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Arylalkylamine Derivatives as Myeloperoxidase Inhibitors, Synthesis and Pharmacological Activity

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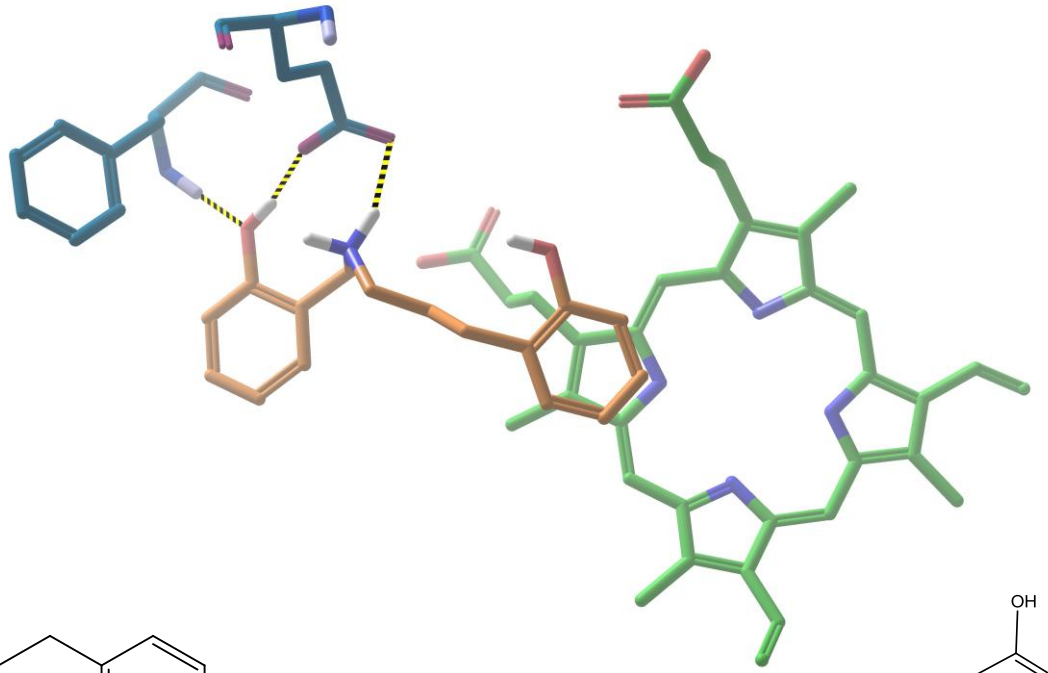
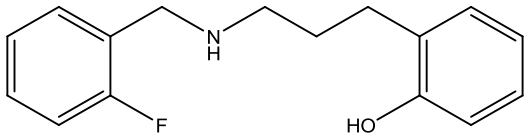
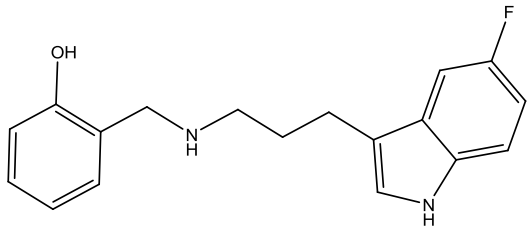
Arylalkylamine Derivatives as Myeloperoxidase Inhibitors, Synthesis and Pharmacological Activity

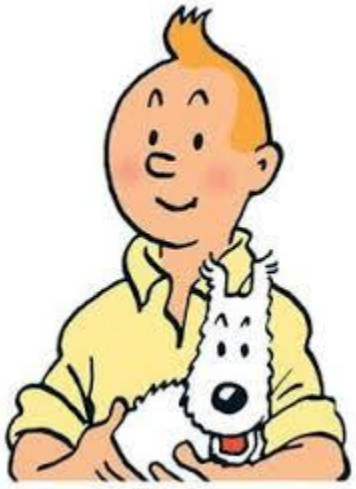




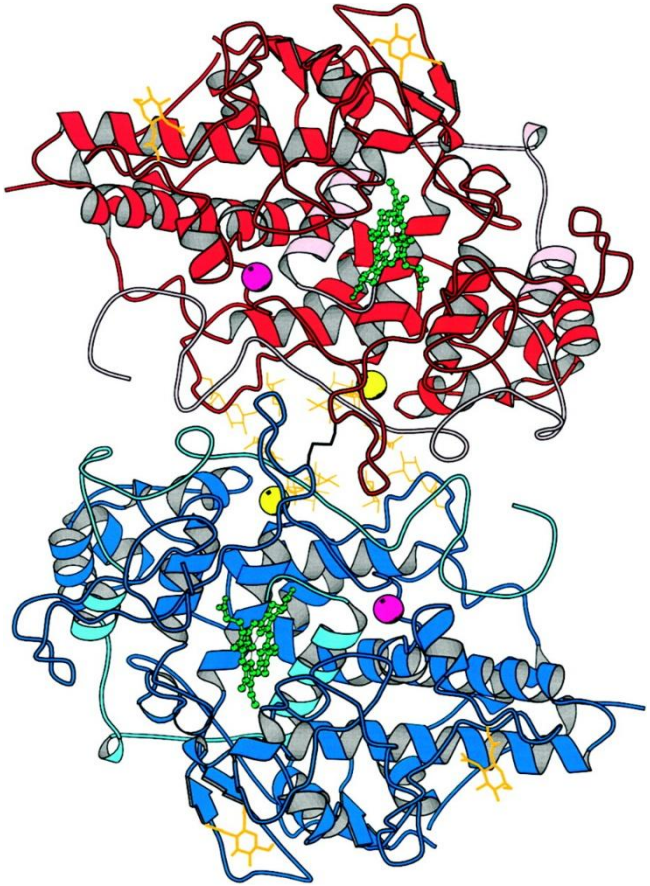


Abstract: Myeloperoxidase (MPO) is an important target for drug design because of its contributing role in many inflammatory syndromes such as atherosclerosis, rheumatoid arthritis, end-stage renal disease or neurodegeneration. Rational drug design assisted by virtual screening is an interesting tool to design new chemical entities that could inhibit MPO. After a high throughput virtual screening of a database, bis-2,2'-[(dihydro-1,3(2H,4H)-pyrimidinediyl)bis(methylene)]phenol was chosen as a starting hit and we used different strategies of chemical synthesis to perform pharmacomodulation described by the three approaches. This led to 36 compounds that have been assessed in an in vitro inhibition MPO test. We found that the arylalkylamine compounds were active but to a lesser extent than the starting hit. Exception for propylamine derivatives with a phenyl cycle should be noticed. As indolic compounds have demonstrated interesting inhibiting properties, we combined indole ring with the phenolhydropyrimidine structure which led to compounds more active than the hit. Among them, propylamine derivatives were new MPO inhibitors with a nanomolar IC_{50}. Kinetics studies for the most potent inhibitors were conducted and reflected a fast reaction with compound I resulting in the accumulation of compound II Structure-activity.
Keywords: Myeloperoxidase; Inhibitors; Arylalkylamine

