SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL CYANOPYRIDONES AND BENZOPYRAN DERIVATIVES

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ABSTRACT: In this investigation our aim is to synthesized a number of new cyanopyridone and benzopyran derivatives. Cyanopyridone was synthesized by reaction of aldehydes, 2-cyano-N-(substituted)acetamides and malononitrile. Benzopyran was synthesized from 2-(Substitutedbenzylidene) malononitrile. The synthesized compounds displayed different degrees of antimicrobial activity against Staphylococcus aureus, Streptococcus pyogenes, P. aeruginosa, E. coli, Pseudomonas aeruginosa and Aspergillus Niger, Candida albicans. Compound 5a found to be more potent on S. aureus, compound CP1 shows good antibacterial activity and BP2 shows good antifungal activity.
Key words: Cyanopyridone, Benzopyran, Ampicillin, Griseofulvin and Minimum inhibitory concentration.

I.INTRODUCTION

Synthesis of new cyanopyridone and benzopyran heterocyclic molecules is important in terms of searching new biologically active substances. Pyridone and their derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance [1-3]. 2-Pyridones represent a unique class of pharmacophore, which are observed in various therapeutic agents [4] and antibiotics [5]. These heterocycles attracted attention because of their applications as bioactive compounds for example as a promising class of HIV- 1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) [6], as antibacterial [7], antifungal [8], sedative [9] and cardiotonic agents [10]. Moreover, such derivatives have recently become important due to their structural similarity to nucleosides [11].

Traditionally benzopyrans have been identified as chromans, chromanones, chromones and 2- and 3-chromenes. Benzopyrans are important chemical synthon, associated with a broad range of biological effects including antioxidant [12,13], anti-HIV [14,15], neuroprotective [16,17], antiepileptic [18,19], antimicrobial [20,21], antidiabetic [22,23], antihypertensive [24,25], and anticancer agents [26,27]. Among the diverse biological activities of benzopyrans, breast cancer is one of the most intriguing since the discovery of ormeloxifene [28], KBU2046 (Phase II) [29], and B43-genistein [30]. Therefore, many benzopyrans have contributed to the search for new anti-breast cancer agents.

In this work, we report for synthesis of a new cyanopyridone and benzopyran, for further investigations in drug development against multidrug-resistant bacteria and fungi. We carried out the antimicrobial screenings of the new compound on *Staphylococcus aureus, Streptococcus pyogenes, P. aeruginosa, E. coli, Pseudomonas aeruginosa and Aspergillus Niger, Candida albicans*.

II.EXPERIMENTAL

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. 1H NMR was determined in DMSO-*d*6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Synthesis of cyanopyridone

General procedure for Synthesis of 2-cyano-N-(substituted) acetamides

Synthesis of 2-cyano-N-(substituted) acetamides was prepared using previously published methods. The solvent-free reaction of arylamines with ethyl cyanoacetate constitutes one of the most widely used methods for the preparation of cyanoacetanilides. Thus, fusion of aromatic amines with an excess amount of ethyl cyanoacetate at 150 °C afforded cyanoacetanilide derivatives. [31]

General procedure for the synthesis of 6-amino-1,2-dihydro-4- (aryl)-2-oxo-1-(2,5-dichlorophenyl) pyridine-3,5-dicarbonitriles

A mixture of 2-cyano-N-(2,5-dichlorophenyl) acetamide (0.01 mol), appropriate aromatic aldehydes (0.01 mol), malononitrile (0.01 mol) and catalytical amount of piperidine in methanol (20 ml) was heated under reflux condition for 15-16 hour. The reaction mixture was kept at room temperature for 2-4 hour. The solid product obtained was isolated and recrystallized from ethanol.

General procedure for the synthesis of 6-amino-1,2-dihydro-4- (aryl)-2-oxo-1-(3,4-dichlorophenyl) pyridine-3,5-dicarbonitriles

