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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

New thiazolidinedione-5-acetic acid amide derivatives: synthesis, characterization and investigation of antimicrobial and cytotoxic properties

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Abstract The present work describes the synthesis, antimicrobial and cytotoxic activity of 2,4-thiazolidinedione-5-acetic acid amides **3a–n**. The structures of the compounds were confirmed by IR, ^{1}H, ^{13}C NMR and elemental analysis. All compounds were tested for antimicrobial activity by twofold serial dilution technique. The preliminary results revealed that the compound **3d** exhibits promising antibacterial and antifungal activity. The cytotoxic (MTT) activity of 2,4-thiazolidinedione-5-acetic acid amides were tested in four tumour cell lines. We found that compound **3j** inhibited proliferation of HeLa, HT29, A549 and MCF-7 cell lines with IC_{50} values of 33, 35, 30 and 36 μM, respectively.

Keywords Thiazolidinedione · Antibacterial activity · Antifungal activity · Cytotoxic activity

Introduction

Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In addition, primary and opportunistic fungal infections continue to increase rapidly because of the increased number of immunocompromised patients. As known, not only biochemical similarity of human cell and fungi forms a handicap for selective activity, but also the easily gained resistance is the main problem encountered in developing safe and efficient antifungal. On the other hand, *Mycobacterium tuberculosis* remains a leading infectious cause of death in the world today. The incidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly to the HIV/AIDS pandemic, which greatly increase the risk of infection proceeding to overt disease (Grange and Zumla, 2002).

The 2,4-thiazolidinedione (TZD) moiety is extensively utilised as a carboxylic acid mimetic to improve the metabolic stability and therapeutic profile of bioactive agents (Boyd, 2007; Mclntyre *et al.*, 2007; Elte and Blickle, 2007). During recent years there has been a vast investigation on different classes of 2,4-thiazolidinediones, many of which were found to have an extensive spectrum of pharmacological activities such as antibacterial and antifungal (Ayhan-kilcigil and Atlantar, 2000; Heerding *et al.*, 2003; Tuncbilek and Atlantar, 2006; Bozdag-Dundar *et al.*, 2007), cardiotonic (Andreani *et al.*, 1993), anti-oedematus and analgesic (De-Lima *et al.*, 1994), cyclooxygenase and lipoxygenase inhibitory (Boschelli *et al.*, 1992), rosiglitazone and pioglitazones (TZD), lower plasma glucose levels by acting as ligands for the peroxisome proliferator-activated receptors (PPARs). In addition, this class of compounds have several other potentially beneficial effects including change in lipid profile, blood pressure lowering and anti-inflammatory effects (Kalaitzidis *et al.*, 2009). TZDs target vascular cells (Kurebayashi *et al.*, 2005), and monocytes/macrophages (Jiang *et al.*, 1998; Ricote *et al.*, 1998) inhibit the production of pro-inflammatory cytokines as well as the expression of inducible nitric oxide synthase and cell adhesion molecules. These drugs may also be beneficial in multiple sclerosis and neurodegenerative diseases, including Alzheimer's and Parkinson's at least partially due to their anti-inflammatory activity (Heneka and

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Landreth, 2007). On the other hand, thiadiazole nucleus constitutes the active part of several biological active compounds, including antibacterial, antifungal (Modzelewska-Banachiewicz *et al.*, 2004; Foroumadi *et al.*, 2005a; Kadi *et al.*, 2007), antitubercular (Solak and Rollas, 2006; Mamolo *et al.*, 2003; Foroumadi et al., 2005c), analgesic (Schenone *et al.*, 2006), anti-inflammatory (Farghaly *et al.*, 2000; Kadi *et al.*, 2007; Schenone *et al.*, 2006), antidepressant (Varvaresou *et al.*, 1998), leishmanicidal (Foroumadi *et al.*, 2005b) agents. In view of these facts, we have designed and synthesised a number 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)acetamide derivatives. The objective of this study was to investigate the benefits of such hybridization on the anticipated biological activities, and to determine whether this would lead to added synergistic biological activity of the target molecules.

Results and discussion

Chemistry

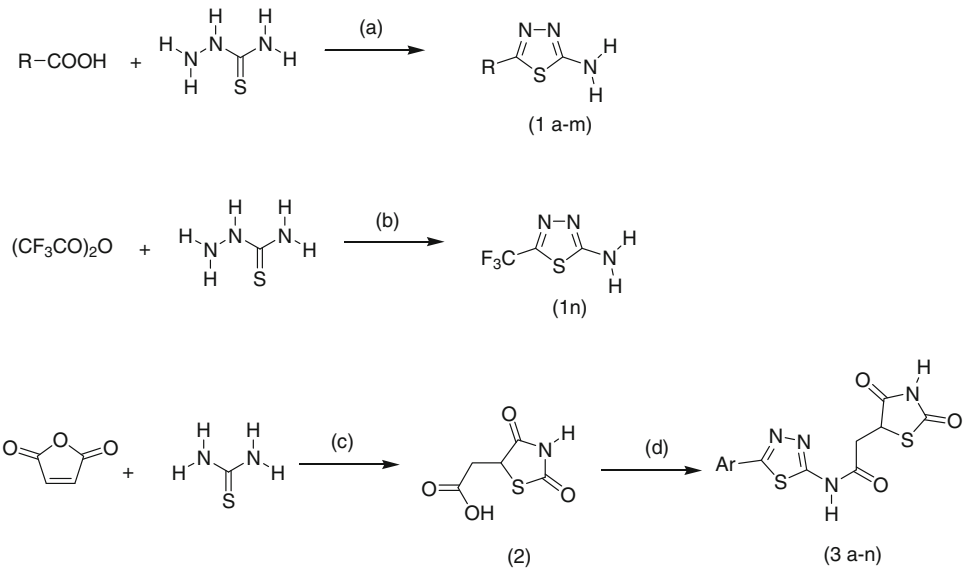
2,4-Thiazolidinedione-5-acetic acid, prepared from thiourea and maleic anhydride in presence of concentrated hydrochloric acid (Zimenkovskii *et al.*, 2006). 2-(2,4-Dioxothiazolidin-5-yl)acetyl chloride was prepared from the 2,4-thiazolidinedione-5-acetic acid and $SOCl_2$, without isolation further reacted with 5-substituted-2-amino-1,3,4-thiadiazols as Scheme 1. Several procedures are available for the one-step synthesis of 2-amino-5-substituted-1,3,4-thiadiazols (Tu *et al.*, 2008) derivatives. Yet the reaction of substituted aryl acid with thiosemicarbazide in presence of dehydrating agent phosphorus oxychloride ($POCl_3$) affords a series of 2-amino-5-substituted-1,3,4-thiadiazols. The structures and physicochemical data of final compounds are illustrated in Table 1.

