# SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF SOME NEW 5-SUBSTITUTED -$N^1$-[(1E)-(2-CARBOXO-1*H* QUINOLIN-3-YL) METHYLENE]-3-PHENYL-1H-INDOLE-2-CARBOHYDRZIDE DERIVATIVES

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**Abstract**

Indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds, because of their varied biodynamic properties. New substituted indole Schiff bases 5-substituted -$N^1$-[(1E)-(2-carboxo-1*H*-quinolin-3-yl)methylene]-3-phenyl-1H-indole-2-carbohydrzide **3a-d** are synthesized by condensation of 5-Substituted-3-phenyl-2-carboxahydrazide (0.01 mol) and substituted 3-formyl-2-carboxo-1*H*-quinolines (0.01 mol) in presence of catalytic amount of the glacial acetic acid. These Schiff bases on further reacting with acetic anhydride/ thioglycolic acid in DMF / $FeCl_3$-AcOH and con Sulphuric acid gives respective pyrrazole **4a-d**, thioazolidine **5a-d**, 1, 3, 4-oxadiazole **6a-d** and oxadiazino **7a-d** indole derivatives. All the above synthesized compounds are conformed by spectral data and elemental analysis. The newly synthesized compounds were screened for their antimicrobial activity.

**Introduction**

Literature survey reveals that indole and its derivatives possess wide spectrum of biological activities. In continuation of our research work on the synthesis of indole derivatives viz, antimicrobial, analgesic (1), anticatatonic (2), and anti-inflammatory (3) activities. Several indole derivatives are reported to possess antiviral (4), antihepatitis-B virus(HBV) (5) and COX-2 inhibitors (6). Qunolines analogues have attracted great attention of medicinal and synthetic chemists because of their presence in natural products and physiological activities. There are many methods available for synthesis qunolines, the Vilsmeier approach has been recently, explored by Katritzky etal (7) and Srivastav etal (8). In recent years, the chemistry of qunolines and their derivatives as gained increasing attention, particularly because substituted qunolines are associated with immense biological activities (8-9). Fused indolo[2,3-c]isoquinolines possesses various biological activities such as bactericidal, fungicidal, anticancer and antihistaminic activity(10-14). Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, oxadiazoles (15-16), thioazolidines (17-18) and oxadiazino (19-20) derivatives have played vital role in the medicinal chemistry. In this paper we report here the synthesis of some pyrrazole, thioazolidine, 1, 3, 4-oxadiazole and oxadiazino ring moieties containing indole and quinoline moieties by making use of 3,5-disubstituted indole-2-carboxyhydrazide and substituted 3-formyl-2-carboxo-1*H*-quinolines as starting materials.

**Experimental:**

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer FT-IR (spectrum 1000); $^1$H NMR spectra on a Bruker AMX (500 MHz) spectrophotometer using DMSO or $CHCl_3$ as solvent and TMS as an internal standard (chemical shifts in □) and mass spectra on a FAB-MS instrument.

**Synthesis of 5-substituted-N$^1$-[(1*E*)-(2-carboxo-*1H*-quinolin-3-yl)methylene]-3-phenyl-1*H*-indole-2-carbohydrzide 3a-d:**

5-substituted-3-phenyl-2-carboxyhydrazide **1a-b** (0.01mol) and substituted-3-formyl-2-hydroxy-quinoline **2a-b** (0.01 mol) and a catalytic amount of glacial acetic acid were taken in ethanol (20 ml) and refluxed for 7-8hr on water bath. The resulting solid were filtered, washed with little alcohol dried and recrystallised to get 5-chloro-N$^1$-[(1*E*)-(2-carboxo-*1H*-quinolin-3-yl)methylene]-3-phenyl-1*H*-indole-2-carbohydrzide **3a-d.**

**Synthesis of 3-[(2*S*)-3-acetyl-5-(-5-susbtituted-3-phenyl-1*H*-indol-2-yl) 2,3-dihydro-1,3,4-oxadiazol-2-yl]quinolin-2-yl acetate 4a-d:**

A mixture of the **3a-d** (0.01mol) and acetic anhydride (10 ml) was refluxed for 3hr on refluxed for 3 hr on oil bath. The reaction mixture was cooled to room temperature, poured into ice-cold water and the solid separated was recrystallised from suitable solvent to yield 3-[(2*S*)-3-acetyl-5-(5-susbtituted -3-phenyl-1*H*-indol-2-yl) 2,3-dihydro-1,3,4-oxadiazol-2-yl]quinolin-2-yl acetate **4a-d.**

