Synthesis of triazole, pyrazole, oxadiazine, oxadiazole, and sugar hydrazone-5-nitroindolin-2-one derivatives: part I

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Objective

The aim of part I is the synthesis of different series of 1H-1,2,4-triazol-3-yl)phenylimino)(methylbenzyl)-5-nitroindolin-2-ones, 1H-pyrazole-1-carbonyl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-ones, 3-(4-(1,3,4-oxadiazin-6-one)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-ones, 1,3,4-oxadiazol-2-yl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-ones, and 4-(-1-(*p*-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) sugar hydrazone derivatives (**4–13)** through the reaction of 4-[1-(*p*-methylbenzyl)-5-nitro-2-oxoindolin-3-ylidineamino]benzohydrazide (**3**) with different reagents to be evaluated biologically.

Materials and methods

Derivatives of (1H-1,2,4-triazol-3-yl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one and (1H-pyrazole-1-carbonyl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**4–6**) were prepared by the reaction of 4-[(1-(*p*-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino)] benzohydrazide (**3**) with benzyl, benzoyl isothiocyanate, or acetyl acetone to form 1H-1,2,4-triazole and 1H-pyrazole-5-nitroindolin-2-one derivatives. The reaction of **3** with ethyl bromoacetate, ethyl acetoacetate, or acetyl chloride afforded 1,3,4 oxadiazin-6-one, 3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole, or 1,3,4-oxadiazole-5-nitroindolin-2-one derivatives (**7–9**), respectively. Sugar hydrazone-5-nitroindolin-2-ones (**10–13**) were archived by the reaction of **3** with D-glucose, D-mannose, D-arabinose, and D-ribose using both conventional and green chemistry.

Results and conclusion

Conventional and microwave methods used for the synthesis of various triazole, pyrazole, oxadiazine, oxadiazole, and sugar hydrazone-5-nitroindolin-2-one derivatives were applied for the synthesis of compounds **4–13**. These methods were simple and gave good yields of the target compounds in short reaction times.

Keywords:
indoline-2,3-dione, oxadiazine, oxadiazoles, pyrazoles, sugar hydrazones, triazoles

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Introduction

Several heterocyclic compounds are widely found in nature and are essential for life. Indoline-2,3-dione is an endogenous compound with pharmacological importance [1]. Many indoline-2,3-dione derivatives are known to possess antimicrobial, anti-inflammatory, analgesic, antiviral, antifungal, antitubercular, and antidepressant activities [2–7]. Moreover, the Schiff's bases [8–11] and the hydrazides [12–13] of indoline-2,3-dione derivatives have been reported and evaluated for different pharmacological activities such as antibacterial, anticonvulsant, antiprotozoal, and antitubercular. Also, 1,2,4 triazoles, pyrazoles, 1,3,4 oxadiazoles derivatives [14–15] and their sugar hydrazones [16–17] possess several biological effects. The objective of the present study is the synthesis of several derivatives of triazole, pyrazole, oxadiazine, oxadiazole, and sugar hydrazone-5-nitroindolin-2-one derivatives from 4-(1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino)benzohydrazide using the conventional and microwave-assisted technique (part I).

Experimental

Chemistry

Melting points were determined in open capillary tubes on an Electro thermal digital melting point apparatus (Stuart, SMP10, UK) and were uncorrected. IR spectra were recorded on a Jasco FT/IR Fourier transform infrared spectrophotometer (USA) using KBr disks. ^{1}H NMR spectra were determined on a JOEL 270 MHz spectrometer (Japan) in DMSO-d_6 using TMS as the internal reference. Mass spectra were recorded on mass spectrometer JOEL at 70 eV. Elemental analyses were performed at the Microanalytical Lab, National Research Center, and the results were found to be in agreement ($\pm$ 0.4%) within the calculated values. The microwave oven used was LG 900 W (LG group, Seoul, South Korea). Purity of the synthesized compounds was checked by thin-layer chromatography (TLC) silica-gel alumina sheet-Merck 60-F254 precoated sheets (Darmstadt, Germany). 5-Nitroindoline-2,3-dione was purchased from Sigma-Aldrich (North Teutonia Avenue, Milwaukee, USA).

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*General procedures for the synthesis of ethyl 4-(5-nitro-2-oxoindolin-3-ylideneamino) benzoate (**1**)*

Method A: An equimolar amount of 5-nitroindoline-2,3-dione (0.03 mol, 5.76 g) and ethyl-4-amino benzoate (0.03 mol, 3.78 g) was dissolved in absolute ethanol (20 ml) containing glacial acetic acid (2 ml). The reaction mixture was heated under reflux at 120°C for 8 h and then kept at room temperature overnight. The solvent was evaporated under vacuum, and the resulting solid was recrystallized from absolute ethanol to afford compound **1** of yield 2.50 g (75%).

Method B: A solution of 5-nitroindoline-2,3-dione (0.01 mol, 1.92 g) and ethyl-4-amino benzoate (0.01 mol, 1.26 g) was dissolved in a mixture of water (10 ml) and absolute ethyl alcohol (10 ml) (1 : 1) and refluxed under stirring for 12 h. After cooling, the formed crystalline product was collected by filtration and dried to give 2.50 g (82%) of compound **1**.

