Synthesis, Characterization and biological evaluation of indole derivatives as potential antioxidant agents

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Abstract

The present study envisaged the development of novel antioxidant candidates using the indole scaffold. Several indole/5-substituted indole-3-acetyl derivatives were synthesized with different heterocyclic moieties and evaluated by two methods- DPPH assay and Reducing ability assay. The library substitution pattern included acetyl group substitution at 3rd as active position. This acetyl moiety was further linked with morpholine, benzimidazole and other heterocyclic rings. The result data showed that compound **3f** showed maximum potency in DPPH assay (IC_{50}=1.74±0.22 μM) and reducing ability assay (IC_{50}=29±5.21 μM). SAR studies concluded that presence of electron withdrawing group at the 5th position of indole is favorable for the activity and also showed the importance of imidazole substitution. It can be concluded that structural modification in indole derivatives makes them able to directly scavenge reactive oxygen and nitrogen species (ROS and RNS, respectively; collectively referred to as RONS) and suggest that the radical stabilization is affected by type of substitution on indole. Ultimately, it is concluded that the indole moiety is mandatory for the good antioxidant activity.

1. Introduction

Oxidative stress is observed when there is increased reactive oxygen species (ROS) formation, leading to disturbed cellular function. ROS shows its effect at cellular level i.e. lipid peroxidation, nucleic acid, and protein alterations. That leads to serious disease conditions such as atherosclerosis, ischemic heart diseases, diabetes etc. (Gupta *et al.*, 2014).

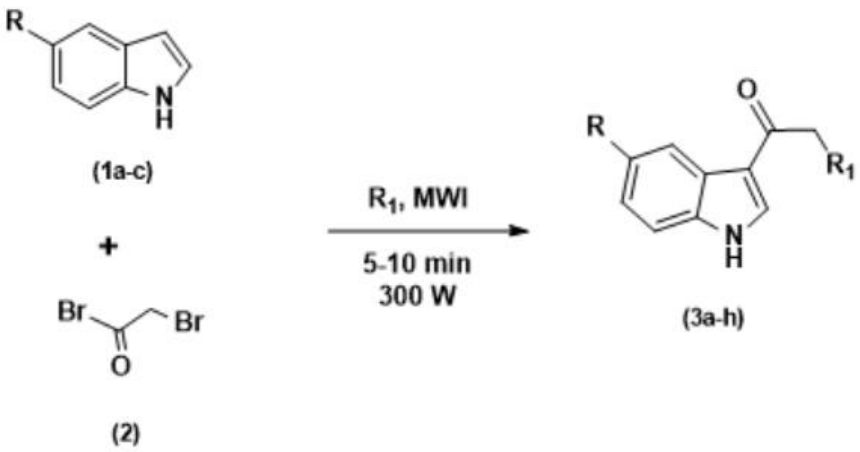
Nowadays, oxidative disease condition is controlled by antioxidant. An antioxidant has the ability to prevent or slow the oxidation of macromolecules. As the data provided by Gautam *et al.*, The word antioxidant comes from the Greek, meaning 'against oxidation'. In 1797, antioxidant activity by few compounds was first observed by

Berthollate and further in 1817 by Davy. In 1843, Deschamps used this technique. The antioxidant may act through various mechanisms i.e. by 1) Complexing with metal ions 2) By reduction of hydro peroxides 3) Inactivation of free radical and ultimately inhibit propagation of reactions.

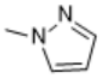
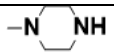
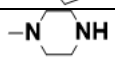
In drug discovery, specific and profound pharmacological activity is a demanding task. It becomes significant to determine and report the study the structure activity relationship of designed and synthesized molecules. Many hetero-cyclic compound derivatives are mentioned in the literature as important antioxidizing agents (Arora et al., 2014; Raghunath & Mathada, 2014). Indole or benzo[b]pyrrole is an organic molecule containing nitrogen as hetero atom and pharmacologically versatile moiety thus becomes a key target of researcher. In indole, the pyrrole ring is very electron rich, as compared to six membered ring and allows the electrophile to attach with five membered ring. The stable cation formation occurs at the C-3 as compared to C-2, making C-3 more prone to attack by electrophile. Strong acids induce the protonation of indole more easily at the C-3 position as compared to 1st position (Lalit *et al*., 2012).

