Supporting Information

Supporting Information for *RSC Advances*

In-silico binding affinity to cyclooxygenase-II and Green synthesis of benzylpyrazolyl coumarin derivatives

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CONTENT:

ESI-1: All the five cavities (labeled as 1, 2, 3, 4 and 5) mapped within COX-II enzyme.

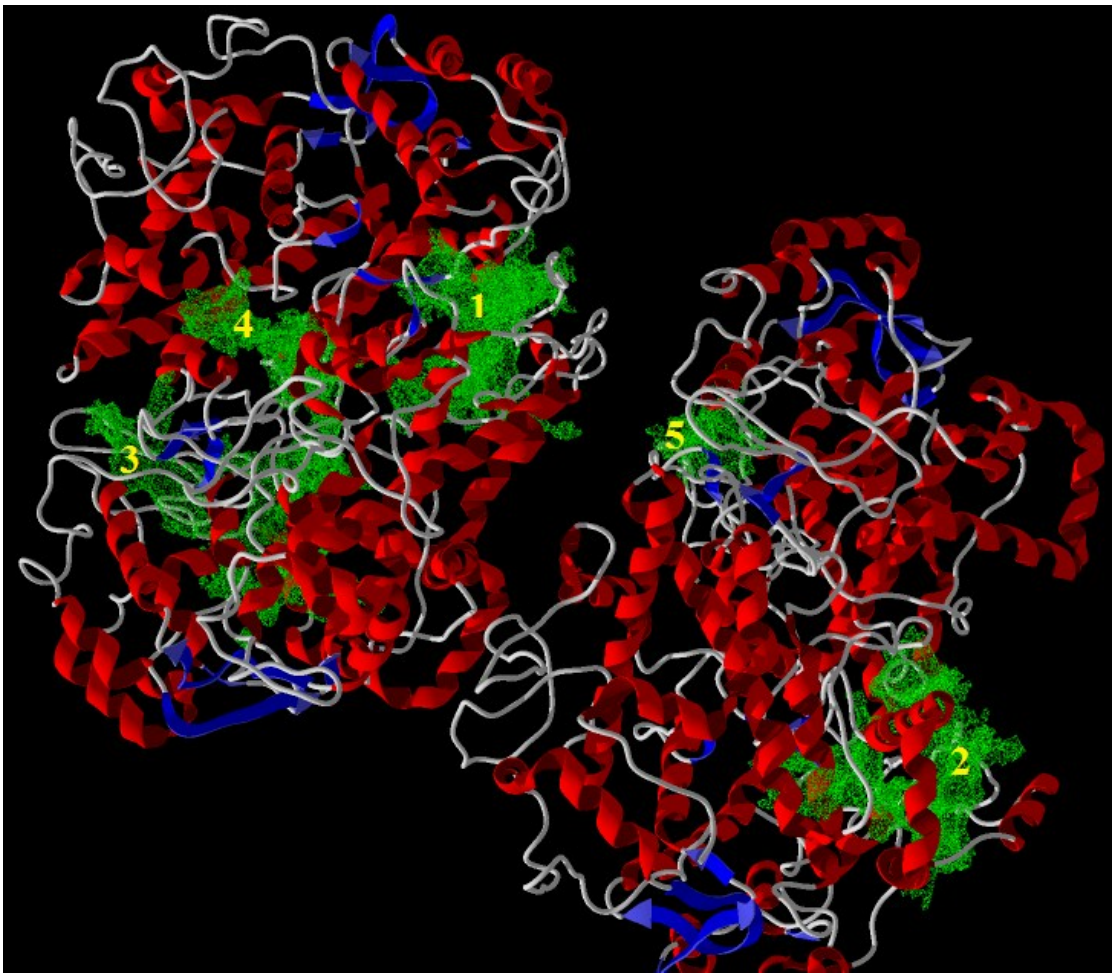


Fig.S1 All the five cavities (labeled as 1, 2, 3, 4 and 5) mapped within COX-II enzyme.

ESI-2: Methods for the Preparation of ionic liquids:

Method for the preparation of Neutral [pmIm]Br : [pmIm]Br has been prepared by refluxing a mixture of 1-bromopentane (20 mmol, 3.02g) and N-methyl imidazolium (20 mmol, 1.64 g) in neat conditions for 48 hrs with continuous stirring. After completion of 48 hrs a golden colour viscous liquid is formed. This viscous liquid is then allowed to cool at room temperature and then washed by ethyl acetate for 5-6 times to remove excess starting materials and finally the solvent was evaporated under vacuum.

Method for the preparation of [AcMIm] Cl : Chloroacitic acid (1.89 g , 20 mmol) is added to a cooled (0-5^{o}C) solution N-methyl imidazolium (1.64 g , 20 mmol) in DCM (15 ml) and the mixture was stirred at 50 ^{o}C for 24 hrs. The crude (white) product obtained is washed with diethyl ether (2 x 5 ml) and dried under vacuum to obtained pure [AcMIm]Cl.

ESI-3: Preparative method for the synthesis of benzylpyrazolyl coumarin derivatives

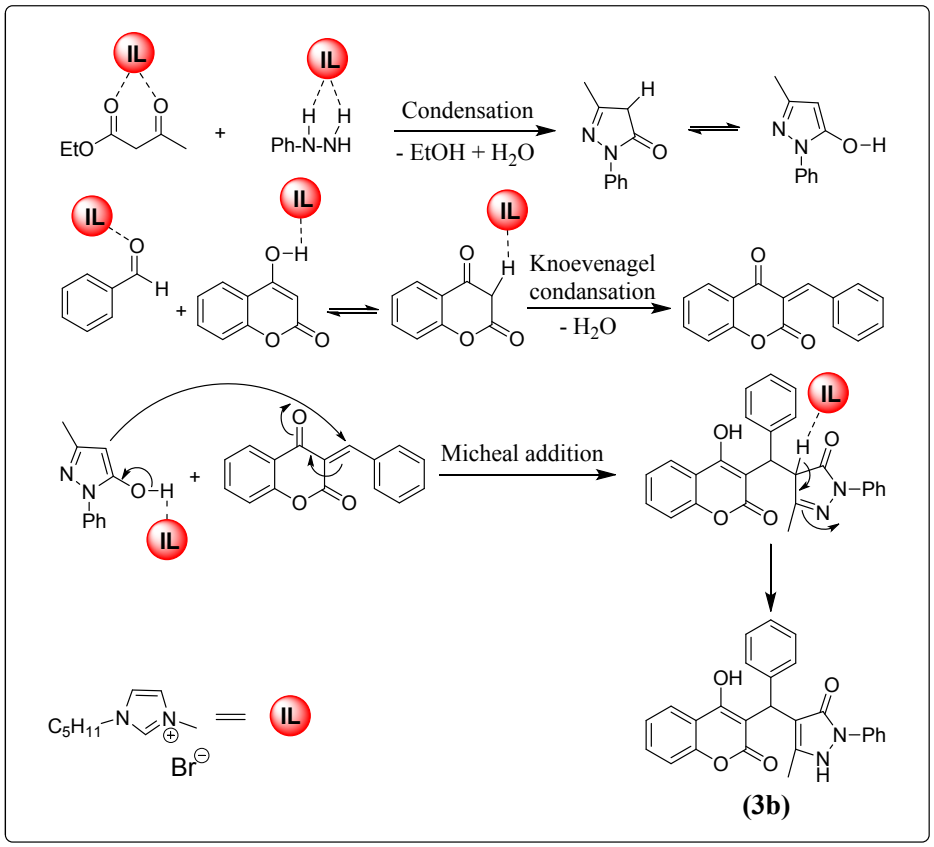
General Method for the Preparation of Benzylpyrazolyl Coumarins using ionic liquid as the catalyst and solvent:

