Convenient methodology for Synthesis a New Series of Heterocyclic Compounds Including The Enamine Moiety

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Abstract

Due to the desire of all researchers to develop methods for preparing heterocyclic compounds because of their wide applications in various fields and also due to their eagerness to invent efficient , fast , clean , environmentally friendly and economical methods .Therefore, green chemistry methods were adopted, represented by grinding technique to prepare a distinctive type of heterocyclic compounds represented by N-phenyl-3-(piperonayl-5`-yl)-4-cyno-5-amino pyrazole through smooth one-pot multicomponent reaction among piperonal, malononitrile and phenyl hydrazine hydrochloride for (4-5min.) with yield enhancement. This pyrazole was converted to it's Schiff base derivatives (2-5) through it's reaction with substituted benzaldehyde in acid media, then these Schiff base were underwent Diels-Alder reaction with diarylidene hydrazine (6-8) via another green chemistry technique represented by microwave irradiation at power (700 watt) for (5-10 min.) to afford 1,2,4-triazine derivatives (9-20). All prepared compounds were illustrated by the available physical and spectral methods .

Key words: 1,2,4-Triazines, Schiff bases, Diels-Alder reaction, Green chemistry, Grinding, Microwave irradiation

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Introduction

Five membered heterocyclic ring are conceded as one of the most important types among the organic compounds , since have wide application in organic synthesis [1],industrial [2], pharmametical , medical [3] and biological field [4]. 5-Amino pyrazole as an active example of the mentioning above possess wide application in medical field as anticancer [5], antirheumatod arthritis [6], and anti fungal [7], anti bacterial[8], anti viral[9], anti tubercular[10], antimicrobial [11], anticonvulsant [12] and also it used in osteoporosis treatment [13] and anti pyretic [14]. Based on the above ,herein in this presentation 2-amino pyrazole (1) have been choosed as active enamine which prepared by using green chemistry technique represented by grinding technique for (4-5min.) among piperonal , malononitrile and phenyl hydrazine hydrochloride , then it converted to it's Schiff base derivative (2-5) via it's reaction with substituted benzaldehyde in acid media followed by Diels-Alder reaction between Schiff base (2-5) and diarylidene hydrazine (6-8) accelerated by microwave irradiation using power (700 watt) for (5-10 min.) to afford 1,2,4-triazine derivatives (9-20) with accepted percentage yield .

The Experimental

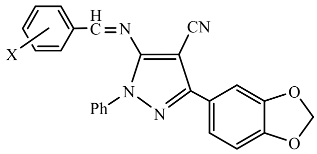
Synthesis of N-phenyl-3-(piperonayl-5`-yl)-4-cyno-5-aminopyrazole (1):[15]

Equimolar (0.01 mole) of piperonal , phenyl hydrazine hydrochloride and malononitrile was well grinded in small mortor for (4-5 minute) as exothermic reaction will yellow fumes . The reaction mixture will converted gradually into viscous mass then solid mass which treated with ethanol until the precipitate is completely separated , followed by filtration and washed thoroughly with pet-ether (6×3ml), dried to afford compound (1) with M.P: 138-140°C, %: 73%, T.L.C(R_f): 0.647. U.V λ_{max}(nm): 340&354(nm). FT-IR (υ cm^{-1}): NH_2 (3210), =CH(3003), CN (2699), C=C (1604), C=N (1500), C-O-C (1257 and 1037).

Synthesis of Schiff bases (2-5): [16]

In round bottomed flask (100 ml) equipped with magnetic bar dissolved (0.0006 mole) of substituted benzaldehyde in methanol (20 ml) in presence of few drops of glacial acetic acid followed by adding dropwise of alcoholic solution of compound (1)(0.0006 mole) with stirring at room temperature for (24 hrs.) then allowed to cool for (15 minute) then poured into beaker with ice-water with continuous stirring , filtration and washed the precipetate thoroughly with water (5×5ml), drying to achieve compounds (2-5) with physical properties listed in Table(1).