Method C: A mixture of 5-nitroindoline-2,3-dione (0.01 mol, 1.92 g) and ethyl-4-amino benzoate (0.01 mol,1.26 g) in polyethylene glycol-600 (PEG-600) (10 ml) was refluxed at 100°C for 2 h. The reaction mixture was cooled and poured onto ice-cold water. The separated solid was filtered off, washed with cold water, and recrystallized from methanol to give product **1** in good yield (2.88 g, 85%).

Method D (microwave): A mixture of 5-nitroindoline-2,3-dione (0.01 mol, 1.92 g) and ethyl-4-amino benzoate (0.01 mol, 1.26 g) in the presence of sodium acetate (0.01 mol, 0.82 g) was taken in an open 125 ml Erlenmeyer flask. After thorough mixing, the reaction was irradiated in an automated microwave oven (LG 900 W and temperature 100°C) for 3 min. The oven was turned off after 2 min of heating to avoid evaporation of the reagent, and the progress of the reaction was monitored by TLC. After completion of the reaction, the flask was cooled, and the product was extracted from the flask. Hot ethanol was added. The solvent was then evaporated under vacuum and the product was filtered and recrystallized from methanol to give the compound. Yield 2.70 g (80%); mp 211–213°C; IR cm^{-1} (KBr): 3395 (NH), 1705 (C = O), 1730 (C = O ester), 1653 (C = N); ^{1}H NMR (DMSO-d_6, ppm): 2.10 (t, 3H, $COOCH_2CH_3$), 4.55–4.75 (q, 2H, $COOCH_2CH_3$), 6.85–7.20 (m, 4H, Ar-H), 7.30–7.50 (m, 3H, Ar-H); MS: *m/z*: 339 [M^+]; Anal. Calcd. (%) for $C_{17}H_{13}N_3O_5$: C: 60.18, H: 3.86, N: 12.38; found: C: 60.12, H: 3.80, N: 12.32.

*Synthesis of ethyl 4-[(1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino)] benzoate (**2**)*

A mixture of compound **1** (0.02 mol, 6.78 g) and 4-methylbenzyl chloride (0.03 mol, 3.4 ml) in dry pyridine (5 ml) was heated under reflux for 6 h. After completion of the reaction, the reaction mixture was cooled and then washed with diluted hydrochloric acid (1 : 1) and then with water (50 ml). The formed precipitate was filtered and crystallized from methanol to give compound **2,** which was used directly for the preparation of compounds **3–13**. Yield 3.28 g (74%); mp 190–192; IR cm^{-1} (KBr): 3395(NH), 1705 (C = O), 1735 (C = O ester), 1648 (C = N); ^{1}H NMR (DMSO-d_6, ppm): 1.8 (s, 3H, CH_3) 2.15 (t, 3H, $-COOCH_2CH_3$), 4.20 (s, 2H, CH_2-benzyl), 4.50–4.70 (q, 2H, $-COOCH_2CH_3$), 6.75–7.00 (m, 4H, Ar-H), 7.20–7.40 (m, 4H, Ar-H), 7.50–7.65 (m, 3H-Ar-H); MS: *m/z* = 443 [M^+]; Anal. Calcd. (%) for $C_{25}H_{21}N_3O_5$: C: 67.71, H: 4.77, N: 9.48; found: C: 67.69, H: 4.70, N: 9.42.

*Synthesis of 4-[(1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino)] benzohydrazide (**3**)*

Compound **2** (2 mmol, 0.90) was dissolved in absolute ethyl alcohol (30 ml), and hydrazine hydrate (2 mmol, 1 ml) was added dropwise with stirring at room temperature. Thereafter, the reaction mixture was heated under reflux with stirring for 8 h. The reaction was monitored by TLC and kept in a refrigerator for 4 h. The separated solid was filtered and washed with water and then with a small amount of absolute ethanol (15 ml). The product was dried and recrystallized with absolute ethanol to give compound **3**. Yield 3.2 g (76%); mp 270–272°C; IR cm^{-1} (KBr): 3380 (NH), 3217 (NH_2), 1705 (C = O), 1665 (C = O amide), 1644 (C = N); ^{1}H NMR (DMSO-d_6, ppm): 2.10 (s, 3H, CH_3), 4.30 (s, 2H, CH_2-benzyl), 5.63 (s, 2H, NH_2), 6.86–7.10 (m, 4H, Ar-H), 7.15–7.40 (m, 4H, Ar-H), 7.50–7.65 (m, 3H, Ar-H), 9.86 (s,1H, NH); MS: *m/z*: 430 [$M^+ + 1$]; Anal. Calcd. (%) for $C_{23}H_{19}N_5O_4$: C: 64.33, H: 4.46, N: 16.31; found: C: 64.30, H: 4.42, N:16.25.

*Synthesis of 3-(4-(4-benzyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (4) and 3-(4-(4-benzoyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenylimino)-1-(4-methylbenzyl)-5-nitroindolin-2-one (**5**)*

Method A: A mixture of compound **3** (1 mmol, 0.43 g), benzyl isothiocyanate (1 mmol, 0.15 ml), or benzoyl isothiocyanate (1 mmol, 0.2 ml) in absolute ethanol (10 ml) and potassium hydroxide solution (10 ml, 10% KOH in absolute ethanol) was taken. The reaction mixture was refluxed under stirring for 8 h, and the progress of the reaction was monitored by TLC. After cooling, the separated product was filtered and acidified with diluted hydrochloric acid (10% HCl). The precipitate formed was collected by filtration and recrystallized from methanol to give compounds **4** and **5** with yields 75 and 78%, respectively.

