Synthesis and Biological Evaluation of Isatin Derivatives as Antibacterial Inhibitors

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ABSTRACT

Herein, 2'-amino-6'-(ethylthio)-2-oxo-1'H-spiro[indoline-3,4'-pyridine]-3',5'-dicarbo-nitrile I and 2-(2-oxoindolin-3-ylidene)hydrazine-1-carbox-imidamide II were served as prestarting intermediates for the production of polyfunctional substituted heterocycles like; pyrazole, pyridine, imidazole, and pyrimidine. Subsequently, representative chemicals of the manufactured series were verified and assessed as antibacterial inhibitors. Spiro-indoline pyridine I was prepared to be used as a beginning material for manufacturing assorted novel heterocyclic compounds containing an isatin moiety. Derivative I was obtained via the reaction of isatydine malononitrile with malononitrile and ethyl thioc in the presence of ammonium acetate. The starting compound I was permitted to combine with carbon disulfide in boiling pyridine to afford the carbamodithioic acid derivative III. Also, the reaction of compound I with triethyl orthoformate, maleic anhydride, dimethylformamide, dimethyl acetal, hydrazine hydrate, and diethyl malonate yielded compounds IV, V, VI, VII, and VIII respectively. Moreover, the reaction of the ketonic carbonyl group of isatin with aminoguanidine salt in aqueous alcohol when there was a catalytic amount of sodium bicarbonate yielded compound II. Likewise, carbonimidamide derivative II reacted with active methylene compounds such as malononitrile and its derivatives; namely, ethoxy methylene malononitrile and chloroacetonitrile to afford compounds XI, XII, and IX, respectively. On the other hand, compound II interaction with dimethyl acetylenedicarboxylate allowed a heterocyclic imidazole derivative to be obtained.

1. Introduction

Isatin derivatives have a long history of applications in the pharmaceutical industry as active pharmacophores. Heterocyclic compounds with an isatin nucleus have assorted biological merits, including anti-inflammatory, analgesic [1-5], anticancer [6-11], antitubercular [12], antimalarial [13-17], antioxidant [18-21], anthelmintic [22], and antianxiety activities [23]. Moreover, they work as anticonvulsants [24, 25], anti-HIV [26-28], antiviral [29], antibacterial [30-34], anti-fungal [35], and anti-tubercular agents [36-39]. Isatin derivatives also have various industrial applications, they are used as corrosion inhibitors [40-42], fluorescent sensors [43-46], and also in the dye industry [47, 48].

2. Materials and Methods

Oxindoline hydrazide carbonimidamide II was synthesized in accordance with literature methods [Krátký et al, 2021] [63]. All chemicals and initial materials were collected from commercial providers and were applied without any additional purification.

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To a well-stirred mixture of carbonyl compounds "such as isatin" (0.147 g, 1.0 mmol), active methylene compounds "such as Malononitrile" (0.123 g, 2.0 mmol), and mercapto "such as ethyl thiol" (0.072 mL, 1.0 mmol) in ethanol, after adding the basic catalyst "diethylamine" (0.1 mL), stirring was carried out for 180 minutes. As soon as the reaction is finished (showed by TLC), ethanol (5.0 mL) was added, and after another 5 minutes of stirring the reaction was finished. The resulting white crude was concentrated by filtration and subsequently rinsed with a blend of cyclohexane and chloroform. (80:20, v/v) and then dried. The resultant crude was recrystallized from alcohol "such as EtOH". Yield: 40%, m.p.: 272 °C (KBr, / cm -3): 3446, 3309, 3242, 3212 (NH2, 2NH), 3088 (C=H, aromatic), 2951 (C=H, aliphatic), 2215, 2176 (CN), 1707 (C=O, amide), 1626 (C=C, aliphatic), 1606 (C=C, aromatic).

\[ ^1H \text{NMR (DMSO-d}_6, 300 \text{MHz, ppm): } \delta/\text{ppm} = 1.27 (3H, CH₃), 3.03 (2H, CH₂), 1.64 (s, 2H, NH₂), 7.52 (m, 5H, Ar-H), 7.34 (t, 1H, Ar-H), 6.80 (s, 1H, NH), 6.14 (d, 1H, Ar-H), 2.83 (s, 2H, CH₂), 1.79 (t, 1H, Ar-H), 1.06 (s, 3H, CH₃). \]

Yield: 60%, m.p.: 272 °C (KBr, / cm -3): 3446, 3309, 3242, 3212 (NH₂, 2NH), 3088 (C=H, aromatic), 2951 (C=H, aliphatic), 2215, 2176 (CN), 1707 (C=O, amide), 1626 (C=C, aliphatic), 1606 (C=C, aromatic).

