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A-Cynocetanilides as Key Precursor to Achieve New Series of Diver Pyrimidine-2-one Derivatives Via Efficient Multicomponent Pathway

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ABSTRACT: Multicomponent reactions received a great deals of attention in organic chemistry due to its ability to perform diver heterocyclic compounds which possess wide applications and activity in different fields via one-pot reaction including three or more component even wet or solid phase with yield enhancement and reducing the reaction time. In this work, α –cynoacetanilide compounds(D1-4) have been prepared firstly via traditional reaction between ethylcynoacetate and aromatic primary amines and then this compounds underwent multicomponent reaction with thiourea and substituted benzaldehyde via Biginelli reaction in ratio (1:1:1)to afford the pytimidine-2-one derivatives (E1-4). All prepared compounds were characterized by FT-IR, 1Hand 13C-NMR spectroscopy.

INTRODUCTION

α-Cyanoacetanilide compounds serve as fundamental building blocks for the synthesis of a wide range of biologically active heterocyclic compounds (Mahmoud, 2019). Their derivatives exhibit diverse biological activities, including anti H1V1 (AIDS) (Huang et al., 2016), antiviral (Chen et al., 2019), antifungal (Borrego-Muñoz et al., 2022), antimalarial (Govindarao et al., 2020), and antibacterial (Al-Joubory et al., 2021) properties which increase When these compounds incorporate heterocyclic moieties (Eftekhari et al., 2020).

These compounds are prepared via nucleophilic substitution reactions, utilizing amines as nucleophiles that attack an electrophilic carbonyl carbon atom bearing a leaving group a process that can occur in either basic or acidic media (Salem et al., 2011). Multicomponent reactions are a supreme type of reactions in which three or more compounds are combined in a one-pot step to perform a pure product incorporating all the participating atoms with yield enhancement (Campos-Prieto et al., 2024).

The Biginelli reaction is an awesome type of multicomponent reaction, which used to achieve fused and non-fused pyrimidine rings through a three-component process (Abatwar et al., 2024). The pyrimidine moiety is found naturally in the nitrogenous bases (uracil, cytosine, and thymine) which are found in (DNA) and (RNA) (Joule et al., 2020). Pyrimidine and its derivatives exhibit significant biological activity, making them important in pharmaceutical applications (Ahmed et al., 2023); They act as anti-inflammatory agents (Islam et al., 2024), anticancer agents (Wei et al., 2022), in cardiovascular drugs(Hu et al., 2019), antioxidants. (Kumar et al., 2023), antibacterial (Nunes et al., 2020), in leukemia drugs (Piya et al., 2020), antiviral (Jadhav et al., 2024), and as anti H1V1 (AIDS) (Patil, 2018).

EXPERIMENTAL

Melting Point (M.P) were measured on Electro thermal Stuart SMP 10. melting Point apparatus.Infrared (FT-IR) spectra were recorded using a Bruker, FT-IR spectrophotometer (Pye unicom SP 2000). Nuclear magnetic sesonance spectrometer (^{1}H-NMR): Measurement of the nuclear magnatic resonance spectrum using Bruker (400 MHz) using DMSO as a solvent and

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TMS as an internal reference. Spectral regions were experessed in (ppm). Then layer chromatography (TLC) was using on silica gel (120 mesh) with (13%) gypsun coated plates (2x10) cm activated at (110-120ºC) for one hour before use and the plates were developed with iodine vapor. using (Benzene:Ethylacetate) solvent system at ratio of (8:2) for preparation (D_{1-4}) and (E_{1-4}) compounds.

Synthesis Methods of α-cyanoacetanilide compounds (D_{1-4}) (Anbu et al., 2019):

Equimolar (0.02 mol) of the primary aromatic amine and ethyl cyanoacetate were placed in a (100 mL) round bottomed flask and dissolved in 30 mL of absolute ethanol in acedic media of(1 mL) glacial acetic acid. The reaction mixture was then refluxed for (6 hrs.), then cooled to room temperature. The resulting precipitate was filtered off, washed with ice-cold water to remove the acid, dried, and recrystallized from absolute ethanol to yield the products **(D_{1-4})** with the physical constants listed in (Table 1).

