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ABSTRACT BOOK

TARGET-ORIENTED DEVELOPMENT OF NOVEL ANTIPROTOZOAL AGENTS: CELASTROL CARBOXAMIDES AS INHIBITORS OF *LEISHMANIA* Hsp90

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The *Leishmania* isoform of the 90kDa Heat Shock Protein (*Ls*Hsp90), a chaperone known to assist the folding of more than 200 client proteins, was reported to be generally involved in parasite differentiation from promastigote to amastigote possessing a pivotal role during heat-induced cellular stress. Moreover, it was demonstrated that an impair of the native functions of *Ls*Hsp90 through the action of active-site inhibitors can exert a detrimental effect on the natural parasite life-cycle ultimately leading to its death.[1,2]

Celastrol (**Figure 1**) is a natural triterpene exhibiting a plethora of *in vitro* and *in vivo* activities. Among them, this pentacyclic compound is reported to possess a promising antiproliferative activity thanks to its ability of interacting with the chaperone cycle of the human isoform of Hsp90 (*h*Hsp90).[3] Moreover, celastrol derivatives (*e.g.* the methyl ester pristimerin, **Figure 1**) have also exhibited an interesting antiprotozoal activity.[4,5]

With the aim of building a target-oriented approach to treat *Leishmania* infections based on the inhibition of *Ls*Hsp90, we prepared two basic carboxamides celastrol derivatives (**SS-1** and **SS-2**, **Figure 1**) to enhance its leishmanicidal activity and selectivity of action by deducting its unspecific cytotoxicity (measured as IC_{50} on HMEC-1 cell lines). Accordingly, celastrol and the two basic derivatives **SS-1** and **SS-2** (**Figure 1**) were *in vitro* tested for their leishmanicidal activity against promastigotes of *Leishmania tropica* and *L. infantum* and, in parallel, their mechanism of action was investigated as well *via ad hoc in vitro* experiments using a recombinant Hsp90 from *L. braziliensis* (LbHsp90).[6]

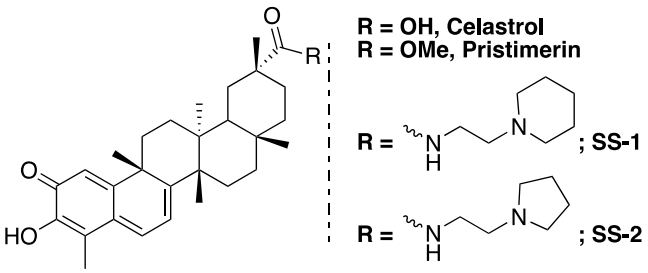

Figure 1. Structures of celastrol, pristimerin and the basic derivatives SS-1 and SS-2.

In virtue of their pH sensitive basic heads, both **SS-1** and **SS-2** were found to be more potent (IC_{50} in the nanomolar range) and selective leishmanicidal agents than celastrol itself. Furthermore, we were able to demonstrate that **SS-1** and **SS-2** successfully (*in vitro*) inhibited the native kinase activity of *Lb*Hsp90 highlighting the key role of the inhibition of this chaperone in their mechanism of action.

References

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