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Synthesis of thiazoloquinoline schiff bases as potential antibacterial agents

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ABSTRACT

The novel synthetic methods of heterocyclic Schiff bases are attracting the science society through their potential bio and medicinal applications which motivated us to develop new quinoline Schiff bases using 2-amino-4(p-methylphenyl)-thiazole as starting precursor. All the newly synthesized Schiff bases by a simple condensation reaction are characterised and confirmed using FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass and CHNS elemental analysis techniques. Titled compounds are screened for their antibacterial activity against different Gram-positive and Gram-negative bacterial strains using disc dilution method. Among the synthesized compounds (2-amino-4(p-methyl phenyl)-thiozole and 8-methoxy and naphthyl substituted quinoline Schiff bases have shown remarkably enhanced activity against *Escherichia coli, Salmonella typhi* and *Staphylococcus aureus*. The minimum inhibition concentration (MIC) values observed from (25-32)µg/mL for three different bacterial strains.

Keywords: 2-amino-4(p-methylphenyl)thiazole, substituted quinoline-3-carbaldehydes, antibacterial activity, Streak dilution method.

1. INTRODUCTION

Infectious diseases constitute a tenacious and major public-health hazard all over the world. The treatment of infectious diseases still remain a challenging task because of combination of factors such as an alarming increase in number of multi-drug-resistant microbial pathogens and advent of newer infectious diseases. Despite the availability of a large number of antibiotics and chemotherapeutics, the inevitable consequence of widespread and injudicious use of antibacterial has been the emergence of antibiotic-resistant pathogens, resulting in a serious threat to global public health [1]. The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibacterial. A potential solution to the antibiotic resistance is to design and explore innovative heterocyclic agents with novel mode of actions. In this context, thiazole derivatives have been playing a crucial role in medicinal chemistry [2-4]. Thiazole nucleus constitutes an integral part of all the available penicillin's, which have transformed the bacterial diseases therapy. They display quite a broad spectrum of biological activities, which have found applications in the treatment of allergies [15], hypertension, inflammation, schizophrenia, cancer [9,10] , microbial infections and HIV infections [14]. Further, thiazoles have emerged as new class of potent antimicrobial agents [8], which are reported to inhibit bacteria by blocking the biosynthesis of certain bacterial lipids and/or by additional mechanism.

2. MATERIALS AND METHODS

Synthetic starting material, reagents and solvents were of analytical reagent grade of the highest quality commercially available and were purchased form Aldrich Chemical Co. (USA) and Merck Chemical Co. (USA) and were dried when necessary. The progress of the reaction was monitored by thin layer chromatography with silica-gel with calcium sulphate binder (Merck Chemical Co., USA) using petroleum ether/ethyl acetate (v/v) as eluent. UV light and iodine vapours were used for detection of compounds. IR spectra were recorded, using KBr pellets, on a Schimadzu FT-IR spectrophotometer. Electron ionization (EI) mass spectra were obtained on Jasco Model (JASCO International Co. Ltd., Japan). ^{1}H-and ^{13}C-NMR spectra, in DMSO-(D_6) solution, was recorded on A Bruker AC 200 instrument at

298 K. Chemical shifts were reported as δ relative to TMS as internal standard. Melting points (ºC) were determined with an open glass capillary tube and uncorrected. Elemental analysis was performed in Perkin Elmer 240 instrument (Perkin Elmer Life and Analytical Sciences Ins., USA).

2.1 Synthesis of 2-amino-4-(p-methyl phenyl) thiazole (I) (Fig. I)

Compound (I) prepared by cyclisation of thiourea with p-methyl phenacyl bromide (α-halo ketone) in accordance with method described in the literature [11] and recrystallized from ethanol (m.p 124-126º C).

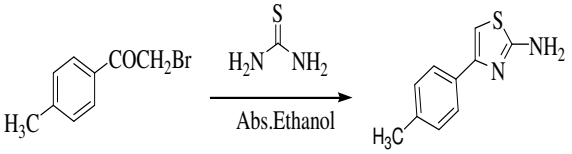

Fig. I 2-amino-4(p-methylphenyl)thiazole

2.2. Scheme 1: Synthesis of Substituted-2-oxoquinoline-3-carbaldehydes 2(a-g) (Fig. II)

The titled compounds 2(a-g) were synthesized from the respective substituted 2-chloro3-formyl quinolines. The O-nucleophilic substitution of chloro group in quinoline3-carbaldehyde (0.01mole) was readily accomplished by refluxing it in 20ml of glacial acetic acid for 4-5hrs. After completion of the reaction, the whole mass was poured into crushed ice, the solid obtained was filtered, washed with water and recrystallized from ethanol and purified by column chromatography (pet. ether/ethyl acetate - 95/5). Their structures were confirmed with reported melting points. [12-13]

