



Chemistry Tipping the Biological Seesaw

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During a biological inflammatory response, patrolling leukocytes (white blood cells) release chemokines - a type of peptide cytokine - to summon other leukocytes. Inhibition of this process could provide a mechanism for new anti-inflammatory drugs.

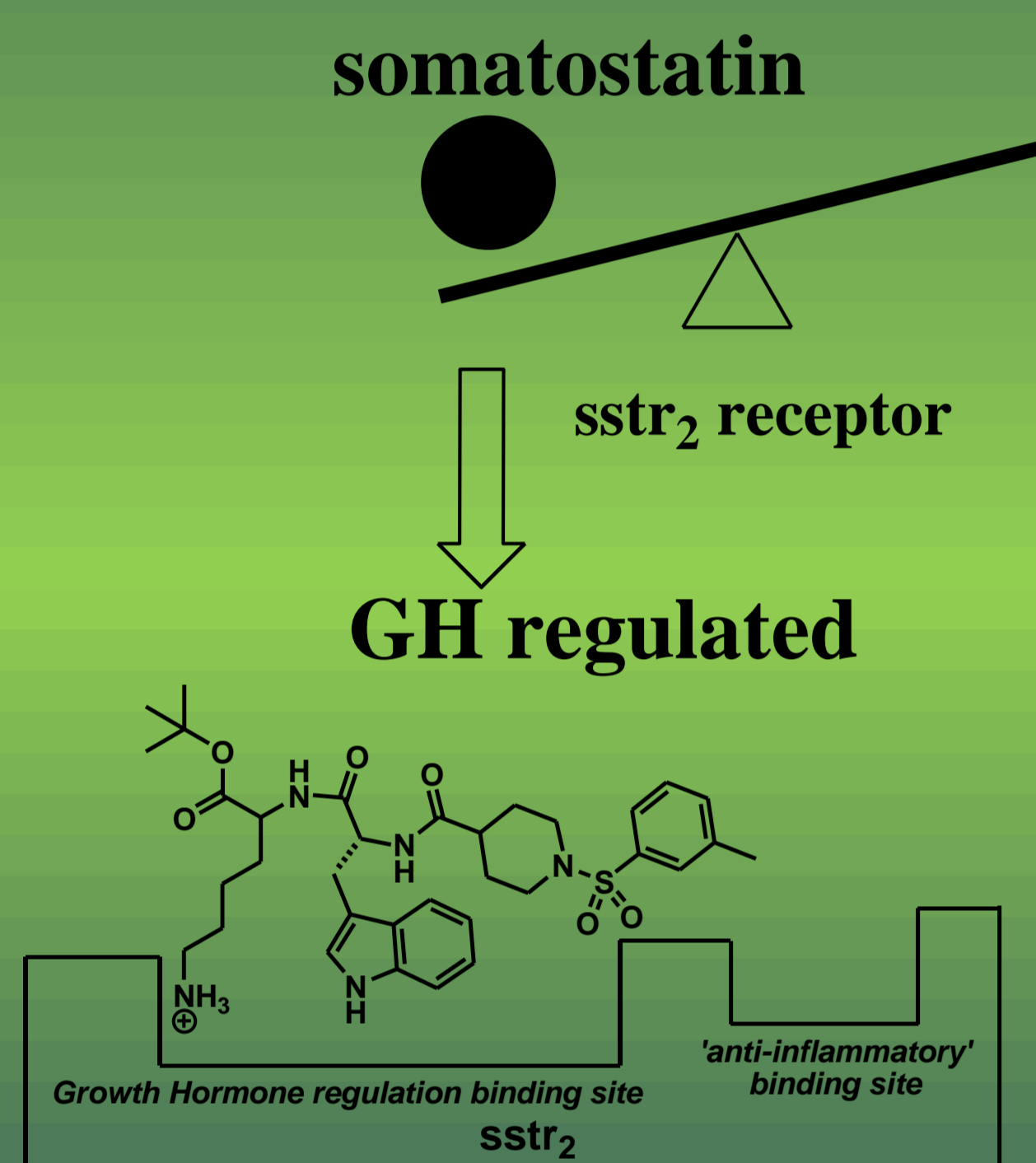
Traditionally inhibition has been sought by blocking chemokine receptors with antagonists, but we have found useful molecules by inhibiting functional cell migration - with great success.

We would not have discovered Broad-Spectrum Chemokine Inhibitors (BSCIs) using a receptor antagonist approach as our functional screening approach has discovered a new biological target for anti-inflammatory drug design - the *sstr₂* receptor.

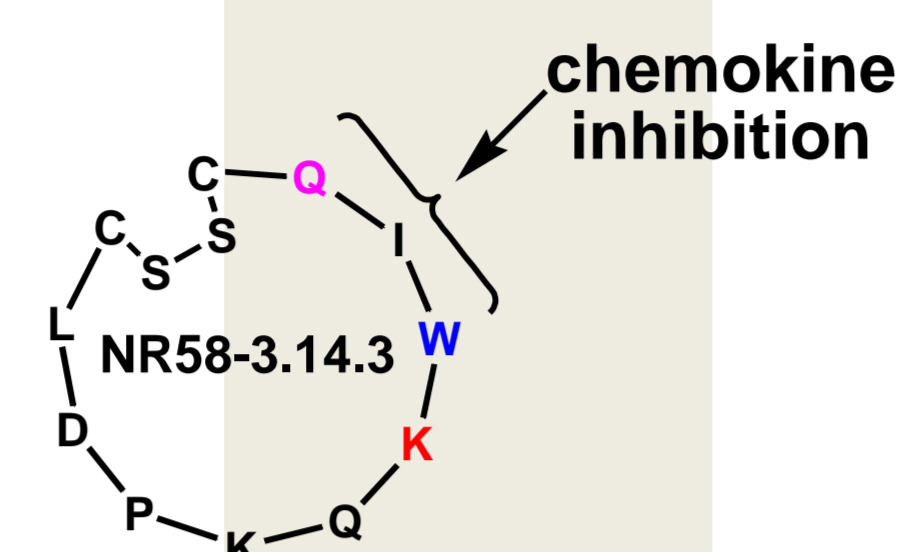
Sometimes inflammation is inappropriate and can exacerbate certain diseases for example cancer, arthritis and asthma.