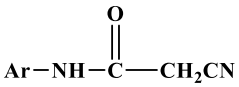


Table (1): The physical properties and spectral data for compounds (D_{1-4}).

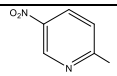
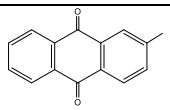
Comp. No.	Ar	M.P ºC	Colour	Yield (%)	R_f	FT-IR (ν cm^{-1})						Others
						NH	CH_2		CN	C=O	C=N	
							assy	sym				
D_1		309-311	Brown	64	0.847	3231	2987	2806	2217	1644	1590	—
D_2		290-293	Deep brown	71	0.684	3312	2932	2832	2200	1630	1581	NO_2 assy 1538, sym 1317
D_3		166-169	Pale brown	68	0.766	3327	3212	2987	2207	1668	1615	C-S assy 1127, sym 1009
D_4		308-310	Brown	66	0.623	3329	3236	3198	2165	1708, 1673	1586	—

Table (2): ^{1}H-NMR and ^{13}C-NMR spectroscopy for compounds (D_{1-4}).

Comp. No.	^{1}H-NMR δ(ppm)	^{13}C-NMR δ(ppm)
D_1	CH_2 (s, 1.869, 2H); Ar-H (m, 6.259-8.806, 3H); NH (s, 11.328, 1H)	CH_2 (14.61); Ar-C (158.47-162.79)
D_2	CH_2 (s, 1.324, 2H); Ar-H (m, 7.099-8.087, 3H); NH (s, 8.990, 1H)	CH_2 (13.73); Ar-C (153.72-160.48)
D_3	CH_2 (s, 1.353, 2H); CH=CH thiazole (d-d, 6.484-6.508+7.745-7.766, 2H); NH (s, 9.780, 1H)	CH_2 (80.10); Ar-C (116.38-191.39)
D_4	CH_2 (s, 4.197, 2H); Ar-H (m, 6.678-8.429, 7H); NH (s, 10.920, 1H)	CH_2 (27.62); Ar-C (110.14-183.80)

Synthesis Methods of 2-pyrimidinone-substituted compounds (E_{1-4}) (Hamed et al., 2017):

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Equimolar (0.02 mol) of substituted benzaldehyde, one of the previously prepared alpha-cyanoacetanilide compounds (D_{1-4}) and urea, were placed in a (50 mL) round bottomed flask and dissolved in (20 mL) of absolute ethanol and triethylamine (1 mL) as a basic catalyst. The mixture was then refluxed for (6 hrs.), then cooled to room temperature. The resulting precipitate was separated by filtration and recrystallized from absolute ethanol to yield the products **(E_{1-4})** with the physical constants listed in (Table 3).

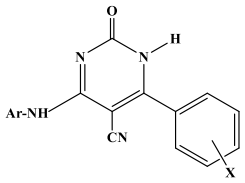


Table (3): The physical properties for compounds (E_{1-4}).

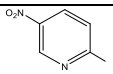
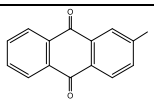
Comp. No.	Ar	X	MP °C	Colour	Yield (%)	R_f
E_1		3-NO_2	331-334	Yellow	88	0.465
E_2		3-NO_2	288-291	Deep brown	91	0.882
E_3		4-OH	195-198	Yellow	82	0.596
E_4		3-NO_2	252-254	Deep yellow	79	0.753

Table (4): FT-IR spectral data for compounds (E_{1-4}).