Method B: A mixture of compound **3** (1 mmol, 0.43 g), benzyl isothiocyanate (2 mmol, 0.30 ml) or benzoyl isothiocyanate (2 mmol, 0.4 ml), *p*-toluenesulfonic acid (1 mmol, 0.17 g), and ammonium acetate (1 mmol, 0.7 g) was mixed together with a pestle and mortar at room temperature. The reaction mixture was solidified. The contents were quenched by adding water and absolute ethanol (5 : 5 ml) with stirring at room temperature for 30 min and then for 3 h at 50°C. The reaction was monitored by TLC. The formed precipitate was washed with 5% $NaHCO_3$ (10 ml) and then with water (25 ml) and dried. The resulting solid product was recrystallized

from methanol to give pure products **4** and **5** (yields 80 and 84%, respectively).

Method C: A mixture of compound **3** (1 mmol, 0.43 g), benzyl isothiocyanate (2 mmol, 0.30 ml) or benzoyl isothiocyanate (2 mmol, 0.40 ml), and polyethylene glycol-600 (PEG-600) (10 ml) was refluxed with stirring at 100°C for 2.30–3 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto cold water. The precipitated substance was filtered and washed with ice-cold water and then recrystallized with methanol to give products **4** and **5** in excellent yields of 90 and 92%, respectively.

Method D: An open 125 ml Erlenmeyer flask containing compound **3** (1 mmol, 0.43 g) and benzyl isothiocyanate (1 mmol, 0.15 ml) or benzoyl isothiocyanate (1 mmol, 0.2 ml) in the presence of a solution of potassium hydroxide (10 ml, 10% KOH in water) was irradiated in an automated microwave oven for 2.30–3.30 min (LG 900 W at 100°C). The reaction was monitored by TLC. The oven was turned off after 2–3 min of heating to avoid evaporation of the reagents. After completion of the reaction the flask was cooled and the product was extracted from the flask by scratching. The product was then acidified by diluted hydrochloric acid and washed with water. The precipitate was collected by filtration and recrystallized from absolute ethanol to give products **4** and **5** in yields of 80 and 82%, respectively.

*3-(4-(4-Benzyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**4**)*
Yield 0.42 g (75%); mp 253–255°C; IR cm^{-1} (KBr): 3399 (NH), 1705 (C = O), 1658 (C = N), 1050 (C = S); ^1H NMR (DMSO-d_6, ppm): 2.10 (s, 3H, CH_3), 3.75 (s, 2H, CH_2-benzyl), 4.20 (s, 2H, benzyl-CH_2), 6.70–6.90 (m, 5H, Ar-H), 7.02–7.26 (m, 4H, Ar-H), 7.30–7.50 (m, 4H, Ar-H), 7.60–7.78 (m, 3H, Ar-H), 11.34 (s,1H, NH); MS: *m/z*: 559 [$M^+ - 1$], Anal. Calcd. (%) for $C_{31}H_{24}N_6O_3S$: C: 66.41, H: 4.31, N: 14.99, S: 5.72; found: C: 66.48, H: 4.25, N: 14.92, S: 5.80.

*3-(4-(4-Benzoyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**5**)*
Yield 0.45 g (78%); mp 280–282°C; IR cm^{-1} (KBr): 3390 (NH), 1705, 1715 (2C = O), 1654 (C = N), 1065 (C = S); ^1H NMR (270 MHz, DMSO-d_6, ppm): 2.00 (s, 3H, CH_3), 4.10 (s, 2H, CH_2-benzyl), 6.75–6.99 (m, 5H, Ar-H), 7.10–7.30 (m, 4H, Ar-H), 7.40–7.60 (m, 4H, Ar-H), 7.65–7.80 (m, 3H, Ar-H), 11.34 (s,1H, NH); MS: *m/z*: 575 [$M^+ + 1$]; Anal. Calcd. (%) for $C_{31}H_{22}N_6O_4S$: C: 64.80, H: 3.86; N: 14.63, S: 5.58; found: C: 64.76, H: 3.80, N: 4.55, S: 5.55.

*Synthesis of 3-(4-(3,5-dimethyl-1H-pyrazole-1-carbonyl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**6**)*
A cold mixture of acetyl acetone (1 mmol, 0.1 ml) and anhydrous sodium acetate (0.01 mol, 0.1 g) in absolute ethanol (10 ml) was added dropwise with stirring for 10 min to a solution of compound **3** (1 mmol, 0.43 g) in ethanol (10 ml) and a few drops of TEA. The reaction mixture was stirred for 5 h at room temperature and the progress of the reaction was monitored by TLC. The mixture was left at room temperature overnight. The solvent was evaporated under vacuum and the residue obtained was washed with water (50 ml), filtered, dried, and recrystallized from absolute ethanol to form compound **6**. Yield 0.33 g (68%), mp 272–274°C; IR cm^{-1} (KBr): 1705,1710 (2C = O), 1655 (C = N); ^1H NMR (DMSO-d_6,ppm): 2.10 (s, 3H, CH_3), 2.30 (s, 3H, CH3, 2.40 (s, 3H, CH_3), 4.20 (s, 2H, CH_2-benzyl), 6.10 (s, 1H, CH pyrazole), 6.80–7.00 (m, 4H, Ar-H), 7.20–7.50 (m, 4H, Ar-H), 7.60–7.75 (m, 3H, Ar-H), MS: *m/z*: 493 [M^+]; Anal. Calcd. (%) for $C_{28}H_{23}N_5O_4$: C: 68.14, H: 4.70, N: 14.19; found: C: 68.10, H: 4.68, N: 14.15.

