Original Article

Synthesis, Characterization, Antimicrobial And Anticancer Evaluation Of 3-(4-(4-Bromophenyl) Thiazol-2-Yl)-2-(Substituted Phenyl) Thiazolidin-4-Ones

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Abstract

A series of 3-(4-(4-bromophenyl)thiazol-2-yl)-2-(substituted phenyl)thiazolidin-4-one derivatives was synthesized and These derivatives were characterized by IR, and 1H NMR spectral data. All the compounds were evaluated for their in vitro antimicrobial activity against two Gram negative strains (Escherichia coli) and two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and fungal strain Candida albicans and Aspergillus niger. All newly synthesized compounds exhibited promising results.

Introduction:

Increasing antimicrobial resistance (AR) results in high morbidity and mortality worldwide. The highest impact of AR is often more evident in developing countries, although AR remains a major global healthcare challenge. The World Health Organization in 2015 released the action plan aimed to fight the antimicrobial resistance among bacterial and fungal pathogens, although despite the efforts the resistance remains one of the leading threats. Therefore, it is crucial to explore novel scaffolds leading to the development of future antimicrobial compounds (Malukaite et al., 2022).

Despite the extensive research and rapid progress in drug science and chemotherapeutic agents for combating cancer, it is still one of the most leading causes of death worldwide. Statistics show that by 2040, cancer incidence will continue to rise to up to 29.5 million cases per year.2 Cancer treatment is still a major issue, owing to the toxicity, resistance, and lack of selectivity of the currently available anticancer medications (Othman et al., 2022).

The thiazole ring is an aromatic heterocyclic ring commonly found in natural and synthetic molecules. It is existing in the structure of alkaloids, steroids, vitamins (Thiamine-vit B1), flavones, pigments and secondary metabolites. Thiazole is a fascinating building block in medicinal chemistry for the design and synthesis of biologically active derivatives (Ayati et al., 2019). For example, thiazoles demonstrated antimicrobial (Bondock et al., 2013), anticancer(Sharma et al., 2020), antifungal (Lino et al., 2018), antioxidant (Djukic et al., 2018), anti-inflammatory(Sharma et al., 2009), antiviral (Osman et al., 2018), antidiabetic(Yin et al., 2021), anticonvulsant(Ahangar et al., 2011) and neuroprotective activities(Goshain et al., 2019) are reported. Many thiazole

analogs exhibited very potent antitumor or cytotoxic activity and many of them have been specially designed to target specific pathways (Mishra et al., 2015).

So there is an immediate need to discover new antimicrobial and anticancer agents.

In view of these findings, we hypothesized that thiazole derivatives would potentially have promising biological potential. As a consequence, it was determined that these molecules would be subjected to bioassays in order to identify their therapeutic potential. As a result, we provide in this work the synthesis of thiazole derivatives with chemical characterization and antimicrobial and anticancer properties.

MATERIALS AND METHODS:

Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded in KBr phase on a Perkin Elmer Spectrum RXI FTIR spectrophotomer. ^{1}H NMR spectra were run on BRUKER spectrometer (400 MHz liquid state NMR spectrometer) using Tetramethylsilane (TMS) as an internal standard. The purity of the synthesized compounds was ascertained by thin layer chromatography on silica gel G in solvent system ethyl acetate: benzene (6:4, v/v) using iodine vapors as detecting agent.

Chemistry

p-Bromo acetophenone, thiourea, and iodine was taken in a round bottom flask and was refluxed for 12 h to yield 4-(4-bromophenyl)-thiazol-2-amine. A mixture of 4-(4-bromophenyl)-thiazol-2-amine and different aromatic aldehydes was refluxed in minimum amount of ethanol in presence of small amount of glacial acetic acid for 6-7 h to yield the N-(subsitutedbenzylidene)-4-(4-bromophenyl)-thiazol-2-amines. Further, reaction of N-(subsitutedbenzylidene)-4-(4-bromophenyl)-thiazol-2-amines with thioglycollic acid to yield thiazoles clubbed with 4-thiazolidinones (**Scheme 1**). Thiazole derivatives were characterized on the basis of the spectral and analytical studies.

