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Efficient Regioselective Three-Component *Domino* Synthesis of 3-(1,2,4-Triazol-5-yl)-1,3-thiazolidin-4-ones as Potent Antifungal and Antituberculosis Agents

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In research for promising antibacterial and antifungal compounds, a series of 2-aryl 3-[1,2,4]triazol-5-yl 4-thiazolidinones **1** were synthesized by a *domino* reaction of 5-amino-1*H*-[1,2,4]triazoles **3**, aromatic aldehydes, and α-mercaptoacids in boiling toluene in the presence of molecular sieves 4 Å. Of the twenty novel 3-[1,2,4]triazol-5-yl 4-thiazolidinone derivatives, four compounds 2-benzo[*d*][1,3]dioxol-6-yl-3-[(3-morpholin-4-yl)-1*H*-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1i**), 2-(4-chlorophenyl)-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1*H*-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1p**), 2-benzo[*d*][1,3]dioxol-6-yl-3-[3-(4-methylpiperazin-1-yl)-1*H*-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1s**), 2-benzo[*d*][1,3]dioxol-6-yl-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1*H*-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1t**) exhibited MICs of 4 μg/mL or less versus *Mycobacterium tuberculosis*. Moreover, these compounds were screened against *Candida albicans*. Compounds **1p**, **1s** gave MICs of 1 μg/mL or less, and were fungicidal. Finally, compound **1s** was evaluated against an expanded fungal panel and showed good activity against *Cryptococcus neoformans*. In addition, compound **1s** also appeared to be fungicidal against *Aspergillus arrhizus*, with MIC <1 μg/mL.

Keywords: 5-Amino-1*H*-[1,2,4]triazoles / Antifungal agents / Antituberculosis agents / *Domino* reaction / 4-Thiazolidinones

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Introduction

The necessity for more potent antimicrobial agents has become vital because of emerged resistance to the currently used antibiotics. Patients suffering from debilitating diseases such as neoplasia who need long term parenteral nutrition may suffer from systemic infections caused by resistant microorganisms [1].

The multi-component reactions (MCRs) are gaining importance in organic and medicinal chemistry [2]. MCRs strategies offer significant advantages over conventional linear-type synthesis [3] through increased contribution on speed, diversity and efficiency in the drug discovery process [4]. In such reactions, three or more reactants are employed in a single reaction vessel to obtain new products constitutive of all components [5]. On the other hand, the *domino* reactions are defined as a special case of MCRs that could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagent [6, 7]. Therefore, these types of reactions would allow an ecologically and economically favorable production [8].

4-Thiazolidinone [9] derivatives possess antibacterial [10–13], antifungal [14–19], and antituberculosis [20, 21] activities. 4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme Mur B [22] which is essential in cell wall biosynthesis.

Cell wall biosynthesis in bacteria involves the assembly of peptidoglycan which serves as a critical structural unit of the cell wall by maintaining the osmotic integrity of the cell. The biosynthesis of peptidoglycan proceeds from UDP

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N-acetylglucosamine with the two-step synthesis of UDP-*N*-acetylmuramic acid catalyzed by the enzymes MurA and MurB. MurA facilitates the addition of an enolpyruvyl moiety from phosphoenolpyruvate to the 3-hydroxyl of UDP-*N*-acetylglucosamine. MurB is responsible for the reduction of the enol ether to the lactyl ether, utilizing 1 equivalent of NADPH and a solvent-derived proton [23].

As part of a research program directed to drug discovery of antimicrobial agents [24–27] and due to the previously reported antimicrobial activity of 4-thiazolidinones we decided to synthesize a series of thiazolidinone derivatives to investigate structure activity relationship (SAR) and their antimicrobial profiles. We report here the synthesis of twenty novel 3-(1,2,4)-triazol-5-yl-1,3-thiazolidin-4-ones derivatives using three-component *domino* reaction and their evaluation against various microbial agents including *Candida albicans* A39, *Aspergillus fumigatus* (strain 168.95), and *Mycobacterium tuberculosis* H37Rv.

Results and discussion

Chemistry

Our strategy for the synthesis of 3-(1,2,4-triazol-5-yl)-1,3-thiazolidin-4-ones is based upon the cycloaddition reaction of α-mercaptoalkalonic acids to an imine group in a three-component *domino* reaction.

The retrosynthetic study of this strategy (Fig. 1) revealed that the 3-(1,2,4)-triazol-5-yl-1,3-thiazolidin-4-ones **1** could be obtained from the reaction of 5-amino-1*H*-(1,2,4)-triazoles **3**, aromatic aldehydes and α-mercaptoacids without isolation of Schiff's bases **2** (c.f. the linear type synthesis). The amine **3** could be accessible by the reaction of cyanocarbonimidodithioic acid dimethyl ester (**5**) with one molar equivalent of an appropriate cyclic amine followed by the reaction with hydrazine hydrate ($NH_2NH_2 \cdot H_2O$) without isolation of isothioureas **4**.

This study was initiated by the synthesis of the starting materials, 5-amino-1*H*-3-substituted (1,2,4)-triazoles in two steps. Therefore, *N*-cyanocarbonimidodithioic acid dimethyl ester **5** reacted smoothly with one molar equiv. of cyclic amines in boiling acetonitrile to give the corresponding isothiourea derivative **4**. Without the isolation of isothioureas, a slight excess of hydrazine was added and the mixture was refluxed till complete evolution of methyl mercaptan furnishing 5-amino-1*H*-3-substituted (1,2,4)-triazoles in excellent yields [28].

Practically, 4-thiazolidinone derivatives **1** were obtained using a three-component *domino* reaction. Therefore, a mixture of 5-amino-1*H*-(1,2,4)-triazoles **3**, the appropriate aldehydes and α-mercaptoacids was reacted in the presence of molecular sieves (4 Å) in toluene at 85°C to give 3-(1,2,4-triazol-5-yl)-1,3-thiazolidin-4-one derivatives **1** (Scheme 1).

