Potent "Clicked" MMP2 Inhibitors: Synthesis, Molecular Modeling and Biological Exploration

Jose María Zapico,[a] Pilar Serra,[a] Josune García-Sanmartín,[b] Kamila Filipiak,[a, c] Rodrigo J. Carbajo,[d] Anne K. Schott,[d] Antonio Pineda-Lucena,[d] Alfredo Martínez,[b] Sonsoles Martín-Santamaría,[a] Beatriz de Pascual-Teresa,*[a] Ana Ramos. *[a]

[a] Departamento de Química, Facultad de Farmacia, Universidad San Pablo CEU, Urbanización Montepríncipe, 28668 Boadilla del Monte, Madrid, Spain. Phone: (+34)913724724, Fax: (+34)913510496 E-mail: bpaster@ceu.es; aramgon@ceu.es;
[b] Center for Biomedical Research of La Rioja (CIBIR) C/ Piqueras 98, 26006 Logroño, Spain.
[c] Department of Molecular Biology, Faculty of Mathematics and Natural Sciences, The John Paul II Catholic University of Lublin, 20-718 Lublin, Poland.
[d] Structural Biology Laboratory, Medicinal Chemistry Department, Centro de Investigación Príncipe Felipe, Avda. Autopista del Saler, 16,46012 Valencia, Spain

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IR, δ_H and δ_C NMR, MS (ESI) and microanalysis data of compounds **14-22**

***N*-Hydroxy-4-({4-[4-(4-methylphenyl)-1*H*-1,2,3-triazole-1-yl]phenyl}sulfonyl)tetrahydro-2*H*-pyran-4-carboxamide (14).** (Found: C, 55.20; H, 5.23; N, 11.76; S, 6.76. $C_{21}H_{22}N_4O_5S{\cdot}H_2O$ requires C, 54.77; H, 5.25; N, 12.17; S, 6.96%); ν_{max} (KBr)/ cm^{-1} 3477, 3139, 1653; δ_H (DMSO-d_6) 1.98 (2H, td, *J* 13.4, 4.3, 2CH*H*), 2.26 (2H, d, *J* 13.4, 2CH*H*), 2.36 (3H, s, CH_3), 3.17 (2H, t, *J* 11.6, 2OCH*H*), 3.91 (2H, dd, *J* 11.6 and 3.7, 2OCH*H*), 7.34 (2H, d, *J* 7.9, ArH), 7.86 (2H, d, *J* 7.9, ArH), 7.97 (2H, d, *J* 9.2, ArH), 8.23 (2H, d, *J* 9.2, ArH),

9.30 (1H, br s, NH), 9.45 (1H, s, Triazole-H) 11.08 (1H, s, OH); n.O.e. $H_{9.45} \rightarrow H_{8.23}$, 2.4%; $\rightarrow H_{7.86}$, 3.0%; δ_C (DMSO-d_6) 20.8, 27.3, 63.9, 69.7, 119.3, 119.9, 125.4, 127.0, 129.6, 132.1, 134.1, 138.0, 140.5, 147.9, 160.4; MS (ESI): *m/z* 443.17 $[M+H]^+$.

***N*-Hydroxy-4-({4-[4-(4-pentylphenyl)-1*H*-1,2,3-triazole-1-yl]phenyl}sulfonyl)tetrahydro-2*H*-pyran-4-carboxamide (15).** (Found: C, 58.69; H, 6.10; N, 10.37; S, 5.94. $C_{25}H_{30}N_4O_5S{\cdot}H_2O$ requires C, 58.12; H, 6.24; N, 10.85; S, 6.21%); ν_{max} (KBr)/ cm^{-1} 3152, 1651; δ_H (DMSO-d_6) 0.87 (3H, t, *J* 6.7, CH_3), 1.23-1.31 (4H, m, $2CH_2$), 1.58-1.63 (2H, m, CH_2), 2.00 (2H, td, *J* 12.8 and 3.7, 2CH*H*), 2.25 (2H, d, *J* 12.8, 2CH*H*), 2.62 (2H, t, *J* 7.3 H, CH_2Ar), 3.18 (2H, t, *J* 11.0, 2OCH*H*), 3.90 (2H, dd, *J* 11.0 and 3.0, 2OCH*H*), 7.34 (2H, d, *J* 8.0, ArH), 7.87 (2H, d, *J* 8.0, ArH), 7.98 (2H, d, *J* 8.5, ArH), 8.23 (2H, d, *J* 8.5, ArH), 9.25 (1H, br s, NH), 9.45 (1H, s, Triazole-H), 11.05 (1H, s, OH); δ_C (DMSO-d_6) 14.1, 22.1, 27.4, 30.7, 31.0, 35.0, 64.0, 69.6, 119.5, 120.0, 125.6, 127.4, 129.1, 132.3, 134.1, 140.6, 143.1, 148.0, 160.4; MS (ESI): *m/z* 499.22 $[M+H]^+$.

