Structure-Based Drug Discovery in Shanghai Hengrui

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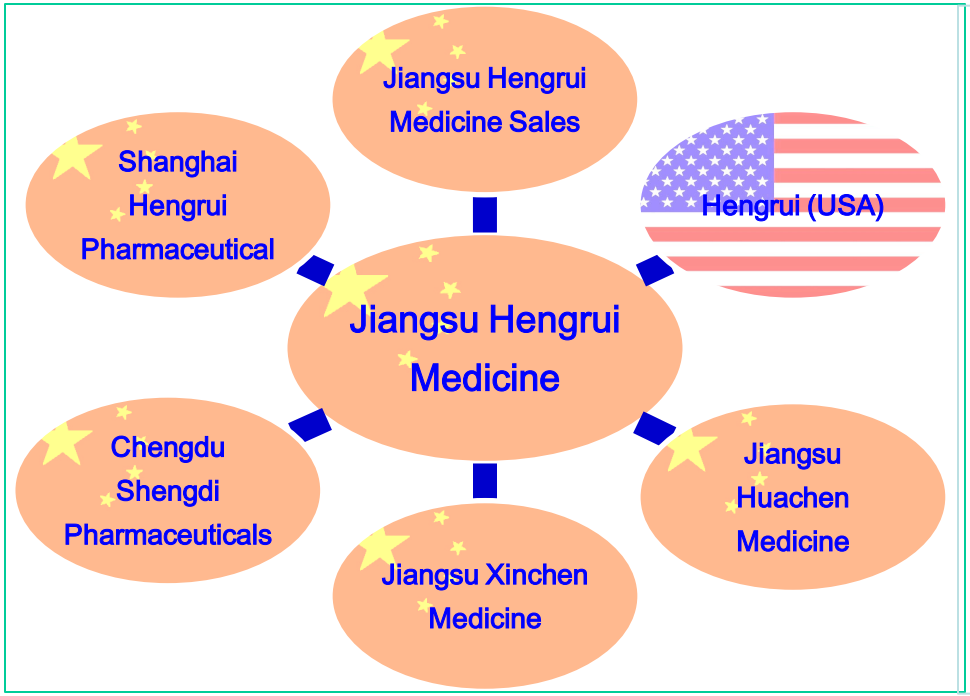
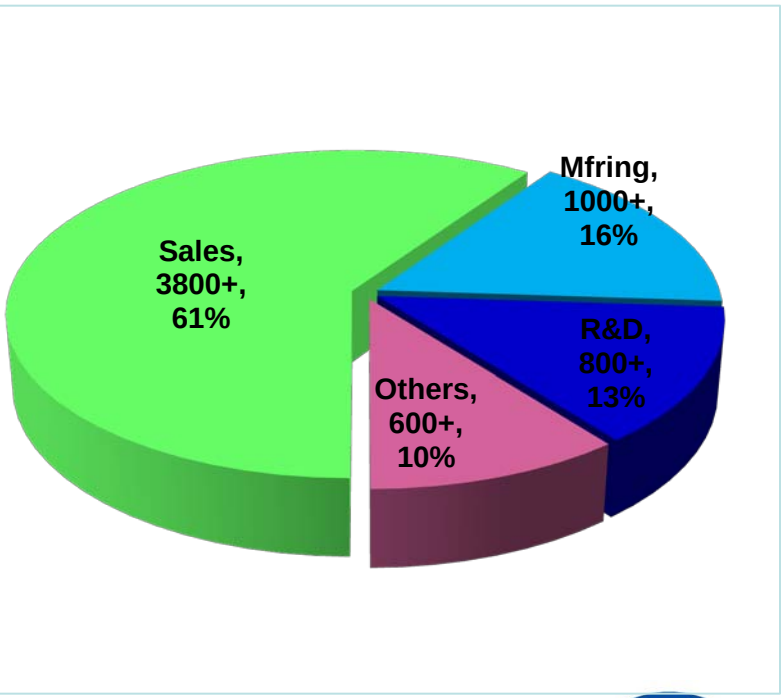
Brief Introduction about Hengrui

- Headquarter in Lianyungang, Jiangsu Province
- Established in 1970
- Listed on Shanghai Stock Exchange in 2000
- >6000 employees over the globe



公司结构



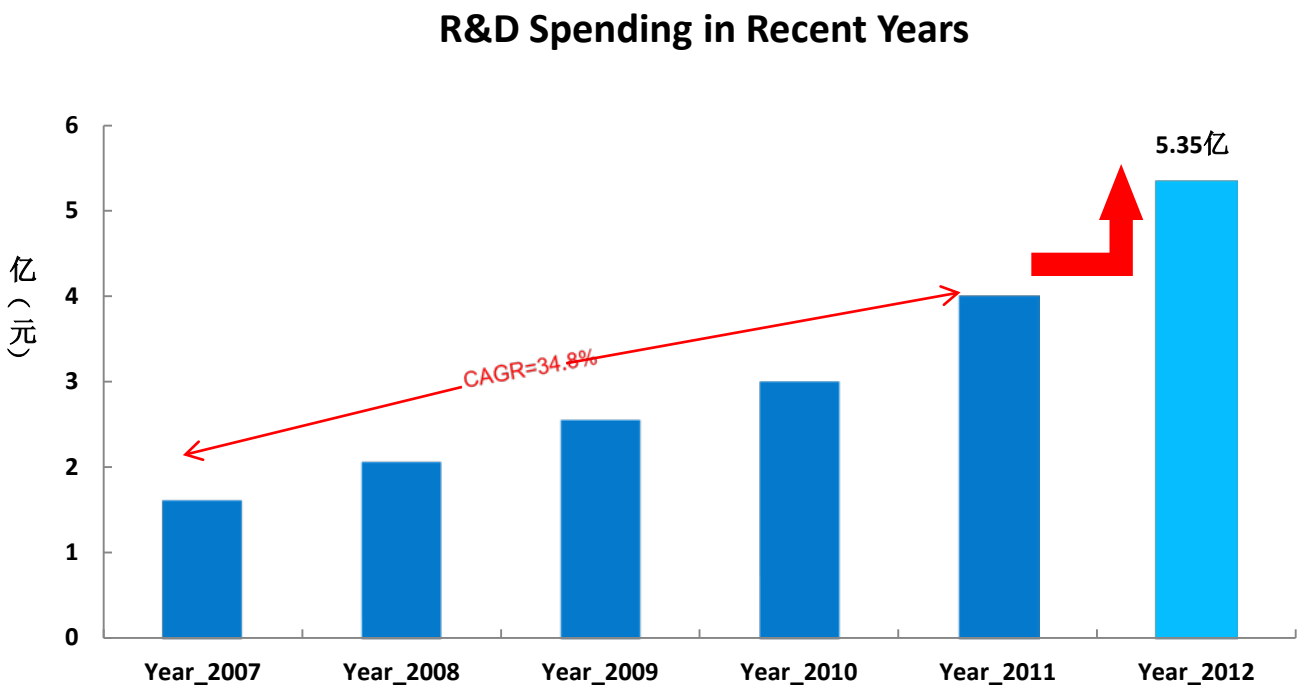
员工

恒瑞创新体系 (R&D system)

