Full Paper

Synthesis and Antibacterial Activity of Various Substituted Oxadiazole Derivatives

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Some new 2-(2-(4(4-substitutedbenzoyl-2-methylphenoxy)acetyl)-*N*-(2-substitutedphenyl) hydrazinecarbothioamides (**4a–4j**) and (4-((5-(2-substitutedphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-3-substitutedphenyl)(phenyl)methanones (**5a–5j**) have been synthesized from 2-(4-(3-substitutedbenzoyl)-2-methylphenoxy)acetohydrazides (**3a**, **3b**). These newly synthesized compounds (**4a–4j** and **5a–5j)** were characterized by elemental and spectral (IR, ^{1}H-NMR and MS) analysis. All the synthesized compounds have been screened for their antibacterial activity against both types of Gram negative and Gram positive bacteria. The most potent antibacterial compound of this series was compound **5i** which has the low MIC 3.75–0.9375 μg/mL value. Both minimal inhibitory concentration (MIC) and inhibition zones were determined in order to monitor the efficacy of the synthesized compounds. Certain compounds inhibit bacterial growth with low MIC (μg/mL) value.

Keywords: Antibacterial activity / Oxadiazole / Toxicity study

Received: May 18, 2010; Revised: September 15, 2010; Accepted: September 17, 2010

DOI 10.1002/ardp.201000141

Introduction

Five membered nitrogen containing heterocycles with oxygen atom are an important class of compounds in medicinal chemistry. Oxadiazole derivatives have attracted much attention among five-membered oxygen containing heterocycles because of their biological and pharmacological properties like antibacterial [1–3], antimicrobial [4, 5], fungicidal [6], anti-inflammatory [7], antipsychotic [8], anticonvulsant [8], and antidepressant [9]. In the light of above discussion we report herein the synthesis of 2-(2-(4-benzoyl-2-methylphenoxy)acetyl)-N-(2-substitutedethoxyphenyl)hydrazinecarbothioamides (**4a–4h**) and (4-((5-(2-substitutedphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-3-methylphenyl)(phenyl)-methanone (**5a–5h**) with the hope to get better antibacterial agents.

Chemistry

The synthetic route of the title compounds is outlined in Scheme 1. The starting compounds 2-(4-(3-substitutedbenzoyl)-2-methylphenoxy) acetates (**2a**, **2b**) were prepared by the reaction of substituted 4-hydroxybenzophenones (**1a**, **1b**) with ethyl bromoacetate. Compounds **2a**, **2b** on treatment with hydrazine hydrate yielded 2-(4-(3-substitutedbenzoyl)-2-methylphenoxy) acetohydrazides (**3a**, **3b**). Further, the compounds **3a**, **3b** were converted into 2-(2-(4-(3-sustituted-benzoyl)-2-methylphenoxy)acetyl)-*N*-(2-substitutedphenyl)hydrazinecarbothioamides (**4a–4j**), on reaction with various substituted phenylisothiocynates. Compounds **4a–4j** reacted with sodium hydroxide and potassium iodide to obtain (3-substitutedphenyl)-(3-methyl-4-((5-(2-substitutedphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanones (**5a–5j**). Structural assignments of the above newly synthesized

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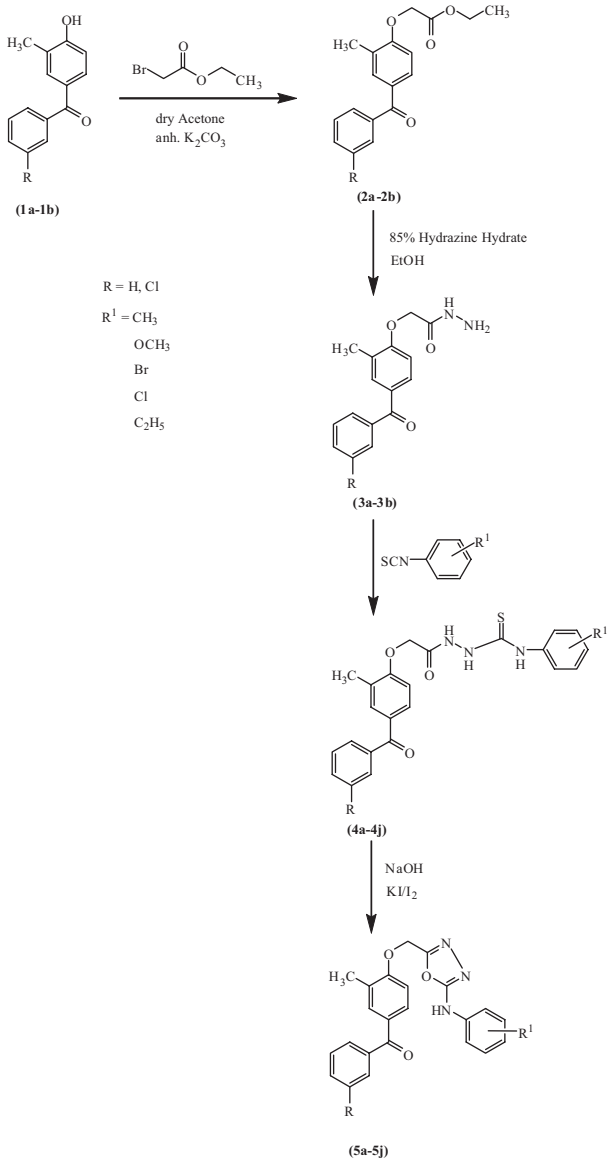


Scheme 1. Synthetic route of oxadiazole derivatives.

compounds were based on elemental (C, H, N) and spectral (IR, ^{1}H-NMR and MS) analysis.

