Chemistry of Heterocyclic Compounds, Vol. 45, No. 5, 2009

SYNTHESIS, ANTIVIRAL AND ANTIMICROBIAL SCREENING OF SOME NEW 2-OXOINDOLINE DERIVATIVES

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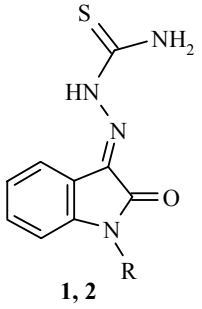
New 3-(2-(5-(aryldiazenyl)-4-methylthiazol-2-yl)hydrazono)indolin-2-ones were prepared by the reaction of isatin β-thiosemicarbazone with different hydrazonoyl chlorides. Imide derivatives were prepared by the reaction of isatin hydrazone with various anhydrides, and a series of new sulfonimides was also synthesized. All new compounds were tested for their biological activities.

Keywords: isatin, 2-oxoindolinylidenaminobenzenesulfonamide, phthalic anhydride, thiazolyl-hydrazone, antimicrobial and antiviral activities.

Isatins (1H-indole-2,3-dione) are synthetically versatile substrates, useful for the synthesis of a large variety of heterocyclic compounds [1]. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives. In nature, isatin is found in plants of the genus *Isatis* [2], in *Calanthe discolor* LINDL. [3], and *Couroupita guianensis* Aubl. [4], and has been also found as a component of the secretion from the parotid gland of *Bufo* frogs [5], and in humans as a metabolic adrenaline derivative [6–8]. Several authors found that isatin β-thiosemicarbazone and its N-Mannich bases were active against various viruses [9–11]. The first clinically approved antiviral agent, N-methylisatin β-thiosemicarbazone (methisazone **1**), and isatin β-thiosemicarbazone (**2**) are active against poxviruses [12]. Antiviral



1, 2

1 R = Me, **2** R = H

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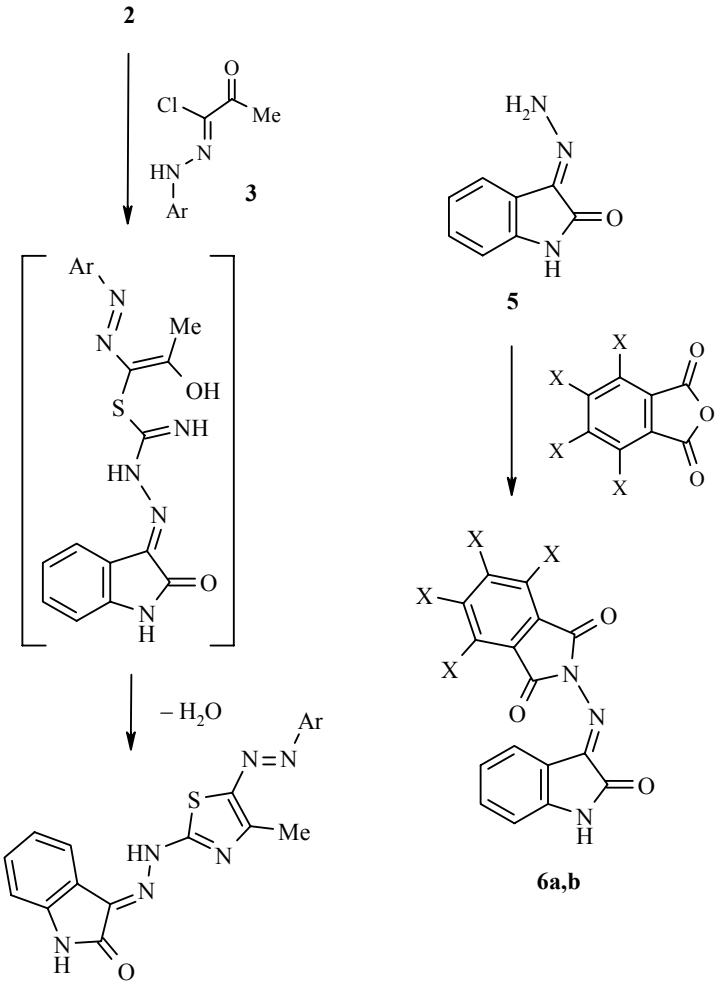
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 689-694, May, 2009. Original article submitted May 5, 2008.

properties of certain semicarbazone derivatives have been reported, in which the antiviral effect is attributed to the presence of the NHC(=S)NH group [13–15]. Prompted by these observations, we report here the synthesis of the new 2-oxoindoline derivatives with the hope to get better antimicrobial and antiviral molecules. All new compounds have been screened for their antibacterial, antifungal, and antiviral activities.

