DABCO-PROMOTED MULTICOMPONENT REACTIONS FOR FACILE SYNTHESIS OF STRUCTURALLY DIVERSE 4-HETEROCYCLIC-2-AMINO- 4*H*-CHROMENES ANALOGUES

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ABSTRACT:
An expedient mild catalyst three component synthesis of 2-amino-3-pivaloyl-4-heterocyclic-4*H*-chromene derivatives are conveying by cyclic condensation with benzoylacetonitrile/ benzothiazoleacetonitrile with thiazolidinedione/1,3cyclohexanedione and salicylaldehyde derivatives has been developed. The main advantages of the existing procedure are existence as a green method, milder reaction conditions, necessary shorter reaction time, and excellent yields.

KEY WORDS:2-amino-3-pivaloyl-4-heterocyclic-4*H*-chromene derivatives,benzoylacetonitrile,benzothiazoleacetonitrile, thiazolidinedione, 1,3cyclohexanedione,salicylaldehyde derivatives.

INTRODUCTION:
Design of highly functionalised chemical reaction afford structural difficulty and diversity with least number of synthetic steps for the formation of compounds with stimulating activities is a major challenge of modern drug discovery process.[1] 4*H*-chromenes are the privileged structural design frequently found in a number of natural products, steroids , pharmaceuticals and biologically active molecules.[2] There are many 4*H*-chromenes synthesis involved wide attention for their biological properties, such as anti-cancer, antifungal, antibacterial, antioxidant, anti-inflammatory, antitumor and antiviral activities.[3-9]Owing to the biological properties and wide spectrum of applications, synthesis of 4*H*-chromene derivatives has been more concern and the development of novel approaches to access the 2-amino-4*H*-chromene scaffold is a challenging task for organic chemists.[10] Due to the prominence of 4H-chromene components focus from a pharmaceutical and biological[11] point of view, there is still the need to develop efficient, mild and environmentally benign procedure for the formation of 2-amino-4*H*-chromene derivatives.Our research group is actively engaged to developing multicomponent reaction protocols for accessing diverse scaffolds, particularly 4-heterocyclic-substituted-4*H*-chromene are emerging highly essential diversity scafold to design and synthesis of building blocks.[12-15] Therefore we disclose the design and synthesis of highly functionalised and heterocyclic substituents at 4 positions of 4*H*-chromenes in an efficient three component manner.

EXPERIMENTAL:
MATERIALS AND PHYSICAL MEASUREMENTS:
All chemicals were reagent grade purchased from Sigma Aldrich, Merck and Alfa aesar used without purification. The reactions were monitored by thin layer chromatography (TLC) on pre-coated Aluminium plate of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F-254), spot were visualised under short UV light. NMR spectra were recorded on a BrukerAvance-II 400FT spectrometer at 400 MHz (1H) and 100(13C) IN DMSO using TMS as an internal reference. Mass spectra were recorded on a Water UPLC-TQD mass spectrometer. Melting points were determined by open glass capillary method and were uncorrected.
4. General procedure for synthesis of 5-(2-amino-3-benzoyl-8-methoxy-4H-chromen-4-yl)-2-thioxoimidazolidin-4-onederivatives. To a stirred solution of ethanol and water (1:1) ratio were added a mixture of Thiazolidinedione/1,3cyclohexanedione, Benzoyl acetonitrile/benzothiazoleacetonitrile and Salicylaldehyde derivatives at room temperature with vigorous stirring for appropriate time (scheme 1). The precipitate was filtered, washed with ethanol. The product were obtained uncontaminated by TLC and spectral techniques.

