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Antibacterial and antifungal activities of some hydroxyacetophenone derivatives

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The investigation of antibacterial and antifungal activity of five synthesized compounds **1**-**5** have been reported. The synthesized compounds have demonstrated poor antifungal, but good antibacterial activity.

Keywords: Antibacterial, antifungal, anticancer, acetophenone, NMR spectroscopy

The acetophenones and their derivatives are important compounds in chemistry, medicine, drug synthesis, *etc*. Due to their different functionality these compounds confer biological activities, such as antimicrobial, antibacterial, antifungal, anticancer, antitubercular, antiviral, anti-inflammatory, antihyperglycemic, *etc*.[1-18]

In this work had been investigated antibacterial, antifungal activities of some hydroxyacetophenone derivatives against *E. coli*, *K. pneumoniae*, S. *aureus*, *A. niger* and *C. albicans*.

Escherichia coli is a gram-negative, anaerobic, rod-shaped bacterium of the genus escherichia, that is commonly found in the lower intestine of warm-blooded organisms (endotherms) and there also exist many pathogenic strains, which that can cause a variety of diarrheal and other diseases in humans and animals[19].

Klebsiella pneumoniae is a gram-negative, non motile, encapsulated, lactose-fermenting, anaerobic, rod-shaped bacterium. The most common condition caused by *K. pneumoniae* bacteria is pneumonia, typically in the form of bronchopneumonia and also bronchitis. These patients have an increased tendency to develop lung abscess, cavitation, empyema, and pleural adhesions. It has a death rate around 50%, even with antimicrobial therapy. The mortality rate can be nearly 100% for people with alcoholism and bacteremia[20].

Staphylococcus aureus is a gram-positive coccal bacterium, which can cause a wide spectrum of infections, ranging from simple to potentially fatal diseases. The literature data show that the incidence of infection due to *S. aureus* seems to be the highest in neonates and immuno deficient individuals with a mortality rate of ~50% with high antibiotic resistance threat[21-23].

Aspergillus niger is a fungus and one of the most common species of the genus Aspergillus. It causes a disease called black mould on certain fruits and vegetables such as grapes, apricots, onions, and peanuts, and is a common contaminant of food. In extremely rare instances, humans may become ill, but this is due to a serious lung disease, aspergillosis, and it is one of the most common causes of otomycosis (fungal ear infections), which can cause pain, temporary hearing loss, and, in severe cases, damage to the ear canal and tympanic membrane[24].

Candida albicans is a diploid fungus pathogen and causes opportunistic human infections, that are transferred through the mouth and genitals. Systemic fungal infections (fungemia) are important causes of morbidity and mortality in immunodeficient patients (such as AIDS, cancer chemotherapy or organ transplant)[25].

Experimental Section

The homogeneity and structure of the synthesized compounds were confirmed by thin layer chromatography (Silufol UV-254, 0.1 mm silica gel plates, iodine vapor as visualizing agent, eluent 5:2 hexane/ethyl acetate) and NMR spectroscopy. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AV-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer (Figures S1−S5, Supplementary Information).

