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Development of Nitromethane catalyzed C-H activation for the preparation of chromeno[3,4-*d*]imidazol-4-ones as hybrid scaffolds

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Abstract: Herein we report a tandem cyclization protocol towards hitherto unprepared hybrid scaffolds of coumarin and imidazole core. The synthetic methodology initiates with linking of aromatic amines with coumarin at 4-position, followed by tandem cyclization with the help of nitromethane leading to the synthesis of title compounds in high to excellent yields (80-97%). Detailed characterization including ^{1}H NMR, ^{13}C NMR and HRMS for all newly synthesized compounds has been reported.

Keywords: hybrid molecules, coumarin, imidazole, nitromethane, tandem cyclization.

Introduction

Designing of novel drug molecules involve multiple parallel and intersecting approaches; howeverbio-inspired design process and rational design process have been two major directions to work at, during last few decades. At the border between bio-inspired design and rational design, one can imagine preparation of hybrid molecules with a dual mode of action to create efficient new drugs. In this account, hybrid molecules canbedefined as chemical entities with two or more structural domains having different biological functions and dual activity, indicating that a hybrid molecule acts as two distinct pharmacophores (a "double-edged sword").[1]

Attracted by potential of hybrid molecules, we took an assignment to design and synthesize novel hybrid molecules for their potential biological application. Owing to our long standing experience[2] and interest in coumarin derivatives[3]due to their profound & wide-ranging biological profile, it was impulsivelyselected as one core of targeted hybrid molecules.

Imidazole core was selected as second scaffold of hybrid molecules looking to the high therapeutic properties of the imidazole based drugs.Medicinal properties of imidazole core include anticancer[4], β-lactamase inhibitors[5], 20-HETE synthase inhibitors[6], carboxypeptidase inhibitors[7], hemeoxygenase inhibitors[8], anti-inflammatory[9], antibacterial[10], antifungal[11], antiviral[12], antitubercular[13].It is noteworthy that one of the most abundant amino acid 'histidine' could be seen as imidazole containing hybrid molecule. Histidine, found in many proteins and enzymes, plays a vital role in the structure and binding functions of hemoglobin. These facts indicate the selection of coumarin and imidazole cores in designing of new hybrid molecules (Figure 1).

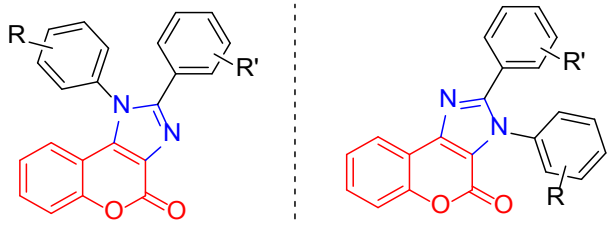
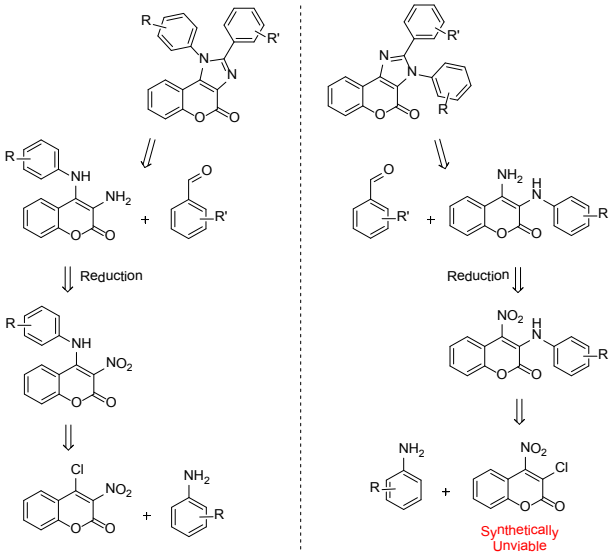


Fig. 1. Proposed hybrid scaffolds

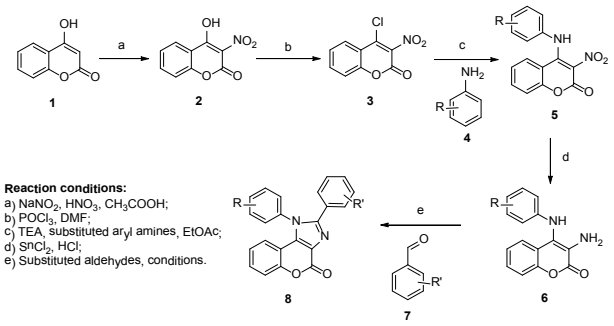
A detailed retrosynthetic analysis was carried out to design environmentally as well as synthetically viable reaction pathway for desired chromeno[3,4-*d*]imidazol-4-ones (Scheme 1).



Scheme 1. Retrosynthetic analysis for two possible hybrid scaffolds.

Following the insights received from retrosynthetic analysis, a multistep reaction sequence was designed (Scheme 2), that basically initiates with linking of aromatic amines with coumarin at 4-position, followed by reduction and a subsequent reaction with aromatic aldehyde to afford the desired chromeno[3,4-d]imidazol-4-ones**8**.Required 4-chloro-3-nitro-2*H*-chromen-2-one**3,** can be prepared by consecutive nitration and chlorination of 4-hydroxy coumarin **1** (Scheme 2).

Result and Discussion



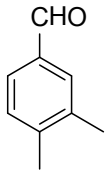
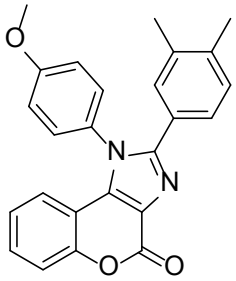
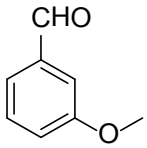
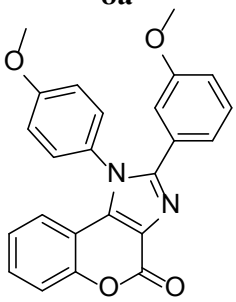
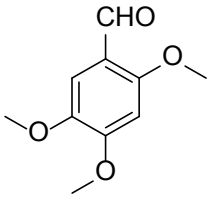
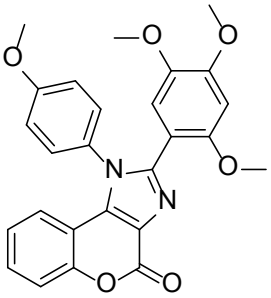
Scheme 2. Synthetic route for the synthesis of chromeno[3,4-*d*]imidazol-4-ones.

