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Article

Ring Transformation of Chromone-3-Carboxamide under Nucleophilic Conditions

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A reatividade química de cromona-3-carboxamida foi estudada para uma série nucleófilos de carbono e de nitrogênio. O tratamento da carboxamida com algumas aminas primárias forneceu cromona-2,4-dionas. A condensação da carboxamida com hidrato de hidrazina, fenilihidrazina e hidrocloridrato de hidroxilamina forneceu cromenopirazóis e cromeno isoxazol, respectivamente. A reação da carboxamida com cloridrato de guanidina, cianoguanidina e tioureia resultou na transformação do anel, produzindo cromenopiridinas. O comportamento químico da carboxamida também foi estudado para etilenodiamina, *o*-fenilenodiamina, 2-aminofenol e 2-aminotiophenol. Uma variedade de produtos foi isolada a partir da reação de carboxamidas com alguns nucleófilos de carbono.

The chemical reactivity of chromone-3-carboxamide was studied towards a series of nitrogen and carbon nucleophiles. Treatment of carboxamide with some primary amines gave chromane-2,4-diones. Condensation of carboxamide with hydrazine hydrate, phenyl hydrazine and hydroxylamine hydrochloride afforded chromenopyrazoles and chromenoisoxazole, respectively. Reaction of carboxamide with guanidine hydrochloride, cyanoguanidine and thiourea resulted in ring transformation producing chromenopyridines. The chemical behavior of carboxamide was also studied towards ethylenediamine, *o*-phenylenediamine, 2-aminophenol and 2-aminothiophenol. A variety of products were isolated from the reaction of carboxamide with some carbon nucleophiles.

Keywords: chromone-3-carboxamide, ring transformation, chromane-2,4-diones, chromeno[4,3-*d*]pyrimidine, nitrogen and carbon nucleophiles, cyclocondensation

Introduction

3-Substituted chromones are very active substrates toward nucleophilic reagents, due to the availability of different electron deficient centers. The diversity of properties of these compounds is due to the fact that they are highly reactive geminally activated push-pull alkenes (α,β-unsaturated ketones) with a good leaving group at the β-carbon atom, whose role is played by the phenolate anion. 3-Substituted chromones have the ability to undergo a nucleophilic 1,4-addition followed by further transformations related to γ-pyrone ring opening and heterocyclizations at the C-4 atom and/or at the substituent in position 3. 3-Formylchromones have been used to prepare a variety of heterocyclic compounds via reaction with different nucleophiles.[1-4] Chromone-3-carbonitriles on treatment with carbon nucleophiles produced chromeno[2,3-*b*]pyridines.[5] A variety of products was obtained from reactions of chromone-3-carboxylic acid with nucleophilic reagents.[6] Furthermore, the heating of chromone-3-carboxylate with concentrated ammonium hydroxide leads to 3-formimidoyl-4-hydroxycoumarin.[7] Primary and secondary amines reacted with 3-bromochromone to yield ring contraction products and 3-aminochromones.[8,9] The work on the chemistry of chromone-3-carboxamide is rare,[10] thus as an extension of the work directed to study the chemical behavior of 3-substituted chromones under nucleophilic conditions, the present investigation describes the chemical reactivity of chromone-3-carboxamide (**1**) towards a variety of nucleophilic reagents.

Results and Discussion

Chromone-3-carboxamide has three electron deficient centers, C-2, C-4 as C=O and the amidic carbon at position 3. In continuation to our interest in the chemistry of chromone-3-carboxamide (**1**),[10] the present work aims to study the chemical reactivity of carboxamide **1** towards a variety of nitrogen and carbon nucleophiles. The treatment

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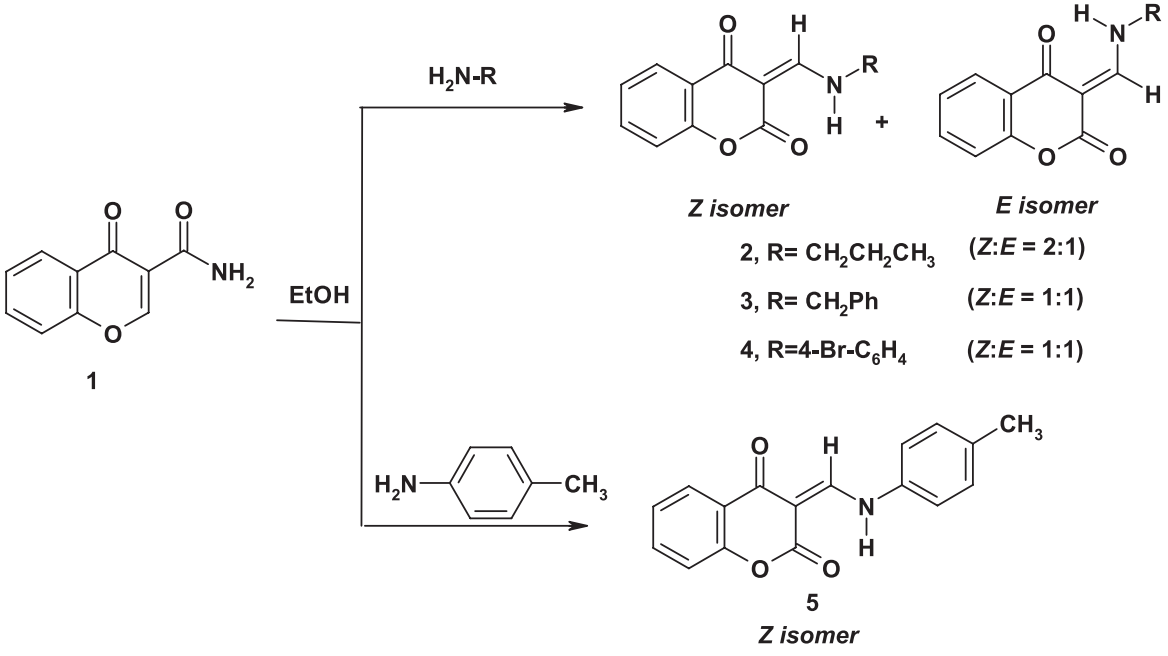
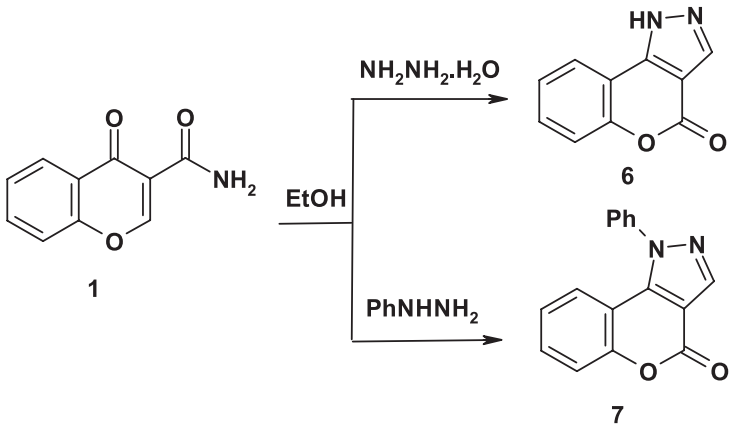
of carboxamide **1** with some primary aliphatic and aromatic amines namely; *n*-propylamine, benzylamine, *p*-bromoaniline and *p*-toluidine, in absolute ethanol resulted in ring transformation via γ-pyrone ring opening followed by lactonization with loss of ammonia to afford the corresponding chromane-2,4-diones **2**-**5** (Scheme 1). Compounds **2**-**4** were isolated as stereoisomeric mixtures of *Z* and *E* isomers, while compound **5** was isolated as a pure isomer (*Z* isomer). The ratio of *Z*:*E* isomers depends on the type of amine used. The *Z*:*E* ratios of compounds **2**-**4** were deduced from studies of their ^{1}H nuclear magnetic resonance (NMR) spectra. The relatively high deshielding effect on the β-hydrogen which is *cis* to the cyclic ester function of an α,β-unsaturated ester compared to that of an α,β-unsaturated ketone helped to distinguish the *Z* and *E* isomers. Also, the higher δ values of NH in *Z* isomers as compared with that of *E* isomers help to differentiate between the *Z* and *E* isomers. The high δ values are attributed to the intramolecular hydrogen bonds in both isomers. The two doublets assigned to the exocyclic C*H* protons, in *E* and *Z* isomers, are usually exchanged to singlets in the presence of D_2O, with concomitant disappearance of the two signals assigned to the NH protons. On the other hand, the ^{1}H NMR spectrum of compound **5** showed one exchangeable signal at δ 13.45 ppm corresponding to the NH proton. The high δ value confirms the *Z* isomer for compound **5**, in addition the spectrum also revealed characteristic singlet at δ 2.33 attributed to the methyl protons. Moreover, the ^{13}C NMR spectrum of compound **5** showed characteristic signals at δ 20.6 and 97.9 assigned to methyl carbon and C-3.

Next, the chemical reactivity of carboxamide **1** was studied towards a variety of 1,2-binucleophiles. Thus, condensation of carboxamide **1** with hydrazine hydrate and phenyl hydrazine in refluxing ethanol achieved the ring transformation of compound **1** producing chromeno[4,3-*c*]pyrazoles **6** and **7**, respectively (Scheme 2). While the reaction of carboxamide **1** with 7-chloro-4-hydrazinoquinoline (**8**) in refluxing ethanol afforded the hydrazone derivative **9**. Also, the condensation of carboxamide **1** with hydroxylamine hydrochloride in refluxing DMF (dimethylformamide) produced chromeno[3,4-*d*]isoxazol-4(4*H*)-one (**10**) (Scheme 3). The ^{1}H NMR spectrum of compound **10** showed characteristic singlet assigned to H-3$_{isoxazole}$ at δ 8.88 ppm.

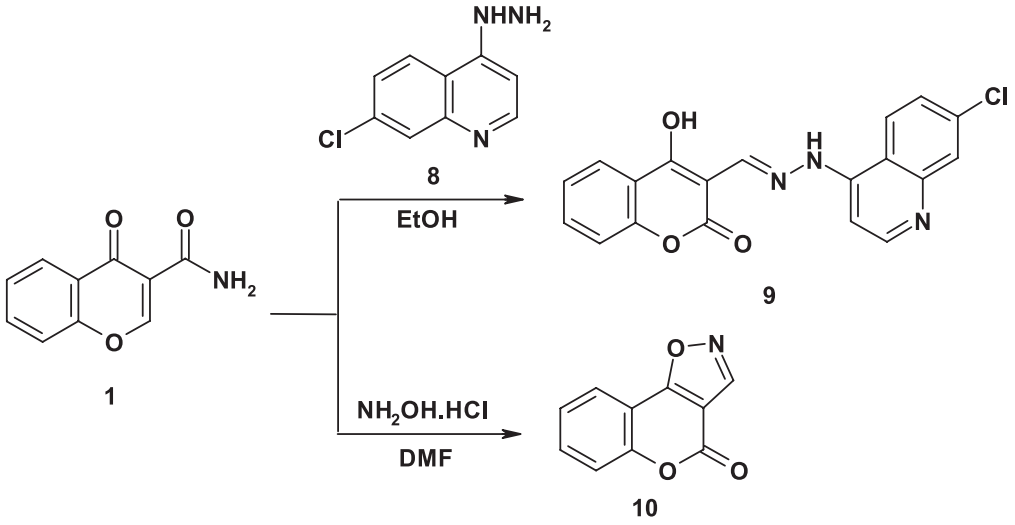
On the other hand, carboxamide **1** was allowed to react with some 1,3-binucleophiles. Thus, the condensation of carboxamide **1** with guanidine hydrochloride, cyanoguanidine and thiourea in ethanolic potassium hydroxide solution produced chromeno[4,3-*d*]pyrimidine derivatives **11**-**13**, respectively (Scheme 4). The infrared (IR) spectra of compounds **11**-**13** showed characteristic absorption band in the range 1701-1734 cm^{-1} assigned to the O–C=O functions, the spectrum of compound **12** showed absorption band at 2259 cm^{-1} attributed to the nitrile function. The ^{1}H NMR spectra of compounds **11**-**13** showed singlet signals attributed to the H-4$_{pyrimidine}$ in the range δ 8.99-9.35 ppm. Structures of compounds **12** and **13** were further deduced from their mass spectra which revealed the molecular ion peaks at *m/z* 238 and 230,



Scheme 1.



Scheme 2.



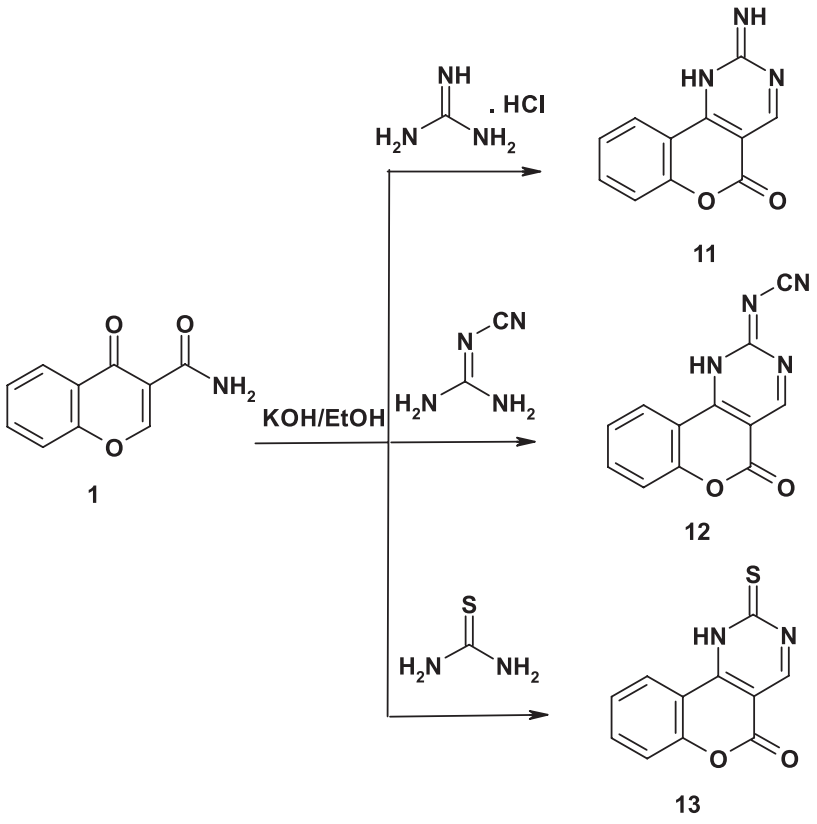
Scheme 3.

respectively, which agree with the formula weights and support the structures.

Further, the chemical behavior of carboxamide **1** was studied towards *o*-phenylenedimine, 2-aminophenol and 2-aminothiophenol. Thus, the condensation of **1** with *o*-phenylenedimine and *o*-aminophenol in refluxing DMF afforded the chromane-2,4-dione derivatives **14** and **15**, respectively, as *Z* isomers (Scheme 5). The ^{1}H NMR spectra of compounds **14** and **15** showed exchangeable doublets assigned to the NH protons at δ 13.42 and 13.75 ppm, respectively, in addition to characteristic doublets exchanged to singlets in D_2O at δ 8.74 and 8.94 ppm, respectively, which were assigned to the exocyclic vinyl protons. The higher δ values of the exocyclic vinyl protons and NH protons confirm the pure *Z* isomers for compounds **14** and **15**. The structure of compound **14** was further deduced from its mass spectrum which revealed the molecular ion peak at *m/z* 280, agreeing with the formula weight 280.29. On the other hand, the treatment of carboxamide **1** with *o*-aminothiophenol in refluxing DMF achieved ring transformation producing benzothiazolylcoumarin derivative **17** via the non-isolable intermediate **16** as shown in Scheme 5.

Ethylenediamine showed different behavior when reacted with carboxamide **1** and produced the *bis* enaminone derivative **18** via the reaction of ethylenediamine with two equivalents of carboxamide **1** (Scheme 6). The mass spectrum of compound **18** showed the molecular ion peak at *m/z* 404 which agrees with the formula weight 404.38 and confirms the structure.

Also, the chemical reactivity of carboxamide **1** was studied towards a variety of carbon nucleophiles. Thus, the treatment of carboxamide **1** with malononitrile in ethanol containing few drops of piperidine afforded the pyridine derivative **19** as depicted in Scheme 7. The reaction proceeds via deprotonation of malononitrile followed by nucleophilic attack at C-2 position and γ-pyrone ring opening with concomitant cycloaddition. The IR spectrum



Scheme 4.

of compound **19** showed characteristic absorption bands at 2222 (C≡N) and 1654 ($C=O_{pyridone}$). Its ^{1}H NMR spectrum showed characteristic singlet at δ 8.64 ppm assigned to the H-$4_{pyridine}$. The mass spectrum showed the molecular ion peak at *m/z* 255 corresponding to its molecular formula $C_{13}H_9N_3O_3$ and supports the structure. Further, the ^{13}C NMR spectrum of compound **19** showed characteristic signals at δ 89.8 (C-$5_{pyridine}$) and 115.5 (C≡N).

In the same manner, the treatment of carboxamide **1** with cyanoacetamide under the same reaction conditions produced the pyridine derivative **20** (Scheme 8). Its ^{1}H NMR spectrum showed characteristic singlet at δ 8.79 ppm due to the H-$4_{pyridine}$.

The reaction of carboxamide **1** with acetophenone in ethanolic potassium hydroxide solution gave the corresponding α,β-unsaturated ketone **21** (Scheme 9). The ^{1}H NMR spectrum of compound **21** showed two doublets at δ 8.97 and 9.50 ppm assigned to the olefinic protons. Finally, the condensation of carboxamide **1** with thiobarbituric acid in ethanolic sodium ethoxide afforded pyrimidine derivative **22**. Its ^{1}H NMR spectrum showed characteristic singlet due to the exocyclic vinyl proton at δ 8.80 ppm, its mass spectrum showed the molecular ion peak at *m/z* 316 corresponding to the molecular formula ($C_{14}H_8N_2O_5S$) and confirms the structure.

