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Synthesis, Characterization and Biological Evaluation of 1,3,4- Oxadiazole Derivatives with hydroxybenzoate and indoline-2-carboxylic acid

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ABSTRACT: The paper presents the synthesis of 1,3,4-oxadiazol derivatives through the reaction between 2-hydroxybenzoate , Hydrazine and indoline-2-carboxylic acid. The newly synthesized compounds have been characterized and their structure configuration have been determined with the help of various elemental analysis, (IR, ^{1}H NMR, ^{13}C NMR, GCMS spectroscopic) techniques. These compounds were tested for their antibacterial inhibition potential against the pathogen *Staphylococcus aureus* and *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginoca, Escherichia coli* and *Salmonella typhi* (as gram negative bacteria). compound (3) (5-(2-hydroxy-5-methylphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-nitroindolin-2-yl)methanone [$C_{18}H_{14}N_4O_5S$] is more biological activity against all pathogens.

Keywords: 1,3,4-Oxadiazole, methyl 2-hydroxybenzoate derivatives, Hydrazine, indoline-2-carboxylic acid, Biological Activity.

1. INTRODUCTION

Medicinal Chemistry or Pharmaceutical Chemistry is a discipline at the intersection of chemistry. It involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It is a part of pharmacology, this latter taken in its etymological sense 'pharmakon' + 'logs': study of drugs [1-5]. The activity of a given drug depends on a sequence of physio-chemical events that begin when the active molecule penetrates into the living organism and which culminates when the active molecule reaches its target and elicits the appropriate biological response. Classically it is admitted that three characteristic phases govern the biological activity of a drug in a living organism. A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements as members of its ring(s) [5-7]. Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties and applications of these heterocycles. In contrast, the rings of homocyclic compounds consist entirely of atoms of the same element. Although heterocyclic compounds may be inorganic, most contain at least one carbon. While atoms, that are neither carbon nor hydrogen are often referred in organic chemistry as heteroatoms. This is usually in comparison to the all-carbon backbone, and does not prevent a compound such as borazine (which has no carbon atoms) from being labelled "heterocyclic" [8.9]. IUPAC recommends the Hantzsch-Widman nomenclature for naming heterocyclic compounds. 1,3,4-Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. It is derived from furan by substitution of two methylene groups [10-12]. (=CH) with two pyridine type nitrogens (-N=). There are three known isomers: 1,2,4-oxadiazole (2), 1,2,3-oxadiazole (3) and 1,2,5-oxadiazole [13]. However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important construction motif for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have

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a broad biological activity spectrum including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and anti-diabetic properties [14,15]. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids, esters and carboxamides. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential. The synthesis of novel 1,3,4-oxadiazole derivatives, and investigation of their chemical properties and biological behavior has accelerated in the last two decades [16]. In recent years the number of scientific studies with these compounds has increased considerably. Considering the period from 2002 to 2015, the Scifinder Scholar database records 2,577 references to 1,3,4-oxadiazole, demonstrating its relevance for heterocyclic chemistry. Taking into account, the importance of these compounds of both heterocyclic and medicinal chemistry, we have decided to present the main synthesis approaches used for obtaining the heterocyclic nucleus, as well as the broad spectrum of pharmacological activities reported in the literature over the past years [17].

