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In silico evaluation of EGFR PROTACs' ADMET properties based on linker structure

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INTRODUCTION & AIM

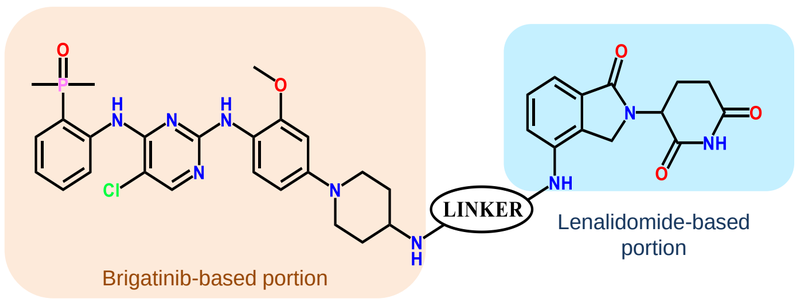
Proteolysis-targeting chimeras (PROTACs) are heterobifunctional molecules consisting of two linked substructures: protein-of-interest-binding ligand (POI ligand) and the E3 ubiquitin ligase-binding ligand (1). Simultaneous binding of the PROTAC to both the POI and the E3 ligase leads to the ubiquitylation of the POI, thus marking it for degradation via the ubiquitin proteosome system (1). First fully-synthetic PROTAC was synthesised in 2001 (2). Since then, an expansion in PROTAC synthesis is seen, though challenges are present in their design, synthesis and application in therapy. In particular, the **evaluation of pharmacokinetic and pharmacodynamic properties of PROTAC molecules is quite difficult** due to their catalytic nature (3). Additionally, they have high molecular weight and they exhibit hooking effect (4,5). To address those issues, scientists started to investigate PROTAC linker characteristics and their impact on the biodegradation efficacy of PROTACs. However**, the impact of linker structure on PROTACs' DMPK properties is still not well understood** (6).

In this poster, I analyse three types of modifications potentially leading to improved bioavailability of PROTACs *in silico*, on an example of EGFR PROTACs' structure. Those modifications include changes to: i) linker length ; ii) linker rigidity; iii) number of hydrogen donors in linker; iv) number of introduced heteroatoms.

METHOD

All PROTACs designed contained brigatinib as EGFR-targeting ligand, and lenalidomide as a ligand targeting cereblon (CRBN) E3 ligase. Brigatinib was chosen due to its effectivenes against C797S/T790M/activating-mutation (triple-mutation) related to osimertinib resistance in treating non-small-cell lung cancer (7). Lenalidomide was chosen due to its ability to create stronger H-bonds at the CRBN–CK1α interface (8).

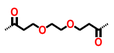
All compounds were tested in silico for the evaluation of their ADMET properties, using freely available online ADMET Tools: SwissADME, ADMETlab 2.0, pkCSM6. Additionally, tools that involve artificial intelligence (AI) calculations were used, and the results obtained from these softwares were compared to non-AI tools. AI software used: ADMET-AI, Simulations Plus. SMILES strings were obtained using SMILES generator by Cheminfo.org. Obtained results were compared and most interesting findings are shown.

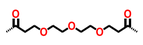


Linkers with changes to:

i) linker length:

1: 

2: 

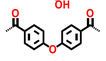
3: 

4:

ii) linker rigidity:

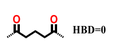
5: 

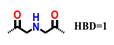
6: 

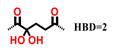
7: 

8:

iii) number of H donors:

9: 

10: 

11: 

12:

iv) number of heteroatoms:

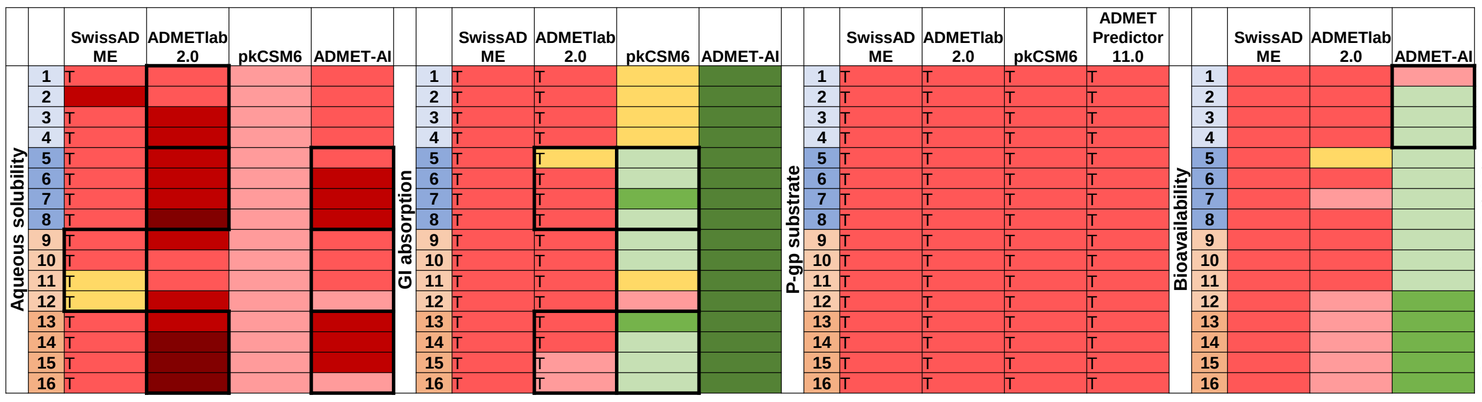
13: 

14: 

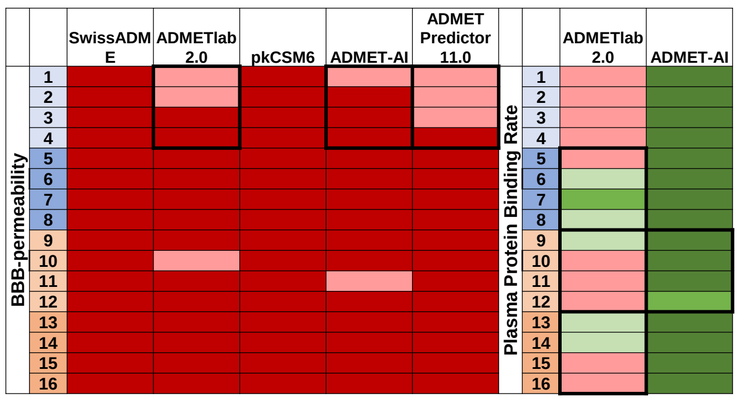
15: 

16:

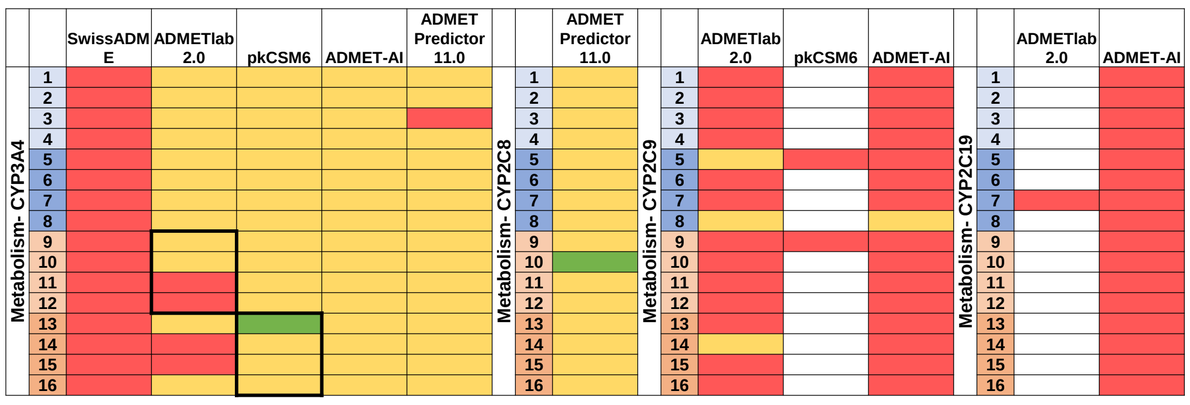
RESULTS & DISCUSSION



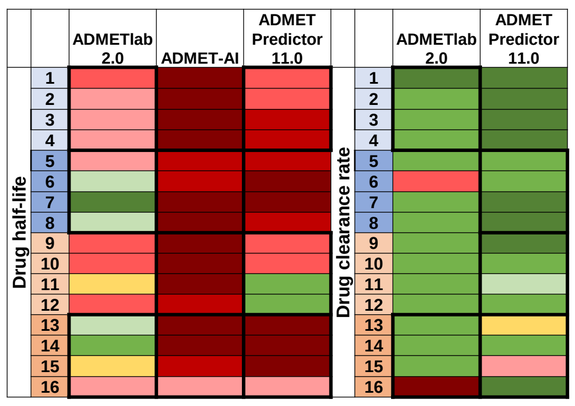
*T- textual result. All textual results are shown as medium values of positive, negative or moderate result. NOTE: Colours are shaded in intervals of ±50% of the minimal value. Grey- no information. Red- undesirable scores. Green- desirable scores. Yellow- moderate scores.



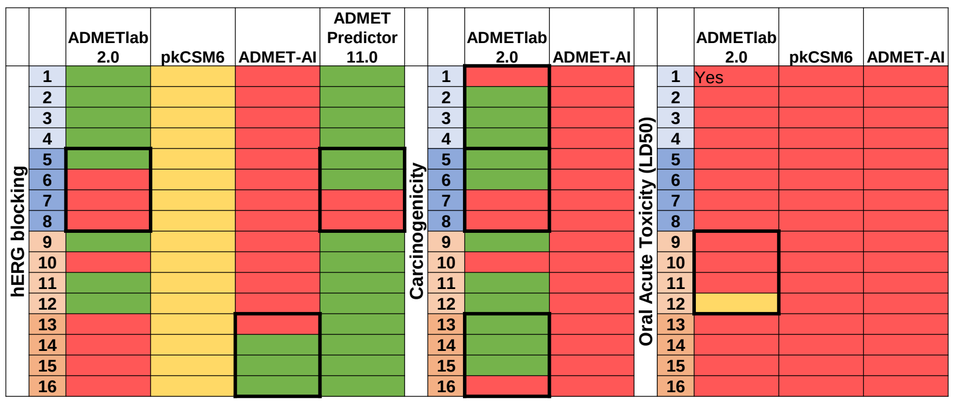
NOTES: i) BBB-permeability: Red- not BBB permeable. Light red- low BBB permeability.
ii) Plasma Protein Binding Rate: Light red: score 70-80%. Light green: score 85-90%. Medium green: score 90-95%. Dark green: score 100%.



NOTE: All results are textual. Green: substrate. Red: inhibitor. Yellow: substrate and inhibitor.



NOTES: i) Drug half-life: reds indicate longer half-lives, greens indicate shorter half-lives, yellow indicates moderate half-life. rate.
ii) Drug clearance rate: greens indicate faster clearance rates, reds indicate slower clearance rates, yellow indicates moderate clearance



NOTE: All results are shown indicating an existence of tox parameters. Green-yes. Red- No. Yellow: hERGII blocked, hREG I not blocked; or low LD50.

CONCLUSION AND FUTURE WORK

Overall, the AI-powered tools gave more precise measurements. It was noted that the increase in linker length contributed to better bioavailability and the reduction of carcinogenicity of PROTACs. Introduction of more rigid structures contributed to increased plasma protein binding (PPB) rate. Increasing number of hydrogen bond donors contributed to improved aqueous solubility and the decrease in oral acute toxicity, however, it also lowered the rate of gastrointestinal absorption of the drugs. The higher the number of heteroatoms, the lower hERG blocking was apparent. Unfortunately, for most other parameters highlighted in the results, it was not possible to determine the relationship with the modifications set in this paper. As the results were not precise and varied greatly between programmes, it is necessary to perform *in vitro* ad *in vivo* tests and determine the drugs' real ADMET properties. So far, the tools seem to not be able to calculate PROTAC's properties with great precision, and are more suitable for small molecules.

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