SUPPORTING INFORMATION

Design, synthesis and biological evaluation of renin inhibitors guided by simulated annealing of chemical potential simulations

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List of fragments used in the simulated annealing of chemical potential*:

Neutral fragments
acetamide
N,*N*-dimethylacetamide
N-methylacetamide, *anti* configuration
N-methylacetamide, *syn* configuration
acetone
propan-2-one O-methyl oxime
acetonitrile
acetophenone
aniline
N-methylaniline
N,*N*-dimethylaniline
anisole
2-chloroanisole
1-methyl-3,4-dihydro-1H-azepin-2(7*H*)-one
N-methylbenzamide
benzene
1,2-dichlorobenzene
1,3-dichlorobenzene
1,3-difluorobenzene
1-chloro-2-methylbenzene
(trifluoromethyl)benzene
chlorobenzene
fluorobenzene
(trifluoromethoxy)benzene
1H-benzo[*d*]imidazole
2-methyl-1*H*-benzo[*d*]imidazole
1*H*-benzo[*d*]imidazol-2-amine
1-methyl-1*H*-benzo[*d*]imidazole
benzo[*d*]isoxazole
benzo[*d*][1,3]dioxole
benzofuran
benzonitrile
benzo[*d*]thiazole
2-methylbenzo[*d*]thiazole
benzo[*d*]thiazol-2-amine
biphenyl
cyclohexane
cyclopentane
ethane
ethanol
ether
isobutane

imidazole
5-methyl-2-(methylthio)-1*H*-imidazole
1-methyl-1*H*-imidazole
2,3-dihydro-1*H*-indene
1*H*-indazole
1*H*-indazol-3-amine
1-methyl-1*H*-indazole
indole
1-(1*H*-indol-1-yl)ethanone
1-methyl-1*H*-indole
isoquinoline
isoxazole
3-methylisoxazole
mesitylene
methanesulfonamide
N,N-dimethylmethanesulfonamide
methanol
methyl acetate
1-morpholinoethanone
4-methylmorpholine
naphthalene
nitrobenzene
1,3,4-oxadiazole
1,2,4-oxadiazole
oxazole
phenol
phthalazine
1,4-dimethylpiperazin-2-one
1-methylpiperazin-2-one
4-methylpiperazin-2-one
piperazine
1-methylpiperidine
propane
9-methyl-9*H*-purine
(*R*)-2-methoxytetrahydro-2*H*-pyran
(*S*)-2-methoxytetrahydro-2*H*-pyran
pyrazine
1*H*-pyrazole
1,3,5-trimethyl-1*H*-pyrazole
1,3-dimethyl-1*H*-pyrazole
3,5-dimethyl-1*H*-pyrazole
1-methyl-1*H*-pyrazole
pyridine
pyridin-2-amine
1,4-dimethylpyridin-2(1*H*)-one
pyrimidine

2,4-dimethoxypyrimidine
2-methoxy-4-methylpyrimidine
pyrimidin-2-amine
4-methoxypyrimidin-2-amine
2-methoxypyrimidin-4-amine
pyrimidin-4-amine
pyrrolidin-2-one
1-methylpyrrolidin-2-one
quinazolin-2(1*H*)-one
quinazolin-2(3*H*)-one
quinazolin-4(1*H*)-one
1-methylquinazolin-4(1*H*)-one
3-methylquinazolin-4(3*H*)-one
quinazoline
3-methylquinolin-2(1*H*)-one
4-methylquinolin-2(1*H*)-one
quinolin-4(1*H*)-one
quinoline
tetrahydrofuran
tetrahydropyran
tetrahydrothiophene
thiazole
2-methylthiazole
thiazol-2-amine
methyl(phenyl)sulfane
dimethylsulfane
1-(1,1-dioxidothiomorpholino)ethanone
4-methylthiomorpholine 1,1-dioxide
thiophene
toluene
1*H*-1,2,4-triazole
4*H*-1,2,4-triazole
1,3-dimethylurea
water
m-xylene
o-xylene
p-xylene

Protonated fragments
4-acetyl-1,4-diazepan-1-ium
ethanaminium
2-amino-4,5-dimethyl-1H-imidazol-3-ium
2-amino-4-methyl-1*H*-imidazol-3-ium
methanaminium
4-methylmorpholin-4-ium
4-acetylpiperazin-1-ium

4-methylpiperazin-1-ium
1,4-dimethylpiperazin-1-ium
2-amino-4-methoxypyridin-1-ium
2,4-diamino-6-methoxypyridin-1-ium
2,4-diaminopyrimidin-1-ium
2,4-diamino-6-methoxypyrimidin-1-ium
2,6-diamino-4-methoxypyrimidin-1-ium
4,6-diamino-2-methylpyrimidin-1-ium
dimethylammonium

*Names were generated from the corresponding structures using the *Structure to Name* algorithm in ChemBioDraw Ultra, Version 12, from Perkin-Elmer Informatics (Waltham, MA).

