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Original Article

Synthesis and Characterization of Halo-Indole Derivatives Reveal Improved Therapeutic Agents for Treatment of Inflammations

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ABSTRACT

Background: Five-membered heterocycle with one neighbouring nitrogen atoms is present in the indole nucleus. Heterocyclic substances feature two adjacent benzene and pyrrole ring atoms. Indoles are heterocyclic compounds with one oxygen ring that have a benzoannelated-pyrrole ring. Indole derivatives are highly valuable chemical synthesis and medicinal intermediates. Recent years have seen a surge in interest in the effective synthesis of indole blocks and associated functionalization's, particularly the alkylation of indoles. The two following factors will be the main emphasis of this research like recent advancements in the alkylation of indoles, namely those involving the N1-, C2- and C3-positions and the synthesis of indoles, which was facilitated by transition metals. **Materials and Methods:** Benzoic acid and ethanoic acid, propionic acid, hydroxylamine, 2,5 Dichloro aniline are used for the synthesis of indole derivatives were used for the synthesis of indole **Results:** Compared to indomethacin, the anti-inflammatory results for the substances or their derivatives like Compound *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-4-aminobenzene-benzene-1,2-diamine:NA5 (Scheme 1B); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-2-aminobenzene-benzene-1,2-diamine (NA6); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-3-aminobenzene-benzene-1,2-diamine: NA7 (Scheme 1B) containing aromatic group. **Conclusion:** Examined were the anti-inflammatory properties of the substances in the title and their derivatives. The compounds containing indole derivatives with an electron-withdrawing group have a higher activity than those containing an electron-donating group, according to research on the link between structure and activity. Summarising the data from the previously reviewed literature, we can say that indole has a broad spectrum of biological activity. Numerous opportunities exist to investigate indole for new therapeutic uses. Researchers worldwide will benefit from this study's coverage of the chemistry of indole derivatives in the design and synthesis of new pharmaceuticals that might be utilised to treat a range of diseases.

Keywords: 5-chloro-1*H*-indole Benzoic acid, Ethanoic acid, Propionic acid, Hydroxylamine, Egg albumin solution, Distilled water/DMSO, Bovine serum albumin, Phosphate buffer (0.5 M, pH 6.3).

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INTRODUCTION

Indole, sometimes called benzopyrrole,[1] is an aromatic compound that has ten π-electrons (two from a lone pair on N and eight from=bonds).[2] On indole, electrophilic substitution happens easily because of high π-electrons delocalization, much like it does on the benzene ring. An essential heterocyclic system, indole supplies the structural framework for alkaloids derived from plants, Strychnine and Lysergic acid Diethylamide (LSD).[3] They have distinct smells and are colourless and crystalline in nature.[4] When the indole nucleus is added to pharmaceuticals with a physiologically active pharmacophore, it becomes a significant heterocyclic molecule with wide-ranging biological action. As a result, scientists were interested in creating alternative indole scaffolds for the purpose of screening diverse pharmacological actions.[5] Indole serves as the parent nucleus in a number of natural chemicals, including tryptophan. Higher plants break down tryptophan to create the plant hormone indole-3-acetic acid.[6] Indole derivatives are of great interest. Indoles having a chemical formula of C_8H_7N and a molecular weight of 117.15 g/mol.[7] Compared to standard medicine, the molecule with

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electron-donating and electron-withdrawing groups attached to the indole rings had a stronger inhibitory capacity against bacterial and fungal strains.[8] Indole has been found to possess broad-spectrum antibacterial, anti-inflammatory, analgesic, anti-tubercular, antihypertensive, anticonvulsant and antiviral properties following a thorough examination of several research and review papers.[9] Indole is manufactured by a range of bacteria and is found in large quantities in the natural world. As a result, various research organisations have worked to find novel antimicrobial medications and the WHO and young scientists worldwide have made significant efforts to treat these infections,[10] such as anti-inflammatory, antibacterial, antifungal, herbicidal and antiviral activity, however, is represented pharmacologically by indole, along with its derivatives.[11] In the Figure 1 below, indole was shown. These days, indoles have a broad variety of pharmacological properties. We have attempted to provide a summary of the significant pharmacological activities of derivatives of indole here. The goal of this study is to provide an overview of the current status of indole syntheses, with a special emphasis on the most recent advancements in novel synthetic methodologies.[12] Preparing natural goods or bioactive chemicals that include the indole unit is emphasised. We give an overview of the synthesis of indole from a historical viewpoint, highlighting the methods used to choose the nitrogen precursors. The research is structured to provide indole synthesis techniques by using various aromatic substrates that include nitrogen-containing functional groups as a source of nitrogen for the indole moiety.[13] The scant attention paid to some functional groups and typical reactions in earlier evaluations on this subject has led to their being especially emphasised and underlined. The most recent published results are highlighted, although other synthetic methodologies that have been more often utilised and addressed in thorough, outstanding studies on the subject are summarised.[14] We are especially interested in the indolization processes and the various ring closure techniques; we pay little attention to changing the indole structures from the beginning.[15] Novel indole syntheses are always being found and the scientific community places a high value on these discoveries because of the tactical significance of molecules and significant attention and uses because of their biological and pharmacological properties.[16]