Introduction



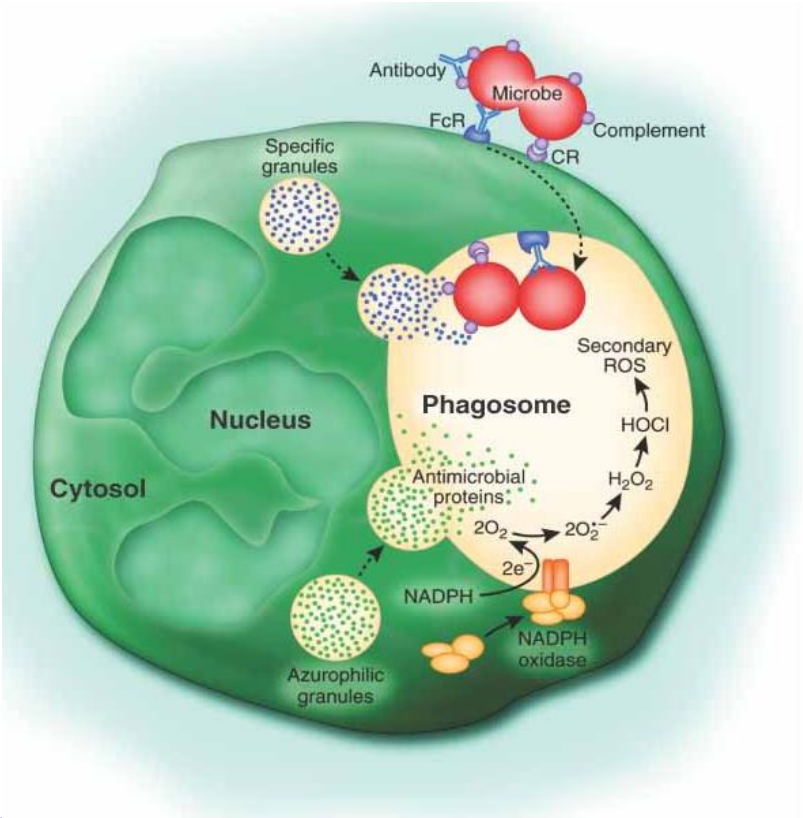
MPO



Introduction

- Neutrophils, monocytes, immune defense system
- Phagocytosis
- Kills microorganisms
- Produces HOCl

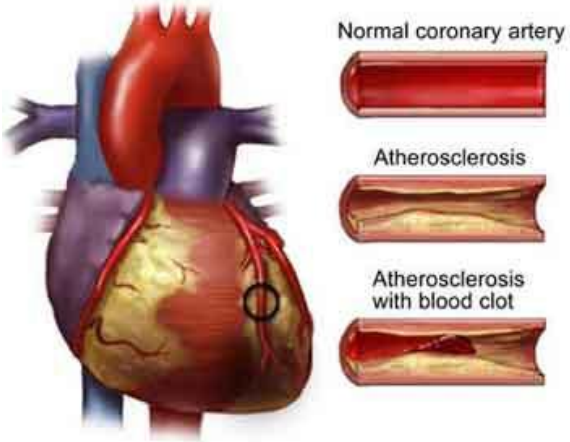
Myeloperoxidase MPO



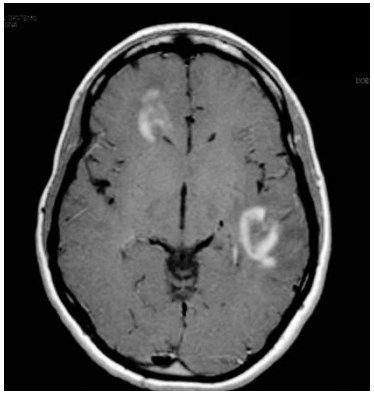
Introduction

MPO is a contributing factor in many inflammatory syndromes such as:

- Atherogenic lesions
- Rheumatoid arthritis
- End-stage renal disease
- Neurodegeneration

