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Pharmacological activities of 5-substituted-N-(substituted-2H-[1, 3]oxazino[6, 5-b]quinolin-3(4H)-yl)-3-phenyl-1H-indole-2-Carboxamides

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Abstract

(E)-5-Substituted-*N*'-[(1, 2-dihydro-substituted-2-oxoquinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrazides **3a-h,** obtained by the reaction of 5-substituted-3-phenyl indole-2-carbohydrazides **1a-b** and 1, 2-dihydro-substituted-2-oxoquinoline-3-carboxaldehydes **2a-d** on further reaction with sodium borohydride followed by treatment with formaldehyde yielded 5-substituted-*N*'-[(1, 2-dihydro-substituted-2-oxoquinoline-3-yl)methyl]-3-phenyl-*1H*-indole-2-carbohydrazides **4a-h** and 5-substituted-*N*-(substituted-*2H*-[1, 3] oxazino[6, 5-b] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamides **5a-h** respectively. Structures of the all the newly synthesized compounds were confirmed by spectral data. All these compounds have been screened for their anti-inflammatory and analgesic activities.

Keywords: Indoles; quinolines; oxazinoquinolines; Pharmacological activities.

1. Introduction

Heterocycles bearing nitrogen, sulphur and oxygen atoms in their structure constitute the core structure of a number of biologically interesting compounds. Indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their varied biodynamic propertiesviz, antiviral [1], antihepatitis-B virus [2], antioxidant activity [3], antituberculosis activity [4] and cyclooxygenase-2 inhibitors [5]. The heterocyclic containing quinoline ring system has attracted the attention of the chemists because of possessing significant biological activities [6-10]. Many indolo [2, 3-c] isoquinolines reported from our laboratory have been found to possess bactericidal and fungicidal activities [11-14]. Several 1,3-benzoxazine derivatives reported in the literature were found to possess antireserpine, analgesic, anti-inflammatory, tranquillizing, sedative, bactericidal, bacteriostatic [15-17], smooth muscle relaxant, cytotoxicity & antiproliferative activity [18] and spermicidal activities [19].

In light of above findings and in continuation of our research work on indoles [20-27], we hereby report the synthesis and antimicrobial activity of some 5-substituted-*N*'-((2-hydroxy-substituted-quinolin-3-yl)methyl)-3-phenyl-*1H*-indole-2-carbohydrazides **4a-h** and 5-substituted-*N*-(substituted-*2H*-[1, 3] oxazino[6, 5-b] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamides **5a-h,** having indole and quinolinooxazine moieties in their structure with the hope getting compound with more potent antimicrobial and antituberculosis activity by making use of (*E*)-5-substituted-*N*'-[(1, 2-dihydro-substituted-2-oxoquinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrazides [28] **3a-h** as starting materials where in nitrogen atom of NH_2 group of 5-substituted-3-phenyl indole-2-carbohydrazide has become the part of oxazine nitrogen of quinolino-1, 3-oxazine system (**Scheme I**).

2. Experimental:

2.1 General procedures:

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr discs (νmax in cm-1) on Perkin- Elmer FT-IR (Spectrum ONE) spectrophotometer, 1H NMR spectra on a Bruker AMX (400 MHz) spectrophotometer using DMSO-d6 as solvent using TMS as an internal standard (chemical shifts in d) and mass spectra on a mass spectrometer JEOL sx-102 (FAB) instrument (m/z in %). Compounds were checked for their purity by TLC on silica gel 60G F254plates and iodine vapours were used as visualizing agent. Elemental analysis carried out using Flash EA1112 series elemental analyzer.

The starting materials (*E*)-5-substituted-*N'*-[(1,2-dihydro-substituted-2-oxoquinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrazides (**3a-h**) was prepared according reported method [23]. We already reported the synthesis part of this work along antimicrobial activity [28].

General method for the preparation of (E)-5-substituted-N'-[(1, 2-dihydro-substituted-2-oxoquinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrazides (3a-h): 5-Substituted-3-phenyl-2-carboxyhydrazides (1a-b) (0.001mol) and 2, 3-dihydro-substituted-3-formyl-2-oxo-quinolines (2a-d) (0.001 mol) and a catalytic amount of glacial acetic acid were taken in ethanol (20 ml) and refluxed for 8h on water bath. The resulting solids were filtered, washed with little alcohol dried and purified by crystallization from dioxane to get 5-chloro-N^1-[(1E)-(2-carboxo-1H-quinolin-3-yl)methylene]-3-phenyl-1H-indole-2-carbohydrzides **3a-h**.

