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Synthesis and Identification of New Derivatives of 1H-benzo[f]indole-2,3-dione

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Abstract

This study synthesizes and identifies novel heterocyclic compounds derived from 1H-benzo[f]indole-2,3-dione. The target compounds were synthesized through Schiff base reactions, utilizing 1H-benzo[f]indole-2,3-dione as the core substrate. The reaction pathways were optimized to enhance yield and selectivity. Comprehensive structural elucidation of the synthesized compounds was performed using spectroscopic techniques, including NMR, FTIR, and mass spectrometry, confirming the successful formation of the desired heterocyclic frameworks. Additionally, preliminary studies were conducted to evaluate the potential applications of these compounds in medicinal chemistry and materials science.

Keywords: Pathways; NMR; FTIR; Mass spectrometry

1. Introduction

Heterocyclic compounds occupy a prominent position in organic and medicinal chemistry due to their diverse biological activities and wide-ranging applications in pharmaceuticals, agrochemicals, and materials science. Among these, nitrogen-containing heterocycles have garnered significant attention for their role as structural frameworks in natural products and synthetic drugs [1, 2]. The 1H-benzo[f]indole-2,3-dione scaffold, a fused bicyclic system combining an indole ring with a quinonoid moiety, represents a versatile starting material for the synthesis of novel heterocyclic derivatives [3]. The reactivity of 1H-benzo[f]indole-2,3-dione enables the formation of complex molecular architectures through nucleophilic addition, cyclization, and condensation reactions. Such transformations have paved the way for the development of compounds with unique physicochemical properties and biological functionalities, including antimicrobial, anticancer, and antiviral activities [4, 5]. The ability of isatin derivatives to intercalate into DNA and induce interferon secretion. Additionally, the toxicity of isatin derivatives is significantly lower than that of the analogous benzoisatin derivatives, although their interferon-inducing activity is also somewhat reduced in comparison [6-8]. Despite the synthetic potential of 1H-benzo[f]indole-2,3-dione, limited studies have been conducted to explore its utility in creating diverse heterocyclic frameworks. This work aims to address this gap by synthesizing and characterizing new heterocyclic derivatives derived from this core structure. The current study also investigates the structural, spectroscopic, and potential biological properties of the synthesized compounds to expand their applicability in various fields.

2. Experimental

2.1. Chemicals, and instrumentation

All materials were purchased from Merck, Sigma, BDH, and GCC. The formation of compounds was confirmed using IR, and NMR spectrometry techniques. Silica gel precoated aluminum sheets (Merck), for thin layer chromatography (TLC), were used for determining Rf and monitoring the reaction progress. The melting points were determined in open

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capillary, using melting point apparatus, provided by Cole-Parmer Ltd, UK. Fourier Transform Infrared Spectrophotometer was recorded on Shimadzu, Japan. Bruker Avance400 MHz NMR spectrometer was used for 1H and 13C NMR using deuterated DMSO as solvent.

