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Original Article

Synthesis, characterization and antimicrobial activity of some new coumarine derivatives

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ABSTRACT

The emergence of microbial strains resistant to the present antibiotics highlights the need for search of new antimicrobial agents. In continuation to this, present work deals with the synthesis and antimicrobial activity of 2 amino-3-(benzo[d] thiazol-2-yl)-4-phenyl pyrano [3,2-c] chromen-5(4H)-one derivatives. The newly synthesized compounds were screened for *in vitro* antimicrobial activity against four Gram positive bacteria, four Gram negative bacteria and four fungi in the solvent Dimethylsulphoxide. Some of the synthesized compounds exhibited better antibacterial activity against Gram positive bacteria than Gram negative bacteria. None of the synthesized compounds showed antifungal activity against the selected fungal strains.

Keywords: Antibacterial activity, Gram positive bacteria, Gram negative bacteria, Dihydropyrano [c]chromenes Dimethylsulphoxide

INTRODUCTION

The majority of problematic infections with respect to failing antibiotic treatment are caused by multi drug resistant pathogens. The heterocyclic compound played important role in regulating biological activities. The heterocyclic compound our interest in synthesizing some coumarine derivatives with the aim of testing their potential as antimicrobial agents. Dihydropyrano[c]chromenes have recently attracted much attention as an important class of heterocycles because of their useful biological and pharmacological properties. These compounds are widely used as antibacterial[1-2], anticoagulant[3], antioxidant[4-5], spasmolytic, anticancer, diuretic and hepatoprotactive agents in the field of drugs and pharmaceuticals [6-7]. Thus, in the present work, some new dihydropyrano[c]chromenes were synthesized. The structure of newly synthesized compounds was confirmed by Mass, ^{1}H NMR and IR spectroscopy. Further, antimicrobial screening of these synthesized compounds was done against some bacterial (Gram positive as well as Gram negative) and fungal strains in the solvent Dimethylsulphoxide.

EXPERIMENTAL

Materials: Reagent grade chemicals were used without further purification. The purity of the synthesized compounds was checked by Thin Layer Chromatography.

Synthesis:

Synthesis of 2-(benzo[d] thiazol-2-yl) acetonitrile: In an equimolar solution of 2-amino thiophenol and malano nitrile in ethanol, 0.5 ml glacial acetic acid was added drop wise. The solution was stirred for 30 min. Light yellow colored solid was formed which was filtered and dried.

Synthesis of dihydropyrano[c]chromene derivatives: In an equimolar methanolic solution of 2-(benzo[d] thiazol-2-yl) acetonitrile and 4-hydroxy coumarin, different substitutes aldehydes were added in the presence of piperidine as a catalyst. The reaction mixture was refluxed for 8-9 hours. The product was filtered and recrystallized with ethanol.

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Characterization: IR spectra were recorded by SHIMADZU-FTIR-8400 spectrophotometer in frequency range of 4000-400 cm-1 by KBr powder method. ^{1}H NMR spectra were recorded by BRUCKER spectrometer (400 MHZ) using internal refences TMS and DMSO – d_6. The Mass spectra were recorded by GCMS- SHIMADZU-QP 2010.

Antimicrobial activity:

Microorganisms tested: The studied microorganisms were obtained from National Chemical Laboratory (NCL), Pune, India. The microorganisms were maintained at 4°C. The Gram positive bacteria studied were *Staphylococcus aureus* ATCC29737 (*SA*), *Corynebacterium rubrum* ATCC14898 (*CR*), *Listeria monocytogenes* ATCC19112 (*LM*), *Bacillus cereus* ATCC11778 *(BC)*; Gram negative bacteria were *Pseudomonas aeruginosa* ATCC27853 (*PA*), *Escherichia coli* NCIM2931 (*EC*), *Klebsiella pneumoniae* NCIM2719 (*KP*), *Salmonella typhimurium* ATCC23564 (*ST*) and Fungi were *Candida albicans* ATCC2091 (*CA*), *Cryptococcus neoformans* NCIM3542 (*CN*), *Candida glabrata* NCIM3448 (*CG*), *Candida epicola* NCIM3367 (*CE*). The organisms were maintained on nutrient agar and MGYP medium (Hi Media, India) for bacteria and fungi respectively, at 4°C and sub-cultured before use. The microorganisms studied are clinically important ones causing several infections and food spoilage.

