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# Synthesis, Characterization, and Antibacterial Activity of Some Thiazoles Derived from Allyl Thioureas[1]

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**Abstract**—Synthesis of thiazoles was carried out from allyl thioureas using different cyclizing agents such as hydrogen chloride gas and bromine. Synthesized compounds were characterized by IR, $^{1}$H and $^{13}$C NMR, mass spectrometry, and elemental analysis. The synthesized thiazoles were evaluated for their antibacterial activity against Gram postitive (*Lactobacillus bulgaris* and *Streptococcus mitis*) and Gram negative (*Yersinia*) as well as antifungal activity against *Aspergillus niger fungi*.

**Keywords:** thiazoles, allyl thioureas, hydrogen chloride, bromine, antibacterial, antfungal

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## INTRODUCTION

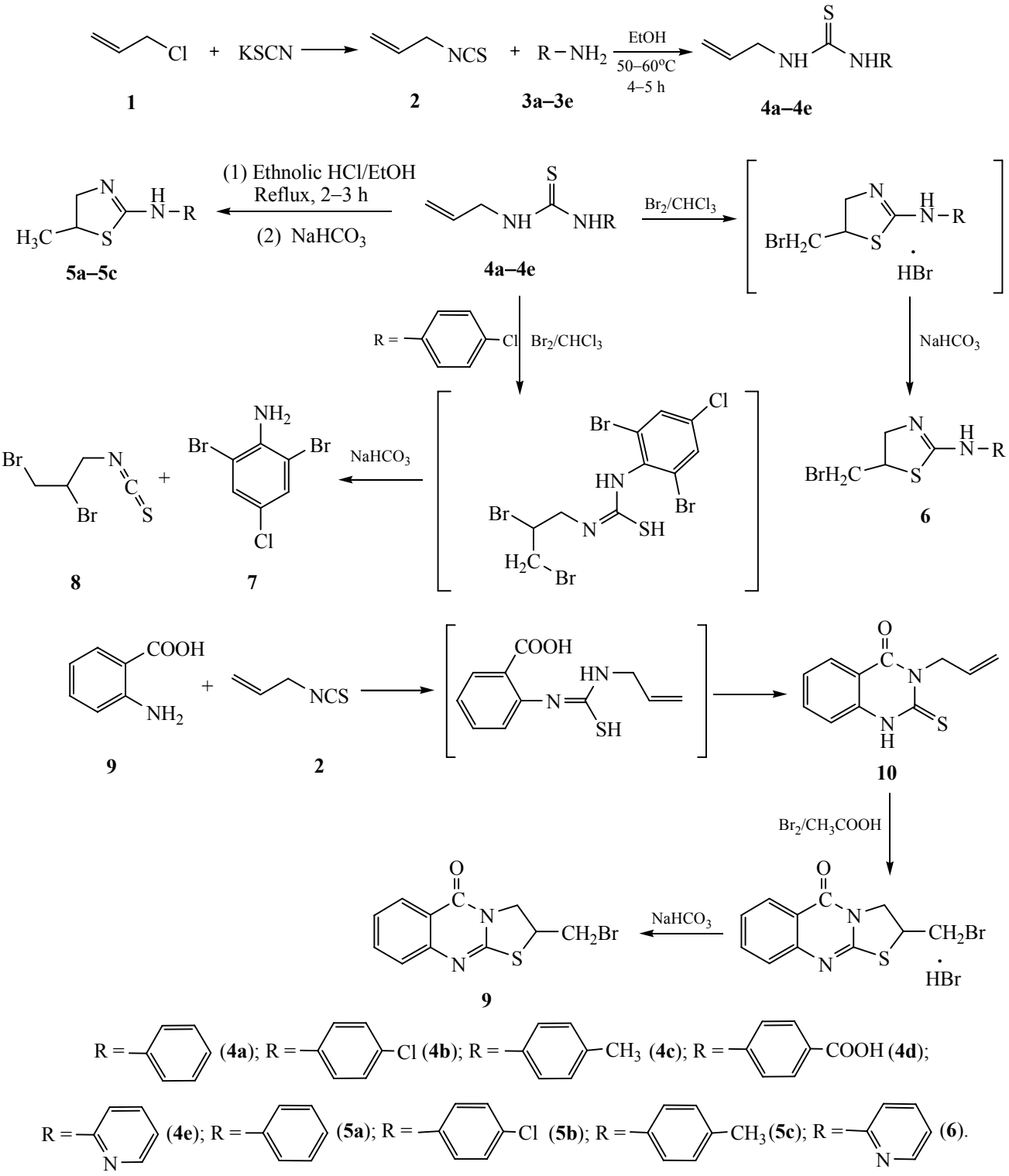
Thiazoles demonstrate a broad spectrum of mild to potential pharmacological activities [1-2] including analgesic [3], anti-microbial [4], anti-inflammatory [5], anticonvulsant [6], antitubercular [7], anthelmintic [8], anticancer [9], diuretic [10], and cardiotonic [11]. Thiazoles are non-carcinogenic [12] readily metabolized compounds and their ring system is applied in drug development for treatment of HIV [13], mental retardation in children and neurodegenerative brain damage (Alzheimer's and Parkinsonism diseases) [13–16]. Herein we report the synthesis of allyl thioureas, their conversion into thiazoles by two simple approaches to cyclization and their evaluation for antibacterial and antifungal activities.

