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National Hellenic Research Foundation

INSTITUTE OF CHEMICAL BIOLOGY

Novel Tocopherol Hybrids and Bioisosteres as Proteasome Activators

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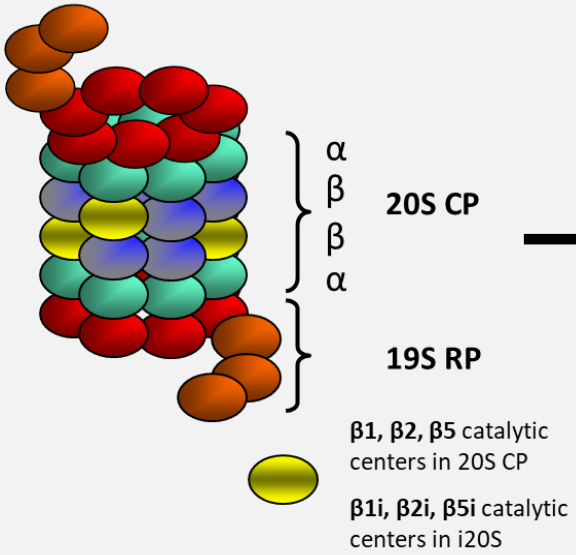
Athens, 21/06/2019

Proteasome 20S



Proteolytic sites

- active sites of 20S complex

β_1 caspase-like (PGPH, acidic aminoacids)

β_2 trypsin-like (basic aminoacids)

β_5 chymotrypsin-like (hydrophobic aminoacids)

- The proteasome constitutes one of the main cellular proteolytic mechanism that maintain protein homeostasis (proteostasis) and participates in almost all cellular functions through the degradation of misfolded, redundant, and damaged proteins.
- The catalytic 20S core constists of two outer rings, made up of seven different alpha subunits and two inner rings made up of seven ß subunits. The 20S proteasome has three well-characterized peptidase activities: chymotryptic-like, tryptic-like and caspase like, which are located in the hollow cavity of the cylinder and associated with ß5, ß2, and ß1 subunits, respectively.
- Proteasome has been reported to decline in terms of quantity and function during ageing and age-related diseases progression.
- Proteasome activation constitutes a pioneer strategy for the deceleration of aging.

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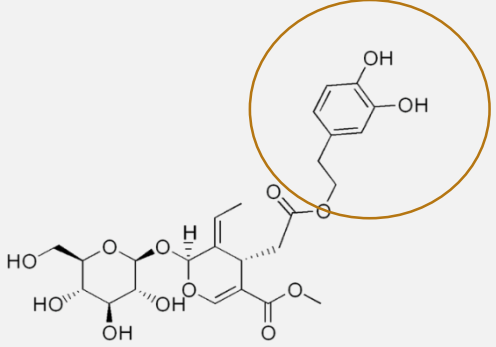
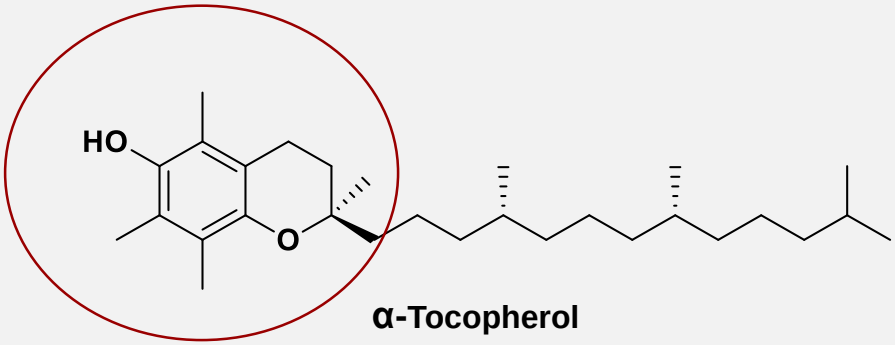
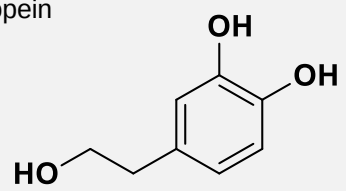


