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Synthesis and antioxidant properties of 2-(3-(hydroxyimino)methyl)-1*H*-indol-1-yl)acetamide derivatives

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Abstract

Background: The main aim of this work was to synthesise a novel *N*-(substituted phenyl)-2-(3-(hydroxyimino) methyl)-1*H*-indol-1-yl) acetamide derivatives and evaluate their antioxidant activity. These compounds were prepared by a condensation reaction between 1*H*-indole carbaldehyde oxime and 2-chloro acetamide derivatives. The newly synthesised compound structures were characterised by FT-IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. Furthermore, the above-mentioned compounds were screened for antioxidant activity by using ferric reducing antioxidant power (FRAP) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) methods.

Result: The antioxidant activity result reveals that most of the compounds were exhibiting considerable activity in both methods and the values are very closer to the standards. Among the synthesised compounds, compound 3j, 3a and 3k were shown remarkable activity at low concentration.

Conclusion: Compounds 3j, 3a and 3k were shown highest activity among the prepared analogues due to the attachment of halogens connected at the appropriate place in the phenyl ring. Hence, these substituted phenyl rings considered as a perfect side chain for the indole nucleus for the development of the new antioxidant agents.

Keywords: Indole, Acetamides, Antioxidant activity, FRAP and DPPH method

Background

The indole framework is one of the most widely distributed heterocyclic nuclei in both natural and synthetic compounds in which benzene and pyrrole are fused in 2, 3 positions [1]. The name indole is derived from the word indigo and oleum [2]. In 1986, Adolf von Bayer prepared indole from oxindole by a simple chemical reaction using zinc dust [3]. Indole and their derivatives are identified as a non-basic nitrogenous pharmacophore exhibiting a broad range of useful biological activities such as anti-inflammatory [4], anti-depressant [5], anti-fungal [6], anti-cancer [7], antihypertensive [8], antibiotic [9], anti-microbial agent [10], anti-viral [11], chelating agents [12], antimalarial [13], anti-HIV [14], anti-diabetic [15], anti-tuberculosis [16], insecticidal [17] and analgesic activity [18]. Because of the dynamic properties, they have been placed in a unique platform of nitrogenous heterocyclic compounds and enhance the interest of the scientist all over the world towards the preparation of the novel indole derivatives. Amide and their analogues are also found in many naturally occurring compounds and received much attention due to their high chemotherapeutic profile and easy way of developing a novel compound through the simple chemical reaction [19]. It has been prepared by the reaction of substituted acid with various aliphatic or aromatic amines. These derivatives are associated with a board spectrum of biological activities such as anti-fungal [20], insecticides [21], anticonvulsant [22], analgesic [23], anti-inflammatory [24], anti-tuberculosis [25] and anti-tumour [26] properties. As a result of a continuous search for the above-mentioned area, a series of novel

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N-(substituted phenyl)-2-(3-(hydroxyimino) methyl)-1*H*-indol-1-yl) acetamide derivatives were synthesised and evaluated their antioxidant activity by using ferric reducing antioxidant power (FRAP) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) method. Most of the compounds were shown admirable anti-oxidant activity due to the presence of indole and amide pharmacophore.

Method

Chemistry

The melting points of prepared analogues were recorded by open capillary tube on an Electrothermal 9100 melting point apparatus and are uncorrected. Functional groups present in the compounds were confirmed by using IR spectra (KBr) were recorded on a Shimadzu FT-IR 8400S spectrophotometer between the ranges from 4000 cm^{-1} to 400 cm^{-1}. ^{1}H-NMR spectra were determined on a Bruker NMR spectrometer (500 MHz). ^{13}C-NMR spectra were performed on a Bruker NMR spectrometer (100 MHz) and fully decoupled. Chemical shifts were reported in parts per million (ppm) using the deuterated solvent peak and tetramethylsilane as an internal standard. X-ray studies were determined by X Calibur diffractometer. The molecular weight of the compound was analysed by the Shimadzu mass spectrometer and element analysis was performed on Perkin Elmer 2400 CHN elemental analyser.

Preparation of 1*H*-indole-3-carbaldehyde [1]

An equimolar mixture of indole (0.001 mol), *N*, *N*-dimethyl formamide (0.001 mol) and 8.75 ml of phosphorous oxychloride was poured into the round bottom. The resulting solution was stirred magnetically for 5 h at 60 °C and transferred into 25 ml of 10% sodium carbonate solution. After complete addition, the mixture again stirred for 2 h at 100 °C. The separated product was washed with water, dried over anhydrous calcium chloride and recrystallised from hot ethanol [27].

Preparation of 1*H*-indole-3-carbaldehyde oxime [2]

1H-indole-3-carbaldehyde (1.66 mmol), sodium hydroxide (0.15 mol) and hydroxylamine hydrochloride (3.4 gm) were dissolved in 10 ml of ethanol and refluxed at 80 °C for 3 h. The progression of the reaction was monitored by TLC using the mixture of n-hexane and ethyl acetate as a mobile phase. After completion of the reaction, the separated product was washed with water and recrystallised from hot ethanol [28].

Preparation of N-(substituted phenyl)-2-(3-(hydroxyimino) methyl)-1*H*-indol-1-yl) acetamide derivatives: [3a–n]

A solution of 2-chloro acetamide derivatives (2 mmol) in 20 ml DMF, indole-3-carbaldehyde oxime [2] (2 mmol), potassium iodide (2 mmol) and potassium carbonate (2 mmol) were added and the resulting mixture was refluxed for 8 h at 80 °C. Then, the hot solution was poured into ice-cold water and the separated product was filtered, washed with water, dried over anhydrous calcium chloride and recrystallised from hot ethanol [29]. The scheme of the synthesis compounds were summarised in Fig. 1.

