

Synthesis of 2-(substituted-phenyl)-5-(aminomethyl)- and (thiomethyl)-1,3,4-oxadiazoles. Oxidation of thiomethyl-oxadiazole derivatives by dimethyldioxirane

Attila Kiss-Szikszai^a, Tamás Patonay*,^a and József Jekő^b

^a Department of Organic Chemistry, University of Debrecen, P.O.Box 20, H-4010 Debrecen, Hungary

^b ICN Hungary Co. Ltd., H-4440 Tiszavasvári, Hungary

E-mail: tpatonay@tigris.klte.hu

Dedicated to Prof. Kalevi Pihlaja on the occasion of his 60th birthday

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Abstract

Various substituted 2-aryl-5-aminomethyl- and -5-thiomethyl-1,3,4-oxadiazoles were synthesized in high yields from the corresponding chloromethyl derivatives. Selective oxidation of the sulfides into 5-sulfinylmethyl and 5-sulfonylmethyl-1,3,4-oxadiazoles by dimethyldioxirane under mild conditions was also demonstrated.

Keywords: Dimethyldioxirane, nucleophilic substitution, 1,3,4-oxadiazole

Introduction

Derivatives of 1,3,4-oxadiazole constitute an important family of heterocyclic compounds.¹ Since many of them display a remarkable biological activity, their synthesis and transformations have been received particular interest for a long time. The 2-aryl-5-(substituted methyl)-1,3,4-oxadiazoles have been reported to show antibacterial,^{2,3} antifungal,⁴ analgesic and anti-inflammatory^{5,6}, and hypoglycemic³ activity. Their synthetic usefulness has also been demonstrated. The 2-azidomethyl-5-(4-chlorophenyl)-1,3,4-oxadiazole, as a 1,3-dipole, added efficiently to norbornene derivatives⁷ while 2-phenyl-5-[(2-pyridylum)methyl]-1,3,4-oxadiazole chloride was found to be a good nitrene precursor⁸. Liebscher and his coworkers reported diastereoselective side-chain alkylation of oxadiazoles by using a prolinolyl group as a chiral auxiliary⁹ and also the synthesis of bicyclic imidazoles carrying oxadiazolyl moiety.¹⁰ To prepare the corresponding substrates, nucleophilic substitution of 2-aryl-5-chloromethyl-1,3,4-oxadiazoles have usually been applied.

The most popular synthesis of 2,5-disubstituted-1,3,4-oxadiazole based on the thermal or

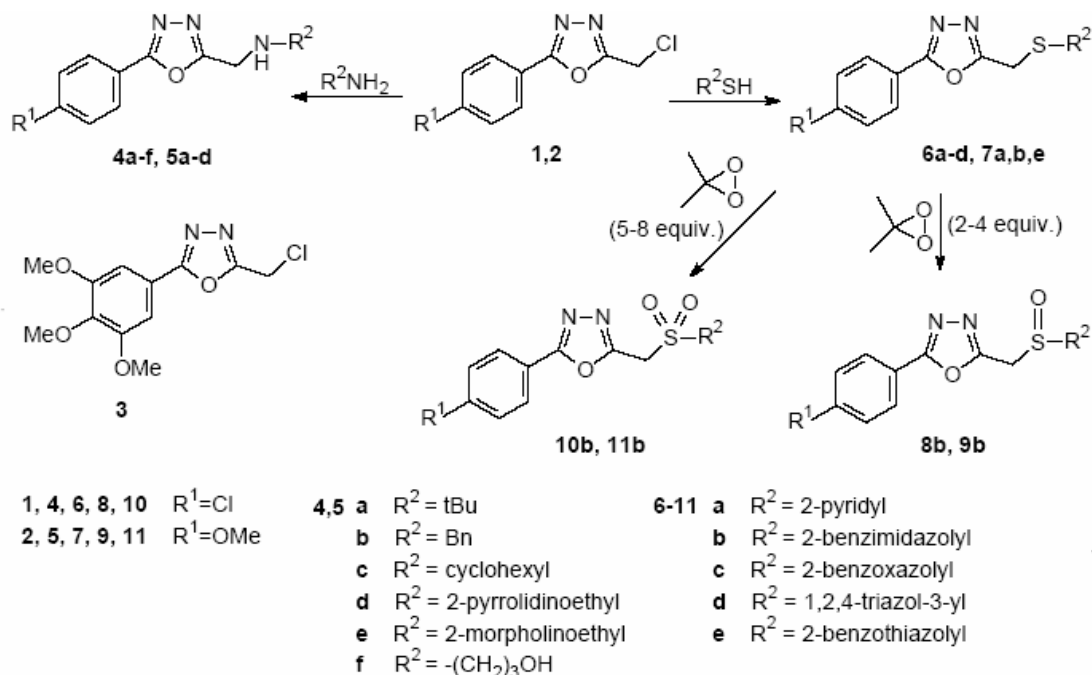
acid-catalysed cyclization of 1,2-diacylhydrazines¹. Ring-closure usually proceeded in the presence of hot phosphorus oxychloride^{3,4,11} although an improved method by using triphenylphosphine/carbon tetrachloride/triethylamine reagent was also reported recently.² Oxidative cyclization of aldehyde or ketone acylhydrazones¹ and thermal acylation of 5-substituted tetrazoles followed by nitrogen elimination¹²⁻¹⁴ also afford the desired derivatives, but these approaches have not been used for the synthesis of 2-aryl-5-chloromethyl-1,3,4-oxadiazoles.

Recently we have studied the preparation of 2-(alkylamino- or dialkylaminomethyl)- and 2-hetarylthiomethyl-5-aryl-1,3,4-oxadiazoles and selected results of this project are presented in this contribution.