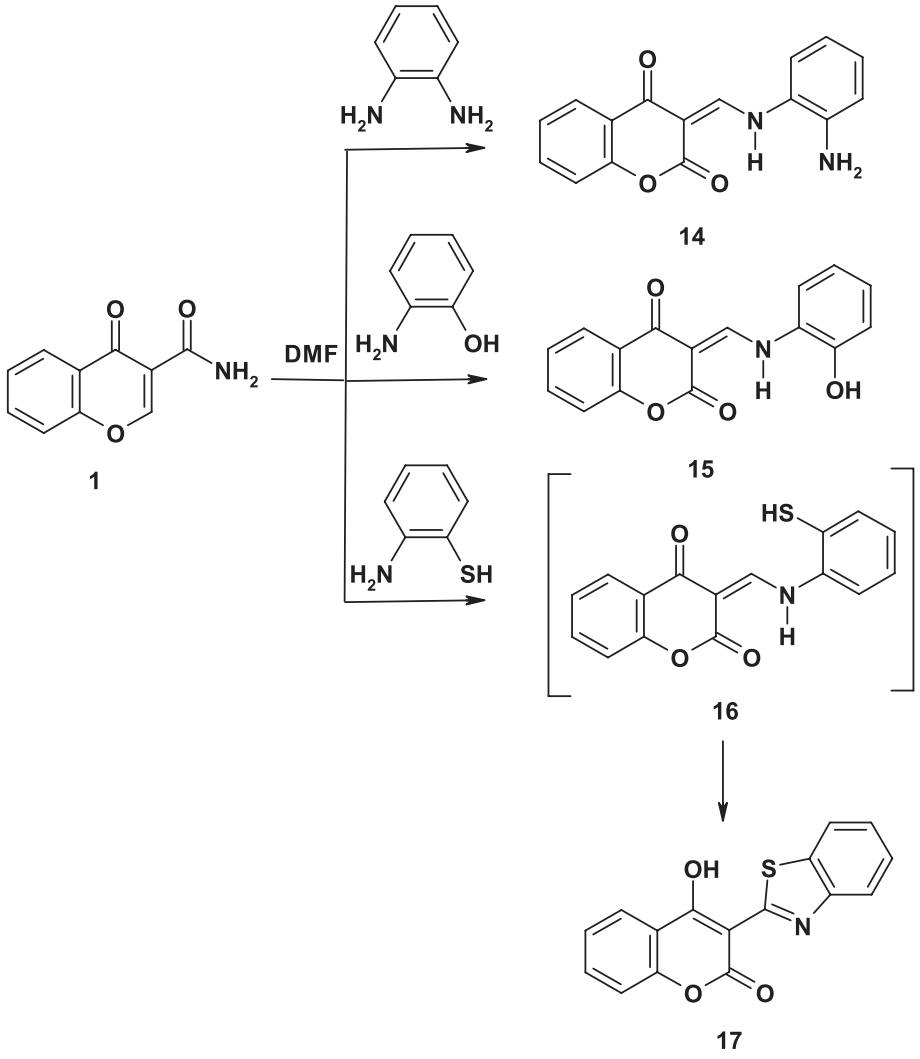
Conclusion

In conclusion, chromone-3-carboxamide has three electron deficient centers, C-2, C-4 and the amidic carbon at position 3. The nucleophilic reagent usually attack at the C-2 position with γ-pyrone ring opening followed by further transformation during the course of the reaction producing a variety of products depending on the nucleophile used.

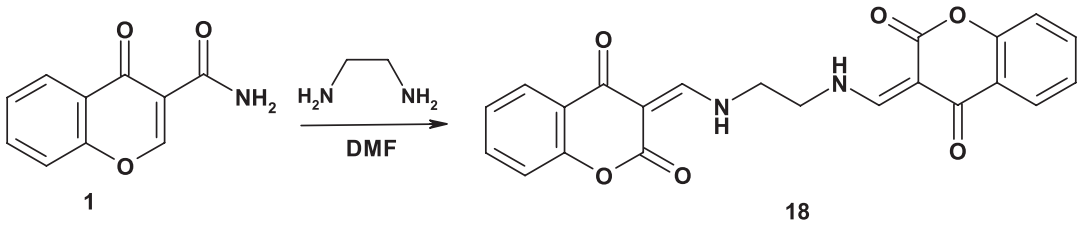
Experimental

General

Melting points are uncorrected and were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR spectra were measured on Gemini (200 MHz) and Mercury-300BB (300 MHz) spectrometers using DMSO-d_6 as a solvent and TMS (tetramethylsilane, δ) as the internal standard. Mass spectra were obtained using GCMS qp 1000 ex Shimadzu instrument (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer at the Chemical War Department, Ministry of Defense, Cairo, Egypt.



Scheme 5.



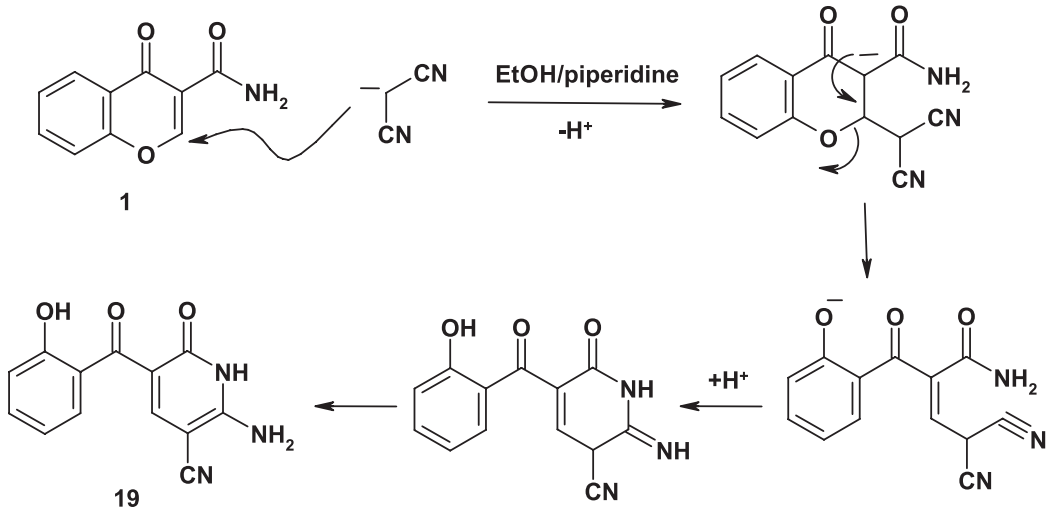
Scheme 6.

General procedure for the reaction of chromone 3-carboxamide (**1**) with aliphatic and aromatic amines

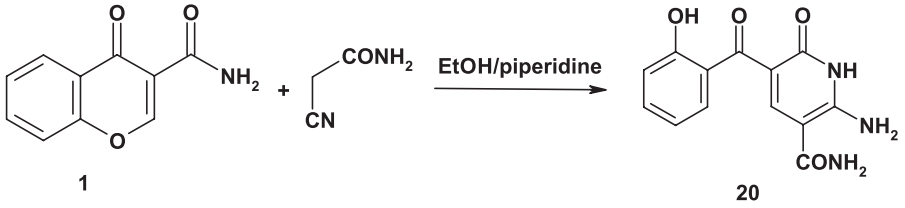
A mixture of carboxamide **1** (0.57 g, 3 mmol) and *n*-propylamine, benzylamine, *p*-bromoaniline and *p*-toluidine (3 mmol), in absolute ethanol (15 mL), was heated under reflux for 1 h. The crystalline products obtained after cooling were filtered off and recrystallized from ethanol to give compounds **2**-**5**, respectively.

3-[(Propylamino)methylidene]chromane-2,4(3*H*)-dione (**2**)

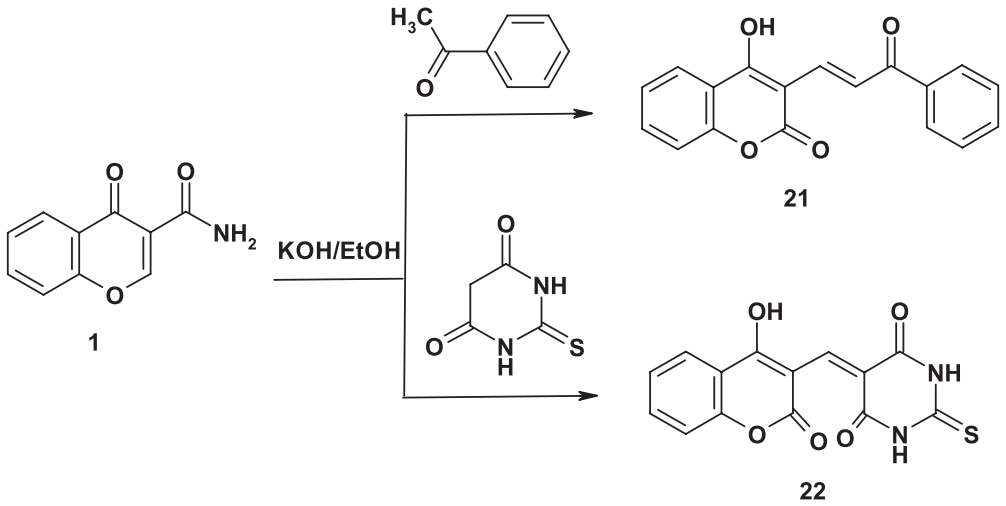
White crystals; mp 156-157 ºC; yield (0.48 g, 69%); IR (KBr) ν/cm^{-1} 3181 (NH), 3028 ($CH_{arom.}$), 2962, 2933, 2876 ($CH_{aliph.}$), 1716 (OC=O), 1636 (C=O), 1590 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (t, 3H, *J* 7.5 Hz, CH_3), 1.59-1.71 (m, 2H, CH_2), 3.56 (t, 2H, *J* 6.9 Hz, CH_2), 7.26-7.33 (m, 2H, H-6 and H-8), 7.65 (t, 1H, *J* 7.8 Hz, H-7), 7.92 (d, 1H, *J* 6.4 Hz, H-5), 8.46 (d, 0.64 H, *J* 12.6 Hz, CH_{vinyl} exchanged to singlet with D_2O, *Z* isomer), 8.56 (d, 0.36 H, *J* 12.6 Hz,



Scheme 7.



Scheme 8.



Scheme 9.

CH_{vinyl} exchanged to singlet with D_2O, *E* isomer), 10.38 (bs, 0.36 H, NH exchangeable with D_2O, *E* isomer), 11.67 (bs, 0.64 H, NH exchangeable with D_2O, *Z* isomer); MS (*m/z*, %) 232 (M + 1, 17), 231 (M^+, 100), 216 (63), 202 (24), 188 (24), 173 (13), 121 (72), 93 (18), 77 (19) and 65 (28); anal. calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06%; found: C, 67.49; H, 5.61; N, 6.03%.

3-[(Benzylamino)methylidene]chromane-2,4(3*H*)-dione (**3**)

White crystals; mp 165-166 ºC; yield (0.44 g, 53%); IR (KBr) ν/cm^{-1} 3363, 3183 (NH), 3025 ($CH_{arom.}$), 2955, 2915 ($CH_{aliph.}$), 1712 (OC=O), 1647 (C=O), 1603 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.45 (d, 2H, *J* 6.0 Hz, CH_2 exchanged to singlet with D_2O, *E* isomer), 4.83 (d, 2H, *J* 6.0 Hz, CH_2 exchanged to singlet with D_2O, *Z* isomer),

6.79-6.88 (m, 1H, Ar-H), 7.05 (d, 1H, *J* 7.8 Hz, Ar-H), 7.12-7.42 (m, 5H, Ar-H), 7.48 (d, 0.5H, *J* 13.2 Hz, CH_{vinyl} exchanged to singlet with D_2O, *Z* isomer), 7.65 (t, 1H, *J* 6.6 Hz, Ar-H), 7.91 (d, 1H, *J* 6.9 Hz, Ar-H), 8.65 (bs, 0.5H, CH_{vinyl} exchanged to singlet with D_2O, *E* isomer), 8.95 (d, 0.5H, NH exchangeable with D_2O, *E* isomer), 11.01 (m, 0.5H, NH exchangeable with D_2O, *Z* isomer); anal. calcd for $C_{17}H_{13}NO_3$ (279.30): C, 73.11; H, 4.69; N, 5.01%; found: C, 73.03; H, 4.78; N, 4.92%.

3-{[(4-Bromophenyl)amino]methylidene}chromane-2,4(3*H*)-dione (**4**)

White crystals; mp 249-250 ºC; yield (0.64 g, 62%); IR (KBr) ν/cm^{-1} 3215, 3187 (NH), 3060 ($CH_{arom.}$), 1688 (OC=O), 1648 (C=O), 1608 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.50 (d, 1H, *J* 8.7 Hz, Ar-H), 7.11 (d, 1H, *J* 9.0 Hz, Ar-H), 7.33-7.39 (m, 3H Ar-H), 7.53 (d, 1H, *J* 7.8 Hz, H-8), 7.64 (t, 1H, *J* 7.8 Hz, H-7), 7.96 (d, 1H, *J* 7.8 Hz, H-5), 8.85 (d, 0.5H, CH_{vinyl} exchanged to singlet with D_2O, *Z* isomer), 8.89 (d, 0.5H, CH_{vinyl} exchanged to singlet with D_2O, *E* isomer), 11.82 (d, 0.5H, NH exchangeable with D_2O, *E* isomer), 13.37 (d, 0.5H, NH exchangeable with D_2O, *Z* isomer), MS (*m/z*, %) 344 (M + 2, 25), 342 (M^+, 25), 173 (100, M^+- 4-BrC_6H_5NH), 157 (7), 155 (7), 121 (42), 92 (28), 77 (11) and 64 (26); anal. calcd for $C_{16}H_{10}BrNO_3$ (344.17): C, 55.84; H, 2.93; N, 4.07%; found: C, 55.78; H, 2.85; N, 4.01%.

(3*Z*)-3-{[(4-Methylphenyl)amino]methylidene}chromane-2,4(3*H*)-dione (**5**)

White crystals; mp 194-195 ºC; yield (0.45 g, 54%); IR (KBr) ν/cm^{-1} 3174 (NH), 3064 ($CH_{arom.}$), 1684 (OC=O), 1648 (C=O), 1603 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.33 (s, 3H, CH_3), 6.46 (d, 1H, *J* 8.4 Hz, Ar-H), 7.81 (d, 1H, *J* 7.8 Hz, Ar-H), 7.28-7.39 (m, 3H, Ar-H), 7.56 (d, 1H, *J* 8.4 Hz, H-8), 7.71 (t, 1H, *J* 8.4 Hz, H-7), 7.98 (d, 1H, *J* 7.8 Hz, H-5), 8.85 (bs, 1H, CH_{vinyl}), 13.45 (bs, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6) 20.6 (CH_3), 97.9 (C3), 113.9, 114.2, 117.1, 119.2, 124.2, 125.7, 129.3, 130.3, 134.9, 135.6, 136.7, 152.0 (C_{vinyl}), 154.3 (C8a), 158.0 (C-2 as C=O), 177.9 (C-4 as C=O); anal. calcd for $C_{17}H_{13}NO_3$ (279.30): C, 73.11; H, 4.69; N, 5.01%; found: C, 73.02; H, 4.62; N, 5.07%.

Chromeno[4,3-*c*]pyrazol-4(1*H*)-one (**6**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and hydrazine hydrate (0.15 mL, 3 mmol), in absolute ethanol (15 mL), was heated under reflux for 2 h. The white crystals obtained after cooling were filtered off and recrystallized from ethanol to give compound **6** as white crystals; mp 225-226 ºC (mp 226-227 ºC);[6] yield (0.31 g, 56%).

1-Phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (**7**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and phenyl hydrazine (0.30 mL, 3 mmol), in absolute ethanol (15 mL), was heated under reflux for 2 h. The pale yellow crystals obtained after cooling were filtered off and recrystallized from ethanol to give compound **7** as white crystals; mp 193-194 ºC (mp 192-193 ºC,[11] 191 ºC);[12] yield (0.36 g, 46%).

3-{[2-(7-Chloroquinolin-4-yl)hydrazinylidene]methyl}-4-hydroxy-2*H*-chromen-2-one (**9**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and 7-chloro-4-hydrazinoquinoline (**8**) (0.58 g, 3 mmol), in absolute ethanol (30 mL), was heated under reflux for 15 min. The yellow crystals obtained during heating were filtered off and recrystallized from DMF/H_2O to give compound **9** as yellow crystals; mp 304-305 ºC; yield (0.65 g, 60%); IR (KBr) ν/cm^{-1} 3363, 3289, 3178 (OH, NH), 3056 ($CH_{arom.}$), 1716 (OC=O), 1660 (C=N), 1614 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.23-7.35 (m, 2H, Ar-H), 7.49 (s, 1H, H-$8_{quinoline}$), 7.55-7.66 (m, 1H, Ar-H), 7.76-7.86 (m, 1H, Ar-H), 7.90 (s, 1H, CH=N), 8.12 (d, 1H, *J* 8.1 Hz, Ar-H), 8.27 (d, 1H, *J* 9.0 Hz, Ar-H), 8.37 (d, 1H, H-$3_{quinoline}$), 8.57 (d, 1H, H-$2_{quinoline}$), 11.60 (bs, 1H, NH exchangeable with D_2O), 16.53 (bs, 1H, OH exchangeable with D_2O); anal. calcd for $C_{19}H_{12}ClN_3O_3$ (365.77): C, 62.39; H, 3.31; N, 11.49%; found: C, 62.37; H, 3.30; N, 11.32%.

