Biomagi Project OxazolCarboxamides

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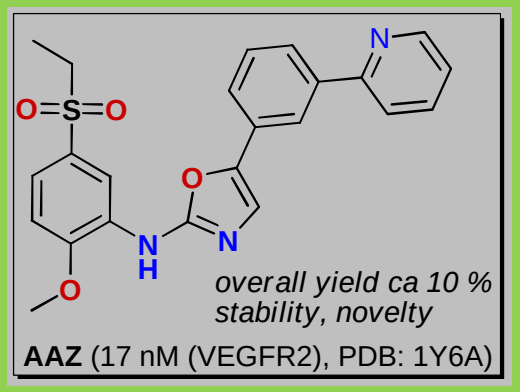
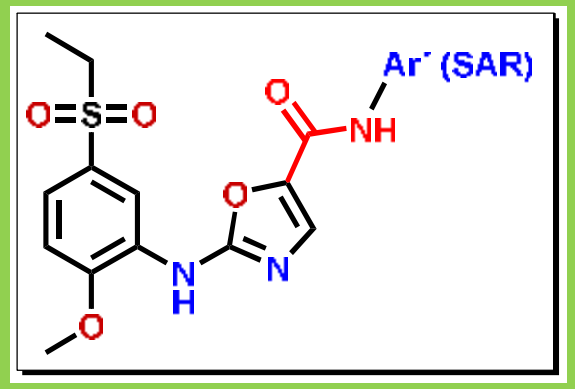
Mgr. Juraj Dobiaš



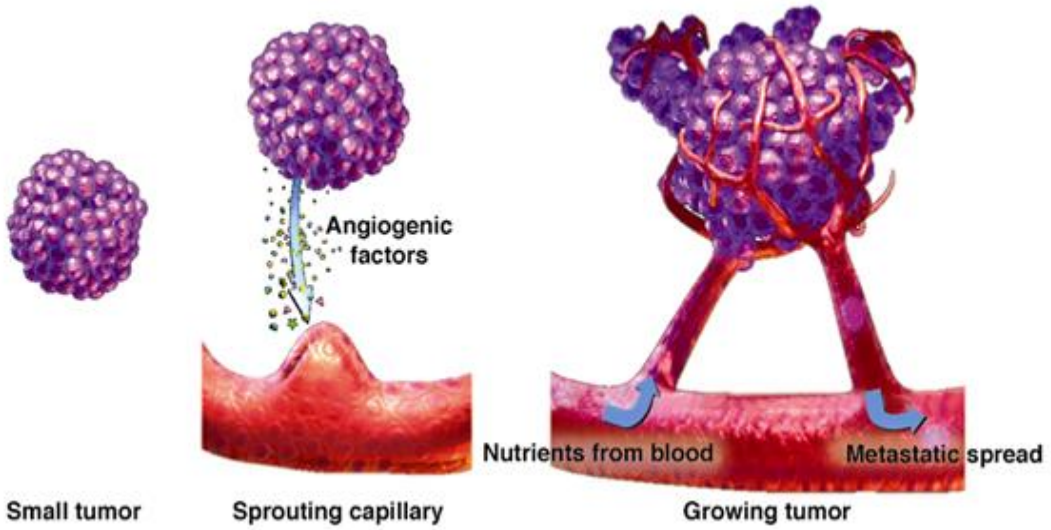


Project aims:

- development of new VEGFR2 inhibitors possessing **structure novelty**
- predicted good VEGFR2 **affinity** and **bioavailability**
- **synthetic feasibility**

Why VEGFR-2

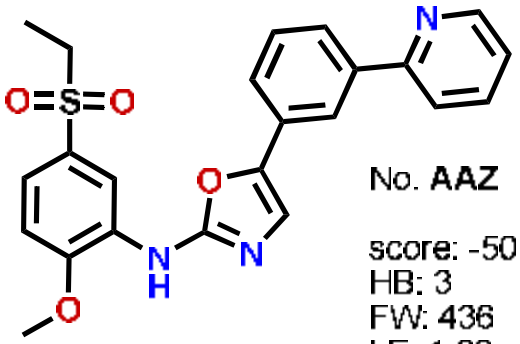
- Main regulator of angiogenesis.



- Inhibition of TK domain leads to slower tumor growth and metastasis spread.

