SYNTHESIS AND CHARACTERIZATION OF HETEROCYCLIC COMPOUNDS OF PHARMACEUTICAL IMPORTANCE

A

THESIS

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SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED (3E)-3-BENZYLIDENE-1-METHYLQUINOLINE-2,4(1H,3H)-DIONES:

1.1 INTRODUCTION

The first synthesis of benzofuran by Perkin[1] in 1870 and its subsequent discovery in coal-tar in 1890 by Kraemer and Spielker[2] triggered off a chain of research publications on benzofurans. Since the end of the second world war, the chemistry of benzofuran derivatives has developed spectacularly. Research in this field has reached to such a scale that the number of research publications after 1950 far exceeds the number before 1950. Several important monographs have been devoted to it and more and more publications still continue to appear [3-8].

This surge of interest is largely due to the fact that the benzofuran ring forms an important part of pharmacodynamically active natural substances. "Coumarone resins" have been the subject of patents, especially for use in building materials[9-10] and as protectives in paints and varnishes[11]. Coumarone-indene copolymer resins are also widely used. When added to rubber, they influence the vulcanizing rate[12] and improve the strength properties of some synthetic rubbers[13-15]. "Coumaronic" derivatives are used for bleaching in the textile industry[16] and as inhibitors in the sulfochlorination of kogasin[17].

1. W.H. Perkin, *J.Chem.Soc.*, **1870** 23, 368.
2. G. Kraemer and A. Spielker, *Ber.*,**1890** 23 78.
3. V.R.Shah, J.L. Bose and R.C.Shah, *J.Org.Chem*,**1960,** 25,677
4. V. B. Meher, *"Heterocyclic compounds"* (Editor H. C. Elderfiels), Vol. II, pp. 1 to 65, *Wiley*, New York, **1951**.
5. T.S. Steuens, "*Chemistry of carbon compounds*", Elserier, (Editor-E. M. Rodd.) Vol. IV A, pp. 168, **1957**.
6. R. Livingstone, *"Rodd's Chemistry of carbon compounds*" II. Edition, Elsevier, Amsterdam, Vol. IV A, pp. 141, **1973.**
7. A. Williams, *"Furans, synthesis and application"*, pp. 1, Noyes data corporation, London, **1973**.
8. A. Mustafa, "*The Chemistry of heterocyclic compounds*", vol. 29, Benzofurans, Pp. 4911, Wiley, New York , **1974**.

The research has progressed along the following three main lines :

(1) Extraction, determination of the structures, partial or total synthesis of the natural benzofuran derivatives.

(2) Synthesis of benzofuran derivatives with physiological, pharmacological, therapeutic or toxic properties.

(3) Studies on the reactivity of benzofuran and its derivatives from the chemical and physical point of view.

1.2 METHODS OF SYNTHESIS

The numerous methods for the synthesis of the benzofuran ring system can be classified under four major heads.

(1) Formation of the heterocyclic ring from an aromatic substrate.

(2) Formation of the heterocyclic ring from a non-aromatic substrate.

(3) Fusion of the benzene ring to a furan substrate.

(4) Formation of the heterocyclic ring from other heterocyclic compounds.

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9. P. Rechner, *French patent*, **1964**, 359, 781,*C. A*. 61, 11735 .

10. M. Inoue, Coal Tar (Tokyo), **1952**, 4, 336 *C. A.*, **1953,** 61, 6121.

11. A. L. Rummelsburg, *U. S. patent,* **1950,** 2, 527, 578 ; *C. A*. **1951** 45, 2234

12. E. Tomczam and M. Gajewski, Muanyag Gumi, **1969,** 6, 403 ; *C. A.* **1970** 72, 22429.

13. J. Pielichowski, Chemi. Stosow, Ser A , **1970**, 13, 343 ; *C. A*. **1970,** 72, 101603.

14. I. I. Yikelson, V. V. legacheva and I. V. Fedotova, *Koks Khim*.,**1970**, 2, 34 ; *C.A*. 72, 113567.

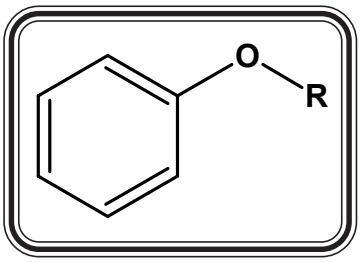
15. W. J. Wald, *U. S. Patent,* 2, 925, 662 ,**1960**; *C.A*., **1961,** 55, 4029.

16. T. Sorensen, Tidsker. Teatiltekn. **1951,** 2. 128; *C.A.* , **1951,**45, 10593.

17. H. Kroepelin, W. Optiz and W. Freiss, Erode Kohle, 19492, 498; *C.A.* **1950,** 44, 2203.

1.2.1 Formation of the heterocyclic ring from an aromatic substrate :

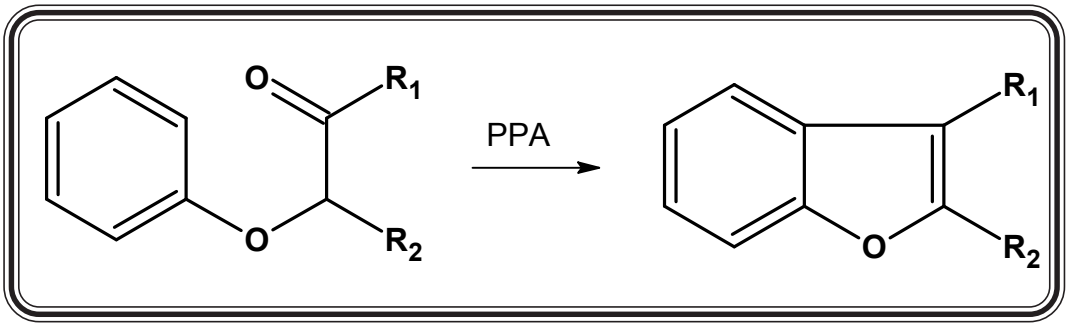
Several methods which come under this head comprise of ring closure, cyclodehydration, heterocyclic ring closure and intra molecular condensation of aryloxylated compounds of the following type.



1.2.1.1 From aryloxyaldehydes and ketones :

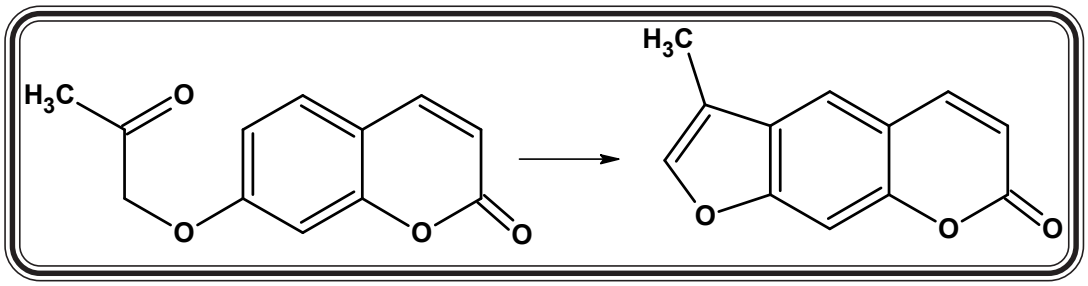
(I) From Aryloxy acetaldehydes :

This method which is due to Stoermer and coworkers[18-20] consists of dehydration of aryloxyacetaldehydes or of their acetals, using polyphosphoric acid or phosphorus pentoxide as a catalyst [21-22].



18. R. Stoermer and F. Bartsch, *Ber.*,**1900**, 33, 3175 .
19. R. Stoermer and F. Bartsch, *Ber.*,**1902**, 35, 3560.
20. R. Stoermer and E. Barthelmes, *Ber*, **1915,** 48, 62 .
21. (a) P. Sigwalt. *J. Polym. Sci.*, **1961**, 52, 15 .
    (b) P. Sigwalt, *C. R. Acad. Sci.*, **1961**, 252, 3800.
22. P. Spagnolo, M. Tiecco, A. Tundo, G. Martalli, *J. Chem. Soc. Perkin*, Trans., **1972,**1, 556.

Similarly an aryloxyketone can give the corresponding 2 and 3 or 2,3-dialkylbenzofuran on dehydration with sulphuric acid, zinc chloride, phosphorus oxychloride or polyphosphoric acid[23-26]. The acetonyl ether of 7-hydroxycoumarin gives 3-methylpsoralene. Cyperaquinone has also been synthesized[27].

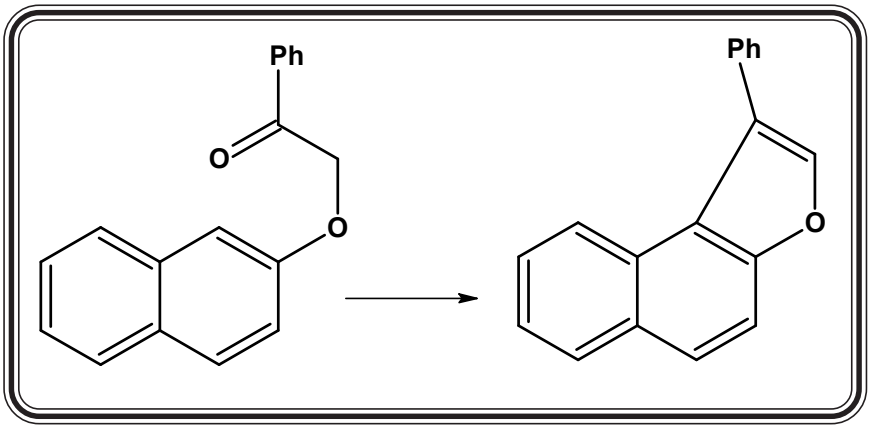


This method has also been applied to the synthesis of 2,3-dimethylbenzofurans[28-29]as well as polycyclic benzofurans like naphtho furans[30],benzodifurans[31],naphthodifurans and thiendo benzofurans [32-33].

23. R. Royer and E. Bisagni, *Bull. Soc., Chem. Fr.*, **1959**, 521.
24. H. Singh and J. C. Verma, *J. Ind. Chem. Soc.*, **1963**, 40, 31.
25. K. Raudsepp and H. Kippze, Tr. Tallin Politekh Inst.; *Ser. A*., **1964,** 216, 79 .
26. J. N. Chatterjee, *J. Ind. Chem. Soc.*, **1953**, 30, 1.
27. T. K. Veselovskaya, I. V. Machinskayae and H. J. Nadeeyarva, Zh. *Obshch. Khim*., **1964,** 34, 560; *C. A*., **1964,** 60, 13218.
28. R. Royer and L. Rene, *Bull. Soc. Chim. Fr.*, **1970**,1036 .
29. J. K. Mcleod and B. R. Worth, *Tetrahedron Lett.*,**1972**, 237-241.
30. R. Royer, M. Hubert – Habart, L. Rene, A. Cheutin and M. L. Desvoye, *Bull. Soc. Chemistry*, **1964**, 1259.
31. R. Royer, E. Bisagni, C. Hudry, A. Cheutin and M. L. Desvoye, ibid., **1963**,1103.
32. R. Royer, E. Bisagni, M. Hubert – Habart, L. Rene and J. P. Marquet, ibid., **1965,** 1794.
33. R. Royer, P. Demerseman and J. P. Lechartier C. R., *acad. Sci.*, **1962**, 254, 2605.

Graffenreid and Kostanecki[34] observed that cyclodehydration aryloxyacetoacetates gave good yields of otherwise difficult obtainable coumarilic esters [35], which on hydrolysis and decarboxylation can give the corresponding benzofurans. Naphthofurans have also been prepared by these methods[36].

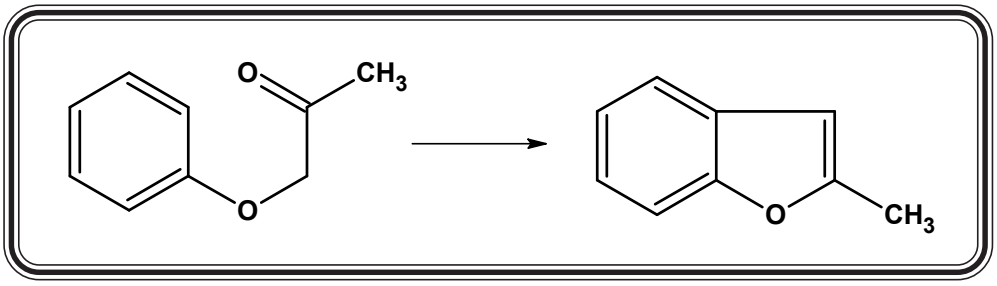
Aryloxy acetophenones on dehydration should give in principle 3-arylbenzofurans[37-38]. Sometimes 2-arylbenzofurans are obtained due to rearrangement dependending on the conditions of the reaction[39]. According to Thomas and Bokadia[40], however, 2-naphthoxy acetophenones give only 2-phenylnaphtho (2,1-b) furan under all conditions



34. A. V. Graffenrid and V. Kostanecki, Ber.,**1910**, 43, 2155 .
35. W. E. Boehme, *Org. Synth*.,**1953,** 33, 43.
36. B. I. Du Pont de Nemours, *British Patent*, 705950, **1954**; C. A., **1955,** 49, 2233 .
37. W. Davies, S. Middleton. *Chem. Ind.* (London), **1957**,1999.
38. E. Bisagni and R. Royer, *Bull. Soc. Chim. Fr.*, 925, **1962**.
39. K. K. Thomas and M. M. Bokadia, *J. Ind. Chem. Soc*., **1968**, 45, 265
40. Idem, ibid., **1966**, 43, 713.

(ii) Photochemical cyclization of α-aryloxyketones :

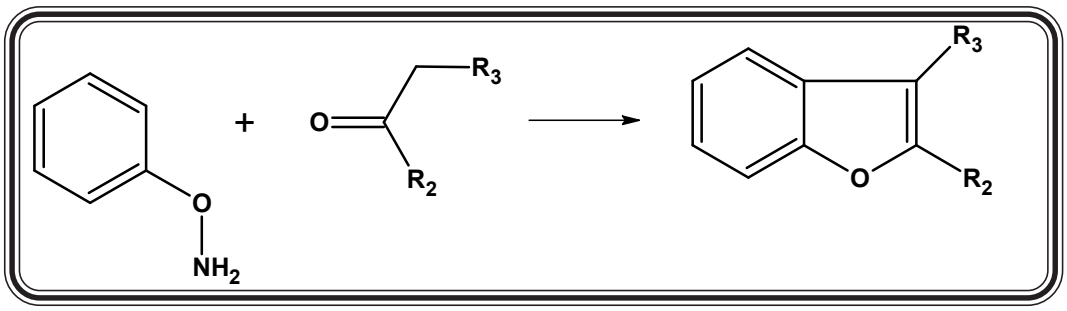
Aryloxy acetones irradiated in methanol at room temperature give the corresponding 2-methylbenzofurans formed through a rearrangement[41-42]. Naphthofurans have also been prepared by this method[43].



(iii) From α-aryloximes :

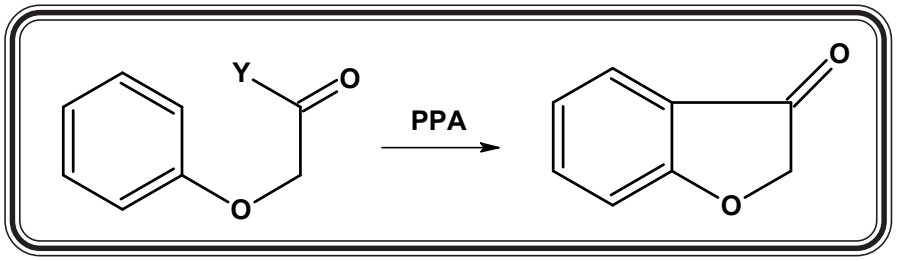
This new method discovered in 1966 by Sheradsky[44], has proved useful for the synthesis of fused benzofurans. 2-Phenyl oximes obtained from phenoxy amiones and appropriate ketones, give substituted benzofurans in good yields when heated in acetic acid with boron trifluoride etherate. The reaction mechanism is similar to that of Fischer-Indole synthesis[45]. Numerous substituted benzofurans, including some nitro derivatives showing anti-inflammatory and anti-bacterial activity, have been prepared by this method[46-47].

41. J. Hill, *Chem. Commu*., **1966**, 260.
42. M. K. M. Dirania and J. Hill. *J. Chem. Soc*. C, **1968,** 1311.
43. J. R. Collier, M. K. M. Dirania and J. Hill, *ibid*., **1970,** 155.
44. T. Sheradsky, *Tetrahedron Lett*., **1966**, 5225.
45. P. E. Dupont, *Ph.D. Thesis*, Rensselaer Polytech. Inst., New York, **1966**; *Diss. Abstr.*, **1969,** 29, 4092; *C. A*., **1969,** 71, 112147.
46. T. Sheradsky, *J. Heterocycl. Chem*., **1967,** 4, 413.
47. A. Moorardian and P. Dupont, *ibid*, 441.



(iv) From aryloxy acetic acids and acid chlorides :

Acids with the general formula (Y = OH) undergo ring closure with the usual reagents like sulphuric acid, phosphorus pentoxide, polyphosphoric acid etc., to give 3-(2H) benzofuranones usually in low yields[48]. According to Elvidge and Foster, acid chlorides (Y = Cl) give the same product by intramolecular Fridel-Crafts reaction[49].



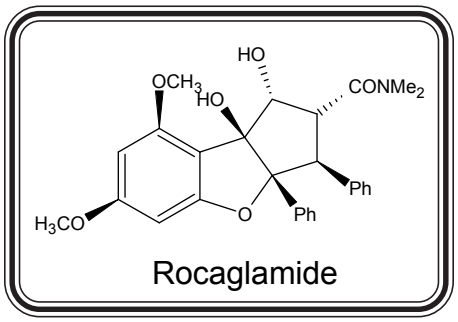
(v) From aryloxy alcohols :

This method which is due to Rindfusz[50-51] leads to dihydrobenzofurans by internal cyclodehydration of aryloxyalcohols in presence of zinc chloride.

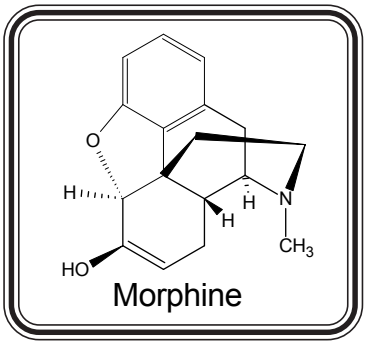
48. J. N. Chatterjee, S. N. P. Gupta, and V. N. Mahrotra, *J. Ind. Chem. Soc.*, **1965,** 42, 205.
49. J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, **1951,** 73, 4296.
50. R. E. Rindfusz, *ibid,* **1919,** 41, 665.
51. R. E. Rindfusz, P. M. Ginnings and V. L. Harnack, *ibid*. **1920,** 42, 157.

1.3 Biological Activity Associated with Benzofuran Derivatives

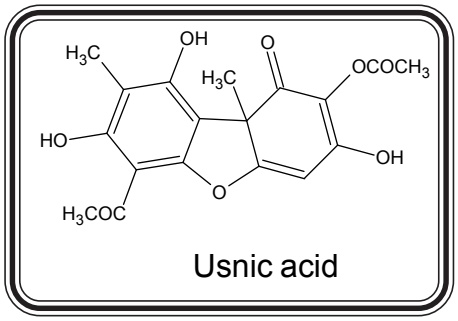
The benzofuran ring is found in many natural products. Several bioactive natural product have been isolated containing benzofuran moiety. The structures of Rocaglamide, 4-O-methylcedrusin, Morphine, Galanthamine, Thebaine, Usnic acid, Furocoumarin (Methoxalen), Aflatoxin.etc are as follows.



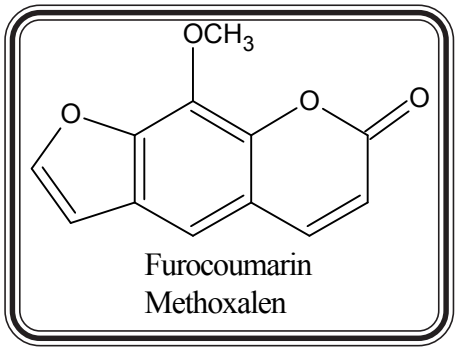
Rocaglamide



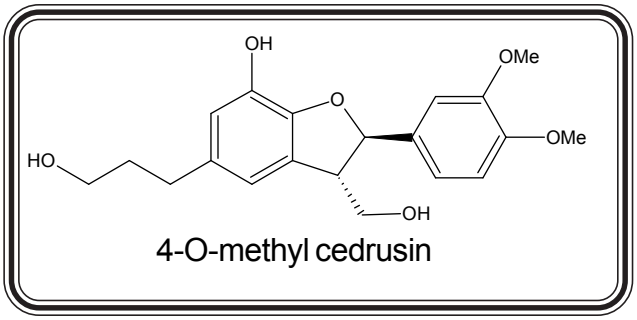
Morphine



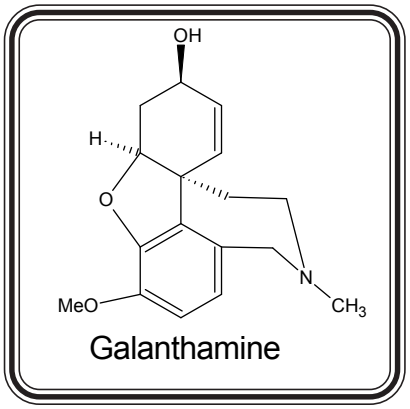
Usnic acid



Furocoumarin
Methoxalen



4-O-methyl cedrusin



Galanthamine

Benzofuran derivatives have been reported to possess biological activities[52-54]. Some derivatives of benzofuran have vasodialating and hypotensive effects[55].Some benzofuran derivatives have hypotensive and arrhythimic activities[56]. The biological activity of Mannich bases as antiamoebic and antiinflammatory agents has also been reported[57]. Some pyrazoline derivatives were used as bacteriostatic,fungicidal and anticancer agents[58]. Isoxazoline compounds have been shown to have antituberculosis and antibiotic activities [59].

Benzofuran ring system is incorporated in many natural products and synthetic pharmaceuticals to varying biological & pharmacological activities.

52. Proksch, P.; Rodriguez, E. *Phytochemistry,* **1983**, *22*, 2335-2348.

53. Isman, M. B.; Proksch, P. *Phytochemistry,* **1985**, *24*, 1949-1951.

54. Proksch, P.; Rodriguez, E. *Biochem. Syst. Ecol.,* **1984**, *12*, 179-181.

55. Isman, M. B.; Proksch, P.; Witte, L. *Arch. Insect. Biochem. Physiol.*, **1987**, *6*, 109-120.

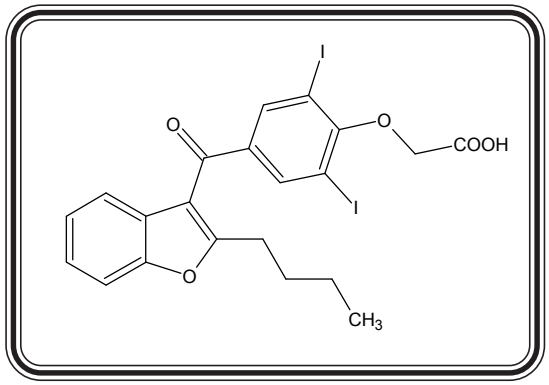
56. Isman, M. B. In *Insecticides of Plant Origin*; Arnason, J. T., Philoge'ne, B. J. R., Morand, P., *ACS Symposium Series 387*: Washington,DC, 1989; pp 44-58.

57. Kunze, A.; Aregulin, M.; Rodriguez, E.; Proksch, P. *J. Chem. Ecol.***1996**, *22*, 491-498.

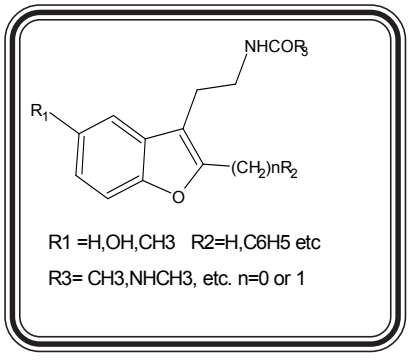
58. Pereda-Miranda, R.; Bernard, C. B.; Durst, T.; Arnason, J. T.;Sa´nchez-Vindas, P.; Poveda, L.; San Roma´n, L., *J. Nat. Prod.,* **1997**,*60*, 282-284.

59. Sosa, M. E.; Tonn, C. E.; Giordano, O. S. *J. Nat. Prod.,* **1994**, *57*, 1262.

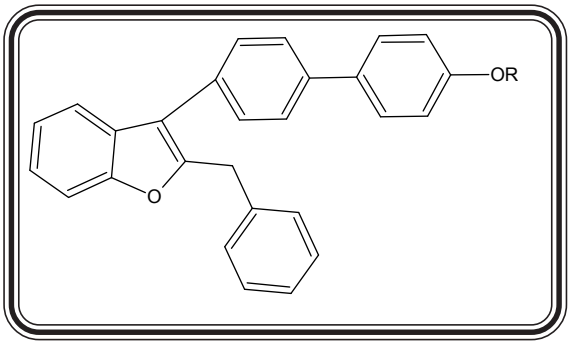
Recent developments in antiarrhythmic therapy have indicated that the best approach to pharmacologically controlling supraventricular arrhythmias and life-threatening ventricular tachyarrhythmias is by prolonging cardiac repolarization rather than by blocking conduction. *Amiodarone* has emerged as the most potent compound, but its universal use has been limited by its toxicity profile. There are data to suggest that an important component of amiodarones antiarrhythmic action might be mediated via inhibition of thyroid hormone action in the heart. Therefore, a new series of carboxymethoxybenzoyl and benzyl derivatives of benzofuran was prepared and evaluated as thyroid hormone receptor antagonists[60].



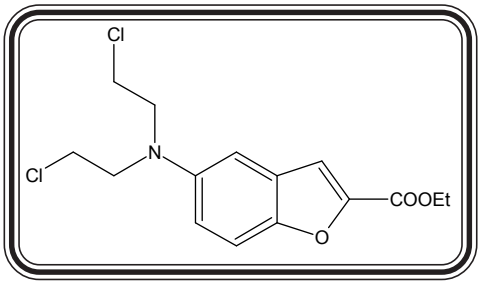
A series of N-(2-phenylbenzofuran-3-yl) ethyl amide and N-(2-arylalkylbenzofuran-3-yl) ethyl amide derivatives were synthesized and evaluated as Melatonin receptor Ligands by Valerie Wallez, et al.[61]



Michael S. Malamas[62] et.al. have synthesized novel benzofuran derivatives as inhibitors of protein tyrosine phosphatase 1 B with antihyperglycemic properties.



Pier Giovanni Baraldi & co workers[63] have designed, synthesized, and carried out in vivo and in vitro antileukemic activity of a novel series of compounds in which different benzoheterocyclic rings, bearing a nitrogen mustard or a benzoyl nitrogen mustard or an R-bromoacryloyl group as alkylating moieties.



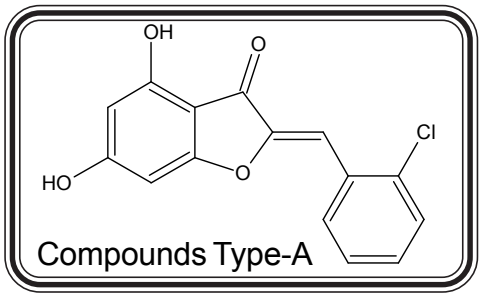
60. Bo Carlsson, B. N. Singh, Marcel Temciuc, Stefan Nilsson, Yi-Lin Li, Charlotta Mellin, and Johan Malm *J. Med. Chem.,* **2002,** *45,* 623-630.

61. Vale´rie Wallez, Sophie Durieux-Poissonnier, Philippe Chavatte, Jean A. Boutin, Vale´rie Audinot, Jean-Paul Nicolas, Caroline Bennejean, Philippe Delagrange, Pierre Renard, and Daniel Lesieur *J. Med. Chem.,* **2002,** *45,* 2788-2800.

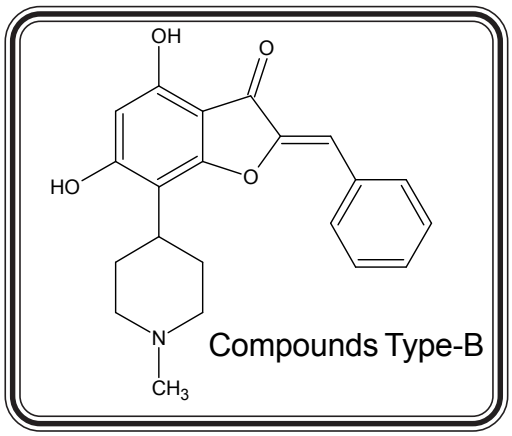
62. Michael S. Malamas,Janet Sredy, Christopher Moxham, Alan Katz, Weixin Xu, Robert McDevitt,Folake O. Adebayo, Diane R. Sawicki, Laura Seestaller, Donald Sullivan, and Joseph R. Taylor *J. Med. Chem.,* **2000,** *43,* 1293-1310.

63. Pier Giovanni Baraldi, Romeo Romagnoli, Italo Beria, Paolo Cozzi, Cristina Geroni, Nicola Mongelli, Nicoletta Bianchi, *J. Med. Chem.,* **2000,** *43,* 2675-2684.

The inhibition of cyclin-dependent kinases (CDK's) has emerged as an important theme in anticancer research. Benzofuran derivatives are able to inhibit the activity of these crucial enzymes in the regulation of the cell division cycle are expected to have antiproliferative properties. Novel 2-benzylidene-benzofuran-3-ones were designed and synthesized to mimic *flavopiridol*, a well-established inhibitor of cyclin-dependent kinases (CDK's) which is currently undergoing clinical evaluation.[64]

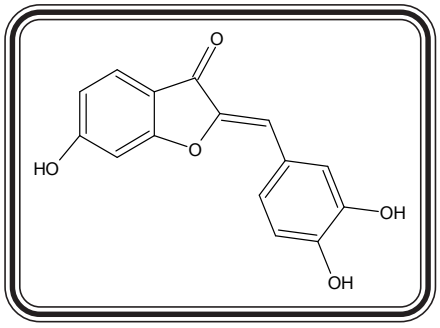


Compounds Type-A

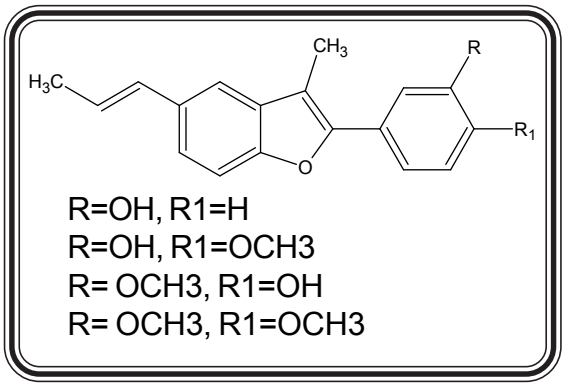


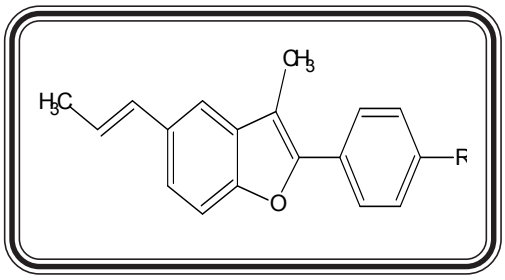
Compounds Type-B

O. Kayser, A. F. Kiderlen, U. Folkens and H. Kolodziej[65] have synthesized 6-hydroxybenzofuran-3 (*2H*)-one is an aurone with activity against promastigotes of *Leishmania* spp. (EC_{50} = 0.09–0.11 µg/ml) and against amastigotes of *L. donovani* (EC_{50} = 1.24 µg/ml), but non-toxic to bone marrow-derived macrophages.

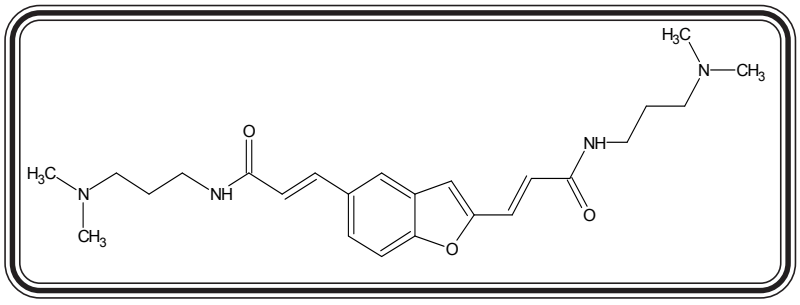


Chauret et al. (1996) have reported for the first time in a species of the Piperaceae, three known neolignans (conocarpan, eupomatenoid-5 and eupomatenoid-6) isolated from Piper decurrens and confirmed the structure. Greisiele Lorena Pessini[65] et. al. have evaluated the activity *against gram-positive and gram-negative bacteria.*





Chris J.Hamilton et. al.[66] has synthesized and evaluated 3,5-disubstituted benzofuran derivatives as time-dependent inhibitors of the protozoan oxidoreductase trypanothione reductase .



64. Joseph Schoepfer, Heinz Fretz, Bhabatosh Chaudhuri, Lionel Muller, Egge Seeber, Laurent Meijer, Olivier Lozach, Eric Vangrevelinghe, and Pascal Furet *J. Med. Chem.* **2002,** *45,* 1741-1747.

65. Greisiele Lorena Pessini ,Benedito Prado Dias Filho,Celso Vataru Nakamura, Diógenes Aparício Garcia Cortez.Mem Inst Oswaldo Cruz, Rio de Janeiro,**2003** Vol.98 (8):1115-1120.

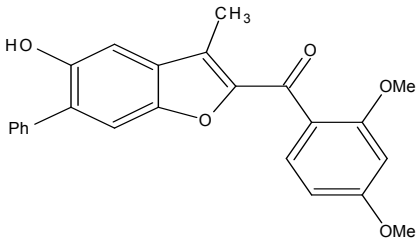
66. Chris J.Hamilton, Ahilan Saravanamuthu,Alan H.Fairlamb and Ian M.Eggleston *Bioorganic & Medicinal Chemistry*, **2003,** 11,3683-3693.

67. Ecker G, Chiba P, Hitzler M, Schmid D, Visser K, Cordes HP, Csollei J, Seydel JK, Schaper KJ., *J Med Chem.,* **1996,** Nov 22; 39(24): 4767-74.

68. Ichiro Hayakawa Rieko Shioya, Toshinori Agatsuma, Hidehiko Furukawa, Shunji Naruto and Yuichi Sugano; *Bioorganic & Medicinal Chemistry Letters*, **2004**, 14, (2), pp. 455-458.

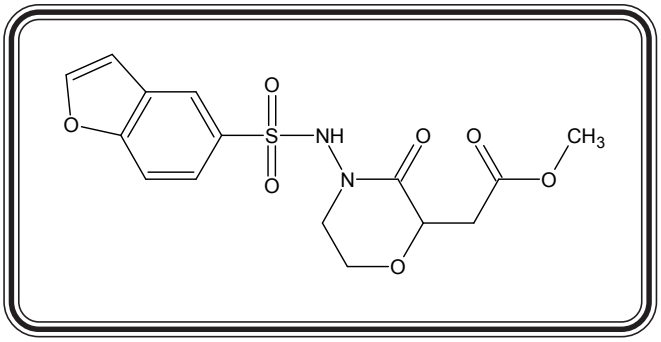
Ecker G et. al.[67] have synthesized a series of benzofurylethanolamine analogs of propafenone whicha have been prepared and evaluated for Multidrug resistance-reversing (mdr) activity as a propafenone-type modulators of tumor cell multidrug resistance.

Ichiro Hayakawa et.al.[68] has worked on the structure of 4-hydroxy-3-methyl-6-phenylbenzofuran-2-carboxylic acid ethyl ester, which exhibits selective cytotoxicity against a tumorigenic cell line.From this, (2,4-dimethoxyphenyl)-(4-hydroxy-3-methyl-6-phenylbenzofuran-2-yl)-methanone was designed and synthesized as a biologically stable derivative containing no ester group. Although the potency of was almost the same as the initial hit compounds expected to last longer in the human body as an anticancer agent.

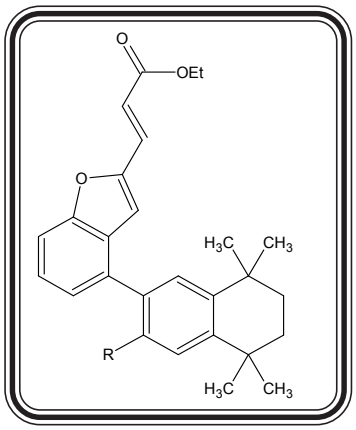


Novel types of anti tumor agent
ED52=40 ng/ml

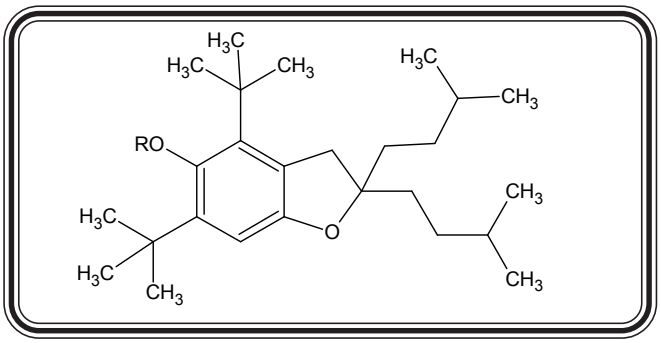
Thromboembolic disorders are the major cause of morbidity and mortality in the developed world. Several acute diseases including deep venous thrombosis. Jonas W. Nilsson et. al.[68] have synthesized and did the SAR of thrombin inhibitors incorporating a novel 4-amino-morpholinone scaffold in benzofuran structures.



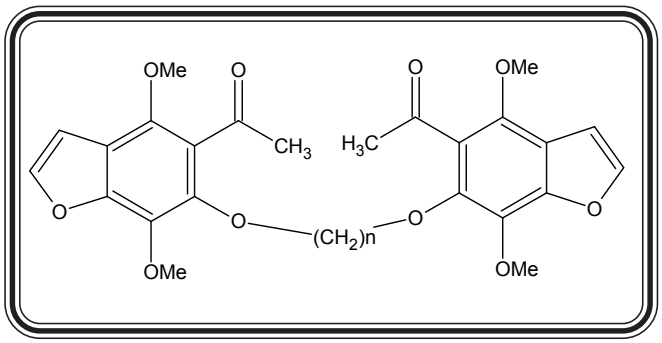
A novel series of tetrahydrobenzofuranyl and tetrahydrobenzothienyl ropenoic acids that showed potent agonist activity against RXRR were synthesized by Curt D. Haffner et al [69].



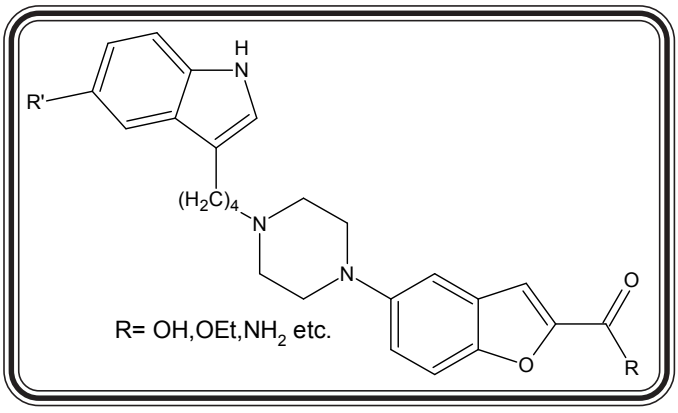
K.Tamura et. al.[70] has designed and synthesized some of 4,6-Di-*tert*-butyl-2,3-dihydro-5-benzofuranols as a novel series of antiatherogenic antioxidants.



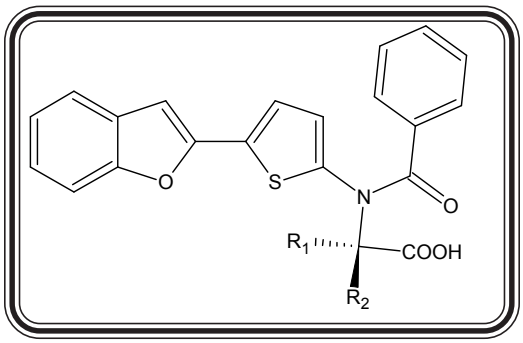
The voltage-gated potassium channel Kv1.3 is critically involved in the activation of human T cells and has therefore long been pursued as a novel target for immunosuppressive therapy. Jonathan B. Baell et.al.[71] has prepared a series of compounds and carried out potassium channel activation study.



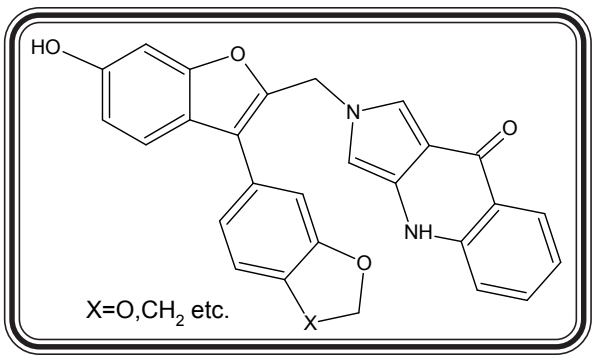
Timo Heinrich, et. al.[72] has synthesized and carried out structure-activity relationship in a class of benzofuran as dual 5-HT_{1A} receptor agonists and serotonin reuptake inhibitors.



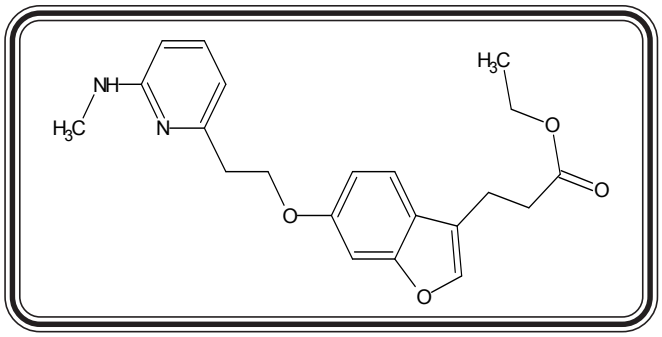
Laval Chan and his group[72] have prepared novel class of inhibitors of hepatitis C NS5B polymerase.



Synthesis of furoyl and benzofuroyl pyrroloquinolones as potent and selective PDE-5 inhibitors was reported. Their in vitro potencies in inhibiting PDE-5 and selectivity in inhibiting other PDE isozymes (PDE1-4 and PDE6) were valuated. Some of these compounds are more potent than *sildenafil* with better selectivity toward PDE1 and PDE6.[73]



A novel series of potent and selective Rva3/Rva5 dual inhibitors was designed, synthesized, and evaluated against several integrins by Juan Jose Maruga et. al.[74]



69. Kunio Tamura, Yoshiaki Kato, Akira Ishikawa, Yasuharu Kato, Motomu Himori, Mitsutaka Yoshida, *J. Med. Chem.,* **2003,** *46,* 3083-3093.

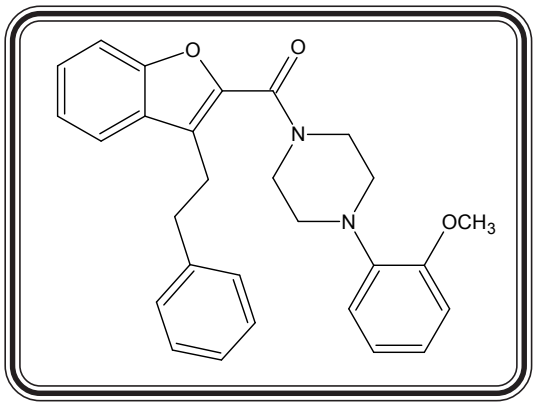
70. Jonathan B. Baell, Robert W. Gable,Andrew J. Harvey, Nathan Toovey, Tanja Herzog, Wolfram H and Heike Wulff, *J. Med. Chem.,* **2004,** *47,* 2326-2336.

71. Timo Heinrich,* Henning Bo¨ttcher, Rolf Gericke, Gerd D. Bartoszyk, Soheila Anzali, Christoph A. Seyfried, *J. Med. Chem.,* **2004,** *47,* 4684-4692.

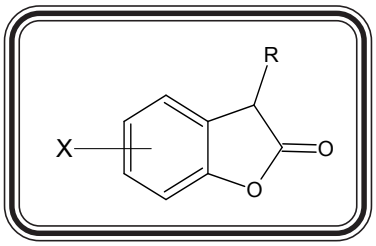
72. Laval Chan T. Jagadeeswar Reddy, Me´lanie Proulx,Sanjoy K. Das, Oswy Pereira, Wuyi Wang, Arshad Siddiqui, Constantin G. Yannopoulos, *J. Med. Chem.,* **2003,** *46,* 1283-1285.

73. Weiqin Jiang, Zhihua Sui, Mark J. Macielag, Shawn P. Walsh, James J. Fiordeliso, James C. Lanter, Jihua Guan, Yuhong Qiu, Patricia Kraft, Sheela Bhattacharjee, Elizabeth Craig, Donna Haynes-Johnson, T. Matthew John, and Joanna Clancy *J. Med. Chem.,* **2003,** *46,* 441-444.

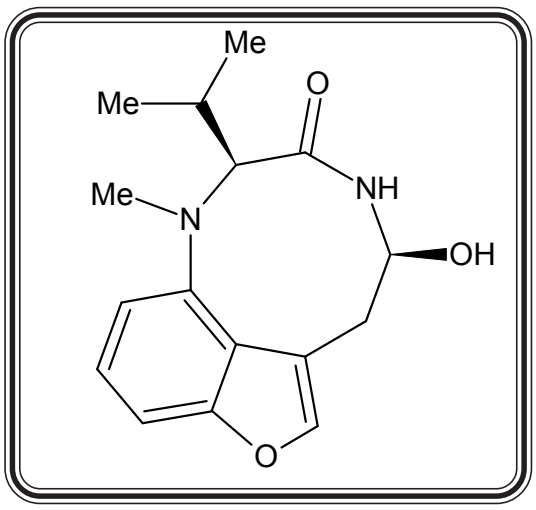
74. Juan Jose´ Maruga´ n,* Carl Manthey, Beth Anaclerio, Lou Lafrance, Tianbao Lu, Tom Markotan,Kristi A. Leonard, Carl Crysler, Stephen Eisennagel, Malini Dasgupta, and Bruce Tomczuk *J. Med. Chem.,* **2004,** 47, 451-458.



A. Closse et. al. have synthesized a new class of 2,3 di-hydrobenzo furan 2-ones derivatives which is power ful anti-inflammatory compound.



The benzofuran analogue of the natural product was synthesized and found to be similar in its activity , exhibiting a K_i of 17.3 ± 3.7 nM in the displacement of [^{3}H]PDBU from PKCa. 4



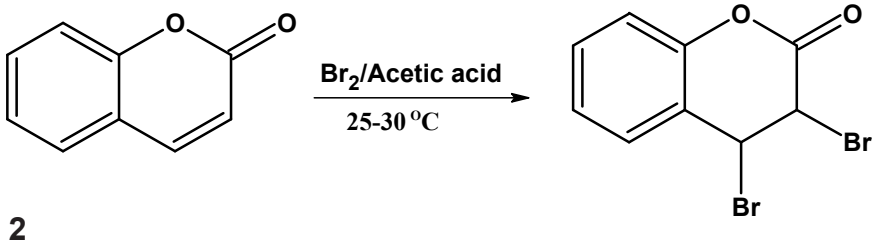
The development of multiple drug resistance represents an increasing problem in cancer treatment as well as in antimicrobial therapy. Within the past decade, several mechanisms of pleiotropic drug resistance of tumor cells have been identified.[26] One type of multidrug resistance (MDR) has been shown to be mediated by an energy dependent, membrane-bound efflux pump termed P-glycoprotein (PGP).[27] PGP represents a member of the ATP-binding casette[28] with low substrate specificity. A broad range of cytostatic drugs such as anthracyclines, epipodophyllotoxins, actinomycin D, vinca alkaloids, colchicines, and taxol are eliminated via PGP-mediated efflux.[29] recently, this mechanism of Drug resistance has attracted additional attention since it was proposed to be involved in multidrug resistance of Gram-negative bacteria[30] as well as in fungi[31-33] and host-mediated resistance of *Mycobacterium tuberculosis* against tuberculostatic drugs[34]. Within the past few years a variety of substances have been shown to inhibit PGP-mediated drug efflux and thereby reestablish sensitivity toward chemotherapeutic agents[35.] Gerhard Ecker et.al. have synthesized a series of benzofuran derivatives.

The current work is aimed at the synthesis of the title compounds in 5 steps.

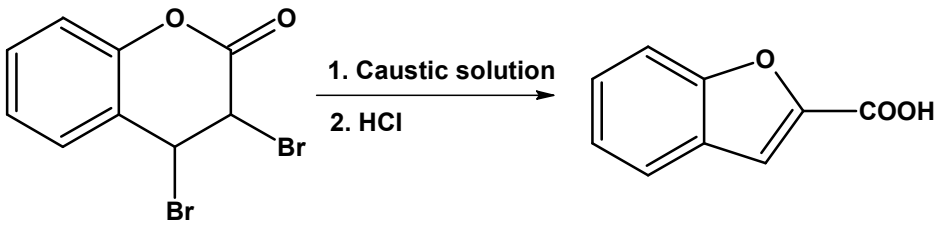
First step involved bromination of coumarin at C_3 and C_4 position, which was subsequently converted into benzo furan 2-carboxylic acid by ring contraction followed by esterification and than conveted into a hydrazide. This hydrazide was subjected to further reaction with several aldehydes to afford *substituted N*'-[(1*Z*)-phenylmethylene]-1-benzofuran-2-carbohydrazides.