4a. 5-(2-amino-3-benzoyl-8-methoxy-4H-chromen-4-yl)-2-thioxoimidazolidin-4-one

Yellow solid, yield 95%; m.p=214-215°C; 1H NMR (400 MHz, DMSO-d_6): δ(ppm)=11.35(s,1H,NH), 9.95(s, 1H,NH), 9.13(s, 2H,NH_2), 7.45-7.42(m, 3H), 7.36(q, J=3.6,3.6Hz,2H), 7.02(t, J=0.8,4.4Hz,2H), 6.54(t, J=4.4,4.8Hz, 1H),4.29(d, J=2.8Hz, 1H), 3.9(d, J=1.6Hz, 1H), 3.83(s,3H); 13C NMR (DMSO-d6, 100 MHz)δ(ppm)=192.1, 183.0, 174.1, 164.1, 146.9, 141.5, 139.7, 129.0, 128.4, 126.2, 124.2, 121.4, 119.5, 111.8, 82.7, 68.4, 55.8, 38.4. HR-MS m/z: calcd for C20H17N3O4S [M+H]+: 396.1013; found: 396.1021.

4b. 5-(2-amino-3-benzoyl-4H-chromen-4-yl)-2-thioxothiazolidin-4-one

Yellow solid, yield 91%; m.p=226-2227°C; 1H NMR (400 MHz, DMSO-d_6): δ(ppm)=9.05(s,2H,NH_2), 7.47-7.42(m,5H), 7.35(t, J=74.4,71.2Hz, 1H), 7.12(t, J=78.0,68.0Hz, 2H), 7.03(d, J=74.0Hz, 1H), 4.65(d, J=34.8Hz, 1H), 4.46(d, J=36.4Hz, 1H); 13C NMR (DMSO-d6, 100 MHz)δ(ppm)=203.5, 192.7, 176.6, 163.7, 150.3, 141.1, 129.5, 128.6, 128.5, 127.4, 126.6, 124.9, 120.5, 116.1, 83.9, 65.7, 25.5. HR-MS m/z: calcd for C19H14N2O3S2 [M+H]+: 382.0446; found: 382.0458.

4c. 5-(2-amino-3-benzoyl-5-(hydroxymethyl)-8-methyl-4H-pyrano[2,3-c]pyridin-4-yl)-2-thioxoimidazolidin-4-one

Pale yellow solid, yield 92%; m.p=238-239°C; 1H NMR (400 MHz, DMSO-d_6): δ(ppm)=11.50(s,1H,NH), 9.76(s,1H,NH), 8.80(s, 2H,NH_2), 8.23(s, 1H), 7.37-7.30(m, 5H), 5.38(t, J=4.8,4.4Hz, 1H), 4.72(d, J=2.8Hz, 1H), 4.52(d, J=36Hz, 2H), 4.29(s, 1H),2.52(s, 3H); 13C NMR (DMSO-d6, 100 MHz)δ(ppm)= 191.9, 183.4, 173.4, 164.8, 146.0, 145.9, 143.7, 140.5, 131.2, 130.3, 129.6, 127.9, 127.8, 79.5, 66.5, 58.5, 35.5, 18.7. HR-MS m/z: calcd for C20H18N4O4S [M+H]+: 411.1122; found: 411.1119.

4d. 2-(2-amino-3-(benzo[d]thiazol-2-yl)-4H-chromen-4-yl)-3-hydroxycyclohex-2-en-1-one

Pale yellow solid, yield 90%; m.p=219-220°C; 1H NMR (400 MHz, DMSO-d_6): δ(ppm)=10.85(s, 1H, NH), 8.33(s, 2H, NH_2), 7.84(d, J=7.6Hz, 1H), 7.67(d, 8.0Hz, 1H), 7.34-7.30(m, 1H), 7.17-7.11(m, 3H), 7.01(q, J=7.2,7.2Hz, 1H), 6.96(d, J=8.0Hz, 1H), 5.24(s, 1H), 2.26(br, 4H), 1.69(t, J=6.4,5.6Hz, 2H); 13C NMR (DMSO-d6, 100 MHz)δ(ppm)=169.3, 156.4, 153.1, 148.9, 131.7, 128.0, 126.9, 125.6, 125.3, 123.8, 121.8, 119.1, 114.7, 103.8, 78.4, 20.42. HR-MS m/z: calcd for C22H19N2O3S [M+H]+: 391.1111; found: 391.1093.

