Journal of the Iranian Chemical Society (2018) 15:2093–2105
https://doi.org/10.1007/s13738-018-1402-3

ORIGINAL PAPER

One-pot synthesis, spectroscopic characterization and DFT study of novel 8-azacoumarin derivatives as eco-friendly insecticidal agents

Sameh A. Rizk[1] · Galal A. Elsayed[1] · Maher A. El-Hashash[1]

Received: 4 January 2018 / Accepted: 13 May 2018 / Published online: 15 June 2018

Abstract

A series of sixteen 8-azacoumarin derivatives bearing aryl moieties at C-5 and C-7 was designed and synthesized by a concise and facile procedure utilizing grinding and ultrasound approaches. The efficient multi-component protocols proceeded smoothly and in the absence of solvent to furnish the target products in moderate to good yields. All the synthesized molecules were characterized via ^{1}HNMR, ^{13}CNMR, IR, mass spectra, and elemental analyses. The density functional theory (DFT) was then used to discover the structural and electronic characteristics of such compounds. Finally, an insecticidal study against *Plutella xylostella* and *Helicoverpa armigera* on the synthesized compounds is reported. The bioassay results indicated that some of the tested compounds showed potency ranging from good to moderate. In particular, analogs **6i** and **6l**, among the tested compounds, showed even more potency than commercial chlorpyrifos. On the other hand, the rest of the tested compounds showed moderate to weak activities.

Keywords Azacoumarin · Chalcones · Ultrasonic irradiation · Grindstone · DFT · Insecticidal activity

Introduction

A plethora of coumarin and coumarin-related compounds in nature and their broad range of therapeutic potential make them 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], and anti-HIV activities [8]. 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, the synthesis of analogs having a coumarin moiety is an urgent demand. Moreover, coumarin has become an important scaffold to construct different analogs 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 have been reported to proceed with high selectivity and yield. Such non-conventional procedures include solid phase catalysts [22, 23] and microwave-assisted irradiation [24]. Accelerated concern about environment and safety has attracted global efforts to develop green eco-friendly procedures. Therefore, ultrasound promoted synthesis in aqueous media and solvent-free synthesis [25, 26] had emerged and increasingly used in organic synthesis. Compared with the aforementioned conventional methods, these methods are much more environmentally tolerant and easily controlled. As an advantage, a large number of organic reactions have been carried out with higher yield, shorter reaction time, and milder condition. In all reactions, organic solvents are always 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

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-018-1402-3) contains supplementary material, which is available to authorized users.

✉ Sameh A. Rizk
samehrizk@sci.asu.edu.eg; samehrizk2006@gmail.com

[1] Department of Chemistry, Faculty of Science, Ain Shams University, Cairo 11566, Egypt

convenient and rapid synthetic procedures that are energy efficient have become highly desirable such as grindstone [27, 28] and one-pot multi-component reactions [29]. This kind of green chemistry is widely used nowadays and has become 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), and 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 the 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 published concerning the preparation of a 7-azacoumarin in water as the reaction medium [31]. Recently, in some studies, 8-azacoumarin derivatives have been synthesized 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 few 8-azacoumarins, however, were prepared 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]. Recently, a couple of articles have been published utilizing better methods for 8-azacoumarin synthesis via the microwave-assisted method [34, 36, 37].

Results and discussion

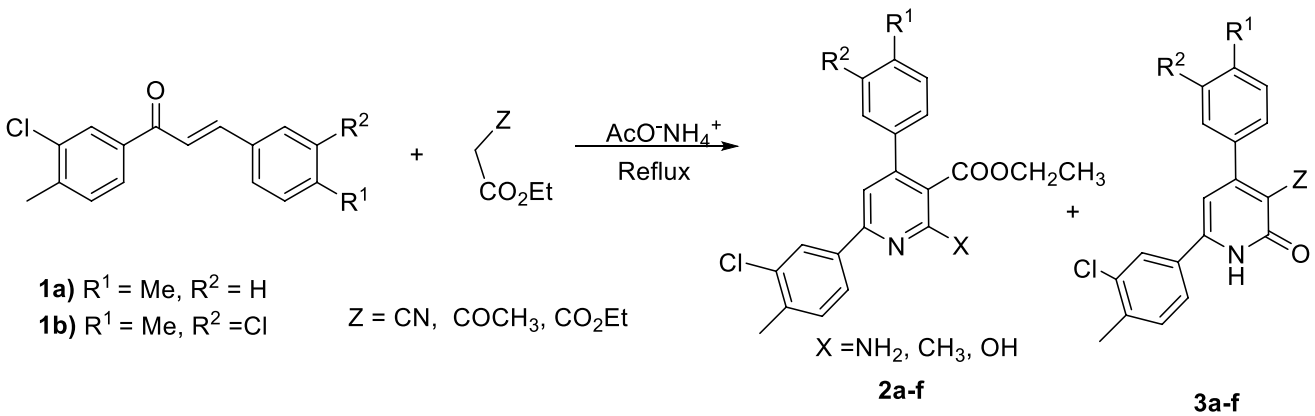
Chemistry

On attempting to synthesize the target compounds under 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.

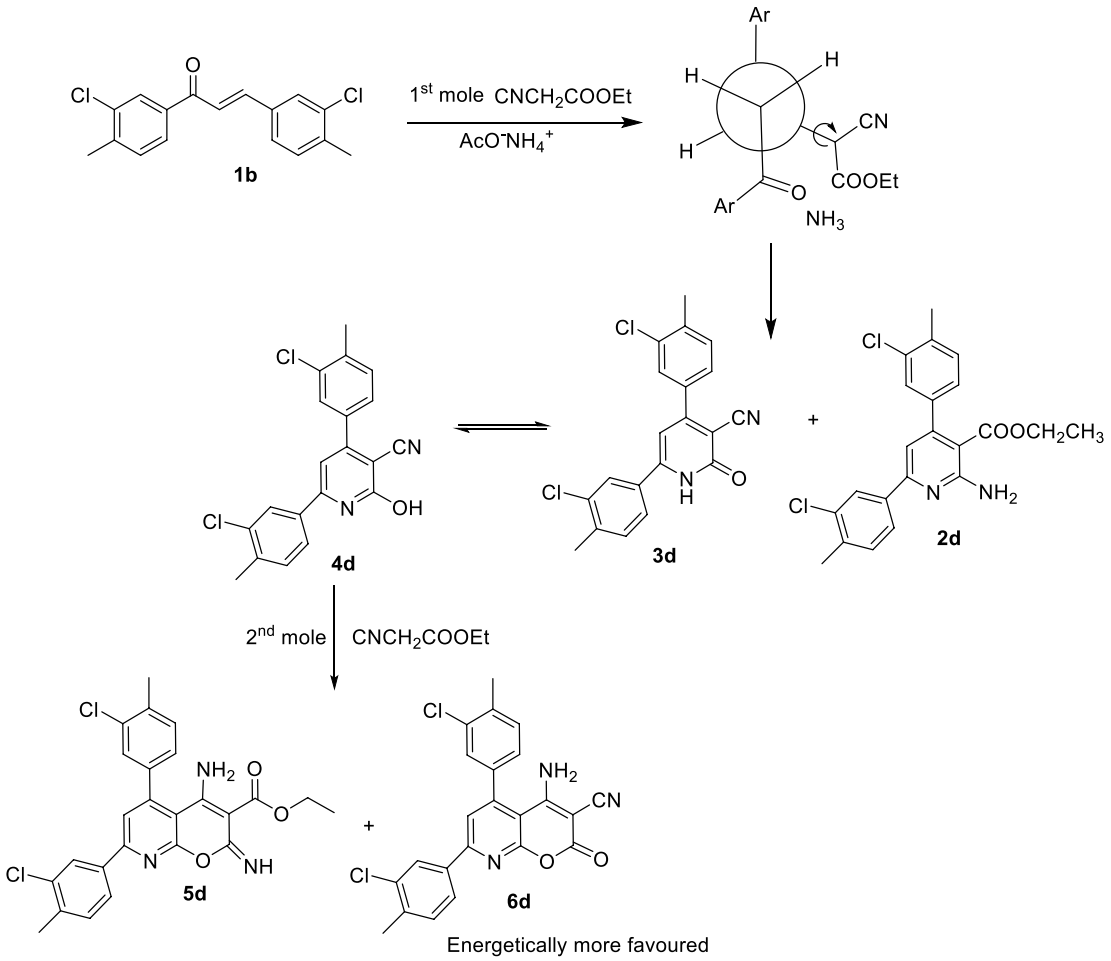
It was previously reported that the reaction of chalcone **1a, b** with different active methylenes such as ethyl cyanoacetate, ethyl acetoacetate, diethyl malonate, and malononitrile in the presence of ammonium acetate afforded the pyridine esters **2a–f** and 2-pyridone derivatives **3a–f** under thermal and microwave reaction conditions [38–41].

