Chapter 5: Section A

HETEROCYCLES FROM 4-HYDROXY COUMARIN

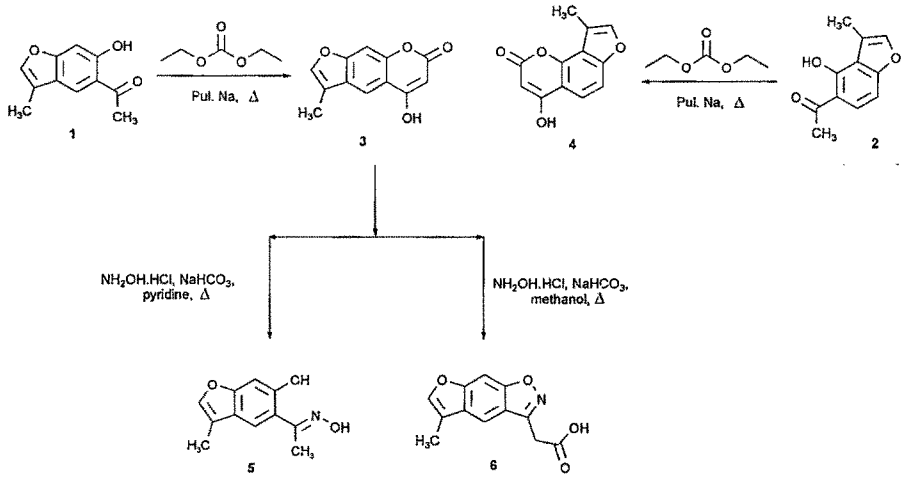
5.A.1 Introduction

Zonisamide, a 1,2-benzisoxazole derivative is an important anti-epilitic agent available in market.[1,2] It has close resemblance to indole and the 1,2-benzisoxazole nucleus can substitute for the indole nucleus as far as auxin (plant cell growth substance) like activity is concerned.[3] Several 3-substituted 1,2-benzisoxazole derivatives have been reported to show anti-convulsant activity.[4] 1,2-benzisoxazole phosphoradiamidates as a novel anti-cancer prodrug via bioreductive activation have also been studied.[5] Flucloxacillin, Oxacillin, Cloxacillin and Dicloxacillin belongs to the class of new isoxazole penicillin in current clinical use.[6]

Some furobenzisoxazole derivatives are reported to possess hypotensive, uricosuric and diuretic activities and hence are useful as therapeutics for treatment of hyperuricemia, edama and hypertension;[7,8] which prompted us to synthesize new furobenzisoxazole derivatives. Several reports are available in literature for the synthesis of 1,2-benzisoxazole,[9-11] but not much work has been done for the synthesis of furobenzisoxazole.[12] We report herein, synthesis of some new furobenzisoxazole derivatives from hydroxy furocoumarin.

5.A.2 Results and Discussion

We have synthesized new hydroxy furocoumarin which on Posner reaction,[13] with hydroxylamine gave furobenzisoxazole. New derivatives of furobenzisoxazole have been synthesized and interesting observations have been recorded during the course of study.

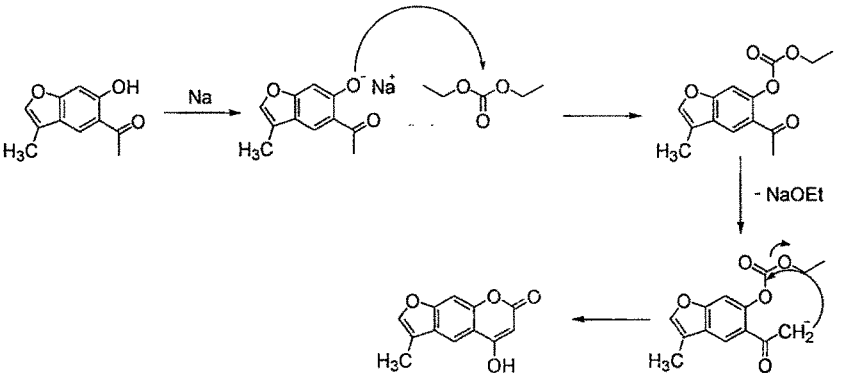


Scheme 1

As shown in **Scheme 1**, 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone **1**,[14] and 1-(4-hydroxy-3-methyl-benzofuran-5-yl)-ethanone **2**,[14] on reaction with pulverized sodium and diethyl carbonate,[15] gave new linear 5-hydroxy-3-methyl-furo[3,2-g]chromen-7-one **3** and angular 7-hydroxy-3-methyl-furo[3,2-g]chromen-7-one **4** isomers respectively. The structures of both the compounds were confirmed by their ^{1}H NMR spectra. Compound **3 (Figure 1)**, showed a singlet at δ 5.74 ppm for one proton at C-6 and another singlet at δ 11.72 ppm corresponding to C5-OH (enolic hydroxyl). Other signals observed were, δ 2.28 (d, J = 1.28 Hz, 3H, C3-CH_3), 7.36 (s, 1H, C9-H), 7.47 (d, J = 1.28 Hz, 1H, C2-H) and 8.01 (s, 1H, C4-H). Whereas, the ^{1}H NMR of compound **4 (Figure 2)**, showed singlets at δ 5.65 ppm and δ 12.00 ppm, both corresponding to one proton

each for C6-H and C5-OH respectively. Other signals observed were, 2.48 (d, J = 1.44 Hz, 3H, C3-CH_3), 7.34-7.36 (d, J = 8.76 Hz, 1H, C9-H), 7.53 (d, J = 1.44 Hz, 1H, C2-H), 7.71-7.73 (d, J = 8.76 Hz, 1H, C8-H).

However, the angular isomer **4** could not be studied further based on the poor yields of 1-(4-hydroxy-3-methyl-benzofuran-5-yl)-ethanone **2.**[14]



Scheme 1a

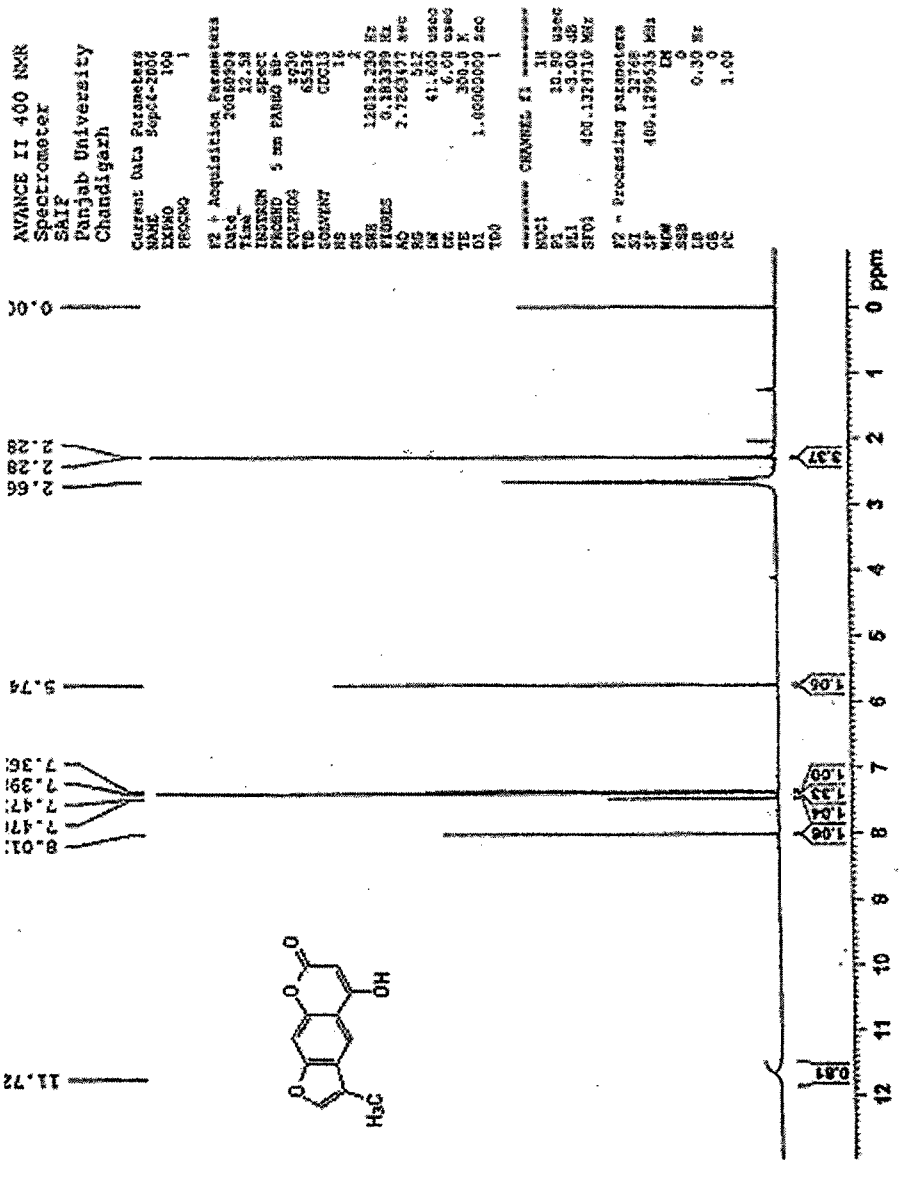


Figure 1: ^{1}H NMR of compound 5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one **3**.

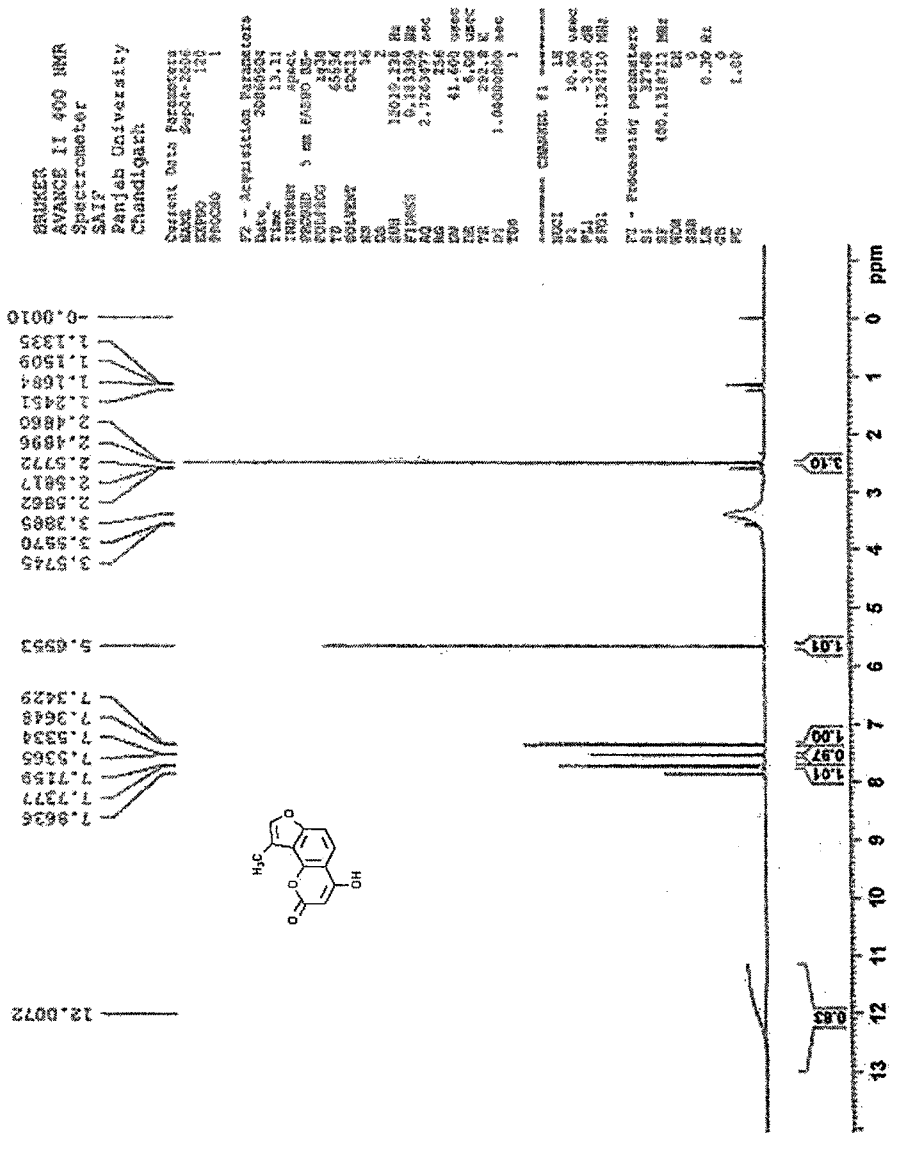


Figure 2: ^{1}H NMR of compound 7-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one **4.** Contd.

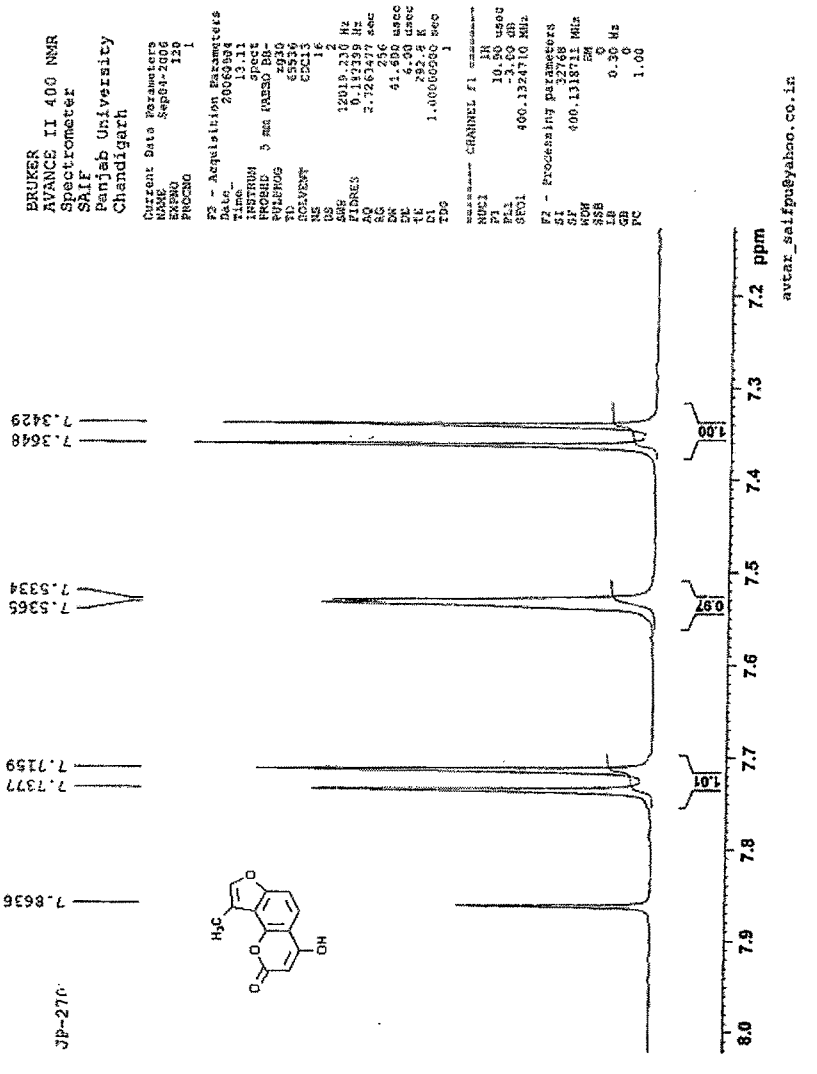


Figure 2: ^{1}H NMR of compound 7-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one **4**.

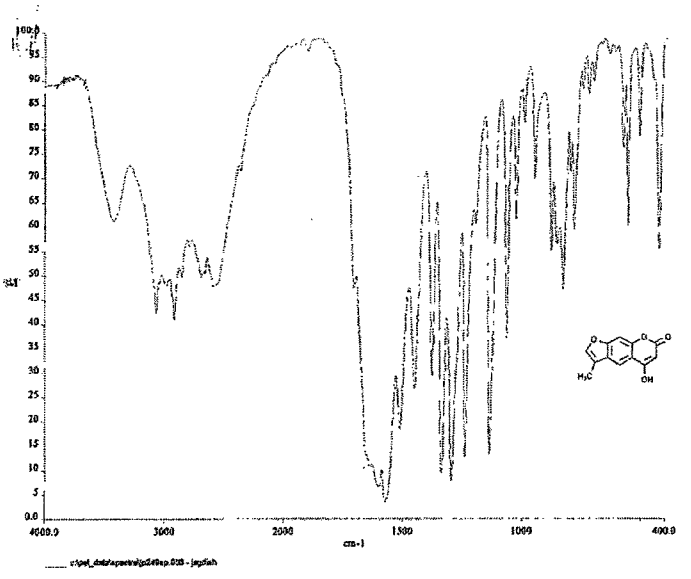


Figure 3: IR of compound5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one 3.

Posner reaction, of 5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one **3** with hydroxylamine hydrochloride using pyridine gave 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone oxime **5** as the major product; but when the reaction was carried out in methanol, the major product obtained was 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)-acetic acid **6** as shown in **Scheme 1.** This indicates that the use of pyridine favours the formation of hydroxy acetophenone oxime **5** via decarboxylation. In the ^{1}H NMR of **5 (Figure 4)**, doublet at δ 2.21 ppm (J = 1.32 Hz) for three protons indicated –CH_3 at C-3, the singlet at δ 2.45 ppm again for three protons indicated –N=C-CH_3 group, singlets at δ 7.03 ppm and 7.52 ppm for one proton each indicated C-7 and C-4 protons, doublet at δ 7.29 ppm (J = 1.32 Hz) for one proton indicated C-2 proton and a singlet at δ 11.48 ppm for one proton indicated C6-OH. The IR spectrum of **5 (Figure 5)**, showed absorption bands at 3374 cm^{-1} (*s*) for hydroxy group of ketoxime and 1596 cm^{-1} (*s*) for >C=N- imine, which further confirmed the structure. The ^{1}H NMR of **6 (Figure 6)**, showed a singlet at δ 4.05 ppm corresponding to two protons of C3-CH_2COO- group and a singlet (broad band) at

9.50 ppm for one proton of carboxylic acid. Other signals observed were, δ 2.28 (d, J = 1.32 Hz, 3H, C5-CH_3), 7.47-7.48 (d, J = 1.32 Hz, 1H, C6-H), 7.54 (d, J = 0.8 Hz, 1H, C8-H) and 7.76 (d, J = 0.56 Hz, 1H, C4-H). The IR spectrum of **6** **(Figure 7)**, showed a broad shallow band at 2547-3128 cm^{-1} for O-H and a band at 1726 cm^{-1} (*s*) for >C=O of carboxylic acid.

Scheme 1b shows the probable reaction mechanism for the formation of the said products by Posner reaction.

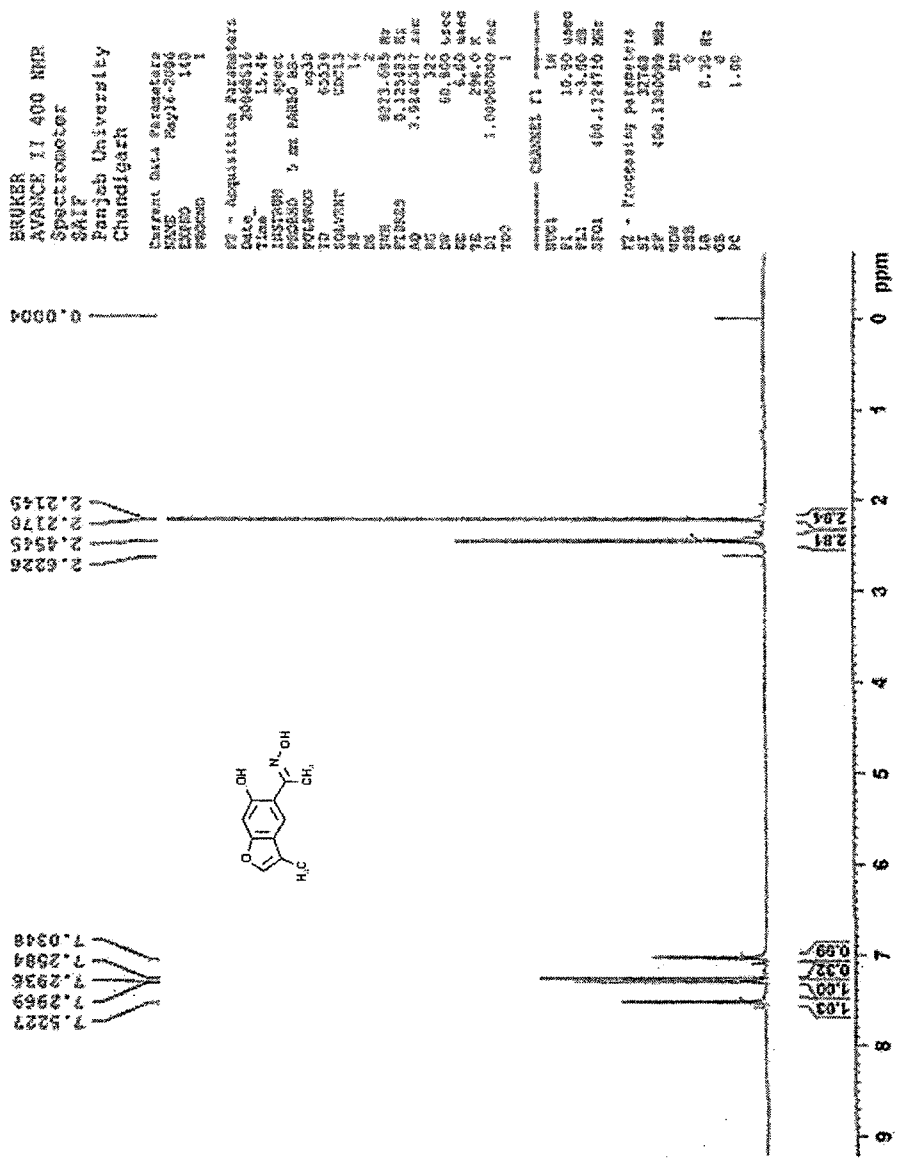


Figure 4: ^{1}H NMR of compound 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone oxime **5**.

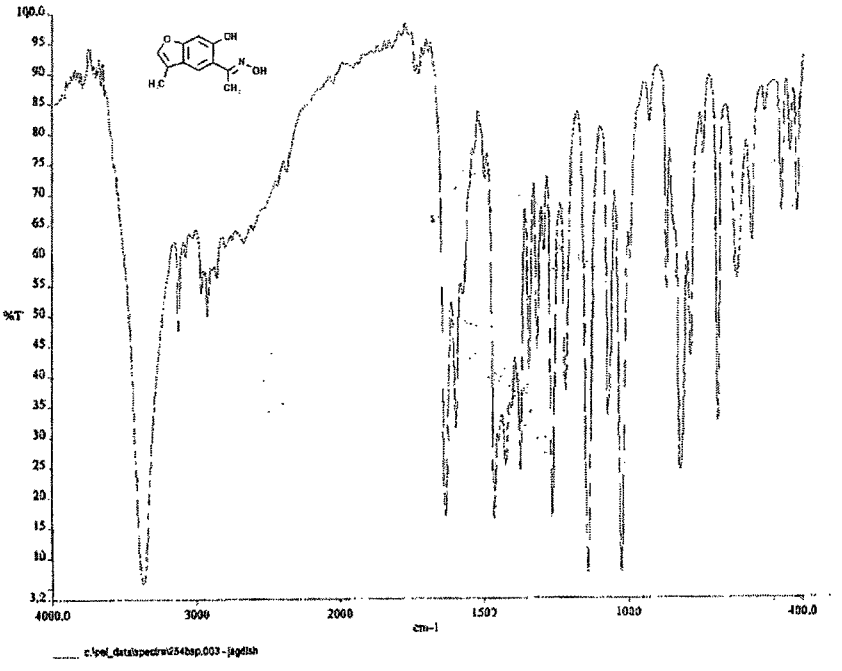


Figure 5: IR of compound 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone oxime **5**.

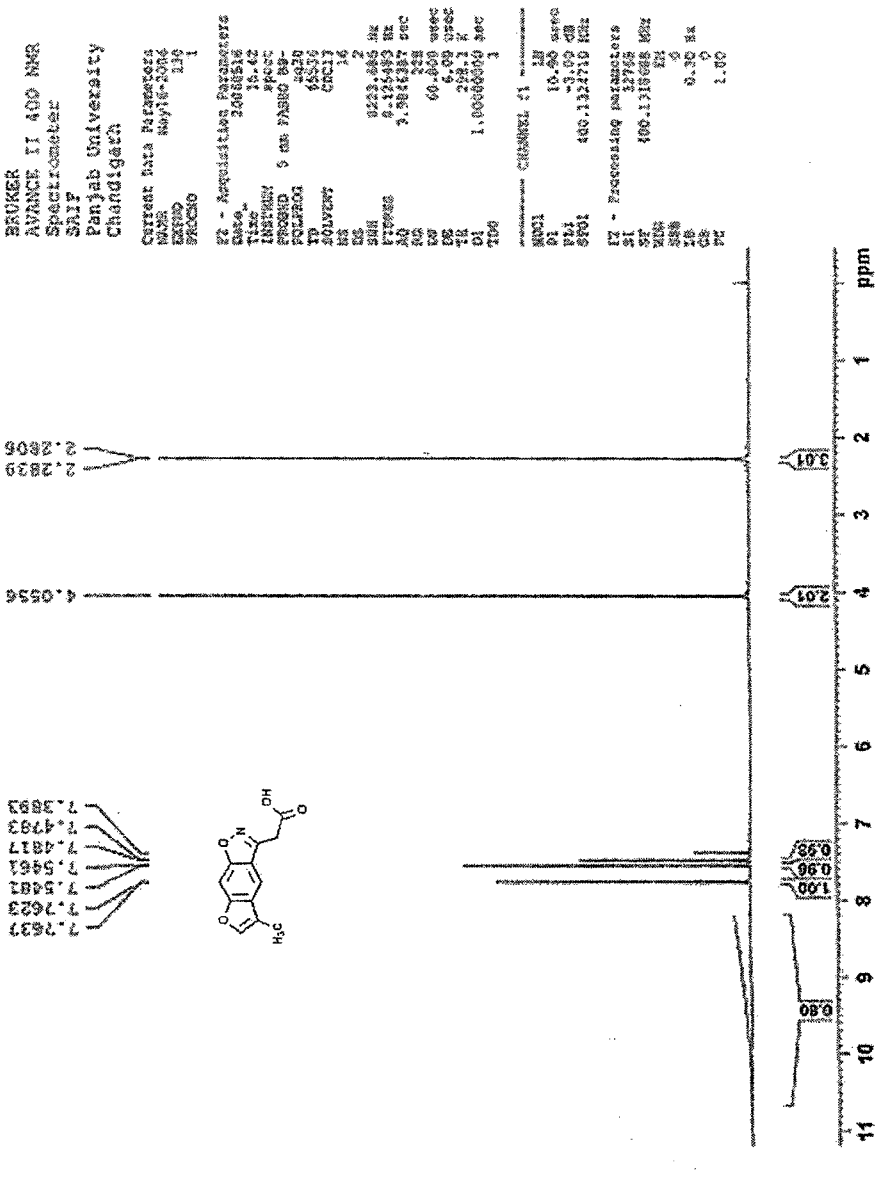


Figure 6: ^{1}H NMR of compound 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)-acetic acid **6**.

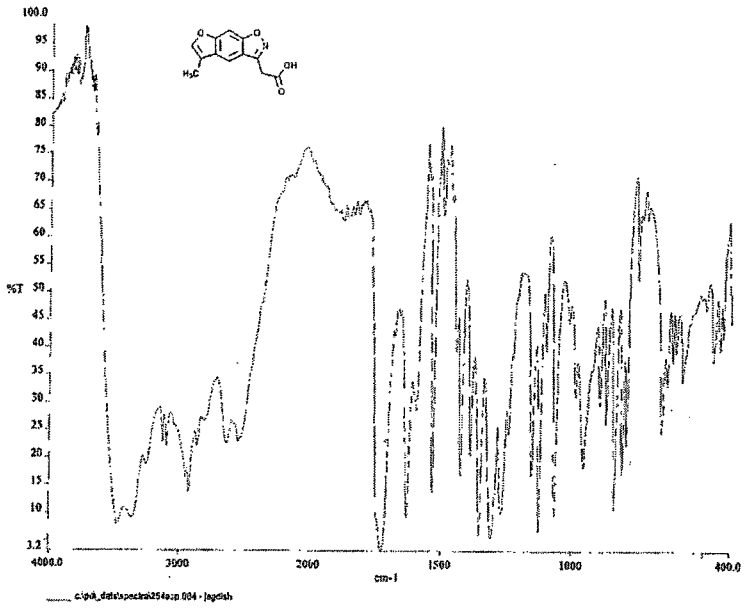
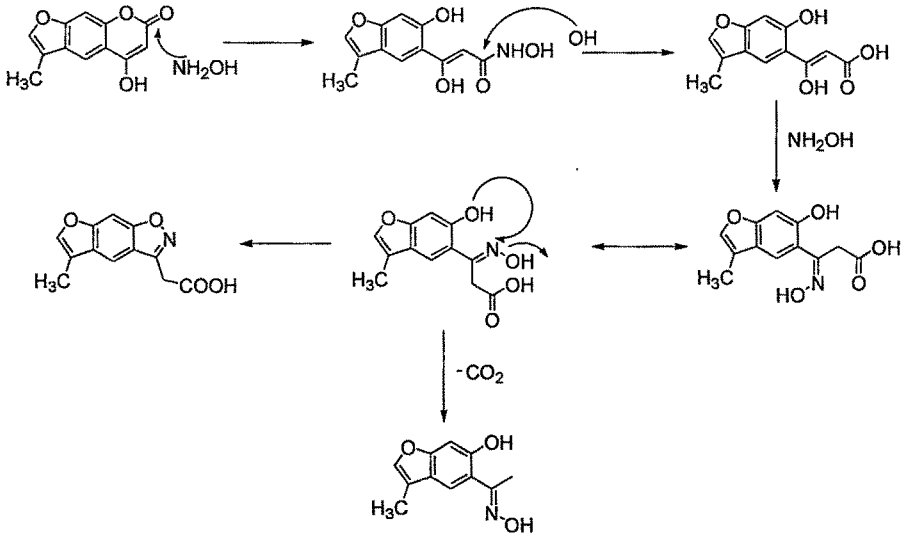
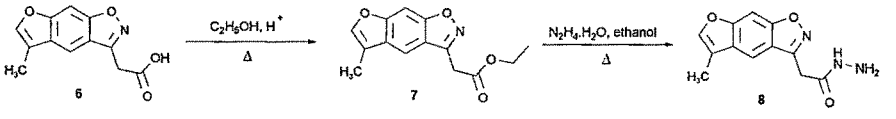


Figure7: IR of compound 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)-acetic acid **6**.



