



# Synthesis of new chiral 1,3,4-thiadiazole-based di- and tri-arylsulfonamide residues and evaluation of in vitro anti-HIV activity and cytotoxicity

Maria Shafique<sup>1</sup> · Shahid Hameed<sup>1</sup> · Muhammad Moazzam Naseer<sup>1</sup> · Najim Aboud Al-Masoudi<sup>2,3</sup>

Received: 12 January 2018 / Accepted: 14 June 2018 / Published online: 2 July 2018  
© Springer International Publishing AG, part of Springer Nature 2018

## Abstract

A series of new chiral 1,3,4-thiadiazole-based bis-sulfonamides **4a–4w** and tri-sulfonamide analogue **5** was synthesized and evaluated as anti-HIV agents. The reaction of chiral amino acids **1** with sulfonyl chlorides **2**, followed by subsequent reaction of resultant *N*-protected amino acids **2a–2f** with thiosemicarbazide in the presence of excess phosphorous oxychloride afforded *N*-(1-(5-amino-1,3,4-thiadiazol-2-yl)alkyl)-4-arylsulfonamides **3a–3f**. Treatment of **2a–2f** with substituted sulfonyl chlorides in portions furnished the target bis-sulfonamide analogues **4a–4w** in good yields, together with the unexpected **5**. The new compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compounds **4s** were the most active in inhibiting HIV-1 with IC<sub>50</sub> = 9.5 μM (SI = 6.6), suggesting to be a new lead in the development of an antiviral agent. Interestingly, compound **5** exhibited significant cytotoxicity of >4.09 μM and could be a promising antiproliferative agent.

**Keywords** Anti-HIV activity · Cytotoxicity · *N*-Protected amino acids · Sulfonamides · 1,3,4-Thiadiazoles

## Introduction

Thiadiazoles represent a class of compounds having immense importance in medicinal chemistry due to their mesoionic nature and good lipophilicity [1–3]. They are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest including antibacterial [4, 5], antifungal [6–8], anti-inflammatory [9, 10], antimicrobial [10–13], antitubercular [14–16], anticancer [17–22], anti-helicobacter pylori [23, 24] and anticonvulsant [25] properties. In recent years, we have synthesized a series of new naphthalene derivatives bearing 1,3,4-thiadiazole backbone as potential anti-HIV agents [26], meanwhile Ijichi et al. [27] reported that 4-(2,6-dichlorophenyl)-1,2,5-thiadiazol-3-

yl *N*-methyl-*N*-alkylcarbamates proved inhibitory to HIV-1 replication in the nanomolar concentration range. Many drugs containing 1,3,4-thiadiazole nucleus such as acetazolamide [28], methazolamide [29], megazol [30], and xanomeline [31] (Fig. 1) are available in the market.

Sulfonamides (sulfa drugs) were the first drugs largely employed and systematically used as preventive and chemotherapeutic agents against various diseases [32]. With the rapid progress in this field, more active and selective sulfonamide derivatives have been prepared by linking various heterocyclic moieties with sulfonamide core [33].

Based on these observations and as continuation of our research interests in sulfonamides and 1,3,4-thiadiazole derivatives [34–36], herein we report the synthesis of a new series of chiral 1,3,4-thiadiazole-based bis-sulfonamides (**4a–4w** and **5**), their structure characterization and evaluation of their anti-HIV activities.

## Results and discussion

### Chemistry

The synthesis of chiral 1,3,4-thiadiazole-based bis-sulfonamides was initiated by the reaction of chiral amino

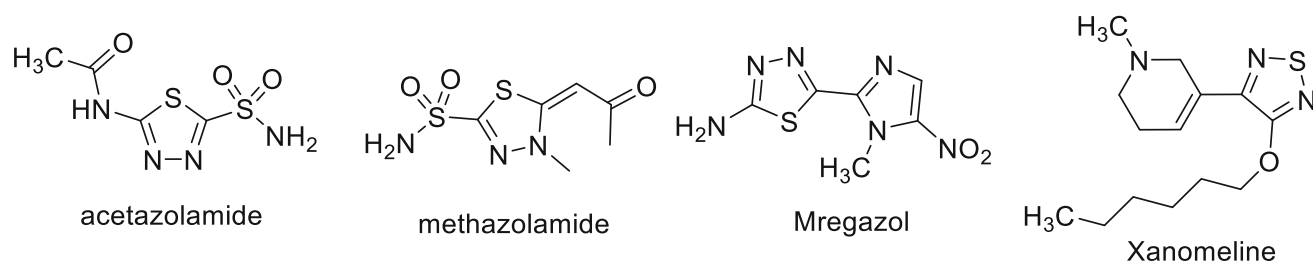
✉ Shahid Hameed  
shameed@qau.edu.pk

✉ Najim Aboud Al-Masoudi  
najim.al-masoudi@gmx.de  
http://www.al-masoudi.de

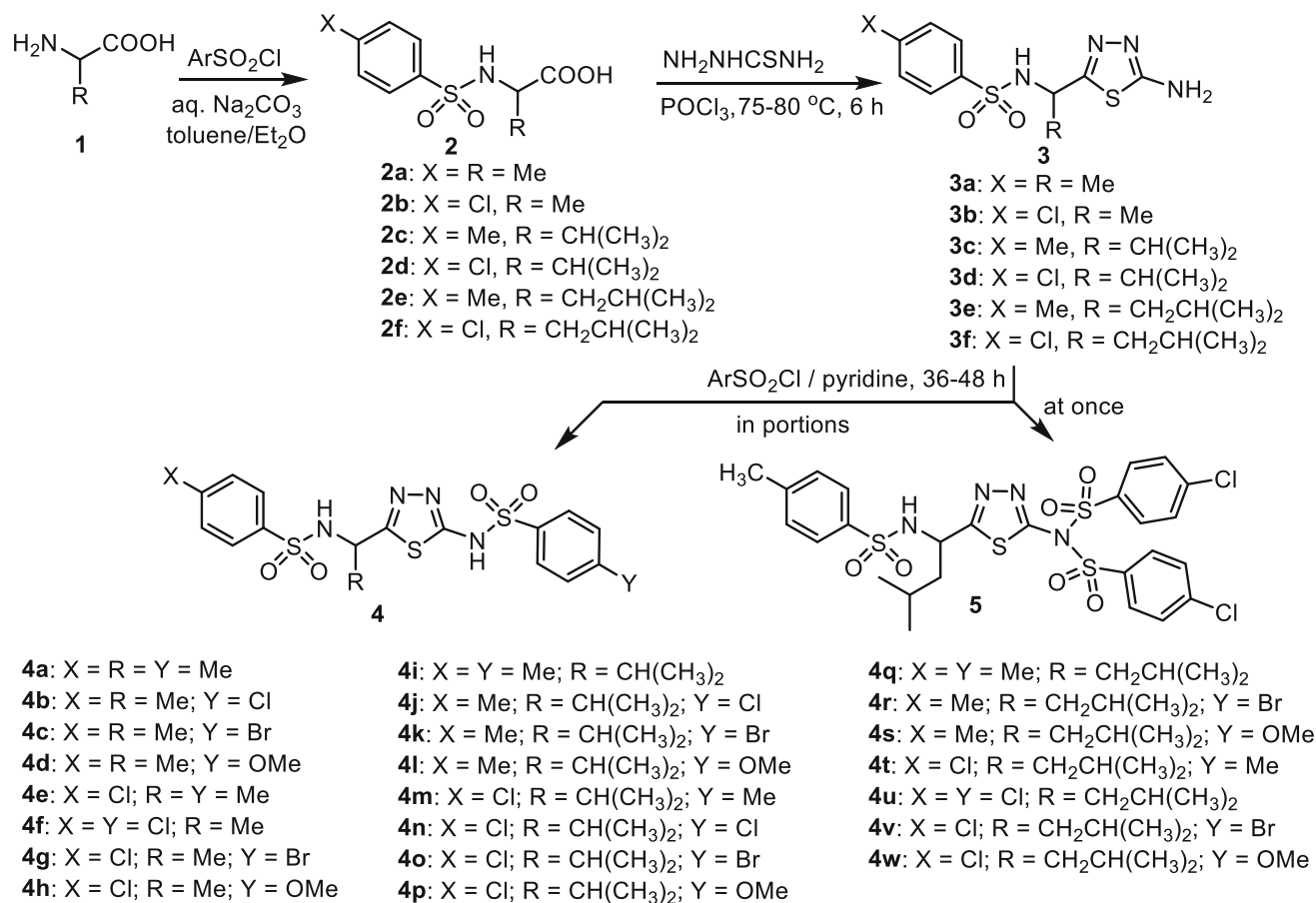
<sup>1</sup> Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

<sup>2</sup> Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq

<sup>3</sup> Present Address: Constance, Germany



**Fig. 1** Commercially available 1,3,4-thiadiazole-based drugs



**Scheme 1** Synthesis of 1,3,4-thiadiazole-based bis-sulfonamide derivatives **4a–4w** and **5**

acids **1** with arylsulfonyl chlorides **2** to furnish the corresponding *N*-arylsulfonamides **2a–2f** (79–9% yield), which were further reacted with thiosemicarbazide in the presence of excess phosphorous oxychloride to afford 2,5-disubstituted 1,3,4-thiadiazole-based arylsulfonamides **3a–3f**. Initially, when the reaction was carried out at high temperature, it resulted in the formation of side products providing low yields of the desired target molecules. However, when the reaction was performed at 75–80 °C (optimizing reaction temperature starting from 0 °C), it provided good yields of the desired products. After successful synthesis of 2,5-disubstituted 1,3,4-thiadiazole-based arylsulfonamides **3a–3f** in 65–76% yields, the synthesis of

bis-arylsulfonamides **4a–4w** was attempted. The reaction of **3a–3f** with the respective arylsulfonyl chloride using pyridine as a base and solvent provided bis-arylsulfonamides **4a–4w** in 67–82% yield (Scheme 1). It is pertinent to mention here that a reasonable amount of unreacted **3a–3f** was recovered when the reaction was performed using equimolar quantities of reactants diminishing the yields of the desired products. Nevertheless, the gradual increase in arylsulfonyl chlorides (1:1.4) under inert argon atmosphere lead to the formation of desired products **4a–4w** in good yields. Furthermore, addition of arylsulfonyl chloride to the reaction mixture in this ratio all at once resulted in the formation of *N,N*-disubstituted product **5** in 50% yield (Scheme 1).

However, the addition of arylsulfonyl chloride in small portions led to the desired monosubstituted product.