Tabel (1): physical properties for compounds (2-5)



Comp.No.	X	M.P (°C)	Yield (%)	T.L.C	Molecular formula
2	m-OMe , p-OH	-104 101	48	0.738	$C_{25}H_{18}N_4O_4$
3	p-NO2	-171 168	40	0.625	$C_{24}H_{15}N_5O_4$
4	m-OH	81-83	55	0.542	$C_{24}H_{16}N_4O_3$
5	p-OH	91-94	67	0.578	$C_{24}H_{16}N_4O_3$

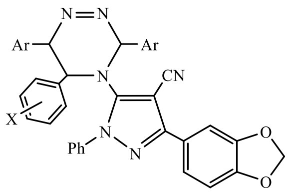
Synthesis of di arylidene hydrazine (6-8):

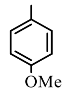
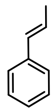
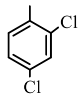
These compounds were prepared according to the literature [17], also it identically conformity in all its physical constant`s.

Synthesis of 1,2,4-triazine derivatives (9-20): [18]

In beaker (50 ml) equimolar (0.0008 mole) of Schiff base (2-5) and diarylidene hydrazine (6-8) were well grinded then irradiated under microwave oven for (5-10 minute) at (700 watt) in the absence of catalyst. cooling then washed thoroughly with water to afford compounds (9-20) with physical properties listed in Table (2).

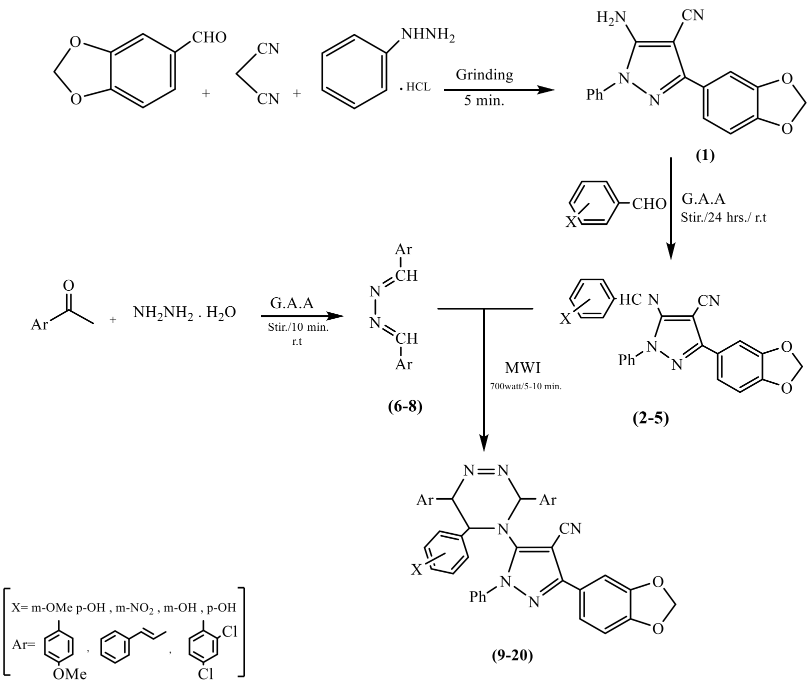
Tabel (2): physical properties for compounds (9-20)



Comp.No.	Ar	X	M.P(ºC)	Yield (%)	T.L.C	Molecular formula
9		m-OMe p-OH	151-153	80	0.413	$C_{41}H_{34}N_6O_6$
10		m-NO_2	160-163	62	0.434	$C_{40}H_{31}N_7O_6$
11		m-OH	157-159	86	0.538	$C_{40}H_{32}N_6O_5$
12		p-OH	160-162	75	0.571	$C_{40}H_{32}N_6O_5$
13		m-OMe P-OH	104-106	89	0.522	$C_{43}H_{34}N_6O_4$
14		m-NO_2	144-147	87	0.476	$C_{42}H_{31}N_7O_4$
15		m-OH	137-140	94	0.579	$C_{42}H_{32}N_6O_3$
16		p-OH	115-117	75	0.7	$C_{42}H_{32}N_6O_3$
17		m-OMe p-OH	187-189	80	0.54	$C_{39}H_{26}Cl_4N_6O_4$
18		m-NO_2	209-211	77	0.615	$C_{38}H_{23}Cl_4N_7O_4$
19		m-OH	200-202	55	0.5	$C_{38}H_{24}Cl_4N_6O_3$
20		p-OH	196-198	62	0.549	$C_{38}H_{24}Cl_4N_6O_3$