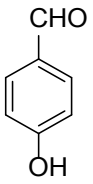
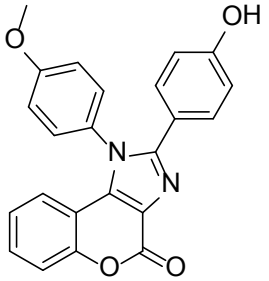
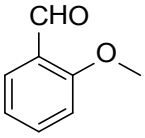
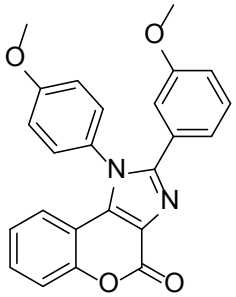
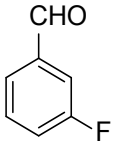
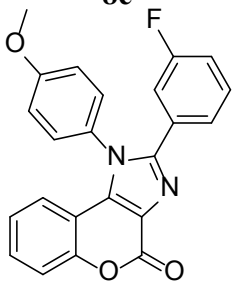
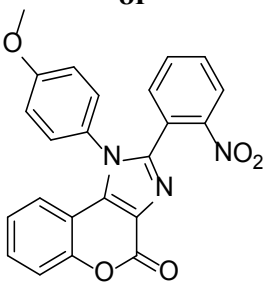
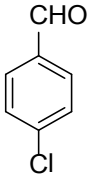
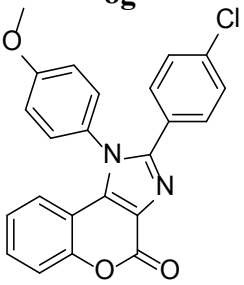
Following the above strategy, initial experiments were carried out to synthesize the necessary 4-chloro-3-nitro coumarin. Under the conditions of 67% HNO_3/HOAc at 80 °C, nitration of the readily available 4-hydroxycoumarin went smoothly to give the corresponding 4-hydroxy-3-nitrocoumarin in high yield (92%). We then decided to convert hydroxy group at 4-position in coumarin into a halogen. Since there are difficulties in preparing 4-bromocoumarins, we turned our attention to 4-chloro-3-nitrocoumarin which could be easily accessed by the reaction of 4-hydroxy-3-nitrocoumarin with $POCl_3$ in DMF at room temperature. One mole of 4-chloro-3-nitrocoumarin was condensed with one mole of aromatic amine in presence of base

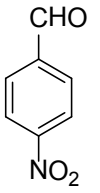
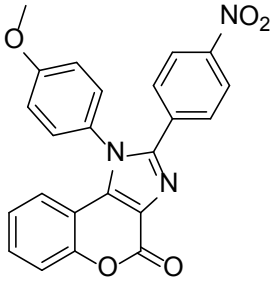
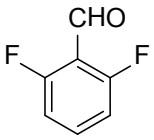
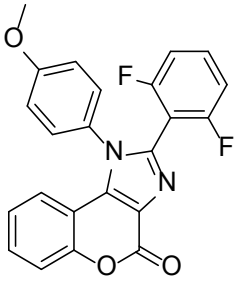
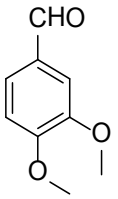
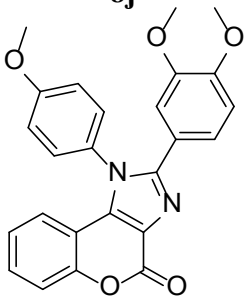
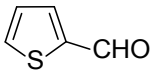
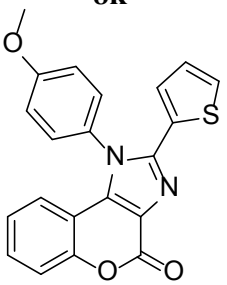
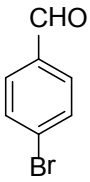
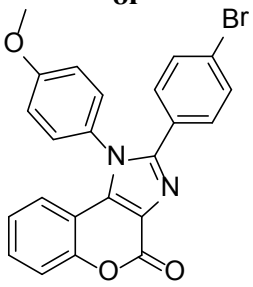
under conventional heating for 3-4 h afforded the compound **5** which was on further metal reduction yielded compound**6**. Compound **6** was reacted with one mole of substituted aldehydes **7**in presence of nitromethane yielded the desired product**8**.

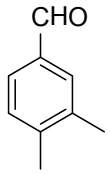
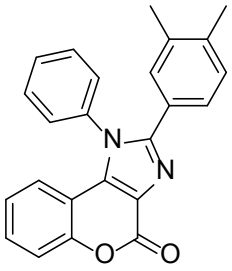
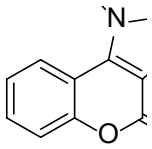
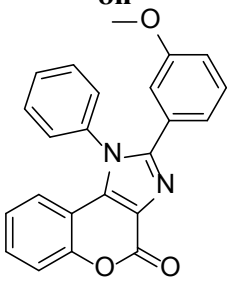
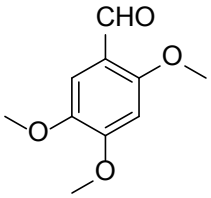
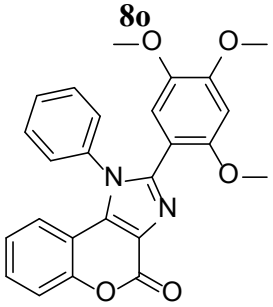
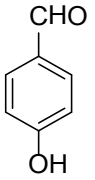
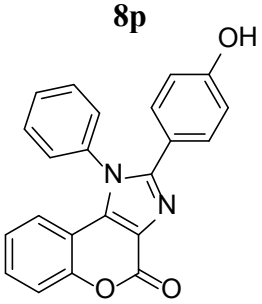
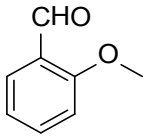
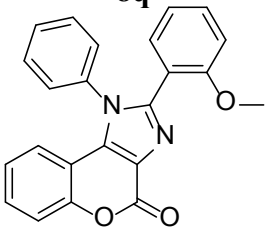
With this well-developed syntheticprocedure in hand, the scope and generality of this methodology were explored using a variety of aromatic aldehydes (**Table1**). To our satisfaction, all the employed aldehydes were compatible with reaction conditions, affording good to excellent yields of the desired products.

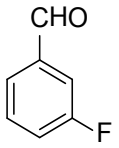
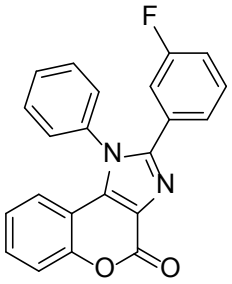
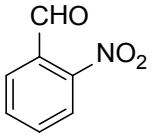
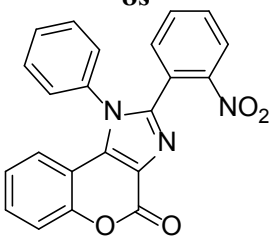
Table 1. Library of newly prepared chromeno[3,4-*d*]imidazol-4-ones.

Entry	Compound	Aldehydes	Product	Yield[a] (%)
1	**6a**		 **8a**	94
2	**6a**		 **8b**	86
3	**6a**		 **8c**	89

4	**6a**		 **8d**	89
5	**6a**		 **8e**	92
6	**6a**		 **8f**	90
7	**6a**		 **8g**	84
8	**6a**		 **8h**	90

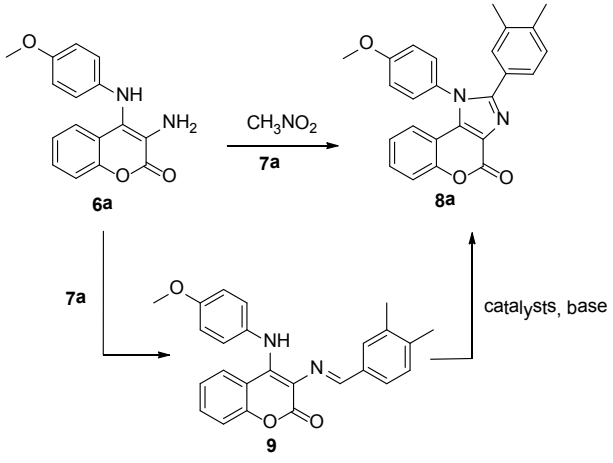
9	**6a**		 **8i**	86
10	**6a**		 **8j**	91
11	**6a**		 **8k**	89
12	**6a**		 **8l**	85
13	**6a**		 **8m**	90

14	**6b**		 **8n**	80
15	**6b**		 **8o**	83
16	**6b**		 **8p**	81
17	**6b**		 **8q**	84
18	**6b**		 **8r**	85

19	**6b**		 **8s**	80
20	**6b**		 **8t**	82

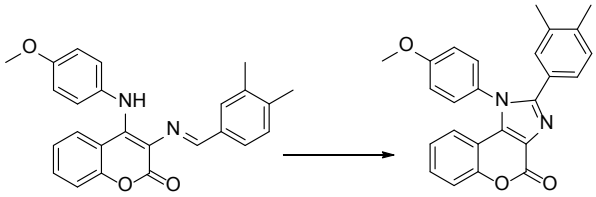
[a]Isolated Yields.