The *N*-arylsulfonylation of amino acids to compounds **2a–2f** was verified by the IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. The IR spectra were characterized by the appearance of bands for symmetric and asymmetric stretchings of the arylsulfonyl group in the regions 1162–1156 and 1328–1311  $\text{cm}^{-1}$ , respectively, meanwhile carbonyl groups appeared in the region of 1729–1717  $\text{cm}^{-1}$ . In the  $^1\text{H}$  NMR spectra of **2a–2f**, NH proton appeared as broad singlets or doublets at the regions  $\delta$  5.13–6.77 ppm, meanwhile the carboxylic acid protons resonated at the regions  $\delta$  8.0–10.33 ppm, exchangeable with  $\text{D}_2\text{O}$ . The structures of **3a–3f** were confirmed by their IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and mass spectra. The IR spectra showed peaks in the regions 3263–3156  $\text{cm}^{-1}$  attributed to the NH stretchings of  $\text{NH}_2$  group, while the peaks at 1729–1717  $\text{cm}^{-1}$  were attributed to the carbonyl group stretching. In the  $^1\text{H}$  NMR spectra of **3a–3f**, the doublets or broad singlets at the regions  $\delta$  8.56–6.43 ppm were assigned to  $\text{NH}_2$  or secondary NH protons, exchangeable with  $\text{D}_2\text{O}$ . In  $^{13}\text{C}$ -NMR spectra of **3a–3f**, C-2 of the thiadiazole moiety appeared at the regions  $\delta$  161.3–162.3 ppm, while C-5 of the same ring resonated at the regions  $\delta$  168.9–169.8 ppm. Furthermore, the structures of **4a–4w** and **5** were assigned on the basis of their IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and mass spectra. The characteristic signals for secondary NH absorption at 3289–3255  $\text{cm}^{-1}$  in the IR spectra indicated the formation of the desired products. In  $^1\text{H}$ -NMR spectra, the aromatic protons appeared as multiplets or doublets in regions  $\delta$  7.86–7.35 ppm, integrating to eight protons, while the aliphatic and substituents protons were fully analyzed (c.f. “Experimental section”). In the  $^{13}\text{C}$ -NMR spectra of **4a–4w**, C-2 and C-5 of the thiazdiazole backbone resonated at the regions  $\delta$  159.3–161.7 and 162.8–169.2 ppm, respectively. The eight signals at the regions  $\delta$  114.0–144.0 ppm were assigned to the aromatic carbon atoms, while CHNH carbon atom resonated at the regions  $\delta$  49.0–59.8 ppm. The aromatic carbon atom C-OMe (of compounds **4d**, **4h**, **4l**, **4p**, **4s** and **4w**) appeared at the regions  $\delta$  158.8–162.8 ppm. The other aliphatic and substituent carbon atoms were fully assigned (c.f. “Experimental section”) Compound **4h** was selected for further NMR experiments. The gradient heteronuclear multiple-bond correlation [37] NMR spectrum of **4h** showed two  $^3J_{\text{H,C}}$  couplings: C-2 carbon atom of the thiadiazole backbone at  $\delta_{\text{C}}$  161.1 ppm coupled with CHMe proton at  $\delta_{\text{H}}$  4.46 ppm as well as methyl protons of the same group at  $\delta_{\text{H}}$  1.47 ppm. Further, a  $^2J_{\text{H,C}}$  coupling between methyl protons of methoxy substituent at  $\delta_{\text{H}}$  3.83 ppm and aromatic carbon atom C-OMe at  $\delta_{\text{C}}$  162.7 ppm was observed. Additionally, a  $^2J_{\text{H,C}}$  coupling between CHMe protons at  $\delta_{\text{H}}$  4.46 ppm with CHMe carbon atom at  $\delta_{\text{C}}$  49.6 ppm was witnessed (Fig. 2).

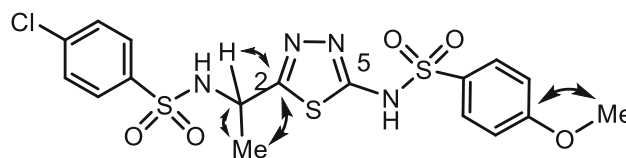


Fig. 2  $J_{\text{H,C}}$  correlations in the HMBC NMR spectrum of **4h**

### In vitro anti-HIV activity

Compounds **3a–3f**, **4a–4w** and **5** were evaluated for their inhibitory activity against HIV-1 (strain III<sub>B</sub>) and HIV-2 (strain ROD) and monitored by the inhibition of the virus-induced cytopathic effect in the human T-lymphocyte (MT-4) cells, using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [38]. The results are summarized in Table 1, in which the data for nevirapin [39], azidothymidine (AZT) [40], and lamivudine (3TC) [41] are included for comparison. The cytotoxicity of the compounds was determined in parallel. None of the tested compounds were active against inhibition of HIV-1 and HIV-2, although they showed cytotoxicity against MT-4 cells at micromolar concentrations. However, **4s** exhibited an  $\text{IC}_{50}$  value of 9.25  $\mu\text{M}$ , with a selectivity index (SI) value of 6.6; however, compound **5** turned out cytotoxic for exponentially growing MT-4 cells (human  $\text{CD4}^+$  lymphocytes) in the low micromolar range ( $\text{CC}_{50}$  4.09  $\mu\text{M}$ ). This study revealed that compounds containing a branched-chain aliphatic group (leucine residue) together with a methoxy substituent at the arylsulfonyl moiety showed significant anti-HIV-1 activity, while the presence of three arylsulfonyl groups bearing a 1,3,4-thiadiazole ring would enhance the cytotoxicity of such molecules (e.g., compound **5**).

### Conclusion

We have synthesized a series of new chiral 1,3,4-thiadiazole-based bis-arylsulfonamides **4a–4w** and **5** in a multistep sequence starting from chiral amino acids. The new synthesized compounds were screened for their inhibitory activity against HIV-1 and HIV-2, where **4s** showed significant inhibition of HIV-1 with  $\text{IC}_{50}$  value of 9.25  $\mu\text{M}$  (SI = 6.6). The anti-HIV activity results suggested that **4s** might act as a new candidate for reverse transcriptase inhibition. Furthermore, compound **5** exhibited significant cytotoxicity of >4.09  $\mu\text{M}$  against human T-lymphocyte (MT-4) cells and could be a promising antiproliferative agent.

**Table 1** In vitro anti-HIV-1 and HIV-2 activity of 1,3,4-thiadiazole derivatives

Compd.	Virus strain	av. IC <sub>50</sub> ( $\mu$ M) <sup>a</sup>	av. CC <sub>50</sub> ( $\mu$ M) <sup>b</sup>	SI <sup>c</sup>
<b>4e</b>	III <sub>B</sub>	>60.53	60.53	<1
	ROD	>60.53	60.53	<1
<b>4s</b>	III <sub>B</sub>	9.25	61.05	6.6
	ROD	>61.05	61.05	<1
<b>4u</b>	III <sub>B</sub>	>59.93	59.93	<1
	ROD	>59.93	59.93	<1
<b>4v</b>	III <sub>B</sub>	>57.63	57.63	<1
	ROD	>57.63	57.63	<1
<b>5</b>	III <sub>B</sub>	>4.09	4.09	<1
	ROD	>4.09	4.09	<1
Nevirapin	III <sub>B</sub>	0.05	>4.00	>80
	ROD	4.00	>4.00	<1
AZT	III <sub>B</sub>	0.0019	>25	>13,144
	ROD	0.0018	>25	>14,245
3TC	III <sub>B</sub>	0.51	>20	>39
	ROD	2.02	>20	>10

Anti-HIV-1 activity measured against strain III<sub>B</sub>

Anti-HIV-2 activity measured against strain ROD

<sup>a</sup>Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and HIV-2-induced cytopathogenic effect

<sup>b</sup>Average CC<sub>50</sub>: compound concentration that reduces the viability of mock-infected MT-4 cells by 50%

<sup>c</sup>SI selectivity index (CC<sub>50</sub>/IC<sub>50</sub>). All data represent the mean values of at least two separate experiments

## Experimental section

### Chemistry

Melting points were measured on a Gallenkamp melting point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FTIR spectrophotometer using ATR (attenuated total reflectance) facility. NMR spectra were acquired on 300 MHz (<sup>1</sup>H) and on 100 MHz (<sup>13</sup>C) spectrometers (Bruker Avance, Germany) with TMS as internal standard and on the  $\delta$  scale in ppm. The mass spectra were recorded on Agilent Technologies mass spectrometer (model: 5973) using ESI method. All the reactions were monitored using pre-coated silica gel-60 F<sub>254</sub> TLC plates purchased from Merck (Germany), using CHCl<sub>3</sub>-MeOH 9:1 as eluent. Thiosemicarbazide was purchased from Sigma-Aldrich.

### General procedure for the synthesis of *N*-(4-chloro/methylbenzenesulfonyl)amino acids **2a–2f**

The respective amino acid (1.00 mmol) was dissolved in an aqueous solution of sodium carbonate (2.00 mmol, 212 mg

in water (5 mL)) and a solution of arylsulfonyl chloride (1.20 mmol) in toluene/diethyl ether (7 mL) was added. The reaction mixture was stirred vigorously and monitored by TLC. After the completion of reaction (20–24 h), the organic layer was separated and the aqueous layer was acidified with dilute hydrochloric acid. The precipitated solid was filtered and recrystallized from aqueous EtOH.

### *N*-(4-Methylbenzenesulfonyl)alanine (**2a**)

From L-alanine (74 mg). Yield: 223 mg (92%) as colorless; m.p.: 137–138 °C; R<sub>f</sub>: 0.45; IR ( $\nu_{\max}$ , neat, cm<sup>-1</sup>): 3400–2450 (OH), 3276 (NH), 1729 (C=O), 1572 (C=C), 1311, 1157 (2 × O=S=O), 1088 (C–O). <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>):  $\delta$  1.33 (d, 3H, *J* = 7.2 Hz, CH<sub>3</sub>CH), 2.42 (s, 3H, Ar-CH<sub>3</sub>), 3.97 (m, 1H, CHCH<sub>3</sub>), 6.77 (d, 1H, *J* = 8.4 Hz, NH), 7.37 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.77 (d, 2H, *J* = 8.1 Hz, Ar-H), 10.33 (s, 1H, CO<sub>2</sub>H).

### *N*-(4-Chlorobenzenesulfonyl)alanine (**2b**)

From L-alanine (74 mg). Yield: 235 mg (89%) as colorless; m.p.: 131–132 °C; R<sub>f</sub>: 0.44; IR ( $\nu_{\max}$ , neat, cm<sup>-1</sup>): 3450–2450 (OH), 3270 (NH), 1720 (C=O), 1574 (C=C), 1319, 1162 (2 × O=S=O), 1082 (C–O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.46 (d, 3H, *J* = 7.2 Hz, CH<sub>3</sub>CH), 4.01 (m, 1H, CHCH<sub>3</sub>), 5.13 (bs, 1H, NH), 7.49 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.82 (d, 2H, *J* = 8.7 Hz, Ar-H), 9.70 (s, 1H, CO<sub>2</sub>H).