Anti-oxidant activity

Ferric reducing antioxidant power (FRAP) method

The FRAP is a quantitative assay for evaluating the antioxidant potency of newly synthesised compounds [30]. The FRAP reagent was prepared by mixing of 2.5 ml of 10 μM ferric TPTZ, 2.5 ml of 20 μM $FeCl_3$ and 25 ml of 0.3 μM of acetate buffer and maintain the pH 3.6. The mixture was prepared freshly and warmed at 37 °C before use. Here, the antioxidants react with ferric tripyridyl triazine complex (colourless) which turn to ferrous 2,4,6-tripyridyl-s-triazine (blue colour). To identify the antioxidant activity, different concentrations (50, 75, 100 μg/ml) of synthesised compounds in DMSO (1 ml) was mixed with FRAP reagent. The content was incubated at 50 °C for 20 min. The specified quantity of the solution was transferred into a cuvette and measured the absorbance at 593 nm using a Shimadzu ultraviolet spectrometer. Standard absorbance was also calibrated. The antioxidant power of acetamide derivatives at different concentration was determined through directly substituting the absorbance in the mentioned formula.

$$\text{FRAP value of sample } (\mu\text{m}) = \frac{\text{Absorbance (sample)} \times \text{FRAP value of standard } (\mu\text{m})}{\text{Absorbance (Standard)}}$$

DPPH radical scavenging method

DPPH is a stable free radical widely used to assess the radical scavenging activity of antioxidant components [31]. DPPH free radical has a stable violet colour in methanol and becomes colourless or yellow colour when paired with antioxidant or reducing agents. These radicals can accept the odd electron or hydrogen from the antioxidant and converted to a stable diamagnetic molecule (yellow). To identify the antioxidant activity, the solution of synthesised compounds has been prepared by dissolving in methanol (100 μg/ml). Simultaneously, a solution of DPPH was also prepared in another container had been shown maximum absorbance at 517 nm due to the presence of stable 1,1-diphenyl 2-picryl hydrazyl stable free radical (violet colour). Each test compound (4 ml) was added to 4 ml of DPPH solution and kept aside for 30 min at room temperature. Absorbance was measured at 517 nm using a Shimadzu ultraviolet spectrometer. Blank and standard absorbances

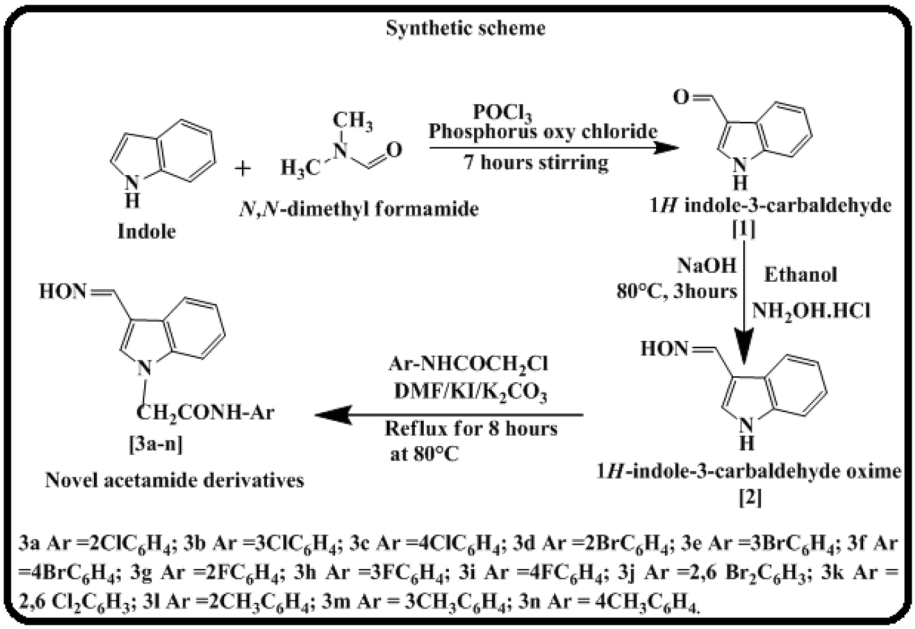

Fig. 1 Synthetic route of various potent *N*-(substituted phenyl)-2-(3-(hydroxyimino)methyl)-1*H*-indol-1-yl) acetamide derivatives [3a–n]

were also calibrated. Antioxidant activity of acetamide derivatives was determined through directly substituting the absorbance in the mentioned formula.

$$\text{Percentage inhibition} = \frac{\text{Absorbance of blank-Absorbance of test}}{\text{Absorbance of blank}} \times 100$$

Computational analysis

Computational science is a relatively new discipline that deals with the development and application of computational models and simulations, often coupled with high-performance computing, to solve the complex problem arising in drug design. Here, conformational analysis and geometric optimization of compound 3a have been performed by using Chemdraw ultra 12. Semi-empirical method PM3 is used for optimising the full geometry of the system using QA algorithm and unrestricted Hatee-Fock (UHF) method in conjunction with the 6-311++ G(d,p) basis set [32].

X-ray crystallography

X-ray crystallography is a tool used to investigate the three-dimensional picture of the atomic and molecular structure of a crystal by using X-ray light, which has wavelengths of 1 Å. The beam of X-ray hits a crystal and causes the diffraction of light in particular directions; it has fed into the computer and finds out the position of every atom in the molecule. Crystallographic data were collected at 296 K, and the structure of crystal was solved by direct method using SHELXS-97 [33].

