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ORIGINAL ARTICLE

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

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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 $IC_{50} = 9.5$ 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-thiadiaziole backbone as potetial 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

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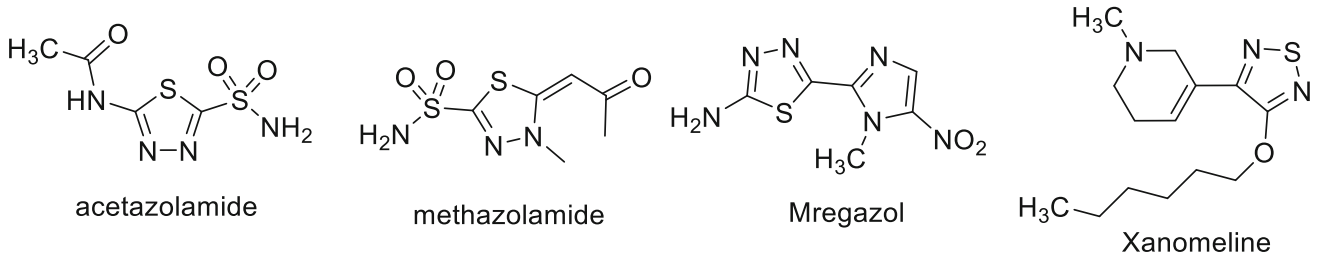
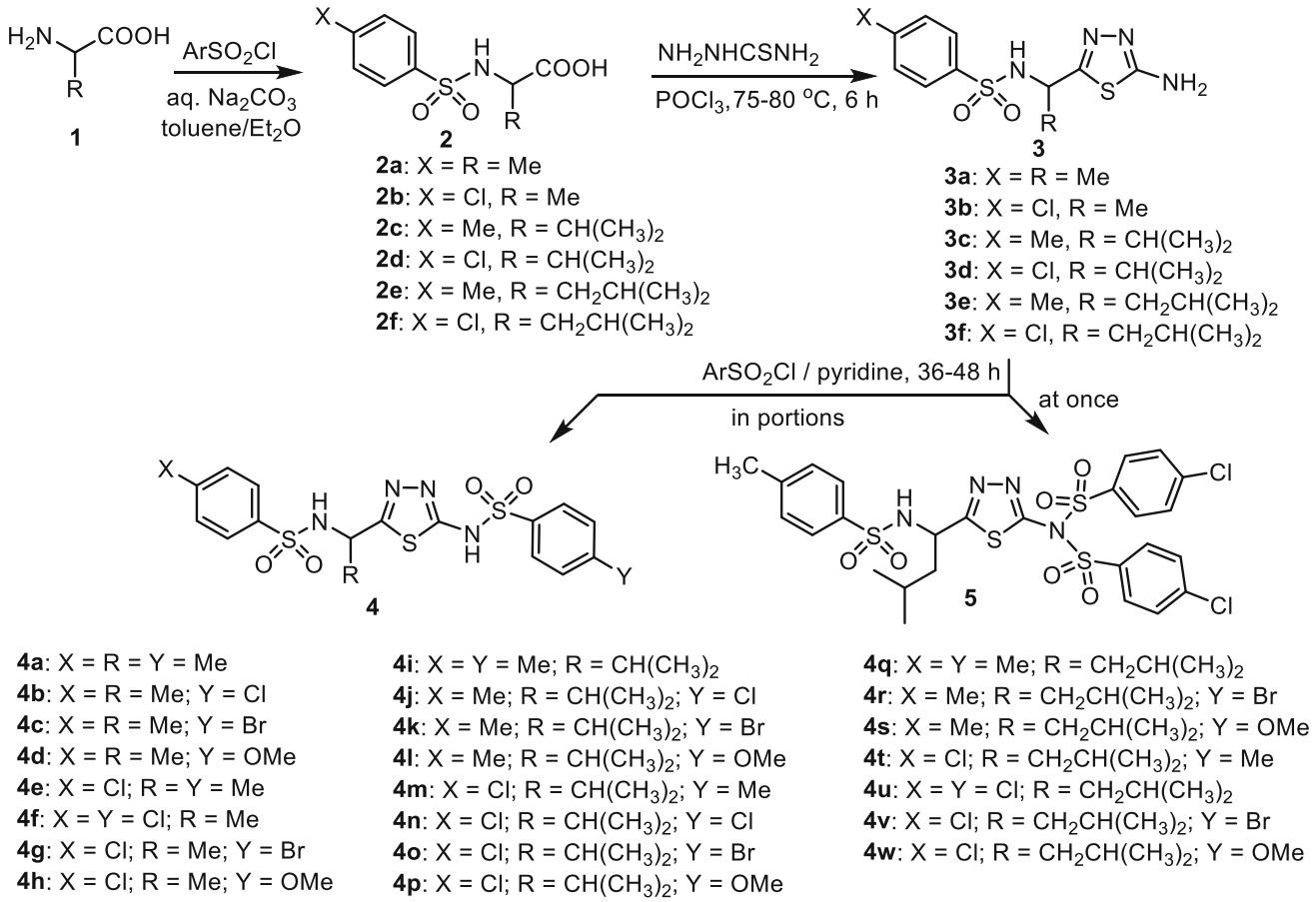


Fig. 1 Commercially available 1,3,4-thiadiazole-based drugs



2a: X = R = Me
2b: X = Cl, R = Me
2c: X = Me, R = $CH(CH_3)_2$
2d: X = Cl, R = $CH(CH_3)_2$
2e: X = Me, R = $CH_2CH(CH_3)_2$
2f: X = Cl, R = $CH_2CH(CH_3)_2$