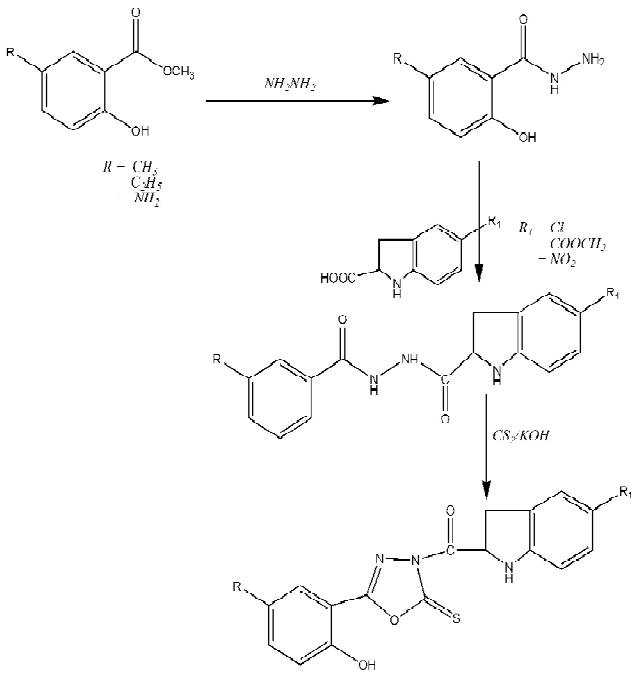
2. EXPERIMENTAL

2.1. Reagents

The entire chemicals used were of the analytical reagent grade, indoline-2-carboxylic acid and 2-hydroxybenzoate procured from s.d.-fine. Hydrazine was purchased from Merck.

2.2. General procedure for the synthesis of compounds 1-9

Methyl 2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazide (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with indoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum (Scheme I).



Scheme I

2.2.1. (5-chloroindolin-2-yl)(5-(2-hydroxy-5-methylphenyl)-2-thioxo-1,3,4 oxadiazol-3(2H)-yl)methanone (Compound 1)

Methyl 2-hydroxy-5-methylbenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-chloroindoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 06H, Ar–H), 4.8.0 (s, H, OH), 2.35 (s, 3x1H, CH), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N^2H) 3244, ν(C=S), 719 , ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{18}H_{14}ClN_3O_3S$, (387.04) calcu. C 55.74, H 3.64, N, 10.83; found C 55.88, H 3.42, N 10.13.

2.2.2. Methyl-2-(5-(2-hydroxy-5-methylphenyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazole-3-carbonyl)indoline-5-carboxylate (Compound 2)

Methyl 2-hydroxy-5-methylbenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-(methoxycarbonyl)indoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 06H, Ar–H), 4.8.0 (s, H, OH), 2.35 (s, 6x1H, CH), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N²H) 3244, ν(C=S), 719 , ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{20}H_{17}N_3O_5S$ (411.08) calcu. C 58.38, H 4.16, N, 10.21;found C 58.88, H 4.42, N 10.13.

2.2.3. (5-(2-hydroxy-5-methylphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-nitroindolin-2-yl)methanone (Compound 3)

Methyl 2-hydroxy-5-methylbenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-nitroindoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 08H, Ar–H), 4.8.0 (s, H, OH), 2.35 (s, 3x1H, CH), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122, (aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N²H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{18}H_{14}N_4O_5S$, (398.06) calcu. C 54.27, H 3.54, N 14.06 found C 54.88, H 3.92, N 14.13.

2.2.4. (5-chloroindolin-2-yl)(5-(5-ethyl-2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methanone(Compound 4)

Methyl 5-ethyl-2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-chloroindoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 06H, Ar–H), 4.8.0 (s, H, OH), 1.24 (s, 3x1H, CH) 2.59 (s, 2x1H, CH aliphatic), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol).

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N²H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{19}H_{16}ClN_3O_3S$, (401.06) calcu. C 56.79, H 4.01, N 10.46; found C 56.88, H 4.08, N 10.43.

2.2.5. Methyl-2-(5-(5-ethyl-2-hydroxyphenyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazole -3-carbonyl) indoline-5-carboxylate (Compound 5)

Methyl 5-ethyl-2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-(methoxycarbonyl)indoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced

pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 06H, Ar–H), 4.8 (s, H, OH), 3.88 (s, 3H, OCH), 1.24 (s, 3x1H, CH) 2.59 (s, 2x1H, CH aliphatic), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N²H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{21}H_{19}N_3O_5S$, (425.10) calcu. C 59.28, H 4.50, N 9.88; found C 59.30, H 4.42, N 9.86.