MATERIALS AND METHODS

Materials

5-chloro-1*H*-indole and 2,5-dichloroaniline hydroxylamine, 2-aminophenol, ethanoic acid, propionic acid, Egg albumin solution, Phosphate buffered saline, distilled water/DMSO; 5 mL of 1.5 mg/mL Bovine Serum Albumin (BSA); 250 µL of phosphate buffer (0.5 M, pH 6.3) are used for the synthesis and biological Activity of indole derivatives Every chemical was of the analytical variety. All of the chemicals were bought from Modern Chemicals in Nashik, while others are offered by the college.

Methods

Every derivative of indoles was created using a traditional process. Melting point was confirmed using the capillary open tube technique. The chemicals' purity was examined using Thin-Layer Chromatography (TLC). Using KBr pellets and a Perkin Elmer Spectrum FTIR equipment, IR spectra have been acquired. A Bruker AVANCE III 500 MHz (AV 500) spectrometer was used to record 1 H-NMR spectrum. Scheme of N-[3-amino-4-(5-chloro-1H-indol-1-yl)phenoxy]benzene-1,2-diamine (Code name: NA) and its derivatives (Code name: NA1 to NA7) were given in Figures 2 and 3.

Experimental Work

Synthesis of 5-chloro-2-(5-chloro-1H-indol-1-yl) aniline (Scheme 1A)

2 g of 5-chloro-1*H*-indole and 7 mL of 2,5-dichloroaniline were combined in a flask with a round bottom. For 2 hr, the mixture was heated to 100º in a heating mantel. Once the liquid had cooled, 10% sodium hydroxide solution was gradually added until it was barely litmus-alkaline. Reaction flask was rinsed with ice-cold water. After recrystallizing the crude product with cold water, it was cleaned using around 25 mL of cold water.

Synthesis of 5-(amino-oxy)-2-(5-chloro-1H-indol-1-yl) aniline: (Scheme 1A)

Add 2 g of the product and two hydroxylamine to a round-bottom flask. Heat the reaction mixture for 3 hr at 100ºC in a heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

Synthesis of N-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]benzene-1,2-diamine: (Scheme 1B) NA

Add 2-aminophenol to a flask with a round bottom, add 2 g of product and heat the reaction mixture for 3 hr at 100ºC in a heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

Synthesis of 2-({5-chloro-2-[(5-chloro-1*H*-indol-1-yl) amino]phenyl}amino)phenyl acetate: NA1 (Scheme 1B)

Add 2-chloro Aniline to a flask with a round bottom, add 2 g of product and heat the reaction mixture for 3 hr at 100ºC in a heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

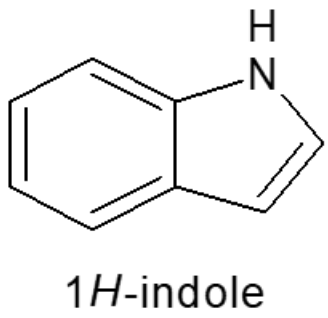

Figure 1: Structure of Indole derivatives.

Synthesis of (2-{[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]amino}phenyl)carbamic acid: NA2 (Scheme 1B)

Add acetic acid to a flask with a round bottom, add 2 g of product and heat the reaction mixture for 3 hr at 100°C in a heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

Synthesis of 2-({5-chloro-2-[(5-chloro-1*H*-indol-1-yl) amino] phenyl} amino) phenyl propanoate: NA3 (Scheme 1B)

In a round-bottomed flask, 2 g of product and add ethanoic acid and treat the reaction mixture for 4 hr at 100°C in heating mantel. After cooling, the reaction mixture was filtered and recrystallized with ethanol. The Product was washed with ice cold water and filtered and dried in hot air oven for 10 min and later naturally.

Synthesis of *N*-(2-{[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy] amino}phenyl) formamide: NA4 (Scheme 1B)

In a round-bottomed flask, 2 gm of product and add formic acid and treat the reaction mixture for 3 hr at 100°C in heating mantel. After cooling, the reaction mixture was filtered and recrystallized with ethanol. The Product was washed with ice cold water and filtered and dried in hot air oven for 10 min and later naturally.