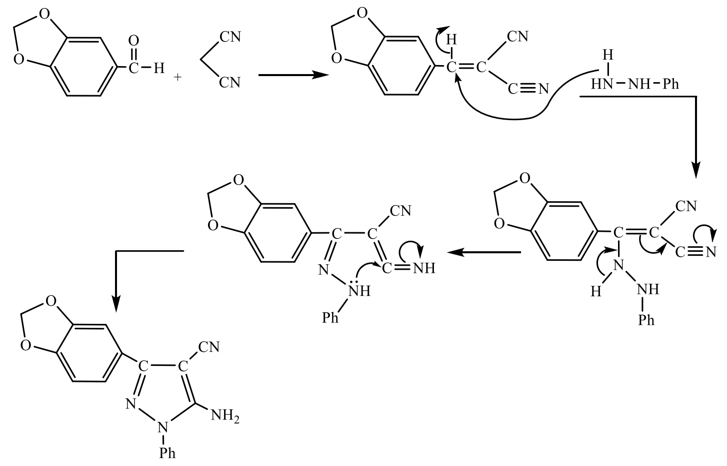
Result and Discussion

All compounds were synthesized through the following synthetic pathway :



Scheme (1): Synthetic pathway for compounds (1-20)

First of all, substituted 5-amino pyrazole (1) was prepared according to the following suggested mechanism :[15]

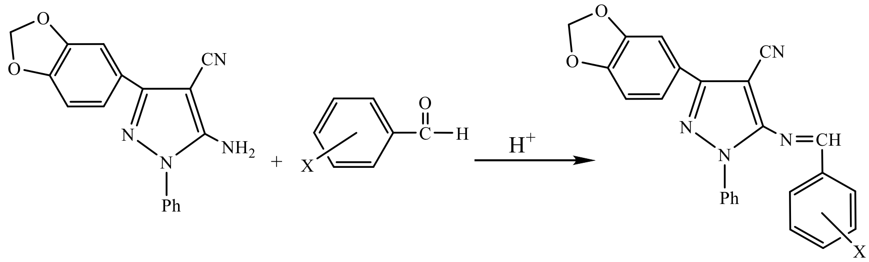


(1)

Scheme (2): The mechanism formation of compound (1)

This compound was identified via spectroscopic methods . So , in U.V spectra it gave absorption band at λ_{max} (nm): (340 and 354) refer to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ respectively . Whereas, in FT-IR it shown stretching vibration band at (υ cm^{-1}): (3210),(2699) refer to the primary aromatic amine and nitrile group in addition to the other absorption bands listed in experimental part which came in the agreement with suggested structure .

Further more, the reaction of compound (1) with substituted benzaldehyde in acidic media from glacial acetic acid afford the corresponding Schiff bases (2-5) as shown in the following equation:



…….(1)

(2-5)

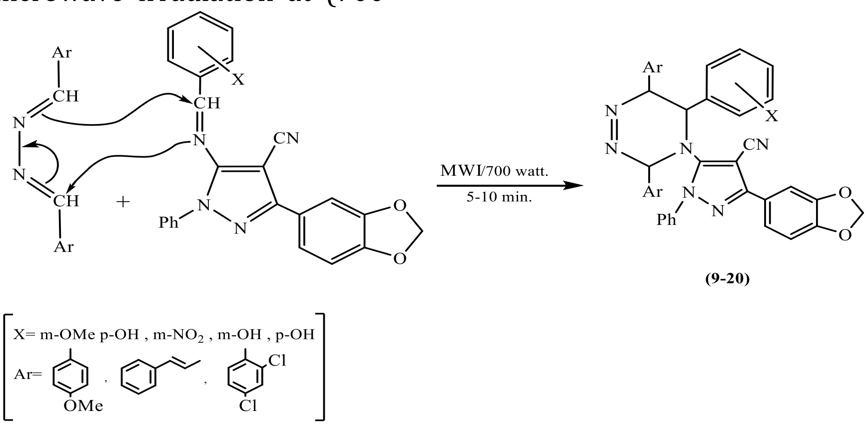
[X= m-OMe p-OH , m-NO_2 , m-OH , p-OH]