4e. 2-(2-amino-3-(benzo[d]thiazol-2-yl)-6-bromo-4H-chromen-4-yl)-3-hydroxycyclohex-2-en-1-one

Yellow solid, yield 80%; m.p=267-268°C; 1H NMR (400 MHz, DMSO-d_6): δ(ppm)=11.0(s, 1H, NH), 8.36(s, 2H, NH_2), 7.85(d, J=7.6Hz, 1H), 7.68(d, J=8.0Hz, 1H), 7.35-7.31(m, 2H), 7.21(d, J=2.4Hz, 1H), 7.16-7.12(m, 1H), 6.96(d, J=8.4Hz, 1H), 5.23(s, 1H), 2.31(d, J=4.8Hz, 4H), 1.71(d, J=5.2Hz, 2H); 13C NMR (DMSO-d6, 100 MHz)δ(ppm)=168.9, 156.0, 153.0, 148.2, 131.7, 130.2, 129.8, 127.9, 125.6, 122.0, 121.1, 119.2, 117.2, 115.0, 77.93, 20.3. HR-MS m/z: calcd for C22H17BrN2O3S [M+H]+:469.0216; found: 469.0202.

RESULTS AND DISCUSSIONS:

Herein we report the simple, effective method high atom economic reaction, a multicomponent organic base mediated green solvent synthesis of 4-heterocyclic-2amino-4*H*-chromene derivatives **4a-e** (scheme 1) by cyclic condensation of Benzoylacetonitrile/ benzothiazoleacetonitrile**3a-b** with Thiazolidinedione/1,3cyclohexanedione **2a-c** and Salicylaldehyde derivatives **1a-d** has been developed.

The reaction mixture was afford with organic base at room temperature, rapid formation of 4*H*-chromene yield formation is 95%(Table 1, Entry 7). As a result, the reaction was performed using mild bases, after screening various bases, DABCO was observed to be the best catalyst as it afforded the product in 3hrs in excellent yield.

At present, the modern organic synthesis widely used green solvents such as water; ethanol and their fusions in the presence of green catalyst have attracted much attention, because these solvents are safe, economical, and environmentally benign. For this reason, we are developing green novel synthetic methods for the preparation 5-(2-amino-3-benzoyl-8-methoxy-4H-chromen-4-yl)-2-thioxoimidazolidin-4-one derivatives. This is a single step three component reaction, which is not only operationally simple, effective, benign and unpolluted but also the consistent products are good to excellent yields. Therefore to find the suitable reaction medium, the reaction was performed with various solvents at room temperature found that ethanol and water was best solvent to desired product. The structure of the product **4a-e** was confirmed by 1H, 13C NMR, IR and HRMS spectra.To extend the scope of this methodology, the three component reaction was further examined with 1,3-cyclohexadione, benzothiazole acetonitrile and salicylaldehyde derivatives **4d** has been developed.Encouraged by this result, a library of 4-heterocyclic substituted 2-amino-4H-chromenes was synthesized and the results were summarized (**fig 1**). All the compounds were characterized by ^{1}H, ^{13}CNMR, IR and HRMS spectra. The ^{1}H, ^{13}CNMR of 4a and 4b compounds are depicted in **fig 2 and fig 3.**

CONCLUSION

We have designed and developed a facile three component reaction protocol for the synthesis of highly substituted 4-heterocyclic-2-amino-4*H*-chromene derivatives with high yield. This 4-heterocyclic substituted-4*H*-chromenes are expected to possess enhanced anticancer activity. The scope of the reaction has been explored by changing the different substrate of the multicomponent reaction and the result have been summarised.

SUPPORTING INFORMATION

The supporting information for this article contains the general information, experimental section, general procedure, spectral data, ^{1}H, ^{13}C spectra for all the synthesized compounds.