It was interesting to note that, in the absence of nitromethane, the desired product was not obtained but a Schiff base **9** was obtained (**Scheme 3**). The Schiff base were also obtained as impurity in some of the reactions even when nitromethane was used. This substrate**9**when treated with a suitable catalyst yielded the desired product**8**. Table **2** shows the varieties of catalyst used out of which a mixture of $Cu(OAc)_2$ and $PdCl_2$ (1:1) was found to be the most promising catalytic system.



Scheme 3. Observation of reaction in presence and absence of nitromethane.

Table 3. Optimization of catalyst system.[a,b]



Entry	Catalytic system (mol%)	Base	Time (h)	Yield[b] (%)
1.	$Cu(OAc)_2$	K_2CO_3	5	70
2.	$Cu(OAc)_2$	Cs_2CO_3	3	64
3.	$PdCl_2$	K_2CO_3	6	69
4.	$PdCl_2$	Cs_2CO_3	4	76
5.	$Cu(OAc)_2 + PdCl_2$	K_2CO_3	4	79
6.	$Cu(OAc)_2 + PdCl_2$	Cs_2CO_3	3	84
7.	$Pd(OAc)_2 + PdCl_2$	Cs_2CO_3	24	-

[a]All reactions were carried out in 3 mL DMF at reflux temperature using compound **9** (1.0 mmol), base (1.5 equiv.) and catalyst (10 mol%). [b]Isolated yields.

Conclusion

Over and above, we have described a novel yet facile and convenient synthesis of chromeno[3,4-*d*]imidazol-4-ones. This synthetic protocol tolerated various substrates to afford title compounds in good to excellent yields and offered several other advantages including short reaction time,simple experimental workup and no toxic byproduct formation. It is noteworthy that the obtained products in the current work are interesting nitrogen heterocyclic molecules containing coumarin scaffold. Further studies and applications on such compounds are ongoing in our laboratory and will be published in due course.

Experimental

All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise specified. Melting points were determined in open capillaries on a Fargo MP-2D melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel G60 F254 (Merck, Merck KGaA, Darmstadt, Germany) using short-wavelength ultraviolet (UV) light for visualization. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Bruker AVANCE Top-Spin spectrometers (400 and 500 MHz) in the solvents indicated. The proton chemical shifts are reported in parts per million (δ ppm) relative to $(CH_3)_4Si$ (TMS), and coupling constants (*J*) are reported in Hertz (Hz). NMR peak splittings are given by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; and brs, broad singlet. High-resolution mass spectra (HRMS) were recorded on a Waters HDMS G1 instrument with ESI^+, centroid mode, and the samples were dissolved in MeOH.

Synthesis of 3-nitro-4-hydroxy coumarin (**2**):
It was prepared according to previously reported synthetic procedure by V. O. Iaroshenko and co-workers.[14]

Synthesis of 3-nitro-4-chloro coumarin (**3**):
It was prepared according to previously reported synthetic procedure by B. R. Dekić and co-workers.[15]

General method for the synthesis of 3-nitro-4-arylamino coumarin (**5**):
Compound **3**(1.0 equiv.)and aryl amines **4** (1.0 equiv.) is dissolved in ethyl acetate followed by dropwise addition of TEA (2.0 equiv.). Reaction was refluxed for 3 h and the product falls out on cooling the reaction. The solid obtained is filtered, washed with ethyl acetate and water.

General method for the synthesis of 3-amino-4-arylamino coumarin (**6**):
To a suspension of $SnCl_2$ (7.0 equiv.) and con HCl (10 vol), compound **5**was added in portion at room temperature. After completion of the reaction, the reaction mass was poured into crushed ice and was made alkaline using 2M sodium hydroxide solution. The resulting suspension was then extracted with diethyl ether twice. The organic layer obtained was washed with water, dried over sodium sulfate and the solvent was evaporated under vacou.

General method for the synthesis of Schiff base (**9**):
Into a solution of compound **6**(1.0 mmol) in MeOH (5 mL), substituted aromatic aldehydes **7**(1.0 mmol)is added slowly and the mixture is allowed to reflux for 3 h. The product falls out which is filtered and washed with MeOH.

General method for the synthesis of chromeno[3,4-d]imidazol-4-ones(**8a-t**):
Into a solution of compound **6**(1.0 mmol) in nitromethane (5 mL), substituted aromatic aldehydes **7**(1.0 mmol)is added slowly and the mixture is allowed to reflux for 3 h. The reaction was then diluted with MeOH and further it was refluxed for 1 h. The product falls out with crystals which is filtered and washed

with MeOH.

By following the above mentionedsynthetic procedure, following compounds (**8a-t**) was prepared:

2-(3,4-dimethylphenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8a**)
Yield 94%; mp 190–192 °C. ^{1}H NMR (DMSO-d_6) δ 2.16 (3H, s, CH_3), 2.19 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 6.66 (1H, d, J = 8.0 Hz, ArH), 7.07 (2H, s, ArH), 7.14 (1H, t, J = 7.5 Hz, ArH), 7.21 (2H, d, J = 8.5 Hz, ArH), 7.39 (1H, s, ArH), 7.47–7.53 (2H, m, ArH), 7.63 (2H, d, J = 8.5 Hz, ArH).^{13}C NMR (DMSO-d_6) 19.6, 19.8, 56.1, 113.3, 115.8, 118.0, 121.0, 124.6, 125.5, 126.4, 126.7, 129.0, 129.7, 130.2, 130.5, 136.8, 138.0, 138.7, 152.2, 152.6, 156.6, 160.9. HRMS [ESI+]: calculated for $C_{25}H_{20}N_2O_3$, 397.1552 $[M+H]^+$, found 397.1607.

2-(3-methoxyphenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8b**)
Yield 86%; mp 183–185 °C. ^{1}H NMR (DMSO-d_6) δ 3.66 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.66 (1H, d, J = 8.0 Hz, ArH), 6.97 (1H, d, J = 8.0 Hz, ArH), 7.03 (1H, s, ArH), 7.09 (1H, d, J = 7.5 Hz, ArH), 7.15 (1H, t, J = 7.5 Hz, ArH), 7.21 (2H, d, J = 9.5 Hz, ArH), 7.28 (1H, t, J = 8.0 Hz, ArH), 7.48–7.54 (2H, m, ArH), 7.66 (2H, d, J = 9.0 Hz, ArH). ^{13}C NMR (DMSO-d_6) 55.5, 56.1, 113.3, 114.5, 115.9, 116.1, 118.0, 121.1, 121.6, 124.7, 125.5, 129.0, 130.0, 130.2, 130.3, 130.4, 138.2, 152.2, 156.6, 159.2, 160.9. HRMS [ESI+]: calculated for $C_{24}H_{18}N_2O_4$, 399.1345 $[M+H]^+$, found 399.1335.