N-(1-Arylethylidene)-N'-[4-(indan-5-yl)thiazol-2-yl]hydrazones have been synthesized by the reaction of acetophenone derivatives with thiosemicarbazide followed by the treatment with 2-bromo-1-(5-indanyl)-ethanone [16]. We used this pathway to prepare thiazoles **4a-d**.

3-[2-(5-Aryldiazenyl-4-methylthiazol-2-yl)hydrazono]indolin-2-ones **4a-d** were prepared according to Scheme 1 by the reaction of thiosemicarbazone **2** with hydrazonyl chlorides **3**. The reaction of hydrazone **5** with phthalic anhydride and tetrachlorophthalic anhydride afforded 2-(2-oxoindolin-3-ylideneamino)isoindoline-1,3-diones **6a**,**b** (Scheme 1).

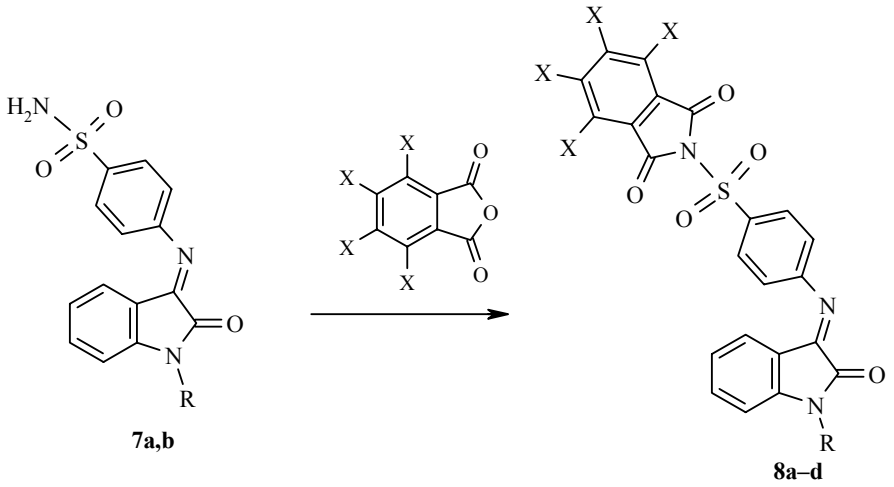
Scheme 1



4 a Ar = Ph, **b** Ar = 4-ClC_6H_4, **c** 4-BrC_6H_4, **d** Ar = 2,4-$Cl_2C_6H_3$;
6 a X = H, **b** X = Cl

Since sulfonamides are used in the treatment of infections, especially for patients intolerant to antibiotics [17], we synthesized new sulfonimides **8a-d** for biological evaluation using the reaction of 3-(4-sulfonamidophenylimino)indolin-2-ones **7a**,**b** with phthalic and tetrachlorophthalic anhydrides (Scheme 2).

Scheme 2



7a,b **8a–d**

7 a R = H, **b** R = Ac; **8 a** R = X = H; **b** R = H, X = Cl; **c** R = Ac, X = H; **d** R = Ac, X = Cl

The ^{1}H NMR spectra of compounds **4a-d** displayed a singlet at about 2.4 ppm attributed to the methyl groups. The IR spectra of compounds **6a,b** showed absorption bands in the region of 1750-1625 cm^{-1} indicating the presence of the C=O groups. Physical data are given in Table 1.

The IR spectra of compounds **8a-d** showed sharp stretching bands at about 1714 cm^{-1} for the carbonyl groups. The mass spectra of all new compounds in each case revealed a peak corresponding to their molecular ion peaks.

