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Design, synthesis, X-ray analysis, and biological screening of new oxime and enaminone thiazoline-2-thione derivatives

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ABSTRACT

An urgent need exists to develop antimicrobial and anticancer drugs that are safer and less prone to the development of resistance. To this end, a series of 12 new thiazoline-2-thione derivatives (oxime and enaminone) were synthesized using an appropriate synthetic route. The characterization of the newly synthesized compounds was performed using X-ray single-crystal diffractometry, elemental analysis, ^{1}H NMR, ^{13}C NMR, IR, and MS techniques. These compounds were then evaluated for their biological activities against a variety of microbes and human cancer cell lines. Our results revealed that the prepared thiazoline derivatives **4a, 4b, 6a, 6c,** and **7** showed potent antifungal activity against *Aspergillus fumigatus*, comparable to the standard drugs. Additionally, all the thiazoline derivatives, except compound **4b**, were effective against *Candida albicans*. The tested thiazolines also demonstrated potent antibacterial activity comparable to the standard drugs for all tested Gram-positive and Gram-negative bacterial species. The cytotoxicity evaluation of synthesized compounds **3, 6b** and **7** against two cancer cell lines (HCT-116 and HepG-2) revealed that they had moderate cytotoxic activities, with compound **6b** showing the best cytotoxic activity against the HCT-116 (IC_{50} = 79 μg/ml) and HepG-2 (IC_{50} = 49 μg/ml) cell lines. These findings open the pathway for the development of new lead compounds with chemotherapeutic properties.

1. Introduction

Microbial infections and cancer are major causes of morbidity and mortality worldwide. Cancer is reported to claim the life of nearly 10 million people yearly, with the major types linked to infections [1]. The number of newly diagnosed cancers is growing rapidly owing to the increase in lifespan and the advances in diagnostic techniques. While infectious disease and cancer treatments are available and effective, the development of resistance and the presence of toxicity remain a hurdle. Indeed, it is the greatest challenge in modern drug development to identify new targets and drugs that effectively combat microbial infections and cancer. Hence, an urgent demand exists for new antimicrobial and anticancer agents with better safety profiles and improved selectivity against microbial and tumor cells [2–5].

The thiazoline scaffold is considered a functional group in thiazolium-based drugs such as penicillin and pioglitazone [6,7]. A series of compounds known as thiazoline derivatives have been synthesized and recognized as bioactive agents. In recent years, thiazoline derivatives have gained much attention, because these compounds exhibit various pharmacological activities, such as anti-inflammatory [8,9], anti-microbial [10–13], anti-diabetic [14–16], anti-cancer [4,17–19], and antioxidant activities [20,21]. The inhibitory activities of thiazoline derivatives have been reported against butyrylcholinesterase and carboxylesterase [22].

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Recently, we reported the synthesis, antimicrobial and cytotoxic activities of a series of thiazoline (thiazoline-2-thione) derivatives [23]. In continuation of our interest in the synthesis and pharmacological screening of thiazoline-2-thione derivatives, the present study outlines additional approaches to synthesize 12 new thiazoline-2-thione derivatives and to screen for their biological activities.

2. Experimental details

2.1. Chemistry

The chemicals and reagents used in this study are commercially available (Sigma-Aldrich, Fluka, Acros Organic) and were used without further purification. Measurements of the melting points of the compounds were done using a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were measured on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Tokyo, Japan) at 70 eV. Infra-red (IR) spectra were measured as KBr on a Perkin Elmer FT-IR spectrophotometer 1000 (PerkinElmer, Waltham, MA, USA). The ^{1}H NMR (500 MHz), and ^{13}C NMR (500 MHz) spectra were performed on a Jeol-500 NMR spectrometer. The chemical shifts were reported in δ units and coupling constants (J) were reported in Hertz (Hz) with respect to solvents (CD_3OD, D_2O, DMSO–d6, $CDCl_3$) by using tetramethylsilane as an internal standard. The multiplicities were given as s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet). Elemental analysis was recorded on a 2400 CHN Elemental Analyzer.

2.1.1. Synthesis compound **2**

Compound **1** (1.25 g, 1 mmol) was dissolved in Xylene with DMF-DMA (2 mmol) in a round bottom flask. The reaction was heated for 2 h, then allowed to cool for a short time. The solid product that formed was filtered, washed with ethanol, and recrystallized with ethanol to afford thiazoline-2-thione derivative **2**.

2.1.1.1. (E)−3-(Dimethylamino)−1-(4-methyl-3-phenyl-2-thioxo-2, 3-dihydrothiazol-5-yl)prop–2-en-1-one (***2***). Yellow crystals,(0.274 g, yield 90%); m.p. 180–185 °C (Ethanol); IR $_{vmax}$ 1639 (*C = O*), 1573 (*C = C*), 1543 (*C = S*); ^{1}H NMR ($CDCl_3$) δ 2.84 (s, 3H, CH_3), 2.25 (s, 6H, -N(CH_3)$_2$), 5.09 (s, 1H, CH=CHN), 7.68 (s, 1H, CHCO), 7.16 – 7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.85 (CH_3), 45.27 (2CH_3), 93.93, 106.00, 123.01, 128.16 (2C), 129.76, 129.94 (2C), 137.69 (Ar-C), 144.07 (*C = C*–N), 154.09 (*C = C* thiazole), 178.68 (*C = O*), 188.42 (*C = S*); MS (*m/z*) (%) 304.07 (M^+, 100%); Anal. Calcd. for $C_{15}H_{16}N_2OS_2$ (304.43): C, 59.18; H, 5.30; N, 9.20; S, 21.06. Found: C, 59.21; H, 5.39; N, 9.31; S, 21.17%.

2.1.2. Synthesis compound ***3***

Hydroxylamine (1 mmol) was dissolved in 20 mL of absolute ethanol, then added to compound **1** (0.31 g, 1 mmol). The reaction mixture was refluxed for 6 h. The formed precipitate was filtered off and recrystallized with ethanol to afford thiazoline-2-thione derivative **3.** The crystal structure of compound 3 was solved using X-ray crystallography.

4.1.2.1. (E)−5-(1-(Hydroxyimino)ethyl)−4-methyl-3-phenylthiazole-2(3H)-thione (***3***). Yellow crystals, (0.198 g, yield 75%); m.p. 217 °C (Ethanol); IR $_{vmax}$ 3160 (OH), 1631 (*C = N*), 1591 (*C = C*), 1491 (*C = S*); ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 3.55 (s, 3H, CH_3), 7.21 – 7.85 (m, 5H, Ph), 11.65 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 13.71 (CH_3), 15.86 (CH_3C=*N*), 119.89 (=*C*–*C = N*), 128.69, 129.95 (2C), 130.85 (2C), 131.24 (Ar-C), 138.11 (=*C*–CH_3), 147.74 (-*C = N*–OH), 187.48 (*C = S*); MS (*m/z*) (%) 264.09 (M^+, 100%), 249.09 (M-CH_3^+, 10%), 77.08 ($C_6H_5^+$, 94%); Anal. Calcd. for $C_{12}H_{12}N_2OS_2$ (264.04): C, 54.52; H, 4.58; N, 10.60; S, 24.25. Found: C, 54.56; H, 4.52; N, 10.65; S, 24.29%.

