Supplementary Material

Rational design and regioselective synthesis of conformationally restricted furan-derived ligands as potential anti-malarial agents

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I. NMR Spectra

3-[(Trityloxy)methyl]furan 5
4-[(trityloxy)methyl]furan-2-carbaldehyde 6a
2-Acetyl-4-[(trityloxy)methyl]furan 6b
2-(3,3-Dimethylbutanoyl)-4-[(trityloxy)methyl]furan 6c
3-[(Trityloxy)methyl]furan-2-carbaldehyde 7a
2-acetyl-3-[(trityloxy)methyl]furan 7b
2-((3,3-dimethylbutanoyl)-3-[(trityloxy)methyl]furan 7c
4-(Hydroxymethyl)furan-2-carbaldehyde 8a
2-Acetyl-1-[4-(Hydroxymethyl)furan 8b
2-(3,3-Dimethylbutanoyl)-1-[4-(hydroxymethyl)]furan 8c
Diethyl (2-formylfuran-4-yl)methyl phosphate 9a
(2-Acetylfuran-4-yl)methyl diethyl phosphate 9b
Diethyl [2-(3,3-dimethylbutanoyl)furan-4-yl]methyl phosphate 9c
(2-Formylfuran-4-yl)methyl dihydrogen phosphate 10a
(2-Acetylfuran-4-yl)methyl dihydrogen phosphate 10b
[2-(3,3-Dimethylbutanoyl)furan-4-yl]methyl dihydrogen phosphate 10c
Diethyl \{2-[[\text{hydroxyimino}]methyl]furan-4-yl\}methyl phosphate 11a
Diethyl [2-([hydroxyimino]ethyl)furan-4-yl]methyl phosphate 11b
Diethyl {2-[1-(hydroxyimino)-3,3-dimethylbutyl]furan-4-yl}methyl phosphate 11c
{(2-[[Hydroxyimino]methyl]furan-4-yl)methyl dihydrogen phosphate 3\textsuperscript{a}}
{2-[1-(Hydroxyimino)ethyl]furan-4-yl}methyl dihydrogen phosphate 3b
{2-[1-(Hydroxyimino)-3,3-dimethylbutyl]furan-4-yl}methyl dihydrogen phosphate 3c
II. *In Silico* Modelling Data

**Figure 1.** Binding energies from Autodock flexible docking. Dashes indicate binding to EcDXR structures; circles to PfDXR structures. Binding is relatively poor to 1QOL across all compounds. In general 3c binds better to the EcDXR structures 2EGH, while 3a and 3b bind better to the PfDXR structures 3AUA and 3AU9 in this set of docking experiments.
Figure 2. Binding energies for Autodock Vina flexible docking. Circles represent binding energies to PfDXR structures, while dashes indicate binding to EcDXR structures. The potential pro-drugs 11a-c show variable but high binding energy to most systems; 3a and 3b bind well to all structures, while 3c binds preferentially to EcDXR systems (with the exception of the PfDXR homology model which was modelled on an EcDXR template).
Table 1. Binding Energies (kcal/mol) for flexible and rigid docking of fosmidomycin, FR900098 and various (de)protonation states of DOXP using Autodock Vina. In each case the pairs of energies are for flexible and rigid docking respectively.