Chromeno[3,4-*d*]isoxazol-4(4*H*)-one (**10**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and hydroxylamine hydrochloride (0.21 g, 3 mmol) in DMF was heated under reflux for 2 h. After cooling, the white precipitate so formed was filtered off and recrystallized from DMF/H_2O to give compound **10** as white crystals; mp 223-224 ºC (225 ºC);[13] yield (0.37 g, 66%).

General procedure for the reaction of chromone-3-carboxamide (**1**) guanidine hydrochloride, cyanoguanidine and thiourea

A mixture of carboxamide **1** (0.57 g, 3 mmol) and guanidine hydrochloride, cyanoguanidine or thiourea (3 mmol), in ethanolic potassium hydroxide solution (2%, 20 mL), was heated under reflux for 2 h. After cooling, the reaction mixture was neutralized with dil. HCl. The separated solid was filtered off and crystallized from the proper solvent to produce compounds **11**, **12** and **13**.

2-Imino-1,2-dihydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one (**11**)

Crystallized from dioxane as white crystals; mp 265-266 ºC (mp 265 ºC,[14] 260 ºC);[15] yield (0.42 g, 66%);

IR (KBr) ν/cm^{-1} 3277 (br, 2NH), 1702 (OC=O), 1663 (C=N), 1608 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32-7.46 (m, 1H, Ar-H), 7.62-7.83 (m, 2H, Ar-H), 8.01 (bs, 1H, NH exchangeable with D_2O), 8.30 (d, 1H, *J* 7.2 Hz, H-10), 8.99 (s, 1H, H-4$_{pyrimidine}$), 12.57 (bs, 1H, NH exchangeable with D_2O); anal. calcd for $C_{11}H_7N_3O_2$ (213.20): C, 61.97; H, 3.31; N, 19.71%; found: C, 61.95; H, 3.32; N, 19.65%.

(5-Oxo-5*H*-chromeno[4,3-*d*]pyrimidin-2-yl)cyanamide (**12**)

Crystallized from AcOH as white crystals; mp 200-201 ºC; yield (0.38 g, 53%); IR (KBr) ν/cm^{-1} 3461 (NH), 2259 (C≡N), 1734 (OC=O), 1609 (C=N), 1559 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.92 (bs, 1H, NH exchangeable with D_2O). 7.46-7.53 (m, 2H, Ar-H), 7.80 (t, 1H, *J* 7.8 Hz, H-8), 8.35 (d, 1H, *J* 7.2 Hz, H-10), 9.22 (s, 1H, H-4$_{pyrimidine}$); ^{13}C NMR (75 MHz, DMSO-d_6) 116.8 (C≡N), 117.4, 119.0, 124.5, 124.9, 125.1, 135.6, 154.3 (C6a), 158.5 (C-5 as C=O), 161.1 (C-2 as C=N), 161.8 (C-4 as C=N), 171.8 (C10b). MS (*m/z*, %) 238 (M$^+$, 83), 212 (13), 187 (30), 175 (77), 121 (99), 105 (20), 92 (55), 77 (34), 65 (49) and 57 (100); anal. calcd for $C_{12}H_6N_4O_2$ (238.21): C, 60.51; H, 2.54; N, 23.52%; found: C, 60.45; H, 2.38; N, 23.41%.

2-Thioxo-1,2-dihydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one (**13**)

Crystallized from AcOH/H_2O as white crystals; mp 246-247 ºC; yield (0.32 g, 46%); IR (KBr) ν/cm^{-1} 3261 (NH), 1701 (OC=O), 1633 (C=N), 1607 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20-7.87 (m, 3H, 2Ar-H and NH), 7.77 (t, 1H, *J* 7.8 Hz, Ar-H), 8.30 (d, 1H, *J* 7.8 Hz, H-10), 9.35 (s, 1H, H-4$_{pyrimidine}$); MS (*m/z*, %) 230 (M$^+$, 11), 214 (11), 173 (76), 149 (66), 121 (84), 105 (34), 92 (45), 77 (37), 65 (60) and 50 (100); anal. calcd for $C_{11}H_6N_2O_2S$ (230.25): C, 57.38; H, 2.63; N, 12.17; S, 13.93%; found: C, 57.27; H, 2.58; N, 12.13; S, 13.82%.

General procedure for the reaction of chromone-3-carboxamide (**1**) with *o*-phenylenediamine, 2-aminophenol and 2-aminothiophenol

A mixture of carboxamide **1** (0.57 g, 3 mmol) and *o*-phenylenediamine, 2-aminophenol and 2-aminothiophenol (3 mmol) in DMF (15 mL) was heated under reflux for 2 h. The crystalline products obtained during heating or after cooling were filtered off and recrystallized to give compounds **14**, **15** and **17**, respectively.

(3*Z*)-3-{[(2-Aminophenyl)amino]methylidene}chromane-2,4(3*H*)-dione (**14**)

Obtained during heating as yellow crystals, recrystallized from DMF; mp 219 ºC; yield (0.39 g, 46%); IR (KBr) ν/cm^{-1} 3407 (NH_2, NH), 3068 (CH$_{arom.}$), 1719 (OC=O), 1640 (C=O), 1558 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.30 (bs, 2H, NH_2 exchangeable with D_2O). 6.76 (t, 1H, *J* 7.8 Hz, Ar-H), 6.92 (d, 1H, *J* 6.9 Hz, Ar-H), 7.10 (t, 1H, *J* 7.5 Hz, Ar-H), 7.36-7.46 (m, 2H, Ar-H), 7.49 (d, 1H, *J* 7.8 Hz, Ar-H), 7.78 (t, 1H, *J* 7.5 Hz, H-7), 8.01 (d, 1H, *J* 7.2 Hz, H-5), 8.74 (d, 1H, *J* 12.6 Hz, CH$_{vinyl}$ exchanged to singlet with D_2O), 13.42 (d, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6) 97.9 (C3), 117.5, 117.8, 118.2, 119.9, 120.0, 124.1, 125.2, 128.1, 129.8, 134.7, 140.5, 154.3 (C8a), 155.8 (C$_{vinyl}$), 162.3 (C-2 as C=O), 179.9 (C-4 as C=O). MS (*m/z*, %) 281 (M + 1, 9), 280 (M$^+$, 48), 159 (25), 119 (100), 105 (9), 92 (13), 77 (11) and 65 (30); anal. calcd for $C_{16}H_{12}N_2O_3$ (280.29): C, 68.57; H, 4.32; N, 9.99%; found: C, 68.54; H, 4.24; N, 9.92%.

(3*Z*)-3-{[(2-Hydroxyphenyl)amino]methylidene}chromane-2,4(3*H*)-dione (**15**)

Obtained after cooling as yellow crystals, recrystallized from DMF/EtOH; mp 290-291 ºC; yield (0.35 g, 42%); IR (KBr) ν/cm^{-1} 3072 (br, NH, OH), 1716 (OC=O), 1629 (C=O), 1548 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.95 (t, 1H, Ar-H), 7.02 (d, 1H, *J* 7.8 Hz, Ar-H), 7.14 (t, 1H, *J* 7.8 Hz, Ar-H), 7.16-7.35 (m, 3H, Ar-H), 7.69 (d, 1H, H-8), 7.99 (d, 1H, *J* 7.8 Hz, H-5), 8.94 (d, 1H, *J* 14.1 Hz, CH$_{vinyl}$ exchanged to singlet with D_2O), 12.10 (d, 1H, OH exchangeable with D_2O), 13.75 (d, 1H, NH exchangeable with D_2O); anal. calcd for $C_{16}H_{11}NO_4$ (281.27): C, 68.33; H, 3.94; N, 4.98%; found: C, 68.41; H, 3.69; N, 4.75%.

3,3'-{Ethane-1,2-diylbis[iminomethylylidene]}bis(2*H*-chromene-2,4(3*H*)-dione) (**18**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and ethylenediamine (0.2 mL, 3 mmol), in absolute ethanol (15 mL), was heated under reflux for 30 min. The white crystals obtained during heating were filtered off and recrystallized from DMF to give compound **18** as white crystals; mp > 300 ºC; yield (0.39 g, 32%); IR (KBr) ν/cm^{-1} 3314 (2NH), 3068 (CH$_{arom.}$), 2925, 2865 (CH$_{aliph.}$), 1748 (OC=O), 1665 (C=O), 1602 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 4H, 2CH$_2$), 5.29 (s, 2H, 2 NH), 7.29-7.31 (m, 4H, Ar-H), 7.60-7.68 (m, 2H, Ar-H), 7.93-7.98 (m, 2H, Ar-H), 8.45 (d, 2H, *J* 12.6 Hz, 2CH$_{vinyl}$ exchanged to singlet with D_2O). MS (*m/z*, %) 404 (M$^+$, 25), 230 (13), 215 (24), 203 (46), 174 (41), 149 (100), 121 (71), 105 (30), 92 (30), 77 (35) and 64 (80); anal. calcd for $C_{22}H_{16}N_2O_6$ (404.37): C, 65.34; H, 3.99; N, 6.93%; found: C, 65.28; H, 3.78; N, 6.85%.

2-Amino-5-(2-hydroxybenzoyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (**19**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and malononitrile (0.2 g, 3 mmol), in absolute ethanol (15 mL) containing two drops of piperidine was heated under reflux for 30 min. The white crystals obtained during heating were filtered off and recrystallized from DMF/H_2O to give compound **19** as white crystals; mp > 300 ºC; yield (0.52 g, 68%); IR (KBr) ν/cm^{-1} 3382, 3314, 3138 (NH_2, NH, OH), 2222 (C≡N), 1654 ($C{=}O_{pyridone}$), 1609 ($C{=}O_{hydrogen\ bonded}$), 1552 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46 (t, 1H, *J* 6.9 Hz, Ar-H), 7.58 (d, 1H, *J* 7.5 Hz, Ar-H), 7.81-7.87 (m, 2H, 1Ar-H and NH), 8.12 (t, 1H, *J* 6.6 Hz, Ar-H), 8.42 (bs, 1H, NH exchangeable with D_2O), 8.64 (s, 1H, NH), 8.81 (s, 1H, H-$4_{pyridine}$); ^{13}C NMR (75 MHz, DMSO-d_6) 89.8 (C-$5_{pyridine}$), 115.5 (C≡N), 118.0, 121.1, 124.9, 125.9, 135.4, 137.9, 144.3, 154.5, 161.5 (C-$6_{pyridine}$), 168.5 (C=O), 174.0 (C=O); MS (*m/z*, %) 256 (M + 1, 7), 255 (M$^+$, 38), 237 (100), 210 (25), 121 (36), 105 (15), 92 (17), 77 (15) and 64 (29); anal. calcd for $C_{13}H_9N_3O_3$ (255.23): C, 61.18; H, 3.55; N, 16.46%; found: C, 61.19; H, 3.65; N, 16.64%.

2-Amino-5-(2-hydroxybenzoyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**20**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and cyanoacetamide (0.25 g, 3 mmol), in absolute ethanol (15 mL) containing two drops of piperidine, was heated under reflux for 30 min. The white crystals obtained during heating were filtered off and recrystallized from DMF/H_2O to give compound **20** as white crystals; mp > 300 ºC; yield (0.43 g, 53%); IR (KBr) ν/cm^{-1} 3424, 3390, 3203 ($2NH_2$, NH, OH), 3064 ($CH_{arom.}$), 1697 ($C{=}O_{amide}$), 1654 ($C{=}O_{pyridone}$), 1636 ($C{=}O_{hydrogen\ bonded}$), 1624 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26 (d, 1H, *J* 6.3 Hz, Ar-H), 7.45-7.52 (m, 3H, 2Ar-H and 1H of NH_2), 7.78 (t, 1H, *J* 7.2 Hz, Ar-H), 7.89 (bs, 2H, NH_2 exchangeable with D_2O), 8.62 (d, 1H, *J* 8.1 Hz, Ar-H), 8.66 (bs, 2H, NH_2 exchangeable with D_2O), 8.79 (s, 1H, H-$4_{pyridine}$), 13.30 (bs, 1H, OH exchangeable with D_2O); anal. calcd for $C_{13}H_{11}N_3O_4$ (273.25): C, 57.14; H, 4.06; N, 15.38%; found: C, 56.92; H, 4.09; N, 15.16%.

4-Hydroxy-3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]-2*H*-chromen-2-one (**21**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and acetophenone (0.36 g, 3 mmol), in ethanolic potassium hydroxide solution (2%, 20 mL), was heated under reflux for 2 h. After cooling, the reaction mixture was neutralized with dil. HCl. The white precipitate so formed was filtered off and crystallized from acetic acid to give compound **21** as white crystals; mp 238-239 ºC (239-240 ºC;[16] yield (0.48 g, 55%).

5-[(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)methylidene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**22**)

A mixture of carboxamide **1** (0.57 g, 3 mmol) and thiobarbituric acid (0.43 g, 3 mmol), in ethanolic potassium hydroxide solution (2%, 20 mL), was heated under reflux for 2 h. After cooling, the reaction mixture was neutralized with dil. HCl. The white precipitate so formed was filtered off and crystallized from DMF to give compound **22** as yellow crystals; mp > 300 ºC; yield (0.55 g, 58%); IR (KBr) ν/cm^{-1} 3506, 3420 (2NH, OH), 3048 ($CH_{arom.}$), 1761, 1713 (3C=O), 1527 (C=C), 1254 (C=S); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.60 (t, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.86 (t, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 8.80 (s, 1H, CH_{vinyl}), 12.29 (bs, 2H, 2NH exchangeable with D_2O). MS (*m/z*, %) 316 (M$^+$, 9), 258 (13), 207 (22), 166 (16), 138 (24), 141 (14), 105 (23), 91 (63), 84 (100), 77 (11) and 65 (30); anal. calcd for $C_{14}H_8N_2O_5S$ (316.29): C, 53.16; H, 2.55; N, 8.86; S, 10.14%; found: C, 53.02; H, 2.34; N, 8.38; S, 9.88%.

Supplementary Information

Data spectra and spectra of synthesized compounds are available free of charge at http://jbcs.sbq.org.br as PDF file.

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Article

Ring Transformation of Chromone-3-Carboxamide under Nucleophilic Conditions

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Chromeno[4,3-*c*]pyrazol-4(1*H*)-one (**6**): IR (KBr) ν/cm^{-1} 3217 (NH), 3054 ($CH_{arom.}$), 1735 (OC=O) and 1603 (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.61 (t, 1H, *J* 7.6 Hz, H-8), 7.79 (d, 1H, *J* 8.2 Hz, H-6), 7.93 (t, 1H, *J* 7.6 Hz, H-7), 8.16 (d, 1H, *J* 8.2 Hz, H-9), 9.12 (s, 1H, H-3), 13.23 ppm (bs, 1H, NH exchangeable with D_2O).

1-Phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (**7**): IR (KBr) ν/cm^{-1} 3117 ($CH_{arom.}$), 1751 (OC=O), 1614 (C=N), 1526 (C=C).

Chromeno[3,4-*d*]isoxazol-4(4*H*)-one (**10**): IR (KBr) ν/cm^{-1}) 3037 ($CH_{arom.}$), 1728 (OC=O), 1621 (C=N), 1591 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.37-7.56 (m, 2H, Ar-H), 7.65 (d, 1H, *J* 6.6 Hz, Ar-H), 7.87 7.65 (d, 1H, *J* 6.9 Hz, Ar-H), 8.88 (s, 1H, H-3$_{isoxazole}$).

3-(1,3-Benzothiazol-2-yl)-4-hydroxycoumarin (**17**): obtained after cooling as yellow crystals, recrystallized from ethanol; mp 281-282 ºC (279-282 ºC);[1] yield (0.32 g, 36%); IR (KBr) ν/cm^{-1} 3334 (OH), 3064 ($CH_{arom.}$), 1667 (OC=O), 1618 (C=N), 1604 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.86 (d, 1H, Ar-H), 7.00 (t, 1H, Ar-H), 7.27-7.44 (m, 2H, Ar-H), 7.58-7.63 (m, 2H, Ar-H), 7.94 (d, 1H, H-8), 8.13 (d, 1H, *J* 6.6 Hz, Ar-H), 9.01 (bs, 1H, OH exchangeable with D_2O).

4-Hydroxy-3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]-2*H*-chromen-2-one (**21**): IR (KBr) ν/cm^{-1} 3081 ($CH_{arom.}$), 1714 (OC=O), 1654 (C=O), 1607 (C=C); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.11-8.49 (m, 7H, Ar-H), 8.62 (d, 1H, *J* 8.6 Hz, Ar-H), 8.73 (d, 1H, *J* 8.0 Hz, Ar-H), 8.97 (d, 1H, *J* 15.2 Hz, $CH_{olefinic}$), 9.50 (d, 1H, *J* 14.8 Hz, $CH_{olefinic}$), 12.97 (bs, 1H, OH exchangeable with D_2O).