- Jiangsu R&D Center: Drug Development & CMC
- Shanghai R&D Center: Early Discovery to Preclinical Candidates
- Chengdu R&D Center: Specialty Pharmaceuticals
- US R&D Center: Early Discovery

恒瑞研发投入 (R&D Investment)

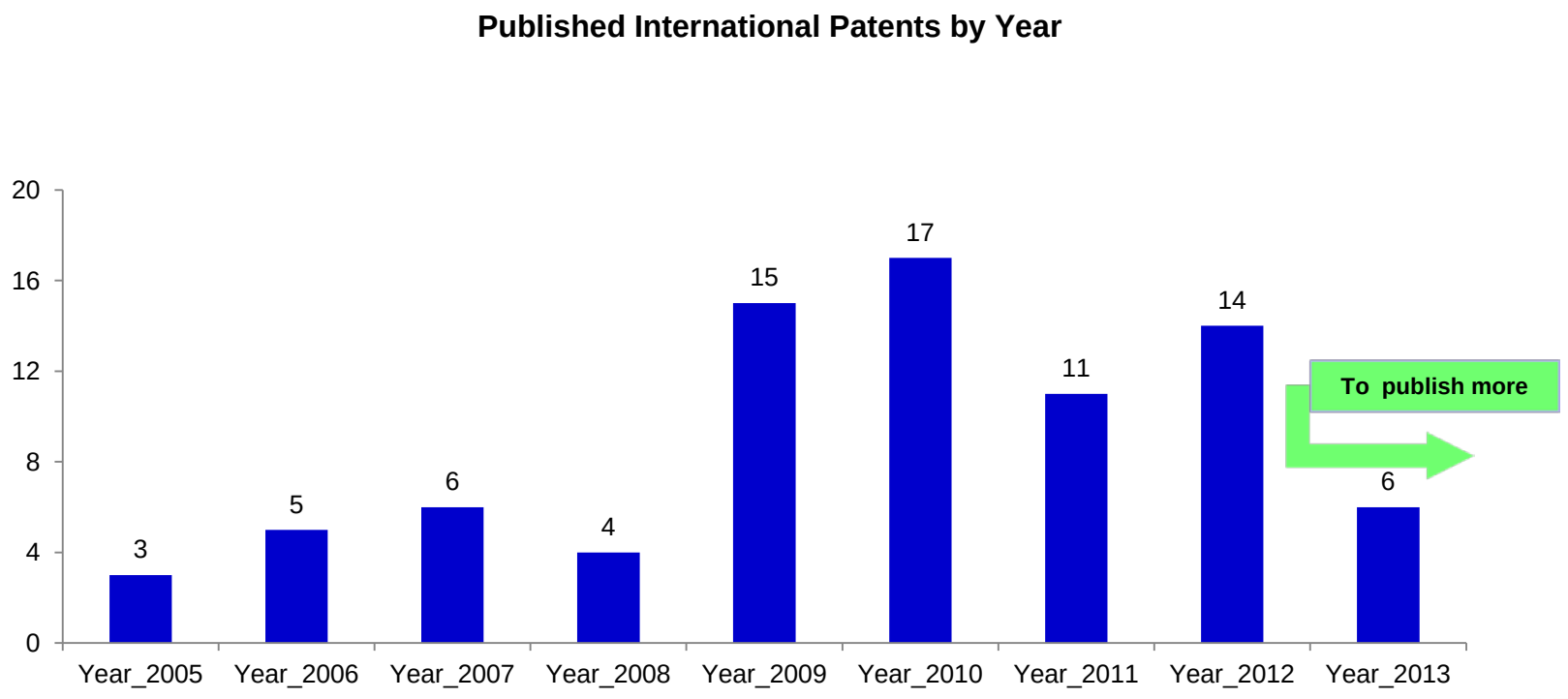
- Yearly R&D spending reaches 10% of total revenue
- R&D budget for 2012 is 5.35亿元 (~56 Million GBP)



恒瑞知识产权 (Intellectual Properties)

By 2013:

- **Total 380 Patent applications**
- **Total 81 published PCT patents worldwide**



SBDD case studies

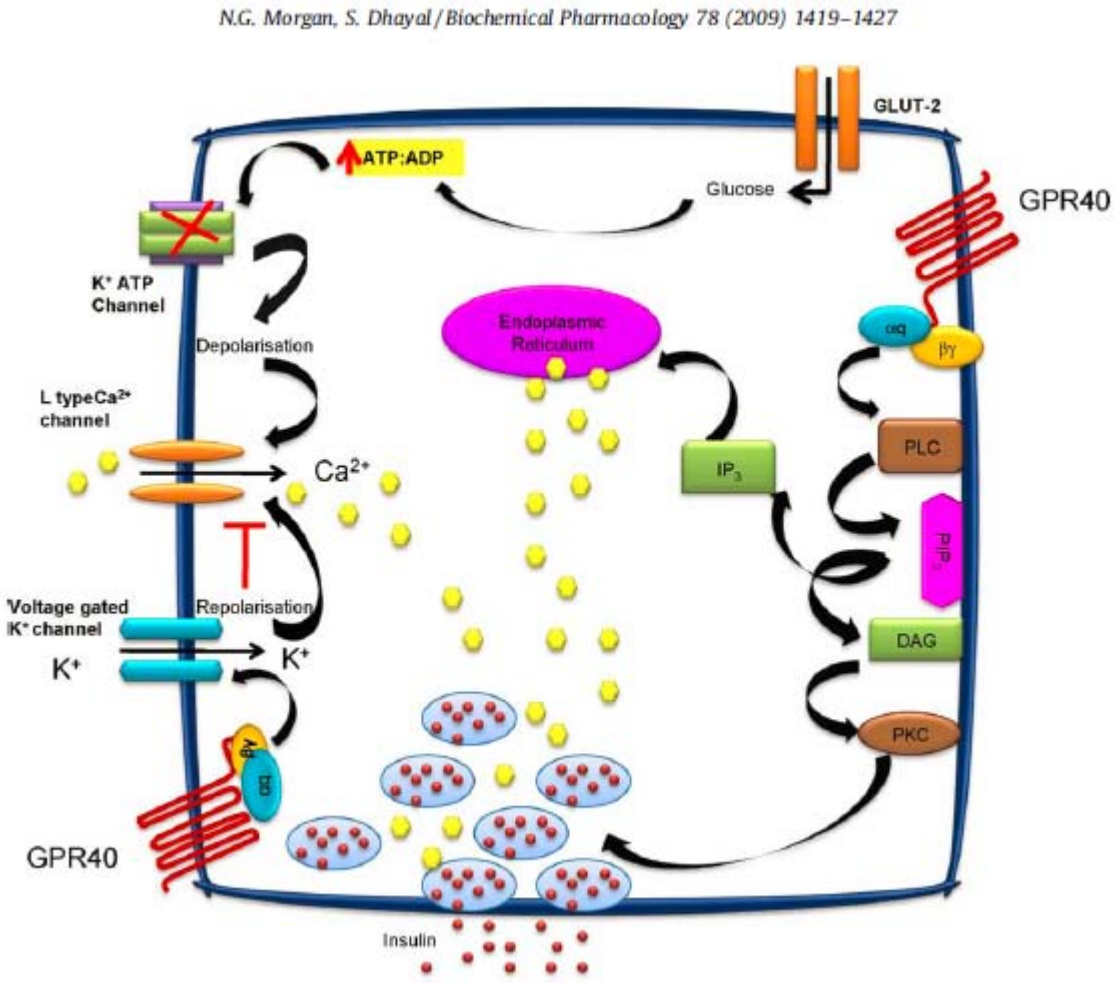
1. **Discovery of novel conformationally restricted small molecular GPR-40 agonists**