## RESULTS AND DISCUSSION

The general objective of our ongoing research is development of simple synthetic approaches to biologically active compounds [17–19]. Earlier we have reported the synthetic approach to thiazole derivatives via thiourea intermediates (Scheme 1). Allyl isothiocyanate **2**, prepared by the reaction of allyl chloride **1** and potassium thiocyanate in ethanol, was used as the starting material for synthesis of thiourea without further purification. Thioureas **4a–4e** were prepared by condensation of amines **3a–3e** and allyl isothiocyanate **2** according to the previously reported procedure [20]. Cyclization of thioureas was carried out under the action of ethanolic hydrogen chloride or bromine to afford the corresponding thiazoles. Under the action of ethanolic hydrogen chloride, thioureas **4a–4c** were converted into respective thiazoles **5–5c**. Cyclization carried out in the presence of bromine in chloroform did not give thiourea **4b** but led to the intermediate which underwent retro-cleavage and gave unexpected products, 2,6-dibromo-4-chloroaniline **7** and 1,2-dibromo-3-isothiocyanatopropane **8**. In case of thiourea **4e**, cyclization with bromine in chloroform gave 5-bromomethylthiazole (**6**). Under similar conditions, the compounds **4a** and **4b** gave gummy materials that were difficult to separate and purify. Anthranilic acid **9** was condensed with allyl isothiocyanate **2** in glacial acetic acid with formation of the corresponding quinazoline **10** which upon reacting with bromine in acetic acid followed by treatment with sodium bicarbonate subsequently cyclized into 2-bromomethylthiazolo[2,3-*b*]quinazoline-5-one (**9**). Conversion of thioureas into the targeted compounds was justified by FT–IR, $^{1}$H, $^{13}$C NMR, and mass spectra. In FT–IR spectra the characteristic absorption band of the C=S group of thioureas was recorded at 1090–1194 cm$^{-1}$ which disappeared upon cyclization indicated. The new band in the range of 870–700 cm$^{-1}$ assigned to the C–S–C group of thiazoles was recorded. Signals of

[1] The text was submitted by the authors in English.

**Scheme 1.**




two –NH protones of thioureas (δ = 6.13–11.86 ppm) simplified into one signal upon cyclization into thiazoles. Formation of thiazoles from thiourea was supported by mass spectra.

