Design and Synthesis of Non-Peptide Mimetics Mapping the Immunodominant Myelin Basic Protein (MBP\textsubscript{83-96}) Epitope to Function as T-cell Receptor Antagonists

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Figure S1. (a) Plot of rms values over time for the Cα atoms of T cell receptor (TCR) residues in complex with compounds 14-19, (b) atomic positional fluctuations for the different residues in the TCR for the different molecular dynamics (MD) simulation runs, and (c) rms values for compounds 14-19, during the MD simulations.

Table S1. The chemical structures and properties of compounds 1-13, purchased from Ambinter Chemicals.

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<th>Ambinter Code</th>
<th>Structure</th>
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<th>logPa</th>
<th>PSA</th>
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LogP and PSA values are reported as shown on Ambinter Chemicals catalogue: [http://www.ambinter.com/](http://www.ambinter.com/)
Table S2. Semi-empirical (SE) binding energy in solvent, for molecule 15 in complex with the whole TCR and with selected binding site residues (kcal/mol).

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<tr>
<th>Method</th>
<th>Whole Receptor</th>
<th>Selected Site Residues</th>
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<tr>
<td>PM7</td>
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<td>-24.09</td>
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<tr>
<td>PM6-D</td>
<td>6.00</td>
<td>0.26</td>
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<tr>
<td>PM6-DH2</td>
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<td>AM1</td>
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Table S3. Interaction energies for 20 MD snapshots of analogue 15, using PM7 in solvent.

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<th>MD Snapshot</th>
<th>Analogue 15 Interaction Energy (Kcal/mol)</th>
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<td>15</td>
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<td>16</td>
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<td>17</td>
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<td>18</td>
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<td>19</td>
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<td>20</td>
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<td>Mean</td>
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<td>Standard Deviation</td>
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<td>Standard Error (SE)</td>
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Table S4. Interaction energy for molecule 15 in solvent as calculated by different density functional theory (DFT) methodologies, employing different basis sets.

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<tr>
<th>DFT Method in Solvent</th>
<th>cc-pVTZ</th>
<th>cc-pVDZ</th>
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<th>6-31G</th>
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<th>6-31+G**</th>
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<td>B97D</td>
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Table S5. Interaction energies for analogues 17-19, using PM7.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Interaction Energy (Kcal/mol)</th>
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<td>17</td>
<td>-35.39</td>
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<tr>
<td>18</td>
<td>-37.28</td>
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<tr>
<td>19</td>
<td>-35.40</td>
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Figure S2. RP-HPLC chromatogram (top) and ESI-MS (bottom) of final analogue 15 (MW\textsubscript{theoretical}: 285.34).

RP-HPLC Conditions:
- i) Column: Agilent ZORBAX Eclipse Plus C18 (3.5μm, 100x4.6mm),
- ii) Solvents: H\textsubscript{2}O (0.08% TFA), AcN (0.08% TFA),
- iii) Gradient elution: from 10% AcN to 100% AcN over 30min.
- iv) t\text{R}: 19.3 min, Purity: 99%
**Figure S3.** $^1$H NMR spectra of analogue 15 (400 MHz, CD$_3$OD) δ 7.27-7.36 (m, 4 H, Ph, Ar), 7.20-7.22 (m, 2 H, Ph), 6.78 (dd, 1 H, $J = 2.8, 2.4$ Hz, Ar), 6.52 (dd, 1 H, $J = 2.8, 2.0$ Hz, Ar), 5.13 (s, 2 H, CH$_2$Ph), 3.46 (t, 2 H, $J = 6.3$ Hz, CH$_2$), 3.35 (t, 2 H, $J = 6.3$ Hz, CH$_2$).

**Figure S4.** $^{13}$C NMR spectra of analogue 15 (100 MHz, CD$_3$OD) δ 168.6 (C=O), 159.0 (C=NH), 139.0 (C Ph), 129.8 (2 × CH Ph), 129.0 (CH), 128.5 (2 × CH Ph), 125.4 (CH), 123.6 (CH), 120.1 (C Ar), 109.0 (CH Ar), 54.5 (CH$_2$Ph), 42.4 (CH$_2$), 39.4 (CH$_2$).
Figure S5. RP-HPLC chromatogram (top) and ESI-MS (bottom) of final analogue 16 (MW\textsubscript{theoretical}: 285.34).

RP-HPLC Conditions:
i) Column: Agilent ZORBAX Eclipse Plus C18 (3.5\textmu m, 100x4.6mm),
ii) Solvents: H\textsubscript{2}O (0.08\% TFA), AcN (0.08\%TFA),
iii) Gradient elution: from 5\% AcN to 100\% AcN over 30min.
iv) t\textsubscript{R}: 20.2 min.

Figure S6. \textsuperscript{1}H NMR spectra of analogue 16 (600 MHz, CD\textsubscript{3}OD) \delta 7.19-7.27 (m, 3 H, Ph), 7.07 (d, 2 H, \textit{J} = 7.8 Hz, Ph), 6.97-6.98 (m, 1 H, Ar), 6.79-6.80 (m, 1 H, Ar), 6.14-6.15 (m, 1 H, Ar), 5.59 (s, 2 H, 3.40 (t, 2 H, \textit{J} = 6.3 Hz, CH\textsubscript{3}), 3.26 (t, 2 H, \textit{J} = 6.3 Hz, CH\textsubscript{3}).
Figure S7. $^{13}$C NMR spectra of analogue 16 (100 MHz, CD$_3$OD) δ 165.2 (C=O), 159.9 (C=NH), 140.6 (Ph), 129.5 (2 × CH Ph), 129.3 (CH), 128.3 (CH), 127.9 (2 × CH Ph), 126.0 (C Ar), 114.9 (CH Ar), 109.0 (CH Ar), 52.7 (CH:Ph), 42.4 (CH$_2$), 39.3 (CH$_2$).