The IR spectra of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)acetamides (**3a**–**n**) exhibited a absorption band in the region of 3566–3233 cm^{-1} attributable to the stretching vibration of NH, and around 1690 cm^{-1} to the carbonyl carbon. The 2,4-thiazolidinedione-5-acetic acid and their derivatives contain diastereotopic protons of methylene group, that is why the fragment $CH^AH^BCH^X$ is presented in ^1H NMR spectra as ABX spin system, which appears as doublet of doublet at ~3.05–3.48 ppm, and ~4.85 ppm with coupling constant $J_{AB} = 15.01–17.76$ Hz, $J_{AX} = 6.9–10.75$ Hz, $J_{BX} = 3.4–5.5$ Hz. High value of J_{AB} agreed with the data of Takahashi ("carbonyl effect") for structurally related 2-thioxo-4-thiazolidinone-acetic acids (Takahashi, 1964).

In order to predict the drug likeliness of the synthesised compounds on the guidelines of Lipinski rule of 5 (Molecular weight $\leq$ 500, log $P \leq 5$, HBD ≤ 5 and HBA ≤ 10) study was carried out using Pallas software (Pallas, 2010) the result are given in Table 2. The relevance of the synthesised molecules with respect to Lipinski rule of five is as follows.

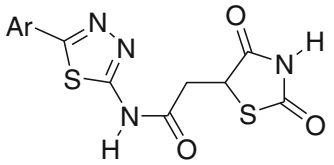
Molecular weight of the compound is important in drug action, if the molecular weight increases beyond a limit, the bulkiness of the compounds also increases, which will affect the drug action (affect the drug receptor/DNA interactions). Molecular weight of compounds lie between 326.29 and 424.28 show that it follows Lipinski rule of 5. So the bulkiness of the compounds is in optimum limit for the action.

Pharmacokinetic property optimization is a rather complex undertaking that is likely to require changes in



Scheme 1 Reagents and conditions: (*a*) $POCl_3$, 110°C; (*b*) 0–40°C; (*c*) HCl 100°C; (*d*) (I) $SOCl_2$, dioxane, (II) **1a**–**n**, Et_3N, dioxane

Table 1 Physical constants of the compounds **3a–n**



Compounds	Ar	Yield (%)	M.p. (°C)	Molecular weight	Molecular formula
3a	C_6H_5	66	256–257	334	$C_{13}H_{10}N_4O_3S_2$
3b	4-Cl-C_6H_4	59	261–262	368	$C_{13}H_9ClN_4O_3S_2$
3c	4-Br-C_6H_4	61	247–248	413	$C_{13}H_9BrN_4O_3S_2$
3d	4-F-C_6H_4	55	239–240	352	$C_{13}H_9FN_4O_3S_2$
3e	2-Cl-C_6H_4	62	231–232	368	$C_{13}H_9ClN_4O_3S_2$
3f	4-CH_3-C_6H_4	58	260–261	348	$C_{14}H_{12}N_4O_3S_2$
3g	3-OCH_3-C_6H_4	54	237–238	364	$C_{14}H_{12}N_4O_4S_2$
3h	4-OCH_3-C_6H_4	69	249–250	364	$C_{14}H_{12}N_4O_4S_2$
3i	3, 4-OCH_3-C_6H_3	62	241–242	394	$C_{15}H_{14}N_4O_5S_2$
3j	3,4,5-OCH_3-C_6H_2	52	260–261	424	$C_{16}H_{16}N_4O_6S_2$
3k	2-NO_2-C_6H_4	56	248–249	379	$C_{13}H_9N_5O_5S_2$
3l	3-NO_2-C_6H_4	50	241–242	379	$C_{13}H_9N_5O_5S_2$
3m	4-NO_2-C_6H_4	54	256–257	379	$C_{13}H_9N_5O_5S_2$
3n	CF_3	49	298–299	402	$C_8H_5F_3N_4O_3S_2$

Table 2 Drug likeliness of the 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)acetamides (**3a–n**)

Compound	TPSA	MW	log *P*	HBD	HBA	Rule-5 violation
3a	101.05	334.39	1.43	2	7	0
3b	101.05	368.83	2.06	2	7	0
3c	101.05	413.28	2.22	2	7	0
3d	101.05	352.38	1.70	2	7	0
3e	101.05	368.83	2.06	2	7	0
3f	101.05	348.42	1.97	2	7	0
3g	110.28	364.42	1.43	2	8	0
3h	110.28	364.42	1.43	2	8	0
3i	119.51	394.45	1.30	2	9	0
3j	128.75	424.48	1.17	2	10	0
3k	146.87	379.39	1.34	2	10	0
3l	146.87	379.39	1.34	2	10	0
3m	146.87	379.39	1.34	2	10	0
3n	101.05	326.29	0.45	2	7	0

TPSA polar surface area, *MW* molecular weight, *HBD* hydrogen bond donors, *HBA* hydrogen bond acceptor, *Lipinski rule of 5* (Molecular weight $\leq$ 500, log $P \leq 5$, HBD ≤ 5 and HBA ≤ 10)

those molecular determinants that are responsible for binding affinity and specificity like hydrogen bonds. Hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) groups in the compound optimise the drug receptor interaction. Number of HBAs ($\leq$10) and HBDs ($\leq$5) in the proposed compounds obeys the Lipinski rule of 5, so it may have good absorption or permeability properties through the biological membrane.

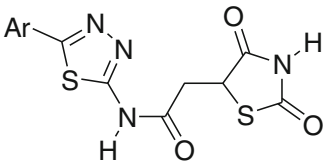
Dissolution is highly interdependent influences of aqueous solubility, ionizability (p*K*a) and lipophilicity (log *P*). Furthermore, log *P* is a crucial factor governing passive membrane partitioning, influencing permeability opposite to its effect on solubility. The log *P* values of the synthesised compounds lie in between 0.45 and 2.22.