Due to their role in initiating inflammation chemokines are therefore a good target for anti-inflammatory drugs - for example BSCIs.

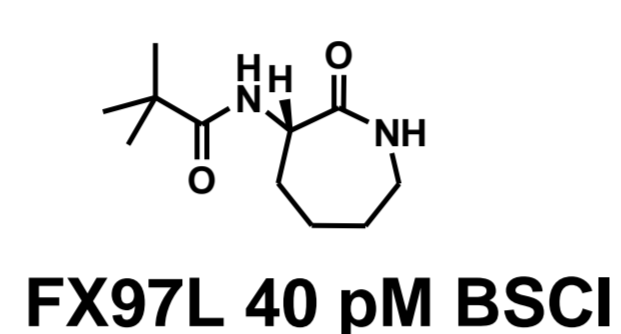
Functional selectivity is the ability for a receptor to have different functions depending on the molecule to which it is bound.



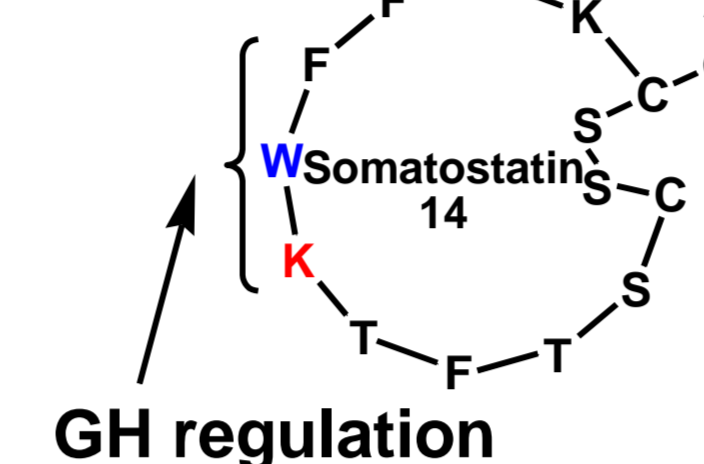
NR58-3.14.3 is a BSCI. It is a cyclic peptide with the critical motif being WIQ.



FX97L is a 40 pM BSCI.¹ The Q motif is mimicked by a caprolactam which retains the amide and has been found to be a successful pharmacological component.



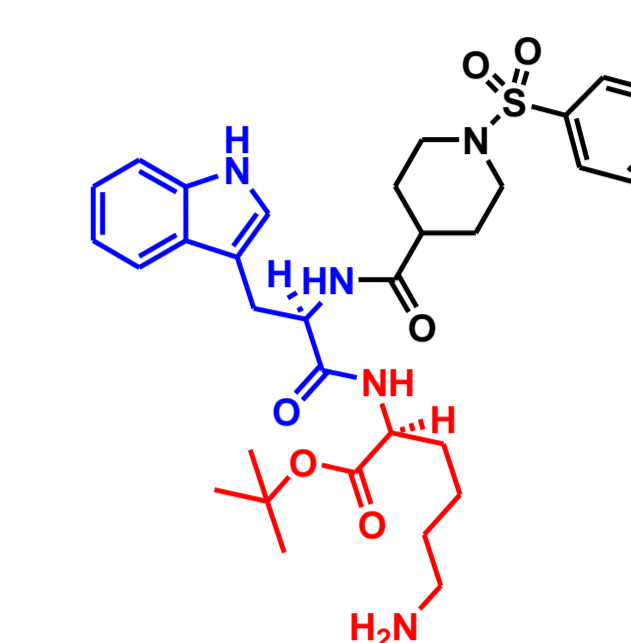
However, it has been discovered that BSCIs do not bind to chemokine receptors but to the *sstr₂* receptor for somatostatin.



