Med Chem Res (2012) 21:212–223
DOI 10.1007/s00044-010-9531-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological activity studies of new hybrid molecules containing tryptamine moiety

Hakan Bektas · Ahmet Demirbas · Neslihan Demirbas · Sengul Alpay Karaoglu

Received: 17 June 2010 / Accepted: 2 December 2010 / Published online: 15 December 2010

Abstract The synthesis of *N*′-(4-substitutedphenylsulfonyl)-2-{4-[2-(1*H*-indol-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetohydrazides (**3a–c**), 2-{4-[2-(1*H*-indol-3-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}-*N*′-aryl methylidene acetohydrazides (**4a–f**) and 4-[2-(1*H*-indol-3-yl)ethyl]-5-(4-substitutedbenzyl)-2-[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**5a**, **b**) was performed starting from the corresponding acid hydrazides (**2a**, **b**) which was reported earlier. The treatment of 1,3,4-oxadiazole derivatives (**5a**, **b**) with hydrazine hydrate produced 4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl derivatives (**6a**, **b**). Then, compound **6b** was converted to the corresponding Schiff base (**7**) by the treatment with anisaldehyde. The synthesis of 5-(4-chlorobenzyl)-4-[2-(1*H*-indol-3-yl)ethyl]-2-[(4-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**8**) and 5-(4-methylbenzyl)-4-[2-(1*H*-indol-3-yl)ethyl]-2-[(4-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**10**) was carried out by the reaction of acid hydrazides (**2a**, **b**) with aryl iso(thio)cyanates either via the formation of the intermediates (**9a**, **b**) (for **10**) or direct cyclization (for **8**). 1,3-Oxa(thia)zol-2(3H)-ylidene]acetohydrazide derivatives (**11a**, **b**) were obtained by the reaction of **9a**, **b** with 4-chlorophenacyl bromide. All newly synthesized compounds were screened for their antimicrobial activities and some of which was found to be active against the test microorganisms.

Keywords 1*H*-indole · 1,2,4-Triazole · Schiff base · 1,3-Oxadiazole · 1,3-Thiazole · Antimicrobial activity

H. Bektas
Department of Chemistry, Faculty of Sciences, Giresun University, 28100
Giresun, Turkey

A. Demirbas · N. Demirbas (✉)
Department of Chemistry, Faculty of Sciences,
Karadeniz Technical University, 61080 Trabzon, Turkey
e-mail: neslihan@ktu.edu.tr

S. A. Karaoglu
Department of Biology, Faculty of Sciences,
Rize University, 53100 Rize, Turkey

Introduction

Research and development of potent and efficient antimicrobial agents possessing the activity not only on the control of serious infections, but also for the prevention and treatment of some infectious diseases constitutes a major challenge in medicinal chemistry. Although these efforts has resulted in the development of a wide variety of antimicrobial agents, as a result of misuse and overuse of antibiotics, pathogenic microorganisms have developed resistance associated with an increase in mortality towards number of antibiotics which have been using clinically as significant drugs, such as β-lactam antibiotics, macrolides, quinolones and vancomycin. Resistance has been defined as the temporary or permanent ability of an organism and its progeny to remain viable and/or multiply under conditions that would destroy or inhibit other members of the strain. Bacteria may be defined as resistant when they are not susceptible to a concentration of antibacterial agent used in practice. Traditionally, resistance refers to instances where the basis of increased tolerance is a genetic change, and where the biochemical basis is known. Such serious global health problem demands a renewed effort seeking the development of new antimicrobial agents, and

much attention has been focused on addressing the problem of multi-drug resistant (MDR) bacteria and fungi resulting from the widespread use and misuse of classical antimicrobial agents (Ozdemir *et al*., 2007; Tuncbilek *et al*., 2009; Giraud *et al*., 2008, 2009; Hester and Nesnow, 2008; Ezabadi *et al*., 2008).

In order to search and synthesize of combinational chemotherapeutic drugs with different mechanisms of action and with low side effects constitute an important part of the methods that aims to overcome the antimicrobial resistance. Beside the development of completely new agents possessing chemical characteristics that clearly differ from those of existing ones, there is another approach containing to combine two or more pharmacophores each with different mode of action, into a single molecule. These merged pharmacophore may be addressing the active site of different targets and offer the possibility to overcome drug resistance. In addition, this approach can also reduce unwanted side effects (Rawal *et al*., 2005; Bonde and Gaikwad, 2004; Rawal *et al*., 2007; Dixit *et al*., 2006; Kaplancikli *et al*., 2008, Solomon *et al*., 2010).

Among the important pharmacophores responsible for antimicrobial activity, the azole scaffold is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antimicrobial agents. Among azole-based drugs, which have been using for the treatment of fungal infections, Conazoles, such as Itraconazole, Fluconazole, Voriconazole and Ravuconazole are widely used and studied class of antimicrobial therapeutics due to their safety profile and high therapeutic index (Yu *et al*., 2007; Gupta *et al*., 2007; Schiller and Fung, 2007; Ashok *et al*., 2007; Rostom *et al*., 2009). In addition, it has been reported that remarkable antibacterial activity against methicillin-resistant strains of *Staphylococcus aureus* (MRSA) has been ascribed to some azoles, particularly miconazole.

It has been reported that the primary structural requirement for the antimicrobial azole class is a weak basic azole nucleus bonded by a nitrogen–carbon linkage to the rest of the structure. In this connection, the amidine nitrogen (in imidazole or triazole) is believed to bind the heme iron of enzyme-bound cytochrome P450 to prevent oxidation of steroidal substrates by the enzyme. Azoles containing aromatic substituents have been believed to mimic the corresponding non-polar steroidal portion of the substrate for the enzyme. The non-polar functionality leads to high degree of lipophilicity to the antifungal azoles. On the other hand, it was reported that incorporation of various halo substituents into the heterocyclic ring systems augments biological activities considerably. Furthermore, introduction a chloro-substituted benzene moiety into triazole scaffold results in increase of broad spectrum of antimicrobial activity due to the ability of halogen to act as polar hydrogen or hydroxy mimic. Substitution of hydrogen by halogen atom has been a strategy in designing molecules having biological activity. Although triazole and imidazole nuclei act by the same mechanism of action, triazoles have been possess advantages over imidazoles, which have slow metabolic rate, oral bioavailability, and less effect on human sterol synthesis. For these reasons, imidazoles have slowly being replaced by triazole molecules (Rostom *et al*., 2009; Sahoo *et al*., 2010).

Ribavirin (antiviral), Rizatriptan (antimigraine) and Alprazolam (anxiolytic) are the other examples of drugs containing triazole moiety (Cai *et al*., 2007; Rao *et al*., 2006; Hancu *et al*., 2007). Other therapeutic effects of 1,2,4-triazole derivatives have been reported on inflammation, cancer, pain, tuberculosis or hypertension (Kuçukguzel *et al*., 1999; Yuksek *et al*., 1997; Tozkoparan *et al*., 2000; Ikizler *et al*., 2000; Demirbas *et al*., 2002; Turan-Zitouni *et al*., 2001). Moreover, a number of triazole derivatives containing an imine bond have intensively been synthesized due to their biological activities (Demirbas *et al*., 1996, 2009; Bayrak *et al*., 2009a, b; Bektas *et al*., 2010a, b; Isloor *et al*., 2009; Karthikeyan *et al*., 2006).

Oxazolidinones are the other important azole derivatives incorporated into new class of totally synthetic antibiotics, such as Linezolid, Eperezolid, AZD2564 and the thiomorpholine analogue of linezolide, PNU-100480 (Das *et al*., 2005; Cui *et al*., 2005). Also Eperezolid derivatives containing five-membered heterocycles have been found to be active. Moreover, the tryptamine sub-structure is present in numerous naturally occurring and synthetic compounds, many of which exhibit important pharmacological activities. For example, a number of 5-alkyltryptamine derivatives which are known as triptans collectively, e.g. sumatriptan, have been using as antimigraine drugs. Some *N,N*-disubstituted tryptamines have been reported to show psychotomimetic activity, although there is evidence to suggest that the tryptamine derivatives are metabolized in vivo to more active forms. In addition, some tryptamine-based sulfonamides have been reported as human β3-adrenergic receptor agonists (Kobeci *et al*., 2005; Sawa *et al*., 2005; Yamazaki *et al*., 2009; Jenkins *et al*., 2008).

Synthetic organic chemistry has always been a vital part of the highly integrated and multidisciplinary process of various drug developments. Hydrazides and their derivatives have been in generally used as the starting materials for the synthesis of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles, 1,3-oxazolidin-2-ones, 1,3-thiazolidin-2-ones (Weidinger-Wells *et al*., 2002; Demirbas *et al*., 2005, 2007). Furthermore, heterocyclic hydrazides are generally utilized as intermediates for the synthesis of several condensed systems containing triazoles and other moieties (Demirbas *et al*., 2005; Holla *et al*., 2002).