**Synthesis of 5- substituted -*N*-[(2*R*)-2-(2-carboxo-*1H* quinolin-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenyll-1*H*-indole-2-carboxamide 5a-d:**

**3a-d** (0.01 mol) was refluxed in DMF (30 ml) containing a pinch of anhydrous zinc chloride and thioglycolic acid (0.01 mol) for 8hr. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered washed and recrystallised from suitable solvent to get 5- substituted -*N*-[(2*R*)-2-(2-carboxo-*1H* quinolin-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenyll-1*H*-indole-2-carboxamide **5a-d**..

**Synthesis of 2-carboxo-1*H*- 3-[5-(5- substituted -3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]quinolin 6a-d:**

To a well stirred solution of **3a-d** (0.01 mol) in acetic acid (15 ml), a solution of ferric chloride (1.5 g) in water (5 ml) was added. The mixture was stirred for 1hr and diluted with water (100) and kept at room temperature for two days. The solid separated was filtered, washed with water and crystallized to get **6a-d**

**Synthesis of 2-(5-chloro-3-phenyl-1*H*-inol-2yl)[1,3,4]oxadiazepino[7,6-b]quinoline 7a-d.**

**3a-d** (0.01mol) was added slowly to concentrated Sulphuric acid (AR grade, 0.015mol) in the cold, with stirring. The resulting mass was allowed to attain room temperature and poured into cold water. After neutralization with liquid ammonia, the product 2-(5-chloro-3-phenyl-1*H*-inol-2yl)[1,3,4]oxadiazepino[7,6-b]quinoline **7a-d** were obtained, filtered washed dried and crystallized from suitable solvents.

**Results and discussion:**

Various substituted schiff's bases of indole prepared by the reaction of substituted indole-2-carboxyhydrazide **1a-b** with 3-formyl-2-hydroxy-quinolines **2a-b** in presence of catalytic amount of glacial AcOH under refluxed conditions gives 5-chloro-N$^1$-[(1*E*)-(2-hydroxyquinolin-3-yl) methylene]-3-phenyl-1*H*-indole-2-carbohydrzide **3a-d**. The structure of these compounds conformed by spectral data. The IR spectrum compound **3a** exhibited absorption peaks at 1610, 1674, 3229, and 3311 cm$^{-1}$, due to C=N, C=O and NH/NH functions respectively. The PMR spectrum of **3a** displayed three singlets at 12.2, 12.0 and 11.5 due to protons of OH, NH of indole and NH-C=O respectively. Azomethine proton has resonated as singlet at 7.35 and a multiplet observed in the region 7.10-7.90 is due to thirteen protons of aromatic function. Mass spectral fragmentation of the compound **3a** has displayed the molecular ion peak at m/z 441, 443 (82%, 27%). It has undergone into fragmentation to generate a fragment of peaks at m/z 254, 256 (100%, 32%), which is the base peak of the compound. Further fragmentation is generated peaks at m/z 219 (15%), m/z 190 (17%) and m/z 89 (20%). These spectral data supports the proposed structure of compound **3a**. Further Cyclization of these schiff bases **3a-d** with acetic anhydride under refluxed conditions gave the desired 3-[(2*S*)-3-acetyl-5-(-5-chloro-3-phenyl-1*H*-indol-2-yl) 2,3-dihydro-1,3,4-oxadiazol-2-yl]quinolin-2-yl acetate **4a-d**. The IR spectrum of substituted oxadiazole **4a** the showed the absorption peaks at 1607, 1699 and 1716 cm$^{-1}$, due to cyclic C=N, C=O, ester C=O functions respectively. The peak due to the indole NH at 3352 cm$^{-1}$. The NMR spectrum shows two singlets at 2.4 and 2.8 due to two methyl protons, a multiplet observed in the region 7.10-8.00 is due to thirteen protons of aromatic function and Azomethine proton. The fine singlet at 11.4 due to the NH of indole. This further supported by the mass spectrum. Compound **4a** has undergone into fragmentation to generate a fragment of molecular ion peak at m/z 524, 526(45%, 15%), other fragmented peaks are at m/z 483, 485(52%, 17%), m/z 439, 441(54%,18%), m/z 296, 298(81%, 27%) and m/z 254, 256(100%, 31%) which is the base peak of the compound. Further these schiff bases **3a-d** on reaction with thioglycolic acid in presence of catalytic amount of $ZnCl_2$, DMF as solvent used, furnishes the thioazolidine derivatives 5-chloro-*N*-[(2*R*)-2-(2-hydroxyquinolin-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenyll-1*H*-indole-2-carboxamide **5a-d**. The formation these compounds conformed by spectral data. The IR spectrum of **5a** shows peaks at 1652, 1657 and 1738 cm$^{-1}$ due to C=O, –C=ONH and C=O of thioazolidine respectively. The absorption peaks appeared at 3267 and 3351 cm$^{-1}$ due to NH/NH functions respectively. The PMR spectrum shows the singlet at 3.21 and 3.81 due to –CH=N and -$CH_2$ functions of thioazolidine respectively. A multiplet observed in the region 6.9-7.9 is due to thirteen protons of aromatic protons, the fine singlet appears at 8.4, 9.4 and 11.9 due to amide NH, NH of indole and OH of quinoline. Mass spectral fragmentation of the compound **5a** has displayed the molecular ion peak at m/z 503,505(82%, 27%). It has undergone into fragmentation to generate a fragment of peaks at m/z 359, 361(72%, 22%), 254, 256 (100%, 32%), which is the base peak of the compound. Further fragmentation is generated peaks at m/z 219 (15%), m/z 190 (17%) and m/z 89 (20%)

