SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL BENZOPYRAN DERIVATIVES

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***ABSTRACT:** Heterocyclic compounds are the major class of organic substrates that contain at least two different types of atoms in the ring. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interesting compounds of benzopyran derivatives. Three new benzopyran derivatives 2a, 2b and 2c were synthesized and their physical characteristics like melting point and % of yield. In the anti-bacterial study, compounds 2a and 2c has significant anti-bacterial against both tested gram positive and gram-negative bacteria while other promising compounds mentioned earlier showed significant narrow spectrum activity. The different spectrum of activity by the test compounds against the tested microorganisms may be due to different substituents present in the substituted pyrazole nucleus.*

I. INTRODUCTION

1.1. Heterocycles in Medicinal Chemistry

Nowadays, the entire pharmaceutical industry is faced with the challenge of increasing productivity and innovation. The major hurdles are the increasing costs of research and development and a simultaneous stagnating number of new chemical entities (NCEs). The cause of this innovation deficit is definitively not the biology. Decoding of the human genome has led to a wealth of drug targets. With more than 30,000 human genes, the assumption is that at least 1,000 are significantly involved in the emergence and course of disease. Furthermore, because each of these genes is linked to the function of between five and ten proteins, the conclusion is that there might be 5,000–10,000 targets for new drugs[1]. Despite the successful introduction of protein therapeutics and the promise of gene therapy, major pharmaceutical companies are still focused on the discovery and development of low-molecular weight compounds. Hence, the challenge is to select the most drugable targets and to find the corresponding drug-like molecules, substances that not only interact with the target, but also have specific pharmacokinetic and toxicological properties, that allow them to be developed as a drug..It seems clear that selecting appropriate molecules to synthesize is one of the most troublesome questions. It has been estimated that the number of possible molecules with a molecular weight of less than 500 Da is 10^{200}, of which only 10^{60} may possess drug-like properties. The proportion of these drug-like molecules synthesized to date has been estimated as one part in 10^{57}, or roughly the ratio of the mass of one proton to the mass of the sun! The issue is therefore the selection of new molecules from this vast universe, which have the potential to be biologically active [3].

Heterocyclic compounds containing nitrogen (N), Oxygen (O) & sulphur(S) exhibits a wide range of biological activities. It is well documented that vast majority of Pyrazole[4-12], Quinazoline[13-20] and Pyrazoline[21-29] derivatives are known to possess pharmacologically proven therapeutic potentials. Novel and Efficient method of synthesis for Nitrogen containing heterocyclic molecule still represent highly pursued target for antimicrobial, antimarerial and other biological activities. A wide investigation or evolution, development of active analog and random discovery is a valuable and employed method for drug discovery.

The drug discovery process is aimed at discovering molecules that can be very rapidly developed into effective treatments to fulfill unmet medical needs. Though this process has become many folds faster as compared to that in the past due to advances in basic science and technology, delivering successful drugs still remain a daunting task. Traditionally, the effects of new drugs were characterized by the pharmacological actions in animal models or in isolated tissue or organ systems. Drug screening was based on the basic knowledge and understanding of biology, the disease symptomatology and the existing drugs used in therapy. Since pharmacological effects were characterized, this process of drug discovery was independent of the understanding of the etiology and pathophysiology of the disease or the mechanism of action of the compound. This was otherwise known as physiology-based drug discovery[30].

However, once hits or leads have been co-crystallized with their targets and exact binding conformations have been established, docking of analogues can be facilitated by the application of algorithms that model compound modification on pre-defined core fragments of leads. At the very least automated analogue design and evaluation makes it possible to quickly eliminate molecules that are too large or do not satisfy binding constraints and shifts focused towards more promising synthetic candidates. Combining docking and designing of analogue libraries

provides a particularly promising route to lead optimization[31].

Drug designing is a tedious process only fewer drugs can reach to the level of clinical applicability. Such compounds have to be given extensive trials before they are tried on human. This adds to the cost of research for new drugs. This means that if the development of new drugs is to remain economically feasible the ratio of output to input must be increased[32-33].

The affinity of the drug to a complementary-structurally unknown receptor drug designing is performed basing on either the structure of the drug structure-based drug design or basing on the receptor to which the drug may bind known as the receptor-based drug design. These techniques employ powerful computers molecular graphic and sophisticated software[34-35].