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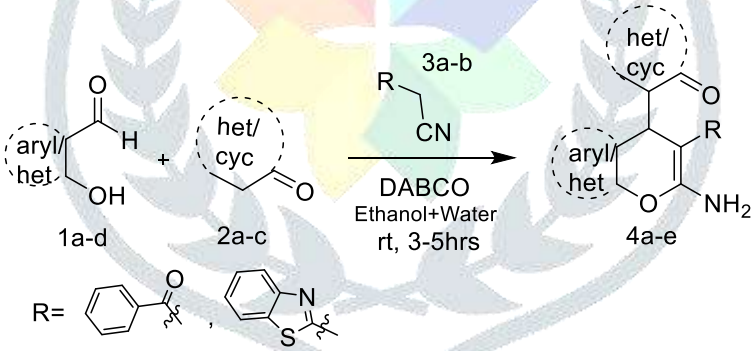
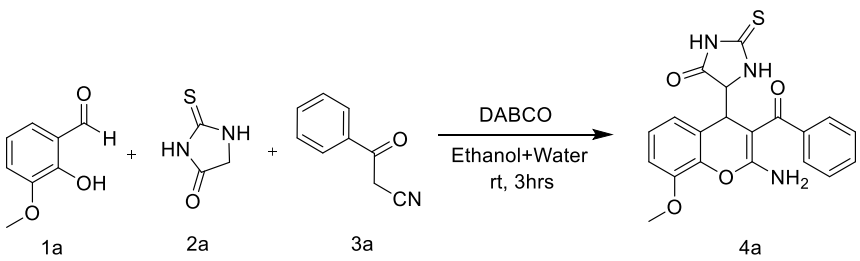
Table-1 Optimization of reaction condition for the synthesis of 4a-e

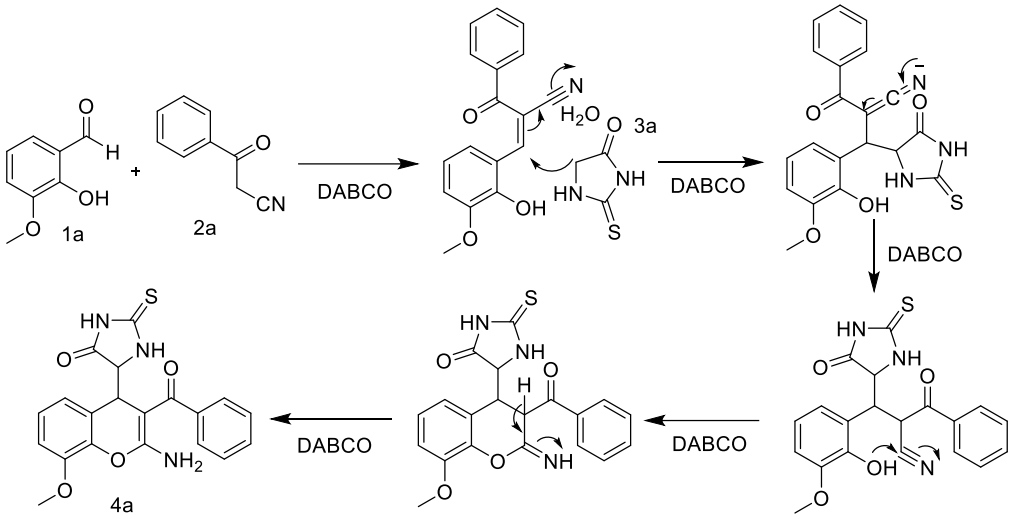
Entry	Solvent	Base	Time (hrs)	Yield (%)
1	MeOH	Piperidine	7	60
2	MeOH	K_2CO_3	8	50
3	MeOH	DABCO	4	75
4	EtOH	DABCO	4	80
5	EtOH	NaOEt	5	60
6	EtOH	Piperidine	4	75
7	EtOH +H_2O	DABCO	3	95
8	EtOH +H_2O	Piperidine	3	80
9	H_2O	K_2CO_3	4	trace
10	EtOH +H_2O	L-proline	6	62
11	MeOH+H_2O	DABCO	3.5	89
12	EtOH +H_2O	K_2CO_3	5.5	78
13	i-PrOH	piperidine	7	55
14	i-PrOH	K_2CO_3	8	65
15	MeCN	DABCO	9	50



