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Original Research Article

Synthesis of N-substituted acetamide derivatives of azinane-bearing 1,3,4-oxadiazole nucleus and screening for antibacterial activity

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Abstract

Purpose: *To synthesize some acetamide derivatives bearing azinane and 1,3,4-oxadiazole heterocyclic cores and to evaluate their antibacterial potentials.*
Methods: *Ethyl piperidin-4-carboxylate (**2**) was converted to ethyl 1-[(4-chlorophenyl)sulfonyl]piperidin-4-carboxylate (**3**), 1-[(4-chlorophenyl)sulfonyl]piperidin-4-carbohydrazide (**4**) and 5-[1-(4-chlorophenylsulfonyl)-4-piperidinyl]-1,3,4-oxadiazol-2-thiol (**5**) using three consecutive steps. The target molecules, 5-{1-[(4-chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(substituted)-2-acetamoyl]thio]}-1,3,4-oxadiazole (**8a-n**) were synthesized by stirring 5 and N-aryl-2-bromoacetamides (**7a-n**) in an aprotic polar solvent. The structures were corroborated by infrared (IR), electron impact mass spectrometry (EI-MS) and proton/carbon nuclear magnetic resonance ($^{1}H/^{13}C$-NMR) spectroscopic techniques. The evaluation of antibacterial activity was based on the effect on the increase in absorbance of the broth medium due to log phase microbial growth.*
Results: *Compound **8g** bearing a 2-methylphenyl group was the most the active growth inhibitor of Salmonella typhi, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis bacterial strains with minimum inhibitory concentrations (MIC) of 10.63±0.97, 10.31±1.00, 10.45 ± 0.94 and 11.77±5.00 µM, respectively. Ciprofloxacin was used as reference standard.*
Conclusion: *All the synthesized compounds are moderate inhibitors but relatively more active against Gram-negative bacterial strains. 5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2-methylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (**8g**) is the most active growth inhibitor of all the strains except Staphylococcus aureus.*

Keywords: *1,3,4-Oxadiazole, Acetamides, Antibacterial activity, Piperidine*

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INTRODUCTION

The search for new drug candidates with more bioactivity potential is a key research interest in synthetic organic chemistry [1]. The derivatives of heterocyclic compounds have been found to be bioactive, including naturally occurring and synthetically prepared ones [2]. Among these compounds, 1,3,4-oxadiazole derivatives have been synthesized and evaluated for a number of biological activities including antidepressant, anticonvulsant, anticancer, antimicrobial, etc.,

during the last two decades [2-11]. Another bioactive heterocyclic moiety, piperidine or azinane, is found to be a part of many natural and synthetic bioactive compounds [12]. Furthermore, this moiety has applications as food additives, solvents, curing agents for rubber and intermediates for inorganic synthesis [13,14]. These different bioactive heterocyclic moieties have been included as a single unit in target molecules with the aim of possibly enhancing their antibacterial potential.

EXPERIMENTAL

General

Chemical reagents were purchased from Sigma Aldrich and Alfa Aesar through local suppliers. The solvents of analytical grade were also obtained from local suppliers. The purity of final compounds was verified by thin-layer chromatography (TLC) performed on silica gel-coated aluminum plates. *n*-Hexane and ethyl acetate were employed as the mobile phase. The TLC plates were visualized under a UV_{254} lamp. A Griffin and George apparatus was used to determine melting points, which were uncorrected. A Jasco-320-A spectrophotometer, Bruker spectrometer and JMS-HX-110 spectrometer were used to record IR (potassium bromide pellet method), ^{1}H-NMR (in $CHCl_3$-d_1, at 300 & 400 MHz) & ^{13}C-NMR (in $CHCl_3$-d_1, at 100 MHz) and EIMS spectra, respectively.

Synthesis of ethyl 1-[(4-chlorophenyl) sulfonyl]piperidin-4-carboxylate (3)

4-Chlorobenzenesulfonyl chloride (**1**; 0.05 mol) was stirred with ethyl piperidin-4-carboxylate (**2**; 0.05 mol) in water for 3 hours. The pH was adjusted to 9 - 10 with 15 % Na_2CO_3 during the reaction. The reaction was monitored by TLC. Chilled distilled water was added to the reaction mixture to obtain the precipitate of compound **3**. The formed precipitate was collected by filtration, washed and dried.

Synthesis of 1-[(4-chlorophenyl)sulfonyl] piperidin-4-carbohydrazide (4)

Compound **3** (0.04 mol) was refluxed with hydrazine hydrate (0.04 mol) in ethanol for 2.5 hours. The reaction was monitored by TLC. After addition of distilled water, the precipitate was obtained by filtration, washed and dried at room temperature.