The compounds **3a-d** on reaction with $FeCl_3$ in presence of acetic acid under stirring at room temperature gives the substituted oxadiazole derivatives 3-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]quinolin-2-ol **6a-d**, these further conformed by the spectral studies. The IR spectrum of compound **6a** gives absorption peaks at 1597, 1618, 1654, 3290 and 3415 cm$^{-1}$ due to the two C=N of oxadiazole, NH of indole and OH of quinoline respectively. The NMR spectrum shows the two singlets at 11.4 and 12.0 due to the NH of indole and OH of quinoline respectively. The multiplet due to thirteen protons of aromatic function at 7.4-8.0. Mass spectral fragmentation of the compound **6a**

has displayed the molecular ion peak at m/z 439, 441 (45%, 14%). It has undergone into fragmentation to generate a fragment of peaks at m/z 412, 414(8%, 2%), 394, 396(100%, 32%), which is the base peak of the compound. Further fragmentation is generated peak at m/z 219 (15%). These schiff base compounds **3a-d** which on Cyclization with Conc.$H_2SO_4$ yielded 2-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3.4-oxadiazepino[7,6-b]quinoline **7a-d**. These oxadiazino derivatives conformed by spectral data. The IR spectrum of **7a** showed peaks at 1609, 1615 and 3225 $cm^{-1}$ due to two C=N of oxadiazino group and NH of indole respectively. The NMR spectrum show peak at 12.0 for NH of indole. The multiplet at 6.9-7.9 due to fourteen aromatic protons. Mass spectral fragmentation of the compound **7a** has displayed the molecular ion peak at m/z 423, 425 (79%, 23%). It has undergone into fragmentation to generate a fragment of peaks at m/z 265, 267 (100%, 32%), which is the base peak of the compound. Further fragmentation is generated peaks at m/z 217(45%) and m/z 191(21%).These spectral data supports the proposed structure of compound **7a**.

