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# Microwave assisted efficient synthesis of Coumarin derivatives

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## Abstract:

Intermediate 5-Hydroxy-8H-1-oxa-8–aza-anthracene-2,7-dione was prepared by environmentally benign microwave assisted method from easily available cheap raw material 4-methyl amino coumarin and malonic acid with catalytic amount of phosphorus oxychloride. From this same intermediate 4,11-dimethyl -6H-1,8-dioxa -6–aza-benzo [a] anthracene-2,5,9-trione was synthesized by using ethyl acito acetate and 11-methyl-6H-8,13-dioxa-6-aza-pyrano benzo [b] anthracene-5,9,14-trione pyrazine was synthesized by using methyl salicylate and catalytic amount of pyridine. Environmentally benign microwave assisted method provides high yield product with quality nature which is convenient to isolation.

**Key Words:** Microwave, Malonic acid, Pyrazine.

## Introduction:

Synthesis of new chemical entities is major bottleneck in drug discovery. Conventional methods for various chemical syntheses is very well documented and practiced. The methods for synthesis (Heating process) of organic compounds has continuously modified from the decade.

Microwave Assisted Organic Synthesis (MAOS), which has developed in recent years, has been considered superior to traditional heating. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. Now day's technique is considered as an important approach toward green chemistry as this technique is more environmentally friendly. Many modern pharmaceuticals are totally synthetic compounds and a large proportion of these are heterocyclic. Among various types of heterocyclic compounds used as drugs, a large number of them are 5 or 6 member's heterocyclic compounds having 1 to 3 hetero atoms in them. Work is done is todevelop potential therapeutic agents and studying their chemistry

## Theoretical:

Coumarin chemistry has become more important since many years, which is documented by thousands of papers and patent on coumarins. This is mainly because of the discovery of the varied biochemical properties [1], industrial uses and analytical application of coumarins. Moreover coumarin moiety is widely distributed in nature and many of the natural products containing this sub unit has showed useful and diverse biological activities such as antifungal [2], anticoagulant [3], carcinogens [4], antibacterial [5], insecticidal [6]. Coumarin reported to

possess biological activity are used in treatment of vitilago psoriasis [7] and other dermal [8]. In recent times it has been extensively used as laser material [9],photosensitizers[10], brighte[11], as intermediate for dyes [12], pesticides and pharmaceutical [13], as well as in perfu formulation [14], in enzymology of biological probes [15]. Many synthetic 4-hydroxy coumari derivatives are reputed as anticoagulant drug [16]. Recognition of 4-hydroxy coumarin unit as its blood anticoagulant activity lead to hectic research on 4-hydroxy coumarin and immediate outcome of it was the introduction of many synthetic 4-hydroxy coumarin derivatives such as Dicoumarol [17], Warfarin, Coumachlar [18], Cyclocoumarol etc. blood anticoagulant within a very short time.

3-Substituted 4-hydroxy coumarin has been reported as HIV protease inhibitors [19] and antiviral agents [20] with high therapeutic index. They are also found to exhibit biological activities such as anticoagulant [21], antibacterial [22], antifungal [23], insecticides [24], estrogenic[25], plant metabolite [16,17], blastcholine effect [18], narcotics and sedatives action [26,27] etc.

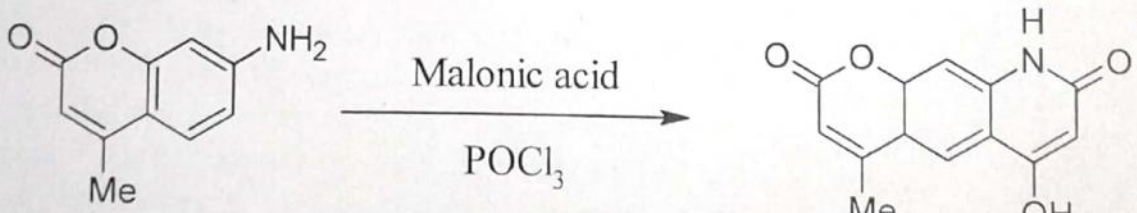
The biological activity of coumarin and its derivatives inspired us to synthesize various heterocyclic compounds derivatives of it.

## Materials and Methods:

All reagents used were obtained from Sigma Aldrich, and are chemically pure or analytical reagent grade. The liquid aldehyde was purified by distillation and purity of solid organic compounds was checked by TLC.Infrared spectra of samples measured in KBr pellets on a Perkin Elmar Version 10.03.07. NMR Spectra were obtained from 300MHz NMR Spectrometer. The purity confirmation and reaction monitoring by TLC on silica gel plates prepared on glass slides.

**1. Synthesis of (2a-d) 5-Hydroxy -8H-1-oxa -8–aza-anthracene - 2, 7-dione.**

Mixture of 4-methyl amino coumarin (0.001 mole) phosphorus oxychlorides (15 ml) and malonic acid (0.001 mole) refluxed in synthetic microwave oven with condenser at intensity of 20% (210W) for 7 min. The mixture was then cooled and basified with NaOH to $P_H$ - 9 and filtered. The filtrate was acidified with conc. HCl to $P_H$ -2.




**2. Synthesis of (3a-d) : 4,11-dimethyl -6H-1,8-dioxa -6–aza-benzo [a] anthracene-2,5,9-trione.**

Mixture of (2a-d) and ethyl acitoacetate was refluxed in synthetic microwave oven with condenser at intensity of 20% (210W) for 7 min. The mixture was then cooled and poured into ice cold water.

