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Preparation of some new 2-cyano-N'-(2-hydroxy-5-(4-methylphenyl diazenyl)benzylidene)acetohydrazides and coumarin derivative

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Abstract

A new ten heterocyclic compounds were prepared starting from aniline derivative which underwent diazotization reaction with salicylaldehyde affording 5-p-tolyl azo salicylaldehyde **2** which further reacted with 2-cyanoacetohydrazide to produce 2-cyano-N'-(2-hydroxy-5-(4-methyl phenyl-diazenyl)benzylidene)acetohydrazide **4** in yield 82%. In order to obtain 2-cyano-N'-(2-hydroxy-5-(p-tolyldiazenyl)benzylidenes **6a-e**, component **4** underwent condensation reaction with several aldehydes, including benzaldehyde, 4-methoxy benzaldehyde, 2,5-dimethoxy benzaldehyde, 4-chloro benzaldehyde, and 2,5-dichloro benzaldehyde. 2-Cyano-N'-(2-hydroxy-5-(p-tolyldiazenyl)benzylidene) **(6a)** in yield 83%, 3-phenylacrylohydrazide acrylohydrazide-3-(4-methoxyphenyl) (**6b**) in yield 82%, 2-Cyano-3-(2,5-dimethoxyphenyl) acrylohydrazide N'-(2-hydroxy-5-(p-tolyldiazenyl)benzylide-3-(chlorophenol) (**6c**) in yield 75%, 2-Cyano-3-(2,4-dichlorophenyl)- N' -(2-hydroxy-5-(p-tolyldiazenyl) benzylidene) (**6d**) in yield 78% and 2-cyano- N' -(2-hydroxy-5-(p-tolyldiazenyl) benzylidene) acrylohydrazide (**6e**) in yield 85%, respectively. Moreover, compound **4** combined with para toluedene and/or aniline to produce 2-cyano-N'- (2-hydroxy-5-p-tolyldiazenyl) benzylidene-2- (phenyldiazenyl) aceto-hydrazide **(8a)** in yield 64% and 2-cyano-N'- (2-hydroxy-5-p-tolyldiazenyl) benzylidene-2- (p-tolyldiazenyl) acetohydrazide **(8b)** in yield 67% respectively. In the end, compound **4** gave rise to N'-(2-hydroxy-5-(p-tolyldiazenyl)benzylidene)-2-oxo-2H-chromene-3-carbohydrazide (**11a**) in yield 69% and 6-Hydroxy-N'-(2-hydroxy-5-(p-tolyldiazenyl) benzylidene)-2-oxo-2H-chromene-3-carbohydrazide (**11b**) in yield 72% via reactions of o-hydroxybenzaldehydes with 2,4-dihydroxybenzaldehyde. Several analytical and spectroscopic techniques, including mass spectroscopy, infrared spectroscopy, carbon thirteen magnetic resonance spectroscopy, proton magnetic resonance spectroscopy, and elemental analysis, were used to illustrate the structures of all produced compounds.

Keywords: Cyanoacetohydrazides, benzylidene, coumarin derivative

1. Introduction

The biological effects of coumarin derivatives included cytotoxic, antiproliferative, and anticancer activities. Not only do they effectively combat cancer, but they also hardly ever have any negative side effects [1]. Traditionally, coumarin-containing herbal remedies were made from a variety of plant, fungal, and bacterial sources [2, 3]. The biological activity of coumarin is often linked to its anticancer [4], antifungal [5], anti-HIV [6, 7], inhibition of lipid peroxidation [8], and anti-clotting properties. A potent selective coronary vasodilator, carbochromen has been used for many years in the treatment of angina pectoris [9]. Figure 1 A shows that whereas novobiocin [10] has antibacte-

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rial qualities and wedelolactone [11] is utilized as a venomous snakebite antidote, serline has been demonstrated to have anti-HIV Activities

As naturally occurring anticancer chemicals, coumarins are a class of natural compounds that are frequently found in a number of plant families [12]. 4-methylumbelliferone inhibits the formation and progression of tumors by hyaluronic acid [13]. It is a chemopreventive and chemotherapeutic medication that efficiently targets cancers of the kidney, prostate, ovaries, breasts, and pancreas [14]. A variety of semi-synthetic coumarin compounds with varied substitution patterns have been found to be potent anticancer medications; some examples of these anticancer coumarin-based derivatives (I–VI) are depicted in Figure 1B [15–18].

