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Synthesis and Chemical Characterization of Some Novel Benzopyrans and Their Biological Activity Studies

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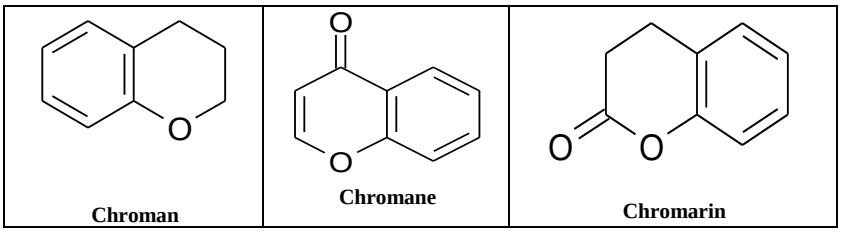
ABSTRACT

Substituted benzopyrans such as chromones and coumarins have received significant consideration during last few decades as they are proficient with diversity of biological activities and have extensive variety of therapeutic properties. A literature review postulates that benzopyran derivatives possess different pharmacological and biological activities, of which the most potent is anti-microbial activity. We thought to synthesize pyrano pyramidine moiety incorporating benzimidazole and benzopyran moiety.

Keywords: Benzopyrans, Chromones, Benzimidazole

INTRODUCTION

Traditionally benzopyrans have been identified as chromans, chromanones, chromones and 2- and 3-chromenes. The coumarins are the leading class of 1-benzopyran derivatives. They are found mainly in higher plants. Most natural coumarins are oxygenated at C-7; Umbelliferone (7-hydroxycoumarin) being regarded as the structural and biogenetic parent of the more highly oxygenated coumarins. Prenylation at carbon and oxygen is mutual in a large number of coumarins. The prenyl groups found in coumarins show the utmost number of biogenetic alterations including cyclisation to dihydropyrans, pyrans, dihydrofurans and furans. In the Type of Compound Index the very numerous coumarins are subdivided into classes of manageable size according to their oxygen substitution pattern, with separate sections for natural products having extra rings; furo-1-benzopyrans and pyrano-1-benzopyrans.



Chroman **Chromane** **Chromarin**

Chromones are renowned naturally occurring oxygen-containing heterocyclic compounds, which execute important biological functions in Nature. The curiosity in their chemistry remains unabated because of their usefulness as biologically active agents [1-3].

The 4 H-1-benzopyran-4-one ring systems is widely found in a number of natural products such as flavonoids. These natural products have demonstrated numerous biological activities such as antiviral, anti-inflammatory, antiallergic, antimutagenic and anticarcinogenic activities [4-9]. The 4H-1-benzopyran-4-one ring system s is extensively disseminated in nature in plant kingdom and forms a significant class of oxygen heterocycle. The most useful medical properties allied with this naturally befalling benzopyran-4-one have lead to the exploration of several synthetic analogues for such properties. This has resulted in a capacious work in this area.

Substituted benzopyrans have received considerable attention during last few decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. A Literature investigation shows that benzopyran derivatives retain different pharmacological and biological activities; which of most potent activity are anti-inflammatory and antibacterial activity.

Benzopyran derivatives have been shown to have very fascinating pharmacological activities, like antibacterial, anti-inflammatory and antifungal. When one biologically active molecule is linked to another, the resultant molecule generally has increased potency.

Hence in the present study, the two systems such as substituted benzopyrans and benzimidazole are fused to obtain highly potent, more specific anti-inflammatory and less toxic antibacterial agents.

MATERIALS AND METHODS

Melting points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. The purity of the compounds were checked by TLC on silica gel G plates using n-hexane, ethyl acetate (1:3) solvent system and U.V lamp used as a visualizing agent. IR spectra were recorded using KBr pellets on a Shemadzu 8000 series spectrophotometer. ^{1}H-NMR spectra on a Varian EM-200, advance 200 MHz spectrophotometer using DMSO as solvent and TMS as internal standard (chemical shift values expressed in ppm).

Experimental

The starting product 2-cyano methyl benzimidazole was synthesized from o-phenylene diamine and ethylcyanoacetate in single step. The benzimidazole derivatives further converted in to respective benzopyran derivative by treating with different aromatic phenols and benzaldehyde in presence of piperidine to afford 2-amino-3-benzimidazolyl benzopyran derivatives. The benzopyran derivative further converted in to cyclized compound i.e., in to benzopyranopyrimidine by condensing with different aromatic aldehydes in the presence of anhydrous $Zncl_2$ in alcohol medium by refluxing for 18-20 h. The synthesized compounds were characterized by TLC and Spectral data.