Figure S8. RP-HPLC chromatogram (top) and ESI-MS (bottom) of final analogue 17 (MW$_{\text{theoretical}}$: 353.48).

RP-HPLC Conditions:

i) Column: Agilent ZORBAX Eclipse Plus C18 (3.5μm, 100x4.6mm),

ii) Solvents: H$_2$O (0.08% TFA), AcN (0.08% TFA),

iii) Gradient elution: from 10% AcN to 100% AcN over 30min.

iv) ts: 17.7 min, Purity: 99%
**Figure S9.** $^1$H NMR spectra of analogue 17 (600 MHz, CD$_3$OD) $\delta$ 7.95 (d, 1 H, $J = 7.8$ Hz, Ar$'$), 7.90 (s, 1 H, Ar$'$), 7.57 (t, 1 H, $J = 7.8$ Hz, Ar$'$), 7.43 (d, 1 H, $J = 7.8$ Hz, Ar$'$), 7.41 (app dd, 1 H, $J = 2.4, 1.8$ Hz, Ar), 6.85 (dd, 1 H, $J = 3.0, 2.4$ Hz, Ar), 6.56 (dd, 1 H, $J = 3.0, 1.8$ Hz, Ar), 5.26 (s, 2 H, CH$_2$Ar$'$), 3.47 (t, 2 H, $J = 6.0$ Hz, CH$_2$), 3.36 (t, 2 H, $J = 6.0$ Hz, CH$_2$).

**Figure S10.** $^{13}$C NMR spectra of analogue 17 (100 MHz, CD$_3$OD) $\delta$ 168.6 (C=O), 159.0 (2 × C=NH), 140.8 (C Ar$'$), 131.5 (CH), 131.1 (CH), 127.7 (CH), 127.2 (CH), 126.3 (C Ar$'$), 125.4 (CH), 123.7 (CH), 120.5 (C Ar), 109.4 (CH Ar), 54.0 (CH$_2$Ar$'$), 42.4 (CH$_2$), 39.5 (CH$_2$).
Figure S11. RP-HPLC chromatogram (top) and ESI-MS (bottom) of final analogue 18 (MW\textsubscript{theoretical} 343.39).

RP-HPLC Conditions:

i) Column: Agilent ZORBAX Eclipse Plus C18 (3.5μm, 100x4.6mm),

ii) Solvents: H\textsubscript{2}O (0.08% TFA), AcN (0.08%TFA),

iii) Gradient elution: from 10% AcN to 100% AcN over 30min.

iv) t\textsuperscript{R}: 16.6 min, Purity: 98%.

Figure S12. ¹H NMR spectra of analogue 18 (600 MHz, CD\textsubscript{3}OD) δ 7.33 (app dd, 1 H, J = 2.4, 1.8 Hz, Ar), 7.27 (d, 2 H, J = 8.1 Hz, Ar′), 7.17 (d, 2 H, J = 8.1 Hz, Ar′), 6.78 (dd, 1 H, J = 3.0, 2.4 Hz, Ar), 6.52 (dd, 1 H, J = 3.0, 1.8 Hz, Ar′), 5.11 (s, 2 H, CH\textsubscript{2}Ar′), 3.59 (s, 2 H, CH\textsubscript{2}CO\textsubscript{2}H), 3.46 (t, 2 H, J = 6.0 Hz, CH\textsubscript{2}), 3.35 (t, 2 H, J = 6.0 Hz, CH\textsubscript{2}).
Figure S13. RP-HPLC chromatogram (top) and ESI-MS (bottom) of final analogue 19 (MW\textsubscript{theoretical} 343.38).

RP-HPLC Conditions:

i) Column: Agilent ZORBAX Eclipse Plus C18 (3.5 μm, 100x4.6mm),

ii) Solvents: H\textsubscript{2}O (0.08% TFA), AcN (0.08% TFA),

iii) Gradient elution: from 5% AcN to 100% AcN over 30 min.

iv) \( t_R \): 18.9 min, Purity: 99%.

Figure S14. \(^1\)H NMR spectra of analogue 19 (400 MHz, CD\textsubscript{3}OD) \( \delta \) 7.98 (d, 2 H, \( J = 8.0 \) Hz, Ar'), 7.36 (app t, 1 H, \( J = 2.0 \) Hz, Ar), 7.28 (d, 2 H, \( J = 8.0 \) Hz, Ar'), 6.81-6.82 (m, 1 H, Ar), 6.55 (dd, 1 H, \( J = 2.8, 2.0 \) Hz, Ar), 5.23 (s, 2 H, CH\textsubscript{2}Ar'), 3.89 (s, 3 H, OCH\textsubscript{3}), 3.47 (t, 2 H, \( J = 6.4 \) Hz, CH\textsubscript{3}), 3.35 (t, 2 H, \( J = 6.4 \) Hz, CH\textsubscript{3}).