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Cesium carbonate as a heterogeneous reusable and efficient catalyst for the synthesis of 2-amino-*4H*-Chromene derivatives

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ABSTRACT

A simple, efficient and environmentally being method for the synthesis of 2-amino 4H-chromene derivatives was developed using Caesium carbonate as a hetrogeneous base catalyst. Three component reaction of an aldehyde, malononitrile and cyclic dimedone in ethanol at room temperature offered the corresponding 2-amino- 4H-chromene derivatives with excellent yields (80-96%) in a short reaction time.

Kewords: Dimedone, Hetrogeneous, Cesium carbonate

INTRODUCTION

4*H*-Benzo[b] pyrans and its derivatives are of considerable interest due to their various pharmacological activities such as spasmolytic, diuretic, anti-coagulant, anti-cancer, anti-ancaphylactia activity. [1] Furthermore, tetrahydrochromene moiety is an important class of benzopyran derivatives found in many natural products [2]. Among these, 2-amino-4*H*-chromene-3-carbonitrile derivatives have been reported to possess antitumor, anticoagulant, antibacterial and fungicidal activities. [3] They are often used in cosmetics, pigments and utilized as potentially biodegradable agrochemicals [4]. One of the most important classes of these reactions is C–C coupling reactions, such as Aldol and Knoevenagel condensations and Michael reaction [5–7].

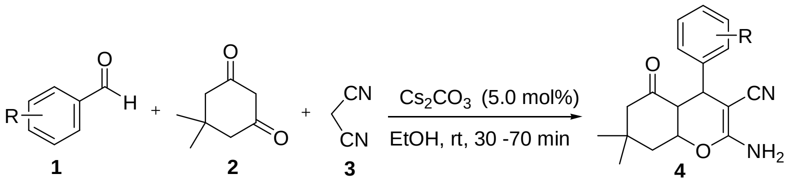
Due to the significant importance of these compounds various approaches and catalysts were reported for the synthesis of tetrahydrochromene derivatives [8-9] such as cyclization of arylidenemalononitriles with dicarbonyl compounds in the presence of piperidine [10], morpholine, pyridine[11], KF-Alumina[12]. Variety of catalyst's such as *N*-methylimidazole [13], Hexadecyltrimethylammonium bromide (HTMAB) [14], Fluoride ion [15], (s)-proline[16], triethylbenzylammonium chloride (TEBA) [17] and microwave irradiation [18] electrosynthesis method [19] are also applied for preparation of this important class of compounds. However, the reported methods still have several drawbacks such as prolonged reaction time, harsh reaction conditions, use of toxic reagents and organic solvents. Therefore, development of a safe and eco-friendly protocol for preparation tetrahydrochromene derivatives is always on demand.

Development and applications of environmentally benign solid catalysts becoming an area of growing interest in organic synthesis. Solid-base catalysts were synthesized by functionalization of various solid-state materials, constitute a class of heterogeneous catalysts that are capable to catalyze various C–C coupling reaction [20]. The solid base catalysts derived from alkali earth metallic precursors has played an important role in heterogeneous catalysis. These catalysts have several advantages over homogeneous organic basic catalysts, such as easy recovery of the catalyst, simple product isolation and reusability. Therefore, the solid base catalysts have been considered as potential alternatives to homogeneous organic basic catalysts.

The use of such heterogeneous catalyst offer advantages in process development, especially with respect to the separation of products from the catalyst and recycling or retaining of the catalyst in the reactor. The application of solid acidic and basic catalysts in clean technologies and sustainable chemistry is a “green” alternative for chemical processes

In recent years, caesium carbonate (Cs_2CO_3) has found extensive catalytic applications as an excellent mild base catalyst for a variety of synthetic organic transformations [21-23]. Additionally, several other important organic protocols have been successfully carried out in the presence of Cs_2CO_3 such as Gewald reaction [24], synthesis of quinazoline-2,4(1H,3H)-diones[25], pyrrolo[1,2-*a*]quinoxalines synthesis[26], chemo-selective alkylation and dialkylation of active methylene compounds [27] and synthesis of biaryl ethers [28]. Furthermore, tandem Ugi condensation and intermolecular substitution at room temperature using Cs_2CO_3 have been also reported [29].

Here in we report the preparation of 2-amino -4*H*-chromene derivatives by the three component reactions with aromatic aldehydes, malononitrile and dimedone in the presence of Cs_2CO_3 as base catalyst (**Scheme 1**). To the best of our knowledge,recently reported in Acetic acid functionlised with ionic liquid [30], this is first report investigating the use of Cs_2CO_3 in the synthesis of 2-amino-4*H*-chromene derivatives.



Scheme 1. Cs_2CO_3 catalysed three component reaction for synthesis of 2-amino -4*H*-chromene derivatives

MATERIALS AND METHODS

General details

All solvents and chemicals were used of commercial grade without further purification. Melting points were determined in open capillary tube. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS.

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General procedure for the synthesis of 4H-chromene derivatives:

A mixture of an aromatic aldehyde (1 mmol), malonitrile (1 mmol) and dimedone (1 mmol) in the presence of 5 mol % Cs_2CO_3 in ethanol is stir at room temperature for 30-70 min. After completion of reaction as indicated on TLC, ethyl acetate added in reaction mixture and stir for 10 min and separate the catalyst by filtaration, organic layer was washed with water and the solvent was evaporated under vacuum to obtained crude product. The obtained product was further purified by recrystallization using solvent ethyl acetate to get the desired compound 4 (a-n)

Spectral data for representative and newly synthesized compounds

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a) White solid, ^1H NMR (300 MHz, $CDCl_3$): δ 7.79-7.89 (m, 2H), 7.41-7.50 (m, 1H), 6.88-7.04 (m, 2H), 6.57 (brs, 2H, NH), 4.29 (s, 1H), 2.58 (s, 2H), 2.26 (m, 1H), 2.01 (m, 1H), 1.23 (s, 3H),0.84 (s, 3H) ; ^{13}C-NMR (300 MHz, $CDCl_3$): δ 201.2,162.3, 155.8, 145.6, 128.7 127.5, 119.2, 112.1, 57.6, 49.9, 40.3, 39.9, 36.1, 27.4; GC-MS *m/z* 294 (M^+);

2-Amino-7,7-dimethyl-5-oxo-4- (3,4,5-trimethoxyphenyl)- 5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e): Yellow solid, ^1H NMR (300 MHz, $CDCl_3$): δ 7.29-7.41 (m, 2H), 6.71 (brs, 2H, NH), 4.22 (s, 1H), 3.73 (s, 9H), 2.51 (s, 2H), 2.23 (m, 1H), 2.17 (m, 1H), 1.10 (s, 3H),0.92 (s, 3H) ; ^{13}C-NMR (300 MHz, $CDCl_3$): δ 201.1, 160.0 157.8, 132.0, 129.6, 129.0, 119.1, 107.2, 106.4, 60.3, 59.3, 57.1, 50.0, 38.0, 32.3, 28.9; GC-MS *m/z* 384 (M^+);