Synthesis of *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-4-aminobenzene-benzene-1,2-diamine:NA5 (Scheme 1B)

In a round-bottomed flask, 2 g of product and add 4 nitro aniline and treat the reaction mixture for 3 hr at 100°C in heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

Synthesis of *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]-2-aminobenzene-benzene-1,2-diamine: NA6 (Scheme 1B)

Put 2 g of the product and 3 g of 2-nitro aniline into a round-bottom flask. Heat the reaction mixture for 3 hr at 100°C in a heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

Synthesis of *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]-3-aminobenzene-benzene-1,2-diamine: NA7 (Scheme 1B)

Add 2 g of the product and 2 g of 3-nitro aniline to a round-bottom flask. Heat the reaction mixture for 3 hr at 100°C in a heating mantel. The reaction mixture was cooled, filtered and then recrystallized with ethanol. The product was cleaned in ice-cold water, filtered and dried for 10 min in a hot air oven before it naturally dehydrated.

RESULTS

Spectral Data

Synthesis of 5-(amino-oxy)-2-(5-chloro-1H-indol-1-yl)aniline: (Scheme 1A): NA (Scheme 1A)

FTIR (KBr) ν cm^{-1}: 1600.92 C=C Stretch(Aromatic), 2952.84 C-H Stretch(Aromatic), 2828.10 C-N bend (Aromatic), 3537.45 N-H Stretch (Aromatic), 2423.21 C-H Stretch (Aliphatic), 771.87 C-Cl Stretch (Aromatic), 1521.84 N-H bend (Aromatic); 1H NMR (400 MHz, DMSO): δ 11.7 N-H (s, 1H, *J*=11.1), δ 12.4 N-H (s, 1H, *J*=11.4), δ 7.3-7.9 Ar C-H (m, 12H, *J*=14.3).

Synthesis of 2-({5-chloro-2-[(5-chloro-1*H*-indol-1-yl) amino]phenyl}amino)phenyl acetate: NA1 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1498.45 C=C Stretch (Aromatic), 1160.01 C-C Stretch (Aromatic), 1301.72 C-N Stretch (Aromatic), 3313 N-H Stretch (Aromatic), 799.5 C-Cl Stretch, 2844 C-H (Aromatic); 1H NMR (400 MHz, DMSO): δ 12.5 N-H (s, 1H, *J*=11.7), 13.3 N-H (s, 1H, *J*=11.4), 7.0-7.8 Ar C-H (m, 17H, *J*=14.3).

Synthesis of (2-{[3-amino-4-(5-chloro-1H-indol-1-yl) phenoxy]amino}phenyl)carbamic acid: NA2 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1586 C=C Stretch (Aromatic), 1132.01 C-C Stretch (Aromatic), 1332.83 C-N Stretch (Aromatic), 3359 N-H Stretch (Aromatic), 1728.10 C=O (Ester), 782 C-Cl bend (Aliphatic); 1H NMR (400 MHz, DMSO): δ 12.5 N-H (s, 1H, *J*=11.7), 13.3 N-H (s, 1H, *J*=11.4), 7.1-7.9 Ar C-H (m, 15H, *J*=14.3), 2.5 CH_3 (s, 3H, *J*=11.0).

Synthesis of 2-({5-chloro-2-[(5-chloro-1*H*-indol-1-yl) amino]phenyl}amino)phenyl propanoate: NA3 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1718.26 C=C Stretch(Aromatic), 1191.63 C-C Stretch(Aromatic), 1266.86 C-N Stretch (Aromatic), 3259.13 N-H Stretch(Aromatic), 747.0 C-Cl bend (Aliphatic), 1728.15 C=O (Ester); 1H NMR (400 MHz, DMSO): δ 2.2 CH_2(s, 2H, *J*=11.7), 13.3 N-H (s, 1H, *J*=11.4), 12.7 N-H(s, 1H, *J*=11.4), (7.0-7.8 Ar C-H (m, 13H, *J*=14.3), 2.8 CH_3 (s, 3H, *J*=11.0).

Synthesis of N-(2-{[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]amino}phenyl) formamide: NA4 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1632.29 C=C Stretch(Aromatic), 1232.5 R-O-R (Aliphatic), 2835.81 C-N bend (Aromatic), 998.02 N-H Bend (Aromatic), 3247.7 O-H bend (Aliphatic), 1728.1 C=O (Diketones), 1550 N-O (Aromatic), 778.4 C-H bend (Aliphatic); 1H NMR (400 MHz, DMSO): δ 3.3 CH_3 (s, 3H, *J*=11.4), 6.4 CH_2 Group (s, 2H, *J*=13.1), 7.0-7.9 Ar C-H (m, 14H, *J*=14.3); Mol.Wt. 374.35.