Results

Spectral data

Preparation of N-(2-chlorophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3a]

Molecular formula: $C_{17}H_{14}N_3O_2Cl$; yield: (77%); melting point: 229–230 °C; FT-IR (ν_{max}/cm^{-1}): 3046 (Ar-H str), 1506 (Ar-C str), 3317 (NH-str), 1646 (NH-bend), 1726 (C=O-str), 623 (Cl); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.71 (s, 2H, CH_2-H), δ 6.46 (d, 2H, *J* = 14.3 Hz, CH-H), δ 6.89 (t,1H, *J* = 9.1 Hz, Ar-H), δ 7.54 (t, 1H, *J* = 10.3 Hz, Ar-H), δ 7.64 (s, 4H, Ar-H) δ 7.74 (d, 1H, *J* = 12.1 Hz, Ar-H), δ 7.96 (d, 1H, *J* = 14.5 Hz, Ar-H), δ 8.31 (s, 1H, NH-H), δ 9.11 (s, 1H, NOH-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 43.9, 106.2, 110.1, 119.2, 122.8, 127.4, 128.1, 128.4, 128.4, 132.2, 134.5, 134.5, 136.1, 136.1, 141.7, 145.7, 166.4; ESI-MS (*m/z*, %): 327 (59) [M^+], 329 (18) [M^++2], 241 (26), 185 (46), 146 (23), 80 (100), 53 (40); anal. calcd for $C_{17}H_{14}N_3O_2Cl$ (327), predicted: C, 62.30; H, 4.31; N, 12.82%. Found: C, 62.47; H, 4.16; N, 12.62%.

Preparation of N-(3-chlorophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3b]

Molecular formula: $C_{17}H_{14}N_3O_2Cl$; yield: (63%); melting point: 257–259 °C; FT-IR (ν_{max}/cm^{-1}): 3037 (Ar-H str), 1521 (Ar-C str), 3305 (NH-str), 1602 (NH-bend), 1757 (C=O-str), 724 (Cl); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.83 (s, 2H, CH_2-H), δ 6.69 (d, 2H, *J* = 14.3 Hz, CH-

H), δ 7.06 (d,1H, *J* = 17.8 Hz, Ar-H), δ 7.29 (s, 1H, Ar-H), δ 7.37 (s, 4H, Ar-H), δ 7.57 (d, 1H, *J* = 14.7 Hz, Ar-H), δ 7.83 (s, 1H, Ar-H), δ 8.15 (s, 1H, NH-H), δ 9.12 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 327 (49) [M^+], 329 (17) [M^++2], 267 (31), 216 (42), 173 (100), 146 (22); 80 (49), 39 (34); Anal. Calcd for $C_{17}H_{14}N_3O_2Cl$ (327), predicted: C, 62.30; H, 4.31; N, 12.82%. Found: C, 62.35; H, 4.28; N, 12.91%.

Preparation of N-(4-chlorophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3c]

Molecular formula: $C_{17}H_{14}N_3O_2Cl$; yield: (89%); melting point: 211–213 °C; FT-IR (ν_{max}/cm^{-1}): 3061 (Ar-H str), 1538 (Ar-C str), 3369 (NH-str), 1646 (NH-bend), 1705 (C=O-str), 689 (Cl); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.69 (s, 2H, CH_2-H), δ 6.68 (d, 2H, *J* = 10.3 Hz, CH-H), δ 7.27 (s, 4H, Ar-H), δ 7.50 (d, 2H, *J* = 12.4 Hz, Ar-H) δ 7.88 (d, 2H, *J* = 14.1 Hz, Ar-H), δ 8.25 (s, 1H, NH-H), δ 9.10 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 327 (57) [M^+], 329 (21) [M^++2], 267 (37), 201 (45), 159 (26), 115 (100), 77 (37), 39 (26); anal. calcd for $C_{17}H_{14}N_3O_2Cl$ (327), predicted: C, 62.30; H, 4.31; N, 12.82%. Found: C, 62.52; H, 4.26; N, 12.84%.

Preparation of N-(2-bromophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3d]

Molecular formula: $C_{17}H_{14}N_3O_2Br$; yield: (72%); melting point: 283–287 °C; FT-IR (ν_{max}/cm^{-1}): 3043 (Ar-H str), 1532 (Ar-C str), 3326 (NH-str), 1628 (NH-bend), 1734 (C=O-str), 578 (Br); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.55 (s, 2H, CH_2-H), δ 6.53 (d, 2H, *J* = 14.3 Hz, CH-H), δ 6.76 (t,1H, *J* = 7.8 Hz, Ar-H), δ 7.23 (s, 5H, Ar-H), δ 7.41 (d, 1H, *J* = 10.8 Hz, Ar-H) δ 7.69 (d, 1H, *J* = 9.1 Hz, Ar-H), δ 8.09 (s, 1H, NH-H), δ 8.93 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 371 (27) [M^+], 373 (25) [M^++2], 254 (47), 216 (30), 173 (63), 159 (43), 115 (100), 53 (30); anal. calcd for $C_{17}H_{14}N_3O_2Br$ (371), predicted: C, 54.86; H, 3.79; N, 11.29%. Found: C, 54.92; H, 3.61; N, 11.08%.

Preparation of N-(3-bromophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3e]

Molecular formula: $C_{17}H_{14}N_3O_2Br$; yield: (59%); melting point: 226–230 °C; FT-IR (ν_{max}/cm^{-1}): 3012 (Ar-H str), 1505 (Ar-C str), 3365 (NH-str), 1638 (NH-bend), 1711 (C=O-str), 615 (Br); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.45 (s, 2H, CH_2-H), δ 6.57(d, 2H, *J* = 11.3 Hz, CH-H), δ 7.03 (s,1H, Ar-H), δ 7.15 (s, 1H, Ar-H), δ 7.35 (s, 4H, Ar-H), δ 7.50 (d, 1H, *J* = 12.1 Hz, Ar-H), δ 7.80 (s, 1H, Ar-H), δ 8.06 (s, 1H, NH-H), δ 9.15 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 371 (29) [M^+], 373 (27) [M^++2], 254 (51), 201 (26), 159 (41), 115 (100), 90 (51), 44 (26); anal. calcd for $C_{17}H_{14}N_3O_2Br$ (371), predicted: C, 54.86; H, 3.79; N, 11.29%. Found: C, 54.73; H, 3.55; N, 11.14%.