3a: X = R = Me
3b: X = Cl, R = Me
3c: X = Me, R = $CH(CH_3)_2$
3d: X = Cl, R = $CH(CH_3)_2$
3e: X = Me, R = $CH_2CH(CH_3)_2$
3f: X = Cl, R = $CH_2CH(CH_3)_2$

4a: X = R = Y = Me
4b: X = R = Me; Y = Cl
4c: X = R = Me; Y = Br
4d: X = R = Me; Y = OMe
4e: X = Cl; R = Y = Me
4f: X = Y = Cl; R = Me
4g: X = Cl; R = Me; Y = Br
4h: X = Cl; R = Me; Y = OMe
4i: X = Y = Me; R = $CH(CH_3)_2$
4j: X = Me; R = $CH(CH_3)_2$; Y = Cl
4k: X = Me; R = $CH(CH_3)_2$; Y = Br
4l: X = Me; R = $CH(CH_3)_2$; Y = OMe
4m: X = Cl; R = $CH(CH_3)_2$; Y = Me
4n: X = Cl; R = $CH(CH_3)_2$; Y = Cl
4o: X = Cl; R = $CH(CH_3)_2$; Y = Br
4p: X = Cl; R = $CH(CH_3)_2$; Y = OMe
4q: X = Y = Me; R = $CH_2CH(CH_3)_2$
4r: X = Me; R = $CH_2CH(CH_3)_2$; Y = Br
4s: X = Me; R = $CH_2CH(CH_3)_2$; Y = OMe
4t: X = Cl; R = $CH_2CH(CH_3)_2$; Y = Me
4u: X = Y = Cl; R = $CH_2CH(CH_3)_2$
4v: X = Cl; R = $CH_2CH(CH_3)_2$; Y = Br
4w: X = Cl; R = $CH_2CH(CH_3)_2$; Y = OMe

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*-arylsulfonylated amino acids **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}H and ^{13}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 cm^{-1}, respectively, meanwhile carbonyl groups appeared in the region of 1729–1717 cm^{-1}. In the ^{1}H NMR spectra of **2a–2f**, NH proton appeared as broad singlets or doublets at the regions δ 5.13–6.77 ppm, meanwhile the carboxylic acid protons resonated at the regions δ 8.0–10.33 ppm, exchangeable with D_2O. The structures of **3a–3f** were confirmed by their IR, 1H, 13C NMR and mass spectra. The IR spectra showed peaks in the regions 3263–3156 cm^{-1} attributed to the NH stretchings of NH_2 group, while the peaks at 1729–1717 cm^{-1} were attributed to the carbonyl group stretching. In the ^{1}H NMR spectra of **3a–3f**, the doublets or broad singlets at the regions δ 8.56–6.43 ppm were assigned to NH_2 or secondary NH protons, exchangeable with D_2O. In ^{13}C-NMR spectra of **3a–3f**, C-2 of the thiadiazole moiety appeared at the regions δ 161.3–162.3 ppm, while C-5 of the same ring resonated at the regions δ 168.9–169.8 ppm. Furthermore, the structures of **4a–4w** and **5** were assigned on the basis of their IR, ^{1}H, ^{13}C NMR and mass spectra. The characteristic signals for secondary NH absorption at 3289–3255 cm^{-1} in the IR spectra indicated the formation of the desired products. In ^{1}H-NMR spectra, the aromatic protons appeared as multiplets or doublets in regions δ 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}C-NMR spectra of **4a–4w**, C-2 and C-5 of the thiazdiazole backbone resonated at the regions δ 159.3–161.7 and 162.8–169.2 ppm, respectively. The eight signals at the regions δ 114.0–144.0 ppm were assigned to the aromatic carbon atoms, while *C*HNH carbon atom resonated at the regions δ 49.0–59.8 ppm. The aromatic carbon atom C-OMe (of compounds **4d**, **4h, 4l**, **4p**, **4s** and **4w**) appeared at the regions δ 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 $^{3}J_{H,C}$ couplings: C-2 carbon atom of the thiadiazole backbone at δ_C 161.1 ppm coupled with *C*HMe proton at δ_H 4.46 ppm as well as methyl protons of the same group at δ_H 1.47 ppm. Further, a $^{2}J_{H,C}$ coupling between methyl protons of methoxy substituent at δ_H 3.83 ppm and aromatic carbon atom C-OMe at δ_C 162.7 ppm was observed. Additionally, a $^{2}J_{H,C}$ coupling between CH*Me* protons at δ_H 4.46 ppm with *C*HMe carbon atom at δ_C 49.6 ppm was witnessed (Fig. 2).

