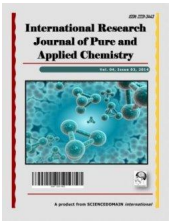

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One Pot Synthesis and Spectroscopic Characterization of Novel 8-Azacoumarin Derivatives as Eco-Friendly Insecticidal Agents

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAAS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author KA managed the analyses of the study. Author SAR managed the literature searches. Author MAAS managed Biological part. All authors read and approved the final manuscript.

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ABSTRACT

A series of five 8-azacoumarin derivatives bearing aryl moieties at C-5 and C-7 designed and synthesised by a concise procedure utilising grinding and ultrasound approaches. The multi-component protocols proceeded smoothly in the absence of solvent to furnish the target products in moderate to good yields. All the synthesised molecules characterised via ^{1}HNMR, ^{13}CNMR, IR, Mass spectra, and elemental analyses. In this article, we examined the insecticidal activity of some of the synthesized 8-azacoumarin derivatives as a new trend to the control cotton leafworm *Spodoptera littoralis* that considered the most serious attacking pest on cotton.

Keywords: Azacoumarin; chalcones; ultrasonic irradiation; grindstone; insecticidal activity; and cotton leafworm Spodoptera littoralis.

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1. INTRODUCTION

A plethora of coumarin and coumarin-related compounds in nature and their broad range of therapeutic potential put them as some of the most promising targets [1]. Natural and synthetic coumarin derivatives have proved for many years to have diverse and significant therapeutic potential such as antimicrobial, [2] anti-inflammatory [3], analgesic [4], anticancer [5], anticoagulant [6], antioxidant [7], anti-HIV [8] activities. In particular, a large number of derivatives have shown cytotoxic activity both in vitro and in vivo [9,10]. Furthermore, coumarins have been widely applied in fluorescent probes and caging chemistry [11]. It is also worthy to mention that coumarin derivatives have shown a wide range of activities as insecticidal and acaricidal agents [12-14]. Due to all of the aforementioned facts, synthesis of analogues having coumarin moiety is an urgent demand. Moreover, coumarin has become an important scaffold to construct different analogues of coumarin-containing compounds to carry out more biological investigations. The synthetic routes for coumarins have been well developed by conventional strategies such as Perkin [15], Knoevenagel [16], Wittig [17], Clasien [18], Michael [19], Reformatsky [20] and Pechmann reactions [21]. In recent years, eco-friendly procedures were reported to proceed with high selectivity and yield. Such non-conventional procedures include solid phase catalysts [22-23], microwave-assisted irradiation [24]. Accelerated concern about environment and safety has attracted global efforts to develop green eco-friendly procedures. Therefore, ultrasound Promoted [25] synthesis in aqueous media and solvent-free synthesis [26] had emerged and increasingly used in organic synthesis. Compared with the aforementioned conventional methods, those methods are much more environmentally tolerant and easily controlled. As an advantage, a large number of organic reactions have been carried out in higher yield, shorter reaction time and milder condition. In all reactions, organic solvents are always being used. Recently, organic reactions in water as the solvent instead of using harmful organic solvents have drawn much more attention, because water is a cheap, safe and environmentally benign solvent. More convenient and rapid synthetic procedures that are energy efficient became highly desirable such as grindstone [27-28] and one pot multi-component reactions [29]. This kind of green chemistry is widely used nowadays and became significant in combinatorial chemistry due to its process simplicity, mild conditions, atomic economy and extension of the scope of substrates. Replacement of a phenyl with a pyridyl in coumarin leads to azacoumarin (isostere of coumarin), such replacement is one of the most successful strategies not only to increase the hydrophilicity but also to improve metabolic stability. Therefore, azacoumarins have emerged as a plausible class of biological candidates but they have not received enough attention. In particular, 8-azacoumarins showed remarkable applications such as fluorophores [30]. Few reports about synthetic strategy regarding 8-azacoumarin derivatives have been reported most likely because access to this scaffold is challenging. The synthetic routes for coumarins have been well developed, but on the other hand, the corresponding synthesis of azacoumarins is difficult and, as far as we know, until 2012 there was only one paper has been published concerning the preparation of a 7-azacoumarin in water as the reaction medium [31]. Recently, in some studies, 8-azacoumarin derivatives have been synthesised by electrophilic aromatic substitution reactions (SEAr), using 2-hydroxyl-6-electron-donating groups of substituted pyridines as the starting material under acidic [32] or PPh_3 activation conditions [33-34]. Only a few 8-azacoumarins, however, were synthesised by this method due to the inherent poor nucleophilicity of pyridines which means that this method is only suitable for those electron-rich pyridines, resulting in a limited number of accessible targets. To address the problem, later on, a new method for the synthesis of 8-azacoumarins that would greatly extend the substrate scope has been reported [35]. Also, it was one of our strategies to synthesise such compounds as objectives target of our work. Recently, a couple of articles have been published utilising better methods for 8-azacoumarin synthesis via microwave-assisted method [34,36-38].