3. Materials and Methods

3.1. Synthesis of Schiff Base Derivatives 1-4: [9-11]

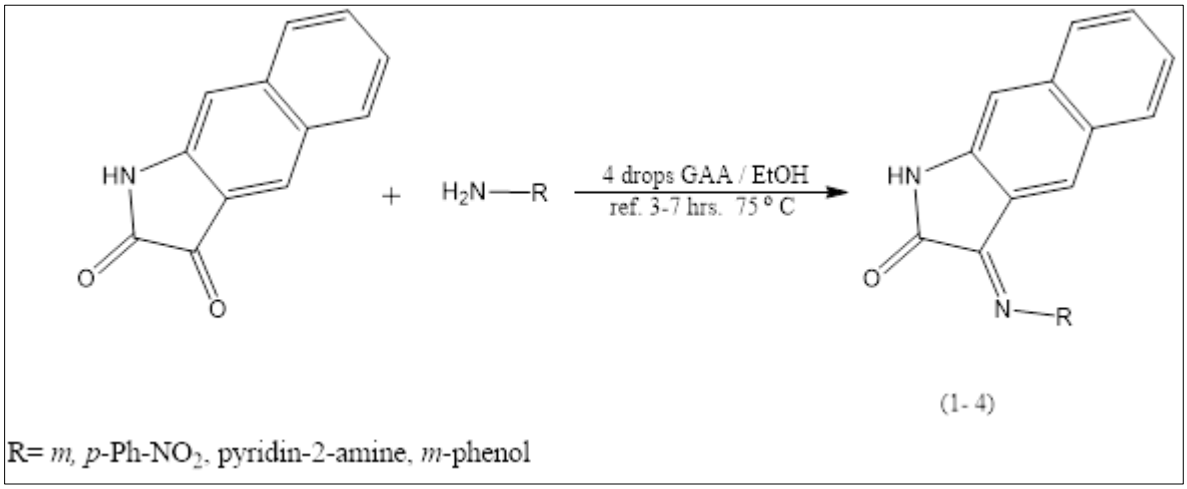

Figure 1 Synthesis of Schiff Base Derivatives

3.1.1. (Z)-3-((3-nitrophenyl)imino)-1,3-dihydro-2H-benzo[f]indol-2-one (1)

Equivalent moles (1:1 mole) of 3-nitroaniline with 1H-benzo[f]indole-2,3-dione, in (50ml) of absolute ethanol with three drops of glacial acetic acid. This mixture was refluxed for (5-7) hours at 75 °C. TLC was used to check the reaction's progress. According to the literature procedure, the solid product obtained was crystallized from ethanol to form (1) .

3.1.2. (Z)-3-((4-nitrophenyl)imino)-1,3-dihydro-2H-benzo[f]indol-2-one (2)

Equivalent moles (1:1 mole) of *P*-nitroaniline with 1H-benzo[f]indole-2,3-dione, in (50ml) of absolute ethanol with three drops of glacial acetic acid. This mixture was refluxed for (4-5) hours at 75 °C. TLC was used to check the reaction's progress. According to the literature procedure, the solid product obtained was crystallized from ethanol to form (2) .

3.1.3. (3Z,3'E)-3,3'-(pyridine-2,3-diylbis(azanylylidene))bis(1,3-dihydro-2H-benzo[f]indol-2-one) (3)

Equivalent moles (1:2 mole) of *o*-phenylendiamine with 1H-benzo[f]indole-2,3-dione, in (50ml) of absolute ethanol with three drops of glacial acetic acid. This mixture was refluxed for (6-7) hours at 75 °C. TLC was used to check the reaction's progress. According to the literature procedure, the solid product obtained was crystallized from ethanol to form (3) .

3.1.4. (Z)-3-((3-hydroxyphenyl)imino)-1,3-dihydro-2H-benzo[f]indol-2-one (4)

Equivalent moles (1:1 mole) of *m*-aminophenol with 1H-benzo[f]indole-2,3-dione, in (50ml) of absolute ethanol with three drops of glacial acetic acid. This mixture was refluxed for (3-5) hours at 75 °C. TLC was used to check the reaction's progress. According to the literature procedure, the solid product obtained was crystallized from ethanol to form (4) .

Table 1 Some Physical Properties of Schiff Base Derivatives

Comp.	Chemical Formula	R_f	m.p. °C	Yield%	Color
1	$C_{18}H_{11}N_3O_3$	0.64	200-202	80%	Orange
2	$C_{18}H_{11}N_3O$	0.65	210-212	85%	Orange
3	$C_{29}H_{17}N_5O_2$	0.54	212-214	88%	Orange
4	$C_{18}H_{12}N_2O_2$	0.7	208-210	89%	Orange