General procedure for the synthesis of (E)-5-substituted-*N'*-[(substituted- 2-hydroxy-6-methyl quinolin-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazides (4a-h) : Sodiumborohydride (0.044 mol) was added to a solution of compound 3a-h(0.001mol) in methanol (10 ml) and the mixture stirred for 30 min. at room temperature. The residue separated, on pouring the reaction mixture into ice-cold water was filtered, washed with water, dried and purified by crystallization from dioxane to furnish 4a-h in a good yield. (*E*)-5-Chloro-*N'*-[(1, 2-dihydro-2-oxoquinoline-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4a: Brown crystals, Yield 75%, m. p. 281 ^{0}C; IR (KBr) in cm^{-1}: 1682, 1723 (CO/CO), 3062, 3188, 3361 and 3381 (NH/NH/NH/NH); ^{1}H NMR (DMSO-d6) in δ: 3.50 (s, 2H, CH_2), 6.90-7.89 (m, 13H, ArH), 5.68 (s, 1H, NH), 10.41 (s, 1H, NH), 10.62 (s, 1H, NH), 11.05 (s, 1H, NH); FAB-MS m/z (in %): 442, 444 (68, 18), 414, 416 (41, 12), 283, 285 (41, 12), 255, 257 (100, 32), 225, 227 (32, 10), 190 (14); Anal. Requires for $C_{25}H_{19}N_4O_2Cl$: C, 67.80; H, 4.29; N, 12.65 %. Found: C, 67.61; H, 4.38; N, 12.59 %.

(*E*)-5-Chloro-N'-[(1, 2-dihydro-6-methyl-2-oxoquinoline-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4b: Yellow solid, Yield 68%, m. p. 245 ^{0}C; IR (KBr) in cm^{-1}: 1679, 1723 (CO/CO), 3061, 3190, 3325 and 3433(NH/NH/NH/NH); ^{1}H NMR in δ: 1.68 (s, 3H, CH_3), 3.44 (s, 2H, CH_2), 7.01-7.65 (m, 12H, ArH), 5.61 (s, 1H, NH), 10.25 (s, 1H, NH), 10.74 (s, 1H, NH), 10.98 (s, 1H, NH);Anal. Requires for $C_{26}H_{21}N_4O_2Cl$: C, 68.35 %; H, 4.60; N, 12.27 %. Found: C, 68.41; H, 4.48; N, 12.28 %.

(*E*)-5-Chloro-*N'*-[(1, 2-dihydro-8-methyl-2-oxoquinoline-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4c: Yellow crystals, Yield 78%, m. p. 256 ^{0}C; IR (KBr) in cm^{-1}: 1680, 1721 (CO/CO), 3061, 3188, 3328 and 3431(NH/NH/NH/NH); ^{1}H NMR in δ: 1.81 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 7.01-8.13 (m, 12H, ArH), 5.65 (s, 1H, NH), 10.41 (s, 1H, NH), 10.78 (s, 1H, NH), 11.04 (s, 1H, NH); Anal. Calcd for $C_{26}H_{21}N_4O_2Cl$: C, 68.35; H, 4.60; N, 12.27 %. Found: C, 68.40; H, 4.52; N, 12.35 %.

(*E*)-5-Chloro-*N'*-[(1, 2-dihydro-8-methoxy-2-oxoquinoline-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4d: Brown crystals, Yield 68%, m. p. 273 ^{0}C; IR (KBr) in cm^{-1}: 1684, 1723 (CO/CO), 3057, 3173, 3271 and 3360 (NH/NH/NH/NH); ^{1}H NMR in δ: 2.18 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2), 7.15-7.80 (m, 12H, ArH), 5.85 (s, 1H, NH), 10.15 (s, 1H, NH), 10.56 (s, 1H, NH), 10.86 (s, 1H, NH); Anal. Requires for $C_{26}H_{21}N_4O_3Cl$: C, 66.03; H, 4.44; N, 11.85 %. Found: C, 65.81; H, 4.52; N, 11.80 %.

(*E*)-5-Methoxy-*N'*-[(1, 2-dihydro-2-oxoquinoline-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4e: Colorless crystals, Yield 71%, m. p. 265 ^{0}C; IR (KBr) in cm^{-1}: 1681, 1723 (CO/CO), 3061, 3188, 3361 and 3432 (NH/NH/NH/NH); ^{1}H NMR in δ: 2.15 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2), 6.81-7.95 (m, 13H, ArH), 5.78 (s, 1H, NH), 10.21 (s, 1H, NH), 10.51 (s, 1H, NH), 10.98 (s, 1H, NH); FAB-MS m/z (in %): 438 (41), 410 (38), 279 (37), 251 (100), 221 (38), 190 (14). Anal. Requires for $C_{26}H_{22}N_4O_3$: C, 71.23; H, 5.02; N, 12.78 %. Found: C, 71.41; H, 4.89; N, 13.00 %.