*Synthesis of 3-(4-(1,3,4-oxadiazin-6-one)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**7**)*
To a solution of compound **3** (1 mmol, 0.43 g) and DMF (10 ml), ethyl bromoacetate (2 mmol, 0.33 ml) was added dropwise with stirring for 30 min. This was followed by addition of anhydrous sodium acetate (2 mmol, 0.139 g). The reaction mixture was heated under reflux at 100°C for 8 h with stirring, and the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and water (50 ml) was added. The product was extracted with ethyl acetate, concentrated under vacuum, washed with water (100 ml), and recrystallized from absolute ethanol to give compound **7**. Yield 0.23 g (65%); mp 260–262°C; IR cm^{-1} (KBr): 3388 (NH), 1705 (C = O), 1740 (C = O ester), 1650–1656 (C = N); ^1H NMR (DMSO-d_6, ppm): 2.10 (s, 3H, CH_3), 4.20 (s, 2H, CH2-benzyl), 4.40 (s, 2H, CH_2), 6.75–7.00 (m,4H, Ar-H), 7.22–7.45 (m, 4H, Ar-H), 7.55–7.75 (m, 3H, Ar-H), 9.60 (s,1H, NH); Anal. Calcd. (%) for $C_{25}H_{19}N_5O_5$: C: 63.96, H: 4.08, N: 14.92; found: C:63.91, H:4.12, N:14.96.

*Synthesis of 3-(4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl) phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**8**)*
A mixture of compound **3** (1 mmol, 0.43 g) and ethyl acetoacetate (2 mmol, 0.26 ml) was heated under reflux without solvent at 100°C for 15 min with stirring. The mixture was then heated under reflux in DMF (10 ml) containing a few drops of triethylamine for 6 h. The reaction was monitored by TLC. After cooling, the precipitate formed was collected by filtration and recrystallized from absolute ethanol to give compound **8**. Yield 0.31 g (64%); mp 272–274°C; IR cm^{-1} (KBr): 1705,1720(2C = O),1690 (C = O), 1645–1655 (C = N); ^1H NMR (DMSO-d_6,ppm): 1.90 (s, 3H, CH_3), 1.90 (s, 3H, CH_3) 2.10 (s, 2H, CH_2), 4.20 (s, 2H, CH_2-benzyl), 6.72–7.00 (m, 4H, Ar-H), 7.20–7.35 (m, 4H, Ar-H), 7.40–7.60 (m, 3H, Ar-H), 9.30; Anal. Calcd. (%) for $C_{27}H_{21}N_5O_5$: C: 65.45, H: 4.72, N: 14.13; found: C: 65.41, H: 4.68, N: 14.09.

*Synthesis of 3-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenylimino)-1-(p-methylbenzyl)-5-nitroindolin-2-one (**9**)*
A mixture of compound **3** (1 mmol, 0.43 g), acetyl chloride (2 mmol, 0.20 ml) in DMF (10 ml), and a few drops of TEA was stirred at room temperature for 8 h. The reaction was monitored by TLC. After completion of

the reaction, the reaction mixture was cooled and then poured onto crushed ice. The solid obtained was filtered and recrystallized from methanol to give compound **9**. Yield 0.29 g (66%); mp 213–215°C; IR cm^{-1} (KBr): 1705(C = O), 1640–1650 (C = N); ^{1}H NMR (DMSO-d_6, ppm): 2.10 (s, 3H, CH_3), 2.35 (s, J = 6 Hz, 3H, CH_3), 4.20 (s, 2H, CH_2-benzyl), 6.80–7.00 (m, 4H, Ar-H), 7.20–7.45 (m, 4H, Ar-H), 7.50–7.70 (m, 3H, Ar-H); MS: *m/z*: 453 [M^+]; Anal. Calcd. (%) for $C_{25}H_{19}N_5O_4$: C: 66.22, H: 4.22, N: 15.44; found: C: 66.25, H: 4.25, N: 15.48.

*General procedure for the synthesis of compounds **6–9** using polyethylene glycol (PEG-600)*

A mixture of compound **3** (0.1 mmol, 0.43 g), acetyl acetone, ethyl bromoacetate, ethyl acetoacetate, and acetyl chloride (0.1 mmol) and polyethylene glycol (PEG-600) (10 ml) in the presence of TEA was heated at 100°C for 2–3 h. The reaction monitored by TLC. The reaction mixture was cooled and poured onto cold water. The precipitated solid was filtered and washed with cold water and then crystallized from methanol to give compounds **6–9** in good yields of 80–82%.

*General procedures for synthesis of compounds **6–9** using a microwave*

Into an open round flask were added compound **3** (1 mmol, 0.43 g) and acetyl acetone, ethyl bromoacetate, ethyl acetoacetate, or acetyl chloride (1 mmol) in the presence of *p*-toluenesulfonic acid (2 mmol, 1.4 g), and DMF (5 ml) absorbed over acidic alumina (1 g). The reaction was mixed at room temperature and then irradiated in an automated microwave oven (900 W LG at 100°C) for 2–3 min. The oven was turned off after 1–2 min of heating to avoid evaporation of the reagents. The reaction was monitored by TLC, and after completion of the reaction the flask was cooled. The product was extracted from the flask by scratching; the solid substance separated was washed with water (30 ml), filtered, and recrystallized from methanol and then weighted to yield compounds **6–9** (78–80%, respectively).