Scheme 1b: Probable reaction mechanism for the Posner reaction products.



Scheme 2

The carboxylic acid **6** was then converted into its ethyl ester **7** which on reaction with hydrazine hydrate gave (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide **8** as shown in **Scheme 2**.

The ^{1}H NMR of **8** **(Figure 8)**, showed doublet at δ 2.30 ppm (J = 1.28 Hz) for three protons of C5-CH_3, singlet at δ 3.97 ppm for two protons of C3-CH_2CO-, doublet at δ 7.49 ppm (J = 1.28 Hz) for one proton at C6-H, two singlets at δ 7.54 ppm and 7.92 ppm for one proton each at C-8 and C-4 respectively, singlet for one proton at δ 9.15 ppm for –CO-NH- which confirmed the structure. It was further supported by IR spectrum, which showed absorption bands at 3320 cm^{-1} (*s*) for N-H stretching of –CO-NH- and N-H stretching of –NH_2- and a band at 1646 cm^{-1} (*s*) for C=O stretching of –CO-NH-.

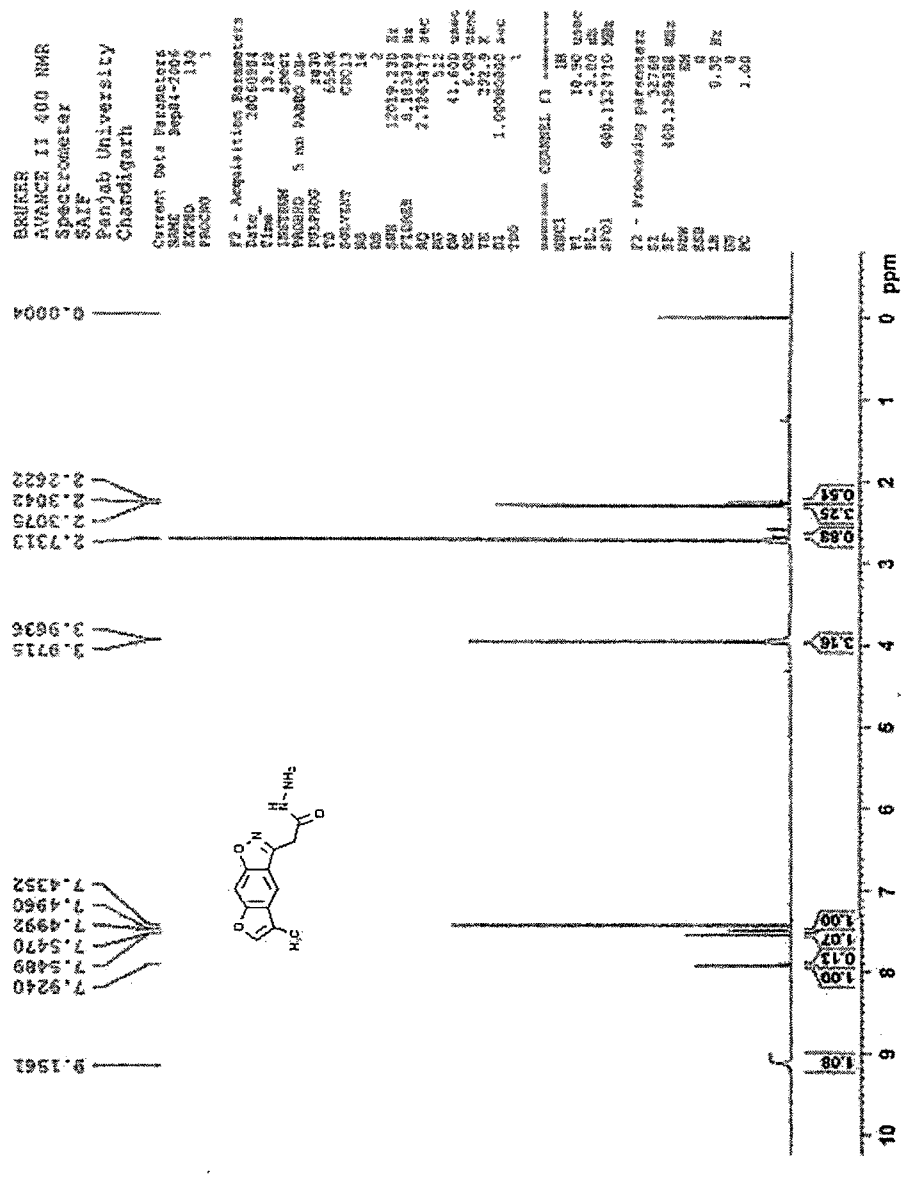


Figure 8: ^{1}H NMR of compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide **8**.

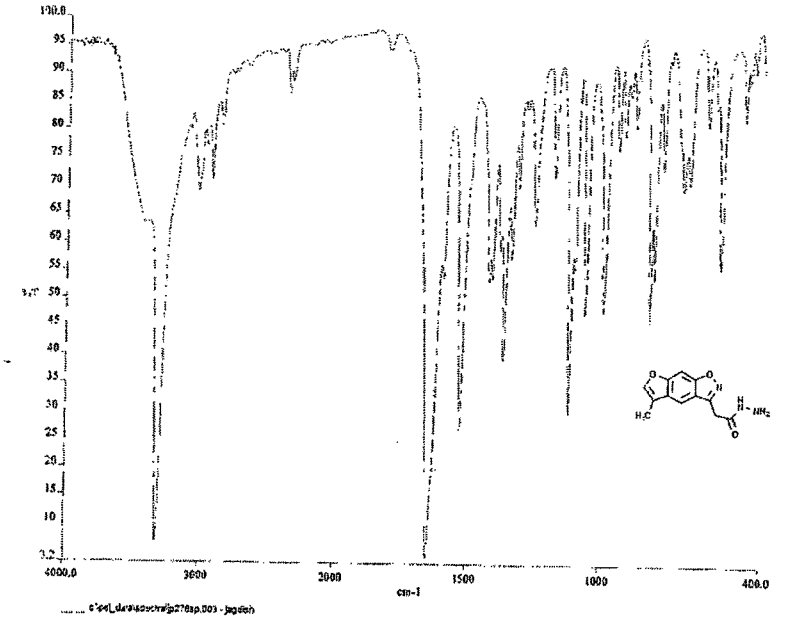
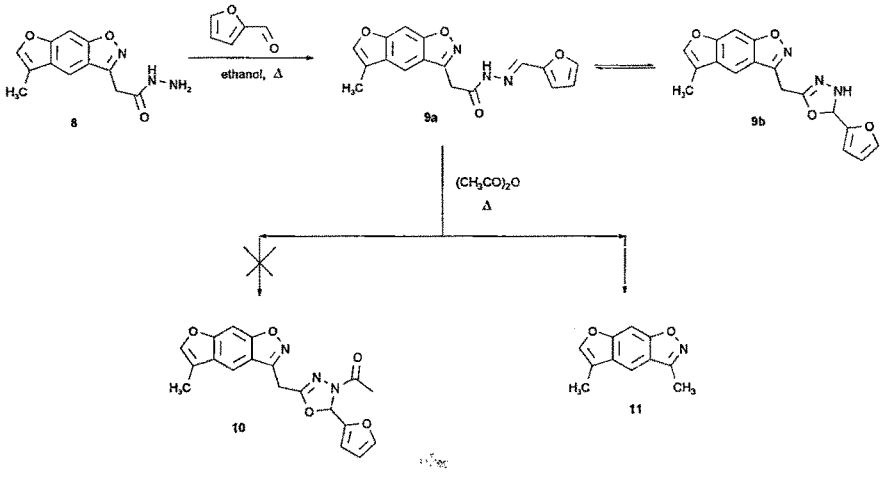
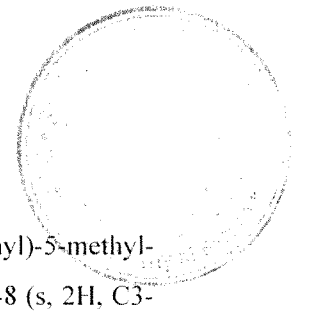


Figure 9: IR of compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide **8**.



Scheme 3

As shown in **Scheme 3**, the reaction of hydrazide **8** with furfuraldehyde gave schiff base (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9**. The ^{1}H NMR of **9** (**Figure 10**), in DMSO indicated the existence of schiff base in two interconverting tautomeric structures; (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9a** and 3-(5-furan-2yl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-5-methyl-furo[2'3':4,5]benzo[1,2-*d*]isoxazole **9b**. The ratio of **9a**: **9b** was found to be approximately 2:1 by integration. Also the signals for the minor tautomer **9b** were found to be slightly deshielded than for the major tautomer **9a**. A singlet at δ 4.07 ppm for one proton at C5'-H and a singlet at δ 11.64 ppm again for one proton at N4'-H confirmed the existence of **9b** tautomer. The –NH- proton of –CO-NH- was observed at 11.45 ppm for the **9a** tautomer. Two doublets at δ 2.22 ppm and δ 2.28 ppm both with J = 1 Hz indicated C5-CH_3 of **9a** and **9b** tautomer respectively. Other signals observed in the ^{1}H NMR spectra for the two tautomers were; (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide (**9a**): δ 4.48 (s, 2H, C3-CH_2-CO-), 6.51-6.52 (m, 1H, C4'-H), 6.73 (d, J = 3 Hz, 1H, C3'-H), 7.49-7.56 (m, 3H, C5'-H, C6-H and –CH=N-), 7.84 (s, 1H, C8-H), 7.95 (s, 1H, C4-H), 11.45 (s, 1H, -



CO-NH-). 3-(5-furan-2yl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-5-methyl-furo[2'3':4,5]benzo[1,2-*d*]isoxazole (**9b**): δ 4.07 (s, 1H, C5'-H), 4.48 (s, 2H, C3-CH_2-C2'), 6.47-6.48 (m, 0.5H, C4"-H), 6.78 (d, J = 3 Hz, 0.5H, C3"-H), 7.49-7.56 (m, 1H, C5"-H and C6-H), 8 (s, 0.5H, C8-H), 8.13 (s, 0.5H, C4-H), 11.64 (s, 0.5H, N4'-H). The LCMS **(Figure 11)** showed the M+1 peak at 324.3.

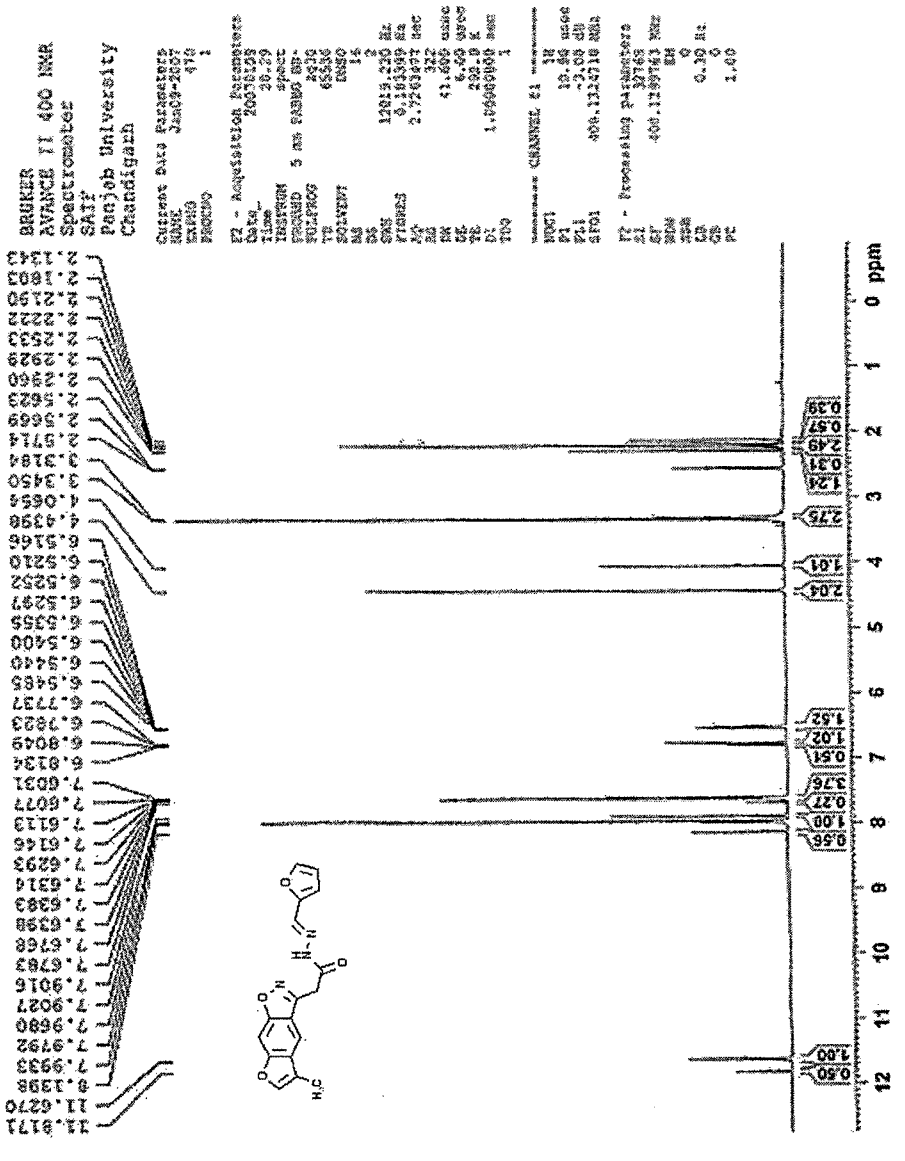


Figure 10: ^{1}H NMR of compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9**. Contd.

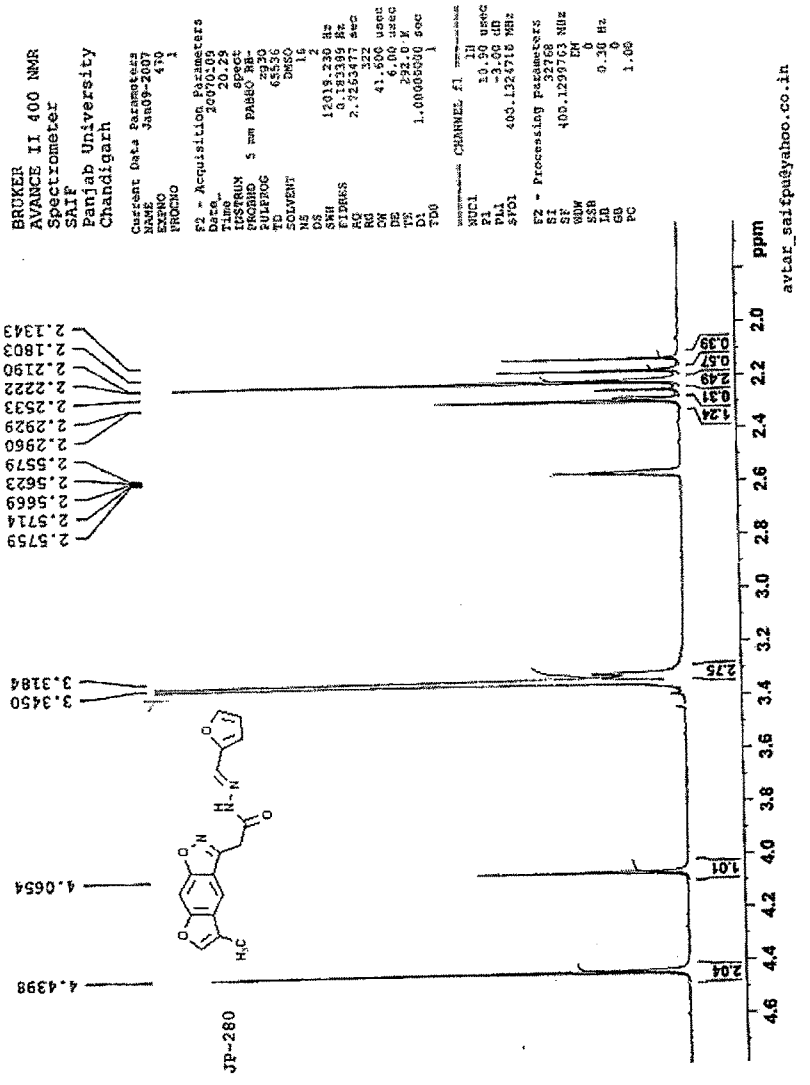


Figure 10: ^{1}H NMR of compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9**. Contd.

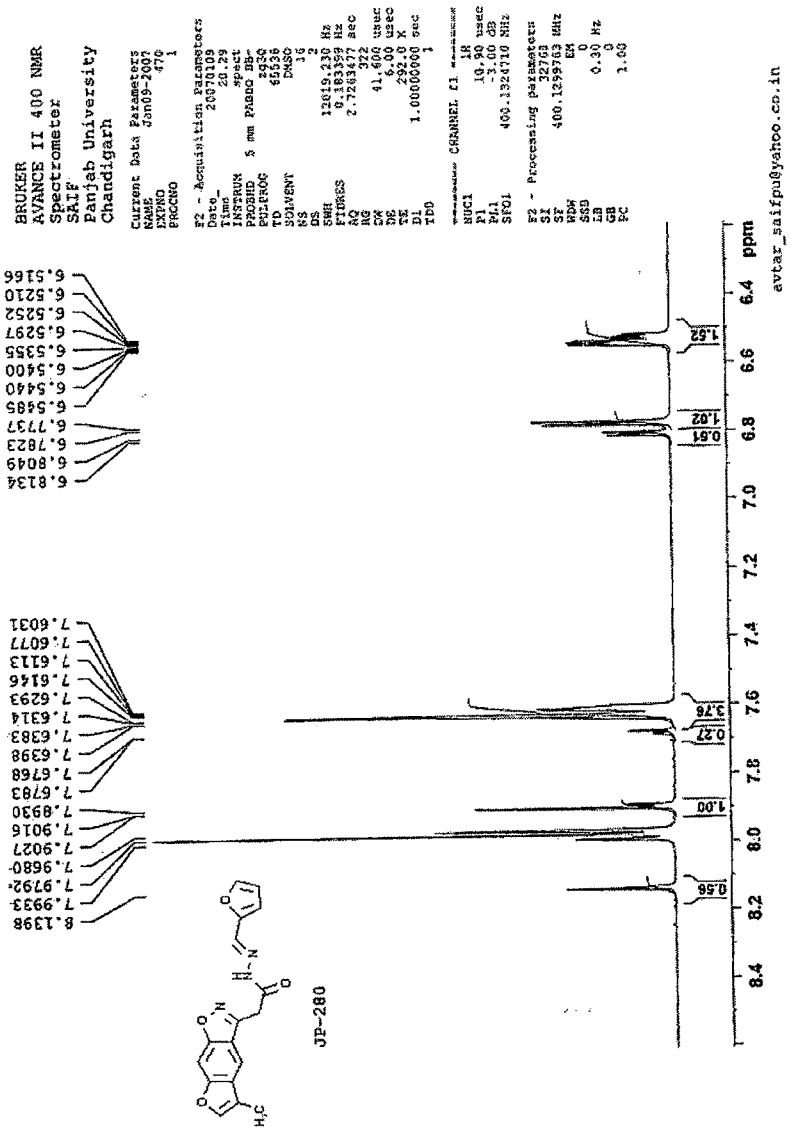


Figure 10: ^{1}H NMR of compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9**.

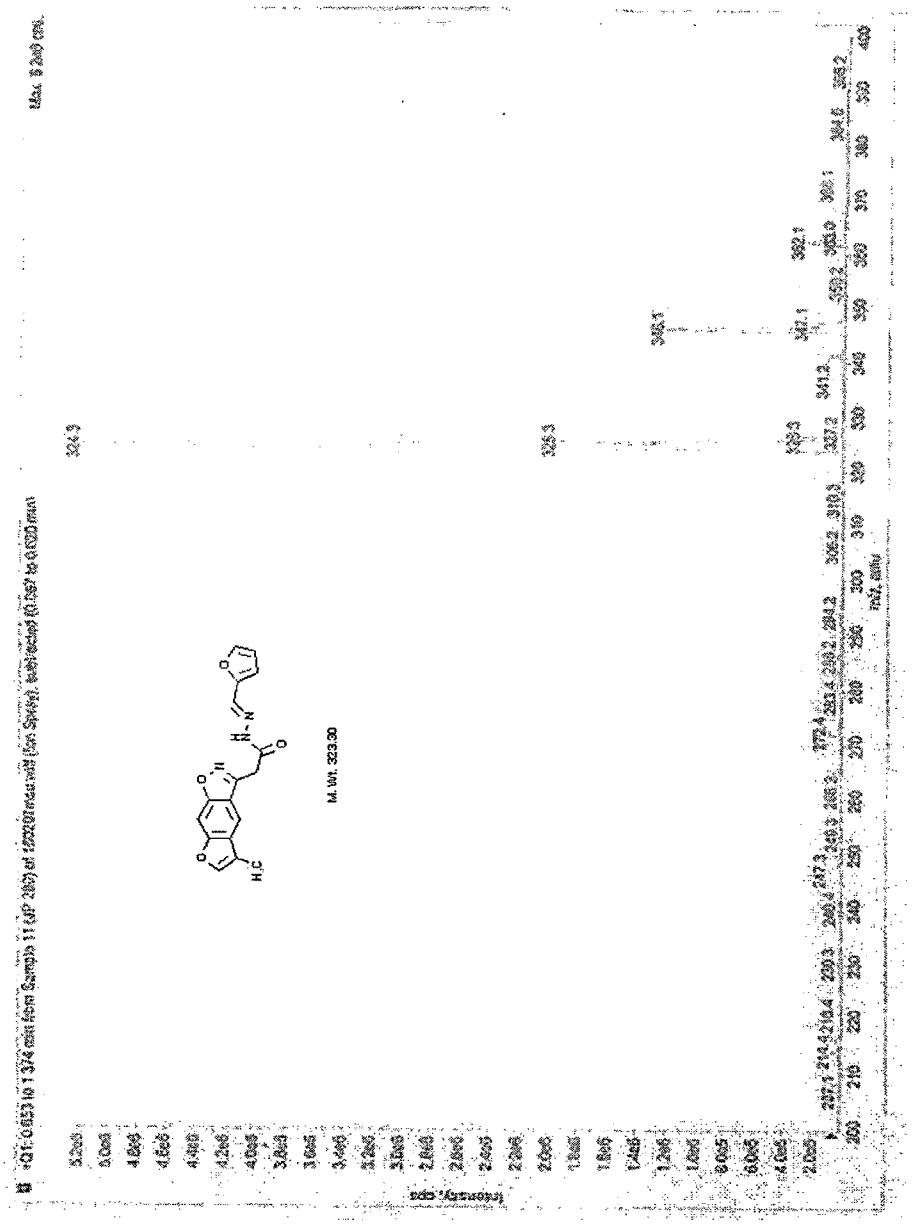


Figure 11: LCMS of compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9**.

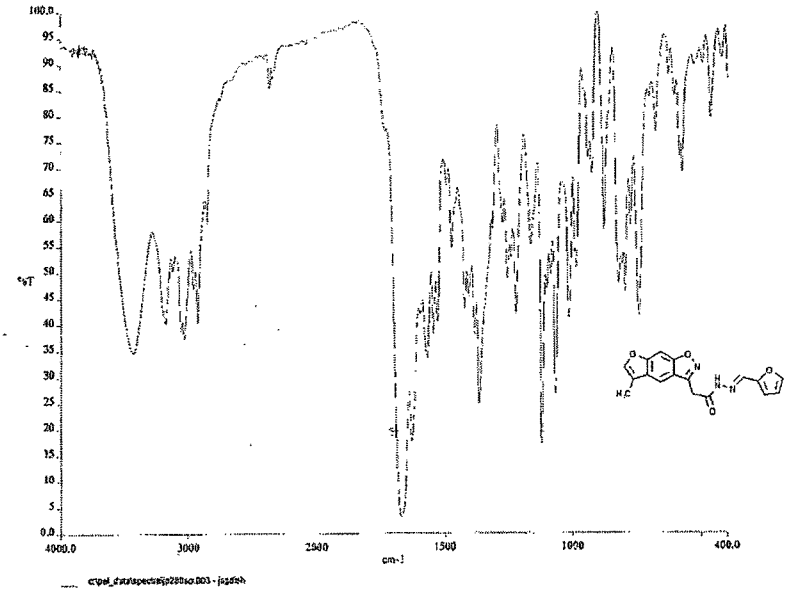


Figure 12: IR compound (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **9**.

To get 1-[2-furan-2-yl-5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazol-3-yl]-ethanone **10**, compound **9** was subjected to cyclization by refluxing in acetic anhydride; but instead of getting **10** as the product, to our surprise the product obtained was identified as 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole **11**. Though from the ^{1}H NMR of compound **9**, it is evident that **9b** exists as minor tautomer, the formation of product **10** was not at all observed. The ^{1}H NMR of **11** **(Figure 13)**, in $CDCl_3$ showed doublet at δ 2.29 ppm (J = 1.24 Hz) for C5-CH_3, a singlet at δ 2.63 ppm for C3-CH_3, a doublet at δ 7.46 ppm (J = 1.24 Hz) for C6-H and two singlets at δ 7.53 ppm and δ 7.63 ppm for C8-H and C4-H respectively. The product was further confirmed by LCMS **(Figure 14)** and IR **(Figure 15)**.

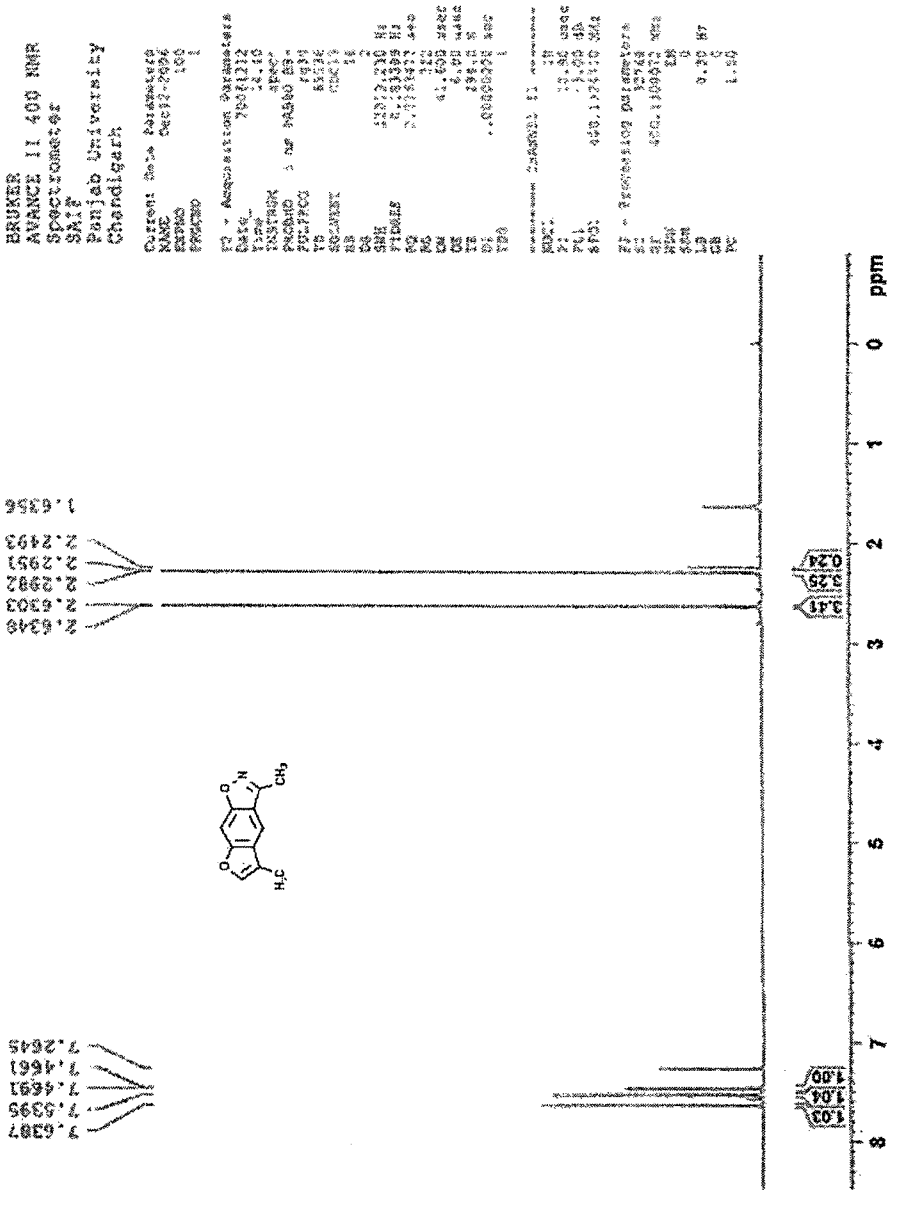


Figure 13: ^{1}H NMR of compound 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole **11**.