In the present work, we report on the one-pot reaction of chalcone (**1a–c**), 2-substituted ethyl acetate, and ammonium acetate in which they were subjected to react in a multi-component reaction (MCR) by grindstone chemistry, together without using tetrahydrofuran (THF) for 25–30 min (Scheme 2). Afterward, the reaction mixture was left overnight at room temperature to yield crude yellow solid products (**6a–p**). Nevertheless, in ultrasonic irradiation, the requisite amount of THF was used to yield the same products. Some comparative data regarding the yield, reaction time, and melting points of both procedures are shown in Table 1. However, in ultrasonic irradiation, 2-pyridone **3** can be isomerized to the reactive lactim compound **4** (Scheme 2) that proceeds to afford the energetically favorable azacoumarin product **6** (see more in DFT section).

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



Scheme 1 Reaction under conventional thermal condition



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

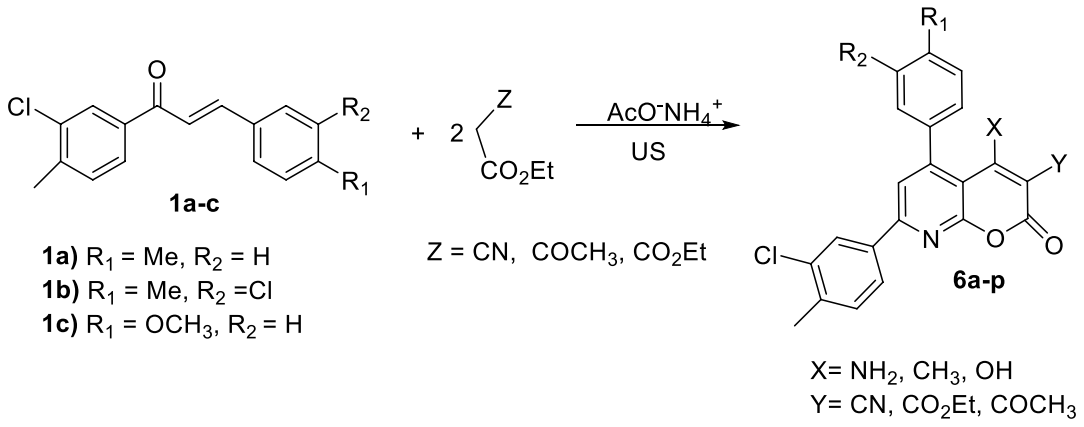
Table 1 Synthesis of 4-X-5-(4-chlorophenyl)-7-(3,4-dimethyl phenyl)-2-oxo-2H-pyrano[2,3-b] pyridine- 3-Y (**6a-p**)

Substrate	Product	R_1	R_2	X	Y	Ultrasonic irradiation T (min).	Yield %	Grinding T (min).	Yield %	m.p. (°C)
1a	**6a**	Me	H	NH_2	CN	25	82	35	40	180–182
1a	**6b**	Me	H	CH_3	$COCH_3$	25	90	30	44	168–170
1a	**6c**	Me	H	OH	$CO_2CH_2CH_3$	20	90	25	45	118–120
1a	**6d**	Me	H	NH_2	$COCH_3$	25	37	30	36	234–236
1a	**6e**	Me	H	CH_3	CN	25	45	30	40	138–140
1a	**6f**	Me	H	NH_2	$CO_2CH_2CH_3$	25	45	30	40	146–148
1a	**6g**	Me	H	OH	CN	25	40	30	30	116–118
1a	**6h**	Me	H	CH_3	$CO_2CH_2CH_3$	25	85	30	50	116–118
1b	**6i**	Me	Cl	NH_2	CN	25	88	25	50	180–182
1b	**6j**	Me	Cl	CH_3	$COCH_3$	25	90	30	43	174–176
1b	**6k**	Me	Cl	OH	$CO_2CH_2CH_3$	20	83	25	50	136–138
1b	**6l**	Me	Cl	NH_2	$COCH_3$	25	40	30	50	202–204
1b	**6m**	Me	Cl	CH_3	CN	20	40	30	40	130–132
1c	**6n**	OMe	H	NH_2	CN	25	80	30	55	194–196
1c	**6o**	OMe	H	CH_3	$COCH_3$	25	75	30	35	156–158
1c	**6p**	OMe	H	OH	$CO_2CH_2CH_3$	25	85	30	35	176–178

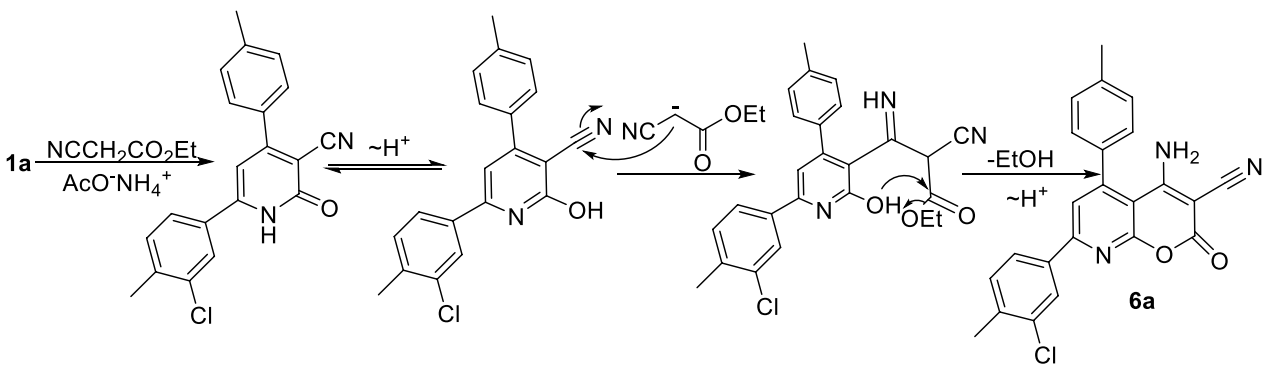
product. For example, when compounds **1a–c** were treated with two moles of ethyl cyanoacetate, ethyl acetoacetate, or diethyl malonate, the azacoumarin derivatives **6a–c**, and **6i–k** and **6n–p**, respectively, were the sole products in each case (Scheme 3). The reaction possibly proceeded according to the following mechanism (Scheme 4).

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–c, 6i–k** and **6n–p** were the sole products 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 produced, 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 produced, respectively. Similarly to the latter reaction with ethyl cyanoacetate and diethyl malonate, chalcone **1** yielded correspondingly **6f** and **6g**. On the other hand, subsequent treating of chalcone **1** with ethyl acetoacetate followed by diethyl malonate in the same manner yielded one product of pyrano[2,3-b]pyridine derivative **6h** that inverses the reactivity of the diethyl malonate precursor rather than ethyl acetoacetate (Table 2 and as outlined in Scheme 5). Figures 1 and 2 indicate the stability of the desired azacoumarin product **6a** than the corresponding chromone product **5a**. 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 shown in Scheme 6.

