Synthesis of Purine Analogues with Trifluoromethyl-Substituents

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Fluoro- and trifluoromethyl-substituents of organic compounds play an important role for pharmaceutical active compounds. These substituents can increase the activity and/or bioavailability of bioactive molecules by tuning the electronical and sterical effects. It is currently in discussion if trifluoromethyl substituents have the capacity to form hydrogen bonds which would lead to interesting interactions with e.g. proteins.[1] A variety of purine analogues in the form of pyrollo[2,3-d]pyrimidines, respectively 7-deazapurines were found in nature as pharmaceutical active compounds such as tubercidin.[2] While these natural materials act as anti-viral, anti-bacterial or respectively anti-tumor agents, they also show a high toxicity and severely lack selectivity. Therefore these compounds are not suitable as pharmaceuticals.

Aim of this work is the synthesis of substituted 7-deazapurines and purines, containing at least one fluorine moiety. By introducing trifluoromethyl-substituents, one hopes to achieve a higher selectivity in biological evaluations.[3] The *de novo* synthetic pathways start from fluorine containing buildings blocks and are first fused to functionalized pyrimidine heterocycles and subsequently to the purine analogue bicycles. A limited amount of synthetic steps are to introduce various substituents in order to establish substance libraries. Subsequent biological evaluations can yield information about the structure-activity relationship of these compounds.

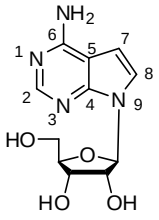

Figure 1: Tubercidin.

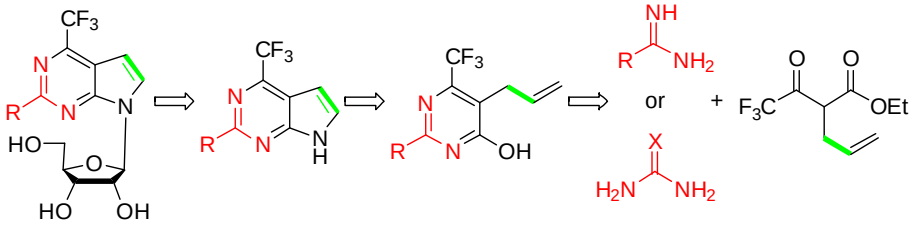

Figure 2: Synthetic pathway to yield 7-deazapurines.

[1] R. Filler, *Organofluorine compounds in medicinal chemistry and biomedical applications*, Elsevier, 1993.

[2] R. Kazlauskas, P. Murphy, R. Wells *et al.*, *Aust. J. Chem.*, 1983, 36, 165-170.

[3] P. Naus, R. Pohl, I. Votruba *et al.*, *J. Med. Chem.*, 2010, 53, 460-470.

Neurons Seeking for the Right Connection: a Molecular Study

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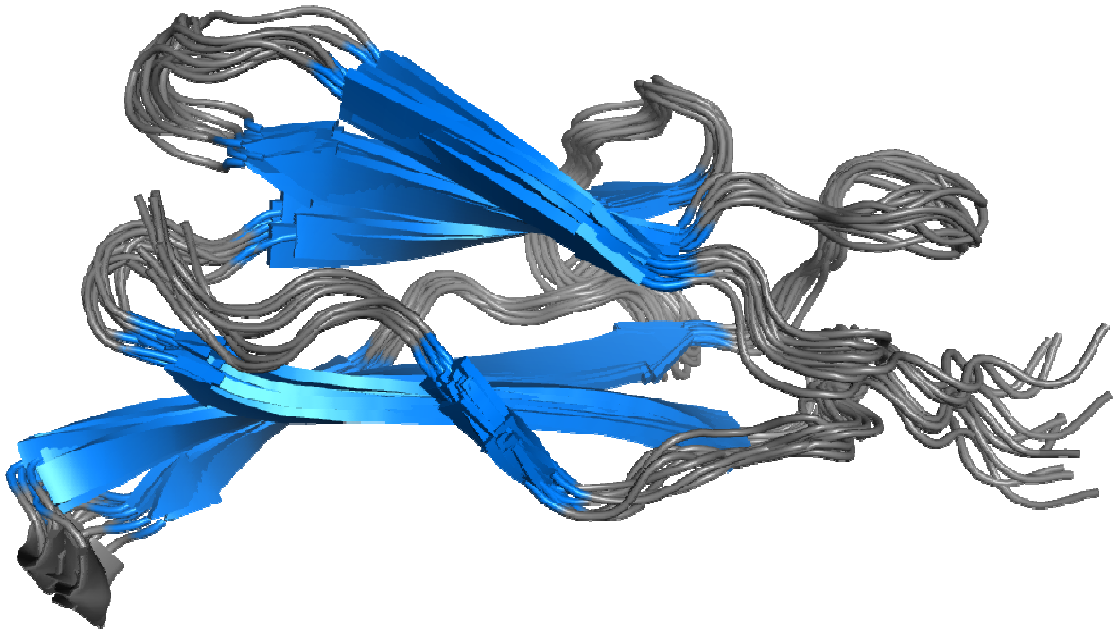
During development of the nervous system, neurons are growing on highly ordered routes to find their target. On a molecular level, multiple cell surface receptors participate in the correct path finding and bundling of neurons. In the present study, one of these receptors is characterized in structure, dynamics and it's interaction to inhibitors and natural ligands.



Thiazolides, GSTP1 and Colon Cancer Cell Apoptosis

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Thiazolides are antibiotics with potent anti-microbial activities used for the treatment of intestinal infections. Although so far no (side) effects on mammalian cells have been described, our lab has recently shown that thiazolides promote apoptosis in colon cancer cells. Thiazolides potently synergized with other apoptosis inducers, such as chemotherapeutic drugs and TRAIL. As the main mammalian target of thiazolides we identified the glutathione S-transferase, GSTP1. Interestingly, GSTP1 enzymatic activity was required for the apoptosis inducing activity of thiazolides. Furthermore, we have seen that cell cycle progression was a prerequisite for Thiazolide-induced apoptosis in colon cancer cells. We are currently investigating the molecular requirements of the thiazolide structure and derivatives to induce a GSTP1-dependent apoptotic cell death in colon cancer cells. Various thiazolides differ in their apoptosis promoting activity in Caco-2 cells. The thiazolide RM4819 induced activation of JNK and p38- MAP kinase, and their inhibition strongly blocked thiazolide-induced cell death. They also induced the expression of the Jun kinase target Bim, a BH3-only protein. Furthermore downregulation of Bim attenuated thiazolide-induced apoptosis. As GSTP1 sequesters and inhibits Jun kinase and other signaling molecules we are currently investigating whether thiazolides induce Jun kinase and p38 activation and subsequent apoptosis induction via the release of these MAP kinases from GSTP1. Interestingly, GSTP1 is barely expressed in normal colonic mucosa, but abundantly expressed in colorectal tumor cells. As we have previously shown that inhibition of cell cycle progression blocks thiazolide-induced cell death in Caco-2 cells, we are examining whether cell cycle arrest causes reduced GSTP1 expression in colon cancer cells or affects GSTP1 enzymatic activity. Current data indicate that GSTP1 expression is not affected by cell cycle arrest.

Our study proposes thiazolides as a novel therapeutic for the treatment of colorectal tumors and GSTP1 as an Achilles' heel of thiazolide-induced cell death.