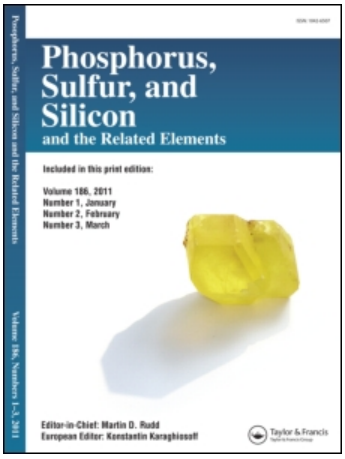


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis and Characterization of Some Novel Quinolinothiazines of Biological Interest

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# Synthesis and Characterization of Some Novel Quinolinothiazines of Biological Interest

**Balakrishna Kalluraya,[1] Janardhana Nayak,[1] Adithya Adhikari,[1] Sujith K.V.,[1] N Sucheta Shetty,[2] and Manuela Winter[3]**
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*A series of 3-aryl-4H-5-($6^1$/$8^1$-substituted-$3^1$-formyl-$2^1$-quinolinyl) thia-1,2,4-triazoles were prepared by the reaction of 2-chloro-3-formyl-6/8-substituted quinoline with 3-substituted 4H-5-mercapto-1,2,4-triazole. These thia-triazoles **5** on reaction with substituted acetophenone gave a novel series of 2-substituted-s-triazolo[5,1-b]-6/8-substituted quinolino-9-arylacetyl[1,3]thiazines **8** rather than the expected 1-aryl-3-[$2^1$-(5-substituted-4H-1,2,4-triazole-5-thia)-$6^1$/$8^1$-substituted quinoline-$3^1$-yl]-2-propen-1-ones 7. The new compounds were screened for their antibacterial activity against Gram-positive and Gram-negative bacteria and antifungal activity against Candida albicans. Most of the tested compounds showed significant antibacterial activity much higher than that of the standard drug Nitrofurazone. The structures of the new compounds were established based on analytical and spectral data. In a typical example, the structure of thiazine **8e** was further confirmed by single crystal x-ray data.*

**Keywords** Biological activity; quinoline; thiazines; triazole

## INTRODUCTION

Heterocycles bearing symmetrical triazole ring are reported to show a broad spectrum of biological activities.[1,2] Likewise, quinoline

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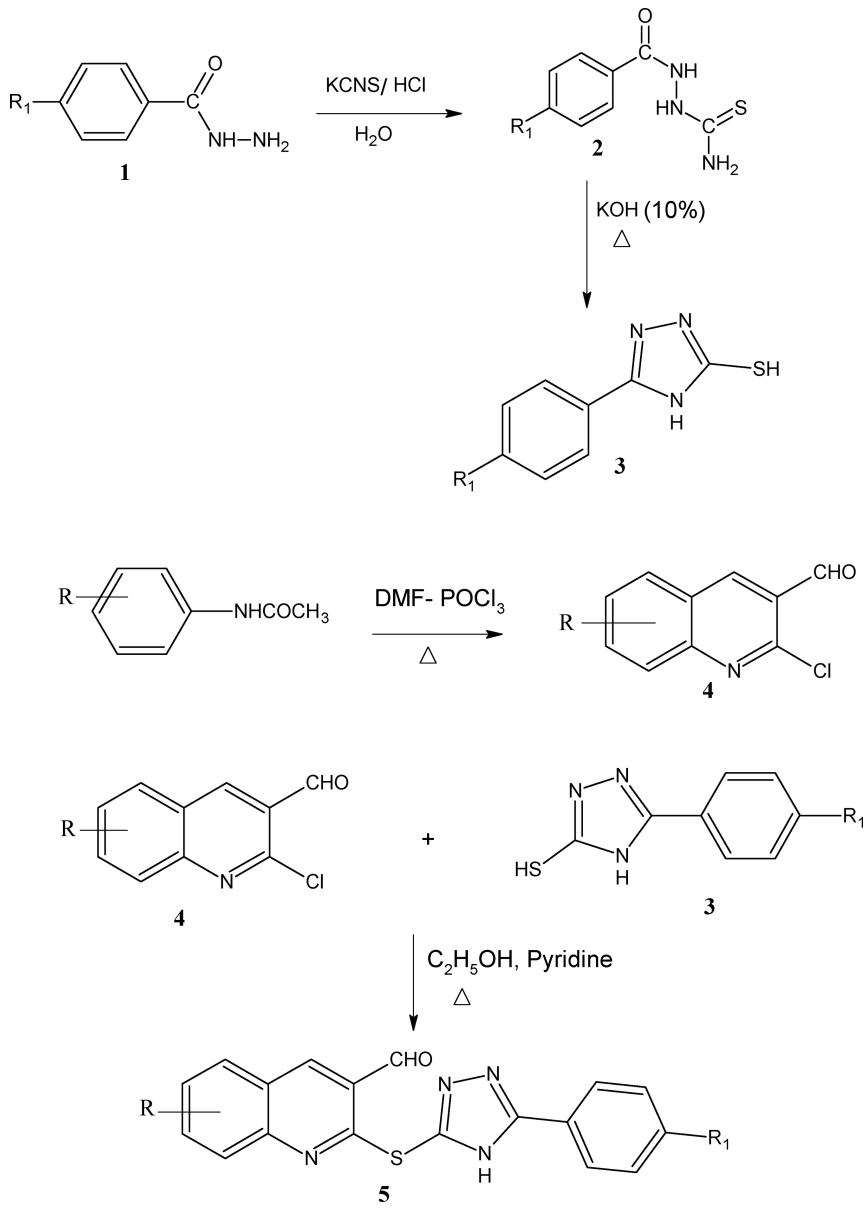
derivatives exhibit a variety of biological activities like antimalarial, anti-inflammatory, antimicrobial, HIV receptors, anticonvulsant, antipyretic, and so on.[3–6]