***N*-Hydroxy-4-({4-[4-(4-pentylbenzyl)-1*H*-1,2,3-triazole-1-yl]phenyl}sulfonyl)tetrahydro-2*H*-pyran-4-carboxamide (16).** (Found: C, 60.04; H, 6.31; N, 10.36; S, 5.86. $C_{26}H_{32}N_4O_5S{\cdot}0.5H_2O$ requires C, 59.87; H, 6.38; N, 10.74; S, 6.15%); ν_{max} (KBr)/ cm^{-1} 3152, 1655; δ_H (DMSO-d_6) 0.85 (3H, br s, CH_3), 1.27 (4H, br s, $2CH_2$), 1.52 (2H, br s, C$H_2$$CH_2$Ar), 1.90-2.05 (2H, m, 2CH*H*), 2.24 (2H, d, *J* 12.8, 2CH*H*), 2.45-2.50 (2H, hidden by DMSO, CH_2CH_2Ar), 3.16 (2H, t, *J* 11.6, 2OCH*H*), 3.86-3.92 (2H, m, 2OCH*H*), 4.07 (2H, s, ArCH_2Ar'), 7.13 (2H, d, *J* 7.2, ArH), 7.19 (2H, d, *J* 7.2, ArH), 7.91 (2H, d, *J* 7.9, ArH), 8.17 (2H, d, *J* 7.9, ArH), 8.80 (1H, s, Triazole-H), 9.27 (1H, br s, NH), 11.08 (1H, s, OH); δ_C (DMSO-d_6) 14.1, 22.1, 27.4, 30.9, 31.0, 34.9, 64.0, 69.6, 119.9, 121.2, 128.6, 132.3, 133.8, 136.3, 140.5, 140.7, 148.2, 160.5; MS (ESI): *m/z* 513.27 $[M+H]^+$.

***N*-Hydroxy-4-{[4-(4-phenyl-1*H*-1,2,3-triazole-1-yl)phenyl]sulfonyl}tetrahydro-2*H*-pyran-4-carboxamide (17).** (Found: C, 53.85; H, 4.84; N, 12.23; S, 7.04. $C_{20}H_{20}N_4O_5S{\cdot}H_2O$ requires C, 53.80; H, 4.97; N, 12.55; S, 7.18%); ν_{max} (KBr)/ cm^{-1} 3218, 1667; δ_H (DMSO-d_6) 1.98 (2H, td, *J* 12.8, 2CH*H*), 2.25 (2H, d, *J* 12.8, 2CH*H*), 3.17 (2H, t, *J* 11.6, 2OCH*H*), 3.91 (2H, dd, *J* 11.6 and 3.1, 2OCH*H*), 7.42 (1H, t, ArH), 7.53 (2H, t, ArH), 7.96-8.00 (4H, m, ArH), 8.24 (2H, d, *J* 8.6, ArH), 9.35 (1H, br s, NH), 9.51 (1H, s, Triazole-H), 11.05 (1H, s, OH); δ_C (DMSO-d_6) 27.3, 63.8, 69.6, 119.7, 119.8, 125.4, 128.4, 128.9, 129.8, 132.1, 134.3, 140.4, 147.8, 160.2; MS (ESI): *m/z* 429.14 $[M+H]^+$.

