Highly efficient organocatalytic synthesis of diverse and densely functionalized 2-amino-3-cyano-4*H*-pyrans under mechanochemical ball milling

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Experimental Section

General

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a fresh distilled sample. The ball mill was a Retsch MM 400 swing mill. 10 mL stainless steel ball mill vessels were applied for 1-5 mmol runs. Two stainless steel balls with 12 mm diameter were used, and the milling frequency was at 28 Hz at the ambient temperatures. Analytical thin layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 Avance spectrometers with $CDCl_3$ as solvent at ambient temperature and tetramethylsilane (TMS) as the internal standard. All chemical shifts are given relative to TMS. Infrared (IR) spectra were acquired on a Shimadzu FT-IR-8400S spectrometer. All yields refer to the isolated products.

General procedure for the preparation of 2-amino-3-cyano-4H-pyran derivatives (5, 8, 10)

A clean and dry 10 mL ball mill vessel with 2 stainless steel balls was charged with malononitrile **2** (1.1 mmol), aromatic aldehydes **3** (1 mmol), phenol or C-H acidic compounds **4**, **7**, **9** (1 mmol), and POPI **1c** (9.2 mg, 5 mol%). The vessel was closed, and the milling was started at ambient temperatures at a speed of 28 Hz for the specific times indicated in Tables 2, 3 and 4 until products **6, 8** or **10** were formed completely. The reaction progress was monitored by TLC. After completion of the reaction, the product was triturated in a 10 mL beaker containing 5 mL of water for 5 minute. The obtained solid was filtered on a Buchner funnel and dried in an oven at 60 ^{o}C to afford the pure products. The filtrate was evaporated to dryness under reduced pressure and then EtOH (1 mL) was added. POPI **1c**, as a white solid, was filtered off and dried in an oven at 75 ^{o}C for the next experiments.

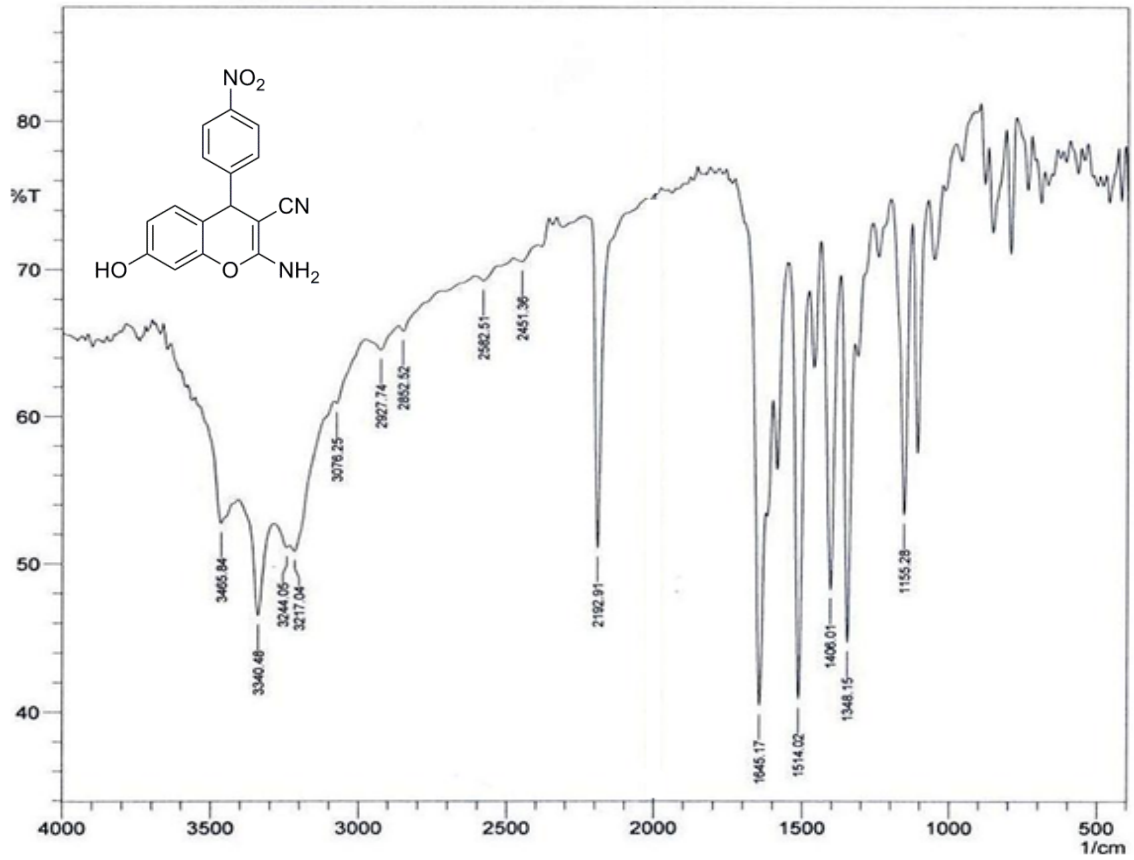

Fig. 1 IR spectra of 2-amino-4-(4-nitropheneyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (**5e**, Table 2, entry 5).

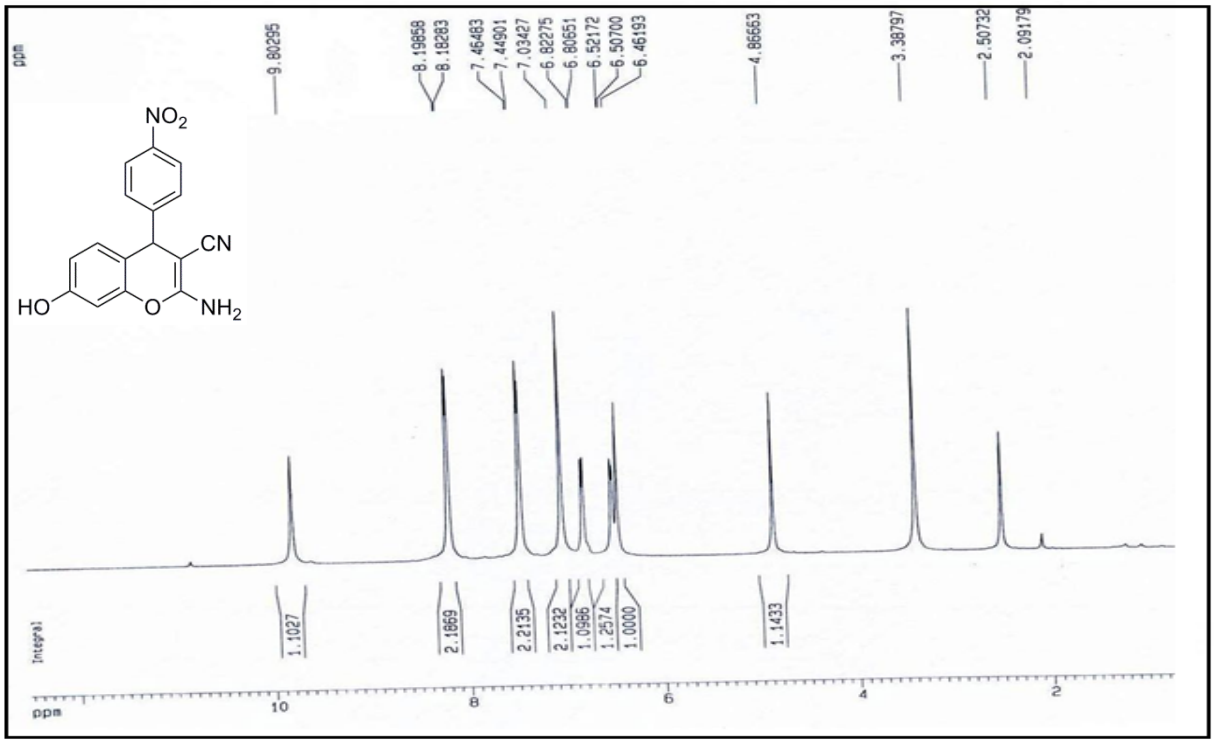

Fig. 2 ^{1}H NMR spectra of 2-amino-4-(4-nitropheneyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (**5e**, Table 2, entry 5)

