



## Research Article

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# Chiral Synthesis of N, S and O Hetero Atoms Containing Heterocyclic Compounds

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## Abstract

DHPMs (Dihydropyrimidin) are chiral compounds having biological properties such as antiviral, antibiotic, anticarcinogenic, antihypertensive, antitubercular, antimycobacterial or anticancer activities due to presence of stereogenic carbon C<sub>4</sub> in their structure. DHPMs derivatives are synthesized via a multicomponent reaction of aldehyde derivative, urea or thiourea and 1,3-dicarbonyl compounds using Biginelli Reaction and microwave irradiation catalyzed by HCl. <sup>1</sup>H NMR, IR, mass spectra and C, H, N analysis data established identification of the compounds.

**Keywords:** Dihydropyrimidines, nmr, mass spectra, synthesis, chemical compounds

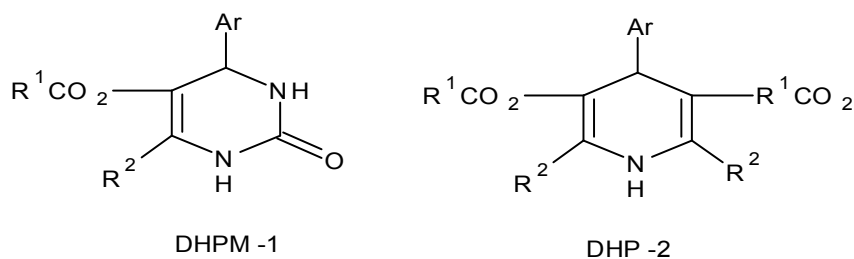
## Introduction

The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry<sup>1</sup>. The diversity, efficiency and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process<sup>2</sup>.

The 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPM-1, Figure 1) have recently emerged as important target molecules due to their therapeutic and pharmacological properties<sup>3</sup> such as antiviral<sup>4</sup>, antimitotic<sup>5a-b</sup>, anticarcinogenic<sup>6</sup>, antihypertensive<sup>7</sup> and noteworthy, as calcium channel modulators<sup>8</sup>. Additionally, their particular structure has been found in natural marine alkaloid batzelladine A and

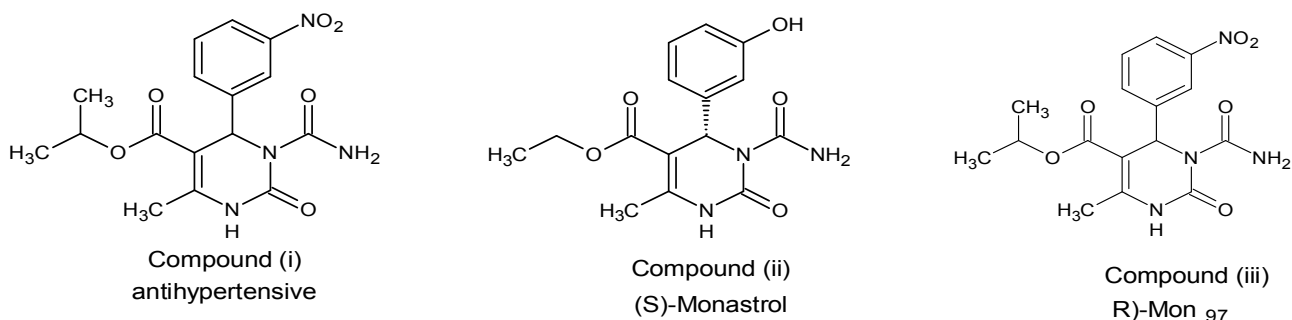
B which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, so disclosing a new field towards the development of AIDS therapy<sup>9</sup>. Also, due to the close related structure of DHPMs with the known dihydropyridine calcium channel modulators of the Hantzsch-type (DHP - 2, Figure 1), an intensive research has been devoted to synthesize the dihydropyrimidinone nucleus and this subject was recently reviewed<sup>10</sup>.

