SYNTHESIS AND EVALUATION OF SOME NOVEL CHROMEN 2 ONES BASED ON ANTIPSYCHOTICS DRUG

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Abstract:
Synthesis of 2-[(4-methyl-2-oxo-2H-chromen-7-yl) oxy-(aryl)] acetamide was the goal of this project activity..CDCl3 was the common solvent for all the compounds. A significant affinity for 5-HT receptors, one of the key properties of atypical antipsychotics, was validated by the literature study. evaluation of their melting temperatures, Rf values (derived from TLC), Spectral of the (1HNMR) or infrared (IR) light were used for the physicochemical characterisation.

Keywords: Chromen 2, NMR, Antipsychotic Drugs

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1.INTRODUCTION

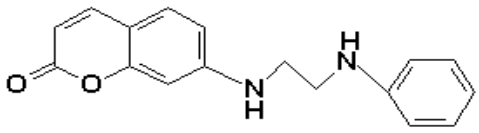
The antipsychotic agents, now more commonly called as the "neuroleptics"(neuro for nerve, and lepsis for seizure), are among those most importantA common types of medications which developed after the Second World War.

A psychotropic, psychoactive or phenotropic drug is one that inhibits, sharpens or alters behavioural, feelings, or attitude. There are two categories of mental disorders: anxiety & schizophrenia. an anxious person usually retains sufficient insight to realize that he is ill while the psychotic patient lives in a world of his own, believes that his own actions are completely rational and is a victim of his hallucinations and delusions.

The antipsychotic Medicines has the ability to calm down or subdue reckless, rough, or harsh sensitive behaviour. behaviour, leaving the higher intellectual functions relatively unaffected. Hence, they are also known as major tranquilizers [1].

Mechanism of Action

As spite of blocking D2 or automatic receptors, almost all neuroleptic drugs also inhibit D1 receptors, notably thioxanthenes, benzene, and a drug called In the beginning of a neuroleptic therapy, DA neurons awake and flow greater DA, yet after several treatments, they enter a state of physiological depolarization activation, with decreased production and elimination of DA as well as ongoing transmitter blockage [2].



PD Chromenone

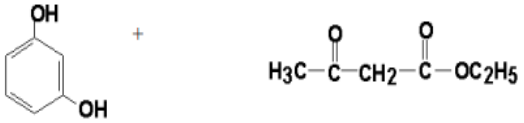
Thus, five different derivatives of chromene-2-one were synthesized which may have better efficiency and pharmacological profile. So, our prime objective is to explore potential of **2[(4-methyl-2-oxo-2*H*–chromen-7-yl)oxy-N-(aryl)]-acetamide derivatives**

2.Material and Methods

1) All the other chemicals used were procured from Merck and were of analytical grade.
2) The silica gel used for TLC was "Silica Gel H" was bought at Bayer & applied to acrylic laboratory plates.
3) Indigo chambers was used to see the plates of TLC.
4) The melting points of final products and the The transparent pipette technique was used to identify the erroneous stages.
5) The chemicals' IR spectrum were taken on “FTIR Schimadzu-3100” at University of Pune, Chemistry Department, Instrumental Section.
6) Each of these chemicals' spectrum from NMR have been obtained on “FTNMR VarianMercury 300” at University of Pune, Chemistry Department, Instrumental Section. The solvent used for all the compounds was $CDCl_3$.

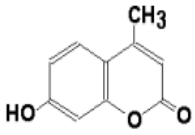
Scheme of synthesis

Step-I: Synthesis of 7-Hydroxy 4-methyl-chromen-2-ones (1)



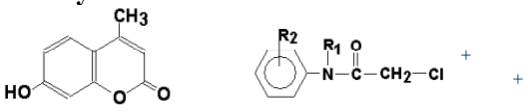
Resorcinol Ethyl acetoacetate

Conc Sulphuric acid
10% NaOH
2M H_2SO_4



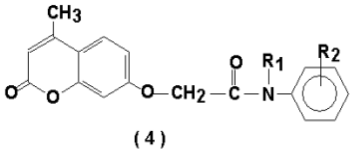
7-Hydroxy 4-methyl-chromen-2-ones(1)

Step-III: synthesis of various derivatives

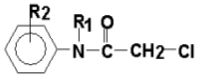


(3) 7-Hydroxy 4-methyl-chromen-2-ones (1)

Reflux for 30 hours Toluene TEA



(4)



(3)

Sr. no.	Compound name	R_1	R_2
1	Chloroacetanilide (3a)	-H	-H
2	4-Methyl chloroacetanilide (3b)	-H	4(-CH_3)
3	2-Methyl chloroacetanilide (3c)	-H	2(-CH_3)
4	4-Methoxy chloroacetanilide (3d)	-H	4(-OCH_3)
5	N-Methyl chloroacetanilide (3e)	N-CH_3	-H
6	**4'-Bromo-2'-chloroacetanilide-(3f)**		
7	**4′-Chloro-2-cyanoacetanilide-3g**		
8	N-(4-Nitrophenyl)acetamide – 3h		

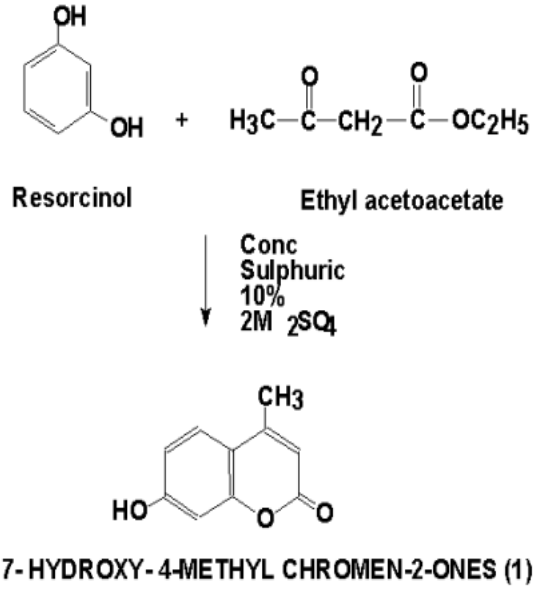
Code no.	Compound name	R_1	R_2
4a	2-[(4-Methyl-2-oxo-2H-chromen-7yl oxy)-Nphenyl] acetamide	-H	-H
4b	2-[(4-Methyl-2-oxo-2H-chromen-7yl oxy)-N-(4methylphenyl)] acetamide	-H	4(-CH_3)
4c	2-[(4-Methyl-2-oxo-2H-chromen-7yl oxy)-N-(2methylphenyl)] acetamide	-H	2(-CH_3)
4d	2-[(4-Methyl-2-oxo-2H-chromen-7yl oxy)-N-(4methoxy phenyl)] acetamide	-H	4(-OCH_3)
4e	2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)-N - methyl-N -phenyl-acetamide	N-CH_3	-H

4f N-(4-methoxyphenyl)-2-[(8-methyl-2-oxo-4-propyl-2H-chromen-7-yl)oxy]acetamide 4g N-(7-Methoxy-4-methyl-2-oxo-2H-chromenyl)-2-bromoacetamide

4h N-(2,3-dimethylphenyl)-2-((4-methyl-2-oxo-2H-chromen-7yl)oxy)acetamide

Synthesis of 7-hydroxy-4-methylchromen-2-one (COUM)

The method of Pechmann and Duisberg was followed for the preparation of 7-hydroxy -4 methylchromen-2-one



7- HYDROXY- 4-METHYL CHROMEN-2-ONES (1)

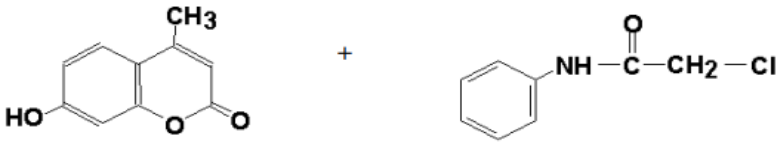
100ml. of conc. H_2SO_4*(A.R. Grade)* was kept in an ice-bath to which sodium chloride was added. When temperature fell below 10°C, a solution of [0.091mole (10 g)] resorcinol and [0.103 mole (13ml)] ethyl acetoacetate (redistilled) was added with continuous stirring for period of 2 hours. Care was taken during this addition that temperature of the solution remained below 10°C. The reaction mixture was maintained at ambient temperature after its addition for a total pf 18 hours.

At that, 200g of broken ice and 300 ml of distilled water were combined, and the response mix was added while being vigorously stirred. The cloud of particles that resulted from this was then vacuum-filtered and recovered. With several 25ml parts, icy water was utilised for cleaning everything.

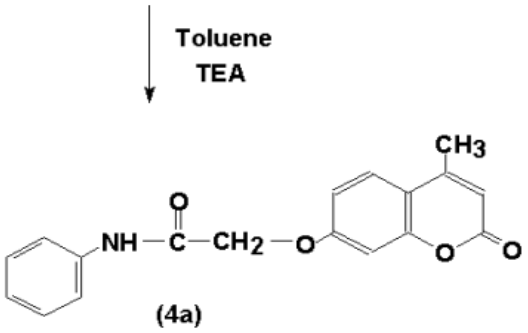
The component was dissolved in 150 ml of 5% NaOH, filtrated and then 2M H2SO4 (approximately 55 ml) was incorporated while being vigorously stirred. Litmus was then used to determine if it was sour. That unprocessed Coumarin is a was filtered and retrieved at the pump. It was washed four times in 25 cc of cold water and dried at a temperature of roughly 100 °C.

With alcohol, the good is recrystallized.

2-[(4-Methyl-2-oxo-2*H*-chromen-7yl oxy)-N-phenyl] acetamide (4a)



7-Hydroxy 4-methyl-chromen-2-ones (1) **Chloroacetanilide (3a)**



(4a)

A mixture of 1.93g (0.011mole) of 7-hydroxy-4-methylcoumarin (1) 1.695g (0.01mole) of chloroacetanilide (2a) and 1.01ml (0.01mole) of triethyl amine in 50ml of toluene retussinated for 30 hours..The resulting mix had been filtered after cool. To get rid of any remaining chromene that hadn't reacted, the reaction mix in the toluene layer was washed with a 5% NaOH solution. To get rid of any remaining triethylamine, 25 cc of water was then used to wash the area.Anhydrous sodium sulphate was covered with a toluene layer that had dried overnight. Under vacuum, toluene was extracted, then the leftover substance had been recreated from acetone.