Synthesis of 5-[1-(4-chlorophenylsulfonyl)-4-piperidinyl]-1,3,4-oxadiazol-2-thiol (5)

Potassium hydroxide (0.04 mol) and carbon disulfide (0.08 mol) were refluxed for 5 hours with compound **4** (0.04 mol) in ethanol. The reaction was monitored by TLC. Cold distilled water and dilute HCl (to adjust pH to 2 - 3) were added to precipitate the target compound. The product was obtained by filtration, washed, dried and re-crystallized from methanol.

Synthesis of *N*-aryl-2-bromoacetamides (7a-n)

Aryl amines (**6a-n**; 0.02 mol) were stirred with 2-bromoacetyl bromide (0.02 mol) in distilled water for 1 hour. The pH was maintained at 9 - 10 with 15 % Na_2CO_3 during the reaction. Completion of reaction was confirmed by TLC. The product was obtained after filtration, washing and drying.

Synthesis of 5-{1-[(4-chlorophenyl)sulfonyl] piperidin-4-yl}-2-{[*N*-(substituted)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8a-n)

Compound **5** (0.005 mol) was stirred with LiH (0.005 mol) in DMF for half an hour. Equimolar *N*-aryl-2-bromoacetamides (**7a-n**) were added and the mixture was stirred for 3 - 4 hours. Completion of reaction was monitored by TLC. Cold distilled water was added to form the precipitate, which was filtered out, washed and dried.

Antibacterial activity assay

The antibacterial activity assay was performed according to the protocol reported in the literature [15-17], in sterile 96-well microplates under aseptic conditions. The increase in absorbance of broth medium was noted which is directly related to log phase of microbial growth.

Statistical analysis

Statistical analysis using Microsoft Excel 2010 was based on three independent experiments, and the results are expressed as mean ± SEM. The minimum inhibitory concentration (MIC) was determined with suitable dilutions (5 - 30 µg/well) for each compound and the results were analyzed using EZ-Fit software (Perrella Scientific Inc, Amherst, USA). The statistical analysis included 85 % CL.

RESULTS

The protocol for synthesis of some new *N*-substituted acetamide derivatives of azinane bearing 1,3,4-oxadiazole is elaborated in

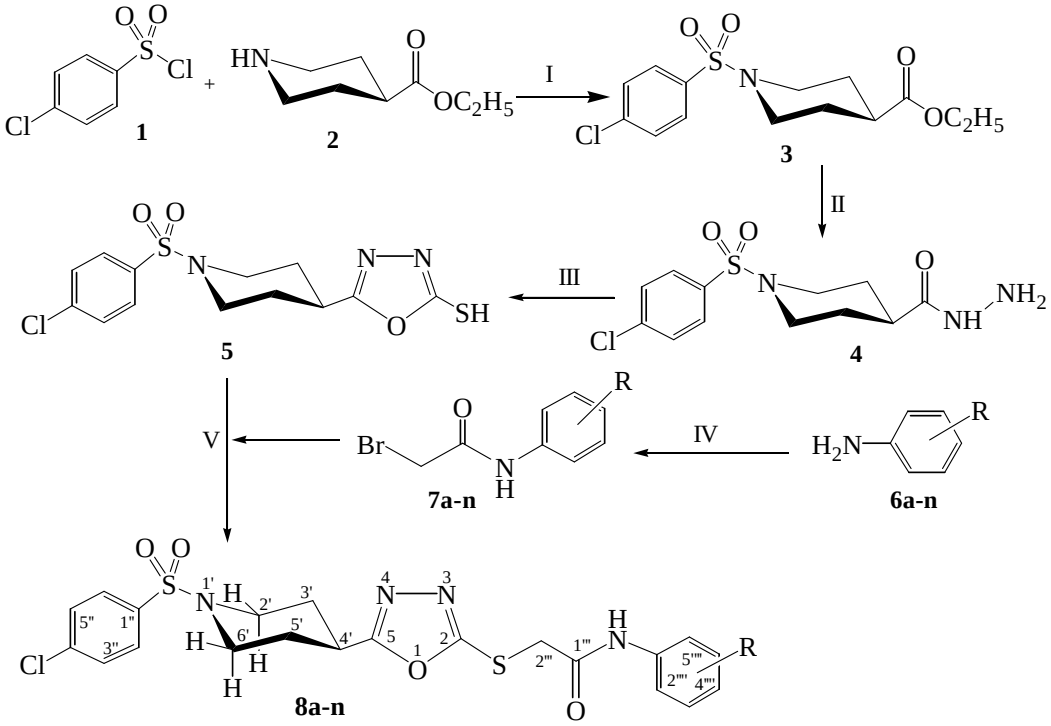

Figure 1: Protocol for synthesis of *N*-substituted acetamide derivatives of azinane bearing 1,3,4-oxadiazole. **Reagents & conditions:** (**I**) 15 % Na_2CO_3 solution, H_2O, stir for 3 hours. (**II**) $N_2H_4.H_2O$, EtOH, reflux for 2.5 hours. (**III**) CS_2, KOH (s), EtOH, reflux for 5 hours. (**IV**) $BrCH_2COBr$, 15 % Na_2CO_3 solution, H_2O, stir for 1 hour. (**V**) Dimethyl formamide, LiH, stir for 3 - 4 hours.