3.2. Synthesis of Imidazolidine Derivatives by [3 + 2] cycloaddition reaction [1H-4H] and [1T-4T]

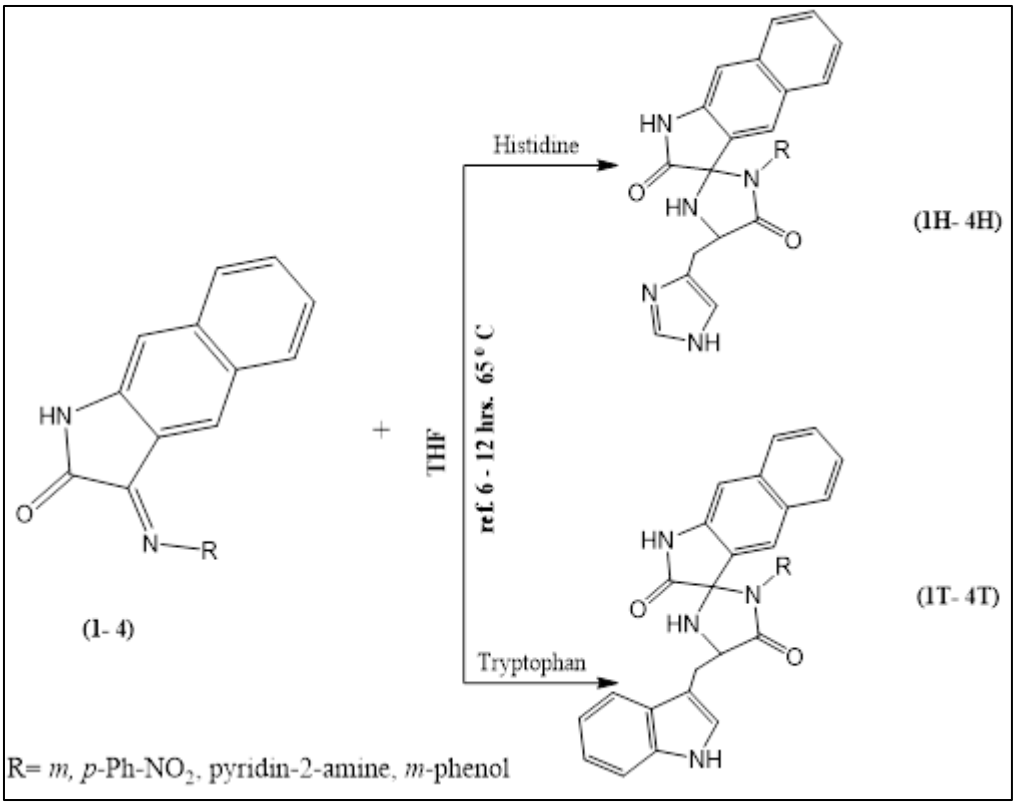

Figure 2 Synthesis of Imidazolidine Derivatives

*3.2.1. 4'-((1H-imidazol-4-yl)methyl)-1'-(3-nitrophenyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione (**1**H)*

(1:1 mole) the equivalent of histidine with the compound 1 in (50ml) of dry benzene. This mixture was refluxed for (6-8) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (1H) according to the literature procedure .

*3.2.2. 4-((1H-indol-3-yl)methyl)-1-(3-nitrophenyl)spiro[imidazolidine-2,3'-indoline]-2',5-dione (**1**T)*

(1:1 mole) the equivalent of tryptophan with compound 1, in (50ml) of dry benzene. This mixture was refluxed for (6-8) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (1T).

*3.2.3. 4'-((1H-imidazol-4-yl)methyl)-1'-(4-nitrophenyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione (**2**H)*

(1:1 mole) the equivalent of histidine with the compound 2 in (50ml) of dry benzene. This mixture was refluxed for (7-10) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (2H).

*3.2.4. 4'-((1H-indol-3-yl)methyl)-1'-(4-nitrophenyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione (**2**T)*

(1:1 mole) the equivalent of tryptophan with compound 2, in (50ml) of dry benzene. This mixture was refluxed for (7-10) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (2T)

*3.2.5. 1',1'''-(pyridine-2,3-diyl)bis(4'-((1H-imidazol-4-yl)methyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione) (**3**H)*

(2:1 mole) the equivalent of histidine with the compound 3 in (50ml) of dry benzene. This mixture was refluxed for (8-12) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (3H)

*3.2.6. 1',1'''-(pyridine-2,3-diyl)bis(4'-((1H-indol-3-yl)methyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione) (**3**T)*

(2:1 mole) the equivalent of tryptophan with compound 3, in (50ml) of dry benzene. This mixture was refluxed for (8-12) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (3T).

4'-((1H-imidazol-4-yl)methyl)-1'-(3-hydroxyphenyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione (4H)

(1:1 mole) the equivalent of histidine with the compound 4 in (50ml) of dry benzene. This mixture was refluxed for (9-11) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (4H)

*3.2.7. 4'-((1H-indol-3-yl)methyl)-1'-(3-hydroxyphenyl)spiro[benzo[f]indole-3,2'-imidazolidine]-2,5'(1H)-dione (**4**T)*

(1:1 mole) the equivalent of tryptophan with compound 4, in (50ml) of dry benzene. This mixture was refluxed for (9-11) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compound (4T)

