



Biological activity of novel pentasubstituted cyclohexanol against some microorganisms

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The aim of this study is to investigate the antibacterial, antifungal activity of the new six membered 4-(4-bromophenyl)-4-hydroxy-2,6-diphenylcyclohexane-1,3-diylbis(4-bromophenyl)methanone and known (E)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one. The investigated products exhibit promising activities.

Keywords: Antimicrobial, antibacterial, aromatic ketone, cyclohexanol

The aromatic ketones are effective compounds in organic synthesis and have important significance for synthesis of different practical compounds¹⁻¹⁰, which have physiological activity. Due to their different functionality these compounds confer biological activities, such as antimicrobial, antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, antihyperglycemic¹¹⁻²¹.

Taking into account of their pharmaceutical actuality the 1,2,3,4,5-pentasubstituted cyclohexanol and its forming chalcone against *S. aureus*, *E. coli*, *KES* (*Klebsiella*, *Enterobacter*, *Serratia*) and *A. niger* were investigated.

Experimental Section

Materials and instrumentation

All the chemicals were obtained from commercial sources (Aldrich) and used as received. NMR experiments have been performed on a BRUKER FT NMR spectrometer (UltraShieldTM Magnet) AVANCE 300 (300.130 MHz for ¹H and 75.468 MHz for ¹³C) with a BVT 3200 variable temperature unit in 5 mm sample tubes using Bruker Standard software (TopSpin 3.1). The ¹H and ¹³C chemical shifts were referenced to internal tetramethylsilane (TMS); the experimental parameters for ¹H: digital resolution = 0.23 Hz, SWH = 7530 Hz, TD = 32 K, SI = 16 K, 90° pulse-length = 10 μs, PL1 = 3 dB, ns = 1, ds = 0, d1 = 1 s; for ¹³C: digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90° pulse-length = 9 μs, PL1 = 1.5 dB, ns = 100, ds = 2, d1 = 3 s (Figure S1-S9,

Supplementary Information). NMR-grade acetone-*d*₆ were used for the solutions of 1 and 2.

Electrospray mass spectra of new **2** was run with an ion-trap instrument (Esquire 6000 Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. For electrospray ionization, the drying gas and flow rate were optimized according to the particular sample with 35 psi nebulizer pressure. Scanning was performed from *m/z* 100 to 1200 in methanol solution. The compounds were observed in the positive mode (capillary voltage = 80–105 V).

The purity of the synthesized compounds were confirmed by thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254), iodine vapor was used as visualizing agent, eluent- 5:2 hexane/ethyl acetate.

Melting points were measured on an Electrothermal 9100 apparatus without correction.

Synthesis

A mixture of 4-bromoacetophenone (1.99 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) in 20 mL ethanol, 0.5 and 5 mL of 10-60 % sodium (or potassium) hydroxide solution was added and stirred at room temperature for 3 hours. The forming precipitate was collected by filtration and recrystallized in ethanol. In the presence of 0.5 and 5 mL of 10-40% sodium or potassium hydroxide solution a white compound **1** was obtained which had been described in the literature (yield 67-90%); in the presence of 5 mL of 50 and 60% sodium or potassium

hydroxide solution a new pale pink compound **2**, yield 26-37%; m.p.180-183°C.

^1H NMR of compound **2** (acetone- d_6 , 300 MHz): δ 1.91 and 3.43 (d-d and t, $^2J=12.4$, $^3J=4.3$, $^3J=7.6$, 2H, CH₂), 4.19 (m, 1H, CH), 4.53 (t, $^3J=4.6$, 1H, CH), 4.31 (d-d, $^3J=12.5$, $^3J=7.6$), 4.91 (d, 1H, OH), 5.13 (d, $^3J=12.5$, 1H, CH), 6.85-7.71 (m, 22H, CH_{arom.}); ^{13}C NMR of compound **2** (acetone- d_6 , 75 MHz): δ 38.7, 40.8, 44.9, 51.3, 52.1, 120.0, 126.1, 126.3, 126.5, 126.6, 127.5, 128.4, 128.5, 128.6, 128.7, 129.8, 131.5, 132.6, 143.2, 147.7, 200.1, 204.6.; ESI-MS: m/z [M+H]⁺ 773, 692, 553, 500, 411, 361, 306.