Similarly, on treatment of **1a** with ethyl cyanoacetate followed by diethyl malonate and vice versa, the corresponding **6f** and **6g** were obtained, respectively. On the other hand, subsequent treatment of chalcone **1a** with ethyl acetoacetate, followed by diethyl malonate in the same manner yielded one



Scheme 3 Synthesis of compounds **6a–p**



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

Table 2 Outline of the one-pot reaction with similar and different active methylene compounds

Comd. no.	Two-component reaction		Three-component reaction		
	Active methylene (2 moles)	Product	Active methylene		Product
			1st molecule	2nd molecule	
1a	$CH_2(CN)COOEt$	**6a**			
1a	$CH_2(COCH_3)COOEt$	**6b**			
1a	$CH_2(COOC_2H_5)_2$	**6c**			
1a			$CH_2(CN)CO_2Et$	$CH_3COCH_2CO_2Et$	**6d, 6e**
1a					
1a			$CH_2(CN)COOEt$	$CH_2(COOC_2H_5)_2$	**6f, 6g**
1a					
1a			$CH_3COCH_2CO_2Et$	$CH_2(COOC_2H_5)_2$	**6h, 6i**
1b	$CH_2(CN)COOEt$	**6j**			
1b	$CH_2(COCH_3)COOEt$	**6k**			
1b	$CH_2(COOC_2H_5)_2$	**6l**			
1b			$CH_2(CN)COOEt$	$CH_2(COCH_3)COOEt$	**6m, 6n**
1b					
1c	$CH_2(CN)COOEt$	**6o**			
1c	$CH_2(COCH_3)COOEt$	**6p**			
1c	$CH_2(COOC_2H_5)_2$	**6q**			

product of pyrano[2,3-b] pyridine derivative **6h** that inversed the reactivity of the diethyl malonate precursor rather than ethyl acetoacetate (Table 2).

The structures of all synthesized 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 ($\nu C=O$) in the IR spectrum of chalcones of **1a–c** disappeared **i**n the IR spectra of all 7-(3-chloro-4-methylphenyl)-5-(aryl)-2-oxo-2H-pyrano[2,3-b]pyridine derivatives (**6a–p**).

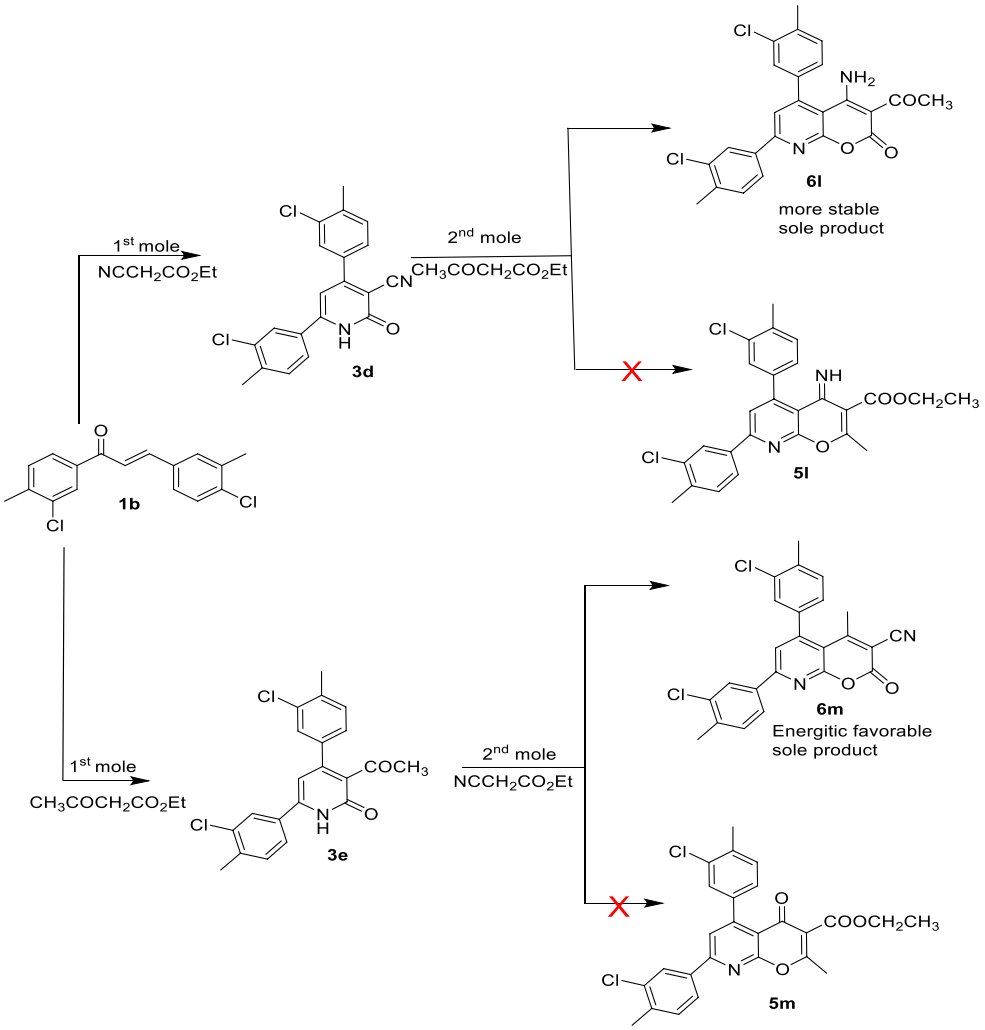
Moreover, the appearance of the stretching vibration of NH_2 as broad bands in the region 3440–3300 and another band at 2216 cm^{-1} corresponding to C≡N confirmed the formation of the desired compounds **6a** and **2i**. The ^{1}H-NMR spectrum of 5-(4-chlorophenyl)-7-(3,4-dimethylphenyl)-2-oxo-2H-pyrano[2,3-b]pyridine derivatives **6c, 6g, 6k**, and **6p** revealed characteristic singlet peaks in the $\delta=10.22$–11.82 ppm region, corresponding to the OH group. On the other hand, ^{1}H-NMR spectra of **6a, 6d, 6f, 6i, 6l**, and **6n** revealed characteristic singlet peaks at the $\delta=10.22$–11.82 ppm region corresponding to NH_2 moieties. In addition, a multiplet peak at the $\delta=6.79$–8.01 ppm region (protons of benzene and 1H proton of pyridyl ring) emerged, which clearly ascertained their corresponding molecular structures.

Bioassay for insecticidal activity of the synthesized compounds

The results listed in Table 3 indicate that most of the title compounds showed weakly insecticidal activity against the two pests. However, some of the compounds displayed good insecticidal activities. For example, compounds **6i** and **6l** showed 100% activities at 500 μg mL^{-1} and 50% activities at 50 μg mL^{-1} against both *Plutella xylostella* and *Helicoverpa armigera*. Meanwhile, the activities of compounds **6i** and **6l** against *Helicoverpa armigera* were better than those of chlorpyrifos at 200 μg mL^{-1}; compound **6i** and **6l** showed 75.0 and 86.1% activity, respectively, against *Helicoverpa armigera* at 200 μg mL^{-1}. In addition, compounds **6j** and **6k** also showed good insecticidal activities, and their mortalities against *Plutella xylostella* were 95.2 and 92.9%, respectively (500 μg mL^{-1}), and with 200 μg mL^{-1} concentration the activity of **6j** against *Plutella xylostella* was still 94.2%. Furthermore, the activity of compounds **6j** against *Helicoverpa armigera* at 200 μg mL^{-1} was 67.9 and 78.1% for **6k**, which is better than that of chlorpyrifos. Moreover, compounds **6c** and **6d** had 55.1 and 55.9% activities on *Plutella xylostella* and *Helicoverpa armigera* at 500 μg mL^{-1}, respectively.

The LC_{50} values of compounds **6i, 6j, 6k**, and **6l** were further evaluated and the results listed in Table 4. The LC_{50} values of **6i, 6j**, and **6l** on *Plutella xylostella* were much lower than that of chlorpyrifos, which indicated that the activities of these compounds on *Plutella xylostella*. On the other hand, the LC_{50} values of **6i, 6k**, and **6l** on *Plutella xylostella* were much lower than that of chlorpyrifos, which indicated that the activities of these compounds on *Helicoverpa armigera* were better than that of chlorpyrifos.