(*E*)-5-Methoxy-N'-[(1,2-dihydro-6-methyl-2-oxoquinoline-3-yl)methylene]-3-phenyl-1H-indole-2-carbohydrazide, 4f: Light yellow crystals, Yield 75%, m. p. 261 ^{0}C; IR (KBr) in cm^{-1}: 1684, 1719 (CO/CO), 3085, 3188, 3361 and 3408 (NH/NH/NH/NH); ^{1}H NMR in δ; 1.61 (s, 3H, CH_3), 2.05 (s, 3H, OCH_3), 3.81 (s, 2H, CH_2),

6.75-7.65 (m, 12H, ArH), 5.72 (s, 1H, NH), 9.91 (s, 1H, NH), 10.35 (s, 1H, NH), 10.89 (s, 1H, NH); Anal. Requires for $C_{27}H_{24}N_4O_3$: C, 71.68; H, 5.31; N, 12.39 %. Found: C, 71.75; H, 5.24; N, 12.55 %.

(*E*)-5-Methoxy-*N'*-[(1, 2-dihydro-8-methyl-2-oxoquinoline-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4g: Colorless crystals, Yield 81%, m. p. 245 ^{0}C; IR (KBr) in cm^{-1}: 1680, 1723 (CO/CO), 3061, 3188, 3315 and 3410 (NH/NH/NH/NH); ^{1}H NMR in δ: 1.74 (s, 3H, CH_3), 2.18 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 6.89-7.75 (m, 12H, ArH), 5.68 (s, 1H, NH), 9.85 (s, 1H, NH), 10.35 (s, 1H, NH), 10.94 (s, 1H, NH); Anal. Requires for $C_{27}H_{24}N_4O_3$: C, 71.68; H, 5.31; N, 12.39 %. Found: C, 71.44; H, 5.44; N, 12.28 %.

(*E*)-5-Methoxy-*N'*-[(1, 2-dihydro-8-methoxy-2-oxoquinoline-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrazide, 4h: Colorless crystals, Yield 74%, m. p. 281 ^{0}C; IR (KBr) in cm^{-1}: 1685, 1723 (CO/CO), 3061, 3189, 3315 and 3433 (NH/NH/NH/NH); ^{1}H NMR in δ: 2.18 (s, 3H, OCH_3), 2.24 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2), 6.91-7.81 (m, 12H, ArH), 5.75 (s, 1H, NH), 9.48 (s, 1H, NH), 10.41 (s, 1H, NH), 10.81 (s, 1H, NH); Anal. Requires for $C_{27}H_{24}N_4O_4$: C, 69.23; H, 5.13; N, 11.96 %. Found: C, 69.42; H, 5.02; N, 11.80 %.

General method for the preparation of 5-substituted-*N*-(substituted-*2H*-[1, 3]oxazino[6, 5-b] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamides,(5a-h)

Compound **4a-h** (0.001mol) and formalin (37%, 1 ml) was refluxed in ethanol (10 ml) for 5 h. The residue obtained after pouring the reaction mixture into ice-cold water was filtered, washed with water, dried and purified by recrystallization from dioxane to give **5a-h** in a good yield. The compounds **5a, 5b, 5e** and **5h** recrystallized from dioxane and compound **5c, 5d, 5f** and **5g** from benzene.

5-Chloro-*N*-(*2H*-[1, 3]oxazino[6, 5-b] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5a: Colorless crystals, Yield: 69%, m. p. 212 ^{0}C; IR (KBr) in cm^{-1}: 1180 (C-O-C), 1670 (CO), 3261 and 3308 (NH/NH);1HNMR in δ: 4.25 (s, 2H, CH_2), 4.68 (s, 2H, CH_2), 7.01-7.89 (m, 13H, ArH), 9.95 (s, 1H, NH), 11.05 (s, 1H, NH); FAB-MS m/z (in %): 454, 456 (100, 34), 425, 427 (38, 11), 255, 257 (52, 16), 225, 227 (38, 12), 190 (14); Anal. RequiresforC$_{26}$H$_{19}$N$_4$O$_2$Cl: C, 68.65; H, 4.18; N, 12.32 %. Found: C, 68.75; H, 4.10; N, 12.19 %.