The original one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones was firstly reported by Pietro Biginelli in 1893 performing the three-component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Brønsted acid catalysis<sup>11</sup>. However, this reaction suffers from the harsh conditions, high reaction times and frequently low yields. Among the



**Figure 1.** The Biginelli (1) and Hantzsch (2) compounds

The following compound (i) exhibits an antihypertensive effect and only (S)-Monastrol (ii) and (R)-Mon- 97(iii) present potential anticancer activity



[Anticancer agent]

diversity of available methodologies in the literature that use lithium salts<sup>12</sup>, TMSI<sup>13</sup>, reactions performed under ionic liquids<sup>14</sup>, solid phase<sup>15</sup>, polymer-supported<sup>16</sup>, heterogeneous catalysis by silica's<sup>17</sup> and montmorillonites<sup>18</sup> or activation by ultrasound<sup>19</sup> and microwave<sup>20</sup> energies as synthetic protocols to prepare DHPMs, special attention has been dedicated to Lewis acids catalysis. Recently, BF<sub>3</sub>.OEt<sub>2</sub> complex was shown to be an excellent promoter of the three-component reaction<sup>21</sup> but anhydrous conditions were required. High yields of DHPMs were obtained using metals halides, such as NiCl<sub>2</sub>.6H<sub>2</sub>O and FeCl<sub>3</sub>.6H<sub>2</sub>O<sup>22</sup>, CoCl<sub>2</sub>.6H<sub>2</sub>O<sup>23</sup>, BiCl<sub>3</sub><sup>24</sup>, In (III)-halides<sup>25</sup>, and ZrCl<sub>4</sub><sup>26</sup>, or lanthanide halides such as LaCl<sub>3</sub>.7H<sub>2</sub>O<sup>27</sup>, and CeCl<sub>3</sub>.7H<sub>2</sub>O<sup>28</sup> as Lewis acid catalysts. Metal triflates, such as Zn(OTf)<sub>2</sub><sup>29</sup>, Cu(OTf)<sub>2</sub><sup>30</sup>, Bi(OTf)<sub>3</sub><sup>31</sup>, and Sc(OTf)<sub>3</sub><sup>32</sup> or lanthanide triflates as Yb(OTf)<sub>3</sub><sup>32</sup>, and La(OTf)<sub>3</sub><sup>33</sup> SnCl<sub>4</sub>.2H<sub>2</sub>O<sup>34</sup> were also reported.

### Antitubercular activity

Dihydropyrimidines are not represented in the current clinical antitubercular regimens, suggesting that this class of compounds may target new biochemical mechanisms potentially allowing treatment of MDR-TB and there are very few investigatory reports on dihydropyrimidines as

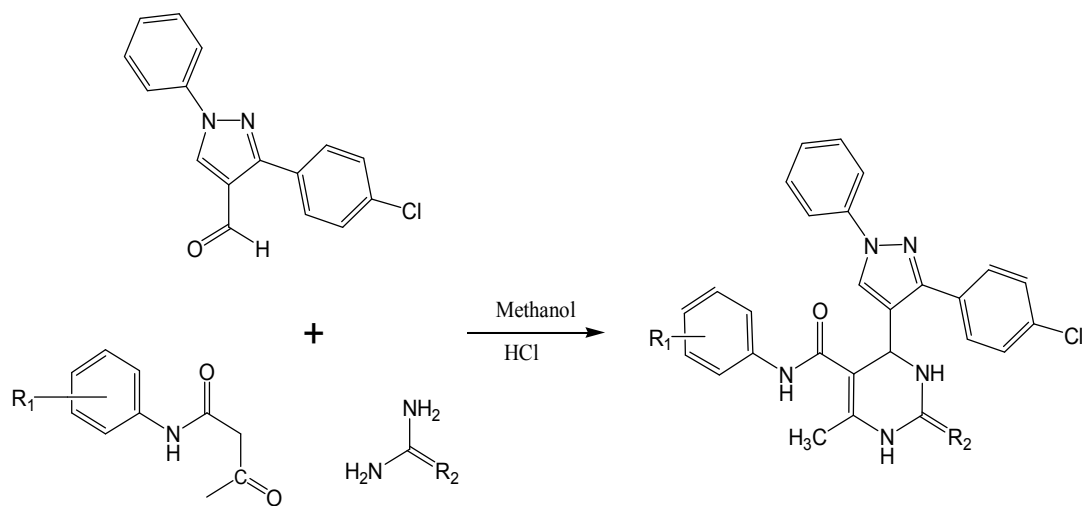
antitubercular agents<sup>35</sup>. Recognizing these facts and in constituents of work on pyrimidine derivatives we set upon a program of making antitubercular agents, using the central dihydropyrimidine as the template and adding versatile constituents on the various positions of dihydropyrimidine ring.

