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Original article

Synthesis and biological evaluation of thiazoline derivatives as new antimicrobial and anticancer agents

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ABSTRACT

N′-(3,4-Diarylthiazol-2(3*H*)-ylidene)-2-(arylthio)acetohydrazides were synthesized and evaluated for their antimicrobial activity and cytotoxicity against NIH/3T3 cells. Compound **22** bearing 1-phenyl-1*H*-tetrazole and *p*-chlorophenyl moieties was found to be the most promising antibacterial agent against *Pseudomonas aeruginosa*, whereas compound **23** bearing 1-phenyl-1*H*-tetrazole and *p*-bromophenyl moieties was the most promising antifungal agent against *Candida albicans*. The most effective derivatives were also evaluated for their cytotoxicity against C6 glioma cells. The results indicated that compound **17** bearing 1-phenyl-1*H*-tetrazole and nonsubstituted phenyl moieties (IC_{50} = 8.3 ± 2.6 μg/mL) was more effective than cisplatin (IC_{50} = 13.7 ± 1.2 μg/mL) against C6 glioma cells. Compound **17** also exhibited DNA synthesis inhibitory activity on C6 cells. Furthermore, compound **17** showed low toxicity to NIH/3T3 cells (IC_{50} = 416.7 ± 28.9 μg/mL).

1. Introduction

Infectious diseases caused by bacteria and fungi have emerged as important causes of morbidity and mortality worldwide due to their ability to thwart therapeutic regimens by rapidly evolving resistance to antimicrobial agents [1–6].

Eukaryotic pathogens such as fungi pose a particular therapeutic challenge since they share a close evolutionary relationship with their human hosts, limiting the number of drug targets that can be exploited to selectively kill the pathogen [6]. The treatment of fungal infections, particularly those caused by drug-resistant fungal pathogens is often complicated by high toxicity, low tolerability, or narrow spectrum of activity [3–7].

In the last few decades, the greatly increased incidence of life-threatening bacterial and fungal infections has resulted in a corresponding increase in demand for new effective antimicrobial agents which inhibit the growth of pathogens or kill them and have no or least toxicity to host cells [1–8].

Thiazoles are found in many biologically active compounds, including natural products and pharmaceutical agents [9,10]. The reduced forms of thiazoles, thiazolines, have attracted a great deal of interest as privileged scaffolds due to their synthetic and biological importance. Compounds bearing thiazoline moiety have been reported to exhibit a wide spectrum of biological effects including antimicrobial activity [11–18]. In addition, hydrazides–hydrazones have received considerable attention as important pharmacophores in medicinal chemistry [19,20]. Isoniazid, which possesses a hydrazide moiety in its molecular structure, is the frontline drug employed in the treatment of tuberculosis [21]. Nifuroxazide, which is a nitrofuran antibacterial agent bearing a hydrazone moiety, is widely used as an intestinal antiseptic. Many studies have also confirmed that hydrazone derivatives of isoniazid and other hydrazides exhibit significant antimicrobial activity [19–26].

1-Substituted-1*H*-tetrazole-5-thiol and 5-methyl-1,3,4-thiadiazole-2-thiol have gained great importance in the synthesis of pharmacologically active drugs. Some synthetic β-lactam antibiotics possess 5-thio-1-methyl-1*H*-tetrazole (MTT) or thio-linked thiadiazole as the side chain [10,27].

Triazole antifungal agents, play a leading role in the treatment of systemic fungal infections due to their broad spectrum and improved safety profile. Fluconazole, itraconazole, voriconazole, and posaconazole are widely used antifungal drugs bearing triazole ring for the treatment of systemic fungal infections [28,29].

Medicinal chemists have also carried out considerable research for novel antimicrobial agents bearing a pyrimidine moiety.