The resulting product produced 1.4 g of 2-[(4-Methyl-2-oxo-2H-chromen-7yl oxy)-N-phenyl] acetamide (4a) upon the recrystallization from acetone**.**

Yield: 1.4 g

Percent Yield : 45.15 %

Melting Point :152-154 ºC

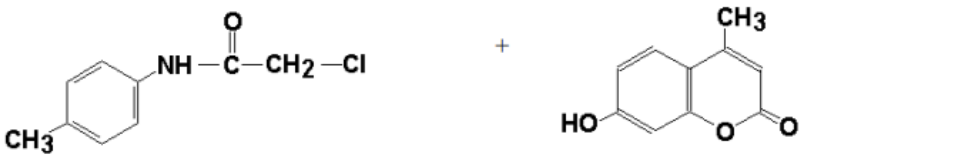
Rf value: 0.39

{Mobile phase: Benzene: Ethyl acetate (4: 1)}

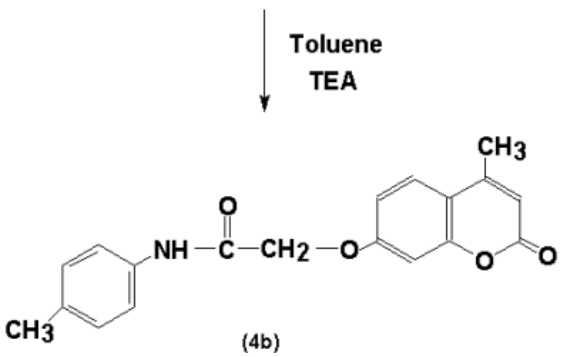
IR (KBr) Data

3303.8 cm^{-1}(s), 3072.4 cm^{-1}(s),2922 cm^{-1}(s),1703 cm^{-1}(s),1596.9-1446.6 cm^{-1} (s), 1342.4 cm^{-1}(s), 1245.4 cm^{-1}(s), 850.5 cm^{-1}(s),

2-[(4-Methyl-2-oxo-2*H*-chromen-7yloxy)-N-(4-methylphenyl)] acetamide (4b)



4-Methyl chloroacetanilide (3b) **7-Hydroxy 4-methyl-chromen-2-ones (1)**



(4b)

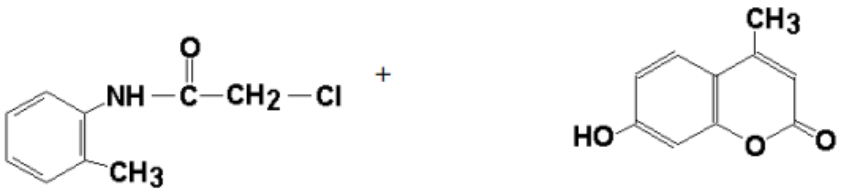
A mixture of 1.93g (0.011mole) of 7-hydroxy-4-methylcoumarin (1) 1.83g (0.01mole) of 4Methyl chloroacetanilide (3b) and 1.01ml (0.01mole) of triethyl amine in 50ml of toluene stirred for thirty hours. The ensuing solution went through filtering upon chilling.. The reaction mixture in toluene layer was washed with 5% NaOH solution to remove traces of unreacted chromene. It was followed by Triethylamine traces should be removed by wiping with 25 cc of water.Anhydrous sodium sulphate (ANS) was covered with a toluene layer that was dried overnight. Under vacuum, toluene was separated out then the leftover substance was reconstituted from acetone.

The residue on recrystallization from acetone afforded 1.gm of 2-[(4-Methyl-2-oxo-2*H*chromen-7yl oxy)-N- (4-methylphenyl)] acetamide (4b)

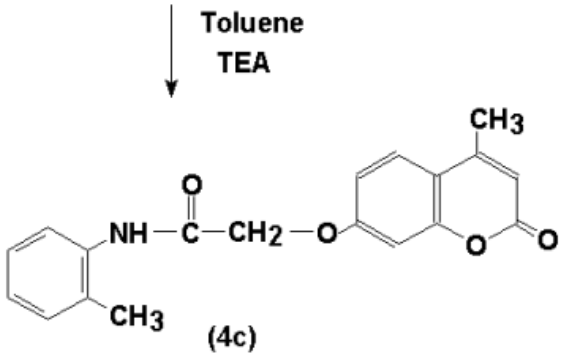
Yield :1.29 g
Percent Yield : 40 %
Melting Point :165-167 °C
Rf value : 0.38
{Mobile phase: Benzene: Ethyl acetate (4: 1)}

IR (KBr) Data
3321.2 cm^{-1}(s), 2922.2 cm^{-1}(s),1703 cm^{-1}(s),1596.9-1446.5 cm^{-1}(s), 1344.3 cm^{-1}(s),1296.1 cm^{-1}(s), 1247.4 cm^{-1}(s), 815.8 cm^{-1}(b),

2-[(4-Methyl-2-oxo-2*H*-chromen-7yloxy)-N-(2- methyl phenyl)] acetamide (4c)



2-Methyl chloroacetanilide (3c)7-Hydroxy 4-methyl-chromen-2-ones(1)



(4c)

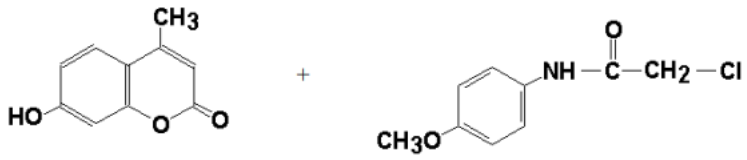
A mixture of 1.93g (0.011mole) of 7-hydroxy-4-methylcoumarin (1) and 1.83gm of 2-Methyl chloroacetanilide (3c) and 1.01ml (0.01mole) of triethyl amine in 50ml of toluene stirred for thirty hours. The reaction mixture was filtered before chilling.. The reaction mixture in toluene layer was washed with 5% NaOH solution to remove traces of unreacted chromene. It was followed by washing Triethylamine residues should be eliminated with 25 cc of water.Anhydrous sodium sulphate was covered with a toluene layer that had been dried overnight. Using sweep, benzene was taken out, and the remaining substance was formed again from acetonitrile.

The residue on recrystallization from acetone afforded 1.56 g of 2-[(4-Methyl-2-oxo-2*H*chromen-7yl oxy)-N-(2- methyl phenyl]acetamide (4c)

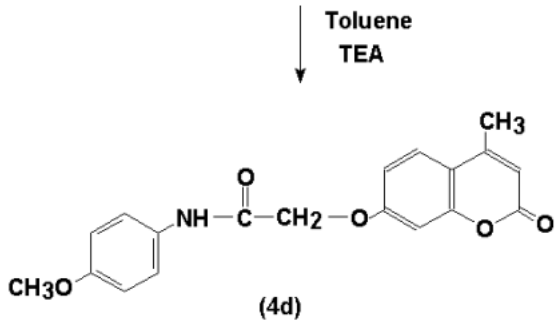
Yield :1.56 g
Percent Yield : 48.39 %
Melting Point :167-169 °C
Rf value :0.9
{Mobile phase: Benzene: Ethyl acetate (5: 1)}

IR (KBr) Data
3319.3 cm^{-1}(s), 3068.5 cm^{-1}(s),2977.9 cm^{-1}(s),1699.2cm^{-1}(s), 1620.1-1448.4 cm^{-1}(s), 1334.6 cm^{-1}(s),1290.3 cm^{-1}(s), 1253.6 cm^{-1}(s), 858.3 cm^{-1}(s),

N- (4-Methoxy phenyl)-2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy) acetamide (4d)



4-Methoxy chloroacetanilide (3d) **7-Hydroxy 4-methyl-chromen-2-ones (1)**
(1)



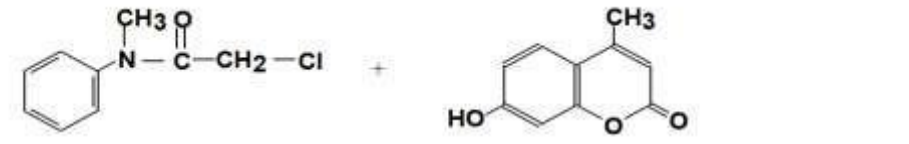
(4d)

A mixture of 1.93g (0.011mole) of 7-hydroxy-4-methylcoumarin and1.99gm of 4-Methoxy chloroacetanilide (3d) and 1.01ml (0.01mole) of triethyl amine in 50ml of toluene 30 hours of refluxing occurred. The ensuing solution underwent filtering following cool. The reaction mixture in toluene layer was washed 5% NaOH solution to get rid of any remaining chromene that hasn't been converted. To get rid of all the remaining triethylamine, 25 cc of water were then utilised for cleaning the area.Anhydrous sodium sulphate was coated with a toluene layer that was dried overnight. Under vacuum, toluene was removed, and the remaining substance was reconstituted form methanol.

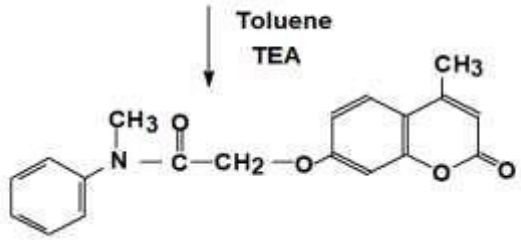
The resulting product produced 1 g of 2-[(4-Methyl-2-oxo-2H-chromen-7yl oxy)-N-(4methoxy phenyl]acetamide (4d) upon re-cry form acetone.
Yield :1.41 g
Percent Yield : 41.7 %
Melting Point :172-174 ^{o}C
Rf value :0.4
{Mobile phase: Benzene: Ethyl acetate (4: 1)}

IR (KBr) Data
3303.8 cm^{-1}(s), 3109.0 cm^{-1}(b),2353 cm^{-1}(s),1706.9cm^{-1}(s), 1606.6-1444.6 cm^{-1}(m), 1365.5 cm^{-1}(s),1328.9 cm^{-1}(s), 1251.7 cm^{-1}(s), 823.5 cm^{-1}(s).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N,N-methyl-phenyl-acetamide (4e)



N-Methyl chloroacetanilide (3e) **7-Hydroxy 4-methyl-chromen-2-ones (1)**



A mixture of 1.93g (0.011mole) of 7-hydroxy-4-methylcoumarin and1.71g of N- methyl chloroacetanilide (3e) and 1.01ml (0.01mole) of triethyl amine in 50ml of toluene 30 hours of refluxing occurred. The reaction mixture was filtered before settlingThe reaction mixture in toluene layer was washed with 5% NaOH solution to remove traces of unreacted chromene. It was

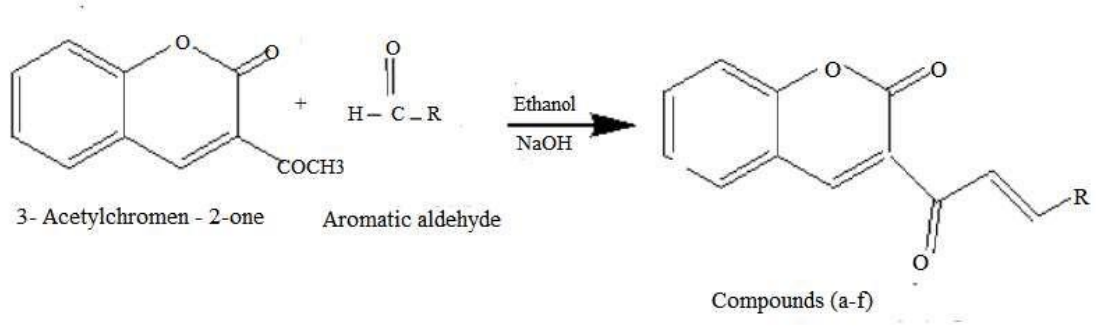
followed by washing Triethylamine traces should be eliminated using 25 cc of solution.Anhydrous sodium sulphate was coated with a toluene layer that was dried overnight. By vacuum, toluene was extracted, and the leftover substance was reconstituted form acetone.