   Bioorganic & Medicinal Chemistry Letters 23 (2013) 2920–2924

2. **Structure-based design and synthesis of bicyclic fused-pyridines as MEK inhibitors**

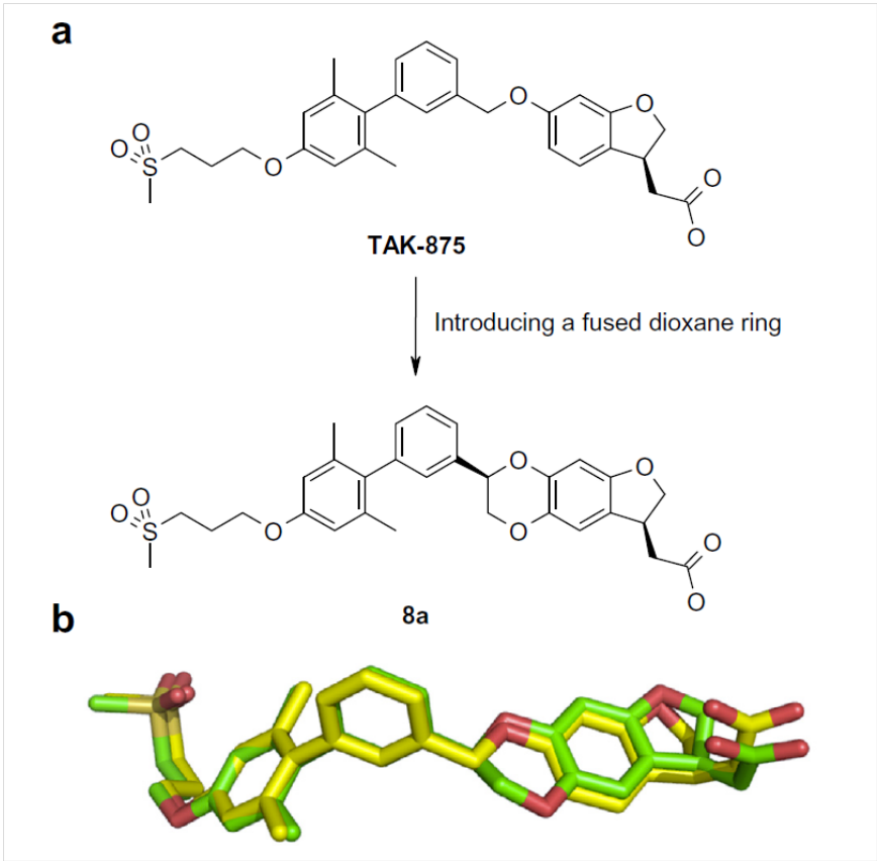
   Bioorganic & Medicinal Chemistry Letters 24 (2014) 2555–2559

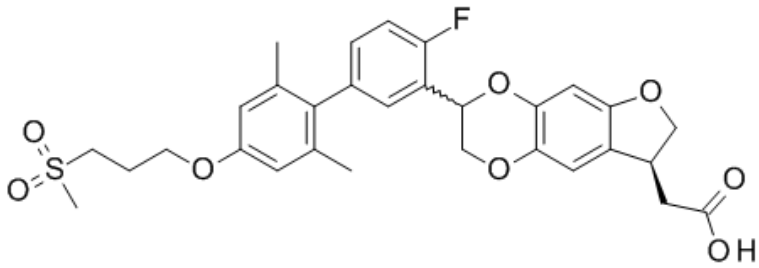
Small molecular GPR-40 agonists



Activation of GPR40 -> Increased Insulin secretion

Conformationally restricted design achieved the same level of *in vivo* potency

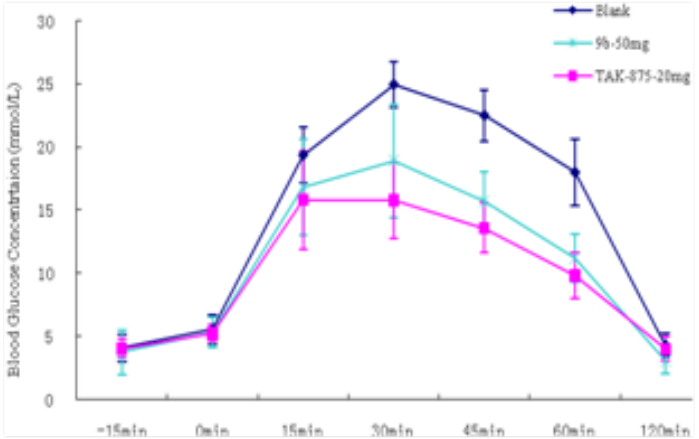




9a EC50 = 46.5 nM, Emax = 87%, Chirality = S
9b EC50 = 67.5 nM, Emax = 83%, Chirality = R

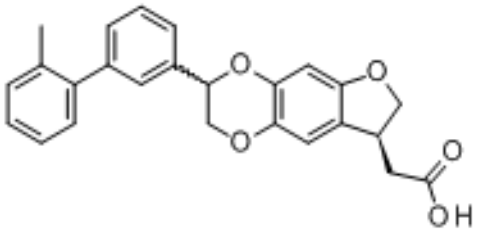
TAK-875 EC50 = 41.8 nM, Emax = 100%

ICR mice OGTT results of compound 9b and TAK-875



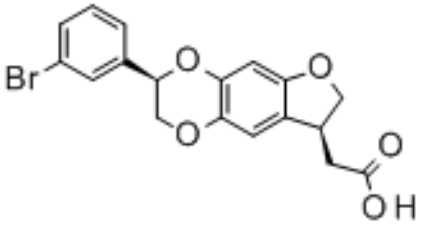
25% AUC ↓
30% AUC ↓

Discrepancy b/t *in vitro* and *in vivo* potencies for the truncated cpds



17a EC50 = 39.3 nM, Emax = 76%, Chirality = R
17b EC50 = 19.1 nM, Emax = 91%, Chirality = S