In our earlier communications,[7,8] we have reported the one-pot synthesis of quinolino thiadiazepines by the reaction of 3-substituted-4-amino-5-mercapto-1,2,4-triazole with 6/8- substituted -2-chloro-3-formyl quinoline. Keeping in view of these observations, we studied the mode of reaction between 6/8-substituted -2-chloro-3-formyl quinoline **4** with the 3-substituted- 4H-5-mercapto-1,2,4-triazole **3** in ethanol medium employing pyridine as catalyst and such reactions resulted in the formation of novel series of 3-aryl -4H-5-($6^1$/$8^1$-substituted-$3^1$-formyl-$2^1$-quinolinyl) thia-1,2,4-triazoles **5** (Scheme 1). Reaction of 3-aryl-4H-5-($6^1$/$8^1$-substituted-$3^1$-formyl-$2^1$-quinolinyl) thia-1,2,4-triazoles **5** with substituted acetophenone **6** in ethanol medium in the presence of sodium hydroxide as catalyst gave novel series of 2-substituted-s-triazolo[5,1-b]-6/8-substituted quinolino-9-arylacetyl[1,3]thiazines **8** instead of 1-aryl-3-[$2^1$-(5-substituted-4H-1,2,4-triazole-5-thia)-$6^1$/$8^1$-substitutedquinoline-$3^1$-yl]-2-propene-1-ones **7** (Scheme 2). 3- Substituted -4H-5-mercapto-1,2,4-triazoles **3** were prepared by the cyclization of appropriate aroyl thiosemicarbazide **2** with potassium hydroxide. These thiosemicarbazide **2** were obtained by the reaction of aroyl hydrazide **1** with potassium thiocyanate, as per the literature method.[9] 6/8-Substituted-2-chloro-3-formylquinolines **4** were prepared according to the literature method.[10] The structures of new compounds were characterized by analytical, spectral data, and X-ray diffraction studies (Tables I, II, III & VI).

