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Biological activity of benzopyran derivatives against some microorganisms

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The aim of this study is to carry out the catalyst-free green synthesis of tetrahydro benzopyran derivatives and investigation their antibacterial, antifungal activity against some microorganisms. The investigated compounds exhibit promising activities.

Keywords: Green synthesis, Antimicrobial, Antibacterial, Pyran

The interest in the discovery of novel approaches for the construction of complex heterocycles has significance, due to their potential in the production of pharmaceutically active compounds. Especially, N-, O-, and S- content heterocycles are effective in drug chemistry and have importance for the synthesis of different practical compounds, which have physiological activity[1-19]. Among these compounds, tetrahydropyrans are important because of their wide range of applications. These molecules are used in many fields of medicine as anticoagulants, anticancer, spasmolytic, antibacterial, anti-anaphylactic activity, and diuretics, *etc*.[20-22]

Considering their pharmaceutical actuality, the biological activity of the known compounds (**5** and **6**)[23,24] against *S. aureus*, *E. coli*, *Salmonella* and *C. Albicans* were investigated (in this work, benzopyran derivatives were synthesized by the catalyst-free green method in glycerol).

Experimental Section

All the chemicals were obtained from commercial sources (Aldrich) and used as received. NMR experiments have been performed on a BRUKER FT NMR spectrometer (Ultra Shield TM Magnet) AVANCE 300 (300.130 MHz for ^{1}H NMR and 75.468 MHz for ^{13}C NMR) with a BVT 3200 variable temperature unit in 5 mm sample tubes using Bruker Standard software (Top Spin 3.1). The ^{1}H and ^{13}C NMR chemical shifts were referenced to internal tetramethylsilane (TMS); the experimental parameters for ^{1}H: 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 ^{13}C: 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. NMR-grade DMSO-d_6 was used for solutions **5** and **6** (see Supplementary Information).

Electrospray mass spectra of **5** and **6** were 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).

FT-IR spectra were obtained as KBr pellets on a Perkin-Elmer 781 spectrophotometer (see Supplementary Information).

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

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected.

General procedure for the synthesis of 2-amino-4-(5-bromo-2-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5) and 2-amino-7,7-dimethyl-5-oxo-4-[(E)-2-phenylethenyl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6).

To a mixture of aldehyde (**1** or **2**, 1 mmol), dimedone (**3**, 1 mmol), and malononitrile (**4**, 1 mmol) in a 10 mL round-bottomed flask connected to a

reflux condenser, was added glycerol (5 mL), and the resulting mixture was stirred in an oil-bath (80°C). After completion of the reaction, warm water (5 mL) was added. The insoluble products were isolated by simple filtration. The crystalline solids were collected and dried. Structural data are identical to the published works[23,24].

2-Amino-4-(5-bromo-2-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile, 5: White powder, yield 81%, m.p.193°C. IR (KBr): 3362, 3200, 3101, 2955, 2214, 1688, 1621 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.90 (s, 3H), 1.01 (s, 3H), 2.04 (d, ^2J = 16.0 Hz, 1H), 2.23 (d, 2 J = 15.6 Hz, 1H), 2.36 (d, 2 J = 16.0 Hz, 1H), 2.47 (d, ^2J = 15.6 Hz, 1H), 4.77 (s, 1H), 6.64 (d, ^3J = 8.4 Hz, 1H), 6.97 (s, 1H), 7.06(d, ^3J = 8.4 Hz, 1H), 9.68 (s, 1H); MS: *m/z* (%) 389.2 (M^+, 100%), 390.2 (18.95%), 391.2 (3.21%). Anal. Calcd for $C_{18}H_{17}BrN_2O_3$: C, 55.54; H, 4.40; N, 7.20. Found: C, 55.62; H, 4.57; N, 7.41.

2-Amino-7,7-dimethyl-5-oxo-4-[(*E*)-2-phenylethenyl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile, 6: White powder, yield 73%, m.p.183°C. IR (KBr): 3298, 3187, 3076, 2932, 2198, 1647, 1609 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.08 (s, 3H), 1.12 (s, 3H), 2.28(d, J = 16.3 Hz, 1H), 2.35 (d, J = 16.3 Hz, 1H), 2.40 (s, 2H), 4.09 (s, 1H), 4.53 (s, 2H), 6.12 (m, 1H), 6.50 (d, J = 16.3 Hz, 1H), 7.18–7.36 (m, 5H); MS: *m/z* (%) 320.2 (M^+, 100%), 321.2 (18.99%), 322.2 (3.28%). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.88; H, 6.44; N, 8.56%.