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



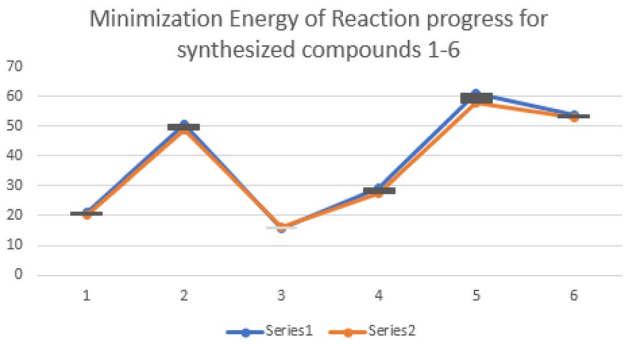


Fig. 1 Outline of the energy value (Kcal/ mol) for two series (1 and 2) of compounds **1–6** during the reaction progress of chalcone **1a** and **1b** with ethyl cyanoacetate, indicating that the thermal stability of 2-pyridone **3** is more than that of chalcone**1 as** represented in Fig. 2 (1a–6a) and scheme 2 (1b, 2d–6d)

The toxic ratio is defined as the ratio of imidacloprid's LC_{50} value for baseline toxicity and the compounds' LC_{50} value.

DFT "studies"

The optimized molecular structures of the synthesized compounds are formed as stable energetic structure geometry. Such geometrical structure of the compounds as an example, compounds **1–6** is gradually optimized and its energy is continuously decreased until the fluctuations in the molecule energy are minimized (Fig. 1). The optimized geometrical structures of two series of compounds **1–6** under ultrasonic reaction condition in addition to their solvation with tetrahydrofuran (THF) displayed wholly distributed energies over every molecular structure (Fig. 2). Frontier molecular orbitals possess the highest occupied molecular orbital (HOMO), excited during ultrasonic energy $HOMO_{-1}$ and the lowest unoccupied molecular orbital (LUMO) (Fig. S1) [42–45]. The regions of highest electron density (HOMO) characterize the electrophilic-attacking sites, while the LUMO imitates the nucleophilic-attacked sites [46, 47]. Quantum chemical computation can be explained the mechanism of the reaction at the different condition to afford the

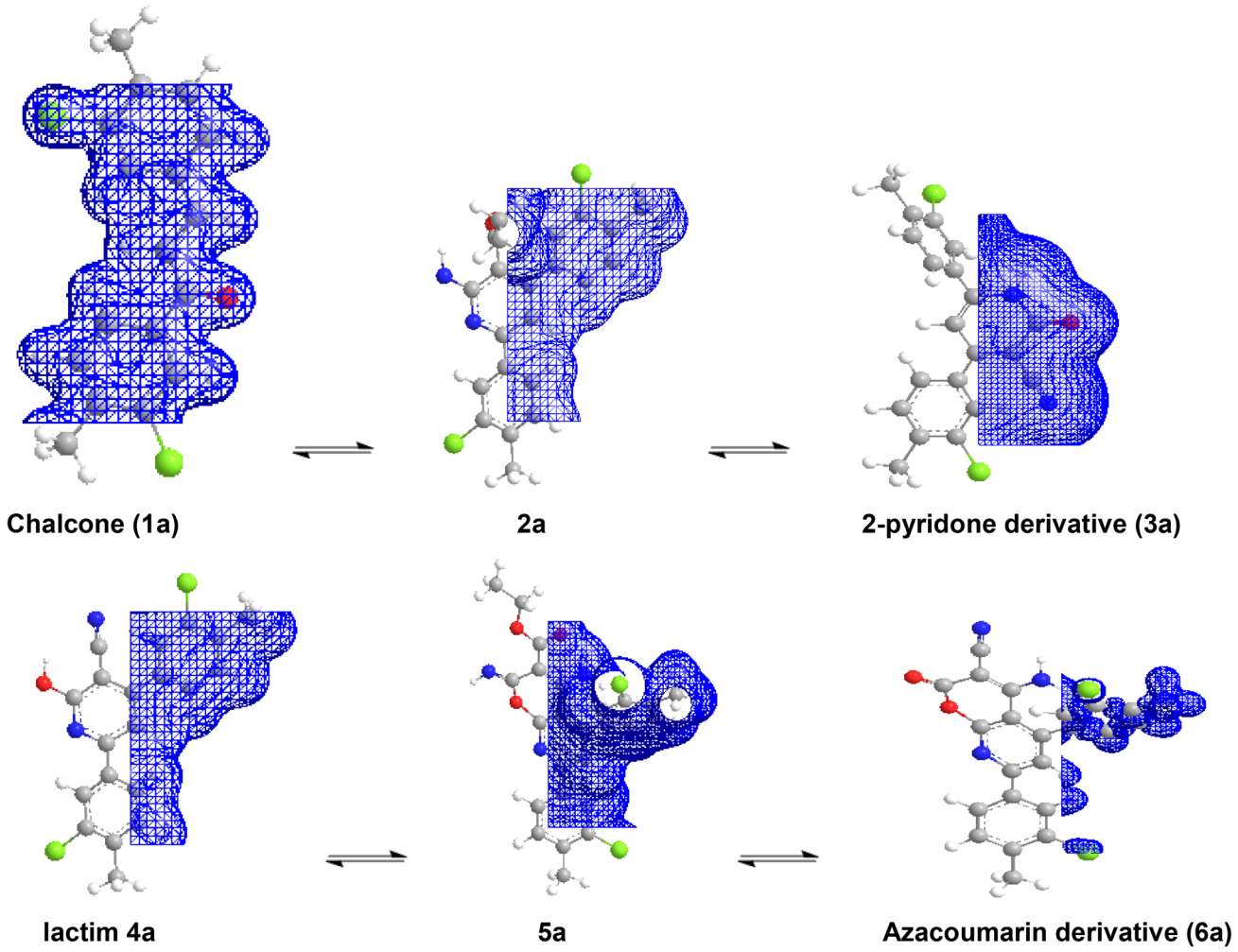
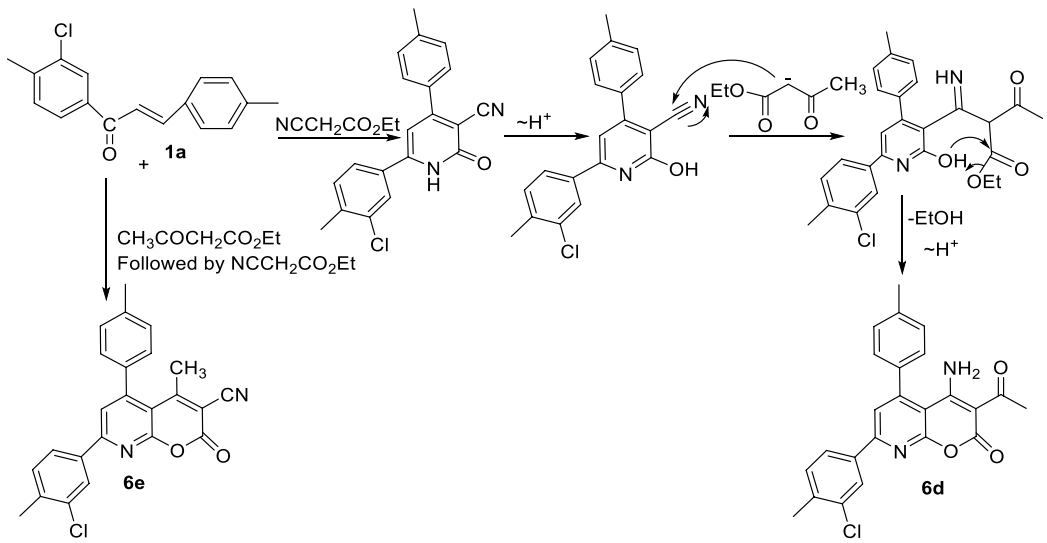