Synthesis of *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-4-aminobenzen e-benzene-1,2-diamine:NA5 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1679.69 C=C Stretch(Aromatic), 1182.78 C-O Stretch (Aromatic), 2828.10 C-N stretch (Aromatic), 1646.80 N-H bend (Aromatic), 3289.2 O-H bend (Aliphatic), 1722.46 C=O (Diketones), 3289.2 O-H Stretch (Aliphatic), 620.66 C-Cl (Aliphatic); 1H NMR (400 MHz, DMSO): δ 2.5 CH_3(s, 3H, *J*=11.7), 3.3 CH_3 (s, 3H, *J*=11.4), 7.7-7.98 Ar C-H (m, 16H, *J*=14.3); Mol.Wt.353.24.

Synthesis of *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]-2-aminobenzene-benzene-1,2-diamine: NA6 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1594.6 C=C Stretch(Aromatic), 1262.2 C-C Stretch(Aromatic), 2828.10 C-N bend (Aromatic), 1496.6 N-H bend (Aromatic), 3279.2 O-H bend (Aliphatic), 1134.5 C=O (Diketones); 1H NMR (400 MHz, DMSO): δ 2.5 CH_3(s, 3H, *J*=11.7), 3.3 CH_3 (s, 3H, *J*=11.4), 7.5-7.98 Ar C-H (m, 15H, *J*=14.3); Mol.Wt.374.35.