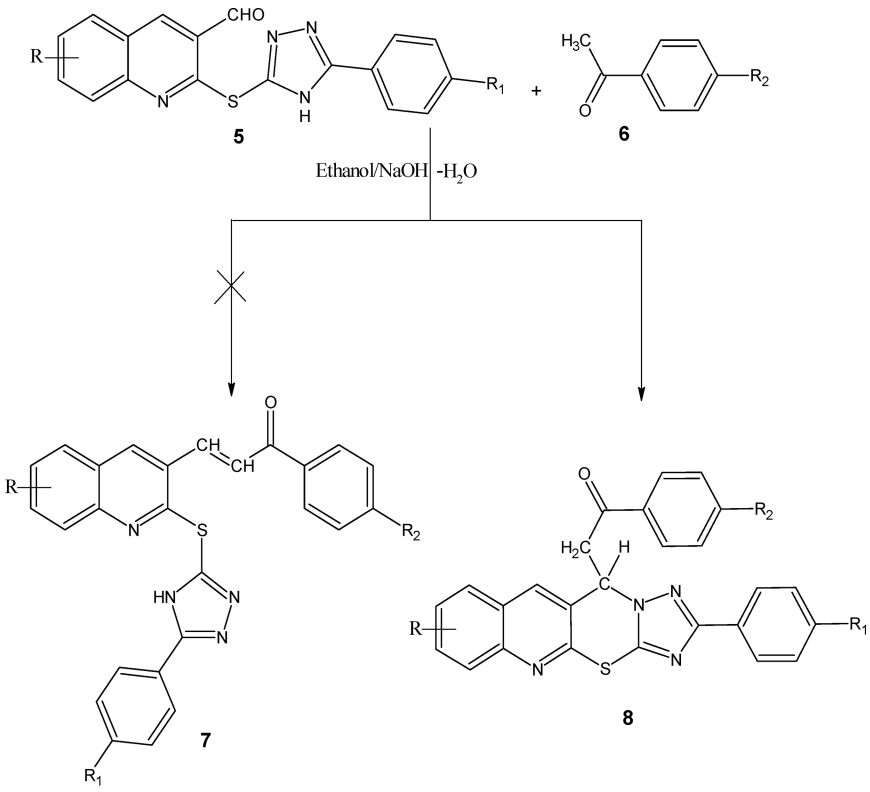


## RESULTS AND DISCUSSION

The structures of the newly synthesized compounds were established based on analytical and spectral data. In the IR spectra of compounds **5,** the aldehyde carbonyl absorption band was observed in the region of 1687-1690 $cm^{-1}$. Further, the $^1$H NMR spectra of compound **5c** the methyl protons of the quinoline moiety came into resonance as a singlet at $\delta$ 2.75 integrating for three protons. The aldehyde proton appeared as a singlet at $\delta$ 10.35 integrating for one proton. The N-H proton appeared as a singlet at $\delta$ 7.11, while the signal due to quinoline 4-H appeared as singlet at $\delta$ 8.43, integrating for one proton. The signal due to the remaining quinoline protons (5H, 7H, and 8H) and aromatic protons overlapped with each other and appeared as multiplets in the region of $\delta$ 7.40–8.12 integrating for eight protons. Similarly, $^1$H NMR spectra for compounds **5d, 5e,** and **5j** were also recorded and the chemical shift values observed are presented in Table I. When




**SCHEME 1**




R = H, 8-methyl,6-methyl

$R_1$ = H, OH

$R_2$ = H, Cl

**SCHEME 2**

these 3-aryl-5-(6/8-substituted-3-formyl quinoline-2-yl)thia-4H-1,2,4-triazole **5** were condensed with appropriately substituted acetophenones in the presence of sodium hydroxide, we expected the formation of 1-aryl-3-[$2^1$-(5-substituted-4H-1,2,4-triazole-5-thia)-$6^1/8^1$-substituted quinoline-$3^1$-yl]-2-propen-1-ones **7**. However, surprisingly this one pot reaction resulted in the formation of a novel series of 2-substituted-s-triazolo[5,1-b]-6/8-substituted quinolino-9-arylacetyl[1,3]thiazines **8** (Scheme 2). A probable mechanistic pathway for the formation of these compounds is suggested in Scheme 3. Further evidence for the proposed structure was obtained by Mass spectral

**TABLE I Selected[1] H NMR ($\delta$, ppm) Spectra of the Compounds**

**5d.** $^1$H NMR ($CDCl_3$+ DMSO-$d_6$)$\delta$ 3.96 (s,3H,$OCH_3$) 10.5 (s,1H, CHO), 7.03 (s, 1H, triazole-NH), 8.36 (s, 1H, quinoline-4H ), 7.89 (d, 1H, quinoline-8H), 7.13–8.15 (m, 7H, Ar-H & quinoline-5H , 7H).

**5e.** $^1$H NMR ($CDCl_3$+ DMSO-$d_6$)$\delta$ 10.5 (s, 1H, CHO), 9.33 (s, 1H, OH), 8.45 (s, 1H, quinoline-4H), 6.91 (d, 2H, ortho-protons of p-hydroxyphenyl), 7.96 (d, 2H, meta-protons of p-hydroxyphenyl ), 7.48–8.02 (m, 5H, quinoline-5H, 6H, 7H, 8H and triazole-NH protons).

**5j.** $^1$H NMR ($CDCl_3$)$\delta$ 2.57 (s, 1H, $CH_3$), 10.55 (s, 1H, CHO), 8.39 (s, 1H, quinoline-4H), 7.44 (d, 2H, ortho protons of p-chlorophenyl), 8.09 (d, 2H, meta protons of p-chlorophenyl), 7.07–7.92 (m, 4H, quinoline-5H, 6H, 8H and triazole-NH protons).

**8d.** $^1$H NMR ($CDCl_3$+ DMSO-$d_6$)$\delta$ 3.87 (dd, 1H, CH), 3.65 (dd, 2H, $CH_2$), 8.43 (s, 1H, quinoline-4H), 6.88 (d, 2H, ortho-protons of p-hydroxyphenyl), 7.78 (d, 2H, meta-protons of p-hydroxyphenyl), 7.37 (d, 2H, ortho-protons of p-chlorophenyl), 7.88 (d, 2H, meta-protons of p-chlorophenyl), 7.54–7.99 (m, 5H, OH, quinoline-5H, 6H, 7H and 8H).

**8e.** $^1$H NMR ($CDCl_3$)$\delta$ 2.73 (s, 3H, $CH_3$), 3.87 (dd, 1H, CH), 3.61 (dd, 2H, $CH_2$), 8.35 (s, 1H, quinoline-4H ), 7.34–8.09 (m, 13H, Ar-H and quinoline-5H, 6H and 7H).

**8j.** $^1$H NMR ($CDCl_3$)$\delta$ 3.92 (s, 3H, $OCH_3$), 3.65 (dd, 1H, CH), 3.55 (dd, 2H, $CH_2$), 7.28–8.15 (m, 13H, Ar-H and quinoline-4H, 5H, 6H and 7H).



data. In the Mass spectra of **5d**, the molecular ion peak is observed at m/z 362 (Molecular Formula $C_{19}H_{14}N_4O_2S$) in agreement with the proposed structure. Similarly the Mass spectrum of compounds **5g** m/z 363 ($M^+$+1 peak) (Molecular Formula $C_{19}H_{14}N_4O_2S$) and **5h** m/z 378 (Molecular Formula $C_{19}H_{14}N_4O_3S$) are in agreement with the proposed structure.

