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The Use of the Carbonyl Group (C-3) of Isatin for the Construction of Pyrazoline Moiety and the Study of its Antioxidant Activity

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Abstract

A series of novel pyrazoline derivatives **5-13** were synthesized in three steps from isatin, with yields ranging from 40 to 72% over the multistep procedure. The first step included the condensation of isatin with *p*-aminoacetophenone to afford the corresponding Schiff base **1** in a 75% yield. In the second step, the enolate form of Schiff base **1** was reacted with different aromatic aldehydes (benzaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde) to give the title chalcone derivatives **2-4** in **60-72** yields. In the third step, pyrazoline derivatives **5-13** were synthesized *via* cycloaddition reactions between compounds **2-4** and hydrazine hydrate, phenyl hydrazine, or *p*-nitrophenyl hydrazine. The cycloaddition produced the target pyrazoline compounds in 40-72% isolated yields. All prepared compounds were characterized by FT-IR and ^{1}H NMR spectroscopy. Some of the prepared compounds were tested for antioxidant properties.

Keywords: Antioxidant activity, Isatin, Pyrazoline.

استخدام مجموعة الكاربونيل (C3) للايستن في بناء شطر البايرازولين و دراسة نشاطها المضاد للاكسدة

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الخلاصة

تم تخليق سلسلة من مشتقات البايرازولين الجديدة **5–13** في ثلاث خطوات من الايزاتين، مع إنتاجية بمدى من 40 الى 72% خلال طريقة عمل متعددة الخطوات. الخطوة الاولى تضمنت تكاثف الايستن مع بارا–امينواسيتوفينون لتحضير قاعدة شف **1** بمنتوج 75%. في الخطوة الثانية تم مفاعلة اينوليت قاعدة شف **1** مع الديهايدات اروماتية مختلفة (بنزلديهايد و بارا–انايتروبنزلديهايد و بارا–كلوروبنزلديهايد) لاعطاء مشتقات الجالكون المعنونة **2–4** بمنتوج 60–72%. في الخطوة الثالثة، تم تخليق مشتقات البيرازولين **5–13** عبر تفاعلات الإضافة الحلقية بين المركبات **2–4** و الهايدرازين المائي، فنيل هايدرازين و بارا–نايتروفنيل هايدرازين. أنتجت الإضافة الحلقية مركبات البايرازولين المستهدفة بنسبة 40–72% من المحصول المعزول. تم تشخيص المركبات الناتجة بواسطة مطيافية FT–IR و ^{1}H NMR. بعض المركبات المحضرة تم اختبارها كمضادات اكسدة.

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1. Introduction

Isatin (indole-1H-2,3-dione) consists of a fused ring system comprising a six-membered aromatic ring and a five-membered anti-aromatic ring. It was first discovered in 1841 by Erdman and Laurent, who synthesized orange monoclinic isatin crystals through the nitric and chromic acid oxidation of indigo dye [1]. It is a privileged scaffold endowed with broad-spectrum biological properties [2], including antitumor [3], anti-mycobacterial [3], antiviral [4], anti-HIV [5], and anti-inflammatory [6]. Also, it plays an important role in the treatment of advanced renal carcinoma, according to the FDA approval of the oxindole-based sunitinib maleate [7]. The chalcone is regarded as one of the most significant compounds due to the presence of two aromatic rings and a double bond with a carbonyl group in its structure. Chalcone, which acts as the focal point for a set of vital biological molecules known as chalconoids or chalcones, is in fact an aromatic enone [8]. Chalcone and its derivatives have important biological activities, such as anticancer [9], anti-tuberculosis [9], anti-antimicrobial [10], and anti-biofilm [10]. Pyrazoline is a dihydropyrazole, a five-membered heterocyclic molecule with two nitrogen atoms in close proximity and just one endocyclic double bond [11]. It has three tautomeric forms that are unsubstituted [12]. Pyrazoline serves as a crucial precursor for the synthesis of new chemical compounds with therapeutic properties [13]. Because of their role in heterocyclic synthesis and medical applications, pyrazolines are regarded as important chemicals in organic chemistry [14]. Moreover, pyrazolines possess a wide range of biological activities, such as anti-inflammatory [15,16], anti-depressant [17], antimicrobial [16,18], calcium channel blockers [19], antihypertensive [20], antitumor [21], antiviral [22], antibacterial [23], monoamine oxidase inhibitor [24], anti-HIV [25], anticancer [26], antimalarial [27], and anti-oxidant [28]. In this work, isatin-derived pyrazoline compounds will be synthesized *via* a three-step procedure. First, isatin will undergo condensation with *p*-aminoacetophenone to form an imine intermediate. This imine will then react with various aromatic aldehydes in the second step to produce chalcone derivatives. Finally, the chalcones will undergo cycloaddition with hydrazines in the third step to yield the target pyrazoline products.

