Original Article

Design, Synthesis, Antimicrobial And Anticancer Evaluation Of Thiazole Clubbed With 4-Thiazolidinone Derivatives

Tanuja[1]*, Harneet Singh[2]

[1] Research Scholar, Department of Pharmaceutical Sciences, Glocal University, Mirzapur Pole, Sharanpur, U.P, India, 247001.
Email: tanu88.pharma@gmail.com (Corresponding Author)

[2] Supervisor, Department of Pharmaceutical Sciences, Glocal University, Mirzapur Pole, Sharanpur, U.P, India, 247001.

DOI: 10.47750/pnr.2022.13.S09.423

Abstract

Twenty derivative of thiazole have been synthesized from 4-(4-bromophenyl)-thiazol-2-amine. Synthesized derivatives were characterized by analysis, 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. Most of the compounds exhibited moderate to significant activities.

Introduction:

In the clinical world, consideration of retardation of pathogenic bacteria towards the available antibiotic was becoming a major worldwide problem as many bacterial pathogens have already established resistance against them. Therefore, there could be the appearance of increasing in the mortality rate for gram-positive and/or gram-negative bacterial diseases. It is mainly due to the over-growth in population and extreme modernization for comfort. Hence, the rapid development of microbial resistance leads to discovering a new effective antimicrobial drug agent, which can reduce the bacterial mortality rate. To set up a revolutionary change in the failure of synthesizing selective antibacterial drugs, researchers have been endeavored by a lot of eminent expertise from last few decades. To achieve a new effective scaffold for an efficient fight against bacterial viruses is required (Mohanty et al., 2022).

Malignant disease is widely prevalent and considered to be the major challenges of this century, which concerns the medical community all over the world. Cancer has sustained cellular proliferative capacity. Although the mechanism of initiation and progression of cancer has been well established, the successful treatment of cancer remains a huge challenge facing the lack of early detection, undefined tumor cell dormancy status, and metastatic properties of malignant tumor. The development of anticancer drug resistance, which leads to the failure of most chemotherapeutic anticancer treatments, is significantly restricted the clinical efficacy of the most commonly prescribed anticancer drug. Consequently, there is an urgent need for the implementation of efficient prevention and treatment strategies to curb cancer deaths. Investigating small molecule antitumor agents, which could decrease drug resistance and reduce unpleasant side effect is more desirable (Alizadeh and Hashemi, 2021)

Heterocyclic compounds have been widely explored in natural products and medicinal chemistry as biologically active scaffolds with significant pharmacological impacts. Among heterocyclic compounds, thiazole-based

heterocycles have demonstrated a wide range of biological activities and are considered the most common class of heterocycles frequently utilized in drug design and synthetic chemistry (Salem et al., 2022). Thiazoles found in many powerful biologically active drugs such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) and Tiazofurin (antineoplastic drug) (Hussein and Zitouni, 2018). Thus, thiazole moiety if it is present in any compound will show numerous biological activities such as 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.

Based upon the above facts, we described the synthesis of certain novel substituted thiazole derivatives clubbed with thiazolidinone and evaluated their biological potential as anticancer and antimicrobial activity.

MATERIALS AND METHODS:

Melting points deliberate in capillary tubes with the help of Sonar melting point equipment and are uncorrected. IR spectra were obtained using FTIR Bruker ATR instrument (cm^{-1}). With the help of Bruker DRX-300 FTNMR instrument, ^{1}H NMR spectrums in DMSO-d_6 were recorded to use a tetramethylsilane reference. TLC using silica gel G in the particular solvent-based ethyl acetate: benzene (6:4, v/v) with iodine vapours as a detecting agent was used to determine the purity of the produced compounds.

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 was yield thiazoles clubbed with 4-thiazolidinones. In the next step, thiazoles clubbed with 4-thiazolidinones was reacted with different substituted aldehydes yielded the title compounds (**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

N-(substituted benzylidene)-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).

(Z)-5-(substituted benzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one(1-20):

A mixture of (0.01 M) 3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (1-20) required aromatic aldehydes (0.01 M) and anhydrous sodium acetate in glacial acetic acid (20 ml) and refluxed for 5–7 h. After cooling, the solution was poured on crushed ice to precipitate the product. The product was recrystallized from rectified spirit (Deep et al., 2015).