The remainder produced 1.33 g of 2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)-N-N methylphenyl-acetamide (4e) upon re-cry from methanol.

Yield :1.33 g
Percent Yield :41.35 %
Melting Point :145-147 ºC
Rf value :0.52
{Mobile phase: Benzene: Ethyl acetate (4: 1)}

IR (KBr) Data
3053.1 cm^{-1}(s), 2858.3 cm^{-1}(s),1687.6 cm^{-1}(s), 1614.3-1434.6 cm^{-1}(s), 1396.4 cm^{-1}(s), 1344.3 cm^{-1}(s), 1276.8 cm^{-1}(s), 835.1 cm^{-1}(s)

Synthesis of some new 3- (substituted) Chromen-2-one (a-f)



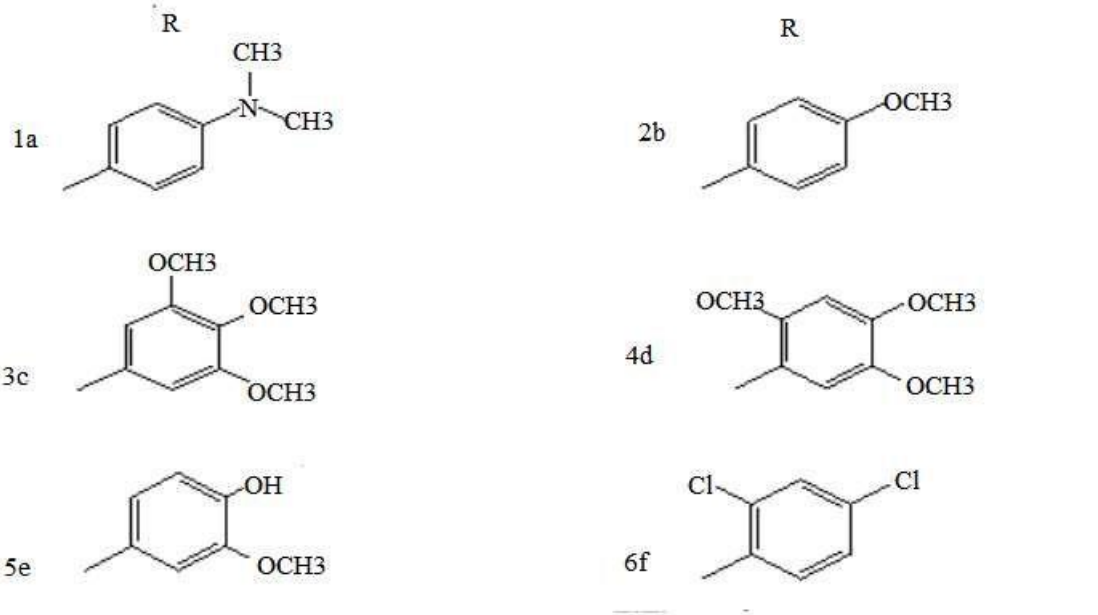


Fig. Synthesis of some new 3- (substituted) Chromen-2-one (a-f)

Table: Name of synthesized compounds

Sr.no.	Compound code	Compound name
1	A	3-(3(4-dimethylamino)Phenylacryloyl)-Chromen-2-one
2	B	3-(3(4-methoxy)Phenylacryloyl)-Chromen-2- one
3	C	3-(3(3, 4, 5-trimethoxy)Phenylacryloyl)-Chromen-2-one

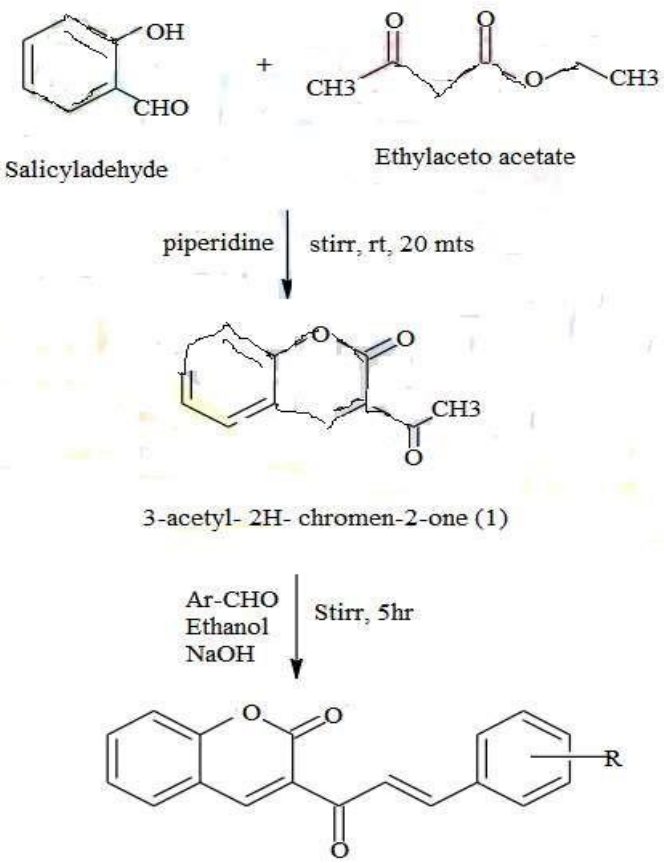
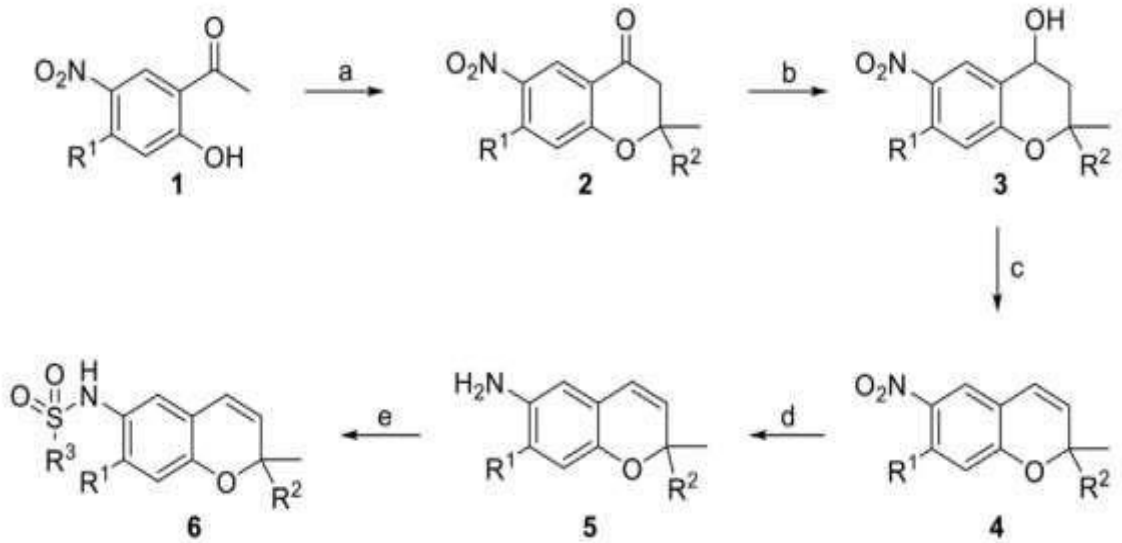


Fig. Synthesis of 3- [(2E)-3-(substituted phenyl) prop-2-enoyl]-2H-chromen-2-one (2a2c)

Table: Synthesized compounds

Sr. no.	Compound code	R
1	2a	-H
2	2b	-4-NH_2
3	2c	-4-NO_2

N-(2,7-dimethyl-2-alkyl-2H-chromen-6-yl) sulfonamide derivatives as selective serotonin 5-HT6 receptor antagonists

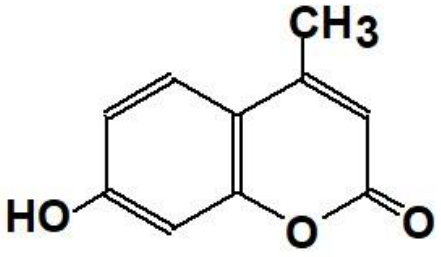


Scheme: Reagents and conditions: (a) R2COCH3, piperidine, toluene, 80 ◦C, 12 h; (b) NaBH4, MeOH/THF, 0 °C, 1 h; (c) PTSA, toluene, reflux, 4 h; (d) Fe, NH4Cl, EtOH/H2O (2:1, v/v), reflux, (4–5) h; (e) R3SO2Cl, DIPEA, DMAP, DCM, 6 h.

3.RESULTS

Chemical Studies

The chemistry part of the project deal with the synthesis of five compounds of N-(aryl)2[(4-methyl-2-oxo-2H-chromen-7-yl)]-derivatives of acetate alongwith physicochemical characterization , which was done by assessment of their melting points, R_f values (calculated from TLC), Spectrum of the proton nuclear magnetic resonance (1HNMR) and infrared wavelengths. The sharp melting points of all five synthesized compounds along with their single spot-on TLC were considered enough to assure their purity. The structure conformation of all the synthesized compounds including the starting compound (1) and one of the intermediate (4b) was done with the help of IR and ^{1}HNMR spectroscopy.