| ligand | 3au rigi 9_A d | 3au rigi 9_B d | 3au rigi a_A d | 3au rigi a_B d | homo rigi logy d | 2eg rigi h_A d | 2eg rigi h_B d | 1q0 rigi I_A |
|--------|---------------|---------------|---------------|---------------|----------------|----------------|----------------|--------------|
| fosmidomycin | -8.2 - | -8.1 - | -7.9 - | -7.9 - | -6.2 - | -7.5 - | -7.3 - | -8.2 - |
| FR900098 | -8.2 - | -8.7 - | -8.9 - | -8.9 - | -8.0 - | -8.5 - | -8.2 - | -8.4 - |
| DOXP | | | | | | | | |
| dp | -7.9 -7.2 | -8.0 -7.3 | -7.8 -7.5 | -7.6 -7.5 | -7.2 -6.4 | -6.5 -6.8 | -6.7 -6.9 | -7.4 -7.1 |
| dpni | -8.0 -7.2 | -7.8 -7.6 | -7.7 -7.1 | -7.8 -7.5 | -6.8 -6.5 | -6.8 -6.6 | -7.1 -7.3 | -7.5 -7.3 |
| dpnii | -8.0 -7.5 | -8.0 -7.6 | -7.8 -7.7 | -7.8 -7.6 | -6.9 -6.1 | -6.9 -7.0 | -6.9 -7.0 | -7.4 -7.4 |
| dpniii | -8.2 -7.5 | -7.7 -7.6 | -7.8 -7.7 | -7.7 -7.6 | -7.1 -6.1 | -6.9 -7.0 | -7.1 -7.0 | -7.4 -7.4 |
| dpniv | -7.9 -7.3 | -7.9 -7.3 | -7.9 -7.7 | -7.8 -7.6 | -6.7 -6.1 | -6.9 -6.9 | -7.0 -7.1 | -7.3 -7.4 |
| dpnii | -8.4 -7.3 | -8.5 -7.3 | -8.1 -7.3 | -7.9 -7.7 | -7.2 -6.6 | -6.9 -6.5 | -7.1 -7.1 | -7.5 -7.0 |
| dpnii | -8.3 -7.5 | -8.2 -7.4 | -7.9 -7.6 | -7.9 -7.5 | -7.2 -6.4 | -6.7 -6.5 | -7.2 -7.2 | -7.5 -7.3 |
| dpnii | -8.2 -7.4 | -7.9 -7.3 | -7.7 -7.5 | -7.9 -7.6 | -6.8 -6.6 | -7.1 -6.6 | -7.1 -7.2 | -7.7 -7.3 |
| dpniv | -8.1 -7.6 | -8.2 -7.5 | -8.0 -7.6 | -8.0 -7.7 | -7.1 -6.7 | -7.0 -6.7 | -7.0 -7.2 | -7.3 -7.5 |
| dpnii | -8.3 -7.6 | -8.3 -7.5 | -7.9 -7.9 | -7.7 -7.9 | -7.1 -6.8 | -7.2 -6.5 | -7.4 -7.0 | -7.8 -7.5 |
| dpnii | -8.4 -7.3 | -8.3 -7.4 | -8.0 -7.7 | -7.4 -7.7 | -7.0 -6.7 | -7.3 -6.5 | -7.0 -7.0 | -7.4 -7.1 |
| dpniiiii | -8.1 -7.3 | -8.1 -7.3 | -7.9 -7.3 | -8.2 -7.3 | -6.7 -6.6 | -7.3 -6.8 | -7.1 -7.4 | -7.6 -7.2 |
| dpniv | -8.0 -7.3 | -7.9 -7.3 | -7.8 -7.3 | -8.2 -7.2 | -6.7 -6.6 | -7.2 -6.9 | -7.4 -7.4 | -7.8 -7.4 |
| dpniv | -8.0 -7.5 | -8.0 -7.5 | -7.8 -7.7 | -8.0 -7.6 | -6.8 -6.5 | -6.8 -7.1 | -7.0 -7.2 | -7.7 -7.5 |
| dpnvi | -8.3 -7.4 | -8.5 -7.6 | -8.1 -7.5 | -7.8 -7.7 | -7.0 -6.2 | -6.9 -6.4 | -7.1 -6.9 | -7.6 -7.1 |
Table 2a. Binding Energies (kcal/mol) for flexible and rigid docking of various (de)protonation states of 3a-c using Autodock Vina. In each case the pairs of energies are for flexible and rigid docking respectively.

