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Research Article

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF IMINO SUBSTITUTED 1, 3, 4 OXA AND THIADIAZOLES

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ABSTRACT

A series of new 2-amino 1, 3, 4oxadiazoles and 1, 3, 4 thiadiazoles Were synthesized followed by condensation with various substituted aldehydes to yield their Schiffbases.The synthesized compounds were evaluated for their antimicrobial activity against two Gram positive bacteria two Gram negative bacteria and two fungal species /yeast strains.All the synthesized compounds showed good antimicrobial activity.

Keywords: Oxadiazoles, Thiadiazoles, Schiff bases, Antimicrobial activity.

INTRODUCTION

The continual emergence of multidrug resistant bacteria creates a need for the synthesis of novel antimicrobial agents. 1, 3, 4 oxadiazoles represent versatile lead molecule as potential bioactive agents [1] This interesting group of compounds possesses diverse biological activites such as antimicrobial[2,3] anti-inflammatory[4] antitubercular, anticonvulsant[6,7], anticancer[8,9], anti-HIV[10] hypoglycemic[11] and genotoxic[12] activities.Substituted 1, 3, 4 thiadiazoles posses a wide spectrum of biological activities including antimicrobial[13] anti-inflammatory[14] antitubercular[15] anticonvulsant[16] and antidiabetic[1] activities. Schiff bases have also been widely reported as biologically versatile compounds having antifungal, herbicidal and plant growth regulating properties [18,19].

A recent rational approach of drug design involve linking two molecules with individual intrinsic activity into a single hybrid molecule with improved efficacy and minimum toxicity[19]this encouraged us to synthesise 1, 3, 4-thiadiazole groups incorporated with schiffs bases and evaluate their antimicrobial activities. The present communication deals with the synthesis and antimicrobial evaluation of fifteen new imino substituted 1, 3, 4 oxa and thiadiazoles.

MATERIALS AND METHODS

Materials, methods

All the chemicals and solvents used in this work were of analytical reagent grade (anhydrous) and purchased from Sigma-Aldrich. Melting points were determined on an electrothermal apparatus in an open capillary tube and are uncorrected. The 1H-NMR recorded on JEOL_JNM Ex-90, 90 MHz using TMS as internal reference in CDCl3. IR spectra were recorded from KBr discs on Perkin ElmerFT IR spectrophotometer.

Elemental Analysis was performed on an Elementar Vario EL elemental analyzer. Satisfactory C, H, N analyses were obtained for all the compounds.

Synthesis of 2-(5-amino-1, 3, 4-oxadiazol-2-yl) phenol (compound 1) and 5-(4-chlorophenyl)-1, 3, 4-oxadiazol-2-amine (compound 2)

A mixture of semicarbazide (0.01mole, 3.6grms), salicylic acid (0.01mole, 1.38 grms) concentrated sulphuric acid (10ml) were taken in a round bottomed flask, refluxed for 3 hours and the mixture was poured on to crushed ice.. The solid separated was filtered, washed with water and recrystallized from ethanol to give the compound 1 compound 2 was synthesized following similar procedure by taking p-chlorobenzoic acid.

Synthesis of schiffs bases of amino oxadiazoles

Synthesis of 2-(5-{[-(4-chlorophenyl) methylidene] amino}-1, 3, 4-oxadiazol-2-yl) phenol(1a)

A mixture of 2-(5-amino-1, 3, 4-oxadiazol-2-yl) phenol (0.01mole), 4-chlorobenzaldehyde (0.01mole) and ethanol (5ml) were taken in a round bottomed flask. The mixture was refluxed at 80°C on water bath for 3 hrs and was poured on crushed ice. The contents were washed with water and recrystallized from ethanol to give compound 2-(5-{[-(4 chlorophenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) phenol(1a) compounds 1b-1e and 2a-2ewere synthesized following similar procedure by condensing with appropriate aldehydes

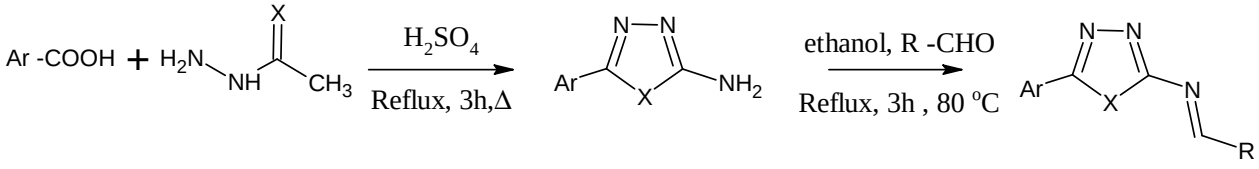
Synthesis of 2-(5-amino-1, 3, 4-thiadiazol-2-yl) phenol (compound 3) and 5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-amine (compound 4)

A mixture of thiosemicarbazide (0.01mole, 3.6grms), salicylic acid (0.01mole, 1.38 grms) concentrated sulphuric acid (10ml) were taken in a round bottomed flask, refluxed for 3 hours and the mixture was poured on to crushed ice.. The solid separated was filtered, washed with water and contents were washed with water and recrystallized from ethanol to give the compound 3. Compound 4 was synthesized following similar procedure by taking p-chlorobenzoic acid

Synthesis of schiffs bases of amino thiadiazoles

Synthesis of 2-(5-{[-(4-chlorophenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) phenol (3a)

A mixture of 2-(5-amino-1, 3, 4-thiadiazol-2-yl) phenol (0.01mole), 4-chlorobenzaldehyde (0.01mole) and ethanol (5ml) were taken in a round bottomed flask. The mixture was refluxed at 80°C on water bath for 3 hrs and was poured on crushed ice. The contents were washed with water and recrystallized from ethanol to give compound 2-(5-{[-(4 chlorophenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) phenol (3a) compounds 3b, 3c and 4a-4c) were synthesized following similar procedure by condensing with appropriate aldehydes.



Scheme 1

X= O for compounds 1a to1d and 2ato 2c compounds 1-4 compounds 1a-1d;2a-2c

X= S for compounds3a to 3c and 4a to 4c 3a-3c and 4a-4c

The strategy employed in the synthesis of the title compounds is depicted in **scheme1.** The structures, Melting points, Rf values(Hexane; Methanol 9:1 ratio), % yield %composition Molecular weight of all the synthesized compounds are given in **Table 1.**

Spectral data

Compound-1a orange crystalline solid

3436 (-OH), 3049.52(Ar-H), 1625.29, 1593.8(-C=N), 1517(C=C)**;** H^1NMR 7.34(N=CH), 8.20-9.01(Ar-H), 9.89(O-H); m/e: 299

Compound-1b: Dark yellow crystals; 3479.8(-OH), (Ar-H), 1610.38, 1596(-C=N), 1515.68(C=C)**;** H^1NMR 7.47(N=CH),

7.30-7.86(Ar-H), 9.90(O-H); m/e: 282.

Compound-1c: orange crystalline solid; 3455(-OH), 3049(Ar-H), 2943(-C-H), 1625, 1593.8(-C=N), 1569(C=C), **;** H^1NMR 2.85(-CH_3), 7.41(N=CH), 7.31-7.87(Ar-H), 9.62(O-H); m/e: 308

Compound-1d: orange yellow crystals; 3470(-OH), 3054(Ar-H), 1673, 1559(-C=N), 1519(C=C)**;** H^1NMR 7.37(N=CH), 8.25-9.03(Ar-H), 9.74(O-H); m/e: 265

Compound-1e: yellow crystals; 3459.12(-OH), 3064.13(Ar-H), 1605.24, 1567.81(-C=N), 1493.23(C=C),) **;** H^1NMR 0.9(-CH_3), 7.35(N=CH), 8.24-9.10(Ar-H), 9.82(O-H); m/e: 280

Compound-2a: Dark yellow crystalline solid; 3040.52(Ar-H), 1610, 1558.8(-C=N), 1517(C=C), 836.25(Substitution) **;** H^1NMR 7.42(N=CH), 8.20-9.02(Ar-H); m/e: 317

Compound-2b: Orange crystalline solid;3456.87(-OH), 3089.52(Ar-H), 1613.29, 1570(-C=N), 1518(C=C), 831(Substitution) **;** H^1NMR 7.43(N=CH), 8.21-9.04(Ar-H), 9.90(O-H); m/e: 300

Compound-2c: Dark orange solid;3037 (Ar-H), 2865, 2949(C-H), 1613, 1551 (-C=N), 1516(C=C), H^1NMR 2.86(-CH_3), 7.36(N=CH), 8.22-9.11(Ar-H); m/e: 327.