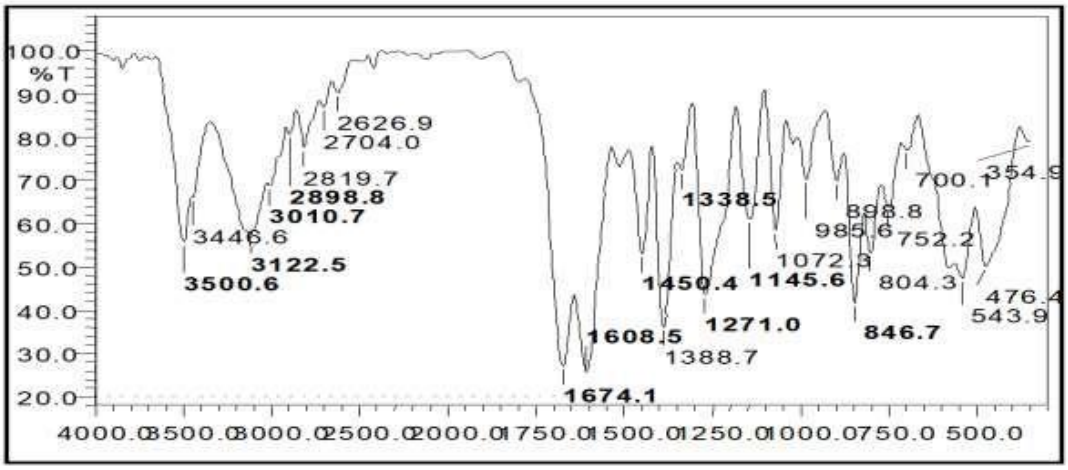
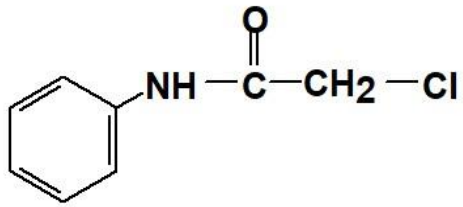


Fig. IR spectrum of 1



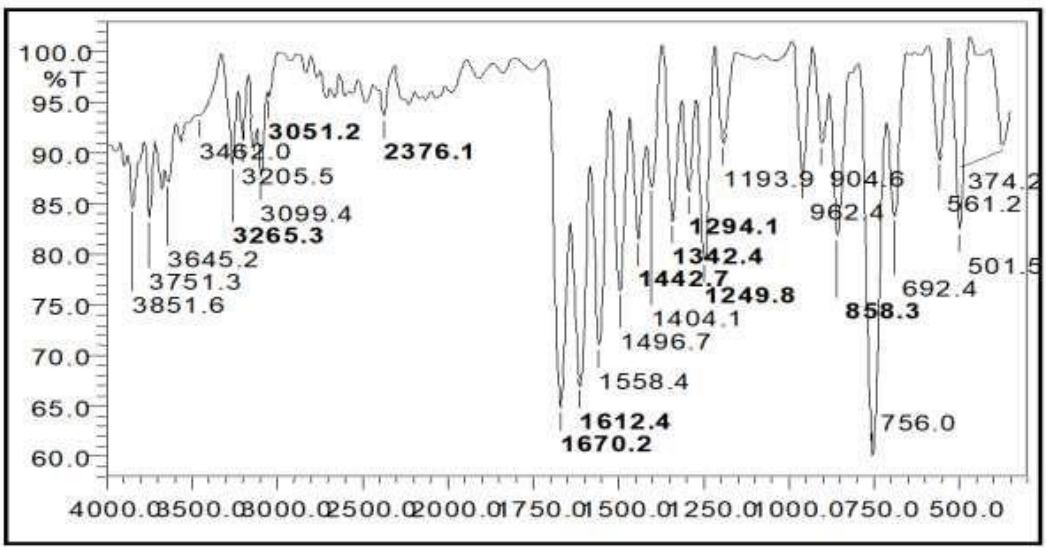
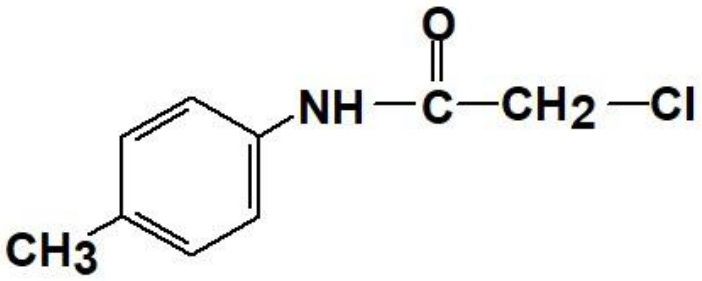


Fig. IR spectrum of 3a



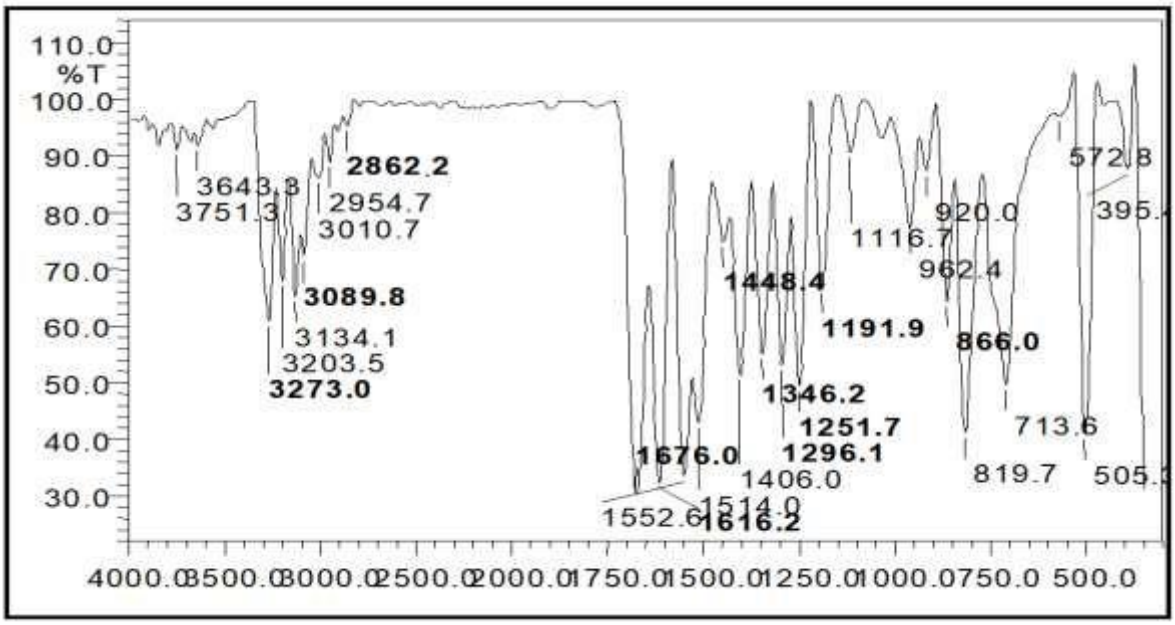
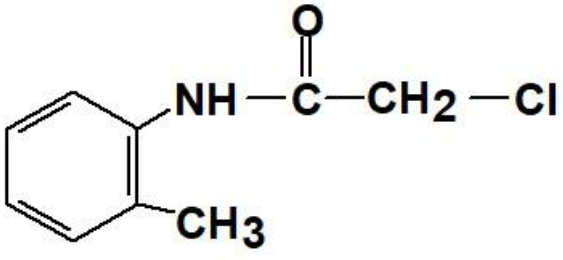


Fig. IR spectrum of 3b

Table: IR DATA – 3b

Sr.No.	*v* (cm^{-1})	Functional group assignment
1.	3273	N-H stretching's
2.	3089.8	Aromatic –CH stretching
3.	2862.2	Aliphatic –CH stretching.
4.	1676.0	C=O stretching(amide).
5.	1616.2-1448.4	Aromatic C=C stretching. (skeletal vibrations)
6.	1346.2	C-O stretching between Carbon no. 7 and oxygen of –OH group.
7.	1296.1	C-O-C stretching in lactones.
8.	1251.7cm	C-N stretching.
9.	866.0	Aromatic –CH out of –plane stretching.



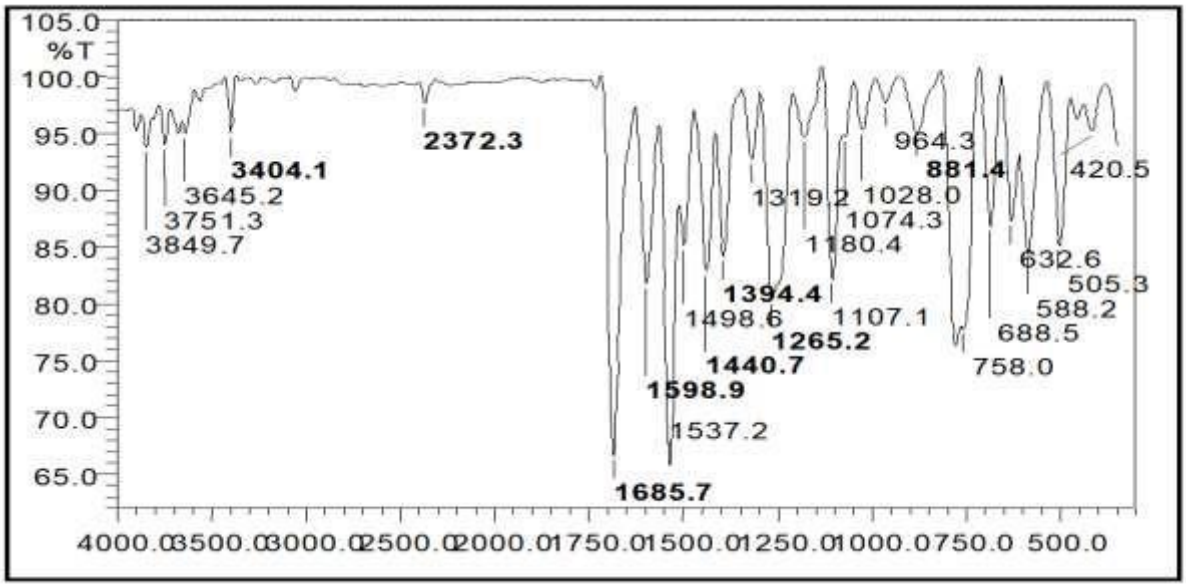
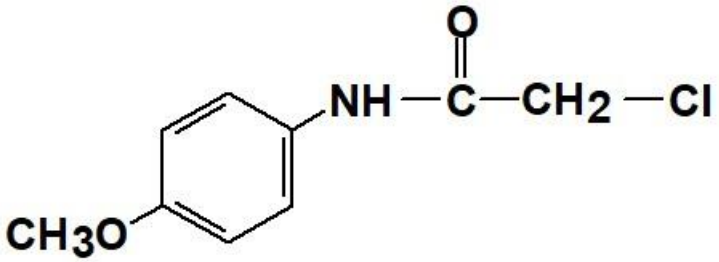
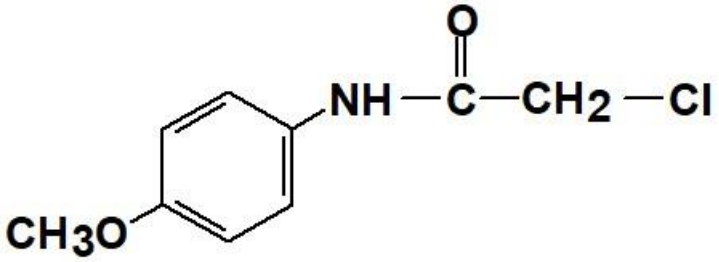