***N*-Hydroxy-4-{[4-(4-biphenyl-4-yl-1*H*-1,2,3-triazole-1-yl)phenyl]sulfonyl}tetrahydro-2*H*-pyran-4-carboxamide (18).** (Found: C, 60.30; H, 4.86; N, 10.49; S, 6.03. $C_{26}H_{24}N_4O_5S{\cdot}H_2O$ requires C, 59.76; H, 5.01; N, 10.72; S, 6.14 %); ν_{max} (KBr)/ cm^{-1} 3224, 1667; δ_H (DMSO-d_6) 1.96-2.03 (2H, m, 2CH*H*), 2.26 (2H, d, *J* 13.4, 2CH*H*), 3.18 (2H, t, *J* 11.6, 2OCH*H*), 3.89-3.93 (2H, m, 2OCH*H*), 7.38-7.43 (1H, m, ArH), 7.48-7.53 (2H, m, ArH), 7.76 (2H, *J* 7.3, ArH), 7.85 (2H, *J* 8.5, ArH), 7.99 (2H, d, *J* 8.5, ArH), 8.07 (2H, d, *J* 8.5, ArH), 8.27 (2H, d, *J* 8.5, ArH), 9.32 (1H, br s, NH), 9.58 (1H, s, Triazole-H), 11.11 (1H, s, OH); δ_C (DMSO-d_6) 27.3, 63.9, 69.6, 120.0, 120.2, 126.0, 126.6, 127.4, 127.8, 128.9, 129.1, 132.3, 134.0, 139.5, 140.2, 140.5, 147.5, 160.5; MS (ESI): *m/z* 505.16 $[M+H]^+$.

***N*-Hydroxy-4-({4-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazole-1-yl]phenyl}sulfonyl)tetrahydro-2*H*-pyran-4-carboxamide (19).** (Found: C, 54.31; H, 4.88; N, 11.80; S, 6.76. $C_{21}H_{22}N_4O_6S{\cdot}0.5H_2O$ requires C, 53.95; H, 4.96; N, 11.98; S, 6.86%); ν_{max} (KBr)/ cm^{-1} 3223, 1690, 1666; δ_H (DMSO-d_6) 1.98 (2H, td, *J* 12.8, 4.3, 2CH*H*), 2.26 (2H, d, *J* 12.8 Hz, 2CH*H*), 3.17 (2H, t, *J* 11.6 Hz, 2OCH*H*), 3.91 (2H,

dd, *J* 11.6 and 3.7, 2OCH*H*), 7.09 (2H, d, *J* 9.2, ArH), 7.90 (2H, d, *J* 9.2, ArH), 7.98 (2H, *J* 9.2, ArH), 8.23 (2H, d, *J* 9.2, ArH), 9.23 (1H, br s, NH), 9.49 (1H, s, Triazole-H), 11.10 (1H, s, OH); δ_C (DMSO-d_6) 27.3, 55.3, 63.9, 69.6, 114.6, 118.8, 119.8, 122.4, 126.9, 132.3, 133.8, 140.6, 147.8, 159.6, 160.5; MS (ESI): *m/z* 459.15 $[M+H]^+$.

4-{[4-(4-Butyl-1*H*-1,2,3-triazole-1-yl)phenyl]sulfonyl}-*N*-hydroxytetrahydro-2*H*-pyran-4-carboxamide (20).(Found: C, 51.42; H, 6.03; N, 12.85; S, 7.33. $C_{18}H_{24}N_4O_5S{\cdot}0.9H_2O$ required C, 50.91; H, 6.12; N, 13.19; S, 7.55 %); ν_{max} (KBr)/ cm^{-1} 3191, 1659; δ_H (DMSO-d_6) 0.92 (3H, t, *J* 7.3, CH_3), 1.33-1.41 (2H, m, CH_2), 1.61-1.71 (m, 2H, CH_2), 1.96 (2H, td, *J* 12.8 and 3.7, 2CH*H*), 2.24 (2H, d, *J* 12.8, 2CH*H*), 2.73 (2H, t, *J* 7.9, C*H*$_2$Ar), 3.16 (2H, t, *J* 11.6 H, 2OCH*H*), 3.89 (2H, dd, *J* 11.6 and 3.0, 2OCH*H*), 7.92 (2H, d, *J* 8.6, ArH), 8.17 (2H, d, *J* 8.6, ArH), 8.79 (s, 1H, Triazole-H) 9.27 (1H, br s, NH), 11.04 (1H, s, OH); δ_C (DMSO-d_6) 13.7, 21.6, 24.6, 27.2, 30.8, 63.9, 69.5, 119.6, 120.4, 132.1, 133.6, 140.6, 148.8, 160.3; MS (ESI): *m/z* 409.17 $[M+H]^+$.