1-(4-methoxyphenyl)-2-(2,4,5-trimethoxyphenyl)chromeno[3,4-d]imidazol-4(1H)-one(**8c**)
Yield 89%; mp 214–216 °C. ^{1}H NMR (DMSO-d_6) δ 3.57 (3H, s, OCH_3), 3.67 (3H, s, OCH_3),3.78 (3H, s, OCH_3),3.81 (3H, s, OCH_3), 6.58 (1H, s, ArH), 6.73 (1H, d, J = 8.0 Hz, ArH), 7.01 (1H, s, ArH), 7.07 (2H, d, J = 9.0 Hz, ArH), 7.14 (1H, t, J = 8.5 Hz, ArH), 7.43 (2H, d, J = 9.0 Hz, ArH), 7.48-7.54 (2H, m, ArH).^{13}C NMR (DMSO-d_6) 55.3, 55.5, 55.6, 56.0, 97.0, 108.3, 112.6, 114.4, 115.4, 117.4, 120.4, 124.1, 124.9, 127.9, 129.2, 129.6, 136.6, 141.9, 151.1, 151.3, 151.6, 151.8, 156.0, 159.8. HRMS [ESI+]: calculated for $C_{26}H_{22}N_2O_6$, 459.1556 $[M+H]^+$, found 459.1589.

2-(4-hydroxyphenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8d**)
Yield 89%; mp 186–188 °C. ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s, OCH_3), 6.64 (1H, d,J = 8.0 Hz, ArH), 6.72 (2H, d, J = 9.0 Hz, ArH), 7.14 (1H, t, J = 8.0 Hz, ArH), 7.21 (2H, d, J = 9.0 Hz, ArH), 7.33 (2H, d, J = 9.0 Hz, ArH), 7.47-7.53 (2H, m, ArH), 7.62 (2H, d, J = 8.5 Hz, ArH), 9.91 (1H, s, OH).^{13}C NMR (DMSO-d_6) 55.5, 112.8, 115.0, 115.3, 117.4, 119.4, 120.3, 124.1, 124.8, 128.6, 129.4, 129.6, 130.3, 137.2, 151.6, 152.3, 156.1, 158.6, 160.2.HRMS [ESI+]: calculated for $C_{23}H_{16}N_2O_4$, 385.1188 $[M+H]^+$, found 385.1160.

2-(2-methoxyphenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8e**)
Yield 92%; mp 196–198 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (6H, s, 2 × OCH_3), 6.99 (2H, d,J = 8.0 Hz, ArH), 7.05 (2H, d, J = 9.0 Hz, ArH), 7.07 (1H, t, J = 8.0 Hz, ArH), 7.32 (2H, d, J = 9.0 Hz, ArH), 7.60–7.62 (4H, m, ArH), 8.40 (1H, t, J = 8.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 58.5, 62.4, 114.6, 116.2, 117.3, 119.4, 121.4, 122.3, 124.1, 124.9, 127.6, 129.5, 129.9, 130.6, 135.2, 152.6, 152.9, 156.1, 158.6, 160.3. HRMS [ESI+]: calculated for $C_{24}H_{18}N_2O_4$, 399.1345 $[M+H]^+$, found 399.1330.

2-(3-fluorophenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8f**)
Yield 90%; mp 170–172 °C. ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s, OCH_3), 6.99 (2H, d,J = 8.0 Hz, ArH), 7.20 (2H, d, J = 9.0 Hz, ArH), 7.32 (1H, t, J = 8.0 Hz, ArH), 7.49 (2H, d, J = 9.0 Hz, ArH), 7.51 (2H, d, J = 9.0 Hz, ArH), 7.62 (2H, m, ArH), 7.76 (1H, d, J = 8.5 Hz, ArH).^{13}C NMR (DMSO-d_6) 55.5, 111.8,

114.9, 115.5, 116.4, 118.4, 120.0, 124.8, 125.7, 127.6, 129.4, 129.9, 130.7, 137.2, 151.8, 152.6, 156.3, 158.7, 160.3. HRMS [ESI+]: calculated for $C_{23}H_{15}FN_2O_3$, 387.1145 $[M+H]^+$, found 387.1141.

1-(4-methoxyphenyl)-2-(2-nitrophenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8g**)
Yield 84%; mp 212–214 °C. ^{1}H NMR (DMSO-d_6) δ 3.80 (3H, s, OCH_3), 6.73 (1H, d,*J* = 7.5 Hz, ArH), 7.09 (2H, d, *J* = 8.5 Hz, ArH), 7.18 (1H, t, *J* = 7.0 Hz, ArH), 7.50 (2H, d, *J* = 8.5 Hz, ArH), 7.52–7.58 (2H, m, ArH), 7.73–7.77 (2H, m, ArH), 7.80–7.83 (1H, m, ArH), 8.13 (1H, d, *J* = 8.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 56.0, 112.9, 115.7, 118.1, 121.0, 124.2, 124.9, 125.1, 125.6, 127.3, 129.6, 130.7, 132.3, 133.6, 134.2, 137.5, 148.9, 149.6, 152.4, 156.4, 160.8.HRMS [ESI+]: calculated for $C_{23}H_{15}N_3O_5$, 414.1090 $[M+H]^+$, found 414.1072.

2-(4-chlorophenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8h**)
Yield90%; mp 197–199 °C. ^{1}H NMR (DMSO-d_6) δ 3.89 (3H, s, OCH_3), 6.66 (1H, d,*J* = 9.5 Hz, ArH), 6.80 (1H, d, *J* = 11.0 Hz, ArH), 7.21 (2H, d, *J* = 11.0 Hz, ArH), 7.44-7.52 (6H, m, ArH), 7.66 (2H, d, *J* = 11.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 55.5, 112.6, 114.1, 115.4, 117.5, 120.5, 124.2, 125.0, 127.6, 128.1, 128.4, 129.5, 130.4, 131.0, 134.5, 137.7, 150.8, 151.7, 156.0, 160.4. HRMS [ESI+]: calculated for $C_{23}H_{15}N_2O_3$, 403.0849 $[M+H]^+$, found 403.0829.

1-(4-methoxyphenyl)-2-(4-nitrophenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8i**)
Yield 86%; mp 195–197 °C. ^{1}H NMR (DMSO-d_6) δ 3.89 (3H, s, OCH_3), 6.99 (2H, d,*J* = 9.5 Hz, ArH), 7.51 (2H, d, *J* = 11.0 Hz, ArH), 7.62 (1H, d, *J* = 11.0 Hz, ArH), 7.72–7.76 (3H, m, ArH), 8.05 (2H, d, *J* = 11.0 Hz, ArH), 8.32 (2H, d, *J* = 10.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 58.5, 112.6, 114.3, 114.4, 116.5, 119.5, 123.2, 126.8, 127.5, 129.1, 129.4, 129.5, 130.7, 131.2, 134.8, 137.9, 150.2, 151.9, 156.2, 160.3. HRMS [ESI+]: calculated for $C_{23}H_{15}N_3O_5$, 414.1090 $[M+H]^+$, found 414.1068.

2-(2,6-difluorophenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8j**)
Yield 91%; mp 185–187 °C. ^{1}H NMR (DMSO-d_6) δ 3.87 (3H, s, OCH_3), 6.99 (2H, d,*J* = 9.5 Hz, ArH), 7.26 (2H, d, *J* = 11.0 Hz, ArH), 7.32 (1H, d, *J* = 11.0 Hz, ArH), 7.51 (2H, m, ArH), 7.62 (2H, d, *J* = 11.0 Hz, ArH), 7.76 (2H, d, *J* = 10.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 56.5, 111.6, 114.0, 115.4, 116.1, 119.1, 123.0, 125.9, 126.5, 129.1, 129.9, 130.5, 130.7, 131.6, 134.4, 137.3, 150.5, 151.8, 156.4, 160.1. HRMS [ESI+]: calculated for $C_{23}H_{14}F_2N_2O_3$, 405.1051 $[M+H]^+$, found 405.1026.