General approach for the Synthesis of thiazole derivatives:

Synthesis of 4-(4-bromophenyl)-thiazol-2-amine:

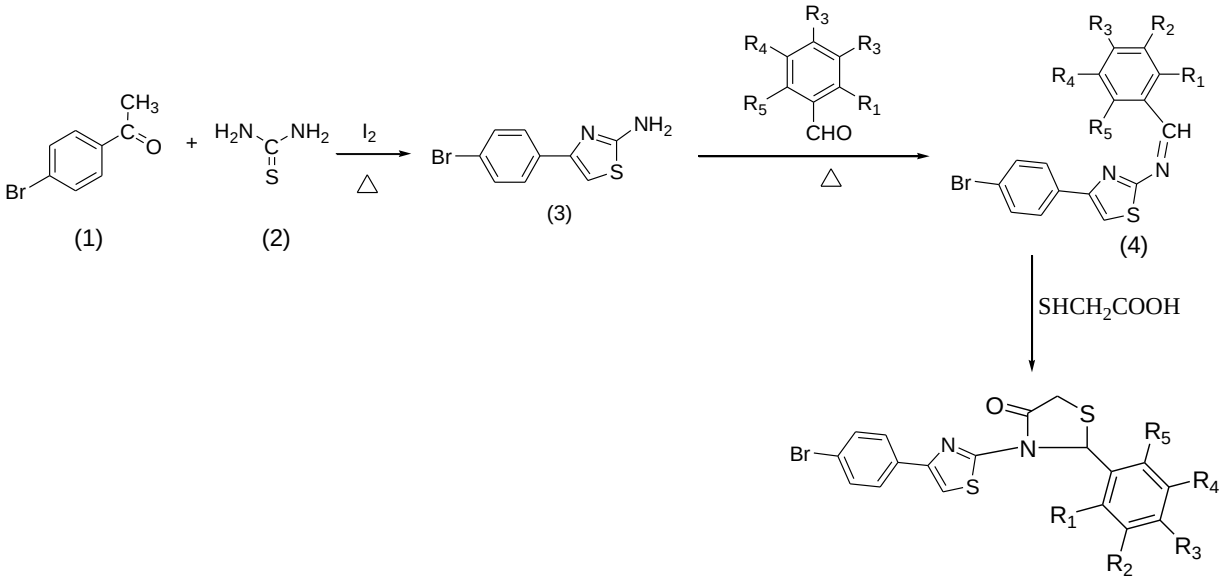
A mixture of p-bromo acetophenone (0.1 mol), thiourea (0.2 mol) and iodine (0.1 mol) was refluxed for 11–12 h. The reaction mixture was cooled and washed with diethyl ether to remove unreacted acetophenone and iodine. The completion of reaction was confirmed by thin layer chromatography. After this reaction mixture was allowed to cool and poured into the solution of ammonium hydroxide, precipitated and then filtered.

Synthesis of N-(subsitutedbenzylidene)-4-(4-bromophenyl)-thiazol-2-amines

A mixture of 4-(4-bromophenyl)-thiazol-2-amine (0.02 mol) and substituted aldehydes (0.02 mol) was refluxed in minimum amount of ethanol in presence of small amount of glacial acetic acid for 6–7 h. The completion of reaction was monitored by TLC. The mixture was cooled and poured in ice cold water. The solid thus obtained was filtered and dried (Sharma et al., 2019)

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(substituted phenyl)thiazolidin-4-one **(1-20):**

N-(subsitutedbenzylidene)-4-(4-bromophenyl)-thiazol-2-amine derivatives and required amount of thioglycolic acid (0.015 M, 1.40 ml) in DMF (50 ml), containing a pinch of anhydrous $ZnCl_2$ was refluxed for about 6 h. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water, and the product was recrystallized from rectified spirit (Deep et al., 2015). Synthetic pathway for formation of title compounds is presented in Scheme 1.



