Medicinal Chemistry – Melanocortin Receptors and Privileged Structures

Problem Questions – 16/11/09

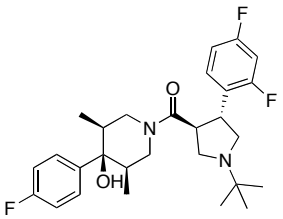
The Melanocortin (MC) receptors are members of the Rhodopsin family of G protein-coupled receptors (GPCR's). There are 5 members of the MC receptor family that bind naturally occurring peptidic melanocortin ligands. The receptors are implicated in many biological processes such as pigmentation and are associated with early-onset obesity and male erectile function.

Early investigation this receptor family was carried out by Mac Hadley *et al.* Going against pretty much all common sense and professional practice Hadley carried out his own style of assessment described in **Hadley M. Peptides, 26, 2005, 1687-1689** –

"During the development of MTI, I served as a proverbial "human pincushion" (a.k.a., guinea pig), that is, I tested the efficacy of the peptide to produce a tan on myself. Therein lies a very interesting story. Our group of University investigators prepared and characterized some fragment MC analogs that proved to be as potent as MTI, even though structurally only half the size (seven amino acids) of the parent analog. In addition, the melanotropin MTII was conformationally restrained by a lactam bridge to provide a cyclic structure of increased lipophilicity. The smaller molecule is just as active as the larger MTI; it is cheaper to synthesize and might gain access more readily into the body. Based upon these and other considerations, a sterile preparation was provided for injection to determine its tanning potential.

One mistake in my deliberations was made, however. MTI had previously been administered at a dose as high as 10 mg without physiological consequences (other than tanning). I forgot, however, that MTII was only about half the molecular weight of MTI. Therefore, when I took an equivalent (10 mg) dose of MTII, I inadvertently received about twice the number of molecules of the peptide. Unlike MTI, however, MTII caused a rather immediate, unexpected response: nausea and, to my great surprise, an erection (no figure provided). While I lay in bed with an emesis pan close by, I had an unrelenting erection (about 8 h duration) which could not be subdued even with a cold pack. When my wife came upon the scene, she proclaimed that I "must be crazy." In response, I raised my arm feebly into the air and answered, "I think we may become rich.""

A few non-peptidic modulators of MCR's have since been developed and currently Pfizer have a drug, PF-00446687, in phase 1 clinical trials. Compounds **1** and **2** were created in the development of PF-00446687.



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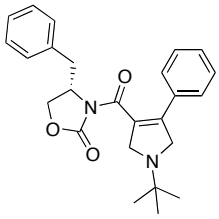

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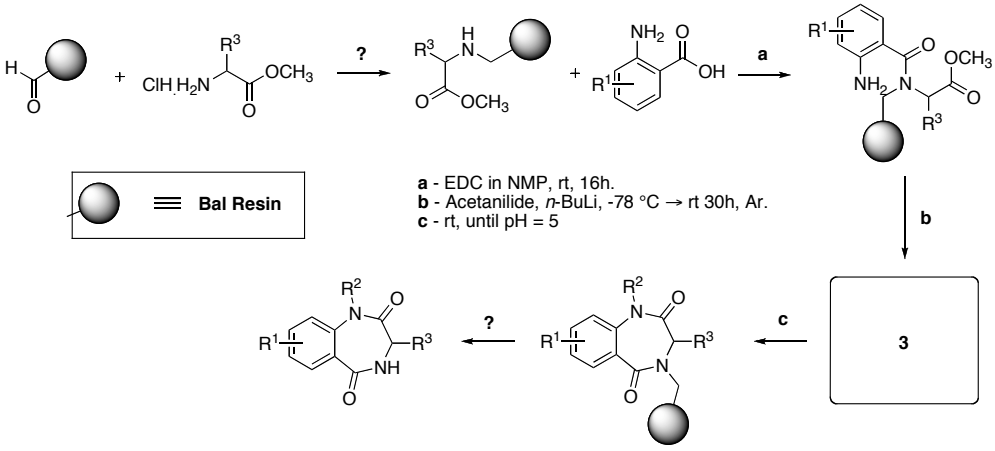
Q1. Suggest an effective retrosynthetic analysis and forward synthetic plan of both compounds.