*Antibacterial activity.* The synthesized compounds (**4a–4e**, **5a–5c**, **7**, and **10**) were screened for their antibacterial activity against Gram postitive *Lactobacillus bulgaris* and *Streptococcus mitis*, and Gram

**Table 1.** Antibacterial activity of compounds **4a–4e**, **5a–5c**, **7**, **10**

| Product | Zone of inhibition, mm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Lactobacillus bulgaris* | | | *Yersinia* | | | *S.mitis* | | |
| | lower | middle | upper | lower | middle | upper | lower | middle | upper |
| **4a** | 0.90 | 0.40 | 0.8 | – | 0.80 | 1.13 | 0.90 | 1.50 | 1.30 |
| **4b** | 3.10 | 1.93 | 2.10 | – | 2.33 | 2.00 | 1.93 | 1.50 | 1.40 |
| **4c** | 1.20 | 1.06 | 0.56 | – | – | – | 1.1 | 0.70 | 1.00 |
| **4d** | 0.50 | 1.20 | 0.10 | – | – | – | – | – | 0.63 |
| **4e** | – | – | – | 1.12 | 0.50 | 1.43 | 0.5 | 1.50 | 1.40 |
| **5a** | 0.53 | 4.93 | 2.23 | – | 3.90 | 1.16 | 2.5 | 2.30 | 1.60 |
| **5b** | 0.53 | 0.83 | – | 0.54 | 0.46 | 0.90 | 0.9 | 0.50 | 0.90 |
| **5c** | – | 1.50 | 1.46 | 1.60 | 1.33 | 1.60 | 1.5 | 1.80 | 1.20 |
| **7** | 1.43 | 0.78 | 0.86 | – | – | 0.66 | – | – | 0.20 |
| **10** | 0.80 | – | 1.76 | 1.00 | – | 1.20 | – | 1.10 | 1.26 |
| Ofloxacin | 4.85 | 5.02 | 0.95 | 1.05 | 4.10 | 3.95 | 2.10 | 0.42 | – |

negative *Yersinia* by well diffusion methods at the concentrations (mg/mL): 9–10, 5–6, and 1–2. The inhibition zones (in mm) were compared with the standard drug Ofloxacin (Table 1). The synthesized compounds demonstrated moderate activity.

**Table 2.** Antifungal activity of compounds **4a–4e, 5a–5c, 7,** and **10**

| Product | Zone of inhibition, mm | | |
|---|---|---|---|
| | *Aspergillus niger* | | |
| | lower | middle | upper |
| **4a** | – | – | – |
| **4b** | 1.70 | 1.40 | 1.50 |
| **4c** | – | 0.80 | – |
| **4d** | 0.80 | 1.50 | – |
| **4e** | – | 1.50 | – |
| **5a** | 0.10 | 0.80 | 1.80 |
| **5b** | 0.50 | 0.80 | – |
| **5c** | – | – | – |
| **7** | 2.20 | 1.91 | 1.58 |
| **10** | – | – | – |
| Fluconazole | – | – | 1.90 |

*Antifungal activity.* The synthesized compounds (**4a–4e**, **5a–5c**, **7**, and **10**) were screened for antifungal activity against *Aspergillus nigerfungus* by the agar well diffusion method. The zone of inhibition (in mm) was compared with the standard drug Fluconazole (Table 2). The synthesized compounds demonstrated moderate activity against the tested fungal strain.

## EXPERIMENTAL

All commercially available chemicals were used without further purification. Melting points were determined in open capillary tubes. Elemental analyses were carried out with a Thermo Scientific analyzer. IR spectra (KBr discs) were recorded on a Perkin Elmer Spectrum 400 IR spectrophotometer. $^{1}H$ and $^{13}C$ NMR were measured on a BRUKER AVANCE II 400 NMR Spectrometer at 400 MHz and 100 MHz respectively using TMS as the internal standard. Progress of the processes was monitored by TLC using silica gel-G.

**3-Isothiocyanatoprop-1-ene (2)** *(general procedure).* The mixture of allyl chloride (1 mmol) and potassium thiocyanate (1.1 mmol) in anhydrous ethanol (10 fold volume of allyl chloride) was refluxed for 1.5–2 h and used further without purification.