Through the inhibition of VEGFR2 [19–21] and topoisomerase II [22–24], studies have recently shown that coumarin-based compounds can inhibit immune regulation, cell growth and differentiation, and cell differentiation. These targets have been deemed appealing for the development of anticancer agents. VEGFR-2, a type III transmembrane receptor tyrosine kinase (RTK) found in a broad range of cancer cells, mediates nearly all cellular responses to VEGF. It is regarded as the primary transducer of angiogenesis and VEGF-dependent apoptosis [25]. Therefore, the VEGFR-2 inhibitory signaling pathway has emerged as a key tactic in the search for and creation of cutting-edge treatments for a range of cancers in humans [26]. Also some interesting coumarin derivatives **VII**, **VIII**, **IX** and **X** showed antitumor activity in vitro on Ehrlich ascites carcinoma in the preliminary testing figure 2 [27, 28].

Table 1: The screening results of compounds VII, VIII**,** IX and X

Compound No.	% of dead tumor cells at 100g/ml
VII	**20%**
VIII	**30%**
IX	**20%**
X	**40%**

hows the resultsscreening of the antitumor activity of coumarin derivatives **VII, VIII, IX** and **X**. Moreover it was clear from the results that compound **X** is the most potent antitumor activity.

From other side, the literature showed that N'-(1-(5-chloro-2-hydroxyphenyl)-ethylidene), pyrazoles [29], triazoles [30], thiazoles [31], pyridines [32], pyridazines [33], and coumarins [34] are among the prominent heterocyclic systems that are synthesized using 2-cyanoacetohydrazide derivatives. The valuable IC50 of -3-(morpholinosulfonyl)-benzohydrazide **XI** is 0.013 μM against many cancer cell types [35]. With an IC50 of 91.83 nM, compound **XII** functions as lysine-specific demethylase (LSD1) [36] (Figure 3). Coumarins also have a wide range of biological functions [37]. As seen in Figure 3, Daphentin **XIII**, for instance, is used to treat neurological diseases, liver fibrosis, and cancer [38].

Based on the combined reports mentioned above and the ability to synthesize various heterocyclic ring systems with biological activity, including antimicrobial, antiviral, and anticancer properties [39], we designed the synthesis of several new coumarins and 2-cyanohydrazide derivatives in the current study. We started with a new key intermediate, cyanohydrazide of arylazosalicyaldehydes, in order to investigate the promising anticancer compounds.

It is clear that for the researchers' the wide applications and importants in different field of hetrocyclic compounds as a whole and specifically the coumarin and hydrazones derivatives among them.

2. Results and Discussion

Condensation of 4-methylphenyldiazenyl) benzaldehyde **2** (which was prepared from diaziunmum salt of 4-methylaniline, followed by coupling with salicylaldehyde) with cyanoacetohydrazide **3** in boiling dioxane afforded the isolated product **4** (Scheme1)**.**

We designed the synthesis of several new coumarins and 2-cyanohydrazide derivatives in the current study. We started with a new key intermediate, cyanohydrazide of arylazosalicyalde-