| ligand | 3au 9_A | rigi 9_B | 3au 9_B | rigi a_A | 3au a_B | homology | 2egh  _A | rigi h_B | 1q0  _A | rigid |
|--------|--------|--------|--------|--------|--------|----------|--------|--------|--------|-------|
| 3a     | -7.4   | -6.4   | -7.5   | -6.7   | -7.0   | -6.5     | -8.6   | -7.2   | -7.7   | -7.8   | -7.9   | -7.7   | -7.8   | -7.6   |
| 3ani   | -7.4   | -6.6   | -7.9   | -7.0   | -7.8   | -6.5     | -8.3   | -7.4   | -7.5   | -7.9   | -7.5   | -7.6   | -7.8   | -7.7   |
| 3anii  | -7.4   | -6.5   | -7.5   | -7.0   | -7.2   | -6.4     | -7.8   | -7.3   | -7.7   | -7.6   | -7.7   | -7.3   | -7.9   | -7.6   |
| 3aniii | -7.5   | -6.5   | -7.6   | -6.9   | -7.4   | -6.4     | -7.7   | -7.4   | -7.7   | -7.6   | -7.8   | -7.4   | -8.4   | -7.6   |
| 3aniiit| -7.7   | -6.5   | -8.1   | -6.6   | -7.7   | -6.4     | -7.9   | -7.3   | -7.5   | -7.2   | -7.6   | -7.2   | -8.2   | -7.7   |
| 3aniit | -8.0   | -6.7   | -7.8   | -6.6   | -7.5   | -6.5     | -7.8   | -7.3   | -7.4   | -7.3   | -7.6   | -7.2   | -8.0   | -7.7   |
| 3anit  | -7.9   | -6.2   | -7.6   | -6.5   | -7.7   | -6.2     | -8.0   | -7.4   | -7.5   | -7.5   | -7.6   | -7.3   | -8.0   | -7.5   |
| 3anni  | -7.2   | -6.7   | -8.0   | -7.1   | -7.3   | -6.7     | -7.7   | -7.3   | -7.4   | -7.7   | -7.6   | -7.4   | -8.1   | -7.7   |
| 3annii | -7.3   | -6.7   | -8.0   | -7.1   | -7.9   | -6.7     | -7.8   | -7.3   | -7.5   | -7.6   | -8.0   | -7.4   | -7.8   | -7.7   |
| 3anniit| -7.4   | -6.4   | -8.0   | -7.0   | -7.6   | -6.4     | -7.9   | -7.5   | -7.3   | -7.1   | -7.4   | -7.3   | -7.8   | -7.5   |
| 3aniiit| -7.5   | -6.4   | -7.8   | -6.7   | -7.8   | -6.4     | -7.8   | -7.5   | -7.6   | -7.0   | -7.2   | -7.1   | -8.2   | -7.6   |
| 3anni  | -8.1   | -6.3   | -8.0   | -6.7   | -8.0   | -6.2     | -8.0   | -7.3   | -7.6   | -7.3   | -7.7   | -7.2   | -7.8   | -7.6   |
| 3annit | -7.3   | -6.3   | -7.6   | -6.6   | -7.8   | -6.3     | -7.8   | -7.3   | -7.7   | -7.3   | -7.7   | -7.2   | -8.1   | -7.6   |
| 3annii | -7.9   | -6.5   | -7.4   | -7.0   | -7.4   | -6.6     | -7.9   | -7.6   | -7.2   | -7.2   | -7.3   | -7.2   | -8.7   | -7.6   |
| 3annt  | -7.7   | -6.3   | -8.0   | -6.7   | -7.6   | -6.2     | -7.7   | -7.5   | -7.3   | -7.0   | -7.2   | -7.1   | -8.0   | -7.4   |
| 3at    | -8.2   | -6.5   | -8.1   | -6.7   | -8.0   | -6.5     | -7.5   | -7.1   | -7.5   | -7.6   | -7.9   | -7.3   | -8.1   | -7.7   |
| 3b     | -7.1   | -6.2   | -8.3   | -6.1   | -7.8   | -6.5     | -7.9   | -6.8   | -8.2   | -7.6   | -7.8   | -7.3   | -7.9   | -7.7   | -8.4   | -7.5   |
| 3bni   | -8.7   | -5.4   | -8.7   | -6.0   | -7.3   | -5.4     | -7.6   | -5.8   | -8.2   | -7.6   | -8.3   | -7.9   | -8.3   | -7.4   | -8.4   | -7.4   |
| 3bnii  | -7.3   | -6.5   | -8.1   | -6.1   | -7.7   | -6.6     | -8.2   | -6.8   | -8.2   | -7.6   | -8.0   | -7.6   | -8.1   | -7.7   | -8.5   | -7.8   |