A mixture of ethyl acetoacetate (1mmol), phenyl hydrazine/hydrazine hydrate (1mmol), aromatic aldehyde (1 mmol), 4-hydroxy coumarin (1 mmol) and ionic liquid (1.5 ml) is stirred at room temperature for a period of time until the reaction mixture gets solidified. The completion of the reaction is checked by TLC. After completion of the reaction, water (10 ml) and ethyl acetate (15 ml) is added and stirred at room temperature for 2 min. then allowed to settle down for some time. Two different layers of immiscible liquids are formed, in water the ionic liquid gets dissolved and the product goes to ethyl acetate layer. These two layers are separated using separation funnel and organic layer was washed with brine, dried with sodium anhydrous Na_2SO_4. Evaporation of solvent under vacuum left the crude product, which was then re-crystallized from ethanol. Primarily, the products were confirmed by checking their melting points and further confirmed by ^{1}H NMR and ^{13}C NMR studies. The ionic liquid was recovered from water layer simply evaporation of water under vacuum and reused for subsequent runs.

General method for the preparation of benzylpyrazolyl coumarin (3b) using [pmIm]Br as the catalyst and solvent: Representative experimental procedure for the synthesis of 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one (3b)

A mixture of ethyl acetoacetate (130 mg, 1mmol), phenyl hydrazine (108 mg, 1mmol), benzaldehyde (106 mg, 1mmol), 4-hydroxy coumarin (162 mg, 1 mmol) and [pmIm]Br (2ml) is stirred at room temperature for 2.5 hours until the reaction mixture get solidified. The completion of the reaction is checked by TLC. The product was separated following the procedure as mentioned above (ESI-3) and purified by re-crystallization from hot ethanol to provide pure 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one (3b, 85%). The formation of product was confirmed spectroscopic analysis.

ESI-4: Plausible mechanism for the synthesis of benzylpyrazolyl coumarin, namely, 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one



Scheme 1 Plausible mechanism for the synthesis of 3b.

ESI-5: Reusability of [pmIm]Br:

After the completion of the reactions for the synthesis of 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one (3b), product was isolated through the extraction with ethyl acetate and water. Then, compound was purified by recrystallization from ethanol. The water layer was then washed several times with ethyl acetate and then dried under vacuum to get the ionic liquid back. The separated ionic liquid was then used for the same reaction to get its recyclability. In this way, [pmIm]Br can easily be recycled six times with a minimum loss of yield of the product.

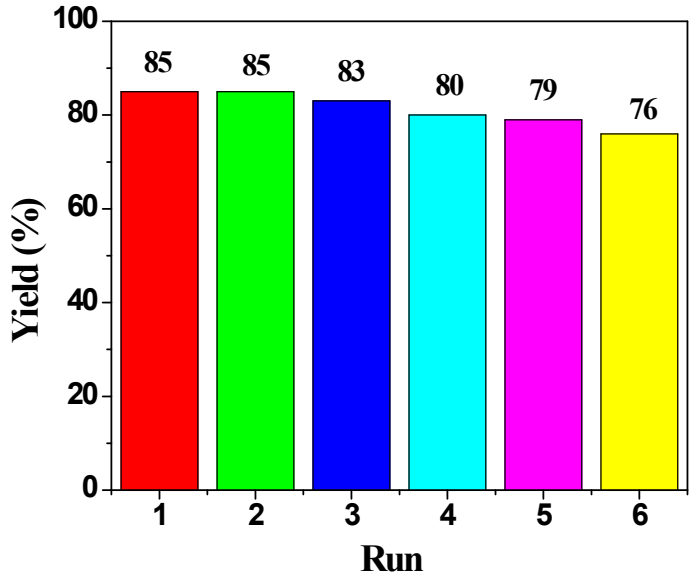
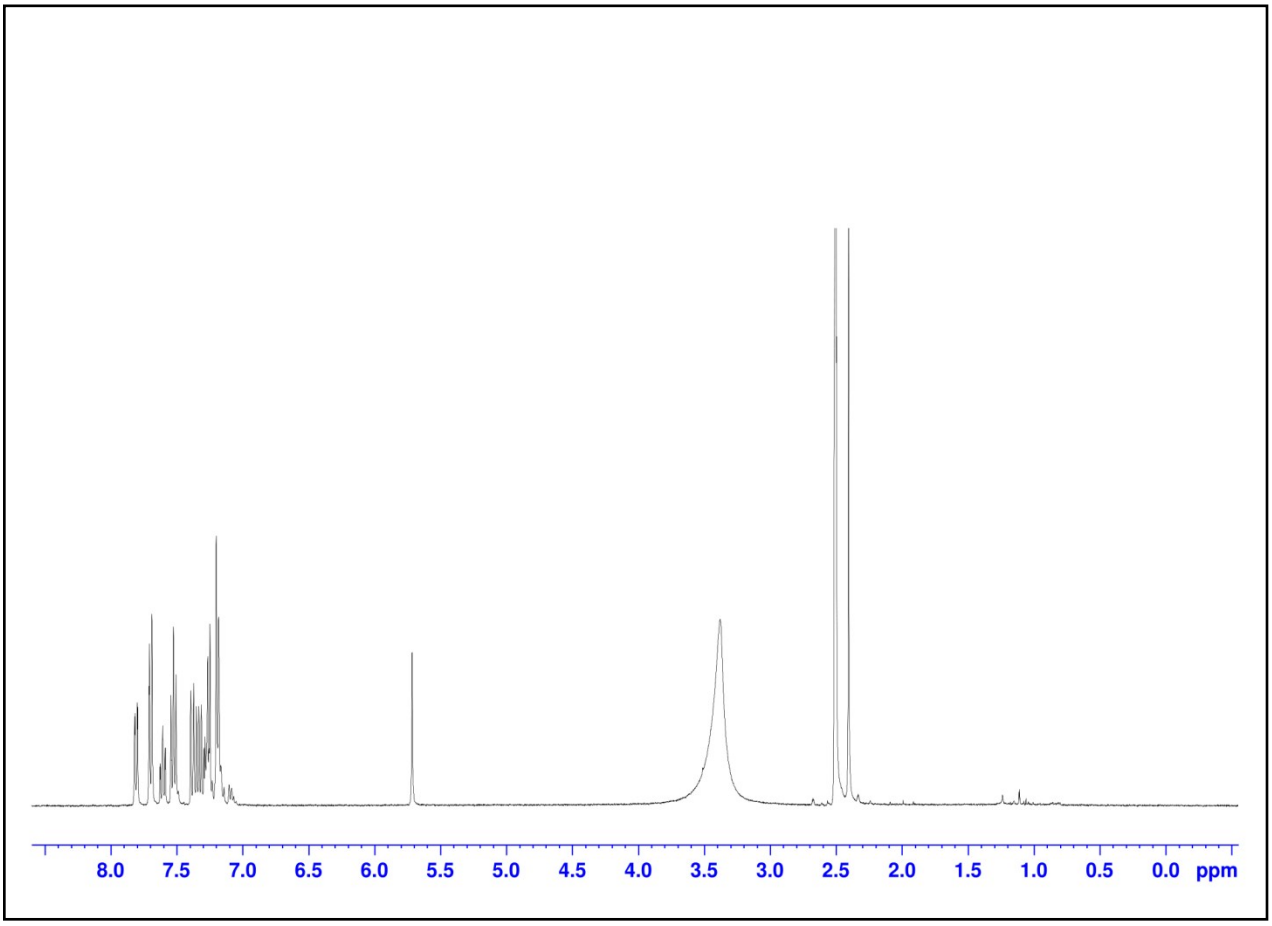
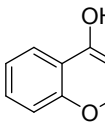


