

OptiMim™

Mimetica's approach to drug development is based on our OptiMim™ technology: **Optimisable Mimetics**. This technology allows accurate mimetics of natural peptides to be made on our proprietary scaffolds and then optimised into candidate drugs for development, as illustrated in Figure 1 below. No other technology offers the ability to rapidly make such accurate mimetics and then effectively optimise them. This capability is due to an unmatched flexibility to vary both the scaffold shape and the attached groups, providing a highly efficient drug development process.

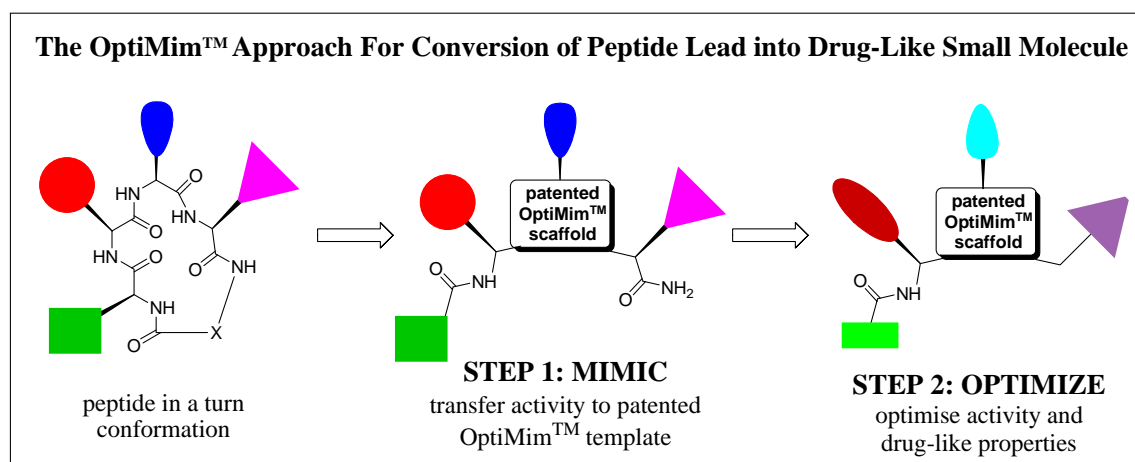


Figure 1. How the OptiMim™ technology is applied. The key side chain groups (coloured) from a biologically active peptide turn are transferred to a scaffold to give a peptide turn mimetic retaining some of the biological activity. Activity and drug-like properties are then optimised by systematic variation of the scaffold and substituent groups, producing a drug candidate.

The mimetics have several advantages over native peptides making them more likely to be useful drugs: increased stability, increased lipophilicity, increased rigidity, decreased size.

Mimetic drug candidates are then tested for their effectiveness in models of disease and for their pharmacological behaviour. The outcomes of this testing may indicate that further optimisation of the mimetic compound is needed to ensure activity, oral availability or acceptable duration of action. Where one of the required characteristics is lacking Mimetica has the advantage over traditional approaches that a new scaffold can be used with the same binding groups – potentially solving the problem with relatively little need for re-optimisation.

Key Competitive Advantages

- Rapid cost effective generation of lead compounds
- Compound novelty
- Superior optimisation and receptor selectivity
- Possibility for extended patent life due to scaffold patent coverage enabling the delay of therapeutic patent filing.

The technology is the best now available for making turn mimetics due to the very high levels of conformational control and large range of side-chain groups that can be included on the scaffold. High levels of biological activity transfer from peptide to mimetics have been achieved due to the ability to make accurate mimetics – difficult with other technologies. The chemistry provides many opportunities for the optimisation of the lead compounds initially generated. We have demonstrated that variation of the scaffold shape can lead to large increases in activity and selectivity.

Table 1. Illustration of how isomer variation can be used to optimise activity and selectivity. All four compounds have identical side-chain groups and the same core scaffold – only the chiral centres are different (radioligand binding affinity against ^{125}I NDP-MSH, nM).

