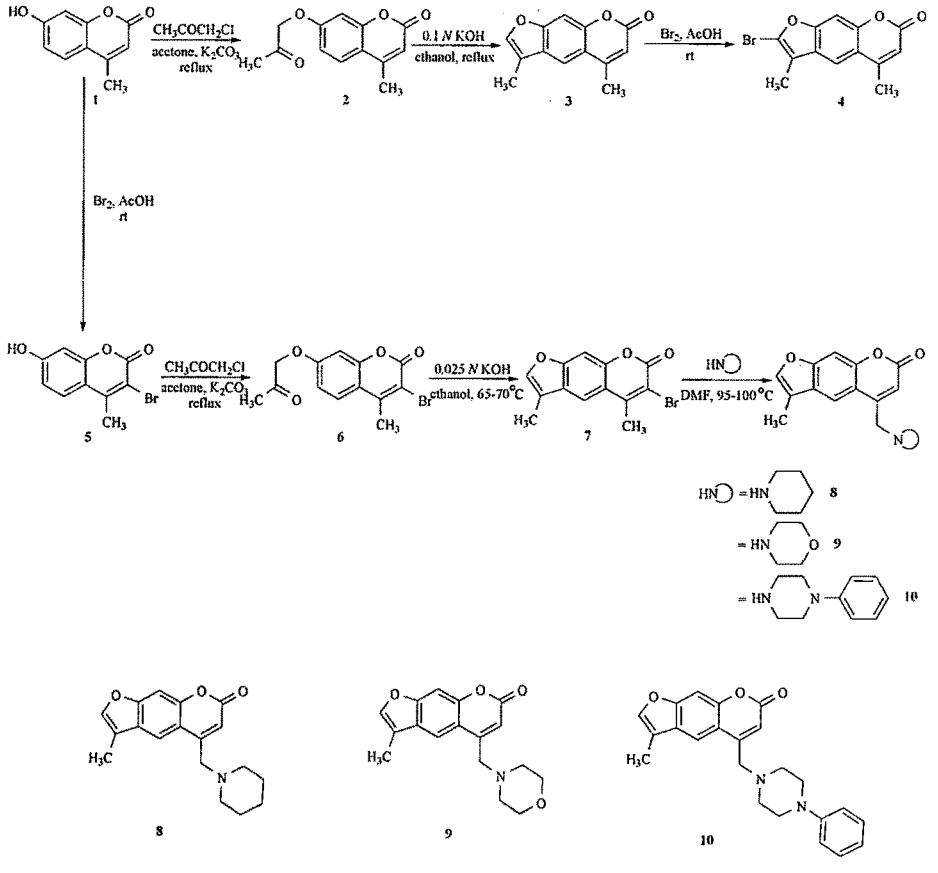
Chapter 4: STUDIES IN SYNTHESIS OF NEW PSORALENAMINES

4.1 Introduction

Furocoumarins such as Psoralens (5-methoxy psoralen or bergapton, 8-methoxy psoralen or xanthotoxin, 4,5',8-trimethyl psoralen) are well known photosensitizing drugs used in PUV-A (Psoralen Ultra Violet-A) therapy for the treatment of dermatological disorders like psoriasis, vitiligo, mycosis and atropic eczema;[1] as well as fungal, viral and bacterial infections.[2] Recently, Psoralen derivatives have also been used in the treatment of cutaneous T cell lymphoma,[3] human immunodeficiency diseases,[4] and prevention of rejection of organ transplants.[5] Introduction of aminomethyl group in furocoumarins enhances antibacterial activity.[6] Aminopsoralens are used for nucleic acid probe preparations, preparation of conjugates, inhibition of cell proliferation, inactivation of virus for vaccine preparation, and in particular, for the inactivation of pathogens in blood products.[7]

Most of the study done hitherto deals with 3-amino psoralens or 2-amino psoralens.[7] Paradkar *et al.* reported a novel synthesis of 4-aminomethyl coumarins by condensing 3-bromo-4-methyl coumarin with secondary amines using DMF as solvent.[8] Madhavrao *et al.* have established a mechanism for the same.[9]

Because of the wide spread and increasing interest in aminopsoralens for its pharmacological action, this study was undertaken to synthesize some new amino psoralen derivatives via bromination. Moreover, it was of considerable interest to study the reactivity and orientation of 3,5-substituted psoralens towards bromination. Although it is evident that the third position of furan ring in psoralens is most reactive towards electrophilic substitution, the behaviour of psoralens in which the third position is blocked has not been reported for bromination. The synthetic pathway followed by MacLeod *et al.*,[10] and Paradkar *et al.*,[8] has been employed to prepare the title compounds as outlined in **Scheme 1**.



Scheme 1

4.2 Results and Discussion

β-Methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) **1**,[11] was condensed with mono chloroacetone using potassium carbonate in dry acetone to give the aryloxyketone 4-methyl-7-(2-oxo-propoxy)-chromen-2-one **2**. The ^{1}H NMR **(Figure 1)** showed signals at δ 2.32 (d, 3H, J = 0.8 Hz, C4-CH_3), 2.42 (s, 3H, -$COCH_3$), 4.66 (s, 2H, -OCH_2CO-), 6.18 (d, 1H, J = 0.8 Hz, C3-H), 6.77-6.78 (d, 1H,

J = 2.8 Hz, C8-H), 6.89-6.92 (dd, 1H, J = 2.8 Hz and J = 8.8 Hz, C6-H), 7.54-7.56 (d, 1H, J = 8.8 Hz, C5-H) which confirmed the structure. Compound **2** when subjected to cyclization in 0.1 *N* ethanolic potassium hydroxide gave the corresponding furocoumarin (psoralen) 3,5-dimethyl-furo[3,2-*g*]chromen-7-one **3** as shown in **Scheme 1**. The ^{1}H NMR of compound **3** showed signals at δ 2.21-2.22 (d, 3H, J = 1.5 Hz, C3-CH_3), 2.51-2.52 (d, 3H, J = 1.08 Hz, C5-CH_3), 6.27-6.28 (d, 1H, J = 1.08 Hz, C6-H), 7.36 (s, 1H, C9-H), 7.52 (d, 1H, J = 1.5 Hz, C2-H), 7.58 (s, 1H, C4-H). Furocoumarin **3** was brominated with bromine in acetic acid to get the desired 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one, but from the ^{1}H NMR it was revealed that the product formed was 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4**. This shows that the second position of the furan ring is more reactive towards halogenation compared to the α-position of the chromen-2-one ring in psoralens. In the ^{1}H NMR of compound 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4** **(Figure 2)**, doublet at δ 6.27-6.28 ppm corresponding to one proton for C6-H (or α-H of chromen-2-one) coupled (J = 1.08 Hz, allylic coupling) with C5-CH_3, the absence of signal at δ 7.5 ppm for C2-H proton and the absence of splitting (due to allylic coupling with C2-H) in the C3-CH_3 signal at δ 2.24 ppm confirmed the structure. Other signals observed were, δ 2.24 (s, 3H, C3-CH_3), 2.52 (d, 3H, J = 1.08 Hz, C5-CH_3), 7.36 (s, 1H, C9-H), 7.58 (s, 1H, C4-H). The ^{13}C NMR **(Figure 3)** values δ 113.76 ppm and 115.26 ppm for C6 and C2 carbon respectively, further confirmed the substitution of bromine at C2 position. Other signals observed were, δ 8.80 (C3-*C*H_3), 19.21 (C5-*C*H_3), 99.48 (C9), 113.92 (C3), 116.60 (C4), 126.58 (C4a), 127.94 (C3a), 151.45 (C8a), 152.45 (C5), 156.14 (C9a), 160.80 (C7). The UV spectrum in dichloromethane showed absorption at 284, 302, 324, 333, 340, 347 nm. Consequently the target aminomethyl psoralens could not be prepared.

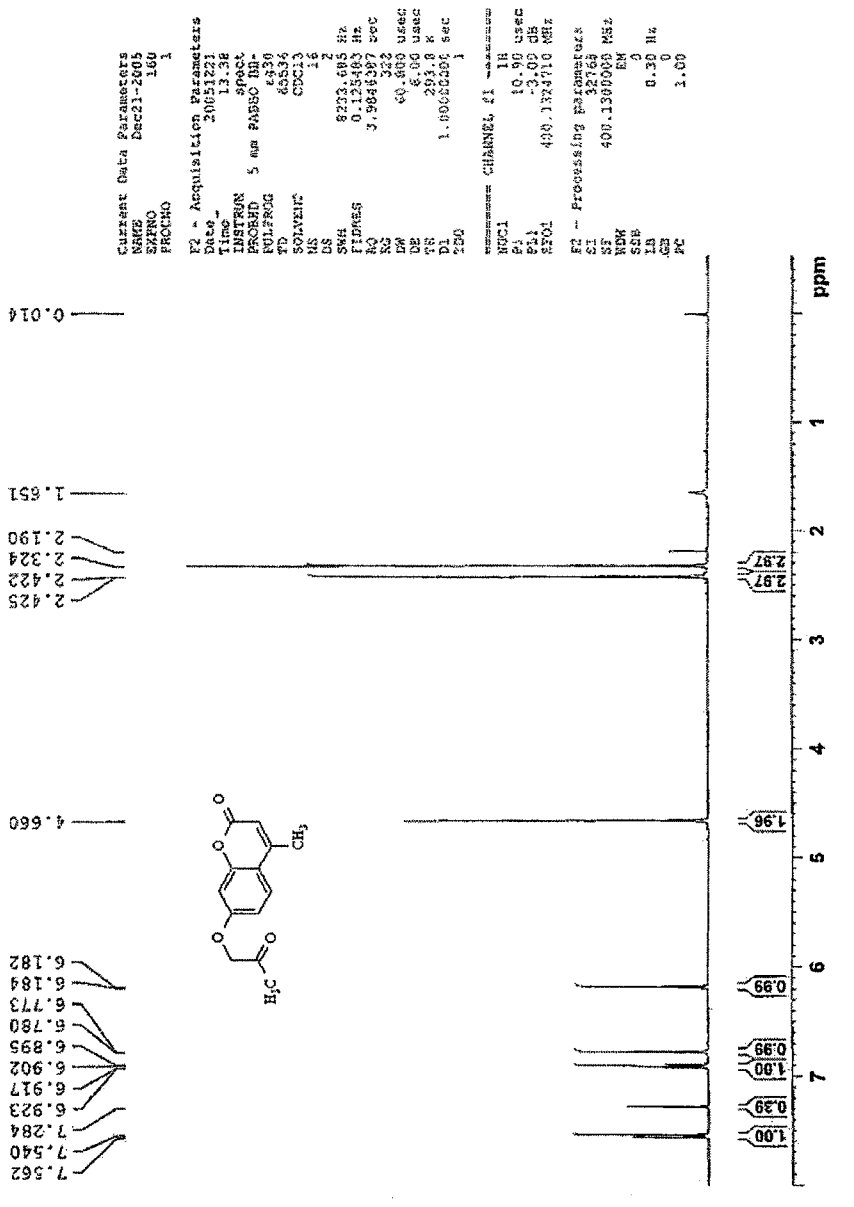


Figure 1: ^{1}H NMR of compound 4-methyl-7-(2-oxo-propoxy)-chromen-2-one **2**.

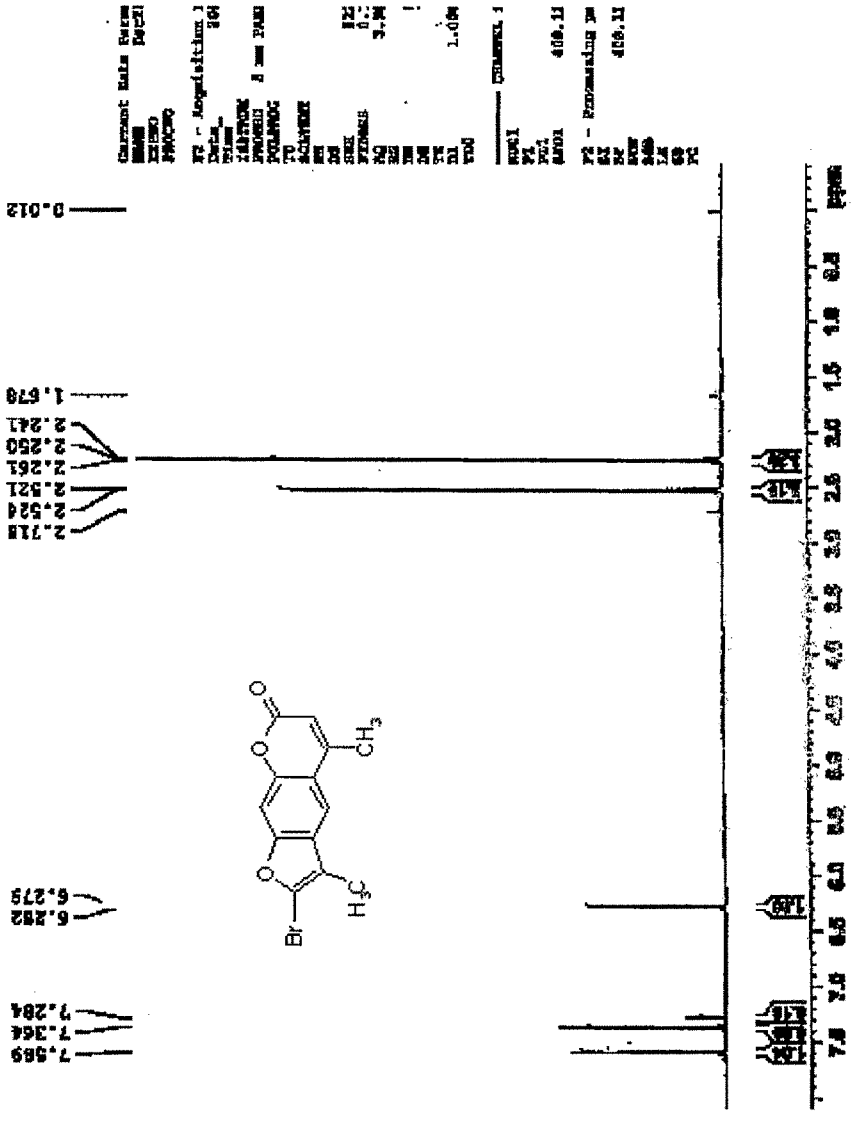


Figure 2: ^{1}H NMR of compound 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4**.

