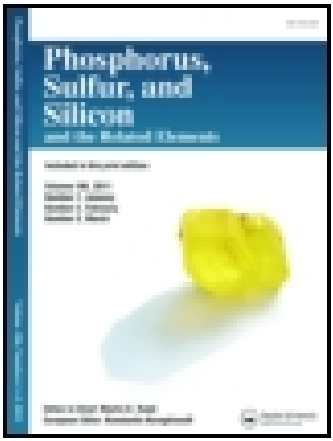

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Synthesis, Characterization, and Antimicrobial Studies of Some Quinolines Containing 1,3-Thiazines

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Synthesis, Characterization, and Antimicrobial Studies of Some Quinolines Containing 1,3-Thiazines

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6/8-Substituted-2-chloroquinoline-3-carboxylic acids, upon reaction with 3-(p-substituted aryl)-4H-5-mercapto-1,2,4-triazoles in the presence of sodium acetate and an acetic anhydride medium, afforded a novel series of 2-(p-substituted aryl)-s-triazolo[5,1-b]-6/8-substituted quinolino [1,3] thiazin-9(H)-ones. The structures of the new compounds were elucidated by IR, ^{1}H NMR, and mass spectral studies. All the newly synthesized compounds have been screened for their antibacterial and antifungal activities. Most of them showed significant activity comparable with that of the standards Furacin and Flucanazol.

Keywords Antibacterial activity; antifungal activity; mercapto-s-triazoles; quinoline carboxylic acids; 1,3-thiazine

INTRODUCTION

Thiazines are found to show a number of biological activities such as anticancer,[1] antileukemic,[2] and antibacterial[3] properties. Some thiazines also show antihypertensive[4] activity. Quinolines are the traditional antimalarial drugs.[5] Many of them also exhibit potent anti-inflammatory and antipyretic action.[6,7] Various 1,2,4-triazole derivatives are found to associated with diverse pharmacological activities such as antiviral,[8] antitubercular,[9] antibacterial,[10] and antifungal[10] properties. Quinoline

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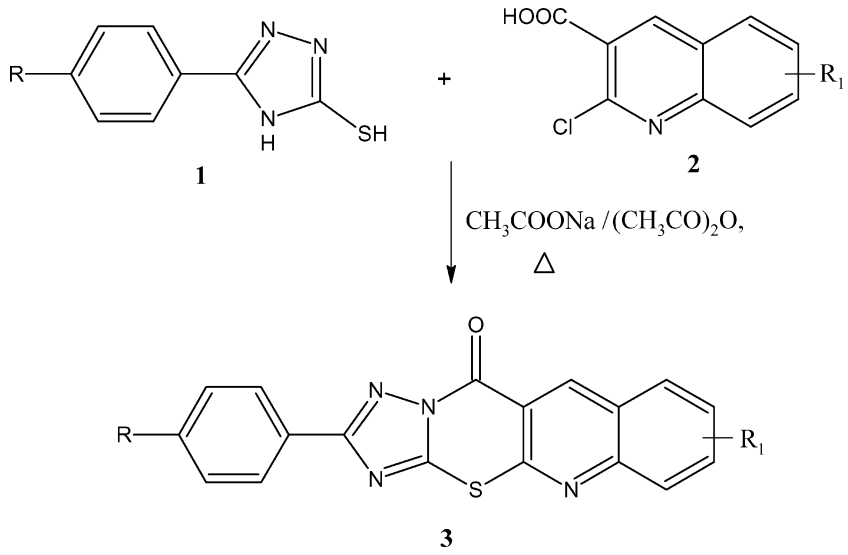

SCHEME 1

moiety flanked with a thiazole ring has been found to possess antibacterial activity.[11] Prompted by these observations and also in continuation of our research work[12,13] on quinoline-containing biologically active compounds, we studied the reactions of 3-substituted-4H-5-mercapto-1,2,4-triazoles with 6/8-substituted-2-chloroquinoline-3-carboxylic acid. Such reactions resulted in the formation of a novel series of 2-aryl-s-triazolo[5,1-b]-6/8-substituted quinolino[1,3]thiazine-9(H)-ones **3**.