Somatostatin is a peptide involved in growth hormone (GH) regulation.²

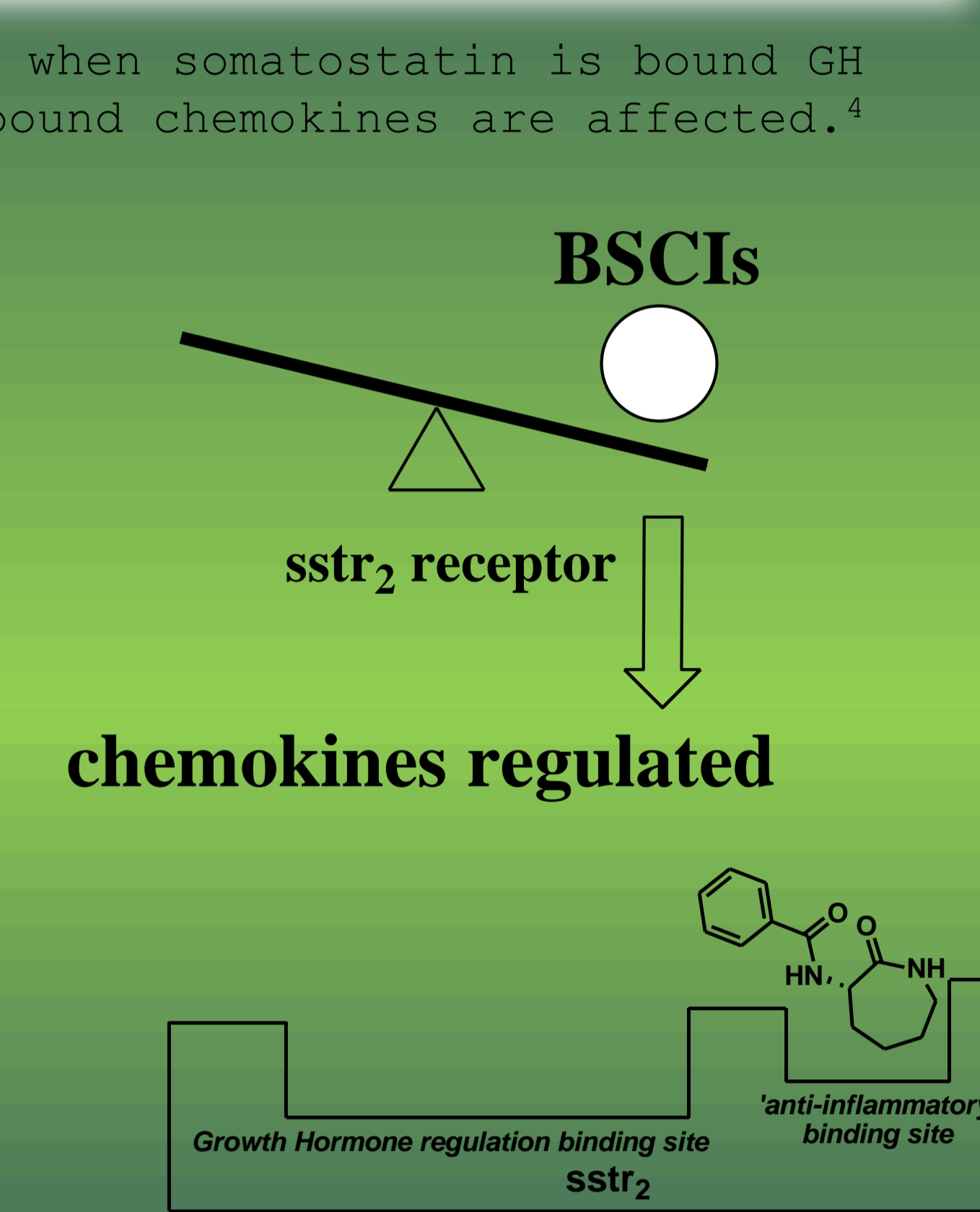
