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SYNTHESIS AND MICROBIOLOGICAL EVALUATION OF SOME NEW BISCHALCONES

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ABSTRACT

A series of bischalcones (4a-j) were synthesized and evaluated for their antimicrobial actions. Bischalcones were prepared by condensing 1,1´-(4,6-dimethyl-1,3-phenylene)diethanone (3) with appropriate aromatic aldehydes in ethanol in presence of KOH. The structures of the synthesized compounds were confirmed on the basis of ^{1}H NMR, Mass and elemental analysis results. The antimicrobial screening of the title compounds was performed at a concentration of 100 µg/mL by cup plate method; the compounds inhibiting growth of one or more of the microorganisms were further tested for their minimum inhibitory concentration (MIC) by turbidity method. The results revealed that the compound 4f showed good activity against *S. aureus*, *E. coli* and *P. aeruginosa* with MIC-12.5 µg/mL. Similar type of activity was shown by the compound 4g against *S. aureus* and *E. coli* and, by the compound 4j against *S. aureus* and *P. aeruginosa* with MIC-12.5 µg/mL.

Keywords: Bischalcone, MIC, Antibacterial, Antifungal.

INTRODUCTION

The increasing incidence of resistance to a number of antibacterial agents is becoming a major concern[1,2]. Moreover, incidences of systemic bacterial and fungal infections are increasing due to an increase in the number of immuno-compromised hosts.

Immunosuppression due to malignancy, immunosuppressive therapies, HIV-infection, broad-spectrum antimicrobial treatment and age, places patients at risk for microbial infections. A small number of antifungal agents are available in the market, and all have some drawbacks regarding their spectrum, tissue distribution, toxicity, and high cost[3,4]. Therefore the need of hour is to search for alternative new and more effective antimicrobial agents with a broad spectrum activity. Among a wide variety of compounds that have been explored for developing antimicrobial agents, Flavonoidal derivatives-chalcones, flavanones and flavones have played an important role[5-9]. Chalcones have attracted considerable attention due to their

marked physiological activity and distinct functions. They form a large group of naturally occurring organic compounds and possess wide range of pharmacological actions including antimicrobial action[5-14]. Also, chalcone derivatives acquire a special place in natural chemistry as well as in heterocyclic chemistry because this system is a frequently encountered structural motif in many pharmacologically relevant compounds[15-18].

Resorcinol is a simple and important aromatic moiety (1,3-benzenediol) that has been chemically incorporated into various compounds to improve their pharmacological profile[19-21]. In view of these points it was considered worthwhile to study some resorcinol-based bischalcones derivatives for their antimicrobial actions.

MATERIALS AND METHODS

Chemistry

Melting points are uncorrected and were recorded in liquid paraffin bath using open end capillaries. ^{1}H-NMR spectra were recorded on Bruker spectropsin DPX-300 MHz in $CDCl_3$; chemical shift (δ) values are reported in parts per million (*ppm*). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; m, multiplet. Mass spectroscopic analyses for compounds were performed on a JEOL JMS-D 300 instrument. Elemental analyses were performed on a Perkin-Elmer 240 analyzer and were in range of ±0.4% for each element analyzed (C, H, N). Thin-layer chromatography was carried out to monitor the reactions using silica gel G as stationary phase and iodine chamber and UV lamp were used for visualization of TLC spots.

Synthesis of 1,1´-(4,6-Dihydroxy-1,3-phenylene)diethanone (2)

It was prepared from resorcinol (**1**) following literature method[19]. It gave a violet colour with ethanolic ferric chloride solution; positive test for phenols. Yield 72%; m.p. 184-186°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 2.65 (s, 6H, 2×-$COCH_3$), 6.65 (s, 1H, H-2), 8.15 (s, 1H, H-5).