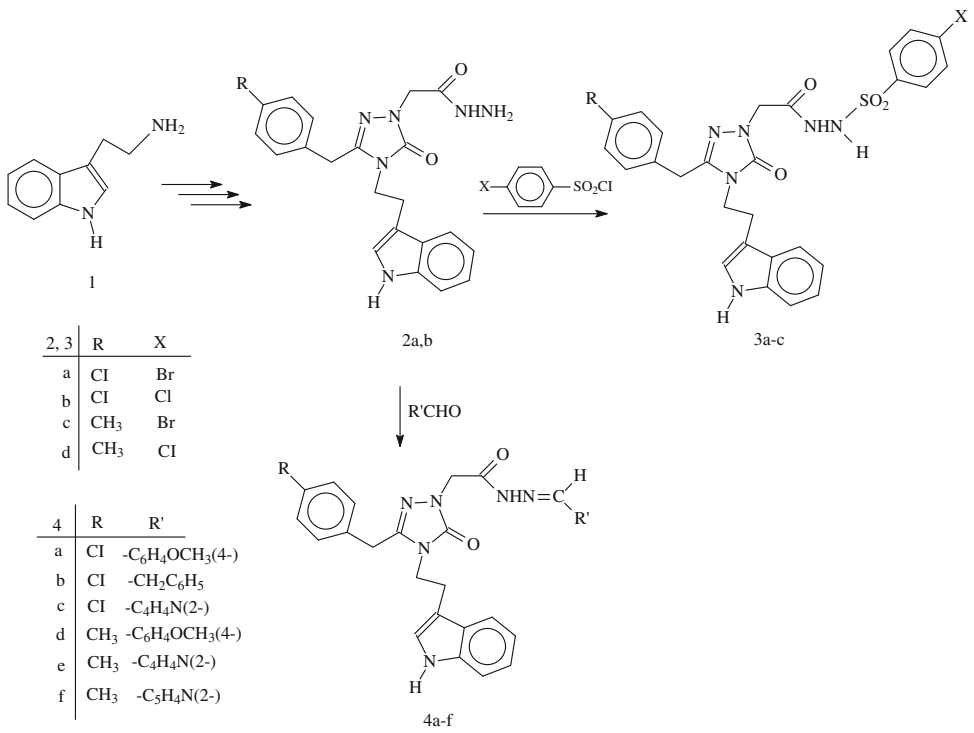
Motivated by these findings and in continuation of our ongoing efforts endowed with the discovery of nitrogenated heterocycles with potential chemotherapeutic activities, we would like to report here the synthesis and investigation of antimicrobial activities of new 1*H*-indole derivatives incorporating such pharmacophore heterocycles in a single structure as 1,2,4-triazole, 1,3-oxazole and/or 1,3-thiazole moieties.

Chemistry, results and discussion

The main aim of the present study is to synthesize and investigate the antimicrobial activity of new hybrid molecules incorporating two or more heterocyclic pharmacophores. The synthesis pathway leading to the title compounds was shown in Fig. 1.

2-{3-(4-substitutedbenzyl)-4-[2-(1*H*-indol-3-yl)ethyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetohydrazides (**2a**, **b**) have been prepared by the way reported by us, recently, starting from tryptamine [2-(1*H*-indol-3-yl)ethylamine] by three steps (Bektas *et al*. 2010a, b). The condensation of compounds **2a** and **2b** with two different aromatic sulfonyl chlorides in boiling ethanol has afforded the corresponding *N*′-(4-substitutedphenylsulfonyl)-2-{4-[2-(1*H*-indol-3-yl) ethyl]-3-(4-substitutedbenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetohydrazides (**3a**, **b**), while the refluxing of the same intermediates (**2a**, **b**) with several aldehydes in ethanol has resulted in the formation of the corresponding Schiff bases (**4a**–**f**) in good yields. This idea originated from the need to incorporate an sulfonamide or imine moiety to molecule, because, so far, the antimicrobial properties of sulfonamides or imine compounds were well documented. The synthesis of 4-[2-(1*H*-indol-3-il)ethyl]-5-(4-substitutedbenzyl)-2-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**6a**, **b**) has been performed starting from hydrazides (**2a**, **b**) via the formation of 4-[2-(1*H*-indol-3-yl)ethyl]-5-(4-substitutedbenzyl)-2-[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**5a**, **b**). Then, the 4-amino group on 1,2,4-triazol-3-yl moiety of compound **6a** has been functionalized to 4-methoxyphenylmethyliden derivative (**7**) with the aim to increase the lipophilicity of the molecule with antimicrobial activity.

The reactions of compounds **2a**, **2b** with benzylisothiocyanate in ethanol under reflux temperature has yielded different type of products (**8** and **9a**); compound **2a** has produced 3-chlorobenzyl-2-({4-[2-(1*H*-indol-3-yl)ethyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetyl)-*N*-benzylhydrazinecarboxamide **9a** by the treatment with benzylisothiocyanate in boiling ethanol, whereas the reaction of compound **2b** has resulted in further ring cyclization in the same reaction conditions, thus, compound **8** has formed (Fig. 2). On the other hand, the synthesis of compound **10** has been performed by intramolecular cyclization of carboxamide side chain of **9a** in the presence of alcoholic KOH under reflux conditions.



2, 3	R	X
a	Cl	Br
b	Cl	Cl
c	CH_3	Br
d	CH_3	Cl

4	R	R'
a	Cl	$-C_6H_4OCH_3$(4-)
b	Cl	$-CH_2C_6H_5$
c	Cl	$-C_4H_4N$(2-)
d	CH_3	$-C_6H_4OCH_3$(4-)
e	CH_3	$-C_4H_4N$(2-)
f	CH_3	$-C_5H_4N$(2-)

Fig. 1 Preparation of compounds **1**–**4**

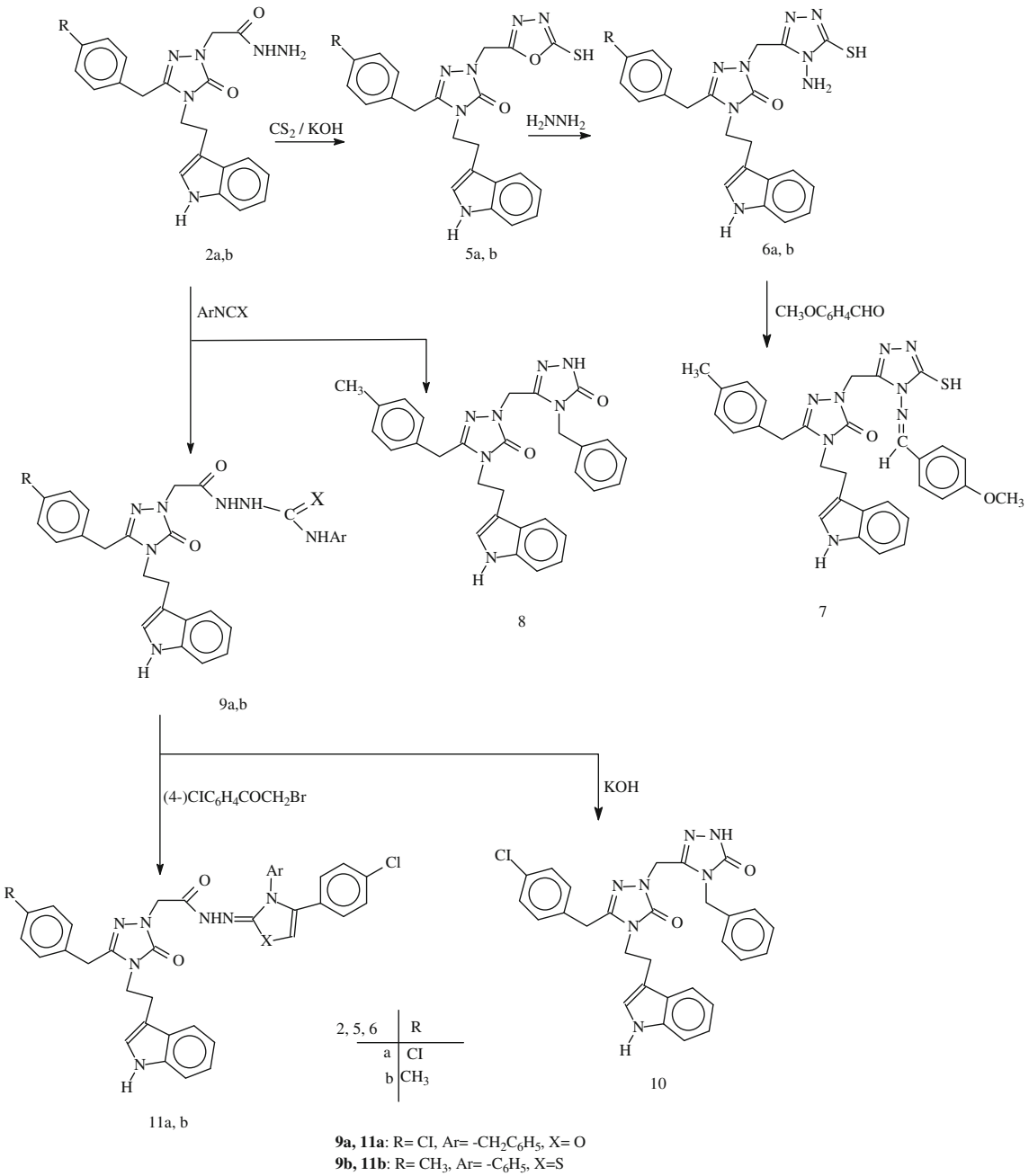


Fig. 2 Synthetic pathway for the preparation of compounds **5–11**

With the aim of introducing of an 1,3-oxazole or 1,3-thiazole nucleus to molecule, compounds **9a** and **9b** were condensed with 4-chlorophenacyl bromide in ethanol in the presence of dried sodium acetate under reflux conditions; thus, the synthesis of **11a** and **11b** has been achieved.