These Schiff base were identified by physical and spectral methods Tables (1 and 3) respectively . Since , in U.V spectra they shown clear absorption bands at λ_{max} (nm): (340-313) and (420-354) refer to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ and due to the increasing of polarity, whereas in FT-IR spectra they shown significant absorptions bands at (υ cm^{-1}): (1598-1502) refer to the (C=N) functional group with the absence of the absorption band of the (NH_2) group and the appearance of the absorption band of nitrile group and other functional groups which gave an indication for the Schiff base formation .

Table(3): The spectral data of compounds (2-5)

Comp. No.	FT- IR υ(cm⁻¹)								Others	U.V/ MeOH λ max (nm)
	OH	=CH	CN	C=C	C=N acyclic	C=N cyclic	C-O-C asym.	C-O-C sym.		
2	3309	3021	2347	1600	1503	1485	1253	1037	CH_3 asym. 2935 sym. 2899	354, 340
3	—	2957	2369	1598	1523	1485	1251	1035	NO_2 asym. 1444 sym. 1346	356, 340
4	3283	3022	2348	1683	1598	1487	1253	1035	—	419,313
5	3417	2926	2319	1600	1502	1487	1253	1037	—	420,340

Finally, these Schiff bases (2-5) were underwent Diels-Alder reaction via it's reaction with diarylidene hydrazine (6-8) and also accelerated by microwave irradiation at (700 watt) for (5-10 minute) these one-pot two component reaction proceeded through the following mechanism [18] to afford 1,2,4-triazine derivatives (9-20)

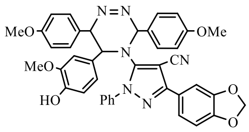
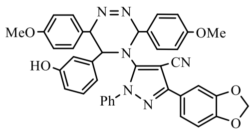
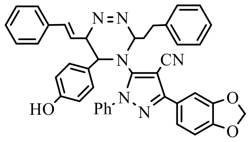
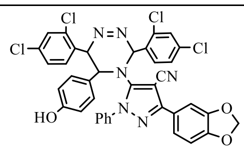


Scheme (3): Synthesis mechanism of compound (9-20)

The 1,2,4-triazine derivatives (9-20) shown an absorption bands in U.V spectra at λ_{max} (nm): (400-317) and (388-211) refer to the n→π* and π→π* and also due to the increasing of the ring system . Whereas in FT-IR they gave stretching vibration bands at (1603-1540 cm^{-1}) refer to the (N=N) functional group with the absence of the absorption bands of (C=N) of Schiff base , this indicate clearly the formation of the Diels-Alder adduct represented by compounds 1,2,4-triazine derivatives (9-20).

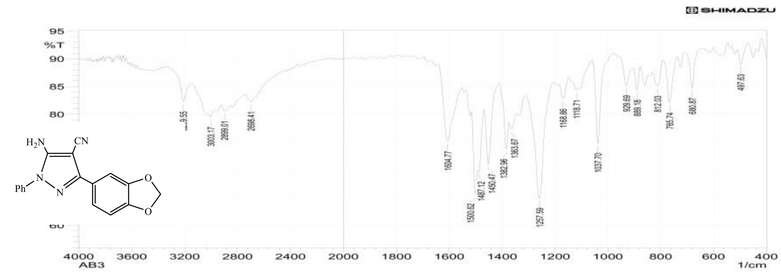
Furthermore, the compounds (9,11,16 and 20) shown a significant peaks at δ(ppm): (1.23-3.93) refer to the 1,2,4-triazine protons in addition to the AB system which appeared as (d-d) peaks in all compounds including para substituent in it's structures Table (4). Which came in good agreement with the suggested structures .