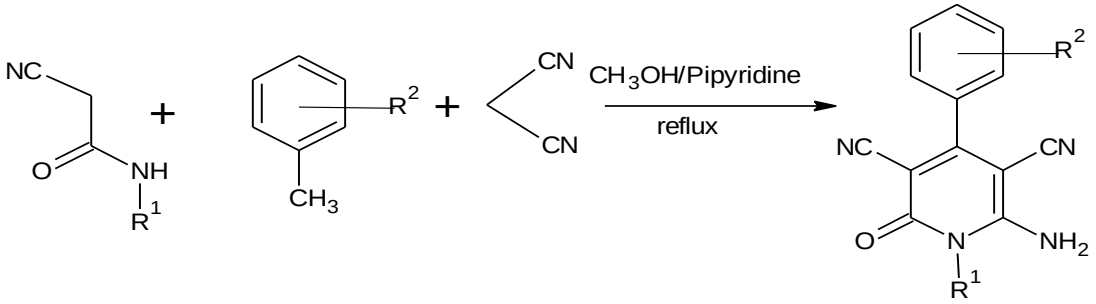
A mixture of 2-cyano-N-(3,4-dichlorophenyl) acetamide (0.01 mol), appropriate aromatic aldehydes (0.01 mol), malononitrile (0.01 mol) and catalytical amount of piperidine in methanol (20 ml) was heated under reflux condition for 15-16 hour. The reaction mixture was kept at room temperature for 2-4 hour. The solid product obtained was isolated and recrystallized from ethanol.

General procedure for the synthesis of 6-amino-1,2-dihydro-4-(aryl)-2-oxo-1-(4-Fluorophenyl) pyridine-3,5-dicarbonitriles

A mixture of 2-cyano-N-(4-Fluorophenyl) acetamide (0.01 mol), appropriate aromatic aldehydes (0.01 mol), malononitrile (0.01 mol) and catalytical amount of piperidine in methanol (20 ml) was heated under reflux condition for 15-16 hour. The reaction mixture was kept at room temperature for 2-4 hour. The solid product obtained was isolated and recrystallized from ethanol.

General procedure for the synthesis of 6-amino-1,2-dihydro-4-(aryl)-2-oxo-1-(2,5-dimethylhenyl) pyridine-3,5-dicarbonitriles

A mixture of 2-cyano-N-(2,5-dimethylphenyl) acetamide (0.01 mol), appropriate aromatic aldehydes (0.01 mol), malononitrile (0.01 mol) and catalytical amount of piperidine in methanol (20 ml) was heated under reflux condition for 20-22 hour. The reaction mixture was kept at room temperature for 2-4 hour. The solid product obtained was isolated and recrystallized from ethanol.



Reaction scheme for synthesis of cyanopyridone

Table 1: Physical Data of synthesized compound

Compound	**R**	**R2**	**M.F**	**M.W. (gm/ mole)**	**M.P. (^{0}C)**	**% of yield**	**R_f value**
CP1	2-Cl-5-Cl-phenyl	4-OCH_3	$C_{20}H_{12}Cl_2N_4O_2$	410	280-284	66	0.87
CP2	3-Cl-4-Cl-phenyl	4-CH_3	$C_{20}H_{12}Cl_2N_4O$	394	245-248	77	0.85

Table 2: Elemental Analysis

Compound	**Molecular formula**	**% of Elemental Analysis**					
		Calculated			**Found**		
		C	**H**	**N**	**C**	**H**	**N**
CP1	$C_{20}H_{12}Cl_2N_4O_2$	58.41	2.94	13.62	58.21	2.45	13.33
CP2	$C_{20}H_{12}Cl_2N_4O$	60.78	3.06	14.18	60.65	3.01	14.15

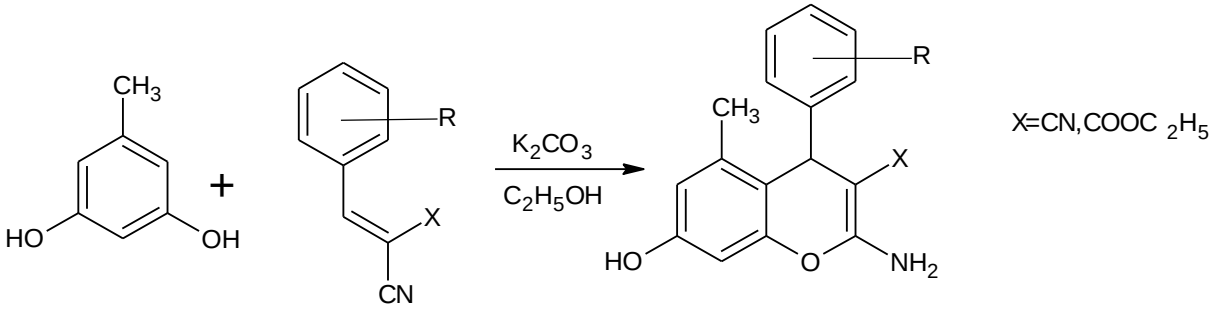
Synthesis of benzopyran

Synthesis of 2-(Substitutedbenzylidene) malononitrile.