2.1.3. Synthesis compound ***4***

Compound **3** (0.26 g, 1 mmol) and phenyl hydrazine (0.1 g, 1 mmol) or hydrazine hydrate (0.1 g, 1 mmol) was dissolved in glacial acetic acid solvent and heated for 5 h. After cooling, the precipitate was filtered, washed with ethanol, dried, and recrystallized from absolute ethanol to give compounds **4a, b**.

2.1.3.1. (E)−4-Methyl-3-phenyl-5-(1-(3-phenyltriazanylidene)ethyl) thiazole-2(3H)-thione (***4a***). Yellow solid, (0.211 g, yield 80%); m.p. 170 °C; IR $_{vmax}$ 3286, 3232 (NH), 1642 (*C = N*), 1599 (*C = C*), 1496 (*C = S*); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 6.69 – 7.23 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 12.50 (CH_3), 14.35 (CH_3), 112.44, 113.50 (2C), 121.16, 128.12, 129.18 (2C), 129.51 (2C), 130.50 (2C), (Ar-C), 145.00 (*C = C*), 147.75(*C = N*), 157.95 (*C = N*), 188.59 (*C = S*); MS (*m/z*) (%) 354 (M^+, 100%); Anal. Calcd. for $C_{18}H_{18}N_4S_2$ (c): C, 60.99; H, 5.12; N, 15.81; S, 18.09. Found: C, 60.87; H, 5.19; N, 15.71; S, 18.16%.

2.1.3.2. (E)−4-Methyl-3-phenyl-5-(1-triazanylideneethyl)thiazole-2(3H)-thione (***4b***). Yellow crystals, (0.237 g, yield 85%); m.p. 255 °C; IR $_{vmax}$ 3208 (NH), 3163 (NH_2), 1674 (*C = N*), 1590 (*C = C*), 1491 (*C = S*); ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.86 (s, 2H, NH_2), 6.69 – 7.22 (m, 10H, 2 Ph), 8.90 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 12.30 (CH_3), 15.10 (CH_3), 104.30, 128.40, 129.61 (2C), 132.51 (2C), 136.90 (Ar-C), 150 (*C = C*), 157.60 (*C = N*), 188.40 (*C = S*); MS (*m/z*) (%) 278 (M^+, 2%), 249.08 (M-CH_3^+, 14%), 247.04 (M^+−NH−NH_2), 77.02 ($C_6H_5^+$, 100%); Anal. Calcd. for $C_{12}H_{14}N_4S_2$ (278.39): C, 51.77; H, 5.07; N, 20.13; S, 23.03. Found: C, 51.81; H, 5.16; N, 20.21; S, 23.12%.

2.1.4. Synthesis compound ***5***

A mixture of compound **2** (0.31 g, 1 mmol) and urea (1 mmol) or thiourea (1 mmol) in glacial acetic acid (10 mL) was refluxed for 5 h. The precipitate was filtered and recrystallized with absolute ethanol to afford compounds **5a, b**.

2.1.4.1. (E)−1-(3-(4-Methyl-3-phenyl-2-thioxo-2, 3-dihydrothiazol-5-yl)−3-oxoprop-1-en-1-yl)urea (***5a***). Yellow crystals, (0.256 g, yield 80%); m.p. 205 °C; IR $_{vmax}$ 3440 (NH), 1622, 1568 (*C = O*), 1537 (*C = C*), 1489 (*C = S*); ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 5.20 (d, 1H, CH), 7.71 (d, 1H, CH), 7.35 – 7.56 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.25 (CH_3), 94.30, 105.34, 128.30, 129 (2C), 131.40 (2C), 132.65 (Ar-C), 147.15 (CH=CH), 158.25, 162.50 (*C = C*), 186 (*C = O*), 188.45 (*C = S*); MS (*m/z*) (%) 319 (M^+, 1%), 304.10 (M-CH_3^+, 84%), 260.05 (M-$NHCONH_2^+$, 30%); Anal. Calcd. for $C_{14}H_{13}N_3O_2S_2$ (319.40): C, 52.65; H, 4.10; N, 13.16; S, 20.08. Found: C, 52.76; H, 4.21; N, 13.22; S, 20.15%.

2.1.4.2. (E)−1-(3-(4-Methyl-3-phenyl-2-thioxo-2, 3-dihydrothiazol-5-yl)−3-oxoprop-1-en-1-yl)thiourea (***5b***). Yellow solid, (0.252 g, yield 75%); m.p. 292 °C; IR $_{vmax}$ 1586 (*C = O*), 1559 (*C = C*), 1516, 1494, (*C = S*); ^{1}H NMR ($CDCl_3$) 2.19 (s, 3H, CH_3), 5.21 (d, 2H, CH), 7.35 – 7.56 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.85 (CH_3), 92.50, 123.65, 128.49, 129.69 (2C), 130.13 (2C), 137.50 (Ar-C), 154.00 (*C = C*–N), 154.00 (*C = C*),176.35, 184.00 (*C = O*), 187.85 (*C = S*); MS (*m/z*) (%) 340 (M^+, 2%), 319.06 (M-H^+, 14%), 317.04 (M-3H^+, 100%), 77.08 ($C_6H_5^+$, 68%); Anal. Calcd. for $C_{14}H_{13}N_3OS_3$ (335.46): C, 50.13; H, 3.91; N, 12.53; S, 28.67. Found: C, 50.20; H, 3.98; N, 12.60; S, 28.75%.

2.1.5. Synthesis compound ***6***

A solution of compound **2** (0.30 g, 1 mmol) in glacial acetic acid was added to aniline derivatives (1 mmol), then refluxed for 6 h. The precipitate formed, was then filtered, washed with ethanol and recrystallized using ethanol to afford compounds **6a-e**.

2.1.5.1. (E)−3-(Hydroxyamino)−1-(4-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)prop–2-en-1-one (***6a***). Yellow crystals, (0.175 g, yield 60%); m.p. 135 °C; IR $_{vmax}$ 3146(NH), 1608 (*C* = *O*), 1589 (*C* = *C*), 1488 (*C* = *S*); ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 6.23 (d, 1H, CH=CH), 7.19 – 7.55 (m, 5H, Ph), 8.24 (s, 1H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 15.77 (CH_3), 101.01, 108.87, 128.07, 130.10, 137.41, 139.82 (Ar-C), 150.58 (*C* = *C*), 160.46 (*C* = *C* thiazole),187.00 (*C* = *O*), 188.86 (*C* = *S*); MS (*m/z*) (%) 292 (M^+, 100%), 274.05 (M-H_2O^+, 22%), 77.06 ($C_6H_5^+$, 100%); Anal. Calcd. for $C_{13}H_{12}N_2O_2S_2$ (292.37): C, 53.41; H, 4.14; N, 9.58; S, 21.93. Found: C, 53.31; H, 4.19; N, 9.63; S, 21.85%.

