

Cu(II) complexes of 4- and 5- nitro-substituted heteroaryl cinnamoyl derivatives and determining their anticoagulant activity

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Abstract

Keywords:

1,3-indandiones
Cu (II)-complexes
IR
PT
INR

Article history:

Received 05.04.2016
Received in revised
form 12.06.2016
Accepted 30.06.2016

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Introduction. This article presents the synthesis of Cu(II) complexes of 4- and 5- nitro-substituted heteroaryl cinnamoyl derivatives and the research on their anticoagulant activity.

Materials and methods. All chemicals used were purchased from Merck and Sigma-Aldrich. The melting points were determined with a digital melting point apparatus SMP 10. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 F₂₅₄, 0.2 mm Merck plates, eluent system (vol. ratio): CH₂Cl₂ : CH₃COCH₃ = 1 : 1. IR spectra were taken on spectrometer Perkin-Elmer FTIR-1600 in KBr discs.

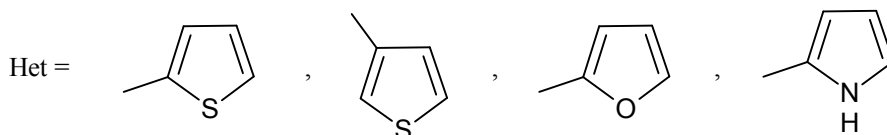
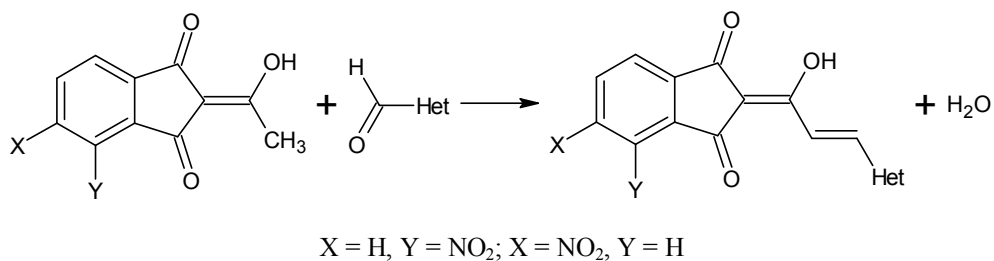
Results and discussion. Ligands, needed for the obtaining of the corresponding complexes, are obtained from 4- and 5-nitro-substituted 2-acyl-1,3-indandiones by two different methods: Mosher and Meier and Rotberg and Oshkaya, and the new thing in our method is the use of pyrrolidine as catalyst. The resulting ligand is dissolved in dioxane and Cu(CH₃COO)₂ · H₂O is dissolved in methanol and this solution is added to the solution of the ligand, wherein the complex crystallizes upon cooling. The physicochemical parameters and the corresponding spectral studies of the newly identified compounds have been defined. Based on the results obtained it is suggested that the composition of the complexes is [M(L)₂]. Based on the experimental data, the most probable structure for the Cu(II) complexes has been suggested with two deprotonated OH groups of 4- and 5-nitro- cinnamoyl derivatives. The spectroscopic data on the amorphous samples indicate a square planar or a tetrahedral structure geometry of the Cu(II) complexes. Anticoagulant activity of the synthesized complexes has been determined by their prothrombin time and has been compared with that of the starting 4- and 5-nitro-cinnamoyl derivatives. It has been shown that the 5-nitroderivatives have a higher anticoagulant activity than the corresponding 4-nitroderivatives.

Conclusion. New Cu(II) complexes of 4- and 5- nitro-substituted heteroaryl cinnamoyl derivatives were successfully obtained and their anticoagulant activity was determined. These complexes may be used in future tests of food products of plant and animal origin.

Introduction

In our previous work [1] we described the synthesis of 4- and 5-nitro-substituted heteroaryl cinnamoyl derivatives from the corresponding 4- and 5-nitro-2-acetyl-1,3-indandiones with heteroaldehydes in the presence of pyrrolidine as catalyst. Their structure has been proved by elemental analysis and spectral analysis methods.

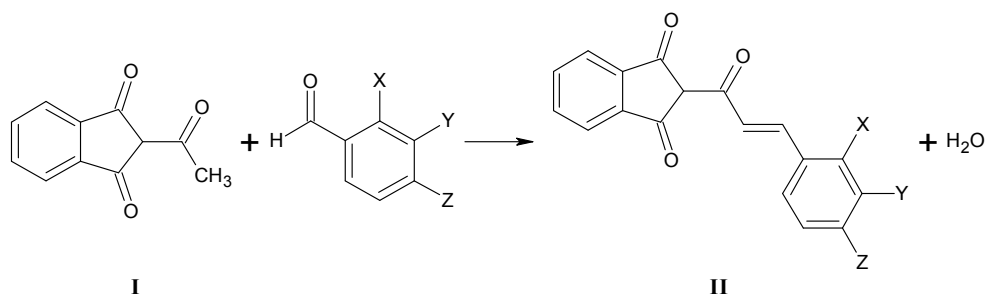
The compounds were obtained from 4- and 5-nitro-substituted 2-acetyl-1,3-indandiones by two different methods: Mosher and Meier [2] and Rotberg and Oshkaya [3], and the new thing in our method was the use of pyrrolidine as catalyst.



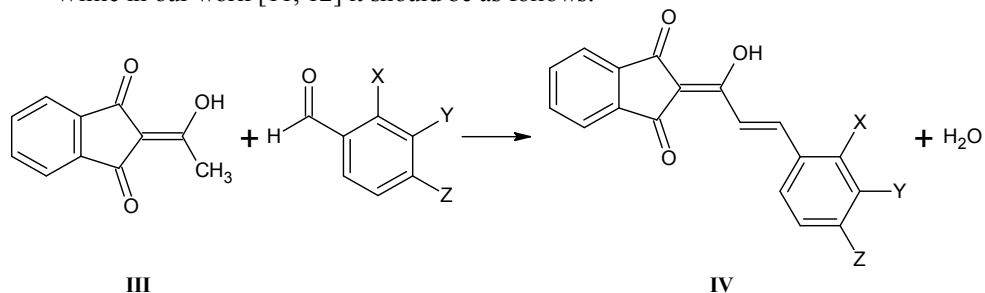
In the literature, there are quite a few examples showing that the replacement of saturated with unsaturated radical very often enhances the physiological effect or have particularly specific effect [4, 5].

But the introduction of an unsaturated radical becomes very difficult through the methods described [2, 3, 6-9]. For this purpose a new methodology [10] has been developed.

In the absence of catalysts, for example, 2-acetyl-1,3-indandione with benzaldehyde does not react, but in particularly hard conditions in the presence of alkaline or acidic catalysts, the reaction proceeds to the obtaining of the corresponding cinnamoyl derivatives. In all of these publications the reaction is indicated to proceed as follows:



While in our work [11, 12] it should be as follows:



The tautomeric form III has been proved to be energetically the most favourable form of the existing five tautomeric forms [13]. While up to now, 4- and 5-nitro cinnamoyl derivatives have not been received, pyrrolidine proved to be particularly successful catalyst.

The structure of the product of the condensation reaction between 2-acetylindan-1,3-dione and aniline was investigated in gas phase, solution and solid state using a combination of quantum-chemical calculations, IR- and ^1H -, ^{13}C -NMR spectroscopy, and by using a combination of 2D NMR experiments, which included ^1H - ^1H COSY, HMQC and HMBC sequences, and X-ray crystallography [14]. A series of six 2-acyl-1,3-indandione derivatives were determined in crystalline state and in gas phase using X-ray diffraction and theoretical methods (HF, DFT and TD-DFT) [12].