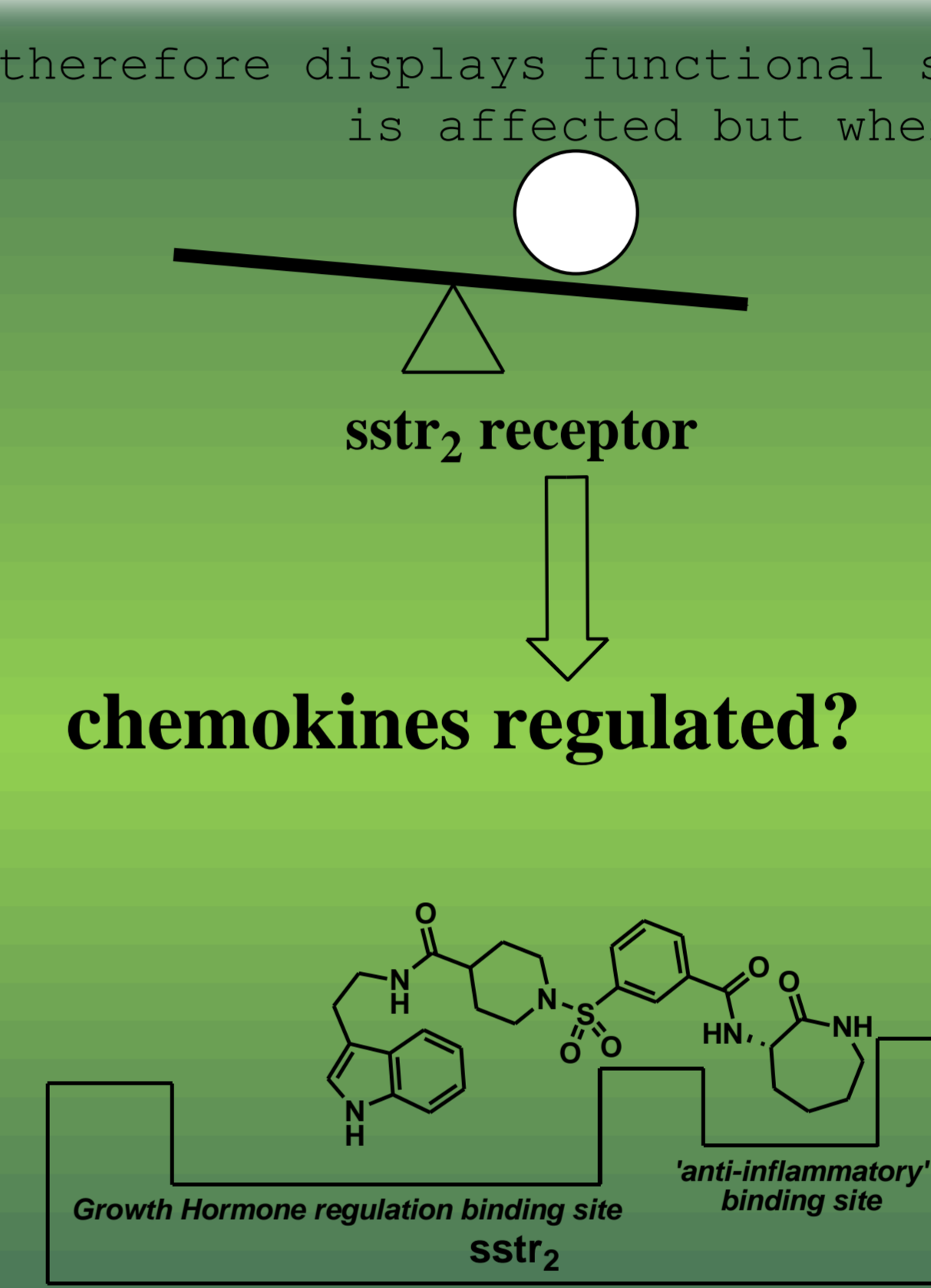
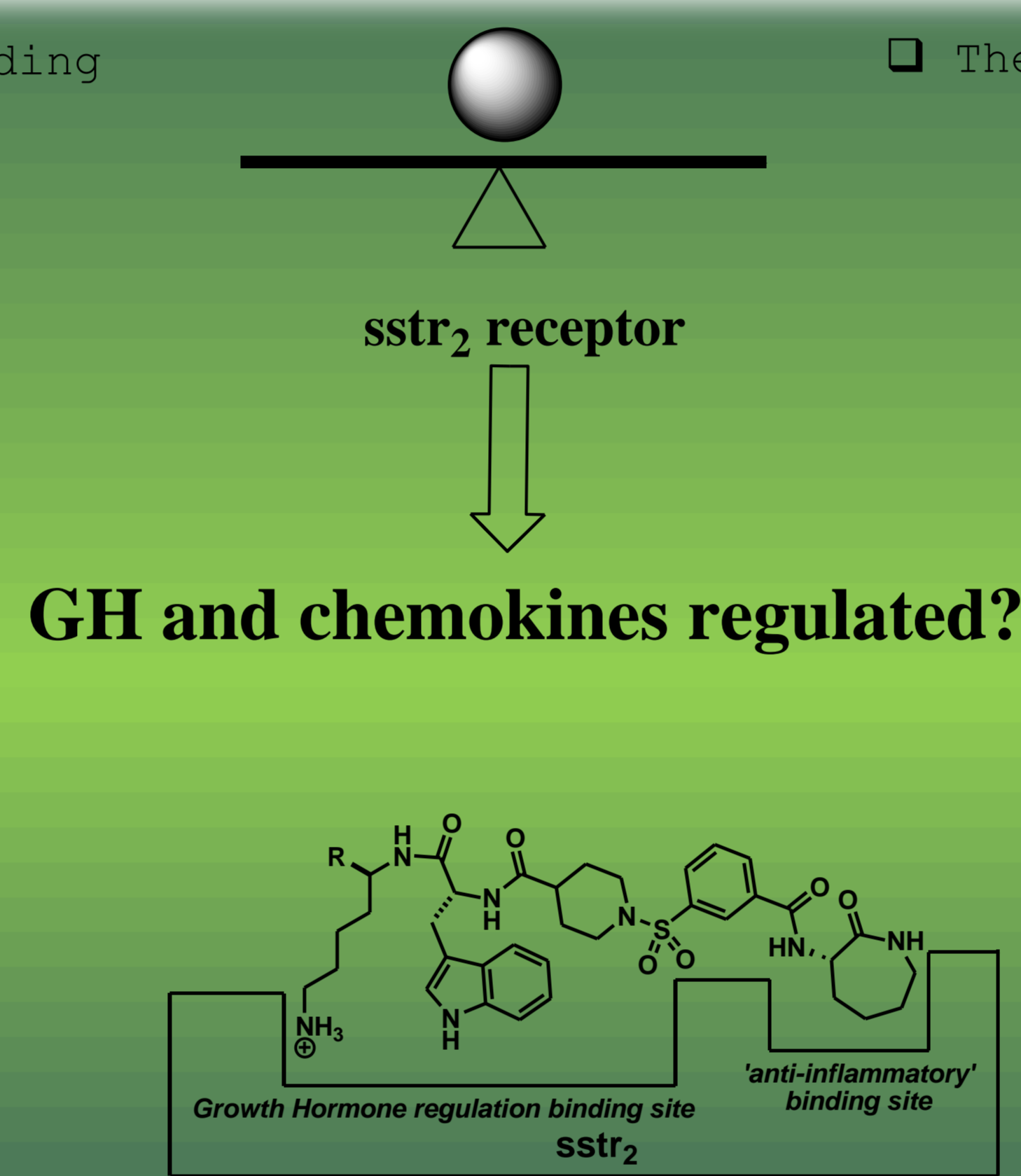
