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Secondary metabolites from *Hypericum scruglii* as potential dual HIV-1 inhibitors effective on HIV-1 replication

Cinzia Sanna[1], Monica Scognamiglio[2], Elisa Rita Ceresola[3], Antonio Fiorentino[2], Angela Corona[1], Filippo Canducci[3], Enzo Tramontano[1] and **Francesca Esposito[1]**

[1]University of Cagliari, Italy

[2]Second University of Naples, Italy

[3]San Raffaele Hospital-IRCCS, Italy

Statement of the Problem: Currently, the approved treatment of HIV infection and prevention on its progression towards AIDS is based on the highly active antiretroviral therapy (HAART) which combines at least 2, and preferably 3, antiviral agents, targeting different steps of the viral replication cycle. The majority of the 30 approved anti-AIDS drugs is represented by reverse transcriptase (RT) inhibitors that target only the DNA polymerase activity. Although the RNase H function is a good target, there are still no pre-clinical drugs that inhibit this viral function. With the application of integrase (IN) inhibitors, the treatment outcome has also been improved. Multi-target ligand drugs have become a hotspot in new drug research and development. Hence, in our ongoing research of natural products inhibiting the replication of HIV-1, some compounds obtained from aerial parts of *Hypericum scruglii* Bacch., Brullo et Salmeri, belonging to the Sardinian endemic flora, have been assayed to evaluate their HIV-1 RT and IN dual inhibition ability.

Methodology: *Hypericum scruglii* methanolic extract along with their main single isolated constituents have been tested for their ability to inhibit the HIV-1 RNase H activity in biochemical assay and the HIV-1 IN strand-transfer catalytic activity in presence of LEDGF cellular cofactor in Homogeneous Time Resolved Fluorescence assay. The active compounds have also been tested on HIV-1 replication in cell-based assays.

Findings: Five of the isolated compounds inhibited IN activity with IC50 values in the 1.58-13.0 μg/mL range, and three inhibited RNase H activity with IC50 values in the 4.1-9.1 μg/mL range. Two compounds inhibited viral replication with an EC50 value of 3 μM.

Conclusion & Significance: We reported some compounds obtained from *Hypericum scruglii* that display strong inhibition against two key viral enzymes, and that could be considered new and attractive leads for the development of multi-targeted antiviral agents.

v_barbakadze@hotmail.com