The product 2-(Substitutedbenzylidene) malononitrile has been synthesized by the reaction of different substituted aldehyde and malononitrial in presence of base (pipyridine). [32]

General method for the Synthesis of 2-amino-7-hydroxy-5-methyl- 4-(substitutedphenyl)-4H-chromene-3-carbonitrile

0.01 mole of 2-(Substitutedbenzylidene) malononitrile and 0.01 mole of 5-methyl resorcinol dissolve in absolute ethanol. Stirring the reaction mixture at room temperature, gradually added the anhydrous potassium carbonate and stirring the reaction mixture at room temperature for 5-6 hours. After completion of reaction, pour the reaction mixture in dilute hydrochloric acid and neutralized it, separated the solid product filter, dry and crystallized from ethanol.



Reaction scheme for synthesis of benzopyran

Table 3: Physical Data of synthesized compound

Compound	**X**	**R**	**M.F**	**M.W. (gm/ mole)**	**M.P. (^{0}C)**	**% of yield**	**R_f value**
BP1	CN	4-OCH_3	$C_{18}H_{16}N_2O_3$	308	210-212	70	0.88
BP2	COOEt	4-OCH_3	$C_{20}H_{21}NO_5$	355	166-168	60	0.84

Table 4: Elemental Analysis

Compound	**Molecular formula**	**% of Elemental Analysis**					
		Calculated			**Found**		
		C	**H**	**N**	**C**	**H**	**N**
BP1	$C_{18}H_{16}N_2O_3$	70.12	5.23	9.09	70.10	5.21	9.0
BP2	$C_{20}H_{21}NO_5$	67.59	5.96	3.94	67.54	5.92	3.91

III.BIOLOGICAL EVALUATION

Antimicrobial Evaluation

All the synthesized compounds (CP1,CP2 and BP1,BP2) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [33, 34] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and two fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282, taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards [33]. Serial dilutions of the test compounds and reference drugs were prepared in Muellere-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL).

Further progressive dilutions with melted Muellere-Hinton agar were performed to obtain the required concentrations. In primary screening 1000 µg mL^{-1}, 500 µg mL^{-1} and 250 µg mL^{-1} concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution at 200 µg mL^{-1}, 100 µg mL^{-1}, 50 µg mL^{-1}, 25 µg mL^{-1}, 12.5 µg mL^{-1}, and 6.25 µg mL^{-1} concentration against all microorganisms. The tubes were inoculated with 108 cfu mL^{-1} (colony forming unit/mL) and incubated at 37 ºC for 24 h. The MIC was the lowest concentration of the tested compound that yields no

visible growth (turbidity) on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO had no effect on the microorganisms in the concentrations studied.

IV.RESULT AND DISCUSSION

Spectral data

Compound (CP1): 6-amino-1-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile

Yield: 66%; MP: 280-2840C; IR (ν, cm^{-1}): 3665 &3522 (N-H, Streching of primary amine), 3194(C-H Streching of aromatic ring), 2218 (C≡N Streching of nitrial group), 1639 (C=O Steching of pyridone ring), 1525 (N-H deformation of NH2 group), 1461 (C=C Steching of aromatic ring), 1252 (C-N Streching of carbon bonded to amine), 1173 (C-O-C symmetrical stretching OCH3 group), 1095 (C-H in plane bending for aromatic ring), 830 (out of plane bending for disubstituted aromatic ring), 774 (C-Cl Streching).

^{1}H-NMR δ: 3.85 (3H, s, OCH3(a)), 7.12-7.15(2H, d, Ar-CH(b-b')J=11.6mHz), 7.52-7.55 (2H, d, Ar-CH(c-c')), 7.68-7.69 (1H, d/q, Ar-CH(d)), 7.75-7.78 (1H, d, Ar-CH(e),J=11.6mHz), 7.85(1H, s, Ar-CH(f)), 8.28(2H, s, NH2(g)); MS: *m/z* 410; Elemental Analysis for $C_{20}H_{12}C_{l2}N_4O_2$: Calculated: C, 58.41; H, 2.94; N, 13.62%.; Found: C, 58.21; H, 2.45; N, 13.33%.