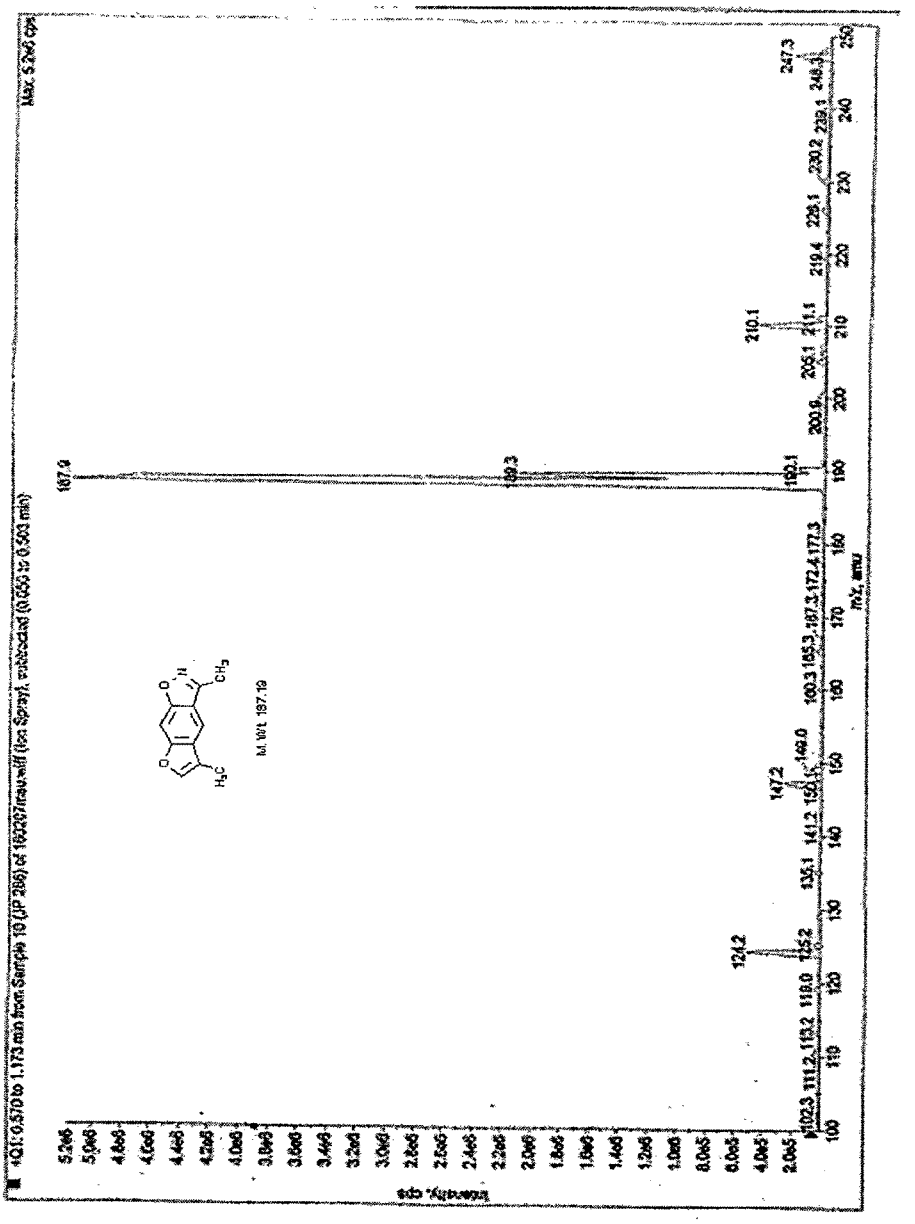


Figure 14: LCMS of compound 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole **11**.

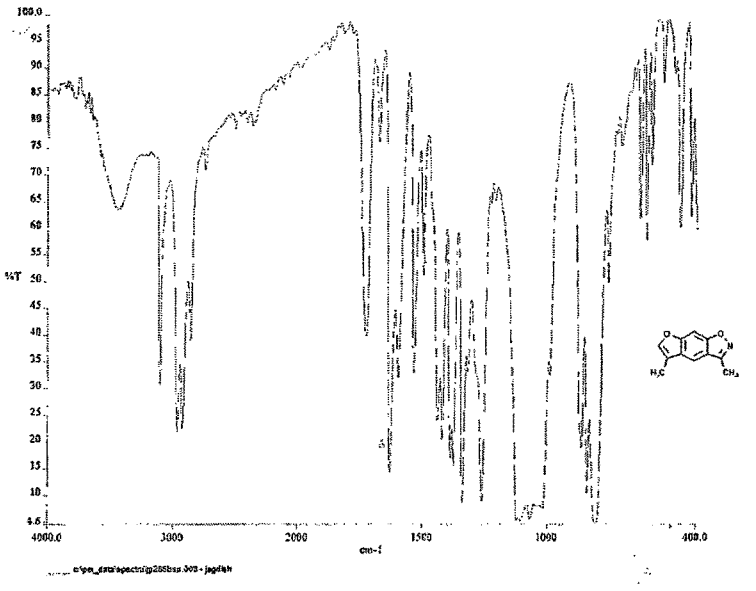
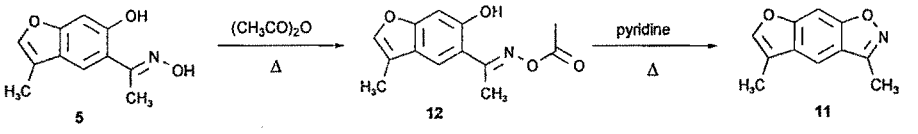
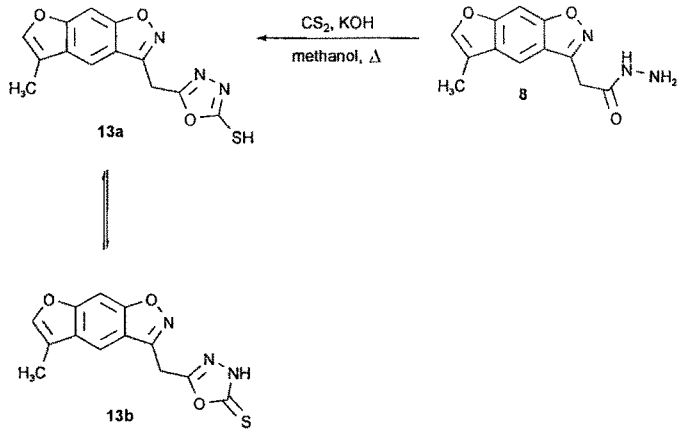


Figure 15: IR of compound 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole **11**.



Scheme 4

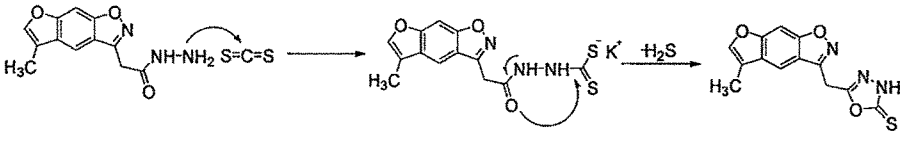
The formation of **11** was further confirmed by synthesizing it from ketoxime **5**, as shown in **Scheme 4**. The acetylation of **5** by refluxing it with acetic anhydride gave acetic acid 5-(1-hydroxyimino-ethyl)-3-methyl-benzofuran-6-yl ester **12**, which on cyclizati on in pyridine gave 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole **11**.[5] The product formation was confirmed by co-tlc and mix melting point in comparison with sample **11**, obtained by earlier method **(Scheme 3)**.



Scheme 5

Since the desired 1,3,4-oxadiazole **10** was not obtained from schiff base **9**, it has been synthesized from hydrazide **8** by reaction with carbon disulfide in presence of methanolic potassium hydroxide, which gave 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13** **(Scheme 5)**. The ^{1}H NMR of **13** in DMSO **(Figure 16)**, showed once again existence of tautomerism between 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13a** and 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-3*H*-[1,3,4]oxadiazole-2-thione **13b**. The ratio of **13a**: **13b** from integration was found to be 2: 1. The ^{1}H NMR of **13** showed a doublet at δ 2.30 ppm (J = 1.32 Hz) for C5'-CH_3, a singlet at δ 4.53 ppm for C5-CH_2-C3', a doublet at 7.56 ppm (J = 1.32 Hz) for C6'-H, two doublets at δ 7.61-7.62 ppm (J = 0.64 Hz) and δ 7.78 ppm (J = 0.4 Hz) for C8'-H and C4'-H respectively, a singlet at δ 7.62 ppm for N3-H of **13b** tautomer and a singlet at δ 14.33 ppm for C2-SH of **13a** tautomer. The LCMS of **13** **(Figure 17)**, showed M+1 peak at 288.3, which is in agreement with its molecular weight 287.3. Further the IR spectrum **(Figure 18)** showed absorption band at 3434 cm^{-1} (*w*) for –N-H- stretching vibration of **13b** tautomer, a band at 2753 cm^{-1} (*m*) for S-H stretching vibration of **13a** tautomer and a band at 1277 cm^{-1} (*m*) for >C=S stretching vibration of **13b** tautomer.

The probable mechanism for the formation of 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13** is shown in **Scheme 5a**.



Scheme 5a

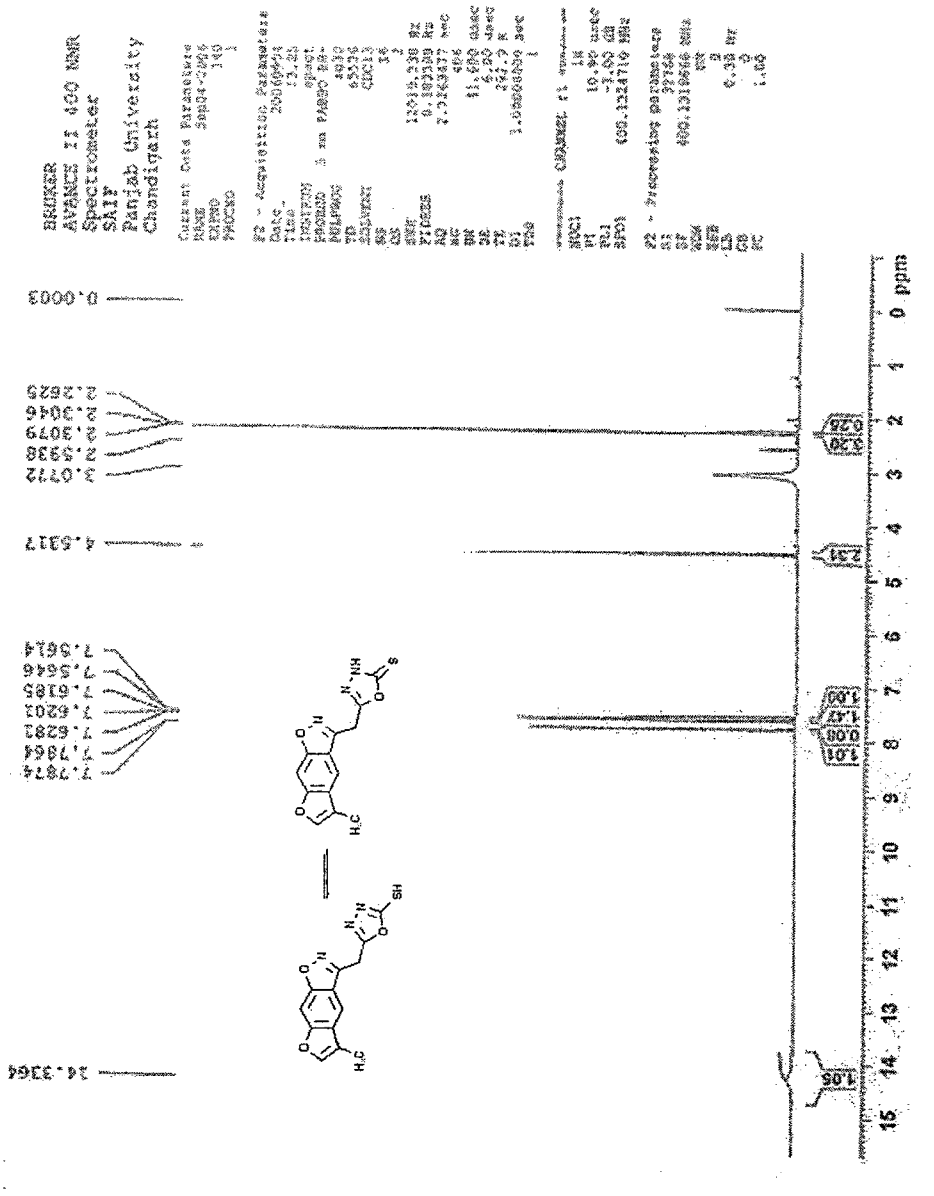


Figure 16: ^{1}H NMR of compound 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13**. Contd.

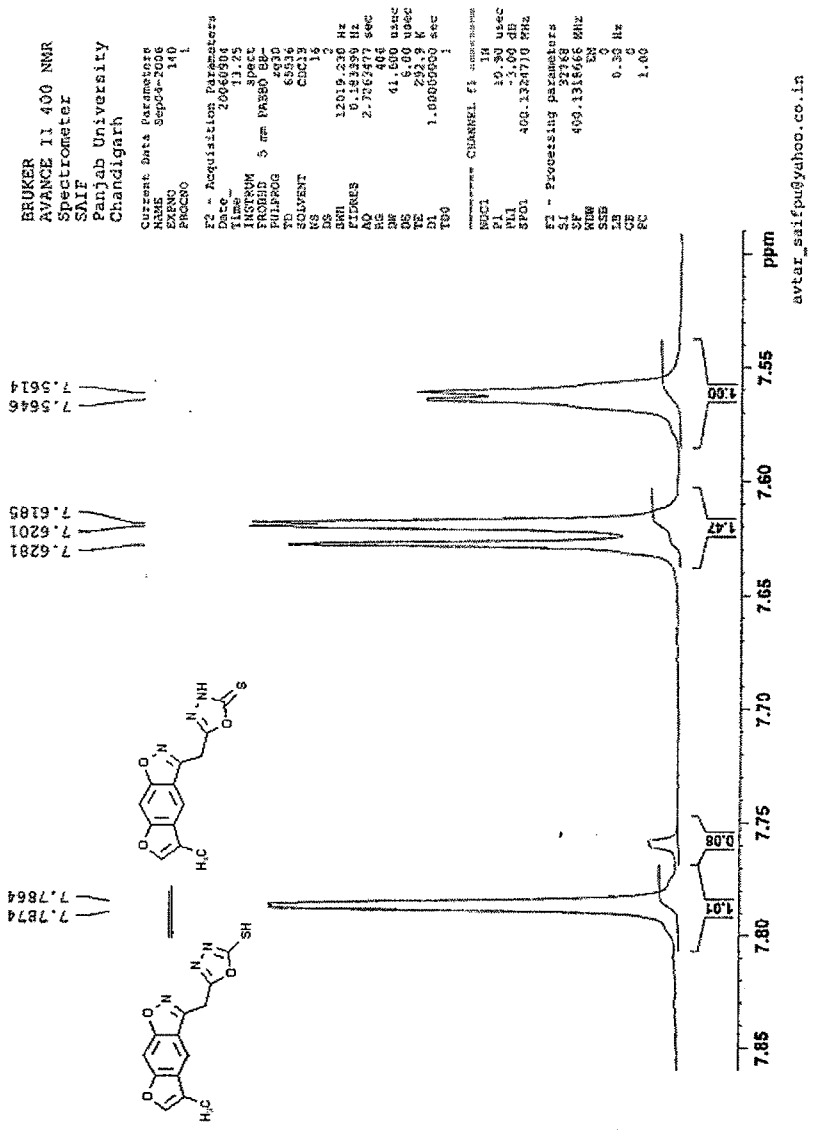


Figure 16: ^{1}H NMR of compound 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13**.

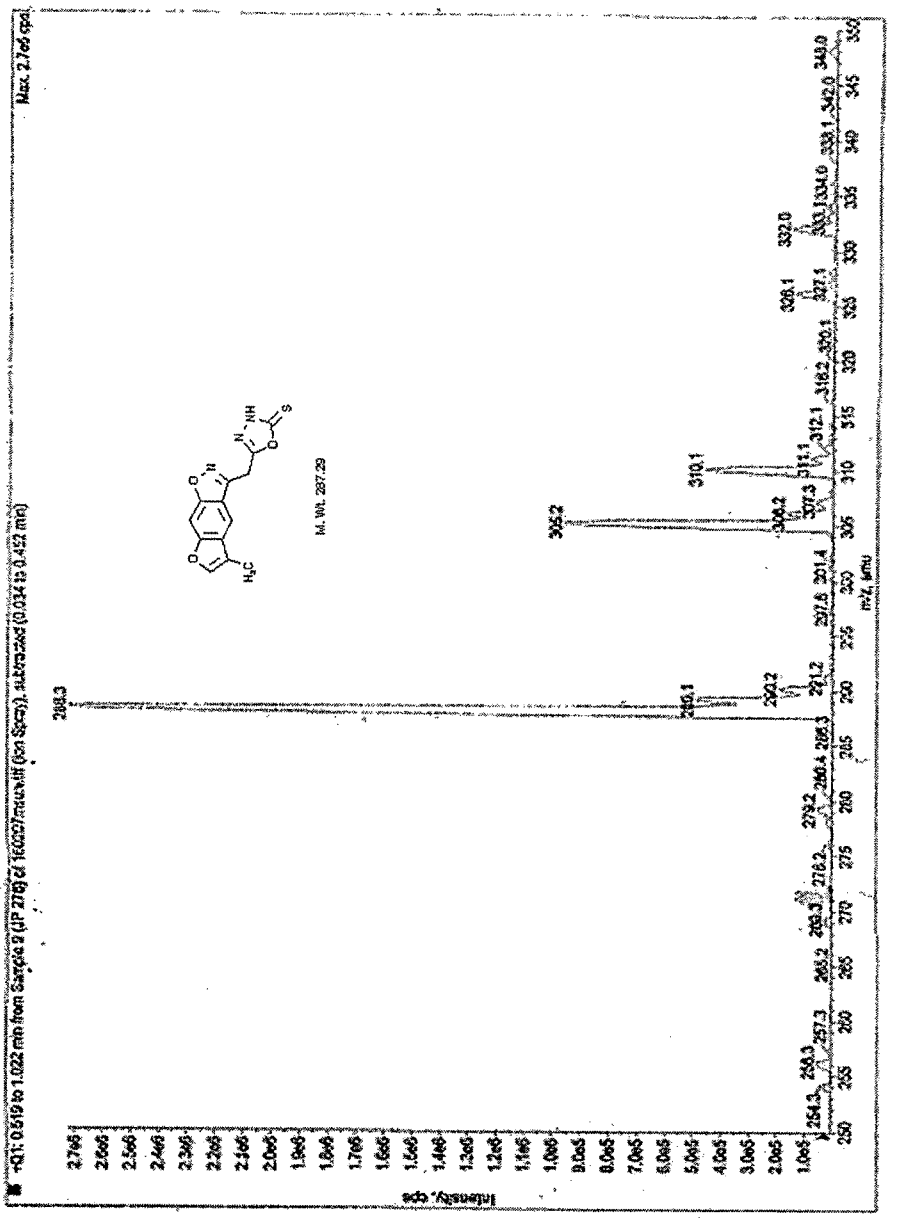


Figure 17: LCMS of compound 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13**.

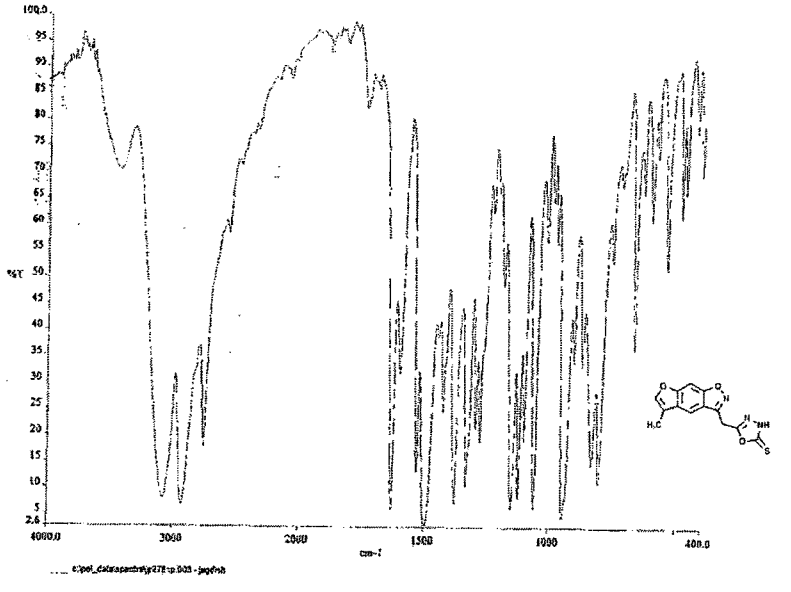
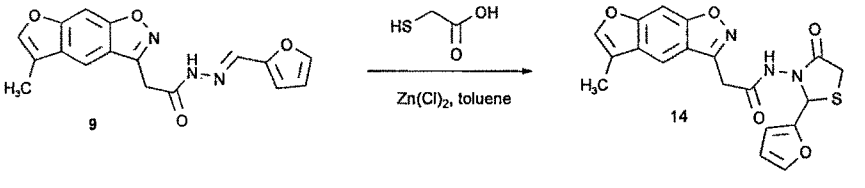


Figure 18: IR of compound 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol **13**.



Scheme 6

β-Lactam derivatives are of utmost importance for their use as antibiotics. Penicillins and Cephalosporins are the two well known antibiotics belonging to this class of family. Schiff base **9** was reacted with thioglycolic acid in presence of zinc chloride to give thiazolidinone derivative - *N*-(2-furan-2-yl-4-oxo-

thiazolidin-3-yl)-2-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetamide **14** as shown in **Scheme 6**.

The ^{1}H NMR **(Figure 19)** showed signals at δ 3.71-3.75 (d, J = 16 Hz, 1H, C5'-H_a of thiazolidinone ring), 3.85-3.89 (d, J = 16 Hz, 1H, C5'-H_b of thiazolidinone ring) and 5.90 (s, 1H, C2'-H of thiazolidinone ring) which confirmed the structure. Other signals observed were, δ 2.27 (d, J = 1.05 Hz, 3H, C5-CH_3), 4.02 (s, 2H, C3-CH_2-CO-), 6.43-6.44 (m, 1H, C4"-H of furan ring), 6.53-6.53 (m, 1H, C3"-H of furan ring), 7.74-8.07 (m, 4H, C4-H, C6-H, C7-H, C5"-H), 10.94 (s, 1H, -CONH-).

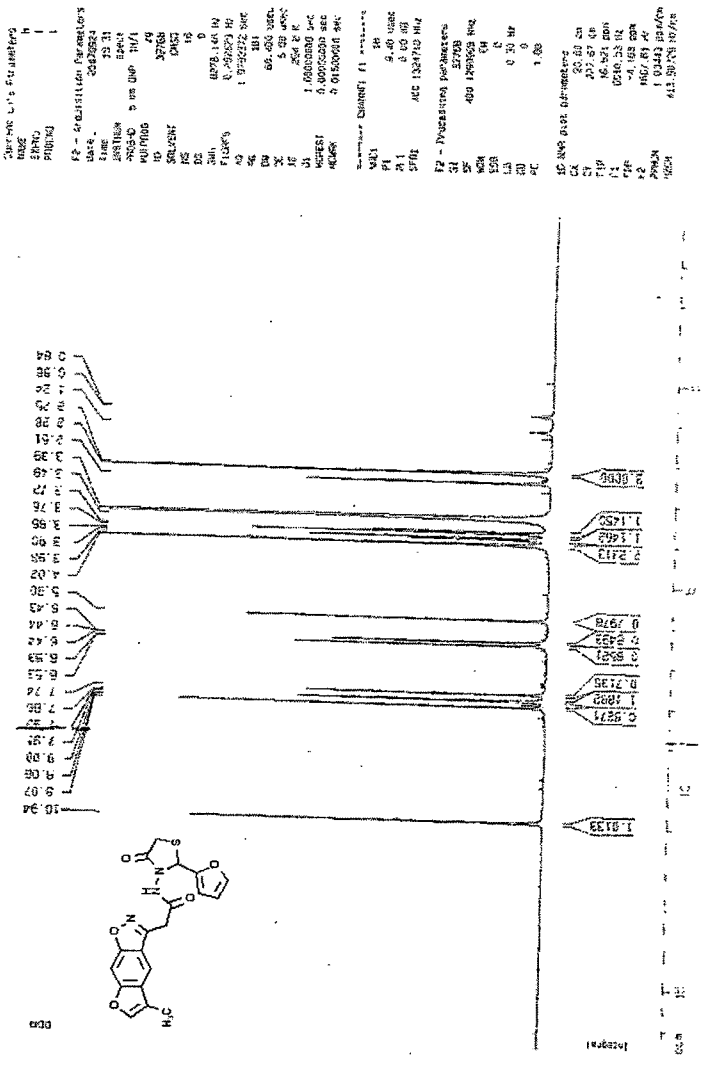


Figure 19: ^{1}H NMR of compound *N*-(2-furan-2-yl-4-oxo-thiazolidin-3-yl)-2-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetamide **14**.

5.A.3 Experimental

Melting points (uncorrected) were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by tlc on Acme's silica gel G plates using UV/Iodine vapour as visualizing agent and Acme's silica gel (60-120 mesh) was used for column chromatographic purification. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400). Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (spectrum RX1) using potassium bromide optics. The mass spectrum was obtained on Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS Mass Spectrometer (EI, 70 eV) (Model-016932) using Ion Spray source. NMR spectra were recorded on Bruker 400 MHz Spectrophotometer. Chemical shifts are relative to tetramethylsilane on δ-scale in ppm. Coupling constants are given in Hz and relative peak areas were in agreement with all assignments.

General procedure for the preparation of (3, 4).

5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one (3).

A solution of 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone (**1**) (2 g, 10.51 mmol) in diethyl carbonate (25 ml) was added gradually to pulverized sodium (0.48 g, 21.03 mmol) under anhydrous conditions. After stirring the reaction mixture for 10 min at room temperature, it was heated gradually to reflux temperature and maintained for 30 min.* It was then allowed to cool and methanol (15 ml) added to decompose the unreacted sodium. Reaction mass was then poured into water (50 ml) and the aqueous layer washed twice with toluene (25 ml). Concentrated hydrochloric acid was slowly added to the aqueous layer until pH 2 and solid obtained was collected by filtration. The crude product was crystallized from acetonitrile/ethanol 9:1 as light cream coloured crystals (1 g, 44 %), m.p. 262-263 °C. IR (KBr): 3426, 1707, 1597, 1575, 1513, 1338, 1296, 1137 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 2.28 (d, J = 1.28 Hz, 3H, C3-CH_3), 5.74 (s, 1H, C6-

* Highly exothermic reaction.

H), 7.36 (s, 1H, C9-H), 7.47 (d, J = 1.28 Hz, 1H, C2-H), 8.01 (s, 1H, C4-H), 11.72 (s, 1H, C5-OH). Anal. Calcd for $C_{12}H_8O_4$ (216.19): C, 66.67; H, 3.73. Found: C, 66.47; H, 3.58 %.

7-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one (4). Light brown crystals (acetonitrile/ethanol) 9:1, yield (41 %), m.p. 284 °C. IR (KBr): 3422, 1710, 1593, 1571, 1518, 1330, 1288, 1135 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 2.48 (d, J = 1.44 Hz, 3H, C3-CH_3), 5.65 (s, 1H, C6-H), 7.34-7.36 (d, J = 8.76 Hz, 1H, C9-H), 7.53 (d, J = 1.44 Hz, 1H, C2-H), 7.71-7.73 (d, J = 8.76 Hz, 1H, C8-H), 12 (s,1H, C7-OH). Anal. Calcd for $C_{12}H_8O_4$ (216.19): C, 66.67; H, 3.73. Found: C, 66.47; H, 3.58 %.

Preparation of 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone oxime (5). To a solution of 5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one (3) (1.5 g, 6.93 mmol) in pyridine (15 ml), a solution of hydroxylamine hydrochloride (1.68 g, 24.28 mmol) in water (5 ml) was added and reaction mixture refluxed for 12 h. It cooled to room temperature, poured into ice-hydrochloric acid and the solid obtained was collected by filtration. The crude product was crystallized from toluene/petroleum ether (60-80 °C) 3:7 mixture as light brown crystals (0.65 g, 45.65 %), m.p. 184-186 °C. IR (KBr): 3374, 1634, 1597, 1464, 1374, 1263, 1139, 1024 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.21 (d, J = 1.32 Hz, 3H, C3-CH_3), 2.45 (s, 3H, -N=C-CH_3), 7.03 (s, 1H, C7-H), 7.29 (d, J = 1.32 Hz, 1H, C2-H), 7.52 (s, 1H, C4-H), 11.48 (s, 1H, C6-OH). Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.11; H, 5.22; N, 6.69 %.

