European Journal of Medicinal Chemistry 44 (2009) 5112–5116

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis and antibacterial activity of some novel bis-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and bis-4-thiazolidinone derivatives from terephthalic dihydrazide

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ARTICLE INFO

Article history:
Received 24 October 2008
Received in revised form
16 July 2009
Accepted 23 July 2009
Available online 30 July 2009

Keywords:
Terephthalic dihydrazide
1,3,4-Oxadiazole/thiadiazoles
1,2,4-Triazole
Antibacterial activity

ABSTRACT

A novel series of 1,4-bis(6-(substituted phenyl)-[1,2,4]-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**5a**–**b**) and 4-bis(substituted phenyl)-4-thiazolidinone derivatives (**7a**–**c**) have been synthesized from terephthalic dihydrazide (**1**) through multistep reaction sequence. 1,4-Bis(5-aryl-1,3,4-oxadiazole-2yl) benzene derivatives (**2a**–**f**) and bis-substituted terephthalohydrazide (**6a**–**e**) were also synthesized from terephthalic dihydrazide by cyclization with various aromatic acids and aldehydes. Terephthalic dihydrazide (**1**) was obtained from poly(ethylene terephthalate) waste from reaction with hydrazine hydrate in good yield (86%). All the synthesized compounds were screened for their antibacterial activities against various bacteria and fungi strains. Several of these compounds showed potential antibacterial activity.

1. Introduction

Oxadiazole derivatives, an important group of heterocyclic compounds, have been the subject of extensive study in the recent past. Numerous reports have highlighted their chemistry and use [1–3]. It has also been reported in literature that certain compounds bearing 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole nucleus possess significant anti-inflammatory activity [4–7]. 4-Thiazolidinone derivatives are also known to possess antibacterial [8–12], antifungal [13–15], antiviral [16–20] and antituberculosis [11,21–23] properties. 4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme [24]. The incidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly due to the HIV/AIDS pandemic, which greatly increase the risk of infectious proceeding to overt disease. During recent years, the microorganisms have developed increasing resistance against drugs. Therefore, there is a need to develop new, potent, fast-acting antimicrobial, antiviral and antimycobacterial drugs with low toxicity.

Poly(ethylene terephthalate) (PET) is a thermoplastic polyester produced in very large quantities since it finds major applications in textile apparel, photographic films and soft drink bottles due to high durability, non-biodegradability, crystal clear transparency and non-toxic nature. On the other hand, this has led to problems of waste disposal [25]. One of the techniques to reduce PET waste disposal problems is to follow chemical recycling through depolymerization and conversion of the products of the reaction into value added materials. In our earlier study, depolymerization of PET was carried through aminolysis using ethanolamine, to give monomer bis-(2-hydroxy ethylene terephthalamide) having terminal reactive hydroxyl group [26]. In the present study, we have synthesized terephthalic dihydrazide from PET bottle waste using excess hydrazine hydrate having terminal reactive NH_2 groups. Five-membered heterocyclic compounds of terephthalic acid derivatives were synthesized. We report herein the synthesis of some potent analogs of bis-1,3,4-oxadiazole, bis-1,2,4-triazole and 4-thiazolidinone derivatives, which have been tested for their antibacterial activity.

2. Chemistry

The terephthalic dihydrazide **1** was prepared by aminolysis of PET bottle waste with hydrazine hydrate at reflux condition in good yield. Various 1,4-bis(5-aryl-1,3,4-oxadiazole-2yl) benzene (**2a**–**f**) were prepared by treatment of dihydrazide with appropriate aromatic acids in the presence of trifluoro acetic acid (Scheme 1). The structures of compounds were established on the basis of their