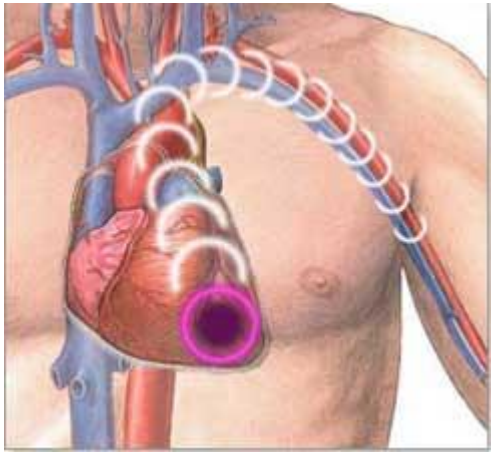


Atherosclerosis



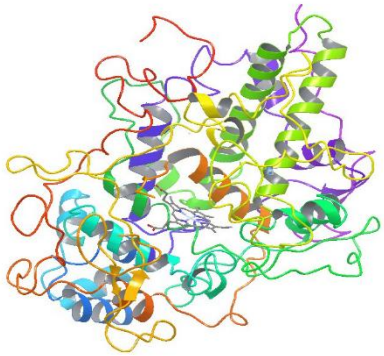
Multiple sclerosis

Parkinson



CVD

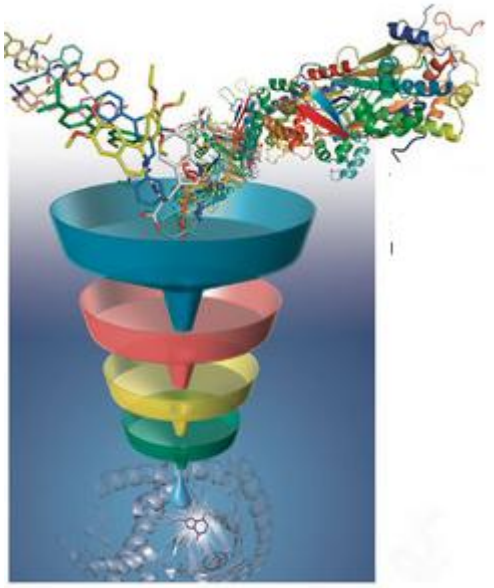
Finding New MPO inhibitors



MPO

ASINEX

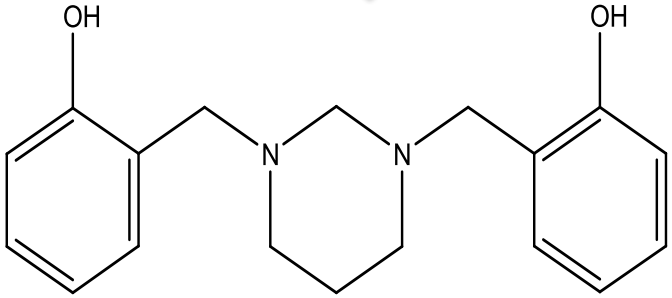
Pharmaceutical Database



HTVS

8 HITS of MPO inhibitors

Selected Hit for pharmacomodulaltion



A1

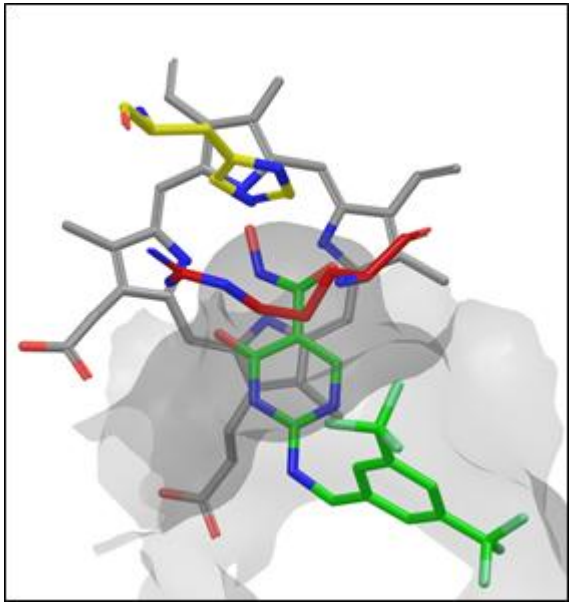
IC_{50} = 0.5 µM

Results and discussion

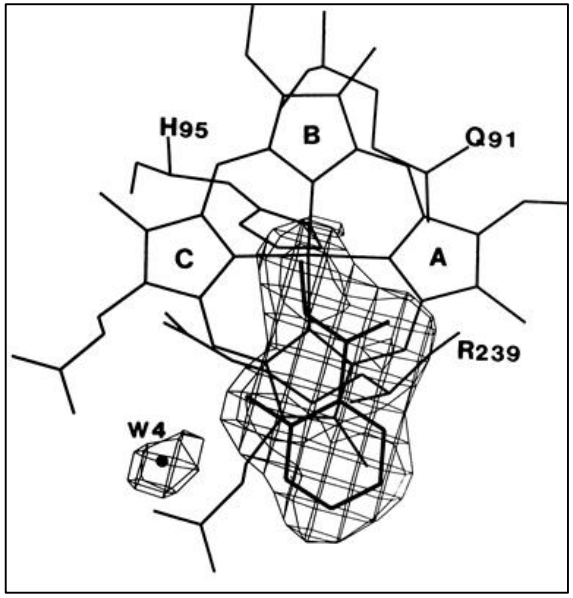
Pharmacomodulation and docking

Docking

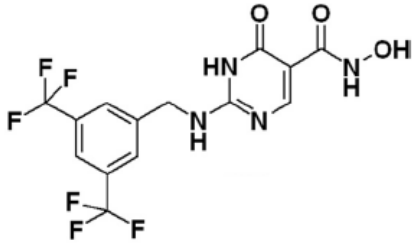
Validation of docking using poses in HX1, SHA X-ray data

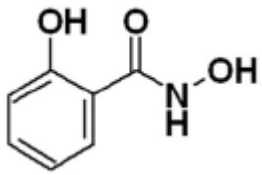


HX1 IN PDB 4C1M



SHA in PDB 1DNW





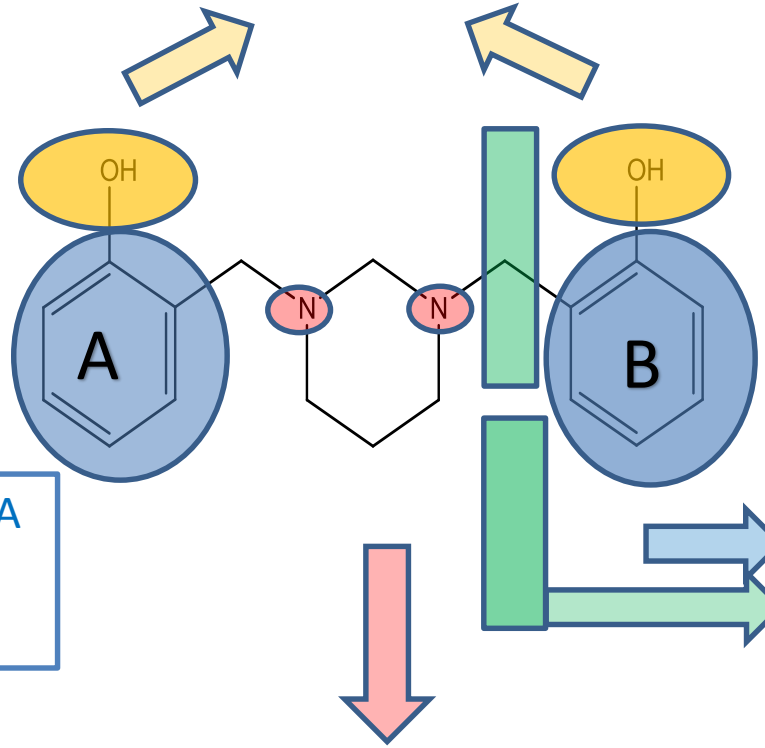
Pharmacomodulation and docking

All compounds were desigend and docked in MPO receptors 1DNW -4C1M

Best poses of the docked compounds were compared with X-Ray data of the known inhibitors HX1 and SHA
And redocked in same receptors