The synthetic route followed for obtaining the title compounds is outlined in Scheme 1. Thus 3-substituted aryl-4H-5-mercapto-1,2,4-triazoles **1** on reaction with 6/8-substituted-2-choroquinoline-3-carboxylic acid **2** in acetic anhydride in the presence of sodium acetate afforded a series of the title compounds 2-(p-substituted aryl)-s-triazolo[5,1-b]-6/8-substituted quinolino[1, 3] thiazine-9H-ones **3**. The 1,2,4-triazole **1** and quinolino carboxylic acids **2** were synthesized according to the procedures in the literature.[14,15]

RESULTS AND DISCUSSION

The structure of newly synthesized thiazines **3** were established on the basis of their analytical and spectral data. The IR spectra of compounds **3** showed absorption bands in the region 1700–1720 cm^{-1},

characteristic of carbonyl stretching, and 1622–1640 cm^{-1} characteristic of carbon nitrogen stretching. In a typical example, the ^1H NMR spectra of **3b** showed a singlet at δ 2.62, integrating for three protons of the methyl group. The quinoline 4-H proton appeared as a singlet at δ 9.43, integrating for one proton, while the signals due to the quinoline 8-H appeared as a doublet at δ 8.01, integrating for one proton. The signals due to the remaining quinoline protons and aromatic protons merged together and appeared as a multiplet in the region of δ 7.42–8.32, integrating for 7 protons. Similarly in the mass spectrum of compound **3b**, the molecular ion peak was observed at m/z, 344 (M.F. $C_{19}H_{12}N_4OS$) in agreement with the proposed structure.

Characterization data of the new compounds are given in Table I, and the spectral data of other compounds are presented in the Experimental section.

Antibacterial and Antifungal Activities

The antibacterial and antifungal activity of the newly synthesized compounds was assessed by minimum inhibitory concentration (MIC) by the serial dilution method.[16] The antibacterial activity of the newly synthesized thiazines **3** were carried out against four different microorganisms, namely *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa.* Furacin was used as the standard. Antifungal activity was carried out on the fungus *Candida albicans*. Flucanazol was employed as the standard.

Among the compounds tested, most of them showed significant antibacterial and antifungal activity comparable with that of the standard. Particularly compound **3f** carrying p-hydroxyphenyl group at position 3 of the triazole moiety and methyl group at position 6 of quinoline moiety showed highest activity against *P. aeruginosa*. Also compounds **3i, 3j, 3k**, and **3l** carrying p-chlorophenyl group at postion 3 of the triazole moiety showed significant antibacterial activities such as **3i** against *P. aeruginosa*, **3j** against *S. aureus*, **3k** against *E. coli* and *P. aeruginosa*, and **3l** against *S. aureus.* Similarly, the compounds **3d, 3i**, and **3l** showed significant antifungal activity against *C. albicans* (Table II).

EXPERIMENTAL

Melting points were determined by capillary method and are uncorrected. IR spectra were recorded on a Nicolet Avatar 330 FT IR

TABLE I Characterization Data of 2-(p-Substituted aryl)-s-triazolo[5,1-b]-6/8-substituted Quinolino[1,3] thiazin-9(H)-ones 3a–l