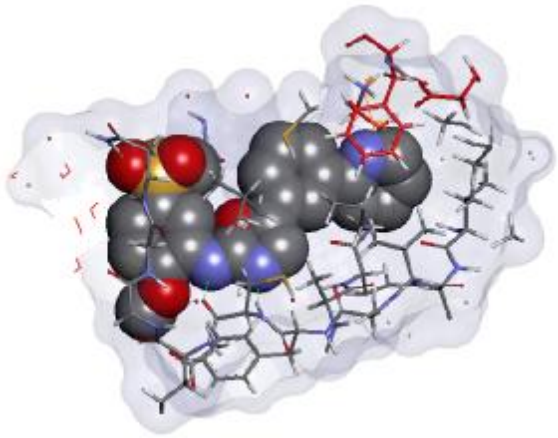
Project rationale:

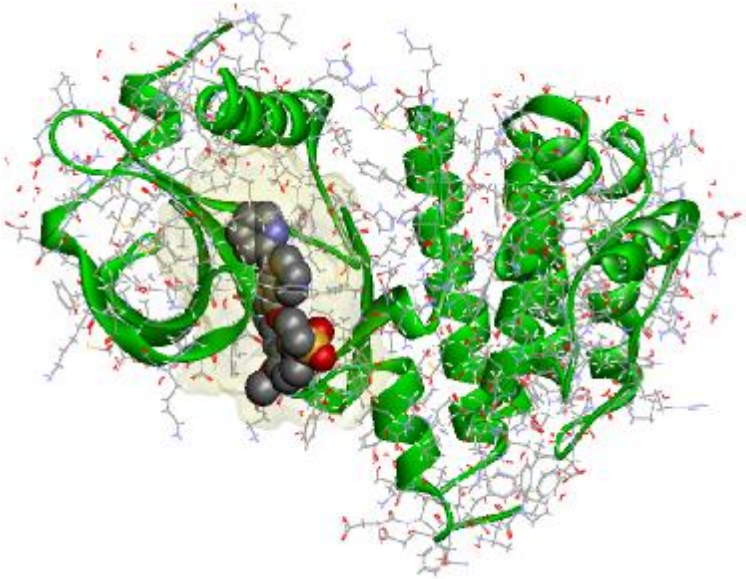
State of the art: AAZ (PDB: 1Y6A), IC_{50}: 17 nM