In the IR spectra of compounds **8,** the carbonyl absorption band was observed in the region of 1670–1681 $cm^{-1}$. In the $^1$H NMR spectra of compound **8a**, the thiazine 4H (i.e., CH) proton came into resonance as doublet of a doublet centered at $\delta$ 3.89 integrating for one proton. The signal due to $CH_2$ protons appeared as two doublets centered at $\delta$ 3.62 integrating for two protons, which indicated that the two protons are magnetically non-equivalent since they are adjacent to a chiral carbon. The quinoline-4H proton appeared as a singlet at $\delta$ 8.43 integrating for one proton, while the signal due to remaining quinoline protons (5H, 6H, 7H, and 8H) and two phenyl ring protons overlapped with each other and appeared as multiplets in the region of $\delta$ 7.26–8.10 integrating for 14 protons. Similarly, the 1H NMR spectra of thiazines **8d**, **8e**, and **8j** were also recorded and the chemical shift assignments are given in Table I. Further evidence for the proposed structure was obtained by Mass-spectral data. The mass spectrum of compound **8a** showed the molecular ion peak at m/z 435, which is $M^+$+1 peak and is in agreement with the molecular formula $C_{26}H_{18}N_4OS$. The other prominent

**TABLE II Characterization Data of 3-Aryl-4H-5-(6/8-substituted-3[1]- formyl-2[1]-quinolinyl) thia-1,2,4-triazoles 5a–l**

| Compd. no. | R | $R_1$ | M.p.°C (yield %) | Mol. formula (mol. weight) | % Analysis found (calculated) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| 5a | H | H | 232–233 (65) | $C_{18}H_{12}N_4OS$ (332) | 65.12 (65.06) | 3.58 (3.61) | 17.01 (16.86) |
| 5b | 6-Methyl | H | 233–234 (64) | $C_{19}H_{14}N_4OS$ (346) | 65.83 (65.89) | 3.95 (4.04) | 16.35 (16.18) |
| 5c | 8-Methyl | H | >300 (71) | $C_{19}H_{14}N_4OS$ (346) | 66.04 (65.89) | 3.81 (4.04) | 16.42 (16.18) |
| 5d | 6-Methoxy | H | 254–255 (68) | $C_{19}H_{14}N_4O_2S$ (362) | 63.10 (62.98) | 3.76 (3.86) | 15.53 (15.46) |
| 5e | H | OH | >300 (72) | $C_{18}H_{12}N_4O_2S$ (348) | 62.23 (62.06) | 3.56 (3.44) | 16.21 (16.09) |
| 5f | 6-Methyl | OH | 227–228 (77) | $C_{19}H_{14}N_4O_2S$ (362) | 63.16 (62.98) | 3.76 (3.86) | 15.52 (15.46) |
| 5g | 8-Methyl | OH | 273–274 (72) | $C_{19}H_{14}N_4O_2S$ (362) | 63.04 (62.98) | 3.78 (3.86) | 15.57 (15.46) |
| 5h | 6-Methoxy | OH | >300 (71) | $C_{19}H_{14}N_4O_3S$ (378) | 60.21 (60.31) | 3.67 (3.70) | 14.96 (14.81) |
| 5i | H | Cl | >300 (70) | $C_{18}H_{11}ClN_4OS$ (366.5) | 58.98 (58.93) | 2.94 (3.00) | 15.38 (15.27) |
| 5j | 6-Methyl | Cl | 281–282 (62) | $C_{19}H_{13}ClN_4OS$ (380.5) | 60.12 (59.92) | 3.35 (3.42) | 14.83 (14.71) |
| 5k | 8-Methyl | Cl | >300 (76) | $C_{19}H_{13}ClN_4OS$ (380.5) | 60.18 (59.92) | 3.53 (3.42) | 14.86 (14.71) |
| 5l | 6-Methoxy | Cl | 275–276 (75) | $C_{19}H_{13}ClN_4O_2S$ (396.5) | 58.01 (57.50) | 3.19 (3.27) | 14.24 (14.12) |

Solvent of crystallization = 1:1 ethanol + dimethylformamide mixture.

**TABLE III Characterization Data of 2-Substituted-s-triazolo[5,1-b]- 6/8-substituted quinolino-9-arylacetyl[1,3]thiazines (8a-l)**