2-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one (**8k**)
Yield 89%; mp 189–191 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s, OCH_3), 3.87 (6H, s, 2 × OCH_3),6.94 (2H, d,*J* = 9.5 Hz, ArH), 6.99 (2H, d, *J* = 11.0 Hz, ArH), 7.25 (1H, d, *J* = 11.0 Hz, ArH), 7.32 (2H, m, ArH), 7.51 (2H, d, *J* = 11.0 Hz, ArH), 7.76 (2H, d, *J* = 10.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 56.5, 58.3, 112.3, 113.9, 115.5, 116.3, 119.7, 123.2, 125.8, 126.4, 129.2, 129.7, 130.7, 130.9, 131.8, 134.2, 137.1, 150.6, 151.9, 156.5, 160.3. HRMS [ESI+]: calculated for $C_{25}H_{20}N_2O_5$, 429.1450 $[M+H]^+$, found 429.1442.

1-(4-methoxyphenyl)-2-(thiophen-2-yl) chromeno[3,4-d]imidazol-4(1H)-one(**8l**)
Yield 85%; mp 169–171 °C. ^{1}H NMR (DMSO-d_6) δ 3.71 (3H, s, OCH_3), 6.85 (2H, d,*J* = 9.5 Hz, ArH), 7.09 (2H, d, *J* = 11.0 Hz, ArH), 7.14 (1H, d, *J* = 11.0 Hz, ArH), 7.39 (2H, m, ArH), 7.55 (2H, d, *J* = 11.0 Hz, ArH), 7.66 (2H, d, *J* = 10.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 55.2, 111.4, 113.9, 115.4, 116.7, 123.3, 124.7, 124.8, 127.8, 130.3, 131.3, 134.6, 143.9, 145.0, 151.4, 151.5, 156.2, 157.1.HRMS [ESI+]: calculated for $C_{21}H_{14}N_2O_3S$, 375.0803 $[M+H]^+$, found 375.0789.

2-(4-bromophenyl)-1-(4-methoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one (**8m**)
Yield 90%; mp 177–179 °C. ^{1}H NMR (DMSO-d_6) δ 3.89 (3H, s, OCH_3), 6.66 (1H, d, *J* = 9.0 Hz, ArH), 7.15 (1H, t, *J* = 10.0 Hz, ArH), 7.21 (2H, d, *J* = 8.0 Hz, ArH), 7.42 (2H, d, *J* = 8.5 Hz, ArH), 7.49 (2H, d, *J* = 9.0 Hz, ArH), 7.53 (2H, d, *J* = 8.0 Hz, ArH), 7.66 (2H, d, *J* = 8.0 Hz, ArH). ^{13}C NMR (DMSO-d_6) 55.6, 112.7, 115.5, 117.5, 120.5, 123.4, 124.2, 125.1, 128.0, 128.1, 129.6, 129.9, 130.7, 131.4, 137.7, 151.0, 156.0, 160.0HRMS [ESI+]: calculated for $C_{25}H_{15}BrN_2O_3$, 447.0344 $[M+H]^+$, found 447.0309.

2-(3,4-dimethylphenyl)-1-phenylchromeno[3,4-d]imidazol-4(1H)-one(**8n**)
Yield 80%; mp 160–162 °C. ^{1}H NMR (DMSO-d_6) δ 2.16 (3H, s, CH_3), 2.19 (3H, s, CH_3), 7.07 (1H, d, *J* = 8.0 Hz, ArH), 7.32 (1H, d, *J* = 8.5 Hz, ArH), 7.45–7.47 (2H, m, ArH), 7.58–7.62 (4H, m, ArH), 7.67–7.70 (2H, m, ArH), 7.76–7.79 (2H, m, ArH). ^{13}C NMR (DMSO-d_6) 19.6, 19.8, 115.8, 118.8, 121.0, 123.2, 125.5, 126.4, 126.7, 129.4, 129.6, 130.3, 136.8, 137.3, 138.7, 150.2, 158.6, 162.8. HRMS [ESI+]: calculated for $C_{24}H_{18}N_2O_2$, 367.1447 $[M+H]^+$, found 367.1442.

2-(3-methoxyphenyl)-1-phenylchromeno[3,4-d] imidazol-4(1H)-one(**8o**)
Yield 83%; mp 189–191 °C. ^{1}H NMR (DMSO-d_6) δ 3.88 (3H, s, OCH_3), 7.04 (1H, d, *J* = 8.0 Hz, ArH), 7.30 (1H, d, *J* = 8.5 Hz, ArH), 7.45–7.47 (3H, m, ArH), 7.56–7.60 (5H, m, ArH), 7.76–7.79 (2H, m, ArH), 7.96 (1H, s, ArH).^{13}C NMR (DMSO-d_6) 56.1, 113.2, 114.8, 115.6, 116.4, 118.9, 121.0, 121.8, 124.6, 125.4, 129.0,130.0, 130.3, 130.9, 138.2, 152.2, 156.8, 159.4, 160.7. HRMS [ESI+]: calculated for $C_{23}H_{16}N_2O_3$, 369.1239 $[M+H]^+$, found 369.1233.

1-phenyl-2-(2,4,5-trimethoxyphenyl) chromeno[3,4-d]imidazol-4(1H)-one(**8p**)
Yield 81%; mp 192–194 °C. ^{1}H NMR (DMSO-d_6) δ 3.57 (3H, s, OCH_3), 3.67 (3H, s, OCH_3),3.78 (3H, s, OCH_3),6.68 (1H, s, ArH), 6.75 (2H, d, *J* = 8.0 Hz, ArH), 7.02 (1H, s, ArH), 7.10 (2H, d, *J* = 9.0 Hz, ArH), 7.16 (1H, t, *J* = 8.5 Hz, ArH), 7.45 (2H, d, *J* = 9.0 Hz, ArH), 7.58–7.64 (2H, m, ArH).^{13}C NMR (DMSO-d_6) 55.5, 55.6, 56.0, 97.6, 108.3, 112.6, 114.6, 115.3, 117.8, 120.9, 124.0, 127.9, 129.0, 136.9, 141.6, 151.0, 151.2, 156.8, 160.8. HRMS [ESI+]: calculated for $C_{25}H_{20}N_2O_5$, 429.1450 $[M+H]^+$, found 429.1442.

2-(4-hydroxyphenyl)-1-phenylchromeno[3,4-d] imidazol-4(1H)-one(**8q**)
Yield 84%; mp 168–178 °C. ^{1}H NMR (DMSO-d_6) δ 3.92 (1H, s, OH), 7.09 (1H, d, *J* = 8.0 Hz, ArH), 7.30 (1H, d, *J* = 8.5 Hz, ArH), 7.45–7.47 (3H, m, ArH), 7.56–7.62 (5H, m, ArH), 7.76–7.79 (2H, m, ArH), 7.96 (1H, s, ArH).^{13}C NMR (DMSO-d_6) 113.8, 115.2, 115.6, 117.9, 119.2, 120.3, 124.4, 124.5, 128.6, 129.7, 129.8, 130.9, 137.2, 156.1, 158.6, 160.2. HRMS [ESI+]: calculated for $C_{22}H_{14}N_2O_3$, 355.1083 $[M+H]^+$, found 355.1093.

