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Microwave-Assisted Synthesis and Biological Activities of Some Chromene Derivatives

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Abstract: ***A series of 4H-chromene derivatives were synthesized under microwave irradiation, a comparative study was done depending upon yield and time. The present study reveals the synthesis of chromene derivative in which pyrazine-2-ol was reacted with chloroethylacetate in presence of K_2CO_3 to form an intermediate which was further treated with hydrazine hydrate to form hydrazino derivative of pyrazine-2-ol and finally the intermediate is condensed by substituted chromene derivatives to form final compound conventionally as well as by using microwave irradiation technique. The synthesized compounds were then characterized by using FT-IR, ^{1}H-NMR and Mass spectrophotometer. All the compounds were screened for their anti-microbial activity, anti-oxidant and anti-inflammatory activity. It was found that the derivatives showed moderate activity as compared to standard.***

Keywords: Microwave assisted synthesis, Chromene, Anti-bacterial activity, Anti-inflammatory activity**.**

1. Introduction

Chromene is a heterocyclic ring system consisting of a benzene ring fused to a pyran ring. Chromene constitute the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins (Qiao Ren *et.al.,* 2011). It is known that certain natural and synthetic chromene derivatives possess important biological activities such as antimicrobial (Chetan BS *et.al.,* 2012), antioxidant (Milan M *et.al.,* 201), antifungal (Suresh T *et.al.,* 2010), anti-inflammatory (Nitin K *et.al.,* 2012) activity. Since varying substituent's is a common method for drug design in medicinal chemistry and a useful medical value of substituted thiourea derivatives containing pyrazine moiety, we aimed to synthesize new pyrazine derivatives and to investigate their antimicrobial and anti inflammatory activities.

2. Material and Method

All raw materials used in the synthesis have been obtained from M/S Fluka AG (Bachs, Switzerland) and M/S Sigma-Aldrich chemicals and Co. Inc. (Milwoukee, WI,USA). Melting points were recorded on a Thermonik Melting point Apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. IR spectra were recorded on a IR-Affinity, Shimadzu using DRS system. ^{1}H-NMR spectra have been recorded on a JEOL AL-400 FT-NMR spectrometer (400 MHz, JEOL Ltd., Tokyo, Japan), using TMS as internal standard in solvent DMSO. Mass data have been recorded on Agilent GC-MS Elemental analysis has been carried out on a C, H, and N Elemental Analyzer (Thermo-Finnigan Flash EA 1112, Italy) GC-MS is carried on GC7890 MS 200 of Agilent, Microwave oven for synthesis Monowave 300 Anton Parr.

3. Experimental

3.1 Synthesis of ethyl (pyrazin-2-yloxy)acetate (Compound 2)

Pyrazin-2-ol (0.01 mol) and K_2CO_3 (0.01 mol) was dissolved in acetone stirred for 30 mins. Reflux the reaction mixture leading to formation of potassium salt of pyrazin-2-ol. After salt formation ethyl chloroacetate (0.012 mol) was added drop wise. Reflux the reaction mixture till completion of reaction. Reaction monitoring was done by TLC. Product was isolated in cold water. Aqueous layer was extracted with10 mL Diethyl ether for three times to extract product.

3.2 Synthesis of 2-(pyrazin-2- yloxy)acetohydrazide (Compound 3)

Compound 2 (0.01 mol) was dissolved in ethyl alcohol, reflux the reaction mixture till it forms clear solution. To this clear solution previously prepared mixture of Hydrazine hydrate and HCl (0.01mol) was added and reflux the reaction mixture for 8-10 hrs leading to completion of product. Reaction was monitoring by TLC. After completion of reaction keep the reaction mixture on standing for overnight, needle shaped crystal formed. Filter the product and wash with water till pH 7-8. Recrystallized the product with Ethyl alcohol.