Comp.	FT-IR (v cm^{-1})								
	NH-C=O	NH	C≡N	C=O	C=N	C=C	NO_2		Others
							assy	sym	
E_1	3335	3262	2380	1660	1603	1575	1553	1337	—
E_2	3349	3106	2201	1632	1617	1581	1526	1349	—
E_3	3185	3346	2210	1644	1586	1504	—	—	C-S 1012
E_4	3434	3334	2113	1700 , 1667	1587	1571	1523	1329	—

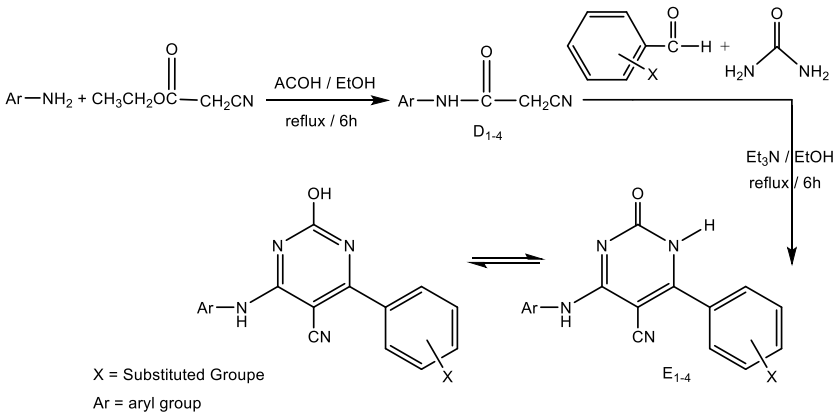
Table (5): ^{1}H-NMR and 13C-NMR spectroscopy for compounds (E_{1-4}).

Comp. No.	^{1}H-NMR δ(ppm)	^{13}C-NMR δ(ppm)
E_1	NH (s, 4.331, 1H); Ar-H (m, 6.426-8.031, 7H); OH-pyrimidine(s, 8.335, 1H)	CN (40.61); Ar-C (113.36-173.27)
E_2	NH (s, 5.457, 1H); Ar-H (m, 6.700-8.676, 7H); OH-pyrimidine (s, 10.132, 1H)	CN (40.57); Ar-C (124.46-192.27)

Comp. No.	^{1}H-NMR δ(ppm)	^{13}C-NMR δ(ppm)
E_3	NH (s, 3.287, 1H); OH (s, 5.497, 1H); Ar-H (m, 6.498-8.592, 6H); OH-pyrimidine (s, 8.850, 1H)	CN (46.04); Ar-C (107.67-160.23)
E_4	NH (s, 5.828, 1H); Ar-H (m, 6.211-8.786, 11H); OH-pyrimidine (s, 10.119, 1H)	CN (59.07); Ar-C (110.13-192.20)