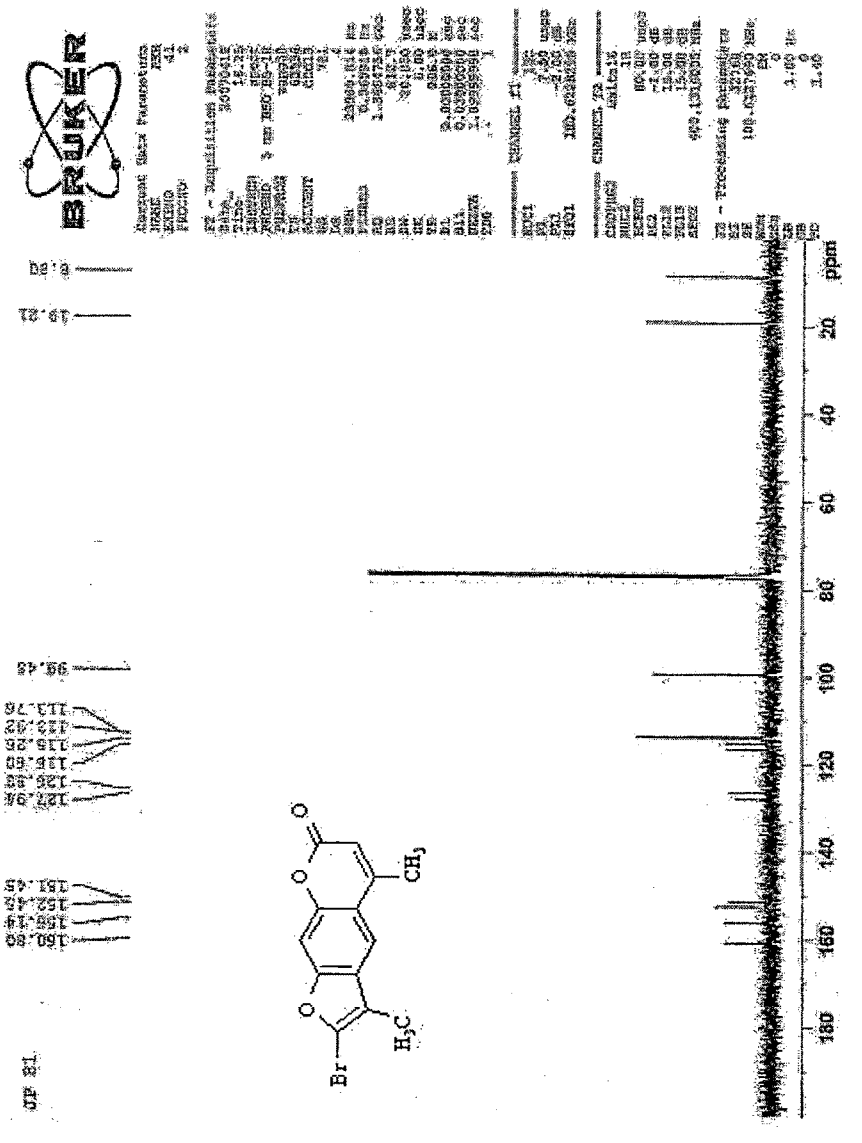


Figure 3: ^{13}C NMR of compound 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4**.

In a slightly modified methodology, β-methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) **1** was first brominated using bromine in acetic acid to give 3-bromo-7-hydroxy-4-methyl-chromen-2-one **5**,[12] in an addition-elimination reaction, which was then condensed with mono chloroacetone in presence of potassium carbonate in dry acetone to give 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one **6**. The ^{1}H NMR **(Figure 4)** showed signals at δ 2.32 (s, 3H, C4-CH_3), 2.62 (s, 3H, -$COCH_3$), 4.67 (s, 2H, -OCH_2CO-), 6.78-6.79 (d, 1H, J = 2.4 Hz, C8-H), 6.92-6.95 (dd, 1H, J = 2.4 Hz and J = 9.2 Hz, C6-H), 7.60-7.62 (d, 1H, J = 9.2 Hz, C5-H). Compound **6** on cyclization in ethanolic potassium hydroxide gave 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7** in a similar fashion as shown in **Scheme 1**.

In the ^{1}H NMR of compound 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7** **(Figure 5)**, the absence of signal at δ 6.28 ppm for C6-H proton and the absence of splitting for C5-CH_3 signal (no allylic coupling) at δ 2.74 ppm confirmed the substitution of bromine at C-6 position. Further doublets at δ 7.50 ppm (1H, J = 1.6 Hz) for C2-H and δ 2.31-2.32 ppm (3H, J = 1.6 Hz) for C3-CH_3 corroborated the structure **7**. In the ^{13}C NMR **(Figure 6)**, signals at δ 99.68 ppm and 143.52 ppm were assigned to C6 and C2 carbon respectively. The mass spectrum (lcms) **(Figure 7)** was obtained as m/z (relative intensity, 100%): 317 (8.88) M+23 (from Na^+), 295.1 (100) M+1, 292.9 (100) M^+ using mobile phase Acetonitrile: Ammonium acetate 1mM (90:10 % v/v). The UV spectrum in dichloromethane showed absorption at 282, 302, 323, 331, 342, 355, 362 nm.

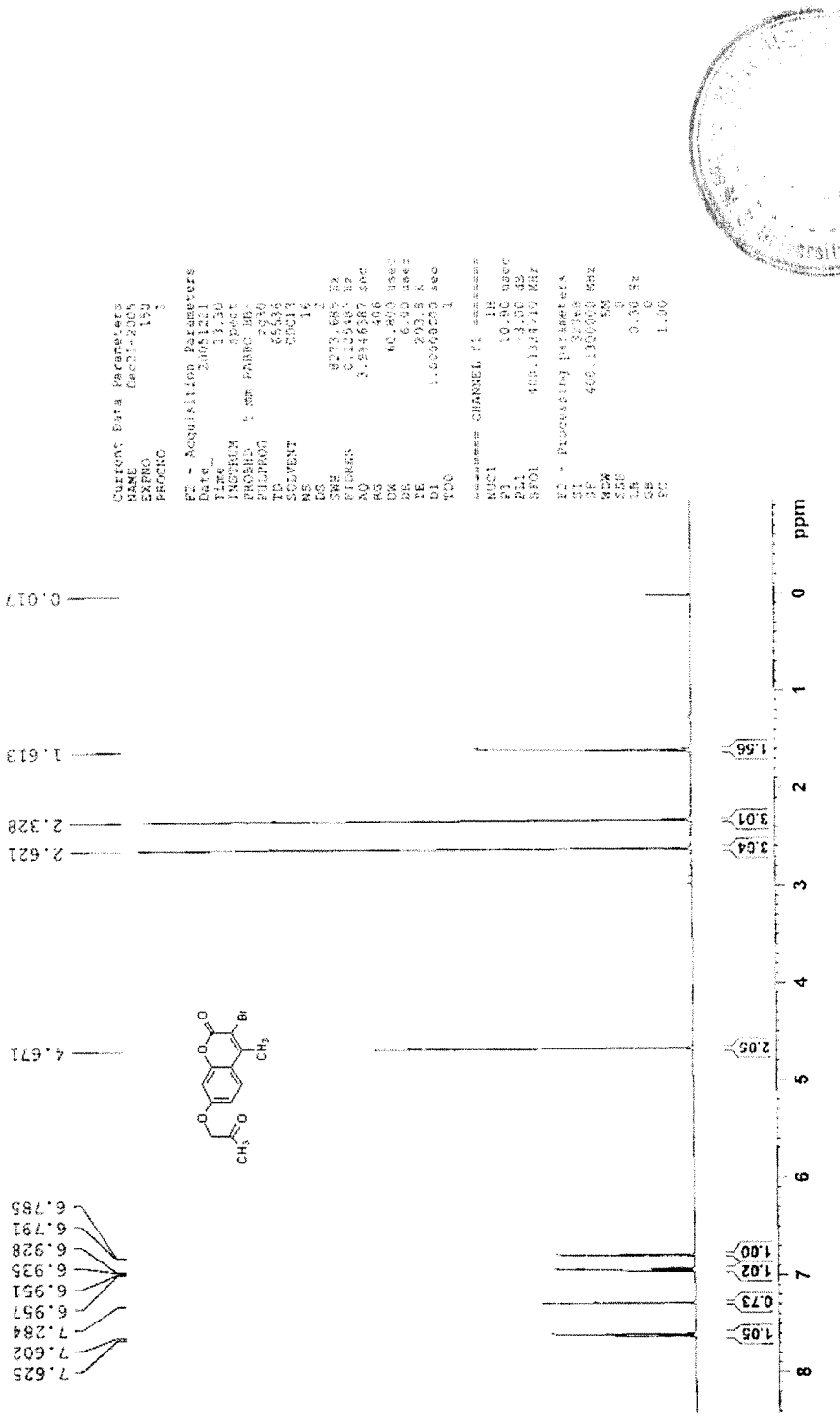


Figure 4: ^{1}H NMR of compound 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-ono **6**.

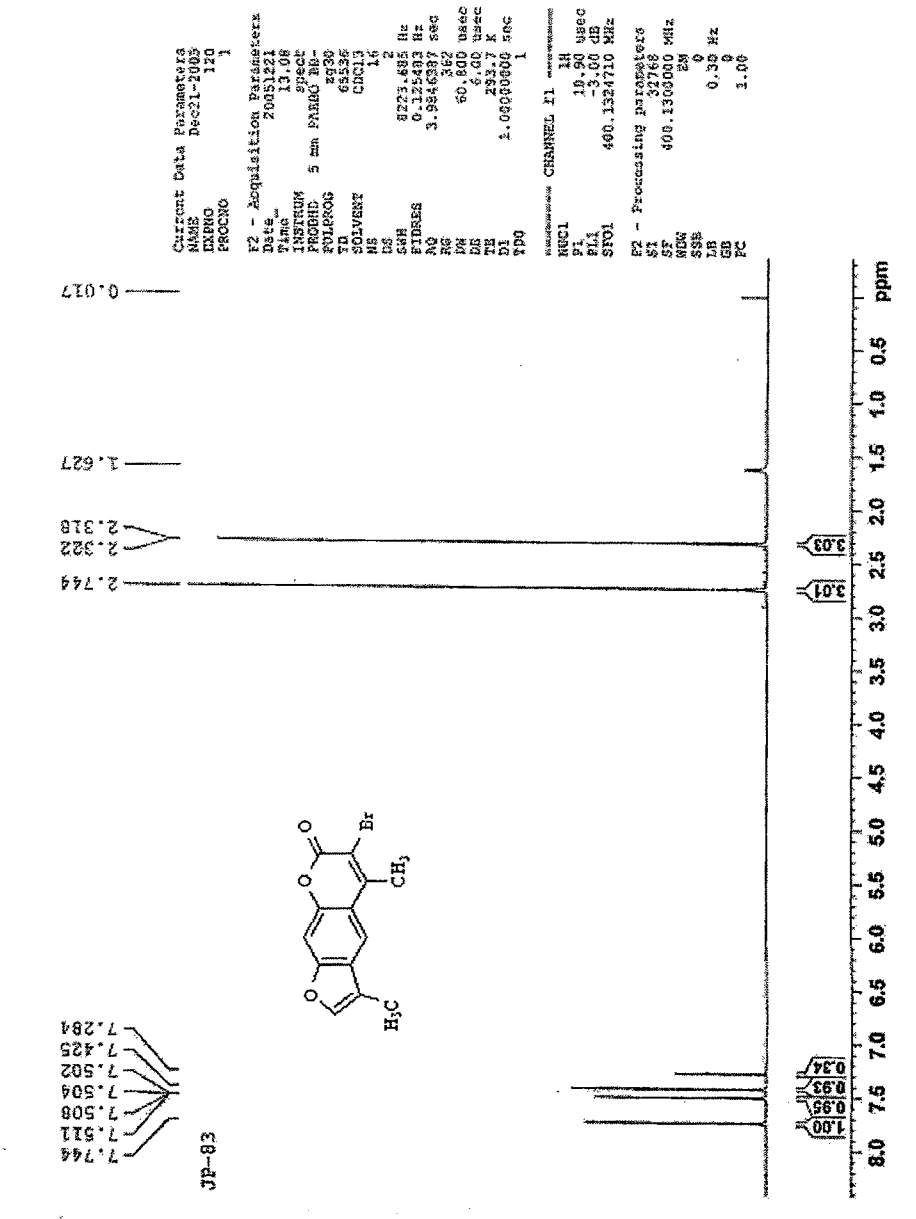


Figure 5: ^{1}H NMR of compound 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7**.