2-(2-methoxyphenyl)-1-phenylchromeno[3,4-d] imidazol-4(1H)-one(**8r**)
Yield 85%; mp 174–176 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s, OCH_3), 6.99 (2H, d, *J* = 8.0 Hz, ArH), 7.05 (2H, d, *J* = 9.0 Hz, ArH), 7.07 (1H, t, *J* = 8.0 Hz, ArH), 7.32 (2H, d, *J* = 9.0 Hz, ArH), 7.60–7.62 (5H, m, ArH), 8.40 (1H, t, *J* = 8.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 58.5, 114.6, 116.2, 117.3, 119.4, 121.4, 122.3, 124.1, 124.9, 127.6, 129.5, 129.9, 130.6, 135.2, 152.6, 156.1, 158.6, 160.3.HRMS [ESI+]: calculated for $C_{23}H_{16}N_2O_3$, 369.1239 $[M+H]^+$, found 369.1245.

2-(3-fluorophenyl)-1-phenylchromeno[3,4-d] imidazol-4(1H)-one(**8s**)
Yield 80%; mp 167–169 °C. ^{1}H NMR (DMSO-d_6) δ 6.98 (2H, d,*J* = 8.0 Hz, ArH), 7.20 (2H, d, *J* = 9.0 Hz, ArH), 7.30 (1H, t, *J* = 8.0 Hz, ArH), 7.49 (2H, d, *J* = 9.0 Hz, ArH), 7.52 (2H, d, *J* = 9.0 Hz, ArH), 7.62–7.64 (3H, m, ArH), 7.76

(1H, d, J = 8.5 Hz, ArH).^{13}C NMR (DMSO-d_6) 55.5, 111.8, 114.9, 115.5, 116.4, 118.4, 120.0, 124.8, 125.7, 127.6, 129.4, 129.9, 130.7, 137.2, 151.8, 152.6, 156.3, 158.7, 160.3.HRMS [ESI+]: calculated for $C_{22}H_{13}FN_2O_2$, 357.1039 $[M+H]^+$, found 357.1023.

2-(2-nitrophenyl)-1-phenylchromeno[3,4-d] imidazol-4(1H)-one(**8t**)

Yield 82%; mp 202–204 °C. ^{1}H NMR (DMSO-d_6) δ 6.73 (1H, d,J = 7.5 Hz, ArH), 7.09 (2H, d, J = 8.5 Hz, ArH), 7.18 (1H, t, J = 7.0 Hz, ArH), 7.50 (2H, d, J = 8.5 Hz, ArH), 7.52–7.58 (3H, m, ArH), 7.73–7.77 (2H, m, ArH), 7.80–7.83 (1H, m, ArH), 8.13 (1H, d, J = 8.0 Hz, ArH).^{13}C NMR (DMSO-d_6) 56.0, 112.9, 115.7, 118.1, 121.0, 124.2, 124.9, 125.1, 125.6, 127.3, 129.6, 130.7, 132.3, 133.6, 134.2, 137.5, 148.9, 149.6, 152.4, 156.4, 160.8. HRMS [ESI+]: calculated for $C_{22}H_{13}N_3O_4$, 384.0984 $[M+H]^+$, found 384.0962.

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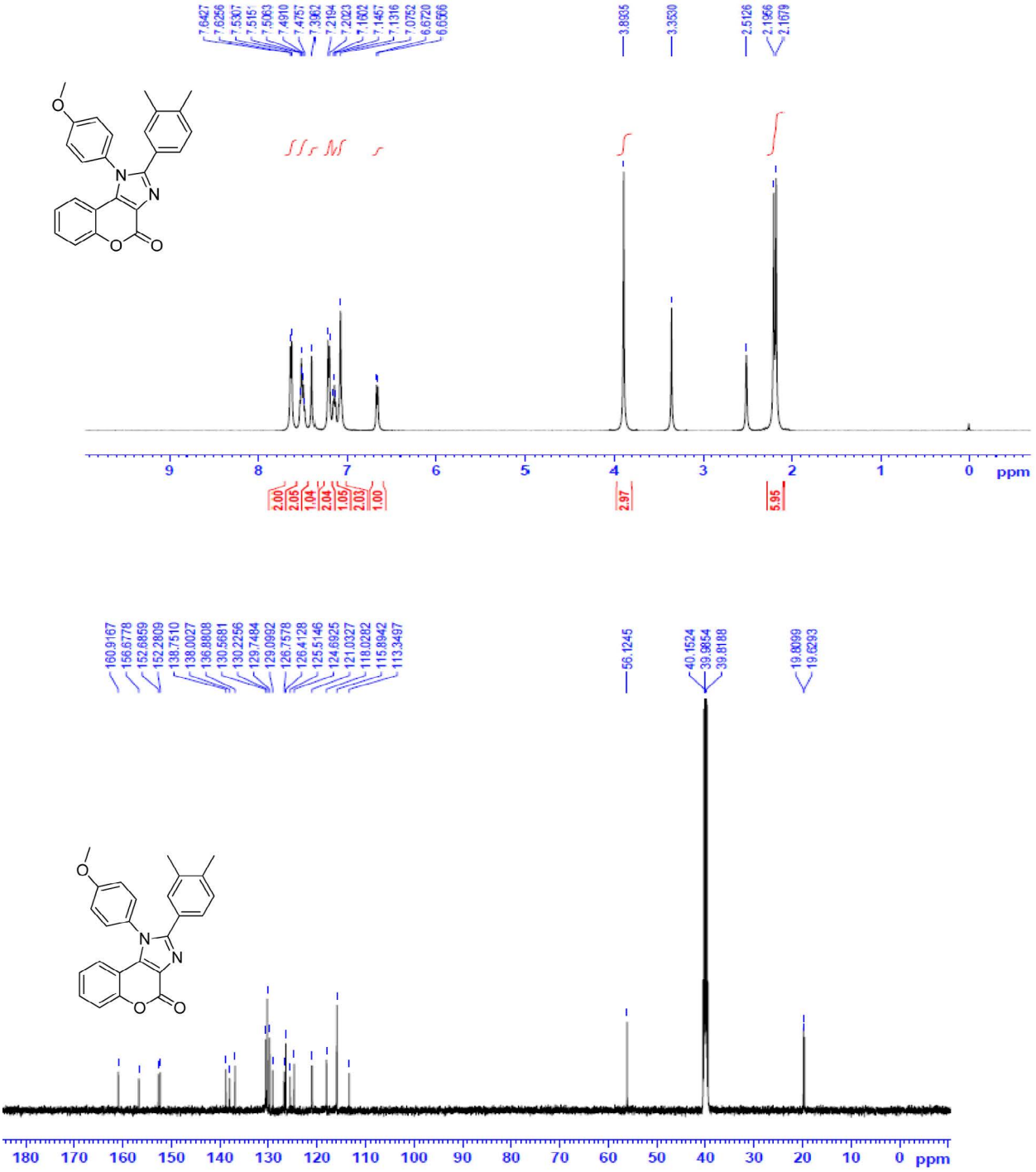
^{1}H and ^{13}C NMR spectra of 8a