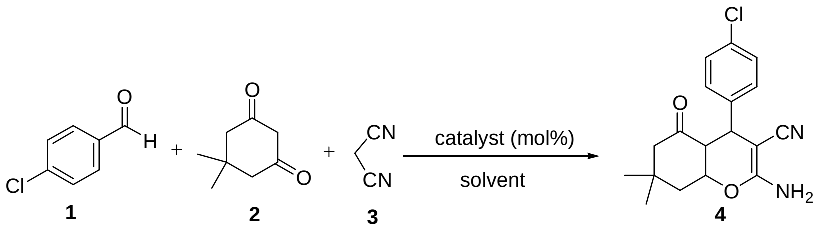
2-Amino-7, 7-dimethyl-5-oxo-4- (2, 3-dichlorophenyl)- 5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l): White solid, ^1H NMR (300 MHz, $CDCl_3$): δ 7.17-7.21 (m, 1H), 7.40-7.47 (m, 1H), 7.82-7.90 (m, 1H), 6.72 (brs, 2H, NH), 4.24 (s, 1H), 2.61 (s, 2H), 2.28 (m, 1H), 2.06 (m, 1H), 0.94 (s, 3H),0.74 (s, 3H) ; ^{13}C-NMR (300 MHz, $CDCl_3$): δ 200.7, 159.8, 154.0, 140.1, 131.3, 130.2, 130.0, 119.2, 113.2, 67.6, 60.0, 44.3, 41.2, 32.1, 28.6; GC-MS *m/z* 363 (M+);

2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-3-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4o): Brownish Solid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17-7.21 (m, 1H), 7.40-7.47 (m, 1H), 7.82-7.90 (m, 1H), 6.72 (brs, 2H, NH), 4.24 (s, 1H), 2.61 (s, 2H), 2.28 (m, 1H), 2.06 (m, 1H), 0.94 (s, 3H),0.74 (s, 3H) ; ^{13}C-NMR (300 MHz, $CDCl_3$): δ 200.0, 161.3, 154.0, 153.6, 142.8, 135.1, 129.9, 122.8, 119.1, 114.1, 59.9, 53.5, 38.1, 37.5, 31.3, 30.7; GC-MS *m/z* 295 (M+);

RESULTS AND DISCUSSION

A mixture of 4-chlorobenzaldehyde (**1**), dimedone (**2**) and malononitrile (**3**) was explored in the presence of Cs_2CO_3 (20.0 mol %) as catalyst in ethanol. The target product **4a** was obtained with 94% yield in 1h at room temperature (Table 1, entry 1). Inspired by this interesting result next we tested the effect of different molar ratios of the catalyst (Cs_2CO_3) and solvents on the reaction yield (Table 1, entries 2-8). We also investigated the effect of temperature on reaction and results are summarised in table 2. It suggests that room temperature is the optimum temperature for this protocol (Table 2, entry 1). Above mentioned screening suggested that in the presence 5.0 mol% of catalyst and ethanol as a solvent the corresponding product (**4a**) was obtained in 94% yield at room temperature in 0.5 h (Table 1, entry 8).

Table 1. Optimization of reaction conditions[a]



Entries	Catalyst (Mol %)	Solvent	Time (hr)	Yield (%)[b]
1	Cs_2CO_3 (20)	EtOH	1.0	94
2	Cs_2CO_3 (10)	EtOH	1.0	94
3	Cs_2CO_3 (5)	$CHCl_3$	10.0	46
4	Cs_2CO_3 (5)	CH_2Cl_2	10.5	49
5	Cs_2CO_3 (5)	CH_3CN	8.0	56
6	Cs_2CO_3 (5)	DMSO	7.5	60
7	Cs_2CO_3 (5)	Water	3.0	82
8	**Cs_2CO_3 (5)**	**EtOH**	**0.5**	**94**

[a]*Reaction conditions: 4-chlorobenzalaldehyde (1 mmol), Malanonitrile (1 mmol), Dimedone (1mmol), at rt.*

.[b]*Isolated yields*

Table 2. Effect of temperature on the reaction progress [a]

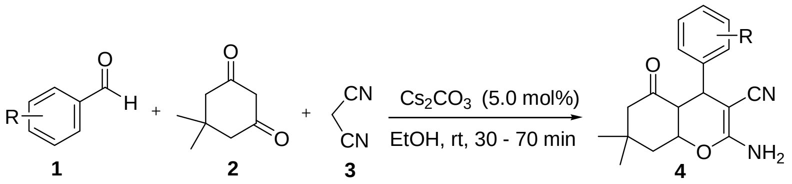
Entries	Temp ^{0}C	Time (h)	Yield (%)[b]
1	RT	0.5	94
2	50	1.5	95
3	60	1.5	95
4	70	1.5	93

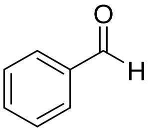
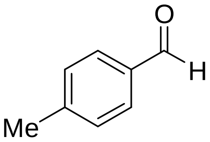
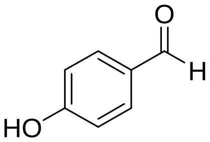
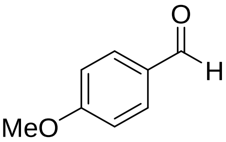
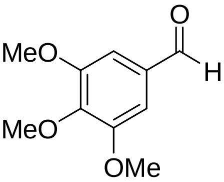
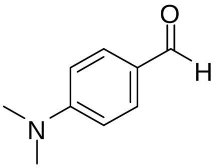
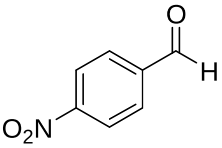
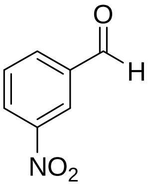
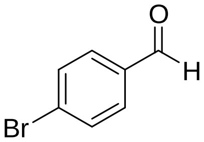
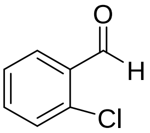
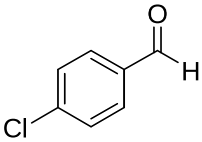
[a]*Reaction conditions: : 4-chlorobenzalaldehyde (1 mmol), Malanonitrile (1 mmol), Dimedone (1mmol), at rt..*
[b]*Isolated yields*

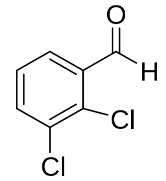
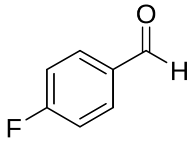
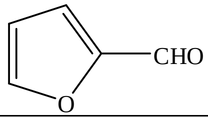
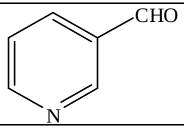
Above evaluation of different parameters suggested that the reaction between 4-chlorobenzaldehyde (**1**), dimedone (**2**) and malononitrile (**3**) in the presence of Cs_2CO_3 (5.0 mol%) completed in 0.5 h and target product (**4a**) formed in 94% yield at room temperature in ethanol (Table 1, entry 8) and condiderd as the optimized condition.

With optimized condition in hand we studied the substrate scope of reaction with differently substituted aromatic and hetero aromatic aldehydes. Various electron-rich, electron deficient group substituted, as well as halogen bearing aromatic aldehydes afforded the correspondingn 2-amino 4*H*-chromene derivatives in excelent yield (80–96%). Comparatively, the rate of reaction of electron-deficient aryl aldehyde is faster than the electron-rich aryl aldehyde (Table-3, entry 1-15). We succesfully extended the scope of present protocol for the aromatic heterocyclic aldehydes and the target 2-amino 4*H*-chromene derivatives formed in excellent yield (Table-3, 14-15). The purification of the 2-amino 4*H*-chromene derivatives can be easily done by recrystallization process.