2. Experimental part

2.1. Materials and instrumentation

All chemicals were purchased from commercial sources and used without additional purification, unless stated otherwise. TLC was performed on Merck silica gel 60 F_{254} and visualized by a UV lamp and aqueous alkaline potassium permanganate. The melting points are uncorrected and were recorded in open capillary tubes using Stuart Scientific SMP3. Infrared spectral data were recorded using a Shimadzu 8400 FTIR spectrometer. The ^{1}H NMR spectra were recorded using a Bruker AV400 spectrometer. Chemical shifts are quoted in ppm downfield from tetramethylsilane (TMS) as an internal standard or deuterated DMSO in ^{1}H NMR as a reference ($\square_H$ 2.50 ppm). The antioxidant activity data were recorded using a spectrophotometer (Shimadzu UV-1800 Spectrophotometer).

2.2. Chemistry

*2.2.1. Preparation of 3-((4-acetylphenyl)imino)indolin-2-one (**1**) [29]*

To a solution of isatin (2 g, 13 mmol, 1.0 eq.) in ethanol (50 mL), glacial acetic acid (4-5 drops) was added before heating at 70 °C for 30 minutes. A solution of *p*-aminoacetophenone (1.84 g, 13 mmol, 1.0 eq.) in ethanol (10 mL) was then added to the reaction mixture and refluxed for 8 hours, as determined by TLC (eluent with petroleum ether/ethyl acetate, 1:1). The solid crude material was filtered, washed with ethanol, and recrystallized from toluene to afford the desired product (**1**). The physical properties and FT-IR spectral data of this product are shown in Tables 1 and 2, respectively.

*2.2.2. General procedure for the synthesis of the chalcone derivatives derived from isatin **2-4** [30,31]*

A mixture of compound **1** (400 mg, 1.5 mol, 1.0 eq.) in dioxane:ethanol (75 mL, 2:1) and NaOH solution (3 drops, 40%) was stirred for 30 minutes. Benzaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde (1.5 mol, 1.0 eq.) was added to the reaction mixture and stirred for 48 hours, as determined by TLC (eluent with petroleum ether/ethyl acetate). The mixture was then added to ice water and subjected to filtration, washing with water, and recrystallization from toluene to provide the desired products (**2**-**5**). The physical properties and FT-IR spectral data of these products are listed in Tables 1 and 2, respectively.

*2.2.3. General procedure for the synthesis of the pyrazoline derivatives **5-13** [32]*

