SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF NOVEL N-PHENYLPROPYL-3-SUBSTITUTED INDOLINE-2-ONE DERIVATIVES

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INTRODUCTION

Infectious diseases are the main cause of mortality in the world and rapid increase of antimicrobial resistance among pathogenic strains (bacterial and fungal) is becoming a serious public health problem because microbes replicate very rapidly and get mutated which help the microbes to survive in the presence of an antimicrobial drug, these will quickly become predominant throughout the microbial population. Free radicals play important roles in many physiological and pathological conditions [1]. In general, the generation and scavenging of oxygen free radicals is balanced and any imbalance or excessive amounts of active radicals may contribute to disease development. It has been found that free radical reactions can produce deleterious modifications in membranes, proteins, enzymes, and DNA [2], increasing the risk of diseases such as cancer [3], Alzheimer’s [4], Parkinson’s [5], angiocardiopathy [6], arthritis [7], asthma [8], diabetes [9] and degenerative eye disease [10]. Owing to increased microbial resistance, and various disorders caused by free radicals, and to develop more potent small molecules with enhanced antimicrobial and antioxidant properties, a series of N-phenylpropyl-3-substituted indoline-2-ones are synthesized by Knoevenagel condensation.

Indole-1H-2, 3-dione or Indoline-2, 3-dione commonly known as Isatin is a well-known natural product found in plants of genus Isatis and in couropita guiananicae aubl [11]. It has also been isolated as a metabolic derivative of adrenaline in humans [12]. The biological and pharmacological properties of isatin and its derivatives have led to extensive use of these compounds as key intermediates in organic synthesis [13]. It is a core constituent of many alkaloids [14], drugs [15], as well as dyes [16]. The literature survey reveals that various derivatives of isatin possess diverse activities such as antibacterial [17], antifungal [18], antiviral [19], HIV [20], antimiocobacterial [21], anticancer [22], anti-inflammatory [23], anticonvulsant activities [24] and acts as a potent antagonist on atrial natriuretic peptide receptors in vitro [25].

It possesses an indole nucleus with two chemically distinct cyclic carbonyl groups keto and lactam. The structure of isatin has provoked tremendous interest in chemists to unfold the interesting aspects of organic reactions and mechanism. Isatins mainly react at three different sites, namely aromatic substitution at C-5, N-allylation and carbonyl reaction at C-3. The most fascinating application of isatins in organic synthesis is undoubtedly due to the highly reactive C-3-carbonyl group that is a prochiral center as well. At the C-3 carbonyl group of isatin, nucleophilic additions or spiro annulation takes place which transforms it into 2-oxindole derivative. 2-oxindoles especially those which are spiro fused to the other cyclic framework, have drawn tremendous interest of researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide because they occur in many natural products such as spirotryprostatins, horstilane, gelsemine, gelseverine, rhyynchophylline and elacoline etc.

So as a part of our research in the area of heterocyclic compounds containing indole moiety, the main focus was on N-allylation and nucleophilic addition at C-3 of isatin with various aromatic and heterocyclic acetonaphone analogues. Herein we report the synthesis of some new N-phenylpropyl-3-substituted indoline-2-one derivatives, their characterization and antimicrobial and antioxidant activities.

The reaction of 5-substituted isatin (1) with 3-chloro propyl benzene in the presence of K2CO3 and N,N-dimethyl formamide gave 1-(3-phenylpropyl) indoline-2,3-dione (2a) and 5-flouro-1-(3-phenylpropyl) indoline-2,3-dione (2b). It was found that the K2CO3-DMF system is an effective promotion for this reaction [26]. Use of K2CO3 as a catalyst has inherent advantages including operational simplicity, low cost and suitability in industrial application. Reaction of 2(a-b) with acetonaphene derivatives viz: acetyl naphthalene 2-acetyl thiope, 3-acetylpyridine, 4-flouro acetonaphene, 4-methoxy acetonaphene, 4-benzonitrile gave 3-hydroxy-3-(2-oxoethylidene)-1-(3-phenylpropyl) indoline-2-one derivatives (3a-I). The tertiary alcohol can easily be dehydrated under acidic conditions to yield 3-(2-oxoethylidene)-1-(3-phenylpropyl) indolin-2-one derivatives (4a-I).
MATERIALS AND METHODS