***N*-Hydroxy-4-[(4-{4-[((phenylsulfonyl)carbamoylamino)methyl]-1*H*-1,2,3-triazole-1-yl}phenyl)sulfonyl]-tetrahydro-2*H*-pyran-4-carboxamide (21).** (Found: C, 44.77; H, 4.46; N, 13.51; S, 9.97. $C_{22}H_{24}N_6O_8S_2{\cdot}2H_2O$ requires C, 43.99; H, 4.70; N, 13.99; S, 10.68 %); ν_{max} (KBr)/ cm^{-1} 3301, 1671; δ_H (DMSO-d_6) 1.97 (2H, td, *J* 12.8 and 4.3, 2CH*H*), 2.24 (2H, d, *J* 12.8, 2CH*H*), 3.17 (2H, t, *J* 11.6, 2OCH*H*), 3.89 (2H, dd, *J* 11.6 and 3.7, 2OCH*H*), 4.26 (2H, d, *J* 4.9 Hz, CONHC*H*$_2$), 6.78 (1H, br s, NHCON*H*CH_2), 7.45-7.48 (3H, m, ArH), 7.82 (2H, d, *J* 6.7, ArH), 7.92 (2H, d, *J* 8.5, ArH), 8.14 (2H, d, *J* 8.5, ArH), 8.63 (1H, s, Triazole-H), 9.34 (1H, br s, N*H*OH), 11.10 (1H, br s, OH); δ_C (DMSO-d_6) 27.3, 34.9, 64.0, 69.6, 120.0, 121.5, 127.3, 129.1, 132.3, 133.2, 133.9, 140.5, 146.5, 152.0, 160.5; MS (ESI): *m/z* 565.18 $[M+H]^+$.

***N*-Hydroxy-4-({[4-(4-phenoxybenzyl)-1*H*-1,2,3-triazole-1-yl]phenyl}sulfonyl)tetrahydro-2*H*-pyran-4-carboxamide (22).** (Found: C, 59.47; H, 4.98; N, 9.85; S, 5.58. $C_{27}H_{26}N_4O_6S{\cdot}0.8H_2O$ requires C, 59.07; H, 5.07; N, 10.21; S, 5.84 %); ν_{max} (KBr)/ cm^{-1} 3148, 1654; δ_H (DMSO-d_6) 1.97 (2H, td, *J* 12.8 and 4.9, 2CH*H*), 2.24 (2H, d, *J* 12.8, 2CH*H*), 3.16 (2H, t, *J* 12.0, 2OCH*H*), 3.89 (2H, dd, *J* 12.0 and 3.7, 2OCH*H*), 4.12 (2H, s, ArCH_2Ar'), 6.96-7.00 (4H, m, ArH), 7.12 (1H, t, *J* 7.3, ArH), 7.32-7.40 (4H, m, ArH), 7.92 (2H, d, *J* 8.6, Ph), 8.20 (2H, d, *J* 8.6, Ph), 8.82 (1H, s, Triazole-H), 9.28 (1H, br s, NH) 11.07 (1H. br s, OH); δ_C (DMSO-d_6) 27.4, 30.5, 64.0, 69.6, 118.5, 119.1, 120.0, 121.3, 123.5, 130.2, 130.3, 132.3, 133.8, 134.3, 140.7, 148.1, 155.2, 157.0, 160.5; MS (ESI): *m/z* 535.24 $[M+H]^+$.

Figure 1S. Evolution of the root-mean-square deviations (RMSD) of the Cα atoms of MMP2, in complex with compound **18**, with respect to the initial structure (pink) and the NMR structure (blue) (1hov, model1) along the 3-ns MD simulation.