### Experimental

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were used throughout the experiment. IR spectra were recorded on Shimadzu-8400 FTIR spectrophotometer by DRS method. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> on a BRUKER AVANCE II 400 spectrometer using TMS as internal standard. The progress of reaction was monitored by TLC run on silica gel G (Merck).

### Conventional method

A mixture of aldehyde derivative (0.01mole), 1,3 -dicarbonyl compound (0.01 mole), urea (0.01 mole) add in a 30ml methanol and add catalytic amount of Hydrochloric acid were placed in a round bottom flask and the mixture was refluxed for about 18 hrs till the reaction was



Where R1 = -Cl, -F, -NO<sub>2</sub>, -OCH<sub>3</sub>  
R2 = O, S

complete (monitored by TLC). The mixture was then cooled to room temperature (RT) and poured into water with continuous stirring when the solid product separated out. The crude solid product was purified by repeated recrystallisation from alcohol or by column chromatography to give the pure products.

### Microwave method

A mixture of aldehyde derivative (0.01mole), 1, 3 –dicarbonyl compound (0.01 mole), urea (0.01 mole) and catalytic amount of Hydrochloric acid were placed in a flask and irradiated in a microwave oven 220 W for the required duration. Now the mixture was cooled to room temperature and water was added with stirring when the solid product precipitated out, which was filtered. The crude product was washed with water and recrystallised from alcohol or purified by column chromatography to give the product in good to excellent yields. All the product were characterized by melting point, <sup>1</sup>H NMR, IR, Mass Spectra and C, H, N analysis.

## Result and Discussion

### Spectral data

**4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-N-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxamide, 1-B**

A mixture of 3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01mole), N-(4-methoxyphenyl)-3-oxobutanamide (0.01 mole), Urea (0.01 mole) and catalytic amount of Hydrochloric acid were placed in a flask and irradiated in a microwave oven 220 W for 10 min. After the completion of the process, the mixture was cooled to room temperature and water was added with stirring when the solid product precipitated out, which was filtered. The crude product was washed with water and recrystallised from alcohol or purified by column chromatography to give 69% yields.

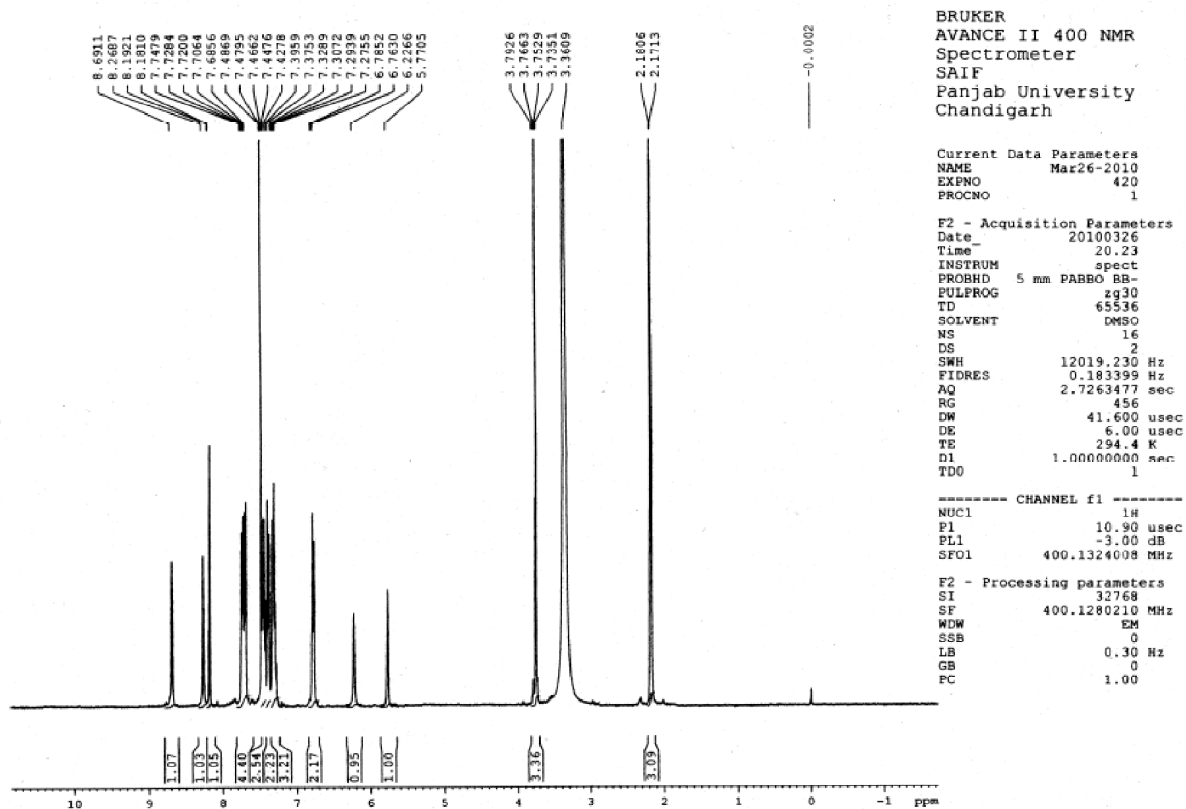
M.P. 245-250°C ; IR-Aromatic 3047, C=O-1690, NH-1596 & 3400, -OCH<sub>3</sub>-2830 2810 and 1460-1440, -CH<sub>3</sub>-2920- and 1470-1430, -Cl-761 cm<sup>-1</sup>, <sup>1</sup>H NMR- (CDCl<sub>3</sub>) $\delta$  3.73 (s, 6H, -OCH<sub>3</sub>), 5.71 (d, 1H, -CH), 2.16 (d, 2H, -NH), 8.0 (d, 1H, -NH) 1.71 (3H, -CH<sub>3</sub>), 6.83-7.65 (13H, ArH); MF- C<sub>28</sub>H<sub>2</sub>ClN<sub>5</sub>O<sub>3</sub>, M.W.-513.16, C=65.16%, H=4.71%, Cl=6.90%, N=13.63%, O=9.34% (Figures 2 and 3).