Synthesis of 1-(5-acetyl-2,4-dimethoxyphenyl)-1-ethanone (3)

A mixture of 1,1´-(4,6-dimethyl-1,3-phenylene)diethanone (**2**) (2.5 mmol), dimethylsulphate (5 mmol) and anhydrous potassium carbonate (11.25 g) in dry acetone (100 mL) was refluxed for 6 h. The contents were then filtered, concentrated to a small volume and poured onto crushed ice. A solid mass separated out which was filtered, washed with water, dried and then crystallized from methanol:dichloromethane mixture to give shiny needles of **3** (it did not give violet colour with ethanolic ferric chloride solution; negative test for phenols). Yield 74%, m.p. 164-166°C. ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 6H, 2×-$COCH_3$), 3.93 (s, 6H, 2×-OCH_3), 6.34 (s, 1H, H-2), 8.37 (s, 1H, H-5). MS: *m/z* 222 (M^+), 207, 177, 175, 149. Anal calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.22.

General procedure for synthesis of Bischalcones (4a-j)[22]

A mixture of compound **3** (5 mmol) in ethanol (20 mL), an aromatic aldehyde (10 mmol) and a solution of potassium hydroxide (3 g) in distilled water (5 mL) was stirred for 2 h at room temperature and then left overnight. It was poured into cold water and acidified with HCl, a solid mass separated out which was filtered, washed with water, sodium bicarbonate solution (2% w/v in water) and again with water. It was crystallized to give **4a-k** (It gave a red colour with conc. sulphuric acid; positive test for chalcones, and no colour with ethanolic ferric chloride solution; negative test for phenols).

1-(2,4-Dimethoxy-5-[3-(3-nitrophenyl) acryloyl]phenyl)-4-(3-nitrophenyl)but-2-en-1-one 4a

Yield: 61%, m.p. 220-222°C. ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 6H, 2×-OCH_3), 6.54 (s, 1H, H-3'), 7.26

(d, 2H, 2xH-α), 7.58 (m, 2H, 2xH-5), 7.87 (dd, 2H, 2xH-4), 8.05 (d, 2H, 2xH-β), 8.26 (dd, 2H, 2xH-6), 8.20 (s, 1H, H-6`), 8.43 (s, 2H, 2xH-2). MS: *m/z* 488 (M^+), 340, 312, 176, 136 . Anal calcd. for $C_{26}H_{20}N_2O_8$: C, 63.93; H, 4.13; N, 5.74. Found: C, 63.81; H, 4.06; N, 5.50.

1-(2,4-Dimethoxy-5-[3-(4-nitrophenyl) acryloyl]phenyl)-4-(4-nitrophenyl)but-2-en-1-one 4b

Yield: 65%, m.p. 234-236°C. ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 6H, 2×-OCH_3), 6.55 (s, 1H, H-3'), 7.04-7.46 (m, 6H, 2xH-3,5,α), 7.78-8.13 (m, 6H, 2xH-2,6,H-β), 8.22 (s, 1H, H-6`). MS: *m/z* 488 (M^+), 340, 176, 148. $C_{26}H_{20}N_2O_8$: C, 63.93; H, 4.13; N, 5.74. Found: C, 63.71; H, 4.12; N, 5.46.

1-(2,4-Dimethoxy-5-[3-(2-chlorophenyl) acryloyl]phenyl)-4-(2-chlorophenyl)but-2-en-1-one 4c

Yield: 58%, m.p. 202-204°C. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 6H, 2×-OCH_3), 6.51 (s, 1H, H-3'), 7.06-7.34 (m, 4H, 2×H-3,5), 7.41-7.53 (m, 6H, 2xH-4,6,α), 7.88 (d, 2H, 2xH-β), 8.19 (s, 1H, H-6'). MS: *m/z* 466 (M^+), 330, 267, 131. Anal calcd. for $C_{26}H_{20}Cl_2O_4$: C, 66.82; H, 4.31. Found: C, 66.56; H, 4.64.

1-(2,4-Dimethoxy-5-[3-(4-chlorophenyl) acryloyl]phenyl)-4-(4-chlorophenyl)but-2-en-1-one 4d

Yield: 62%, m.p. 195-196°C. ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 6H, 2×-OCH_3), 6.53 (s, 1H, H-3'), 6.86 (d, 4H, 2×H-3,5), 7.23(d, 2H, 2xH-α), 7.49 (d, 4H,2×H-2,6), 7.78 (d, 2H, 2xH-β), 8.18 (s, 1H, H-6'). MS: *m/z* 466 (M^+), 302, 295, 131. Anal calcd. for $C_{26}H_{20}Cl_2O_4$: C, 66.82; H, 4.31. Found: C, 66.74; H, 4.57.