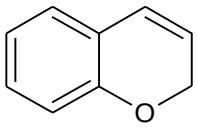
Hence this proposal will succeed in the discovery of new lead molecules. Which can held promise therapeutically in near future. This may endow them with different physical, pharmacological & chemotherapeutic properties. This nitrogen containing heterocyclic compounds played increasingly expanded role in chemotherapy. Despite of the widespread use of heterocyclic compound in medicine as a chemotherapeutic agent in last few decades but the recent evaluation still remains unabated.

It is earnestly believed that towards the beginning of new century (2001 AD) keeping in view the tremendous global technological competition, one is left with no other choice than to intertionalize research and development of pharmaceutical drugs to achieve the common objective "better drugs for a better world".

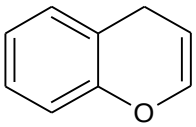
1.2. Introduction to benzopyran

Benzopyran is an polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring. According to current IUPAC nomenclature, the name chromene used in previous recommendations is retained; however, systematic 'benzo' names, for example 2*H*-1-benzopyran, are preferred IUPAC names for chromene, isochromene, chromane, isochromane, and their chalcogen analogues.[36] There are two isomers of benzopyran that vary by the orientation of the fusion of the two rings compared to the oxygen, resulting in 1-benzopyran (chromene) and 2-benzopyran (isochromene)—the number denotes where the oxygen atom is located by standard naphthalene-like nomenclature.

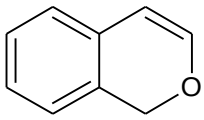
. Therefore, there are many structural isomers owing to the multiple possible positions of the oxygen atom and the tetrahedral carbon atom:



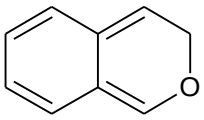
2H-chromene (2H-1-benzopyran)



4H-chromene (4H-1-benzopyran)



1H-isochromene (1H-2-benzopyran)



3*H*-isochromene (3*H*-2-benzopyran)

A search of chemical abstracts revealed the 2,2-Dimethyl- 2*H*benzopyran moiety to be present in more than 4000 compounds including natural products and designed structures.

The relatively high incidence of this benzopyran unit in natural products is partially attributable to the numerous prenylation and cyclization reactions in many polyketide biosynthesis pathways. Examining the characteristics of many biologically active, natural products like benzopyran compounds, reveals their diverse structural properties, and more importantly, their wide-ranging biological actions, suggesting that derivatives of the benzopyran motif may be capable of interacting with a variety of cellular targets. In addition, the fact that many of the structures are active in cell-based assays suggested that derivatives of the benzopyran unit remain sufficiently lipophilic to cross cell membranes, a key feature of any biologically relevant small molecule library [37- 39]

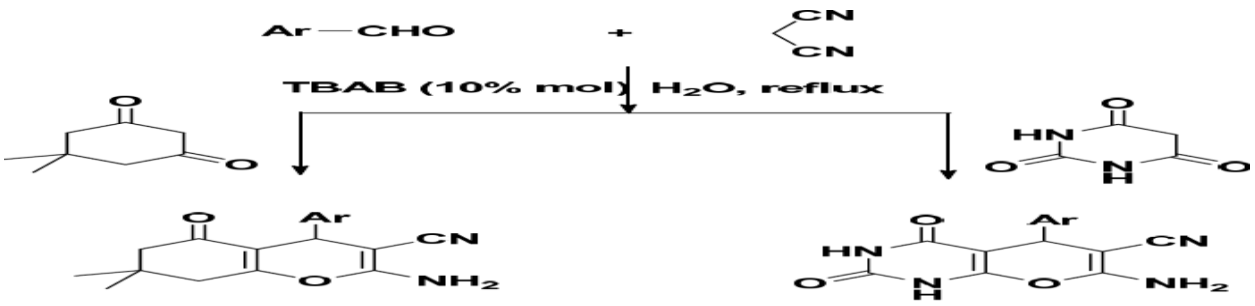
II. REVIEW OF LITERATURE

Benzopyran derivatives

4*H*-benzo[*b*]pyrans using TBAB as a catalyst

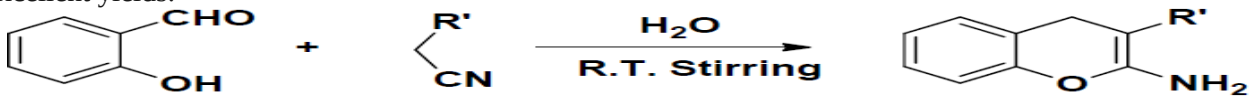
Fard *et al.* [40] reported a highly efficient procedure for the preparation of 4*H*-benzo[*b*]pyrans and pyrano[2,3-*d*]pyrimidinones via a domino Knoevenagelcyclo-condensation reaction using TBAB as a catalyst in water.