2.1.5.2. (E)−3-Hydrazinyl-1-(4-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)prop–2-en-1-one (***6b***). Yellow solid, (0.146 g, yield 50%); m.p. 229 °C; IR $_{vmax}$ 3290 (OH), 3160 (NH), 1621 (*C* = *O*), 1589 (*C* = *C*), 1490 (*C* = *S*); ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H, CH_3), 3.31 (s, 2H, NH_2), 6.52 (s, 1H, CH=CH), 7.37 – 7.60 (m, 5H, Ph), 7.87 (s, 1H, CH=CH), 13.14 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.92 (CH_3), 102.15, 115.65, 128.51, 129.67 (2C), 130.50 (2C), 136.50 (Ar-C), 138.50 (*C* = *C*–N), 141.95 (*C* = *C*), 184 (*C* = *O*), 187.85 (*C* = *S*); MS (*m/z*) (%) 291 (M^+, 100%), 262.17 (M-N_2H^+, 26%), 43.12 (CH_3CO^+, 100%); Anal. Calcd. for $C_{13}H_{13}N_3OS_2$ (291.39): C, 53.59; H, 4.50; N, 14.42; S, 22.01. Found: C, 53.51; H, 4.58; N, 14.49; S, 22.11%.

2.1.5.3. (E)−3-((4-Chlorophenyl) amino)−1-(4-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)prop–2-en-1-one (***6c***). Yellow crystals, (0.31 g, yield 80%); m.p. 220 °C; IR $_{vmax}$ 1634 (CO), 1565 (*C* = *C*), 1483 (*C* = *S*); ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H, CH_3), 6.54 (d, 1H, CH=CH), 7.10 – 7.58 (m, 10H, Ph), 11.37 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.30 (CH_3), 93.45, 106.65, 119.2 (2C),128.70, 129.50 (2C), 129.65 (2C), 130.21 (2C), 132.70, 136.50, 137.61 (Ar-C), 155.70 (CH=CH), 162.32 (*C* = *C*), 187.00 (*C* = *O*), 188.45 (*C* = *S*); MS (*m/z*) (%) 388 (M^{+2}, 40%), 386 (M^+, 92%), 77.07 ($C_6H_5^+$, 78%); Anal. Calcd. for $C_{19}H_{15}ClN_2OS_2$ (386.91): C, 58.98; H, 3.91; Cl, 9.16; N, 7.24; S, 16.57. Found: C, 58.91; H, 3.86; Cl, 9.16; N, 7.32; S, 16.63%.

2.1.5.4. (E)−3-((4-Methoxyphenyl) amino)−1-(4-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)prop–2-en-1-one (***6d***). Yellow powder,(0.314 g, yield 82%); m.p. 195 °C; IR $_{vmax}$ 1636 (CO), 1571 (*C* = *C*), 1478 (*C* = *S*); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.10 (d, 1H, CH=CH), 6.83 (d, 1H, CH=CH), 6.95 – 7.51 (m, 10H, 2Ph), 11.85 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 15.93 (CH_3), 55.65 (OCH_3), 65.45, 94.00, 115.30 (2C), 118.19 (2C), 128.21, 129.97 (2C), 130.00, 133.45 (2C), 137.80, 144.21 (Ar-C), 154.55 (*C* = *C*), 157.21 (*C* = *C* thiazole),178.90 (*C* = *O*), 187.65 (*C* = *S*); MS (*m/z*) (%) 382 (M^+, 100%), 383.07 (*M* + 1, 30%), 305.14 (M-$C_6H_5^+$, 10%), 77.05 ($C_6H_5^+$, 50%); Anal. Calcd. for $C_{20}H_{18}N_2O_2S_2$ (382.50): C, 62.80; H, 4.74; N, 7.32; S, 16.76. Found: C, 62.72; H, 4.84; N, 7.29; S, 16.66%.

2.1.5.5. (E)−3-((1H-Benzo[d]imidazol-2-yl)amino)−1-(4-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)prop–2-en-1-one (***6e***). Yellow crystals, (0.216 g, yield 55%); m.p. 208 °C; IR $_{vmax}$ 1621 (*C* = *O*), 1567 (*C* = *C*), 1488 (*C* = *S*); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 3.09 (s,1H,NH), 2.88 (s, 1H, NH), 5.09 (d, 1H, CH), 7.67 (d, 1H, CH), 7.16 – 7.52 (m, 9H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 15.85 (CH_3), 94.02, 117.30, 123.01 (2C), 128.21, 129.77 (2C), 129.96 (2C), 130.50 (2C), 137.75 (2C) (Ar-C), 154.11 (*C* = *C*–N), 178.74 (*C* = *C*), 188.00 (*C* = *O*), 192.30 (*C* = *S*); MS (*m/z*) (%) 392 (M^+, 100%), 77.07 ($C_6H_5^+$, 44%); Anal. Calcd. for $C_{20}H_{16}N_4OS_2$ (392.50): C, 61.20; H, 4.11; N, 14.27; S, 16.34. Found: C, 61.02; H, 4.21; N, 14.15; S, 16.44%.

2.1.6. Synthesis compound ***7***

Compound **2** (0.30 g, 1 mmol) was completely dissolved in glacial acetic acid (10 mL), then ammonium acetate (0.3 g, 1 mmol) was added to reaction mixture. The reaction mixture was then heated for 5 h. After cooling, the precipitate was collected and washed with absolute ethanol, then recrystallized from ethanol to afford the desired compound **7**.

2.1.6.1. (4-Methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)(6-(4-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)pyridin-3-yl)methanone (***7***). Yellow crystals, (0.311 g, yield 60%); m.p. 243 °C; IR $_{vmax}$ 1644 (*C* = *O*), 1571 (*C* = *C*), 1488 (*C* = *S*); ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 6H, CH_3), 7.23 – 7.65 (m, 10H, Ar-H), 7.90 (s, 1H, CH), 8.10 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 12.10 ($2CH_3$), 98.80, 121.80, 125.90, 128.40 (2C), 129.10 (4C), 131.30, 134.35 (4C), 135.90 (2C), 137.85, 147.00 (*C* = *C* thiazole), 154.25, 157.00 (*C* = *C*), 162.10 (Pyridine and Ar-C), 186.70 (*C* = *O*), 188.95 (*C* = *S*); MS (*m/z*) (%) 517 (M^+, 8%), 77.05 ($C_6H_5^+$, 100%); Anal. Calcd. for $C_{26}H_{19}N_3OS_4$ (517.70): C, 60.32; H, 3.70; N, 8.12; S, 24.77. Found: C, 60.22; H, 3.65; N, 8.28; S, 24.57%.