**Allyl thioureas (4a–4e)** (*general procedure*). Allyl isothiocyanate (1mmol) was added drop wise to ethanolic solution of an appropriate amine (1 mmol)

upon stirring. The reaction mixture was heated at 50–60°C for 3.5–4 h followed by stirring at room temperature for 24 h. The reaction mixture was filtered off to give the corresponding thiourea that was crystallized from either ethanol or glacial acetic acid.

**1-Allyl-3-phenylthiourea (4a).** Yield 50%, mp 101–103°C. IR spectrum, ν, $cm^{-1}$: 3348 (N–H); 3006 (Ar–CH); 1589 and 1533 (ArC=C); 1443 (N–H) ; 1387 (C–N); 1186 (C=S). $^1$H NMR spectrum, δ, ppm: 4.17–4.19 d (2H, $–CH_2$); 5.09–5.22 m (2H, $=CH_2$); 5.85–5.95 m (1H, =CH); 7.06–7.44 m (5H, Ar–H); 7.66 s (1H, ArN–H); 9.45 s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 47.62, 117.04, 125.25, 127.2, 130.12, 133.27, 136.15, 180.41. *M* 193 $[M + H]^+$. Found, %: C 62.16, H 6.15, N 14.03. $C_{10}H_{12}N_2S$. Calculated, %: C 62.46, H 6.29, N 14.57.

**1-Allyl-3-(4-chlorophenyl)thiourea (4b).** Yield 56%, mp 97–99ºC. IR spectrum, ν, $cm^{-1}$: 3233 (N–H), 3052 (Ar–CH), 1599 and 1548 (Ar–C=C), 1490 (N–H), 1411 (C–N), 1091 (C=S). $^1$H NMR spectrum, δ, ppm: 4.25 s (2H, $–CH_2$), 5.15–5.20 d.d (2H, $=CH_2$), 5.81–5.91 m (1H, =CH), 6.13 br.s (1H, Ar N–H), 7.19–7.39 m (4H, Ar–H), 8.83 br.s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 47.63, 117.40, 126.53, 130.16, 132.6, 133.02, 134.81, 180.42. *M* 227 $[M + H]^+$. Found, %: C 52.76, H 4.69, N 11.98. $C_{10}H_{11}ClN_2S$. Calculated, %: C 52.97, H 4.89, N 12.36.

**1-Allyl-3-*p*-tolylthiourea (4c).** Yield 42%, mp 98–100ºC. IR spectrum, ν, $cm^{-1}$: 3295 (N–H), 3010 (Ar–CH), 1586 and 1532 (Ar–C=C), 1449 (N–H), 1315 (C–N), 1191 (C=S). $^1$H NMR spectrum, δ, ppm: 2.29 s (3H, $–CH_3$), 4.14 s (2H, $–CH_2$), 5.08–5.20 m (2H, $=CH_2$), 5.84-5.93 m (1H, =CH), 7.10–7.27 m (4H, Ar–H), 7.60 br.s (1H, Ar N–H), 9.39 br.s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 21.08, 47.81, 116.99, 125.69, 130.83, 133.11, 133.33, 137.78, 180.90. *M* 207 $[M + H]^+$. Found, %: C 63.66, H 6.53, N 13.00. $C_{11}H_{14}N_2S$. Calculated, %: C 64.04, H 6.84, N 13.58.

