Synthesis of new heterocyclic isosteres of L-buthionine sulfoximine (L-BSO)

Thomas P.; Armijo R.; Tapia R. A.; Salas C.

Facultad de Química Orgánica, Pontificia Universidad Catolica de Chile

Vicuña Mackenna 4860, Macul, 7820436, Santiago, Chile

** E-mail*: *cosalas@uc.cl*

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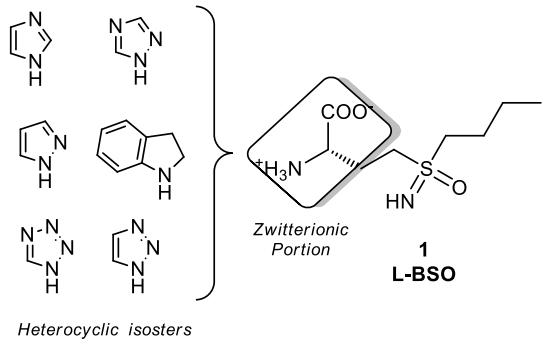
INTRODUCTION

Glutathione (GSH) in *Trypanosoma cruzi*, is a pivotal precursor of trypanothione, $T(SH)_2$, the main molecule that protects this parasite of the toxic effects produced by certain drugs, hydrogen peroxide and free radicals[1]. In GSH synthesis, Glutamate Cysteine Ligase (GCL) plays a fundamental role because it catalyzes the limiting step and is inhibited by L-Buthionine Sulfoximine **1** (L-BSO)[2]. Recent studies have shown that the reduction in the synthesis of GSH by L-BSO increase the trypanocidal effect of nifurtimox and benznidazol in *in vitro* models of Chagas's diseases[3]. In this context, we were interested in developing new heterocyclic isosters of L-BSO. With this purpose we first carried out a 3D model of GCL of *T. cruzi*, to design new derivatives of L-BSO[4].

RESULTS AND DISCUSSION

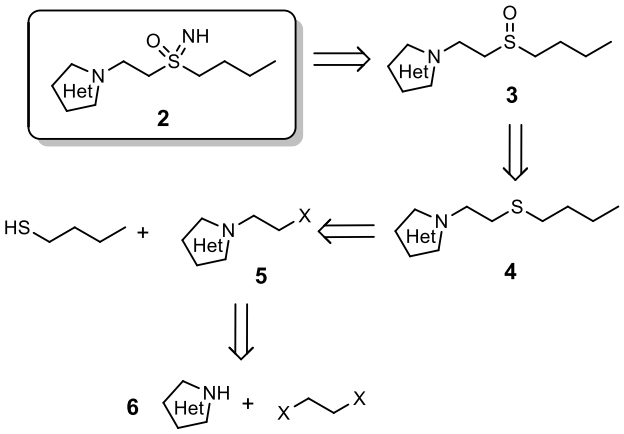
Using the information provided by the 3D model, we modified the zwitterionic part of L-BSO with different heterocyclic rings. This new analogs may act as heterocyclic isosters of BSO with improved biodisponibility (Fig.1).

Figure 1. Chemical structure of L-BSO and heterocyclic isosters.



With this information in hand, a synthetic pathway to obtain these compounds is based on the retrosynthetic scheme shown in figure 2.

Figure 2. Retrosynthetic analysis for obtain isosters of L-BSO.



Alkylation of selected heterocyclics (**6**) with 1,2-dihaloethane followed by S_N2 type reaction of **5** with 1-buthanetiol gave sulfide intermediates **4**. These sulfides were oxidized with *m*-chloroperbenzoic acid (MCPBA) under usual conditions, to obtain sulfoxides **3** in good yields (57-78%). Finally, sulfoxides **3**, were treated with *o*-mesitylenesulfonylhydroxylamine (MSH) to afford sulfoximines **2** (34-75%).

CONCLUSION

We have obtained a series of new heterocyclic isosters of L-BSO, which are under study to evaluate their trypanocidal effects.

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