Pharmacomodulation

The role of hydroxyl groups on both aromatic cycles A and B

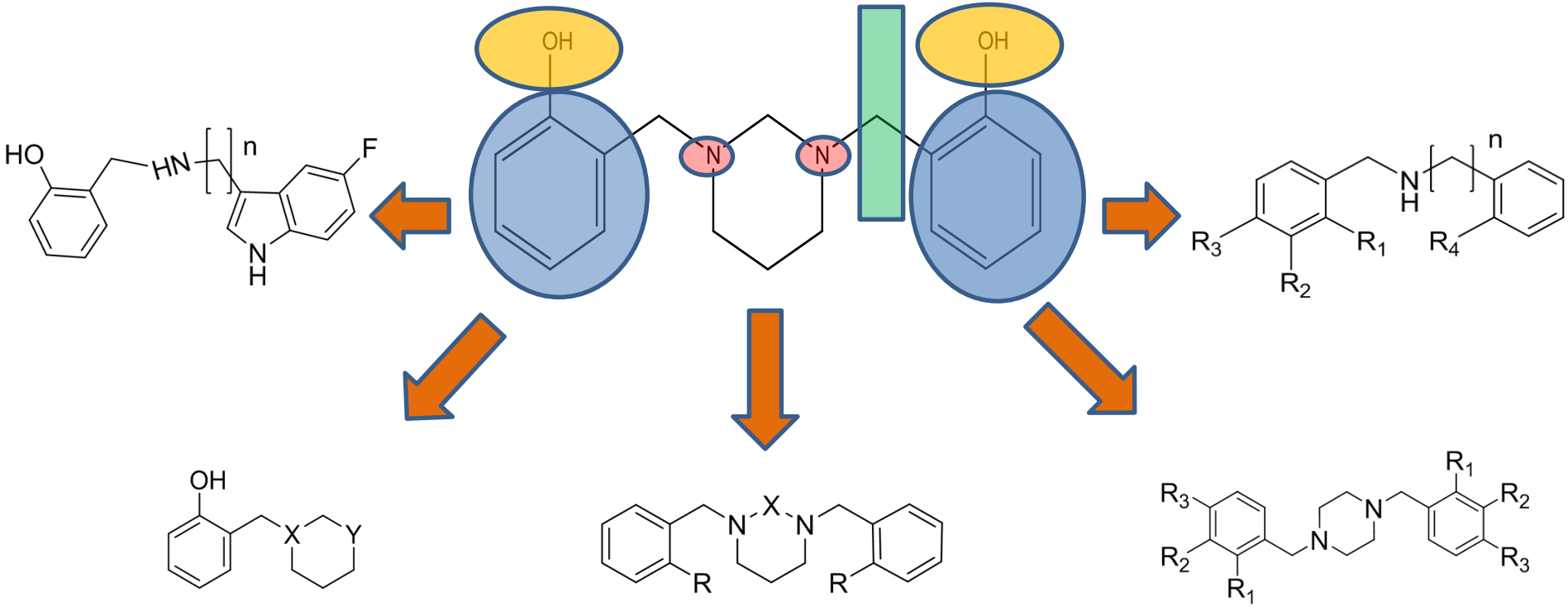


The role of aromatic cycle A and one atom of nitrogen.

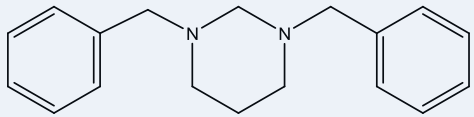
The role of bridge length between one nitrogen atom and cycle B after removing the hexadrodroperimidine cycle and different substitution on both cycles A and B.

The role of the position of the two nitrogen atoms

Pharmacomodulation



Designed compounds



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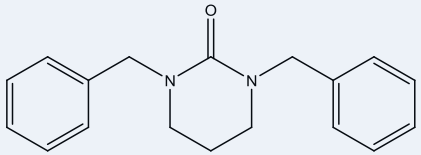

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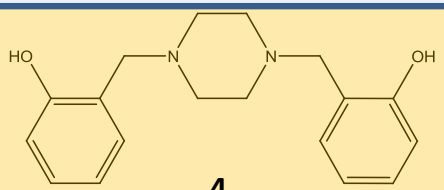

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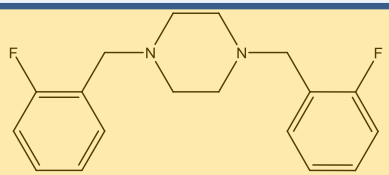

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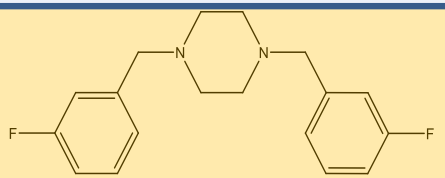

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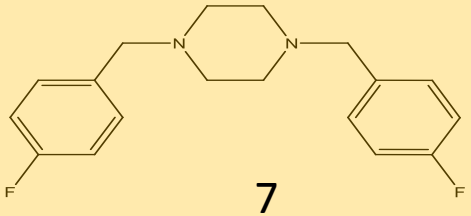

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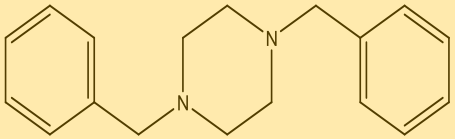

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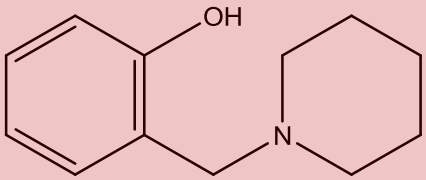

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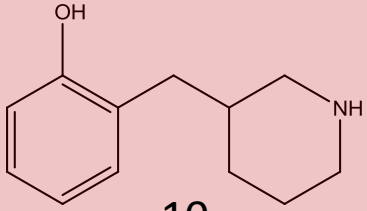
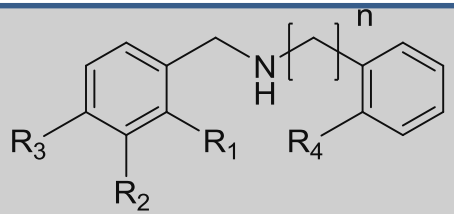
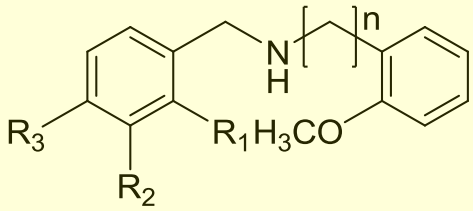


10

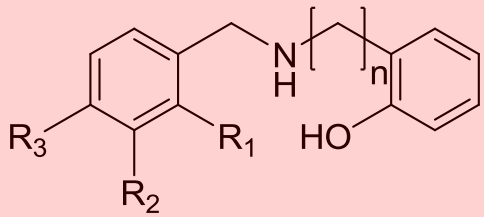
Designed compounds



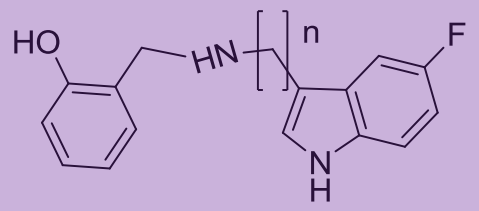
R_1=OH, R_2= R_3= R_4= H	n= 2	**11**
R_1=OH, R_2= R_3= R_4= H	n= 3	**12**
R_1=R_2= R_3=R_4=H	n= 2	**13**
R_1=R_2= R_3=R_4=H	n= 3	**14**
R_1=OH, R_2= R_3=H, R_4= F	n= 2	**15**
R_1=OH, R_2= R_3=H, R_4= F	n= 3	**16**



