Synthesis, Antimicrobial, Antioxidant, Toxicity and Anticancer Activity of a New Azetidinone, Thiazolidinone and Selenazolidinone Derivatives Based on Sulfonamide

Zainab Kadhim Al-Khazragie, Bushra Kamel Al-Salami, and Adnan Jassim Mohammed Al-Fartosy*

Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq, PO BOX 781, Basrah, Iraq

** **Corresponding author:***

tel: +964-7704051812
email: zezit1993aa@yahoo.com

Received: January 21, 2022
Accepted: April 1, 2022

DOI: 10.22146/ijc.72454

Abstract: *A new series of azetidinone (Z_2a-Z_2e, Z_2g), thiazolidinone and selenazolidinone derivatives (Z_2B, Z_2E, Z_2B', Z_2E') based on sulfonamide have been synthesized and characterized by different instrumental techniques, such as elemental analyses, FTIR, multinuclear NMR (^{1}H, ^{13}C) and mass spectrometry. The tested compound containing selenium (Z_2E') was less toxic than its analogs containing sulfur (Z_2E) based on the LD_{50} value determined by Dixon's up and down method. All compounds showed antibacterial properties, however, Z_2E' was more active against Gram-negative bacteria:* Escherichia coli *and* Pseudomonas aeruginosa *than Gram-positive ones:* Streptococcus aureus *and* Bacillus*, with the lowest MIC value of 5 mg/mL. All compounds showed good antioxidant activity at a lower rate than the standard compound BHT (82%). More precisely, Z_2b was the main compound that possess strong activity as an antioxidant (73%). MTT viability assay showed that all tested compounds had cytotoxic effects on MCF-7 cells after 72 h of treatment. Our results revealed that Z_2E' and Z_2E compounds possessed strong activity (IC_{50} = 24.8 and 90.9 µg/mL, respectively) against MCF-7 cells at a higher rate than the standard compound 5-FU (IC_{50} = 97.47 µg/mL). Our results indicated that Z_2E' had a promising bioactive scaffold of great medicinal interest due to their numerous pharmacological and biological activities.*

Keywords: *2-azetidinone; 4-thiazolidinone; 4-selenazolidinone; sulfonamide; biochemical activities*

■ INTRODUCTION

Sulfonamides are the first effective chemotherapeutic agents used for bacterial disease in humans. They are widely used for prophylaxis and treatment of bacterial infections although they are bacteriostatic rather than bactericidal. Their value lies in the ability to slow down or prevent growth in wounds or infected organs without appreciable toxicity to normal tissues [1]. A large number of sulfonamide derivatives have been synthesized, which made it possible to establish a correlation between specific structural characteristics and the antimicrobial activity of newly synthesized molecules. A free aromatic NH_2 group in the para position, relative to the sulfonamide group, is essential for the activity of sulfonamides [2]. The presence of the additional substituent in the ortho and meta position of the benzene ring reduces the sulfonamide activity. On the other hand, the *N*1-monosubstituted derivatives of sulfanilamide produce active compounds. The activity degree of such compounds increased by introducing heteroaromatic substituents. The introduction of various substituents resulted in the products with different physicochemical, pharmacokinetic (a degree of protein binding, metabolism, excretion), and pharmacodynamic properties [3]. Recent studies demonstrated that sulfonamides are active to prevent cancerous cells [4]. 2-Azetidinones (β-lactams) are saturated four-membered ring heterocyclic compounds containing three carbon atoms, a nitrogen atom, and a carbonyl group [5]. The name "β-Lactam" is given to cyclic amides because the nitrogen atom is associated with the β-carbon atom relative to the carbonyl group.

2-Azetidinones, a structural unit found in the most widely used antibiotics [6], have occupied a basic

position in medicinal chemistry for almost a century now. The microbe's basic position in medicinal chemistry for almost a century now. With the microbes responding to the traditional antibiotics through β-lactamases, the need for novel antibiotics prevails, making the synthesis of newer β-lactams ever more important. In addition to their use as antibiotics, 2-azetidinones are increasingly being used as synthons for other biologically important molecules [7-10]. 2-Azetidinones have been found to act as cholesterol acyl transferase inhibitors, thrombin inhibitors, human cytomegalovirus protease inhibitors, matrix metalloprotease inhibitors, cysteine protease, and apoptosis inductors [6]. The biological activity is usually associated with the nature of the groups linked to *N*-1, *C*-3, and *C*-4 of the 2-azetidinone molecules [11]. 2-Azetidinone derivatives containing β-lactam nucleus have a wide range of pharmaceutical activity and have become an integral part of the chemotherapeutic arsenal available to today's medical practitioners [12].

Thiazolidinones (or selenazolidinones) are thiazolidine (or selenazolidine) derivatives and have an atom of sulfur (or selenium) at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 4 [13-14]. However, thiazolidinone derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature [15]. Thiazo- and selenazolidine-4-ones are an important class of compounds in organic and medicinal chemistry [16-17]. The 4-thiazolidinone or 4-selenazolidinone ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as antitubercular, antibacterial, anti-inflammatory, antioxidant agents, antiviral agents, especially as anti-HIV agents, and their use as anticancer drugs [13,18-20]. They received considerable attention during the last two decades as they are gifted with a variety of activities and have a wide range of therapeutic properties [16-17].

In the present work, we synthesized a new series of 2-azetidinone, 4-thiazolidinone and 4-selenazolidinone derivatives through cycloaddition reaction of imines with ketene, thioglycolic acid and 2-selenoglycolic acid, respectively. The compounds were studied *in vivo* acute toxicity, antioxidant, antibacterial, and anticancer activity.

■ EXPERIMENTAL SECTION

Materials

All the chemicals and solvents used were of analytical grade supplied from BDH, Fluka, USP, Merck, MOLBASE and Aldrich. 2-Chloroquinoline-3-carbaldehyde, *p*-toluenesulphonic acid (PTSA), 2-amino-4-chlorobenzenesulfonamide, sulfamerazine, sulfisoxazole, sulfamethazine, sulfathiazole, sulfanilamide, chloroacetylchloride, thioglycolic acid, and zinc chloride ($ZnCl_2$) as well as butylated hydroxyl toluene (BHT) were obtained from Sigma-Aldrich. 2-Seleno-glycolic acid and β-carotene were supplied from MOLBASE and USP respectively. Tween-20 (Polyoxyethylene (20) sorbitan monolaurate), linoleic acid, 1,4-dioxane and dimethylformamide were obtained from Fluka. Sodium azide, triethylamine, Na_2SO_4 and $NaHCO_3$ from Merck. Sulfuric acid, ethanol, acetone, methanol, and chloroform were obtained from BDH. Thin-layer chromatography (TLC) was carried out by using an aluminium sheet coated with silica gel $60F_{254}$ (Merck), iodine and ultraviolet (UV) light was used for visualized TLC plates.

Instrumentation

The FTIR spectra as KBr discs were recorded in the range 4000–400 cm^{-1} using a Shimadzu FT-IR model 8400s instrument. The experimental values of ^{1}H and ^{13}C-NMR spectra for the studied compounds were obtained in a Brucker spectrophotometer (400 and 75 MHz, respectively) and using DMSO-d_6 as a solvent and TMS as an internal standard (Central Laboratory, University of Tehran, Iran). The mass spectra were measured by the EI technique at 70 eV using an Agilent Technologies 5975C spectrometer. Elemental analysis (C,H,N,S) was calculated using CHNS-932 LECO apparatus. Melting points were determined with a Bauchi 510 melting point apparatus and are uncorrected.

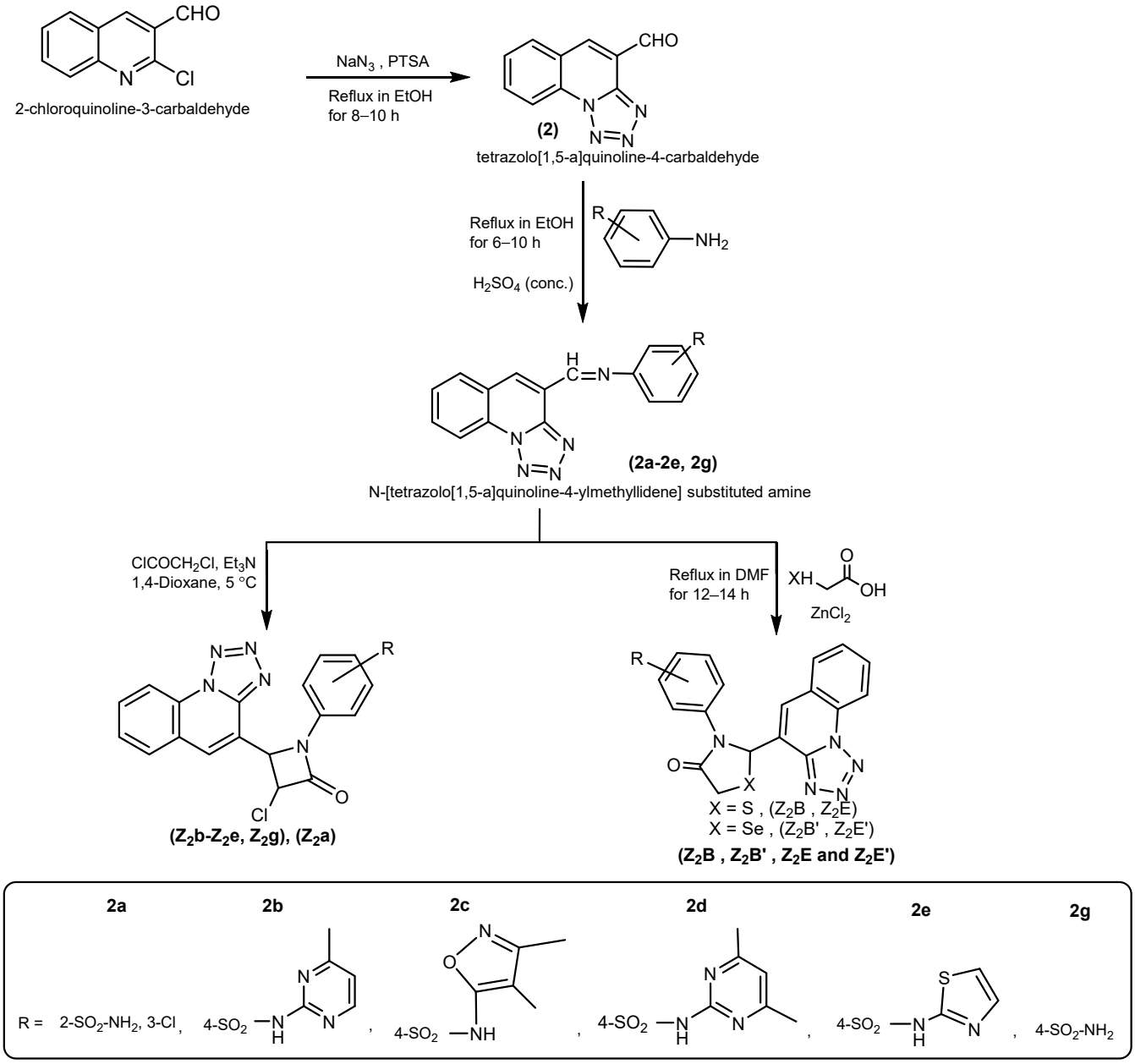
Synthesis

The compound tetrazolo[1,5-a]quinoline-4-carbaldehyde (**2**) was prepared and characterized as

previously described in the literature [21]. This compound gave satisfactory elemental analysis and spectroscopic data, and they are not reported. The synthetic procedure for the preparation of compound **(2)** is presented in Scheme 1.

Synthesis of sulfonamide imines (2a-2e, 2g)

The following general method was used to prepare compounds **2a**-**2e** and **2g** according to the literature method [21]. An equimolar quantity of sulfonamide derivatives (2-amino-4-chlorobenzenesulfonamide (5 mmol, 1.03 g), sulfamerazine (5 mmol, 1.32 g), sulfisoxazole (5 mmol, 1.34 g), sulfamethazine (5 mmol, 1.4 g), sulfathiazole (5 mmol, 1.3 g) sulfanilamide (5 mmol, 0.861 g) and tetrazolo[1,5-a]quinoline-4-carbaldehyde (**2**) (5 mmol, 0.99 g) were dissolved in a 25 mL of ethanol, then a catalytic amount of concentrated H_2SO_4 (2 drops) was added and the reaction mixture refluxed for about 6–10 h, the progress of the reaction was



Scheme 1. Synthesis of 2-azetidinones, 4-thiazolidinones and 4-selenazolidinones

monitored by TLC using ethyl acetate/*n*-hexane (v/v 2:8) as eluent and UV light as appearance, the resulted compounds were obtained by pouring the reaction mixture onto crushed ice. The precipitated solids were filtered off from the reaction mixture and washed with cold water, dried, followed by recrystallized in ethanol to get the target compounds. The synthetic procedures for the preparation of compounds (**2a**-**2e** and **2g**) are presented in Scheme 1.

4-Chloro-2-((tetrazolo[1,5-a]quinolin-4-ylmethylene) amino)benzenesulfonamide (2a). Pale yellow powder; yield: 63%; Rf: 0.90; m.p: 218–222 °C; Elemental analysis for $C_{16}H_{11}ClN_6O_2S$ (386.82 g/mol); Calcd: C, 49.68; H, 2.87; N, 21.73; S, 8.29. Found: C, 49.71; H, 2.89; N, 21.69; S, 8.24. IR (KBr) cm^{-1}: 3344 $\nu_{str.}(NH_2$, asymmetrical), 3178 $\nu_{str.}(NH_2$, symmetrical), 1654 ν(C=N, tetrazole ring), 1600 ν(CH=N), 1500–1473 ν(C=C), 1323 $\nu_{str.}(SO_2$, asymmetrical), 1168 $\nu_{str.}(SO_2$, symmetrical), 1249 ν(N-N=N, tetrazole ring), 952 ν(S-N), 860 ν(C-Cl), 632 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 8.68 (d, 1H, *J* = 12 Hz, Ar-H), 8.58 (s, 1H, CH=N), 8.35 (s, 1H, pyridine-H), 8.08 (t, 1H, J_1 = 8, J_2 = 12 Hz, Ar-H), 8.01 (s, 1H, Ar-H), 7.88 (t, 1H, $J_1 = J_2$ = 12 Hz, Ar-H), 7.66 (d, 1H, *J* = 12 Hz, Ar-H), 7.07 (s, 2H, NH_2), 6.89 (d, 1H, *J* = 16 Hz, Ar-H), 6.60 (d, 1H, *J* = 16 Hz, Ar-H).