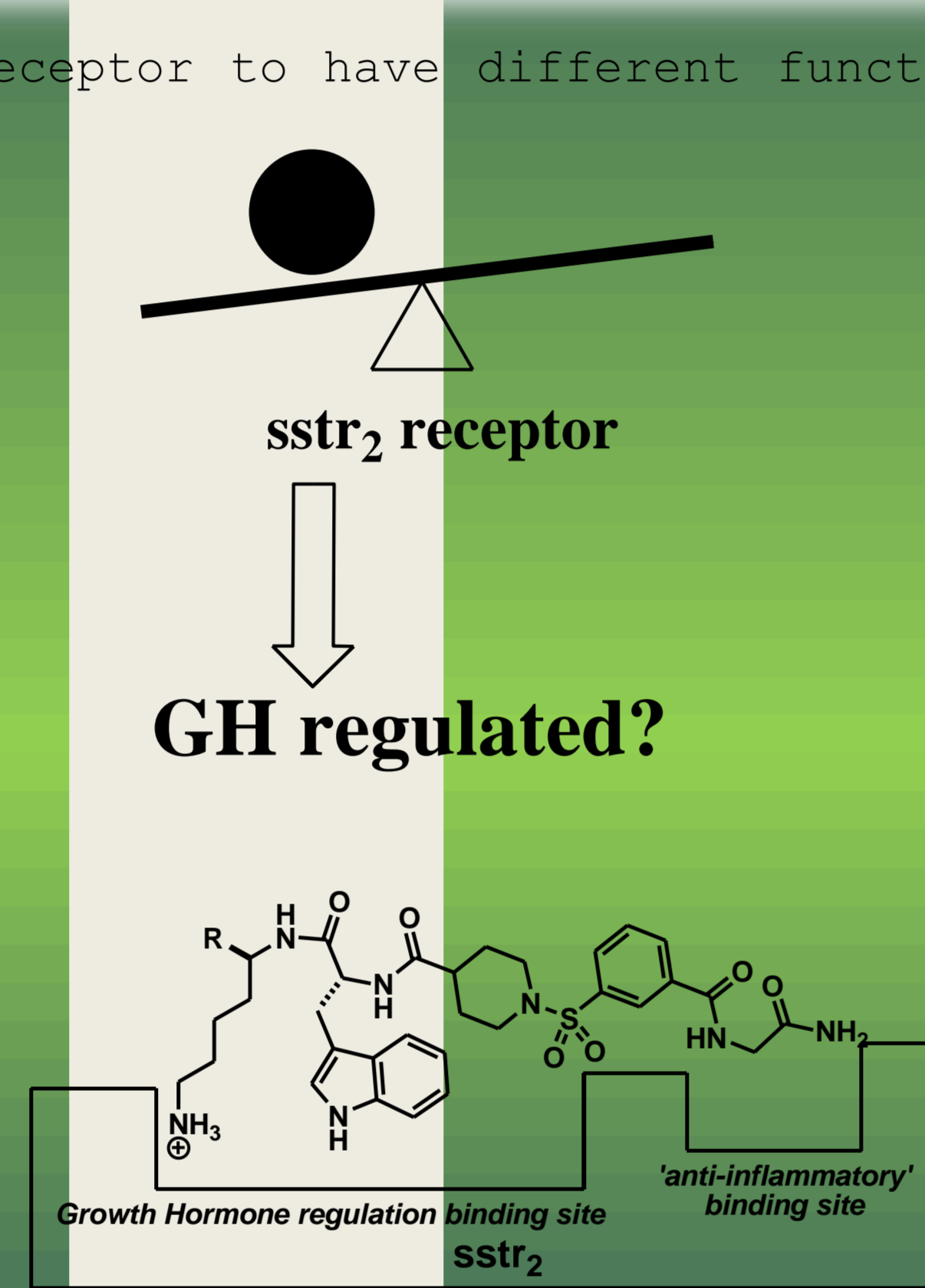
It is a cyclic peptide with the critical motif being KWF.³