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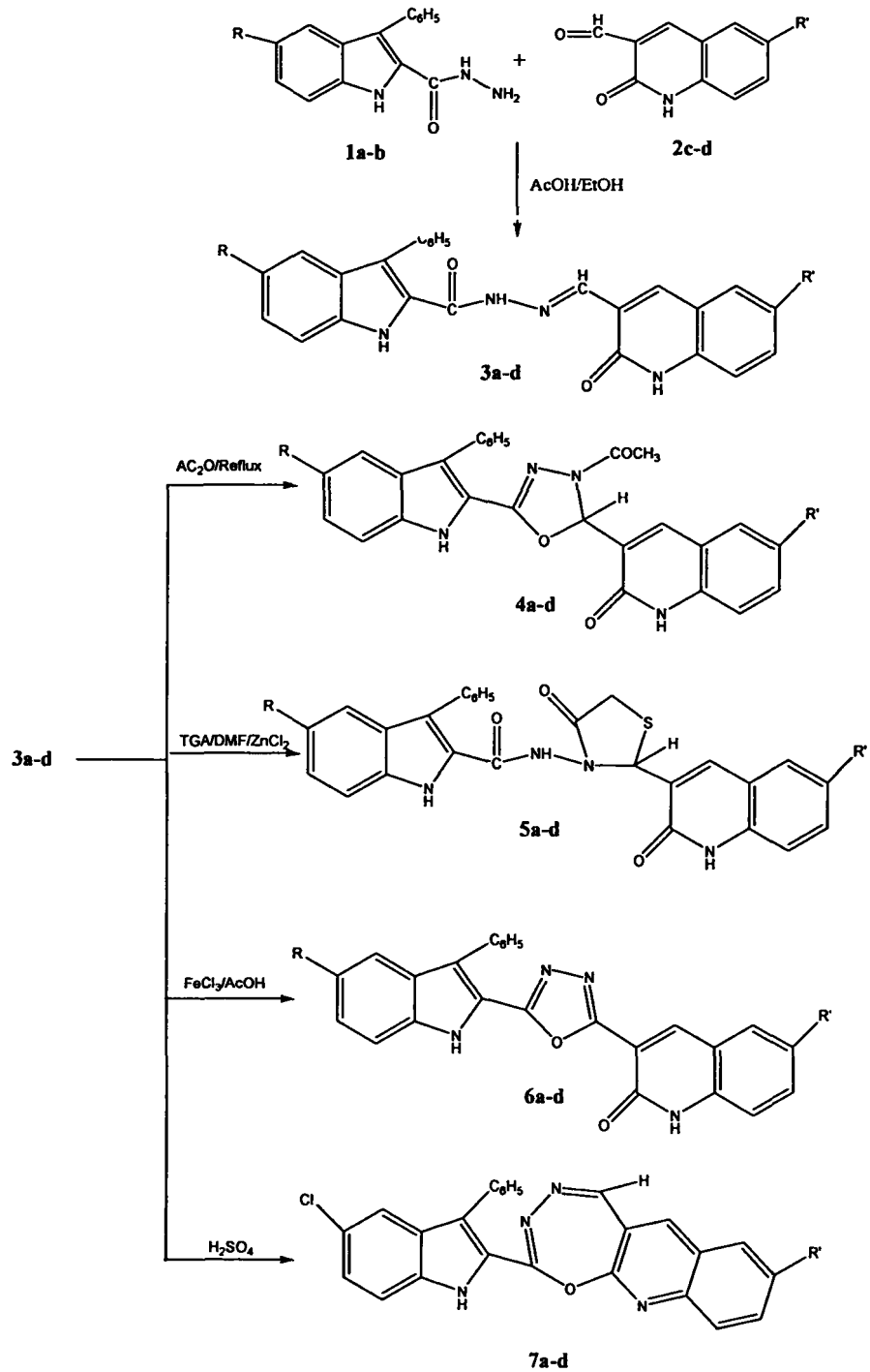
**Table-I: Characterization data of synthesized compounds**