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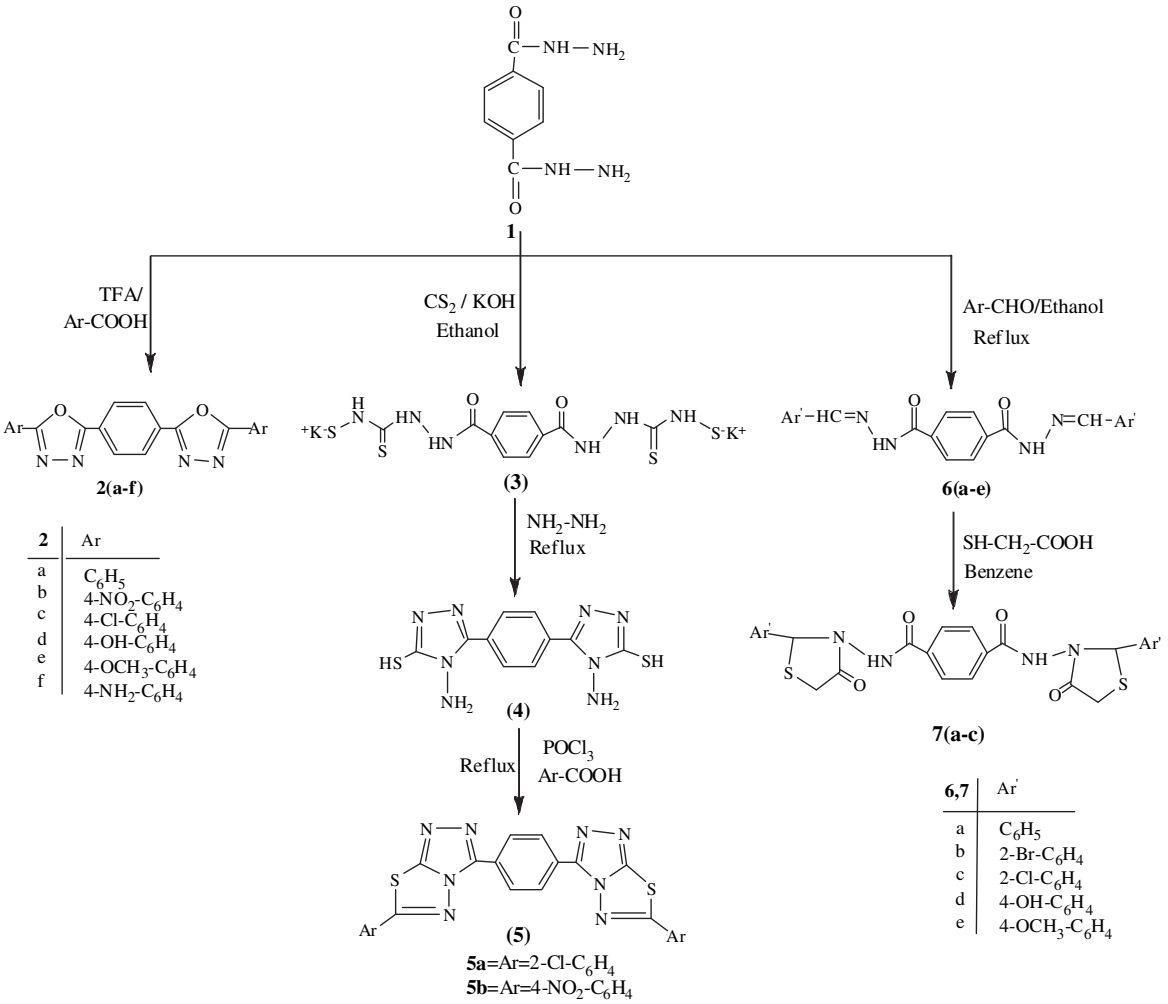
doi:10.1016/j.ejmech.2009.07.023



Scheme 1.

spectral data. The required bis-dithiocarbazinate (**3**) was synthesized by reacting dihydrazide with carbondisulfide and potassium hydroxide in ethanol. This salt (**3**) underwent ring closure with an excess of 99% hydrazine hydrate to give the 1,4-phenylene-bis(4-amino-4*H*-1,2,4-triazole-3-thiol) (**4**). Thus resulted triazole was then further converted to the title compounds (**5a**–**b**) in a one-pot reaction, by condensation with aromatic acids in the presence of $POCl_3$. Hydrazones **6a**–**e** were obtained from condensation of compound **1** with aromatic aldehyde in ethanol. Another series of 4-thiazolidinone (**7a**–**c**) were prepared by cyclocondensation of some substituted hydrazones with thioglycolic acid in benzene. The yield and physical data of synthesized compounds are summarized in Table 1.