An example of an *sstr₂* ligand based on the KWF motif.

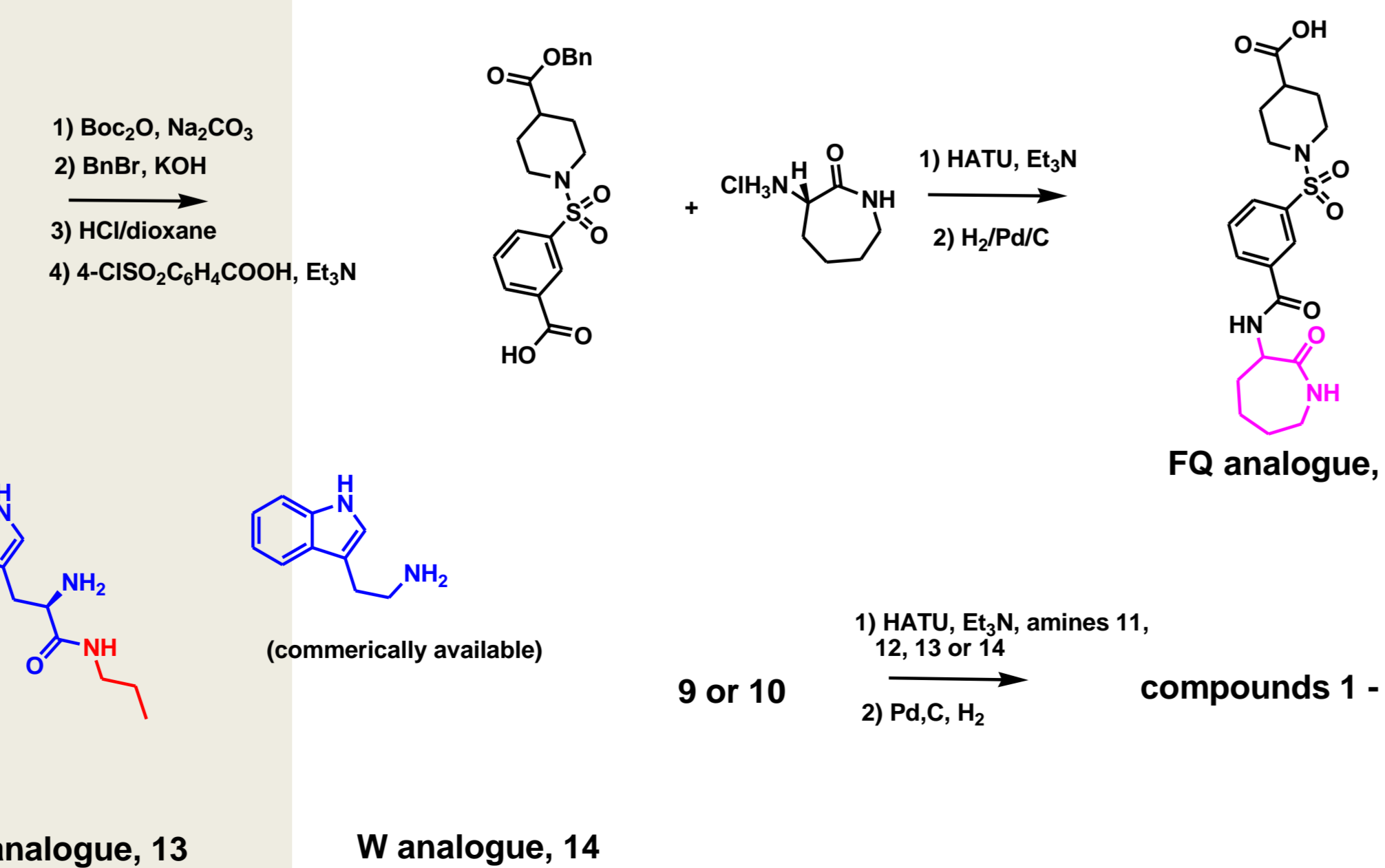