Table 1: Different substituted aryl group

Comp	R	Comp	R	Comp	R
8a	2-CH_3, 4-CH_3	**8f**	3-CH_3, 5-CH_3	**8k**	4-OCH_2CH_3
8b	2-CH_3, 3-CH_3	**8g**	2-CH_3	**8l**	2-OCH_2CH_3
8c	2-CH_3, 5-CH_3	**8h**	4-CH_3	**8m**	2-CH_2CH_3, 6-CH_3
8d	2-CH_3, 6-CH_3	**8i**	2-CH_2CH_3	**8n**	2-OCH_3
8e	3-CH_3, 4-CH_3	**8j**	4-CH_2CH_3		

Figure 1 and different *N*-substituted groups are given in Table 1. The spectral characterization of synthesized compounds is described below.

Spectral characterization of synthesized molecules (8a-n)

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2,4-dimethylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8a)

White amorphous solid; Yield: 84 %; M.P. 139-140 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 $gmol^{-1}$; IR (KBr, u_{max}, cm^{-1}): 3312, 3043, 1648, 1666, 1603, 1385, 1173, 1034, 678; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.60 (br.s, 1H, -NH), 7.70 (d, J = 8.4 Hz, 1H, H-6""), 7.68 (d, J = 8.4 Hz, 2H, H-2" & H-6"), 7.50 (d, J = 8.4 Hz, 2H, H-3" & H-5"), 6.98 (d, J = 8.8 Hz, 1H, H-5""), 6.96 (s, 1H, H-3""), 3.96 (s, 2H, H-2"'), 3.69-3.66 (m, 2H, H_e-2' & H_e-6'), 2.95-2.89 (m, 1H, H-4'), 2.62 (dt, J = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.26 (s, 3H, CH_3-4""), 2.15 (s, 3H, CH_3-2""), 2.14-2.12 (m, 2H, H_e-3' & H_e-5'), 1.99-1.96 (m, 2H, H_a-3' & H_a-5'); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.4 (C-5), 165.3 (C-2), 165.1 (C-1'"), 139.5 (C-1"), 135.1 (C-4"), 134.8 (C-1""), 132.9 (C-2""), 132.4 (C-4""), 131.2 (C-5""), 129.5 (C-3" & C-5"), 129.0 (C-2" & C-6"), 127.2 (C-3""), 122.6 (C-6""), 44.9 (C-2' & C-6'), 35.9 (C-2'"), 32.4 (C-4'), 28.1 (C-3' & C-5'), 20.8 (CH_3-4""), 17.8 (CH_3-2""); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2,3-dimethylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8b)

White crystalline solid; Yield: 79 %; M.P. 172-173 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 $gmol^{-1}$; IR (KBr, u_{max}, cm^{-1}): 3308, 3042, 1646, 1661, 1608,

1387, 1175, 1032, 632; ^{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''), 7.54 (d, *J* = 8.0 Hz, 1H, H-6'''), 7.50 (d, *J* = 8.4 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'''), 3.73-3.70 (m, 2H, H_e-2' & H_e-6'), 2.90-2.85 (m, 1H, H-4'), 2.58 (dt, *J* = 10.4, 2.0 Hz, 2H, H_a-2' & H_a-6'), 2.26 (s, 3H, CH_3-3'''), 2.15-2.10 (m, 2H, H_e-3' & H_e-5'), 2.09 (s, 3H, CH_3-2'''), 2.02-1.95 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2,5-dimethylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8c)

Off-white amorphous solid; Yield: 76 %; M.P. 166-167 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 gmol^{-1}; IR (KBr, u_{max}, cm^{-1}): 3316, 3048, 1642, 1660, 1606, 1386, 1178, 1030, 676; ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* (ppm) 8.53 (br.s, 1H, -NH), 7.15 (s, 1H, H-6'''), 7.63 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.46 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.06 (d, *J* = 8.4 Hz, 1H, H-3'''), 6.91 (d, *J* = 8.0 Hz, 1H, H-4'''), 3.94 (s, 2H, H-2'''), 3.68-3.64 (m, 2H, H_e-2' & H_e-6'), 2.97-2.93 (m, 1H, H-4'), 2.59 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.31 (s, 3H, CH_3-2'''), 2.20 (s, 3H, CH_3-5'''), 2.16-2.13 (m, 2H, H_e-3' & H_e-5'), 1.98-1.94 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2,6-dimethylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8d)

