3,4-Oxadiazoles because of their antimicrobial activities.[1–6] The heterocycle, 3,4-methylenedioxyphenyl ring is also the part of active drugs. The molecules employed as antitumor and anticancer possessing this ring are lycoricidine, narciclasine and pancratistatin.[7] Moreover, the antidepressant drugs such as paroxetine also bear this moiety.[8]

The structural modification leads to variation in antimicrobial activities of the molecules. This prompted us to extend our previous work[9–11] to synthesize 5-substituted-2-((6-chloro-3,

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4-methylenedioxyphenyl)methylthio)-1,3,4-Oxadiazole derivatives with an aim to observe their antibacterial activity. The synthesized molecules were found to be better inhibitors of *Escherichia coli* and *Pseudomonas aeroginosa* relative to ciprofloxacin.

2. Materials and methods

2.1. General

The reagents, purchased from Alfa Aesar and Sigma–Aldrich, were of synthetic grade and the solvents, obtained through commercial suppliers, were of analytical grade. Melting points of the synthesized molecules were measured on Griffin-George apparatus in an open capillary tube and were uncorrected. Purity and reaction progress were monitored through thin layer chromatography (TLC) on coated silica gel G-25-UV_{254} plates using different ratios of ethyl acetate and *n*-hexane as solvent systems. KBr (potassium bromide) pellet procedure was used to record I.R. spectra on a Jasco-320-A spectrophotometer. Wave number is given in cm^{-1}. Bruker spectrometers are employed for ^{1}H NMR & ^{13}C NMR spectra in $CDCl_3$ at 400–100 MHz. Chemical shifts are given in ppm relative to TMS and coupling constant in Hz. EIMS were recorded through JMS-HX-110 spectrometer, with a data system.

2.2. General procedure for the synthesis of esters (**2a–l**)

The aryl/aralkyl carboxylic acids (**1a–l**; 2.0 g) were dissolved in 8.0 mL absolute ethanol followed by the addition of 1.0 mL concentrated sulfuric acid in a 100 mL round bottom (RB) flask. The mixture was refluxed for 2–5 h. After reaction completion, established by TLC (ethyl acetate:*n*-hexane, 20%:80%), the mixture was poured into a 250 mL separating funnel. Then 80 mL distilled water and concentrated aqueous sodium carbonate solution were added to set a pH [9,10]. The solvent, 30 mL diethyl ether was added and upper ether layer containing required ester was collected after shaking. The solvent was distilled off to afford the transparent esters, **2a–l**, with yields ranging 62–76%.[9–10]

2.3. General procedure for the synthesis of hydrazides (**3a–l**)

The esters (**2a–l**; 0.02 mol) were added to 20.0 mL ethanol in a 100 mL RB flask followed by 4.0 mL 80% hydrazine hydrate. The mixture was stirred or refluxed accordingly for 3–6 h till reaction completion, supervised by TLC (ethyl acetate:*n*-hexane, 40%:60%). The precipitates of solid products were generated after addition of excess of distilled water which were filtered and washed with distilled water to afford **3a–l**, with yields ranging 71–87%.[9,10]

2.4. General procedure for the synthesis of 5-substituted-1,3,4-Oxadiazol-2-thiols (**4a–l**)

The carbohydrazides (**3a–l**; 0.02 mol) were suspended in 20.0 mL absolute ethanol in a 100 mL RB flask, basified with potassium hydroxide (0.02 mol) and refluxed to homogenize the mixture. Carbon disulfide (0.04 mol) was poured to the mixture and refluxed it for 4–6 h. TLC (ethyl acetate:*n*-hexane, 30%:70%) was developed to verify the reaction completion. The mixture was diluted by 30–50 mL distilled water and dilute HCl was added to acidify up to pH = 3–4. The precipitates, **4a–l**, were collected through filtration and washed by distilled water. The compounds were obtained with yields ranging 74–81%.[9,10]

2.5. General procedure for the synthesis of 5-substituted-2-((6-chloro-3,4-methylenedioxyphenyl)methylthio)-1,3,4-Oxadiazole (**6a–l**)

5-substituted-1,3,4-Oxadiazol-2-thiols (**4a–l**; 0.2 mmol) were homogeneously dissolved in 15.0 mL *N,N*-dimethylformamide (DMF) in a 50 mL RB flask. After activation of **4a–l** by sodium hydride (0.2 mmol) on stirring for half an hour, 6-chloro-3,4-methylenedioxybenzyl chloride (**5**; 0.2 mmol) was added and further stirred for 3–5 h. After complete reaction, monitored through TLC (ethyl acetate:*n*-hexane, 30%:70%), cold distilled water was added and the products were isolated by filtration or solvent extraction. The final solid products were re-crystallized from methanol.