9.7% AUC ↓ in mice OGTT @50mpk

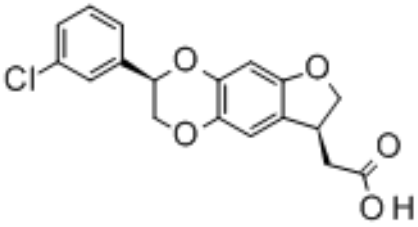


28a EC50 = 13.5 nM, Emax = 120%

Rat@5mpk,
PO AUC = 529,516 ng h/ml
Cmax = 17,775 ng/ml
T1/2 = 26.8 h

Monkey@6mpk,
PO AUC = 136,301 ng h/ml
Cmax = 5357 ng/ml
T1/2 = 16.4 h

4.9% AUC ↓ in mice OGTT @50mpk



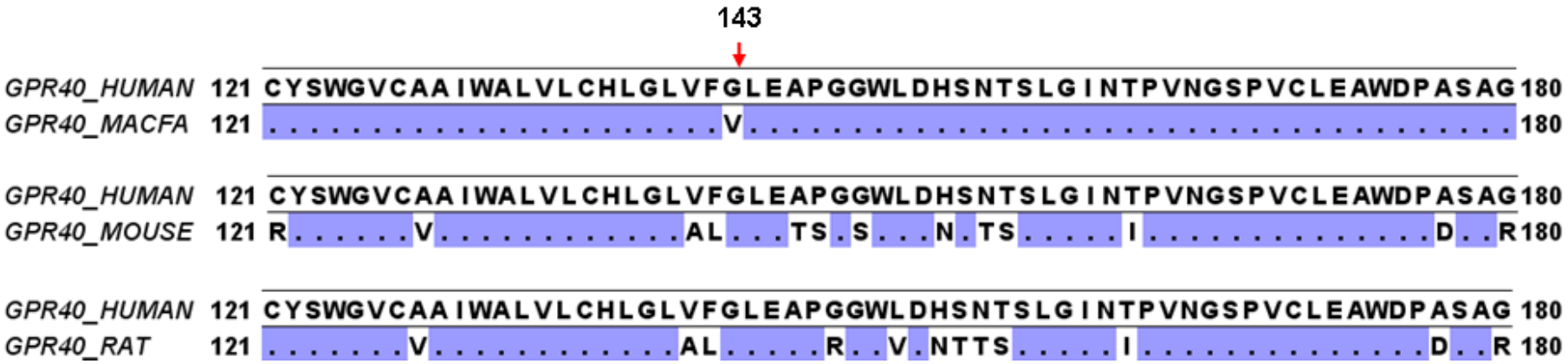
30a EC50 = 34.2 nM, Emax = 87%

Rat@5mpk,
PO AUC = 665,884 ng h/ml
Cmax = 21,950 ng/ml
T1/2 = 27.5 h

Monkey@6mpk,
PO AUC = 126,223 ng h/ml
Cmax = 19,712 ng/ml
T1/2 = 12.9 h

11.0% AUC ↓ in mice OGTT @50mpk

Species differences – Sequences Comparison of GPR40



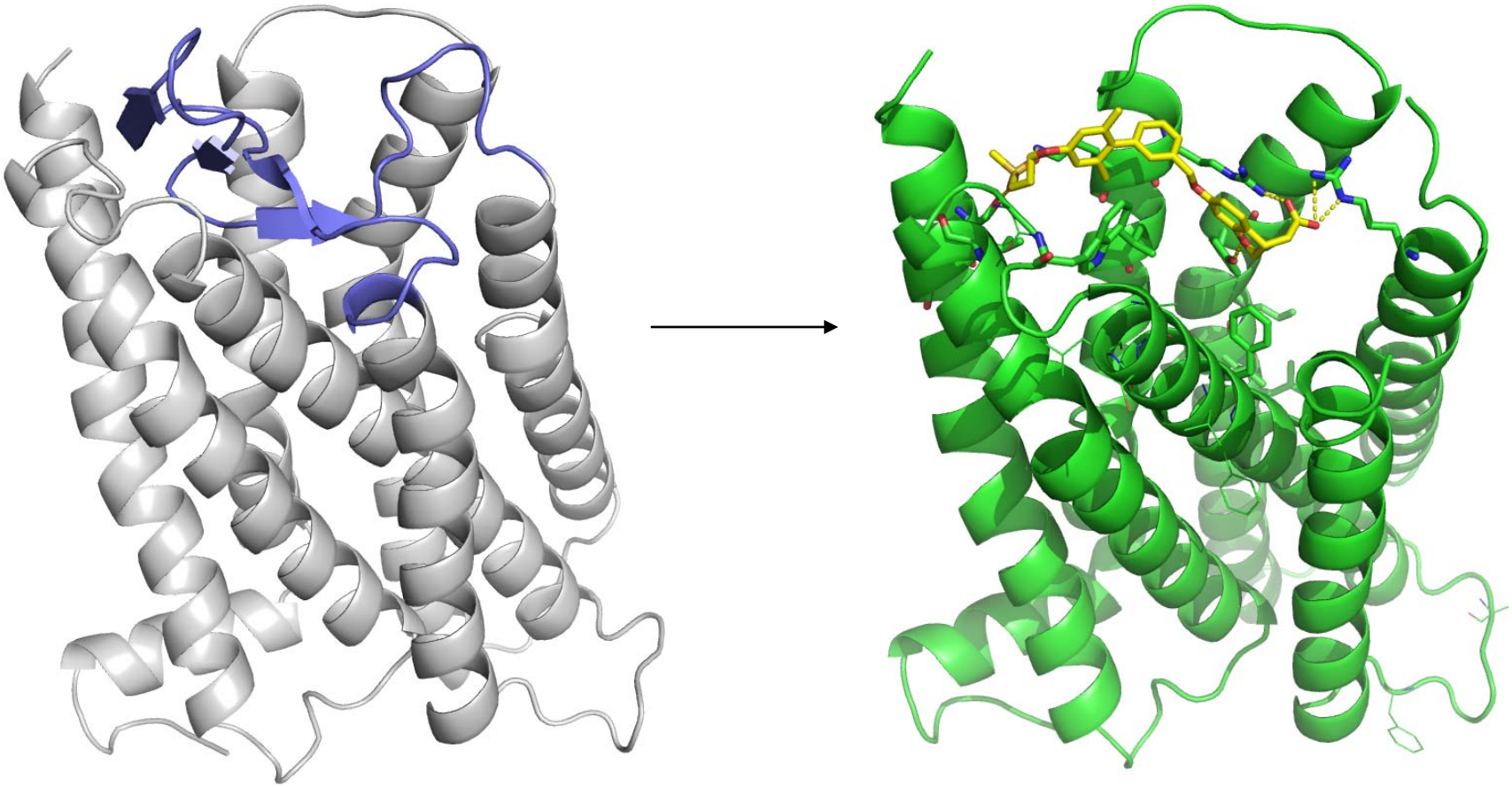
Although whole seq. similarity among human/mouse/rat/monkey are all > 90%. The blue loops (a.a. 143-180) among human, rat and mouse are quite different.

At the same time, between human and monkey, the blue loops are almost identical with one exception at residue 143.