Thiazole clubbed with thiazolidinone derivatives(**1-20**)

Table 1: Physical data of Thiazole derivatives (1-20)

Comp.	M. Formula	X	M. Pt. (^{o}C)	M. Wt.	R_f value*	% yield
1	**$C_{18}H_{13}BrN_2OS_2$**	Benzaldehyde	137-139	**417.34**	0.62	74
2	**$C_{18}H_{12}BrClN_2OS_2$**	2-chloro benzaldehyde	142-144	**451.79**	0.67	85
3	**$C_{18}H_{13}BrN_2O_2S_2$**	2-hydroxy benzaldehyde	131-133	**433.34**	0.71	71
4	**$C_{18}H_{12}BrN_3O_3S_2$**	3-nitro benzaldehyde	125-127	**462.34**	0.78	77
5	**$C_{21}H_{19}BrN_2O_4S_2$**	3,4,5-methoxy benzaldehyde	117-119	**507.42**	0.64	69
6	**$C_{19}H_{15}BrN_2O_2S_2$**	3-methoxy benzaldehyde	161-163	**447.37**	0.62	81
7	**$C_{18}H_{12}Br_2N_2OS_2$**	4-bromo benzaldehyde	141-143	**496.24**	0.63	86
8	**$C_{20}H_{18}BrN_3OS_2$**	4-dimethyl amino benzaldehyde	176-178	**460.41**	0.79	67
9	**$C_{18}H_{12}BrN_3O_3S_2$**	4-nitro benzaldehyde	123-125	**462.34**	0.73	71
10	**$C_{18}H_{12}BrClN_2OS_2$**	3-chloro benzaldehyde	166-168	**451.79**	0.70	70
11	**$C_{19}H_{15}BrN_2OS_2$**	4-methyl benzaldehyde	129-131	**431.37**	0.69	72
12	**$C_{22}H_{22}BrN_3OS_2$**	4-dimethylamino benzaldehyde	133-135	**488.46**	0.74	78
13	**$C_{19}H_{15}BrN_2O_3S_2$**	4-hydroxy-3-methoxy benzaldehyde	179-181	**463.37**	0.67	62
14	**$C_{18}H_{12}BrFN_2OS_2$**	4-fluorobenzaldehyde	155-157	**435.33**	0.63	63
15	**$C_{18}H_{12}BrClN_2OS_2$**	4-chloro benzaldehyde	151-153	**451.79**	0.76	67
16	**$C_{18}H_{11}BrCl_2N_2OS_2$**	2,4-dichloro benzaldehyde	137-139	**486.23**	0.88	60
17	**$C_{18}H_{12}Br_2N_2OS_2$**	3-bromo benzaldehyde	147-149	**496.24**	0.65	59
18	**$C_{18}H_{12}BrFN_2OS_2$**	3-fluorobenzaldehyde	188-189	**435.33**	0.62	71
19	**$C_{19}H_{15}BrN_2O_2S_2$**	2-methoxy benzaldehyde	159-161	**447.37**	0.71	64
20	**$C_{18}H_{12}Br_2N_2OS_2$**	2-bromo benzaldehyde	153-155	**496.24**	0.58	67

Solvent system: *Benzene

Spectral data:

3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (1) IR (KBr, cm^{-1}): 3010 (C-H Ar), 1772 (C=O), 1638 (C=N str), 1603 (C=C Ar), 1366 (C-N), 693(C-S) 647 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.89-7.77 (m, 9H, ArH), 6.96 (s, 1H, -CH thiazol), 6.79 (s, 1H, -NCHS), 3.87 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(2-chlorophenyl)thiazolidin-4-one (2) IR (KBr, cm^{-1}): 1742 (C=O), 1649 (C=N str), 1622 (C=C Ar), 1365 (C-N), 754(C–Cl), 719(C-S) 670 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.69-7.20 (m, 8H, ArH), 6.98 (s, 1H, -CH thiazol), 6.63 (s, 1H, -NCHS), 3.83 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one (3) IR (KBr, cm^{-1}): 3614 (OH), 3119 (C-H Ar), 1715 (C=O), 1649 (C=N str), 1622 (C=C Ar), 1363 (C-N), 736(C-S), 667 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.13-8.10 (m, 8H, ArH), 6.94 (s, 1H, -CH thiazol), 6.917 (s, 1H, -NCHS), 6.913 (s, 1H, -OH), 3.38 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(3-nitrophenyl)thiazolidin-4-one (4) IR (KBr, cm^{-1}): 3075 (C-H Ar), 1626 (C=N str), 1607 (C=C Ar), 1521 (N–O str, NO2), 1341 (C-N), 717(C-S) 676 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.17-7.33 (m, 8H, ArH), 6.97 (s, 1H, -CH thiazol), 6.91 (s, 1H, -NCHS), 3.75 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(3,4,5-trimethoxyphenyl)thiazolidin-4-one (5) IR (KBr, cm^{-1}): 3013 (C-H Ar), 1746 (C=O), 1696 (C=N str), 1630 (C=C Ar), 1345 (C-N), 1252–1205(C–O–C str), 680(C-S) 631 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.22-7.92 (m, 6H, ArH), 7.14 (s, 1H, -CH thiazol), 7.10 (s, 1H, -NCHS), 3.97 (s, 2H, CH2), 3.39 (s, 9H, $–OCH_3$).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(3-methoxyphenyl)thiazolidin-4-one (6) IR (KBr, cm^{-1}): 3025 (C-H Ar), 1658 (C=N str), 1564 (C=C Ar), 1388 (C-N), 1260–1218(C–O–C str), 684(C-S) 680 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.07-7.98 (m, 8H, ArH), 7.72 (s, 1H, -CH thiazol), 7.54 (s, 1H, -NCHS), 3.80 (s, 2H, CH2), 3.42 (s, 3H, –OCH3).