R_1=OH, R_2= R_3= H,	n= 2	**17**
R_1=OH, R_2= R_3= H,	n= 3	**19**
R_1= R_2= R_3=H,	n= 2	**21**
R_1= R_2= R_3=H,	n= 3	**23**
R_1=F, R_2= R_3=H	n= 2	**25**
R_1=F, R_2= R_3=H	n= 3	**27**
R_1=R_2= H, R_3=F	n= 2	**29**
R_1=R_2= H, R_3=F	n= 3	**31**
R_1=H, R_2=F, R_3=H	n= 2	**33**
R_1=H, R_2=F, R_3=H	n= 3	**35**

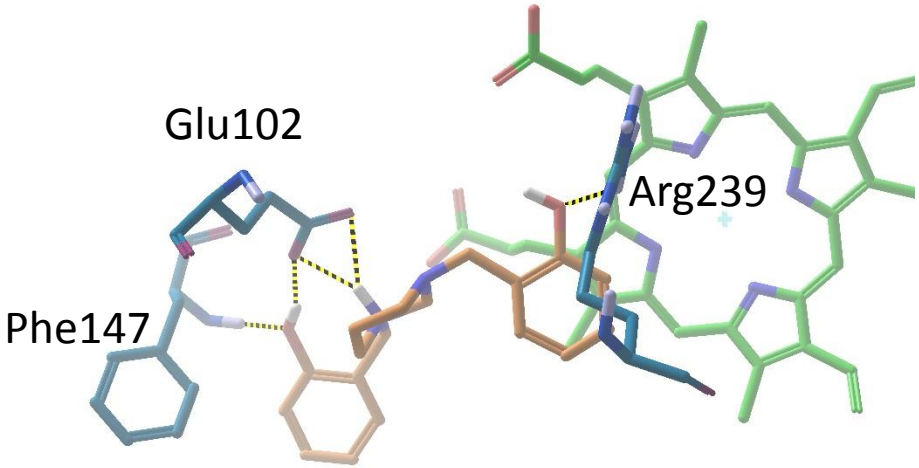


R_1=OH, R_2= R_3= H,	n= 2	**18**
R_1=OH, R_2= R_3= H,	n= 3	**20**
R_1= R_2= R_3=H,	n= 2	**22**
R_1= R_2= R_3=H,	n= 3	**24**
R_1=F, R_2= R_3=H	n= 2	**26**
R_1=F, R_2= R_3=H	n= 3	**28**
R_1=R_2= H, R_3=F	n= 2	**30**
R_1=R_2= H, R_3=F	n= 3	**32**
R_1=H, R_2=F, R_3=H	n= 2	**34**
R_1=H, R_2=F, R_3=H	n= 3	**36**

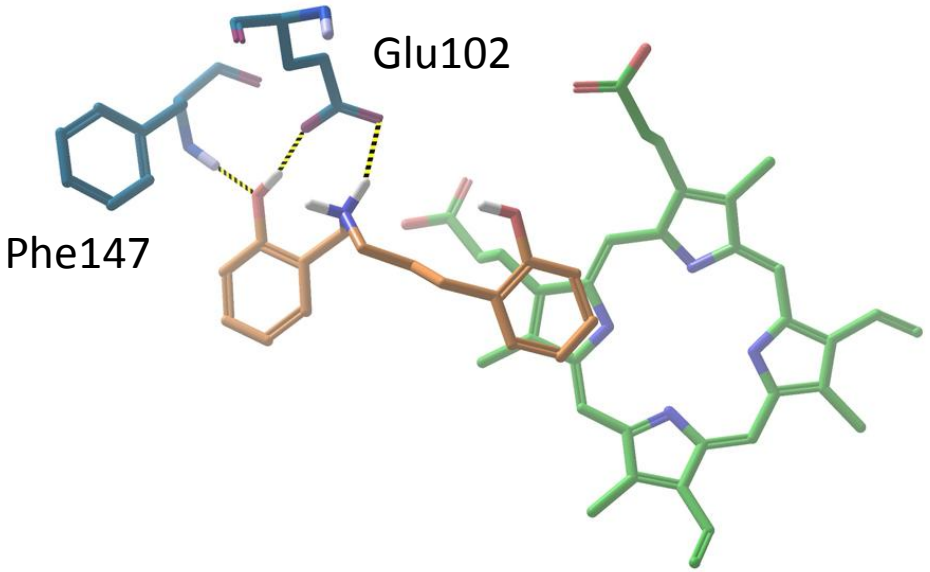


n=2 **37**
n=3 **38**

Some docked poses of the designed compounds in MPO Receptor



Compound 4 Shows hydrogen bonds with Glu102 and Phe147 Arg239 and salt bridge with Glu102

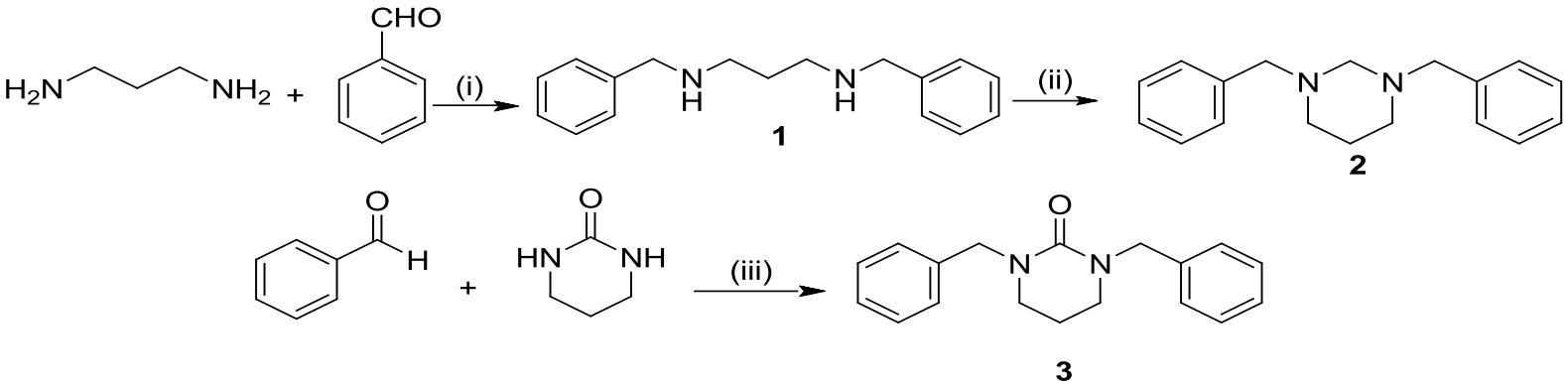


Compound 20 Shows hydrogen bonds with Glu102 and Phe147 and salt bridge with Glu102