Species differences - GPR40 human homology model

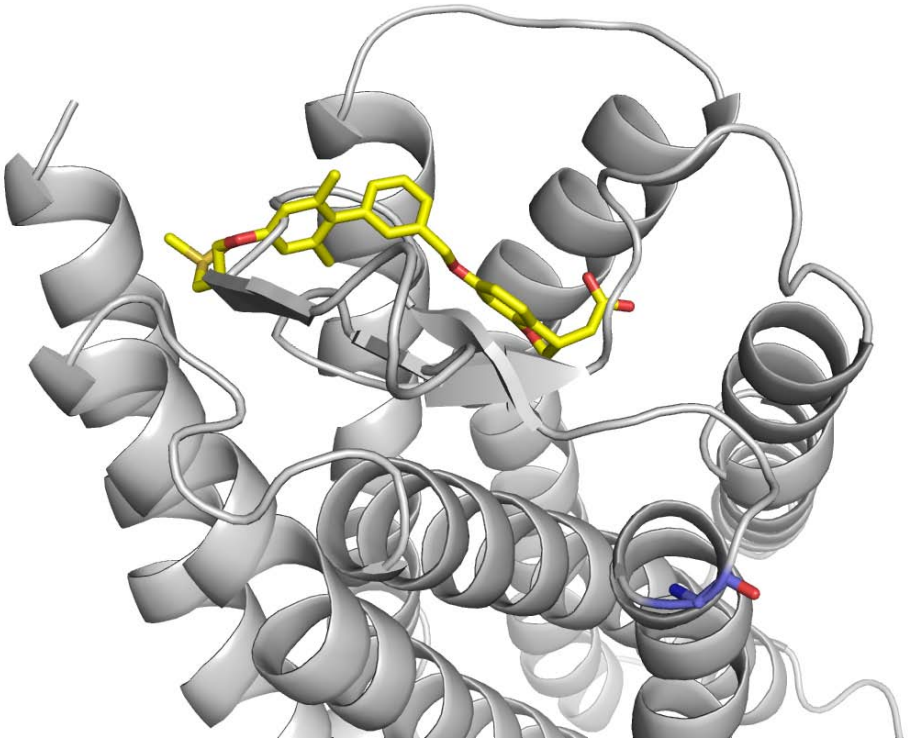
Full model

Truncated model



To model the active site binding of TAK-875, Truncation of the extracellular loop (highlighted as the Blue Loop in the Full model) was originally used by scientists in Takeda (Negoro and et al, ACS Med. Chem. Lett. 2011).

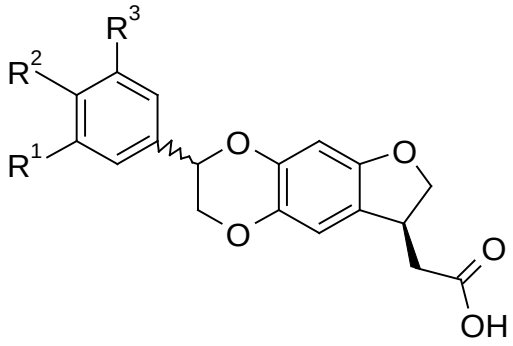
Species differences – Putative ligand binding sites of human and monkey are identical.



Residue 143 (shown in blue stick) is quite far away from the putative ligand binding site.

Monkey may serve as a better animal model for the translation between *in vitro* and *in vivo* GPR40 activity.

Species specificity were confirmed by Rat GSIS INS-1 assay of selected GPR40 agonists



No.	R^1	R^2	R^3	Chirality	[a]EC_{50} (nM)	E_{max} (%)
TAK-875					93	100
28a	Br	H	H	R	77	40
30a	Cl	H	H	R	-	36.8
31a	Cl	Cl	H	R	-	46.8
32a	CF_3	H	H	R	-	43.6

[a] Values are means of three experiments.

In vivo efficacy achieved in monkey model

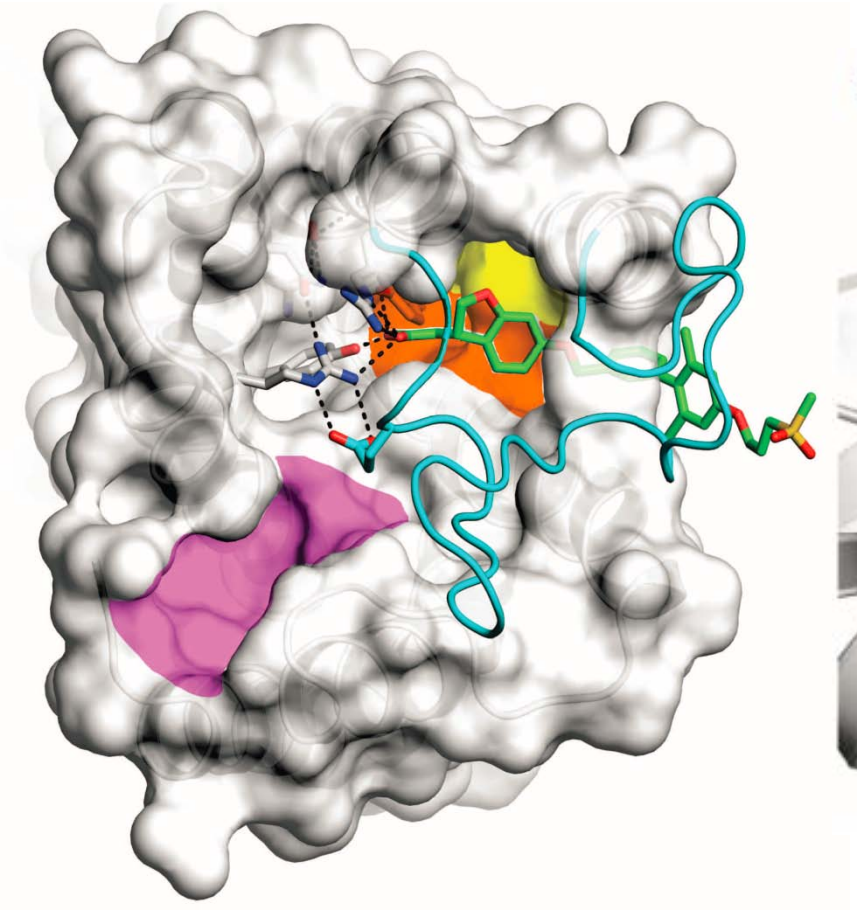
IVGTT of selected GPR40 agonists in an obese type 2 diabetes rhesus monkey model