TABLE 1. Physical and analytical data for the compounds **4**, **6,** and **8**

Compound*	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
4a	$C_{18}H_{14}N_6OS$	59.68 / 59.65	3.85 / 3.89	23.24 / 23.19	8.91 / 8.85	279-280	83
4b	$C_{18}H_{13}ClN_6OS$	54.52 / 54.48	3.29 / 3.30	21.28 / 21.18	8.22 / 8.08	300-302	79
4c	$C_{18}H_{13}BrN_6OS$	49.21 / 48.99	3.12 / 2.97	18.99 / 19.04	7.52 / 7.27	282-283	81
4d	$C_{18}H_{12}Cl_2N_6OS$	50.34 / 50.13	2.97 / 2.80	19.71 / 19.49	7.61 / 7.43	262-263	84
6a	$C_{16}H_9N_3O_3$	66.09 / 65.98	3.19 / 3.11	14.71 / 14.43	—	>300	74
6b	$C_{16}H_5Cl_4N_3O_3$	45.02 / 44.79	1.22 / 1.17	9.98 / 9.79	—	>300	76
8a	$C_{22}H_{13}N_3O_5S$	61.43 / 61.25	3.29 / 3.04	9.77 / 9.74	7.68 / 7.43	>300	62
8b	$C_{22}H_9Cl_4N_3O_5S$	46.65 / 46.42	1.98 / 1.59	7.51 / 7.38	5.64 / 5.63	>300	66
8c	$C_{24}H_{15}N_3O_6S$	61.02 / 60.88	3.29 / 3.19	8.89 / 8.88	6.89 / 6.77	>300	70
8d	$C_{24}H_{11}Cl_4N_3O_6S$	47.32 / 47.16	1.99 / 1.81	7.03 / 6.87	5.41 / 5.25	>300	67

* Color: red (compounds **4a-c**), yellow (compound **4d**), colorless (compounds **6a,b, 8a-d**).

The antimicrobial and antiviral activities were studied for all new compounds. Amoxicillin (antibacterial) and fluconazole (antifungal) were used as references. Among all the tested compounds only compound **6b** showed antibacterial activity against *Bacillus subtilis* in about 25 mm inhibition zone. No antiviral activities were found for any of the compounds examined.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in potassium bromide using Perkin Elmer 1650 and Pye-Unicam SP300 IR spectrophotometers. The ^{1}H NMR spectra were recorded in DMSO-d_6 with TMS as an internal standard using a Varian Gemini 300 NMR spectrometer (300 MHz). Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu and GCMS 5988-A HP spectrometers. Elemental analyses were carried out in the Micro-analytical Laboratory of Cairo University, Giza, Egypt. 1-(2-Oxoindolin-3-ylidene)thiosemicarbazide **2** [18], 3-(4-sulfonamidophenylimino)indolin-2-one derivatives **7a,b** [19], and 3-hydrazonoindolin-2-one **5** [20] were prepared according to the methods reported.

3-(2-(5-(Aryldiazenyl)-4-methylthiazol-2-yl)hydrazono)indolin-2-ones 4a-d. A mixture of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide **2** (2.2 g, 10 mmol) and the appropriate hydrazonyl chloride (10 mmol) in ethanol (100 ml) containing a few drops of triethylamine was refluxed for 1.5 h, left to cool at room temperature, and the products were separated by filtration, vacuum dried, and recrystallized from ethanol/DMF.

3-(2-(4-Methyl-5-(phenyldiazenyl)thiazol-2-yl)hydrazono)indolin-2-one (4a). IR spectrum, ν, cm^{-1}: 1692 (C=O, st.); 3251 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 2.39 (3H, s, CH_3); 6.82–7.45 (9H, m, H Ar); 8.12 (1H, s, NH); 8.36 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 363 [M^++1] (3.5); 362 [M^+] (100).

3-(2-(5-[(4-Chlorophenyl)diazenyl]-4-methylthiazol-2-yl)hydrazono)indolin-2-one (4b). IR spectrum, ν, cm^{-1}: 1690 (C=O, st.); 3221 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 2.41 (3H, s, CH_3); 6.91–7.45 (8H, m, H Ar); 8.22 (1H, s, NH), 8.42 (2H, 2s, 2NH). Mass spectrum, *m/z* (*I*, %): 398 [M^++2] (3); 397 [M^++1] (14); 396 [M^+] (100).

3-(2-(5-[(4-Bromophenyl)diazenyl]-4-methylthiazol-2-yl)hydrazono)indolin-2-one (4c). IR spectrum, ν, cm^{-1}: 1690 (C=O, st.); 3198 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 2.42 (3H, s, CH_3); 6.83–7.23 (8H, m, H Ar); 8.15 (1H, s, NH); 8.42 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 442 [M^++2] (18); 441 [M^++1] (89); 440 [M^+] (100).