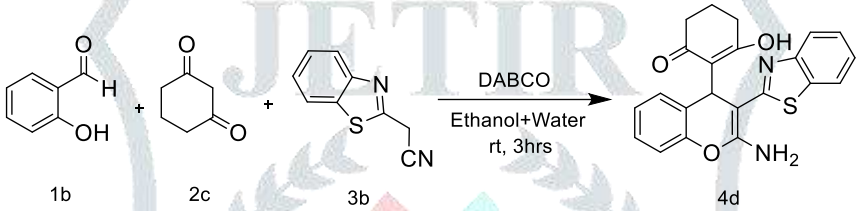
Scheme-1 Three component reaction for the synthesis of 4a-e



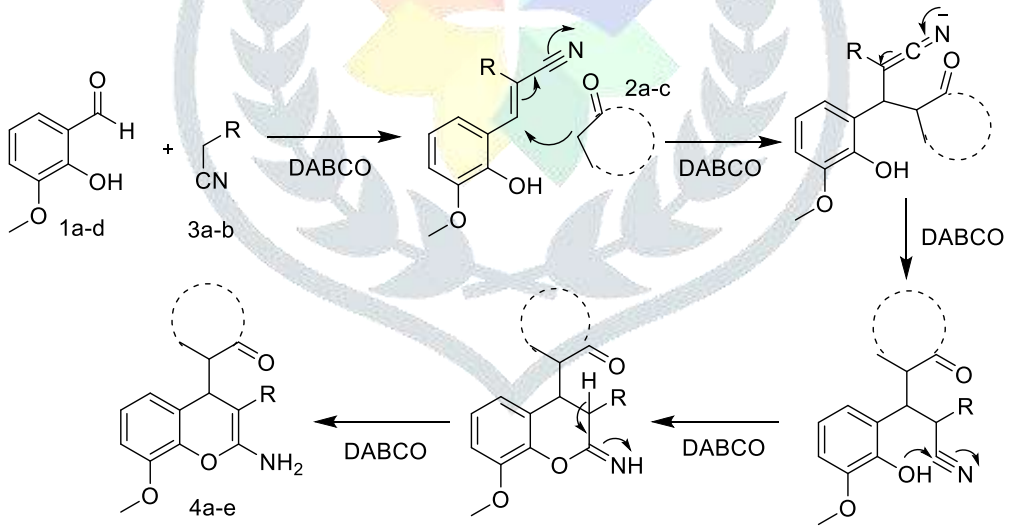
Scheme 2 Three c-mponent reaction for the synthesis of 4a