Table 3. Cs_2CO_3 catalyzed synthesis of 2-amino 4*H*-chromene derivatives [a]



Entries	**R**	**Product 4**	**Time (min)**	**Yield (%)**	**M.P. (°C) Observed**
1		a	70	94	235-237
2		b	60	92	208-210
3		c	70	93	223-225
4		d	60	94	200-202
5		e	70	90	247-249
6		f	70	80	210-215
7		g	30	96	152-154
8		h	50	96	209-211
9		i	60	89	199-200
10		j	70	94	201-203
11		k	60	96	213-214

12		l	70	88	225-227
13		m	60	90	210-212
14		n	70	84	201-203
15		o	60	87	187-189

^{a}*Reaction conditions: : Aromatic aldehyde (1 mmol), Malanonitrile (1 mmol), Dimedone (1mmol), at rt..*
^{b}*Isolated yields*

Reusability of the catalyst was also investigated. For this purpose, the reaction of benzaldehyde with dimedone and malononitrile was studied at room temperature in the presence of cesium carbonate. After completion of reaction, the catalyst was separated by a simple filtration from the resulting heterogeneous mixture, washed with methanol & dried at 120°C for 2.0 hr and re-used for consecutive run under the same reaction conditions. As it is shown in Figure-1, the catalyst could be reused at least three times without significant loss of activity.

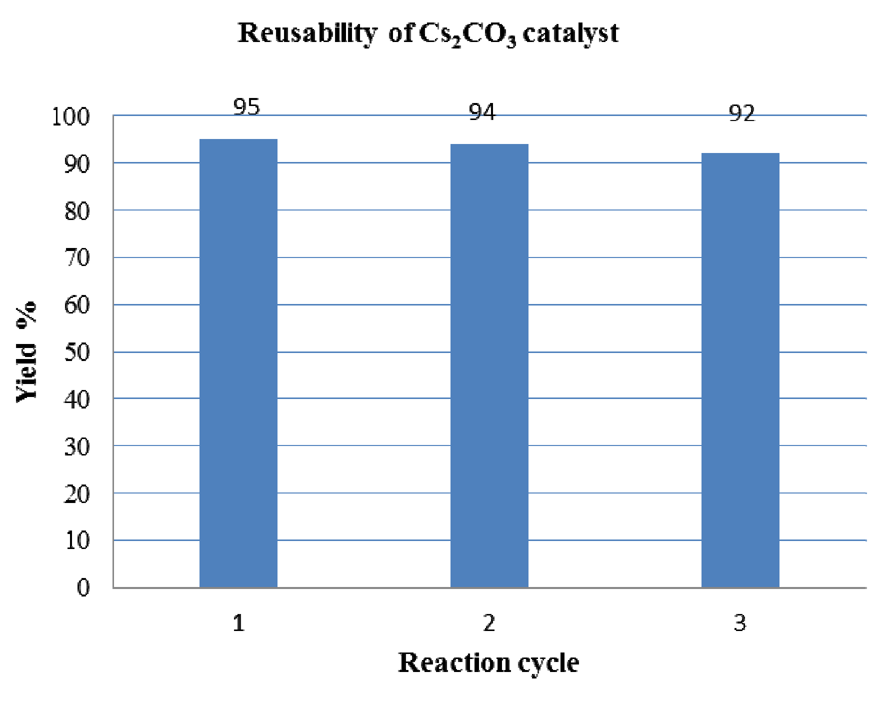
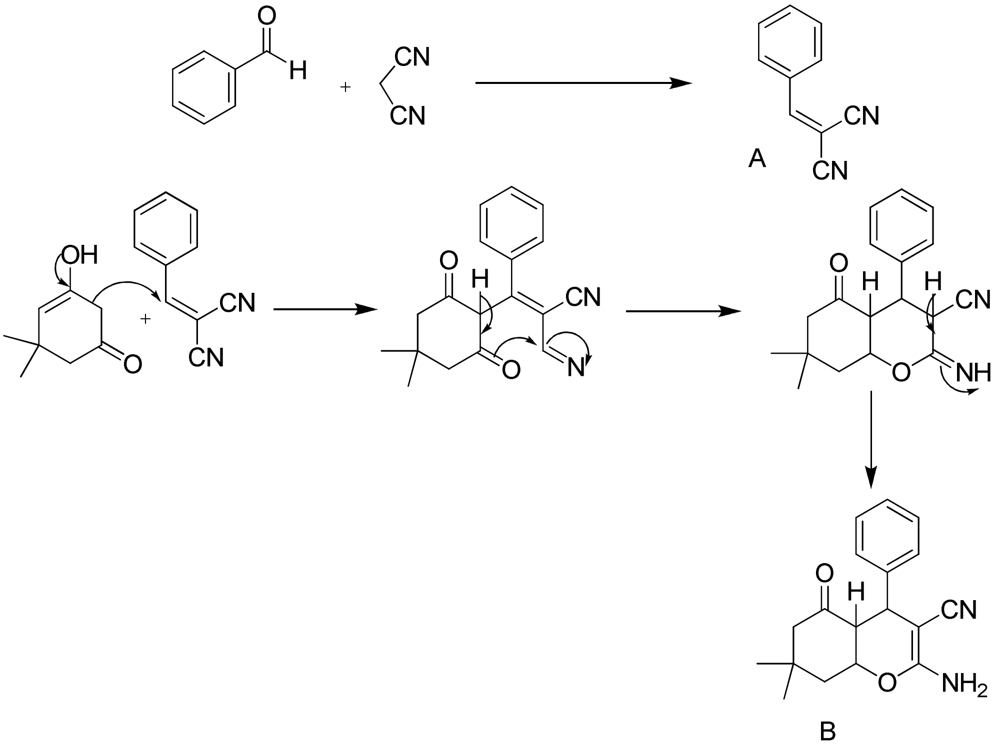


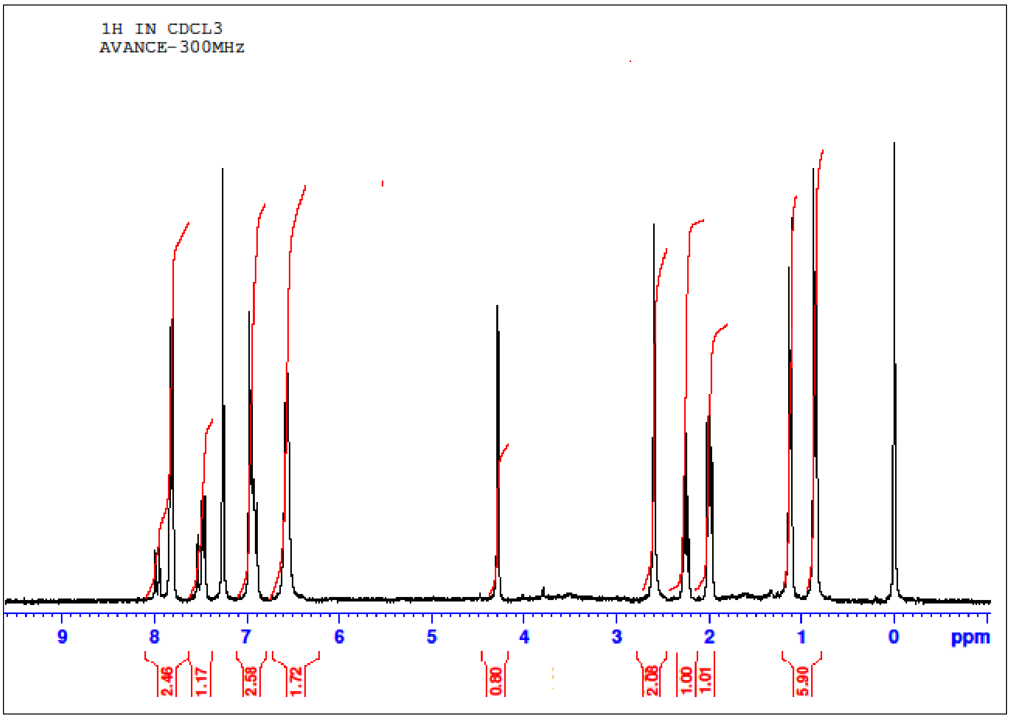
Figure 1: Reusability of solid Cs_2CO_3 as a catalyst for the synthesis of 4a