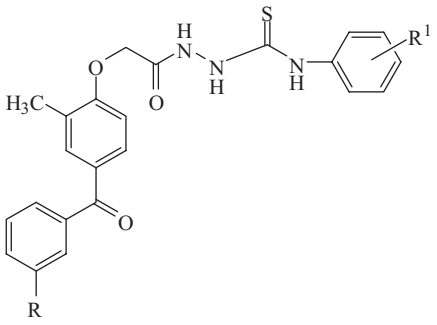
Results and discussion

The antibacterial activity of all the newly synthesized compounds (**4a–4j** and **5a–5j**) and the standard drugs ciprofloxacin and gatifloxacin were carried out against both types of Gram negative bacteria (*Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* CIP 53153, *Escherichia coli* ATCC 25922) and Gram positive bacteria (*Staphylococcus aureus* ATCC 25923). Diameter of zone of inhibition in mm and minimal inhibitory concentration (MIC) in μg/mL of all the compounds were given in Tables 1 and 2. Dimethyl sulfoxide treated group served as a control. The compounds **4a–4j** exhibited varying antibacterial response against different types of bacterial strains, but the compounds having electronegative groups such as Br and Cl, showed better results than the other compounds. The compounds **4e**, **4f** and **4j** (having ethylphenyl, methylphenyl, and ethylphenyl moieties, respectively) were devoid of antibacterial activity against Gram negative bacteria *P. aeruginosa* ATCC 27853 and *K. pneumoniae* CIP 53153. These compounds showed mild antibacterial activity against *E. coli* ATCC 25922 with MIC 120, 250, and 120 μg/mL, respectively. The compounds **4e** and **4f** exhibited moderate activity against Gram positive bacteria *S. aureus* ATCC 25923 with MIC 60 and 90 μg/mL, respectively. Among the compounds **4a–4j**, compound **4i** having chlorophenyl ring exhibited good antibacterial activity against Gram negative bacteria *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 and Gram positive bacteria *S. aureus* ATCC 25923 with MIC 15 μg/mL for each. Moreover, compound **4h** having bromophenyl ring showed good activity against Gram negative bacteria *E. coli* ATCC 25922 with MIC 15 μg/mL and moderate antibacterial activity against *K. pneumoniae* CIP 53153 with MIC 30 μg/mL. Formation of the compounds **5a-5j** (having oxadiazole ring) markedly enhanced the antibacterial activity against both types of bacteria. Out of these compounds, **5f**, **5g**, **5h** and **5j** exhibited significant antibacterial activity against different types of bacterial strains. Furthermore, the compound **5i** (having chlorophenyl ring) has shown most potent antibacterial activity against Gram negative bacteria *P. aeruginosa* ATCC 27853 (MIC 3.75 μg/mL), *K. pneumoniae* CIP 53153 (MIC 1.875 μg/mL), *E. coli* ATCC 25922 (MIC 3.75 μg/mL). The later compound exhibited maximum antibacterial activity against Gram positive bacteria *S. aureus* ATCC 25923 with lowest MIC 0.9375 μg/mL as compared to the standard drugs ciprofloxacin (MIC 3.75 μg/mL) and gatifloxacin (MIC 1.875 μg/mL). The newly synthesized compounds were also tested for approximate lethal dose LD_{50} and were found to exhibit a higher value of LD_{50} i.e. more than 800 mg/kg except compound **5i** which exhibited LD_{50} of more than 1600 mg/kg (maximum dose tested). The compounds have shown high value of LD_{50} indicating good safety margin.

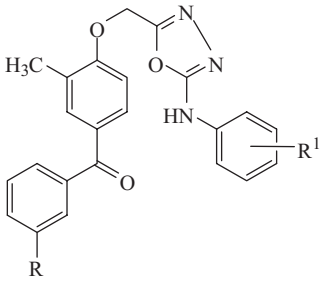
Conclusion

1. In general oxadiazole derivatives (*i.e.* **5a–5j**) are more active than their parent compounds (**4a–4j**).
2. Compounds having a substitution with 2-chlorophenyl ring (*i.e.* compound **5i**) showed promising antibacterial activity against both types of bacteria.

Table 1. Inhibitory-zone diameter (in mm) of the synthesized compounds **4a–4j** and **5a–5j** against the tested bacterial strains.



(4a-4j)



(5a-5j)

Comp. No.	R	R'	Antibacterial activity[a] Diameter of the inhibition zone (in mm)				LD_{50} mg/kg
			Pseudomonas aeruginosa ATCC 27853	***Klebsiella pneumoniae*** CIP 53153	***Escherichia coli*** ATCC 25922	***Staphylococcus aureus*** ATCC 25923	
4a	H	CH_3	–	6	9	–	>800
4b	H	OCH_3	7	–	7	–	>800
4c	H	Br	10	15	–	11	>800
4d	H	Cl	12	10	17	13	>800
4e	H	C_2H_5	–	–	8	15	>800
4f	Cl	CH_3	–	–	7	12	>800
4g	Cl	OCH_3	10	10	10	10	>800
4h	Cl	Br	13	16	21	12	>800
4i	Cl	Cl	20	16	21	20	>800
4j	Cl	C_2H_5	–	–	10	–	>800
5a	H	CH_3	–	12	10	–	>800
5b	H	OCH_3	10	14	12	10	>800
5c	H	Br	16	18	–	13	>800
5d	H	Cl	20	8	12	10	>800
5e	H	C_2H_5	15	6	15	15	>800
5f	Cl	CH_3	–	18	20	14	>800
5g	Cl	OCH_3	18	20	12	12	>800
5h	Cl	Br	21	19	16	20	>800
5i	Cl	Cl	27	28	26	28	>1600
5j	Cl	C_2H_5	7	19	10	16	>800
Ciprofloxacin	–	–	24	21	22	25	
Gattifloxacin	–	–	22	26	25	23	

3. All the compounds exhibited $LD_{50} > 800$ mg/kg, except compound **5i** (having 2-chlorophenyl ring) which showed $LD_{50} > 1600$ mg/kg.