RESULTS AND DISCUSSION

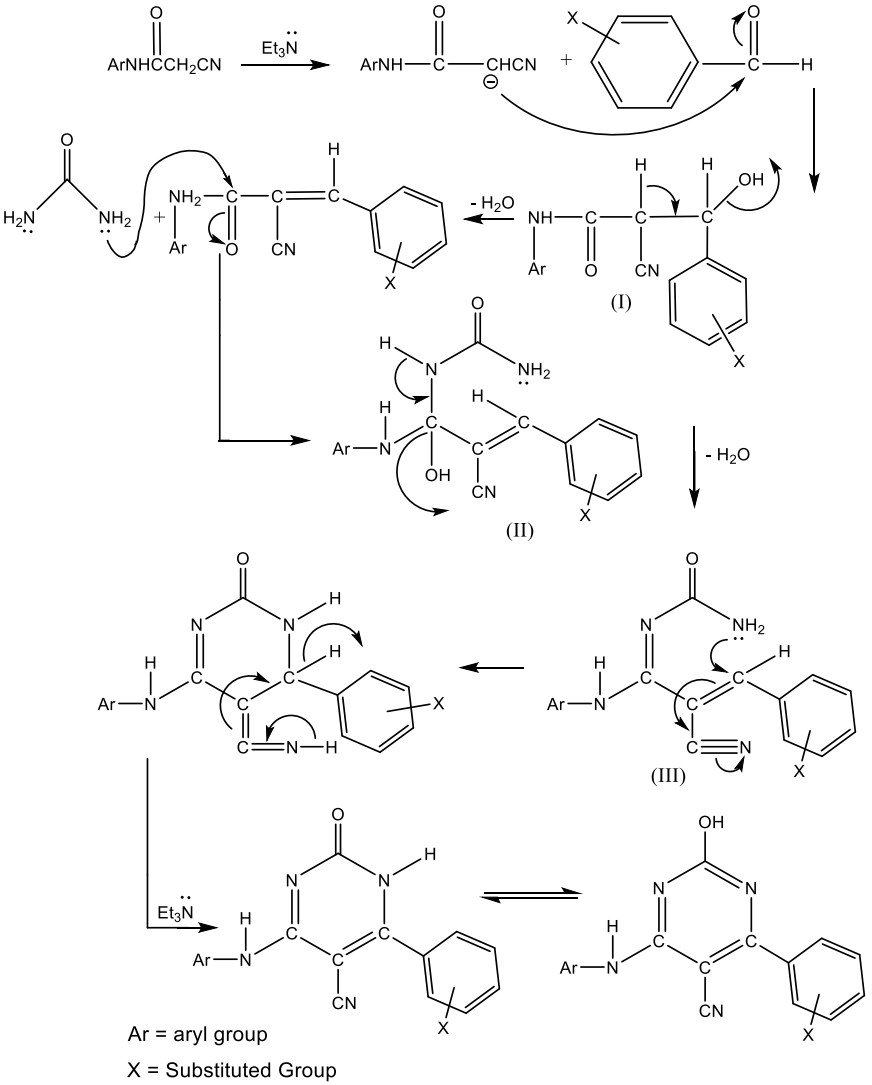
2-Cyno-N-aryl acetamide (D_{1-4}) act as active synthon through multicomponent reaction with substituted benzaldehyde and thiourea to achieve tetra substituted pyrimidine (E_{1-4}) according to the following pathway, Scheme(1)



Scheme (1): The synthetic pathway for compounds (D_{1-4}) and (E_{1-4}).

It is supposed that the reaction was proceeded initially via the formation of an anion induced by the base which acts as a nucleophile to attack the aldehyde carbonyl, yielding the intermediate (I) which subsequently undergoes a second nucleophilic attack by the ione pair of the urea nitrogen atom to form the intermediate (II) followed by the losing of a water molecule to form the intermediate (III). Finally, an intramolecular cyclization occurs by the action of ione pair in the second urea nitrogen atom and accompanied by intramolecular proton shifts facilitated by the basic medium to give the compounds (E_{1-4}) (Scheme 2) (Eman et al., 2024).

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Scheme (2): The synthetic mechanism of compounds (E_{1-4}).

The substituted 2-pyrimidinone compounds were characterized spectroscopically, so In infrared (IR) spectra, the compounds (E_{1-4}) exhibited characteristic absorption bands at (1238–2110 cm^{-1}), (3185–3434 cm^{-1}), and (3106–3346 cm^{-1}), corresponding to C–N, secondary amine N–H, and cyclic amide NH–C=O groups, respectively, in addition to other diagnostic absorption bands listed in (Table 4).

Regarding to the ^{1}H-NMR spectroscopy, compounds (E_{1-4}) demonstrated tautomerism although singlet signals corresponding to the pyrimidine OH group at the 2-position appeared at (δ ppm) (8.031–10.132), indicating the compound's (Keto-Enol Tautomerism) (Table 5)

On the other hand, the ^{13}C-NMR spectrum, signals for the (CN) group appeared at (40.61–59.07 (δ) ppm), and signals for (Ar-C) appeared at (δ ppm) (107.67–192.27) (Table 5). The figures below describe their spectroscopy.