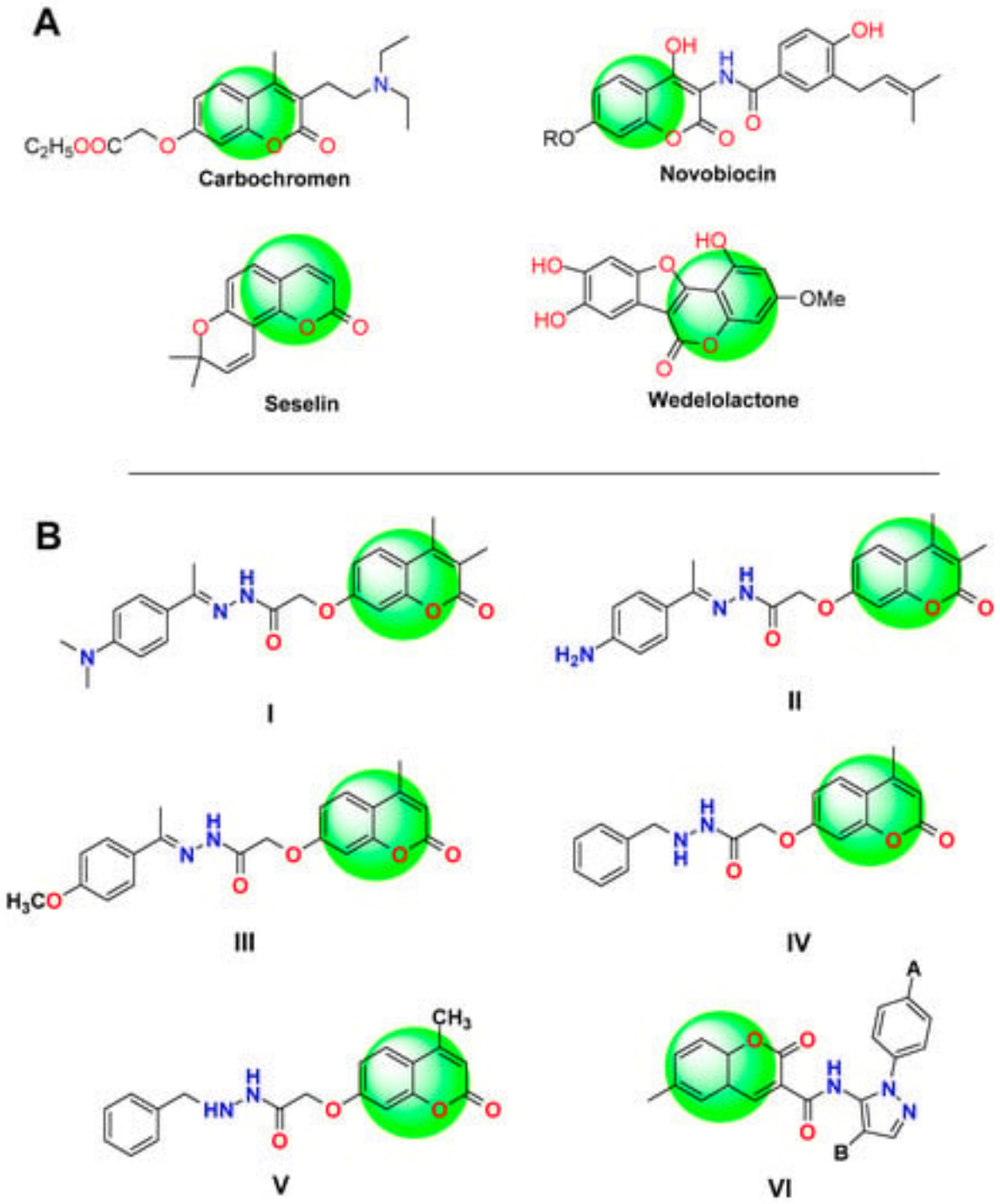


Figure 1: (**A**): Representative biological active coumarins; (**B**) Structures of some of anticancer coumarin derivatives through VEGFR2 inhibition.

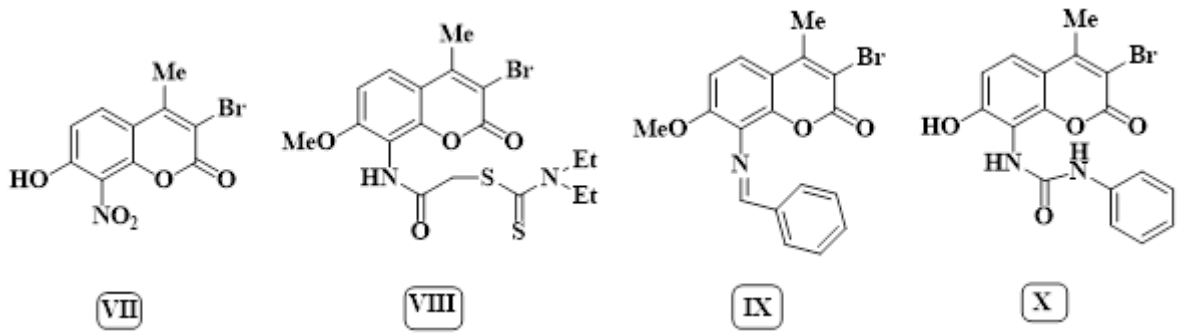


Figure 2: Some coumarin derivatives VII, VIII, IX and X which possess antitumor activity