Fig.S2. Reusability of [pmIm]Br for the synthesis of 3b.

ESI-6: 1HNMR copy of benzylpyrazolyl coumarin derivatives:





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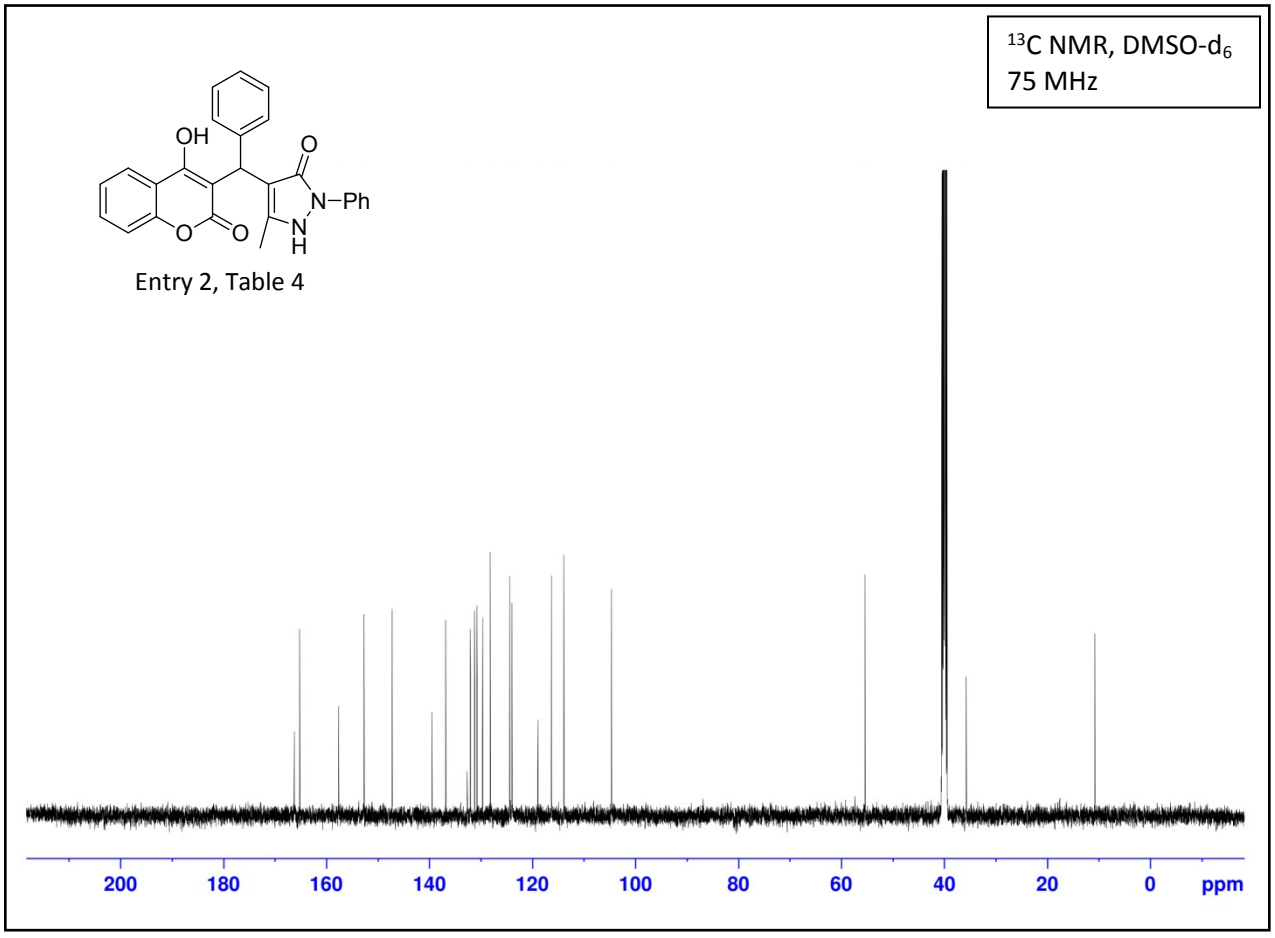
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OH
O
N–Ph
N
H
O
O
Entry 2, Table 4
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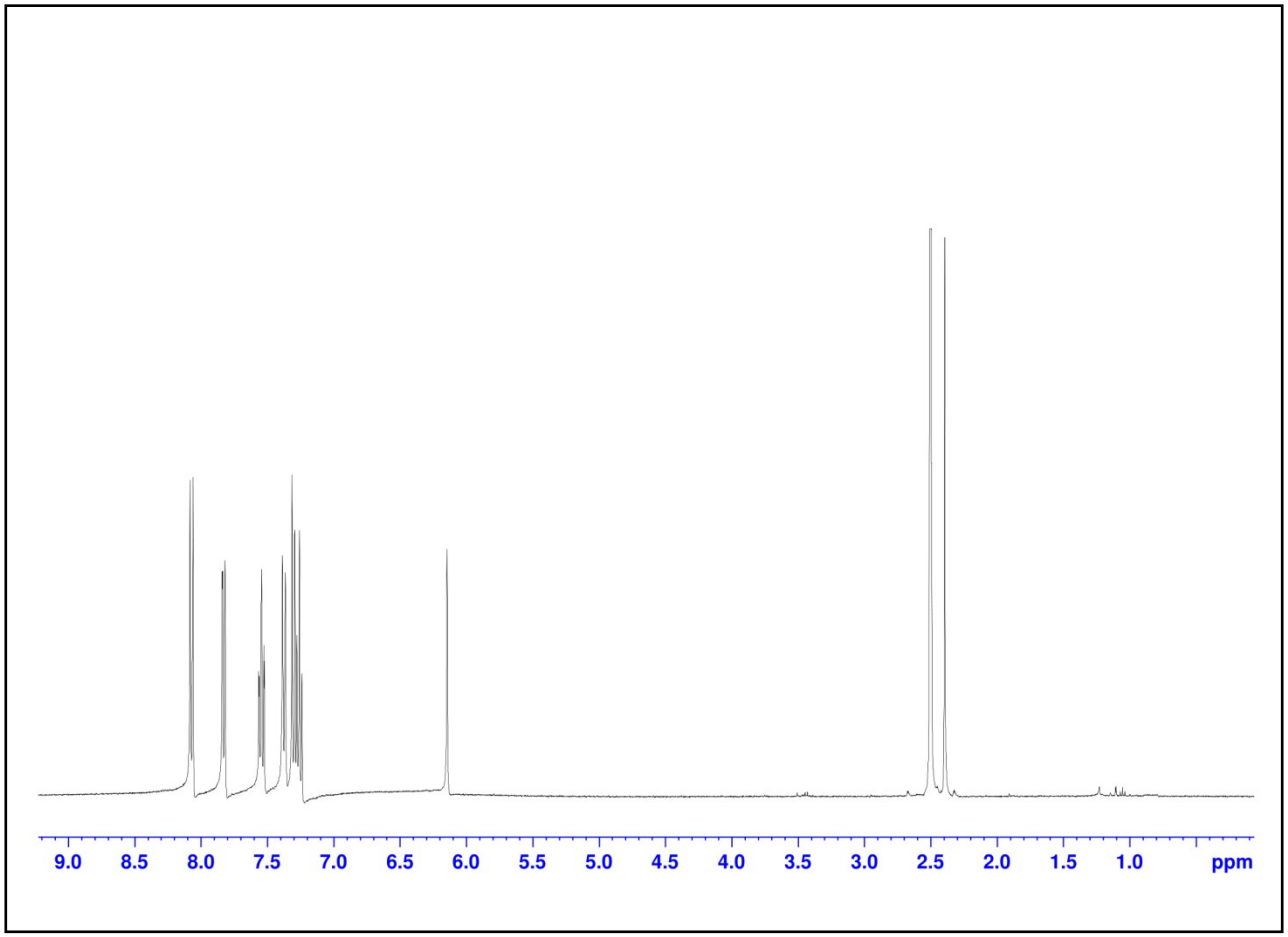
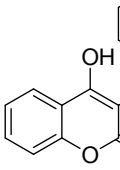
140
120
100
80
60
40
20
0
ppm