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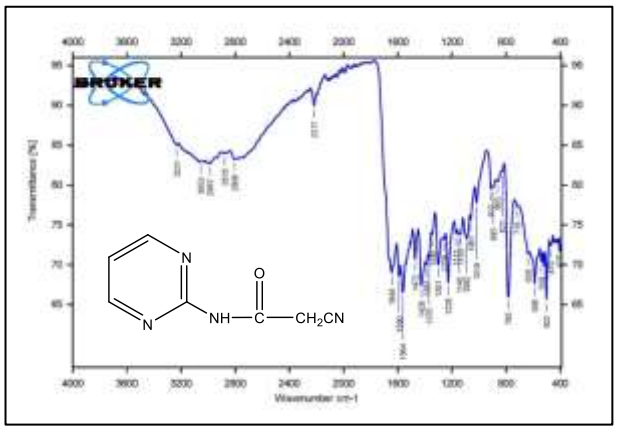


Fig. (1): FT-IR of compound (D_1).

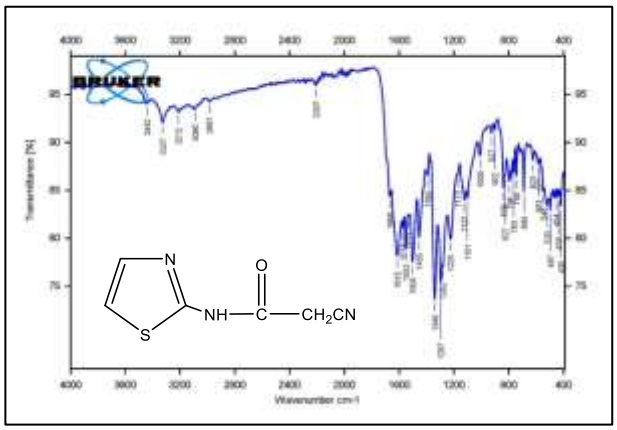


Fig. (2): FT-IR of compound (D_3).

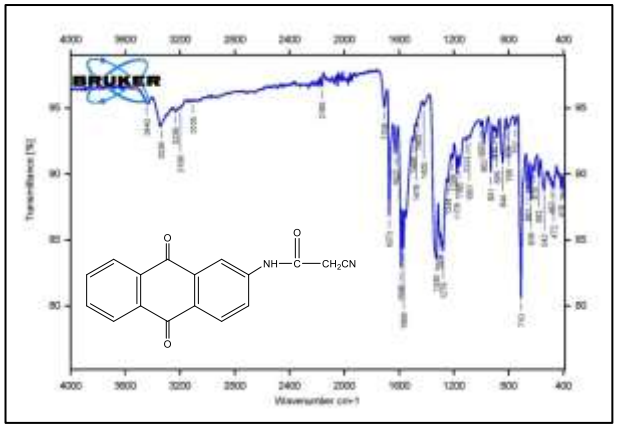


Fig. (3): FT-IR of compound (D_4).

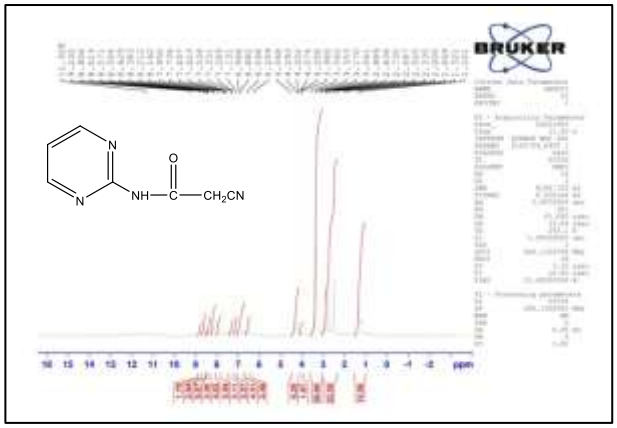


Fig. (4): ^{1}H-NMR of compound (D_1).