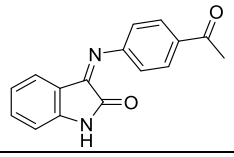
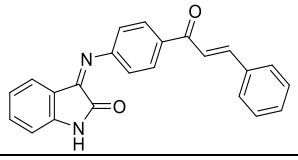
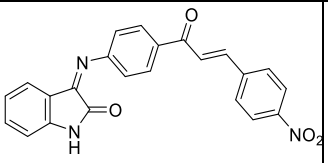
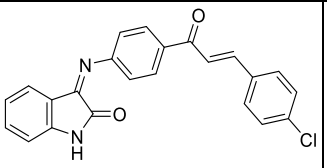
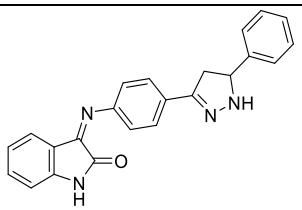
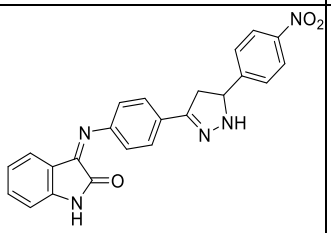
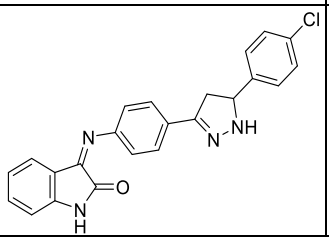
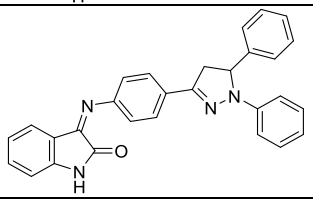
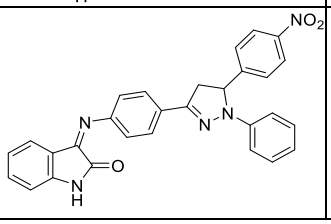
To a mixture of compounds **2-4** (400 mg, 0.75-0.85□□mol, 1.0 eq.) in EtOH (25 mL) and glacial acetic acid (3 drops), hydrazine hydrate, phenyl hydrazine, or *p*-nitrophenyl hydrazine (38-130 mg, 0.75-0.85 □mol, 1.0 eq.) was then slowly added. This mixture was then heated to reflux for 10-15 hours, as mentioned by TLC (eluent with petroleum ether/ethyl acetate). The mixture was then allowed to cool to room temperature before adding ice water, undergoing filtration, and washing with water, recrystallizing with a suitable solvent, and providing the desired products **5-13**. The physical properties and FT-IR spectral data of these products are listed in Tables 1 and 2, respectively.

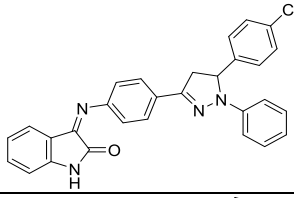
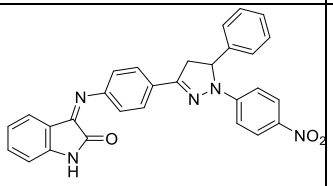
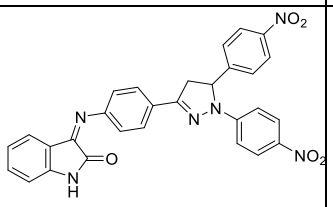
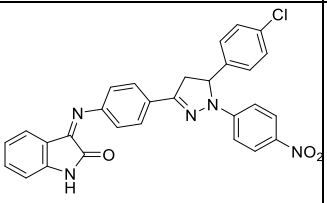
2.3. Antioxidant activity test [33]

The scavenging activity of the produced compounds against free radicals was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test. A 100 mL stock solution of DPPH was prepared by dissolving DPPH (4 mg) in methanol. This solution was kept in a volumetric flask wrapped with aluminum foil to protect it from light. A stock solution was prepared by dissolving the tested compound (1 mg) in methanol (10 mL) to prepare a 100-ppm concentration. This stock solution was then diluted to obtain the other two concentrations (25 and 50 ppm). In addition, similar concentrations of ascorbic acid (vitamin C) were prepared for comparison. A volume of 1 mL for each concentration (25, 50, and 100 ppm) of the tested compound was added to 1 mL of DPPH solution and incubated for 30 minutes at room temperature. The blank solution only contained DPPH solution (1 mL). The absorbance of each solution was measured on a spectrophotometer at 517 nm wavelength. Equation 1 was applied to determine the potential for scavenging DPPH radicals.

