Journal of Enzyme Inhibition and Medicinal Chemistry, 2011; 26(5): 668–680

ISSN 1475-6366 print/ISSN 1475-6374 online
DOI: 10.3109/14756366.2010.546792

informa
healthcare

RESEARCH ARTICLE

Synthesis, QSAR and anti-HIV activity of new 5-benzylthio-1,3,4-oxadiazoles derived from α-amino acids

Tayyaba Syed[1], Tashfeen Akhtar[1], Najim A. Al-Masoudi[2], Peter G. Jones[3], and Shahid Hameed[1]

[1]Department of Chemistry, Quaid-I-Azam University, Islamabad, Pakistan, [2]Chemistry Department, College of Basrah, Basrah, Iraq (previous address: Fachbereich Chemie, Universität Konstanz, Konstanz, Germany), and [3]Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Braunschweig, Germany

Abstract

2-(1-[(4-Chloro/methylphenylsulfonylamino)alkyl]-5-thioxo-4,5-dihydro-1,3,4-oxadiazoles (**4a–e**) were synthesized, in four steps, *via* the sulfonyl derivatives of L-amino acids (L-alanine, L-methionine and L-phenylalanine) **1a–e**, the esters **2a–e**, the hydrazides **3a–e** and finally the cyclization to **4a–e**. Alkylation of **4a–e** with 1.0 mole eq. of substituted benzyl halides furnished *S*-benzyl derivatives **5a–t**, while 1.1 mole eq. yielded major **5a–t** and minor amount of **6a–d**. Alternatively, treatment of **4a–e** with 2.0 mole eq. of substituted benzyl halides furnished **6a–d** only. The structures of **5b** and **5l** were further confirmed by single crystal X-ray analysis. Compounds **5a–t** and **6a–d** showed no selective inhibition against HIV-1 and HIV-2 replication in MT-4 cells. However, **5f** and **5j–5q** exhibited some inhibitory activity against both types with EC_{50} values (>11.50 – >13.00 μg/mL). These results suggest that the structural modifications of these compounds might lead to the development of new antiviral agents. The quantum structure-activity relationship of these novel structural congeners is discussed.

Keywords: Anti-HIV activity, α-amino acids, 5-benzylthio-1,3,4-oxadiazoles, QSAR

Introduction

Among the various viral human ailments, acquired immunodeficiency syndrome is perhaps the most complicated disease, and as yet no effective drugs or methods of control are available owing to the mutational changes in HIV virus[1]. In spite of the beneficial effects of the drugs in use, the side effects are intensified with the combination therapy[2]. Therefore, synthesis or design of novel potent, selective, and less toxic drugs remains one of the most challenging tasks that chemists are facing. 1,3,4-oxadiazole is a versatile molecule[3–6] for designing potential antiviral agents. The safety and efficacy of Raltegravir[7], a new anti-HIV drug containing the 1,3,4-oxadiazole moiety, has recently been described. On the other hand, sulphonamides attract significant attention because of their chemotherapeutic importance[8–11]. Cyclotriazadisulphonamide compounds are new effective HIV entry inhibitors[12]. We selected in the present work, two backbones: 1,3,4-oxadiazole and a sulphonamide since both having potential anti-HIV activity, which might lead to a remarkable potent anti-HIV agent with high therapeutic index. In continuation of our interest in the synthesis of biologically active azoles[13–17], we report here the synthesis of chiral sulphonamides bearing 1,3,4-oxadiazole derivatives and evaluation of their anti-HIV activity.

Experimental section

General

Melting points were measured on a Gallenkamp melting point apparatus (MP-D) and are uncorrected. The R_f values were determined using pre-coated silica gel aluminium packed plates, Kieselgel 60 HF_{254} from Merck (Germany). Infrared (IR) spectra were recorded on a FTS 3000 MX, Bio-RAD Merlin spectrophotometer (Excalibur Model, USA). Nuclear magnetic resonance (NMR) spectra were recorded on a 300 (^{1}H) and 75 MHz (^{13}C) NMR spectrometer (Bruker Avance, Switzerland) with tetramethylsilane

Address for Correspondence: Shahid Hameed, Department of Chemistry, Quaid-I-Azam University, Islamabad, 45320, Pakistan. Tel: +92 51 9064 2133; Fax: +92 51 9064 2241. E-mail: S. Hameed, shameed@qau.edu.pk or N. Al-Masoudi, najim almasoudi@gmx.de

(Received 01 June 2010; revised 07 December 2010; accepted 07 December 2010)

as internal standard on a δ scale in ppm, multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, ad = apparent doublet, aq = apparent quartet, qn = quintet and m = multiplet. Electron impact (EI) mass spectra were recorded on a Agilent technologies 6890N (GC) mass spectrometer and an inert selective detector 5973 (Agilent Technologies, USA). Elemental analyses were recorded on CHNS-932 Leco (Leco Corporation, USA).

General procedure for synthesis of the hydrazides (3a–e)

The hydrazides **3a–e** were synthesized from the appropriate amino acids *via* three steps of sulfonylation furnishing **1a–e**, followed by esterfication with acidic MeOH to give **2a–e** and finally treatment with the hydrazine hydrate. The hydrazides were characterized by comparison of their physical data with the literature values[3,17].

General procedure for the synthesis of *N*-[1-(5-mercapto-1,3,4-oxadiazol-2-yl)alkyl]-4-chloro/methylbenzenesulphonamides (4a-e)

A mixture of 2-(4-chloro/methylphenylsulfonylamino) alkane hydrazide (5.40 mmol), CS_2 (10.80 mmol) and KOH (10.80 mmol) in MeOH (25 mL) was heated under reflux for 18–20 h. The solvent was evaporated to 5 mL, poured into ice-cooled water, and acidified with HOAc to pH 5. The resulting precipitate was collected, dried and recrystallized from aq. EtOH, except **4d,** which was purified by column chromatography using *n*-hexane and ethyl acetate (8:2) as an eluent.

N-[1-(5-Mercapto-1,3,4-oxadiazol-2-yl)ethyl]-4-methylbenzenesulphonamide (4a)

Yield: 0.93 g (58%); m.p. 190–192°C; R_f: 0.39 (*n*-hexane: ethyl acetate 3:2); IR (υ_{max}, cm^{-1}): 3278, 2925, 2936, 1474, 1327, 1261, 1160; ^{1}H-NMR (300 MHz, acetone-d_6): δ 12.86 (1H, s, N-H), 7.73 (2H, d, J = 8.4 Hz, Ar-H), 7.37 (2H, d, J = 7.8 Hz, Ar-H), 7.31 (1H, d, J = 8.4 Hz, N-H), 4.65 (1H, q, J = 7.2 Hz, CH), 2.41 (3H, s, CH_3), 1.49 (3H, d, J = 7.2Hz, CH_3). ^{13}C-NMR (75 MHz, acetone-d_6): δ 178.6, 162.8, 143.5, 137.8, 129.6, 126.8, 45.5, 20.6, 18.2. Anal. calcd. for $C_{11}H_{13}N_3O_3S_2$ (299.37): C, 44.13; H, 4.38; N, 14.04%. Found: C, 44.24; H, 4.33; N, 13.57%. EI-MS [m/z (%)]: 299 [M^+].

4-Chloro-*N*-[1-(5-mercapto-1,3,4-oxadiazol-2-yl)ethyl] benzenesulphonamide (4b)

Yield: 0.94 g (52%); m.p. 191–193°C; R_f:0.39 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3297, 2939, 1496, 1333, 1261, 1168. ^{1}H-NMR (300 MHz, acetone-d_6): δ 9.30 (1H, s, N-H), 7.85 (2H, d, J = 8.7 Hz, Ar-H), 7.61 (2H, d, J = 8.7 Hz, Ar-H), 7.54 (1H, d, J = 8.1 Hz, N-H), 4.71 (1H, aq, J = 7.2 Hz, CH), 1.52 (3H, d, J = 6.9 Hz, CH_3). ^{13}C-NMR (75 MHz, acetone-d_6): δ 178.6, 162.6, 139.7, 138.5, 129.3, 128.6, 45.5, 18.2. EI-MS [m/z (%)] 286 (55), 218 (100), 175 (75), 111 (70), 75 (20). Anal. calcd. for $C_{10}H_{10}N_3O_4S_2Cl$ (335.79): C, 37.56; H, 3.15; N, 13.1%4. Found: C, 38.06; H, 3.37; N, 12.60%.

N-[1-(5-Mercapto-1,3,4-oxadiazol-2-yl)-3-(methylthio) propyl]-4-methylbenzenesulphonamide (4c)

Yield: 1.24 g (64%); m.p. 144–146°C; R_f: 0.41 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3261, 2910, 1472, 1331, 1291, 1160, 1086. ^{1}H-NMR (300 MHz, acetone-d_6): δ 14.35 (1H, s, N-H), 8.65 (1H, d, J = 8.4 Hz, N-H), 7.60 (2H, d, J = 8.4 Hz, Ar-H), 7.33 (2H, d, J = 8.1 Hz, Ar-H), 4.50 (1H, aq, J = 7.8 Hz, CH), 2.50 (2H, m, -CH_2), 2.36 (3H, s, CH_3), 2.03–1.93 (2H, m, CH_2), 1.93 (3H, s, CH_3). ^{13}C-NMR (75 MHz, acetone-d_6): δ 178.1, 170.5, 143.6, 137.8, 130.0, 126.9, 48.3, 31.6, 29.2, 21.5, 14.7. Anal. calcd. for $C_{13}H_{17}N_3O_3S_3$ (359.49): C, 45.52; H, 3.80; N, 8.33%. Found: C, 46.02; H, 3.87; N, 8.35%. EI-MS [m/z (%)]: 258 (52), 171 (5), 155 (32), 91 (100), 73 (86), 61 (83).

4-Chloro-*N*-[1-(5-mercapto-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]benzenesulphonamide (4d)

Yield: 1.37 g (67%); m.p. 148–150°C; R_f: 0.40 (*n*-hexane: ethyl acetate 3:2); IR (υ_{max}, cm^{-1}): 3256, 1467, 1336, 1278, 1161, 1090. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 14.38 (1H, s, N-H) 8.67 (1H, d, J = 8.4 Hz, N-H), 7.72 (2H, d, J = 8.7 Hz, Ar-H), 7.61 (2H, d, J = 8.7 Hz, Ar-H), 4.55 (1H, q, J = 8.1 Hz, CH), 2.50–2.35 (2H, m, -CH_2), 2.01–1.91 (2H, m, CH_2), 1.95 (3H, s, CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 178.0, 161.9, 139.5, 138.2, 129.7, 128.7, 48.3, 31.5, 29.2, 14.8. EI-MS [m/z (%)]: 191 (33), 175 (30), 144 (8), 128 (28), 111 (100), 75 (82), 61 (5). Anal. calcd. for $C_{12}H_{14}N_3O_3S_3Cl$ (379.91): C, 37.94; H, 3.71; N, 11.06%. Found: C, 37.55; H, 3.61; N, 11.03%.