Table 2 Some Physical Properties of Imidazolidine Derivatives

Comp.	Chemical Formula	R_f	m.p.˚C	Yield%	Color
1H	$C_{24}H_{18}N_6O_4$	0.65	220-222	80	Light Orange
1T	$C_{29}H_{21}N_5O_4$	0.68	222-224	82	Light Orange
2H	$C_{24}H_{18}N_6O_4$	0.64	202-204	93	Burnt Orange
2T	$C_{29}H_{21}N_5O_4$	0.61	217-219	93	Burnt Orange
3H	$C_{37}H_{29}N_{11}O_4$	0.73	221-223	90	Orange
3T	$C_{47}H_{35}N_9O_4$	0.7	218-220	88	Orange
4H	$C_{24}H_{19}N_5O_3$	0.55	211-213	85	Burnt Orange
4T	$C_{29}H_{22}N_4O_3$	0.5	214-216	84	Burnt Orange

4. Results and discussion

The Schiff base compounds (1–4) were synthesized through the condensation reaction of 1H-benzo[f]indole-2,3-dione with primary aromatic amines in absolute ethanol, using a few drops of glacial acetic acid as a catalyst. Furthermore, the derivatives (1–4)H and (1–4)T were obtained by reacting the Schiff base compounds (1–4) with histidine and tryptophan, respectively, in a mixture of ethanol and tetrahydrofuran (THF).

The chemical compositions of compounds were asserted by IR, ^1H & ^{13}C NMR spectroscopy. In the FT-IR spectrum of compounds (1-4) we notice that disappearance of asymmetric and symmetric stretching vibration of primary amine (NH_2) group and presence of stretching vibration for (C=N imine) bands at υ =1650–1630 cm^{-1} [15] initially attributes to Schiff base derivatives formation.

The Fourier transform infrared (FT-TR) spectra of compounds (1-4) H and T, the IR spectra of these compounds showed the absence of any absorption bands corresponding to the presence of stretching vibration for the azomethine group (CH = N) at υ = 1650–1630 cm^{-1}. And appearance stretching vibration for (C-H aliphatic) at υ = 3060-2900 cm^{-1}. And the secondary of amin (NH) (3330- 3360) cm^{-1} [16]. And (OH) group at 3338 cm^{-1} [17]. And C=O (amide) at 1693- 1705 cm^{-1} [18].

The ^{1}H NMR spectra of compounds (1-4) showed sharp signals at δ 11.00–10.80 ppm due to the protons of imide (N-H) [19, 20], Protons of the aromatic ring (CH=CH), were observed within the expected chemical shift regions at δ 6.00-8.9 ppm [21] and exhibited the expected integral values.

Furthermore, the ^{1}H NMR spectra of compounds (1-4) H and T showed signals in the region of δ= 11.50-13.20 ppm due to the protons of (N-H amine) [19, 20]. Regarding compound, 4H, proton appeared as singlet signal at δ 9.50 ppm due to the protons of (O-H) [17, 21]. Protons of the aromatic ring (CH=CH) were observed within the expected chemical shift regions and exhibited the expected integral values δ 6.50- 8.90 ppm [15].

The ^{13}C NMR spectra of compounds (1-4) revealed characteristic carbon signals at 150-165 due to the carbons of imine groups (C=N). The carbon signals of carbonyl function (C=O) of amide groups in the compounds spectra appeared at δ 160–145 ppm [19, 20].

The 13C NMR spectra of Compounds (1-4) a and b disappear Carbon signals assigned to carbons the azomethine groups (CH = N). Characteristic carbon signals in the region at δ 80-140ppm revealed the carbons of aromatic rings (CH=CH) [21, 22].

5. Recommendations and conclusion

- **Expanding the Scope of Research:** Investigate the potential inhibitory effects of the synthesized compounds on a broader range of cancers.
- **Exploration of Antimicrobial Activity:** Conduct in-depth studies to evaluate the antimicrobial efficacy of the prepared compounds against various resistant strains of bacteria and fungi for possible pharmaceutical applications.
- **Development of Derivatives:** Continue synthesizing new derivatives of imidazolidine by reacting Schiff base derivatives with other bioactive compounds such as peptides or natural products to explore their multifunctional applications in medicine and agriculture.
- **In Vivo Studies:** Perform comprehensive preclinical evaluations of the anticancer properties of the synthesized compounds using animal models to better understand their therapeutic potential and safety profiles.
- **Environmental Applications:** Assess the potential use of synthesized compounds in agrochemistry, such as bio-pesticides or plant growth regulators, due to their expected biological activity and environmental compatibility.
- **Mechanistic Studies:** Investigate the detailed mechanisms of action of these compounds on cellular pathways in both microbial and cancer models to elucidate their therapeutic targets and optimize their efficacy.

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