2.2.6. (5-(5-ethyl-2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-nitroindolin-2-yl)methanone (Compound 6)

Methyl 5-ethyl-2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-nitroindoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 08H, Ar–H), 4.8.0 (s, H, OH), 1.24 (s, 3x1H, CH) 2.59 (s, 2x1H, CH aliphatic), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N²H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{19}H_{16}N_4O_5S$, (412.08) calcu. C 55.33, H 3.91, N 13.58; found C 55.38, H 3.88, N 13.60.

2.2.7. (5-(5-amino-2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-chloroindolin-2-yl)methanone (Compound 7)

Methyl 5-amino-2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-chloroindoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 06H, Ar–H), 4.8.0 (s, H, OH), 11.35 (s, 2x1H, NH), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N²H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{17}H_{13}ClN_4O_3S$, (388.03) calcu. C 52.51, H 3.37, N 14.41; found C 52.38, H 3.42, N 14.43.

2.2.8. Methyl-2-(5-(5-amino-2-hydroxyphenyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazole-3-carbonyl)indoline-5-carboxylate (Compound 8)

Methyl 5-amino-2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-(methoxycarbonyl)indoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 08H, Ar–H), 4.8.0 (s, H, OH), 11.35 (s, 2x1H, NH), 3.88 (s, 3H, OCH), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3,

128.8, 127.5, 122,(aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1× 10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N^2H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{19}H_{16}N_4O_5S$, (412.08) calcu. C 55.33, H 3.91, N 13.58; found C 55.38, H 3.92, N 13.60.

2.2.9. (5-(5-amino-2-hydroxyphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-nitroindolin-2-yl)methanone (Compound 9)

Methyl 5-amino-2-hydroxybenzoate (12 mmol) in ethanol (20 mL) was added to a solution of hydrazine (1 mmol) in ethanol (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and react with 5-nitroindoline-2-carboxylic acid which further refluxed for 6h in the presence of CS2/KOH the solvent removed under reduced pressure by rotarvapour until a solid product was formed that was washed with cold ethanol and dried under vacuum. Melting point 145°C, Yield 70–75% (scheme 1). ^{1}H NMR (300MHz, DMSO): δ = 7.22-7.48 (m, 08H, Ar–H), 4.8.0 (s, H, OH), 11.35 (s, 2x1H, NH), 4.77 (s, 1H, -NH, indol), 3.4 (d, 2x1H, H of indol)

^{13}C NMR (300MHz, DMSO, 300 K): 139.3 (C=N), 186.0 (C=S), 145.7, 135.8, 133.1, 129.3, 128.8, 127.5, 122, (aromatic carban). One quaternary carbon was not detected. UV/vis (Nujol mul (nm)): λ = 278, 332, 342. UV/vis (1×10^{-4} mol, DMSO): λ = 261, 289, 355. IR (KBr): ν(N^2H) 3244, ν(C=S), 719, ν(C=N) 1678 s, ν(N–N) 1144 s cm^{-1}. Elemental analysis for $C_{17}H_{13}N_5O_5S$, (399.06) calcu. C 51. 12, H 3.28, N 17.54; found C 51.18, H 3.32, N 17.58.

3. RESULTS AND DISCUSSION

3.1. FAB Mass spectra

All the spectra exhibit parent peaks due to molecular ion (M^+). The proposed molecular formula of these complexes was confirmed by comparing their molecular formula weight with m/e values. The molecular ion (M^+) peaks obtained from various complexes are as follows: m/e = 386.04 (compound 1), m/e = 410.08 (compound 2), m/e = 397.06 (compound 3), m/e = 400.06 (compound 4), m/e = 424.10 (compound 5), m/e = 411.08 (compound 6), m/e = 387.03 (compound 7), m/e = 411.08 (compound 8), m/e = 398.06 (compound 9). This data is in good agreement with the proposed molecular formula for these complexes (table 1). In addition to the peaks due to the molecular ion, the spectra exhibit peaks assignable to various fragments arising from the thermal cleavage of the complexes. The peal intensity gives an idea of the stability of the fragments.