***N*-(4-Methylpyrimidin-2-yl)-4-((tetrazolo[1,5-a]quino line-4-ylmethylene)amino)benzenesulfonamide (2b).** Yellow powder; yield: 91%; Rf: 0.86; m.p: 232–234 °C; Elemental analysis for $C_{21}H_{16}N_8O_2S$ (444.47 g/mol); Calcd: C, 56.75; H, 3.63; N, 25.21; S, 7.21. Found: C, 56.72; H, 3.59; N, 25.25; S, 7.18. IR (KBr) cm^{-1}: 3225 ν(N-H), 1631 ν(C=N, tetrazole, pyrimidine ring), 1589 ν(CH=N), 1465–1496 ν(C=C), 1323 $\nu_{str.}(SO_2$, asymmetrical), 1153 $\nu_{str.}(SO_2$, symmetrical), 1278 ν(N-N=N, tetrazole ring), 979 ν(S-N), 678 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 12.06 (s, 1H, NH), 8.60 (s, 1H, CH=N), 8.54 (t, 1H, $J_1 = J_2$ = 4 Hz, Ar-H), 8.40 (d, 1H, *J* = 4 Hz, pyrimidine-H), 8.30 (d, 1H, *J* = 12 Hz, Ar-H), 8.08 (s, 1H, pyridine-H), 7.97 (t, 1H, J_1 = 8, J_2 = 12 Hz, Ar-H), 7.83 (d, 2H, *J* = 12 Hz, Ar-H), 7.23 (d, 2H, *J* = 4 Hz, Ar-H), 7.08 (t, 1H, $J_1 = J_2$ = 8 Hz, Ar-H), 6.67 (d, 1H, *J* = 20 Hz, pyrimidine-H), 2.10 (s, 3H, CH_3).

***N*-(3,4-Dimethylisoxazol-5-yl)-4-((tetrazolo[1,5-a]qui nolin-4-ylmethylene)amino)benzenesulfonamide (2c).** Yellow crystals; yield: 60%; Rf: 0.91; m.p: 190–193 °C; Elemental analysis for $C_{21}H_{17}N_7O_3S$ (447.47 g/mol); Calcd: C, 56.37; H, 3.83; N, 21.91; S, 7.17. Found: C, 56.41; H, 3.86; N, 21.88; S, 7.19. IR (KBr) cm^{-1}: 3383 ν(N-H), 2924 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1651 ν(C=N, tetrazole, isoxazole ring), 1597 ν(CH=N), 1462–1531 ν(C=C), 1338 $\nu_{str.}(SO_2$, asymmetrical), 1161 $\nu_{str.}(SO_2$, symmetrical), 1253 ν(N-N=N, tetrazole ring), 875 ν(S-N), 671 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 12.25 (s, 1H, NH), 9.02 (s, 1H, CH=N), 8.86 (s, 1H, pyridine-H), 8.69 (d, 1H, *J* = 8 Hz, Ar-H), 8.47 (d, 1H, *J* = 8 Hz, Ar-H), 8.15 (t, 1H, J_1 = 8, J_2 = 12 Hz, Ar-H), 7.92 (t, 1H, J_1 = 12, J_2 = 8 Hz, Ar-H), 7.60 (d, 2H, *J* = 8 Hz, Ar-H), 7.45 (d, 2H, *J* = 12 Hz, Ar-H), 2.10 (s, 3H, CH_3), 1.58 (s, 3H, CH_3).

***N*-(4,6-Dimethylpyrimidin-2-yl)-4-((tetrazolo[1,5-a] 4uinoline-4-ylmethylene)amino)benzenesulfonami de (2d).** Pale orange powder; yield: 59%; Rf: 0.67; m.p: 276–278 °C; Elemental analysis for $C_{22}H_{18}N_8O_2S$ (458.50 g/mol); Calcd: C, 57.63; H, 3.96; N, 24.44; S, 6.99. Found: C, 57.59; H, 3.98; N, 24.41; S, 7.03. IR (KBr) cm^{-1}: 3352 ν(N-H), 1662, 1643 ν(C=N, tetrazole, pyrimidine ring), 1593 ν(CH=N), 1469–1500 ν(C=C), 1338 $\nu_{str.}(SO_2$, asymmetrical), 1149 $\nu_{str.}(SO_2$, symmetrical), 1253 ν(N-N=N, tetrazole ring), 914 ν(S-N), 678 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 10.68 (s, 1H, NH), 9.01 (s, 1H, CH=N), 7.92 (d, 1H, *J* = 10 Hz, Ar-H), 7.68 (s, 1H, pyridine-H),7.44 (t, 1H, $J_1 = J_2$ = 5 Hz, Ar-H), 7.25 (dd, 2H, *J* = 20 Hz, Ar-H), 7.18 (t, 1H, $J_1 = J_2$ = 5 Hz, Ar-H), 6.86 (d, 1H, *J* = 5 Hz, Ar-H), 6.75 (dd, 2H, *J* = 10 Hz, Ar-H), 6.60 (s, 1H, pyrimidine-H), 3.03 (s, 6H, $2CH_3$).

4-((Tetrazolo[1,5-a]quinolin-4-ylmethylene)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (2e). Dark yellow crystals; yield: 90%; Rf: 0.91; m.p: 204–205 °C; Elemental analysis for $C_{19}H_{13}N_7O_2S_2$ (435.48 g/mol); Calcd: C, 52.40; H, 3.01; N, 22.51; S, 14.73. Found: C, 52.38; H, 2.98; N, 22.54; S, 14.71. IR (KBr) cm^{-1}: 3379 ν(N-H), 2920 ν(CH, asymmetrical, aliph.), 2850 ν(CH, symmetrical, aliph.), 1651 ν(C=N, tetrazole, thiazole

ring), 1608 ν(CH=N), 1419–1462 ν(C=C), 1330 $\nu_{str.}(SO_2$, asymmetrical), 1168 $\nu_{str.}(SO_2$, symmetrical), 1284 ν(N-N=N, tetrazole ring), 925 ν(S-N), 636 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 12.86 (s, 1H, NH), 9.07 (s, 1H, CH=N), 7.97 (d, 1H, *J* = 12 Hz, Ar-H), 7.83 (d, 1H, *J* = 12 Hz, Ar-H), 7.70 (d, 2H, *J* = 12 Hz, Ar-H), 7.50 (t, 1H, J_1 = 4, J_2 = 8 Hz, Ar-H), 7.31 (s, 1H, pyridine-H), 7.23 (d, 2H, *J* = 4 Hz, Ar-H), 7.08 (d, 1H, *J* = 12 Hz, thiazole-H), 6.90 (d, 1H, *J* = 8 Hz, thiazole-H), 6.79 (t, 1H, J_1 = 8, J_2 = 12 Hz, Ar-H).

4-((Tetrazolo[1,5-a]quinoline-4-ylmethylene)amino) benzenesulfonamide (2g). Maroon crystals; yield: 93%; Rf: 0.89; m.p: 192–194 °C; Elemental analysis for $C_{16}H_{12}N_6O_2S$ (352.37 g/mol); Calcd: C, 54.54; H, 3.43; N, 23.85; S, 9.10. Found: C, 54.57; H, 3.42; N, 23.89; S, 9.07. IR (KBr) cm^{-1}: 3448 $\nu_{str.}(NH_2$, asymmetrical), 3417 $\nu_{str.}(NH_2$, symmetrical), 2924 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1651 ν(C=N, tetrazole ring), 1608 ν(CH=N), 1550–1446 ν(C=C), 1334 $\nu_{str.}(SO_2$, asymmetrical), 1153 $\nu_{str.}(SO_2$, symmetrical), 1242 ν(N-N=N, tetrazole ring), 918 ν(S-N), 690 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 8.89 (s, 1H, CH=N), 8.31 (d, 1H, *J* = 10 Hz, Ar-H), 8.03 (s, 1H, pyridine-H), 7.89 (d, 1H, *J* = 5 Hz, Ar-H), 7.71 (dd, 2H, *J* = 10 Hz, Ar-H), 7.47 (t, 1H, J_1 = 10, J_2 = 15 Hz, Ar-H), 7.36 (t, 1H, $J_1 = J_2$ = 10 Hz, Ar-H), 7.10 (dd, 2H, *J* = 10 Hz, Ar-H), 6.97 (s, 2H, NH_2).

Synthesis of 2-azetidinone derivatives (Z_2a-Z_2e, Z_2g)

A mixture of imine **2a** (2 mmol, 0.77 g), **2b** (2 mmol, 0.89 g), **2c** (2 mmol, 0.895 g), **2d** (2 mmol, 0.92 g), **2e** (2 mmol, 0.87 g), **2g** (2 mmol, 0.7g), respectively and triethyl amine (4 mmol, 0.40 g) were dissolved in dry 1,4-dioxane (25 mL), cooled at 5 °C and stirred. To this well-stirred cooled solution, a solution of chloroacetyl chloride (4 mmol, 0.45 g) in dry 1,4-dioxane (25 mL) was added dropwise within a period of 20 min, at 5 °C with constant stirring. The reaction mixture was then stirred for an additional 8 h and left at room temperature for 48 h, and the solution was filtered to separate the white triethylamine hydrochloride salt. The filtrate was concentrated to half of its initial volume and then poured onto crushed ice. The progress of the reaction was monitored by TLC. The precipitated products were filtered, washed with cold ethanol absolute several times, dried in air, and recrystallized from ethanol to get the purified 2-azetidinones [22-23]. The Rf values of 2-azetidinones were determined by using ethyl acetate:benzene (3:7) as solvent system. The synthetic procedures for preparing compounds (**Z_2a**-**Z_2e** and **Z_2g**) are presented in Scheme 1.

4-Chloro-2-(3-chloro-2-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)azetidin-1-yl)benzenesulfonamide (Z_2a). White powder; yield: 54%; Rf: 0.74; m.p: 202–203 °C; Elemental analysis for $C_{18}H_{12}C_{l2}N_6O_3S$ (463.30 g/mol); Calcd: C, 46.66; H, 2.61; N, 18.14; S, 6.92. Found: C, 46.70; H, 2.63; N, 18.11; S, 6.99. IR (KBr) cm^{-1}: 3344 $\nu_{str.}(NH_2$, asymmetrical), 3136 $\nu_{str.}(NH_2$, symmetrical), 2924 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1701 ν(C=O, azetidin-2-one ring), 1535 ν(C-N, azetidin-2-one ring), 1654 ν(C=N, tetrazole ring), 1500–1469 ν(C=C), 1319 $\nu_{str.}(SO_2$, asymmetrical), 1168 $\nu_{str.}(SO_2$, symmetrical), 1226 ν(N-N=N, tetrazole ring), 914 ν(S-N), 860 ν(C-Cl), 636 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 8.68 (d, 1H, *J* = 6 Hz, Ar-H), 8.55 (s, 1H, pyridine-H), 8.34 (d, 1H, *J* = 6 Hz, Ar-H), 8.00 (s, 1H, Ar-H), 7.87 (t, 1H, $J_1 = J_2$ = 9 Hz, Ar-H), 7.62 (d, 1H, *J* = 9 Hz, Ar-H), 7.04 (s, 2H, NH_2), 6.88 (t, 1H, $J_1 = J_2$ = 21 Hz, Ar-H), 6.56 (d, 1H, *J* = 9 Hz, Ar-H), 6.05 (d, 1H, *J* = 12 Hz, CH-Cl, 2-azetidinone ring), 4.17 (dd, 1H, *J* = 20 Hz, CH-N, 2-azetidinone ring); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 168.72, 148.33, 140.25, 138.42, 132.36, 131.53, 130.09, 129.81, 128.23, 125.65, 123.92, 123.14, 120.03, 119.74, 118.83, 115.93, 60.53, 55.37; The EI-MS m/z (%): 463 $[M]^+$ (3.5), 431 $[C_{18}H_{16}ClN_6O_3S]^+$ (2.5), 373 $[C_{18}H_{14}C_{l2}N_4O]^{\bullet+}$ (3.3), 314 $[C_{18}H_{12}N_5O]^+$ (5.2), 194 $[C_9H_7ClN_2O]^{\bullet+}$ (65.3), 148 $[C_9H_{10}NO]^+$ (100).

4-(3-Chloro-2-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl) azetidin-1-yl)-*N*-(4-methylpyrimidin-2-yl)benzene sulfonamide (Z_2b). Dark brown powder; yield: 68%; Rf: 0.48; m.p: 240–242 °C; Elemental analysis for $C_{23}H_{17}ClN_8O_3S$ (520.95 g/mol); Calcd: C, 53.03; H, 3.29; N, 21.51; S, 6.16. Found: C, 53.10; H, 3.28; N, 21.57; S, 6.21. IR (KBr) cm^{-1}: 3483 ν(N-H), 2920 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1697 ν(C=O, azetidin-2-one ring), 1519 ν(C-N, azetidin-

2-one ring), 1573 ν(C=N, tetrazole ring), 1481–1435 ν(C=C), 1334 $\nu_{str.}(SO_2$, asymmetrical), 1161 $\nu_{str.}(SO_2$, symmetrical), 1257 ν(N-N=N, tetrazole ring), 922 ν(S-N), 821 ν(C-Cl), 663 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 10.69 (s, 1H, NH), 8.31 (s, 1H, pyridine-H), 8.00 (d, 1H, *J* = 9 Hz, pyrimidine ring), 7.78 (d, 1H, *J* = 9 Hz, Ar-H), 7.69 (d, 2H, *J* = 9 Hz, Ar-H), 7.53 (t, 1H, $J_1 = J_2$ = 9 Hz, Ar-H), 6.96 (d, 1H, *J* = 6 Hz, Ar-H), 6.83 (d, 2H, *J* = 12 Hz, Ar-H), 6.77 (t, 1H, $J_1 = J_2$ = 9 Hz, Ar-H), 6.57 (d, 1H, *J* = 9 Hz, pyrimidine ring), 4.26 (d, 1H, *J* = 6 Hz, CH-Cl, 2-azetidinone ring), 3.02 (d, 1H, *J* = 15 Hz, CH-N, 2-azetidinone ring), 1.18 (s, 3H, CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 170.13, 158.07, 151.98, 148.68, 144.76, 141.96, 135.82, 132.30, 130.22, 129.90, 128.98, 126.23, 125.38, 120.68, 119.92, 119.42, 116.73, 113.17, 61.48, 58.47, 26.72; The EI-MS m/z (%): 522 $[M]^+$ (1.7), 365 $[C_{18}H_{14}ClN_6O]^+$ (2), 225 $[C_9H_9N_2O_3S]^+$ (3.4), 195 $[C_9H_8ClN_2O]^+$ (6.2), 148 $[C_9H_{10}NO]^+$ (100).