Preparation of N-(4-bromophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3f]

Molecular formula: $C_{17}H_{14}N_3O_2Br$; yield: (62%); melting point: 247–249 °C; FT-IR (ν_{max}/cm^{-1}): 3072 (Ar-H str), 1563 (Ar-C str), 3317(NH-str), 1620 (NH-bend), 1757 (C=O-str), 636 (Br); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.79 (s, 2H, CH_2-H), δ 6.75 (d, 2H, *J* = 14.1 Hz, CH-H), δ 7.07 (s, 4H, Ar-H), δ 7.34 (d, 2H, *J* = 13.3 Hz, Ar-H), δ 7.60 (d, 2H, *J* = 13.8 Hz, Ar-H), δ 8.23 (s, 1H, NH-H), δ 9.00 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 371 (27) [M^+], 373 (24) [M^++2], 267 (35), 216 (62), 173 (26), 104 (100), 69 (55), 40 (41); anal. calcd for $C_{17}H_{14}N_3O_2Br$ (371), predicted: C, 54.86; H, 3.79; N, 11.29%. Found: C, 54.80; H, 3.58; N, 11.32%.

Preparation of N-(2-flurophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3g]

Molecular formula: $C_{17}H_{14}N_3O_2F$; yield: (88%); melting point: 213–217 °C; FT-IR (ν_{max}/cm^{-1}): 3047 (Ar-H str), 1524 (Ar-C str), 3328(NH-str), 1641 (NH-bend), 1760 (C=O-str), 968 (F); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.58 (s, 2H, CH_2-H), δ 6.48 (d, 2H, *J* = 10.3 Hz, CH-H), δ 6.82-7.00 (m, 3H, Ar-H), δ 7.26 (s, 4H, Ar-H), δ 7.65 (t, 1H, *J* = 10.8 Hz, Ar-H), δ 8.04 (s, 1H, NH-H), δ 9.07 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 311 (24) [M^+], 254 (36), 216 (24), 203 (49), 137 (66), 96 (100), 41 (39); anal. calcd for $C_{17}H_{14}N_3O_2F$ (311), predicted: C, 65.59; H, 4.53; N, 13.50%. Found: C, 65.40; H, 4.52; N, 13.46%.

Preparation of N-(3-flurophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3h]

Molecular formula: $C_{17}H_{14}N_3O_2F$; yield: (72%); melting point: 244–247 °C; FT-IR (ν_{max}/cm^{-1}): 3012 (Ar-H str), 1593 (Ar-C str), 3329(NH-str), 1611 (NH-bend), 1728 (C=O-str), 1038 (F); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.74 (s, 2H, CH_2-H), δ 6.63 (t, 1H, *J* = 8.4 Hz, Ar-H), δ 6.82 (d, 2H, *J* = 10.8 Hz, CH-H), δ 7.13 (s, 4H, Ar-H), δ 7.23-7.42 (m, 1H, Ar-H), δ 7.56 (d, 1H, *J* = 11.1 Hz, Ar-H), δ 7.81 (d, 1H, *J* = 14.3 Hz, Ar-H), δ 8.16 (s, 1H, NH-H), δ 8.85 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 311 (34) [M^+], 267 (24), 201 (53), 162 (34), 121 (60), 80 (100), 42 (27); anal. calcd for $C_{17}H_{14}N_3O_2F$ (311), predicted: C, 65.59; H, 4.53; N, 13.50%. Found: C, 65.38; H, 4.47; N, 13.62%.

Preparation of N-(4-flurophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3i]

Molecular formula: $C_{17}H_{14}N_3O_2F$; yield: (90%); melting point: 211–213 °C; FT-IR (ν_{max}/cm^{-1}): 3097 (Ar-H str), 1502 (Ar-C str), 3311 (NH-str), 1624 (NH-bend), 1755 (C=O-str), 1137 (F); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, CH_2-H), δ 6.37 (d, 2H, *J* = 13.3 Hz, CH-H), δ 6.76 (t, 2H, *J* = 12.8 Hz, Ar-H), δ 7.27 (s, 4H, Ar-H), δ 7.62 (t, 2H, *J* = 10.1 Hz, Ar-H), δ 7.99 (s, 1H, NH-

H), δ 9.14 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 311 (21) [M^+], 254 (39), 216 (31), 159 (58), 115 (100), 77 (31), 41 (39); anal. calcd for $C_{17}H_{14}N_3O_2F$ (311), predicted: C, 65.59; H, 4.53; N, 13.50%. Found: C, 65.47; H, 4.36; N, 12.55%.

Preparation of N-(2,6-dichlorophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3j]

Molecular formula: $C_{17}H_{13}N_3O_2Cl_2$; yield: (78%); melting point: 225–229 °C; FT-IR (ν_{max}/cm^{-1}): 3071 (Ar-H str), 1536 (Ar-C str), 3328 (NH-str), 1612 (NH-bend), 1739 (C=O-str), 724 (Cl); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.53 (s, 2H, CH_2-H), δ 6.54 (d, 2H, *J* = 14.3 Hz, CH-H), δ 6.81 (d,1H, *J* = 14.1 Hz, Ar-H), δ 7.19 (d, 2H, *J* = 17.4 Hz, Ar-H), δ 7.59 (s, 4H, Ar-H) δ 8.21 (s, 1H, NH-H), δ 9.09 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 361 (39) [M^+], 363 (27) [M^++2], 365 (15) [M^++4] 288 (57), 201 (20), 159 (46), 115 (57), 90 (100), 44 (24); anal. calcd for $C_{17}H_{13}N_3O_2Cl_2$ (361), predicted: C, 56.37; H, 3.62; N, 11.60%. Found: C, 56.17; H, 3.57; N, 11.62%.