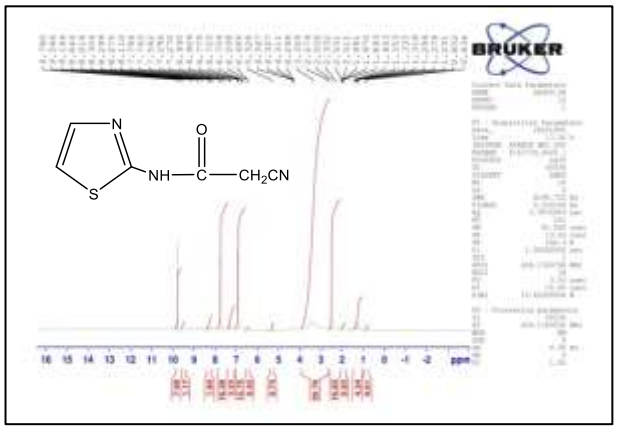


Fig. (5): ^{1}H-NMR of compound (D_3).

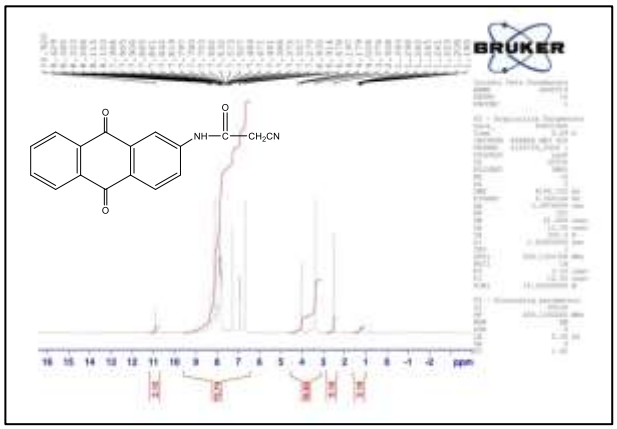


Fig. (6): ^{1}H-NMR of compound (D_4).

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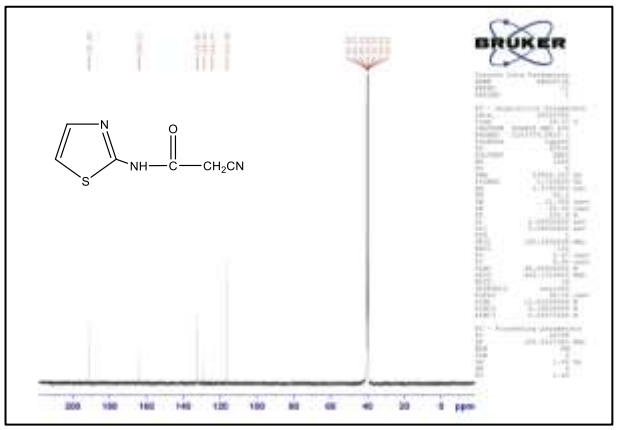


Fig. (7): ^{13}C-NMR of compound (D_3).

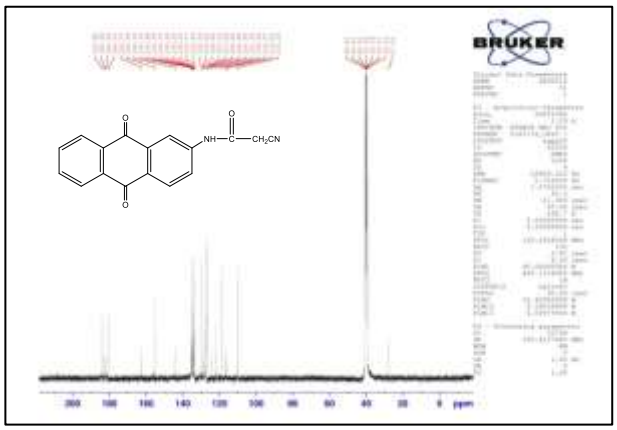


Fig. (8): ^{13}C-NMR of compound (D_4).