The structures of all newly synthesized compounds were confirmed based on FT-IR, LC-MS, ^{1}H NMR and ^{13}C NMR spectral data and elemental analysis.

None of the synthesized compounds displayed antifungal activity against *Candida albicans* (Ca), *Saccharomyces cerevis* (Sc) and *Candida tropicalis* (Ct) (data not shown). Compounds **3a–d** were found to be active against Gram negative bacillus, *Pseudomonas aeruginosa* (Pa), Gram positive cocci *Staphylococcus aureus* (Sa), Gram positive spore bacillus *Bacillus cereus* (Bc) and *M. smegmatis* (Ms). Nonpigmented rapidly growing mycobacteria (*M. smegmatis* is one of them) constitute a group of species of the genus Mycobacterium that share some characteristics. On the contrary of expected, compounds **4a**, **4b**, **4d–f**) which contains an imine functionality in their structures, exhibited no antimicrobial activity towards the

test microorganisms (data not shown). Only marginal activity was observed for compound **4c** on *M. smegmatis*. The compounds having 1,3,4-oxadiazole nucleus, **5a** and **5b**, demonstrated marginal activities on Sa, moderate activities on Bc and good activities on Ef. The conversion of 1,3,4-oxadiazole ring into 4-amino 1,2,4-triazole nucleus caused to loss of antimicrobial activity against Sa and Ef for compounds **6a** and **6b**, whereas these compounds found to posses moderate activity against Bc and marginal activity against Ms. The introduction of more lipophylic 4-methoxyphenylmethylene moiety into position 4 of 5-sulfanyl-1,2,4-triazole scaffold in compound **6a** increased the antimicrobial activity on the test microorganisms except Ef. Compounds **8** and **10**, which have the same chemical skeletons with the difference of a methyl or chlor substituent at the position 4 of phenyl group, displayed similar activities on Pa, Bc and Ms. As an comparison in the antimicrobial activities of compounds **8** and **10**, the substitution of methyl group by more polar chlor atom caused an increase. The incorporation of 1,3-thiazole nucleus into structure (for compound **11b**) resulted in no antimicrobial activity, whereas 1,3-oxadiazole moiety caused slight activity on Sa and Ms for compound **11a**.

Conclusion

This study reports the synthesis of some new 1*H*-indole derivatives incorporating several other pharmacophore heterocycles in a single structure. Hence, herein we combined all these potential chemotherapeutic units, namely 1,2,4-triazole, 1,3-oxazole and/or 1,3-thiazole moieties. The antimicrobial screening studies were also performed in the study. 1,2,4-Triazole nucleus is one of the active components present in many standard drugs and it is known to increase the pharmacological activity of the molecules. The presence of 1*H*-indole, 1,3-oxazole or 1,3-thiazole nucleus is also instrumental in contributing to the net biological activity of a system.

The antimicrobial screening suggests that among the newly synthesized compounds, compounds, **3a–d** exhibited activity against *P. aeruginosa* (Pa), *S. aureus* (Sa), *B. cereus* (Bc) and *M. smegmatis* (Ms). On the other hand, among compounds **4**, only compound **4c** displayed activity on *M. smegmatis*. The compounds having 1,3,4-oxadiazole nucleus, **5a** and **5b**, were found to be active on Sa, Bc and Ef. Compounds **6a** and **6b,** which contain 4-amino-1,2,4-triazole moiety instead of 1,3,4-oxadiazole nucleus, demonstrated moderate activity against Bc and marginal activity against Ms. Compounds **8** and **10**, which have the same chemical skeletons with the difference of a methyl or chlor substituent at the position 4 of phenyl group, displayed similar activities on Pa, Bc and Ms. On the other hand, compound **11a** exhibited slight activity on Sa and Ms, while **11b** displayed no activity against the test microorganisms.

Experimental

All the chemicals were purchased from Fluka Chemie AG Buchs (Switzerland), and they were used without further purification. Melting points of the synthesized compounds are determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. Reactions are monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminium sheets. The mobile phase was ethanol and ethyl acetate (1:1) and detection was made using UV light. IR spectra are recorded as potassium bromide pellets using a PerkineElmer 1600 series FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AVENE II 400 MHz NMR Spectrometer (Chemical shift in ppm down field from TMS as an internal reference). Splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; m: multiplet. The elemental analysis was performed on a Costech Elemental Combustion System CHNS-O elemental analyzer. All the compounds gave C, H and N analysis within ±0.4% of the theoretical values. The mass spectra were obtained for compounds **3**, **6a–c** and **11a** at a Quattro LC-MS (70 eV) Instrument. Compounds **2a**, **b** were prepared by the way reported previously (Bektas *et al*. 2010a, b).

General method for the synthesis of compounds **3a–c**

To a solution of the corresponding compound **2** in tetrahydrofurane (10 mmol) 4-chlorobenzensulfonylchloride (10 mmol) was added and the reaction mixture was refluxed in the presence of triethylamine (20 mmol) for 4 h. Then, the reaction content was allowed to reach to room temperature and water was added into it. The formed solid was filtered off, recrystallized from ethanol–water (1:2) to obtain the pure product.

*N′-(4-Bromophenylsulfonyl)-2-{4-[2-(1H-indol-3-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetohydrazide (**3a**)*

Yield 78%, mp. 185–186°C; Anal. Calcd. (%) for: $C_{27}H_{24}BrClN_6O_4S$: C, 50.36, H, 3.76, N, 13.05, S, 4.98, Found; C, 50.42, H, 3.82, N, 13.14, S, 4.87; IR (KBr, ν, cm^{-1}): 3256, 3134 (NH), 2978, 2832 (CH_2), 1702, 1695 (–C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.81 (2H, bs, tryp-CH_2), 3.47 (2H, s, benzyl-CH_2), 3.66 (2H, bs, tryp-CH_2), 4.27 (2H, s, CH_2), 7.00–7.10 (6H, m, ar–H), 7.32–7.36 (4H, m, ar–H), 7.75 (3H, s, ar–H), 10.16 (1H, s, NH), 10.38 (1H,

s, NH), 10.93 (1H, s, NH); ^{13}C NMR (DMSOd_6) δ (ppm): 23.89 (tryp-CH_2), 30.18 (benzyl-CH_2), 42.09 (tryp-CH_2), 45.69 (CH_2), ar–C: [110.14 (C), 111.49 (C), 117.99 (C), 118.56 (C), 121.17 (C), 123.31 (C), 126.81 (C), 127.76 (C), 128.42 (2C), 129.57 (C), 129.91 (2C), 130.47 (C), 131.62 (C), 132.46 (C), 133.74 (C), 136.12 (C), 138.08 (C), 145.20 (C)], 153.72 (triazole C-3), 165.80 (triazole C-5), 170.85 (C=O).

*N′-(4-Chlorophenylsulfonyl)-2-{4-[2-(1H-indol-3-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetohydrazide (**3b**)*

Yield 75%, mp. 192–193°C; Anal. Calcd. (%) for: $C_{27}H_{24}Cl_2N_6O_4S$: C, 54.10, H, 4.04, N, 14.02, S, 5.35, Found; C, 54.17, H, 4.12, N, 14.14, S, 5.32; IR (KBr, ν, cm^{-1}): 3252, 3145 (NH), 2973, 2856 (CH_2), 1700, 1695 (–C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.78 (2H, bs, trp-CH_2), 3.44 (2H, s, benzyl-CH_2), 3.62 (2H, bs, tryp-CH_2), 4.32 (2H, s, CH_2), 7.12–7.18 (6H, m, ar–H), 7.36–7.45 (4H, m, ar–H), 7.79 (3H, s, ar–H), 10.08 (1H, s, NH), 10.43 (1H, s, NH), 10.92 (1H, s, NH); ^{13}C NMR (DMSOd_6) δ (ppm): 23.94 (tryp-CH_2), 29.18 (benzyl-CH_2), 43.09 (tryp-CH_2), 46.34 (CH_2), ar–C: [110.43 (C), 111.28 (C), 117.96 (C), 118.58 (C), 121.17 (C), 123.36 (C), 126.89 (C), 127.74 (C), 128.49 (2C), 129.57 (C), 129.87 (2C), 130.43 (C), 131.62 (C), 132.56 (C), 133.78 (C), 136.12 (C), 138.18 (C), 146.68 (C)], 154.39 (triazole C-3), 165.82 (triazole C-5), 170.88 (C=O).