*General procedure for the synthesis of N′-ethylidene 4-(-1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) sugar hydrazone derivatives (**10–13**)*

D-Glucose (1 mmol, 0.20 g), D-mannose (1 mmol, 0.20 g), D-arabinose (1 mmol, 0.15 g), or D-ribose (1 mmol, 0.15 g) mixed in water (1 ml) was added to a solution of compound **3** (1 mmol, 0.43 g) in ethanol (20 ml) and acetic acid (0.5 ml). The reaction mixture was stirred at room temperature for 1 h, and then refluxed with stirring at 50°C for 5–6 h. Water (0.5 ml) was added after 3 h. The reaction was monitored by TLC. After cooling, the mixture was evaporated under vacuum, and the resulting mixture was washed with absolute ethanol to afford the respective hydrazone derivatives **10–13** in yields of 70–74%.

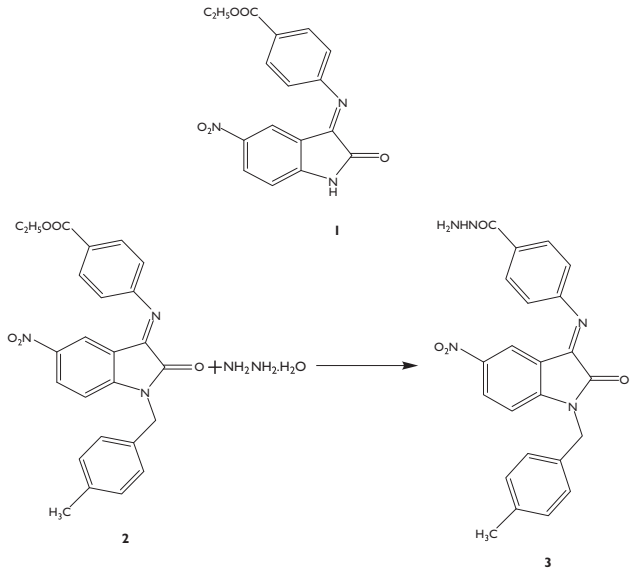
D-Glucose-4-(-1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) hydrazone derivative (10): Yield 0.44 g (74%), mp 175–177°C; IR cm^{-1} (KBr): 3420–3445(OH), 1705 (C = O), 1664 (C = O amide), 1652 (C = N), 1635(N = CH); ^{1}H NMR (MeOD-d_4, ppm): 2.10 (s, 3H, CH_3), 3.70–3.80 (m, 2H, CH_2-OH), 3.90–4.10 (m, 5H, OH, exchangeable D_2O), 4.20 (s, 2H, CH_2-benzyl), 4.30–4.50 (m, 2H, H-2, H-1a), 4.60 (dd,1H, J = 12.1, 6.7 Hz, H-1b), 4.70 (1H, dd, J = 7.5, 2.3 Hz, H-3), 4.80 (dd,1H, J = 3.8, 2.5 Hz, H-4), 5.00 (dd, 1H, J = 7.8, 3.6 Hz, H-5), 5.10 (d,1H, J = 7.6 Hz, H-6), 6.80–7.10 (m, 4H, Ar-H), 7.30–7.50 (m, 4H, Ar-H), 7.60–7.75 (m, 3H, Ar-H), 8.10 (d, 1H, N = CH), 9.30 (s,1H, NH); Anal. Calcd. (%) for $C_{29}H_{29}N_5O_9$: C: 58.88, H, 4.94, N, 11.84; found: C: 58.83, H: 4.90, N: 11.80.

D-Mannose-4-(-1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) hydrazone derivative (11): Yield 0. 41 g(70%), mp 183–185°C; IR cm^{-1} (KBr): 3425–3440 (OH), 1715(C = O), 1665 (C = O amide) 1650 (C = N), 1630 (N = CH),); ^{1}H NMR (MeOD-d4, ppm): 2.10 (s, 3H, CH_3), 3.60–3.70 (m, 2H, CH_2-OH), 3.90–4.10 (m, 5H, OH, exchangeable D_2O), 4.25 (s, 2H, CH_2-benzyl), 4.40 (d, 1H, m, J = 3.5Hz, H-6) 4.60 (1H, dd, J = 8.3, 3.2 Hz, H-5), 4.70 (1H, d, J = 8.2 Hz, H-4), 4.96 (1H, d, J = 7.7 Hz, H-3), 5.20 (1H, m, H-2), 5.40 (d, 1H, H-1a), 3.56 (1H, dd, J = 11.2, 3.6 Hz, H-1b), 6.90–7.20 (m, 4H, Ar-H), 7.30–7.50 (m, 4H, Ar-H), 7.60–7.80 (m, 3H, Ar-H), 8.20 (d, 1H, N = CH), 9.40 (s,1H, NH); MS: *m/z*: 590 [$M^+ - 1$]; Anal. Calcd. (%) for $C_{29}H_{29}N_5O_9$: C: 58.88, H: 4.94, N: 11.84; found: C: 58.83, H: 4.90, N: 11.80.