Pharmacology

Antimicrobial activity

The synthesised compounds were tested for their in vitro antibacterial activity against the Gram-positive *Staphylococcus aureus* (ATCC25923), *Enterococcus faecalis* (ATC C35550), Gram-negative *Escherichia coli* (ATCC35218), *Pseudomonas aeruginosa* (ATCC25619) bacteria and *Candida albicans* (ATCC2091), *Aspergillus flavus* (NCIM No. 524), *Aspergillus niger* (ATCC6275) and *Cryptococcus neoformans* (Clinical isolate) fungi. The MIC values were determined by using the twofold serial dilution technique (National Committee for Clinical Laboratory Standards, 2000) in Mueller–Hinton broth and Sabouraud dextrose agar for the antibacterial and antifungal assays,

Table 3 Results of antibacterial and antifungal activities of compounds (**3a–n**) [minimum inhibitory concentration (MIC) values]



Compound	Ar	*E.c*	*P.a*	*S.a*	*E.f*	*C.a*	*C.n*	*A.f*	*A.n*
3a	C_6H_5	64	64	32	64	64	64	64	64
3b	4-Cl-C_6H_4	32	32	4	32	16	16	16	16
3c	4-Br-C_6H_4	32	32	8	32	16	16	16	16
3d	4-F-C_6H_4	8	8	4	4	8	8	8	4
3e	2-Cl-C_6H_4	32	32	16	16	16	16	32	16
3f	4-CH_3-C_6H_4	16	16	8	4	16	32	32	32
3g	3-OCH_3-C_6H_4	16	32	4	8	16	16	16	32
3h	4-OCH_3-C_6H_4	32	16	16	4	16	16	32	16
3i	3,4-OCH_3-C_6H_3	16	16	16	32	16	16	16	32
3j	3,4,5-OCH_3-C_6H_2	16	16	16	16	16	32	16	16
3k	2-NO_2-C_6H_4	64	64	32	64	64	64	64	16
3l	3-NO_2-C_6H_4	64	32	32	64	64	64	64	64
3m	4-NO_2-C_6H_4	64	64	32	32	64	64	32	64
3n	CF_3	32	32	32	32	16	16	32	16
Amp.		NT	NT	2	2	NT	NT	NT	NT
Cip.		2	2	NT	NT	NT	NT	NT	NT
Ket.		NT	NT	NT	NT	2	2	1	2

E.c, *Escherichia coli*; *P.a*, *Pseudomonas aeruginosa*; *S.a*, *Staphylococcus aureus*; *E.f*, *Enterococcus faecalis*; *C.a*, *Candida albicans*; *C.n*, *Cryptococcus neoformans*; *A.f*, *Aspergillus flavus*; *A.n*, *Aspergillus niger*; NT, not tested; Amp., ampicillin; Cip., ciprofloxacin; Ket., ketoconazole

respectively. Ampicillin and ciprofloxacin were used as the reference antibacterial agents; ketoconazole was used as the reference antifungal agents. All the biological results of the tested compounds are given in Table 3. The combined data were reported that the synthesised compounds (**3a–n**) showing MIC values between 64 and 4 μg/ml were able to have an in vitro inhibitory effect against the screened microorganisms.

All compounds were found to be active against Gram-positive bacteria especially *Staphylococcus aureus* at 4–32 μg/ml concentration. Compound **3a** which has no substitution at the *para* position of phenyl ring attached to 5th position of the thiadiazole moiety did not promote much activity against the tested microbial strains, whereas compounds **3f–j** which have electron donating $–CH_3$ group at the *para* position of phenyl ring and $–OCH_3$ group at different position of the phenyl ring exhibits moderate activity. The introduction of –Cl, –Br groups at the *para* position of phenyl ring were found to enhance the antibacterial potency significantly. Thus, the compounds **3b** and **3c** active against Gram-positive especially *Staphylococcus aureus* at 4–8 μg/ml concentration, while **3d** which has electron withdrawing –F functional group substituted at the *para* position of phenyl ring exerted excellent antibacterial activity by inhibiting the growth of all the tested bacterial strains at 4–8 μg/ml.

Compounds like **3k**, **3l**, and **3m** showed moderate antibacterial activity against all the tested bacterial strains. Antifungal results indicated that compounds **3b–d** exhibit good activity against all the tested fungal strains.

Cytotoxic activity

In vitro cytotoxic studies of thiazolidinedione-5-acetic acid amide derivatives **3a–n** were carried out on different cancer cell lines and results of cytotoxicity studies were summarised in Table 4. Among the 14 compounds **3j** which was 3,4,5-trimethoxyphenyl, exhibited the good inhibitory activity against HeLa, HT29, A549 and MCF-7 cell lines, with the inhibitory concentration (IC_{50}) values of 33, 35, 30 and 36 μM, respectively. Compounds **3g**, **3h** and **3i** showed moderate cytotoxic activities against all tested human tumour cell lines with IC_{50} values of 35–60 μM. In general, structures with donor substituents showed activity, the position of substituents appears to play an important role in activity too.

Table 4 In vitro cytotoxicity of compounds (**3a–n**) against four different human cancer cell lines (IC_{50}, μM)

Compound	Ar	HeLa	HT29	A549	MCF7
3a	C_6H_5	62	78	80	80
3b	4-Cl-C_6H_4	62	64	60	68
3c	4-Br-C_6H_4	52	60	68	72
3d	4-F-C_6H_4	50	42	50	60
3e	2-Cl-C_6H_4	60	66	62	84
3f	4-CH_3-C_6H_4	50	58	46	52
3g	3-OCH_3-C_6H_4	54	56	60	58
3h	4-OCH_3-C_6H_4	42	44	45	42
3i	3,4-OCH_3-C_6H_3	40	42	35	38
3j	3,4,5-OCH_3-C_6H_2	33	35	30	36
3k	2-NO_2-C_6H_4	50	68	72	78
3l	3-NO_2-C_6H_4	68	72	78	67
3m	4-NO_2-C_6H_4	50	60	68	72
3n	CF_3	42	50	60	62
Cisplatin		7	4	2	3

Cell lines include cervical carcinoma (HeLa), colorectal cancer (HT29), lung cancer (A549) and breast adenocarcinoma (MCF-7)

Conclusion

We report the synthesis of a series of 2,4-thiazolidinedione-5-acetic acid amides in good yields and are characterised by their physical and analytical data. The antibacterial and antifungal studies carried out to by twofold serial dilution technique. The preliminary structural-activity relationship study showed that 4-fluorophenyl and 3,4,5-trimethoxyphenyl ring are important for activity and selectivity of 2,4-thiazolidinedione-5-acetic acid amides. Moreover, the cytotoxic activity of this series suggests that 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*-(5-(-3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-yl)acetamide **3j** offers a novel template for development of a new class of anticancer agents.

Experimental protocols

General conditions

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting point was determined by electrothermal melting point apparatus and is uncorrected. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel (60GF-254) plates and visualised with UV light. Column chromatography was performed on silica gel (200–300 mesh). Infra red (IR) spectra was recorded on using KBr disk on a Nicolet MX-1 FTIR spectrophotometer, ^{1}H and ^{13}C NMR spectra were recorded on AMX-400, Bruker-400 liquid-state NMR spectrometer using tetramethylsilane (TMS) as internal standard (chemical shift in δ ppm). Elemental analysis was carried out using a Perkin Elmer 2400-CHN Analyzer. Spectral analysis was carried out by Sophisticated Analytical Instruments Facility (SAIF) division of Indian Institute of Science, Bangalore, India.

Chemistry

General procedure for synthesis of 5-substituted-1,3,4-thiadiazol-2-amine ***1a–m*** *(Tu et al., 2008)*

A stirring mixture of benzoic acid (50 mmol), thiosemicarbazide (50 mmol) and phosphorus oxychloride (15 ml) was heated at 75°C for 1 h. After cooling to room temperature, water was added; the reaction mixture was further refluxed for 4 h. After cooling, the mixture was basified to pH 8 by the dropwise addition of 50% potassium hydroxide solution under stirring. Thus, obtained precipitate was filtered and recrystallised from ethanol.

Synthesis of 5-phenyl-1,3,4-thiadiazol-2-amine ***1a*** This compound was obtained as white solid in a yield of 78%. M.p.: 225–227°C; IR (KBr, ν, cm^{-1}); 3590, 3126 (ν_{NH}), 1620 ($\nu_{C=N}$), 690(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.76 (s, 2H), 7.5 (m, 5H).

Synthesis of 5-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine ***1b*** This compound was obtained as white solid in a yield of 75%. M.p.: 212–214°C; IR (KBr, ν, cm^{-1}); 3345, 3156 (ν_{NH}), 1626 ($\nu_{C=N}$), 685(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.50 (d, $J = 6.56$ Hz, 2H), 7.47 (d, $J = 6.23$ Hz, 2H), 7.44 (s, 2H).

Synthesis of 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine ***1c*** This compound was obtained as white solid in a yield of 74%. M.p.: 225–226°C; IR (KBr, ν, cm^{-1}); 3394, 3136 (ν_{NH}), 1626 ($\nu_{C=N}$), 665(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.78-7.82 (dd, $J_1 = 8.42$ Hz, $J_2 = 16.63$ Hz, 4H), 7.44(s, 2H).

Synthesis of 5-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine ***1d*** This compound was obtained as white solid in a yield of 80%. M.p.: 232°C; IR (KBr, ν, cm^{-1}); 3294, 3156 (ν_{NH}), 1633 ($\nu_{C=N}$), 682(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.79–7.84 (dd, $J_1 = 6.36$ Hz, $J_2 = 8.46$ Hz, 2H), 7.42 (s, 2H), 7.28–7.34 (m, 2H).

Synthesis of 5-(2-chlorophenyl)-1,3,4-thiadiazol-2-amine ***1e*** This compound was obtained as white solid in a yield of 82%. M.p.: 228–230°C; IR (KBr, ν, cm^{-1}); 3384, 3136 (ν_{NH}), 1643 ($\nu_{C=N}$), 672(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.97–8.01 (m, 2H), 7.57–7.60 (m, 1H), 7.44–7.47 (m, 1H), 7.42 (s, 2H).

Synthesis of 5-(4-methylphenyl)-1,3,4-thiadiazol-2-amine ***1f*** This compound was obtained as white solid in a yield of 88%. M.p.: 212°C; IR (KBr, ν, cm^{-1}); 3578, 3143 (ν_{NH}), 1651 ($\nu_{C=N}$), 681(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.60–7.63 (d, $J = 9.96$ Hz, 2H), 7,31 (s, 2H), 7.26 (d, $J = 7.93$ Hz, 2H), 2.32 (s, 3H, CH_3).

Synthesis of 5-(3-methoxyphenyl)-1,3,4-thiadiazol-2-amine ***1g*** This compound was obtained as light yellow solid in a yield of 84%. M.p.: 220°C; IR (KBr, ν, cm^{-1}); 3448, 3155 (ν_{NH}), 1650 ($\nu_{C=N}$), 1231 (ν_{Ar-O-C}), 676(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.25–7.35 (m, 3H), 6.97–7.01 (dd, 1H), 7,40 (s, 2H), 3.79 (s, 3H, OCH_3).

Synthesis of 5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-amine ***1h*** This compound was obtained as light yellow solid in a yield of 80%. M.p.: 196°C; IR (KBr, ν, cm^{-1}); 3548, 3126 (ν_{NH}), 1660 ($\nu_{C=N}$), 1243 (ν_{Ar-O-C}), 676(ν_{C-S}); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.62 (d, $J = 7.83$ Hz, 2H), 7.50 (d, $J = 8.01$ Hz, 2H), 7,27 (s, 2H), 3.53 (s, 3H, OCH_3).

Synthesis of 5-(3,4-dimethoxyphenyl)-1,3,4-thiadiazol-2-amine ***1i*** This compound was obtained as white solid in a yield of 79%. M.p.: 210°C; IR (KBr, ν, cm^{-1}); IR (KBr, ν, cm^{-1}); 3578, 3156 (ν_{NH}), 1640 ($\nu_{C=N}$), 1258 (ν_{Ar-O-C}), 670(ν_{C-S}); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 8.65–8.69 (m, 3H), 7.61 (s, 2H), 3.71 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3).

Synthesis of 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-amine ***1j*** This compound was obtained as greyish solid in a yield of 90%. M.p.: 206°C; IR (KBr, ν, cm^{-1}); 3590, 3126 (ν_{NH}), 1620 ($\nu_{C=N}$), 1266 (ν_{Ar-O-C}), 690(ν_{C-S}); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.85 (s, 2H), 6.95 (s, 2H, NH_2), 3.83 (s, 6H, OCH_3), 3.80 (s, 3H, OCH_3).