5-Chloro-*N*-(7-methyl-*2H*-[1, 3]oxazino[6, 5-*b*] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5b: Colorless crystals, Yield 78%, m. p. 195 ^{0}C; IR (KBr) in cm^{-1}: 1170 (C-O-C), 1660 (CO), 3211 and 3327 (NH/NH);1HNMR in δ: 1.75 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 6.81-7.65 (m, 12H, ArH), 10.25 (s, 1H, NH), 10.95 (s, 1H, NH); Anal. Requires for $C_{27}H_{21}N_4O_2Cl$: C, 69.16; H, 4.48; N, 11.95 %. Found: C, 68.95; H, 4.70; N, 11.78 %.

5-Chloro-*N*-(9-methyl-*2H*-[1, 3]oxazino[6, 5-*b*] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5c: Colorless crystals, Yield76%, m. p. 155 ^{0}C; IR (KBr) in cm^{-1}: 1180 (C-O-C), 1660 (CO), 3060 and 3310 (NH/NH); ^{1}H NMR in δ: 1.74 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 6.95-7.71 (m, 12H, ArH), 10.45 (s, 1H, NH), 10.98 (s, 1H, NH); Anal. Requires for $C_{27}H_{21}N_4O_2Cl$: C, 69.16; H, 4.48; N, 11.95 %. Found: C, 69.25; H, 4.61; N, 12.08 %.

5-Chloro-*N*-(9-methoxy-*2H*-[1, 3]oxazino[6, 5-*b*] quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5d: Colorless crystals, Yield 65%, m. p. 168 ^{0}C; IR (KBr) in cm^{-1}: 1178 (C-O-C), 1661 (CO), 3301 and 3332 (NH/NH); ^{1}H NMR in δ: 2.05 (s, 3H, OCH_3), 4.38 (s, 2H, CH_2), 4.71 (s, 2H, CH_2), 6.85-7.65 (m, 12H, ArH), 10.48 (s, 1H, NH), 11.10 (s, 1H, NH); Anal. Requires for $C_{27}H_{21}N_4O_3Cl$: C, 66.87; H, 4.33; N, 11.56 %. Found: C, 66.67; H, 4.41; N, 11.31 %.

5-Methoxy-*N*-(2H-[1, 3]oxazino[6, 5-*b*]quinolin-3-(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5e: Colorless crystals, Yield 73%, m. p. 185 ^{0}C; IR (KBr) in cm^{-1}: 1171 (C-O-C), 1671 (CO), 3271 and 3305 (NH/NH); ^{1}H NMR in δ: 2.13 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 4.67 (s, 2H, CH_2), 6.85-7.78 (m, 13H, ArH), 10.65 (s, 1H, NH), 11.05 (s, 1H, NH); FAB-MS m/z (in %): 450 (100), 421 (48), 251 (52), 221 (34), 190 (14). Anal. Requires for $C_{27}H_{22}N_4O_3$: C, 72.00; H, 4.89; N, 12.44 %. Found: C, 71.85; H, 4.98; N, 12.65 %.

5-Methoxy-*N*-(7-methyl-*2H*-[1, 3] oxazino[6, 5-*b*]quinolin-3-(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5f: Brown crystals, Yield 76%, m. p.155 ^{0}C; IR (KBr) in cm^{-1}: 1174 (C-O-C), 1678 (CO), 3064 and 3383 (NH/NH); ^{1}H NMR in δ: 1.81 (s, 3H, CH_3), 2.15 (s, 3H, OCH_3), 4.31 (s, 2H, CH2), 4.74 (s, 2H, CH_2), 6.95-7.81 (m, 12H, ArH), 10.58 (s, 1H, NH), 10.95 (s, 1H, NH); Anal. Requires for $C_{28}H_{24}N_4O_3$: C, 72.41; H, 5.17; N, 12.07 %. Found: C, 71.50; H, 5.31; N, 11.95 %.

5-Methoxy-*N*-(9-methyl-*2H*-[1, 3] oxazino[6, 5-*b*] quinolin-3-(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5g: Colorless crystals, Yield 78%, m. p. 210-212 ^{0}C; IR (KBr) in cm^{-1}: 1166 (C-O-C), 1668 (CO), 3258 and 3309 (NH/NH); ^{1}H NMR in δ: 1.78 (s, 3H, CH_3), 2.18 (s, 3H, OCH_3), 4.28 (s, 2H, CH_2), 4.68 (s, 2H, CH_2), 6.85-7.67 (m, 12H, ArH), 10.68 (s, 1H, NH), 11.15 (s, 1H, NH); Anal. Requires for $C_{28}H_{24}N_4O_3$: C, 72.41; H, 5.17; N, 12.07 %. Found: C, 71.29; H, 5.29; N, 11.88 %.