Reaction Scheme : -

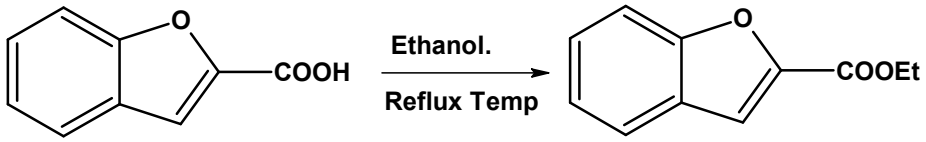
Step - 1



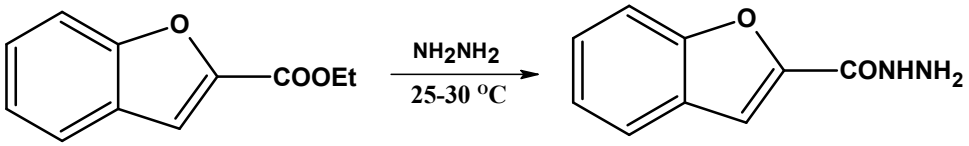
Step - 2



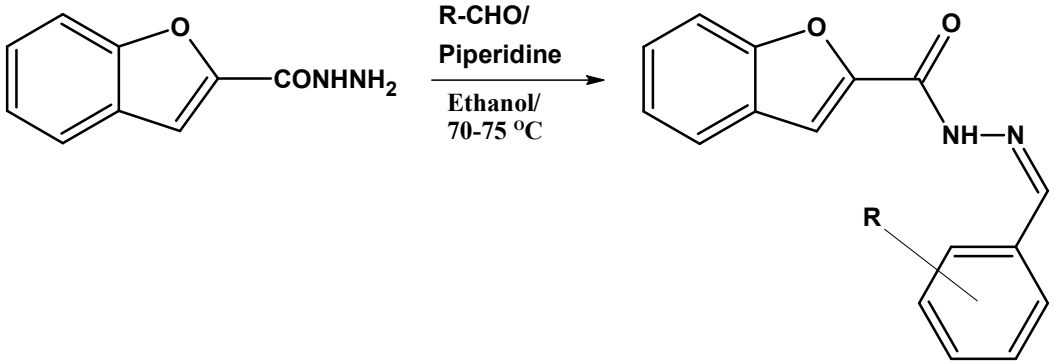
Step - 3



Step - 4



Step - 5



Experimental

(1) Preparation of 3,4-dibromo coumarin.

Take 14.6 gm of coumarin into a clean dry RBF and to this add 150 ml of acetic acid in the stirring condition so that the reaction mixture is developed. The temperature of this reaction is to be kept at around 25-30°C. Take 10 gm (5.2 ml) liquid bromine in to addition funnel & add dropwise to RBFby maintaining temp. 25-30 °C. After completion of addition stirr for one hour at same temperature , then to this add 500 ml water and is furthur stirred for 30 min. Aqueous layer extracted with 3X 100 ml of chloroform. The combined organic layer is washed with 100 ml brine solution. Then chloroform layer dry over anhy. sodium sulphate.

Take chloroform layer into RBF & distilled out chloroform completely. Cool to 25-30 °C. 25 ml ether was added and stirred for 10 min.The product obtained was filtered. Yield~70%, m.p. 103-104 (Reported[75] m.p 102-105)

(2) Preparation of 1-benzofuran-2-carboxylic acid

Take 7.5 gm 3,4 -dibromo coumarin into RBF. Charge 25 ml 30 % aqueous KOH solution into RBF drop wise at 25-30 °C. Heat reaction mixture upto reflux temperature & maintain for two hours. Cool to 25 °C and adjust pH 3 to 4 with help of conc. hydrochloric acid. Filter the product & wash with water. Dry the product & crystallized from methanol. Yield~82-88%, m.p. 191-192 (Reported[75] m.p.190-193)

(3) Preparation of 1-benzofuran-2-carboxylic acid ethyl ester

Take 5 gm 1-benzofuran-2-carboxylic acid into RBF. Charge 25 ml ethanol into RBF at 25-30 °C. Add 2-3 drop Conc. Sulphuric acid into RBF. Heat reaction mixture upto reflux temperature & maintain for two hours. Cool to 25 °C and quench into ice cold water. Separate the layer. Organic layer washed with saturated sodium bicarbonate solution till neutral pH. Yield~85 to 90%.The ester was used for further reaction without purification.

(4) Preparation of 1-benzofuran-2-carboxylic acid hydrazide

Take 5.0 gm 1-benzofuran 2-carboxylic acid into RBF. Add 25 ml ethanol into RBF as a solvent. Charge 5.0 gm hydrazine monohydrate into RBF & keep at room temperature for overnight. Filter the product & dry in air oven. The melting point of crude product was 72-75 ^{0}C. It was used without further purification. Yield~ 80 to 85%.

(5) Preparation of substituted *N*'-[(1*Z*)-phenylmethylene]-1-benzofuran-2-carbohydrazides (Schiff base)

General Procedure:-

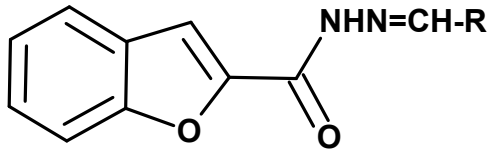
0.1 mole 1-benzofuran 2-carboxylic acid hydrazide was taken into RBF. Charge 0.1 mole substituted aromatic aldehyde into RBF with 10 ml of ethanol as a solvent & heat to reflux temperature in presence of base catalyst. Maintain refluxed temp. for five hrs. Cool to room temperature & filter the product. Dry in air oven. Yield~70 to 85%.

All the reaction were monitored by TLC using ethyl acetate:hexan (6:4) solvent system.

A series of compounds were prepared by the similar method. A physical data are given as Table **1.1.**

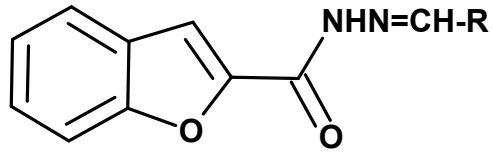
75. *Organic synthesis, Col. Vol. III*, **1955**, 209.

Table: -1.1 Physical constants ofsubstituted N'-[(1Z)-phenylmethylene]-1-benzofuran-2-carbohydrazides



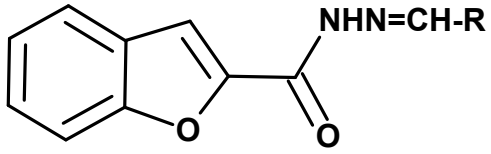
Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
1	SB-1	$-C_6H_5$	$C_{16}H_{12}N_2O_2$	264.27	142-143	72.71 (72.69)	4.58 (4.55)	10.60 (10.62)
2	SB-2	$4\text{-Cl-}C_6H_5$	$C_{16}H_{11}N_2O_2Cl$	298.72	162-165	64.33 (64.32)	3.71 (3.70)	9.38 (9.33)
3	SB-3	$4,5,6\text{-Tri-}OCH_3$ C_6H_5	$C_{19}H_{18}N_2O_5$	354.35	153-155	64.40 (64.38)	5.12 (5.10)	7.91 (7.90)
4	SB-4	$4\text{-F-}C_6H_5$	$C_{16}H_{11}FN_2O_2$	282.26	147-150	66.08 (66.10)	3.93 (3.90)	9.92 (9.93)
5	SB-5	$3\text{-}OCH_3\text{-}C_6H_5$	$C_{17}H_{14}N_2O_3$	294.30	150-151	69.38 (69.40)	4.49 (4.50)	9.52 (9.55)
6	SB-6	$2\text{-Cl-}C_6H_5$	$C_{16}H_{11}N_2O_2Cl$	298.72	163-165	64.33 (64.30)	3.71 (3.73)	9.38 (9.40)
7	SB-7	$3\text{-Cl-}C_6H_5$	$C_{16}H_{11}N_2O_2Cl$	298.72	158-160	64.33 (64.30)	3.71 (3.69)	9.38 (9.40)

Table: -1.1 Contd.



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
8	SB-8	2-NO_2-C_6H_5	$C_{16}H_{11}N_3O_4$	309.27	165-168	62.14 (62.10)	3.58 (3.55)	13.59 (13.60)
9	SB-9	3-NO_2-C_6H_5	$C_{16}H_{11}N_3O_4$	309.27	162-165	62.14 (62.15)	3.58 (3.60)	13.59 (13.63)
10	SB-10	4-NO_2-C_6H_5	$C_{16}H_{11}N_3O_4$	309.27	170-174	62.14 (62.14)	3.58 (3.60)	13.59 (13.55)
11	SB-11	2-OH-C_6H_5	$C_{16}H_{12}N_2O_3$	280.27	145-146	68.56 (68.55)	4.32 (4.30)	9.99 (10.02)
12	SB-12	4-OH-C_6H_5	$C_{16}H_{12}N_2O_3$	280.27	158-160	68.56 (68.52)	4.32 (4.29)	9.99 (10.01)
13	SB-13	4-N,N-Di-CH_3 C_6H_5	$C_{18}H_{17}N_3O_2$	307.34	130-132	70.34 (70.30)	5.58 (5.55)	13.67 (13.65)
14	SB-14	9-Anthracine	$C_{19}H_{14}N_2O_2$	302.32	167-170	75.48 (75.45)	4.67 (4.68)	9.27 (9.30)

Table: -1.1 Contd.



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
15	SB-15	3-Indole	$C_{18}H_{13}N_3O_2$	303.31	173-175	71.28 (71.30)	4.32 (4.30)	13.85 (13.87)
16	SB-16	3-Br-C_6H_5	$C_{16}H_{11}BrN_2O_2$	343.17	152-155	56.00 (55.99)	3.23 (3.25)	8.16 (8.19)
17	SB-17	3-OCH_3-C_6H_5	$C_{17}H_{14}N_2O_3$	294.30	136-140	69.38 (69.40)	4.79 (4.80)	9.52 (9.50)
18	SB-18	4-OCH_3-C_6H_5I	$C_{17}H_{14}N_2O_3$	294.30	145-146	69.38 (69.41)	4.79 (4.77)	9.52 (9.51)
19	SB-19	3,4-Di-OCH_3 C_6H_5	$C_{18}H_{16}N_2O_4$	324.33	163-164	66.66 (66.62)	4.97 (5.00)	8.64 (8.60)
20	SB-20	3-OC_6H_5-C_6H_5	$C_{22}H_{16}N_2O_3$	356.37	180-183	74.15 (74.20)	4.53 (4.50)	7.86 (7.85)

SPECTRAL ANALYSIS : (IR)

Instrument : SHIMADZU FT IR-8400 Spectrophotometer

Sample technique : KBr pellet

Frequency range : 400-4000 cm^{-1}

The region of infrared spectrum which is of greatest importance lies between 4000 cm^{-1} to 400 cm^{-1}. Absoption bands in the spectrum result from the energy changes arising as a consequence of molecular vibrations of the bond stretching and bending type. The aromaticity of the compounds is determined from the significant absoprtion around 1600-1400cm-1 and 850-600cm-1. Various functional groups shows specific absorption in the finger print region which becomes the key point in their indentification.

Spectral data of final compounds are included using the instrument, SHIMAZDU FT IR-8400, sample technique, KBr pellet, for the frequency range 4000-400 cm-1.

Looking to the spectral study of the newly synthesized benzofuran derivatives, the carbonyl group of the hydrazide functionality shows a band at around 1680-1650 cm-1 indicating amidic linkage. A broad band for the secondary amine group in the amidic functionality is seen at around 3350-3290 cm-1 which indicates the presence of (-NH) in the compound.

The stretching vibrations for the fused aromatic ring are seen at 3100-3000 cm-1. The substitutions of the aromatic ring are observed in the region of 750-650 cm-1. The ether linkage for furan ring (C-O-C) is observed at around 1210-1190 cm-1.

The stretching for the C-N appears at around 1400-1200 cm-1 which furthur adds up the evidence of the presence of the secondary amine group.

SPECTRAL ANALYSIS : (MASS)

Instrument : VG 70-S (70eV) Spectrograph for EI

Instrument : JEOL SX 102/DA-6000 Spectrograph for FAB

The mass spectrometry is used for the accurate determination of the molecular weight. It also provides information about the structure of compounds by an examination pattern. When the organic compound are bombarded with the electrons under high vaccum, each molecule looses electron by various fission processes giving rise to ions and neutral fragments.The positive ions are expelled from the ionization chamber and resolved by the means of magnetic field,. When these ions arrive at the detector, they are recorded. The intensity of the peak in the spectrum indicates the abundance of the ions. The most intense peak is called the base peak. When a single electron is removed from the molecule it give rise to molecular ion peak (M+) and has the highest mass: charge (m/z) ratio. The base peak is given the arbitrary value of 100% and the height of each othe peak is determined relative to that value.

For the current study, Instrument used was **JEOL SX 102/DA-6000** for FAB (**Fast Atom Bombardment**). The molecular ion peaks (M+) of the compounds in mass spectra were in total agreement with its molecular weight.

In case of ***SB-3***, the molecular ion peak is observed at 354 m/z (M+) peak, while the base peak is obtained at 245.0 m/z.

In case of ***SB-19***, the molecular ion peak is observed at 324 m/z (M+) peak, while the base peak is obtained at 154.0 m/z.

^{1}H NMR Spectral Study :-

Instrument :BRUKER AC 300 MHz FT-NMR

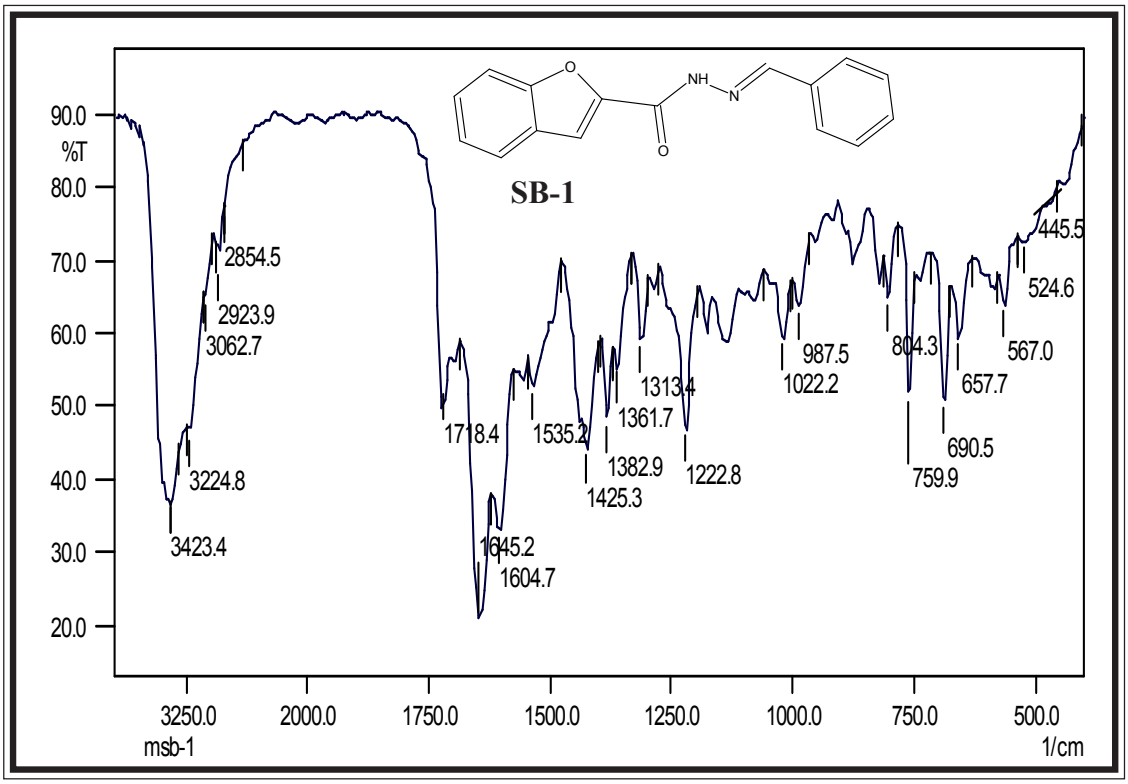
Internal reference :TMS

Solvent :$CDCl_3$ or DMSO+ d_6

In ^{1}H NMR Spectrum of N'-[(1E)-phenylmethylene]-1-benzofuran-2-carbohydrazide (SB-1), the signal at 7.46 δppm observed as multiplet for the $C_{18,19}$ protons exhibiting ortho-, meta- coupling. Along with this signal, the signal for the proton of C_{14} is merged and obtained as multiplet which can be calculated by the number of protons. The signal for the protons of $C_{18,19,14}$ is observed as multiplet at 7.91 δppm. A singlet for the proton of N_{12} is observed in very down field at 9.55 δppm.

For the signals of benzo furan ring protons, it can be observed that a doublet for the C_{10} proton is seen at 7.258 δppm due to meta coupling with the C_8 proton. A quartet is observed at 6.70 δppm for the C_7 & C_8 protons due to ortho and meta coupling with each other.

IR Spectrum of N'-[(1E)-phenylmethylene]-1-benzofuran-2-carbohydrazide (SB-1)



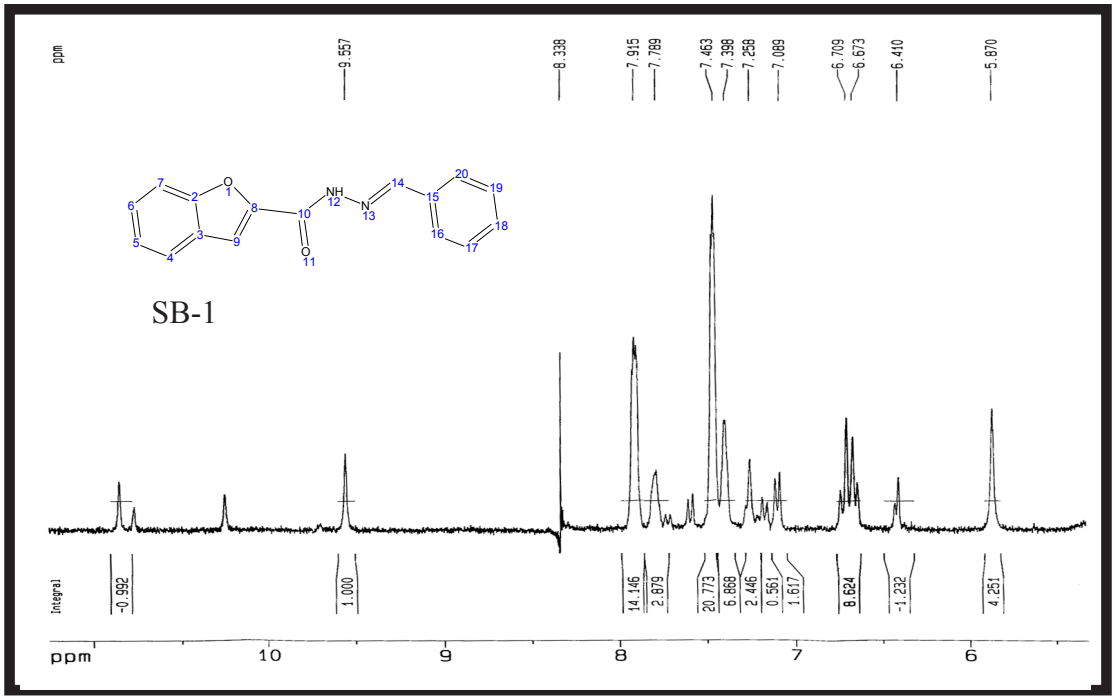
Instrument : SHIMADZU FT IR-8400

Sample technique : KBr Pellet

Frequency range : 4000-400 cm^{-1}

Type	Vibration mode	Frequency cm^{-1}
Carbonyl	>C=O Str (Ring)	1718.4
	>C=O Str (Amide)	1654.2
Amine	-NH Str.	3423.4
Aromatic	ring skeleton vib.	1604.7 1535.2 1425.3
	o.o.p.bending vib. (1,2,3-tri sub.)	804.3 759.9

^{1}H NMR Spectra of N'-[(1E)-phenylmethylene]-1-benzofuran-2-carbohydrazide (SB-1)



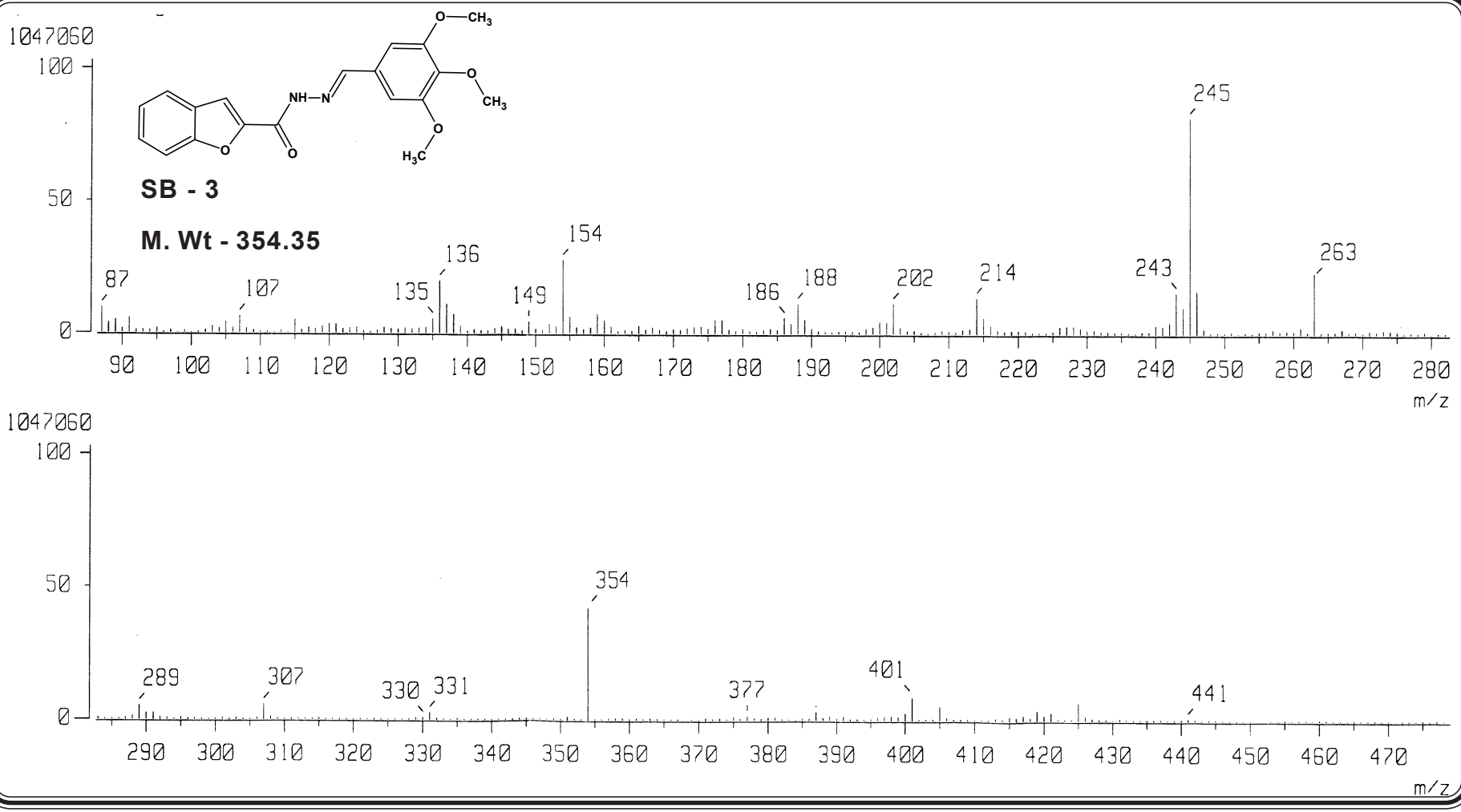
Instrument : BRUKER AC 300 MHz FT-NMR

Standard : TMS

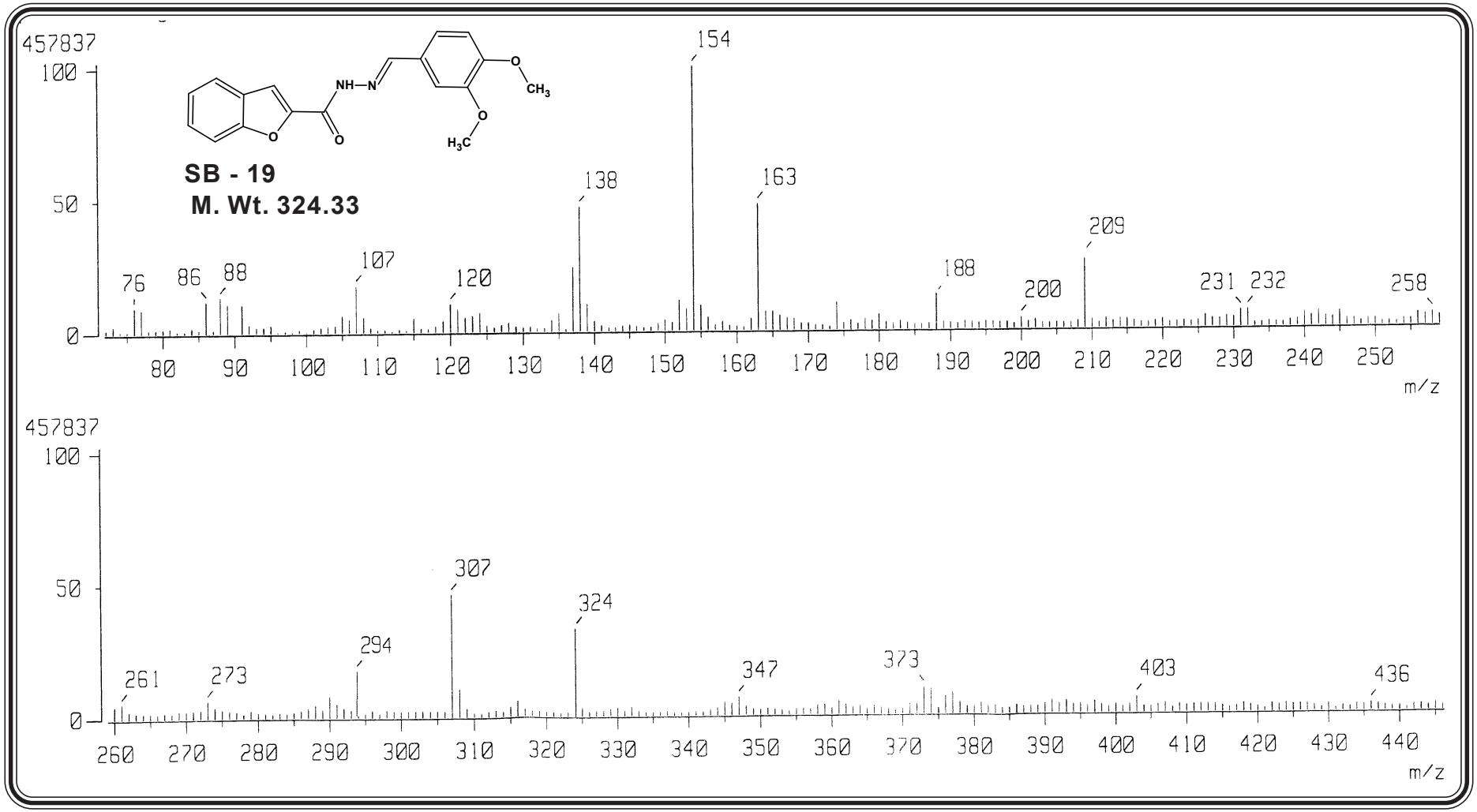
Solvent : DMSO d_6

Chemical Shift δ ppm	No. of Proton	Muliplicity	Inference
5.87	1H	S	C(9)
6.67-6.70	2H	Q	C(7,4)
7.258	2H	D	C(6,5)
7.39-7.46	2H+1H	M	C(20,16,14)
7.78-7.91	3H	M	C(17,18,19)
9.55	1H	S	N(12)

MASS Spectrum of N'-[(1E)-(3,4,5-trimethoxyphenyl)methylene]-1-benzofuran-2-carbohydrazide:- (SB-3)



MASS Spectrum of N'-[(1E)-(3,4-dimethoxyphenyl)methylene]-1-benzofuran-2-carbohydrazide:- (SB-19)



INTRODUCTION.

Multi-drug resistant Gram postitive bacterial pathogens[1-3], including methicillin resistant Staphyllococcous aureus[4] (MRSA) and Staphyllo coccus epidermidis (MRSE), vancomycin-resisitant enterococci (VRE)[5,6] and penicillin and cephalosporin resistant streptococci[7] have become a serious problem for the human community. More troublsome are the patterns of resistance that can be magnified by transfer of the genetic information among species[8]. Recent studies suggest that resistant bacteria are persistant in the nature due to the stability of resistance genes and transfer elements[9].

Few coumarins were recently indentified as anti-HIV agents and found to be useful as integrease as well as protease inhibitors arousing new interest in small molecules possessing this moieties[10-15].Due to easy acccpetibility in the biological system than its tautomeric chromone nuclues[16-19] these best known aromatic lactones were selected to study their anti-microbial activity.

1. Swartz, M.N., Hospital-acquired Infections., *Proc. Natu. Acad. Sci.*,USA, **1994**, 91, 2420.
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3. Fekete, T. The crucial interplay in Emerging Resistance Percept. *Bio.Med*, **1995,** 38, 363.
4. Brumfitt, W., Hamilton-Miller, *Drugs. Exp. Clin. Res*., **1994**, XX, 215.
5. Low, D.E., Willey, B.M., *Am. Jour. Surg*., SA **1995**, 85, 125.
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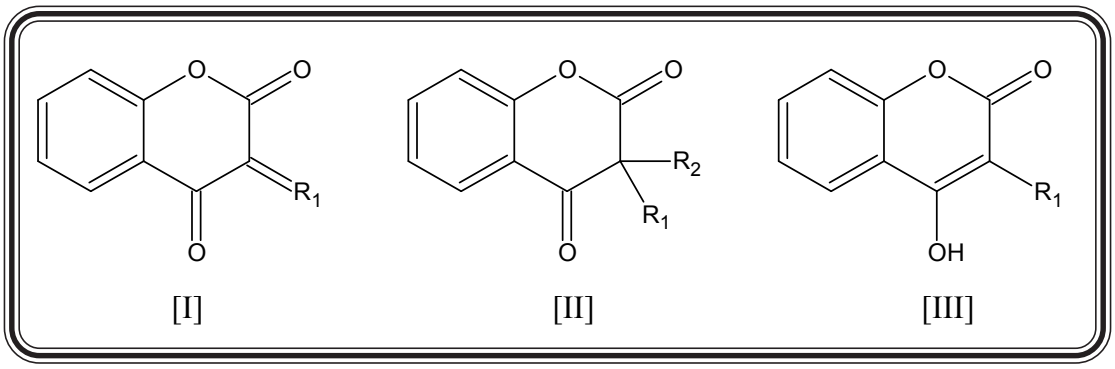
9. Salyers A. A., Amabile Cuevas, C.E., *Antimicro. Agents. Chemother.,* **1997**,41, 2321.
10. Thaisrivongs, S. Janakiraman,M. M. et. al. *J. Med. Chem*., **1996**,39, 2400.

Anti-microbial and anti-tubercular activity of 2,4-dichromane dione system were observed by Chavda and Shah et. al.[20] They observed that the introduction of electron withdrawing group like nitro or fluoro at the benzenoid part of the benzopyran ring may help in increasing the potency at much lower concentration.

In continution of this research work, the synthesis of a series of N-(methyl-ene-4-oxo coumarinyl)-carbamates by the condensation of various carbamates with 4-hydroxy coumarins in the presence of triethyl orthoformate was under taken to obtain series of compounds in 50-55% yield.[21]

Earlier to that historically very few work is reported in literature on such systems. 2, 4-chromanedione is essentially a nomenclature limited to the compounds of general formula [I] and [II]. The compounds of types [II, R1= H] are probably more closely releated to the 4-Hydroxy coumarins, being represented by the general formula [III]. Many methods are used to prepare 2,4-chromandiones and 2,3,4-chromantriones in which the ketonic nature of 4-hydroxy coumarin is established.



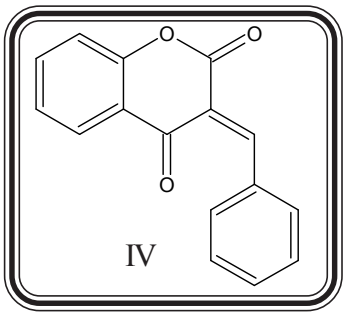
4-hydroxy coumarins [III, R_1 = H] frequently reacted with aldehydes to give 3-benzylidene-2, 4-chromandiones. The condition have been used are

(i) Heating in acetic anhydride in the presence of a little piperdine[22].

(ii) Ethanol at room[23] temperature or at reflux temperature[24].

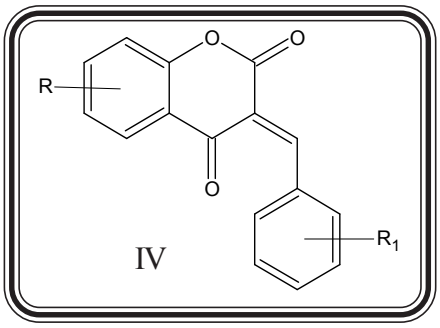
(iii) Refluxing in methanol in the presence of sodium ammonium phos phate[25].

(iv) Heating in formic acid and triethyl amine.

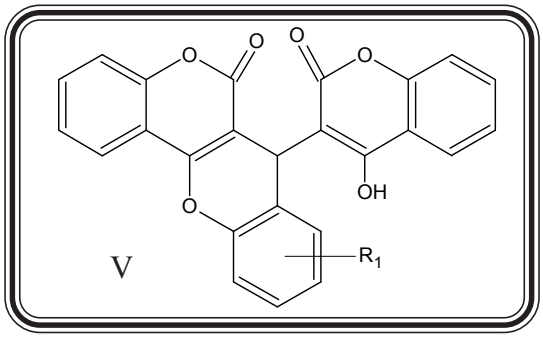


IV

In many of the reported reactions, salicylaldehyde or it's analogues were used and many multicyclic compounds of type [IV] have been isolated either as the sole product or in addition to salicylalidene derivatives.



IV



V

11. Fesen, m. R., Kohn k. W. *Nat. Acad. Sci.*, USA, **1993**, 90, 2399.

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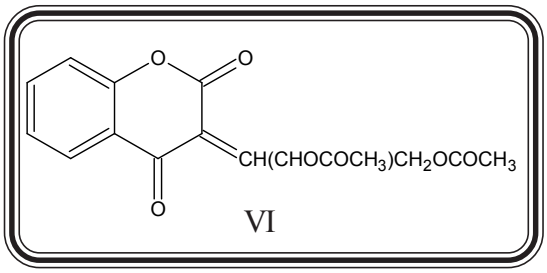
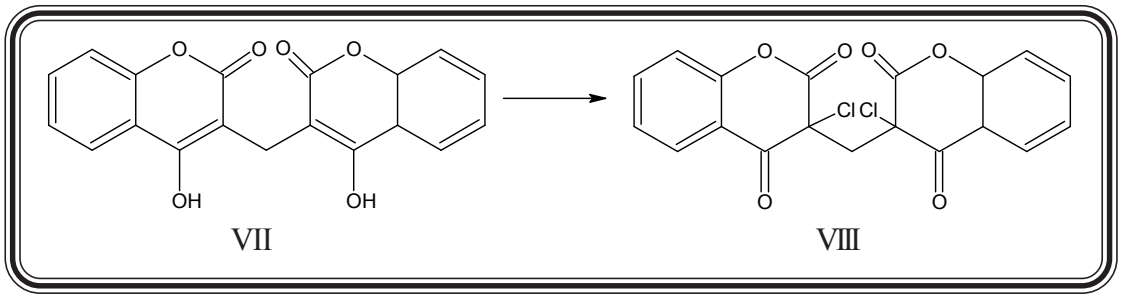
4-hydroxy coumarin has been refluxed with completely acetylated aldehydohexose in ethanol for 24 hrs.to give compounds of the type [VI] 5 the hexoses used were derived from D-glucose,D-manose,And D-galactose and yield were reported 33,48and 43 percent respsctively. Good yield of the deacetylated product were obtained on heating in methanol with few drops of perchloric acid.[26]



VI

4-hydroxy coumarin was reacted with chlorine in a suitable solvent[27] or sulfuryl chloride[28] to give 3,3-dichloro-2,4-chromandiones. When 3,3'-methylene bis(4-hydroxy coumarin) [VII] was treated[29] with sulfuryl chloride afforded to give 3,3'-methylenebis(3-chloro-2,4-chromandione) [VIII].



VII VIII

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19. Nagesam, M., Raju. M. S., *J. Ind. Chem. Soc,* **1987**, 64, 418.

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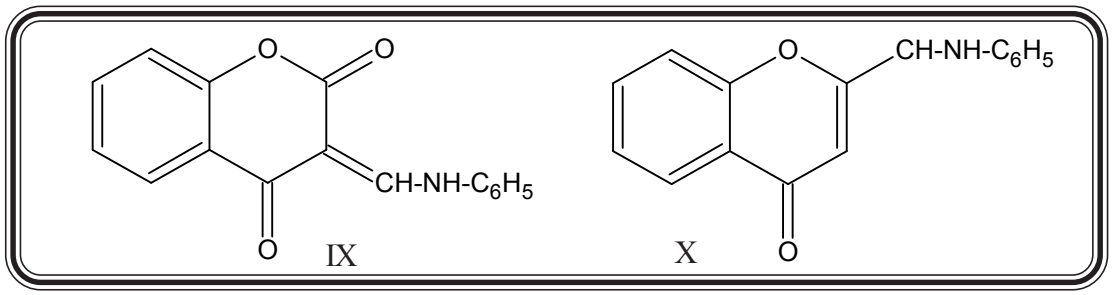
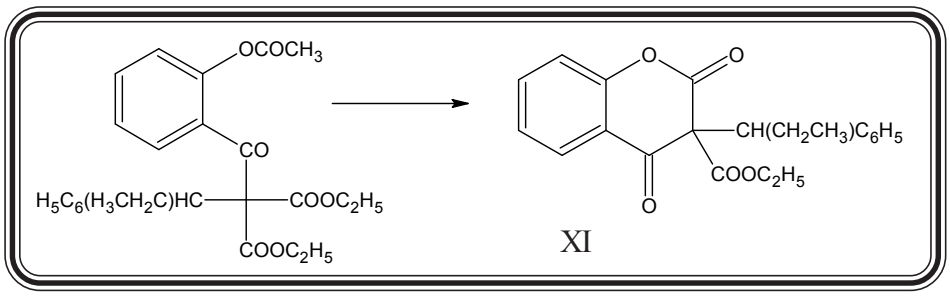
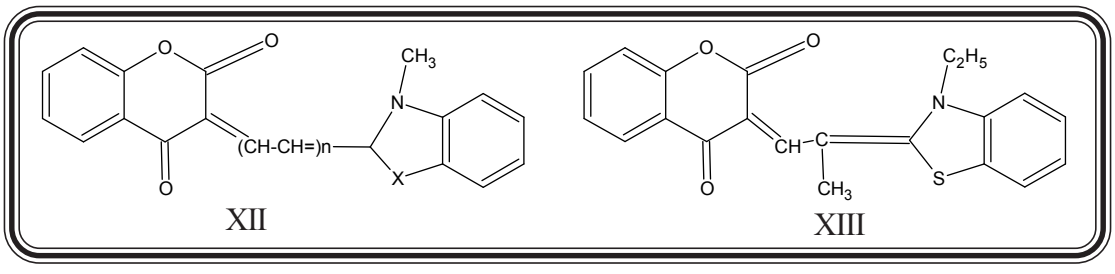
When a mixture of (2-hydroxy benzoyl) acetanilide, ethyl orthoformate, and acetic anhydride was heated at 100-110°C for 7 min., 3-anilinomethylene-2,4-chromandione [IX] was isolated in 44 percent yield together with 4 percent of the chromone-3-carboxanilide [X][30].



3-Ethoxycarbonyl-3-(1-phenyl propyl)-2,4-chromandione [XI] has been prepared by the addition of sodium methoxide to the substituted malonic ester[31].



A number of merocyanine dyes of the type [XII] have been synthesized from 4-hydroxy coumarins and 2-acetanilidovinylbenzothiazole methiodide and related compounds by refluxing for few minutes in acetic anhydride and triethyl amine1. Analogus compounds [XII] have been prepared by treatment of 4-hydroxy coumarin with 2-(2-chloro propenyl)-3-ethylbenzothiazolonium chloride[32].



Webster and Mc. Golgin[33] have prepared dimethyl aminophenyl propylidene-2,4-chromandione and it was used in the production of visible laser radiation.

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44. Ziegler, E., Junek, H., Nolken, E.; *Mh. Chem.,* **1958**, 89, 678.
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48. Ziegler, E., Hradetzky, F., Eder, M.; *Mh. Chem*., **1966**, 97,1394.
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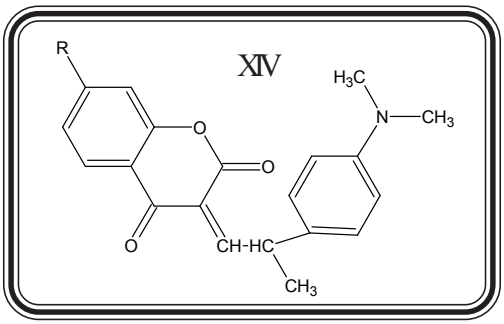
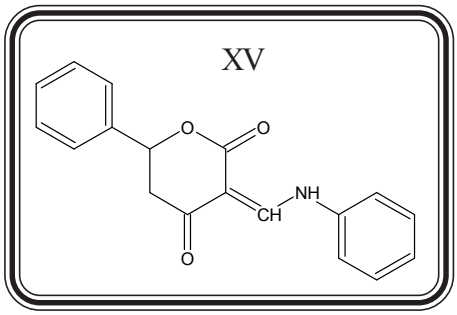
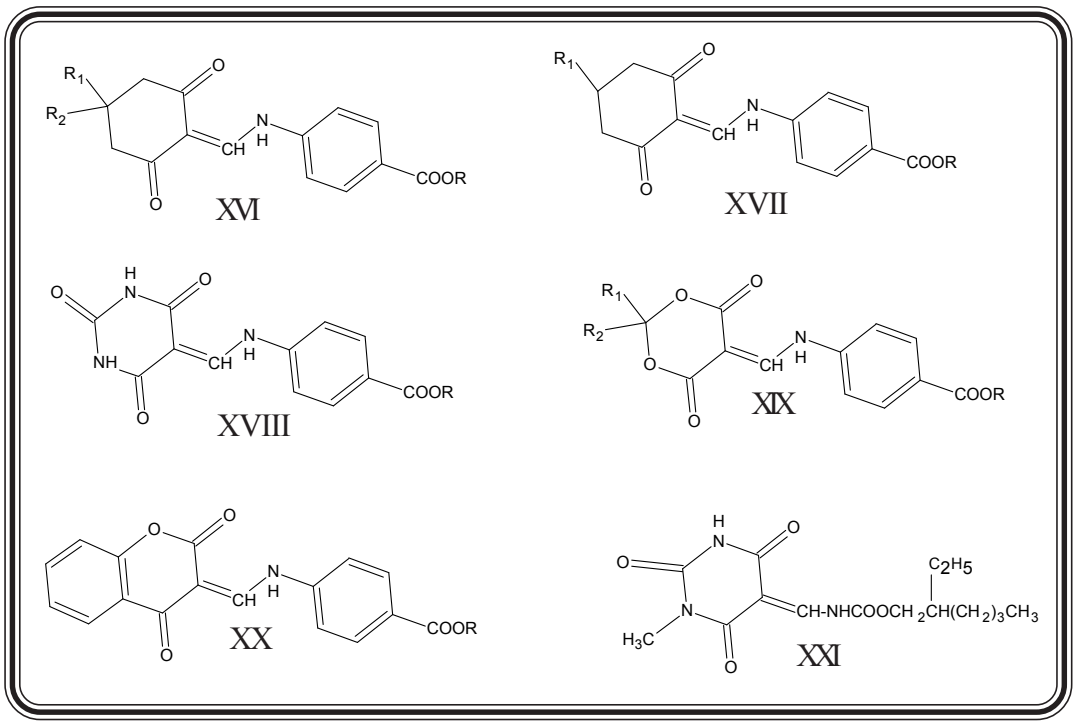
50. Peinhardt, G., Reppel, L.; *Pharmazine*, **1970**, 25, 68.

4-Hydroxy-6-phenyl-2-pyrone when condensed with triethyl orthoformate and aniline in ethanol, gave the compound of the type[34] [XV], which was cleaved in refluxing aqueous acetic acid-hydrochloric acid into 2-phenyl-4-pyrone in 62% yield.

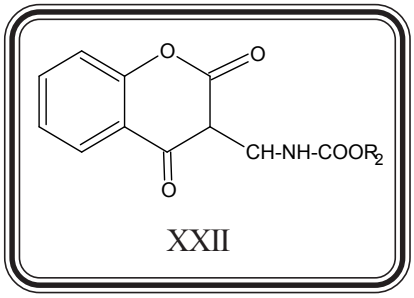




Yasude and Hukuoka[35] have reported many compounds of the type [XVI-XXI] which were claimed as UV absorbing agents, weather-resistant organic polymer compound and a cosmetic ingredient also [XVII-XXI]. It was also observed that these derivatives have an excellent UV absorption ability and a high light stability.

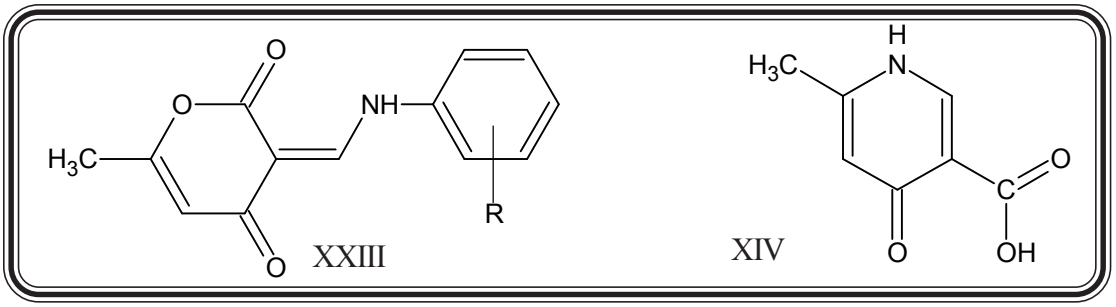


Stankovicova and coworkers[36] have studied the skeletons of the compounds of the type [XXII]. The semiempirical PM3 method has also been used for the calculatuion of the heats of formation and optimal structure of 4-chromanes [XXII].

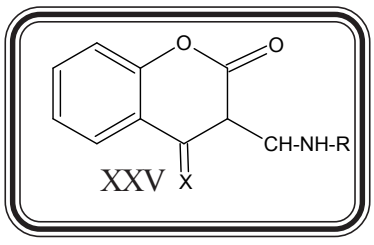


XXII

Zhengming and coworkers[37] have reported that when pyranones [XXIII] were refluxed with aqueous hydrochloric acid for 1 hr., afforded pyridine derivatives [XXIV] with 46-72 percent yield.



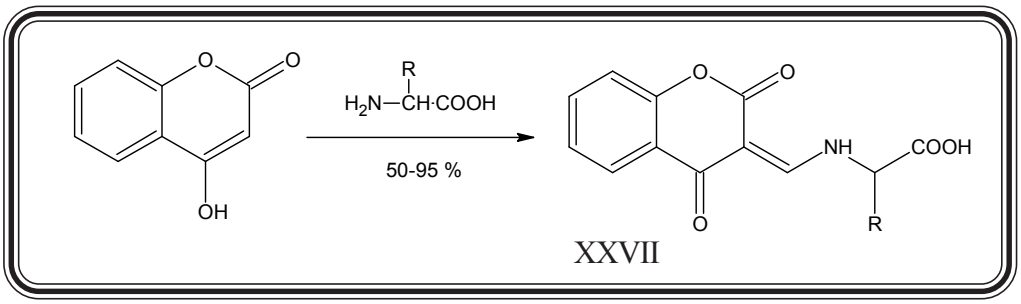
The equilibrium between Z and E isomers of the type [XXV, where X=S, Se] derived from 3-formyl-4-thio (seleno) coumarin resulting from the hindered rotation around the exocyclic carbon-carbon bond in the stable ketoamine tautomeric forms have been stuided[38] by means of IR, 1D and 2D (NOESY), NMR spectroscopy and also by ab initio and semi empirical calculation.



XXV

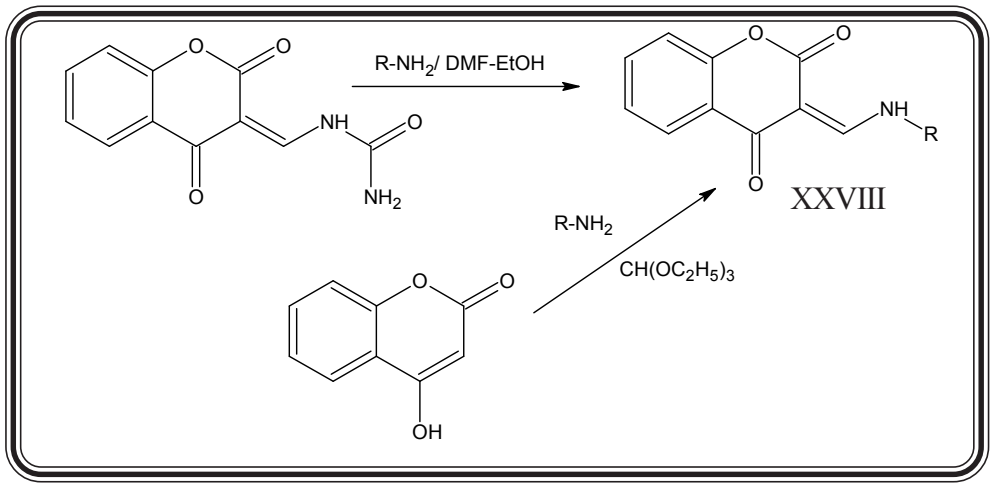
Hamdi and coworkers[39] synthesized many new compounds N-(methylene-4-oxo-coumarinyl) carbamates [XXVI] by the condensation of carbamates with 4-hydroxy coumarin in the presence of triethyl orthoformate with good yield.