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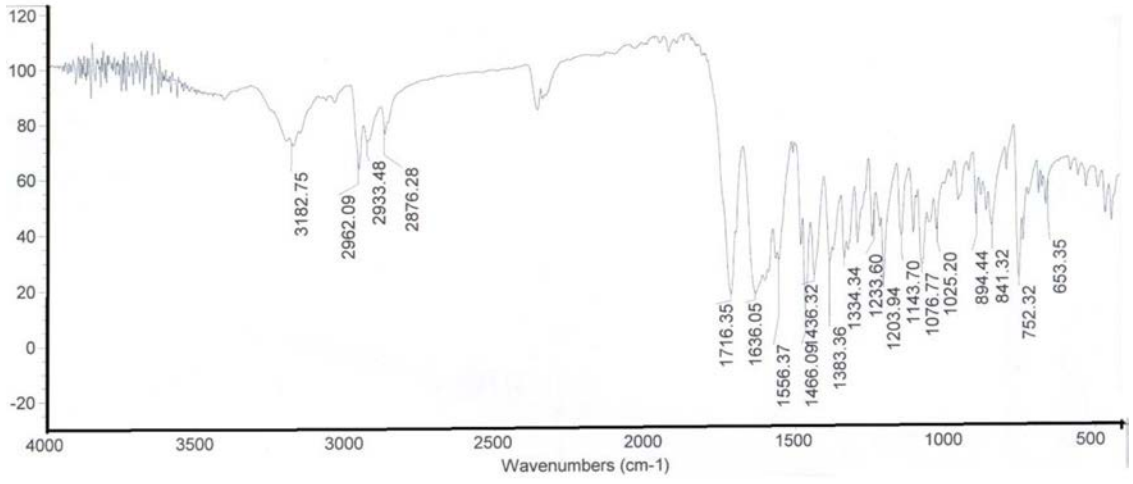

Figure S1. IR spectrum of compound **2**.

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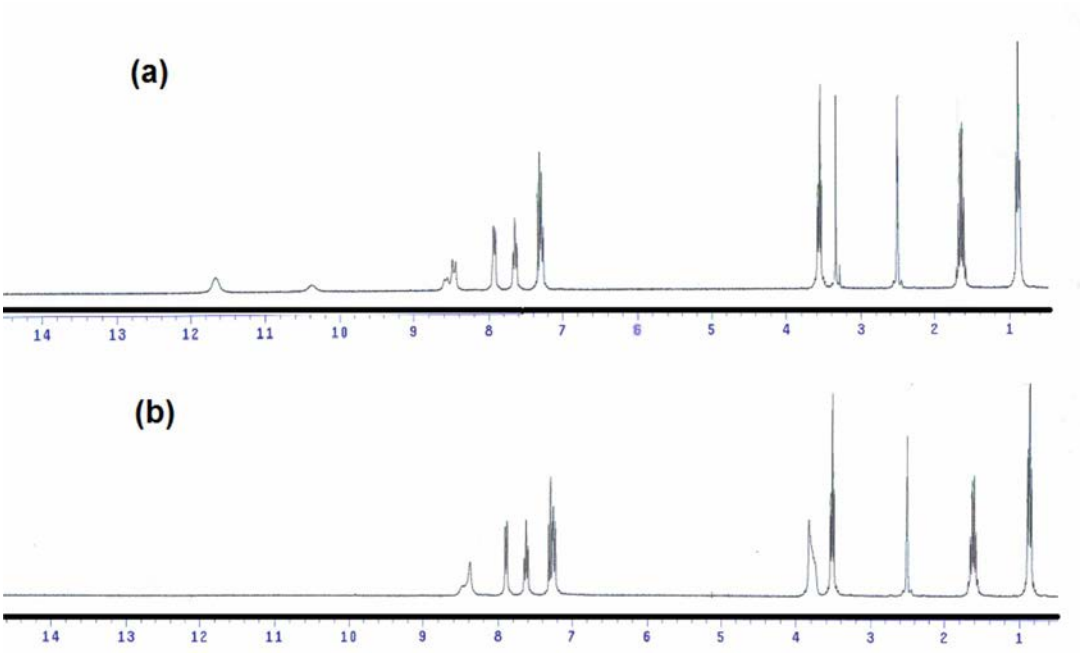

Figure S2. ^{1}H NMR spectrum of compound **2** in DMSO-d_6 (a) and DMSO-D_2O (b).

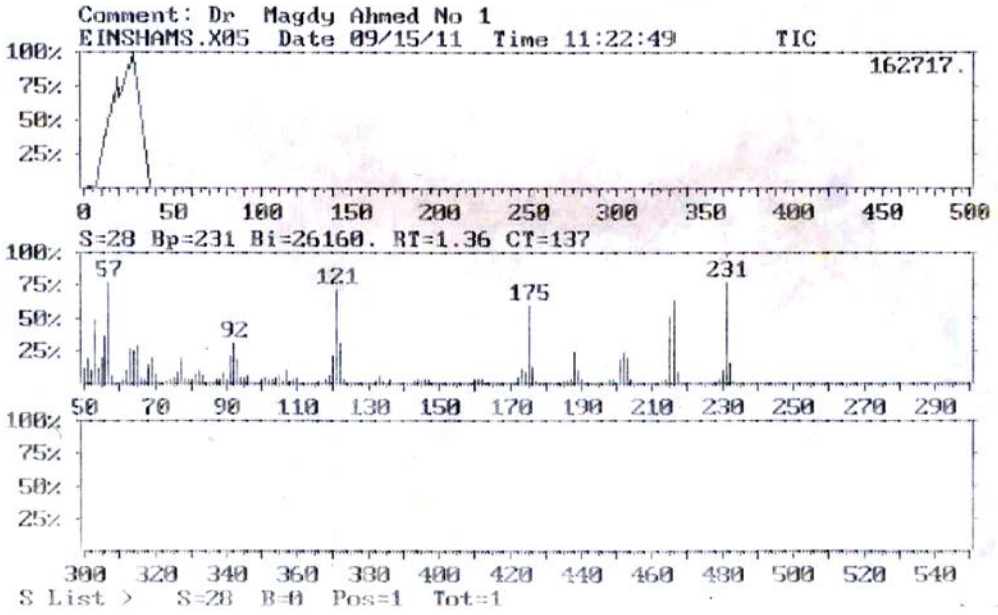

Figure S3. Mass spectrum of compound **2**.

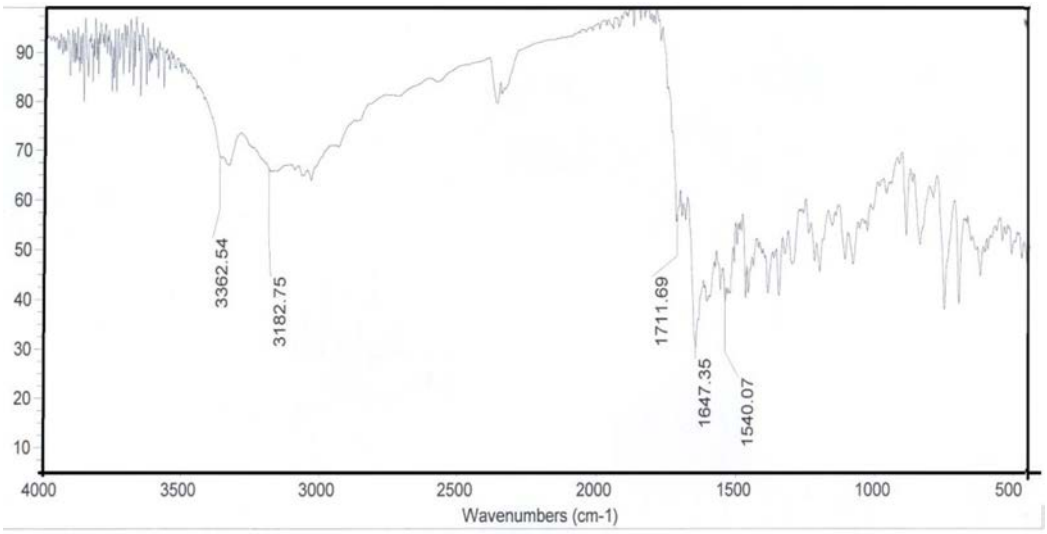

Figure S4. IR spectrum of compound **3**.

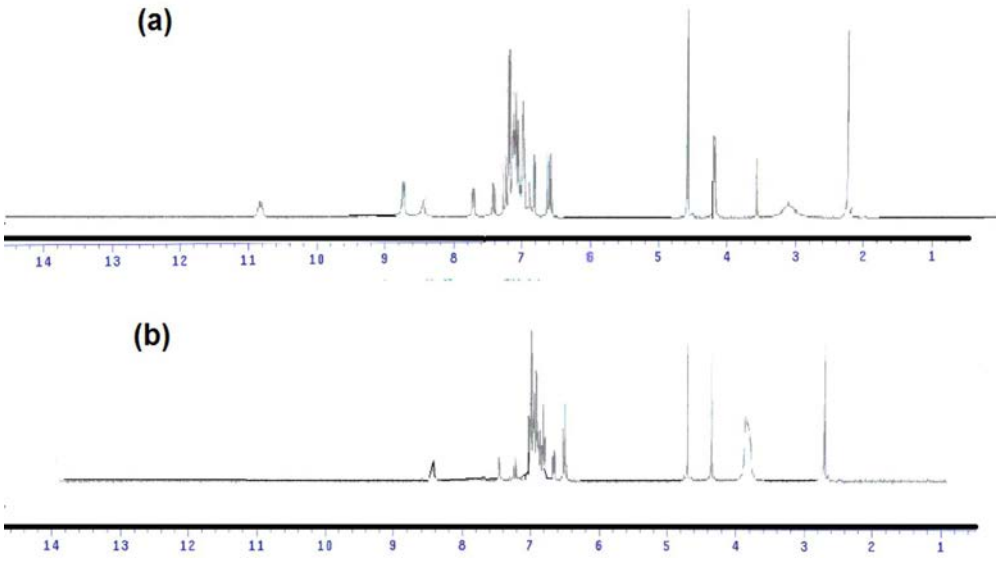

Figure S5. ^{1}H NMR spectra of compound **3** in DMSO-d_6 (a) and DMSO-D_2O (b).

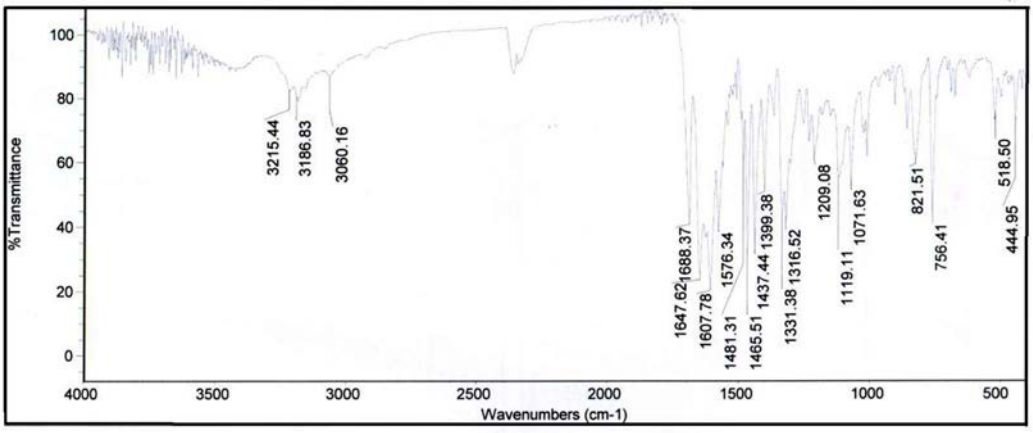

Figure S6. IR spectrum of compound **4**.

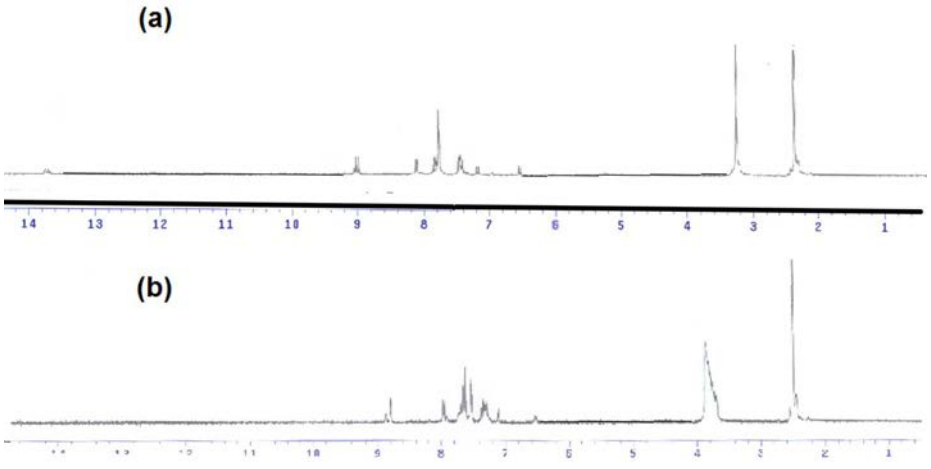

Figure S7. ^{1}H NMR spectrum of compound **4** in DMSO-d_6 (a) and DMSO-D_2O (b).

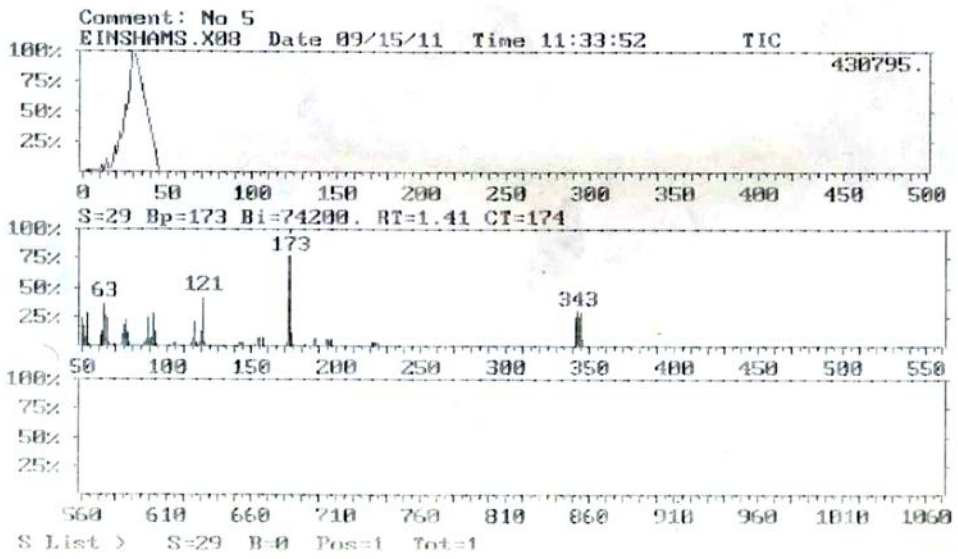

Figure S8. Mass spectrum of compound **4**.

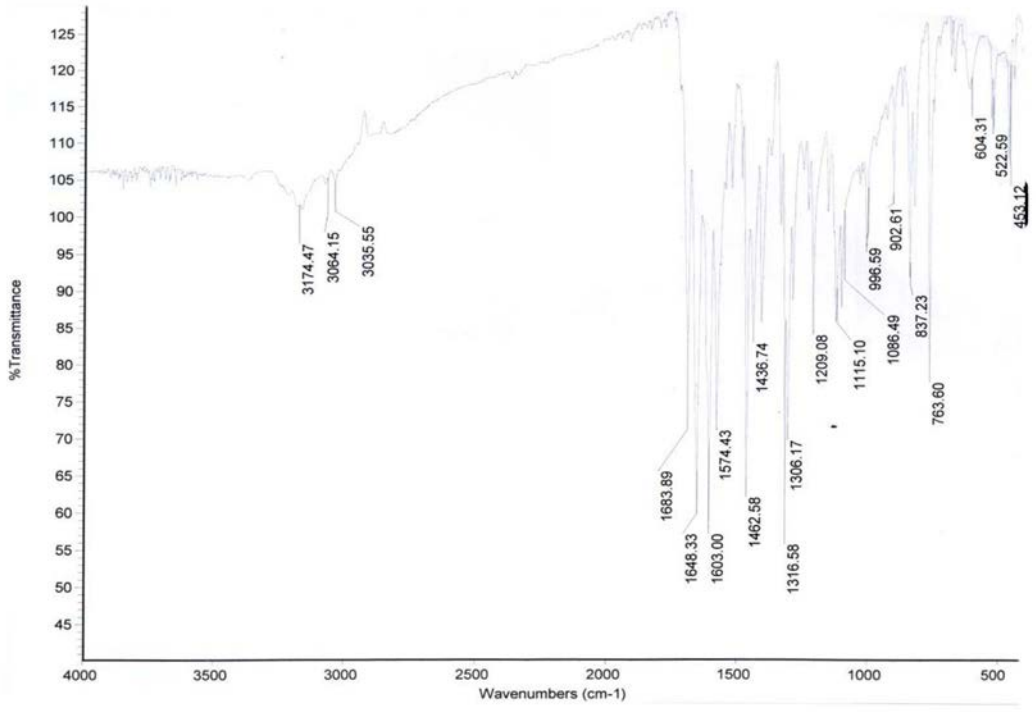

Figure S9. IR spectrum of compound **5**.

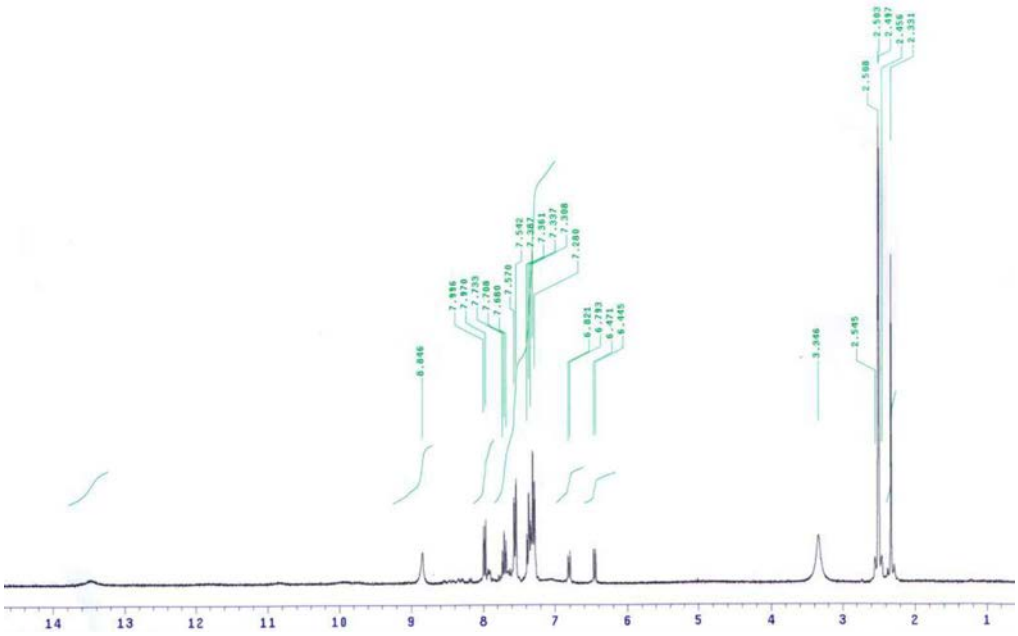

Figure S10. [1]H NMR spectrum of compound **5** in DMSO-d_6.