Compd	R	R_1	Product description	Yield (%) mp (°C)	Mol. Formula	Found% (Calcd)		
						C	H	N
3a	H	H	White crystals	72 >300	$C_{18}H_{10}N_4OS$	65.49 (65.45)	2.98 (3.03)	17.03 (16.96)
3b	H	6-Methyl	White crystals	70 >300	$C_{19}H_{12}N_4OS$	66.31 (66.27)	3.39 (3.48)	16.32 (16.27)
3c	H	8-Methyl	Pale yellow crystals	67 286–87	$C_{19}H_{12}N_4OS$	66.38 (66.27)	3.43 (3.48)	16.18 (16.27)
3d	H	6-Methoxy	Yellow crystals	71 >300	$C_{19}H_{12}N_4O_2S$	63.28 (63.33)	3.28 (3.33)	15.62 (15.55)
3e	OH	H	Yellow crystals	74 >300	$C_{18}H_{10}N_4O_2S$	62.38 (62.42)	2.94 (2.89)	16.23 (16.18)
3f	OH	6-Methyl	Yellow crystals	77 >300	$C_{19}H_{12}N_4O_2S$	63.30 (63.33)	3.26 (3.33)	15.64 (15.55)
3g	OH	8-Methyl	Yellow crystals	72 >300	$C_{19}H_{12}N_4O_2S$	63.26 (63.33)	3.42 (3.33)	15.45 (15.55)
3h	OH	6-Methoxy	Yellow crystals	71 >300	$C_{19}H_{12}N_4O_3S$	60.72 (60.63)	3.23 (3.19)	14.93 (14.89)
3i	Cl	H	White crystals	70 >300	$C_{18}H_9ClN_4OS$	59.34 (59.25)	2.39 (2.46)	15.43 (15.36)
3j	Cl	6-Methyl	Pale yellow crystals	65 >300	$C_{19}H_{11}ClN_4OS$	60.31 (60.24)	3.02 (2.91)	14.83 (14.79)
3k	Cl	8-Methyl	Pale yellow crystals	69 295–96	$C_{19}H_{11}ClN_4OS$	60.16 (60.24)	3.11 (2.91)	14.68 (14.79)
3l	Cl	6-Methoxy	Yellow crystals	73 >300	$C_{19}H_{11}ClN_4O_2S$	57.84 (57.79)	2.72 (2.79)	14.24 (14.19)

Solvent of crystallization dimethylformamide.

TABLE II Antibacterial and Antifungal Activity Data of Compounds 3a–l

Compd	Antibacterial activity(MIC in μg/mL)				Antifungal activity(MIC in μg/mL)
	E. coli	*S. aureus*	*P. aeruginosa*	*B. subtilis*	*C. Albicans*
3a	6.25	12.5	6.25	12.5	6.25
3b	6.25	6.25	6.25	6.25	6.25
3c	6.25	12.5	6.25	6.25	6.25
3d	6.25	6.25	6.25	6.25	**3.125**
3e	6.25	6.25	6.25	12.5	6.25
3f	12.5	6.25	**3.125**	25	6.25
3g	6.25	12.5	6.25	6.25	6.25
3h	6.25	6.25	6.25	6.25	6.25
3i	6.25	6.25	**3.125**	25	**3.125**
3j	6.25	**3.125**	6.25	6.25	6.25
3k	**3.125**	6.25	**3.125**	12.5	6.25
3l	6.25	**3.125**	6.25	6.25	**3.125**
Furacin	6.25	6.25	6.25	6.25	—
Flucanazol	—	—	—	—	6.25
DMF (Control)	—	—	—	—	—

Index for biological activity: disc size: 5.5 mm; duration: 24 h; *E. coli*: *Escherichia coli*; *S. aureus*: *Staphylloococcus aureus*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *B. subtilis*: *Bacillus subtilis*; *C. albicans*: *Candida albicans.*

spectrophotometer ($\nu_{max.}$ in cm^{-1}) using KBr pellets. ^1H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer using DMSO-d_6 or $CDCl_3$ as solvent (chemical shift in δ, ppm) and TMS as internal standard. Mass spectra were recorded on a JEOL-SX 102/DA-6000 mass spectrometer using Argon/Xenon (6kV, 10 mA) as the FAB gas operating at 10 KV. The purity of compounds were checked by TLC.