| Compd. No. | R | $R_1$ | $R_2$ | M.p.°C (yield %) | Mol. formula (mol. weight) | Analysis % found (calculated) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| 8a | H | H | H | 189–190 (69) | $C_{26}H_{18}N_4OS$ (434) | 71.84 (71.88) | 4.10 (4.14) | 12.95 (12.90) |
| 8b | H | H | Cl | 227–128 (71) | $C_{26}H_{17}ClN_4OS$ (468.5) | 66.62 (66.59) | 3.60 (3.63) | 11.92 (11.95) |
| 8c | H | OH | H | >300 (67) | $C_{26}H_{18}N_4O_2S$ (450) | 69.29 (69.33) | 3.98 (4.00) | 12.47 (12.44) |
| 8d | H | OH | Cl | 254–255 (68) | $C_{26}H_{17}ClN_4O_2S$ (484.5) | 64.42 (64.39) | 3.48 (3.51) | 11.53 (11.56) |
| 8e | 8-Methyl | H | H | 215–216 (72) | $C_{27}H_{20}N_4OS$ (448) | 72.28 (72.32) | 4.50 (4.46) | 12.47 (12.50) |
| 8f | 8-Methyl | H | Cl | 220–221 (70) | $C_{27}H_{19}ClN_4OS$ (482.5) | 67.11 (67.15) | 3.95 (3.93) | 11.58 (11.60) |
| 8g | 8-Methyl | OH | H | >300 (69) | $C_{27}H_{20}N_4O_2S$ (464) | 69.86 (69.83) | 4.28 (4.31) | 12.02 (12.06) |
| 8h | 8-Methyl | OH | Cl | 138–139 (68) | $C_{27}H_{19}ClN_4O_2S$ (498.5) | 64.96 (64.99) | 3.85 (3.81) | 11.20 (11.23) |
| 8i | 6-Methoxy | H | H | 173–174 (71) | $C_{27}H_{20}N_4O_2S$ (464) | 69.86 (69.82) | 4.28 (4.31) | 12.03 (12.06) |
| 8j | 6-Methoxy | H | Cl | 217–218 (72) | $C_{27}H_{19}ClN_4O_2S$ (498.5) | 65.02 (64.99) | 3.84 (3.81) | 11.25 (11.23) |
| 8k | 6-Methoxy | OH | H | 250–251 (73) | $C_{27}H_{20}N_4O_3S$ (480) | 67.47 (67.50) | 4.13 (4.17) | 11.71 (11.67) |
| 8l | 6-Methoxy | OH | Cl | >300 (65) | $C_{27}H_{19}ClN_4O_3S$ (514.5) | 62.94 (62.97) | 3.73 (3.69) | 10.92 (10.88) |

Solvent of crystallization = 1:1 Ethanol+ DMF mixture.

**TABLE IV Antibacterial Activities of 3-Aryl-5-(6/8 substituted-3-formyl-2-yl) thia-4H-1,2,4-triazoles 5a–l**

| | Minimum inhibitory concentration (MIC) ($\mu$g/ml) | | | |
|---|---|---|---|---|
| Compound no. | *E. coli* | *K. pneu.* | *P. aer.* | *S. aur.* |
| **5a** | **10** | 12.5 | 25 | 25 |
| **5b** | 25 | 25 | 25 | 25 |
| 5c | 25 | **12.5** | 25 | **12.5** |
| 5d | 25 | 25 | 25 | 25 |
| 5e | **12.5** | **12.5** | 25 | **12.5** |
| 5f | **12.5** | 25 | 25 | 25 |
| 5g | 25 | **12.5** | 25 | **12.5** |
| 5h | 25 | 25 | 25 | 25 |
| 5i | 25 | 25 | 25 | 25 |
| 5j | **12.5** | **12.5** | 25 | **12.5** |
| 5k | **12.5** | **12.5** | **12.5** | **12.5** |
| 5l | 25 | 25 | 25 | 25 |
| Nitrofurazone | **12.5** | **12.5** | **12.5** | **12.5** |
| DMF (control) | — | — | — | — |

*E. coli = Escherichia coli; K. pneu = Klebsiella pneumonia; P. aer = pseudomonas aeruginosa; and S. aur = Staphylococcus aureus*



peak at m/z 329 is due to loss of benzoyl cation from the molecular ion. Similarly, the peak at m/z 105 is due to benzoyl cation. The mass spectrum of compound **8d** showed molecular ion peak at m/z 485 ($M^+$+1) in agreement with molecular formula $C_{26}H_{17}ClN_4O_2S$. The peak at m/z 345 is due to the loss of benzoyl cation. Similarly, for the mass spectrum of the compound **8e, the** molecular ion peak was observed at m/z 448 in agreement with the molecular formula $C_{27}H_{20}N_4OS$. The base peak at m/z 343 is due to the loss of benzoyl cation. The formation of thiazine rather than the expected chalcone is confirmed by recording single crystal X-ray for the compound **8e** (Figure 1). The crystallographic data are summarized in Table VI.

## EXPERIMENTAL

The melting points of the newly synthesized compounds were determined in open capillaries and were uncorrected. The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer or NICOLET AVATAR 330 FT IR spectrophotometer in KBr pellets. The $^1$H-NMR spectra were recorded on a Bruker AC 300F (300MHz) NMR spectrometer using DMSO-$d_6$ or $CDCl_3$ as solvent and TMS as internal standard. All chemical shift values are expressed in $\delta$ scale. Mass spectra was recorded on a Jeol-JMS-D300 mass spectrometer operating at 70eV or