Antibacterial and antifungal testing

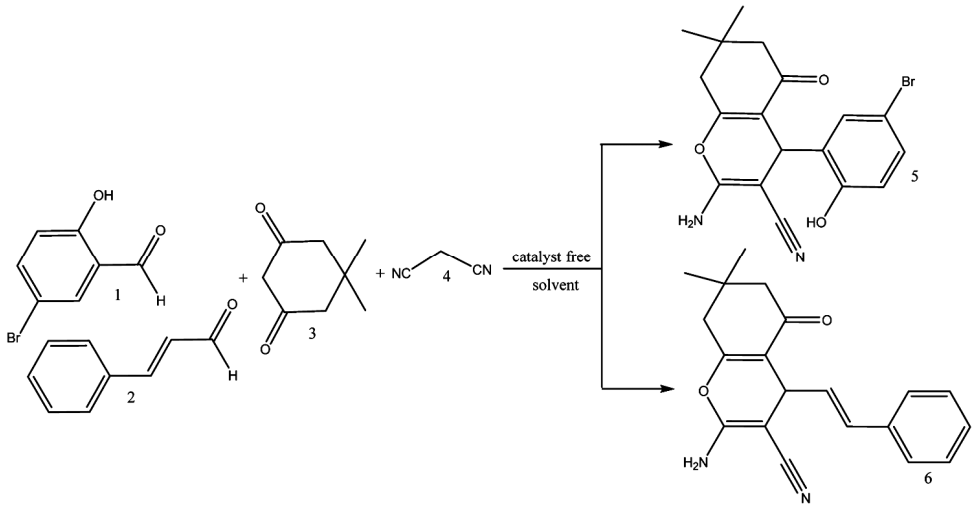
Compounds **5** and **6** were evaluated for their *in vitro* antibacterial and antifungal activities by the disc-diffusion method (used Mueller-Hinton-, Endo-, Baird-Parker-, SS-, Sabouraud agars growth media)[25]. Stock solutions of test compounds were diluted in dimethyl sulfoxide (DMSO) to give a final concentration of 10 mg/mL. The DMSO alone was used as a control and it was revealed that the solvent does not influence antibacterial / antifungal properties (the zone of inhibition was 1-1.5 mm). The plates with bacterial suspensions and disk of investigated compounds were incubated at 37°C, for 24 h for the bacteria and fungi. After incubation, growth was surveyed by measuring the diameter of the growth inhibition zones.

This work used differential microorganisms and culture media from the company "*Liofil-chem*" (Italy): *Staphylococcus aureus (ATCC 25923)*, *Escherichia coli (ATCC 25922)*, *Salmonella (ATCC 13076)* and *Candida albicans (ATCC 90028).*

Results and Discussion

Despite the fact that investigated compounds are known in the literature[23,24], we suggested a catalyst-free green synthesis method in glycerol. The synthesis route and mechanism of the tetrahydro benzopyran derivatives are given in Scheme 1 and Scheme 2.

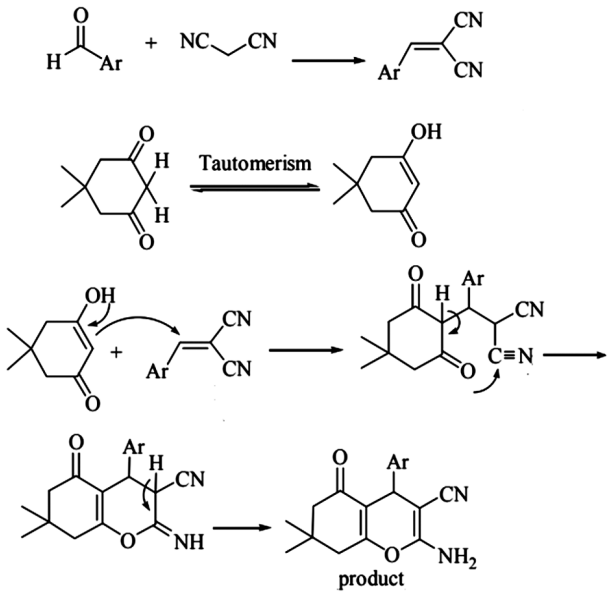
Our goal in this work was the examine of antimicrobial and antifungal activity of 2-amino-4-(5-bromo-2-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **5** and 2-amino-7,7-dimethyl-5-oxo-4-[(E)-2-phenylethenyl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **6**. The



Scheme 1 — Synthesis route of the tetrahydro benzopyran derivatives **5** and **6**

Table 1 — Antibacterial and antifungal activity of **5** and **6** in DMSO solution (10 mg/mL) by disc-diffusion method

Compd	Microorganism	Antimicrobial activity (zone of inhibition in mm)				
		M. Hinton	Endo	B. Parker	SS	Sabour
5	*S. aureus*	16	–	18	–	–
	E. coli	16	23	–	–	–
	S. enterica	10	–	–	13	–
	C. albicans	13	–	–	–	15
6	*S. aureus*	11	–	14	–	–
	E. coli	13	18	–	–	–
	S. enterica	08	–	–	11	–
	C. albicans	12	–	–	–	13



Scheme 2 — Synthesis mechanism of the tetrahydro benzopyran derivatives

in vitro antibacterial activities of compounds **5**, **6** were evaluated against gram-positive and gram-negative bacteria and fungi using the cultures of different standard microorganisms: *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* and *Candida albicans.* Our investigations demonstrated that compound **5** in minimal concentration exhibited better antibacterial activity than **6** against investigated microorganisms in all growth media. But for compound **5**, the best result is demonstrated in Endo agar growth medium against *E-coli* (zone of inhibition was 23 mm). The high biological activity of the **5** can probably be caused by the presence of bromine atom and hydroxyl group in the molecule. Bromine and the hydroxyl group in compound **5** exhibit antibacterial activity suggesting that the bromine participates in a hydrophobic (as a halogen bond donor), –OH in a hydrophilic interaction (as a hydrogen bond acceptor). The fact indicates that hydrogen bonding impacts the antibacterial activity of **5**. Thus, halogen bonding, which has lately been demonstrated to be often beneficial for bioactivity, is most likely involved in the antibacterial activity of **5**[26,27].

These compounds also demonstrate antifungal activities in minimal concentration. The results are shown in Table 1.

Conclusions

In the presented work, we demonstrated a one-pot catalyst-free green synthetic simple method in glycerol solvent, which provides the fast and synchronous preparation of two practical important compounds **5** and **6**. This allows for the fast testing of pharmacological activities of these tetrahydro benzopyran derivatives. The simplicity, minimal concentration effect, inexpensive starting materials, easy setup, simple workup and good yields are notable features of the presented study.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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