4-(3-Chloro-2-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)azetidin-1-yl)-*N*-(3,4-dimethylisoxazol-5-yl)benzenesulfonamide (Z_2c). Dark brown powder; yield: 42%; Rf: 0.77; m.p: 140–142 °C; Elemental analysis for $C_{23}H_{18}ClN_7O_4S$ (523.95 g/mol); Calcd: C, 52.72; H, 3.46; N, 18.71; S, 6.12. Found: C, 52.80; H, 3.51; N, 18.69; S, 6.17. IR (KBr) cm^{-1}: 3448 ν(N-H), 2974 ν(CH, asymmetrical, aliph.), 2870 ν(CH, symmetrical, aliph.), 1705 ν(C=O, azetidin-2-one ring), 1570 ν(C-N, azetidin-2-one ring), 1651, 1616 ν(C=N, tetrazole, Isoxazole ring), 1462–1427 ν(C=C), 1338 $\nu_{str.}(SO_2$, asymmetrical), 1161 $\nu_{str.}(SO_2$, symmetrical), 1284 ν(N-N=N, tetrazole ring), 922 ν(S-N), 763 ν(C-Cl), 690 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 10.80 (s, 1H, NH), 7.93 (d, 1H, *J* = 9 Hz, Ar-H), 7.82 (s, 1H, pyridine-H), 7.77 (d, 2H, *J* = 15 Hz, Ar-H), 7.69 (t, 1H, $J_1 = J_2$ = 6 Hz, Ar-H), 7.34 (t, 1H, J_1 = 6, J_2 = 9 Hz, Ar-H), 6.78 (d, 1H, *J* = 12 Hz, Ar-H), 6.59 (d, 2H, *J* = 9 Hz, Ar-H), 4.30 (d, 1H, *J* = 15 Hz, CH-Cl, 2-azetidinone ring), 3.56 (d, 1H, *J* = 3 Hz, CH-N, 2-azetidinone ring), 2.07 (s, 3H, CH_3), 1.61 (s, 3H, CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 172.15, 157.00, 151.90, 149.54, 140.64, 139.62, 131.89, 131.38, 129.07, 127.05, 123.30, 122.90, 119.45, 118.96, 118.17, 113.59, 110.36, 65.44, 61.23, 17.24, 12.58; The EI-MS m/z (%): 523 $[M]^+$ (1), 413 $[C_{18}H_{12}ClN_5O_3S]^{\bullet+}$ (1), 253 $[C_{11}H_{13}N_2O_3S]^+$ (35.8), 181 $[C_9H_8ClNO]^{\bullet+}$ (43.8), 161 $[C_9H_{11}N_3]^{\bullet+}$ (100), 135 $[C_8H_9NO]^{\bullet+}$ (86.9), 104 $[C_3H_3ClNO]^+$ (23.4).

4-(3-Chloro-2-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)azetidin-1-yl)-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide (Z_2d). Pale yellow powder; yield: 47%; Rf: 0.56; m.p: 230–233 °C; Elemental analysis for $C_{24}H_{19}ClN_8O_3S$ (534.98 g/mol); Calcd: C, 53.88; H, 3.58; N, 20.95; S, 5.99. Found: C, 53.91; H, 3.54; N, 20.98; S, 6.03. IR (KBr) cm^{-1}: 3383 ν(N-H), 2924 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1712 ν(C=O, azetidin-2-one ring), 1531 ν(C-N, azetidin-2-one ring), 1658,1585 ν(C=N, tetrazole, pyrimidine ring), 1465–1427 ν(C=C), 1334 $\nu_{str.}(SO_2$, asymmetrical), 1153 $\nu_{str.}(SO_2$, symmetrical), 1257 ν(N-N=N, tetrazole ring), 979 ν(S-N), 871 ν(C-Cl), 663 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 12.06 (s, 1H, NH), 8.48 (d, 1H, *J* = 30 Hz, Ar-H), 8.28 (s, 1H, pyridine-H), 7.97 (d, 2H, *J* = 27 Hz, Ar-H), 7.79 (d, 1H, *J* = 6 Hz, Ar-H), 7.51 (d, 2H, *J* = 9 Hz, Ar-H), 7.19 (t, 1H, J_1 = 39, J_2 = 30 Hz, Ar-H), 6.87 (s, 1H, pyrimidine ring), 6.69 (t, 1H, $J_1 = J_2$ = 9 Hz, Ar-H), 4.22 (d, 1H, *J* = 9 Hz, CH-Cl, 2-azetidinone ring), 3.40 (s, 1H, CH-N, 2-azetidinone ring), 2.35 (s, 6H, $2CH_3$); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 169.63, 153.86, 148.05, 140.94, 138.71, 132.43, 130.75, 129.38, 127.91, 127.65, 124.81, 124.57, 120.13, 119.82, 118.65, 116.83, 113.74, 61.53, 58.41, 25.32; The EI-MS m/z (%): 536 $[M]^+$ (2.2), 428 $[C_{18}H_{13}ClN_6O_3S]^{\bullet+}$ (1.8), 331 $[C_{15}H_{15}N_4O_3S]^+$ (2.3), 274 $[C_{16}H_{12}N_5]^+$ (51.2), 160 $[C_9H_{10}N_3]^+$ (34.4), 148 $[C_9H_{10}NO]^+$ (100), 93 $[C_6H_7N]^{\bullet+}$ (71.6).

4-(3-Chloro-2-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)azetidin-1-yl)-*N*-(thiazol-2-yl)benzenesulfonamide (Z_2e). Pale brown powder; yield: 77%; Rf: 0.92; m.p: 130–133 °C; Elemental analysis for $C_{21}H_{14}ClN_7O_3S_2$ (511.96 g/mol); Calcd: C, 49.27; H, 2.76; N, 19.15; S, 12.53. Found: C, 49.22; H, 2.80; N, 19.10; S, 12.56. IR (KBr) cm^{-1}: 3375 ν(N-H), 2924 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1701 ν(C=O, azetidin-2-one ring), 1527 ν(C-N, azetidin-2-one ring), 1651,1600 ν(C=N, tetrazole, thiazole ring), 1455–1400 ν(C=C), 1327 $\nu_{str.}(SO_2$, asymmetrical), 1138 $\nu_{str.}(SO_2$, symmetrical), 1276 ν(N-N=N, tetrazole ring), 929 ν(S-N), 848 ν(C-Cl), 636 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR

(400 MHz, DMSO-d_6) (δ/ppm): 10.68 (s, 1H, NH), 7.92 (d, 1H, J = 4 Hz, Ar-H), 7.84 (s, 1H, 1H, pyridine-H), 7.73 (d, 2H, J = 8 Hz, Ar-H), 7.67 (d, 1H, J = 8 Hz, Ar-H), 7.44 (t, 1H, $J_1 = J_2$ = 4 Hz, Ar-H), 7.18 (t, 1H, $J_1 = J_2$ = 4 Hz, Ar-H), 6.77 (d, 2H, J = 8 Hz, Ar-H), 6.74 (d, 1H, J = 4 Hz, thiazole ring), 6.60 (d, 1H, J = 4 Hz, thiazole ring), 4.28 (d, 1H, J = 4 Hz, CH-Cl, 2-azetidinone ring), 3.20 (d, 1H, J = 20 Hz, CH-N, 2-azetidinone ring); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 168.48, 163.03, 152.50, 151.50, 149.72, 147.99, 142.14, 139.31, 132.03, 128.34, 128.19, 127.53, 124.75, 119.41, 118.51, 113.02, 111.51, 68.98, 62.47; The EI-MS m/z (%): 513 $[M]^+$ (2.3), 309 $[C_{12}H_{11}N_3O_3S_2]^{\bullet+}$ (2.8), 279 $[C_{12}H_{10}ClN_3OS]^{\bullet+}$ (2.8), 256 $[C_9H_{10}N_3O_2S_2]^+$ (3.4), 239 $[C_9H_7N_2O_2S_2]^+$ (3.4), 105 $[C_7H_7N]^{\bullet+}$ (100).

4-(3-Chloro-2-oxo-4-(tetrazolo[1,5-a]quinolin-4-yl)azetidin-1-yl)benzenesulfonamide (Z_2g). Pale gray powder; yield: 81%; Rf: 0.63; m.p: 208–210 °C; Elemental analysis for $C_{18}H_{13}ClN_6O_3S$ (428.85 g/mol); Calcd: C, 50.41; H, 3.06; N, 19.60; S, 7.48. Found: C, 50.49; H, 3.01; N, 19.63; S, 7.41. IR (KBr) cm^{-1}: 3448 $\nu_{str.}$(NH_2, asymmetrical), 3417 $\nu_{str.}$(NH_2, symmetrical), 2974, 2935 ν(CH, asymmetrical, aliph.), 1743 ν(C=O, azetidin-2-one ring), 1546 ν(C-N, azetidin-2-one ring), 1647 ν(C=N, tetrazole ring), 1477–1442 ν(C=C), 1338 $\nu_{str.}$(SO_2, asymmetrical), 1157 $\nu_{str.}$(SO_2, symmetrical), 1260 ν(N-N=N, tetrazole ring), 914 ν(S-N), 817 ν(C-Cl), 690 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 8.02 (s, 1H, pyridine-H), 7.95 (d, 1H, J = 9 Hz, Ar-H), 7.69 (d, 2H, J = 9 Hz, Ar-H), 7.50 (t, 1H, J_1 = 9, J_2 = 6 Hz, Ar-H), 7.00 (t, 1H, $J_1 = J_2$ = 9 Hz, Ar-H), 6.99 (s, 2H, NH_2), 6.79 (d, 1H, J = 9 Hz, Ar-H), 6.67 (d, 2H, J = 9 Hz, Ar-H), 4.30 (d, 1H, J = 6 Hz, CH-Cl, 2-azetidinone ring), 3.23 (s, 1H, CH-N, 2-azetidinone ring); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 169.05, 154.64, 151.12, 142.74, 142.50, 137.64, 137.10, 134.03, 132.01, 127.84, 127.61, 124.93, 120.49, 111.52, 56.46, 45.71; The EI-MS m/z (%): 429 $[M]^+$ (1), 351 $[C_{18}H_{14}ClN_5O]^{\bullet+}$ (1.1), 225 $[C_9H_9N_2O_3S]^+$ (1.2), 197 $[C_9H_{10}ClN_2O]^+$ (1.4), 149 $[C_9H_{11}NO]^{\bullet+}$ (2.8), 86 $[C_4H_8NO]^+$ (100).

Synthesis of 4-thiazolidinone or 4-selenazolidinone (Z_2B, Z_2E, Z_2B', Z_2E')

A mixture of Schiff base **2b** (10 mmol, 4.4 g), **2e** (10 mmol 4.35 g) and a catalytic amount of zinc chloride (0.05 g) in DMF (10 mL) was reacted with thioglycolic acid (20 mmol, 1.84 g) or 2-seleno-glycolic acid (20 mmol, 2.78 g) in DMF (10 mL). The mixture was refluxed for 12–14 h. The reaction mixture was then poured into crushed ice. The separated solid was neutralized by sodium bicarbonate to remove excess thioglycolic acid. Solid compounds obtained were filtered, washed several times with water and recrystallized from ethanol. The completion of the reaction and the purity of the products were confirmed by the TLC using methanol:carbon tetrachloride (2:8) [21]. The synthetic procedures for the preparation of compounds (**Z_2B**, **Z_2E**, **Z_2B'** and **Z_2E'**) are presented in Scheme 1.

***N*-(4-Methylpyrimidin-2-yl)-4-(4-oxo-2-(tetrazolo[1,5-a]quinolin-4-yl)thiazolidin-3-yl)benzenesulfonamide (Z_2B).** Reddish orange powder; yield: 72%; Rf: 0.81; m.p: 138–140 °C; Elemental analysis for $C_{23}H_{18}N_8O_3S_2$ (518.57 g/mol); Calcd: C, 53.27; H, 3.50; N, 21.61; S, 12.37. Found: C, 53.31; H, 3.55; N, 21.57; S, 12.44. IR (KBr) cm^{-1}: 3225 ν(N-H), 2924 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1691 ν(C=O, thiazolidinone ring), 1519 ν(C-N, thiazolidinone ring), 1627,1573 ν(C=N, tetrazole, pyrimidine ring), 1481–1438 ν(C=C), 1338 $\nu_{str.}$(SO_2, asymmetrical), 1157 $\nu_{str.}$(SO_2, symmetrical), 1273 ν(N-N=N, tetrazole ring), 976 ν(S-N), 725 $\nu_{str.}$(C-S-C, asymmetrical), 678 $\nu_{str.}$(C-S-C, symmetrical), 624 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 11.24 (s, 1H, NH), 8.33 (d, 1H, J = 6 Hz, Ar-H), 8.00 (d, 1H, J = 9 Hz, pyrimidine-H), 7.70 (t, 1H, J_1 = 9, J_2 = 3 Hz, Ar-H), 7.52 (d, 2H, J = 9 Hz, Ar-H), 6.96 (d, 1H, J = 6 Hz, Ar-H), 6.85 (s, 1H, pyridine-H), 6.77 (t, 1H, $J_1 = J_2$ = 9 Hz, Ar-H), 6.76 (d, 2H, J = 9 Hz, Ar-H), 6.59 (d, 1H, J = 9 Hz, pyrimidine-H), 6.00 (s, 1H, CH-N, thiazolidinone ring), 3.67 (s, 2H, CH-CO, thiazolidinone ring), 2.98 (s, 3H, CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 167.87, 156.07, 151.62, 147.28, 140.36, 132.83, 130.75, 130.12, 129.87, 128.74, 126.63, 124.71, 124.11, 122.37, 119.43, 118.55, 115.73, 111.96, 57.25, 33.82, 22.18; The EI-MS m/z (%): 518 $[M]^+$ (1.6), 364 $[C_{15}H_{16}N_4O_3S_2]^{\bullet+}$ (1.2), 272 $[C_{12}H_{10}N_5OS]^+$ (6.2), 250 $[C_{10}H_{10}N_4O_2S]^{\bullet+}$ (30.3), 147 $[C_5H_{11}N_2OS]^+$ (3.5), 105 $[C_3H_7NOS]^{\bullet+}$ (100).