Results and Discussion

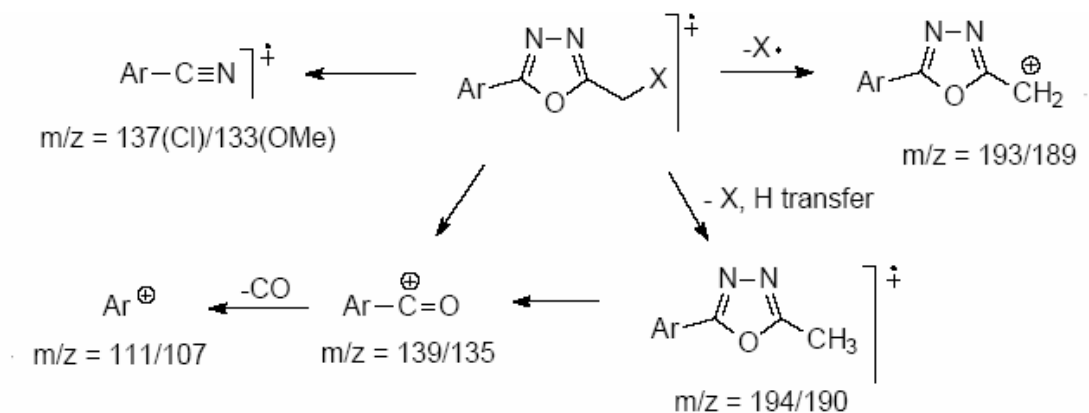
The starting materials **1-3** were synthesized from the corresponding aroyl hydrazides and chloroacetyl chloride according to a reported procedure^{4,15}. From the various conditions of their nucleophilic substitution reported in the literature (2 equiv. of nucleophile in dioxane,^{5,6} 1-1.2 equiv. of nucleophile in methanol or ethanol solution in the presence of potassium carbonate³, sodium acetate⁴ or triethyl amine,⁹ 1 equiv. of nucleophile and 1 equiv. of sodium hydride in DMF¹⁰, 1 equiv. of nucleophile and potassium carbonate in DMSO solution¹⁵), the last one was found to give the highest yields. The reaction of chloromethyl derivatives **1,2** with various amines or hetarenethiols and potassium carbonate in DMSO solution at room temperature gave the expected amines **4,5** and sulfides **6,7** in good yields in 4-6 hrs (Scheme 1). Surprisingly, no reaction was observed upon analogous treatment of 2-chloromethyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (**3**) even at a longer reaction period. At higher temperatures the starting material was consumed but the expected product was not obtained. It is very likely that under these conditions the concurrent attack of the nucleophile(s) on the C-2, C-5 carbon atoms of the oxadiazole ring takes place which leads to ring cleavage.¹

When sulfides **6b,7b** were treated with dimethyldioxirane¹⁶ (DMD), the corresponding sulfoxides **8b,9b** and sulfones **10b,11b** were obtained in excellent yields depending on the amount of oxidizing agent used. Treatment of the sulfides with 2-4 equiv. of DMD resulted in the formation of sulfoxides, the synthesis of sulfones required a higher amount (5-8 equiv.) of oxidizing agent. The oxadiazole moiety remained intact (Scheme 1). The measured sulfoxide/sulfone ratio of the crude product in the synthesis of sulfoxides was higher than 9/1 which indicates a good chemoselectivity for the attack of DMD on the sulfur atom of the sulfide unit. This reactivity pattern is characteristic of DMD oxidation although exceptional deviations have also been reported.¹⁷ It is noteworthy that a complete decomposition of the starting **6,7** sulfides without the formation of considerable amount of any sulfoxide or sulfone was found in the attempted oxidation by hydrogen peroxide in acetic acid. Once again, these results demonstrate the synthetic value of DMD in oxygen transfer under mild and neutral conditions.



Scheme 1

The structures of the obtained products were proven by spectroscopic methods. The characteristic $\text{C}=\text{N}$ band ($1616\text{-}1594\text{ cm}^{-1}$) of medium intensity and a medium-strong band at $1025\text{-}1000\text{ cm}^{-1}$ were identified in each IR spectra, the latter could be attributed to the C-O-C vibration or heteroatom ring deformation of the oxadiazole ring.¹⁸ The presence of the 1,3,4-oxadiazole unit was supported by the appearance of two quaternary signals (C-2, C-5) in the range $\delta = 162.5\text{-}166.6\text{ ppm}$ of their ^{13}C NMR spectrum. The oxadiazole ring was found to exert a slight upfield shift (ca. -5 ppm) on the *ipso*-carbon of the 2-aryl group. In their MS spectra 5-chloromethyl derivatives **1-3** and 5-thiomethyl derivatives **6,7** gave molecular ions of medium intensity and the base peak usually belonged to the corresponding acylium ions and nitrile radical ions which formed by the cleavage of the heteroatom ring. Both of these have been reported as characteristic for this family. However, only very weak molecular ion were detected in the spectra of the aminomethyl derivatives **4,5** as the ArCO^+ fragment appeared as a peak of medium intensity and the base peak usually came from the amine side chain. The most important fragmentation pathways are shown by Scheme 2.



Scheme 2

Experimental Section

General Procedures. Dimethyldioxirane solution was prepared according to literature procedure¹⁹ and its peroxide content was determined iodometrically. Chromatographic separations were performed using silica gel (Merck, 70-230 mesh). Thin-layer chromatography was carried out on Macherey-Nagel precoated silica plate (0.25 mm layer thickness). Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded with a Gemini 200 spectrometer in CDCl₃ solution unless otherwise specified (internal standard TMS, $\delta = 0$ ppm). Mass spectra were taken on a VG Trio-2 (EI, 70 eV) apparatus. IR spectra were recorded with a Perkin-Elmer 283 instrument in KBr disks.

2-Aryl-5-(chloromethyl)-1,3,4-oxadiazoles **1**, **2**, **3** were prepared by a direct reaction of aromatic acidhydrazides and ClCH₂COCl according to the procedure of Vakula *et al.*¹⁵

5-Chloromethyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (1). Colourless needles, yield 67%, mp 80.5-81 °C (PhMe-hexane) (lit.¹¹ 85 °C). IR: 3012, 2960, 1604 (C=N), 1481, 1410, 1255, 1092 (Ar-Cl), 1011, 835, 735, 727 cm⁻¹. ¹H NMR (DMSO-d₆): 5.15 (s, 2H, CH₂), 7.70 (d, $J = 8.7$ Hz, 2H, 3',5'-H), 8.05 (d, $J = 8.7$, 2H, 2',6'-H). ¹³C NMR (DMSO-d₆): 33.1 (CH₂), 121.9 (C-1'), 128.7 (C-2',6'), 129.9 (C-3',5'), 137.4 (C-4'), 163.3, 164.5 (C-2, C-5). MS: 228/230/232 (35/21/5, M⁺, Cl₃₅/Cl₃₇/2xCl₃₇), 193 (28, M - Cl), 179 (10, M - CH₂Cl), 139 (100, 4-ClC₆H₄CO⁺), 137 (29, 4-ClC₆H₄CN), 123 (16), 111 (50, 4-ClC₆H₄⁺), 75(53).