2.2. X-Ray crystallography

Compound **3** was obtained as single crystals by slow evaporation from an ethanol solution of the pure compound at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer equipped with graphite monochromatic Mo Kα radiation, λ = 0.71073 Å at 296 (2) K. Cell refinement and data reduction were carried out by Bruker SAINT. A SHELXT [24,25] was used to reveal the structure. The final refinement was carried out by the full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on *f*.

2.3. Biological evaluation

2.3.1. Antimicrobial activity

The antifungal and antibacterial activities of selected synthesized compounds were screened using the agar diffusion method [26–28]. The *in vitro* antimicrobial activity of the chosen compounds was performed against two different fungi (*Aspergillus fumigatus* [RCMB 002,008] and *Candida albicans* [RCMB 05,036]), two Gram-positive bacterial strains (*Streptococcus pneumonia* [RCMB010010] *and Bacillis subtilis* [RCMB 010,067]) and two Gram-negative bacterial strains (*Salmonella sp* [RCMB 010,043], and *E. coli* [RCMB 010,052]). Amphotericin B (antifungal), ampicillin (Gram-positive antibacterial), and gentamicin (Gram- negative antibacterial) were used as the standard antimicrobial agents. Each experiment was performed in triplicate. The Mueller-Hinton agar medium for bacteria and the Sabouraud's agar medium for fungi were used in this study. Briefly, 100 μl of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately108 cells/ml for bacteria or 105 cells/mL for fungi. A suspension of the organisms was added to the sterile nutrient agar media at 45 °C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 6 mm in diameter were made using a cork borer. The samples of the test compounds, as well as the reference drugs, were dissolved in DMSO to generate a solution of 10 mg mL^{-1}. 100 µL of each sample and reference were added to each well. Dimethylsulfoxide (DMSO) was used as a negative control and showed no inhibition zones. The plates were incubated for 24 h at 37 °C (for bacteria) and for 48 h at 28 °C (for fungi). After incubation, the microorganism's growth was observed. The diameters of the inhibition zones were measured and compared with that of the reference drug. The observed inhibition zones were measured in millimeters and the percentage val-

ues of the inhibition zones compared to the reference drugs were recorded (Tables 4).

2.3.2. Cytotoxic activity

The cytotoxic activity of selected compounds against colon cancer (HCT-116) and liver cancer (HepG-2) cells was investigated using the standard 3-(4,5-dimethyl-2-thiazolyl)−2,5-diphenyl-2H-tetrazolium bromide (MTT) assay [29]. A soluble tetrazolium salt was used in the MTT colorimetric assay method. The effects of the tested compounds on the cell viability of the HCT-116 and HepG-2 cell lines were determined using MTT colorimetric assay. The HCT-116 and HepG-2 cells were seeded in 96-well plates at 5×10^4 cells/mL. The compounds' were dissolved in dimethyl sulfoxide, diluted in the medium and added to each well. Experimental sets containing different concentrations of the compounds and the positive control doxorubicin were prepared and the cells were incubated for 24 h. After 24 h of contact with the cells, 25 μL of MTT solution (5 mg/mL) was added to each well. The plates were left for another 4 h in an incubator at 37 °C and the supernatant was aspirated after the incubation period. Absorbance at 550 nm was recorded with an ELISA micro-plate reader. GraphPad Prism software Version 7.02 (La Jolla, California, USA) was used to analyze the data. The cell viability% was calculated in relation to the control group without treatment. Concentration response curves were generated to determine IC_{50} using the non-linear least square fits of a log (inhibitor) *versus* normalized response model. Each sample was tested in triplicate in three independent experiments.

2.4. Docking studies

All molecular modeling calculations were carried out using Autodock 4.0 [30]. The target compounds were drawn on ChemBio-Draw Ultra 14.0 and converted into 3D structures using Hyperchem pro 8.0 software (www.hyper.com). Autodock tools (ADT) version 1.5.6 (www.autodock.scrips.edu) was used to prepare molecular docking. The X-ray crystal structure of the epidermal growth factor receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib (PDB ID: 1M17) was retrieved from the www.rcsb.org [31]. The enzyme was protonated, where hydrogen atoms were added at their standard geometry, the partial charges were computed and the system was optimized. The grid box size was set to a dimension of 20×−0.53×58 in x, y, z coordinates to cover the active site of the kinase while virtual screening was performed by AutoDock 4.2.5.1. The best binding conformation was selected from the docking log (.dlg) file for each ligand and further interaction analysis was done using PyMol and Discovery Studio Visualizer 4.0.

3. Results and discussion

3.1. Chemistry

The synthetic strategy adopted for the preparation of thiazoline-2-thiones **2, 3** and **4a,b** is outlined in Scheme 1, while that of thiazoline-2-thiones **5a,b, 6a-e,** and **7** are in Scheme 2. The synthesis of 12 new oxime and enaminone of thiazoline-2-thione derivatives was carried out at a yield of 50–90% using the proposed methods (Schemes 1 and 2). The synthesis of thiazoline-2-thione **1** was reported previously [23]. Compound **1** was obtained in high yields by stirring 3-chloropentane-2,4–dione with aniline and carbon disulfide in ethanol at room temperature. The compound containing an active methylene group (compound **1)** was condensed o with DMF-DMA in xylene using a thermal method afforded enamine **2** in high yield [32,33]. The ^{1}H spectral data exhibited a doublet, integrated with one proton at δ 5.09 and 7.68 due to the resonance of an α, β-keto-unsaturated proton in the structure.

Oxime **3** was prepared by the treatment of compound **1** with hydroxylamine (via nucleophilic addition to the carbonyl group) (Scheme 1). Thus, the IR spectra of compound **3** showed a disappearing band for CO stretching. In addition, the ^{13}C NMR spectra of **3** displayed a signal of CO in the molecule, and contained a singlet integrated with one proton, which represents $C = N$–OH at δ 11.65 ppm. The structure of thiazoline-2-thione **3** was confirmed by single crystal X-ray analysis. The crystallographic data confirm the structure of the molecule.

Then compound **3** was mixed with hydrazine or phenyl hydrazine in the presence of AcOH, which yielded the targeted compounds **4a,b** in good yield. ^{1}H, ^{13}C NMR and mass spectral data were consistent with the structures of the prepared **4a,b.** The presence of electron deficient (electrophile) and electron rich centers (nucleophile) in the *N,N*-dimethyl enamine derivatives initiated a wide range of diverse block acyclic and cyclic hetero-compounds [34].