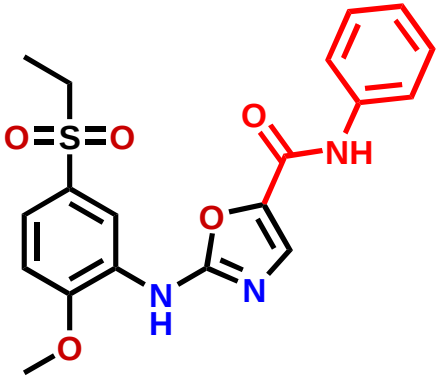
No. **AAZ**

score: -50.34
HB: 3
FW: 436
LE: 1.62
xLogP 4.12
charge: 0
NRB: 7

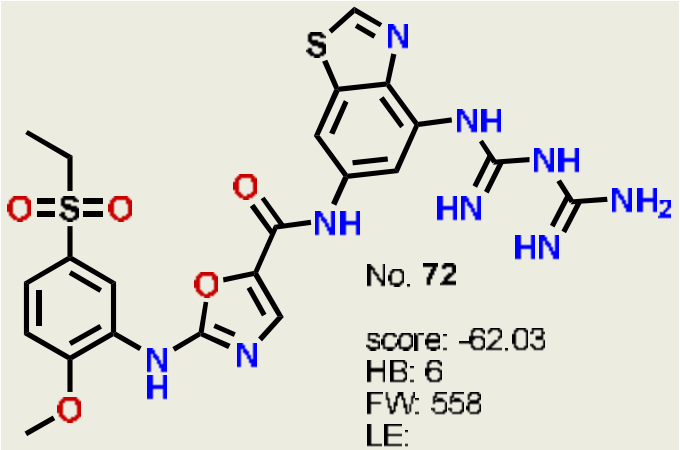




New leading skeleton **and** **the best predicted derivative:**



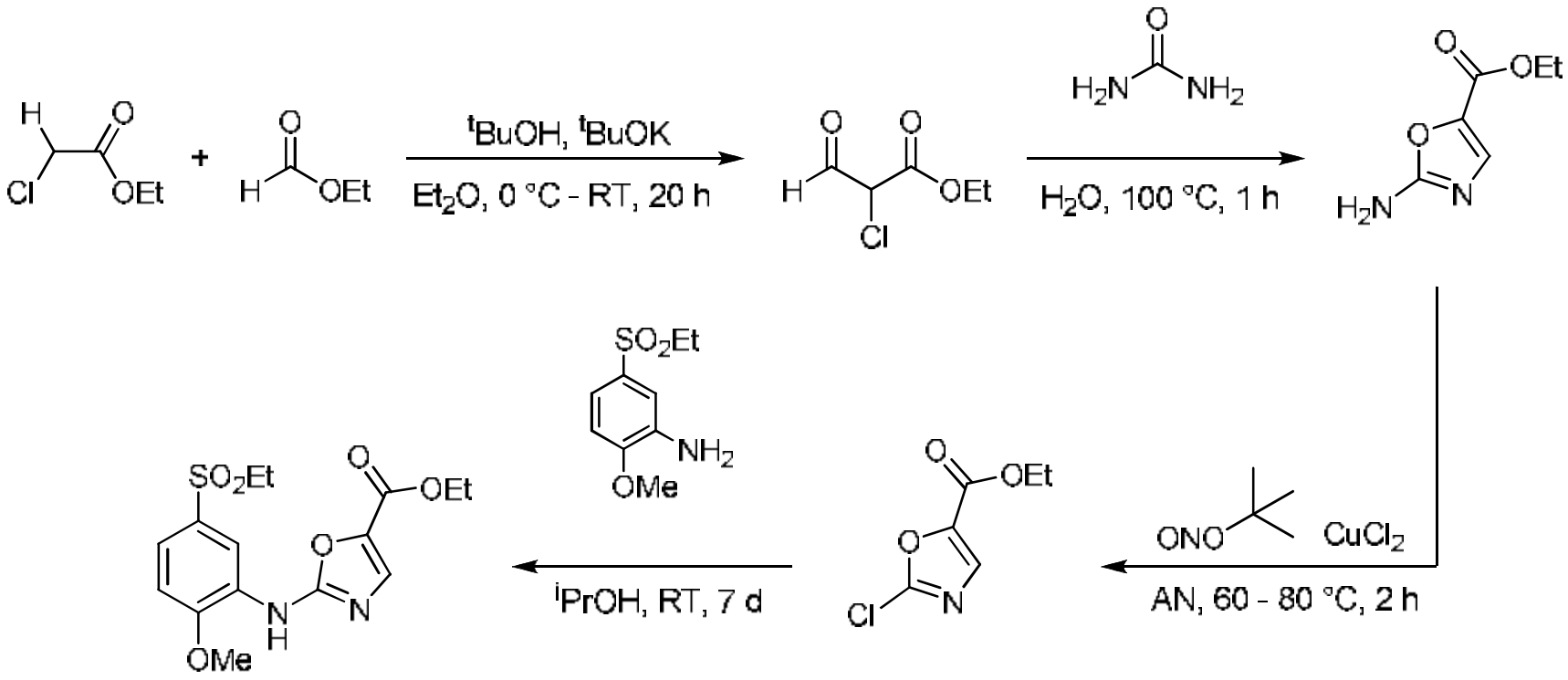
score: -46.50
HB: 3
FW: 401
LE: 1.66
xLogP 2.70
charge: 0
NRB: 7



No. **72**

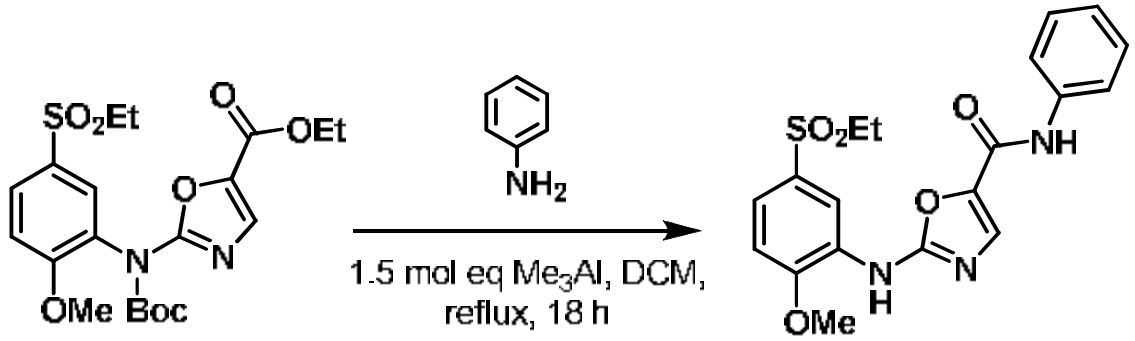
score: -62.03
HB: 6
FW: 558
LE:
cLogP 2.4
charge:
NRB:

Ester precursor synthesis

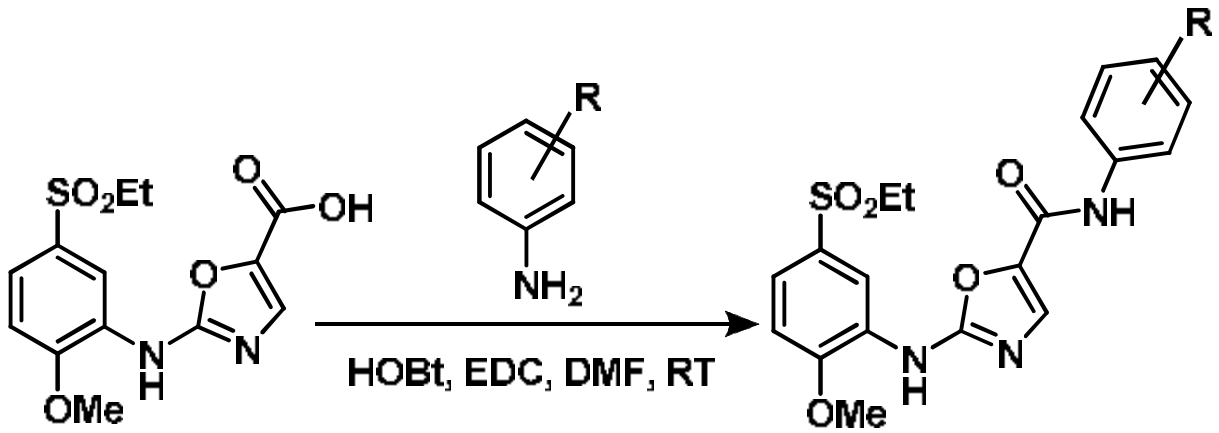


Key synthetic step

Basic skeleton:



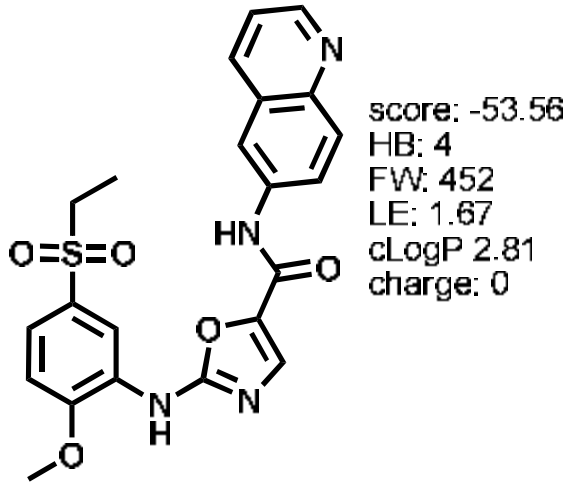
Broadened scope with activated esters



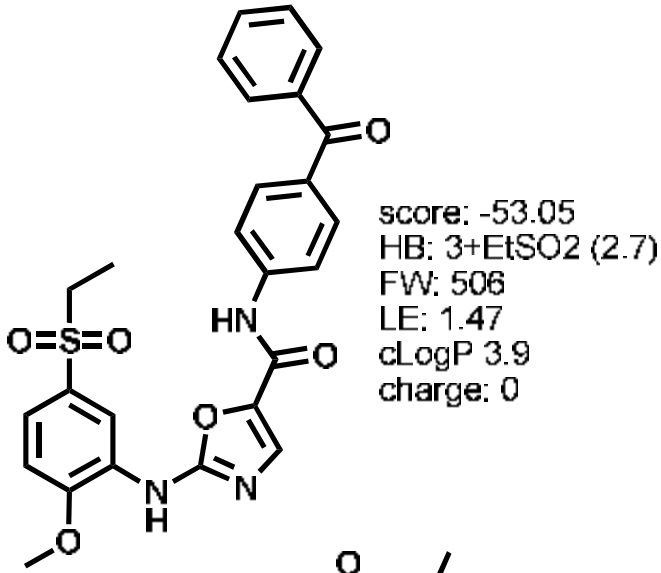
Deactivated anilines react slowly with low yields

Anilines from commercial sources

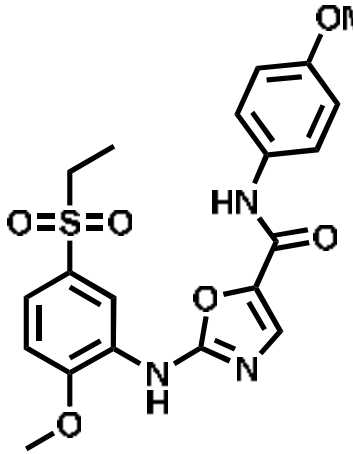
Structures and predicted properties



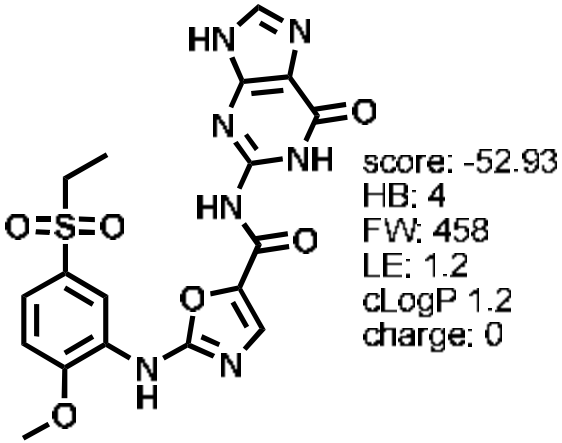
score: -53.56
HB: 4
FW: 452
LE: 1.67
cLogP 2.81
charge: 0