Fig. 2 The effect of ultrasonic energy for optimized isomerization by computational chemical calculation converted chalcone **1a** to azacoumarin **6a** via 2-pyridone **3a**. Color index: white H, gray C, blue N, red O, green Cl and blue wire mesh THF solvent



Scheme 6 Mechanistic illustration for the three-component strategy

Table 3 Insecticidal activity (%) at different concentrations (μg mL^{-1}) of the synthesized compounds against *Plutella xylostella* and *Helicoverpa armigera*

Comp. no	Insecticidal activity (%) at different concentrations (μg mL^{-1})									
	Plutella xylostella					*Helicoverpa armigera*				
	500	200	100	50	25	500	200	100	50	25
6a	40	33	22	10	5	35.6	18.7	5.8	–	–
6b	30.8	22.7	16.9	11.4	8.2	36.0	11.7	7.7	3.6	–
6c	55.1	19.4	12.6	7.1	2.3	34.2	10.8	5.3	1.8	–
6d	55.9	40.1	36.2	20.2	11.9	35.1	13.3	–	–	–
6e	24.6	14.0	12.2	9.5	7.2	36.7	14.9	4.4	–	–
6f	22.3	16.5	8.9	–	–	38.2	14.6	–	–	–
6g	28.2	11.2	3.2	–	–	11.2	–	–	–	–
6h	29.6	12.3	6.1	3.3	–	31.3	16.4	7.5	3.2	–
6i	100	80.0	66.4	53.7	37.1	100	75.0	63.2	50.4	27.8
6j	95.2	94.2	43.8	34.5	25.2	89.4	67.9	45.1	31.2	26.7
6k	92.9	56.2	33.8	23.8	16.9	92.2	78.1	45.2	24.5	17.9
6l	100	87.2	63.7	53.7	24.1	95.2	86.1	67.2	51.0	22.8
6m	90.4	76.2	55.1	33.8	19.6	88.7	66.6	52.0	29.8	11.9
6n	44.6	29.8	14.3	9.0	6.2	45.2	23.5	11.4	9.8	2.3
6o	33.5	24.1	19.6	10.2	7.8	24.1	13.5	7.7	2.8	–
6p	24.7	14.2	9.9	7.6	–	33.1	23.6	14.2	3.3	1.9
Chlorpyrifos	100	100	100	92	81	84.2	67.9	56.9	33.1	20.1

Table 4 LC_{50} values of **6i, 6j, 6 k, 6 l** and chlorpyrifos against *Plutella xylostella* and *Helicoverpa armigera*

Insects	Compd.	LC_{50} (mg/L)	$y = a + bx$	Toxic ratio[a]
Plutella xylostella	**6i**	43.85	$\boldsymbol{y = 3.1852 + 1.0493x}$	0.98
	6j	95.58	$y = 2.35527 + 1.59130x$	0.98
	6k	167.7	$y = 2.15892 + 1.2746x$	0.99
	6l	50.77	$y = 2.09929 + 1.7009x$	0.98
	Chlorpyrifos	7.64	$y = 3.732 + 1.46x$	0.98
Helicoverpa armigera	**6i**	58.8	$y = 2.3643 + 1.5001x$	0.99
	6j	111.76	$y = 2.6981 + 1.1224x$	0.98
	6k	77.10	$y = 3.4268 + 0.8336x$	0.98
	6l	65.29	$y = 2.3290 + 1.4716x$	0.97
	Chlorpyrifos	103.56	$y = 2.2280 + 1.3748x$	0.97

[a]Toxic ratio

different products. The competitive reaction of the second molecule of ethyl cyanoacetate, under ultrasonic reaction conditions, preferred to attack 2-pyridone **3** that has lower $\Delta E = \text{LUMO–HOMO}_{-1} = 2.930$ ev than chalcone **1** that has $\Delta E = \text{LUMO–HOMO} = 5.664$ ev to yield the desired product **6**. In the thermal reaction condition, it prefers attacking chalcone **1** that has $\Delta E = \text{LUMO–HOMO} = 10.044$ ev to yield 2-pyridone **3** (Table 5). So, the 2-pyridone product **3** was preferred to yield in the thermal reaction condition as outlined in Fig. 1. On the other hand, dipole moment (μ) is a promising measurable parameter for molecular polarity. It is clearly evident from Table 5 that compounds **6** (j, k and l) exhibit high polarities, and so they have the most potent insecticidal activity [48]. The hydration energy echoes the more solvated parts of azacoumarin that be contributed to attack the insect, resulting in the most potent activity of such compounds (Tables 4, 5) [49, 50]. The nucleophilicity index (ω) and the surface area can be confirmed the insecticidal activity and followed the order: 6i > 6l > 6j > 6k > 6d and conforms to environmental insecticidal activity [51–53]. Accordingly, the DFT data are in accordance with the previously obtained results (cf. Tables 3, 4, 5).

Experimental

Materials and methods

Melting points were determined in open glass capillaries and were uncorrected. The IR spectra (υ_{max} in cm^{-1}) were

Table 5 DFT parameters calculated for the synthesized compounds

Comp no	E_{HOMO} (eV)	E_{HOMO-1} (eV)	E_{LUMO} (eV)	ΔE thermal$_{(LUMO-HOMO)}$	ΔE ultrasonic (LUMO–HOMO^{-1})	Dipole moment μ (Debye)	Hydration E (k cal mol^{-1})	Surface area, A (nm^2)	Nucleophilicity, ω (eV)
1	−10.93	−6.55	−0.886	10.044	5.664	−0.526	−20.691	1183.34	4.12
2	−7.42	−3.82	−0.342	7.078	3.478	0.4520	−50.462	909.23	4.34
3	−11.05	−3.84	−0.910	10.140	2.930	−6.682	−15.84	1122.25	5.24
4	−8.17	−3.62	−1.261	6.909	2.359	3.810	−29.331	1034.24	3.38
5	−7.85	−3.49	−0.752	7.089	2.738	4.733	−59.942	1187.32	3.27
6d	−7.87	−3.43	−0.821	7.049	2.609	12.318	−53.321	1209.58	2.61
6i	−7.75	−3.84	−0.810	6.940	3.030	13.879	−55.453	1354.25	5.24
6j	−8.07	−3.58	−0.861	7.209	2.719	13.863	−54.765	1314.67	4.83
6k	−7.85	−3.89	−0.798	7.052	3.092	14.121	−55.963	1281.15	3.93
6l	−7.97	−3.53	−0.872	7.98	2.658	14.118	−54.621	1336.34	5.11
6m	−7.72	−3.29	−0.843	6.877	2.447	12.256	−53.272	1126.34	2.47

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, 400 MHz) using $CDCl_3$/DMSO-d_6 as solvents. TMS was taken as the internal standard. ^{13}C-NMR spectra were recorded on the same spectrometer (Rheinstetten, Germany) at 100 MHz and referenced to solvent signals $\delta = 39.50$ ppm for DMSO-d_6. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) using the electron ionization technique at 70 e.v. Elentar Vario EL III automatic CHN analyzer was used for elemental analyses. The CHN analyses were recorded at the Central Armed Force in Egypt. Sonication was performed in a Toshcon model SW 4 cleaner with a frequency of 37 KHz and operating at maximum power of 150 W. The purity of compounds was checked by TLC using silica gel (60–120) mesh as adsorbent, UV light, or iodine to accomplish visualization. All common reagents and solvents were used as obtained from commercial suppliers without further purification. Chalcone (**1**) was prepared by the method described in literature [54].

General procedure for the synthesis of 7-(3-chloro-4-methyl phenyl)-5-(4-methylphenyl)- 2-oxo-2H-pyrano[2,3-b] pyridine derivatives (6a–p)

Method (i): Chalcone (**1a–c**) (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 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 the solvent system. Sonication was continued until the 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): Chalcone (**1a–c**) (0.05 mol), active methylene compounds, e.g., ethyl cyanoacetate, ethyl acetoacetate, and/or diethylmalonate (0.05 mol), and ammonium acetate (0.04 mol) were ground together in an agate mortar and pestle for 25–30 min. The color of the reaction mixture turned into light yellow from colorless 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 recrystallized from 95% aqueous ethanol.