Cotton leafworm *Spodoptera littoralis* is considered as the most serious pest on cotton in Egypt. Larvae of this pest also attack other crops such as vegetables, ornamental and orchard trees in the Mediterranean area [39]. After extensive and misuse of broad-spectrum chemical insecticides in controlling cotton leafworm created high levels of resistance to organophosphorus, carbamates and pyrethroids [40]. To decrease the negative effect of the classical insecticides, there is a recognised need to find an alternative route to control of cotton leaf worm [41]. In this article, we will examine

the insecticidal activity of the azacoumarin derivatives as a new trend to control cotton leaf worm.

2. EXPERIMENTAL

2.1 Materials and Methods

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra (υ_{max} in cm^{-1}) were recorded on FT-IR Shimadzu -8400S Spectrophotometer using KBr pellets (New York, NY, USA). ^{1}H-NMR spectra were recorded on JEOL-AL 300 spectrophotometer (Rheinstetten, Germany, 400MHz) using $CDCl_3$/DMSO-d_6 as solvents. TMS was taken as an internal standard. ^{13}C-NMR spectra were recorded on the same spectrometer (Rheinstetten, Germany) at 100MHz and referenced to solvent signals δ = 39.50 ppm for DMSO-d_6. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) used the electron ionisation technique at 70 e.v. Elentar Vario EL III automatic CHN analyser was used for elemental analyses. The CHN analyses were recorded at Central forced armed (CFA), Lucknow, India. Sonication was performed in a Toshcon model SW 4 cleaner (with a frequency of 37 KHz and operating at a maximum power of 150 W.(The purity of compounds was checked by TLC using silica gel (60-120) mesh) as an adsorbent, UV light, or iodine accomplished visualisation. All common reagents and solvents were used as obtained from commercial suppliers without further purification. Chalcone (1) were prepared by the method described in literature [42].

2.1.1 General procedure for the synthesis of 7-(Diphenyl)-5-(3-chlorophenyl)- 2-oxo-2H-pyrano[2,3-b]pyridine derivatives (6a-e).

Method (i): Chalcone (1) (0.05 mol), active methylene compounds, e.g. ethyl cyanoacetate, ethyl acetoacetate and/or diethyl malonate (0.05 mol), and ammonium acetate (0.04 mol) were ground together in a mortar. Then, this mixture was transferred into a 250-mL round bottom flask with the addition of ethanol (5 mL). The reaction flask was then placed in the maximum energy area in an ultrasonic cleaning bath (observation of the surface of the reaction solution during vertical adjustment of flask depth shows the optimum position by the point at which maximum surface disturbance occurs). The bath temperature was controlled by the addition or removal of water at 30°C. The progress of the reaction was monitored by TLC using C_6H_6: EtOAc v/v 95:5 as a solvent system. Sonication was continued until starting reactants disappeared as indicated by TLC. A yellow solid product was obtained within 20-25 min of irradiation (Table 1). After the completion of the reaction, the mixture was poured into crushed ice with constant stirring to obtain a yellow solid mass, which was dried and recrystallized from 95% ethanol.

Method (ii): A mixture of chalcone (1) (0.05 mol), active methylene compounds, e.g. ethyl cyanoacetate, ethyl acetoacetate and/or diethyl malonate (0.05 mol), and ammonium acetate (0.04 mol) was ground together in an agate mortar and pestle for 25-30 min. The colour of the reaction mixture turned into light yellow from colourless starting reactants. The progress of the reaction was monitored by TLC using C_6H_6: EtOAc 95:5 as a solvent system. Then the reaction mixture was left overnight whereby a yellow solid crude product was obtained which was recrystallised from 95% aqueous ethanol.