Table 1
FAB mass spectral data of the trivalent chromium, manganese and iron complexes derived from macrocyclic ligand

Complexes	*Mol. wt.*	*Molecular ion peak [M]$^+$*	*Important peak due to complex fragmentation*
$C_{18}H_{14}ClN_3O_3S$	387.04	387.04	15.02, 77.04, 93.04, 100.98, 107.07, 146.06, 152.03, 180.02, 193.07, 207.03, 235.02, 280.00, 352.02, 372.02
$C_{20}H_{17}N_3O_5S$	411.08	411.08	15.02, 77.04, 93.04, 100.98, 107.07, 146.06, 176.07, 193.07, 204.07, 207.03, 235.02, 304.07, 352.02, 396.07
$C_{18}H_{14}N_4O_5S$	398.06	398.06	15.02, 77.04, 93.04, 100.98, 107.07, 146.06, 163.05, 191.05, 193.07, 207.03, 235.02, 291.02, 352.02, 383.04
$C_{19}H_{16}ClN_3O_3S$	401.06	401.06	15.02, 77.04, 93.04, 100.98, 121.02, 146.06, 152.04, 180.02, 193.07, 221.04, 249.04, 280.00, 366.08, 372.02
$C_{21}H_{19}N_3O_5S$	425.10	425.10	15.02, 77.04, 93.04, 100.98, 121.07, 146.06, 176.07, 193.07, 204.07, 221.04, 249.04, 304.04, 366.09, 396.07
$C_{19}H_{16}N_4O_5S$	412.08	412.08	15.02, 77.04, 93.04, 100.98, 121.07, 146.06, 163.05, 191.05, 193.07, 221.04, 249.04, 291.02, 366.09, 383,05
$C_{17}H_{13}ClN_4O_3S$	388.03	388.03	15.02, 77.04, 93.04, 100.98, 108.05, 128.98, 146.06, 152.02, 180.02, 193.07, 208.02, 236.02, 353.07, 372.02
$C_{19}H_{16}N_4O_5S$	412.08	412.08	15.02, 77.04, 93.04, 100.98, 108.05, 146.06, 176.07, 193.07, 204.07, 208.02, 236.02, 304.03, 353.07, 396.07
$C_{17}H_{13}N_5O_5S$	399.06	399.06	15.02, 77.04, 93.04, 100.98, 108.05, 146.06, 163.05, 191.02, 191.05, 193.07, 208.02, 236.02, 353.07, 382.05

3.2. IR Spectra

The IR spectra of all compounds showed that behaves as a neutral pentadentate of the type ONSNO with two coordinating sites (ON and SNO). This behaviour was proved by: (i) the shift of ν(C=O), ν(C=S), ν(C=N) signals to lower frequencies (4–18, 2–17, and 12–39cm^{-1}, respectively) together with their weak appearance; (ii) the occurrence of the ν(N–N) band at higher wave numbers; [18] and (iii) the presence of the NH group indicating the neutrality.

The appearance of two characteristic bands in the ranges 1561–1559cm^{-1} and 1370–1367 cm^{-1} in the case of complexes was attributed to $\nu_{asym}(COO^-)$ and $\nu_{sym}(COO^-)$, respectively, indicating the participation of the carboxylate oxygen in the complexes formation. The mode of coordination of carboxylate group has often been deduced from the magnitude of the observed separation between the $\nu_{asym}(COO^-)$ and $\nu_{sym}(COO^-)$. The separation value, $\Delta\nu(COO^-)$, between $\nu_{asym}(COO^-)$ and $\nu_{sym}(COO^-)$, in these complexes were more than 190 cm^{-1} (191–193 cm^{-1}) suggesting the coordination of carboxylate group in a monodentate fashion [19].