5-Methoxy-*N*-(9-methoxy-*2H*-[1, 3] oxazino[6, 5-*b*] quinolin-3-(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamide, 5h: Colorless crystals, Yield 71%, m. p. 133-136 ^{0}C; IR (KBr) in cm^{-1}: 1155 (C-O-C), 1681 (CO), 3199 and 3362 (NH/NH); ^{1}H NMR in δ: 2.18 (s, 3H, OCH_3), 2.31 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 4.71(s, 2H, CH_2), 6.91-7.85 (m, 12H, ArH), 10.41 (s, 1H, NH), 11.01 (s, 1H, NH); Anal. Requires for $C_{28}H_{24}N_4O_4$: C, 70.00; H, 5.00; N, 11.67 %. Found: C, 69.89; H, 5.05; N, 11.87 %.

2.2. Pharmacological activities.

2.2a. Antinflammatory activity by paw-edema method [29]:

Inflammation is a tissue reaction to infection, irritation or foreign substance. It is the part of the host defense mechanism but when it becomes great it causes acute inflammatory conditions. There are several tissue factors or mechanisms that are known to be involved in the inflammatory reactions such as release of histamine, bradykinin and prostaglandins. Inflammation is not one event, but a series of events occurring in an orderly sequence, though not necessarily dependent on each other for their development.

Materials and methods:

Anti-inflammatory activity was evaluated by carrageen an induced rat hind paw oedema method. Albino rats of either sex weighing between 150-200 g were divided into groups of six animals each. The first group served as the control and received vehicle only (Tween-80, 1%), second group of animals were administered with standard drug Indomethacin 25 mg/kg body weight, orally. The animals of the other groups were treated with synthesized compounds at a dose of 25 mg/kg body weight, orally. A mark was made on both the hind paws just below the tibio-tarsal junction so that every time the paw could be dipped in the mercury column of plethysmo graph upto the mark to ensure constant paw volume. The normal paw volume was measured for both the legs, after 30 min. of above

treatment an inflammation was induced in the left hind paw by injecting 0.1 ml of carrageen an (1%, w/v) in the planter tissue of the paw of all animals. The right paw served as a reference to non-inflammed paw for comparison. The initial paw volume was measured plethysmo graphically within 30 sec. of the injection. The relative increase in the paw served as a reference to non-inflammed paw for comparison. The relative increase in the paw volume was measured in control, standard and treated group, for 4 hr after carrageen an injection. The percent increase in paw volume over the initial reading was also calculated. This increase in paw volume in animals treated with standard drug and the synthesized indole and thiazole derivatives were compared with the increase in paw volume of control animals. Thus, percent inhibition of paw volume was calculated using the formula,

% inhibition = (1-Vt / Vc) x 100.

Where, **Vt** and **Vc** are mean relative changes in the paw volume of the test and control respectively.

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control. The results of anti-inflammatory testing of all the tested compounds are summarized in the following **Tables-1**.

2.2b. Analgesic activity by Tail flick method [30].

Tail flick method was followed for the evaluation of analgesic activity using the instrument analgesiometer. Albino mice of either sex weighing between 25-30 g were randomly distributed into groups consisting of six animals in each group. The first group served as a control group and animals were administered with vehicle (Tween-80, 1%) orally. The second group was administered with standard drug analgin at a dose of 25 mg/kg body weight, orally. The animals of the other groups were treated with indole derivatives at a dose of 25 mg/kg body weight, orally. The reaction time was noted at 0, 30, 60 and 90 min. of time intervals after the drug administration. Percent protection against tail flicking was calculated using the formula: **% Protection = (1-Wc/Wt) x 100**

Where Wc and Wt are the mean time for the tail flicking in the test and control groups, respectively.

All the newly synthesized indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control. The results of analgesic testing of all the tested compounds are summarized in the following **Tables-2**.

3. Results and Discussion

3.1. Chemistry

The various Schiff bases **3a-h** were prepared according to the procedure reported by us[28]. These compounds **3a-h** when reacted with sodium borohydride in dry methanol at room temperature afforded 5-substituted-*N*'-[(1, 2-dihydro-substituted-2-oxoquinoline-3-yl) methyl]-3-phenyl-*1H*-indole-2-carbohydrazides **4a-h** in a good yield. Compound **4a** in its IR spectrum showed absorption bands at 1682 1723, 3062, 3188, 3361 and 3381 cm^{-1} due to C=O/C=O and NH/NH/NH/NH functions respectively. Five singlets and a multiplet, observed at 3.50, 5.68, 10.41, 10.62, 11.05 and 6.90-7.89 δ in its ^1H NMR spectrum of compound **4a** were due to the two protons of methelene function attached to 3-position of quinoline moiety, four protons of four NH functions and thirteen aromatic protons respectively. Mass spectrum of compound **4a** exhibited molecular ion peak $M^{+\cdot}$ at 442, 444 (68%, 18%), which corresponds to its molecular weight. Due to the sequentiontial loss of CO molecule, 2-methylindole, CO molecule, N_2H_2 molecule and chloride radical from the molecular ion of compound **4a** gave fragment ions recorded at m/z 414, 416 (41%, 12%), 283, 285 (41%, 12%), 255, 257 (100%, 32%, base peak), 225, 227 (32%, 10%) and 190 (14%) respectively. All these data proves the formation of compound **4a** from compound **3a**.

Compounds **4a-h** when allowed to react with formalin in ethanol under refluxed conditions furnished 5-substituted-*N*-[substituted-*2H*-(1, 3) oxazino(6, 5-b) quinolin-3(*4H*)-yl]-3-phenyl-*1H*-indole-2-carboxamides **5a-h** in good yield. The IR spectrum of **5a** exhibited absorption bands at 1180, 1670, 3261 and 3308 cm^{-1} due to C-O-C, C=O and NH/NH functions respectively. In the ^1H NMR (in δ) spectrum of **5a** four protons of two methelene protons of oxazine moiety have resonated as two distinct singlets at 4.25 & 4.68, A multiplet appeared in the region 7.01-7.89 accounts for thirteen aromatic protons. Two distinct singlets observed at 9.95 and 11.05 are due to proton on indole NH and proton of amide function respectively. Mass spectrum **5a** displayed molecular ion peak $M^{+\cdot}$ at 454, 456 (100%, 34%), which is equivalent to its molecular weight and base peak of the compound. Further fragment ions recorded at m/z 425, 427 (38%, 11%), 255, 257 (52%, 16%), 225, 227 (38%, 12%) and 190 (14%) are due to sequential expulsion of CHO radical, $C_{10}H_8N_3$, a simultaneous expulsion of CHO radical & hydrogen radical followed by a chloride radical respectively from the molecular ion. These data clearly proves the formation of compound **5a** from **4a**.

3.2. Pharmacological activities.

3.2a. Antinflammatory activity

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control.

From **Table-1** of the results of anti-inflammatory activity of indole derivatives, it is clear that the compounds **4a, 4b, 4d, 5a, 5b** and **5d** have exhibited good anti-inflammatory activity as compared with that of standard drug indomethacin. The compounds **4c, 4e, 4f, 5c, 5e** and **5f** showed moderate anti-inflammatory activity as compared with that of standard drug indomethacin. The remaining compounds **4g, 4h, 5g** and **5h** were less active when compared with that of standard drug indomethacin. Under these conditions, the standard drug indomethacin used exhibited 73.02 % anti-inflammatory activity and control 1% Tween-80 used as a control did not show any anti-inflammatory activity.

3.2b. Analgesic activity

All the newly synthesized indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control.

From the **Table-2**, it is clearly that the compounds **4a, 4b, 4d, 5a, 5b** and **5d** exhibited good analgesic activity as compared with that of standard drug analgin. The compounds **4c, 4e, 4f, 5c, 5e** and **5f** showed moderate analgesic activity as compared with that of standard drug analgin. The remaining compounds **4g, 4h, 5g** and **5h** were less active when compared with that of standard drug. Under these conditions the standard drug analgin used exhibited 63.18% analgesia, after 60 min drug administration and 1% Tween-80 used as a control did not show any analgesic activity.

4. Conclusion

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control. The results of anti-inflammatory activity of indole derivatives, it is clear that the compounds **4a, 4b, 4d, 5a, 5b** and **5d** have exhibited good anti-inflammatory activity as compared with that of standard drug indomethacin.

All the newly synthesized indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control. From the **Table-2**, it is clearly that the compounds **4a, 4b, 4d, 5a, 5b** and **5d** exhibited good analgesic activity as compared with that of standard drug analgin.

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Table -1. Anti-inflammatory activity of indole compounds.