In a typical experimental procedure, a mixture of aromatic aldehyde, malononitrile, dimedone or barbituric acid in water under reflux condition, was stirred in the presence of a catalytic amount of TBAB (10 mol%) to afford the 4*H*-benzo[*b*]pyrans and pyrano[2,3- *d*] pyrimidinones.



2.1.2 Benzopyran using uncatalyzed aqueous media.

In aqueous media uncatalyzed reaction of o-hydroxy benzaldehyde with malenonitrial or ethylcyanoacetate, the first formed Knoevenagel condensation products underwent cyclization as a result of nucleophilic attack by the hydroxyl group on the cyano group. Thus 2-amino-2H-1-benzopyrane- 3-carbonitriale or carboxylate were formed in excellent yields.[41]



R'=CN, COOEt

Scheme 2.7

III. MATERIALS AND METHODS

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a Shimadzu-fourier transform infra-red **(FTIR)-8400 Spectrophotometer** using **KBr** disc. 1H NMR spectra were recorded on a **Bruker DPX-400 MHz** spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. The mass spectral data were obtained with a **SHIMADZU-GCMS-QC-2010.**

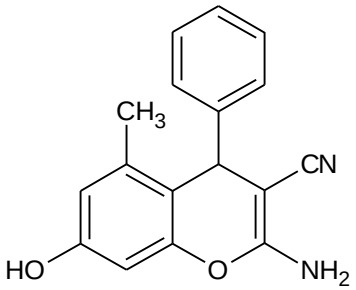
Synthesis of 2-(Substituted benzylidene) malononitrile.

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

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

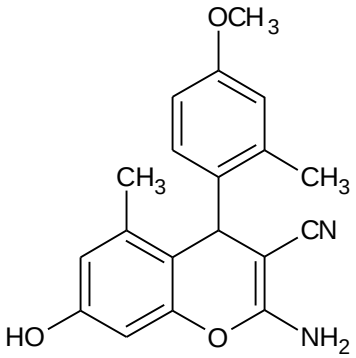
0.01 mole of 2-(Substituted benzylidene) malononitrile and 0.01 mole of 5-methyl resorcinol dissolve in absolute ethanol. Stirring the reaction mixture at room temperature, gradually added the anhydrous potassium carbonate and stirring the reaction mixture at room temperature for 5-6 hours. After completion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

2-amino-7-hydroxy-5-methyl-4-phenyl-4H-cromene-3-carbonitrile



Yield: 60%; MP: 205-2070C; MS: *m/z* 278;
Elemental Analysis for C17H14N2O2:
Calculated: C, 73.37; H, 5.07; N, 10.07; %.
Found: C, 73.27; H, 5.0; N, 10.01; %.

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



Yield: 70%; MP: 210-2120C; MS: *m/z* 308;
Elemental Analysis for C18H16N2O3:
Calculated: C, 70.12; H, 5.23; N, 9.09; %.
Found: C, 70.10; H, 5.21; N, 9.0; %.

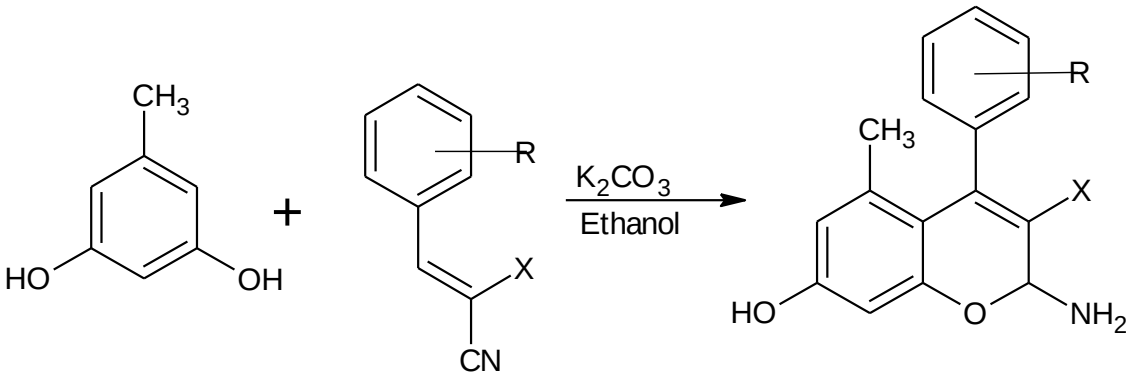
Synthesis of Ethyl-2-cyano-3-Substitutedphenylacrylate.