The reaction pathway involves the *in-situ* formation of intermediate 5-triazolylimines **2** by condensation of the amine **3** and the appropriate aldehydes. The next step involves the nucleophilic attack of the thiol group to the imine carbon–nitrogen double bond giving the intermediate **6**, which has two possible nucleophilic nitrogens for reaction with the thioacid carboxyl group. This would lead to the formation of either 1,2,4-triazol-5-yl-1,3-thiazolidin-4-one **1** or [1,2,4]triazolo[5,1-*d*][1,3,5]thiadiazepin-8(7*H*)one ring **7**. It seems of much interest to note that the present cyclization proceeds regiospecifically to exclusively give 4-thiazolidinone. This is in striking contrast to the reported formation of [1,2,4]triazolo[5,1-*d*][1,3,5]thiadiazepin-8(7*H*)one ring **7** in an analogous reaction with 3-amino pyrazole [29, 30] (Scheme 2).

It is worthy to note that the product obtained from α-mercaptopropionic acid gave a mixture of *cis* and *trans* isomers. ^{1}H-NMR spectra of such mixtures showed that a 2-Hz coupling between hydrogens on carbons 2 and 5 corresponds to the *cis*-form. The *cis*-form is better able to adopt a ''W'' configuration favoring indirect coupling which is often

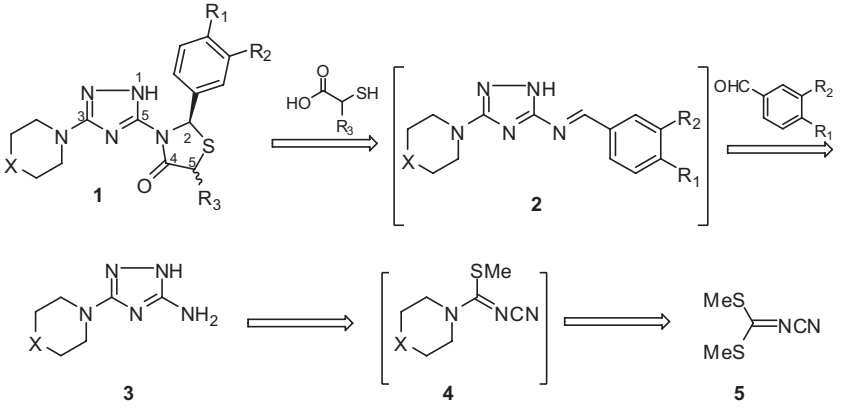
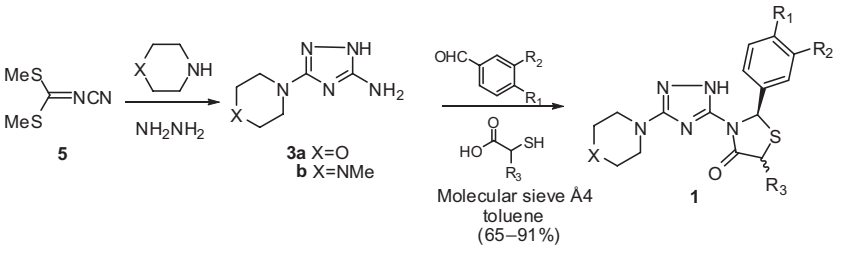


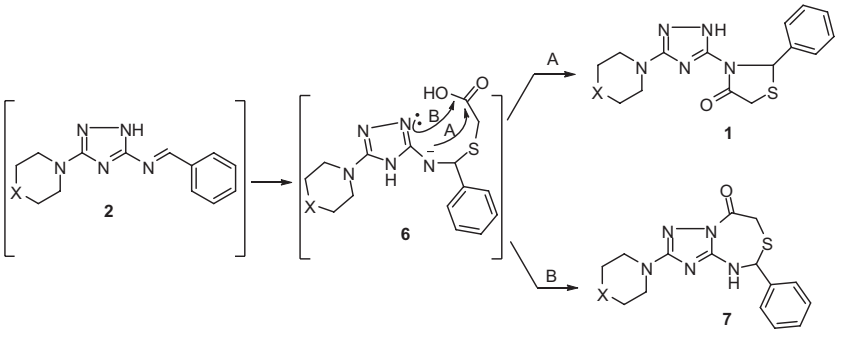
Figure 1. Retrosynthetic study of 3-[1,2,4]-triazol-5-yl 4-thiazolidinones.



1	X	R_1	R_2	R_3	Yield (%)
a	O	H	H	H	83
b	O	H	H	Me	86
c	O	Me	H	H	91
d	O	Me	H	Me	88
e	O	Cl	H	H	79
f	O	Cl	H	Me	81
g	O	OMe	H	H	73
h	O	OMe	H	Me	79
I	O	$-OCH_2O-$		H	69
J	O	$-OCH_2O-$		Me	71

1	X	R_1	R_2	R_3	Yield (%)
k	NMe	H	H	H	69
l	NMe	H	H	Me	65
m	NMe	Me	H	H	67
n	NMe	Me	H	Me	65
o	NMe	Cl	H	H	77
p	NMe	Cl	H	Me	73
q	NMe	OMe	H	H	78
r	NMe	OMe	H	Me	79
s	NMe	$-OCH_2O-$		H	73
t	NMe	$-OCH_2O-$		Me	70

Scheme 1. Synthesis of 3-[1,2,4]triazol-5-yl-4-thiazolidinones.



Scheme 2. Mechanism of formation of 3-[1,2,4]triazol-5-yl 4-thiazolidinones.

invoked to rationalized hydrogen spin-spin splitting across four single bonds [31].

Biology

2-Aryl 3-(1,2,4-triazol-5-yl)-1,3-thiazolidin-4-ones **1a–t** were screened for their potential antifungal activities against *Candida albicans* and *Aspergillus fumigates*. These were also tested against *Mycobacterium tuberculosis* for their antituberculosis activity. The antimicrobial data for these compounds are summarized in Table 1. The greatest activity among the twenty compounds **1a–t** was found for (**1i**, **1p**, **1s**, **1t**) which showed good *in-vitro* activity against *C. albicans* with MIC values of <4 μg/mL. Compounds **1p** and **1s** were fungicidal against *C. albicans* with MIC values of <1 μg/mL in comparison with fluconazole, a known antibiotic possessing a MIC value of 0.25 μg/mL. Compounds **1i**, **1n**, **1s** showed good *in-vitro* activity against *M. tuberculosis* with MIC values of <1 μg/mL. Compounds **1m**, **1n**, **lp**, **lq** and **lt** showed activity against *A. fumigatus* producing MIC values of 10 μg/mL. Subsequently, compound **ls** showed excellent antifungal activity against *A. fumigatus* with a MIC value of <1 μg/mL.