Compound-2d: Yellow solid; 3470(-OH), 3054(Ar-H), 1673, 1559(-C=N), 1519(C=C), **;** H^1NMR 7.35(N=CH), 8.25-9.10(Ar-H); m/e: 283.7

Compound 3a: Brown solid 3480(-OH), 3095(Ar-H), 1620, 1590(-C=N), 1516(C=C), 1134(C-S) **;** H^1NMR 7.40(N=CH), 8.23-9.21(Ar-H), 9.42(O-H); m/e: 315

Compound3b: light brown crystalline solid; 3465(-OH), 3037(Ar-H), 1620, 1590(-C=N), 1516(C=C), 1141(C-S) **;** H^1NMR 7.42(N=CH), 8.33-9.32(Ar-H), 9.87(O-H); m/e: 298

Compound3c: Dark brown crystalline solid; 3480(-OH), 3052(Ar-H), 2952, 2893(-C-H), 1654, 1612(-C=N), 1518(C=C), 1128(C-S) **;** H^1NMR 2.84(-CH_3), 7.44(N=CH), 8.33-9.41(Ar-H), 9.90(O-H); m/e: 325.

Compound 4a: brown amorphous solid; 3037(Ar-H), 1612, 1551(-C=N), 1516(C=C), 1136(C-S)**;** H^1NMR 7.36(N=CH), 8.23-9.11(Ar-H); m/e: 334

Compound4b: light brown amorphous solid; 3037(Ar-H), 1613, 1551(-C=N), 1516(C=C), 1145(C-S)**;** H^1NMR 7.34(N=CH), 8.27-9.12(Ar-H), 9.68(O-H); m/e: 316\

Compound4c: brown solid; 3038(Ar-H), 2958, 2893(-C-H), 1688, 1590(-C=N), 1518(C=C), 1128(C-S)**;** H^1NMR 2.84(-CH_3), 7.42(N=CH), 8.25-9.11(Ar-H), m/e: 343

Antimicrobial Activity

Microbial culture maintenance

The microbial cultures were procured from Dept. of Microbiology, GIS, and GITAM University. The bacterial cultures were cultured in nutrient broth prior to the screening of antimicrobial activity each isolate was checked for its purity and several colonies were emulsified into 50 ml nutrient broth. The inoculated flasks were incubated at 37ºC for 18 h on a rotary shaker at 150 rpm. The bacteria were subcultured on agar slants and maintained at 4^0C until further use.

The fungal cultures were grown on Sabouraud's dextrose agar medium containing streptomycin. The plates were incubated in an environmental chamber set at 25^0C±2^0C, 90 % relative humidity (RH), and 16:8hrs light: dark regime. An aqueous conidial suspension of 10^7 conidia/ml containing 105mg/ml Tween 80 was prepared from 14 day old culture. The conidial viability of the fungi was tested and inoculated with more than 95% germination.

Evaluation of antimicrobial activity

Evaluation of antimicrobial activities of the test compounds was performed by agar well diffusion method. Wells of 6mm diameter were made and the compounds were loaded using a micropipette. The plates were incubated at 37^0C for bacteria and 25^0C for fungi. Following incubation the plates were observed for zones of inhibition. The inhibition zone around the disc as calculated edge to edge zone of confluent growth which is usually corresponds to the sharpest edge of the zone and to be measured diameter in millimeter.