5-Chloromethyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (2). Colourless prisms, yield 61%, mp 88.5-90 °C (PhMe-hexane) (lit.¹¹ 94-95 °C, lit.¹⁹ 92 °C). IR: 3018, 1616 (C=N), 1497, 1428, 1310, 1259 (C-O-C), 1178, 1008, 843, 744, 737 cm⁻¹. ¹H NMR (DMSO-d₆): 3.87 (s, 3H, MeO), 5.12 (s, 2H, CH₂), 7.15 (d, $J = 9.0$ Hz, 2H, 3',5'-H), 7.95 (d, $J = 9.0$ Hz, 2H, 2',6'-H). ¹³C NMR (DMSO-d₆): 33.2 (CH₂), 55.5 (MeO), 115.2 (C-3',5'), 115.3 (C-1'), 128.8 (C-2',6'), 162.6, 165.3 (C-2, C-5, C-4'). MS: 224/226 (29/9, M⁺, Cl₃₅/Cl₃₇), 189 (20, M - Cl), 135 (100, 4-

MeOC₆H₄CO⁺), 133 (20, 4-MeOC₆H₄CN), 119 (8), 92 (15), 77 (23).

5-Chloromethyl-2-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (3). Colourless needles, yield 68%, mp 106.5-110 °C (PhMe-hexane) (lit.¹⁵ 215 °C). IR: 3008, 1594 (C=N), 1498, 1462, 1418, 1322, 1240 (C-O-C, OMe), 1130 (C-O-C, OMe), 996, 846, 744, 728 cm⁻¹. ¹H NMR: 3.92 (s, 3H, 4-OMe), 3.96 (s, 6H, 3,5-OMe), 4.80 (s, 2H, CH₂), 7.90 (s, 2H, 2,6-H). ¹³C NMR: 32.9 (CH₂), 56.3 (3',5'-MeO), 60.9 (4'-MeO), 104.3 (C-2',6'), 118.2 (C-1'), 141.4 (C-4'), 153.6 (C-3',5'), 162.0, 165.8 (C-2, C-5). MS: 284/286 (48/16, M⁺, Cl₃₅/Cl₃₇), 269 (20, M - Me), 249 (4, M - Cl), 195 (100, (MeO)₃C₆H₂CO⁺).

2-(4-(Chlorophenyl)-5-(tert-butylamino)methyl-1,3,4-oxadiazole (4a). **Typical procedure.** 1.37 mL (13.037 mmol) of *tert*-butylamine and 1.86 g (13.5 mmol) of anhydrous K₂CO₃ were added to a stirred solution of **1** (1.498 g, 6.540 mmol) in DMSO (30 mL) at room temperature and the reaction was monitored by TLC (MeOH-PhMe = 10:1, v/v). After 4 hours it was poured into water (200 mL). The precipitate was filtered off and washed with hexane (2x10 mL) to obtain 1.165 g (67%) of **4a** as white microcrystalline powder. mp 72.5-73.5 °C (EtOAc-hexane). IR: 3339 (NH), 2967 (CH₃), 1607 (C=N), 1584, 1482, 1409, 1364, 1091 (Ar-Cl), 1010, 844, 729 cm⁻¹. ¹H NMR: 1.19 (s, 9H, tBu), 1.51 (s, 1H, NH), 4.10 (s, 2H, CH₂), 7.46 (d, *J* = 6.8 Hz, 2H, 3',5'-H), 8.00 (d, *J* = 6.8 Hz, 2H, 2',6'-H). ¹³C NMR: 28.7 (CMe₃), 37.8 (CH₂), 51.0 (CMe₃), 122.5 (C-1'), 128.3 (C-2',6'), 129.5 (C-3',5'), 138.1 (C-4'), 164.4, 166.6 (C-2, C-5). MS: 250 (54, M - CH₃), 193 (5, M - tBuNH), 181 (12), 139 (29, 4-ClC₆H₄CO⁺), 111 (15, 4-ClC₆H₄⁺), 95 (20), 70 (100, C₄H₈N). Anal. Calcd. for C₁₃H₁₆ClN₃O (265.74): C, 58.76; H, 6.07; N, 15.81. Found: C, 58.77; H, 5.89; N, 15.44.

5-(Benzylamino)methyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (4b). From chloride **1** (1.541 g, 6.727 mmol) and benzylamine (1.48 mL, 13.549 mmol) as given for **4a**. Yield 86%, mp 69.5-71 °C. IR: 3372 (NH), 2923, 1606 (C=N), 1484, 1453, 1412, 1412, 1133, 1097, (Ar-Cl), 1016, 830, 742, 736 cm⁻¹. ¹H NMR: 1.90 (s, 1H, NH), 3.90 (s, 2H, PhCH₂), 4.10 (s, 2H, HetCH₂), 7.25-7.36 (m, 5H, Ph), 7.50 (d, *J* = 6.9 Hz, 2H, 3',5'-H), 7.96 (d, *J* = 6.9 Hz, 2H, 2',6'-H). ¹³C NMR: 42.8 (HetCH₂), 52.9 (PhCH₂), 122.4 (C-1'), 127.5 (C-4'), 128.3, 128.4, 128.7, 129.6 (C-2',6', C-3',5', C-2'',6'', C-3'',5''), 138.2, 139.1 (C-4', C-1''), 164.5, 165.6 (C-2, C-5). MS: 298 (<1, M - 1), 194 (20, M - PhCH=NH), 139 (10, 4-ClC₆H₄CO⁺), 137 (8, 4-ClC₆H₄CN), 106 (100, PhCH₂NH⁺), 91 (41, PhCH₂⁺). Anal. Calcd. for C₁₆H₁₄ClN₃O (299.75): C, 64.11; H, 4.71; N, 14.02. Found: C, 63.94; H, 4.58; N, 14.22.

2-(4-Chlorophenyl)-5-(cyclohexylamino)methyl-1,3,4-oxadiazole (4c). From chloride **1** (1.513 g, 6.605 mmol) and cyclohexylamine (1.52 mL, 13.287 mmol) as given for **4a**. Yield 94%, mp 82.5-85 °C. IR: 3310 (NH), 2930 (CH₂), 2853, 1584, 1483, 1413, 1203, 1133, 1095 (Ar-Cl), 1011, 855, 834, 732 cm⁻¹. ¹H NMR: 1.20 (m, 4H, cyclohexyl CH₂), 1.70 (m, 4H, cyclohexyl CH₂), 1.92 (m, 2H, cyclohexyl CH₂), 3.56 (m, 1H, cyclohexyl CH), 4.12 (s, 2H, HetCH₂), 7.50 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 8.00 (d, *J* = 8.7 Hz, 2H, 2',6'-H). ¹³C NMR: 24.6 (C-3'',5''), 25.8 (C-4''), 33.0 (C-2',6''), 40.9 (HetCH₂), 55.9 (C-1''), 122.5 (C-1'), 128.3, 129.6 (C-2',6', C-3',5'), 138.1 (C-4'), 164.5, 166.1 (C-2, C-5). MS: 291 (<1, M⁺), 290 (<1, M - 1), 248 (10, M - C₃H₇), 194 (12), 139 (13, 4-ClC₆H₄CO⁺), 111 (6, 4-ClC₆H₄⁺), 98 (100, cHxNH⁺). Anal.