Materials
All the chemicals and solvents were of laboratory reagent grade and used as received from Sigma Aldrich and SD fine. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC using silica gel-coated aluminium plates (Merck) and spots were visualized by exposing the dry plates to iodine vapors. The IR (KBr) spectra were recorded on a Perkin-Elmer spectrometer on FT-IR spectrometer. The 1H NMR (DMSO-d6) spectra were recorded on a Bruker (400 MHz) and the chemical shifts were expressed in ppm (δ scale) downfield from TMS. Mass spectral data were recorded by electron impact method on JEDL-GCMATE II GC-MS mass spectrometer. Elemental analysis was carried out using Flash EA 1112 series elemental analyzer. All the compounds gave C, H and N analysis within ±0.5% of the theoretical values.

General procedure for the synthesis of 5-substituted-1-(3-phenylpropyl)indoline-2,3-dione (2a-b)
To a stirred solution of indoline-2,3-dione/5-flouro indoline-2,3-dione (1-(3-phenylpropyl)indoline-2,3-dione (2a)

3-2-(4-fluorophenyl)-2-oxoethyl-1-(3-phenylpropyl)indolin-2-one (3d)
IR (KBr) (λmax): 1640 (NHCO), 1720 (C=O), 3523 (OH). 1H NMR (400 MHz, CDCl3) δ (ppm): 2.62 (t, 2H, CH2), 1.9 (m, 2H, CH2), 3.8 (t, 2H, N-CH2), 6.8-7.15 (m, 13H, Ar-H), 3.5 (s, 2H, CH2), 4.18 (s, 1H, OH). LCMS: m/z = 403 [M]+. Analysis: Cacld for C25H23N05: (403): C, 74.43; H, 5.00; N, 3.45

3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-(3-phenylpropyl)indolin-2-one (3e)
IR (KBr) (λmax): 1630 (NHCO), 1710 (C=O), 3500 (OH). 1H NMR (400 MHz, CDCl3) δ (ppm): 2.62 (t, 2H, CH2), 1.9 (m, 2H, CH2), 3.8 (t, 2H, N-CH2), 6.9-7.8 (m, 13H, Ar-H), 3.3 (s, 2H, CH2), 4.24 (s, 1H, OH). LCMS: m/z = 415 [M]+. Analysis: Cacld for C26H25NO6: (415): C, 75.16; H, 6.03; N, 3.37. Found: C, 75.16; H, 6.05; N, 3.44

4-(2-hydroxy-2-oxo-3-(naphthalen-2-yl)acetyl)-1-(3-phenylpropyl)indolin-3-yl)acetil benzonitrile (3f)
IR (KBr) (λmax): 1645 (NHCO), 1720 (C=O), 3523 (OH). 1H NMR (400 MHz, CDCl3) δ (ppm): 2.62 (t, 2H, CH2), 1.9 (m, 2H, CH2), 3.8 (t, 2H, N-CH2), 6.5-8.11 (m, 13H, Ar-H), 3.78 (s, 2H, CH2), 4.20 (s, 1H, OH). LCMS: m/z = 419 [M]+. Analysis: Cacld for C26H25N05: (419): C, 76.68; H, 5.40; N, 6.82; O, 11.69. Found: C, 76.70; H, 5.32; N, 6.84; O, 11.67.
General procedure for the synthesis of 3-(2-oxyethyldiene)-1-(3-phenylpropyl)indolin-2-one derivatives 4(a-l)

To a stirred solution of 3(a-l) (0.91 mmol) in ethanol (15 ml) was added concentrated HCl (5 ml) and the reaction mixture was refluxed for 6 h. The progress of the reaction was monitored on TLC using several solvent systems of different polarity. Reaction mixture was filtered, dried and purified by recrystallization from ethanol to obtain the desired product as bright red needles.