Preparation of N-(2,6-dibromophenyl)-2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)acetamide: [3k]

Molecular formula: $C_{17}H_{13}N_3O_2Br_2$; yield: (62%); melting point: 198–201 °C; FT-IR (ν_{max}/cm^{-1}): 3053 (Ar-H str), 1517 (Ar-C str), 3325 (NH-str), 1618 (NH-bend), 1712 (C=O-str), 527 (Br); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 4.55 (s, 2H, CH_2-H), δ 6.57 (s, 1H, Ar-H), δ 6.89 (d, 2H, *J* = 14.8 Hz, CH-H), δ 7.54 (s, 4H, Ar-H), δ 7.90 (d, 2H, *J* = 16.2 Hz, Ar-H), δ 8.35 (s, 1H, NH-H), δ 9.07 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 451 (16) [M^+], 453 (34) [M^++2], 318 (25), 216 (31), 173 (39), 159 (21), 115 (100), 77 (50), 54 (31); anal. calcd for $C_{17}H_{13}N_3O_2Br_2$ (451), predicted: C, 45.26; H, 2.90; N, 9.31%. Found: C, 45.40; H, 2.75; N, 9.47%.

Preparation of 2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)-N-O-tolylacetamide: [3l]

Molecular formula: $C_{18}H_{17}N_3O_2$; yield: (87%); melting point: 175–177 °C; FT-IR (ν_{max}/cm^{-1}): 3063 (Ar-H str), 1549 (Ar-C str), 3312 (NH-str), 1624 (NH-bend), 1720 (C=O-str); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 2.46 (s, 3H, CH_3-H), δ 4.75 (s, 2H, CH_2-H), δ 6.43 (d, 2H, *J* = 11.3 Hz, CH-H), δ 6.59-6.64 (m,1H, Ar-H), δ 7.11 (d, 1H, *J* = 14.8 Hz, Ar-H), δ 7.32 (s, 1H, Ar-H), δ 7.52 (s, 4H, Ar-H), δ 7.85 (d, 1H, *J* = 16.1 Hz, Ar-H), δ 8.13 (s, 1H, NH-H), δ 9.03 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 307 (20) [M^+], 254 (30), 201 (19), 159 (39), 115 (100), 89 (20), 52 (39), 40 (25); anal. calcd for $C_{18}H_{17}N_3O_2$ (307), predicted: C, 69.61; H, 5.15; N, 14.33%. Found: C, 69.58; H, 5.19; N, 14.42%.

Preparation of 2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)-N-m-tolylacetamide: [3m]

Molecular formula: $C_{18}H_{17}N_3O_2$; yield: (92%); melting point: 184–187 °C; FT-IR (ν_{max}/cm^{-1}): 3026 (Ar-H str), 1514 (Ar-C str), 3367 (NH-str), 1608 (NH-bend), 1704 (C=O-str); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 2.70 (s, 3H, CH_3-H), δ 4.79 (s, 2H, CH_2-H), δ 6.41 (d, 3H, *J* = 13.5 Hz, CH-H), δ 7.02 (t,1H, *J* = 10.8 Hz, Ar-H), δ 7.44 (s, 4H, Ar-H), δ 7.67 (s, 1H, Ar-H), δ 7.87 (s, 1H, Ar-H), δ 8.36 (s, 1H, NH-H), δ 9.15 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 307 (21) [M^+], 267 (39), 242 (18), 216 (60), 159 (32), 115 (100), 77 (51), 39 (31); anal. calcd for $C_{18}H_{17}N_3O_2$ (307), predicted: C, 69.61; H, 5.15; N, 14.33%. Found: C, 69.29; H, 5.58; N, 14.70%.

Preparation of 2-(3-((hydroxyimino)methyl)-1H-indol-1-yl)-N-p-tolylacetamide: [3n]

Molecular formula: $C_{18}H_{17}N_3O_2$; yield: (81%); melting point: 193–197 °C; FT-IR (ν_{max}/cm^{-1}): 3072 (Ar-H str), 1583 (Ar-C str), 3305 (NH-str), 1623 (NH-bend), 1729 (C=O-str); ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): δ 2.60 (s, 3H, CH_3-H), δ 4.66 (s, 2H, CH_2-H), δ 6.43 (d, 2H, *J* = 13.2 Hz, CH-H), δ 7.01 (d, 2H, *J* = 16.8 Hz, Ar-H), δ 7.50 (s, 4H, Ar-H), δ 7.79 (d, 2H, *J* = 17.4 Hz, Ar-H), δ 8.32 (s, 1H, NH-H), δ 9.13 (s, 1H, NOH-H); ESI-MS (*m/z*, %): 307 (18) [M^+], 254 (26), 201 (18), 159 (26), 132 (35), 96 (100), 56 (60), 39 (24); anal. calcd for $C_{18}H_{17}N_3O_2$ (307), predicted: C, 69.61; H, 5.15; N, 14.33%. Found: C, 69.72; H, 5.16; N, 14.68%.

Anti-oxidant activity

FRAP method

The method measured the anti-oxidant potency of different *N*-(substituted phenyl)-2-(3-(hydroxyimino) methyl)-1*H*-indol-1-yl) acetamide derivative by reducing the Fe^{3+} into Fe^{2+} ion. Most of the compounds were shown admirable antioxidant activity. The antioxidant values of some of the tested acetamide derivatives are very closer to standard drugs. The anti-oxidant activity of synthesised compounds was shown in Table 1.