Synthesis, structure, spectral and coordination properties of a crown ether derivative of 1,3-indandione were presented by Ahmedova et al. [15]. The crystal structure of the newly synthesized crown ether derivative of 2-benzylidene-1,3-indandione was determined by means of single-crystal X-ray diffraction. The compound crystallizes in the monoclinic P21/n space group. There are four molecules in the unit cell. The structure of complexes with alkaline and alkaline-earth metal ions (K^+ , Na^+ , Mg^{2+} , Sr^{2+} and Ba^{2+}) were verified by elemental analyses, IR-, UV-Vis and also studied by means of quantum chemical methods. A racemic mixture of an octahedral Fe(III) complex was studied by means of single-crystal X-ray diffraction, Mössbauer and EPR spectroscopy [16]. Six organophosphine/phosphite silver(I) complexes of 2-acetyl-1,3-indandione (2-AID) have been obtained and characterized by elemental analysis, ^1H -, $^{13}\text{C}\{\text{H}\}$ NMR, IR spectroscopy, and thermal analysis (TG and DSC), respectively. The molecular structure of one of them has been determined by X-ray single crystal analysis in which the silver atom is in a distorted trigonal geometry [17]. Eu^{+3} complexes with 2-AID, 2-isovaleryl-1,3-indandion and 2-benzyl-1,3-indandion have been synthesized and characterized by Teotonio et al. [18]. A series of new Cu(II), Zn(II), Pb(II) Cd(II) complexes of 2AID were synthesized and based on NMR (in solution and solid state) and EPR spectroscopy for paramagnetic complexes were characterized [19]. Some of the studies concern excited state twisting, as for N,N-dimethylaminobenzylidene-1,3-indandione and derivatives [20-22]. Recently, selective electrochemical fluorination (SEF) of 1-indanone, 2-indanone and 1,3-indandione were carried out in $\text{Et}_3\text{N}\cdot 4\text{HF}$ ionic liquid by Ilayaraja and Noel [23]. Extensive publications and review, mainly from Alfimov et al., focus on the study of the molecular receptors based on photochromic crown ethers and complex formation [24]. No complexes with 4- and 5-nitro-substituted heteroaryl cinnamoyl derivatives have been obtained, so their anticoagulant activity has not been examined.

That is why, the research described here is focused on the synthesis of Cu(II) complexes of 4- and 5-nitro-substituted heteroaryl cinnamoyl derivatives and their characterization by elemental analysis, UV-Vis and IR spectroscopy.

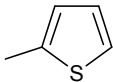
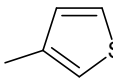
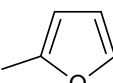
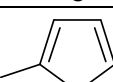
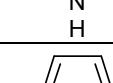
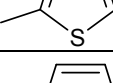
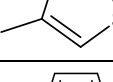
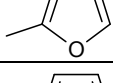
Materials and methods

All chemicals used were purchased from Merck and Sigma-Aldrich. The melting points were determined with a digital melting point apparatus SMP 10. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 F₂₅₄, 0.2 mm Merck plates, eluent system (vol. ratio): CH₂Cl₂ : CH₃COCH₃ = 1 : 1. IR spectra were taken on spectrometer Perkin-Elmer FTIR-1600 in KBr discs. UV/Vis spectra was measured on a Lambda 9 Perkin-Elmer UV/Vis/NIR Spectrophotometer from 200 nm to 1000 nm.

The obtaining of the Cu (II) complexes of the 4- and 5-nitro-cinnamoyl derivatives was conducted according to the following common methodology.

In a flask of joint of 100 ml, 0.001 mol of the corresponding nitro-cinnamoyl derivative are dissolved by refluxing. 0.0005 mol of the copper salt (Cu(CH₃COO)₂).H₂O are dissolved with gentle heating. The ligand is dissolved in a medium of dioxan (7 ml), and the copper salt – in an medium of methanol (10 ml). After addition of the solution of the copper salt to that of the nitro-cinnamoyl product, the solution is cooled to room temperature. The resulting complex is filtered and dried at room temperature and then in a desiccator over silica gel. The resulting complexes are light brown to dark brown crystalline substances with melting points above 370 °C. The yields, melting points and R_f are given in Table 1.

Table 1

X	Y	Het	Yeld, %	M.p., °C	R _f
H	NO ₂		57.17	> 370	0.47
H	NO ₂		18.00	> 370	0.49
H	NO ₂		43.77	> 370	0.40
H	NO ₂		38.33	> 370	0.45
NO ₂	H		48.71	> 370	0.48
NO ₂	H		50.62	> 370	0.42
NO ₂	H		53.51	> 370	0.51
NO ₂	H		39.13	> 370	0.40

Results and discussion

Through spectroscopic methods for structural analysis the structure of 2-acetyl-1,3-indandione and its derivatives have been defined in detail. Based on this, the possibility for receiving of several tautomeric forms, as well as a tautomeric equilibrium, have been established. V. Enchev et. al. [13] in 1999 demonstrated the realization of intramolecular proton transfer. The proof of proton transfer and the failure to register a high energy form led to the assumption of reversible and relatively fast transfer of passing of enol forms in one another.

A number of researchers have been directed to synthesis, determining the structure and properties of derivatives of 2-acetyl-1,3-indandione. Of particular interest is the nitro group introduced in the phthaloyl ring, due to the strong electron acceptor character due to a significant degree to the change of the distributed electron density, as a result of which change in acidity and other physicochemical properties of 2-acetyl-1,3-indandione can be expected. It has been found that the introduction of a nitro group in the phthaloyl core of 2-acetyl-1,3-indandiones greatly increases the acidity of the triketones. The increase in the acid properties is associated with an increase in the acidity of the anionic form, which in its turn is explained by the involvement of the nitro group in the negatively charged delocalized anion of the 5-nitro-2-acetyl-1,3-indandione. The nitro group in the fourth position due to the spatial problems, does not detract from the plain position and thus does not have such a strong negative conjugation effect to the triketone group as the nitro group located in the fifth place.

Despite the well-known chelato-creating ability of the 2-acetyl-1,3-indandiones and their derivatives, significantly small is the number of the studies in this area. That is why we turned to the study of the 4- and 5- nitro-cinnamoyl derivatives with five-cycle heteroaldehyde and the ability to form complexes with transition metals, in this case Cu^{2+} .

The relative stability of the potential enol tautomers in the cinnamoyl derivatives, unsubstituted in the phthaloyl core, has been established [25] through optimization by HF and DTF methods [25]. The resulting relative energies indicate that the exocyclic enol form (a) is the most favourable. In accordance with the Hartree-Fock calculations the endocyclic enol form (b) and the rotamer acis are very poor in energy. DFT results show energy differences between these two isomers as the rotamer acis is more stable than the tautomer (c) (Fig. 1).

Due to the existence of geometrical isomerism, the number of isomers has been increased to eight, as energetically most advantageous is structure (a), and this is namely the E-form (a) (Fig. 2).

The names of the respective forms, depending on the substituents, are given in the Table. 2.

UV/Vis spectra were measured on a Lambda 9 Perkin-Elmer UV/Vis/NIR Spectrophotometer from 200 nm to 1000 nm.

All UV-Vis spectra were registered in DMSO. Maxima in the electronic spectra of Cu(II) complexes with 4-nitro-substituted heteroaryl cinnamoyl derivatives were observed at 255, 305, 376 for Va (Cu(II) complexes with 4-nitro-cinnamoyl derivatives); 256, 323, 382 for Vb; 256, 320, 411 for Vc nm, respectively. Maxima in the UV-Vis spectra of the Cu(II) complexes with 5-nitro-substituted heteroaryl cinnamoyl derivatives were observed at 256, 395 for Va₁ (Cu(II) complexes with 5-nitro-cinnamoyl derivatives); 256, 284 for Vb₁; 256, 317, 386 for Vc₁ nm, respectively.

