Molecular Medicinal Chemistry

IDECEFYN

vol 13 May-August 2007, **19-21** http://www.idecefyn.com.ar ISSN 1666-888X

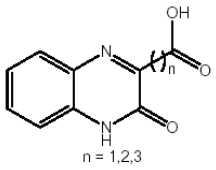
Synthesis of quinoxalines and benzoquinoxalines with potential pharmacologic activity

Romina Julieta Glisoni, Beatriz M. Fernández and Albertina G. Moglioni*.

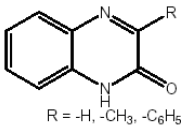
Cátedra de Química Medicinal, Departamento de Farmacología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, C1113AAD Ciudad Autónoma de Buenos Aires, Argentina.
*amoglio@ffyb.uba.ar

Introduction

Some 3-quinoxalin-2-one carboxylic acids (**I**) and its esters showed some anticancer activity, further revealing moderate antibacterial and antifungal activity (Di Nardo *et al.*, 1984; Sanna *et al.*, 1998; Vitale *et al.*, 1998). Moreover, 3-alkyl substituted derivatives of quinoxalin-2(*1H*)-one (**II**) proved to have a similar moderate anti-tumor activity (Sanna *et al.*, 1999).

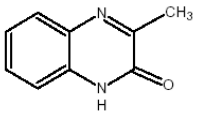


I

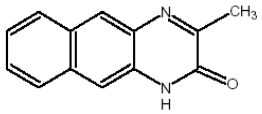


II

The introduction of a benzene ring in the quinoxalinone (**III**) resulted in the corresponding benzoquinoxalinone (**IV**), which showed activity on human lung tumor cells (EKVX cell line), human kidney tumor cells (LC A498), and on tumor cells of the central nervous system (SNB-75 line) (Rodrigo *et al.*, 1997).



III



IV

Furthermore, the search for effective agents for the AIDS treatment is an open field of research in medicinal chemistry. In that sense, compounds with different chemical structures have been prepared, including quinoxalines, which act as non-nucleoside inhibitors of HIV reverse transcriptase.

On the basis of these considerations the organic synthesis of quinoxalinones and benzoquinoxalinones was carried out by the traditional method of Hinsberg (1887). Since the conventional reaction of Hinsberg shows difficulties for the preparation of quinoxalinic heterocycles and produces, when the benzene ring is substituted, a mixture of position isomers very difficult to separate, an alternative synthetic route of quinoxaline derivatives was explored: a reaction of biocatalysis using yeasts. This technique led to yields of 90-95%, while the amount used as starting material was not a limiting factor for this reaction, but it is for the traditional Hinsberg reaction. Furthermore, it has been observed that the enantioselective reactions were possible when using the enzymatic route, thus leading to a unique final product of higher purity, and hence to higher yields.

The biocatalysis is a new synthetic route that uses the enzymatic machinery of some species of microorganisms to carry out reactions of oxidation-reduction, condensation, acylation and cyclization, among others. This new approach has the advantage of being economic and less toxic than the traditional routes, since the reactions occur in aqueous layer and not in organic solvents. In addition, the induction of the enzymes of interest can be achieved, in case of obtaining low yields, as well as also the inhibition of other enzymes that give secondary products of reaction.

Methodology

Saccharose (10 g) was dissolved in 100 ml of distilled water in a 1l-Erlenmeyer, and *S. cereviciae* (10 g) was added, leaving the mixture under stirring for 1 hour at room temperature. *o*-Phenylenediamine or 2,3-diaminonaphthalene (100 mg; 1 mmol) and different types of α-ketoacids (1.4 mmols) in excess were added to the mixture. The mixture was further stirred for 48 hours at the same temperature. Once the reaction was ended, the mixture was centrifuged, the acidic pellet was isolated and finally resuspended in methanol. The mixture was