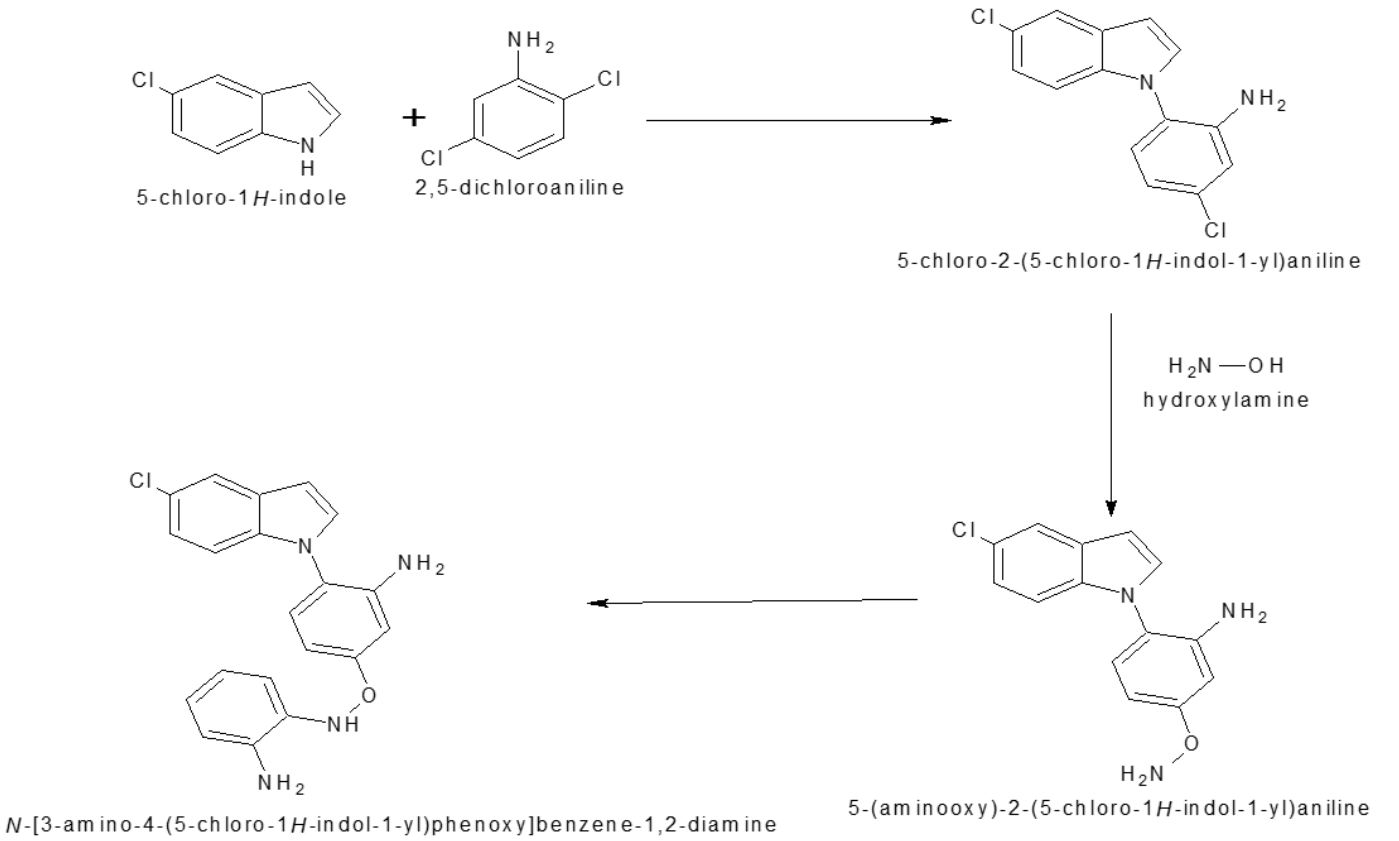

Figure 2: Scheme of N-[3-amino-4-(5-chloro-1H-indol-1-yl)phenoxy]benzene-1,2-diamine.

Synthesis of *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]-3-aminobenzene-benzene-1,2-diamine: NA7 (Scheme 1B)

FTIR (KBr) ν cm^{-1}: 1495.45 C=C Stretch(Aromatic), 1145.12 C-C Stretch(Aromatic), 2431 C-N Stretch(Aromatic), 3313 N-H Stretch(Aromatic), 1699.5 C=O Stretch (Carboxylic Acid), 3471 and 3537 O-H Stretch (Aliphatic), 1670.10 C=O (Diketones), 2844 C-H(Aromatic); 1H NMR (400 MHz, DMSO): δ 3.63 CH_3(s, 3H, *J*=11.7), 3.71 CH_3 (s, 3H, *J*=11.4), 5.44 CH_2 Group (s, 2H, *J*=13.1), 6.36-6.38 CH_2 Group (s, 2H, *J*=13.1), 7.18-7.25 Ar C-H (m, 15H, *J*=14.3); 5.98-5.56 OH (2H, s, *J*=17.4); Mol.Wt. 404.46.

Biological evaluation

Preparation of 1% of egg albumin solution

A 1% egg albumin solution may be made using either fresh hen's eggs or easily found egg albumin powder from shops. To correctly make egg-albumin solution from a fresh hen's egg, fracture it gently, then add 1 mL of the transparent part to 100 mL of distilled water with a thorough swirling motion. Egg albumin is the name of the transparent part of the egg. When creating the solution, the water has to be cold. When water reaches a boil, it will coagulate. Graphical Representation of Albumin Denaturation Inhibitory Activity of Synthesized N-[3-amino-4-(5-chloro-1H-indol-1-yl)