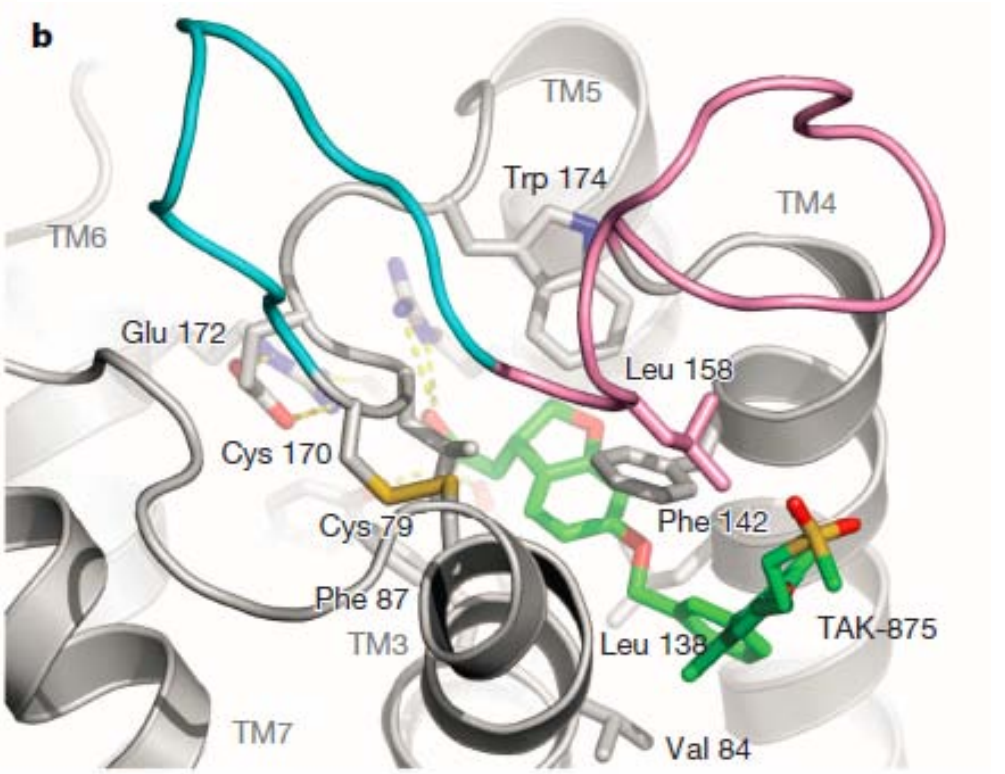
No.	Dosage (mg/kg)	Inhibition of AUC_{Glu}	
		0-60min (%)	0-120min (%)
TAK-875	20.0	14.73	15.02
28a	6.0	32.09	24.45
30a	6.0	7.71	10.71
30a	20.0	16.43	13.16

[a] Values are means of three experiments.

- **Selectivity against GPR41, GPR43 and GPR120 >=10 uM**
- **no hERG inhibition (IC50 >30 uM)**
- **CYPs DDI > 50 uM**

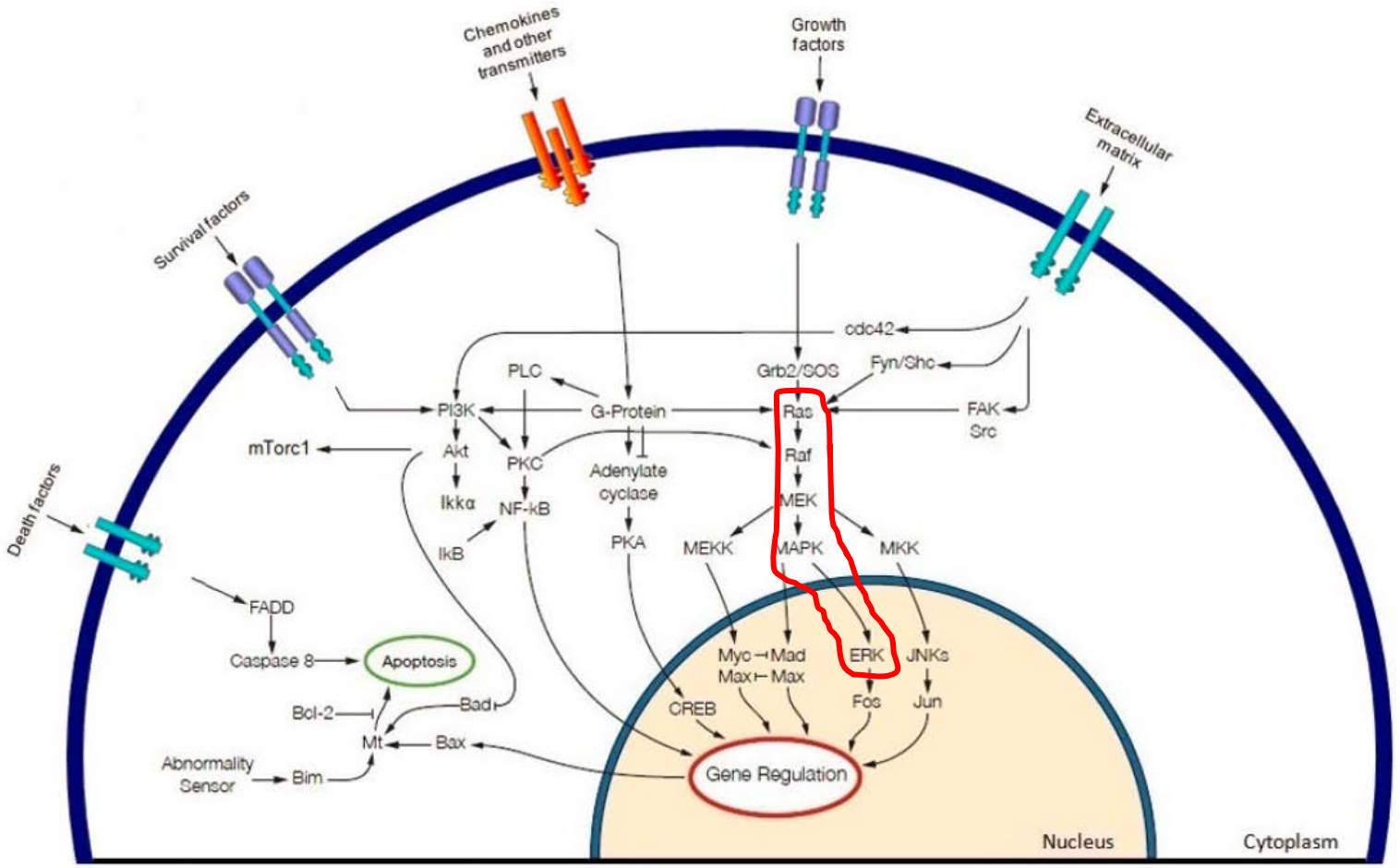
co-Crystal structure of TAK-875 with GPR40 was published*





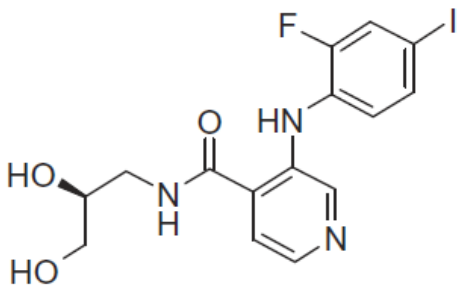
* High-resolution structure of the human GPR40 receptor bound to allosteric agonist TAK-875. Srivastava, A. and et al. **Nature 513, 124–12, 2014**

RAS-RAF-MEK-ERK pathway

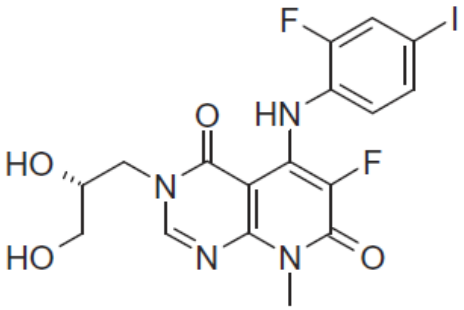


Neil Thompson and John Lyons. Expert Opin Ther Targets. 2012 January ; 16(1): 103–119.