D-Arabinose-4-(-1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) hydrazone derivative (12): Yield 0.41 g (73%), mp 180–182°C; IR cm^{-1} (KBr): 3425–3445 (OH), 1715 (C = O), 1660 (C = O amide); 1649 (C = N); 1630 (N = CH).^{1}H NMR (DMSO-d_6, ppm): 2.10 (s, 3H, CH_3), 3.60–3.70 (2H, m,H-3, H-1a), 3.80 (1H, dd, J = 7.3, 4.5 Hz, H-2), 4.00 (1H, dd, J = 12.3, 7.3 Hz, H-1b), 4.20 (s, 2H, CH_2 -benzyl), 4.40 (1H, Br, H-4), 4.60 (1H, d, J = 10.3 Hz, H-5), 4.80–5.10 (1H, t, J = 6.4 Hz, CH_2-OH), 5.20–5.40 (m, 5H, OH, exchangeable D_2O), 6.80–7.15 (m, 4H, Ar-H), 7.20–7.50 (m, 4H, Ar-H), 7.60–7.80 (m, Hz, 3H, Ar-H), 8.15 (d, 1H, N = CH), 9.25 (s,1H, NH); MS (relative intensity): *m/z*: 560 [$M^+ + 1$]; Anal. Calcd. (%) for $C_{28}H_{27}N_5O_8$: C: 59.89, H: 4.85, N: 12.47; found: C: 59.83, H: 4.80, N, 12.42.

D-Ribose-4-(-1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) hydrazone derivative (13): Yield 0.39 g (71%), mp 179–181°C; IR cm^{-1} (KBr): 3425–3440 (OH), 1715 (C = O), 1665 (C = O amide); 1650 (C = N); 1635 (N = CH) ^{1}H NMR (DMSO-d_6, ppm): 2.10 (s, 3H, CH_3), 3.70–3.80 (m, 2H, CH_2-OH), 3.90–4.10 (m, 4H, OH, exchangeable D_2O), 4.25 (s, 2H, CH_2 -benzyl), 4.40 (1H, dd, J = 11.2, 3.5 Hz, H-1a), 4.60–4.70 (2H, m, H-3, H-1b); 4.80 (1H, d, J = 3.2 Hz, H-5), 5.18 (1H, dd, J = 8.7, 3.3 Hz, H-4), 5.44 (1H, dd, J = 9.3, 5.6 Hz, H-2),6.80–7.10 (m, 4H, Ar-H), 7.20–7.40 (m, 4H, Ar-H), 7.50–7.70 (m, 3H, Ar-H), 8.35 (d, 1H, N = CH), 9.35 (s,1H, NH); Anal. Calcd. (%) for $C_{28}H_{27}N_5O_8$: C: 59.89, H: 4.85, N: 12.47; found: C: 59.83, H: 4.80, N: 12.42.