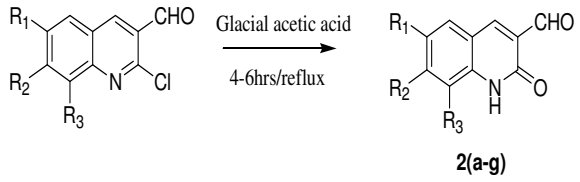

Fig. II Substituted 2-oxo-quinoline-3-carbaldehydes

2.3. Scheme 2: Synthesis of substituted 3-[(4-p-Tolyl-thiazol-2ylimino)-methyl](1H)quinolin-2-ones 3(a-g) (Fig.III)

Condensation of equimolar quantities of 2-amino-4(p-methyl phenyl) thiazole (I) (0.01mole) in 20ml of glacial acetic acid with a serious of methyl, methoxy, and naphthyl substituted 3-formyl quinolin(1H)-2-ones 2(a-g) (0.01mole) in ethanol (30ml) was refluxed with few a drops of glacial acetic acid for 6-8hrs. After completion of the reaction, the whole reaction mass was poured into crushed ice, the solid obtained was filtered, washed with water and recrystallized from ethanol. The structure of Schiff bases were confirmed by using spectroscopic (FT-IR, ^{1}H-NMR, ^{13}C-NMR, Mass) and elemental analysis.

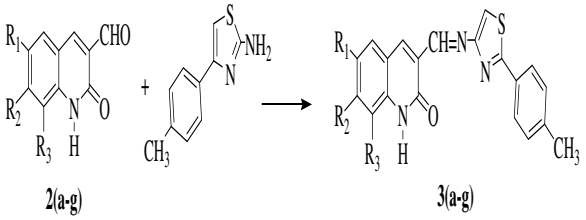

Fig. III Substituted 3-[(4-p-Tolyl-thiazol-2ylimino)-methyl]1H-quinolin-2-ones

2.4 Anti bacterial activity

Antibacterial activity of newly synthesized compounds (1) and 3(a-g) were evaluated against *Escherichia coli, Salmonella typhi* and *Staphylococcus aureus* bacterial strains by disc dilution method using nutrient agar medium. The sterilized medium (120℃ for 30 min) was inoculated (1ml/100ml of medium) with the suspension (105CFU/ml) of the micro organism and poured into the petridish to a depth of 3-4mm. The paper impregnated with the test compounds (50µg/ml in dimethyl sulfoxide) was placed on the solidified medium. The plates were preincubated for 1h at room temperature and incubated at 37℃ for 24 hours. Neomycin was used as standard for antibacterial activity. The observed zone inhibitions of the standard and test elements are presented in Table I. Minimum inhibitory concentrations (MIC) of the test compounds were determined by agar streak dilution method.

3. RESULTS AND DISCUSSION

The spectral data of synthesized Schiff bases were as follows:

3.1. 3-[(4-p-Tolyl-thiazol-2ylimino)methyl]-1H-quinolin-2-one (3a)

IR (KBr, cm^{-1}): υ = 1653 (C=N of azomethine), 1523 (C=N thiazole), 3308 (C-OH), 696 (C-S-C). ^{1}H-NMR (200MHz, [D_6] DMSO): δ = 2.37(C_5-CH_3), 8.50(s,1H,C_4-H), 7.34 (d,1H,C_5-H J=8.1Hz), 7.50(t,1H,C_6-H), 7.61(t,1H,C_7-H), 7.63(d,1H,C_8-H) 6.62(s,1H,CS-H), 7.17-7.21 (dd,2H,C'$_2$,C_5'-H), 7.27-7.65(dd,2H,C_3,C_5-H), 9.19(s,1H,N=CH). MF $C_{20}H_{15}N_3OS$ m.p 210-214°C, Yield: 63%, Calcd: C 69.54, H 4.37, N 12.16 Found: C 69.52, H 4.33, N 12.15, Ms (EI, 70eV): m/z: 347.43 [M+2] - 439.