Preparation of 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)-acetic acid (6). To a solution of 5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one (3) (2.5 g, 11.56 mmol) in methanol (25 ml), hydroxylamine hydrochloride (2.81 g, 40.47 mmol) and sodium bicarbonate (3.40 g, 40.47 mmol) was added and the reaction mixture refluxed for 15 h. Excess of methanol was distilled off and the reaction mass was dissolved in 10 % sodium bicarbonate solution (100 ml) and filtered. Concentrated hydrochloric acid was slowly added to the filtrate until pH 2 and the

solid obtained was collected by filtration. The crude compound was purified by column chromatography using chloroform/methanol 9:1 mixture to get white crystals (1.45 g, 54.23 %), m.p. 170-172 °C dec. of 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)-acetic acid. IR (KBr): 3471, 3095, 2924, 2638, 1726, 1630, 1532, 1352, 1307, 1126 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 2.28 (d, J = 1.32 Hz, 3H, C5-CH_3), 4.05 (s, 2H, C3-CH_2-COO-), 7.47-7.48 (d, J = 1.32 Hz, 1H, C6-H), 7.54 (d, J = 0.8 Hz, 1H, C8-H), 7.76 (d, J = 0.56 Hz, 1H, C4-H), 9.50 (s (broad), 1H, -COOH). Anal. Calcd for $C_{12}H_9NO_4$ (231.20): C, 62.34; H, 3.92; N, 6.06. Found: C, 62.31; H, 3.88; N, 5.93 %.

Preparation of 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid ethyl ester (7). To a solution of 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)-acetic acid (**6**) (1.5 g, 6.48 mmol) in absolute ethanol (25 ml), one drop of concentrated sulphuric acid was added and the solution refluxed for 5 h. Excess of ethanol was removed under reduced pressure and the reaction mixture poured into ice-water. The product was extracted twice with diethyl ether (25 ml) and washed with 10 % sodium bicarbonate solution (25 ml) followed by washing with water (25 ml). Diethyl ether was distilled off to get 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid ethyl ester (1.2 g, 71.34 %). The product was used without further purification for the next reaction.

Preparation of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide (8). To a solution of hydrazine hydrate 99 % (0.35 g, 6.94 mmol) in absolute ethanol (15 ml), a solution of 5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid ethyl ester (1.2 g, 4.62 mmol) in absolute ethanol (5 ml) was added drop wise at reflux temperature. After completion of addition it was further refluxed for 6 h. Excess of ethanol was distilled off and the reaction mass was cooled to room temperature. The crystals obtained were filtered and washed with ethanol. The product recrystallized from ethanol to get white crystals (0.8 g, 70.48 %), m.p. 193-194 °C of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide. IR (KBr): 3320, 1646, 1529, 1368, 1121

cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 2.30 (d, J = 1.28 Hz, 3H, C5-CH_3), 3.97 (s, 2H, C3-CH_2-CO-), 7.49 (d, J = 1.28 Hz, 1H, C6-H), 7.54 (s, 1H, C8-H), 7.92 (s, 1H, C4-H), 9.15 (s,1H, -CO-NH-). Anal. Calcd for $C_{12}H_{11}N_3O_3$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.49; H, 4.38; N, 17.01 %.

Preparation of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide (9a) OR 3-(5-furan-2yl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-5-methyl-furo[2'3':4,5]benzo[1,2-*d*]isoxazole (9b). A solution of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide (**8**) (0.5 g, 2.03 mmol) and freshly distilled furfuraldehyde (0.19 g, 2.03 mmol) in absolute ethanol (15 ml) was refluxed for 6 h. Excess of ethanol was distilled off and the reaction mass cooled to room temperature. The crystals obtained were filtered and washed with ethanol. The product was recrystallized from ethanol to get light yellow crystals (0.45 g, 68.26 %), m.p. 195 °C dec. of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide or 3-(5-furan-2yl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-5-methyl-furo[2'3':4,5]benzo[1,2-*d*]isoxazole. IR (KBr): 3435, 3031, 1670, 1630, 1571, 1547,1368, 1123 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide (**9a**): δ 2.22 (d, J = 1 Hz, 3H, C5-CH_3), 4.48 (s, 2H, C3-CH_2-CO-), 6.51-6.52 (m, 1H, C4'-H), 6.73 (d, J = 3 Hz, 1H, C3'-H), 7.49-7.56 (m, 3H, C5'-H, C6-H and –CH=N-), 7.84 (s, 1H, C8-H), 7.95 (s, 1H, C4-H), 11.45 (s, 1H, -CO-NH-). 3-(5-furan-2yl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-5-methyl-furo[2'3':4,5]benzo[1,2-*d*]isoxazole (**9b**): δ 2.28 (d, J = 1 Hz, 1.5H, C5-CH_3), 4.07 (s, 1H, C5'-H), 4.48 (s, 2H, C3-CH_2-C2'), 6.47-6.48 (m, 0.5H, C4"-H), 6.78 (d, J = 3 Hz, 0.5H, C3"-H), 7.49-7.56 (m, 1H, C5"-H and C6-H), 8 (s, 0.5H, C8-H), 8.13 (s, 0.5H, C4-H), 11.64 (s, 0.5H, N4'-H). LCMS (EI): *m/z* (%) 362.1(5.76, M+K), 346.1 (23.07, M+Na), 325.3 (36.53, M+2), 324.3 (100, M+1). Anal. Calcd for $C_{17}H_{13}N_3O_4$ (323.30): C, 63.16; H, 4.05; N, 13.00. Found: C, 62.91; H, 3.88; N, 12.73 %.

Preparation of 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole (11). A solution of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide (**9a**) (0.5 g, 1.54 mmol) in acetic anhydride (15 ml) refluxed for 8 h. Excess of acetic anhydride distilled off under reduced pressure and the reaction mass poured into ice water. The solid obtained was collected by filtration and purified by column chromatography using petroleum ether (60-80 °C):ethyl acetate 7:3 mixture, which gave white crystals (0.15 g, 51.81 %), m.p. 135 °C of 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole. IR (KBr): 3102, 2963, 1726, 1631, 1598, 1388, 1340, 1261, 1106, 1066 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.29 (d, J = 1.24 Hz, 3H, C5-CH_3), 2.63 (s, 3H, C3-CH_3), 7.46 (d, J = 1.24 Hz, C6-H), 7.53 (s, 1H, C8-H), 7.63 (s, 1H, C4-H). LCMS (EI): *m/z* (%) 210.1 (9.61, M+Na), 189.3 (40.38, M+2), 187.9 (100, M+1), 147.2 (3.84), 124.2 (9.61). Anal. Calcd for $C_{11}H_9NO_2$ (187.19): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.33; H, 4.68; N, 7.23 %.

Preparation of acetic acid 5-(1-hydroxyimino-ethyl)-3-methyl-benzofuran-6-yl ester (12). A solution of 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone oxime (**5**) (0.5 g, 2.43 mmol) refluxed in acetic anhydride (25 ml) for 4 h. Excess of acetic anhydride distilled off under reduced pressure and the reaction mass poured into ice water. The solid obtained was collected by filtration. The crude product (0.42 g, 69.71 %) was used without further purification for the next step.

Preparation of 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole (11) from acetic acid 5-(1-hydroxyimino-ethyl)-3-methyl-benzofuran-6-yl ester (12). A solution of crude acetic acid 5-(1-hydroxyimino-ethyl)-3-methyl-benzofuran-6-yl ester (**12**) in dry pyridine (15 ml) was refluxed for 4 h. The reaction mass was cooled to room temperature and then poured into ice-hydrochloric acid mixture. The solid obtained was filtered and purified by column chromatography using petroleum ether (60-80 °C):ethyl acetate 7:3 mixture, which gave white crystals (0.15 g, 47.17 %), m.p. 135 °C of 3,5-dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole.

Preparation of 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol (13a) or 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-3H-[1,3,4]oxadiazole-2-thione (13b). A solution of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide **(8)** (1 g, 4.07 mmol) and carbon disulfide (0.31 g, 4.07 mmol) in 1 % methanolic potassium hydroxide (20 ml) was refluxed for 8 h until the evolution of hydrogen sulfide gas ceases. Excess of methanol was distilled off and the reaction mass poured into ice water. The aqueous solution was made alkaline by addition of potassium hydroxide (1 g, 17.8 mmol), stirred for 15 min and filtered. The filtrate, acidified with concentrated hydrochloric acid until pH 2 and the product was filtered and purified by column chromatography using chloroform:methanol 9:1 mixture, which gave yellowish brown crystals (0.7 g, 59.75 %), m.p. 222 °C of 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol or 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-3*H*-[1,3,4]oxadiazole-2-thione. IR (KBr): 3434, 3076, 2926, 2753, 1628, 1596, 1529, 1494, 1377, 1333, 1295, 1277, 1149, 1121, 1058 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 2.30 (d, J = 1.32 Hz, 3H, C5'-CH_3), 4.53 (s, 2H, C5-CH_2-C3'), 7.56 (d, J = 1.32 Hz, 1H, C6'-H), 7.61-7.62 (d, J = 0.64 Hz, 1H, C8'-H), 7.62 (s, 0.5H, N3-H – 13b tautomer), 7.78 (d, J = 0.4 Hz, 1H, C4'-H), 14.33 (s, 1H, C2-SH – 13a tautomer). LCMS (EI): *m/z* (%) 326.1 (3.70, M+K), 310.1 (16.66, M+Na), 305.2 (35.18, M+NH_4), 289.1 (18.51, M+2), 288.3 (100, M+1). Anal. Calcd for $C_{13}H_9N_3O_3S$ (287.29): C, 54.35; H, 3.16; N, 14.63; S, 11.16. Found: C, 54.11; H, 3.01; N, 14.41; S, 10.94 %.

***N*-(2-furan-2-yl-4-oxo-thiazolidin-3-yl)-2-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetamide 14.** A solution of (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide **(9a)** (0.5 g, 1.54 mmol), thioglycolic acid (0.21 g, 2.31 mmol) and catalytic amount of fused zinc chloride in dry toluene (20 ml) was subjected to azeotropic distillation for 12 h. The reaction mixture washed with water and toluene removed under reduced

pressure. The crude product purified by column chromatography using petroleum ether (60-80 °C):ethyl acetate 8:2 mixture, which gave light yellow crystals (0.21 g, 34.20 %), m.p. 236 °C dec. of *N*-(2-furan-2-yl-4-oxo-thiazolidin-3-yl)-2-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetamide. ^{1}H NMR ($(CD_3)_2SO$): δ 2.27 (d, J = 1.05 Hz, 3H, C5-CH_3), 3.71-3.75 (d, J = 16 Hz, 1H, C5'-H_a of thiazolidinone ring), 3.85-3.89 (d, J = 16 Hz, 1H, C5'-H_b of thiazolidinone ring), 4.02 (s, 2H, C3-CH_2-CO-), 5.90 (s, 1H, C2'-H of thiazolidinone ring), 6.43-6.44 (m, 1H, C4"-H of furan ring), 6.53-6.53 (m, 1H, C3"-H of furan ring), 7.74-8.07 (m, 4H, C4-H, C6-H, C7-H, C5"-H), 10.94 (s, 1H, -CONH-). Anal. Calcd for $C_{19}H_{15}N_3O_5S$ (397.40): C, 57.42; H, 3.80; N, 10.57. Found: C, 57.11; H, 3.64; N, 9.98 %.

5.A.4 Conclusions

- The present investigation provides with new heterocyclic derivatives from 4-hydroxy coumarins.

- The Posner reaction of 4-hydroxy coumarin is known to give mixture of 1,2-benzisoxazole-3-acetic acid and 2-hydroxyacetophenone oximes. When pyridine is used as solvent, 2-hydroxyacetophenone oximes is the major product, which can be minimized by the use of methanol as solvent.

- The compounds can be explored for possible pharmacological activities.

5.A.5 References

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Chapter 5: Section B

STUDIES IN THE SYNTHESIS AND TAUTOMERISM OF NEW WARFARINS

5.B.1 Introduction

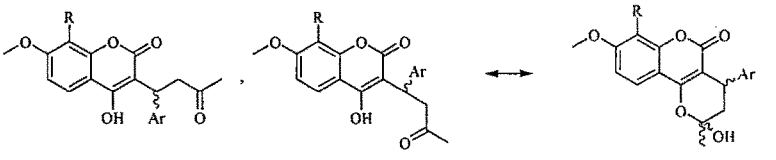
Warfarins today dominate coumarin anticoagulant owing to its excellent potency and good pharmacokinetic profile.[1] Warfarin decreases blood coagulation by interfering with vitamin K metabolism. It inhibits specifically the vitamin K epoxide reductase subunit,[2, 3] thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues. So they are referred as vitamin K antagonists. Warfarin and its derivatives have also been used as non-peptidic HIV protease inhibitor.[4] Some common clinical uses of warfarin are fibrillation, artificial heart valves, deep venous thrombosis and pulmonary embolism.[5] Warfarins have also used as rodenticides.

Owing to the importance of warfarin in natural and synthetic organic chemistry, we report herein the synthesis of some new warfarin derivatives and their existence in three interconverting tautomers from NMR studies.[6]

The Michael condensation of benzalacetone with 4-hydroxy coumarins under the usual conditions in ethanol with either sodium ethoxide, hydrochloric acid or piperidine as catalyst are known to give a mixture of normal condensation product and the cyclic ketal formed by reaction with ethanol.[7] Earlier, from our laboratory, cyclo-dehydrated products have been reported by Michael condensation reaction of benzalacetone with 4-hydroxy coumarins in methanol.[8] Reactions were thus carried out in pyridine. We have synthesized new warfarin derivatives from 8-substituted 4-hydroxy-7-methoxy-benzopyran-2(*H*)-one and different α,β-enones viz. benzalacetone,[9] anisalacetone,[9] and salicylalacetone.[10]

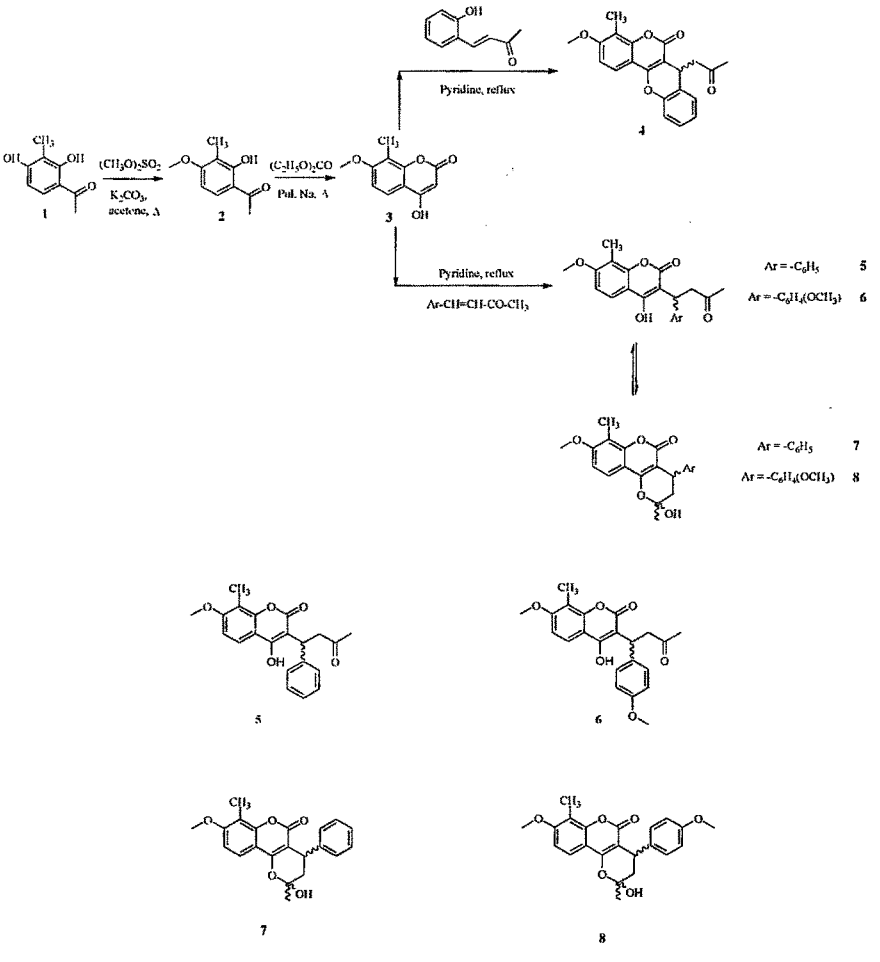
^{1}H NMR studies of these compounds in deuteriochloroform shows three interconverting tautomeric structures, two of which are cyclic diastereomeric hemiketals, while the third one is the open chain intermediate form; whereas the ^{1}H NMR in deuteriodimethylsulfoxide shows existence of only two

diastereomeric hemiketal forms as shown in **Figure 1**. The reaction sequence for different title compounds is outlined in **Scheme 1** and **Scheme 2**.



Open chain Cyclic hemiketal

Figure 1: Tautomers of Warfarin.


Pyridine, reflux
Pyridine, reflux
Ar-CH=CH-CO-CH3
Ar = -C6H5 5
Ar = -C6H4(OCH3) 6
Ar = -C6H5 7
Ar = -C6H4(OCH3) 8

Scheme 1

5.B.2 Results and Discussion

Methyl resacetophenone **1**,[11] was monomethylated using dimethyl sulfate in potassium carbonate and dry acetone to give 1-(2-hydroxy-4-methoxy-3-methyl-phenyl)-ethanone **2**, which on Hoesch[12] condensation with diethyl carbonate and pulverized sodium gave 4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one **3**. ^{1}H NMR of compound **3** showed signals at δ 2.2 (s, 3H, C8-CH_3), 3.9 (s, 3H, C7-OCH_3), 5.6 (s, 1H, C3-H), 7.08-7.11 (d, J = 8.8 Hz, 1H, C6-H), 7.59-7.61 (d, J = 8.8 Hz, 1H, C5-H), 14.1 (s, 1H, C4-OH) which confirmed the structure. The C4-OH being enolic hydroxy, was highly deshielded. Michael condensation of **3** with salicylalacetone, benzalacetone and anisalacetone and gave different title compounds **(4-6)** respectively.

4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one **3** when condensed with anisalacetone in pyridine gave 4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-8-methyl-benzopyran-2[*H*]-one **6**. ^{1}H NMR of this compound in deuteriodimethylsulfoxide **(Figure 2)** can be interpreted in terms of two cyclic diastereomeric hemiketals. The Michael condensation product obtained is a δ-hydroxy ketone **(Scheme 1)** and can therefore undergo ring closure to the corresponding cyclic hemiketal as shown in **Figure 1**. Two distinct methyl proton resonances at δ 1.54-1.60 ppm for three protons indicate presence of methyl group at C-2. Resonance spread over δ 1.83-2.30 ppm for two protons corresponds to diastereotopic methylene protons at C-3, whereas multiplet at δ 3.71-3.90 ppm for one proton indicates presence of methine proton resonance at C-4; which clearly indicates the cyclic hemiketal structure 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2,7-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **8**. The lack of methylene resonance at δ 3.2-3.3 ppm and a methine resonance at δ 4.6-4.8 ppm excludes a significant contribution by the open chain form **(6)** in deuteriodimethylsulfoxide. The methyl proton resonance for the major hemiketal tautomer appears down field from that for the minor hemiketal tautomer in the relative ratio of 70:30 approximately by integration.

However, the ^{1}H NMR spectrum of this compound when recorded in deuteriochloroform **(Figure 3)** showed mixture of open chain **(6)** and two cyclic diastereomeric hemiketal forms **(8)**. The numbers of signals obtained were doubled and were in the ratio of 1:1 by integration, which shows the existence of open chain tautomer as an entirely different molecule. Methyl (C2-CH_3) resonance for three protons at δ 1.65-1.69 ppm and methylene (-CH_2-) resonance for two protons at δ 1.96-2.54 ppm corresponds to two diastereomeric hemiketal tautomers. The methyl proton resonance for the major hemiketal tautomer now appears upfield from that for the minor hemiketal tautomer in the relative ratio of 60:40 approximately by integration. Two singlets at δ 2.24 ppm and δ 2.31 ppm were observed for methyl group attached to aromatic ring for the open chain and cyclic tautomers. Resonance at δ 3.22-3.26 ppm was assigned to diastereotopic methylene protons of open chain tautomer. The methine proton resonance for cyclic hemiketal and open chain tautomer was observed at δ 4.07-4.12 ppm and δ 4.23-4.24 ppm respectively. All ^{1}H NMR signals for compound **6** and **8** in DMSO and $CDCl_3$ are shown below.

^{1}H NMR ($(CD_3)_2SO$, 400 MHz) **(Figure 2)**: δ 1.54-1.60 (two singlets, 3H, C2-CH_3 resonance), 1.83-2.30 (m, 2H, -CH_2- resonance), 2.15 (s, 3H, C7-CH_3), 3.71 (s, 3H, C4'-OCH_3), 3.90 (m, 4H, C8-OCH_3 and -CH- resonance), 6.77-6.79 (d, J = 8.4 Hz, 2H, C3'-H and C5'-H), 7.07-7.30 (m, 3H, C9-H, C2'-H and C6'-H), 7.65-7.67 (d, J = 8.8 Hz, 1H, C10-H), 11.39 (s, 1H, C2-OH).

^{1}H NMR ($CDCl_3$, 400 MHz) **(Figure 3)**: δ 1.65-1.69 (two singlets, 3H, C2-CH_3 resonance), 1.96-2.54 (m, 2H, -CH_2- resonance in hemiketal tautomer), 2.24 (s, 3H, C7-CH_3 in hemiketal tautomer), 2.31 (s, 3H, C8-CH_3 in open chain tautomer), 3.22-3.26 (m, 2H, -CH_2- resonance in open chain tautomer), 3.76-3.93 (m, 12H, C8-OCH_3 and C4'-OCH_3 in hemiketal tautomer and C7-OCH_3 and C4'-OCH_3 in open chain tautomer), 4.07-4.12 (m, 1H, -CH- resonance in hemiketal tautomer), 4.23-4.24 (m, 1H, -CH- resonance in open chain tautomer), 6.79-6.86 (m, 4H, C3'-H and C5'-H in hemiketal tautomer and C3'-H and C5'-H in open chain

tautomer), 7.13-7.23 (m, 6H, C9-H, C2'-H and C6'-H in hemiketal tautomer and C6-H, C2'-H and C6'-H in open chain tautomer), 7.63-7.71 (d, J = 8.76 Hz, 1H, C10-H in hemiketal tautomer), 7.70-7.72 (d, J = 8.76 Hz, 1H, C5-H in open chain tautomer).

Similar observations were recorded for Michael condensation of 4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one **3** with benzalacetone. ^{1}H NMR of cyclic hemiketal tautomer - 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **7** in DMSO is shown in **Figure 4**. ^{13}C NMR of this compound in DMSO **(Figure 5)** and DMSO plus $CDCl_3$ **(Figure 6)** did not show much of a difference. Moreover, the solid state ^{13}C NMR **(Figure 7)** reveals that the compound exists in different forms, even in crystalline state.

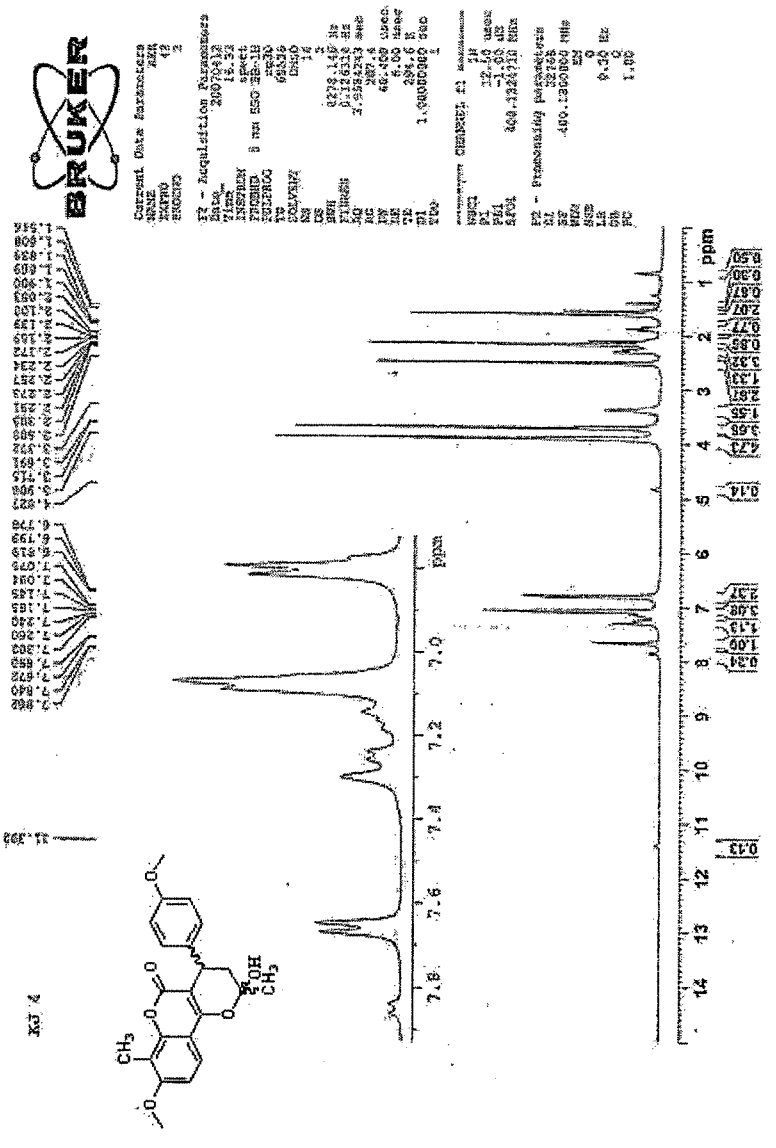


Figure 2: ^{1}H NMR of cyclic hemiketal tautomer - 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2,7-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **8** in DMSO.

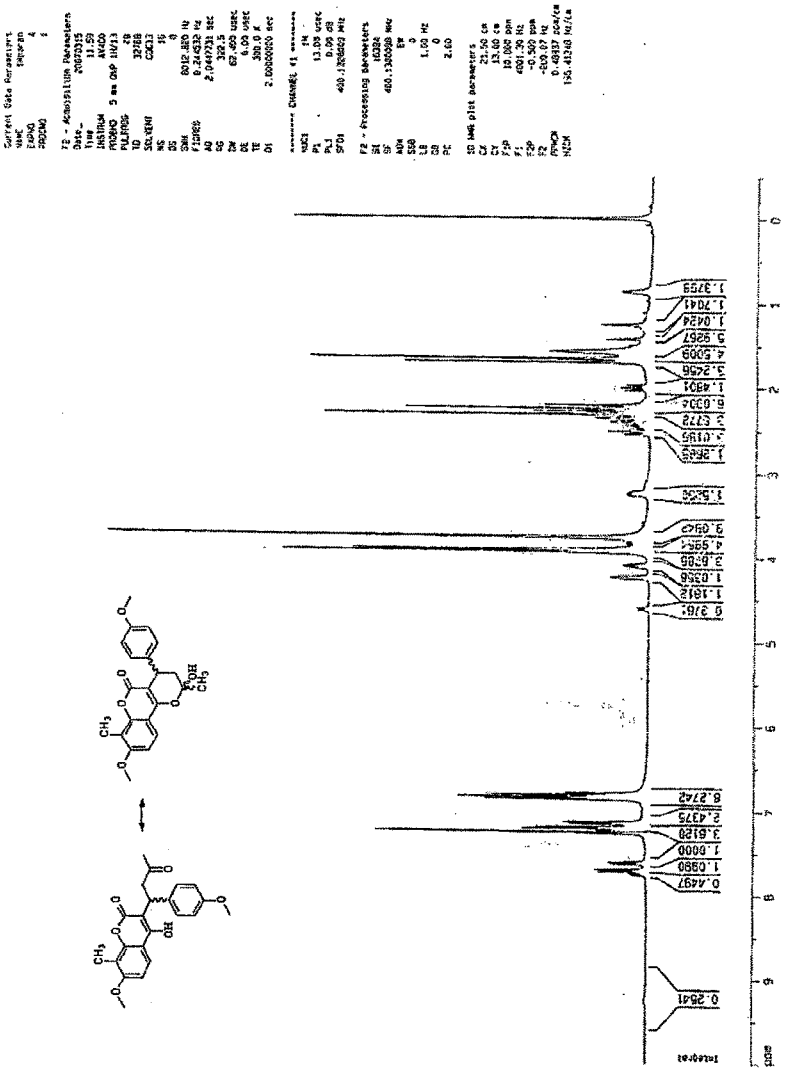


Figure 3: ^{1}H NMR of open chain tautomer - 4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-8-methyl-benzopyran-2[*H*]-one **6** and cyclic hemiketal tautomer - 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2,7-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **8** in $CDCl_3$. Contd.