Synthetic pathway for formation of title compounds is presented in Scheme 1.

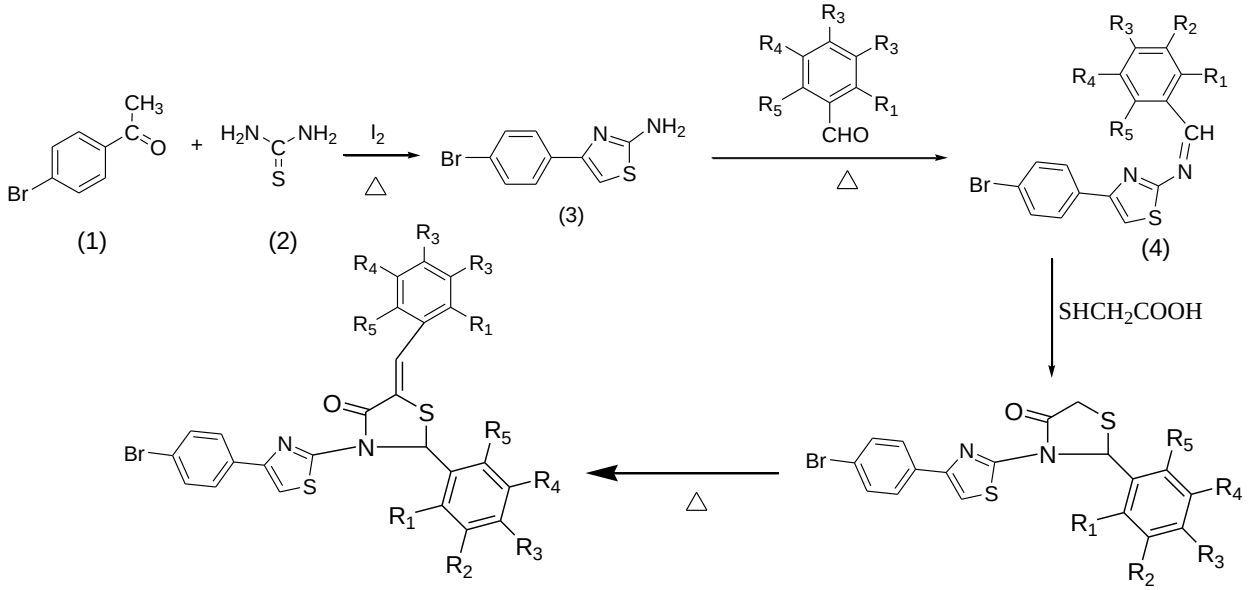

Table 1: Physical data of Thiazole derivatives (1-20)

Table-1 Physical data of Thiazole derivatives

Comp.	M. Formula	X	X'	M. Pt. (^oC)	M. Wt.	R_f value*	% yield
1	**$C_{25}H_{17}BrN_2OS_2$**	Benzaldehyde	Benzaldehyde	225-227	**505.45**	0.68	84
2	**$C_{25}H_{16}BrClN_2OS_2$**	Benzaldehyde	2-chloro benzaldehyde	199-201	**539.89**	0.72	76
3	**$C_{25}H_{17}BrN_2O_2S_2$**	Benzaldehyde	2-hydroxy benzaldehyde	233-235	**521.45**	0.67	75
4	**$C_{25}H_{16}BrN_3O_3S_2$**	Benzaldehyde	3-nitro benzaldehyde	176-178	**550.45**	0.75	68

