From the search for CHIKV inhibitors to the discovery of a potent anti-HIV infection agent

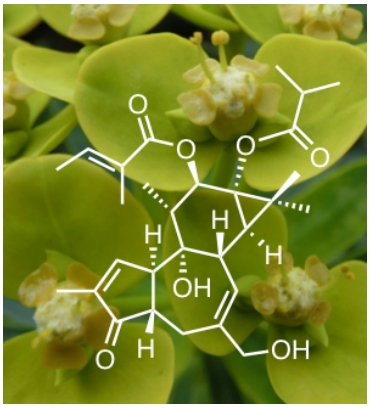
LITAUDON Marc

[1]Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France.

Keywords : Euphorbiaceae, *Euphorbia amygdaloides*, phorbol esters, chikungunya, HIV

As part of an ongoing program aiming at the discovery of novel inhibitors of chikungunya virus (CHIKV) replication from tropical plants, we discovered by chance that daphnane-type diterpenoids isolated from *Trigonostemon cherrieri*, a critically endangered endemic Euphorbiaceae from New Caledonia, exhibited significant and selective antiviral activity. This result was the starting point for the phytochemical and biological investigation of other Euphorbiaceae species originating from different tropical and Mediterranean regions leading to the characterization of several bioactive tigliane-type diterpenoids, some of which possessing extremely potent and selective anti-CHIKV properties.[1] To further explore the structure-activity relationships of such diterpenoids, the anti-CHIKV and anti-HIV activities of about 40 tiglianes isolated from different Euphorbiaceae species or commercially available were evaluated.[2] Surprisingly, the results showed that there was a strong correlation between both activities, suggesting that the anti-CHIKV activity of the diterpene esters might result from their ability to modulate the activity of protein kinase C isozymes as is the case for their anti-HIV activity. Among the most interesting compounds, a 4β-deoxyphorbol ester (4β-dPE, figure below) isolated from *Euphorbia amygdaloides* was found to have a 20-100 times more potent anti-HIV activity than prostratin, which had raised considerable interest in early 2000s owing to a potential clinical application.[3] Further, it has been shown that 4β-dPE reactivates HIV-1 from latency and could potentially contribute to decrease the viral reservoir, downregulates the expression of the HIV-1 receptors CD4, CCR5 and CXCR4, and that combination of 4β-dPE with various antiretroviral drugs showed a consistent synergistic effect, suggesting that 4β-dPE represents a new lead compound for the treatment of HIV-1 latency in combination with antiretroviral drugs.[4]

I. Image:



II. Reference:

1 Bourjot, M., Delang, L., Nguyen,V.H., Neyts, J., Guéritte, F., Leyssen, P., Litaudon. M. Prostratin and 12-*O*-Tetradecanoylphorbol 13-acetate are potent and selective inhibitors of chikungunya virus Replication. J. Nat. Prod. 2012, 75, 2183-2187.

2 Nothias-Scaglia, L.F., Pannecouque, C., Renucci, F., Delang, L., Neyts, J., Roussi, F., Costa, J., Leyssen, P., Litaudon, M., Paolini, J. Antiviral activity of diterpene esters on chikungunya virus and HIV replication. J. Nat. Prod. 2015, 78, 1277-1283

3 Nothias, L.F., Boutet-Mercey, S., Cachet, X., De La Torre, H.E., Laboureur, L., Gallard, J.F., Retailleau, P., Brunelle, A., Dorrestein, P.C. Costa, J., Bedoya, L.M., Roussi, F., Leyssen, P., Alcami, J., Paolini, J., Litaudon, M., Touboul, D. Environmentally friendly procedure based on supercritical fluid chromatography and tandem mass spectrometry molecular networking for the discovery of potent antiviral compounds from *Euphorbia semiperfoliata*. J. Nat. Prod. **2017**, 80, 2620-2629

2. De La Torre, H.E., Jimenez, R., Bueno, P., Camarero, S., Roman, L., Fernandez-Garcia, J.L., Beltran, M., Nothias, L.F., Cachet, X., Paolini, J., Litaudon, M., Alcami, J. Bedoya, L.M. 4-Deoxyphorbol inhibits HIV-1 infection and reactivate viral reservoirs through PKC/MEK activation synergizing with vorinostat and anti-retroviral drugs. Biochem. Pharmacol. 2020, submitted

III. Biography:

Marc Litaudon has completed his PhD in 1991 from University Paris-Sud, France and Postdoctoral Studies from University of Canterbury (New Zealand). In 1994 he served in New Caledonia as the Head of "Laboratory of Medicinal Plants" (CNRS). In 2001, he joined the ICSN and since has led its phytochemical laboratory and the management and scientific development of the "ICSN Extracts Library". He was appointed deputy director of ICSN in 2020. He has published more than 200 papers in reputed journals and has been serving as an editorial board member of "Phytochemistry" and "Plants".

IV. Presenting author details



Full Name: LITAUDON
Contact number: +33 (0)1 69 82 30 85
Twitter account:
Linked In account:
Session name/ number:
Category: (Oral presentation/ Poster presentation) : Oral Presentation
Passport Number: 11AL84107