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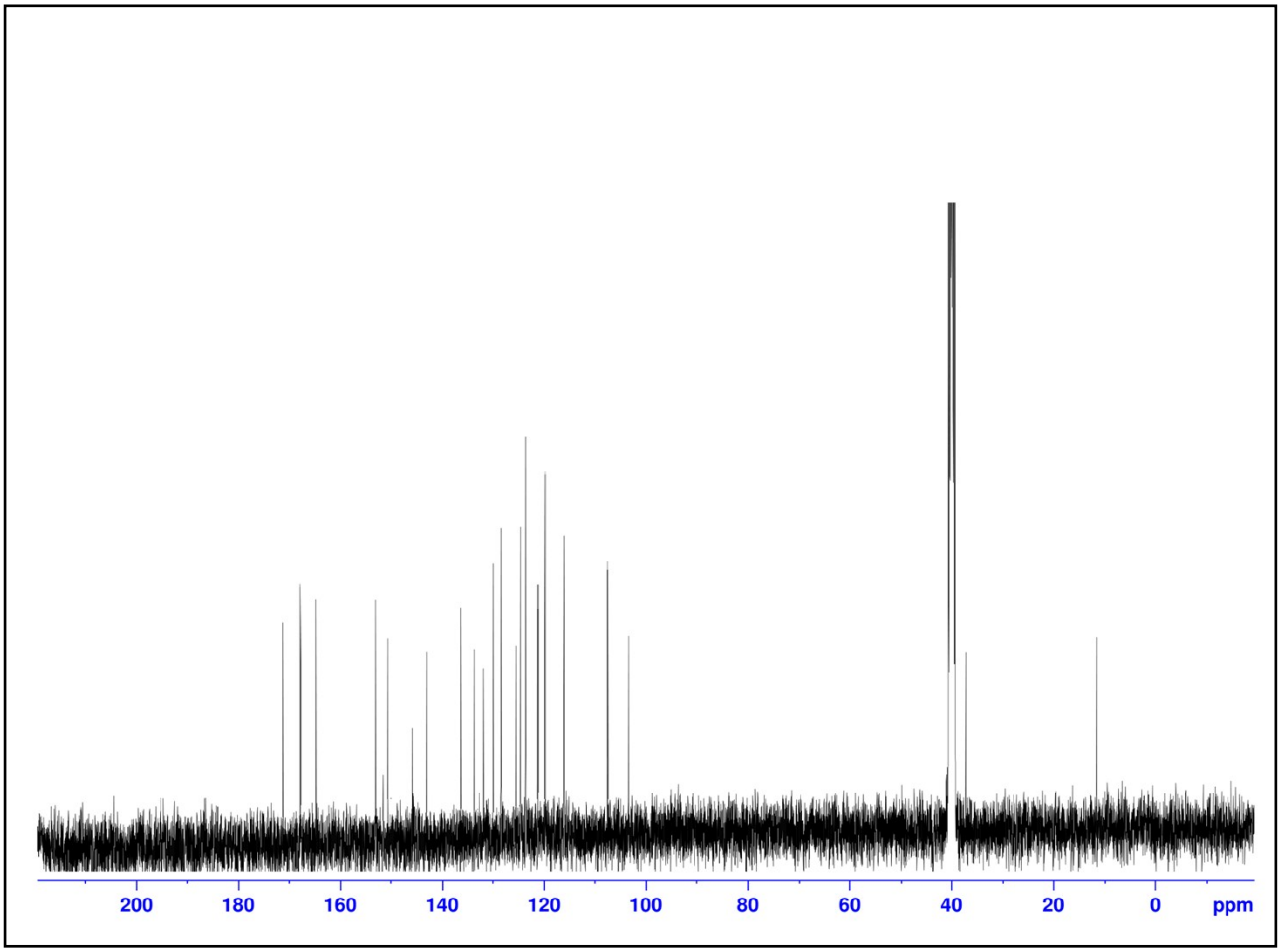