*N′-(4-Bromophenylsulfonyl)-2-{4-[2-(1H-indol-3-yl)ethyl]-3-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetohydrazide (**3c**)*

Yield 80%, mp. 175–177°C; Anal. Calcd. (%) for: $C_{28}H_{27}BrN_6O_4S$: C, 53.94, H, 4.36, N, 13.48, S, 5.14, Found; C, 53.84, H, 4.31, N, 13.52, S, 5.22; IR (KBr, ν, cm^{-1}): 3217, 3125 (NH), 2924, 2852 (CH_2), 1710, 1690 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.77 (2H, t, tryp-CH_2, $J = 6.2$ Hz), 3.42 (2H, s, benzyl-CH_2), 3.61 (2H, t, tryp-CH_2, $J = 6.2$ Hz), 4.28 (2H, s, CH_2), 6.85–6.89 (3H, d, ar–H, $J = 7.6$), 6.94–7.12 (5H, m, ar–H), 7.34–7.39 (2H, m, ar–H), 7.59 (3H, s, ar–H), 10.15 (1H, s, NH), 10.38 (1H, s, NH), 10.90 (1H, s, NH); ^{13}C NMR (DMSOd_6) δ (ppm): 20.55 (CH_3), 23.83 (tryp-CH_2), 30.55 (benzyl-CH_2), 42.01 (tryp-CH_2), 45.60 (CH_2), ar–C: [110.11 (C), 111.43 (C), 117.99 (C), 118.43 (C), 121.01 (C), 124.13 (C), 126.63 (C), 128.18 (2C), 129.07 (2C), 129.53 (2C), 131.65 (2C), 132.44 (C), 135.96 (C), 138.09 (C), 145.03 (C), 147.85 (C)], 153.72 (triazole C-3), 165.78 (triazole C-5), 170.18 (C=O).

*N′-(4-Chlorophenylsulfonyl)-2-{4-[2-(1H-indol-3-yl)ethyl]-3-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetohydrazide (**3d**)*

Yield 83%, mp. 203–205°C; Anal. Calcd. (%) for: $C_{28}H_{27}ClN_6O_4S$: C, 58.08, H, 4.70, N, 14.51, S, 5.54, Found; C, 58.15, H, 4.75, N, 14.83, S, 5.63; IR (KBr, ν, cm^{-1}): 3225, 3180 (NH), 2932, 2856 (CH_2), 1706, 1692 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.26 (3H, s, CH_3), 2.80 (2H, t, tryp-CH_2, $J = 5.8$ Hz), 3.40 (2H, s, DMSO-d_6-benzyl-CH_2), 3.62 (2H, bs, tryp-CH_2), 4.29 (2H, s, CH_2), 6.85-6.89 (2H, m, ar–H), 6.95–7.07 (5H, m, ar–H), 7.35–7.39 (2H, m, ar–H), 7.48–7.64 (2H, m, ar–H), 7.73–7.85 (2H, m, ar–H), 10.17 (1H, s, NH), 10.41 (1H, s, NH), 10.92 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 20.56 (CH_3), 23.87 (tryp-CH_2), 30.56 (benzyl-CH_2), 42.03 (tryp-CH_2), 45.67 (CH_2), ar–C: [110.17 (C), 111.46 (C), 118.02 (C), 118.49 (C), 121.14 (C), 123.26 (C), 126.82 (C), 128.36 (2C), 129.10 (2C), 129.51 (2C), 131.67 (2C), 136.00 (C), 136.15 (C), 137.65 (C), 137.96 (C), 145.58 (C)], 153.78 (triazole C-3), 165.83 (triazole C-5), 170.14 (C=O).

General method for the synthesis of compounds **4a**–**f** and **7**

A mixture of the corresponding compound **2** (for **4a**–**f**) or **6b** (for **7**) (10 mmol) and appropriate aldehyde (10 mmol) in absolute ethanol was refluxed for 3 h. After cooling the mixture to room temperature, a white solid appeared. This crude product recrystallized from dimethyl sulfoxide/water (1:2). The obtained solid was washed several times with water and dried in vacuum to yield the target product.

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-(4-methoxyphenylmethyliden)acetohidrazide (**4a**)*

Yield 78%, mp. 238–239°C; Anal. Calcd. (%) for: $C_{29}H_{27}N_6O_3Cl$; IR (KBr, ν, cm^{-1}): 3339 (NH), 1707 (triazole C=O), 1688 (hydrazide-C=O), 1607 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.84 (bs, 2H, tryp-CH_2), 3.45 (s, 2H, benzyl-CH_2), 3.70 (bs, 2H, tryp-CH_2), 3.79 (s, 3H, OCH_3), 4.46, 4.85 (s, 2H, CH_2), 6.96–7.14 (m, 7H, ar–H), 7.30–7.45 (m, 4H, ar–H), 7.65–7.68 (d, 2H, arH, $J = 7.0$ Hz), 7.96 and 8.14 (s, 1H, *cis–trans* amid conformers), 10.95 (s, 1H, tryp-NH), 11.55 (d, 1H, NH). MS (ESI): *m/z* (%) 543 (M, 82), 545 (M + 2, 40), 565 (100), 357 (40), 229 (84). ^{13}C NMR (DMSO-d_6) δ (ppm): 23.61 (trp-CH_2), 32.46 (benzil-CH_2), 42.34 (trp-CH_2), 47.84 (N-CH_2), 55.42 (OCH_3), ar–C: [111.90 (C), 112.56 (C), 115.94 (2C), 117.58 (C), 119.59 (C), 121.28 (C), 124.38 (C), 127.39 (C), 127.53 (C), 129.30 (2C), 129.67 (2C), 132.43

(2C), 135.71 (C), 136.90 (C), 161.56 (C), 163.98 (C)], 142.62 (–N=CH), 145.02 (triazol C-5), 155.39 (triazol C-3), 168.28 (C=O).

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-(2-phenylethyliden)acetohydrazide (**4b**)*

Yield 75%, mp. 242–243°C; Anal. Calcd. (%) for: $C_{29}H_{28}N_7O_3Cl$: C, 62.42, H, 5.06, N, 17.57, Found; C, 62.32, H, 5.15, N, 17.43; IR (KBr, *v*, cm^{-1}): 3305 (NH), 1697, 1710 (C=O), 1569 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.82 (bs, 2H, tryp-CH_2), 3.42 (s, 2H, benzyl-CH_2), 3.68 (bs, 2H, tryp-CH_2), 4.27 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 6.96–7.29 (m, 7H, ar–H), 7.31–7.42 (m, 7H, ar–H), 8.05 (s, 1H, NH), 9.26 (s, 1H, NH), 9.89 (s, 1H, NH), 10.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.85 (tryp-CH_2), 31.07 (benzyl-CH_2), 41.12 (trp-CH_2), 42.14 (N–CH_2), 46.24 (CH_2), ar–C: [110.05 (C), 111.76 (C), 115.19 (C), 116.89 (C), 117.55 (C), 118.38 (C), 120.56 (C), 121.13 (C), 123.36 (2C), 124.84 (2C), 125.72 (2C), 128.06 (2C), 129.18 (C), 131.56 (C), 136.08 (C), 137.89 (C)], 144.56 (triazole C-3), 145.02 (triazol C-5), 154.01 (triazol C-3), 167.98 (C=O). MS (ESI): *m/z* (%) 513 ([M^+], 38), 535 (M + Na, 100), 357 (20), 144 (34).

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-(pyrrol-2-ylmethyliden)acetohydrazide (**4c**)*

IR (KBr, *v*, cm^{-1}): 3280, 3110 (NH), 1693 (triazole C=O), 1668 (hydrazide-C=O), 1574 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.84 (t, 2H, tryp-CH_2, 6.8 Hz), 3.47 (s, 2H, benzyl-CH_2), 3.74 (t, 2H, tryp-CH_2, 6.8 Hz), 4.42, 4.84 (s, 2H, CH_2), 6.11 (s, 1H, ar–H), 6.44 (bs, 1H, ar–H), 6.90–7.14 (m, 6H, ar–H), 7.32–7.44 (m, 4H, ar–H), 7.83, 8.04 (s, 1H, *cis–trans* amid conformers), 10.98 (s, 1H, trp-NH), 11.38, 11.42 (s, 2H, 2NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 24.66 (trp-CH_2), 30.90 (benzil-CH_2), 42.84 (tryp-CH_2), 47.05 (N–CH_2), ar–C: [109.93 (C), 110.91 (C), 112.23 (C), 113.42 (C), 118.76 (C), 119.31 (C), 121.92 (C), 122.66 (C), 124.14 (C), 127.41 (C), 127.58 (C), 129.16 (2C), 131.20 (2C), 132.33 (C), 134.61 (C), 136.87 (C)], 146.00 (N=CH), 154.93 (triazole C-3), 163.21 (triazole C-5), 168.32 (C=O). MS (ESI): *m/z* (%) 502 ([M^+]+1, 48), 524 (M + Na, 100), 345 (22), 144 (28).

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-(4-methoxyphenylmethyliden)acetohydrazide (**4d**)*

Yield 80%, mp. 256–257°C; Anal. Calcd. (%) for: $C_{30}H_{30}N_6O_3$; IR (KBr, *v*, cm^{-1}): 3323(NH), 1707 (triazole C=O), 1687 (hydrazide-C=O), 1606(C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.25 (s, 3H, CH_3), 2.81 (t, 2H, tryp-CH_2), 3.41 (s, 2H, benzyl-CH_2), 3.66 (t, 2H, tryp-CH_2), 3.79 (s, 3H, OCH_3), 4.87 (s, 2H, CH_2), 6.86–7.15 (m, 9H, ar–H), 7.36–7.45 (m, 2H, ar–H), 7.84 (d, 2H, arH), 7.98, 8.16 (s, 1H, *cis–trans* amid conformers), 10.95 (s, 1H, tryp-NH), 11.56 (d, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.28 (CH_3), 24.61 (tryp-CH_2), 31.27 (benzyl-CH_2), 42.73 (tryp-CH_2), 46.94 (NCH_2), 55.96 (OCH_3), ar–C: [110.90 (C), 112.20 (C), 114.97 (2C), 118.79 (C), 119.23 (C), 121.88 (C), 124.08 (C), 127.21 (C), 127.53 (C), 129.11 (2C), 129.65 (2C), 132.48 (2C), 136.71 (C), 136.86 (C), 144.66 (C), 161.50 (C)], 146.30 (N=CH), 154.84 (triazole C-3), 163.70 (triazole C-5), 168.56 (C=O). MS (ESI): *m/z* (%) 523 ([M^+]+1, 88), 545 ([M^+]+Na, 100), 380 (24), 144 (28).

