



Società
Chimica
Italiana

XXVIII

Congresso
Nazionale

MILANO, 26 - 30 Agosto 2024



SCI 2024
Chimica
**ELEMENTI
DI FUTURO**

Atti del XXVIII Congresso

Allianz MiCo – Milano Convention Centre – Fiera Milano
Milano, 26-30 agosto 2024

Volume 2

ISBN:

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Conferenze e Comunicazioni



FAR-PO-016

Structural simplification of imipridones to speed up the knowledge on the nature of the interactions with the human ClpP, a mitochondrial protease strictly linked to DIPG

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The human ClpP (*hClpP*), a mitochondrial matrix caseinolytic protease, is responsible for the mitochondria proteostasis by degradation of misfolded and damaged proteins under the physiological regulation of the AAA+ ATPase chaperone ClpX. By consuming ATP, ClpX recognizes, unfolds, and translocates the tagged proteins into the *hClpP* tetradecamer proteolytic cylindrical chamber to be degraded. High *hClpP* expression levels were found in multiple tumor tissues in which may play an oncogenic role. Given that *hClpP* inhibition by small molecule inhibitors has shown therapeutic effects in several tumour types, the chemo-activation of mitochondrial *hClpP* can also exhibits promising anticancer properties¹. The most successful ClpP activators belong to the class of imipridones and ONC201, also named dordaviprone, is the first-in-class of the series (Figure 1). Currently ONC201 is worldwide evaluated in a Phase 3 study in H3K27-altered glioma, including Diffuse Intrinsic Pontine Glioma (DIPG)². Through a *rational drug design approach*, the tetrahydropyridopyrimidinone (THPPD) was identified as a new scaffold for *hClpP* potent activators development (e.g. TR57). Structure optimization led to a novel series of piperazine derivatives as putative *hClpP* activators. A structure-activity relationship study aimed at deeply knowing the nature of the interactions with the *hClpP* to identify a better *hClpP* activator will be presented.

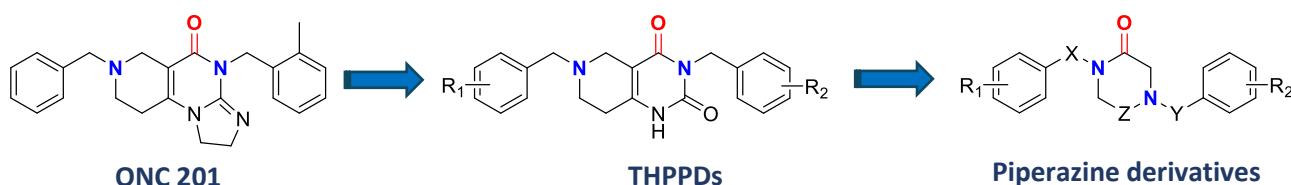


Figure 1: From ONC201 to novel piperazine derivatives as *hClpP* activators.

References:

- [1] M. Miciaccia, F. Rizzo, M.G. Perrone, A. Scilimati, et al. Harmaline to Human Mitochondrial Caseinolytic Serine Protease Activation for Pediatric Diffuse Intrinsic Pontine Glioma Treatment. *Pharmaceuticals (Basel)*. 2024, 17(1):135.
- [2] M.G. Perrone, A. Ruggiero, A. Centonze, A. Carrieri, S. Ferorelli, A. Scilimati. *Curr. Med. Chem.* 2021, 28(17), 3287-3317.



ISBN: