Ideas for the ddesign and synthesis of new ALM-DAI analogues

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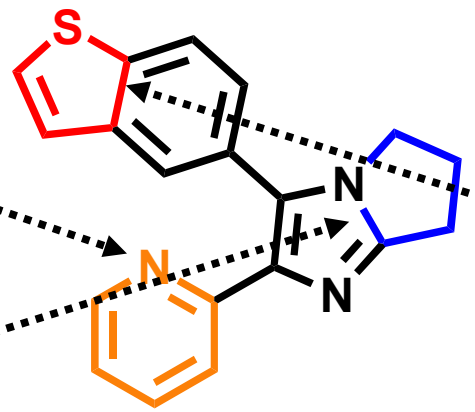
Summary

Enhance potency/solubility

Further exploration of the pyridine ring

Combinations of ALM-DAI-28 with the different cores

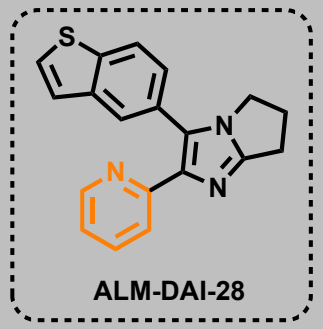


ALM-DAI-28

Improve matebolic stability

Decrease the electron density of the methylene from the 5-benzothienyl group

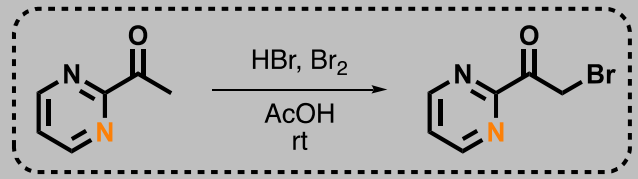
Further exploration of the pyridine ring of ALM-DAI-28



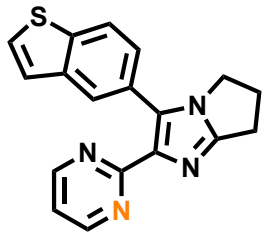
Log P: 3,64

Starting with the corresponding 2-bromo-1-(aryl)ethanone # using the same procedure employed for the preparation of ALM-DAI compounds; or the appropriate 2-acetyl derivative and subsequent bromination at α-position* [PMID: 24967731, 26318065].

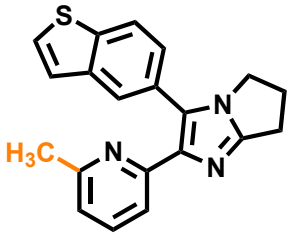
*



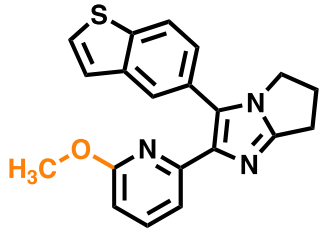
Pyridine analogues
(Potency improvement?)



* Log P: 3,51

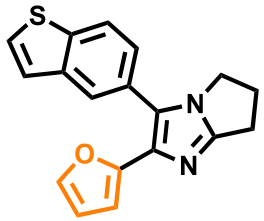


* Log P: 4,35

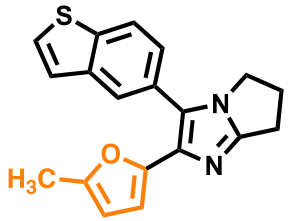


* Log P: 4,23

Furan analogues
(Interesting Log P reduction)



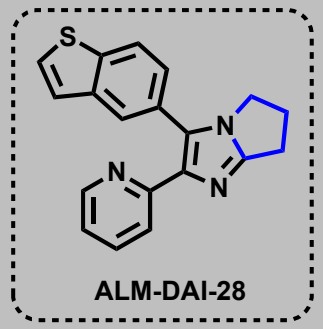
Log P: 1,85



Log P: 1,47

Log P values calculated with Chemdraw

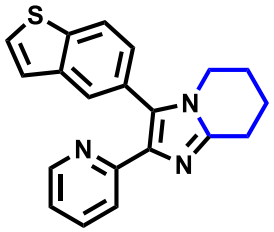
Modifications to the imidazole core of ALM-DAI-28



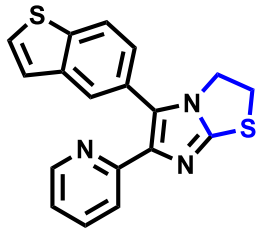
ALM-DAI-28

Once ALM-DAI-28 has been identified as the most active compound (MIC = 2 g/mL), the imidazole core could be changed with the different imidazole combinations used in the ALM-DAI library to see if the 6,7-dihydro-[5H]pyrrolo[1,2-a]imidazole is still the best core. However the Log P values are higher in these analogues.