3. Results and discussion

3.1. Antibacterial activity

The antibacterial activities of the synthesized compounds were determined by the well-diffusion method [27]. In this work, *Escherichia coli* (ATTC-25922), *Klebsiella pneumoniae* (ATCC 10031), *Bacillus cereus* (ATTC-10702), *Salmonella typhimurium* (ATTC-23564) were used to investigate the antibacterial activities. The prepared compounds were tested against the Gram +ve bacteria (*B. cereus*) and Gram −ve bacteria (*E. coli*). The bacterial liquid cultures were prepared in infusion broth for their activity tests. The compounds were dissolved in DMSO at concentration of 1 mg ml^{-1}. Antibacterial activity of DMSO against the test organisms was investigated, and was found to be nil. Approximately 1 cm^3 of a 24 h broth culture containing 10^6 cfu cm^{-3} was placed in sterile Petri dishes. Molten nutrient agar (15 cm^3), kept at 45°C, was then poured into the Petri dishes and allowed to solidify. Six millimetre diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37°C. After 24 h, the inhibition zone that appeared around the holes in each plate was measured. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin and sulphametoxazol as standards [28,29]. These results are summarized in Table 2.

Compounds **2a**–**2e**, showed comparatively good activity against all the strains, which is attributed to the presence of groups having inductively electron withdrawing but mesomerically electron donating substituents on phenyl group. These were found to be the most active compounds against the test microorganisms. Compounds **2b** and **2c** have higher antibacterial activity against *E. coli* and *B. cereus* than the compounds containing parallel polar groups (OH, NH_2). It has been observed that compound **4** having 1,2,4-triazole-3-thiol moiety has comparatively good activity against all the fungal strains. In the 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole series, compounds **5a** and **5b** showed similar activities as compared to compound **4**. These results indicate that additional

Table 1
Yield and physical data of the synthesized compounds.

Compound	Ar	Crystallization solvent	m.p. (°C)	UV, λ_{max} (nm)	Yield[a] (%)	Mol formula/ mol wt
2a	C_6H_5	Ethanol/H_2O	335–336	301	90	$C_{22}H_{14}N_4O_2$/366
2b	4-NO_2-C_6H_4	Ethanol/H_2O	354–356	245	87	$C_{22}H_{12}N_6O_6$/458
2c	4-Cl-C_6H_4	Ethanol/H_2O	370–372	245	83	$C_{22}H_{12}N_4O_2Cl_2$/ 435
2d	4-OH-C_6H_4	Ethanol/H_2O	353–355	246	75	$C_{22}H_{14}N_4O_4$/ 398
2e	4-OCH_3-C_6H_4	Ethanol/H_2O	327–329	245	85	$C_{24}H_{18}N_4O4$/ 428
2f	4-NH_2-C_6H_4	Ethanol/H_2O	276–278	252	70	$C_{22}H_{16}N_6O_2$/ 396
4	–	DMF/H_2O	312–314	314	82	$C_{10}H_{10}N_8S_2$/ 306
5a	2-Cl	DMF/H_2O	267–268	336	76	$C_{24}H_{12}Cl_2N_8S_2$/ 546
5b	4-NO_2	DMF/H_2O	324–326	343	72	$C_{24}H_{12}N_{10}O_4S_2$/ 568
6a	C_6H_5	DMF/H_2O	365–366	314	88	$C_{22}H_{18}N_4O_2$/ 370
6b	2-Br-C_6H_4	DMF/H_2O	346–348	313	86	$C_{22}H_{16}N_4O_2Br_2$/ 526
6c	2-Cl-C_6H_4	DMF/H_2O	342 (decom)	314	83	$C_{22}H_{16}N_4O_2Cl_2$/ 438
6d	4-OH-C_6H_4	DMF/H_2O	348 (decom)	309	86	$C_{22}H_{18}N_4O_4$/ 402
6e	4-OCH_3-C_6H_4	DMF/H_2O	348–350	317	87	$C_{24}H_{22}N_4O_4$/ 430
7a	C_6H_5	DMF/H_2O	352–354	309	73	$C_{26}H_{22}N_4O_4S_2$/ 518
7b	2-Br-C_6H_4	DMF/H_2O	338–340	316	75	$C_{26}H_{20}Br_2N_4O_4S_2$/ 674
7c	2-Cl-C_6H_4	DMF/H_2O	355 (decom)	314	72	$C_{26}H_{20}Cl_2N_4O_4S_2$/ 586