4-Amino-7-(3-chloro-4-methyl phenyl)-5-(4-methylphenyl)-2-oxo-2H-pyrano[2,3-b]pyridine-3-carbonitrile (6a) Yellow crystal, IR (ν, 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.

3-Acetyl-7-(3-chloro-4-methyphenyl)-4-methyl-5-(*p*-tolyl)-2H-pyrano[2,3-b]pyridin-2-one (6b) Yellow crystal, IR (ν, 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.

Ethyl-7-(3-chloro-4-methylphenyl)-5-(4-methylphenyl)-4-methyl-2-oxo-2H-pyrano [2,3-b]pyridin-2-on-3-yl acetate (6c) Yellow crystal, IR (ν, 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.

3-Acetyl-4-amino-7-(3-chloro-4-methylphenyl)-5-(4-methylphenyl)-2H-pyrano [2,3-b] pyridin-2-one (6d) Yellow crystal, IR (ν, cm^{-1}): 3243, 3186, (NH_2), 3055 (CH), 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,

7-(3-Chloro-4-methylphenyl)-5-(4-methylphenyl)-4-methyl-2-oxo-2H-pyrano[2,3-b]pyridin-3-carbonitrile (6e) Yellow crystal, IR)ν, 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.

Ethyl-4-amino-7-(3-chloro-4-methylphenyl)-5-(4-methylphenyl)-2-oxo-2H-pyrano[2,3-b] pyridin-3-yl acetate (6f) Yellow crystal, IR (ν, cm^{-1}): 3445 and 3380 (NH_2), 3090 (ArH), 1745, 1738 (C=O), MS (*m/z*) 450/448. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.2 (t, 3H, CH_3), 2.29 (s, 6H, 2Me), 4.24 (q, 2H, CH_2), 7.11–7.87 (m, 8H, ArH), 10.62 (s, 2H, NH_2 exchangeable in D_2O). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7. 20.2, 22.4, 60.8, 101.2, 104.9, 123.3, 123.79, 127.4, 127.5 (2), 129.8 (2), 131.6, 132.8, 133.8, 134.2, 134.7, 138.5, 144.6, 146.4, 159.1, 164.0, 165.4, 174.1; *Anal*. Calcd. for $C_{25}H_{21}ClN_2O_4$ (448.5): C 66.89, H 4.72, N 6.24. Found: C 66.78, H 4.32, N 6. 49.

7-(3-Chloro-4-methylphenyl)-5-(4-methylphenyl)-2,4-dioxo2H-pyrano[2,3-b] pyridin-3-carbonitrile (6g) Yellow crystal, IR (ν, cm^{-1}): 3460 (OH), 3087 (ArH), 2217(CN), 1732 (C=O), 1620 MS (*m/z*) 404/402. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.29 (s, 6H, 2Me), 7.18–7.99 (m, 8H, ArH), 11.22 (s, 1H, OH exchangeable in D_2O). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.9, 21.8, 71.5, 104.8, 116.3, 123.4, 123.9, 127.4 (2), 127.8, 129.1 (2), 131.4, 132.8, 134.6, 134.8, 135.1, 136.5, 146.3, 146.9, 155.6, 165.9, 169.6; *Anal*. Calcd. for $C_{23}H_{15}ClN_2O_3$ (402.5): C 68.58, H 3.75, N 6.95. Found: C 69.31, H 3.97, N 7.21.

Ethyl-7-(3-chloro-4-methylphenyl)-5-(4-methylphenyl)-4-methyl-2-oxo-2H-pyrano[2,3-b] pyridin-3-yl acetate (6h) Yellow crystal, IR (ν, cm^{-1}): 3050, 2913 (CH), 1748, 1732 (C=O), MS (*m/z*) 449/447. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.2 (t, 3H, CH_3), 2.29 (s, 6H, $2CH_3$), 2.54 (s, 3H, CH_3), 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: 15.1, 19.9, 21.3, 21.8, 62.8, 103.9, 111.2, 121.3, 124.1, 126.4, 128.3 (2), 129.5 (2), 131.6, 133.4, 134.6, 134.8, 135.8, 137.5, 145.9, 147.0, 160.2, 162.8, 163.9, 167.0; *Anal*. Calcd. for $C_{26}H_{22}ClNO_4$ (447.5): C 69.72, H 4.95, N 3.13. Found: C 69.33, H 4.67, N 3.45.

4-Amino-5-(3-chloro-4-methylphenyl)-7-(3-chloro-4-methyl phenyl)-2-oxo-2H-pyrano[2,3-b]pyridine-3-carbonitrile (6i) Yellow crystal, IR (ν, cm^{-1}): 3315 and 3175 (NH_2), 3051 (ArH), 2215 (CN), 1745 (C=O), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 6H, $2CH_3$), 5.62 (s, 2H, NH_2), 7.38–7.79 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.5 (2), 76.4, 103.9, 116.3, 121.7, 124.2, 125.8, 127.4, 127.7, 131.5 (2), 133.3, 134.3, 135.1 (2), 136.9 (2), 144.4, 145.7, 157.7, 163.5, 181; *Anal*. Calcd. for $C_{23}H_{15}Cl_2N_3O_2$ (435): C 63.32, H 3.47, N 9.63. Found: C 62.01, H 3.77, N 9.91.

3-Acetyl-5-(3-chloro-4-methylphenyl)-7-(3-chloro-4-methylphenyl)-4-methyl-2H-pyrano[2,3-b] pyridin-2-one (6j) Yellow solid, IR (ν, cm^{-1}): 3060, 2900, 2868(CH), 1739, 1689 (C=O), MS (*m/z*) 439/436. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.25 (s, 6H, $2CH_3$), 2.62 (s, 3H, CH_3), 7.43–8.19 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.9 (2), 22.4, 29.59, 104.8, 123.7, 124.2, 125.1, 126.9, 127.7, 129.4, 131.3 (2), 134.6, 134.8 (2), 135.7, 137.4 (2), 144.6, 147.4, 159.4, 160.1, 163.9, 197.6; *Anal*. Calcd. for $C_{25}H_{19}Cl_2NO_3$ (451): C 68.38, H 4.23, N 3.10. Found: C 68.71, H 4.66, N 3.39.

Ethyl-5-(3-chloro-4-methylphenyl)-7-(3-chloro-4-methylphenyl)-4-methyl-2-oxo-2H-pyrano[2,3-b] pyridin-2-on-3-yl acetate (6 k) Yellow solid, IR (ν, cm^{-1}): 3502 (OH), 3045 (ArH), 1750, 1734, 1670 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (t, 3H, CH_3), 2.19 (s, 6H, 2Me), 4.74 (q, 2H, CH_2), 7.18–8.13 (m, 7H, ArH), 11.82 (s, 1H, OH exchangeable in D_2O). ^{13}C NMR (100 M Hz, $CDCl_3$) δ: 14.2, 19.5 (2), 60.9, 101.3, 105.1, 122.1, 122.7, 126.5, 126.9, 131.3 (2), 133.9, 134.2, 134.8 (2), 136.1 (2), 144.8, 145.3, 147.6, 160.4, 165.0, 165.2, 171.4; *Anal*. Calcd. for $C_{25}H_{19}Cl_2NO_5$ (483): C 62.00, H 3.95, N 2.89. Found: C 61.88, H 3.65, N 2.63.