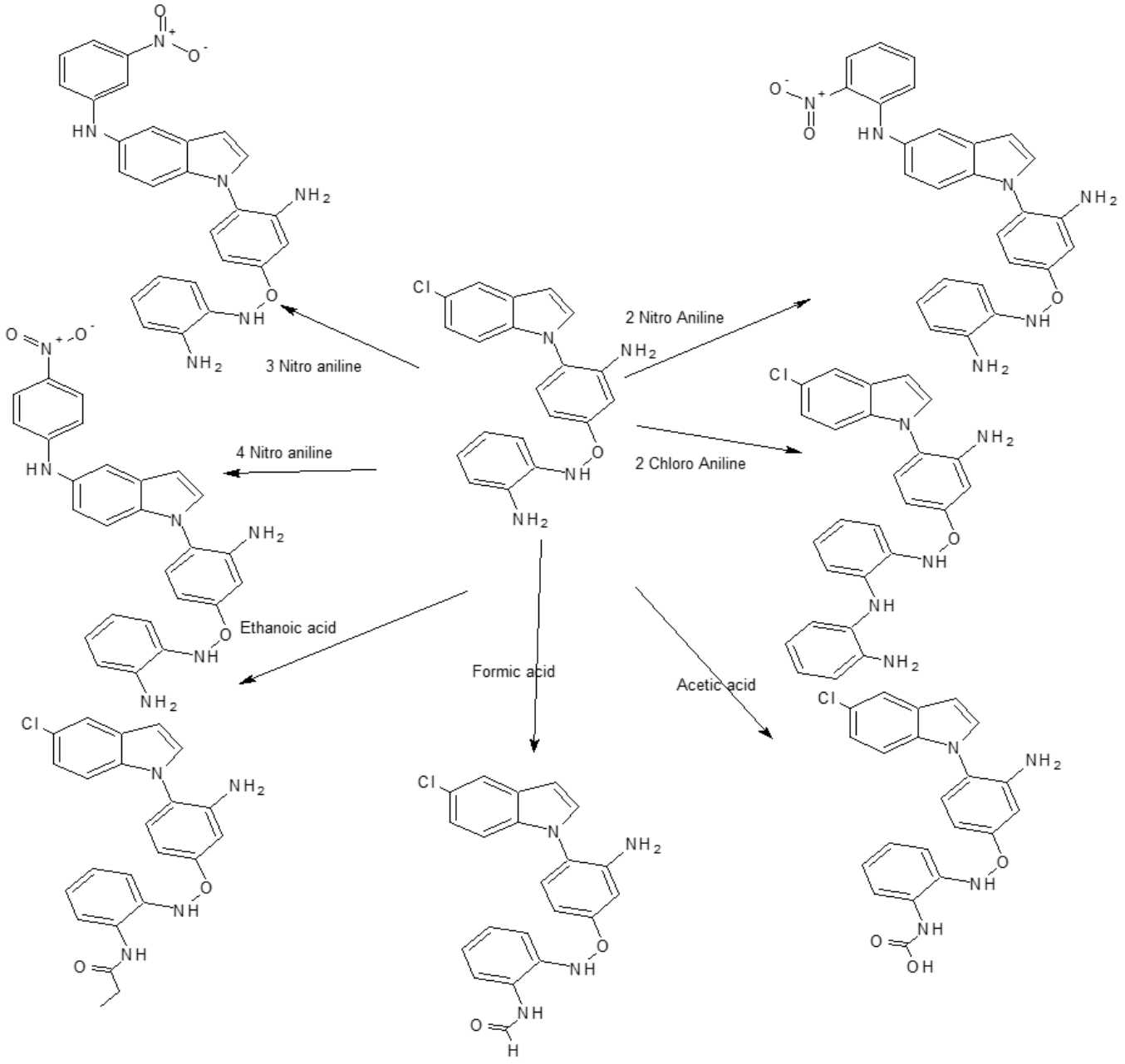

Figure 3: Scheme of N-[3-amino-4-(5-chloro-1H-indol-1-yl) phenoxy] benzene-1,2-diamined Derivatives.

phenoxy] benzene-1,2-diamined Derivatives were given in Figure 4.

Evaluation of Albumin Denaturation Inhibitory Activity of Synthesized Compounds

Protein denaturation is one of the most well-known causes of inflammation. As part of the investigation, seven test samples (NA1-NA7) had their ability to reduce inflammation assessed. A test for denaturation of proteins has been carried out. Multiple concentrations (50, 100, 200 and 300 µg/mL) of test samples were produced. 0.5 mL of 1.5 mg/mL Bovine Serum Albumin (BSA) was added to each reaction mixture and it was then incubated for 20 min at 37°C. The reaction mixtures were then heated for 3 min to 57°C. Before adding 250 µL of phosphate buffer (0.5 M, pH 6.3), each mixture had to be thoroughly blended. When all of the molecules in each reaction mixture had been evenly distributed, 100 µL of each mixture was transferred into separate test tubes and the same amount of Folin-Ciocalteu's reagent was added. The tubes were allowed to cool after a 10 min incubation time at 55°C. The absorbance at 650 nm was then measured using a UV/Vis spectrophotometer, with triple distilled water acting as the blank. The collected data was juxtaposed to the reference medicine, indomethacin sodium (100 µg/mL). The inhibition percentage of protein denaturation was calculated using the procedure given Table 2.

$$\%\text{denaturation inhibition} = [\text{Abs control} (\text{Abs test}/\text{Abs control})] \times 100$$

DISCUSSION

Following Scheme 1B, the synthesis of Novel Substituted Indole derivatives from NA1 to NA7 was started. Physical Data of Indole derivatives were given in Table 1. A comparative chart demonstrates the anti-inflammatory properties of novel substituted indole-derived compounds at various doses, such as 50, 100, 200 and 300 µg/mL, as well as how well they can stop the spread of inflammation. indomethacin was prescribed as usual medication. Table 2 provided a snapshot of the anti-inflammatory findings for the named compounds (NA1-NA8). Compounds NA7 and NA6 had greater absorbance at lower dosage levels of 50 µg/mL and 100 µg/mL. (2-{[3-amino-4-(5-chloro-1H-indol-1-yl) phenoxy]amino} phenyl) carbamic acid: NA2 (Scheme

