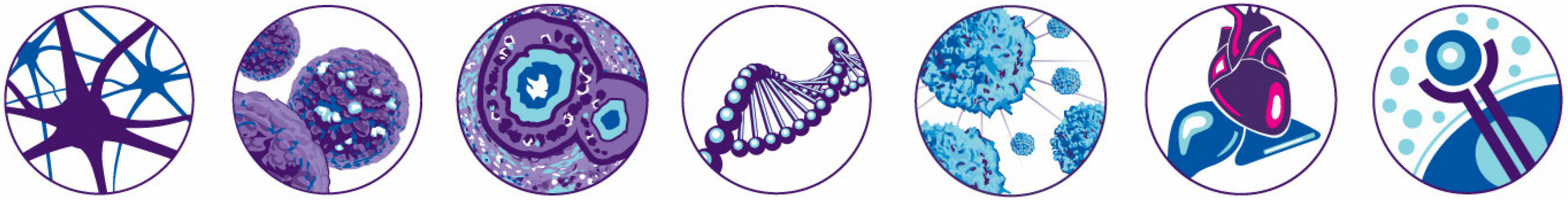


Potency Prediction:
What do a Practitioner Wish For?

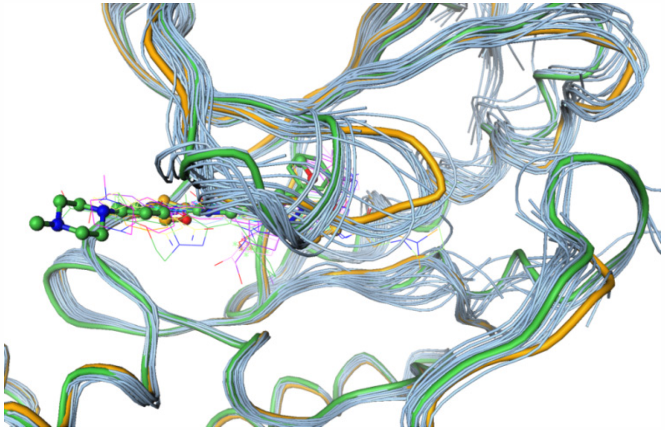
Xinjun Hou and Simone Sciabola

Neuroscience & Pain Medicinal Chemistry

Pfizer Worldwide Research and Development

Analyses of MAP4K4 Structures

- Flexible ATP site with a diverse conformations of multiple loops
  - p-loop "In" representative: MAP_01
  - p-Loop "Out" representative: MAP_20
- Reference: MAP_20 ligand
- Free/Constraint shells: 3.5Å/4Å, 5Å, 5+Å
- Ranking ordering
  - $\Delta\Delta G_{calc} = 0.3 * \Delta\Delta E_{calc}$



Structure	Binding Motif	p-Loop Tyr	E69 Helix	T181 Loop	Lys-54
MAP_01	EX	In	Out	Y	No HB
MAP_02	EX	Out-X	Out	X	No HB
MAP_03	A	In-X	X	X	No HB
MAP_04	EX	Out	In	X	E69-HB
MAP_05	EX	Out	In	X	No HB
MAP_06	A+	Out	In	X	E69-HB
…	…	…	…	…	…
MAP_20	A	Out	In	X	E69-HB
…	…	…	…	…	…

Pilot Study: MAP4K4 (4ZK5) and GNE-495 SAR

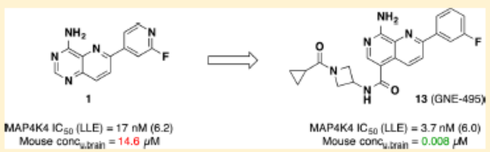
ACS Medicinal Chemistry Letters
Letter
pubs.acs.org/acsmedchemlett

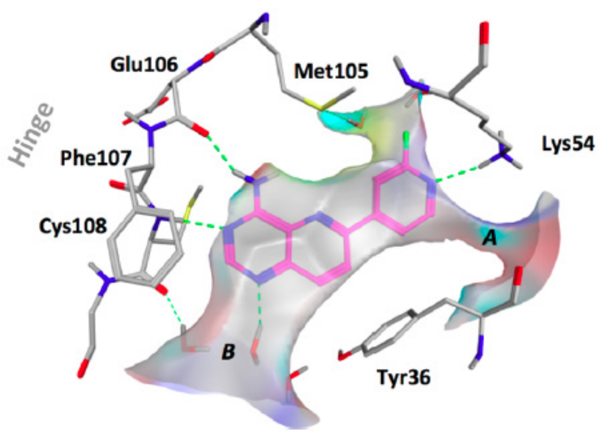
Structure-Based Design of GNE-495, a Potent and Selective MAP4K4 Inhibitor with Efficacy in Retinal Angiogenesis