Experimental

General

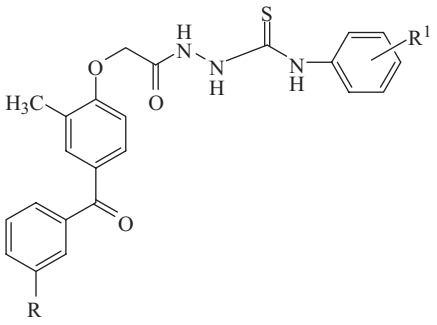
Melting points were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded in KBr on Perkin-Elmer-spectrum RX-I instrument and ν_{max} was recorded in cm^{-1}. ^{1}H-NMR spectra were recorded on a Hitachi 300 MHz using TMS as internal standard (chemical shifts (δ) in ppm) and Elemental analysis (C, H, N) of all the compounds were performed on CHN analyzer, Carlo Erba 1108 analyzer at the Central Drug Research Institute (Lucknow, India). ^{13}C-NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using solvent peak as internal standard. Mass spectra were determined on a Jeol SX 102 (FAB) spectrometer. The progress of the reaction is monitored by TLC and product are purified through recrystallization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G coated plate of 0.5 mm thickness.

Chemistry

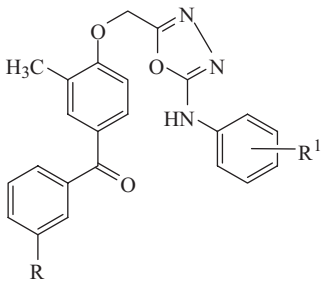
General procedure for synthesis of 2-(4-(3-substitutedbenzoyl)-2-methylphenoxy) acetates ***2a–2b***

A mixture of substituted 4-hydroxybenzophenones (**1a–1b**) (2.0 mol), ethyl bromoacetate (2.0 mol) and potassium carbonate

Table 2. Minimal inhibitor concentration (MIC) μg/mL of synthesized compounds **4a–4j** and **5a–5j** against the tested bacterial strains.



(4a-4j)



(5a-5j)

			Pseudomonas aeruginosa ATCC 27853	*Klebsiella pneumoniae* CIP 53153	*Escherichia coli* ATCC 25922	*Staphylococcus aureus* ATCC 25923
4a	H	CH_3	–	300	150	–
4b	H	OCH_3	60	–	240	–
4c	H	Br	150	180	180	270
4d	H	Cl	180	130	60	120
4e	H	C_2H_5	–	–	120	60
4f	Cl	CH_3	–	–	150	90
4g	Cl	OCH_3	120	150	150	120
4h	Cl	Br	60	30	15	30
4	Cl	Cl	15	120	15	15
4j	Cl	C_2H_5	–	–	120	–
5a	H	CH_3	–	120	60	120
5b	H	OCH_3	30	15	60	90
5c	H	Br	120	60	–	150
5d	H	Cl	15	60	15	30
5e	H	C_2H_5	15	60	60	30
5f	Cl	CH_3	–	30	15	15
5g	Cl	OCH_3	15	30	15	30
5h	Cl	Br	7.50	15	15	7.50
5i	Cl	Cl	3.75	1.875	3.75	0.9375
5j	Cl	C_2H_5	30	60	15	30
Control	–	–	Nil	Nil	Nil	Nil
Ciprofloxacin	–	–	15	3.75	7.5	3.75
Gattifloxacin	–	–	7.5	3.75	3.75	1.875

(10 g) in dry acetone (150 mL) were refluxed for 6 h. To the cooled reaction mixture, water (150 mL) was added and extracted with ether. The ether layer washed with 5% aqueous sodium hydroxide and with water and dried over anhydrous sodium sulphate and evaporated. The crude product on recrystallization from appropriate solvents yielded **2a–2b**.

Ethyl-2-(4-benzoyl-2-methylphenoxy)acetate ***2a***

Yield 88% (methanol); m.p. 76°C. IR (KBr) ν 2990 (C-H aromatic), 1690 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.86–6.90 (m, 8H, J = 8.6 Hz, aromatic-H), 3.60 (q, 2H, J = 7 Hz, CH_2CH_3), 2.50 (s, 2H, CH_2), 1.34 (t, 3H, J = 7 Hz, CH_2CH_3), 2.32 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) 187.0, 171.0, 166.4, 137.8, 132.2, 131.8, 130.1, 130.0, 128.2, 128.1, 123.0, 113.7, 75.9, 59.5, 13.6, 11.0. MS (*m*/*z*): 298.12 [M^+]. Anal. calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.49; H, 6.0.10%.

Ethyl-2-(4-(3-chlorobenzoyl)-2-methylphenoxy)acetate ***2b***

Yield 80% (acetone); m.p. 73°C. IR (KBr) ν 2995 (C-H aromatic), 1688 (C=O), 748 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.82–6.92 (m, 7H, J = 8.7 Hz, aromatic-H), 3.70 (q, 2H, J = 7 Hz, CH_2CH_3), 2.48 (s, 2H, CH_2), 1.40 (t, 3H, J = 7 Hz, CH_2CH_3), 2.30 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 171.0, 166.4, 139.2, 133.5, 132.6, 131.8, 130.5, 130.0, 129.6, 128.2, 128.1, 123.0, 113.7, 75.9, 59.5, 13.6, 11.0. MS (*m*/*z*): 332.78 [M^+]. Anal. calcd. for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15. Found: C, 64.90; H, 5.18%.

General procedure for synthesis of 2-(4-(3-substitutedbenzoyl)-2-methylphenoxy)acetohydrazides ***3a–3b***

To an ethanolic solution (25 mL) of ester (1.2 mol), hydrazine monohydrate (1.2 mol) was added and the reaction mixture was

kept aside for 2 h. The white crystalline solid separated was filtered, washed with ethanol dried and recrystallized from hot suitable solvents to give **3a–3b**.