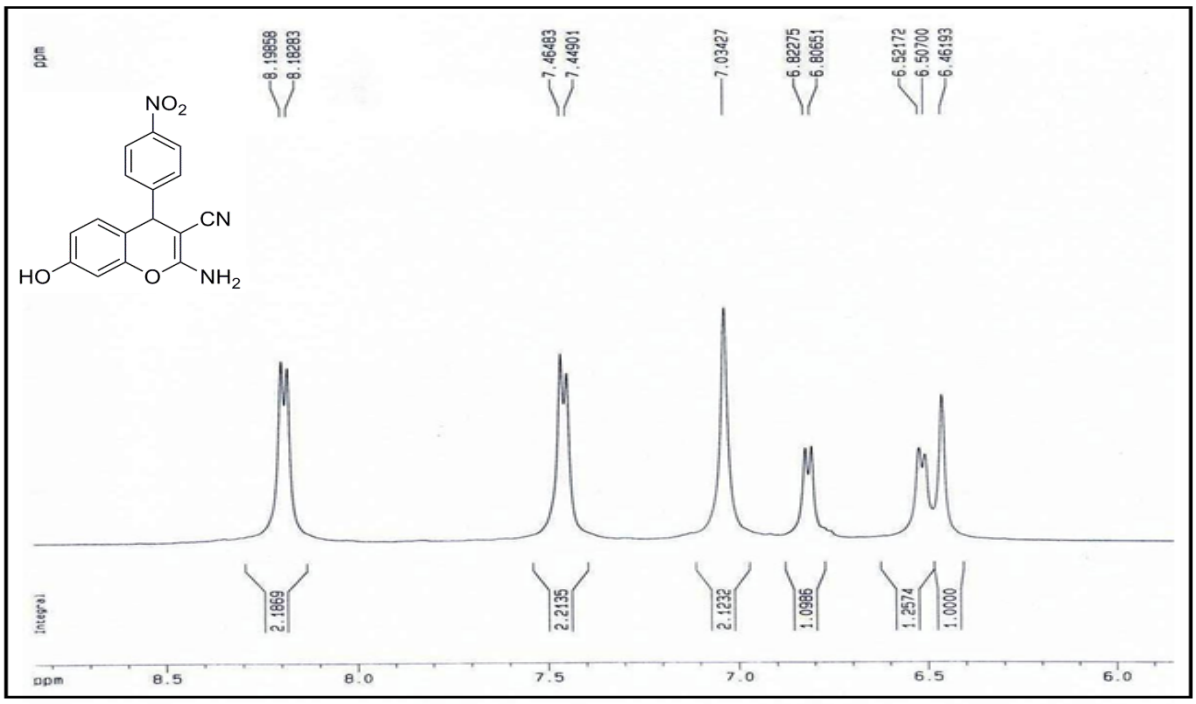

Fig. 3 [1]H NMR spectra (expanded aromatic region) of 2-amino-4-(4-Nitropheneyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (**5e**, Table 2, entry 5)

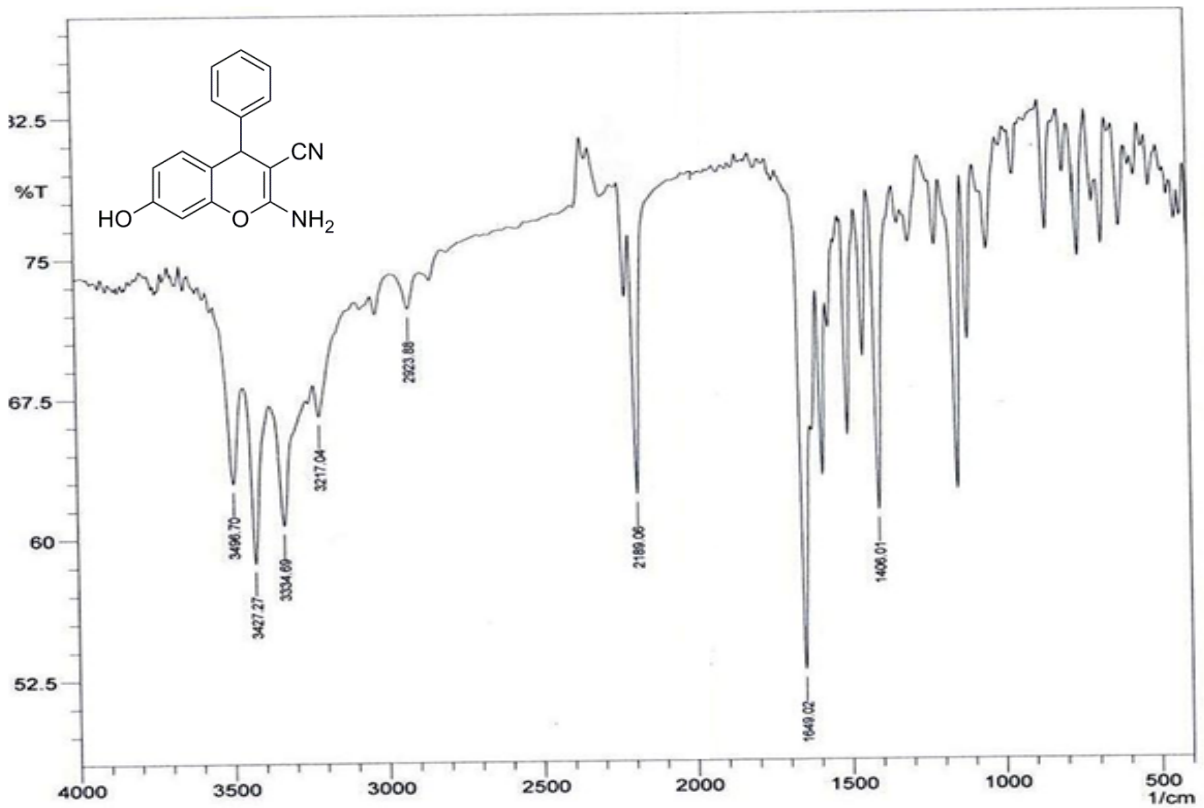

Fig. 4 IR spectra of 2-amino-4-(pheneyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (**5g**, Table 2, entry 7).