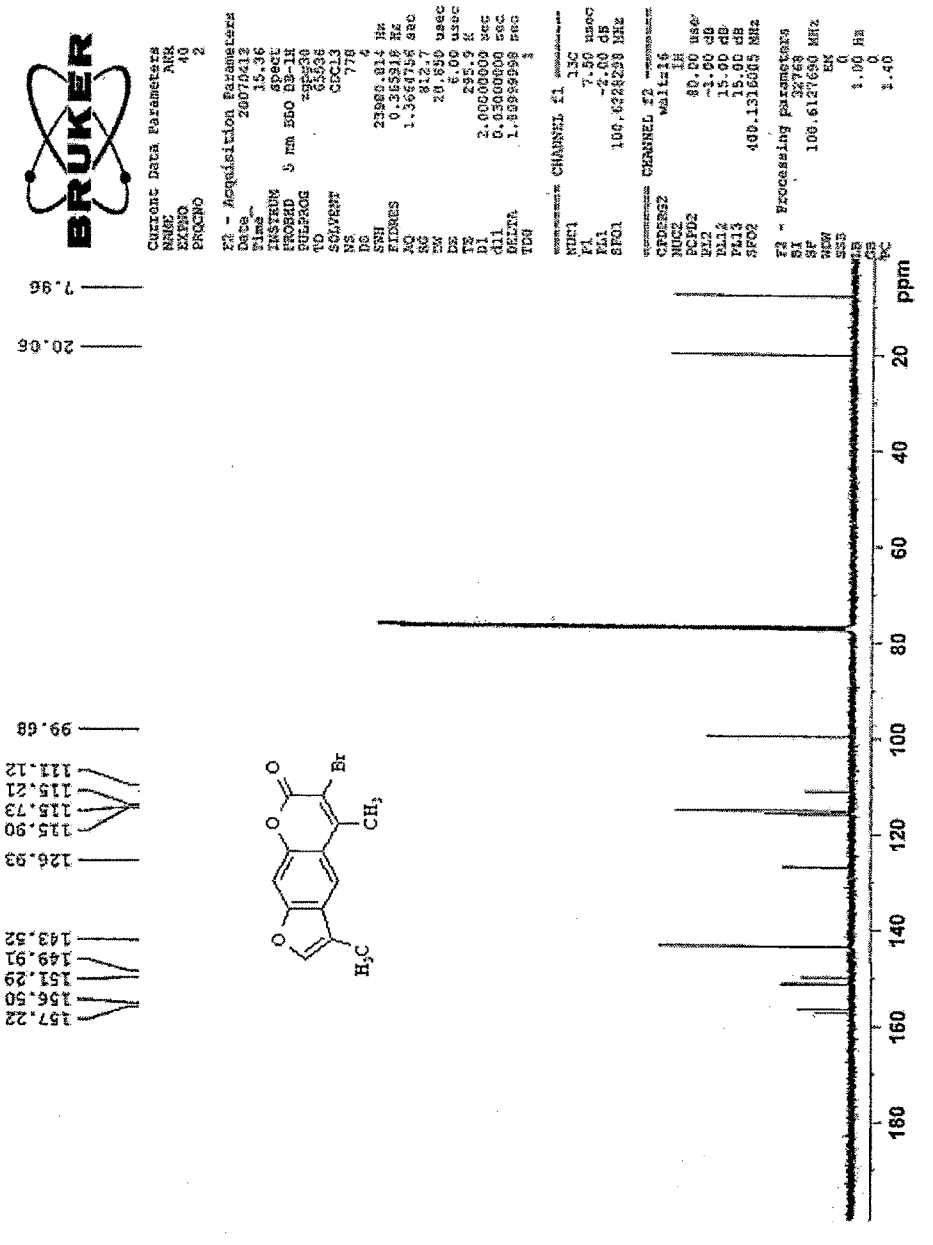


Figure 6: ^{13}C NMR of compound 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one 7.

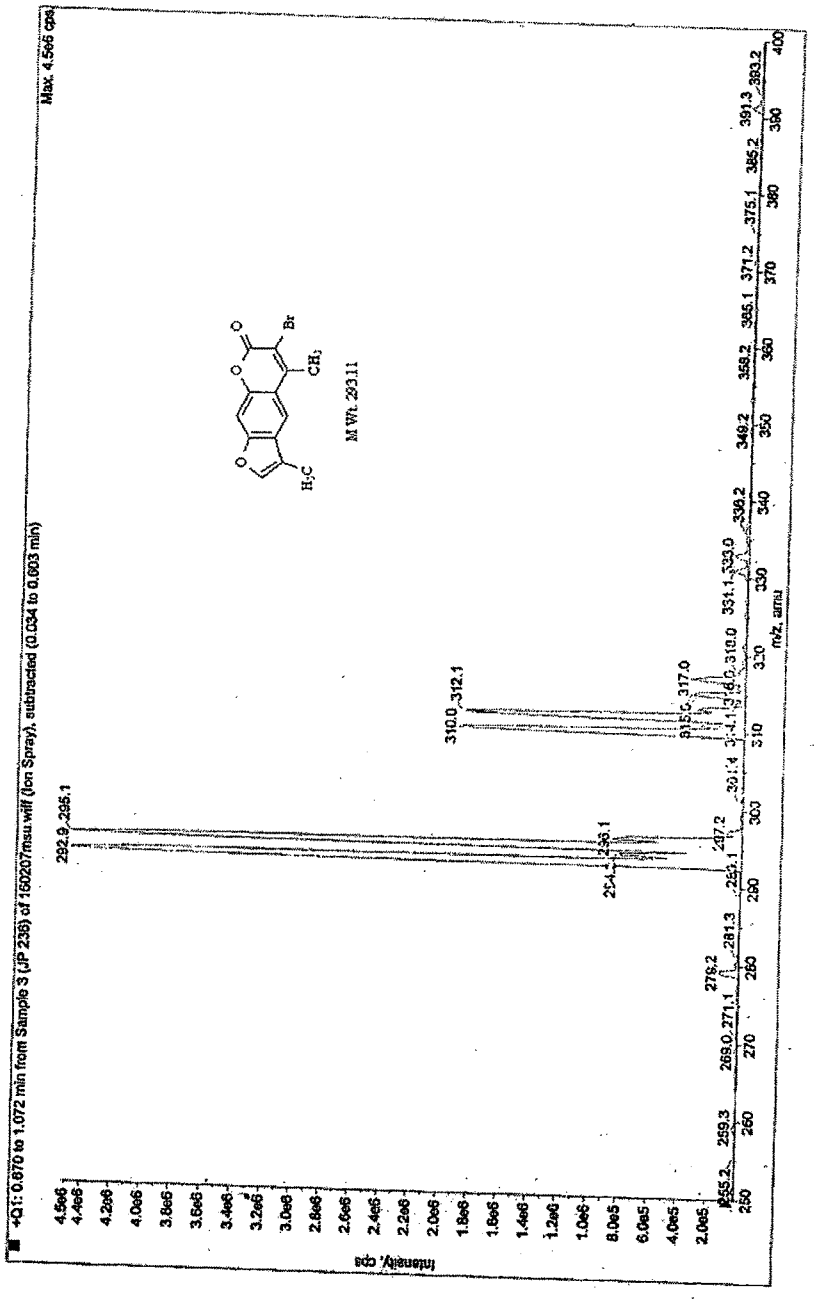
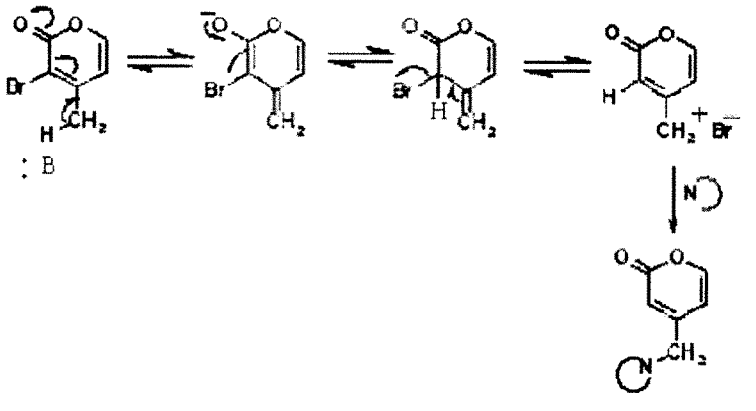


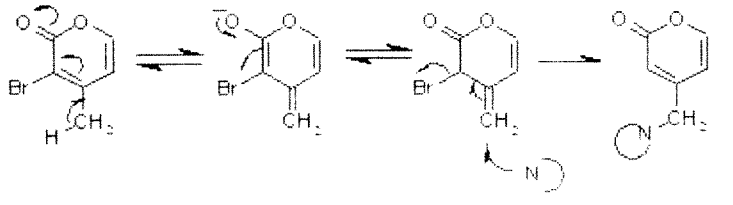
Figure 7: LCMS of compound 6-bromo-3,5-dimethyl-furo[3.2-g]chromen-7-one **7**.

Finally, 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7** was condensed with different amines to give the corresponding aminomethyl psoralens **(8, 9, 10)**. The probable reaction mechanism is outlined in **Scheme 2.**

^{1}H NMR of compound 3-methyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one **8 (Figure 8)**, showed singlets at δ 6.51 ppm corresponding to one proton for C6-H proton and δ 3.66 ppm corresponding to two protons for C5-CH_2-, which confirmed the formation of 5-amino methyl psoralens. Other signals observed were, δ 1.47-1.48 (t, 2H, C4'-CH_2-), 1.59-1.65 (m, 4H, C3'-CH_2- and C5'-CH_2-), 2.27-2.28 (d, 3H, J = 1.2 Hz, C3-CH_3), 2.51 (t, 4H, C2'-CH_2- and C6'-CH_2-), 7.35 (s, 1H, C9-H), 7.43-7.44 (d, 1H, J = 1.2 Hz, C2-H), 7.92 (s, 1H, C4-H). In the ^{13}C NMR **(Figure 9)**, δ values 99.59 ppm for C6 and 59.91 ppm for C5-*C*H_2- further confirmed the structure. Other signals observed were, at δ 7.84 (C2-*C*H_3), 24.10 (C3' and C5'), 26.07 (C4'), 55.05 (C2' and C6'), 112.51 (C9), 114.92-115.73 (C4, C4a and C3), 126.23 (C3a), 143 (C2), 151.86 (C8a), 153.04 (C9a), 156.42 (C5), 161.57 (C7). The UV spectrum in dichloromethane showed absorption at 281, 301, 305, 329, 337 nm. The mass spectrum (lcms) **(Figure 10)** for 3-methyl-5-morpholin-4-ylmethyl-furo[3,2-*g*]chromen-7-one **9** was obtained as m/z (relative intensity, 100%): 338.1 (7.27) M+39 (from K^+), 322.2 (38.18) M+23 (from Na^+), 301.2 (70.90) M+2, 299.9 (100) M+1 using mobile phase Acetonitrile: Ammonium acetate 1mM (90:10 % v/v).



Scheme 2: Probable mechanism for the formation of 4-aminomethyl psoralens. (S_N1)



Scheme 2: Probable S_N^2 mechanism for the formation of 4-aminorthyl Psoralens.

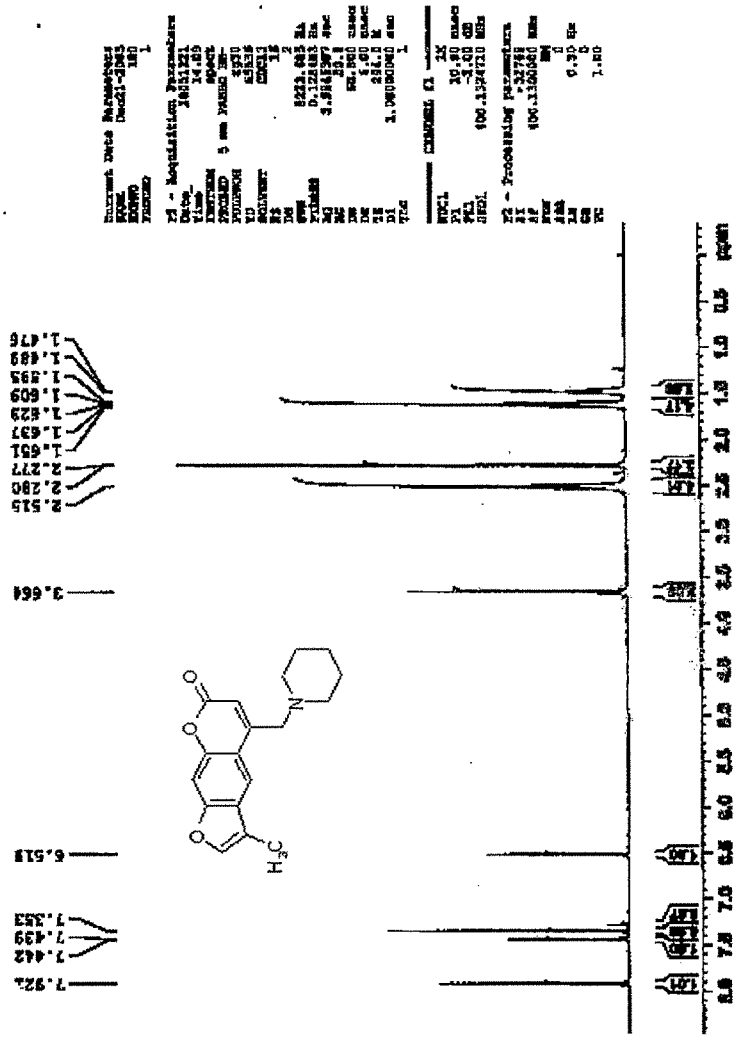


Figure 8: ^{1}H NMR of compound 3-methyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one **8**.