2-(4-bromophenyl)-3-(4-(4-bromophenyl)thiazol-2-yl)thiazolidin-4-one (7) IR (KBr, cm^{-1}): 3107 (C-H Ar), 1634 (C=N str), 1533 (C=C Ar), 1344 (C-N), 723(C-S) 627 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.72-7.29 (m, 8H, ArH), 6.38 (s, 1H, -CH thiazol), 6.29 (s, 1H, -NCHS), 4.71 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(4-(dimethylamino)phenyl)thiazolidin-4-one (8) IR (KBr, cm^{-1}): 3007 (C-H Ar), 2875 (C-H str., -CH3), 1749 (C=O), 1697 (C=N str), 1639 (C=C Ar), 1395 (C-N), 624(C-S) 629 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.09-7.47 (m, 8H, ArH), 7.27 (s, 1H, -CH thiazol), 6.97 (s, 1H, -NCHS), 2.50 (s, 2H, CH2), 2.38 (s, 6H, N $(CH3)_2$).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (9) IR (KBr, cm^{-1}): 3012 (C-H Ar), 1675 (C=N str), 1626 (C=C Ar), 1510 (N–O str, NO2), 1362 (C-N), 694(C-S) 634 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.08-8.01(m, 8H, ArH), 7.74 (s, 1H, -CH thiazol), 7.28 (s, 1H, -NCHS), 3.74 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(3-chlorophenyl)thiazolidin-4-one(10) IR (KBr, cm^{-1}): 3110 (C-H Ar), 1723 (C=O), 1629 (C=N str), 1602 (C=C Ar), 1470 (C-N), 746(C–Cl), 676(C-S) 636 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.12-8.09 (m, 8H, ArH), 6.96 (s, 1H, -CH thiazol), 6.93 (s, 1H, -NCHS), 3.36 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-p-tolylthiazolidin-4-one (11) 3068 (C-H Ar), 2836 (C-H str., -CH3), 1697 (C=O), 1671 (C=N str), 1620 (C=C Ar), 1367 (C-N), 703(C-S) 666 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.39-7.24 (m, 8H, ArH), 6.98 (s, 1H, -CH thiazol), 6.95 (s, 1H, -NCHS), 3.78 (s, 2H, CH2), 2.31 (s, 3H, N-CH_3).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(4-(diethylamino)phenyl)thiazolidin-4-one (12) IR (KBr, cm^{-1}): 3002 (C-H Ar), 2946(-CH_2CH3), 1670 (C=O), 1558 (C=C Ar), 1393 (C-N), 685(C-S) 635(Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.62-7.50 (m, 8H, ArH), 7.19 (s, 1H, -CH thiazol), 7.07 (s, 1H, -NCHS), 2.49 (s, 2H, CH2), 2.30(m, 6H, CH_3), 2.05(m, 4H, CH_2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (13) IR (KBr, cm^{-1}): 3448(OH) 3118 (C-H Ar), 1678 (C=O), 1558 (C=N str), 1525 (C=C Ar), 1328 (C-N), 1268–1207(C–O–C str), 721(C-S) 672 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.11-7.87 (m, 7H, ArH), 7.53 (s, 1H, -CH thiazol), 7.28 (s, 1H, -NCHS), 3.93 (s, 2H, CH2), 3.38 (s, 3H, –OCH_3).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(4-fluorophenyl)thiazolidin-4-one (14) IR (KBr, cm^{-1}): 3178 (C-H Ar), 1673 (C=N str), 1590 (C=C Ar), 1327 (C-N), 1269 (C–F), 722(C-S) 667 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.57-7.22 (m, 8H, ArH), 7.06 (s, 1H, -CH thiazol), 7.03 (s, 1H, -NCHS), 3.60 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(4-chlorophenyl)thiazolidin-4-one (15) IR (KBr, cm^{-1}): 3120 (C-H Ar), 1630 (C=O), 1585 (C=N str), 1532 (C=C Ar), 1332 (C-N), 727(C–Cl), 669(C-S) 587 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.50-9.14 (m, 8H, ArH), 6.97 (s, 1H, -CH thiazol), 6.94 (s, 1H, -NCHS), 3.78 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(2,4-dichlorophenyl)thiazolidin-4-one (16) IR (KBr, cm^{-1}): 3060 (C-H Ar), 1700 (C=O), 1599 (C=N str), 1525 (C=C Ar), 1392 (C-N), 749(C–Cl), 695(C-S) 652 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.44-7.27 (m, 7H, ArH), 7.16 (s, 1H, -CH thiazol), 6.13 (s, 1H, -NCHS), 3.38 (s, 2H, CH2).