3-(2-naphthalen-2-yl)-2-oxoethyldiene)-1-(3-phenylpropyl)indolin-2-one derivatives 4(a-l)

IR (KBr) \(\lambda_{\text{max}}\) in cm\(^{-1}\): 1660 (N=O), 1706 (C=O), 3054 (Ar C-H stretch). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 2.06 (m, 2H, CH\(_2\)), 2.75 (t, 2H, CH\(_2\)), 3.82 (t, 2H, N-CH\(_2\)), 6.72 (s, 1H, CH), 7.03-8.85 (m, 13H, Ar-H). LCMS: \(m/z = 386\) [M]. Analysis: Calcd for C\(_{25}\)H\(_{26}\)FNO\(_2\): 386; C, 78.57; H, 5.83; N, 3.69.

3-(2-oxy-2-thiophen-2-yl)-1-(3-phenylpropyl)indolin-2-one (4d)

IR (KBr) \(\lambda_{\text{max}}\) in cm\(^{-1}\): 1649 (N=O), 1711 (C=O), 3080 (Ar C-H stretch) 650 (C=C). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 2.06 (m, 2H, CH\(_2\)), 2.75 (t, 2H, CH\(_2\)), 3.82 (t, 2H, N-CH\(_2\)), 6.71 (s, 1H, CH), 7.0-8.5 (m, 13H, Ar-H). LCMS: \(m/z = 368\) [M]. Analysis: Calcd for C\(_{25}\)H\(_{26}\)FN: 368; C, 75.17; H, 5.34; N, 3.37.

3-(2-(2-oxo-1-(3-phenylpropyl)indolin-3-yldiene)acetyl)benzonitrile (4f)

IR (KBr) \(\lambda_{\text{max}}\) in cm\(^{-1}\): 1598 (C=C stretch). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 2.09 (m, 2H, CH\(_2\)), 2.75 (t, 2H, CH\(_2\)), 3.82 (t, 2H, N-CH\(_2\)), 6.72 (s, 1H, CH), 7.27-8.1 (m, 13H, Ar-H). LCMS: \(m/z = 397\) [M]. Analysis: Calcd for C\(_{26}\)H\(_{26}\)FNO\(_2\): 397; C, 77.90; H, 5.23; N, 3.63. Found: C, 77.92; H, 5.25; N, 3.69.

Antimicrobial activity

The antibacterial activities of compounds 4(a-l), were carried out using the Cup plate diffusion method [25]. This method depends on the diffusion of the antibiotic from a cavity through the solidified agar layer in a petri dish to an extent such that the growth of the added microorganism is prevented in a circular zone around the cavity containing a solution of the antibiotic. For antibacterial activity, bacterial species used are two Gram negative species, Escherichia coli (ATCC 9637), Salmonella typhi (ATCC 6539) and two Gram positive species, Bacillus subtilis (ATCC 6633), Staphylococcus aureus (ATCC 29277). Two fungal strains Aspergillus niger (ATCC 16509), Aspergillus fumigatus (ATCC 16406) were used for antifungal activity. Solution of each compound at a concentration of 100µg/ml in DMSO was prepared and the inhibition zone diameter in millimeter was used as the criterion for measuring the microbial activity after 24 h for bacteria and 72 h for fungi. Ciprofloxacin is used as bacterial standards and Amphotericin B is used as fungal standards for references to evaluate the efficacy of the tested compounds under the same conditions. DMSO used as control and solvent to prepare compound solutions. Measurements of results are shown in table 2.
Table 1: Physical Properties of 3-(2-oxoethylidene)-1-(3-phenylpropyl)indolin-2-one derivatives 4(a-l)