5	**$C_{28}H_{23}BrN_2O_4S_2$**	Benzaldehyde	3,4,5-methoxy benzaldehyde	171-173	**595.53**	0.63	71
6	**$C_{26}H_{19}BrN_2O_2S_2$**	Benzaldehyde	3-methoxy benzaldehyde	152-154	**535.48**	0.78	59
7	**$C_{25}H_{16}Br_2N_2OS_2$**	Benzaldehyde	4-bromo benzaldehyde	191-193	**584.35**	0.65	82
8	**$C_{27}H_{22}BrN_3OS_2$**	Benzaldehyde	4-dimethyl amino benzaldehyde	185-187	**548.52**	0.71	79
9	**$C_{25}H_{16}BrN_3O_3S_2$**	Benzaldehyde	4-nitro benzaldehyde	183-185	**550.45**	0.75	72
10	**$C_{25}H_{16}BrClN_2OS_2$**	Benzaldehyde	3-chloro benzaldehyde	169-171	**539.89**	0.69	69
11	**$C_{26}H_{19}BrN_2OS_2$**	Benzaldehyde	4-methyl benzaldehyde	182-184	**519.48**	0.63	62
12	**$C_{29}H_{26}BrN_3OS_2$**	Benzaldehyde	4-diethylamino benzaldehyde	203-205	**576.57**	0.64	74
13	**C26H19BrN2O3S2**	Benzaldehyde	4-hydroxy-3-methoxy benzaldehyde	188-190	**551.47**	0.69	68
14	**$C_{25}H_{16}BrFN_2OS_2$**	Benzaldehyde	4-fluorobenzaldehyde	200-202	**523.44**	0.78	83
15	**$C_{25}H_{16}BrClN_2OS_2$**	Benzaldehyde	4-chloro benzaldehyde	194-196	**539.89**	0.65	65
16	**$C_{25}H_{15}BrCl_2N_2OS_2$**	Benzaldehyde	2,4-dichloro benzaldehyde	175-177	**574.34**	0.81	61
17	**$C_{25}H_{16}Br_2N_2OS_2$**	Benzaldehyde	3-bromo benzaldehyde	222-224	**584.35**	0.83	76
18	**$C_{25}H_{16}BrFN_2OS_2$**	Benzaldehyde	3-fluorobenzaldehyde	188-190	**523.44**	0.67	64
19	**$C_{26}H_{19}BrN_2O_2S_2$**	Benzaldehyde	2-methoxy benzaldehyde	177-179	**535.48**	0.72	60
20	**$C_{25}H_{16}Br_2N_2OS_2$**	Benzaldehyde	2-bromo benzaldehyde	215-217	572.33	0.66	63

Solvent system: *Benzene

Spectral data:

(Z)-5-benzylidene-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (1) IR (KBr, cm^{-1}): 3008 (C-H Ar), 1740 (C=O), 1644 (C=N str), 1626 (C=C Ar), 1373 (C-N), 696(C-S) 666 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.69-7.22 (m, 14H, ArH), 7.11 (s, 1H, C=CH), 6.65 (s, 1H, -CH thiazol), 6.02 (s, 1H, -NCHS), 4.79 (s, 2H, CH2).

(Z)-5-(2-chlorobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (2) IR (KBr, cm^{-1}): 2996 (C-H Ar), 1705 (C=O), 1658 (C=N str), 1613 (C=C Ar), 1374 (C-N), 743(C–Cl), 680(C-S) 657 (Br); ^{1}H NMR

(DMSO-d6, 400 MHz): 8.90-8.10 (m, 13H, ArH), 7.76 (s, 1H, C=CH), 7.24 (s, 1H, -CH thiazol), 6.88 (s, 1H, -NCHS), 3.81 (s, 2H, CH2).

(Z)-5-(2-hydroxybenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (3) IR (KBr, cm^{-1}): 3608 (OH), 3026 (C-H Ar), 1740 (C=O), 1690 (C=N str), 1633 (C=C Ar), 1344 (C-N), 699(C-S) 648 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.92-7.96 (m, 13H, ArH), 7.47 (s, 1H, C=CH), 7.15 (s, 1H, -CH thiazol), 7.04 (s, 1H, -OH), 7.01 (s, 1H, -NCHS), 3.87 (s, 2H, CH2).

(Z)-5-(3-nitrobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (4) IR (KBr, cm^{-1}): 2946 (C-H Ar), 1741 (C=O), 1692 (C=N str), 1639 (C=C Ar), 1517 (N–O str, NO2), 1342 (C-N), 692(C-S) 646 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.12-7.78 (m, 13H, ArH), 7.63 (s, 1H, C=CH), 7.29 (s, 1H, -CH thiazol), 7.23 (s, 1H, -NCHS), 3.48 (s, 2H, CH2).