3.2. 6-methyl-[3-(4-tolyl-thiazol-2ylimino)-methyl]-1H-quinolin-2-one (3b)

IR (KBr, cm^{-1}): υ = 1653 (C=N of azomethine), 1522 (C=N thiazole), 3307 (C-OH), 682 (C-S-C). ^{1}H-NMR (200MHz, [D_6] DMSO): δ = 2.32(s,3H,C_6-CH_3)), 2.37(C_5-CH_3), 8.50 (s,1H, C_4-H), 7.34 (d,1H,

C_5-H), 7.62(d, 1H,(C_7-H), 7.64(d,1H,C_8-H), 6.63(s,1H,CS-H), 7.19-7.23 (dd, 2H, C'$_2$, C_5'-H), 7.31-7.64(dd, 2H, C_3, C_5-H), 9.19(s, 1H, N=CH) $C_{21}H_{17}N_3OS$ m.p 212-215°C, Yield: 64%, Calcd: C 70.17, H 4.76, N 11.69, Found: C 70.14, H 4.75, N 11.67, Ms (EI, 70eV) m/z : 359.44, [M+2] 361.

3.3. 8-methyl-3-[(4-p-Tolyl-thiazol-2ylimino)methyl]-*1H*-quinolin-2-one (3c)

IR (KBr, cm^{-1}): υ = 1612 (C=N of azomethine), 1529 (C=N thiazole), 3316 (C-OH), 684 (C-S-C), ^{1}H-NMR (200MHz, [D_6] DMSO): δ = 2.41(s, 3H, (C_8-CH_3)), 2.37(C_5-CH_3), 8.50 (s,1H, C_4-H), 7.34 (d,1H, C_5-H), 7.50(t, 1H, C_6-H), 7.61(d, 1H,(C_7-H), 6.66(s, 1H, CS-H), 7.17-7.21 (dd, 2H, C'$_2$, C_5'-H), 7.27-7.65(dd, 2H, C_3, C_5-H), 9.19(S, 1H, N=CH). ^{13}C-NMR (200MHz, [D_6] DMSO): δ=20.69(C_5'-CH_3), 17.10(C_8-CH_3), 163.9(C-2), 156.3(C-4),123.5(C-5), 123.8(C-6), 128.7(C-7), 129.6(C-8), 136.2(C-9), 126.5(C-10), 165.32(CH=N), 154.10(C_1'), 114.24(C_2'), 156(C_3'), 133.7(C_4'), 126.7(C_5', C_9'), 129.2(C_6', C_8'), 137.9(C_7'). m.p 186-190°C, Yield: 63%, Calcd: C 70.17, H 4.76, N 11.69 Found: C 70.16, H 4.71, N 11.72 $C_{21}H_{17}N_3OS$ (359.44) MS(EI, 70eV): m/z(%)=73(100)$[M]^+$ [M+2] 361.

3.4 6,8-Dimethyl-3-[(4-p-tolyl-thiazol-2ylimino)methyl]-1H-quinolin-2-one (3d)

IR (KBr, cm^{-1}): υ = 1644 (C=N of azomethine), 1525 (C=N thiazole), 3303 (C-OH), 677 (C-S-C) ^{1}H-NMR (200MHz, [D_6] DMSO): δ = 2.31(s, 3H, (C_8-CH_3)), 2.33 (s,3H, C_6-CH_3) 2.37(C_5-CH_3), 8.50 (s,1H, C_4-H), 7.34 (d,1H, C_5-H), 7.62(d, 1H,(C_7-H), 6.65(s, 1H, CS-H), 7.17-7.21 (dd,2H,C'$_2$,C_5'-H), 7.27-7.65(dd,2H,C_3,C_5-H), 9.19(s,1H,N=CH). $C_{22}H_{19}N_3OS$ M.Pt: 200-206°C, Yield: 69% Calcd: C 70.71, H 5.12, N 11.25 Found: 70.68, H 5.13, N 11.22.Ms (EI, 70eV): m/z 373.47 [M+2] - 375.