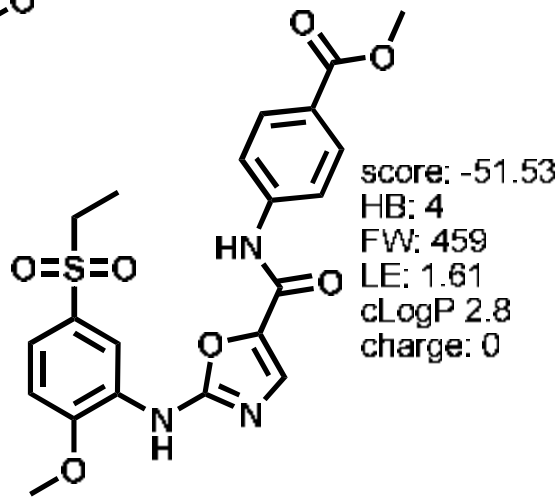
score: -53.05
HB: 3+EtSO2 (2.7)
FW: 506
LE: 1.47
cLogP 3.9
charge: 0



score: -51.14
HB: 4
FW: 431
LE: 1.7
cLogP 2.7
charge: 0



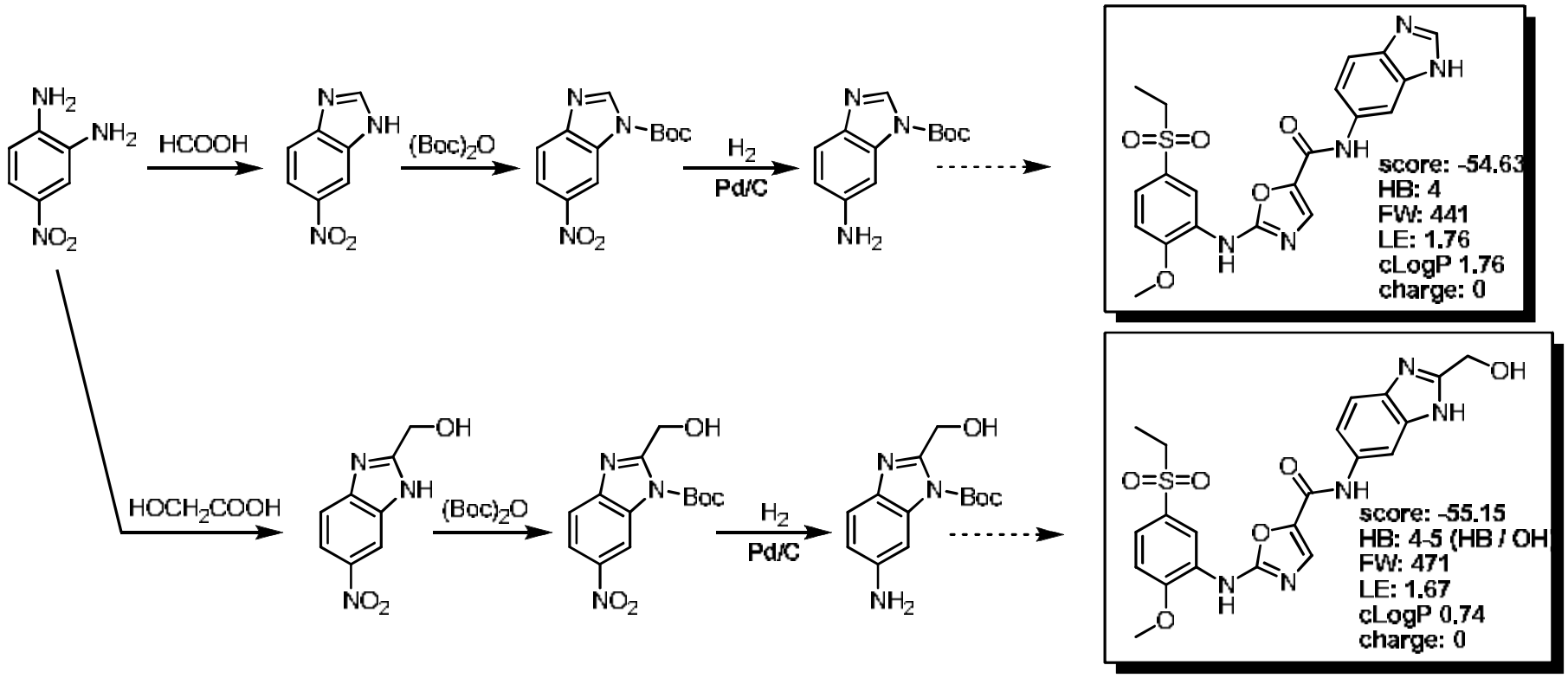
score: -52.93
HB: 4
FW: 458
LE: 1.2
cLogP 1.2
charge: 0



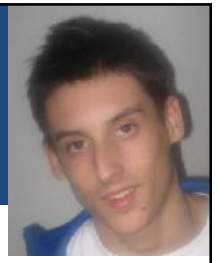
score: -51.53
HB: 4
FW: 459
LE: 1.61
cLogP 2.8
charge: 0

Anilines for preparation

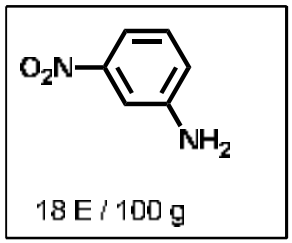
Synthesis:

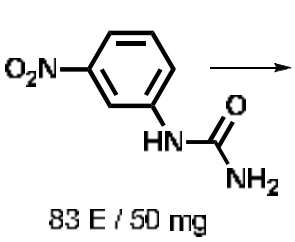


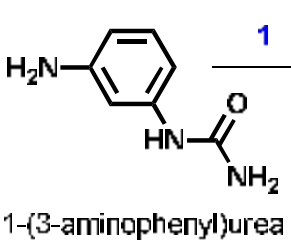
Anilines for preparation



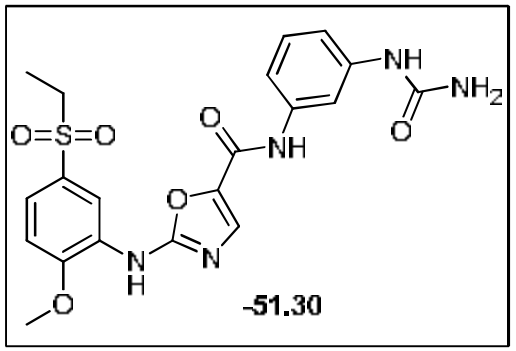
Synthesis:

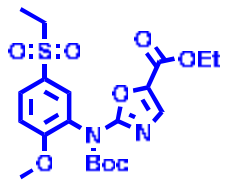


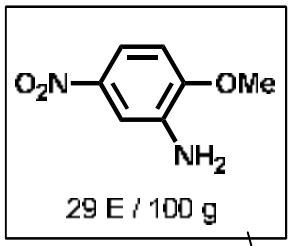


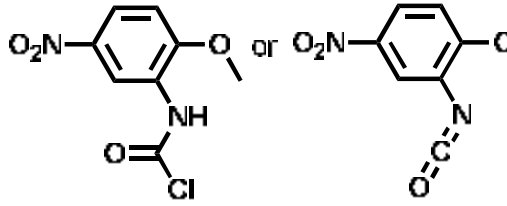


1



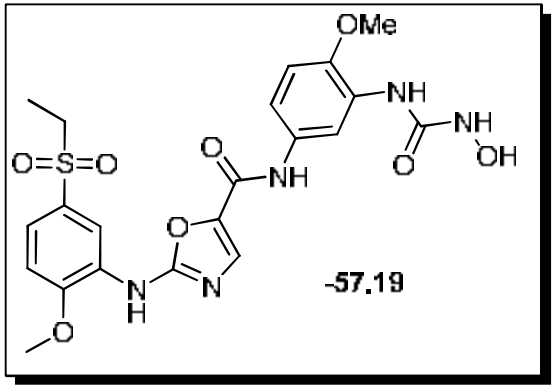


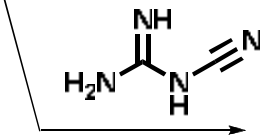




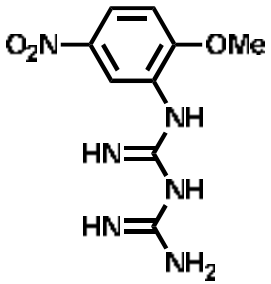
a/ NH_2OH
b/ H_2, Pd/C