(Z)-5-(3,4,5-trimethoxybenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (5) IR (KBr, cm^{-1}): 3005 (C-H Ar), 1653 (C=N str), 1610 (C=C Ar), 1374 (C-N), 1259–1206(C–O–C str), 679(C-S) 643(Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.44-7.90 (m, 11H, ArH), 7.74 (s, 1H, C=CH), 7.56 (s, 1H, -CH thiazol), 7.47 (s, 1H, -NCHS), 4.81 (s, 2H, CH2), 4.12 (s, 9H, –OCH_3).

(Z)-5-(3-methoxybenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (6) IR (KBr, cm^{-1}): 3012 (C-H Ar), 1740 (C=O), 1652 (C=N str), 1618 (C=C Ar), 1368 (C-N), 1260–1239(C–O–C str), 689(C-S) 639 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.16-7.08 (m, 13H, ArH), 7.05 (s, 1H, C=CH), 6.65 (s, 1H, -CH thiazol), 6.51 (s, 1H, -NCHS), 3.48 (s, 2H, CH2), 3.30 (s, 3H, –OCH_3).

5-(4-bromophenyl)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (7) IR (KBr, cm^{-1}): 2973 (C-H Ar), 1700 (C=O), 1650 (C=N str), 1614 (C=C Ar), 1375 (C-N), 683(C-S) 665 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.68-7.64 (m, 13H, ArH), 7.48 (s, 1H, C=CH), 6.70 (s, 1H, -CH thiazol), 6.67 (s, 1H, -NCHS), 4.43 (s, 2H, CH2).

(Z)-5-(4-(dimethylamino)benzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (8) IR (KBr, cm^{-1}): 3006 (C-H Ar), 2897 (C-H str., -CH3), 1714 (C=O), 1662 (C=N str), 1617 (C=C Ar), 1377 (C-N), 681(C-S) 646 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.65-7.93 (m, 13H, ArH), 7.65 (s, 1H, C=CH), 7.62 (s, 1H, -CH thiazol), 7.27 (s, 1H, -NCHS), 3.32 (s, 2H, CH2), 2.50 (s, 6H, N $(CH3)_2$).

(Z)-5-(4-nitrobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (9) IR (KBr, cm^{-1}): 2990 (C-H Ar), 1659 (C=N str), 1620 (C=C Ar), 1550 (N–O str, NO2), 1339 (C-N), 680(C-S) 647 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.99-7.42 (m, 13H, ArH), 7.40 (s, 1H, C=CH), 7.02 (s, 1H, -CH thiazol), 6.50 (s, 1H, -NCHS), 4.12 (s, 2H, CH2).

(Z)-5-(3-chlorobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (10) IR (KBr, cm^{-1}): 3049 (C-H Ar), 1595 (C=C Ar), 1453 (C-N), 775(C–Cl), 682(C-S) 646 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.67-7.32 (m, 13H, ArH), 7.23 (s, 1H, C=CH), 6.97 (s, 1H, -CH thiazol), 6.76 (s, 1H, -NCHS), 3.89 (s, 2H, CH2).

(Z)-5-(4-methylbenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (11) IR (KBr, cm^{-1}): 3032 (C-H Ar), 2838 (C-H str., -CH3), 1711 (C=O), 1659 (C=N str), 1559 (C=C Ar), 1377 (C-N), 681(C-S) 653 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.63-7.23 (m, 13H, ArH), 7.13 (s, 1H, C=CH), 6.85 (s, 1H, -CH thiazol), 6.51 (s, 1H, -NCHS), 4.63 (s, 2H, CH2), 2.90 (s, 3H, N-CH_3).

(Z)-5-(4-(diethylamino)benzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (12) IR (KBr, cm^{-1}): 3028 (C-H Ar), 2963(-CH_2CH3), 1685 (C=O), 1633 (C=N str), 1604 (C=C Ar), 1346 (C-N), 692(C-S)

663 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.93-7.37 (m, 13H, ArH), 7.29 (s, 1H, C=CH), 7.22 (s, 1H, -CH thiazol), 6.94 (s, 1H, -NCHS), 3.31(m, 6H, CH_3), 2.50(m, 4H, CH_2).