Across the broad sample, compound **1s** showed impressive activity against all three organisms with a MIC value of ≤ 1.0 μg/mL and MFC levels of ≤ 1.0 μg/mL against both fungal species *C. albicans* and *Aspergillus fumigatus*. Finally, it is of interest to note that the methylenedioxy substituted compounds exhibited the greatest antimicrobial activity. The replacement of the morpholine with *N*-methyl piprazine on methylenedioxy substituted compounds lowers the activity as antifungal but without effect on the antituberculosis activity. Chloro substituted compounds with *N*-methyl piperazine moiety exhibited similar antimicrobial activity to methylenedioxy substituted compounds.

Next in an expanded fungal panel, summarized in Table 2, **1s** was screened for MIC_{80}, MIC_{100} and MFC concentrations against seven *C. albicans* isolates, five *A. fumigates* isolates and three isolates of *Fusarium solani*, *Rhizopus arrhizus* and *Cyrptococcus neoformans.* The compound **1s** showed MIC_{80} of

Table 1. MIC and MFC values of 2-aryl 3-[1,2,4]triazolyl 4-thiazolidinone compounds.

Compound No	X	R_1	R_2	R_3	*C. albicans*		*A. fumigatus*		*M. tuberculosis*
					MIC (μg/mL)	MFC (μg/mL)	MIC (μg/mL)	MFC (μg/mL)	MIC (μg/mL)
1a	O	H	H	H	10	100	100	100	16
1b	O	H	H	CH_3	25	50	100	100	8
1c	O	CH_3	H	H	12.5	25	100	>100	3.13
1d	O	CH_3	H	CH_3	nt	nt	nt	nt	1.56
1e	O	Cl	H	H	25	50	nt	nt	1.56
1f	O	Cl	H	CH_3	>100	nt	100	>100	≤ 6.25
1g	O	OCH_3	OCH_3	H	>100	nt	100	>100	nd[a]
1h	O	OCH_3	OCH_3	CH_3	10	100	100	100	16
1i	O	$-OCH_2O-$		H	1.04	2.08	33.4	33.4	≤1
1j	O	$-OCH_2O-$		CH_3	12.2	25	100	100	4
1k	NCH_3	H	H	H	10	10	100	100	8
1l	NCH_3	H	H	CH_3	nt	nt	nt	nt	nt
1m	NCH_3	CH_3	H	H	10	>100	10	>100	nt
1n	NCH_3	CH_3	H	CH_3	10	10	10	100	≤1
1o	NCH_3	Cl	H	H	100	100	100	nt	nt
1p	NCH_3	Cl	H	CH_3	≤1	10	10	>100	2
1q	NCH_3	OCH_3	OCH_3	H	10	>100	10	>100	nt
1r	NCH_3	OCH_3	OCH_3	CH_3	100	>100	>100	nt	8
1s	NCH_3	$-OCH_2O-$		H	≤1	≤1	≤1	≤1	≤1
1t	NCH_3	$-OCH_2O-$		CH_3	3.12	6.25	10	10	3.13
Fluconazole					0.25	NA			
Voriconazole							13.5	NA	
Rifampin									0.062

[a] No activity observed at 6.25 μg/mL
NA: Not active
nt: Not tested

Table 2. Evaluation of **1s** against an expanded fungal panel.

Genus	Species	Isolate No.	MIC (80%)	MIC (100%)	MFC
Candida	*albicans*	116.98	1.56	1.56	>100
Candida	*albicans*	159.95	0.79	1.58	3.12
Candida	*albicans*	149.97	0.78	1.56	6.25
Candida	*albicans*	156.97	1.56	3.15	>100
Candida	*albicans*	126.97	1.56	3.12	3.12
Candida	*albicans*	117.00	0.78	3.12	25
Candida	*albicans*	A39	1.56	1.56	25
Aspergillus	*fumigatus*	168.95	10	50	>100
Aspergillus	*fumigatus*	182.99	3.12	50	>100
Aspergillus	*fumigatus*	119.00	3.12	50	>100
Aspergillus	*fumigatus*	165.86	50	50	>100
Aspergillus	*fumigatus*	153.90	3.12	50	>100
Fusarium	*solani*	152.89	3.12	50	50
Rhizopus	*arrhizus*	117.89	0.78	1.56	1.56
Cryptococcus	*neoformans*	H99	1.56	1.56	>100

3 μg/mL values against all tested strains except, *A. fumigatus* isolates 168.95 and 153.90. It has a MIC_{100} of 3 μg/mL or less against all *C. albicans* and *C. neoformans* strains. Also, **ls** showed MFC activity at 3 μg/mL against *C. albicans* 159.995 and 126.97 and *Rhizopus arrihizus.* Subsequently, the results show that sample **ls** shows great potential as an antifungal and anti-tuberculosis agent and thus it warrants further study.

In conclusion, the three-component *domino* reaction described in this paper is a very regioselective, facile and practical method for the synthesis of 4-thiazolidinone. The ease of the reaction procedure, the work-up and the significantly high yields prove this procedure to be a useful and an attractive alternative method to current linear-type synthesis of 4-thiazolidinone.

Experimental section

Biology

Mycobacterium tuberculosis susceptibility testing

The compounds were tested against *M. tuberculosis* H37Rv in BACTEC 12B medium using a fluorometric broth microdilution assay, the Microplate Alamar Blue Assay (MABA) [32]. Compounds were initially assessed at 6.25 μg/mL, and those effecting a reduction in fluorescence of at least 90% relative to untreated cultures were further evaluated for MIC by testing at lower concentrations. The MIC was defined as the lowest concentration of compound effecting a reduction of ≥90% of the relative fluorescence units relative to a control culture. Rifampin (control antibiotic) is typically used to treat *Mycobacterium* infections, including tuberculosis and Hansen's disease.