[a] Isolated yield.

bulky substituents deteriorate the antibacterial activity of these triazole analogs. Compound **5a** showed comparatively good activity against *B. cereus* in which chloro group is present at ortho position to the phenyl ring. Hydrazones **6a**–**6e** show moderate activity against all the bacterial strains. The compounds containing electron withdrawing substituents at ortho position such as compounds **6b** and **6c** show good activity against *B. cereus* and *S. typhi*. Compounds **7b** and **7c**, wherein electron withdrawing substituents Br and Cl are attached ortho to phenyl group of thiazolidinone ring show moderate biological activity. From these results it is clear that substituents affect the activity of compounds in different series such as chloro group present in **2c** of oxadiazole system has good activity while in case of 1,3,4-thiadiazole (compound **5b**) and 4-thiazolidinones (compound **7c**) series activity varies. Also in case of compound **2b** in oxadiazole series has very good activity against all the test organisms with NO_2 substituent while same substituent in thiadiazole system has moderate activity (compound **5b**).

Table 2
Results of antibacterial activity of the tested compounds.

Sample ID	Antibacterial activity (in mm/ conc. 1 mg/ml^{-1})			
	Escherichia coli	*Klebsiella pneumoniae*	*Bacillus cereus*	*Salmonella typhi*
2a	8	7	8	7
2b	9	8	9	8
2c	8	4	8	6
2d	6	6	5	4
2e	7	5	6	4
2f	6	5	6	5
4	7	6	5	6
5a	6	6	7	6
5b	5	5	5	5
6a	6	5	4	4
6b	6	5	5	6
6c	5	6	8	7
6d	5	5	6	5
6e	6	6	6	4
7a	8	6	8	7
7b	7	7	7	6
7c	7	6	6	6
Sulphametoxazol	12	10	10	11
Ciprofloxacin	20	21	18	23

3.2. Spectroscopic data

The IR spectra of **1** showed absorption peak at 1630 cm^{-1} due to amide group and broad peak at 3254 cm^{-1} due to NH. Its ^{1}H spectrum revealed a singlet at δ 7.86 for aromatic protons, broad peaks at δ 9.87 and δ 4.55 due to the amide and NH protons. ^{13}C spectra of **1** shows peak at δ 126.9, 135.4 and 165.1 for aromatic CH, Ar–C–CO and CO groups respectively. These spectral values of synthesized terephthalic dihydrazide are in good agreement with those reported in the literature [30]. The IR spectrum of compound **2a** showed absorption peak at 1676 cm^{-1} due to C═N streching vibrations. The absence of CO peak at 1630 cm^{-1} confirms the formation of oxadiazole ring. Its ^{1}H NMR spectrum revealed a multiplet at δ 7.7–7.9 due to aromatic protons. Physical and spectral data of these compounds are in good agreement with those reported in the literature [31].