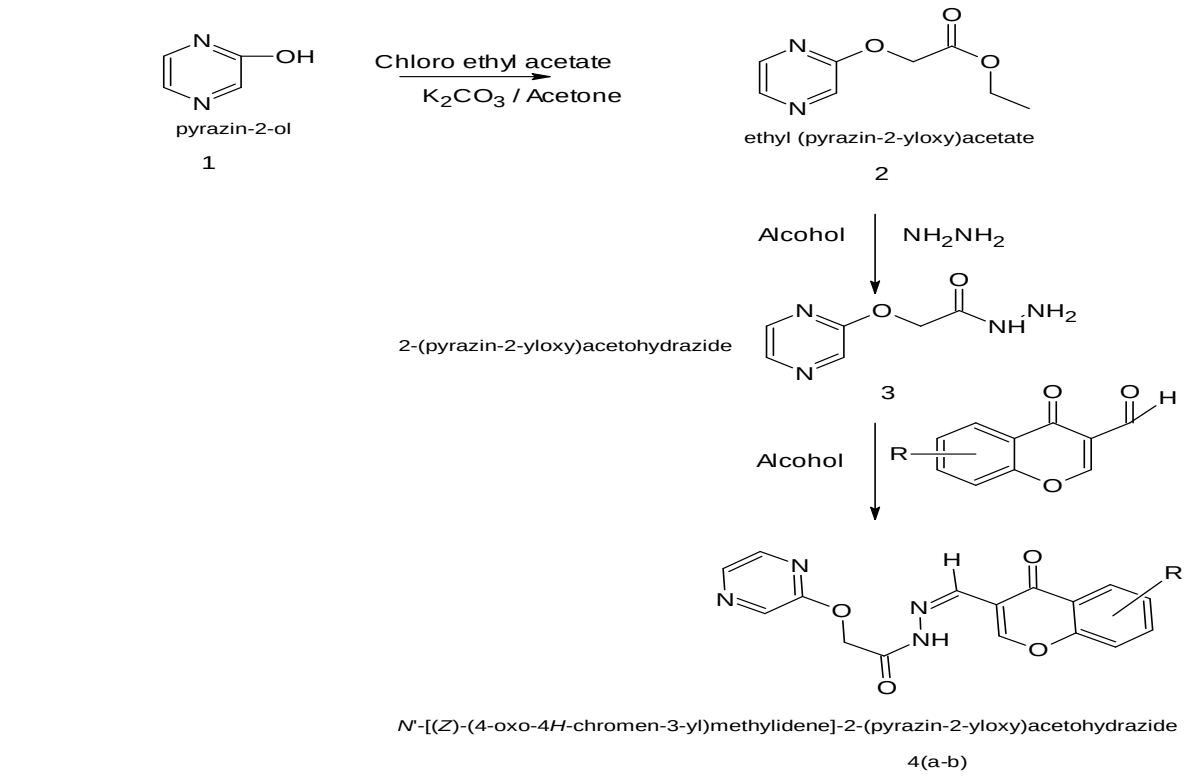
3.3 Synthesis of N'-[(Z)-(4-oxo-4H-chromen-3-yl) methylidene]-2-(pyrazin-2-yloxy)acetohydrazide (Compound 4a)

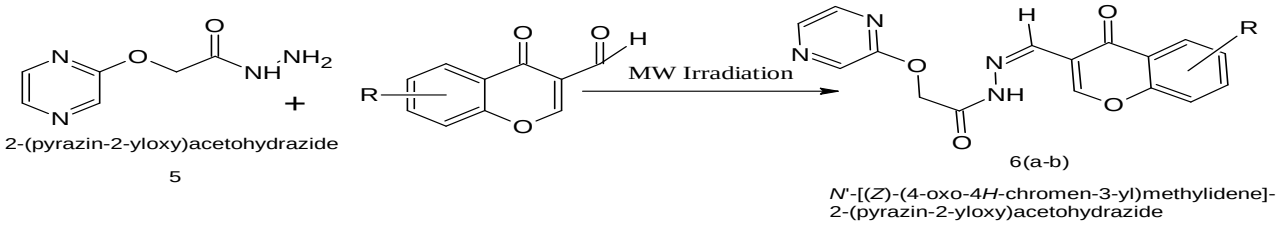
Conventional method

Compound 3 (0.01mol)was dissolved in alcohol. To this solution glacial acetic acid was added followed by addition of 4-oxo-4H-chromene-3yl (0.01mol) Refluxed the reaction mixture for 6-8 hrs. Completion of reaction was monitored by TLC. The crude product was cooled to room temperature, pour the reaction mixture to ice cold water, product was obtained. Filtered the product; wash with water. Recrystallized the product with Ethyl alcohol

Microwave Method

Compound 5 (0.01mol) was dissolved in DMF. To this solution glacial acetic acid was added followed by addition of 4-oxo-4H-chromene-3yl (0.01mol). The reaction mixture was irradiated for 210seconds. The crude product was cooled to room temperature, pour the reaction mixture to ice cold water, product was obtained. Filtered the product; wash with water. Recrystallized the product with Ethyl alcohol