Antifungal test organisms

The fungi used in this study for all the compounds in Table 1 included two reference strains, *C. albicans* A39 and *A. fumigatus* (strain 168.95). Expanded studies on **1s-p** employed the fungi listed in Table 2.

Medium

Antifungal susceptibility testing was performed with RPMI 1640 medium (Sigma Chemical Co., St. Louis, MO) with glutamine, but without sodium bicarbonate, and was buffered at pH 7.0 with 0.165 M morpholinopropanesulfonic acid.

Antifungal in-vitro susceptibility testing

Experiments for determination of MICs of yeasts were performed by the broth macrodilution method according to the recommendations of the National Committee for Clinical Laboratory Standards [32]. The only difference compared to the standardized method was the choice of drug dilutions, which ranged from 100 to 0.09 μg/mL. Briefly, this method specifies the use of an inoculum grown at 35°C and adjusted to a concentration of 0.5×10^3 to 2.5×10^3 CFU/mL. Readings were taken at 48 h for all yeasts except for *C. neoformans*, for which the results are interpreted at 72 h. The MIC was defined as the culture with the lowest drug concentration in which a visual turbidity less than or equal to 80% inhibition compared to that produced by the growth control tube was observed.

The minimum fungicidal concentration (MFC) was determined by plating 100-μL aliquots from tubes showing complete inhibition of growth on Sabouraud agar plates. The lowest drug concentration that yielded three or fewer colonies was recorded as the MFC.

Moulds were tested by the same method [33], but with the following modifications. Isolates were grown on Sabouraud dextrose agar at 30°C; after adequate sporulation occurred (4–14 days), conidia were harvested by flooding the colonies with a sterile solution of 0.85% NaCl and 0.05% Tween 80 in sterile distilled water. Inocula were prepared with a hemocytometer for counting and were then diluted with RPM1 1640 medium to obtain a final inoculum size of approximately 0.5×10^3 to 2.5×10^3 CFU/mL. The inoculum size was verified by plating an aliquot of the inoculum. The cultures were incubated at 30°C for 48 to 72 h or until growth in the control tube was visible.

Synthetic protocols

Melting ranges (°C) were recorded on a Fischer-Johns apparatus (Fischer-Scientific, Pittsburgh, PA, USA) and were uncorrected. IR spectra were recorded on a Schimadzu IR-470 spectrometer (Schimadzu, Kyoto, Japan). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian EM-360 L NMR spectrometer at 300 MHz and 75 MHz, respectively. (Varian Inc., Palo Alto, CA, USA) Chemicals (Aldrich, Merck, Whitehouse Station, NJ, USA). Chemical shifts are expressed in δ-values (ppm) relative to TMS as internal standard and using CD_3Cl as solvent. High resolution MS were determined with a JEOL JMS-SX 102A spectrometer. Microanalytical data (C, N, H) agreed with the proposed structures within +0.4% of the theoretical values. Thin layer chromatography was performed on precoated silica gel plates (Kieselgel, 0.25 mm, 60G F 254, Merck). A developing solvent system of chloroform/methanol (8:2) was used and the spots were detected by ultraviolet light.

*Synthesis of 3-(substituted)-1H-1,2,4-triazole 5-amine (**3a,b**) [28]*

To a solution of *N*-cyanocarbonimidodithioic acid dimethyl ester (**5**) (36.5 g, 0.25 mol) in 100 mL MeCN was added morpholine or 4-methylpiprazine (0.25 mmol). The mixture was refluxed for 2 h, cooled and 15 mL $NH_2NH_2 \cdot H_2O$ was added and refluxed for additional 5 h. The solvent was evaporated under vacuum to give solid products. Recrystallization from appropriate solvent afforded **3**.

*3-(1-Morpholin-4-yl)-1H-1,2,4-triazol-5-amine (**3a**)*

Yield (89%), m.p. 167–168°C (2-PrOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.23 (t, J = 4.8 Hz, 4H, H-3 & 5-mor), 3.70 (t, J = 4.8 Hz, 4H, H-2 & 6-mor), 5.65 (brs, 2H, NH_2), 9.96 (br, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 46.6, 66.2, 158.6,163.4. IR ($CHCl_3$): $\bar{\nu}$ = 3220, 3130, 1630 cm^{-1}.

*3-(4-Methylpiprazin-1-yl)-1H-1,2,4-triazol-5-amine (**3b**)*

Yield (90%), m.p. 89–91°C (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33 (t, J = 6.2 Hz, 4H, H-3 & 5-pip), 3.35 (t, J = 6.2 Hz, 4H, H-2 & 6-pip), 5.80 (brs, 2H, NH_2), 11.0 (br, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 45.6, 45.4, 58.2, 159.3, 163.9. IR ($CHCl_3$): $\bar{\nu}$ = 3230, 3135, 1653 cm^{-1}.

*Synthesis of 3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-2-substituted phenyl-1,3-thiazolidin-4-one (**1a–j**)*

To a solution of 5-amino-3-(1-morpholino)-1*H*-[1,2,4]triazole **3a** (1.69 g, 10 mmol) in toluene (50 mL) was added aromatic aldehydes (10 mmol), α-mercaptoacids (10 mmol) and 1 g molecular sieves (4 Å). The mixture was heated at 100°C for 8 h. The solution was filtered and evaporated under vacuum. H_2O (100 mL) was added and the mixture was extracted with AcOEt (2 × 250 mL) and the organic layer was dried (Na_2SO_4) and solvent was evaporated under vacuum to give solid residues. Recrystallization from an appropriate solvent gave **1a–j**.

*3-[(3-Morpholino-1H-1,2,4-triazol-5-yl)]-2-phenyl-1,3-thiazolidin-4-one (**1a**)*

Yield (83%), m.p. 201–203°C (Hex/EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.25 (dt, J = 3, 4.7 Hz, 4H, H-3 & 5-mor), 3.71 (t, J = 4.7 Hz, 4H, H-2 & 6-mor), 3.77 (d, J = 16.8 Hz, 1H, H-5), 4.06 (dd, J = 1.3, 16.8 Hz, 1H, H-5), 6.38 (d, J = 1.3 Hz, 1H, H-2), 7.29–7.34 (m, 5H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 39.8, 46.7, 46.6, 59.8, 66.3, 66.5, 126.4, 126.6, 129.3, 129.5, 137.3, 138.5, 184.2, 196.9. IR ($CHCl_3$): $\bar{\nu}$ = 1706 cm^{-1}. MS m/z = 331 (100, M^+). HR-MS; 331.1117 for $C_{15}H_{17}N_5O_2S$ (331.1119).