Further when 4-hydroxy coumarin reacted with á-amino acids in the presence of excess triethyl orthoformate gave the compounds of the type [XXVII] with good yield. The amino acids like glycine, alanine, leucine, phenyl alanine, tyrosine, tryptophan, L-dopa, serine, crysteine, glutamic acid and glutamine were used[40].



XXVII

It was also revealed[41] that N-(methylene-4-oxo coumarinyl) amines of the type [XXVIII] have been prepared by aliphatic and aromatic amines with 3-ureido methylenecoumarins. The compounds of the type [XXVIII] were prepared by the reaction of amines with 4-hydroxy coumarin and triethyl orthoformate with 40-90 % yield.

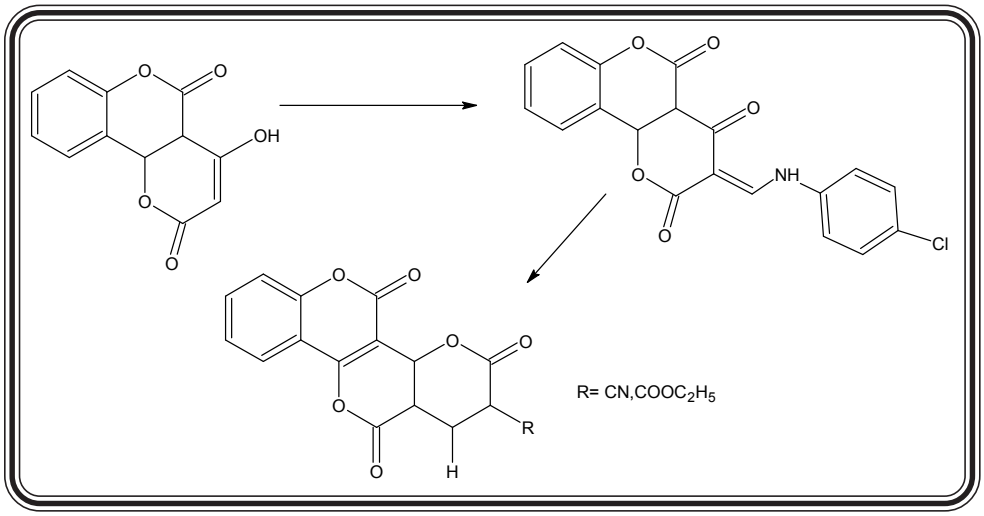


XXVIII

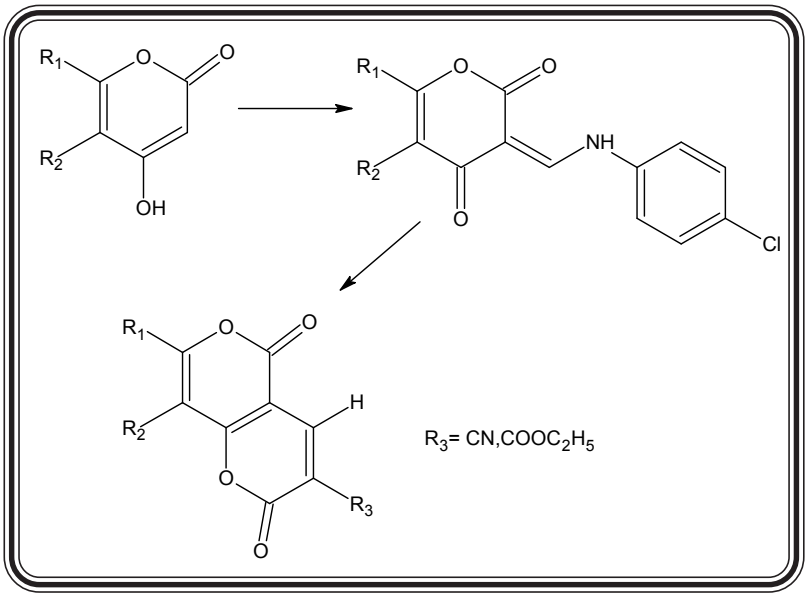
It was also observed that the addition of the amine at site C_3 of the unsaturated α–β ketone system with elimination of urea indicated that the –NHR group is a poor leaving group. This reaction can also be carried out with substituted 3-ureidomethylenecoumarin with elimination of the substituted urea.

Numerous applications of methylene oxopyrone amines as an intermediate have been found from different literature and are summarized as below.

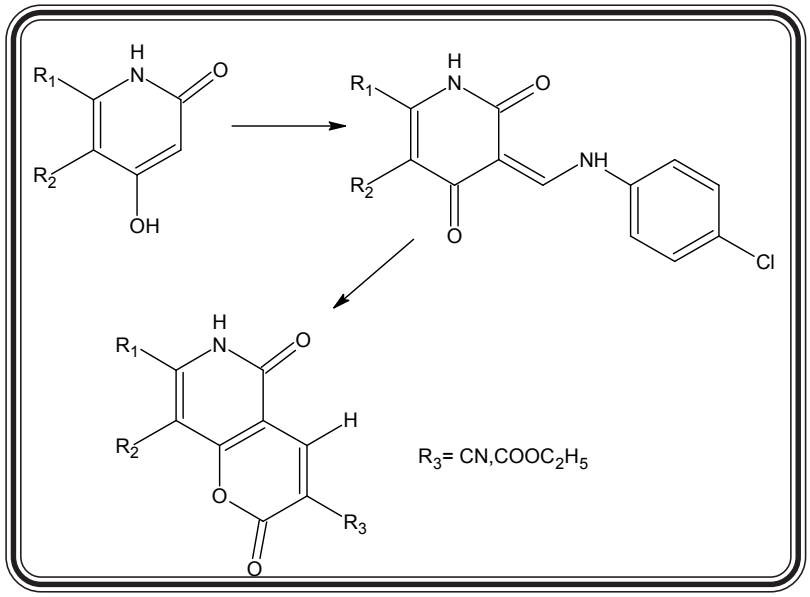
- Ziegler, E. and co workers[42].



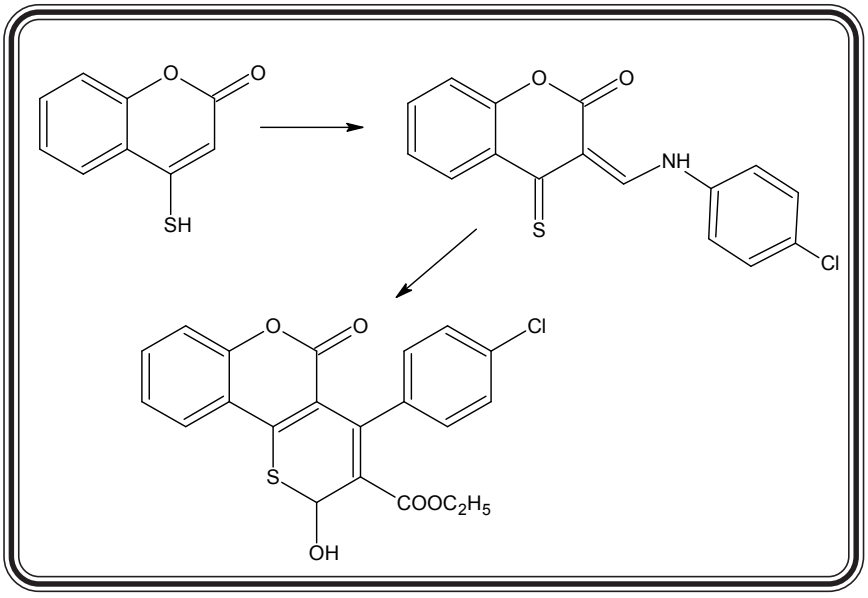
- Butt, M.A. and co workers.;[43], Ziegler, E., Junek, H.;[44]; Wolfebeis, O.S.[45].



- Zielger, E. and co workers[46-48]; Kappe, Th.[49]



- Peinhardt, G., Roppel, L.[50]



SYNTHETIC ASPECT :

Many modifications on 2,3,4-chromantriones were studied[51] in this laboratory for their anti-HIV, antitubercular and anticancer activities. Recently, it was found that the C_3 position on the coumarin nucleus led to antimicrobial properties by introducing appropriate functional groups containing an aliphatic chain.

In the present chapter, the tautomeric 4-hydroxy coumarin systems were used to be attacked by basic nitrogen of different amino acids to obtain newer molecules.

All reaction schemes are outlined on page no. **13**

51. a) Thaker, D.; *Ph.D Thesis*, Saurashtra University, **1996**.
    b) Sureja, D.; *Ph.D Thesis*, Saurashtra University, **1997**.
    c) Naliyapara, Y.; *Ph.D Thesis*, Saurashtra University, **1998**.
    d) Desai, B.; *Ph.D Thesis,* Saurashtra University, **2000**.
    e) Chavda, M.; *Ph.D Thesis*, Saurashtra University, **2000**.
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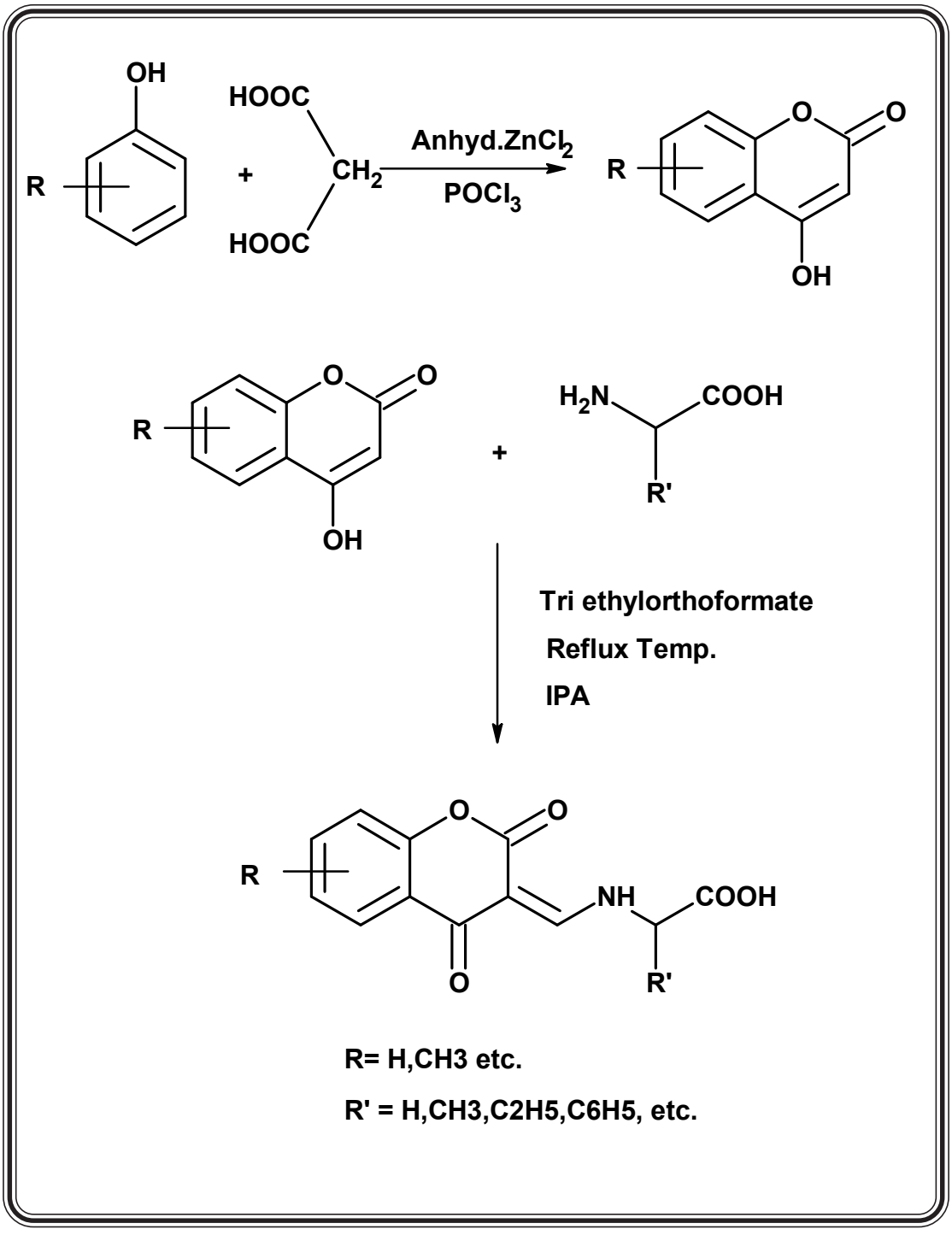
Reaction Secheme



R= H,CH3 etc.

R' = H,CH3,C2H5,C6H5, etc.

EXPERIMENTAL

1) Preparation of 7-Methyl 4-hydroxy coumarins :

It was prepared according to the method of Shah and co-workers[52].

3-methyl phenol (0.1 mole) and malonic acid (0.1 mole) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 ml), And the reaction mixture was heated on water bath at 70 ^{o}C for 10 Hrs. The reaction mixture cooled to room temperature & quench into ice water to afford a brown yellow color solid, which was filtered and wash with water. The solid material was dissolved in to 10% sodium carbonate solution & filtered to remove undissolved material. The filtrate was slowly acidified with dilute hydrochloric acid. Solid product separated, which was filtered and washed with water, dried and recrystallised from ethanol. m. p. 240-242 ^{0}C (Reportd[52] m.p. 241-242 ^{0}C)

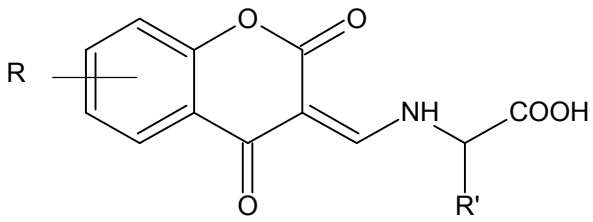
2) Preparation of 2-[(*Z*)-(7-methyl-2,4-dioxo-2*H*-chromen-3(4*H*)-ylidene) Methyl] amino}] acid

General method:-

A mixture of 7-methyl 4-hydroxy coumarin (0.01 mol), tri ethyl orthoformate (0.015 mol.) & different amino acid (0.01 mol.) in 25 ml Isopropyl alcohol was refluxed under stirring for 4 hrs. The precipitates formed after cooling the reaction mixture, was filtered and washed with chilled isopropyl alcohol. The crude product crystallized from appropriate solvent. Yield ~ 45-50%.

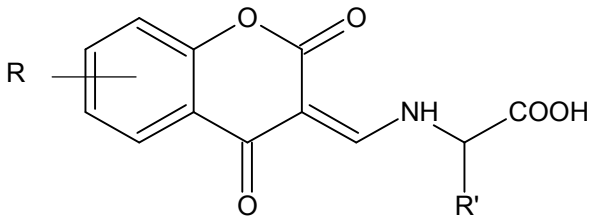
The compound gave satisfactory elemental analysis. A series of compounds were also prepared using different amino acid. The physical and analytical data of this compounds are given in table No. **2.1**

Table 2.1 Physical constants of substituted-2-{[(*Z*)-(2,4-dioxo-2*H*-chromen-3(4*H*)-ylidene)methyl]amino}propanoic acids



Sr. No.	Code No.	Substitution		Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
		R	R'				C	H	N
1	MB/01	7-CH_3	H	$C_{13}H_{11}NO_5$	261.23	252-254	59.77 (59.79)	4.24 (4.22)	5.38 (5.39)
2	MB/02	7-CH_3	C_2H_5	$C_{15}H_{15}NO_5$	289.28	260-262	62.28 (62.25)	5.23 (5.20)	4.84 (4.89)
3	MB/03	7-CH_3	CH_2COOH	$C_{15}H_{13}NO_7$	319.26	235-237	56.43 (56.40)	4.10 (5.07)	4.39 (4.42)
4	MB/04	7-CH_3	CH_2SH	$C_{14}H_{13}NO_5S$	30732	220-222	54.71 (54.73)	4.26 (4.23)	4.56 (4.53)
5	MB/05	7-CH_3	$(CH_2)_3NH_2$	$C_{16}H_{18}N_2O_5$	318.32	188-191	60.37 (60.39)	5.70 (5.66)	8.80 (8.91)

Table 2.1 Contd.



Sr. No.	Code No.	Substitution		Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
		R	R'				C	H	N
6	MB/06	7-CH_3	CH_3CHOH	$C_{15}H_{15}NO_6$	305.28	235-237	59.01 (59.05)	4.95 (4.92)	4.59 (4.60)
7	MB/07	7-CH_3	$C_6H_5CH_2$	$C_{20}H_{17}NO_5$	351.35	255-260	68.37 (68.40)	4.88 (4.89)	3.99 (4.01)
8	MB/08	7-CH_3	$(CH_3)_2CH_2CH$	$C_{17}H_{19}NO_5$	317.33	237-240	64.34 (64.31)	6.03 (6.00)	4.41 (4.37)
9	MB/09	7-CH_3	HO-C_6H_4-CH_2	$C_{20}H_{17}NO_6$	367.35	248-251	65.39 (65.42)	4.66 (4.63)	3.81 (3.77)

SPECTRAL ANALSIS : (IR)

Instrument : SHIMAZDU FT-IR-8400 Spectrophotometer.

Sample Technique : KBr pellet

Frequency range : 4000-400cm-1.

In general, the IR Spectrum of the newly synthsized amino acid derivatives can be explained as : The carboxylic acid funcitionality gives the broad peak around 3400-2900 cm-1. The secondary amine of the amino acid group linked to the ethylinic carbon gives a peak in the range of 3300-3200 cm-1.The frequency for the ketone group of the coumarin ring is observed at around 1715-1700 cm-1. The aromatic ring gives stretching band at 3030-3000 cm-1.

In the IR spectrum of MB-2,MB-3,MB-4, a broad band for the -OH functionality of acidic group is observed at around 3400-2800 cm-1 indicating intermolecular bonding. The ketone group of the coumarin is observed at 1717-1710 cm-1 which indicates presence of the two ketone group. The ketone group of the acid functional group is seen at around 1680 cm-1. A sharp band for the secondary functional group (-NH) of amino acid is observed at 3300-3250 cm-1.

The bending vibratiions for the aromatic group are observed at around 1650-1400 cm-1. In all the sample IR spectrum, the bending for the methyl group ($-CH_3$) of aromatic ring is seen at 1385 cm-1. In case of ***MB-2***, the bending vibration for the ($-CH_2$) group is observed at around 1450 cm-1.

^{1}H NMR Spectral Study :-

Instrument :BRUKER AC 300 MHz FT-NMR

Internal reference :TMS

Solvent :$CDCl_3$ or DMSO+ d_6

Looking to the NMR spectra of the compound MB-1 and MB-2, a singlet of aromatic methyl proton (-CH_3) was observed in the range of δ 2.40 to 2.50. The multiplet of proton due to -NH-CH-COOH was observed at around δ 6.5ppm. The aromatic proton were observed in range of δ 7.25-7.60 ppm.

Singlet of acidic proton (-COOH) was observed in range of δ 10.80 to 10.90. The doublet of -NH protonis observed at δ 9.87.

SPECTRAL ANALYSIS : (MASS)

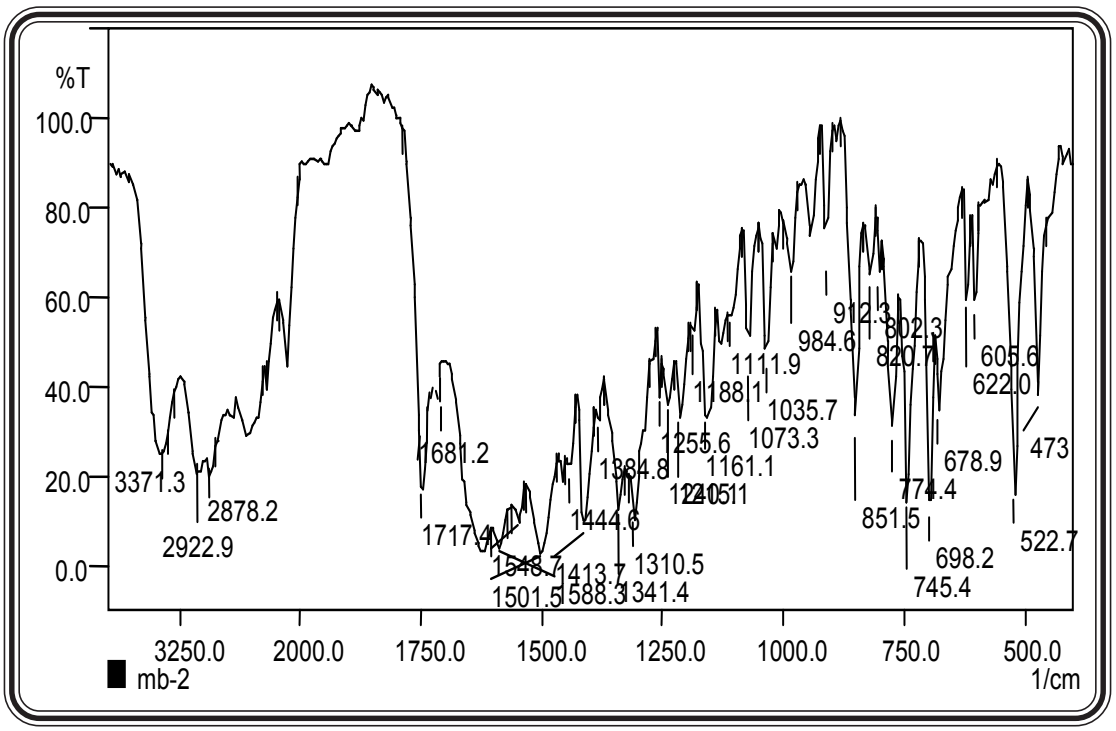
Instrument : VG 70-S (70eV) Spectrograph for EI

Instrument : JEOL SX 102/DA-6000 Spectrograph for FAB

For curunt study, Instrument used was **JEOX SX 102/DA-6000** for FAB. The molecular ion peaks (M^+) of the compunds in mass spectra were total agreement with its molecular weight.

In case of **MB-1**, the molecular ion peak is observed at 262 m/z (M^+) peak, while the base peak is obtained at 154 m/z.

IR Spectrum of 1-ethyl-2-[(*Z*)-(7-methyl-2,4-dioxo-2*H*-chromen -3(4*H*)-ylidene)methyl]hydrazinecarboxylic acid: - (MB-2)



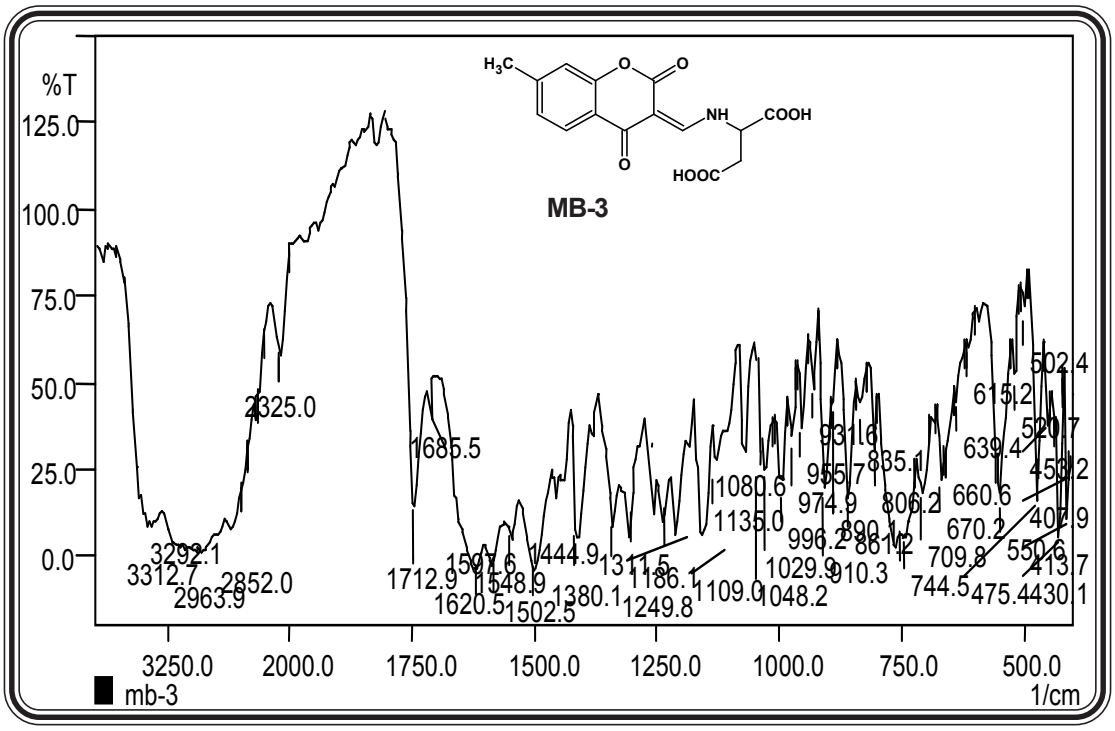
Sample Technique : KBr Pellet

Instrument : SHIMADZU FT-IR-8400

Frequency range : 4000-400cm^{-1}

Vibration Mode	Observed cm^{-}	Refrence cm^{-}
-NH- (Strech.)	3389	3400-3300
-C=O (cyclic)	1717	1715-1735
-C=O (acidic)	1681	1700-1715
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-CH_2-(Rocking)	1459	1470-1400
-CH_3 (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H) (OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

IR Spectrum of 1-(carboxymethyl)-2-[(*Z*)-(7-methyl-2,4-dioxo-2*H*-chromen-3(4*H*)-ylidene)methyl]hydrazinecarboxylic acid:- (MB-3)



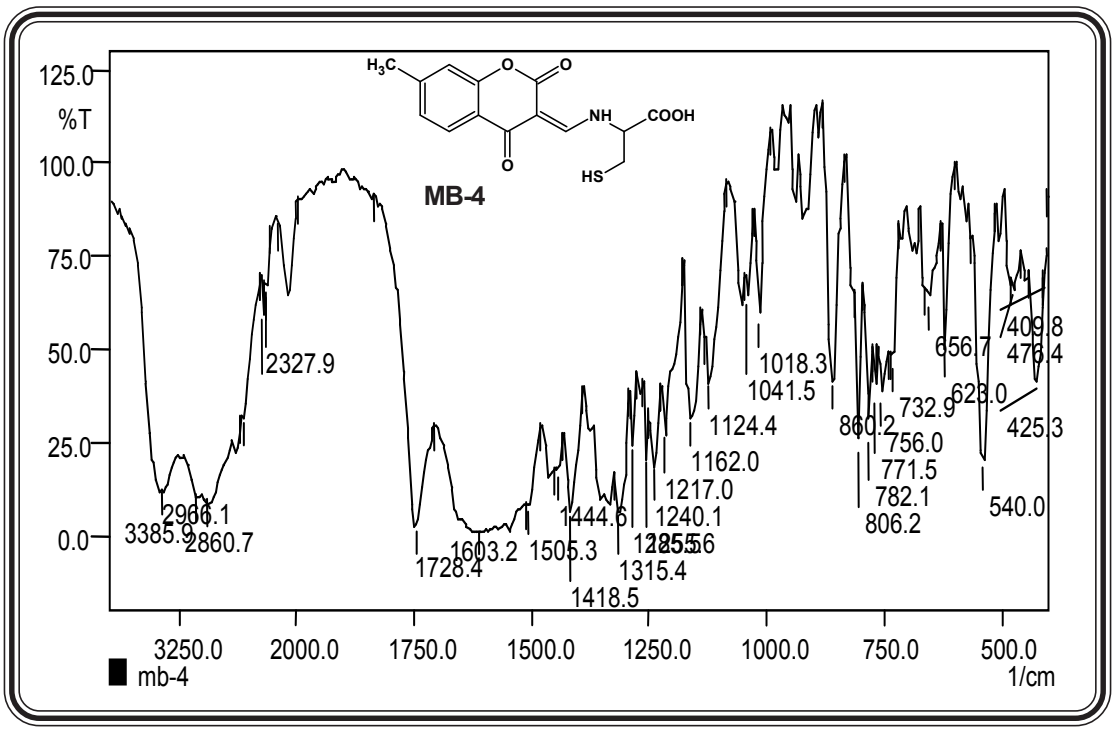
Sample Technique : KBr Pellet

Instrument : SHIMADZU FT IR-8400

Frequency range : 4000-400cm^{-1}

Vibration Mode	Observed cm^{-}	Refrence cm^{-}
-NH- (Strech.)	3389	3400-3300
-C=O-(cyclic)	1712	1715-1735
-C=C- (acidic)	1685	1700-1715
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-CH_2- (Rocking)	1459	1470-1400
-CH_3 (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H) (OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

IR Spectrum of 1-(mercaptomethyl)-2-[(*Z*)-(7-methyl-2,4-dioxo-2*H*-chromen-3(4*H*)-ylidene)methyl]hydrazinecarboxylic acid:- (MB-4)



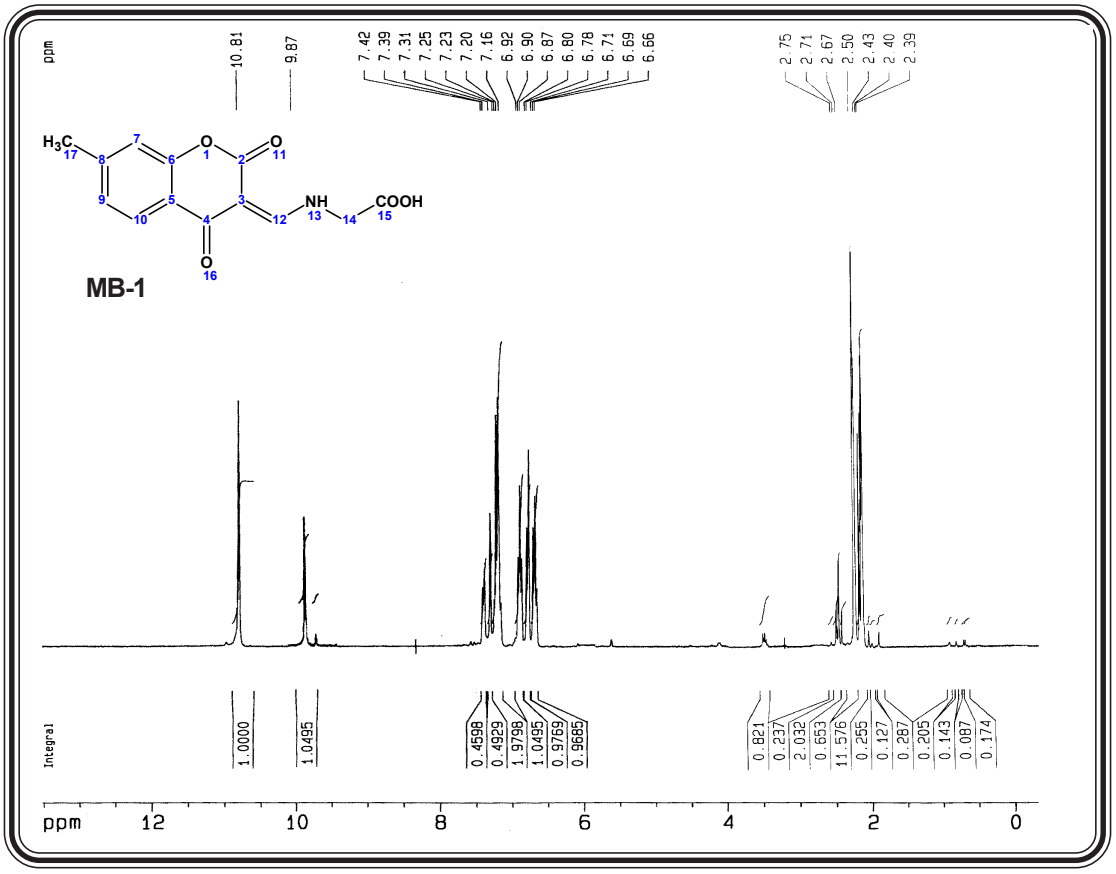
Sample Technique : KBr Pellet

Instrument : SHIMADZU FT IR-8400

Frequency range : 4000-400cm^{-1}

Vibration Mode	Observed cm^{-}	Refrence cm^{-}
-NH- (Strech.)	3389	3400-3300
-C=O- (Strech.)	1728	1715-1735
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-CH_2-(Rocking)	1459	1470-1400
-CH_3 (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H) (OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

^{1}H NMR Spectrum of [(*Z*)-(7-methyl-2,4-dioxo-2*H*-chromen-3(4*H*)-ylidene)methyl]amino}acetic acid:- (MB-1)



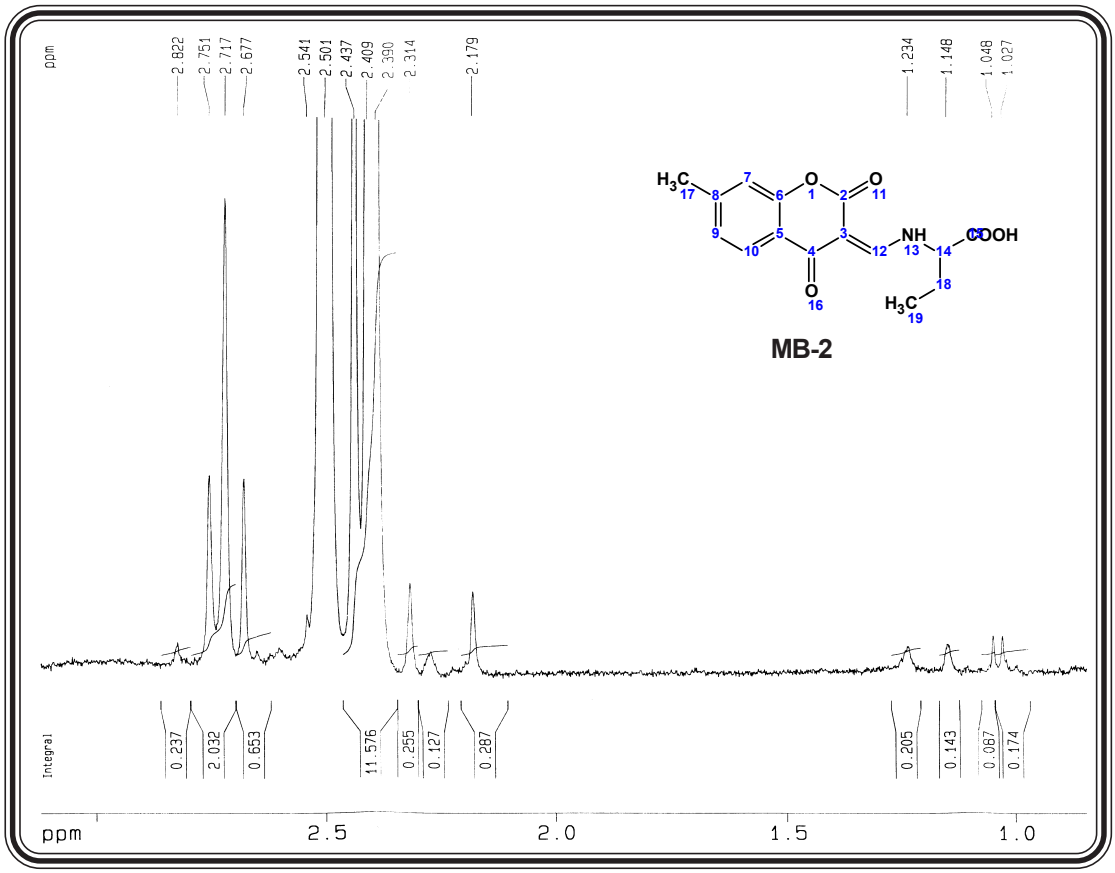
Instrument : BRUKER AC 300 MHz FT-NMR

Standard : TMS

Solvent : $DMSOd_6$

Type	No. of Proton	Multiplicity	δ PPM
-Acidic H	1	Singlet	10.81
$-CH_2$	2	Singlet	2.75
=CH	1	Singlet	7.16-7.42
Ar-H	3	Multiplet	6.66-7.42
$-CH_3$	3	Singlet	2.50
-NH-	1	Triplet	9.87

^{1}H NMR Spectrum of 1-ethyl-2-[(*Z*)-(7-methyl-2,4-dioxo-2*H*-chromen -3(4*H*)-ylidene)methyl]hydrazinecarboxylic acid:- (MB-2)



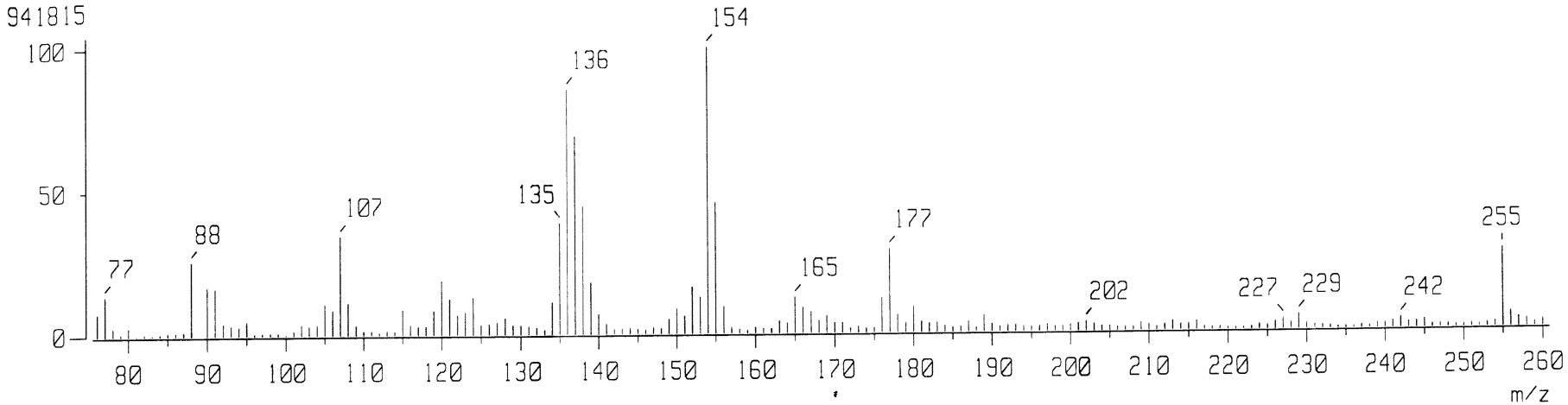
Instrument : BRUKER AC 300 MHz FT-NMR

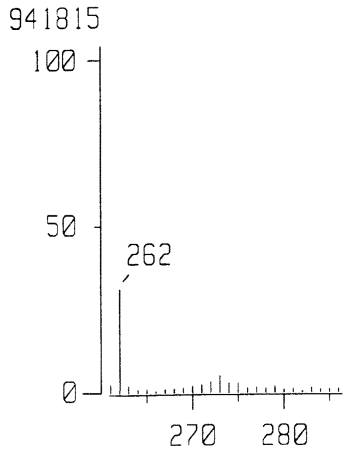
Standard : TMS

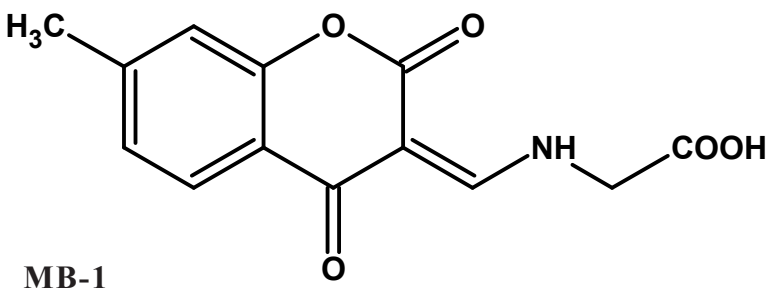
Solvent : $DMSOd_6$

Type	No. of Proton	Multiplicity	δ PPM
$-CH_3$	6	Singlet	2.50
$-CH_2$	2	Singlet	2.75
=CH	1	Singlet	7.5
Ar-H	3	Multiplet	6.50-7.50
-NH-	1	Doublet	9.87
Acidic H	1	Singlet	10.80-10.90

Mass Spectra of (*Z*) - (7-methyl-2,4-dioxo-2*H*-chromen-3(4*H*)-ylidene)methyl]amino}acetic acid:- (MB-1)





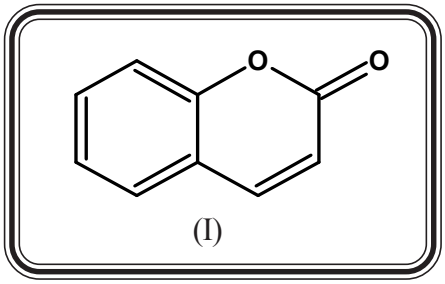


MB-1

M. Wt. = 261.230

INTRODUCTION

First Vogel[1] reported the isolation of coumarin from *tonka beans*, bearing the aroma of cutted grass in 1820. Coumarin (I) was synthesized in 1868 on treatment of sodium salt of ortho hydroxy benzaldehyde with acetic anhydride by W .H. Perkin et. al[2-3].



(I)

The coumarin ring skeleton is found in many natural products such as a novobiocine, coumermycin, psoralen, bergapten, imperatorin, gerbera coumarin, ferulenol, etc.

The coumarin ring skeleton is also used as a versatile synthon for the preparation of number of heterocyclic compounds with different biological & pharmacological activity. Extensive studies were carried out on isolation, structure elucidation and its pharmacological studies of natural occurring coumarin and its derivatives by many researchers[4-14].

---

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SYNTHESIS OF 4-HYDROXY COUMARIN

Several methods are reported for synthesis of 4-Hydroxy coumarin and their substituted derivatives namely.

1. Anschutz method[15].
2. Kaneyuki method[16].
3. Paul-Lokermann Synthesis[17].
4 Robertson Synthesis[18].
5. Sonn's Synthesis[19].
6. Mentzer Synthesis[20].
7. Garden's method[21].
8. Ziegler & Junek method[22].
9. Resplandy Method[23].
10. Jain, Rohatagi & Sheshadri method[24].
11. Shah, Bose & Shah method[25-6].

Shah and co workers[6] have prepared 4-hydroxy coumarin derivatives in good yield & quality by condensation of different phenol /substituted phenols with malonic acid in the presence of anhydrous zinc chloride and phosphorus oxychloride. This method is very simple & useful for the preparation of 4-hydroxy coumarin & substituted 4-hydroxy coumarins.

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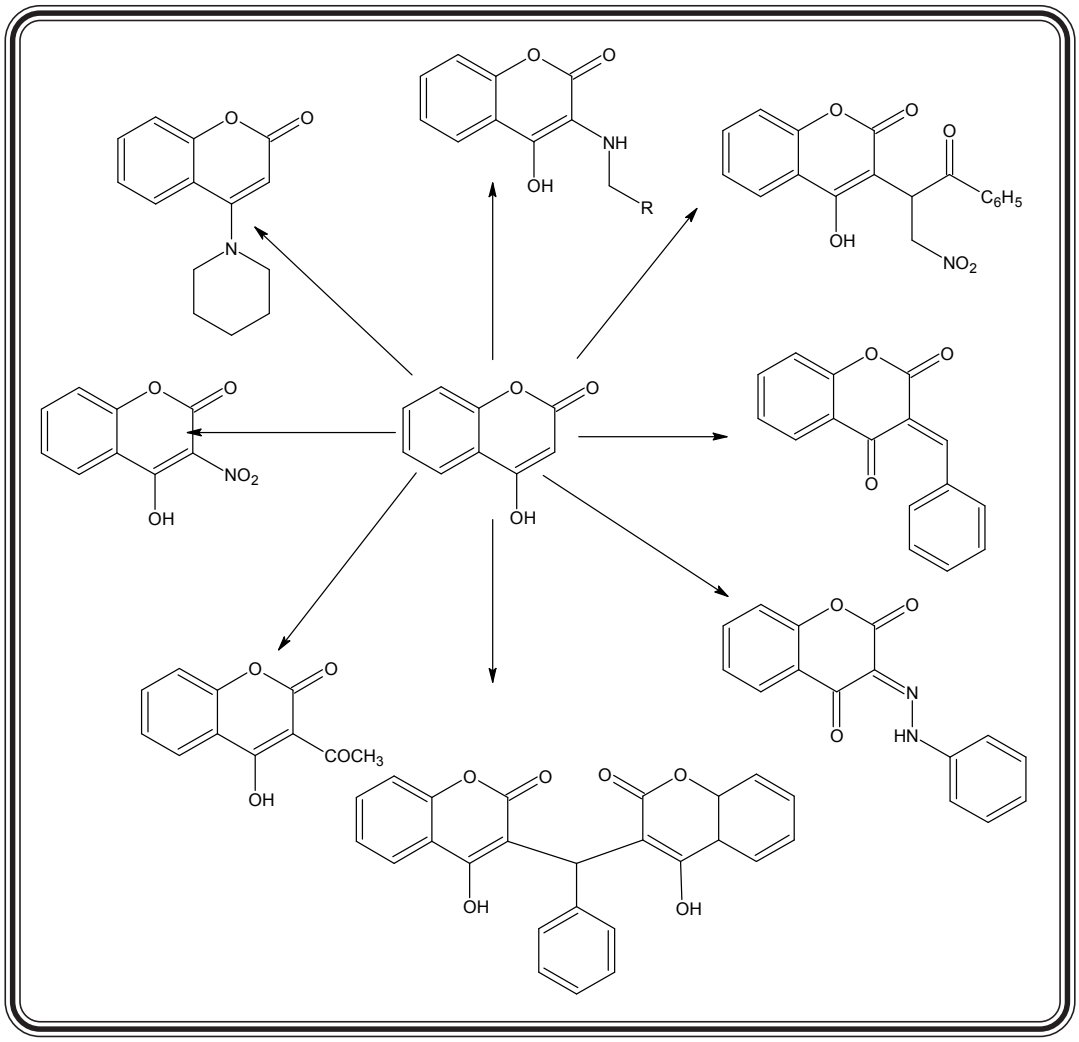
4-HYDROXY COUMARIN : - A VERSATILE SYNTHON

4-Hydroxy coumarin came out as versatile synthon. Numbers of heterocyclic compounds have been synthesized from 4-hydroxy coumarin.



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BIOLOGICAL ACTIVITY ASSOCIATED WITH COUMARIN DERIVATIVES

Coumarin derivatives posses different types of pharmacological activities such as anti-coagulant[26], antipsorratic[27], antifungal, antibacterial[28], anticancer, psychotropic, tuberculostatic, pesticidal, fungicidal, rodenticidal, as well as insecticidal activity against mosquito larvae.

Natural occurring coumarins such as psoralen, bergapten and imperatorin are used as anti psoriatic drug against psoriasis[29]. They have also have been reported as antifungal agents[30].

Buu-Hoi and coworkers[31] have synthesized 3-aryl coumarins as potential anticancer & antiviral agents.

Elderfield & Roy[32] have synthesized nitrogen mustard coumarins as a potential anti cancer agents.

Warfarin, Dicoumarol & acenocoumarole found active as anti-coagulant drugs. Tetrameric & dimeric coumarins also found to be HIV integrase inhibitors[33].

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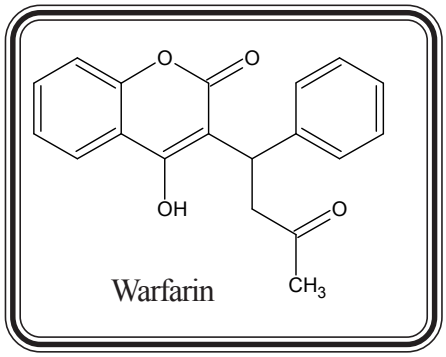
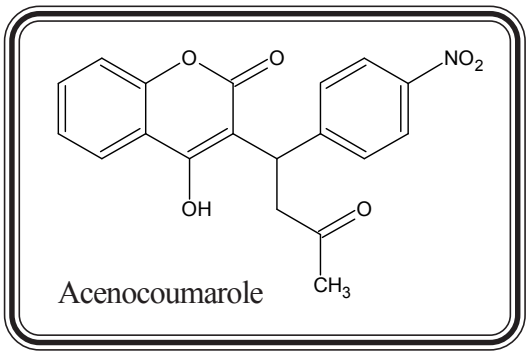


Warfarin



Acenocoumarole

Christopher Gleye et. al.[33] have carried out acaricidal activity of tonaka bean extract.

The natural occurring coumarin derivatives have attracted much attention mainly because of their potent anti bacterial & anti HIV activity. The coumarin derivatives are a class of molecule that exhibits antimicrobial activity also.

SYNTHETIC ASPECTS

Vora[34] have synthesized many 4-aryl aminocoumarins and studied their anti HIV activity . All the synthesized compounds were tested against the replication of HIV-1(III-B) and HIV-2 (ROD) at subtoxic concentration in acutely infected MT-4 cell lines.

The tested compounds were found to be very less active. The poor activity may be attributed to the solubility of compounds. It may conclude that substitution present on the coumarin skeleton as well as on C-4 carbon; phenyl ring did not play any important role in anti HIV activity. These results help us to design new set of synthetic molecules possessing improved solubility & with basic structure modification required for anti HIV activity.