Off-white amorphous solid; Yield: 86 %; M.P. 96-97 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 gmol^{-1}; IR (KBr, u_{max}, cm^{-1}): 3346, 3038, 1644, 1680, 1616, 1376, 1158, 1020, 656; ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* (ppm) 8.46 (br.s, 1H, -NH), 7.65 (d, *J* = 8.0 Hz, 2H, H-2'' & H-6''), 7.49 (d, *J* = 8.0 Hz, 2H, H-3'' & H-5''), 7.10-7.07 (m, 3H, H-3''' to H-5'''), 3.95 (s, 2H, H-2'''), 3.68-3.65 (m, 2H, H_e-2' & H_e-6'), 2.98-2.93 (m, 1H, H-4'), 2.55 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.23 (s, 6H, CH_3-2''' & CH_3-6'''), 2.18-2.15 (m, 2H, H_e-3' & H_e-5'), 2.02-1.96 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(3,4-dimethylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8e)

White amorphous solid; Yield: 71 %; M.P. 196-197 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 gmol^{-1}; IR (KBr, u_{max}, cm^{-1}): 3342, 3034, 1642, 1684, 1612, 1372, 1154, 1022, 655; ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* (ppm) 8.83 (br.s, 1H, -NH), 7.69 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.50 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.26 (s, 1H, H-2'''), 7.22 (d, *J* = 8.4 Hz, 1H, H-5'''), 7.03 (d, *J* = 8.0 Hz, 1H, H-6'''), 3.90 (s, 2H, H-2'''), 3.73-3.70 (m, 2H, H_e-2' & H_e-6'), 2.88-2.84 (m, 1H, H-4'), 2.59 (dt, *J* = 10.4, 2.0 Hz, 2H, H_a-2' & H_a-6'), 2.21 (s, 3H, CH_3-4'''), 2.18 (s, 3H, CH_3-3'''), 2.16-2.12 (m, 2H, H_e-3' & H_e-5'), 2.02-1.96 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(3,5-dimethylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8f)

White amorphous solid; Yield: 74 %; M.P. 207-208 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 gmol^{-1}; IR (KBr, u_{max}, cm^{-1}): 3345, 3037, 1645, 1687, 1615, 1376, 1157, 1022, 657; ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* (ppm) 8.54 (br.s, 1H, -NH), 7.64 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.52 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.14 (s, 2H, H-2''' & H-6'''), 6.97 (s, 1H, H-4'''), 3.95 (s, 2H, H-2'''), 3.69-3.65 (m, 2H, H_e-2' & H_e-6'), 2.99-2.95 (m, 1H, H-4'), 2.57 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.28 (s, 6H, CH_3-3''' & CH_3-5'''), 2.19-2.16 (m, 2H, H_e-3' & H_e-5'), 2.01-1.97 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2-methylphenyl)-2-acetamoyl]thio}-1,3,4-oxadiazole (8g)

White amorphous; Yield: 79 %; M.P. 148-149 °C; M.F.: $C_{22}H_{23}ClN_4O_4S_2$; M.M.: 507 gmol^{-1}; IR (KBr, u_{max}, cm^{-1}): 3340, 3031, 1631, 1683, 1611, 1372, 1159, 1027, 651; ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* (ppm) 8.73 (br.s, 1H, -NH), 7.88 (d, *J* = 8.0 Hz, 1H, H-6'''), 7.69 (d, *J* = 8.8 Hz, 2H, H-2'' & H-6''), 7.50 (d, *J* = 8.8 Hz, 2H, H-3'' & H-5''), 7.17 (t, *J* = 7.6 Hz, 1H, H-5'''), 7.14 (d, *J* = 8.0 Hz, 1H, H-3'''), 7.04 (t, *J* = 7.6 Hz, 1H, H-4'''), 3.97 (s, 2H, H-2'''), 3.70-3.67 (m, 2H, H_e-2' & H_e-6'), 2.91-2.85 (m, 1H, H-4'), 2.61 (dt, *J* = 12.0, 2.4 Hz, 2H, H_a-2' & H_a-6'), 2.20 (s, 3H, CH_3-2'''), 2.15-2.11 (m, 2H,

H_e-3' & H_e-5'), 2.02-1.93 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 509 $[M+2]^+$, 507 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 134 $[C_8H_8NO]^+$, 106 $[C_7H_8N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(4-methylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8h)