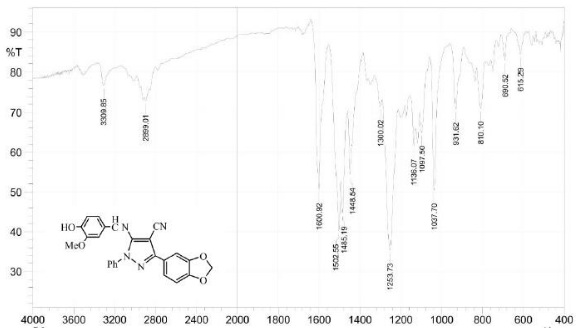
Table(4): ^{1}H-NMR spectral data of compounds (9,11,16,20)

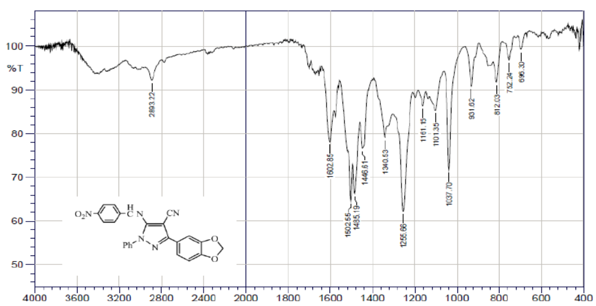
Comp .No.	Structure	^{1}H-NMR δ(ppm)
9		(s,3.74,3 OCH_3);(m,3.82-3.93,Triazine);(s,5.98,CH_2-piperonal);(m,6.04-6.98,piperonal ring);(AB system)(d-d,7.04-7.83,p-OCH_3 and p-OH phenyl) ;(m,7.87-8.64,phenyl ring) ;(s,9.90,OH)
11		(s,3.74,2 OCH_3);(m,3.82-3.93,Triazine);(s,6.08,CH_2-piperonal ; (m,6.12-6.98,piperonal ring);(AB system)(d-d,7.07-7.84,p-OCH_3 ,phenyl);(m,7.87-8.64,phenyl ring);(s,9.80,OH)
16		(d,1.24,4H cinnamaldehyde);(m,2.41-2.45,Triazine) ;(s,5.98 ,CH_2-piperonal);(m,6.04-6.13,piperonal ring);(m,6.98-7.92, and 8.50, phenyl ring);(s,8.39,OH);(AB system)(d-d,8.63-8.73,p-OH phenyl ring)
20		(m,1.23-1.25,Triazine);(s,5.97,CH_2-piperonal);(m,6.04-6.14, piperonal ring);(m,6.62-7.81,phenyl ring);(s,7.97,OH);(AB system)(d-d,8.10-8.92,p-OH phenyl)

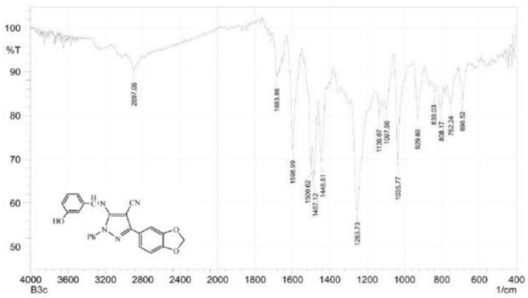
Conclusion

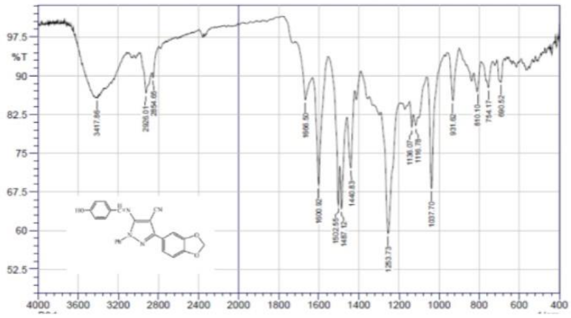
Actually, substituted 5-amino pyrazole (1) and the 1,2,4-triazine derivatives (9-20) have been prepared through one-pot green chemistry grinding and microwave irradiation techniques respectively, which gave yield enhancement with simple, efficient method and reducing the reaction time . Furthermore, thin layer chromatography (T.LC) measurement clearly indicate the formation and purity of the prepared compounds by comparing it's (R_f) value with those of starting materials