The IR spectrum of **4** displayed stretching bands at 3313 cm^{-1} due to NH. ^{1}H NMR spectrum of this sample displayed a singlet at δ 9.88 and δ 5.55 which were accounted for SH and NH_2, respectively. ^{13}C NMR spectrum of **4** showed signals at δ 168.10 and δ 135.4 due to C═S of triazole and C_5 carbon of triazole, respectively. The mass spectrum of **4** displayed a molecular ion peak at *m*/*z* 306 which confirmed its molecular weight. Compounds **6**(**a**–**e**) showed carbonyl amide stretching at 1645 cm^{-1} and N–H bands in 3200–3228 cm^{-1} region. ^{1}H NMR and ^{13}C NMR data were also in agreement with the formation of hydrazones. ^{1}H NMR spectra of **6a** showed two singlets at δ 12.0 and δ 8.4 which were attributed to the CO–NH and N═CH protons, respectively. IR absorption bands due to the 4-thiazolidiones **7**(**a**–**c**) give C═O stretching at 1653 cm^{-1} and at 3314 cm^{-1} due to the –NH stretching. Their ^{1}H NMR spectra exhibited resonances at 5.86–6.35, 3.61–3.98 and 3.69–4.13 ppm assigned for 4-thiazolidinone, –CH and S–CH_2, respectively. The structure of synthesized compounds was confirmed by spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass). The characterization data of all the compounds are summarized in Table 3.

4. Conclusion

In this report, an easy and useful method to synthesize antibacterial active derivatives containing novel series of 1,4-bis(6-(substituted phenyl)-[1,2,4]-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**5a**–**b**) and 4-bis(substituted phenyl)-4-thiazolidinone derivatives (**7a**–**c**) from terephthalic dihydrazide which is being obtained from PET waste. Bis-oxadiazole and bis-hydrazone derivatives have also been synthesized. Most of these compounds show moderate antibacterial activity comparable with to commercial compounds. And therefore become lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly holds great promise towards pursuit to discover novel class of antibacterial agents. Further studies are being conducted to acquire more information about quantitative structure–activity relationships.

Table 3
Spectral data of compounds.