General Procedure for the Preparation of 2-(p-Substituted aryl)-s-triazolo[5,1-b]-6/8-substituted Quinolino[1,3] thiazin-9(H)-ones 3

A mixture of 3-substituted aryl-4H-5-mercpto-1,2,4-triazole **1** (0.01 mol), 6/8-substituted-2-chloroquinoline-3-carboxylic acid **2** (1.64 g, 0.01 mol), and fused sodium acetate (0.02 mol) in acetic anhydride (20 mL) was refluxed on an oil bath (120–125 °C) for 6 h. It was allowed to cool to room temperature and diluted with water. The solid, thus separated,

was filtered, washed with water, and recrystallized from dimethylformamide.

Spectral data for other compounds are presented here: **3a:** ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ, 9.41 (s,1H, quinoline-4H), 7.12–8.51 (m, 9H, Ar-H & Quinoline protons). Mass: m/z, 331(M^++1 Peak) (M.F.: $C_{18}H_{10}N_4SO$). 3c: **^{1}H NMR (DMSO-d_6): δ, 2.68 (s, 3H, CH_3), 9.38 (s,1H, quinoline-4H), 7.28–8.46 (m, 8H, Ar-H & quinoline protons). Mass: m/z, 344 (M.F.: $C_{19}H_{12}N_4SO$). 3d:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 3.91 (s, 3H, OCH_3), 9.35 (s, 1H, quinoline-4H), 7.31–8.22 (m, 8H, Ar-H & quinoline protons). Mass: m/z, 361 (M^++1 peak) (M.F.: $C_{19}H_{12}N_4SO_2$). **3e:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 9.51, (s, 1H, OH), 9.38 (s, 1H, quinoline-4H), 6.81 (d, 2H, ortho protons of p-hydroxyphenyl), 7.91 (d, 2H, meta protons of p-hydroxyphenyl), 7.48–8.21 (m, 4H, quinoline-5H, 6H, 7H & 8H). Mass: m/z, 346 (M.F.: $C_{18}H_{10}N_4SO_2$). **3f:** ^{1}H NMR (DMSO-d_6): δ, 2.64, (s, 3H,CH_3), 9.46, (s, 1H, OH), 9.36 (s, 1H, quinoline-4H), 6.76 (d, 2H, ortho protons of p-hydroxyphenyl), 8.01 (d, 2H, meta protons of p-hydroxyphenyl), 7.41–8.21 (m, 3H, quinoline-5H, 7H & 8H).Mass: m/z, 360(M^++1Peak) (M.F.: $C_{18}H_{10}N_4SO_2$). **3g:** ^{1}H NMR (DMSO-d_6): δ, 2.80 (s, 3H, CH_3), 9.46 (s, 1H, OH), 9.44 (s, 1H, quinoline-4H), 6.92 (d, 2H, ortho protons of p-hydroxyphenyl), 8.10 (d, 2H, meta protons of p-hydroxyphenyl), 7.57–8.32 (m, 3H, quinoline-5H, 6H and 7H). **3h:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 3.82, (s, 3H, OCH_3), 9.48 (s, 1H, OH), 9.36 (s, 1H, Quinoline-4H), 6.84 (d, 2H, ortho protons of p-hydroxyphenyl), 8.19 (d, 2H, meta protons of p-hydroxyphenyl), 7.38–8.191 (m, 3H, quinoline-5H, 7H & 8H). Mass: m/z, 376 (M.F.: $C_{19}H_{12}N_4SO_3$). **3i:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 9.34 (s, 1H, Quinoline-4H), 6.81 (d, 2H, ortho protons of p-chloroyphenyl), 7.81 (d, 2H, meta protons of p-chlorophenyl), 7.43–8.11 (m, 4H, quinoline-5H,6H, 7H & 8H). Mass: m/z, 365/367 (M^++1&M^++3 peak) (M.F.: $C_{19}H_{12}N_4SO_3$). **3j:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 2.38, (s, 3H, CH_3), 9.28 (s, 1H, quinoline-4H), 7.31 (d, 2H, ortho protons of p-chloroyphenyl), 7.84 (d, 2H, meta protons of p-chlorophenyl), 7.81–8.19 (m, 3H, Quinoline-5H, 7H & 8H). Mass: m/z, 378/380 (M.F.: $C_{19}H_{11}ClN_4SO$). **3k:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 2.39, (s, 3H, CH_3), 9.18 (s, 1H, quinoline-4H), 7.29 (d, 2H, ortho protons of p-chloroyphenyl), 7.91 (d, 2H, meta protons of p-chlorophenyl), 7.43–8.08 (m, 3H, quinoline-5H, 6H & 7H). Mass: m/z, 378/380 (M.F.: $C_{19}H_{11}ClN_4SO$). **3l:** ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ, 3.81, (s, 3H, OCH_3), 9.21 (s, 1H, quinoline-4H), 7.36 (d, 2H, ortho protons of p-chloroyphenyl), 8.01 (d, 2H, meta protons of p-chlorophenyl), 7.43–8.18 (m, 3H, Quinoline-5H, 7H & 8H). Mass: m/z, 394/396 (M.F.: $C_{19}H_{11}ClN_4SO_2$).