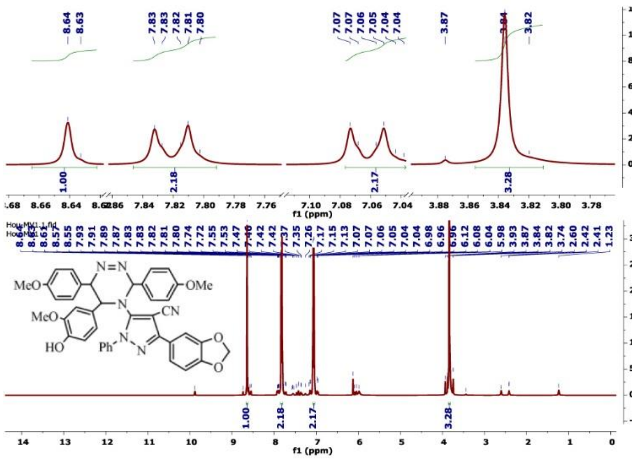












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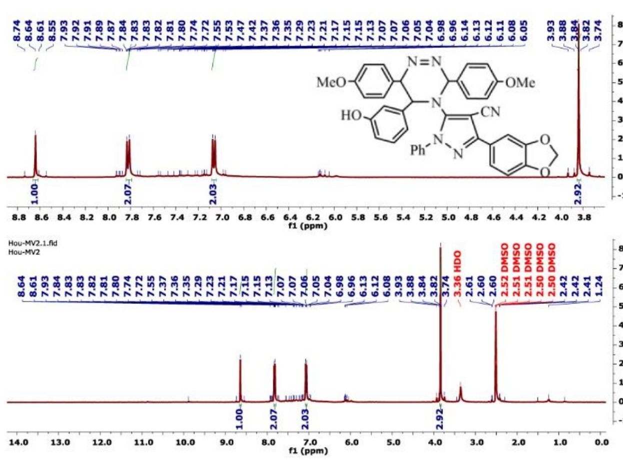

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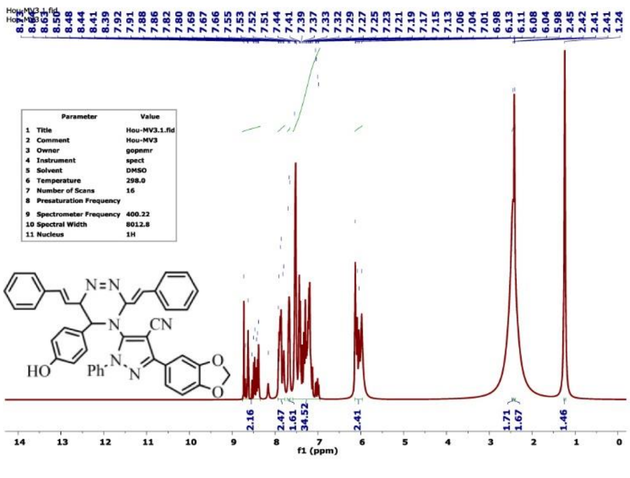

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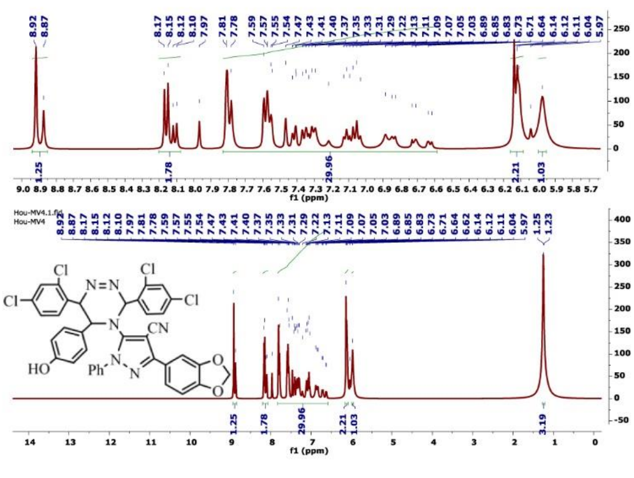

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