***N*-(4-Methylpyrimidin-2-yl)-4-(4-oxo-2-(tetrazolo[1,5-a]quinolin-4-yl)-1,3-selenazolidin-3-yl)benzenesulfonamide (Z_2B').** Maroon powder; yield: 51%; Rf: 0.51; m.p: 194–196 °C; Elemental analysis for $C_{23}H_{18}N_8O_3SSe$ (565.47 g/mol); Calcd: C, 48.85; H, 3.21; N, 19.82; S, 5.67. Found: C, 48.89; H, 3.18; N, 19.79; S, 5.63. IR (KBr) cm^{-1}: 3360 ν(N-H), 2920 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1701 ν(C=O, thiazolidinone ring), 1519 ν(C-N, thiazolidinone ring), 1597,1570 ν(C=N, tetrazole, pyrimidine ring), 1481-1438 ν(C=C), 1330 $\nu_{str.}(SO_2$, asymmetrical), 1157 $\nu_{str.}(SO_2$, symmetrical), 1273 ν(N-N=N, tetrazole ring), 972 ν(S-N), 574 $\nu_{str.}$(C-Se); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 10.58 (s, 1H, NH), 8.32 (s, 1H, pyridine-H), 7.98 (d, 1H, *J* = 9 Hz, Ar-H), 7.77 (d, 1H, *J* = 6 Hz, pyrimidine-H), 7.69 (d, 2H, *J* = 9 Hz, Ar-H), 7.52 (d, 1H, *J* = 9 Hz, Ar-H), 6.95 (t, 1H, J_1 = 9, J_2 = 6 Hz, Ar-H), 6.82 (d, 2H, *J* = 18 Hz, Ar-H), 6.77 (t, 1H, J_1 = 9, J_2 = 6 Hz, Ar-H), 6.59 (d, 1H, *J* = 9 Hz, pyrimidine-H), 6.03 (s, 1H, CH-N, thiazolidinone ring), 3.25 (s, 2H, CH-CO, thiazolidinone ring), 2.73 (s, 3H, CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 167.86, 162.78, 157.38, 153.35, 151.60, 142.13, 138.23, 132.18, 130.29, 129.88, 129.68, 129.35, 125.76, 123.28, 120.36, 118.94, 115.90, 112.53, 56.19, 31.22, 29.83; The EI-MS m/z (%): 566 $[M]^+$ (1.2), 407 $[C_{18}H_{13}N_6OSe]^+$ (0.8), 303 $[C_9H_9N_2O_3SSe]^+$ (1.3), 227 $[C_9H_{10}NOSe]^+$ (30.7), 199 $[C_{10}H_9N_5]^{\bullet+}$ (51.4), 134 $[C_8H_8NO]^+$ (100).

4-(4-Oxo-2-(tetrazolo[1,5-a]quinolin-4-yl)thiazolidin-3-yl)-*N*-(thiazol-2-yl)benzenesulfonamide (Z_2E). Brown powder; yield: 67%; Rf: 0.75; m.p: 160–162 °C; Elemental analysis for $C_{21}H_{15}N_7O_3S_3$ (509.58 g/mol); Calcd: C, 49.50; H, 2.97; N, 19.24; S, 18.88. Found: C, 49.56; H, 3.01; N, 19.28; S, 18.82. IR (KBr) cm^{-1}: 3363 ν(N-H), 2920 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1693 ν(C=O, thiazolidinone ring), 1535 ν(C-N, thiazolidinone ring), 1597 ν(C=N, tetrazole, thiazole ring), 1420 ν(C=C), 1369 $\nu_{str.}(SO_2$, asymmetrical), 1138 $\nu_{str.}(SO_2$, symmetrical), 1280 ν(N-N=N, tetrazole ring), 929 ν(S-N), 748 $\nu_{str.}$(C-S-C, asymmetrical), 686 $\nu_{str.}$(C-S-C, symmetrical), 628 $\nu_{str.}$(C-S, sulfonamide); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 10.55 (s, 1H, NH), 8.90 (d, 1H, *J* = 9 Hz, thiazole-H), 8.32 (d, 1H, *J* = 6 Hz, Ar-H), 7.95 (s, 1H, pyridine-H), 7.73 (d, 2H, *J* = 9 Hz, Ar-H), 7.44 (d, 1H, *J* = 9 Hz, Ar-H), 7.34 (t, 1H, J_1 = 9, J_2 = 12 Hz, Ar-H), 7.11 (t, 1H, J_1 = 6, J_2 = 18 Hz, Ar-H), 7.10 (d, 2H, *J* = 6 Hz, Ar-H), 6.75 (d, 1H, *J* = 6 Hz, thiazole-H), 6.03 (s, 1H, CH-N, thiazolidinone ring), 3.03 (s, 2H, CH-CO, thiazolidinone ring); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 170.68, 157.20, 147.03, 141.75, 134.23, 131.93, 130.83, 130.37, 129.86, 129.69, 123.67, 122.12, 120.30, 119.18, 115.29, 110.44, 109.16, 56.17, 32.45; The EI-MS m/z (%): 509 $[M]^+$ (1.4), 267 $[C_{10}H_9N_3O_2S_2]^{\bullet+}$ (1.8), 239 $[C_9H_7N_2O_2S_2]^+$ (2.2), 195 $[C_{10}H_5N_5]^{\bullet+}$ (5.0), 177 $[C_9H_9N_2S]^+$ (2.8), 86 $[C_3H_4NS]^+$ (64), 64 $[O_2S]^+$ (100).

4-(4-oxo-2-(tetrazolo[1,5-a]quinolin-4-yl)-1,3-selenazolidin-3-yl)-*N*-(thiazol-2-yl)benzenesulfonamide (Z_2E'). Yellowish brown powder; yield: 58%; Rf: 0.61; m.p: 178–180 °C; Elemental analysis for $C_{21}H_{15}N_7O_3S_2Se$ (556.48 g/mol); Calcd: C, 45.33; H, 2.72; N, 17.62; S, 11.52. Found: C, 45.31; H, 2.69; N, 17.66; S, 11.48. IR (KBr) cm^{-1}: 3367 ν(N-H), 2920 ν(CH, asymmetrical, aliph.), 2854 ν(CH, symmetrical, aliph.), 1689 ν(C=O, thiazolidinone ring), 1523 ν(C-N, thiazolidinone ring), 1600 ν(C=N, tetrazole, thiazole ring), 1431–1408 ν(C=C), 1365 $\nu_{str.}(SO_2$, asymmetrical), 1138 $\nu_{str.}(SO_2$, symmetrical), 1276 ν(N-N=N, tetrazole ring), 933 ν(S-N), 555 $\nu_{str.}$(C-Se); ^{1}H-NMR (300 MHz, DMSO-d_6) (δ/ppm): 10.52 (s, 1H, NH), 8.32 (d, 1H, *J* = 5 Hz, Ar-H), 7.70 (s, 1H, pyridine-H), 7.37 (d, 2H, *J* = 10 Hz, Ar-H), 7.29 (t, 1H, J_1 = 10, J_2 = 5 Hz, Ar-H), 7.24 (d, 1H, *J* = 10 Hz, Ar-H), 7.06 (t, 1H, J_1 = 10, J_2 = 5 Hz, Ar-H), 6.70 (d, 2H, *J* = 5 Hz, Ar-H), 6.56 (d, 1H, *J* = 10 Hz, thiazole-H), 6.54 (d, 1H, *J* = 5 Hz, thiazole-H), 4.92 (s, 1H, CH-N, thiazolidinone ring), 3.74 (s, 2H, CH-CO, thiazolidinone ring); ^{13}C-NMR (300 MHz, DMSO-d_6) (δ/ppm): 173.82, 166.23, 148.68, 144.76, 135.82, 132.30, 130.22, 129.90, 128.98, 128.71, 125.38, 124.96, 122.86, 120.68, 119.92, 116.73, 113.17, 58.47, 35.66; The EI-MS m/z (%): 557 $[M]^+$ (1.2), 435 $[C_{19}H_{13}N_7O_2S_2]^{\bullet+}$ (2.5), 320 $[C_{12}H_{10}N_5OSe]^+$ (1.2), 279 $[C_{10}H_9N_5Se]^{\bullet+}$ (31.7), 239 $[C_9H_7N_2O_2S_2]^+$ (2.8), 174 $[C_{10}H_{12}N_3]^+$ (60.1), 64 $[O_2S]^+$ (100).

Biological Activity

Acute toxicity (LD_{50})

Healthy albino mice of either sex (male and female),

aged from 7 to 9 weeks and whose body weight ranged between 23–33 g, were used to study the acute toxicity of 4-thiazolidinone (**Z_2E**) and 4-selenazolidinone (**Z_2E'**) derivatives. The animals were injected intraperitoneally with the first dose of 500 mg/kg. The result was read death X or life O after 24 h and increases or decreases the amount of dose was constant 50 mg/kg and repeat dosing up or down for 4 mice after changing the result death to life and versa. LD_{50} was calculated based on the diagram and equation of Dixon

$$LD_{50} = Xf + Kd$$

where Xf: the last dose, K: the interval between dose levels, d: the tabulated value, Table 1 [24].

Antibacterial activity

The compounds (**Z_2B**, **Z_2E**, **Z_2B'** and **Z_2E'**) were screened *in vitro* for antibacterial properties. The panel of pathogens involved *Staphylococcus aureus* and *Bacillus* as a Gram-positive bacterium, *Escherichia coli* and *Pseudomonas aeruginosa* as a Gram-negative bacterium, using the agar diffusion method. The antibiotic tetracycline was used to calibrate and compare with the antibacterial stuff. 0.2 mL of bacterial inoculums were uniformly spread using a sterile cotton swab on a sterile petri dish Mueller Hinton Agar (MHA). The tested compounds and tetracycline drug was dissolved in DMSO with concentrations including 1, 5, 25,125, 250, and 500 mg/mL for each compound. 50 µL from 1–500 mg/mL concentrations of tested compounds and tetracycline were added to every well (7 mm diameter holes cut within the agar gel, 20 mm aside from one another). The plates were incubated for 24 h at 36 °C ± 1 °C, under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in mm [25]. Furthermore, values of minimum inhibitory concentration (MIC) of those compounds [26]. The MIC was recorded because of the lowest concentration at which no visible growth was observed.

Table 1. The tabulated Dixon values

	O	OO	OOO	OOOO	
XOOO	0.157-	0.154-	0.154-	0.154-	OXXX
XOOX	0.878-	0.861-	0.860-	0.860-	OXXO
XOXO	0.701	0.747	0.741	0.741	OXOX
XOXX	0.084	0.169	0.181	0.182	OXOO
XXOO	0.305	0.372	0.380	0.381	OOXX
XXOX	0.305-	0.169	0.144-	0.142-	OOXO
XXXO	1.288	1.500	1.544	1.549-	OOOX
XXXX	0.555	0.0897	0.985	1.000	OOOO
	X	XX	XXX	XXXX	

K represented serial tests started with: -

Antioxidant activity

The antioxidant activity of the azetidin-2-one (**Z_2a**-**Z_2e**, **Z_2g**), 4-thiazolidinone (**Z_2B**, **Z_2E**) and 4-selenazolidinone (**Z_2B'**, **Z_2E'**) were determined according to the β-carotene bleaching method [27]. The β-carotene bleaching method is based on the loss of the yellow color of β-carotene because of its reaction with radicals formed by linoleic acid oxidation in an emulsion and according to previous methods [28]. A solution of β-carotene was prepared by dissolving 0.01 g of β-carotene in 50 mL of chloroform. As much as 1 mL of this solution was then pipetted into a round-bottom rotary flask containing 0.02 mL of linoleic acid and 0.2 mL of Tween-20. After removing the chloroform by vacuum evaporation using a rotary evaporator at room temperature, 50 mL of distilled water was added to the flask with manual shaking as the first stage. The emulsion (3.8 mL) was added to tubes containing 0.2 mL of the prepared compounds and the reference (BHT) compound which was prepared by dissolving 0.01 g of these compounds in 0.2 mL of DMSO. The absorbance was read at 470 nm, and the samples were then subjected to thermal autoxidation at 45°C in a water bath for 2 h. Absorbance was measured every 15 min [27]. Antioxidant activity (AA) was calculated as the percent of inhibition relative to the control using the equation

$$\%AA = 1 - [(Ai - At) / (Ai^* - At^*)] \times 100$$

where, Ai: is the measured absorbance value of the sample at zero time. At: is the measured absorbance value of the sample after incubation 105 min at 45 °C. Ai*: is the measured absorbance value of control at zero time, At*: is the measured absorbance value of control after incubation 105 min at 45 °C.

Anti-breast cancer activity

In vitro *MTT cellular viability assay*. The cytotoxicity of samples on the MCF-7 cell line was determined by the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl tetrazolium

bromide (MTT) cell viability assay [29]. Cells at a density of 1 × 10^4 cells/mL (100 µL/well) were seeded in 96-well plates and incubated overnight under 5% CO_2 at 37 °C, followed by exposure to a series of concentrations (6.25, 12.5, 25, 50, 75, and 100 µg/mL) of the tested compounds (**Z_2E** and **Z_2E'**) and 5-Fluorouracil as reference drug. At the same time, a group only containing culture medium was set as blank control. Each group had three biological repeats. After dosing for 72 h, the cells were washed, and then fresh medium (100 µL) supplemented with 28 µL of 2 mg/mL solution of MTT was added to each well. After incubated in the dark for 2 h at 37 °C, removing the MTT solution and the crystals remaining in the wells were solubilized by adding 100 µL of DMSO followed by 37 °C incubation for 15 min with shaking [30]. The optical density at 620 (OD620) of each well was measured by a plate reader (Synergy H4: Bio-Tek, Winooski, VT, USA). The results are presented as mean ± standard deviation (SD). The survival rate of control cells treated without the tested compounds was 100%. Cell viability was calculated using the following equation

$$\text{Cell viability}(\%) = \frac{\text{dosing cell OD} - \text{blank OD}}{\text{control cell OD} - \text{blank OD}} \times 100$$

Acridine orange/Ethidium bromide staining. Morphological apoptosis of MCF-7 cells treated with different concentrations of the newly prepared compounds (**Z_2E** and **Z_2E'**) and standard (5-Fluorouracil) were assessed using an acridine orange/ethidium bromide (AO/EB) staining kit (Solarbio, Beijing, China, Cat No. CA1140). The density of 1 × 10^4 MCF-7 cells/mL was plated in 6-well plates (1 mL/well) and incubated overnight. The medium was replaced with the tested compounds-containing 6.25, 12.5, 25, 50, 75, and 100 µg/mL medium and incubated for 48 h under the same conditions mentioned before. Cells were washed with PBS and stained with AO/EB solution (20 µL AO/EB freshly mixed solution of equal volume in 1 mL PBS) for 2–3 min in the dark. After the successive washes, the fluorescent images were taken with an inverted fluorescence microscope (Olympus Corporation, Beijing, China) [31].