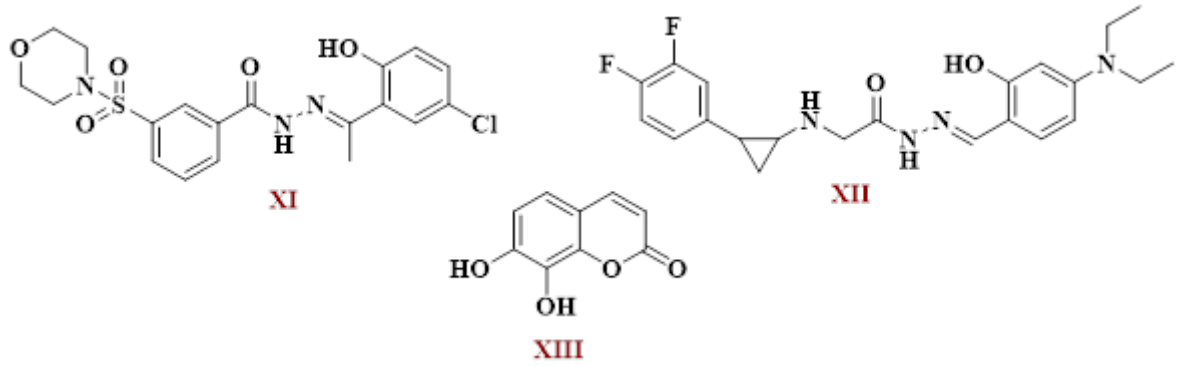
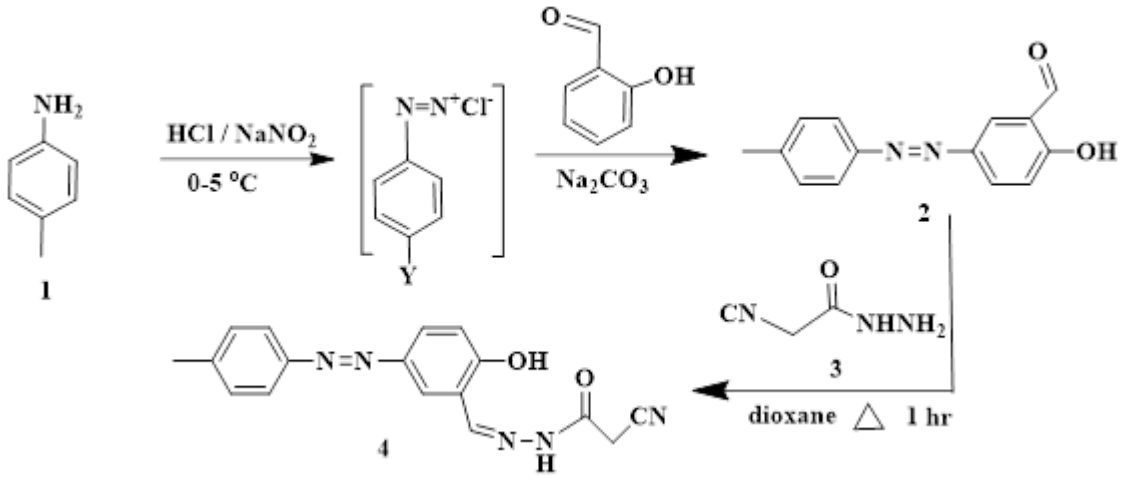


Figure 3: Anticancer activity of hydrazones XI, XII, and coumarin XIII



Scheme 1:

hydes, in order to investigate the promising anticancer compounds. Furthermore, D_2O exchangeable singlet signals for OH also emerged in **4** at = 11.79, and 11.30 ppm. Compound 4's ^{13}C NMR spectra revealed distinctive signals for the CH_3, CH_2, CN, and CO at 24.9, 36.6, 116.5, and 165.2 ppm, respectively.