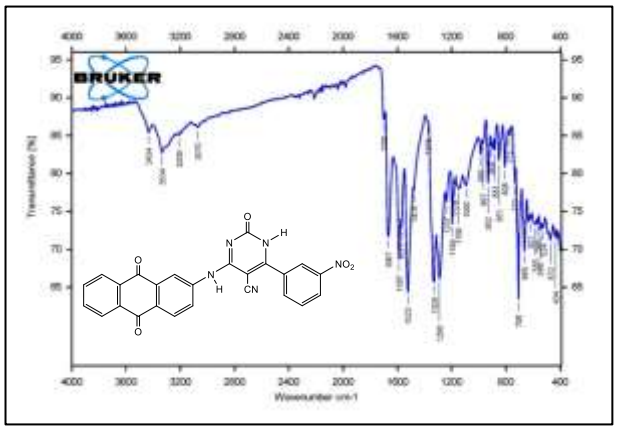


Fig. (9): FT-IR of compound (E_4).

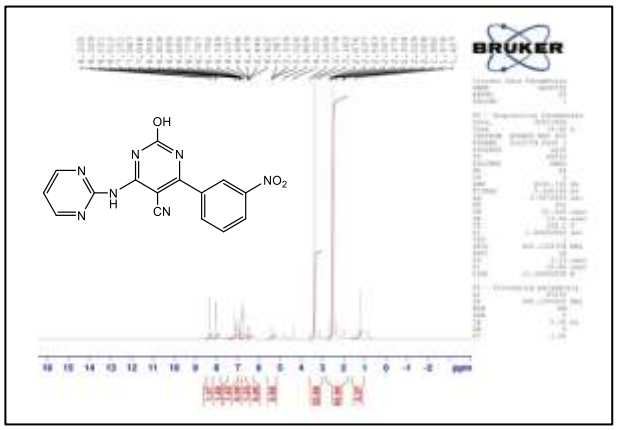


Fig. (10): ^{1}H-NMR of compound (E_1).

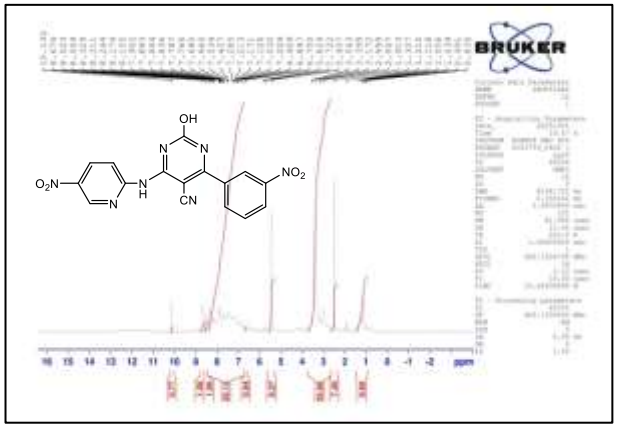


Fig. (11): ^{1}H-NMR of compound (E_2).

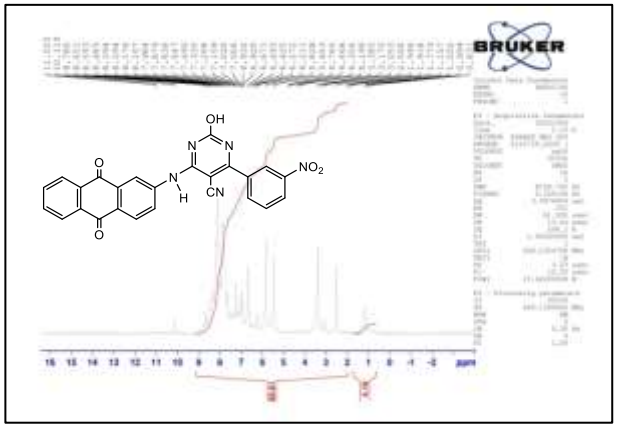


Fig. (12): ^{1}H-NMR of compound (E_4).