Agar well diffusion method: *In vitro* antimicrobial activity of the new dihydropyrano [c]chromenes derivatives were studied against pathogenic microbial strains by the agar well diffusion method [8]. Mueller Hinton No. 2 / Sabouraud dextrose agar (Hi-media) was used for the antibacterial and antifungal susceptibility test respectively. The new dihydropyrano [c]chromenes derivatives were dissolved in 100% DMSO to give a concentration of 20 mg ml^{-1}. The Mueller Hinton agar / Sabouraud dextrose agar was melted and cooled to 48-50°C and a standardized inoculum (1.5×10^8 CFU/ ml, 0.5 McFarland) was then added aseptically to the molten agar and poured into sterile Petri dishes; wells (8.5 mm) were prepared in the seeded agar plates. The test compound (100 µl) was introduced into the well. The plates were incubated overnight at 37°C and 28°C for 24 h and 48 h respectively, for bacteria and fungi. DMSO were used as negative control. The microbial growth was determined by measuring the diameter of the zone of inhibition and the mean values are presented with ± SEM.

RESULTS AND DISCUSSION

IR, ^{1}H NMR and Mass spectral data of 2-amino-3-(benzo[*d*]thiazol-2-yl)-4-(3- methoxy phenyl) pyrano[3,2-*c*]chromen-5(4H)-one (ABR-8):

IR: 3439.19 (N-H str), 1746.60 (C=O), 1306.82 (C-N str), 1271.13 (C-O-C str assymetrical),) 1114.89 (C-O-C str sym), 1586.50 (C=C str aromatic), 3042.81(C-H str aromatic)

^{1}H NMR (δ ppm): 3.698 (3H, s,-OCH_3), 4.766 (1H,s, -CH), 8.670 (2H, s, -NH_2), 6.755-8.670 (12H, multiplate, aromatic)

Mass: (M/Z) 454,410, 347, 291, 279, 265, 249, 174

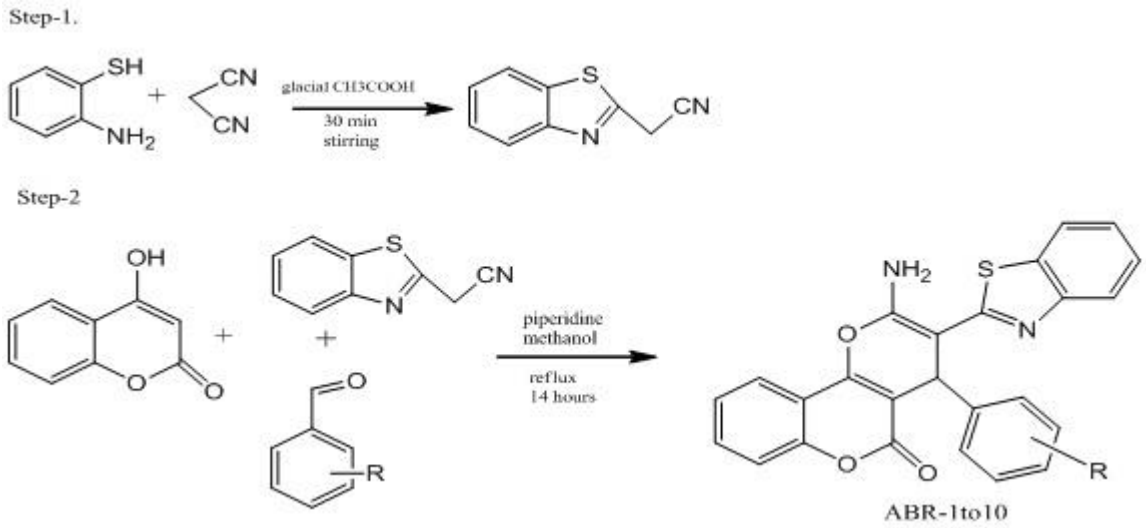
The 10 synthetic compounds and their respective controls produced different inhibition zones against the tested bacterial strains. The *in vitro* antibacterial activity of the ten compounds in DMSO against medically important Gram positive and Gram-negative bacteria is shown in Fig. 1. All the 10 compounds showed inhibitory activity against *B. cereus* but ABR-7, ABR-9 and ABR-10 showed highest activity than all other strains studied. Only ABR-4 exhibited activity against *S. aureus.* ABR-2, ABR-4, ABR-7, ABR-9 showed lesser activity against *L. monocytogenes*. ABR-7, ABR-9, ABR-10 showed lesser activity against *C. rubrum. B. cereus* was the most susceptible bacteria, getting inhibited by all the 10 synthesized compounds (Fig. 1A).

None of the compounds in DMSO showed antibacterial activity against *E. coli*. ABR-1, ABR-2, ABR-4, ABR-7, ABR-10 compound showed lesser inhibitory activity against *K. pneumonia.* ABR-1, ABR-2, ABR-4, ABR-8 and ABR-10 showed some inhibitory activity against *P. aeruginosa*. ABR-1, ABR-2, ABR-4, ABR-8 and ABR-10 showed inhibitory activity against *S. typhimurium*. *E. coli* and *P. aeruginosa* were the most resistant bacterial strains not getting inhibited by any of the tested compounds (Fig. 1B).