**TABLE V Antibacterial and Antifungal Activity Data of Compounds 8a–l**

| Compd. no. | Antibacterial activity (MIC in $\mu$g/ml) | | | | Antifungal activity (MIC in $\mu$g/ml) |
|---|---|---|---|---|---|
| | *E. coli* | *S. aureus* | *P. aeruginosa* | *B. subtilis* | *C. albicans* |
| 8a | **6.25** | 6.25 | **6.25** | **6.25** | 6.25 |
| 8b | **6.25** | 6.25 | **6.25** | **6.25** | 6.25 |
| 8c | **6.25** | 12.5 | **6.25** | **6.25** | 6.25 |
| 8d | **6.25** | 6.25 | **6.25** | **6.25** | **3.125** |
| 8e | **6.25** | 6.25 | **6.25** | 12.5 | 6.25 |
| 8f | 12.5 | 25 | 12.5 | 25 | 6.25 |
| 8g | 12.5 | 12.5 | **6.25** | **6.25** | 6.25 |
| 8h | **6.25** | 6.25 | **6.25** | **6.25** | 6.25 |
| 8i | 50 | 25 | 25 | 25 | 6.25 |
| 8j | **6.25** | 6.25 | **6.25** | **6.25** | 6.25 |
| 8k | **6.25** | 12.5 | **6.25** | 12.5 | 6.25 |
| 8l | **6.25** | 6.25 | **6.25** | **6.25** | **3.125** |
| Nitrofurazone | 12.5 | 6.25 | 12.5 | 12.5 | — |
| Fluconazole | — | — | — | — | 6.25 |
| DMF (Control) | — | — | — | — | — |

Disc size = 5.5 mm; Duration = 24 h; *E. coli = Escherichia coli; S. aur = Staphylococcus aureu; P. aer = pseudomonas aeruginosa; B. subtilis = Bacillus subtilis; and C. albicans = Candida albicans.*



JEOL SX 102/DA-6000 mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the FAB gas operating at 10 kV. CHN analysis was carried out on a Vairo-EL(Elementa) model. The purity of all compounds was confirmed by TLC. The single crystal X-ray was measured on an Oxford Excalibur 2 Diffractometer [R(int) = 0.0515]. The structural solution and refinement was done using SHELXS-97[11] and SHELXL-97[12] programs. The yield, melting point and other characterization data of compounds **8** are given in Table III.

## 3-Aryl-5-mercapto-4H-1,2,4-triazoles 3

A mixture of aroyl hydrazine **1** (0.01 mol), potassium thiocyanate (1.9 g, 0.02 mol), conc. HCl (10 mL) and water (20 mL) was refluxed for 3 h. After cooling, the resulting aroyl thiosemicarbazide **2** was collected by filtration, washed with water, dried, and recrystallized from ethanol. A mixture of aroyl thiosemicarbazide **2** (0.05 mol) and 10% KOH (50 mL) was refluxed for 3 h. The mixture was then cooled to room temperature and filtered. The filtrate was neutralized by the gradual addition of glacial acetic acid. The resulting solid 3-aryl-5-mercapto-4H-1,2,4-triazole **3** was collected by filtration, dried and recrystallized from ethanol.

**TABLE VI Crystal Data and Structure Refinement for $C_{27}H_{20}N_4OS$ (8e)**

| | |
|---|---|
| Identification code | cvd113 |
| Empirical formula | $C_{27}H_{20}N_4OS$ |
| Formula weight | 448.54 |
| Temperature | 106(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Triclinic, P-1 |
| Unit cell dimensions | a = 10.2601(6) A alpha = 61.041(9) deg.<br>b = 11.1491(10) A beta = 69.497(8) deg.<br>c = 11.2440(10) A gamma = 76.479(7) deg. |
| Volume | 1050.86(15) A^3 |
| Z, Calculated density | 2, 1.421 Mg/m^3 |
| Absorption coefficient | 0.184 mm^-1 |
| F(000) | 470 |
| Crystal size | 0.15 × 0.10 × 0.06 mm |
| Theta range for data collection | 2.57 to 25.00 deg. |
| Limiting indices | -12<=h<=12, -13<=k<=13, -13<=l<=13 |
| Reflections collected / unique | 13756/3681 [R(int) = 0.0515] |
| Observed reflns[I>2sigma(I)] | 2453 Fo > 4sig(Fo) |
| Completeness to theta = 25.00 | 99.6% |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on F^2 |
| Data/restraints/parameters | 3681/0/274 |
| Goodness-of-fit on F^2 | 0.895 |
| Final R indices [I>2sigma(I)] | R1 = 0.0365, wR2 = 0.0836 |
| R indices (all data) | R1 = 0.0598, wR2 = 0.0877 |
| Largest diff. peak and hole | 0.361 and -0.644 e.A^-3 |