| 3bniii | -7.5   | -6.3   | -7.9   | -6.3   | -8.0   | -6.6     | -8.2   | -7.6   | -7.9   | -7.6   | -8.1   | -7.6   | -8.3   | -7.8   |
| 3bniit | -8.6   | -7.0   | -8.1   | -7.2   | -8.3   | -7.0     | -8.3   | -7.1   | -8.8   | -7.7   | -8.1   | -7.7   | -8.4   | -7.6   | -8.6   | -7.9   |
| 3bnit  | -8.6   | -7.0   | -8.6   | -7.2   | -8.3   | -7.1     | -8.3   | -7.2   | -8.2   | -7.6   | -8.2   | -7.8   | -8.1   | -7.7   | -8.7   | -7.9   |
| 3bni   | -8.3   | -6.7   | -8.1   | -6.9   | -8.2   | -6.7     | -8.0   | -7.1   | -8.0   | -7.6   | -8.0   | -7.8   | -8.3   | -7.7   | -8.6   | -7.7   |
| 3bnii  | -7.3   | -6.1   | -8.3   | -6.1   | -8.3   | -6.4     | -8.3   | -7.9   | -8.1   | -7.8   | -8.2   | -7.6   | -8.6   | -8.0   |
Table 2b. Binding Energies (kcal/mol) for flexible and rigid docking of various (de)protonation states of 3a-c using Autodock Vina. In each case the pairs of energies are for flexible and rigid docking respectively.

| ligand | 3au 9_A  | rigi 9_B  | 3au 9_A  | rigi a_A  | 3au 9_A  | rigi a_A  | Homo- | 2egh _A  | rigi h_B  | 1qOl_ A  | rigi d  |
|--------|---------|-----------|---------|-----------|---------|-----------| -----|----------|-----------|----------|---------|
| 3bnnii | -7.4    | -6.1      | -8.2    | -6.1      | -8.2    | -6.4      | -8.1  | -6.6     | -8.3     | -7.8     | -8.0    | -7.8    | -8.2   | -7.5    | -8.6   | -8.0    |
| 3bnnii | -7.3    | -6.3      | -8.5    | -6.4      | -7.5    | -6.5      | -7.6  | -6.8     | -8.3     | -7.7     | -8.1    | -7.3     | -7.7   | -7.8    | -8.7   | -7.7    |
| 3bnniit| -7.9    | -6.9      | -7.9    | -7.0      | -8.3    | -6.9      | -7.8  | -7.0     | -8.2     | -7.6     | -8.0    | -7.5     | -8.1   | -7.6    | -8.9   | -7.9    |
| 3bnniit| -8.4    | -6.7      | -8.5    | -6.8      | -8.2    | -6.9      | -7.9  | -7.0     | -8.2     | -7.7     | -8.2    | -7.7     | -8.4   | -7.6    | -8.7   | -7.8    |
| 3bnnit | -8.4    | -6.6      | -8.6    | -6.8      | -8.3    | -6.7      | -7.9  | -6.9     | -8.2     | -7.7     | -8.2    | -7.7     | -8.3   | -7.6    | -8.6   | -7.8    |
| 3bnn   | -7.4    | -6.0      | -8.0    | -6.1      | -7.9    | -6.2      | -7.8  | -6.5     | -8.2     | -7.9     | -7.8    | -7.6     | -7.6   | -7.7    | -8.8   | -7.8    |
| 3bnnnt | -8.1    | -6.5      | -8.2    | -6.9      | -8.2    | -6.6      | -7.9  | -6.8     | -8.4     | -7.6     | -7.8    | -7.4     | -7.9   | -7.6    | -8.7   | -7.8    |
| 3bt    | -8.6    | -6.9      | -8.6    | -7.1      | -8.2    | -7.0      | -8.1  | -7.2     | -8.1     | -7.7     | -8.1    | -8.0     | -8.1   | -7.9    | -8.7   | -7.9    |
| 3c     | -4.5    | -4.9      | -6.7    | -5.1      | -4.9    | -5.0      | -6.2  | -5.0     | -9.0     | -8.6     | -8.9    | -8.4     | -9.6   | -7.8    | -8.9   | -5.7    |