2.1.1.1 4-Amino-7-(diphenyl)-5-(3-chlorophenyl)- 2-oxo-2H-pyrano[2,3-b]pyridine-3-carbonitrile (6a).

Yellow crystal, IR (v, cm^{-1}): 3284, 3180 (NH_2), 3050 (ArH), 2216 (C≡N), 1743 (C=O), MS (m/z) 403.5/401.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 6H, 2Me), 5.62 (s, 2H, NH_2), 7.38-7.79 (m, 8H, ArH): ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.4, 21.7, 77.8, 103.9, 115.1, 123.3, 123.9, 126.4 (2), 128.4, 129.1 (2), 130.2, 131.7, 134.2 (2), 134.5, 135.2, 137.4, 144.2, 145.9, 156.1, 163.5 181.2; *Anal*. Calcd. for $C_{23}H_{16}ClN_3O_2$ (401.5): C 68.75, H 4.01, N 10.46. Found: C 68.39, H 4.35, N 10.01.

2.1.1.2 3-Acetyl-7-(diphenyl)-4-methyl-5-(3-chlorophenyl)-2H-pyrano[2,3-b]pyridin-2-one (6b).

Yellow crystal, IR (v, cm^{-1}): 3045 (ArH), 1741, 1682 (C=O), MS (m/z) 419/417. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 6H, 2Me), 2.62 (s, 3H, CH_3), 7.43-8.19 (m, 8H, ArH): ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 22.4, 25.6, 58.1, 105.5, 121.6, 122.7, 127.4, 127.9 (2), 129.1 (2), 131.3, 132.6, 134.2, 134.4, 134.7, 138.1, 141.6, 143.0, 145.2, 1456.7, 158.5, 164.3; *Anal*. Calcd. for $C_{24}H_{20}ClNO_3$ (417.5): C 71.02, H 4.97, N 3.45. Found: C 71.43, H 4.72, N 3.77.

2.1.1.3 Ethyl-7-(biphenyl)-5-(3-chlorophenyl)-4-methyl-2-oxo-2H-pyrano[2,3-b]pyridin-2-on-3-ylacetate (6c).

Yellow crystal, IR (v, cm^{-1}): 3460 (OH), 3045 (ArH), 1750, 1734, 1670 (C=O). MS (m/z) 451.5/449.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.2 (t, 3H, CH_3), 2.29 (s, 6H, 2Me), 4.2 (q, 2H, CH_2), 7.18-7.99 (m, 8H, ArH), 11.82(s, 1H, OH exchangeable in D_2O). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 20.3, 61.9, 99.7, 103.7, 123.0, 123.5, 126.4 (2), 127.9 (2), 129.1 (2), 131.0, 132.4, 134.2, 134.5, 134.8, 136.4, 144.7, 146.2, 158.9, 164.2, 165.6; *Anal*. Calcd. for $C_{25}H_{20}ClNO_5$ (449.5): C 66.74, H 4.48, N 3.11. Found: C66.72, H 4.21, N, 3.40.

2.1.1.4 3-Acetyl-4-amino-7-(biphenyl)-5-(3-chlorophenyl)- 2H-pyrano [2,3-b] pyridin-2-one (6d).

Yellow crystal, IR (v, cm^{-1}): 3243, 3186, (NH_2), 3055 (ArH), 1738, 1681 (C=O), MS (m/z) 420/418. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 6H, 2Me), 2.6 (s, 3H, CH_3), 7.06-7.67 (m, 8H, ArH), 12.12 (s, 2H, NH_2 exchangeable in D_2O). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 21.8, 30.3, 103.2, 108.7 123.7, 123.9, 127.4, 127.7, 129.7 (2), 130.5, 131.8 (2), 133.4, 134.2, 134.6, 138.1, 145.5, 147.4, 160.6, 163.7, 170.8, 197.5; *Anal*. Calcd. for $C_{24}H_{19}ClN_2O_3$ (418.5): C 68.82, H 4.57, N 6.69. Found: C 68.56, H 4.17, N 6.31,

2.1.1.5 7-(Biphenyl)-5-(3-chlorophenyl)-4-methyl-2-oxo-2H-pyrano[2,3-b]pyridin-3-carbonitrile (6e).