A huge data on the antioxidizing properties of indole is mentioned in the literature of natural products and also medicinal (synthetic) compounds with diverse therapeutic activity.

Among this, indole moiety containing compounds melatonin and serotonin and their derivatives, as 5-hydroxytryptofol, 5-methoxytryptamine, and 5-methoxytryptofol, found to have special antioxidant properties (Yılmaz *et al*., 2012). Among the marketed antioxidants i.e. Quercetin, Resveratrol etc. have some minor to major side effects occurs such as flatulence, nausea, stomach pain, and/or diarrhea (Salehi *et al*., 2018). It becomes essential for the scientists to develop novel antioxidizing agents with negligible side-effects. Moreover, the C-3 substituted indole displayed profound antioxidant properties as reported by Silveira *et al*. and also antioxidant properties of indole derivatives, tryptamine, tryptophan encouraged us to design, synthesize and evaluate the antioxidant potency of C-3 substituted indole derivatives (Noland *et al*., 1966). In the present research, indole/5-substituted indole-3-actyl derivatives attached with different heterocylic moieties were developed (Ummadi *et al*., 2017) (Scheme 1) and evaluated by DPPH assay and Reducing ability assay to study ROS scavenging activity. It aims to highlight the oxidative stress, and its prevention by novel synthetic indole derivatives.



Scheme 1

Compound name	R	R_1	Compound name	R	R_1
3a	H		**3e**	$-OCH_3$	
3b	H		**3f**	$-NO_2$	
3c	$-OCH_3$		**3g**	$-NO_2$	
3d	$-OCH_3$		**3h**	$-NO_2$	

2. Materials and Methods

2.1 Chemistry

Pure CDH chemicals and reagents were used, purchased from Sigma Aldrich. Dried and commercial-grade solvents were used for synthesis and evaluation purposes. ^{1}H-NMR spectra were recorded on a Bruker advance Neo 500-MHz NMR spectrometer. Spectra were calculated in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. BIO-RAD FTS FT-IR spectrophotometer was used for IR spectra. Elemental analyses were performed using Perkin Elmer model 2400 CHN analyzer.

2.1.1 General procedure for the synthesis of substituted hetero cyclic linked indole derivatives (3a-3h)

For the synthesis of novel indole derivatives, multi-component technique was applied. The solution of 1H-indole/5-substituted indole (4.3 mmol) (1a-c) was prepared in ethanol (10 ml) in a conical flask. To this, bromoacetyl bromide (4.4 mmol) (2) was added dropwise at 0-5 °C. To this, anhydrous potassium carbonate (4.4 mmol) as a catalyst and appropriate nitrogen containing hetero cyclic compounds (R_1) (4.4 mmol) was added. The reaction mixture was irradiated under microwave for 5-10 min at 300 W. After completion of reaction confirmed by TLC, the products were filtered, evaporated to get the yellow-brownish viscous oily products (3a-3h).

1-(1*H*-indol-3-yl)-2-morpholinoethanone (3a): Yield: (85%); IR KBr (cm^{-1}): 3115 (C-H), 1726 (C=O), 1597 & 1420 (C=C), 1221 (C-C); ^{1}H-NMR: δ 2.56 (4H, t, 2xCH_2), 3.60 (4H, t, 2xCH_2), 3.70 (2H, s, CH_2), 7.17 (1H, t, Ar-H), 7.31 (1H, t, Ar-H), 7.49 (1H, d, Ar-H), 8.17 (1H, d, Ar-H), 8.47 (1H, s, pyrrole), 12.03 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 55.6, 66.4, 69.6, 111.1, 116.2, 119.8, 121.7, 121.8, 124.7, 133.4, 137.1, 195.3; Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.54; N, 11.40.

(1*H*-benzo[d]imidazol-1-yl)(1*H*-indol-3-yl)methanone (3b):Yield: (68%); IR KBr (cm^{-1}): 3020 (C-H), 1760 (C=O), 1588 & 1428 (C=C), 1212 (C-C); ^{1}H-NMR: δ 7.35 (1H, t, Ar-H), 7.33 (1H, t, Ar-H), 7.35 (1H, t, Ar-H), 7.45 (1H, d, Ar-H), 7.55 (1H, d, Ar-H), 8.08 (1H, s, Ar-H), 8.38 (1H, s, pyrrole), 8.40 (IH, d, Ar-H), 12.21 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 112.7, 113.9, 120.7, 121.7, 122.8, 121.1, 125.2, 125.7, 132.0, 143.2; Anal. Calcd. For $C_{44}H_{40}N_8O_5$: C, 73.55; H, 4.24; N, 16.08; Found: C, 73.49; H, 4.19; N, 16.06.