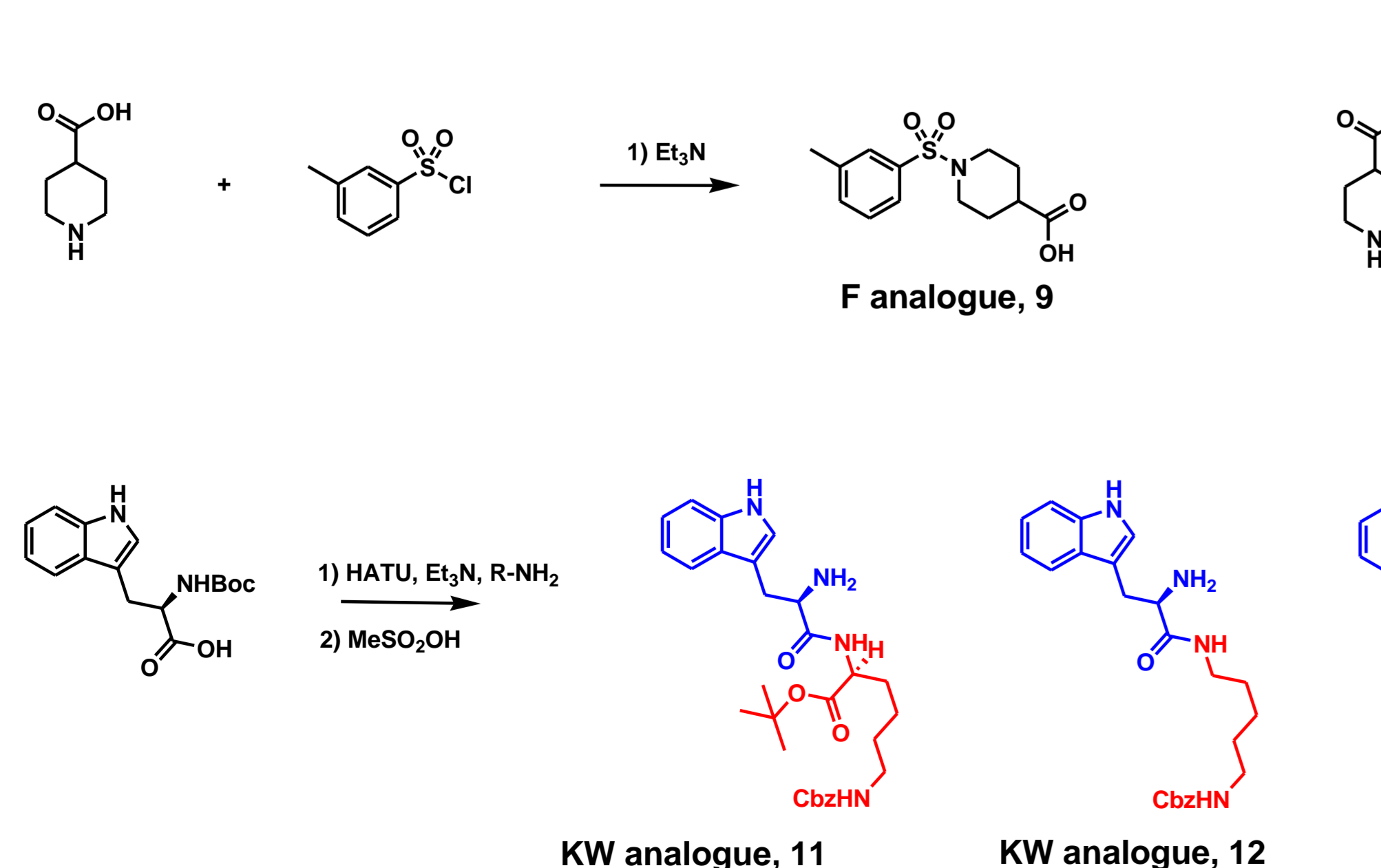
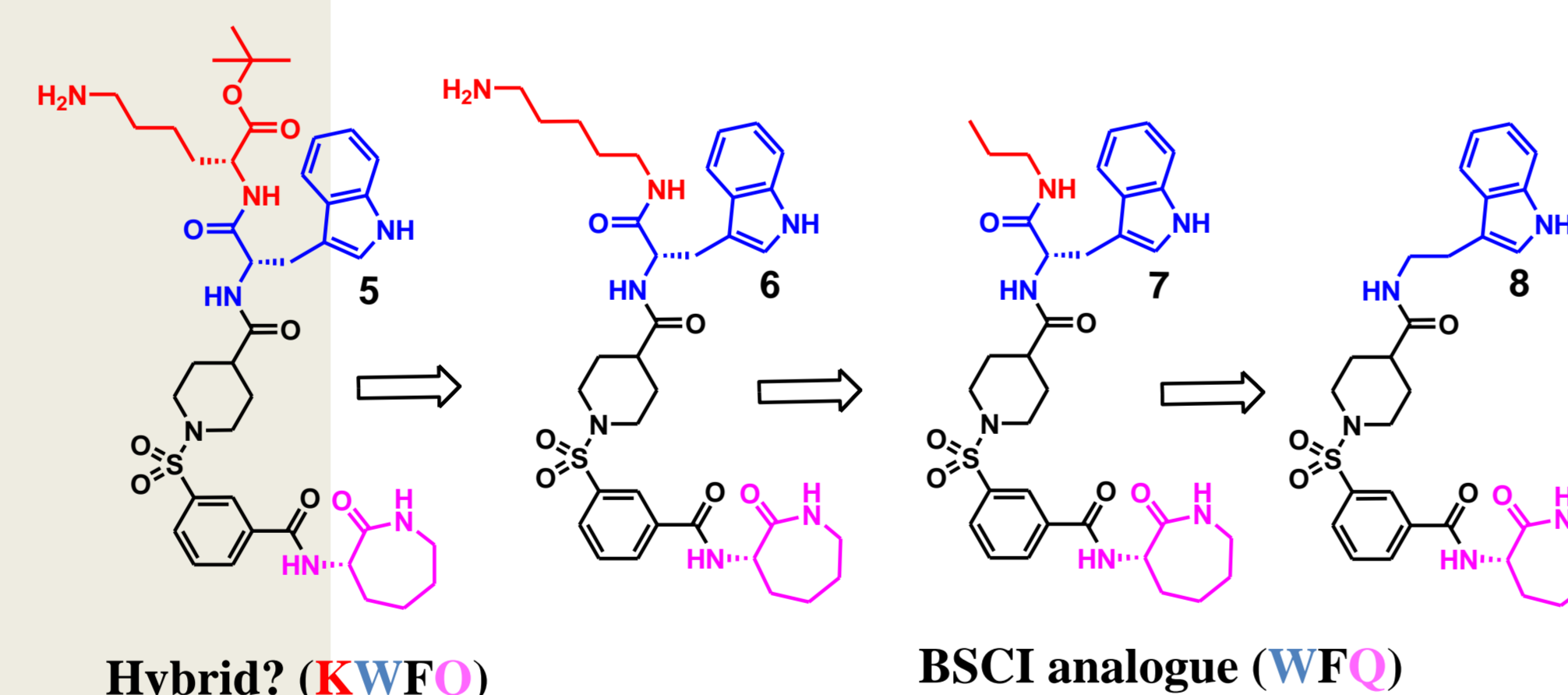
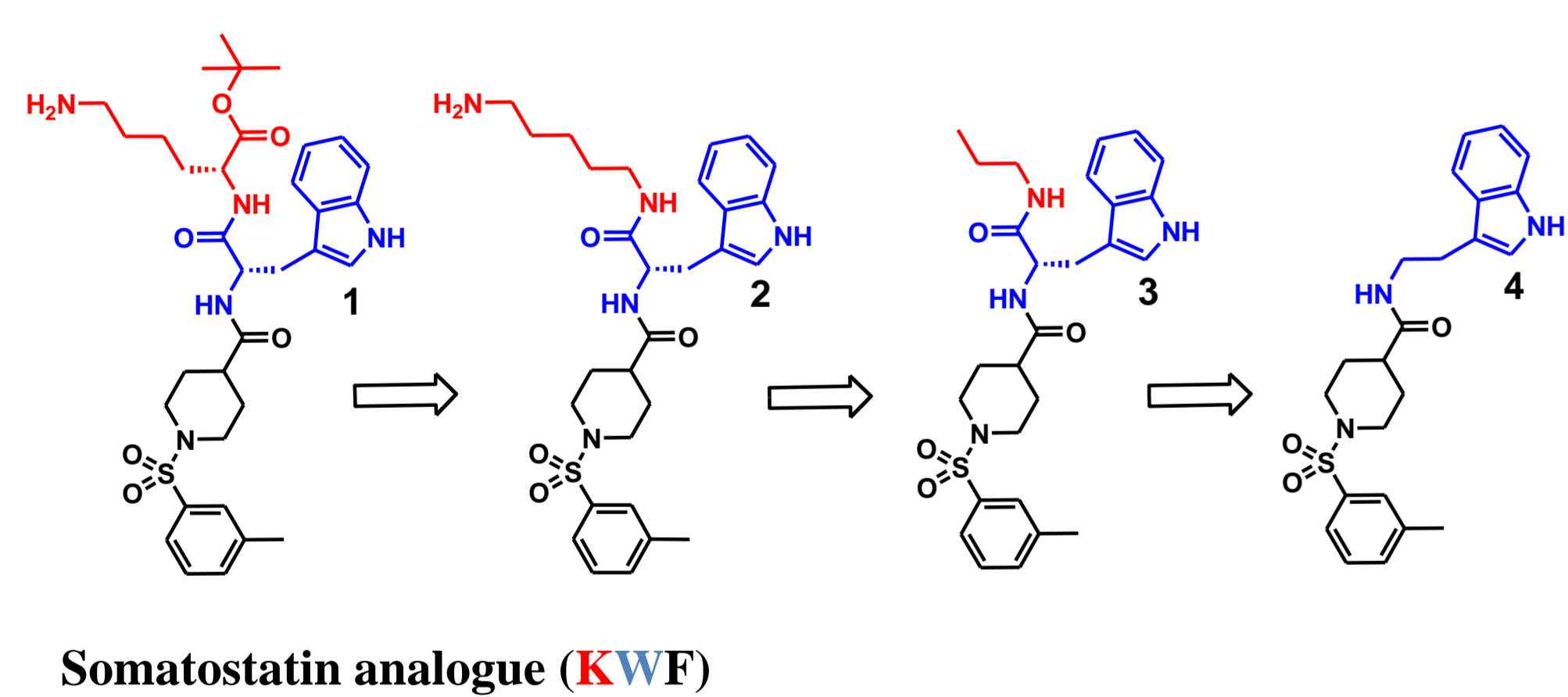