(Z)-5-(4-hydroxy-3-methoxybenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (13) IR (KBr, cm^{-1}): 3749(OH), 3051 (C-H Ar), 1681 (C=O), 1632 (C=N str), 1603 (C=C Ar), 1348 (C-N), 1256–1216(C–O–C str), 695(C-S) 646 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.45-7.59 (m, 12H, ArH), 7.56 (s, 1H, C=CH), 6.72 (s, 1H, -CH thiazol), 6.69 (s, 1H, -NCHS), 3.43 (s, 2H, CH2), 3.41 (s, 3H, –OCH_3).

(**Z)-5-(4-fluorobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one** (14) IR (KBr, cm^{-1}): 3030 (C-H Ar), 1602 (C=N str), 1506 (C=C Ar), 1368 (C-N), 1249 (C–F), 713(C-S) 627 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.13-7.29 (m, 13H, ArH), 7.25 (s, 1H, C=CH), 6.49 (s, 1H, -CH thiazol), 6.44 (s, 1H, -NCHS), 4.45 (s, 2H, CH2).

(Z)-5-(4-chlorobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (15) IR (KBr, cm^{-1}): 3079 (C-H Ar), 1641 (C=N str), 1578 (C=C Ar), 1324 (C-N), 714(C–Cl), 697(C-S) 672 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.92-7.33 (m, 13H, ArH), 7.00 (s, 1H, C=CH), 6.95 (s, 1H, -CH thiazol), 6.82 (s, 1H, -NCHS), 4.65 (s, 2H, CH2).

(Z)-5-(2,4-dichlorobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (16) IR (KBr, cm^{-1}): 3011 (C-H Ar), 1672 (C=O), 1634 (C=N str), 1602 (C=C Ar), 1368 (C-N), 733(C–Cl), 686(C-S) 634 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.93-7.27 (m, 12H, ArH), 7.25 (s, 1H, C=CH), 7.22 (s, 1H, -CH thiazol), 6.96 (s, 1H, -NCHS), 3.41 (s, 2H, CH2).

(Z)-5-(3-bromobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (17) IR (KBr, cm^{-1}): 3024 (C-H Ar), 1689 (C=O), 1634 (C=N str), 1352 (C-N), 707(C-S) 637 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.38-7.14 (m, 13H, ArH), 7.11 (s, 1H, C=CH), 6.74 (s, 1H, -CH thiazol), 6.62 (s, 1H, -NCHS), 4.13 (s, 2H, CH2).

(Z)-5-(3-fluorobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (18) IR (KBr, cm^{-1}): 3067 (C-H Ar), 1672 (C=O), 1638 (C=N str), 1602 (C=C Ar), 1378 (C-N), 1238 (C–F), 709(C-S) 619 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 7.67-7.39 (m, 13H, ArH), 7.13 (s, 1H, C=CH), 7.12 (s, 1H, -CH thiazol), 6.84 (s, 1H, -NCHS), 4.61 (s, 2H, CH2).

(Z)-5-(2-methoxybenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (19) IR (KBr, cm^{-1}): 3004 (C-H Ar), 1685 (C=O), 1634 (C=N str), 1609 (C=C Ar), 1378 (C-N), 1322(C–O–C str), 688(C-S) 667 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.39-7.62 (m, 13H, ArH), 7.51 (s, 1H, C=CH), 7.04 (s, 1H, -CH thiazol), 6.98 (s, 1H, -NCHS), 4.31 (s, 2H, CH2), 2.59 (s, 3H, –OCH_3).

(Z)-5-(2-bromobenzylidene)-3-(4-(4-bromophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (20) IR (KBr, cm^{-1}): 3053 (C-H Ar), 1636 (C=N str), 1599 (C=C Ar), 1351 (C-N), 711(C-S) 649 (Br); ^{1}H NMR (DMSO-d6, 400 MHz): 8.10-7.73 (m, 13H, ArH), 7.65 (s, 1H, C=CH), 7.17 (s, 1H, -CH thiazol), 6.77 (s, 1H, -NCHS), 3.31 (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	12.5	12.5	12.5	50	50
2	**1.56**	12.5	**1.56**	25	25
3	12.5	12.5	12.5	12.5	12.5
4	50	50	3.12	50	25
5	25	12.5	3.12	6.25	25
6	12.5	12.5	6.25	12.5	12.5
7	50	50	25	50	25
8	12.5	25	50	12.5	12.5
9	12.5	12.5	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	25	25	12.5	12.5
16	12.5	**1.56**	25	25	12.5
17	12.5	12.5	6.25	12.5	25
18	25	12.5	25	3.12	25
19	12.5	12.5	6.25	**1.56**	**3.12**
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	200.50
2	168.23
3	**78.07**
4	254.69
5	171.45
6	106.25
7	175.45
8	138.76
9	435.56
10	293.37
11	275.70
12	234.65
13	**45.89**
14	227.67
15	238.55
16	**65.19**
17	107.27
18	159.32
19	194.21
20	182.23
Doxorubicin (Standard drug)	**16.12**