1-(2,4-Dimethoxy-5-[3-(2-methylphenyl) acryloyl]phenyl)-4-(2-methylphenyl)but-2-en-1-one 4e

Yield: 54%, m.p. 188-190°C. ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H, 2×-CH_3), 3.95 (s, 6H, 2×-OCH_3), 6.39 (s, 1H, H-3'), 6.81-7.47 (m, 8H, 2×H-3,4,5,6), 7.50 (d, 2H, 2xH-α), 7.98 (d, 2H, 2xH-β), 8.16 (s, 1H, H-6'). MS: *m/z* 426 (M^+), 309, 281, 145, 117, 105. Anal calcd. for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14. Found: C, 78.66; H, 6.25.

1-(2,4-Dimethoxy-5-[3-(4-hydroxy-3-methoxyphenyl)acryloyl]phenyl)-4-(4-hydroxy-3-methoxyphenyl)but-2-en-1-one 4f

Yield: 61%, m.p. 208-209°C. ^{1}H NMR ($CDCl_3$) δ 3.92 (s, each, 6H, 2×-OCH_3), 3.98 (s, each, 6H, 2×-OCH_3), 6.48 (s, 1H, H-3'), 6.87 (d, 2H, 2×H-5), 7.16-7.23 (m, 4H, 2xH-2,6), 7.36 (d, 2H, 2xH-α), 7.64 (d, 2H, 2xH-β), 8.18 (s, 1H, H-6'). MS: *m/z* 490 (M^+), 341, 295, 103, 91. Anal calcd. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.42; H, 5.31.

1-(2,4-Dimethoxy-5-[3-(2,6-dichlorophenyl) acryloyl]phenyl)-4-(2,6-chlorophenyl)but-2-en-1-one 4g

Yield: 58%, m.p. 180-182°C. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 6H, 2×-OCH_3), 6.51 (s, 1H, H-3'), 7.22-7.36 (m, 4H, 2xH-4 + 2xH-α), 7.48-7.56 (m, 4H, 2×H-3,5), 7.88 (d, 2H, 2xH-β), 8.15 (s, 1H, H-6'). MS: *m/z* 550 (M^+), 293, 267, 131. Anal calcd. for $C_{27}H_{20}Cl_4O_4$: C, 58.93; H, 3.66. Found: C, 59.28; H, 3.46.

1-(2,4-Dimethoxy-5-[3-(2-hydroxyphenyl) acryloyl]phenyl)-4-(2-hydroxyphenyl)but-2-en-1-one 4h

Yield: 54%, m.p. 221-222°C. ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 6H, 2×-OCH_3), 6.45 (s, 1H, H-3'), 6.99-7.53 (m, 10H, 2×H-3,4,5,6,α), 7.82 (d, 2H, 2xH-β), 8.17 (s, 1H, H-6'). MS: *m/z* 430 (M^+), 311, 295, 103, 91. Anal calcd. for $C_{26}H_{22}O_6$: C, 72.55; H, 5.15. Found: C, 72.40; H, 5.20.

1-(2,4-Dimethoxy-5-[3-(3-hydroxyphenyl) acryloyl]phenyl)-4-(3-hydroxyphenyl)but-2-en-1-one 4i

Yield: 51%, m.p. 214-215°C. ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 6H, 2×-OCH_3), 6.50 (s, 1H, H-3'), 7.26

(d, 2H, 2xH-α), 7.31-7.36 (m, 2H, 2xH-5), 7.67 (dd, 2H, 2xH-4), 7.88 (d, 2H, 2xH-β), 7.98 (dd, 2H, 2xH-6), 8.18 (s, 1H, H-6`), 8.26 (s, 2H, 2xH-2). MS: *m/z* 430 (M^+), 309, 295, 103, 91. Anal calcd. for $C_{26}H_{22}O_6$: C, 72.55; H, 5.15. Found: C, 72.48; H, 5.08.

1-(2,4-Dimethoxy-5-[3-(4-fluorophenyl) acryloyl]phenyl)-4-(4-fluorophenyl)but-2-en-1-one (4j)

Yield: 60%, m.p. 196-198°C. ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 6H, 2×-OCH_3), 6.48 (s, 1H, H-3'), 7.03-7.84 (m, 12H, 2×H-2,3,5,6,α,β), 8.12 (s, 1H, H-6'). MS: *m/z* 434 (M^+), 313, 285, 149, 131, 77. Anal calcd. for $C_{26}H_{20}F_2O_4$: C, 71.88; H, 4.64. Found: C, 71.96; H, 4.41.

Microbiology

The synthesized compounds were evaluated for their antimicrobial activity[23,24] against three bacterial strains and two fungal strains at a concentration of 100 µg/mL by cup plate method. Compounds inhibiting growth of one or more of the test microorganisms were further tested for their minimum inhibitory concentration (*MIC*).

Antibacterial Activity

The compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATCC-25923), *Escherichia coli* (ATCC-25922), and *Pseudomonas aeruginosa* (ATCC-27853) bacterial strains at a concentration of 100 µg/mL by cup plate method[23]. Ciprofloxacin was used as standard drug for comparison. Freshly prepared liquid agar medium (25 mL/petridish) was poured into each petridishes and the plates were dried by placing in an incubator at 37°C for 1 h. Then standardized culture of microorganism was spread on each petridishes by L-shaped spreader. Wells (6 mm) were made using an agar punch and, each well was labeled accordingly. A control (solvent) was also included in the test. The test compound and standard drug solutions (100µg/mL) were made in dimethylsulfoxide (DMSO) and added in each well separately and petridishes kept aseptically for 1h for diffusion of the sample. After the completion of diffusion, all the petridishes were kept for incubation at 37°C for 24 h and then diameter of the zone of inhibition was measured in mm (Table 1).

Compounds inhibiting growth of one or more of the test microorganisms were further tested for their minimum inhibitory concentration (*MIC*) by broth dilution technique. A solution of the compounds (100 µg/mL) was prepared in DMSO and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile test tubes a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The inoculum consisting of an overnight broth culture of microorganisms was added to separate tubes. The tubes were incubated at 37° for 24 h and examined for turbidity. The highest dilution (lowest concentration) required to stop the growth of bacteria was regarded as *MIC*. Results are presented in Table 2.

Antifungal Activity

Antifungal activity of the synthesized compounds was determined against *Candida albicans* (ATCC-10231) and *Aspergillus niger* (ATCC-16404) by agar diffusion method[23]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Agar media (20 mL) was poured into each petridish and the plates were dried by placing in an incubator at 37°C for 1 h. Wells were made using an agar punch and, each well was labeled accordingly. A control was also prepared in triplicate and maintained at 37°C for 3-4 days. The test compounds and standard drug (Griseofulvin) solutions (100 µg/mL) were made

in dimethylsulfoxide (DMSO) and added in each well separately and petridishes kept aseptically for 1h for diffusion of the sample. After the completion of diffusion, all the petridishes were kept for incubation at 37°C for 3-4 days and then diameter of the zone of inhibition was measured in mm (Table 1). Compounds inhibiting growth of one or more of the fungal strains were further tested for their minimum inhibitory concentration (*MIC*). A solution of the compounds (100 µg/mL) was prepared in DMSO and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile test tubes a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The tubes were inoculated with approximately $1.6x10^4$-$6x10^4$ c.f.u. mL^{-1} and incubated for 48 h at 37°C and examined for growth. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as *MIC*. Results are presented in Table 2.

RESULTS AND DISCUSSION

Chemistry

The protocol for synthesis of title compounds is presented in Scheme-1. The starting material, 1,1´-(4,6-dihydroxy-1,3-phenylene)diethanone (2), prepared from resorcinol (1), was treated with dimethylsulphate in dry acetone in presence of anhydrous potassium carbonate to get 1,1´-(4,6-dimethyl-1,3-phenylene)diethanone (3), which gave negative ferric chloride test showing the absence of phenolic-hydroxyl group. Compound (3) was then condensed with different aromatic aldehydes in presence of potassium hydroxide following Claisen-Schmidt reaction conditions[22] to furnish 10 new bischalcones (4a-j). These compounds gave a red colour with conc. sulphuric acid; positive test for chalcones, and no colour with ethanolic ferric chloride solution; negative test for phenolic-hydroxyl group. The structures of the synthesized compounds were further supported by ^{1}H NMR, Mass spectral data and elemental analysis results.