### *N*-(4-Methylbenzenesulfonyl)valine (**2c**)

From L-valine (117 mg). Yield: 184 mg (85%) as colorless crystals; m.p.: 151–153 °C; R<sub>f</sub>: 0.45; IR ( $\nu_{\max}$ , neat, cm<sup>-1</sup>): 3400–2400 (OH), 3280 (NH), 1729 (C=O), 1586 (C=C), 1318, 1160 (2 × O=S=O), 1081 (C–O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.87 (d, 3H, *J* = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.96 (d, 3H, *J* = 6.6 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 2.12 (m, 1H, CHCH(CH<sub>3</sub>)<sub>2</sub>), 2.42 (s, 3H, Ar-CH<sub>3</sub>), 3.80 (m, 1H, NHCH), 5.24 (d, 1H, *J* = 9.9 Hz, NH), 7.29 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.73 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.20 (s, 1H, CO<sub>2</sub>H).

### *N*-(4-Chlorobenzenesulfonyl)valine (**2d**)

From L-valine (117 mg). Yield: 240 mg (82%) as colorless crystals; m.p.: 125–127 °C; R<sub>f</sub>: 0.45; IR ( $\nu_{\max}$ , neat, cm<sup>-1</sup>): 3450–2400 (OH), 3277 (NH), 1728 (C=O), 1578 (C=C), 1328, 1159 (2 × O=S=O), 1084 (C–O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.76 (d, 3H, *J* = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, 3H, *J* = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 2.14 (m, 1H, CHCH(CH<sub>3</sub>)<sub>2</sub>), 3.93 (m, 1H, NHCHCH), 5.65 (bs, 1H, NH), 7.66 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.83 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.60 (s, 1H, CO<sub>2</sub>H).

***N*-(4-Methylbenzenesulfonyl)leucine (2e)**

From L-leucine (131 mg). Yield: 234 mg (82%) as colorless crystals; m.p.: 126–128 °C;  $R_f$ : 0.47; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3400–2450 (OH), 3269 (NH), 1717 (C=O), 1576 (C=C), 1318, 1158 ( $2 \times \text{O}=\text{S}=\text{O}$ ), 1080 (C–O).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.83 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.90 (d, 3H,  $J = 6.8$  Hz,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.51 (m, 2H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.79 (m, 1H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.43 (s, 3H, Ar- $\text{CH}_3$ ), 3.93 (m, 1H,  $\text{NHCH}_2$ ), 5.25 (d, 1H,  $J = 9.6$  Hz, NH), 7.29 (d, 2H,  $J = 8.4$  Hz, Ar-H), 7.74 (d, 2H,  $J = 8.4$  Hz, Ar-H), 8.60 (s, 1H,  $\text{CO}_2\text{H}$ ).

***N*-(4-Chlorobenzenesulfonyl)leucine (2f)**

From L-leucine (131 mg). Yield: 242 mg (79%) as colorless crystals; m.p.: 111–114 °C;  $R_f$ : 0.48; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3450–2450 (OH), 3275 (NH), 1728 (C=O), 1577 (C=C), 1319, 1156 ( $2 \times \text{O}=\text{S}=\text{O}$ ), 1082 (C–O).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.87 (d, 3H,  $J = 6.3$  Hz,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.93 (d, 3H,  $J = 6.5$  Hz,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.56 (m, 2H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.80 (m, 3H, m,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 3.98 (m, 1H,  $\text{NHCH}_2$ ), 5.23 (d, 1H,  $J = 9.9$  Hz, NH), 7.24 (d, 2H,  $J = 9.0$  Hz, Ar-H), 7.80 (m, 1H, Ar-H), 10.02 (s, 1H,  $\text{CO}_2\text{H}$ ).

**General procedure for the synthesis of *N*-(1-(5-amino-1,3,4-thiadiazol-2-yl)alkyl)-4-arylsulfonamides 3a–3f**

To an ice-cooled mixture of thiosemicarbazide (165 mg, 1.00 mmol) and corresponding *N*-(4-chloro/methyl benzenesulfonyl)amino acid (1.0 mmol), an excess of phosphorus oxychloride (25 mL) was added slowly under continuous stirring. Subsequently, the temperature was raised gradually to 75–80 °C. The reaction was stirred at this temperature for 6 h, cooled and quenched with crushed ice. The resulting solution was refluxed for 4 h. The solution was then cooled and neutralized with solid  $\text{KHCO}_3$ . The solid thus separated was filtered, washed with cold water and recrystallized from EtOH.

***N*-(1-(5-Amino-1,3,4-thiadiazol-2-yl)ethyl)-4-methylbenzenesulfonamide (3a)**

From **2a** (243 mg). Yield: 226 mg (76%) as colorless crystals; m.p.: 230–232 °C;  $R_f$ : 0.34; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3421, 3416 ( $2 \times \text{NH}$ , pri.), 3263 (NH, sec.), 1567 (C=C), 1321, 1162 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.24 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.38 (s, 3H, Ar- $\text{CH}_3$ ), 4.49 (m, 1H,  $\text{CHCH}_3$ ), 7.06 (s, 2H,  $\text{NH}_2$ ), 7.37 (d, 2H,  $J = 8.4$  Hz, Ar- $H_{3,3'}$ ), 7.67 (d, 2H,  $J = 8.4$  Hz, Ar- $H_{2,2'}$ ), 8.37 (d, 1H,  $J = 5.7$  Hz,  $\text{NHCH}$ ).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  21.1 ( $\text{CH}(\text{CH}_3)_2$ ), 21.4 (Ar- $\text{CH}_3$ ), 49.5 ( $\text{CHCH}_3$ ), 127.0 (Ar- $C_{3,3'}$ ), 130.1 (Ar-

$C_{2,2'}$ ), 138.4 (Ar- $C_1$ ), 143.4 (Ar- $C_4$ ), 162.3 ( $\text{C}_{\text{thiadiazole}}^2$ ), 169.8 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  299  $[\text{M}+\text{H}]^+$ .

***N*-(1-(5-Amino-1,3,4-thiadiazol-2-yl)ethyl)-4-chlorobenzenesulfonamide (3b)**

From **2b** (264 mg). Yield: 222 mg (70%) as colorless crystals; m.p.: 207–209 °C;  $R_f$ : 0.36; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3428, 3418 ( $2 \times \text{NH}$ , pri), 3244 (N–H, sec.), 1578 (C=C), 1311, 1157 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.28 (d, 3H,  $J = 6.9$  Hz,  $\text{CHCH}_3$ ), 4.56 (m, 1H,  $\text{CHCH}_3$ ), 7.09 (s, 2H,  $\text{NH}_2$ ), 7.69 (d, 2H,  $J = 6.6$  Hz, Ar- $H_{3,3'}$ ), 7.76 (d, 2H,  $J = 6.6$  Hz, Ar- $H_{2,2'}$ ), 8.59 (d, 1H,  $J = 8.1$  Hz,  $\text{NHCH}$ ).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  21.3 ( $\text{CHCH}_3$ ), 49.6 ( $\text{CHCH}_3$ ), 128.9 (Ar- $C_{2,2'}$ ), 129.7 (Ar- $C_{3,3'}$ ), 137.8 (Ar- $C_4$ ), 140.4 (Ar- $C_1$ ), 161.3 ( $\text{C}_{\text{thiadiazole}}^2$ ), 169.7 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  317/319  $[\text{M}+\text{H}]^+$ .

***N*-(1-(5-Amino-1,3,4-thiadiazol-2-yl)-2-methylpropyl)-4-methylbenzenesulfonamide (3c)**

From **2c** (271 mg). Yield: 213 mg (65%) as mauve solid; m.p.: 253–254 °C;  $R_f$ : 0.36; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3358, 3350 ( $2 \times \text{NH}$ , pri), 3156 (NH, sec.), 1594 (C=C), 1328, 1159 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (DMF- $d_7$ ):  $\delta$  0.96 (3H, d,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.16 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.22 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.56 (3H, s, Ar- $\text{CH}_3$ ), 4.50 (1H, m,  $\text{NHCH}$ ), 7.28 (s, 2H,  $\text{NH}_2$ ), 7.50 (d, 2H,  $J = 8.1$  Hz, Ar- $H_{3,3'}$ ), 7.84 (2H, d,  $J = 8.1$  Hz, Ar- $H_{2,2'}$ ), 8.24 (1H, d,  $J = 1.6$  Hz,  $\text{NHCH}$ ).  $^{13}\text{C}$  NMR (DMF- $d_7$ ):  $\delta$  18.7 ( $\text{CH}(\text{CH}_3)_2$ ), 18.9 ( $\text{CH}(\text{CH}_3)_2$ ), 20.8 ( $\text{CH}(\text{CH}_3)_2$ ), 33.6 (Ar- $\text{CH}_3$ ), 60.1 ( $\text{NHCH}$ ), 127.1 (Ar- $C_{3,3'}$ ), 129.6 (Ar- $C_{2,2'}$ ), 139.1 (Ar- $C_1$ ), 143.0 (Ar- $C_4$ ), 160.7 ( $\text{C}_{\text{thiadiazole}}^2$ ), 169.6 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  327  $[\text{M}+\text{H}]^+$ .

***N*-(1-(5-Amino-1,3,4-thiadiazol-2-yl)-2-methylpropyl)-4-chlorobenzenesulfonamide (3d)**

From **2d** (292 mg). Yield: 239 mg (69%) as light pink crystals; m.p.: 251–253 °C;  $R_f$ : 0.35; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3457, 3448 ( $2 \times \text{NH}$ , pri), 3252 (NH, sec.), 1576 (C=C), 1318, 1160 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (DMF- $d_7$ ):  $\delta$  0.76 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.93 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.25 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 4.33 (m, 1H,  $\text{NHCH}$ ), 7.66 (d, 2H,  $J = 7.8$  Hz, Ar- $H_{3,3'}$ ), 7.83 (d, 2H,  $J = 8.1$  Hz, Ar- $H_{2,2'}$ ), 8.04 (bs, 2H,  $\text{NH}_2$ ), 8.65 (bs, 1H,  $\text{NHCH}$ ).  $^{13}\text{C}$  NMR (DMF- $d_7$ ):  $\delta$  18.4 ( $\text{CH}(\text{CH}_3)_2$ ), 18.8 ( $\text{CH}(\text{CH}_3)_2$ ), 21.1 ( $\text{CH}(\text{CH}_3)_2$ ), 32.0 ( $\text{NHCH}$ ), 128.8 (Ar- $C_{2,2'}$ ), 129.6 (Ar- $C_{3,3'}$ ), 138.0 (Ar- $C_4$ ), 140.3 (Ar- $C_1$ ), 161.6 ( $\text{C}_{\text{thiadiazole}}^2$ ), 169.3 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  345/347  $[\text{M}+\text{H}]^+$ .