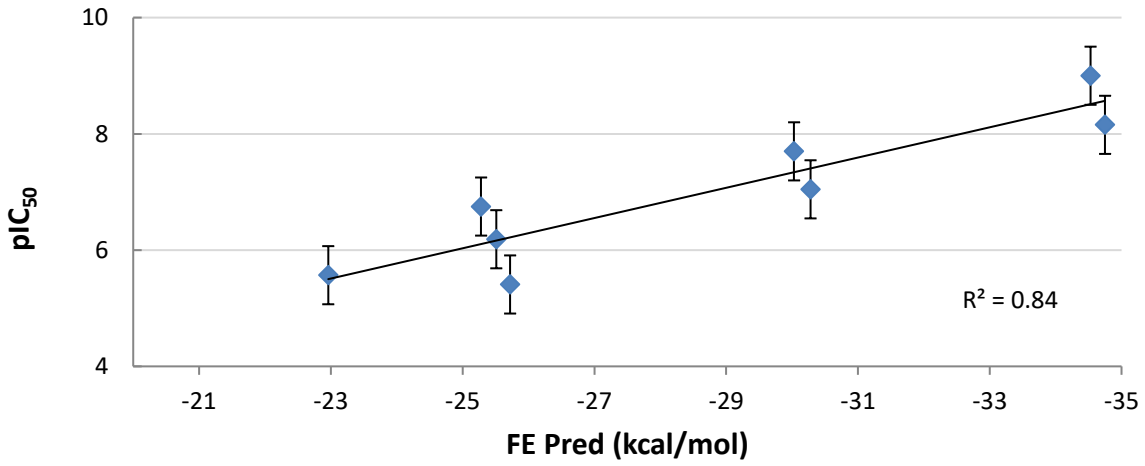

Figure A. Correlation plot of pIC_{50} versus predicted relative Free Energies for compounds **6a-d** and **7a-d** determined using Constrained Fragment Analysis in the 2G1Y crystal structure.

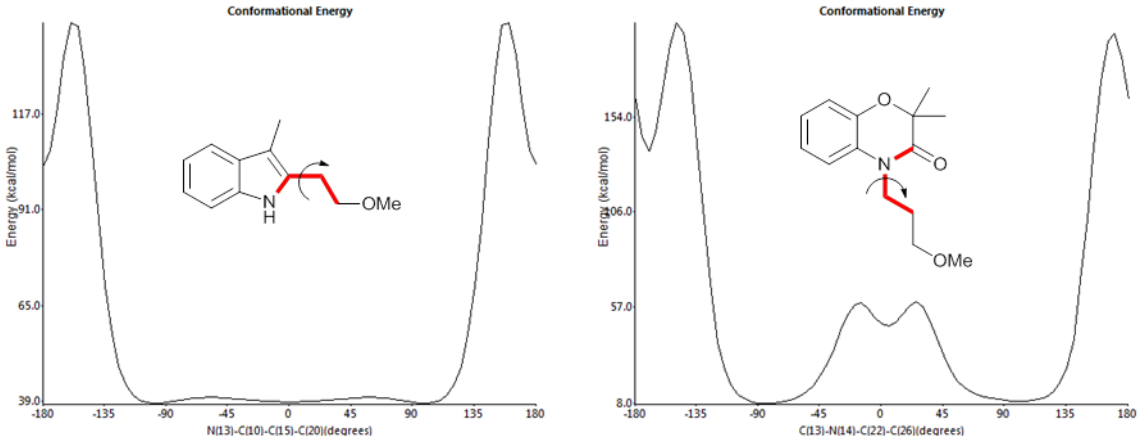

Figure B. Torsion angle energy analysis of a representative 2-alkylindole and representative *N*-alkylbenzoxazinone. Starting from a minimized conformation, the dihedral shown (red) for each compound was analyzed using the Dihedral Driver function in ChemBio 3D Ultra, Version 12, from Perkin-Elmer Informatics (Waltham, MA).