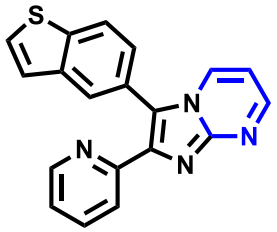
Log P: 3,64



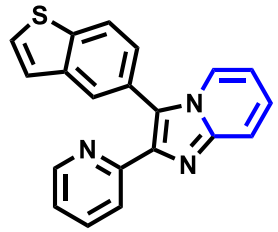
Log P: 4,06



Log P: 4,41



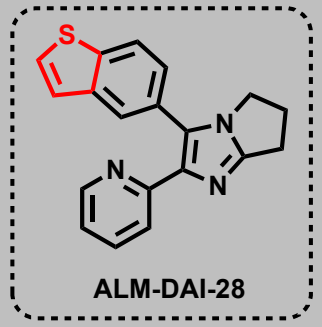
Log P: 3,88



Log P: 4,17

Log P values calculated with Chemdraw

Improve metabolic stability of ALM-DAI-28



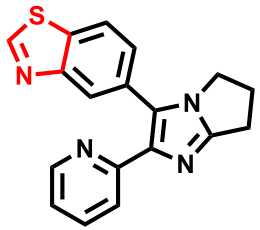
ALM-DAI-28

Log P: 3,64

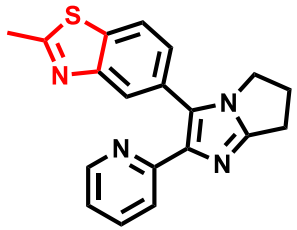
Decrease of the electron density:

- Introduction of heteroatoms to the thiophen ring (e.g.: thiazole analogues).
- Delocalizing the electrons from the methylene of the thiopen ring (e.g.: dibenzothiophene group).

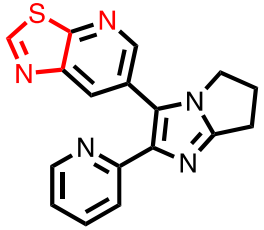
Compounds can be easily prepared by Suzuki couplings following the ALM-DAI procedure.



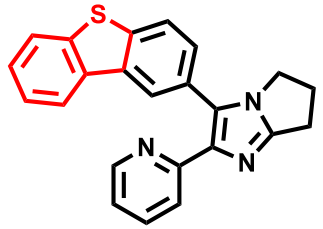
Log P: 3,22



Log P: 3,34



Log P: 2,6

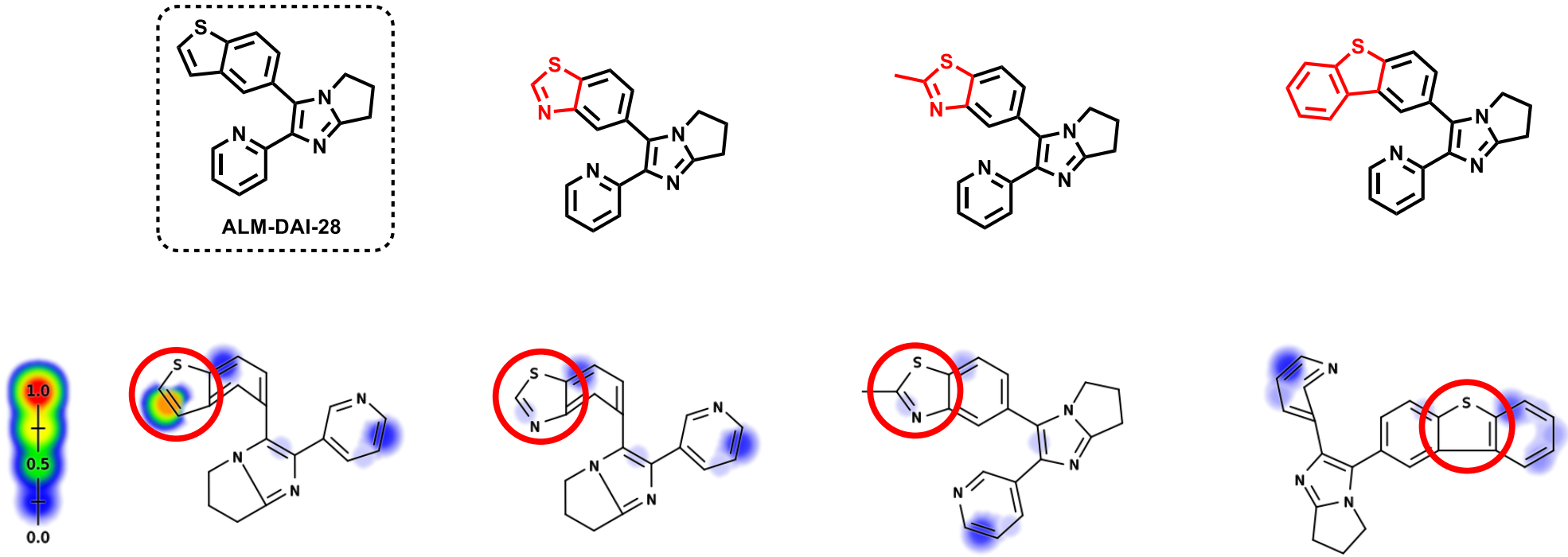


Log P: 4,84

Boronic ester/acid or BrR comercially availables: CAS = 1073354-91-2 (BEster); CAS = 590417-67-7 (BAcid); CAS= 886372-88-9 (BrR); CAS = 668983-97-9 (BAcid).

Log P values calculated with Chemdraw

Metabolic stability of ALM-DAI-28 vs thiophene and dibenzothiophene analogues



XenoSite prediction of P450-mediated metabolism of ALM-DAI-28 and analogues.