| 3cnii  | -4.2    | -4.9      | -7.3    | -5.3      | -4.7    | -5.0      | -7.0  | -4.9     | -9.2     | -8.7     | -8.5    | -7.9     | -9.1   | -8.0    | -8.9   | -5.4    |
| 3cnii  | -4.7    | -4.9      | -7.0    | -4.9      | -6.5    | -4.8      | -6.7  | -4.9     | -8.6     | -8.5     | -9.1    | -8.4     | -8.8   | -8.0    | -9.0   | -5.6    |
| 3cnii  | -4.6    | -4.9      | -7.0    | -5.0      | -4.8    | -4.8      | -6.6  | -5.0     | -8.8     | -8.6     | -9.4    | -8.3     | -9.5   | -7.7    | -8.8   | -5.3    |
| 3cnii  | -4.6    | -5.1      | -7.1    | -5.2      | -4.5    | -5.0      | -5.1  | -5.3     | -8.8     | -8.5     | -8.5    | -7.6     | -8.8   | -7.8    | -7.3   | -5.4    |
| 3cnii  | -4.5    | -5.0      | -7.0    | -5.1      | -4.9    | -5.0      | -6.7  | -5.2     | -8.8     | -8.4     | -8.4    | -7.5     | -8.7   | -7.7    | -7.4   | -5.4    |
| 3cnit  | -4.4    | -4.7      | -6.9    | -4.8      | -4.5    | -4.7      | -6.9  | -4.8     | -8.9     | -8.4     | -9.2    | -7.9     | -9.3   | -8.1    | -8.0   | -5.4    |
| 3cnni  | -4.4    | -5.0      | -7.1    | -5.1      | -6.7    | -4.9      | -6.7  | -5.0     | -9.0     | -8.8     | -8.8    | -7.8     | -8.7   | -8.0    | -9.1   | -5.6    |
| 3cnnii | -4.8    | -4.9      | -7.7    | -4.9      | -6.5    | -4.8      | -7.1  | -5.0     | -8.8     | -8.6     | -9.1    | -7.8     | -9.0   | -8.1    | -9.3   | -5.5    |
| 3cnnii | -4.0    | -4.6      | -6.7    | -4.7      | -6.5    | -4.6      | -6.5  | -4.8     | -8.9     | -8.5     | -9.1    | -7.9     | -9.0   | -7.3    | -8.9   | -5.0    |
| 3cnnii | -4.6    | -4.8      | -6.7    | -4.9      | -4.5    | -4.8      | -6.7  | -5.1     | -8.8     | -8.1     | -8.1    | -7.2     | -8.6   | -7.2    | -7.8   | -5.0    |
| 3cnn   | -4.4    | -4.8      | -4.4    | -4.9      | -6.5    | -4.7      | -6.8  | -5.0     | -8.9     | -8.3     | -8.8    | -7.8     | -9.0   | -7.9    | -8.3   | -5.6    |
| 3cnn   | -4.7    | -4.9      | -4.8    | -5.0      | -4.3    | -4.8      | -6.7  | -4.9     | -8.9     | -8.4     | -8.6    | -7.7     | -8.8   | -7.8    | -8.4   | -5.5    |
| 3cnn   | -4.1    | -4.7      | -6.4    | -4.9      | -4.5    | -4.7      | -6.8  | -4.9     | -8.9     | -8.6     | -8.5    | -7.6     | -9.1   | -7.3    | -9.1   | -5.2    |
| 3cnnnt | -4.5    | -4.5      | -4.6    | -4.7      | -4.5    | -4.6      | -6.7  | -4.8     | -9.1     | -8.3     | -8.7    | -7.2     | -8.5   | -7.7    | -7.7   | -5.0    |
| 3ct    | -5.0    | -5.0      | -7.0    | -5.1      | -4.3    | -5.1      | -5.0  | -5.2     | -8.4     | -8.4     | -8.8    | -7.5     | -8.8   | -7.9    | -7.9   | -5.3    |
Table 3. Binding Energies (kcal/mol) for flexible and rigid docking of various (de)protonation states of 9a-c, 10a-c and 11a-c using Autodock Vina. In each case the pairs of energies are for flexible and rigid docking respectively.