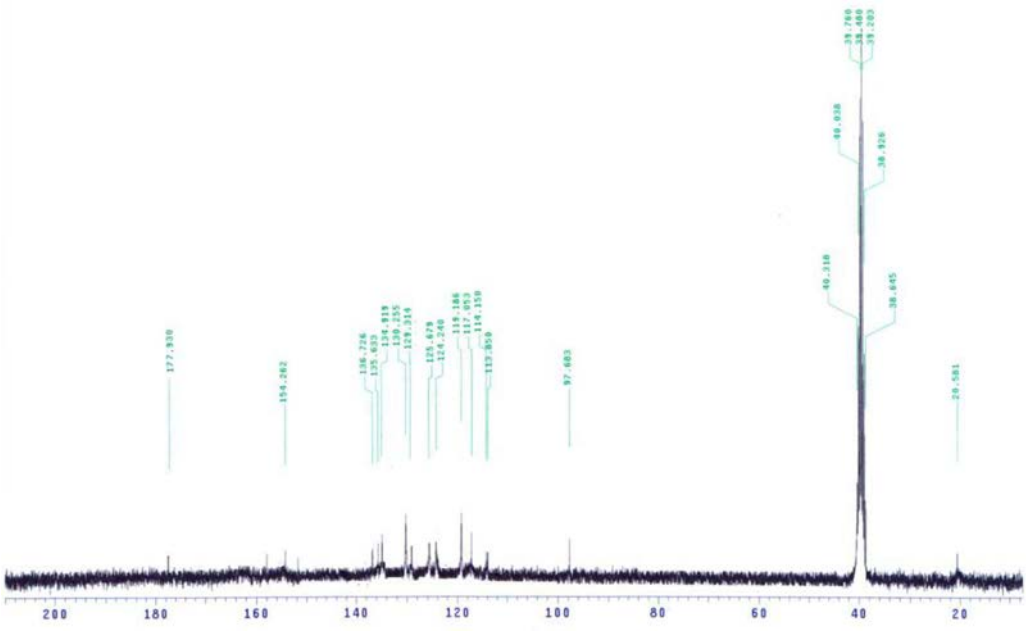

Figure S11. [13]C NMR spectrum of compound **5** in DMSO-d_6.

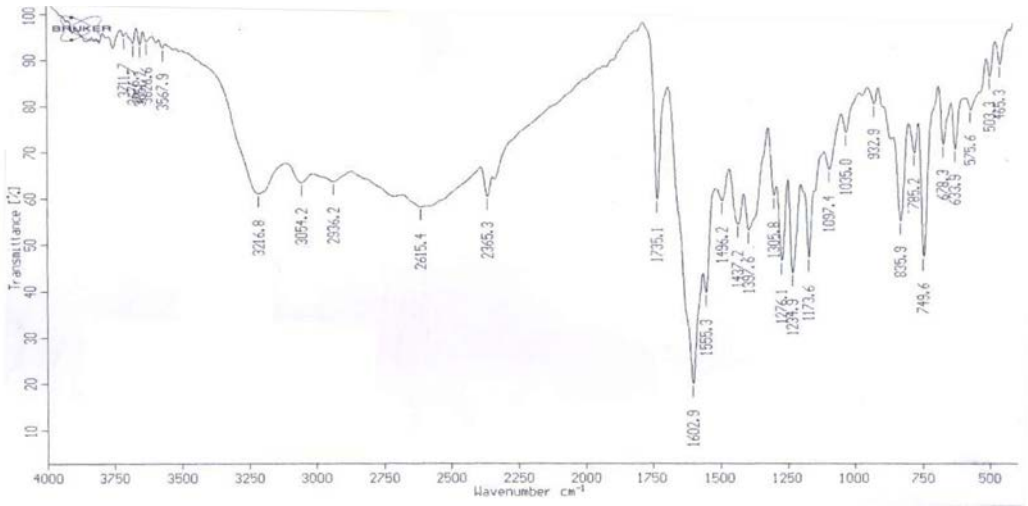

Figure S12. IR spectrum of compound **6**.

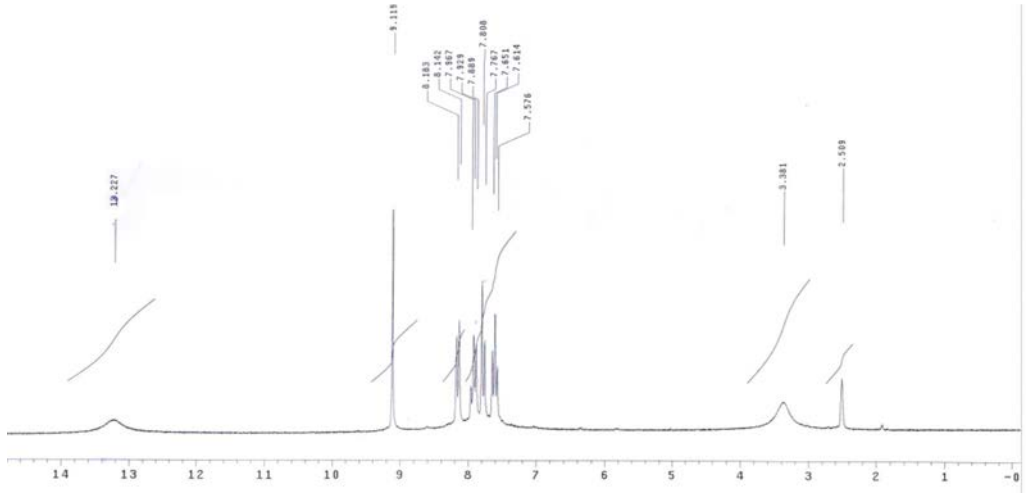

Figure S13. ^{1}H NMR spectrum of compound **6** in DMSO-d_6.

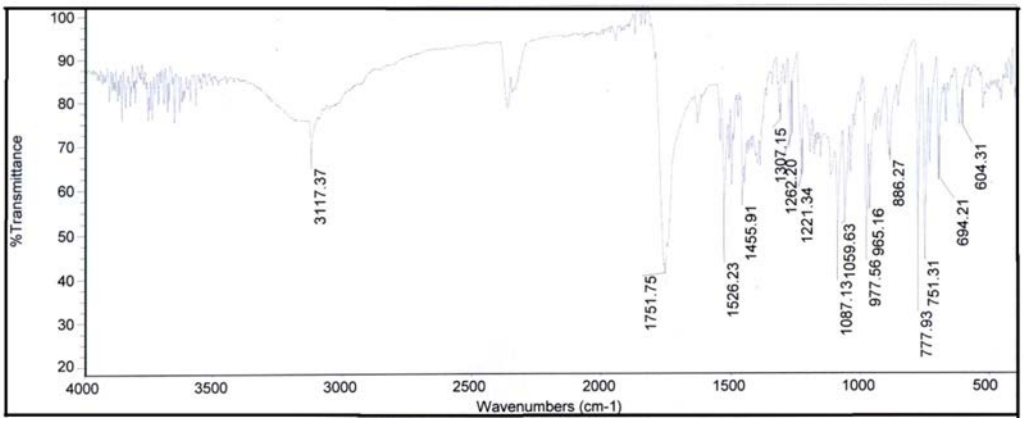

Figure S14. IR spectrum of compound **7**.

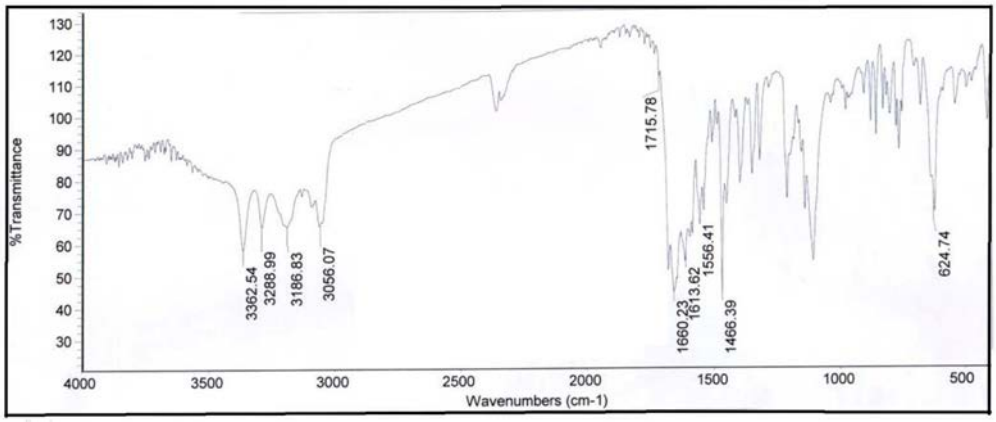

Figure S15. IR spectrum of compound **9**.

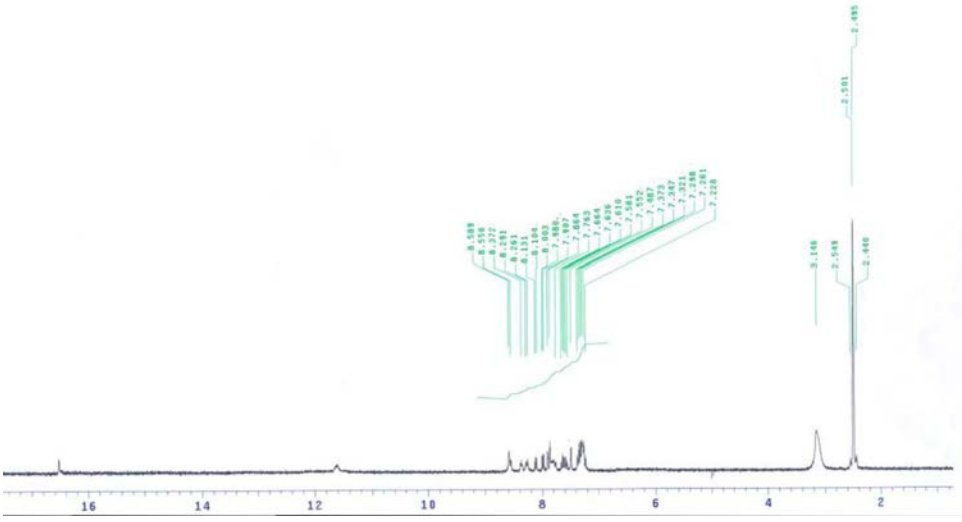

Figure S16. ^{1}H NMR spectrum of compound **9** in DMSO-d_6.

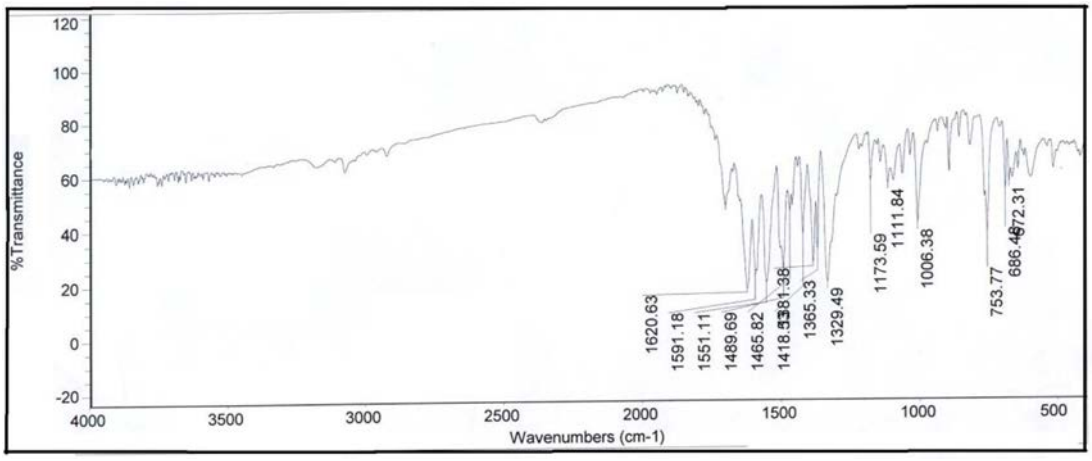

Figure S17. IR spectrum of compound **10**.

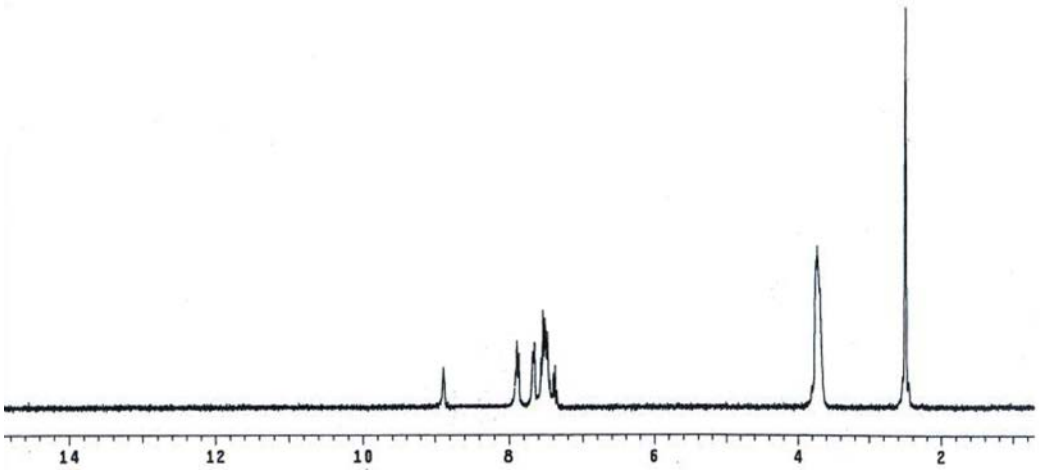

Figure S18. [1]H NMR spectrum of compound **10** in DMSO-d_6.

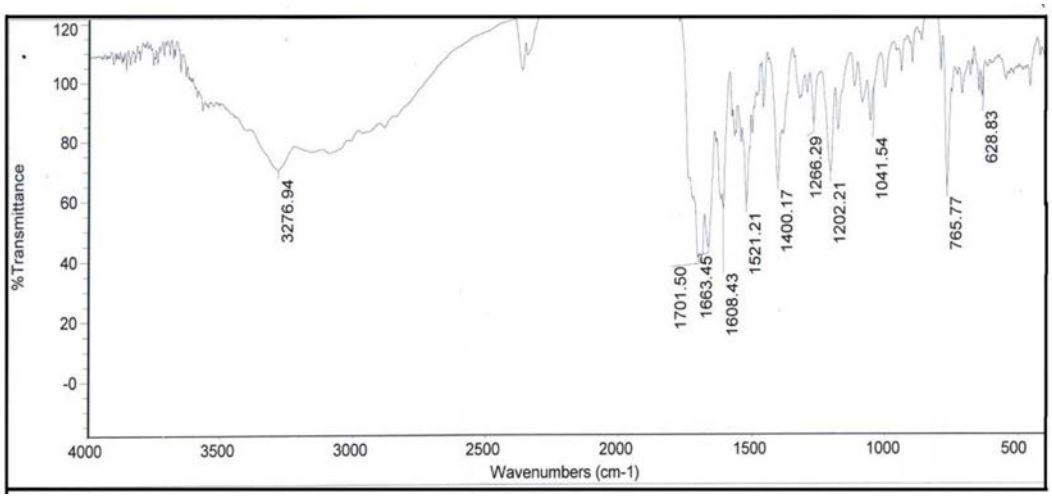

Figure S19. IR spectrum of compound **11**.

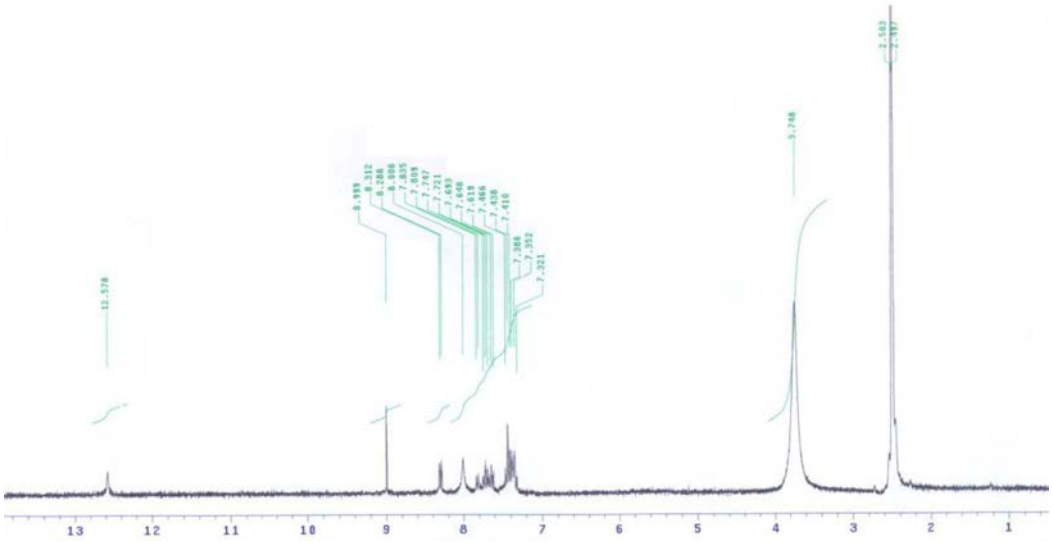

Figure S20. [1]H NMR spectrum of compound **11** in DMSO-d_6.