N-[1-(5-Mercapto-1,3,4-oxadiazol-2-yl)-2-phenylethyl]-4-methylbenzenesulphonamide (4e)

Yield: 1.45 g (72%); m.p. 150–152°C; R_f: 0.42 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3279, 2950, 1462, 1334, 1270, 1156, 1085. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.80 (1H, s, N-H), 8.67 (1H, d, J = 8.4 Hz, N-H), 7.72 (2H, d, J = 8.7 Hz, Ar-H), 7.61 (2H, d, J = 8.7 Hz, Ar-H), 7.21–7.11 (5H, m, Ar-H), 4.55 (1H, aq, J = 8.1 Hz, CH), 2.50–2.35 (2H, m, CH_2), 2.01–1.91 (2H, m, CH_2), 1.95 (3H, s, CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 178.0, 161.6, 143.4, 137.6, 136.0, 129.8, 129.6, 128.8, 128.4, 127.4, 126.6, 51.1, 38.2, 21.5. EI-MS [m/z (%)]: 274 (82), 155 (72), 91 (100), 77 (5), 65 (25). Anal. calcd. for $C_{17}H_{17}N_3O_3S_2$ (375.47): C, 54.38; H, 4.56; N, 11.19%. Found: C, 54.56; H, 4.61; N, 11.03%.

N-[1-(5-benzylthio/4-halobenzylthio)-1,3,4-oxadiazol-2-yl)alkyl]-4-methyl/4-halobenzenesulphonamides (5a-t)

A mixture of **4a–e** (0.92 mmol), 4-halobenzyl halide (0.92 mmol) and K_2CO_3 (2.76 mmol) was stirred in acetone (30 mL) at room temperature for 3–4 h. The reaction mixture was filtered, the filtrate concentrated and poured into ice-cold water. The resulting solid was filtered and recrystallized from acetone - water or purified by column chromatography using *n*-hexane and ethyl acetate (4: 1) as eluent.

N-[1-(5-Benzylthio-1,3,4-oxadiazol-2-yl)ethyl]-4-methylbenzenesulphonamide (5a)

Yield: 0.308 g (86%); m.p. 98–100°C; R_f: 0.57 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3275, 1596, 1570, 1328, 1153, 1087. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (2H, d, *J* = 8.4 Hz, Ar-H), 7.41–7.31 (5H, m, Ar-H), 7.24 (2H, d, *J* = 7.8 Hz, Ar-H), 4.75 (1H, q, *J* = 7.2 Hz, CH), 4.36 (3H, s, NH, CH_2), 2.39 (3H, s, CH_3), 1.54 (3H, d, *J* = 7.2 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.8, 164.6, 143.9, 136.6, 135.6, 129.7, 129.1, 128.8, 128.2, 127.1, 45.5, 36.7, 21.6, 20.4. EI-MS [m/z (%)]: 389 [M^+], 234 (2), 198 (10), 155 (18), 91 (100), 77 (4), 65 (20). Anal. calcd. for $C_{18}H_{19}N_3O_3S_2$ (389.49): C, 55.51; H, 4.92; N, 10.79%. Found: C, 55.70; H, 4.99; N, 10.52%.

N-[1-(5-(4-Bromobenzylthio)-1,3,4-oxadiazol-2-yl) ethyl]-4-methylbenzenesulphonamide (5b)

Yield: 0.335 g (80%); m.p. 135–137°C; R_f: 0.56 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3142, 1593, 1578, 1334, 1167, 1093, 1032. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (2H, d, *J* = 8.1 Hz, Ar-*H*), 7.46 (2H, d, *J* = 8.4 Hz, Ar-H), 7.24–7.30 (4H, m, Ar-*H*), 4.74 (1H, q, *J* = 6.9 Hz, CH), 4.50 (1H, s, NH), 4.31 (2H, s, CH_2), 2.39 (3H, s, CH_3), 1.53 (3H, d, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.0, 164.3, 143.9, 136.6, 134.5, 131.9, 130.8, 129.7, 127.1, 122.2, 45.5, 35.9, 21.6, 20.3; EI-MS [m/z (%)]: 467 /469 [M^+], 314/312 (3), 298 (1), 198 (41), 171 /169 (90), 155 (53), 91 (100), 65 (27). Anal. calcd. for $C_{18}H_{18}BrN_3O_3S_2$ (456.38): C, 46.16; H, 3.87; N, 8.97%. Found: C, 45.47; H, 3.96; N, 8.76%.

N-[1-(5-(4-Fluorobenzylthio)-1,3,4-oxadiazol-2-yl) ethyl]-4-methylbenzenesulphonamide (5c)

Yield: 0.36 g (96%); m.p. 106–108°C; R_f: 0.57 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3283, 1597, 1575, 1336, 1223, 1150, 1086. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.4 Hz, Ar-*H*), 7.36–7.40 (2H, m, Ar-H), 7.25 (2H, d, *J* = 8. Hz, Ar-H), 7.05 (2H, at, *J* = 8.4 Hz, Ar-H), 4.74 (1H, q, *J* = 6. Hz, CH), 4.41 (2H, s, CH_2), 4.35 (1H, s, NH), 2.39 (3H, s, CH_3), 1.54 (3H, d, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.0, 164.5, 162.0 (*J* = 246.0 Hz), 144.0, 136.6, 131.2 (*J* = 3.7 Hz), 130.9 (*J* = 8.2 Hz), 129.0, 127.0, 115.7 (^2J = 21.7 Hz), 45.5, 35.8, 21.6, 20.4. EI-MS [m/z (%)]: 407 (1), 392 (1), 252 (2), 198 (20), 155 (25), 109 (100), 91 (32), 65 (15). Anal. calcd. for $C_{18}H_{19}FN_3O_3S_2$ (408.49): C, 53.06; H, 4.45; N, 10.31%. Found: C, 52.48; H, 4.53; N, 10.09%.

N-[1-(5-(4-Chlorobenzylthio)-1,3,4-oxadiazol-2-yl) ethyl]-4-methylbenzenesulphonamide (5d)

Yield: 0.319 g (82%); m.p. 103–105°C; R_f: 0.57 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3134, 1597, 1578, 1334, 1167, 1129, 1092, 1032. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.4 Hz, Ar-H), 7.35 (2H, d, *J* = 8.7 Hz Ar-H), 7.30 (2H, d, *J* = 8.7 Hz, Ar-H), 7.25 (2H, d, *J* = 8.1 Hz, Ar-H), 4.75 (1H, q, *J* = 6.9 Hz, CH), 4.61 (1H, s, NH), 4.33 (2H, s, CH_2), 2.39 (3H, s, CH_3), 1.53 (3H, d, *J* = 7.2 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.9, 164.4, 143.9, 136.6, 134.1, 134.0, 130.5, 129.7, 128.9, 127.1, 45.5, 35.8, 21.6, 20.3. EI-MS (m/z %) 423/425 [M^+], 268 (1), 198 (19), 155 (32), 125/127 (100), 113/111 (2), 91 (60), 65 (17). Anal. calcd. for $C_{18}H_{18}ClN_3O_3S_2$ (423.94): C, 51.00; H, 4.28; N, 9.91%. Found: C, 51.00; H, 4.31; N, 9.83%.

N-[1-(5-Benzylthio-1,3,4-oxadiazol-2-yl)ethyl]-4-chlorobenzenesulphonamide (5e)

Yield: 0.233 g (62%); m.p. 98–100°C; R_f: 0.49 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3243, 1580, 1568, 1330, 1165, 1083. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.44 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.31–7.40 (5H, m, Ar-H), 4.81 (1H, s, NH), 4.75 (1H, q, *J* = 7.2 Hz, CH), 4.39 (2H, s, CH_2), 1.58 (3H, d, *J* = 7.2 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.5, 164.9, 139.5, 138.2, 135.1, 129.4, 129.1, 128.8, 128.6, 128.2, 45.6, 36.7, 20.3. EI-MS [m/z (%)]: 409 [M^+], 332 (1), 218 (10), 177/175 (16), 113/111 (25), 91 (100), 77 (6), 65 (16). Anal. calcd. for $C_{17}H_{16}ClN_3O_3S_2$ (409.91): C, 49.81; H, 3.93; N, 10.25%. Found: C, 49.67; H, 4.00; N, 10.00%.

N-[1-(5-(4-Bromobenzylthio)-1,3,4-oxadiazol-2-yl) ethyl]-4-chlorobenzenesulphonamide (5f)

Yield: 0.292 g (65%); m.p. 114–116°C; R_f: 0.50 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3225, 1585, 1510, 1342, 1171, 1083, 1032. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.4 Hz, Ar-H), 7.44 (4H, d, *J* = 9.0 Hz, Ar-H), 7.29 (2H, d, *J* = 8.1 Hz, Ar-H), 5.83 (1H, d, *J* = 8.7 Hz, NH), 4.78 (1H, aq, *J* = 6.9 Hz, CH), 4.33 (2H, s, CH_2), 1.57 (3H, d, *J* = 7.2 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.6, 164.6, 139.5, 138.1, 134.3, 131.9, 130.8, 129.4, 128.6, 122.3, 45.6, 35.9, 20.2. EI-MS [m/z (%)]: 489 /487 [M^+], 288 /286 (2), 218 (13), 175 (22), 171 /169 (100), 111 (48), 75 (20), 28 (17). Anal. calcd. for $C_{17}H_{15}BrClN_3O_3S_2$ (488.81): C, 41.77; H, 3.09; N, 8.60%. Found: C, 42.01; H, 3.15; N, 8.80%.

N-[1-(5-(4-Fluorobenzylthio)-1,3,4-oxadiazol-2-yl) ethyl]-4-chlorobenzenesulphonamide (5g)

Yield: 0.232 g (59%); m.p. 92–94°C; R_f: 0.48 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3274, 1599, 1569, 1331, 1158, 1229, 1089. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8. Hz, Ar-H), 7.43 (2H, d, *J* = 8.7 Hz, Ar-H), 7.36–7.39 (2H, m, Ar-H), 7.03 (2H, at, *J* = 8.4 Hz, Ar-H), 6.05 (1H, d, *J* = 8.1 Hz, NH), 4.79 (1H, at, *J* = 7.2 Hz, CH), 4.35 (2H, s, CH_2), 1.57 (3H, d, *J* = 6.9 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.6, 164.7, 162 (^1J = 246 Hz), 139.5, 138.2, 131.0 (overlapped), 130.9 (^3J = 8.2 Hz), 129.4, 128.6, 115.8 (^2J = 21.7 Hz), 45.5, 35.9, 20.1. EI-MS [m/z (%)]: 427 [M^+], 332 (1), 252 (2), 218 (8), 175 (12), 109 (100); Anal. calcd. for $C_{17}H_{15}ClFN_3O_3S_2$ (427.9): C, 47.72; H, 3.53; N, 9.82%. Found: C, 48.08; H, 3.79; N, 9.65%.

N-[1-(5-(4-Chlorobenzylthio)-1,3,4-oxadiazol-2-yl) ethyl]-4-chlorobenzenesulphonamide (5h)

Yield: 0.236 g (63%); m.p. 87–89°C; R_f: 0.47 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): δ3129, 1577, 1332, 1170, 1083, 1032. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* = 8.7 Hz, Ar-H), 7.44 (2H, d *J* = 8.7 Hz Ar-H), 7.31 (2H, d, *J* = 8.7 Hz, Ar-H);7.36 (2H, d, *J* = 8.7 Hz, Ar-H), 5.58 (1H, s, NH), 4.75 (1H, q, *J* = 6.9 Hz, CH); 4.35 (2H, s, CH_2), 1.58

(3H, d, J=7.2 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.5, 164.6, 139.6, 138.1, 134.2, 133.7, 130.6, 129.4, 129.0, 128.6, 45.5, 35.9, 20.3. EI-MS [m/z (%)]: 218 (12), 175 (24), 159/157 (4), 127/125 (100), 113/111 (39). Anal. calcd. for $C_{17}H_{15}ClN_3O_3S_2$ (408.9): C, 45.95; H, 3.40; N, 9.46%. Found: C, 46.29; H, 3.65; N, 8.94%.