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-(pyrrol-2-ylmethyliden)acetohydrazide (**4e**)*

Yield 88%, mp. 238–239°C; Anal. Calcd. (%) for: $C_{27}H_{27}N_7O_2$; IR (KBr, *v*, cm^{-1}): 3221, 3146 (NH), 1692 (triazole C=O), 1671 (hydrazide-C=O), 1577 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.28 (s, 3H, CH_3), 2.83 (t, 2H, tryp-CH_2, 7.4 Hz), 3.44 (s, 2H, benzyl-CH_2), 3.67 (t, 2H, tryp-CH_2, J = 7.4 Hz), 4.88 (s, 2H, CH_2), 6.15 (t, 1H, ar–H), 6.48 (bs, 1H, ar–H), 6.89–7.14 (m, 8H, ar–H), 7.38–7.47 (m, 2H, ar–H), 7.87, 8.08 (s, 1H, *cis–trans* amid conformers), 10.97 (s, 1H, tryp-NH), 11.40, 11.52 (s, 2H, 2NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.52 (CH_3), 23.81 (tryp-CH_2), 30.48 (benzyl-CH_2), 41.97 (tryp-CH_2), 46.17 (NCH_2), ar–C: [104.21 (C), 109.11 (C), 110.117 (C), 111.39 (C), 112.59 (C), 117.98 (C), 118.42 (C), 121.07 (C), 123.28 (C), 126.60 (C), 126.76 (C), 127.03 (C), 128.28 (2C), 129.06 (2C), 131.73 (C), 136.06 (C)], 145.50 (N=CH), 154.17 (triazole C-3), 162.40 (triazole C-5), 167.54 (C=O). MS (ESI): *m/z* (%) 482 (M + 1, 46), 504 (M + Na, 64), 345 (22), 229 (100), 108 (40).

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-(pyridin-2-ylmethyliden)acetohydrazide (**4f**)*

Yield 90%, mp. 244–245°C; Anal. Calcd. (%) for: $C_{28}H_{27}N_7O_2$; IR (KBr, *v*, cm^{-1}): 3327 (NH), 1704 (triazole C=O), 1691 (hydrazide-C=O), 1581 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.25 (s, 3H, CH_3), 2.80 (t, 2H, tryp-CH_2), 3.41 (s, 2H, benzyl-CH_2), 3.66 (t, 2H, tryp-CH_2), 4.53, 4.93 (s, 2H, CH_2), 6.87 (d, 2H, ar–H), 6.97–7.14 (m, 5H, ar–H), 7.35–7.44 (t, 3H, ar–H, J = 8.2 Hz), 7.83–7.86 (t, 1H, ar–H), 7.92–8.01 (d, 2H, ar–H), 8.24 and 8.62 (s, 1H, *cis–trans* amid conformers), 10.95 (s, 1H, tryp-NH),

11.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.30 (CH_3), 24.64 (tryp-CH_2), 31.27 (benzyl-CH_2), 42.72 (tryp-CH_2), 46.93 (NCH_2), ar–C: [110.88 (C), 112.19 (C), 118.78 (C), 119.20 (C), 120.60 (C), 121.87 (C), 124.06 (C), 125.07 (C), 127.55 (C), 129.07 (2C), 129.85 (2C), 132.51 (C), 136.70 (C), 136.86 (C), 137.58 (C), 150.18 (C), 153.25 (C)], 145.74 (N=CH), 154.78 (triazole C-3), 164.27 (triazole C-5), 169.07 (C=O). MS (ESI): *m/z* (%) 494 ([M^+]+1, 96), 516 ([M^+]+Na, 98), 351 (32), 144 (38).

*4-[2-(1H-Indol-3-yl)ethyl]-5-(4-methylbenzyl)-2-{[4-(4-methoxyphenylmethylidenamino) -5-sulfanyl-4H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one (**7**)*

Yield 72%, mp. 211–212°C; Anal. Calcd. (%) for: $C_{31}H_{30}N_8O_2S$: C, 64.32, H, 5.23, N, 19.36, S, 5.54, Found; C, 64.42, H, 5.43, N, 19.38, S, 5.59; IR (KBr, *v*, cm^{-1}): 3181 (NH), 2923, 2846 (CH_2), 1689 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.17 (3H, s, CH_3), 2.47 (3H, s, CH_3), 2.82 (2H, s, tryp-CH_2), 3.36 (2H, s, benzyl-CH_2), 3.65 (2H, s, tryp-CH_2), 4.86 (2H, s, CH_2), 6.92–7.24 (7H, m, ar–H), 7.27–7.79 (6H, m, ar–H), 9.82 (1H, s, CH), 10.53 (1H, s, NH), 13.67 (1H, s, SH). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.37 (CH_3), 23.46 (tryp-CH_2), 32.25 (benzyl-CH_2), 38.87–41.38 (DMSO-d_6 + tryp-CH_2), 43.87 (NCH_2), 55.52 (OCH_3), ar–C: [110.66 (C), 111.18 (C), 112.21 (C), 112.34 (C), 115.52 (C), 118.78 (C), 119.24 (C), 120.94 (2C), 121.84 (C), 123.02 (C), 125.56(2C), 127.52 (C), 129.14 (2C), 129.86 (2C), 132.32 (C), 136.46 (C)], 142.18 (CH), 145.76 (triazole C-3), 148.58 (triazole C-5), 155.68 (oxadiazole C-2), 167.54 (oxadiazole C-5); MS (ESI): *m/z* (%) 579 ([M^+]+1, 25), 302 (10), 152 (100).

General method for the synthesis of compounds **5a**, **b**

The corresponding compound **2** (10 mmol) and CS_2 (0.60 ml, 10 mmol) were added to a solution of KOH (0.56 g, 10 mol) in 50 ml H_2O and 50 ml ethanol. The reaction mixture was allowed to reflux for 3 h. Then, the reaction content was acidified with conc. HCl. The precipitate formed was filtered off, washed with H_2O and recrystallized from ethanol to afford the desired compound.

*4-[2-(1H-Indol-3-yl)ethyl]-5-(4-chlorobenzyl)-2-[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**5a**)*

Yield 92%, mp. 165–166°C; Anal. Calcd. (%) for: $C_{22}H_{19}ClN_6O_2S$: C, 56.59, H, 4.10, N, 18.00, S, 6.87, Found; C, 56.55, H, 4.17, N, 18.12, S, 6.84; IR (KBr, *v*, cm^{-1}): 3330 (NH), 2950, 2776 (CH_2), 1682 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.82 (2H, s, tryp-CH_2), 3.42 (2H, bs, DMSO-d_6 + benzyl CH_2), 3.66–3.70 (2H, d, tryp-CH_2, $J = 6.4$ Hz), 5.06 (2H, s, NCH_2), 6.91–7.02 (5H, m, ar–H), 7.28–7.36 (4H, m, ar–H), 10.91 (1H, s, NH), 13.49 (1H, s, SH). ^{13}C NMR (DMSO-d_6) δ (ppm): 24.52 (tryp-CH_2), 30.85 (benzyl-CH_2), 41.37 (tryp-CH_2), 43.18 (NCH_2), ar–C: [110.87 (C), 112.22 (C), 118.54 (C), 119.32 (C), 121.88 (C), 124.05 (C), 127.59 (C), 129.17 (2C), 131.25 (2C), 132.35 (C), 134.22 (C), 136.82 (C)], 147.09 (triazole C-3), 153.96 (triazole C-5), 159.83 (oxadiazole C-2), 178.71 (oxadiazole C-5); MS (ESI): *m/z* (%) 467 ([M^+]+1, 14), 203 (42), 143 (100).

*4-[2-(1H-Indol-3-yl)ethyl]-5-(4-methylbenzyl)-2-[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**5b**)*

Yield 90%, mp. 158–159°C; Anal. Calcd. (%) for: $C_{23}H_{22}N_6O_2S$: C, 61.87, H, 4.97, N, 18.82, S, 7.18, Found; C, 61.82, H, 4.92, N, 18.88, S, 7.25; IR (KBr, *v*, cm^{-1}): 3321 (NH), 2921, 2857 (CH_2), 1694 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.24 (3H, s, CH_3), 2.83 (2H, t, tryp-CH_2, 7.0 Hz), 3.46 (2H, bs, DMSO-d_6 + benzyl CH_2), 3.71 (2H, t, tryp-CH_2, $J = -7.0$ Hz), 5.09 (2H, s, NCH_2), 6.83–6.87 (2H, m, ar–H), 6.96–6.99 (1H, m, ar–H), 7.03–7.10 (4H, m, ar–H), 7.33–7.38 (2H, m, ar–H), 10.92 (1H, s, NH), 13.85 (1H, s, SH). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.24 (CH_3), 24.35 (tryp-CH_2), 31.14 (benzyl-CH_2), 41.04 (tryp-CH_2), 43.21(NCH_2), ar–C: [110.85 (C), 112.17 (C), 118.51 (C), 119.35 (C), 121.92 (C), 123.81 (C), 127.49 (C), 129.08 (2C), 129.87 (2C), 131.92 (C), 136.62 (C), 136.89 (C)], 147.61 (triazole C-3), 154.08 (triazole C-5), 159.80 (oxadiazole C-2), 178.56 (oxadiazole C-5); MS (ESI): *m/z* (%) 447 ([M^+]+1, 10), 405 (35), 143 (100).