Antimicrobial activity screening

All synthesized compounds 1a-1e and 2a-2d 3a-3c and 4a-4c were screened for their antimicrobial activity against two gram +ve bacteria, *Staphylococcus aureus, Bacillus subtilis*, two gram-ve bacteria *Pseudomonas aeruginosa, Escherichia coli* and two fungal species *Aspergillus niger* and *Trichoderma viride* by agar well diffusion method. The inhibition zone was measured in mm using Ampicillin and Ketoconazole.as standards in DMSO. DMSO showed no inhibition zone.. All the compounds were tested at a concentration of 200 µg/ml. Each experiment was repeated twice and the average of the two determinations was recorded. The results are summarized in **Table 2**

RESULTS AND DISCUSSION

The IRspectra of the compounds 1a-4c the aromatic C-H streaching absorption appeared in the region 3037-3094 cm-1.The band at 3450-3400 hundred is due to O-H streaching vibration the band at 1620-1600 for all the compounds is due to C=N streach.The singlet in H^1 nmr at 7.35 is due to N=CH.the O-H proton signal which appeared at 9.67-9.93 were further characterized by D2Oexchange the aromatic protons appeared between d 7.2-7.9 as a multiplet in all synthesized compounds.

Antimicrobial screening

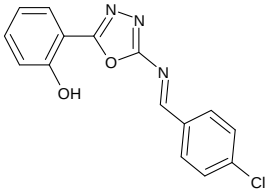
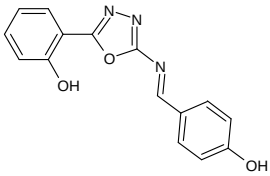
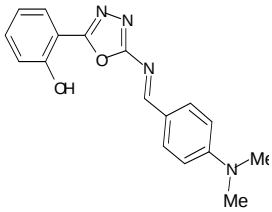
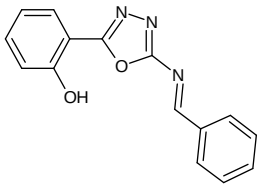
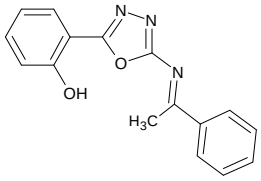
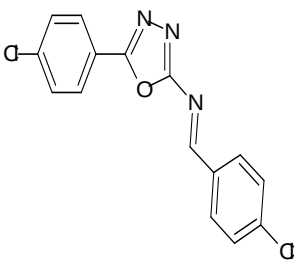
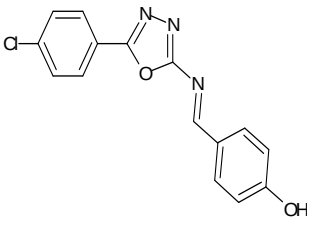
In the study of antimicrobial assay copounds1b (25mm);3b(18)4b(17);1e(19)2a(20) and 2b(26) are more potent than ampicillin against *Staphylococcus aureus, Bacillus subtilis and Pseudomonas aeruginosa* respectively compounds 4b;2c, 2a; and 2c, 3a 3c are equally potent as ampicillin against *Staphylococcus aureus, Bacillus subtilis and Pseudomonas aeruginosa.* all the newly synthesized fifteen title compounds showed significant activity against Escherichia coli with inhibition zones of 14to 19mm.

Based on the zones shown by these compounds against all the bacterial strains, the antibacterial activity is maximum for the compounds 1b and 3b possessing two phenolic hydroxyl groups It is demonstrated good electron mobility in the aromatic ring may enhance the activity increasing hydroxy groups which are electron donating in nature on the phenyl ring resulted in more antibacterial activity. Compound 2a with chloro- substitution was found to be less efficient than the other synthesized compounds against all the tested bacteria but surprisingly the efficacy of the compounds 2d containing two chlorine moieties one in the oxadiazole ring and the other in the Schiff's base was increased.. Compound 1d without any substitution on the Schiff's base and 1e with an alkyl substituent were found to be moderately effective. Compound 3c which possesses N, N-dimethyl amino group in the Para position of the phenyl ring of the Schiff's base showed similar effect as 3a which

contain a chlorosubstitution against pseudomonas.The efficacy of the compounds is more prominent if they are substituted with electron donating groups on the phenyl ring of schiffs base rather than the phenyl ring of oxa or thia diazole.The observation is derived from the fact that the efficacy of 2b (a hydroxyl group on schiffs bse)is more against all the tested bacteria than 1a(cl substitution on schiffs base)and 1e (without any substitution on schiffs base) similarly a hydroxyl substitution on schiffs base in compound4a made it more efficient than all other compounds in thiadiazole series Molecules with oxadiazole skeleton are found better antimicrobial agents than thia diazoles.