*5-Methyl-3-[(3-morpholin4-yl)-1H-1,2,4-triazol-5-yl)]-2-phenyl-1,3-thiazolidin-4-one (**1b**)*

Yield (86%), m.p. 179–181°C (Hex/EtOAc) as diastereomeric mixture (*cis*/*trans*; 2:1).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.62 (d, J = 6.9 Hz, 3H, CH_3), 3.25 (dt, J = 1.2, 9.6 Hz, 4H, H-3 & 5-mor), 3.82 (t, J = 9.6 Hz, 4H, H-2 & 6-mor), 4.35 (dq, J = 0.6, 6.9 Hz, 1H, H-5), 6.31 (s, 1H, H-2), 7.37–7.25 (m, 5H, H-Ar).

trans-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, J = 6.9 Hz, 3H, CH_3), 3.20 (d, J = 15 Hz, 4H, H-3 & 5-mor), 3.73 (t, J = 15 Hz, 4H, H-2 & 6-mor), 4.11 (q, J = 6.9 Hz, 1H, H-5) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.3, 44.9, 46.7, 46.7, 59.8, 66.3, 66.6, 125.9, 126.5, 129.3, 129.5, 137.2, 158.5, 159.4 184.3. IR ($CHCl_3$): $\bar{\nu}$ = 1709 cm^{-1}; MS m/z = 345 (100, M^+); HR-MS; 345.1254 for $C_{16}H_{19}N_5O_2S$ (345.1259).

*2-(4-Methylphenyl)-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1c**)*

Yield (91%), m.p. 158–159°C (Hex/EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.26 (dt, J = 1.8, 4.8 Hz, 4H, H-3 & 5-mor), 3.72 (t, J = 4.8 Hz, 4H, H-2 & 6-mor), 3.76 (d, J = 16.5, 1H, H-5), 4.06 (dd, J = 1.2, 16.5 Hz, 1H, H-5), 6.36 (s, 1H, H-2), 7.14 (d, J = 8.1 Hz, 2H, H-Ar), 7.02 (d, J = 8.1 Hz, 2H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.6, 33.8, 46.7, 46.7, 59.8, 66.3, 66.5, 123.2, 123.6, 129.3, 129.5, 137.3, 138.4, 157.4, 158.5, 184.2. IR ($CHCl_3$): $\bar{\nu}$ = 1706 cm^{-1}; MS m/z = 345 (100, M^+), 135 (57). HR-MS; 345.1260 for $C_{16}H_{19}N_5O_2S$ (345.1259).

*5-Methyl-2-(4-methylphenyl)-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1d**)*

Yield (88%), m.p. 179–180°C (Hex/EtOAc) as diastereomeric mixture (*cis*/*trans*; 2:1).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 6.9 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.24 (t, J = 4.2 Hz, 4H, H-3 & 5-mor), 3.68–3.74 (m, 4H, H-2 & 6-mor), 4.25 (q, J = 6.9 Hz, 1H, H-5), 6.29 (s, 1H, H-2), 7.13 (d, J = 8 Hz, 2H, H-Ar), 7.21 (d, J = 8Hz, 2H, H-Ar)

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.71 (d, J = 6.9 Hz, 3H, CH_3), 4.09 (q, J = 6.9 Hz, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.3, 21.2, 40.9, 46.7, 46.7, 59.8, 66.3, 66.6, 125.7, 126.5, 129.3, 129.5, 137.2, 138.5, 157.4, 158.5, 184.3. IR ($CHCl_3$): $\bar{\nu}$ = 1706 cm^{-1}. MS m/z = 359 (100, M^+), 149 (35.7) 135 (17.2). HR-MS; 359.1419 for $C_{17}H_{21}N_5O_2S$ (359.1416).

*2-(4-Chlorophenyl)-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)1,3-thiazolidin-4-one (**1e**)*

Yield (79%), m.p. 202–203°C (Hex/EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.25 (dt, J = 2.1, 5.1 Hz, 4H, H-3 & 5-mor), 3.74 (t, J = 5.1 Hz, 4H, H-2 & 6-mor), 3.79 (d, J = 16.5 Hz, 1H, 5-H_1), 4.03 (dd, J = 1.4, 16.5 Hz, 1H, H-5), 6.34 (d, J = 1.2 Hz, 1H, H-2), 7.25–7.33 (m, 4H, H-Ar) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 34.7, 46.6, 59.8, 65.7, 66.3, 127.5, 129.0, 134.6, 138.7, 157.3, 158.6, 171.7 ppm; IR ($CHCl_3$): $\bar{\nu}$ = 1706 cm^{-1}. MS m/z = 367 (38.7, M^++2), 365 (100, M^+), 135 (47.8). HR-MS; 365.0718 for $C_{15}ClH_{16}N_5O_2S$ (365.0713).

*2-(4-Chlorophenyl)-5-methyl-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1f**)*

Yield (81%), m.p. 219–220°C (Hex/EtOAc) as diastereomeric mixture (*cis*/*trans*; 5:1).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.71 (d, J = 6.9 Hz, 3H, CH_3), 3.19–3.26 (m, 4H, H-3 & 5-mor), 3.69–3.74 (m, 4H, H-2 & 6-mor), 4.11 (q, J = 6.9 Hz, 1H, H-5), 6.26 (s, 1H, H-2), 7.47–738 (m, 4H, H-Ar). *trans*-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.62 (d, J = 6.9 Hz, 3H, CH_3), 3.9–3.26 (m, 4H, H-3 & 5-mor), 3.69–3.74 (m, 4H, 2 H-2 & 6-mor), 4.28 (q, J = 6.9 Hz, 1H, H-5), 6.26 (s, 1H, H-2), 7.47–7.38 (m, 4H, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 42.7, 46.6, 59.8, 66.3, 127.5, 129.0, 134.6, 138.8, 157.4, 158.5, 171.7. IR ($CHCl_3$): $\bar{\nu}$ = 1706 cm^{-1}. MS m/z = 381 (38.5, M^++2), 379 (100, M^+), 135. HR-MS; 379.0867 for $C_{16}ClH_{18}N_5O_2S$ (379.0869).