Group (Compound)	Dose mg/kg b.w	Mean values (± SE) of oedema volume at different intervals				% inhibition at 2hr
		0	30	60	90	
1 (Control)	1 ml	0.232 (±0.026)	0.225 (±0.021)	0.215 (±0.024)	0.201 (±0.016)	-
2 (Indomethacin)	25	0.181** (±0.009)	0.157 (±0.010)	0.058*** (±0.005)	0.061 (±0.009)	73.02
4a	25	0.159*** (±0.005)	0.139** (±0.009)	0.086*** (±0.008)	0.079 (±0.014)	60.00
4b	25	0.167*** (±0.016)	0.121 (±0.015)	0.075*** (±0.011)	0.042 (±0.009)	65.12
4c	25	0.200* (±0.009)	0.177 (±0.020)	0.121** (±0.016)	0.126 (±0.021)	43.72
4d	25	0.165** (±0.014)	0.170 (±0.017)	0.091*** (±0.008)	0.101 (±0.014)	57.67
4e	25	0.208* (±0.026)	0.159 (±0.019)	0.115** (±0.021)	0.110 (±0.014)	46.51
4f	25	0.201 (±0.016)	0.141 (±0.014)	0.118 (±0.007)	0.108 (±0.015)	45.13
4g	25	0.285 (±0.016)	0.219 (±0.018)	0.210 (±0.021)	0.181* (±0.017)	12.33
4h	25	0.208 (±0.009)	0.178* (±0.016)	0.148 (±0.011)	0.142 (±0.021)	31.16
5a	25	0. 215* (±0.011)	0.160 (±0.005)	0.114 (±0.017)	0.119** (±0.026)	46.98
5b	25	0.201* (±0.013)	0.154 (±0.017)	0.108** (±0.026)	0.115 (±0.014)	49.77
5c	25	0.192 (±0.008)	0.169 (±0.021)	0.155* (±0.018)	0.145 (±0.009)	27.90
5d	25	0.177*** (±0.016)	0.125 (±0.015)	0.080*** (±0.011)	0.042 (±0.009)	59.12
5e	25	0.181 (±0.012)	0.141** (±0.014)	0.118** (±0.022)	0.140 (±0.025)	45.11
5f	25	0.170 (±0.014)	0.167*** (±0.016)	0.122** (±0.007)	0.135 (±0.021)	43.26
5g	25	0.178 (±0.020)	0.182* (±0.016)	0.142 (±0.027)	0.139** (±0.025)	33.95
5h	25	0.280 (±0.009)	0.164** (±0.016)	0.139 (±0.009)	0.128** (±0.021)	32.00

No. of animals for each group=6, Control= 1% Tween-80

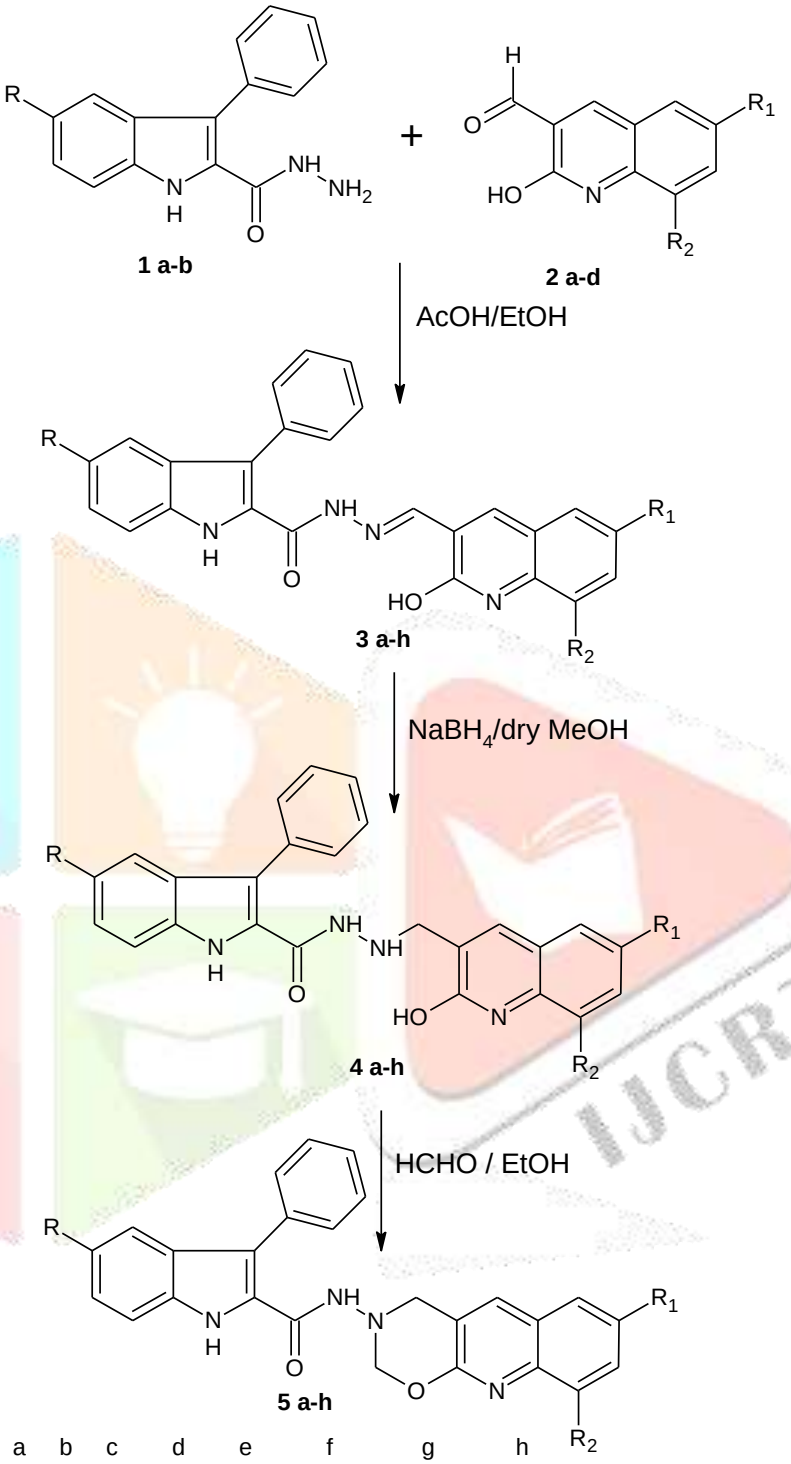
Significance levels *P< 0.05, **P<0.01, ***P<0.001 compared with respective control (**ANOVA followed by Dunnet's test**). Each value represents ±SE (n=6).