2.5.1. 5-Phenyl-2-((6-chloro-3,4-methylenedioxyphenyl)methylthio)-1,3,4-Oxadiazole (**6a**)

White amorphous solid; Yield: 99%; M.P: 155 °C; HR-MS: $[M]^+$ 346.0176 (Calcd. for $C_{16}H_{11}ClN_2O_3S$; 346.0183); IR (KBr): ν_{max} (cm^{-1}): 3053 (Ar—H stretching), 1533 (Ar C=C stretching), 1125 (C—O stretching), 711 (C—Cl stretching), 610 (C—S stretching); ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.98 (dd, J = 8.0, 1.2 Hz, 2H, H-2″ & 6″), 7.50–7.45 (m, 3H, H-3″ to 5″), 7.09 (s, 1H, H-2′), 6.84 (s, 1H, H-5′), 5.94 (s, 2H, H-7′), 4.53 (s, 2H, H-8′); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 165.4 (C-5), 164.6 (C-2), 150.3 (C-4′), 148.7 (C-3′), 135.2 (C-3″ & 5″), 132.8 (C-2″ & 6″), 130.4 (C-4″), 129.8 (C-1″), 129.5 (C-1′), 125.7 (C-6′), 110.9 (C-5′), 110.2 (C-2′), 101.9 (C-7′), 32.7 (C-8′); EIMS (m/z): 348 $[M+2]^+$ (0.3%), 346 $[M]^+$ (1%), 311 (100%), 200 (2%), 178 (2%), 169 (8%), 145 (12%), 139 (4%), 134 (3%), 119 (7%), 105 (8%), 104 (4%), 103 (5%), 77 (9%), 51 (3%).

2.5.2. 5-(2-Methylphenyl)-2-((6-chloro-3,4-methylenedioxyphenyl)methylthio)-1,3,4-Oxadiazole (**6b**)

White amorphous solid; Yield: 90%; M.P: 109 °C; HR-MS: $[M]^+$ 360.0332 (Calcd. for $C_{17}H_{13}ClN_2O_3S$; 360.0341); IR (KBr): ν_{max} (cm^{-1}): 3058 (Ar—H stretching), 1539 (Ar C=C stretching), 1121 (C—O stretching), 707 (C—Cl stretching), 617 (C—S stretching); ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.84 (d, J = 7.6 Hz, 1H, H-6″), 7.40 (t, J = 7.2 Hz,1H, H-4″), 7.32 (d, J = 7.6 Hz, 1H, H-3″), 7.28 (t, J = 7.6 Hz, 1H, H-5″), 7.12 (s, 1H, H-2′), 6.85 (s, 1H, H-5′), 5.95 (s, 2H, H-7′), 4.53 (s, 2H, H-8′), 2.67 (s, 3H, H-7″); ^{13}C NMR ($CDCl_3$, 100 MHz, δ/ppm): 164.8 (C-5), 164.1 (C-2), 150.1 (C-4′), 149.4 (C-3′), 134.3 (C-2″), 131.6 (C-1′), 130.9 (C-4″), 128.8 (C-3″), 128.1 (C-1″), 127.6 (C-5″), 126.8 (C-6′), 126.2 (C-6″), 111.2 (C-5′), 110.6 (C-2′), 101.8 (C-7′), 32.5 (C-8′), 20.1 (C-7″); EIMS (m/z): 362 $[M+2]^+$ (0.5%), 360 $[M]^+$ (1.5%), 325 (100%), 200 (2%), 192 (5%), 169 (8%), 160 (2%), 139 (8%), 134 (3%), 133 (6%), 119 (4%), 117 (3%), 104 (9%), 91 (30%), 51 (2%).