Scheme 3: Plausible mechanism for the formation of 4a



Scheme 4 Three component reaction for the synthesis of 4d



Scheme 5: overall mechanism for the formation of 4a-e

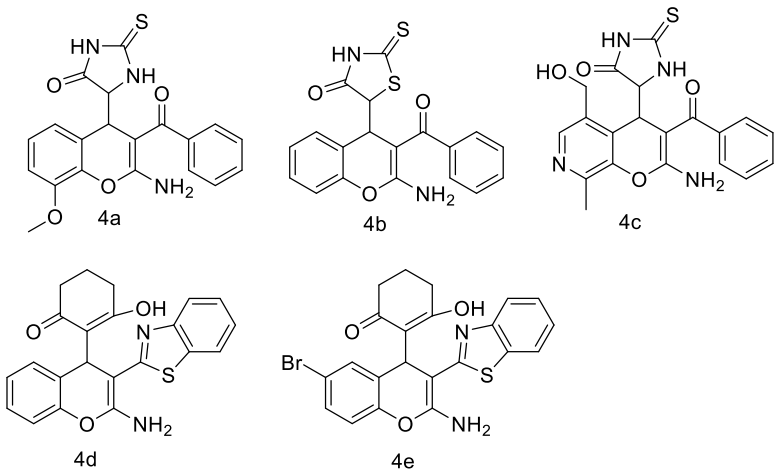
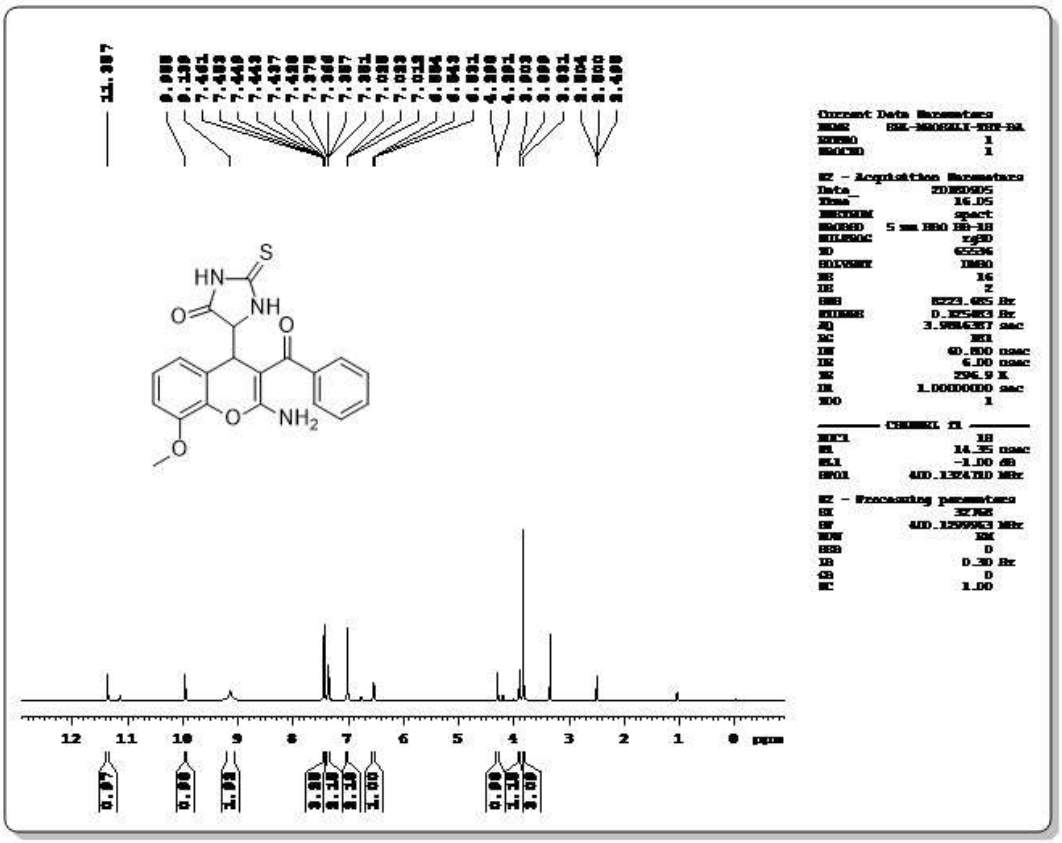