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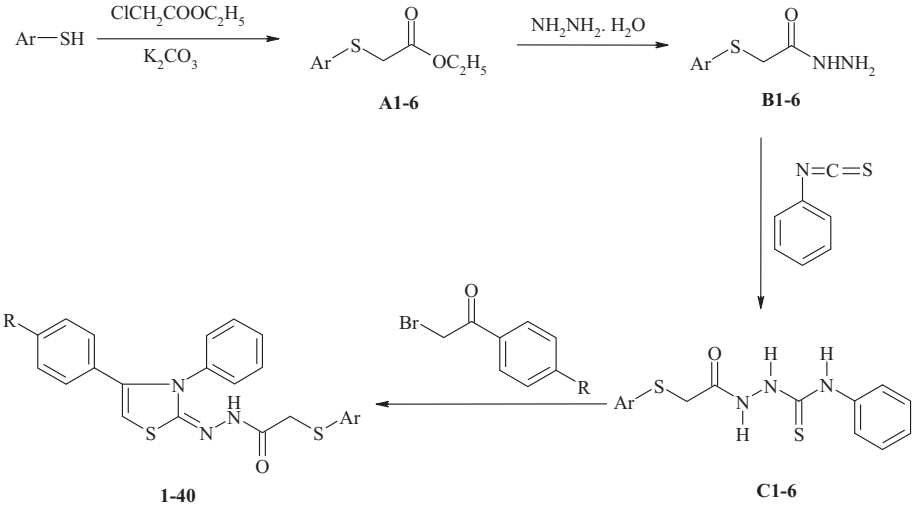

Scheme 1. The synthetic route for the preparation of the target compounds (**1**–**40**).

Trimethoprim and sulfadiazine are chemotherapeutic drugs containing a pyrimidine moiety currently used in the treatment of infectious diseases [10,30].

On the basis of these findings, herein we reported the synthesis of a series of thiazoline derivatives bearing a hydrazone moiety and focused on their potential antimicrobial effects and cytotoxicity. Thio-linked triazole, tetrazole, thiadiazole and pyrimidine were preferred as the side chain while designing the molecules. Furthermore, all compounds were evaluated for their cytotoxic effects against NIH/3T3 cell lines. The most effective antimicrobial derivatives were also

Table 1
Some properties of the compounds (**1**–**40**).