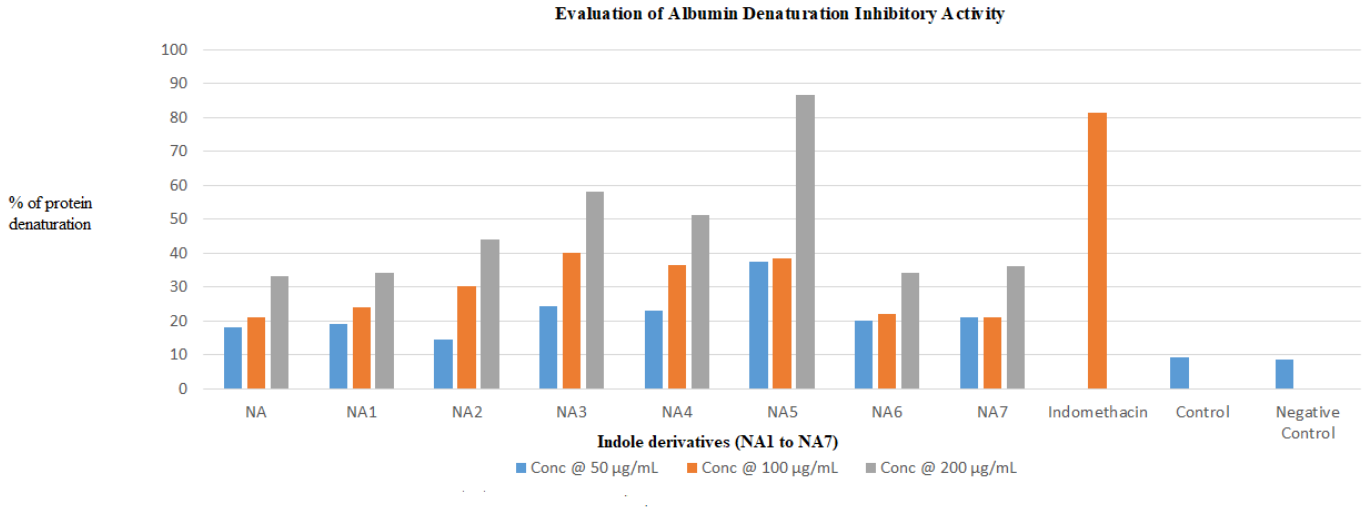

Figure 4: Graphical Representation of Albumin Denaturation Inhibitory Activity of Synthesized N-[3-amino-4-(5-chloro-1H-indol-1-yl) phenoxy] benzene-1,2-diamined Derivatives.

Table 1: Physical Data of Indole derivatives.

Compounds Code	Yield %	M.P.(°C)	Molecular Formula	Molecular weight
NA	94	130-132	$C_{20}H_{16}N_2$	284.35
NA 1	98	302-304	$C_{22}H_{20}N_2O_2$	344.15
NA 2	94	170-173	$C_{22}H_{20}N_2O_4$	376.41
NA 3	90	132-134	$C_{20}H_{16}N_2O_2$	316.35
NA 4	94	124-126	$C_{20}H_{14}N_4O_2$	374.35
NA 5	98	124-126	$C_{20}H_{14}Cl_2N_2$	353.24
NA 6	94	184-186	$C_{20}H_{14}N_4O_4$	353.24
NA 7	92	166-168	$C_{24}H_{24}N_2O_4$	353.24

Table 2: Albumin Denaturation Inhibitory Activity of Indole derivatives (inhibition percentage of protein denaturation).

Indole derivatives	%denaturation inhibition			
	Conc @ 50 μg/mL	Conc @ 100 μg/mL	Conc @ 200 μg/mL	Conc @ 300 μg/mL
NA	18.25±1.22	21.12± 1.88	33.22±2.01	48.13±3.25
NA 1	19.23±1.02	24.12±1.86	34.28±2.34	50.42±3.45
NA 2	14.65± 1.24	30.24±2.01	44.21±2.96	62.29±3.25
NA 3	24.36± 1.63	40.27±2.34	58.22±3.48	70.35±3.95
NA 4	23.14± 1.34	36.49±2.65	51.23±2.98	56.32±3.46
NA 5	37.55± 1.96	38.55±3.54	86.69±4.08	92.26±4.66
NA 6	20.25± 1.25	22.25±1.76	34.22±2.11	51.13±3.37
NA 7	21.23± 1.11	21.23±1.72	36.28±2.21	52.63±3.22
Indomethacin		81.53±3.25	---	---
Control	9.47±0.04	---	---	---
Negative control (DMSO @ 0.1%)	8.60 ±0.03	---	---	---