The product Ethyl-2-cyano-3-Substitutedphenylacrylate has been synthesized by the reaction of different substituted aldehyde and ethyl cyano acetate in presence of base (pipyridine).

General method for the Synthesis of Ethyl-2-amino-7-hydroxy-5-Methyl -4 (substituted phenyl)-4H-chromene-3-carboxylate.

0.01 mole of Ethyl-2-cyano-3-Substitutedphenylacrylate 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 8-10 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.

SCHEME



X= CN, COOEt

IV. RESULTS AND DISCUSSION

Compound 2-amino-7-hydroxy-5-methyl-4-phenyl-4H-cromene-3-carbonitrile

IR (cm^{-1}): 3630 (O-H stretching of free primary alcohol), 3585, 3321 & 3298, (N-H stretching of free primary amine), 3146 (C-H stretching vibration of aromatic region), 2200 (C≡N stretching of the nitrile group), 1651 (N-H deformation, in plane bending of N-H), 1508-1350 (O-H in plane bending), 1350 (C-N stretching for carbon bonded to amino group), 997 (C-H in plane bending of phenyl ring), 671 (C-H out of plane bending for 1,3-disubstituted phenyl nucleus)

^{1}H NMR (DMSO-d_6) δ ppm: 6.25 (s, 2H, H1), 4.57 (s, 1H, H2), 7.25 (s, 1H, H3 *J*=3.2 Hz), 7.32 (d, 1H, H4, *J*=9.2 Hz), 7.15-7.20 (m, 2H, H5 & H6, *JH5*=8 Hz, *JH6=7.2 Hz*), 6.72 (d, 1H, H7, *J*= 8.4 Hz.), 6.48-6.51 (d, 1H, H8, *J*= 10.8 Hz), 6.46 (s, 1H, H9, *J*=2.4 Hz.), 9.41 (s, 1H, H10)

MS: *m/z:* 278.00; Elemental Analysis for $C_{17}H_{14}N_2O_2$: Calculated: C, 73.37; H, 5.07; N, 10.07;%. Found: C, 73.27; H, 5.0; N, 10.01; %.

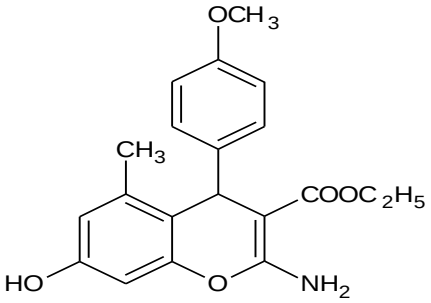
Compound 2-amino-7-hydroxy-4-(4-methoxyphenyl)-5-methyl-4Hcromene- 3-carbonitrile

IR (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 (DMSO-d_6) δ ppm: 1.89 (3H, Singlet, -CH3(a)), 3.7 (3H, Singlet, -OCH3(b)), 4.46 (1H Singlet, -H(c)), 6.32 (1H, Singlet, Ar-H(d)), 6.37 (1H, Singlet, Ar-H(e)), 6.72 (2H, Singlet, -NH2(f)), 6.82-6.84 (2H, Doublet, Ar-H(g,g')), 6.93-6.96 (2H, Doublet, Ar-H(h,h')), 9.59 (1H, Singlet, -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 Ethyl-2-amino-7-hydroxy-4-(4-methoxyphenyl)-5-methyl-4Hchromene- 3-carboxylate



Yield: 60%; MP: 166-1680C; MS: *m/z* 355;

Elemental Analysis for C20H21NO5:

Calculated: C, 67.59; H, 5.96; N, 3.94; %.

Found: C, 67.54; H, 5.96; N, 3.91; %.

IR (cm^{-1}): 3414 (O-H Stretching of primary alcohol), 3298 (N-H Stretching of primary amine), 2972 (C-H Stretching of aromatic ring), 1660 (C=O Stretching frequency of ester), 1618 (N-H deformation of NH_2 group), 1512 (O-H in plane bending), 1462 (C=C Stretching of aromatic ring), 1311 (C-N Stretching of carbon bonded to amine), 1245 (C-O-C asymmetrical stretching for ethers), 1145 (C-O-C symmetrical stretching OCH3 group), 1069 (C-H in plane bending of phenyl ring), 842 (Out of plane bending for disubstituted aromatic ring)