plausible mechanism

The plausible mechanism for the reaction proceeds via initial formation of cyanoolefin [A] through condensation between aryl aldehyde and malanonitrile. Due to more acidic protons of malanonitrile as compaired to dimedone, the preferential attack of malononitrile take place on electron deficient carbon of an aldehyde. dimedone can be easily converted to its enolate form in the presence of Cs_2CO_3 that could readily react with cyanoolefin [A], affording the Michael addition product, followed by tautomerism, intramolecular O-cyclization and proton transfer reactions forming the desired product tetrahydrbenzo[*b*]pyran [B]



^{1}H NMR spectra for Compound 4a



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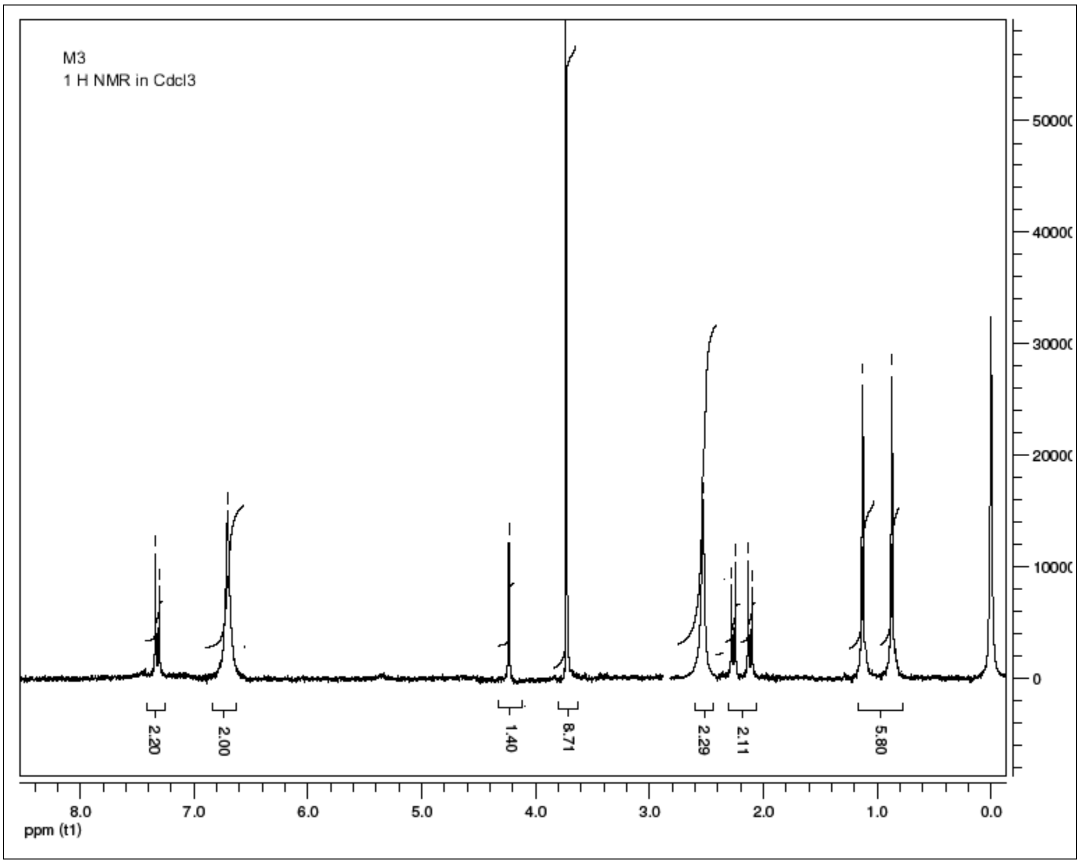
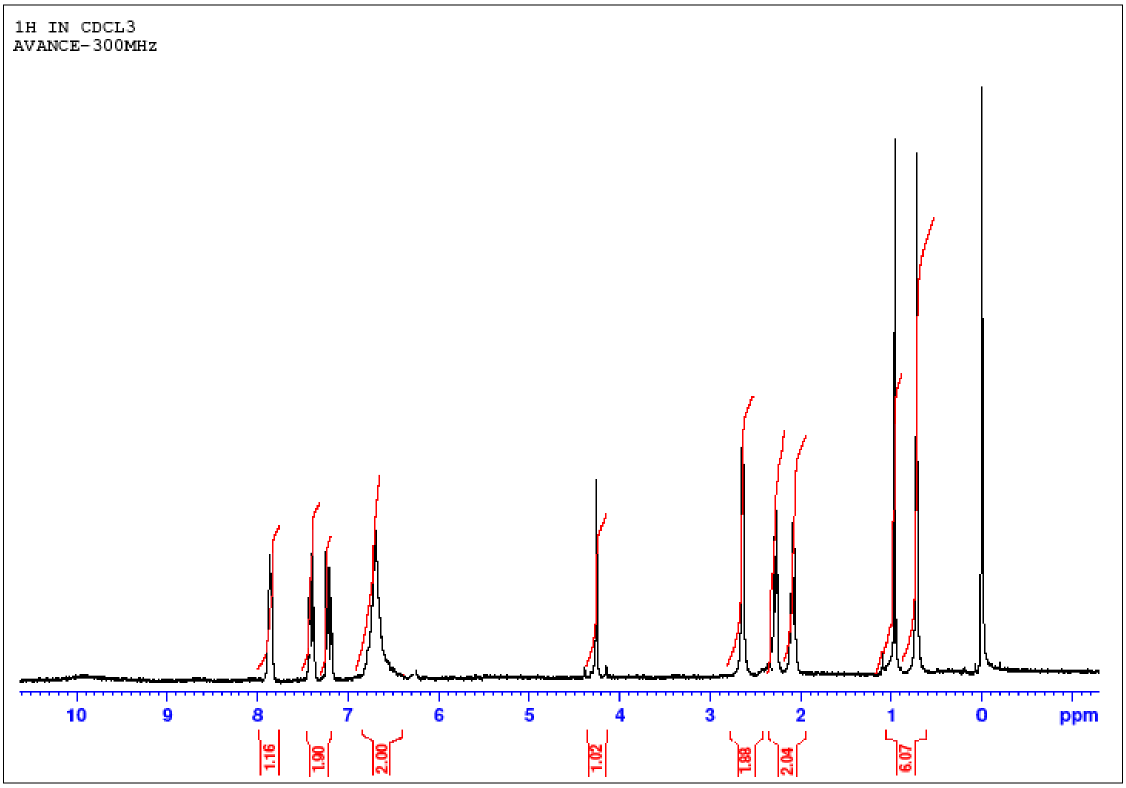
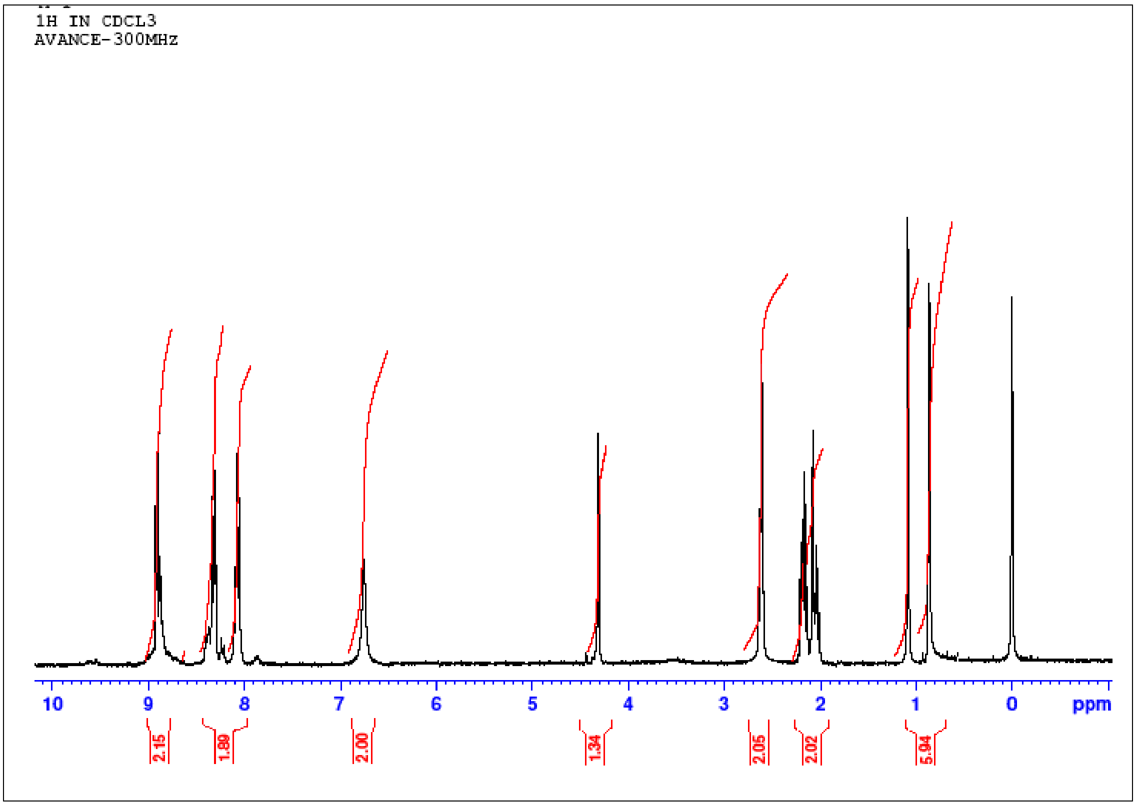
^{1}H NMR spectra for Compound 4e