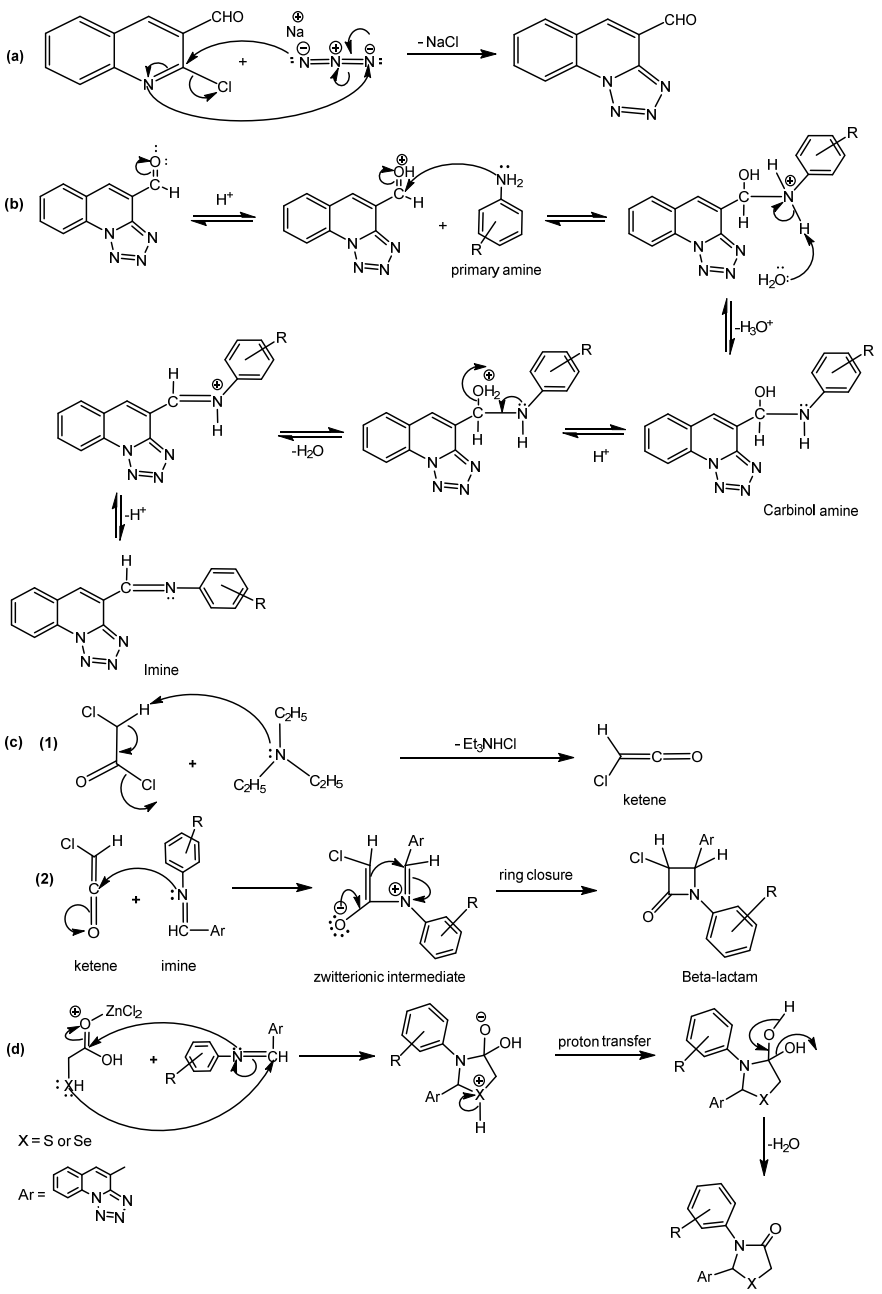
■ RESULTS AND DISCUSSION

The 2-azetidinone (**Z_2a**-**Z_2e**, **Z_2g**), 4-thiazolidinone (**Z_2B**, **Z_2E**) and 4-selenazolidinone (**Z_2B'**, **Z_2E'**) compounds were prepared via reaction of imines with ketene, thioglycolic acid, and 2-selenoglycolic acid, respectively. The prepared thiazolidin-4-ones and selenazolidine-4-one are obtained as solid compounds, often melting with decomposition but the attachment of an alkyl group to the nitrogen lowered its melting point compared to the β-Lactam compounds. 2-Azetidinones, 1,3-thiazolidin-4-ones and 1,3-selenazolidine-4-ones are stable in air, and they are soluble in most polar solvents. The suggested mechanisms for preparing a 2-azetidinone and thiazo- or selenazolidin-4-one ring are shown in Scheme 2. Also, the existence of interactive unsaturated ketone group in 2-azetidinones and thiazo- or selenazolidin-4-one are accountable for their biological activities [32]. The elemental analysis results C, H, N, and S of the studied compounds are in agreement with the theoretical values.

Spectroscopic Analysis

Infrared spectra (FTIR)

All the infrared spectra of the compounds were characterized by a medium to a weak band at 1226–1284 cm^{-1} which corresponds to the ν(N-N=N) stretching vibration for tetrazole ring [33]. Also, the IR spectra of all the prepared compounds show featured bands in the range 1319–1369 and 1138–1168 cm^{-1}, which are assigned to asymmetrical and symmetrical stretching vibration, respectively, of SO_2 group [34]. The compounds (**2a**, **2g**, **Z_2a** and **Z_2g**) show two bands within the range 3136–3448 cm^{-1}, which is attributed to asymmetric and symmetric stretching of ν(NH_2) groups. In addition, the medium to weak bands at 3225–3448 cm^{-1} can correspond to the ν(N-H) stretching vibration. IR spectra of the Schiff bases **2a**-**2e**, **2g** showed the absence of band at 1681 cm^{-1} which attribute to carbonyl ν(C=O) stretching vibration which was apparent in the tetrazolo[1,5-a]quinoline-4-carbaldehyde compound (**2**) and instead, the appearance of a strong new band at 1589–1608 cm^{-1} that assigned to the imine ν(CH=N) linkage, which indicates the reaction between the amino and aldehyde moieties of the starting reagents which are no more existed and have been



Scheme 2. The suggested mechanisms of (a) Tetrazole ring, (b) Schiff bases, (c) β-Lactam compounds and (d) 4-thiazolidinone or 4-selenazolidinone compounds), respectively

converted into the respective Schiff base linkages [4,21].

The structure of 2-azetidinones (i.e., compounds **Z_2a**-**Z_2e** and **Z_2g**) was established by IR spectroscopy which showed the disappearance of CH=N bands in the region 1589–1608 cm^{-1} combined with the appearance of absorption bands at 1697–1743 and 1519–1546 cm^{-1} due to ν(C=O) and ν(C-N), respectively [21-22]. Ring closure in 4-thiazolidinones and 4-selenazolidinones can be observed by the appearance of strong bands at 1689–1701 and 1519–1535 cm^{-1} which attributed to the stretching vibration of the carbonyl group ν(C=O) and ν(C-N), respectively [20-21]. The spectrum was distinguished by the appearance of distinct absorption bands for ν(C-S-C) at the range 725–748 and 678–686 cm^{-1}, which assigned to asymmetrical and symmetrical stretching vibration respectively for the 1,3-thiazolidin-4-ones

(**Z_2B** and **Z_2E**) [12,34]. Furthermore, the strong to medium bands which appeared in the range 555–574 cm^{-1} are attributed to the ν(C-Se) stretching vibration for the 4-selenazolidinones (**Z_2B'** and **Z_2E'**) [35]. All the prepared compounds show strong to medium bands in the range 914–979 and at 624–690 cm^{-1} in IR spectrum can be related to stretching of ν(S-N) and ν(C-S), respectively [4].

^{1}H-NMR and ^{13}C-NMR spectra

The ^{1}H-NMR spectra of the prepared compounds show a singlet signal at the range δ 10.52–12.86 ppm, which is attributed to the N-H protons. Furthermore, (**2a**, **2g**, **Z_2a** and **Z_2g**) compounds have a singlet signal at δ 6.97–7.07 ppm due to the presence of two protons of NH_2 group of sulfonamide which innervate the desired results [4]. The proton of azomethine group (CH=N) of compounds (**2a**-**2e**, **2g**) appears at δ 8.58–9.07 ppm [21]. The 2-azetidinone compounds (**Z_2a**-**Z_2e** and **Z_2g**) are characterized by showing doublet signal at δ 3.02–4.17 ppm and at δ 4.22–6.05 ppm, which can be assigned to the (CH-N) and (CH-Cl) protons, respectively and disappearing the azomethine signal that exists in Schiff bases (**2a**-**2e** and **2g**) [11,36]. The ^{1}H-NMR spectra of the 4-thiazolidinones and 4-selenazolidinones (**Z_2B**, **Z_2E**, **Z_2B'** and **Z_2E'**) are characterized by showing singlet signals at δ 3.03–3.67 ppm and at δ 3.25–3.74 ppm, which attributed to the (CH_2-S) and (CH_2-Se) protons respectively [21,37]. Also, singlet signal that appears at δ 4.92–6.03 can be attributed to the (CH-N) proton of these compounds [21]. The compounds (**2b**, **2c**, **2d**, **Z_2b**, **Z_2c**, **Z_2d**, **Z_2B** and **Z_2B'**) shows a singlet signal at δ 1.18–3.03 ppm due to methyl protons [4,21]. In addition, multiple signals that appear at δ 6.54–8.86 ppm can be attributed to aromatic rings of all the studied compounds [21,38]. Therefore, the ^{1}H-NMR result supports the formation of four- or five-membered rings.

The ^{13}C-NMR spectra of azetidine-2-ones, 1,3-thiazolidin-4-ones and 1,3-selenazolidin-4-ones show signals at the range δ 168.48–172.15 ppm, δ 167.87–170.68 ppm and signal at δ 167.86–173.82 ppm which attribute to cyclic carbonyl carbon (C=O), respectively [20-21]. The 2-azetidinone compounds are characterized by showing two signals at δ 56.46–68.98 and δ 45.71–62.47 ppm and which can be assigned to the C-Cl and C-N in lactam ring, respectively [11]. Also, the spectra of the thiazolidine-4-one or selenazolidin-4-one derivatives exhibited two signals at δ 56.17–58.47 and δ 31.22–35.66 ppm, which can be assigned to the 2-C and 5-C in 1,3-thiazo or 1,3-selenazolidin-4-one ring, respectively [21,39]. The ^{13}C-NMR spectra of the prepared compounds (**Z_2b**, **Z_2c**, **Z_2d**, **Z_2e**, **Z_2B**, **Z_2B'**, **Z_2E** and **Z_2E'**) show signals at the range δ 151.62–166.23 ppm is due to the imine functional group (C=N) in sulfonamide ring. Additionally, the compounds (**Z_2b**, **Z_2c**, **Z_2d**, **Z_2B**, and **Z_2B'**) show signals at δ 12.58–29.83 ppm that can be attributed to methyl groups [4]. Furthermore, the signals of aromatic carbons of these synthesized compounds are represented at δ 111.52–154.64 ppm [4]. The ^{13}C-NMR spectral data of the 2-azetidinones and thiazolidine-4-ones or selenazolidin-4-ones are in accord with the suggested structures.

EI-mass

The mass spectrum of all studied compounds detects the molecular ion peaks $[M]^+$ are in excellent acceptance with the suggested structures. The potential suggested ion fragments with the appearance of the result of fragmentation of these synthesized compounds are shown in Scheme 3, furthermore, the peaks intensity gives an idea about the stability of fragments primarily with the base peaks.

The mass spectrum of the compound **Z_2b** shows several fragments peaks at m/z 365, 225, 195, and m/z 148, and these peaks can be assigned to $[C_{18}H_{14}ClN_6O]^+$, $[C_9H_9N_2O_3S]^+$, $[C_9H_8ClN_2O]^+$ and $[C_9H_{10}NO]^+$ ions, respectively. The mass spectrum of the compound **Z_2B** shows five fragments peaks at m/z 364, 272, 250, 147 and m/z 105, and these peaks can be attributed to $[C_{15}H_{16}N_4O_3S_2]^{\bullet+}$, $[C_{12}H_{10}N_5OS]^+$, $[C_{10}H_{10}N_4O_2S]^{\bullet+}$, $[C_5H_{11}N_2OS]^+$ and $[C_3H_7NOS]^{\bullet+}$ ions, respectively. On the other hand, the mass spectrum of compound **Z_2B'** is characterized by the appearance of five fragmentation peaks at m/z 407, 303, 227, 199 and 134 which can be attributed to $[C_{18}H_{13}N_6OSe]^+$, $[C_9H_9N_2O_3SSe]^+$, $[C_9H_{10}NOSe]^+$, $[C_{10}H_9N_5]^{\bullet+}$ and $[C_8H_8NO]^+$ ions respectively. The base peaks at m/z 86 can be assigned to the $[C_4H_8NO]^+$ ion for most 2-azetidinone compounds. Successive degradation of the target compound and the appearance of different peaks due to various fragments

are good evidence for the molecular structure of the investigated compounds.

Biological Activity

The median lethal dose (LD_{50})

The lethal dose (LD_{50}) of the studied compounds (**Z_2E** and **Z_2E'**) *in-vivo* was determined in mice via intraperitoneally injecting dosages ranging from 500–750 mg/kg with equal spacing (concentrations) between doses. Our data revealed that LD_{50} values were 658.45 and 758.45 mg/kg for the compounds **Z_2E** and **Z_2E'**, respectively. The results may give an indication about the moderate toxicity effect of the studied compounds and clinical change observed in the mice after giving different doses. The toxic signs observed in injected mice may be manifested in some behaviors such as tremors, straight tail, salivation, urination, lacrimation, defecation, shortness of breath, excitation, muscle fasciculations, capillary bulge, convulsions and also the tortuous reflex in some treatments, and finally death at high toxic doses, Table 2 [40-41].

Antibacterial activity

The sensitivity of four human pathogenic microbes (two of Gram-positive bacteria: *S. aureus*, *Bacillus* and two of Gram-negative bacteria: *E. coli*, *P. aeruginosa*) to the new synthetic heterocyclic compounds (**Z_2B**, **Z_2B'**, **Z_2E** and **Z_2E'**) was tested and compared to that of the commercially available antibacterial antibiotic tetracycline. Our study confirmed that the thiazolidine-4-one and selenazolidin-4-one compounds had antibacterial activity (increases as the compound concentration increases) against the studied bacteria, also minimum inhibitory concentration MIC which can define as the lowest concentration of the compound in the medium which out visible growth of the test organisms in a concentration ranging from 1–500 mg/mL, as shown in Table 3–6.