General method for the synthesis of compounds **6a**, **b**

The mixture of corresponding compound **5** (10 mmol) and hydrazine hydrate (25 mmol) in ethanol was heated under reflux with stirring for 2 h, then reaction was maintained at room temperature for an additional 3 h. Water added to the reaction mixture and was left to cool overnight. The precipitate formed was filtered off and recrystallized from ethanol: water (1:4) to obtain the target compound.

*4-[2-(1H-Indol-3-yl)ethyl]-5-(4-chlorobenzyl)-2-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**6a**)*

Yield 78%, mp. 189–190°C; Anal. Calcd. (%) for: $C_{22}H_{21}ClN_8OS$: C, 54.94, H, 4.40, N, 23.30, S, 6.67, Found; C, 54.90, H, 4.43, N, 23.28, S, 6.62; IR (KBr, *v*, cm^{-1}): 3277, 3079 (NH), 2924 (CH_2), 1685 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.78 (2H, s, tryp-CH_2), 3.46 (2H, s, benzyl-CH_2), 3.65 (2H, d, tryp-CH_2), 4.95 (2H, s, NCH_2), 5.57

(2H, s, NH_2), 6.65–7.06 (5H, m, ar–H), 7.28–7.33 (4H, m, ar–H), 10.90 (1H, s, NH), 13.71 (1H, s, SH). ^{13}C NMR (DMSO-d_6) δ (ppm): 23.83 (tryp-CH_2), 30.13 (benzyl-CH_2), 38.07–40.58 (DMSO-d_6 + tryp-CH_2), 42.14 (NCH_2), ar–C: [110.05 (C), 111.42 (C), 117.90 (C), 118.48 (C), 121.10 (C), 123.30 (C), 126.75 (C), 128.41 (2C), 130.38 (2C), 131.53 (C), 133.72 (C), 136.04 (C)], 145.61 (triazole C-3), 147.57 (triazole C-5), 153.42 (oxadiazole C-2), 166.35 (oxadiazole C-5); MS (ESI): *m/z* (%) 483 (M + 2, 100), 503 (M + Na, 18), 156 (30).

*4-[2-(1H-Indol-3-yl)ethyl]-5-(4-methylbenzyl)-2-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**6b**)*

Yield 69%, mp. 180–185°C; Anal. Calcd. (%) for: $C_{23}H_{24}N_8OS$: C, 59.98, H, 5.25, N, 24.33, S, 6.96, Found; C, 59.92, H, 5.21, N, 24.38, S, 6.98; IR (KBr, *v*, cm^{-1}): 3373, 3269, 3170 (NH + NH_2), 2923 (CH_2), 1686 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.21 (3H, s, CH_3), 2.74 (2H, s, tryp-CH_2), 3.52 (2H, s, benzyl-CH_2), 3.60 (2H, s, tryp-CH_2), 4.95 (2H, s, CH_2), 5.78 (2H, s, NH_2), 6.87–7.04 (7H, m, ar–H), 7.31–7.42 (2H, m, ar–H), 10.88 (1H, s, NH), 13.70 (1H, s, SH). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.30 (CH_3), 24.56 (tryp-CH_2), 31.28 (benzyl-CH_2), 38.82–41.33 (DMSO-d_6+ tryp-CH_2), 42.87 (NCH_2), ar–C: [110.85 (C), 113.21 (C), 112.17 (C), 118.70 (C), 119.18 (C), 121.85 (C), 124.02 (C), 127.52 (C), 129.04 (2C), 129.87 (2C), 132.38 (C), 136.74 (C)], 146.77 (triazole C-3), 148.37 (triazole C-5), 154.21 (oxadiazole C-2), 167.10 (oxadiazole C-5); MS (ESI): *m/z* (%) 460 (M, 35), 461 ([M^+]+1, 58), 148 (100).

General method for the synthesis of compounds **8**, **9a** and **9b**

A mixture of the corresponding compound **2** (10 mmol) and phenyl isothiocyanate (for compound **9b**) or benzylisothiocyanate (for compounds **8** and **9a**) (15 mmol) was refluxed in ethanol for 4 h. On cooling the resulting solution to room temperature, a white solid was obtained. This crude product was filtered and recrystallized from ethanol (**9a**, **b**) or dimethyl sulfoxide/water (**8**) (1:2) to afford the desired product.

*5-(4-Chlorobenzyl)-4-[2-(1H-indol-3-yl)ethyl]-2-[(4-benzyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**8**)*

Yield 88%, mp. 204–205°C; Anal. Calcd. (%) for: $C_{30}H_{29}N_7O_2$: C, 69.35, H, 5.63, N, 18.87, Found; C, 68.72, H, 5.58, N, 18.72; IR (KBr, *v*, cm^{-1}): 3241 (NH), 2952, 2851 (CH_2), 1709, 1684 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.58 (2H, t, tryp-CH_2, J = 6.8 Hz), 3.63 (2H, t, tryp-CH_2, J = 7.0 Hz), 4.23 (2H, s, CH_2), 4.43 (2H, s, CH_2), 6.85–6.99 (2H, m, ar–H), 7.03–7.27 (5H, m, ar–H), 7.30–7.41 (6H, m, ar–H), 8.05 (1H, s, ar–H), 9.90 (1H, s, NH), 10.93 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.58 (CH_3), 22.74 (tryp-CH_2), 31.52 (benzyl-CH_2), 38.49–40.24 (DMSO-d_6 + CH_2), 41.46 (tryp-CH_2), 42.48 (CH_2), ar–C: [110.10 (C), 111.38 (C), 117.64 (2C), 118.44 (2C), 121.13 (C), 123.06 (2C), 126.34 (C), 127.28 (C), 128.76 (2C), 129.13 (C), 129.38 (2C), 131.34 (C), 132.74 (C), 136.17 (C), 136.18 (C)], 146.44 (triazole C-3), 147.26 (triazole C-3), 152.56 (triazole C-5), 168.42 (triazole C-5); MS (ESI): *m/z* (%) 520 ([M^+]+1, 62), 405 (56), 229 (40), 143 (100).

*3-Chlorobenzyl-2-({4-[2-(1H-indol-3-yl)ethyl]-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetyl)-N-benzylhydrazinecarboxamide (**9a**)*

Yield 75%, mp. 242–243°C; Anal. Calcd. (%) for: $C_{29}H_{28}N_7O_3Cl$: C, 62.42, H, 5.06, N, 17.57, Found; C, 62.32, H, 5.15, N, 17.43; IR (KBr, *v*, cm^{-1}): 3305 (NH), 1697, 1710 (C=O), 1569 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.82 (bs, 2H, tryp-CH_2), 3.42 (s, 2H, benzyl-CH_2), 3.68 (bs, 2H, tryp-CH_2), 4.27 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 6.96–7.29 (m, 7H, ar–H), 7.31–7.42 (m, 7H, ar–H), 8.05 (s, 1H, NH), 9.26 (s, 1H, NH), 9.89 (s, 1H, NH), 10.95 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 23.85 (tryp-CH_2), 31.07 (benzyl-CH_2), 41.12 (tryp-CH_2), 42.14 (NCH_2), 46.24 (CH_2), ar–C: [110.05 (C), 111.76 (C), 115.19 (C), 116.89 (C), 117.55 (C), 118.38 (C), 120.56 (C), 121.13 (C), 123.36 (2C), 124.84 (2C), 125.72 (2C), 128.06 (2C), 129.18 (C), 131.56 (C), 136.08 (C), 137.89 (C)], 144.56 (triazole C-3), 153.82 (triazole C-5), 165.74 (C=O), 175.61 (C=O); MS (ESI): *m/z* (%) 558.10 (M, 15), 425 (20), 168 (40), 156 (100).

*Synthesis of 5-(4-methylbenzyl)-4-[2-(1H-indol-3-yl)ethyl]-2-[(4-benzyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**10**)*

A solution of compound **9a** (10 mmol) in 2 N NaOH was heated under reflux for 3 h. The resulting solution was allowed to reach to room temperature and acidified to pH 3–4 with 37% HCl. The precipitate formed was filtered off, washed with water and recrystallized from ethanol/water (1:1) to afford the desired compound. Yield 85%, mp. 206–208°C; Anal. Calcd. (%) for: $C_{29}H_{26}ClN_7O_2$: C, 64.50, H, 4.85, N, 18.16, Found; C, 64.73, H, 4.80, N, 18.22; IR (KBr, *v*, cm^{-1}): 3232 (NH), 2950, 2845 (CH_2), 1712, 1690 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.56 (2H, t, tryp-CH_2, J = 6.8 Hz), 3.60 (2H, t, trp-CH_2,

$J = 7.0$ Hz), 4.14 (2H, s, CH_2), 4.48 (2H, s, CH_2), 6.80–6.92 (2H, m, ar–H), 7.13–7.32 (5H, m, ar–H), 7.35–7.55 (6H, m, ar–H), 8.02 (1H, s, ar–H), 9.87 (1H, s, NH), 10.95 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 22.45 (tryp-CH_2), 30.52 (benzyl-CH_2), 38.49–40.24 (DMSO-d_6+ CH_2), 41.32 (tryp-CH_2), 43.57 (CH_2), ar–C: [110.17 (C), 111.35 (C), 117.56 (2C), 118.44 (2C), 121.13 (C), 123.12 (2C), 126.65 (C), 127.28 (C), 128.76 (2C), 129.13 (C), 129.38 (2C), 131.34 (C), 132.74 (C), 135.68 (C), 136.22(C)], 145.45 (triazole C-3), 147.84 (triazole C-3), 153.36 (triazole C-5), 165.3642 (triazole C-5); MS (ESI): *m/z* (%) 542 (M+2, 15), 464 (24), 176 (25), 148 (100).