Fig. IR spectrum of 3c

Table: IR DATA – 3c

Sr.No.	*v* (cm^{-1})	Functional group assignment
1.	3404.1	N-H stretching's
2.	3089.8	Aromatic –CH stretching
3.	2372.3	Aliphatic –CH stretching.
4.	1685.7	C=O stretching.
5.	1598.9-1440.7	Aromatic C=C stretching. (skeletal vibrations)
6.	1394.4	C-O stretching between Carbon no. 7 and oxygen of –OH group.
7.	1265.2	C-O-C stretching in lactones.
8.	1251.7cm	C-N stretching.
9.	881.4	Aromatic –CH out of –plane stretching.





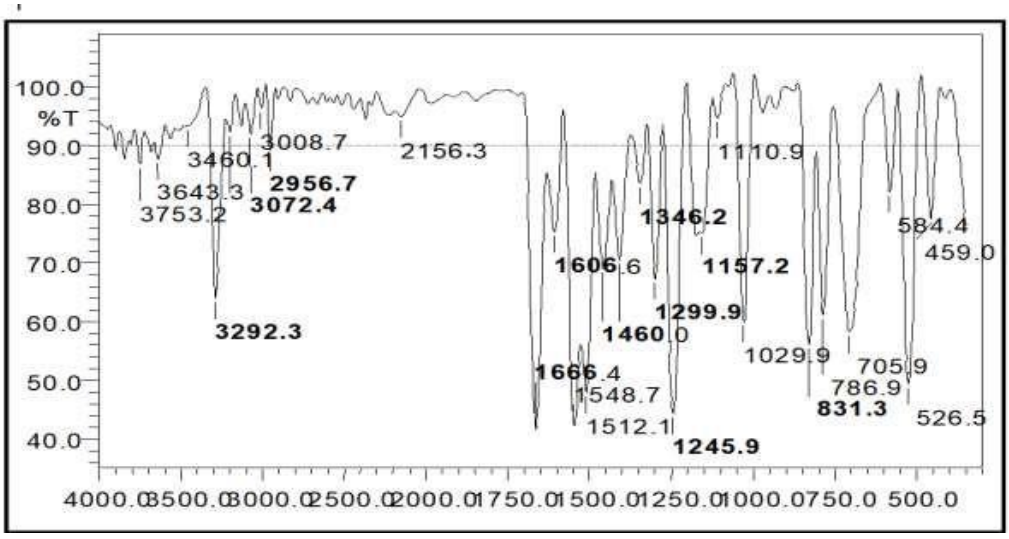
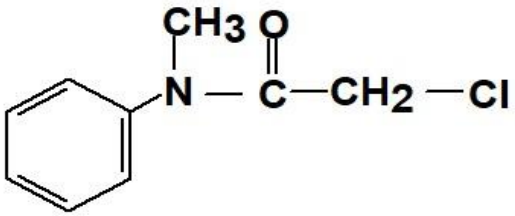


Fig. IR spectrum of 3d

Table: IR DATA – 3d

Sr.No.	ν (cm^{-1})	Functional group assignment
1.	3292.3	N-H stretching's
2.	3072.4	Aromatic –CH stretching
3.	2956.7	Aliphatic –CH stretching.
4.	1666.4	C=O stretching.
5.	1606.7-1460.7	Aromatic C=C stretching. (skeletal vibrations)
6.	1346.2	C-O stretching between Carbon no. 7 and oxygen of –OH group.
7.	1299.9	C-O-C stretching in lactones.
8.	1245.9cm	C-N stretching.
9.	831.3	Aromatic –CH out of –plane stretching.



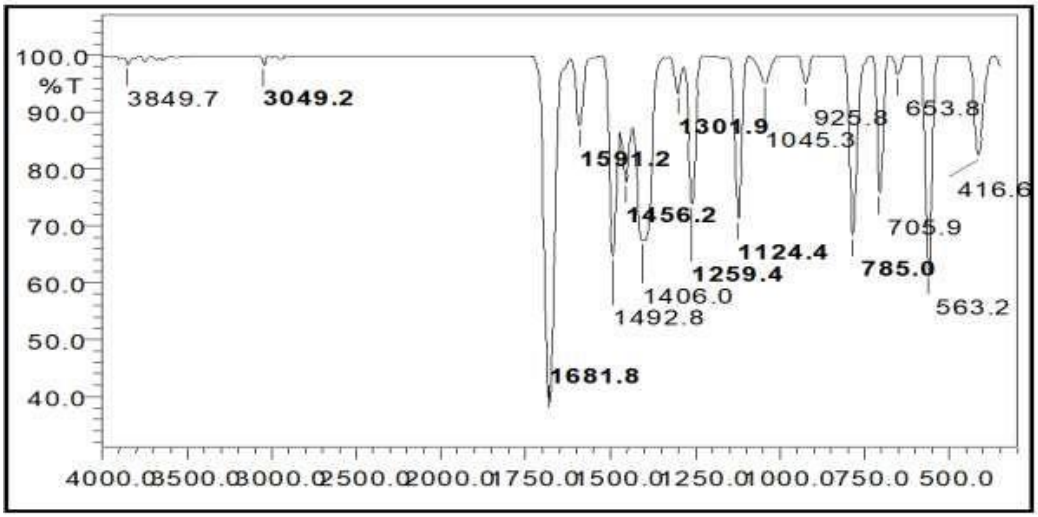
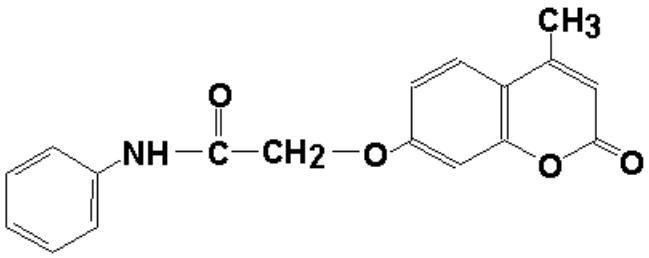


Fig. IR spectrum of 3e

Table: IR DATA – 3e

Sr.No.	***v*** **(cm^{-1})**	**Functional group assignment**
1.	3049.2	Aromatic –CH stretching
2.	2956.7	Aliphatic –CH stretching.
3.	1681.8	C=O stretching.
4.	1591.2- 1456.2	Aromatic C=C stretching. (skeletal vibrations)
5.	1346.2	C-O stretching between Carbon no. 7 and oxygen of –OH group.
6.	1301.9	C-O-C stretching in lactones.
7.	1259.4cm	C-N stretching.
8.	785.0	Aromatic –CH out of –plane stretching.



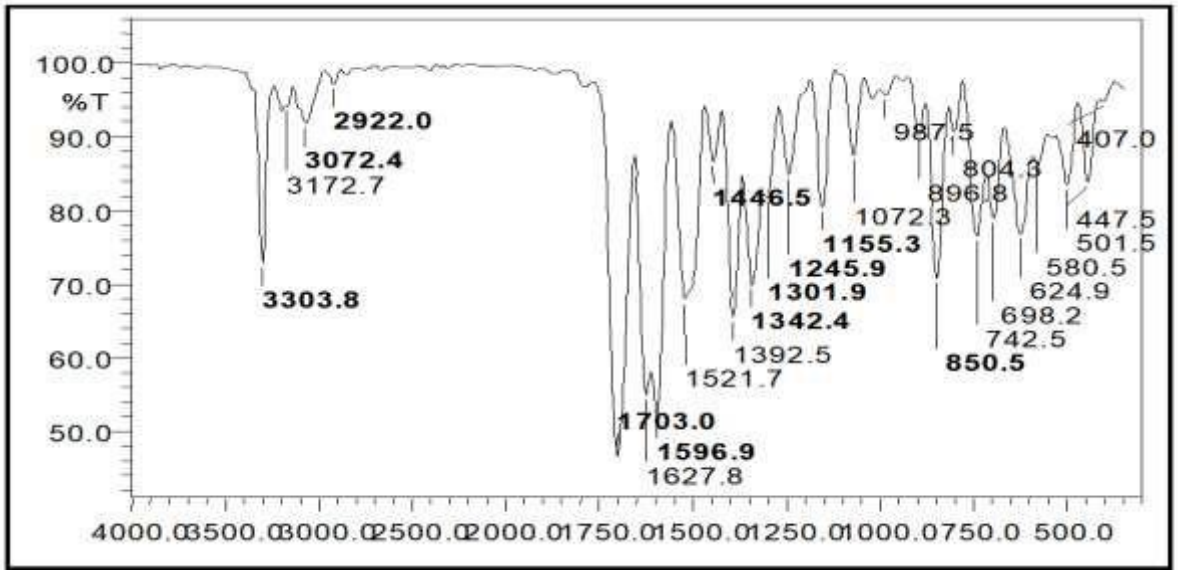
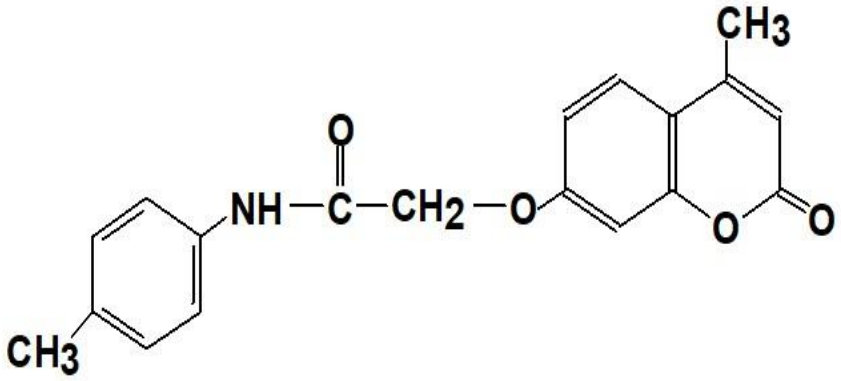