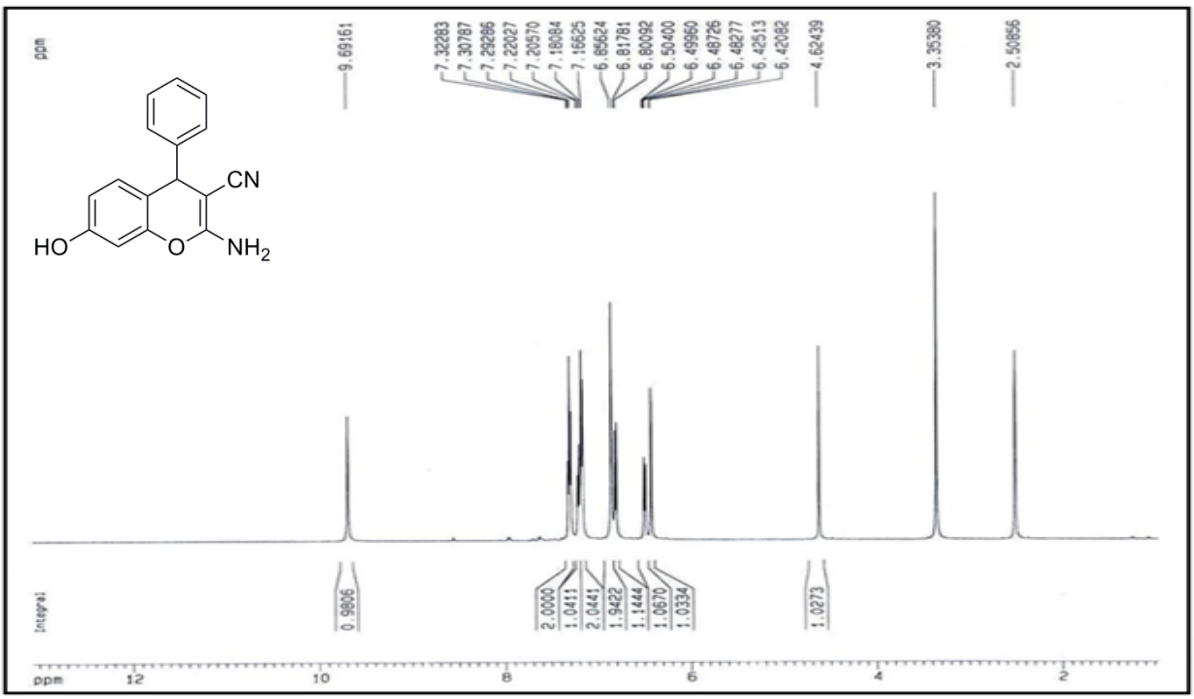

Fig. 5 [1]H NMR spectra of 2-amino-4-(pheneyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (**5g**, Table 2, entry 7).

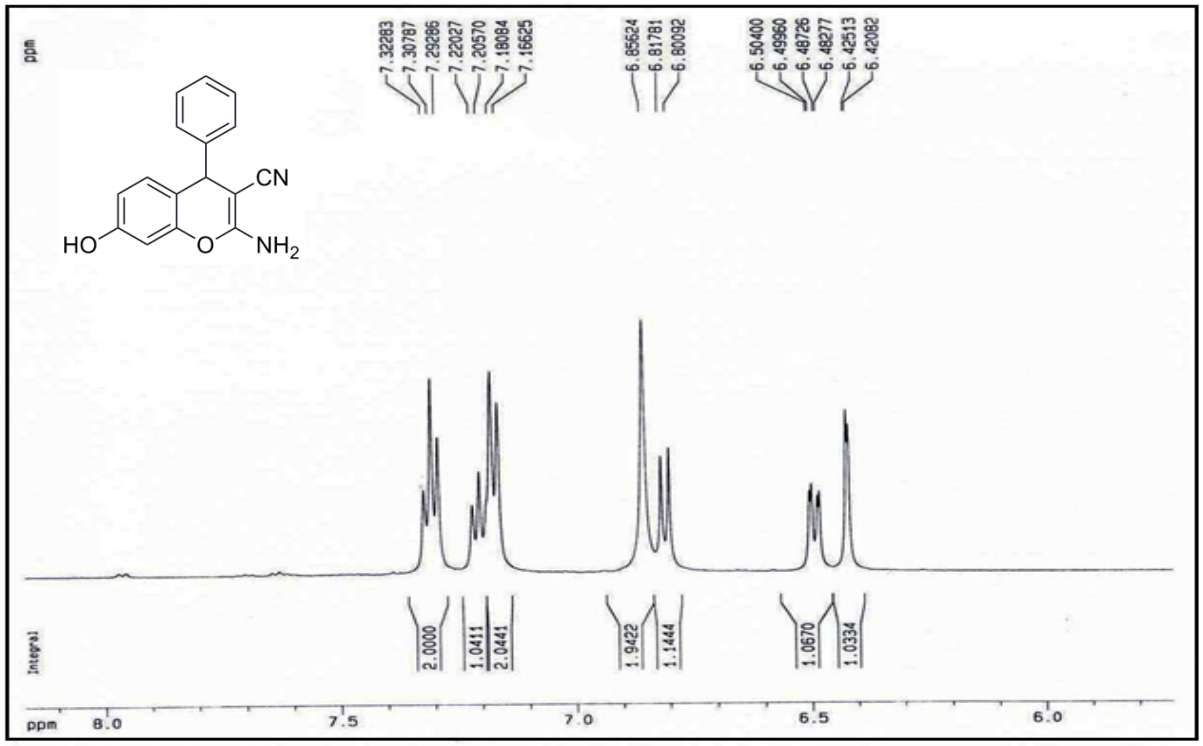

Fig. 6 [1]H NMR spectra (expanded aromatic region) of 2-amino-4-(pheneyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (**5g**, Table 2, entry 7).

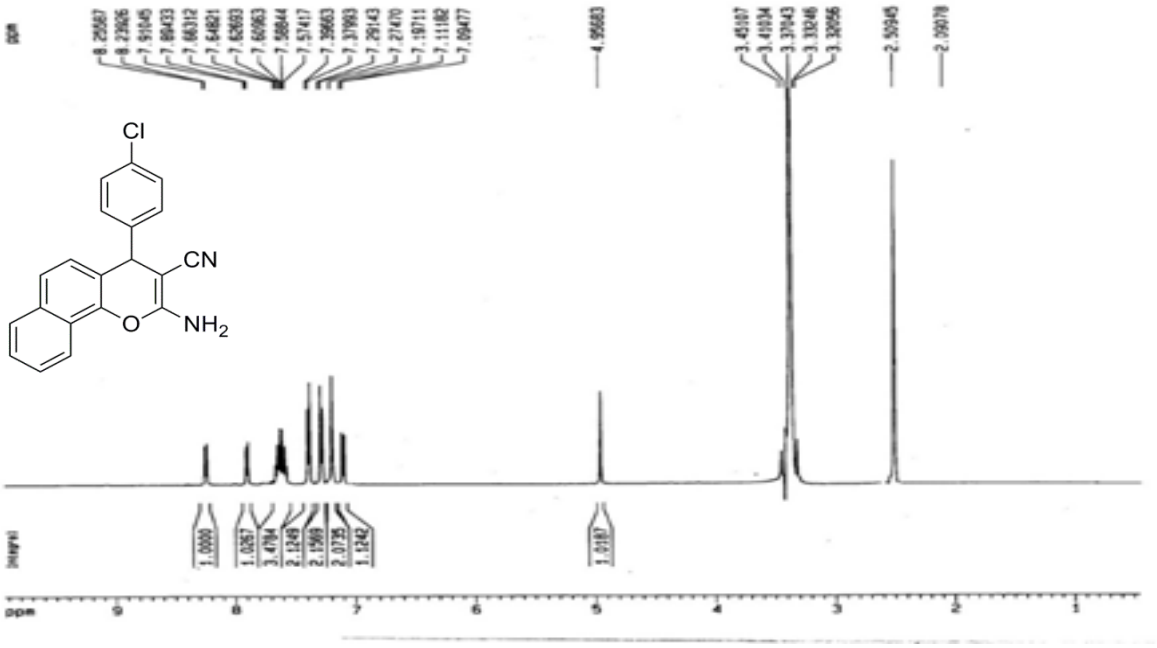

Fig. 7 [1]H NMR spectra of 2-amino-4-(4-chlorophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile (**8a**, Table 3, entry 1).