General method for the synthesis of compounds **11a** and **11b**

The mixture of corresponding compound **9** (10 mmol), 4-chlorophenacyl bromide (10 mmol) and in ethanol was refluxed in the presence of dried sodium acetate (200 mmol) for 8 h. Then, the reaction content was cooled to room temperature, poured into ice-cold water while stirring and left overnight in cold. The formed solid was filtered, washed with water three times and recrystallized from dimethyl sulfoxide-water (1:1) to afford pure compounds.

*3-(4-Chlorobenzyl)-2-{4-[2-(1H-indol-3-yl)ethyl]-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-[3-benzyl-4-(4-chlorophenyl)-1,3-oxazol-2(3H)-ylidene]acetohydrazide (**11a**)*

Yield 82%, mp. 167–168°C; Anal. Calcd. (%) for: $C_{35}H_{31}N_7O_3Cl_2$: C, 64.16, H, 4.51, N, 14.16, Found; C, 64.22, H, 4.61, N, 14.20; IR (KBr, *v*, cm^{-1}): 3240, 3233 (NH), 2975, 2842 (CH_2), 1715, 1688 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.82 (2H, bs, tryp-CH_2), 3.44 (2H, s, CH_2), 3.67 (2H, bs, tryp-CH_2), 4.22 (2H, s, CH_2), 4.41 (2H, s, CH_2), 5.47 (1H, s, thiazole), 6.96–7.38 (15H, m, ar–H), 7.61–7.65 (1H, d, ar–H, $J = 7.4$ Hz), 7.95–8.03 (2H, t, ar–H, $J = 7.4$ Hz), 9.87 (1H, s, NH), 10.93 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 23.45 (tryp-CH_2), 31.46 (benzyl-CH_2), 38.42–40.24 (DMSO-d_6 + CH_2), 41.46 (tryp-CH_2), 41.84 (thiazole C5), 45.70 (CH_2), ar–C: [110.124(C), 111.42 (C), 116.96 (2C), 118.60 (2C), 121.34 (2C), 122.49 (2C), 124.82 (CH + thiazole C5), 126.62 (C), 127.58 (C), 128.73 (2C), 129.39 (C), 129.69 (2C), 131.50 (C), 132.72 (C), 135.29 (2C), 136.91 (2C), 136.98 (C)], 150.15 (triazole C-3), 151.3 (triazole C-3), 152.68 (thiazole C-4), 153.92 (thiazole C-2), 190.44 (C=O); MS (ESI): *m/z* (%) 693 ([M^+]+1, 32), 715 (M + Na, 58).

*2-{4-[2-(1H-Indol-3-yl)ethyl]-3-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}-N′-[3-phenyl-4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetohydrazide (**11b**)*

Yield 75%, mp. 170–171°C; Anal. Calcd. (%) for: $C_{37}H_{32}N_7O_2SCl$: C, 65.91, H, 4.78, N, 14.54, S, 4.76, Found; C, 65.88, H, 4.75, N, 14.56, S, 4.72; IR (KBr, *v*, cm^{-1}): 3255, 3241 (NH), 2978, 2838 (CH_2), 1719, 1685 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.43 (2H, t, tryp-CH_2, $J = 6.8$ Hz), 3.60 (2H, t, tryp-CH_2, $J = 7.0$ Hz), 3.92 (2H, s, CH_2), 4.33 (2H, s, CH_2), 4.92 (1H, s, thiazole), 6.92 (1H, bs, ar–H), 7.10–7.55 (10H, m, ar–H), 7.66–7.82 (5H, m, ar–H), 8.05 (2H, s, ar–H), 9.86 (1H, s, NH), 10.22 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.51 (CH_3), 22.64 (tryp-CH_2), 30.65 (benzyl-CH_2), 38.49–40.24 (DMSO-d_6+ CH_2), 40.46 (tryp-CH_2), 40.58 (thiazole C5), 42.48 (CH_2), ar–C:[110.12 (C), 111.38 (C), 116.96 (2C), 118.65 (2C), 122.34 (2C), 123.45 (2C), 125.94 (CH + thiazole C5), 126.34 (C), 127.28 (C), 128.76 (2C), 129.13 (C), 129.38 (2C), 131.34 (C), 132.74 (C), 136.17 (2C), 136.18 (2C), 135.12 (C)], 150.12 (triazole C-3), 151.84 (triazole C-3), 152.48 (thiazole C-4), 153.94 (thiazole C-2), 191.14 (C=O); MS (ESI): *m/z* (%) 675 ([M^+]+1, 45), 415 (85), 229 (34), 143 (100).

Antimicrobial activity assessment

All bacterial and yeast strains were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 25923, *B. cereus* 709 ROMA, Ms: *Mycobacterium smegmatis* ATCC607, *C. albicans* ATCC 60193, Sc: *Saccharomyces cerevisiae* RSKK 251. All the newly synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) and ethanol to prepare chemicals of stock solution of 10 mg/1 ml.

Agar-well diffusion method

Simple susceptibility screening test using agar-well diffusion method as adapted earlier (Ahmad *et al*., 1998) was used. Each microorganism was suspended in Mueller–Hinton (MH) (Difco, Detroit, MI) broth and diluted approximately to 106 colony forming unit (cfu)/ml. They were 'flood-inoculated' onto the surface of MH agar and Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI) and then dried. For *C. albicans* and *C. tropicalis*, SDA were used. Five-millimetre diameter wells were cut from the agar using a sterile cork-borer, and 50 ml of the extract substances was delivered into the wells. The plates were incubated for 18 h at 35°C. Antimicrobial activity was

Table 1 Screening for antimicrobial activity of the compounds (50 µl)

Compound no.	Microorganisms and inhibition zone (mm)				
	Pa	Sa	Ef	Bc	Ms
3a	12	8	–	12	9
3b	12	11		12	14
3c	10	–	–	8	7
3d	10	7	–	10	9
4c	–	–	–	–	6
5a	–	8	10	6	–
5b	–	12	12	8	8
6a	–	–	–	7	7
6b	–	–	–	7	6
7	12	11	–	12	6
8	6	–	–	7	10
9a	–	–	–	–	–
9b	–	–	–	–	–
10	10	–	–	12	10
11a	–	5	–	6	–
11b	–	–	–	–	–
Amp.	18	35	10	15	
Strep.					35

Ms, *Mycobacterium smegmatis* ATCC607; Pa, *Pseudomonas aeruginosa* ATCC 43288; Sa, *Staphylococcus aureus* ATCC 25923; Ef, *Enterococcus faecalis* ATCC 29212; Bc, *Bacillus cereus* 702 Roma; Amp., ampicillin; Strep., streptomycin; –, no activity

evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10 mg) and Fluconazole (5 mg) were used as standard drugs. Dimethyl sulfoxide and ethanol were used as solvent controls. The antimicrobial activity results are summarized in Table 1.

Acknowledgments This project was supported by Scientific and Technological Research Council of Turkey (TUBITAK, Project no: 107T333) and Karadeniz Technical University, BAP, Turkey (Ref. No. 2007.111.002.6) and is gratefully acknowledged.

References

Ahmad I, Mehmood Z, Mohammed F (1998) Screening of some Indian medicinal plants for their antimicrobial properties. J Ethnopharmacol 62:183–193

Ashok M, Holla BS, Poojary B (2007) Convenient one pot synthesis and antimicrobial evaluation of some new Mannich bases carrying 4-methylthiobenzyl moiety. Eur J Med Chem 42: 1095–1101

Bayrak H, Demirbas A, Demirbas N, Alpay-Karaoglu S (2009a) Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. Eur J Med Chem 44:1057–1066

Bayrak H, Demirbas A, Demirbas N, Alpay-Karaoglu S (2009b) Synthesis of some new 1,2,4-triazoles starting from isonicotinic acid hydrazide and evaluation of their antimicrobial activities. Eur J Med Chem 44:4362–4366

Bektas H, Karaali N, Sahin D, Demirbaş A, Alpay-Karaoglu S, Demirbas N (2010a) Synthesis of some new 1,2,4-triazoles starting from isonicotinic acid hydrazide and evaluation of their antimicrobial activities. Molecules 15:2427–2438

Bektas H, Demirbas N, Demirbas A, Alpay-Karaoglu S (2010b) Synthesis of some new biheterocyclic triazole derivatives and evaluation of their antimicrobial activity. Turk J Chem 34:165–180