---

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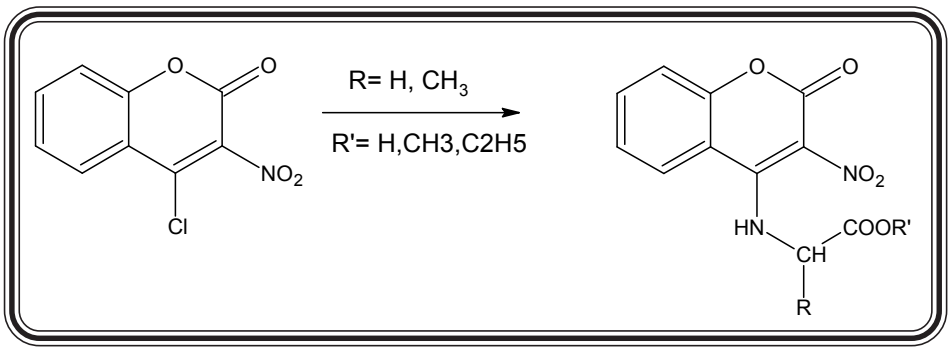
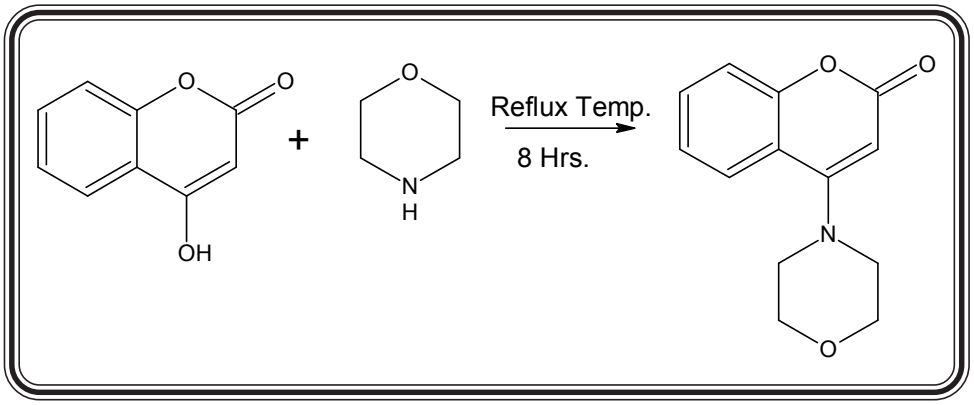
SYNTHESIS OF 4-PIPERIZINO COUMARINS.

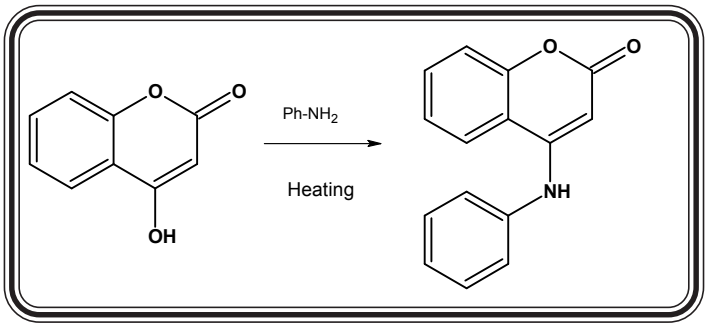
Chansok et. al.[35] prepared 3 & 4 morpholino coumarin from 4-bromo coumarin. They got mixture of 3 & 4 morpholino coumarins. Stannic & co workers[35a] have synthesized N-substituted 3-Nitro coumarinyl amino acid from 4-chloro 3- nitro coumarin.



Chakrabarty & coworkers[36] have synthesized 4- morpholino coumarin by refluxing 4-hydroxy coumarin in morpholine for 8 hrs.



Anschutz[36a] reported the synthesis of 4-anilino coumarin by heating 4-hydroxy coumarin with aniline.



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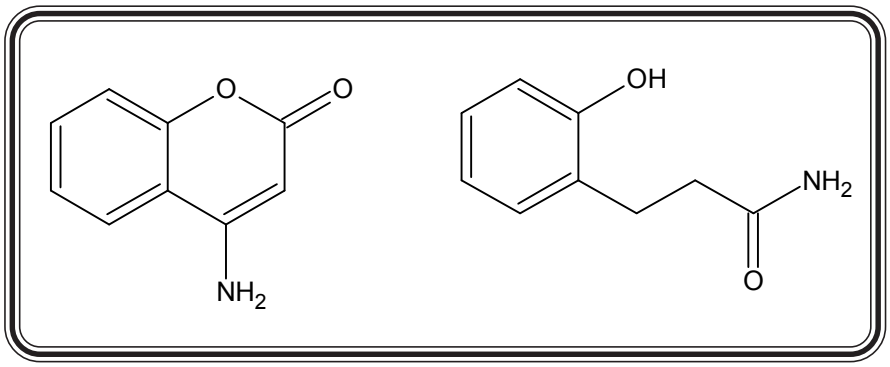
35a. Tabakovic, Stunic Z., M., LAcan, R., *J. of Heterocycl. Chem.*, **1997**, 34, 1821.

Zagorevaskii[37] reported that the action of liq. Ammonia on 4-chloro coumarin in the presence of copper powder exclusively afforded-amino coumarin. In another method 4-chloro coumarin, when treated with conc. ammonium hydroxide in dioxan for 40 Hrs at room temp. afforded 4-amino coumarin in 25 % yield &o-hydroxy phenyl propionamide in 52 % yield due to opening of the lactone ring.



Barden et. al.[38], El-Ebrashi[39] have prepared 4-amino coumarin by condensation of primary & secondary amine with 4-chloro coumarin under reflux in xylene.

Bhatt and Thakor[40] have synthesized 4-aryl amino coumarins by direct condensation of 4- hydroxy coumarin with different aryl amines.

Tabakovic et. al.[40a] synthesize 4-anilino coumarin by direct condensation of 4-hydroxy coumarin with aryl amine without using solvent.

---

36. Chakraborty,D. P.,Gupta, A. D.,Bose,P. K., *Ann. Biochem. Exp. Med.,***1958**,17,59.

36a. Anschutz, R., Liebigs, *Ann. Chem. Soc.*, **1909**,367, 204.

37. Zagorevskii, V. A. & Dudykina, N. V., Zh., *Obsch. Khim.*, **1962**, 32, 2384.

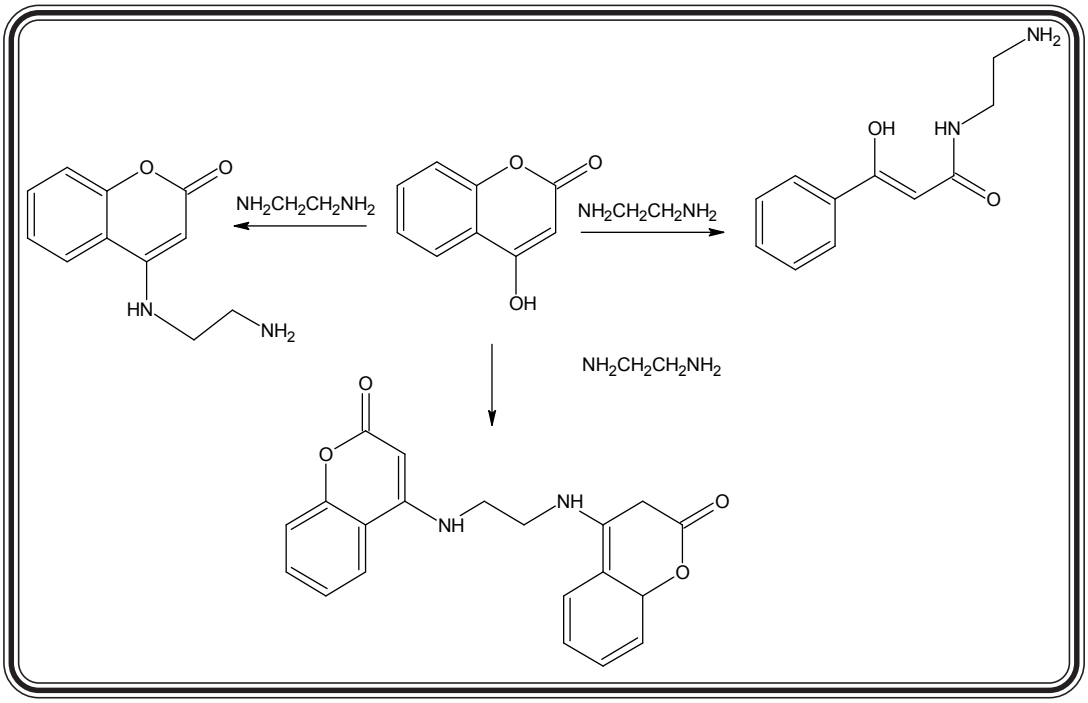
38. Badran, M. M.; El-Ansari, A. K & El-Meligie, S., *Egyptian J. of Pharm. Sci.*, **1989**, 30 (1-4), 379-87.

39. El-Ebrashi, Nabila M. A.; Nasef, Atiat M. M.; Magd-El-Din & Asmaa, A.;*Egyptian J. of Pharm. Sci.*, **1986**, 27(1-4), 7-16.

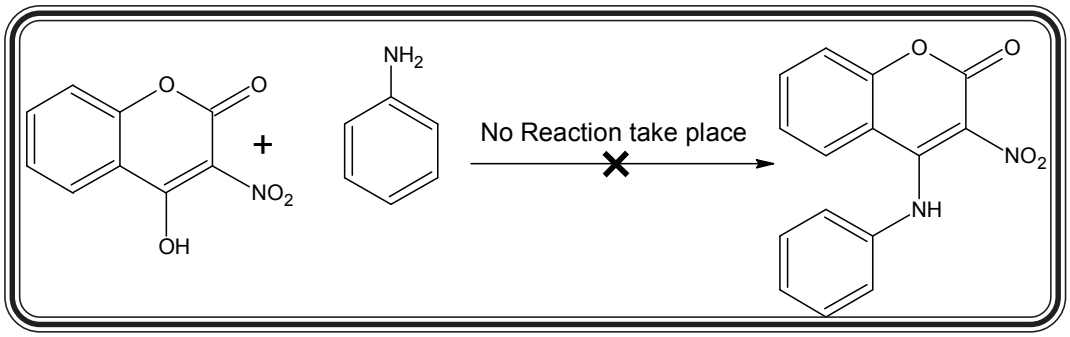
40. Bhatt, N. S. ; *Ph. D. Thesis*, Saurashtra University, Rajkot, **1983**.

40a. Tabakovic, K., Tabakovic, I., Ajdini, N., Leci, O., *Synthesis,* **1987**, 308.

Hamdi and co workers[41] have tried to explain three different possibility on reaction of 4-hydroxy coumarin with 1, 2 di-amino ethane in iso propanol solvent.

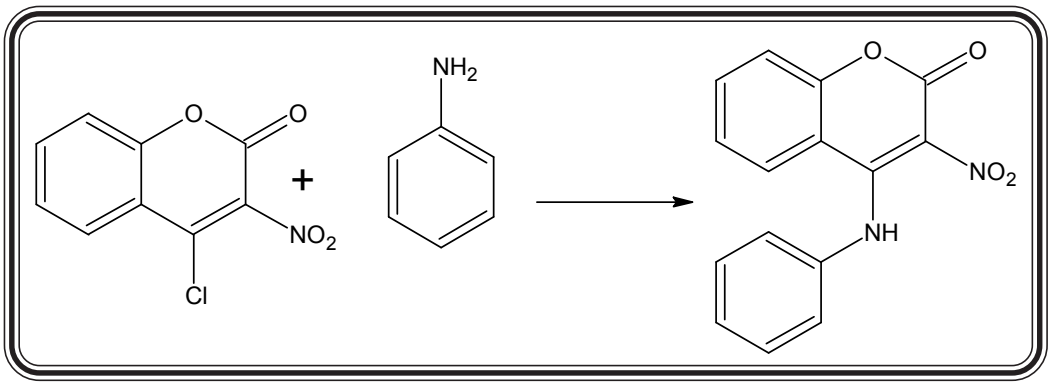


They observed that when 3-nitro 4-hydroxy coumarin is used for the direct condensation with different aryl amine, no reaction take place.

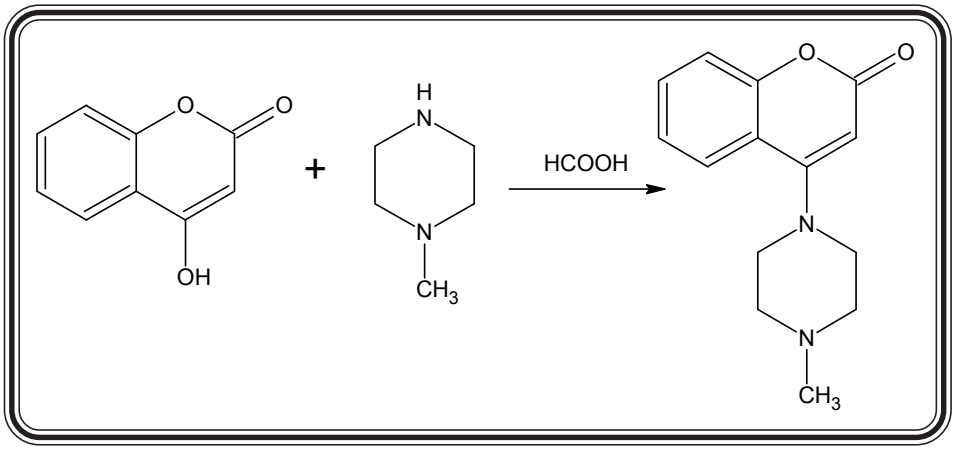


But by different method, we can prepare 3-nitro 4-aryl amino coumarin coumarin as below.

41. Hamdi, M., Cottet, S., Tedenchi, C., Speziale, V., *J. Heterocyclic Chem.*, **1997**, 34, 1851.

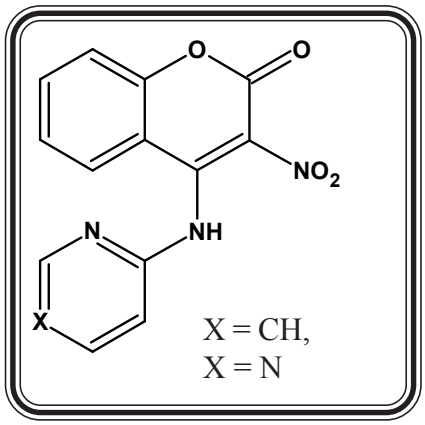


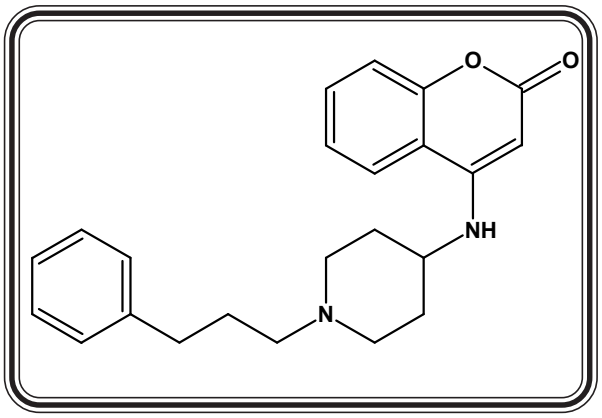
Above observation state that reaction of 4- hydroxy coumarin with amine followed by Leuckart reaction condition.



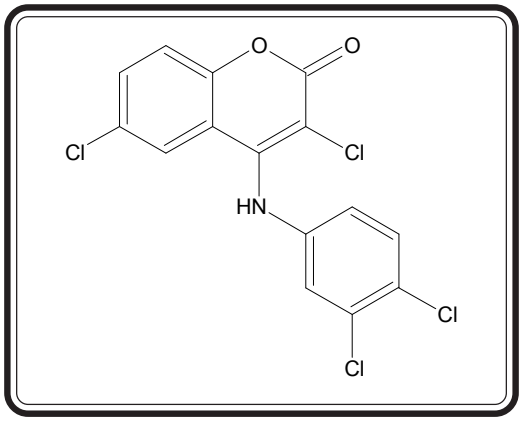
ACTIVITY ASSOCIATED WITH 4-ARYL AMINO COUMARIN DERIVATIVES.

Bachman[42] have synthesized 3 - nitro - 4 - (2-pyridylamino) coumarin and tested for their antimicrobial activity against *S. aureus, E. Coli. & C. allbicans* [43].





Bachmann also prepareed 4-aryl coumarin compound by treating 3,4,6-trichloro coumarin and 3,4-dichloro aniline at 200 ^{0}C.



Spalding et. al.[44] studied 4- morpholino coumarin as a analogue of camaquin (quinoline antimalarial) for antimalarial activity in the plasmodium gallinacean infection but compound found inactive in the Plasmodium Gallinaceum infection in chicks. While 7-(4-amino sulphonamido) coumarins were found to possess strong tuberculosis activity.[45]

Di Braccio et. al.[46] have synthesized N-Substituted 4-amino coumarins derivative & tested *in vitro* for their antiproliferative activity (DNA synthesis inhibition in Ehric cells). The compound showed an appreciable antiproliferative activity.

42. Bachman, G. L., *U.S.Patent*, **1972**, 3, 625, 980; *C.A.*, **1972**, 76, 72404.

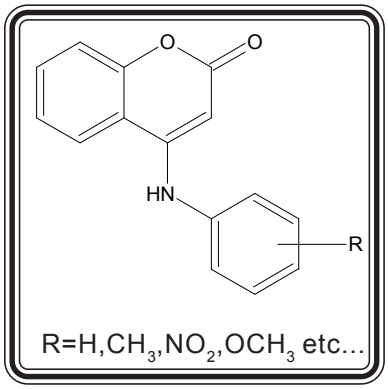
43. Govori, S. Rapic., V., Leci, O., Cacic, M., Tabakovic, I., *J. Heterocycl. Chem.*, **1996**, 33, 351.

44. Spalding,D.P.,Mosher, H.S.,Whitmore, F.C., *J.Am.Chem.Soc.*,**1950**,72, 5338.

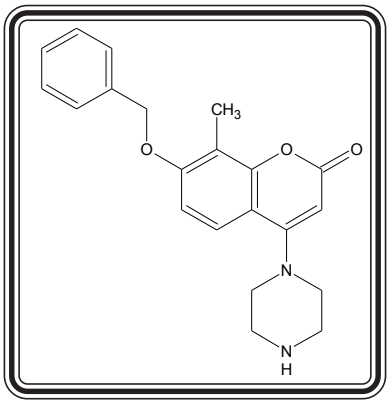
45. Hauo, K., Ruchiro, I., Yakugagu Zassi, **1963**, 83, 1169-71; *C. A.*, **1964**, 60, 492b.

46. Di Braccio, Mario; G., Giancarlo; R., Giorgio; M. & Cristina; *Farmaco*, **2003**, 58 (11), 1083-1097.

Shah and Chavada[47] have screened various N-substituted aminocoumarins for their antimicrobial activity.



Giorgio and co-workers[48-49] have synthesized substituted 4- (1-piperazinyl) coumarins and studied *in vitro* activity on human platelet aggregation.



Zagoreveskii and group[50-51] have prepared several 3-nitro-4-amino coumarins possessing neurotropic activity, generally inhibiting spontaneous locomotor activity, and decreasing hypertensitivity induced by phenamine and prolonging sleep due to a barbiturate drug-thiopental.

47. Shah, A. Chavada, M. & Karia,D., *Ind. J. of Chem.*, **2003**, 42B, 1502-1507.

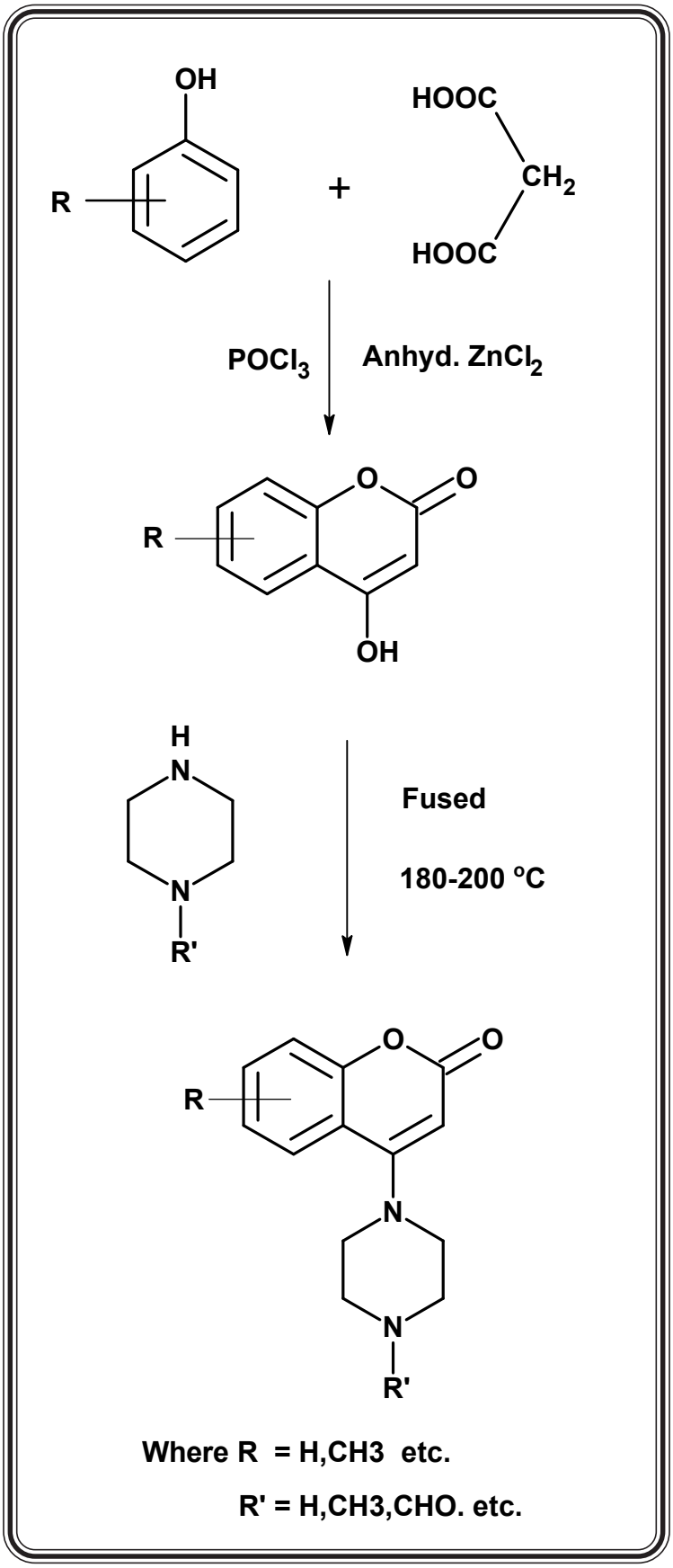
48. Giorgio, R., Mario, D.B., Antonio C., Giancarlo, G., Giuliana, L., Maria, G.S. & Angelo, C., *Bioorg. & Med. Chem.,* **2003**, 11(1), 123-138.

49. Giorgio, R., Mario, D.B.,Giancarlo, G., Giuliana, L., Maria, G.S. & Angelo,C. *Euro.J.of Med. Chem.*, **2004**, 39(5), 397-409.

50. Zagorevskii,V.A., Savel'ev,V.L. & Artamonova,O.S., Otkrytiya Isobret prom Obraztsy, *Tovarnyl Znaki*, **1973**, 50(37), 93; *C.A.*, **1974**, 80, 36999.

51. Zagorevskii,V.A., Savel'ev,V.L., Prynishnikovam,N.T., Artamonova,O.S., Shavyrina,V.V. & Afanoslevam,T.G., *Khim. Farm.Zh.*, **1975**, 9, 10-12.

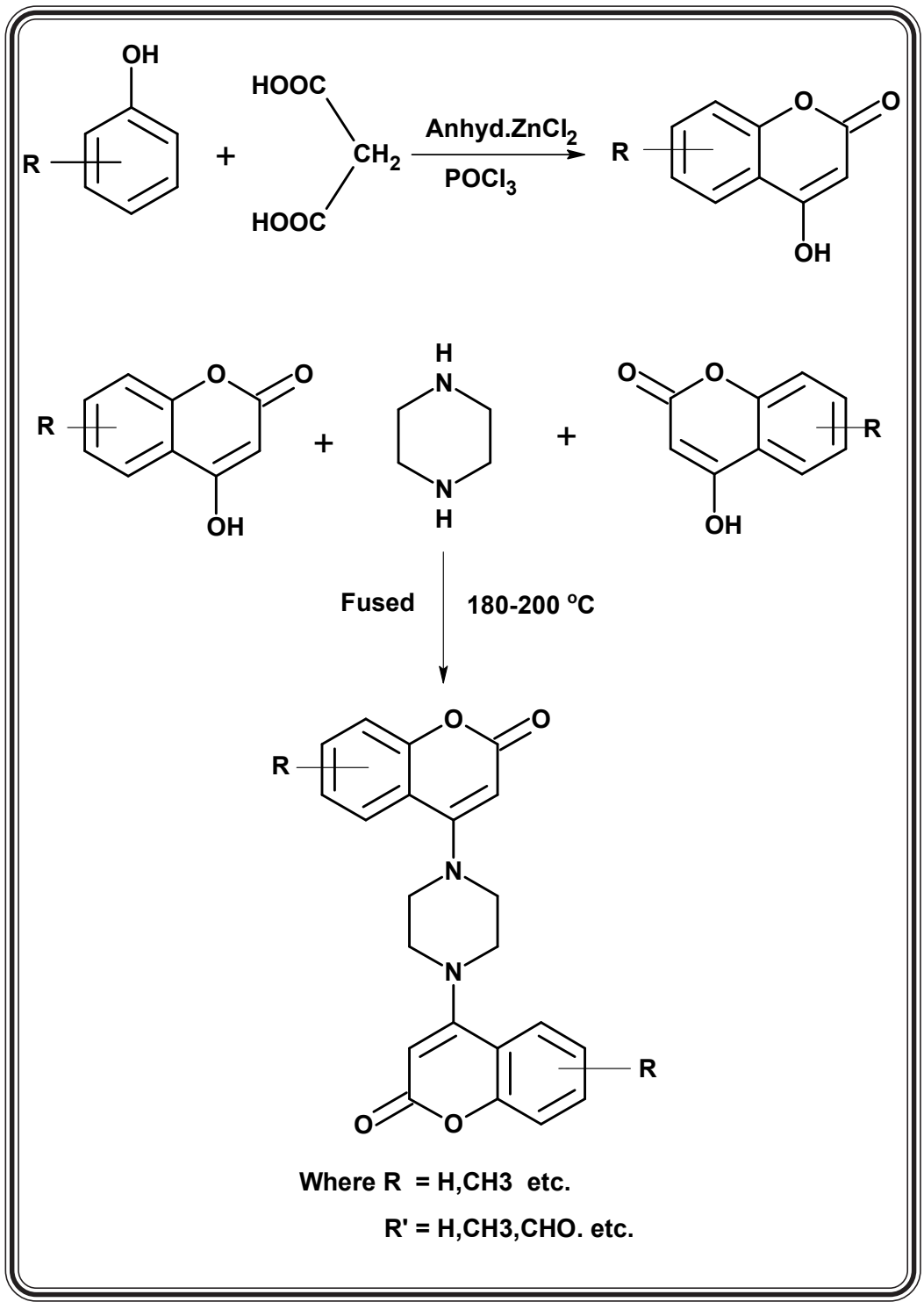
Reaction Scheme - 1



Where R = H,CH3 etc.

R' = H,CH3,CHO. etc.

Reaction Scheme - 2



Where R = H,CH3 etc.

R' = H,CH3,CHO. etc.

EXPERIMENTAL

1) Preparation of substituted 4-hydroxy coumarins :

It was prepared according to the method of Shah and co-workers[6]. Substituted phenol (0.1 mole) and malonic acid (0.1 mole) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 ml) and the reaction mixture was heated on water bath at 70 ^{o}C for 10 hrs. The reaction mixture then cooled to room temperature & quench into ice water to afford a brown yellow color solid, which was filtered and wash with water. The solid material was dissolved in to 10% sodium carbonate solution & filtered to remove undissolved material. The filtrate was slowly acidified with dilute hydrochloric acid. Solid product separated, which was filtered and washed with water, dried and recrystallised from ethanol. Yield~55 to 65%

2) Preparation of substituted 4-Piperazino coumarins.

General precedure:-

4- hydroxy coumarin (0.1 mole) was mixed piperazine (0.1 mole) and heated up to 150- 170 ^{O}C with continuous stirring. Then reaction mass was cooled to room temperature and treated with methanol (25 ml). Reaction mixture was filtered and wash with methanol. The product was dried and recrystallised from methanol. Yield ~65 to 75 %.

Similarly, other derivatives were synthesized. The physical and analytical data of these compounds are given in Table No. **3.1**

3)Preparation of substituted 4- (4- Formyl Piperazino) coumarins (General precedure)

4- hydroxy coumarin (0.1 mole) was mixed Piperazine (0.1 mole) and heated up to 150- 170 ^{O}C with continuous stirring. Then reaction mass was cooled to room temperature and treated with methanol (25 ml). Reaction mixture was filtered and wash with methanol. This product was refluxed with 3-volume formic acid for one hrs. It was cooled to room temperature & quenched in to ice-water. The product was filter and washed with water. The product was dried and recrystallised from methanol. Yield ~60 to 70%

Similarly, other derivatives were synthesized. The physical and analytical data of these compounds are given in Table No. **3.2**

4) Preparation of substituted 4-(4-methyl Piperazino) coumarins (General precedure)

4- hydroxy coumarin (0.1 mole) was mixed 4-Methyl Piperazine (0.1 mole) and heated up to 150- 170 ^{O}C with continuous stirring. Then reaction mass was cooled to room temperature and treated with methanol (25 ml). Reaction mixture was filtered and washed with methanol. The product was dried and recrystallised from methanol. Yield ~65 to 70 %

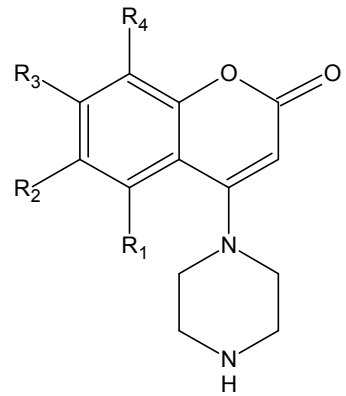
Similarly, other derivatives were synthesized. The physical and analytical data of these compounds are given in Table No. **3.3**

5) Preparation of 4-[4-(2-oxo-2*H*-chromen-4-yl) piperazin-1-yl]-2*H*- chromen-2-one:- (General precedure)

4- hydroxy coumarin (0.2 mole) was mixed Piperazine (0.1 mole) and heated up to 180- 200 ^{O}C with continuous stirring. Then reaction mass was cooled to room temperature and treated with methanol (25 ml). Reaction mixture was filtered and washed with methanol. The product was dried and recrystallised from methanol. Yield ~55 to 65 %

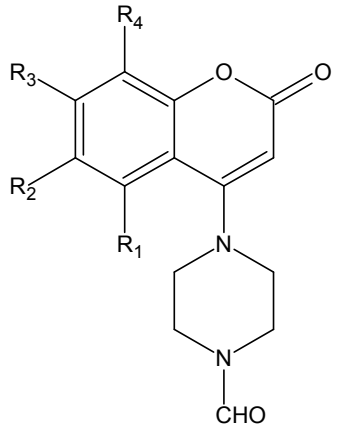
Similarly, other derivatives were synthesized. The physical and analytical data of these compounds are given in Table No.**3.4**

Table 3.1 Physical constants of substituted-4- (Piperazine)-2H-chromene-2-ones



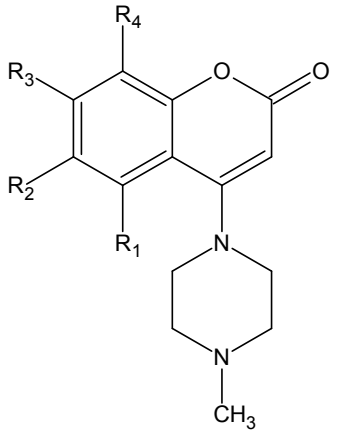
Sr. No.	Code No.	Substitution				Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
		R_1	R_2	R_3	R_4				C	H	N
1	AM-01	H	H	H	H	$C_{13}H_{14}N_2O_2$	230.26	210-214	67.81 (67.80)	6.12 (6.10)	12.17 (12.10)
2	AM-02	H	H	CH_3	H	$C_{14}H_{16}N_2O_2$	244.28	225-258	66.83 (66.81)	6.60 (6.65)	11.47 (11.44)
3	AM-303	H	CH_3	H	H	$C_{14}H_{16}N_2O_2$	244.28	218-220	66.83 (66.85)	6.60 (6.55)	11.47 (11.45)
4	AM-04	H	CH_3	CH_3	H	$C_{15}H_{18}N_2O_2$	258.31	235-237	69.74 (69.70)	7.02 (7.00)	10.84 (10.80)
5	AM-05	H	H	H	CH_3	$C_{14}H_{16}N_2O_2$	244.28	220-222	66.83 (66.80)	6.60 (6.62)	11.47 (11.40)

Table 3.2 Physical constant of substituted-4- (2-oxo-2H-chromen-4-yl) piperazine-1-carbaldehydes



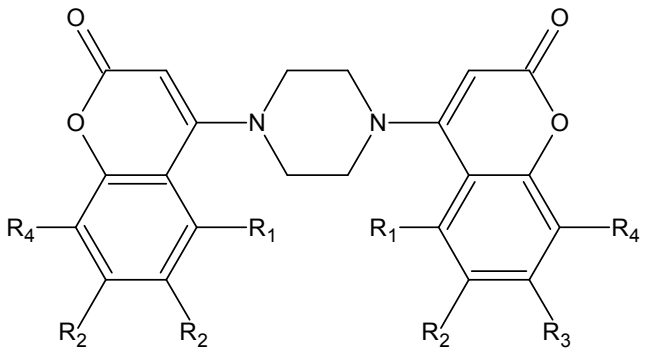
Sr. No.	Code No.	Substitution				Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
		R_1	R_2	R_3	R_4				C	H	N
6	AM-06	H	H	H	H	$C_{14}H_{14}N_2O_3$	258.27	180-182	65.11 (65.01)	5.46 (5.42)	10.85 (10.90)
7	AM-07	H	H	CH_3	H	$C_{15}H_{16}N_2O_3$	272.3	175-178	66.16 (66.15)	5.92 (5.92)	10.29 (10.30)
8	AM-08	H	CH_3	H	H	$C_{15}H_{16}N_2O_3$	272.3	165-163	66.16 (66.11)	5.92 (5.90)	10.29 (10.25)
9	AM-09	H	CH_3	CH_3	H	$C_{16}H_{18}N_2O_3$	286.32	179-182	67.12 (67.10)	6.34 (6.32)	9.78 (9.80)
10	AM-10	H	H	H	CH_3	$C_{15}H_{16}N_2O_3$	272.3	187-190	66.16 (66.14)	5.92 (5.95)	10.29 (10.25)

Table 3.3 Physical constants of substituted-4-(4-methylpiperazin-1-yl)-2H-chromen-2-ones



Sr. No.	Code No.	Substitution				Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
		R_1	R_2	R_3	R_4				C	H	N
11	AM-11	H	H	H	H	$C_{14}H_{14}N_2O_3$	258.27	217-219	65.11 (66.08)	5.46 (5.45)	10.85 (10.95)
12	AM-12	H	H	CH_3	H	$C_{15}H_{16}N_2O_3$	272.3	202-205	66.16 (66.07)	5.92 (5.90)	10.29 (10.23)
13	AM-13	H	CH_3	H	H	$C_{15}H_{16}N_2O_3$	272.3	193-195	66.16 (66.08)	5.92 (5.95)	10.29 (10.24)
14	AM-14	H	CH_3	CH_3	H	$C_{16}H_{18}N_2O_3$	286.32	189-192	67.12 (66.12)	6.34 6.32)	9.78 (9.70)
15	AM-15	H	H	H	CH_3	$C_{15}H_{16}N_2O_3$	272.3	213-215	66.16 (66.13)	5.92 (5.85)	10.29 (10.25)

Table 3.4 Physical constants of substituted-4- [4-(2-oxo-2H-chromen-4-yl) piperazin-1-yl]-2H-chromen-2-one



Sr. No.	Code No.	Substitution				Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
		R_1	R_2	R_3	R_4				C	H	N
16	AM-16	H	H	H	H	$C_{22}H_{20}N_2O_4$	376.40	>280	70.20 (70.21)	5.36 (5.40)	7.44 (7.40)
17	AM-17	H	H	CH_3	H	$C_{24}H_{24}N_2O_4$	402.45	>280	71.27 (71.21)	5.98 (6.00)	6.93 (7.00)
18	AM-18	H	CH_3	H	H	$C_{24}H_{24}N_2O_4$	402.45	>280	71.27 (71.25)	5.98 (6.01)	6.93 (6.90)
19	AM-19	H	CH_3	CH_3	H	$C_{26}H_{28}N_2O_4$	432.5	>280	72.20 (72.21)	6.53 (6.62)	6.48 (6.40)
20	AM-20	H	H	H	CH_3	$C_{24}H_{24}N_2O_4$	402.45	>280	71.27 (70.20)	5.98 (5.95)	6.93 (6.95)

SPECTRAL ANALSIS : (IR)

Instrument : SHIMAZDU FT-IR-8400 Spectrophotometer.

Sample Technique : KBr pellet

Frequency range : 4000-400cm-1.

The IR spectrum of the newly synthesized aryl amine compounds can be explained as : The carbonyl group is observed at frequency range of 1715-1690 cm-1, while the -NH linkage can be confirmed by the presence of band at 3400-3200 cm-1. Ether linkage of lactone can be confirmed by observing sharp band in the region of 1200 cm-1. Aromatic skeleton frequencies are observed in the range of 1650-1400 cm-1.

In ***(AM-1),*** the IR spectra is indicated by the functionalities observed as below. The aromatic skeleton of the coumarin ring is observed at the streching vibration of 3030-3000 cm-1.The bending vibrations are in the frequency range of 1600-1450 cm-1. The stretching vibration for the ketone group of the coumarin ring is observed at 1713.9 cm-1.The secondary amine group of the piperazine functional group is confirmed by the stretching band obtained at around 3401.2 cm-1.

Similarly, in case ***(AM-6),*** the aromatic skeleton is observed same as in case of ***(AM-1)***, the aldehyde functional group is confirmed by bands obtained as doublet at 2852 and 2741 cm-1 resp. The another functionality of the ketone group is seen as a sharp band at 1711 cm-1.

SPECTRAL ANALYSIS : (MASS)

Instrument : VG 70-S (70eV) Spectrograph for EI

Instrument : JEOL SX 102/DA-6000 Spectrograph for FAB

For the current study

For the current study, Instrument used was **JEOL SX 102/DA-6000** for FAB (**Fast Atom Bombardment**). The molecular ion peaks (M+) of the compounds in mass spectra were in total agreement with its molecular weight.

In case of ***AM-1***, the molecular ion peak is observed at 230.0 m/z (M+) peak, while the base peak is obtained at 154.0 m/z.

In case of ***AM-2***, the molecular ion peak is observed at 245.0 m/z (M+) peak, while the base peak is obtained at 154.0 m/z.

^{1}H NMR Spectral Study :-

Instrument :BRUKER AC 300 MHz FT-NMR

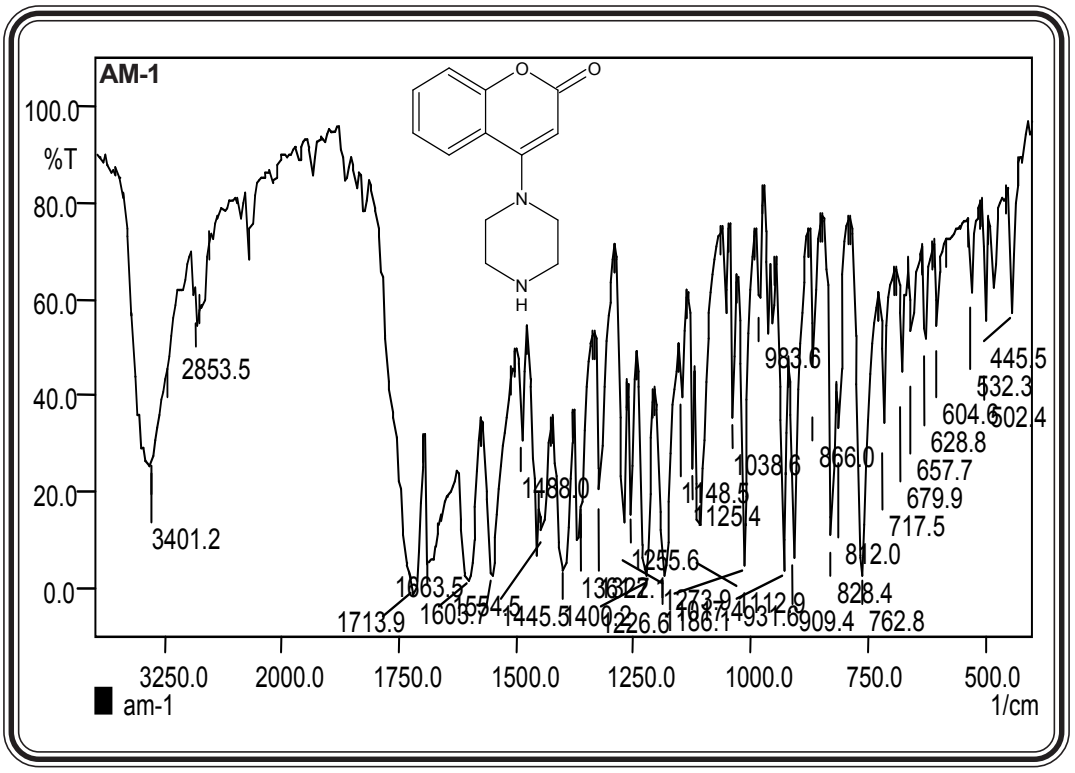
Internal reference :TMS

Solvent :$CDCl_3$ or DMSO+ d_6

In ^{1}H NMR Spectrum of ***AM-1*****,** aromatic protons were observed at d 7.50to 8.00 ppm. Doble coublet of methylen proton (-CH_2) was observed at δ 3.31 to 3.36 ppm. Singlet of aromatic CH (3) was observed at δ 5.78 ppm.

In case of ***AM-2***, aromatic methyl proton (-CH_3) was observed at δ 2.3 to 3.00 ppm. Aromatic protons were observed in between δ 7.1 to 7.65ppm.