*2-(4-Benzoyl-2-methylphenoxy)acetohydrazide **3a***

Yield 75% (ethanol); m.p. 167°C. IR (KBr) ν 3340 (NH), 2992 (C-H aromatic), 1686 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.40 (brs, 1H, NH, D_2O exchangeable), 8.30 (brs, 2H, NH_2, D_2O exchangeable), 7.80–6.91 (m, 8H, J = 8.9 Hz, aromatic-H), 2.50 (s, 2H, CH_2), 2.33 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 170.3, 166.4, 137.8, 132.2, 131.8, 131.0, 130.1, 130.0, 128.2, 128.1, 123.0, 121.1, 113.7, 78.3, 11.0. MS (*m*/*z*): 284.31 [M^+]. Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.63; H, 5.63; N, 9.86%.

*2-(4-(3-Chlorobenzoyl)-2-methylphenoxy)acetohydrazide **3b***

Yield 73% (ethanol); m.p. 163°C. IR (KBr) ν 3347 (NH), 2996 (C-H aromatic), 1684 (C=O), 748 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.44 (brs, 1H, NH, D_2O exchangeable), 8.28 (brs, 2H, NH_2, D_2O exchangeable), 7.90–6.71 (m, 7H, J = 9 Hz, aromatic-H), 2.56 (s, 2H, CH_2), 2.37 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 170.3, 166.4, 139.2, 133.5, 132.6, 131.8, 131.0, 130.5, 130.0, 129.6, 128.2, 128.1, 123.0, 113.7, 78.3, 11.0. MS (*m*/*z*): 318.75 [M^+]. Anal. calcd. for $C_{16}H_{15}ClN_3O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.39; H, 4.76; N, 8.80%.

*General procedure for synthesis of 2-(2-(4-(3-substitutedbenzoyl)-2-methylphenoxy)acetyl)-N-(2-substitutedphenyl)hydrazinecarbothioamides **4a–4j***

A mixture of compounds **3a–3b** (0.6 mol) and substituted phenylisothiocyanates (0.6 mol) in 30 mL of absolute ethanol was refluxed for 5–6 h. After completion of the reaction, the reaction mixture was concentrated and kept overnight at room temperature. The needle shaped crystals thus obtained were purified by repeated washing with appropriate solvents to obtain compounds **4a–4j**.

*2-(2-(4-Benzoyl-2-methylphenoxy)acetyl)-N-(2-methylphenyl)hydrazinecarbothioamide **4a***

Yield 78% (ethanol); m.p. 187°C. IR (KBr) ν 3450 (NH), 3010 (C-H aromatic), 1682 (C=O), 1304 (CN), 1129 (C=S) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.90 (brs, 1H, NH-Ar, D_2O exchangeable), 8.75 (brs, 1H, NHC=S, D_2O exchangeable), 8.60 (brs, 1H, CONH, D_2O exchangeable), 7.80–6.91 (m, 12H, J = 8.6 Hz, aromatic-H), 2.70 (s, 2H, CH_2), 2.35 (s, 6H, 2 × CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 170.3, 186.0, 166.4, 140.1, 137.8, 134.5, 132.2, 131.8, 130.1, 130.0, 129.5, 128.2, 125.8, 125.2, 124.4, 123.0, 113.7, 78.9, 12.4, 11.0. MS (*m*/*z*): 433.52 [M^+]. Anal. calcd. for $C_{24}H_{23}N_3O_3S$: C, 66.49; H, 5.35; N, 9.69. Found: C, 66.43; H, 5.34; N, 9.72%.

*2-(2-(4-Benzoyl-2-methylphenoxy)acetyl)-N-(2-methoxyphenyl)hydrazinecarbothioamide **4b***

Yield 75% (methanol); m.p. 198°C. IR (KBr) ν 3450 (NH), 3008 (C-H aromatic), 1687 (C=O), 1310 (CN), 1130 (C=S) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.94 (brs, 1H, NH-Ar, D_2O exchangeable), 8.75 (brs, 1H, NHC=S, D_2O exchangeable), 8.60 (brs, 1H, CONH, D_2O exchangeable), 7.80–6.91 (m, 12H, J = 9 Hz, aromatic-H), 3.56 (s, 3H, OCH_3), 2.72 (s, 2H, CH_2), 2.32 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 186.0, 170.3, 166.4, 158.8, 137.8, 132.2, 131.8, 130.1, 130.0, 128.2, 128.1, 123.0, 125.5, 126.3, 125.0, 121.1, 114.4, 113.7, 78.9, 56.0, 11.0. MS (*m*/*z*): 449.52 [M^+]. Anal. calcd. for $C_{24}H_{23}N_3O_4S$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.17; H, 5.11; N, 9.37%.

*2-(2-(4-Benzoyl-2-methylphenoxy)acetyl)-N-(2-bromophenyl)hydrazinecarbothioamide **4c***

Yield 74% (acetone); m.p. 204°C. IR (KBr) ν 3452 (NH), 3014 (C-H aromatic), 1689 (C=O), 1305 (CN), 1128 (C=S), 610 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.92 (brs, 1H, NH-Ar, D_2O exchangeable), 8.75 (brs, 1H, NHC=S, D_2O exchangeable), 8.50 (brs, 1H, CONH, D_2O exchangeable), 7.86–6.76 (m, 12H, J = 8.6 Hz, aromatic-H), 2.75 (s, 2H, CH_2), 2.30 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 186.0, 170.3, 166.4, 142.7, 132.2, 132.1, 137.8, 130.0, 130.1, 131.8, 127.5, 127.8, 126.7, 128.2, 128.1, 123.0, 119.9, 113.7, 78.9, 11.0. MS (*m*/*z*): 498.39 [M^+]. Anal. calcd. for $C_{23}H_{20}BrN_3O_3S$: C, 55.43; H, 4.04; N, 8.43. Found: C, 55.49; H, 4.08; N, 8.40%.

