Supplementary Material

Thio-glycomimetics with enhanced lipophilicity and their biological activity

Zbigniew J. Witczak,*a Anastasia Mauger,a Roman Bielski,a and Donald E. Mencerb

aDepartment of Pharmaceutical Sciences, bDepartment of Chemistry and Biochemistry, Wilkes University, 84W South Street, Wilkes-Barre, PA 18766, USA
Email: zbigniew.witczak@wilkes.edu

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1. General information

All reagents and solvents were used as purchased without further purification. Unless otherwise stated, all reactions were carried out under inert atmosphere in oven-dried glassware with dried solvents. All solvents were dried and degassed by standard methods before use. Optical rotation was measured using a JASCO P-2000 Digital Polarimeter. 1H NMR and 13C NMR spectra were recorded on 400MHz Bruker Avance.2D experiments (COSY and HSQC) were performed to enhance assignments. Chemical shifts (δ-scale) are reported in ppm with TMS (0 ppm) as internal standard for 1H NMR and the residual solvent signals (CDCl3: 7.26, for H NMR and (CDCl3: 77.0 ppm) for 13C NMR. Thin layer chromatography was performed on silica gel coated TLC plates and visualized under UV light (at 254nm); detection was executed by exposing to iodine (I2) vapor. The melting points (mp) were obtained on an ElectroThermal FARGO MP- 2D capillary melting point apparatus and were uncorrected. Chemical names were generated by ChemDraw Professional V.15.1.0.144 software.

Crystal Structure Report for compound 10

(1R,2R,5S,6R)-8-(((3S,5S,7S)-adamantan-1-yl)thio)-3,11-dioxa-7,9-diazatricyclo[4.3.1.12,5]undec-8-en-1-ol

A specimen of C_{17}H_{24}N_{2}O_{3}S was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 12.20 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a tetragonal unit cell yielded a total of 5025 reflections to a maximum θ angle of 26.00° (0.81 Å resolution), of which 2963 were independent (average redundancy 1.696, completeness = 94.0%, R_{int} = 2.16%, R_{sig} = 3.44%) and 2733 (92.24%) were greater than 2σ(F^2). The final cell constants of a = 11.730(7) Å, b = 11.730(7) Å, c = 24.056(15) Å, volume = 3310.(4) Å^3, are based upon the refinement of the XYZ-centroids of 9858 reflections above 20 σ(I) with 4.850° < 2θ < 64.14°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.945. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 41 21 2, with Z = 8 for the formula unit, C_{17}H_{24}N_{2}O_{3}S. The final anisotropic full-matrix least-squares refinement on F^2 with 304 variables converged at R1 = 3.03%, for the observed data and wR2 = 7.39% for all data. The goodness-of-fit was 1.060. The largest peak in the final difference electron density synthesis was 0.389 e^-/Å^3 and the largest hole was -0.167 e^-/Å^3 with an RMS deviation of 0.038 e^-/Å^3. On the basis of the final model, the calculated density was 1.350 g/cm^3 and F(000), 1440 e^-.
Table 2. Data collection and structure refinement for compound 10.

| Property                        | Value       |
|---------------------------------|-------------|
| Formula weight                  | 336.44 g/mol|
| Temperature                     | 120(2) K    |
| Wavelength                      | 0.71073 Å   |
| Crystal system                  | tetragonal  |
| Space group                     | P41212      |
| Unit cell dimensions            |             |
| a                               | 11.730(7) Å |
| b                               | 11.730(7) Å |
| c                               | 24.056(15) Å|
| α                               | 90°         |
| β                               | 90°         |
| γ                               | 90°         |
| Volume                          | 3310.4(4) Å³|
| Z                               | 8           |
| Density (calculated)            | 1.350 g/cm³ |
| Absorption coefficient          | 0.212 mm⁻¹  |
| F(000)                          | 1440        |

Theta range for data collection
1.93 to 26.00°

Index ranges
Reflections collected
Independent reflections
Coverage of independent reflections
Absorption correction
Structure solution technique
Structure solution program
Refinement method
Refinement program
Function minimized
Data / restraints / parameters Goodness-of-fit on $F^2$
Final R indices

