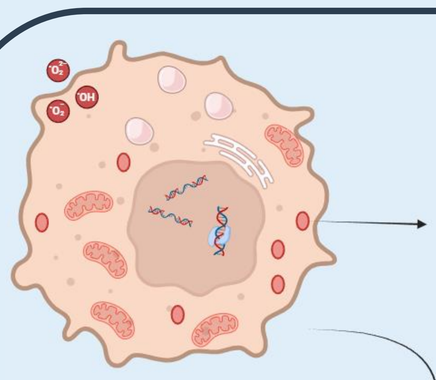
JQ1-conjugates as anti-aging compounds

Alessandro Raffa[a], Federico Berti[a], Fulvia Felluga[a]

[a]Department of Chemical and Pharmaceutical Sciences, University of Trieste, via L.Giorgieri, 1, 34127 Trieste.
alessandro.raffa@phd.units.it

Interreg Italia–Österreich
Co-funded by the European Union

Introduction



Senescent Cell (SC)

Causes:

- Extensive replication
- Oxidative stress
- Genotoxic damage
- Oncogene activation
- Proteasome inhibition

Features:

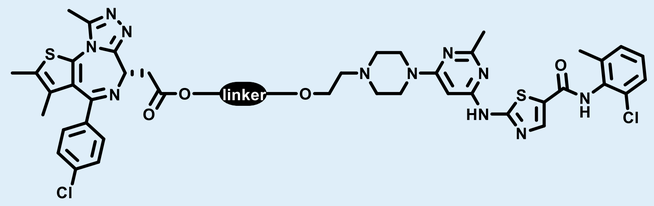
- Enlarged and irregular cell shape
- Accumulation of mitochondria
- Enlarged nuclear size
- Increased lysosomal content
- DNA damage
- **OVEREXPRESSION OF SENESCENT ASSOCIATED β-GALACTOSIDASE**

Consequences:

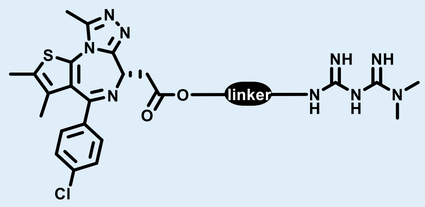
- Accumulation of SCs
- Chronic oxidative stress
- Inflammation
- Age-related diseases

Aim of the work

Cellular senescence is a state characterized by the arrest of cellular division and growth, and it can be caused by many stimuli; additionally, **senescent cells** (SCs) secrete a Senescence Associated Secretory Phenotype (**SASP**), which perpetuates the senescent state and induces neighboring cells into senescence.[1] Among potential therapeutic targets, this study exploit the function of **BET protein** subfamily that, interacting with acetylated lysines, act as transcription regulating factor.[2] **(+)-JQ1** binds the same pocket of acetylated lysine with high affinity.[3]
On the other hand, it was demonstrated both *in vitro* and *in vivo* the efficacy of **Dasatinib**,[4] and, moreover, in the last years several studies have uncovered multiple mechanisms of Metformin as anti-aging agent.[5]
Addressed by this evidence, the aim of the work was to link (+)-JQ1 to Dasatinib or **Metformin**, directly or through different linkers, in order to develop **conjugates** possibly displaying enhanced senolytic activity.