2-(1*H*-imidazol-1-yl)-1-(5-methoxy-1*H*-indol-3-yl) ethanone (3c): Yield: (82%); IR KBr (cm^{-1}): 3224 (C-H), 1725 (C=O), 1610 & 1455 (C=C), 1216 (C-O), 1215 (C-C); ^{1}H-NMR: δ 3.87 (3H, s, CH_3), 5.64 (2H, s, CH_2), 6.79 (1H, d, Ar-H), 6.96 (1H, d, Ar-H), 7.10 (1H, d, Ar-H), 7.28 (1H, d, Ar-H), 7.59 (1H, s, Ar-H), 7.62 (1H, s, Ar-H), 8.40 (1H, s, pyrrole), 12.04 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 55.8, 56.2, 104.8, 112.1, 112.2, 116.2, 119.1, 127.3, 128.1, 129.4, 133.4, 137.8, 154, 190.9; Anal. Calcd. For $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46; Found: C, 65.79; H, 5.08; N, 16.41.

1-(5-methoxy-1*H*-indol-3-yl)-2-(piperazin-1-yl) ethanone (3d): Yield: (79%); IR KBr (cm^{-1}): 3310 (C-H), 1745 (C=O), 1600 & 1485 (C=C), 1213 (C-C), 1167 (C-O); ^{1}H-NMR: δ 2.54 (4H, t, 2xCH_2), 2.58 (4H, t, 2xCH_2), 3.70 (2H, s, CH_2), 3.87 (3H, s, CH_3), 6.79 (1H, d, Ar-H), 7.28 (1H, d, Ar-H), 7.62(1H, s, Ar-H), 8.40 (1H, s, pyrrole), 12.15 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 45.9, 57.1, 55.8, 69.3, 104.8, 112.1, 112.2, 116.2, 127.3, 129.4, 133.4, 154, 195.3; Anal. Calcd. For $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37; Found: C, 65.88; H, 7.00; N, 15.30.

(5-methoxy-1*H*-indol-3-yl)(1*H*-pyrazol-1-yl)methanone (3e): Yield: (70%); IR KBr (cm^{-1}): 3035 (C-H), 1750 (C=O), 1591 & 1432 (C=C), 1220 (C-C), 1230 (C-O);^{1}H-NMR: δ 3.87 (3H, s, CH_3), 6.25 (1H, t, Ar-H), 6.79 (1H, d, Ar-H), 7.28 (1H, d, Ar-H), 7.51 (1H, d, Ar-H), 7.62 (1H, s, Ar-H), 7.77 (IH, d, Ar-H), 8.38 (1H, s, pyrrole), 12.09 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 55.71, 104.33, 108, 4, 113.5, 113.8, 129.1, 133, 136.1; Anal. Calcd. For $C_{44}H_{40}N_8O_5$: C, 69.46; H, 5.30; N, 14.73 Found: C, 69.40; H, 5.22; N, 14.68.

2-(1*H*-imidazol-1-yl)-1-(5-nitro-1*H*-indol-3-yl)ethanone (3f): Yield: (75%); IR KBr (cm^{-1}): 3185 (C-H), 1778 (C=O), 1599 & 1457 (C=C), 1482 (-NO2), 1193 (C-C); ^{1}H-NMR: δ 5.64 (2H, s, CH_2), 6.96 (1H, d, CH), 7.10 (1H, d, CH), 7.59 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.40 (1H, s, pyrrole), 9.00 (IH, s, Ar-H), 12.03 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 53.9, 112.3, 117.5, 119.1, 119.8, 129.7, 133.1, 138.1; Anal. Calcd. For $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.68; N, 20.73; Found: C, 57.75; H, 3.62; N, 20.6.