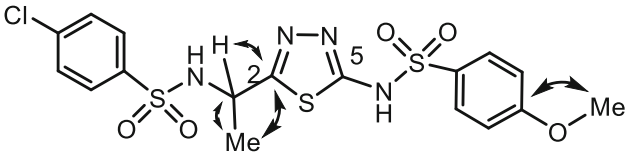


Fig. 2 $J_{H,C}$ correlations in the HMBC NMR spectrum of **4h**

In vitro anti-HIV activity

Compounds **3a–3f**, **4a–4w** and **5** were evaluated for their inhibitory activity against HIV-1 (strain III_B) 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 IC_{50} value of 9.25 μM, with a selectivity index (SI) value of 6.6; however, compound **5** turned out cytotoxic for exponentially growing MT-4 cells (human $CD4^+$ lymphocytes) in the low micromolar range (CC_{50} 4.09 μM). This study revealed that compounds containing a branched-chain aliphatic group (leucine residue) together with a methoxy substituent at the arylsulfonamide moiety showed significant anti-HIV-1 activity, while the presence of three arylsulfonamido 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 IC_{50} value of 9.25 μM (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 μM 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_{50} (μM)[a]	av. CC_{50} (μM)[b]	SI[c]
4e	III_B	>60.53	60.53	<1
	ROD	>60.53	60.53	<1
4s	III_B	9.25	61.05	6.6
	ROD	>61.05	61.05	<1
4u	III_B	>59.93	59.93	<1
	ROD	>59.93	59.93	<1
4v	III_B	>57.63	57.63	<1
	ROD	>57.63	57.63	<1
5	III_B	>4.09	4.09	<1
	ROD	>4.09	4.09	<1
Nevirapin	III_B	0.05	>4.00	>80
	ROD	4.00	>4.00	<1
AZT	III_B	0.0019	>25	>13,144
	ROD	0.0018	>25	>14,245
3TC	III_B	0.51	>20	>39
	ROD	2.02	>20	>10

Anti-HIV-1 activity measured against strain III_B
Anti-HIV-2 activity measured against strain ROD
[a]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and HIV-2-induced cytopathogenic effect
[b]Average CC_{50}: compound concentration that reduces the viability of mock-infected MT-4 cells by 50%
[c]*SI* selectivity index (CC_{50}/IC_{50}). 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 (^{1}H) and on 100 MHz (^{13}C) spectrometers (Bruker Avance, Germany) with TMS as internal standard and on the δ 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_{254} TLC plates purchased from Merck (Germany), using $CHCl_3$-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_f: 0.45; IR (υ_{max}, neat, cm^{-1}): 3400–2450 (OH), 3276 (NH), 1729 (C=O), 1572 (C=C), 1311, 1157 (2 × O = S = O), 1088 (C–O). ^{1}H NMR (acetone-d_6): δ 1.33 (d, 3H, J = 7.2 Hz, CH_3CH), 2.42 (s, 3H, Ar-CH_3), 3.97 (m, 1H, CHCH$_3$), 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_2H).

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

From L-alanine (74 mg). Yield: 235 mg (89%) as colorless; m.p.: 131–132 °C; R_f: 0.44; IR (υ_{max}, neat, cm^{-1}): 3450–2450 (OH), 3270 (NH), 1720 (C=O), 1574 (C=C), 1319, 1162 (2 × O = S = O), 1082 (C–O). ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3H, J = 7.2 Hz, CH_3CH), 4.01 (m, 1H, CHCH$_3$), 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_2H).

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

From L-valine (117 mg). Yield: 184 mg (85%) as colorless crystals; m.p.: 151–153 °C; R_f: 0.45; IR (υ_{max}, neat, cm^{-1}): 3400–2400 (OH), 3280 (NH), 1729 (C=O), 1586 (C=C), 1318, 1160 (2 × O = S = O), 1081 (C–O). ^{1}H NMR ($CDCl_3$): δ 0.87 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 0.96 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 2.12 (m, 1H, CHCH(CH$_3$)$_2$), 2.42 (s, 3H, Ar-CH_3), 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_2H).

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

From L-valine (117 mg). Yield: 240 mg (82%) as colorless crystals; m.p.: 125–127 °C; R_f: 0.45; IR (υ_{max}, neat, cm^{-1}): 3450–2400 (OH), 3277 (NH), 1728 (C=O), 1578 (C=C), 1328, 1159 (2 × O = S = O), 1084 (C–O). ^{1}H NMR ($CDCl_3$): δ 0.76 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 0.88 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 2.14 (m, 1H, CHCH(CH$_3$)$_2$), 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_2H).

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 (υ_{max}, neat, cm^{-1}): 3400–2450 (OH), 3269 (NH), 1717 (C=O), 1576 (C=C), 1318, 1158 (2 × O = S = O), 1080 (C–O). ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 3H, J = 6.6 Hz, $CH_2CH(CH_3)_2$), 0.90 (d, 3H, J = 6.8 Hz, $CH_2CH(CH_3)_2$), 1.51 (m, 2H, $CH_2CH(CH_3)_2$), 1.79 (m, 1H, $CH_2CH(CH_3)_2$), 2.43 (s, 3H, Ar-CH_3), 3.93 (m, 1H, $NHCHCH_2$), 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, CO_2H).

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 (υ_{max}, neat, cm^{-1}): 3450–2450 (OH), 3275 (NH), 1728 (C=O), 1577 (C=C), 1319, 1156 (2 × O = S = O), 1082 (C–O). ^{1}H NMR (acetone-d_6): δ 0.87 (d, 3H, J = 6.3 Hz, $CH_2CH(CH_3)_2$), 0.93 (d, 3H, J = 6.5 Hz, $CH_2CH(CH_3)_2$), 1.56 (m, 2H, $CH_2CH(CH_3)_2$), 1.80 (m, 3H, m, $CH_2CH(CH_3)_2$), 3.98 (m, 1H, $NHCHCH_2$), 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, CO_2H).