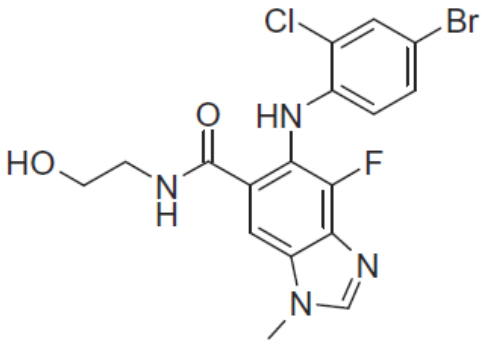
MEK inhibitors in clinical trials



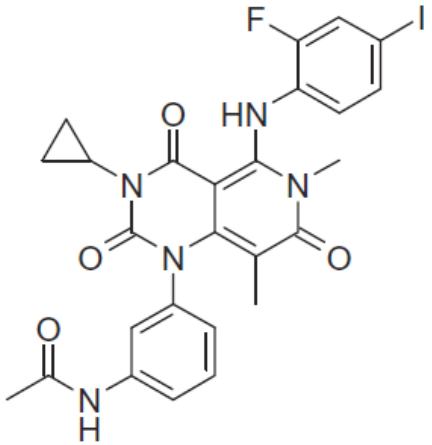
AS-703026



TAK-733

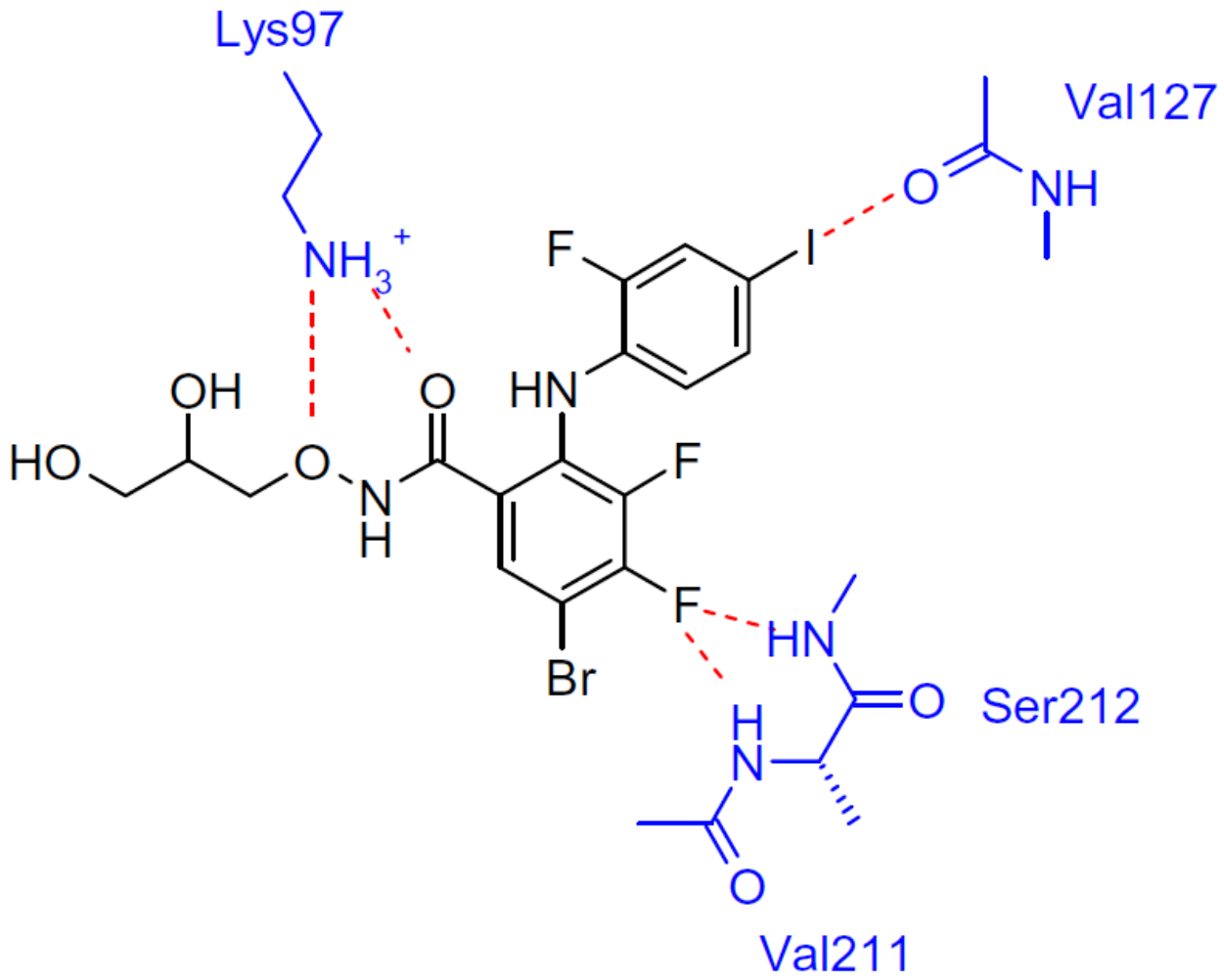


Selumetinib



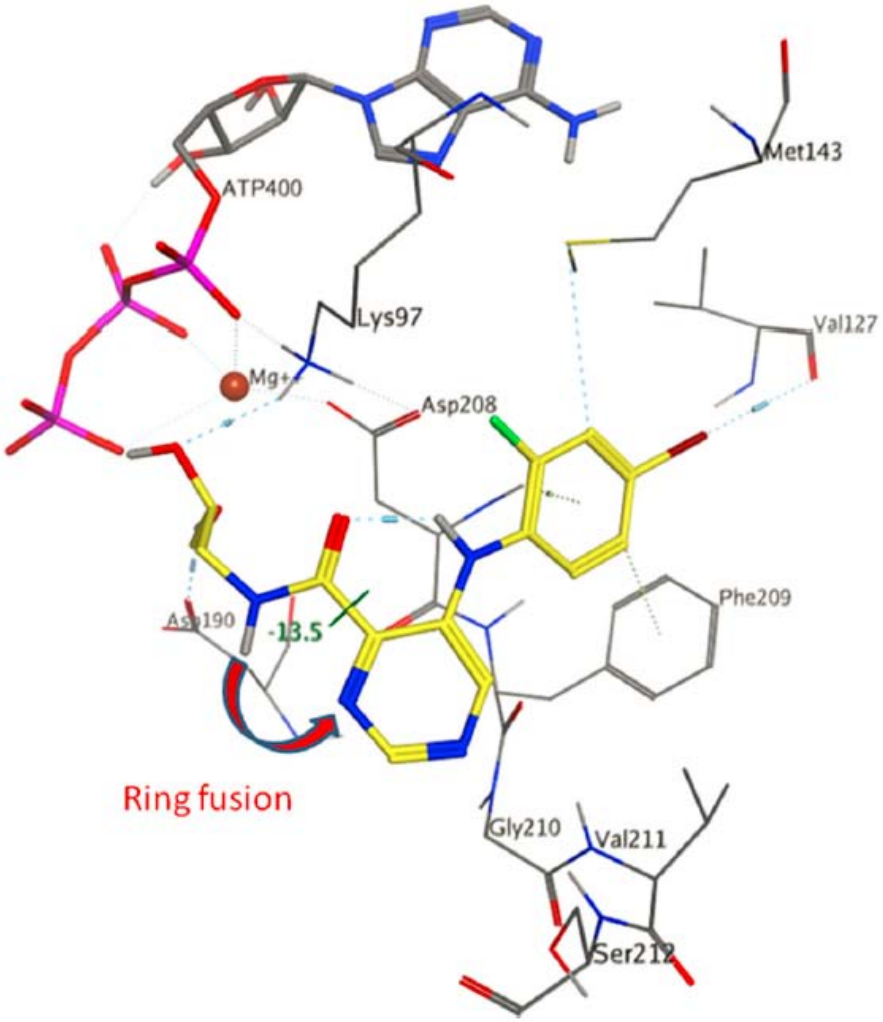
Trametinib

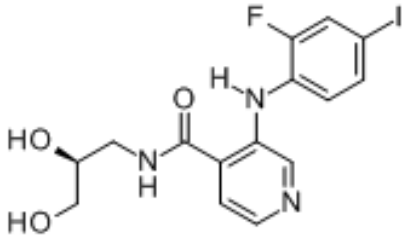
Key interactions of non-ATP competitive MEK Allosteric inhibitor*