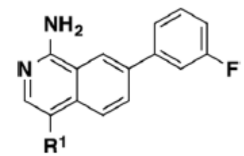
Chudi O. Ndubaku,*,† Terry D. Crawford,† Huifen Chen,† Jason W. Boggs,†,§ Joy Drobnick,† Seth F. Harris,† Rajiv Jesudason,† Erin McNamara,† Jim Nonomiya,† Amy Sambrone,† Stephen Schmidt,† Tanya Smyczek,† Philip Vitorino,†,∥ Lan Wang,† Ping Wu,† Stacey Yeung,† Jinhua Chen,‡ Kevin Chen,‡ Charles Z. Ding,‡ Tao Wang,‡ Zijin Xu,‡ Stephen E. Gould,† Lesley J. Murray,† and Weilan Ye†

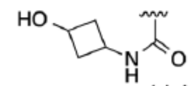
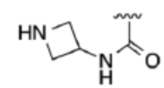
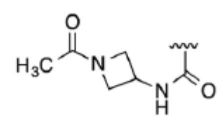
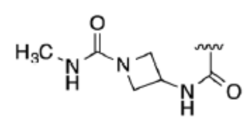
†Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States
‡Wuxi Apptec Co., Ltd., 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131, People's Republic of China

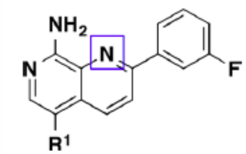
Supporting Information

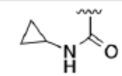
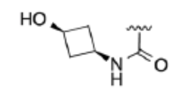
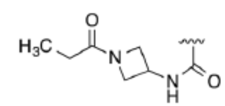
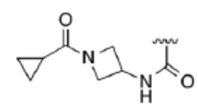
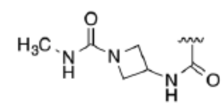






Compound	R^1	MAP4K4 IC_{50} (nM)
6	 (cis/trans)	41 ± 8.7
7		401 ± 12
8		32 ± 0.8
9		15 ± 0.5



Compound	R^1	MAP4K4 IC_{50} (nM)
10		1.4 ± 0.2
11		3.7 ± 0.7
12		3.5 ± 1.3
13 (GNE-495)		3.7 ± 1.4
14		1.6 ± 0.1

GNE-495 SAR

Sum of Interaction and deSolvation Energy

van der Waals Interactions

Desolvation

Ligand & Protein Conformational Strain Energy

Electrostatic Interactions

Total Binding Energy

Cpd	IC50	dGexp	ES	VdW	dGB	dSA	ISE	Lig Strain	Pro Strain	dE	RMS_L0	RMS_L1	RMS_P0
4ZK5_cpd06	41	-10.1	-15.5	-36.3	26.5	-5.1	-30.4	1.8	2.60	-26.0	0.62	0.48	0.24
4ZK5_cpd08	32	-10.2	-24.5	-35.1	33.5	-5.1	-31.2	3.6	4.80	-22.7	0.59	0.82	0.33
4ZK5_cpd09	15	-10.7	-28.4	-40.8	38.3	-5.5	-36.4	2.7	3.00	-30.7	0.63	1.06	0.24
4ZK5_cpd11	3.7	-11.5	-23.6	-35.8	31.7	-5	-32.6	3.8	2.50	-26.4	0.98	0.42	0.35
4ZK5_cpd12	3.5	-11.5	-31.2	-37.9	39.5	-5.5	-35.1	4.6	4.80	-25.7	0.59	1.01	0.31
4ZK5_cpd13	3.7	-11.5	-19.3	-39.9	30.6	-5.6	-34.3	1.6	2.60	-30.1	0.70	0.73	0.24
4ZK5_cpd14	1.6	-12.0	-40.8	-38.3	47.1	-5.4	-37.4	4.3	5.10	-27.9	0.53	1.24	0.26

Structure Integrity

$$\Delta G\,(aq) \approx ES + VdW + \Delta G_{solv} + \Delta E^{L}_{Strain}(aq) + \Delta E^{P}_{Strain}(aq)$$