Table -2. Analgesic activity of indole compounds.

Group (Compound)	Dose mg/kg b.w	Average (± SE) reaction time (sec.) Time after drug treatment (min.)				Percent analgesia at 60 min
		0	30	60	90	
1 (Control)	1 ml	3.245 (±0.219)	3.260 (±0.223)	3.271 (±0.230)	3.257 (±0.212)	-
2 (Analgin)	25	3.895** (±0.219)	5.278** (±0.223)	8.884** (±0.208)	9.057 (±0.218)	63.18
4a	25	3.705 ** (±0.145)	5.001 (±0.223)	7.971** (±0.281)	8.025 (±0.108)	58.96
4b	25	3.741 ** (±0.070)	5.208 (±0.223)	7.041** (±0.218)	6.197 (±0.208)	53.54
4c	25	3.205 ** (±0.243)	3.578 (±0.235)	3.874* (±0.210)	3.957 (±0.108)	15.57
4d	25	3. 724** (±0.219)	4.648 (±0.223)	6. 127** (±0.210)	6. 725** (±0.208)	46.61
4e	25	3.025 ** (±0.219)	3.178 (±0.213)	3.874* (±0.210)	3.957 (±0.108)	15.57
4f	25	3.281 (±0.219)	3.289 (±0.223)	4.071 (±0.2108)	3. 725 (±0.2108)	19.65
4g	25	3.311* (±0.019)	3.548 (±0.224)	3.451 (±0.219)	3.657 (±0.2108)	05.22
4h	25	3. 425* (±0.219)	3. 826 (±0.293)	3.794 (±0.2108)	3. 721 (±0.2108)	13.78
5a	25	3.725 ** (±0.145)	5.231 (±0.223)	8.071** (±0.281)	8.025 (±0.108)	59.47
5b	25	3.681 ** (±0.076)	5.358 (±0.233)	7.215** (±0.218)	6.197 (±0.208)	54.66
5c	25	3. 524** (±0.278)	3. 628 (±0.420)	4. 940 (±0.112	6.1 25 (±0.140)	33.78
5d	25	3.985 (±0.246)	5. 821 (±0.24)	5.991** (±0.210)	6.75 (±0. 115)	45.40
5e	25	3.254 (±0.219)	4. 628** (±0.223)	5.210 (±0.2108)	5.275 (±0.2108)	37.21
5f	25	3.885 ** (±0.219)	5.218 (±0.223)	5.104* (±0.2108)	5.027 (±0.2108)	35.91
5g	25	3.279* (±0.209)	4.286* (±0.243)	4.071 (±0.210)	4.257 ** (±0.208)	19.61
5h	25	3.215* (±0.037)	3.818 (±0.223)	3.801 (±0.215)	3.957 (±0.216)	13.94

No. of animals for each group=6, Control= 1% Tween-80

Significance levels *P< 0.05, **P<0.01, ***P<0.001 compared with respective control (**ANOVA followed by Dunnet's test**). Each value represents ±SE (n=6).



	a	b	c	d	e	f	g	h
R=	-Cl	-Cl	-Cl	-Cl	$-OCH_3$	$-OCH_3$	$-OCH_3$	$-OCH_3$
R_1=	-H	$-CH_3$	-H	-H	-H	$-CH_3$	-H	-H
R_2=	-H	-H	$-CH_3$	$-OCH_3$	-H	-H	$-CH_3$	$-OCH_3$

Scheme-I