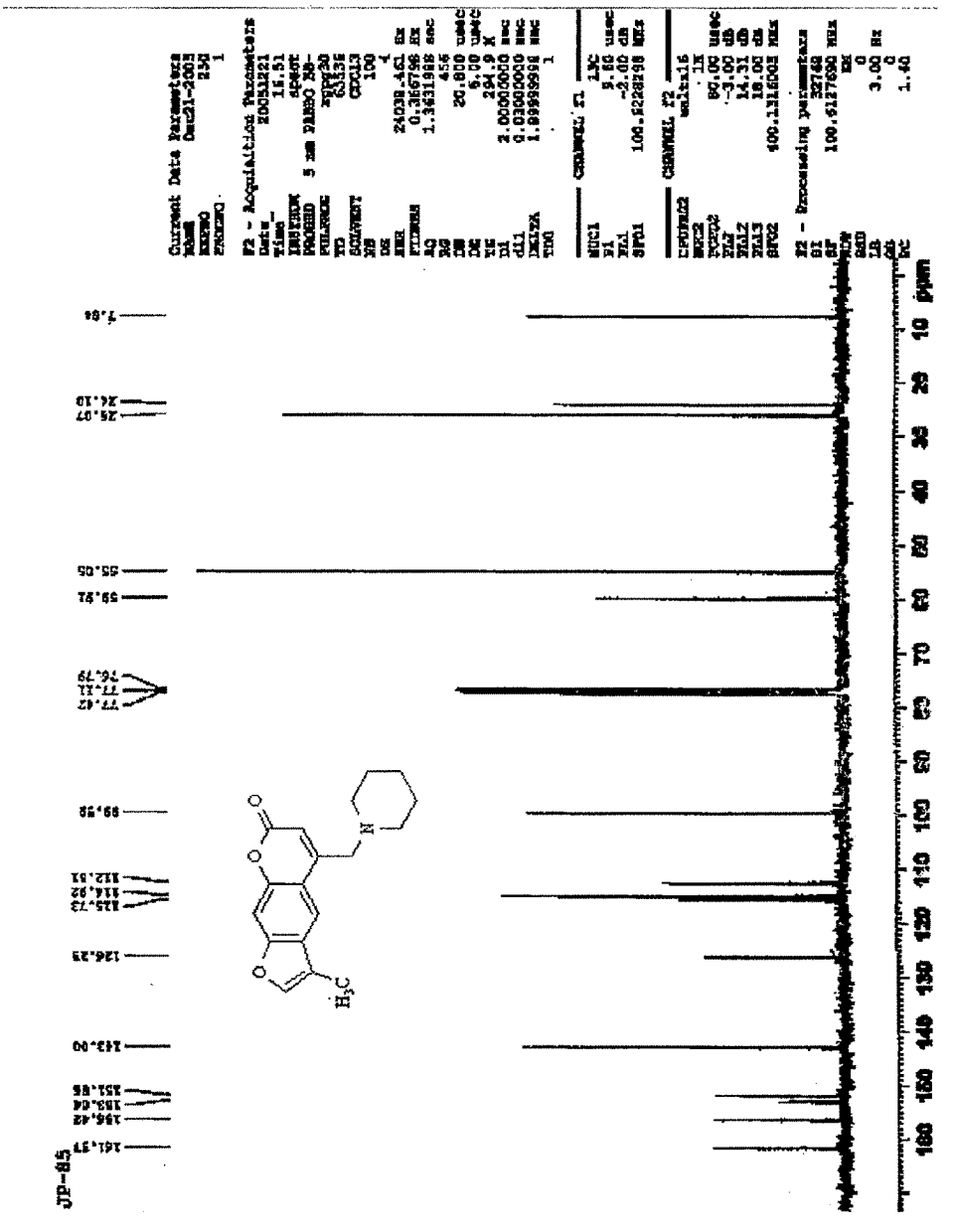


Figure 9: ^{13}C NMR of compound 3-methyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one **8**.

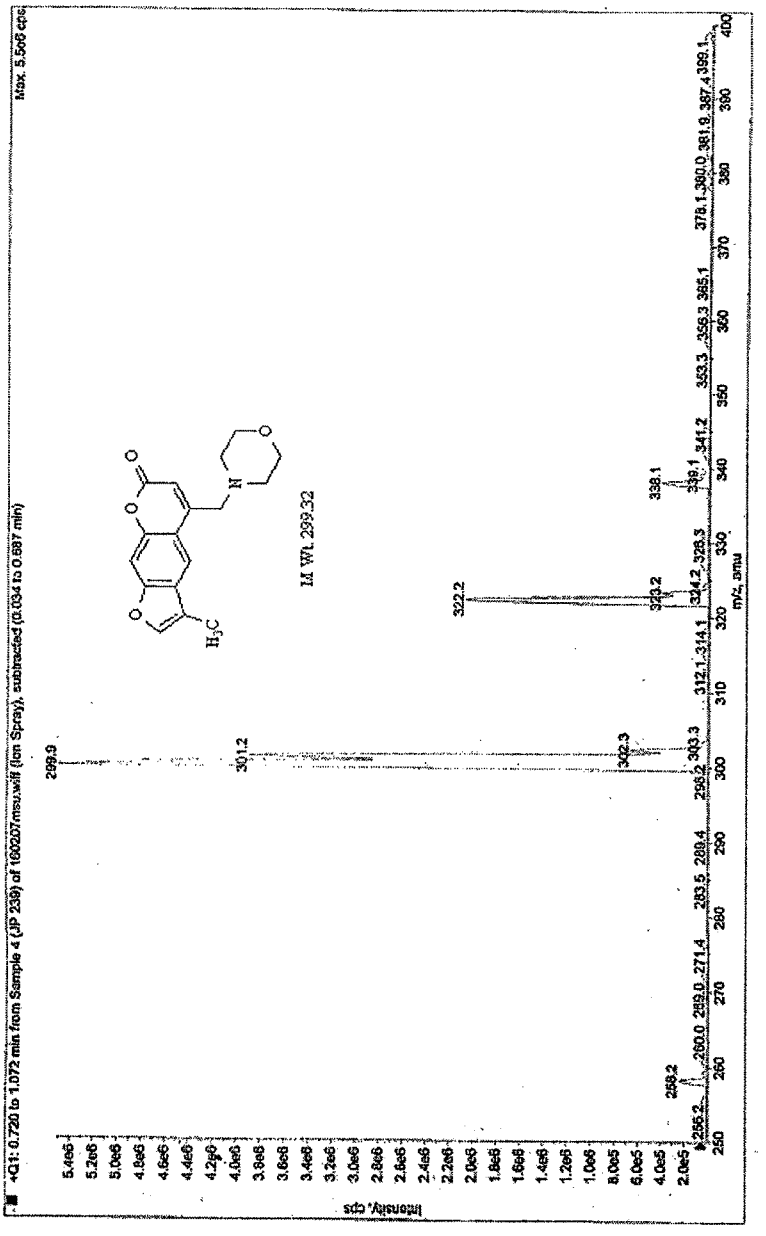
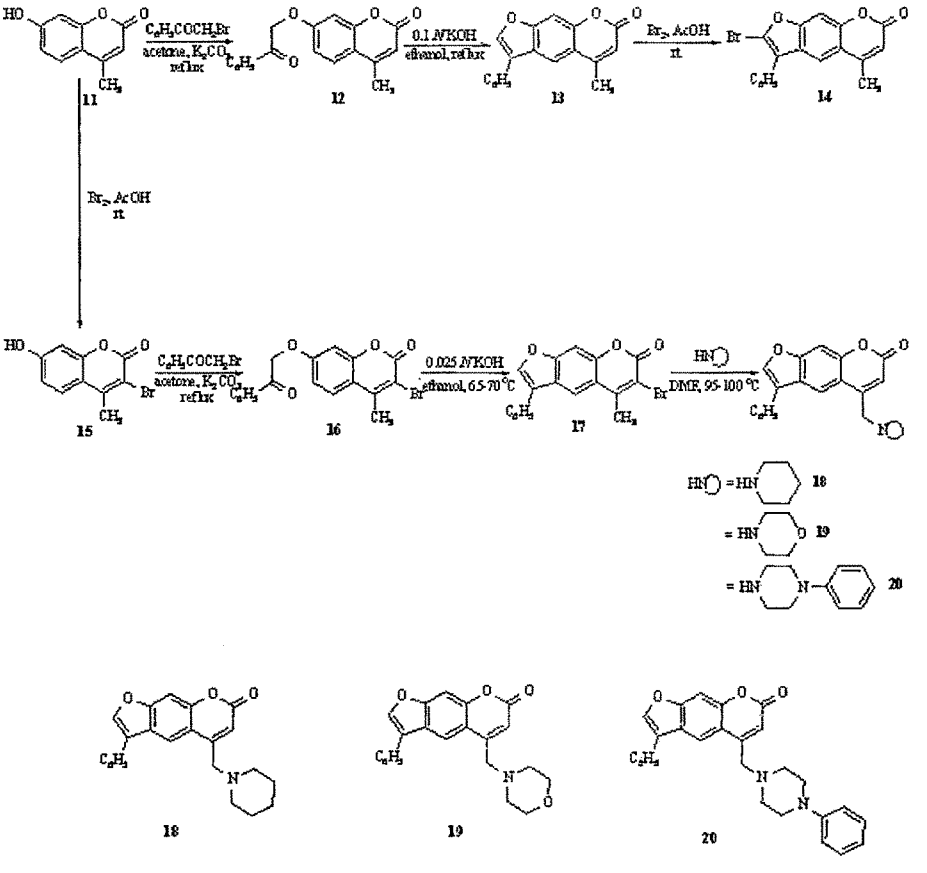


Figure 10: LCMS of compound 3-methyl-5-morpholin-4-ylmethyl-furo[3,2-*g*]chromen-7-one **9**.



Scheme 3

Similar observations were recorded for reaction of β-methyl umbelliferone with phenacyl bromide as shown in **Scheme 3**.

β-methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) **11** when condensed with phenacyl bromide gave 4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one **12**, which on cyclization in 0.1 *N* ethanolic potassium hydroxide gave 5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **13**. Compound **13** on bromination with bromine in acetic acid gave 2-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **14**. The ^{1}H NMR **(Figure 11)** showed signals at δ 2.46 (d, 3H, J = 1.05 Hz, C5-CH_3), 6.28 (d, 1H, J = 1.05 Hz, C6-H), 7.47-7.64 (m, 6H,

C3-phenyl protons and C9-H) and 7.75 (s, 1H, C4-H) which confirmed bromination at C-2.

To synthesize 6-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **17**, 7-hydroxy-4-methyl-chromen-2-one **11** was first brominated using bromine in acetic acid, which gave 3-bromo-7-hydroxy-4-methyl-chromen-2-one **15**.[12] Compound **15** on condensation with phenacyl bromide in potassium carbonate/dry acetone gave 3-bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one **16**, which on subsequent cyclization in ethanolic potassium hydroxide gave 6-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **17**. ^{1}H NMR **(Figure 12)** showed signals at δ 2.69 (s, 3H, C5-CH_3), 7.47-7.49 (m, 1H, C4'-H), 7.54-7.58 (m, 2H, C3'-H and C5'-H), 7.56 (s, 1H, C9-H), 7.64-7.66 (m, 2H, C2'-H and C6'-H), 7.87 (s, 1H, C2-H) and 8.02 (s, 1H, C4-H). The disappearance of signal at δ 6.2 – 6.3 ppm for C6-H proton confirmed the bromination at C-6 position. Compound **17** was condensed with different amines, *viz*, piperidine, morpholine and *N*-phenyl piperazine as shown in **Scheme 3**. The ^{1}H NMR of 3-phenyl-5-(4-phenyl-piperazin-1-ylmethyl)-furo[3,2-*g*]chromen-7-one **20 (Figure 13)**, showed signals at δ 2.79 (t, 4H, C3'-CH_2- and C5'-CH_2-), 3.3 (t, 4H, C2'-CH_2- and C6'-CH_2-), 3.80 (s, 2H, C5-CH_2-), 6.57 (s, 1H, C6-H), 6.92-7.68 (m, 10H, C3-phenyl protons and N4'-phenyl protons), 7.55 (s, 1H, C9-H), 7.86 (s, 1H, C2-H) and 8.45 (s, 1H, C4-H).