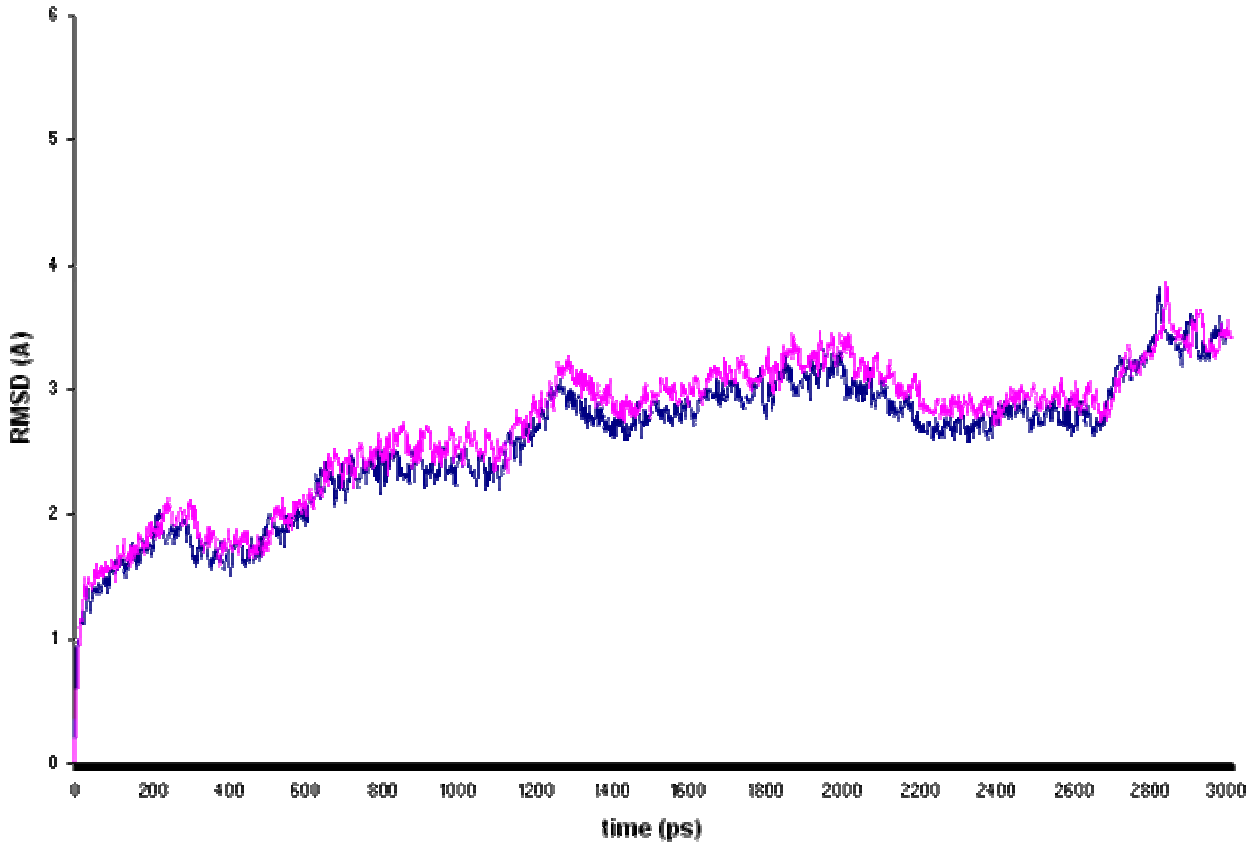

Figure 2S. Evolution of the root-mean-square deviations (RMSD) of the Cα atoms of MMP2, in complex with compound **19**, with respect to the initial structure (pink) and the NMR structure (blue) along the 3-ns MD simulation.