3.5. 6-Methoxy-3-[(4-p-tolyl-thiazol-2ylimino)methyl]-1H-quinolin-2-one (3e)

IR (KBr, cm^{-1}): υ = 1617 (C=N of azomethine), 1506 (C=N thiazole), 3315 (C-OH), 685 (C-S-C). ^{1}H-NMR (200MHz, [D_6] DMSO): δ = 4.04(s,3H,C_6-OCH_3), 2.37(C_5-CH_3), 8.46(s,1H, C_4-H), 7.31(d,1H, C_5-H J=8.70Hz), 7.52(t, 1H, C_6-H), 7.63(d, 1H,(C_7-H,J=8.2Hz), 6.53(s, 1H,C-H), 7.12-7.21(dd,2H,C'$_2$,C_5'-H), 7.27-7.40(dd,2H,C_3,C_5-H), 9.17(s,1H,N=CH). $C_{21}H_{17}N_3O_2S$, M.Pt: 191-195°C, Yield: 60%, Calcd: C 73.01, H 4.56, N 11.19 Found: C 73.0, H 4.52, N 11.18, Ms (EI, 70eV) m/z: 375.44 [M+2] – 377.

3.6. 8-Methoxy-3-[(4-p-tolyl-thiazol-2ylimino)methyl]-1H-quinolin-2-one (3f)

IR (KBr, cm^{-1}): υ = 1648 (C=N of azomethine), 1566 (C=N thiazole), 3344 (C-OH), 673(C-S-C), ^{1}H-NMR (200MHz, [D_6] DMSO): δ = 4.02 (s,3H, C_8-OCH_3), 2.37(C_5-CH_3), 8.46(s,1H, C_4-H), 7.31(d,1H,C_5-HJ=8.70Hz), 7.52(t,1H,C_6-H), 7.63(d,1H,C_7-H,J=8.03Hz), 6.53(s,1H,C-H), 7.13-7.20(dd,2H,C'$_2$,C_5'-H), 7.27-7.40(dd,2H,C_3,C_5-H), 9.17(s,1H,N=CH). $C_{21}H_{17}N_3O_2S$ m.p 180-185°C, Yield: 64%, Calcd: C 70.17, H 4.76, N 11.69, Found: C 70.18, H 4.73, N 11.67, Ms (EI, 70 eV) m/z = 375.44 [M+2] – 377.

3.7. 3-[(4-p-Tolyl-thiazol-2ylimino)methyl]-1H-benzo[h]-quinolin-2-one (3g)

IR (KBr, cm^{-1}): υ = 1685 (C=N of azomethine), 1570 (C=N thiazole), 3344 (C-OH), 748 (C-S-C).^{1}H-NMR(200MHz,[D_6]DMSO):δ = 2.37(C_5-CH_3), 7.32-7.68(m,6H,C_5,C_6,C_7,C_8,C_9,C_{10}), 8.51 (s,1H, C_4-H), 7.34 (d,1H, C_5-H), 7.50(t,1H,C_6-H), 7.61(d,1H,(C_7-H), 6.61(s,1H,CS-H), 7.17-7.21(dd,2H,C'$_2$,C_5'-H), 7.27-7.65(dd, 2H,C_3,C_5-H), 9.19(s,1H,N=CH). $C_{24}H_{17}N_3O_2S$ m.p.190-194°C, Yield: 68%, Calcd: C 72.88, H 4.33, N 10.62, Found: C 72.85, H 4.31, N 10.63, Ms (EI,70eV) m/z : 395.47 [M+2] - 396.

Table - 1: Antibacterial activity of synthesized compounds against Gram negative and positive bacterial strains

Compound	In vitro activity-zone of inhibition in mm(MIC in µg/ml)		
	Escherichia coli	***Salmonella typhi***	***Staphylococcus aureus***
1	6(32)	6(25)	2(31)
3a	1(45)	1.5(41)	1(46)
3b	3(40)	1.5(43)	-
3c	2(44)	1(48)	-
3d	1(40)	1.5(36)	-
3e	1(38)	1.5(34)	0.5(49)
3f	3(34)	5(28)	4(30)
3g	3(32)	5(26)	6(27)
Neomycin	25(0.3)	23(0.4)	24(0.3)
DMSO	-	-	-

In IR spectra absence of aldehyde, amino functional group peaks and appearance of azomethine peaks evidenced that the expected imino compound was formed by condensation of 2-amino-4(p-methylphenyl)thiazole (I) and various substituted 2-oxo-quinoline-3-aldehydes 2(a-g) and the absence of residual staring materials. In ^{1}H-and ^{13}C-NMR peaks at δ 9.19, δ 165.32 and $[M]^{+}$ peak at 359, [M+2] 361 in mass spectra also revealed the formation of Schiff bases.