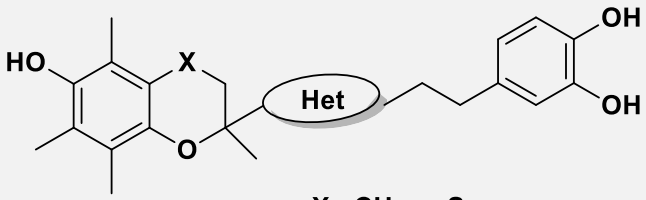
Oleuropein



α-Tocopherol

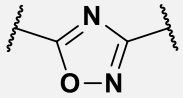


Hydroxytyrosol

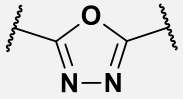


X= CH_2 or S

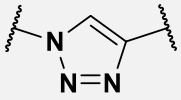
Het =



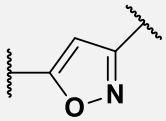
1,2,4-oxadiazole



1,3,4-oxadiazole



1,2,3-triazole



isoxazole

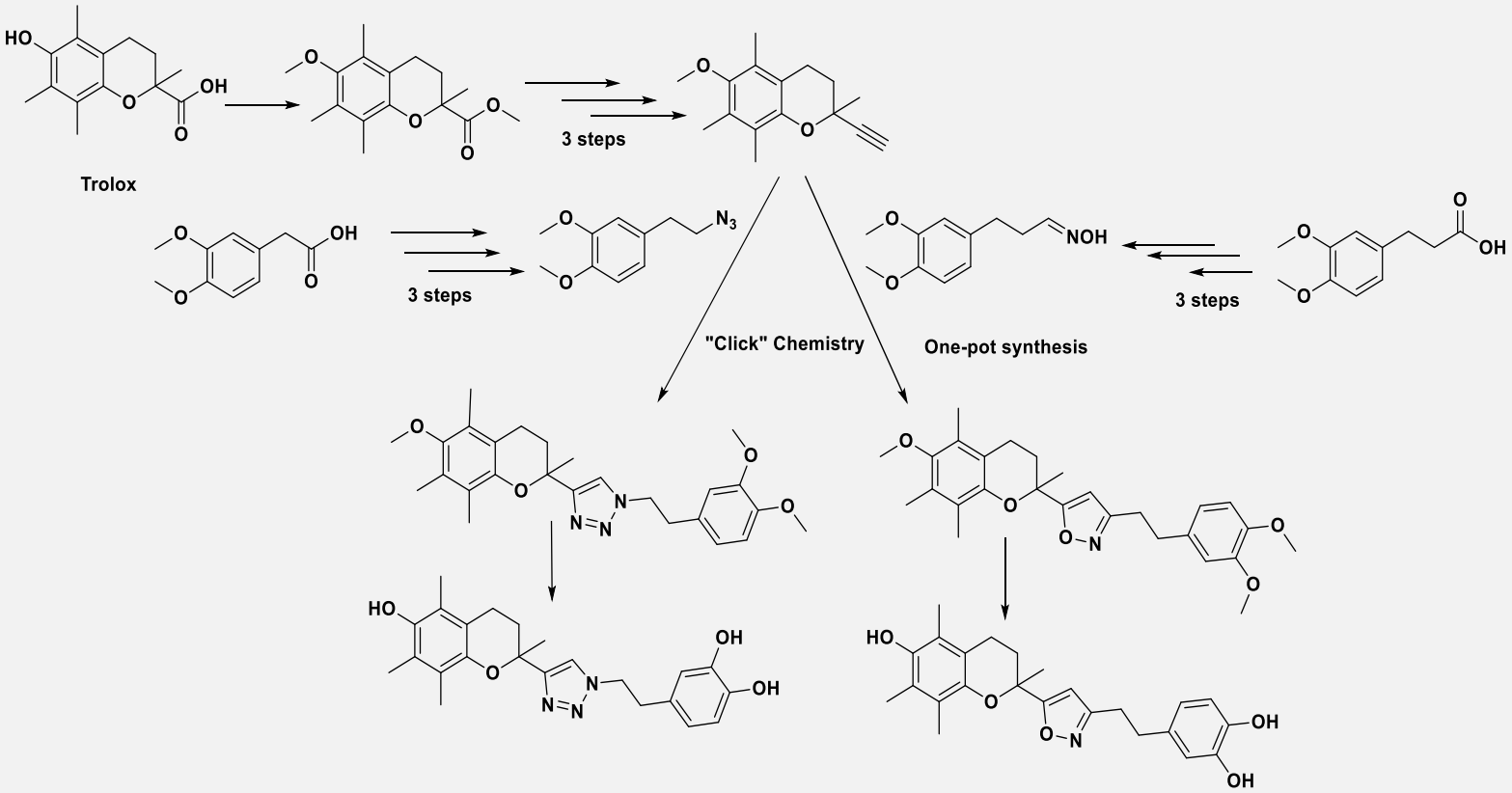
Bioisosterism:

is a strategy of Medicinal Chemistry for the rational design of new drugs, as a special process of molecular modification of a lead compound.

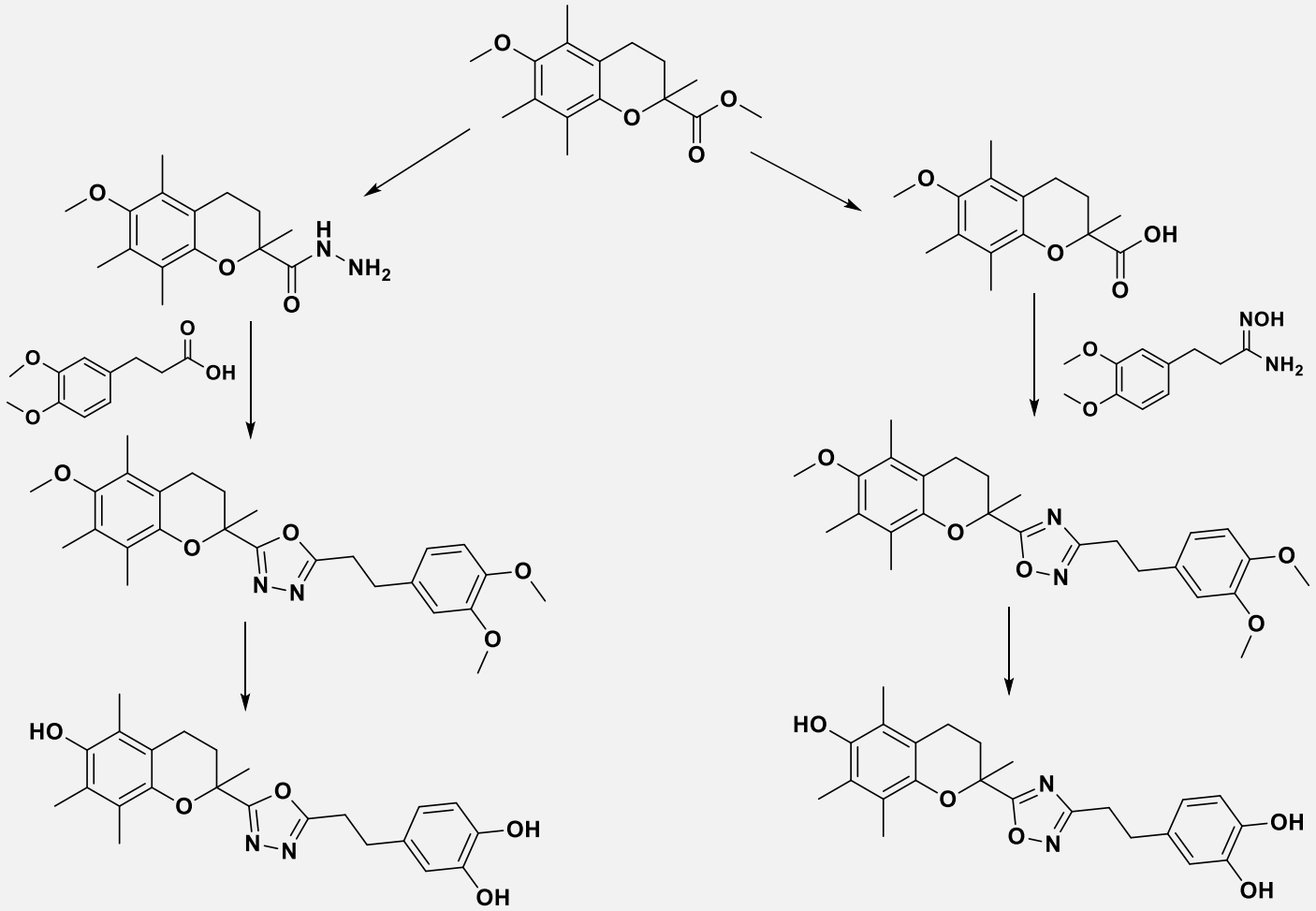
This strategy can result in compounds presenting:

- Improved selectivity
- Fewer side effects and decreased toxicity
- Improved pharmacokinetics: solubility/hydrophobicity
- Increaced metabolic stability
- Simplified synthetic routes
- Patented lead compounds

1,4-disubstituted-1,2,3-triazoles and 3,5-disubstituted isoxazoles

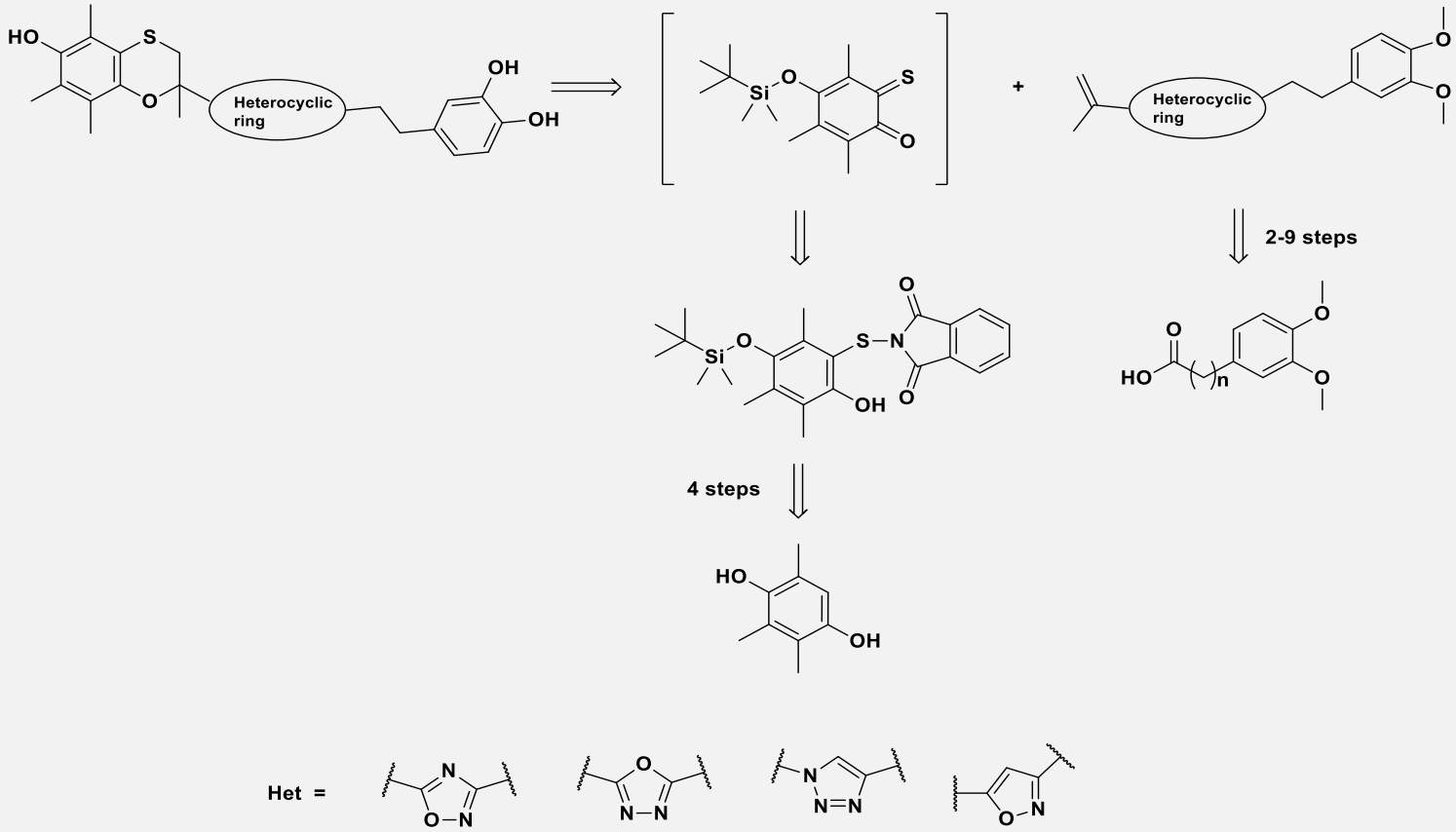