*2-(2-(4-Benzoyl-2-methylphenoxy)acetyl)-N-(2-chlorophenyl)hydrazinecarbothioamide **4d***

Yield 70% (methanol); m.p.190°C. IR (KBr) ν 3450 (NH), 3012 (C-H aromatic), 1682 (C=O), 1302 (CN), 1132 (C=S), 752 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.90 (brs, 1H, NH-Ar, D_2O exchangeable), 8.72 (brs, 1H, NHC=S, D_2O exchangeable), 8.61 (brs, 1H, CONH, D_2O exchangeable), 7.84–6.94 (m, 12H, J = 9 Hz, aromatic-H), 2.60 (s, 2H, CH_2), 2.28 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 186.0, 170.3, 166.4, 139.8, 137.8, 132.2, 131.8, 130.6, 130.1, 130.0, 129.2, 128.2, 128.1, 126.9, 126.7, 126.7, 125.9, 123.0, 113.7, 78.9, 11.0. MS (*m*/*z*): 453.94 [M^+]. Anal. calcd. for $C_{23}H_{20}ClN_3O_3S$: C, 60.86; H, 4.44; N, 9.26. Found: C, 60.88; H, 4.45; N, 9.20%.

*2-(2-(4-Benzoyl-2-methylphenoxy)acetyl)-N-(2-ethylphenyl)hydrazinecarbothioamides **4e***

Yield 68% (methanol); m.p. 200°C. IR (KBr) ν 3455 (NH), 3009 (C-H aromatic), 1684 (C=O), 1304 (CN), 1130 (C=S) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.87 (brs, 1H, NH-Ar, D_2O exchangeable), 8.62 (brs, 1H, NHC=S, D_2O exchangeable), 8.50 (brs, 1H, CONH, D_2O exchangeable), 7.83–6.74 (m, 12H, J = 9 Hz, aromatic-H), 3.02 (q, 2H, J = 6.5 Hz, CH_2CH_3), 2.66 (s, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.20 (t, 3H, J = 6.6 Hz, CH_2CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 194.3, 166.3, 181.1, 162.3, 138.4, 135.8, 134.6, 132.4, 131.9, 131.5, 130.3, 128.4, 128.3, 128.2, 126.2, 124.9, 124.2, 128.4, 119.5, 113.9, 15.4, 67.2, 23.7, 14.5. MS (*m*/*z*): 447.55 [M^+]. Anal. calcd. for $C_{25}H_{25}N_3O_3S$: C, 67.09; H, 5.63; N, 9.39. Found: C, 67.03; H, 5.62; N, 9.45%.

*2-(2-(4-(3-Chlorobenzoyl)-2-methylphenoxy)acetyl)-N-(2-methylphenyl)hydrazinecarbothioamide **4f***

Yield 72% (DMF); m.p. 179°C. IR (KBr) ν 3448 (NH), 3013 (C-H aromatic), 1686 (C=O), 1306 (CN), 1129 (C=S), 744 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.93 (brs, 1H, NH-Ar, D_2O exchangeable), 8.70 (brs, 1H, NHC=S, D_2O exchangeable), 8.60 (brs, 1H, CONH, D_2O exchangeable), 7.84–6.94 (m, 11H, J = 8.7 Hz, aromatic-H), 2.63 (s, 2H, CH_2), 2.35 (s, 6H, 2 × CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.0, 186.0, 170.3, 140.1, 139.2, 134.5, 133.5, 132.6, 131.8, 130.0, 129.6, 128.2, 125.8, 125.2, 124.4, 113.7, 78.9, 12.4, 11.0. MS (*m*/*z*): 467.97 [M^+]. Anal. calcd. for $C_{24}H_{22}ClN_3O_3S$: C, 61.60; H, 4.74; N, 8.98. Found: C, 61.69; H, 4.78; N, 8.92%.

2-(2-(4-(3-Chlorobenzoyl)-2-methylphenoxy)acetyl)-N-(2-methoxyphenyl)hydrazinecarbothioamide ***4g***

Yield 75% (ethanol); m.p. 189°C. IR (KBr) ν 3443 (NH), 3010 (C-H aromatic), 1690 (C=O), 1302 (CN), 1131 (C=S), 751 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.83 (brs, 1H, NH-Ar, D_2O exchangeable), 8.73 (brs, 1H, NHC=S, D_2O exchangeable), 8.62 (brs, 1H, CONH, D_2O exchangeable), 7.89–6.84 (m, 11H, $J = 9$ Hz, aromatic-H), 3.58 (s, 3H, OCH_3), 2.67 (s, 2H, CH_2), 2.38 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 186.0, 170.3, 166.4, 158.8, 139.2, 133.5, 132.6, 131.8, 130.5, 130.0, 129.6, 128.2, 128.1, 126.3, 125.5, 125.0, 123.0, 121.1, 114.4, 78.9, 11.0. MS (*m*/*z*): 483.97 [M^+]. Anal. calcd. for $C_{24}H_{22}ClN_3O_4S$: C, 59.56; H, 4.58; N, 8.68. Found: C, 59.59; H, 4.50; N, 8.67%.

N-(2-Bromophenyl)-2-(2-(4-(3-chlorobenzoyl)-2-methylphenoxy)acetyl)hydrazinecarbothioamide ***4h***

Yield 73% (methanol); m.p. 209°C. IR (KBr) ν 3460 (NH), 3012 (C-H aromatic), 1685 (C=O), 1306 (CN), 1134 (C=S), 748 (C-Cl), 614 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.88 (brs, 1H, NH-Ar, D_2O exchangeable), 8.69 (brs, 1H, NHC=S, D_2O exchangeable), 8.61 (brs, 1H, CONH, D_2O exchangeable), 7.78–6.92 (m, 11H, $J = 8.8$ Hz, aromatic-H), 2.62 (s, 2H, CH_2), 2.32 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 194.3, 181.1, 166.3, 162.3, 141.1, 138.3, 137.2, 132.5, 132.2, 131.9, 131.5, 131.4, 130.5, 129.8, 128.4, 128.3, 128.0, 124.4, 124.2, 113.9, 67.2, 15.4. MS (*m*/*z*): 532.84 [M^+]. Anal. calcd. for $C_{23}H_{19}BrClN_3O_3S$: C, 51.84; H, 3.59; N, 7.89. Found: C, 51.88; H, 3.63; N, 7.84%.

