Mechanism of Action of Broad-Spectrum Chemokine Inhibitors

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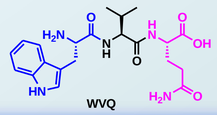
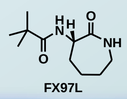
➢Inflammation is the bodies response to a harmful stimuli; however inappropriate inflammation is a key component in many diseases, for example; asthma, hay fever, rheumatoid arthritis and cancer.

➢Leukocytes are recruited to the affected area by chemokines. Therefore chemokines are important pharmaceutical targets. There are over 50 different chemokines and 20 different chemokine receptors; consequently there is much redundancy in the chemokine system therefore a Broad-Spectrum Chemokine Inhibitor - one which inhibits a number of different chemokines - is necessary.

➢'Peptide 3' derived from chemokine MCP-1 was one the first BSCI discovered; the critical motif for reactivity was found to be the tripeptide WVQ, from this a molecule, FX97L, with a potency of 40 pM has been produced.[1]





➢It has been discovered that BSCIs do not bind to chemokine receptors but to the $sstr_2$ receptor for somatostatin.

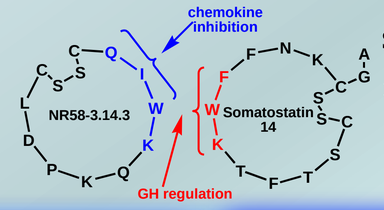
➢Somatostatin is a peptide of the nervous and endocrine system which regulates the secretion of growth hormone (GH).[2] It previously has only weak association with the immune system, the tripeptide KWF was found to be crucial for GH regulation.

➢This is a display of functional selectivity at the $sstr_2$ receptor. Functional selectivity is the effect of one ligand having one agonism when bound to the receptor and another ligand having a different agonism at that same receptor.[3]

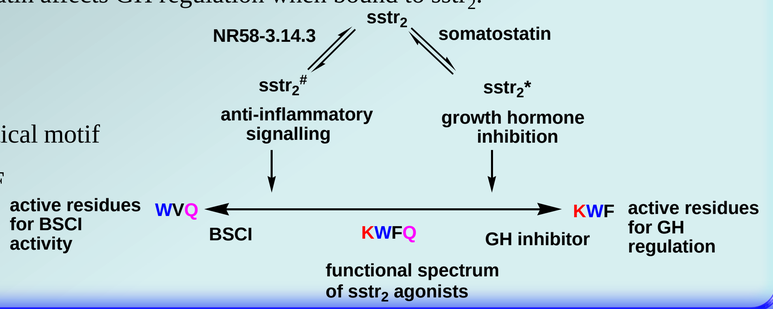
➢BSCIs produce an anti-inflammatory affect when bound to $sstr_2$ and somatostatin affects GH regulation when bound to $sstr_2$.

NR58-3.14.3 a cyclic peptide is a 1 nM BSCI

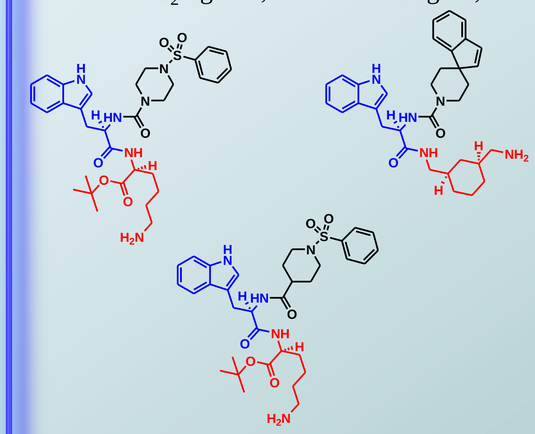
Critical motif for activity is WIQ[4]



Somatostatin critical motif for activity KWF



➢Current $sstr_2$ ligands; all KWF analogues;[2]