Synthesis of 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-amine ***1k*** This compound was obtained as yellow solid in a yield of 73%. M.p.: 242°C; IR (KBr, ν, cm^{-1}); 3577, 3132 (ν_{NH}), 1667 ($\nu_{C=N}$), 676(ν_{C-S}); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 8.41–8.48 (m, 1H), 8.27 (d, $J = 8.84$ Hz, 2H), 8.01 (m, 1H), 7.70 (s, 2H).

Synthesis of 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine ***1l*** This compound was obtained as light yellow solid in a yield of 71%. M.p.: 219°C; IR (KBr, ν, cm^{-1}); 3532, 3151 (ν_{NH}), 1637 ($\nu_{C=N}$), 651(ν_{C-S}); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.99 (d, $J = 8.14$ Hz, 2H), 7.75–7.87 (m, 2H), 7.70 (s, 2H).

Synthesis of 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine ***1m*** This compound was obtained as yellow solid in a yield of 78%. M.p.: 260°C; IR (KBr, ν, cm^{-1}); 3568, 3147 (ν_{NH}), 1658 ($\nu_{C=N}$), 656(ν_{C-S}); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 8.29 (d, $J = 8.92$ Hz, 2H), 7.98 (d, $J = 8.92$ Hz, 2H), 7.69 (s, 2H).

Synthesis of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine ***1n*** A mixture of trifluoroaceticacid anhydride (50 mmol), thiosemicarbazide (50 mmol) was heated at 40°C on a water bath for 1 h. The reaction mixture was cooled, diluted with water and made alkaline with ammonia; the crystalline precipitate was recrystallised with ethanol gave white crystals in a yield of 81%. M.p.: 226°C; IR (KBr, ν, cm^{-1}); 3468 (ν_{NH}), 1647 ($\nu_{C=N}$); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 7.96 (s, 2H).

Synthesis of 2,4-dioxothiazolidine-5-acetic acid ***2*** *(Zimenkovskii et al., 2006)*

A mixture of thiourea (25 mmol) and maleic anhydride (25 mmol) in 15 ml of concentrated hydrochloric acid was refluxed for 5 h. After cooling down to room temperature, the precipitate was separated by filtration, washed with cooled water, and recrystallised from water to yield 2,4-dioxothiazolidine-5-acetic acid.

IR (KBr, ν, cm^{-1}): 3227 (ν_{NH}), 2850, 1690 ($\nu_{C=O}$); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.60 (s, 1H), 11.90 (s, 1H), 4.86 (m, 1H), 3.03 (dd, $J = 15.23$ Hz, $J = 4.6$ Hz, 1H), 2.89 (dd, $J = 11.46$ Hz, $J = 4.2$ Hz, 1H).

General procedure for synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-substituted-1,3,4-thiadiazol-2-yl)acetamide ***3a–n***

A mixture of 2,4-dioxothiazolidine-5-acetic acid (50 mmol) and 1.2 g of thionyl chloride in 5 ml of dioxane was heated under reflux for 5 h, cooled, and treated with 15 ml of hexane. The precipitate was separated by filtration and used without further purification. To a solution of corresponding 5-substituted-1,3,4-thiadiazol-2-amine (10 mmol) and 1 ml of triethylamine in 10 ml of anhydrous dioxane was added the solution of acid chloride (50 mmol) in 10 ml of same solvent. The mixture was heated for 10 min at 100°C, cooled, and diluted with 100 ml of water. The precipitate was separated by filtration and recrystallised with appropriate solvent.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acetamide ***3a*** This compound was obtained as white solid in a yield of 66%. M.p.: 256°C; IR (KBr, ν, cm^{-1}): 3325, 3255 (ν_{NH}), 2881, 1699 ($\nu_{C=O}$); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.90 (s, 1H), 12.10 (s, 1H), 7.95–7.92 and 7.51 (m, 5H), 4.80 (m, 1H), 3.42 (dd, $J = 17.11$ Hz, $J = 4.71$ Hz, 1H), 3.29 (dd, $J = 16.12$ Hz, $J = 4.32$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 169.23, 166.78, 165.63, 162.45, 152.65, 132.12, 129.33, 128.31, 126.34, 51.02, 35.12. Calcd. for $C_{13}H_{10}N_4O_3S_2$: C, 46.70; H, 3.01; N, 16.76; Found: C, 46.65; H, 3.00; N, 16.84%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-4-chlorophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3b*** This compound was obtained as light brown solid in a yield of 59%. M.p.: 261°C; IR (KBr, ν, cm^{-1}): 3566, 3498 (ν_{NH}), 2966, 1690 ($\nu_{C=O}$); ^1H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.89 (s, 1H), 12.12 (s, 1H), 7.55 (d, $J = 6.71$ Hz, 2H), 7.51 (d, $J = 7.26$ Hz, 2H), 4.78 (m, 1H), 3.41 (dd, $J = 15.53$ Hz, $J = 4.61$ Hz, 1H), 3.27 (dd, $J = 17.13$ Hz, $J = 4.82$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 170.03, 168.21, 166.53, 162.13, 153.19, 133.23, 129.74, 128.17, 126.89, 50.12, 34.09. Calcd. for $C_{13}H_9ClN_4O_3S_2$: C, 42.34; H, 2.46; N, 15.19; Found: C, 42.26; H, 2.40; N, 15.29%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-4-bromophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3c*** This compound