Synthesis

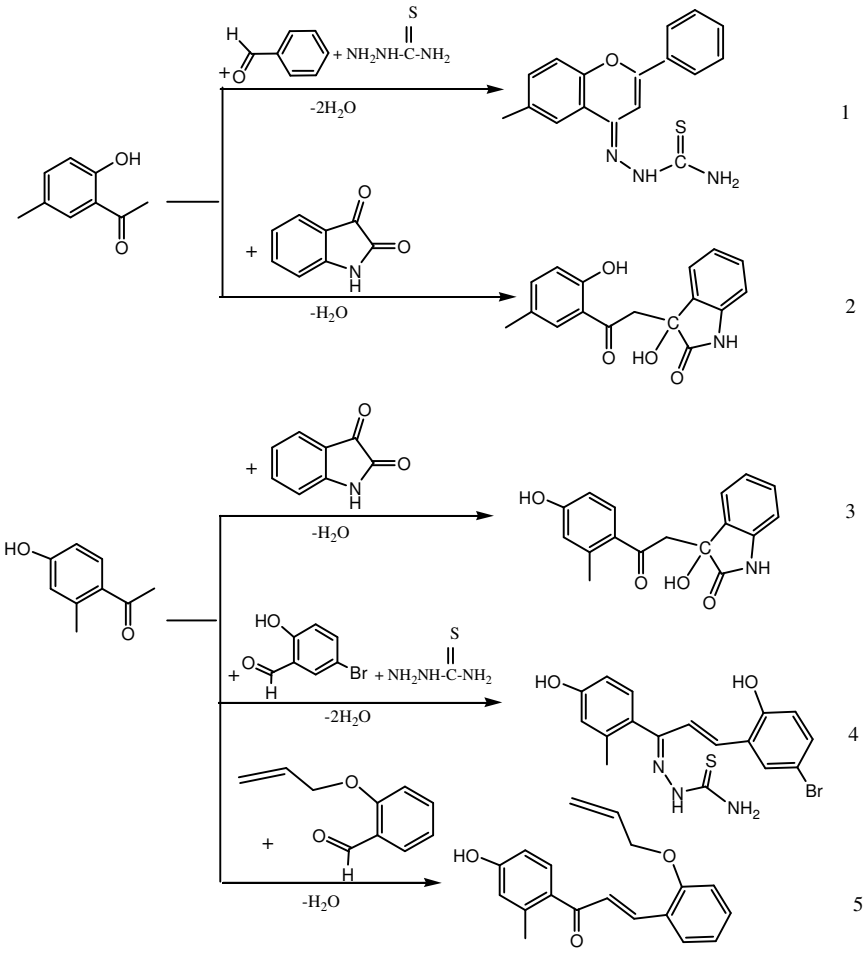
The compound 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one thiosemicarbazone (**1** is known compound in the literature, m.p.240-42°C, yield ~78%), 3-hydroxy-3-[2-(2-hydroxy-5-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (**2**, m.p.128-30°C, yield ~76%), 3-hydroxy-3-[2-(4-hydroxy-2-methylphenyl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (**3**, m.p.122-24°C, yield ~68%), (*E,E*)-3-(5-bromo-2-hydroxyphenyl)-1-(4-hydroxy-2 methylphenyl) prop-2-en-1-one thiosemicarbazone (**4**, m.p.228-30°C, yield ~59%) and (2*E*)-1-(4-hydroxy-2-methylphenyl)-3-[2-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (**5**, m.p.157°C, yield ~63%) have been prepared by the known literature methods (Scheme I)[26-29].

Compound 1: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.28 (s, 3H, CH_3), 2.84 and 3.53 (d-d, 2H, CH_2, $^2J_{H\text{-}H}$ = -17.1 Hz, $^3J_{H\text{-}H}$ = 12.0 and $^3J_{H\text{-}H}$ = 3.0 Hz), 5.19 (d-d, 1H, CH, $^3J_{H\text{-}H}$ = 12.0 and $^3J_{H\text{-}H}$ = 3.0 Hz), 6.85-8.31 (m, 9H, arom. and =CH), 8.01 (s, 2H, NH_2), 10.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 20.64, 32.48, 76.56, 117.65, 120.82, 125.61, 126.77, 128.82, 129.37, 132.44, 140.33, 142.60, 155.37, 179.25.

Compound 2: ^{1}H NMR (acetone-d_6, 300 MHz): δ 2.31 (s, 3H, CH_3), 3.72 and 4.15 (d, 2 H, CH_2, $^3J_{H\text{-}H}$ = 18.0 Hz), 6.03 (s, 1H, OH), 6.79-7.82 (m, 7H, arom.), 10.17 (s, 1H, OH), 11.52 (s, 1H, NH); ^{13}C NMR (acetone-d_6, 300 MHz): δ 19.74, 46.25, 73.41, 109.71, 117.69, 119.84, 121.31, 123.88, 128.22, 129.10, 130.75, 131.87, 137.45, 143.39, 159.62, 178.46, 203.01.