For the course of the reaction, we judge not only by the colour changes, but also by the spectral data of the resulting complexes, compared with those of the starting cinnamoyl

derivatives published by us earlier [1]. The full reaction is traced with TLC. First, there has been a reduction of the frequency of oscillation of the hydroxyl group with $40-85\text{ cm}^{-1}$ for the various complex compounds. The oscillations of one of the carbonyl groups have been retained, unengaged with the chelato-creation, as well as the double $\text{C}=\text{C}$ bond, while for the other change it is significant, the difference is $20-45\text{ cm}^{-1}$. Coordination of the 2-cinnamoyl-1,3-indandiones after deprotonation of the enolic OH group is supposed after comparing the IR spectra of the metal complexes with that of the free ligands. The physicochemical parameters, as well as the IR-spectral data for Cu(II) complexes with 4- and 5-nitro-substituted heteroaryl cinnamoyl derivatives, are listed in Table 1, Table 3 and Table 4.

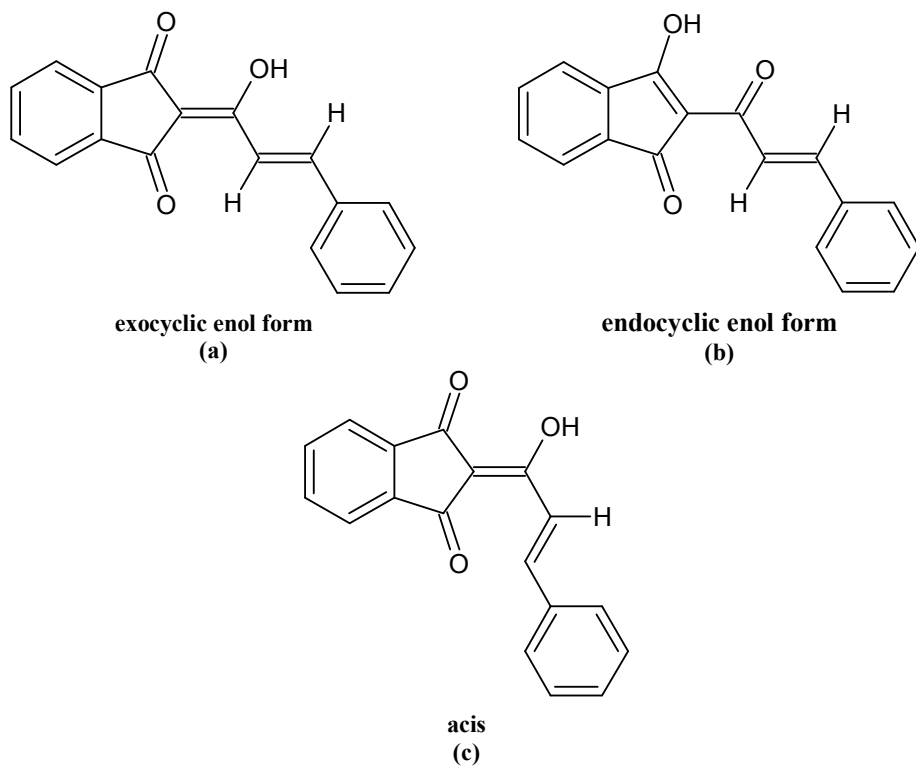


Fig. 1

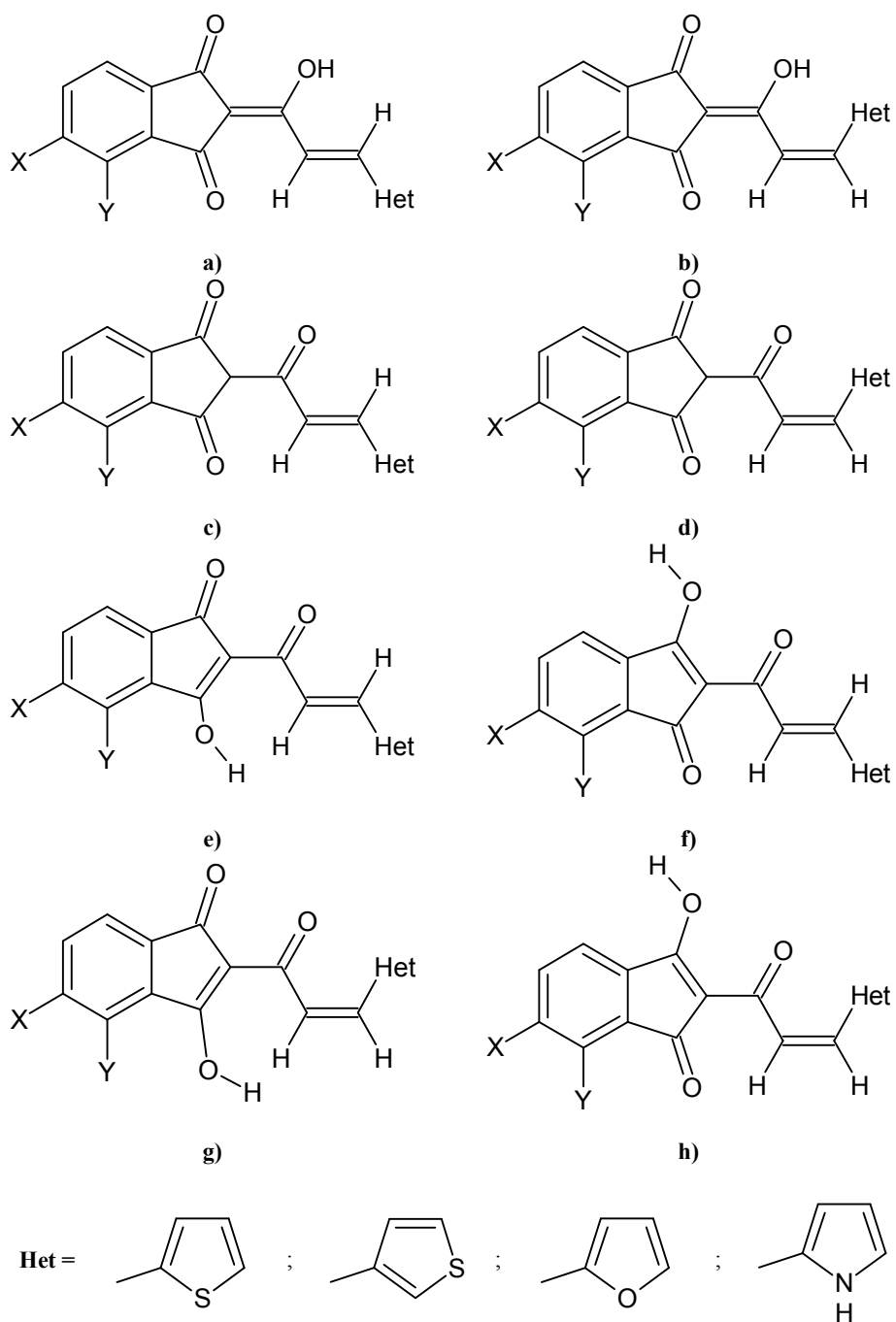
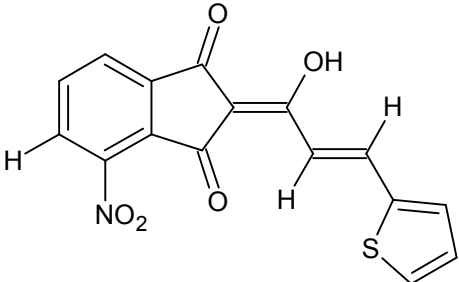
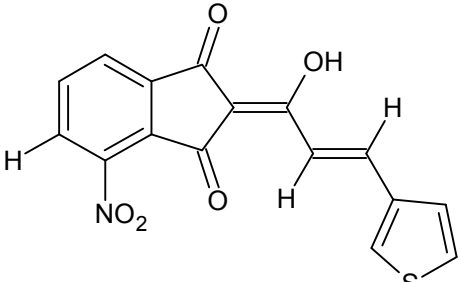
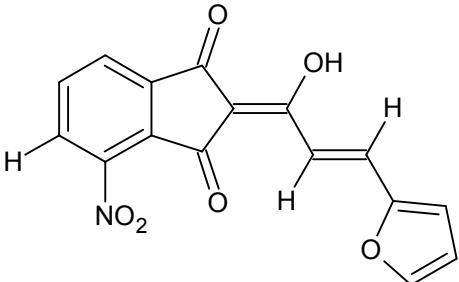
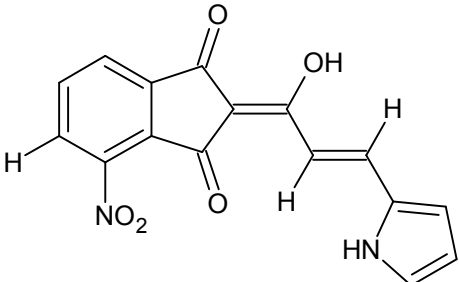
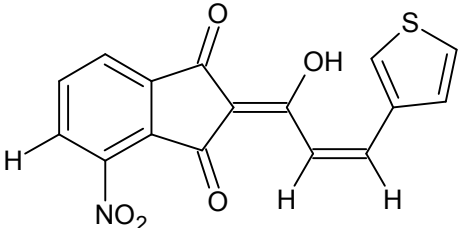
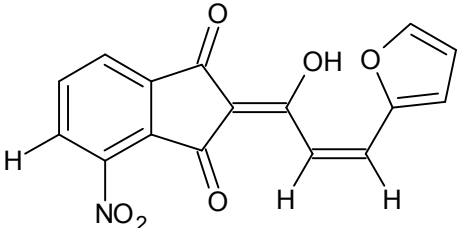
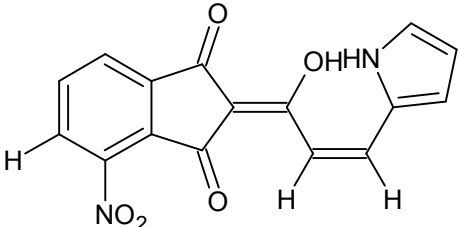
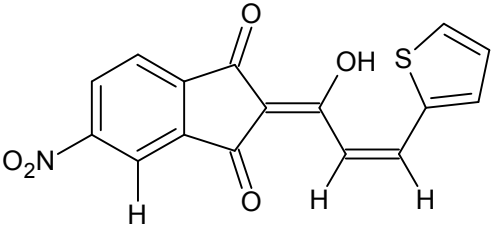
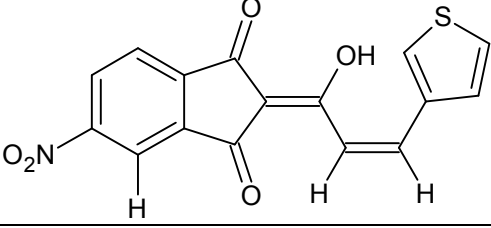
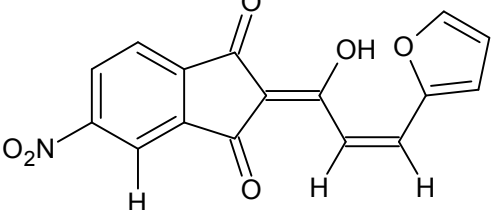