| Compds | R | $R^1$ | M.P $^0$C (Yield%) | Spectral data* (IR (KBr)$\nu_{max}$ *in* $cm^{-1}$;$^1$HNMR *in* δ; Mass *in m/z*) |
|---|---|---|---|---|
| 1a | Cl | H | 324-327(65) | 1608 (C=N), 1661,1674 (C=O/C=O), 3162, 3229, 3311(NH/NH/NH); 7.1-8.2 (m, 13H, ArH), 8.4 (s, 1H, 1CH) 11.6 (s, 1H, NH), 12.0 (s, 1H, CONH), 12.2 (s, 1H, CONH); 440, 442(82%,27%), 254, 256(100%,33%), 219(15%), 191(21%) |
| 1b | Cl | $CH_3$ | 315(69) | 1594 (C=N), 1661, 1675 (C=O/C=O), 3165, 3226, 3311 (NH/NH/NH) |
| 1c | $OCH_3$ | H | 309(74) | 1593 (C=N), 1661, 1673 (C=O/C=O), 3129, 3296, 3382 (NH/NH/NH) |
| 1d | OCH | $CH_3$ | 288-291(60) | 1593 (C=N), 1661, 1673 (C=O/C=O), 3189, 3297, 3373 (NH/NH/NH) |
| 2a | Cl | H | 168(68) | 1180 (C-O-C), 1607 (C=N), 1699, 1716 (C=O/C=O), 3352 (NH); 2.4 (s, 3H, $CH_3$),2.7 (s, 3H, $CH_3$), 6.6 -7.8 (m, 13H,ArH), 8.1(s, 1H, CH), 11.8(s, 1H, NH); 524, 526(45%,15%), 481, 483(52%,17%), 438, 440(19%,54%), 294, 296(18%, 41%), 252, 254(33%,100%) |
| 2b | Cl | $CH_3$ | 194(72) | 1180 (C-O-C), 1615 (C=N), 1660, 1715 (C=O /C=O), 3358 (NH) |
| 2c | $OCH_3$ | H | 188(69) | 1180 (C-O-C), 1616 (C=N), 1661, 1716 (C=O/C=O), 3351 (NH) |
| 2d | OCH | $CH_3$ | 201(75) | 1180 (C-O-C), 1605 (C=N), 1661, 1715 (C=O/C=O), 3345 (NH) |
| 3a | Cl | H | 188(79) | 663 (C-S-C), 1652,1657, 1738 (C=O /C=O/C=O),3259, 3267,3351 (NH/NH/NH); 3.42 (s, 2H, $CH_2$), 6.9-8.0 (m, 14H, ArH& CH), 8.2 (s, 1H, NH), 9.0 (s, 1H, CONH), 11.9 (s, 1H,CONH); 514, 516(4%, 1%), 357, 359(52%, 18%), 254, 256(100%, 33%), 219(18%), 190(23%) |
| 3b | Cl | $CH_3$ | 165(69) | 663 (C-S-C),1656, 1688, 1737 (C=O /C=O/C=O), 3264,3293, 3351 (NH/NH/NH) |
| 3c | $OCH_3$ | H | 175(67) | 670 (C-S-C),1621, 1681, 1721 (C=O /C=O/C=O), 3189,3246, 3346 (NH/NH/NH) |
| 3d | OCH | $CH_3$ | 212(74) | 657 (C-S-C),1654, 1660, 1715 (C=O /C=O/C=O) ,3164, 3229, 3340 (NH/NH/NH) |
| 4a | Cl | H | 235(79) | 1174 (C-O-C), 1597, 1618 (C=N/C=N), 1654 (C=O), 3258, 3312 (NH/NH); 7.4-8.2(m, 13H, ArH), 11.7(s, 1H, NH), 12.0(s, 1H, CONH); 438, 440(40%, 13%), 410, 412(8%,2%), 394, 396(100%,33%), 359(15%) |

| | | | | |
|---|---|---|---|---|
| 4b | Cl | $CH_3$ | 198(64) | 1176 (C-O-C), 1563,1605 (C=N/C=N), 1644 (C=O), 3229, 3310 (NH/NH) |
| 4c | $OCH_3$ | H | 191(71) | 1166 (C-O-C), 1579,1615 (C=N/C=N), 1687 (C=O), 3225, 3421 (NH/NH) |
| 4d | OCH | $CH_3$ | 254-257(59) | 1172 (C-O-C), 1548,1612 (C=N/C=N), 1644 (C=O) , 3229, 3390 (NH/NH) |
| 5a | Cl | H | 240(79) | 1180 (C-O-C), 1571,1609,1654 (C=N/C=N/C=N), 3308 (NH); 7.1-7.8 (m, 13H,ArH),7.0 1(s, 1H, CH), 12.0 (s,1H, NH); 422, 424(79%, 23%), 265, 267(100%, 31%), 266,268(26%,7%) 238,240(12%,44%), 217(45%), 191(21%) |
| 5b | Cl | $CH_3$ | 221(63) | 1166 (C-O-C),1566,1602,1668 (C=N/C=N/C=N), 33 08 (NH) |
| 5c | $OCH_3$ | H | 265(67) | 1166 (C-O-C),1566,1602,1660 (C=N/C=N/C=N), 3307 (NH) |
| 5d | OCH | $CH_3$ | 271-275(61) | 1180 (C-O-C),1571,1605,1654 (C=N/C=N/C=N), 3309 (NH) |

*All the compounds gave satisfactory analysis for C, H and N.




| | a | b | c | d |
|---|---|---|---|---|
| R | Cl | Cl | $OCH_3$ | $OCH_3$ |
| R' | H | $CH_3$ | H | $CH_3$ |

**Scheme 1**