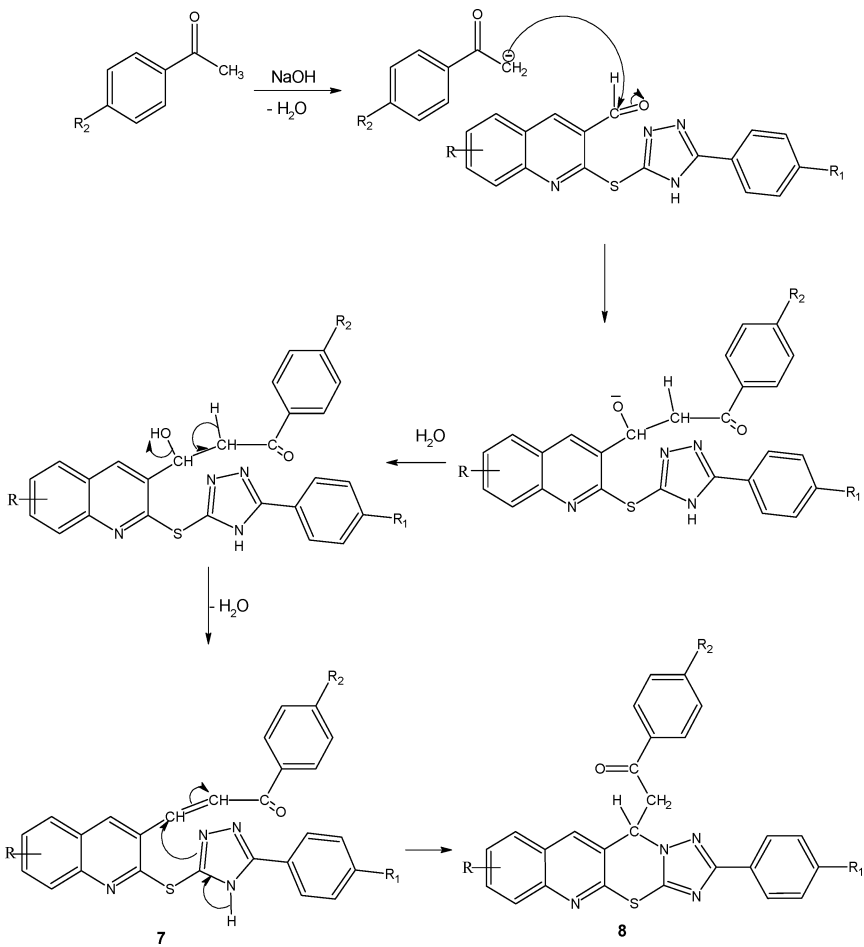


## 6/8-Substituted 2-chloro-3-formyl quinoline 4

Dimethyl formamide (9.13 g, 9.9 ml, 0.125 mol) was cooled to 0°C in a flask equipped with a drying tube; phosphorous oxychoride (53.7 g, 32.2 ml. 0.35 mol) was added drop wise with stirring. To this solution, acetanilide (6.55 g, 0.05 mol) was added and the solution was heated under reflux for 16 h. The reaction mixture was poured into ice water and stirred for 30 min at 0–10°C until 6/8-substituted-2-chloro-3-formyl quinoline **4** separated as yellow precipitate. It was filtered, washed with water, and recrystallized from ethyl acetate.

## 3-Aryl-4H-5-($6^1$/$8^1$-substituted-$3^1$-formyl-$2^1$-quinolinyl) thia-1,2,4-triazole 5

A mixture of 3-aryl-5-mercapto-4H-1,2,4-triazole **3** (0.01 mol), 6/8- substituted -2-chloro-3-formyl quinoline **4** (0.01mol) were dissolved in ethanol (20 mL). Pyridine (1 mL) was added as a catalyst to the above mixture and the contents were refluxed on water bath for 4 to 5 h. After




**SCHEME 3**

the completion of reaction, the excess solvent was removed by distillation, and the contents were cooled to room temperature. The solid product separated was collected by filtration, dried, and recrystallized from a mixture of ethanol and dimethylformamide (Table II).

## 2-Substituted-s-triazolo[5,1-b]-6/8-substituted quinolino-9-arylacetyl[1,3]thiazines 8

To a thoroughly stirred solution of 3-aryl-5-($6^1$/$8^1$-substituted-$3^1$-formyl-$2^1$-yl)thia-1,2,4-triazole **5** (0.01 mol) and p-substituted acetophenone **6** (0.01 mol) in ethanol (25 mL) was added 40% NaOH (3 mL). The reaction mixture was stirred for 24 h. It was poured into