| Comp. No | R   | R₁    | M. For. | M. Wt. | % Yield | M. P. °C |
|----------|-----|-------|---------|--------|---------|----------|
| 4a       | H   |       | C₂₉H₂₃NO₂ | 417    | 67%     | 149-51   |
| 4b       | H   |       | C₂₉H₂₁NO₃S | 373    | 60%     | 172-73   |
| 4c       | H   |       | C₂₉H₂₃N₂O₂ | 368    | 63%     | 160-62   |
| 4d       | H   |       | C₂₉H₂₀FNO₃ | 385    | 67%     | 173-75   |
| 4e       | H   |       | C₂₉H₂₀NO₂ | 397    | 67%     | 146-47   |
| 4f       | H   |       | C₂₉H₂₀N₂O₂ | 392    | 58%     | 187-89   |
| 4g       | F   |       | C₂₉H₁₉FNO₂ | 436    | 83%     | 204-05   |
| 4h       | F   |       | C₂₉H₁₉FNO₃S | 391    | 62%     | 154-56   |
| 4i       | F   |       | C₂₉H₁₉F₃O₂ | 386    | 63%     | 210-12   |
| 4j       | F   |       | C₂₉H₁₉F₂NO₂ | 403    | 56%     | 194-95   |
| 4k       | F   |       | C₂₉H₁₉FNO₃ | 415    | 64%     | 140-42   |
| 4l       | F   |       | C₂₉H₁₉F₃O₂ | 410    | 61%     | 197-99   |

Comp. No.–Compound number. M. for.–Molecular formula, M. wt.–Molecular weight, M. pt.–Melting point.

Antioxidant activity assay

1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity (RSA)

The free radical scavenging activity (RSA) of all the compounds at concentrations of 25, 50, 75 and 100 μg/ml was carried out in the presence of a freshly prepared solution of stable free radical DPPH (0.04% w/v) following a Hatano’s method [26,27]. Ascorbic acid (AA) is used as standards. All the test analyses were performed on three replicates and the results are averaged. The results in percentage are expressed as the ratio of absorption decrease of DPPH in the presence of test compounds and absorption of DPPH in the absence of test compounds at λ 517 nm on ELICO SL 171 Mini Spec spectrophotometer. The percentage scavenging activity of the DPPH free radical was measured using the following equation:

\[
\% \text{ of DPPH RSA} = \frac{\text{Absorbance of Control} - \text{Absorbance of Sample}}{\text{Absorbance of Control}} \times 10
\]

RESULTS AND DISCUSSION

Chemistry

The Synthesis of title compounds was on account of the biological activity of indole and was carried out using a general, simple and straightforward pathway. 5-Substituted-1H-indole-2,3-dione was used as basic material for the synthesis of resultant derivatives. The treatment of 5-substituted 1H-indole-2,3-dione and (3-chloropropyl) benzene in N,N-Dimethyl formamidide with K₂CO₃ yielded substituted N-phenyl propyl isatins 2(a-b). These on condensation with acetophenone analogues resulted into compounds 3(a-l) which on dehydration yielded compounds 4(a-l) (Scheme 1).

The structure elucidation of the final products was carried out by IR, ¹H-NMR and Mass spectral data. IR peaks of the compound were recognized from 1700-1720 cm⁻¹ for C=O stretching, 1640-1660 cm⁻¹ for NHCO stretching, 3075-2850 cm⁻¹ for C-H aliphatic and aromatic correspondently, some stretching bands were also found for C=C at 517 mm. In ¹H-NMR spectra typical proton signals for C-H aliphatic and aromatic were observed between δ 2.36-3.68, and δ 8.06-6.38 respectively.

Scheme 1: Synthesis of compounds 3 (a-l) and 4 (a-l)
Antioxidant activity

In vitro method of scavenging of the stable DPPH radical is extensively used to evaluate the antioxidant activity in less time than other methods. DPPH is a stable free radical that can accept hydrogen radical or an electron and must thus be converted to a stable diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm. When this electron becomes paired off, the absorption decreases stoichiometrically with respect to the number of electrons or hydrogen atoms taken up. The DPPH antioxidant assay measures the hydrogen donating capacity of the molecules under study. When the free-radical DPPH is reduced by the sample, its colour changes from violet to yellow. Based on the structure activity relationship, it is indicated that the presence of substitution at the 5-position of isatin ring and on the side chain influences the antioxidant potency of the molecule. Halogen substitution at position 5 of isatin ring exhibited good antioxidant activity and aromatic substitution at R1 with electronegative atom either in the ring or as a substituent, such compounds were found to be less active. Highest activity is shown by a aromatic ring with methoxy as a substituent.