1,3,4- and 1,2,4- Oxadiazole Analogues

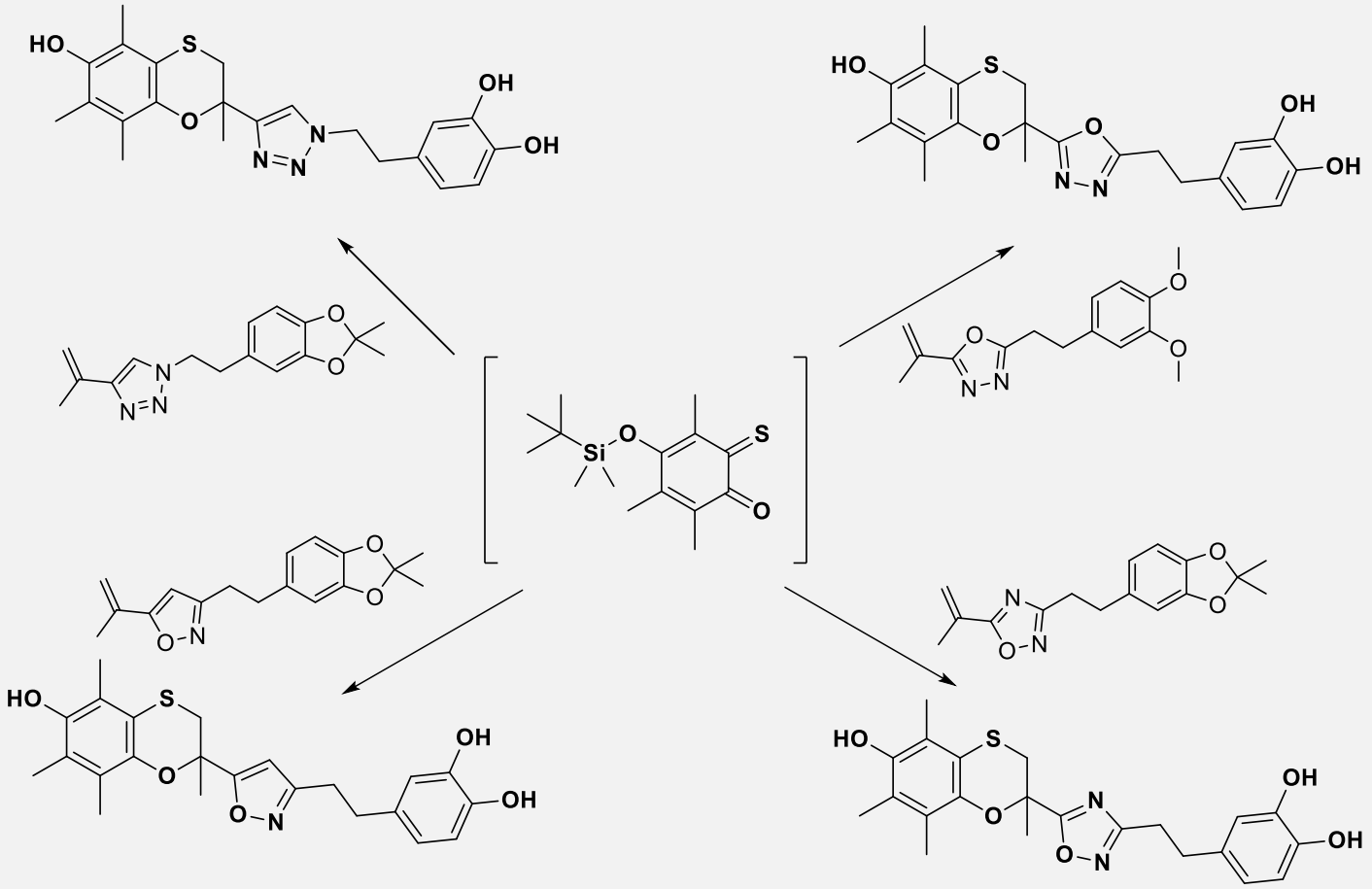


PCT/GR2019/000018, Bioinspired proteasome activators with antiageing activity. Applicant: National Hellenic Research Foundation. Inventors: Koufaki M., Calogeropoulou T., Chondrogianni N., Papahatjis D., Gonos E., Fotopoulou T., Prousis C. K., Chazapi E.