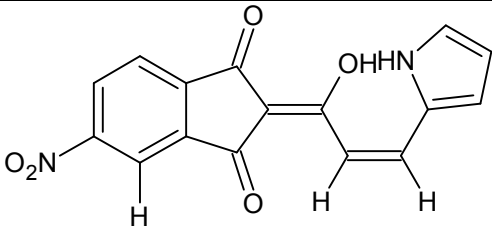
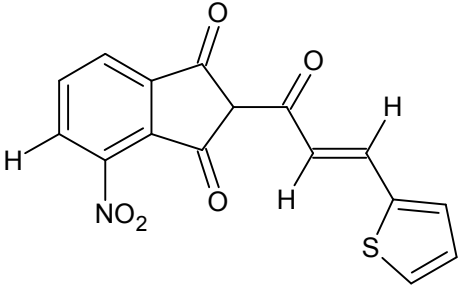
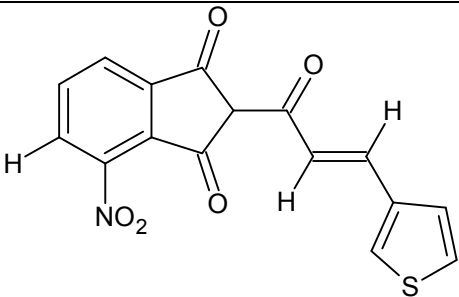
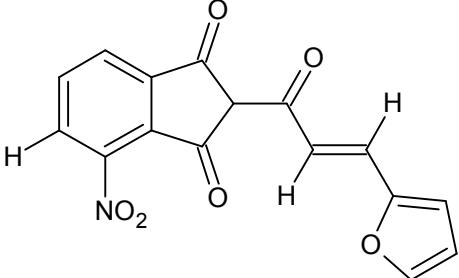
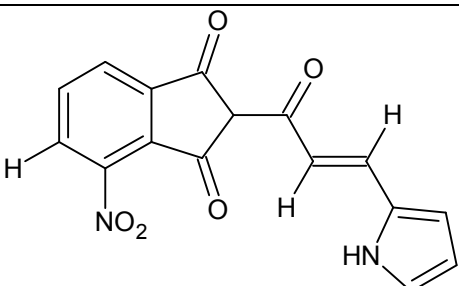
Fig. 2

Table 2

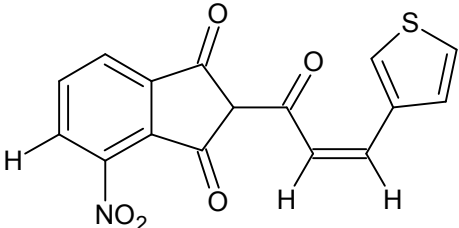
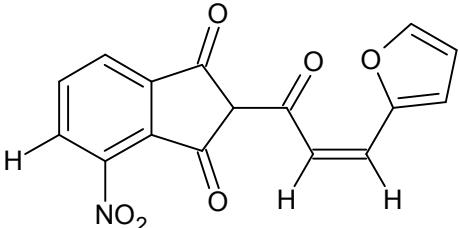
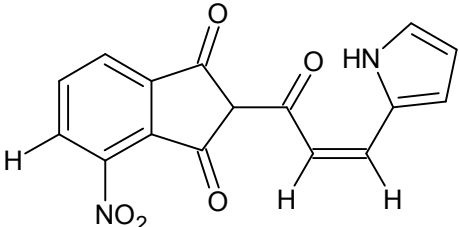
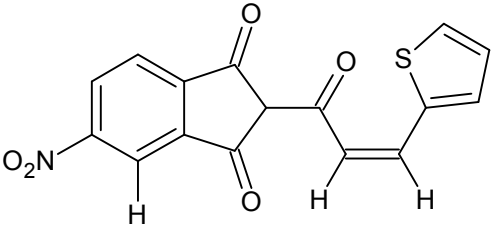
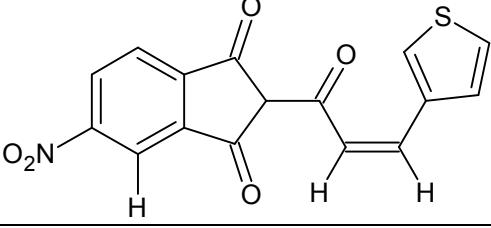
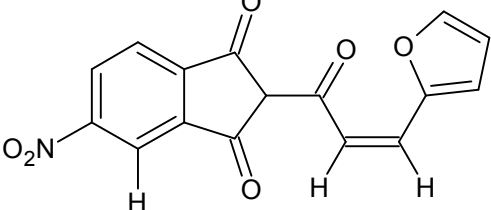
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		<p>(2E)-2-[(2E)-1-hydroxy-3-(thiophen-3-yl)prop-2-en-1-ylidene]-4-nitro-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>
		<p>(2E)-2-[(2E)-3-(furan-2-yl)-1-hydroxyprop-2-en-1-ylidene]-4-nitro-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>
		<p>(2E)-2-[(2E)-1-hydroxy-3-(1<i>H</i>-pyrrol-2-yl)prop-2-en-1-ylidene]-4-nitro-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>