Calcd. for $C_{15}H_{18}ClN_3O$ (291.78): C, 61.75; H, 6.22; N, 14.40. Found: C, 61.85; H, 6.25; N, 14.27.

2-(4-Chlorophenyl)-5-[(2-pyrrolidinoethyl)amino]methyl-1,3,4-oxadiazole (4d). From chloride **1** (1.501 g, 6.553 mmol) and 1-(2-aminoethyl)pyrrolidine (1.65 mL, 13.019 mmol) as given for **4a**. Yield 94%, mp 63.5-65 °C. IR: 3285 (NH), 2929, 1607 (C=N), 1559, 1488, 1411, 1130, 1092 (Ar-Cl), 1001, 841, 818, 738 cm^{-1} . 1H NMR: 1.75 (m, 4H, 3'',4''-H), 2.15 (br s, 1H, NH), 2.50 (m, 4H, 2'',5''-H), 2.62, 2.81 (2xt, $J = 6.2$ Hz, 2x2H, $NHCH_2CH_2N$), 4.12 (s, 2H, $HetCH_2$), 7.50 (d, $J = 8.6$ Hz, 2H, 3',5'-H), 8.00 (d, $J = 8.6$ Hz, 2H, 2',6'-H). ^{13}C NMR: 23.3 (C-3',4''), 43.8 ($HetCH_2$), 47.6 ($NHCH_2CH_2N$), 54.0 (C-2'',5''), 55.4 ($NHCH_2CH_2N$), 122.5 (C-1'), 128.3, 129.5 (C-2',6', C-3',5'), 138.1 (C-4'), 164.5, 165.8 (C-2, C-5). MS: 306 (<1, M^+), 194 (1), 166 (1), 139 (5, 4- $ClC_6H_4CO^+$), 84 (100, $(CH_2)_4NCH_2^+$). Anal. Calcd. for $C_{15}H_{19}ClN_4O$ (306.79): C, 58.72; H, 6.24; N, 18.26. Found: C, 58.79; H, 6.02; N, 17.99.

2-(4-Chlorophenyl)-5-[(2-morpholinoethyl)amino]methyl-1,3,4-oxadiazole hydrochloride (4e.2HCl). From chloride **1** (1.508 g, 6.583 mmol) and 1-(2-aminoethyl)morpholine (1.70 mL, 12.953 mmol) as given for **4a**. The oily product was treated with saturated HCl solution in abs. diethyl ether to give 2.226 g (99%) of hydrochloride. Mp 205-208°C. IR: 2953 (CH_2), 2666, 2441, 2363 (NH^+), 1611 (C=N), 1591, 1484, 1111, 1095 (Ar-Cl), 1012, 732 cm^{-1} . 1H NMR (DMSO- d_6): 3.40, 3.75, 3.92 (br m's, 15H, $6xCH_2 + NH_2^+ + NH^+$), 4.75 (s, 2H, $HetCH_2$), 7.74 (d, $J = 8.6$ Hz, 2H, 3',5'-H), 8.09 (d, $J = 8.6$ Hz, 2H, 2',6'-H). ^{13}C NMR (DMSO- d_6): 51.5 (C-2'',6''), 51.6 (CH_2 -morpholino), 63.2 (C-3'',5''), 122.0 (C-1'), 128.8, 130.0 (C-2',6', C-3',5'), 137.5 (C-4'), 160.0, 164.5 (C-2, C-5). $NHCH_2$ and $HetCH_2$ overlapped with the DMSO signal. Anal. Calcd. for $C_{15}H_{21}Cl_3N_4O_2$ (395.71): C, 45.53; H, 5.35; N, 14.16. Found: C, 45.00; H, 5.18; N, 13.79.

2-(4-Chlorophenyl)-5-[(3-hydroxypropyl)amino]methyl-1,3,4-oxadiazole (4f). From chloride **1** (1.501 g, 6.553 mmol) and 3-hydroxypropylamine (1.00 mL, 13.074 mmol) as given for **4a**. Yield 85%, mp 95-96.5 °C. IR: 3250 (NH), 3154 (OH), 2932 (CH_2), 2858, 1607 (C=N), 1485, 1411, 1090 (Ar-Cl), 1067, 1012, 956, 913, 831, 731 cm^{-1} . 1H NMR: 1.80 (m, 2H, $NHCH_2CH_2CH_2OH$), 2.78 (br s, 2H, NH, OH), 2.95 (t, $J = 5.9$ Hz, 2H, $NHCH_2CH_2CH_2OH$), 3.82 (t, $J = 5.9$ Hz, 2H, $NHCH_2CH_2CH_2OH$), 4.12 (s, 2H, $HetCH_2$), 7.50 (d, $J = 8.6$ Hz, 2H, 3',5'-H), 8.00 (d, $J = 8.6$ Hz, 2H, 2',6'-H). ^{13}C NMR: 31.0 ($NHCH_2CH_2CH_2OH$), 43.6 ($HetCH_2$), 48.3 ($NHCH_2CH_2CH_2OH$), 62.9 ($NHCH_2CH_2CH_2OH$), 122.3 (C-1'), 128.3, 129.6 (C-2',6', C-3',5'), 138.3 (C-4'), 163.5, 165.3 (C-2, C-5). MS: 267 (2, M^+), 222 (10), 194 (22, $M - CH_2CH_2OH$), 139 (35, 4- $ClC_6H_4CO^+$), 137 (16, 4- ClC_6H_4CN), 111 (12), 102 (5), 74 (100, $^+NHCH_2CH_2CH_2OH$). Anal. Calcd. for $C_{12}H_{14}ClN_3O_2$ (267.71): C, 53.84; H, 5.27; N, 15.70.