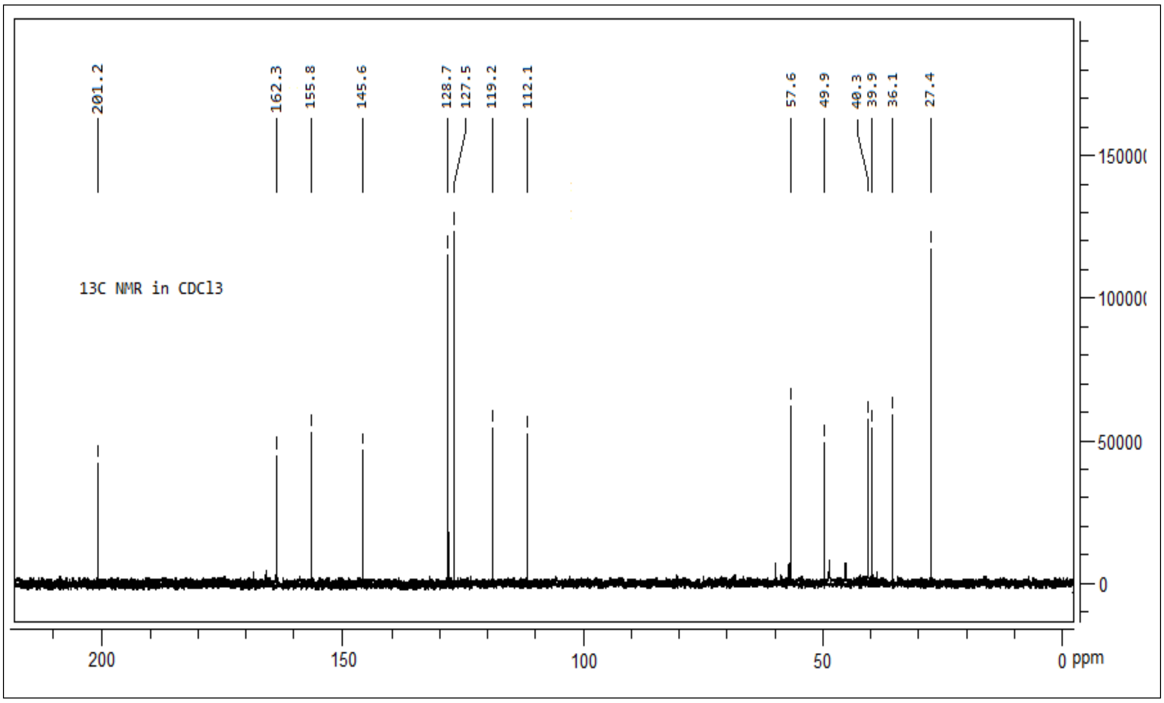
^{1}H NMR spectra for Compound 4l



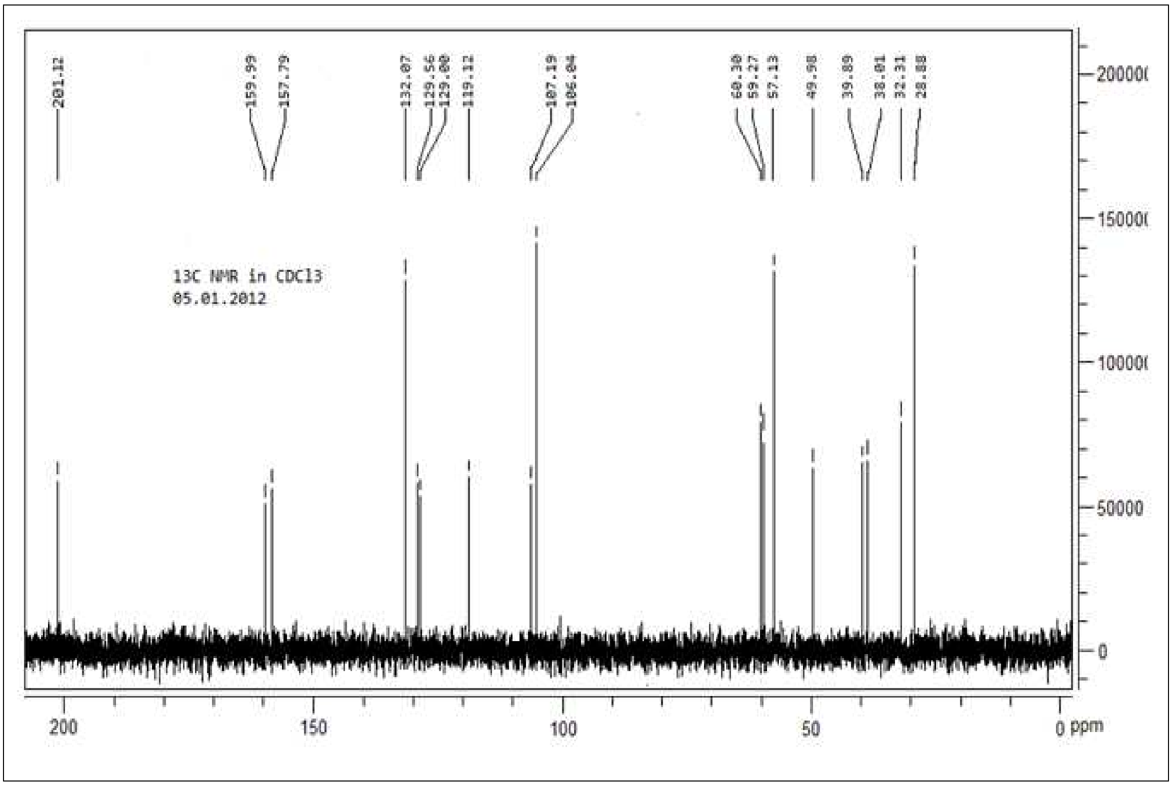
^{1}H NMR spectra for Compound 4o



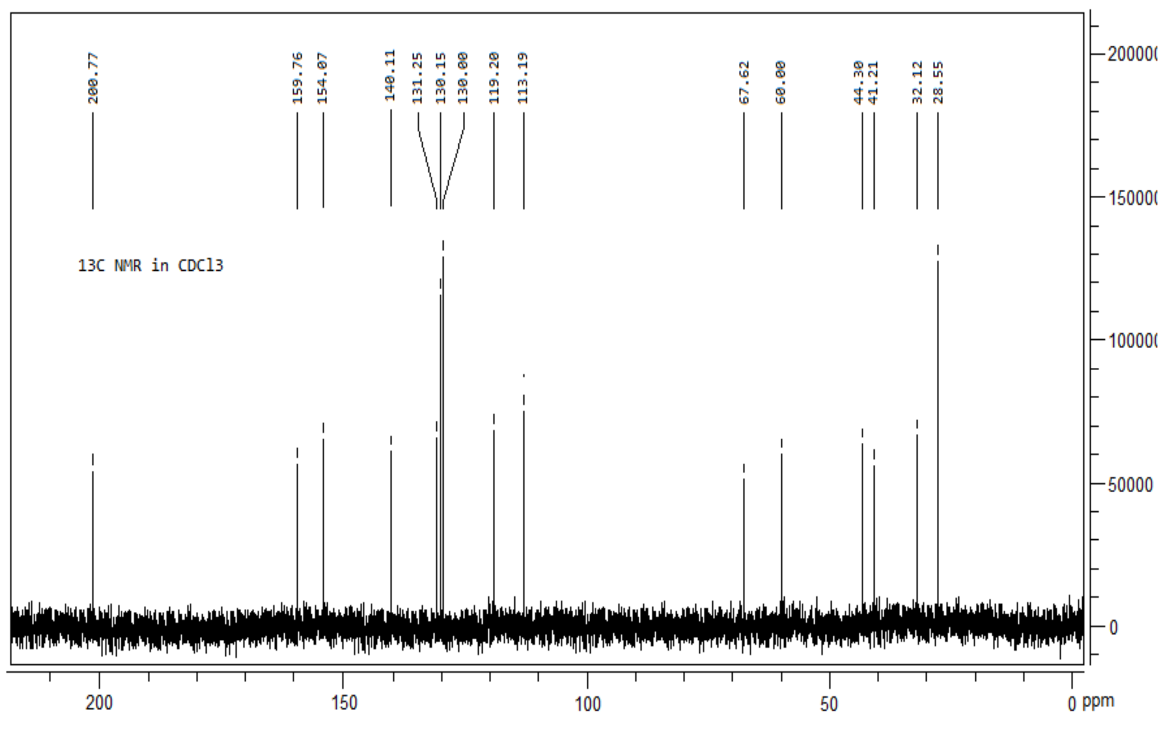