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A blend of 2-indolone derivative II (0.203 g, 1.0 mmol), chloro compound "such as Chloroacetonitrile" (0.063 mL, 1.0 mmol), and catalytic droplets of base "like piperidine" in alcohol "such as ethanol" (5.0 mL) was boiled for 8 hours. Red precipitate was segregated through reflux. The resultant solid was separated by filtration and purification from alcohol "such as EtOH" as red needles. Yield: 42%, m.p.: over 360 °C, IR (KBr, υ/cm⁻¹): 3413, 3390, 3346, 3295 (NH), 3092, 2923 (CH, aliphatic), 1712 (C=O, amide), 1666 (C≡N). 1616 (C=C); MS(EI) (C₁₁H₁₅N₃O, M.wt = 242); m/z(%) = 242 (M⁺, 2.43 %), 262 (2.81%), 185 (30.38%), 159 (21.5%), 157 (21.96%), 145 (2.52%), 129 (59.44%), 103 (77.79%), 77 (25.47%), 52 (55.89%), 43 (100%, CHNO).

2.9. Methyl-2-(5-oxo-2-(2-oxoindolin-3-ylidene)hydrazinyl)-1,5-di-hydro-4H-imidazol-4-ylidene)acetate (X).

To a mixture of 2-indolone derivative II (0.203 g, 1.0 mmol) and a few droplets of base catalyst "such as piperidine" in alcohol "such as ethanol" as solvent (5.0 mL), dimethyl acetylene dicarboxylate (0.122 mL, 1.0 mmol) was included. The time of reaction was finished by refluxing for four hours. The resultant pale brown crude was designed on hot the crude precipitate was separated by filtration and purified via recrystallization from EtOH. Yield: 45 %, m.p.: over 300 °C, IR (KBr, υ/cm⁻¹): 3351, 3309, 3193 (3NH), 2926 (CH, aliph.), 1731 (C=O, ester), 1666 (C=O, amide), 1612 (C≡N); MS(EI) (C₁₃H₁₅N₃O, M.wt = 313); m/z(%) = 313 (M⁺, 223 %), 282 (2.25%), 254 (2.63%), 199 (2.34%), 186 (28.5%), 156 (20.04%), 129 (82.1%), 103 (100%, CH₃N), 76 (57.45%), 52 (22.46%). Math. Calcd for C₁₃H₁₅N₃O: C: 51.07, H: 3.37, N: 21.27. Found: C: 50.81, H: 3.07, N: 20.93.

2.10. 3-(2-(4,6-Diaminopyrimidin-2-yl)hydrazono)indolin-2-one (XI).

A blend of 2-indolone derivative II (0.203 g, 1.0 mmol), active methylene compound "such as malononitrile" (0.066 g, 1.0 mmol), and 3 drops of piperidine in dimethyl formamide (5.0 mL) was boiled for 6 hours. The built dark crude was obtained by filtration and then cleaned by washing with hot dimethyl formamide. The resultant dark needle was pure enough for making analysis. Yield 77 %, m.p.: over 300 °C, IR (KBr, υ/cm⁻¹): 3395, 3351, 3302, 3201 (2NH₃, 2NH), 1720 (C=O, amide), 1644 (C≡N), 1616 (C≡N); MS(EI) (C₁₃H₁₅N₃O₂, M.wt = 269); m/z(%) = 269 (M⁺, 23.14 %), 230 (11.38%), 188 (17.14%), 173 (18.17%), 157 (74.55%), 129 (100%, CH₃N₃), 103 (47.51%), 77 (28.38%), 51 (18.88%). Math. Calcd for C₁₃H₁₅N₃O₂: C: 53.53, H: 4.12, N: 36.41. Found: C: 52.77, H: 3.78, N: 34.96.

2.11. 4-Amino-2-(2-oxoindolin-3-ylidene)hydrazinyl)pyrimidine-5-carbonitrile (XII).

