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# Synthesis and Characterisation of Biologically Important (*E*)-1-(2-Chloro/hydroxy-6/8-substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1, 3, 4-thiadiazol-2-yl]methanimines

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**ABSTRACT**

A new series of (*E*)-1-(2-chloro/hydroxy-6/8-substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1,3,4-thiadiazol-2-yl]methanimine derivatives were synthesized by the condensation of 5-(4-substituted phenyl)-1,3,4-thiadiazole-2-amine with 6/8-substituted-2-chloroquinoline-3-carbaldehyde and 6/8-substituted-2-hydroxy quinoline-3-carbaldehyde.

The novel quinoline-thiadiazole derivatives were confirmed by Mass, NMR and IR spectroscopy. These newly formed quinoline-thiadiazole derivatives shows antibacterial and antifungal activities. Among them few of the novel compounds showed biological activities comparable with that of standard drug.

**KEY WORDS:** Thiosemicarbazide, Thiadiazole, Antibacterial, Antifungal.

## 1. INTRODUCTION

In heterocyclic chemistry quinoline derivatives are very useful since they show diverse pharmacological properties. The derivatives of quinoline shows a various medicinal properties such as antimalarial (Vlabhov, 1990), antibacterial (Nathesh Ramesh kumar, 2003; Pramod, 2011), antifungal (Monika Guptha, 2010), antiviral (Pandey, 2001) and antituberculotic (Vijay Agraval, 1999) etc. 1, 3, 4-Thiadiazole also nitrogen containing compounds and exhibit broad spectrum of pharmacological action such as antimicrobial (Jumat Salimon, 2010; Varasha Jatav, 2006; Khosrow Zamani, 2004), antioxidant (Venkatapuram Padmavathi, 2009), anti-inflammatory (Schenone, 2006) and wound healing activity (Jayakumar Swamy, 2012). In the present work the two heterocyclic moieties are combined together to enhance their antimicrobactirial and antifungal activities.

## 2. MATERIALS AND METHODS

All the materials used from Sigma Aldrich, Alfa, and Spctrochem Chemicals Pvt. Ltd. Melting points of all the synthesised compounds were recorded by melting point instrument. The completions of the process were checked by TLC. IR spectra were found on a NICOLET AVATAR 330 FTIR spectrophotometer, $^1$H-NMR was recorded on BRUKER 400 MHz spectrophotometer and mass of the compound was determined by LCMS: SHIMAZD LCMS2010A instrument.

The 2-amino-5-(4-substituted phenyl)-(1, 3, 4)-thiadiazoles (1) were synthesized by the reaction between thiosemicarbazide, benzoic acid and concentrated $H_2SO_4$ (Scheme.1).

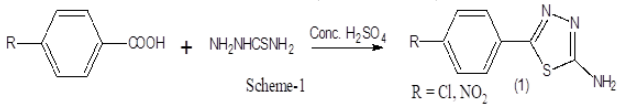



**Figure.1. Synthesis of 2-Amino-5-(4-substituted phenyl)-(1,3,4)-thiadiazoles**

The 6/8 Substituted-2-chloro-3-formyl quinolones (2) were synthesized by the reaction between substituted acetanilide, phosphorous oxychloride and dimethyl formamide. 6/8-substituted-2-chloro-3-formyl quinolones (2) on hydrolysis with hydrochloric acid yielded 6/8 Substituted-2-hydroxy-3-formyl quinolones (3) (Scheme.2).

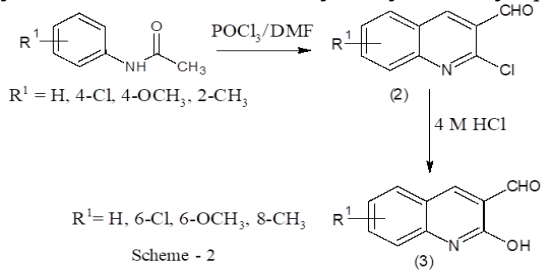
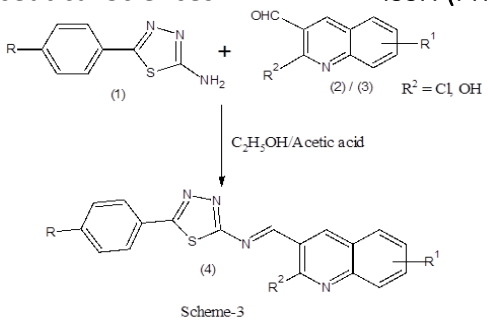



**Figure.2. Synthesis of 6/8-Substituted-2-chloro/hydroxy-3-formyl quinolones**

The (*E*)-1-(2-chloro/hydroxyl-6/8-substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1,3,4-thiadiazol-2-yl]methanimines (4) were synthesized by the reaction between2-amino-5-(4-substituted phenyl)-(1,3,4)-thiadiazoles(1) and 6/8 Substituted-2-chloro/hydroxy-3-formyl quinolones using ethanol and acetic acid(2)/(3) (Scheme 3).