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 $KHCO_3$. 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 (υ_{max}, neat, cm^{-1}): 3421, 3416 (2×NH, pri.), 3263 (NH, sec.), 1567 (C=C), 1321, 1162 (2 × O = S = O). ^{1}H NMR (DMSO-d_6): δ 1.24 (d, 3H, J = 6.9 Hz, $CHCH_3$), 2.38 (s, 3H, Ar-CH_3), 4.49 (m, 1H, $CHCH_3$), 7.06 (s, 2H, 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, NHCH). ^{13}C-NMR (DMSO-d_6): δ 21.1 ($CHCH_3$), 21.4 (Ar-CH_3), 49.5 ($CHCH_3$), 127.0 (Ar-$C_{3,3'}$), 130.1 (Ar-$C_{2,2'}$), 138.4 (Ar-C_1), 143.4 (Ar-C_4), 162.3 ($C^2_{thiadiazole}$), 169.8 ($C^5_{thiadiazole}$). ESI–MS: m/z 299 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3428, 3418 (2×NH, pri), 3244 (N–H, sec.), 1578 (C=C), 1311, 1157 (2 × O = S = O). ^{1}H NMR (DMSO-d_6): δ 1.28 (d, 3H, J = 6.9 Hz, $CHCH_3$), 4.56 (m, 1H, $CHCH_3$), 7.09 (s, 2H, 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, NHCH). ^{13}C NMR (DMSO-d_6): δ 21.3 ($CHCH_3$), 49.6 ($CHCH_3$), 128.9 (Ar-$C_{2,2'}$), 129.7 (Ar-$C_{3,3'}$), 137.8 (Ar-C_4), 140.4 (Ar-C_1), 161.3 ($C^2_{thiadiazole}$), 169. 7 ($C^5_{thiadiazole}$). ESI–MS: m/z 317/319 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3358, 3350 (2×NH, pri), 3156 (NH, sec.), 1594 (C=C), 1328, 1159 (2 × O = S = O). ^{1}H NMR (DMF-d_7): δ 0.96 (3H, d, J = 6.6 Hz, $CH(CH_3)_2$), 1.16 (d, 3H, J = 6.6 Hz, $CH(CH_3)_2$), 2.22 (1H, m, $CH(CH_3)_2$), 2.56 (3H, s, Ar-CH_3), 4.50 (1H, m, NHCH), 7.28 (s, 2H, 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, NHCH). ^{13}C NMR (DMF-d_7): δ 18.7 ($CH(CH_3)_2$), 18.9 ($CH(CH_3)_2$), 20.8 ($CH(CH_3)_2$), 33.6 (Ar-CH_3), 60.1 (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 ($C^2_{thiadiazole}$), 169.6 ($C^5_{thiadiazole}$). ESI–MS: m/z 327 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3457, 3448 (2×NH, pri), 3252 (NH, sec.), 1576 (C=C), 1318, 1160 (2 × O = S = O). ^{1}H NMR (DMF-d_7): δ 0.76 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 0.93 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 2.25 (m, 1H, $CH(CH_3)_2$), 4.33 (m, 1H, 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, NH_2), 8.65 (bs, 1H, NHCH). ^{13}C NMR (DMF-d_7): δ 18.4 ($CH(CH_3)_2$), 18.8 ($CH(CH_3)_2$), 21.1 ($CH(CH_3)_2$), 32.0 (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 ($C^2_{thiadiazole}$), 169.3 ($C^5_{thiadiazole}$). ESI–MS: m/z 345/347 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3464, 3450 (2×NH, pri), 3263 (NH, sec.), 1572 (C=C), 1319, 1156 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.78 (d, 3H, J = 3.3 Hz, CH(CH_3)$_2$), 0.84 (d, 3H, J = 3.3 Hz, CH(CH_3)$_2$), 1.63 (m, 3H, CH_2CH(CH$_3$)$_2$), 2.41 (s, 3H, Ar-CH_3), 4.64 (m, 1H, NHCHCH$_2$), 6.41 (s, 2H, NH$_2$), 7.09 (d, 1H, J = 8.1 Hz, 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}C NMR (acetone-d_6): δ 20.5 (CH(CH_3)$_2$), 21.2 (CH(CH_3)$_2$), 21.7 (CHCH_2), 24.2 (CH(CH$_3$)$_2$), 44.8 (Ar-CH_3), 52.2 (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 ($C^2_{thiadiazole}$), 168.9 ($C^5_{thiadiazole}$). ESI–MS: m/z 341 [M + 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 (υ_{max}, neat, cm^{-1}): 3420, 3412 (2×NH, pri), 3212 (NH, sec.), 1576 (C=C), 1318, 1158 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.72 (d, 3H, J = 6.3 Hz, CH(CH_3)$_2$), 0.79 (d, 3H, J = 6.3 Hz, CH(CH_3)$_2$), 1.46 (m, 3H, CH_2CH(CH$_3$)$_2$), 4.42 (m, 1H, NHCHCH$_2$), 7.07 (s, 2H, 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, NHCH). ^{13}C NMR (acetone-d_6): δ 21.6 (CH(CH_3)$_2$), 23.0 (CH(CH_3)$_2$), 24.4 (CHCH_2), 34.5 (CH(CH$_3$)$_2$), 44.6 (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 ($C^2_{thiadiazole}$), 169.5 ($C^5_{thiadiazole}$). ESI–MS: m/z 359/361 [M + 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 × 50 mL). The organic extracts were washed with 2 N HCl, followed by brine and dried over anhyd. Na_2SO_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 (υ_{max}, neat, cm^{-1}): 3262 (NH, sec.), 1592 (C=C), 1321, 1167 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 1.44 (d, 3H, J = 6.9 Hz, CH_3CH), 2.38 (s, 3H, Ar-CH_3), 2.42 (s, 3H, Ar-CH_3), 4.67 (m, 1H, CH$_3$CH), 7.35 (s, 1H, NHCH), 7.40–7.37 (m, 2H, Ar–H), 7.75–7.71 (m, 4H, Ar–H), 12.60 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 19.6 (CH_3CH), 20.5, 20.6 (2xAr-CH_3), 49.9 (CH$_3$CH), 126.1, 127.1, 129.4, 129.68, 138.0, 139.8, 143.0, 143.7 (8× C$_{arom.}$), 161.1 ($C^2_{thiadiazole}$), 167.6 ($C^5_{thiadiazole}$). ESI–MS: m/z 453 [M + 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 (υ_{max}, neat, cm^{-1}): 3270 (NH, sec.), 1578 (C=C), 1311, 1152 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 1.43 (d, 3H, J = 7.8 Hz, CH_3CH), 2.39 (s, 3H, Ar-CH_3), 4.69 (m, 1H, CH$_3$CH), 7.36 (bs, 1H, 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, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 19.6 (CH_3CH), 20.6 (Ar-CH_3), 49.9 (CH$_3$CH), 127.1, 127.9, 129.1, 129.7, 137.8, 137.9, 141.4, 143.7 (8×C$_{arom.}$), 161.7 ($C^2_{thiadiazole}$), 168.1 ($C^5_{thiadiazole}$). ESI–MS: m/z 472/474 [M + 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 (υ_{max}, neat, cm^{-1}): 3280 (NH, sec.), 1586 (C=C), 1328, 1160 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 1.44 (d, 3H, J = 6.8 Hz, CH_3CH), 2.40 (s, 3H, Ar-CH_3), 4.68 (m, 1H, CH$_3$CH), 7.40 (s, 1H, NHCH), 7.79–7.74 (m, 4H, Ar–H), 7.39–7.36 (m, 4H, Ar–H), 12.73 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 19.6 (CH_3CH), 20.6 (Ar-CH_3), 49.8 (CH$_3$CH), 126.3, 127.1, 128.1, 129.7, 132.1, 138.0, 141.9, 143.7 (8×Ar-C$_{arom.}$), 161.6 ($C^2_{thiadiazole}$), 168.1 ($C^5_{thiadiazole}$). ESI–MS: m/z 516/518 [M + 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 (υ_{max}, neat, cm^{-1}): 3287 (NH, sec.), 1576 (C=C), 1348, 1151 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 1.43 (d, 3H, J = 7.2 Hz, CH_3CH), 2.39 (s, 3H, Ar-CH_3), 3.89 (s, 3H, OCH$_3$) 4.67 (m, 1H, CH$_3$CH), 7.11–7.01 (m, 2H, Ar–H), 7.31 (bs, 1H, NHCH), 7.37 (m, 2H,