Preparation of 1H-benzimidazol-2-yl acetonitrile (I)

o-phenyl diamine (10.8 g, 0.1 mol) and ethyl cyano acetate (17 g, 0.15 mol) were placed in a round bottom flask fitted with a condenser and the mixture was refluxed for 1 h. Then the liquid was evaporated to small volume and cooled. The separated solid was filtered, washed with ether and dried. The product was recrystallized from ethanol. Thus the product obtained was light pink in colour. Melting point was 205 to 207 ^{o} C and the yield percentage was 75%.

Preparation of 2-amino-3-(1H-benzimidazol-2-yl)-4-phenyl-4H-chromen-7-ol (II)

1H-benzimidazol-2-yl acetonitrile (15.6 g, 0.1 mol), Benzaldehyde (10.6 g, 0.1 mol) and Resorcinol (11 g, 0.1 mol) in ethanol (80 ml) was treated with piperidine (1 ml) and stirred at room temperature for 1 h. Thus the solid separated was filtered, washed with ethanol and dried. The product was recrystalized from acetone. Thus the product obtained was light green colour. Melting point 222-224°C and percentage of yield was 82%.

Preparation of 9-hydroxy-5, 12-diphenyl-12H-benzopyrano [3,2-E] benzimidazolyl [1,5-C] pyrimidine (III a)

To a mixture of 2-amino-3-(1H-benzimidazol-2-yl)-4-phenyl-4H-chromen-7-ol (3.54 g, 0.01 mol) and Benzaldehyde (1.06 g, 0.01 mol) in 50 ml of ethanol 100 mg of anhydrous zinc chloride was added and refluxed for 18 to 20 h. The reaction mixture was poured in to crushed ice and the reaction mixture was kept in refrizirator for overnight. Then the separated solid was filtered and dried. The product was recrystallized from methanol, percentage of yield was 68%, melting point 206-208°C. The remaining compounds of this series from III b to III j were synthesized by using same procedure as described for IIIa (Table 1).

Table 1: Characteristic data of Benzopyran Derivatives (II and III a-j)

S. No.	Compound code	Mol. formula	Molecular Wt.	Solvent for crystallization (Yield %)	Melting point (°c)
1	II	$C_{22}H_{17}N_3O_2$	355	Aq.Acetone, (82%)	224-226°C
2	III a	$C_{29}H_{19}N_3O_2$	441	Ethanol, (68%)	205-207°C
3	III b	$C_{29}H_{18}ClN_3O_2$	475	Methanol, (66%)	194-196°C
4	III c	$C_{29}H_{18}ClN_3O_2$	475	Methanol, (67%)	196-198°C
5	III d	$C_{31}H_{24}N_4O_2$	484	Aq.Ethanol, (72%)	182-184°C
6	III e	$C_{29}H_{18}N_4O_4$	486	Ethanol, (60%)	178-180°C
7	III f	$C_{30}H_{21}N_3O_3$	471	Methanol, (71%)	188-190°C
8	III g	$C_{32}H_{25}N_3O_5$	531	Ethanol, (69%)	206-208°C
9	III h	$C_{29}H_{19}N_3O_3$	457	Ethanol, (71%)	209-211°C
10	III i	$C_{29}H_{19}N_3O_3$	457	Methanol, (69%)	211-213°C
11	III j	$C_{27}H_{17}N_3O_3$	431	Ethanol, (63%)	190-192°C

Preparation of 3-(1H-Benzimidazol-2-yl)-4-phenyl-4H-benzo (g) chromen-2-amine (IV)

1H-benzimidazol-2-yl acetonitrile (15.6 g, 0.1 mol), Benzaldehyde (10.6 g, 0.1 mol) and β -napthol (14.4 g, 0.1 mol) in ethanol (80 ml) was treated with piperidine (1 ml) and refluxed for 6 h. Thus the separated solid was filtered, washed with ethanol and dried. The product was obtained recrystalized with ethanol. The yield percentage was 76%, melting point 220-222°C (Table 2).

Preparation of 5, 14-diphenyl-14H-napthopyrano [3,2-E] benzimi- dazolyl [1,5-C] pyrimidine (Va)

To a mixture of 3-(1H-Benzimidazol-2-Yl)-4-Phenyl-4H-Benzo (g) Chromen-2-amine (3.89 g, 0.01 mol) and Benzaldehyde (1.06 g, 0.01 mol) in 50 ml of ethanol, 100 mg of anhydrous zinc chloride was added and then refluxed for 18-20 h. The reaction mixture was then poured in to crushed ice and the reaction mixture was kept in refrizirator for overnight. Then the separated solid was filtered and dried. The product was recrystallized from ethanol. The percentage of yield was 69% and melting point 215-217°C.
The remaining compounds of this series from Vb to Vj were synthesized by using same procedure as described for V a (Table 2).