### *N*-(1-(5-Amino-1,3,4-thiadiazol-2-yl)-3-methylbutyl)-4-methylbenzenesulfonamide (3e)

From **2e** (285 mg). Yield: 245 mg (72%) as colorless crystals; m.p.: 240–242 °C;  $R_f$ : 0.42; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3464, 3450 ( $2 \times \text{NH}$ , pri), 3263 (NH, sec.), 1572 (C=C), 1319, 1156 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.78 (d, 3H,  $J = 3.3$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.84 (d, 3H,  $J = 3.3$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.63 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.41 (s, 3H, Ar- $\text{CH}_3$ ), 4.64 (m, 1H,  $\text{NHCH}_2$ ), 6.41 (s, 2H,  $\text{NH}_2$ ), 7.09 (d, 1H,  $J = 8.1$  Hz,  $\text{NHCH}$ ), 7.32 (d, 2H,  $J = 7.8$  Hz, Ar- $H_{3,3'}$ ), 7.68 (d, 2H,  $J = 8.4$  Hz, Ar- $H_{2,2'}$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  20.5 ( $\text{CH}(\text{CH}_3)_2$ ), 21.2 ( $\text{CH}(\text{CH}_3)_2$ ), 21.7 ( $\text{CHCH}_2$ ), 24.2 ( $\text{CH}(\text{CH}_3)_2$ ), 44.8 (Ar- $\text{CH}_3$ ), 52.2 ( $\text{NHCHCH}_2$ ), 127.1 (Ar- $C_{3,3'}$ ), 129.4 (Ar- $C_{2,2'}$ ), 138.5 (Ar- $C_1$ ), 143.0 (Ar- $C_4$ ), 161.9 ( $\text{C}_{\text{thiadiazole}}^2$ ), 168.9 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  341  $[\text{M}+\text{H}]^+$ .

### *N*-(1-(5-Amino-1,3,4-thiadiazol-2-yl)-3-methylbutyl)-4-chlorobenzenesulfonamide (3f)

From **2f** (306 mg). Yield: 267 mg (74%) as colorless crystals; Yield: 74%; m.p.: 227–229 °C;  $R_f$ : 0.44; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3420, 3412 ( $2 \times \text{NH}$ , pri), 3212 (NH, sec.), 1576 (C=C), 1318, 1158 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.72 (d, 3H,  $J = 6.3$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.79 (d, 3H,  $J = 6.3$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.46 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 4.42 (m, 1H,  $\text{NHCHCH}_2$ ), 7.07 (s, 2H,  $\text{NH}_2$ ), 7.63 (m, 2H, Ar- $H_{3,3'}$ ), 7.67 (m, 2H,  $-H_{2,2'}$ ), 8.54 (d, 1H,  $J = 8.1$  Hz,  $\text{NHCH}$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  21.6 ( $\text{CH}(\text{CH}_3)_2$ ), 23.0 ( $\text{CH}(\text{CH}_3)_2$ ), 24.4 ( $\text{CHCH}_2$ ), 34.5 ( $\text{CH}(\text{CH}_3)_2$ ), 44.6 ( $\text{NHCH}$ ), 128.6 (Ar- $C_{2,2'}$ ), 129.2 (Ar- $C_{3,3'}$ ), 137.3 (Ar- $C_4$ ), 140.3 (Ar- $C_1$ ), 161.4 ( $\text{C}_{\text{thiadiazole}}^2$ ), 169.5 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  359/361  $[\text{M}+\text{H}]^+$ .

### General procedure for the synthesis of *N*-(1-(5-(*N*-arylsulfonyl)amino-1,3,4-thiadiazol-2-yl)alkyl)-4-arylsulfonamides 4a–4w and 5

To a stirred solution of *N*-(1-(5-amino-1,3,4-thiadiazol-2-yl)alkyl)-4-arylsulfonamide (1.0 mmol) in pyridine (15 mL), arylsulfonyl chloride (1.40 mmol) was added under argon at 0 °C in four equal portions. The reaction mixture was stirred at 0 °C for 30 min and then at ambient temperature for 36–48 h. After the completion of reaction (tlc), water was added and the product was extracted with ethyl acetate ( $2 \times 50$  mL). The organic extracts were washed with 2 N HCl, followed by brine and dried over anhyd.  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the residue was recrystallized from EtOH to give the desired product.

### 4-Methyl-*N*-(1-(5-(4-methylphenylsulfonamido)-1,3,4-thiadiazol-2-yl)ethyl)benzenesulfonamide (4a)

From **3a** (298 mg). Yield: 372 mg (82%) as colorless crystals; m.p.: 228–230 °C;  $R_f$ : 0.44; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3262 (NH, sec.), 1592 (C=C), 1321, 1167 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.44 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}_3\text{CH}$ ), 2.38 (s, 3H, Ar- $\text{CH}_3$ ), 2.42 (s, 3H, Ar- $\text{CH}_3$ ), 4.67 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.35 (s, 1H,  $\text{NHCH}$ ), 7.40–7.37 (m, 2H, Ar-H), 7.75–7.71 (m, 4H, Ar-H), 12.60 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.6 ( $\text{CH}_3\text{CH}$ ), 20.5, 20.6 ( $2 \times \text{Ar-CH}_3$ ), 49.9 ( $\text{CH}_3\text{CH}$ ), 126.1, 127.1, 129.4, 129.68, 138.0, 139.8, 143.0, 143.7 ( $8 \times \text{C}_{\text{arom.}}$ ), 161.1 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.6 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  453  $[\text{M}+\text{H}]^+$ .

### 4-Chloro-*N*-(5-(1-(4-methylphenylsulfonamido)ethyl)-1,3,4-thiadiazol-2-yl)benzenesulfonamide (4b)

From **3a** (298 mg). Yield: 378 mg (80%) as colorless crystals; m.p.: 199–201 °C;  $R_f$ : 0.42; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3270 (NH, sec.), 1578 (C=C), 1311, 1152 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.43 (d, 3H,  $J = 7.8$  Hz,  $\text{CH}_3\text{CH}$ ), 2.39 (s, 3H, Ar- $\text{CH}_3$ ), 4.69 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.36 (bs, 1H,  $\text{NHCH}$ ), 7.40 (m, 2H, Ar-H), 7.64 (m, 2H, Ar-H), 7.75 (d, 2H,  $J = 8.3$  Hz, Ar-H), 7.86 (m, 2H, Ar-H), 12.73 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.6 ( $\text{CH}_3\text{CH}$ ), 20.6 (Ar- $\text{CH}_3$ ), 49.9 ( $\text{CH}_3\text{CH}$ ), 127.1, 127.9, 129.1, 129.7, 137.8, 137.9, 141.4, 143.7 ( $8 \times \text{C}_{\text{arom.}}$ ), 161.7 ( $\text{C}_{\text{thiadiazole}}^2$ ), 168.1 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  472/474  $[\text{M}+\text{H}]^+$ .

### 4-Bromo-*N*-(5-(1-(4-methylphenylsulfonamido)ethyl)-1,3,4-thiadiazol-2-yl)benzenesulfonamide (4c)

From **3a** (298 mg). Yield: 372 mg (72%) as colorless crystals; m.p.: 202–204 °C;  $R_f$ : 0.42; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3280 (NH, sec.), 1586 (C=C), 1328, 1160 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.44 (d, 3H,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}$ ), 2.40 (s, 3H, Ar- $\text{CH}_3$ ), 4.68 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.40 (s, 1H,  $\text{NHCH}$ ), 7.79–7.74 (m, 4H, Ar-H), 7.39–7.36 (m, 4H, Ar-H), 12.73 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.6 ( $\text{CH}_3\text{CH}$ ), 20.6 (Ar- $\text{CH}_3$ ), 49.8 ( $\text{CH}_3\text{CH}$ ), 126.3, 127.1, 128.1, 129.7, 132.1, 138.0, 141.9, 143.7 ( $8 \times \text{Ar-C}_{\text{arom.}}$ ), 161.6 ( $\text{C}_{\text{thiadiazole}}^2$ ), 168.1 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  516/518  $[\text{M}+\text{H}]^+$ .

### 4-Methoxy-*N*-(5-(1-(4-methylphenylsulfonamido)ethyl)-1,3,4-thiadiazol-2-yl)benzenesulfonamide (4d)

From **3a** (298 mg). Yield: 328 mg (70%) as white powder; m.p.: 229–231 °C;  $R_f$ : 0.44; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3287 (NH, sec.), 1576 (C=C), 1348, 1151 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.43 (d, 3H,  $J = 7.2$  Hz,  $\text{CH}_3\text{CH}$ ), 2.39 (s, 3H, Ar- $\text{CH}_3$ ), 3.89 (s, 3H,  $\text{OCH}_3$ ), 4.67 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.11–7.01 (m, 2H, Ar-H), 7.31 (bs, 1H,  $\text{NHCH}$ ), 7.37 (m, 2H,

Ar–H), 7.81–7.68 (m, 2H, Ar–H), 12.56 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.5 ( $\text{CH}_3\text{CH}$ ), 20.6 (Ar- $\text{CH}_3$ ), 49.8 ( $\text{CH}_3\text{CH}$ ), 55.2 ( $\text{OCH}_3$ ), 114.0, 127.1, 128.2, 128.5, 129.7, 134.5, 143.7 ( $7 \times \text{C}_{\text{arom.}}$ ), 160.9 ( $\text{C}_{\text{thiadiazole}}^2$ ), 162.8 ( $\text{C}_{\text{arom.}-\text{OMe}}$ ), 167.3 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  469  $[\text{M} + \text{H}]^+$ .

#### 4-Chloro-*N*-(1-(5-(4-methylphenylsulfonamido)-1,3,4-thiadiazol-2-yl)ethyl)benzenesulfonamide (4e)

From **3b** (319 mg). Yield: 326 mg (69%) as colorless crystals; m.p.: 212–213 °C;  $R_f$ : 0.42; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3269 (NH, sec.), 1585 (C=C), 1321, 1142 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.47 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}_3\text{CH}$ ), 2.42 (s, 3H, Ar- $\text{CH}_3$ ), 4.74 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.38 (d, 2H,  $J = 8.1$  Hz, Ar–H), 7.55 (bs, 1H,  $\text{NHCH}$ ), 7.61–7.57 (m, 2H, Ar–H), 7.75–7.72 (m, 2H, Ar–H), 7.38 (d, 2H,  $J = 8.1$  Hz, Ar–H), 12.62 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.7 ( $\text{CH}_3\text{CH}$ ), 20.5 (Ar- $\text{CH}_3$ ), 49.9 ( $\text{CH}_3\text{CH}$ ), 126.1, 128.8, 129.2, 129.4, 138.5, 139.7, 139.7, 143.0 ( $8 \times \text{C}_{\text{arom.}}$ ), 160.8 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.5 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  472/474  $[\text{M} + \text{H}]^+$ .