Retrosynthetic scheme of tocopherol bioisosteres



Novel 4-Thiatocopherol hybrids



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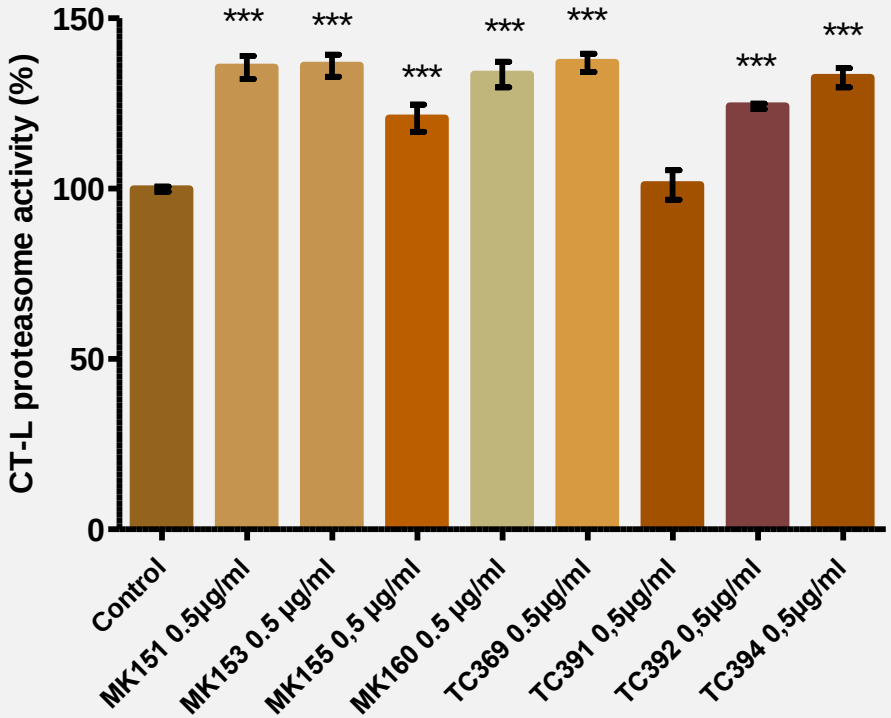
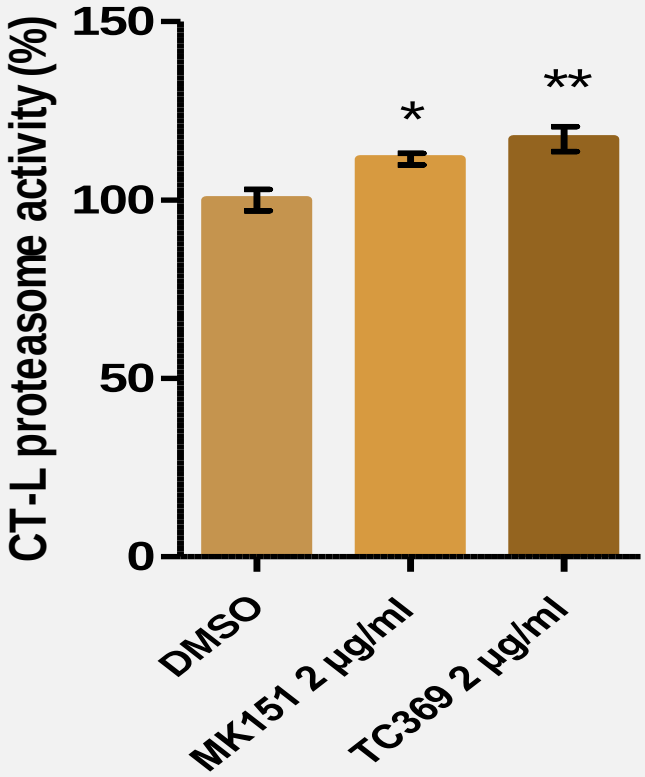
Proteasome activation following treatment of HFL-1 normal fibroblasts with the compounds (0.5 μg/ml concentration)