All the final synthesized derivatives were taken for preliminary screening to evaluate antibacterial activity by cup plate method, in the nutrient agar medium against two gram-positive and two gram-negative bacterial strains at concentration of 1000 μg/ml. The zone of inhibition (mm) of each derivative was ascertained and compared with Ciprofloxacin taken as standard drug for antibacterial activity.

Amphotericin B standard drug. The compounds 4c, 4d, 4e, 4f and 4j were found to be more potent. Results are given in fig. 1.

Table 2: Antibacterial activity, size of inhibition zone (mm) formed at concentration 1000 μg/ml of synthesized compounds 4a-1

| Compound | Antimicrobial activity | Antifungal activity |
|----------|------------------------|---------------------|
|          | Bacillus subtilis | Staphylococcus aureus | Escherichia coli | Salmonella typhi | Aspergillus fumigates | Aspergillus niger |
| 4a       | 32.47               | 31.5±23             | 31.8±13           | 34.5±23           | 30.8±38             | 25.6±24           |
| 4b       | 31.6±27             | 32.9±12             | 30.6±27           | 33±27             | 31±471              | 22±34             |
| 4c       | 22.47               | 28.6±27             | 28.6±27           | 28.7±32           | 32.5±24             | 30.7±32           |
| 4d       | 20.6±54             | 22.8±13             | 20.3±27           | 33.4±4.9          | 29.3±27             |                  |
| 4e       | 34.6±27             | 32.5±24             | 33.6±272          | 35.5±23           | 34.9±42             | 27.6±44           |
| 4f       | 32.47               | 28.2±16             | 25.2±15           | 25.7±30           | 32.3±27             | 28.6±27           |
| 4g       | 24.6±27             | 22.8±13             | 20.6±27           |                  | 22.5±235            | 19.6±25           |
| 4h       | 21.3±27             | 21.7±32             |                  | 21.3±27           |                  | 22.3±27           |
| 4i       | 19.4±7              | 21.3±27             |                  |                  | 29.5±235            | 19.6±25           |
| 4j       | 18.3±27             | 19.5±23             |                  |                  | 33.3±38             | 21.5±24           |
| 4k       | 19.3±47             | 21.6±25             | 15.5±23           |                  | 31.6±25             | 27±47             |
| 4l       | 17.6±28             | 24.5±24             | 19.8±36           | 17±09             | 26.7±32             | 24.7±32           |

Antifungal activity

A series of twelve compounds novel 5-substituted N-phenylpropyl-3-substituted indoline-2-one derivatives 4a-1 was prepared and characterized by TLC, M. P, spectral and analytical data. All the synthesized compounds were evaluated for in vitro antimicrobial activity and antioxidant activity against different bacterial and fungal strains. Compounds 4a, 4b, 4e and 4f were highly active against gram positive and gram negative bacteria, 4e is found to be more potent against all the bacterial strains. Compounds 4c, 4d, 4i and 4j exhibited good antioxidant activity. All the experiments were found in triplicate and the mean were calculated.

Fig 1: DPPH radical scavenging activity of synthesized compounds at Conc. 25, 50, 75, 100 μg/ml. The graph represents the mean±SEM, (n=3), P<0.01-significant compared to the standard group

Table 2: Antibacterial activity, size of inhibition zone (mm) formed at concentration 1000 μg/ml of synthesized compounds 4a-1

CONCLUSION

A series of twelve compounds novel 5-substituted N-phenylpropyl-3-substituted indoline-2-one derivatives 4a-1 was prepared and characterized by TLC, M. P, spectral and analytical data. All the synthesized compounds were evaluated for in vitro antimicrobial activity and antioxidant activity against different bacterial and fungal strains. Compounds 4a, 4b, 4e and 4f were highly active against gram positive and gram negative bacteria, 4e is found to be more potent against all the bacterial strains. Compounds 4c, 4d, 4e, 4f, 4i and 4j exhibited good antioxidant activity. All the experiments were found in triplicate and the mean were calculated.

AUTHORS CONTRIBUTION

All the authors have contributed in various degrees to commencement, design, acquisition of data, analysis, interpretation of data and writing present article.

No activity = --------, Note: Values are expressed in mean±SD (n=3)
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CONFLICT OF INTERESTS

Declared none

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