#### 4-Chloro-*N*-(1-(5-(4-chlorophenylsulfonamido)-1,3,4-thiadiazol-2-yl)ethyl)benzenesulfonamide (4f)

From **3b** (319 mg). Yield: 350 mg (71%) as colorless crystals %; m.p.: 221–223 °C;  $R_f$ : 0.42; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3275 (NH, sec.), 1567 (C=C), 1329, 1146 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.47 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}_3\text{CH}$ ), 4.76 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.64 (bs, 1H,  $\text{NHCH}$ ), 7.91–7.84 (m, 4H, Ar–H), 7.63–7.59 (m, 4H, Ar–H), 12.69 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.7 ( $\text{CH}_3\text{CH}$ ), 49.9 ( $\text{CH}_3\text{CH}$ ), 127.9, 128.9, 129.1, 129.4, 137.9, 138.6, 139.7, 141.3 ( $8 \times \text{C}_{\text{arom.}}$ ), 161.2 ( $\text{C}_{\text{thiadiazole}}^2$ ), 168.0 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  492/494  $[\text{M} + \text{H}]^+$ .

#### 4-Bromo-*N*-(5-(1-(4-chlorophenylsulfonamido)ethyl)-1,3,4-thiadiazol-2-yl)benzenesulfonamide (4g)

From **3b** (319 mg). Yield: 364 mg (68%) as colorless crystals; m.p.: 233–235 °C;  $R_f$ : 0.43; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3278 (NH, sec.), 1580 (C=C), 1320, 1145 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.44 (d, 3H,  $J = 7.8$  Hz,  $\text{CH}_3\text{CH}$ ), 4.64 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.21 (bs, 1H,  $\text{NHCH}$ ), 7.35 (m 2H, Ar–H), 7.38 (n, 2H, Ar–H), 7.77–7.73 (m, 4H, m, Ar–H), 12.05 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.6 ( $\text{CH}_3\text{CH}$ ), 49.9 ( $\text{CH}_3\text{CH}$ ), 126.4, 128.0, 128.9, 129.4, 132.2, 138.5, 139.7, 141.8 ( $8 \times \text{C}_{\text{arom.}}$ ), 161.2 ( $\text{C}_{\text{thiadiazole}}^2$ ), 168.0 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  536/538  $[\text{M} + \text{H}]^+$ .

#### 4-Chloro-*N*-(1-(5-(4-methoxyphenylsulfonamido)-1,3,4-thiadiazol-2-yl)ethyl)benzenesulfonamide (4h)

From **3b** (319 mg). Yield: 365 mg (75%) as white powder; m.p.: 222–224 °C;  $R_f$ : 0.45; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3259 (NH, sec.), 1578 (C=C), 1326, 1126 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.47 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}_3\text{CH}$ ), 3.83 (s, 3H,  $\text{OCH}_3$ ), 4.56 (m, 1H,  $\text{CH}_3\text{CH}$ ), 7.12–7.08 (m, 2H, Ar–H), 7.64–7.60 (m, 2H, Ar–H), 7.71–7.67 (m, 4H, Ar–H), 8.78 (d, 1H,  $J = 8.1$  Hz,  $\text{NHCH}$ ), 13.96 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  20.2 ( $\text{CH}_3\text{CH}$ ), 49.6 ( $\text{CH}_3\text{CH}$ ), 56.1 ( $\text{OCH}_3$ ), 114.8, 128.3, 129.0, 129.8, 134.0, 138.2, 139.9 ( $7 \times \text{C}_{\text{arom.}}$ ), 161.1 ( $\text{C}_{\text{thiadiazole}}^2$ ), 162.7 ( $\text{C}_{\text{arom.}-\text{OMe}}$ ), 167.5 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  488/490  $[\text{M} + \text{H}]^+$ .

#### 4-Methyl-*N*-(5-(2-methyl-1-(4-methylphenylsulfonamido)propyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4i)

From **3c** (326 mg). Yield: 331 mg (69%) as colorless crystals; m.p.: 220–221 °C;  $R_f$ : 0.49; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3286 (NH, sec.), 1586 (C=C), 1323, 1160 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.04 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.12 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.24 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.38 (s, 3H, Ar- $\text{CH}_3$ ), 2.41 (s, 3H, Ar- $\text{CH}_3$ ), 4.67 (m, 1H,  $\text{NHCH}$ ), 7.35 (s, 1H,  $\text{NHCH}$ ), 7.64–7.59 (m, 4H, Ar–H), 7.86–7.74 (m, 4H, Ar–H), 12.48 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  21.0 ( $\text{CH}(\text{CH}_3)_2$ ), 24.1, 24.3 ( $2 \times \text{Ar-CH}_3$ ), 39.4 ( $\text{CH}(\text{CH}_3)_2$ ), 52.2 ( $\text{NHCH}$ ), 126.4, 128.8, 129.4, 130.0, 136.4, 137.3, 143.0, 144.0 ( $8 \times \text{C}_{\text{arom.}}$ ), 159.5 ( $\text{C}_{\text{thiadiazole}}^2$ ), 165.2 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  481  $[\text{M} + \text{H}]^+$ .

#### 4-Chloro-*N*-(5-(2-methyl-1-(4-methylphenylsulfonamido)propyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4j)

From **3c** (326 mg). Yield: 336 mg (67%) as light pink powder; m.p.: 212–214 °C;  $R_f$ : 0.47; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3276 (NH, sec.), 1575 (C=C), 1322, 1148 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.92 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.04 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.28 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.38 (s, 3H, Ar- $\text{CH}_3$ ), 4.27 (m, 1H,  $\text{NHCH}$ ), 7.23 (s, 2H,  $J = 8.1$  Hz, Ar–H), 7.35 (br, 1H,  $\text{NHCH}$ ), 7.66–7.62 (m, 2H, Ar–H), 7.86–7.82 (m, 4H, Ar–H) 12.60 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  20.0 ( $\text{CH}(\text{CH}_3)_2$ ), 20.5 (Ar- $\text{CH}_3$ ), 43.4 ( $\text{CH}(\text{CH}_3)_2$ ), 59.8 ( $\text{NHCH}$ ), 127.1, 128.0, 129.3, 132.1, 138.0, 138.0, 142.1, 143.3 ( $8 \times \text{C}_{\text{arom.}}$ ), 161.2 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.7 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI–MS:  $m/z$  500/502  $[\text{M} + \text{H}]^+$ .

#### 4-Bromo-*N*-(5-(2-methyl-1-(4-methylphenylsulfonamido)propyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4k)

From **3c** (326 mg). Yield: 365 mg (67%) as colorless crystals; m.p.: 209–211 °C;  $R_f$ : 0.49; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3274 (NH, sec.), 1586 (C=C), 1325, 1150 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR



(acetone- $d_6$ ):  $\delta$  0.88 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.03 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.22 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.29 (s, 3H, Ar- $\text{CH}_3$ ), 4.32 (m, 1H,  $\text{NHCH}$ ), 7.21 (d, 2H,  $J = 8.1$  Hz, Ar-H), 7.25 (s, 1H,  $\text{NHCH}$ ), 7.65 (d, 2H,  $J = 8.2$  Hz, Ar-H), 7.82–7.75 (m, 4H, Ar-H), 12.88 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  18.4 ( $\text{CH}(\text{CH}_3)_2$ ), 20.5 (Ar- $\text{CH}_3$ ), 42.7 ( $\text{CH}(\text{CH}_3)_2$ ), 59.8 ( $\text{NHCH}$ ), 126.2, 127.1, 128.0, 129.3, 132.1, 138.0, 142.1, 143.3 ( $8 \times \text{C}_{\text{arom.}}$ ), 160.1 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.7 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  544/546 [ $\text{M} + \text{H}$ ] $^+$ .

#### 4-Methoxy-*N*-(5-(2-methyl-1-(4-methylphenylsulfonamido)propyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4l)

From **3c** (326 mg). Yield: 342 mg (69%) as colorless crystals; m.p.: 230–231 °C;  $R_f$ : 0.48; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3255 (NH, sec.), 1575 (C=C), 1328, 1158 ( $2 \times \text{O} = \text{S} = \text{O}$ ).  $^1\text{H}$ -NMR (acetone- $d_6$ ):  $\delta$  0.88 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.03 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.15 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.38 (s, 3H, Ar- $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 4.25 (m, 1H,  $\text{NHCH}$ ), 7.31 (bs, 1H,  $\text{NHCH}$ ), 7.13–7.09 (m, 2H, Ar-H), 7.20 (d, 2H,  $J = 7.8$  Hz, Ar-H), 7.79–7.76 (m, 4H, Ar-H), 12.60 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$ -NMR (acetone- $d_6$ ):  $\delta$  21.8 ( $\text{CH}(\text{CH}_3)_2$ ), 21.9 (Ar- $\text{CH}_3$ ), 48.9 ( $\text{CH}(\text{CH}_3)_2$ ), 52.5 ( $\text{NHCH}$ ), 55.5 ( $\text{OCH}_3$ ), 113.2, 128.0, 128.9, 129.4, 139.2, 139.8, 141.2 ( $7 \times \text{C}_{\text{arom.}}$ ), 159.3 ( $\text{C}_{\text{thiadiazole}}^2$ ), 160.3 ( $\text{C}_{\text{arom.}}-\text{OMe}$ ), 167.7 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  497 [ $\text{M} + \text{H}$ ] $^+$ .

#### 4-Chloro-*N*-(2-methyl-1-(5-(4-methylphenylsulfonamido)-1,3,4-thiadiazol-2-yl)propyl)benzene sulfonamide (4m)

From **3d** (347 mg). Yield: 351 mg (70%) as colorless crystals; m.p.: 244–246 °C;  $R_f$ : 0.42; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3258 (NH, sec.), 1578 (C=C), 1320, 1146 ( $2 \times \text{O} = \text{S} = \text{O}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.73 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.89 (d, 3H,  $J = 6.7$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.95 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.38 (s, 3H, Ar- $\text{CH}_3$ ), 4.20 (m, 1H,  $\text{NHCH}$ ), 8.71 (d, 1H,  $J = 8.7$  Hz,  $\text{NHCH}$ ), 7.46–7.39 (m, 4H, Ar-H), 7.69–7.63 (m, 4H, Ar-H), 13.94 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  19.9 ( $\text{CH}(\text{CH}_3)_2$ ), 21.5 (Ar- $\text{CH}_3$ ), 32.6 ( $\text{CH}(\text{CH}_3)_2$ ), 59.7 ( $\text{NHCH}$ ), 126.2, 128.9, 129.9, 130.1, 137.9, 139.8, 139.4, 143.3 ( $8 \times \text{C}_{\text{arom.}}$ ), 159.4 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.4 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  500/502 [ $\text{M} + \text{H}$ ] $^+$ .