2-(3-bromophenyl)-3-(4-(4-bromophenyl)thiazol-2-yl)thiazolidin-4-one (17): IR (KBr, cm^{-1}): 3077 (C-H Ar), 1688 (C=O), 1636 (C=N str), 1602 (C=C Ar), 1349 (C-N), 757(C-S) 693 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 9.34-7.30 (m, 8H, ArH), 6.92 (s, 1H, -CH thiazol), 6.72 (s, 1H, -NCHS), 3.47 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(3-fluorophenyl)thiazolidin-4-one (18) IR (KBr, cm^{-1}): 3036 (C-H Ar), 1673 (C=O), 1637 (C=N str), 1539 (C=C Ar), 1354 (C-N), 1239 (C–F), 695(C-S) 648 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.96-7.41 (m, 8H, ArH), 6.99 (s, 1H, -CH thiazol), 6.61 (s, 1H, -NCHS), 3.53 (s, 2H, CH2).

3-(4-(4-bromophenyl)thiazol-2-yl)-2-(2-methoxyphenyl)thiazolidin-4-one (19) IR (KBr, cm^{-1}): 3200 (C-H Ar), 1699 (C=O), 1628 (C=N str), 1583 (C=C Ar), 1294(C–O–C str), 695(C-S) 630 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.50-7.11 (m, 8H, ArH), 6.86 (s, 1H, -CH thiazol), 6.74 (s, 1H, -NCHS), 2.50 (s, 3H, –OCH_3).

2-(2-bromophenyl)-3-(4-(4-bromophenyl)thiazol-2-yl)thiazolidin-4-one (20) IR (KBr, cm^{-1}): 3032 (C-H Ar), 1739 (C=O), 1664 (C=N str), 1637 (C=C Ar), 1365 (C-N), 701(C-S) 623 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.00-7.45 (m, 8H, ArH), 6.98 (s, 1H, -CH thiazol), 6.73 (s, 1H, -NCHS), 3.55 (s, 2H, CH2).

Antimicrobial assay: Determination of Minimum Inhibitory Concentrations (MIC). The antimicrobial activity of synthesized compounds was performed against Gram-positive bacteria: Staphylococcus aureus Microbial Type Culture Collection (MTCC) 3160, Bacillus subtilis MTCC 441, Gram-negative bacterium: Escherichia coli MTCC 443 and fungal strains: Candida albicans MTCC 227 and Aspergillus niger MTCC 281 using tube dilution method. Dilutions of test and standard compounds were prepared in double strength nutrient broth – I.P. (bacteria) or Sabouraud dextrose broth I.P. (fungi). The samples were incubated at 37 ^{0}C for 24 h (bacteria), at 25 ^{0}C for 7 d (A. niger) and at