Molecular Medicinal Chemistry

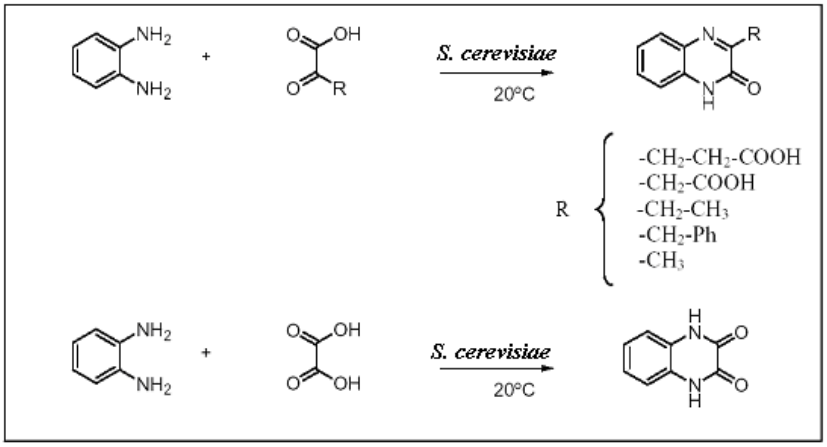
IDECEFYN

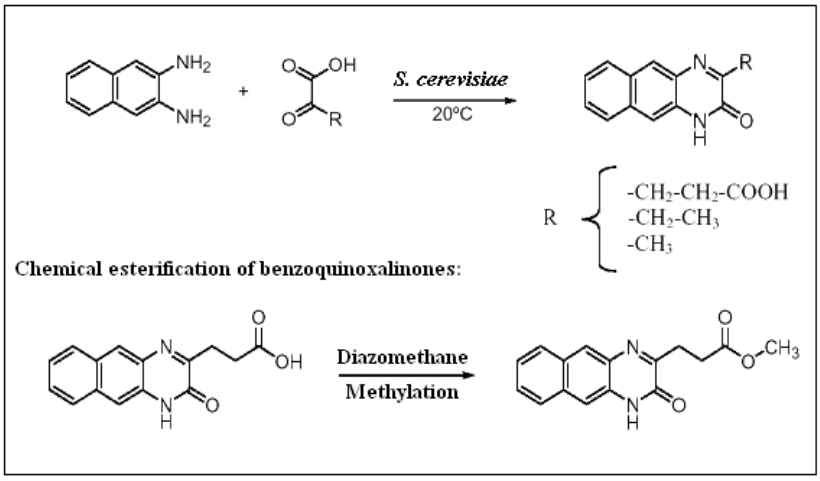
vol 13 May-August 2007, **19-21** http://www.idecefyn.com.ar ISSN 1666-888X

stirred further for 24 hours, and then centrifuged. The upper layer was separated and the solvent evaporated. The solid obtained was washed to remove the residue of saccharose in excess, rendering the final product of synthesis. The structure of the final products was confirmed by their physical and spectroscopic properties.

Results

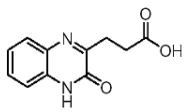
Quinoxaline and benzoquinoxaline derivatives obtained through the reaction of biocatalysis using yeasts.



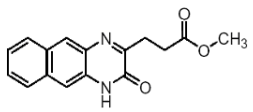


A route of effective and versatile synthesis was found for the preparation of a quinoxalinic and benzoquinoxalinic series of compounds. Two of the products of synthesis were evaluated (by the fellow Romina Glisoni and specialized personnel) against HIV in the National Reference Center for AIDS (Faculty of Medicine, University of Buenos Aires, Argentina).

The biological activity against HIV has been proved for the following two synthetic products obtained by the enzymatic method:



Product 1



Product 2

Analyzing the inhibition curves of the synthesis products **1** and **2**, it was realized that:

• The products **1** and **2** did not show, in the range of work concentrations, virus inhibition by

Molecular Medicinal Chemistry
IDECEFYN
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comparing data with the inhibition curve of Efavirenz (Control).

• Both products did not show toxicity in this range of concentrations.

Conclusions

Quinoxalines and benzoquinoxalines were synthesized by a simple and versatile route of synthesis. This route turned out to be cheaper and less toxic than the traditional Hinsberg´s route, as it avoids the use of organic solvents, just using water water as solvent reaction. Moreover, in this enzymatic method, the amount of starting material is not a limiting factor for the reaction, while it is for the Hinsberg reaction. Products of high purity and higher yield were obtained in comparison with those obtained by traditional routes.

Finally, it has been proved biological activity against the HIV virus for two synthetic products.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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