B. cereus was the most susceptible Gram-positive bacteria, getting inhibited by 10 out of 10 tested compounds. These differences may be attributed to fact that the cell wall in Gram positive bacteria is of a single layer, whereas the Gram-negative cell wall is multilayered structure [9] *E. coli was* the most resistant Gram-negative bacteria not getting inhibited by any of the tested compounds. None of the compounds were active against the tested fungi; may be because of the tougher cell wall they possess. The difference in the response towards bacterial strains is also because of the difference in the cell wall structure of Gram positive and negative bacterial.

Antimicrobial activity of some new dihydropyrano[c]chromenes dissolved in the solvent DMF was evaluated by Bhalu et al. [10]. The compounds showed good antibacterial activity towards Gram positive bacteria but showed very poor activity against Gram negative bacteria. The compounds in DMF solvent showed better antibacterial activity against Gram positive bacteria while the same compounds in DMSO solvent showed better antibacterial activity towards Gram negative bacteria.

In both the studies the central moiety in all the compounds is dihydropyrano [c]chromenes with different side chains, and the solvent used is different. Therefore, differential antibacterial activity was observed. From this study, it can be concluded that it cannot be assumed that one solvent is better than the other. It is also dependent on the molecular structure and the particular bacterial strain considered [11].



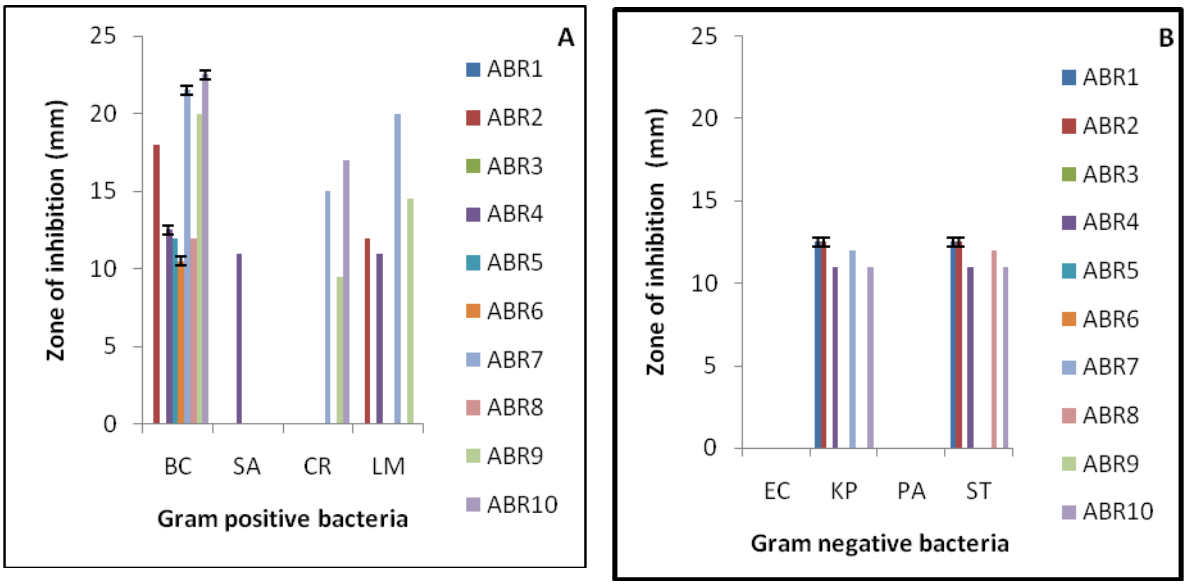


Fig.1. Antibacterial activity of dihydropyrano [c]chromenes in DMSO against (A) Gram positive and (B) Gram negative bacteria.

Table 1: Physical constants of synthesized compounds.

Sr.No.	Compound Code	R	M.F.	M.W.(gm/mol)	% Yield
1	ABR-1	-H	$C_{25}H_{15}N_2O_3S$	424	76
2	ABR-2	4-CH_3	$C_{26}H_{15}N_2O_3S$	438	73
3	ABR-3	3,4-di OCH_3	$C_{27}H_{20}N_2O_5S$	484	72
4	ABR-4	4-F	$C_{25}H_{15}N_2O_3SF$	442	75
5	ABR-5	4-OCH_3	$C_{26}H_{18}N_2O_4S$	454	74
6	ABR-6	4-Br	$C_{25}H_{15}N_2O_3SBr$	502	70
7	ABR-7	3-Br	$C_{25}H_{15}N_2O_3SBr$	502	77
8	ABR-8	3-OCH_3	$C_{26}H_{18}N_2O_4S$	454	69
9	ABR-9	2,5-di OCH_3	$C_{27}H_{20}N_2O_5S$	484	74
10	ABR-10	3-Cl	$C_{25}H_{15}N_2O_3SCl$	453	73

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