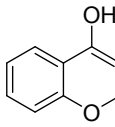

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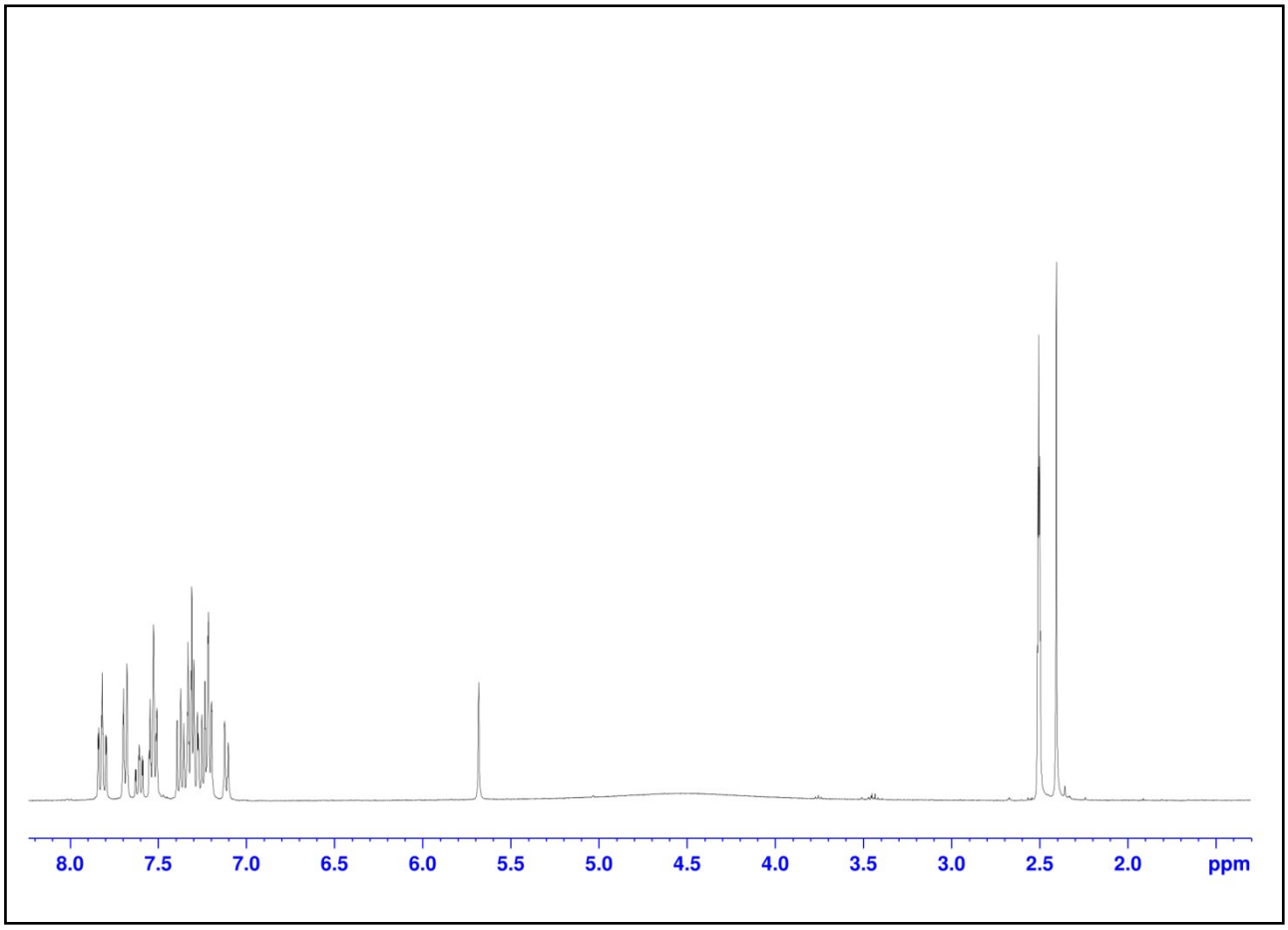

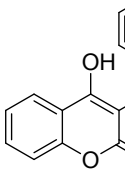

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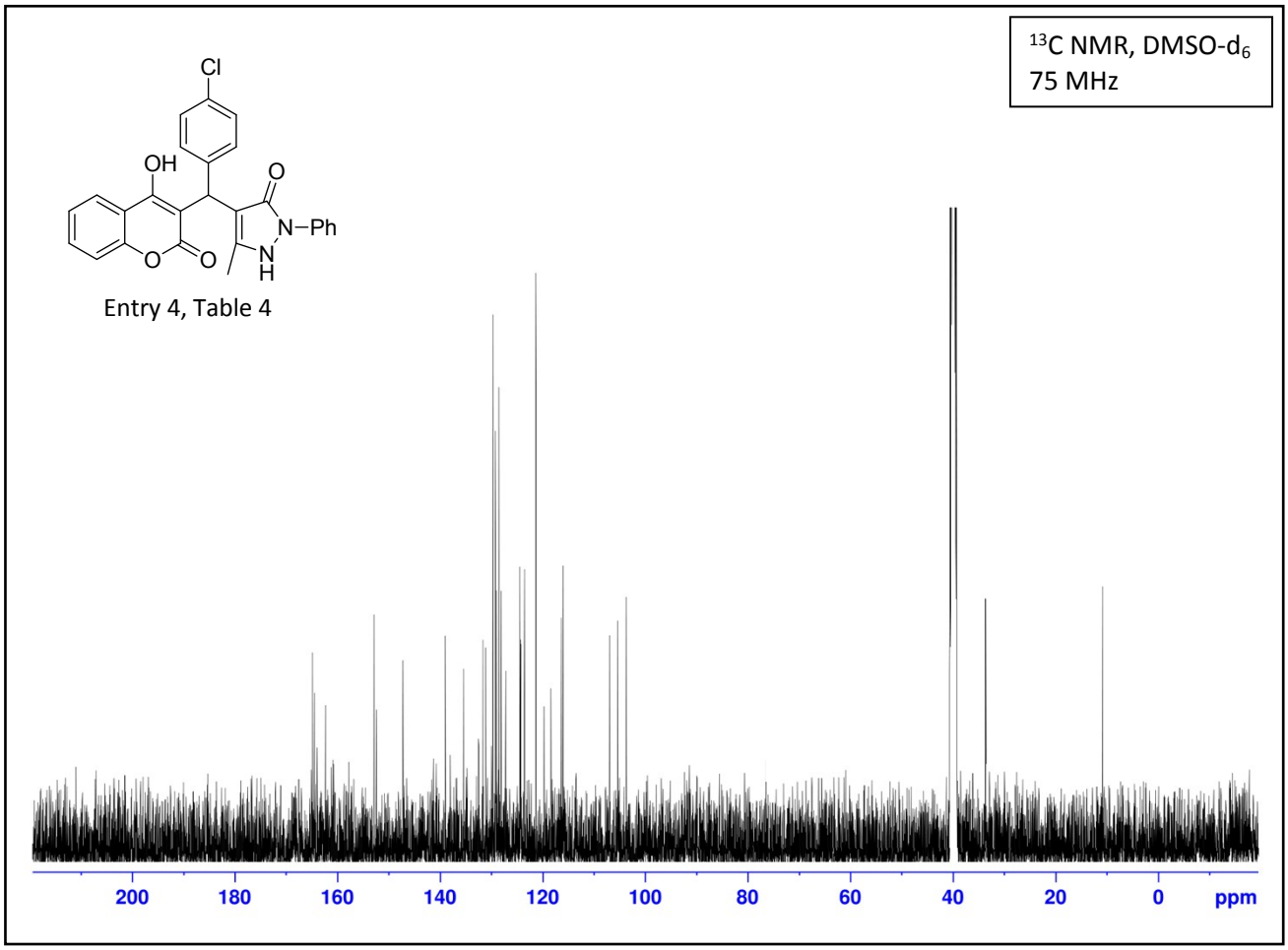
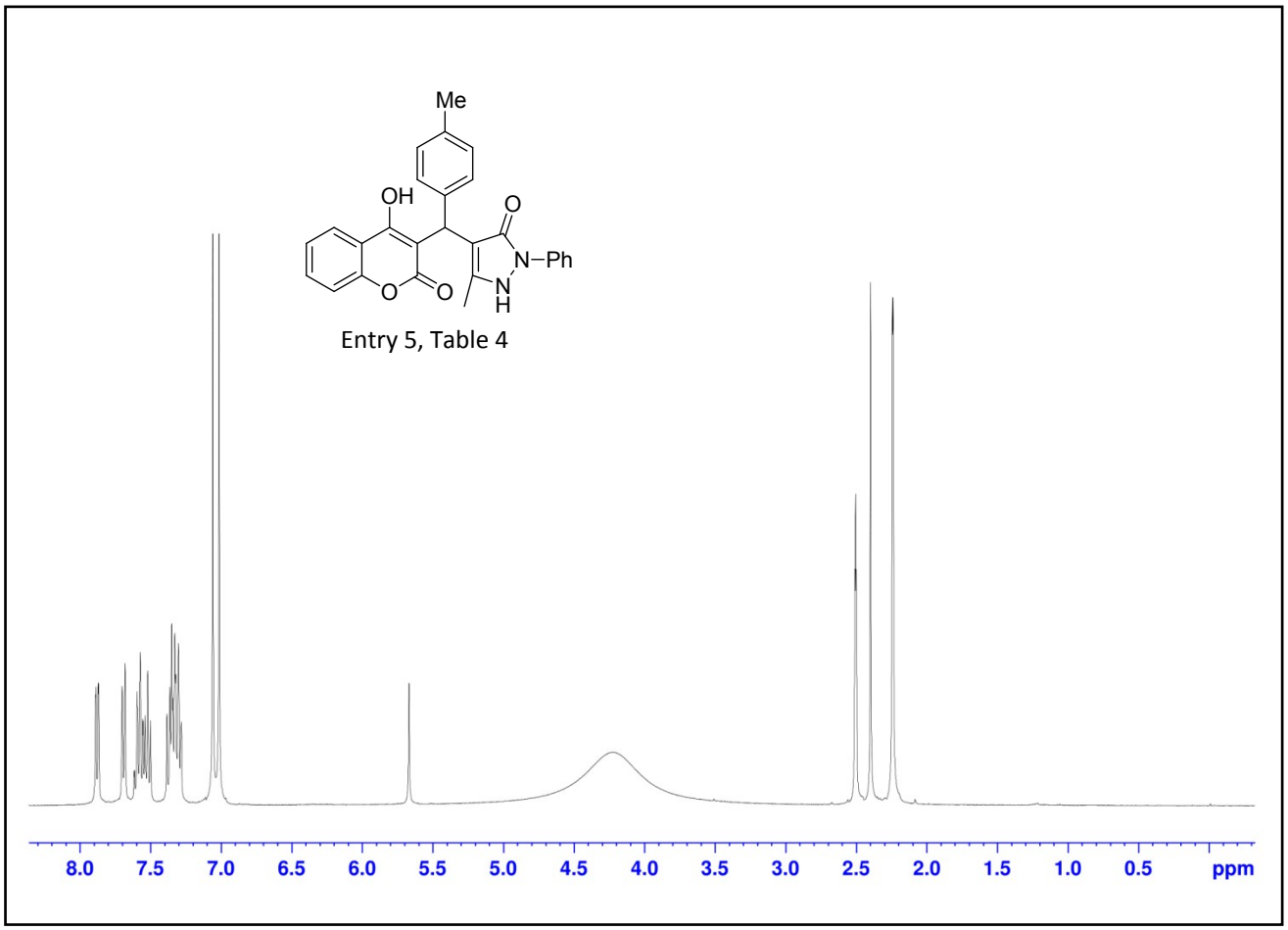