was obtained as brown solid in a yield of 61%. M.p.: 247°C; IR (KBr, ν, cm^{-1}): 3362, 3271 (ν_{NH}), 2942, 1693 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.99 (s, 1H), 12.13 (s, 1H), 7.78–7.74 (m, 4H), 4.81 (m, 1H), 3.39 (dd, $J = 16.52$ Hz, $J = 4.71$ Hz, 1H), 3.08 (dd, $J = 17.11$ Hz, $J = 4.36$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 169.87, 167.01, 164.21, 162.09, 153.12, 135.11, 129.89, 128.45, 126.61, 51.18, 34.41. Calcd. for $C_{13}H_9BrN_4O_3S_2$: C, 37.78; H, 2.20; N, 13.56; Found: C, 37.70; H, 2.18; N, 13.63%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-4-fluorophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3d*** This compound was obtained as light yellow solid in a yield of 55%. M.p.: 239°C; IR (KBr, ν, cm^{-1}): 3434, 3246 (ν_{NH}), 2963, 1698 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.90 (s, 1H), 12.10 (s, 1H), 7.71 (d, 2H), 7.67 (d, 2H), 4.83 (m, 1H), 3.33 (dd, $J = 17.41$ Hz, $J = 4.43$ Hz, 1H), 3.06 (dd, $J = 15.23$ Hz, $J = 4.62$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 171.23, 167.12, 165.13, 163.15, 151.45, 132.34, 129.78, 128.11, 126.69, 50.72, 33.09. Calcd. for $C_{13}H_9FN_4O_3S_2$: C, 44.31; H, 2.57; N, 15.90; Found: C, 44.23; H, 2.51; N, 15.98%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-2-chlorophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3e*** This compound was obtained as white solid in a yield of 62%. M.p.: 231°C; IR (KBr, ν, cm^{-1}): 3421, 3233 (ν_{NH}), 2982, 1690 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.89 (s, 1H), 12.00 (s, 1H), 8.01–7.92 (m, 4H), 4.81 (m, 1H), 3.43 (dd, $J = 17.14$ Hz, $J = 4.20$ Hz, 1H), 3.19 (dd, $J = 15.51$ Hz, $J = 4.34$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 168.97, 165.86, 164.34, 161.56, 151.875, 136.31, 133.32, 129.59, 128.38, 127.78, 126.28, 50.11, 35.29. Calcd. for $C_{13}H_9ClN_4O_3S_2$: C, 42.34; H, 2.46; N, 15.19; Found: C, 42.24; H, 2.39; N, 15.28%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-4-methylphenyl-1,3,4-thiadiazol-2-yl)acetamide ***3f*** This compound was obtained as light yellow solid in a yield of 58%. M.p.: 260°C; IR (KBr, ν, cm^{-1}): 3372, 3259 (ν_{NH}), 2961, 1697 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.89 (s, 1H), 12.00 (s, 1H), 7.62 (d, $J = 7.4$ Hz, 2H), 7,52 (d, $J = 6.7$ Hz, 2H), 4.82 (m, 1H), 3.39 (dd, $J = 16.87$ Hz, $J = 4.69$ Hz, 1H), 3.08 (dd, $J = 15.54$ Hz, $J = 4.81$ Hz, 1H), 2.63 (s, 3H, CH_3),. ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 169.65, 167.21, 165.28, 161.64, 151.73, 131.19, 130.11 129.37, 128.21, 51.02, 35.12 29.15. Calcd. for $C_{14}H_{12}N_4O_3S_2$: C, 48.26; H, 3.47; N, 16.08; Found: C, 48.27; H, 3.41; N, 16.20%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-3-methoxyphenyl-1,3,4-thiadiazol-2-yl)acetamide ***3g*** This compound was obtained as brown solid in a yield of 54%. M.p.: 237°C; IR (KBr, ν, cm^{-1}): 3357, 3241 (ν_{NH}), 2979, 1689 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.87 (s, 1H), 12.21 (s, 1H), 7.35–7.32 (m, 3H), 7.16–7.9 (m, 1H), 4.83 (m, 1H), 3.80 (s, 3H, OCH_3), 3.31 (dd, $J = 17.34$ Hz, $J = 4.23$ Hz, 1H), 3.05 (dd, $J = 15.71$ Hz, $J = 4.78$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 171.76, 168.12, 165.97, 161.78, 151.61, 132.87, 130.12, 129.23, 128.31, 127.13 126.44, 56.28, 50.34, 34.45. Calcd. for $C_{14}H_{12}N_4O_4S_2$: C, 46.15; H, 3.32; N, 15.37; Found: C, 46.11; H, 3.24; N, 15.45%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-4-methoxyphenyl-1,3,4-thiadiazol-2-yl)acetamide ***3h*** This compound was obtained as white solid in a yield of 69%. M.p.: 249°C; IR (KBr, ν, cm^{-1}): 3561, 3315 (ν_{NH}), 2955, 1698 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 13.00 (s, 1H), 12.15 (s, 1H), 7.59 (d, 2H), 7.52 (d, 2H), 4.78 (m, 1H), 3.89 (s, 3H, OCH_3), 3.43 (dd, $J = 16.21$ Hz, $J = 4.78$ Hz, 1H), 3.07 (dd, $J = 15.12$ Hz, $J = 4.65$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 170.29, 168.81, 165.24, 163.11, 153.32, 130.11, 129.24, 128.22, 125.41, 54.21, 49.89, 34.31. Calcd. for $C_{14}H_{12}N_4O_4S_2$: C, 46.15; H, 3.32; N, 15.37; Found: C, 46.10; H, 3.26; N, 15.43%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-(-3,4-dimethoxyphenyl)-1,3,4-thiadiazol-2-yl)acetamide ***3i*** This compound was obtained as white solid in a yield of 62%. M.p.: 241°C; IR (KBr, ν, cm^{-1}): 3448, 3278 (ν_{NH}), 2957, 1698 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.97 (s, 1H), 12.21 (s, 1H), 7.31–7.27 (m, 3H), 4.78 (m, 1H), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). 3.41 (dd, $J = 17.26$ Hz, $J = 4.47$ Hz, 1H), 3.12 (dd, $J = 15.44$ Hz, $J = 4.53$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 171.33, 169.28, 165.11, 162.47, 152.31, 130.79, 129.66, 127.38, 126.12, 124.21, 57.37, 51.45, 49.23, 33.97. Calcd. for $C_{15}H_{14}N_4O_5S_2$: C, 45.68; H, 3.58; N, 14.20; Found: C, 45.69; H, 3.53; N, 14.31%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-(-3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-yl)acetamide ***3j*** This compound was obtained as light yellow solid in a yield of 52%. M.p.: 260°C; IR (KBr, ν, cm^{-1}): 3412, 3253 (ν_{NH}), 2966, 1700 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.81 (s, 1H), 12.14 (s, 1H), 7.21 (d, 2H), 4.81 (m, 1H), 3.87 (s, 6H, $2OCH_3$), 3.71 (s, 3H, OCH_3). 3.38 (dd, $J = 16.43$ Hz, $J = 4.32$ Hz, 1H), 3.27 (dd, $J = 15.23$ Hz, $J = 4.6$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 170.23, 169.67, 166.71, 163.67, 152.39, 131.28, 129.57, 128.49, 125.38, 108.34, 57.34, 50.89, 33.29. Calcd.