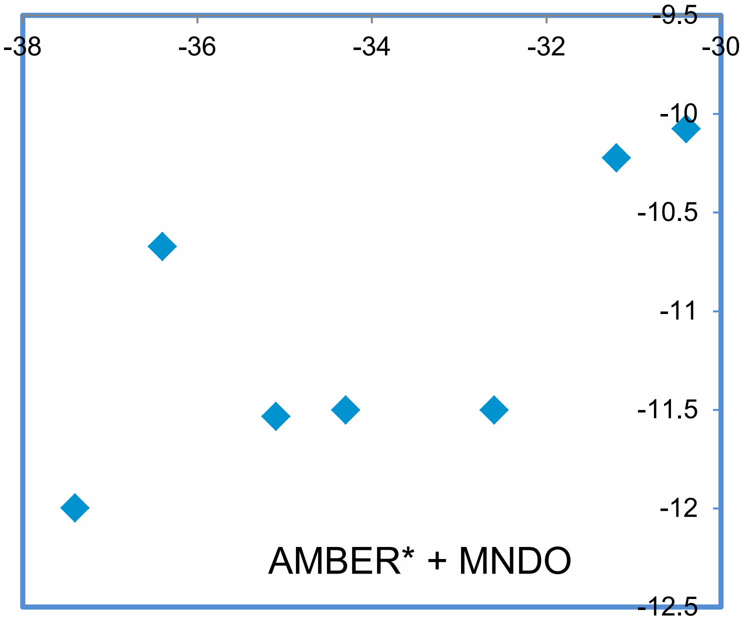
Xinjun Hou, Ben Burke , Bob Kumpf, Tom Hendrickson, Steve Bender, Bob Babine

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT
Medicinal Chemistry

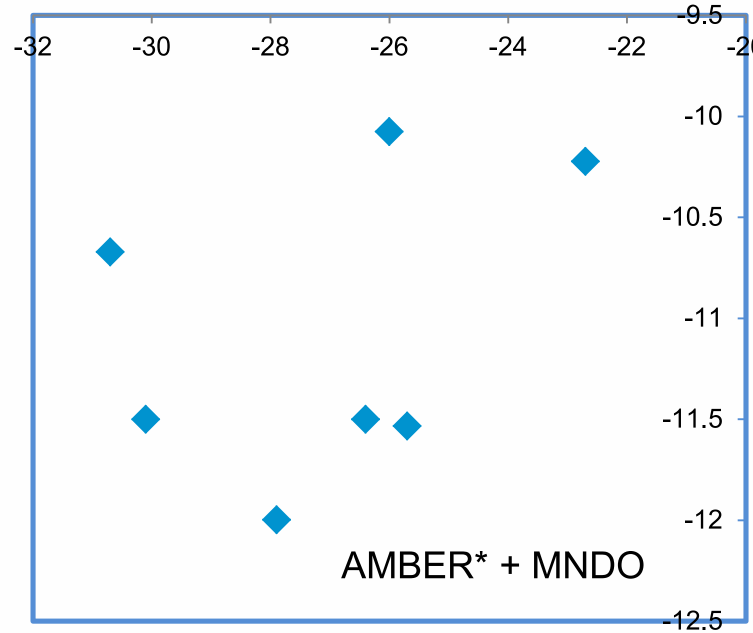
GNE-495 SAR: ligand and protein strains energy terms introduce more “noise”?

$$\Delta E \approx ES + VdW + \Delta G_{solv} + \Delta E^{L}_{Strain}(aq) + \Delta E^{P}_{Strain}(aq)$$

Use ISE Term



Use ΔE Term



PLIERS with MAP_01 & MAP_20

- AMBER* + MNDO
- OPLS2

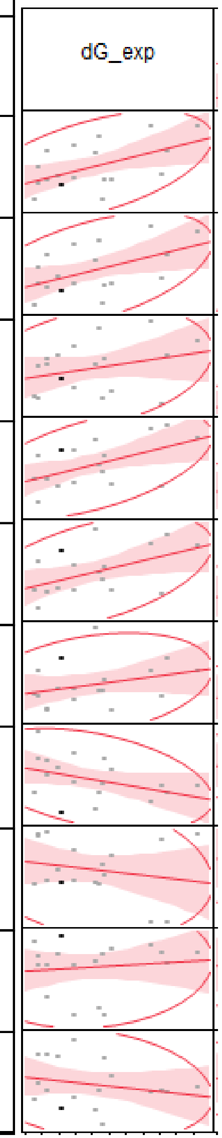
Multiple calculations with a similar workflow

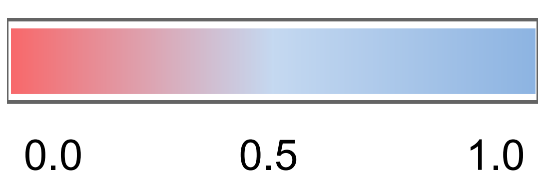
Energy Term	Name	Parameters	Proteins
ES + VdW + dSolv	ISE	OPLS2	MAP_01 & MAP_20
ES + VdW + dSolv	ISE	OPLS3	MAP_01 & MAP_20
ES + VdW + dSolv	ISE	AMBER*+MNDO	MAP_01 & MAP_20
ES + VdW + dSolv	ISE	OPLS2	Individual
ES + VdW + dSolv + Lig Strain	dE1	OPLS2	Individual
ES + VdW + dSolv + Lig Strain + Pro Strain	dE	OPLS2	Individual