Scheme-3

**Figure.3. Synthesis of (*E*)-1-(2-Chloro/hydroxyl-6/8-substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1,3,4-thiadiazol-2-yl]methanimines**

**Experimental Procedures:**

**General procedure for the synthesis of 2-amino-5-(4-substituted phenyl)-(1,3,4)-thiadiazoles (1) (Scheme-1): (Mahendrasinh & Raj, 2013):** A mixture of thiosemicarbazide (9.11g, 0.1mol), benzoic acid (12.2g, 0.1mol) and conc.$H_2SO_4$ (5ml) in 50 ml ethanol was refluxed for 1.5 hours. After cooling the liquid content was poured into ice. The product separated was filtered, washed and purified from ethyl alcohol to separate the product.

**General procedure for the synthesisof 6/8 substituted-2-chloro-3-formyl quinolones (2) (Scheme-2): (Ambika Srivastava, 2005):** To a solution of substituted acetanilide (5 mmoles) in dry dimethyl formamide (15 mmoles) at 0-5$^0$C with stirring $POCl_3$ (60 mmoles) was added drop wise and the mixture stirred at 80-90$^0$C for time ranging between 4-16 hr. The product obtained was poured into crushed ice, stirred for 5 min and the resulting solid mass was filtered, washed well with water and dried. The compounds were recrystallized from either ethyl acetate or acetonitrile.

**General procedure for thesynthesisof 6/8 substituted-2-hydroxy-3-formyl quinolones (3) (Scheme-2) (Pramod, 2011):** A mixture of 6/8-substituted chloroquinolines (0.01M) and HCl (35ml, 4M) was subjected to heating for 4 hours. The product was poured into crushed ice. When hydroxyl quinolines separated as yellow solid, it was purified. It was recrystallized from aqueous acetic acid into yellow sticky needles.

**General procedure for the synthesis of (*E*)-1-(2-chloro/hydroxyl -6/8 substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1, 3, 4-thiadiazol-2-yl]methanimine(4) (Scheme-3):** The solution of 2-amino-5-(4-substituted phenyl)-(1,3,4)-thiadiazole (0.01 mol) and 6/8 substituted-2-chloro/hydroxy-3-formyl quinolines (0.01mol) in ethanol (100-200ml) and glacial acetic acid (2ml) was added and refluxed for 16-24 hours. The crude product obtained was purified by recrystallization from ethanol/glacial acetic acid, to obtain pure crystalline compounds.

**Spectral data:**

4a: IR (KBr) cm$^{-1}$: 1674 (-C=N stretch), 1550(C=C stretch), 2991(-C-H stretch), 1089(-C-N stretch). $^1$HNMR (DMSO) δ ppm: 7.25-8.52 (m, 9H, Ar-H), 10.25(s, 1H,-N=CH-), ESIMS (m/z): 385 (M+).

4e: IR (KBr) cm$^{-1}$:1679(-C=N stretch), 1603(C=C stretch), 2828 (-C-H stretch), 1105 (-C-Nstretch). $^1$HNMR (DMSO) δ ppm: 7.25- 8.52 (m, 9H, Ar-H), 10.25(s, 1H,-N=CH-), ESIMS (m/z): 396 (M+).

4i: IR (KBr) cm$^{-1}$: 1677 (-C=Nstretch), 1550(C=Cstretch), 2987, (-C-H stretch), 1105(-C-N stretch). $^1$HNMR (DMSO) δ ppm: 7-7.8 (m, 9H, Ar-H), 8.5(s, 1H, N-H) 10.5(s, 1H,-N=CH-), ESIMS (m/z): 367 (M+).