for $C_{16}H_{16}N_4O_6S_2$: C, 45.28; H, 3.80; N, 13.20; Found: C, 45.26; H, 3.76; N, 13.23%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-2-nitrophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3k*** This compound was obtained as light yellow solid in a yield of 56%. M.p.: 248°C; IR (KBr, ν, cm^{-1}): 3423, 3304 (ν_{NH}), 2946, 1688 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.92 (s, 1H), 12.18 (s, 1H), 7.72–7.69 (m, 4H), 4.44 (m, 1H), 3.42 (dd, $J = 16.37$ Hz, $J = 4.23$ Hz, 1H), 3.08 (dd, $J = 17.13$ Hz, $J = 4.47$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 170.87, 168.78, 164.25, 163.49, 150.87, 142.31, 130.78, 128.11, 126.65, 125.12, 121.43, 50.72, 32.28. Calcd. for $C_{13}H_9N_5O_5S_2$: C, 41.16; H, 2.39; N, 18.46; Found: C, 41.15; H, 3.33; N, 18.53%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-3-nitrophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3l*** This compound was obtained as light yellow solid in a yield of 50%. M.p.: 241°C; IR (KBr, ν, cm^{-1}): 3453, 3219 (ν_{NH}), 2982, 1697 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 13.12 (s, 1H), 12.13 (s, 1H), 7.78 (d, 2H), 7.74–7.72 (m, 2H), 4.31 (m, 1H), 3.41 (dd, $J = 16.41$ Hz, $J = 4.38$ Hz, 1H), 3.21 (dd, $J = 15.43$ Hz, $J = 4.78$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 171.91, 167.57, 163.41, 162.12, 151.13, 141.54, 130.38, 128.87, 126.11, 124.42, 51.76, 34.81. Calcd. for $C_{13}H_9N_5O_5S_2$: C, 41.16; H, 2.39; N, 18.46; Found: C, 41.14; H, 3.34; N, 18.54%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-4-nitrophenyl-1,3,4-thiadiazol-2-yl)acetamide ***3m*** This com pound was obtained as light yellow solid in a yield of 54%. M.p.: 256°C; IR (KBr, ν, cm^{-1}): 3418, 3312 (ν_{NH}), 2944, 1691 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 12.92 (s, 1H), 12.14 (s, 1H), 8.27 (d, $J = 7.2$ Hz, 2H), 7.98 (d, $J = 6.23$ Hz,2H), 4.12 (m, 1H), 3.42 (dd, $J = 15.83$ Hz, $J = 4.62$ Hz, 1H), 3.13 (dd, $J = 16.41$ Hz, $J = 4.23$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 169.24, 167.98, 165.46, 161.59, 150.22, 130.54, 128.43, 126.63, 125.65, 52.43, 34.21. Calcd. for $C_{13}H_9N_5O_5S_2$: C, 41.16; H, 2.39; N, 18.46; Found: C, 41.17; H, 3.35; N, 18.50%.

Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)-N-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)acetamide ***3n*** This compound was obtained as white solid in a yield of 49%. M.p.: 198°C; IR (KBr, ν, cm^{-1}): 3417, 3319 (ν_{NH}), 1689 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 13.00 (s, 1H), 12.23 (s, 1H), 4.33 (m, 1H), 3.43 (dd, $J = 17.38$ Hz, $J = 4.78$ Hz, 1H), 3.11 (dd, $J = 15.33$ Hz, $J = 4.23$ Hz, 1H). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 170.45, 168.33, 165.27, 156.85, 150.18, 121.44, 50.12, 34.21. Calcd. for $C_8H_5N_4O_3S_2$: C, 29.45; H, 1.54; N, 17.17; Found: C, 29.40; H, 1.51; N, 17.56%.

Microbiology

For the antibacterial and antifungal activity, the compounds were dissolved in dimethylsulfoxide (DMSO). Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 128, 64, 32, 16, 8, 4, 2, 1 μg/ml concentrations with Mueller–Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MICs) were determined using the twofold serial dilution technique (National Committee for Clinical Laboratory Standards, 2000). A control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in our experiments and found inactive in the culture medium. All the compounds were tested for their in vitro growth inhibitory activity against different bacteria and fungi.

Antibacterial and antifungal activity

The cultures were obtained from Mueller–Hinton broth for all the bacterial strains after 24 h of incubation at 37 ± 1°C. Fungi were maintained in Sabouraud dextrose broth after incubation for 24 h at 25 ± 1°C. Testing was carried out in Mueller–Hinton broth and Sabouraud dextrose broth at pH 7.4 and the twofold serial dilution technique was applied. The final inoculums size was 10^5 CFU/ml for the antibacterial assay and 10^4 CFU/ml for the antifungal assay. A set of tubes containing only inoculated broth was used as controls. For the antibacterial assay after incubation for 24 h at 37 ± 1°C and after incubation for 48 h at 25 ± 1°C for antifungal assay, the tube with no growth of microorganism was recorded to represent the MIC expressed in μg/ml. Every experiment in the antibacterial and antifungal assay was replicated twice.

Cytotoxic activity evaluation

The MTT [3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide] cell proliferation assay (Mosmann, 1983) was used to evaluate cytotoxic activity of the synthesised compounds against four human cancer cell lines including HeLa (cervical carcinoma), HT29 (colorectal cancer), A549 (lung cancer) and MCF-7 (breast adenocarcinoma) cell lines. The inhibition of the cell proliferation was determined 24 h after cells were exposed to the tested compounds. The IC_{50} (the concentration that causes 50% growth inhibition) values were determined.

