SYNTHESIS AND BIOLOGICAL EVALUATION OF SCHIFF BASE DERIVATIVES OF FURFURAL BASED HETEROCYCLIC FLAVONES

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Abstract - Synthesized a total of twelve new furfural flavone Schiff base derivatives starting from commercially available phloroglucinol. In the first stage the corresponding acetophenone key intermediate was synthesized from the starting material and was condensed with furfural followed by cyclisation, and formylation. Finally, the formylated flavone was condensed with various aromatic primary amines to obtain the desired Schiff base derivatives. All the synthesized furfural flavone Schiff base derivatives were tested for their anticancer and antibacterial activities and the results were analysed in the light of their structural activity.

Index Terms - Furfuralflavone, Aromatic Amines, Schiff Bases, Antibacterial Activity.

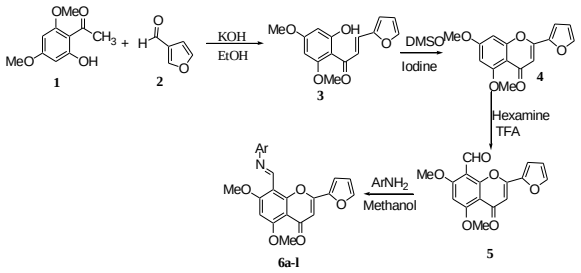
I. INTRODUCTION

Flavone scaffold is an important structure found in many pharmaceutically active compounds with γ-pyrone ring fused with benzene and attached to an aryl ring at 2nd position with good bio importance [1]. They have been classified as neutraceuticals and are found in broad range of plant species including mango, kaju, custard apple, green tea, grapes etc [2-4]. They show wide range of biological activities such as antiviral, anticancer, anti-inflammatory, antibacterial and antioxidant properties [5-15]. In the present study we wish to report structurally diverse flavones-schiff base derivatives consisting of 5-membered heterocyclic ring furan attached to γ-pyrone at 2nd position instead of aryl ring and a Schiff base unit on the fused aromatic system at 8th position (**Scheme 1**), as the heterocyclic system is known for significant biological activity.

II. MATERIALS AND METHODS

Acetophenone and other chemicals used were of AR grade (Merck). Melting points were taken in open glass capillary by using Remi melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Brucker 400 MHz and ^{13}C NMR was on Brucker 100 MHzspectrophotometers. Mass spectra recorded on LC-MS Agilent LC-1100 series.

The targeted compounds were synthesized starting from 2-hydroxy-4,6-dimethoxy acetophenone (**1**) which was obtained from phloroglucinol by known methods. The acetophenone (**1**) was condensed with furfural aldehyde (**2**) in the presence of potassium hydroxide in ethanol solvent at room temperature to produce corresponding chalcone (**3**) with good yield. The cyclisation of chalcones was carried out in dimethyl sulphoxide and catalytic amount of iodine at 70 ºC yielded corresponding flavone (**4**) and was formylated at 8th position of ring with hexamine in TFA to yield **5**. The formylated flavone (**5**) was then condensed with different aromatic amines in methanol at reflux temperatures to yield flavone Schiff base derivatives (**6**) (**Scheme-1**).



6a: o-NO_2, p-Cl; **6b:** p-NO_2; **6c:** m,p-tri-F; **6d:** p-F; **6e:** p-CH_3CO-; **6f:** p-Cl; **6g:** o,p-di-Cl; **6h:** o-CF_3, p-Br, **6i:** o-di-Cl; **6j:** o-OMe, m-Nitro, **6k:** o-di-F; **6l:** Ph

Scheme-1: Synthesis of Schiff base derivatives of furfural flavones

III. RESULTS AND DISCUSSION

Synthesized a total of twelve new furfural flavone Schiff base derivatives (**6a-l**) with good yields (65-85%) from 2-hydroxy-4,6-dimethoxy acetophenone (**1**). In the first stage the acetophenone was condensed with furfural aldehyde followed by cyclisation, and formylation. Finally, the formylated flavone was condensed with various aromatic primary amines to obtain the desired Schiff base derivatives. All the synthesized compounds were confirmed by their ^{1}H NMR, ^{13}C NMR and mass spectral data. Further, the synthesized compounds were also screened for their antibacterial activity by well diffision method on three Gram positive and three Gram negative organisms. The results of the study were provided in the following table 1 and the results were analyzed in the light of their structural activity.