White amorphous solid; Yield: 77 %; M.P. 195-196 °C; M.F.: $C_{22}H_{23}ClN_4O_4S_2$; M.M.: 507 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3344, 3034, 1640, 1683, 1617, 1371, 1156, 1029, 658; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.52 (br.s, 1H, -NH), 7.67 (d, *J* = 8.0 Hz, 2H, H-2'' & H-6''), 7.59 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.34 (d, *J* = 8.0 Hz, 2H, H-2'''' & H-6''''), 6.97 (d, *J* = 8.0 Hz, 2H, H-3'''' & H-5''''), 3.93 (s, 2H, H-2'''), 3.70-3.65 (m, 2H, H_e-2' & H_e-6'), 3.01-2.96 (m, 1H, H-4'), 2.58 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.28 (s, 3H, CH_3-4''''), 2.17-2.13 (m, 2H, H_e-3' & H_e-5'), 2.01-1.95 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 509 $[M+2]^+$, 507 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 134 $[C_8H_8NO]^+$, 106 $[C_7H_8N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2-ethylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8i)

White amorphous solid; Yield: 84 %; M.P. 134-135 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3320, 3021, 1650, 1671, 1602, 1393, 1170, 1034, 672; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.71 (br.s, 1H, -NH), 7.82 (d, *J* = 8.0 Hz, 1H, H-6''''), 7.69 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.50 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.20 (t, *J* = 7.2 Hz, 1H, H-5''''), 7.18 (d, *J* = 7.2 Hz, 1H, H-3''''), 7.09 (t, *J* = 7.2 Hz, 1H, H-4''''), 3.98 (s, 2H, H-2'''), 3.69-3.66 (m, 2H, H_e-2' & H_e-6'), 2.90-2.87 (m, 1H, H-4'), 2.62 (dt, *J* = 11.6, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.52 (q, *J* = 7.6 Hz, 2H, $CH_3\underline{CH_2}$-2''''), 2.15-2.11 (m, 2H, H_e-3' & H_e-5'), 2.02-1.95 (m, 2H, H_a-3' & H_a-5'), 1.08 (t, *J* = 7.6 Hz, 3H, $\underline{CH_3}CH_2$-2''''); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(4-ethylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8j)

Off-white amorphous solid; Yield: 79 %; M.P. 200-201 °C; M.F.: $C_{23}H_{25}ClN_4O_4S_2$; M.M.: 521 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3332, 3023, 1637, 1654, 1587, 1454, 1230, 1024, 718; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.94 (br.s, 1H, -NH), 7.69 (d, *J* = 8.8 Hz, 2H, H-2'' & H-6''), 7.50 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.40 (d, *J* = 8.0 Hz, 2H, H-2'''' & H-6''''), 7.11 (d, *J* = 8.4 Hz, 2H, H-3'''' & H-5''''), 3.91 (s, 2H, H-2'''), 3.73-3.70 (m, 2H, H_e-2' & H_e-6'), 2.89-2.83 (m, 1H, H-4'), 2.61 (q, *J* = 8.0 Hz, 2H, $CH_3\underline{CH_2}$-4''''), 2.60-2.55 (m, 2H, H_a-2' & H_a-6'), 2.16-2.12 (m, 2H, H_e-3' & H_e-5'), 2.02-1.92 (m, 2H, H_a-3' & H_a-5'), 1.18 (t, *J* = 7.6 Hz, 3H, $\underline{CH_3}CH_2$-4''''); EIMS (*m/z*): 523 $[M+2]^+$, 521 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 148 $[C_9H_{10}NO]^+$, 120 $[C_8H_{10}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(4-ethoxyphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8k)

Pink amorphous solid; Yield: 75 %; M.P. 189-190 °C; M.F.: $C_{23}H_{25}ClN_4O_5S_2$; M.M.: 537 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3335, 3024, 1643, 1651, 1583, 1452, 1232, 1021, 713; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.86 (br.s, 1H, -NH), 7.65 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.52 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 6.94 (d, *J* = 8.4 Hz, 2H, H-2'''' & H-6''''), 6.76 (d, *J* = 8.4 Hz, 2H, H-3'''' & H-5''''), 3.93 (s, 2H, H-2'''), 3.84 (q, *J* = 7.6, 2H, $CH_3\underline{CH_2}O$-4''''), 3.72-3.68 (m, 2H, H_e-2' & H_e-6'), 2.91-2.87 (m, 1H, H-4'), 2.63-2.58 (m, 2H, H_a-2' & H_a-6'), 2.15-2.10 (m, 2H, H_e-3' & H_e-5'), 2.01-1.94 (m, 2H, H_a-3' & H_a-5'), 1.32 (t, *J* = 7.6 Hz, 3H, $\underline{CH_3}CH_2O$-4''''); EIMS (*m/z*): 539 $[M+2]^+$, 537 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 164 $[C_9H_{10}NO_2]^+$, 136 $[C_8H_{10}NO]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2-ethoxyphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8l)