^{13}C NMR spectra for Compound 4a



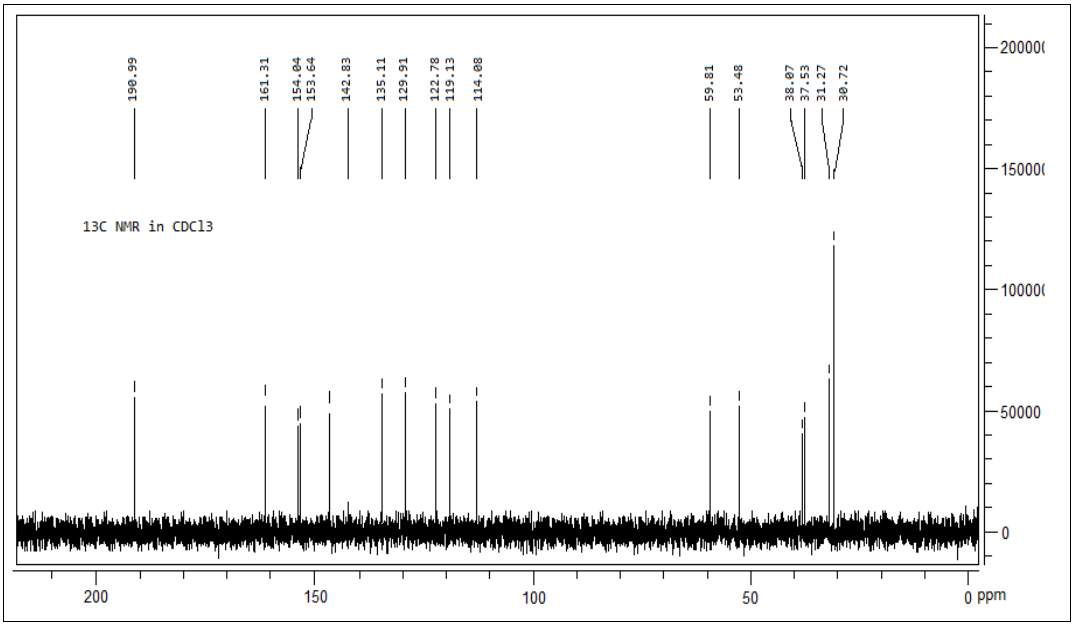
^{13}C NMR spectra for Compound 4e



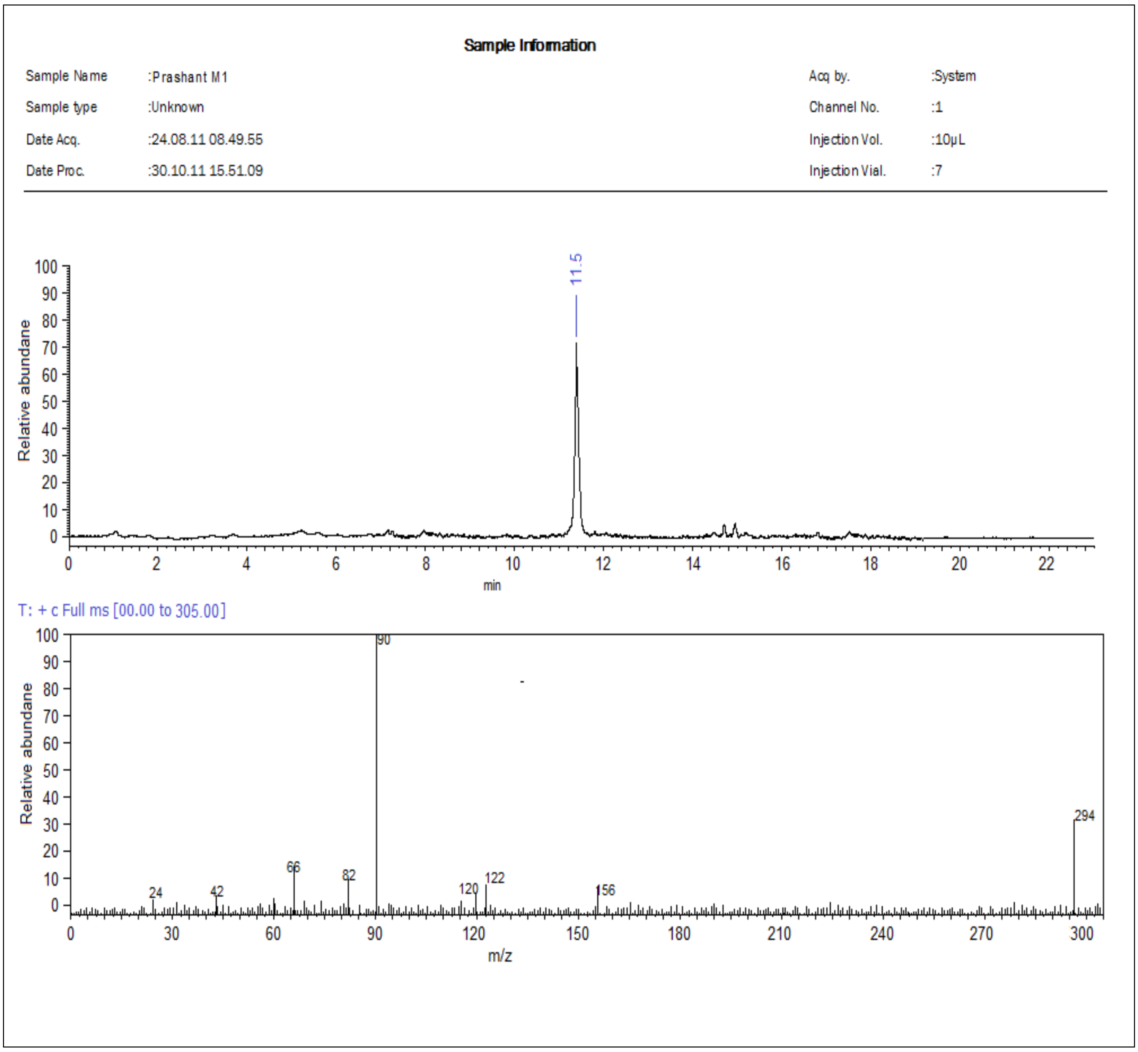
^{13}C NMR spectra for Compound 4l