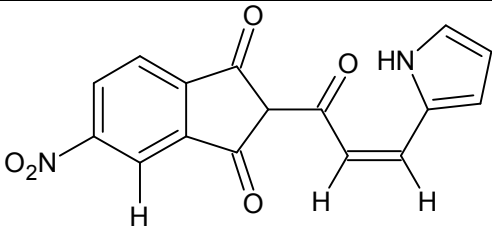
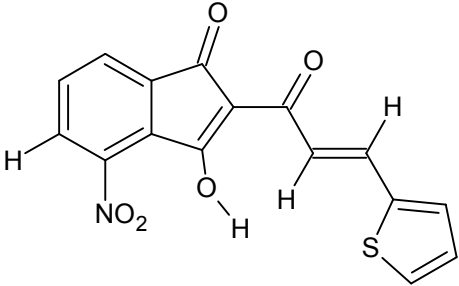
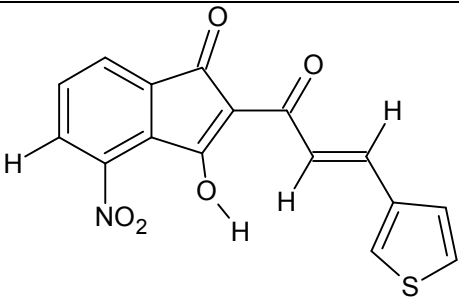
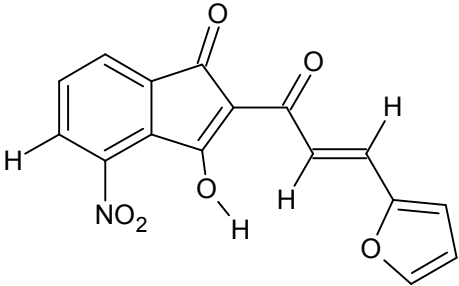
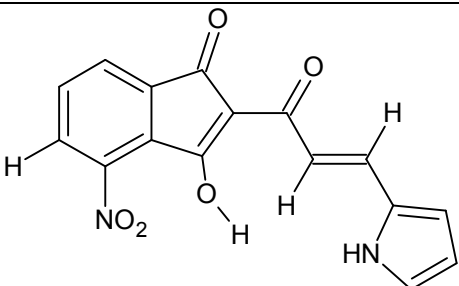
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		<p>(2E)-2-[(2E)-3-(furan-2-yl)-1-hydroxyprop-2-en-1-ylidene]-5-nitro-1H-indene-1,3(2H)-dione</p>
		<p>(2E)-2-[(2E)-1-hydroxy-3-(1H-pyrrol-2-yl)prop-2-en-1-ylidene]-5-nitro-1H-indene-1,3(2H)-dione</p>
b		<p>(2E)-2-[(2Z)-1-hydroxy-3-(thiophen-2-yl)prop-2-en-1-ylidene]-4-nitro-1H-indene-1,3(2H)-dione</p>

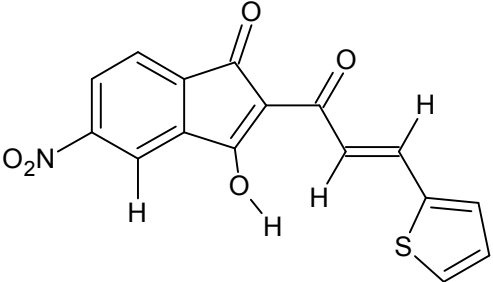
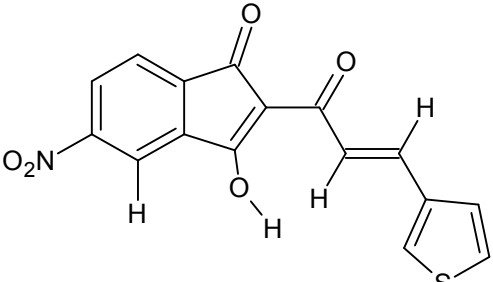
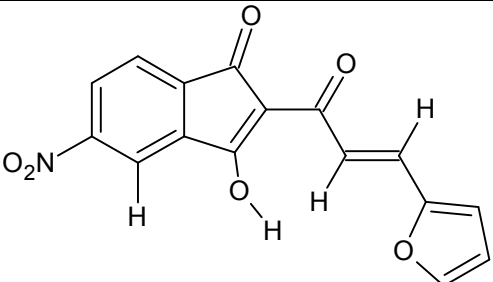
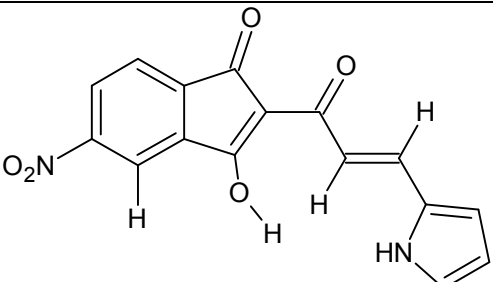
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	<p>(2E)-2-[(2Z)-3-(furan-2-yl)-1-hydroxyprop-2-en-1-ylidene]-4-nitro-1H-indene-1,3(2H)-dione</p>
	<p>(2E)-2-[(2Z)-1-hydroxy-3-(1H-pyrrol-2-yl)prop-2-en-1-ylidene]-4-nitro-1H-indene-1,3(2H)-dione</p>
	<p>(2E)-2-[(2Z)-1-hydroxy-3-(thiophen-2-yl)prop-2-en-1-ylidene]-5-nitro-1H-indene-1,3(2H)-dione</p>
	<p>(2E)-2-[(2Z)-1-hydroxy-3-(thiophen-3-yl)prop-2-en-1-ylidene]-5-nitro-1H-indene-1,3(2H)-dione</p>
	<p>(2E)-2-[(2Z)-3-(furan-2-yl)-1-hydroxyprop-2-en-1-ylidene]-5-nitro-1H-indene-1,3(2H)-dione</p>

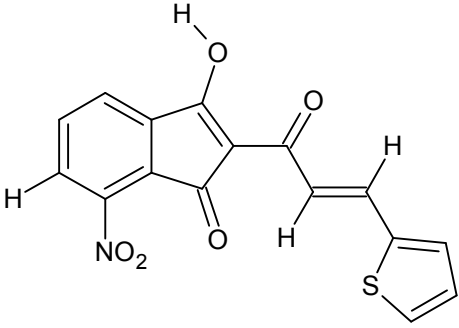
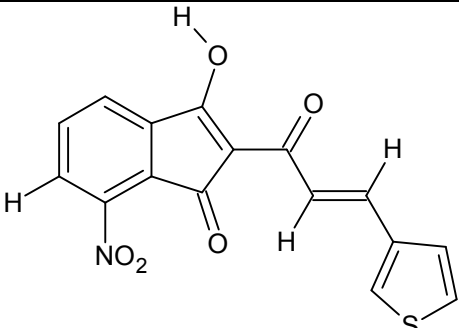
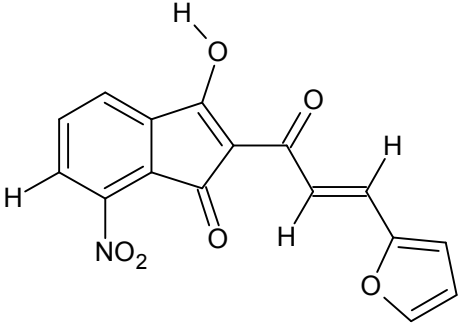
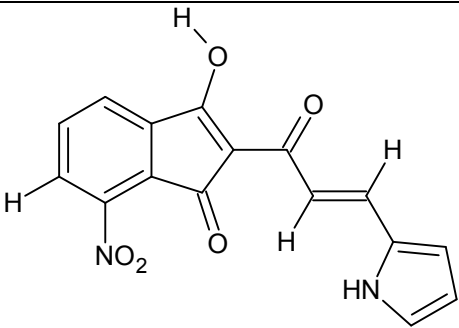
		<p>(2E)-2-[(2Z)-1-hydroxy-3-(1H-pyrrol-2-yl)prop-2-en-1-ylidene]-5-nitro-1H-indene-1,3(2H)-dione</p>
c		<p>4-nitro-2-[(2E)-3-(thiophen-2-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>
		<p>4-nitro-2-[(2E)-3-(thiophen-3-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>
		<p>2-[(2E)-3-(furan-2-yl)prop-2-enoyl]-4-nitro-1H-indene-1,3(2H)-dione</p>
		<p>4-nitro-2-[(2E)-3-(1H-pyrrol-2-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>