Weighting scheme
Absolute structure parameter
Largest diff. peak and hole
R.M.S. deviation from mean

-14<=h<=4, -9<=k<=12, -8<=l<=29 5025
2963 [R(int) = 0.0216]
94.0%

Multi-Scan
direct methods

XT, VERSION 2014/4 Full-matrix least-squares on $F^2$ SHELXL-2014/7 (Sheldrick, 2014)

2963 / 0 / 304
1.060
2733 data; I>2$\sigma$(I)

\[ R1 = 0.0347, \text{ wR2} = 0.0739 \]

all data

\[ w=1/[\sigma^2(F_o^2)+(0.0395P)^2+0.4573P] \text{ where } P=(F_o^2+2F_c^2)/3 \]
-0.1(0)
0.389 and -0.167 eÅ$^{-3}$
0.038 eÅ$^{-3}$
Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å²) for compound 10.

\( U(\text{eq}) \) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

|   | x/a      | y/b    | z/c    | \( U(\text{eq}) \) |
|---|----------|--------|--------|----------------------|
| S1| 0.60339(6)| 0.13124(6) | 0.47987(2) | 0.01858(16) |
| O1| 0.24982(16) | 0.34650(16) | 0.43494(7)  | 0.0198(4)   |
| O2| 0.53477(16) | 0.46250(16) | 0.41065(7)  | 0.0204(4)   |
| O3| 0.37126(17) | 0.53325(16) | 0.37394(7)  | 0.0244(4)   |
| N1| 0.5636(2)  | 0.2388(2)  | 0.38374(9)  | 0.0185(5)   |
| N2| 0.43146(18) | 0.27116(18) | 0.45642(8)  | 0.0150(5)   |
| C1| 0.5396(2)  | 0.2905(2)  | 0.46352(9)  | 0.0162(5)   |
| C2| 0.4123(2)  | 0.9864(2)  | 0.47898(11) | 0.0218(6)   |
| C3| 0.3665(3)  | 0.8649(2)  | 0.46968(11) | 0.0262(6)   |
| C4| 0.4332(3)  | 0.7812(3)  | 0.50683(11) | 0.0285(7)   |
| C5| 0.5595(3)  | 0.7853(2)  | 0.49243(10) | 0.0233(7)   |
| C6| 0.5775(3)  | 0.7517(3)  | 0.43119(10) | 0.0224(6)   |
| C7| 0.5107(3)  | 0.8342(2)  | 0.39390(10) | 0.0219(6)   |
| C8| 0.5560(2)  | 0.9564(2)  | 0.40222(9)  | 0.0177(6)   |
| C9| 0.3832(3)  | 0.8304(3)  | 0.40856(12) | 0.0275(7)   |
| C10| 0.6051(3) | 0.9068(2)  | 0.50105(10) | 0.0214(6)   |
| C11| 0.5223(2) | 0.2243(2)  | 0.43615(9)  | 0.0156(5)   |
| C12| 0.5012(2) | 0.3111(2)  | 0.34460(10) | 0.0204(6)   |
| C13| 0.3744(3) | 0.2995(2)  | 0.35902(10) | 0.0196(6)   |
| C14| 0.3650(2) | 0.3448(2)  | 0.41847(9)  | 0.0160(5)   |
| C15| 0.4155(2) | 0.4679(2)  | 0.41936(10) | 0.0179(6)   |
| C16| 0.4533(3) | 0.5221(3)  | 0.32924(11) | 0.0296(7)   |
| C17| 0.5394(3) | 0.4361(2)  | 0.35209(10) | 0.0234(6)   |

Table 4. Bond lengths (Å) for compound 10.