Compound 3: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.36 (s, 3H, CH_3), 3.48 and 4.03 (d, 2 H, CH_2, $^3J_{H\text{-}H}$ = 18.0 Hz), 6.03 (s, 1H, OH), 6.78-7.79 (m, 8H, arom. and NH), 10.24 (s, 1H, OH).

Compound 4: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.0 (s, CH_3), 6.48 (d-d, 1H, =CH, $^3J_{H\text{-}H}$ = 12.7 Hz), 6.8 (m, 2H, arom.), 6.95 (d-d, 1H, =CH, $^3J_{H\text{-}H}$ = 12.7



Scheme I — General synthesis reaction scheme of investigated compounds

Hz), 7.22 (m, arom.), 8.05 and 8.27 (s, NH_2), 8.02 (s, arom.), 8.54 (s, OH), 9.83 (s, OH), 10.15 s (1H, NH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 19.3, 111.1, 114.5, 118.0, 118.5, 120.3, 125.5, 129.5, 130.1, 130.9, 132.3, 132.7, 137.6, 152.2, 154.9, 158.9, 177.8.

Compound 5: ^{1}H NMR (acetone-d_6, 300 MHz): δ 2.47 (s, 3H, CH_3), 4.69 (d, 2H, OCH_2, $^3J_{H\text{-}H}$ = 6 Hz), 5.29 and 5.45 (d, 2H, =CH_2, $^3J_{H\text{-}H}$ = 9 Hz, $^3J_{H\text{-}H}$ = 15 Hz), 6.11 (m, 1H, =CH), 6.8-8.0 (m, 9H, arom. and CH=CH), 9.06 (s, 1H, OH); ^{13}C NMR (acetone-d_6, 300 MHz): δ 20.61, 68.84, 112.20, 112.75, 116.85, 119.54, 120.92, 122.32, 126.30, 128.50, 130.71, 131.53, 131.59, 133.41, 138.25, 140.89, 157.46, 159.79, 192.52.

Antibacterial and antifungal testing

Compounds **1-5** were evaluated for their *in vitro* antibacterial and antifungal activities by agar disc-diffusion method[30]. Stock solutions of test compounds were diluted in dimethyl sulfoxide (DMSO) to give a final concentration of 1 mg/mL. The DMSO alone was used as a control and it was revealed, that solvent doesn't influence to antibacterial-antifungal properties (zone of inhibition was 1-1.5 mm). The plates with bacterial suspensions and disk of investigated compounds were incubated at 37°C, at 24 h for the bacteria and fungi. After incubation, growth was surveyed by measuring the diameter of the growth inhibition zones.

In this work used differential microorganisms and culture media from the company "*Liofilchem*" (Italy): *Escherichia coli* (*ATCC 25922*), *Klebsiella pneumoniae* (ATCC 13883), *Staphylococcus aureus* (ATCC 25923), *Aspergillus niger* (ATCC 16404) and *Candida albicans* (ATCC 10231).

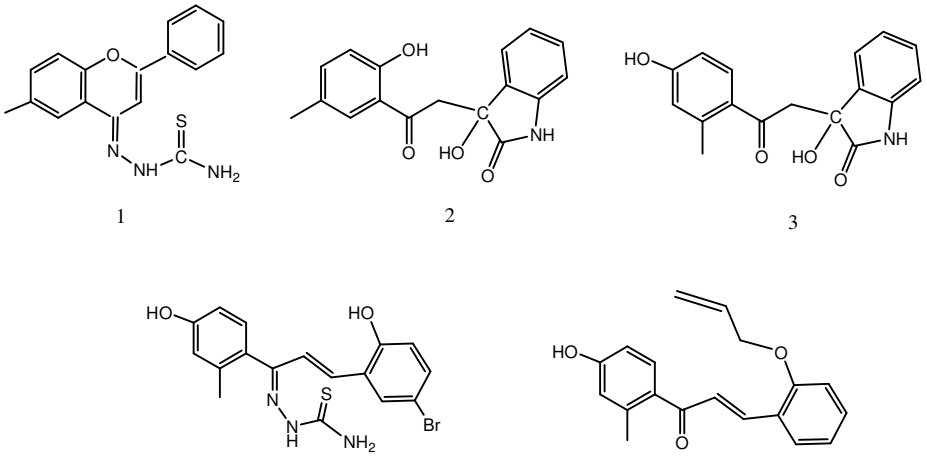
Results and Discussion

In presented work antibacterial, antifungal activities of some hydroxyacetophenone derivatives **1**-**5** against *E. coli*, *K. pneumoniae*, S. *aureus*, *A. niger*, *C. albicans* have been investigated. The molecular structures of investigated compounds were shown in Scheme II (**1** is known compound in the literature).