3-(2-(5-[(2,4-Dichlorophenyl)diazenyl]-4-methylthiazol-2-yl)hydrazono)indolin-2-one (4d). IR spectrum, ν, cm^{-1}: 1688 (C=O, st.); 3219 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 2.44 (3H, s, CH_3); 6.87–7.33 (7H, m, H Ar); 8.17 (1H, s, NH); 8.40 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 432 [M^++1] (34); 431 [M^+] (17.5); 430 (100).

2-(2-Oxoindolin-3-ylideneamino)isoindoline-1,3-diones 6a,b. A mixture of 3-hydrazonoindolin-2-one **5** (0.48 g, 3 mmol) and the appropriate phthalic anhydride (3 mmol) in 50 ml of glacial acetic acid was heated under reflux for 6 h. The reaction mixture was evaporated under reduced pressure; the obtained residue was solidified with ether, filtered off, and crystallized from acetic acid–water to yield compounds **6a**,**b**.

2-(2-Oxoindolin-3-ylideneamino)isoindoline-1,3-dione (6a). IR spectrum, ν, cm^{-1}: 1751 (C=O, st.); 1625 (C=O, st.); 3235 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 7.11–8.02 (8H, m, H Ar); 8.45 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 291 [M^+] (22); 132 (100).

4,5,6,7-Tetrachloro-2-(2-oxoindolin-3-ylideneamino)isoindoline-1,3-dione (6b). IR spectrum, ν, cm^{-1}: 1750 (C=O, st.); 1631 (C=O, st.); 3241 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 6.99–7.34 (4H, m, H Ar); 8.32 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 430 [M^+] (0.45); 429 [M^+ +1] (1.9); 132 (100).

2-(4-(2-Oxoindolin-3-ylideneamino)arylsulfonyl)isoindoline-1,3-diones 8a-d. A mixture of 3-(4-sulfonamidophenylimino)indolin-2-one **7a** or 1-acetyl-3-(4-sulfonamidophenylimino)indolin-2-one **7b** (3 mmol) and the appropriate phthalic anhydride (3 mmol) in 50 ml of glacial acetic acid was heated under reflux for 8 h. The obtained solid product was filtered off and crystallized from acetic acid–water to yield compounds **8a-d**.

2-(4-(2-Oxoindolin-3-ylideneamino)phenylsulfonyl)isoindoline-1,3-dione (8a). IR spectrum, ν, cm^{-1}: 1718 (C=O, st.); 1621 (C=O, st.); 3190 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 6.89–7.98 (12H, m, Ar-H); 8.45 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 432 [M^++1] (0.45); 431 [M^+] (1.9); 285 (100).

4,5,6,7-Tetrachloro-2-(4-(2-oxoindolin-3-ylideneamino)phenylsulfonyl)isoindoline-1,3-dione (8b). IR spectrum, ν, cm^{-1}: 1714 (C=O, st.); 1625 (C=O, st.); 3252 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 7.11–7.68 (8H, m, H Ar); 8.21 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 569 [M^+] (12); 285 (100).

2-(4-(1-Acetyl-2-oxoindolin-3-ylideneamino)phenylsulfonyl)isoindoline-1,3-dione (8c). IR spectrum, ν, cm^{-1}: 1714 (C=O, st.); 1638 (C=O, st.); 3254 (NH, st.). ^{1}H NMR spectrum, δ, ppm: 2.39 (3H, s, CH_3); 7.11–8.03 (12H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 473 [M^+] (3.5); 327 (100).

2-(4-(1-Acetyl-2-oxoindolin-3-ylideneamino)phenylsulfonyl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (8d). IR spectrum, ν, cm^{-1}: 1714 (C=O, st.); 1625 (C=O, st.); 3243 (NH). ^{1}H NMR spectrum, δ, ppm: 2.38 (3H, s, CH_3); 6.88–7.76 (8H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 612 (0.4); 611 [M^+] (2.4); 327 (100).

Antimicrobial Activities. *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus fulvous* were used to verify the antimicrobial activity of the synthesized compounds. The bacterial strains were cultivated on nutrient agar medium, while the fungal strains were cultivated on potato dextrose agar medium. The antimicrobial activities of the tested compounds were investigated by the disk diffusion methods [21].

Antiviral Activity. All the prepared compounds were submitted to test for antiviral activity against HBV (hepatitis B viruses). The test was carried out according to the method [22].

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