Compound (CP2): 6-amino-1-(3,4-dichlorophenyl)-2-oxo-4-(p-tolyl)-1,2-dihydro pyridine-3,5-dicarbonitrile

Yield**:** 77%**;** Melting Point**:** 245-248^{0}C; IR (ν, cm^{-1}): 3457 & 3299(N-H Streching of primary amine), 3202(C-H Streching of aromatic ring), 2837(C-H, Streching of CH3 group), 2213(C≡N Streching of nitrial group), 1685(C=O Steching of pyridone ring), 1617(N-H deformation of NH2 group), 1514 & 1456(C=C Steching of aromatic ring), 1253(C-N Streching of carbon bonded to amine), 1027(C-H in plane bending for aromatic ring), 828(Out of plane bending for disubstituted aromatic ring), 771(C-Cl Streching); ^{1}H-NMR δ: 2.02(3H,s, CH_3(a)), 7.12-7.15(2H, d, Ar-CH(b-b')J=11.6mHz), 7.44-7.51(3H, m, Ar-CH(d,e,f)), 7.85-7.87(2H, d, Ar-CH(c-c')), 8.00(2H,s, NH_2(g));MS: *m/z***:** 394; Elemental Analysis for $C_{20}H_{12}Cl_2N_4O$: Calculated: C, 60.78; H, 3.06; N, 14.18%. Found: C, 60.65; H, 3.01; N, 14.15%.

Compound (BP1): 2-amino-7-hydroxy-4-(4-methoxyphenyl)-5-methyl-4Hcromene-3-carbonitrile

Yield: 70 %, Melting Point: 210-212 ^{0}C, IR (ν, cm^{-1}): 3441(O-H Streching of primary alcohol), 3337(N-H Streching of primary amine), 3048(C-H Streching of aromatic ring), 2963(C-H Streching of CH3 group), 2180(C≡N Streching of nitrial group), 1648(N-H deformation of NH2 group), 1505-1408(O-H in plane bending), 1296(C-N Streching of carbon bonded to amine), 1138(C-O-C symmetrical stretching for ethers), 1068(C-H in plane bending of phenyl ring), 836(out of plane bending for disubstituted aromatic ring); ^{1}H-NMR δ: 1.89(3H,s, CH_3(a)), 3.7(3H, s, -OCH3(b)), 4.46(3H, s, -H(c)), 6.32(1H, s, Ar-H(d)), 6.37(1H, s, Ar-H(e)), 6.72(2H,s, NH2(f)), 6.82-6.84(2H, d, Ar-H(g,g')), 6.93-6.96(2H,d, Ar-H(h,h')), 9.59(1H, -OH(i)); MS: *m/z***:** 308; Elemental Analysis for $C_{18}H_{16}N_2O_3$:; Calculated: C, 70.12; H, 5.23; N, 9.09; %.; Found: C, 70.10; H, 5.21; N, 9.0; %

Compound (BP2): Ethyl-2-amino-7-hydroxy-4-(4-methoxyphenyl)-5-methyl-4Hchromene-3-carboxylate

Yield: 60%, Melting point: 166-168 ^{0}C; IR (ν, cm^{-1}): 3414(O-H Streching of primary alcohol), 3298(N-H Streching of primary amine), 2972(C-H Streching of aromatic ring), 1660(N-H deformation of NH2 group), 1618(O-H in plane bending), 1512(N-H deformation of NH2 group), 1462(C=C Steching of aromatic ring), 1311(C-N Streching of carbon bonded to amine), 1245(C-O-C asymmetrical stretching for ethers), 1145(C-O-C symmetrical stretching OCH_3), 1069(C-H in plane bending of phenyl ring), 842(Out of plane bending for disubstituted aromatic ring); ^{1}H-NMR δ: 1.17-1.22(3H, t, -CH_2CH_3(a)), 1.99(3H, s, -CH_3(b)), 3.66(3H,s, -OCH_3(c)), 3.99-4.04(2H,q, -CH_2(d)CH_3), 4.70(1H, s, -H(e)), 6.35(2H,s, Ar-H(f,f')), 6.74-6.76(2H, d, Ar-H(g,g')), 6.97-6.99(2H,d, Ar-H(h,h')), 7.44(2H, s, -NH_2(i)), 9.49(1H,s, -OH(j)); MS: *m/z***:** 355; Elemental Analysis for $C_{20}H_{21}NO_5$ Calculated: C, 67.59; H, 5.96; N, 3.94; %. Found: C, 67.54; H, 5.96; N, 3.91; %

V.CONCLUSION

In this dissertation we have synthesized two cyano pyrimidine (CP1, CP2) and two benzopyran (BP1, BP2) by using the above discussed reaction scheme in experimental section. After synthesis of all these compounds the compounds are taken for spectral analysis like IR, NMR and Mass spectroscopy to conform their molecular structure, presence of functional group and to know the molecular mass.

All the four synthesized compounds CP1, CP2, BP1 and BP2 were screened for their anti-microbial properties against the selected bacteria and fungi stains. The antimicrobial activity of the synthesized compound was compared with standard antibacterial agent Ampicillin and antifungal agent Griseofulvin. In the antimicrobial

screening it as found that CP1 shows good acntibacterial activity and BP2 shows good antifungal activity.

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