#### 4-Chloro-*N*-(1-(5-(4-chlorophenylsulfonamido)-1,3,4-thiadiazol-2-yl)-2-methylpropyl)benzene sulfonamide (4n)

From **3d** (347 mg). Yield: 359 mg (69%) as colorless crystals; m.p.: 229–231 °C;  $R_f$ : 0.43; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3278 (NH, sec.), 1574 (C=C), 1322, 1143 ( $2 \times \text{O} = \text{S} = \text{O}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.75 (d, 3H,  $J = 6.8$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.82 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.95 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 4.10 (m, 1H,  $\text{NHCH}$ ), 7.23 (d, 1H,  $J = 8.8$  Hz,  $\text{NHCH}$ ),

7.44–7.39 (m, 4H, Ar-H), 7.84–7.79 (m, 4H, Ar-H) 12.20 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  21.8 ( $\text{CH}(\text{CH}_3)_2$ ), 34.2 ( $\text{CH}(\text{CH}_3)_2$ ), 52.4 ( $\text{NHCH}$ ), 127.0, 127.3, 128.9, 129.3, 137.9, 138.7, 140.6, 141.4 ( $8 \times \text{C}_{\text{arom.}}$ ), 160.3 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.6 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  520/522 [ $\text{M} + \text{H}$ ] $^+$ .

#### 4-Bromo-*N*-(5-(1-(4-chlorophenylsulfonamido)-2-methylpropyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4o)

From **3d** (347 mg). Yield: 407 mg (72%) as pale yellow powder; m.p.: 221–223 °C;  $R_f$ : 0.43; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3289 (NH, sec.), 1587 (C=C), 1329, 1158 ( $2 \times \text{O} = \text{S} = \text{O}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.65 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.81 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.90 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 4.10 (m, 1H,  $\text{NHCH}$ ), 7.42–7.36 (m, 4H, Ar-H), 7.69 (d, 1H,  $J = 9.0$  Hz,  $\text{NHCH}$ ), 7.80–7.75 (m, 4H, Ar-H) 12.27 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  20.5 ( $\text{CH}(\text{CH}_3)_2$ ), 32.5 ( $\text{CH}(\text{CH}_3)_2$ ), 55.0 ( $\text{NHCH}$ ), 126.4, 127.3, 128.3, 129.2, 132.2, 138.4, 140.7, 141.8 ( $8 \times \text{C}_{\text{arom.}}$ ), 160.5 ( $\text{C}_{\text{thiadiazole}}^2$ ), 167.6 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  564/566 [ $\text{M} + \text{H}$ ] $^+$ .

#### 4-Chloro-*N*-(1-(5-(4-methoxyphenylsulfonamido)-1,3,4-thiadiazol-2-yl)-2-methylpropyl)benzene sulfonamide (4p)

From **3d** (347 mg). Yield: 362 mg (70%) as white powder; m.p.: 211–213 °C;  $R_f$ : 0.42; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3268 (NH, sec.), 1582 (C=C), 1326, 1160 ( $2 \times \text{O} = \text{S} = \text{O}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.91 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.03 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 3.50 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 4.36 (m, 1H,  $\text{NHCH}$ ), 7.10 (m, 2H, Ar-H), 7.43 (bs, 1H,  $\text{NHCH}$ ), 7.45 (m, 2H, Ar-H), 7.80–7.75 (m, 4H, Ar-H), 12.48 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  18.5 ( $\text{CH}(\text{CH}_3)_2$ ), 32.7 ( $\text{CH}(\text{CH}_3)_2$ ), 55.2 ( $\text{NHCH}$ ), 59.9 ( $\text{OCH}_3$ ), 114.0, 128.2, 128.7, 128.8, 134.4, 138.3, 139.8 ( $7 \times \text{C}_{\text{arom.}}$ ), 158.8 ( $\text{C}_{\text{arom.}}-\text{OMe}$ ), 162.8 ( $\text{C}_{\text{thiadiazole}}^2$ ), 166.8 ( $\text{C}_{\text{thiadiazole}}^5$ ). ESI-MS:  $m/z$  516/518 [ $\text{M} + \text{H}$ ] $^+$ .

#### 4-Methyl-*N*-(5-(3-methyl-1-(4-methylphenylsulfonamido)butyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4q)

From **3e** (340 mg). Yield: 371 mg (75%) as colorless crystals; m.p.: 234–236 °C;  $R_f$ : 0.52; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3287 (NH, sec.), 1587 (C=C), 1328, 1164 ( $2 \times \text{O} = \text{S} = \text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.88 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.90 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.77–1.69 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.48 (s, 3H, Ar- $\text{CH}_3$ ), 4.53 (m, 1H,  $\text{NHCH}$ ), 7.33 (d, 1H,  $J = 8.4$  Hz,  $\text{NHCH}$ ), 7.42–7.37 (m, 4H, Ar-H), 7.74–7.63 (m, 4H, Ar-H) 12.09 (s, 1H,  $\text{NHSO}_2$ ).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  20.6 ( $\text{CH}(\text{CH}_3)_2$ ), 21.7 ( $\text{CH}(\text{CH}_3)_2$ ), 24.1 (Ar- $\text{CH}_3$ ), 41.7 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 49.9 ( $\text{NHCH}$ ), 126.1, 127.2, 129.4, 1297 137.9, 139.8, 143.0, 143.7 ( $8 \times \text{C}_{\text{arom.}}$ ),



161.2 ( $C^2_{\text{thiadiazole}}$ ), 167.6 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  495 [M+H]<sup>+</sup>.

**4-Bromo-*N*-(5-(3-methyl-1-(4-methylphenylsulfonamido)butyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4r)**

From **3e** (340 mg). Yield: 436 mg (78%) as white powder; m.p.: 254–256 °C;  $R_f$ : 0.53; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3269 (NH, sec.), 1572 (C=C), 1320, 1166 ( $2 \times \text{O}=\text{S}=\text{O}$ ). <sup>1</sup>H NMR (acetone- $d_6$ ):  $\delta$  0.81 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.86 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.79–1.64 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.48 (s, 3H, Ar- $\text{CH}_3$ ), 4.60 (m, 1H, NHCH), 7.27 (d, 2H,  $J = 8.1$  Hz, Ar-H), 7.33 (d, 1H,  $J = 8.4$  Hz, NHCH), 7.68 (d, 2H,  $J = 8.4$  Hz, Ar-H), 7.82–7.75 (m, 4H, Ar-H), 12.09 (s, 1H,  $\text{NH}\text{SO}_2$ ). <sup>13</sup>C NMR (acetone- $d_6$ ):  $\delta$  20.9 ( $\text{CH}(\text{CH}_3)_2$ ), 21.8 ( $\text{CH}(\text{CH}_3)_2$ ), 24.1 (Ar- $\text{CH}_3$ ), 43.5 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 52.5 (NHCH), 126.3, 127.5, 128.0, 129.5, 132.2, 137.9, 141.9, 143.6 ( $8 \times C_{\text{arom.}}$ ), 160.9 ( $C^2_{\text{thiadiazole}}$ ), 167.7 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  560/558 [M+H]<sup>+</sup>.

**4-Methoxy-*N*-(5-(3-methyl-1-(4-methylphenylsulfonamido)butyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4s)**

From **3e** (340 mg). Yield: 367 mg (72%) as colorless crystals; m.p.: 233–234 °C;  $R_f$ : 0.54; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3281 (NH, sec.), 1587 (C=C), 1328, 1150 ( $2 \times \text{O}=\text{S}=\text{O}$ ). <sup>1</sup>H NMR (acetone- $d_6$ ):  $\delta$  0.91 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.03 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.80–1.69 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.36 (s, 3H, Ar- $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 4.52 (m, 1H, NHCH), 7.35 (m, 1H, NHCH), 7.18 (m, 2H, Ar-H), 7.49 (m, 2H, Ar-H), 7.79–7.67 (m, 4H, Ar-H), 12.05 (s, 1H,  $\text{NH}\text{SO}_2$ ). <sup>13</sup>C NMR (acetone- $d_6$ ):  $\delta$  20.1 ( $\text{CH}(\text{CH}_3)_2$ ), 22.1 ( $\text{CH}(\text{CH}_3)_2$ ), 24.2 (Ar- $\text{CH}_3$ ), 41.2 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 53.1 (NHCH), 54.2 ( $\text{OCH}_3$ ), 116.1, 126.5, 128.2, 129.6, 133.2, 138.4, 139.7 ( $7 \times C_{\text{arom.}}$ ), 159.3 ( $C^2_{\text{thiadiazole}}$ ), 160.1 ( $C_{\text{arom.}}-\text{OMe}$ ), 169.2 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  511 [M+H]<sup>+</sup>.

**4-Chloro-*N*-(3-methyl-1-(5-(4-methylphenylsulfonamido)-1,3,4-thiadiazol-2-yl)butyl)benzene sulfonamide (4t)**

From **3e** (340 mg). Yield: 386 mg (75%) as colorless crystals; m.p.: 215–217 °C;  $R_f$ : 0.55; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3276 (NH, sec.), 1583 (C=C), 1329, 1153 ( $2 \times \text{O}=\text{S}=\text{O}$ ). <sup>1</sup>H NMR (acetone- $d_6$ ):  $\delta$  0.85 (d, 3H,  $J = 6.2$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.89 (d, 3H,  $J = 6.2$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.78–1.69 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.48 (s, 3H, Ar- $\text{CH}_3$ ), 4.66 (m, 1H, NHCH), 7.47–7.44 (m, 2H, Ar-H), 7.60 (s, 1H, NHCH), 7.63–7.53 (m, 2H, Ar-H), 7.87–7.71 (m, 4H, Ar-H), 12.62 (s, 1H,  $\text{NH}\text{SO}_2$ ). <sup>13</sup>C NMR (acetone- $d_6$ ):  $\delta$  20.9 ( $\text{CH}(\text{CH}_3)_2$ ), 21.9 ( $\text{CH}(\text{CH}_3)_2$ ), 24.2 (Ar- $\text{CH}_3$ ), 43.5 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 52.7 (NHCH), 126.4, 128.8, 129.4, 130.0,

132.4, 138.4, 139.7, 144.0 ( $8 \times C_{\text{arom.}}$ ), 160.1 ( $C^2_{\text{thiadiazole}}$ ), 167.1 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  514/516 [M+H]<sup>+</sup>.