Sample	Zone of inhibition in mm					
	Escherichia coli	Pseudomonas aeruginosaMT	Proteus vulgaris	Bacillus megateriumMTCC 428	Streptococcus muta	Staphylococcus aureu

	MTCC 1687	**MTCC 1688**	**MTCC 426**		**nsMTCC 497**	**sMTCC 737**
Furfuralflavone Schiff base derivatives						
6a	5.00 ±1.00	4.33±0.57	4.33 ±0.57	**5.33±0.57**	2.00± 0.00	0.00±0.00
6b	2.33 ±0.57	**6.33±0.57**	**6.00 ±1.00**	2.00±0.00	2.00± 0.00	0.00±0.00
6c	4.20 ±0.57	**5.23±1.00**	**6.20 ±0.57**	3.15±0.57	2.00± 0.00	0.00±0.00
6d	3.33 ±0.57	**6.33±0.57**	**7.00 ±1.00**	2.33±0.57	2.00± 0.00	**5.33±0.57**
6e	5.52 ±0.00	4.35±1.00	3.00 ±0.57	3.10±0.57	2.20± 0.57	0.00±0.00
6f	4.33 ±0.57	**6.00±1.00**	**5.66 ±0.57**	3.42±0.57	2.00± 0.00	0.00±0.00
6g	3.33 ±0.57	3.33±0.57	3.00 ±0.00	2.33±0.57	2.33± 0.57	0.00±0.00
6h	2.20 ±1.00	3.30±0.57	3..80±0.00	4.70±0.57	2.43± 0.57	0.00±0.00
6i	2.00 ±0.00	**7.00±1.00**	4.33 ±0.57	2.33±0.57	2.00± 0.00	0.00±0.00
6j	4.35 ±0.57	2.35±1.00	4.00 ±0.00	2.33±0.57	2.40± 0.57	0.00±0.00
6k	4.60 ±1.00	**5.10±0.57**	2.42 ±0.57	3.52±0.57	3.00± 0.00	0.00±0.00
6l	3.80 ±1.00	4.13±0.57	3.50 ±0.57	3.85±0.57	3.40± 0.00	0.00±0.00
Streptomycin	**8.00 ±0.00**	**7.00±0.00**	**7.00 ±0.00**	**7.00±0.00**	**8.00± 0.00**	**6.00±0.00**

Table 1: Antibacterial activity results of Schiff base derivatives of furfural flavones

The results revealed that some of the compounds were showed good to excellent antibacterial activity. Especially the compound with **6d** with p-fluoro substitution showed potent activity against Pseudomonas aeruginosa, Proteus vulgaris and Staphylococcus aureus compared with standard Streptomycin. The compound with **6i** with o-di-chlorosubstitution was found to be more prominent against Pseudomonas aeruginosa compared to standard. Further, the compound **6b** with p-nitro substitution and **6c** with m,p-tri-fluoro substitutions also showed significant activities against Pseudomonas aeruginosa, and Proteus vulgaris. The results of these studies clearly revealed that the new structurally diverse Schiff base derivatives of furfural heterocyclic flavones generated a new array for potential antibacterial compounds. The scope of this work includes other heterocyclic flavones such as thiophene , indole, etc flavones Schiff base for potential biological activities.

CONCLUSION

In the present study we wish to report structurally diverse flavones consisting of 5-membered heterocyclic ring furan attached to γ-pyrone at 2nd position instead of aryl ring and a Schiff base unit at fused aromatic system, as the heterocyclic system is known for significant biological activity.

ACKNOWLEDGMENTS

The authors are thankful to Laila Impex R & D centre, Vijayawada, India and Acharya Nagarjuna University, India for support and encouragement.

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