All the synthesized compounds possess antimicrobial activity against the tested bacteria and fungi. The zones of inhibition of the tested compounds were depicted in Table2. The antifungal activity of the compounds was better in comparison with antibacterial activity. All the compounds were effective as antimicrobial agents and further research is required to modify the structure of the compounds in order to make them more potent antimicrobials.

Table 1: The physicochemical parameters of the compounds 1a-4c

Compounds	Names	structures	Mol.formula	Rf	M.Wt	M.P°C	%yield	Composition
1a	2-(5-{[-(4 chlorophenyl)methylidene]amino}-1, 3, 4-oxadiazol-2-yl)phenol		$C_{15}H_{10}ClN_3O_2$	0.85	299.7	194-196	60 %	C(60.11%) H(3.36%) Cl(11.83%) N(14.02%) O(10.68%)
1b	2-(5-{[-(4-hydroxyphenyl)methylidene]amino}-1, 3, 4-oxadiazol-2-yl)phenol		$C_{14}H_9N_3O_2$	0.71	281.08	216-218	67 %	C(64.05%) H(3.94%) N(14.94%) O(17.07%)
1c	2-[5-({-[4-(dimethylamino)phenyl]methylidene }amino)-1, 3, 4-oxadiazol-2-yl]phenol		$C_{17}H_{16}N_4O_2$	0.86	308.3	198-200	58 %	C(66.22%) H(5.23%) N(18.17%) O(10.38%)
1d	2-(5-{-phenyl methylidene]amino}-1, 3, 4-oxadiazol-2-yl)phenol		$C_{15}H_{11}N_3O_2$	0.81	265.2	130-132	52 %	C(67.92%) H(4.18%) N(15.84%) O(12.06%)
1e	2-(5-{[-1-phenylethylidene]amino}-1, 3, 4-oxadiazol-2-yl)phenol		$C_{14}H_{11}N_3O_2$	0.78	279.10	118-120	50 %	C(68.81%) H(4.69%) N(15.05%) O(11.46%)
2a	5-(4-chlorophenyl)-*N*-[-(4-chlorophenyl)methylidene]-1, 3, 4-oxadiazol-2-amine		$C_{15}H_9Ci_2N_3O$	0.84	318.1	142-144	72 %	C(56.63%) H(2.85%) Cl(22.29%) N(13.21%) O(5.03%)
2b	4-[-{[5-(4-chlorophenyl)-1, 3, 4-oxadiazol-2-yl]imino}methyl]phenol		$C_{15}H_{10}ClN_3O_2$	0.76	299.7	192-194	67 %	C(60.11%) H(3.36%) Cl(11.83%) N(14.02%) O(10.68%)