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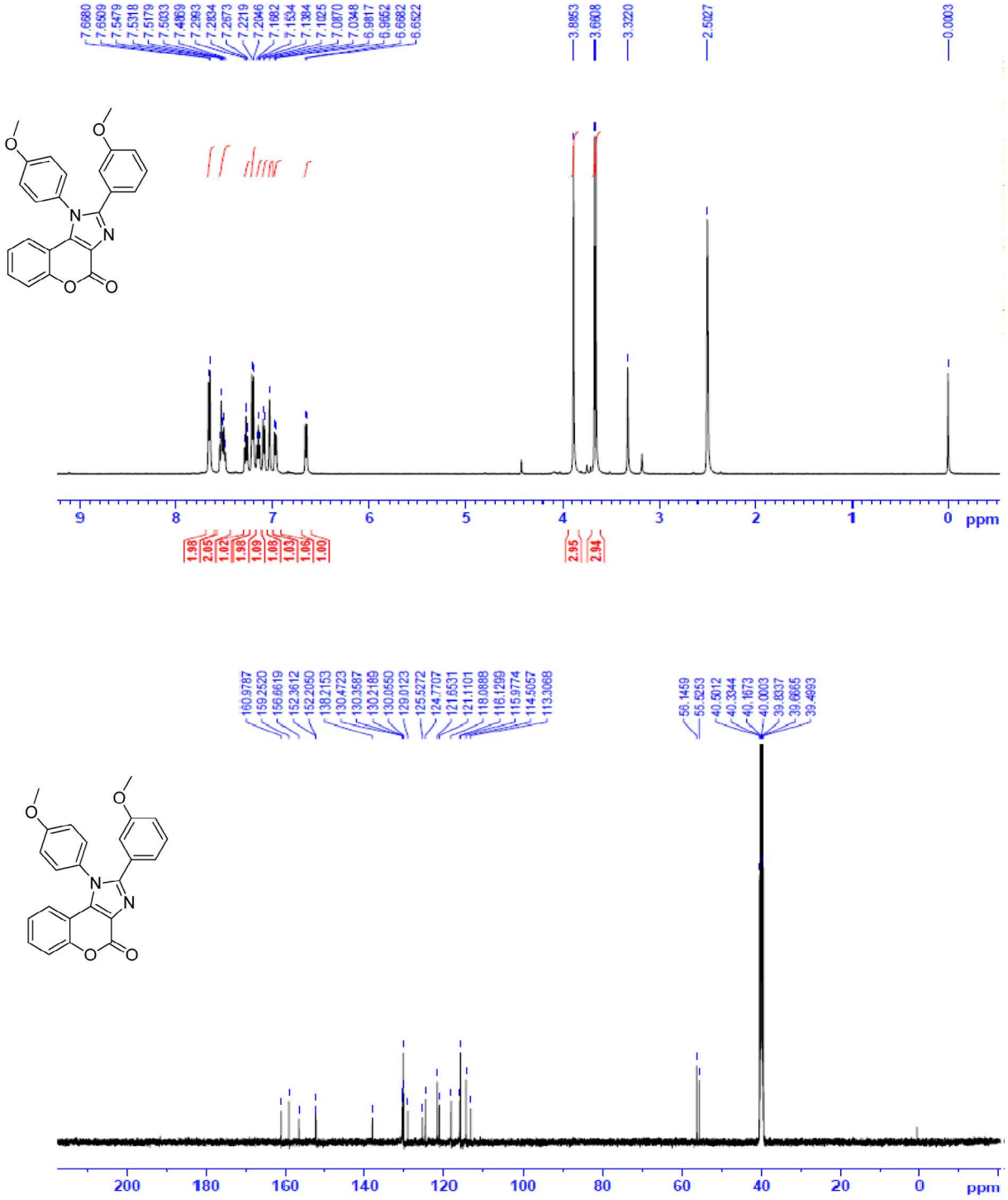

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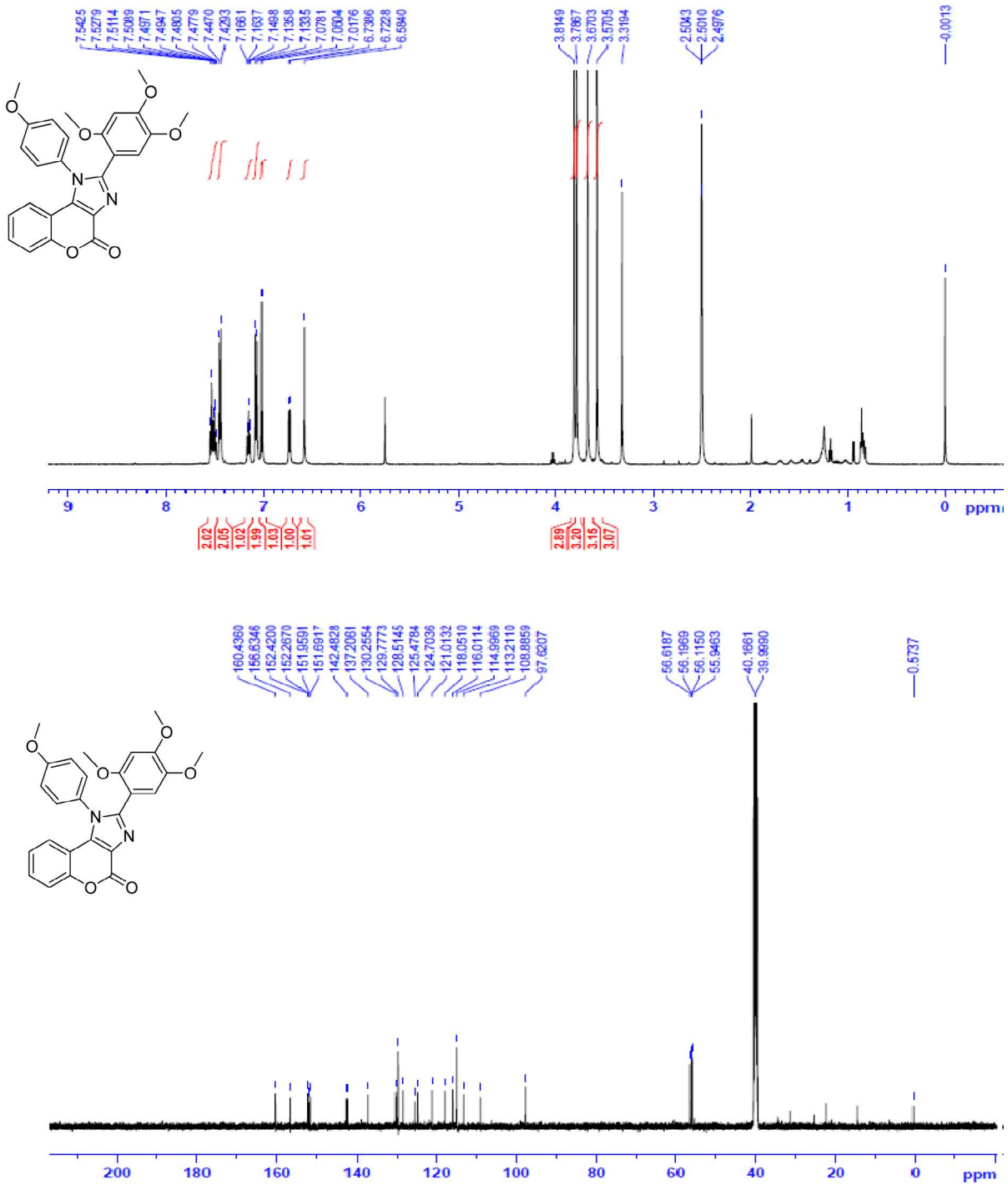