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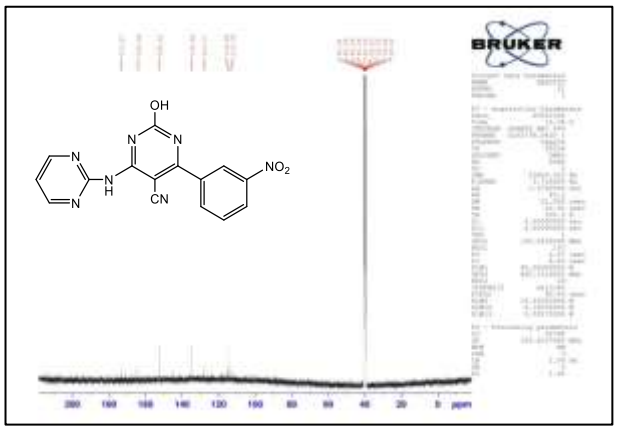


Fig. (13): ^{13}C-NMR of compound (E_1).

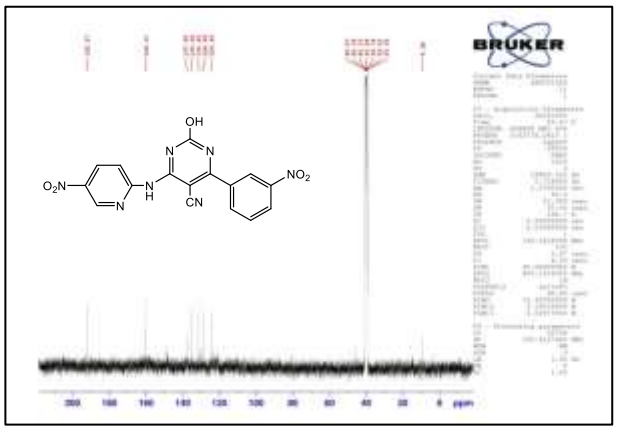


Fig. (14): ^{13}C-NMR of compound (E_2).

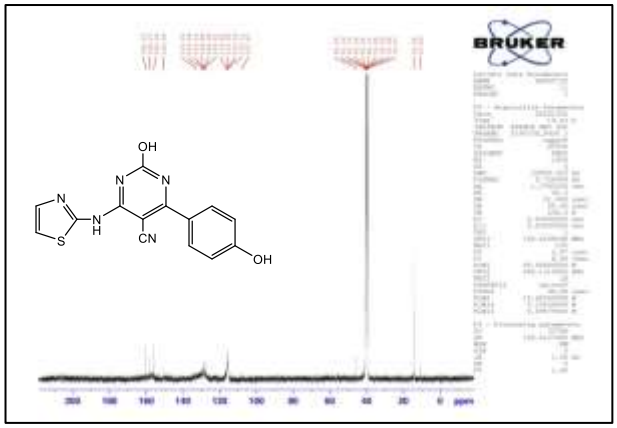


Fig. (15): ^{13}C-NMR of compound (E_3).

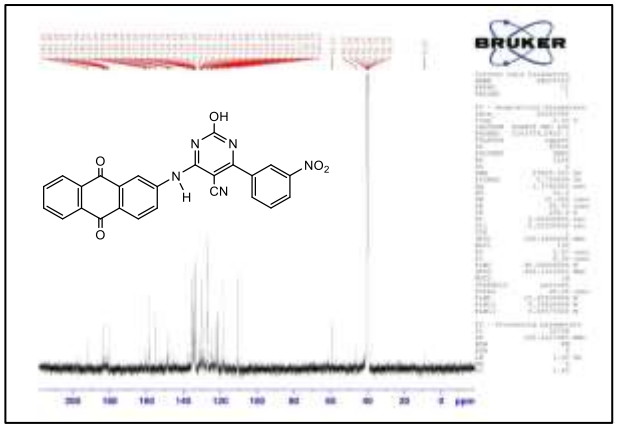


Fig. (16): ^{13}C-NMR of compound (E_4).

CONCLUSION

The current study have been successfully prepared and characterized a new series of heterocyclic compounds. These synthezide pathways have demonstrated good efficiency through the use of one-pot multicomponent reactions and microwave irradiation. These approaches contributed to reducing the reaction times and green eco-friendly reaction conditions compared with conventional methods.

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