37 ^{0}C for 48 h (C. albicans) and the results were recorded in terms of MIC(Cappucino, 1999 and Indian Pharmacopoeia, 1996)

Anticancer Evaluation

The anticancer activity of synthesized (Z)-N-(5-(benzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide derivatives were determined against HeLa Cervical cancer cell Line. Cancer cell line was purchased from the American Type Culture Collection (ATCC), Manassas, VA, USA. Cell line was cultured in RPMI 1640 (Sigma) supplemented with 10% heat inactivated fetal bovine serum (FBS) (PAA Laboratories) and 1% penicillin/streptomycin (PAA Laboratories). Culture was maintained in a humidified incubator at 37 °C in an atmosphere of 5% CO_2. Cytotoxicity of synthesized compounds at various concentrations was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) (Sigma) assay, as described by Mosmann, 1983 but with minor modification, following 72 h of incubation. Assay plates were read using a spectrophotometer at 520 nm. Data generated were used to plot a doseresponse curve of which the concentration of test compounds required to kill 50% of cell population (IC50) was determined. Anticancer activity was expressed as the mean IC_{50} of three independent experiments(Mosmann, 1983)

Table 2. In Vitro Antimicrobial Activity of the Title Compounds (**1-20)**

Compound	Minimum inhibitory concentration (µg ml^{-1})				
	Bacterial Strains			Fungal Strains	
	E. coli	S. aureus	B. subtilis	C. albicans	A. Niger
1	3.12	12.5	25	50	25
2	3.12	12.5	3.12	6.25	25
3	12.5	3.12	6.25	12.5	12.5
4	3.12	3.12	**1.56**	50	25
5	3.12	12.5	3.12	6.25	25
6	12.5	12.5	6.25	12.5	12.5
7	3.12	12.5	25	50	25
8	12.5	25	50	12.5	12.5
9	**1.56**	**1.56**	6.25	6.25	25
10	12.5	12.5	6.25	12.5	12.5
11	3.12	12.5	25	50	25
12	3.12	12.5	3.12	6.25	25
13	12.5	12.5	6.25	12.5	12.5
14	12.5	25	12.5	50	25
15	6.25	3.12	3.12	**1.56**	**3.12**
16	25	25	25	25	12.5
17	3.12	12.5	25	50	25
18	3.12	12.5	3.12	6.25	25
19	12.5	12.5	6.25	12.5	12.5
20	12.5	25	12.5	50	25
Ciprofloxacin (standard drug)	0.01	0.15	0.12	---	--

Clotrimazole (standard drug)	--	--	--	0.10	0.30

Table 3: Anticancer activity of titled compounds (PT1-PT20)

Compounds	**HeLa Cervical Cell Line** **IC_{50}(µM)**
1	188.30
2	96.83
3	78.07
4	254.69
5	382.89
6	453.30
7	233.89
8	84.37
9	**15.56**
10	93.37
11	75.70
12	134.65
13	211.79
14	207.56
15	180.67
16	48.75
17	325.95
18	250.72
19	290.81
20	**32.20**
Doxorubicin (Standard drug)	**16.12**

Results and Discussion

Thiazole derivatives clubbed with thiazolidinone (**1-20**) were synthesized using the synthetic procedure given in Scheme 1. The synthesized compounds were characterized by physicochemical as well as spectral means. Physicochemical properties of the synthesized compounds are presented in Table 1.

Antimicrobial activity

The antimicrobial activity results (Table 2) indicated that the synthesized compounds were having good antimicrobial activity and compound **2** (MIC = 1.56 µg/ml, Table 2) was the most potent antibacterial agent against B. subtilis. Compound **9** was found to be most active against E. coli (MIC = 1.56µg/ml) and S. aureus(MIC = 1.56µg/ml). In the case of antifungal activity against C. albicans, and A. niger, compound **15** (MIC = 1.56 µg/ml, MIC = 3.12 µg/ml) was found most effective among the synthesized series. All the above mentioned compounds having comparable antimicrobial potential to standard drugs ciprofloxacin and Clotrimazole.

Anticancer activity

Anticancer activity results (Table 3) indicated that besides having good antimicrobial activity, the synthesized compounds were also having good anticancer activity against cervicalcancer cell line and compounds **9**(IC_{50} = 15.56 µM) and **15** (IC_{50} = 32.20 µM) were found to be most potent anticancer agents compared to the standard drug Doxorubicin (IC_{50} =16.12 µM).