*2-(3,4-Dimethoxyphenyl)-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1g**)*

Yield (73%), m.p. 148–150°C (Hex/EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.27 (dt, J = 1.8, 5.0 Hz, 4H, H-3 & 5-mor), 3.73 (t, J = 5.0 Hz, 4H, H-2 & 6-mor), 3.77 (d, J =16.5 Hz, 1H, H-5), 3.89, 3.90 (s, 3H each, 2 MeO), 4.04 (dd, J = 1.2, 16.5 Hz, 1H, H-5), 6.35 (d, J =1.2 Hz, 1H, H-2), 6.77–6.80 (m, 1H, H-Ar),

6.86–6.88 (m, 2H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.9, 46.6, 55.9, 55.9, 62.4, 65.8, 66.3, 115.7, 117.9, 122.3, 132.4, 149.2, 149.4, 157.4, 158.5, 171.9. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}. MS $m/z = 391$ (100, M^+), 165 (31.4). HR-MS; 391.1308 for $C_{17}H_{21}N_5O_2S$ (391.1314).

*2-(3,4-Dimethoxyphenyl)-5-methyl-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1h**)*

Yield (79%), m.p. 193–194°C (Hex/EtOAc) as diastereomeric mixture (*cis*/*trans*; 1:1).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.62 (d, $J = 6.9$ Hz, 3H, CH_3), 3.22–3.30 (m, 4H, H-3 & 5-mor), 3.72 (q, $J = 9.6$ Hz, 4H, H-2 & 6-mor), 3.86 (s, 6H, 2 OMe), 4.10 (q, $J = 9.6$ Hz, 1H, H-5), 6.29 (d, $J = 2.4$ Hz, 1H, H-2), 6.76–6.89 (3H, m, H-Ar).

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.72 (d, $J = 6.9$ Hz, 3H, CH_3), 4.26 (q, $J = 6.9$ Hz, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.7, 42.2, 46.1, 55.2, 55.3, 62.0, 66.2, 66.3, 116.6, 117.3, 122.2, 131.3, 147.8, 148.6, 157.3, 158.4, 171.8. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}. MS $m/z = 405$ (100, M^+), 179 (24.2). HR-MS; 405.1473 for $C_{18}H_{23}N_5O_2S$ (405.1470).

*2-(Benzo[d][1,3]dioxol-6-yl)-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1i**)*

Yield (69%), m.p. 191–192°C (Hex/EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.28 (dt, $J = 2.0$, 3.6 Hz, 4H, H-3 & 5-mor), 3.74 (t, $J = 3.6$ Hz, 4H, H-2 & 6-mor), 3.83 (d, $J = 16.5$ Hz, 1H, H-5), 4.05 (dd, $J = 1.3$, 16.5 Hz, 1H, H-5), 5.96 (d, $J = 1.2$ Hz), 2H, 6.31 (s, 1H, H-2), 6.72–6.82 (m, 3H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 35.6, 46.7, 65.7, 66.5, 67.0, 101.6, 117.9, 116.4, 125.8, 132.7, 149.7, 148.9, 157.8, 158.8, 172.4. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}. MS $m/z = 375$ (100, M^+), 150 (15.9). HR-MS; 375.1011 for $C_{16}H_{17}N_5O_2S$ (375.1001).

*2-(Benzo[d][1,3]dioxol-6-yl)-5-methyl-3-[(3-morpholin-4-yl)-1H-1,2,4-triazol-5-yl)]-1,3-thiazolidin-4-one (**1j**)*

Yield (71%), m.p. 182–183°C (Hex/EtOAc) as diastereomeric mixture (*cis*/*trans*; 1:1).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.61 (d, $J = 6.9$ Hz, 3H, CH_3), 3.22–3.31 (m, 4H, H-3 & 5-mor), 3.70–3.75 (m, 4H, H-2 & 6-mor), 4.09 (q, $J = 6.9$ Hz, 1H, H-5), 5.96 (d, $J = 1.2$ Hz), 6.24 (s, 1H, H-2), 6.70–6.86 (m, 3H, H-Ar).

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.72 (d, $J = 6.9$ Hz, 3H, CH_3), 4.25 (q, $J = 6.9$ Hz, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.8, 44.4, 46.5, 65.2, 66.3, 66.7, 101.1, 117.2, 116.2, 125.2, 131.6, 148.6, 148.9, 157.9, 158.9, 172.4. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}. MS $m/z = 389$ (100, M^+), 165 (18.8). HR-MS; 389.1153 for $C_{17}H_{19}N_5O_2S$ (389.1157).

*Synthesis of 3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-2-substituted phenyl-1,3-thiazolidin-4-one (**1k–t**)*

To a solution of 5-amino-3-(4-methylpiperazin-1-yl)-1*H*-[1,2,4]-triazole **3b** (1.82 g, 10 mmol) in toluene (50 mL) was added aromatic aldehydes (10 mmol), α-mercaptoacids (10 mmol) and 1 g molecular sieves (4 Å). The mixture was heated at 100°C for 8 h. The solution was filtered, evaporated under vacuum, dissolved in H_2O (100 mL) and the mixture was extracted with AcOEt (2 × 250 mL) and the organic layer was dried (Na_2SO_4) and solvent was evaporated under vacuum to give solid residues. Recrystallization from an appropriate solvent gave **1k-t**.