Results and Discussion

Thiazole derivatives **(1-20)** were synthesized according to synthetic procedure described in Scheme 1. The structure of synthesized compounds was confirmed by NMR and IR spectroscopy which were in full agreement with assigned molecular structures. The physicochemical properties of synthesized compounds are given in Table 1.

Antimicrobial activity

The antimicrobial activity of the synthesized compounds was carried out using the tube dilution method (Cappuccino and Sherman, 1999) and results indicated that none of the synthesized compounds was found to be better antimicrobial agent than standard drugs, ciprofloxacin and clotrimazole (Table 2). The antimicrobial activity results of the synthesized compounds indicated that compound **2** was found to be the most potent antimicrobial agent against B. subtilis (MIC = 1.56 µg/ml) and E.coli (MIC = 1.56 µg/ml). In case of S. aureus compound **16** (MIC = 1.56 µg/ml) was found to be most potent antimicrobial agent. In case of fugal strain against A. niger, C. albicans compound **19** (MIC = 3.12 µg/ml and MIC = 1.56 µg/ml) was found to be most potent antifungal agent as compared to the standard drugs.

Anticancer activity

The in vitro anticancer activity of the synthesized compounds was determined against Cervical cancer cell line using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay (Mosmann, 1983) and the results are presented in Table 3. In general, the synthesized compounds showed average anticancer activity as none of the synthesized compounds displayed better anticancer potential than standard drug Doxorubicin (IC_{50} = 16.12 µM) and compounds **3**, (IC_{50} =78.07µM) **13**, (IC_{50} =45.89 µM) and **16**(IC_{50} =65.19 µM) showed good anticancer potential as compared to standard drug Doxorubicin (IC_{50} =16.12 µM). Compound **13** (IC_{50} =45.89 µM) was found to be the most potent anticancer agent.

Conclusion

A series of thiazole (1-20) derivatives was synthesized and evaluated for its in vitro antimicrobial and anticancer activities. Antimicrobial activity results revealed the synthesized compounds displayed average antimicrobial and anticancer potentials and compounds **2, 16** and **19** were found to be most potent antimicrobial and in case of anticancer activity compound 3 were found be most active compound against the cervical cancer cell line.

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. Alizadeh SR and Hashemi SM (2021) Development and therapeutic potential of 2-aminothiazole derivatives in anticancer drug discovery. Medicinal Chemistry Research 30:771–806.
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. Hussein W and Zitouni GT (2018) Synthesis of new thiazole and thiazolyl derivatives of medicinal significant-a short review. MOJ Biorg Org Chem. 2(2):52–55.
9. Indian Pharmacopoeia Commission (2007) Pharmacopoeia of India vol. I, Controller of Publications, Ministry of Health Department, Govt. of India, New Delhi. 37.
10. 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.
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. Mohanty P et al., (2022) Antibacterial Activity of Thiazole and its Derivatives: A Review. Biointerface Research in applied chemistry. 12(2): 2171 – 2195
13. Mosmann T (1983) Colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays J. Immunol. Methods, 65: 55-63
14. 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.
15. Salem MG et al., (2022) Novel 1,3-Thiazole Analogues with Potent Activity against Breast Cancer: A esign, Synthesis, In Vitro, and In Silico Study. Molecules 27:4898.
16. 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.
17. Sharma PC et al., (2020) Thiazole-containing compounds as therapeutic targets for cancer therapy. Eur. J. Med. Chem. 188 :112016
18. 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.
19. 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.