Oxindole derivative II (0.203 g, 1.0 mmol) was dissolved in alcohol "such as EtOH" (10.0 mL). Ethylenemethylene malononitrile (0.122 g, 1 mmol) was included in the blend. The blend was boiled under heating for four hours. During reflux, a reddish-brown precipitate was formed then isolated by filtration and purified via recrystallization from alcohol "such as ethanol". Yield: 50 %, m.p.: over 300 °C, IR (KBr, υ/cm⁻¹): 3368, 3320 (2NH₃), 3120:3193 (NH), 2217 (CN), 1666 (C≡N), 1612 (C≡N), 1600 (C≡C); MS(EI) (C₁₃H₁₅N₄O, M.wt: 279); m/z(%) = 279 (M⁺, 26.60 %), 252 (2.82%), 250 (22.94%), 186 (114.7%), 185 (62.65%), 129 (62.95%), 102 (100%, CH₃N), 76 (62.26%), 52 (39.61%).

2.12. Antimicrobial assay

The antimicrobial activity of products under research was estimated against Gram-positive bacteria "such as Bacillus subtilis and Staphylococcus aureus" and Gram-negative bacteria "like Escherichia coli and Pseudomonas aeruginosa". Drug chloramphenicol was applied as a controller standard for in vitro antibacterial activity. Antimicrobial activity of recently-manufactured samples, as opposed to multi-pathological strains, was indicated as inhibition diameter zones in millimeters (mm) as follows in Table 1.

Table 1: Examined compounds’ in vitro antibacterial effects.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Gram (+)ve bacteria</th>
<th>Gram (-)ve bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Staphylococcus aureus</td>
<td>Bacillus subtilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Activity index</td>
<td>% Activity index</td>
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<tr>
<td></td>
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<td>LZ ± S.D.*</td>
<td>LZ ± S.D.*</td>
</tr>
<tr>
<td>1</td>
<td>I</td>
<td>111.1</td>
<td>51.8</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
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<td>3</td>
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<td>111.1</td>
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<td>VII</td>
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<td>12</td>
<td>XII</td>
<td>111.1</td>
<td>51.8</td>
</tr>
<tr>
<td>13</td>
<td>Control</td>
<td>111.1</td>
<td>51.8</td>
</tr>
</tbody>
</table>

* LZ: Inhibition diameter regions expressed in millimeters (mm); S.D: Standard deviation. αNA: antimicrobial inactivity sensed

The studied chemicals presented differences in their antibacterial activities (Table). Samples II, V, and VI were active against all studied bacteria (Table; entries 2, 5, and 6, respectively). Compounds I, IV, XI, and XII were not active against Staphylococcus aureus (Table; entries 1, 4, 11, and 12, respectively) while samples I and XII were inactive against Pseudomonas aeruginosa (Table; entries 1 and 12, respectively). Compounds II, VII, VIII, IX, and X were active against all tested pathogens except Escherichia coli (Table; entries 3 and 7-10, respectively). Compound VII gave the highest activity against Staphylococcus aureus and Pseudomonas aeruginosa bacteria in this test (Table; entry 7). In addition, compound II gave the highest activity against Bacillus subtilis and Escherichia coli (Table; entry 2).
2.1. Antimicrobial activity assay.

According to techniques described in the literature, the antibacterial effect of the chemicals under study was detected via a specific bacteria [Russell et al, 1977] [64]. Also, the common medication chloramphenicol had its antibacterial properties tested under the same parameters.

3. Results and discussion

That is generally known pyridine-3,5-dicarbonitriles could be assembled through the condensation of carbonyl derivatives with active methylene compounds and aliphatic thiols. In this work, ethyl thiol was used along with isatin as a carbonyl compound and malononitrile as an active methylene-containing reactant to have access to the product (I). In such a reaction, various reaction conditions, including the utilization of assorted bases [49-54], acids [55], amino acids [56], and catalytic ionic salts were explored [57-61]. However, many of the above-mentioned conditions possess considerable disadvantages, such as the creation of unavoidable side products, low yields, difficult reaction conditions, prolonged reaction times, time-consuming workup, and the employment of costly and naturally harmful catalysts and solvents. As a result, we have tried to overcome these flaws and find effective procedures for these points using less toxic and less expensive pathways.

Several procedures have been adopted to obtain the final product I. The most appropriate and high-yield pathway was a one-pot four-component procedure, including the stirring of an ethanolic solution of one mole of isatin, two moles of malononitrile, and one mole of ethyl mercaptan in a basic catalytic amount of diethyl amine at normal temp. (Scheme 1). In comparison to other methods, this one not only utilized available catalysts and solvents but also the reaction was accomplished in a shorter time with a cleaner profile.

Scheme 1, Production of compounds I and II.