3.3. ^{1}H NMR

A survey of literature reveals that the NMR spectroscopy has been proved useful in establishing the structure and nature of many Schiff base ligand and their complexes. The ^{1}H NMR spectra of Schiff base ligand (HL) was recorded in d_6-dimethylsulfoxide (DMFO-d_6) solution using Me_4Si (TMS) as internal standard. The ^{1}H NMR spectra of the ligand shows broad signal at 9.4-12.1 ppm due to the –NH [48,]. The multiplets in the region 7.54-8.76 ppm may be assigned to aromatic proton [20, 21]

^{13}C NMR of the Schiff base ligand, the signal appeared in the region 113-158 are assigned to aromatic carbon. The signal at 198.3-185.6, 182.8-171.2, 165.4-150.7 and 148.1- 15.8 ppm are due to C=S, C=N, C=O and CH_3 respectively.

3.4. Antibacterial Activity

Antibacterial activity was determined by Agar-ditch method [22]. The investigated microorganisms were *Staphylococcus aureus* and *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginoca, Escherichia coli* and *Salmonella typhi* (as gram negative bacteria). The metal complexes were dissolved in the solvent DMF to obtained final concentration 1mg/0.1ml. A loop full of the given test strain was inoculated in 30 ml of nutrient broth and incubated for 24 hour in an incubator at 30°C in order to activate the bacterial strain activity. 18-20 ml of the nutrient agar media was added in to a 100 mm diameter pantry-plate. 0.1 ml of the activated strain was inoculated in to the media when it reaches the temperature of 40°C. The medium was allowed to solidify. After solidification of the media a hole was made in the plates with the help of a

Table 4
Bactericidal screening data of the ligand and their corresponding metal complexes (inhibition zone in mm)

Microorganism	*Complexes*									*Imipenem*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	
Gram-positive										
Staphylococcus aureus	57	65	87	09	17	36	25	19	57	100
Bacillus subtilis	53	62	85	38	23	35	33	24	55	100
Gram-negative										
Escherichia coli	08	40	64	07	14	31	36	17	27	100
Salmonella typhi	56	34	59	10	23	33	37	23	30	100
Pseudomonas aeruginosa	35	23	56	06	16	27	31	20	60	100

[a] Excellent activity (90-100% inhibition), Good activity (60-70% inhibition), Significant activity (30-50% inhibition), negligible activity (08-20% inhibition),

[b] Compound 1 = $C_{18}H_{14}ClN_3O_3S$, 2 = $C_{20}H_{17}N_3O_5S$, 3 = $C_{18}H_{14}N_4O_5S$, 4 = $C_{19}H_{16}ClN_3O_3S$, 5 = $C_{21}H_{19}N_3O_5S$, 6 = $C_{19}H_{16}N_4O_5S$, 7 = $C_{17}H_{13}ClN_4O_3S$, 8 = $C_{19}H_{16}N_4O_5S$, 9 = $C_{17}H_{13}N_5O_5S$,

[c] Imipenem = Standard drug.

cup-borer, which was then filled with one of the test sample solution [23]. The plates were incubated for 24 hours at 35°C. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activity of the synthetic complexes. The compound (3) (5-(2-hydroxy-5-methylphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-nitroindolin-2-yl) methanone [$C_{18}H_{14}N_4O_5S$] shows the best antimicrobial activity against the entire test strain (table 2). The mean value obtained for three individual replicates was used to calculate the zone of growth inhibition of each sample.

CONCLUSION

These complexes were tested for their antibacterial inhibition potential against some pathogens studies reveals that, metal compound (3) (5-(2-hydroxy-5-methylphenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)(5-nitroindolin-2-yl)methanone [$C_{18}H_{14}N_4O_5S$] is more biological activity against all pathogens.

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