**4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-N-(4-methoxyphenyl)-6-methyl-2-thiopyrimidine-5-carboxamide, 2-B**

A mixture of 3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01mole), N-(4-methoxyphenyl)-3-oxobutanamide (0.01 mole), Thiourea (0.01 mole) and catalytic amount of Hydrochloric acid were placed in a flask and irradiated in a microwave oven 220 W for 12 min.

**Table 1.** Summary

Entry	R1	R2	Product	Yield (%)	M.P.	Microwave time (minutes)
1	H	O	1-A	78	270-80	5
2	<i>p</i> -OCH <sub>3</sub>	O	1-B	72	245-50	10
3	<i>o</i> -F	O	1-C	65	192-94	7
4	<i>p</i> -F	O	1-D	82	214-20	12
5	<i>m</i> -F	O	1-E	56	208-10	15
6	<i>o</i> -Cl	O	1-F	78	156-60	8
7	<i>p</i> -Cl	O	1-G	65	211-22	5
8	<i>m</i> -Cl	O	1-H	88	255-60	9
9	<i>o</i> -NO <sub>2</sub>	O	1-I	74	201-10	3
10	<i>p</i> -NO <sub>2</sub>	O	1-J	80	245-25	5
11	<i>m</i> -NO <sub>2</sub>	O	1-K	73	235-47	7
12	H	S	2-A	78	179-88	5
13	<i>p</i> -OCH <sub>3</sub>	S	2-B	69	200-11	12
14	<i>o</i> -F	S	2-C	83	268-77	9
15	<i>p</i> -F	S	2-D	71	260-74	4
16	<i>m</i> -F	S	2-E	77	206-17	6
17	<i>o</i> -Cl	S	2-F	73	178-89	9
18	<i>p</i> -Cl	S	2-G	82	209-20	8
19	<i>m</i> -Cl	S	2-H	78	235-38	6
20	<i>o</i> -NO <sub>2</sub>	S	2-I	85	200-05	4
21	<i>p</i> -NO <sub>2</sub>	S	2-J	70	250-55	7
22	<i>m</i> -NO <sub>2</sub>	S	2-K	89	190-95	9