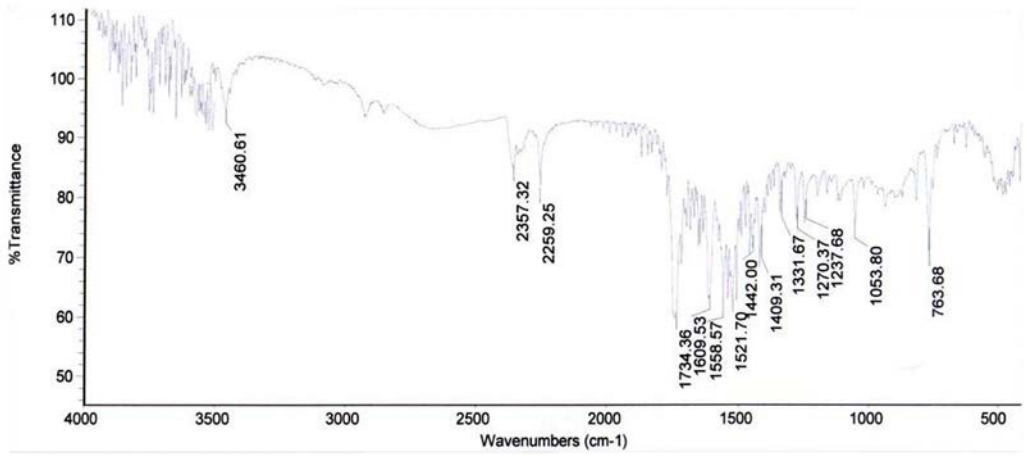

Figure S21. IR spectrum of compound **12**.

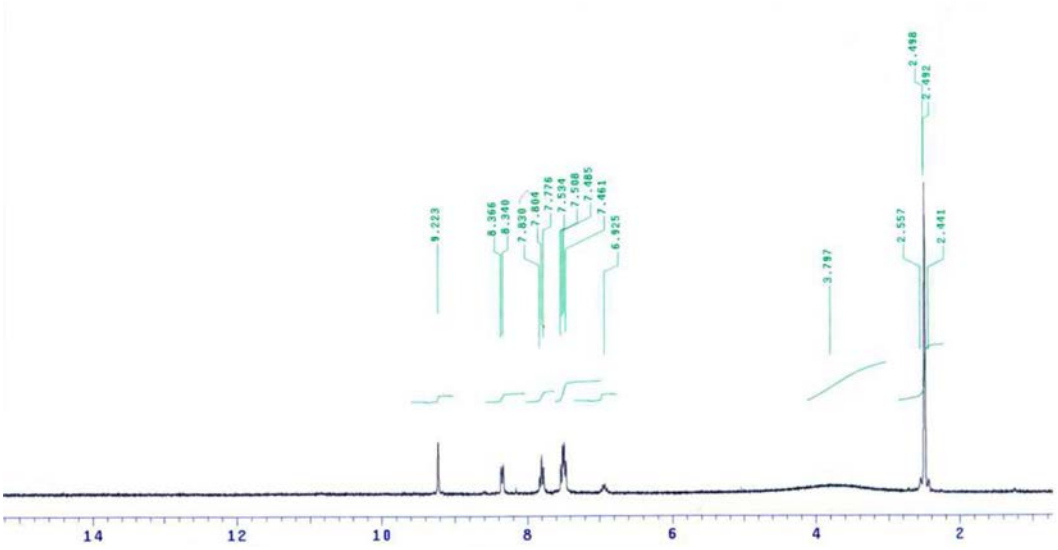

Figure S22. ^{1}H NMR spectrum of compound **12** in DMSO-d_6.

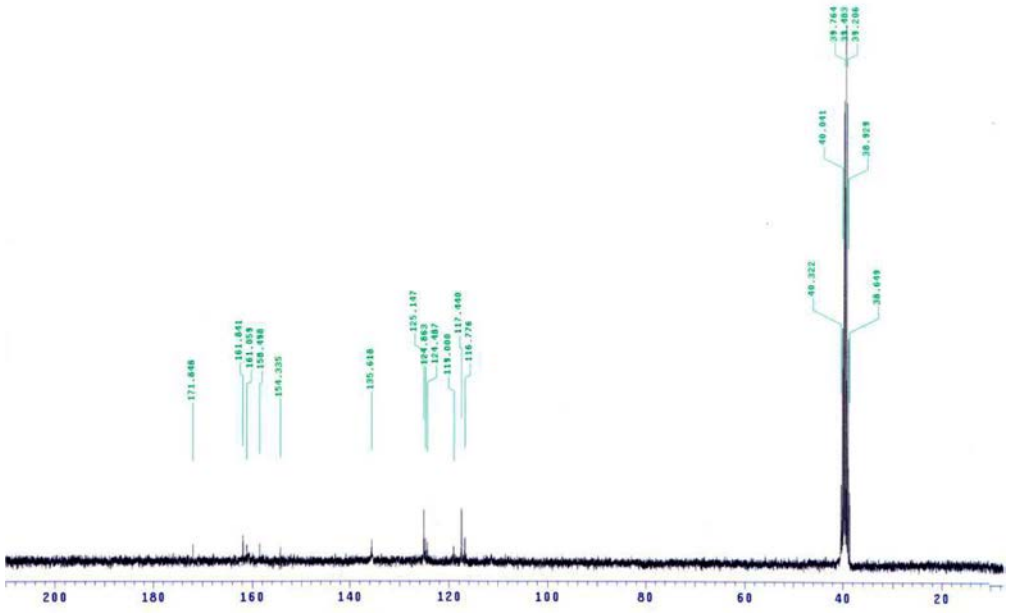

Figure S23. ^{13}C NMR spectrum of compound **12** in DMSO-d_6.

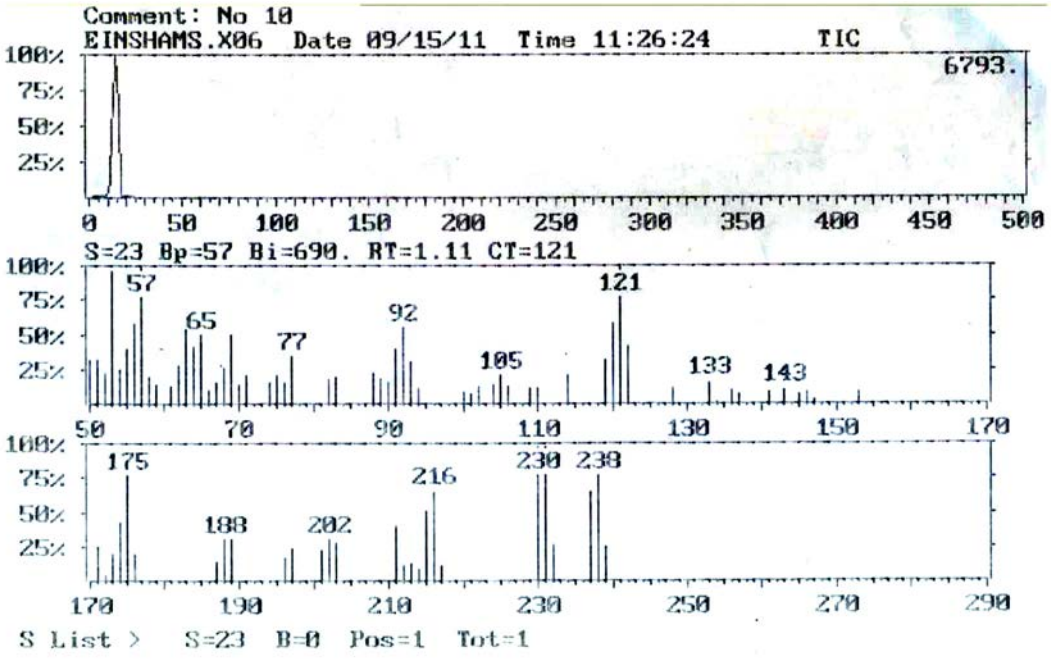

Figure S24. Mass spectrum of compound **12**.

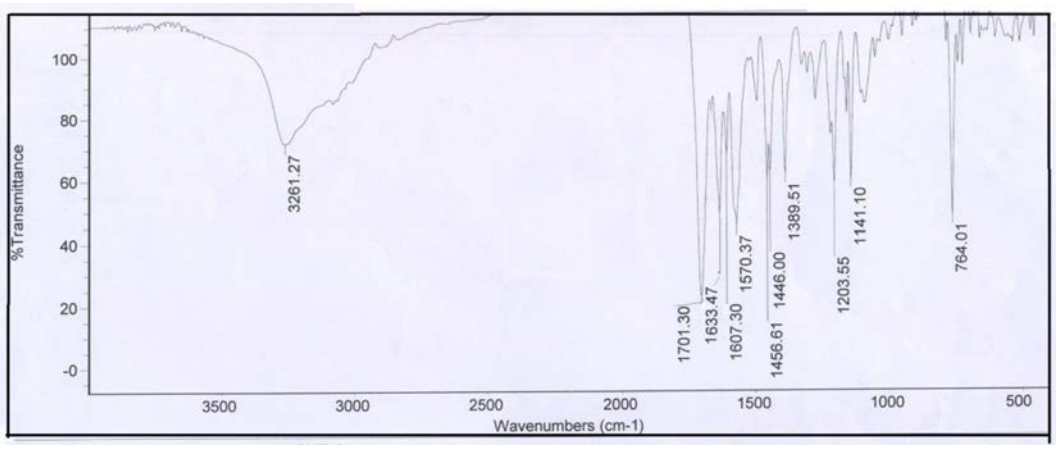

Figure S25. IR spectrum of compound **13**.

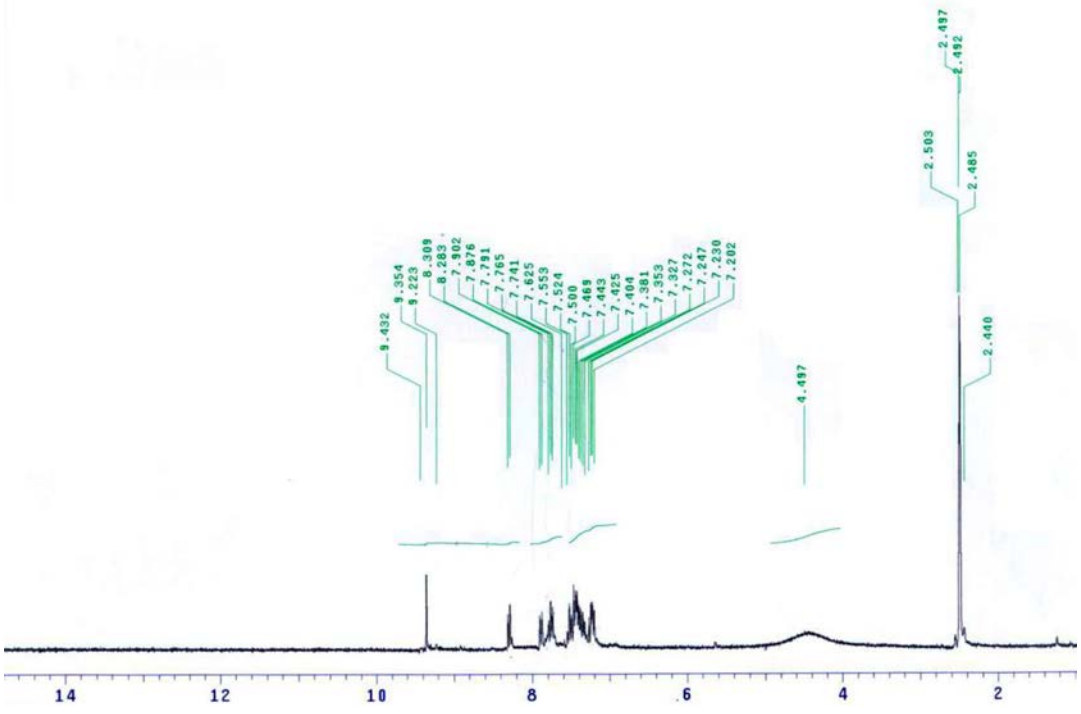

Figure S26. ^{1}H NMR spectrum of compound **13** in DMSO-d_6.

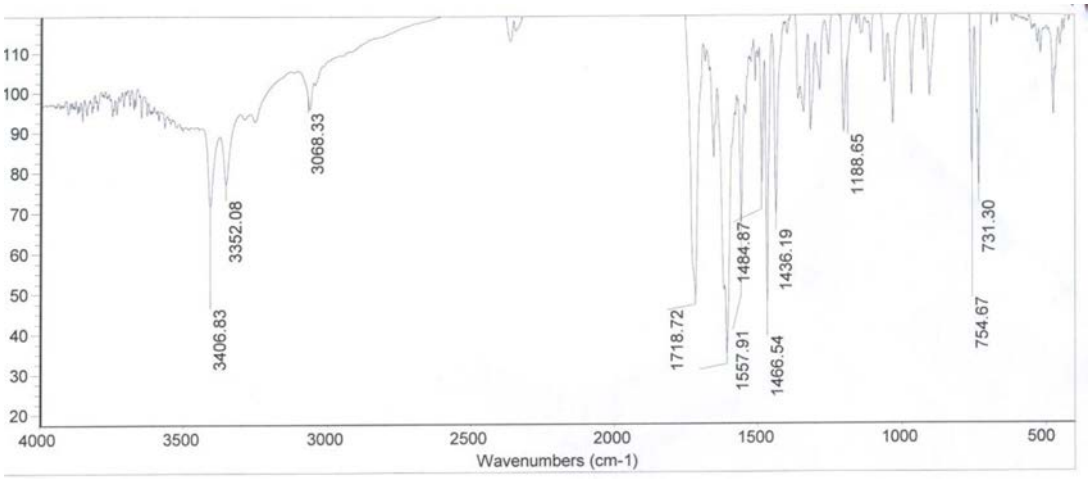

Figure S27. IR spectrum of compound **14**.

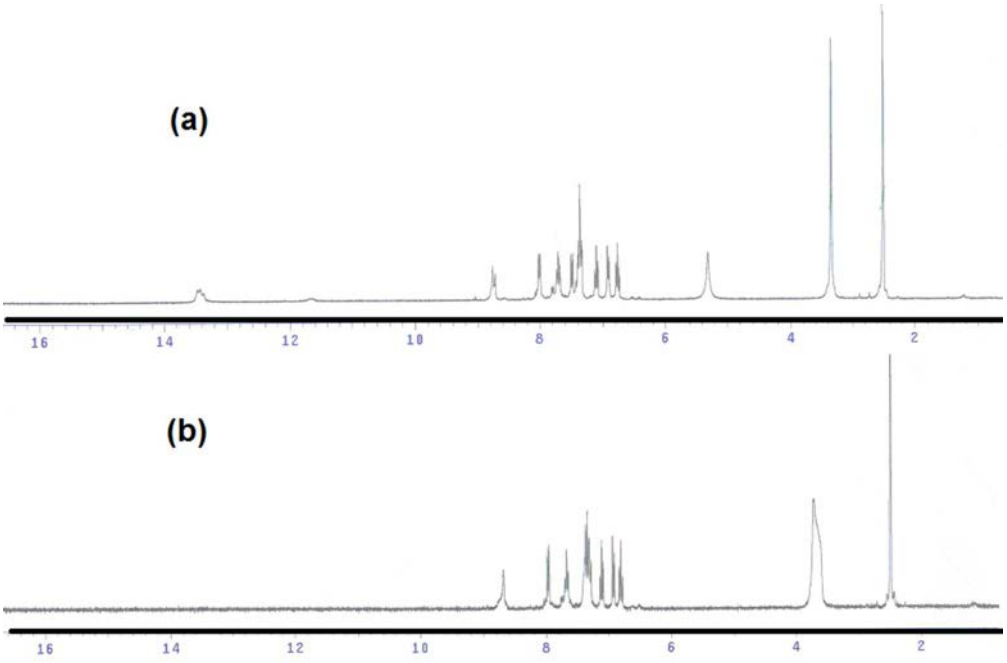

Figure S28. ^{1}H NMR spectra of compound **14** in DMSO-d_6 (a) and DMSO-D_2O (b).

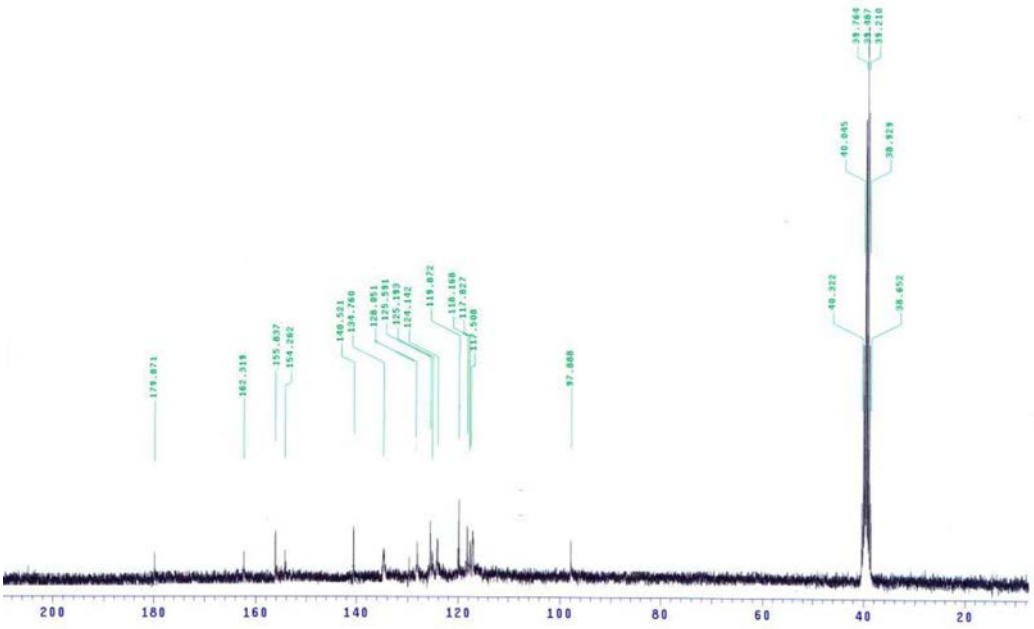

Figure S29. ^{13}C NMR spectrum of compound **14** in DMSO-d_6.