IR spectrum of 4-piperazin-1-yl-2*H*-chromen-2-one:- (AM-1)



Sample Technique : KBr Pellet

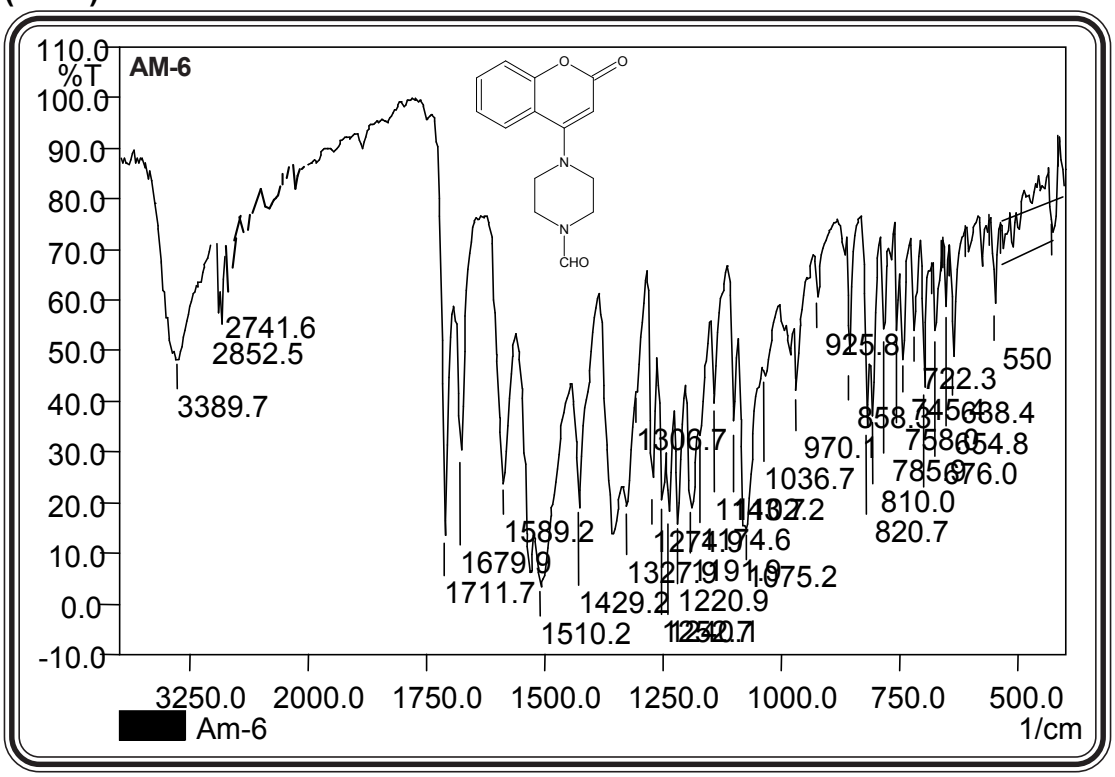
Instrument : SHIMADZU FI IT-8400

Frequency range : 4000-400cm^{-1}

Vibration Mode	Observed cm^{-1}	Refrence cm^{-1}
-NH- (Strech.)	3389	3400-3300
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-C=O- (Strech.)	1713	1710-1725
-CH_2- (Rocking)	1459	1470-1400
-CH_3 (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H)(OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

IR spectrum of 4-(2-oxo-2*H*-chromen-4-yl)piperazine-1-carbaldehyde:-

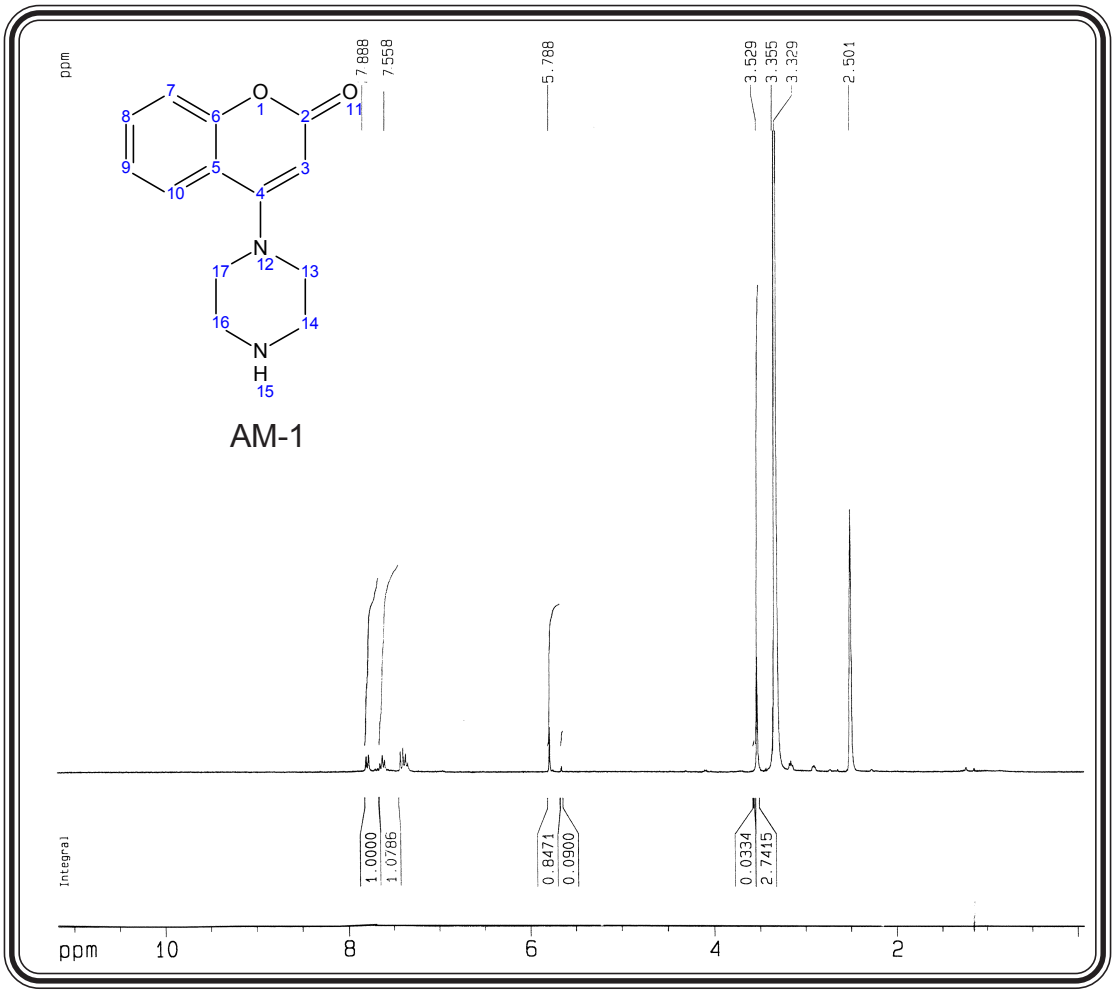
(AM-2)



Sample Technique	:	KBr Pellet
Instrument	:	SHIMADZU FI IT-8400
Frequency range	:	4000-400cm^{-1}

Vibration Mode	Observed cm^{-1}	Refrence cm^{-1}
-NH- (Strech.)	3389	3400-3300
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-C=O (cyclic)	1711	1710-1725
-C=O (ald.)	1679	1680-1690
-CH_2- (Rocking)	1459	1470-1400
-CH_3 (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H)(OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

^{1}H NMR spectrum of 4-piperazin-1-yl-2*H*-chromen-2-one:- (AM-1)



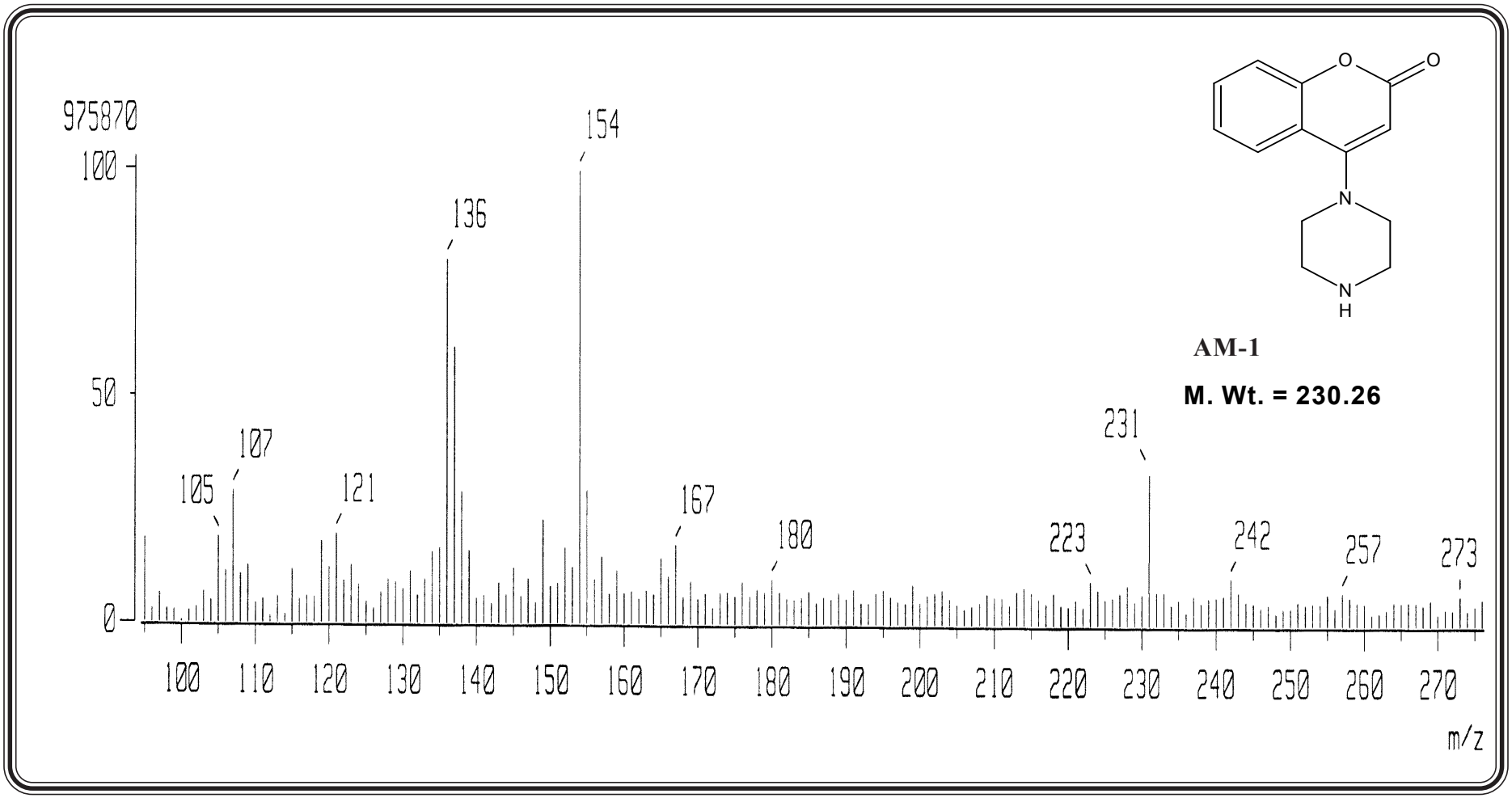
Instrument : BRUKER AC 300 MHz FT-NMR

Standard : TMS

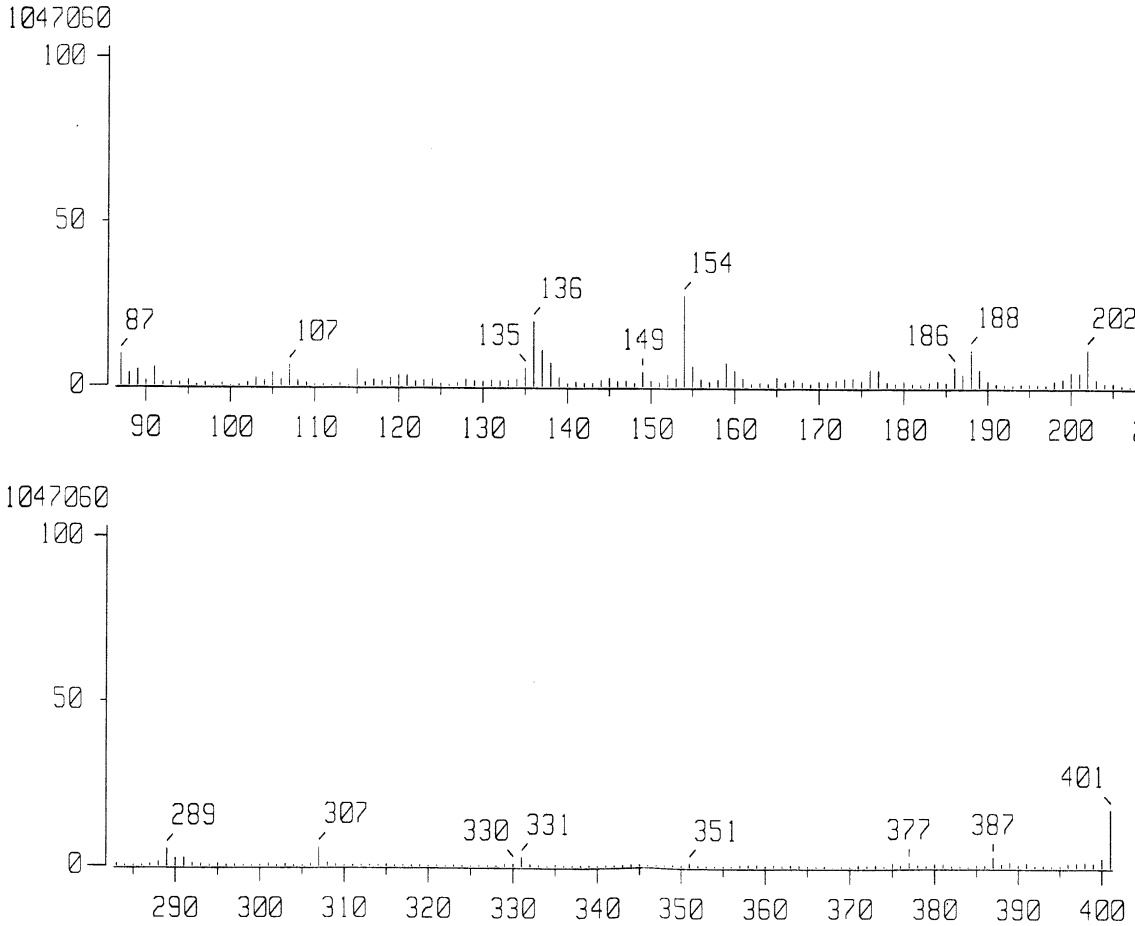
Solvent : DMSO

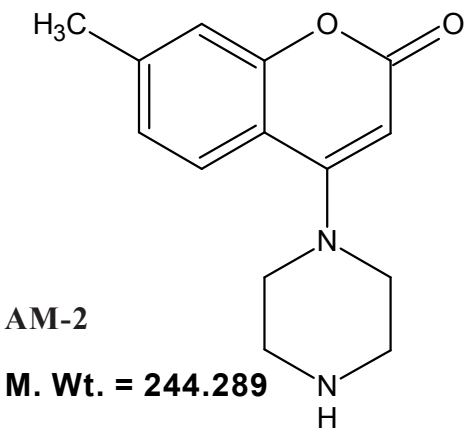
Type	No. of Proton	Multiplicity	δ PPM
$-CH_2$	8	Double Doublet	3.31-3.36
-CH(3)	1	Singlet	5.72
Ar-H	4	Multiplet	7.50-8.00
-NH-	1	Singlet	3.52

Mass Spectra of 4-piperazin-1-yl-2*H*-chromen-2-one:- (AM-1)



Mass Spectra of 7-methyl-4-piperazin-1-yl-2*H*-chromen-2-one:- (AM-2)





AM-2

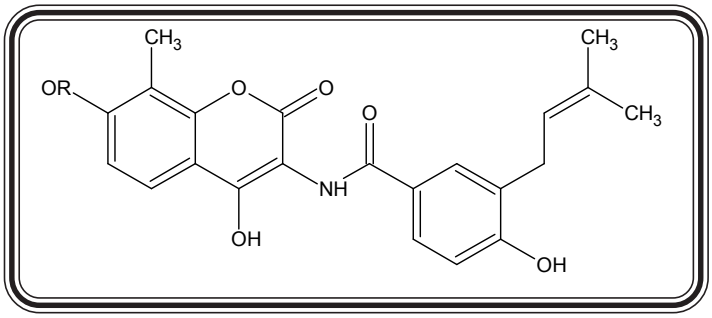
M. Wt. = 244.289

Introduction

Pyrazole derivatives have a long history of application in the pharmaceutical industry[1] as part of biologically active pharmaceuticals.[2,3] Celebrex 3a **(**1), a currently marketed selective COX-II inhibitor, is a diaryl Pyrazole derivative. 3-Hydroxy pyrazoles and 3-amino pyrazoles have been shown to be versatile intermediates to access a variety of biologically active heterocycles.[4] A novel COX-II inhibitor [5] began with the discovery that diaryl hydrazone showed high affinity for the COX-II enzyme. This compound, however,also showed high affinity for the COX-I enzyme.To improve the COX-II enzyme selectivity of compound, a series of conformationally restricted N-acylydrazones such as compound 3. Acyl hydrazones have been reported [6] in the literature to exhibit anti-inflammatory and analgesic activity. Compound **3** showed a 100-fold selectivity for COX-II over COX-I enzyme in the in vitro assay (Table 3). Cyclic aryl hydrazones such as 4,5-diaryl-*2*H-pyridazine-3-one and Fused heterocyclic systems containing pyrazole ring are ranked among the most versatile bioactive compounds,[7,9] *1*H-Pyrazolo[3,4-b]pyridine is an example of such fused system, which is known to possess remarkable and significant biological and medicinal importance.[10-14] It has been reported that pyrazolo[3,4-b]pyridines were potential specific antagonists of nucleic acid metabolism. Derivatives of this heterocyclic ring system have been shown to be substrate inhibitors of purine-requiring enzymes and also exhibit potential nonsedative anxiolytic activity.[15] The pyrazolopyridine system can be viewed as an aminoquinoline analogue, and the aminoquinoline derivatives such as chloroquine and amodiaquine have presented a high antimalarial activity. They are still in use, although their use is limited due to development of resistant parasites. However, concerning leishmaniasis, amodiaquine was never been used.

1. Vadim A. Makarov, Olga B. Riabova, Vladimir G. Granik, Hans-Martin Dahse, Axel Stelzner, Peter Wutzler and Michaela Schmidt, *Bioorganic & Medicinal Chemistry Letters*, **2005,** 15, 37.
2 Laxminarayan Bhat, Bernd Jandeleit, Tracy M. Dias, Tristen L. Moors and Mark A. Gallop, *Bioorganic & Medicinal Chemistry Letters,* **2005,** 15, 857.
3. K. T. Potts, S. Husain , *Chem. Comm*. **1970**, 1360.
4. K. T. Potts, S. Husain, *J. Org. Chem*., **1971**, 36, 3368
5. Michael G. Organ", Stanislas Mayer, Franck Lepifre, Blaise N'Zemba & Jayantilal Khatri, *Molecular Diversity* **7:***Kluwer Academic Publishers* **2003,** 211–227.
6. H. Kato, S. Nakazawa, T. Kiyasawa and K. Hirakawa, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 672.
7. H. Gotthardt, C. M. Weisshuhn, *Chem. Ber.*, **1978**, 111, 3037.
8. H. Gotthardt in A. R. Katrisky and C. W. Ress (Eds.), *Comprehensive Heterocyclic Chemistry Vol. 6*, Pergamon Press, Oxford, **1984**, 813.
9. H. Gotthardt and B. Christl, *Tetrahedron Lett*., **1968**, 4747.
10. Ali A. ABDEL HAFEZ, Ibrahim M. A. AWAD and Raga A. AHMED, *Czechoslovak Chemical Communications,* **1993**, 58(5), 1198-1202
11. Zhao W.G.; Li Z.M.; Yuan D.K.*Journal of Chemical Research*, Volume 2, Number 9, **2002**, pp. 454-455(2).
12. Adapted from Witherington et al, *Bioorg Med Chem Lett.* **2003** Sep 15;13(18):3055-7 & Zhang et al, *Bioorg Med Chem Lett*. **2003** Sep 15; 13(18): 3049-53
13. Raj N. Misra, Hai-yun Xiao, David B. Rawlins, Weifang Shan, Kristen A. Kellar, Janet G. Mulheron, John S. Sack, John S. Tokarski, S. David Kimball, Kevin R. Webster, *Bristol-Myers Squibb Pharm. Res. Inst*., *cheminform*, vol.34, issue 42, **2003.**
14. Misra RN, Rawlins DB, Xiao HY, Shan W, Bursuker I, Kellar KA, Mulheron JG, Sack JS, Tokarski JS, Kimball SD, Webster KR. *Bioorg Med Chem Lett.* **2003** Mar 24;13(6):1133-6.
15. Talaat I. El-Emary, *J. Chin. Chem. Soc., **1999**, Vol. 46, No.4,* 585.

The structure relationship of the antibiotics novobiocin[16] and coumarmycin[17] with 3-amino-4-hydroxy coumarin has promoted serious work on derivatives of 3-amino-4-hydroxy coumarins.



Arndt and co workers[18] prepared 2-methyl-4H-1-benzopyrano (3,4-d)oxazole-4-one by heating 3-amino-4-hydroxycoumarin with acetic anhydride while Dallaker et.al.[19] reported the synthesis of 5-(o-hydroxy phenyl)-2-ethyl-4-oxazole carboxylic acid γ lacton and 5-(2-hydroxy-3-isopropyl-6methylphenyl))-2-ethyl-4-oxazole carboxylic acid γ lacton from the corresponding 3-aryl amino-4-hydroxy coumarin by boiling with proionic anhydride. 5-(2,4-di-hydroxyphenyl-m-tolyl)-2-methyl-4oxazole carboxylic acid α -lactone acetate has been isolated[17] as one of the products of degradation of coumermycin.

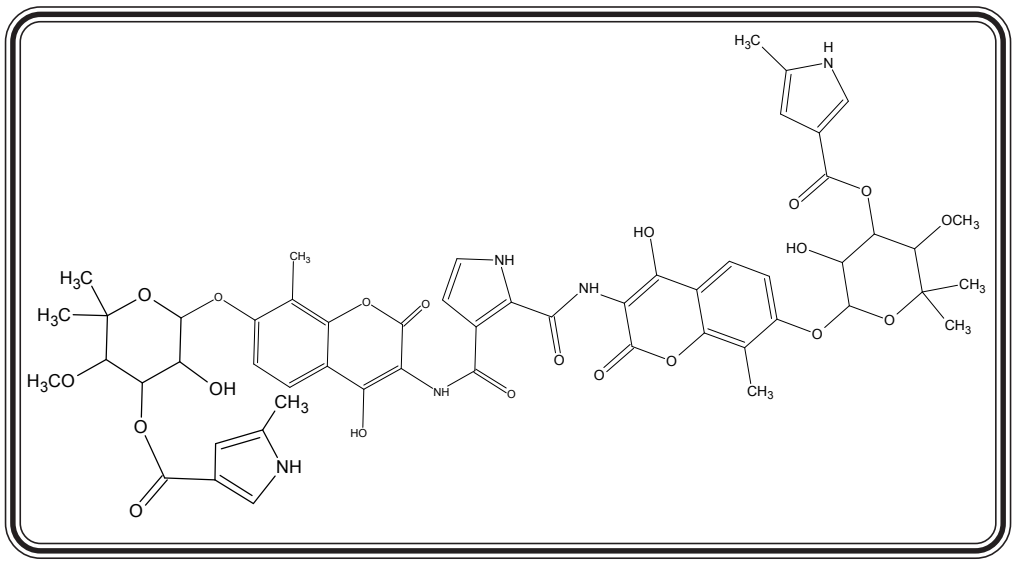
Merchant & desai[20] synthesized a number of benzopyrano(3,4-d) oxazoles by cyclisation of the Schiff bases (obtaining from 3-amino-4-hydroxy coumarins).

Merchant & Shirali[21] reported a new and convenient method for the preparation of 2-aryl-4H-1-benzopyrano-(3,4-d) oxazole-4-one by heating 3-amino-4-hydroxy coumarin hydrochloride with substituted aromatic acids in the presence of polyphosphoic acid.

In the course of previous work on the synthesis of benzopyrano oxazines, it was found that during the cyclisation of 4-hydroxy-3-(N-chloroacetyl) coumarins if instead of anhydrous potassium acetate a mixture of polyphosphoric acid and phosphorus oxychloride was used , the resulting compounds were 2-chloromethyl-4H-1-benzopyrano (3,4-d)oxazole-4-ones

obtained as crystalline solids in about 60 to 70 % yields. Such an observation has also been made by Van der Burg et.al.[22] during the course of their work on the synthesis of substituted piperazine derivatives with high anti serotonin activity.

A typical compound of this type,2-chloromethyl-6-methyl-4H-1-benzopyrano (3,4-d)oxazole-4-one showed in its uv spectra γ max (EtOH) 276 (4.12),285 (4.14) and305 (3.97)nm.



Vadim A.Makarov, et. al.[23] have synthesized and carried out anti-coxsackie virus B_3 activity of 2-amino-3-nitropyrazolo [1,5-a] pyrimidines and their analogs.

Recently, Laxminarayan Bhat et. al.[24] have synthesized and biological evaluation of novel steroidal pyrazoles as substrates for bile acid transporters.

16. K.S.R. Krishna Mohan Rao and N.V. Subba Rao, *Current. Sci.*,**1964**,33,614.

17. Kawaguchi, H., Naito, T., Tsukima, H., *Antibiotics*, **1965**, 18,11.

18. Arndt, F., Loewe, L., Ayaca, K., *Ber.*, **1951**, 84, 319.

19. Dallacker, F., Katzer, P., *Ann.*, **1961**, 643, 97.

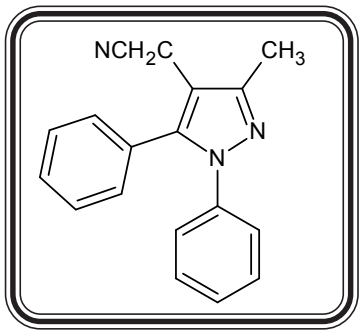
20. Merchant, J. R., Desai, H. K., *Ind. Jour. Chem.*, **1973**, 11, 433.

21. Merchant, J. R., Shirali, S. S., *Chem. Ind.* , **1977**, 33.

22. W.J. Van der Burg, J.J. Bonta,C. Raman, *J. Med Chem.*;**1970**, 13, 35.

The pyrazole derivatives are used in reverse transcriptase implicated in the infectious life cycle of Human Immuno Virus (HIV). The compounds which interfere with the prevention of this enzyme have shown utility in the treatment of condition cause d by HIV and genetically related retroviruses such as Acquired Immuno Deficiency Syndrome (AIDS). There is a continous effort to prove new and better modulators, especially inhibitor of HIV reverse transcriptase. Since the virus is able to mutant becomes resistant to the effects of known modulator.[25]

Antiviral activity is ascribe as a class of N-(hydroxy ethyl) pyrazole derivative in patent. A number of pyrazoles are disclosed as reverse transcriptase including a class of N-phenyl pyrazoles.



The well known ability of human immuno deficiency (HIV) to effeciently generate the resistance to both protease inhibitors and reverse transcriptase inhibitor (RTI's) has compelled researchers in these areas to develop novel analogues with enhanced activity against such mutants. The discovery of the bis(heteroaryl) piperazine (BHAP) class of nucleoside RTI's at Pharmacia and Upjohn's led to the deveopment of delaviride mesylate which is currently been marketed as Rescriptor for treatment of patients suffering from HIV infection and AIDS.[26]

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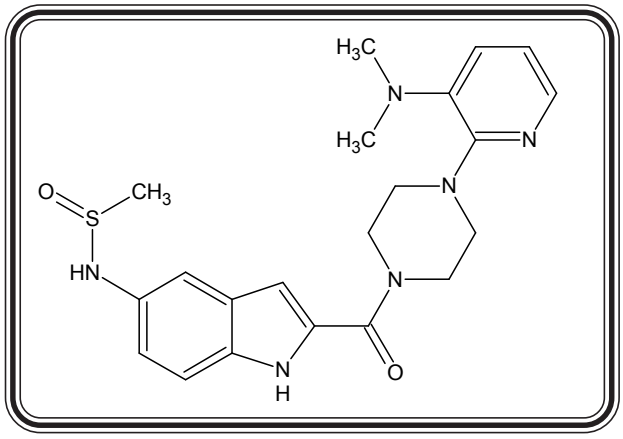
23. Makarov, V.A.,Riabova,O.B.,Granik,V.G.,Schmidtke,M.,*Bio.& Med.Chem. Lett.*, **2000**, 15, 39.

24. Bhat,L.,Jandeleit,B.,Dias,T. M.,Gallop,M. A., *Bio. &Med. Chem. Lett.*,**2005**,15,85

25. *US Patent,* **6933 312**

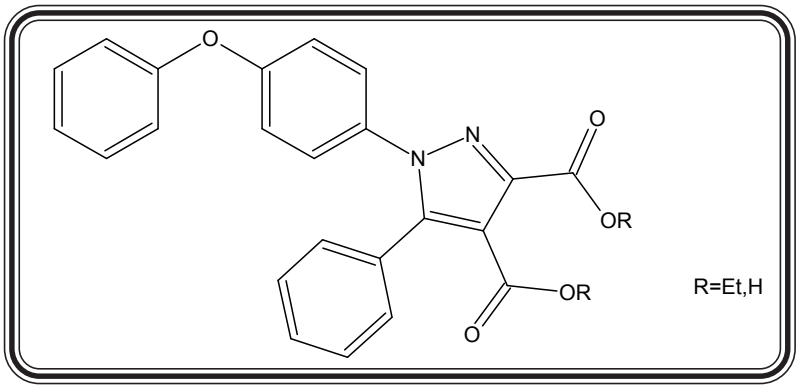
26. Genin, M. J., Carolin, b., *Jour. Med. Chem.*, **2000**, 43, 1034.



The major reverse transcriptase(RT) mutant selected by serial HIV-1 passage in vitro in the presence of increasing concentration of delaviride contains a proline to leucine substitution. Thus a new analogue with enchanced activity against the P236L mutants, a new class of non-nucleoside RTI's with the desire activity profile have synthesized against deliviride resistant viruses.

Recently it was seen that aryl substituted pyrazoles, triazoles and tetrazoles as anti-convulsants and acts as blockers (Na+) sodium channel. Several class of therapeutically useful drug including local anaesthetics such as lidocaine and bupivacaine, anti-arrhythmics such as propafenone and anti convulsants such as lamotriagine, phenytoin and carbamazepine have been shown to have common mechanism of action by blocking the modulator of Na+ channel.[27]

Each of the synthesized agents were believed to act by interfereing with the rapid influence of Na+ ion.

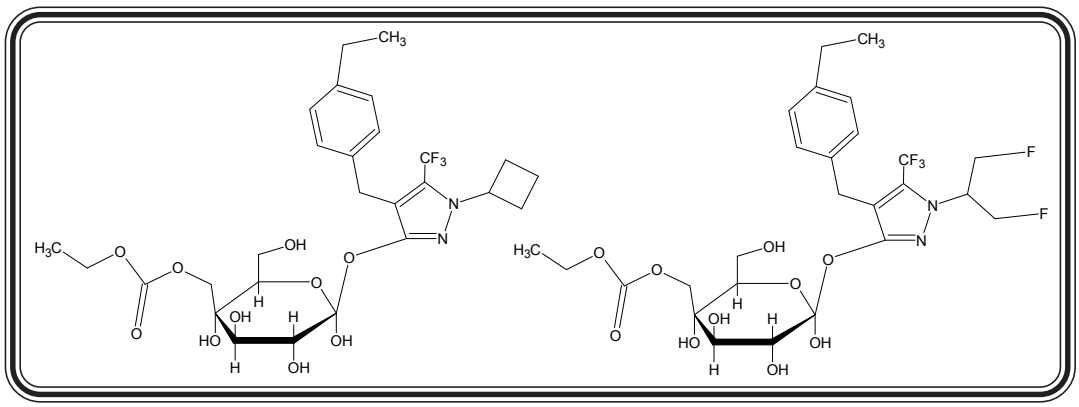


Recently other Na+ channel blocker such as BW 619C89 and lifarizine have been shown to be neuroprotective in animal model of global and focal ischemia and are presently in clinical trials.[28]

It has been established there are at least five to six sites on the voltage sensitive Na+ channel which binds to neurotoxic specifically.[29]

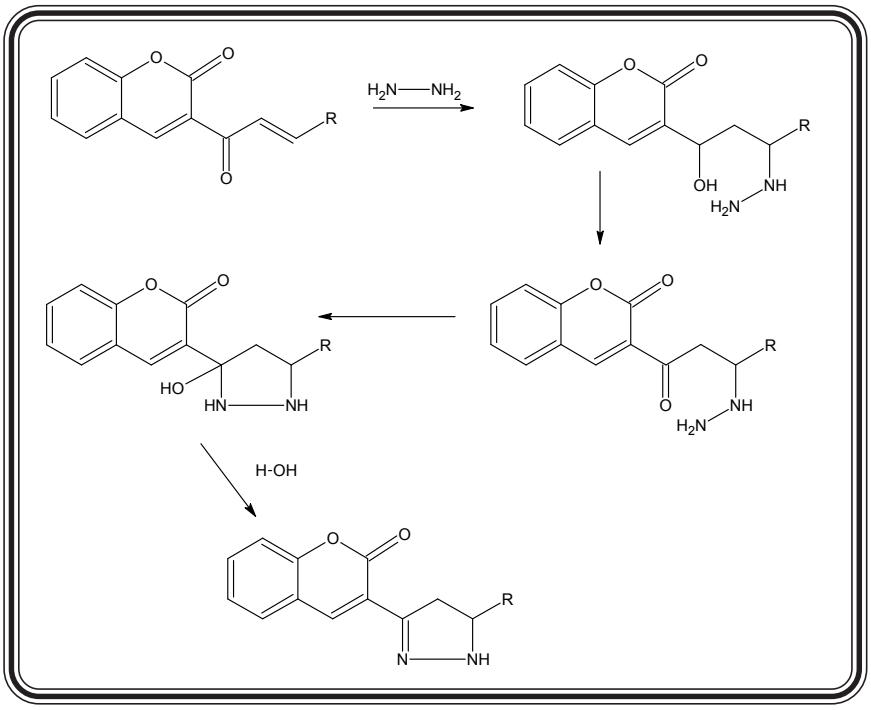
Na+ depedent glucose transproter (SGLT) is a membrane protein which transports glucose, and SGLT-1 and SGLT-2 are known. Glucose that is filtered in glomeruli is reabsored at renal uniferous tubules via SGLT and the glucose taken is reused in the body through the bloodstream. When the SGLT-2 is inhibited the amount of glucose reabsored at renal uniferous tubules lowers and the glucose excreted in urine. Therefore it is considered that an SGLT inhibitor which is effective when administered orally is useful for treating diabetes.

Koji et. al[30] has synthesized compounds as shown below for the above activity.



27. Catherall, W. A., et. al., *Trends Pharma. Sci.*, **1987**, 8,57.
28. Graham et. al., *J. Pharmacol. exp. Ther.*, **1994,** 269, 854.
29. Derk, J., Hogen, K., *US Patent,* **699 363.**
30. Koji, O., MAtsuda, K., Tokyo, *US Patent,* **690 905.**

Biological activity of 3-substituted coumarin[1-3] & pyrazolines[4-6] encouraged us to prepare molecules containing both moieties in one molecular frame which may have promising biological activity.



2-hydroxychalcones, which have structures similar to many natural pigments containing polyhydroxyand polymethoxychalcones and related flavones and flavonols, are some of the most interesting derivatives of b-phenylacrylophenones. Chalcones are known to be convenient synthons for various heterocyclic compounds. Pyrazoline derivatives possess various biological activity. Compounds characterized by antispasmodic, bactericidal, fungicidal, antiestrogen, and therapeutic activity and monoamineoxidase inhibitors have been found among them [1]. In order to prepare new bioactive compounds, we studied the reaction of 1,3-benzodioxane and 1,4-benzodioxane analogs of chalcone with hydrazine hydrate. Reaction of hydrazine hydrate with **1**-**4** [2-4] in alcohol at the boiling point of the reaction mixture produced a pyrazoline ring to form 3-(2-hydroxyphenyl)-5-hetarylpyrazolines **5**-**8** [5].

Earlier, Kulin Parmar[31] reported the synthesis of various 3- aceto acetyl4-hydroxycoumarin.Few pyranopyran,benzopyrano pyrazole, benzophenondiazepine,isoxazole,methyl pyrazole derivatives were synthesized by known methods.[2-3] He also studied antimicrobial as well as antifungal activities of these compounds.

Recently, Denish Karia[32] has also prepared 3-acetyl and 3-aceto acetyl 4-hydroxy coumarin, which were further utilized for derivatization of heterocycles like pyrano chromendiones, benzo pyrano pyrazoles. These all compounds were tested for anti-HIV activity.

In another synthetic approach, Mungra[32a] synthesized few derivatives on basis of earlier findings and comparative effect of substitution in following six types of series. They are obtained as under:

(1) 1-hydroxy-2-acetoacetyl-(substituted)-2H-chromen-3-one with 2N hydrochloric acid when refluxed in ethanol for 2 hours, afforded 2-methyl-4H-pyrano[3,2-c] (substituted) 2H-chromene-4,5-diones.

(2) 1-hydroxy-2-acetoacetyl-(substituted)-2H-chromen-3-one in 80% hydrazine hydrate was refluxed for 1 hour led to the formation of 3-acetonyl-(substituted)-hydrazone-4-oxo-1H,4H-benzopyran [4,3-c] pyrazoles.

(3) 1-hydroxy-2-acetoacetyl-(substituted)-2H-chromen-3-one reacted with o-phenylene diamine and acetic acid was refluxed for 3 hours afforded seven membered system derivatives, 1-hydroxy-2-[4-methyl, 3H-benzo [b] 1,4-diazepin-2-yl] (substituted) 2H-chromen-3-ones.

(4) When 1-hydroxy-2-acetoacetyl-(substituted)-2H-chromen-3-one treated with hydroxylamine hydrochloride and ethanol, 1-hydroxy-2-(5-methyl-isoxazole-3-yl) (substituted) 2H-chromen-3-ones were obtained.

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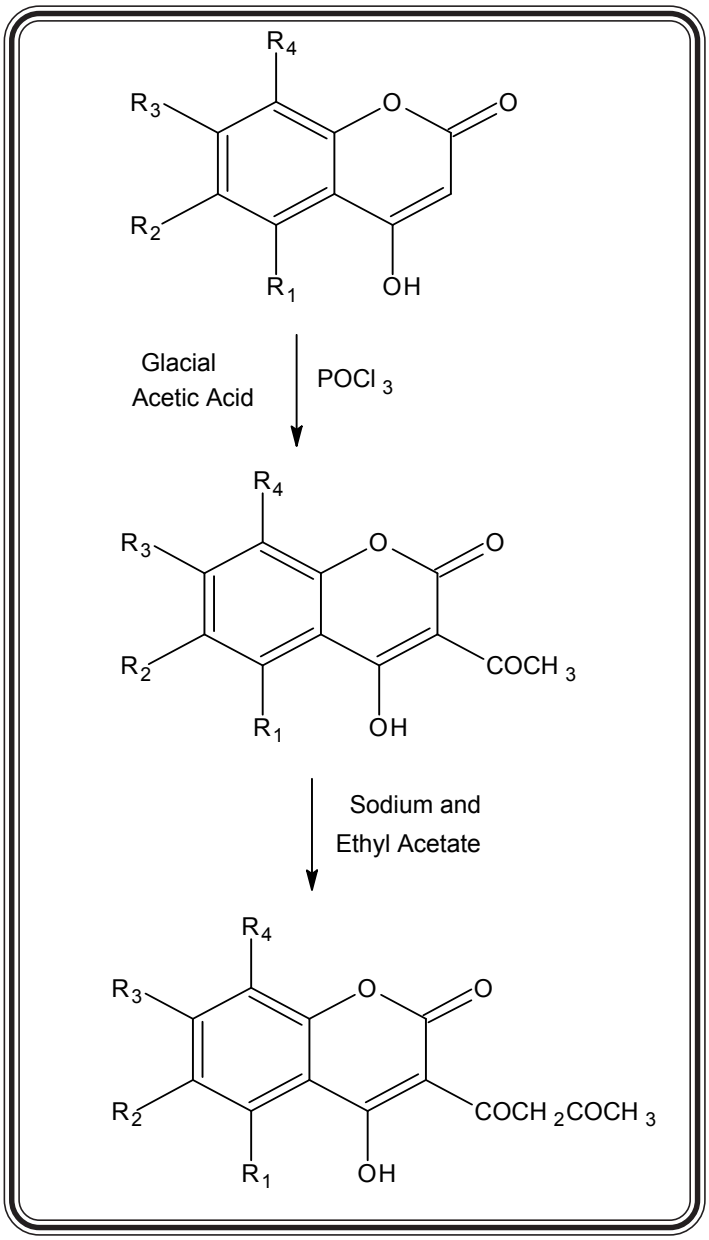
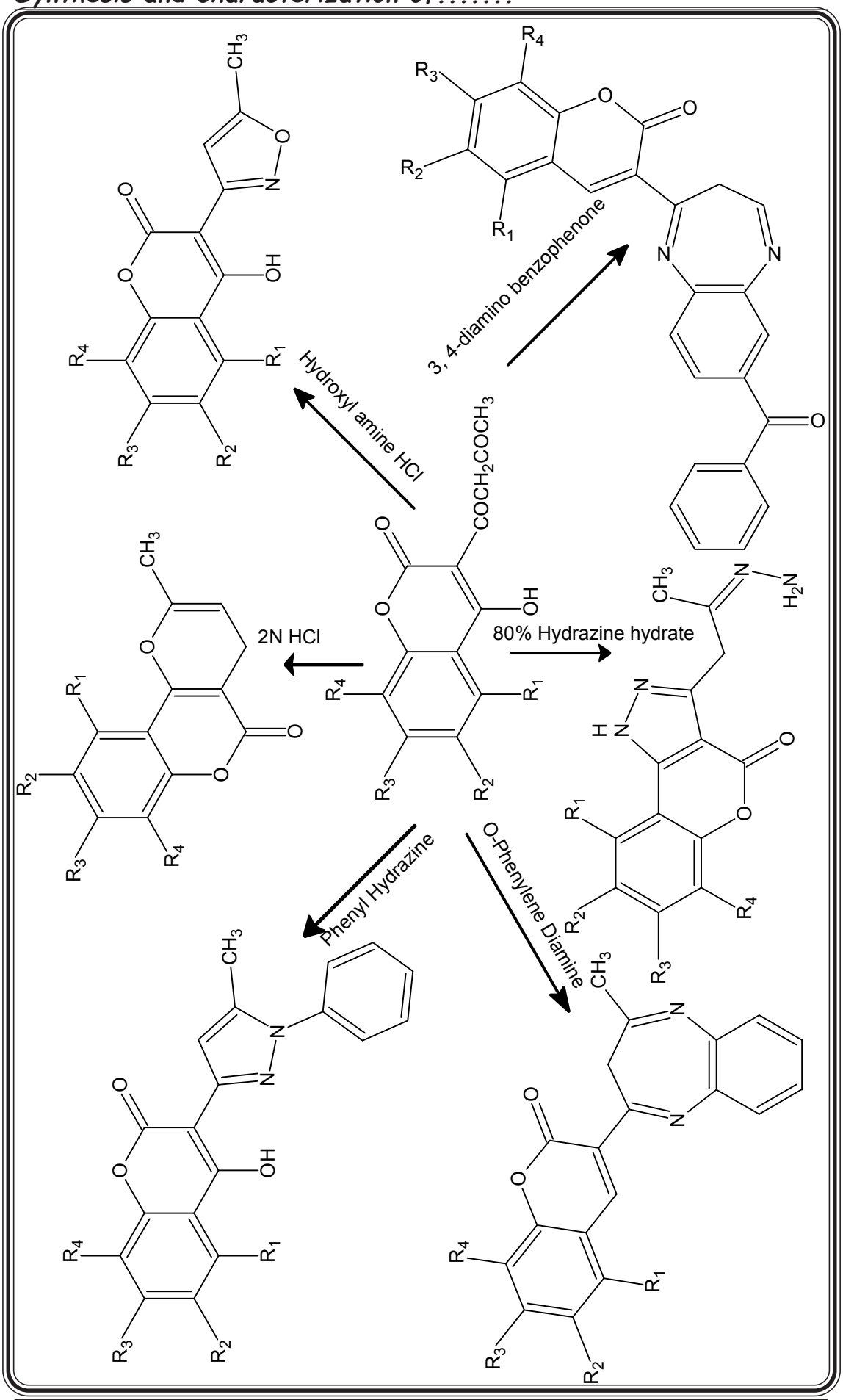
31. Kulin Parmar, Ph.D Thesis, Saurashtra University, 1992
32. Denish Karia, Ph.D Thesis, Saurahstra University, 1999.
32a. Nimish Mungara, Ph. D. Thesis, Saurashtra University, 1999.

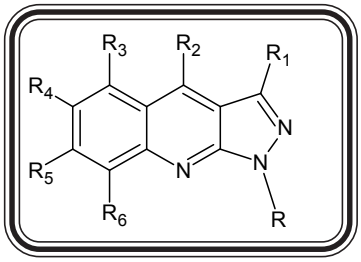
(5) 1-hydroxy-2-acetoacetyl-(substituted)-2H-chromen-3-one when condensed with 3,4-diaminobenzophenone in glacial acetic acid for 3 hours, gave 1-hydroxy-2-4-methyl (substituted), 3H-benzo [b] 1,4-diazepin phenyl-2H-chromen-3-ones.

(6) When 1-hydroxy-2-[4-methyl, 3H-benzo [b] 1,4-diazepin-2-yl] (substituted) 2H-chromen-3-ones was treated with phenyl hydrazine and refluxed in ethanol for 2 hours, 1-hydroxy-2-(5-methyl-1-phenyl-pyrazol-3-l) (substituted) 2H-chromen-3-ones were obtained in good yields.

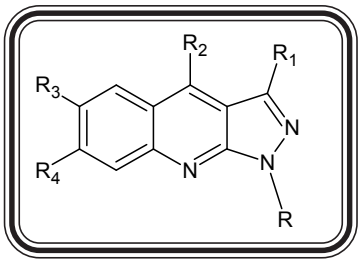



3, 4-diamino benzophenone
Hydroxyl amine HCl
2N HCl
80% Hydrazine hydrate
Phenyl Hydrazine
O-Phenylene Diamine

Andrez Daniel et. al. reported that aromatic aldehydes reacts with 5-anilino pyrazoles in the presence of $ZnCl_2$ to give the corresponding benzylidenopyrazoles. A new facile route of micro-wave assisted synthesis of 1H- pyrazole [3,4-b] quinolones has been adopted by them.[33]



1-Methyl-3-phenyl-1H-pyrazolo[3,4-b]quinoline(PAQ derivatives)carry different substituents have been synthesized by Tao's group3[34] as emitting material.They also reported that diethylamino-substituted pyrazoloquinoline could generate a sharp green electroluminence[35].The substitution effects of PAQ derivatives with electron-withdrawing and electron-donating substituents were investigated according to their photo-physical properties and electroluminescent behavior.



33. Danel, A., Chaczatrian, K., *Arkat USA*., **1998**, 52, 841.

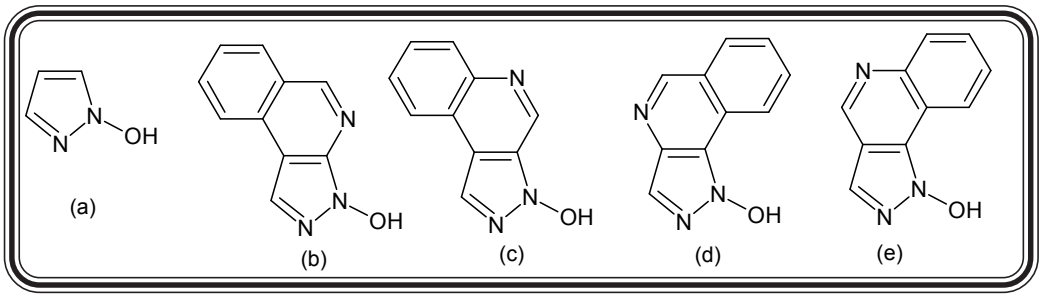
34. Tao, Y. T., Balasubramaniam, E., *Chem. Matter.*, **2001**, 13, 1207.

35. Tao, Y. T., Balasubramaniam, E., *Apply. Phy. Lett.*, **2000**, 77, 1575.

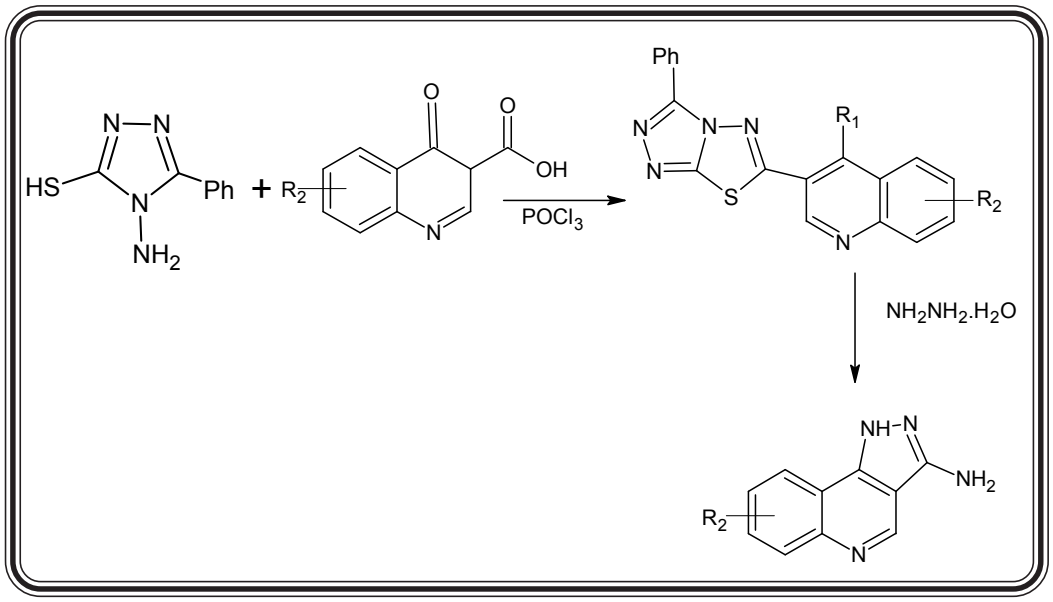
36. Jeremy, R., Greenwood, T., *ECCC7 Article,* **2004**.

37. RenZhong, Q., Zhao, F., *Gen. Org. Phosphorous Chem.*, **2004**.

The recently-synthesised novel heterocyclic isomers 3-hydroxy-*3H* -pyrazolo[3,4-*c*]isoquinoline (**b**), 3-hydroxy-*3H* -pyrazolo[3,4-*c*]quinoline (**c**), 1-hydroxy-*1H* -pyrazolo[4,3-*c*]isoquinoline (**d**) and 1-hydroxy-*1H* -pyrazolo [4,3-*c*]quinoline(**e**)show remarkable differences in properties and reactivity, both between each other and compared with the simpler parent compound 1-hydroxypyrazole (**a**), despite their great structural similarity. *Ab initio* calculations were performed with a view to investigating their preferred tautomeric forms and proton affinities in gas phase and in aqueous solution[36].

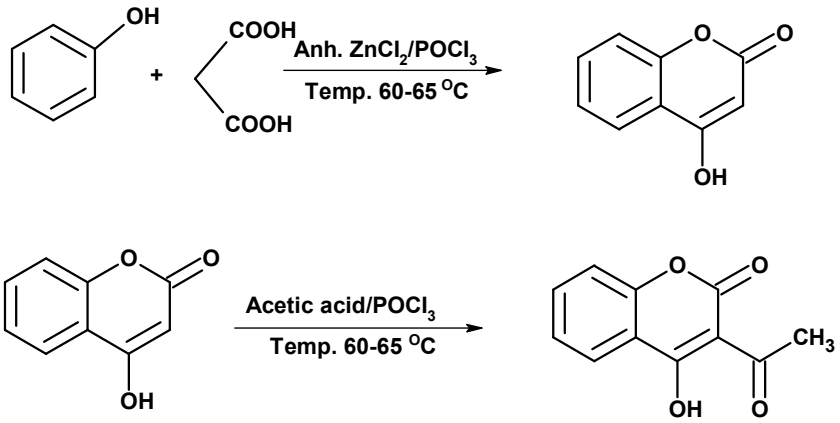


A simple and efficient for the synthesis of condensed pyrazole derivatives *via* closed ring reactionof *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives with 4-dihydro-4-oxo-quinoline-3- carboxylic acid derivatives in the presence of $POCl_3$ and the ring-opening reaction in the presence of hydrazine hydrate is described by RenZhong et. al.[37].

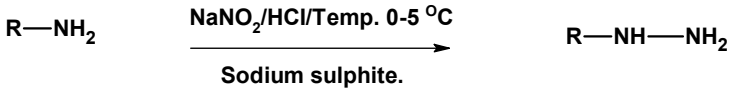


REACTION SCHEME

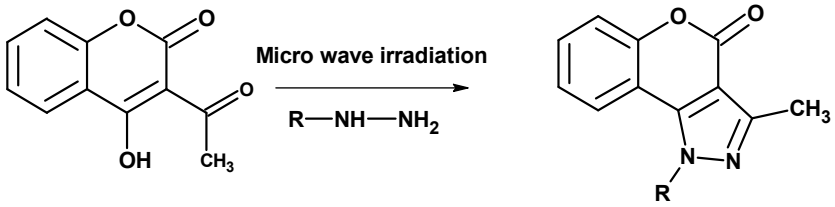
Step-1



Step-2



Step-3



R =C_6H_5F, C_6H_5Br, C_6H_5Cl, etc.

EXPERIMENTAL

A) Preparation of 4-hydroxy coumarins. :

It was prepared according to the method of Shah and co-workers[38]. Phenol (0.1 mole) and malonic acid (0.1 mole) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 ml) and the reaction mixture was heated on water bath at 70 ^{o}C for 10 Hrs. The reaction mixture cooled to room temperature & quench into ice water to afford a brown yellow color solid, which was filtered and wash with water. The solid material was dissolved in to 10% sodium carbonate solution & filtered to remove undissolved material. The filtrate was slowly acidified with dilute hydrochloric acid. Solid product separated, which was filtered and washed with water, dried and recrystallised from ethanol. Yield~65%, m.p. 209-210 ^{0}C(Reported[38] m.p.209-211^{0}C)

B) Preparation of 4-hydroxy 3-acetyl coumarin:

To a mixture of glacial acetic acid(40 ml) and 4-hdyroxy coumarin (8.1gm, 0.05m) in a RBF is added phosphorous oxychloride (33ml). Then reaction mixture was heated on water bath at 65-70 ^{O}C for 10 hrs. Then reaction mixture cooled to room temperature and poured in to crushed ice. A pale yellow solid product separated out, filtered and washed with water to remove excess of glacial acetic and $POCl_3$ and dried. The product was recrystallised from ethanol. yield~85%, m.p. 112-115 ^{0}C (Reported[39] m.p. 113-114 ^{0}C)

38. V. R. Shah, J. L. Bose and R. C. shah; *J. Org. Chem,* ***1960,*** 25, 677.
39. Kariya D., *Ph. D. Thesi*s, Saurashtra Universtiy, **1999.**

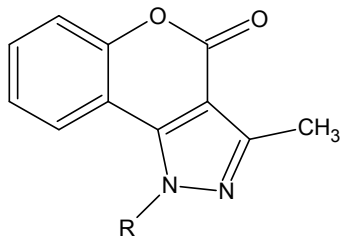
C) Preparation of substituted 3-methylchromeno[4,3-c]pyrazol-4(1H)-ones:-

General Procedure:-

A mixture of 4-hydroxy 3-acetyl coumarin (0.1 mole) and substituted phenyl hydrazine (0.1 mole) was subjected to microwave irradiation (70 w) for 10 minute to give title compound. The yield was found to be ~ 85%.