Antibacterial and antifungal testing

Compounds **1** and **2** were evaluated for their *in vitro* antibacterial, antifungal activities by the agar disc-diffusion and diffusion zone method.²¹ Stock solutions of test compounds were diluted in dimethyl sulfoxide (DMSO) to give a final concentration of 10 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 hours 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): *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and KES (*Klebsiella*,

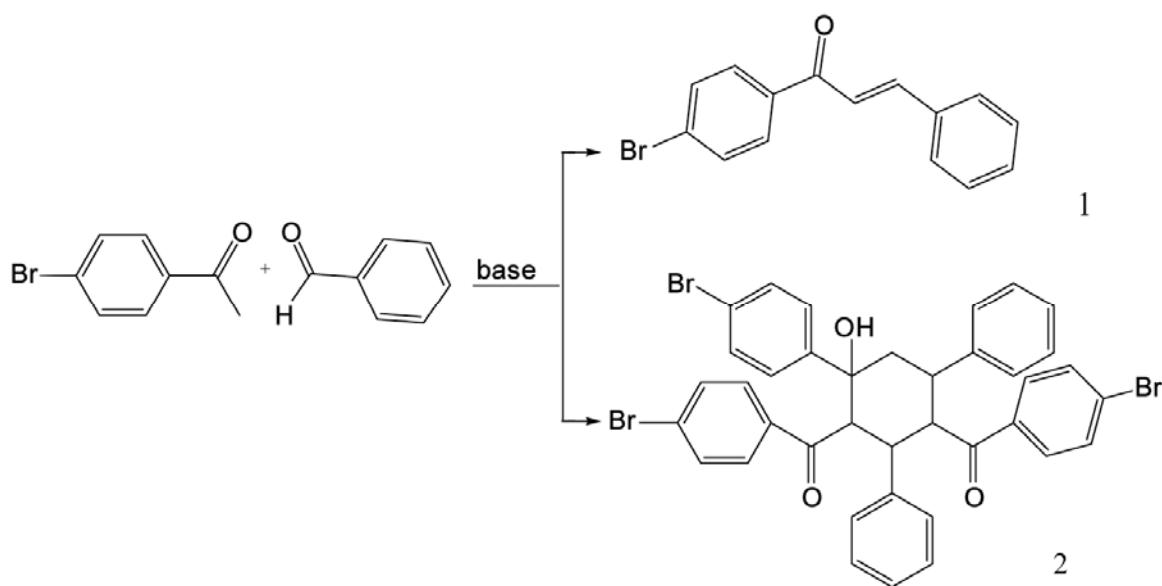
Enterobacter, *Serratia*), *Aspergillus niger* (the isolates from the different foods and water).

Results and Discussion

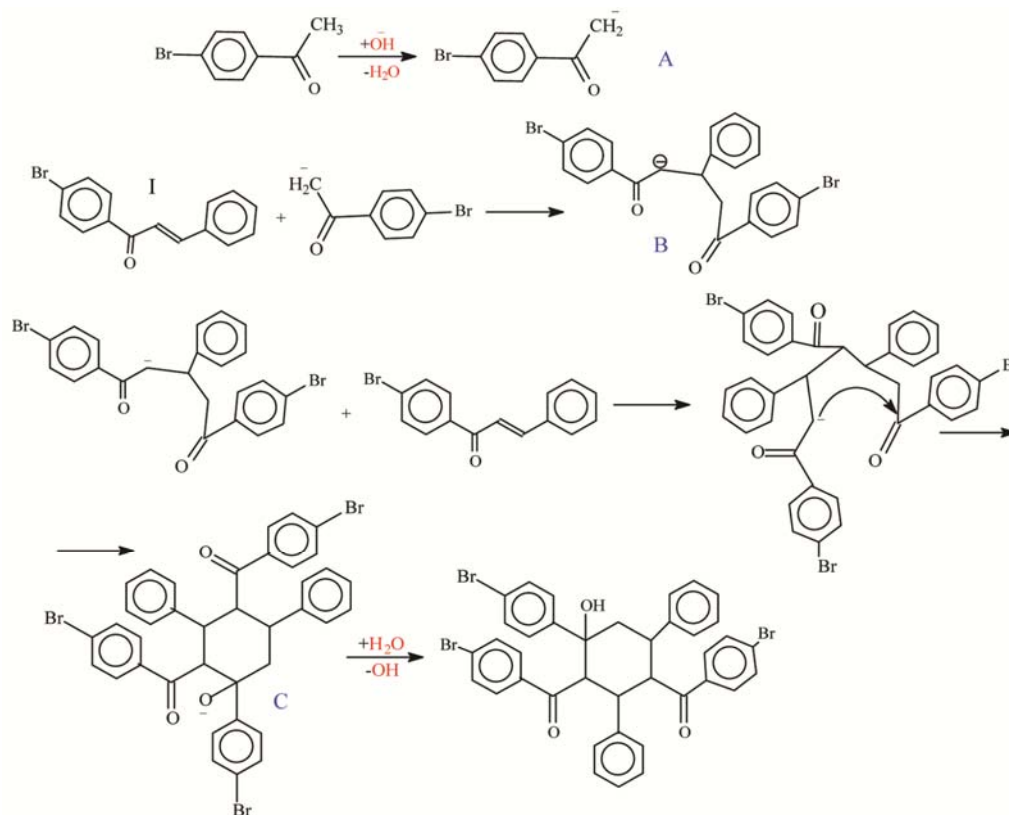
In our previous work is reported about the synthesis methods, reaction mechanism and 3D structure determination of new polysubstituted cyclohexanol by NMR and quantum-chemical methods.¹⁰ The compound **2** was characterized by ^1H , ^{13}C NMR spectroscopy and ESI-MS methods (Figure S1-9, Supplementary Information). Condensation of 4-bromoacetophenone with benzaldehyde can lead to formation of two different compounds, as given in Scheme I.