1B);2-({5-chloro-2-[(5-chloro-1*H*-indol-1-yl)amino]phenyl} amino)phenyl propanoate: NA3 (Scheme 1B); N-(2-{[3-amino-4-(5-chloro-1H-indol-1-yl)phenoxy]amino}phenyl)formamide: NA4 (Scheme 1B) displayed lower absorbance at higher dose level of 300 µg/mL. Compound *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]-4-aminobenzene-benzene-1,2-diamine:NA5 (Scheme 1B); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-2-aminobenzene-benzene-1,2-diamine (NA6); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-3-aminobenzen e-benzene-1,2-diamine: NA7 (Scheme 1B) containing aromatic group, showed higher absorbance at lower dose level of 200 µg/mL. Table 2 displayed the outcomes of the produced compounds' anti-inflammatory tests. The anti-inflammatory properties of recently synthesised compounds have been investigated in relation to the Albumin Denaturation Inhibitory Activity. Tests have been performed on all the substances at 50, 100, 200 and 300 µg/mL. Table 2 summarises the study's findings. It is interesting to point out that all the compounds of the present series showed some anti-inflammatory activity. *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-4-aminobenzene-benzene-1,2-diamine:NA5 (Scheme 1B); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-2-aminobenzene-benzene-1,2-diamine (NA6); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-3-aminobenzen e-benzene-1,2-diamine: NA7 (Scheme 1B) had more anti-inflammatory properties than the ones that matched them. Nitro aniline compounds showed more activity than other derivatives, while their indole derivatives showed less percentage inhibition by albumin denaturation inhibitory action. It has been observed that the *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl) phenoxy]-4-aminobenzene-benzene-1,2-diamine:NA5 (Scheme 1B); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-2-aminobenzene-benzene-1,2-diamine (NA6); *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)phenoxy]-3-aminobenzen e-benzene-1,2-diamine: NA7 (Scheme 1B) having amino at ortho, meta and para position on phenyl ring was the most active and it was studied at three graded doses (50, 100, 200 and 300 µg/mL). The compound *N*-[3-amino-4-(5-chloro-1*H*-indol-1-yl)pheno xy]-2-aminobenzene-benzene-1,2-diamine (NA6) showed the strongest and most dose-dependent anti-inflammatory action of all the newly created compounds. Because indole derivatives have so many uses in medicinal chemistry, both traditional and green synthetic techniques have been devised for their production. Compared to conventional procedures, the green methodology offers several benefits such as quick reaction times, low costs for reagents, high yields and environmental friendliness.[17] To get beyond the limitations of traditional techniques, researchers in both academia and the pharmaceutical industry are now working on creating a variety of green methodologies for the chemical synthesis of molecules based on indole. This study incorporates the advancements over the past ten years in environmentally friendly techniques for the synthesis of indole derivatives, including the use of microwaves, ionic liquids, water, ultrasound, nanocatalysts, green catalysts, multicomponent reactions and solvent-free reactions (please refer to the scheme below for a breakdown of the methodology).[18] Additionally, this research has demonstrated the use of green chemistry in the production of medicines containing indole and their biological investigations. One of the busiest fields of heterocyclic chemistry research has been indole chemistry. Particularly, 3-substituted indole derivatives have drawn a lot of interest as starting points for the synthesis of several naturally occurring substances as well as additional substances with biological activity. In this paper, a three-component reaction involving aromatic amine and carboxylic acid with a catalytic quantity of acid under convectional conditions effectively created a synthetic process for multi-substituted indole derivatives.[19] The benefits of this process are high atom utilisation, easy operation and easily accessible raw materials.

CONCLUSION

Convectional technique was used to synthesised several Indole derivatives. The seven Indole derivatives in all were synthesised. Good yields of every chemical were produced. The albumin denaturation inhibitory activity was used to provide the biological anti-inflammatory effect. According to this study, indole derivatives exhibited more potent anti-inflammatory activity against various forms of inflammation. Several of the compounds generated have been demonstrated to have potent anti-inflammatory characteristics. When synthesised compounds were compared to other Indole, higher activity was observed. There are several compounds with a variety of biological applications that possess the indole moiety. Many synthetic medicinal compounds embrace an indole nucleus as part of their pharmacophore structure, which helps pharmaceuticals bind to the residual residues of target molecules' binding sites. Derivatives having indole core have a variety of biological consequences, including antidiabetic, anticancer, antibacterial, anti-HIV, antiviral, anti-inflammatory, antioxidant, anticholinesterase, antitubercular and antimalarial defining features. In their hunt for novel chemical entities, these behaviors have attracted indole to the attention of researchers. These ingredients might be used to create more effective and less hazardous drugs for an assortment of ailments.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FTIR: Fourier transform infrared spectroscopy; **NMR spectroscopy:** Nuclear Magnetic spectroscopy; **MS:** Mass spectroscopy; **KBr:** Potassium Bromide; **% Yield:** Percentage yields; **M.P:** Melting point; **mg/kg:** Milligram/ kilograms; **sec:** Seconds; **δ:** Chemical shift; Mol. **Wt:** Molecular Weight; **g:** Gram.

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