**4-(3-Allylthioureido) benzoic acid (4d).** Yield 59%, mp 180–182ºC. IR spectrum, ν, $cm^{-1}$: 3363 (N–H), 3016 (Ar–CH), 1693 (C=O), 1606 and 1532 (Ar–C=C), 1420 (N–H), 1306 (C–N), 1171 (C=S). $^1$H NMR spectrum, δ, ppm: 4.16 s (2H, $–CH_2$), 5.11–5.24 m (2H, $=CH_2$), 5.86–5.95 m (1H, =CH), 7.63–7.89 m (4H, Ar–H), 8.13 s (1H, Ar N–H), 9.88 s (1H, N–H), 12.46 br.s (1H, O–H). $^{13}$C NMR spectrum, δ, ppm: 46.02, 115.99, 121.02, 125.24, 129.96, 134.36, 143.73, 166.94, 180.21. *M* 237.0 $[M + H]^+$. Found, %: C 54.56, H 5.24, N 10.00. $C_{11}H_{12}N_2O_2S$. Calculated, %: C 54.9, H 5.12, N 10.26.

**1-Allyl-3-(pyridin-2-yl)thiourea (4e).** Yield 40%, mp 98–100ºC. IR spectrum, ν, $cm^{-1}$: 3229 (N–H), 2956 (Ar–CH), 1598 and 1541 (Ar–C=C), 1452 (N–H), 1331 (C–N), 1194 (C=S). $^1$H NMR spectrum, δ, ppm: 4.29–4.36 m (2H, $–CH_2$), 5.16–5.30 m (2H, $=CH_2$), 5.95–6.04 m (1H, =CH), 6.96-8.18 m (4H, Ar–H), 10.61 s (1H, Ar N–H), 11.86 s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 47.76, 112.37, 116.36, 118.01, 133.24, 138.65, 145.60, 153.56, 179.60. *M* 194.0 $[M + H]^+$. Found, %: C 55.67, H 5.66, N 19.17. $C_9H_{11}N_3S$. Calculated, %: C 55.93, H 5.74, N 19.74.

**Cyclization of thioureas in presence of HCl (5a–5c)** *(general procedure)*. To a solution of thiourea (1 mmol) in ethanol was added ethanolic HCl (4 mmol). The mixture was refluxed for 2–2.5 h, cooled down and neutralized with aqueous $NaHCO_3$ to make the product to precipitate. The solid was filtered off, repeatedly washed with distilled water and crystallized from ethanol.

**5-Methyl-*N*-phenyl-4,5-dihydrothiazol-2-amine (5a)**. Yield 75%, mp 114–116ºC. IR spectrum, ν, $cm^{-1}$: 3466 (N–H), 3027 (Ar–CH), 1631 and 1585 (Ar–C=C), 1491 (N–H), 1318 (C–N). $^1$H NMR spectrum, δ, ppm: 1.31–1.32 d (3H, $–CH_3$), 3.40–3.59 d.d (1H, –CH), 3.84–3.96 m (2H, $–CH_2$), 6.89–7.44 m (4H, Ar–H), 8.78 br.s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 21.11, 44.40, 63.91, 118.64, 121.39, 128.53, 144.51, 156.28. *M* 193.0 $[M + H]^+$. Found, %: C 64.25, H 6.15, N 15.07. $C_{10}H_{12}N_2S$. Calculated, %: C 62.46, H 6.29, N 14.57.

***N*-(4-Chlorophenyl)-5-methyl-4,5-dihydrothiazol-2-amine (5b).** Yield 63%, mp 116–118ºC. IR spectrum, ν, $cm^{-1}$: 3088 (Ar–CH), 1625 and 1581 (Ar–C=C), 1485 (N–H), 1320(C–N). $^1$H NMR spectrum, δ, ppm: 1.30–1.31 d (3H, $–CH_3$), 3.54–3.57 d (1H, –CH), 3.84–3.95 m (2H, $–CH_2$), 7.24–7.43 m (4H, Ar–H), 8.91 br.s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 21.04, 44.45, 63.83, 120.27, 125.01, 128.35, 143.58, 156.58.*M* 227.0 $[M + H]^+$. Found, %: C 54.70, H 4.91, N 12.60. $C_{10}H_{11}ClN_2$. Calculated, %: C 54.97, H 4.89, N 12.36.