Compound no.	Spectral values
2a	IR (cm^{-1}) = 2923 (C–H), 1676 (C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 7.97 (m, 14H, Ar-H) ^{13}C NMR (DMSO-d_6) (δ ppm) = 163.5, 155.8, 155.5, 135.2, 127.6, 118,115.2
2b	IR (cm^{-1}) = 2921 (C–H), 1669 (C=N), 1519 (NO_2) ^{1}H NMR (DMSO-d_6) (δ ppm) = 8.3 (d, J = 9.2 Hz, Ar-H), 8.1 (d, J = 8.8 Hz, Ar-H), 7.9 (s, 4H, Ar-H) ^{13}C NMR (DMSO-d_6) (δ ppm) = 166.2, 149.6, 130.5, 127.6, 123.6, 123.5
2c	IR (cm^{-1}) = 2929(C–H), 1668(C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 8.01 (d, J = 9.0 Hz, Ar-H), 7.9 (d, J = 8.6 Hz, Ar-H), 7.5 (s, 4H, Ar-H)
2d	IR (cm^{-1}) = 3226 (O–H), 2935 (CH), 1662 (C=N) ^{1}H NMR(DMSO-d_6) (δ ppm) = 11.8(bs, –OH), 11.0(d, J = 8.4 Hz, Ar-H), 8.0(s, 4H, Ar-H), 7.5(d, J = 8.4 Hz, 4H, Ar-H)
2e	IR (cm^{-1}) = 2925(C–H), 1672(C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 8.01 (s, 4H, Ar-H), 7.9 (d, J = 8.8 Hz, Ar-H), 7.0 (d, J = 8.8 Hz, Ar-H), 3.8 (s, 3H, –OCH_3)
2f	IR (cm^{-1}) = 3307 (N–H), 2991 (C–H), 1664 (C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 11.4 (bs, –NH), 8.0 (s, 4H, Ar-H), 7.9 (d, J = 8.2 Hz, 4H, Ar-H), 7.8 (d, J = 8.0 Hz, 4H, Ar-H)
4	IR (cm^{-1}) = 3313 (N–H), 2935 (CH), 2554 (SH), 1604 (C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 9.88 (bs, 1H, SH), 7.8 (s, 4H, Ar-H), 4.57 (bs, NH_2) ^{13}C NMR (DMSO-d_6) (δ ppm) = 165.1, 135.4, 126.8 MS(m/z) = 307(M^+), 261, 163, 146
5a	IR (cm^{-1}) = IR (cm^{-1}) = 2925(C-H), 1672(C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 8.1 (s, Ar-H), 8.0 (d, 2H, Ar-H), 7.9 (d, 2H, Ar-H), 7.75-7.5(m, Ar-H) ^{13}C NMR (DMSO-d_6) (δ ppm) = 165, 131.5, 131, 129.7, 128.6, 127.8, 126.4, 125.6, 124.5 MS (m/z) = 546(M^+), 382, 284, 164
5b	IR (cm^{-1}) = 2954 (C–H), 1656 (C=N) ^{1}H NMR (DMSO-d_6) (δ ppm) = 10.9 (d, 4H, Ar-H), 8.4 (s, 4H, Ar-H), 8.1 (d, 4H, Ar-H) MS (m/z) = 569 (M^+), 526, 164, 101
6a	IR (cm^{-1}) = 3201 (N–H), 2837 (C–H), 1645 (amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 12.0 (s, 1H, CO–NH), 8.4 (s, 2H, –CH=N), 8.0 (d, 4H, Ar-H), 7.75 (d, J = 8.1 Hz, 4H, Ar-H), 7.46 (s, 6H, Ar-H) ^{13}C NMR (DMSO-d_6) (δ ppm) = 162.4, 148.3, 136.1, 134.2, 130.2, 128.8, 127.7, 127.1
6b	IR (cm^{-1}) = 3220 (N–H), 2864 (C–H), 1642 (amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 12.2 (s, 2H, C0-NH), 8.8 (s, 2H, –CH=N), 8.09 (s, 4H, Ar-H), 7.73 (d, J = 8Hz, 2H, Ar-H),7.50 (d, J = 7.2 Hz, 2H, Ar-H), 7.41(d, J = 7.8 Hz, 2H, Ar-H)
6c	IR (cm^{-1}) = 3201(N–H), 2837(C-H), 1645 (amide C=O) ^{1}H NMR(DMSO-d_6) (δ ppm) = 12.2(s, 2H, CO–NH), 8.9 (s, 2H, –CH=N), 8.09(s, 4H, Ar-H), 7.56(d, J = 8 Hz, 2H, Ar-H), 7.46(d, J = 7.2 Hz, 2H, Ar-H), 7.41(d, J = 8.0 Hz, 2H, Ar-H) ^{13}C NMR (DMSO-d_6) (δ ppm) = 163, 144.1, 138.2, 133.2, 131.5, 129.9, 127.8, 127.6, 126.9
6d	IR (cm^{-1}) = 3210 (O–H, N–H), 2995 (C-H), 1641 (amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 11.80 (s, 1H, C0-NH), 9.91 (s, 1H, O-H), 8.37 (s, 1H,-CH=N), 8.03 (s, 2H, Ar-H), 7.60 (d, J = 8.4 Hz, 2H, Ar-H), 6.8 (d, J = 8 Hz, 2H, Ar-H)
6e	IR (cm^{-1}) = 3228(N–H), 2985(C–H), 1647(amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 11.86(s, 2H, CO–NH), 8.42 (s, 2H, -CH=N), 8.03(s, 4H, ArH), 7.71(d, J = 8.8 Hz, 4H, Ar-H), 7.05(d, J = 8.4 Hz, 4H, Ar-H)
7a	IR (cm^{-1}) = 3213 (N–H), 2914 (C–H), 1627 (thiazolidinone C=O), 1606(amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 11.8 (s, 2H, C0-NH), 8.3 (s, 4H, Ar-H), 7.4 (m, 10 H, Ar-H), 5.1 (s, 2H, C-H), 3.8 (d, J = 7.2 Hz, 4H),
7b	IR (cm^{-1}) = 3314 (N–H), 2965 (C–H), 1653 (thiazolidinone C=O), 1628 (amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 12.2(s, 2H, CO–NH), 8.8(s, 4H, Ar-H), 7.4–8.0(m, 8H, Ar-H), 5.2(s, 2H, C–H), 3.9(d, J = 7.2 Hz, 4H),
7c	IR (cm^{-1}) = 3201 (N–H), 2835 (C–H), 1643 (thiazolidinone C=O), 1606 (amide C=O) ^{1}H NMR (DMSO-d_6) (δ ppm) = 8.9 (s, 2H, CO–NH), 8.1 (s, 4H, Ar-H), 7.4–7.6 (m, 8H, Ar-H), 5.2 (s, 2H, C–H), 3.9 (d, 4H, J = 7.2 Hz)