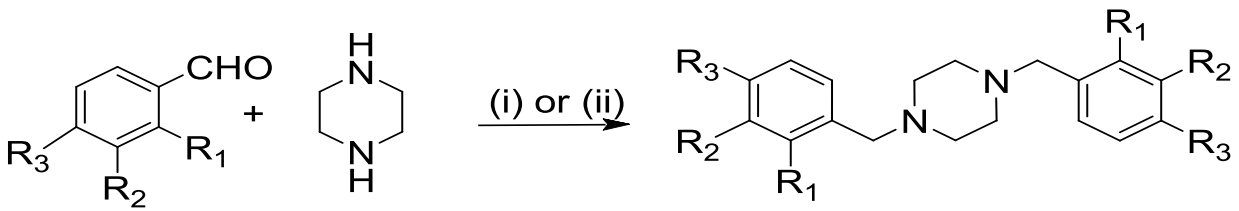
Docking results gave some similar interactions as with HX1 and SHA A1 and different free Energy levels -ΔG or affinities with MPO receptors

Chemistry

Chemistry



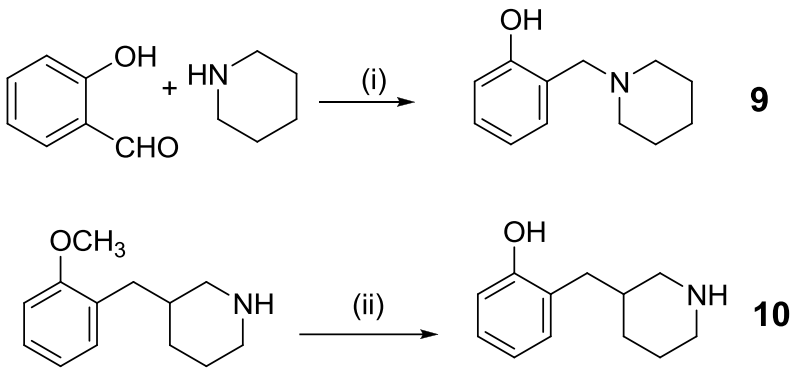
Reagents and conditions
(i) $NaBH_4$, EtOH
(ii)formaldehyde (37 wt % aqueous solution),EtOH
(iii) BnCl, NaH, DMF, Reflux



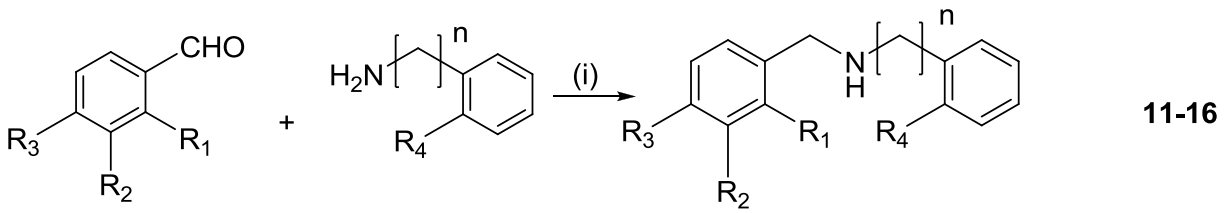
Reagents and conditions:
(i) $NaBH_4$, acetic acid,EtOH for **4**
(ii) $NaBH_3CN$, acetic acid,EtOH for **5-8**

R_1=OH; R_2=R_3=H;	**4**
R_1=F; R_2=R_3=H	**5**
R_2=F; R_1=R_3=H	**6**
R_3=F; R_1=R_3=H	**7**
R_1=R_2=R_3= H	**8**

Chemistry



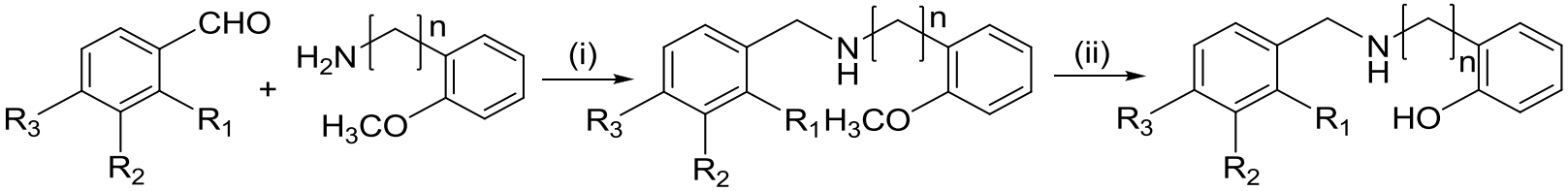
Reagents and conditions: (i) $NaBH_3CN$, acetic acid,EtOH (ii) $BBr_{3,}DCM$



11-16

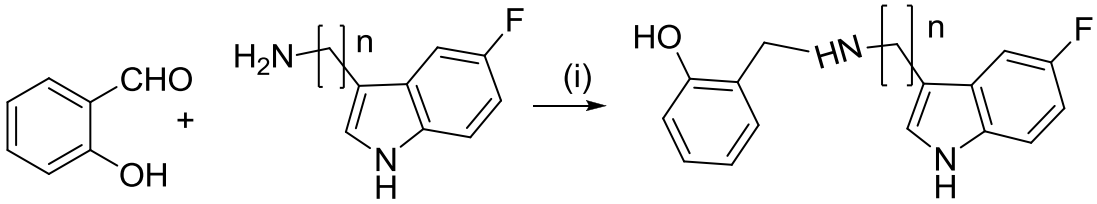
Reagents and conditions: (i) NaBH4, MeOH