5-(tert-Butylamino)methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (5a). From chloride **2** (1.505 g, 6.670 mmol) and *tert*-butylamine (0.70 mL, 6.661 mmol) as given for **4a**. Yield 57%, mp 75-77 °C. IR: 3316 (NH), 2970 (CH_3), 1616 (C=N), 1591, 1502, 1426, 1363, 1307, 1259 (C-O-C, OMe), 1185, 1085, 1025, 832, 740, 702 cm^{-1} . 1H NMR: 1.15 (s, 9H, *t*Bu), 3.85 (s, 3H, MeO), 4.01 (s, 2H, $HetCH_2$), 6.95 (d, $J = 8.9$ Hz, 2H, 3',5'-H), 7.96 (d, $J = 8.9$ Hz, 2H, 2',6'-H). ^{13}C NMR: 28.7 (CMe_3), 37.8 ($HetCH_2$), 50.9 (CMe_3), 55.3 (OMe), 114.5 (C-3',5'), 116.6 (C-1'), 128.8 (C-2',6'), 162.5, 165.2, 165.8 (C-2, C-5, C-4'). MS: 261 (1, M^+), 246 (80, $M - Me$), 189

(53, M – tBuNH), 177 (13), 135 (100, 4-MeOC₆H₄CO⁺), 133 (29, 4-MeOC₆H₄CN), 92 (10), 77 (16), 70 (56, C₄H₈N). Anal. Calcd. for C₁₄H₁₉N₃O₂ (261.32): C, 64.35; H, 7.33; N, 16.08. Found: C, 64.30; H, 7.48; N, 15.99.

5-(Benzylamino)methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole hydrochloride (5b.HCl).

From chloride **2** (1.508 g, 6.713 mmol) and benzylamine (0.74 mL, 6.774 mmol) as given for **4a**. The oily product was treated with saturated HCl solution in abs. diethyl ether to give 1.447 g (65%) of hydrochloride. Mp 141-143 °C. IR: 2929, 2728, 2600 (NH⁺), 1616 (C=N), 1500, 1450, 1308, 1255 (C-O-C, OMe), 1176, 1024, 844, 743, 701 cm⁻¹. ¹H NMR (DMSO-d₆): 3.87 (s, 3H, OMe), 4.35 (s, 2H, PhCH₂CH₂), 4.59 (s, 1H, HetCH₂), 7.19 (d, *J* = 8.9 Hz, 2H, 3',5'-H), 7.43 (m, 3H, 2",4",6"-H), 7.59 (m, 2H, 3",5"-H), 7.98 (d, *J* = 8.9 Hz, 2H, 3',5'-H), 10.4 (br s, 2H, NH₂⁺). ¹³C NMR (DMSO-d₆): 50.0, 55.6 (PhCH₂CH₂, HetCH₂), 115.2 (C-3',5'), 115.4 (C-1'), 128.8 (C-2',6' + C-3",5"), 129.3 (C-4")*, 130.6 (C-2",6"), 131.7 (C-1")*, 159.6, 162.6, 165.2 (C-2, C-5, C-4'). *Interchangeable assignment. MS: 190 (60, 2-Ar-5-Me-1,3,4-oxadiazole), 135 (27, 4-MeOC₆H₄CO⁺), 133 (30, 4-MeOC₆H₄CN), 106 (100, PhCH₂NH), 91 (65, PhCH₂), 77(16). Anal. Calcd. for C₁₆H₂₁N₃O₂ (287.36): C, 66.88; H, 7.37; N, 14.62. Found: C, 67.01; H, 7.17; N, 14.39.

5-(Cyclohexylamino)methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (5c).

From chloride **2** (1.497 g, 6.664 mmol) and cyclohexylamine (0.77 mL, 6.731 mmol) as given for **4a**. Yield 64%, mp 80-82.5 °C. IR: 3313 (NH), 2926 (CH₂), 2851 (CH₂), 1616 (C=N), 1504, 1426, 1309, 1256 (C-O-C, OMe), 1181, 1086, 1032, 1005, 844, 740 cm⁻¹. ¹H NMR: 1.09-1.31 (m, 4H, cyclohexyl CH₂), 1.62-1.98 (m, 6H, cyclohexyl CH₂), 2.05 (m, 1H, NHCH), 3.92 (s, 3H, OMe), 4.12 (s, 2H, HetCH₂), 7.01 (d, *J* = 9.0 Hz, 2H, 3',5'-H), 8.00 (d, *J* = 9.0 Hz, 2H, 2',6'-H). ¹³C NMR: 24.5 (C-3",5"), 25.7 (C-4"), 32.9 (C-2",6"), 40.7 (HetCH₂), 55.3, 55.8 (C-1", MeO), 114.5 (C-3',5'), 116.5 (C-1'), 128.8 (C-2',6'), 162.5, 165.2 (C-2, C-5, C-4'). MS: 244 (2, M – C₃H₇), 224 (32), 189 (20), 135 (100, 4-MeOC₆H₄CO⁺), 133 (22, 4-MeOC₆H₄CN), 119 (8), 92 (13), 77 (20). Anal. Calcd. for C₁₆H₂₁N₃O₂ (287.36): C, 66.88; H, 7.37; N, 14.62. Found: C, 66.95; H, 7.21; N, 14.55.

2-(4-Methoxyphenyl)-5-[(2-pyrrolidinoethyl)amino]methyl-1,3,4-oxadiazole hydrochloride (5d.2HCl).

From chloride **2** (1.498 g, 6.668 mmol) and 1-(2-aminoethyl)pyrrolidine (0.85 mL, 6.707 mmol) as given for **4a**. The oily product was treated with saturated HCl solution in abs. diethyl ether to give 1.047 g (46%) of hydrochloride. Mp 195-200 °C. IR: 2947 (CH₂), 2924 (CH₂), 2675, 2600, 2363 (NH⁺), 1616 (C=N), 1500, 1260 (C-O-C, OMe), 1175, 1025, 841, 741 m⁻¹. ¹H NMR (DMSO-d₆): ~3.40 (br s, 3H, NH⁺, NH₂⁺), 3.65, 3.86, 3.89 (3xs, 12H, CH₂), 4.74 (s, 2H, HetCH₂), 7.22 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 8.04 (d, *J* = 8.8 Hz, 2H, 2',6'-H). ¹³C NMR (DMSO-d₆): 22.6 (C-3",4"), 42.7 (HetCH₂), 49.2, 55.6 (NCH₂CH₂N), 53.2 (C-2",5"), 115.2 (C-3',5'), 115.4 (C-1'), 128.9 (C-2',6'), 159.4, 162.7, 165.2 (C-2, C-5, C-4'). MS: 302 (1, M⁺ of free base), 190(1), 135 (15, 4-MeOC₆H₄CO⁺), 111 (3), 84 (100, (CH₂)₄NCH₂⁺), 78 (38). Anal. Calcd. for C₁₆H₂₄Cl₂N₄O₂ (375.29): C, 51.21; H, 6.45; N, 14.93. Found: C, 50.56; H, 6.41; N, 14.58.

2-(4-Chlorophenyl)-5-[(2-pyridyl)thio]methyl-1,3,4-oxadiazole (6a).

From chloride **1** (1.506 g, 6.575 mmol) and 2-mercaptopyridine (0.734 g, 6.603 mmol) as given for **4a**. Yield 86%, mp 89-90.5 °C. IR: 2914, 1606 (C=N), 1578, 1558, 1483, 1456, 1412, 1256, 1130, 1092

(Ar-Cl), 1008, 834, 756, 733 cm^{-1} . ^1H NMR (DMSO- d_6): 4.80 (s, 2H, HetCH $_2$), 7.20 (dd, $J = 7.3$, 5.2 Hz, 1H, 5''-H), 7.45 (d, $J = 8.1$ Hz, 1H, 3''-H), 7.70 (m, 3H, 3',5'-H), 7.94 (d, $J = 8.6$ Hz, 2H, 2',6'-H), 8.43 (d, $J = 5.8$ Hz, 1H, 6''-H). ^{13}C NMR (DMSO- d_6): 22.7 (HetCH $_2$), 120.9, 122.2 (C-1', C-3'', C-5''), 128.4, 129.9 (C-2',6', C-3',5'), 137.0 (C-4'), 137.4 (C-4''), 149.8 (C-6''), 155.8 (C-2''), 163.8, 165.0 (C-2, C-5). MS: 303/305 (63/21, M^+ , $\text{Cl}_{35}/\text{Cl}_{37}$), 270 (6), 230 (8), 194 (6), 164 (47), 139 (77, 4- $\text{ClC}_6\text{H}_4\text{CO}^+$), 137 (43, 4- $\text{ClC}_6\text{H}_4\text{CN}$), 124 (75, 2-pySCH $_2^+$), 123 (100), 111 (83, 2-pySH), 78 (80, py $^+$). Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{OS}$ (303.76): C, 55.36; H, 3.32; N, 13.83. Found: C, 55.35; H, 3.11; N, 14.02.

5-[(2-Benzimidazolyl)thio]methyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (6b). From chloride **1** (1.501 g, 6.553 mmol) and 2-mercaptobenzimidazol (0.985 g, 6.558 mmol) as given for **4a**. Yield 86%, mp 205-206 $^{\circ}\text{C}$. IR: 3073, 2985, 2881, 2811, 1609 (C=N), 1566, 1483, 1403, 1356, 1280, 1092 (Ar-Cl), 1011, 834, 752, 724 cm^{-1} . ^1H NMR (DMSO- d_6): 4.45 (s, 2H, HetCH $_2$), 7.18 (m, 2H, 5'',6''-H), 7.50 (br s, 2H, 4'',7''-H), 7.62 (d, $J = 8.3$ Hz, 2H, 3',5'-H), 7.90 (d, $J = 8.3$ Hz, 2H, 2',6'-H), 12.80 (s, 1H, NH). ^{13}C NMR: 25.3 (HetCH $_2$), 122.2 (C-1'), 128.4, 129.8 (C-2',6', C-3',5'), 137.0 (C-4'), 147.7 (C-2''), 163.9, 164.5 (C-2, C-5). C-4'', C-3a'', C-5'', C-6'', C-7'', C-7a'' carbon signals appeared as highly broadened singlets at $\delta \sim 111$, 117.5, 122 ppm due to the exchange of hydrogen between the two nitrogens. MS: 342, 344 (43/15, $\text{Cl}_{35}/\text{C}_{37}$), 194 (26), 163 (38, benzimidazolyl-SCH $_2^+$), 162 (80), 150 (90, 2-HS-benzimidazole), 139 (100, 4- $\text{ClC}_6\text{H}_4\text{CO}^+$), 123 (43), 111 (43, 4- ClC_6H_4^+), 90 (15), 75(38). Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{ClN}_4\text{OS}$ (342.80): C, 56.06; H, 3.23; N, 16.34. Found: C, 55.97; H, 3.54; N, 16.20.

5-[(2-Benzoxazolyl)thio]methyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (6c). From chloride **1** (1.515 g, 6.614 mmol) and 2-mercaptobenzoxazol (0.999 g, 6.608 mmol) as given for **4a**. Yield 84%, mp 105-106 $^{\circ}\text{C}$. IR: 3084, 1606 w (C=N), 1586, 1502, 1486, 1453, 1403, 1238, 1224, 1140, 1095 (Ar-Cl), 1009, 850, 754, 744, 731 cm^{-1} . ^1H NMR (DMSO- d_2): 4.81 (s, 2H, HetCH $_2$), 7.32 (m, 2H, 5'',6''-H), 7.46 (d, $J = 8.5$ Hz, 2H, 3',5'-H), 7.48, 7.65 (2xm, 2x1H, 4'',7''-H), 7.92 (d, $J = 8.5$ Hz, 2H, 2',6'-H). ^{13}C NMR (DMSO- d_6): 25.6 (HetCH $_2$), 110.2 (C-7''), 119.0 (C-4''), 122.0 (C-1'), 124.6, 124.8 (C-5'',C-6''), 128.4, 129.6 (C-2',6', C-3',5'), 138.5 (C-4'), 141.8 (C-3a''), 152.5 (C-7a''), 162.1, 162.9, 165.1 (C-2, C-5, C-2''). MS: 343/345 (35/12, M^+ , $\text{Cl}_{35}/\text{Cl}_{37}$), 270 (3), 193 (25), 151 (15, 2-HS-benzoxazole), 139 (100, 4- $\text{ClC}_6\text{H}_4\text{CO}^+$), 123 (22), 111 (30, 4- ClC_6H_4^+), 91 (9), 75(15). Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{ClN}_3\text{O}_2\text{S}$ (343.78): C, 55.90; H, 2.93; N, 12.22. Found: C, 56.12; H, 2.77; N, 12.21.

2-(4-Chlorophenyl)-5-[(1,2,4-triazol-3-yl)thio]methyl-1,3,4-oxadiazole (6d). From chloride **1** (1.502 g, 6.557 mmol) and 3-mercapto-1,2,4-triazole (1.327 g, 13.122 mmol) as given for **4a**. Yield 78%, mp 138.5-139 $^{\circ}\text{C}$. IR: 3249 (NH), 3137, 1606 (C=N), 1565, 1484, 1460, 1410, 1274, 1232, 1092 (Ar-Cl), 1012, 845, 729 cm^{-1} . ^1H NMR (DMSO- d_6): 4.69 (s, 2H, HetCH $_2$), 7.69 (d, $J = 8.6$ Hz, 2H, 3',5'-H), 7.98 (d, $J = 8.6$ Hz, 2H, 3',5'-H), 8.60 (s, 1H, triazole-H), 14.20 (br s, 1H, NH). ^{13}C NMR (DMSO- d_6): 25.4 (HetCH $_2$), 122.2 (C-1'), 128.4, 129.9 (C-2',6', C-3',5'), 137.0 (C-4'), 145.6 br (triazole CH), 163.8, 164.7 (C-2, C-5). MS: 293/295 (25/8, M^+ , $\text{Cl}_{35}/\text{Cl}_{37}$), 193 (8), 139 (100, 4- $\text{ClC}_6\text{H}_4\text{CO}^+$), 113 (61), 111(61, 4- ClC_6H_4^+), 75(40). Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{ClN}_5\text{OS}$ (293.73): C, 44.98; H, 2.75; N, 23.84. Found: C, 45.21; H, 2.88; N, 23.44.