Next, the reaction of the thiazoline-2-thione derivative **2** was reacted with urea or thiourea in the presence of acetic acid to afford targeted products **5a,b** through a condensation reaction via dimethylamine elimination (Scheme 2). The structures of these products were confirmed on the basis of their spectroscopic data. Similarly, compound **2** reacted with the derivatives of amine under the identical experimental conditions of the above synthesis, yielded thiazoline-2-thione derivative **6a–e** (Scheme 2). Additionally, a thiazoline-2-thione derivative with a pyridine moiety (compound **7)** was obtained by heating enamine **2** with ammonium acetate in acetic acid (Scheme 2).

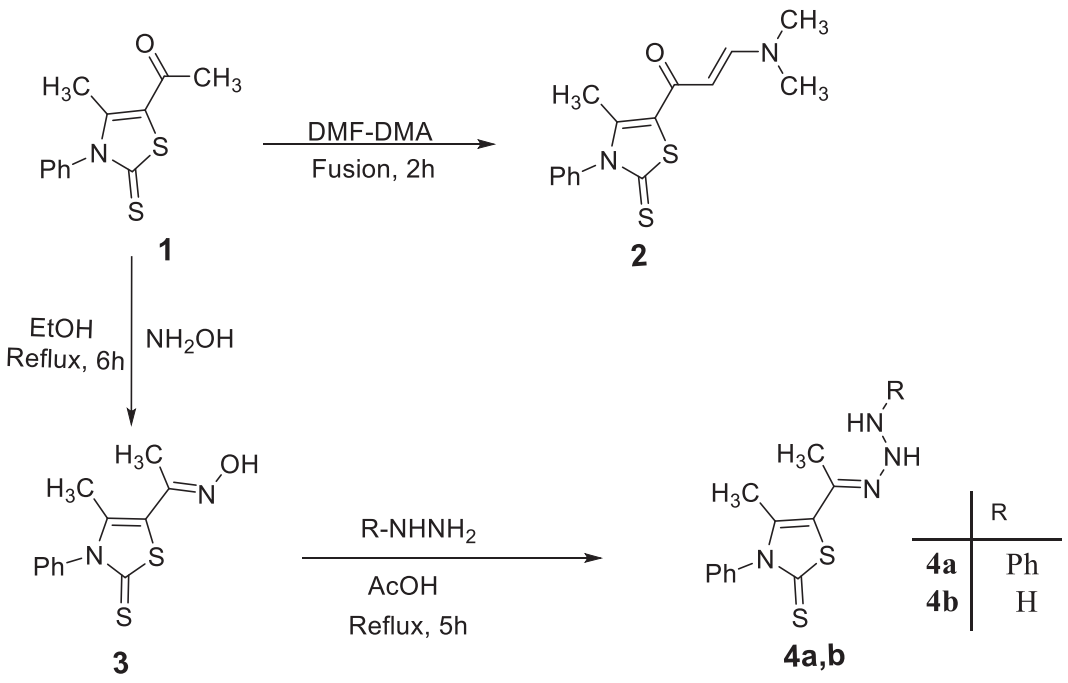
3.2. X-ray crystallography

The thiazoline-2-thione derivative **3** crystal of the dimensions 0.47 × 0.26 × 0.14 mm was selected for X-ray crystallography analysis. Crystallographic data were collected on a Bruker APEX-II diffractometer equipped with a CCD detector. The crystallographic data and refinement information of the thiazoline derivative **3** ($C_{12}H_{12}N_2OS_2$) are summarized in Table 1. The selected bond lengths and bond angles are listed in Table 2. The asymmetric unit contains one independent molecule, as shown in Fig. 1. All the bond lengths and angles are within normal ranges [35]. The thiazoline ring makes a dihedral angel with the phenyl ring equal to 83.63(2)°, nearly perpendicular planes. The N2-C4 is a double bond, its bond length is 1.294(5) Å and the oxime group found in the trans conformation as shown in Fig. 1, which stabilized by weak intramolecular hydrogen bond between C5—H5A···O1. In the crystal packing shown in Fig. 2, the molecules are linked *via* one inter-molecular hydrogen bond between the hydroxyl hydrogen of oxime moiety in one molecule with the S2 in another molecule through a and b axes (Table 3).