Possible formation mechanism of **2** at the presence of a base catalyst is given in Scheme II.

Our goal in this work were to examine of antimicrobial and antifungal activity of (*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (**1**) and new 4-(4-bromophenyl)-4-hydroxy-2,6-diphenylcyclohexane-1,3-diyl)bis(4-bromophenyl)methanone (**2**). The *in vitro* antibacterial activities of compounds **1**, **2** were evaluated against gram-positive and gram-negative bacteria and fungi using the cultures of different standard microorganisms: *Staphylococcus aureus*, *Escherichia coli*, KES (*Klebsiella*, *Enterobacter*, *Serratia*), and *Aspergillus niger* (the isolates from the different foods and water). Our investigations demonstrated that, compound **2** in minimal concentration exhibited better antibacterial activity,



Scheme I — Synthesis of the chalcone **1** and its cyclohexenol derivative **2**

Scheme II — Formation mechanism of the compound **2** at the presence of base catalystTable I — Antibacterial, antifungal activity of **1** and **2** in DMSO solution (10 mg/mL) (diffusion zone method and disc-diffusion method)

Compd	Microorganisms	Antimicrobial activity (zone of inhibition in mm)	
		diffusion zone method	disc-diffusion method
1	<i>S. aureus</i>	37	24
	<i>KES</i>	18	12
	<i>Escherichia coli</i>	28	16
	<i>Aspergillus</i>	11	7
2	<i>S. aureus</i>	30	16
	<i>KES</i>	42	24
	<i>Escherichia coli</i>	32	21
	<i>Aspergillus</i>	16	9

than **1** against of *KES* (*Klebsiella*, *Enterobacter*, *Serratia*), that can be probably caused by the presence of five aromatic ring and three bromine atom in the molecule. The results demonstrated that, compound **2** had good growth-inhibiting activity against of *Escherichia coli*. But compound **1** in minimal concentration exhibited the best growth-inhibiting effects against of *Staphylococcus aureus*, which can be explained by the presence of

unsaturated bond, aromatic ring and bromine atom in the molecule **1**. These compounds demonstrate also antifungal activities in minimal concentration. The results are shown in Table I.

Conclusions

In presented work we demonstrated one-pot practical simple method, which provides the fast and synchronous preparation of two practical important compounds: ((*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (**1**) and 4-(4-bromophenyl)-4-hydroxy-2.6-diphenylcyclohexane-1.3-diyl)bis(4-bromophenyl)-methanone (**2**) with good yields. This allows to make fast pharmacological activities test of these novel polysubstituted cyclohexanol derivatives and known chalcone. The simplicity, minimal concentration effect, inexpensive starting materials, easy setup, simple workup, good yields are features of presented study.

Supplementary Information

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

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