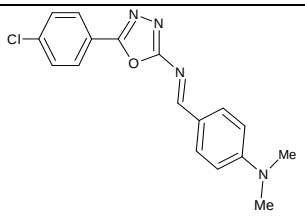
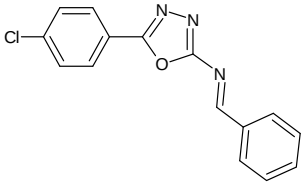
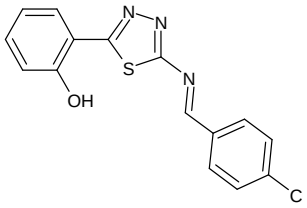
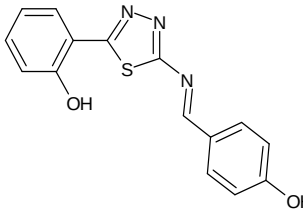
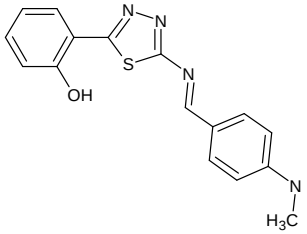
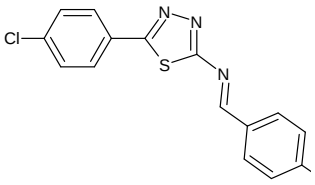
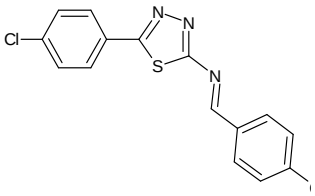
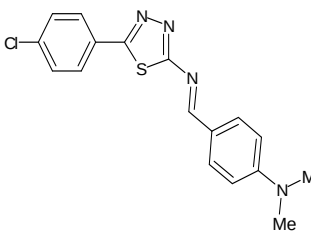
2c	5-(4-chlorophenyl)-*N*-{-[4-(dimethylamino)phenyl]methylidene}-1, 3, 4-oxadiazol-2-amine		$C_{17}H_{15}ClN_4O$	0.80	326.7	184-186	57 %	C(62.48%) H(4.63%) Cl(10.85%) N(17.15%) O(4.90%)
2d	5-(4-chlorophenyl)-*N*-[-phenylmethylidene]-1, 3, 4-oxadiazol-2-amine		$C_{15}H_{10}ClN_3O$	0.79	283.7	138-140	62 %	C(63.50%) H(3.55%) Cl(12.50%) N(14.81%) O(5.64%)
3a	2-(5-{[-(4-chlorophenyl)methylidene]amino}-1, 3, 4-thiadiazol-2-yl)phenol		$C_{15}H_{10}ClN_3OS$	0.81	315.77	204-206	65 %	C (59.56%) H(4.41%) Cl(10.34%) N(16.34%) S(9.35%)
3b	2-(5-{[-(4-hydroxyphenyl)methylidene]amino}-1, 3, 4-thiadiazol-2-yl)phenol		$C_{15}H_{11}N_3O_2S$	0.68	297.33	216-218	67 %	C (60.59%) H(3.73%) N(14.13%) O(10.76%) S(10.78%)
3c	2-[5-({-[4-(dimethylamino)phenyl]methylidene}amino)-1, 3, 4-thiadiazol-2-yl]phenol		$C_{17}H_{16}N_4OS$	0.80	324.42	192-194	62 %	C (62.94%) H(4.97%) N(17.27%) O(4.93%) S(9.88%)
4a	5-(4-chlorophenyl)-*N*-[-(4-chlorophenyl)methylidene]-1, 3, 4-thiadiazol-2-amine		$C_{15}H_9Cl_2N_3S$	0.73	334.22	142-144	72 %	C (53.90%) H(2.71%) Cl(21.22%) N(12.57%) S(9.59%)
4b	4-[-{[5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl]imino}methyl]phenol		$C_{15}H_{10}ClN_3OS$	0.71	315.77	192-194	67 %	C (57.05%) H(3.19%) Cl(11.23%) N(13.31%) O(5.07%) S(10.15%)
4c	5-(4-chlorophenyl)-*N*-{-[4-(dimethylamino)phenyl]methylidene}-1, 3, 4-thiadiazol-2-amine		$C_{17}H_{15}ClN_4S$	0.82	342.84	126-128	57 %	C (59.56%) H(4.41%) Cl(10.34%) N(16.34%) S(9.35%)

Table 2: Zone of inhibition in mm for the compounds1a-4c

Names of the organisms	Ampicillin	1a	1b	1c	1d	1e	2a	2b	2c	2d	3a	3b	3c	4a	4b	4c
Staphylococcus aureus	21	12	25	13	19	12	20	17	19	18	13	12	12	15	21	18
Bacillus subtilis	16	14	17	14	13	13	16	15	16	15	18	14	14	18	18	14
Pseudomonas aeruginosa	18	13	19	15	17	19	20	26	18	17	14	14	15	18	18	16
Escherichia coli	16	14	17	16	18	19	18	15	15	14	15	11	11	15	16	12
	Ketokonazole															
Trichodermaviride	18	20	21	20	15	24	20	22	21	21	17	15	12	16	18	10
Aspergillus Niger	23	14	20	14	15	18	19	17	18	20	17	14	17	15	22	18
Yeast							20	17	17	19	15	16	18	19	23	17

CONCLUSION

In conclusion, fifteen novel imino substituted oxa and thia diazoles (1a-4c) were synthesized and have been subjected to in vitro antimicrobial activity against various pathogenic bacteria and fungi to evaluate their effect on different bacteria and fungal strains. The screening results indicate that all the compounds exhibited moderate activity against bacteria and fungi. The difference in activity depends on the substitution of different reactive groups on the aromatic moiety

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