| ligand | 3au9_A rigid | 3au9_B rigid | 3au_A rigid | 3au_a_A rigid | Homology rigid | 2eg_h_A rigid | 2eg_h_B rigid | 1q01_l_A rigid |
|--------|--------------|--------------|-------------|--------------|---------------|---------------|---------------|---------------|
| 9a     | -6.4 -5.5    | -7.0 -6.0    | -7.3 -5.4   | -7.6 -6.2    | -7.8 -7.1     | -6.6 -6.7     | -7.3 -7.0     | -7.2 -6.5     |
| 9b     | -6.4 -4.4    | -7.2 -5.1    | -7.4 -5.0   | -7.1 -5.8    | -8.0 -7.3     | -6.9 -7.1     | -7.6 -7.4     | -7.5 -5.0     |
| 9c     | -3.8 -4.7    | -6.4 -4.8    | -5.7 -4.7   | -6.3 -4.9    | -7.8 -7.4     | -7.7 -6.6     | -7.8 -6.6     | -7.3 -4.6     |
| 10a    | -7.3 -6.6    | -7.4 -6.9    | -7.5 -6.2   | -7.3 -6.4    | -7.7 -6.7     | -7.1 -7.0     | -7.0 -6.9     | -7.4 -7.2     |
| 10ani  | -7.5 -6.9    | -7.6 -7.0    | -7.5 -6.6   | -7.6 -6.5    | -7.6 -6.8     | -7.1 -6.8     | -7.2 -6.7     | -7.6 -7.4     |
| 10anii | -7.4 -6.9    | -7.6 -7.0    | -7.6 -6.6   | -7.7 -6.5    | -7.2 -6.8     | -7.4 -6.9     | -7.5 -6.8     | -7.6 -7.4     |
| 10ann  | -8.1 -6.8    | -8.1 -7.0    | -7.5 -6.6   | -7.5 -6.6    | -7.4 -6.8     | -6.8 -6.6     | -6.8 -6.7     | -7.6 -7.3     |
| 10b    | -7.5 -6.7    | -7.6 -7.1    | -7.7 -6.6   | -7.8 -6.9    | -8.4 -7.0     | -7.6 -7.4     | -7.5 -7.5     | -8.2 -7.6     |
| 10bni  | -7.3 -6.8    | -8.4 -7.2    | -7.9 -6.6   | -7.5 -6.9    | -8.0 -7.1     | -7.4 -7.3     | -7.6 -7.3     | -7.9 -7.6     |
| 10bnn  | -7.3 -6.9    | -7.9 -7.3    | -7.9 -6.6   | -8.0 -7.0    | -8.5 -7.1     | -7.4 -7.1     | -7.5 -7.3     | -7.9 -7.7     |
| 10c    | -7.3 -4.8    | -7.3 -4.7    | -7.0 -4.8   | -6.8 -4.9    | -8.4 -8.0     | -8.3 -7.8     | -8.6 -8.2     | -8.8 -6.1     |
| 10cni  | -7.0 -4.7    | -7.3 -4.7    | -7.2 -4.7   | -6.2 -4.8    | -8.5 -8.0     | -8.2 -7.8     | -8.1 -8.1     | -8.2 -6.1     |
| 10cnii | -6.5 -4.8    | -7.0 -4.7    | -7.0 -4.8   | -7.1 -4.8    | -8.6 -8.2     | -8.3 -7.8     | -8.5 -8.0     | -8.8 -6.0     |
| 10cnn  | -4.3 -4.6    | -6.8 -4.6    | -6.6 -4.6   | -6.1 -4.6    | -8.8 -7.8     | -8.0 -7.4     | -7.7 -7.8     | -8.2 -5.9     |
| 11a    | -7.3 -4.5    | 7.4 -5.7     | -6.7 -5.4   | -6.9 -5.8    | -7.2 -8.0     | -7.2 -7.0     | -7.7 -7.3     | -7.1 -5.9     |
| 11an   | -6.8 -4.4    | -7.0 -5.5    | -7.0 -5.0   | -7.4 -5.7    | -8.1 -7.9     | -7.2 -7.0     | -7.5 -7.3     | -8.1 -5.3     |
| 11ant  | -6.2 -4.4    | -7.4 -5.0    | -6.1 -4.3   | -6.9 -4.7    | -7.6 -7.9     | -7.3 -7.2     | -7.2 -7.2     | -8.6 -5.1     |
| 11at   | -6.2 -4.4    | -7.0 -5.1    | -7.2 -4.5   | -7.1 -4.5    | -8.0 -8.0     | -7.0 -7.0     | -7.4 -7.3     | -7.6 -5.1     |