^{1}H NMR (DMSO-d_6) δ ppm: 1.17-1.22 (3H, Triplet, -CH2CH3(a)), 1.99 (3H, Singlet, -CH3(b)), 3.66 (3H, Singlet, -OCH3(c)), 3.99-4.04 (2H, Quartet, -CH2(d)CH3), 4.70 (1H, Singlet, -H(e)), 6.35 (2H, Singlet, Ar-H(f,f')), 6.74-6.76 (2H, Doublet, Ar-H(g,g')), 6.97-6.99 (2H, Doublet, Ar-H(h,h'))**,** 7.44 (2H, Singlet, -NH2(i)), 9.49 (1H, Singlet, -OH(j))

MS: *m/z* 355; Elemental Analysis for C20H21NO5: Calculated: C, 67.59; H, 5.96; N, 3.94; %. Found: C, 67.54; H, 5.96; N, 3.91; %.

Antibacterial and antifungal activity of synthesized compounds

Code	**Antibacterial Activity**				**Antifungal Activity**		
	Minimal Bactericidal Concentration µg/ml				**Minimal Fungicidal Concentration µg/ml**		
	Gram +ve Bacteria		**Gram –ve Bacteria**				
	S.a.	**S.p.**	**E.c.**	**P.a.**	**C.a.**	**A.n.**	**A.c.**
2a	**200**	**500**	**62.5**	**500**	**1000**	**500**	**500**
2b	**100**	**200**	**500**	**500**	**250**	**1000**	**1000**
2c	**500**	**100**	**62.5**	**100**	**500**	**500**	**1000**

Minimal Inhibition Concentration

Standard Drugs	**S.aureus**	**S.pyogenus**	**E.coli**	**P.aeruginosa**
	(microgramme/ml)			
Ampicillin	**250**	**100**	**100**	**100**
Chloramphenicol	**50**	**50**	**50**	**50**
Ciprofloxacin	**50**	**50**	**25**	**25**
Norfloxacin	**10**	**10**	**10**	**10**

Minimal Fungicidal Concentration

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		

Nystatin	100	100	100
Greseofulvin	500	100	100

Three new benzopyran derivatives 2a, 2b and 2c were synthesized and their physical charecteristics like melting point and % of yield was presented in table 1. The synthesized compounds were studied for spectral analysis which was discussed in experimental section. All the newly synthesized benzopyran analogous were screened for their antimicrobial activity and the result was shown in table 2 in experimental section.

All the newly synthesized compounds (**2a, 2b & 2c**) series were screened for their antimicrobial activity in-vitro at the doses of 100 µg in 0.1ml of DMF on *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Pseudomonas aeruginosa* and three fungal strains *Candida albicans*, *Aspergillus Niger*, *Aspergillus clavatus* The results cited in Table 2 represents that many compounds registered mild to moderate to strong antibacterial activity against the tested microorganisms while some compounds does not showed any activity. The Compounds **2a**, **2b** and **2c** showed the marked zone of inhibition between **24, 14 and 27mm** against S. aureus while standard drug Ampicillin registered **27mm**. Similarly, compound nos. **2a, 2b** and **2c** registered zone of inhibition between **21, 12** and **23mm** against B. subtilis while the standard drug exhibited **24mm**. The most promising compounds among all the synthesized compounds showing a maximum zone of inhibition are **2c (27mm)** against *S. aureus* and for *B. subtilis*, the compounds are **2c (23mm).**

In case of Gram-negative bacteria, compound nos. **2a** and **2c** possess zone of inhibition **25** and **28**mm while the standard drug Ampicillin registered **22mm** against E. coli. Compounds **2b** shows **18mm** towards E. coli. Similarly, compound **2a** and **2c** showed zone of inhibition between **26 to 31mm**, at the same time the standard drug resulted zone of inhibition of **20mm** against P.aeruginosa. Compounds 2**b** shows **14 mm** towards P.aeruginosa. The most promising compounds against gram-negative bacteria are **2a** and **2c** against E. coli and against P. aeruginosa.

In the anti-bacterial study, compounds **2a** and **2c** has significant anti-bacterial against both tested gram positive and gram-negative bacteria while other promising compounds mentioned earlier showed significant narrow spectrum activity. The different spectrum of activity by the test compounds against the tested microorganisms may be due to different substituents present in the substituted pyrazole nucleus. The experiment was performed in triplicate in order to minimize the errors and results are presented in Table 2.

In the study of antibacterial activity, the synthesized had shown comparatively better activity against tested bacteria. The difference spectrum of activity against bacteria may be due to chemical modification of test compounds which relate to the Structure Activity Relationship (SAR).

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