**Table.1. Characterization data of (*E*)-1-(2-chloro/hydroxyl -6/8 substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1,3,4-thiadiazol-2-yl]methanimines (4a-4l)**

| Comp. | R | R$^1$ | R$^2$ | Molecular formula | Mol. Wt. (g) | Melting point ($^0$C) | Yield (%) | Calculated % | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H | N |
| 4a | Cl | H | Cl | $C_{18}H_{10}Cl_2N_4S$ | 385 | 280$^0$C | 82 | 56.11 | 2.62 | 14.15 |
| 4b | Cl | 6-Cl | Cl | $C_{18}H_9Cl_3N_4S$ | 419 | 283$^0$C | 56 | 51.51 | 2.16 | 13.35 |
| 4c | Cl | 6-$OCH_3$ | Cl | $C_{19}H_{12}Cl_2N_4OS$ | 415 | 277$^0$C | 62 | 54.95 | 2.91 | 13.49 |
| 4d | Cl | 8-$CH_3$ | Cl | $C_{19}H_{12}Cl_2N_4S$ | 399 | 273$^0$C | 73 | 57.15 | 3.03 | 14.03 |
| 4e | $NO_2$ | H | Cl | $C_{18}H_{10}ClN_5O_2S$ | 396 | 270$^0$C | 79 | 54.62 | 2.55 | 17.69 |
| 4f | $NO_2$ | 6-Cl | Cl | $C_{18}H_9Cl_2N_5O_2S$ | 430 | 278$^0$C | 53 | 50.25 | 2.11 | 16.28 |
| 4g | $NO_2$ | 6-$OCH_3$ | Cl | $C_{19}H_{12}ClN_5O_3S$ | 426 | 267$^0$C | 61 | 53.59 | 2.84 | 16.45 |
| 4h | $NO_2$ | 8-$CH_3$ | Cl | $C_{19}H_{12}ClN_5O_2S$ | 409 | 265$^0$C | 69 | 55.68 | 2.95 | 17.09 |
| 4i | Cl | H | OH | $C_{18}H_{11}ClN_4OS$ | 367 | 295$^0$C | 77 | 58.94 | 3.02 | 15.27 |
| 4j | Cl | 6-Cl | OH | $C_{18}H_{10}Cl_2N_4OS$ | 401 | 303$^0$C | 59 | 53.88 | 2.51 | 13.96 |
| 4k | Cl | 6-$OCH_3$ | OH | $C_{19}H_{13}ClN_4O_2S$ | 397 | 293$^0$C | 62 | 57.50 | 3.30 | 14.12 |
| 4l | Cl | 8-$CH_3$ | OH | $C_{19}H_{13}ClN_4OS$ | 381 | 288$^0$C | 65 | 59.92 | 3.44 | 14.71 |

## 3. RESULTS AND DISCUSSION

The quinoline-thiadiazole derivatives were tested for antibacterial and antifungal activities using minimum inhibitory concentration (MIC) (Schwalbe, 2007) by the serial dilution method (Stokes, 1980; Metin, 2013). The antibacterial activities on the bacteria *Escherichia Coli* and *Bacillus Subtilis.* Furacin was used as the standard. Antifungal activity was on the fungus *Aspergillus Niger*. Fluconazole was employed as the standard. Among the tested compounds 4d and 4hshown highest antibacterial activity. Compounds 4j and 4l shown potent antifungal activities. The data's are given in table.2.

**Table.2. Antibacterial and Antifungal activity Data of novel compounds.**

| **Compound** | **Minimum inhibitory concentration in µg/mL** | | |
|---|---|---|---|
| | **Antibactirial** | | **Antifungal** |
| | ***E. Coli*** | ***B. Subtilis*** | ***A. Niger*** |
| 4d | 10 | 10 | 6 |
| 4f | 5 | 6 | 5 |
| 4g | 6 | 5 | 7 |
| 4h | 10 | 10 | 7 |
| 4j | 6 | 10 | 10 |
| 4k | 10 | 7 | 5 |
| 4l | 7 | 6 | 10 |
| Furacin | 10 | 10 | - |
| Flucanzol | - | - | 10 |
| DMF(control) | - | - | - |

Index for biological activity: disc size: 5.5 mm; duration: 24 hours.

## 4. CONCLUSION

Quinoline-thiadiazole compounds show biological and pharmacological activities. Twelve novel (*E*)-1-(2-chloro/hydroxyl -6/8 substituted quinolin-3-yl)-*N*-[5-(4-substitued phenyl)-1,3,4-thiadiazol-2-yl]methanimines were synthesized and some of them characterized by IR, $^{1}$HNMR and Mass spectroscopy. A few of them were subjected for antibacterial and anti-fungal activities. The results have shown that some of compounds showed powerful antibacterial and antifungal activities.