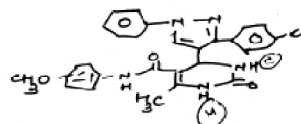
avtar\_saifpu@yahoo.co.in

Fig 2. NMR Spectra of 1 B

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Sample Information

Analyzed by : G. J. KHER  
Analyzed : 3/3/2010 3:44:09 PM  
Sample Name : VC-01  
Sample ID : VC-01  
Data File : C:\GCMSolution\Data\Project\VC-01.QGD  
Method Name : C:\GCMSolution\Data\Project\1DI.qm



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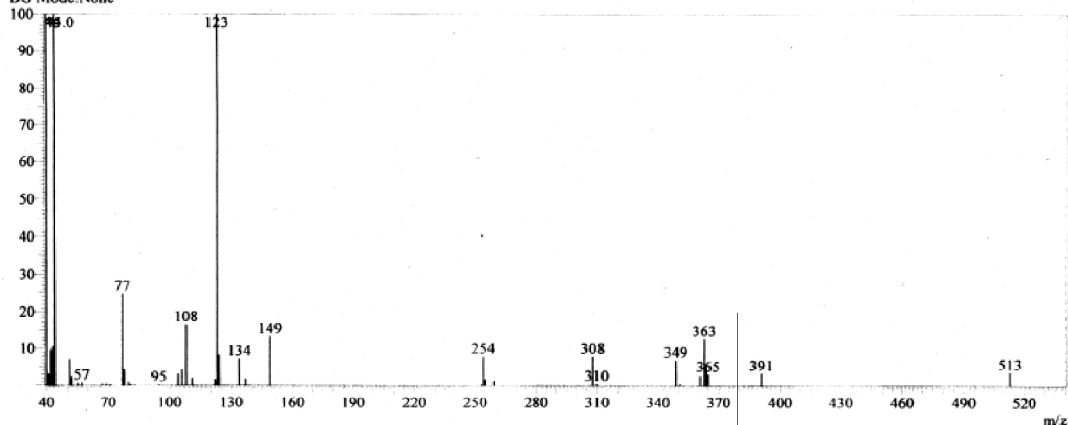