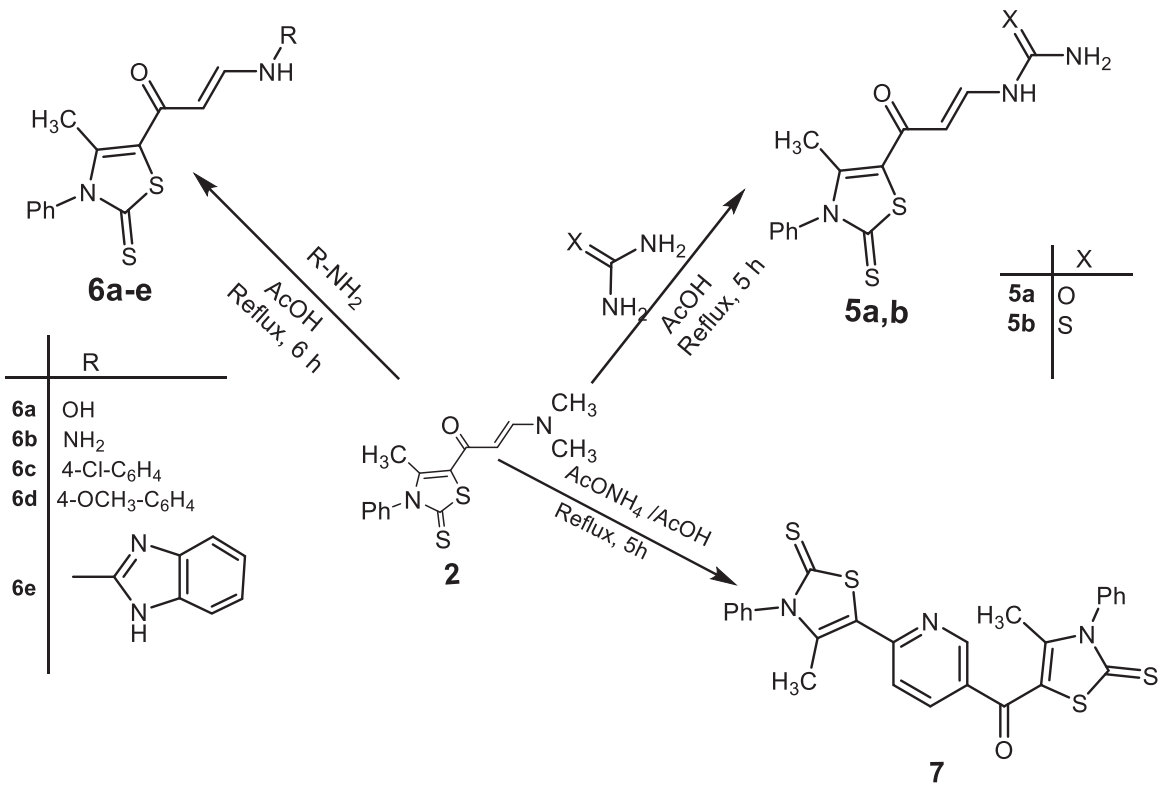
3.3. Biological evaluation

3.3.1. Antimicrobial activity

The antifungal and antibacterial activities of the selected synthesized compounds and the reference drugs were investigated using the agar diffusion method [26–28]. Amphotericin B (antifungal), ampicillin (Gram positive antibacterial) and gentamicin (Gram negative antibacterial) were used as positive controls. The antimicrobial activity was screened against two fungal species (*Aspergillus fumigatus* (RCMB 002,008 (4)) and *Candida albicans* (RCMB 05,036)), two Gram-positive bacteria (*Staphylococcus aureus* (RCMB010010) and *Bacillus subtilis* (RCMB 010,067)), and two-Gram negative bacteria (*Salmonella sp*. (RCMB 010,043) and *E. coli* (RCMB 010,052)). The results of the *in vitro* antimicrobial assessment of the synthesized compounds are depicted in Table 4.



Scheme 1. Synthesis of thiazoline (thiazoline-2-thione) derivatives **2, 3** and **4a, b**.



Scheme 2. Synthesis of thiazoline (thiazoline-2-thione) derivatives **5a, b, 6a-e**, and **7**.

Thiazoline derivatives **4a,4b, 6a,6c** and **7** showed potent antifungal activity comparable to amphotericin B when investigated against *Aspergillus fumigatus*. Additionally, all the thiazoline derivatives, except compound **4b**, were effective against *Candida albicans.* Furthermore, thiazoline derivatives namely **4a,4b, 6a,6c** and **7** displayed good fungicidal activities with small substituents, such as **4a** (R = Ph), **6a** (R = OH), and **6c** (R = −4-Cl-C_6H_4). However, compound 4b without substituent ($R = H$) did not show any fungicidal activity against *Candida albicans*.

The newly prepared thiazoline derivatives **3, 4a,b, 5a,b, 6a–e** and **7** were also screened for their antibacterial (Gram-positive and Gram-negative) activity. All compounds, except for **6e**, showed no activity against *Bacillus subtilis,* but demonstrated potent antibacterial activity against the Gram-positive bacteria *Staphylococcus au-*

Table 1
The crystal and experimental data of thiazoline derivative **3**.

Crystal data	
Chemical formula	$C_{12}H_{12}N_2OS_2$
Mr	264.36
Crystal system, space group	Triclinic, *P*-1
Temperature (K)	296
a, *b*, *c* (Å)	6.7932 (14), 7.2346 (14), 14.280 (3)
α, β, γ (°)	80.934 (6), 89.366 (7), 63.769 (6)
V (Å3)	620.3 (2)
Z	2
Radiation type	Mo *Kα*
μ (mm^{-1})	0.41
Crystal size (mm)	0.48 × 0.37 × 0.07
Data collection	
Diffractometer	Bruker APEX-II D8 venture diffractometer
Absorption correction	Multi-scan SADABS Bruker 2014
Tmin, Tmax	0.880, 0.972
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	12,532, 2966, 2288
R_{int}	0.064
Refinement	
R[$F^2 > 2\sigma(F^2)$], w$R(F^2)$, S	0.077, 0.208, 1.08
No. of reflections	2836
No. of parameters	160
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	1.50, −0.58

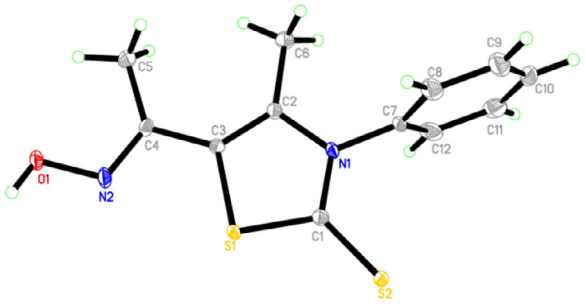


Fig. 1. ORTEP diagram of thiazoline derivative **3**. Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

reus and *Bacillus subtilis*. In addition, all the tested compounds were effective against the Gram-negative bacteria (*Salmonella sp,* and *E. coli)*. The MIC values obtained from all compounds were promising compared to the values of the reference drug, gentamicin (*c.f.* Table 4). Compounds **4a, 4b, 5a, 5b, 6a**, and **6e** were more effective against *Salmonella sp* than gentamicin, while compounds **4a, 6a**, and **6e** were more effective against *E. coli*.

3.3.2. Cytotoxic activity

The cytotoxic activity of some selected thiazoline derivatives and the reference drug doxorubicin were investigated using the MTT assay [29] against colon carcinoma cells (HCT-116) and a human hepatocellular carcinoma cell line (HepG-2). The cytotoxic activity was expressed as a viability% based on three independent experiments (Fig. 3). The concentration of the tested compounds needed to inhibit 50% of HCT-116 cells (IC_{50}) is presented in Table 5. Compounds **6b** (IC_{50} = 79 μg/ml) and **7** (IC_{50} = 133 μg/ml) showed moderate cytotoxic activity on the HCT-116 cell line,

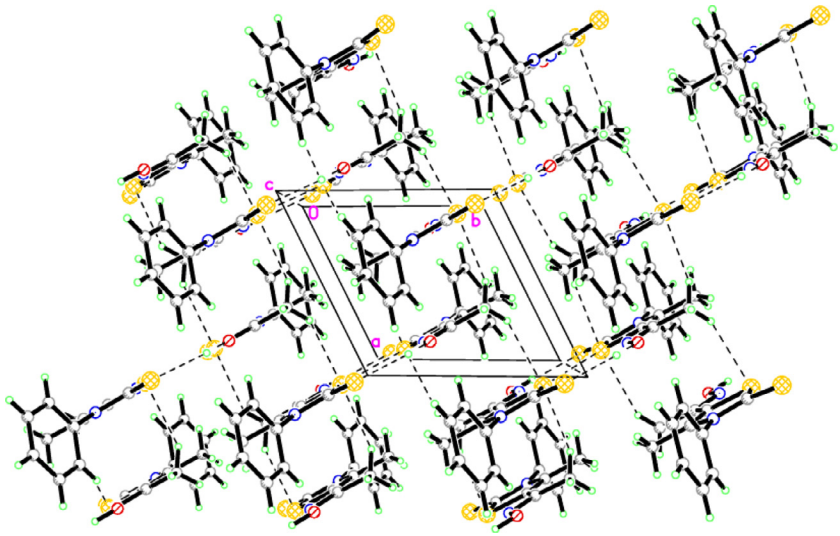


Fig. 2. Molecular packing of thiazoline derivative **3** viewed hydrogen bonds which are drawn as dashed lines along *a* and *b* axes.