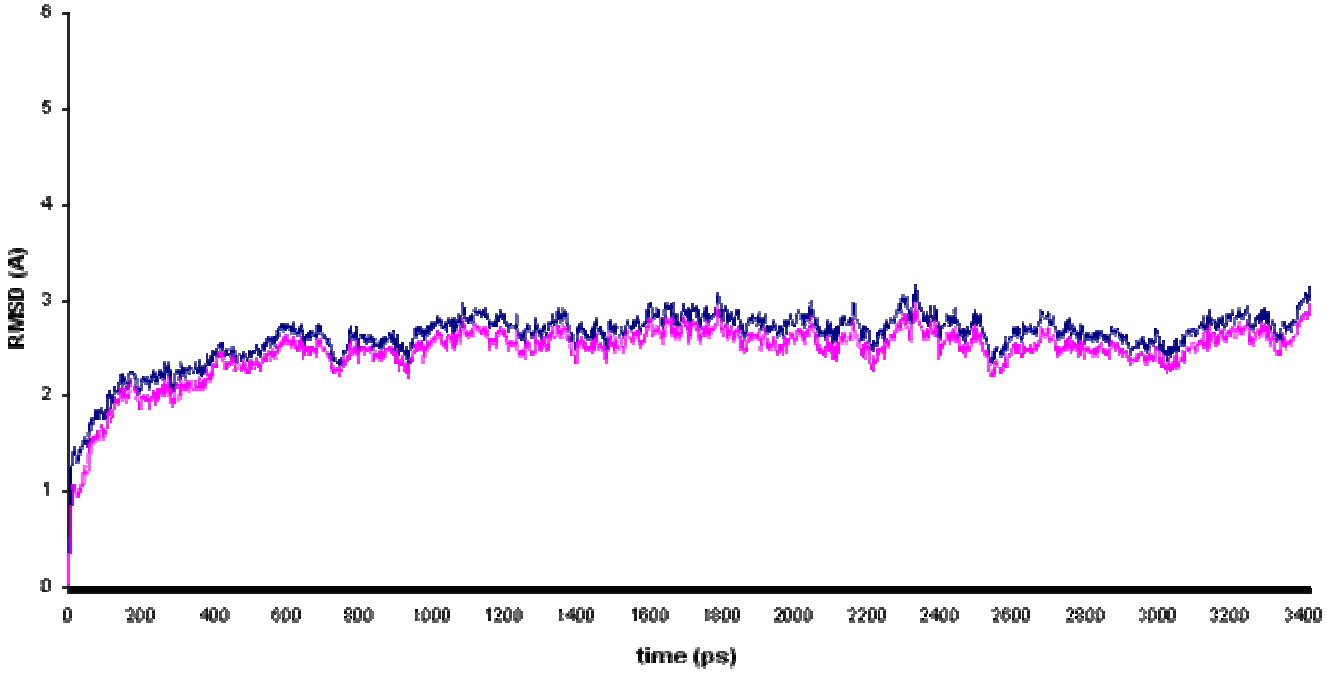

Figure 3S. Evolution of the distances with Zn ion involving hydroxamate oxygens of compound **18** (CO-Zn distance in blue; HO-Zn distance in pink) along the 3-ns MD simulation.

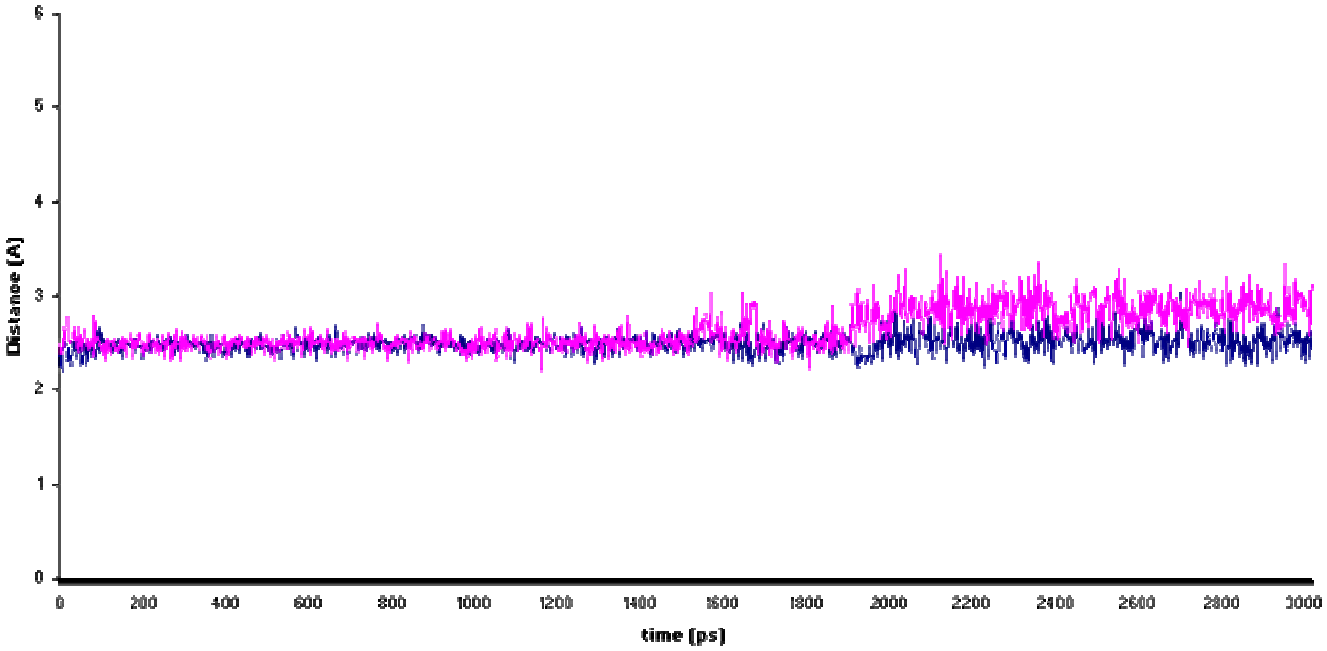

Figure 4S. Evolution of the distances with Zn ion involving hydroxamate oxygens of compound **19** (CO-Zn distance in blue; HO-Zn distance in pink) along the 3-ns MD simulation.