I% = (Abs blank - Abs sample) / Abs blank × 100 [34]

Table 1: Physical properties of compounds **1-13**

No.	Compound structure	Compound formula	Reaction time (hours)	M.Wt (g/mol)	m.p. (°C)	Color	Yield (%)
1		$C_{16}H_{12}N_2O_2$	8	264.28	250-252	Light orange	75
2		$C_{23}H_{16}N_2O_2$	48	354.41	308-310	Light yellow	65
3		$C_{23}H_{15}N_3O_4$	48	397.39	326-328	Off-white	60
4		$C_{23}H_{15}ClN_2O_2$	48	386.84	318-320	Off-white	72
5		$C_{23}H_{18}N_4O$	12	366.42	145-148	Yellow	40
6		$C_{23}H_{17}N_5O_3$	15	411.42	196-198	Pale yellow	57
7		$C_{23}H_{17}ClN_4O$	13	400.87	176-180	Yellow	60
8		$C_{29}H_{22}N_4O$	11	442.52	105-108	Light brown	63
9		$C_{29}H_{21}N_5O_3$	13	487.52	156-160	Dark brown	72

10		$C_{29}H_{21}ClN_4O$	10	476.96	172-176	Brown	67
11		$C_{29}H_{21}N_5O_3$	12	487.52	224-226	Yellow	70
12		$C_{29}H_{20}N_6O_5$	14	532.52	280-284	Light brown	70
13		$C_{29}H_{20}ClN_5O_3$	11	521.96	290-292	Light orange	68

3. Results and discussion

3.1. Chemistry

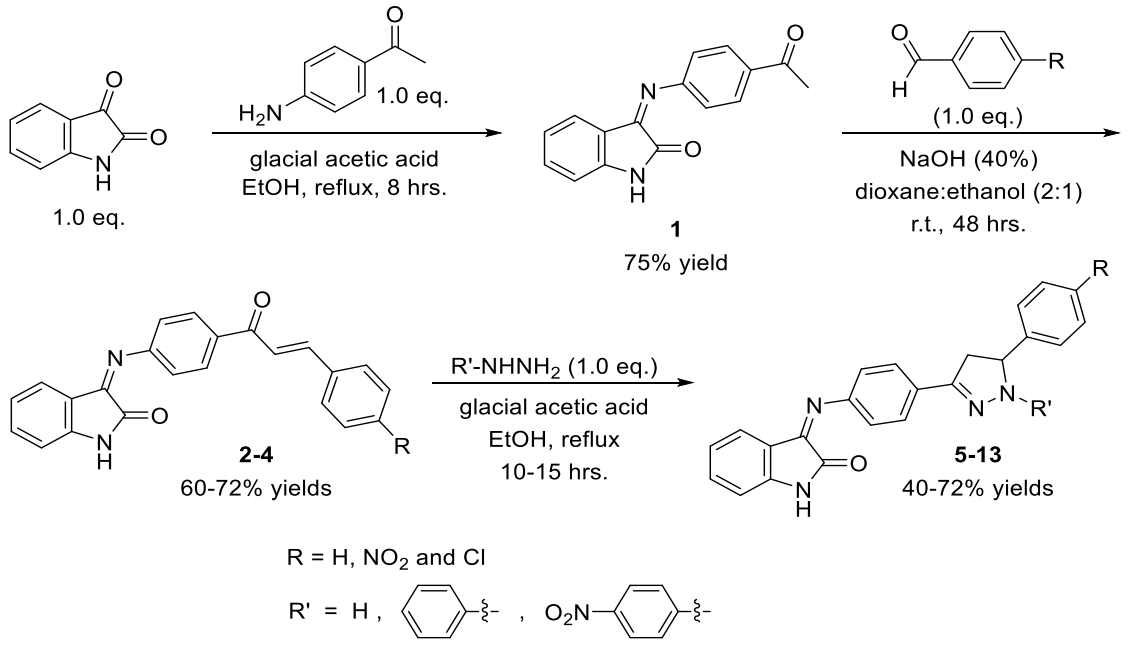
The synthetic route for the preparation of compounds **1-13** is shown in Scheme 1. Compound **1** was prepared in 75% yield *via* the condensation of isatin with *p*-aminoacetophenone. The FT-IR spectral data of compound **1** showed a new absorption at 1741 cm^{-1}, which was attributed to the carbonyl group of the new ketone. The carbonyl group absorption of the ketone at isatin was observed at 1747 cm^{-1}, which was shifted to 1653 cm^{-1} when changing it to the C=N group at compound **1**. The Claisen-Schmidt reaction of compound **1** with three types of aromatic aldehydes (benzaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde) in an ethanoic sodium hydroxide solution as a basic medium was used to successfully make chalcone derivatives **2-4**. The enolate of compound **1** is more reactive towards reactions with aldehydes than the ketone form. The FT-IR spectral data of compounds **2-4** revealed new stretching vibrations from 1595 to 1603 cm^{-1} due to the olefinic bond of the α,β-unsaturated carbonyl [35]. The absorption band of the C=N bond at compounds **2-4** appeared at 1620-1659 cm^{-1}. In addition, the absorptions of the carbonyl groups at compounds **2-4** observed from 1722 to 1731 cm^{-1} were lower than those of the carbonyl group in compound **1** (at 1741 cm^{-1}). This is due to the conjugation of the double bond with the carbonyl group. Two absorption bands at 1535 and 1356 cm^{-1} observed in product **3** for the asymmetric and symmetric stretching vibrations of the NO_2 group, respectively [36]. The cycloaddition reaction between compounds **2-4** and hydrazine or its derivatives was then successfully achieved to give the desired pyrazolines **5-13** in yields ranging from 40 to 72%. Each product of **5-13** is likely to be a mixture of two enantiomers. This reaction included using glacial acetic acid as a catalyst to accelerate the nucleophilic addition to α,β-unsaturated compound by the attack of the NH_2 group, followed by the proton transfer to the OH group, which prepares the oxonium ion and then removes H_2O molecules. The conversion to the desired products **5-13** was monitored by TLC, which indicated that all the reactants **2-4** were consumed in the reaction. The FT-IR spectral data of compounds **5-13**