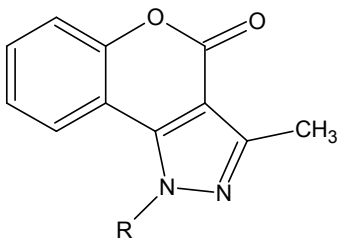
With same procedure, series of compounds have been synthesized and physical data of compounds were recorded in Table No. 4.1on page No.99,100,101

Table No. 4.1 Physical constants of 3-methyl-1-Substituted-phenyl chromeno [4,3-c] pyrazol-4 (1H)-ones



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
1	PYZ-1	$-C_6H_5$	$C_{17}H_{12}N_2O_2$	264.27	170-171	72.71 (72.68)	4.58 (4.55)	10.60 (10.65)
2	PYZ-2	$4\text{-Cl-}C_6H_5$	$C_{17}H_{11}N_2O_2Cl$	310.72	164-165	65.71 (65.73)	3.71 (3.75)	9.08 (9.11)
3	PYZ-3	$4\text{-CH}_3\text{-}C_6H_5$	$C_{18}H_{14}N_2O_2$	290.32	199-203	74.47 (74.50)	4.86 (4.82)	9.65 (9.64)
4	PYZ-4	$4\text{-F-}C_6H_5$	$C_{17}H_{11}FN_2O_2$	294.28	194-196	69.38 (69.40)	3.77 (3.74)	9.52 (9.50)
5	PYZ-5	$3\text{-CH}_3\text{-}C_6H_5$	$C_{18}H_{14}N_2O_2$	290.32	205-207	74.47 (74.45)	4.86 (4.88)	9.65 (9.63)
6	PYZ-6	$2\text{-Cl-}C_6H_5$	$C_{17}H_{11}N_2O_2Cl$	310.72	199-201	65.71 (65.69)	3.71 (3.68)	9.08 (9.05)
7	PYZ-7	$3\text{-Cl-}C_6H_5$	$C_{17}H_{11}N_2O_2Cl$	310.72	178-180	65.71 (65.75)	3.71 (3.74)	9.08 (9.05)

Table No. 4.1 Contd.



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
8	PYZ-8	2-NO_2-C_6H_5	$C_{17}H_{11}N_3O_4$	321.20	200-202	63.55 (63.56)	3.45 (3.44)	13.08 (13.05)
9	PYZ-9	3-NO_2-C_6H_5	$C_{17}H_{11}N_3O_4$	321.20	215-218	63.55 (63.54)	3.45 (3.48)	13.08 (13.09)
10	PYZ-10	4-NO_2-C_6H_5	$C_{17}H_{11}N_3O_4$	321.20	206-207	63.55 (63.58)	3.45 (3.50)	13.08 (13.10)
11	PYZ-11	3-Cl 4 -F-C_6H_5	$C_{17}H_{10}ClFN_2O_2$	328.72	185-187	62.11 (62.12)	3.07 (3.10)	8.52 (8.46)
12	PYZ-12	3-OCH_3-C_6H_5	$C_{18}H_{14}N_2O_3$	306.31	165-168	70.58 (70.60)	4.61 (4.57)	9.15 (9.18)
13	PYZ-13	4-OCH_3-C_6H_5	$C_{18}H_{14}N_2O_3$	306.31	173-175	70.58 (70.55)	4.61 (4.62)	9.15 (9.18)
14	PYZ-14	4-CH_3-C_6H_5	$C_{18}H_{14}N_2O_2$	290.32	190-192	74.47 (74.49)	4.86 (4.84)	9.65 (9.66)

SPECTRAL ANALYSIS : (IR)

Instrument : SHIMAZDU FT-IR-8400 Spectrophotometer.

Sample Technique : KBr pellet

Frequency range : 4000-400cm-1.

Theoritically IR spectrum of newly synthesized pyrazolo fused coumrin compounds can be characterized as : The aromatic region of the coumarin as well as the pyrazole ring can be characterized by stretching bands obtained at 3096-3019 cm-1 and the bending vibrations bands at 1650-1400 cm-1. The bending vibrations for -CH_3 group of the fused pyrazole group is seen at 1385 cm-1 as well as its stretching vibrations at 2956-2850 cm-1. The cabonly group(>C=O) of the coumarin ring is seen at 1710-1690 cm-1 which confirms the presence of keto group.

In IR spectrum of ***PYZ-1,*** the stetching as well as bending vibrations are seen for the aromatic as well as the aliphatic group. The ketone group of the coumarin ring is confirmed by the sharp band obtained at 1708 cm-1 while the -CH_3 group is confimed by seeing the bending vibration at 1381 cm-1. The C-N band is observed in the In plane bending region 1090 cm-1.The substitution on the aryl ring of the fused pyrazole group is seen in the region of 850-650 cm-1.

Similarly IR spectrum for other compounds can also be explained.

SPECTRAL ANALYSIS : (MASS)

Instrument : Shimazdu-QP-2010

Detector : Electron Impact (EI)

Mass Analyzer : Quardropole mass analyzer

Injection System : Direct Inlet System (DI)

For the Mass Spectral analysis of compounds of this series the GC-MS (Gas Chramatograph coupled with MASS) technique was used. The molecular ion peaks (M+) of the comounds in mass spectra were in total agreement with it's molecular weight.

In case of ***PYZ-4,*** the molecular ion peak is observed at 294.0 m/z (M+) peak while the base peak is observed at 121.0 m/z.

In case of ***PYZ-5,*** the molecular ion peak is observed at 290.0 m/z (M+) peak while the base peak is observed at 204.0 m/z.

^{1}H NMR Spectral Study :-

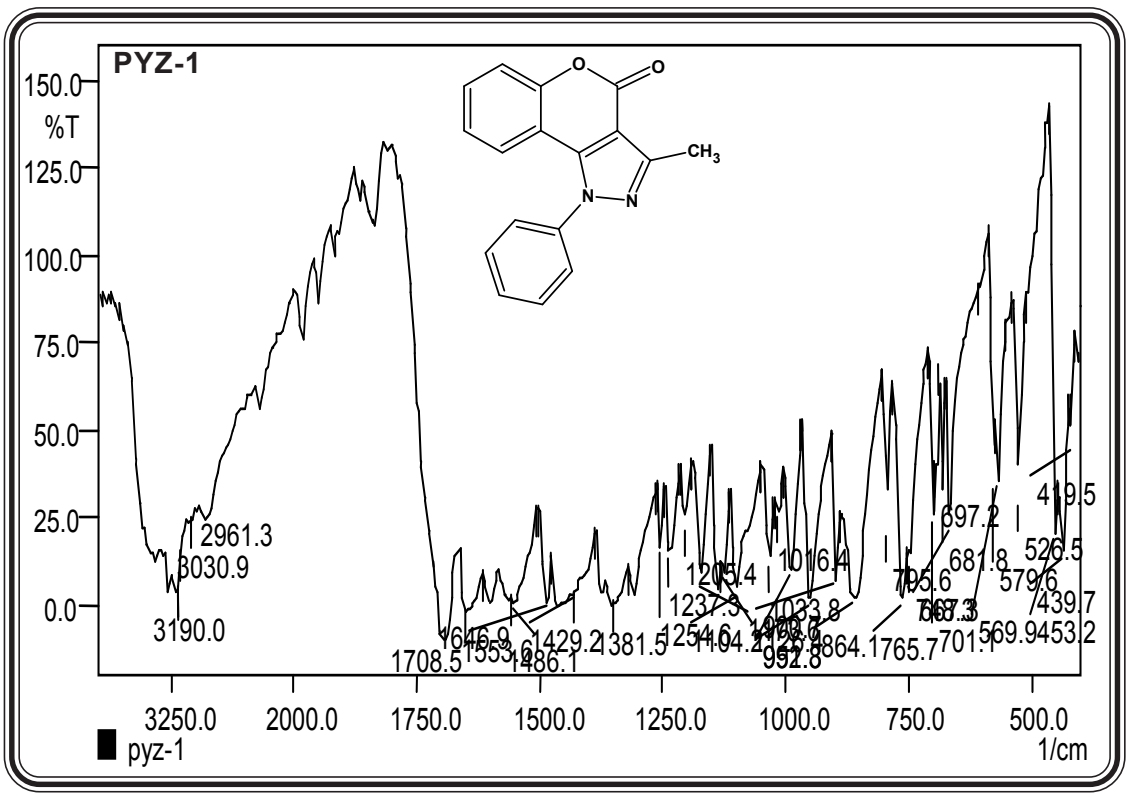
Instrument :BRUKER AC 300 MHz FT-NMR

Internal reference :TMS

Solvent :$CDCl_3$ or DMSO+ d_6

1H NMR spectra of **PYZ-1**, two typical doublet observed at δ 7.39 and δ 7.46ppm is due to ortho coupling of -CH (C_{17}, C_{18})with -CH (C_{18}, C_{20}). Quatret of -CH (C_{12},C_{11}) is observed at δ 6.67to 6.70 ppm.Two triplet due to aromatic proton of -CH (C_{10},$_{13}$) is observed at δ 7.08 and δ 7.25ppm. One triplet observed at δ 7.00 ppm due to aromatic proton of C_{19}.

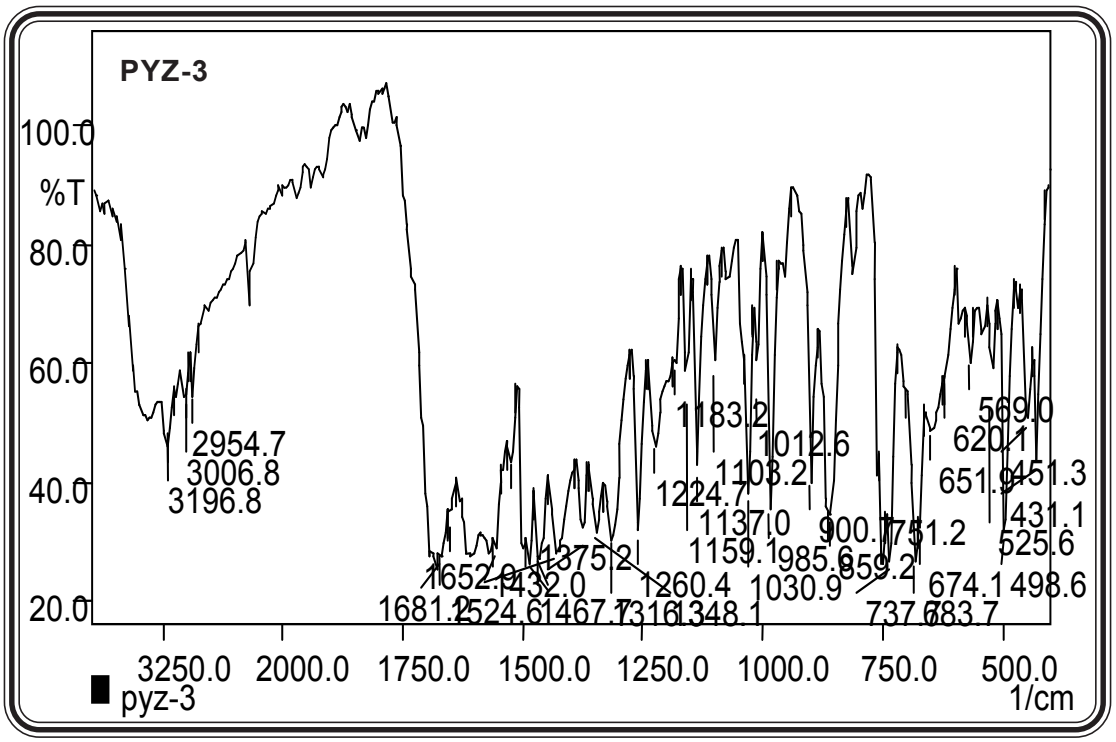
IR Spectrum of 3-methyl-1-phenyl chromeno[4,3-*c*]pyrazol-4(1*H*)-one.



Sample Technique	:	KBr Pellet
Instrument	:	SHIMADZU FTIR-8400
Frequency range	:	4000-400cm^{-1}

Vibration Mode	Observed cm^{-1}	Refrence cm^{-1}
-NH- (Strech.)	3389	3400-3300
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-C=O-	1708	1710-1725
-CH$_2$-(Rocking)	1459	1470-1400
-CH$_3$ (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H) (OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

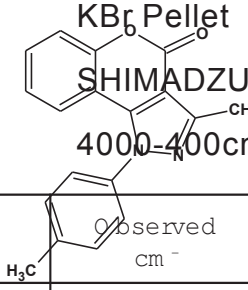
IR Spectrum of 3-methyl-1-(4-methylphenyl)chromeno[4,3-*c*] pyrazol-4(1*H*)-one



Sample Technique : KBr Pellet

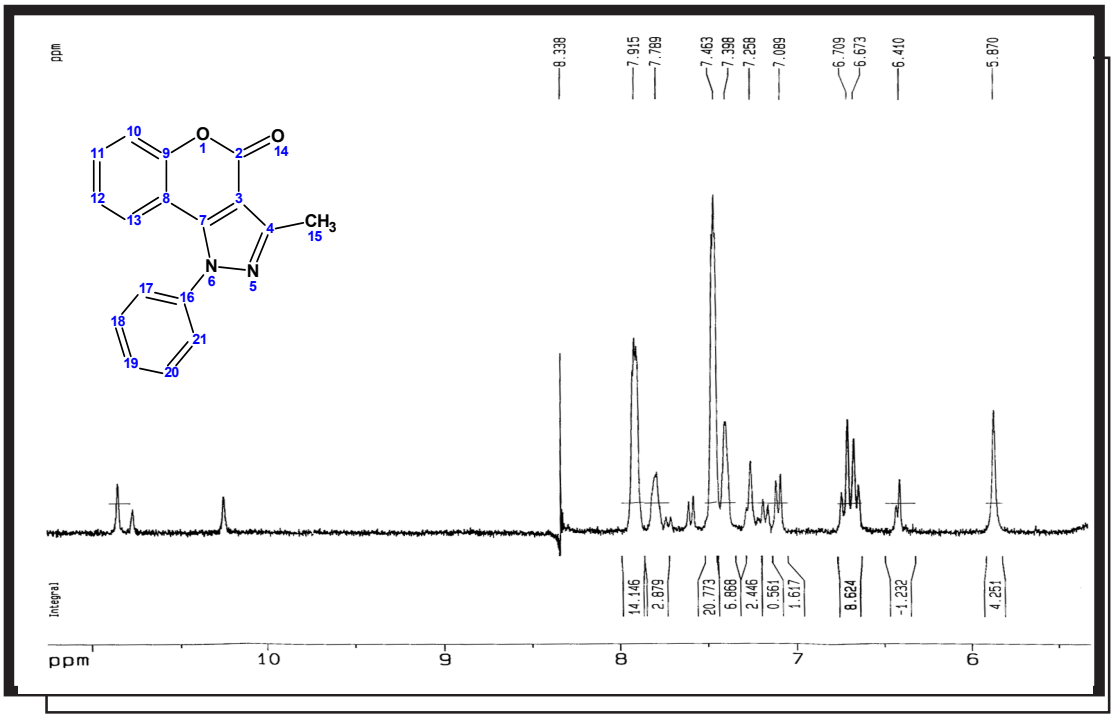
Instrument : SHIMADZU FTIR-8400

Frequency range : 4000-400cm^{-1}



Vibration Mode	Observed cm^{-1}	Refrence cm^{-1}
-NH- (Strech.)	3389	3400-3300
-C=C-(Ring Skeletone)	1557 1487	1600-1500
-C=O-	1681	1710-1725
-CH_2-(Rocking)	1459	1470-1400
-CH_3 (Bending)	1340	1390-1370
-C-N (Strech.)	1243	1250-970
Arenes (C-H) (OOP Bending)	748 846	690-900
-C-C (Bending)	1013 1083	950-1100

^{1}H NMR Spectra of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4 (1*H*)-one:- (PYZ-1)



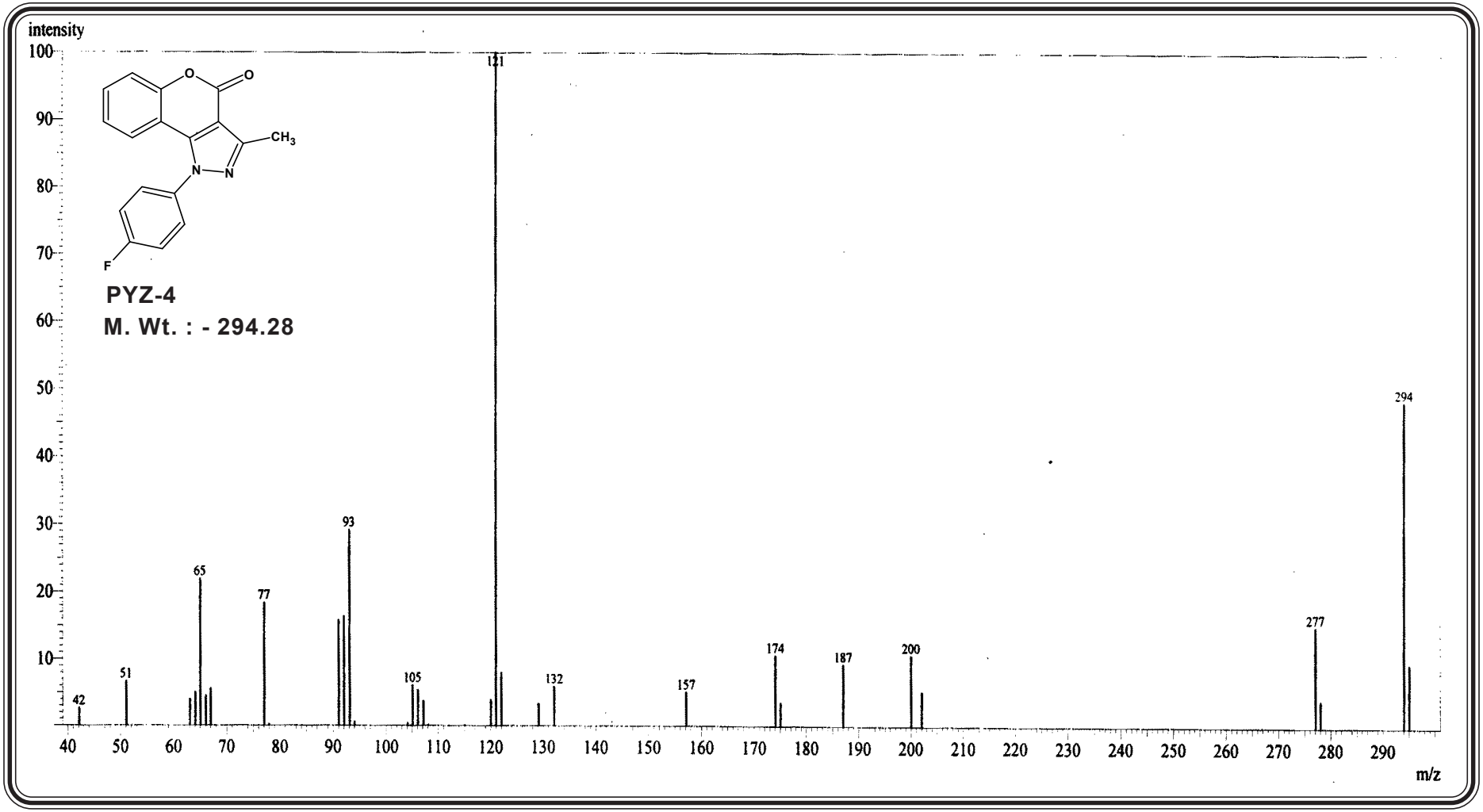
Instrument :BRUKER AC 300 MHz FT-NMR

Standard :TMS

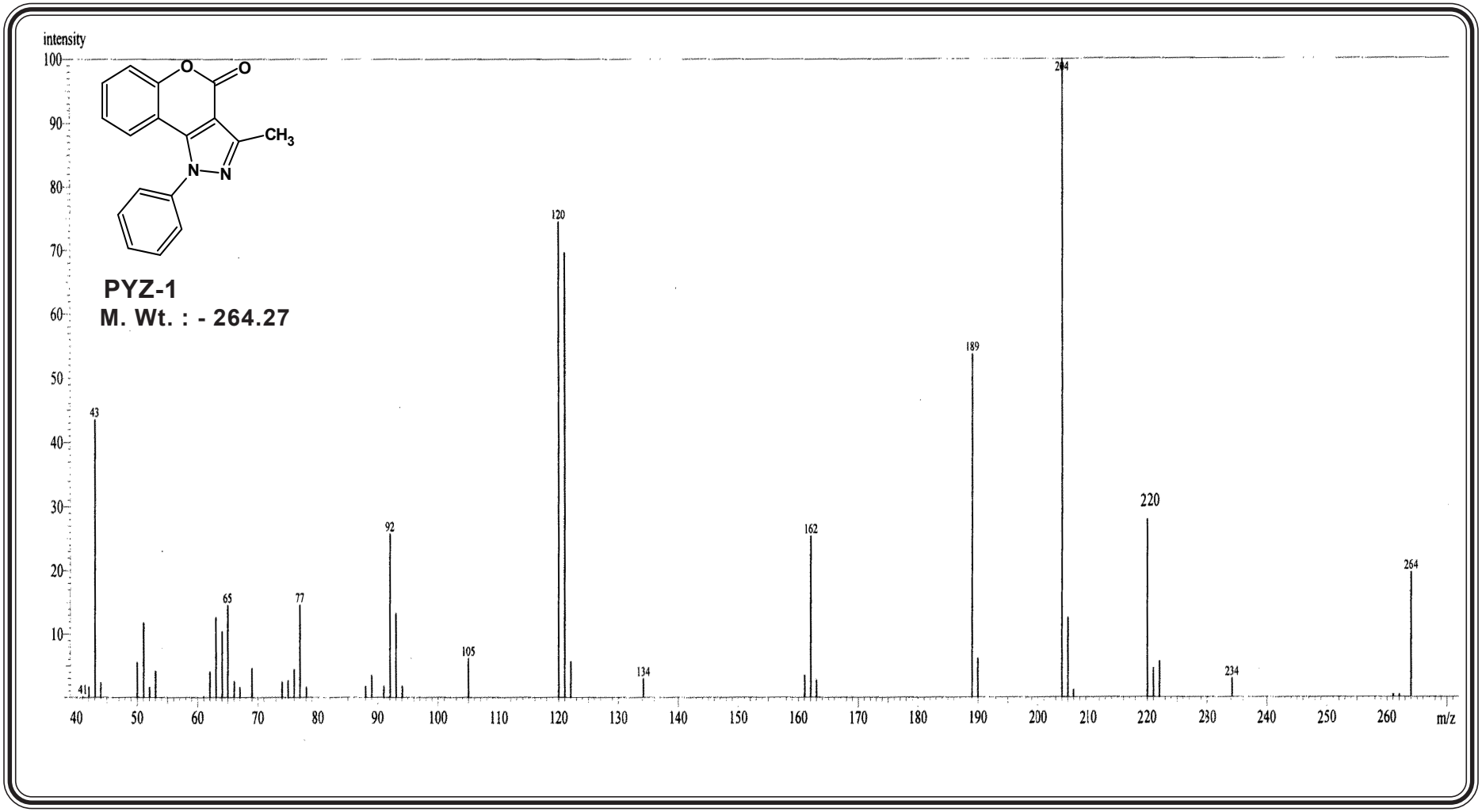
Solvent :DMSO d_6

Inference	No. of Proton	Muliplicity	Chemical Shift δ ppm
C(15)	3H	Singlet	2.26
C(10)	1H	Triplet	7.08
C(11,12)	2H	Quartet	6.67-6.70
C(13)	1H	Triplet	7.25
C(17,21)	2H	Doublet	7.39 7.46
C(18,20)	2H	Doublet	7.78 7.91
C(19)	1H	Triplet	7.00

MASS Spectrum of 1-(4-chlorophenyl)-3-methylchromeno[4,3-*c*]pyrazol-4(1*H*)-one :- (PYZ-4)



MASS Spectrum of 3-methyl-1-(3-phenyl)chromeno[4,3-*c*]pyrazol-4(1*H*)-one : (PYZ-1)

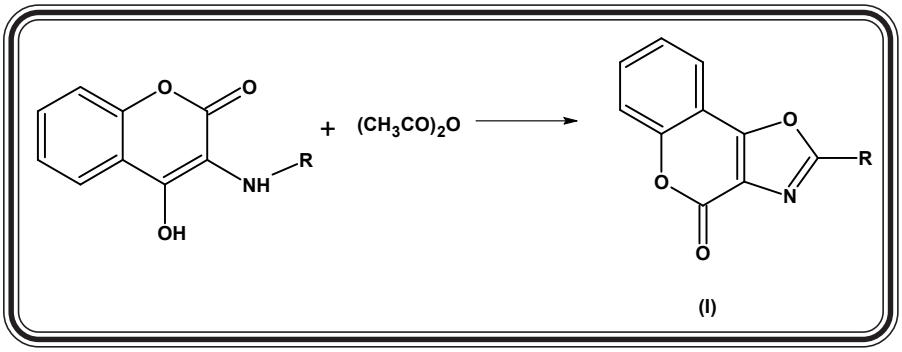


INTRODUCTION :

Five, six or seven membered rings containing oxygen and nitrogen as hetero atoms have been studied by many researchers. The biological importance of coumarin derivatives has led to considerable study in the field of synthetic coumarins with 3,4-carbocyclic and 3,4-fused heterocyclic ring systems. Darbarwar and Sundermurthy[1] reviewed entirely the reaction of 4-hydroxycoumarin leading to 3,4-fused ring systems and their physiological activity.

FIVE MEMBERED RINGS CONTAINING OXYGEN AND NITROGEN AS HETERO ATOMS :

3-amino-4-hydroxy coumarin when heated with acetic anhydride, afforded 2-methyl-benzopyrano[3,4-d] oxazol-4-one[2,3].

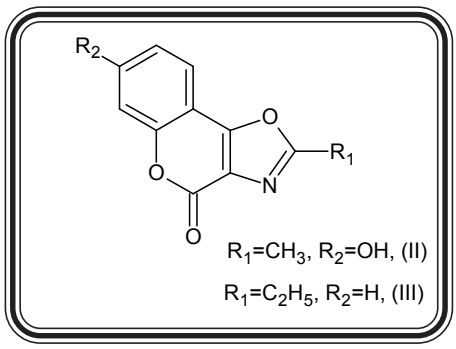


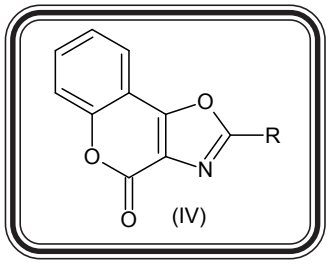
(I)

During the structural investigation, novobiocin was treated with acetic anhydride undergoing cleavage at the amide and glycosidic linkage and cyclising to (II) N-methyl analogue[4], while 3-amino-4-hydroxycoumarin when refluxed with propionic anhydride gave the 2-ethyl derivative (III)[5].

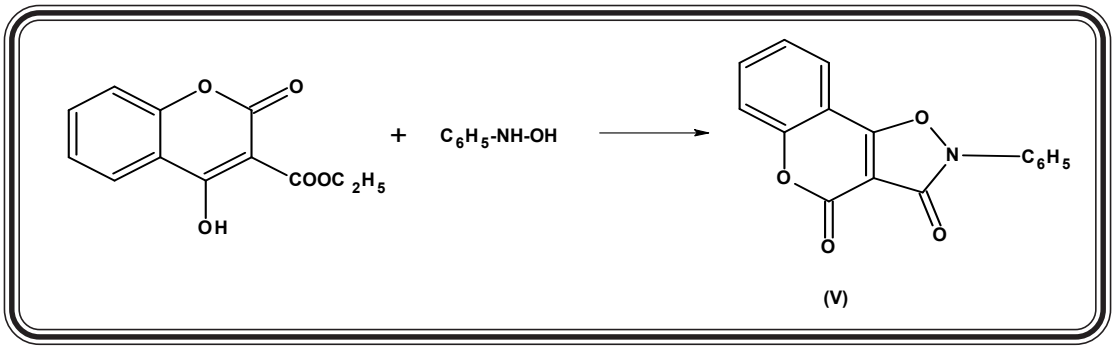
1. Darbarwar, M., *Synthesis*, **1982**, 337.
2. Arndt, F., Loewe, L., *Chem. Ber.,* **1951**, 84, 319.
3. Klosa, J., *Pharmazie*, **1953**, 8, 221.
4. Darbarwar, M., *Synthesis*, **1982**, 337.

A different route to synthesize 2-substituted coumarino-oxazoles (IV) involves the condensation of 3-amino-4-hydroxy coumarin with various aromatic aldehydes in nitrobenzene.[6,7]



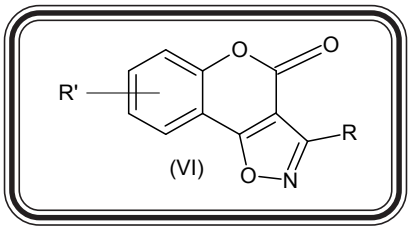


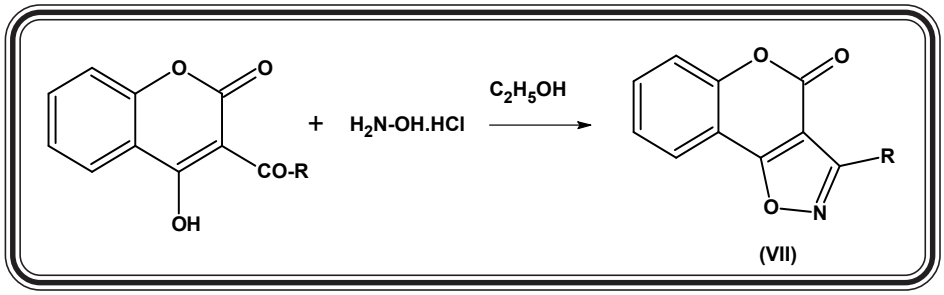
The isoxazoles containing 5-memebred ring system have also been prepared by different methods. 2-N-phenyl benzopyrano-[3,4-d]isoxazole-3,4-dione (V) and its derivatives were achieved by heating correspondi ng 3-ethoxycabonyl coumarin with phenylhydroxylamine.[8]



Various coumarino-isoxazoles (VI) having substituents in benzene ring have been prepared by refluxing the oximes of substituted 4-chloro-3-formyl coumarins using sodium acetate in alcohol.[9]

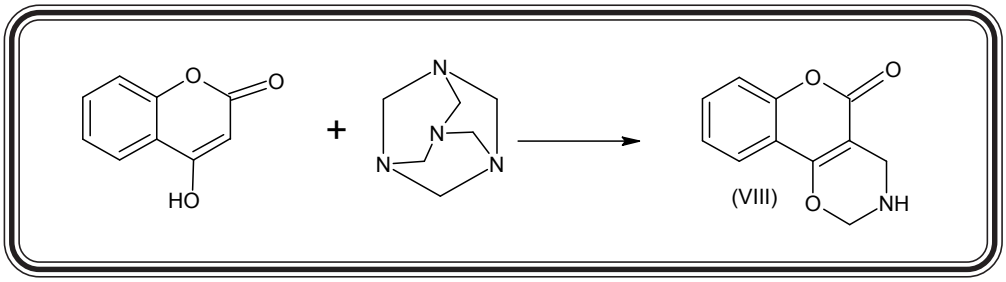
Action of hydroxylamine hydrochloride on 3-acyl or 3-benzoyl-4-hydroxy coumarins (VII) have been reported by Desai et. al.[10]





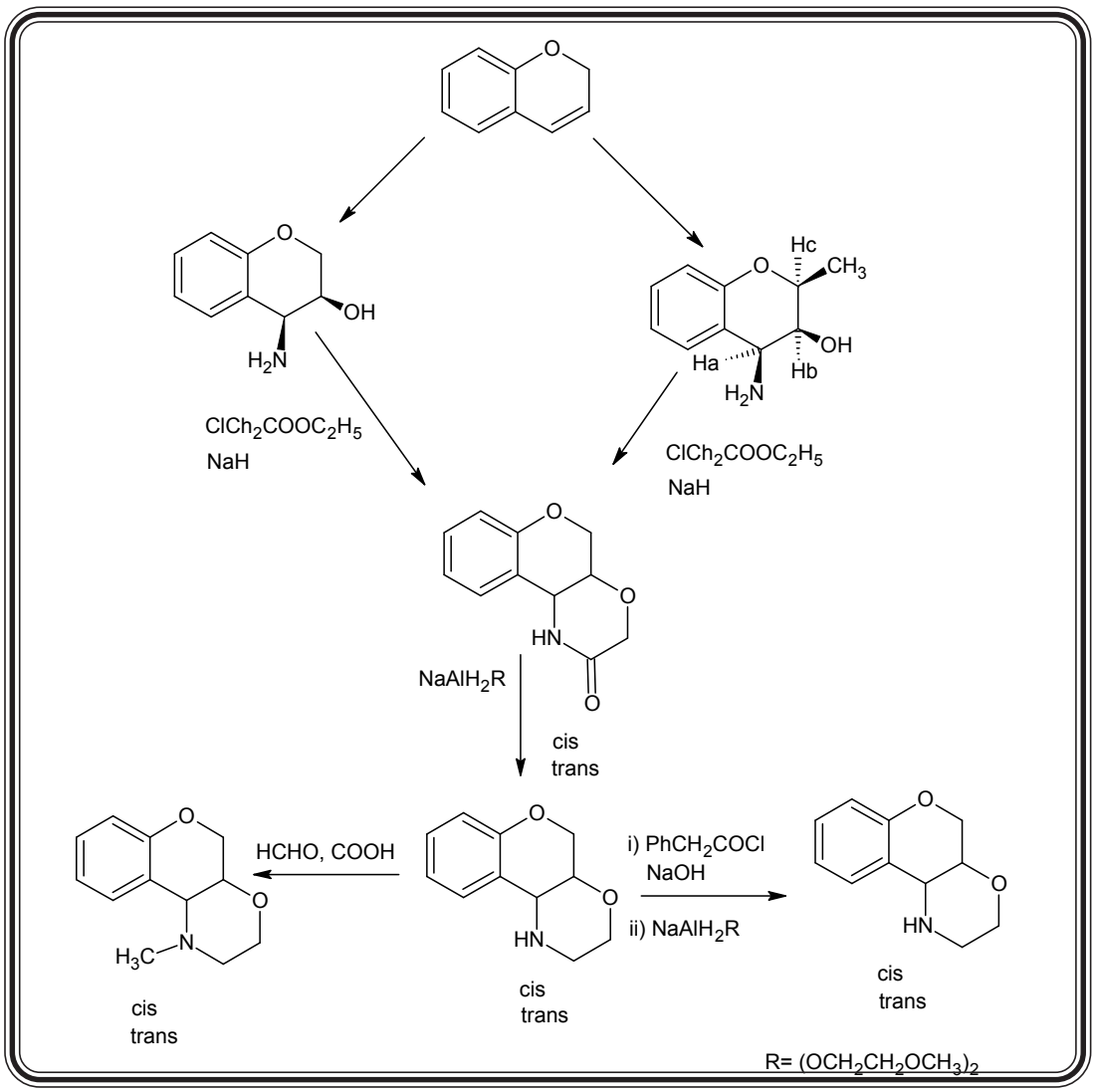
SIX MEMEBERED RINGS CONTAINING OXYGEN AND NITROGEN AS HETERO ATOMS :

4-hydroxycoumarin when mixed together with hexamethylenetetraamine (HMTA) and stirred for 5 minutes at 180-190°C gave 3,4-dihydro-1,3-oxazino[5,6-c][1,2]benzopyran-5-one (VIII)[11]. The furthur work on other 4-hydroxycoumarins was also carried out by Chavda and Shah.[12]



Julian and Matusiak[13] have studied the stereoselective synthesis of [1]benzopyrano [3,4-b][1,4]oxazines as potential antidepressants.

5. Arndt, F., Loewe, L., *Chem. Ber.,* **1951**, 84,319.
6. Klosa, J., *Pharmazie*, **1953**,8,221.
7. Hinman, J. W., Jackson, W. G., *J. Ame. Chem. Soc.*, **1956**, 78, 1072.
8. Dallacker, F., Kratzer, P., *Justus Liebigs Ann, Chem.*, **1961**, 97, 643.
9. Rao, K. S., Subba Rao, N. V., *Curr. Sci.*, **1964**,33,614.
10. Merchant, K. R., Desai, H. K., *Ind. J. Chem.*, **1973**, 11, 433.
11. Kentaro, O., Kazuhiko, K., *Japan Kokai*, **1968,**68,11916, *C.A*. **1969**,70,11572.
12. Chavda, M., Ph. D Thesis, *Saurashtra University.*, **2000**.

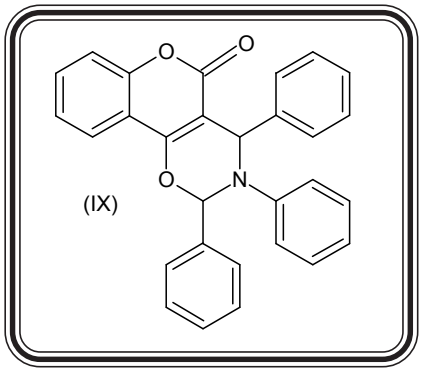


According to the recent paper of Manolov[15], the condensation products of 4-hydroxycoumarin and Schiff bases were studied under different conditions led to the conclusion that outcome of reaction product was not as per Dike and Merchant[14] who had predicted the benzopyrano-oxazine structure (IX) having molecular mass (M+ = 431).

13. Jullian, D. R., Matusaik, Z. S., *Jour. Heterocyclic. Chem.*, **1975**,12,1179.

14. Dike, S. Y., Merchant, J. R., *Tetrahedron Lett.*, **1978**,38,,3607.

15. Manolov, I. I., *Tetrahedron Lett.*, **1998,** 39,3041.

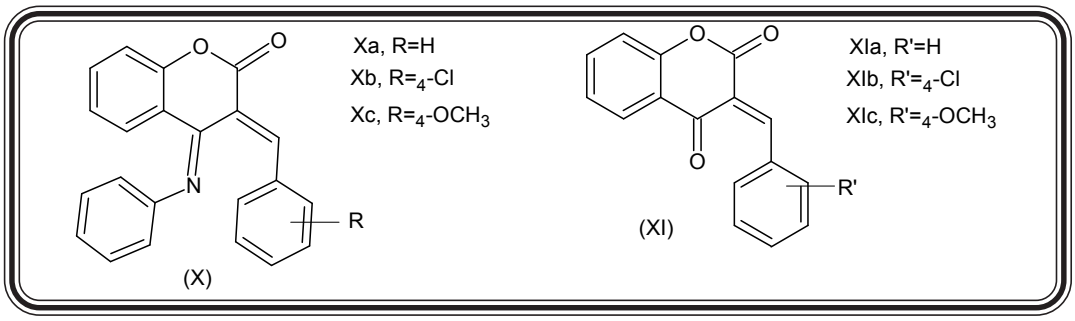


(IX)

In continuation of our study on 3,4 fused coumarins[16] and coumarin derivative,[17] when Shah et. al[18], investigated the entire reaction with changed molar proportions and reaction conditions as suggested by Manolov, different results were obtained. Merchant suggested to carry out condensation by one mole of 4-hydroxy coumarin with two moles of Schiff base in glacial acetic acid at 30°C for 1 to 3 hours.

According to Manolov, the reaction of 4-hydroxycoumarin carried out with Schiff bases like benzylideneaniline, p-methoxy benzylideneaniline and p-chloro benzylideneaniline under the experimental conditions of Merchant and coworkers, even failed to react and no product except starting substances were obtained. He furthur reported that the mixture after refluxed for 13 hrs. (which is naturally a different reaction conditions altogather from reflux and reaction hrs. point of view) afforded a compound which was assigned as structure (X) and thus, 3-benzylidine-phenyliminocoumarin was identified as the sole reaction product.

Contrary to these findings, Shah et. al.[18], has attempted reaction with the same reaction conditions, using 1:2 molar ratio of 4-hydroxycoumarin and Schiff base with vigorous stirring in glacial acetic acid at 30°C for 1-3 hrs. have afforded to give an off-white product when benzylideneaniline was used. The furthur experiments for the condensation of 4-hydroxycoumarin with p-methoxy and p-chloro benzylideneaniline also gave the products precipitated out at 30°C.



The melting points of all these compounds definitely matches with that of observed by Merchant, but the elemental analysis suggests the absence of nitrogen which led to a molecular formula $C_{16}H_{10}O_3$ having the only possible structure XIa[19-21] and thus rejecting possibility of oxazine ring formation also. Thus structure (IX) and (X) are not formed. The TLC of these compounds XIa-c were giving single spot on glass plates prepared from Silica Gel G. The solvent system used was acetone : benzene and visualization was carried out in iodine chamber.

16. Shah, A., Naliapara, Y. T., Motohashi, N., Kawase, M., *Anticancer Res.*, **1998**, 18, 3001.
17. Shah, A., Bhatt, N., Raval, R., Thakor, V., *Science and Culture*, **1986**,52(7),2289.
18. Vora, V. B., Ph.D Thesis, *Saurashtra University*., **2000**.
19. Jesthi, P. K., Rout, M. K., *Indian J. Chem*., **1965**, 3,461.
20. Velezheva, V. S., Erofeev, Yu., *J. Org. Chem*. USSR, **1973**,9,183.
21. Sullivan, W. R., Hueber, C. F., *J. Am. Chem. Soc.*, **1943**,65,2288.
22. Caddick, S. *Tetrahedro*n, **199**5, *5*1, 10403*.*
23. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacqnault, P., *Synthesis,* **1998,**1213.
24. Perreux, L.; Loupy, A. *Tetrahedron,* **200**1, *5*7, 9199.
25. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron,* **200***1, 5*7, 9225.
26. Khadizah M. Al-Zaydi., *Molecules*., **2003**,8,551

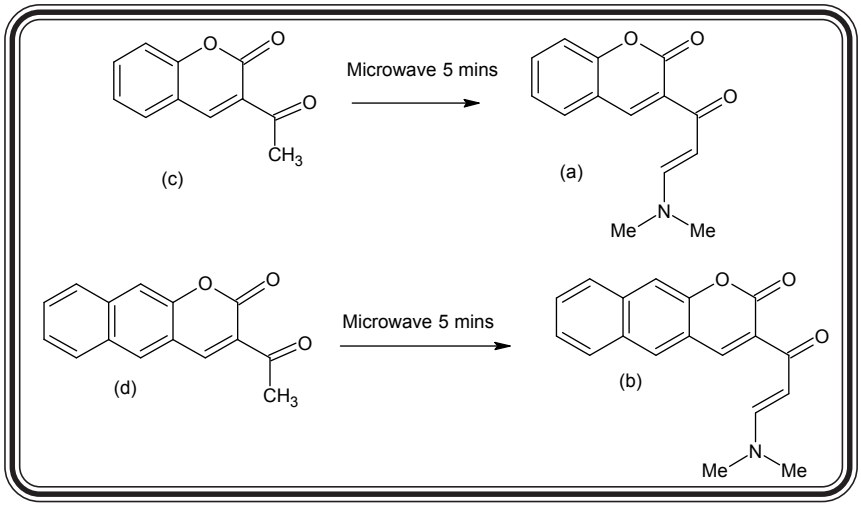
The highest peak (M+= 250) observed by Merchant in 70 ev MS study of the reaction product was probably due to XIa and not IX, but the explanation for 30 ev Mass result is intriguing and unexpectable in the present study.

CONCLUSION :

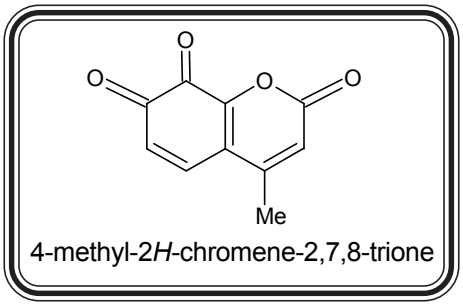
This led to the confirmation of 3-(substituted-benzal)-2,4-diketochroman type compounds instead of 3,4-fused benzopyrano oxazine derivatives. Further, elemental analysis data also support the absence of nitrogen, thus eleminating benzylidene phenyliminochroman structure suggested by earlier authors.

The utility of microwaves in heterocyclic synthesis is now receiving considerable attention[22-25] and, although enaminones has been recently extensively utilized as precursors for the synthesis of heteroaromatics, the solventless reaction of enaminones with nucleophilic reagents under microwave irradiation has not, to our knowledge, been previously investigated. The potential utility of microwaves as an energy source for heterocyclic synthesis, Khadiza M. Al-Zyadi[26] reported synthesis of 3-heteroarylsubstituted coumarins and benzo coumarins of potential interest as pharmaceuticals and/or photochromic dyes [27-29] and investigated the possibility of conducting these reactions under microwave irradiation in addition to the standard thermal conditions.

Enaminones **a** and **b** were smoothly obtained by reacting compounds **c** and **d** with dimethylformamide dimethylacetal (DMFDMA) in a domestic microwave for a very short time, the yield being much higher than that obtained by conventional heating with a solvent. Compound **1** has been recently synthesized by Elnagdi *et a*l.,[30] by refluxing 3-acetylcoumarin with DMFDMA in xylene solution. However, under such conditions the yield of the enaminone was much lower than that obtained by the solvent less procedure.



The coumarin molecule has been shown to possess unique antiedema and antiinflammatory activities, and these make it particularly effective in the treatment of all high-protein edemas.[31,32] Several natural or synthetic coumarins with various hydroxy and other substituents were found to inhibit lipid peroxidation and to scavenge hydroxyl radicals, superoxide radicals and hypochlorous acid.[33] The dihydroxylated coumarins (vicinal OH groups) and flavonoids [34] (a closely related class) were all also active. Furthermore furocoumarins, pyranocoumarins, geiparvarin analogues[35] and some more newly synthesized coumarins condensed with an heteroaromatic ring were found to act as antiinflammatories,[36–38] antioxidants[36–38] cytostatic agents [35] and to inhibit viral proteases [39] and viral replication.