Compound	R	Ar	Yield (%)	M.p. (°C)	Molecular formula	Molecular weight
1	H	4-Methyl-4*H*-1,2,4-triazol-3-yl	70	123–126	$C_{20}H_{18}N_6OS_2$	422
2	NO_2	4-Methyl-4*H*-1,2,4-triazol-3-yl	80	100–103	$C_{20}H_{17}N_7O_3S_2$	467
3	CH_3	4-Methyl-4*H*-1,2,4-triazol-3-yl	70	109–112	$C_{21}H_{20}N_6OS_2$	436
4	OCH_3	4-Methyl-4*H*-1,2,4-triazol-3-yl	71	148–151	$C_{21}H_{20}N_6O_2S_2$	452
5	F	4-Methyl-4*H*-1,2,4-triazol-3-yl	72	167–169	$C_{20}H_{17}FN_6OS_2$	440
6	Cl	4-Methyl-4*H*-1,2,4-triazol-3-yl	75	260–262	$C_{20}H_{17}ClN_6OS_2$	456
7	Br	4-Methyl-4*H*-1,2,4-triazol-3-yl	76	260–263	$C_{20}H_{17}BrN_6OS_2$	501
8	CN	4-Methyl-4*H*-1,2,4-triazol-3-yl	81	246–247	$C_{21}H_{17}N_7OS_2$	447
9	H	1-Methyl-1*H*-tetrazol-5-yl	75	202–206	$C_{19}H_{17}N_7OS_2$	423
10	NO_2	1-Methyl-1*H*-tetrazol-5-yl	80	78–80	$C_{19}H_{16}N_8O_3S_2$	468
11	CH_3	1-Methyl-1*H*-tetrazol-5-yl	74	224–225	$C_{20}H_{19}N_7OS_2$	437
12	OCH_3	1-Methyl-1*H*-tetrazol-5-yl	72	124–125	$C_{20}H_{19}N_7O_2S_2$	453
13	F	1-Methyl-1*H*-tetrazol-5-yl	75	218–219	$C_{19}H_{16}FN_7OS_2$	441
14	Cl	1-Methyl-1*H*-tetrazol-5-yl	77	223–227	$C_{19}H_{16}ClN_7OS_2$	457
15	Br	1-Methyl-1*H*-tetrazol-5-yl	78	229–230	$C_{19}H_{16}BrN_7OS_2$	502
16	CN	1-Methyl-1*H*-tetrazol-5-yl	81	244–245	$C_{20}H_{16}N_8OS_2$	448
17	H	1-Phenyl-1*H*-tetrazol-5-yl	78	71–74	$C_{24}H_{19}N_7OS_2$	485
18	NO_2	1-Phenyl-1*H*-tetrazol-5-yl	85	235–237	$C_{24}H_{18}N_8O_3S_2$	530
19	CH_3	1-Phenyl-1*H*-tetrazol-5-yl	75	232–233	$C_{25}H_{21}N_7OS_2$	499
20	OCH_3	1-Phenyl-1*H*-tetrazol-5-yl	73	230–231	$C_{25}H_{21}N_7O_2S_2$	515
21	F	1-Phenyl-1*H*-tetrazol-5-yl	75	237	$C_{24}H_{18}FN_7OS_2$	503
22	Cl	1-Phenyl-1*H*-tetrazol-5-yl	83	246–248	$C_{24}H_{18}ClN_7OS_2$	519
23	Br	1-Phenyl-1*H*-tetrazol-5-yl	84	242–243	$C_{24}H_{18}BrN_7OS_2$	564
24	CN	1-Phenyl-1*H*-tetrazol-5-yl	86	233–234	$C_{25}H_{18}N_8OS_2$	510
25	H	5-Methyl-1,3,4-thiadiazol-2-yl	79	156–160	$C_{20}H_{17}N_5OS_3$	439
26	NO_2	5-Methyl-1,3,4-thiadiazol-2-yl	88	250–252	$C_{20}H_{16}N_6O_3S_3$	484
27	CH_3	5-Methyl-1,3,4-thiadiazol-2-yl	76	240–241	$C_{21}H_{19}N_5OS_3$	453
28	OCH_3	5-Methyl-1,3,4-thiadiazol-2-yl	75	248–249	$C_{21}H_{19}N_5O_2S_3$	469
29	F	5-Methyl-1,3,4-thiadiazol-2-yl	78	228–231	$C_{20}H_{16}FN_5OS_3$	457
30	Cl	5-Methyl-1,3,4-thiadiazol-2-yl	85	244–245	$C_{20}H_{16}ClN_5OS_3$	473
31	Br	5-Methyl-1,3,4-thiadiazol-2-yl	86	237–239	$C_{20}H_{16}BrN_5OS_3$	518
32	CN	5-Methyl-1,3,4-thiadiazol-2-yl	89	254–255	$C_{21}H_{16}N_6OS_3$	464
33	H	Pyrimidin-2-yl	80	77–78	$C_{21}H_{17}N_5OS_2$	419
34	NO_2	Pyrimidin-2-yl	89	260–263	$C_{21}H_{16}N_6O_3S_2$	464
35	CH_3	Pyrimidin-2-yl	77	84–87	$C_{22}H_{19}N_5OS_2$	433
36	OCH_3	Pyrimidin-2-yl	75	218–219	$C_{22}H_{19}N_5O_2S_2$	449
37	F	Pyrimidin-2-yl	79	241–242	$C_{21}H_{16}FN_5OS_2$	437
38	Cl	Pyrimidin-2-yl	87	247–248	$C_{21}H_{16}ClN_5OS_2$	453
39	Br	Pyrimidin-2-yl	88	245–246	$C_{21}H_{16}BrN_5OS_2$	498
40	CN	Pyrimidin-2-yl	90	256–258	$C_{22}H_{16}N_6OS_2$	444