Table 2: Characteristic data of benzopyran derivatives (IV and V a-j)

S. No.	Compound code	Mol. formula	Molecular Wt.	Solvent for crystallization (Yield %)	Melting point (c)
1	IV	$C_{26}H_{19}N_3O$	389	Ethanol, (76%)	220-222°C
2	V a	$C_{33}H_{21}N_3O$	475	Ethanol, (69%)	215-217°C
3	V b	$C_{33}H_{20}N_3OCl$	509	Ethanol, (66%)	204-206°C
4	V c	$C_{33}H_{20}N_3OCl$	509	Ethanol, (66%)	213-215°C
5	V d	$C_{35}H_{26}N_4O$	518	Ethanol, (72%)	192-194°C
6	V e	$C_{33}H_{20}N_4O_3$	520	Ethanol, (58%)	197-199°C
7	V f	$C_{34}H_{23}N_3O_2$	505	Ethanol, (70%)	199-201°C
8	Vg	$C_{36}H_{27}N_3O_4$	565	Ethanol, (71%)	205-207°C
9	V h	$C_{33}H_{21}N_3O_2$	491	Methanol, (64%)	214-216°C
10	V i	$C_{33}H_{21}N_3O_2$	491	Ethanol, (66%)	212-214°C
11	V j	$C_{31}H_{19}N_3O_2$	465	Ethanol, (61%)	202-204°C

INTERPRETATION

Compound III f

IR: 3579 cm^{-1} OH str, 3091 cm^{-1} CH str (Aromatic), 2904 cm^{-1} CH str (OCH_3), 1624 cm^{-1} C=N str, 1593 cm^{-1} C=C str, 1085 cm^{-1} C-O-C str.

NMR: 7.0-8.6 δ ppm for aromatic and aliphatic (17H), 12.5-12.8 δ ppm for H of OH, 3.8- 4.0 ppm for 3H of OCH_3 (Table 3).

Compound V d

IR: 2968 cm^{-1} CH str (Aromatic), 2902 cm^{-1} CH str N $(CH_3)_2$, 1643 cm^{-1} C=N str, 1573 cm^{-1} C=C str, 1083 cm^{-1} C-O-C str.

NMR: 7.0-8.6 δ ppm for 20H aromatic and Aliphatic, 2.6-3.1 δ ppm for 6H of N $(CH_3)_2$.

Antibacterial activity

Anti-bacterial activity is carried out by disc-diffusion method, using *Staphylococus aureus*, *Bacillus subtilis*, *Bacillus pumilis*, *Escherichia coli* and *Pseudomonous aeruginosa* organisms for antibacterial activity. The potency of the synthesized compounds was determined against standard drugs Gentamycin and Ampicillin by measuring the zone of inhibition (Table 4).

Table 3: Antibacterial activity of newly synthesized benzopyran derivatives

Sample Code	*Inhibition zone diameter in mm									
	Staphylococus aureus		*Bacillus subtilis*		*Bacillus pumilis*		*Escherichia coli*		*Pseudomonous aeruginosa*	
	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
III a	3	7	4	8	5	9	4	9	6	10
III b	7	11	8	14	6	13	12	14	8	12
III c	5	7	4	9	4	8	7	10	5	8
III d	7	16	7	17	7	15	11	17	7	15
III e	3	10	5	12	3	9	6	12	6	11
III f	8	19	8	18	9	18	12	20	11	22
III g	7	18	8	19	8	18	8	19	10	20
III h	8	17	7	17	8	16	8	17	9	18
III i	6	15	6	16	7	13	10	16	8	18
III j	2	8	5	11	4	9	-	8	-	-
Gentamycin	13	19	12	17	15	20	13	24	15	25
Ampicillin	15	23	14	24	13	23	14	22	14	23
DMF	-	-	-	-	-	-	-	-	-	-

*Average of triplicate ± Standard deviation

Note: '-'denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 above good

Table 4: Antibacterial activity of newly synthesized benzopyran derivatives

Sample code	*Inhibition zone diameter in mm									
	Staphylococus aureus		*Bacillus subtilis*		*Bacillus pumilis*		*Escherichia coli*		*Pseudomonous aeruginosa*	
	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
V a	-	-	5	11	3	10	5	12	-	-
V b	6	12	4	13	5	12	6	14	6	13
V c	5	10	5	10	5	9	4	10	7	11
V d	9	17	8	17	10	18	9	20	10	19
V e	5	12	5	13	7	15	6	13	6	14
V f	10	19	9	19	10	20	10	20	10	21
V g	8	16	7	17	11	20	10	20	9	18
V h	7	16	7	16	8	19	9	19	8	18
V i	6	15	5	15	7	17	6	18	7	16
V j	4	9	3	8	6	12	5	11	4	10
Gentamycin	13	19	12	17	15	20	13	24	15	25
Ampicillin	15	23	14	24	13	23	14	22	14	23
DMF	-	-	-	-	-	-	-	-	-	-

