Synthesis of potencial inhibitors of HIV-1Nef.

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INTRODUCTION

A decreasing of the expression of CD4 receiver in the surface of the infected cells by Nef is one of the most important events during the infection by HIV-1. The identification of Nef inhibitors is very important to the treatment of HIV infection. The development of new therapies and methods of synthesis of Nef antagonists is a new and highly specific therapeutic approach and aims at eliminating the side effects involved with the existing anti-retroviral cocktail. To achieve this goal, we propose to synthesize a series of inhibitors of degradation of CD4 by Nef beginning with molecular modeling studies of the Nef protein and its catalytic domains involved in this function.[1] In this sense, compound **1** seems to be one of the most promising (Figure 1).[2]

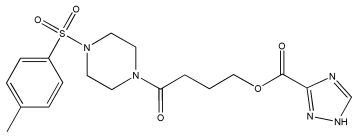
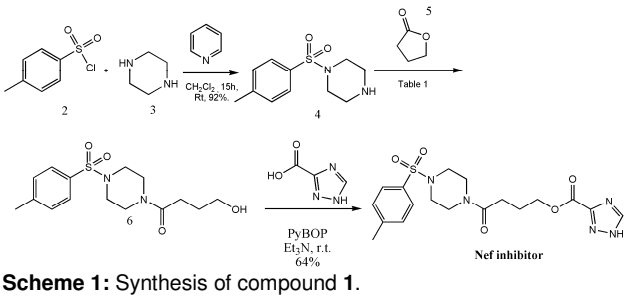


Figure 1: Structure of a potential Nef inhibitor.

RESULTS AND DISCUSSION

The first step of the synthesis of compound **1** is the sulfonation of piperazine **3** in the presence of pyridine in dichloromethane, affording compound **4** in 92% yield (Scheme 1).



Scheme 1: Synthesis of compound **1**.

The next step involved the opening of γ-butyrolactone by compound **4**. Among the different experimental conditions investigated, the use of μw irradiation (130 °C, 200 W, 1 h), was the only one to furnish compound **6** (Table 1, entry 5), thus demonstrating the efficiency of the microwave assisted reaction in contrast to the reactions under reflux.

Table 1. Experimental conditions for the opening of γ-butyrolactone opening by compound 4.

Entry	Time (h)	Temperature (°C)	Solvent	Pressure (atm)	Yield (%)
1	15	Reflux	Metanol	1	-
2	0,25	Reflux	CH_2Cl_2	-	-
3	72	60	$CHCl_3$	120	-
4	1	40/ μw	CH_2Cl_2	-	-
5	1	130/ μw	-	-	**79**

In the final stage of the synthesis, compound **6** was coupled with 1,2,4-triazole-3-carboxylic acid **7**. Some coupling agents were tested, such as DCC / DMAP, EDC and PYBOP. Only the latter was able to provide compound **1** in 84% yield **(Scheme 2).**[3]

CONCLUSION

Compound **1**, a potential inhibitor of HIV-1 Nef, was efficiently obtained from piperazine by a 3-step sequence and its pharmacological properties will be now evaluated.

ACKNOWLEDGEMENTS

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