2-(2-(4-(3-Chlorobenzoyl)-2-methylphenoxy)acetyl)-N-(2-chlorophenyl)hydrazinecarbothioamide ***4i***

Yield 70% (ethanol); m.p. 210°C. IR (KBr) ν 3447 (NH), 3013 (C-H aromatic), 1690 (C=O), 1302 (CN), 1130 (C=S), 754 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.97 (brs, 1H, NH-Ar, D_2O exchangeable), 8.76 (brs, 1H, NHC=S, D_2O exchangeable), 8.66 (brs, 1H, CONH, D_2O exchangeable), 7.74–6.84 (m, 11H, $J = 9$ Hz, aromatic-H), 2.61 (s, 2H, CH_2), 2.35 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 194.3, 181.1, 166.3, 162.3, 141.1, 138.3, 135.9, 133.9, 132.5, 131.9, 131.5, 130.2, 131.4, 130.5, 129.8, 128.4, 128.3, 124.4, 124.3, 124.2, 113.9, 67.2, 15.4, 13.4. MS (*m*/*z*): 488.39 [M^+]. Anal. calcd. for $C_{23}H_{19}Cl_2N_3O_3S$: C, 56.56; H, 3.92; N, 8.60. Found: C, 56.60; H, 3.90; N, 8.67%.

2-(2-(4-(3-Chlorobenzoyl)-2-methylphenoxy)acetyl)-N-(2-ethylphenyl)hydrazinecarbothioamide ***4j***

Yield 70% (methanol); m.p. 196°C. IR (KBr) ν 3457 (NH), 3015 (C-H aromatic), 1686 (C=O), 1300 (CN), 1127 (C=S), 749 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.93 (brs, 1H, NH-Ar, D_2O exchangeable), 8.70 (brs, 1H, NHC=S, D_2O exchangeable), 8.60 (brs, 1H, CONH, D_2O exchangeable), 7.87–6.90 (m, 11H, $J = 9$ Hz, aromatic-H), 3.05 (q, 2H, $J = 6.6$ Hz, CH_2CH_3), 2.60 (s, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.25 (t, 3H, $J = 6.6$ Hz, CH_2CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 194.3, 181.1, 166.3, 162.3, 141.1, 135.8, 134.6, 132.5, 131.5, 131.4, 131.3, 130.3, 129.8, 128.4, 128.3, 128.2, 126.2, 124.9, 124.2, 119.5, 113.9, 109.8, 67.2, 23.7, 15.4, 14.5. MS (*m*/*z*): 481.99 [M^+]. Anal. calcd. for $C_{25}H_{24}ClN_3O_3S$: C, 62.30; H, 5.02; N, 8.72. Found: C, 62.32; H, 5.00; N, 8.75%.

General procedure for synthesis of (3-substitutedphenyl)-(3-methyl-4-((5-(2-substitutedphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanones ***5a–5j***

A solution of substituted hydrazinecarbothioamides **4a–4j** (0.07 mol) and sodium hydroxide (10 mL) in 50 mL of ethanol was cooled under continuous stirring for 30 min. To this mixture, iodine in KI (5%) was added dropwise till the color of iodine persisted at room temperature. After that the mixture was refluxed for 2h. After completion of the reaction, the reaction mixture was poured onto crushed ice. The solid thus obtained was washed with sodium thiosulphate solution and recrystallized from suitable solvents to yielded compounds **5a–5j**.

(3-Methyl-4-((5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)phenyl)methanone ***5***

Yield 71% (methanol); m.p. 230°C. IR (KBr) ν 3442 (NH), 2972 (C-H aromatic), 1712 (C=O), 1312 (CN), 1004 (C-O-C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.60 (brs, 1H, NH, D_2O exchangeable), 7.89–6.70 (m, 12H, $J = 9$ Hz, aromatic-H), 3.24 (s, 2H, CH_2), 3.10 (s, 6H, $2 \times CH_3$) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 147.4, 137.8, 132.2, 131.8, 130.1, 130.0, 128.2, 128.1, 128.0, 126.3, 124.3, 123.0, 118.4, 115.0, 72.3, 12.1, 11.0. MS (*m*/*z*): 399.44 [M^+]. Anal. calcd. for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.19; H, 5.28; N, 10.58%.

(4-((5-(2-Methoxyphenylamino)-1,3,4-oxadiazol-2-yl) methoxy)-3-methylphenyl)phenyl)methanone ***5b***

Yield 75% (acetone); m.p. 236°C. IR (KBr) ν 3448 (NH), 2980 (C-H aromatic), 1710 (C=O), 1314 (CN), 1009 (C-O-C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.50 (brs, 1H, NH, D_2O exchangeable), 7.86–6.74 (m, 12H, $J = 8.6$ Hz, aromatic-H), 3.60 (s, 3H, OCH_3), 3.26 (s, 2H, CH_2), 3.15 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 148.6, 137.8, 132.3, 132.2, 131.8, 130.1, 131.0, 130.0, 128.2, 128.1, 123.0, 121.6, 119.5, 116.1, 114.9, 113.7, 72.3, 56.0. MS (*m*/*z*): 415.44 [M^+]. Anal. calcd. for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11. Found: C, 69.45; H, 5.12; N, 10.18%.