In the present work, the antibacterial activity of the new synthetic compounds may be attributed to the fact that these two groups of bacteria differ by their cell wall component and their thickness. The ability of these new

Table 2. Toxicity results (LD_{50}) and toxic signs on mice

Test characterization	Results	
	Z_2E	**Z_2E'**
Doses range	500–650 = 150 mg/kg	500–750 = 250 mg/kg
First dose	500 mg/kg	500 mg/kg
Last dose	650 mg/kg	750 mg/kg
Up and down dose	50 mg/kg	50 mg/kg
Median lethal dose (LD_{50}) mg/kg	658.45 mg/kg	758.45 mg/kg
Effective dose (LD_{50} /10) mg/kg	65.845 mg/kg	75.84 mg/kg
No. of mice	8 (XOXXOXOO)	8 (XXOXOOXO)
Onset of toxic signs	5–16 min	5–24 min
Toxic signs	Rolling convulsions, excitation, salivation, choreoathetosis, tremors, death	Salivation, dyspnoea, convulsions, excitation, tremors, muscle fasciculation, death

Table 3. The inhibition zones (mm) against *Staphylococcus aureus*

Coms.	Diameter of inhibition zone (mm) *Staphylococcus aureus*						
	Concentration (mg/mL)						
	1	**5**	**25**	**125**	**250**	**500**	**MIC**
Z_2B	NI	13	14	29	33	37	5
Z_2B'	NI	NI	NI	NI	NI	15	500
Z_2E	NI	NI	NI	10	12	14	125
Z_2E'	NI	NI	17	18	21	23	25
Tetracycline*	NI	4	10	14	25	48	5

* Standard, NI = No Inhibition

Table 4. The inhibition zones (mm) against *Bacillus*

Coms.	Diameter of inhibition zone (mm) *Bacillus*						
	Concentration (mg/mL)						
	1	**5**	**25**	**125**	**250**	**500**	**MIC**
Z_2B	NI	11	18	40	45	50	5
Z_2B'	NI	NI	NI	12	15	16	125
Z_2E	NI	NI	NI	14	16	18	125
Z_2E'	NI	NI	18	20	21	26	25
Tetracycline*	5	11	14	22	30	50	1

* Standard, NI = No Inhibition

Table 5. The inhibition zones (mm) against *Pseudomonas aeruginosa*

Coms.	Diameter of inhibition zone (mm) *Pseudomonas aeruginosa*						
	Concentration (mg/mL)						
	1	**5**	**25**	**125**	**250**	**500**	**MIC**
Z_2B	NI	NI	10	11	12	22	25
Z_2B'	NI	NI	NI	12	12	13	125
Z_2E	NI	NI	NI	NI	30	40	250
Z_2E'	NI	NI	19	20	24	26	25
Tetracycline*	NI	6	8	17	30	52	5

* Standard, NI = No Inhibition

Table 6. The inhibition zones (mm) against *Escherichia coli*

Coms.	Diameter of inhibition zone (mm) *Escherichia coli*						
	Concentration (mg/mL)						
	1	**5**	**25**	**125**	**250**	**500**	**MIC**
Z_2B	NI	NI	10	10	14	20	25
Z_2B'	NI	NI	NI	NI	10	12	250
Z_2E	NI	NI	NI	20	25	29	125
Z_2E'	NI	13	20	20	20	24	5
Tetracycline*	NI	8	11	15	21	44	5

* Standard, NI = No Inhibition

compounds to cause the bacterial colonies to disintegrate probably results from their interference with the bacterial cell wall, thereby inhibiting the microbial growth [42]. Among the new synthetic heterocyclic compounds, **Z_2E'** was found to be more effective than the positive control (tetracycline) against Gram-negative bacteria (*E. coli*) with an inhibition zone (IZ) of 13, 20 and 20 mm at the concentration of 5, 25 and 125 mg/mL, respectively. This result may come from the fact that the membrane of Gram-negative bacteria is surrounded by an outer membrane containing lipopolysaccharides, which makes the compound able to combine with the lipophilic layer in order to enhance the permeability of the membrane to Gram-negative bacteria. In conclusion, the antibacterial activity of any compound may be related to the cell wall structure of bacteria due to the importance of this wall for bacterial survival. Thus, the ability of antibiotics to kill or inhibit the growth of bacteria may be through inhibition of a step in peptidoglycan synthesis by gram-positive bacteria [43-44].

In the case of antibacterial activity against Gram-positive bacteria (*S. aureus* and *Bacillus*), all compounds were found to have activity ranging between high and moderate. Our results indicated that the compound **Z_2B**

possessed the highest antibacterial activity against Gm+Ve (*S. aureus*) with an IZ of 13, 14, 29, and 33 mm at concentrations of 5, 25, 125, and 250 mg/mL, respectively. Also, the **Z_2B** compound showed more potent compared to the positive control IZ = 4–25 mm at the same concentration. On the other hand, our data pointed out that compound **Z_2B** showed a good antibacterial activity against Gm+Ve (*Bacillus*) with an IZ ranging from 11–45 mm as compared to tetracycline IZ = 11–30 mm at the concentrations 5–250 mg/mL.

All the thiazolidine-4-one or selenazolidin-4-one drugs are selective inhibitors of bacterial cell wall synthesis and therefore active against growing bacteria [44]. The biological activity of 4-thiazolidinone skeleton is believed to be associated with the chemical reactivity of the ring and on the substituents, especially in the nitrogen of 4-thiazolidinone ring [44]. Furthermore, the mechanism of action of sulfonamide is inhibition of the action of dihydropteroate synthase and blocking the net biosynthesis of folate coenzymes. Therefore, it represents bacteriostatic compounds [45].

The MIC of tested compounds in this study against the test organisms ranged between 1–500 mg/mL, Table 3–6. Antimicrobial agents with low activity against an organism had a high MIC while a highly active antimicrobial agent gave a low MIC. The most resistant microorganisms were *E. coli* and *P. aeruginosa*, whereas the most sensitive microorganisms were *S. aureus* and *Bacillus*. The lowest MIC value of 5 mg/mL was recorded on *S. aureus* and on *Bacillus* with compound **Z_2B**. The compound **Z_2E'** was more active as compared with its precursors and had the lowest MIC value of 5 mg/mL obtained on *E. coli* and on *P. aeruginosa*. However, the highest MIC value of 250 mg/mL was recorded on *E. coli* and on *P. aeruginosa* with compounds (**Z_2B'** and **Z_2E**), whereas the highest MIC values of 500 and 125 mg/mL were obtained on *S. aureus* and on *Bacillus* with compounds **Z_2B'** and **Z_2E**, respectively. The results of the present study suggest that the thiazolidine-4-one and selenazolidin-4-one compounds possess remarkable toxic activity against bacteria and may assume pharmacological importance [46].

Antioxidant activity

Reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, hydroxyl, and nitric oxide radicals are generated during the bioorganic redox process and normal cellular metabolism. They play a significant role in oxidative stress related to the development and pathogenesis of life-limiting various diseases such as cancer, diabetes mellitus, arteriosclerosis, rheumatoid arthritis, and others [27].

The results in Table 7 and Fig. 1–4 indicated an increase in the antioxidant activity of the synthetic compounds and standard in the order of **Z_2d** < **Z_2B'** < **Z_2e** < **Z_2g** < **Z_2E'** < **Z_2b** < BHT with corresponding percentages values of 50.0, 53.0, 57.2, 57.7, 68.8, 73.0, and 82.3%, respectively. On the other hand, the lowest activity was observed for compounds **Z_2B**, **Z_2a**, **Z_2E**, and **Z_2c** with corresponding inhibition ratios 48.4, 47.4, 35.8,

Table 7. Antioxidant activity of prepared compounds, the values are the mean ± SD

Comp. symbol	Aj	At	Aj*	At*	AA%
BHT	0.582 ± 0.01	0.544 ± 0.011	0.456 ± 0.031	0.241 ± 0.016	82.3
Z_2a	0.527 ± 0.015	0.414 ± 0.023	0.456 ± 0.031	0.241 ± 0.016	47.4
Z_2b	0.479 ± 0.004	0.421 ± 0.019	0.456 ± 0.031	0.241 ± 0.016	73
Z_2c	0.474 ± 0.003	0.329 ± 0.028	0.456 ± 0.031	0.241 ± 0.016	32.6
Z_2d	0.573 ± 0.017	0.466 ± 0.008	0.456 ± 0.031	0.241 ± 0.016	50
Z_2e	0.561 ± 0.013	0.469 ± 0.014	0.456 ± 0.031	0.241 ± 0.016	57.2
Z_2g	0.463 ± 0.005	0.372 ± 0.018	0.456 ± 0.031	0.241 ± 0.016	57.7
Z_2B	0.540 ± 0.009	0.429 ± 0.012	0.456 ± 0.031	0.241 ± 0.016	48.4
Z_2B'	0.487 ± 0.007	0.386 ± 0.021	0.456 ± 0.031	0.241 ± 0.016	53
Z_2E	0.557 ± 0.013	0.419 ± 0.008	0.456 ± 0.031	0.241 ± 0.016	35.8
Z_2E'	0.459 ± 0.003	0.392 ± 0.014	0.456 ± 0.031	0.241 ± 0.016	68.8

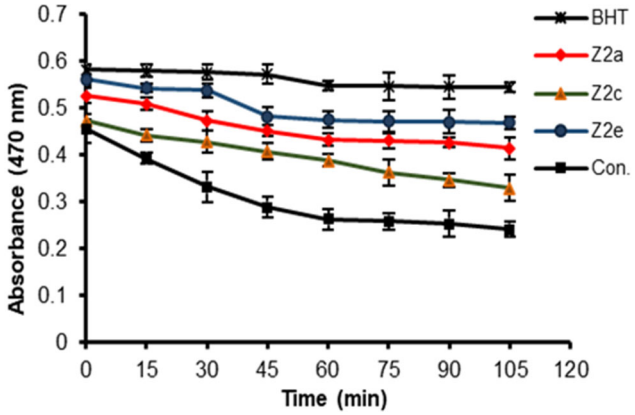


Fig 1. Antioxidant activity of compounds **Z_2a**, **Z_2c** and **Z_2e**

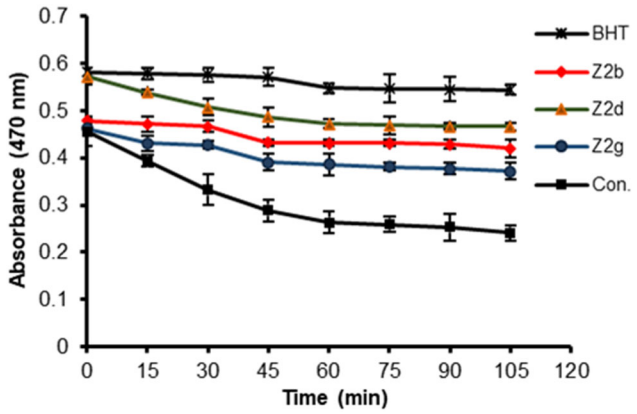


Fig 2. Antioxidant activity of compounds **Z_2b**, **Z_2d** and **Z_2g**

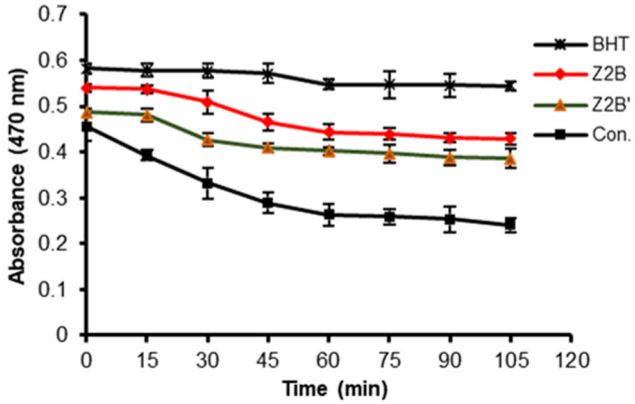


Fig 3. Antioxidant activity of compounds **Z_2B** and **Z_2B'**

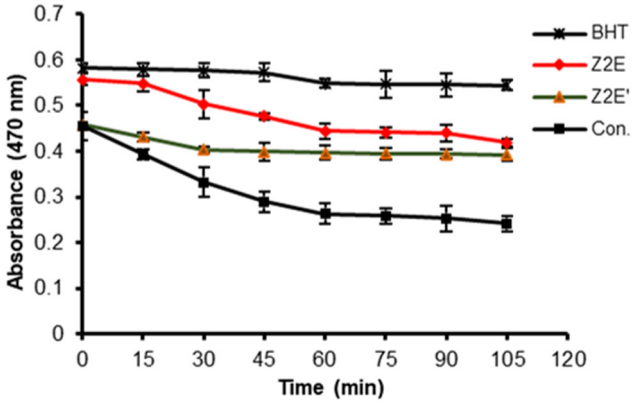


Fig 4. Antioxidant activity of compounds **Z_2E** and **Z_2E'**

and 32.6%, respectively. A possible explanation for the higher antioxidant activity of these compounds (**Z_2b**, **Z_2E'**, **Z_2g**, **Z_2e**, **Z_2B'** and **Z_2d**) might be due to the following reasons. First, since compounds **Z_2b** and **Z_2d** have an additional methyl group which increases the antioxidant activity, this activity may be correlated with the introduction of electron donor substituent which stabilizes the generated radical during oxidation [47]. Second, compounds **Z_2E'** and **Z_2B'** have Se-C moieties in 4-selenazolidinone ring which increase the antioxidant activity by the interaction with the active site of protein to form a new seleno-protein (Enz-Se) moiety in the active site [51]. Furthermore, the organoselenium compounds had the ability to catalyze the reduction of harmful peroxides by glutathione (GSH) and thereby protect the biomolecules against oxidative damage. Third, compounds (**Z_2b**, **Z_2g**, **Z_2e** and **Z_2d**) have a β-lactam ring which can act as a scavenger for radicals to prevent oxidative cellular damage and thus enhance antioxidant properties [48].

The finding that compound **Z_2b** possessed a strong protective effect is interesting and points to the potential use of this new compound as an agent to overcome oxidative stress that is associated with cellular metabolism and disease conditions [52]. The mechanism by which **Z_2b** protects the body's cells from oxidative damage may require further study and investigation.

Interestingly, the relative antioxidant effect of some β-lactam or 4-thiazo and 4-selenazolidinone antibiotics such as ampicillin on oxygen-reactive species (ROS) has been reported, and a possible therapeutic role for β-lactam agents in protecting host tissues from oxidative damage has been proposed. The keto lactam ring or thiazolidine ring is responsible for initiating the free radical scavenging activity due to its N-H and C=O moieties [49-50].

Notably, scientific studies have confirmed that compounds in general, including those that have antioxidant properties, may be subjected to metabolism *in vivo* through specialized enzymatic systems in the body, which often convert lipophilic chemical compounds into polar products that are easily secreted. Therefore, we expect that **Z_2d** and other new synthetic compounds enter different metabolic pathways in the body that may modify differently from their structure and/or toxicity, and this requires further research. Again, the exact possible mechanism via which compound **Z_2b** and the new other synthetic compounds protect against oxidative damage will be a matter of future studies and must be confirmed in a more controlled experimental design [27].