^{13}C NMR spectra for Compound 4o



Mass spectra for Compound 4a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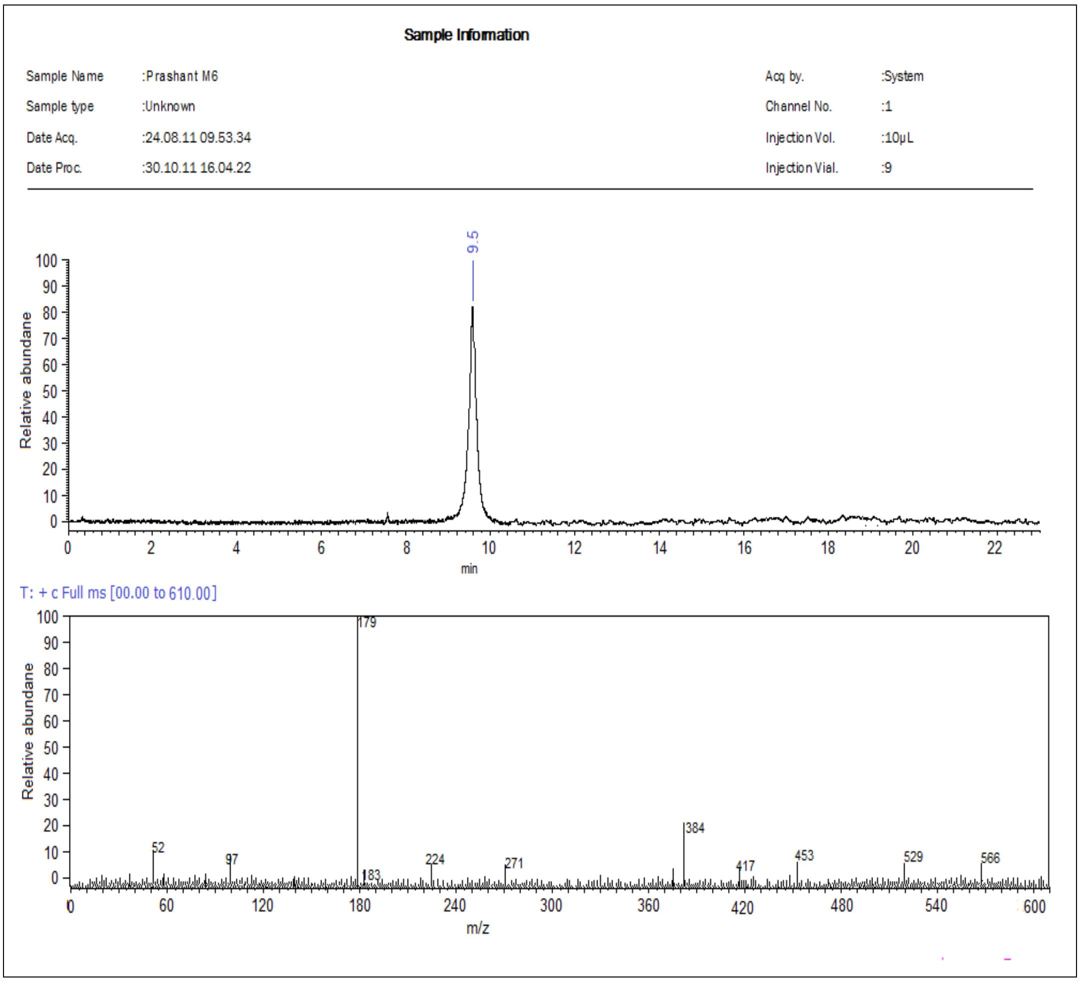
Injection Vial. :7