2-cyano-N'-(2-hydroxy-5-(4-methylphenyl diazenyl) benzylidene) acetohydrazide (**4**) was condensed with different aromatic aldehydes **5a-e** in boiling N,N-dimethylformamide (DMF) to provide the corresponding arylmethylene derivatives **6a-e** (Scheme 2). Using spectroscopic methods, the structure of **6a-e** was clarified (IR, ^1H NMR and MS). Compound **6e**, for instance, exhibits distinctive signals in its ^1H NMR chart, including two D_2O

exchangeable singlet signals at δ = 9.44 and 10.78 ppm in addition to a singlet signal at 2.36 (s, 3H, CH_3). The following wavelengths showed peaks in the infrared spectrum: 3431 (OH), 3021 (NH), 2375 (CN), and 1621 (CO). M/z = 478.08 (M++1.54%), 479.07 (M+ + 2, 2.30%), and other values in the MS spectrum are consistent with the chemical formula $C_{24}H_{17}C_{l2}N_5O_2$.

Furthermore, the corresponding arylhydrazo derivatives **8a,b** were produced by coupling **4** with various aryl diazonium chlorides (which were created by diazotizing primary aromatic amines **7a,b** with a solution of sodium nitrite) in dry DMF in the presence of solid sodium hydroxide (Scheme 3). Using the arylhydrazo derivative **8a** as an example, the ^{1}H NMR spectrum revealed three D_2O exchangeable singlet signals (2NH and OH protons) at δ = 9.60, 10.65, and 11.46 ppm, respectively, along with a singlet signal at δ = 2.43 ppm due to the methyl protons and a multiplet signal at δ = 7.43-8.14 ppm for aryl and CH protons. Additionally, absorption bands were visible in the infrared spectrum of sample **8a** at 3433, 2206, and 1617 cm^{-1} in relation to OH, CN, and C=O groups, respectively.

Furthermore, compounds **4** were cyclocondensed with o-hydroxybenzaldehyde **9a** and 2,4-dihydroxybenzaldehyde **9b**, respectively, under reflux in DMF containing a small quantity of piperidine, to yield the coumarin derivatives **11a,b** (Scheme 4). Their spectral data was used to establish the structures **11a,b**. The OH, NH, and two C=O functions, respectively, are responsible for the absorption bands that example compound **11a** displayed in its IR chart at 3430, 3203, 1667, and 1627 cm^{-1}. The methyl protons in **11a** appeared at 3.32 in ^{1}H NMR as a singlet signal, aryl protons for a multiplet signal at δ = 7.39-8.80 ppm, and the NH and OH groups for two signals at δ = 10.47 and 11.68 ppm respectively.

3. Experimental

All melting points were uncorrected and calculated using an Electro thermal (9100) device. Using KBr pellets, the IR spectra were captured using a Perkin Elmer 1430 Spectrophotometer. Using DMSO-d6 as a solvent, the NMR spectra were recorded at 300 and 75 MHz (^{1}H and ^{13}C NMR spectra, respectively) using a Varian Mercury VXR-300 NMR spectrometer. The results are reported as δ values. A Shimadzu GCMS-QP 1000 Ex mass spectrometer operating at 70 eV was used to capture mass spectra. The Vario EL III Elemental CHNS analyzer was used to do elemental studies at Cairo University's Microanalyses Center. The compounds methylphenyldiazenyl)benzaldehyde (**1**) and 2-cyanoacetohydrazide **(2)** were prepared according the published procedures [40, 41]

3.1. Preparation of 2-cyano-N'-(2-hydroxy-5-(4-methylphenyldiazenyl) benzylidene) - acetohydrazide (4).

After refluxing for an hour in dioxane (15 ml) containing a mixture of 2-hydroxy-5-(4-methylphenyldiazenyl)benzaldehyde **(1)** (0.01 mol) and 2-cyanoacetohydrazide **(2)** (0.01 mol), the mixture was allowed to cool at room temperature. After forming, the solid was filtered out of the DMF and recrystallized from DMF.