Yellow crystal, IR (v, cm^{-1}): 3070 (ArH), 2215 (CN), 1745 (C=O); MS (m/z) 402/400. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.21 (s, 6H, 2Me), 2.5 (s, 3H, CH_3), 7.32-7.87 (m, 8H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 19.2, 22.0, 97.1, 104.6, 116.8, 123.2, 123.8, 127.4, 127.7 (2), 129.1 (2), 131.1, 132.5, 134.3, 134.5, 134.8, 138.3, 146.3, 146.9, 156.8, 165.1, 170.2; *Anal*. Calcd. for $C_{24}H_{17}ClN_2O_2$ (400.5): C 71.91, H 4.27, N 6.99. Found: C 70.98, H 4.68, N 6.58.

2.2 Effect of Azacoumarin Derivatives against Cotton Leaf Worm *Spodoptera littoralis* (boised)

2.2.1 Insects:

Rearing of cotton leaf worm carried out on Central Agricultural Pesticides Laboratory (CAPL) under room temperature (25 ± 2ºC with 65 ± 5 Rh) and at a 12: 12 h (light: dark). The larvae provided daily with clean and dry castor leaves then transferred into clean suitable containers [41].

2.2.2 Susceptibility test

The response of the fourth instar larvae towards various compounds (6a-e) was determined by using the leaf-dipping technique. A series of concentrations 25, 50, 100, 200, 400 and 800 ppm were prepared in (ethanol, water and tween 80) mixture solution, where controls were treated by (tween 80 and water) mixture only for every compound. Castor bean leaves dipped in prepared solutions with varying concentrations for 10 seconds for every compound. Treated castor bean leaves left in the air – dry at room temperature. Ten 4 instar larvae placed with treated leaves into Petri-dishes and hold at room temperature. Three replicates for every concentration were treated. Mortality recorded after 24 hrs of treatment. Mortality percentage corrected according to controls using Abbott's formula (1925) [43]. The LC_{50}, LC_{90}, slope and toxicity index was estimated [44].

3. RESULTS AND DISCUSSION

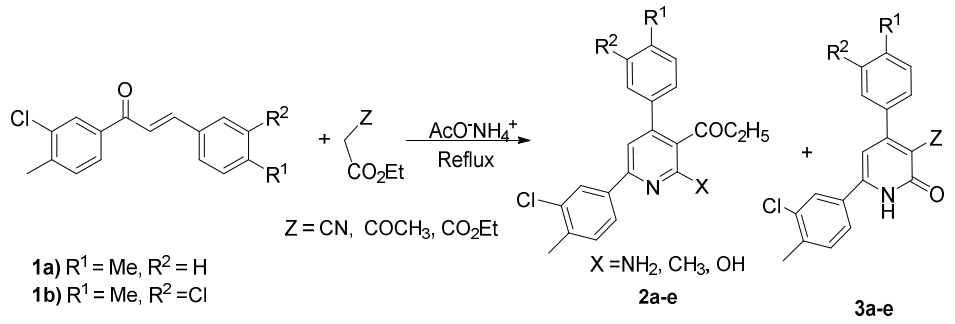
3.1 Chemistry

On attempting to synthesise the target compounds under the conventional condition of thermal heating, the reactions did not proceed to completion, and only one molecule of the active methylene compound was incorporated as shown in scheme 1. It was previously reported that the reaction of chalcone 1 with different active methylene such as ethyl cyanoacetate, ethyl acetoacetate, diethyl malonate, and malononitrile in the presence of ammonium acetate afforded the pyridine esters 2a-e and 2-pyridone derivatives 3a-e under thermal and microwave reaction conditions. [45-48]