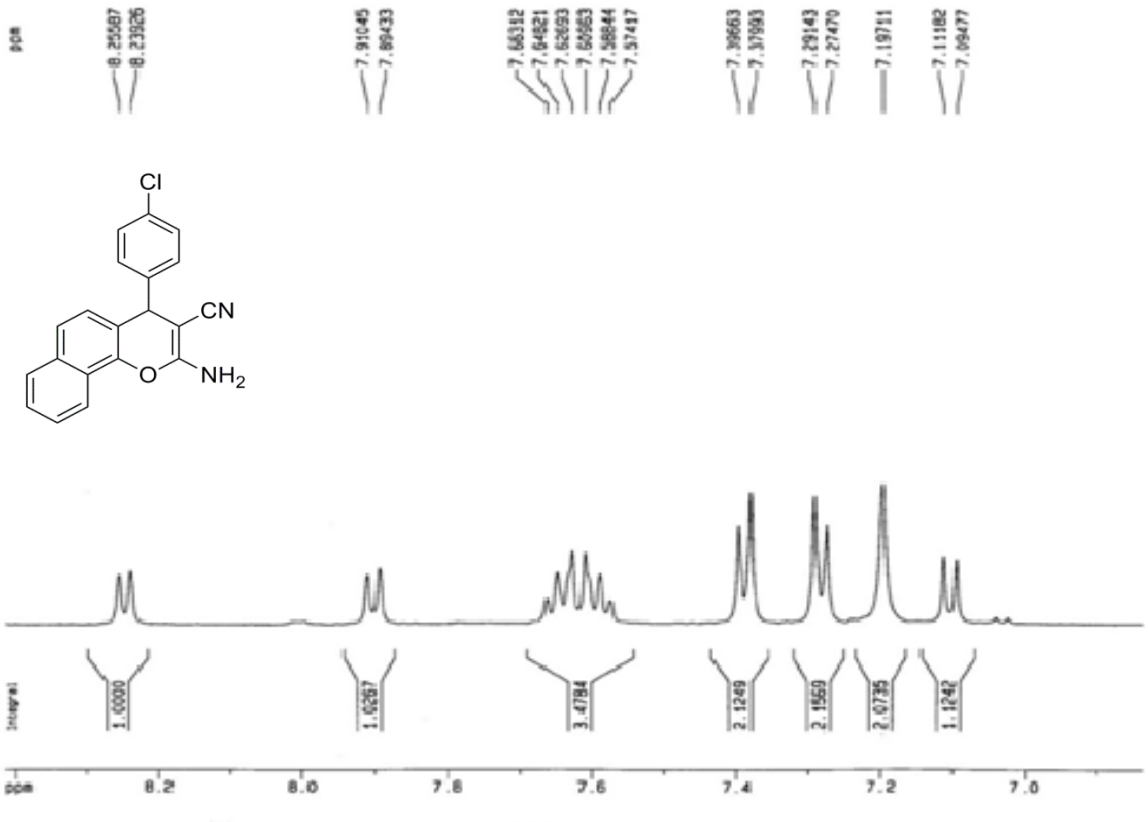

Fig. 8 [1]H NMR spectra (expanded aromatic region) of 2-amino-4-(4-chlorophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile (**8a**, Table 3, entry 1).

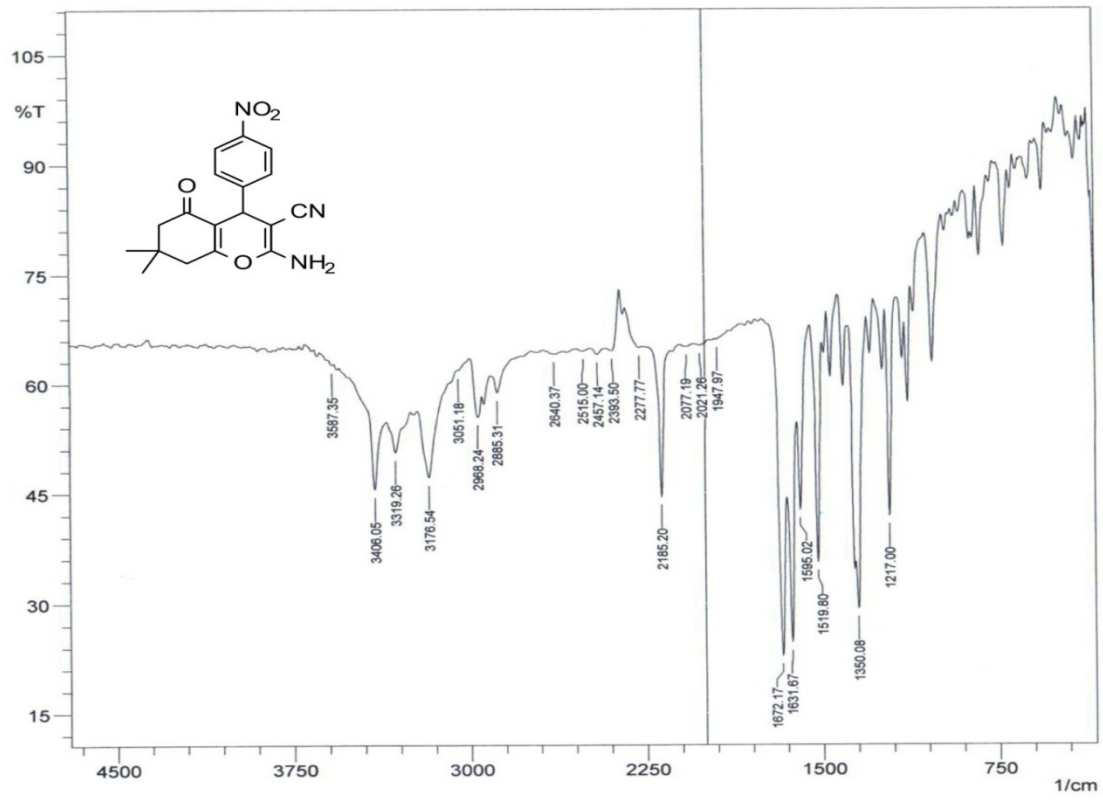

Fig. 9 IR spectra of 2-amino-4-(4-Nitropheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10d**, Table 4, entry 4).