Fig. IR spectrum of 4a

Table: IR DATA – 4a



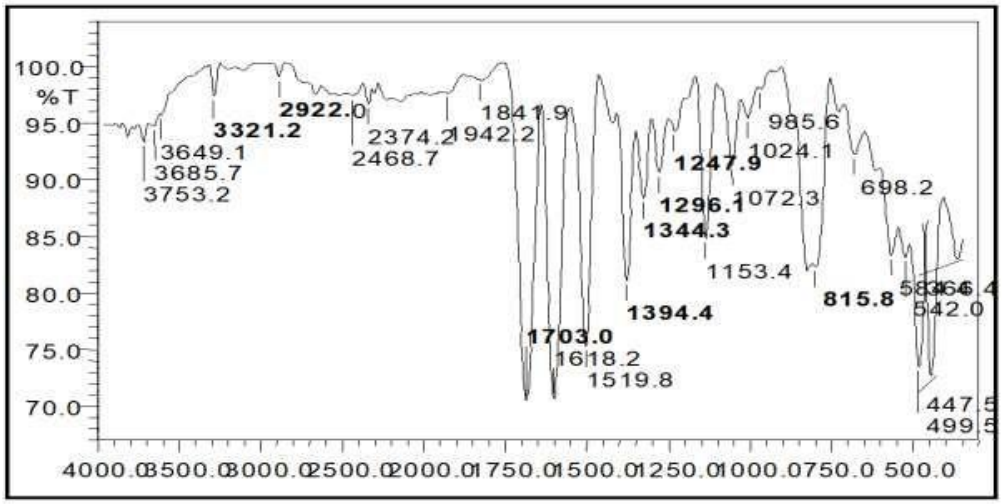
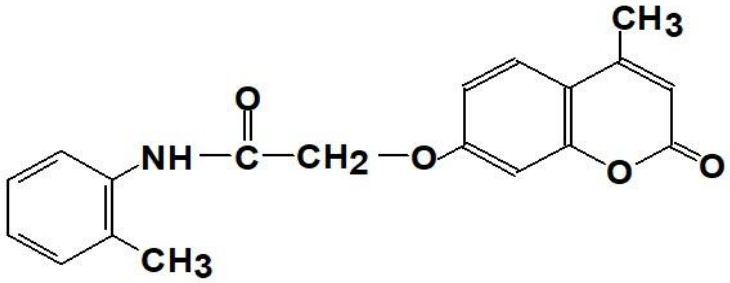


Fig. IR spectrum of 4b

Table: IR DATA – 4b

Sr.No.	*v* (cm^{-1})	Functional group assignment
1.	3321.2	N-H stretching's
2.	2922.0	Aliphatic –CH stretching.
3.	1703.0	C=O stretching.
4.	1596.9-1446.5	Aromatic C=C stretching. (skeletal vibrations)
5.	1344.3	C-O stretching between Carbon no. 7 and oxygen of –OH group.
6.	1296.1	C-O-C stretching in lactones.
7.	1247.9cm	C-N stretching.
8.	815.8	Aromatic –CH out of –plane stretching.



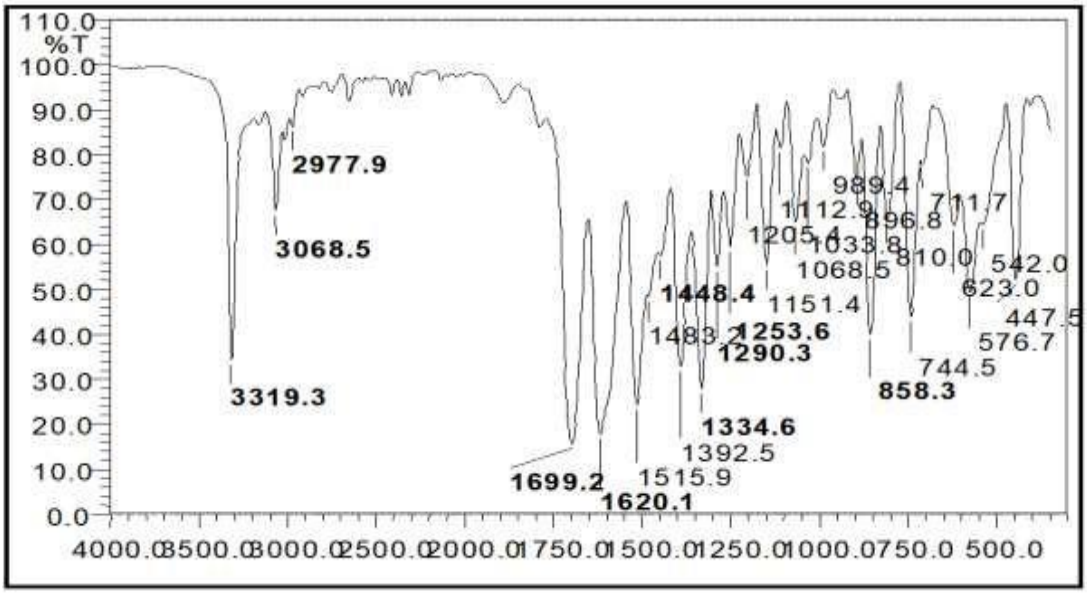
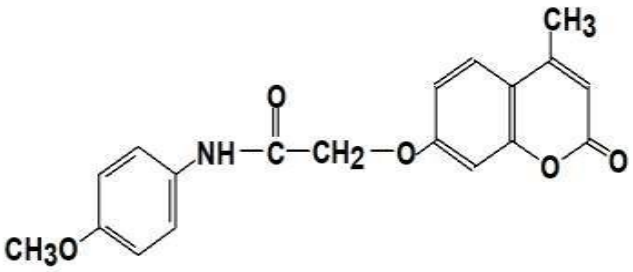


Fig. IR spectrum of 4c

Table: IR DATA – 4c

Sr.No.	ν (cm^{-1})	Functional group assignment
1.	3319	N-H stretching's
2.	3068.5	Aromatic –CH stretching
3.	2977.9	Aliphatic –CH stretching.
4.	1699.2	C=O stretching.
5.	1620.1-1448.4	Aromatic C=C stretching. (skeletal vibrations)
6.	1334.6	C-O stretching between Carbon no. 7 and oxygen of –OH group.
7.	1290.3	C-O-C stretching in lactones.
8.	1253.6cm	C-N stretching.
9.	858.3	Aromatic –CH out of –plane stretching.