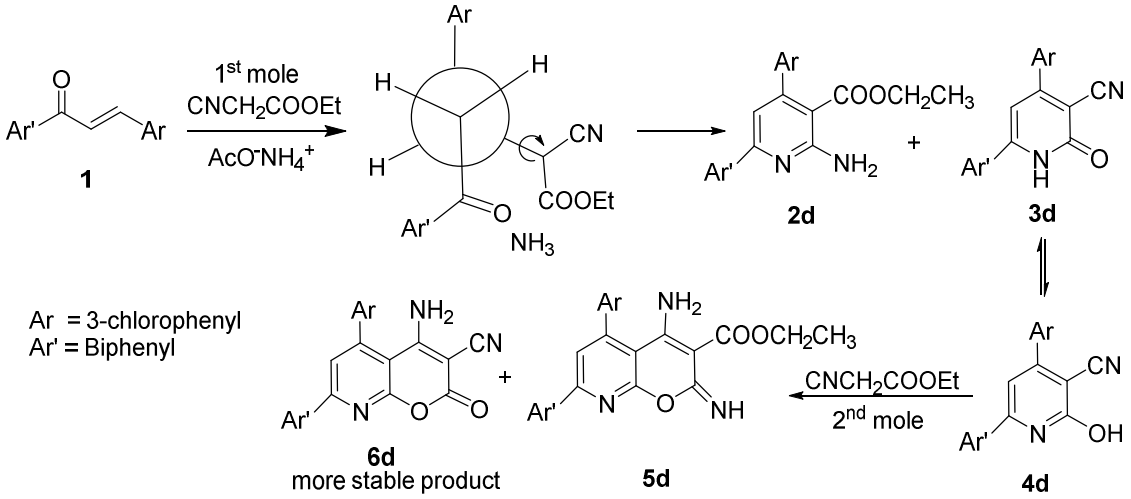
In the present work, we can report the one-pot reaction of Chalcone (1), 2-substituted ethyl acetate and ammonium acetate in which they were submitted to react in a multicomponent response (MCR) by grindstone chemistry altogether without using tetrahydrofuran (THF) for 25-30 minutes (Scheme 2). Afterwards, the reaction mixture was left overnight at room temperature to yield crude yellow solid products (6a-e). Nevertheless, in ultrasonic irradiation, the requisite amount of THF was used to yield the same products. Some data regarding the yield, reaction time and melting points of both

procedures are tabulated in Table 1. However, an ultrasonic irradiation, the 2-pyridone 3 can be isomerised to the reactive lactim compound 4 (Scheme 2).

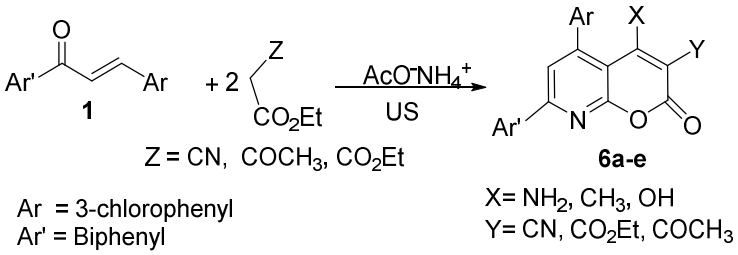
Upon using two equivalents of the same active methylene such as ethyl cyanoacetate, ethyl acetoacetate, or diethyl malonate in a two-component reaction, the pyrano[2,3-b]pyridine derivative was obtained as a sole product. For example, when compounds 1 were treated with two moles of ethyl cyanoacetate, ethyl acetoacetate or diethyl malonate, the azacoumarin derivatives 6a-e respectively afforded as sole product in each case (Scheme 3). The reaction possibly proceeded according to the following mechanism (Scheme 4).



Scheme 1. Reaction under the conventional thermal condition



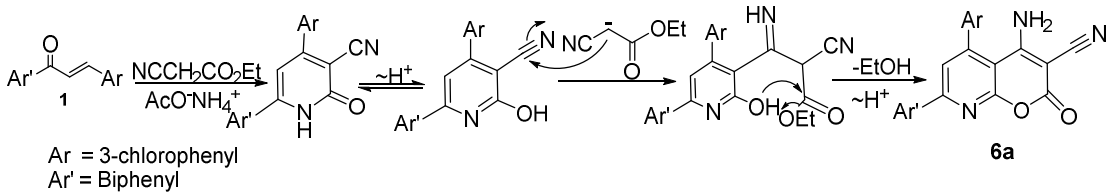
Scheme 2. Outline the course of the reaction via ultrasonic irradiation



Scheme 3. Synthesis of compounds 6a-e

Table 1. Synthesis of 4-X-5-(Biphenyl)-7-(3-chlorophenyl)-2-oxo-2H-pyrano[2,3-b]pyridine-3-Y (6a-e)