Ar–H), 7.81–7.68 (m, 2H, Ar–H), 12.56 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 19.5 (CH_3CH), 20.6 (Ar-CH_3), 49.8 (CH_3CH), 55.2 (OCH_3), 114.0, 127.1, 128.2, 128.5, 129.7, 134.5, 143.7 (7×$C_{arom.}$), 160.9 ($C^2_{thiadiazole}$), 162.8 ($C_{arom.}$-OMe), 167.3 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 469 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3269 (NH, sec.), 1585 (C=C), 1321, 1142 (2 × O = S = O). ^1H NMR (acetone-d_6): δ 1.47 (d, 3H, J = 6.9 Hz, CH_3CH), 2.42 (s, 3H, Ar-CH_3), 4.74 (m, 1H, CH_3CH), 7.38 (d, 2H, J = 8.1 Hz, Ar–H), 7.55 (bs, 1H, 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, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 19.7 (CH_3CH), 20.5 (Ar-CH_3), 49.9 (CH_3CH), 126.1, 128.8, 129.2, 129.4, 138.5, 139.7, 139.7, 143.0 (8×$C_{arom.}$), 160.8 ($C^2_{thiadiazole}$), 167.5 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 472/474 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3275 (NH, sec.), 1567 (C=C), 1329, 1146 (2 × O = S = O). ^1H NMR (acetone-d_6): δ 1.47 (d, 3H, J = 6.9 Hz, CH_3CH), 4.76 (m, 1H, CH_3CH), 7.64 (bs, 1H, NHCH), 7.91–7.84 (m, 4H, Ar–H), 7.63–7.59 (m, 4H, Ar–H), 12.69 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 19.7 (CH_3CH), 49.9 (CH_3CH), 127.9, 128.9, 129.1, 129.4, 137.9, 138.6, 139.7, 141.3 (8×$C_{arom.}$), 161.2 ($C^2_{thiadiazole}$), 168.0 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 492/494 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3278 (NH, sec.), 1580 (C=C), 1320, 1145 (2 × O = S = O). ^1H NMR (acetone-d_6): δ 1.44 (d, 3H, J = 7.8 Hz, CH_3CH), 4.64 (m, 1H, CH_3CH), 7.21 (bs, 1H, 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, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 19.6 (CH_3CH), 49.9 (CH_3CH), 126.4, 128.0, 128.9, 129.4, 132.2, 138.5, 139.7, 141.8 (8×$C_{arom.}$), 161.2 ($C^2_{thiadiazole}$), 168.0 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 536/538 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3259 (NH, sec.), 1578 (C=C), 1326, 1126 (2 × O = S = O). ^1H NMR (acetone-d_6): δ 1.47 (d, 3H, J = 6.9 Hz, CH_3CH), 3.83 (s, 3H, OCH_3), 4.56 (m, 1H, CH_3CH), 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, NHCH), 13.96 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 20.2 (CH_3CH), 49.6 (CH_3CH), 56.1 (OCH_3), 114.8, 128.3, 129.0, 129.8, 134.0, 138.2, 139.9 (7 × $C_{arom.}$), 161.1 ($C^2_{thiadiazole}$), 162.7 ($C_{arom.}$-OMe), 167.5 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 488/490 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3286 (NH, sec.), 1586 (C=C), 1323, 1160 (2 × O = S = O). ^1H NMR (acetone-d_6): δ 1.04 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 1.12 (d, 3H, J = 6.6 Hz, $CH(CH_3)_2$), 2.24 (m, 1H, $CH(CH_3)_2$), 2.38 (s, 3H, Ar-CH_3), 2.41 (s, 3H, Ar-CH_3), 4.67 (m, 1H, NHCH), 7.35 (s, 1H, NHCH), 7.64–7.59 (m, 4H, Ar–H), 7.86–7.74 (m, 4H, Ar–H), 12.48 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 21.0 ($CH(CH_3)_2$), 24.1, 24.3 (2xAr-CH_3), 39.4 ($CH(CH_3)_2$), 52.2 (NHCH), 126.4, 128.8, 129.4, 130.0, 136.4, 137.3, 143.0, 144.0 (8×$C_{arom.}$), 159.5 ($C^2_{thiadiazole}$), 165.2 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 481 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3276 (NH, sec.), 1575 (C=C), 1322, 1148 (2 × O = S = O). ^1H NMR (acetone-d_6): δ 0.92 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 1.04 (d, 3H, J = 6.6 Hz, $CH(CH_3)_2$), 2.28 (m, 1H, $CH(CH_3)_2$), 2.38 (s, 3H, Ar-CH_3), 4.27 (m, 1H, NHCH), 7.23 (s, 2H, J = 8.1 Hz, Ar–H), 7.35 (br, 1H, NHCH), 7.66–7.62 (m, 2H, Ar–H), 7.86–7.82 (m, 4H, Ar–H) 12.60 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 20.0 ($CH(CH_3)_2$), 20.5 (Ar-CH_3), 43.4 ($CH(CH_3)_2$), 59.8 (NHCH), 127.1, 128.0, 129.3, 132.1, 138.0, 138.0, 142.1, 143.3 (8×$C_{arom.}$), 161.2 ($C^2_{thiadiazole}$), 167.7 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 500/502 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3274 (NH, sec.), 1586 (C=C), 1325,1150 (2 × O = S = O). ^1H NMR