For the comparative characterization of compounds, we investigated sensitivity of antibiotics such as, *Gentamicin* (***Gn***), *Amoxicillin* (***An***), *Cefazoline* (***Ce***) against *E.coli*, *K. pneumoniae*, S. *aureus* and *Posaconazole* (***Pe***), *Caspofungin* (***Cn***) against *A. niger*, *C. albicans* and obtained results are given in Table I.

The results showed that compounds **1-5** in DMSO solution at concentration of 1 mg/mL didn't exhibit antifungal properties, whereas compounds **2-5** were displayed good antibacterial activity against *E. coli* and *K. pneumoniae* (Table I).

The compounds **2** was displayed good antibacterial activity against *E. coli* (zone of inhibition was 11 mm), than antibiotic *Cefazoline* (zone of inhibition was 10 mm). The compound **3** was displayed good antibacterial activity against *E. coli* (zone of inhibition was 14 mm) and *K. pneumoniae* (zone of inhibition was 20 mm), than antibiotics *Amoxicillin* and *Cefazoline* (zone of inhibition accordingly were 12, 10 mm (for the *E. coli*) and 15, 16 mm for the *K. pneumoniae*). The compound **4** was displayed high antibacterial activity against *E. coli* (zone of inhibition was 18 mm) and *K. pneumoniae* (zone of inhibition was 20 mm), than antibiotics *Gentamicin*, *Amoxicillin* and *Cefazoline* (zone of inhibition



Scheme II — The molecular structure of investigated componds

Table I — Antibacterial and anti-fungal activity of **1-5** in DMSO solution (1 mg/mL) (disc-diffusion method)

Microorganisms	Zone of inhibition (mm)									
						Antibiotics				
	1	**2**	**3**	**4**	**5**	***Gn***	***An***	***Ce***	***Pe***	***Cn***
E. coli	7	11	14	18	15	16	12	10		
K. pneumoniae	6	8	20	20	13	18	15	16		
S. *aureus*	10	6	21	18	17	32	29	45		
A. niger	12	8	12	18	12				24	28
C. albicans	14	15	15	22	17				24	28
DMSO	1-1.5	1-1.5	1-1.5	1-1.5	1-1.5					

accordingly were 16, 12, 10 mm (for the *E. coli*) and 18, 15, 16 mm for the *K. pneumoniae*). The compound **5** was displayed good antibacterial activity against *E. coli* (zone of inhibition was 15 mm), than antibiotics *Amoxicillin* and *Cefazoline* (zone of inhibition accordingly were 12, 10 mm (for the *E. coli*).

To summarize the obtained data, high antibacterial activity of compound **4** against *E. coli*, *K. pneumoniae* may be related to the presence of two free phenol hydroxyl groups, bromine atom, unsaturated bond and thiosemicarbazone fragment with high molecular mobility in the molecule.

Conclusion

We have reported the biological activities of some hydroxyacetophenone derivatives in DMSO solutions. All the synthesized compounds have demonstrated poor antifungal activity, but compounds **2-5** show good antibacterial activity against *E. coli* and *K. pneumoniae*.

Our investigations demonstrated that high antibacterial activity of compound **4** against *E. coli* and *K. pneumoniae* may be related to the presence of two free phenol hydroxyl groups, bromine atom, unsaturated bond and thiosemicarbazone fragment in the compound.

For the comparative characterization of investigated compounds as antibiotics used *Gentamicin*, *Amoxicillin*, *Cefazoline*, *Posaconazole*, *Caspofungin*.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/ 123456789/60.

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