Fig 3. Mass Spectra of 1 B

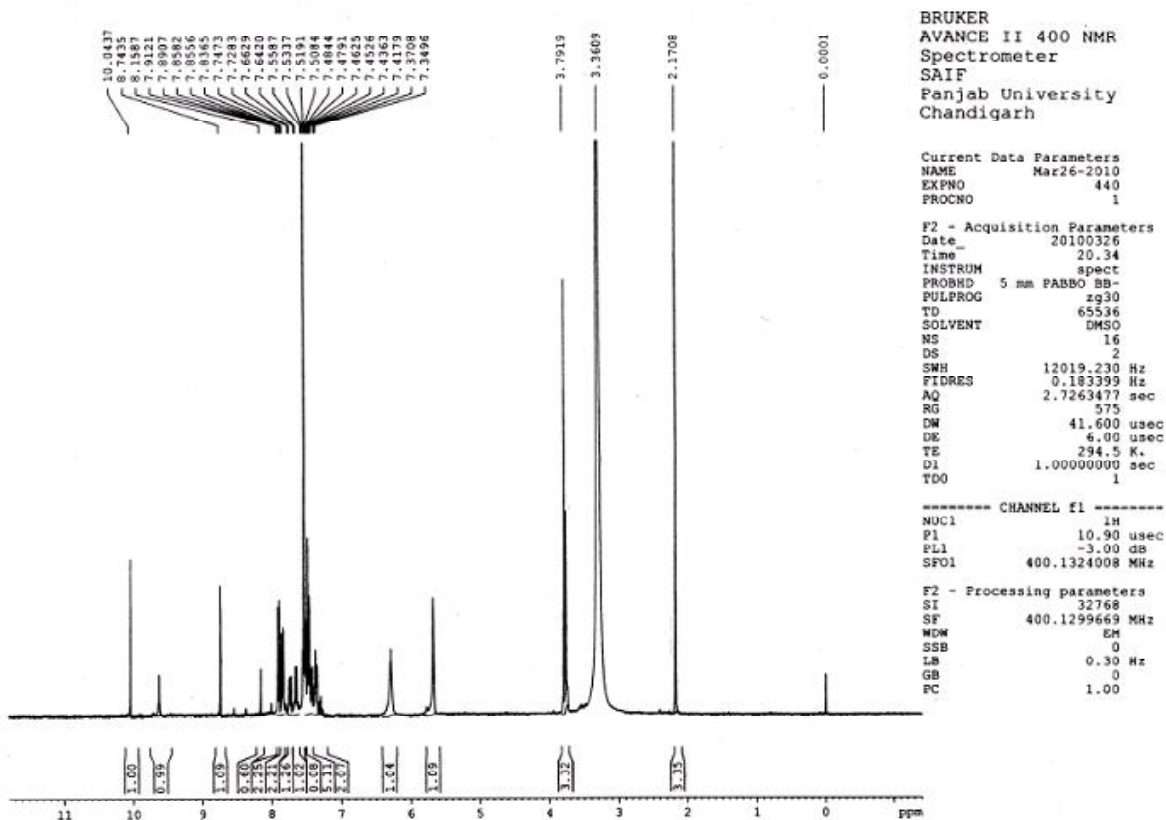


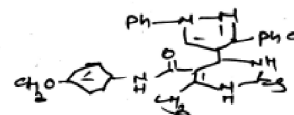
Fig 4. NMR Spectra of 2 B

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Sample Information

Analyzed by : G. J. KHER  
 Analyzed : 3/3/2010 3:02:17 PM  
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 Sample ID : VC-11  
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 Method Name : C:\GCMSolution\Data\Project\VD1.qm



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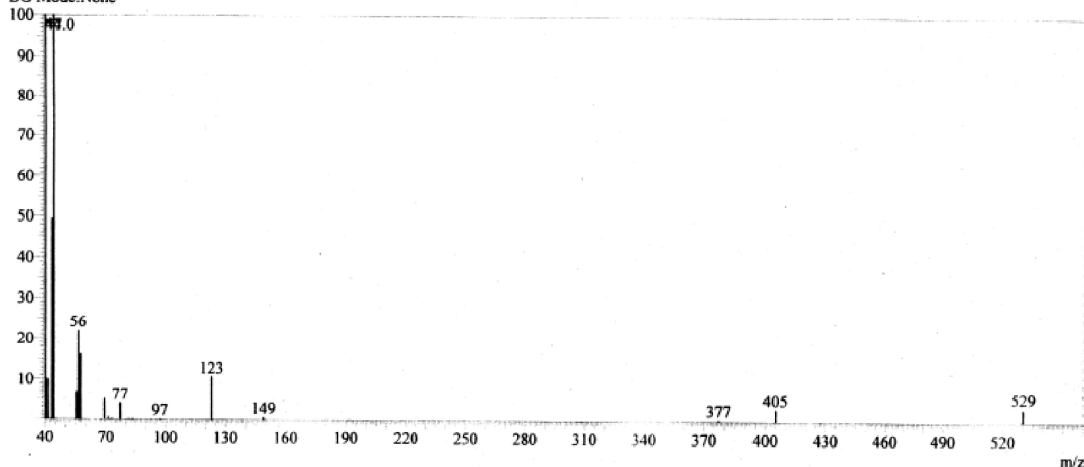


Fig 2. Mass Spectra of 2

After the completion of the process the mixture was cooled to room temperature and water was added with stirring when the solid product precipitated out, which was filtered. The crude product was washed with water and recrystallised from alcohol or purified by column chromatography to give 72% yields.

M.P. 200-211°C ; IR-Aromatic 3037, C=O - 1690, NH-1650-1550, -SH-2590-2550, -OCH<sub>3</sub>-2830-2810 and 1460-1440, -CH<sub>3</sub>-2882-2862 and 1470-1430, -Cl-600-800 cm<sup>-1</sup>, <sup>1</sup>H NMR (CDCl<sub>3</sub>)δ 3.73(s, 3H, -OCH<sub>3</sub>), 5.77(d, 1H, -CH), 6.22(d, 1H, -NH), 8.18 (d, 1H, -NH) 1.71(3H, -CH<sub>3</sub>) , 6.22-8.69(14H, ArH); MF- C<sub>28</sub>H<sub>24</sub>N<sub>5</sub>ClO<sub>2</sub>S; M.W.-530.04, C=65.97%, H=4.96%, Cl=6.71%, N=13.26%, O=9.09%. (Figures 4 and 5).

Results are summarised in Table 1.

### Acknowledgments

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