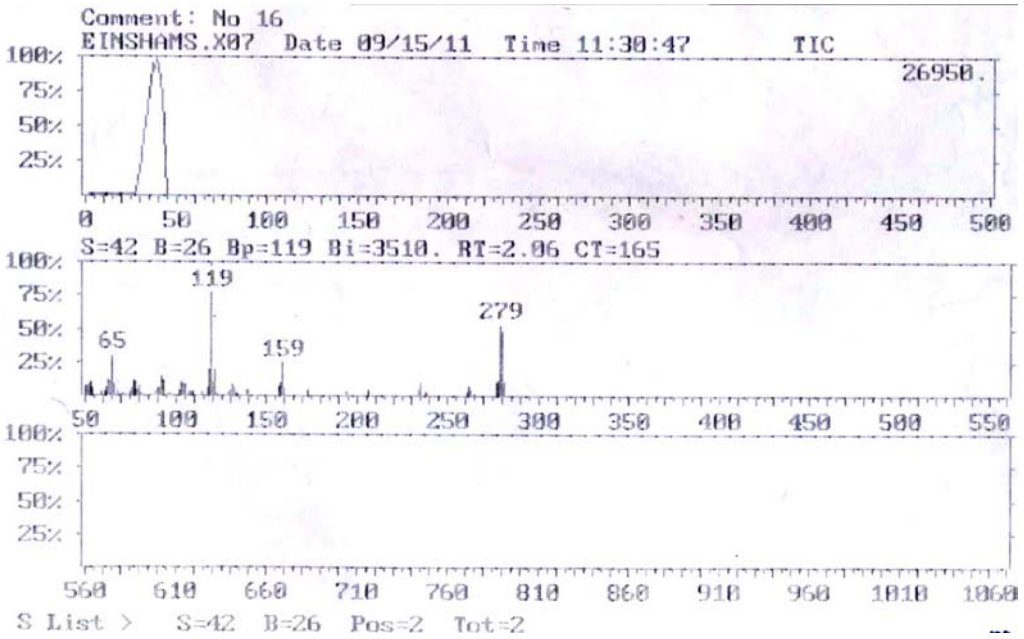

Figure S30. Mass spectrum of compound **14**.

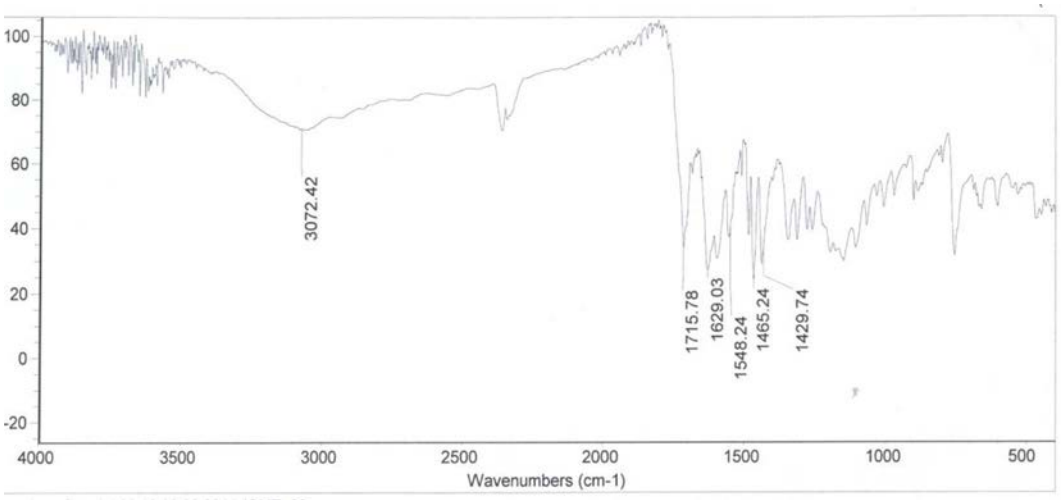

Figure S31. IR spectrum of compound **15**.

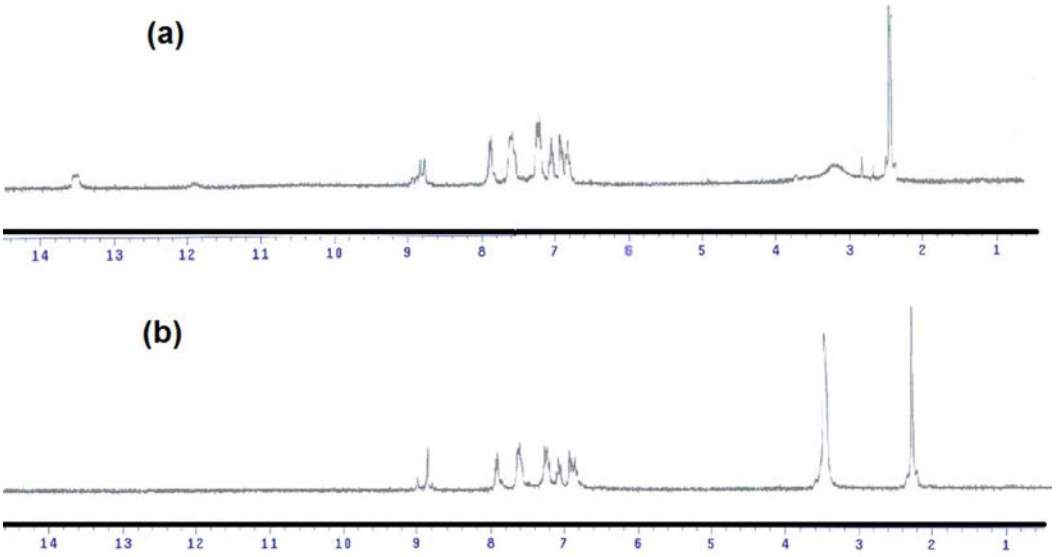

Figure S32. ^{1}H NMR spectra of compound **15** in DMSO-d_6 (a) and DMSO-D_2O (b).

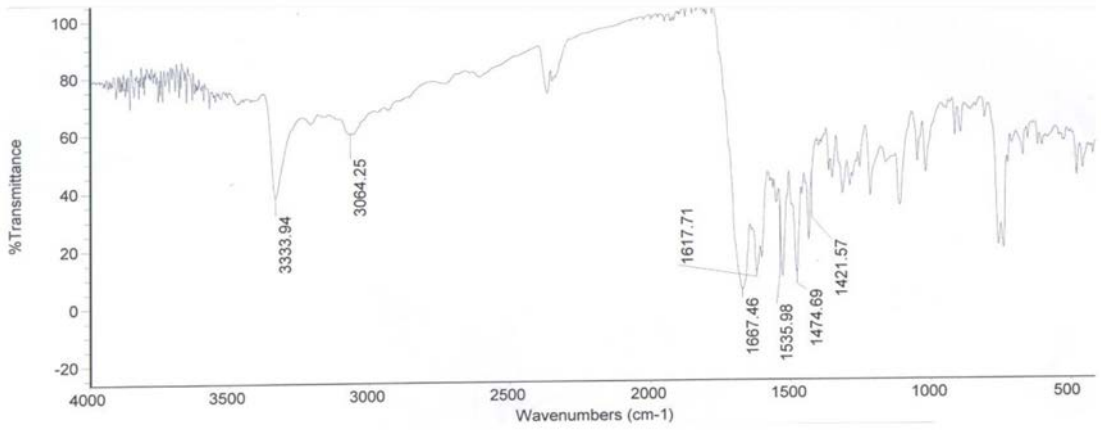

Figure S33. IR spectrum of compound **17**.

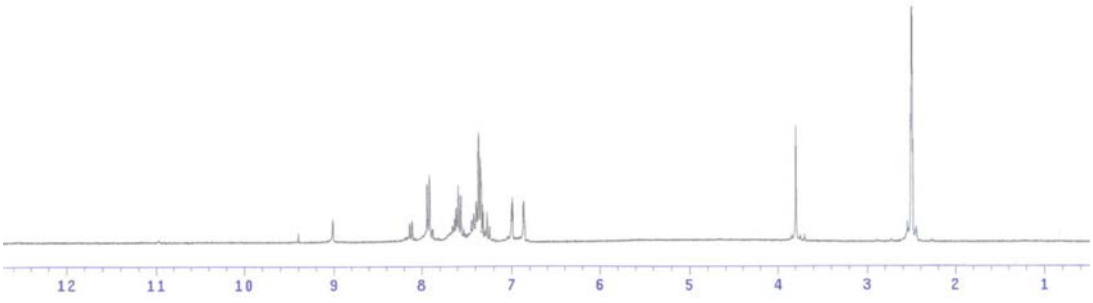

Figure S34. ^{1}H NMR spectra of compound **17** in DMSO-d_6.

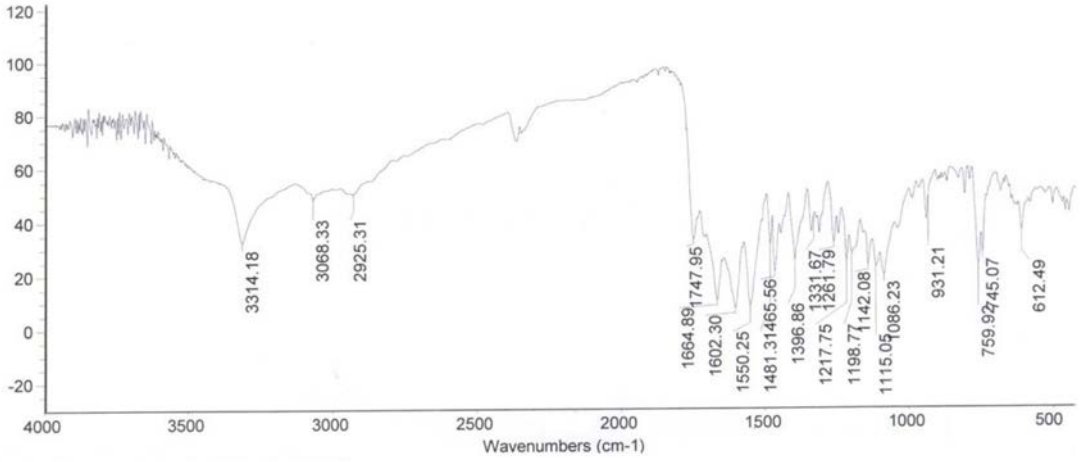

Figure S35. IR spectrum of compound **18**.

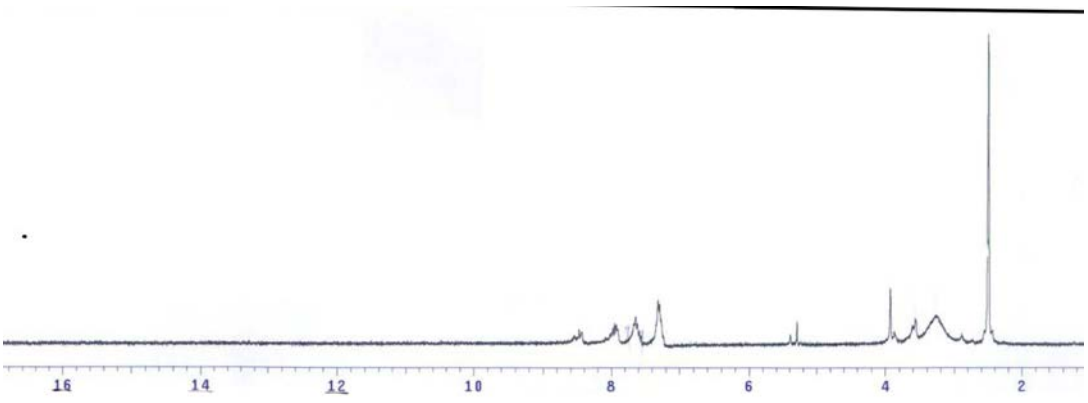

Figure S36. [1]H NMR spectra of compound **18** in DMSO-d_6.

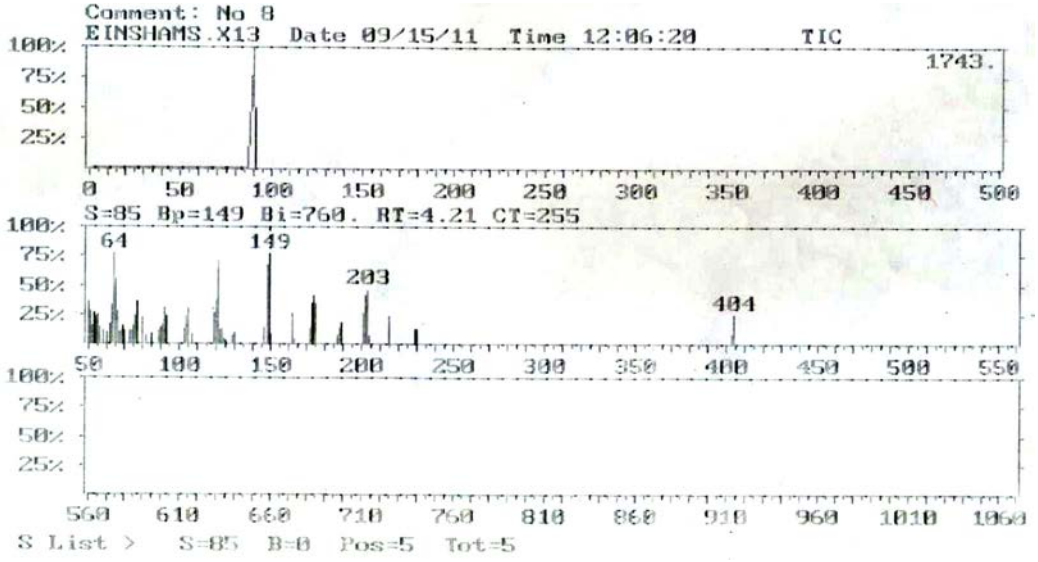

Figure S37. Mass spectrum of compound **18**.

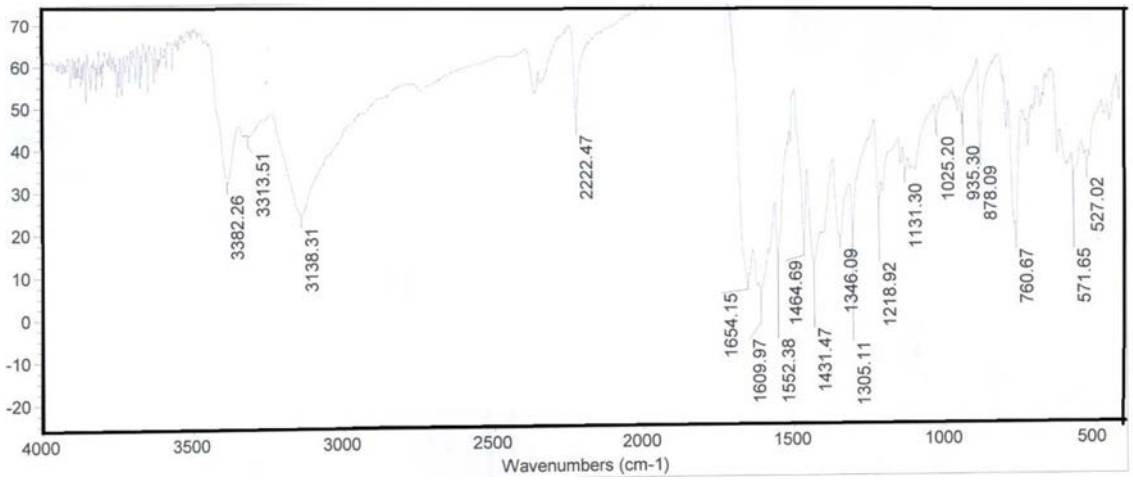

Figure S38. IR spectrum of compound **19**.

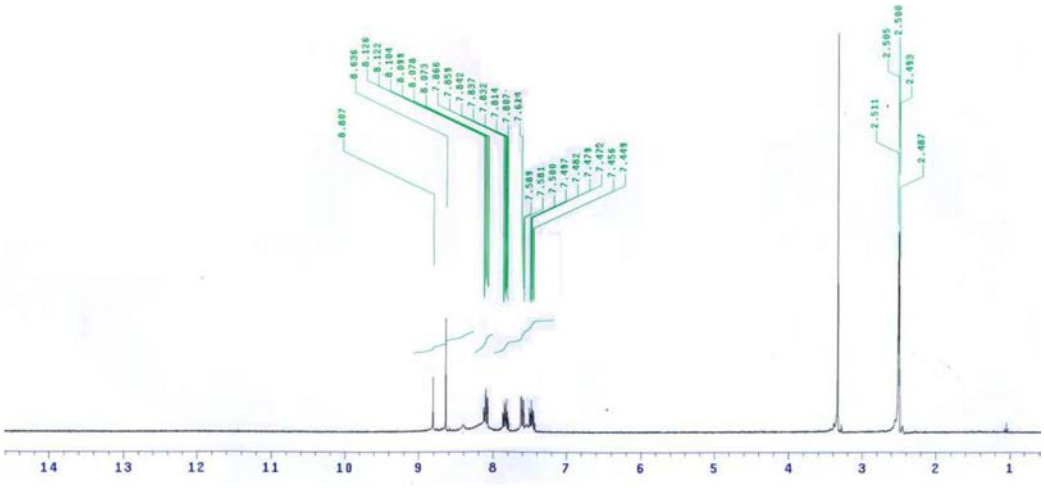

Figure S39. ^{1}H NMR spectrum of compound **19** in DMSO-d_6.