DPPH method

DPPH is a perfect method to evaluate the antioxidant activity of newly synthesised compounds due to the short time required for the analysis and high reliability. The result reveals that decreases the absorbance due to the antioxidant molecule may supply the electron to the DPPH free radical. Most of the compounds were shown excellent antioxidant activity. The anti-oxidant activity of synthesised compounds was shown in Table 2.

Computational analysis

To gain a better understanding of the geometrical structure of the investigated compound, 3D molecular modelling

Table 1 The result of antioxidant activity of synthesised compounds using ferric reducing antioxidant power (FRAP)

Compounds	Ferric ion (Fe^{3+}) reducing antioxidant power in nm		
	50 μg/ml	75 μg/ml	100 μg/ml
3a	0.804*	0.820**	0.856*
3b	0.757*	0.764*	0.782*
3c	0.738*	0.759*	0.781**
3d	0.716	0.751**	0.802
3e	0.671**	0.690*	0.741**
3f	0.658*	0.673*	0.716**
3g	0.451**	0.476**	0.514*
3h	0.420*	0.431*	0.497*
3i	0.402**	0.425*	0.440
3j	0.814*	0.837*	0.863*
3k	0.792*	0.813**	0.850*
3l	0.590*	0.615*	0.631*
3m	0.612*	0.630*	0.657**
3n	0.620**	0.643*	0.683**
BHA	0.942*	1.136**	1.352*
TBHQ	0.956*	1.257*	1.394**

*$P < 0.05$, **$P < 0.01$ as compared to blank and standard respectively; statistical analysis—one way ANOVA

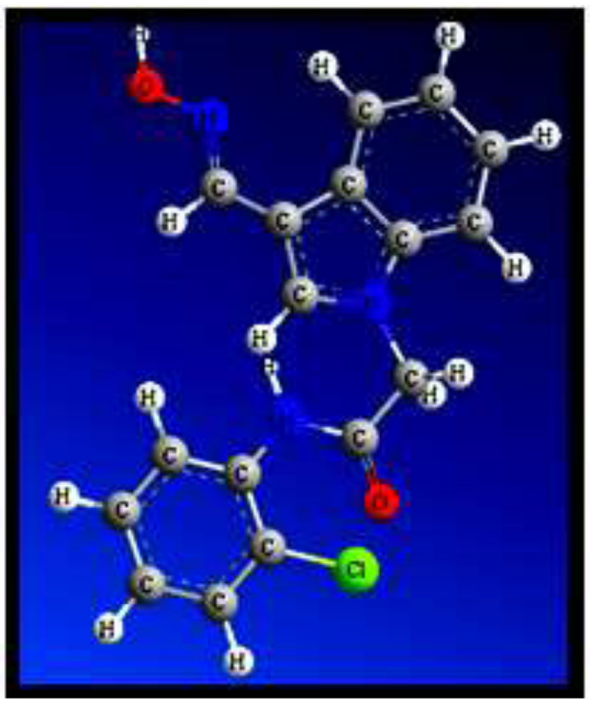

Fig. 2 Stereochemical structure of *(E) N*-(2-chlorophenyl)-2-(3-((hydroxyimino)methyl)-1*H*-indol-1-yl) acetamide [3a]

studies have been done. It gives the knowledge of the molecular structure of the compound, geometric optimization and conformational analysis as reported in a recent study [34]. The optimised structure with the atom labelling of a compound 3a is represented in Fig. 2. Some selected bond lengths and angle are listed in Table 3.

Table 2 The result of antioxidant activity of synthesised compounds with percentage scavenging

Compounds	Absorbance	Percentage scavenging
3a	0.387 ± 0.002*	55.72
3b	0.417 ± 0.006**	52.28
3c	0.472 ± 0.003*	45.99
3d	0.396 ± 0.005*	54.69
3e	0.491 ± 0.006*	43.82
3f	0.536 ± 0.005*	38.67
3g	0.730 ± 0.004*	16.47
3h	0.781 ± 0.005**	10.64
3i	0.804 ± 0.004*	08.00
3j	0.339 ± 0.003*	61.21
3k	0.392 ± 0.006**	55.14
3l	0.692 ± 0.002*	20.82
3m	0.618 ± 0.005*	29.29
3n	0.564 ± 0.004**	35.46
Ascorbic acid	0.324 ± 0.001*	62.92
Blank	0.874 ± 0.002**	NA

*$P < 0.05$, **$P < 0.01$ as compared to blank and standard respectively; statistical analysis—one way ANOVA

X-ray crystallography determination and refinement

Diffraction data of the compound 3a were collected from 7351 reflections using X Calibur diffractometer equipped with area detector and a graphite monochromator (λ = 0.83452) at 296 K. The dimension of the crystal employed for data collection was 0.30 × 0.28 × 0.28 mm at 30% probability of selected bond angle and bond length. The refinement was carried out by full-matrix least-squares using SHELXL 97. The different parameters, conditions and data collections of the refinement process of compound 3a were furnished in Table 4. The ORTEP view of

Table 3 Geometrical data of compound 3a

Atoms	Bond length (A°)	Atoms	Bond angle (°)
C(9)-N(1)	1.376	C(9)-N(1)-C(19)	124.87
C(8)-C(9)	1.399	H(31)-C(12)-C(13)	120.43
C(7)-C(8)	1.398	C(13)-C(12)-C(11)	119.99
C(6)-C(7)	1.393	H(30)-C(11)-C(16)	119.99
C(14)-Cl(21)	1.719	H(30)-C(11)-C(12)	119.99
N(1)-C(19)	1.470	C(16)-C(11)-C(12)	120.00
C(18)-O(20)	1.208	H(29)-C(10)-N(22)	116.54
C(18)-C(19)	1.509	C(3)-C(10)-N(22)	123.59
N(17)-C(18)	1.369	C(3)-C(10)-N(22)	120.00
C(13)-N(17)	1.345	C(9)-N(1)-C(19)	124.87