showed new stretching vibrations ranging from 1610 to 1618 cm^{-1} attributed to the C=N bond of the pyrazoline rings [37,38]. The FT-IR spectra of some compounds (**7**, **9**, and **13**) did not show the absorption band of the C=N bond due to the overlap with other absorption bands. All details of the FT-IR spectral data for the prepared compounds **1**-**13** are listed in Table 2. The ^{1}H NMR spectral data of compounds **5**, **10**, and **11** showed singlet signals at 11.47-11.57 ppm, which belong to the N-H proton of the isatin part. The aromatic protons were observed in the normal range of the chemical shifts (**5** at 8.04-7.21, **10** at 8.04-6.98, and **11** at 8.16-7.21 ppm [35,39]. Finally, the chemical shifts of the aliphatic protons of the pyrazoline ring appeared to be in the range 3.35-3.19 ppm for C-H protons and 2.43-2.10 ppm for CH_2 protons [40]. The olefinic protons of the chalcone derivatives **2**-**4** (normally at 4.5-5.5 ppm) did not appear in the ^{1}H NMR spectra of compounds **5**, **10**, and **11**, which could be good evidence for the conversion to the desired pyrazoline products. All the details of the ^{1}H NMR data are shown in Table 3.

Table 2: Characteristic FT-IR spectral data (υ, cm^{-1}) of compounds **1**-**13**

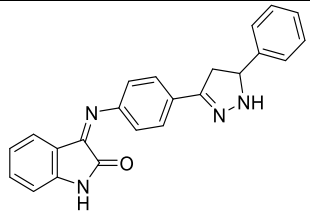
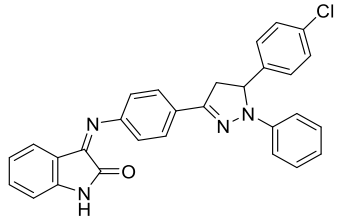
No.	N-H	C-H Alkene	C-H Aromatic	C-H Aliphatic	C=O Ketone	C=O Amide	C=N Imine	C=C Aliphatic	C=C Aromatic	Other bands
1	3252	-	3003	2982	1741	1682	1653	-	1576	-
2	3238	3190	3003	2935	1724	1674	1659	1603	1510	-
3	3227	3171	3097	2928	1731	1668	1620	1595	Overlap with 1535	1535 NO_2 (asym.) 1356 NO_2 (sym.)
4	3254	3195	3007	2932	1722	1674	Overlap with 1595	1595	1516	1074 C-Cl
5	3157 3360	-	3018	2889 2806	-	1688	1657 1610	-	1553	-
6	3358	-	3070	2935	-	1680	1647 1612	-	1552	1516 NO_2 (asym.) 1302 NO_2 (sym.)
7	3157 3357	-	Overlap with 3157	2889 2804	-	1686	1659 Overlap	-	1550	1099 C-Cl
8	3130	-	3057	2934 2893	-	1680	1663 1618	-	1556	-
9	3178	-	3057	2980 2930	-	1680	1660 Overlap	-	1526	
10	3171	-	3059	2932 2924	-	1684	1659 1616	-	1556	1076 C-Cl
11	3171	-	3059	2900 2820	-	1680	Overlap 1616	-	1555	