Mass spectra for Compound 4e



Sample Information

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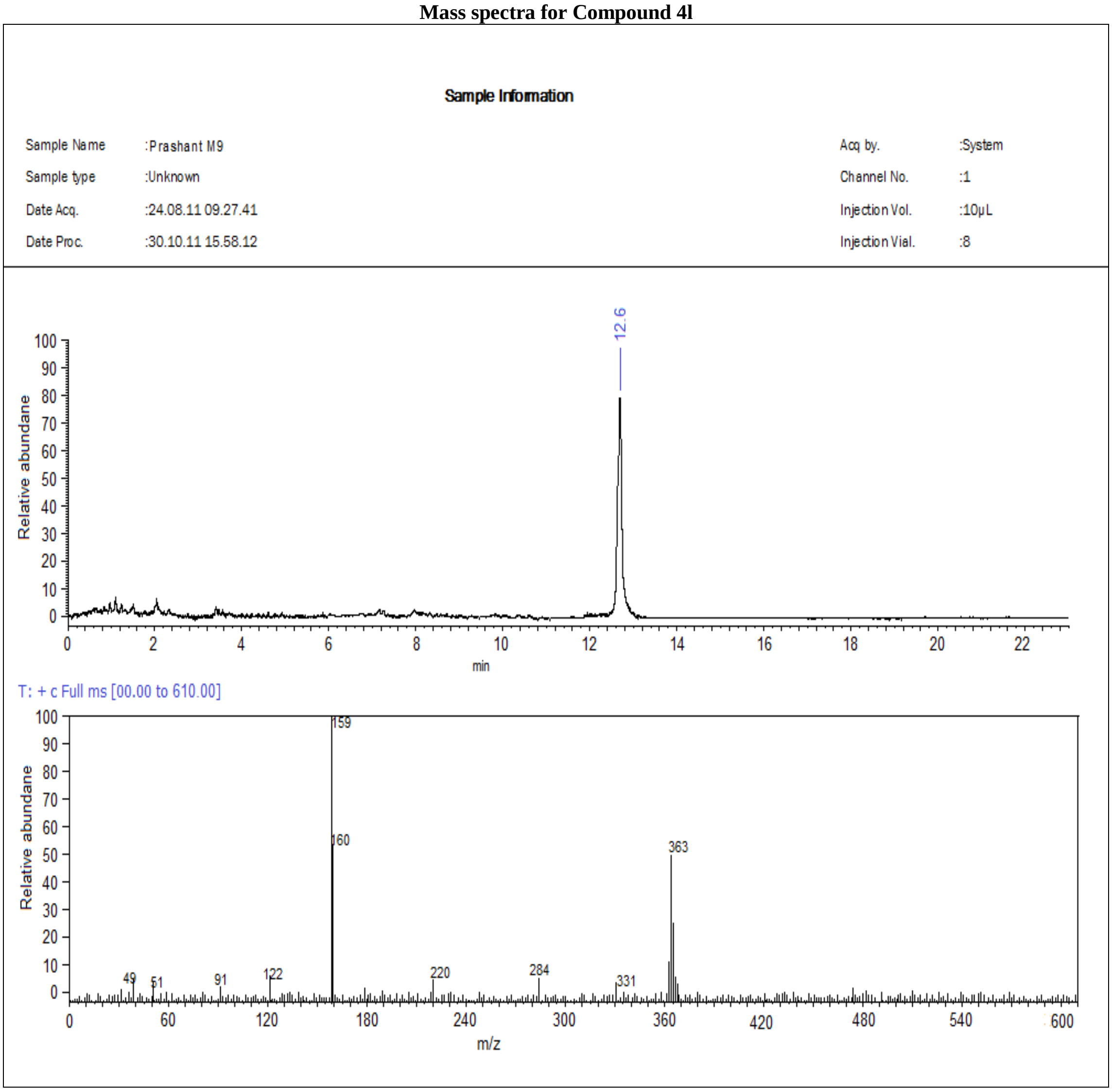
Mass spectra for Compound 4l



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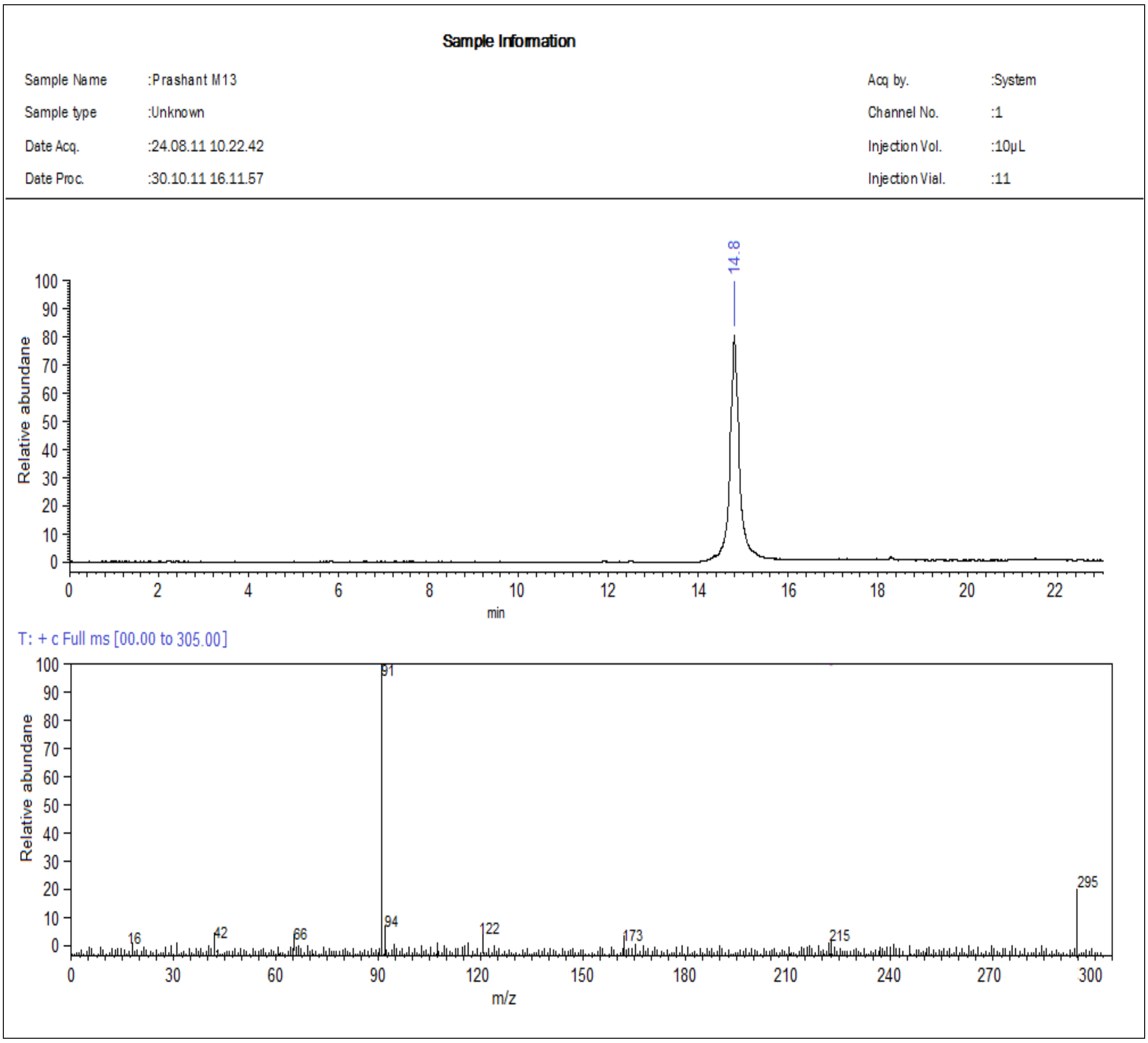
Mass spectra for Compound 4o



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CONCLUSION

In summary, we have developed a simple and efficient protocol for the synthesis of 2-amino-4*H*-chromene derivatives under mild conditions in short time, using cesium carbonate green heterogeneous catalyst in ethanol. This simple and facile method will be a useful addition to green chemistry with solid base heterogeneous recyclable catalyst.

Acknowledgement
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