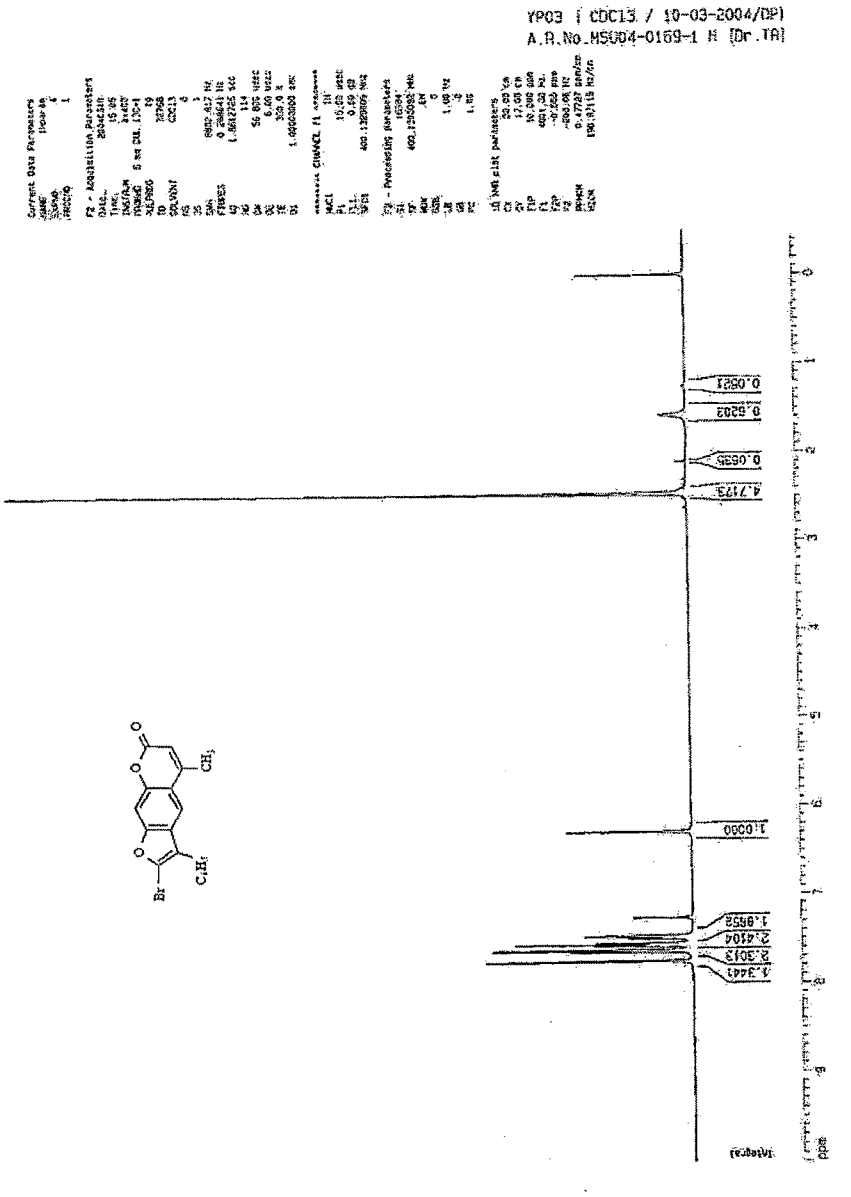


Figure 11: ^{1}H NMR of compound 2-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **14**.

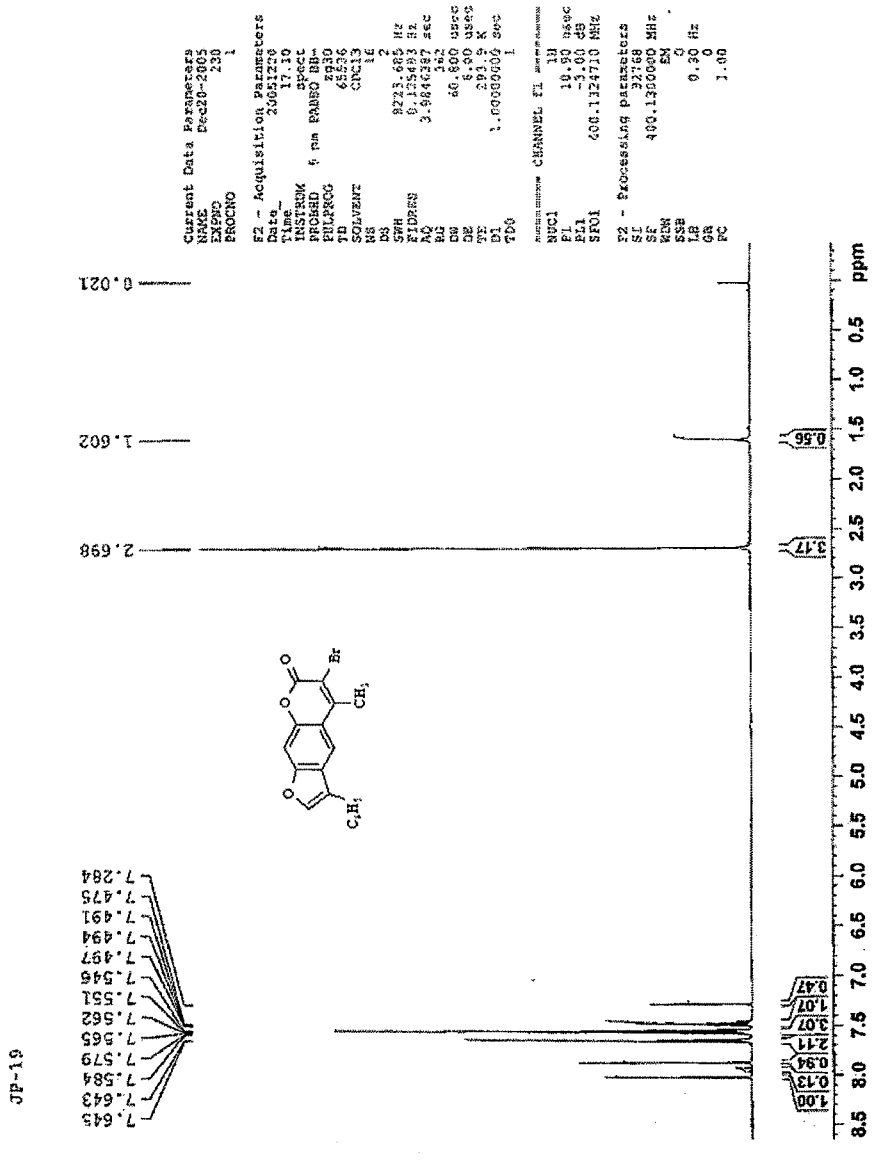


Figure 12: ^{1}H NMR of compound 6-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **17**.

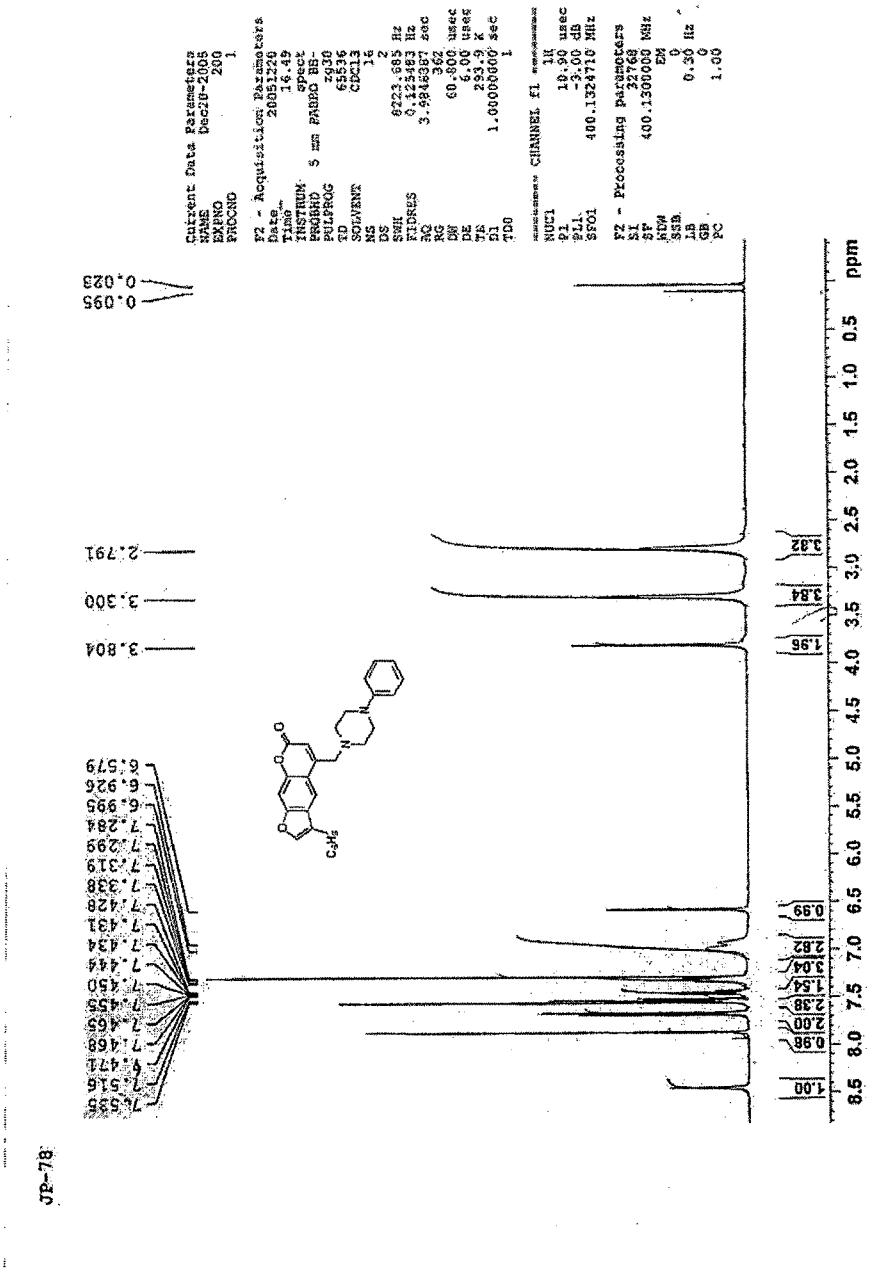


Figure 13: ^{1}H NMR of compound 3-phenyl-5-(4-phenyl-piperazin-1-ylmethyl)-furo[3,2-*g*]chromen-7-one **20**.

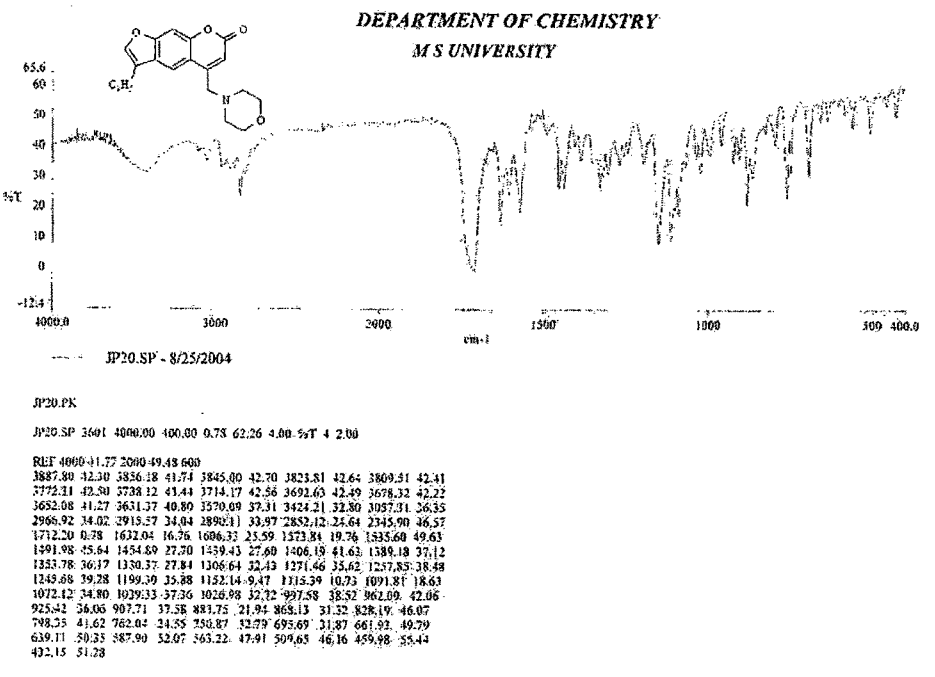
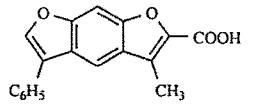


Figure 14: ^{1}H NMR of compound 5-morpholin-4-ylmethyl-3-phenyl-furo[3,2-*g*]chromen-7-one **19**.

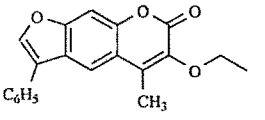
Cyclization of 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one **6** and 3-bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one **16** to 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7** and 6-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **17** respectively, was the bottleneck of the process. Cyclization in 0.1 *N* ethanolic potassium hydroxide at reflux temperature lowered the over all yield of the reaction drastically due to the formation of mixture of products. One of the product was identified as furocoumarilic acid formed due to alkaline ring contraction,[13] which has been confirmed from the ^{1}H NMR **(Figure 15)** and IR **(Figure 16)** spectra of 3-methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid **21**, obtained during cyclization of 3-bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one **16**. ^{1}H NMR of compound **21** showed signals at δ 2.58 (s, 3H, C3-CH_3), 7.32-7.36 (m, 1H, C4'-H), 7.44-7.47 (m, 2H, C2'-H and C6'-H), 7.63-7.66 (m, 3H, C8-H, C3'-H and C5'-H), 7.93 (s, 1H, C6-H), 7.96 (s, 1H, C4-H).