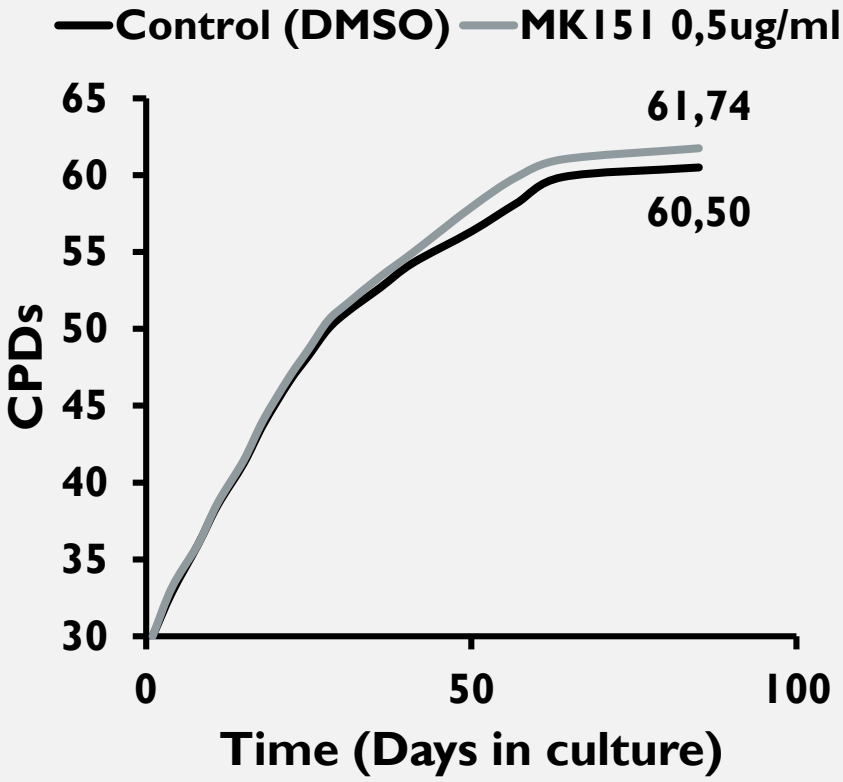
***P-value<0.001

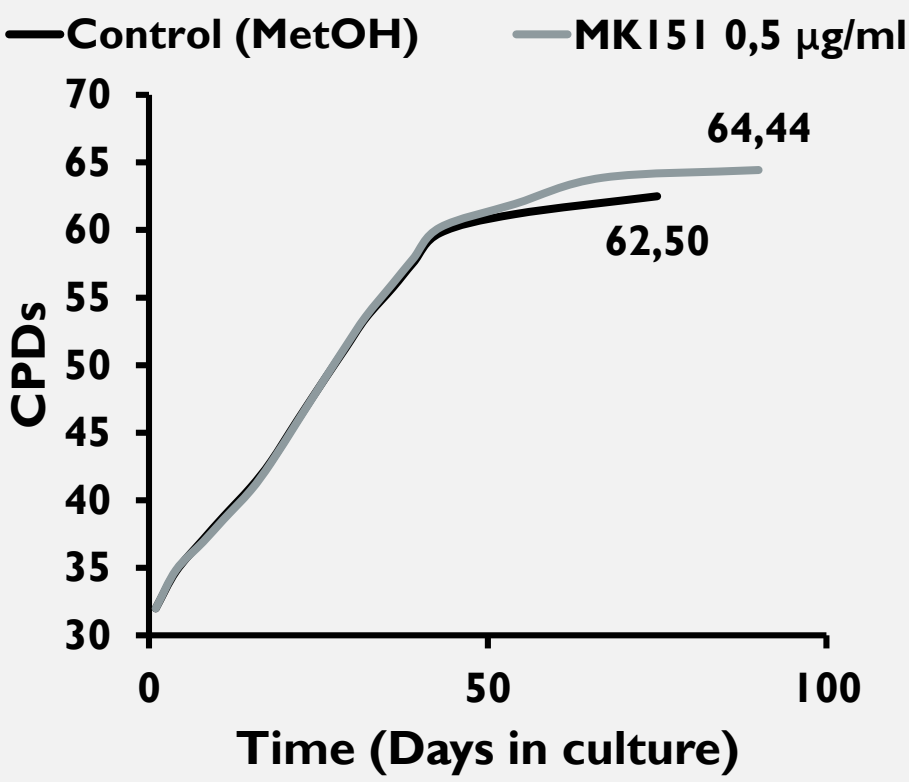
Direct activation of purified 20S complex by MK151 and TC369