N-[1-(5-Benzylthio-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-methylbenzenesulphonamide (5i)

Yield: 0.256 g (62%); m.p. 120–122°C; R_f: 0.52 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3280, 1596, 1327, 1153, 1083. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68 (2H, d, J=8.4 Hz, Ar-H), 7.31–7.41 (5H, m, Ar-H), 7.23 (2H, d, J=8.1 Hz, Ar-H), 5.70 (1H, d, J=9.3 Hz, NH), 4.83 (1H, m, CH), 4.36 (2H, s, CH_2), 2.55 (2H, m, CH_2), 2.38 (3H, s, CH_3), 2.16–2.08 (2H, m, CH_2), 2.05 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.0, 164.6, 143.9, 136.5, 135.0, 129.7, 129.1, 128.8, 128.2, 127.1, 48.6, 36.7, 33.2, 29.6, 21.6, 15.3. EI-MS [m/z (%)]: 358 (4), 326 (3), 312 (25), 171 (2), 155 (11), 109 (100), 91 (40), 75 (10), 61 (38). Anal. calcd. for $C_{20}H_{23}N_3O_3S_3$ (449.61): C, 53.43; H, 5.16; N, 9.35%. Found: C, 53.45; H, 5.15; N, 9.10%.

N-[1-(5-(4-Bromobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-methylbenzenesulphonamide (5j)

Yield: 0.33 g (68%); m.p. 119–121°C; R_f: 0.55 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3264, 1597, 1327, 1153, 1080, 1069. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (2H, d, J=8.4 Hz, Ar-H), 7.47 (2H, d, J=8.4 Hz, Ar-H), 7.22–7.29 (4H, m, Ar-H), 5.70 (1H, d, J=9.3 Hz, NH), 4.83 (1H, m, CH), 4.31 (2H, s, CH_2), 2.53 (2H, t, J=6.9 Hz, CH_2), 2.38 (3H, s, CH_3), 2.16–2.08 (2H, m, CH_2), 2.04 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.3, 164.3, 143.9, 136.5, 134.5, 131.9, 130.8, 129.7, 127.1, 122.2, 48.5, 35.9, 33.1, 29.6, 21.6, 15.3. EI-MS [m/z (%)]: 372 /370 (27), 300 /298 (36), 258 (5), 169 /171 (85), 91 (100), 75 (18), 65 (21), 61 (82), 28 (95). Anal. calcd. for $C_{20}H_{22}BrN_3O_3S_3$ (528.51): C, 45.45; H, 4.20; N, 7.95%. Found: C, 45.32; H, 4.24; N, 7.60%.

N-[1-(5-(4-Fluorobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-methylbenzenesulphonamide (5k)

Yield: 0.342 g (78%); m.p. 108–110°C; R_f: 0.45 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3262, 1597, 1569, 1326, 1154, 1142, 1089. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (2H, d, J=8.4 Hz, Ar-H), 7.35–7.40 (2H, m, Ar-H), 7.24 (2H, d, J=8.1 Hz, Ar-H), 7.03 (2H, at, J=8.7 Hz, Ar-H), 5.42 (1H, s, NH), 4.83 (1H, at, J=7.2 Hz, CH), 4.34 (2H, s, CH_2), 2.54 (2H, t, J=6.7 Hz, CH_2), 2.39 (3H, s, CH_3), 2.16–2.06 (2H, m, CH_2), 2.04 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.2, 164.5, 162.0 (J=246 Hz), 149.3, 136.5, 131.1 (J=3.0 Hz), 130.9 (J=8.2 Hz), 129.7, 127.1, 115.7 (J=21.7 Hz), 48.6, 35.9, 33.1, 29.6, 21.6, 15.3. EI-MS [m/z (%)]: 358 (4), 326 (3), 312 (25), 171 (2), 155 (11), 109 (100), 91 (40), 75 (10), 61 (38). Anal. calcd. for $C_{20}H_{22}FN_3O_3S_3$ (467.6): C, 51.37; H, 4.74; N, 8.99%. Found: C, 51.39; H, 4.91; N, 8.77%.

N-[1-(5-(4-Chlorobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-methylbenzenesulphonamide (5l)

Yield: 0.338 g (76%); m.p. 114–116°C; R_f: 0.45 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3261, 1596, 1567, 1325, 1153, 1089, 1039. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (2H, d, J=8.4Hz, Ar-H), 7.35 (2H, d, J=8.1 Hz, Ar-H), 7.31 (2H, d, J=9.0 Hz, Ar-H), 7.24 (2H, d, J=8.1 Hz, Ar-H), 4.83 (1H, at, J=6.9 Hz, CH), 4.81 (1H, s, NH), 4.33 (2H, s, CH_2), 2.53 (2H, t, J=6.9 Hz, CH_2), 2.39 (3H, s, CH_3), 2.16–2.06 (2H, m, CH_2), 2.04 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.2, 164.4, 143.9, 136.5, 134.1, 133.9, 130.5, 129.7, 129.1, 127.1, 48.6, 35.9, 33.1, 29.6, 21.6, 15.3; EI-MS [m/z (%)]: 358 (2), 328 (28), 313 (2), 155 (15), 125 (100), 91 (72), 65 (12), 61 (65). Anal. calcd. for $C_{20}H_{22}ClN_3O_3S_3$ (484.05): C, 49.63; H, 4.58; N, 8.68%. Found: C, 50.00; H, 4.73; N, 8.73%.

N-[1-(5-Benzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-chlorobenzenesulphonamide (5m)

Yield: 0.25 g (58%); m.p. 102–104°C; R_f: 0.48 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3132, 1579, 1338, 1167, 1083. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (2H, d, J=8.7 Hz, Ar-H), 7.44 (2H, d, J=8.7Hz, Ar-H), 7.33–7.38 (5H, m, Ar-H), 5.71 (1H, d, J=9.3 Hz, NH), 4.88 (1H, m, CH), 4.39 (2H, s, CH_2), 2.58 (2H, t, J=7.2 Hz, CH_2), 2.10–2.18 (2H, m, CH_2), 2.08 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.5, 165.0, 139.6, 137.9, 134.9, 129.4, 129.1, 128.8, 128.6, 128.2, 48.6, 36.8, 33.0, 29.6, 15.4. EI-MS [m/z (%)]: 294 (52), 111 (5), 91 (100), 65 (20), 28 (51). Anal. calcd. for $C_{19}H_{20}ClN_3O_3S_3$ (470.03): C, 48.55; H, 4.29; N, 8.94%. Found: C, 47.98; H, 4.38; N, 8.52%.

N-[1-(5-(4-Bromobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-chlorobenzenesulphonamide (5n)

Yield: 0.308 g (61%); m.p. 98–100°C; R_f: 0.48 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3150, 1575, 1330, 1163, 1084, 1070. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (2H, d, J=8.7 Hz, Ar-H), 7.48 (2H, d, J=8.4 Hz, Ar-H), 7.43 (2H, d, J=8.4 Hz, Ar-H), 7.29 (2H, d, J=8.4 Hz, Ar-H), 4.86 (1H, at, J=6.9 Hz, CH), 4.45 (1H, s, NH), 4.33 (2H, s, CH_2), 2.54 (2H, t, J=6.6 Hz, CH_2), 2.09–2.16 (2H, m, CH_2), 2.05 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.2, 164.6, 139.5, 138.2, 134.2, 132.0, 129.4, 128.9, 128.6, 122.3, 48.7, 36.0, 33.0, 29.6, 15.3; EI-MS [m/z (%)]: 346 (3), 171/169 (100), 111 (10), 75 (16), 28 (62). Anal. calcd. for $C_{19}H_{19}BrClN_3O_3S_3$ (548.92): C, 41.57; H, 3.49; N, 7.65%. Found: C, 41.60; H, 3.52; N, 7.55%.

N-[1-(5-(4-Fluorobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-chlorobenzenesulphonamide (5o)

Yield: 0.246 g (55%); m.p. 94–96°C; R_f: 0.48 (*n*-hexane: ethyl acetate 3: 2); IR (υ_{max}, cm^{-1}): 3226, 1573, 1326, 1227, 1165, 1084. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, J=8.7 Hz, Ar-H), 7.43 (2H, d, J=8.7 Hz, Ar-H), 7.37–7.40

(2H, m, Ar-H), 7.04 (2H, at, J = 8.4 Hz, Ar-H), 4.88 (1H, at, J = 7.2 Hz, CH), 4.37 (3H, s, CH_2, NH), 2.57 (2H, t, J = 6.9 Hz, CH_2), 2.10–2.18 (2H, m, CH_2), 2.07 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.8, 164.8, 163.0 (J = 246 Hz), 139.6, 138.0, 130.9 (J = 8.4 Hz), 312 (21), 191 (3), 175 (10), 109 (100), 111 (20), 75 (10), 61 (35). 130.9, 129.4, 128.6, 115.8 (J = 21 Hz), 48.6, 35.9, 32.9, 29.6, 15.4. EI-MS [m/z (%)]: 378 (3), 346 (2). Anal. calcd. for $C_{19}H_{19}ClFN_3O_3S_3$ (488.02): C, 46.76; H, 3.92; N, 8.61%. Found: C, 46.96; H, 3.90; N, 8.49%.

N-[1-(5-(4-Chlorobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-chlorobenzenesulphonamide (5p)

Yield: 0.233 g (54%); m.p. 85–87°C; R_f: 0.48 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3241, 1574, 1326, 1190, 1165, 1093; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, J = 8.7 Hz, Ar-H), 7.43 (2H, d, J = 8.7 Hz, Ar-H), 7.35 (2H, d, J = 8.7 Hz, Ar-H), 7.31 (2H, d, J = 8.7 Hz, Ar-*H*), 4.92 (1H, s, NH), 4.88 (1H, at, J = 7.5 Hz, CH), 4.35 (2H, s, CH_2), 2.65 (2H, t, J = 6.9 Hz, CH_2), 2.10–2.18 (2H, m, CH_2), 2.06 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.9, 164.7, 139.6, 137.9, 134.2, 133.7, 130.5, 129.4, 129.0, 128.6, 48.5, 35.9, 32.9, 29.6, 15.4. EI-MS [m/z (%)]: 278 (12), 175 (14), 127/125 (10), 113/111 (45), 73 (91), 61 (100), 28 (35). Anal. calcd. for $C_{19}H_{20}ClN_3O_3S_3$ (470.03): C, 45.52; H, 3.80; N, 8.33%. Found: C, 46.02; H, 3.87; N, 8.35%.

N-[1-(5-Benzylthio)-1,3,4-oxadiazol-2-yl)-2-phenylethyl]-4-methylbenzenesulphonamide (5q)

Yield: 0.325 g (76%); m.p. 155–157°C; R_f: 0.47 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3210, 1570, 1330, 1163, 1088. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (2H, d, J = 8.4 Hz, Ar-H), 7.34–7.38 (5H, m, Ar-*H*), 7.21–7.24 (3H, m, Ar-H), 7.17 (2H, d, J = 8.1 Hz, Ar-H), 6.98–7.01 (2H, m, Ar-H), 5.02 (1H, s, NH), 4.88 (1H, aq, J = 6.9 Hz, CH), 4.33 (2H, s, CH_2), 3.16 (2H, m, CH_2), 2.37 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.8, 164.5, 143.9, 136.1, 135.2, 134.1, 129.7, 129.3, 129.1, 128.9, 128.8, 128.3, 127.6, 127.1, 50.7, 40.4, 36.7, 21.6. EI-MS [m/z (%)]: 374 (20), 310 (13), 274 (3), 155 (24), 91 (100), 77 (3), 65 (14). Anal. calcd. for $C_{24}H_{23}N_3O_3S_2$ (465.59): C, 61.91; H, 4.98; N, 9.03%. Found: C, 62.46; H, 5.37; N, 9.02%.

N-[1-(5-(4-Bromobenzylthio)-1,3,4-oxadiazol-2-yl)-2-phenylethyl]-4-methylbenzenesulphonamide (5r)

Yield: 0.37 g (74%); m.p. 150–152°C; R_f: 0.47 (*n*-hexane: ethyl acetate; 3: 2); IR (υ_{max}, cm^{-1}): 3256, 1595, 1567, 1330, 1162, 1091, 1075. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (2H, d, J = 8.4 Hz, Ar-H), 7.48 (2H, d, J = 8.4 Hz, Ar-H), 7.22–7.25 (3H, m, Ar-H), 7.18 (2H, d, J = 8.1 Hz, Ar-H), 7.05 (2H, d, J = 8.7 Hz, Ar-H), 6.97–7.01 (2H, m, Ar-H), 5.18 (1H, d, J = 8.7 Hz, NH), 4.87 (1H, aq, J = 6.9 Hz, CH), 4.29 (2H, s, CH_2), 3.09–3.22 (2H, m, CH_2), 2.38 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.0, 164.2, 143.9, 136.1, 134.5, 134.1, 132.0, 130.8, 129.7, 129.3, 128.9, 127.6, 127.1, 122.3, 50.7, 40.3, 35.9, 21.6. EI-MS (m/z %) 274 (3), 171/169 (100), 155 (11), 91 (60), 65 (22). Anal. calcd. for $C_{24}H_{22}BrN_3O_3S_2$ (544.48): C, 52.94; H, 4.07; N, 7.72%. Found: C, 52.94; H, 4.30; N, 7.57%.

N-[1-(5-(4-Fluorobenzylthio)-1,3,4-oxadiazol-2-yl)-2-phenylethyl]-4-methylbenzenesulphonamide (5s)

Yield: 0.355 g (80%); m.p. 140–142°C; R_f: 0.47 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3129, 1599, 1540, 1331, 1226, 1157, 1089. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 (2H, d, J = 8.4 Hz, Ar-H), 7.36 (2H, m, Ar-H), 7.22–7.24 (3H,m, Ar-*H*), 7.18 (2H, d, J = 8.1 Hz, Ar-H), 7.03 (2H, at, J = 8.7 Hz, Ar-H), 6.97–6.99 (2H, m, Ar-H), 5.18 (1H, d, J = 8.4 Hz, NH), 4.87 (1H, aq, J = 6.9 Hz, CH), 4.32 (2H, s, CH_2), 3.09–3.22 (2H, m, CH_2), 2.38 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.9, 164.3, 162.5 (J = 243 Hz), 143.9, 136.1, 134.1, 131.2 (J = 3.7 Hz), 130.9 (J = 7.5 Hz), 129.7, 129.3, 128.9, 127.6, 127.1, 50.7, 40.3, 35.9, 21.6. EI-MS [m/z (%)]: 483 [M$^+$], 392 (22), 328 (18), 274 (5), 155 (51), 109 (100), 91 (95), 65 (15). Anal. calcd. for $C_{24}H_{22}FN_3O_3S_2$ (483.58): C, 59.61; H, 4.59; N, 8.69%. Found: C, 60.03; H, 4.74; N, 8.75%.

N-[1-(5-(4-Chlorobenzylthio)-1,3,4-oxadiazol-2-yl)-2-phenylethyl]-4-methylbenzenesulphonamide (5t)

Yield: 0.345 mg (75%); m.p: 146–148° C; R_f: 0.47 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 3139, 1598, 1568, 1331, 1163, 1090, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 (2H, d, J = 8.1Hz, Ar-H), 7.30 (4H, m, Ar-H), 7.21–7.23 (3H, m, Ar-H), 7.18 (2H, d, J = 8.4 Hz, Ar-H), 6.97–6.99 (2H, m, Ar-H), 5.18 (1H, d, J = 8.4 Hz, NH), 4.87 (1H, at, J = 6.9 Hz, CH), 4.31 (2H, s, CH_2), 3.08–3.23 (2H, m, CH_2), 2.38 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.1, 164.2, 143.9, 136.2, 134.2, 134.1, 133.9, 130.5, 129.7, 129.3, 129.0, 128.9, 127.6, 127.1, 50.7, 40.3, 35.9, 21.6.; EI-MS [m/z (%)]: 499 [M$^+$], 410/408 (23), 344 (15), 155 (48), 127/125 (80), 91 (100), 65 (14). Anal. calcd. for $C_{24}H_{22}ClN_3O_3S_2$ (500.03): C, 57.65; H, 4.43; N, 8.40%. Found: C, 57.03; H, 4.51; N, 8.26%.

Synthesis of 2-{*N*-[4-halobenzyl]-1-(4-chloro/methyl-phenylsulphonylamino)alkyl}-5-benzylthio-1,3,4-oxadiazoles (6a-d)

Compounds **6a–d** were prepared by following the same procedure as for the preparation of **5a–d** from treatment of **4a–e** with 1.1 mol. eq. of 4-halobenzyl halides to give a mixture of mono- and disubstituted products. Compounds **5** and **6** were separated by SiO_2 column chromatography, using *n*-hexane and ethyl acetate (4:1) as an eluent.

N-(4-Bromobenzyl)-*N*-[1-(5-(4-bromobenzylthio)-1,3,4-oxadiazol-2-yl)ethyl]-4-methylbenzenesulphonamide (6a)

Yield: 0.135 g (23%); m.p. 156–158°C; R_f: 0.64 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 2982, 1593, 1565, 1486, 1469, 1327, 1155, 1070. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (2H, d, J = 8.1 Hz, Ar-H), 7.49 (2H, d, J = 8.4 Hz, Ar-H), 7.30–7.36 (6H, m, Ar-H), 7.10 (2H, d, J = 8.1 Hz, Ar-H), 5.36 (1H, q, J = 6.9 Hz, CH), 4.47 (1H, d, J = 15.9 Hz, CH), 4.30

(1H, d, J=15.2 Hz, CH), 4.26 (2H, s, CH_2), 2.45 (3H, s, CH_3), 1.46 (3H, d, J=6.9 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.8, 164.7, 144.1, 136.9, 135.3, 134.5, 131.9, 130.9, 129.9, 129.8, 127.2, 122.2, 121.7, 48.5, 47.3, 35.8, 21.6, 15.7. EI-MS [m/z (%)]: 281 (6), 212/210 (11), 198 (25), 171/169 (65), 155 (145), 133 (27), 91 (100), 73 (10), 65 (18), 28 (85). Anal. calcd. for $C_{25}H_{23}Br_2N_3O_3S_2$ (639.42): C, 47.11; H, 3.64; N, 6.59%. Found: C, 45.37; H, 3.45; N, 5.94%.

N-(4-Bromobenzyl)-*N*-[1-(5-(4-bromobenzylthio)-1,3,4-oxadiazol-2-yl)ethyl]-4-chlorobenzenesulphonamide (6b)

Yield: 0.125 g (19%); m.p. 144–146°C; R_f: 0.65 (*n*-hexane: ethyl acetate; 3:2); IR (υ_{max}, cm^{-1}): 2990, 1596, 1570, 1480, 1468, 1331, 1156, 1069. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, J=8.7 Hz, Ar-H), 7.48 (4H, d, J=8.7 Hz, Ar-H), 7.37 (2H, d, J=8.4 Hz, Ar-H), 7.31 (2H, d, J=8.4 Hz, Ar-H), 7.11 (2H, d, J=8.1 Hz, Ar-H), 5.35 (1H, q, J=7.2 Hz, CH), 4.32 (1H, d, J=15.7 Hz, CH), 4.31 (1H, d, J=17.1 Hz, CH), 4.30 (2H, s, CH_2), 1.49 (3H, d, J=7.2 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.5, 164.9, 139.7, 138.3, 134.9, 134.4, 131.9, 131.6, 130.9, 129.8, 129.6, 128.6, 122.2, 121.9, 48.8, 47.6, 35.8, 16.2; EI-MS [m/z (%)]: 300/298 (70), 212/210 (30), 183 (5), 171/169 (100), 143 (12), 89 (31), 75 (15), 63 (20). Anal. calcd. for $C_{24}H_{20}Br_2ClN_3O_3S_2$ (659.84): C, 43.82; H, 3.06; N, 6.39%. Found: C, 44.14; H, 3.47; N, 6.03%.

N-(4-Fluorobenzyl)-*N*-[1-(5-(4-fluorobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]-4-methylbenzenesulphonamide (6c)

Yield: 0.143 g (27%); brownish oil; R_f: 0.65 (*n*-hexane: ethyl acetate 3:2); IR (υ_{max}, cm^{-1}): 2950, 1597, 1560, 1486, 1472, 1340, 1158, 1069. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (2H, d, J=8.4 Hz, Ar-H), 7.48 (2H, d, J=8.7 Hz, Ar-H), 7.37–7.42 (2H, m, Ar-H), 7.30 (2H, d, J=8.1 Hz, Ar-H), 7.05 (2H, at, J=8.4 Hz, Ar-H), 6.9 (2H, at, J=8.7 Hz, Ar-H), 5.39 (1H, t, J=7.5 Hz, CH), 4.38 (1H, d, J=15.9 Hz, CH), 4.30 (1H, d, J=15.2 Hz, CH), 4.30 (2H, s, CH_2), 2.30–2.55 (3H, m, CH_2, CH), 2.43 (3H, s, CH_3), 1.90–1.96 (1H, m, CH), 1.96 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.4, 164.0, 162.5 (J=246 Hz), 162.3 (J=245 Hz), 144.1, 136.8, 131.8 (J=3.7 Hz), 131.1 (J=3.7 Hz), 130.5 (J=8.2 Hz), 130.4 (J=8.2 Hz), 129.8, 127.3, 115.8 (J=21.7 Hz), 115.3 (J=21.7 Hz), 51.7, 48.4, 35.7, 30.2, 29.7, 21.6, 15.2. EI-MS [m/z (%)]: 500 (3), 420 (11), 297 (2), 155 (3), 109 (100), 91 (8), 65 (5), 61 (10).

N-(4-bromobenzyl)-*N*-[1-(5-(4-bromobenzylthio)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl-4-methylbenzenesulphonamide] (6d)

Yield: 0.109 g (17%); brownish oil; R_f: 0.63 (*n*-hexane: ethyl acetate 3:2); IR (υ_{max}, cm^{-1}): 2917, 1601, 1562, 1508, 1472, 1340, 1155, 1220. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (2H, d, J=8.4 Hz, Ar-H), 7.48 (2H, d, J=8.4 Hz, Ar-H), 7.37 (2H, d, J=8.4 Hz, Ar-H), 7.28–7.32 (4H, m, Ar-H), 7.15 (2H, d, J=8.4 Hz, Ar-H), 5.39 (1H, at, J=7.5 Hz, CH), 4.30 (1H, d, J=13.5 Hz, CH), 4.29 (1H, d, J=13.5 Hz, CH), 4.27 (2H, s, CH_2), 2.52–2.23 (3H, m, CH_2, CH), 2.43 (3H, s, CH_3), 1.89–1.96 (1H, m, CH), 1.95 (3H, s, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.7, 144.1, 136.7, 135.5, 134.4, 131.9, 131.6, 130.9, 130.1, 129.9, 127.3, 122.3, 121.9, 51.8, 48.4, 35.8, 29.7, 21.6, 15.2. EI-MS [m/z (%)]: 697/695 (2), 276/274 (2), 186/184 (95),157/155 (20), 75 (31), 65 (45), 28 (15).

X-ray structure determinations

Crystal data and refinement details are presented in Table 1. *Data collection and reduction*: Crystals were mounted in inert oil on glass fibres and transferred to the cold gas stream of an Oxford Diffraction diffractometer (**5b**: Xcalibur S with monochromated Mo-$K\alpha$ radiation, λ=0.71073 Å; **5l**: Xcalibur Nova E with mirror-focussed Cu-$K\alpha$ radiation, λ=1.54184 Å). Absorption corrections were performed on the basis of multi-scans. *Structure refinement*: The structures were refined anisotropically against F^2 (program SHELXL-97[19]). Hydrogens of NH groups were refined freely; methyl groups were refined as idealized rigid groups allowed to rotate but not tip; other hydrogen atoms were included with a riding model. For **5b**, restraints to displacement parameters were employed to improve stability of refinement. For both structures, the absolute configuration was confirmed by the *Flack* parameter.

Table 1. Crystallographic data for compounds **5b** and **5l.**

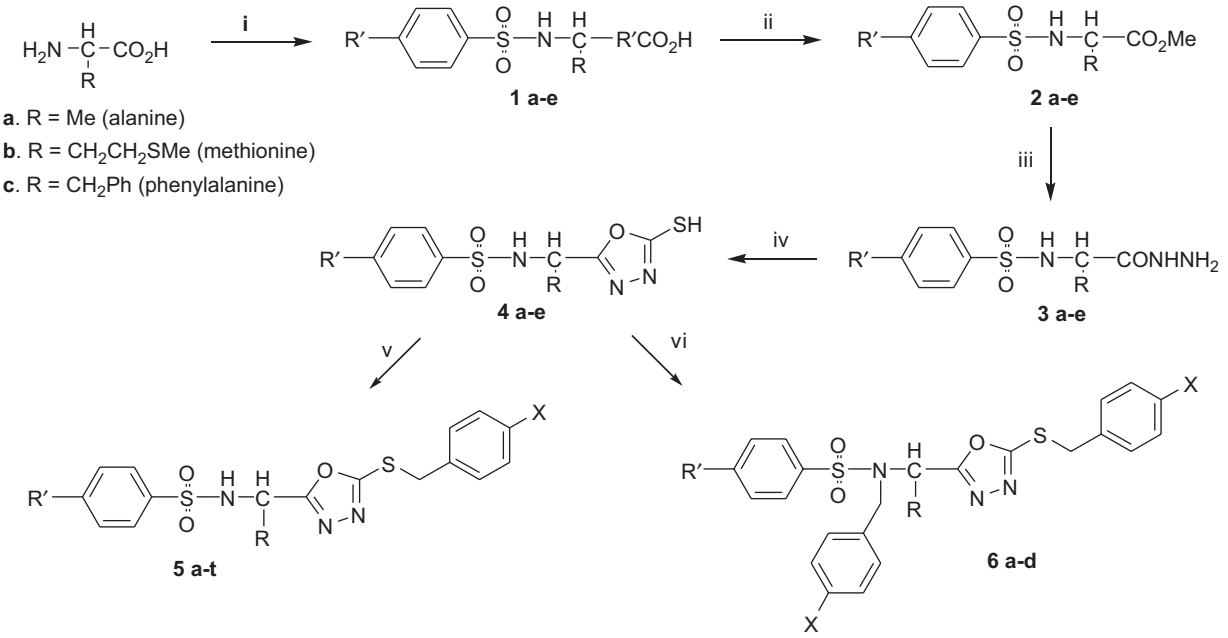
Data	**5b**	**5l**
Formula	$C_{18}H_{18}BrN_3O_3S_2$	$C_{20}H_{22}ClN_3O_3S_3$
M_r	468.38	484.04
Habit	Colourless tablet	Colourless tablet
Crystal size (mm)	0.2×0.2×0.1	0.2×0.2×0.1
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
Cell constants		
a (Å)	5.5822 (1)	14.8104 (5)
b (Å)	17.8004 (3)	5.1998 (2)
c (Å)	20.1547 (4)	15.9657 (6)
α (°)	90	90
β (°)	90	111.615 (4)
γ (°)	90	90
V (Å^3)	2002.68	1143.08
Z	4	2
D_x (Mg m^{-3})	1.553	1.406
μ (mm^{-1})	2.29	4.27
Radiation	Mo-$K\alpha$	Cu-$K\alpha$
Wavelength (Å)	0.71073	1.54184
F(000)	952	504
T (°C)	–173	–173
$2\theta_{max}$	60	152
Completeness (%)	99.7	99.9 (to 2θ 145°)
Reflux measured	102274	24447
Reflux independant	5848	4320
R_{int}	0.039	0.037
Parameters	250	277901
Restraints	162	1
wR (F^2, all refluxes)	0.040	0.064
R (F, >4σ (F))	0.020	0.024
Flack parameter	–0.006 (3)	0.007 (10)
S	0.97	1.04
maximum $\Delta\rho$ (e Å^{-3})	0.50	0.22

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the numbers CCDC-762468 (**5b**) and 762469 (**5l**). Copies may be requested free of charge from http://www.ccdc.cam.ac.uk/products/csd/request/.

Results and discussion

Three different amino acids: L-alanine, L-methionine and L-phenylalanine (**a–c**) were selected in our present work to synthesize the desired chiral compounds. The L-amino acids were converted into the corresponding sulphonamides **1a–e** by reaction with 4-chlorobenzenesulfonyl chloride and 4-methylbenzenesulfonyl chloride (Scheme 1). Compounds **1a–e** were converted into their respective methyl esters **2a–e**[20], followed by treatment with the hydrazine hydrate to yield the corresponding acid hydrazides **3a–e**[21]. The hydrazides **3a–e** were cyclized to 1,3,4-oxadiazoles **4a–e**[22], using CS_2 in the presence of KOH. The 1,3,4-oxadiazoles **4a–e** were further derivatized with 4-substituted benzylhalides[13]. Thus, treatment of **4a–e** with a slight excess (1.1 equiv.) of 4-substituted benzyl halides resulted in the substitution at *S*- as well as *N*-(sulphonamide), giving a mixture of two products: *S*-substituted and *S*,*N*-disubstituted products. However, repetition of the experiment using equimolar ratios of 4-substituted benzylhalide and 1,3,4-oxadiazoles led to the *S*-substitution only and furnished **5a–t**.

The structures of **4a–e** were confirmed from the NMR, IR and mass spectra. In the IR spectra, the C=N absorption appeared in the region υ_{max} 1496–1462 cm^{-1} at the



	R	R′	X
1a-4a	Me	Me	-
1b-4b	Me	Cl	-
1c-4c	$(CH_2)_2SMe$	Me	-
1d-4d	$(CH_2)_2SMe$	Cl	-
1e-4e	CH_2Ph	Me	-
5a	Me	Me	H
5b	Me	Me	Br
5c	Me	Me	F
5d	Me	Me	Cl
5e	Me	Cl	H
5f	Me	Cl	Br
5g	Me	Cl	F
5h	Me	Cl	Cl
5i	$(CH_2)_2SMe$	Me	H
5j	$(CH_2)_2SMe$	Me	Br

	R	R′	X
5k	$(CH_2)_2SMe$	Me	F
5l	$(CH_2)_2SMe$	Me	Cl
5m	$(CH_2)_2SMe$	Cl	H
5n	$(CH_2)_2SMe$	Cl	Br
5o	$(CH_2)_2SMe$	Cl	F
5p	$(CH_2)_2SMe$	Cl	Cl
5q	CH_2Ph	Me	H
5r	CH_2Ph	Me	Br
5s	CH_2Ph	Me	F
5t	CH_2Ph	Me	Cl
6a	Me	Me	Br
6b	Me	Cl	Br
6c	$(CH_2)_2SMe$	Me	F
6d	$(CH_2)_2SMe$	Me	Br

Scheme 1. Reagents and conditions. (i) 4-Chloromethyl/methylbenzenesulphonyl chlorides, K_2CO_3, $CHCl_3$; (ii) MeOH, H_2SO_4, reflux 4 h; (iii) $N_2H_4.H_2O$, MeOH, reflux 3–4 h; (iv) CS2, KOH, MeOH, reflux 18–20 h; (v) 1.0 eq. $YCH_2C_6H_4X$, acetone, K_2CO_3, r.t.; (vi) 2.0 eq. $YCH_2C_6H_4X$, acetone, K_2CO_3, r.t.

expense of strong carbonyl absorption of the hydrazides **3a–e** (υ_{max} 1686–1664 cm^{-1}). The weak absorption for C-S in the range of υ_{max} 1291–1261 cm^{-1} was a further support for formation of the desired molecules. In the ^{1}H-NMR spectra, the signals at δ 14.38–9.30 ppm were assigned to the N-H proton. The two signals in the ^{13}C-NMR spectra at δ 178.6–178.0 ppm and δ 170.5–161.6 ppm were assigned to the C-2 and C-5 of the oxadiazole ring respectively. The mass spectra demonstrated a common fragment for **4a**, **4c** and **4e** at *m/z* 155 and for **4b** and **4d** at *m/z* 175, resulting by cleavage of the sulphonamide linkage. The base peak observed for compounds **4a–e** was attributed to the tropyllium cation at *m/z* 91 or the chlorotropyllium cation at *m/z* 127/125. Analogously, the structures of **5a–t** were confirmed by the ^{1}H-, ^{13}C-NMR and mass spectra. In the ^{1}H-NMR spectra of **5a–t**, two signals for four aromatic protons in the range δ 7.75–7.03 ppm together with two protons singlet (δ 4.88–4.74 ppm) assigned to the benzylic protons were observed. The ^{13}C-NMR spectra showed new signals corresponding to the methylene carbons of the benzyl group resonating in the range δ 48.6–45.5 ppm. In the mass spectra, the most abundant fragments were observed at *m/z* 91 or 90 + X (X = Cl). The fragments at *m/z* 155 (*R′* = CH_3) and *m/z* 175 (*R′* = Cl) were generated due to the cleavage of the sulphonamide moiety.