|   |   |   |   |   |
|---|---|---|---|---|
| S1-C11| 1.789(3) | S1-C1| 1.855(3) |
| O1-C14| 1.408(3) | O1-H1O| 0.81(3) |
| O2-C15| 1.416(3) | O2-C17| 1.443(3) |
| O3-C15| 1.432(3) | O3-C16| 1.449(3) |
| N1-C11| 1.361(3) | N1-C12| 1.463(3) |
| N1-H1N| 0.81(3) | N2-C11| 1.294(3) |
| N2-C14| 1.480(3) | C1-C10| 1.539(4) |
| C1-C8| 1.540(3) | C1-C2| 1.541(4) |
C2-C3  1.539(4)  C2-H2A  0.95(3)
C2-H2B  0.98(3)  C3-C9  1.538(4)
C3-C4  1.541(4)  C3-H3  1.00(3)
C4-C5  1.523(4)  C4-H4A  0.97(3)
C4-H4B  1.02(3)  C5-C10  1.536(4)
C5-C6  1.540(3)  C5-H5  0.98(3)
C6-C7  1.535(4)  C6-H6A  0.99(3)
C6-H6B  0.99(3)  C7-C9  1.537(5)
C7-C8  1.542(4)  C7-H7  1.00(2)
C8-H8A  1.04(3)  C8-H8B  0.97(3)
C9-H9A  0.99(3)  C9-H9B  0.95(3)
C10-H10A  0.96(3)  C10-H10B  1.01(3)
C12-C13  1.534(4)  C12-C17  1.544(4)
C12-H12  0.98(3)  C13-C14  1.530(3)
C13-H13A  0.99(3)  C13-H13B  1.02(3)
C14-C15  1.561(4)  C15-H15  0.94(2)
C16-C17  1.529(4)  C16-H16A  1.01(3)
C16-H16B  1.01(4)  C17-H17  0.93(3)

Table 5. Bond angles (°) for compound 10.

| Bond Angles | Value (°) |
|-------------|-----------|
| C11-S1-C1   | 101.78(12)|
| C15-O2-C17  | 101.0(2)  |
| C11-N1-C12  | 119.4(2)  |
| C12-N1-H1N  | 121.2(2)  |
| C10-C1-C8   | 109.5(2)  |
| C8-C1-C2    | 110.1(2)  |
| C8-C1-S1    | 112.56(18)|
| C3-C2-C1    | 109.3(2)  |
| C1-C2-H2A   | 107.6(18) |
| C1-C2-H2B   | 108.5(17) |
| C9-C3-C2    | 109.8(2)  |
| C2-C3-C4    | 109.2(2)  |
| C2-C3-H3    | 108.2(2)  |
| C5-C4-C3    | 109.9(2)  |
| C3-C4-H4A   | 110.3(17) |
| C3-C4-H4B   | 109.5(17) |
| C4-C5-C10   | 109.8(2)  |
C10-C5-C6 108.6(2)  C4-C5-H5 109.0(18)
C10-C5-H5 109.6(18)  C6-C5-H5 109.8(17)
C7-C6-C5 109.1(2)  C7-C6-H6A 107.3(18)
C5-C6-H6A 112.0(17)  C7-C6-H6B 109.1(17)
C5-C6-H6B 110.1(17)  H6A-C6-H6B 109.3(3)
C6-C7-C9 110.1(2)  C6-C7-C8 109.5(2)
C9-C7-C8 109.5(2)  C6-C7-H7 110.2(17)
C9-C7-H7 109.3(17)  C8-C7-H7 108.2(17)
C1-C8-C7 108.8(2)  C1-C8-H8A 108.1(14)
C7-C8-H8A 110.4(16)  C1-C8-H8B 108.6(16)
C7-C8-H8B 111.4(17)  H8A-C8-H8B 109.2(2)
C7-C9-C3 109.6(2)  C7-C9-H9A 108.9(17)
C3-C9-H9A 110.1(16)  C7-C9-H9B 110.3(19)
C3-C9-H9B 108.6(16)  H9A-C9-H9B 109.2(2)
C5-C10-C1 109.8(2)  C5-C10-H10A 111.3(17)
C1-C10-H10A 108.1(16)  C5-C10-H10B 109.6(17)
C1-C10-H10B 108.4(16)  H10A-C10-H10B 110.2(2)
N2-C11-N1 126.1(2)  N2-C11-S1 118.37(18)
N1-C11-S1 115.6(2)  N1-C12-C13 106.7(2)
N1-C12-C17 109.3(2)  C13-C12-C17 109.8(2)
N1-C12-H12 108.9(16)  C13-C12-H12 109.7(16)
C17-C12-H12 112.2(16)  C14-C13-C12 104.5(2)
C14-C13-H13A 110.6(17)  C12-C13-H13A 111.8(17)
C14-C13-H13B 108.6(14)  C12-C13-H13B 111.8(16)
H13A-C13-H13B 109.2(2)  O1-C14-N2 109.89(19)
O1-C14-C13 109.7(2)  N2-C14-C13 109.6(2)
O1-C14-C15 109.4(2)  N2-C14-C15 109.4(2)
C13-C14-C15 105.6(2)  O2-C15-O3 110.3(2)
O2-C15-C14 109.4(2)  O3-C15-C14 110.1(15)
O2-C15-H15 109.0(16)  O3-C15-H15 110.1(15)
C14-C15-H15 112.3(16)  O3-C16-C17 103.4(2)
O3-C16-H16A 108.8(18)  C17-C16-H16A 113.3(18)
O3-C16-H16B 107.3(18)  C17-C16-H16B 113.5(19)
H16A-C16-H16B 110.2(2)  O2-C17-C16 100.6(2)
O2-C17-C12 107.8(2)  C16-C17-C12 113.1(3)
O2-C17-H17 108.9(18)  C16-C17-H17 113.3(18)
C12-C17-H17 112.2(19)
Table 6. Anisotropic atomic displacement parameters (Å²) for compound 10.