The reaction possibly took place via the following mechanism [50]:
The configuration of compound I was established from their chemical analysis and spectroscopy information. The IR chart of start I indicated sturdy absorption bands for the primary amine group at $v = 3309$ and $3242$, for the secondary amino groups at $v = 3446$ and $3212$ cm$^{-1}$, according to the cyano group at $v = 2215$ and $2176$ cm$^{-1}$, and because of the (C=O) carbonyl group of an amide at $v = 1707$ cm$^{-1}$. Furthermore, the $^1$H NMR (DMSO-$d_6$) spectrum of the product I presented a singlet signal at $\delta = 10.51$ ppm appointed to (NH) proton of isatin, singlet signals around $\delta = 9.46$ ppm of the (dihydropyridine-NH) one proton, signals around $\delta = 6.84-7.28$ ppm assigned to the four protons of isatin aromatic ring, a singlet signal around $\delta = 6.16$ ppm of (NH$_2$) two protons, a quartet signal around $\delta = 3.03$ ppm for the two protons of (CH$_2$) group, and a triplet signal around 1.27 ppm for the 3 protons of the terminal (CH$_3$) group. Also, the mass spectroscopy spectrum presented the peak of molecular ion at $m/z = 327$ (M$^+4$), which corresponds with the chemical structure that has been proposed. [62]. Compound I reacted with different substances such as carbon disulfide, triethyl orthoformate, $N$, $N$-dimethylformamide dimethyl acetal, and maleic anhydride to afford several valuable heterocyclic derivatives (Scheme 3).
(3',5'-Dicyano-2'-{ethylthio}sio[1,8]naphtha[3,4'-pyridin]-6'-yl]carbamido-dithioic acid III was produced by reacting compound I with carbon disulfide in pyridine under reflux conditions for 12 hours (Scheme 3). The construction of compound III was examined by chemical investigation and spectroscopy results. The IR chart spectrum of sample III recorded the absence of the amino group (NH₂) absorption band and the presence of a new sturdy absorption band at 1214 cm⁻¹ equivalent to (C=O) group. Furthermore, The predicted chemical formula was confirmed by the mass spectrum, which revealed the peak of molecular ion at m/z = 399.

To further study the synthetic potential of derivative I, its mixture with triethyl orthofomate was observed. Thus, refluxing compound I with triethyl orthofomate in anhydride or ethanol solution gave compound IV (Scheme 3). The construction of the last compound was asserted given basic chemical analysis and spectroscopy information. The IR spectrum of chemical IV presented the absence of the amino group (NH₂) absorption band. The ²H NMR (DMSO-d₆) results supplied still more support for compound IV's proposed structure, which discovered three new peaks at δ 1.32 ppm according to the three protons of (CH₂) groups, a quartet signal around δ 3.38 ppm for the two protons of (CH₂) group, and at δ 4.33 ppm confirming the assert of (CH) proton.

Additionally, the reaction of sample I with maleic anhydride in an acid "such as CH₂COOH" afforded the maleic acid derivative V. Spectroscopic and analytical information were used to verify the compound's V configuration. Thus, IR spectra of compound V exhibited a broad absorption band at 3000-3600 cm⁻¹ corresponding to (OH) group. Another piece of suggestion for the proposed construction of compound V was gained from the ¹H NMR (DMSO-d₆) chart, which revealed three singlet resonances at δ 5.70, 5.42, and 11.61 ppm, approving the existence of 2(CH) and (OH) groups, respectively.

Moreover, N, N-dimethylformamidomethyl acetal in refluxing dioxane (Scheme 3). The construction of product VI was verified founded on its investigative and spectroscopic information, as the infrared spectrum presented an absorption band at 1627 cm⁻¹ equivalent to (C=O) groups. Further confirmation for the proposed formation of the product V was gained from the ¹H NMR (DMSO-d₆) data, which revealed two singlet resonances at δ 3.29 ppm integrating for six protons of two terminal methyl groups and at δ 8.82 ppm confirming the existence of (CH) proton.

The synthetic scheme for developing a pyrazole ring converged with the pyridine moiety of compound I was based on its reaction with hydrazine hydrate in ethanol under reflux conditions followed by a subsequent cyclization reaction of the product to give spiro[dipyrazolo]pyridine derivative VII (Scheme 3). The product's VII IR spectra revealed the absence of the two cyano groups (CN) absorption bands. Furthermore, the mass spectra revealed a molecular ion peak at m/z = 308 which corresponds to the calculated molecular composition.