Table 4 Crystal data and structural refinement of compound 3a

Identification code	Compound 3a
Empirical formula	$C_{17}H_{14}N_3O_2Cl$
Formula weight	327
Crystal system	Monoclinic
Crystal size (mm)	0.30 × 0.28 × 0.28
Temperature (K)	296
Space group	$P\,21/n$
Wave length (Å)	0.83452
Volume (Å^3)	1038.63 (8)
Absorption coefficient (mm^{-1})	0.049
$F(000)$	739
Z	3
Calculated density (Mg/m^3)	1.046
Theta range for data collection	2.38°–26.46°
Index range	$-9 \le h \le 10$ $-14 \le k \le 14$ $-19 \le l \le 19$
Measured reflections	7351
Independent/observed reflections	2787
Data/restraints/parameters	10371/0/539
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.158
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0518$, $\omega R_2 = 0.1427$
R indices [all data]	$R_1 = 0.0119$, $\omega R_2 = 0.1712$
Extinction coefficient	0.0062 (18)
Largest diff. Peak and hole (e Å^3)	0.345/−0.28

the crystal bond angle and bond length was shown in Fig. 3 and Table 5.

To bridge our theoretical computational results with experimental synthesis, we have selected (E) *N*-(2-chlorophenyl)-2-(3-(hydroxyimino)methyl)-1*H*-indol-1-yl)acetamide (3a). As shown in Fig. 2, the molecule structure of compound 3a consists of a *N*-(2-chlorophenyl) acetamide group linked with 1*H*-indole-3-carbaldehyde oxime. A comparison of optimised geometry and single-crystal XRD structure for compound 3a has been made to see the reliability of our used method. It can be seen that our calculated geometry and all the ring conformation using the B3LYP method match very well with the experiment. As per the 3D molecular structure of compound 3a, the observed bond length and bond angle around C(9)-N(1) and C(9)-N(1)-C(19) were 1.376 A° and 124.87° respectively. Similar kind of geometrical data were collected from the X-ray crystallography study. It is seen that no significant differences in bond length and bond angle were observed in the optimised and experimental structures. Therefore, the obtained results are in a good agreement with the experimental results and hence strongly support them. These studies have provided great insights into the chemical properties such as predicting reactivity, the most available site for substitution, as well as their bioactive conformation of (E) *N*-(2-chlorophenyl)-2-(3-(hydroxyimino)methyl)-1*H*-indol-1-yl) acetamide (3a). Comparison of the experimental and the calculated selected bond lengths and bond angles were mentioned in Table 6.

Discussion

The route of synthesis of indole acetamide derivatives was depicted in the synthetic scheme outlines the preparation part of the synthetic analogues. Here, the key intermediate 1*H*-indole-3-carbaldehyde oxime was obtained by refluxing the mixture of 1*H*-indole-3-carbaldehyde and hydroxylamine in ethanol. The synthetic compounds *N*-(substituted phenyl)-2-(3-(hydroxyimino)methyl)-1*H*-indol-1-yl) acetamide derivatives were obtained from the interaction of

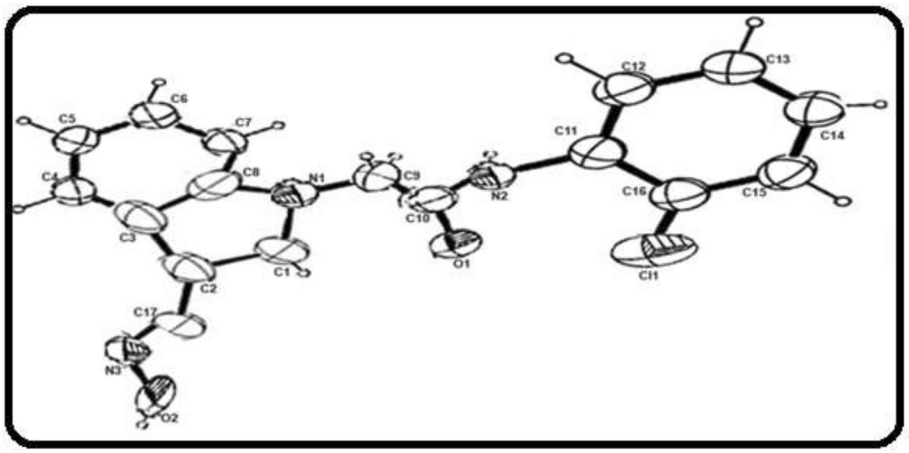

Fig. 3 An ORTEP view of compound 3a at 30% probability level

1*H*-indole-3-carbaldehyde oxime and 2-chloro acetamide derivatives. The FT-IR and ^{1}H-NMR spectrum of compounds were shown peaks due to different functional groups and proton present in the synthesised compounds. In FT-IR spectrum, strong bands at the region of 623, 724, 689, 724, 578, 615, 636, 527, 968, 1038 and 1137 cm^{-1}could be attributed to the chloro, bromo and fluro group respectively. The aryl ring was raised stretching peak in between 3097–3012 cm^{-1} and 1502–1593 cm^{-1}. A strong absorption peak at 3369–3305 cm^{-1} and 1602–1646 cm^{-1} is due to the presence of the NH group, whereas a strong peak in the region of 1704–1760 cm^{-1} indicated that the carbonyl group exists in the synthesised compounds. The number of protons present in the analogues was identified by ^{1}H-NMR spectroscopy from the chemical shift. The spectra showed a singlet at δ 2.34–2.82 ppm corresponding to a methyl proton (CH_3-H); a singlet at δ 4.39–4.92 ppm corresponding to methylene proton (CH_2-H) and a singlet at δ 6.31–6.89 ppm corresponding to CH proton; a singlet at δ 6.98–7.90 ppm corresponding to aromatic protons(Ar-H); a doublet at δ 6.37–8.04 ppm corresponding to aromatic protons (Ar-H); a triplet at δ 6.62–7.81 ppm corresponding to aromatic protons (Ar-H); a multiplet at δ 6.59–7.42 ppm corresponding to aromatic protons (Ar-H); a singlet at δ 8.00–8.39 ppm to amine (-NH-H) and a singlet at δ 8.79-9.21