4-methyl-2*H*-chromene-2,7,8-trione

27. Al-Zaydi,K. M. *J., Saudi. Chem. Society*, **2002**, 477.

28. Al-Zaydi, K. M.; Hafez, E. A.; Elnagdi, M. H., *J. Chem. Res,* **2000***, (S)* 4, 510.

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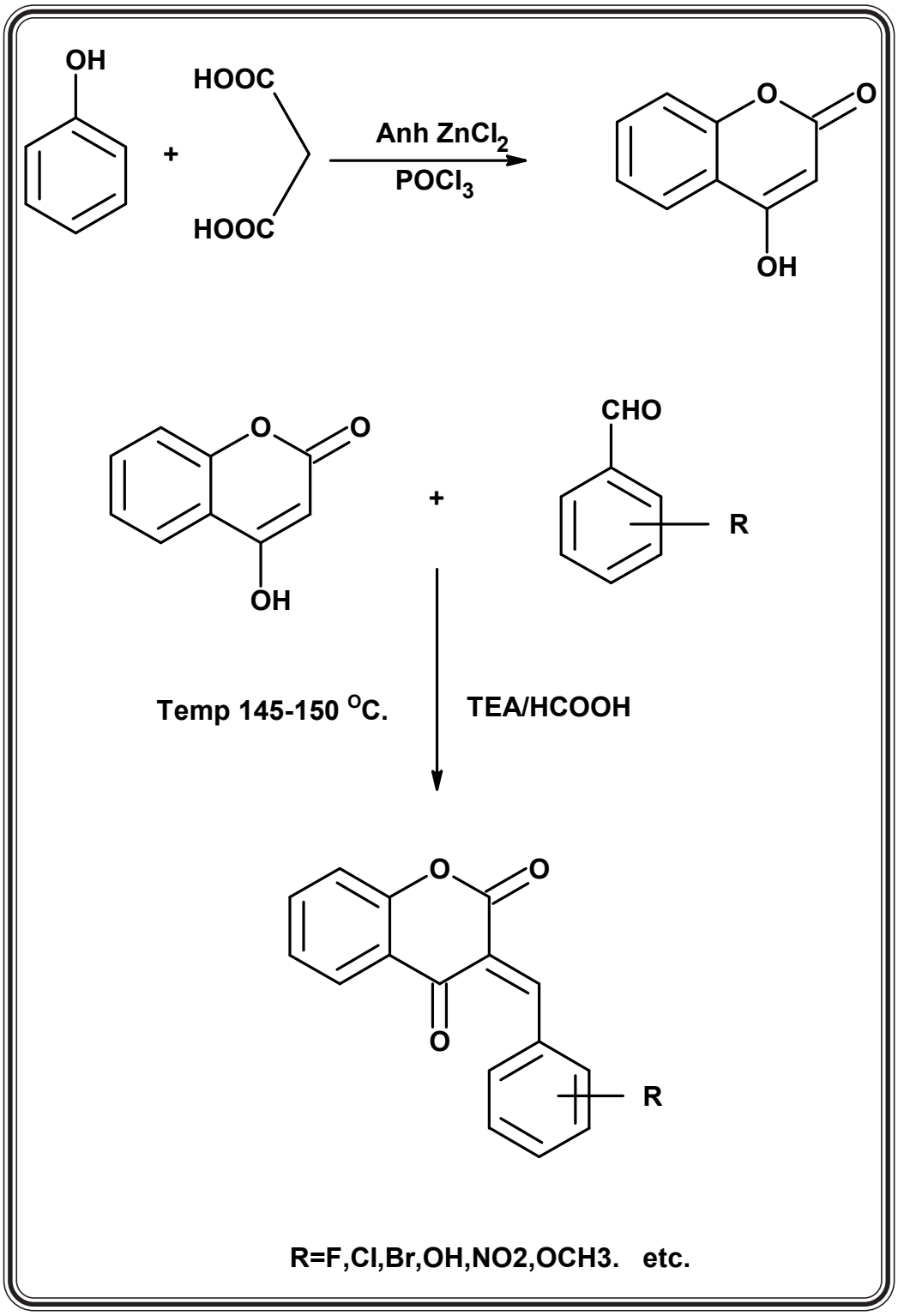
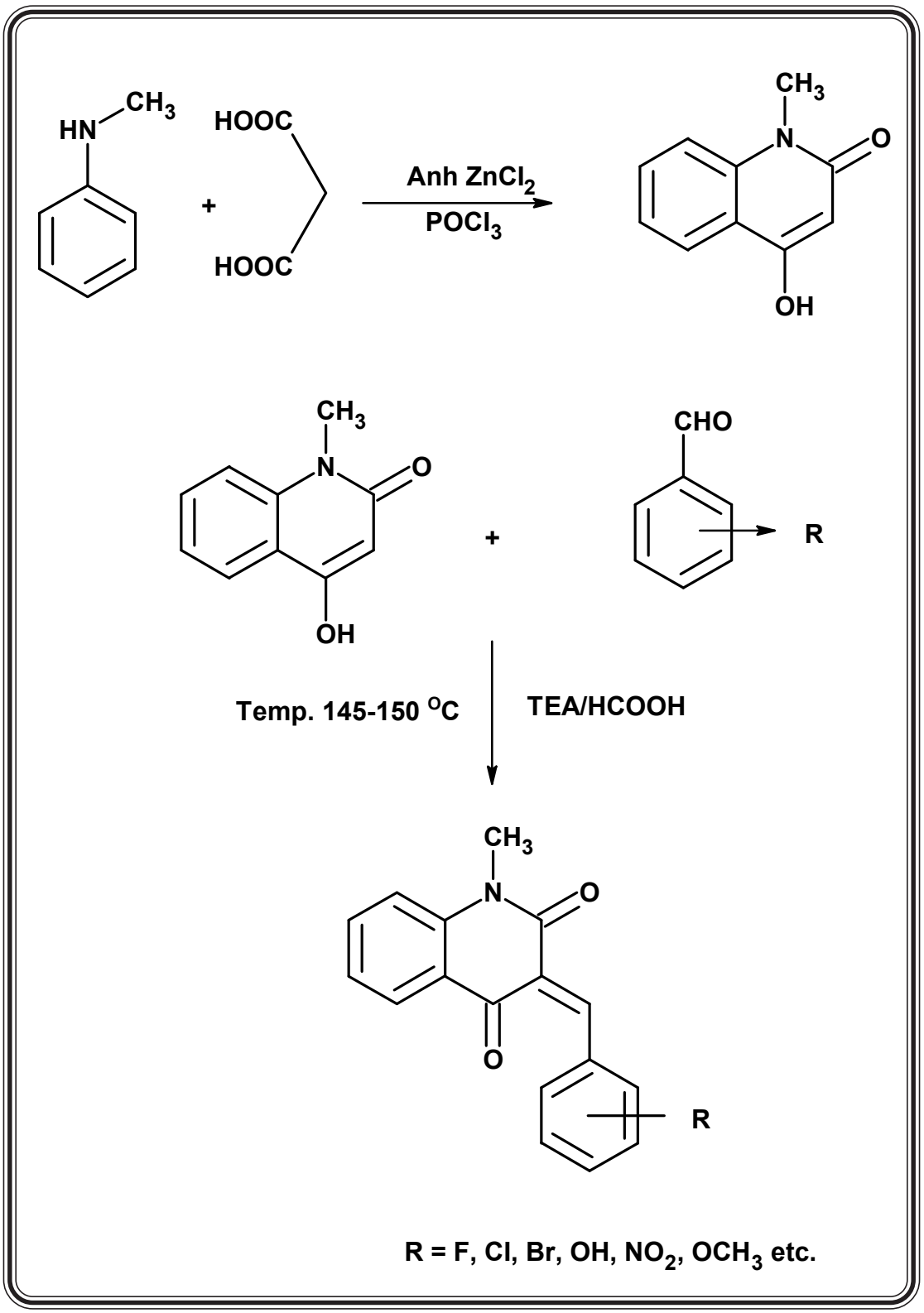
In the curent chapter, two different series of compounds from 4-hydroxy coumarin and N-methyl, 2,4-dihydroxy quinoline were prepared as per the reaction schemes **5.1** and **5.2**.

Reaction Scheme - 5.1



Reaction Scheme - 5.2



EXPERIMENTAL

A) Preparation of 4-hydroxy coumarin :

It was prepared according to the method of Shah and co-workers[31].

Phenol (0.1 mole) and malonic acid (0.1 mole) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 ml) and the reaction mixture was heated on water bath at 70 ^{o}C for 10 Hrs. The reaction mixture cooled to room temperature & quench into ice water to afford a brown yellow color solid, which was filtered and wash with water. The solid material was dissolved in to 10% sodium carbonate solution & filtered to remove undissolved material. The filtrate was slowly acidified with dilute hydrochloric acid. Solid product separated, which was filtered and washed with water, dried and recrystallised from ethanol. yield~65%, m.p. 210 (Reported[31] m.p. 209-210)

B) Preparation of 4-hydroxy N-methyl quinolone[32] :

It was prepared according to the method of Shah and co-workers. N-methyl aniline (0.1 mole) and malonic acid (0.1 mole) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 ml), and the reaction mixture was heated on water bath at 70 ^{o}C for 10 Hrs. The reaction mixture cooled to room temperature & quench into ice water to afford a brown yellow color solid, which was filtered and wash with water. The solid material was dissolved in to 10% sodium carbonate solution & filtered to remove undissolved material. The filtrate was slowly acidified with dilute hydrochloric acid. Solid product separated, which was filtered and washed with water, dried and recrystallised from ethanol. yield~82%, m.p 256-258 ^{0}C. (Reported[32] m.p. 256-257 ^{0}C)

C) Preparation of substituted (3*E*)-3-benzylidene-2*H*-chromene-2,4 (3*H*)-dione:- (General Preocedure)

To a mechanically stirred mixture of 4-hydroxy coumarin (0.01 mole), substituted aldehyde (0.01 mole), tri ethyl amine (0.015 mole) and formic acid was refluxed at 145 to 150 ^{o}C. for 7 hrs. The precipitates formed after cooling was filtered, washed with cold methanol and dried as amorphous solid. Yield ~ 52 to 60 %

D) Preparation of substituted (3*E*)-3-benzylidene-1-methyl quinoline -2,4(1*H*,3*H*)-dione:- (General Preocedure)

To a mechanically stirred mixture of N-methyl quinolin-2-one (0.01 mole), substituted aldehyde (0.01 mole), tri ethyl amine (0.015 mole) and formic acid was refluxed at 145 to 150 ^{o}C. for 7 hrs. The precipitates formed after cooling was filtered, washed with cold methanol and dried as amorphous solid. Yield ~ 52 to 60 %

Similarly many analogs of both above compounds were also prepared. The physical data table of these compounds are recorded as Table **5.1** and **5.2**

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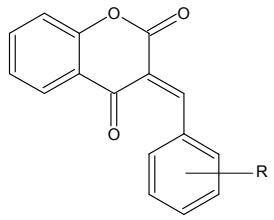
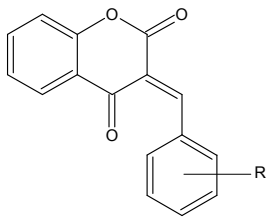
Table 5.1 Physical constant of substituted (3*E*)-3-benzylidene-2*H*-chromene-2,4(3*H*)-diones



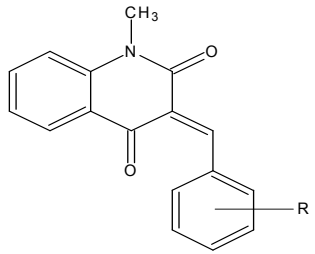
Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %	
						C	H
1	CT-1	H	$C_{16}H_{12}O_3$	252.28	202-204	76.79 (76.80)	4.03 (4.00)
2	CT-2	2-Cl	$C_{16}H_{11}ClO_3$	286.70	235-237	67.03 (67.00)	3.87 (3.85)
3	CT-3	3-Cl	$C_{16}H_{11}ClO_3$	286.70	190-191	67.03 (67.05)	3.87 (3.90)
4	CT-4	2-NO_2	$C_{16}H_{11}NO_5$	297.26	222-225	64.65 64.62	3.73 (3.70)
5	CT-5	3-NO_2	$C_{16}H_{11}NO_5$	297.26	223-224	64.65 (64.68)	3.73 (3.75)

Table 5.1 Contd.



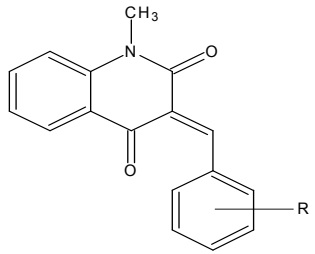
Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %	
						C	H
6	CT-6	4-NO_2	$C_{16}H_{11}NO_5$	297.26	236-238	65.09 (65.10)	3.07 (3.10)
7	CT-7	3-OH	$C_{16}H_{12}O_4$	268.26	175-177	71.64 (74.65)	4.51 (4.53)
8	CT-8	3-OCH_3	$C_{17}H_{14}O_4$	282.91	215-219	72.33 (72.35)	5.0 (5.02)
9	CT-9	4-F	$C_{16}H_{11}FO_3$	270.25	239-240	71.11 (71.15)	4.10 (4.11)
10	CT-10	4-N, N, Di-CH_3	$C_{18}H_{17}NO_3$	295.33	210-211	73.20 (73.22)	5.80 (5.77)

Table 5.2 Physical constant of substituted (3E)-3-benzylidene-1-methylquinoline-2,4(1H,3H)-dione



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
11	QT-1	H	$C_{17}H_{15}NO_2$	265.30	188-189	77.55 (77.52)	4.98 (5.00)	5.32 (5.30)
12	QT-2	2-Cl	$C_{17}H_{14}ClNO_2$	299.751	195-198	68.12 (68.15)	4.71 (4.69)	4.67 (4.70)
13	QT-3	3-Cl	$C_{17}H_{14}ClNO_2$	299.751	223-225	68.12 (68.10)	4.71 (4.75)	4.67 (4.65)
14	QT-4	2-NO2	$C_{17}H_{14}N_2O_4$	310.304	210-211	65.80 (65.83)	4.55 (4.59)	9.09 (9.10)
15	QT-5	3-NO2	$C_{17}H_{14}N_2O_4$	310.304	198-200	65.80 (65.77)	4.55 (4.52)	9.09 (9.07)

Table 5.2 Contd.



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %		
						C	H	N
16	QT-6	4-NO2	$C_{17}H_{14}N_2O_4$	310.30	235-236	65.80 (65.81)	4.55 (4.56)	9.09 (9.06)
17	QT-7	3-OH	$C_{17}H_{15}NO_3$	281.30	178-182	72.58 (72.60)	5.37 (5.40)	4.98 (4.96)
18	QT-8	3-OCH3	$C_{18}H_{17}NO_3$	295.33	245-246	73.20 (73.25)	5.80 (5.83)	4.78 (4.75)
19	QT-9	4-Cl	$C_{17}H_{14}ClNO_2$	299.75	228-230	68.12 (68.15)	4.71 (4.75)	4.67 (4.65)
20	QT-10	4-OH	$C_{17}H_{15}NO_3$	281.30	202-204	72.58 (72.60)	5.37 (5.35)	4.98 (5.00)

SPECTRAL ANALYSIS : (IR)

Instrument : SHIMAZDU FT-IR-8400 Spectrophotometer.

Sample Technique : KBr pellet

Frequency range : 4000-400cm-1.

Theoritically IR spectrum of newly synthesized chromane trione compounds can be characterized as : The aromatic region of the coumarin as well as the aryl ring at 3-position can be characterized by stretching bands obtained at 3096-3019 cm-1 and the bending vibrations bands at 1650-1400 cm-1. The bending vibrations for -CH_3 group secondary amine is seen at 1390-1370 cm-1 as well as its stretching vibrations at 2990-2850 cm-1. The cabonly group(>C=O) of the coumarin ring is seen at 1710-1690 cm-1 which confirms the presence of ketone group.

In the IR spectrum of ***CT-5,*** the stretching as well as bending vibrations are seen for the aromatic as well as the aliphatic group. The ketone group of the coumarin ring is confirmed by the sharp band obtained at 1708 cm-1, while the -CH_3 group is confimed by seeing the bending vibration at 1381 cm-1. The C-N band is observed in the In-plane bending region of 1090 cm-1.The substitution on the aryl ring of the fused pyrazole group is seen in the region of 850-650 cm-1.

Similarly IR spectrum for other compounds can also be explained.

^{1}H NMR Spectral Study :-

Instrument :BRUKER AC 300 MHz FT-NMR

Internal reference :TMS

Solvent :$CDCl_3$ or DMSO+ d_6

^{1}H NMR Spectra of **QT-1**, a singlet observed at δ 3.72 ppm confirmed the presence of methyl (C_{11}) protons. A singlet at δ 5.62 ppm confirms presence of C_{13} proton. Two typical doublet of para coupling observed at δ 7.33 ppm and δ 7.58 ppm is due to ortho coupling of -CH (C_{16}, C_{18}) with -CH (C_{15}, C_{19}). Two doublet of -CH (C_8, C_9) is observed at δ 7.87 and δ 8.14 ppm respectively. Two triplet due to aromatic protons of -CH (C_7, C_{10}) is observed at δ 7.90 ppm and δ 7.60 ppm.

Similarly observation are seen in ^{1}H NMR spectra of **CT_2** on page No. **130.**

SPECTRAL ANALYSIS : (MASS)

Instrument : Shimazdu-QP-2010

Detector : Electron Impact (EI)

Mass Analyzer : Quardropole mass analyzer

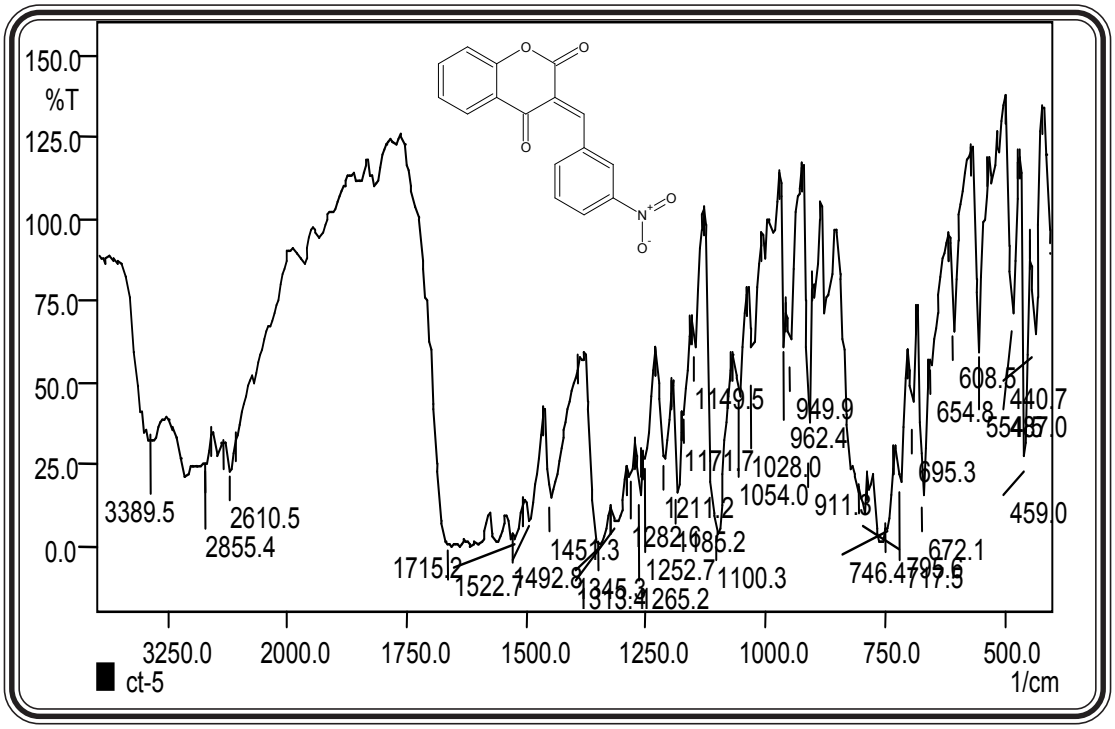
Injection System : Direct Inlet System (DI)

For the Mass Spectral analysis of compounds of this series the GC-MS (Gas Chramatograph coupled with MASS) technique was used. The molecular ion peaks (M+) of the comounds in mass spectra were in total agreement with it's molecular weight.

In case of ***CT-7,*** the molecular ion peak is observed at 294.0 m/z (M+) peak, 295 (M+1) peak while the base peak is observed at 278.0 m/z.

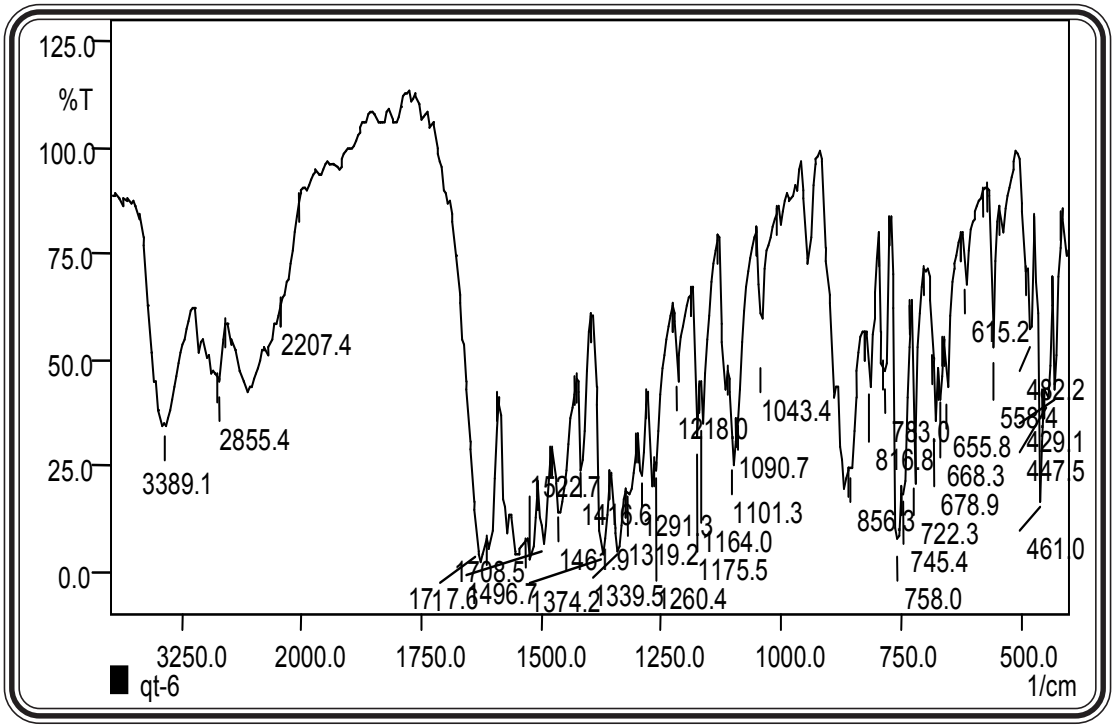
In case of ***QT-3,*** the molecular ion peak is observed at 472.0 m/z (M+) peak while the base peak is observed at 262.0 m/z.

IR Spectrum of (3*E*)-3-(3-nitrobenzylidene)-2*H*-chromene-2,4(3*H*)-dione:- (CT-5)



Sample Technique	:	KBr Pellet
Instrument	:	SHIMADZU FI IT-8400
Frequency range	:	4000-400cm^{-1}

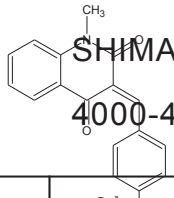
IR spectrum of (3E)-1-methyl-3-(4-nitrobenzylidene)quinoline-2,4 (1H,3H)-dione:- (QT-6)



Sample Technique : KBr Pellet

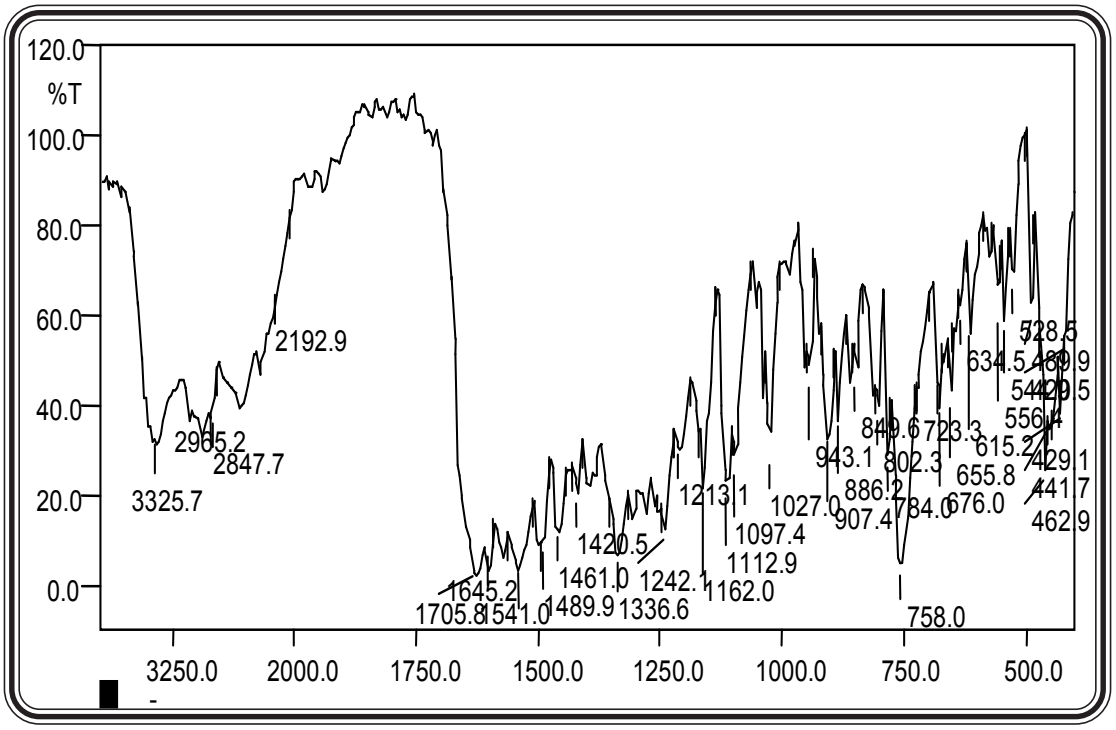
Instrument : SHIMADZU FI IT-8400

Frequency range : 4000-400cm^{-1}



Vibration Mode	Observed cm^{-1}	Refrence cm^{-1}
-NH- (Stretch.)	3389	3400-3300
-C=O- (Stretch.)	1717 1708	1715-1735
-C=C- (Ring Skeleton)	1522 1496	1600-1500
-CH_2- (Rocking)	1461	1470-1400
-CH_3 (Bending)	1339	1390-1370
-C-NO_2	1374	1350-1400
-C-N (Stretch.)	1260	1250-970
Arenes (C-H) (OOP Bending)	745 856	690-900
-C-C (Bending)	1013 1090	950-1100

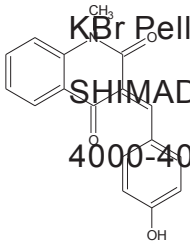
IR spectrum of (3E)-1-methyl-3-(4-hydroxybenzylidene)quinoline-2,4 (1H,3H)-dione:- (QT-10)



Sample Technique : KBr Pellet

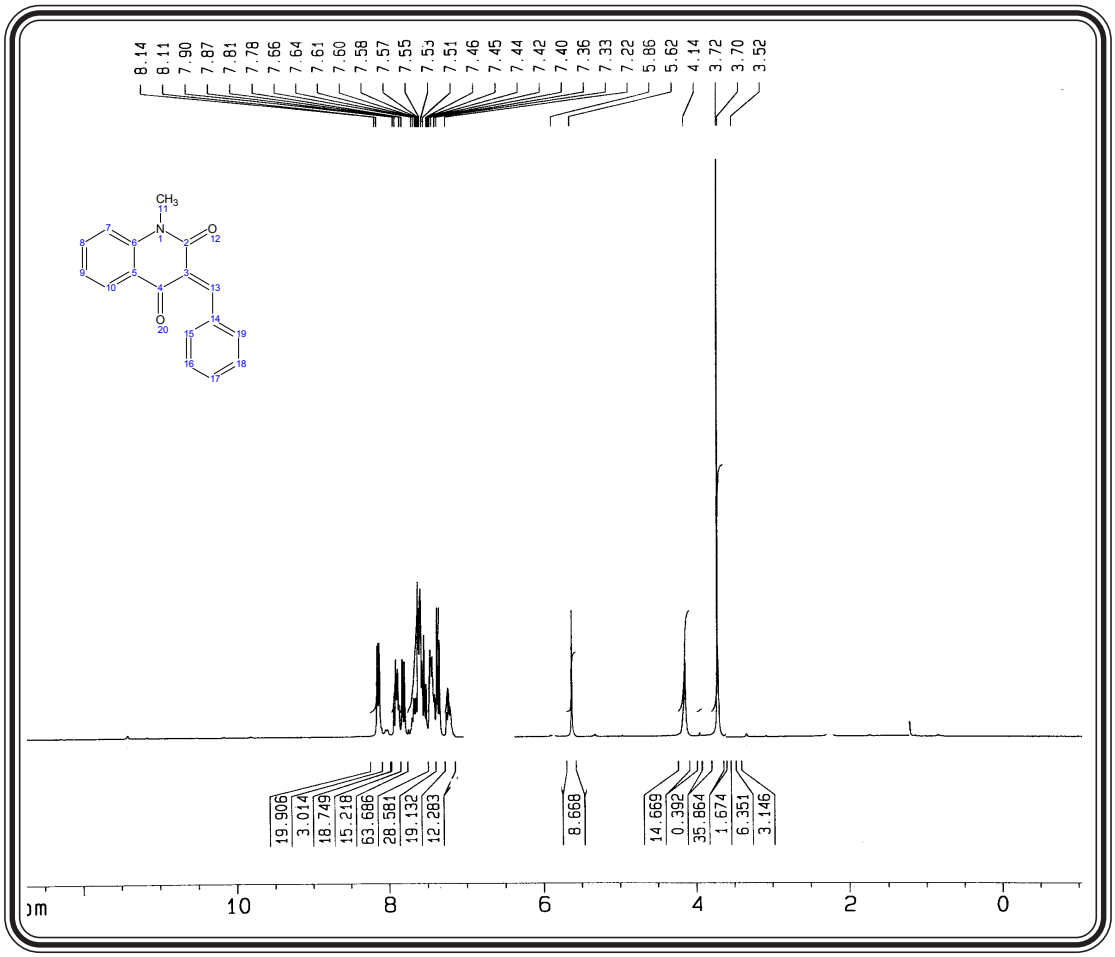
Instrument : SHIMADZU FI IT-8400

Frequency range : 4000-400cm^{-1}



Vibration Mode	Observed cm^{-1}	Refrence cm^{-1}
-NH- (Strech.)	3325	3400-3300
-OH (Strech.)	3325	3300-3500
-C=O-(Strech.)	1705	1710-1725
-C=C-(Ring Skeletone)	1541 1489	1600-1500
-CH_2-(Rocking)	1461	1470-1400
-CH_3 (Bending)	1336	1390-1370
-C-N (Strech.)	1242	1250-970
Arenes (C-H) (OOP Bending)	758 849	690-900
-C-C (Bending)	1027 1097	950-1100

^{1}H NMR spectrum of (3*E*)-3-benzylidene-1-methylquinoline-2,4(1*H*,3*H*)-dione:- (QT-1)



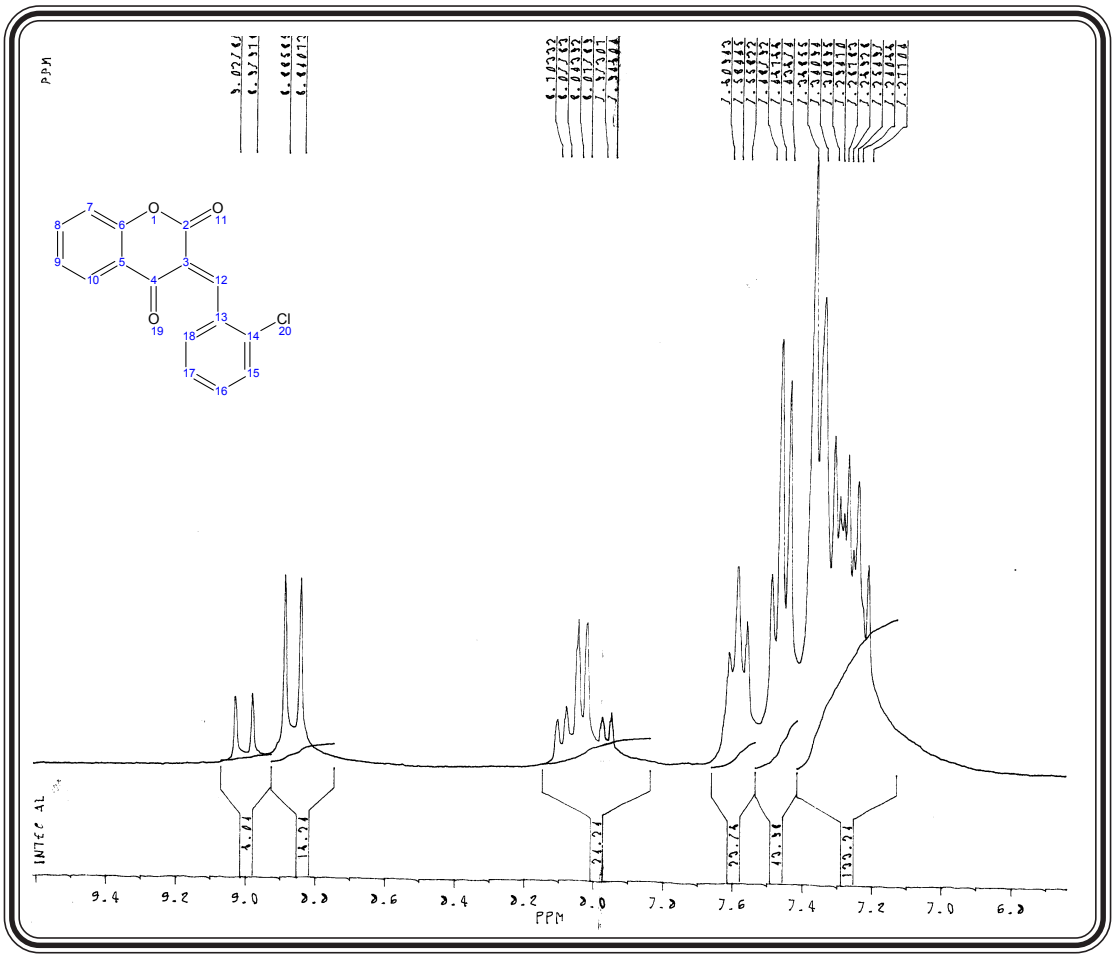
Instrument : BRUKER AC 300 MHz FT-NMR

Standard : TMS

Solvent : $DMSOd_6$

Type	No. of Proton	Multiplicity	d PPM
-CH_3(11)	3H	singlet	3.72
-CH(13)	1H	singlet	5.62
-CH(17)	2H	triplet	7.22
-CH(16,18)	2H	doublet	7.33
-CH(15,19)	2H	doublet	7.58
-CH(9)	1H	doublet	7.87
-CH(7)	1H	triplet	7.90
-CH(8)	1H	doublet	8.14
-CH(10)	1H	triplet	7.60

^{1}H NMR spectrum of (3*E*)-3-(2-chlorobenzylidene)-2*H*-chromene-2, 4(3*H*)-dione (CT-2)



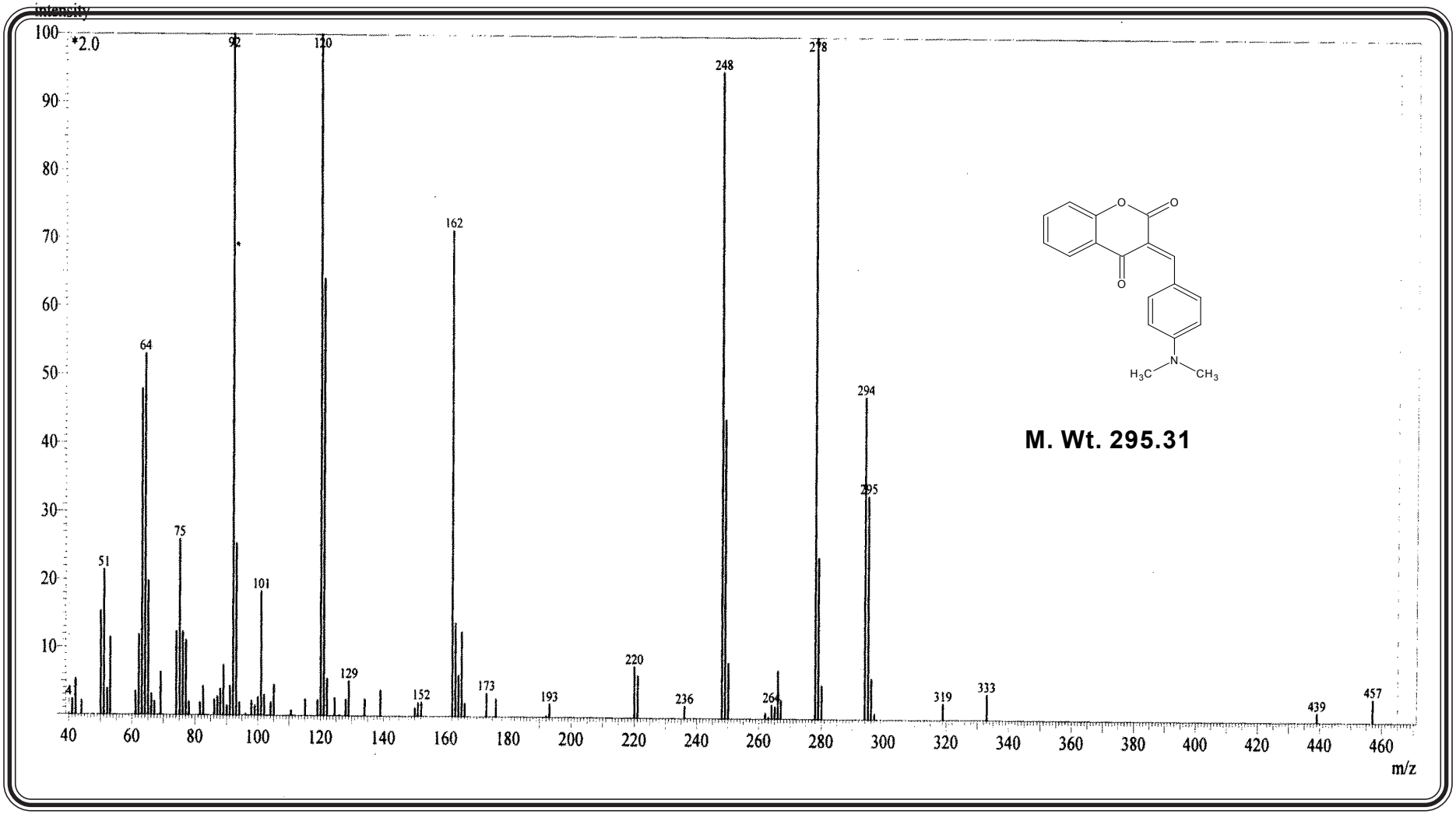
Instrument : BRUKER AC 300 MHz FT-NMR

Standard : TMS

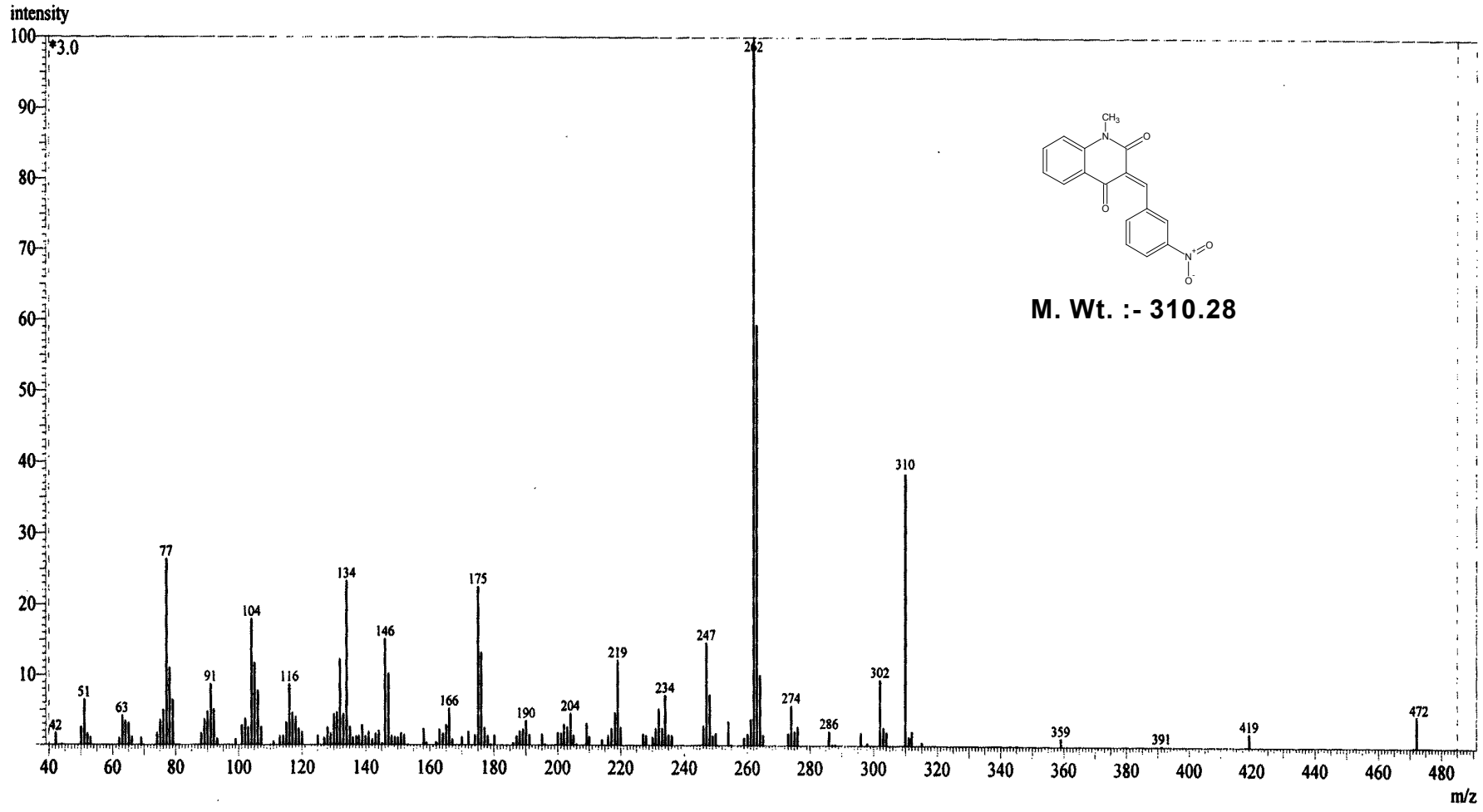
Solvent : $DMSOd_6$

Type	No. of Proton	Multiplicity	d PPM
-CH(12)	1H	singlet	5.62
-CH(16)	1H	triplet	7.22
-CH(15,17)	2H	doublet	7.33
-CH(18)	1H	doublet	7.58
-CH(9)	1H	double	7.87
-CH(7)	1H	triplet	7.90
-CH(8)	1H	double	8.14
-CH(10)	1H	triplet	7.60

IR Spectrum of (3*E*)-3-(N<N-dimethylaminobenzylidene)-2*H*-chromene-2,4(3*H*)-dione (CT-10)



Mass spectrum of (3E)-1-methyl-3-(3-nitrobenzylidene)quinoline-2,4 (1H,3H)-dione:- (QT-5)



INTRODUCTION

Nature is still an excellent source of new drugs; Out of 20 leading drugs in last decade, 9 of them were derived from natural products.[1] Almost 40% of the 520 new drugs approved for the drug market between 1983-2004 were natural products. Greater than 60% of the anticancer and anti infective agents that are on the market or in clinical trials are of natural products or derived from natural products.[2]

Several chalcones are found to occur in nature. The natural chalcones are found to contain phloroglucinol, pyrogallol, catechol and hydroquinone nuclei[3-6]. Some chalcones are found to occur in nature as glycosides like carathamine and iscoarthamine present in *Carthamus tinctrius* [7].

The chalcones are also natural biocides, [8-10] and are well known intermediates in the synthesis of heterocyclic compounds exhibiting various biological activities like antimalarial[11.] antiviral[15], antitumar[13], herbicidal[14], antioxidant[15], and also bactericidal.[16,17]

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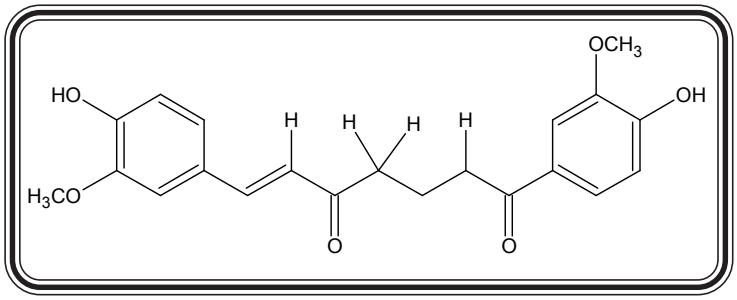
Curcumin is a yellow pigment isolated from the rhizone of perennial herb *Curcuma longa L (turmeric)*. Lampe et. al [18] elucidated the chemical structure of Curcumin.



Curcumin has several biological activities like anti-inflammatory, antioxidative, antibacterial, antihepatotoxic, hypertensive and hypocholesterolemic[19-23]. Tonnesen[24] describes Curcumin as a non-toxic compound even at high dosages.

Modification of groups on the terminal aromatic rings of Curcumin reveals that electron donating group increase anti-inflammatory activity[25]. The structure similarity of chalcones like molecule is expected to exhibit either antagonize or potentiate the biological activity. Therefore it was very essential to study few chalcones derivatives of such type derived from 3-acetyl coumarin.

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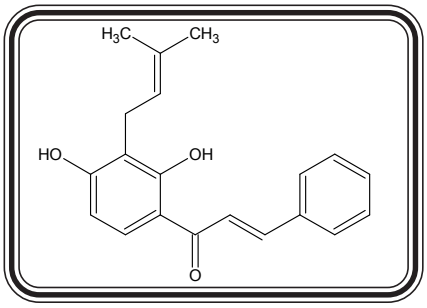
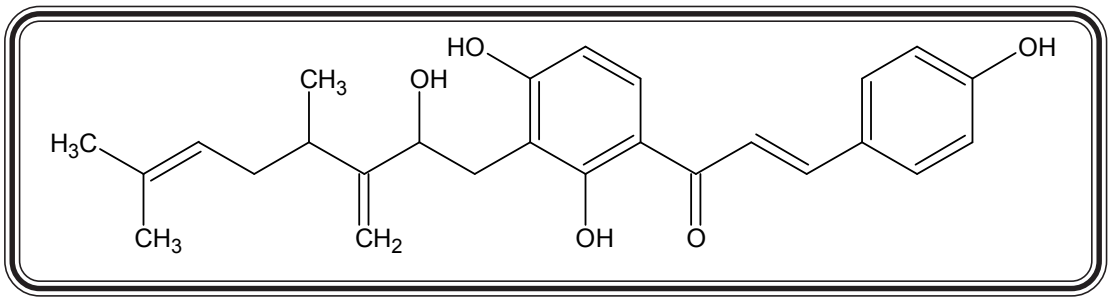
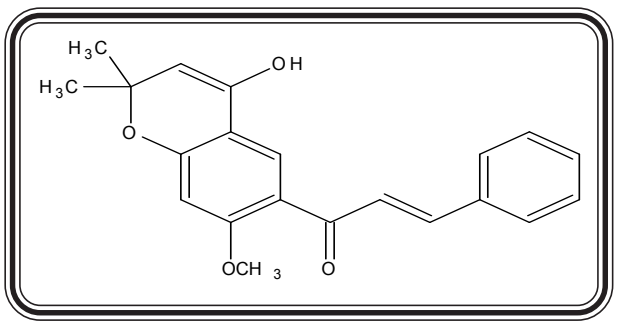
The isocordoin reported as a potential antitumour agent .The isocordoin was isolated from *Lonchocarpus neuroscapha* and the chemical structure of isocordoin was elucidated by P. G. Waterman,[26] et. al



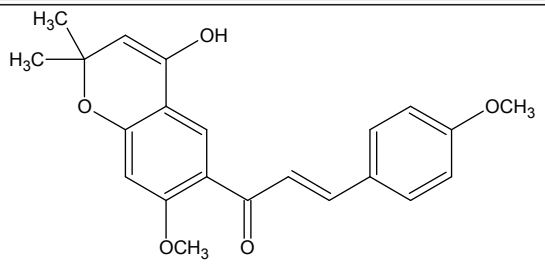
G. Delle Monache[27],et. al had carried out biological study of New geranyl chalcone derivatives with antifungal and radical scavenging properties from the leaves of *Artocarpus nobilis.*



J. S.Calderon[28] et al had isolated naturally occurring novel chalcone coumarin obavatachalcone & confirmed structure as below.

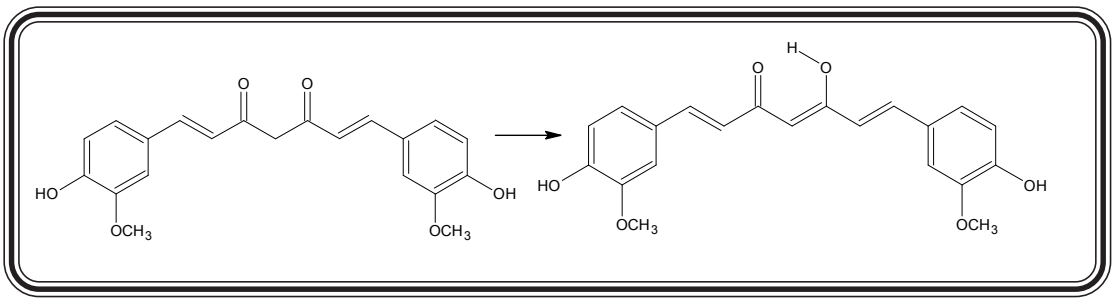


L. Jayasinghe[29] et. al had isolated and confirmed chemical structure of naturally occurring new coumarin chalcone for which biological study is under progress.



2'-methoxy-4,6-dihydroxylonchocarpin
Lonchocarpus xuul

The natural product curcumin (diferuloylmethane, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), obtained from the spice turmeric, exhibits numerous biological activities including anti-cancer, anti-inflammatory, and anti-angiogenesis activities. Some of these biological activities may derive from its anti-oxidant properties. There are conflicting reports concerning the structural/electronic basis of the anti-oxidant activity of curcumin. Curcumin is a symmetrical diphenolic dienone. A series of enone analogues of curcumin were synthesized that included: (1) curcumin analogues that retained the 7-carbon spacer between the aryl rings; (2) curcumin analogues with a 5-carbon spacer; and (3) curcumin analogues with a 3-carbon spacer (chalcones). These series included members that retained or were devoid of phenolic groups. Anti-oxidant activities were determined by the TRAP assay and the FRAP assay. Most of the analogues with anti-oxidant activity retained the phenolic ring substituents similar to curcumin. However, a number of analogues devoid of phenolic substituents were also active; these non-phenolic analogues are capable of forming stable tertiary carbon-centered radicals.



Tannins and lignins are natural compounds contained in plants such as tea leaves. Previously it was demonstrated that tannic acid represses 12-*o*-tetra-decanoyl phorbol-13-acetate (TPA)-induced human immunodeficiency virus (HIV) promoter activity. Furthermore it was demonstrated that a 30-bp element located just downstream of the NF-êB element in the HIV promoter responds negatively to tannic acid. However, the kinds of molecules responsible for this suppressive effect have remained unknown, because tannic acid is a mixture of various galloylglucoses. Furthur study of structure-defined natural compounds for HIV promoter-suppressive effects showed that ellagitannins suppress TPA-induced HIV promoter activity to the same extent as tannic acid. It is well documented that 3-Phenylcoumarins, isoflavone and chalcones have more suppressive effects than ellagitannins.

BIOLOGICAL ACTIVITY ASSOCIATED WITH CHALCONES

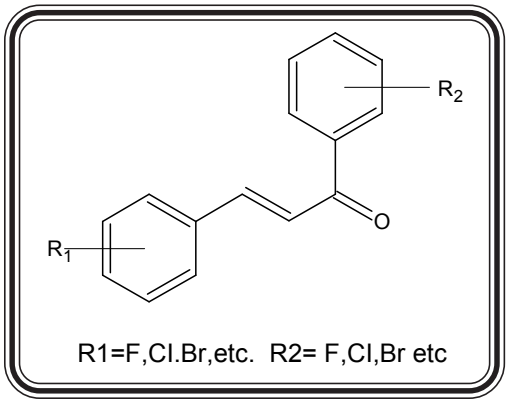
The chalcones have exhibited different biological activities like antimalarial[30], antiviral[31], antitumar[32], herbicidal[33] and also bactericidal[34]. They are also well known as antioxidants[35].