The ^{1}H NMR spectrum of 1,1´-(4,6-dimethyl-1,3-phenylene)diethanone (3) showed a singlet at δ 2.61, which could be accounted for six protons of two acetyl groups. The two methoxyl groups appeared as singlet at δ 3.93. The ring protons, H-2 and H-5, gave singlet at δ 6.34 and 8.37, respectively. The mass spectrum of the compound (3) showed a peak at *m/z* 222, which was the molecular ion of the compound, other peaks were observed at *m/z* 207, 177, 175 and 149. The proposed fragmentation pattern has been presented in Chart 1.

The ^{1}H NMR spectra of the title bischalcones (4a-j) revealed the presence of two methoxyl groups as singlet at around δ 3.9, and two -CH=CH- groups as two doublets at around δ 7.3 and δ 8.0 integrating for two CH-α and two CH-β protons, respectively. Chalcone ring protons H-3` & H-6`appeared as singlet at δ 6.5 and δ 8.2, respectively. Other signals were observed at appropriate δ values integrating for the protons of two substituted phenyl rings. The mass spectra of bischalcones showed the presence of molecular ion peaks in reasonable intensities. The observed fragmentation pattern of bischalcones (4a-j) is presented in Chart 2. Elemental analyses values of the synthesized compounds were found within ±0.4% of theoretical values.

Antibacterial and Antifungal Activity

The newly prepared compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATCC-25923), *Escherichia coli* (ATCC-25922) and *Pseudomonas aeruginosa* (ATCC-27853) bacterial species, and antifungal activity against *Candida albicans* (ATCC-10231) and *Aspergillus niger* (ATCC-16404). The antimicrobial screening data showed that compounds 4f, 1-(2,4-dimethoxy-5-[3-(4-hydroxy-3-methoxyphenyl)acryloyl]phenyl)-4-(4-hydroxy-3-methoxyphenyl)but-2-en-1-one, exhibited good activity against *S. aureus, E. coli* & *P. aeruginosa* with *MIC*-12.5 µg/mL. Similar type of activity was shown by the compound 4g,

1-(2,4-dimethoxy-5-[3-(2,6-dichlorophenyl) -acryloyl]phenyl)-4-(2,6-chlorophenyl)but-2-en-1-one, against *S. aureus* & *E. coli*, and by the compound 4j, 1-(2,4-dimethoxy-5-[3-(4-fluorophenyl)acryloyl]phenyl)-4-(4-fluorophenyl)but-2-en-1-one, against *S. aureus* & *P. aeruginosa* with MIC-12.5 µg/mL. Another compound, Compounds 4d, 1-(2,4-dimethoxy-5-[3-(4-chlorophenyl)acryloyl]phenyl)-4-(4-chlorophenyl)but-2-en-1-one, was active against *S. aureus* with MIC-12.5 µg/mL. Rest of the compounds showed moderate to low antimicrobial activities. The standard drugs showed *MIC* values of 6.25 µg/mL (Table1 & 2).

An analysis of results indicated that the bischalcones 4a-j were appreciable in their antibacterial and antifungal actions. Presence of chloro or fluoro group(s) increased the antimicrobial activity of the bischalcones.

CONCLUSION

10 New bischalcones derivatives (4a-j) were successfully synthesized starting from resorcinol. The antimicrobial studies showed that the synthesized compounds were having appreciable antibacterial and antifungal activities. 1-(2,4-dimethoxy-5-[3-(4-hydroxy-3-methoxyphenyl)acryloyl]phenyl)-4-(4-hydroxy-3-methoxyphenyl)but-2-en-1-one (4f) emerged as lead compound among the synthesized compounds. Presence of chloro or fluoro group(s) increased the antimicrobial activity of the bischalcones. It is conceivable that the derivatives showing significant anti-microbial activity can be further modified to exhibit better potency than the standard drugs.