Chemistry



Reagents and conditions: (i) NaBH4, MeOH
(ii) BBr3, DCM

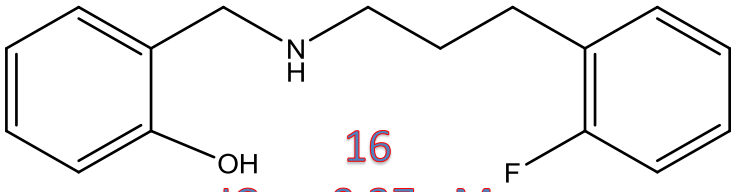
17- 36



Reagents and conditions: (i) NaBH4, MeOH

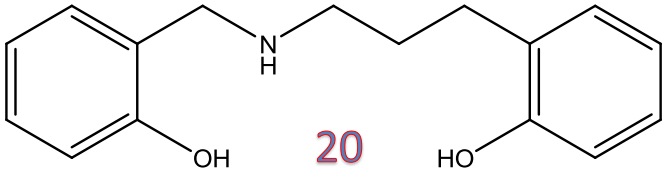
37-38

MPO inhibition assay
Best synthesized compounds with its IC50



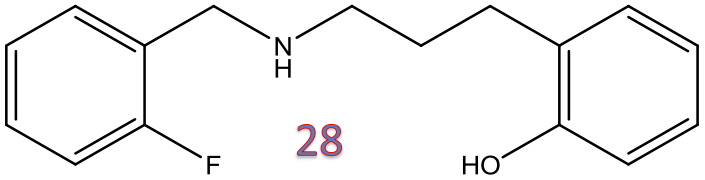
16

IC_{50}= 0.37 µM



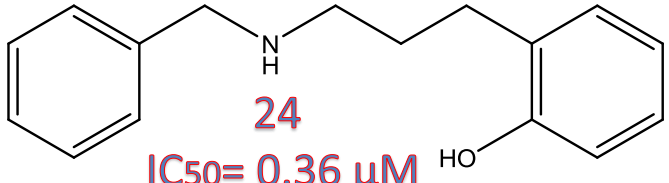
20

IC_{50}= 0.37 µM



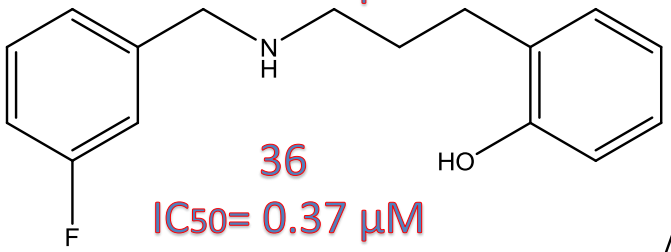
28

IC_{50}= 0.27 µM



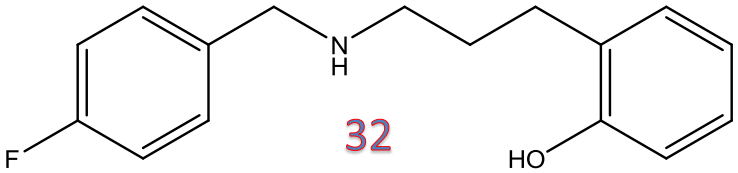
24

IC_{50}= 0.36 µM



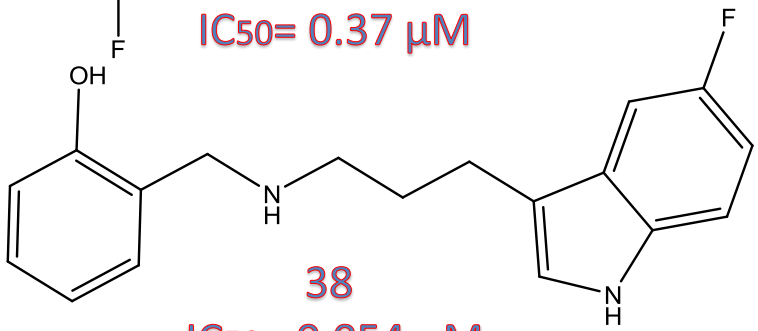
36

IC_{50}= 0.37 µM



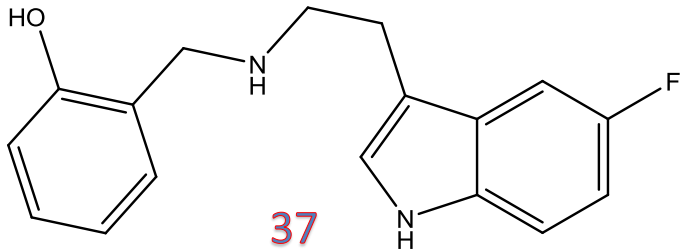
32

IC_{50}= 0.49 µM



38

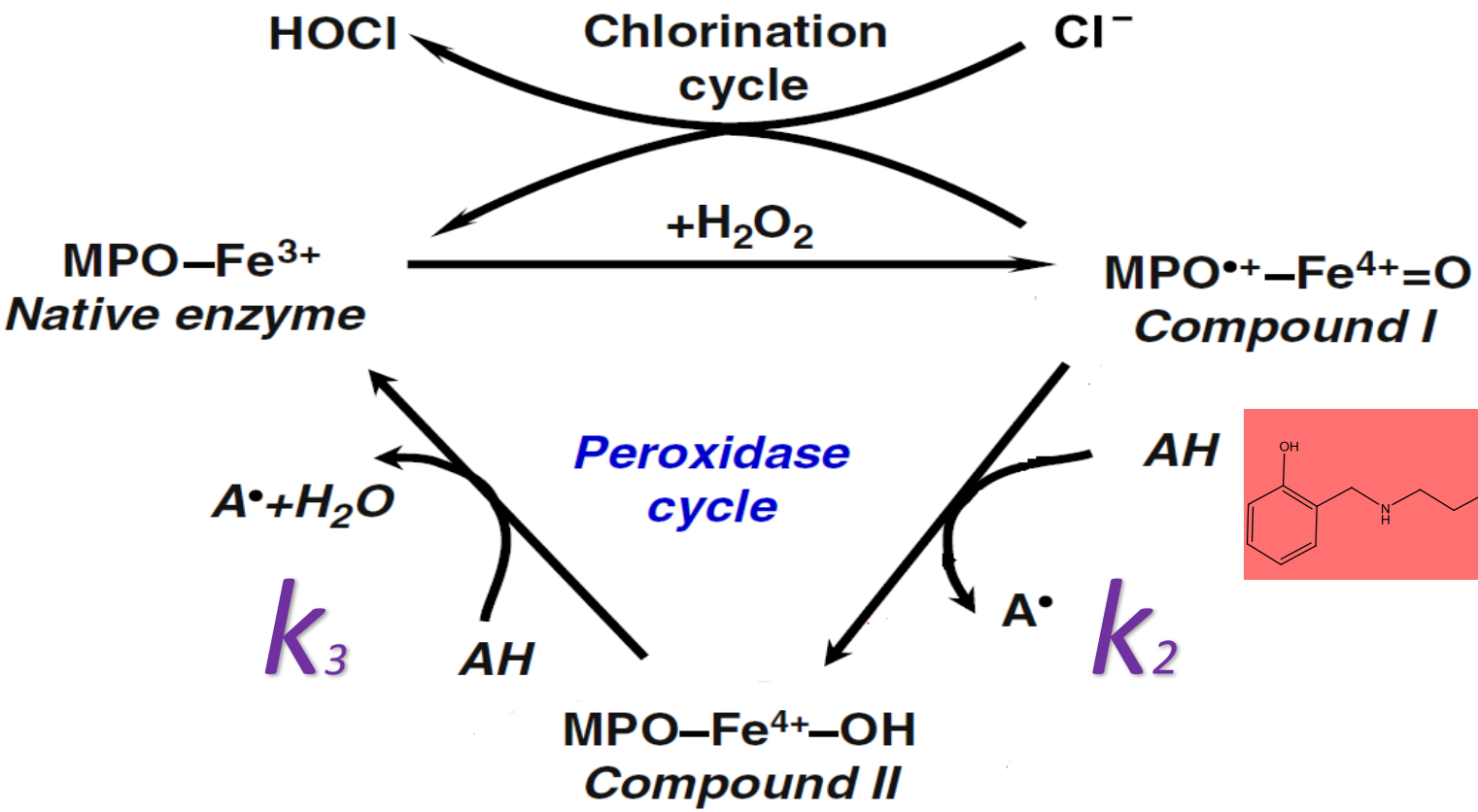
IC_{50}= 0.054 µM



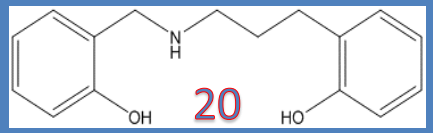
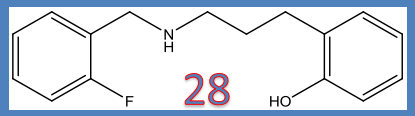
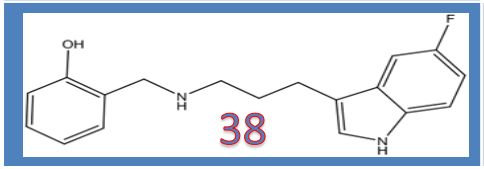
37