Substrate	Product	X	Y	Ultrasonic irradiation T (min).	Yield %	Grinding T (min).	Yield %	m.p.(°C)
1	**6a**	NH_2	CN	25	82	35	40	180-182
1	**6b**	OH	$CO_2CH_2CH_3$	25	90	30	44	168-170
1	**6c**	CH_3	$COCH_3$	20	90	25	45	118-120
1	**6d**	CH_3	CN	25	37	30	36	234-236
1	**6e**	NH_2	$COCH_3$	25	45	30	40	138-140



Scheme 4. Mechanistic illustration of the two-component strategy for 6a synthesis

When the reactions were carried out using two equivalents of the same active methylene such as ethyl cyanoacetate, ethyl acetoacetate, or diethyl malonate in a pseudo-three component reaction, one pyrano[2,3-b]pyridine derivative was obtained as a sole product. For example, when compounds 1 were treated with two moles of ethyl cyanoacetate, ethyl acetoacetate or diethyl malonate, the azacoumarin derivatives 6a-e were afforded as sole product in each case. On the other hand, by applying a three-component reaction strategy using a mixture of two different active methylene compounds, e.g. ethyl cyanoacetate and ethyl acetoacetate and vice versa, two pyrano[2,3-b]pyridine derivatives 6d and 6e were afforded respectively. Both of the above-supposed techniques provided products in good to excellent yields with simple and mild reaction conditions. But in case of using ethyl cyanoacetate and ethyl acetoacetate with chalcone 1 via three-component reaction, two products of pyrano[2,3-b]pyridine derivatives 6d and 6e were afforded respectively that inverses the reactivity of the diethyl malonate precursor rather than ethyl acetoacetate as outlined in (Scheme 5).

As stated vide supra, both of the above-supposed techniques provided products in good to excellent yields with simple and mild reaction conditions. A mechanistic illustration of the three-component strategy for 6d and 6e formation is illustrated in Scheme 6.

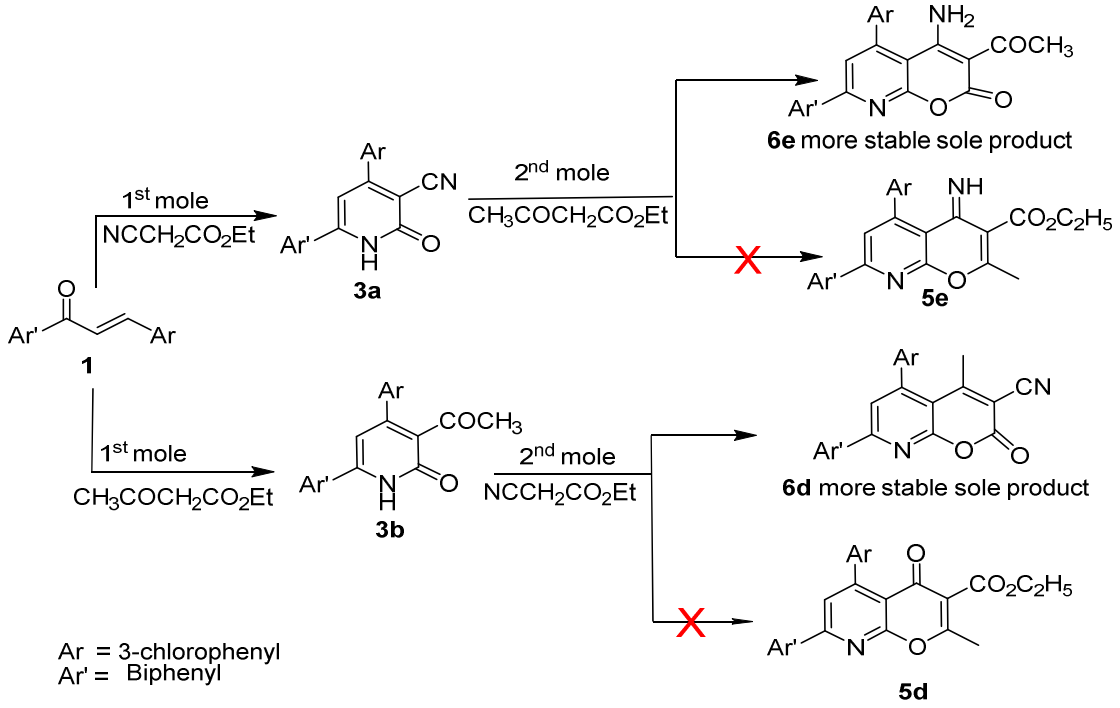
Structures of all synthesised compounds were established on the basis of elemental and spectral analyses (IR, NMR and MS). As an evidence, the characteristic peak at 1660 cm^{-1} corresponding to (vC=O) in the IR spectrum of chalcones of 1 disappeared in the IR spectra of all 7-(Dilphenyl)-5-(3-chlorophenyl)-2-oxo-2H-pyrano[2,3-b]pyridine derivatives (6a-e).