Cell cytotoxicity (anticancer) study

One of the first goals of researchers and scientists is to discover and develop a new anti-cancer drug that has good efficacy and does not cause any of the side effects of current chemotherapy drugs. Therefore, the need for a time-saving, low-cost, high-throughput drug efficacy testing system has led to the emergence of an *in vitro* model cytotoxicity testing on human cancer cell lines [50-51].

In this work, the cytotoxic effects of the synthesized compounds against breast cancer cell line (MCF-7) were evaluated using 5-fluorouracil (5-FU) as a reference cytotoxic drug. The IC_{50} and cell viability percent of MCF-7 cancerous at different concentrations ranging from 6.25–100 µg/mL are given in Table 8 and Fig. 5–7. The results showed that compound **Z_2E** was comparable to that of 5-FU (positive control), while compound **Z_2E'** (IC_{50} = 24.87 µg/mL) is a more cytotoxic agent than 5-FU (IC_{50} = 97.47 µg/mL), Table 8. It is evident that the tested compounds showed anticancer activity in all concentrations and the effects of these compounds were dose-dependent, *i.e.*, by increasing the concentration in the culture media; the percentage of cells viability is decreased (this means that the percentage of dead cells has increased). IC_{50} values ranged from 24.87 to 97.47 µg/mL. Also, we can note that the cytotoxic activity of compound **Z_2E'** was higher in cancerous cells when compared with the compound **Z_2E**,

Table 8. The IC_{50} values and the percent of cell viability of the tested compounds in breast cancer cell line MCF-7, the values are the mean ± SD

Coms.	Cell viability %						IC_{50} (µg/mL)
	Concentration (µg/mL)						
	6.25	12.5	25	50	75	100	
Z_2E	99.06 ± 0.83	98.68 ± 0.91	96.13 ± 1.15	94.10 ± 0.09	79.41 ± 0.52	34.35 ± 0.08	90.92
Z_2E'	98.84 ± 1.12	97.57 ± 1.09	49.11 ± 1.44	18.17 ± 2.01	17.48 ± 0.15	16.99 ± 0.02	24.87
5-Fluorouracil	83.13 ± 0.86	80.69 ± 1.07	72.76 ± 0.86	66.57 ± 1.06	58.93 ± 0.61	49.29 ± 0.06	97.47

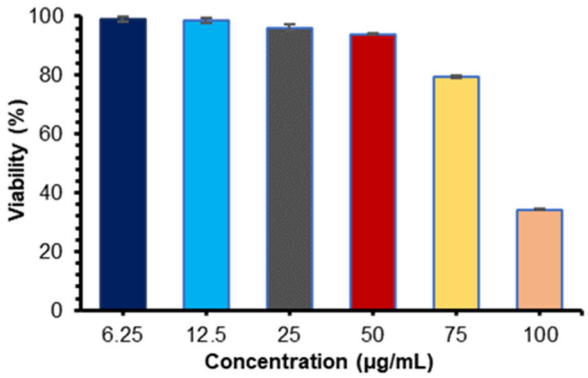


Fig 5. Anticancer activity of compound **Z_2E** at 6.25–100 µg/mL

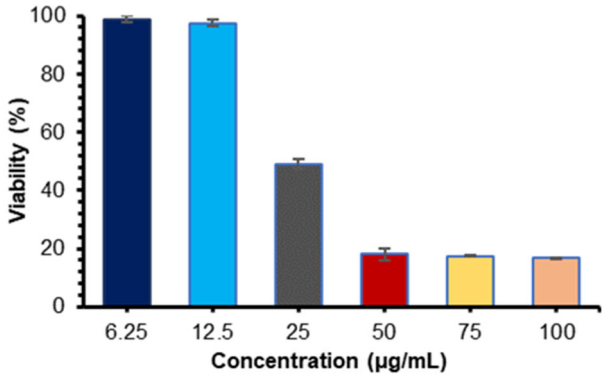


Fig 6. Anticancer activity of compound **Z_2E'** at 6.25–100 µg/mL

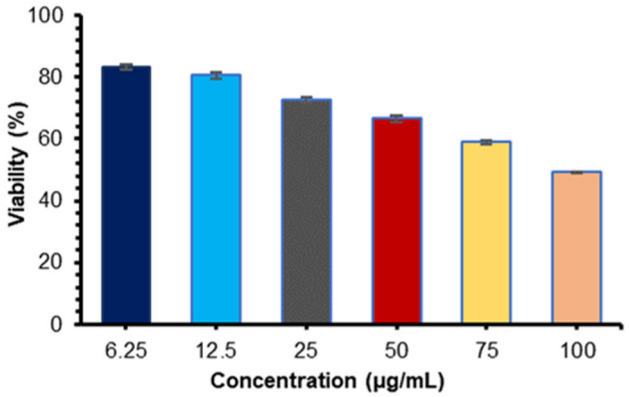


Fig 7. Anticancer activity of drug **5-Fluorouracil** at 6.25–100 µg/mL

especially at a concentration of 25 µg/mL.

Thiazolidine-4-one compounds revealed their pharmaceutical significance as anticancer agents. Numerous antitumor thiazolidinones are currently used to treat cancer, such as anthracyclines, bleomycin, mitomycin C, dactinomycin, and mithramycin. The major mechanism of action for these antitumor thiazolidinones is inhibition of cell wall synthesis, DNA intercalation or inhibition of DNA synthesis [51-52]. The presence of 4-thiazolidinone ring in the molecular structure of compounds **Z_2E** and **Z_2E'** is related to anticancer activity by inhibiting the transpeptidase enzyme, which catalyzes the cross-linking of the peptidoglycan strands in the cell wall phase of the cancer cell wall biosynthesis. The thiazolidinone or selenazolidinone ring can bind to the active site of the transpeptidase enzyme since its structure resembles that

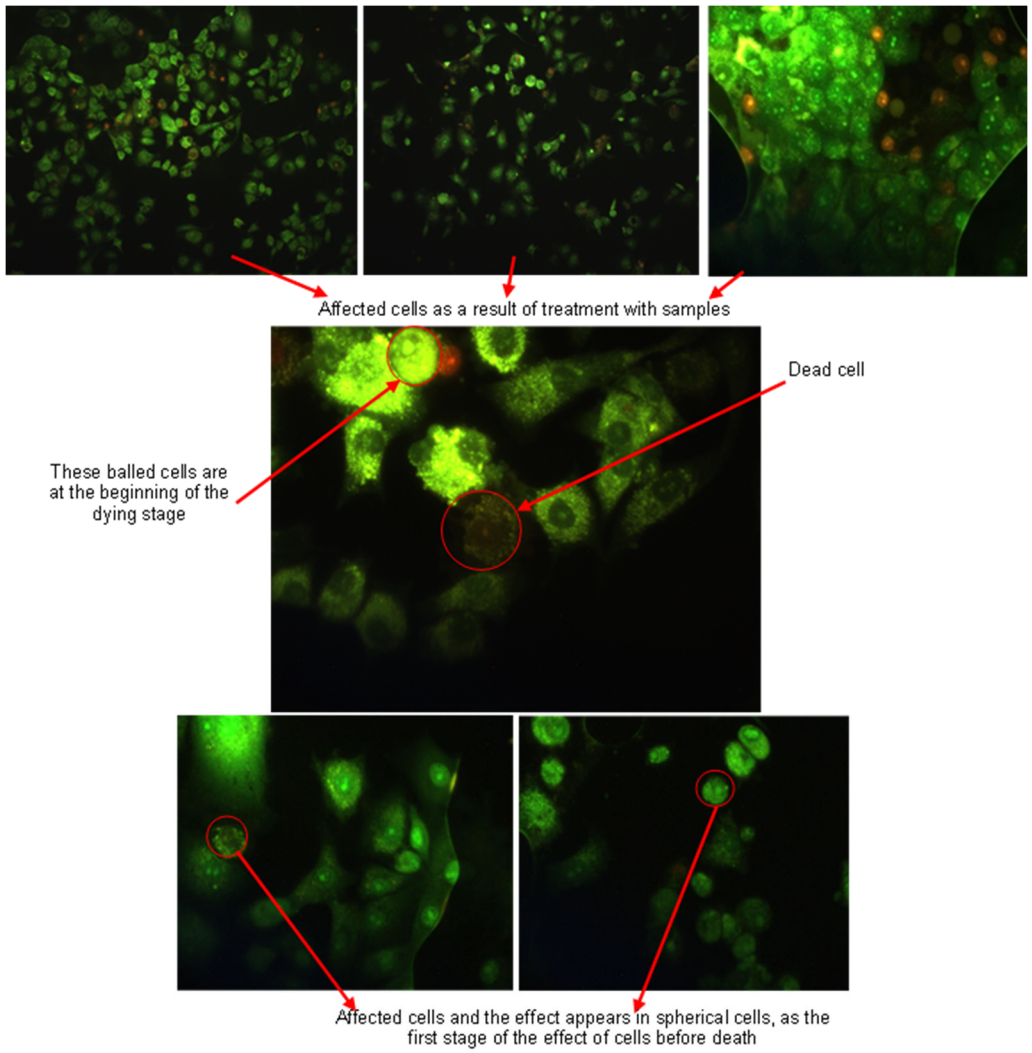


Fig 8. Anticancer activity of compound **Z_2E** at 75–100 µg/mL

of the substrate, which is the terminal D-ala-D-ala dipeptide of the pentapeptide of each monomer unit [47]. Note that D-ala-D-ala dipeptide of the substrate can exist in multiple conformations formed by rotation around the C-C single bonds but a thiazolidine-4-one molecule has a limited variety of conformation because of the rigidity of the five-membered ring [48]. Of the many conformations possible for the terminal dipeptide the one that binds to the enzyme resembles the structure of the thiazolidine-4-one ring, and thus, the two can compete for binding to the active site of the enzyme. The -C(O)-N bond of the thiazolidine-4-one or selenazolidin-4-one mimics the -C(O)-N of the peptide bond of the terminal dipeptide. Therefore, inhibition the formation of the cancer cell wall, which leads to cells death [46,49]. Banik et al. [50,52] also show that thiazolidine-4-ones with polyaromatic substituents induce tumor cell death in a variety of breast cancer cell lines. As well, the presence of (-S-C-N- and -Se-C-N-) moieties in the tested compounds is related to anticancer activity by the interaction with the active site of protein through hydrogen bonding bringing about the hindrance development of cells [50]. However, several novel classes of thiazolidine-4-ones and selenazolidin-4-ones have been shown to possess anticancer properties as well [52].

On the other hand, the present results clearly indicated that the compounds **Z_2E** and **Z_2E'** had an ability to induce apoptosis of MCF-7 Cells, as illustrated in Fig. 8–9. Acridine orange (AO) is a vital dye and will stain the nuclei of both live and dead cells to green while ethidium bromide (EB) will stain only cells that have lost membrane integrity to red. Thus, live cells will appear uniformly green while early apoptotic cells will have condensed or fragmented nuclei with bright green color. Late apoptotic cells will show condensed and fragmented orange chromatin. The results showed that increased the compound **Z_2E'** concentration resulted in gradual increases in orange and red staining accompanied by reductions in green staining of nuclei, indicating cell damage and apoptosis (Fig. 9). Therefore, a high concentration (100 µg/mL) of **Z_2E'** could cause serious membrane damage in around 84% of cells. Moreover, these results indicate that the apoptotic rate gradually increases with the **Z_2E** and **Z_2E'** concentrations and treatment time. It is verified that at around 25 µg/mL **Z_2E'** can induce half of the cells to undergo apoptosis at 48 h, consistent with the IC_{50} results.

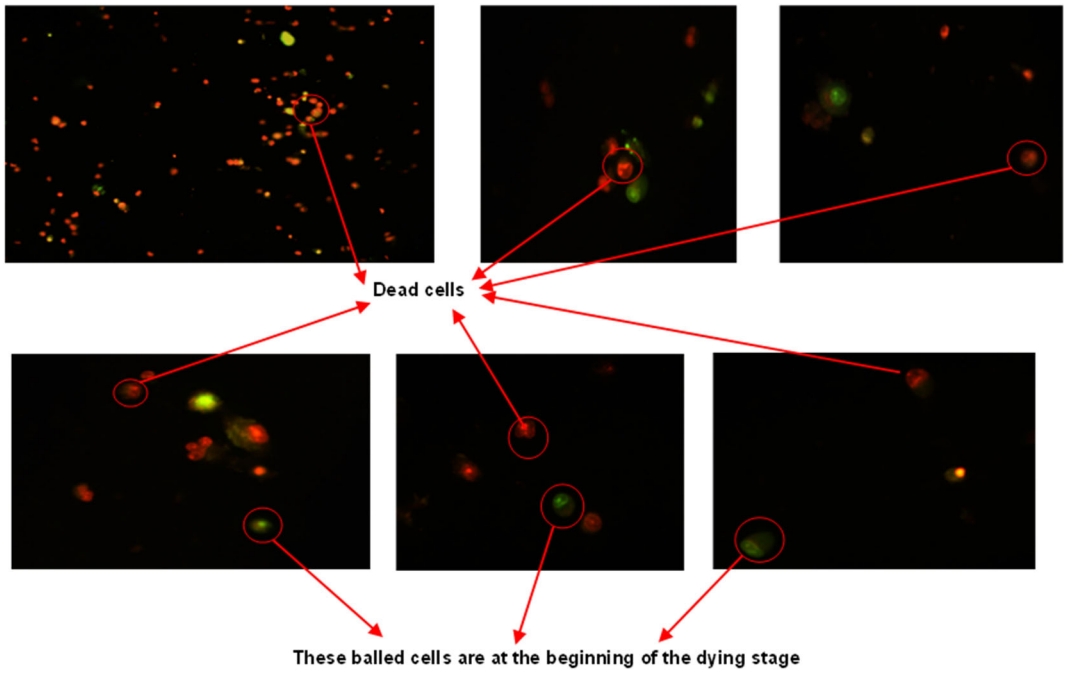


Fig 9. Anticancer activity of compound **Z_2E'** at 12.5–25 µg/mL

■ CONCLUSION

In this study new series of 2-azetidinone (**Z_2a**-**Z_2e**, **Z_2g**), thiazolidinone and selenazolidinone derivatives (**Z_2B**, **Z_2E**, **Z_2B'**, **Z_2E'**) have been designed and synthesized starting based on sulfonamide. The proposed structures of all the synthesized compounds were proved using spectral methods. The newly synthesized compounds were evaluated for their *in vitro* antibacterial, antioxidant, toxicity, and anticancer activities. Results of the LD_{50} test using Dixon's up and down method indicated that the compound containing selenium (**Z_2E'**) was less toxic than its analogs containing sulfur (**Z_2E**). Although their antimicrobial potential was good, **Z_2E'** compound was more active against Gram-negative bacteria with the lowest MIC value of 5 mg/mL. All compounds showed antioxidant activity, but **Z_2b** was the main compound that possesses strong activity as antioxidants (73%). *In vitro* MTT viability assay indicated that all tested compounds had cytotoxic effects on MCF-7 cells after 72 h of treatment. The results revealed that **Z_2E'** and **Z_2E** compounds possessed strong activity with good IC_{50} = 24.8 and 90.9, respectively at a higher rate than the standard compound 5-FU, IC_{50} = 97.47. These results support that **Z_2E'** has potential properties as a promising drug in several diseases such as breast cancer due to their numerous pharmacological and biological activities.