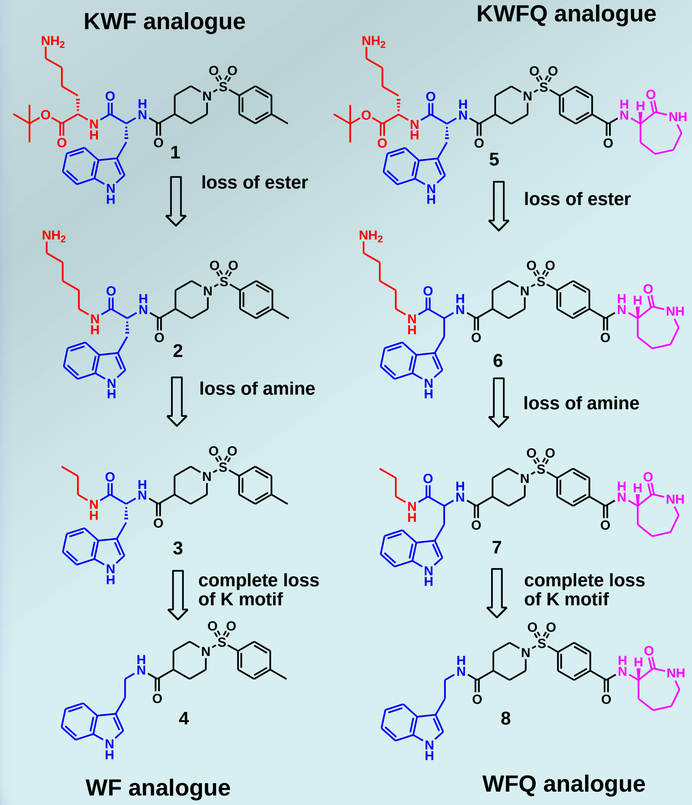
➢The aim of my project is to synthesis a catalogue of structures starting off as GH regulators (KWF analogues) and moving along the scale to potential BSCIs (KWFQ) analogues.

➢The Q mimic will be a lactam which retains the amide and has been found to be successful pharmacological component.

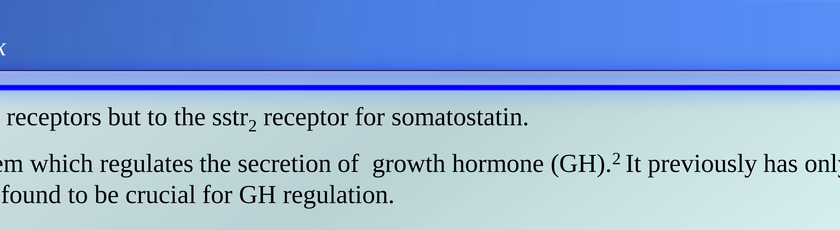
➢These compounds will all be tested for their BSCI potency and GH inhibition.

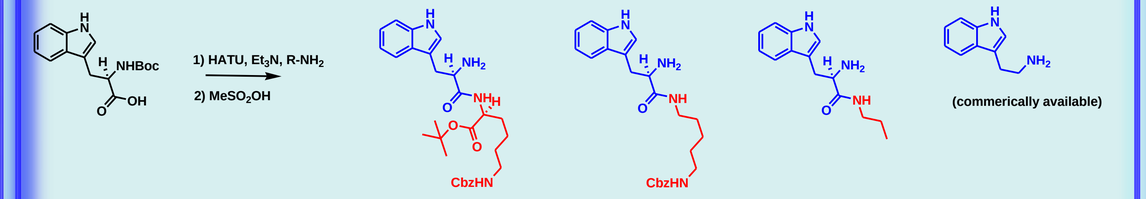
➢This will enable the structure activity relationship to be quantified and the Functional Selectivity balance to be determined.

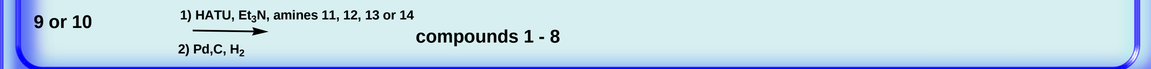
Synthetic targets; stepwise change of KWF and KWFQ analogues for structure activity relationship testing regarding BSCI and $sstr_2$ inhibition ability.



Synthesis;







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