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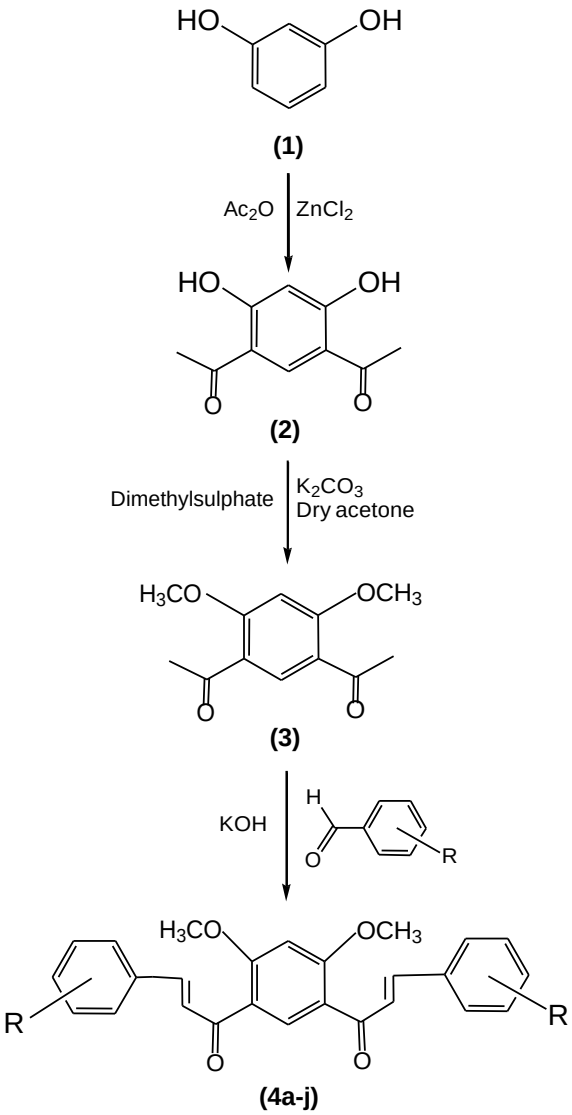

Scheme 1: Protocol for synthesis of title compounds.

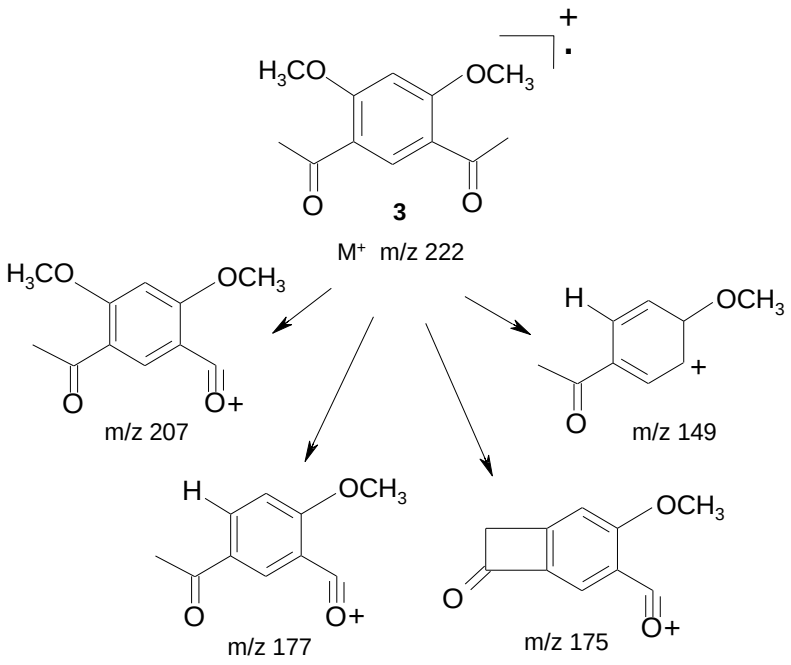

Chart 1: Mass fragmentation pattern of compound 3.