The anisotropic atomic displacement factor exponent takes the form:

\[-2\pi^2 \left( a^2 U_{11} + \ldots + 2hk a^* b^* U_{12} \right) \]

|       | U₁₁  | U₁₂  | U₁₃  | U₁₄  | U₁₅  |
|-------|------|------|------|------|------|
| S1    | 0.0188(4) | 0.0169(4) | 0.0201(3) | -0.0029(2) | -0.0033(2) | 0.0030(3) |
| O1    | 0.0149(10) | 0.0263(11) | 0.0182(8) | -0.0076(8) | -0.0010(7) | 0.0013(8) |
| O2    | 0.0206(10) | 0.0185(10) | 0.0222(8) | -0.0020(7) | 0.0016(8) | -0.0028(9) |
| O3    | 0.0326(12) | 0.0203(10) | 0.0204(8) | 0.0020(8) | -0.0003(8) | 0.0074(9) |
| N1    | 0.0220(14) | 0.0188(13) | 0.0198(10) | -0.0012(9) | 0.0049(9) | 0.0070(11) |
| N2    | 0.0152(12) | 0.0127(11) | 0.0171(9) | -0.0030(8) | -0.0003(8) | 0.0001(9) |
| C1    | 0.0180(14) | 0.0147(14) | 0.0159(10) | -0.0012(9) | -0.0004(10) | 0.0023(11) |
| C2    | 0.0197(14) | 0.0192(15) | 0.0263(13) | 0.0012(11) | 0.0037(11) | 0.0046(13) |
| C3    | 0.0212(16) | 0.0184(15) | 0.0391(15) | 0.0027(11) | 0.0053(12) | 0.0019(14) |
| C4    | 0.044(2) | 0.0187(16) | 0.0251(13) | 0.0029(11) | 0.0101(12) | 0.0031(14) |
| C5    | 0.0358(18) | 0.0176(15) | 0.0165(11) | 0.0029(10) | -0.0001(11) | 0.0086(13) |
| C6    | 0.0325(19) | 0.0149(15) | 0.0199(12) | -0.0019(10) | 0.0019(11) | 0.0061(13) |
| C7    | 0.0335(18) | 0.0179(15) | 0.0144(11) | -0.0013(10) | -0.0028(10) | 0.0030(13) |
| C8    | 0.0235(16) | 0.0147(14) | 0.0148(10) | 0.0008(10) | -0.0019(10) | 0.0027(12) |
| C9    | 0.0332(19) | 0.0176(16) | 0.0316(14) | 0.0011(11) | -0.0098(12) | -0.0027(14) |
| C10   | 0.0271(17) | 0.0223(15) | 0.0147(11) | -0.0008(10) | -0.0025(10) | 0.0092(13) |
| C11   | 0.0174(14) | 0.0110(13) | 0.0183(11) | -0.0024(9) | -0.0001(9) | -0.0005(11) |
| C12   | 0.0271(16) | 0.0197(14) | 0.0145(11) | -0.0017(10) | 0.0029(11) | 0.0031(12) |
| C13   | 0.0239(16) | 0.0178(14) | 0.0171(11) | -0.0053(10) | -0.0028(11) | 0.0014(13) |
| C14   | 0.0152(13) | 0.0166(14) | 0.0161(11) | -0.0025(9) | -0.0006(10) | -0.0001(11) |
| C15   | 0.0206(15) | 0.0154(14) | 0.0177(12) | -0.0020(10) | -0.0024(10) | 0.0029(12) |
| C16   | 0.0416(19) | 0.0234(17) | 0.0238(13) | 0.0049(12) | 0.0057(13) | 0.0025(15) |
| C17   | 0.0274(17) | 0.0225(16) | 0.0203(12) | 0.0019(11) | 0.0057(12) | -0.0006(13) |