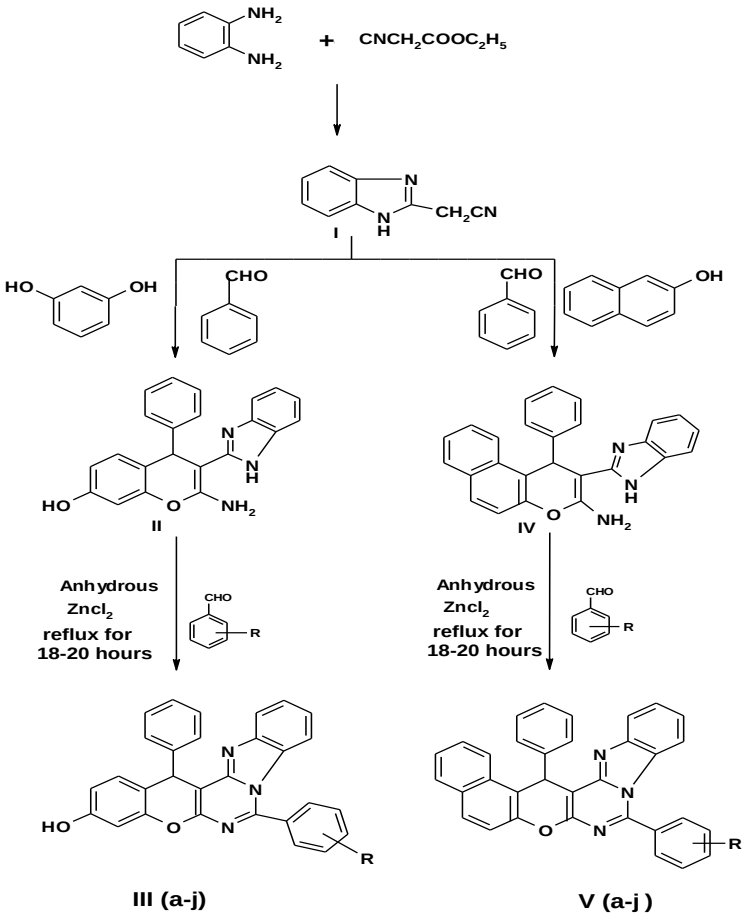
*Average of triplicate ± Standard deviation

Note: '-'denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 above good

RESULTS AND DISCUSSION

All the synthesized compounds III a-j and V a-j were screened for their antibacterial activity. The compounds III f and V f were found to possess good activity against both gram positive and gram-negative bacteria. While compounds IIIg, IIIh, IIIi, Vd, Vg, Vh and Vi were found to exhibit moderate activities. Among these various compounds III f, III g, V f and Vg were showed good activities.

From the anti-bacterial screening it was found that the compounds showed significant activity, some are moderate and equipotent to that of the standard employed for comparison. Hence these compounds appear to be promising anti-bacterial agents. Perhaps the presence of OCH_3 as a substituent on aromatic nucleus attached to 2nd position of pyrimidino pyran nucleus may be responsible for good anti-bacterial activity (Scheme 1).



Scheme 1: I, V- R=a=H, b=4- Cl, c=2- Cl, d=4- N $(CH_3)_2$, e=2- NO_2 f=2- OCH_3, g=3, 4, 5- OCH_3, h=2-OH, i=4-OH, j=Furfuryl

CONCLUSION

The three moieties, i.e., benzopyrans, benzimidazole and pyrimidino pyran moieties independently are antibacterial agents. Here when the three moieties are fused and screened for antibacterial studies they showed a broad spectrum of antibacterial activity. Benzopyran molecule is responsible for antibacterial activity, but it is interesting to note that benzimidazole moiety when fused with other moieties showed a good antibacterial activity.

The above results establish the fact that benzopyrans can be a rich source for exploitation. Therefore, in search of new generation of active compounds, it may be worthwhile to explore the possibility in this area by fusing and substituting different moieties and increase the potency.
Hence in the present study, the two systems such as pyrimidine substituted benzopyrans and benzimidazole are linked to each other and show highly potent, more and less toxic antibacterial agent. In this combination is expected to result in a significant increase in activity.

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