The broad band between 2500 cm^{-1} and 3433 cm^{-1} in the IR spectrum for the carboxylic acid group confirmed the formation of **21**. The furocoumarilic acid was obtained as white amorphous powder; mp 250°C dec. and whose sodium and potassium salts are hydrophobic. The other product was identified as 6-ethoxy-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **22** formed by nucleophilic attack of ethanol, which also has been confirmed from ^{1}H NMR **(Figure 17)**. Signals at δ 1.46-1.50 (t, 3H, C6-OCH_2CH_3) and 4.46-4.51 (q, 2H, C6-OCH_2CH_3), and the disappearance of signal at δ 6.2-6.3 ppm for C6-H proton confirmed substitution at C6 position.

The yields of compounds 7 and 17 were lowered due to these side reactions.



3-Methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid (21)

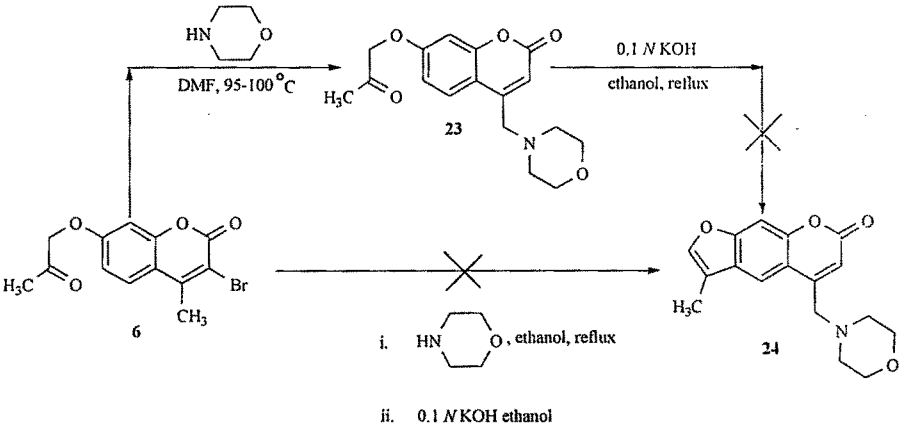


6-Ethoxy-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one (22)

Weaker bases like tri ethylamine and potassium carbonate failed to give the expected results. Cyclization in polyphosphoric acid and phosphorus (III) oxychloride failed. Even the idea of first condensing 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one **6** with amine, followed by cyclization to yield aminomethyl psoralens failed, since the cyclization reaction gave mixture of products **(Scheme 4)**. Condensation of 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one **6** with morpholine gave 4-morpholin-4-ylmethyl-7-(2-oxo-propoxy)-chromen-2-one **23** as confirmed from ^{1}H NMR **(Figure 18)**, but could not be cyclized to aminomethyl psoralens. ^{1}H NMR of **23** showed signals at δ 2.30 (s, 3H, $-COCH_3$), 2.53-2.55 (t, 4H, C3'-CH_2- and C5'-CH_2-), 3.59 (s, 2H, C4-CH_2-), 3.72-3.74 (t, 4H, C2'-CH_2- and C6'-CH_2-), 4.64 (s, 2H, C7-OCH_2CO-), 6.40 (s, 1H, C3-H), 6.75-6.76 (d, 1H, J = 2.56 Hz, C8-H), 6.86-6.89 (dd, 1H, J = 2.6 Hz and J = 8.88 Hz, C6-H) and 7.78-7.80 (d, 1H, J = 8.88 Hz, C5-H) which confirmed the structure.

Consequently the concentration of ethanolic potassium hydroxide was reduced from 0.1 *N* to 0.025 *N* and the cyclization of 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one **6** and 3-bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one **16** to 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7** and 6-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **17** respectively was carried out at 65-70 °C, which gave the desired results.

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



Scheme 4

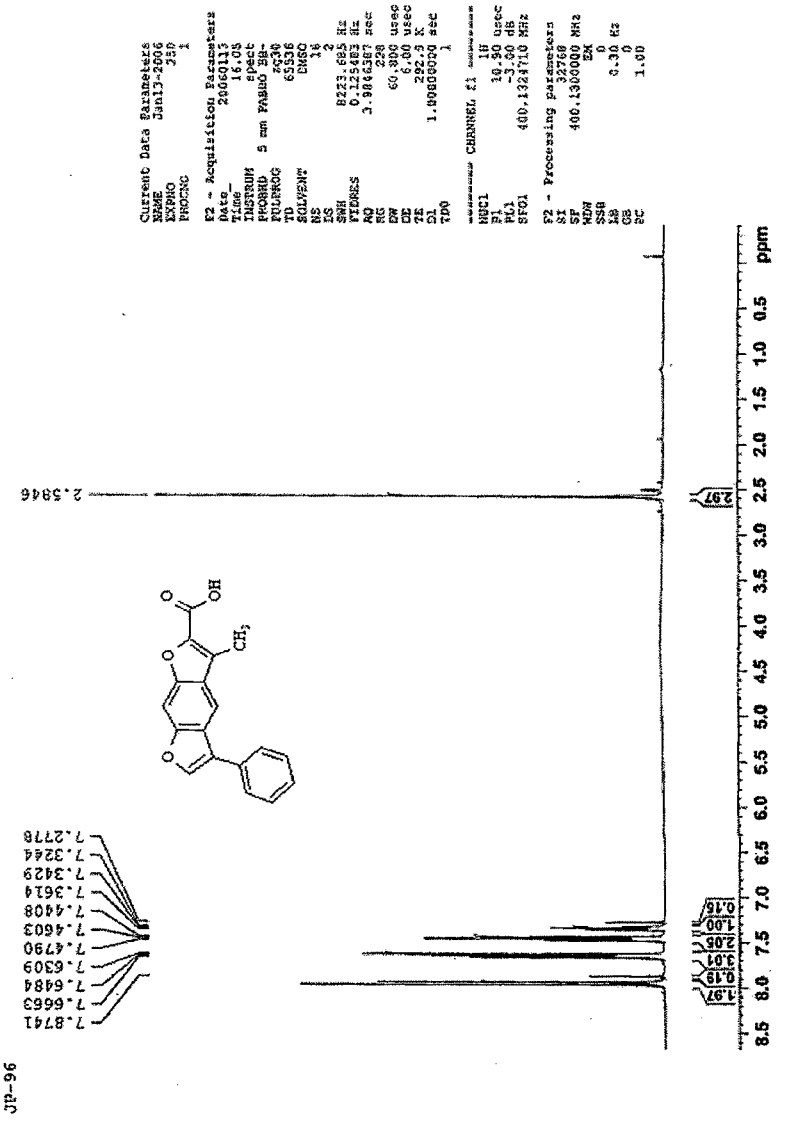


Figure 15: ^{1}H NMR of compound 3-methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid **21**.

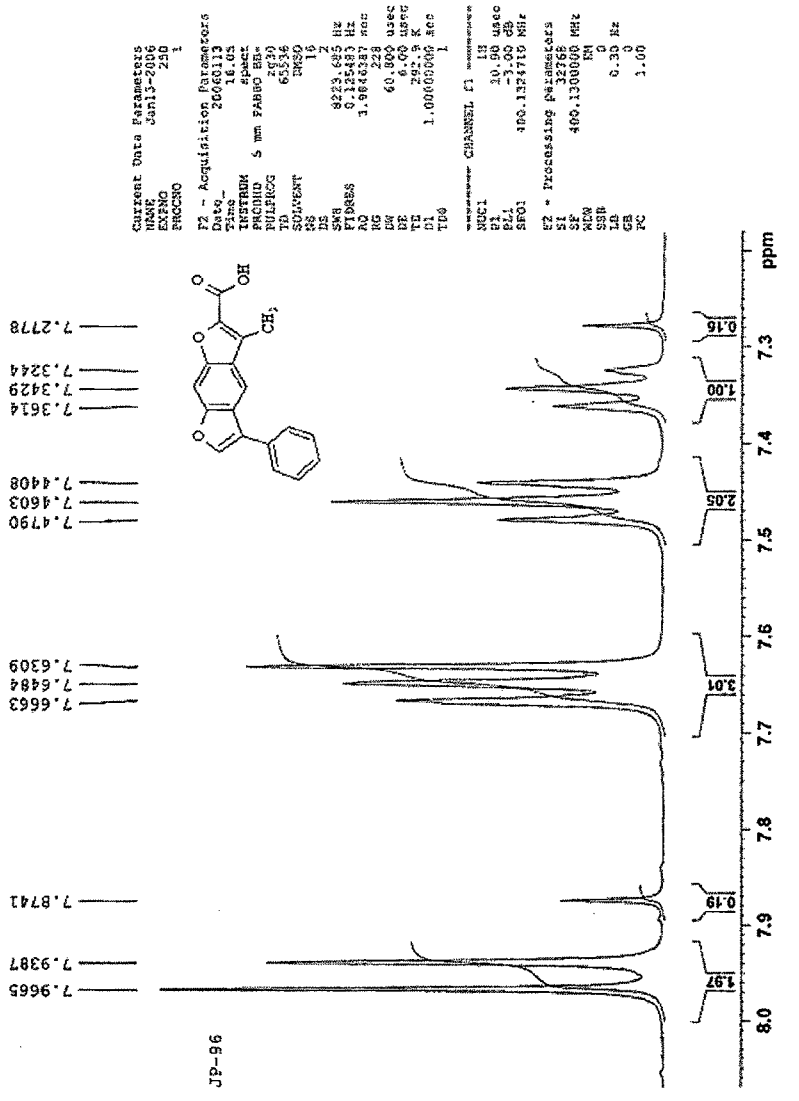


Figure 15: ^{1}H NMR of compound 3-methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid **21**.

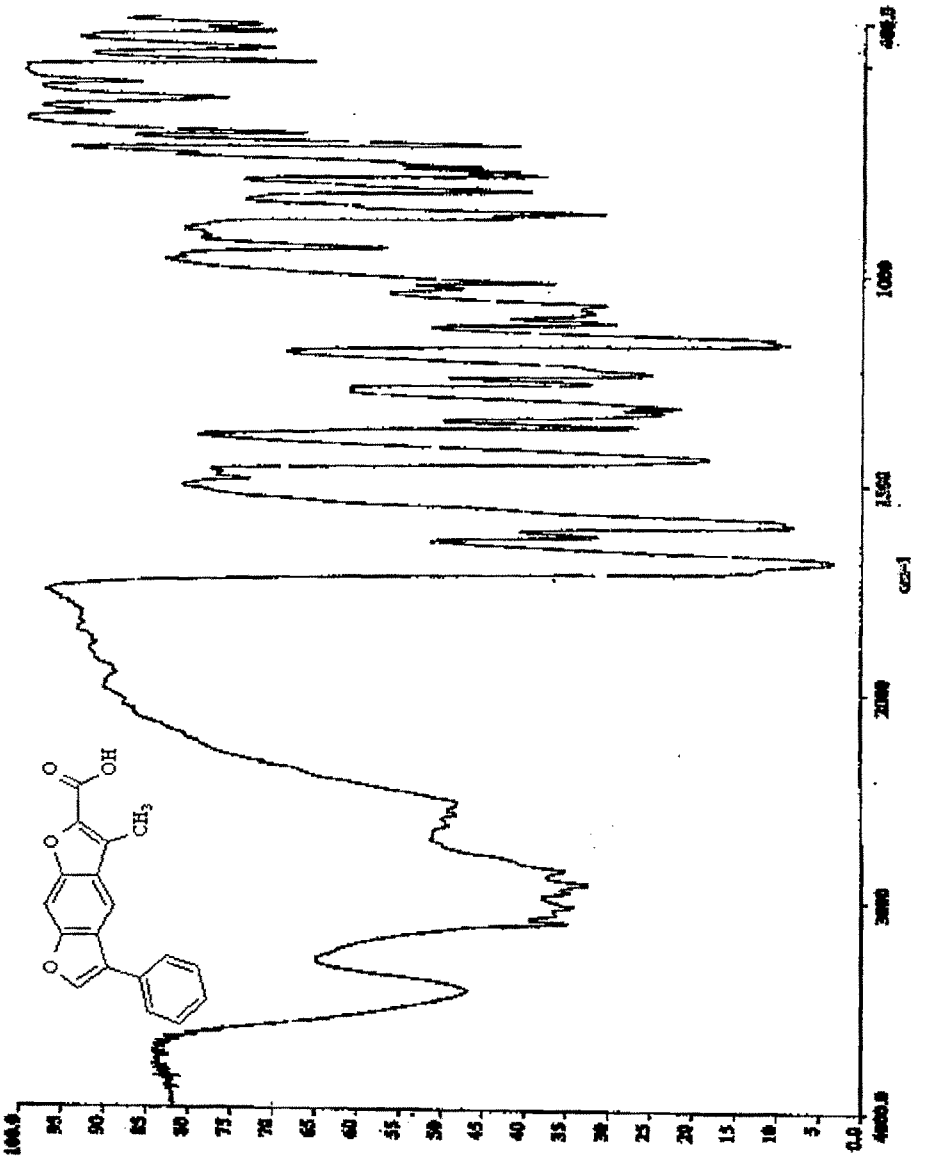


Figure 16: IR of compound 3-methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid **21**.