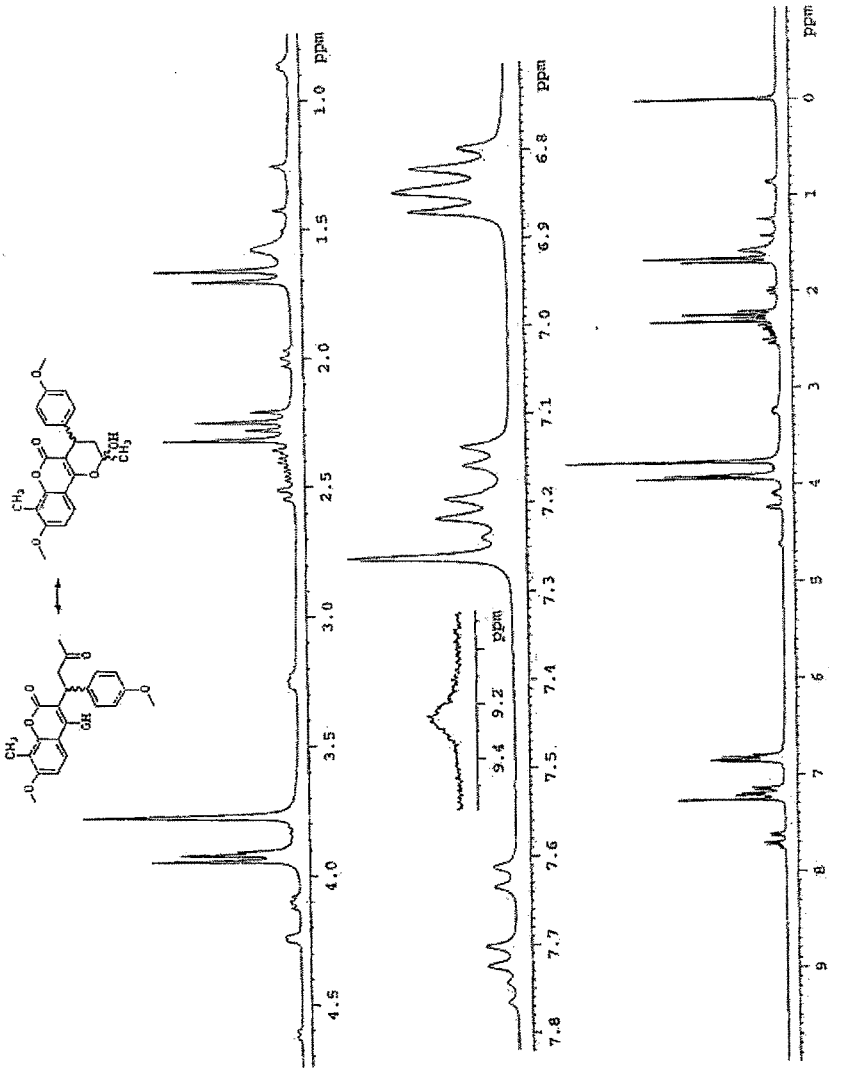


Figure 3: ^{1}H NMR of open chain tautomer - 4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-8-methyl-benzopyran-2[*H*]-one **6** and cyclic hemiketal tautomer - 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2,7-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **8** in $CDCl_3$.

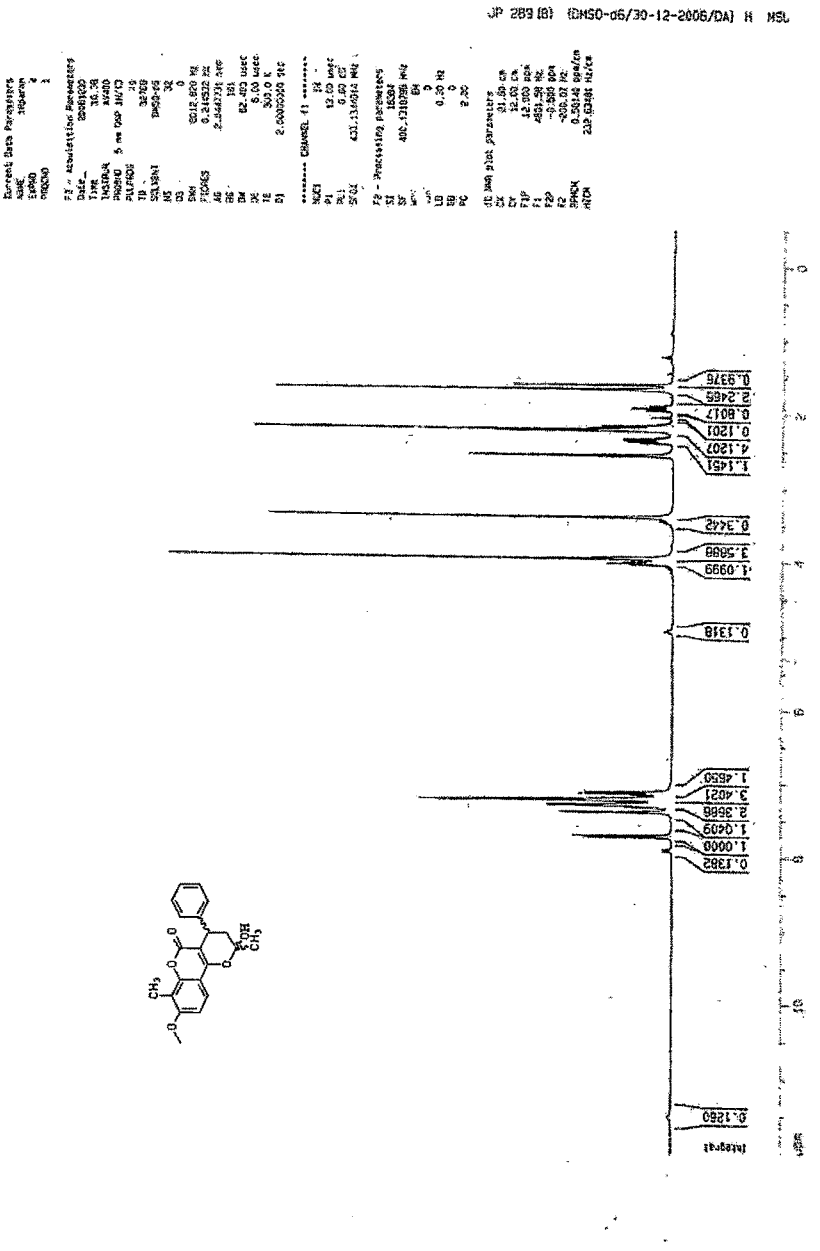


Figure 4: ^{1}H NMR of cyclic hemiketal tautomer - 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one 7 in DMSO. Contd

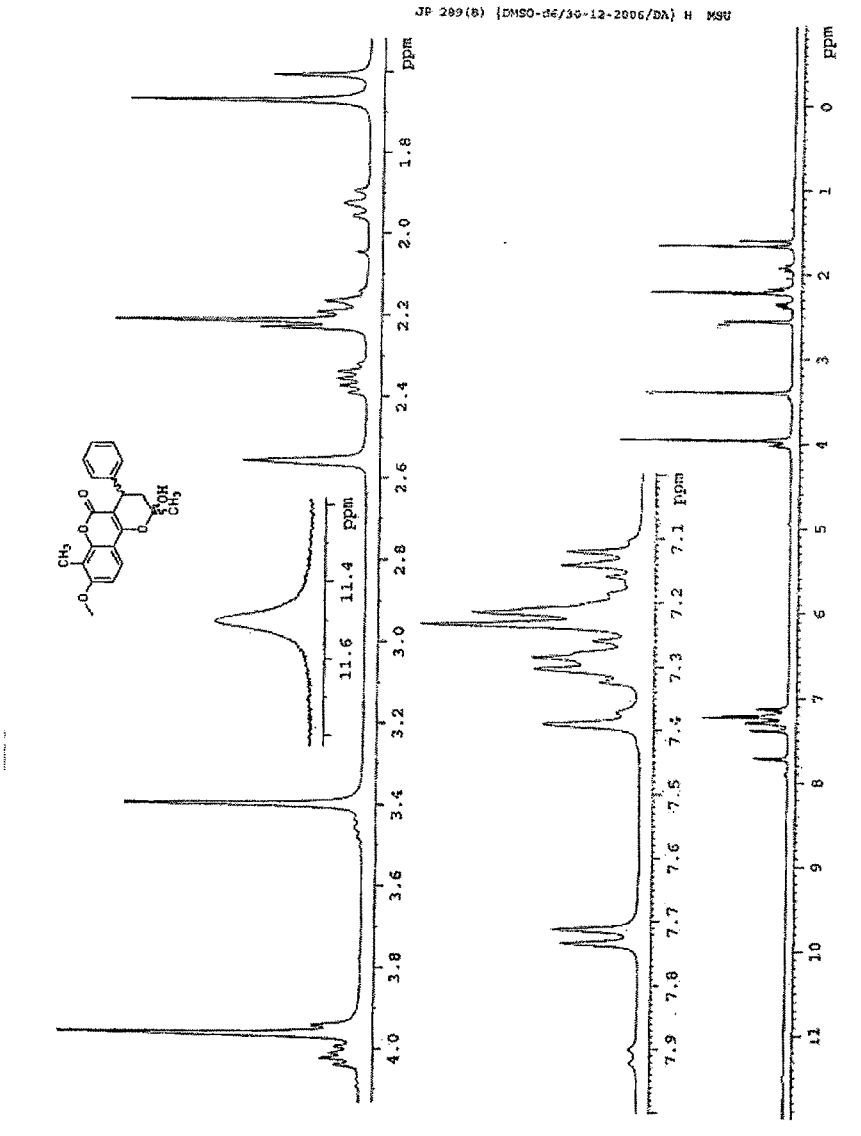


Figure 4: ^{1}H NMR of cyclic hemiketal tautomer - 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one 7 in DMSO.

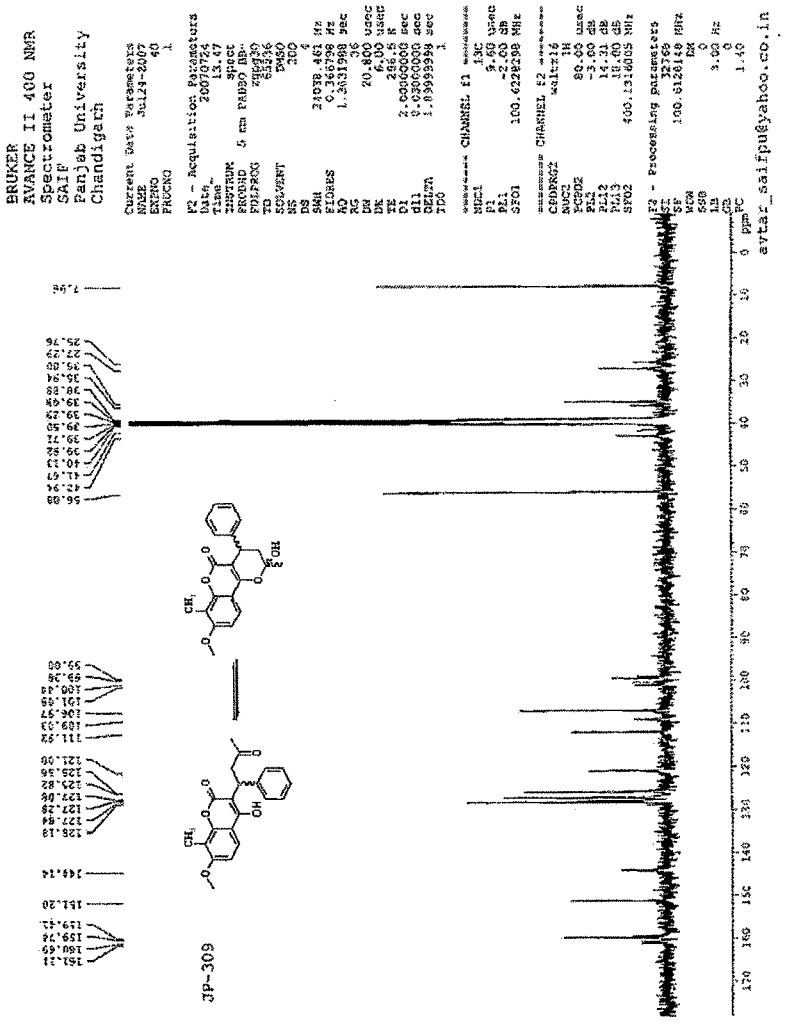


Figure 5: ^{13}C NMR of 4-hydroxy-7-methoxy-8-methyl-3-(3-oxo-1-phenyl-butyl)-benzopyran-2[*H*]-one **5** (open chain tautomer) OR 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **7** (hemiketal tautomer) in DMSO.

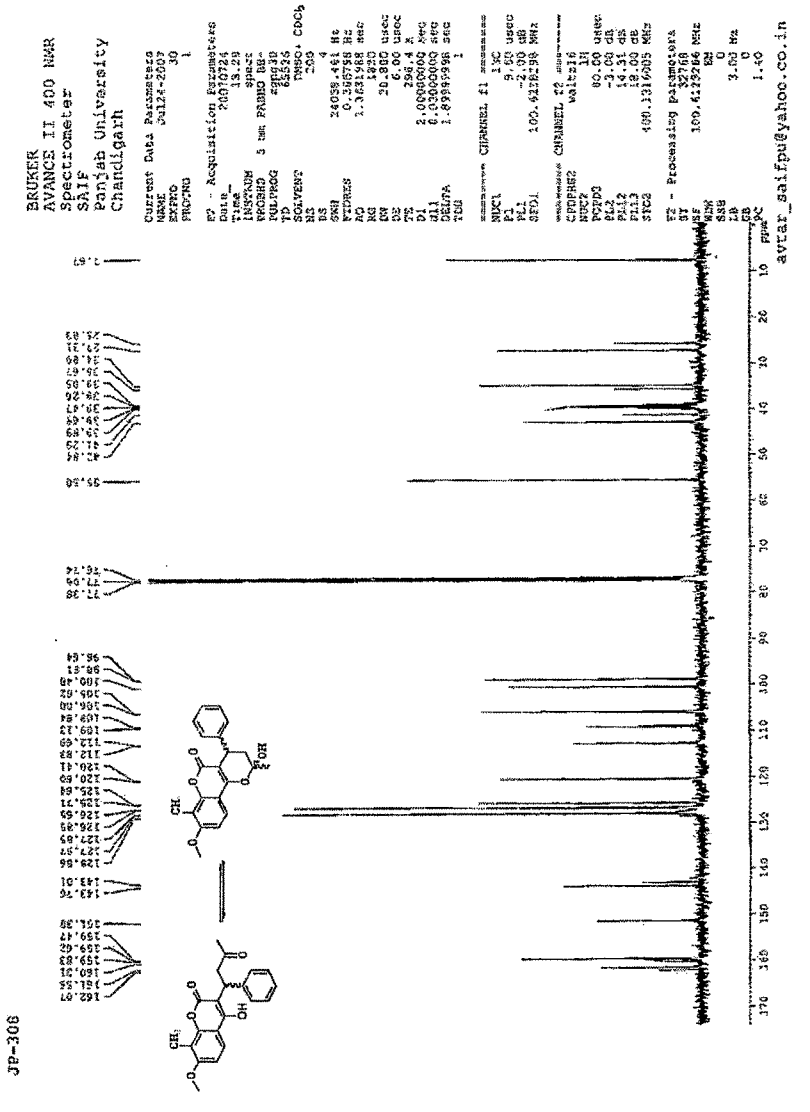


Figure 6: ^{13}C NMR of 4-hydroxy-7-methoxy-8-methyl-3-(3-oxo-1-phenyl-butyl)-benzopyran-2[*H*]-one **5** (open chain tautomer) OR 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **7** (hemiketal tautomer) in DMSO plus $CDCl_3$.

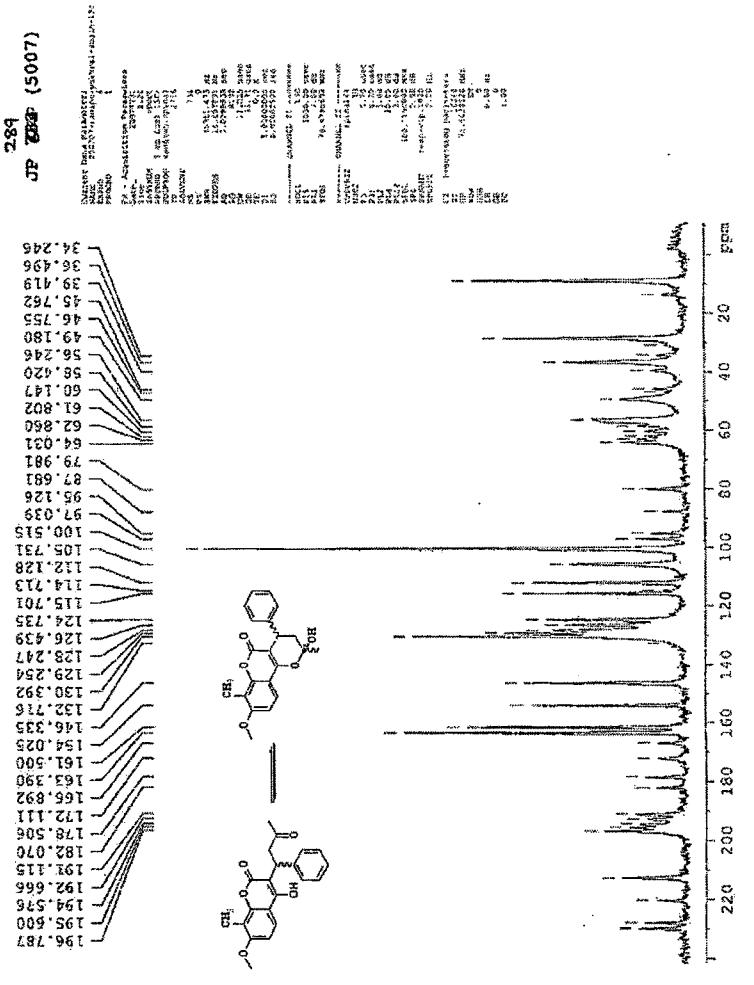


Figure 7: Solid state ^{13}C NMR of 4-hydroxy-7-methoxy-8-methyl-3-(3-oxo-1-phenyl-butyl)-benzopyran-2[*H*]-one **5** (open chain tautomer) OR 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **7** (hemiketal tautomer).

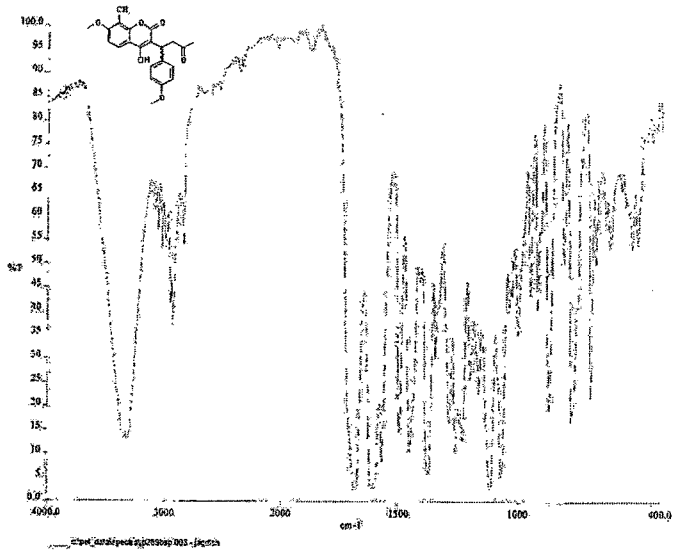


Figure 8: IR of compound 4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-8-methyl-benzopyran-2[*H*]-one **6**.

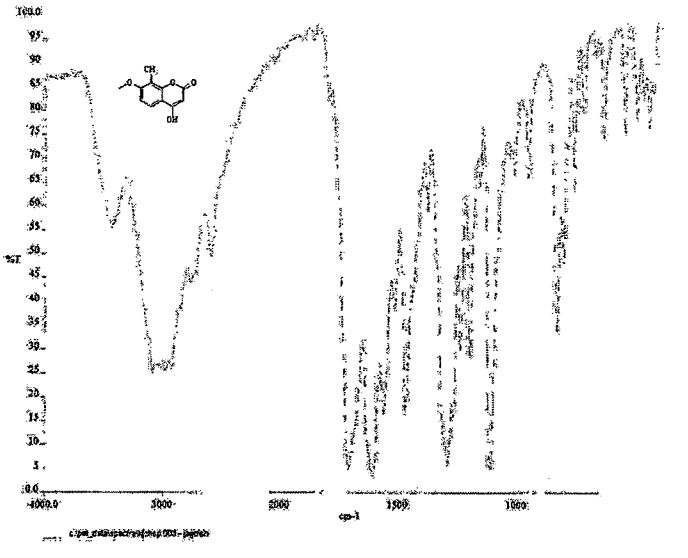


Figure 9: IR of compound 4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one **3**.

However, when 4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one **3** was condensed with salicylalacetone by refluxing in pyridine, the product obtained was 3-methoxy-4-methyl-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one **4**. Here the Michael condensation product spontaneously eliminates water to give alkali insoluble dehydrated product **4**.[8] In the ^{1}H NMR **(Figure 10)**, two double doublets at δ 2.19-2.23 ppm ($J_{vicinal}$ = 3.16 Hz, $J_{geminal}$ = 13.24 Hz) and δ 2.27-2.31 ppm ($J_{vicinal}$ = 2.92 Hz, $J_{geminal}$ = 13.24 Hz) both corresponding to one proton each, were assigned to C7-CH_2- diastereotopic protons; whereas a doublet of doublet at δ 4.26-4.28 ppm ($J_{vicinal}$ = 2.92 Hz, $J_{vicinal}$ = 3.16 Hz) for one proton was assigned to C7-H methine proton. The absences of –OH group further confirmed the dehydrated product. Other signals observed were, δ 1.98 (s, 3H, C4-CH_3), 2.23 (s, 3H, -$COCH_3$), 3.88 (s, 3H, C3-OCH_3), 6.76-6.78 (d, J = 8.8 Hz, 1H, C2-H), 6.85-6.91 (m, 2H, C8-H and C9-H), 7.08-7.13 (m, 1H, C10-H), 7.46-7.48 (dd, J = 1.4 Hz and J = 7.48 Hz, 1H, C11-H), 7.59-7.61 (d, J = 8.84 Hz, 1H, C1-H). IR of this compound is shown in **Figure 11.**

The structures of all the compounds were confirmed on the basis of their elemental analyses and spectral (IR and NMR) data.

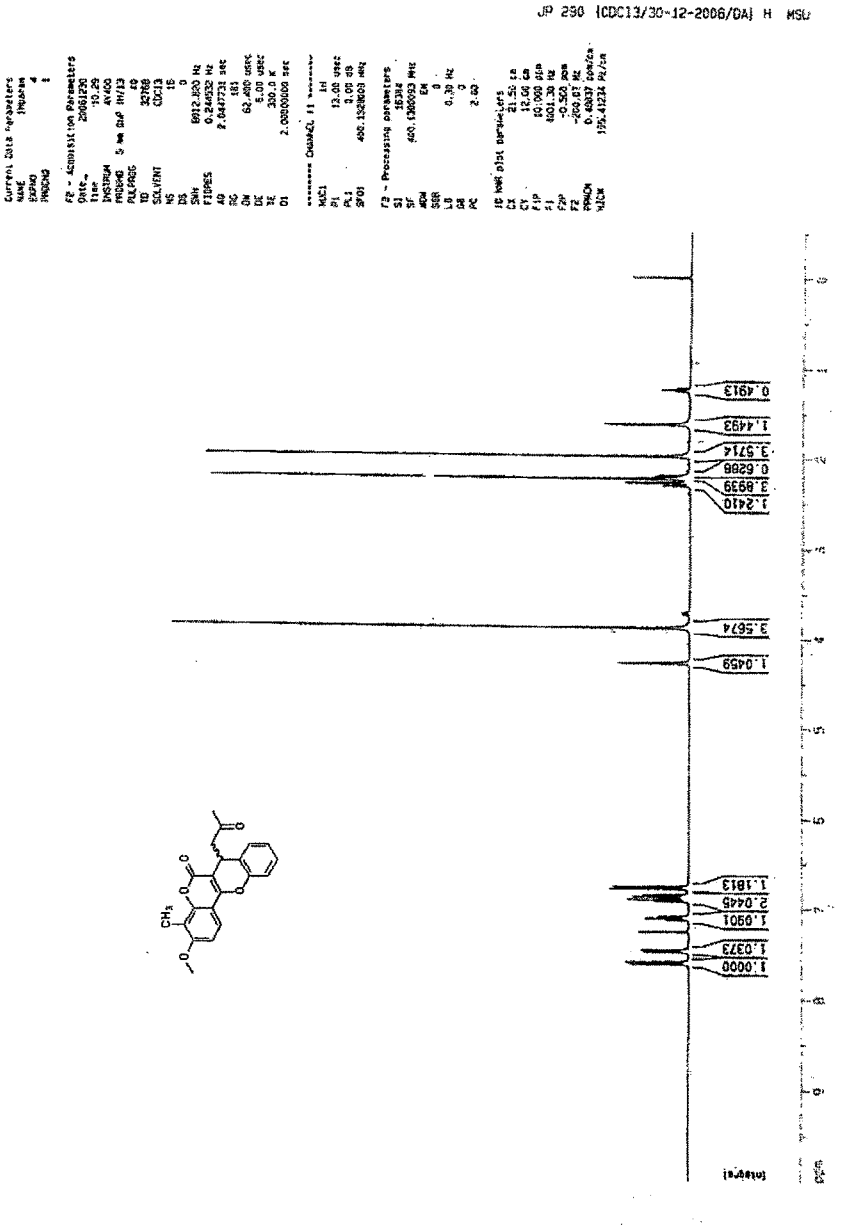


Figure 10: ^{1}H NMR of 3-methoxy-4-methyl-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one **4**. Contd.

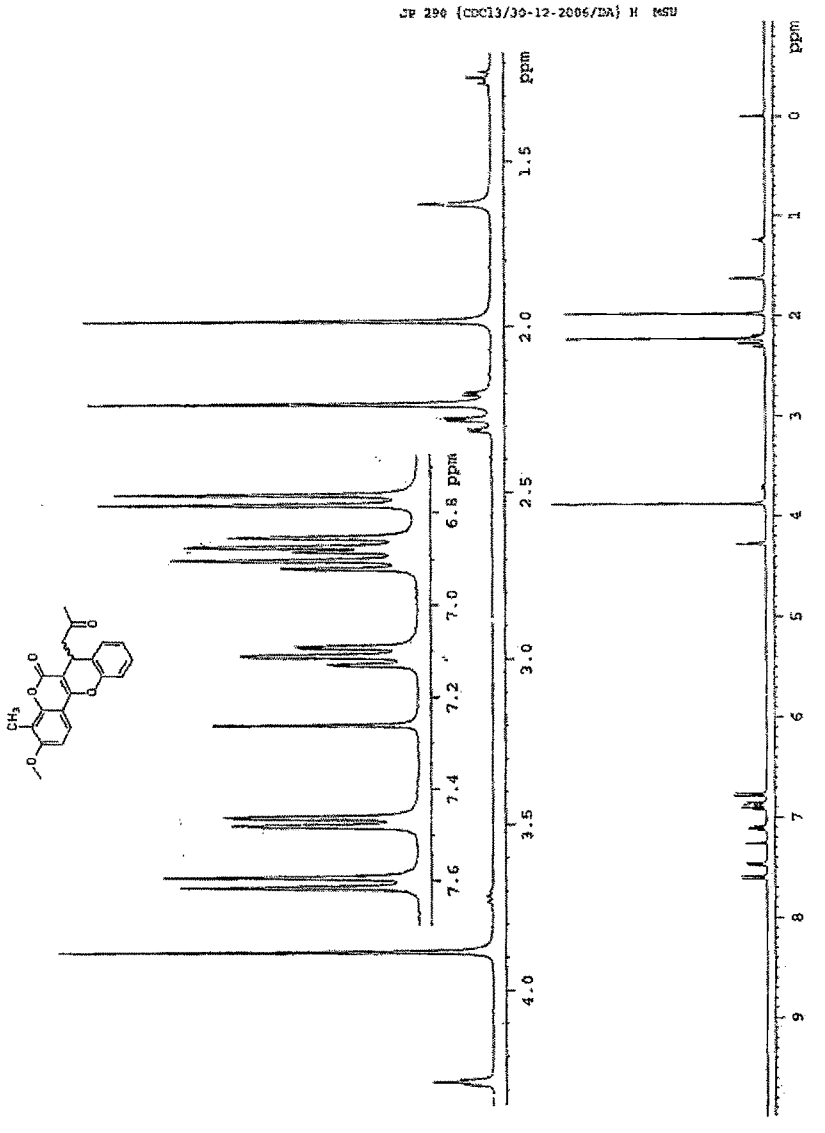


Figure 10: ^{1}H NMR of 3-methoxy-4-methyl-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one **4**.