NMR SPECTRUM OF 3a

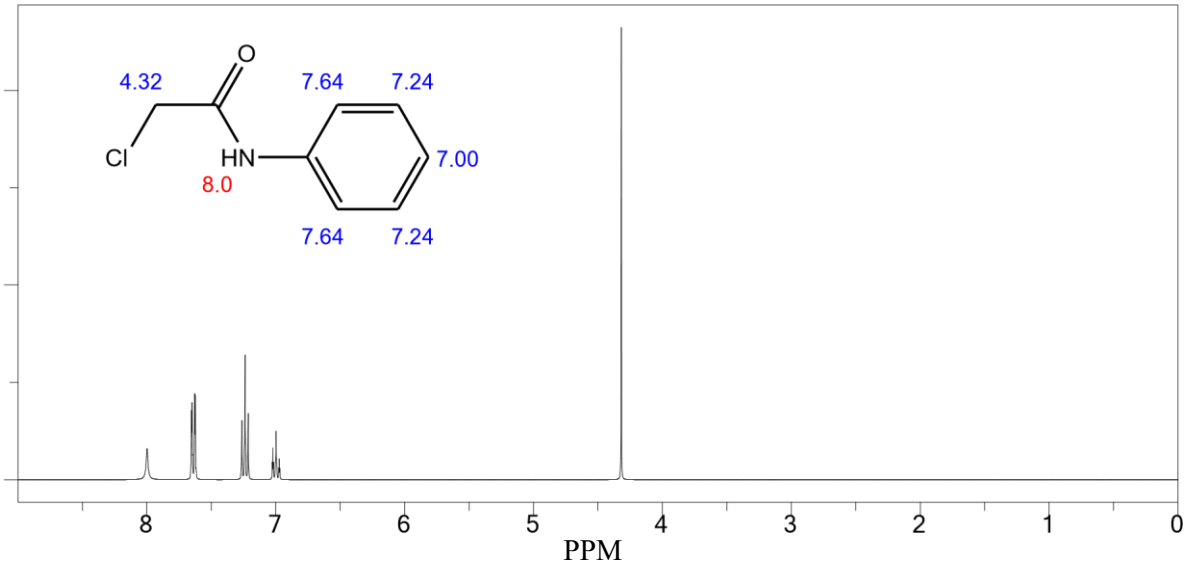


Fig. NMR Spectrum of 3b

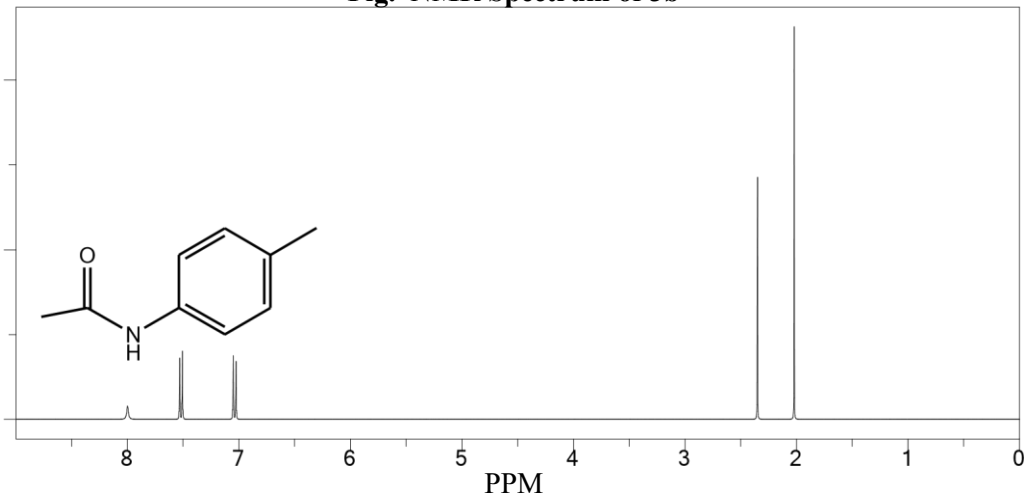
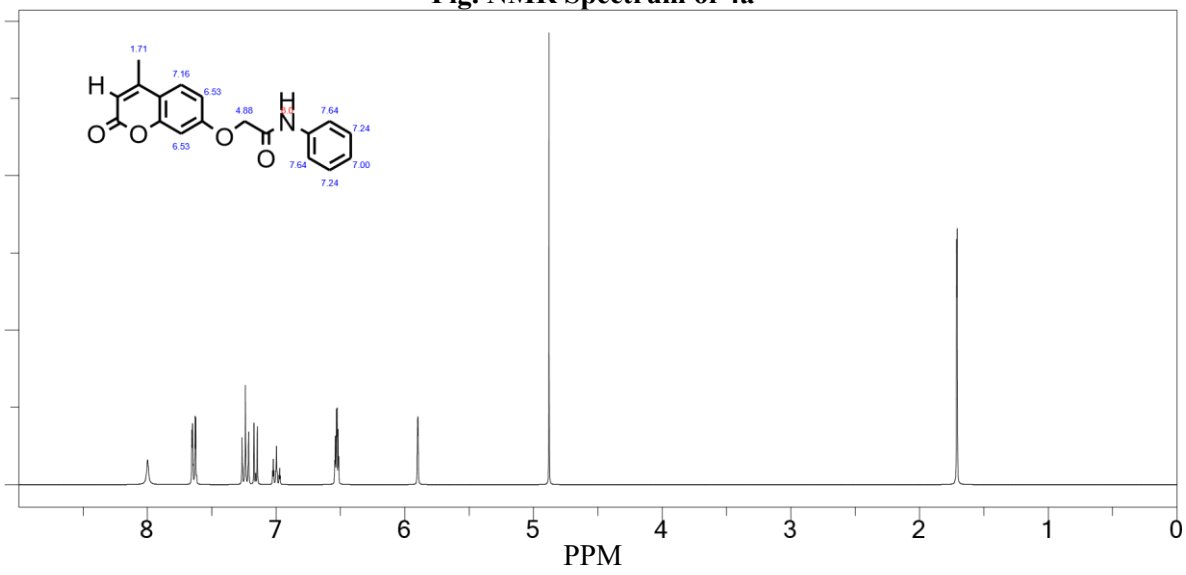
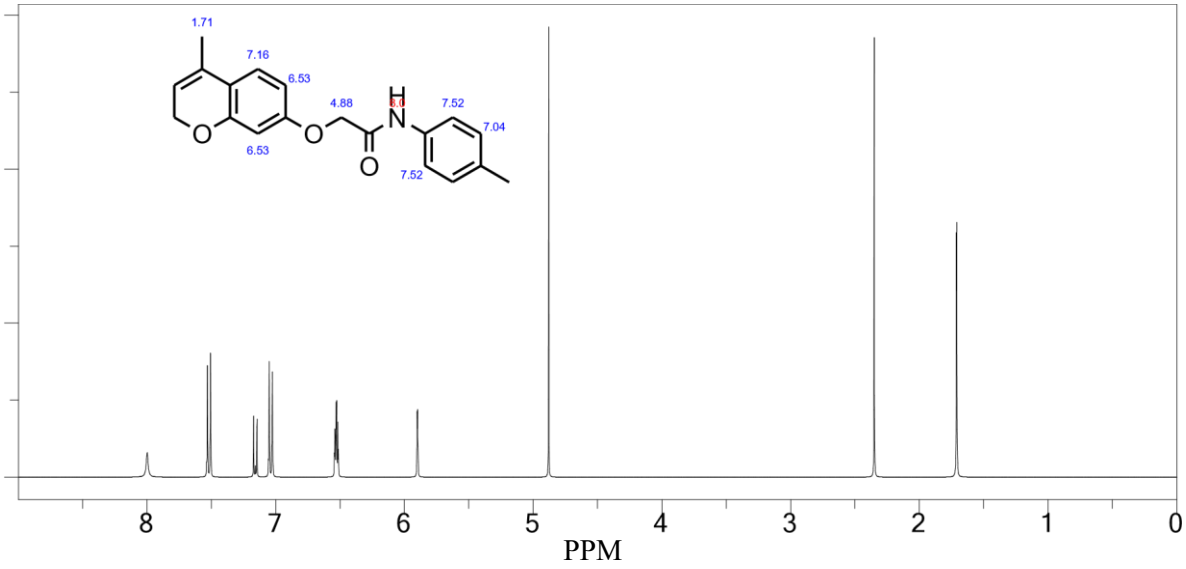