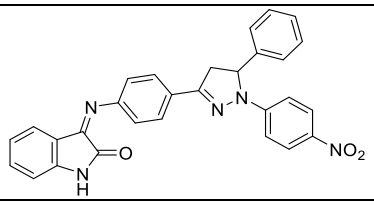
12	3213	-	3022	2891 2808	-	1686	1639 1610	-	1556	1514 NO_2 (asym.)1339 NO_2 (sym.)
13	3286	-	Not observed	2976	-	1684	1639 Overlap	-	1558	Overlap NO_2 (asym.) 1335 NO_2 (sym.). 1063 C-Cl



Scheme 1: Synthesis of pyrazoline derivatives **5-13** derived from isatin

Table 3: ^{1}H NMR spectral data (δ, ppm) of compounds **5, 10,** and **11**

No.	Compound structure	^{1}H NMR spectral data (δ, ppm)
5		11.53 (s, 1H, NH), 8.04-7.21 (m, 13H, Ar-H), 6.46 (s, 1H, NH), 3.33 (t, 1H, *J* = 7.5 Hz, CH), 2.41-2.32 (m, 1H, CH), 2.14-2.10 (m, 1H, CH)
10		11.47 (s, 1H, NH), 8.04-6.98 (m, 17H, Ar-H), 3.19 (t, 1H, *J* = 7.4 Hz, CH), 2.41-2.31 (m, 2H, CH_2)

11		11.57 (s, 1H, NH), 8.16-7.21 (m, 17H, Ar-H), 3.35 (t, J = 7,5 Hz, 1H, CH), 2.43-2.26 (m, 2H, CH_2)

3.2. Antioxidant activity

The antioxidant activity of compounds **5**, **6**, and **8-12** was evaluated in vitro using the DPPH radical scavenging assay at concentrations of 25, 50, and 100 ppm. Among the compounds tested, **8** exhibited the highest DPPH radical scavenging activity at 100 ppm, comparable to ascorbic acid. Compounds **9** and **10** displayed moderate antioxidant activity at 100 ppm in relation to DPPH. All the results of the antioxidant activity are shown in Table 4.

Table 4: Free radical-scavenging activity (%) for some of the prepared compounds (**5**, **6**, and **8-12**)

Compound number	Inhibition (%) for the concentrations (ppm)		
	25	**50**	**100**
5	40	31	24
6	13	13	41
8	32	48	65
9	26	38	50
10	14	37	55
11	22	27	31
12	32	38	43
Ascorbic acid	83.23	84.11	85.29

4. Conclusion

A novel series of pyrazoline-isatin derivatives **5-13** was successfully synthesized in three steps starting from isatin and *p*-aminoacetophenone. The compounds were obtained in moderate to good yields ranging from 40 to 72% over the multistep synthesis. Select pyrazoline products (**5**, **6** and **8**) were evaluated for their antioxidant properties. These compounds showed moderate to good results compared to ascorbic acid. For example, compound **8** was the best at 100 ppm concentration, which had a good scavenging effect compared to the others at the same concentration. The compounds **5** and **8** were the best at 25 and 50 ppm concentrations, respectively, and showed medium effects at these concentrations.

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