Table 7. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å²) for compound 10

|       | x/a   | y/b   | z/c   | U(eq) |
|-------|-------|-------|-------|-------|
| H1N   | 0.616(3) | 0.200(3) | 0.3732(12) | 0.021(8) |
| H1O   | 0.244(3) | 0.373(3) | 0.4660(14) | 0.036(9) |
| H3    | 0.283(3) | -0.135(3) | 0.4774(13) | 0.040(9) |
| H2A   | 0.374(3) | 0.041(3) | 0.4566(11) | 0.021(7) |
| H2B   | 0.404(2) | 0.007(2) | 0.5182(11) | 0.019(7) |
| H5    | 0.601(3) | -0.268(3) | 0.5167(12) | 0.030(8) |
| H4A   | 0.425(2) | -0.198(3) | 0.5457(11) | 0.021(7) |
|   | x/a   | y/b   | z/c   | U(eq) |
|---|-------|-------|-------|-------|
| H4B | 0.401(3) | -0.299(3) | 0.5019(11) | 0.026(8) |
| H7  | 0.521(2) | -0.187(2) | 0.3541(10) | 0.020(7)  |
| H6A | 0.549(3) | -0.326(3) | 0.4232(12) | 0.032(9)  |
| H6B | 0.660(3) | -0.244(3) | 0.4215(12) | 0.027(8)  |
| H8A | 0.643(3) | -0.040(2) | 0.3933(10) | 0.020(7)  |
| H8B | 0.515(2) | 0.011(3)  | 0.3790(12) | 0.021(7)  |
| H9A | 0.341(3) | -0.116(3) | 0.3838(11) | 0.027(8)  |
| H9B | 0.354(3) | -0.244(3) | 0.4036(11) | 0.023(8)  |
| H10A| 0.685(3) | -0.088(2) | 0.4918(10) | 0.014(7)  |
| H10B| 0.593(2) | -0.070(2) | 0.5411(11) | 0.023(7)  |
| H12 | 0.515(2) | 0.283(2)  | 0.3068(11) | 0.018(7)  |
| H13A| 0.326(3) | 0.345(3)  | 0.3335(12) | 0.027(8)  |
| H13B| 0.348(2) | 0.216(3)  | 0.3586(10) | 0.017(7)  |
| H15 | 0.401(2) | 0.506(2)  | 0.4533(10) | 0.008(6)  |
| H17 | 0.613(3) | 0.448(3)  | 0.3393(11) | 0.025(8)  |
| H16A| 0.412(3) | 0.494(3)  | 0.2948(12) | 0.028(8)  |
| H16B| 0.487(3) | 0.600(3)  | 0.3224(12) | 0.036(9)  |