^{13}C NMR, DMSO-d$_6$
75 MHz
Cl
OH
O
N–Ph
N
H
O
O
Entry 4, Table 4
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
OH
O
N–Ph
N
H
O
O
Entry 5, Table 4
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7.0
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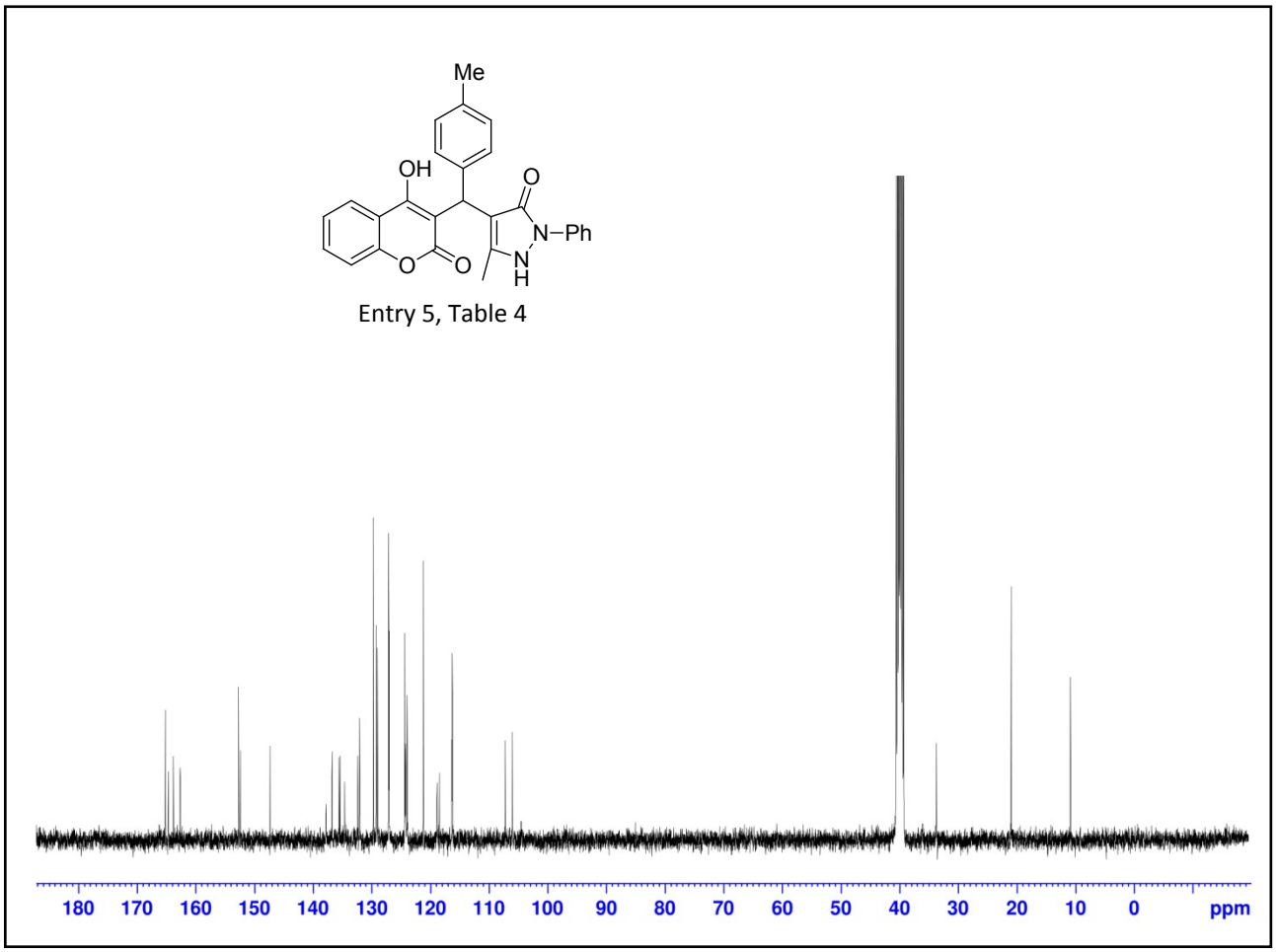
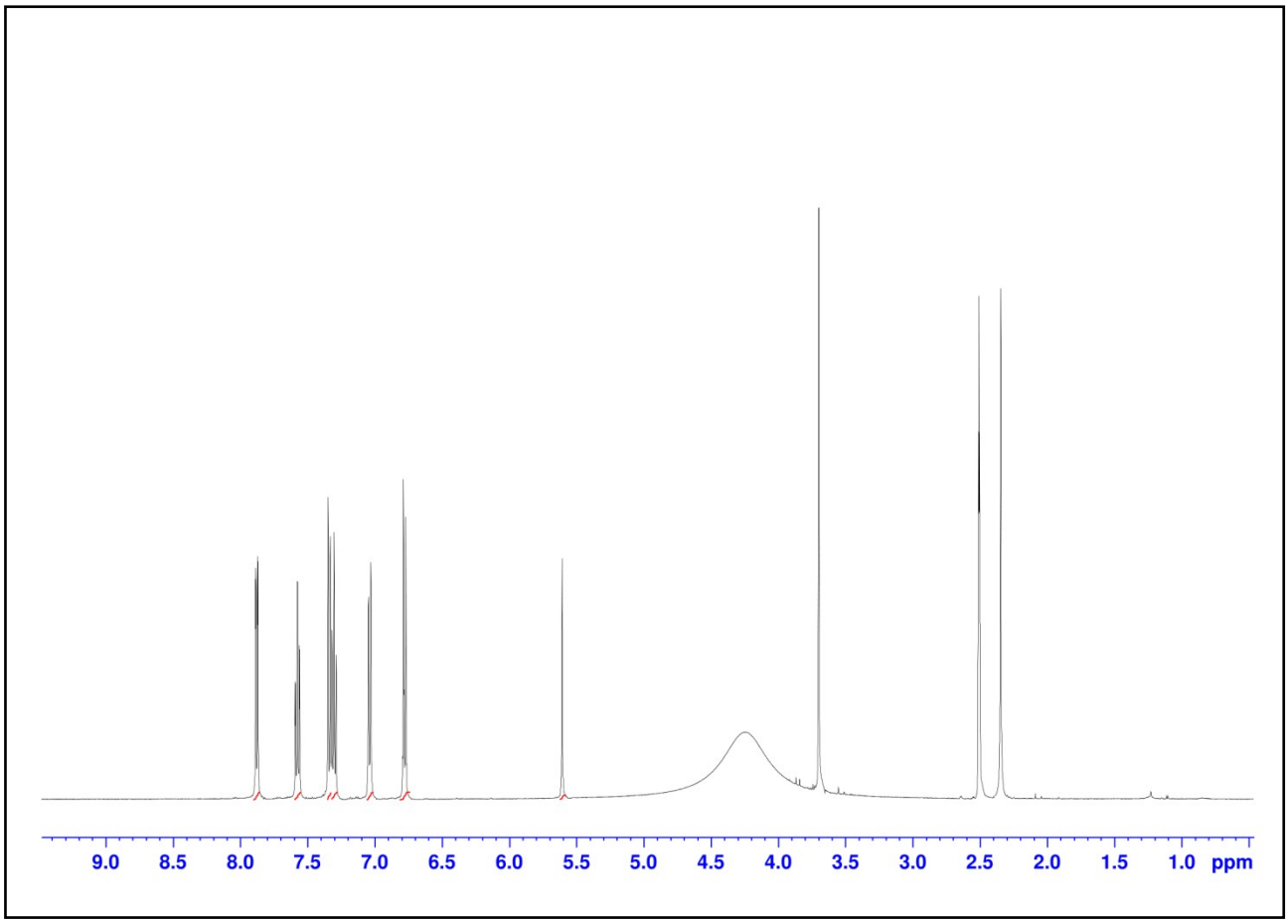
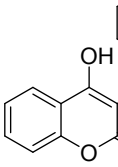
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