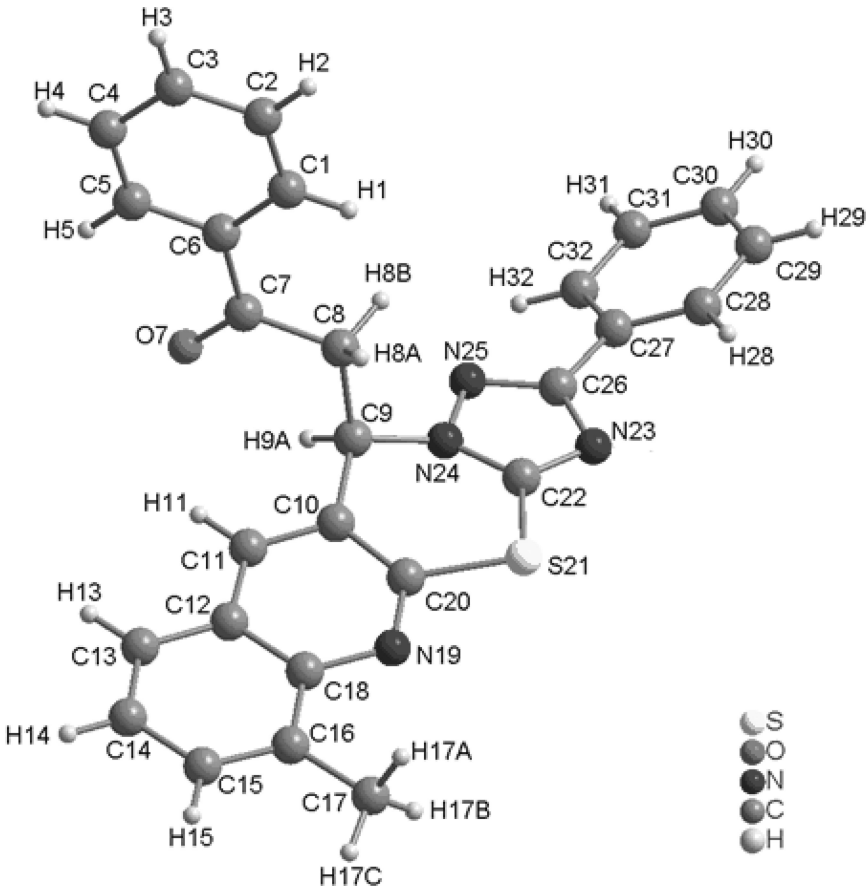



**FIGURE 1** Single crystal X-ray structure of the compound 8e. Selected bond angles (Å) and angles (deg.): S(21)-C(22) 1.7287(19); S(21)-C(20) 1.7663(19); C(22)-S(21)-C(20) 100.63(9); N(19)-C(20)-S(21) 110.56(14); N(23)-C(22)-S(21) 124.97(14); N(24)-C(22)-S(21) 124.26(14); C(10)-C(20)-S(21) 124.32(15); O(7)-C(7) 1.218(2); N(24)-N(25) 1.372(2).

ice water, acidified with dil.HCl, filtered, and recrystallized from a mixture of ethanol and dimethylformamide to give **8** (Table III).

## BIOLOGICAL ACTIVITY

### Antibacterial Activity

The antibacterial activity of the newly synthesized compounds **5** were carried out against four different pathogenic organisms. They are

*Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella pneumonia,* and *Staphylococcus aureus*. The antibacterial activity of the newly synthesized compounds in the present investigation was assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method[13] (Table-IV). Among the compounds tested compound **5k** carrying p-chlorophenyl group at the third position of the triazole and methyl group at the eighth position of the quinoline showed highest activity among all the organisms tested at 10$\mu$g/mL concentration comparable with that of standard drug Nitrofurazone. Apart from these compounds, **5e** carrying p-hydroxyphenyl group at the third position of the triazole and **5j** carrying p-chlorophenyl group at the third position of the triazole and methyl substituent at the sixth position of quinoline showed considerable activity against *E. coli., K. pneumonia,* and *S. aureus*. In addition, compound **5a,** carrying the phenyl group at the third position of the triazole, showed activity against *E. coli*; **5c,** carrying phenyl group at the third position of the triazole and methyl substituent at the eighth position of the quinoline moiety, showed activity against *K. pneumoniae* and *S. aureus*; and **5f,** carrying p-hydroxy phenyl group at the third position of the triazole and methyl group at the sixth position of the quinoline moiety, showed activity against *E. coli*. Compound **5g,** carrying p-hydroxy phenyl group at the third position of the triazole and methyl group at the eight position of the quinoline moiety, showed activity against *K. pneumoniae* and *S. aureus*.

The antibacterial activity of the newly synthesized thiazines **8** were carried out against four different pathogenic organisms—two each of Gram-negative and Gram-positive. They are *Staphylococcus aureus* (Gram-positive), *Bacillus subtilis* (Gram-positive), *Escherichia coli* (Gram-negative), and *Pseudomonas aeruginosa* (Gram-negative). The concentration at which there is no turbidity was taken as Minimum Inhibitory Concentration (MIC) and the results are tabulated in Table-V. Among the compounds tested most of the compounds showed significant antibacterial activity comparable with that of standard drug Nitrofurazone.[14]

## Antifungal Activity

Antifungal activity of thiazines **8** was carried out on the fungus *Candida albicans.* Fluconazole was employed as the standard. The results of antifungal activity data are also given in Table V. Among the compounds tested, the compounds **8d** and **8l** showed the highest antifungal activity comparable with that of standard drug Fluconazole.

## CONCLUSION

A novel series of thiazines **8** were obtained in the one-pot reaction of 3-aryl-5-(6/8-substituted-3-formyl quinoline-2-yl)thia-4H-1,2,4-triazole **5** with various substituted acetophenones **6**, instead of the expected 1-aryl-3-[$2^1$-(5-substituted-4H-1,2,4-triazole-5-thia)-$6^1/8^1$-substituted quinoline-$3^1$-yl]-2-propen-1-ones **7**. The biological activity studies of intermediate and final thiazines indicates that the thiazines are more potent antibacterial agents and the activity is comparable with that of the standard drug Nitrofurazone which is an effective antibacterial agent against urinary infections, particularly against the bacteria *E. coli*.

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