Scheme 1

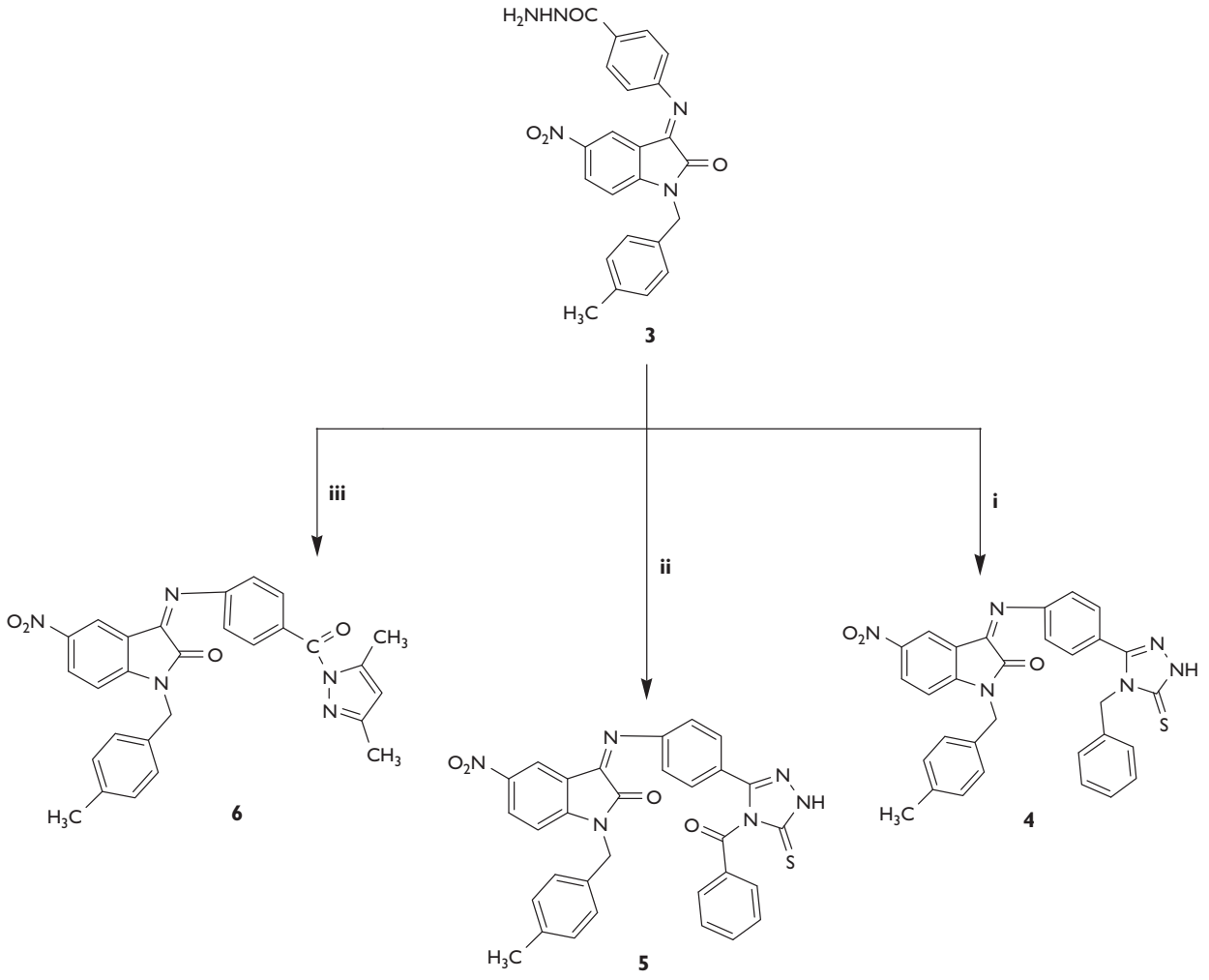


Synthesis of 5-nitroindoline-2-one derivatives **1–3**.

Results and discussion

Indole and related compounds have shown diverse biological activities. Furthermore, some of their derivatives have also been reported to exhibit significant biological activities. Considerable interest has arisen in the design and synthesis of oxoindoline derivatives containing oxadiazole, pyrazole, triazole, and sugar hydrazone to explore their pharmacological activities such as antibacterial and anti-inflammatory activities. Compound **1** was prepared by the reaction of 5-nitro indoline-2,3-dione with ethyl-4-amino benzoate to give the corresponding ethyl(-5-nitro-2-oxoindolin-3-ylideneamino) benzoate (**1**), which reacted with *p*-methyl benzyl chloride to form ethyl 4-(1-(*p*-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino)benzoate (**2**). The hydrazinolysis of compound **2** with hydrazine hydrate gave the corresponding 4-(1-(*p*-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) benzohydrazide (**3**) (Scheme 1). On the basis of elemental analyses and spectral data, structures of compounds **1**, **2**, and **3** were confirmed. The mass spectrum of compound **1** exhibited the molecular ion peak (M^+) at *m/z* 339 and the mass spectrum of compound **2** showed the molecular ion

Scheme 2



Synthesis of 1H-1,2,4-traizole and 1H-pyrazole-5-nitroindoline-2-one derivatives **4–6**. Conditions and reagents: (i) benzyl isothiocyanate/10% KOH/reflux, (ii) benzoyl isothiocyanate/10% KOH/reflux, (iii) acetyl acetone/anhydrous sodium acetate/RT.

peak at *m/z* 443 (M^+). The IR spectrum of compound **3** was characterized by absorption bands C = N at 1644 cm^{-1}, C = O at 1705 cm^{-1}, NH at 3380 cm^{-1}, and NH_2 at 3217 cm^{-1}.

The reaction of compound **3** with benzyl isothiocyanate or benzoyl isothiocyanate in the presence of an aqueous solution of 10% KOH provided the corresponding 3-(4-(4-benzyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)phenylimino)-1-(4-methylbenzyl)-5-nitroindolin-2-one (**4**) and 3-(4-(4-benzoyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**5**). The IR spectrum of compound **5** exhibited two absorption bands for C = O stretching at 1705 and 1715 cm^{-1} and for C = S at 1065 cm^{-1}.

In addition, condensation reaction of 4-(1-(*p*-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) benzohydrazide (**3**) with acetyl acetone afforded the corresponding -3-(4-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**6**) (Scheme 2). The IR spectrum of compound **6** displayed two absorption bands at 1705 and 1710 cm^{-1} for C = O.

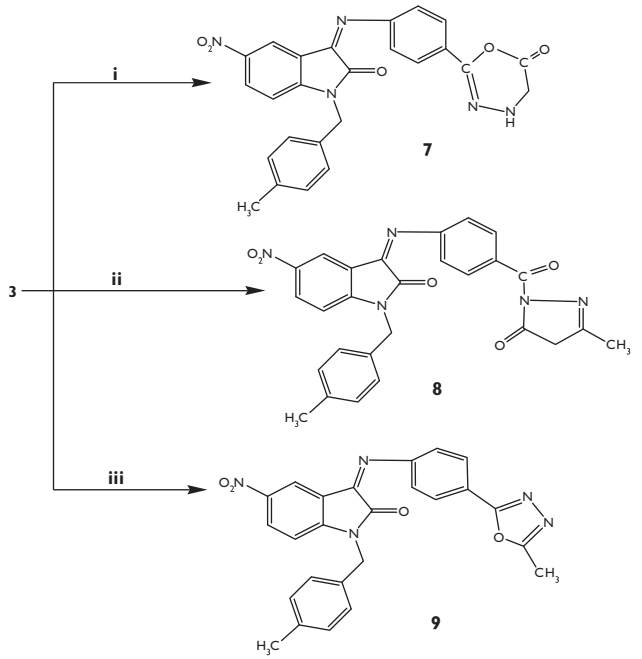
Moreover, compound **3** was reacted with ethyl bromoacetate to afford the corresponding 3-(4-(1,3,4-oxadiazin-6-one)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**7**). The IR spectrum of compound **7** showed absorption bands at 3388 cm^{-1} for NH, 1740 cm^{-1} and 1705 cm^{-1} for C = O ester, and carbonyl groups, respectively, and 1656–1650 cm^{-1} for C = N.