Table 5 Crystal bond angle and bond length of compound 3a in ORTEP view

Atoms	Bond length (A°)	Atoms	Bond angle (°)
C(9)-N(1)	1.341(2)	C(9)-N(1)-C(19)	125.02(12)
C(8)-C(9)	1.358(2)	H(31)-C(12)-C(13)	120.43(14)
C(7)-C(8)	1.372(3)	C(13)-C(12)-C(11)	119.78(13)
C(6)-C(7)	1.407(2)	H(30)-C(11)-C(16)	120.17(12)
C(14)-Cl(21)	1.735(3)	H(30)-C(11)-C(12)	120.28(14)
N(1)-C(19)	1.425(2)	C(16)-C(11)-C(12)	120.13(13)
C(18)-O(20)	1.241(3)	H(29)-C(10)-N(22)	117.73(12)
C(18)-C(19)	1.514(2)	C(3)-C(10)-N(22)	122.87(12)
N(17)-C(18)	1.357(2)	C(3)-C(10)-N(22)	121.49(13)
C(13)-N(17)	1.340(2)	C(9)-N(1)-C(19)	125.38(12)

Table 6 Comparison of the selected value of experimental and calculated bond length, bond angle of compound 3a

Compounds	DFT/B3LYP with 6-311G(d,p)	X-ray
Bond length (A°)		
C(9)-N(1)	1.376	1.341(2)
C(8)-C(9)	1.399	1.358(2)
C(7)-C(8)	1.398	1.372(3)
C(6)-C(7)	1.393	1.407(2)
C(14)-Cl(21)	1.719	1.735(3)
N(1)-C(19)	1.470	1.425(2)
C(18)-O(20)	1.208	1.241(3)
C(18)-C(19)	1.509	1.514(2)
N(17)-C(18)	1.369	1.357(2)
C(13)-N(17)	1.345	1.340(2)
Bond angle (°)		
C(9)-N(1)-C(19)	124.87	125.02(12)
H(31)-C(12)-C(13)	120.00	120.43(14)
C(13)-C(12)-C(11)	119.99	119.78(13)
H(30)-C(11)-C(16)	119.99	120.17(12)
H(30)-C(11)-C(12)	119.99	120.28(14)
C(16)-C(11)-C(12)	120.00	120.13(13)
H(29)-C(10)-N(22)	116.54	117.73(12)
C(3)-C(10)-N(22)	123.59	122.87(12)
C(3)-C(10)-N(22)	120.00	121.49(13)
C(9)-N(1)-C(19)	124.87	125.38(12)

ppm corresponding to oxime proton (-NOH-H). The mass and element of the synthetic compound were confirmed by the Shimadzu mass spectrometer and Perkin Elmer 2400 CHN elemental analyser. Finally, these synthesised compounds were screened for antioxidant activity using FRPH and DPPH methods. Most of the synthesised compounds were shown promising antioxidant activity by reducing ferric tripyridyl triazine complex and radical scavenging property. Some of the tested acetamide derivatives were found as a potent antioxidant activity as a standard drug. Synthesised compounds in which the halogenated compounds at *ortho* position were showing better antioxidant activities when compared to *meta* and *para-substituted* compounds. Therefore, compounds 3j, 3a, 3k and 3d were constituted with chloro, bromo at the *ortho* position of the phenyl ring had shown admirable antioxidant activity. Compounds 3b, 3c, 4b and 4c have been constituted with chloro and bromo at the *meta/para* position of the phenyl ring offered an interesting antioxidant activity, whereas fluro substituted compounds (3g, 3h, 3i) furnished a reasonable level of antioxidant activity. The result of the antioxidant activity of synthesised analogues was denoted in Table 1 and Table 2. The order of antioxidant potency of novel *N*-(substituted phenyl)-2-(3-(hydroxyimino) methyl)-1*H*-indol-1-yl) acetamide derivatives was found to be 3j>3a>3k>3d>3b>3c>3e>3f>3n>3m>3l>3g>3h>3i.

Conclusion

In this study, novel *N*-(substituted phenyl)-2-(3-(hydroxyimino)methyl)-1*H*-indol-1-yl) acetamide derivatives were synthesised and characterised by FT-IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. Moreover, the antioxidant activities of prepared indole acetamide derivatives were studied by using FRAP and DPPH methods. Compound 3j, 3a and 3k were shown highest activity among the prepared analogues due to the attachment of halogens connected at the appropriate place in the phenyl ring. Hence, these substituted phenyl rings considered as a perfect side chain for the indole nucleus for the development of the new antioxidant agents.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s43094-020-00090-6.

Additional file 1:. Supplementary files

Abbreviations

FT-IR: Fourier transform infrared spectroscopy; TPTZ: 2,4,6-Tri(2-pyridyl)-s-triazine; ^{1}H-NMR: Nuclear magnetic resonance spectroscopy; ESI-MS: Electrospray ionisation mass spectrometry; FRAP: Ferric reducing antioxidant power; DMSO: Dimethyl sulfoxide; DMF: Dimethyl formamide; TLC: Thin-layer chromatography; DPPH: 1,1-Diphenyl-2-picrylhydrazyl

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Authors' contributions

CG designed the study, synthesis, characterisation and computational analysis of the titled compounds. MDD has contributed to the major work in the anti-oxidant activity of the synthesised compounds, analysing the data and writing the manuscript in a journal format. All the authors read and approved the final manuscript.

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Availability of data and materials

Data and materials are available upon request.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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