Compound	Isomer	MC1	MC3	MC4	MC5
MTC173	1	4,000	>10,000	2,500	3,500
MTC176	2	2,000	>5,000	950	500
MTC180	3	10,000	>5,000	1,500	10
MTC185	4	-	>5,000	2,000	1,500

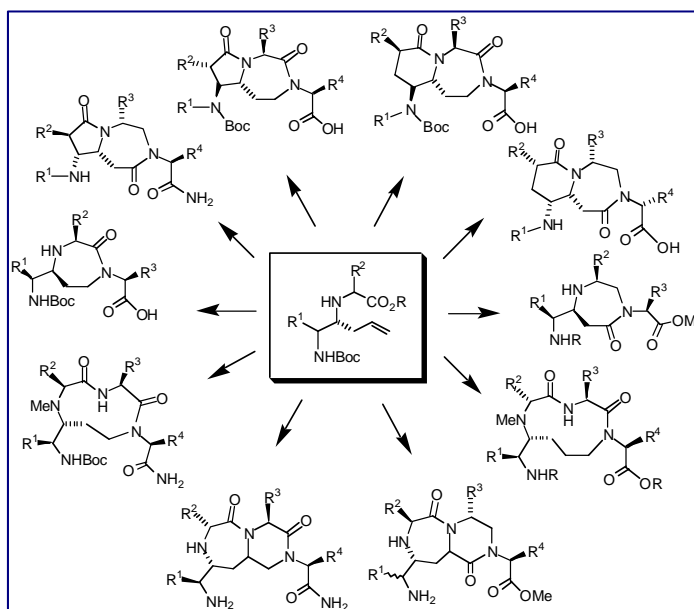


Figure 2. Some of the different scaffolds that can be made from the allylated dipeptide compounds that form the basis of Mimetica's technology platform.

The Technology is Broadly Applicable

The transfer of the biological activity of a GPCR ligand to one of Mimetica's proprietary scaffolds has been achieved in all attempts so far made, resulting in active compounds against the receptors listed in Table 2. Optimisation of initial active compounds has also been achieved, as shown in the table.

Table 2. Activity of OptiMim™-generated compounds designed for different GPCR targets.

Receptor	Activity from first iteration IC ₅₀	Number of iterations	Activity from latest cycle IC ₅₀
MC-1	5 µM	3	0.8 µM
MC-4	10 µM	6	0.9 µM
MC-5	10 µM	14	0.004 µM >500 fold selective over MC1-4
C5a	> 100 µM	4	20 µM
Urotensin II	10 µM	2	8 µM
SST-4	< 10 µM	3	0.3 µM
SST-5	< 10 µM	3	1 µM
GPIIB-IIIA	< 10 µM	1	NA

In addition Mimetica has shown the potential to selectively optimise for the desired activity type – usually agonism. Both agonism and antagonism have been demonstrated at both MC1 and MC4.

Further optimisation, required to develop products, will be conducted on the prime commercial targets (See Product Development).

Drug-like Characteristics of Mimetica's Chemistry

Representative mimetics have been tested for toxicity, microsomal stability, permeability and oral availability. The range of values obtained was consistent with the scaffolds being a suitable basis for oral drug development. In particular good levels of microsomal stability were found, and no evidence of toxicity was detected.

An assessment of Mimetica's lead compounds has been carried out by the Centre for Drug Candidate Optimisation (Monash University). The studies were conducted to obtain baseline and indicative data regarding the physicochemical, metabolic and biopharmaceutical properties of analogues based on the 1,4-diazacycloheptane scaffold, in particular focusing on the potential limitations for developing drugs for oral administration.

The study found that: "The preliminary assessment of the physicochemical, metabolic and biopharmaceutical characteristics suggest that the chemical scaffold forming the basis of the four analogues examined display reasonable "drug-like" properties with no obvious or inherent issues that would preclude oral administration."