The synthesis of compounds **5a–t** was further confirmed by the single crystal X-ray structure analysis of compounds **5b** and **5l**. Compound **5b** (Figure 1) is a disc-shaped molecule in which all three rings lie at the periphery of the disc and are approximately perpendicular to the mean molecular plane (interplanar angles 86° to the five-membered ring, 81° to the ring C8–13, 86° to the ring C16–21). Compound **5l** is also disc-shaped, the height of the disc being approximately the breadth of a phenyl ring (Figure 2); the rings C10–15 and C18–23 subtend angles of 86° and 84°, respectively, to the mean molecular plane, but the angle from the five-membered ring is 27°. A least-squares fit of both molecules in the region C-5,6,7 and *N*-tosyl gives a root mean squared (RMS) deviation of 0.13 Å. Figure 3 shows clearly that the molecules differ significantly in the torsion angles involving the rotation of the five-membered ring (N5-C6-C5-O1 = -47.5° for **5b** and 65.9° for **5l**) and about the short C-S chain (C2-S1-C15-C16 -84.7° for **5b**, C2-S3-C17-C18 169.8° for **5l**). The crystallographic data for **5b** and **5l** are listed in Table 1.

The structures of the disubstituted 1,3,4-oxadiazole derivatives **6a–d** were confirmed by the NMR, IR and mass spectra. The IR spectra demonstrated the disappearance of NH stretchings in the range of υ_{max} 3256–3297 cm^{-1} with the appearance of the strong C–X (X = Cl, Br, F) absorptions in the range υ_{max} 1220–1069 cm^{-1}. The ^{1}H-NMR spectra of **6a–d** demonstrated eight additional aromatic protons in the range of δ 7.75–6.90 ppm, the singlets' oriented in the region δ 4.51–4.19 ppm corresponding to CH_2 protons of the benzylthio group, and the two doublets (^2J couplings) in the region δ 4.47–4.30 ppm

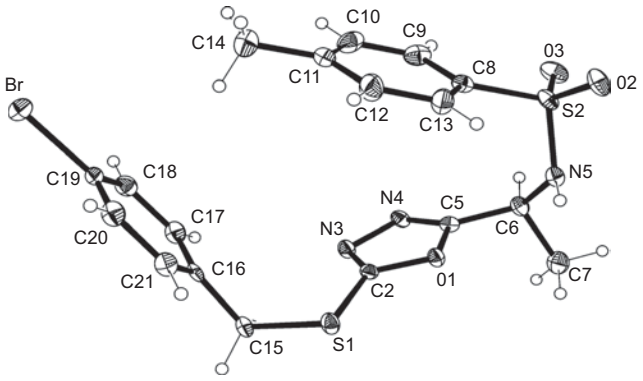


Figure 1. The molecule of compound **5b** in the crystal. Ellipsoids represent 50% probability levels.

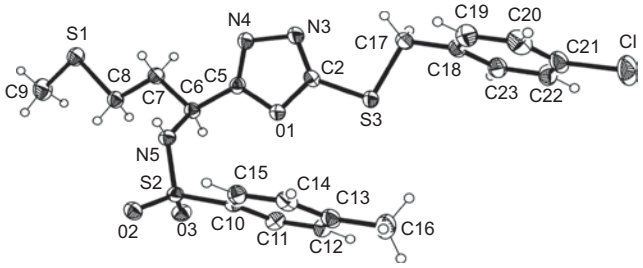


Figure 2. The molecule of compound **5l** in the crystal. Ellipsoids represent 50% probability levels.

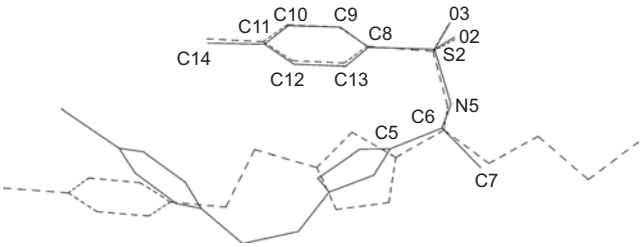


Figure 3. Least-squares fit of the *N*-tosyl regions of **5b** (numbered) and **5l** (dashed bonds).

attributed to the *N*-benzyl group. In the ^{13}C-NMR spectra, eight new signals corresponding to aromatic portion of halobenzyl groups were observed. Further, two methylene carbons appeared in the range of δ 51.7–47.3 ppm. In the mass spectra, the most abundant fragments were observed at *m/z* 91 or 90 + X.

In vitro anti-HIV assay

Compounds **5a–t** and **6a–d** were tested for their anti-HIV-1 and HIV-2 activity, *in vitro*, using III_B and ROD strain in human T-lymphocyte (MT-4) cells, and the results are summarized in Table 2, in which the data for Nevirapine (BOE/BIRG587[23]) and azidothymidine (DDN/AZT[24]) have been included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity. None of the new 1,3,4-oxadiazole derivatives were found to inhibit HIV-1 or HIV-2 replication, *in vitro*, at EC_{50} lower than the CC_{50} in comparison to the Nevirapine and AZT.

Table 2. *In vitro* anti-HIV-1[a] and HIV-2[b] of some new sulphonamide derivatives.

Compound	Virus strain	EC_{50} (μg/mL)[c]	CC_{50} (μg/mL)[d]	SI[e]
5a	III_B	>59.58	59.58	<1
	ROD	>59.58	59.58	<1
5b	III_B	>75.33	75.33	<1
	ROD	>75.33	75.33	<1
5c	III_B	>70.80	70.80	<1
	ROD	>70.80	70.80	<1
5d	III_B	>27.93	27.93	<1
	ROD	>27.93	27.93	<1
5e	III_B	>65.63	>65.63	<1
	ROD	>65.63	>65.63	<1
5f	III_B	>12.33	>12.33	<1
	ROD	>12.33	>12.33	<1
5g	III_B	>58.75	58.75	<1
	ROD	>58.75	>58.75	<1
5h	III_B	>14.08	14.08	<1
	ROD	>14.08	14.08	<1
5i	III_B	>30.48	30.48	<1
	ROD	>30.48	30.48	<1
5j	III_B	>11.75	11.75	<1
	ROD	>11.75	11.75	<1
5k	III_B	>11.50	≥11.50	<orX1
	ROD	>11.50	≥11.50	<orX1
5l	III_B	>13.00	13.00	<1
	ROD	>13.00	13.00	<1
5m	III_B	>12.67	12.67	<1
	ROD	>12.67	12.67	<1
5n	III_B	>12.30	12.30	<1
5o	ROD	>12.30	>12.30	<1
	III_B	>13.65	13.65	<1
	ROD	>13.65	13.65	<1
5p	III_B	>11.88	11.88	<1
	ROD	>11.88	11.88	<1
5q	III_B	>11.67	11.67	<1
	ROD	>11.67	11.67	<1
5r	III_B	>82.10	82.10	<1
	ROD	>82.10	82.10	<1
5s	III_B	>90.83	90.83	<1
	ROD	>90.83	90.83	<1
5t	III_B	>99.40	99.40	<1
	ROD	>99.40	99.40	<1
6a	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
6b	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
6c	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
6d	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
Nevirapine	III_B	0.050	>4.00	>80
	ROD	>4.00	>4.00	<1
DDN/AZT	III_B	0.0022	>25.00	>11587
	ROD	0.00094	>25.00	>26731

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.
[c]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect.
[d]Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e]SI, selectivity index (CC_{50}/EC_{50}).

Theoretical calculations and quantum structure-activity relationship

Semi-empirical self-consistent-field molecular orbital (SCF-MO) method at PM3[18] level within restricted Hartree–Fock[25]. Formalism has been considered to optimize fully the geometry of the 5-benzylthio-1,3,4-oxadiazole molecule in its ground state. Geometry optimization was carried out by using a conjugate gradient method (Polak-Ribiere algorithm[26]). The SCF convergence was set at 0.001 kcal/mol and the RMS gradient was set to 0.001 kcal/(mol) in the calculations.

We performed all the calculations using the HyperChem-7.52 program (Hypercube Inc., USA). In addition, the correlation analysis and the regression analysis for quantum parameters were performed by using Minitab program release 11.11 (Minitab Inc., USA). all calculations were performed on a windows XP workstation in Pentium IV PC.

Acceptability of the regression model was judged by examining the correlation coefficient (r), squared correlation coefficient (R^2), Fisher's value (F) and standard deviation (s). The selected descriptors have obtained and listed in Tables 3 and 4.

A data set of twenty compounds (**5a–5t)** concerning their anti-HIV activity was used for the present quantum structure-activity relationship (QSAR) study. QSAR studies of the 5-benzylthio-1,3,4-oxadiazoles series resulted in several QSAR equations. The four best equations are:

$$\mathrm{LogEC_{50}} = -26.1 - 0.128\,\mathrm{Log\,P} + 0.135\mu - 2.06\,\mathrm{E_{HOMO}} - 119\,\mathrm{N_{10}} \quad (1)$$
$$n = 20, s = 0.2243, r = 0.850, R^2 = 0.723, q^2 = 0.649, F = 9.79$$

$$\mathrm{LogEC_{50}} = -10.2 + 0.567\,\Delta\mathrm{E} - 0.0231\,\mathrm{P} - 0.00172\,\mathrm{S} - 126\,\mathrm{N_{10}} \quad (2)$$
$$n = 20, s = 0.2245, r = 0.850, R^2 = 0.722, q^2 = 0.648, F = 9.75$$

$$\mathrm{LogEC_{50}} = -11.9 - 0.606\,\mathrm{E_{HOMO}} - 0.0171\,\mathrm{P} - 0.00197\,\mathrm{S} - 133\,\mathrm{N_{10}} \quad (3)$$
$$n = 20, s = 0.2226, r = 0.853, R^2 = 0.727, q^2 = 0.654, F = 9.99$$

$$\mathrm{LogEC_{50}} = -17.3 - 1.25\,\mathrm{E_{HOMO}} + 0.147\,\mu - 0.00339\,\mathrm{S} - 121\,\mathrm{N_{10}} \quad (4)$$
$$n = 20, s = 0.2130, r = 0.866, R^2 = 0.750, q^2 = 0.683\,F = 11.25$$

In the above equations, n is the number of compounds used to derive the model and q^2 is the predictive capability.

