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Cycloheptathiophene-3-carboxamide as useful sulfur-containing scaffold for inhibiting essential targets of HIV-1 and influenza virus.

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Keywords: *cycloheptathiophene, sulfur-containing compounds, virus.*

Highlights

Searching for new anti-influenza agents, we have discovered the cycloheptathiophene-3-carboxamide (cHTC) as particularly suitable scaffold;
cHTC derivatives inhibit the PA-PB1 protein-protein interaction;
many cHTC analogues were designed and synthesized through hit-o-lead optimization strategy;
cHTC-based compounds are also able to inhibit the ribonuclease H, an essential function of the HIV-1 reverse transcriptase .

Abstract

Many FDA-approved drugs exert their action thanks to the presence of sulfur-containing moieties.
We have been involved for many years in the synthesis of heterocyclic chemotherapeutic agents and many of them are indeed characterized by the presence of a sulfur atom, which has emerged as essential in imparting the desired biological activity. Following rufloxacin, a quinolone derivative that is in therapy for the treatment of many bacterial infections, various other sulfur-containing small molecules were synthesized by us that showed nice biological activity.
In this presentation, I'll focus on the cycloheptahiophene-3-carboxamide (cHTC) that emerged as very suitable scaffold to inhibit important targets within the replicative cycle of influenza virus (flu) and HIV-1.
The cHTC scaffold was identified thanks to an initial structure-based virtual screening aimed at disrupting the PA-PB1 heterodimerization of the flu RNA-dependent-RNA-polymerase (RdRp). Successive hit-to-led optimization phases led to very interesting derivatives able to inhibit both the PA-PB1 interaction and the viral growth in the low micromolar range.[1-4]
Assaying these compounds within an in-house library of derivatives, we have found that the cHTC scaffold, when properly functionalized, could also grant HIV-1 ribonuclease H inhibitory activity , thus opening the way for an alternative therapeutic application.[5]

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