| 11b    | -6.1 -4.8    | -6.6 -4.9    | -7.2 -5.0   | -7.1 -5.4    | -8.0 -7.9     | -7.8 -7.4     | -7.9 -7.5     | -7.6 -5.1     |
| 11bn   | -6.8 -4.5    | -6.3 -4.7    | -6.4 -4.5   | -7.2 -4.9    | -8.1 -7.8     | -7.8 -7.4     | -7.7 -7.4     | -8.7 -5.1     |
| 11bnt  | -6.6 -4.5    | -6.5 -4.6    | -7.1 -4.5   | -6.6 -4.7    | -8.1 -8.0     | -7.5 -7.7     | -8.1 -7.8     | -7.4 -4.9     |
| 11bt   | -6.2 -4.8    | -6.9 -4.8    | -7.4 -4.9   | -6.9 -4.9    | -8.4 -8.0     | -7.6 -7.4     | -7.8 -7.6     | -8.3 -4.9     |
| 11c    | -3.9 -4.5    | -5.7 -4.6    | -6.3 -4.5   | -4.3 -4.6    | -7.7 -7.7     | -8.2 -7.0     | -7.9 -6.6     | -7.7 -4.9     |
| 11cn   | -4.2 -4.7    | -4.5 -4.8    | -6.6 -4.6   | -4.4 -4.8    | -8.0 -8.0     | -8.1 -7.1     | -8.0 -6.6     | -7.5 -5.0     |
| 11cnt  | -4.2 -4.6    | -6.0 -4.7    | -6.0 -4.6   | -4.0 -4.5    | -7.9 -7.8     | -8.3 -6.8     | -8.5 -7.3     | -6.7 -4.8     |
| 11ct   | -4.4 -4.7    | -5.8 -4.8    | -6.2 -4.8   | -4.5 -5.0    | -8.1 -7.7     | -8.2 -6.7     | -8.3 -7.4     | -7.0 -4.9     |

III. Saturation Transfer Difference (STD) NMR binding protocol

The STD experiment [1,2] was run on the ligands as follows: EcDXR enzyme, stored in sodium phosphate buffer (pH 7.0), was freeze-dried and re-suspended in D₂O to make a final concentration of 20 µM. Each set of ligands was dissolved in the protein solution to give a final ligand concentration of 800 µM and thus a protein:ligand molar ratio of 1:40. The STD experiment was carried out using parameters optimized in a previous study in our group. [1] The saturating on-resonance and off-resonance pulses were set at frequencies of 0.73 ppm and 20
ppm, respectively, while cycling between the on- and off-resonance phases was used to reduce the effects of changes in temperature or magnetic field homogeneity. A 3-9-19 water suppression pulse was applied at 4.7 ppm and 6000 scans were acquired. The on- and off-resonance spectra were subtracted from each other and processed using Bruker Topspin software.

[1] Mayer, M.; Meyer, B. Angew Chem. Int. Ed. 1999, 38, 1784-1788. DOI 10.1002/(SICI)1521-3773(19990614)38:12<1784::AID-ANIE1784>3.0.CO;2-Q.
[2] Marchioro C.; Davalli S.; Provera S.; Heller M.; Ross A.; Senn, H. Experiments in NMR Based Screening, in BioNMR in Drug Research, Zerbe O., Ed.; Wiley-VCH: Weinheim, 2003, Vol. 16, pp. 321-339.
[3] Conibear A. C., Synthesis and Evaluation of Novel Inhibitors of 1-Deoxy-D-xylulose-5-phosphate Reductoisomerase as Potential Antimalarials, MSc. Thesis, Rhodes University, Grahamstown, 2010.
Figure 3. STD NMR correlations for binding of furan derivatives 3a and 3b to EcDXR.