White amorphous solid; Yield: 78 %; M.P. 198-199 °C; M.F.: $C_{23}H_{25}ClN_4O_5S_2$; M.M.: 537 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3337, 3026, 1644, 1656, 1587, 1454, 1236, 1024, 716; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.99 (br.s, 1H, -NH), 8.29 (d, *J* = 8.0 Hz, 1H, H-6''''), 7.68 (d, *J* = 8.8 Hz, 2H, H-2'' & H-6''), 7.49 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.01 (dt, *J* = 8.0, 1.2 Hz, 1H, H-5''''), 6.90 (t, *J* = 8.0 Hz, 1H, H-4''''), 6.88 (d, *J* = 8.0 Hz, 1H, H-3''''), 4.05 (q, *J* = 6.8 Hz, 2H, $CH_3\underline{CH_2}O$-2''''), 4.02 (s, 2H, H-2'''), 3.69-3.66 (m, 2H, H_e-2' & H_e-6'), 2.87-2.83 (m, 1H, H-4'), 2.60 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.14-2.09 (m, 2H, H_e-3' & H_e-5'), 2.02-1.93 (m, 2H, H_a-3' & H_a-5'), 1.42 (t, *J* = 7.2 Hz, 3H, $\underline{CH_3}CH_2O$-2''''); EIMS (*m/z*): 539 $[M+2]^+$, 537 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 164 $[C_9H_{10}NO_2]^+$, 136 $[C_8H_{10}NO]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2-ethyl-6-methylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8m)

Light brown amorphous solid; Yield: 73 %; M.P. 98-99 °C; M.F.: $C_{24}H_{27}ClN_4O_4S_2$; M.M.: 535 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3338, 3027, 1637, 1658, 1588, 1456, 1238, 1028, 715; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.78 (br.s, 1H, -NH), 7.68 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.54 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 6.98-7.14 (m, 3H, H-3''' to H-5'''), 3.94 (s, 2H, H-2'''), 3.75-3.69 (m, 2H, H_e-2' & H_e-6'), 2.96-2.90 (m, 1H, H-4'), 2.46 (q, *J* = 7.6 Hz, 2H, $CH_3\underline{CH_2}$-2''''), 2.62-2.58 (m, 2H, H_a-2' & H_a-6'), 2.15-2.12 (m, 2H, H_e-3' & H_e-5'), 2.01-1.95 (m, 2H, H_a-3' & H_a-5'), 1.94 (s, 3H, CH_3-6''''), 1.02 (t, *J* = 7.6 Hz, 3H, $\underline{CH_3}CH_2$-2''''); EIMS (*m/z*): 537 $[M+2]^+$, 535 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 162 $[C_{10}H_{12}NO]^+$, 134 $[C_9H_{12}N]^+$.

5-{1-[(4-Chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[N-(2-methoxyphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (8n)

White amorphous solid; Yield: 86 %; M.P. 142-143 °C; M.F.: $C_{22}H_{23}ClN_4O_5S_2$; M.M.: 523 gmol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3330, 3028, 1647, 1650, 1589, 1450, 1230, 1029, 712; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.94 (br.s, 1H, -NH), 8.28 (d, *J* = 8.0 Hz, 1H, H-6''''), 7.69 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.52 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.01 (t, *J* = 8.4 Hz, 1H, H-5''''), 6.92 (t, *J* = 8.0 Hz, 1H, H-4''''), 6.83 (d, *J* = 8.0 Hz, 1H, H-3''''), 3.98 (s, 2H, H-2'''), 3.83 (s, 3H, CH_3O-2''''), 3.70-3.66 (m, 2H, H_e-2' & H_e-6'), 2.89-2.84 (m, 1H, H-4'), 2.57 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.16-2.12 (m, 2H, H_e-3' & H_e-5'), 2.00-1.95 (m, 2H, H_a-3' & H_a-5'); EIMS (*m/z*): 529 $[M+2]^+$, 527 $[M]^+$, 300 $[C_{12}H_{13}ClN_2O_3S]^{\bullet+}$, 286 $[C_{12}H_{13}ClNO_3S]^+$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 150 $[C_8H_8NO_2]^+$, 122 $[C_7H_8NO]^+$.