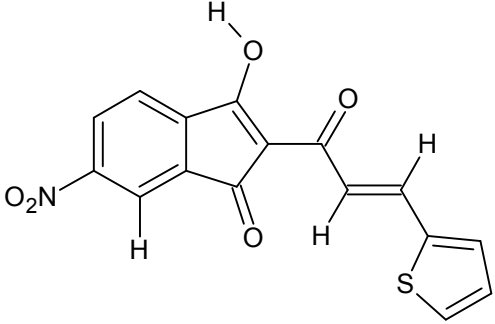
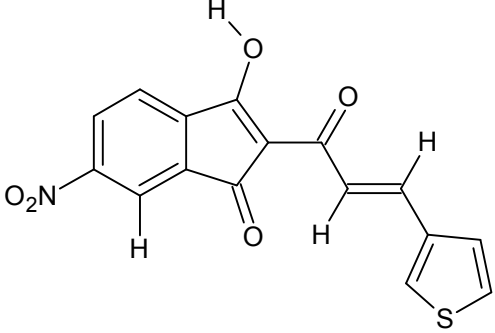
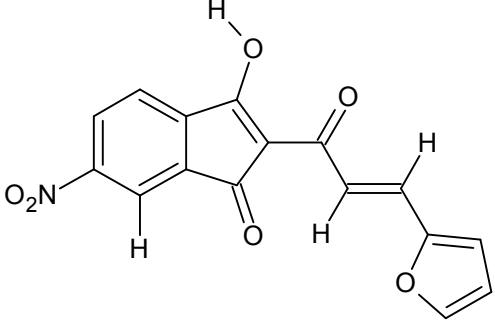
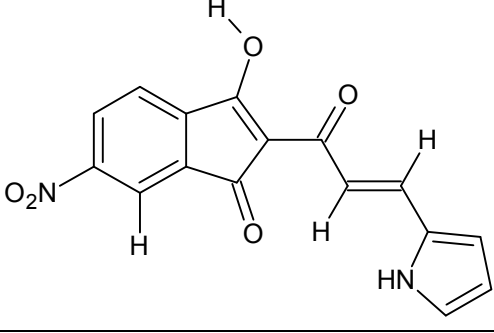
		<p>5-nitro-2-[(2<i>E</i>)-3-(thiophen-2-yl)prop-2-enoyl]-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>
		<p>5-nitro-2-[(2<i>E</i>)-3-(thiophen-3-yl)prop-2-enoyl]-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>
		<p>2-[(2<i>E</i>)-3-(furan-2-yl)prop-2-enoyl]-5-nitro-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>
		<p>5-nitro-2-[(2<i>E</i>)-3-(1<i>H</i>-pyrrol-2-yl)prop-2-enoyl]-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>
d		<p>4-nitro-2-[(2<i>Z</i>)-3-(thiophen-2-yl)prop-2-enoyl]-1<i>H</i>-indene-1,3(2<i>H</i>)-dione</p>

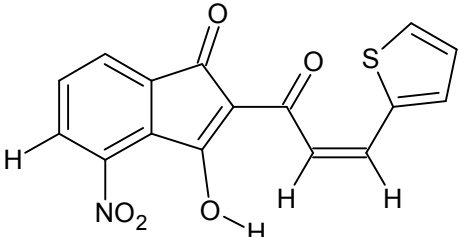
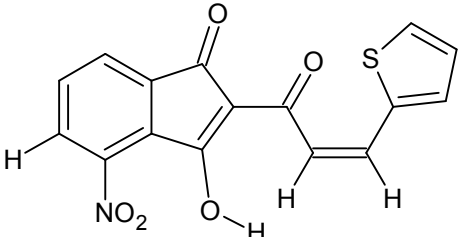
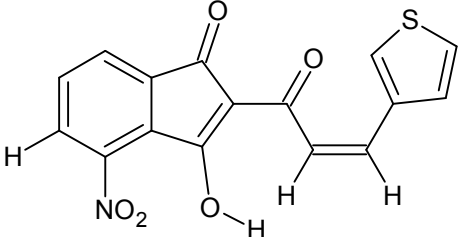
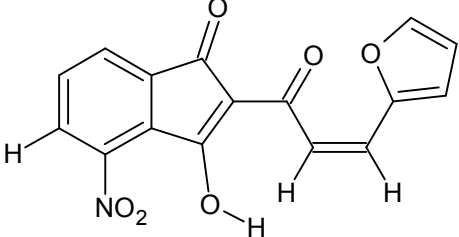
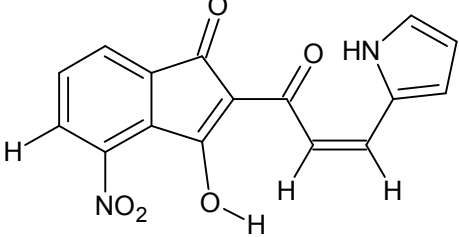
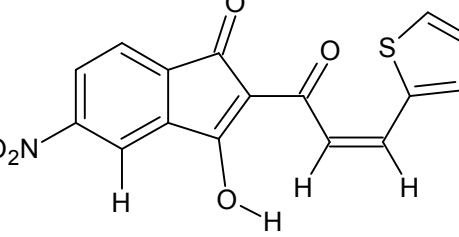
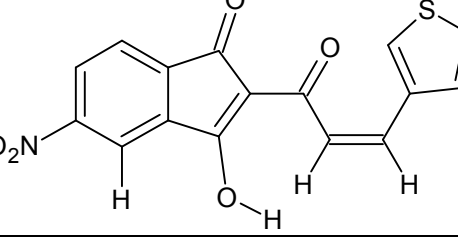
	<p>4-nitro-2-[(2Z)-3-(thiophen-3-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>
	<p>2-[(2Z)-3-(furan-2-yl)prop-2-enoyl]-4-nitro-1H-indene-1,3(2H)-dione</p>
	<p>4-nitro-2-[(2Z)-3-(1H-pyrrol-2-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>
	<p>5-nitro-2-[(2Z)-3-(thiophen-2-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>
	<p>5-nitro-2-[(2Z)-3-(thiophen-3-yl)prop-2-enoyl]-1H-indene-1,3(2H)-dione</p>
	<p>2-[(2Z)-3-(furan-2-yl)prop-2-enoyl]-5-nitro-1H-indene-1,3(2H)-dione</p>