2-(4-Methoxyphenyl)-5-[(2-pyridyl)thio]methyl-1,3,4-oxadiazole (7a). From chloride **2** (1.531 g, 6.815 mmol) and 2-mercaptopyridine (0.761 g, 6.845 mmol) as given for **4a**. Yield 84%, mp 49.5-51 °C. IR: 2999, 1615 (C=N), 1591, 1557, 1500, 1458, 1425, 1261 (C-O-C, OMe), 1130, 1086, 1029, 838, 756 cm⁻¹. ¹H NMR (DMSO-d₆): 3.85 (s, 3H, OMe), 4.73 (s, 2H, HetCH₂), 6.96 (d, *J* = 9.0 Hz, 2H, 3',5'-H), 7.06 (ddd, *J* = 7.1, 4.9, 1.0 Hz, 1H, 5''-H), 7.26 (dd, *J* = 8.2, 1.1 Hz, 1H, 3''-H), 7.54 (ddd, *J* = 8.2, 7.1, 1.9 Hz, 1H, 4''-H), 7.91 (d, *J* = 9.0 Hz, 2H, 2',6'-H), 8.48 (dd, *J* = 4.9, 1.9 Hz, 1H, 6''-H). ¹³C NMR (DMSO-d₆): 23.2 (HetCH₂), 55.3 (OMe), 114.5 (C-3',5'), 116.4 (C-1'), 120.4, 122.4 (C-3',5''), 128.7 (C-2',6'), 136.5 (C-4''), 149.7 (C-6''), 156.0 (C-2''), 162.5, 163.8, 165.4 (C-2, C-5, C-4'). MS: 299 (56, M⁺), 226 (10), 164 (25), 149 (10), 135 (100, 4-MeOC₆H₄CO⁺), 124 (43, 2-pySCH₂⁺), 123 (50), 111 (19, 2-pySH), 92 (26), 78 (50, py⁺). Anal. Calcd. for C₁₅H₁₃N₃O₂S (299.34): C, 60.19; H, 4.38; N, 14.04. Found: C, 59.89; H, 4.29; N, 14.05.

5-[(2-Benzimidazolyl)thio]methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (7b). From chloride **2** (1.510 g, 6.722 mmol) and 2-mercaptobenzimidazole (1.011 g, 6.731 mmol) as given for **4a**. Yield 89%, mp 199-203 °C. IR: 1616 (C=N), 1558, 1499, 1410, 1307, 1261 (C-O-C, OMe), 1177, 1017, 1007, 843, 824, 735 cm⁻¹. ¹H NMR (DMSO-d₆): 3.83 (s, 3H, OMe), 4.90 (s, 2H, HetCH₂), 7.08 (d, *J* = 8.9 Hz, 1H, 3',5'-H), 7.15 (m, 2H, 5'',6''-H), 7.43, 7.55 (2xbr s, 2x1H, 4'',7''-H), 7.81 (d, *J* = 8.9 Hz, 2H, 2',5'-H), 12.80 (s, 1H, NH). ¹³C NMR (DMSO-d₆): 25.2 (HetCH₂), 55.4 (MeO), 110.8* (C-7''), 114.9 (C-3',5'), 115.7 (C-1'), 117.9* (C-4''), 121.6*, 122.2* (C-5'',6''), 128.4 (C-2',6'), 135.8*, 143.8* (C-3a'',C-7a''), 147.7 (C-2''), 162.3, 163.5, 164.6 (C-2, C-5, C-4'). Signals denoted with * slightly broadened due to the exchange of hydrogen between the two nitrogens. MS: 338 (20, M⁺), 190 (8), 189 (5), 163 (12, benzimidazolyl-SCH₂⁺), 162 (20), 150 (19, 2-SH-benzimidazole), 135 (100, 4-MeOC₆H₄CO⁺), 107(8, 4-MeOC₆H₄⁺), 92 (20), 77 (22). Anal. Calcd. for C₁₇H₁₄N₄O₂S (338.38): C, 60.34; H, 4.17; N, 16.56. Found: C, 60.66; H, 3.99; N, 16.47.

5-[(2-Benzothiazolyl)thio]methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (7e). From chloride **2** (1.859 g, 8.275 mmol) and 2-mercaptobenzothiazole (1.390 g, 8.311 mmol) as given for **4a**. Yield 76%, mp 88-92 °C. IR: 1613 (C=N), 1585, 1500, 1463, 1427, 1307, 1225 (C-O-C, OMe), 1175, 1018, 997, 846, 755 cm⁻¹. ¹H NMR: 3.86 (s, 3H, OMe), 4.89 (s, 2H, HetCH₂), 6.96 (d, *J* = 9.0 Hz, 2H, 3',5'-H), 7.34, 7.46 (2xm, 2x1H, 5'',6''-H), 7.79 (dd, *J* = 7.6, 1.5 Hz, 1H, 8''-H), 7.90 (m, 3H, 2',6'-H, 4''-H). ¹³C NMR: 26.4 (HetCH₂), 55.3 (OMe), 114.5 (C-3',5'), 116.1 (C-1'), 121.2, 122.1, 124.9, 126.4 (C-4'', C-5'', C-6'', C-7''), 128.8 (C-2',6'), 135.8 (C-7a''), 153.0 (C-2''), 162.4, 162.7, 163.6, 165.7 (C-2, C-5, C-4', C-3a''). MS: 355 (12, M⁺), 179 (8), 167 (15, 2-HS-benzothiazole), 135 (100, 4-MeOC₆H₄CO⁺), 108 (10), 92 (10), 77 (12). Anal. Calcd. for C₁₇H₁₃N₃O₂S₂ (355.42): C, 57.45; H, 3.69; N, 11.82. Found: C, 54.55; H, 3.34; N, 11.90.