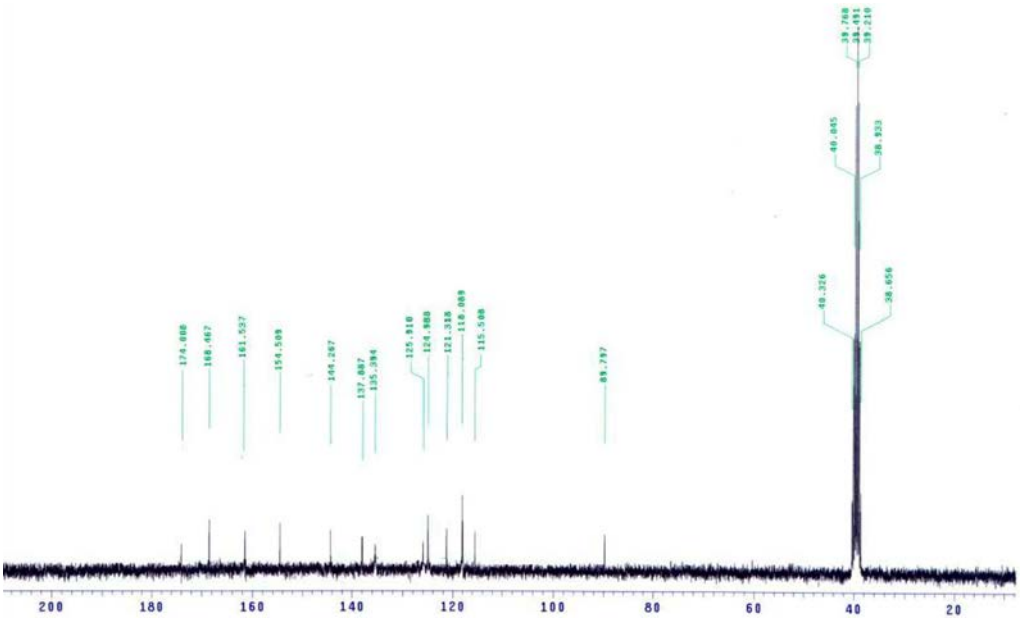

Figure S40. ^{13}C NMR spectrum of compound **19** in DMSO-d_6.

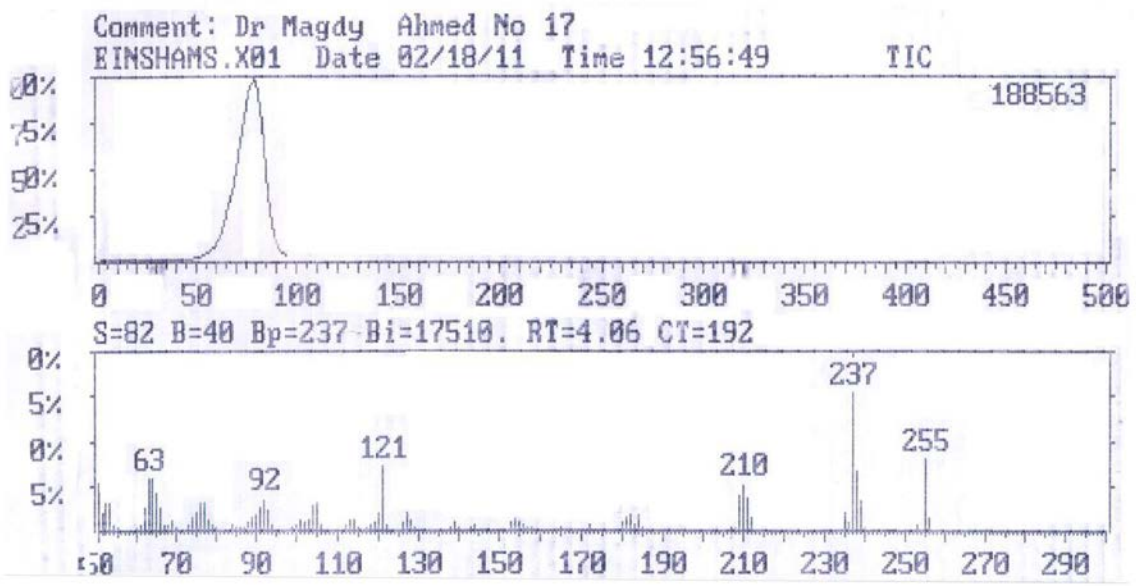

Figure S41. Mass spectrum of compound **19**.

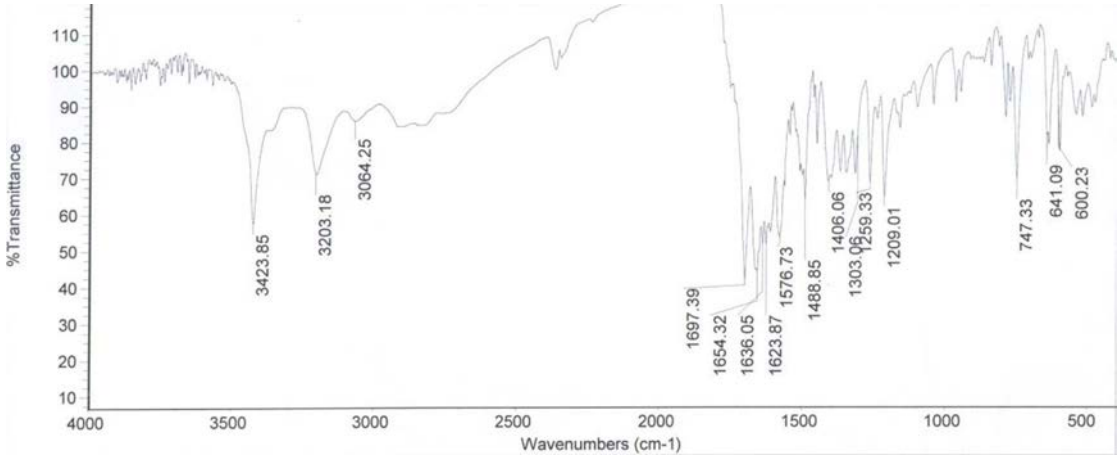

Figure S42. IR spectrum of compound **20**.

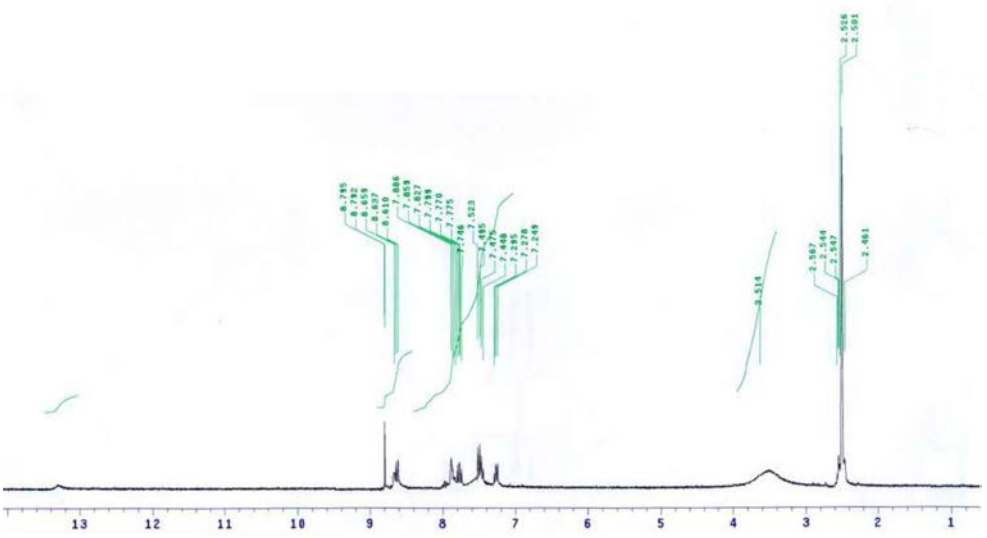

Figure S43. ^{1}H NMR spectrum of compound **20** in DMSO-d_6.

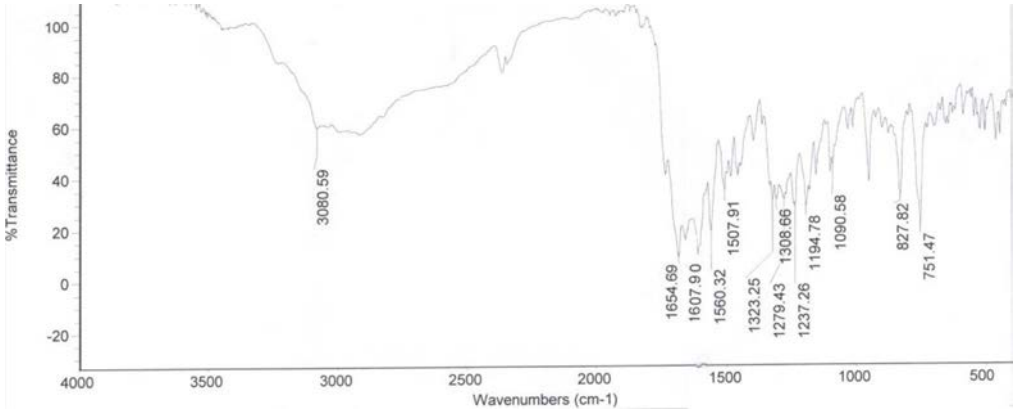

Figure S44. IR spectrum of compound **21**.

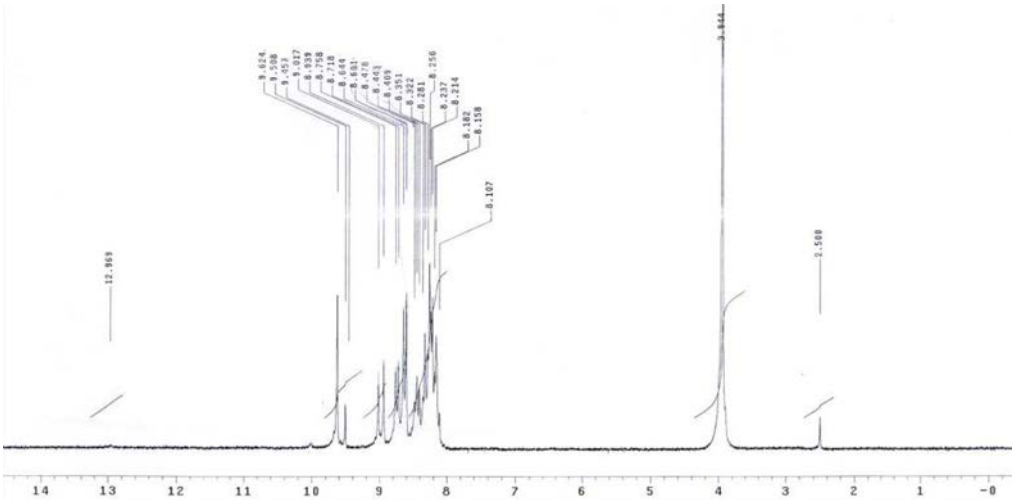

Figure S45. ^{1}H NMR spectrum of compound **21** in DMSO-d_6.

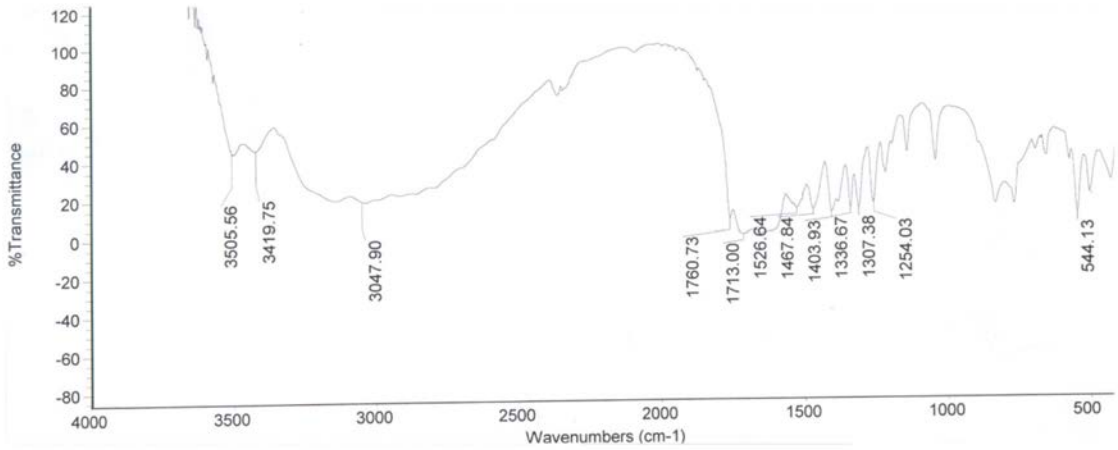

Figure S46. IR spectrum of compound **22**.

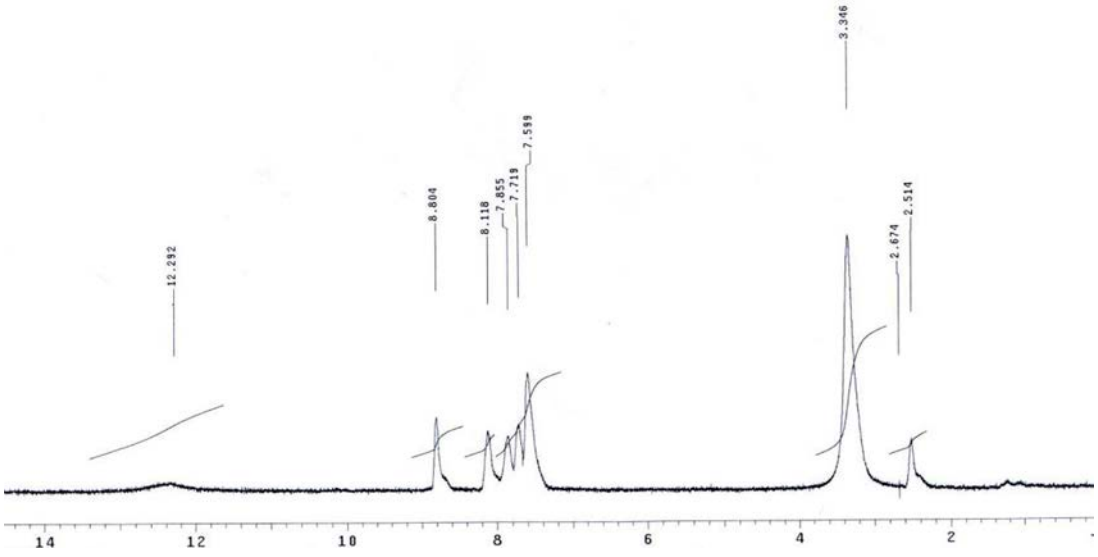

Figure S47. ^{1}H NMR spectrum of compound **22** in DMSO-d_6.

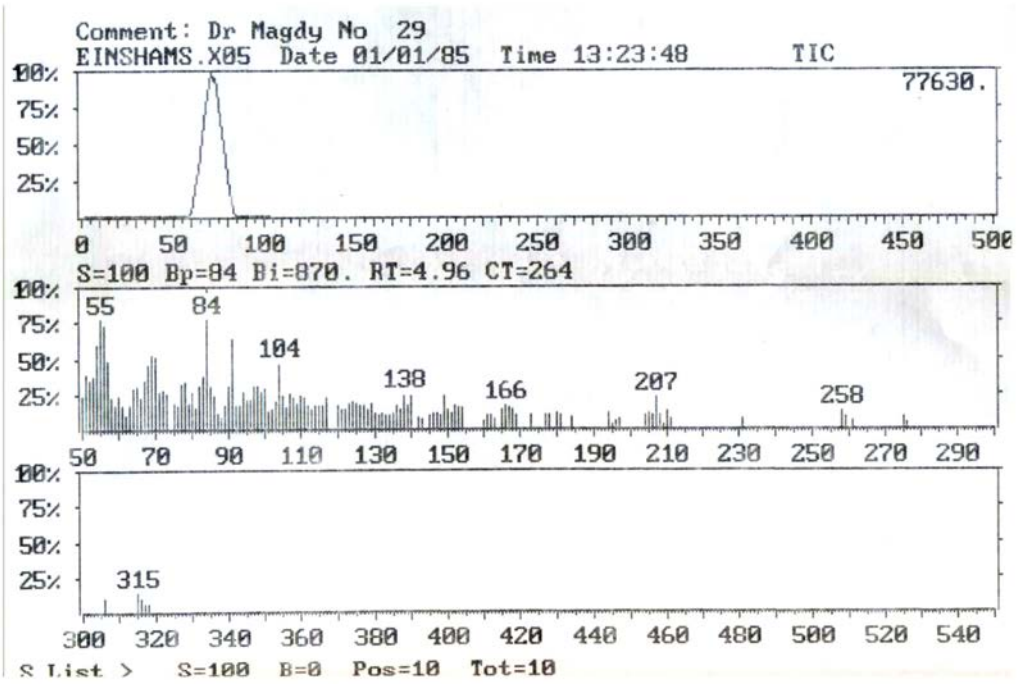

Figure S48. Mass spectrum of compound **22**.