(acetone-d_6): δ 0.88 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 1.03 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 2.22 (m, 1H, CH(CH$_3$)$_2$), 2.29 (s, 3H, Ar-CH$_3$), 4.32 (m, 1H, NHCH), 7.21 (d, 2H, J = 8.1 Hz, Ar–H), 7.25 (s, 1H, NHCH), 7.65 (d, 2H, J = 8.2 Hz, Ar–H), 7.82–7.75 (m, 4H, Ar–H), 12.88 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 18.4 (CH(CH_3)$_2$), 20.5 (Ar-CH_3), 42.7 (CH(CH$_3$)$_2$), 59.8 (NHCH), 126.2, 127.1, 128.0, 129.3, 132.1, 138.0, 142.1, 143.3 (8×C$_{arom.}$), 160.1 ($C^2_{thiadiazole}$), 167.7 ($C^5_{thiadiazole}$). ESI–MS: m/z 544/546 [M + 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 (υ_{max}, neat, cm^{-1}): 3255 (NH, sec.), 1575 (C=C), 1328, 1158 (2 × O = S = O). ^{1}H-NMR (acetone-d_6): δ 0.88 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 1.03 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 2.15 (m, 1H, CH(CH$_3$)$_2$), 2.38 (s, 3H, Ar-CH_3), 3.90 (s, 3H, OCH$_3$), 4.25 (m, 1H, NHCH), 7.31 (bs, 1H, 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, NHSO$_2$). ^{13}C-NMR (acetone-d_6): δ 21.8 (CH(CH_3)$_2$), 21.9 (Ar-CH_3), 48.9 (CH(CH$_3$)$_2$), 52.5 (NHCH), 55.5 (OCH$_3$), 113.2, 128.0, 128.9, 129.4, 139.2, 139.8, 141.2 (7×C$_{arom.}$), 159.3 ($C^2_{thiadiazole}$), 160.3 ($C_{arom.}$-OMe), 167.7 ($C^5_{thiadiazole}$). ESI–MS: m/z 497 [M + 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 (υ_{max}, neat, cm^{-1}): 3258 (NH, sec.), 1578 (C=C), 1320, 1146 (2 × O = S = O). ^{1}H NMR (DMSO-d_6): δ 0.73 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 0.89 (d, 3H, J = 6.7 Hz, CH(CH_3)$_2$), 1.95 (m, 1H, CH(CH$_3$)$_2$), 2.38 (s, 3H, Ar-CH_3), 4.20 (m, 1H, NHCH), 8.71 (d, 1H, J = 8.7 Hz, NHCH), 7.46–7.39 (m, 4H, Ar–H), 7.69–7.63 (m, 4H, Ar–H), 13.94 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 19.9 (CH(CH_3)$_2$), 21.5 (Ar-CH_3), 32.6 (CH(CH$_3$)$_2$), 59.7 (NHCH), 126.2, 128.9, 129.9, 130.1, 137.9, 139.8, 139.4, 143.3 (8×C$_{arom.}$), 159.4 ($C^2_{thiadiazole}$), 167.4 ($C^5_{thiadiazole}$). ESI–MS: m/z 500/502 [M + 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 (υ_{max}, neat, cm^{-1}): 3278 (NH, sec.), 1574 (C=C), 1322, 1143 (2 × O = S = O). ^{1}H NMR (DMSO-d_6): δ 0.75 (d, 3H, J = 6.8 Hz, CH(CH_3)$_2$), 0.82 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 1.95 (m, 1H, CH(CH$_3$)$_2$), 4.10 (m, 1H, NHCH), 7.23 (d, 1H, J = 8.8 Hz, NHCH), 7.44–7.39 (m, 4H, Ar–H), 7.84–7.79 (m, 4H, Ar–H) 12.20 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 21.8 (CH(CH_3)$_2$), 34.2 (CH(CH$_3$)$_2$), 52.4 (NHCH), 127.0, 127.3, 128.9, 129.3, 137.9, 138.7, 140.6, 141.4 (8×C$_{arom.}$), 160.3 ($C^2_{thiadiazole}$), 167.6 ($C^5_{thiadiazole}$). ESI–MS: m/z 520/522 [M + 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 (υ_{max}, neat, cm^{-1}): 3289 (NH, sec.), 1587 (C=C), 1329, 1158 (2 × O = S = O). ^{1}H NMR (DMSO-d_6): δ 0.65 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 0.81 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 1.90 (m, 1H, CH(CH$_3$)$_2$), 4.10 (m, 1H, NHCH), 7.42–7.36 (m, 4H, Ar–H), 7.69 (d, 1H, J = 9.0 Hz, NHCH), 7.80–7.75 (m, 4H, Ar–H) 12.27 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 20.5 (CH(CH_3)$_2$), 32.5 (CH(CH$_3$)$_2$), 55.0 (NHCH), 126.4, 127.3, 128.3, 129.2, 132.2, 138.4, 140.7, 141.8 (8×C$_{arom.}$), 160.5 ($C^2_{thiadiazole}$), 167.6 ($C^5_{thiadiazole}$). ESI–MS: m/z 564/566 [M + 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 (υ_{max}, neat, cm^{-1}): 3268 (NH, sec.), 1582 (C=C), 1326, 1160 (2 × O = S = O). ^{1}H NMR (DMSO-d_6): δ 0.91 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 1.03 (d, 3H, J = 6.9 Hz, CH(CH_3)$_2$), 3.50 (m, 1H, CH(CH$_3$)$_2$), 3.90 (s, 3H, OCH$_3$), 4.36 (m, 1H, NHCH), 7.10 (m, 2H, Ar–H), 7.43 (bs, 1H, NHCH), 7.45 (m, 2H, Ar–H), 7.80–7.75 (m, 4H, Ar–H), 12.48 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 18.5 (CH(CH_3)$_2$), 32.7 (CH(CH$_3$)$_2$), 55.2 (NHCH), 59.9 (OCH$_3$), 114.0, 128.2, 128.7, 128.8, 134.4, 138.3, 139.8 (7×C$_{arom.}$), 158.8 ($C_{arom.}$-OMe), 162.8 ($C^2_{thiadiazole}$), 166.8 ($C^5_{thiadiazole}$). ESI–MS: m/z 516/518 [M + 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 (υ_{max}, neat, cm^{-1}): 3287 (NH, sec.), 1587 (C=C), 1328, 1164 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.88 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 0.90 (d, 3H, J = 6.6 Hz, CH(CH_3)$_2$), 1.77–1.69 (m, 3H, CH_2CH(CH$_3$)$_2$), 2.48 (s, 3H, Ar-CH_3), 4.53 (m, 1H, NHCH), 7.33 (d, 1H, J = 8.4 Hz, NHCH), 7.42–7.37 (m, 4H, Ar–H), 7.74–7.63 (m, 4H, Ar–H) 12.09 (s, 1H, NHSO$_2$). ^{13}C NMR (acetone-d_6): δ 20.6 (CH(CH_3)$_2$), 21.7 (CH(CH$_3$)$_2$), 24.1 (Ar-CH_3), 41.7 (CH$_2$CH(CH$_3$)$_2$), 49.9 (NHCH), 126.1, 127.2, 129.4, 1297 137.9, 139.8, 143.0, 143.7 (8×C$_{arom.}$),