1-(5-nitro-1*H*-indol-3-yl)-2-(piperazin-1-yl)ethanone (3g): Yield: (80%); IR KBr (cm^{-1}): 3037 (C-H), 1769 (C=O), 1597 & 1438 (C=C), 1510 (-NO2), 1197 (C-C);^{1}H-NMR: δ 2.54 (4H, t, 2xCH_2), 2.58 (4H, t, 2xCH_2), 3.70 (2H, s, CH_2), 7.60 (1H, d, Ar-H), 7.95 (1H, d, Ar-H), 8.44 (1H, s, pyrrole), 9.01 (IH, s, Ar-H), 12.06 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 45.9, 57.1, 69.3, 112, 114, 116.2, 126.7, 127.2, 132.2, 133.4, 142.2, 195.3; Anal. Calcd. For $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43; Found: C, 58.28; H, 5.50; N, 19.37.

(5-nitro-1*H*-indol-3-yl)-2-(pyrrolidin-1-yl)ethanone (3h): Yield: (80%); IR KBr (cm^{-1}): 3036 (C-H), 1768 (C=O), 1598 & 1436 (C=C), 1511 (-NO2), 1196 (C-C);^{1}H-NMR: δ 1.71 (4H, quint, 2xCH_2), 2.39 (4H, t, 2xCH_2), 3.53 (2H, s, CH_2), 7.60 (1H, d, Ar-H), 7.95 (1H, d, Ar-H), 8.44 (1H, s, pyrrole), 9.01 (IH, s, Ar-H), 12.15 (1H, s, NH; exchangeable with D_2O); ^{13}C-NMR (DMSO-d_6) δ (ppm): 23.78, 53.90, 62.44, 112.2, 117.4, 119.8, 132.6; Anal. Calcd. For $C_{14}H_{16}N_4O_3$: C, 61.53; H, 5.53; N, 15.38; Found: C, 61.48; H, 5.47; N, 15.32.

2.2 Antioxidant evaluation

a. DPPH activity

According to the method provided by (Kedare & Singh, 2011) DPPH assay was used for the evaluation of the antioxidant activity of compound under study that involves the mechanism of hydrogen transfer and converting the purple DPPH to 1, 1-diphenyl-2- picryl hydrazine (DPPH-H), resulting in the bleaching of the colored solutions.

In DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging assay, ascorbic acid was used as standard. For DPPH solution preparation, 0.1 mM DPPH was dissolved in methanol and kept in dark for 2 h. After 2 h, 2 mL of this DPPH solution was taken, added 2 mL of different concentrations of test samples (2, 4, 6, 8 and 10 µg/mL), mixed thoroughly, incubated for 30 min at room temperature and checked absorbance at a wavelength of 517 nm. The assay was performed in triplicate and values were expressed as IC_{50}, SEM, SD (Table 1) (Kedare & Singh, 2011).

Table 1. Antioxidant activity of synthesized derivatives 3a to 3h measured by DPPH assay.

Sr. no	Molecule	IC_{50} (µM)	SEM	SD
1.	**3a**	3.27	0.56	0.112
2.	**3b**	2.10	0.176	0.088
3.	**3c**	2.00	0.205	0.162
4.	**3d**	2.69	0.215	0.107
5.	**3e**	2.56	0.219	0.109
6.	**3f**	**1.74**	0.221	0.11
7.	**3g**	1.98	0.238	0.119
8.	**3h**	2.03	0.231	0.13
9.	**Ascorbic Acid**	1.18	0.09	0.04

b. Reducing ability assay

The reducing power of the test compounds were determined according to the method previously described in literature. Different concentrations of the test compounds mixed with phosphate buffer (2.5 mL, 0.2M, pH 6.6) and potassium ferricyanide (2.5 mL, 1%). The mixture was incubated at 50^0C for 20 min. A portion (2.5 mL) of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged at 3000 rpm for 10 min. A portion of the solution (2.5 mL) was mixed with distilled water (2.5 mL) and $FeCl_3$ (0.5 mL, 0.1%) and the absorbance was measured at 700 nm. Ascorbic acid was taken as the standard. Phosphate buffer (pH 6.6) was used as blank solution. Activity is measured in terms of IC_{50}, SEM, SD (Liu & Ng, 2000; Jayanthi & Lalitha, 2011; Saundane *et al*., 2013) (Table 2).

Table 2. Antioxidant activity of synthesized derivatives 3a to 3h measured by Reducing ability assay.