All the four models have one outlier's compounds **6**, because their residual values exceeded twice the standard error of estimate. When this outlier has been removed from the data set, four highly significant equations (5, 6, 7 and 8 respectively) have been obtained.

$$\mathrm{LogEC_{50}} = -23.5 - 0.133\,\mathrm{Log\,P} - 1.87\,\mathrm{E_{HOMO}} + 0.038\,\mu - 115\,\mathrm{N_{10}} \quad (5)$$
$$n = 19, s = 0.1751, r = 0.913, R^2 = 0.834, q^2 = 0.787, F = 17.64$$

$$\mathrm{LogEC_{50}} = -13.5 + 1.03\,\Delta\mathrm{E} - 0.0433\,\mathrm{P} + 0.00055\,\mathrm{S} - 111\,\mathrm{N_{10}} \quad (6)$$
$$n = 19, s = 0.1798, r = 0.909, R^2 = 0.826, q^2 = 0.776, F = 16.56$$

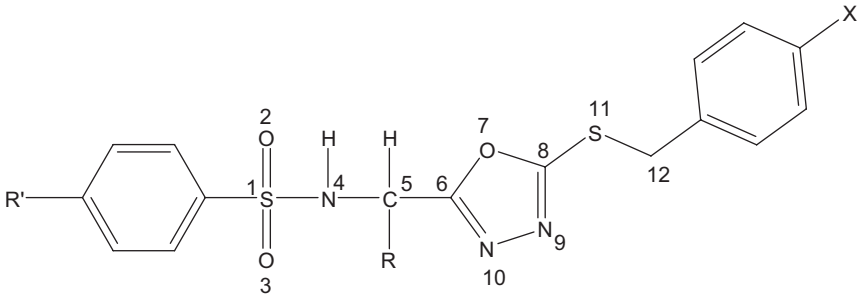
$$\mathrm{LogEC} - = -17.0 - 1.15\,\mathrm{E_{HOMO}} - 0.0341\,\mathrm{P} + 0.00033\,\mathrm{S} - 124\,\mathrm{N_{10}} \quad (7)$$
$$n = 19, s = 0.1694, r = 0.0.919, R^2 = 0.845, q^2 = 0.801, F = 19.08$$

Table 3. Calculated value of descriptors.

Compound	LogP	P	V	S	E_{HOMO}	E_{LUMO}	ΔE	E_{total}	μ	Binding energy	ΔH
75a	5.22	38.32	1095.9	611.90	−9.212	−0.995	8.217	−96002.3	4.015	−4719.94	−3.506
5b	6.01	40.95	1153	655.55	−9.32	−1.148	8.172	−103797.2	3.618	−4686.4	4.667
5c	5.36	38.23	1100.28	622.88	−9.366	−1.041	8.325	−105798.6	3.618	−4728.1	−44.92
5d	5.73	40.25	1130.56	645.94	−9.307	−1.013	8.294	−102950.7	3.508	−4701.0	−7.722
5e	5.27	38.42	1080.49	604.01	−9.321	−1.053	8.268	−99197.7	2.869	−4416.13	2.092
5f	6.06	41.04	1140.28	646.91	−9.418	−1.103	8.315	−107293.0	2.378	−4382.95	9.907
5g	5.41	38.33	1194.81	612.75	−9.423	−1.187	8.236	−109297	3.048	−4427.84	−42.831
5h	5.78	40.35	1129.09	637.29	−9.351	−1.174	8.177	−106451	3.189	−4402.25	−7.135
5i	5.20	44.99	1253.95	704.06	−8.956	−1.018	7.938	−107184.3	5.653	−5335.2	−2.178
5j	6.00	47.62	1310.64	746.42	−9.006	−1.046	7.96	−114977.57	5.4	−5300.0	7.649
5k	5.34	44.90	1258.38	714.86	−9.016	−1.053	7.963	−116980.66	5.516	−5343.4	−43.638
5l	5.72	46.92	1292.59	738.48	−9.008	−1.022	7.986	−114133.02	5.37	−5316.6	−6.766
5m	5.25	45.09	1243.09	698.25	−8.976	−1.099	7.877	−110681.36	4.649	−5033.0	1.768
5n	6.05	47.71	1299.70	739.96	−9.022	−1.053	7.969	−118474.66	4.176	−4997.9	11.562
5o	5.39	45.00	1249.18	708.36	−9.028	−1.147	7.881	−120477.72	4.197	−5041.3	−39.694
5p	5.77	47.02	1281.97	731.12	−9.019	−1.123	7.896	−117630.32	4.23	−5014.7	−3.060
5q	6.90	47.98	1304.85	679.53	−9.169	−0.964	8.205	−113803.33	4.063	−5924.5	25.629
5r	7.69	50.61	1360.85	725.56	−9.312	−0.994	8.318	−121597.32	3.473	−5890.1	34.726
5s	7.04	47.89	1309.33	692.79	−9.34	−0.979	8.361	−123599.93	3.657	−5933.0	−16.071
5t	7.42	49.91	1342.96	716.71	−9.292	−0.945	8.347	−120752.32	3.463	−5906.3	20.758

Binding energy in kcal/mol and heat of formation ΔH in kcal/mol of given series of compounds.
Energy difference (ΔE) in (eV); dipole moments (Δ) in Debye; frontier molecular orbitals energies (E_{HOMO} and E_{LUMO}); molecular surface (S); molecular volume (V); partition coefficient (LogP); polarizability (P); total energy E_{total} in kcal/mol.

Table 4. Mulliken charges of the selected atoms.



Compound	Mulliken charges											
	S_1	O_2	O_3	N_4	C_5	C_6	O_7	C_8	N_9	N_{10}	S_{11}	C_{12}
5a	2.252	−0.821	−0.845	−0.498	0.094	−0.032	−0.072	−0.133	−0.119	−0.072	0.169	−0.094
5b	2.245	−0.823	−0.845	−0.487	0.089	−0.027	−0.072	−0.134	−0.116	−0.073	0.172	0.099
5c	2.245	−0.823	−0.846	−0.486	0.089	−0.026	−0.072	−0.134	−0.113	−0.074	0.178	−0.105
5d	2.245	−0.823	−0.846	−0.486	0.089	−0.026	−0.072	−0.134	−0.113	−0.074	0.178	−0.105
5e	2.246	−0.823	−0.842	−0.489	0.089	−0.029	−0.071	−0.136	−0.110	−0.074	0.178	−0.103
5f	2.246	−0.824	−0.841	−0.491	0.088	−0.027	−0.070	−0.137	−0.109	−0.073	0.180	−0.108
5g	2.250	−0.828	−0.836	−0.498	0.091	−0.030	−0.075	−0.141	−0.100	−0.073	0.166	−0.098
5h	2.247	−0.829	−0.834	−0.501	0.091	−0.033	−0.072	−0.135	−0.113	−0.069	0.169	−0.097
5i	2.262	−0.818	−0.841	−0.513	0.099	−0.034	−0.069	−0.129	−0.124	−0.075	0.173	−0.096
5j	2.262	−0.819	−0.840	−0.512	0.096	−0.029	−0.071	−0.132	−0.119	−0.074	0.183	−0.109
5k	2.260	−0.819	−0.840	−0.509	0.095	−0.029	−0.071	−0.132	−0.118	−0.073	0.181	−0.104
5l	2.260	−0.820	−0.841	−0.508	0.094	−0.029	−0.073	−0.131	−0.118	−0.072	0.180	−0.104
5m	2.249	−0.819	−0.838	−0.493	0.087	−0.031	−0.072	−0.128	−0.121	−0.074	0.171	−0.093
5n	2.251	−0.820	−0.838	−0.495	0.086	−0.027	−0.073	−0.131	−0.116	−0.073	0.182	−0.108
5o	2.253	−0.820	−0.837	−0.497	0.087	−0.027	−0.074	−0.131	−0.115	−0.073	0.180	−0.102
5p	2.253	−0.820	−0.838	−0.497	0.087	−0.029	−0.073	−0.131	−0.116	−0.072	0.180	−0.103
5q	2.251	−0.821	−0.844	−0.499	0.082	−0.025	−0.070	−0.132	−0.119	−0.073	0.167	−0.093
5r	2.252	−0.822	−0.842	−0.502	0.080	−0.019	−0.064	−0.141	−0.106	−0.077	0.176	−0.108
5s	2.251	−0.822	−0.842	−0.500	0.077	−0.018	−0.066	−0.141	−0.104	−0.077	0.175	−0.105
5t	−2.249	−0.822	−0.842	−0.499	0.077	−0.017	−0.065	−0.143	−0.101	−0.078	0.174	−0.106

$$\mathrm{LogEC_{50}} = -16.4 - 1.24\,\mathrm{EHOMO} + 0.0621\,\mu - 0.00272\,\mathrm{S} - 111\,\mathrm{N_{10}} \quad (8)$$

$$n = 19, s = 0.1751, r = 0.0.913, R^2 = 0.834, q^2 = 0.787, F = 17.64$$

Model–5 shows a good correlation coefficient (r) of 0.913 between descriptors (LogP, E_{HOMO}, μ, and N_{10}) and the anti-HIV activity. Squared correlation coefficient (r^2) of 0.834 explains 83.7% variance in biological activity. This model also indicates statistical significance > 99.9% with values $F = 17.64$. Cross-validated squared correlation coefficient (q^2) of this model was 0.787, which shows remarkable internal predication power of this model.

Similarly, **model–6** shows a remarkable correlation coefficient (r) of 0.909 between descriptors (ΔE, P, S, and N_{10}) and the anti-HIV activity. Squared correlation coefficient (r^2) of 0.826 explains 82.6% variance in biological activity. This model also indicates statistical significance > 99.9% with values $F = 16.56$. Cross-validated squared correlation coefficient (q^2) of this model was 0.776, which shows the good internal predication power of this model.

Further, **model–7** demonstrates an interesting correlation coefficient (r) of 0.919 between descriptors (E_{HOMO}, P, S, and N_{10}) and anti-HIV activity. Squared correlation coefficient (r^2) of 0.845 explains 84.5% variance in biological activity. This model also indicates statistical significance > 99.9% with values $F = 19.09$. Cross-validated squared correlation coefficient (q^2) of this model was 0.801, which shows the good internal predication power of this model.

Finally, **model–8** shows a desirable correlation coefficient (r) of 0.913 between descriptors (E_{HOMO}, μ, S and N_{10}) and the anti-HIV activity, where squared correlation coefficient (r^2) of 0.834 explains 83.4% variance in biological activity. This model also indicates statistical significance > 99.9% with values $F = 17.64$. Cross-validated squared correlation coefficient (q^2) of this model was 0.787, which shows reasonable internal predication power of this model.

According to 5, 6, 7, and 8 models, the calculated and experimental activities (EC_{50}) of the title compounds were obtained and listed in Table 5. These models showed good correlation between the experimental and calculated EC_{50} ($r = 0.893$, 0.868, 0.903, and 0.912 for 5, 6, 7 and 8 models, respectively). Models 7 and 8 can be considered as most suitable models for predicting the anti-HIV activity with both statistical significant and excellent predictive ability (Figure 4).

Table 5. Observed and calculated anti-HIV activity (EC_{50}) of given series of compounds.