161.2 ($C^2_{thiadiazole}$), 167.6 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 495 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3269 (NH, sec.), 1572 (C=C), 1320, 1166 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.81 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 0.86 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 1.79–1.64 (m, 3H, $CH_2CH(CH_3)_2$), 2.48 (s, 3H, Ar-CH_3), 4.60 (m, 1H, NHC*H*), 7.27 (d, 2H, J = 8.1 Hz, Ar–H), 7.33 (d, 1H, J = 8.4 Hz, N*H*CH), 7.68 (d, 2H, J = 8.4 Hz, Ar–*H*), 7.82–7.75 (m, 4H, Ar–H), 12.09 (s, 1H, N*H*SO_2). ^{13}C NMR (acetone-d_6): δ 20.9 ($CH(CH_3)_2$), 21.8 ($CH(CH_3)_2$), 24.1 (Ar-CH_3) 43.5 ($CH_2CH(CH_3)_2$), 52.5 (NH*C*H), 126.3, 127.5, 128.0, 129.5, 132.2, 137.9, 141.9, 143.6 (8×$C_{arom.}$) 160.9 ($C^2_{thiadiazole}$), 167.7 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 560/558$[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3281 (NH, sec.), 1587 (C=C), 1328, 1150 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.91 (d, 3H, J = 6.6 Hz, $CH(CH_3)_2$), 1.03 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 1.80–1.69 (m, 3H, $CH_2CH(CH_3)_2$), 2.36 (s, 3H, Ar-CH_3), 3.90 (s, 3H, OCH_3), 4.52 (m, 1H, NHC*H*), 7.35 (m, 1H, N*H*CH), 7.18 (m, 2H, Ar–H), 7.49 (m, 2H, Ar–H), 7.79–7.67 (m, 4H, *Ar–H*), 12.05 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 20.1 ($CH(CH_3)_2$), 22.1 ($CH(CH_3)_2$), 24.2 (Ar-CH_3) 41.2 ($CH_2CH(CH_3)_2$), 53.1 (NH*C*H), 54.2 (OCH_3), 116.1, 126.5, 128.2, 129.6, 133.2, 138.4, 139.7 (7×$C_{arom.}$), 159.3 ($C^2_{thiadiazole}$), 160.1 ($C_{arom.}$-OMe), 169.2 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 511 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3276 (NH, sec.), 1583 (C=C), 1329, 1153 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.85 (d, 3H, J = 6.2 Hz, $CH(CH_3)_2$), 0.89 (d, 3H, J = 6.2 Hz, $CH(CH_3)_2$), 1.78–1.69 (m, 3H, $CH_2CH(CH_3)_2$), 2.48 (s, 3H, Ar-CH_3), 4.66 (m, 1H, NHC*H*), 7.47–7.44 (m, 2H, Ar–H), 7.60 (s, 1H, N*H*CH), 7.63–7.53 (m, 2H, Ar–H), 7.87–7.71 (m, 4H, Ar–H), 12.62 (s, 1H, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 20.9 ($CH(CH_3)_2$), 21.9 ($CH(CH_3)_2$), 24.2 (Ar-CH_3), 43.5 ($CH_2CH(CH_3)_2$), 52.7 (NH*C*H), 126.4, 128.8, 129.4, 130.0, 132.4, 138.4, 139.7, 144.0 (8×$C_{arom.}$), 160.1 $C^2_{thiadiazole}$), 167.1 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 514/516 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3279 (NH, sec.), 1574 (C=C), 1328, 1154 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.83 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 0.89 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 1.80–1.66 (m, 3H, $CH_2CH(CH_3)_2$), 4.66 (m, 1H, NHC*H*), 7.58 (s, 1H, N*H*CH), 7.66–7.51 (m, 4H, Ar–H), 7.86–7.80 (m, 4H, Ar–H), 12.71 (s, 1H, N*H*SO_2). ^{13}C NMR (acetone-d_6):δ 20.8 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$), 43.4 ($CH_2CH(CH_3)_2$), 52.4 (NH*C*H), 127.0, 127.9, 128.9, 129.2, 137.9, 138.4, 139.7, 141.4 (8×$C_{arom.}$), 160.5 ($C^2_{thiadiazole}$), 167.5 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 534/536 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3276 (NH, sec.), 1569 (C=C), 1326, 1159 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.82 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 0.89 (d, 3H, J = 6.2 Hz, $CH(CH_3)_2$), 1.80–1.69 (m, 3H, $CH_2CH(CH_3)_2$), 4.65 (m, 1H, NHC*H*), 7.54–7.51 (4H, m, Ar–*H*), 7.57 (s, 1H, N*H*CH) 7.84–7.75 (m, 4H, Ar–H), 12.00 (1H, s, $NHSO_2$). ^{13}C NMR (acetone-d_6): δ 21.8 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$), 43.5 ($CH_2CH(CH_3)_2$), 52.5 (NH*C*H), 126.4, 128.0, 128.9, 129.8, 132.2, 138.4, 139.7, 141.8 (8×$C_{arom.}$), 160.5 ($C^2_{thiadiazole}$), 167.6 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 579/581 $[M+H]^+$.