(4-((5-(2-Bromophenylamino)-1,3,4-oxadiazol-2-yl) methoxy)-3-methylphenyl)phenyl)methanone ***5c***

Yield 75% (acetone); m.p. 250°C. IR (KBr) ν 3455 (NH), 2970 (C-H aromatic), 1710 (C=O), 1314 (CN), 1012 (C-O-C), 612 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.20 (brs, 1H, NH, D_2O exchangeable), 7.89–6.70 (m, 12H, $J = 8.7$ Hz, aromatic-H), 3.28 (s, 2H, CH_2), 3.17 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 160.0, 150.0, 137.8, 132.6, 131.8, 130.1, 130.0, 128.3, 128.2, 128.1, 123.0, 120.7, 117.3, 113.7, 109.7, 72.3, 32.2, 28.2, 11.0. MS (*m*/*z*): 464.31 [M^+]. Anal. calcd. for $C_{23}H_{18}BrN_3O_3$: C, 59.50; H, 3.91; N, 9.05. Found: C, 59.47; H, 3.95; N, 9.02%.

(4-((5-(2-Chlorophenylamino)-1,3,4-oxadiazol-2-yl) methoxy)-3-methylphenyl)phenyl)methanone ***5d***

Yield 74% (methanol); m.p. 246°C. IR (KBr) ν 3448 (NH), 2982 (C-H aromatic), 1720 (C=O), 1308 (CN), 1008 (C-O-C), 756 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.30 (brs, 1H, NH, D_2O exchangeable), 7.99–6.80 (m, 12H, $J = 9$ Hz, aromatic-H), 3.25 (s, 2H, CH_2), 3.17 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 147.1, 137.8, 131.8, 132.2, 130.1, 130.0, 129.7, 128.2, 128.1, 127.4, 123.0, 120.4, 119.9, 116.5, 113.7, 72.3, 11.0. MS (*m*/*z*): 419.86 [M^+]. Anal. calcd. for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; N, 10.01. Found: C, 65.71; H, 4.30; N, 10.07%.

(4-((5-(2-Ethylphenylamino)-1,3,4-oxadiazol-2-yl) methoxy)-3-methylphenyl)phenyl)methanone ***5e***

Yield 72% (ethanol); m.p. 261°C. IR (KBr) ν 3455 (NH), 2982 (C-H aromatic), 1718 (C=O), 1310 (CN), 1010 (C-O-C) cm^{-1}; ^{1}H-NMR

($CDCl_3$) δ: 10.33 (brs, 1H, NH, D_2O exchangeable), 7.70–6.78 (m, 12H, J = 8.7 Hz, aromatic-H), 3.45 (q, 2H, J = 6.6 Hz, CH_2CH_3), 3.29 (s, 2H, CH_2), 3.20 (s, 3H, CH_3), 1.25 (t, 3H, J = 6.5 Hz, CH_2CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 146.1, 137.8, 132.2, 131.8, 130.0, 130.1, 128.7, 128.2, 128.1, 126.5, 126.8, 123.0, 118.4, 115.0, 113.7, 72.3, 19.8, 16.1, 11.0. MS (*m*/*z*): 413.47 [M^+]. Anal. calcd. for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.66; H, 5.67; N, 10.0%.

(3-Chlorophenyl)(3-methyl-4-((5-(2-methylphenylamino)-1,3,4-oxadiazol-2-yl)methoxy) phenyl) methanone ***5f***

Yield 70% (methanol); m.p. 215°C. IR (KBr) ν 3454 (NH), 2986 (C-H aromatic), 1712 (C=O), 1304 (CN), 1014 (C-O-C), 752 (C-Cl) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 10.24 (brs, 1H, NH, D_2O exchangeable), 7.86–6.78 (m, 11H, J = 9 Hz, aromatic-H), 3.23 (s, 2H, CH_2), 3.17 (s, 6H, 2 × CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 147.4, 139.2, 133.5, 132.6, 131.3, 130.5, 130.0, 129.6, 128.2, 128.1, 126.3, 124.3, 123.0, 118.4, 115.0, 113.7, 72.3, 12.1, 11.0. MS (*m*/*z*): 433.89 [M^+]. Anal. calcd. for $C_{24}H_{20}ClN_3O_3$: C, 66.44; H, 4.65; N, 9.68. Found: C, 66.49; H, 4.69; N, 9.66%.

(3-Chlorophenyl)(4-((5-(2-methoxyphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-3-methylphenyl) methanone ***5g***

Yield 69% (methanol); m.p. 242°C. IR (KBr) ν 3448 (NH), 2990 (C-H aromatic), 1730 (C=O), 1312 (CN), 1008 (C-O-C), 749 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.50 (brs, 1H, NH, D_2O exchangeable), 7.80–6.77 (m, 11H, J = 9 Hz, aromatic-H), 3.66 (s, 3H, OCH_3), 3.22 (s, 2H, CH_2), 3.16 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 148.6, 139.2, 132.6, 133.5, 132.3, 131.8, 130.5, 130.0, 129.6, 128.2, 128.1, 123.0, 121.6, 119.5, 116.1, 114.9, 113.7, 72.0, 56.0, 11.0. MS (*m*/*z*): 449.89 [M^+]. Anal. calcd. for $C_{24}H_{20}ClN_3O_4$: C, 64.07; H, 4.48; N, 9.34. Found: C, 64.00; H, 4.46; N, 9.39%.

(4-((5-(2-Bromophenylamino)-1,3,4-oxadiazol-2-yl) methoxy)-3-methylphenyl)(3-chlorophenyl) methanone ***5h***

Yield 70% (acetone); m.p. 254°C. IR (KBr) ν 3450 (NH), 2995 (C-H aromatic), 1722 (C=O), 1310 (CN), 1006 (C-O-C), 749 (C-Cl), 614 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.54 (brs, 1H, NH, D_2O exchangeable), 7.69–6.70 (m, 11H, J = 9.1 Hz, aromatic-H), 3.20 (s, 2H, CH_2), 3.13 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 150.0, 139.2, 133.5, 132.6, 131.8, 130.5, 130.0, 129.6, 128.3, 128.2, 128.1, 123.0, 120.7, 109.7, 113.7, 72.3, 11.0. MS (*m*/*z*): 498.76 [M^+]. Anal. calcd. for $C_{23}H_{17}BrClN_3O_3$: C, 55.39; H, 3.44; N, 8.42. Found: C, 55.42; H, 3.48; N, 8.40%.