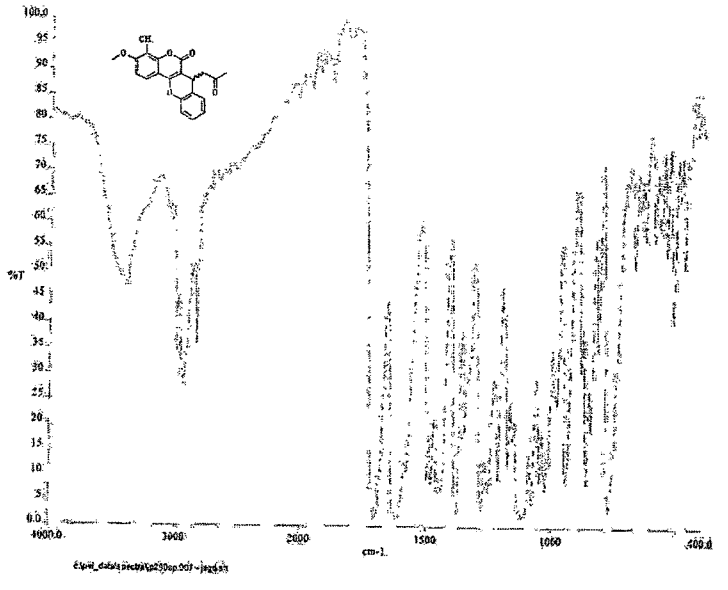
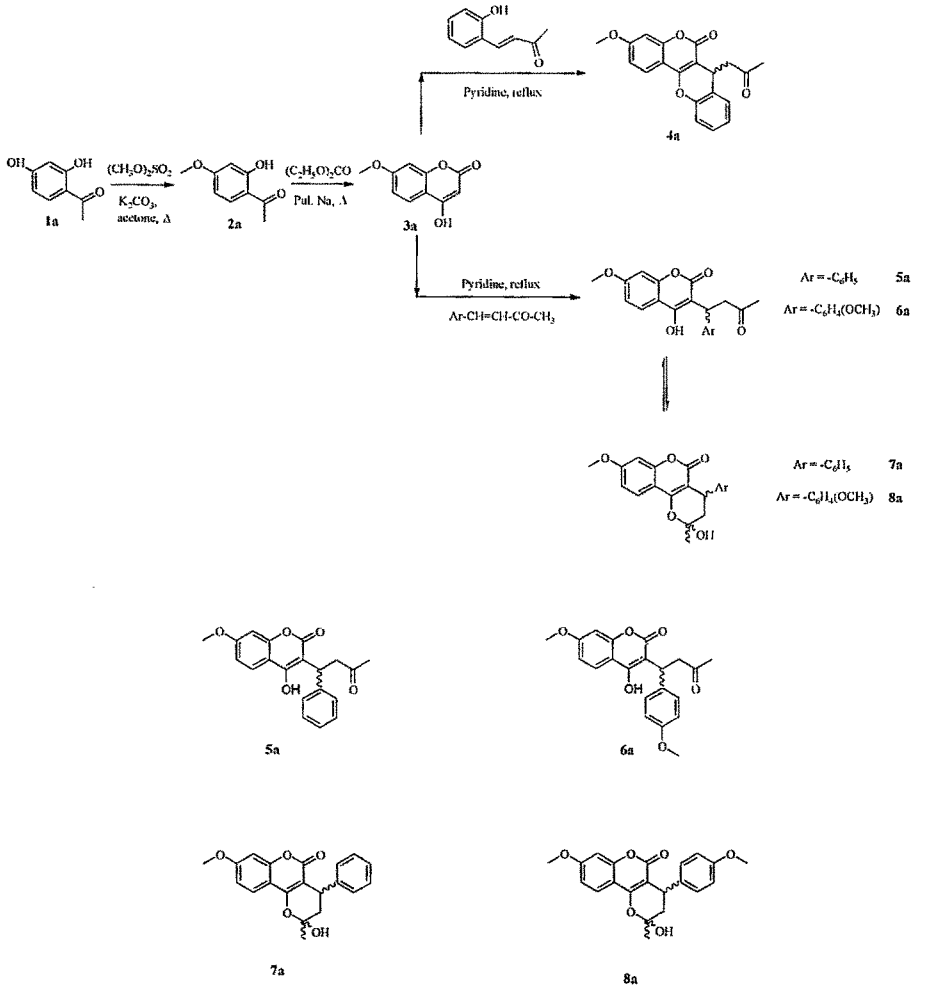


Figure 11: IR of compound 3-methoxy-4-methyl-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one **4**.



Scheme 2

Similar series of reactions were carried out with Resacetophenone **1a**,[10] as shown in **Scheme 2.**

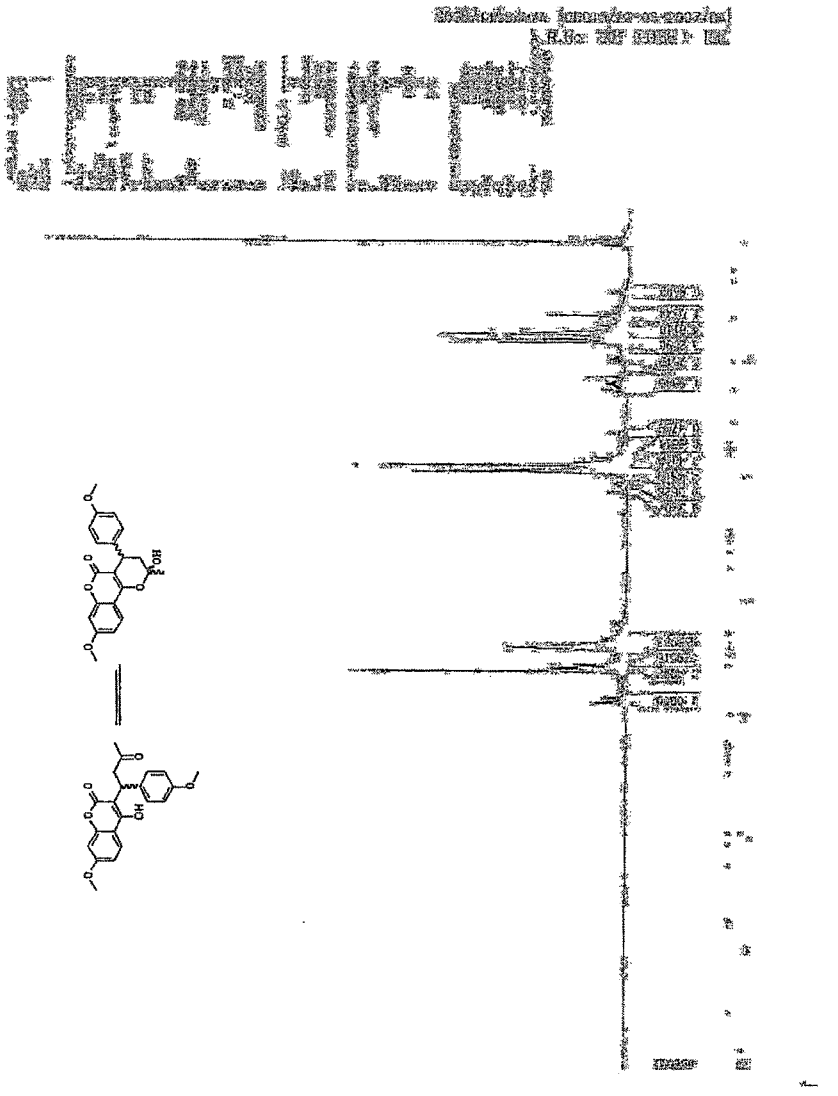


Figure 12: ^{1}H NMR of 4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-benzopyran-2[*H*]-one **6a** (open chain tautomer) OR 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2-methyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **8a** (hemiketal tautomer) in $CDCl_3$. Contd.

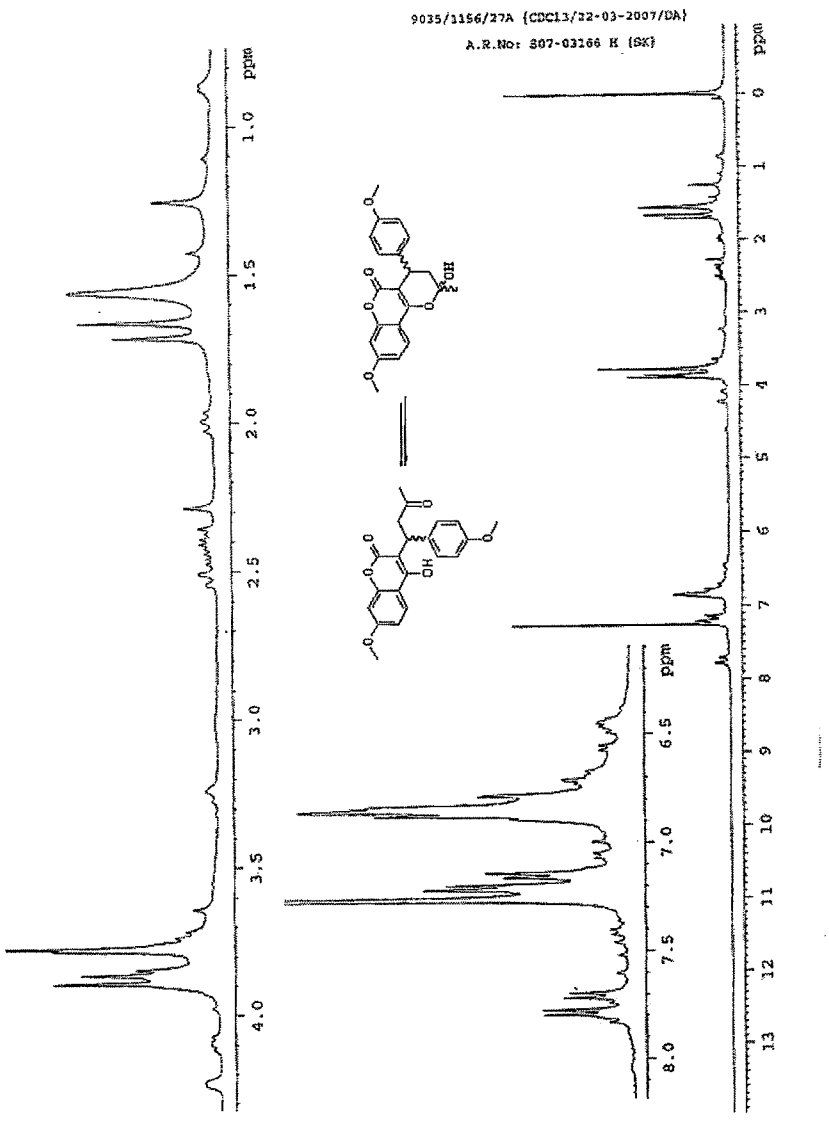


Figure 12: ^{1}H NMR of 4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-benzopyran-2[*H*]-one **6a** (open chain tautomer) OR 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2-methyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one **8a** (hemiketal tautomer) in $CDCl_3$.

5.B.3 Experimental

All chemicals used were of LR grade and were obtained from Merck chemicals. Melting points (uncorrected) were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by TLC on Acme's silica gel G plates using UV/Iodine vapour as visualizing agent and Acme's silica gel (60-120 mesh) was used for column chromatographic purification. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400). Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (spectrum RX1) using potassium bromide optics. NMR spectra were recorded on Brucker 400 MHz. Spectrophotometer. Chemical shifts are relative to tetramethylsilane on δ-scale. Coupling constants are given in Hz and relative peak areas were in agreement with all assignments.

General procedure for the preparation of 2 and 2a.

1-(2-hydroxy-4-methoxy-phenyl)-ethanone (2a).

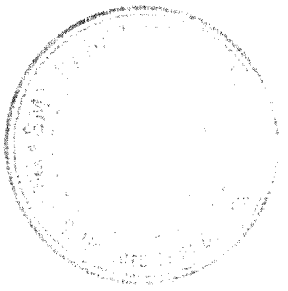
A mixture of 1-(2,4-dihydroxy-phenyl) ethanone **1a** (5g, 0.0328 moles), dimethyl sulfate (1.71 mL, 0.0180 moles) and anhydrous potassium carbonate (6.81g, 0.0492 moles) was refluxed in dry acetone (50 mL) for 18 hours. Excess acetone was distilled off and reaction mixture poured into ice water and solid collected by filtration. The crude product was purified by column chromatography using petroleum ether (60-80 °C): ethyl acetate eluent (8:2) to obtain white crystals (2.6g, 47.61 %) of 1-(2-hydroxy-4-methoxy-phenyl)-ethanone **2a**, mp 48 °C (lit. 48-50 °C).

Anal. Calcd. for $C_9H_{10}O_3$ (166.17): C, 65.05; H, 6.06. Found: C, 65.01; H, 5.98.

1-(2-hydroxy-4-methoxy-3-methyl-phenyl)-ethanone (2).

This compound was obtained as light brown crystals (ethanol), 80 % yield, mp 245 °C (lit. 252 °C).

Anal. Calcd. for $C_{10}H_{12}O_3$ (180.20): C, 66.65; H, 6.71. Found: C, 66.31; H, 6.38.



General procedure for the preparation of 3 and 3a.

4-hydroxy-7-methoxy-benzopyran-2[*H*]-one (3a).*

A solution of 1-(2-hydroxy-4-methoxy-phenyl)-ethanone **2a** (1g, 0.0060 moles) in diethyl carbonate (25 mL) was added slowly to pulverized sodium metal (1g, 0.02174 moles) under anhydrous conditions and stirred for 15 minutes.* It was gradually heated to reflux and maintained for 30 minutes. Reaction mixture was then cooled to room temperature and methanol added to decompose excess sodium metal. Reaction mixture was then poured into ice hydrochloric acid and solid collected by filtration was crystallized from acetonitrile to give white powder (0.52g, 44.96 %) of 4-hydroxy-7-methoxy-benzopyran-2[*H*]-one **3a**, mp 263 °C dec. [lit (13) 263-265 °C dec.]; IR (KBr): ν_{max}, cm^{-1}: 3433, 3083, 2978, 1712, 1606, 1560, 1511, 1470, 1288, 1271, 1238, 1119.

Anal. Calcd. for $C_{10}H_8O_4$ (192.16): C, 62.50; H, 4.19. Found: C, 62.14; H, 4.02.

4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one (3).

This compound was obtained as light brown crystals (acetonitrile), 48.5 % yield, mp 258-260 °C dec. (lit. 261 °C dec.); IR (KBr): ν_{max}, cm^{-1}: 3429, 3089, 2971, 1706, 1606, 1558, 1514, 1468, 1289, 1266, 1236, 1112; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz): δ 2.2 (s, 3H, C8-CH_3), 3.9 (s, 3H, C7-OCH_3), 5.6 (s, 1H, C3-H), 7.08-7.11 (d, J = 8.8 Hz, 1H, C6-H), 7.59-7.61 (d, J = 8.8 Hz, 1H, C5-H), 14.1 (s, 1H, C4-OH).

Anal. Calcd. for $C_{11}H_{10}O_4$ (206.196): C, 64.07; H, 4.88. Found: C, 63.71; H, 4.69.

General procedure for the preparation of 4, 4a, 5, 5a, 6 and 6a.

3-methoxy-4-methyl-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one (4).

A solution of 4-hydroxy-7-methoxy-8-methyl-benzopyran-2[*H*]-one **3** (0.5g, 0.00242 moles) and salicylalacetone (0.393g, 0.00242 moles) in dry pyridine (10

* Highly exothermic reaction.

mL) was refluxed for 22 hours. The reaction was monitored on tlc. It was then poured into ice hydrochloric acid and solid collected by filtration. The crude product was crystallized from ethanol to obtain white crystals (0.62g, 72.97 %) of 3-methoxy-4-methyl-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one **4**, mp 196-198 °C; IR (KBr): $\nu_{max,}$ cm^{-1}: 3036, 2993, 2941, 1704, 1628, 1500, 1482, 1456, 1382, 1349, 1281, 1257, 1216, 1175, 1118, 1082, 1030, 865, 772; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.98 (s, 3H, C4-CH_3), 2.19-2.23 (dd, $J_{vicinal}$ = 3.16 Hz and $J_{geminal}$ = 13.24 Hz, 1H, C7-CH_2CO-), 2.23 (s, 3H, -$COCH_3$), 2.27-2.31 (dd, $J_{vicinal}$ = 2.92 Hz and $J_{geminal}$ = 13.24 Hz, 1H, C7-CH_2CO-), 3.88 (s, 3H, C3-OCH_3), 4.26-4.28 (dd, $J_{vicinal}$ = 2.92 Hz and $J_{vicinal}$ = 3.16 Hz, 1H, C7-H), 6.76-6.78 (d, J = 8.8 Hz, 1H, C2-H), 6.85-6.91 (m, 2H, C8-H and C9-H), 7.08-7.13 (m, 1H, C10-H), 7.46-7.48 (dd, J = 1.4 Hz and J = 7.48 Hz, 1H, C11-H), 7.59-7.61 (d, J = 8.84 Hz, 1H, C1-H).

Anal. Calcd. for $C_{21}H_{18}O_5$ (350.36): C, 71.99; H, 5.17. Found: C, 71.84; H, 4.91.

3-methoxy-7-(2-oxo-propyl)-7*H*-benzopyrano[4,3-*b*]benzopyran-6-one (4a).
This compound was obtained as white crystals (ethanol), 76.2 % yield, mp 214-215 °C; IR (KBr): $\nu_{max,}$ cm^{-1}: 3030, 2995, 1701, 1632, 1501, 1460, 1380, 1356, 1259, 1212, 1175, 1122, 1033, 869, 771.

Anal. Calcd. for $C_{20}H_{16}O_5$ (336.34): C, 71.42; H, 4.79. Found: C, 71.22; H, 4.59.

4-hydroxy-7-methoxy-3-(3-oxo-1-phenyl-butyl)-benzopyran-2[*H*]-one (5a-open chain tautomer) OR 2-hydroxy-8-methoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one (7a-hemiketal tautomer).
This compound was obtained by column chromatographic purification using chloroform: methanol (9:1) eluent, as light brown crystals, 49.20 % yield, mp 228 °C; IR (KBr): $\nu_{max,}$ cm^{-1}: 3430, 1716, 1618, 1519, 1393, 1250, 1178, 1163, 1036.

Anal. Calcd. for $C_{20}H_{18}O_5$ (338.35): C, 70.99; H, 5.36. Found: C, 70.56; H, 5.21.

4-hydroxy-7-methoxy-8-methyl-3-(3-oxo-1-phenyl-butyl)-benzopyran-2[*H*]-one (5-open chain tautomer) OR 2-hydroxy-8-methoxy-2,7-dimethyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one (7-hemiketal tautomer).

This compound was obtained by column chromatographic purification using chloroform: methanol (9:1) eluent, as light brown crystals, 49.50 % yield, mp 170-171 °C; IR (KBr): $\nu_{max,}$ cm^{-1}: 3426, 1713, 1616, 1511, 1393, 1246, 1176, 1160, 1030; ^1H NMR ($(CD_3)_2SO$, 400 MHz): δ 1.60-1.67 (two singlets, 3H, C2-CH_3 resonance), 1.89-2.39 (m, 2H, -CH_2- resonance), 2.21 (s, 3H, C7-CH_3), 3.94-4.04 (m, 1H, -CH- resonance), 3.96 (s, 3H, C8-OCH_3), 7.12-7.14 (d, J = 8.8 Hz, 1H, C9-H), 7.18-7.39 (m, 5H, C4-phenyl protons), 7.71-7.73 (d, J = 8.8 Hz, 1H, C10-H), 11.50 (s, 1H, C2-OH).

Anal. Calcd. for $C_{21}H_{20}O_5$ (352.38): C, 71.57; H, 5.72. Found: C, 71.51; H, 5.59.

4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-benzopyran-2[*H*]-one (6a-open chain tautomer) OR 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2-methyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one (8a-hemiketal tautomer).

This compound was obtained by column chromatographic purification using chloroform: methanol (9:1) eluent, as light brown crystals, 43.48 % yield, mp 100-102 °C; IR (KBr): $\nu_{max,}$ cm^{-1}: 3319, 2960, 1692, 1613, 1570, 1494, 1458, 1382, 1291, 1244, 1239, 1121, 1077, 784; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.66-1.71 (two singlets, 3H, C2-CH_3 resonance), 2.28-2.54 (m, 2H, -CH_2- resonance in hemiketal tautomer), 3.23-3.76 (m, 2H, -CH_2- resonance in open chain tautomer), 3.76-3.88 (m, 12H, C8-OCH_3 and C4'-OCH_3 in hemiketal tautomer and C7-OCH_3 and C4'-OCH_3 in open chain tautomer), 4.09-4.11 (m, 1H, -CH- resonance in hemiketal tautomer), 4.22-4.23 (m, 1H, -CH- resonance in open chain tautomer), 6.70-6.89 (m, 6H, C7-H, C3'-H, C5'-H in hemiketal tautomer and C8-H, C3'-H, C5'-H in open chain tautomer), 7.13-7.21 (m, 6H, C9-H, C2'-H, C6'-H in hemiketal tautomer and C6-H, C2'-H, C6'-H in open chain tautomer), 7.69-7.71

(d, J = 8.76 Hz, 1H, C10-H in hemiketal tautomer), 7.77-7.79 (d, J = 8.72 Hz, 1H, C5-H in open chain tautomer).

Anal. Calcd. for $C_{21}H_{20}O_6$ (368.38): C, 68.46; H, 5.47. Found: C, 68.29; H, 5.19.

4-hydroxy-7-methoxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-8-methyl-benzopyran-2[*H*]-one (6-open chain tautomer) OR 2-hydroxy-8-methoxy-4-(4-methoxy-phenyl)-2,7-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]benzopyran-5[*H*]-one (8-hemiketal tautomer).

This compound was obtained by column chromatographic purification using chloroform: methanol (9:1) eluent, as light brown crystals, 46.85 % yield, mp 112-114 °C; IR (KBr): ν_{max}, cm^{-1}: 3317, 2955, 1690, 1613, 1572, 1499, 1454, 1377, 1290, 1265, 1246, 1234, 1120, 1072, 780; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz): δ 1.54-1.60 (two singlets, 3H, C2-CH_3 resonance), 1.83-2.30 (m, 2H, -CH_2- resonance), 2.15 (s, 3H, C7-CH_3), 3.71 (s, 3H, C4'-OCH_3), 3.90 (m, 4H, C8-OCH_3 and -CH- resonance), 6.77-6.79 (d, J = 8.4 Hz, 2H, C3'-H and C5'-H), 7.07-7.30 (m, 3H, C9-H, C2'-H and C6'-H), 7.65-7.67 (d, J = 8.8 Hz, 1H, C10-H), 11.39 (s, 1H, C2-OH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65-1.69 (two singlets, 3H, C2-CH_3 resonance), 1.96-2.54 (m, 2H, -CH_2- resonance in hemiketal tautomer), 2.24 (s, 3H, C7-CH_3 in hemiketal tautomer), 2.31 (s, 3H, C8-CH_3 in open chain tautomer), 3.22-3.26 (m, 2H, -CH_2- resonance in open chain tautomer), 3.76-3.93 (m, 12H, C8-OCH_3 and C4'-OCH_3 in hemiketal tautomer and C7-OCH_3 and C4'-OCH_3 in open chain tautomer), 4.07-4.12 (m, 1H, -CH- resonance in hemiketal tautomer), 4.23-4.24 (m, 1H, -CH- resonance in open chain tautomer), 6.79-6.86 (m, 4H, C3'-H and C5'-H in hemiketal tautomer and C3'-H and C5'-H in open chain tautomer), 7.13-7.23 (m, 6H, C9-H, C2'-H and C6'-H in hemiketal tautomer and C6-H, C2'-H and C6'-H in open chain tautomer), 7.63-7.71 (d, J = 8.76 Hz, 1H, C10-H in hemiketal tautomer), 7.70-7.72 (d, J = 8.76 Hz, 1H, C5-H in open chain tautomer).

Anal. Calcd. for $C_{22}H_{22}O_6$ (382.41): C, 69.09; H, 5.79. Found: C, 68.89; H, 5.55.

5.B.4 Conclusions

- The new warfarin derivatives synthesized exists in solution as three interconverting tautomeric structures. ^{1}H NMR studies of these compounds in deuteriochloroform shows the existence of all the three tautomeric structures, two of which are cyclic diastereomeric hemiketals, while the third one is the open chain intermediate form; whereas in deuteriodimethylsulfoxide only two diastereomeric hemiketal forms are observed. The methyl (C2-CH_3) proton resonance for the major hemiketal tautomer appears down field from that for the minor hemiketal tautomer when the ^{1}H NMR is recorded in deuteriodimethylsulfoxide; whereas in deuteriochloroform, the methyl (C2-CH_3) proton resonance for the major hemiketal tautomer appears up field. This shows that the percentage of two cyclic diastereomeric hemiketals varies with the solvent used.

- The Michael condensation product of 8-substituted 4-hydroxy-7-methoxy-benzopyran-2[*H*]-one and benzalacetone or anisalacetone is a δ-hydroxy ketone but when salicylalacetone is used, the Michael product undergoes spontaneous dehydration to give alkali insoluble cyclic compound **(4, 4a)**.

- The compounds synthesized could be explored for possible anti-coagulant properties.

5.B.5 References

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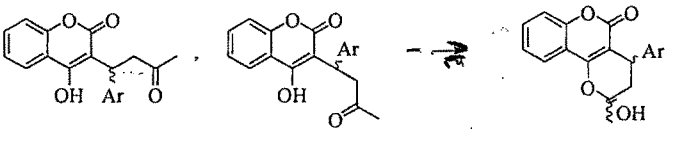
Chapter 5: Section C

SYNTHESIS OF NEW WARFARINS VIA HETERO-DIELS-ALDER CYCLOADDITION

5.C.1 Introduction

Warfarins today dominate coumarin anticoagulant owing to its excellent potency and good pharmacokinetic profile. Coumadin – a sodium salt of warfarin is available in the market. Coumachlor and acenocoumarol are the other well-known derivatives belonging to the same class. Some common clinical uses of warfarin are fibrillation, artificial heart valves, deep venous thrombosis and pulmonary embolism.[1] Warfarins have also been used as rodenticides.

Most of the study shows the synthesis of warfarins by Michael condensation of 4-hydroxy coumarins with α, β – unsaturated ketones.[2] Depending upon the conditions used the product obtained is a mixture of normal condensation product and cyclic ketal or cyclic dehydrated product.[3] Number of modifications using catalyst has been reported.[4] We have already studied tautomerism of new warfarins in Chapter 5: Section B and proved from NMR studies, that in solutions, warfarin exists in three interconverting tautomeric structures, two of which are cyclic diastereomeric hemiketals, while the third one is the open chain intermediate form as shown in **Figure 1**.



Open chain Cyclic diastereomeric hemiketals

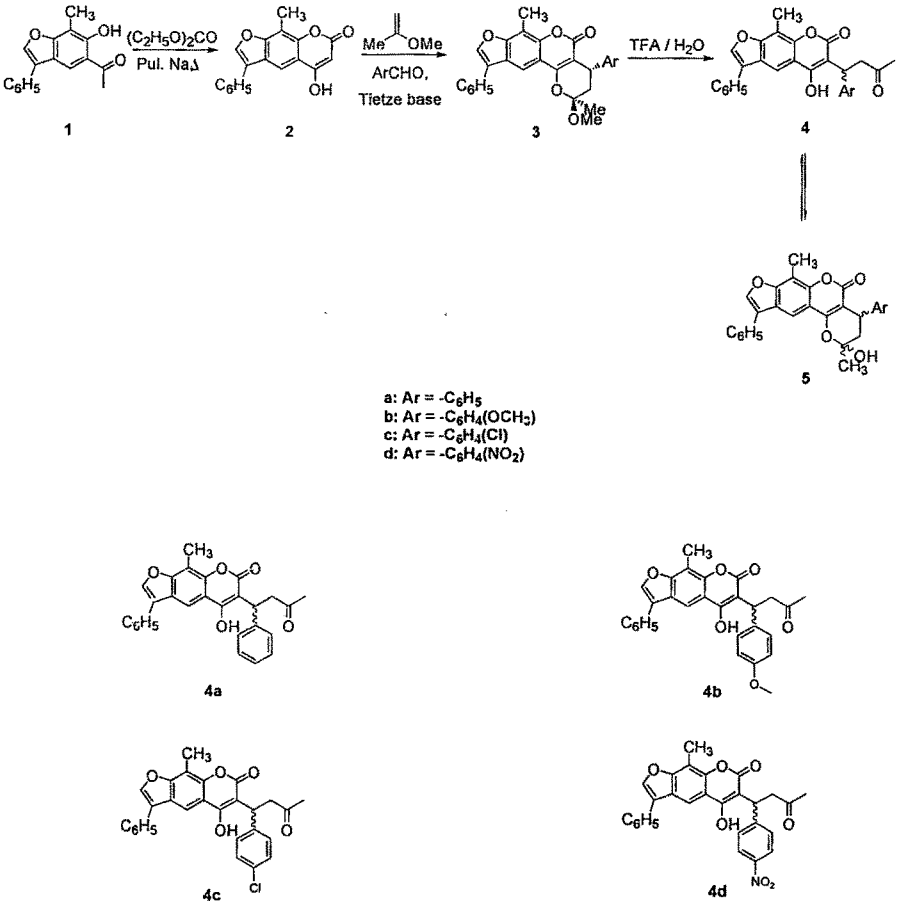
Figure 1: Tautomers of Warfarin.

Literature reveals not much of the work is documented for the synthesis of warfarins via Hetero Diels Alder (HDA) cycloaddition except as reported by Giancarlo Cravotto *et al.*[5] Moreover, no reports have been found for the synthesis

of furowarfarins. Benzo[*c*]furans are susceptible to Diels-Alder reaction, so it was thought of to start with Benzo[*b*]furan.

The present investigation reports the synthesis of a new class of furowarfarins via tandem Knoevenagel-hetero-Diels-Alder cycloaddition reaction, which could be explored further for anticoagulant properties.

The reaction sequence for different title compounds is outlined in **Scheme 1**.



Scheme 1: Synthesis of warfarin derivatives via HDA cycloaddition reaction.

5.C.2 Results and Discussion

1-(6-Hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-ethanone **1**,[6] on reaction with diethyl carbonate and pulverized sodium gave 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2**.[7] The ^{1}H NMR **(Figure 2)** of this compound showed singlets at δ 5.74 ppm and δ 11.84 ppm for C6-H and C5-OH (enolic) protons respectively, which confirmed the structure. Other signals observed were, δ 2.60 (s, 3H, C9-CH_3), 7.38-7.42 (m, 1H, C4'-H), 7.48-7.52 (m, 2H, C3'-H and C5'-H), 7.65-7.68 (m, 2H, C2'-H and C6'-H), 7.92 (s, 1H, C2-H) and 8.15 (s, 1H, C4-H). In the LCMS, the molecular ion peak was observed at 293.1 *m/z*, amu with maximum abundance **(Figure 3)**. The O-H stretching vibration in the IR spectrum **(Figure 4)** was observed at 3430 cm^{-1} (*m*) whereas, a band at 1664 cm^{-1} (*s*) contributed to the >C=O stretching of the lactone ring.