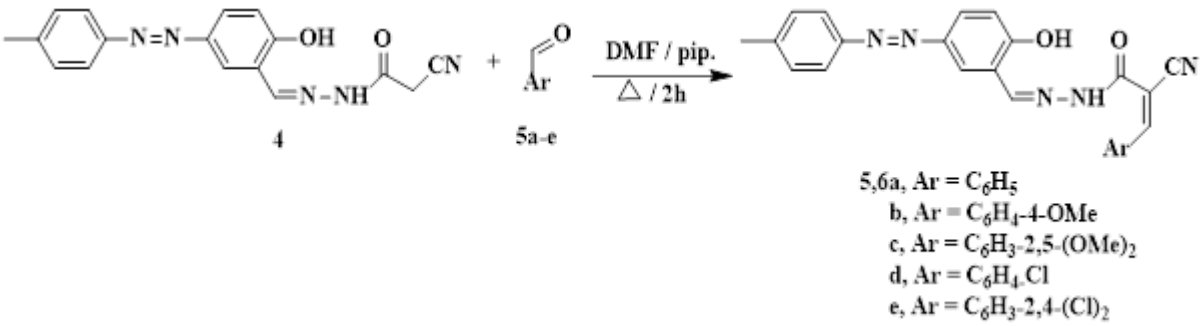
Orange crystals; yield 82%; m.p 295 ^{o}C; ν_{max} / cm^{-1} (KBr) 3435 (OH), 3214 (NH), 2360 (CN), 1671 (CO); protons appeared at δ=2.38 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 7.05-7.11 (m, 2H, Ar), 7.35-7.37 (m, 2H, Ar), 7.39-8.51 (m, 4H, Ar and CH), 11.0 (s, 1H, NH), 11.79 (s, 1H, OH); carbon atoms appeared at δ = 24.9, 36.6, 115.6, 116.5, 117.5, 121.2, 124.3, 124.7, 128.9, 129.9, 130.1, 145.4, 151.0, 165.2; C:H:N for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79 Found: C, 63.62; H, 4.82; N, 21.95%.

Preparation of compounds 6a-e.

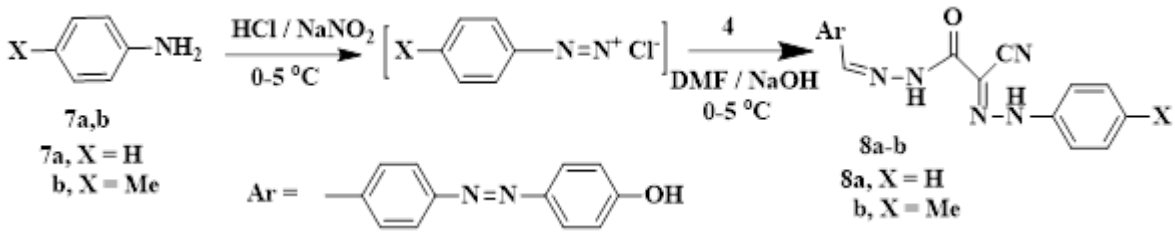
After boiling DMF (10 ml) for two hours and condensing compounds **4** (0.01 mol) with various aromatic aldehydes **5a–e** (0.01 mol) with piperidine drops, the mixture was cooled to room temperature to yield the corresponding arylmethylene derivatives **6a–e**, which were then filtered off, cleaned with absolute ethanol, and recrystallized from DMF.

(2-Cyano - N'-(2-hydroxy -5- (p-tolyl diazenyl) benzyl idene) -3- phenyl acrylohydrazide (6a).

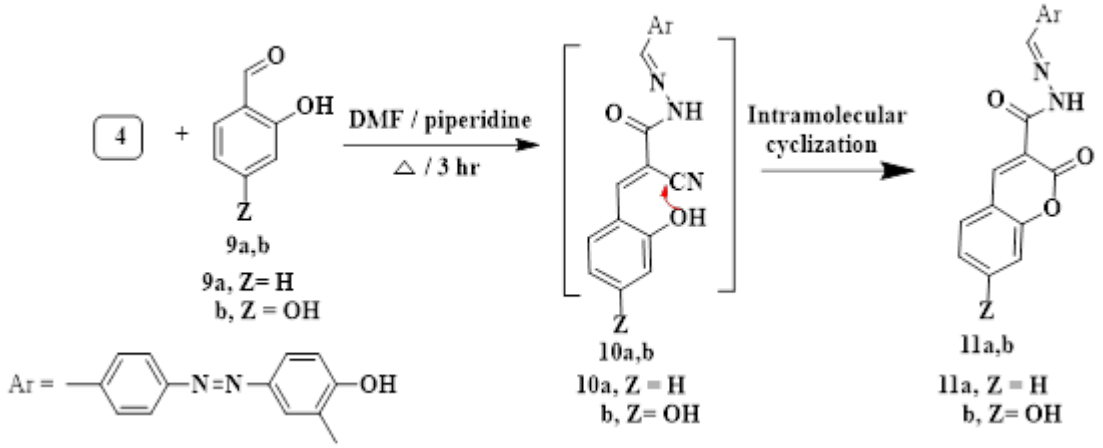
Orange crystals; m.p > 300 ^{o}C; yield 83% ν_{max} / cm^{-1} (KBr) 3388 (OH), 3299 (NH), 2240 (CN), 1627 (CO); protons appeared at δ =2.40 (s, 3H, CH_3),