An additional synthetic method for the manufacturing of ethyl-5'-amino-3'-cyano-2'-{ethylthio}-2,7'-dioxo-7'-8'-dihydro-1'H-spiro[indoline-3,4'-[1,8]naphtha-1'-pyridin]-6'-carboxylate (VIII) was completed through refluxing compound I and diethyl malonate in glacial acetic acid for 12 hours (Scheme 3). The compound's VIII IR spectra displayed the absence of the cyano group (CN) absorption band at 2176 cm⁻¹ and the appearance of a strong absorption band for ester (C=O) at δ 1708 cm⁻¹. A strong verification for the suggested structure of product VIII was won from the ¹H NMR (DMSO-d₆) records, which indicated the triplet-quartet design of the ethoxy group at δ 1.29 and 1.56 ppm substantiates the presence of (CH₂) and (CH₃) groups, respectively.

Moreover, building up an imidazole ring was available through the alkylation reaction of compound (II) with chloro reagent "such as chloroacetanitrite", followed by a subsequent cyclization reaction of the alkylated produce in a basic condition. The alkylation reaction occurred in ethanol having drops of piperidine to have 5-amino-4H-imidazole derivative IX (Scheme 4). The construction of compound IX was proved from spectroscopic figures such as IR, which exhibited the presence of a new absorption band at δ 2923 cm⁻¹ for aliphatic (CH). Also, The molecular ion peak at m/z = 242 which corresponds to the molecular composition C₁₂H₁₄N₄O was identified by the mass spectroscopy of compound IX.

Scheme 3. Reactions of Compound I
Furthermore, a novel imidazole ring connected to oxindole derivative \( \text{II} \) was available through the reaction of dimethyl acetylene dicarboxylate with 2-indolone derivative \( \text{II} \) in ethanol under reflux conditions to give methyl-2-(5-oxo-2-(2-oxoindolin-3-ylidene)hydrazinyl)-1,5-dihydro-4H-imidazol-4-ylideneacetate (\( \text{X} \)) (Scheme 4). The configuration of compound \( \text{X} \) was proved via spectral data. IR presented no absorption bands for the amino group (NH\(_2\)) but exposed the appearance of two new absorption bands at \( \nu \) 2962 cm\(^{-1}\) for aliphatic (CH) and at \( \nu \) 1731 cm\(^{-1}\) for ester (C=O). The mass spectral data for compound \( \text{X} \) indicated the molecular ion peak at \( m/z = 313 \) according to the molecular installation \( C_{14}H_{11}N_5O_4 \).

Moreover, 4,6-diaminopyrimidine derivative \( \text{XI} \) could be manufactured via the condensation of 2-indolone derivative \( \text{II} \) with an active methylene compound "like malononitrile" in refluxing DMF containing droplets of piperidine (Scheme 4). The configuration of the construction of product \( \text{XI} \) was dependent on fundamental analysis and spectroscopic information. Thus, the IR chart discovered the appearance of a new absorption band for (NH\(_2\)) group. Additionally, the mass spectroscopy spectrum of product \( \text{XI} \) indicated the molecular ion peak at \( m/z = 269 \) analogous to the molecular installation \( C_{12}H_{11}N_7O \).

Finally, 4-amino-pyrimidine-5-carbonitrile derivative \( \text{XII} \) was obtained by boiling 2-indolone derivative \( \text{II} \) with ethoxy methylene malononitrile in ethanol (Scheme 4). Fundamental analysis and data from spectroscopy were used to confirm the manufacturing of product \( \text{XII} \). The IR spectrum of product \( \text{XII} \) revealed the existence of a different absorption band at \( \nu \) 2217 cm\(^{-1}\) for (CN) group. Finally, the mass spectral data for sample \( \text{XII} \) presented the molecular ion peak at \( m/z = 279 \), which matched the chemical formula that was suggested.

\[ \text{Scheme 4, Reactions of compound II.} \]

4. Conclusions

To prepare spiro[indoline-pyridine]dikarbonitrile derivative (\( \text{I} \)), we find that it is one of the best ways to obtain high efficiency and less reaction time with the use of available, cheap, and energy-saving chemicals, as the reaction takes place between isatin, active methylene "such as malononitrile", and mercaptan when there was diethylamine as a basic catalyst in cold alcohol. In addition to the ease of forming derivatives with different open chains and heterocyclic compounds by interacting with different reagents, for example, carbon disulfide, maleic anhydride, triethyl orthoformate, hydrazine hydrate, diethyl malonate, and dimethyl formamide dimethyl acetal.

Similarly, indolinylidene hydrazine derivative (\( \text{II} \)) is also highly active when interacting with different reagents to form heterocyclic compounds. All synthesized compounds were tried in vitro opposite four types of bacteria to study their antibacterial activity.

Author Contribution

All authors have contributed equally.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
References


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