Fig. 1 Substrate scope for the three component reaction



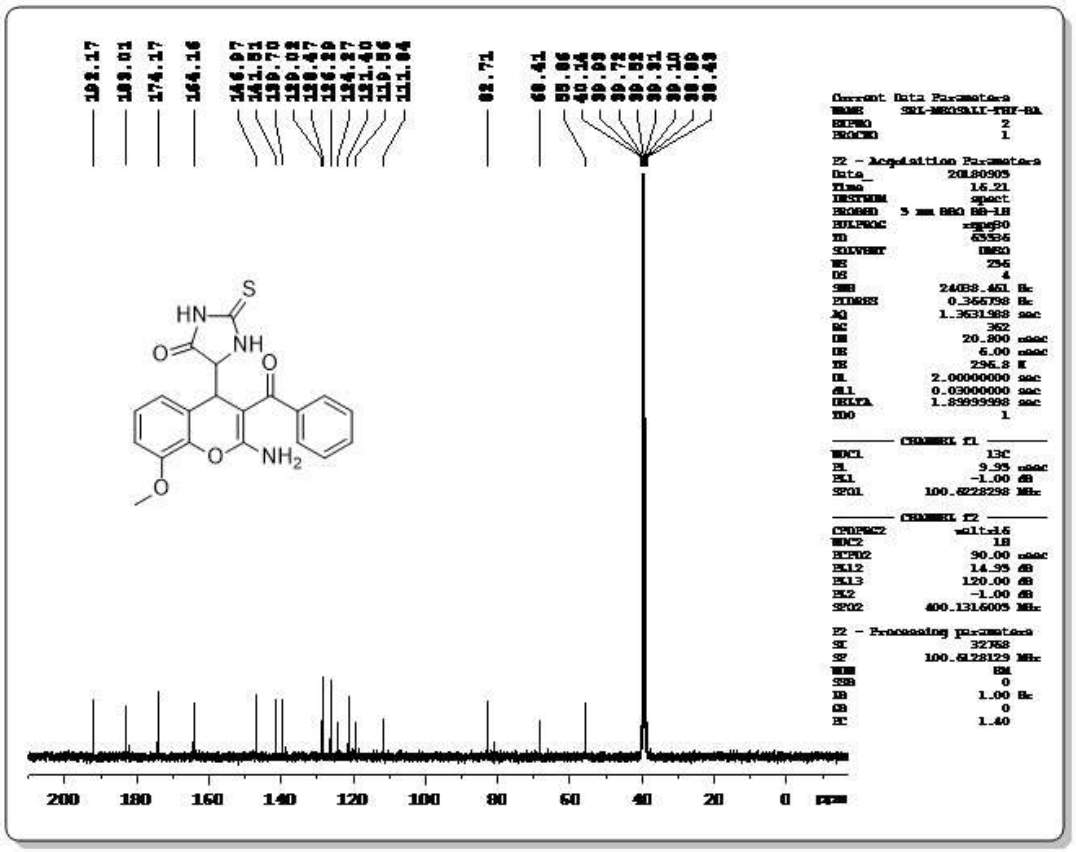
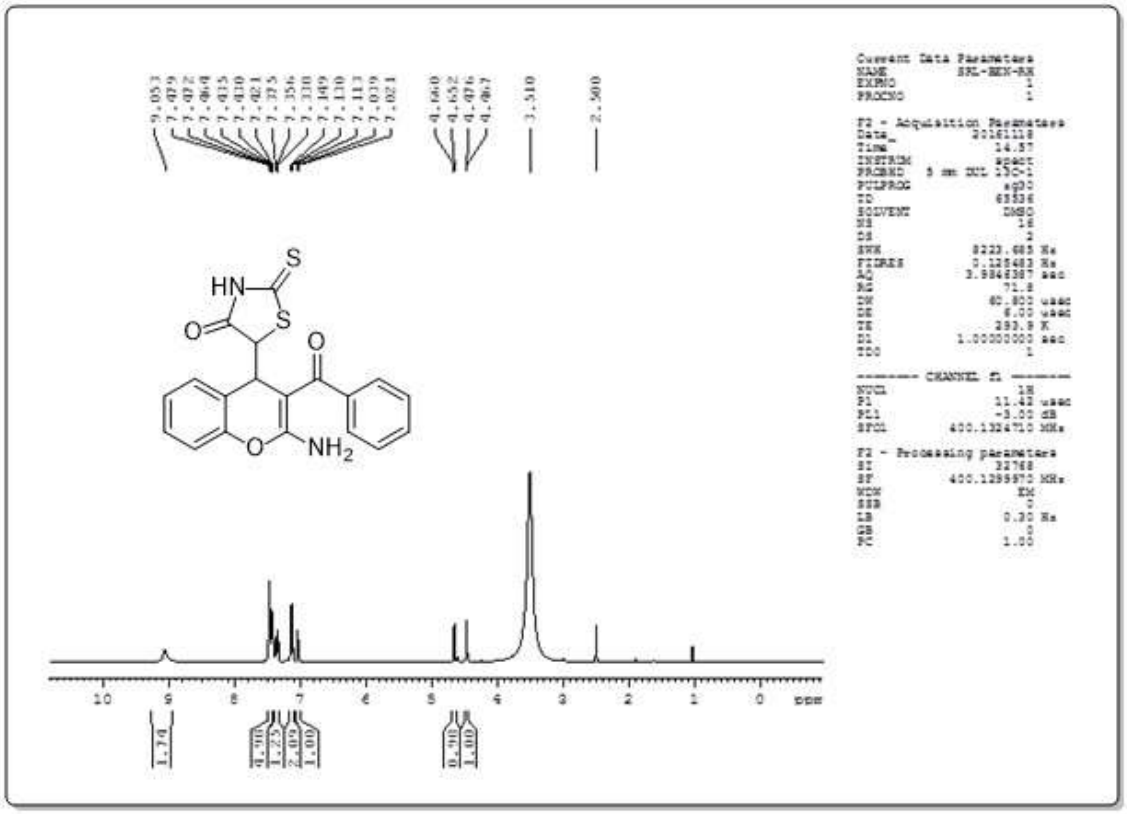