5-[(2-Benzimidazolyl)sulfinyl]methyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (8b). **Typical procedure.** 21 mL of 0.074 M dimethyldioxirane solution in acetone (ca. 2.1 equiv.) was added to a solution of **6b** (0.256 g, 0.747 mmol) in acetone (5 mL). The mixture was stirred for 30 minutes at room temperature and monitored by TLC (MeOH-PhMe = 5:1, v/v). After completion (30 min), the solvent was removed under reduced pressure to obtain 239 mg

yellowish crystalline solid which proved to be a 92/8 mixture of sulfoxide **8b** and sulfone 10b by ^1H NMR analysis. The crude product was purified by column chromatography (hexane- Me_2CO = 1:1, v/v) to give 198 mg (74%) of pure **8b**. mp 187-190 °C. IR: 3220 (NH), 2928, 1606 (C=N), 1554, 1484, 1400, 1270, 1094 (Ar-Cl), 1058, 1050 (S=O), 1012, 832, 746, 730 cm^{-1} . ^1H NMR (DMSO- d_6): 4.94 (d, J = 14.1 Hz, 1H, one of HetCH $_2$), 5.26 (d, J = 14.1 Hz, 1H, the other HetCH $_2$), 7.34 (m, 2H, 5'',6''-H), 7.48 (A $_2$ B $_2$, 4H, 2',3',5',6'-H), 7.65 (br s, 2H, 4'',7''-H). MS: 358 (70, M $^+$), 284 (93), 282 (42), 240 (82, M – benzimidazole), 210 (100), 208 (58), 181 (19), 150 (36, 2-HS-benzimidazole), 139 (69, 4-ClC $_6$ H $_4$ CO $^+$), 111 (36, 4-ClC $_6$ H $_4$ $^+$). Anal. Calcd. for C $_{16}$ H $_{11}$ ClN $_4$ O $_2$ S (358.80): C, 53.56; H, 3.09; N, 15.61. Found: C, 53.64; H, 2.99; N, 15.82.

5-[(2-Benzimidazolyl)sulfinyl]methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (9b). From sulfide **7b** (0.251 g, 0.742 mmol) with 61 mL 0.049 M dimethyldioxirane solution (ca. 4.0 equiv.) according to the procedure given for **8b** 0.247 g crude product (**9b/11b** = 9/1, ^1H NMR) was obtained which yielded 0.197 mg (75%) pure **9b** after column chromatography. mp 155-158.3°C. IR: 2928, 1612 (C=N), 1498, 1428, 1402, 1306, 1260 (C-O-C, OMe), 1174, 1064 (S=O), 1028, 838, 740 cm^{-1} . ^1H NMR (DMSO- d_6): 3.80 (s, 3H, MeO), 4.91 (d, J = 13.9 Hz, 1H, one of HetCH $_2$), 5.23 (d, J = 13.9 Hz, 1H, the other HetCH $_2$), 6.94 (d, J = 8.4 Hz, 2H, 3',5'-H), 7.34 (m, 2H, 5'',6''-H), 7.41 (d, J = 8.4 Hz, 2H, 2',6'-H), 7.64 (br s, 2H, 4'',7''-H). MS: 355 (5, M + 1), 354 (2, M $^+$), 338 (1, M – O), 336 (2, M – H $_2$ O), 321 (3, M – H $_2$ O – Me), 237 (8), 190 (30), 150 (37, 2-HS-benzimidazole), 135 (100, 4-MeOC $_6$ H $_4$ CO $^+$), 133 (25, 4-MeOC $_6$ H $_4$ CN), 73 (35). Anal. Calcd. for C $_{17}$ H $_{14}$ N $_4$ O $_3$ S (354.38): C, 57.62; H, 3.98; N, 15.81. Found: C, 57.66; H, 4.15; N, 15.97.

5-[(2-Benzimidazolyl)sulfonyl]methyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (10b). From sulfide **6b** (0.252 g, 0.732 mmol) with 58 mL 0.065 M dimethyldioxirane solution (ca. 5.2 equiv.) according to the procedure given for **8b** after removal of the solvent 0.247 g (90%) pure **10b** sulfone was obtained. mp 190-193.4°C. IR: 3088 (NH), 1608 (C=N), 1482, 1412, 1356, 1344 (SO $_2$), 1200, 1160, 1142 (SO $_2$), 1094, 1012, 836, 806, 746 cm^{-1} . ^1H NMR (DMSO- d_6): 5.68 (s, 2H, HetCH $_2$), 7.46 (br s, 2H, 5'',6''-H), 7.58 (d, J = 8.4 Hz, 2H, 3',5'-H), 7.66 (d, J = 8.4 Hz, 2H, 2',6'-H), 7.84 (br s, 2H, 4'',7''-H). MS: 310, 312 (48/15, M – SO $_2$, Cl $_{35}$ /Cl $_{37}$), 268 (44), 194 (16), 173 (56), 139 (100, 4-ClC $_6$ H $_4$ CO $^+$), 111 (56, 4-ClC $_6$ H $_4$ $^+$), 90 (35). Anal. Calcd. for C $_{16}$ H $_{11}$ ClN $_4$ O $_3$ S (374.80): C, 51.27; H, 2.96; N, 14.95. Found: C, 51.02; H, 3.13; N, 15.11.

5-[(2-Benzimidazolyl)sulfonyl]methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (11b). From sulfide **7b** (0.252 g, 0.745 mmol) with 76 mL 0.079 M dimethyldioxirane solution (ca. 8.1 equiv.) according to the procedure given for **8b** after removal of the solvent 0.250 g (91%) pure **11b** sulfone was obtained. mp 192-194 °C. IR: 3082 (NH), 1614 (C=N), 1498, 1340 (SO $_2$), 1262 (C-O-C), 1186, 1176, 1144 (SO $_2$), 1020, 1006, 840, 806, 742 cm^{-1} . ^1H NMR (DMSO- d_6): 3.82 (s, 3H, OMe), 5.64 (s, 2H, HetCH $_2$), 7.02 (d, J = 9.1 Hz, 2H, 3',5'-H), 7.45 (m, 2H, 5'',6''-H), 7.58 (d, J = 9.1 Hz, 2H, 2',6'-H), 7.74 (br s, 2H, 4'',7''-H). MS: 306 (31, M – SO $_2$), 264 (24), 221 (45), 189 (15), 173 (17), 157 (20), 135 (100, 4-MeOC $_2$ H $_6$ CO $^+$), 118 (9), 81(40). Anal. Calcd. for C $_{17}$ H $_{14}$ N $_4$ O $_4$ S (370.38): C, 55.13; H, 3.81; N, 15.13. Found: C, 55.42; H, 3.85; N, 15.02.

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