All the Schiff base derivatives moderately inhibited the growth of Gram positive and negative bacteria and among them (2-amino-4(p-methyl phenyl)-thiozole (I) and 8-methoxy (3f) and benzo (3g) substituted quinoline Schiff bases showed enhanced antibacterial activity. Pure thiazole compound is proved as a prominent antibacterial to treat Gram negative *Escherichia coli* and *Salmonella typhi* and naphthyl substituted Schiff base is suitable to stamp down Gram positive *Staphylococcus aureus*. The compounds containing methyl group showed minimum inhibitory activity for Gram negative bacterial strains and evidenced as inactive towards Gram positive strain.

4. CONCLUSION

The new thiazolo quinoline Schiff base compounds 3(a-g) were synthesized successfully and examined for their antibacterial activity. The compounds exhibited reasonable antibacterial activity as compared to the standard. The results obtained validate the hypothesis that Schiff bases having substitution with benzo, methoxy group in 8th position of quinoline ring were suitable for antibacterial activity while methyl substituted at different positions in the aromatic ring is unfit to be used as bacterial resistant. The results also ensured that the thiazole and 8-methoxy and naphthyl substituted quinoline Schiff bases can be used as proficient pathogenic bacteria resistant compared to other derivatives.

5. REFERENCES

1. Laura Freire- Moran. Critical shortage of new antibiotics in development against multidrug-resistant bacteria—Time to react is now, **Drug resist update**. 2011; 14: 118-124.
2. Narendra Singh. Synthesis and antimicrobial activity of some novel 2-amino thiazole derivatives, **J. Chem. Pharm. Res**. 2010; 2 (3): 691-698.
3. Bharti SK and Nath G. **Eur. J. Med. Chem.** 2010: 45:651-660.
4. Nuray Ulusay and Guzelde mirci. Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadizoles bearing imidazo[2,1,b] thiazole moiety. **J. Med. Chem.** 2010; 45: 63-68.
5. Sandhya Bawa and Suresh Kumar. Synthesis of Schiff's bases of 8-methyl- tetrazole [1, 5, α]quinoline as potential anti inflammatory and antimicrobial agents, **Eur. J. Med. Chem.** 2009; 48B: 142-145.
6. Rajan S Giri and Hardik M Thakar. Design, synthesis and characterization of novel 2(2,4-disubstituted – thiozole-5-yl)-3-aryl-3H-quinoline-4-one derivatives as inhibitors of NF-Kb and AP-1 mediated transcription activation and as potential inflammatory agents, **Eur. J. Med. Chem**. 2009; 44: 2184-2189.
7. Kalkhambar RG and Kulkarni GM. Synthesis of novel triheterocyclic thiazoles as anti-inflammatory and analgesic agents, **Eur. J. Med. Chem**. 2007; 42: 1272-1276.
8. Prakash Karegoudar and Mari Sithambaram. Synthesis of some novel 2,4-disubstituted thiazoles as possible anti microbial agents, **Eur. J. Med. Chem.** 2008; 43: 261-267.
9. Zeng-Chen Liu and Bao-Dui Wang. Crystal structure, DNA binding and cytotoxic activities studies of (Cu II) complexes with 2-oxoquinoline-3-carbaldehyde, ***Eur. J. Med. Chem.*** 2010; 45: 5353-5361.
10. Nadeem Siddiqui and Satish Kumar Arya. Diverse biological activities of Thiazoles: A Retrospect, **Int. J. Drug Dev. & Res.,** 2011; 3 (4): 55-67.
11. Ahluwalia VH and Pooja Bhagat. **Intermediates of Organic Synthesis**, IK International private limited, Chapter 5 Heterocyclic compounds, 2005; 275-276.
12. Ambika Srivastava and Singh RM. Vilsmeier-Haack reagent: A facile synthesis of 2- Chloro 3-formylquinolines from N-aryl acetamides and transformation into different Functionalities, **Indian J. Chem. Sect B.** 2005; 44 (B): 1868- 1875.
13. Meth-Cohn O and Narine B. Anti microbial activity and synthesis of quinoline-based Chalcones, **Tetrahedron Lett.** 1978; 23: 2045-2048.
14. Lakshmana Doss M and Lalitha KG. Molecular docking studies of thiazole schiff's bases as HIV1-protease inhibitors, **J. Curr. Chem. Pharm. Sci**. 2011; 1(1): 52-58.
15. Hargrave KD, Hess FK and Oliver JT. Palladium (II) Schiff base complexes derived from sulphanilamide and aminobenzothiazoles, **J. Med. Chem.,**1983; 26: 1158-1163.