Antibacterial activity

The results of antibacterial activity are given as % inhibition and MIC in Table 2 and Table 3, respectively. The synthesized compounds exhibited better activity against the Gram-negative bacterial strains used. Compound **8g** bearing a 2-methylphenyl group was the most active against all the Gram-negative bacterial strains considered and one of the Gram-positive bacterial strains.

DISCUSSION

Compound **8a** was a white amorphous solid with a melting point of 139-140 °C, showing a yield of 84 %. Its molecular mass was justified by the molecular ion peak at *m/z* 521 with an isotopic peak at *m/z* 523. The molecular formula was well supported by EIMS spectrum and the proton integration curves in ^{1}H-NMR spectrum.
The IR spectrum absorption peaks (υ_{max}, cm^{-1}) confirmed all the functionalities, carbonyl for acetamoyl at 1648, sulfamoyl at 1385 and oxadiazole at 1666 (C=N), 1173 & 1034 (C-O-C).

Table 2: Percent inhibition of selected Gram-positive and -negative bacteria by the synthesized compounds

Compound	Inhibition (%)				
	Gram-negative bacteria			*Gram-positive bacteria*	
	S. typhi	***E. coli***	***P. aeruginosa***	***S. aureus***	***B. subtilis***
8a	52.64±1.09	55.93±2.22	60.77±2.40	47.55±3.00	54.14±0.91
8b	69.27±1.21	49.07±1.02	62.45±3.27	53.92±1.27	44.19±3.45
8c	46.36±2.34	53.56±1.71	63.98±4.90	31.37±2.67	44.55±3.43
8d	54.65±1.56	53.19±2.36	59.59±3.47	53.82±1.99	60.81±0.71
8e	57.64±0.76	47.18±2.82	45.82±2.45	49.02±2.54	49.55±0.96
8f	61.45±1.42	48.52±1.57	51.28±0.97	54.31±1.55	49.75±0.76
8g	62.64±1.00	65.60±0.65	64.69±1.12	47.25±3.04	57.93±1.97
8h	49.36±2.87	49.81±2.22	30.87±3.72	41.18±3.77	46.11±0.56
8i	49.55±3.47	52.27±5.00	46.99±1.79	52.94±1.95	48.94±2.47
8j	55.45±1.88	48.24±1.37	52.14±3.47	44.41±2.87	56.16±1.21
8k	55.45±2.03	62.36±2.64	54.23±5.00	50.49±1.90	61.62±2.02
8l	52.82±1.31	53.61±4.54	51.07±2.09	28.04±4.00	53.28±1.67
8m	55.09±1.82	42.08±3.01	47.24±4.69	43.43±3.24	59.19±3.03
8n	75.09±2.92	51.02±3.98	48.83±1.38	58.04±2.00	68.43±1.57
Ciprofloxacin	**91.79±1.45**	**90.87±0.56**	**92.13±0.97**	**90.45±2.98**	**91.18±1.22**

Table 3: MIC of the synthesized compounds

Compound	MIC(µg/ mL)				
	Gram-negative bacteria			*Gram-positive bacteria*	
	S. typhi	***E. coli***	***P. aeruginosa***	***S. aureus***	***B. subtilis***
8a	11.38±1.25	-	12.88±1.06	10.59±1.96	-
8b	16.65±1.09	13.74±2.53	10.22±1.88	-	15.88±1.50
8c	-	17.56±1.00	13.67±1.38	-	-
8d	13.54±1.71	14.05±0.98	11.35±1.75	14.08±1.15	10.84±1.70
8e	16.89±1.50	-	-	-	-
8f	16.46±2.23	-	18.42±0.94	17.19±5.00	-
8g	10.63±0.97	10.31±1.00	10.45±0.94	-	11.77±5.00
8h	-	-	-	-	-
8i	-	18.21±0.34	-	16.83±5.00	-
8j	17.90±3.45	-	18.79±1.69	-	18.06±5.00
8k	17.47±1.22	15.78±1.67	17.37±1.25	19.64±2.50	15.12±1.79
8l	13.90±1.93	11.97±1.98	16.91±1.19	-	17.07±4.93
8m	15.11±1.17	-	-	-	14.39±2.79
8n	15.00±2.15	19.48±2.00	-	16.12±4.86	15.55±4.29
Ciprofloxacin	**7.15±1.29**	**7.90±1.87**	**8.21±1.21**	**8.00±2.98**	**7.12±2.11**

In EIMS spectrum, the mass fragments at *m/z* 300 due to partial breakage of 1,3,4-oxadiazole ring, at *m/z* 258 due to 1-[(4-chlorophenyl)sulfonyl]piperidin-4-yl cation and at *m/z* 148 for *N*-(2,4-dimethylphenyl)amino carbonyl cation collectively corroborated the whole structure of the molecule.