- Proteins
  - MAP_01 for “in” & MAP_20 for “out” ligands
  - Or ligand’s own protein
- Use MAP_20 ligand as reference point (0.0)
- Free and constraint shells: 3.5Å, 4Å, 5Å, 5+Å
- Ranking ordering with
  - $\Delta\Delta G_{calc} = 0.3 * \Delta\Delta E_{calc}$

Pearson R, (Molecule 1 to 19)

Energy Terms	Parameters	Full Set, N = 18	
		R	p-value (Prob > F)
ES + VdW + dSolv	OPLS2	0.533	0.023
ES + VdW + dSolv	OPLS3	0.509	0.031
ES + VdW + dSolv	AMBER*+MNDO	0.297	0.233
ES + VdW + dSolv	OPLS2/Individual Complex	0.541	0.020
ES + VdW + dSolv + Lig Strain	OPLS2/Individual Complex	0.498	0.035
ES + VdW + dSolv + Lig Strain + Pro Strain	OPLS2/Individual Complex	0.307	0.216
	ClogP	0.399	0.101
	MW	0.205	0.414
	TPSA	0.118	0.646
	ClogD	0.230	0.358





Pearson R: P-Loop “in” and “out” groups

Energyy Term	Parameters	Full Set, N = 18		p-Loop IN, n = 12		p-loop OUT, n = 6	
		R	p-value (Prob > F)	R	p-value (Prob > F)	R	p-value (Prob > F)
ES + VdW + dSolv	OPLS2	0.533	0.023	0.453	0.140	0.795	0.059
ES + VdW + dSolv	OPLS3	0.509	0.031	0.427	0.167	0.787	0.063
ES + VdW + dSolv	AMBER*+MNDO	0.297	0.233	0.063	0.834	0.647	0.166
ES + VdW + dSolv	OPLS2/Individual Complex	0.541	0.020	0.341	0.279	0.840	0.036
ES + VdW + dSolv + Lig Strain	OPLS2/Individual Complex	0.498	0.035	0.311	0.325	0.901	0.014
ES + VdW + dSolv + Lig Strain + Pro Strain	OPLS2/Individual Complex	0.307	0.216	0.176	0.587	0.877	0.022
	ClogP	0.399	0.101	0.346	0.285	0.628	0.177
	MW	0.205	0.414	0.290	0.362	0.024	0.883
	TPSA	0.118	0.646	0.032	0.923	0.277	0.593
	ClogD	0.230	0.358	0.235	0.463	0.270	0.633

Spearman's ρ

Energy	Parameters	Full Set, N = 18		p-Loop IN, n = 12		p-loop OUT, n = 6	
		Rho	p-value (Prob > F)	Rho	p-value (Prob > F)	Rho	p-value (Prob > F)
ES + VdW + dSolv	OPLS2	0.426	0.078	0.417	0.178	0.943	0.005
ES + VdW + dSolv	OPLS3	0.399	0.101	0.364	0.245	0.886	0.019
ES + VdW + dSolv	AMBER*+MNDO	0.283	0.255	0.133	0.681	0.829	0.042
ES + VdW + dSolv	OPLS2/Individual Complex	0.408	0.093	0.126	0.687	0.829	0.042
ES + VdW + dSolv + Lig Strain	OPLS2/Individual Complex	0.399	0.101	0.161	0.618	0.886	0.019
ES + VdW + dSolv + Lig Strain + Pro Strain	OPLS2/Individual Complex	0.253	0.311	0.091	0.779	0.714	0.074
Molecular Property	ClogP	-0.356	0.101	-0.218	0.497	-0.771	0.072
Molecular Property	MW	-0.172	0.494	-0.140	0.665	-0.428	0.397
Molecular Property	TPSA	0.148	0.556	-0.053	0.871	-0.257	0.623
Molecular Property	ClogD	-0.172	0.493	-0.137	0.672	-0.058	0.913

P-value questionable (n=6)

Potency prediction – still hopeful?

Aspirational goals for a practitioner:

1. To know the scope of applicability of a method
2. Rank order compounds without training set
3. Method is robust to deal with diverse chemotypes
   - Core/scaffold hopping and ring size changing
   - High quality force field parameter and solvation model
4. **<u>Interpretable to provide a new hypotheses to guide design</u>**
5. Able to work with flexible binding sites
6. Calculation turn around time
7. Inform a user when a calculation result is not reliable