3-Acetyl-4-amino-5-(3-chloro-4-methylphenyl)-7-(3-chloro-4-methylphenyl)-2H-pyrano[2,3-b]pyridin-2-one (6 l) Yellow solid, IR (ν, cm^{-1}): 3310, 3267 (NH_2), 3100, 2975 (CH), 1738, 1681 (C=O), MS (*m*/*z*) 455/452. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 6H, 2Me), 2.6 (s, 3H, CH_3), 7.06–7.67 (m, 7H, ArH), 12.12 (s, 2H, NH_2 exchangeable in D_2O). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.9 (2), 30.2, 103.8, 110.3, 121.9, 124.2, 124.6, 127.6, 127.8, 131.3 (2), 134.6, 134.8 (2), 135.1, 136.1 (2), 146.6, 148.1, 159.1, 165.9, 171.7, 197.4; *Anal*. Calcd. for $C_{24}H_{18}Cl_2N_2O_3$ (452): C 63.59, H 4.00, N 6.18. Found: C 63.22, H 4.35, N 6.34.

5,7-Bis(3-chloro-4-methylphenyl)-4-methyl-2-oxo-2H-pyrano[2,3-b]pyridine-3-carbonitrile (6 m) Yellow solid, IR (ν, cm^{-1}): 3070 (ArH), 2215 (CN), 1745 (C=O); MS (*m*/*z*) 437.5/435.5 ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.21–2.23 (s, 6H, $2CH_3$), 2.51 (s, 3H, CH_3), 7.32–7.87 (m, 7H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 21.0 (2), 97.9, 104.7, 115.1, 123.5, 123.9, 126.5, 127.4, 127.9, 130.2 (2), 134.6, 134.8 (2), 135.1, 136.8 (2), 146.2, 146.8, 155.6, 165.6, 170.6; *Anal*. Calcd. for $C_{24}H_{16}Cl_2N_2O_2$ (434): C 66.22, H 3.70, N 6.44. Found: C 66.65, H 3.81, N 6.16.

4-Amino-7-(3-chloro-4-methylphenyl)-5-(4-methoxyphenyl)-2-oxo-2H-pyrano[2,3-b]pyridine-3-carbonitrile (6n) Yellow solid, IR (ν, cm^{-1}): 3284 and 3180 (NH_2), 3050 (ArH), 2216 (CN), 1743 (C=O), MS (*m*/*z*) 419/417. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, Me), 4.71 (s, 3H, OCH_3), 5.62 (s, 2H, NH_2), 7.38–7.79 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2, 56.8, 78.4, 104.7, 115.2 (2), 115.9, 123.2, 124.2, 128.4, 129.3 (2), 131.5, 133.2, 134.1, 134.6, 135.1, 146.1, 146.7, 157.2, 160.7, 165.9, 181.2; *Anal*. Calcd. for $C_{23}H_{16}ClN_3O_3$ (417.5): C 66.11, H 3.86, N 10.06. Found: C 66.32, H 3.96, N 10.33.

3-Acetyl-7-(3-chloro-4-methylphenyl)-5-(4-methoxyphenyl)-4-methyl-2H-pyrano[2,3-b]pyridin-2-one (6o) Yellow solid, IR (ν, cm^{-1}): 3045, 2912 (CH), 1745, 1689 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, Me), 2.62 (s, 3H, CH_3), 2.87 (s, 3H, $COCH_3$), 4.63 (s, 3H, OCH_3), 7.43–8.19 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 25.3, 56.4, 58.9, 103.8, 115.1 (2), 121.9, 124.1, 127.3, 129.0 (2), 131.3, 132.9, 133.6, 134.2, 134.8, 136.2, 140.5, 143.4, 146.3, 146.9, 160.1, 161.4, 165.3; *Anal*. Calcd. for $C_{25}H_{20}ClNO_4$ (421.11): C 68.33, H 4.78, N 3.32. Found: C 68.71, H 4.56, N 3.61.

Ethyl 7-(3-chloro-4-methylphenyl)-4-hydroxy-5-(4-methoxyphenyl)-2-oxo-2H-pyrano [2,3-b]pyridine-3-carboxylate (6p) Yellow solid, IR (ν, cm^{-1}): 3460 (OH), 3045 (ArH), 1751, 1732, 1674 (C=O). ^{1}H NMR (3400 MHz, $CDCl_3$) δ: 1.2 (t, 3H, CH_3), 2.29 (s, 3H, Me), 4.2 (q, 2H, CH_2), 4.91 (s, 3H, OCH_3), 7.18–7.99 (m, 8H, ArH), 11.82 (s, 1H, OH exchangeable in D_2O). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 19.5, 56.4, 61.8, 101.7, 105.4, 115.0 (2), 123.4, 123.8, 128.3, 129.4 (2), 131.6, 133.7, 134.2, 134.7, 135.9, 146.4, 146.9, 160.3, 161.8, 165.0, 165.9, 171.9; *Anal*. Calcd. for $C_{25}H_{20}ClNO_6$ (465.89): C 64.45, H 4.33, N 3.01. Found: C 64.88, H 4.04, N 3.39.

Insecticidal activity

The insecticidal activities of compounds **6a–p** were measured against *Plutella xylostella* and *Helicoverpa armigera* according to the standard test[38] with a slight modification. The test analogs were dissolved in DMF and serially diluted with water containing Triton X-80 (0.1 mg/L) to obtain the required concentrations. The insects were reared at 25 (± 1)°C and groups were transferred to glass Petri dishes. All experiments were carried out in three replicates for the purpose of statistic requirements. Assessments of mortality were calculated 72 h by the number and size of the live insects relative to those in the negative control. Evaluations were based on a percentage scale of (0 = no activity and 100 = complete eradication). The mortality rates were subjected to probity analysis [39]. Chlorpyrifos was used as positive control, while water containing Triton X-80 (0.1 mg/L) was used as negative control.

Computational methods

DFT studies were carried out for the azacoumarin compounds (**6a-p**) using Materials Studio 6.0 (MS 6.0) software from Accelrys, Inc. DMol3 module was used to perform the DFT calculations using Perdew and Wang LDA exchange–correlation functional and DND basis set. The calculated parameters involved the electron density, dipole moment and frontier molecular orbitals, and the molecular surface area. Frontier molecular orbitals include the

highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs) [38, 39].

Conclusion

The present report is the first study of the synthesis and insecticidal activities of some 8-azacoumarin derivatives. 8-Azacoumarin derivatives **6a–p** were synthesized via two-step, simple, novel and eco-friendly synthetic protocols. Comparative study regarding the outcome yields and the time or reactions was done on ultrasound-assisted and grinding strategies. Full structural elucidations for all synthesized compounds were based on elemental and spectroscopic analyses. Insecticidal evaluations were done on all of the products. In particular, compounds **6i, 6j, 6k**, and **6l** showed much better activities against *Plutella xylostella* and *Helicoverpa armigera* than the rest of the tested compounds. DFT-based bioassay of such compounds that have introduction of N at C-8 instead of CH= in coumarin enhanced the possibility of binding with insecticidal arginine 265, which in turn favored the insecticidal activities. However, the structures of the synthesized compounds need to be optimized and structural modification and biological evaluation are currently underway to explore the full potential of this kind of azacoumarin derivatives with various hydrophobic and hydrophilic substituents based on these findings.