Scheme 2:



Scheme 3:



Scheme 4:

7.32-9.03 (m, 12H, Ar), 8.55 (s, 1H, CH), 8.68 (s, 1H, CH), 10.30 (s, 1H, NH), 11.60 (s, 1H, OH); carbon atoms appeared at δ = 24.9, 102.2, 115.6, 116.2, 118.6, 119.7, 120.2, 132.6, 132.8, 135.6, 132.2, 138.2, 139.2,142.5, 142.7, 160.7; C:H:N for $C_{24}H_{19}N_5O_2$: C, 70.40; H, 4.68; N, 17.10. Found: C, 70.48; H, 4.73; N, 17.45%.

2- Cyano- N'-(2-hydroxy-5-(p-tolyldiazenyl) benzyl idene)-3-(4-methoxy phenyl) acryl ohydrazide (6b).

Yellowish brown crystals; yield 82%; m.p > 300 ^{o}C; ν_{max} / cm^{-1} (KBr) 3370 (OH), 3250 (NH), 1625 (CO), 2283 (CN); protons appeared at δ =3.37 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.04-7.11 (m, 4H, Ar), 7.70-8.02 (m, 5H, Ar), 8.46-8.68 (m, 4H, Ar and CH), 10.90 (s, 1H, NH), 11.50 (s, 1H, OH); C:H:N for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94. Found: C, 68.38; H, 4.86; N, 15.98%.

2-Cyano-3-(2,5-dimethoxyphenyl)- N'-(2-hydroxy-5-(p-tolyldiazenyl)benzylidene) acrylohydrazide (6c).

Brown crystals; yield 75%; m.p >300 ^{o}C; ν_{max} / cm^{-1} (KBr) 3391 (OH), 3206 (NH), 2230 (CN), 1627(CO); protons appeared at δ=2.43 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.73-7.03 (m, 10H, Ar), 8.16 (s, 1H, CH), 8.38 (s, 1H, CH),

10.53 (s, 1H, NH), 11.72 (s, 1H, OH); C:H:N for $C_{26}H_{23}N_5O_4$: C, 66.51; H, 4.94; N, 14.92 found: C, 66.54; H, 4.99; N, 14.98%.

3-(4-Chlorophenyl)-2-cyano- N' -(2-hydroxy-5-(p-tolyldiazenyl)benzylidene) acrylohydrazide (6d).

Brown crystals; m.p >300 ^{o}C; yield 78%; ν_{max} / cm^{-1} (KBr) 3398 (OH), 3171 (NH), 2236 (CN), 1628 (CO);protons appeared at δ =2.61 (s, 3H, CH_3), 7.32-9.06 (m, 9H, Ar), 8.19-8.77 (m, 4H, Ar and CH), 9.66 (s, 1H, NH), 10.89 (s, 1H, OH); C:H:N for $C_{24}H_{18}ClN_5O_2$: C, 64.94; H, 4.09; Cl, 7.99; N, 15.78. Found: C, 64.98; H, 4.14; N, 15.83%.

2-Cyano-3-(2,4-dichlorophenyl)- N' -(2-hydroxy-5-(p - tolyldiazenyl) benzylidene) acrylohydrazide (6e).

Reddish brown crystals; m.p >300 ^{o}C; yield 85%; ν_{max} / cm^{-1} (KBr) 3431 (OH), 3021 (NH), 2375 (CN), 1621 (CO); protons appeared at δ =2.36 (s, 3H, CH_3), 7.92-9.03 (m, 12H, Ar), 9.44 (s, 1H, NH), 10.78 (s, 1H, OH), Mass: m/z = 478.08 (M^++1.54%), 479.07 (M^++ 2,2.30%), 459.35 (33.2%), 373.30 (27%), 371.07 (1.2%), 265.37 (0.46%), 210.48 (2.56%), 165.2 (3.1%), 119 (17.62%), 91 (100%); C:H:N for $C_{24}H_{17}Cl_2N_5O_2$: C, 60.26; H, 3.58; Cl, 14.82; N, 14.64. Found: C, 60.32; H, 3.63; Cl, 14.86; N, 14.71%.