Conclusion

A series of thiazole derivatives (**1–20**) was synthesized and tested in vitro for its antimicrobial and anticancer potentials. In general, the synthesized compounds were found to be potent antimicrobial agents than anticancer agents. Anticancer screening results indicated that compounds **9**(IC_{50} = 15.56 µM) and **15** (IC_{50} = 32.20 µM) were the most active anticancer agents and Antimicrobial activity results indicated that compound 2, 9 and 15 were the most active antibacterial and antifungal agents and may serve as important lead for the discovery of novel antimicrobial agents.

References:

1. Ahangar N et al., (2011) 1-[(2-arylthiazol-4-yl) methyl] azoles as a new class of anticonvulsants: design, synthesis, in vivo screening, and in silico drug-like properties. Chem. Biol. Drug Des. 78(5): 844–852.
2. Ayati A, Emami S, Moghimi S, Foroumadi A. Thiazole in the targeted anticancer drug discovery. Future Med Chem. 2019 Aug;11(15):1929-1952.
3. Bondock S, et al., (2013) Synthesis of some new 2-(3-pyridyl)-4,5-disubstituted thiazoles as potent antimicrobial agents. Eur. J. Med. Chem. 62: 270–279
4. Cappucino JG and Sherman N (1999). Microbiology – A Laboratory Manual, Addison Wesley, California, 263.
5. Deep A et al., (2015) Synthesis, Antimicrobial, Anticancer Evaluation of 2-(aryl)-4-thiazolidinone derivatives and their QSAR studies. Curr Topics Med Chem, 15: 990-1002.
6. Djukic M et al.(2018) In vitro antioxidant activity of thiazolidinone derivatives of 1,3-thiazole and 1,3,4-thiadiazole. Chem. Biol. Interact. 286: 119–131.
7. Goshain O and Ahmed B (2019) Antihypertensive activity, toxicity and molecular docking study of newly synthesized xanthon derivatives (xanthonoxypropanolamine). PLoS ONE 14: e0220920.
8. Indian Pharmacopoeia Commission (2007) Pharmacopoeia of India vol. I, Controller of Publications, Ministry of Health Department, Govt. of India, New Delhi. 37.
9. Lino CI et al. (2018) Synthesis, molecular modeling studies and evaluation of antifungal activity of a novel series of thiazole derivatives. Eur. J. Med. Chem. 151: 248–260.
10. Malukaite D et al., (2022) Synthesis of Novel Thiazole Derivatives Bearing β-Amino Acid and Aromatic Moieties as Promising Scaffolds for the Development of New Antibacterial and Antifungal Candidates Targeting Multidrug-Resistant Pathogens. Molecules 27: 74.
11. Mishra CB et al., (2015) Thiazole: a promising heterocycle for the development of potent CNS active agents. Eur. J. Med. Chem. 92: 1–34.
12. Mosmann T (1983) Colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays J. Immunol. Methods, 65: 55-63
13. Osman H et al. (2018) New thiazolyl-coumarin hybrids: design, synthesis, characterization, x-ray crystal structure, antibacterial and antiviral evaluation. J. Mol. Struct. 1166: 147–154.
14. Othman IMM et al., (2022) Synthesis and biological evaluation of new derivatives of thieno-thiazole and dihydrothiazolothiazole scaffolds integrated with a pyrazoline nucleus as anticancer and multi-targeting kinase inhibitors. RSC Adv 12: 561
15. Sharma D et al., (2019) 4-(4-Bromophenyl)-thiazol-2-amine derivatives: synthesis, biological activity and molecular docking study with ADME profile. BMC Chemistry 13:60.
16. Sharma PC et al., (2020) Thiazole-containing compounds as therapeutic targets for cancer therapy. Eur. J. Med. Chem. 188 :112016
17. Sharma RN et al., (2009) Synthesis of 4-benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: an analogue-based drug design approach. J. Enzyme Inhib. Med. Chem. 24(3): 890–897.
18. Yin L et al., (2021) Design and development of novel thiazolesulfonamide derivatives as a protective agent against diabetic cataract in Wistar rats via inhibition of aldose reductase. Heterocyclic Communications 27: 63–70.