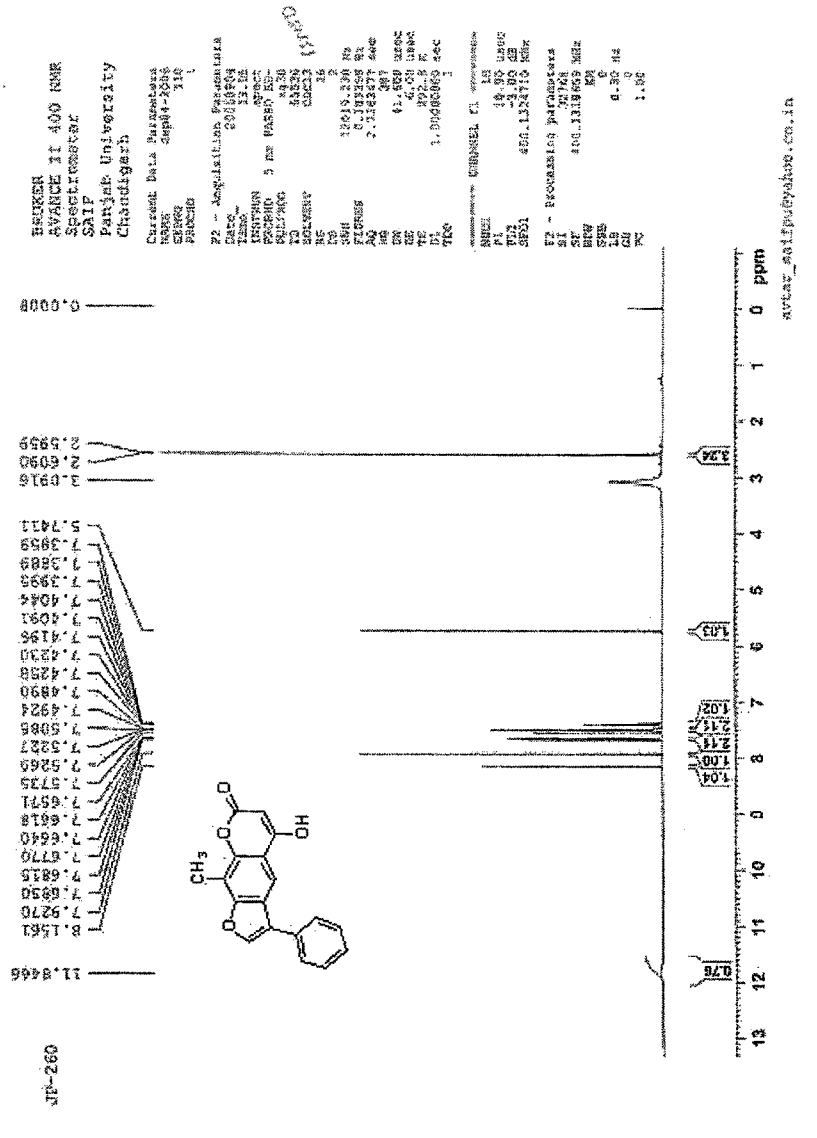


Figure 2: ^{1}H NMR of compound 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2**.

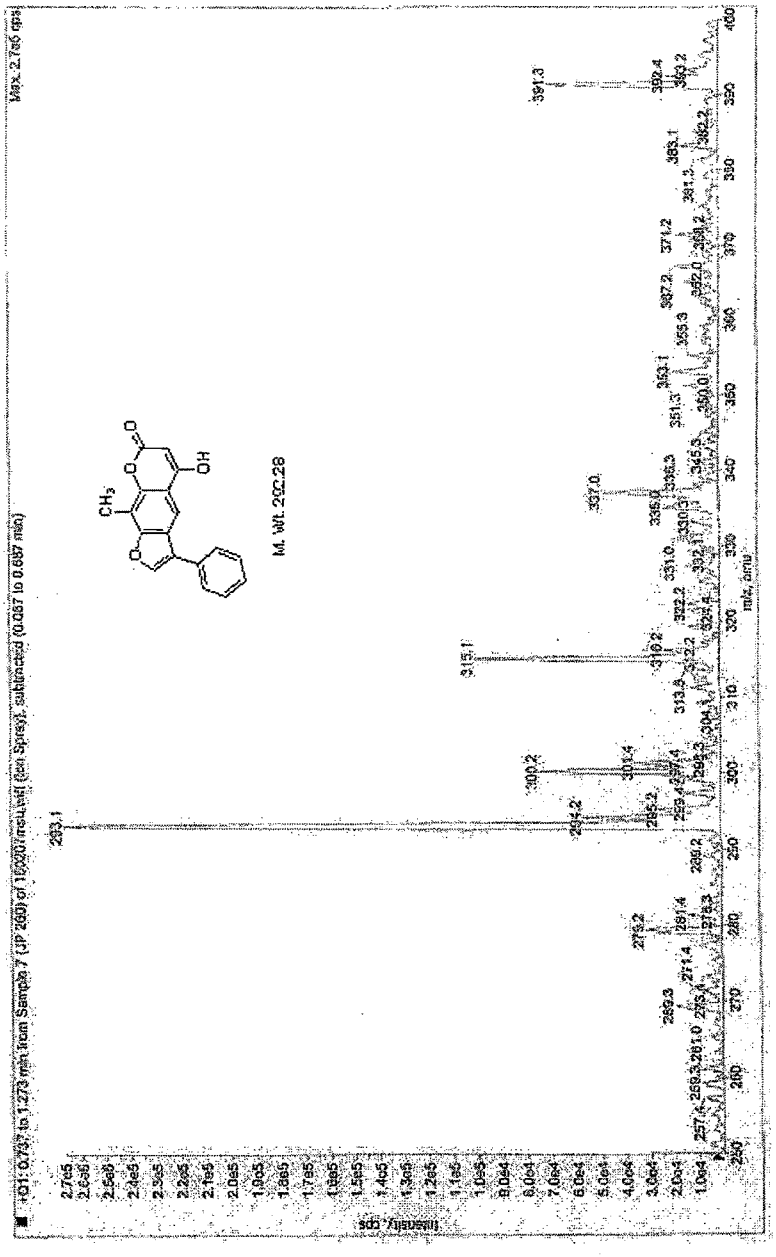


Figure 3: LCMS of compound 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2**.

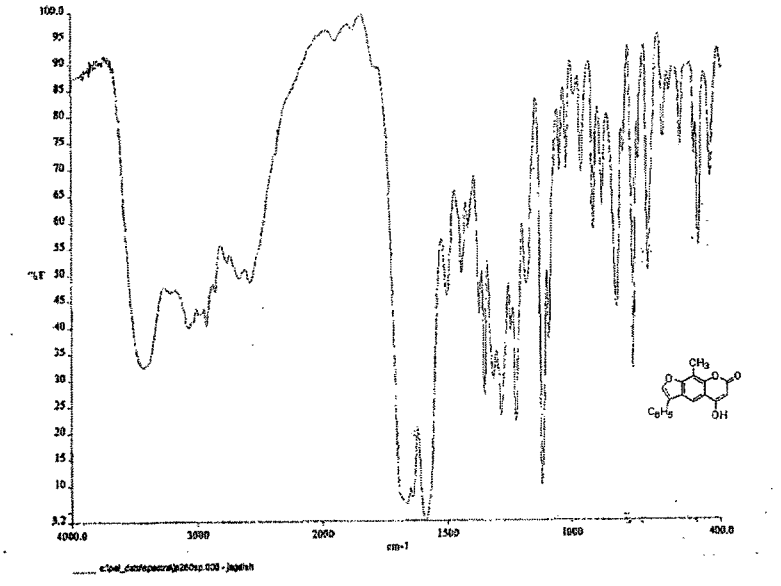
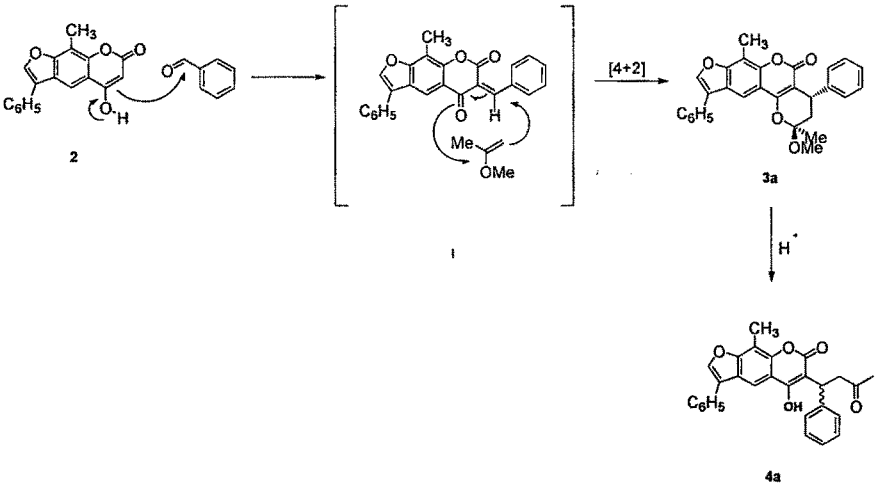


Figure 4: IR of compound 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2**.



Scheme 2: Probable mechanism for the formation of warfarin derivatives.

Compound 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2** when subjected to one-pot multicomponent reaction with benzaldehyde and 2-methoxy propene in dry dioxane (85-90 °C, 6 h, screw cap pressure tube) in the presence of catalytic ethylenediammonium diacetate (Tietze base) and powdered oven-dried 5 Å molecular sieves, gave 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a**. The *in situ* generated 3-arylidene-2,4-chromanedione (I) derived from the Knoevenagel condensation of 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2** with benzaldehyde, undergoes HDA cycloaddition with 2-methoxy propene to give 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one **3a** as shown in **Scheme 2**. Heterodienes (3-arylidene-2,4-chromanedione) are electron-deficient 4π-systems that may undergo inverse-electron-demand Diels-Alder reactions with suitable electron-rich 2π-systems such as enol ethers dienophiles. These are usually concerted non-synchronous transformations that preserve the configuration of the dienophile and usually exhibit high regioselectivity. Based on previous results, it was assumed that the reaction proceeds with *endo (cis)* – selectivity.[5] The product was purified by column chromatography using neutral alumina powder, since the ketals are susceptible to acidic silica. The ^{1}H NMR **(Figure 5)** of **3a** showed a singlet at δ 1.71 ppm for C2-CH_3 and a singlet at δ 3.33 ppm for C2-OCH_3. Double doublets at δ 1.96-2.03 ppm ($J_{vicinal}$ = 11.76 Hz, $J_{geminal}$ = 13.96 Hz) and δ 2.47-2.52 ppm ($J_{vicinal}$ = 7 Hz, $J_{geminal}$ = 14 Hz) both corresponding to one proton each indicated C3-H_A and C3-H_B protons respectively. Whereas, a double doublet at δ 4.08-4.12 ppm ($J_{vicinal}$ = 7 Hz, $J_{vicinal}$ = 11.72 Hz) again corresponding to one proton indicated C4-H proton thus forming an ABX system. The ^{1}H NMR obtained was of the pure compound, but it could not be concluded, whether the cycloadduct formed was *cis* or *trans* isomer.

However, when the single crystal X-ray analysis of compound **3a** was carried out, it was observed that the cycloadduct exists in *trans* configuration. This was contradictory to the results obtained by Giancarlo Cravotto *et al.* which had no X-

ray data.[5] Thus it can be concluded that the reaction proceeds with good diastereoselectivity favouring the *exo* (*trans*) isomer. The C2-OMe group is ψ – axial and C4-phenyl ring is ψ – equatorial in all the cases. The ratio of isomers in the crude product could not be concluded since the difference in rf values for both the isomers was very less and moreover, other isomer being minor, separation was extremely difficult. HPLC of the crude product could not be done because of limitations. The ^{1}H NMR of the crude compound **3a (Figure 6)**, also could not reflect much on the isomer ratios.

The results of the single crystal X-ray diffraction analysis have been discussed latter.

Thus it can be concluded that the reaction proceeds with good distereoselectivity favoring exo (trans) isomer due to anomeric effect, which always places exocyclic acetal oxygen in axial position in chair like conformation and phenyl ring at equatorial position.

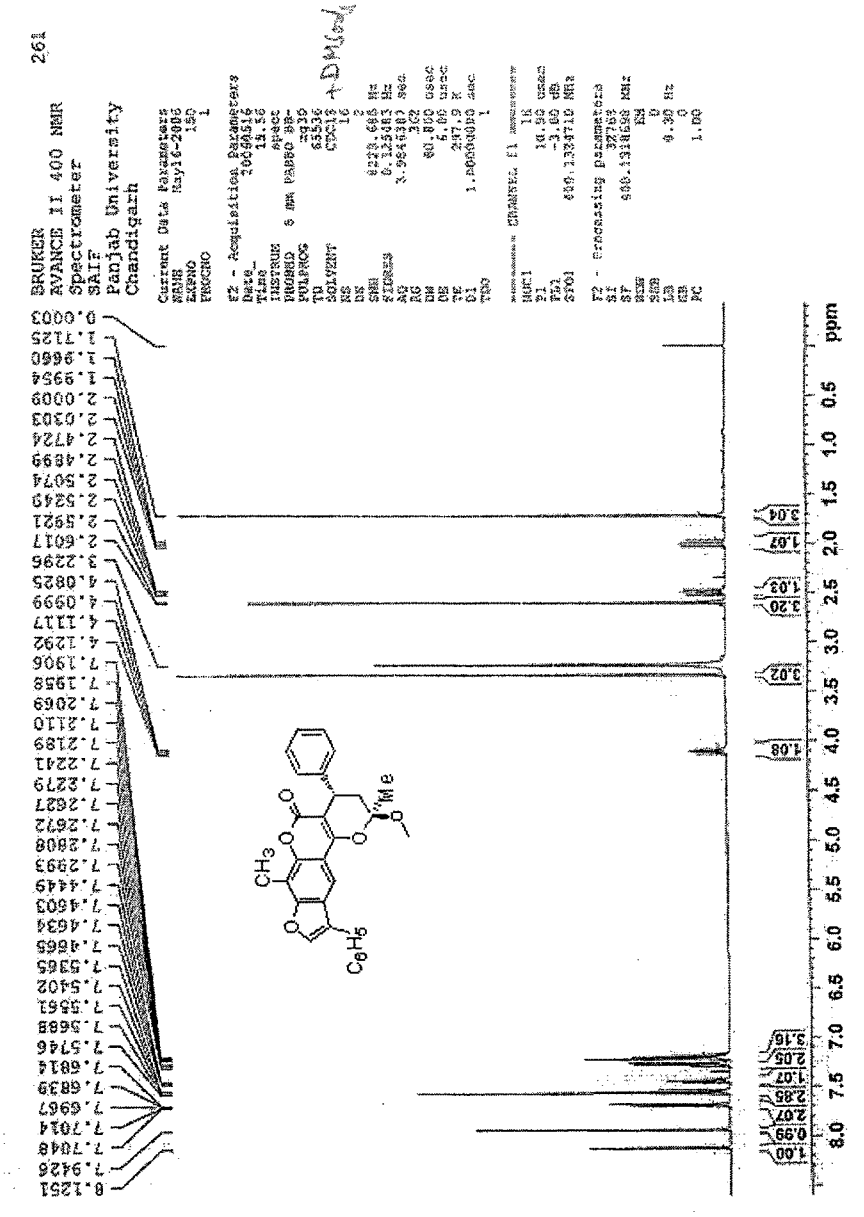


Figure 5: ^{1}H NMR of compound 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a**. Contd.

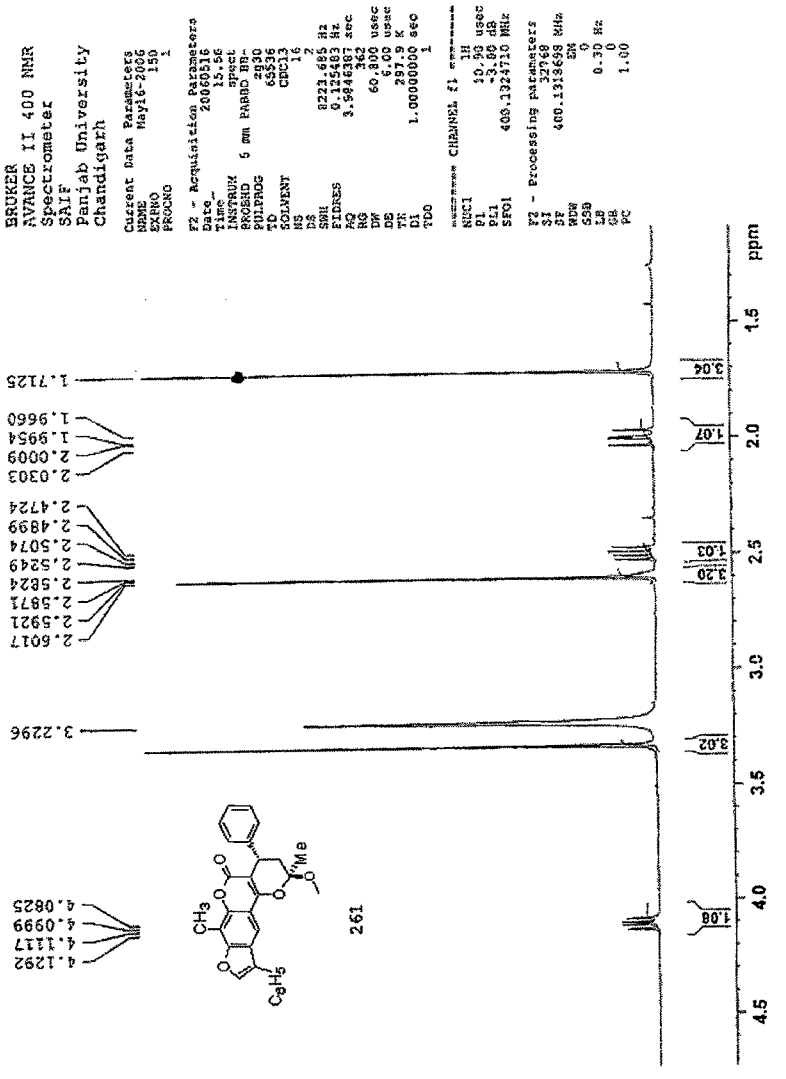


Figure 5: ^{1}H NMR of compound 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a**.

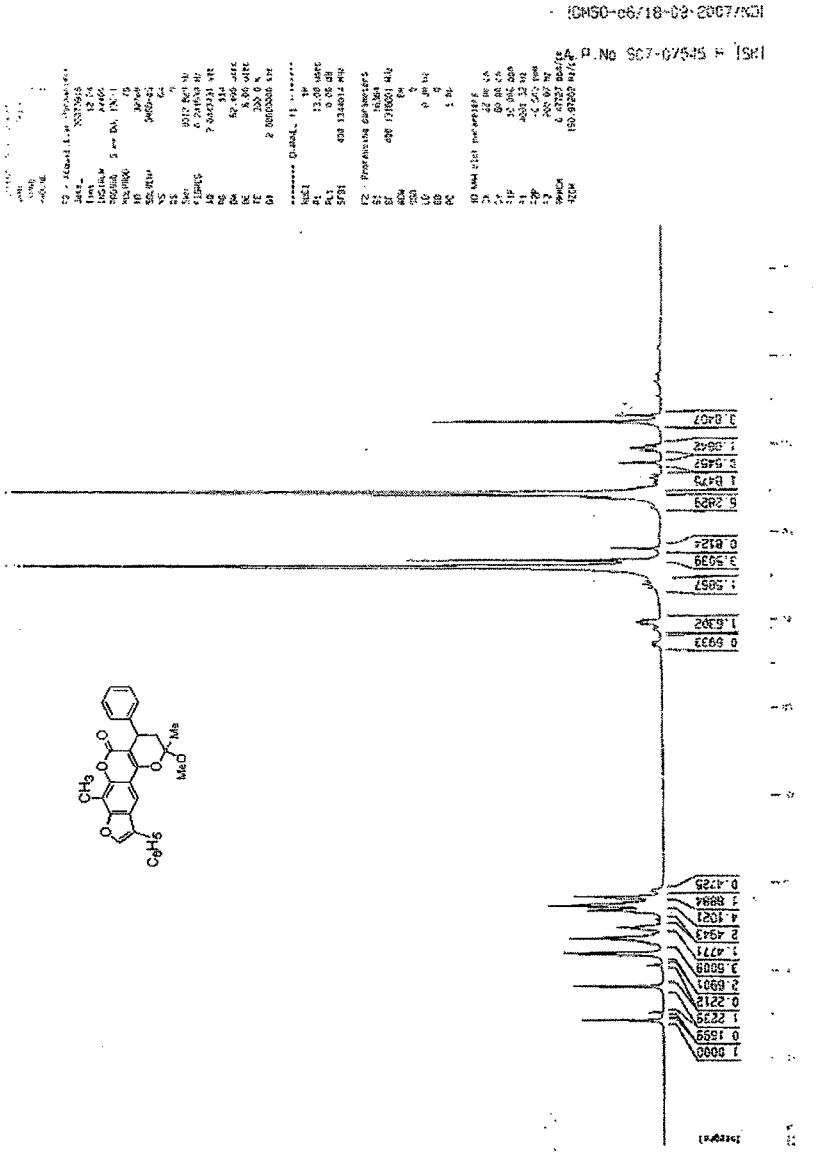


Figure 6: ^{1}H NMR of compound (crude) 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a.**

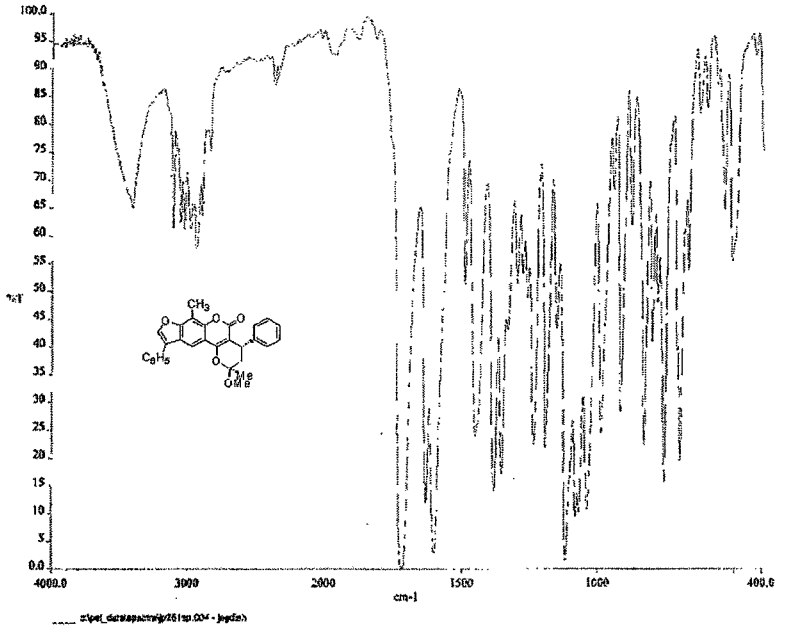


Figure 7: IR of compound 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a**.

The unmasking of the carbonyl function in **3a** was carried out using trifluoro acetic acid / water, which gave 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one **4a**.

The ^{1}H NMR **(Figure 8)** was obtained as a highly complicated spectrum because of their existence in solution as an equilibrium mixture of open-chain keto tautomer - 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one **4a** and two diastereomeric cyclic hemiketal tautomers - 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **5a**.[8] The hydrolysis product is a δ-hydroxy ketone and can therefore undergo ring closure to cyclic hemiketal. The LCMS **(Figure 9)** of **4a** showed a molecular ion peak at 439.2 *m/z*, amu with maximum abundance, which confirmed the structure.

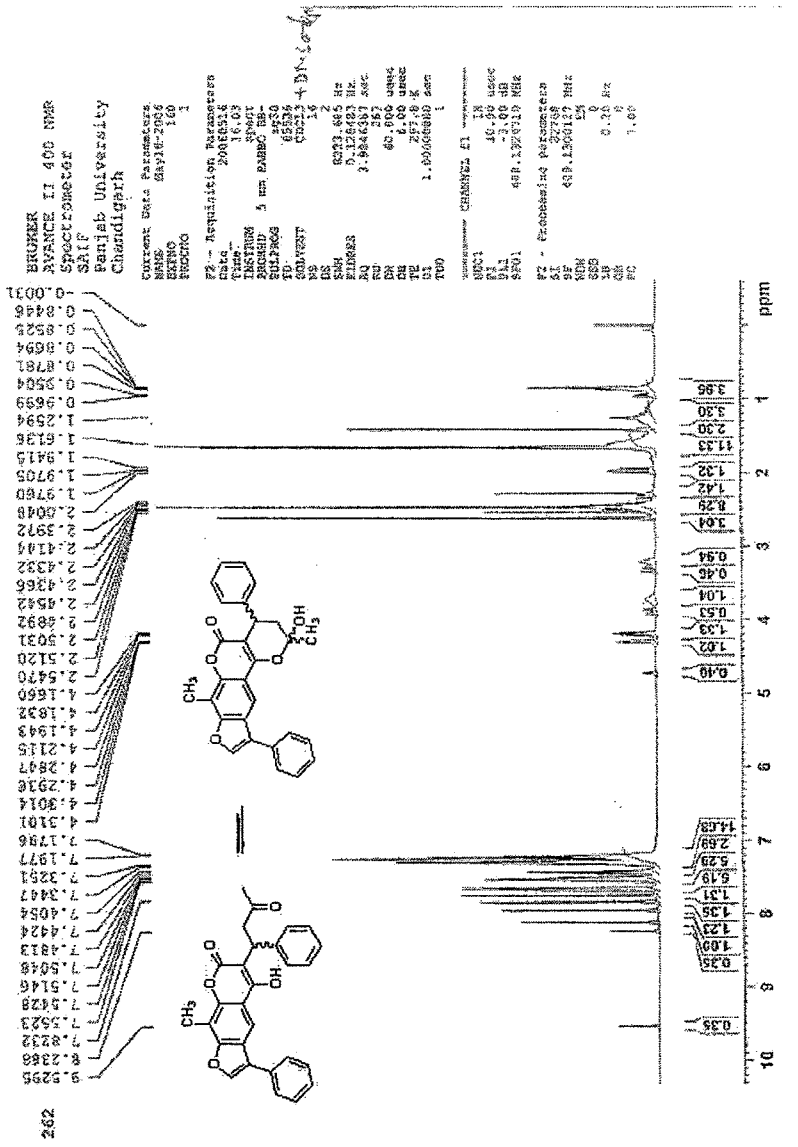


Figure 8: ^{1}H NMR of open-chain keto tautomer - 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one **4a** and diastereomeric cyclic hemiketal tautomer - 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2H-1,6,8-trioxa-cyclopenta[b]phenanthren-5-one **5a**.

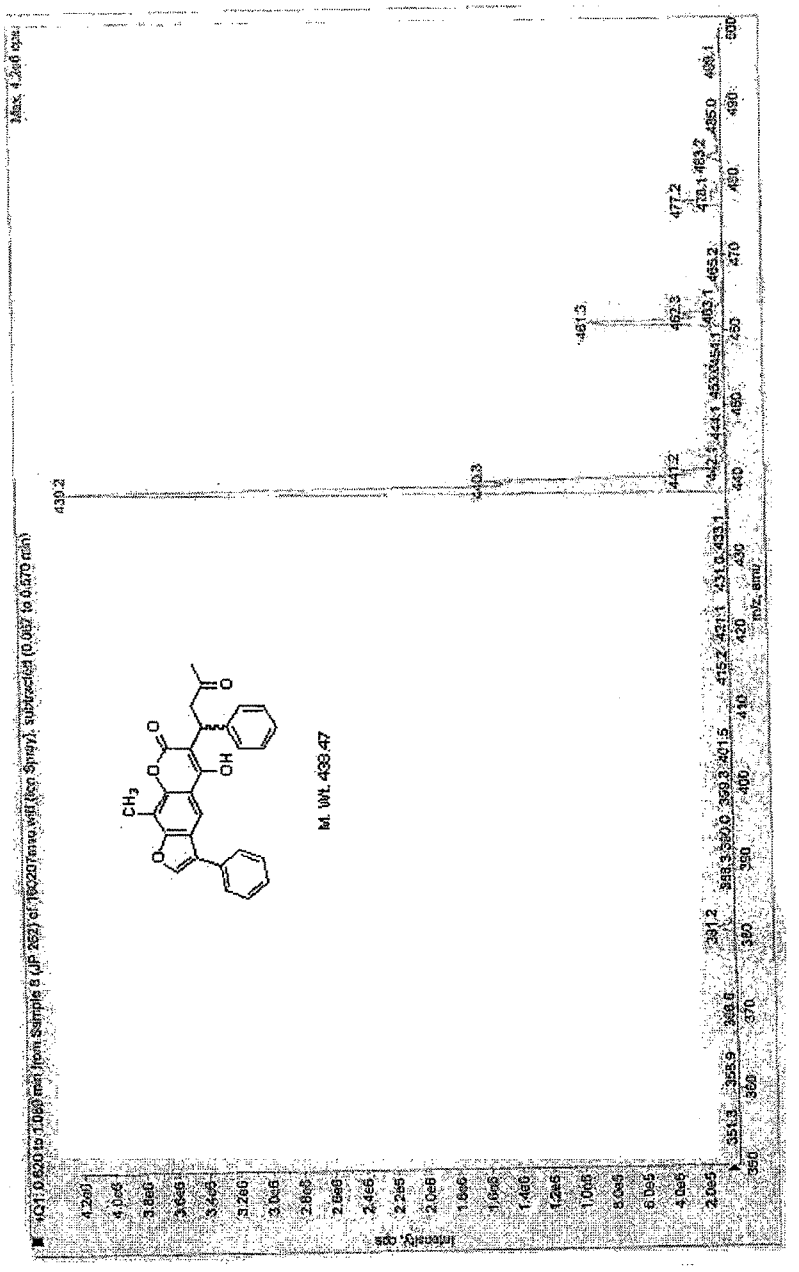


Figure 9: LCMS of compound 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one **4a**.