References

Andreani A, Rambaldi M, Locatelli A, Leoin A, Bossa R, Chiericozzi M, Galatulas I, Salvatore G (1993) Synthesis of lactams with potential cardiotonic activity. Eur J Med Chem 28:825–829

Ayhan-kilcigil G, Altanlar N (2000) Synthesis of 3-substituted phenacyl-5-[2-phenyl-4H–4-oxo-1-benzopyran-6-yl-methylenyl]-thiazolidine-2, 4-dione and their antimicrobial activity. Arzneimittelforschung 50:154–157

Boschelli DH, Connor DT, Kuipers PJ, Wright CD (1992) Synthesis and cyclooxygenase and 5-lipoxygenase inhibitory activity of some thiazolidine-4-one analogs of meclofenamic acid. Bioorg Med Chem Lett 2:705–708

Boyd AS (2007) Thiazolidinedione in dermatology. Int J Dermatol 46:557–563

Bozdag-Dundar O, Ozgen O, Mentese A, Altanlar N, Ath O, Kendi E, Ertan R (2007) Synthesis and antimicrobial activity of some new thiazolil thiazolidine-2,4-dione derivatives. Bioorg Med Chem 15:6012–6017

DeLima JG, Perrissin M, Chantegrel J (1994) Synthesis and pharmacological evaluation of some 3-phenacyl-5-benzylidene-thiazolidine-2,4-diones. Arzneimittelforschung 44:831–834

Elte JWF, Blickle JF (2007) Thiazolidinedione for the treatment of type 2 diabetes. Eur J Inter Med 18:18–25

Farghaly AA, Bekhit AA, Park JY (2000) Design and synthesis of some oxadiazolyl, thiazolidinyl and thiazolyl derivatives of 1H-pyrazole as anti-inflammatory and antimicrobial agents. Arch Pharm Pharm Med Chem 333:53–57

Foroumadi A, Emami S, Hassanzadeh A, Rajaee M, Sokhanvar K, Moshafi MH, Shafiee A (2005a) Synthesis and antibacterial activity of N-(5-benzylthio-1,3,4-thiadiazole-2-yl) and N-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl)piperazinyl quinolone derivatives. Bioorg Med Chem Lett 15:4488–4492

Foroumadi A, Emami S, Pournourmohammadi S, Kharazmi A, Shafiee A (2005b) Synthesis and in vitro leishmanicidal activity of 2-(1-methyl-5-nitro-1H-imidazol-2-yl)-5-substituted-1,3,4-thiadiazole derivatives. Eur J Med Chem 40:1346–1350

Foroumadi A, Soltani F, Moallemzadeh-Haghighi H, Shafiee A (2005c) Synthesis, in-vitro-antimycobacterial activity and cytotoxicity of some alkyl α-(5-aryl-1,3,4-thiadiazole-2-ylthio)acetates. Arch Pharm Chem Life Sci 338:112–116

Grange JM, Zumla A (2002) The global emergency of tuberculosis: what is the cause? J R Soc Health 122:78–81

Heerding DA, Cristmann LT, Clark TJ, Holmes DJ, Rittenhouse SF, Takata DT, Venslavsky JW (2003) New benzylidenethiazolidinedione as antibacterial agents. Bioorg Med Chem Lett 13: 3771–3773

Heneka MT, Landreth GE (2007) PPARs in the brain. Biochim Biophys Acta 1771:1031–1045

Jiang C, Ting AT, Seed B (1998) PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 391:82–86

Kadi AA, El-Brollosy NR, Al-Deeb OA, Habib EE, Ibrahim TM, El-Emam AA (2007) Synthesis, antimicrobial, and anti-inflammatory activites of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazole and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. Eur J Med Chem 42:235–242

Kalaitzidis RG, Sarafidis PA, Bakeis GL (2009) Effects of thiazolidinedione beyond glycaemic control. Curr Pharm Des 15:529–536

Kurebayashi S, Xu X, Ishii S, Shirashi M, Kouhara H, Kasayama S (2005) A novel thiazolidinedione MCC-555 down-regulates tumor necrosis factor-α-induced expression of vascular cell adhesion molecule-1 in vascular endothelial cells. Atherosclerosis 182:71–77

Mamolo MG, Falagiani V, Zampieri D, Vio L, Banfi E, Scialino G (2003) Synthesis and antimycobacterial activity of (3,4-diaryl-3H-thiazol-2-ylidene)-hydrazide derivatives. IL Farmaco 58: 631–637

Mclntyre RS, Soczynska JK, Woldeyohannes HO, Lewis GF, Leiter LA, MacQueen GM, Miranda A, Fulgosi D, Konarski JZ, Kennedy SH (2007) Thiazolidinedione: noval treatments for cognitive deficits in mood disorders. Expert Opin Pharmacother 8:1615–1628

Modzelewska-Banachiewicz B, Banachiewicz J, Chodkowska A, Jagiello-Wojtowicz E, Mazur L (2004) Synthesis and biological activity of new derivatives of 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid. Eur J Med Chem 39:873–877

Mosmann T (1983) Rapid colorimetric assay for cellular growth and survrvial. Application to proliferation and cytotoxicity assays. J Immunol Methods 65:55–63

National Committee for Clinical Laboratory Standards (2000) Method for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard document M-7: A5. National Committee for Clinical Laboratory Standards, Villanova, PA

Pallas 3.7.1.2 (2010) ADME-Tox software. CompuDrug International Inc, USA

Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK (1998) The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 391:79–82

Schenone S, Brullo C, Bruno O, Bondavalli F, Ranise A, Filippelli W, Rinaldi B, Capuano A, Falcone G (2006) New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activity. Bioorg Med Chem 14:1698–1705

Solak N, Rollas S (2006) Synthesis and antituberculosis activity of 2-(aryl-alkylamino)-5-(4-aminophenyl)-1,3,4-thiadiazoles and their Schiff bases. Arkivoc xii:173–181

Takahashi T (1964) Spincoupling constants for methylene groups adjacent to carbonyl groups. Tetrhedron Lett 5:565–572

Tu GG, Li SH, Huang HM, Li G, Xiong F, Mai X, Zhu HW, Kuang BH, Xu WF (2008) Novel aminopeptidase N inhibitors derived from 1,3,4-thiadiazole scaffold. Bioorg Med Chem 16:6663–6668

Tuncbilek M, Altanlar N (2006) Synthesis of new-(substituted phenycyl)-5-[3-(4H-oxo-1-benzopyran-2yl)-benzylidene]-2,4-thiazolidinedione and their antimicrobial activity. Arch Pharm Chem Life Sci 339:213–216

Varvaresou A, Siatra-Papastaikoudi T, Tsotinis A, Tsantili-Kakoulidou A, Vamvakides A (1998) Synthesis, lipophilicity and biological evaluation of indole-containing derivatives of 1,3,4-thiadiazole and 2,2,4-triazole. Il Farmaco 53:320–326

Zimenkovskii BS, Kutsyk RV, Lesyk RB, Matyichuk VS, Obushak ND, Klyufinska TI (2006) Synthesis and antimicrobial activity of 2,4-dioxothiazolidine-5-acetic acid amides. Pharm Chem J 40: 303–306