Table 2
Selected geometric parameters (Å, °) of thiazoline derivative **3**.

S1—C1	1.715 (4)	N1—C2	1.401 (5)
S1—C3	1.758 (4)	N1—C7	1.448 (5)
S2—C1	1.677 (4)	N1—C1	1.362 (5)
O1—N2	1.409 (4)	N2—C4	1.294 (5)
C1—S1—C3	92.0 (2)	N1—C2—C3	112.2 (3)
C1—N1—C2	115.7 (3)	N1—C2—C6	117.9 (3)
C1—N1—C7	121.1 (3)	S1—C3—C4	116.9 (3)
C2—N1—C7	123.2 (3)	S1—C3—C2	110.7 (3)
O1—N2—C4	112.6 (3)	N2—C4—C3	112.4 (3)
S1—C1—S2	124.4 (2)	N2—C4—C5	125.7 (4)
S1—C1—N1	109.5 (3)	N1—C7—C8	118.6 (4)
S2—C1—N1	126.1 (3)	N1—C7—C12	119.9 (4)

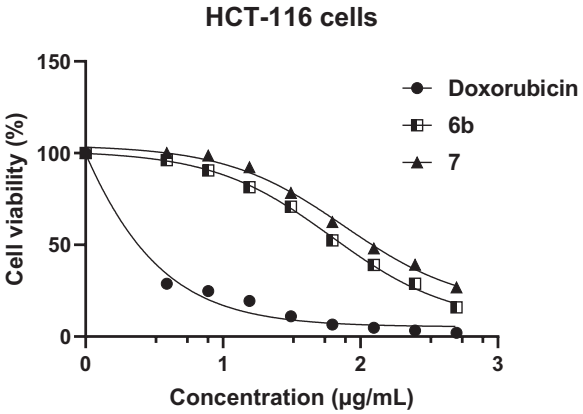


Fig. 3. The cytotoxic activity of the most active thiazoline derivatives and doxorubicin tested in HCT-116 cell line using MTT assay ($n = 3$).

Table 3
Hydrogen-bond geometry (Å, °) of thiazoline derivative **3**.

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O1···S2^{i}	0.92 (8)	2.30 (8)	3.212 (3)	171 (6)

Symmetry codes: (i) $-x, -y + 2, -z + 1$.

while the inhibitory activity of the standard drug doxorubicin against HCT-116 cells exhibited an IC_{50} of 3.2 µg/ml. Furthermore, compound **6b** demonstrated the highest effectiveness against the HepG-2 cell lines compared to the other thiazoline derivatives,

Table 5
IC_{50} values of tested thiazoline derivatives and doxorubicin in MTT assay.

Compound	IC_{50} (95% CI) (µg/mL)
HCT-116	
Doxorubicin	3.2 (1.8–5)
6b	79 (70–89)
7	133 (108–164)
HepG-2	
Doxorubicin	3 (1.6–5.3)
3	136 (118–156)
6b	49 (43.8–55)
7	60 (49–73.5)

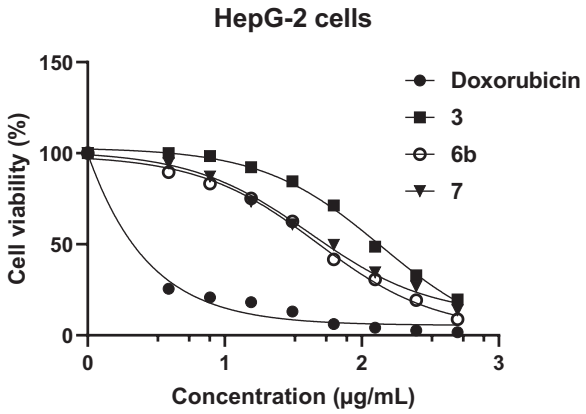


Fig. 4. The cytotoxic activity of the most active thiazoline derivatives and doxorubicin tested in liver cancer cells (HepG-2) using MTT assay ($n = 3$).

with an IC_{50} value of 49 µg/ml (Table 5 and Fig. 4). Interestingly, thiazoline-2-thione derivative **6b** with small substituent (R- NH_2) showed the highest inhibition of HCT-116 and HepG-2 cell lines compared to the other thiazoline-2-thione derivatives.

3.4. Molecular docking studies

Molecular docking of the three promising compounds into the crystal structure of the EGFR kinase domain along with erlotinib (PDB ID code 1M17) was performed. The X-ray crystal

Table 4
The *in vitro* antimicrobial assessment of the synthesized compounds **(3, 4a, 4b, 5a, 5b, 6a-e** and **7)** expressed as inhibition zones diameter in millimeters (mm).

Compound	Microorganisms					
	Fungi		Gram Positive Bacteria		Gram negative Bacteria	
	AF	*CA*	*SA*	*BS*	*SSP*	*EC*
3	NA	12	9	10	12	10
4a	13	14	15	15	16	18
4b	12	NA	8	12	14	13
5a	NA	10	10	12	14	10
5b	NA	10	9	13	14	12
6a	13	12	14	10	14	14
6b	NA	12	10	13	12	13
6c	12	10	11	11	13	13
6d	NA	14	11	12	12	13
6e	NA	13	NA	NA	13	15
7	11	12	11	11	11	13
Amphotericin B	23	25	–	–	–	–
Ampicillin	–	–	23	32	–	–
Gentamicin	–	–	–	–	17	19

NA: No activity; results of the antimicrobial evaluation are expressed as mean of inhibition zone diameter (mm) for different compounds tested in triplicate; *Aspergillus fumigatus* (RCMB 002,008(4)) (AF), *Candida albicans* (RCMB 05,036) (CA), *Staphylococcus aureus* (RCMB010010) (SA), *Bacillus subtilis* (RCMB 010,067) (BS), *Salmonella* sp. (RCMB 010,043) (SSP), *E. coli* (RCMB 010,052 (EC).

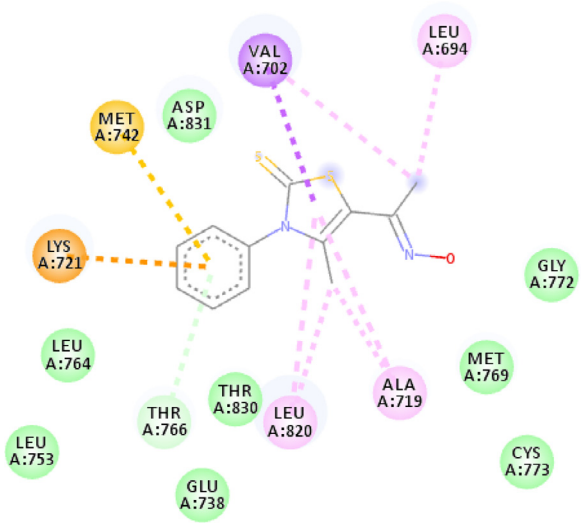


Fig. 5. 2D binding interactions of compound **3** at the active site of EGFR kinase.