**4-Chloro-*N*-(1-(5-(4-chlorophenylsulfonamido)-1,3,4-thiadiazol-2-yl)-3-methylbutyl)benzene sulfonamide (4u)**

From **3f** (361 mg). Yield: 417 mg (78%) as colorless crystals; m.p.: 218–221 °C;  $R_f$ : 0.54; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3279 (NH, sec.), 1574 (C=C), 1328, 1154 ( $2 \times \text{O}=\text{S}=\text{O}$ ). <sup>1</sup>H NMR (acetone- $d_6$ ):  $\delta$  0.83 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.89 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.80–1.66 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 4.66 (m, 1H, NHCH), 7.58 (s, 1H, NHCH), 7.66–7.51 (m, 4H, Ar-H), 7.86–7.80 (m, 4H, Ar-H), 12.71 (s, 1H,  $\text{NH}\text{SO}_2$ ). <sup>13</sup>C NMR (acetone- $d_6$ ):  $\delta$  20.8 ( $\text{CH}(\text{CH}_3)_2$ ), 24.1 ( $\text{CH}(\text{CH}_3)_2$ ), 43.4 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 52.4 (NHCH), 127.0, 127.9, 128.9, 129.2, 137.9, 138.4, 139.7, 141.4 ( $8 \times C_{\text{arom.}}$ ), 160.5 ( $C^2_{\text{thiadiazole}}$ ), 167.5 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  534/536 [M+H]<sup>+</sup>.

**4-Bromo-*N*-(5-(1-(4-chlorophenylsulfonamido)-3-methylbutyl)-1,3,4-thiadiazol-2-yl)benzene sulfonamide (4v)**

From **3f** (361 mg). Yield: 416 mg (72%) as white powder; m.p.: 218–220 °C;  $R_f$ : 0.54; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3276 (NH, sec.), 1569 (C=C), 1326, 1159 ( $2 \times \text{O}=\text{S}=\text{O}$ ). <sup>1</sup>H NMR (acetone- $d_6$ ):  $\delta$  0.82 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.89 (d, 3H,  $J = 6.2$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.80–1.69 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 4.65 (m, 1H, NHCH), 7.54–7.51 (4H, m, Ar-H), 7.57 (s, 1H, NHCH), 7.84–7.75 (m, 4H, Ar-H), 12.00 (1H, s,  $\text{NH}\text{SO}_2$ ). <sup>13</sup>C NMR (acetone- $d_6$ ):  $\delta$  21.8 ( $\text{CH}(\text{CH}_3)_2$ ), 24.1 ( $\text{CH}(\text{CH}_3)_2$ ), 43.5 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 52.5 (NHCH), 126.4, 128.0, 128.9, 129.8, 132.2, 138.4, 139.7, 141.8 ( $8 \times C_{\text{arom.}}$ ), 160.5 ( $C^2_{\text{thiadiazole}}$ ), 167.6 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  579/581 [M+H]<sup>+</sup>.

**4-Chloro-*N*-(1-(5-(4-methoxyphenylsulfonamido)-1,3,4-thiadiazol-2-yl)-3-methylbutyl)benzene sulfonamide (4w)**

From **3f** (361 mg). Yield: 370 mg (70%) as colorless crystals; m.p.: 231–233 °C;  $R_f$ : 0.53; IR ( $\nu_{\text{max}}$ , neat,  $\text{cm}^{-1}$ ): 3259 (NH, sec.), 1566 (C=C), 1320, 1164 ( $2 \times \text{O}=\text{S}=\text{O}$ ). <sup>1</sup>H NMR (acetone- $d_6$ ):  $\delta$  0.85 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.89 (d, 3H,  $J = 6.0$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.78–1.64 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 4.64 (m, 1H, NHCH), 7.12–7.07 (m, 2H, Ar-H), 7.52–7.48 (m, 2H, Ar-H), 7.55 (bs, 1H, NHCH), 7.84–7.75 (m, 4H, Ar-H), 12.50 (s, 1H,  $\text{NH}\text{SO}_2$ ); <sup>13</sup>C NMR (acetone- $d_6$ ):  $\delta$  21.8 ( $\text{CH}(\text{CH}_3)_2$ ), 24.2 ( $\text{CH}(\text{CH}_3)_2$ ), 48.9 ( $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 52.5 (NHCH), 55.2 ( $\text{OCH}_3$ ), 114.0, 128.2, 128.9, 129.2, 134.3, 138.4, 139.7 ( $7 \times C_{\text{arom.}}$ ), 159.9 ( $C^2_{\text{thiadiazole}}$ ), 162.8 ( $C_{\text{arom.}}-\text{OMe}$ ), 166.8 ( $C^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  530/532 [M+H]<sup>+</sup>.

***N*-(1-(5-(*N,N*-dichlorobenzenesulfonyl)amino-1,3,4-thiadiazol-2-yl)-3-methylbutyl)-4-methylbenzenesulfonamide (5)**

From **3f** (361 mg). Yield: 345 mg (50%) as colorless crystals; m.p.: 223–224 °C;  $R_f$ : 0.53; IR ( $\nu_{\max}$ , neat,  $\text{cm}^{-1}$ ): 3283 (NH, sec.), 1715 (C=O), 1520 (C=C), 1328, 1165 ( $2 \times \text{O}=\text{S}=\text{O}$ ).  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.88 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.90 (d, 3H,  $J = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 2.05 (m, 3H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.32 (s, 3H, Ar- $\text{CH}_3$ ), 4.64 (m, 1H, NHCH), 7.43 (s, 1H, NHCH), 8.01–7.27 (m, 12H, Ar-H).  $^{13}\text{C}$  NMR (acetone- $d_6$ ):  $\delta$  20.5 (Ar- $\text{CH}_3$ ), 21.4 ( $\text{CH}(\text{CH}_3)_2$ ), 25.2 ( $\text{CH}(\text{CH}_3)_2$ ), 43.0 (NHCH+ $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 127.2, 128.1, 129.1, 129.4, 129.7, 131.2, 134.0, 137.6, 139.0, 139.6, 141.9, 143.9 ( $12 \times \text{C}_{\text{arom.}}$ ), 160.3 ( $\text{C}^2_{\text{thiadiazole}}$ ), 168.2 ( $\text{C}^5_{\text{thiadiazole}}$ ). ESI-MS:  $m/z$  689/691 [M+H] $^+$ .

### Biological activity assays

#### In vitro anti-HIV assay

Evaluation of the antiviral activity of **3a–3f**, **4a–4w** and **5** against the HIV-1 strain (III<sub>B</sub>) and the HIV-2 strain (ROD) in MT-4 cells was performed using an MTT assay as described previously [38]. In brief, stock solutions (10-times final concentration) of test compounds were added in 25- $\mu\text{L}$  volumes to two series of triplicate wells to allow simultaneous evaluation of their effects on mock and HIV-infected cells at the beginning of each experiment. Serial fivefold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Beckman instruments). Untreated control, HIV- and mock-infected cell samples were included for each sample. HIV-1 (III<sub>B</sub>) [42] or HIV-2 (ROD) [43] stock (50  $\mu\text{L}$ ) at 100–300 CCID<sub>50</sub> (50% cell culture infectious dose) or culture medium was added to either of the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compounds. Exponentially growing MT-4 cells [44] were centrifuged for 5 min at 1000 rpm (Minifuge T, rotor 2250; Heraeus, Germany), and the supernatant was discarded. The MT-4 cells were resuspended at  $6 \times 10^5$  cells per mL, and volumes of 50  $\mu\text{L}$  were transferred to the microtiter tray wells. Five days after infection, the viability of the mock- and HIV-infected cells was examined spectrophotometrically.

**Acknowledgements** We thank Prof. C. Pannecoque of Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium, for the anti-HIV screening.

### References

- Li Y, Geng J, Liu Y, Yu S, Zhao G (2013) Thiadiazole a promising structure in medicinal chemistry. *ChemMedChem* 8:27–41. <https://doi.org/10.1002/cmdc.201200355>
- Hu Y, Li C-Y, Wang X-M, Yang Y-H, Zhu H-L (2014) 1,3,4-Thiadiazole: synthesis, reactions, and applications in medicinal, agricultural, and materials chemistry. *Chem Rev* 114:5572–5610. <https://doi.org/10.1021/cr400131u>
- Jain AK, Sharma S, Vaidya A, Ravichandran V, Agrawal RK (2013) 1,3,4-Thiadiazole and its derivatives: a review on recent progress in biological activities. *Chem Biol Drug Des* 81:557–576. <https://doi.org/10.1111/cbdd.12125>
- Ezabadi IR, Camoutsis C, Zoumpoulakis P, Geronikaki A, Soković M, Glamocilija 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. <https://doi.org/10.1016/j.bmc.2007.10.082>
- Kumura K, Wakiyama Y, Ueda K, Umemura E, Watanabe Yamamoto M, Yoshida T, Ajito K (2018) Synthesis and antibacterial activity of novel lincomycin derivatives. III. Optimization of a phenyl thiadiazole moiety. *J Antibiot* 71:104–112. <https://doi.org/10.1038/ja.2017.59>
- Chen C, Song B, Yang S, Xu G, Bhadury PS, Jin L, Hu D, Li Q, Liu F, Xue W, Lu P, Chen Z (2007) Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. *Bioorg Med Chem* 15:3981–3989. <https://doi.org/10.1016/j.bmc.2007.04.014>
- Liu X-H, Shi Y-X, Ma Y, Zhang C-Y, Dong W-L, Pan L, Wang B-L, Li B-J, Li Z-M (2009) Synthesis, antifungal activities and 3D-QSAR study of *N*-(5-substituted-1,3,4-thiadiazol-2-yl)cyclopropanecarboxamides. *Eur J Med Chem* 44:2782–2786. <https://doi.org/10.1016/j.ejmech.2009.01.012>
- Klip NT, Capan G, Gursoy A, Uzun M, Satana D (2010) Synthesis, structure, and antifungal evaluation of some novel 1,2,4-triazolylmercaptoacetylthiosemicarbazide and 1,2,4-triazolylmercaptomethyl-1,3,4-thiadiazole analogs. *J Enz Inhib Med Chem* 25:126–131. <https://doi.org/10.3109/14756360903040439>
- Kadi AA, Al-Abdullah ES, Shehata IA, Habib EE, Ibrahim TM, El-Emam AA (2010) Synthesis, antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives. *Eur J Med Chem* 45:5006–5011. <https://doi.org/10.1016/j.ejmech.2010.08.007>
- Tozkoparan B, Aytac SP, Gursoy S, Gunal S, Aktay G (2012) Novel 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives as dual analgesic/anti-inflammatory and antimicrobial agents. *Lett Drug Des Discov* 9:204–212. <https://doi.org/10.2174/157018012799079626>
- Bhat AR, Tazeem Azam A, Choi I, Athar F (2011) 3-(1,3,4-Thiadiazole-2-yl)quinoline derivatives: synthesis, characterization and antimicrobial activity. *Eur J Med Chem* 46:3158–3166. <https://doi.org/10.1016/j.ejmech.2011.04.013>
- Bansode S, Kamble R (2011) Synthesis of novel 2-(3'-aryl-sydnnon-4'-ylidene)-5'-substituted-[1,3,4]-thiadiazolylamines and [1,3,4]-thiadiazol-2'-yl-3-oxo-[1,2,4]-triazoles as antimicrobial agents. *Med Chem Res* 21:867–873. <https://doi.org/10.1007/s00044-011-9596-2>
- Onkol T, Doğruer DS, Uzun L, Adak S, Ozkan S, Sahin MF (2008) Synthesis and antimicrobial activity of new 1,2,4-triazole and 1,3,4-thiadiazole derivatives. *J Enzyme Inhib Med Chem* 23:277–284. <https://doi.org/10.1080/14756360701408697>