5. Experimental procedures

5.1. Chemical protocols

Chemicals were purchased from Merck Chemical Company, S.D. Fine (India). Melting points was determined in an open capillary and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrophotometer and reported in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively. NMR spectra were obtained in solutions of DMSO (d_6) and chemical shifts reported in parts per million (ppm) and TMS as internal standard. Analytical TLC of all reactions was performed on Merck prepared plates. Column chromatography was performed using silica gel (100–200 mesh).

5.1.1. General procedure for the synthesis of 1,4-bis(5-aryl-1,3,4-oxadiazole-2yl) benzene (**2a–2f**)

A mixture of terephthalic dihydrazide (1 mmol) and the appropriate aromatic acid (2 mmol) in trifluoroacetic acid (10 ml) was refluxed for 4–6 h. The reaction mixture was slowly poured over crushed ice and kept overnight. The solid thus separated out was neutralized with $NaHCO_3$, filtered and washed with water and recrystallized from ethanol.

5.1.2. Synthesis of bis-potassium dithiocarbazinate (**3**)

Potassium hydroxide (3 mmol) was dissolved in absolute ethanol (25 mL). The solution was cooled in ice bath and terephthalic dihydrazide (1 mmol) was added with stirring. To this carbondisulfide (5 mmol) was added in small portions with constant stirring. The reaction mixture was agitated continuously for 12 h at room temperature. The precipitated potassium dithiocarbazinate was collected by filtration, washed with cold ethanol (50 mL) and dried in vacuum. The potassium salt thus obtained was used in the next step without further purification.

5.1.3. Synthesis of bis-4-amino-1,2,4-triazole-3-thiol (**4**)

A suspension of potassium dithiocarbazinate (1 mmol) in water (5 mL) and hydrazine hydrate (99%, 3 mmol) was heated for 18–20 h at 100 °C with occasional shaking. The colour of the reaction mixture changed to green with the evolution of hydrogen sulfide gas. A homogeneous reaction mixture was obtained during the reaction process. The reaction mixture was cooled to room temperature and diluted with cold water (20 mL). On acidification with HCl the required triazole was precipitated out, which was recrystallized with DMF–water mixture.

5.1.4. Synthesis of 1,4-bis(6-substituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**5a–b**)

An equimolar mixture of 1,4-bis(6-substituted-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles **4** (1 mmol), aromatic acids (2 mmol) in phosphorus oxychloride (5 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature and then gradually poured onto crushed ice with stirring. The mixture was neutralized with $NaHCO_3$ solution and allowed to stand overnight. The solid separated out was filtered and washed thoroughly with cold water.

5.1.5. Synthesis of N′,N′-bis(substituted benzylidene) terephthalohydrazide (**6a–e**)

Equimolar quantities of terephthalic dihydrazide (1 mmol) and different aromatic aldehydes (2 mmol) was refluxed in alcohol for 4 h in the presence of few drops of glacial acetic acid. The reaction mixture on cooling was poured into cold water, filtered and dried. The crude solid was recrystallized in DMF–water mixture to give the products.

*5.1.6. Synthesis of 4-bis(substituted phenyl)-4-thiazolidinone derivatives (**7a–c**)*

A mixture of hydrazone (1 mmol) and thioglycolic acid (2 mmol) was refluxed in dry benzene (25 ml) for 8–10 h. After completion of reaction excess benzene was evaporated in vacuo. The resulting residue was neutralized with saturated $NaHCO_3$ solution until CO_2 evolution ceased. The solid product was washed with water, dried and recrystallized from DMF–water mixture.

Acknowledgement

The authors express their thanks to University Grants Commission, New Delhi, India for the financial support.

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