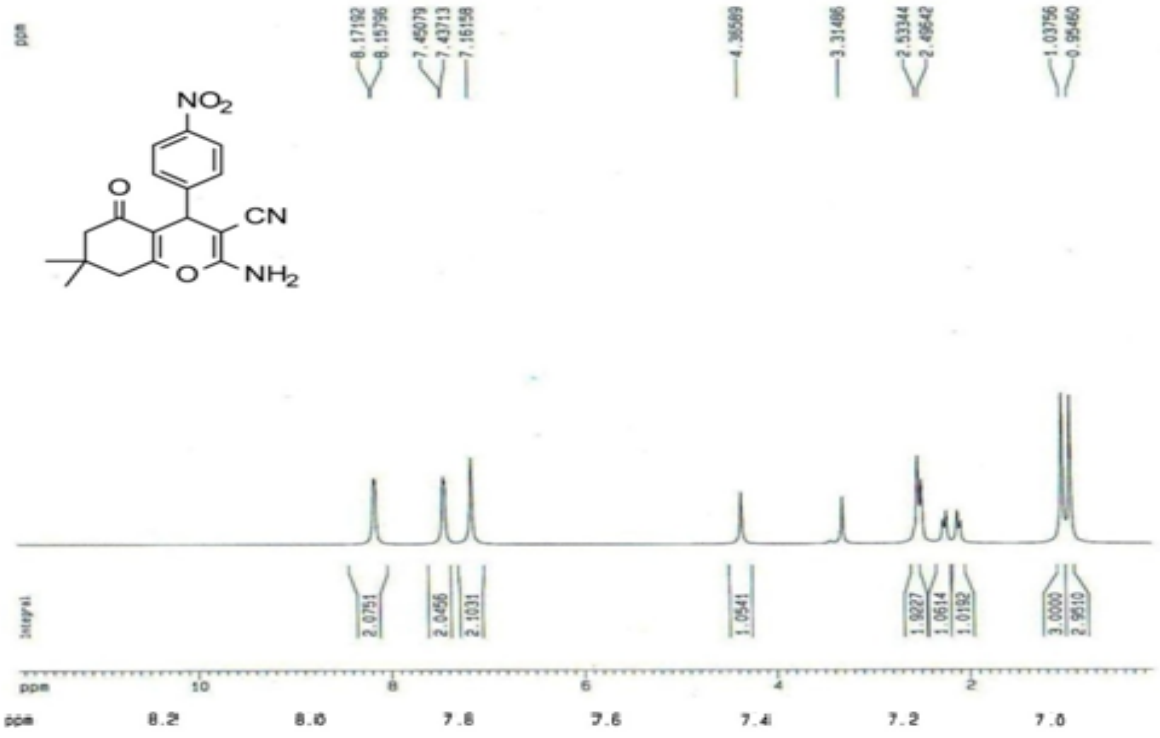

Fig. 10 [1]H NMR spectra (expanded aromatic region) of 2-amino-4-(4-nitropheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10d**, Table 4, entry 4).

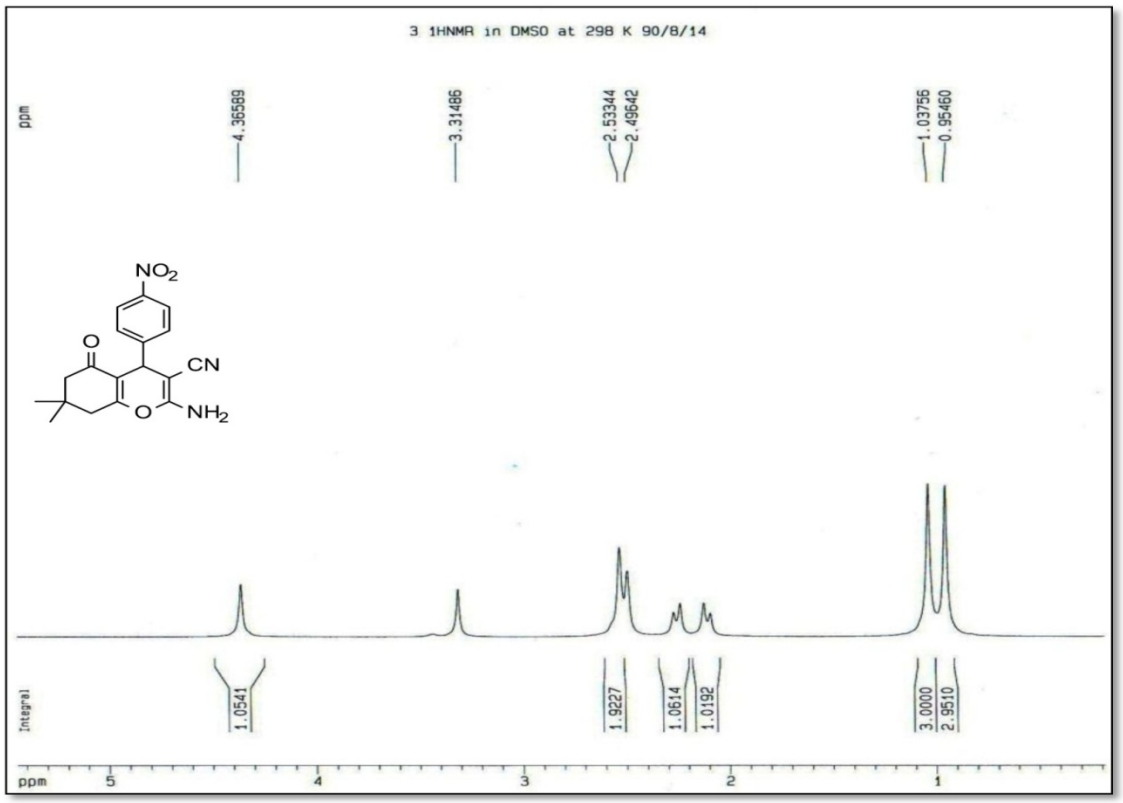

Fig. 11 [1]H NMR spectra (expanded aliphatic region) of 2-amino-4-(4-Nitropheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10d**, Table 4, entry 4).