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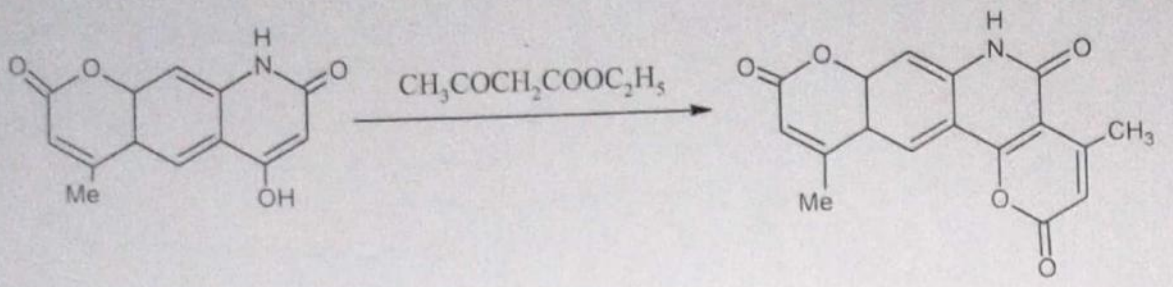
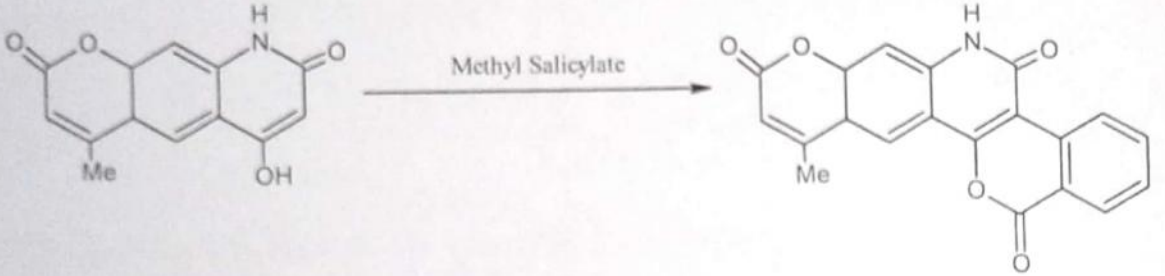



**3. Synthesis of (4a-d) : 11-methyl -6H-8,13-dioxa -6–aza- pyrano benzo [b] anthracene-5,9,14-trione pyrazine.**

Mixture of 2a-d (0.001 mole), catalytic amount of pyridine (0.5 mole) and methyl salicylate (0.002 mole) was refluxed in synthetic microwave oven with condenser at intensity of 20% (210W) for 7 min. The mixture was then cooled and poured into conc. HCl. The product obtained was filtered, washed initially with sodium bicarbonate and then with dil. Sodium hydroxide and finally with water.




## Result and discussion:

**1. (2a-d) 5-Hydroxy -8H-1-oxa -8–aza-anthracene - 2, 7-dione.**

M. F. $C_{12}H_{11}NO_4$, Yield 73.00%, M. P. 210$^0$C

**2. (3ad): 4,11-dimethyl -6H-1,8-dioxa -6–aza-benzo [a] anthracene-2,5,9-trione.**

M. F. $C_{17}H_{13}NO_5$, Yield 72.00%, M. P. 220$^0$C

**Spectral interpretation:**

**I.R. (KBR):**(-NH Stretch) 3440, 3050, ($C_2$>C=O and $C_9$>C=O) 1724, 1650, ($C_8$>C=O) (Ring C=C Stretch) 1600, (C (= O)-O Stretch) 1215, (O-C = C Asymetric Stretch) 1195 cm$^{-1}$

**$^1$HNMR (DMSO):** δ 2.30 (S,3H), δ 2.45 (S,3H), δ 7.46(S,1H); δ 8.10(S,1H) δ 5.90(S,1H),(S,1H); δ 6.29(S,1H); δ 8.1(S,1H)

**2. (4ad) : 11-methyl -6H-8,13-dioxa -6–aza- pyrano benzo [b] anthracene -5,9,14-trione pyrazine.**

M.F.: $C_{19}H_{13}NO_5$, Yield 74.00%, M. P. 237$^0$C

**Spectral interpretation:**

**I.R. (KBR):**(-NH Stretch) 3470, 3040, ($C_9$>C=O and $C_{14}$>C=O) 1724, ($C_5$>C=O) 1650, (Ring C=C Stretch) 1610, (C (= O)-O Stretch) 1220, (O-C = C Asymetric Stretch) 1175 cm$^{-1}$

**$^1$HNMR (DMSO):** δ 2.5 (S,3H), δ 6.29(S,1H),δ 7.45(d,1H); δ 7.8(d,1H), δ 8.0(S,1H)

## Discussion and conclusion:

From references it was conclude that, the synthesized product i.e. 5-Hydroxy -8H-1-oxa -8–aza-anthracene- 2,7-dione; 4,11-dimethyl -6H-1,8-dioxa -6–aza-benzo [a] anthracene-2,5,9-trione; 11-methyl -6H-8, 13-dioxa -6–aza- pyrano benzo [b] anthracene-5,9,14-trione pyrazine posses diverse biological properties as Quinolones derivatives are well known to exhibit antimalerial[28], antiviral[29], antiallergic[30], antseptic[31], antiulser[32] activities along with CNS depressant[33] action. Several quinolones derivatives are also active against asthama[34], pyranoqunolones [35] are known to act as $H_1$ antihistamine and also useful for cell stage preparation more ever, Coumarins are known as potent anti coagulants[36],as well as antibacterial [37], and antifungal[38,39] agents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