*3-[3-(4-Methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-2-phenyl-1,3-thiazolidin-4-one (**1k**)*

Yield (69%), m.p. 168–170°C (Hex/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, NMe), 2.41 (t, $J = 5.1$ Hz, 4H, H-3 & 5-pipzin), 3.29 (dt, $J = 1.8$, 3.6 Hz, 4H, H-2 & 6-pipzin), 3.76 (d, $J = 16.5$ Hz, 1H, H-5), 4.04 (dd, $J = 1.2$, 16.5 Hz, 1H, H-5), 6.39 (d, $J = 1.2$ Hz, 1H, H-2), 7.31–7.33 (m, 5H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.7, 46.2, 46.3, 54.3, 62.3, 78.8, 125.9, 128.7, 198.8, 140.2, 171.9, 184.3, 184.3. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}. MS $m/z = 344$ (56.5, M^+), 274 (100) 200 (61.5), 71 (82.1), 70 (30.7), 43 (60.2). HR-MS; 344.1417 for $C_{16}H_{20}N_6OS$ (344.1419).

*5-Methyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-2-phenyl-1,3-thiazolidin-4-one (**1l**)*

Yield (65%), m.p. 159–160°C (Hex/EtOAc).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.61 (d, $J = 6.9$ Hz, 3H, CH_3), 2.28 (s, 3H, NMe), 2.42 (t, $J = 5.1$ Hz, 4H, H-3 & 5-pipzin), 3.31 (dd, $J = 4.2$, 6.3 Hz, 4H, H-2 & 6-pipzin), 4.24 (q, $J = 6.9$ Hz, 1H, H-5), 6.32 (d, J =1.2 Hz, 1H, H-2), 7.28–7.34 (m, 5H, H-Ar);

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.70 (d, $J = 6.9$, 3H, CH_3), 2.27 (s, 3H, NMe), 4.10 (q, $J = 6.9$ Hz, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.3, 20.4, 40.9, 42.4, 46.2, 46.2, 46.3, 54.3, 54.3, 59.9, 60.9, 46.3, 54.3, 54.3, 59.9, 60.9, 125.8, 126.6, 128.8, 128.6, 140.9, 125.8, 126.6, 128.8, 128.6, 145.2, 184.3. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}; MS $m/z = 358$ (51.4, M^+), 288 (100), 200 (59.3), 71 (67.8), 70 (24.3), 43 (46.9). HR-MS; 358.1578 for $C_{17}H_{22}N_6OS$ (358.1576).

*2-Methylphenyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1m**)*

Yield (67%), m.p. 149–150°C (Hex/EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, NMe), 2.33 (s, 3H, CH_3), 2.42 (t, $J = 5.1$ Hz, 4H, H-3 & 5-pipzin), 3.31 (t, J =5.1 Hz, 4H, H-2 & 6-pipzin), 3.75 (d, $J = 16.5$, 1H, H-5), 4.04 (dd, $J = 1.2$, 16.5 Hz, 1H, H-5), 6.37 (s, 1H, H-2), 7.13 (d, $J = 8.4$ Hz, 2H, H-Ar), 7.21 (d, $J = 8.4$ Hz, 2H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.2, 32.8, 46.3, 54.4, 62.2, 115.3, 125.9 × 2, 129.4 × 2, 137.2, 138.6, 171.9, 184.3, 197.0. IR ($CHCl_3$): $\overline{\nu} = 1706$ cm^{-1}; MS $m/z = 358$ (56.1, M^+), 288 (100), 214 (58.0), 71 (68.6), 70 (25.1), 43 (48.4). HR-MS; 358.1571 for $C_{17}H_{22}N_6OS$ (358.1576).

*5-Methyl-2-methylphenyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1n**)*

Yield (65%), m.p. 154–156°C (Hex/EtOAc).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.72 (d, J = 7.2 Hz, 3H, CH_3), 2.28 (s, 3H, NMe), 2.32 (s, 3H, CH_3), 2.39–2.43 (m, 4H, H-3 & 5-pipzin), 3.25–3.30 (m, 4H, H-2 & 6-pipzin), 4.12 (q, J = 7.2 Hz, 1H, H-5), 6.30 (s, 1H, H-2), 7.12 (t, J = 8.1 Hz, 2H, H-Ar), 7.21 (t, J = 8.1 Hz, 2H, H-Ar) ppm;

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.62 (3H, d, J = 7.2 Hz), 2.29 (3H, s, NMe), 2.33 (3H, s), 4.24 (1H, q, J = 7.2 Hz, 5-H_1). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 20.4, 21.2, 42.4, 46.2, 46.3, 54.2, 54.3, 60.8, 125.7, 126.5 × 2, 129.3 × 2, 129.5, 174.8, 184.3, 197.6. IR ($CHCl_3$): $\bar{\nu}$ = 1706 cm^{-1}; MS m/z = 372 (50.3, M^+), 302 (100), 214 (54.5), 71 (59.2), 70 (21.0), 43 (43.2). HR-MS; 372.1730 for $C_{18}H_{24}N_6OS$ (372.1732).

*2-(4-Chlorophenyl)-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1o**)*

Yield (77%), m.p. 139–140°C (Hex/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, NMe), 2.43 (t, J = 5.1 Hz, 4H, H-3 & 5-pipzin), 3.30 (t, J = 1.2, 5.1 Hz, 4H, H-2 & 6-pipzin), 3.78 (d, J = 16.5 Hz, 1H, H-5), 4.02 (d, J = 16.5 Hz, 1H, H-5), 6.35 (d, J = 1.2 Hz, 1H, H-2), 7.25–7.33 (4H, m, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 34.7, 46.6, 59.8, 65.7, 66.3, 127.5, 129.0, 134.6, 138.7, 157.3, 158.6, 171.7. IR ($CHCl_3$): $\bar{\nu}$ = 1709 cm^{-1}. MS m/z = 380 (14.6, M^++2), 378 (38.6, M^+), 308 (71.4), 234 (46.9), 71 (100), 70 (47.9), 43 (82.1), 42 (41.9). HR-MS; 378.1032 for $C_{16}ClH_{19}N_6OS$ (378.1029).