Sr. no	Molecule	IC_{50} (µM)	SEM	SD
1.	**3a**	38	3.2	1.6
2.	**3b**	30	3.5	1.7
3.	**3c**	37	3.76	1.88
4.	**3d**	49.2	3.93	1.96
5.	**3e**	45	4.68	2.32
6.	**3f**	**29**	5.21	2.6
7.	**3g**	35	6.8	3.4
8.	**3h**	39	7.53	3.76
9.	**Ascorbic Acid**	**28**	2.42	1.12

4. Results and Discussion

The 3-substituted indole derivatives are accepted for their amazing therapeutic nature. Synthesis and evaluation of novel indole/5-substituted indole derivatives are reported. In the synthesis, Microwave irradiated multi-component technique was applied. The solution of 1H-indole/5-substituted indole was dissolved in the ethanol (10 ml) and bromoacetyl bromide and appropriate nitrogen containing heterocyclic compounds was added to this in the presence of suitable catalyst. Reaction was irradiated under microwave for 5–8 min at 300 W. After completion of reaction, yellow-brownish viscous oily products were collected. Novel synthesized derivatives were analyzed by ^{1}H and ^{13}C-NMR, IR spectra and CHN elemental analysis.

For the antioxidant evaluation, two reliable methods were employed- DPPH assay and Reducing ability assay. Different concentrations of test samples were used, measured the absorbance at wavelength of 517 nm in DPPH

assay and at 700 nm in Reducing ability assay. Ascorbic acid was used as standard in both. Among the all synthesized compounds, **3f** showed maximum potency in DPPH assay (IC_{50}=1.74±0.22 μM) and Reducing ability assay (IC_{50}=29±5.21 μM) as compared with standard.

Few points of structure-activity relationship

1. It can be seen that 5-nitro substituted indole derivatives showed better results as compared to unsubstituted and 5-methoxy substituted indole (Terzioglu *et al*.,2006; Archie *et al.*, 2017).

2. It is also seen that imidazole substitution at 3rd position of indole through acetyl linker is favorable for the antioxidant activity (Claudio *et al*., 2013; Ghorbani-Vaghei *et al*., 2018).

5. Conclusions

In this article, main motive of conducted study was to report synthesis and evaluation of antioxidant activity of synthesized novel 3-and 5-substituted indole derivatives. Synthesized compounds were evaluated by different analytical techniques-IR, NMR (^{1}H and ^{13}C) and elemental analysis. Characterization of synthesized derivatives was performed by different analytical methods. In IR spectroscopy, all compounds showed aromatic C-H stretching frequency at 3020-3310cm^{-1} and C=O absorption at 1725-1778 cm^{-1}. Whereas, C=C and C-C aromatic stretching was attributed to the strong absorption at 1420-1485 cm^{-1} and 1193-1221 cm^{-1} respectively. However, strong absorption near 1193-1221cm^{-1} and 1482-1512 cm^{-1} indicated the presence of C-O and NO_2 groups respectively.

Similarly, ^{1}H NMR (DMSO-d_6) spectra of novel morpholine derivatives display triplet at δ 2.56-3.60 ppm. Similarly, singlet at δ 3.87-5.64 ppm was observed in imidazole derivatives. Similar triplet delta values were seen for all piperazine derivatives, i.e. at 2.54 ppm. All the aromatic protons were found between δ 6.79-9.01 ppm as singlet, doublet and triplet protons. NH proton exchange with D_2O was also observed at 12.03-12.21 ppm. Protons of acetyl chain displays singlet at δ at 3.52-6.07ppm. In ^{13}C spectra, values near 23.7-69.3 ppm shows the presence of aliphatic carbons. Whereas, Carbon signals near 104.3-195.3 ppm displays aromatic carbons. Signals at 124.7-137.1 ppm indicated the presence of condensed carbons.

Varied activities of derivatives 3a to 3h were evaluated by DPPH assay and Reducing ability assay as antioxidant agents. It was observed that the 5-substituted indole along with the attachment of heterocyclic moieties improves the activity of compounds. The 5-substituted indole derivatives showed good results as compared with standard drugs.

The results showed that the among tested compounds few are effective scavengers of ROS and RNS, due to radical stabilization. Antioxidant activity is effected by the presence and position of substitution on indolic moiety.

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