14. Talath S, Gadad AK (2006) Synthesis, antibacterial and antitubercular activities of some 7-[4-(5-amino-[1,3,4]thiadiazole-2-sulfonyl)-piperazin-1-yl]fluoroquinolonic derivatives. *Eur J Med Chem* 41:918–924. <https://doi.org/10.1016/j.ejmech.2006.03.027>
15. Foroumadi A, Soltani F, Jabini R, Moshafi MH, Rasnani FM (2004) Antituberculosis agents X. Synthesis and evaluation of in vitro antituberculosis activity of 2-(5-nitro-2-furyl)- and 2-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-1,3,4-thiadiazole derivatives. *Arch Pharm Res* 27:502–506. <https://doi.org/10.1007/BF02980122>
16. Chitra S, Paul N, Muthusubramanian S, Manisankar P, Yogeewari P, Sriram D (2011) Synthesis of 3-heteroarylthioquinoline derivatives and their in vitro antituberculosis and cytotoxicity studies. *Eur J Med Chem* 46:4897–4903. <https://doi.org/10.1016/j.ejmech.2011.07.046>
17. Kumar D, Kumar NM, Chang K-H, Shah K (2010) Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles. *Eur J Med Chem* 45:4664–4668. <https://doi.org/10.1016/j.ejmech.2010.07.023>
18. Bhole RP, Bhusari KP (2010) Synthesis and antitumor activity of (4-hydroxyphenyl)[5-substituted alkyl/aryl]-2-thioxo-1,3,4-thiadiazol-3-yl]methanone and [(3,4-disubstituted)-1,3-thiazol-2-ylidene]-4-hydroxybenzohydrazide. *Med Chem Res* 20:695–704. <https://doi.org/10.1007/s00044-010-9371-9>
19. Chou J, Lai S, Pan S, Jow G, Chern J, Guh J (2003) Investigation of anticancer mechanism of thiadiazole-based compound in human non-small cell lung cancer A549 cells. *Biochem Pharmacol* 66:115–124. [https://doi.org/10.1016/S0006-2952\(03\)00254-5](https://doi.org/10.1016/S0006-2952(03)00254-5)
20. Matysiak J, Opolski A (2006) Synthesis and antiproliferative activity of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles. *Bioorg Med Chem* 14:4483–4489. <https://doi.org/10.1016/j.bmc.2006.02.027>
21. Wei M, Feng L, Li X, Zhou X, Shao Z (2009) Synthesis of new chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing  $\gamma$ -butenolide moiety and preliminary evaluation of in vitro anticancer activity. *Eur J Med Chem* 44:3340–3344. <https://doi.org/10.1016/j.ejmech.2009.03.023>
22. Sun S, Yang Y, Li W, Zhang Y, Wang X, Tang J, Zhu H (2011) Synthesis, biological evaluation and molecular docking studies of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan as potential antitumor agents. *Bioorg Med Chem Lett* 21:6116–6121. <https://doi.org/10.1016/j.bmcl.2011.08.039>
23. Moshaf MH, Sorkhi M, Emami S, Nakhjiri M, Yahya-Meymandi A, Negahbani AS, Siavoshi F, Omrani M, Alipour E, Vosooghi M, Shafiee A, Foroumadi A (2011) 5-Nitroimidazole-based 1,3,4-thiadiazoles: heterocyclic analogs of metronidazole as anti-helicobacter pylori agents. *Arch Pharm Chem Life Sci* 344:178–183. <https://doi.org/10.1002/ardp.201000013>
24. Mirzaei J, Siavoshi F, Emami S, Safari F, Khoshayand MR, Shafiee A, Foroumadi A (2008) Synthesis and in vitro anti-helicobacter pylori activity of N-[5-(5-nitro-2-heteroaryl)-1,3,4-thiadiazol-2-yl]thiomorpholines and related compounds. *Eur J Med Chem* 43:1575–1580. <https://doi.org/10.1016/j.ejmech.2007.11.019>
25. Rajak H, Deshmukh R, Aggarwal N, Kashaw S, Kharya MD, Mishra P (2009) Synthesis of novel 2,5-disubstituted 1,3,4-thiadiazoles for their potential anticonvulsant activity: pharmacophoric model studies. *Arch Pharm Chem Life Sci* 342:453–461. <https://doi.org/10.1002/ardp.200800213>
26. Hamad NS, Al-Haidery NH, Al-Masoudi IA, Sabri M, Sabri L, Al-Masoudi NA (2010) Amino acid derivatives, part 4: synthesis and anti-HIV activity of new naphthalene derivatives. *Arch Pharm Chem Life Sci* 343:397–403. <https://doi.org/10.1002/ardp.200900293>
27. Ijichi K, Fujiwara M, Nagano H, Matsumoto Y, Hanasaki Y, Ide T, Katsuura K, Takayama H, Shirakawa S, Aimi N, Shigeta S, Konno K, Matsushima M, Yokota T, Baba M (1996) Anti-HIV-1 activity of thiadiazole derivatives: structure-activity relationship, reverse transcriptase inhibition, and lipophilicity. *Antivir Res* 31:87–94. [https://doi.org/10.1016/0166-3542\(96\)00950-3](https://doi.org/10.1016/0166-3542(96)00950-3)
28. Sneader W (2005) Drug discovery: a history. Wiley, West Sussex. <https://doi.org/10.1002/0470015535>
29. Iyer G, Bellantone R, Taft D (1999) In vitro characterization of the erythrocyte distribution of methazolamide: a model of erythrocyte transport and binding kinetics. *J Pharmacokin Biopharm* 27:45–66. <https://doi.org/10.1023/A:1020630712388>
30. Hall BS, Wilkinson SR (2012) Activation of benzimidazole by trypanosomal type I nitroreductases results in glyoxal formation. *Antimicrob Agents Chemother* 56:115–123. <https://doi.org/10.1128/AAC.05135-11>
31. Messer WS (2002) The utility of muscarinic agonists in the treatment of Alzheimer's disease. *J Mol Neurosci* 19:187–193. <https://doi.org/10.1007/s12031-002-0031-5>
32. Hansch C, Sammes PG, Taylor JB (1990) Comprehensive medicinal chemistry, vol 2. Pergamon Press, Oxford, Chap 7.1
33. Supuran Claudiu T (2017) Special issue: sulfonamides. *Molecules* 22:1642–1646. <https://doi.org/10.3390/molecules22101642>
34. Iqbal Z, Hameed S, Ali S, Tehseen Y, Shahid M, Iqbal J (2015) Synthesis, characterization, hypoglycemic and aldose reductase inhibition activity of arylsulfonylspiro[fluorene-9,5'-imidazolidine]-2',4'-diones. *Eur J Med Chem* 98:127–138. <https://doi.org/10.1016/j.ejmech.2015.05.011>
35. Abbas MA, Hameed S, Farman M, Kressler J, Mahmood N (2015) Conjugates of degraded and oxidized hydroxyethyl starch and sulfonylureas: synthesis, characterization, and in vivo antidiabetic Activity. *Bioconj Chem* 26:120–127. <https://doi.org/10.1021/bc500509a>
36. Khan MH, Hameed S, Farman M, Al-Masoudi NA, Stoeckli-Evans HZ (2015) Synthesis, anti-HIV activity and molecular modeling study of 3-aryl-6-adamantylmethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives. *Z Naturforsch* 70b:609–616. <https://doi.org/10.1515/znb-2015-0032>
37. Willker W, Leibfritz D, Kerssebaum R, Bermel W (1993) Gradient selection in inverse heteronuclear correlation spectroscopy. *Magn Reson Chem* 31:287–292. <https://doi.org/10.1002/mrc.1260310315>
38. Pannecouque C, Daelemans D, De Clercq E (2008) Tetrazolium-based colorimetric assay for the detection of HIV replication inhibitors: revisited, 20 years later. *Nat Protoc* 3:427–434. <https://doi.org/10.1038/nprot.2007.517>
39. Hargrave KD, Proudfoot JR, Grozinger KG, Cullen E, Kapadia SR, Patel UR, Fuchs VU, Mauldin SC et al (1991) *J Med Chem* 34:2231–2241. <https://doi.org/10.1021/jm00111a045>
40. Mitsuya H, Weinhold KJ, Furman PA, St Clair MH, Lehrmann SN, Gallo RC, Bolognesi D, Barry DW, Broder S (1985) 3'-Azido-3'-deoxythymidine (BW A509U), an antiviral agent that inhibits the inefficiency and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. *Proc Natl Acad Sci USA* 82:7096–7100
41. Coates JA, Cammack N, Jenkinson HJ, Jowett AJ, Pearson BA, Penn CR, Rouse PL, Viner KC, Cameron JM (1992) The separated enantiomers of 2'-deoxy-3'-thiacytidine (BCH 189) both inhibit human immunodeficiency virus replication in vitro. *Antimicrob Agents Chemother* 36:733–739. <https://doi.org/10.1128/AAC.36.4.733>
42. Popovic M, Sarngadharan MG, Read E, Gallo RC (1984) Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science* 224:497–500. <https://doi.org/10.1126/science.6200935>

43. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dautet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 220:868–871. <https://doi.org/10.1126/science.6189183>
44. Miyoshi I, Taguchi H, Kobonishi I, Yoshimoto S, Ohtsuki Y, Shiraishi Y, Akagi T (1982) Type C virus-producing cell lines derived from adult T cell leukemia. *Gann Monogr Cancer Res* 28:219–228