*2-(4-Chlorophenyl)-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1p**)*

Yield (73%), m.p. 168–170°C (Hex/EtOAc).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 6.9 Hz, 3H, CH_3), 2.29 (s, 3H, NMe), 2.38–2.45 (m, 4H, H-3 & 5-pipzin), 3.25–3.33 (m, 4H, H-2 & 6-pipzin), 4.18 (q, J = 6.9 Hz, 1H, H-5), 6.29 (d, J = 2.4 Hz, 1H, H-2), 7.18–7.32 (m, 4H, H-Ar);

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.69 (d, J = 6.9 Hz, 3H, CH_3), 2.28 (s, 3H, NMe), 4.11(q, J = 6.9 Hz, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.5, 42.7, 45.7, 46.8, 60.1, 66.2, 127.1, 129.3, 134.7, 138.9, 157.6, 158.5, 171.9 ppm; IR ($CHCl_3$): $\bar{\nu}$ = 1710 cm^{-1}. MS m/z = 394 (13.8, M^++2), 392 (36.4, M^+), 322 (73.2), 234 (48.9), 71 (100), 70 (45.7), 43 (81.7), 42 (39.4). HR-MS; 392.1188 for $C_{17}ClH_{21}N_6OS$ (392.1186).

*2-(3,4-Dimethoxyphenyl)-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1q**)*

Yield (78%), m.p. 122–124°C (Hex/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, NMe), 2.43 (t, J = 5.1 Hz, 4H, H-3 & 5-pipzin), 3.33 (t, J = 5.1 Hz, 4H, H-2 & 6-pipzin), 3.72 (d, J = 16.5 Hz, 1H, H-5), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.03 (dd, J = 1.5, 16.5 Hz, 1H, H-5), 6.38 (d, J = 1.5 Hz, 1H, H-2), 6.69–6.89 (m, 3H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.6, 46.1, 45.6, 46.6, 54.8, 55.8, 55.9, 62.7, 109.2, 110.6, 118.5, 132.9, 149.4, 171.5, 184.7, 197.2. IR ($CHCl_3$): $\bar{\nu}$ = 1707 cm^{-1}; MS m/z = 404 (65.9, M^+), 332 (100), 244 (41.9), 71 (73.4), 70 (27.0), 43 (53.8), 42 (27.4). HR-MS; (404.1633) for $C_{18}H_{24}N_6O_3S$ (404.1631).

*2-(3,4-Dimethoxyphenyl)-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1r**)*

Yield (79%), m.p. 138–139°C (Hex/EtOAc).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.73 (d, J = 7.2 Hz, 3H, CH_3), 2.29 (s, 3H, NMe), 2.42 (t, J = 5.1 Hz, 4H, H-3 & 5-pipzin), 3.34 (t, J = 5.1 Hz, 4H, H-2 & 6-pipzin), 3.85 (s, 6H, 2OMe), 4.12 (q, J = 7.2 Hz, 1H, H-5), 6.28 (d, J = 1.5 Hz, 1H, H-2), 6.77–6.92 (m, 3H, H-Ar) ppm;

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.63 (d, J = 7.2 Hz, 3H, CH_3), 2.31 (s, 3H, NMe), 4.23 (q, J = 7.2 Hz, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21. 2, 42.7, 46.1, 45.7, 54.6, 55.3, 62.0, 66.2, 66.3, 116.6, 117.3, 122.2, 131.3, 147.8, 148.6, 157.3, 158.4, 171.8. IR ($CHCl_3$): $\bar{\nu}$ = 1707 cm^{-1}; MS m/z = 418 (63.1, M^+), 332 (100), 244 (44.5), 71 (76.7), 70 (24.0), 43 (51.8), 42 (25.1). HR-MS; (418.1785) for $C_{18}H_{22}N_6O_3S$ (418.1787).

*2-(Benzo[d][1,3]dioxol-6-yl)-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1s**)*

Yield (73%), m.p. 155–157°C (Hex/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, NMe), 2.11 (t, J = 5.1 Hz, 4H, H-3 & 5-pipzin), 3.26 (t, J = 5.1 Hz, 4H, H-2 & 6-pipzin), 3.72 (d, J = 16.5 Hz, 1H, H-5), 4.01 (d, J = 16.5 Hz, 1H, H-5), 5.94 (s, 2H, OCH_2O), 6.27 (d, J = 2.5 Hz, 1H, H-2), 6.70–6.86 (m, 3H, H-Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 33.6, 45.5, 46.7, 54.7, 56.1, 65.7, 110.2, 112.6, 113.8, 122.8, 132.7, 148.4, 149.4, 159.8, 161.8, 171.4. IR ($CHCl_3$): $\bar{\nu}$ = 1708. MS m/z = 388 (68.3, M^+), 332 (100), 244 (46.2), 71 (77.8), 70 (25.9), 43 (55.1), 42 (26.6). HR-MS; (388.1320) for $C_{18}H_{22}N_6O_3S$ (388.1318).

*2-(Benzo[d][1,3]dioxol-6-yl)-5-methyl-3-[3-(4-methylpiperazin-1-yl)-1H-1,2,4-triazol-5-yl]-1,3-thiazolidin-4-one (**1t**)*

Yield (70%), m.p. 129–1130°C (Hex/EtOAc).

cis-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.60 (d, J = 6.9 Hz, 3H, CH_3), 2.30 (s, 3H, NMe), 2.12 (t, J = 5.1 Hz, 4H, H-3 & 5-pipzin), 3.24 (t, J = 5.1 Hz, 4H, H-2 & 6-pipzin), 4.27 (q, J = 6.9 Hz, 1H, H-5) 5.92 (s, 2H, OCH_2O), 6.27 (d, J = 2.5 Hz, 1H, H-2), 6.70–6.86 (m, 3H, H-Ar);

trans-Isomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.71 (d, J = 6.9 Hz, 3H, CH_3), 2.29 (s, 3H, NMe), 4.09 (, J = 6.9 Hz, 1H, H-5) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.8, 42.4, 45.5, 46.5, 54.7, 63.2, 110.2, 112.1, 117.2, 122.2, 131.6, 148.6, 148.9, 158.9, 161.9, 174.1. IR ($CHCl_3$): $\bar{\nu}$ = 1706; MS m/z = 402 (70.3, M^+), 332

(100), 244 (46.2), 71 (76.4), 70 (27.8), 43 (57.5), 42 (23.6). HR-MS; 402.1467 for $C_{18}H_{22}N_6O_3S$ (402.1474).

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