References

1. R.I. Al-Bayati, A.A. Hussain Al-Amiery, Y.K. Al-Majedy, J. Afr. Pure Appl. Chem. **4**, 74–86 (2010)
2. A. Behrami, I. Krasniqi, J Chem. Pharm. Res. **4**, 2495–2508 (2012)
3. A.R. Togna, O. Firuzi, V. Latina, V.S. Parmar, A.K. Prasad, A. Salemme, G.I. Togna, L. Saso, Biol. Pharm. Bull. **37**, 60–66 (2014)
4. K.K. Sivakumar, A. Rajasekaran, P. Senthilkumar, P.P. Wattamwar, Bioorg. Med. Chem. Lett. **24**, 2940–2944 (2014)
5. D. Cao, Y. Liu, W. Yan, C. Wang, P. Bai, T. Wang, M. Tang, X. Wang, Z. Yang, B. Ma, L. Ma, L. Lei, F. Wang, B. Xu, Y. Zhou, T. Yang, L. Chen, J. Med. Chem. **59**, 5721 – 5739 (2016)
6. S. Weigt, N. Huebler, R. Strecker, T. Braunbeck, T. Broschard, Reprod. Toxicol. **33**, 133–141 (2012)
7. A. Witaicenis., L.N. Seito., A. Chaqas, L.D. de almeida Jr., A.C. Luchini, P. Rodrigues-Orsi, S.H. Cestari, L.C. Di Stasi, 21, 240–246 (2014)
8. S. Kirkiacharian, D.T. Thuy, S. Sicsic, R. Bakhchinian, R. Kurkjian, T. Tonnaire, J. Il Farmaco **57**, 703–708 (2002)
9. N. Nida, M.R. Farshori, A.A. Banday, U.K. Asad, A. Rauf, Med. Chem. Res. **20**, 535–541 (2011)
10. S. Fioravanti, L. Pellacani, P.A. Tardella, M.C. Vergari, Org. Lett. **10**, 1449–1451 (2008)
11. A.K. Mitra, S.K. Misra, A. Patra, New synthesis of 3-alkyl coumarins. Synth. Commun. **10**, 915–919 (1980)
12. P.E.S. De Oliveira, L.M. Conserva, A.C. Brito, R.P.L. Lemos, Pharm. Biol. **43**, 53–57 (2005)
13. C.C. Joseph, M.M. Ndoile, R.C. Malima, M.H.H. Nkunya, Trans. R. Soc. Trop. Med. Hyg. **98**, 451–455 (2004)
14. M.E. Sinka, M.J. Bangs, S. Manguin, Parasites Vectors **3**, 117–127 (2010)
15. W.H. Perkin, J. Chem. Soc. **32**, 660–674 (1877)
16. E. Knoevenagel, Berichte der deutschen chemischen Gesellschaft **31**, 2596–2619 (1898)
17. R.S. Mali, V.J. Yadav, J. Synth. **12**, 464–465 (1977)
18. S.E. Drewes, N.D. Emslie, N. Karodia, G. Loizou, J. Synth. Commun. **20**, 1437–1443 (1990)
19. G. Speranza, A.D. Meo, S. Zanzola, G. Fontanna, P. Manitto, J. Synth. **32**, 931–936 (1997)
20. R.L. Shriner, The reformatsky reaction. Org. React. **1**, 15–46 (1942)
21. V.H. Pechmann, C. Duisberg, J Chem. Ber. **17**, 929–979 (1884)
22. A. Hoefnagel, E. Gunnewegh, R. Downing, H. van Bekkum, J. Chem. Soc. Chem. Commun. **2**, 225–226 (1995)
23. F.M. Al-Haj-Hussien, M.K. Alzobar, J. Merza, A. Karam, Inter. Lett. Chem. Phys. Astronomy. **69**, 66–73 (2016)
24. V. Vahabi, F. Hatamjafari, Molecules **19**, 13093–13103 (2014)
25. B.R. Chaudhari, Eur. J. Pharma. Med. Res. **3**, 592–597 (2016)
26. T. Sugino, K. Tanaka, Chem. Lett. **30**, 110–111 (2001)
27. F. Toda, K. Tanaka, A. Sekikawa, J. Chem. Soc. Chem. Commun. **4**, 279–280 (1987)
28. A.K. Bose, S. Pednekar, S.N. Ganguly, G. Chakraborty, M.S. Manhasa, Tetrahedron Lett. **45**, 8351–8353 (2004)
29. J. Muškinja, N. Janković, Z. Ratković, G. Bogdanović, Mol. Divers. **20**, 591–604 (2016)
30. M.D. Alexander, M.D. Burkart, M.S. Leonard, P. Portonovo, B. Liang, X. Ding, M.M. Joullié, B.M. Gulledge, J.B. Aggen, A.R. Chamberlin, J. Sandler, W. Fenical, J. Cui, S.J. Gharpure, A. Polosukhin, H.R. Zhang, P.A. Evans, A.D. Richardson, M.K. Harper, C.M. Ireland, B.G. Vong, T.P. Brady, E.A. Theodorakis, J.J. La Clair, Chem. Bio. Chem. **7**, 409 – 416 (2006)
31. G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, Heterocycles **45**, 1715–1721 (1997)
32. R.L. Atkins, D.E. Bliss, J. Org. Chem. **43**, 1975 – 1980 (1978)
33. H. Takano, T. Narumi, N. Ohashi, A. Suzuki, T. Furuta, W. Nomura, H. Tamamura, Tetrahedron **70**, 4400 – 4404 (2014)
34. I. Yavari, M. Adib, L. Hojabri, Tetrahedron **58**, 6895–6899 (2002)
35. D. Wang, Y. Wang, J. Zhao, M. Shen, J. Hu, Z. Liu, L. Li, F. Xue, P. Yu, Org. Lett. **19**, 984–987 (2017)
36. T. Narumi, H. Takano, N. Ohashi, A. Suzuki, T. Furuta, H. Tamamura, Org. Lett. **16**, 1184–1187 (2014)
37. H. Takano, T.N.W. Nomura, H. Tamamura, J. Org. Chem. **82**, 2739–2744 (2017)
38. A.R. Katritzky, L. Serdyuk, C. Chassaing, D. Toader, X.J. Wang, B. Forood, B. Flatt, C.C. Sun, K. Vo, J. Comb. Chem. **2**, 182–185 (2000)
39. I.O. Zhuravel', S.M. Kovalenko, A.V. Ivachtchenko, K.V. Balakin, V.V. Kazmirchuk, Bioorg. Med. Chem. Lett. **15**, 5483–5487 (2005)
40. J. Trilleras, P. De La Torre, D.J. Pacheco, J. Quiroga, M. Nogueras, J. Cobo, Lett. Org. Chem. **8**, 652–655 (2011)
41. C.B. Miao, Y.H. Wang, C.P. Dong, H.T. Yang, Q. Meng, X.Q. Sun, Heterocycles. **87**, 2599–2605 (2013)
42. L. González, D. Escudero, L. Serrano-Andrés, Chem. Phys. Chem. **13**, 28–51 (2012)
43. S. Qiang, C. Hui, Sci. China Chem. **56**, 1271–1276 (2013)
44. M. Winghart, J. Yang, M. Ku¨hn, A. Unterreiner, T.J.A. Wolf, P.D. Dau, H. Liu, D. Huang, W. Klopper, L. Wang, M.M. Kappes, Phys.Chem. Chem. Phys. **15**, 6726–6736 (2013)
45. F. Furche, D. Rappoport. ed. M. Olivucci, *Theoretical and Computational Chemistry* (Elsevier, Amsterdam, 2005)

46. S.A. Rizk, A.M. El-Naggar, A.E. Badawy, J. Mol. Struct. **1155**, 720–733 (2018)
47. J.R. McClean, M.E. Kimchi-Schwartz, J. Carter, W.A. deJong, Phys. Rev. A **95**, 042308 (2017)
48. J.A. Lynch, A.D. Peel, A. Drechsler, M. Averof, S. Roth, Curr Biol **20**(11), 1042–1047 (2010)
49. T. Kumagai, J.N. Ladenthin, Y. Litman, M. Rossi, L. Grill, S. Gawinkowski, J. Waluk, M. Persson, J. Chem. Phys. **148**, 102330 (2018)
50. M.D. Halls, H.B. Schlegel, Chem. Mater. **13**,, 2632–2640 (2001)
51. H. B¨ockmann, S. Liu, J. Mielke, S. Gawinkowski, J. Waluk, L. Grill, M. Wolf, T. Kumagai, Nano Lett. **16**, 1034–1041 (2016)
52. A. Kandala, A. Mezzacapo, K. Temme, M. Takita, M. Brink, J.R. Chow, J.M. Gambetta, Nature **549**, 242–245 (2017)
53. S. Kühsel, A. Brückner, S. Schmelzle, M. Heethoff, N. Blüthgen, Insect Sci. **24**, 829–841 (2017)
54. F. El-Taib Heakal, S.A. Rizk, A.E. Elkholy, J. Mol. Struct. **1152**, 328–336 (2018)