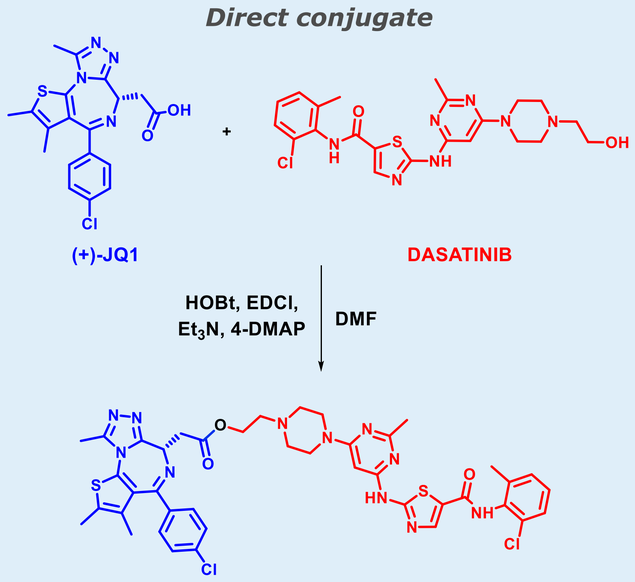
(+)-JQ1 Dasatinib



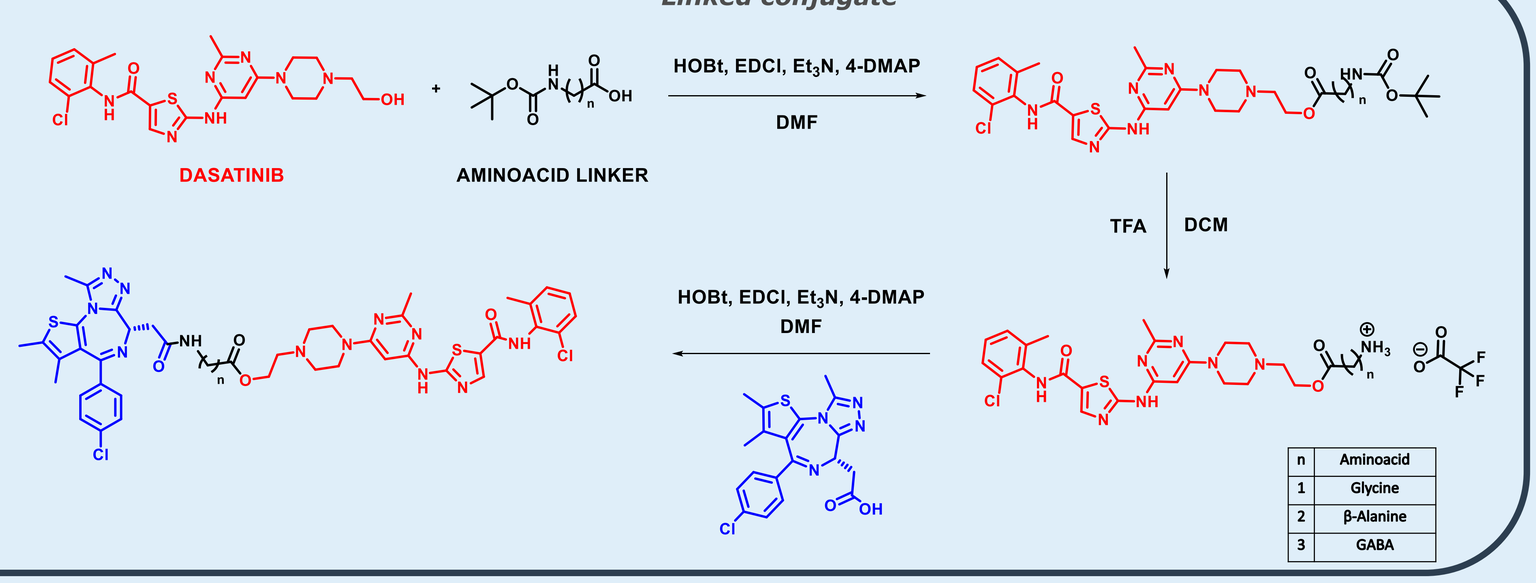
(+)-JQ1 Metformin

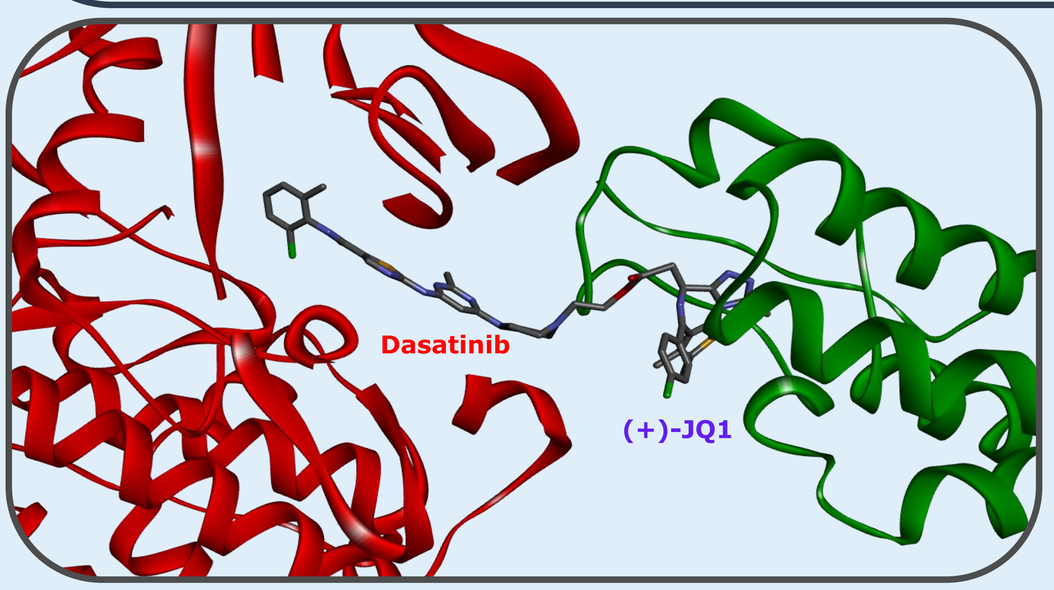
Synthesis of JQ1-Dasatinib conjugates

Direct conjugate

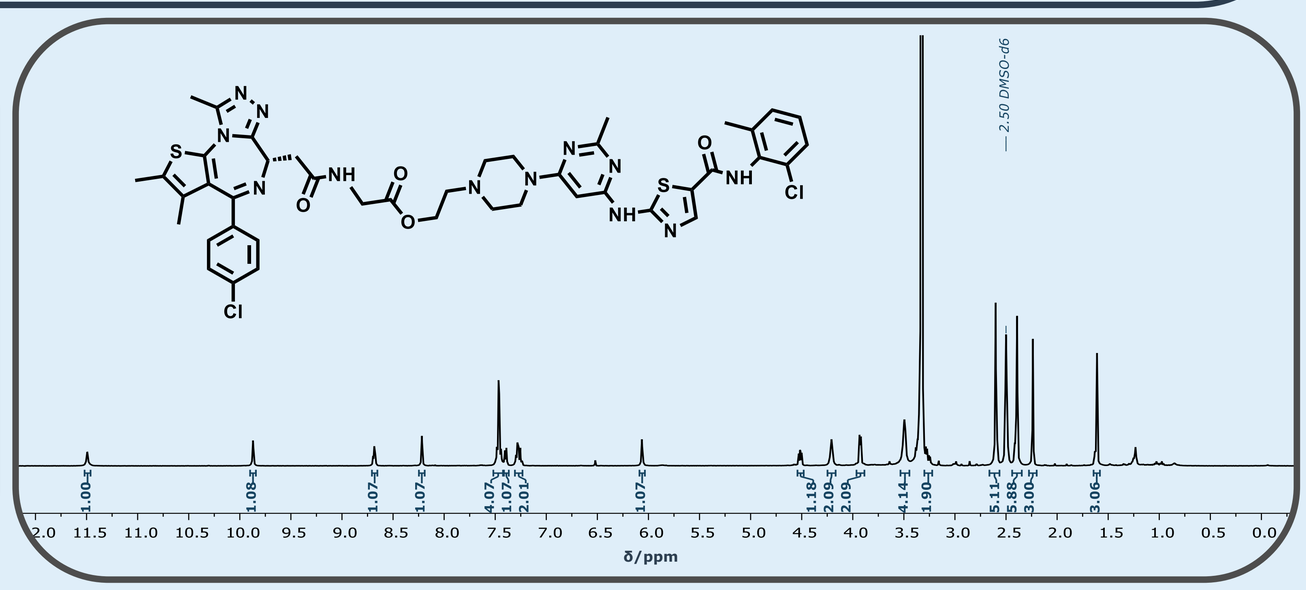


Linked conjugate



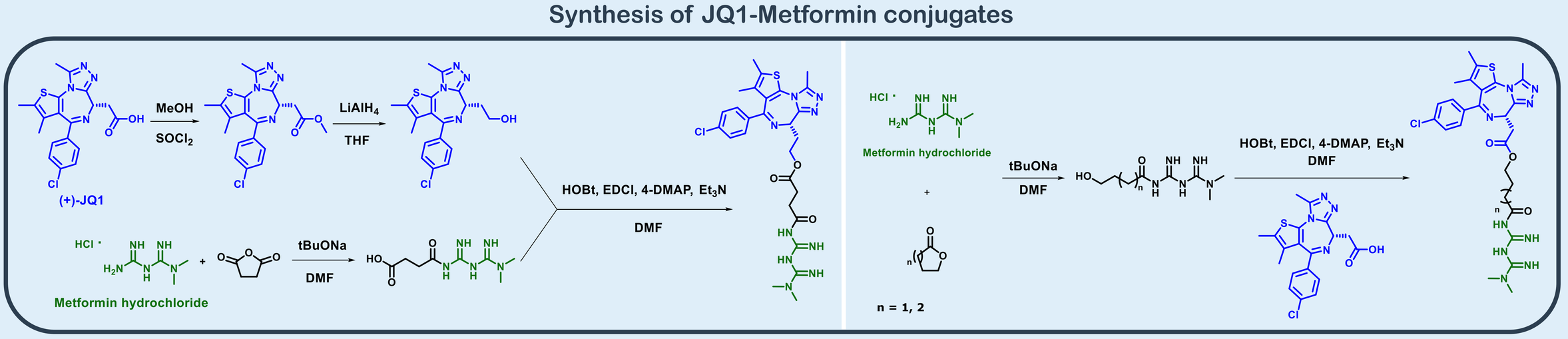


Dasatinib in MYT1 kinase directly bonded with (+)-JQ1 in BRD4



^{1}H NMR of glycine-linked (+)-JQ1-Dasatinib conjugate

Synthesis of JQ1-Metformin conjugates



Conclusions and future perspectives

Two (+)-JQ1-conjugates sets, with Dasatinib and Metformin respectively, were prepared under standard esterification/amidation method (HOBt, EDCl), that allowed to obtain pure products in yields ranging from 65% to 95%.
Currently, biological assays are in progress and based on the results that will be observed, the shown sets of compounds will be enlarged by the choice of linkers of different length and chemical-physical properties.
As far as the linker, the overexpression of SA-β-Galactosidase is a useful tool for targeting and deliverying, to obtain selective action in SCs and reduce the side effects related to off-target interactions.

References

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