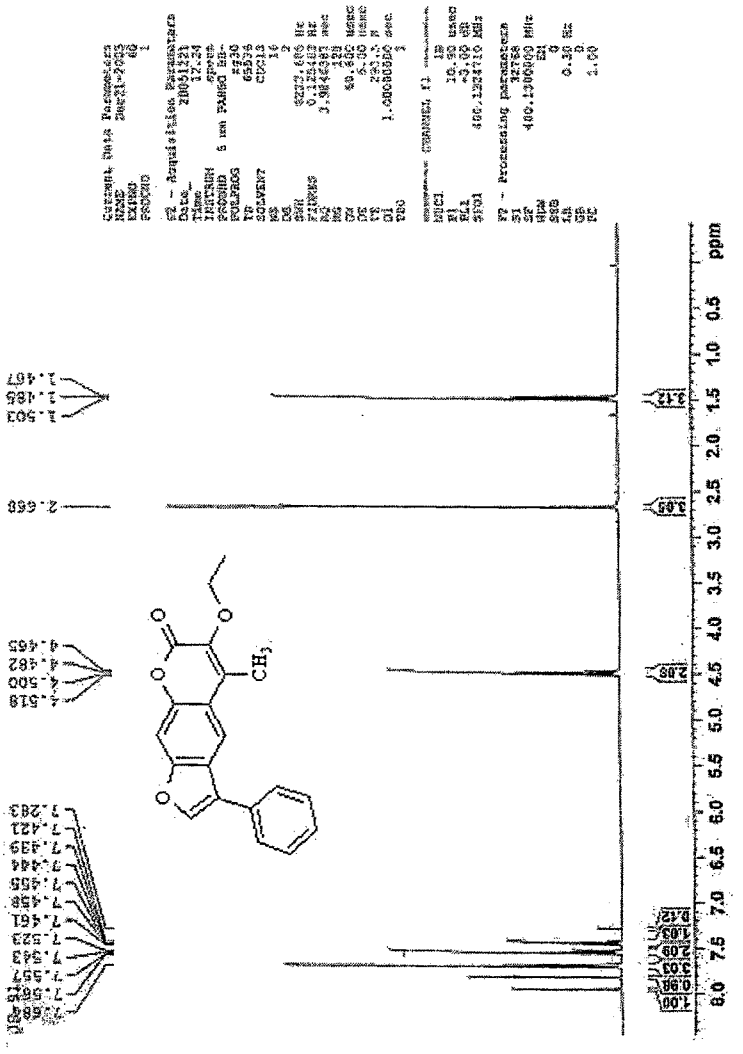


Figure 17: ^{1}H NMR of compound 6-ethoxy-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **22**.

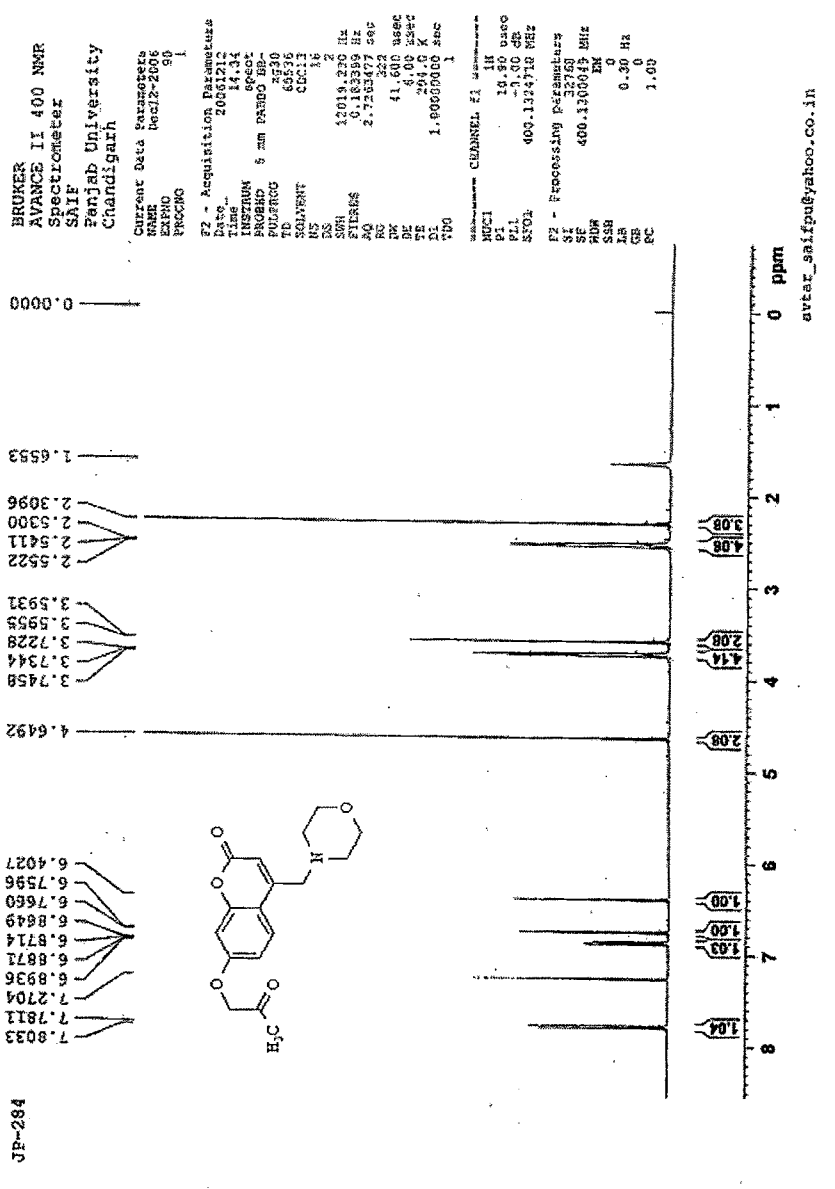


Figure 18: ^{1}H NMR of compound 4-morpholin-4-ylmethyl-7-(2-oxo-propoxy)-chromen-2-one **23**.

4.3 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. UV spectra were recorded on Perkin Elmer Lambda 35 UV/Vis spectrophotometer. The mass spectrum was obtained on Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS Mass Spectrometer (Model-016932) using Ion Spray source. 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, 12, 6 and 16.

To a stirred solution of 7-hydroxy-4-methyl-chromen-2-one **1** (5 g, 0.028 moles), anhydrous potassium carbonate (4.90 g, 0.035 moles) and catalytic amount of potassium iodide in (40 ml) dry acetone; a solution of mono chloroacetone (2.62 g, 0.028 moles) in (20 ml) dry acetone was added dropwise at reflux temperature. It was refluxed for 12 hours. The reaction mixture was concentrated to dryness and then poured into ice water and the solid collected by filtration. The crude product was crystallized from ethanol to give white crystals (3 g, 45.51 %) of 4-methyl-7-(2-oxo-propoxy)-chromen-2-one **2**, mp 154-156 °C lit. [14] 157 °C; ir (KBr): ν_{max}, cm^{-1}: 3061, 1705, 1609, 1591, 1454, 1384, 1360, 1288, 1220, 1166, 958; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.32 (d, 3H, J = 0.8 Hz, C4-CH_3), 2.42 (s, 3H, -$COCH_3$), 4.66 (s, 2H, -OCH_2CO-), 6.18 (d, 1H, J = 0.8 Hz, C3-H), 6.77-6.78 (d, 1H, J = 2.8 Hz, C8-H), 6.89-6.92 (dd, 1H, J = 2.8 Hz and J = 8.8 Hz, C6-H), 7.54-7.56 (d, 1H, J = 8.8 Hz, C5-H).

Anal. Calcd. for $C_{13}H_{12}O_4$ (232.23): C, 67.23; H, 5.20. Found: C, 67.02; H, 5.11.

Potassium iodide is not required for the preparation of compounds **12** and **16**.

4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one (12).

This compound was obtained by column chromatographic purification using petroleum ether (60-80 °C): ethyl acetate (7:3) eluent, as white crystals, 43.2 % yield, mp 169-171 °C lit. [15] 173 °C; ir (KBr): ν_{max}, cm^{-1}: 3071, 1698, 1612, 1596, 1451, 1391, 1366, 1283, 1230, 1160, 968; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.34 (d, 3H, J = 0.9 Hz, C4-CH_3), 4.58 (s, 2H, -OCH_2CO-), 6.19 (d, 1H, J = 0.9 Hz, C3-H), 6.79-6.80 (d, 1H, J = 2.8 Hz, C8-H), 6.89-6.93 (dd, 1H, J = 2.8 Hz and J = 8.8 Hz, C6-H), 7.52-7.68 (m, 6H, C5-H and C2'-H to C6'-H phenyl protons).

Anal. Calcd. for $C_{18}H_{14}O_4$ (294.30): C, 73.46; H, 4.79. Found: C, 72.99; H, 4.34.

3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one (6).

This compound was obtained as white crystals (DMF / ethanol), 67.82 % yield, mp 204-206 °C; ir (KBr): ν_{max}, cm^{-1}: 3062, 2910, 1719, 1698, 1628, 1593, 1392, 1218; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.32 (s, 3H, C4-CH_3), 2.62 (s, 3H, -$COCH_3$), 4.67 (s, 2H, -OCH_2CO-), 6.78-6.79 (d, 1H, J = 2.4 Hz, C8-H), 6.92-6.95 (dd, 1H, J = 2.4 Hz and J = 9.2 Hz, C6-H), 7.60-7.62 (d, 1H, J = 9.2 Hz, C5-H).

Anal. Calcd. for $C_{13}H_{11}O_4Br$ (311.12): C, 50.18; H, 3.56. Found: C, 50.06; H, 3.23.

3-bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one (16).

This compound was obtained as white crystals (toluene), 62.65 % yield, mp 181-182 °C; ir (KBr): ν_{max}, cm^{-1}: 3060, 2907, 1717, 1698, 1623, 1598, 1384, 1210; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H, C4-CH_3), 4.61 (s, 2H, -OCH_2CO-), 6.79-6.80 (d, 1H, J = 2.4 Hz, C8-H), 6.93-6.95 (dd, 1H, J = 2.4 Hz and J = 9.2 Hz, C6-H), 7.50-7.66 (m, 6H, C5-H and C2'-H to C6'-H phenyl protons).

Anal. Calcd. for $C_{18}H_{13}O_4Br$ (373.20): C, 57.93; H, 3.51. Found: C, 57.61; H, 3.31.

General procedure for the preparation of 3, 13, 7 and 17.

Compound 4-methyl-7-(2-oxo-propoxy)-chromen-2-one **2** (1 g, 0.0043 moles) was dissolved in 0.1 *N* ethanolic potassium hydroxide (100 ml) and refluxed for 12

hours. The excess ethanol was removed by distillation *in vacuo* and the reaction mixture was poured into ice-hydrochloric acid and the solid collected by filtration. The crude product was crystallized from ethanol to give white crystals (0.38 g, 41.19 %) of 3,5-dimethyl-furo[3,2-*g*]chromen-7-one **3**, mp 224-226 °C lit. [14] 220 °C; ir (KBr): ν_{max}, cm^{-1}: 3090, 1728, 1639, 1610, 1580, 1388, 1144, 1082; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.21-2.22 (d, 3H, J = 1.5 Hz, C3-CH_3), 2.51-2.52 (d, 3H, J = 1.08 Hz, C5-CH_3), 6.27-6.28 (d, 1H, J = 1.08 Hz, C6-H), 7.36 (s, 1H, C9-H), 7.52 (d, 1H, J = 1.5 Hz, C2-H), 7.58 (s, 1H, C4-H).

Anal. Calcd. for $C_{13}H_{10}O_3$ (214.21): C, 72.88; H, 4.70. Found: C, 72.62; H, 4.51.

In the preparation of compounds **7** and **17** the concentration of ethanolic potassium hydroxide was reduced from 0.1 *N* to 0.025 *N* and the reaction was maintained at 65-70 °C for 12 hours.

5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one (13).

This compound was obtained as white crystals (ethanol), 40.57 % yield, mp 181-182 °C lit. [15] 185 °C; ir (KBr): ν_{max}, cm^{-1}: 3090, 1720, 1632, 1612, 1575, 1385, 1142, 1075; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.48-2.49 (d, 3H, J = 1.1 Hz, C5-CH_3), 6.29-6.30 (d, 1H, J = 1.1 Hz, C6-H), 7.48-7.49 (m, 1H, C4'-H), 7.54-7.59 (m, 2H, C3'-H and C5'-H), 7.54 (s, 1H, C9-H), 7.65-7.67 (m, 2H, C2'-H and C6'-H), 7.86 (s, 1H, C2-H), 7.90 (s, 1H, C4-H).

Anal. Calcd. for $C_{18}H_{12}O_3$ (276.28): C, 78.25; H, 4.37. Found: C, 77.85; H, 4.30.

6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one (7).

This compound was obtained as yellow crystals (toluene), 26.92 % yield, mp 224-226 °C; ir (KBr): ν_{max}, cm^{-1}: 3088, 2925, 1733, 1693, 1639, 1602, 1556, 1350, 1151, 1074; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.31-2.32 (d, 3H, J = 1.6 Hz, C3-CH_3), 2.74 (s, 3H, C5-CH_3), 7.42 (s, 1H, C9-H), 7.50 (d, 1H, J = 1.6 Hz, C2-H), 7.74 (s, 1H, C4-H); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 7.86 (C3-CH_3), 20.06 (C5-CH_3), 99.68 (C6), 111.12 (C9), 115.21 (C3), 115.73 (C4), 115.90 (C4a), 126.93 (C3a), 143.52 (C2),

149.91 (C8a), 151.29 (C9a), 156.50 (C5), 157.22 (C7); lcms: m/z (relative intensity, 100%): 317 (8.88) M+23 (from Na^+), 295.1 (100) M+1, 292.9 (100) M^+.

Anal. Calcd. for $C_{13}H_9O_3Br$ (293.11): C, 53.27; H, 3.09. Found: C, 52.98; H, 3.11.

6-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one (17).

This compound was obtained as yellow crystals (ethanol), 23.64 % yield, mp 208-210 °C; ir (KBr): ν_{max}, cm^{-1}: 3085, 2925, 1734, 1687, 1631, 1605, 1559, 1345, 1154, 1070; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.69 (s, 3H, C5-CH_3), 7.47-7.49 (m, 1H, C4'-H), 7.54-7.58 (m, 2H, C3'-H and C5'-H), 7.56 (s, 1H, C9-H), 7.64-7.66 (m, 2H, C2'-H and C6'-H), 7.87 (s, 1H, C2-H), 8.02 (s, 1H, C4-H).

Anal. Calcd. for $C_{18}H_{11}O_3Br$ (355.18): C, 60.86; H, 3.12. Found: C, 60.50; H, 3.07.

General procedure for the preparation of 4 and 14.

Compound 3,5-dimethyl-furo[3,2-g]chromen-7-one 3 (1 g, 0.0046 moles) was dissolved in acetic acid (40 ml) by warming and to this stirred solution, a solution of bromine (0.24 ml, 0.0046 moles) in acetic acid (10 ml) was added gradually. It was stirred for 3 hours at room temperature and then poured into ice water and the solid collected by filtration. The crude product crystallized from ethanol to give yellow crystals (0.9 g, 65.77 %) of 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4**, mp 230-232 °C; ir (KBr): ν_{max}, cm^{-1}: 3085, 1758, 1689, 1640, 1577, 1341, 1121; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, C3-CH_3), 2.52 (d, 3H, J = 1.08 Hz, C5-CH_3), 6.27-6.28 (d, 1H, J = 1.08 Hz, C6-H), 7.36 (s, 1H, C9-H), 7.58 (s, 1H, C4-H); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 8.80 (C3-CH_3), 19.21 (C5-CH_3), 99.48 (C9), 113.76 (C6), 113.92 (C3), 115.26 (C2), 116.60 (C4), 126.58 (C4a), 127.94 (C3a), 151.45 (C8a), 152.45 (C5), 156.14 (C9a), 160.80 (C7).

Anal. Calcd. for $C_{13}H_9O_3Br$ (293.11): C, 53.27; H, 3.09. Found: C, 52.98; H, 3.11.

2-bromo-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one (14).

This compound was obtained as yellow crystals (ethanol), 61.2 % yield, mp 238-239 °C; ir (KBr): ν_{max}, cm^{-1}: 3084, 1750, 1686, 1636, 1578, 1347, 1110; ^1H nmr

($CDCl_3$, 400 MHz): δ 2.46 (d, 3H, J = 1.05 Hz, C5-CH_3), 6.28 (d, 1H, J = 1.05 Hz, C6-H), 7.47-7.64 (m, 6H, C3-phenyl protons and C9-H), 7.75 (s, 1H, C4-H).
Anal. Calcd. for $C_{18}H_{11}O_3Br$ (355.18): C, 60.86; H, 3.12. Found: C, 60.82; H, 2.94.

General procedure for the preparation of (8-10, 18-20).

A solution of 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7** (0.5 g, 0.0017 moles) and piperidine (0.35 ml, 0.0035 moles) in dry DMF (10 ml) was heated at 95-100 °C for 1 hour. The reaction mixture was poured into ice water and the solid collected by filtration. The crude product was crystallized from ethanol to give light brown crystals (0.28 g, 55.20 %) of 3-methyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one **8**, mp 185 °C; ir (KBr): ν_{max}, cm^{-1}: 3059, 2971, 1718, 1639, 1616, 1579, 1454, 1337, 1158, 1120, 1096; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.47-1.48 (t, 2H, C4'-CH_2-), 1.59-1.65 (m, 4H, C3'-CH_2- and C5'-CH_2-), 2.27-2.28 (d, 3H, J = 1.2 Hz, C3-CH_3), 2.51 (t, 4H, C2'-CH_2- and C6'-CH_2-), 3.66 (s, 2H, C5-CH_2-), 6.51 (s, 1H, C6-H), 7.35 (s, 1H, C9-H), 7.43-7.44 (d, 1H, J = 1.2 Hz, C2-H), 7.92 (s, 1H, C4-H); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 7.84 (C2-*C*H_3), 24.10 (C3' and C5'), 26.07 (C4'), 55.05 (C2' and C6'), 59.91 (C5-*C*H_2-), 99.59 (C6), 112.51 (C9), 114.92-115.73 (C4, C4a and C3), 126.23 (C3a), 143 (C2), 151.86 (C8a), 153.04 (C9a), 156.42 (C5), 161.57 (C7).
Anal. Calcd. for $C_{18}H_{19}O_3N$ (297.35): C, 72.70; H, 6.44; N, 4.71. Found: C, 72.56; H, 6.18; N, 4.44.

3-phenyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one (18).

This compound was obtained by column chromatographic purification using petroleum ether (60-80 °C): ethyl acetate eluent, as light brown crystals, 52.3 % yield, mp 158-160 °C; ir (KBr): ν_{max}, cm^{-1}: 3051, 2971, 1710, 1633, 1611, 1571, 1450, 1333, 1158, 1122, 1091; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.51 (t, 2H, C4'-CH_2-), 1.64-1.66 (t, 4H, C3'-CH_2- and C5'-CH_2-), 2.52 (t, 4H, C2'-CH_2- and C6'-CH_2-), 3.67 (s, 2H, C5-CH_2-), 6.52 (s, 1H, C6-H), 7.43-7.70 (m, 5H, C3-phenyl protons), 7.55 (s, 1H, C9-H), 7.86 (s, 1H, C2-H), 8.50 (s, 1H, C4-H).

Anal. Calcd. for $C_{23}H_{21}O_3N$ (359.42): C, 76.86; H, 5.88; N, 3.89. Found: C, 76.52; H, 5.61; N, 3.67.

3-methyl-5-morpholin-4-ylmethyl-furo[3,2-*g*]chromen-7-one (9).

This compound was obtained as light brown crystals (DMF / ethanol), 59.6 % yield, mp 236-238 °C; ir (KBr): $\nu_{max,}$ cm^{-1}: 3060, 2969, 1719, 1632, 1611, 1577, 1455, 1337, 1153, 1115, 1094; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.30 (d, 3H, J = 1.2 Hz, C3-CH_3), 2.62-2.63 (t, 4H, C3'->N-CH_2- and C5'->N-CH_2-), 3.75-3.79 (m, 6H, C2'-OCH_2- C6'-OCH_2- and C5-CH_2-), 6.56 (s, 1H, C6-H), 7.41 (s, 1H, C9-H), 7.48 (d, 1H, J = 1.2 Hz, C2-H), 7.92 (s, 1H, C4-H); lcms: m/z (relative intensity, 100%): 338.1 (7.27) M+39 (from K^+), 322.2 (38.18) M+23 (from Na^+), 301.2 (70.90) M+2, 299.9 (100) M+1.

Anal. Calcd. for $C_{17}H_{17}O_4N$ (299.32): C, 68.21; H, 5.72; N, 4.67. Found: C, 67.91; H, 5.56; N, 4.33.

5-morpholin-4-ylmethyl-3-phenyl-furo[3,2-*g*]chromen-7-one (19).

This compound was obtained by column chromatographic purification using petroleum ether (60-80 °C): ethyl acetate (7:3), as light brown crystals, 57 %, mp 185-187 °C; ir (KBr): $\nu_{max,}$ cm^{-1}: 3057, 2966, 1712, 1632, 1606, 1573, 1454, 1330, 1152, 1115, 1091; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.64-2.66 (t, 4H, C3'->N-CH_2- and C5'->N-CH_2-), 3.76-3.79 (m, 6H, C2'-OCH_2-, C6'-OCH_2- and C5-CH_2-), 6.59 (s, 1H, C6-H), 7.45-7.76 (m, 6H, C9-H and C3-phenyl protons), 7.80 (s, 1H, C2-H), 8.13 (s, 1H, C4-H).

Anal. Calcd. for $C_{22}H_{19}O_4N$ (361.39): C, 73.11; H, 5.29; N, 3.87. Found: C, 72.88; H, 5.10; N, 3.77.

3-methyl-5-(4-phenyl-piperazin-1-ylmethyl)-furo[3,2-*g*]chromen-7-one (10).

This compound was obtained as light brown crystals (ethanol), 64.2 % yield, mp 214-216 °C; ir (KBr): $\nu_{max,}$ cm^{-1}: 3064, 2963, 1720, 1637, 1619, 1579, 1460, 1340, 1158, 1119, 1084; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.31 (d, 3H, J = 1.2 Hz, C3-CH_3), 2.80 (t, 4H, C3'-CH_2- and C5'-CH_2-), 3.27-3.30 (t, 4H, C2'-CH_2- and C6'-CH_2-),

3.83 (s, 2H, C5-CH_2-), 6.60 (s, 1H, C6-H), 6.89-7.32 (m, 5H, N4'-phenyl protons), 7.45 (s, 1H, C9-H), 7.49 (d, 1H, J = 1.2 Hz, C2-H), 7.98 (s, 1H, C4-H).

Anal. Calcd. for $C_{23}H_{22}O_3N_2$ (374.43): C, 73.77; H, 5.92; N, 7.48. Found: C, 73.51; H, 5.77; N, 7.09.

3-phenyl-5-(4-phenyl-piperazin-1-ylmethyl)-furo[3,2-*g*]chromen-7-one (20).

This compound was obtained as light brown crystals (ethanol / toluene), 61.9 % yield, mp 180 °C dec.; ir (KBr): ν_{max}, cm^{-1}: 3061, 2963, 1713, 1631, 1611, 1578, 1450, 1337, 1157, 1108, 1088; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.79 (t, 4H, C3'-CH_2- and C5'-CH_2-), 3.3 (t, 4H, C2'-CH_2- and C6'-CH_2-), 3.80 (s, 2H, C5-CH_2-), 6.57 (s, 1H, C6-H), 6.92-7.68 (m, 10H, C3-phenyl protons and N4'-phenyl protons), 7.55 (s, 1H, C9-H), 7.86 (s, 1H, C2-H), 8.45 (s, 1H, C4-H).

Anal. Calcd. for $C_{28}H_{24}O_3N_2$ (436.50): C, 77.04; H, 5.54; N, 6.41. Found: C, 76.72; H, 5.41; N, 6.22.

4-morpholin-4-ylmethyl-7-(2-oxo-propoxy)-chromen-2-one (23).

This product was obtained by column chromatographic purification using petroleum ether (60-80 °C): ethyl acetate eluent (8:2), as white crystals, 50.3 % yield, mp 138-140 °C; ^1H nmr ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H, -$COCH_3$), 2.53-2.55 (t, 4H, C3'->N-CH_2- and C5'->N-CH_2-), 3.59 (s, 2H, C4-CH_2-), 3.72-3.74 (t, 4H, C2'-OCH_2- and C6'-OCH_2-), 4.64 (s, 2H, C7-OCH_2CO-), 6.40 (s, 1H, C3-H), 6.75-6.76 (d, 1H, J = 2.56 Hz, C8-H), 6.86-6.89 (dd, 1H, J = 2.6 Hz and J = 8.88 Hz, C6-H), 7.78-7.80 (d, 1H, J = 8.88 Hz, C5-H).

Anal. Calcd. for $C_{17}H_{11}O_5N$ (309.27): C, 66.02; H, 3.58; N, 4.52. Found: C, 66.01; H, 3.33; N, 4.41.

3-methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid (21).

This compound was obtained as white amorphous powder (ethanol), mp 250 °C dec.; ir (KBr): ν_{max}, cm^{-1}: 3433, 3107, 3030, 2922, 1682, 1627, 1598, 1440, 1366, 1332, 1318, 1165, 1119; ^1H nmr ($(CD_3)_2SO$, 400 MHz): δ 2.58 (s, 3H, C3-CH_3),

7.32-7.36 (m, 1H, C4'-H), 7.44-7.47 (m, 2H, C2'-H and C6'-H), 7.63-7.66 (m, 3H, C8-H, C3'-H and C5'-H), 7.93 (s, 1H, C6-H), 7.96 (s, 1H, C4-H).

Anal. Calcd. for $C_{18}H_{12}O_4$ (292.28): C, 73. 96; H, 4.13. Found: C, 73.84; H, 4.03.

6-ethoxy-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one (22).

This compound was obtained by column chromatographic purification using petroleum ether (60-80 °C): ethyl acetate eluent (9:1), as white crystals, mp 169-171 °C; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 1.46-1.50 (t, 3H, C6-OCH_2CH_3), 2.67 (s, 3H, C5-CH_3), 4.46-4.51 (q, 2H, C6-OCH_2CH_3), 7.42-7.46 (m, 1H, C4'-H), 7.52-7.56 (m, 2H, C2'-H and C6'-H), 7.68-7.70 (m, 3H, C9-H, C3'-H and C5'-H), 7.81 (s, 1H, C2-H), 7.94 (s, 1H, C4-H).

Anal. Calcd. for $C_{20}H_{16}O_4$ (320.34): C, 74.98; H, 5.03. Found: C, 74.73; H, 4.98.

4.4 Conclusions

- Furan ring is more reactive towards electrophilic substitution reaction than the pyrone ring.

- Cyclization of 3-bromo aryloxyketones to 6-bromo psoralens can be achieved by carrying out reactions at low temperature and low alkali concentrations. Higher alkali concentration and high temperature are found to give Furocoumarilic acid, formed due to alkaline ring contraction; as well as other side reaction products.

- Compounds could be explored as a possible PUVA reagent.

4.5 References

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