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 (υ_{max}, neat, cm^{-1}): 3259 (NH, sec.), 1566 (C=C), 1320, 1164 (2 × O = S = O), ^{1}H NMR (acetone-d_6): δ 0.85 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 0.89 (d, 3H, J = 6.0 Hz, $CH(CH_3)_2$), 1.78–1.64 (m, 3H, $CH_2CH(CH_3)_2$), 3.90 (s, 3H, OCH_3), 4.64 (m, 1H, NHC*H*), 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, $NHSO_2$); ^{13}C NMR (acetone-d_6): δ 21.8 ($CH(CH_3)_2$), 24.2 ($CH(CH_3)_2$), 48.9 ($CH_2CH(CH_3)_2$), 52.5 (NH*C*H), 55.2 (OCH_3), 114.0, 128.2, 128.9, 129.2, 134.3, 138.4, 139.7 (7×$C_{arom.}$), 159.9 ($C^2_{thiadiazole}$), 162.8 ($C_{arom.}$-OMe), 166.8 ($C^5_{thiadiazole}$). ESI–MS: *m/z* 530/532 $[M+H]^+$.

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

From **3f** (361 mg). Yield: 345 mg (50%) as colorless crystals; m.p.: 223–224 °C; $R_{f:}$ 0.53; IR (υ_{max}, neat, cm^{-1}): 3283 (NH, sec.), 1715 (C = 0), 1520 (C=C), 1328, 1165 (2 × O = S = O). ^{1}H NMR (acetone-d_6): δ 0.88 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 0.90 (d, 3H, J = 6.9 Hz, $CH(CH_3)_2$), 2.05 (m, 3H, $CH_2CH(CH_3)_2$), 2.32 (s, 3H, Ar-CH_3), 4.64 (m, 1H, NHC*H*), 7.43 (s, 1H, N*H*CH), 8.01–7.27 (m, 12H, Ar–H). ^{13}C NMR (acetone-d_6): δ 20.5 (Ar-CH_3), 21.4 ($CH(CH_3)_2$), 25.2 ($CH(CH_3)_2$), 43.0 ($NHCH + CH_2CH(CH_3)_2$), 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×$C_{arom.}$), 160.3 ($C^2_{thiadiazole}$), 168.2 ($C^5_{thiadiazole}$). 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_B) 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-μL 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 (IIIB) [42] or HIV-2 (ROD) [43] stock (50 μL) at 100–300 CCID50 (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 × 105 cells per mL, and volumes of 50 μL were transferred to the microtiter tray wells. Five days after infection, the viability of the mock- and HIV-infected cells was examined spectrophotometrically.

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