The ^{1}H-NMR spectrum displayed two *ortho* coupled doublets with two proton integration at *δ* 7.68 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6'') and 7.50 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5'') for the 4-chlorobenzenesulfonyl group. Two doublets & three singlets in aromatic and aliphatic regions, at *δ* 7.70 (d, *J* = 8.4 Hz, 1H, H-6''''), 6.98 (d, *J* = 8.8 Hz, 1H, H-5''''), 6.96 (s, 1H, H-3''''), 2.26 (s, 3H, CH_3-4'''') and 2.15 (s, 3H, CH_3-2''''), collectively confirmed the presence of 2,4-dimethylphenyl ring. Two singlets at *δ* 8.60 (br.s, 1H, -NH) and 3.96 (s, 2H, H-2''') were assigned to the acetamoyl group. The piperidine or azinane moiety showed signals at *δ* 3.69-3.66 (m, 2H, H_e-2' & H_e-6'), 2.95-2.89 (m, 1H, H-4'), 2.62 (dt, *J* = 12.8, 2.8 Hz, 2H, H_a-2' & H_a-6'), 2.14-2.12 (m, 2H, H_e-3' & H_e-5') and 1.99-1.96 (m, 2H, H_a-3' & H_a-5').

The molecule was also well supported by ^{13}C-NMR (Broad Band and Distorsionless Enhancement by Polarization Transfer). This spectrum showed nineteen signals for two methyl, five methylene, eight methine and eight quaternary carbons. The quaternary carbons appeared at *δ* 169.4 (C-5), 165.3 (C-2), 165.1 (C-1'''), 139.5 (C-1''), 135.1 (C-4''), 134.8 (C-1''''), 132.9 (C-2'''') and 132.4 (C-4''''). The methine carbons demonstrated six signals at *δ* 131.2 (C-5''''), 129.5 (C-3'' & C-5''), 129.0 (C-2'' & C-6''), 127.2 (C-3''''), 122.6 (C-6'''') and 32.4 (C-4'). The methylene carbons were confirmed by three signals at *δ* 44.9 (C-2' & C-6'), 28.1 (C-3' & C-5') and 35.9 (C-2'''). The methyl carbons showed two signals at *δ* 20.8 (CH_3-4'''') and 17.8 (CH_3-2'''').

The analysis of spectral data corroborated the structure of **8a** to be 5-{1-[(4-chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[*N*-(2,4-dimethylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole. The structures of the other molecules were likewise elucidated from their spectral data.

The synthesized compounds exhibited antibacterial activity against Gram-negative bacterial strains used. Against *S. typhi*, **8a** bearing a 2,4-dimethylphenyl group and **8g** bearing a 2-methylphenyl group were the most active ones with MIC values of 11.38 ± 1.25 and 10.63 ± 0.97 µg/mL, respectively, compared to ciprofloxacin (reference antibiotic) with a MIC of 7.15 ± 1.29 µg/mL. Against *E. coli*, the most effective were **8g** and **8l** (2-ethoxyphenyl group) with MIC values of 10.31 ± 1.00 and 11.97 ± 1.98 µg/mL, respectively, compared to the reference value of 7.90 ± 1.87 µg/mL. Against *P. aeruginosa*, compounds **8b** (2,3-dimethylphenyl group), **8d** (2,6-dimethylphenyl group) and **8g** were the most effective with MIC values of 10.22 ± 1.88, 11.35 ± 1.75 and 10.45 ± 0.94 µg/mL, respectively, in comparison to the reference of 8.21 ± 1.21 µg/mL. *S. aureus* growth was effectively inhibited by **8a** with a MIC of 10.59 ± 1.96 µg/mL relative to 8.00 ± 2.98 µg/mL. *B. subtilis* growth was effectively inhibited by **8d** and **8g** with MIC values of 10.84 ± 1.70 and 11.77 ± 5.00 µg/mL, respectively, with reference to 7.12 ± 2.11 µg/mL. Compound **8g** bearing a 2-methylphenyl group was the most active against

all the Gram-negative bacterial strains and one of the Gram-positive bacterial strains.

CONCLUSION

All target compounds were synthesized in reasonable yields by a series of benign methods. The compounds are excellent to moderate growth inhibitors of the bacterial strains studied. Among these biologically active compounds, 5-{1-[(4-chlorophenyl)sulfonyl]piperidin-4-yl}-2-{[*N*-(2-methylphenyl)-2-acetamoyl]thio]}-1,3,4-oxadiazole (**8g**) is the most potent against all the strains except *S. aureus*. This molecule can be further evaluated for cytotoxic behavior and may be considered as a candidate in drug discovery programs.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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