A series of chalcones derivatives have been reported to have potent anti-inflammatory activity. In an effort to continually develop potent anti-inflammatory agents, novel series of chalcones, 2'-hydroxy- and 2',5'-dihydroxychalcones were synthesized and their inhibitory effects on the activation of mast cells, neutrophils, microglial cells and macrophages were evaluated in-vitro.[36]

A chalcone derivative was found to be an inhibitor of tyrosine kinases and the inhibition was ATP-competitive. Three of chalcone derivatives, were found to have an ability to inhibit the tyrosine kinase activity of epidermal growth factor receptor (EGFR) in vitro.Svetaz, L.[37] et al have isolated an antifungal Chalcones and new caffeic acid esters from *Zuccagnia punctata* Acting against soybean infecting fungi.

Stoll, R[38] et.al. have synthesized chalcone derivatives antagonized interactions between the Human Oncoprotein MDM-2 [38]

Wilairat[39] and coworkers prepared series of alkoxylated and hydroxylated chalcones and carried out antimalarial activity & Structure-Activity Relationship Analysis.



R1=F,Cl.Br,etc. R2= F,Cl,Br etc

26, P. G. Waterman*, R. Borges-Argáez, L. M. Pena-Rodríguez, *Phytochemistry*, **2002**, 60(5), 533-540

27. A. Vitali, F. Ferrari, G. Delle Monache*, E. Bombardelli, B. Botta, *Planta Med.*, **2001**, 67(5), 475-477

28 F. Gomez-Garibay, M. De la O Arciniega, C. L. Cespedes, J. Taboada, J. S., Calderon *Z. Naturforsch., Sect. C*, **2001**, 56(11-12), 969-972

29 L. Jayasinghe, B. A. I. S. Balasooriya, W. C. Padmini, N. Hara, Y. Fujimoto *Phytochemistry*, **2004**, 65(9), 1287-1290

30 Prescott B., Int.J.Pharmacol, Bio,Pharm, **1975**, 11(4**),**322, *Chem. Abstr.*, **1975**, 83**,** 126292d.

31 Binder D,Noc C.R., Holzer W. and Roscnwirth B. **1989,** *arch. Pharm.*, **1985**, 318 (1), 48**,** *chem. Abstr.,* 102, 149025u.

Recently Kumar, S. K et al [40] have synthesized and evaluated novel series of Boronic-chalcone derivatives as antitumor Agents.

De Tommasi[41] and coworkers had carried out anti oxidant activity studies of naturally occurring chalcone glycosides and flavanones from *Maclura (Chlorophora) tinctoria.*

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32 Dore,J.C. and Viel C., *J.Pharma,Bell,* **1974**, 29 (4)**,** 341, *chem.Abstr*, **1975**, 83, 90650c.

33 Matsunaka.S, J.Agric., *Food.Chem*, **17,**191 (1969)

34 Devaux,Guy, Nuhrich A. Dargelos V. Vincent. Capdepay M, Fr. Demande, **1978**, 2,357,247 (CI.A. A 61 K 31/345)

35 Saradjiman s.s., Hakin R.L. Vander Goot H. and Timmerman H. Eur. *J. Med.Chem.*, **1997**, 32, 625-630.

36, F. Gomez-Garibay, M. De la O Arciniega, C. L. Cespedes, J. Taboada, J. S., Calderon* Z. *Naturforsch, Sect. C*, **2001,** 56(11-12), 969-972

37. Svetaz, L.; Tapia, A.; Lopez, S. N.; Furlan, R. L. E.; Petenatti, E.; Pioli, Schmeda-Hirschmann, G.; Zacchino, S. A.; *J. Agric. Food Chem*.; (Article); **2004**, 52(11); 3297-3300.

38. Stoll, R.; Renner, C.; Hansen, S.; Palme, S.; Klein, C.; Belling, A.; Zeslawski, W.; amionka, M.; Rehm, T.; Muhlhahn, P.; *Biochemistry; (Article)*; **2001**; 40(2); 336-344.

39 Liu, M.; Wilairat, P.; Go, M. L.; *Med. Chem*.; **2002**; 45(8); 1735-1735

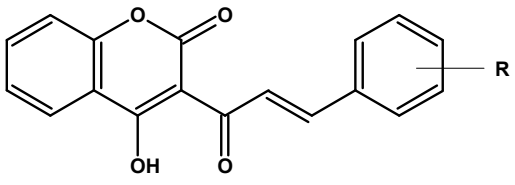
40 Kumar, S. K.; Hager, E.; Pettit, C.; Gurulingappa, H.; Davidson, N. E.; Khan, S. R, *J. Med. Chem.; (Letter)*; 2003; 46(14); 2813-2815

41 Cioffi, G.; Escobar, L. M.; Braca, A.; De Tommasi, N, *J. Nat. Prod.; (Article);* **2003**; 66(8); 1061-1064.

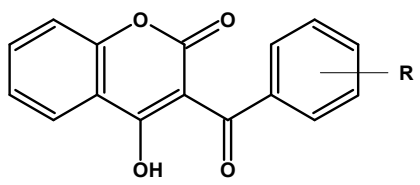
On the other hand, other flavonoids and acetogenins have no suppressive effect. 3-Phenylcoumarins and chalcones showed no suppressive effect on the cytomegalovirus (CMV) promoter, suggesting that they act specifically on the HIV promoter. These results suggest that 3-phenylcoumarin or chalcone compounds could be used to develop novel anti-HIV drugs with an action targeted at HIV promoter activity.

The design and synthesis of non peptidic inhibitors that incorporate S1 S2 binding sites of HIV-1 protease are also well studied by earlier workers. Further using an interactive docking procedure the coumarin and chromone series of compounds were docked into the active site of the enzyme and their binding mode were analyzedby moleculer dynamics simultaneous for 50 ps. All these results helped to identified some 4-hydroxy coumarin-3-yl (un) substituted styryl ketones which exhibited comparatively low inhibition of HIV-1 protease at 10 wm concentration respectively.

Further advances in molecular modeling and structure based drug design have resulted in the development of non peptidic several 4-Hydroxy -2-oxo-2H-coumarin-3-yl (un)substituted styryl ketones (Va-d), 4-hydroxy-2-oxo-2H-coumarin-3-yl- substituted phenyl ketones (VI) and 2-(4'-substituted phenyl)-3-hydroxy-4-oxo-4H-1-benzopyrans (VII, b) inhibitors of HIV-1 protease were studied with different approaches.



a R= 4-F
b R = 4-Cl
c R = 4- OCH_3
d R = 3-NO_2



a R = OCH_3
b R = F

In earlier study chalcone of 4-OH coumarins was studied. The present study is aimed to design compounds devoid of hydroxy group at C_4 position. Thus in present chapter, the series of chalcones of 3-acetyl coumarin were synthesized and studied comparatively.

SYNTHETIC ROUTE FOR PREPARTION:

The two routes have been applied for the synthesis of title compounds. First route consists of the preparation of styryl derivatives from o-hydroxy acetophenone and p-substituted benzaldehydes. The resulting styryl intermediates were further cyclized in presence of hydrogen peroxide and sodium hydroxide. In an another route, the 4-hydroxy coumarin were directly condensed with various cinnamoyl chlorides. when various aldehydes were condensed with malonic acid in presence of pyridine, substituted cinnamic acid derivatives were obtained which were converted into respective acid chlorides. the 4-hydroxy coumarin on further treatment with acid chloride resulted in formation 3-styryl-4-hydroxy coumarins.

These methods established to arrive at the target compounds are rather multistep and involves the use of expensive aldehyde for conversion into cinnamic acids. the yields reported for these compounds are ranging between 40-60 %.

We have found that the alternative synthetic route adopted by us has many advantages because:

1. The route is useful for a single step preparation for various 4-hydroxy coumarins substituted at benzenoid part.
2. The use of aldehyde in the first steps resulting into loss of yield can be eliminated.

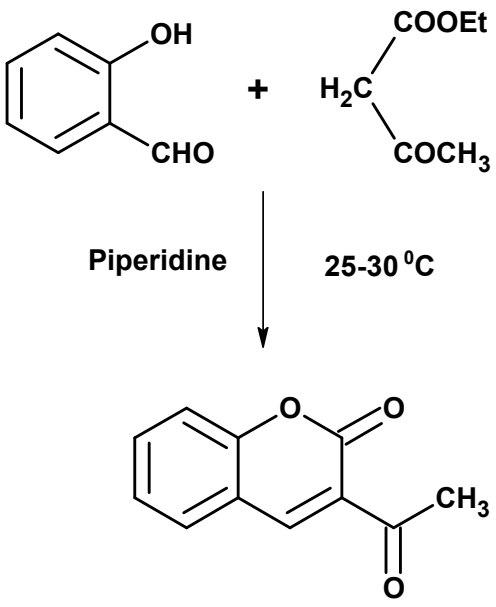
3. The acetylation is accomplished with glacial acetic acid in presence of phosphoryl chloride. the reactivity of third position of coumarin system greatly facilitates direct formation of 3-acetyl-4-hydroxy coumarins avoiding any possibility of acetylation of hydroxyl group at C_4 position.
4. The 3-acetyl-4-hydroxy coumarins are prepared in more than 70% yield in most of the cases and therefore providing better methods with igher yields with less expensive starting materials.
5. The respective chalcones can be prepared in a single step from various 3-acetyl-4-hydroxy coumarins. thus this method offer a better diversity of molecular structures and is of wide applicability. the use of the aldehydes in last step increases the overall yield of chalcone and the purity profile is also maintained.
6. The styryl coumarins are available in low geometrical isomeric forms. fortunately in the investigational molecules selected in this chapter, one isomer is soluble in methanol and another is absolutely insoluble (probably trans), thus leading to a very easy isolations of isomers. some of the chalcones as mentioned in the current list are possessing trans isomers only.
7. The use of chloroform as a solvent is very convenient for this method. in very few instance, chloroform is reported as reaction medium. we found it very convenient.

The current work deals with the application of above advantageous method for the purpose of synthesizing series of 3-acetyl coumarin derived chalcones.

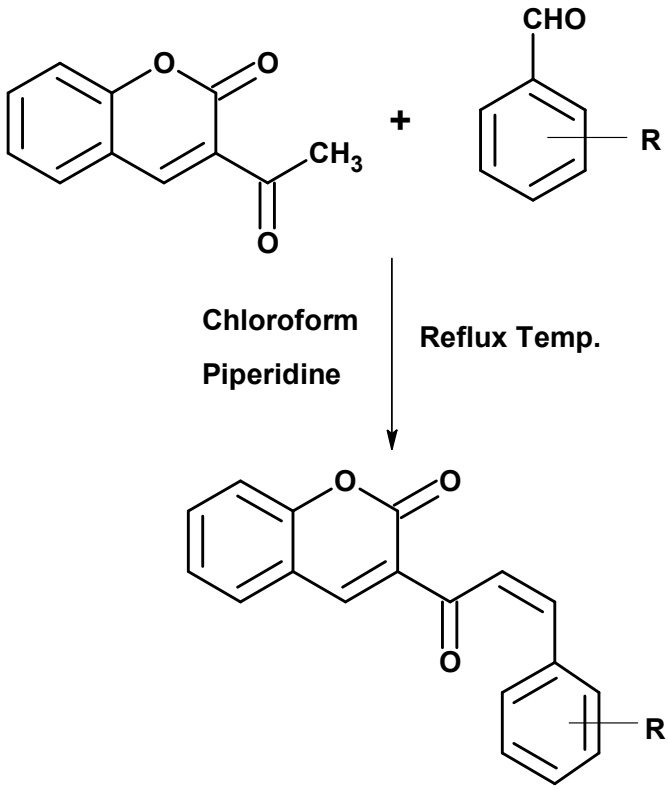
These chalcones were readily availble for cyclocondensation with phenyl hydrazine to afford new pyrazolyl derivatives also.

REACTION SCHEME

Step:1

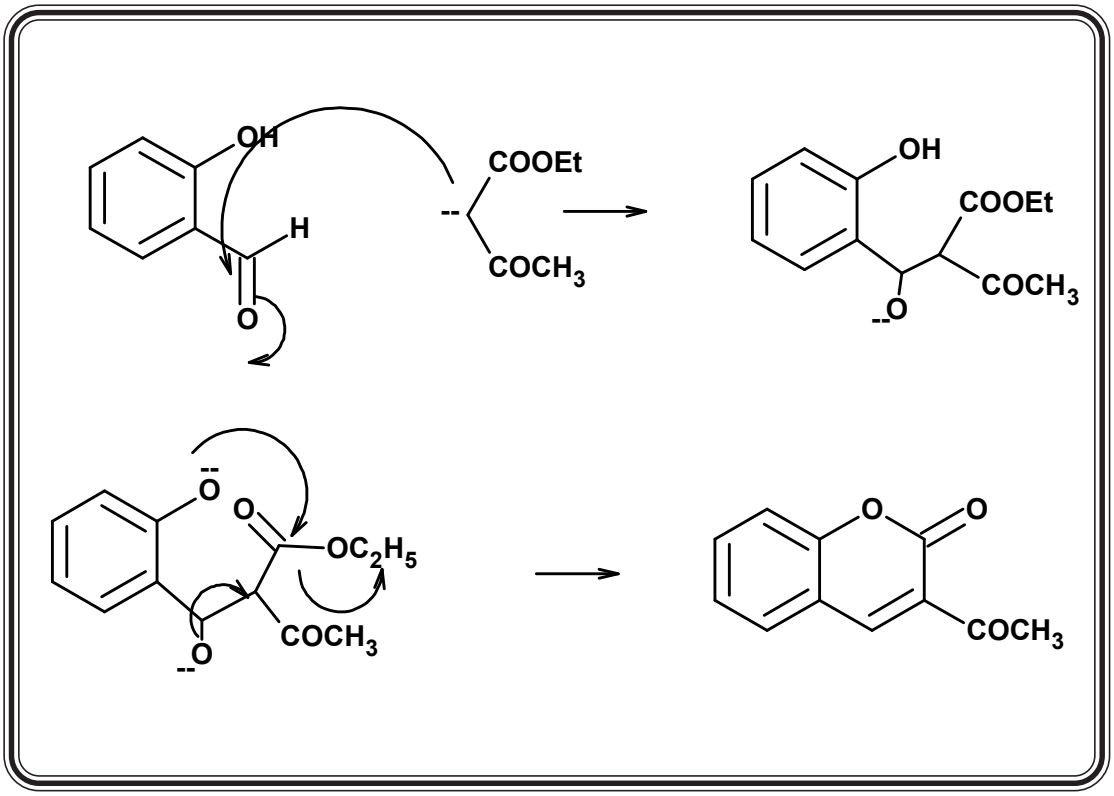


Step:2



R=Cl,F,Br,NO_2,OCH_3,OH etc.

REACTION MECHANISM



EXPERIMENTAL:-

Preparation of 3-acetyl coumarin[42] :

2 –hydroxy benzaldehyde (0.01 mole) and ethyl acetoacetate (0.01 mole) taken into flask and 2-3 drops of piperdine was added as catalyst. Reaction mixture kept at 25-30 ^{o}C Temp.for 2 Hrs. .A pale yellow poduct was obtained. It was filtered& washed with di ethyl ether .The product was recrystallised from ethyl acetate.

TLC system :- Ethyl Acetate : Hexane (3 : 7)

Yield:~65%

Melting Point:-118-199 ^{0}C(Reported[42] m.p. 120^{0}C)

Preparation of 3-[(3-(un.) substituted phenyl) prop-2-enoyl]-2H-chromen-2-one :-

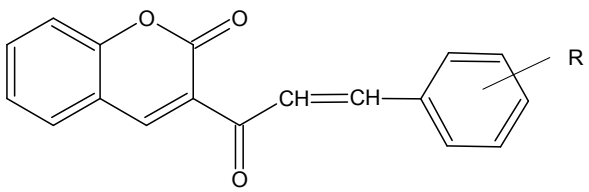
General Procedure:-

In a 100 ml round bottom flask, 3-acetyl coumarin (0.01 mole) and (un) substituted aromatic aldehyde (0.01mole) were dissolved in 100 ml chloroform .The catalytic amount of piperdine (2-3 drop) was added and the reaction mixture was refluxed for 2 hrs. The reaction progress was monitored by TLC. After completion of the reaction chloroform was distilled out completely and 10 ml methanol was added, stirred for 15 min at 25 -30 ^{O}C. The product was filtered & dried in air oven. It was recrystallised from methanol.

With the same procedure, a series of compounds have been synthesized and physical data of compounds were recorded in Table No. **6.1**

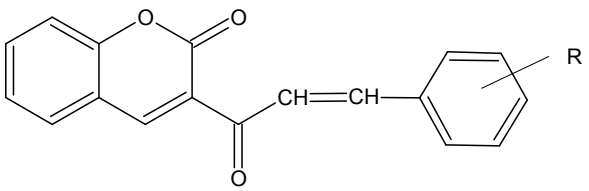
42. Shah A. K., Bhatt N. S., Raval R. V., Thakor V. M., *Curr. Sci.,* **1984**, 53, 1289-1290.

Table 6.1 Physical constants of 3-[3-(Substituted phenyl) -prop-2-enyl]-2H-chromen-2-ones



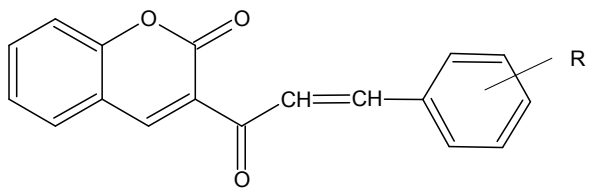
Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %	
						C	H
01	CH/01	H	$C_{18}H_{14}O_3$	278.30	170-172	78.25 (78.20)	4.38 (4.30)
02	CH/02	4-F	$C_{18}H_{13}FO_3$	296.29	143-146	73.47 (73.20)	3.77 (3.75)
03	CH/03	4-Cl	$C_{18}H_{13}ClO_3$	312.74	151-153	69.58 (69.20)	3.57 (3.55)
04	CH/04	3-Cl	$C_{18}H_{13}ClO_3$	312.74	147-149	69.58 (69.42)	3.57 (3.57)
05	CH/05	3-Br	$C_{18}H_{13}BrO_3$	357.19	198-200	60.87 (60.86)	3.12 (3.10)
06	CH/06	3-NO_2	$C_{18}H_{13}NO_5$	323.30	169-172	67.29 (67.25)	3.45 (3.47)

Table 6.1 Contd.



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %	
						C	H
07	CH/07	2-Cl	$C_{18}H_{13}ClO_3$	312.74	145-147	69.58 (69.55)	3.57 (3.50)
08	CH/08	4-OCH_3	$C_{19}H_{16}O_4$	308.32	172-174	74.50 (74.50)	4.61 (4.56)
09	CH/09	2-OCH_3	$C_{19}H_{16}O_4$	308.32	163-165	74.50 (74.43)	4.61 (4.55)
10	CH/10	3-OCH_3	$C_{19}H_{16}O_4$	308.32	185-188	74.50 (74.52)	4.61 (4.58)
11	CH/11	4-OH	$C_{18}H_{14}O_4$	294.30	200-203	73.97 (73.95)	4.14 (4.15)
12	CH/12	3,4,5-Tri-OCH_3	$C_{21}H_{20}O_6$	368.38	210-212	68.85 (68.80)	4.95 (5.00)

Table 6.1 Contd.



Sr. No.	Compound Code	Substitution-R	Molecular Formula	Molecular Weight gm/mol	M.P. [°C]	Elemental analysis %	
						C	H
13	CH/13	2-NO_2	$C_{18}H_{13}NO_5$	323.30	145-147	67.29 (67.20)	3.45 (3.42)
14	CH/14	2-OH	$C_{18}H_{14}O_4$	294.30	170-172	73.97 (73.94)	4.14 (4.10)
15	CH/15	4-NO_2	$C_{18}H_{13}NO_5$	323.30	165-168	67.29 (67.24)	3.45 (3.40)
16	CH/16	3,4-Di-OCH_3	$C_{20}H_{16}NO_5$	336.33	180-183	71.42 (71.40)	4.79 (4.75)
17	CH/17	Anthraldehyde	$C_{26}H_{16}NO_3$	376.40	190-192	82.96 (83.00)	4.28 (4.25)
18	CH/18	Indole-3 carbaldehyde	$C_{20}H_{13}NO_3$	315.32	198-200	76.18 (76.20)	4.16 (4.17)

SPECTRAL ANALYSIS : (IR)

Instrument : SHIMAZDU FT-IR-8400 Spectrophotometer.

Sample Technique : KBr pellet

Frequency range : 4000-400cm^{-}1.

The chalcones synthesised in this chapter exhibits characteristics IR bands which can be explained as : The coumarin ring in the chalcone moiety shows stretching as well as the bending vibrations in the region of 2990-2850 cm^{-}1 and 1640-1400 cm^{-}1 resp. The carbonyl group (>C=O) of the system shows a very sharp bend at 1725-1710 cm^{-}1 which proves the presence of two ketone groups. Moreover, the sharp band obtained is due to the presence of ethylinic bond in neighbouring carbon atoms. Other characteristic bends of the aryl ring of benzaldehyde can be seen in the respective IR spectrum.

In the IR spectrum of ***CH-1,*** the characteristic stretching band for the ethylinic bond in the structure can be seen at around 3125 cm^{-}1, while the presence of two ketone groups (carbonyl frequencies >C=O) in the structure can be seen as a sharp band in the region of 1718 cm^{-}1. The two protons of the ethylinic group shows a band in the out of plane bending region at around 995 cm-1, which is for the cis as well trans positions.

In the case of ***CH-2,*** the frequencies of the respective groups are almost identical to the expected theoritical values. Moreover, a sharp band for the -OCH_3 functional group can be seen at 1384.2 cm^{-}1. In compound ***CH-14,*** the hydroxyl group of the aryl substitution can be seen as a sharp band at 3324 cm^{-}1.The ketone group is proved by the presence of sharp band at 1725 cm^{-}1.

In case of these series, second keto gp. is observed at 1685 cm^{-}1 around in most of the cases. Only in case of CH-14, a stong effect of hydrogen bonding has lowered the value as low as 1666^{-}cm.

^{1}H NMR Spectral Study :-

Instrument :BRUKER AC 300 MHz FT-NMR

Internal reference :TMS

Solvent :$CDCl_3$ or DMSO+ d_6

^{1}H NMR spectra of CH-1, a singlet observed at δ 6.01 ppm confirmed presence of C_4 proton of coumarin ring. Two typical doublet of para coupling observed at δ 6.37 ppm due to ortho coupling of -CH (C_{18},C_{20}) with -CH (C_{17},C_{21}). Two doulet of -CH (C_8,C_9) observed at δ 7.24 ppm. Two triplet due to atomatic proton of -CH (C_7,C_{10}) is observed at δ 7.04 and d 7.42 ppm and one triplet is observed at δ 7.22 ppm due to C19 proton of aromatic ring. Two doublet of vinylic proton C_{14a} and C_{15a} is observed at δ 6.12 and δ 2.49 ppm. Here C_{14a} proton value obseved in down field due to presence of neighbouring keto (C_{14}).

SPECTRAL ANALYSIS : (MASS)

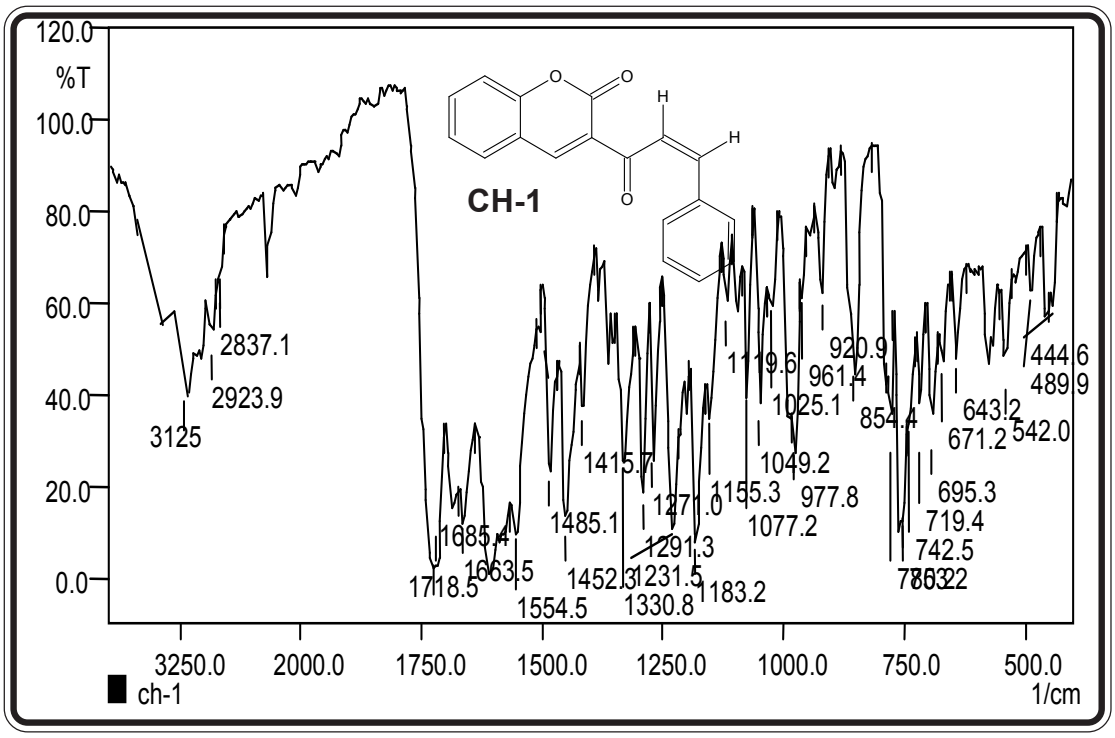
For the current study, Instrument used was **JEOL SX 102/DA-6000** for FAB (**Fast Atom Bombardment**). The molecular ion peaks (M+) of the compounds in mass spectra were in total agreement with its molecular weight.

In case of ***CH-11***, the molecular ion peak is observed at 306.0 m/z (M+) peak, while the base peak is obtained at 173.0 m/z.

In case of ***CH-2***, the molecular ion peak is observed at 366.0 m/z (M+) peak, while the base peak is obtained at 154.0 m/z.

IR spectra of 3-[(2Z)-3-phenylprop-2-enoyl]-2H-chromen-2-one:-

(CH-1)



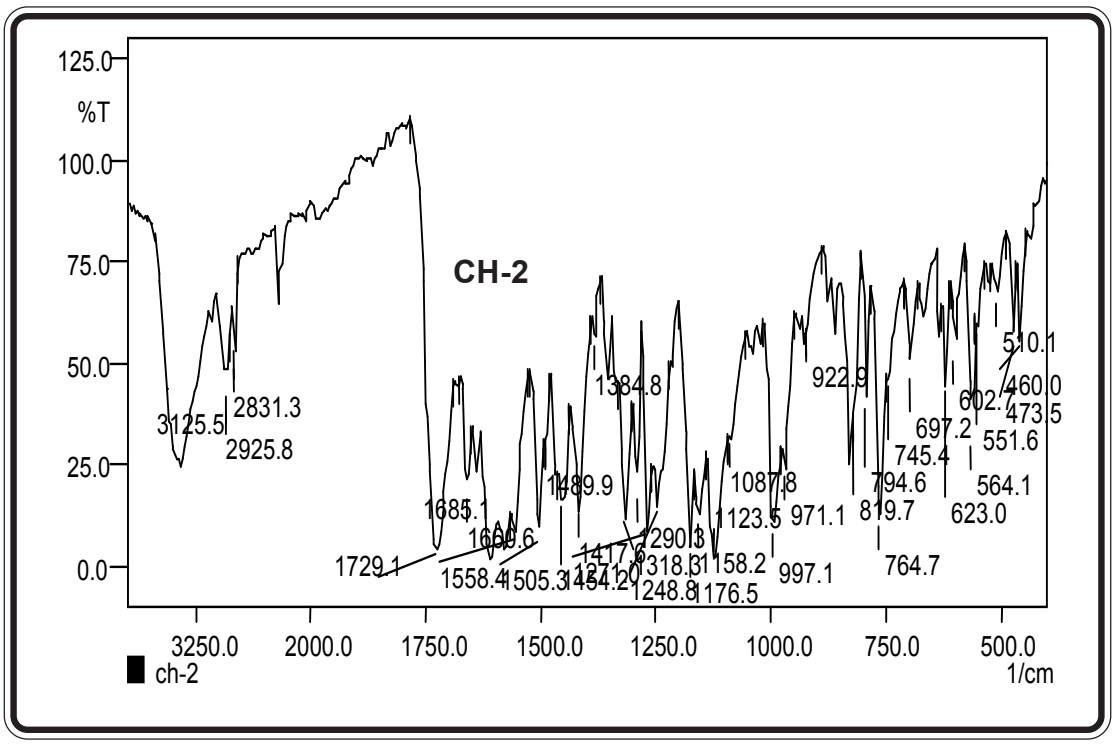
Sample Technique : KBr Pellet

Instrument : SHIMADZU FT IR-8400

Frequency range : 4000-400cm^{-1}

Vibration Mode		Observed cm^{-1}	Refrence cm^{-1}
-CH=CH- (Strech.)		3125	3200-3100
-C=C- (Ring Skeletone)		1554.5 1485.1	1600-1500
Arenes (C-H) (OOP Bending)		780.2 742.5	690-900
Carbonyl	-C=O-O (cyclic)	1718.5	1735-1720
	-C-C=O	1685.4	1700-1680

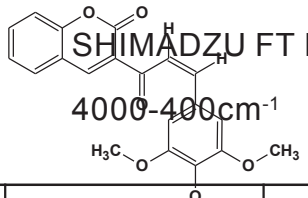
Mass Spectrum of 3-[(2*Z*)-3-(3,4,5-trimethoxyphenyl)prop-2-enoyl]-2*H*-chromen-2-one:- (CH-2)



Sample Technique : KBr Pellet

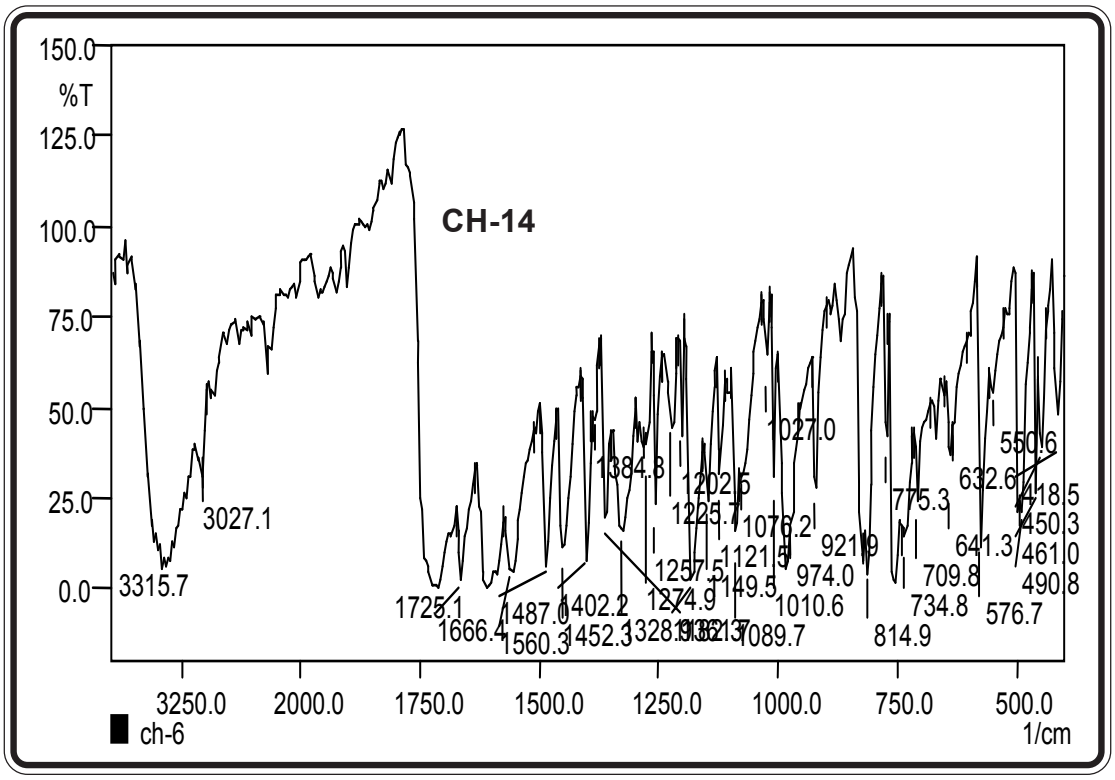
Instrument : SHIMADZU FT IR-8400

Frequency range : 4000-400cm^{-1}



Vibration Mode		Observed cm^{-1}	Refrence cm^{-1}
-CH=CH- (Strech.)		3125.5	3200-3100
-C=C- (Ring Skeletone)		1558.4 1505.3	1600-1500
Arenes (C-H) (OOP Bending)		819.7 745.4	690-900
Carbonyl	-C=O-O (cyclic)	1729.1	1735-1720
	-C-C=O	1685.1	1700-1680
Ether (C-O-C)		1248.5	1250-1225

IR Spectra of 3-[(2*Z*)-3-(2-hydroxyphenyl)prop-2-enoyl]-2*H*-chromen-2-one:- (CH-14)



Sample Technique : KBr Pellet

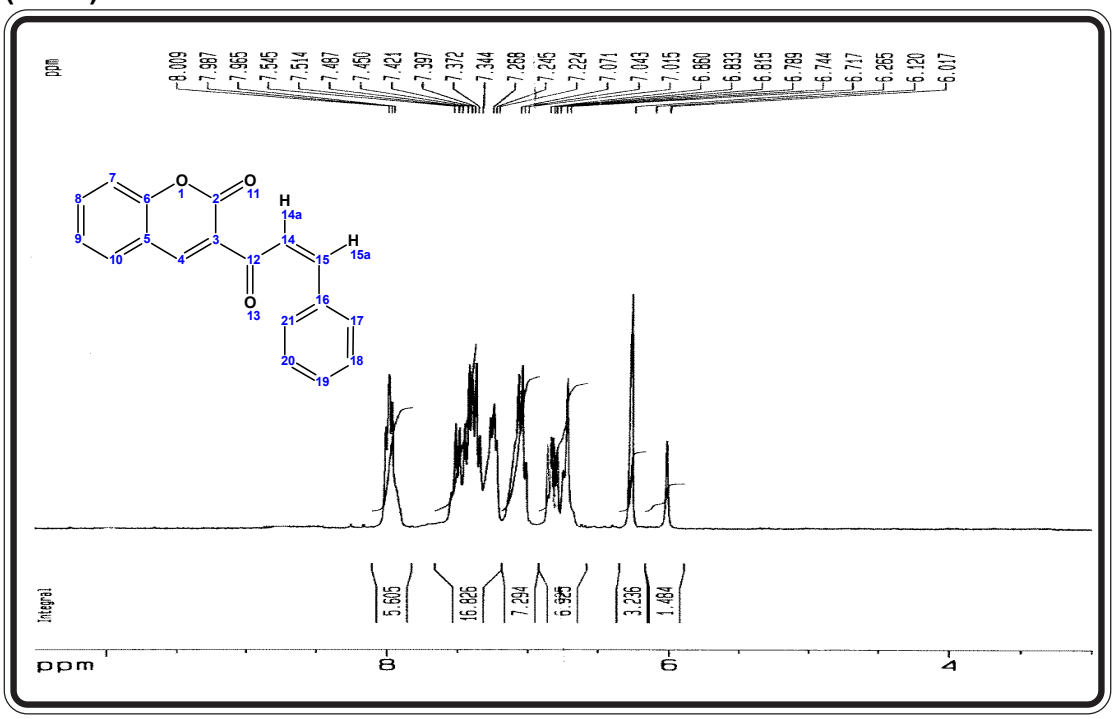
Instrument : SHIMADZU FT IR 8400

Frequency range : 4000-400cm^{-1}

Vibration Mode		Observed cm^{-1}	Refrence cm^{-1}
-OH		3315.7	3450-3300
-CH=CH- (Strech.)		3027.1	3200-3100
-C=C- (Ring Skeletone)		1560.3 1487.0	1600-1500
Arenes (C-H) (OOP Bending)		814.9 734.8	690-900
Carbonyl	-C=O-O (cyclic)	1725.1	1735-1720
	-C-C=O	1666.4	1700-1680

^{1}H NMR spectrum of 3-[(2*Z*)-3-phenylprop-2-enoyl]-2*H*-chromen-2-one:-

(CH-1)



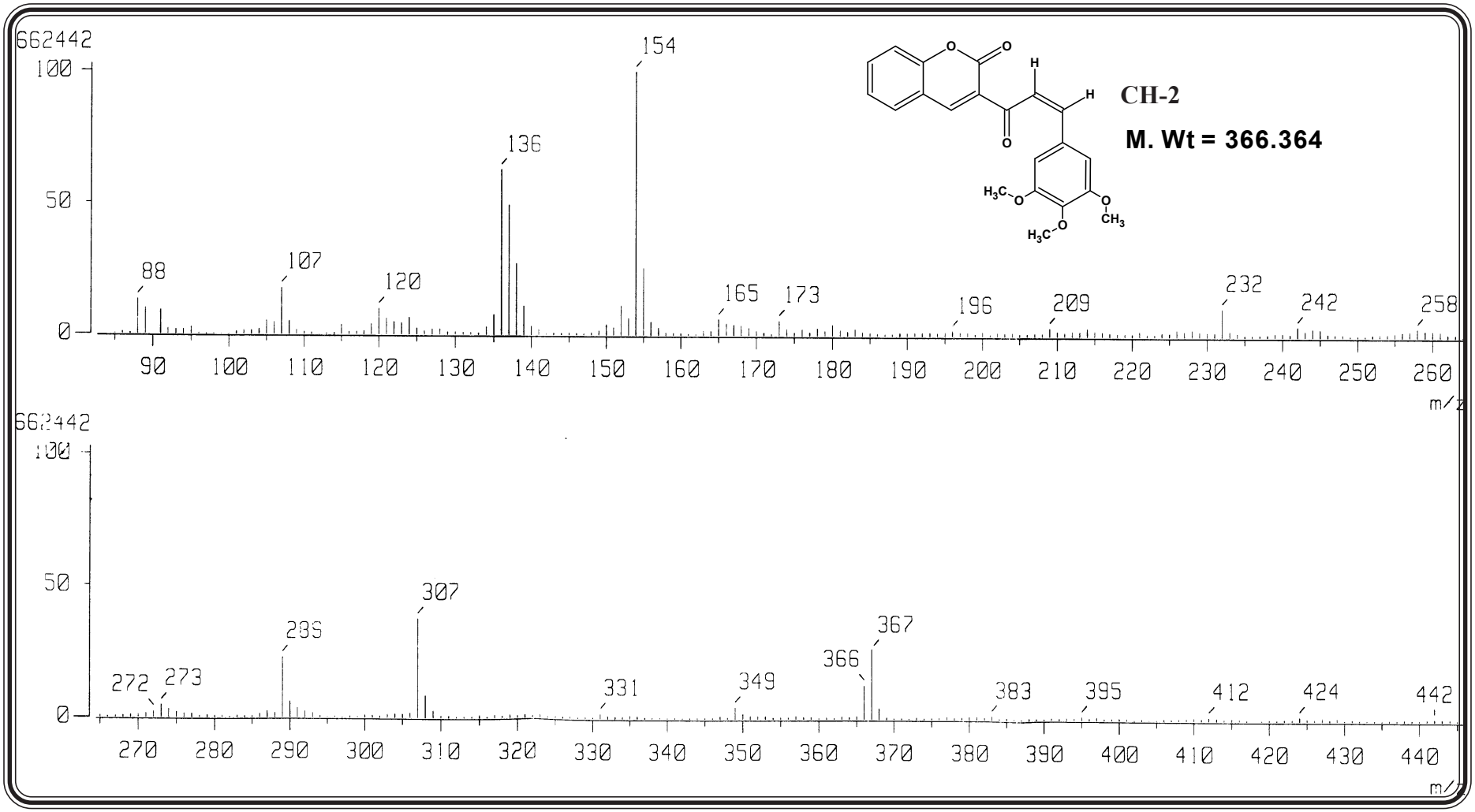
Instrument : BRUKER AC 300 MHz FT-NMR

Standard : TMS

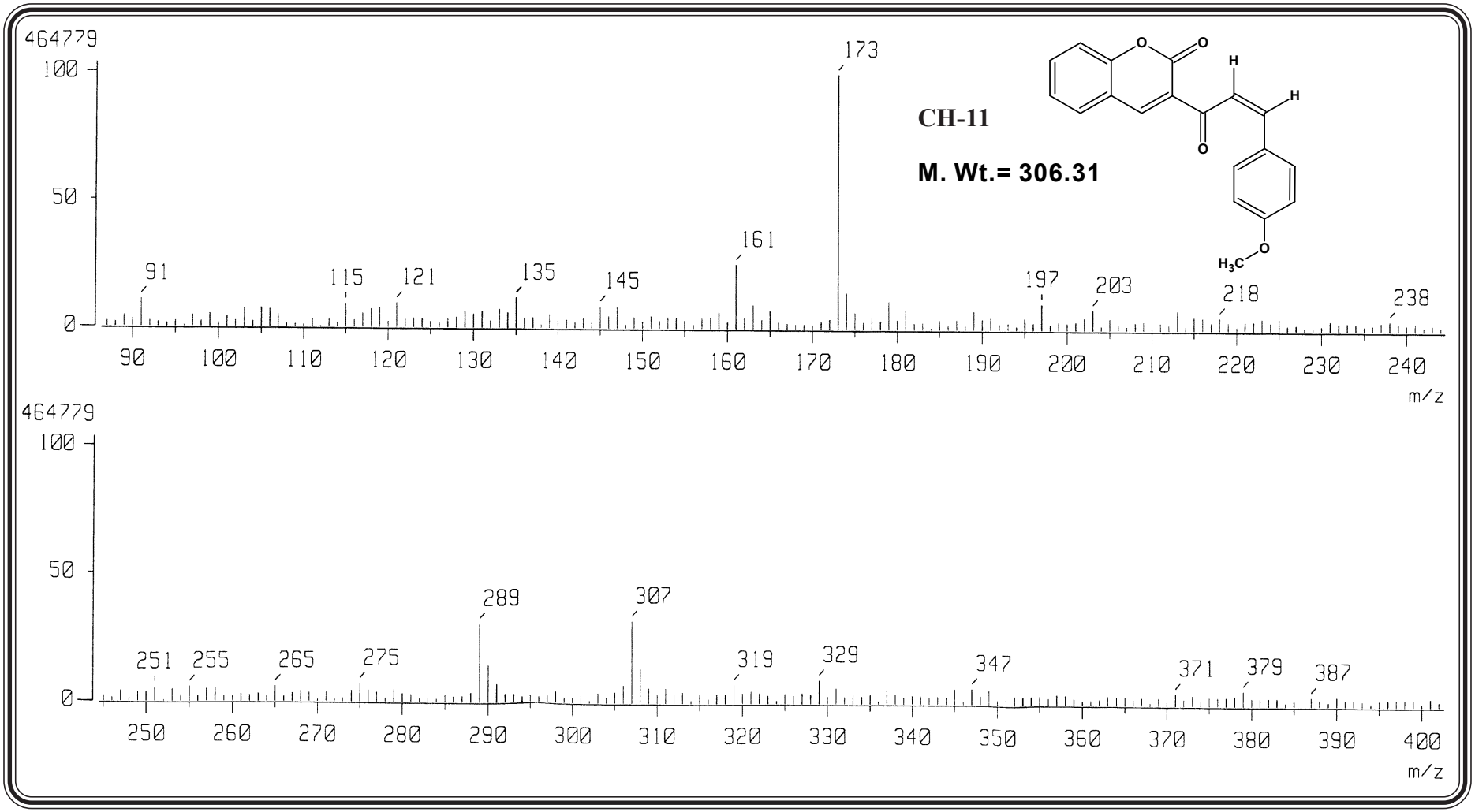
Solvent : DMSO d_6

Type	No. of proton	multiplicity	δ PPM
-CH(15a)	1H	doublet	2.49
-CH(4)	1H	singlet	6.01
-CH(18,20)	2H	doublet	6.37
-CH(17,21)	2H	doublet	6.74
-CH(19)	1H	triplet	7.22
-CH(7)	1H	triplet	7.04
-CH(8,9)	2H	doublet	7.24
-CH(10)	1H	triplet	7.42
-CH(14a)	1H	doublet	6.12

Mass Specta Of 3-[(2*Z*)-3-(3,4,5-trimethoxyphenyl)prop-2-enoyl]-2*H*-chromen-2-one



Mass Specta of 3-[(2*Z*)-3-(4-methoxyphenyl)prop-2-enoyl]-2*H*-chromen-2-one



SUMMARY

The work presented in the thesis is entitled ‘’*synthesis & characterization study of some pharmaceutical important heterocyclic compounds”* are divided into six chapter.

CHAPTER-1

SYNTHESIS AND CHARACTERIZATION OF *SUBSTITUTED N*’-[(1*E*)-PHENYL METHYLENE]-1-BENZO FURAN-2-CARBOHYDRAZIDES

This chapter deals with benzofuran derivatives. The benzofuran skeletons have been associated with different types of pharmacological activities. The brief review about benzofuran derivatives are given which covers synthesis & pharmacological activities of different types of benzofuran derivatives. The series of 20 compounds have been synthesized from coumarin by modified coumarin-benzofuran ring contraction rearrangement.

CHAPTER-2

SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED 2-{[(Z)-(7-METHYL-2,4-DIOXO-2H-CHROMEN-3(4H)-YLIDENE)METHYL]AMINO} ACETIC ACID

The title compounds have been synthesized by using 7-methyl 4-hydroxy coumarin, triethylorthoformate and different amino acid in suitable solvent. The structure of the compounds have been confirmed by NMR, IR, and Mass spectroscopy.

CHAPTER-3

SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED 4-PIPERAZIN-1-YL-2*H*-CHROMEN-2-ONES:

This chapter covers detail study of 4-substituted piperazine coumarins. Aryl amino linked heterocycles have recently identify as small molecules behaving as a tyrosine kinase inhibitors against variety of cancer cell lines .The series of 20 compounds were prepared from substituted 4-hydroxy coumarin condensed with various piperazines. The structure of the compounds have been confirmed by NMR, IR, UV, and Mass spectroscopy.

CHAPTER-4

SYNTHESIS AND CHARACTERIZATION OF SUBSTITITED 3-METHYL-1-PHENYL-CHROMENO[4,3-C]PYRAZOL-4(1H)-ONES

In this chapter, the series of 14 compounds have been synthesized from 3- acetyl 4-hydroxy coumarin and various phenyl hydrazines. The structure of the compounds have been confirmed by NMR, IR, UV, and Mass spectroscopy.

CHAPTER-5

SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED 3-[(2Z)-3-PHENYL-PROP-2-ENOYL]-2H-CHROMEN-2-ONES

In this chapter, two series of compounds have been synthesized. The title compounds have been synthesized from 4-hydroxy coumarin/4-hydroxy quinoline and various aromatic aldehydes in formic acid solvent. The structure of the synthesized compounds have been confirmed from NMR, IR, UV and Mass spectroscopy.

CHAPTER-6

SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED (3E)-3-BENZYLIDENE-1-METHYLQUINOLINE-2,4(1H,3H)-DIONES:

This chapter deals with coumarin chalcones & its derivatives. The brief review of literature survey, synthetic method & pharmacological applications are given.

The series of 18 compounds have been synthesized from 3-acetyl coumarin and various substituted aldehyde in suitable solvent and catalyst. The structure of the compounds have been confirmed by NMR, IR, and Mass spectroscopy.

The chalcones derivatives have been synthesized from different chalcones and hydrazines /substituted hydrazines as micro wave assisted reaction. The structure of the compounds have been confirmed by NMR, IR, and Mass spectroscopy.

PAPER PRESENTED AT NATIONAL/INTERNATIONAL CONFERENCE.

1. Structural requirements detrimental to Antitubercular activity in 1,4- Di hydro pyridines at Gujarat Science Congress February 2004

2. "Synthesis and Antimicrobial Profile of Some 1-[5-acetyl-2-hydroxy-2-methyl-4-alkyl/aryl imino-6- (substituted phenyl) cyclohexyl] ethanones" at 2nd International Symposium Current Trends in Drug Discovery Research DDR-2004, Lucknow (India)

3. "Design, Synthesis and Antimicrobial activity of Some Benzofuran Derivatives." at 9th ISCB-2005 National Conference on Bioactive Heterocycles and Drug Discovery Paradigm Including One Day International Symposium on Recent Trends in Drug Discovery, Rajkot (India).

4. "Clay supported Microwave synthesis of bioactive coumarins." at 9th ISCB-2005 National Conference on Bioactive Heterocycles and Drug Discovery Paradigm Including One Day International Symposium on Recent Trends in Drug Discovery, Rajkot (India).

5. "Synthesis and Characterization of Bis-â (á-Methyl Indole) Methane Derivatives." at 9th ISCB-2005 National Conference on Bioactive Heterocycles and Drug Discovery Paradigm Including One Day International Symposium On Recent Trends in Drug Discovery, Rajkot (India).

PARTICIPATION AT WORKSHOPS/CONFERENCES

1. IUPAC International Conference on Biodiversity and Natural Products: Chemistry and Medical Applications 26-31 January-2004. New Delhi (India).

2. 2nd International Symposium Current Trend in Drug Discovery Research, 17-20 February 2004 at Central Drug Research Institute Lucknow.

3. UGC sponsored National Level Workshop on "Understanding Reaction Mechanism" at Department of Chemistry, Saurashtra University, Rajkot, 28-29th February 2004.

4. XVIII Gujarat Science Congress, at Saurashtra University, Rajkot March 13, 2004.

5. Three-day workshop on Drug Discovery, "From Target to Clinic" at B.V.Patel PERD Centre Ahmedabad. 15th-17th July 2004.

6. One Day Seminar on Global Positioning of Pharma Sector: Challenges and Opportunities for India at B. V. Patel PERD Centre, Ahmedabad, on 18th December-2004.