*P-value<0.05, **P-value<0.01

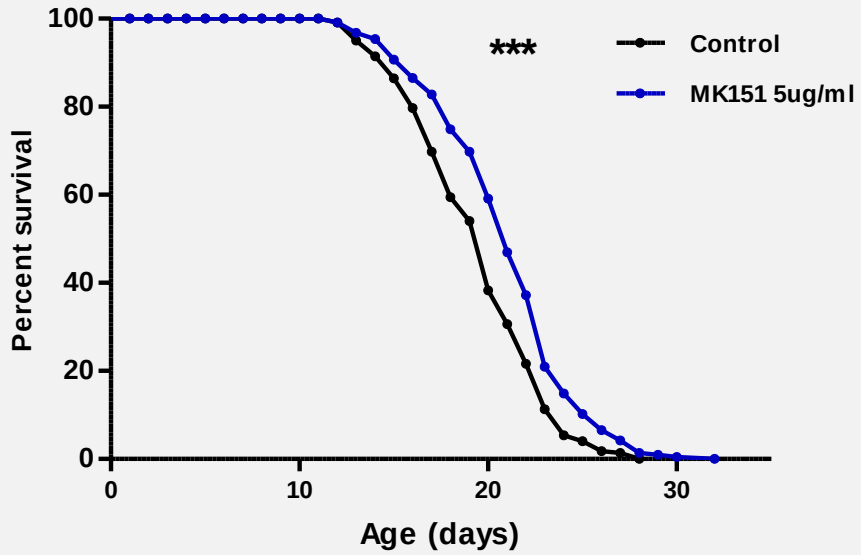
Treatment with MK151 leads to cellular lifespan extension



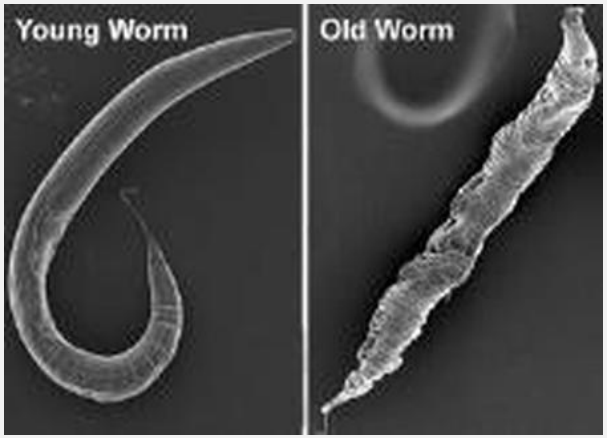


Treatment with MK151 leads to organismal lifespan extension

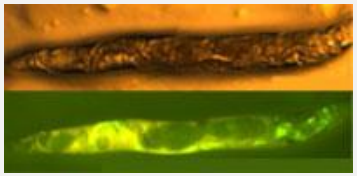
C. elegans lifespan (wt)



Median lifespan (compound/diluent): 21/20
Max lifespan (compound/diluent): 32/28



Day 4



Day 16

Conclusions

- **8** novel hybrid compounds were designed and synthesized.
- The majority of the new compounds showed proteasome activation in young primary HFL-1 fibroblasts.
- **MK151** possess anti-ageing properties that lead to cellular lifespan extension.
- Treatment with **MK151** leads to organismal lifespan extension.
- Direct activation of purified 20S complex by **MK151** and **TC369**, leads to promising structural proteasome activators.

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Evanthia Chazapi Msc, PhD fellow

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Dr. Nikoletta Papaevgeniou, Postdoctoral Reseacher
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