**5-Methyl-*N*-*p*-tolyl-4,5-dihydrothiazol-2-amine (5c).** Yield 57%, mp 103–105ºC. IR spectrum, ν, $cm^{-1}$: 3103 (Ar–CH), 1651 and 1607 (Ar–C=C), 1505 (N–H), 1307 (C–N). $^1$H NMR spectrum, δ, ppm: 1.42–1.44 d (3H, $–CH_3$ with aromatic ring), 2.33 s (3H, $–CH_3$ on thiazole ring), 3.35–3.39 d.d (1H, –CH), 3.78–3.88 m (2H, $–CH_2$), 6.99–7.12 m (4H, Ar–H), 7.66 br.s (1H, NH). $^{13}$C NMR spectrum, δ, ppm: 20.32, 20.86, 43.17,

56.30, 121.34, 129.48, 132.55, 145.94, 162.14. *M* 207.0 $[M + H]^+$. Found, %: C 66.64, H 6.8, N 14.00. $C_{11}H_{14}N_2S$. Calculated, %: C 66.04, H 6.84, N 13.58.

**Cyclization in presence of bromine in $CHCl_3$ (6, 7)** *(general procedure).* To a solution of thiourea (1 mmol) in chloroform was added bromine (2 mmol) dissolved in the same solvent over a period of 1–1.5 h. The resulting mixture was neutralized with $NaHCO_3$ solution. The hard gummy mass thus obtained was washed repeatedly by diethyl ether. The solid thus obtained was recrystallized from ethanol.

***N*-(5-(Bromomethyl)-4,5-dihydrothiazol-2-yl)-pyridin-2-amine (VI)**. Yield 71%, mp 144–146ºC. IR spectrum, ν, $cm^{-1}$: 3410, 3095 (N–H), 1630 and 1580 (Ar–C=C), 1476 (N–H), 1353 (C–N). $^1$H NMR spectrum, δ, ppm: 3.84–3.93 m (2H, $–CH_2$), 4.08–4.19 d (2H, $–CH_2Br$), 4.45 s (1H, –CH), 7.28–8.40 m (4H, Ar–H), 11.49 br.s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 35.21, 46.81, 64.58, 109.93, 113.61, 120.98, 139.90, 146.67, 166.71. *M* 207.0 $[M + H]^+$. Found, %: C 66.64, H 6.8, N 14.00. $C_9H_{10}BrN_3S$. Calculated, %: C 66.04, H 6.84, N 13.58.

**2,6-Dibromo-4-chloroaniline (7).** Yield 85%, mp 93–95ºC. IR spectrum, ν, $cm^{-1}$: 3420 and 3313 (N–H), 3076 (Ar–CH), 1614 and 1568 (Ar–C=C), 1456 (N–H). $^1$H NMR spectrum, δ, ppm: 4.46 s (2H, $–NH_2$), 7.30 s (2H, Ar–H). Found, %: C 24.81, H 1.49, N 4.18. $C_6H_4Br_2ClN$. Calculated, %: C 25.25, H 1.41, N 4.91.

**3-Allyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (10).** Anthranilic acid (1 mmol) was condensed with allyl isothiocyanate (1.1 mmol) to make thiourea which cyclized further into the final product, quinazoline derivative, in presence of acetic acid upon refluxing for 2.5–3 h. Yield 51%, mp 191–193ºC. IR spectrum, ν, $cm^{-1}$: 3259 (N–H), 3042 (Ar–CH), 1653 (C=O), 1622 and 1530 (Ar–C=C), 1416 (N–H), 1321 (C–N), 1186 (C=S). $^1$H NMR spectrum, δ, ppm: 5.02–5.03 d (2H, $–CH_2$), 5.12–5.16 m (2H, $=CH_2$), 5.86–5.95 m (1H, =CH), 7.29–7.94 m (4H, Ar–H), 12.96 s (1H, N–H). $^{13}$C NMR spectrum, δ, ppm: 47.55, 115.34, 115.58, 117.06, 124.44, 127.22, 131.71, 135.43, 139.03, 158.94, 174.97. *M* 207.0 $[M + H]^+$.Found, %: C 60.21, H 4.53, N 12.45. $C_{11}H_{10}N_2OS$. Calculated, %: C 60.53, H 4.62, N 12.83.

**2-(Bromomethyl)-2,3-dihydrothiazolo[2,3-*b*]quinazolin-5-one (11)**. Bromine (2 mmol) dissolved in acetic acid was added to a solution of quinazoline (1mmol) in acetic acid drop wise with continuous stirring for 1–1.5 h. The reaction mixture was stirred for 0.5 h at room temperature. Upon completion of the process, the reaction mixture was neutralized with sodium bicarbonate and the precipitate formed was recrystallized from acetic acid to give 2-bromomethyl-2,3-dihydroythiazolo[2,3-*b*]quinazolin-5-one. Yield 57%, mp >250ºC. IR spectrum, ν, $cm^{-1}$: 3047 (Ar–CH), 1655 (C=O), 1623 and 1532 (Ar–C=C), 1417 (N–H), 1324 (C–N). $^1$H NMR spectrum, δ, ppm: 3.85–3.88d.d (2H, $–CH_2$), 4.31–4.43 m (2H, $–CH_2Br$), 4.53–4.57 d.d (1H, –CH), 7.36–8.06 m (4H, Ar–H). $^{13}$C NMR spectrum, δ, ppm: 23.79, 47.61, 116.35, 116.53, 119.11, 122.62, 126.62, 132.60, 134.07, 160.17, 174.94. Found, %: C 44.55, $H_3$.27, N 9.93. $C_{11}H_9BrN_2OS$. Calculated, %: C 44.46, $H_3$.05, N 9.43.

*Anti-bacterial activity.* Synthesized compounds were studied for their antibacterial activity by well diffusion method in DMSO (Dimethylsulfoxide) as a solvent against various pathogenic strains of bacteria, Gram positive (*Lactobacillus bulgaris*, *S.mitis*) and Gram negative (*Yersinia*) [21], obtained from Maharishi Markandeshwar Medical College, Maharishi Markandeshwar University, Mullana (Haryana) India. 25 mL of nutrient agar medium was poured into Petri plates and the agar plates were swabbed with 100 µL inocula of each test bacterium and stored for 15 min for adsorption. Using sterile cork borer of 3 mm diameter, wells were bored into the seeded agar plates and those were loaded with 10–12 µL volumes. Solutions of the test compounds and standards were prepared in DMSO at concentration of 1000 µg/mL. From this stock solution, diluted solutions of the compounds (0.2, 0.4, …, 1 mg/mL) were inoculated to the corresponding wells. All plates were incubated at 37°C for 24 h. Antibacterial activity of each synthesized compound was evaluated by measuring the zone of inhibition with zone reader (Hi Antibiotic zone scale). MIC was determined as the lowest concentration of the tested compound tested able to inhibit visible growth of the microbes. DMSO was used as the control. Ofloxacin was used as the reference drug. The study was made at three concentrations: high (9–10 mg/mL), middle (5–6 mg/mL), and low (1–2 mg/mL).

*Anti-fungal activity.* Antifungal activity of synthesized compounds was evaluated by the agar well diffusion method against *Aspergillus niger* [21]. The molds were grown on Potato dextrose agar (PDA) at 25ºC for 7 days and used as inocula. 15 mL Of molten PDA (45ºC) was poisoned by addition of 50 µL of each compound, poured into a sterile Petri plate and allowed to solidify at room temperature. Solutions of

the tested compounds and standards were prepared in DMSO (2.000 μg/mL). From the stock solution, two fold dilutions of the compounds (2, 4, …, 64 μg/mL) were inoculated to the corresponding wells. The solidified poisoned agar plates were inoculated at the center with fungal plugs (8 mm diameter), obtained from the actively growing colony and incubated at 25ºC for 7 days. DMSO was used as the negative control. Fluconazole was used as the reference drug. The experiments were carried out in triplicates.

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