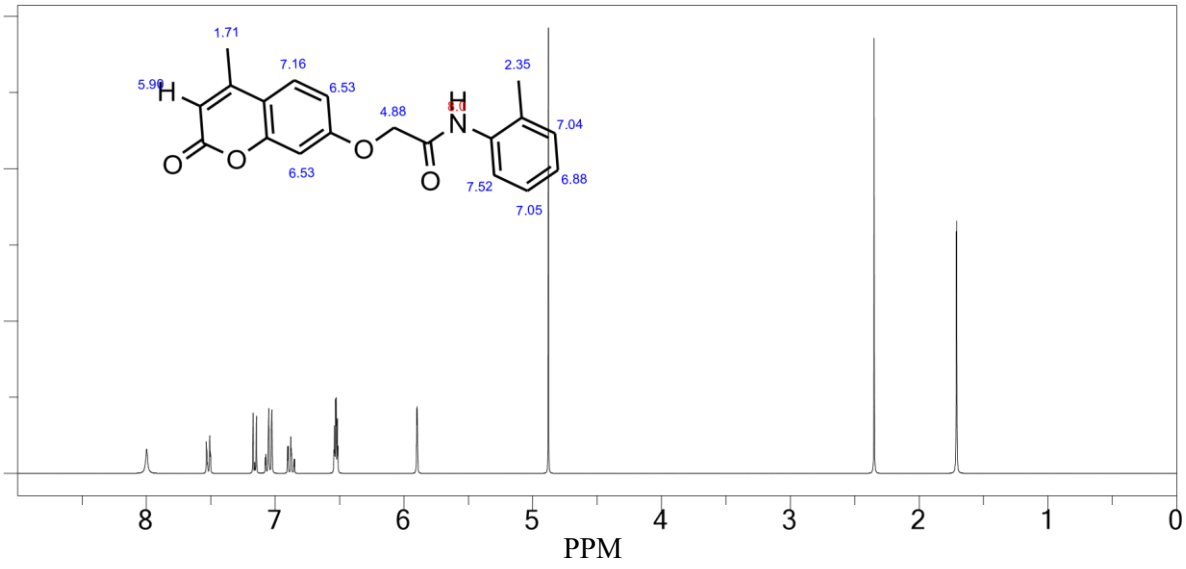
Fig. NMR Spectrum of 4a



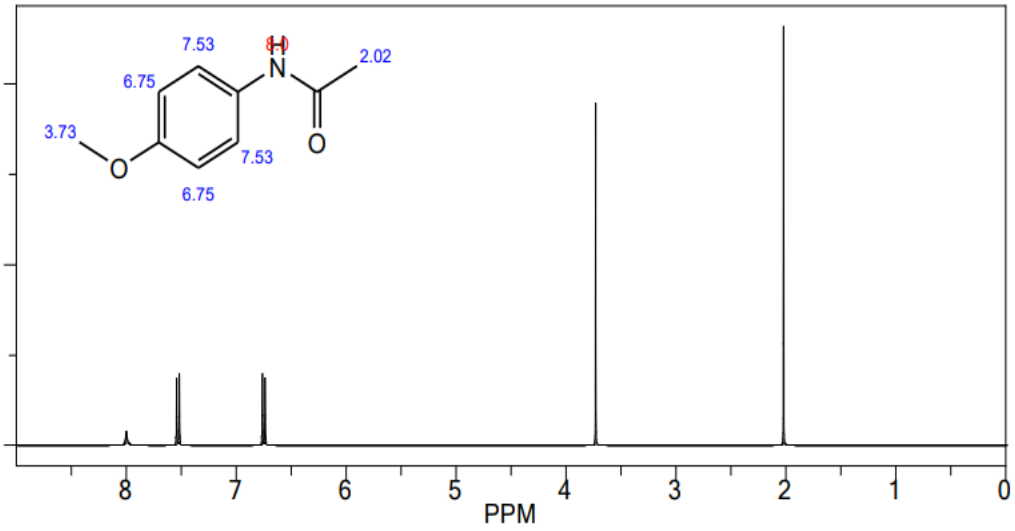
NMR SPECTRUM OF 4b



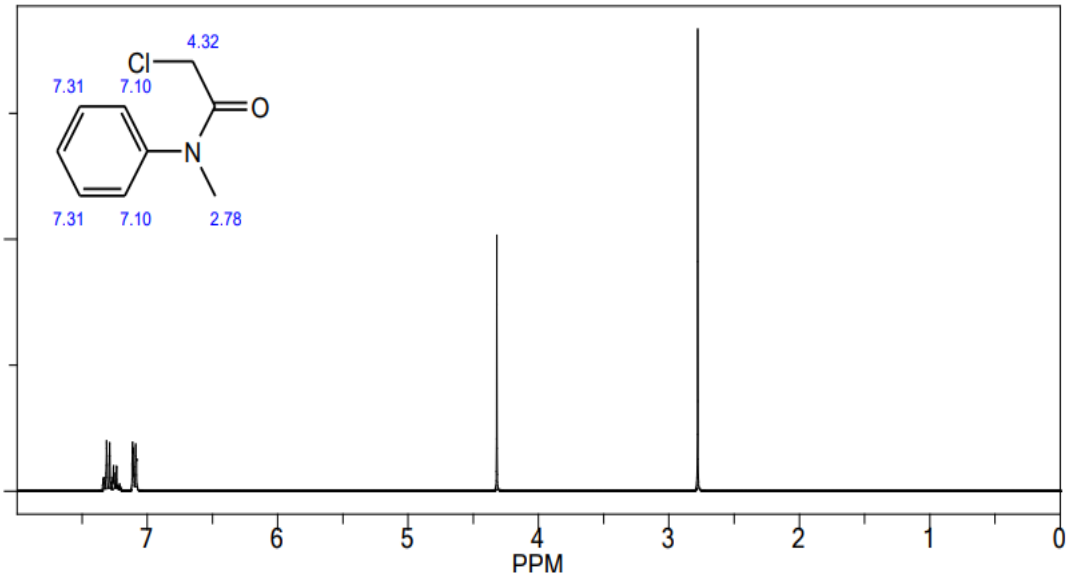
NMR SPECTRUM OF 4c



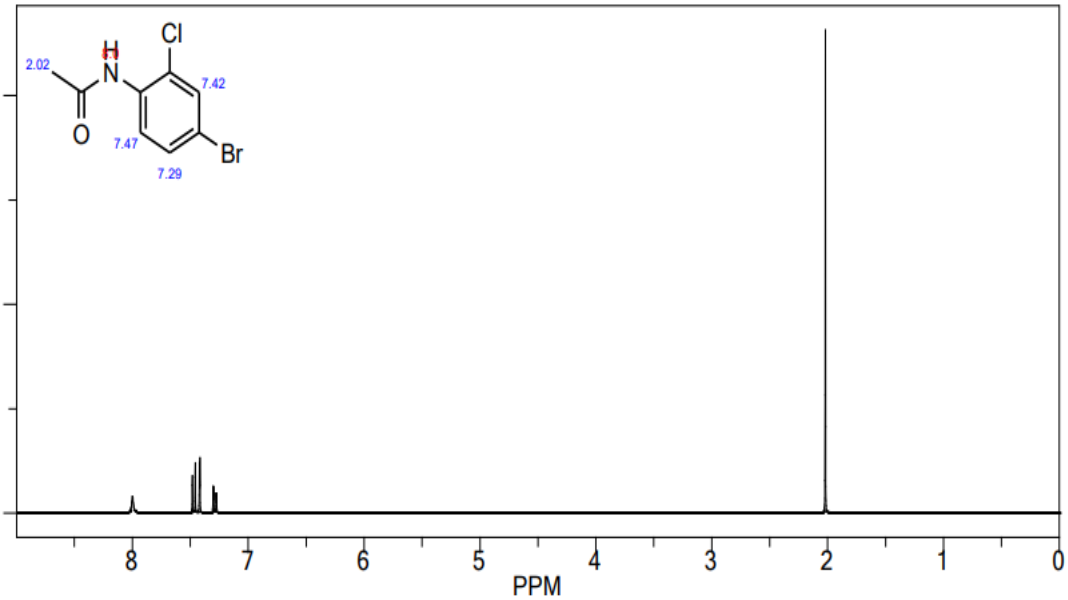
4-Methoxy chloro Acetanilide-(3d)

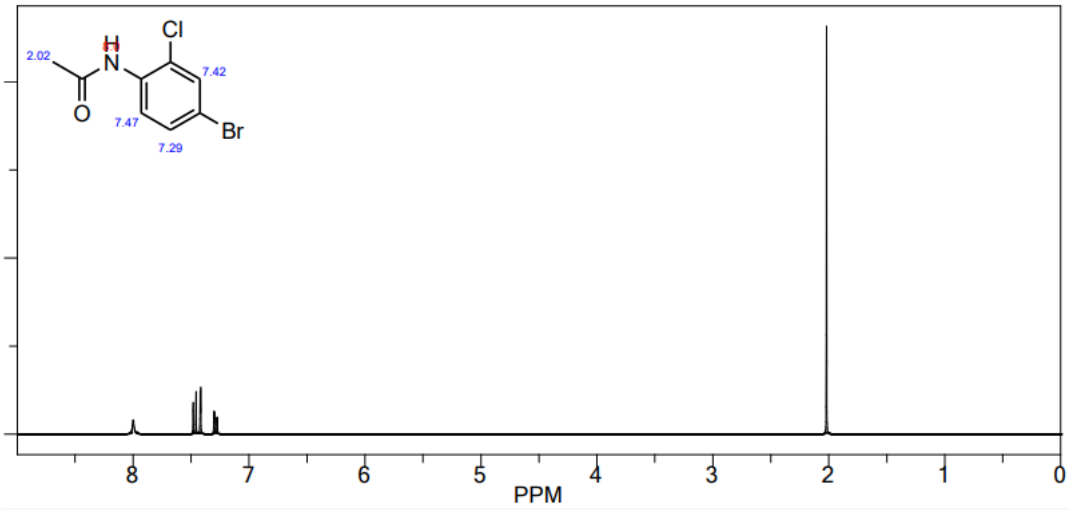


N-Methyl chloroacetanilide-(3e) N-Methyl-2-chloroacetanilide



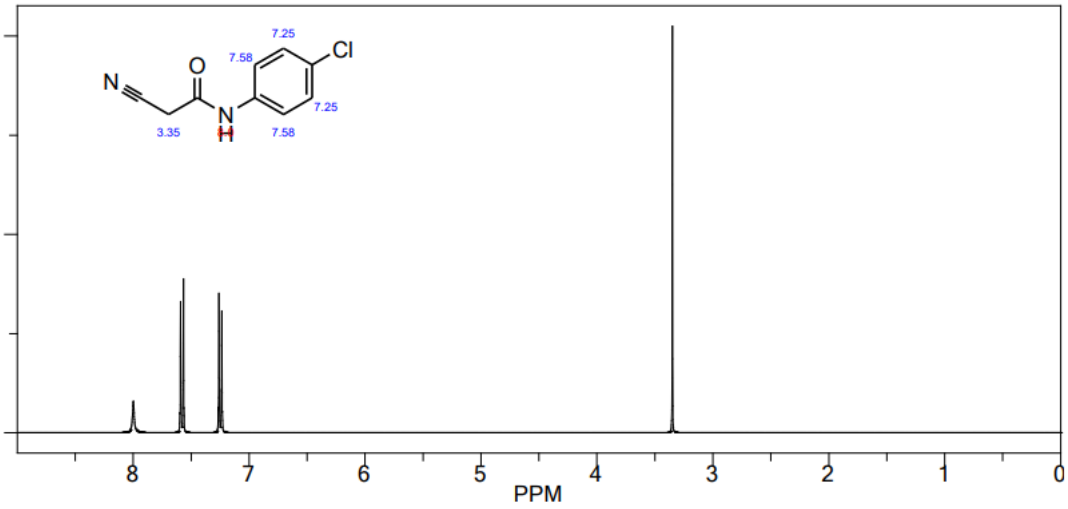
4'-Bromo-2'-chloroacetanilide-(3f)





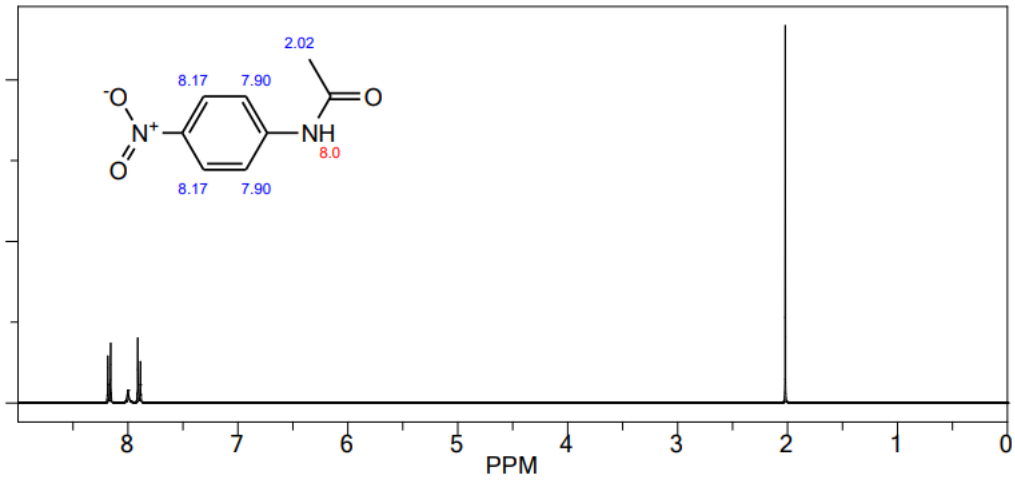
NMR SPECTRUM OF 3g

4′-Chloro-2-cyanoacetanilide



NMR SPECTRUM OF 3h

N-(4-Nitrophenyl)acetamide



4.Conclusion

The aim of the undertaken research work was to make an effort in the direction of synthesizing a molecule, which could have capability of treating, positive as well as negative symptoms of schizophrenia i.e. to synthesize a molecule having atypical profile. Further, the review of literature supported strong affinity of the present molecule for 5-HT receptors, which is one of the main characteristics of atypical antipsychotics. Keeping into consideration these factors, 2-[(4-methyl-2-

oxo-***2H***-chromen-7-yl) oxy- (aryl)] acetamide was selected as lead molecule.
The aim of this project work was to synthesis of 2-[(4-methyl-2-oxo-*2H*-chromen-7-yl) oxy(aryl)] acetamide.

Synthesized derivatives were
2-[(4-Methyl-2-oxo-2*H*-chromen-7yl oxy)-N-phenyl] acetamide (4a)
2-[(4-Methyl-2-oxo-2*H*-chromen-7yl oxy)-N- (4-methylphenyl)] acetamide (4b)
2-[(4-Methyl-2-oxo-2*H*-chromen-7yl oxy)-N- (2-methylphenyl)] acetamide (4c)
2-[(4-Methyl-2-oxo-2*H*-chromen-7yl oxy)-N- (4-methoxy phenyl)] acetamide (4d)
2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N, N-methyl-phenyl-acetamide (4e)

The starting compound was 7-hydroxy-4-methylchromen-2-one which was prepared by taking resorcinol and ethyacetoacetate as starting material 7-hydroxy-4-methyl chromen-2one was first synthesized by reported method. This on treatment with various substituted chloroacetanilide in toluene and in presence of triethylamine resulted in the formation of 2[(4-methyl-2-oxo-2*H*–chromen-7-yl) oxy-N- (aryl))]-acetamide derivatives.

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