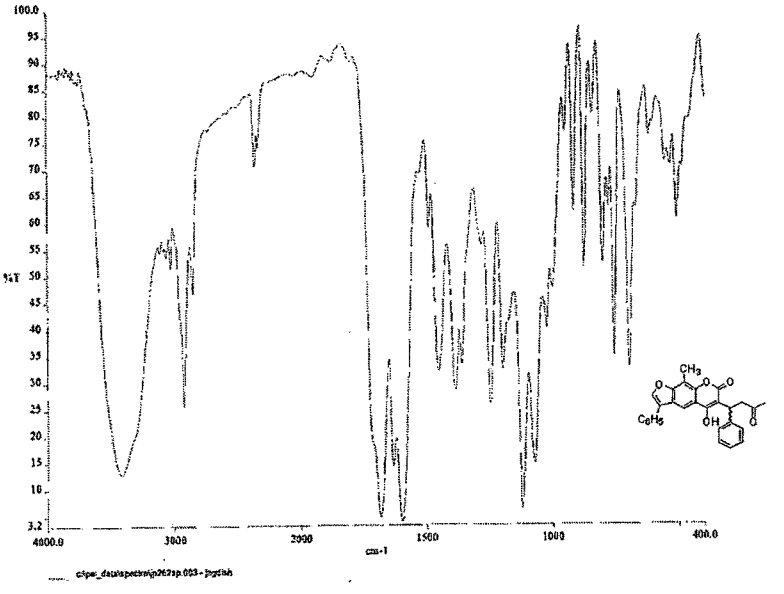


Figure 10: IR of compound 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one **4a**.

Similar observations were recorded using *p*-anisaldehyde, *p*-chloro benzaldehyde and *p*-nitro benzaldehyde. Cycloadducts **3b**, **3c** and **3d** were subjected to hydrolysis without any purification.

The structures of all the compounds have been established on the basis of their elemental analyses and spectral data (IR, NMR and LCMS).

Crystal Structure of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one 3a.

Compound **3a** crystallizes in a centro symmetric monoclinic space group $P2_1/n$. **Figure 11** shows the ORTEP diagram with atom numbering scheme (40% probability factor for the thermal ellipsoids). **Figure 12** shows the crystal structure of **3a**; whereas the packing structure can be seen in **Figure 13** generated by using Mercury 1.4.2 software.[9] The asymmetric unit consists of a single molecule at a normal position. As can be seen from these figures, the C9-OMe group is ψ-axial in a half-chair conformation with respect to C7-phenyl ring, which is ψ-equatorial. This configuration corresponds to *exo* (*trans*) isomer of the cycloadduct **3a**. The torsion angle, -56.63 for O5/C9/C8/C7 and165.15 for C6/C7/C8/C9 shows the *exo* configuration. Further torsion angle, -43.81 for C6/C7/C8/$H8_A$ and -177.99 for O5/C9/C8/$H8_A$ supports the existence of C7 - phenyl ring in equatorial position, with C9 – OMe group axial. The crystal structure shows the (*S*)-configuration at C-7 and C-9 for the molecule. All the atoms apart from C-9 are coplanar. Atom C9 deviates from the plane formed by C7/C8/O1/C10/C11 by 0.630 Å.

The values of final R indices R1 = 0.0800, wR2 = 0.1670 indicates the crystal structure is well resolved.

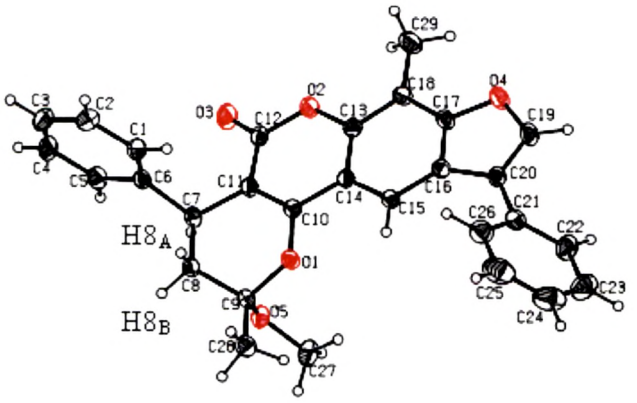


Figure11: ORTEP diagram of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a** with atom numbering scheme (40% probability factor for the thermal ellipsoids).

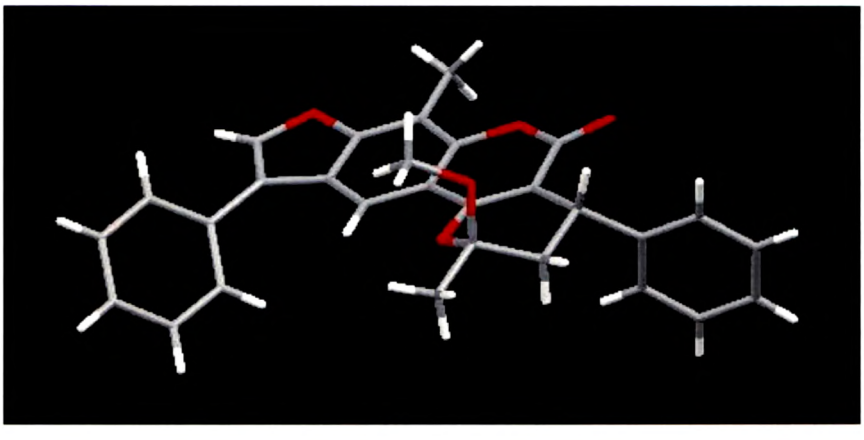


Figure 12: Crystal structure of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a**.

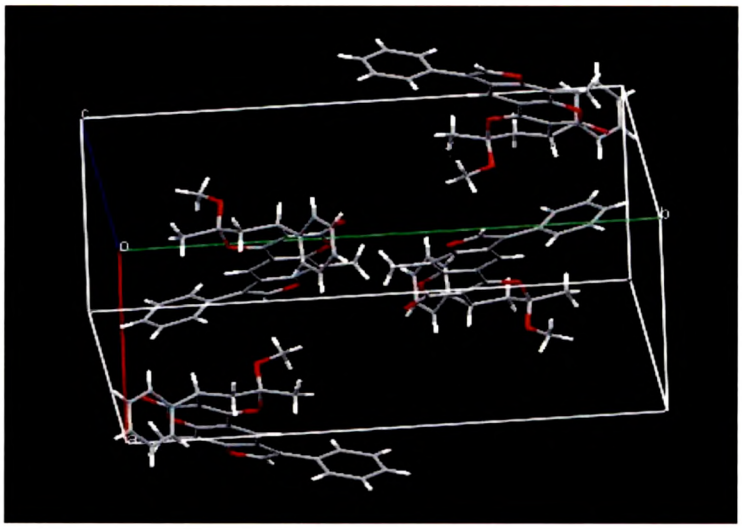
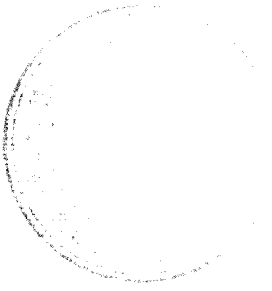


Figure 13: Packing structure of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a**.

Table 1: Crystal data and structure refinement.

Identification code	2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one
Empirical formula	C29 H24 O5
Formula weight	452.48
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 9.9765(13) A,



	alpha = 90 deg. b = 21.684(3) A, beta = 106.461(2) deg. c = 11.0838(15) A, gamma = 90 deg.
Volume	2299.5(5) A^3
Z	4
Density (calculated)	1.307 Mg/m^3
Absorption coefficient	0.089 mm^-1
F(000)	952
Crystal size	0.80 x 0.30 x 0.05 mm
Theta range for data collection	1.88 to 27.50 deg.
Index ranges	-12<=h<=12, -24<=k<=28, -10<=l<=14
Reflections collected	13548
Independent reflections	5197 [R(int) = 0.0300]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9956 and 0.9323
Refinement method	Full-matrix least-squares On F^2
Data / restraints / parameters	5197 / 0 / 310
Goodness-of-fit on F^2	1.221
Final R indices [I>2sigma(I)]	R1 = 0.0800, wR2 = 0.1670
R indices (all data)	R1 = 0.0963, wR2 = 0.1747
Largest diff. peak and hole	0.254 and -0.250 e.A^-3

Table 2: Atomic coordinates (x 10^4) and equivalent Isotropic displacement parameters (A^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4707(2)	2436(1)	6461(2)	35(1)
O(2)	3873(2)	4193(1)	5033(2)	42(1)
O(3)	3987(2)	4567(1)	6897(2)	52(1)
O(5)	3155(2)	2391(1)	7683(2)	37(1)
O(4)	2968(2)	3360(1)	914(2)	45(1)
C(1)	7297(3)	3922(1)	8774(2)	42(1)
C(2)	8364(3)	4271(1)	9529(3)	52(1)
C(3)	8153(3)	4599(1)	10517(3)	55(1)
C(4)	6875(3)	4585(1)	10744(3)	53(1)
C(5)	5802(3)	4231(1)	9990(2)	42(1)
C(6)	6011(3)	3891(1)	9006(2)	34(1)
C(7)	4886(2)	3447(1)	8260(2)	34(1)
C(8)	5386(2)	2787(1)	8619(2)	34(1)
C(9)	4559(2)	2312(1)	7718(2)	31(1)
C(10)	4507(2)	3029(1)	6068(2)	31(1)
C(11)	4560(2)	3516(1)	6851(2)	32(1)
C(12)	4138(3)	4119(1)	6315(2)	37(1)
C(13)	3882(2)	3704(1)	4238(2)	33(1)
C(14)	4207(2)	3108(1)	4717(2)	31(1)
C(15)	4191(2)	2616(1)	3897(2)	32(1)
C(16)	3796(2)	2737(1)	2612(2)	32(1)
C(17)	3433(2)	3338(1)	2201(2)	35(1)
C(18)	3488(3)	3846(1)	2961(2)	36(1)
C(19)	3056(3)	2764(1)	521(2)	43(1)
C(20)	3556(2)	2369(1)	1471(2)	35(1)
C(21)	3857(3)	1710(1)	1354(2)	40(1)
C(22)	2912(3)	1330(1)	521(3)	55(1)
C(23)	3219(5)	716(2)	406(4)	80(1)
C(24)	4477(6)	478(2)	1117(4)	85(1)
C(25)	5426(5)	852(2)	1926(4)	77(1)
C(26)	5122(3)	1461(1)	2056(3)	55(1)
C(27)	2208(3)	1941(1)	6986(3)	51(1)
C(28)	5094(3)	1665(1)	8023(3)	42(1)
C(29)	3082(3)	4481(1)	2453(3)	54(1)

Symmetry transformations used to generate equivalent atoms.

Table 3: Bond lengths [A] and angles [deg].

O(1)-C(10)	1.354(3)
O(1)-C(9)	1.466(3)
O(2)-C(13)	1.379(3)
O(2)-C(12)	1.379(3)
O(3)-C(12)	1.200(3)
O(5)-C(9)	1.402(3)
O(5)-C(27)	1.425(3)
O(4)-C(17)	1.370(3)
O(4)-C(19)	1.375(3)
C(1)-C(6)	1.380(3)
C(1)-C(2)	1.380(4)
C(1)-H(1)	0.9300
C(2)-C(3)	1.371(4)
C(2)-H(2)	0.9300
C(3)-C(4)	1.368(4)
C(3)-H(3)	0.9300
C(4)-C(5)	1.387(4)
C(4)-H(4)	0.9300
C(5)-C(6)	1.381(3)
C(5)-H(5)	0.9300
C(6)-C(7)	1.532(3)
C(7)-C(11)	1.509(3)
C(7)-C(8)	1.529(3)
C(7)-H(7)	0.9800
C(8)-C(9)	1.508(3)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-C(28)	1.504(3)
C(10)-C(11)	1.359(3)
C(10)-C(14)	1.452(3)
C(11)-C(12)	1.447(3)
C(13)-C(18)	1.392(3)
C(13)-C(14)	1.400(3)
C(14)-C(15)	1.398(3)
C(15)-C(16)	1.391(3)
C(15)-H(15)	0.9300
C(16)-C(17)	1.393(3)
C(16)-C(20)	1.457(3)

C(17)-C(18)	1.379(3)
C(18)-C(29)	1.499(4)
C(19)-C(20)	1.339(4)
C(19)-H(19)	0.9300
C(20)-C(21)	1.472(4)
C(21)-C(22)	1.389(4)
C(21)-C(26)	1.390(4)
C(22)-C(23)	1.379(5)
C(22)-H(22)	0.9300
C(23)-C(24)	1.379(6)
C(23)-H(23)	0.9300
C(24)-C(25)	1.370(6)
C(24)-H(24)	0.9300
C(25)-C(26)	1.372(4)
C(25)-H(25)	0.9300
C(26)-H(26)	0.9300
C(27)-H(27A)	0.9600
C(27)-H(27B)	0.9600
C(27)-H(27C)	0.9600
C(28)-H(28A)	0.9600
C(28)-H(28B)	0.9600
C(28)-H(28C)	0.9600
C(29)-H(29A)	0.9600
C(29)-H(29B)	0.9600
C(29)-H(29C)	0.9600

C(10)-O(1)-C(9)	115.80(17)
C(13)-O(2)-C(12)	122.32(19)
C(9)-O(5)-C(27)	115.78(19)
C(17)-O(4)-C(19)	105.26(19)
C(6)-C(1)-C(2)	120.8(2)
C(6)-C(1)-H(1)	119.6
C(2)-C(1)-H(1)	119.6
C(3)-C(2)-C(1)	120.1(3)
C(3)-C(2)-H(2)	119.9
C(1)-C(2)-H(2)	119.9
C(4)-C(3)-C(2)	119.9(3)
C(4)-C(3)-H(3)	120.1
C(2)-C(3)-H(3)	120.1
C(3)-C(4)-C(5)	120.1(3)
C(3)-C(4)-H(4)	120.0
C(5)-C(4)-H(4)	120.0
C(6)-C(5)-C(4)	120.5(3)
C(6)-C(5)-H(5)	119.7
C(4)-C(5)-H(5)	119.7

C(1)-C(6)-C(5)	118.5(2)
C(1)-C(6)-C(7)	120.5(2)
C(5)-C(6)-C(7)	120.8(2)
C(11)-C(7)-C(8)	108.78(18)
C(11)-C(7)-C(6)	113.91(19)
C(8)-C(7)-C(6)	108.20(19)
C(11)-C(7)-H(7)	108.6
C(8)-C(7)-H(7)	108.6
C(6)-C(7)-H(7)	108.6
C(9)-C(8)-C(7)	112.94(19)
C(9)-C(8)-H(8A)	109.0
C(7)-C(8)-H(8A)	109.0
C(9)-C(8)-H(8B)	109.0
C(7)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
O(5)-C(9)-O(1)	108.65(17)
O(5)-C(9)-C(28)	114.1(2)
O(1)-C(9)-C(28)	105.07(18)
O(5)-C(9)-C(8)	106.80(18)
O(1)-C(9)-C(8)	108.69(18)
C(28)-C(9)-C(8)	113.3(2)
O(1)-C(10)-C(11)	123.9(2)
O(1)-C(10)-C(14)	114.37(19)
C(11)-C(10)-C(14)	121.8(2)
C(10)-C(11)-C(12)	119.0(2)
C(10)-C(11)-C(7)	122.7(2)
C(12)-C(11)-C(7)	117.9(2)
O(3)-C(12)-O(2)	116.3(2)
O(3)-C(12)-C(11)	125.3(2)
O(2)-C(12)-C(11)	118.5(2)
O(2)-C(13)-C(18)	115.4(2)
O(2)-C(13)-C(14)	120.7(2)
C(18)-C(13)-C(14)	123.9(2)
C(15)-C(14)-C(13)	120.0(2)
C(15)-C(14)-C(10)	122.8(2)
C(13)-C(14)-C(10)	117.2(2)
C(16)-C(15)-C(14)	118.0(2)
C(16)-C(15)-H(15)	121.0
C(14)-C(15)-H(15)	121.0
C(15)-C(16)-C(17)	118.9(2)
C(15)-C(16)-C(20)	135.6(2)
C(17)-C(16)-C(20)	105.4(2)
O(4)-C(17)-C(18)	123.4(2)
O(4)-C(17)-C(16)	110.7(2)
C(18)-C(17)-C(16)	125.9(2)

C(17)-C(18)-C(13)	113.3(2)
C(17)-C(18)-C(29)	123.0(2)
C(13)-C(18)-C(29)	123.6(2)
C(20)-C(19)-O(4)	113.3(2)
C(20)-C(19)-H(19)	123.3
O(4)-C(19)-H(19)	123.3
C(19)-C(20)-C(16)	105.3(2)
C(19)-C(20)-C(21)	126.2(2)
C(16)-C(20)-C(21)	128.4(2)
C(22)-C(21)-C(26)	118.6(3)
C(22)-C(21)-C(20)	121.2(3)
C(26)-C(21)-C(20)	120.2(2)
C(23)-C(22)-C(21)	120.5(3)
C(23)-C(22)-H(22)	119.7
C(21)-C(22)-H(22)	119.7
C(22)-C(23)-C(24)	119.9(4)
C(22)-C(23)-H(23)	120.0
C(24)-C(23)-H(23)	120.0
C(25)-C(24)-C(23)	120.0(3)
C(25)-C(24)-H(24)	120.0
C(23)-C(24)-H(24)	120.0
C(24)-C(25)-C(26)	120.4(4)
C(24)-C(25)-H(25)	119.8
C(26)-C(25)-H(25)	119.8
C(25)-C(26)-C(21)	120.5(3)
C(25)-C(26)-H(26)	119.7
C(21)-C(26)-H(26)	119.7
O(5)-C(27)-H(27A)	109.5
O(5)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
O(5)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(9)-C(28)-H(28A)	109.5
C(9)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(9)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(18)-C(29)-H(29A)	109.5
C(18)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(18)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5

Symmetry transformations used to generate equivalent atoms.

Table 4: Anisotropic displacement parameters (A^2 x 10^3).

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	48(1)	30(1)	29(1)	0(1)	15(1)	3(1)
O(2)	63(1)	30(1)	32(1)	-1(1)	9(1)	2(1)
O(3)	76(1)	37(1)	40(1)	-11(1)	10(1)	10(1)
O(5)	34(1)	43(1)	34(1)	-7(1)	9(1)	-1(1)
O(4)	59(1)	49(1)	27(1)	2(1)	14(1)	4(1)
C(1)	52(2)	41(1)	35(1)	-6(1)	15(1)	-2(1)
C(2)	53(2)	47(2)	55(2)	0(1)	11(1)	-12(1)
C(3)	66(2)	38(2)	51(2)	-6(1)	-1(2)	-9(1)
C(4)	81(2)	37(2)	36(2)	-14(1)	8(2)	2(1)
C(5)	54(2)	38(1)	35(1)	-5(1)	12(1)	9(1)
C(6)	45(1)	30(1)	26(1)	-2(1)	7(1)	3(1)
C(7)	37(1)	38(1)	26(1)	-4(1)	9(1)	2(1)
C(8)	35(1)	39(1)	26(1)	0(1)	5(1)	-1(1)
C(9)	32(1)	37(1)	24(1)	2(1)	8(1)	2(1)
C(10)	33(1)	32(1)	28(1)	0(1)	10(1)	0(1)
C(11)	35(1)	34(1)	26(1)	-3(1)	7(1)	0(1)
C(12)	43(1)	35(1)	31(1)	-5(1)	6(1)	-2(1)
C(13)	36(1)	31(1)	33(1)	-3(1)	13(1)	-2(1)
C(14)	31(1)	34(1)	28(1)	-2(1)	8(1)	-2(1)
C(15)	37(1)	31(1)	29(1)	-1(1)	12(1)	-1(1)
C(16)	32(1)	37(1)	31(1)	-2(1)	14(1)	-3(1)
C(17)	37(1)	44(1)	27(1)	2(1)	12(1)	-2(1)
C(18)	40(1)	36(1)	34(1)	5(1)	11(1)	0(1)
C(19)	52(2)	54(2)	26(1)	-7(1)	15(1)	-2(1)
C(20)	36(1)	44(1)	27(1)	-6(1)	14(1)	-6(1)
C(21)	49(2)	45(2)	33(1)	-6(1)	24(1)	-5(1)
C(22)	64(2)	60(2)	49(2)	-18(1)	26(2)	-13(2)
C(23)	120(3)	61(2)	72(3)	-28(2)	51(3)	-32(2)
C(24)	147(4)	44(2)	88(3)	-4(2)	73(3)	3(2)
C(25)	102(3)	58(2)	81(3)	14(2)	44(2)	22(2)
C(26)	66(2)	50(2)	51(2)	1(1)	21(2)	2(2)
C(27)	41(1)	62(2)	47(2)	-13(1)	6(1)	-6(1)
C(28)	43(1)	40(1)	41(1)	3(1)	11(1)	4(1)

C(29)	79(2)	42(2)	40(2)	9(1)	14(2)	7(1)

Table 5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3).

	x	y	z	U(eq)
H(1)	7445	3704	8100	50
H(2)	9229	4283	9368	63
H(3)	8877	4830	11031	66
H(4)	6726	4813	11405	64
H(5)	4936	4224	10149	51
H(7)	4026	3516	8502	40
H(8A)	6363	2755	8643	41
H(8B)	5314	2700	9457	41
H(15)	4436	2220	4202	38
H(19)	2795	2647	-321	52
H(22)	2065	1490	36	66
H(23)	2579	463	-149	95
H(24)	4681	63	1047	102
H(25)	6282	692	2389	92
H(26)	5766	1710	2619	65
H(27A)	2437	1849	6221	77
H(27B)	1271	2098	6789	77
H(27C)	2277	1572	7479	77
H(28A)	4893	1529	8777	62
H(28B)	6086	1658	8145	62
H(28C)	4645	1396	7340	62
H(29A)	2557	4680	2946	81
H(29B)	2520	4453	1595	81
H(29C)	3909	4716	2494	81

5.C.3 Experimental

Melting points (uncorrected) were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by tlc on Acme's silica gel G plates using UV/Iodine vapour as visualizing agent. Acme's silica gel (60-120 mesh) and neutral alumina powder was used for column chromatographic purification. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400). Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (spectrum RX1) using potassium bromide optics. The mass spectrum was obtained on Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS Mass Spectrometer (EI, 70 eV) (Model-016932) using Ion Spray source. NMR spectra were recorded on Bruker 400 MHz Spectrophotometer. Chemical shifts are relative to tetramethylsilane on δ-scale in ppm. Coupling constants are given in Hz and relative peak areas were in agreement with all assignments.
X-ray diffraction data were collected using Mo Kα (λ=0.71073A°) radiation on a SMART APEX diffractometer equipped with a CCD area detector. Data collection, data reduction, structure solution/refinement were carried out using the software package of SMART APEX. Graphics were generated using MERCURY 1.4.1.[9]

Single crystal X-ray diffraction

X-ray quality single crystals of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **3a** were grown in a slow evaporation condition at room temperature. Crystals were obtained from a mixture of ethanol and toluene. The structure was solved by direct methods and refined in a routine manner. All hydrogen atoms were geometrically fixed and refined.

Preparation of 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one 2.

A solution of 1-(6-hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-ethanone **1** (1 g, 3.75 mmol) in diethyl carbonate (25 ml) was added to pulverized sodium (0.21 g, 9.38 mmol) and stirred for 15 min under anhydrous conditions. It was then gradually heated to reflux and maintained for 30 min.* The reaction mixture was cooled to room temperature and methanol (10 ml) added to decompose unreacted sodium. The reaction mass was poured into water (50 ml). The aqueous solution was then washed twice with toluene (25 ml) and acidified with concentrated hydrochloric acid until pH 2. The product obtained was filtered and crystallized from ethanol to get cream coloured crystals (0.5 g, 45.55 %), m.p. 255 °C of 5-hydroxy-9-methyl-3-phenyl-furo[3,2-g]chromen-7-one **2**; IR (KBr): 3430, 3071, 1664, 1589, 1501, 1375, 1353, 1285, 1228, 1120 cm^{-1}; ^1H NMR ($(CD_3)_2SO$): δ 2.60 (s, 3H, C9-CH_3), 5.74 (s, 1H, C6-H), 7.38-7.42 (m, 1H, C4'-H), 7.48-7.52 (m, 2H, C3'-H and C5'-H), 7.65-7.68 (m, 2H, C2'-H and C6'-H), 7.92 (s, 1H, C2-H), 8.15 (s, 1H, C4-H), 11.84 (s, 1H, C5-OH); LCMS (EI): *m/z* (%) 315.1 (37.03, M+Na), 293.1 (100, M+1), 279.2 (11.11), 269.3 (7.40).

Anal. Calcd for $C_{18}H_{12}O_4$ (292.29): C, 73.97; H, 4.14. Found: C, 73.81; H, 4.03 %.

General procedure for the synthesis of (3a-3d).

Preparation of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one 3a.

To a solution of 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **2** (0.5 g, 1.71 mmol), freshly distilled benzaldehyde (0.18 g, 1.71 mmol) and 2-methoxy propene 97 % (0.28 g, 3.76 mmol) in dry dioxane (25 ml), powdered oven-dried 5 Å molecular sieves and catalytic amount of ethylenediammonium diacetate (2 mol %) were added and the reaction mixture heated to 85-90 °C for 6 hours in a screw

* Highly exothermic reaction.

cap pressure tube. It was then filtered and washed with dioxane. The filtrate poured into ice water and solid obtained was collected by filtration. The crude product was purified by column chromatography using neutral alumina powder and petroleum ether 60-80 °C: ethyl acetate 9:1 mixture, which gave light yellow crystals (0.35 g, 45.21 %), m.p. 225 °C of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one **3a**; IR (KBr): 3057, 1718, 1633, 1602, 1454, 1383, 1357, 1237, 1194, 1119, 1082, 1069 cm^{-1}; ^1H NMR ($(CD_3)_2SO$): δ 1.71 (s, 3H, C2-CH_3), 1.96-2.03 (dd, $J_{vicinal}$ = 11.76 Hz and $J_{geminal}$ = 13.96 Hz, 1H, C3-H_A), 2.47-2.52 (dd, $J_{vicinal}$ = 7 Hz and $J_{geminal}$ = 14 Hz, 1H, C3-H_B), 2.60 (s, 3H, C7-CH_3), 3.33 (s, 3H, C2-OCH_3), 4.08-4.12 (dd, $J_{vicinal}$ = 7 Hz and $J_{vicinal}$ = 11.72 Hz, 1H, C4-H), 7.19-7.22 (m, 3H, C3'-H, C4'-H and C5'-H), 7.26-7.29 (m, 2H, C2'-H and C6'-H), 7.42-7.46 (m, 1H, C4"-H), 7.53-7.57 (m, 2H, C3"-H and C5"-H), 7.67-7.70 (m, 2H, C2"-H and C6"-H), 7.94 (s, 1H, C2-H), 8.12 (s, 1H, C4-H).

Anal. Calcd for $C_{29}H_{24}O_5$ (452.50): C, 76.98; H, 5.35. Found: C, 76.78; H, 5.11 %.

General procedure for the synthesis of (4a-4d):

Preparation of 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one 4a OR 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2H-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one 5a.

A solution of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one **3a** (0.5 g, 1.10 mmol) in trifluoro acetic acid/water (9.5:0.5) (10 ml) was stirred at room temperature for 6 hours. The reaction mass was then poured into ice water and solid obtained collected by filtration. The crude product was purified by column chromatography using silica gel and chloroform/methanol (9:1) mixture, which gave white crystals (0.4 g, 82.55 %), m.p.198 °C of 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-*g*]chromen-7-one **4a**; IR (KBr): 3422, 2926, 1682, 1632, 1598, 1453,

1385, 1361, 1246, 1121, 1072 cm^{-1}; LCMS (EI): *m/z* (%) 477.2 (4.76, M+K), 461.3 (21.42, M+Na), 439.2 (100, M+1).

Anal. Calcd for $C_{28}H_{22}O_5$ (438.47): C, 76.70; H, 5.06. Found: C, 76.58; H, 4.91 %.

5-Hydroxy-6-[1-(4-methoxy-phenyl)-3-oxo-butyl]-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one 4b.

Cream coloured crystals (81 %), m.p. 180 °C.

6-[1-(4-Chloro-phenyl)-3-oxo-butyl]-5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one 4c.

Off white coloured crystals (75 %), m.p. 212-214 °C.

5-Hydroxy-9-methyl-6-[1-(4-nitro-phenyl)-3-oxo-butyl]-3-phenyl-furo[3,2-*g*]chromen-7-one 4d.

Cream coloured crystals (88 %), m.p. 230-232 °C.

5.C.4 Conclusions

- Single crystal X-ray analysis of compound 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one **3a** shows that the HDA-cycloadduct exists in *exo (trans)* configuration. This was contradictory to the results obtained by Giancarlo Cravotto *et al.* (who had reported formation of *cis* isomer) which had no X-ray data. Thus it can be concluded that the Hetero-Diels-Alder reaction proceeds with good diastereoselectivity favouring the *exo* (*trans*) isomer in this case i.e. C2-OMe and C4-phenyl ring on opposite side. The C2-OMe is ψ-axial with C4-phenyl ring in ψ-equatorial position.

- The process can be explored for the asymmetric synthesis of warfarin derivatives using various chiral auxiliaries.

- The pyran ring of the molecule adopts the half chair conformation.

- The ^{1}H NMR shows the existence of an equilibrium mixture of open-chain keto tautomer - 5-hydroxy-9-methyl-6-(3-oxo-1-phenyl-butyl)-3-phenyl-furo[3,2-g]chromen-7-one **4a** and two diastereomeric cyclic hemiketal tautomers - 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **5a**, in solutions.

- The compounds could be explored for possible anti-coagulant properties.

5.C.5 References

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