Entry 5, Table 4





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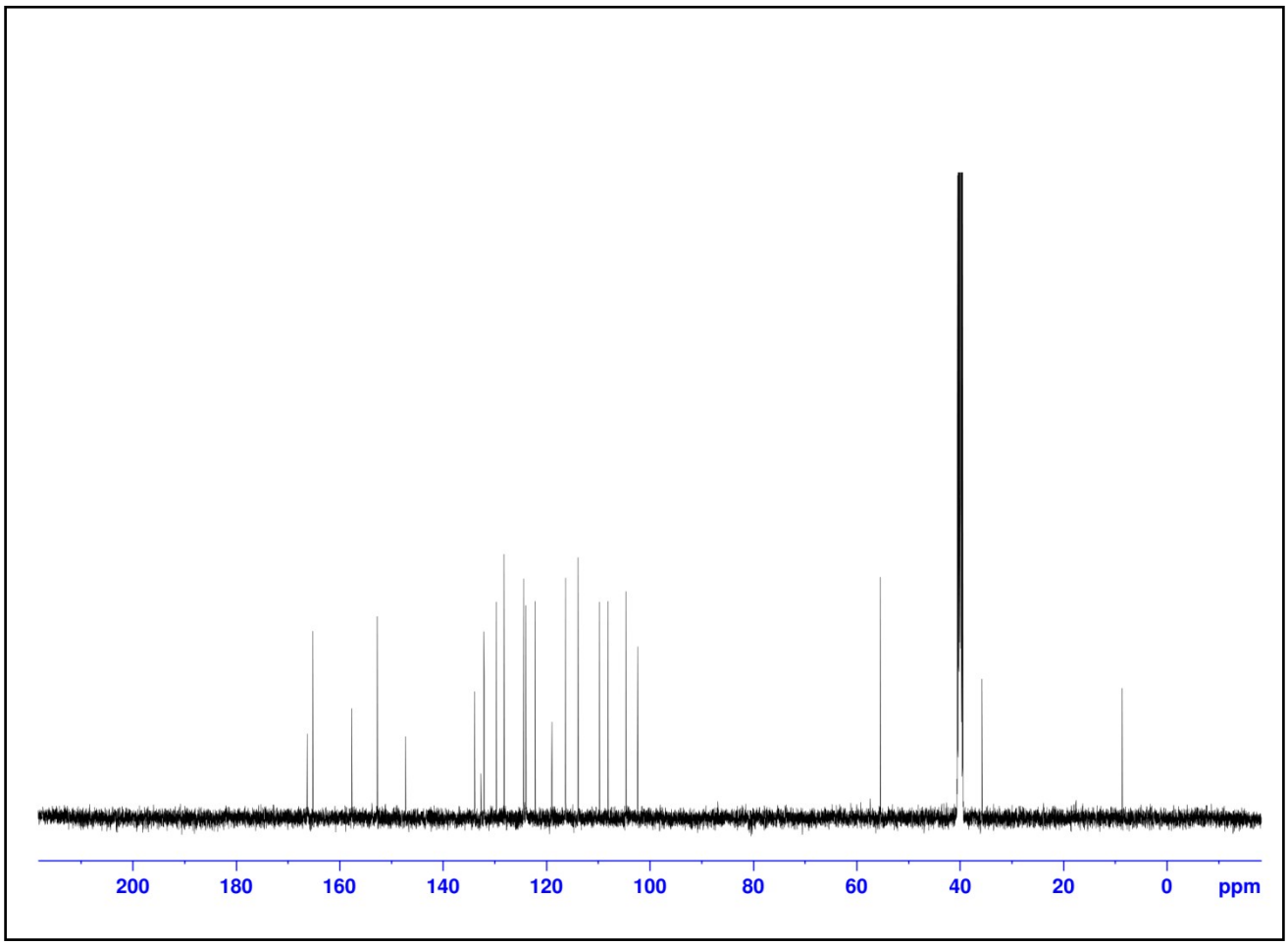