Fig. 2:[1]H, [13]C spectrum of 5-(2-amino-3-benzoyl-8-methoxy-4H-chromen-4-yl)-2-thioxoimidazolidin-4-one 4a



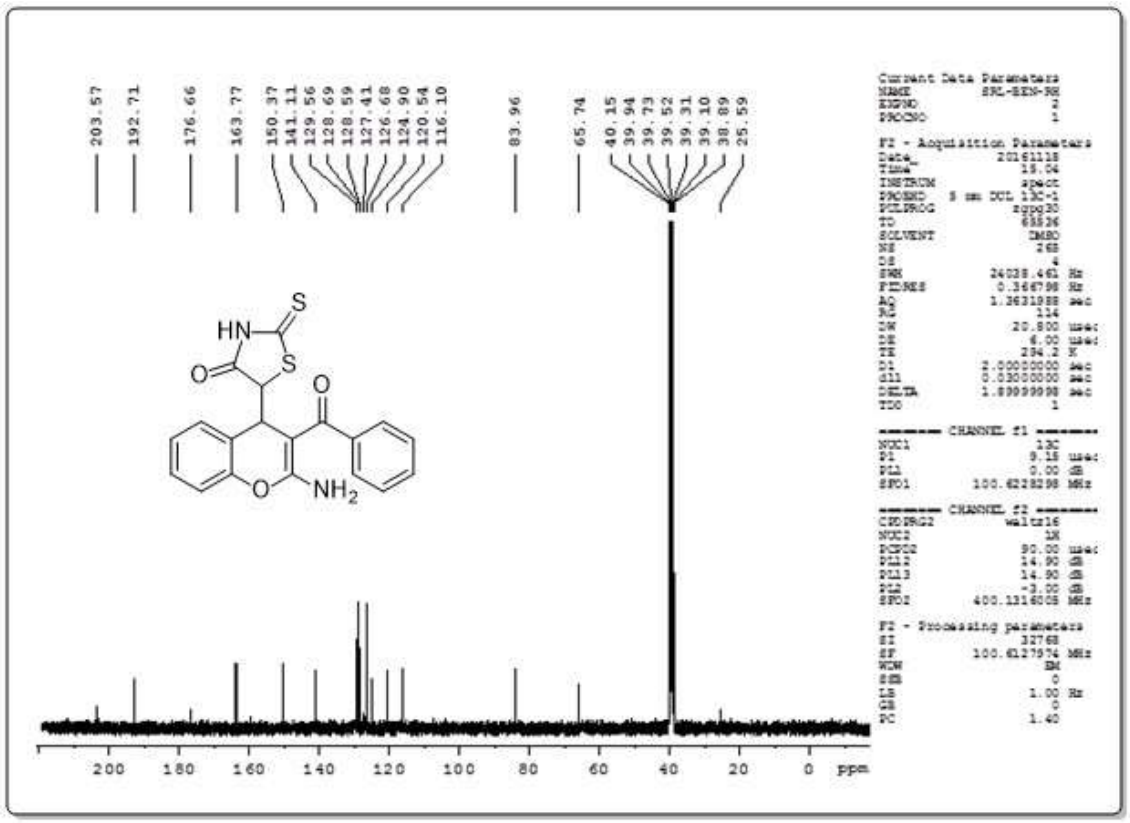


Fig. 3:^{1}H, ^{13}C spectrum of 5-(2-amino-3-benzoyl-4H-chromen-4-yl)-2-thioxothiazolidin-4-one 4b

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