In a similar manner, compound **3** converted into 3-(4-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbonyl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**8**) by reacting with ethyl acetoacetate to form compound **8**. Compound **8** showed absorption bands at around 1705, 1720, 1690, and 1645–1655 cm^{-1} regions, resulting from the C = O and C = N functions. In contrast, treatment of compound **3** with acetyl chloride led to the formation of 3-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**9**) (Scheme 3). The latter compound showed C = O absorption band at 1705 cm^{-1} and C = N at 1640–1650 cm^{-1}. Green chemistry is an approach for the synthesis of most of the synthesized compounds **1–9** using polyethylene glycol (PEG-600), which is a very effective, efficient, and more environmentally friendly solvent (cf. Materials and methods section).

In recent years, microwave-assisted synthesis has become a powerful synthetic tool for rapid synthesis of a variety of beneficial organic intermediates and biologically active compounds. Therefore, we applied microwave conditions to synthesize ethyl-5-nitro-2-oxoindolin-3-ylideneamino) benzoate (**1**), 3-(4-(4-benzyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**4**), 3-(4-(4-benzoyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**5**), and compounds **6–9**.

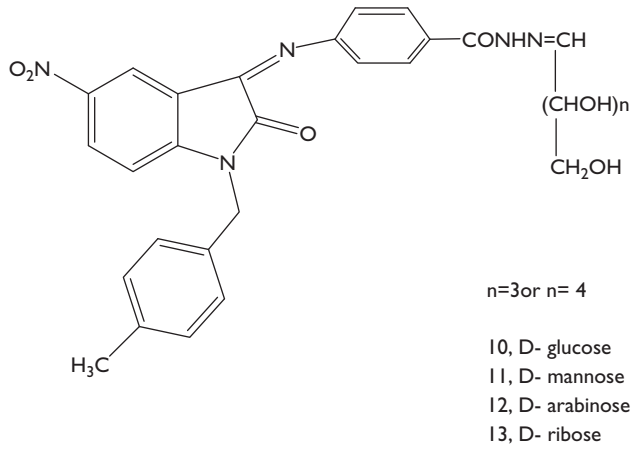
Synthesis of the sugar hydrazone derivatives **10–13** was accomplished by reaction of target **3** with monosaccharides, namely, D-glucose, D-mannose, D-arabinose, or D-ribose, in the presence of water and a few drops of acetic acid to give the respective sugar hydrazones **10–13** (Scheme 4). The IR spectra gave strong absorption bands at 3420–3445 cm^{-1} characterized by the presence of CHOH function groups and an absorption band at 1705 cm^{-1} for the C = O group in addition to N = CH at 1630–1635 cm^{-1}. 4-(1-(*p*-Methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) benzohydrazide (**3**) was attached to a series of open-chain monosaccharides linked to the nitrogen atom of the benzohydrazide group to give sugar hydrazone-5-nitroindolin-2-one derivatives.

Scheme 3



Synthesis of 1,3,4 oxadiazin-6-one, 1H-pyrazole, and 1,3,4-oxadiazole-5-nitroindolin-2-one derivatives **7–9**. Conditions and reagents: (i) ethyl bromoacetate/anhydrous sodium acetate/DMF/reflux, (ii) ethyl acetoacetate/DMF/reflux, (iii) acetyl chloride/DMF/RT.

Scheme 4



Synthesis of sugar hydrazone-5-nitroindolin-2-one derivatives **10–13**. Conditions and reagents: D-glucose, D-mannose, D-arabinose, and D-ribose/water/acetic acid.

Effects of microwave power and reaction time

Microwave heating is a powerful technique for promoting a variety of chemical reactions. The reaction time has an impact on the microwave-assisted method for the synthesis of ethyl 4-(5-nitro-2-oxoindolin-3-ylideneamino)benzoate (**1**) using sodium acetate, 3-(4-(4-benzyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one derivatives, and 3-(4-(4-benzoyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**4** and **5**) in the presence of aqueous KOH. In addition, 3-(4-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**6**), 3-(4-(1,3,4-oxadiazin-6-one)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**7**), 3-(4-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbonyl)phenylimino)-1-(4-methylbenzyl)-5-nitroindolin-2-one (**8**), and 3-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenylimino)-1-(*p*-methylbenzyl)-5-nitroindolin-2-one (**9**) in the presence of *p*-toluenesulfonic acid are also used. When a microwave was used for irradiation, the reaction time was markedly reduced from several hours (in conventional heating) to a few minutes under solvent-free conditions; other advantages of using a microwave are low cost, high yield, and simplicity in processing and handling [18].

Conclusion

A series of triazole, pyrazole, oxadiazine, oxadiazole, and sugar hydrazone-5-nitroindolin-2-one derivatives were synthesized from 4-(1-(p-methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino) benzohydrazide in good yields using conventional and microwave-assisted techniques.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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