(3-Chlorophenyl)(4-((5-(2-chlorophenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-3-methylphenyl) methanone ***5i***

Yield 72% (ethanol); m.p. 248°C. IR (KBr) ν 3448 (NH), 2990 (C-H aromatic), 1730 (C=O), 1312 (CN), 1008 (C-O-C), 759 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.57 (brs, 1H, NH, D_2O exchangeable), 7.9–6.80 (m, 11H, J = 9 Hz, aromatic-H), 3.27 (s, 2H, CH_2), 3.16 (s, 3H, CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 147.1, 139.2, 133.5, 132.6, 131.8, 130.5, 130.0, 129.7, 129.6, 128.2, 128.1, 127.4, 123.0, 120.4, 119.9, 116.5, 113.7, 72.3, 11.0. MS (*m*/*z*): 454.31 [M^+]. Anal. calcd. for $C_{23}H_{17}Cl_2N_3O_3$: C, 60.81; H, 3.77; N, 9.25. Found: C, 60.88; H, 3.70; N, 9.23%.

(3-Chlorophenyl)(4-((5-(2-ethylphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-3-methylphenyl) methanone ***5j***

Yield 73% (methanol); m.p. 238°C. IR (KBr) ν 3454 (NH), 2988 (C-H aromatic), 1735 (C=O), 1311 (CN), 1013 (C-O-C), 756 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.62 (brs, 1H, NH, D_2O exchangeable), 7.89–6.60 (m, 11H, J = 8.8 Hz, aromatic-H), 3.45 (q, 2H, J = 6.5 Hz, CH_2CH_3), 3.24 (s, 2H, CH_2), 3.19 (s, 3H, CH_3), 1.35 (t, 3H, J = 6.5 Hz, CH_2CH_3) ppm; ^{13}C-NMR ($CDCl_3$) 187.0, 166.4, 146.1, 139.2, 133.5, 132.6, 131.8, 130.5, 130.0, 129.6, 128.7, 128.2, 128.1, 126.8, 126.5, 123.0, 118.4, 113.7, 115.0, 72.3, 19.8, 16.1, 11.0. MS (*m*/*z*): 447.91 [M^+]. Anal. calcd. for $C_{25}H_{22}ClN_3O_3$: C, 67.04; H, 4.95; N, 9.38. Found: C, 67.09; H, 4.99; N, 9.30%.

Biological studies

Antibacterial activity

The newly synthesized compounds **4a–4j** and **5a–5j** were screened for antibacterial activity against bacterial strains namely *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* CIP 53153, *Escherichia coli* ATCC 25922, and *Staphylococcus aureus* ATCC 25923 at a concentration of 300 μg/mL by the filter paper disc-method [10]. For comparison, ciprofloxacin and gattifloxacin were used as the standard drugs. DMSO served as control and there was no visible change in bacterial growth due to this. The discs of Whatman filter paper were prepared with standard size (7 mm) and kept into one-Oz screw-capped wide-mouthed containers for sterilization. These bottles are kept in the hot-air oven at 150°C. Now, solution is put into each bottle. The discs are transferred to the inoculated plates with a pair of fine pointed tweezers. To prevent contamination, tweezers may be kept with their tips in 70% alcohol and flamed off before use. Before using the test organisms, grown on nutrient agar, they were subcultured on nutrient broth at 37°C for 18–20 h. Each disc was carefully applied to the surface of the agar without lateral movement once the surface had been touched. Now, the plates incubated for 24 h at 37°C.

Minimal inhibitory concentration (MIC)

The antibacterial activity was assayed in vitro by two-fold broth dilution [11] against the bacterial strains *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* CIP 53153, *Escherichia coli* ATCC 25922, and *Staphylococcus aureus* ATCC 25923. The minimal inhibitory concentrations (MIC, in μg/mL) were defined as the lowest concentrations of compound that completely inhibited the growth of each strain. All compounds dissolved in dimethylsulfoxide were added to the culture media. Mueller-Hinton Broth for bacteria was used to obtain the final concentrations ranging from 300 to 0.9375 μg/mL. The amounts of dimethylsulfoxide never exceed 1% v/v. Inocula consisted of 5.0 × 10^4 bacteria/mL. The MICs were read after incubation at 37°C for 24 h. (bacteria). Media and media with 1% v/v dimethylsulfoxide were employed as growth controls. Ciprofloxacin and gattifloxacin were used as reference antibacterial activity, subcutaneous were performed by transferring 100 μL of each mixture remaining clear in 1 mL of fresh medium. The minimal bactericidal concentrations (MBC, μg/mL) were read after incubation at 37°C for 48 h.

Approximate lethal dose (LD_{50})

The compounds were investigated for this acute toxicity (LD_{50}) in albino mice by following the method of Q. E. Smith [12]. Test compounds were administered orally in one group and the same volume of normal saline in another group of animals consisting six mice each in graded doses. During the study, the animals were allowed to take water and food ad libidum. After 24 h of

drug administration percent mortality in each group was observed. From the data obtained LD_{50} was calculated.

We are thankful to SAIF Punjab University, Chandigarh CDRI Lucknow, India for spectral and analytical analysis of newly synthesized compounds. One of the author, Hemlata Kaur is also thankful to UGC New Delhi, India, for the award of J.RF.-Rajiv Gandhi National Junior Research Fellowship and financial support for this work.

The authors have declared no conflict of interest.

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