Moreover, the appearance of the stretching vibration of NH_2 as broad bands in the region 3440-3300 and another band at 2216 cm^{-1} corresponding to C≡N confirmed the formation of desired compounds 6a and 2. The ^{1}H-NMR spectrum of 5-(diphenyl)-7-(3-chlorophenyl)-2-oxo-2H-pyrano[2,3-b]pyridine derivatives 6 revealed characteristic singlet peaks δ=10.22-11.82 ppm region corresponding to OH group. On the other hand, ^{1}H-NMR spectra of 6a, 6b, 6c, 6d and 6e revealed characteristic singlet peaks at δ=10.22-11.82 ppm region corresponding to NH_2 moieties. Also, a multiplet peak at δ= 6.79-8.01 ppm region (protons of benzene and 1H proton of pyridyl ring) emerged which ascertained their corresponding molecular structures.

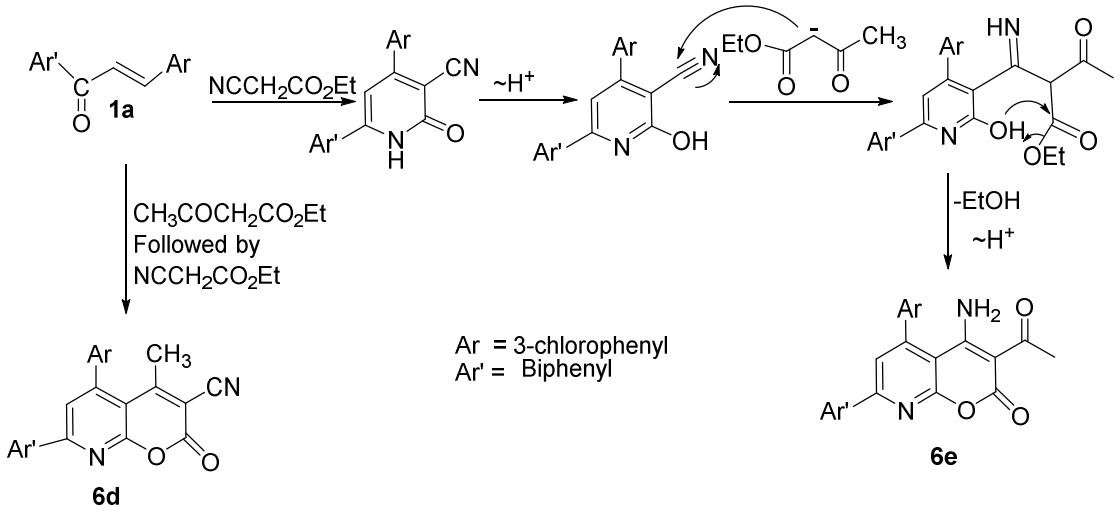
3.2 Biological Activity

Data in Table 2 represented that, compound 6b was the most effective compound against cotton leafworm where its LC_{50} was 24.01 ppm followed by compounds 6a and 6e where their LC_{50} values were 30.46 and 41.23 ppm, while compounds 6c and 6d were the lowest effective compound against cotton leafworm where LC_{50} was 194.38 and 225.27 ppm. The toxicity index of compounds was 100, 78.82, 58.23,

12.35 and 10.66% for compounds 6b, 6e, 6a, 6c and 6d respectively. According to the structure-activity relationship (SAR), the substituent in position 4 of the main molecules 8-azacoumarin had different substituted OH group for compound 6b where it has highly electronegative electron withdrawing group, which decreases the electron density of tested nuclei and increases its reactivity. On the other hand, the substituent groups of compounds 6a and 6e are NH_2 groups while CH_3 for compounds 6c and 6d which all are not strong as electron withdrawing groups compared with OH so their nuclei are less reactive than 6b [49-52].