Compound	Observed EC_{50}	Calculated EC_{50}			
		Model-5	Model-6	Model-7	Model-8
5a	59.58	29.15748	40.01327	35.615	39.79637
5b	75.33	45.87267	37.56644	54.21975	50.27844
5c	70.80	88.92503	88.07061	96.79234	90.84148
5d	27.93	60.99637	68.70131	72.74313	65.39883
5e	65.63	70.53132	73.86845	82.64822	80.77886
5g	58.75	81.71542	54.0463	82.87232	81.30566
5h	14.08	18.78503	14.21674	19.24086	20.83762
5i	30.48	24.88479	25.41575	28.34484	29.27171
5j	11.75	18.13093	16.7519	20.8732	19.34272
5k	11.50	17.96007	16.52532	19.16386	19.09697
5l	13.00	11.702	11.35492	12.39915	12.21044
5m	12.67	18.77293	16.75089	22.12425	21.56269
5n	12.30	13.18797	13.03788	16.12007	13.70624
5o	13.65	16.59495	13.36934	19.46695	17.04569
5p	11.88	10.93604	9.004799	12.54827	11.20977
5q	11.67	18.95501	20.71958	21.57613	29.96061
5r	82.10	75.44735	61.08112	85.12498	86.30384
5s	90.83	105.547	85.42559	108.8894	117.8449
5t	99.40	97.89804	89.67306	112.2172	111.0916

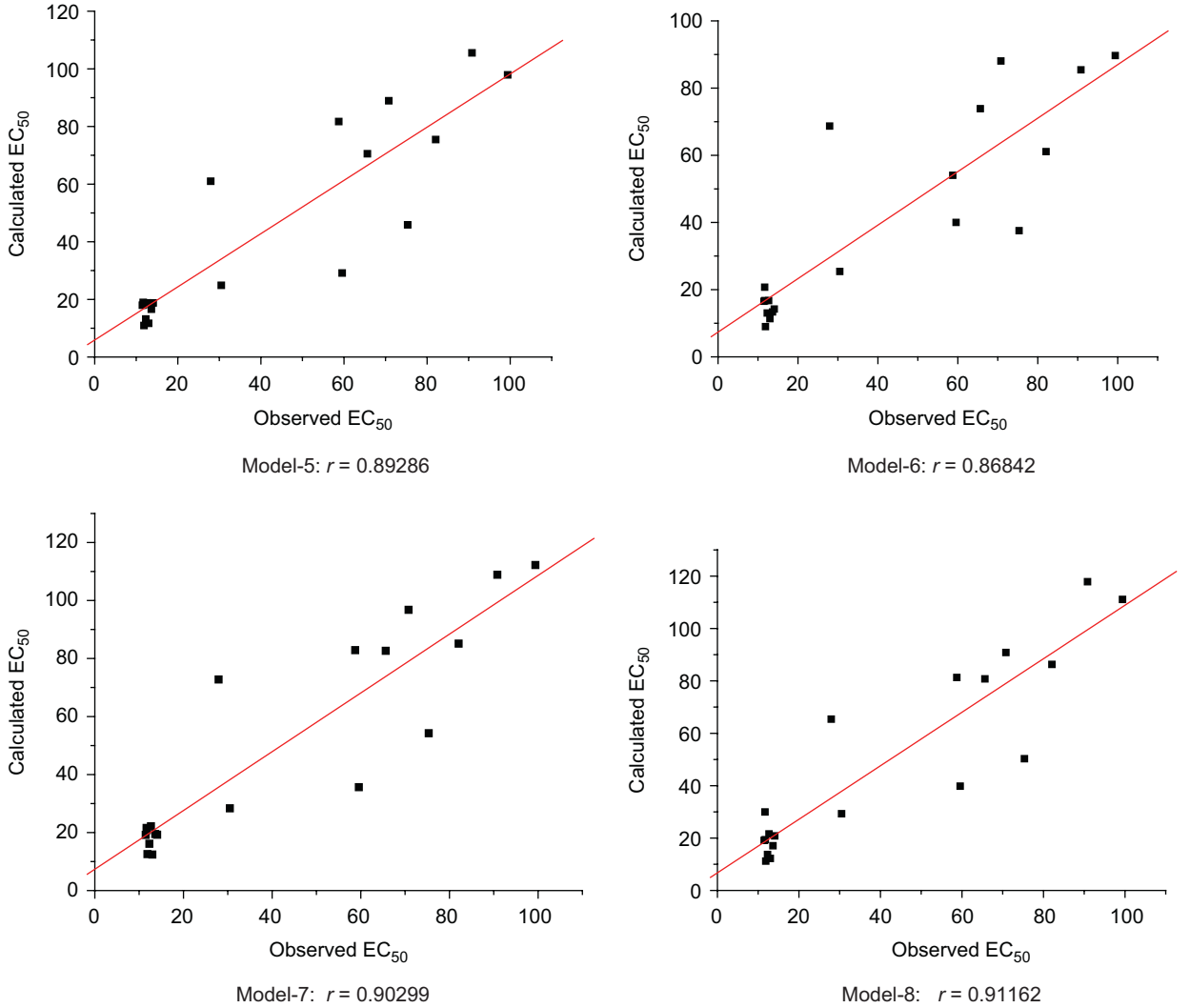


Figure 4. A plot between observed activity and calculated activity for 5, 6, 7, and 8 models. (A) Model-5: $r = 0.89286$. (B) Model-6: $r = 0.86842$. (C) Model-7: $r = 0.90299$. (D) Model-8: $r = 0.91162$.

Conclusion

In conclusion, the above data showed no selective anti-HIV activity. However, compounds **5f, j–5q** did show some inhibitory activity against both HIV-1 and HIV-2 with EC_{50} value ranging from >11.50 to >14.08 μg/mL, but with Si <1.

Acknowledgements

The authors thank Professor C. Pannecouque of Rega institute for medical research, Katholieke Universiteit Leuven, Belgium for the anti-HIV screening.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Hijikata M, Ohta Y, Baba K. Iwata K, Matsumoto M, Mishiro S, Kanai K. Instability of the NS5A ISDR of hepatitis C virus during natural course: take-over of wild type by mutant type or vice-versa driven by immune pressure. Hepatology Res 1998;11:19–25.
2. Bartenschlager R, Lohmann V. Novel cell culture systems for the hepatitis C virus. Antiviral Res 2001;52:1–17.
3. Zareef M, Iqbal R, Al-Masoudi NA, Zaidi JH, Arfan M, Shahzad SA. Synthesis, anti-HIV and antifungal activity of new benzensulphonamides bearing 2,5-disubstituted 1,3,4-oxadiazole moiety. Phosphorus Sulfur Silicon Relat Elem 2007;182:281–298.
4. Iqbal R, Zareef M, Ahmed S, Zaidi JH, Arfan M, Shafique M, Al-Masoudi NA. Synthesis, antimicrobial and anti-HIV activity of some novel benzenesulfonamides bearing 2,5-disubstituted-1,3,4-oxadiazole moiety. J Chin Chem Soc 2006;53:689–696.
5. El-Emam AA, Al-Deeb OA, Al-Omar M, Lehmann J. Synthesis, antimicrobial, and anti-HIV-1 activity of certain 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones. Bioorg Med Chem 2004;12:5107–5113.
6. Johns BA, Weatherhead JG, H., Allen SH, Thompson JB, Garvey EP, Foster SA, Jeffrey JL, Miller WH. The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: Establishing the pharmacophore. Bioorg Med Chem Lett 2009;19:1802–1806.
7. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS et al.; STARTMRK investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009;374:796–806.
8. Yan S, Appleby T, Larson G, Wu JZ, Hamatake RK, Hong Z et al. Thiazolone-acylsulfonamides as novel HCV NS5B polymerase allosteric inhibitors: convergence of structure-based drug design and X-ray crystallographic study. Bioorg Med Chem Lett 2007;17:1991–1995.
9. Yannopoulos CG, Xu P, Ni F, Chan L, Pereira OZ, Reddy TJ et al. HCV NS5B polymerase-bound conformation of a soluble sulfonamide inhibitor by 2D transferred NOESY. Bioorg Med Chem Lett 2004;14:5333–5337.
10. Selvam P, Murugesh N, Chandramohan M, Sidwell RW, Wandersee MK, Smee DF. Anti-influenza virus activities of 4-[(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)amino]-*N*-(4,6-dimethyl-2-pyrimidin-2-yl)benzenesulphonamide and its derivatives. Antiviral Chem Chemother 2006;17:269–274.
11. Li X, Yang X, Liang X, Kai Z, Yuan H, Yuan D, Zhang J, Wang R, Ran F, Qi S, Ling Y, Chen F, Wang D. Synthesis and biological activities of 2-oxocycloalkylsulfonamides Bioorg Med Chem 2008;16:4538–4544.
12. Vermeire K, Schols D. Cyclotriazadisulfonamides: promising new CD4-targeted anti-HIV drugs. J Antimicrob Chemother 2005;56:270–272.
13. Akhtar T, Hameed S, Al-Masoudi NA, Loddo R, La Colla P. *In vitro* antitumor and antiviral activities of new benzothiazole and 1,3,4-oxadiazole-2-thione. Acta Pharm 2008;58:135–149.
14. Akhtar T, Hameed S, Al-Masoudi NA, Khan KM. Synthesis, and anti-HIV activity of new chiral 1,2,4-triazoles and 1,3,4-thiadiazoles. Heteroatom Chem 2007;18:316–322.
15. Zahid M, Yasin KA, Akhtar T, Rama NH, Hameed S, Al-Masoudi NA., Loddo R, La Colla P. New 2-(4-aryl)-5-(2-adamantylthiazol-4-yl)-1,3,4-oxadiazoles as potential antiproliferative and antiviral agents, ARKIVOC 2009;xi: 85–93.
16. Serwar M, Akhtar T, Hameed S, Khan KM. Synthesis, urease inhibition and antimicrobial activities of some chiral 5-aryl-4-(1-phenylpropyl)-2*H*-1,2,4-triazole-3-(4*H*)-thione. ARKIVOC 2009;vii:210–221.
17. Akhtar T, Hameed S, Khan KM, Choudhary MI. Syntheses, urease inhibition, and antimicrobial studies of some chiral 3-substituted-4-amino-5-thioxo-1H,4H-1,2,4-triazoles. Med Chem 2008;4:539–543.
18. Stewart JJP. Optimization of parameters for semi-empirical methods. I Method J Comput Chem 1989;10:209–220.
19. Sheldrick GMA. Short history of *SHELX*. Acta Cryst 2008;A64:112–122.
20. Zareef M, Iqbal R, De Dominguez NG, Rodrigues J, Zaidi JH, Arfan M, Supuran CT. Synthesis andantimalarial activity of novel chiral and achiral benzenesulfonamides bearing 1, 3, 4-oxadiazole moieties. J Enz Inhib Med Chem 2007;22:301–308.
21. Zarghi A, Faizi M, Shafaghi B, Ahadian A, Khojastehpoor HR, Zanganeh V et al. Design and synthesis of new 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles as benzodiazepine receptor agonists. Bioorg Med Chem Lett 2005;15:3126–3129.
22. Koparir M, Cetin A, Cansiz A. 5-Furan-2-yl[1,3,4]oxadiazole-2-thiol, 5-furan-2yl-4*H* [1,2,4] triazole-3-thiol and their thiol-thione tautomerism. Molecules 2005;10:475–480.
23. Hargrave KD, Proudfoot JR, Grozinger KG, Cullen E, Kapadia SR, Patel UR et al. Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase. 1. Tricyclic pyridobenzo- and dipyridodiazepinones. J Med Chem 1991;34:2231–2241.
24. Mitsuya H, Weinhold KJ, Furman PA, St Clair MH, Lehrman SN, Gallo RC et al. 3′ -Azido-3′ -deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. Proc Natl Acad Sci USA 1985;82:7096–7100.
25. Fletcher P. Practical Methods of Optimization. New York: Wiley, 1990.
26. Rui OM, Qian L. I. 2D-QSAR studies on phenoxybenzoic acid derivatives: A novel class of 5α -reductase inhibitors. Chinese J Struct Chem 2008; 27: 105–111.