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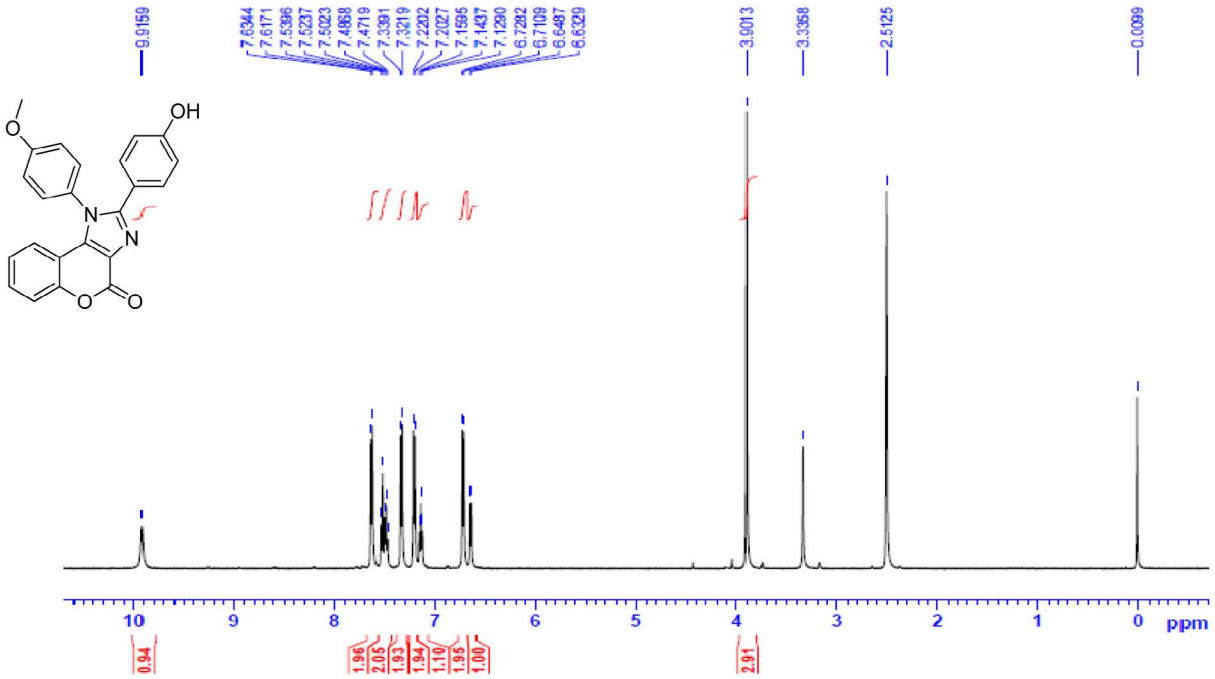

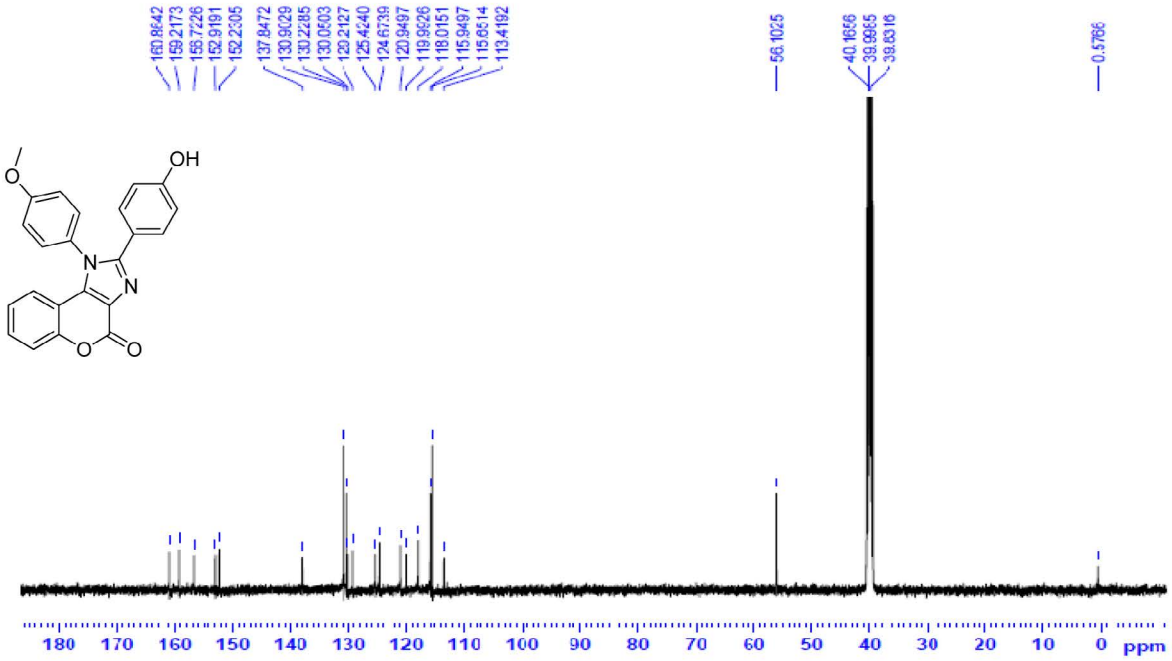

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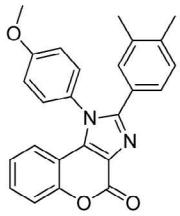

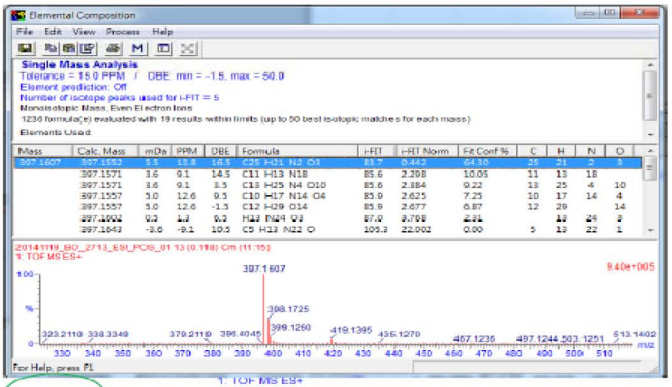

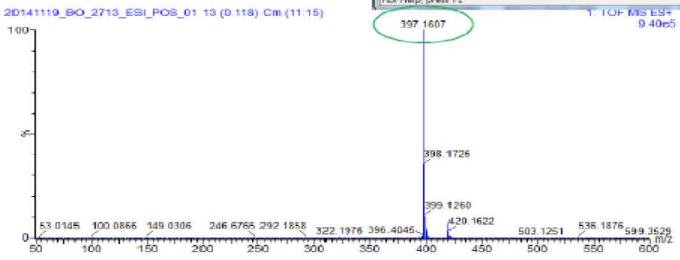

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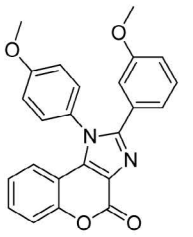

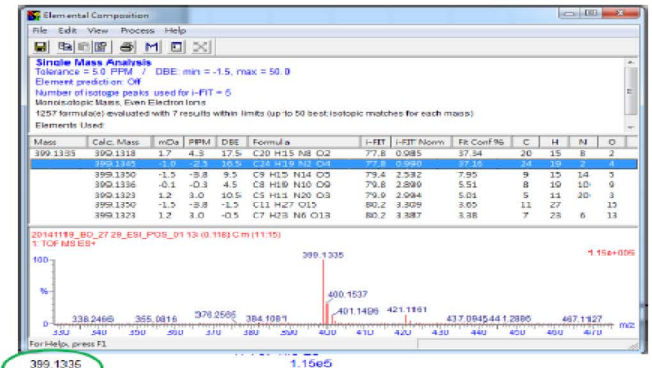

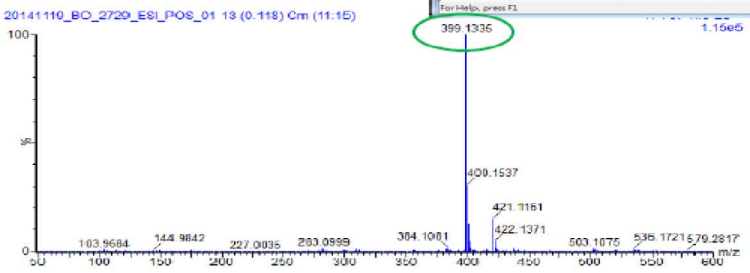

HRMS of 8c