■ ACKNOWLEDGMENTS

The authors are highly thankful to the head of the Chemistry Department, College of Science, the University of Basrah for providing their kind support and facilities to accomplish the present research project within time.

■ REFERENCES

[1] Mansour, A.M., 2014, Selective coordination ability of sulfamethazine Schiff-base ligand towards copper (II): Molecular structures, spectral and SAR study, *Spectrochim. Acta, Part A*, 123, 257–266.

[2] Claudel, M., Schwarte, J.V., and Fromm, K.M., 2020, New antimicrobial strategies based on metal complexes, *Chemistry*, 2 (4), 849–899.

[3] Tačić, A., Nikolić, V., Nikolic, L., and Savić, I., 2017, Antimicrobial sulfonamide drugs, *Adv. Technol.*, 6 (1), 58–71.

[4] Al-Atbi, H.S., Al-Assadi, I.J., Al-Salami, B.K., and Badr, S.Q., 2020, Study of new azo-azomethine derivatives of sulfanilamide: Synthesis, characterization, spectroscopic, antimicrobial, antioxidant and anticancer activity, *Biochem. Cell. Arch.*, 20 (2), 4161–4174.

[5] Bytyqi-Damoni, A., Genç, H., Zengin, M., Demir, D., Gençer, N., and Arslan, O., 2020, Novel β-lactam compounds as activators for polyphenoloxidase, *ChemistrySelect*, 5 (25), 7671–7674.

[6] Elkanzi, N.A.A., 2013, Short review on synthesis of thiazolidinone and *β*-lactam, *World J. Org. Chem.*, 1 (2), 24–51.

[7] Martelli, G., and Giacomini, D., 2018, Antibacterial and antioxidant activities for natural and synthetic dual-active compounds, *Eur. J. Med. Chem.*, 158, 91–105.

[8] Piens, N., 2017, Synthesis of new β-lactam building blocks and their application in heterocyclic Chemistry, *Dissertation*, Faculty of Bioscience Engineering, Ghent University, Belgium.

[9] Elkanzi, N.A.A., and Mohamed, N.M.M., 2014, Synthesis and antimicrobial activity of β-lactams: Antibacterial activities and antifungal activities, *Heterocycl. Lett.*, 4 (1), 153–182.

[10] Salamanca, C.H., Yarce, C.J., Roman, Y., Davalos, A.F., and Rivera, G.R., 2018, Application of nanoparticle technology to reduce the anti-microbial resistance through β-lactam antibiotic-polymer inclusion nano-complex, *Pharmaceuticals*, 11 (1), 19.

[11] Bhalla, A., Bari, S.S., Berry, S., Bhalla, J., Vats, S., Mandal, S., and Khullar, S., 2015, Facile synthesis of novel monocyclic *trans*- and *cis*-3-oxy/thio/seleno-4-pyrazolyl-β-lactams, *ARKIVOC*, 2015 (7), 10–27.

[12] Patel, J.A., Mistry, B.D., and Desai, K.R., 2008, Conventional and microwave induced synthesis of various azetidinone and thiazolidinone derivatives from 3-[(1E)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol and their antimicrobial screening, *Indian J. Chem., Sect. B*, 47B (10), 1695–1700.

[13] Chaban, Z., Harkov, S., Chaban, T., Klenina, O., Ogurtsov, V., and Chaban, I., 2017, Recent advances in synthesis and biological activity evaluation of condensed thiazoloquinazolines: A review, *Pharmacia*, 64 (3), 52–66.

[14] Neri, R., and Bossmann, S.H., 2021, Isoselenocyanates: Synthesis and their use for preparing selenium-based heterocycles, *Synthesis*, 53 (12), 2015–2028.

[15] Nirwan, S., Chahal, V., and Kakkar, R., 2019, Thiazolidinones: Synthesis, reactivity, and their biological applications, *J. Heterocycl. Chem.*, 56 (4), 1239–1253.

[16] Trotsko, N., 2021, Antitubercular properties of thiazolidin-4-ones–A review, *Eur. J. Med. Chem.*, 215, 113266.

[17] Banerjee, B., and Koketsu, M., 2017, Recent developments in the synthesis of biologically relevant selenium-containing scaffolds, *Coord. Chem. Rev.*, 339, 104–127.

[18] Abd Al-khaliq, Z.M., 2015, Synthesis, characterization and antibacterial activity of new series of sulfamethoxazole derivatives, *Thesis*, College of Pharmacy, University of Al-Mustansiriyah, Baghdad, Iraq.

[19] Sahu, P.K., Kim, G., Yu, J., Ahn, J.Y., Song, J., Choi, Y., Jin, X., Kim, J.H., Lee, S.K., Park, S., and Jeong, L.S., 2014, Stereoselective synthesis of 4′-selenonucleosides via seleno-Michael reaction as potent antiviral agents, *Org. Lett.*, 16 (21), 5796–5799.

[20] Desai, N.C., Harsora, J.P., Monapara, J.D., and Khedkar, V.M., 2021, Synthesis, antimicrobial capability and molecular docking of heterocyclic scaffolds clubbed by 2-azetidinone, thiazole and quinoline derivatives, *Polycyclic Aromat. Compd.*, 0, 1–15.

[21] Ramachandran, S., Cheriyan, B.V., and Aanandhi, M.V., 2021, Activities of thiazolidine-4-one and azetidine-2-one derivatives-A review, *Res. J. Pharm. Technol.*, 14 (8), 4513–4516.

[22] Jarrahpour, A., Rezaei, S., Sinou, V., Latour, C., and Brunel, J.M., 2017, Synthesis of some novel 3-spiro monocyclic β-lactams and their antibacterial and antifungal investigations, *Iran. J. Sci. Technol., Trans. A: Sci.*, 41 (2), 337–342.

[23] Al-Masoudi, W.A., Al-Diwan, M.A., and Hassan, I.J., 2015, Synthesis, acute toxicity and modelling docking studies of azo compound derived from sulphonamide and pyrimidine derivative, *Pharma Chem.*, 7 (9), 1–5.

[24] Ahmad, M.F., 2018, *Ganoderma lucidum*: Persuasive biologically active constituents and their health endorsement, *Biomed. Pharmacother.*, 107, 507–519.

[25] Al-Fregi, A.A., Al-Fadhly, A.L., and Al-Salami, B.K., 2017, Synthesis, characterization and biological activity study of some new palladium(II) complexes containing amine or azomethine groups, *Eur. J. Chem.*, 8 (2), 155–161.

[26] Rusmana, D., Wahyudianingsih, R., Elisabeth, M., Balqis, B., Maesaroh, M., and Widowati, W., 2017, Antioxidant activity of Phyllanthus niruri extract, rutin and quercetin, *InaBJ*, 9 (2), 84–90.

[27] Al-Fartosy, A.J.M., 2011, Antioxidant properties of methanolic extract from *Inula graveolens* L., *Turk. J. Agric. For.*, 35 (6), 591–596.

[28] Al-Shammari, A.M., Al-Esmaeel, W.N., Al-Ali, A.A., Hassan, A.A., and Ahmed, A.A., 2019, Enhancement of oncolytic activity of Newcastle disease virus through combination with retinoic acid against digestive system malignancies, *Mol. Ther.*, 27 (4), 126–127.

[29] Sharma, A., and Puhar, A., 2019, Gentamicin protection assay to determine the number of intracellular bacteria during infection of human TC7 intestinal epithelial cells by *Shigella flexneri*, *Bio-Protoc.*, 9 (13), e3292.

[30] Liu, K., Liu, P.C., Liu, R., and Wu, X., 2015, Dual AO/EB staining to detect apoptosis in osteosarcoma cells compared with flow cytometry, *Med. Sci. Monit. Basic Res.*, 21, 15–20.

[31] Mahdi, I.S., Yousif, S.A., and Khammas, S.J., 2019, Synthesis and characterization of some new (tetrazole, thiazolidin-4-one) compounds derived from drugs and evaluation of their biological activities, *Int. J. Pharm. Qual. Assur.*, 10 (4), 720–727.

[32] Bhaskar, V.H., and Mohite, P.B., 2011, Synthesis analgesic, Anti-Inflammatory and antimicrobial activities of some 1-[5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-5-phenyl-1*H*-tetrazole, *J. Optoelectron. Biomed. Mater.*, 3 (1), 7–16.

[33] Verma, V.A., Saundane, A.R., Meti, R.S., Shamrao, R., and Katkar, V., 2020, Synthesis, biological evaluation and docking studies of some new indolyl-pyridine containing thiazolidinone and azetidinone analogs, *Polycyclic Aromat. Compd.*, 42 (4), 1545–1559.

[34] Al-Rubaie, A.Z., Al-Masoudi, W.A., Hameed, A.J., Yousif, L.Z., and Graia, M., 2008, Synthesis, reaction and antiviral activity of 2,4-diaryl-1,3-selenazoles, *J. Korean Chem. Soc.*, 52 (1), 36–46.

[35] Alam, S., Hasan, P., Aneja, B., Ahmad, M.B., and Abid, M., 2016, $POCl_3$ mediated Staudinger reaction of imines with ketenes: Synthesis of monocyclic β-lactam and 1,3-oxazinone derivatives, *Rasayan J. Chem.*, 9 (2), 101–111.

[36] Xie, Y., Liu, J., and Li, J., 2011, Selective synthesis of novel 2-imino-1,3-selenazolidin-4-ones and 2-amino-1,3,4-selenadiazin-5-ones from isoselenocyanates, *Tetrahedron Lett.*, 52 (8), 932–935.

[37] Saini, N., Sharma, A., Thakur, V.K., Makatsoris, C., Dandia, A., Bhagat, M., and Sharma, P.C., 2020, Microwave assisted green synthesis of thiazolidin-4-one derivatives: A perspective on potent antiviral and antimicrobial activities, *Curr. Res. Green Sustainable Chem.*, 3, 100021.

[38] Rafique, J., Canto, F.S.R., Saba, S., Barbosa, F.A.R., and Braga, A.L., 2016, Recent advances in the synthesis of biologically relevant selenium-containing 5-membered heterocycles, *Curr. Org. Chem.*, 20 (2), 166–188.

[39] Sharp, D.J., Rogers, G.C., and Scholey, J.M., 2000, Microtubule motors in mitosis, *Nature*, 407 (6800), 41–47.

[40] Usui, K., Nishida, S., Sugita, T., Ueki, T., Matsumoto, Y., Okumura, H., and Sekimizu, K., 2016, Acute oral toxicity test of chemical compounds in silkworms, *Drug Discoveries Ther.*, 10 (1), 57–61.

[41] Thomba, D.U., Mirgane, S.R., Ambhure, R.U., Pawar, R.P., and Ameta, K.L., 2017, Synthesis and antimicrobial study of novel Schiff bases and metal complexes, *Biochem. Biophys.*, 3, 7–11.

[42] Sevgi, F., Bagkesici, U., Kursunlu, A. N., and Guler, E., 2018, Fe (III), Co (II), Ni (II), Cu (II) and Zn (II) complexes of Schiff bases based-on glycine and phenylalanine: Synthesis, magnetic/thermal properties and antimicrobial activity, *J. Mol. Struct.*, 1154, 256–260.

[43] Opoku-Temeng, C., Naclerio, G.A., Mohammad, H., Dayal, N., Abutaleb, N.S., Seleem, M.N., and Sintim, H.O., 2018, N-(1,3,4-oxadiazol-2-yl)benzamide analogs, bacteriostatic agents against methicillin-and vancomycin-resistant bacteria, *Eur. J. Med. Chem.*, 155, 797–805.

[44] Dhanya, S., and Aravind, A., 2015, Synthesis, characterization and evaluation of antioxidant activities of some new quinazolino-acetidinone derivatives, *J. Chem. Pharm. Res.*, 7 (12), 849–856.

[45] AL-Salami, B.K., AL-Khazragie, Z.K., and Al-Fregi, A.A., 2018, Synthesis, characterization, antimicrobial activity and antioxidant of azo Schiff bases containing sulfanilamide, *J. Global Pharma Technol.*, 10 (3), 952–962.

[46] Kuhn, D., Coates, C., Daniel, K., Chen, D., Bhuiyan, M., Kazi, A., Turos, E., and Ping Dou, Q., 2004, Beta-lactams and their potential use as novel anticancer chemotherapeutics drugs, *Front. Biosci.*, 9 (4), 2605–2617.

[47] Mohana, K.N., and Kumar, C.B.P., 2013, Synthesis and antioxidant activity of 2-amino-5-methylthiazol derivatives containing 1,3,4-oxadiazole-2-thiol moiety, *Int. Scholarly Res. Not.*, 2013, 620718.

[48] Singh, F.V., and Wirth, T., 2018, "Synthesis of Organoselenium Compounds with Potential Biological Activities" in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*, Eds. Jain V.K., and Priyadarsini K.I., The Royal Society of Chemistry, London, UK, 77–121.

[49] Eruygur, N., Koçyiğit, U.M., Taslimi, P., Ataş, M., Tekin, M., and Gülçin, İ., 2019, Screening the *in vitro* antioxidant, antimicrobial, anticholinesterase,

antidiabetic activities of endemic *Achillea cucullata* (Asteraceae) ethanol extract, *S. Afr. J. Bot.*, 120, 141–145.

[50] Bhattacharjee, M.K., 2016, "Antibiotics That Inhibit Cell Wall Synthesis" in *Chemistry of Antibiotics and Related Drugs*, Springer, Cham, Switzerland, 49–94.

[51] Al-Fartosy, A.J.M., and Ati, M.H., 2021, A predictive clinical markers to make prostate cancer and benign prostate hyperplasia easy diagnosis, *Biochem. Cell. Arch.*, 21 (2), 2939–2947.

[52] El-Desoky, S.I., Badria, F.A., Abozeid, M.A., Kandeel, E.A., and Abdel-Rahman, A.H., 2013, Synthesis and antitumor studies of novel benzo pyrano-1,2,3-selenadiazole and spiro[benzopyrano]-1,3,4-thiadiazoline derivatives, *Med. Chem. Res.*, 22 (5), 2105–2114.