sstr₂ ligand based on WKF critical motif

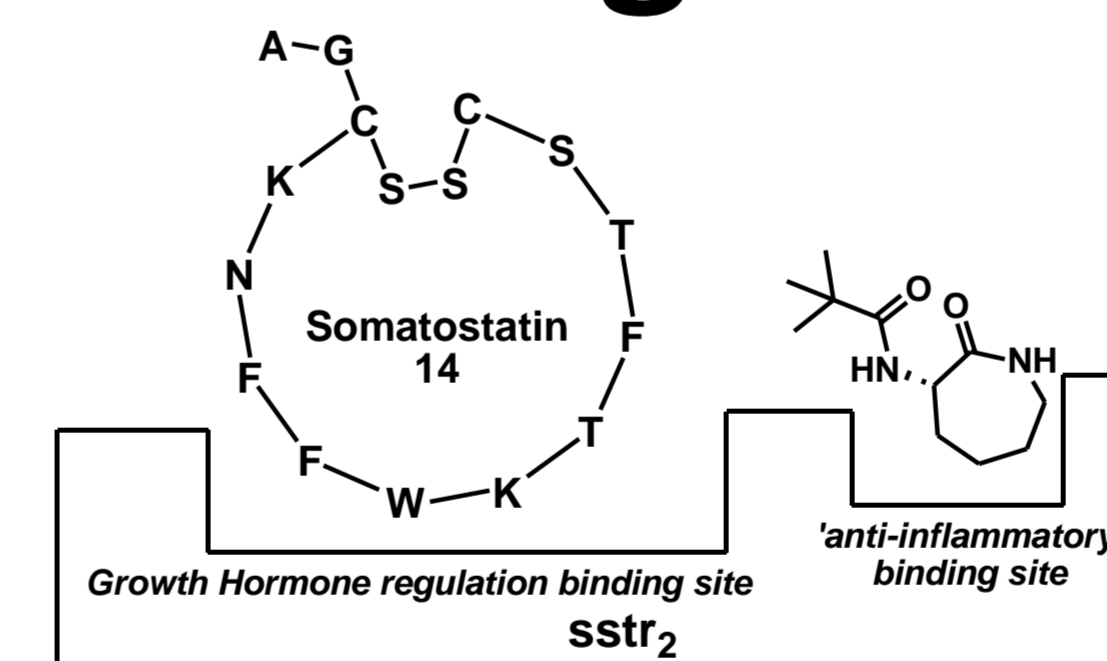
The *sstr₂* receptor therefore displays functional selectivity - when somatostatin is bound GH is affected but when BSCIs are bound chemokines are affected.⁴



The aim of my project is to synthesise a catalogue of molecules analogous to both somatostatin and BSCIs to investigate the important part of the mechanism tipping *sstr₂* from GH to BSCI function.



Binding: Competitive or non-competitive



The smaller BSCIs such as FX97L or a benzoyl analogue are non-competitive in their binding with regards to somatostatin.

The larger BSCIs such as BN83250 are competitive in their binding with regards to somatostatin however.

A series of benzoyl amino lactams were synthesised with different length alkyl chains to determine the point at which they start becoming competitive with somatostatin.



To determine the competitive nature of the ligands they will be subjected to an *sstr₂* binding assay measuring the percentage displacement of somatostatin and a GH regulation assay.

To determine their abilities as BSCIs they will be subjected to an *in vitro* leukocyte migration assay and an *in vivo* anti-inflammatory activity assay.

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2. B. A. Hay, B. M. Cole, F. DiCapua, G. W. Kirk, M. C. Murray, R. A. Nardone, D. J. Pelletier, A. P. Ricketts, A. S. Robertson and T. W. Siegel, *Bioorg. Med. Chem. Lett.*, 2001, 11, 2731-2734.
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