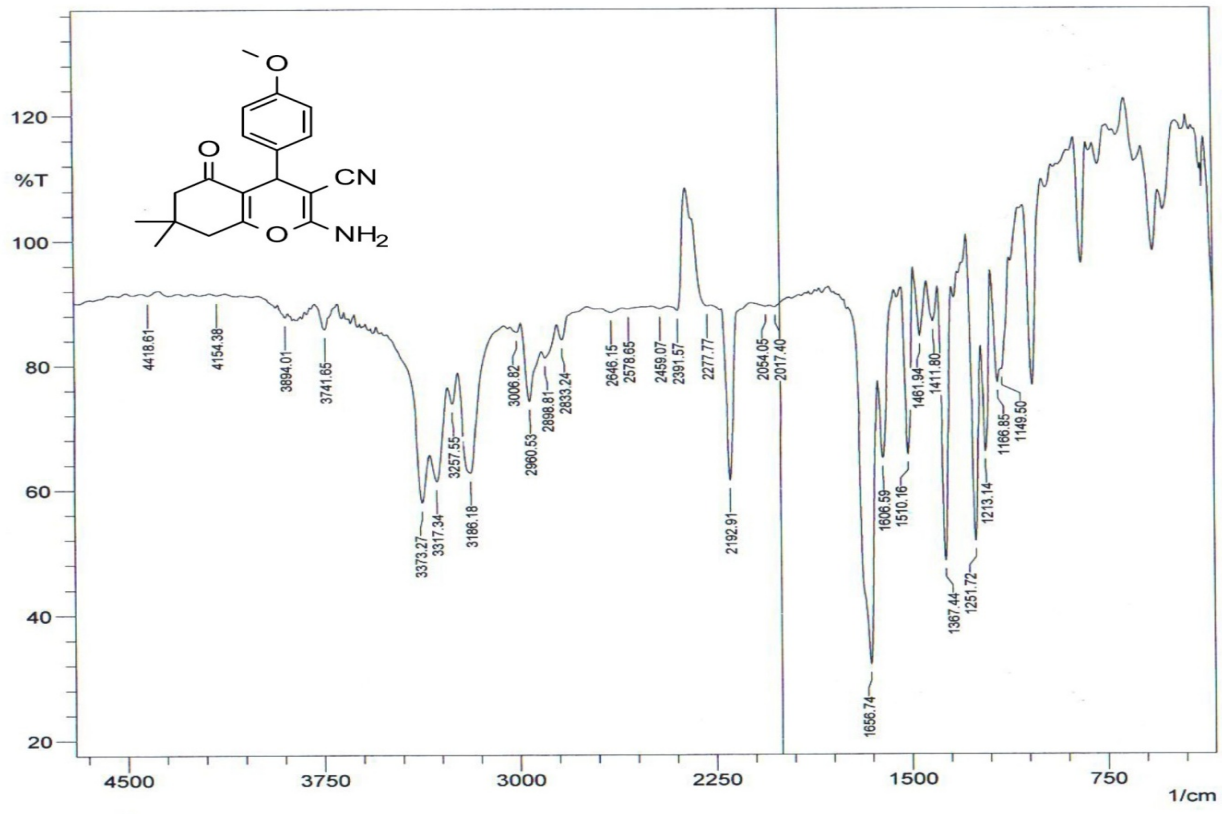

Fig. 12 IR spectra of 2-amino-4-(4-methoxypheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10i**, Table 4, entry 9).

Fig. 13 [1]H NMR spectra of 2-amino-4-(4-methoxypheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10i**, Table 4, entry 9).

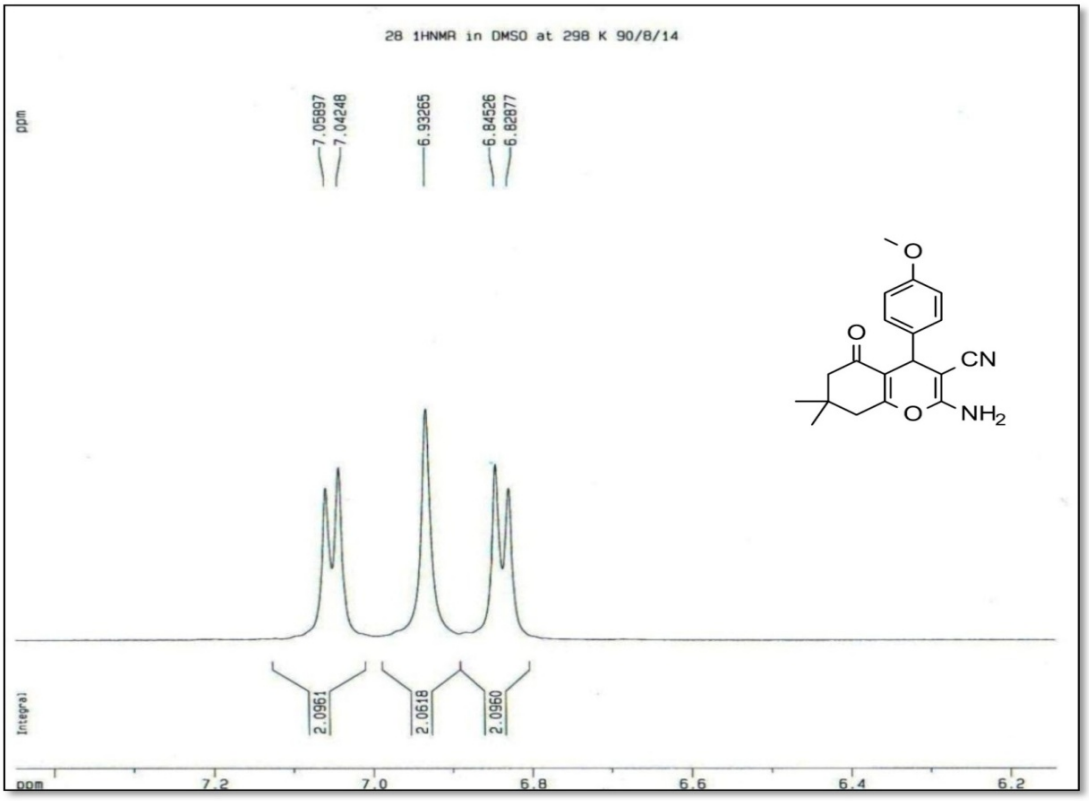

Fig. 14 [1]H NMR spectra (expanded aromatic region) of 2-amino-4-(4-methoxypheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10i**, Table 4, entry 9).

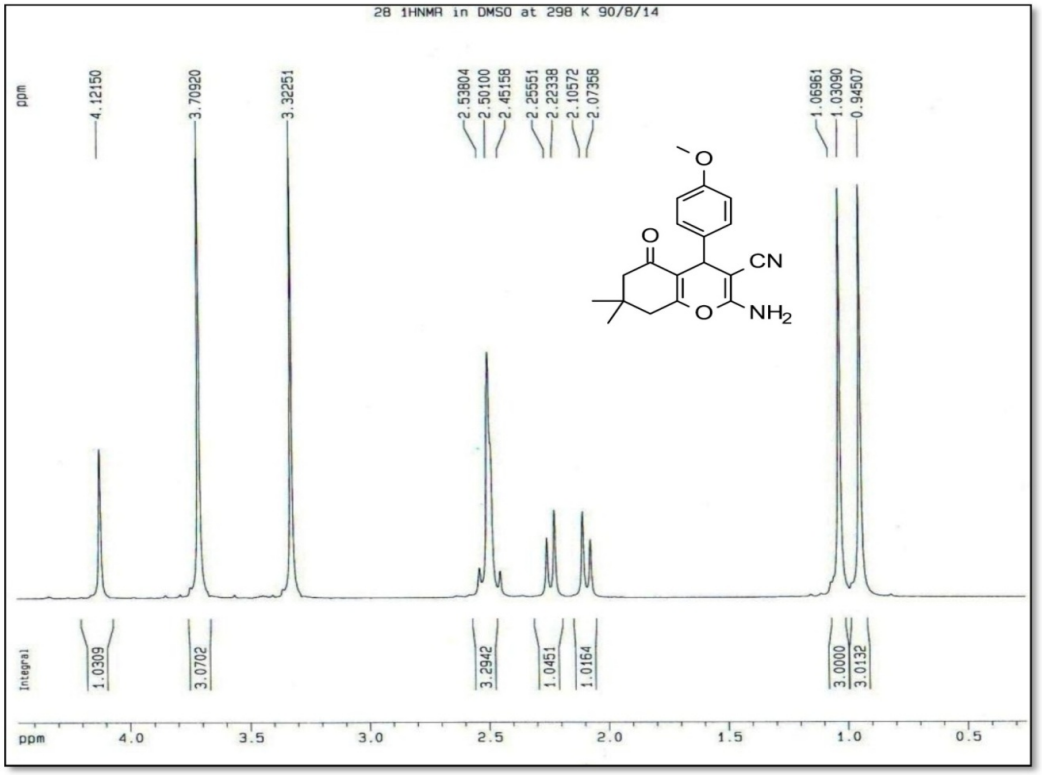

Fig. 15 [1]H NMR spectra (expanded aliphatic region) of 2-amino-4-(4-methoxypheneyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**10i**, Table 4, entry 9).