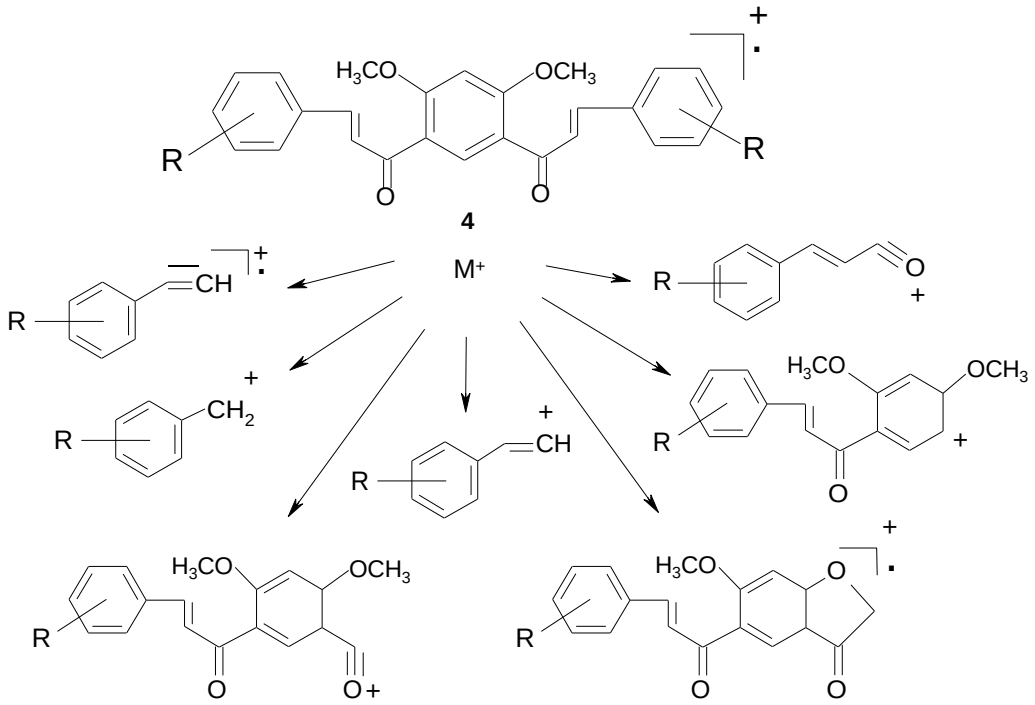

Chart 2: Mass fragmentation pattern of compounds 4.

Table 1: Preliminary antibacterial and antifungal activities of the title compounds

Compd.	Substituent (R)	Antibacterial activity[#]			Antifungal activity[#]	
		S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
4a	3-Nitro	-	-	+	+	-
4b	4-Nitro	+	-	+	+	+
4c	2-Chloro	++	++	+	++	+
4d	4-Chloro	+++	++	++	++	-
4e	2-Methyl	-	-	-	+	-
4f	4-Hydroxy-3-methoxy	+++	+++	+++	++	++
4g	2,6-Dichloro	+++	+++	++	++	+
4h	2-Hydroxy	+	+	++	++	-
4i	3-Hydroxy	+	-	+	+	+
4j	4-Fluoro	+++	++	+++	++	+
Standard-1†		++++	++++	++++	nt	nt
Standard-2†		nt	nt	nt	++++	++++

[#]Zone of inhibition: - = < 5 mm (insignificant or no activity), + = 5-9 mm (weak activity), ++ = 10-14 mm (moderate activity), +++ = 15-20 mm (good activity), ++++ = > 20 mm.

[†]Standard-1 = Ciprofloxacin, Standard-2 = Griseofulvin, nt = not tested.

Table 2: Antibacterial and antifungal activities (MIC, μg/mL) of the title compounds

Compd.	Substituent (R)	Antibacterial activity			Antifungal activity	
		S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
4a	3-Nitro	>100	>100	50	50	>100
4b	4-Nitro	50	>100	50	50	50
4c	2-Chloro	25	25	50	25	50
4d	4-Chloro	12.5	25	25	25	>100
4e	2-Methyl	>100	>100	>100	>100	>100
4f	4-Hydroxy-3-methoxy	12.5	12.5	12.5	25	25
4g	2,6-Dichloro	12.5	12.5	25	25	>100
4h	2-Hydroxy	50	50	25	50	>100
4i	3-Hydroxy	>100	>100	50	>100	50
4j	4-Fluoro	12.5	25	12.5	25	50
Standard-1†		6.25	6.25	6.25	nt	nt
Standard-2†		nt	nt	nt	6.25	6.25

nt = not tested; †Standard-1 = Ciprofloxacin, Standard-2 = Griseofulvin.

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