Bonde CG, Gaikwad NJ (2004) Synthesis and preliminary evaluation of some pyrazine containing thiazolines and thiazolidinones as antimicrobial agents. Bioorg Med Chem 12:2151–2161

Cai S, Li QS, Borchardt RT, Kuczera K, Schowen RL (2007) The antiviral drug ribavirin is a selective inhibitor of *S*-adenosyl-l-homocysteine hydrolase from *Trypanosoma cruzi*. Bioorg Med Chem 15:7281–7287

Cui Y, Dang Y, Yang Y, Zhang S, Ji R (2005) Syntheses and antibacterial activity of a series of 3-(pyridine-3-yl)-2-oxazolidinone. Eur J Med Chem 40:209–214

Das B, Rudra S, Yadav A, Raj A, Rao AVSR, Srinivas ASSV, Soni A, Saini S, Shukla S, Pandya M, Bhateja P, Malhotra S, Mathur T, Arora SK, Rattan A, Mehta A (2005) Synthesis and SAR of novel oxazolidinones: discovery of ranbezolid. Bioorg Med Chem Lett 15:4261–4267

Demirbas A, Johansson CB, Duman N, Ikizler AA (1996) Synthesis and biological activities of some 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives. Acta Pol Pharm 53:117–123

Demirbas N, Ugurluoglu R, Demirbas A (2002) Synthesis of 3-alkyl(aryl)-4-alkylidenamino-4,5-dihydro-1H–1,2,4-triazol-5-ones and 3-alkyl-4-alkylamino-4,5-dihydro-1H–1,2,4-triazol-5-ones as antitumor agents. Bioorg Med Chem 10:3717–3723

Demirbas N, Demirbas A, Alpay-Karaoglu S, Çelik E (2005) Synthesis and antimicrobial activities of some new [1,2,4] triazolo[3,4-b] [1,3,4]thiadiazoles and [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines. Arkivoc i:75–91

Demirbas A, Ceylan S, Demirbas N (2007) Synthesis of some new five membered heterocycles, a facile synthesis of oxazolidinones. J Heterocycl Chem 44:1271–1280

Demirbas A, Sahin D, Demirbas N, Alpay-Karaoglu S (2009) Synthesis of some new 1,3,4-thiadiazol-2-ylmethyl-1,2,4-triazole derivatives and investigation of their antimicrobial activities. Eur J Med Chem 44:2896–2903

Dixit PP, Patil VJ, Nair PS, Jain S, Sinha N, Arora SK (2006) Synthesis of 1-[3-(4-benzotriazol-1/2-yl-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-3-substituted-thiourea derivatives as antituberculosis agents. Eur J Med Chem 41:423–428

Ezabadi IR, Camoutsis C, Zoumpoulakis P, Geronikaki A, Soković M, Glamočilija J, Cirić A (2008) Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: synthesis, biological evaluation, lipophilicity, and conformational studies. Bioorg Med Chem 16:1150–1161

Giraud F, Guillon R, Logé C, Pagniez F, Picot C, Le Borgne M, Le Pape P (2008) Design, synthesis, and evaluation of 1-(N-benzylamino)-2-phenyl-3(1H-1,2,4-triazol-1-yl)propan-2-ols as antifungal agents. Bioorg Med Chem Lett 18:1820–1824

Giraud F, Guillon R, Logé C, Pagniez F, Picot C, Le Borgne M, Le Pape P (2009) Synthesis and structure-activity relationships of 2-phenyl-1-[(pyridinyl- and piperidinylmethyl)amino]-3-(1H–1,2,4-triazol-1-yl)propan-2-ols as antifungal agents. Bioorg Med Chem Lett 19: 301–304

Gupta A, Unadkat JD, Mao Q (2007) Interface interactions of azole antifungal agents with the human breast cancer resistance protein. J Pharm Sci 96:3226–3235

Hancu G, Gaspar A, Gyeresi A (2007) Separation of 1,4-benzodiazepines by micellar electrokinetic capillary chromatography. J Biochem Biophys Methods 69:251–259

Hester SD, Nesnow S (2008) Transcriptional responses in thyroid tissues from rats treated with a tumorigenic and a non-

tumorigenic triazole conazole fungicide. Toxicol Appl Pharm 227:357–369

Holla BS, Poojary NK, Rao SB, Shivananda MK (2002) New bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents. Eur J Med Chem 37:511–517

Ikizler AA, Uzunali E, Demirbaş A (2000) Synthesis of some 1,2,4-triazole derivatives as potential antitumor agents. Indian J Pharm Sci 5:289–292

Isloor AM, Kalluraya B, Shetty P (2009) Regioselective reaction: synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1,2,4-triazoles. Eur J Med Chem 44:3784–3787

Jenkins PR, Wilson J, Emmerson D, Garcia MD, Smith MR, Gray SJ, Britton RG, Mahale S, Chaudhuri B (2008) Design, synthesis and biological evaluation of new tryptamine and tetrahydro-beta-carboline-based selective inhibitors of CDK4. Bioorg Med Chem 16:7728–7739

Kaplancikli ZA, Turan-Zitouni G, Ozdemir A, Revial G (2008) New triazole and triazolothiadiazine derivatives as possible antimicrobial agents. Eur J Med Chem 43:155–159

Karthikeyan MK, Prasad DJ, Poojary B, Bhat KS, Holla BS, Kumari NS (2006) Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorg Med Chem 14:7482–7489

Kobeci GC, Slatford PA, Whittlesey MK, Williams JMJ (2005) N-alkylation of phenethylamine and tryptamine. Bioorg Med Chem Lett 15:535–537

Kuçukguzel SG, Rollas S, Erdeniz H, Kiraz M (1999) Synthesis, characterization and antimicrobial evaluation of ethyl 2-arylhydrazono-3-oxobutyrates. Eur J Med Chem 34:153–160

Ozdemir A, Zitouni GT, Kaplancikli ZA, Revial G, Guven K (2007) Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. Eur J Med Chem 42:403–409

Rao BM, Sangaraju S, Srinivasu MK, Madhavan P, Devi ML, Kumar PR, Chandrasekhar KB, Arpitha C, Balaji TS (2006) Development and validation of a specific stability indicating high performance liquid chromatographic method for rizatriptan benzoate. J Pharm Biomed Anal 41:1146–1151

Rawal RK, Phabhakar YS, Kati SB, De Clercq E (2005) 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT inhibitors. Bioorg Med Chem 13:6771–6776

Rawal RK, Tripathi R, Kati SB, Pannecouque C, De Clercq E (2007) Design, synthesis, and evaluation of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones as anti-HIV agents. Bioorg Med Chem 15: 1725–1731

Rostom SAF, Ashour HMA, Abd El Razik HA (2009) Azole antimicrobial pharmacophore-based tetrazoles: synthesis and biological evaluation as potential antimicrobial and anticonvulsant agents. Bioorg Med Chem 17:2410–2422

Sahoo PK, Sharma ER, Pattanayak EP (2010) Synthesis and evaluation of 4-amino-5-phenyl-4H-[1,2,4]-triazole-3-thiol derivatives as antimicrobial agents. Med Chem Res 19:127–135

Sawa M, Mizuno K, Harada H, Tateishi H, Arai Y, Suzuki S, Oue M, Tsujiuchi H, Furutanic Y, Kato S (2005) Tryptamine-based human beta 3-adrenergic receptor agonists. Part 3: improved oral bioavailability via modification of the sulfonamide moiety. Bioorg Med Chem Lett 15:1061–1064

Schiller SD, Fung HB (2007) Posaconazole: an extended-spectrum triazole antifungal agent. Clin Ther 29:1862–1886

Solomon VR, Hua C, Lee H (2010) Design and synthesis of anti-breast cancer agents from 4-piperazinylquinoline: a hybrid pharmacophore approach. Bioorg Med Chem 18:1563–1572

Tozkoparan B, Gökhan N, Aktay G, Yeşilada E, Ertan M (2000) 6-Benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones substituted with ibuprofen: synthesis, characterization and evaluation of anti-inflammatory activity. Eur J Med Chem 35:743–750

Tuncbilek M, Kiper T, Altanlar N (2009) Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA. Eur J Med Chem 44:1024–1033

Turan-Zitouni G, Sıvacı M, Kılıç FS, Erol K (2001) Synthesis of some triazolyl-antipyrine derivatives and investigation of analgesic activity. Eur J Med Chem 36:685–689

Weidinger-Wells MA, Boggs CM, Foleno BD, Melton J, Bush K, Goldschmidt RM, Hlasta DJ (2002) Novel piperidinyloxy oxazolidinone antibacterial agents. Diversification of the N-substituent. Bioorg Med Chem 10:2345–2351

Yamazaki Y, Kawano Y, Yamanaka A, Maruyama S (2009) N-[(Dihydroxyphenyl)acyl]serotonins as potent inhibitors of tyrosinase from mouse and human melanoma cells. Bioorg Med Chem Lett 19:4178–4182

Yu LT, Ho MT, Chang CY, Yang TK (2007) Asymmetric zinc-Reformatsky reaction of Evans chiral imide with acetophenones and its application to the stereoselective synthesis of triazole antifungal agents. Tetrahedron 18:949–962

Yuksek H, Demirbaş A, Ikizler A, Johansson CB, Çelik C, Ikizler AA (1997) Synthesis and antibacterial activities of some 4,5-dihydro-1H-1,2,4-triazol-5-ones. Arzn-Forsh Drug Res 47:405–409