IC_{50}= 0.058 µM

Transient-State Kinetics

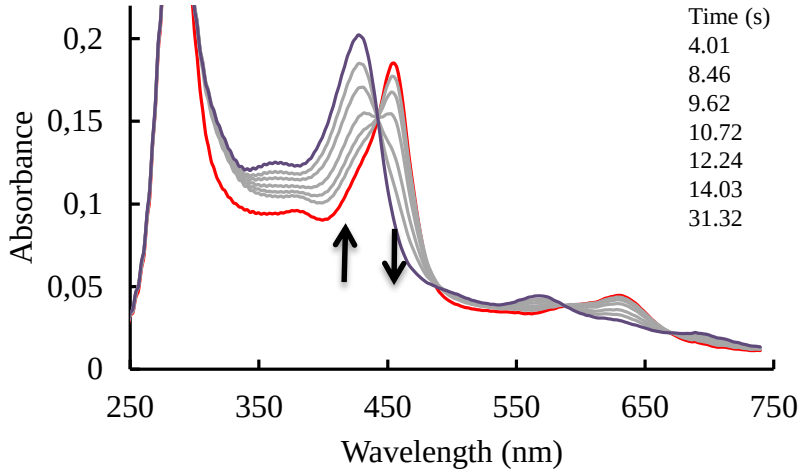


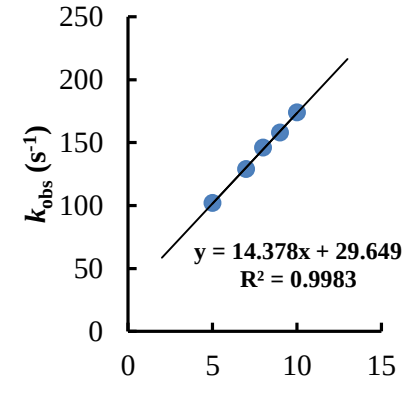
Mechanism of action
Transient-State Kinetics

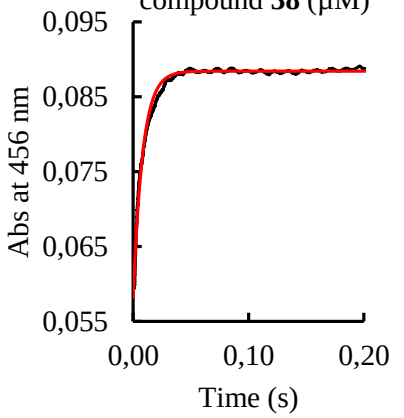
Compound	Compound I reduction rate constant ($M^{-1}s^{-1}$)	Compound II reduction rate constant ($M^{-1}s^{-1}$)	Ratio of compound I rate to compound II rate
 20	1.5×10^6	4.8×10^3	313
 28	5.7×10^6	1.4×10^3	4071
 38	1.4×10^7	3.5×10^3	4000

Mechanism of action
Transient-State Kinetics

The kinetic rate constant of reaction of the three best compounds with MPO/compound I /compound II have been measured.





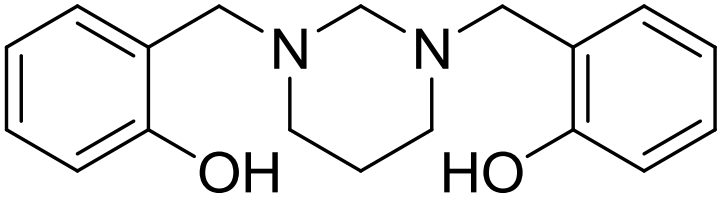


The reaction from compound I to compound II is too fast but the reaction with compound II is slow leading to the accumulation of compound II

Conclusion

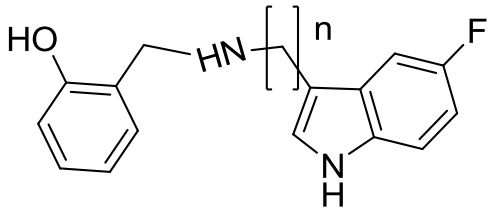
Conclusion

Pharmacomodulation



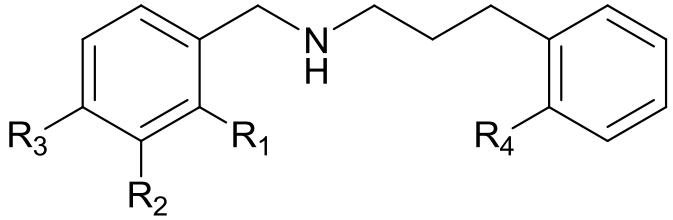
A1-IC_{50} 0.5 µM

MPO
IC_{50}



n=2 **37**
n=3 **38**

with IC_{50} 0.3-0.05 µM .
More active to 2-10 times than the A1

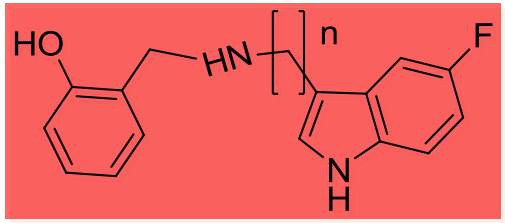


R_1=OH, R_2= R_3=H, R_4= F	**16**
R_1=OH, R_2= R_3=H, R_4= OH	**20**
R_1=R_2= R_3=H, R_4= OH	**24**
R_1=F, R_2= R_3=H, R_4= OH	**28**
R_1=R_2= H, R_3=F R_4= OH	**32**
R_1=H, R_2=F, R_3=H R_4= OH	**36**

Conclusion

***best compounds have shown high reduction rate constants of compound I and II and their ratio can explain the accumulation of compound II, illustrating a reversible mechanism of inhibition..**

***Arylpropylamine derivatives and adding the indole structure to the original scaffold A1 have given us new effective MPO inhibitors**



IC_{50} = 0.3-0.05 µM

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