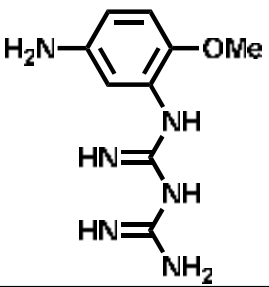
1



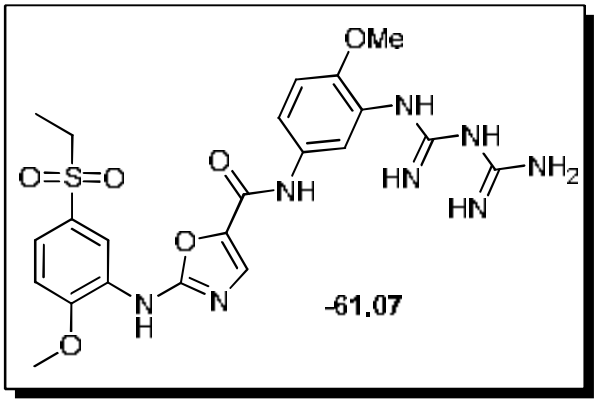


N-cyanoguanidine
29 E / 1000 g
CAS 461-58-5



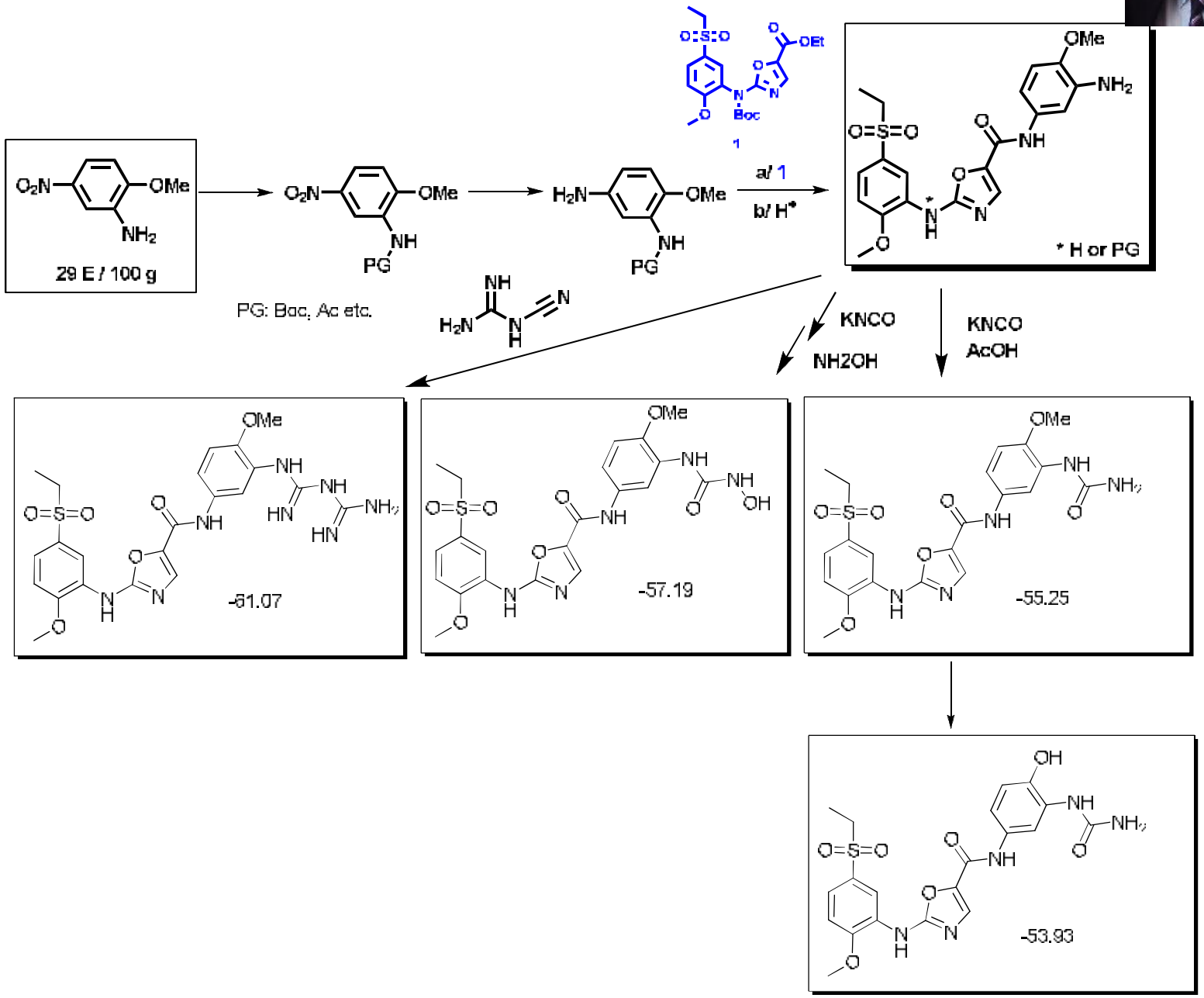


a/ 1
b/ H^+

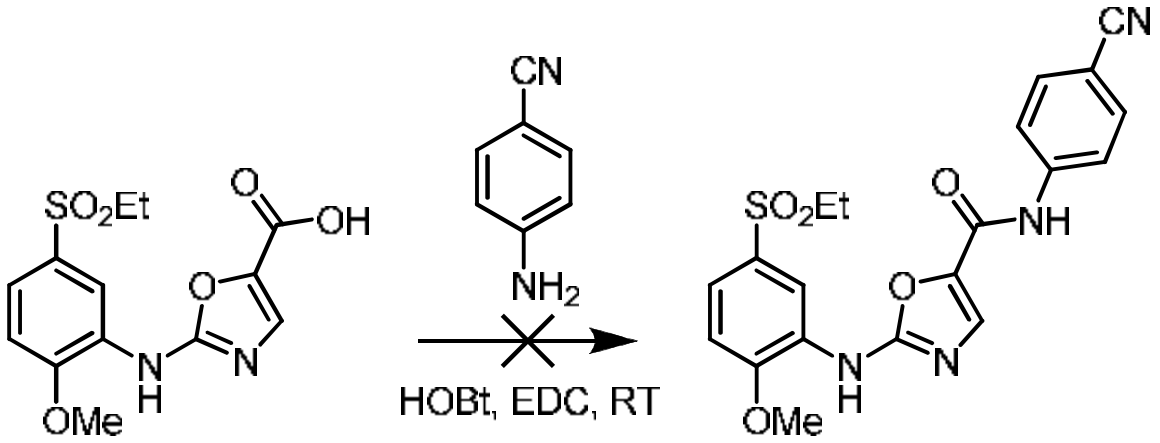


Other approaches

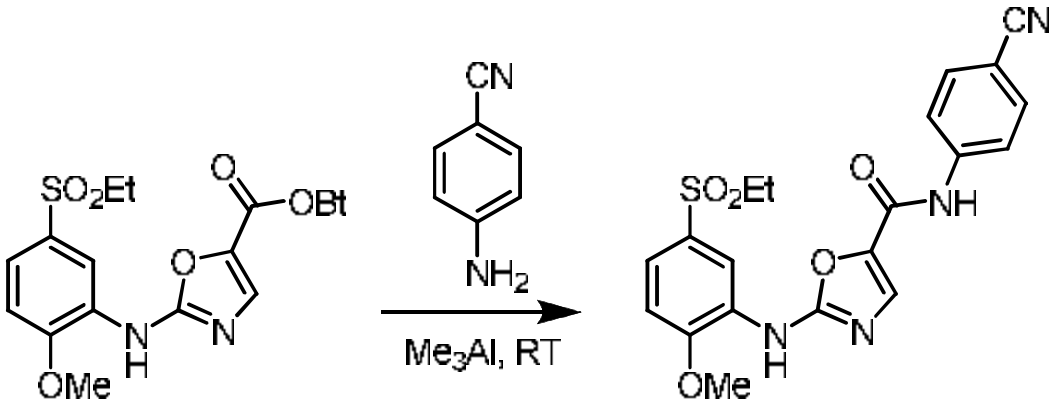
Synthesis:



Problem with anilines nucleophilicity



Only with higher temperatures and with low yield.

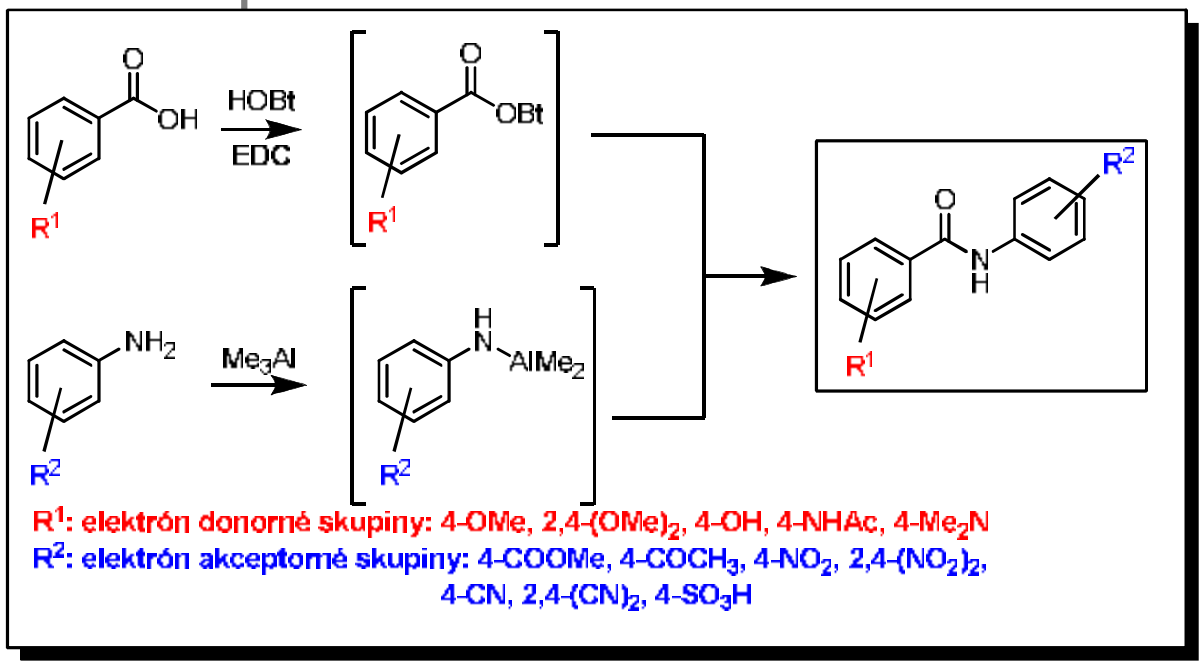


- activation of both reagents
- very quick reaction
- not described in literature

Project for a bachelor diploma work

Methodology for effective synthesis of amide VEGFR2 inhibitors from deactivated ArCOOH and deactivated $ArNH_2$

- Aims:
  - Verification of reaction versatitlity on chosen substrates.
  - One pot synthesis design.
  - Mechanism of activation suggestion.
  - Preparation of predicted VEGFR-2 inhibitors.



Proposed activation mechanism