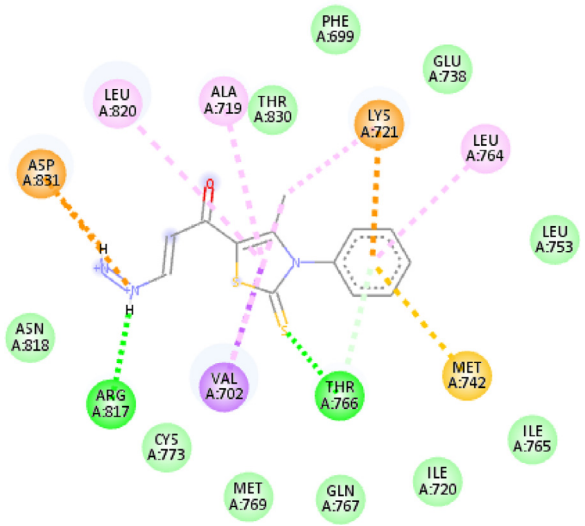


Fig. 6. 2D binding interactions of compound **6b** at the active site of EGFR kinase.

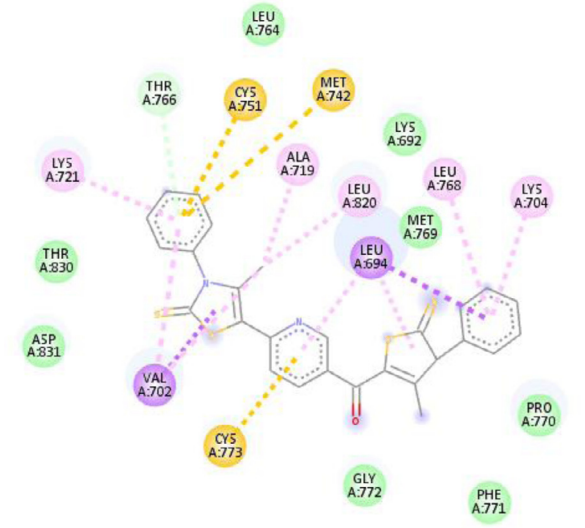


Fig. 7. 2D binding interactions of compound **7** at the active site of EGFR kinase.

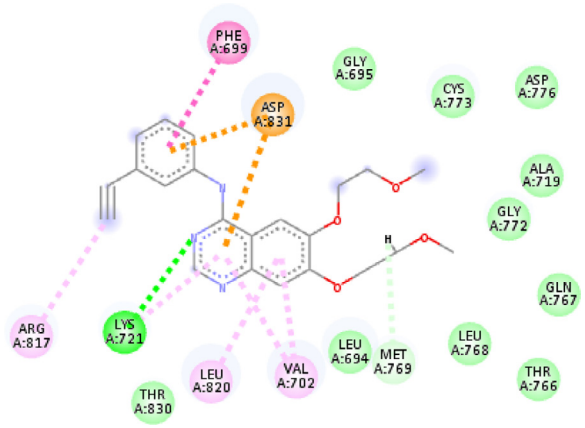


Fig. 8. 2D binding interactions of standard drug erlotinib at the active site of EGFR kinase.

structure illustrates that erlotinib binds to the ATP binding cleft, where the N-1 of the quinazoline ring is hydrogen bonded to the Lys721, whereas the phenyl ring formed π-π stacking with Phe699 and Asp831 formed two π-anion bonds with phenyl and quinazoline ring. Among the compounds **3**, **6b**, and **7**, only compound **6b** showed two hydrogen bonds. The binding free energies of compounds **3**, **6b**, and **7** were −6.9, −7.2 and −8.8 kcal/mol, respectively, compared to the standard erlotinib −6.6 kcal/mol, indicating sufficient affinity between ligands and protein. The thioxo group of compound 6b projects into the oxyanion binding hole and forms hydrogen bonds with the Thr766 whereas, the amino group formed a hydrogen bond with Arg817. The docked conformations of the three ligands **3**, **6b**, **7**, and erlotinib bound to the active site of EGFR kinase are shown in Figure 5, 6, 7 and 8. Overall, it was observed that all the above said ligands occupied the same active site and bound firmly as compared to the standard drug erlotinib.

4. Conclusions

The current study aimed to synthesize and screen the biological activity of a series of thiazoline (thiazoline-2-thione) derivatives. A series of 12 new thiazoline-2-thione derivatives (oxime and enaminone) were synthesized. The structures of the synthesized compounds were confirmed by various spectroscopic methods, such as 1H–NMR, 13C–NMR, mass spectrometry, and elemental analysis. Besides, the molecular structure of **3** was confirmed with the aid of X-ray crystallography. These thiazoline-2-thione derivatives were evaluated for their biological activities in various *in vitro* biological assays. Compounds **4a**, **4b**, **6a**, **6c,** and **7** showed the most effective antifungal activity against *Aspergillus fumigatus*. Additionally, all the thiazoline derivatives except compound **4b** were effective against *Candida albicans. Also,* all thiazoline derivatives demonstrated substantial antibacterial activities compared to reference drugs. In *vitro* cytotoxicity studies revealed that the thiazoline-2-thione derivatives had moderate cytotoxic activity toward all tested cell lines (HepG-2, and HCT-116). Compound **6b** showed the best cytotoxic activity on the HCT-116 and HepG-2 cell lines (IC50 = 79, 49 µg/ml, respectively). The *in-vitro* studies findings also corroborated well with the molecular docking studies. These findings may serve as a template for developing new potential lead compounds with promising chemotherapeutic effects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yahya I. Asiri: Conceptualization, Methodology, Writing - original draft. **Abdullatif Bin Muhsinah:** Conceptualization, Methodology, Writing - review & editing. **Abdulrhman Alsayari:** Conceptualization, Methodology, Writing - review & editing. **Hazem A. Ghabbour:** Conceptualization, Methodology, Software. **Zainab M. Almarhoon:** Conceptualization, Methodology, Software. **Faiz A. Alaizari:** Conceptualization, Methodology, Software. **Kumar Venkatesan:** Methodology, Writing - original draft, Writing - review & editing. **Syed Tasqeeruddin:** Writing - review & editing. **Syeda Shaheen Sulthana:** Writing - review & editing. **Yahia N. Mabkhot:** Conceptualization, Methodology, Software, Writing - review & editing.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2020.128977.

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