REFERENCES

[1] D. A. Shirley, K. Sen, and J. C. Gilmer; *J. Org. Chem.*, **26,** 3587 (1961).
[2] Y. Guindon, V. Girard, C. K. Lau, and R. Fortin, U.S. 4,011,056 (1986); *Chem. Abstr.*, 106330082 (1987).
[3] R. Sharma, R. D. Goyal, and L. Prakash, *Phosphorous, Sulfur, and Silicon*, **80,** 23 (1993).
[4] J. W. Skiles, J. T. Suh, B. E. Williams, P. R. Menard, J. N. Barton, B. Love, H. Jones, E. S. Neiss, A. Schwah, and V. S. Mann, *J. Med. Chem.*, **29**(5), 784 (1986).
[5] P. A.Claret, In *Comprehensive Organic Chemistry*, P. G. Sammes, Ed. (Pergamon, Oxford, UK, 1979), vol. 4, pp. 155 & 205.
[6] M. A. Khan and J. J. Rocha, *Heterocycles*, **6,** 1229 (1977).
[7] F. Spartere, F. Savelli, and G. Cordella, *Formaco Ed. Sci.*, **35,** 735 (1980); *Formaco Ed. Sci.*, **93,** 215405s (1980).
[8] O. G. Todo Uloa, A. E. Papdaki-Valiraki, S. Ikeda, and E. De Clercq, *Eur. J. Med. Chem.*, **29,** 611 (1994).
[9] S. D. Joshi, H. M. Vagdevi, V. P. Vaidya, G. S. Gadaginamath, and S. S. Purohit, *Indian J. Heterocycl. Chem.*, **17,** 367 (2008).
[10] B. Kalluraya, J. Nayak, A. Adhikari, K. V. Sujith, S. Shetty, and M. Wintre, *Phosphorous, Sulfur, and Silicon*, **183**, 1870 (2008).
[11] J. Nayak, K. S. Girisha, and B. Kalluraya, *Indian J. Heterocycl. Chem.*, **17,** 209 (2008).
[12] B. Kalluraya, R. Gururaja, and G. Rai, *Indian J. Chem*, **42B,** 211 (2003).
[13] B. Kalluraya, J. Nayak, and H. M. Vagdevi, *Indian J. Heterocycl. Chem*, **14,** 257, (2005).
[14] B. Kalluraya, S. N. Shetty, and K. J. Jancy, *Chemica Acta Turnica*, **20,** 173 (1992).
[15] K. Rama Rao, N. Bhanumathi, and P. B. Sattur, *J. Heterocycl. Chem*, **28,** 1339 (1991).
[16] E. J. Stokes and G. L. Ridway, *Clinical Bacteriology* (Edward Arnold, London, 1980), p. 226.