4. Tables

Table 1: Characterization Table

Code	*^{1}H NMR (400 MHz, DMSO-δ6) δ (ppm)*	*IR (KBr) cm^{-1}*	*MS (m/z)*
2	5.6 (s, 2H), 2.3(q, 2H), 3.8(t, 3H) 7.11-8.28 (m, 3H, Ar-H)	1210(C-O), 1724 (C=O), 3456 (-N=)	182[M^+]($C_8H_{10}N_2O_3^+$), 138($C_6H_6N_2O_2$)
3	5.4 (s, 2H), 6.1(s, 1H), 9.2(s, 2H), 7.12-8.48 (m, 3H, Ar-H)	3345(-N=), 3434 (-NH), 1212 (C-O)	200 [M^+] ($C_6H_8N_4O_2^+$) 169 ($C_6H_5N_2O_2$)
4a	5.23 (s, 2H), 6.82(s,1H), 2.2 (s,1H), 7.29-8.27 (m, 7H, Ar-H)	3642(-N=), 3215 (-NH), 1212 (-CO), 2212, (-C=C	308 [M^+] ($C_{16}H_{12}N_4O_4^+$) , 162 ($C_7H_5N_4O_2$)
4b	1.5(s,1H), 4.12 (s,1H), 2.8 (s,3H), 7.28-8.16(m, 13H, Ar-H)	1232(C-O), 1827(C=O), 3458 (-NH).	338 [M^+] ($C_{17}H_{14}N_4O_4^+$) 308($C_{16}H_{12}N_4O_4$)

Table 2: Comparison table for conventional and microwave technique

Comp.	*Conventional*		*Microwave*		*Melting Point*
	Time in (Hours)	Yield in (%)	Time in (Seconds)	Yield in (%)	(in ^{0}C) M.P/B.P
4a	6	74	210	94	232
4b	9	65	209	85	244

Table 3: Anti-Bacterial activity of synthesized compounds

Code	R	*Anti-Microbial Activity (µg/ml) [MIC]*				
		Bacterial strains				
		E. coli	*S. typhi*	*P. aeroginosa*	*Kleb pneumoniae*	*Vibrio chlorae*
4a	H	NA	200	NA	100	100
4b	CH_3	200	200	NA	200	50

Table 4: Anti-fungal activity of synthesized compounds

Code	R	Anti-Microbial Activity (µg/ml) [MIC]	
		Fungal strains	
		C. albican	*A. Niger*
4a	H	200	100
4b	CH_3	100	50

- Ampicillin (MIC-0.04 µg/ml) used as standard against *S. aureus, Kleb pneumonia, Vibrio chlorae*

- Trimethoprim (MIC 0.01 µg/ml) used as standard against *S. typhi, P. aeroginosa*
- Miconazole (MIC 6.25 µg/ml) as standard against *C. albicans* and *A. niger*

Table 5: Anti-oxidant activity & Anti-inflammatory activity of synthesized compounds

Code	*R*	*Anti-oxidant*	*Anti-inflammatory*
		IC_{50}±*SD*	IC_{50}±*SD*
4a	H	12.00±2.64	18.32±1.09
4b	$-CH_3$	13.21±0.99	16.54±0.65
std		8.25±0.336	11.70±0.987

- Standard for Anti-oxidant Butyrated Hydrogen Toulene (BHT)
- Standard for Anti-Inflammatory Sodium Diclofenac

5. Result and Discussion

Compound 6a has shown yield of 94% when synthesized by using microwave-technique where as conventional method has produced yield of 74%, same in case for 6b yield from conventional method is low as 65% than in microwave technique with 85%

Synthesized compound were screened for anti-microbial activity by tube dilution method. The compound was tested on Bacterial stains *E. coli, S. typhi, P. aeroginosa, Kleb Pneumoniae, Vibrio chlorae and* Fungal Stains *C. Albicans, A. niger* . The activity was then monitored for 24-48 hours and the data is presented in the Table 3 and 4. The compounds showed mild to moderate anti-microbial activity. Compound 6a has shown low activity for all the microbial stains but the compound 6b has shown moderate activity for *Vibrio chlorae*, while the compound has not shown much activity for other bacterial and fungal stains.

In Free Radical scavenging activity done by DPPH method, standard drug BHT shows IC_{50} at 8.25µg/mL. All synthesized compounds compared with standard, we observed that comp. 6a and 6b has comparatively same activity as compared with standard.

In Anti-inflammatory activity done by HRBC membrane stabilization method, standard drug shows IC_{50} at 11.70µg/mL. Compound 6a shows IC_{50} 16.54µg/mL which when compared with the other synthesized compound showed maximum activity but moderately as compared with standard.

6. Conclusion

The microwave method was found to be better than conventional method in terms of reaction time, yield and relatively simple method to perform synthesis. The series of derivatives of chromenone were synthesized and evaluated for anti-microbial activity. Among which both compound showed moderate activity towards specific bacteria. In anti oxidant and in Anti Inflammatory activity study both substituent was found to have moderate activity as compared with standard.

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