Synthesis of compounds 8a,b.

The coupling of **4** (0.01 mol) in dry dimethyl formamide with several aryl diazonium chlorides (0.01 mol) produced by diazotizing primary aromatic amine salts with a sodium nitrite solution (0.01 mol) while solid sodium hydroxide (0.01 mol) was present. The combination was agitated in an ice bath for two hours, and the resultant solid was filtered, washed with water, and then recrystallized from DMF.

2-Cyano-N'- (2-hydroxy-5-p-tolyldiazenyl) benzylidene-2- (phenyldiazenyl) aceto-hydrazide (8a).

Pale orange crystals; yield 64%; m.p 280 ^{o}C; ν_{max} / cm^{-1} (KBr) 3433 (OH), 3150 (NH), 2206 (CN), 1617 (CO); protons appeared at δ=2.43 (s, 3H, CH_3), 7.43-8.14 (m, 14H, Ar and CH), 9.60 (s, 1H, NH), 10.65 (s, 1H, NH), 11.46 (s, 1H, OH); C:H:N for $C_{23}H_{19}N_7O_2$: C, 64.93; H, 4.50; N, 23.05. Found: C, 64.98; H, 4.61; N, 23.15%.

3.1.1.

2-Cyano-N'- (2-hydroxy-5-p-tolyldiazenyl benzylidene-2- (p-tolyldiazenyl acetohydrazide (8b. Deep brown crystals; m.p 286 ^{o}C ; yield 67%; ν_{max} / cm^{-1} (KBr) 3380 (OH), 3250 (NH), 2225 (CN), 1636 (CO); protons appeared at δ=2.48 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 7.12-7.83 (m, 13H, Ar and CH), 9.45 (s, 1H, NH), 10.71 (s, 1H, NH), 11.35 (s, 1H, OH); C:H:N for $C_{24}H_{21}N_7O_2$: C, 65.59; H, 4.82; N, 22.31. Found: C, 65.40; H, 4.64; N, 22.08%.

Synthesis of compounds 11a,b.

Compound **4** (0.01 mol), various o-hydroxybenzaldehydes **9a, b** (0.01 mol), and a few drops of piperidine were heated under reflux in DMF (10 ml) for three hours, cooled to room temperature, filtered the resultant liquid, and then recrystallized from DMF.

N'-(2-hydroxy-5-(p-tolyldiazenyl)benzylidene)-2-oxo-2H-chromene-3-carbo-hydra-zde (11a).

Pale orange crystals; m.p >300 ^{o}C ; yield 69 %; ν_{max} / cm^{-1} (KBr) 3430 (OH), 3203 (NH), 1667 (CO), 1627 (CO); protons appeared at δ = 3.32 (s, 3H, CH_3), 7.39-8.80 (m, 12H, Ar), 8.43 (s, 1H, CH), 10.47 (s, 1H, NH), 11.68 (s, 1H, OH); C:H:N for $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found. C, 67.79; H, 4.25; N, 13.39%.

6-Hydroxy-N'- (2-hydroxy-5- (p-tolyldiazenyl) benzylidene) -2-oxo-2H-chromene-3-carbo hydrazide (11b).

Reddish brown crystals; m.p > 300 ^{o}C ; yield 72%; ν_{max} / cm^{-1} (KBr) 3358 (OH), 3155 (NH), 1667 (CO), 1629 (CO); protons appeared at δ = 2.34 (s, 3H, CH_3), 6.14-8.43 (m, 12H, Ar), 8.79 (s, 1H, CH), 10.60 (s, 1H, NH), 11.79 (s, 1H, OH); C:H:N for $C_{24}H_{18}N_4O_5$: C, 65.15; H, 4.10; N, 12.66, found: C, 65.35; H, 4.28; N, 12.91%.

4. Conclusion

As a result of the importance of hydrazone compounds in different applications such as medicinal chemistry, we managed to prepare some novel derivatives starting from 2-cyano-N'-(2-hydroxy-5-(4-methylphenyldiazenyl)benzylidene)-acetohydrazide, a series of 2-cyanoacetohydrazides and coumarin derivatives were produced in excellent yield. Appropriate analysis was used to

support the chemicals that were created.

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