## REFERENCES

Ambika Srivastava and Singh R.M, The VIlsmeier-Haack reagent, A facile synthesis of 2- chloro-3-formylquinolines from N aryl acetamides and transformation into different functionalities, Ind. J. Chem, 42B, 2005, 1868-1875.

Jayakumar Swamy B.H.M, Thiadiazole-Quinoline derivaives as Potential Wound Healing Activity, International Journal of Phytopharmacology, 3 (2), 2012, 157-162.

Jumat Salimon, Synthesis and antibacterial activity of some new 1, 3, 4-oxadiazole and 1, 3, 4-thiadiazole derivatives, Journal of applied Sciences Research, 6 (7), 2010, 866-870.

Khosrow Zamani, Synthesis and antimicrobial activity of some pyridyl and naphhyl substituted 1, 2, 4-trizole and 1, 3, 4- thiadiazole derivatives, Trunk J. Chem., 28, 2004, 95-100.

Mahendrasinh Raj M, Hemul Patel V, Laa Raj M and Nainika Patel V, Synthesis and biological evaluation of some 1, 3, 4-thiadiazole derivatives for their antimicrobial activities, International Journal of Pharmaceutical, Chemical and Biological Sciences, 3 (3), 2013, 814-819.

Metin K, Cahit O, Akif EP, Abdurrazak S, Pelin K, Mustafa K, Sevgi DD, Synthesis and biological activities of some novel aminomethyl derivatives of 4-substituted-5-(2-thienyl)-2, 4dihydro-3H-1, 2, 4-triazole-3-thiones, Eur. J. Med. Chem., 63, 2013, 340– 346.

Monica Guptha, Satyapaul, Rajiv Guptha, One pot synthesis of antifungal active 9-substituted-3-aryl-5H, 13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4] triazepines, Ind. J. Chem., 42B, 2010, 475-481.

Nathesh Ramesh Kumar, Mohan Ashok Kumar, Ekamaram Harihara Subramaninan, The synthesis of 6-fluoro -1, 4-dihydro-4-oxo-quinoline-3-carboxylic acid as potential antimicrobial agents, Eur. J. Med Chem., 38, 2003, 1001-1004.

Pandey VK, Meenal Tandon, Synthesis of some new quinolylimidazoles for the anti-viral and antifungal activities, Ind. J. Chem., 42B, 2001, 527-529.

Pramod N and Jayakumarswamy, Synthesis and antimicrobial activity of furoquinolines, Ind.J. Het. Chem., 21, 2011, 61-64.

Pramod N and Jayakumarswamy, Synthesis, Charecterisation and Wound Healing Activity of 1-(8-Methyl-Furo [2,3-b] Quinolin-2yl) Ethanone Derivatives, International J. of Chemical and Pharmaceutical Sciences, 2 (3), 2011, 9-14.

Schenone S, Brullo C, Bruno O, Bondavalli F, Ranise A, Filippelli W, Rinaldi B, Capuano A, Falcone G, New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities, Bioorganic & Medicinal Chemistry, 14 (6), 2006, 1698-1705.

Schwalbe R, Steele-Moore L, Goodwin A.C, Antimicrobial Susceptibility Testing Protocols, CRC Press, 2007.

Strokes EJ, Ridway GL, Clinical Bacteriology, 5th edition, Edward Arnold London, 1980, 234.

Varsha Jatav, Synthesis and Antimicrobial activity of Novel 2-Mehyl-3-(1, 3, 4-thiadiazoyl)-4-(3H) Quinazolinones, Indian Journal of pharmaceutical Sciences, 1, 2006, 360-363.

Venkatapuram Padmavathi, Synthesis, antimicrobial and antioxidant activities of sulfone linked bis heterocycles-pyrazolyl oxadiazoles and pyrazolyl thiadiazole, Chem. Pharm. Bull, 57 (12), 2009, 1376-1380.

Vijay Agrawal K, Shahnaz Bano, Keshav Mathur C, Padmakumar Khadikar V, Quantitaive Structure-activity relationship studies on antituberculotic$N_1$-cyclopropylquinolones using Szeged Index (Sz), Ind. J Chem, 38A, 1999, 1203-1208.

Vlabhov R, Parushev St, Vlahov J, Nickel P, Snatzke G, Synthesis of some new quinoline derivatives-potential antimalarial drugs, Pure Appl. Chem., 62 (7), 1990, 1303-1306.