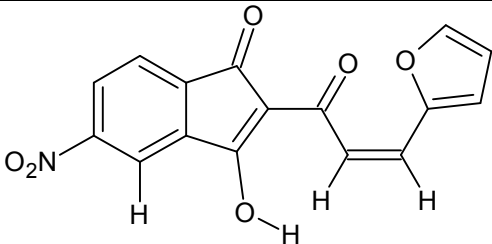
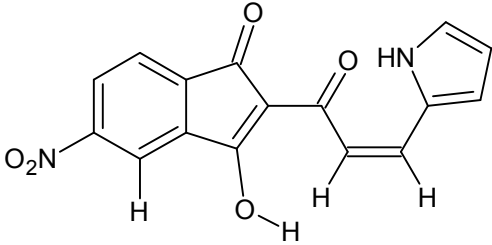
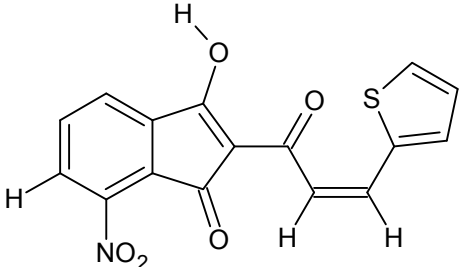
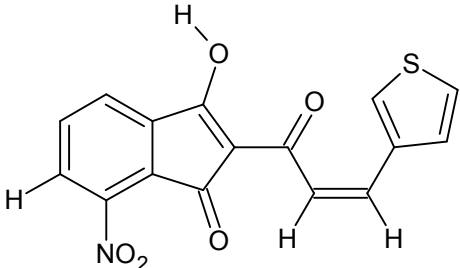
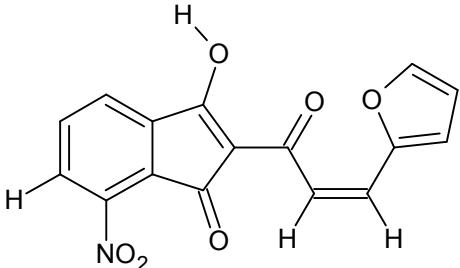
		<p>5-nitro-2-[(2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-indene-1,3(2H)-dione</p>
e		<p>3-hydroxy-4-nitro-2-[(2E)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one</p>
		<p>3-hydroxy-4-nitro-2-[(2E)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one</p>
		<p>2-[(2E)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-4-nitro-1H-inden-1-one</p>
		<p>3-hydroxy-4-nitro-2-[(2E)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one</p>

	<p>3-hydroxy-5-nitro-2-[(2E)-3-(thiophen-2-yl)prop-2-enoyl]-1H-inden-1-one</p>
	<p>3-hydroxy-5-nitro-2-[(2E)-3-(thiophen-3-yl)prop-2-enoyl]-1H-inden-1-one</p>
	<p>2-[(2E)-3-(furan-2-yl)prop-2-enoyl]-3-hydroxy-5-nitro-1H-inden-1-one</p>
	<p>3-hydroxy-5-nitro-2-[(2E)-3-(1H-pyrrol-2-yl)prop-2-enoyl]-1H-inden-1-one</p>

<p>f</p>		<p>3-hydroxy-7-nitro-2-[(2E)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one</p>
		<p>3-hydroxy-7-nitro-2-[(2E)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one</p>
		<p>2-[(2E)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-7-nitro-1H-inden-1-one</p>
		<p>3-hydroxy-7-nitro-2-[(2E)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one</p>

 <p>The structure shows a 1H-inden-1-one core with a hydroxyl group at position 3 and a nitro group at position 6. At position 2, it is substituted with a prop-2-enyl chain in the (2E) configuration, which is further substituted at the 3-position with a thiophen-2-yl ring.</p>	<p>3-hydroxy-6-nitro-2-[(2E)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one</p>
 <p>The structure is similar to the first one, but the thiophen-2-yl ring is replaced by a thiophen-3-yl ring.</p>	<p>3-hydroxy-6-nitro-2-[(2E)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one</p>
 <p>The structure is similar to the first one, but the thiophen-2-yl ring is replaced by a furan-2-yl ring.</p>	<p>2-[(2E)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-6-nitro-1H-inden-1-one</p>
 <p>The structure is similar to the first one, but the thiophen-2-yl ring is replaced by a 1H-pyrrol-2-yl ring.</p>	<p>3-hydroxy-6-nitro-2-[(2E)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one</p>

		3-hydroxy-4-nitro-2-[(2Z)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one
		3-hydroxy-4-nitro-2-[(2Z)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one
		2-[(2Z)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-4-nitro-1H-inden-1-one
		3-hydroxy-4-nitro-2-[(2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one
		3-hydroxy-5-nitro-2-[(2Z)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one
		3-hydroxy-5-nitro-2-[(2Z)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one

		<p>2-[(2Z)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-5-nitro-1H-inden-1-one</p>
		<p>3-hydroxy-5-nitro-2-[(2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one</p>
h		<p>3-hydroxy-7-nitro-2-[(2Z)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one</p>
		<p>3-hydroxy-7-nitro-2-[(2Z)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one</p>
		<p>2-[(2Z)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-7-nitro-1H-inden-1-one</p>

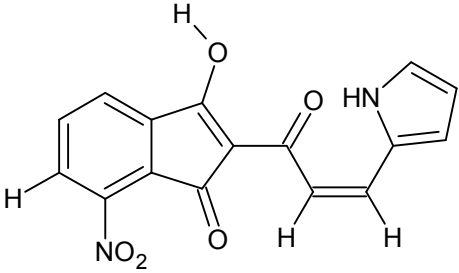
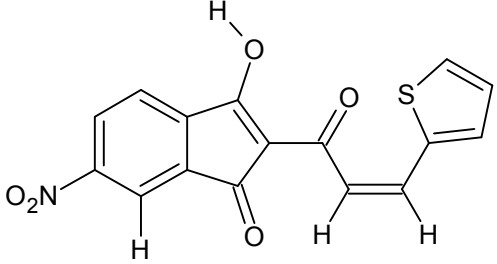
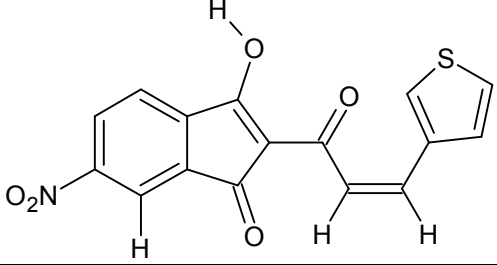
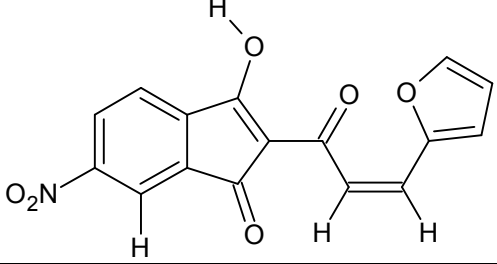
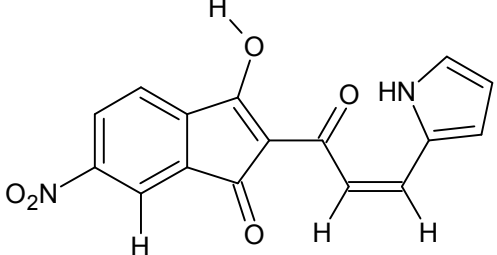
 <p>The structure shows a 1H-inden-1-one core with a hydroxyl group at position 3 and a nitro group at position 7. At position 2, it is substituted with a (2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl group.</p>	<p>3-hydroxy-7-nitro-2-[(2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one</p>
 <p>The structure shows a 1H-inden-1-one core with a hydroxyl group at position 3 and a nitro group at position 6. At position 2, it is substituted with a (2Z)-3-(thiophen-2-yl)prop-2-enyl group.</p>	<p>3-hydroxy-6-nitro-2-[(2Z)-3-(thiophen-2-yl)prop-2-enyl]-1H-inden-1-one</p>
 <p>The structure shows a 1H-inden-1-one core with a hydroxyl group at position 3 and a nitro group at position 6. At position 2, it is substituted with a (2Z)-3-(thiophen-3-yl)prop-2-enyl group.</p>	<p>3-hydroxy-6-nitro-2-[(2Z)-3-(thiophen-3-yl)prop-2-enyl]-1H-inden-1-one</p>
 <p>The structure shows a 1H-inden-1-one core with a hydroxyl group at position 3 and a nitro group at position 6. At position 2, it is substituted with a (2Z)-3-(furan-2-yl)prop-2-enyl group.</p>	<p>2-[(2Z)-3-(furan-2-yl)prop-2-enyl]-3-hydroxy-6-nitro-1H-inden-1-one</p>
 <p>The structure shows a 1H-inden-1-one core with a hydroxyl group at position 3 and a nitro group at position 6. At position 2, it is substituted with a (2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl group.</p>	<p>3-hydroxy-6-nitro-2-[(2Z)-3-(1H-pyrrol-2-yl)prop-2-enyl]-1H-inden-1-one</p>