Scheme 5. Ultrasonic reaction of chalcone 1 with active methylene via three-component reaction



Scheme 6. Mechanistic illustration for the three-component strategy

Table 2. The insecticidal activity of some azacoumarin derivatives against cotton leafworm (*Spodoptera littoralis)*

		Concentrations in ppm							Slope	LC_{50}	LC_{90}	Toxicity Index
		12.5	25	50	100	200	400	800				
Mortality percentage	6a	28.58	40.63	53.64	66.27	77.29	85.92	92.01	1.091	41.23	616.01	58.23
	6b	40.32	50.60	60.85	70.39	78.70	85.45	90.59	0.865	24.01	728.77	100
	6c	6.23	12.54	22.35	35.49	50.63	65.70	78.59	1.290	194.38	1915.91	12.35
	6d	8.37	14.69	23.61	34.90	47.74	60.81	72.75	1.100	225.27	3294.68	10.66
	6e	37.30	47.13	57.15	66.73	75.32	82.56	88.27	0.838	30.46	1031.59	78.82

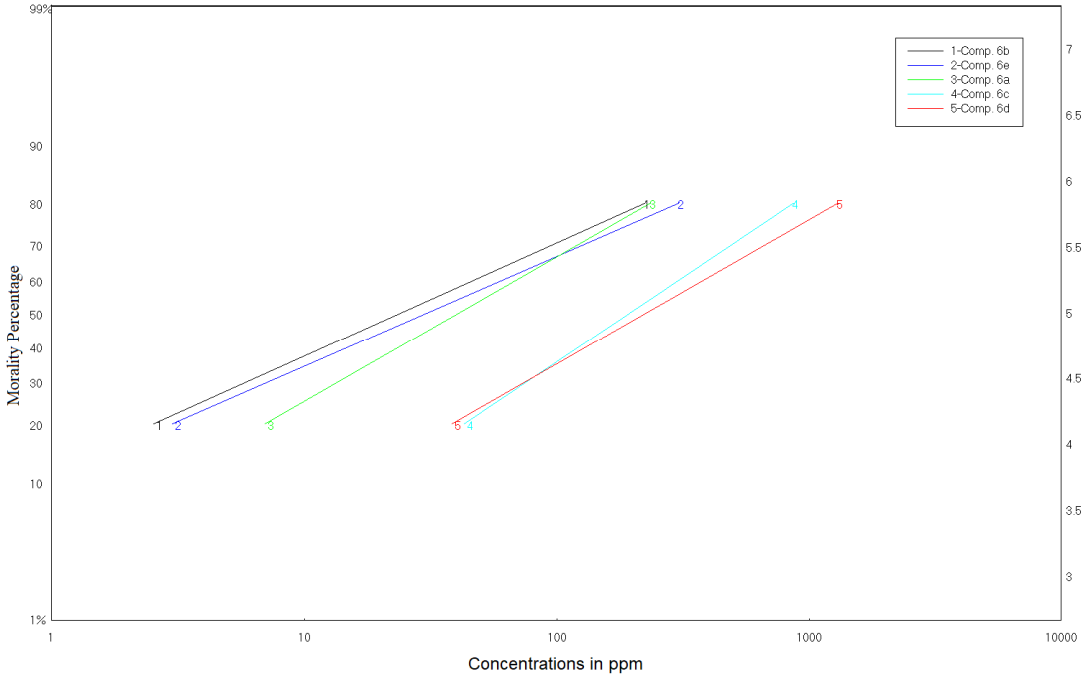


Fig. 1. Ldp lines of 8-azacoumarin derivatives against *Spodoptera littoralis*

4. CONCLUSION

In this article, the synthesis and insecticidal activities of some 8-Azacoumarin derivatives are reported. Firstly, 8-Azacoumarin derivatives 6a-e were synthesized via two-step, simple, novel and eco-friendly synthetic protocols. Comparative study regarding the outcome yields and the time or reactions has been done on those ultrasound-assisted and grinding strategies. Full structural elucidations for all synthesised compounds are based on elemental and spectroscopic analyses. Secondly, assessment of the insecticidal activities of the synthesised compounds was investigated.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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