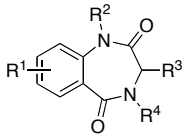
A class of benzodiazepines have been identified as highly active modulators of the entire family of MCR's. Synthesis was achieved using an efficient 5 step solid support based method (Fig. 1)

Q2. Fill in the blanks and give mechanism for each step.



Benzodiazapines are described as privileged structures in biology due to their ability to provide ligands for diverse receptors. The Ugi 4CC reaction has been used to affect their synthesis on many occasions.

Q3. Give disconnections of the general benzodiazapine structure **4** back to the Ugi substrates and draw a mechanism for the formation of **4**. (Hint – synthesis formally requires 2 steps)



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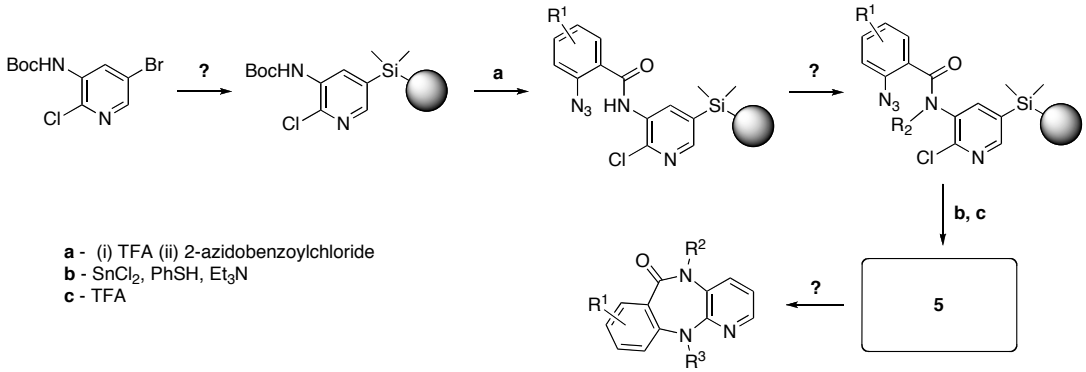
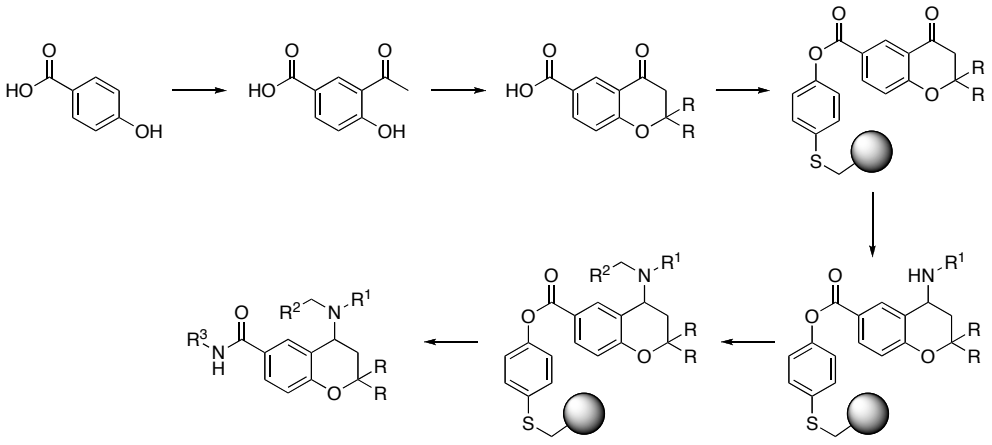
Combinatorial synthesis of privileged structures has been heavily investigated -

Q4. Fill in the blanks and give mechanism for each step in the synthesis of the pyrido-annulated benzodiazepines below.



Q5. Give reaction conditions for the steps in the synthesis of the dihydrobenzofuran below.



Q6. Propose retro sytnesis for the compound below –