Table 3









№	Het	ν _{OH}	ν _{NH}	ν _{ar}	ν _{C=O}	ν _{C=O'}	ν _{C=C}	ν _{C=C(Het)}	ν _{asNO2}	ν _{sNO2}	ν _{OH}	ν _{=CH}	ν _{2-tioph}	ν _{3-tioph}
Va		3444		3062	1701	1632	1614	1571	1537	1351	1254	962	825	
Vb		3443		3088	1697	1632	1610	1573	1537	1351	1276	967		768
Vc		3483		3071	1698	1636	1612	1572	1548	1351	1271	968		
Vd		3471	3364	3055	1697	1633	1610	1572	1538	1351	1271	967		

Table 4

№	Het	ν _{OH}	ν _{NH}	ν _{ar}	ν _{C=O}	ν _{C=O'}	ν _{C=C}	ν _{C=C(Het)}	ν _{asNO2}	ν _{sNO2}	ν _{OH}	ν _{=CH}	ν _{2-tioph}	ν _{3-tioph}
Va ₁		3495		3096	1698	1625	1607	1563	1533	1342	1254	951	838	
Vb ₁		3427		3096	1697	1626	1608	1586	1533	1342	1253	955		798
Vc ₁		3495		3097	1698	1631	1612	1571	1549	1342	1254	950		
Vd ₁		3475	3381	3096	1697	1626	1610	1573	1540	1342	1253	951		

Data from the elemental analysis of the ligands and the complexes are shown in Table 5 and Table 6. The elemental analyses data show composition of the complexes with 1 : 2 metal-to-ligand ratio ($[M(L)_2]$). The ligands coordinate in a bidentate way as monoanions after deprotonation of the enolic OH group. This is confirmed by the IR data of the metal complexes, which are compared with those of the free ligands and presented in Table 3 and 4. The IR data of the 4- and 5-nitro-substituted heteroaryl cinnamoyl derivatives are presented in reference 1.

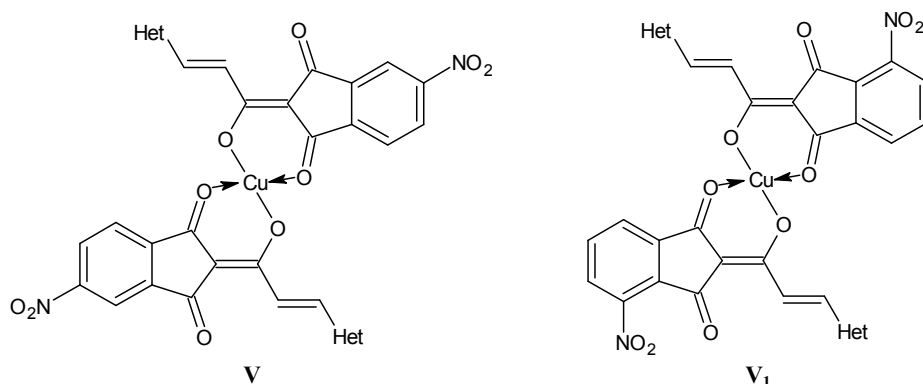
Table 5

Compound	C, %		H, %		N, %		S, %		Cu, %	
	calc.	found	calc.	found	calc.	found	calc.	found	calc.	found
L-Va	58.71	58.65	2.77	2.71	4.28	4.25	9.80	9.59		
CuL	53.67	53.55	2.25	2.17	3.91	3.83	8.95	8.77	8.87	8.75
L-Vb	58.71	58.58	2.77	2.64	4.28	4.18	9.80	9.64		
CuL	53.67	53.48	2.25	2.13	3.91	3.86	8.95	8.79	8.87	8.69
L-Vc	61.74	61.65	2.91	2.83	4.50	4.44				
CuL	56.19	56.00	2.36	2.27	4.10	3.95			9.29	9.18
L-Vd	61.94	61.89	3.25	3.15	9.03	8.94				
CuL	56.35	56.29	2.66	2.51	8.21	8.06			9.32	9.22

Table 6

Compound	C, %		H, %		N, %		S, %		Cu, %	
	calc.	found	calc.	found	calc.	found	calc.	found	calc.	found
L-Va ₁	58.71	58.57	2.77	2.61	4.28	4.24	9.80	9.67		
CuL	53.67	53.48	2.25	2.21	3.91	3.79	8.95	8.78	8.87	8.71
L-Vb ₁	58.71	58.57	2.77	2.63	4.28	4.08	9.80	9.59		
CuL	53.67	53.61	2.25	2.15	3.91	3.82	8.95	8.83	8.87	8.79
L-Vc ₁	61.74	61.55	2.91	2.81	4.50	4.35				
CuL	56.19	56.03	2.36	2.27	4.10	3.95			9.29	9.11
L-Vd ₁	61.94	61.66	3.25	3.15	9.03	8.97				
CuL	56.35	56.17	2.66	2.55	8.21	8.06			9.32	9.26

The most probable structure of the resulting complexes, in our opinion, can be presented as follows:



Based on the results obtained it is suggested that the composition of the complexes is $[M(L)_2]$. Based on the experimental data, the most probable structure for the Cu(II) complexes has been suggested with two deprotonated OH groups of 4- and 5-nitrocinnamoyl derivatives. The spectroscopic data on the amorphous samples indicate a square planar or a tetrahedral structure geometry of the Cu(II) complexes.

Anticoagulant activity of the synthesized complexes has been determined by their prothrombin time and has been compared with that of the starting 4- and 5-nitrocinnamoyl derivatives (Table 7 and Table 8).

Table 7

N ^o	PT, %	INR	PT, s
Va	76.0	1.32	16.4
Va+Cu ²⁺	95.6	1.57	25.4
Vb	129.5	0.44	6.6
Vb+Cu ²⁺	135.6	0.55	9.3
Vc	106.4	0.58	8.5
Vc+Cu ²⁺	114.7	0.76	12.2

PT – Prothrombin Time

INR – International Normal Ratio

Table 8

N ₂	PT, %	INR	PT, s
Va ₁	82.0	1.41	19.6
Va ₁ +Cu ²⁺	101.5	1.63	31.3
Vb ₁	132.3	0.64	10.5
Vb ₁ +Cu ²⁺	140.1	0.66	13.8
Vc ₁	108.4	0.68	9.5
Vc ₁ +Cu ²⁺	111.1	0.84	16.6

PT – Prothrombin Time

INR – International Normal Ratio

It is evident that the 5-nitroderivatives and their complexes manifest a higher anticoagulant activity.

Conclusion

Synthesized and characterized, still not described in the literature, are new 4- and 5-nitro-cinnamoyl derivatives of five-cycle hetero-aldehyde with Cu²⁺. A series of non-charged complexes with Cu(II) has been isolated and analyzed by elemental analyses, UV-Vis and IR spectroscopy. For the paramagnetic Cu(II) complexes a tetrahedral or square planar structure has been proposed.

The anticoagulant activity of the resulting complexes has been determined by defining their prothrombin time, it has been shown that the 5-nitroderivatives have a higher anticoagulant activity than the corresponding 4-nitroderivatives.

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