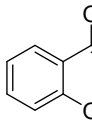

Ent

ESI-7: Representative HPLC data of benzylpyrazolyl coumarin derivatives

All the HPLC data were taken using C-18 column (SHIMADZU make) and methanol-water mixture (1:9) was used as the eluting solvent.

SHIMADZU LabSolutions **Analysis Report**

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Sample ID	: 2		
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Method Filename	: melatonine.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 2 uL		
Date Acquired	: 10/15/2015 3:34:31 PM	Acquired by	: System Administrator
Date Processed	: 11/5/2015 12:29:07 PM	Processed by	: System Administrator

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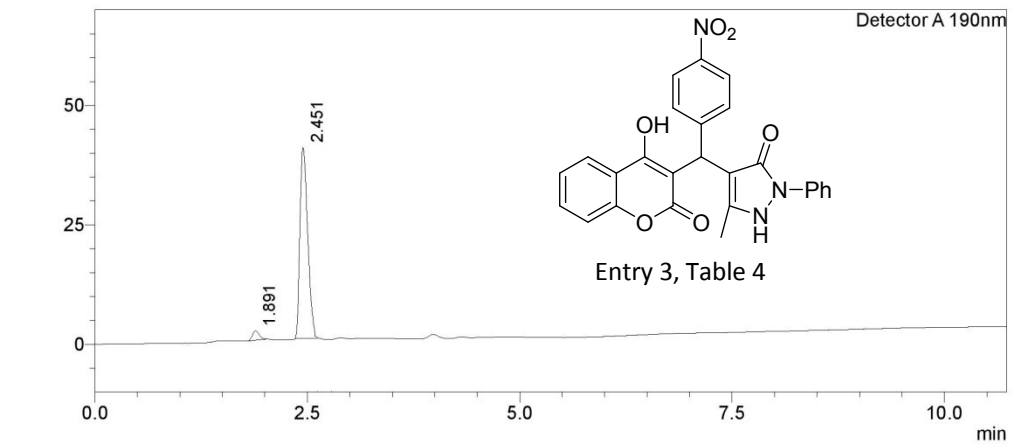

Entry 3, Table 4

<Peak Table>

Detector A 190nm

Ret. Time	Area	Height	Area%	Height%
1.891	10792	1979	3.685	4.547
2.451	282025	41538	96.315	95.453
	292817	43517	100.000	100.000

11/5/2015 12:53:16 PM Page 1 / 1

SHIMADZU LabSolutions

Analysis Report

<Sample Information>

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Sample ID	: 2		
Data Filename	: BPC4.lcd		
Method Filename	: melatonine.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 2 uL		
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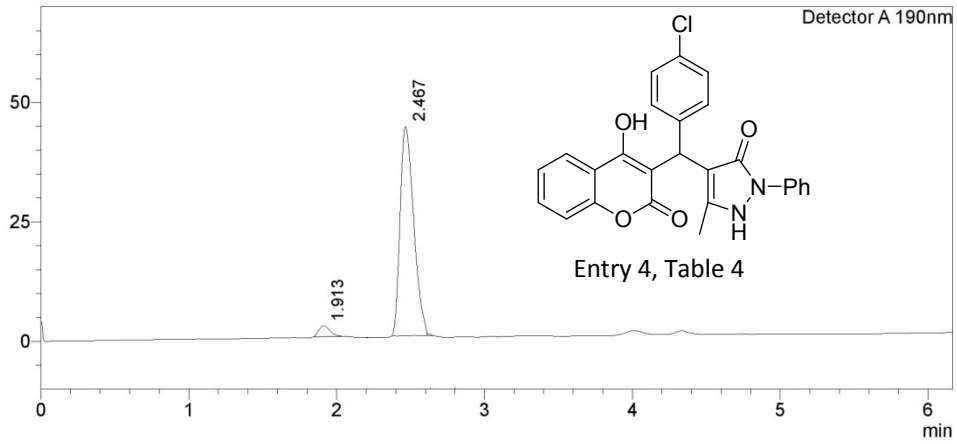

Entry 4, Table 4

<Peak Table>

Detector A 190nm

Ret. Time	Area	Height	Area%	Height%
1.913	11726	2257	3.264	4.537
2.467	347511	47479	96.736	95.463
	359237	49735	100.000	100.000

SHIMADZU LabSolutions

Analysis Report

<Sample Information>

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Sample ID	: BPC-2a		
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Batch Filename	:		
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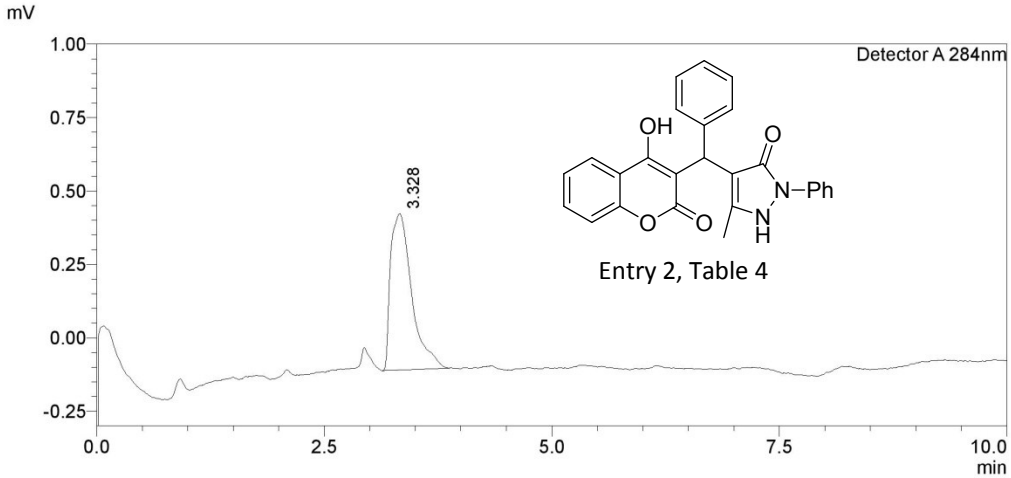

Entry 2, Table 4

<Peak Table>

Detector A 284nm

Ret. Time	Area	Height	Area%	Height%
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	8668	533	100.000	100.000