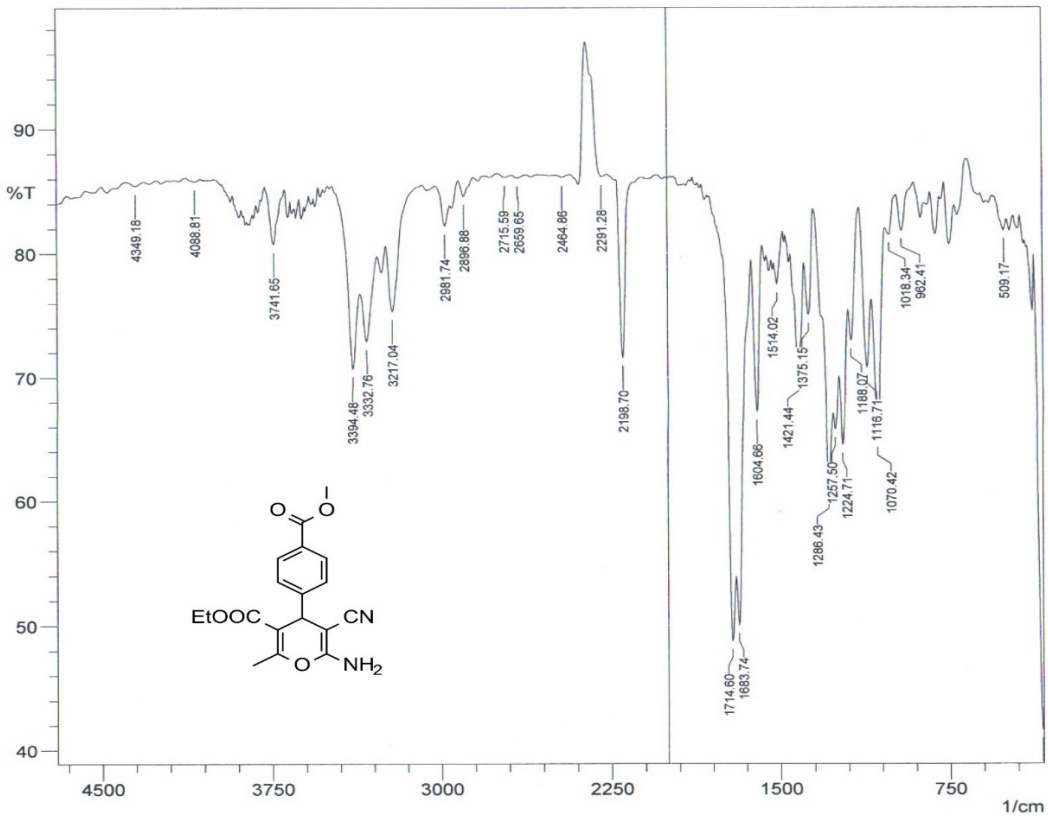

Fig. 16 IR spectra of ethyl 6-amino-5-cyano-4-(4-(methoxycarbonyl)phenyl)-2-methyl-4*H*-pyran-3-carboxylate (**10q**, Table 4, entry 17).

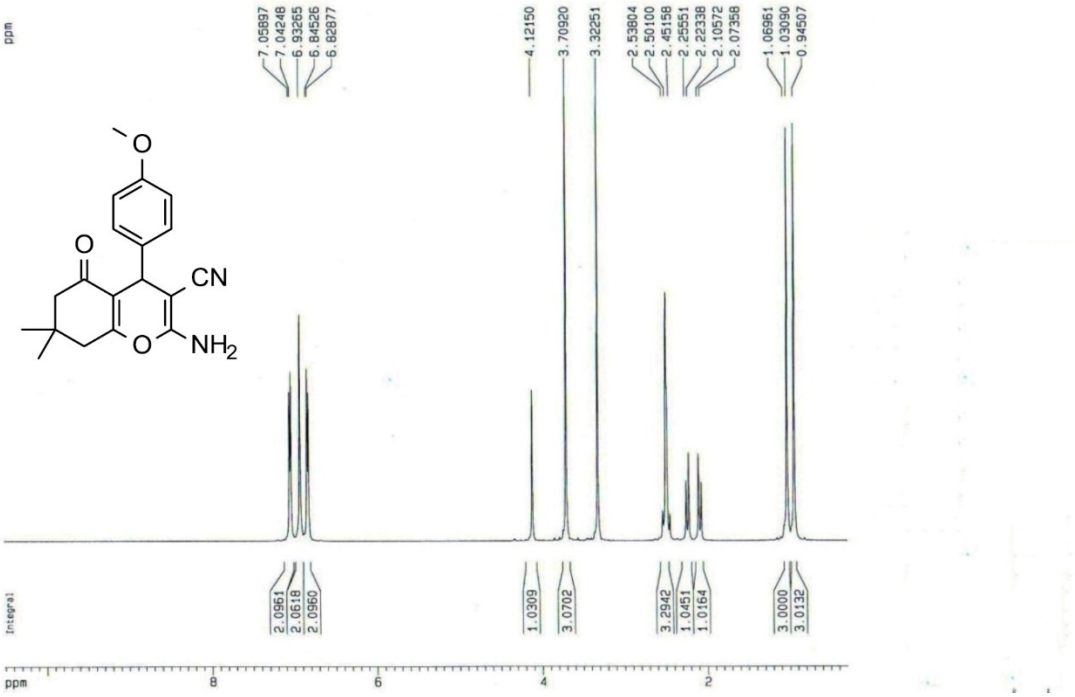

Fig. 17 [1]H NMR spectra of ethyl 6-amino-5-cyano-4-(4-(methoxycarbonyl)phenyl)-2-methyl-4*H*-pyran-3-carboxylate (**10q**, Table 4, entry 17).

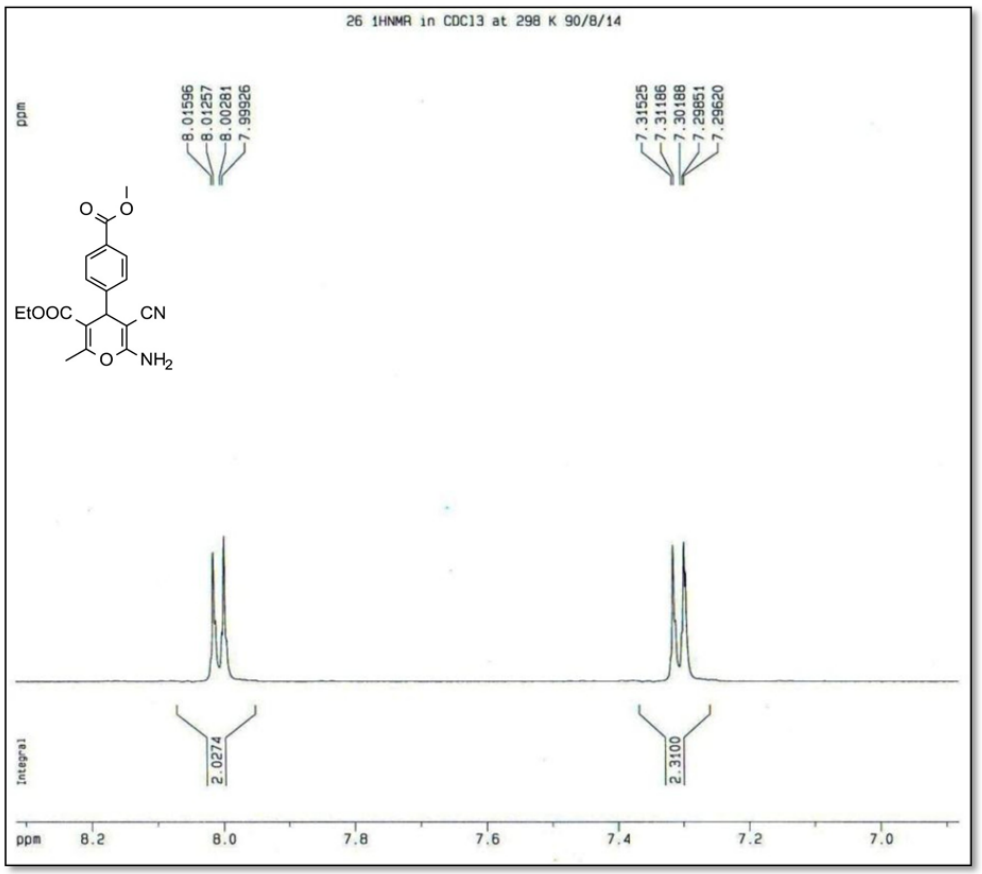

Fig. 18 [1]H NMR spectra (Expanded aliphatic region) of ethyl 6-amino-5-cyano-4-(4-(methoxycarbonyl)phenyl)-2-methyl-4*H*-pyran-3-carboxylate (**10q**, Table 4, entry 17).

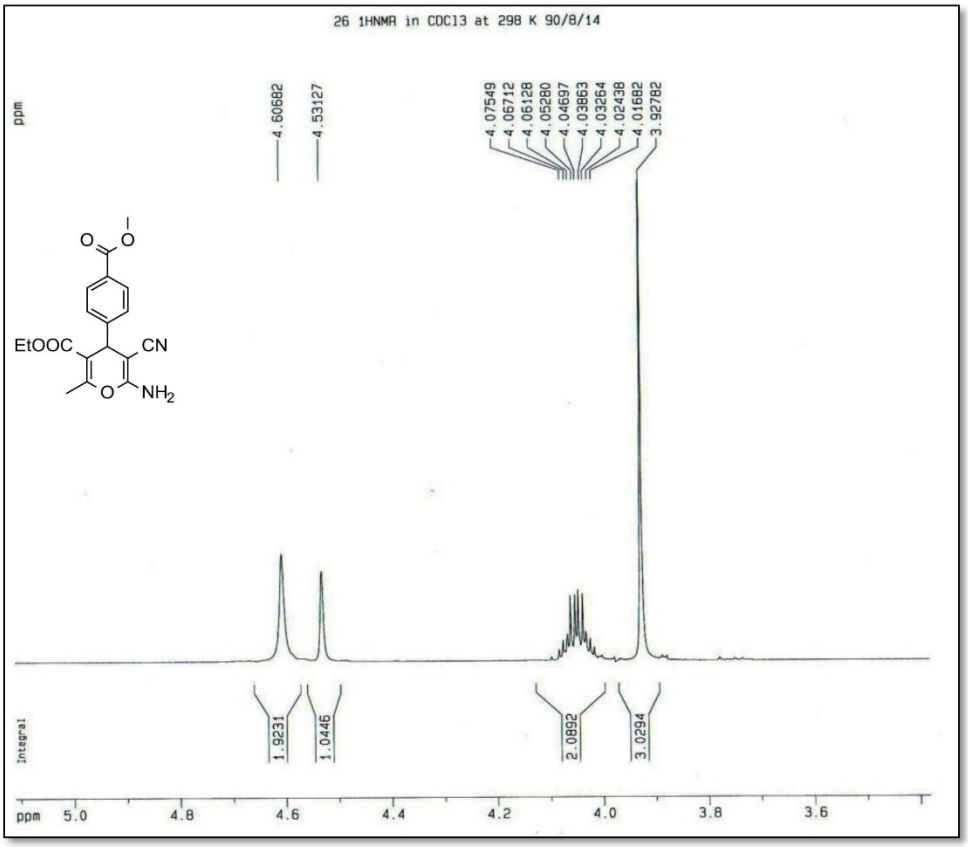

Fig. 18 [1]H NMR spectra of ethyl 6-amino-5-cyano-4-(4-(methoxycarbonyl)phenyl)-2-methyl-4*H*-pyran-3-carboxylate (Table 4, entry 9) (**10q**) (Expanded aliphatic region).

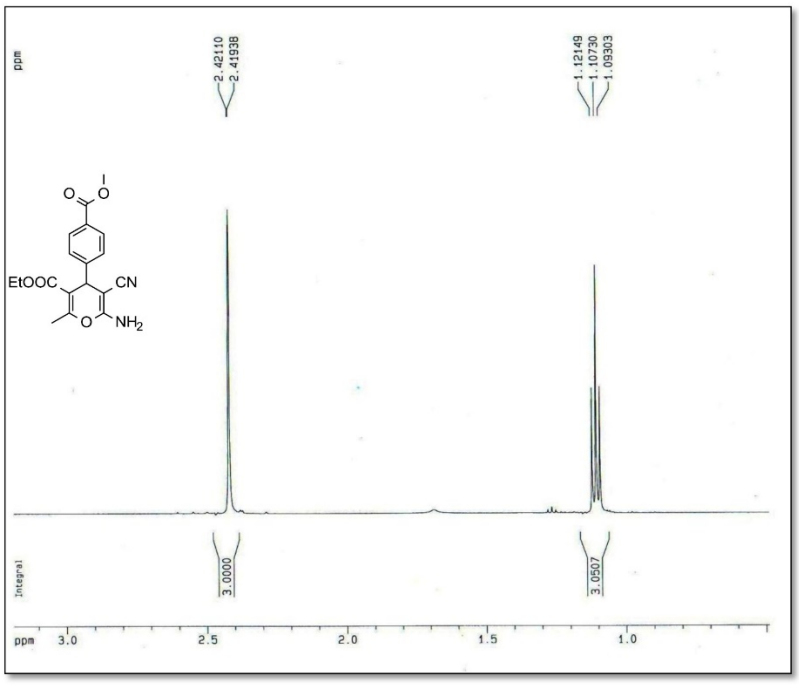

Fig. 19 [1]H NMR spectra (expanded aliphatic region) of ethyl 6-amino-5-cyano-4-(4-(methoxycarbonyl)phenyl)-2-methyl-4*H*-pyran-3-carboxylate (**10q**, Table 4, entry 17).