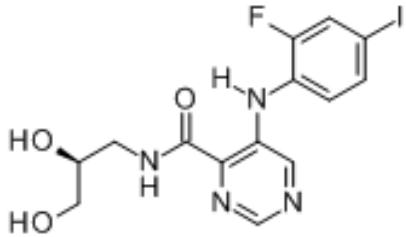
*Ohren, J. F. and et al. Nat. Struct. Mol. Biol. 2004, 11, 1192.

Pyridine to Pyrimidine



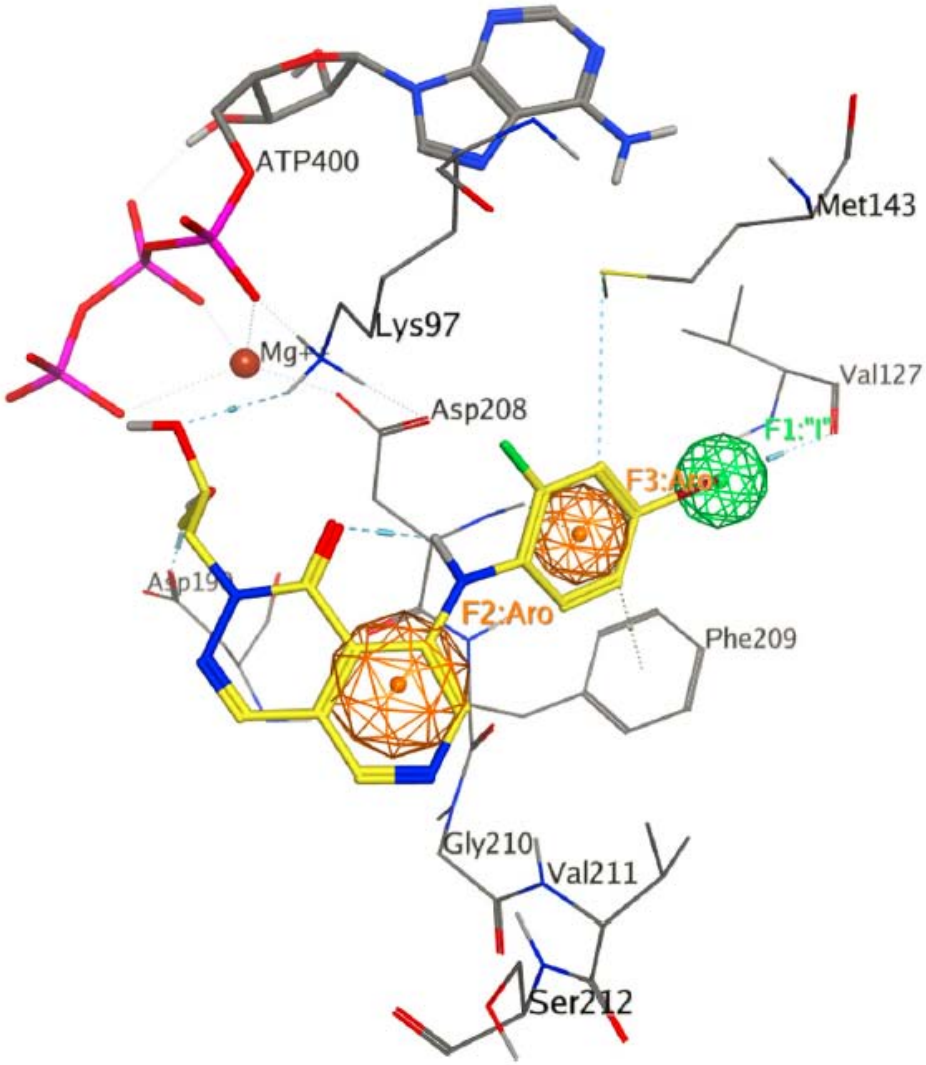


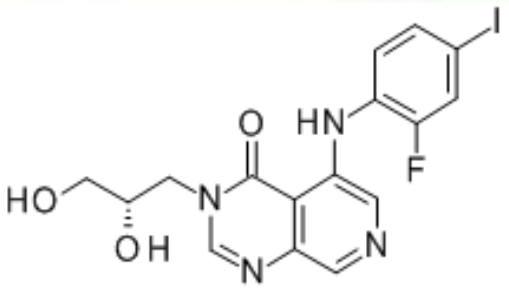
AS-703026
MEK1 IC50 = 3.4 nM
Colo-205 IC50 = 1.8 nM



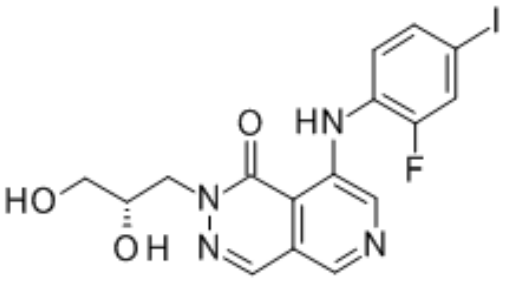
1a
MEK1 IC50 = 5.4 nM
Colo-205 IC50 = 3.4 nM

Novel bicyclic series





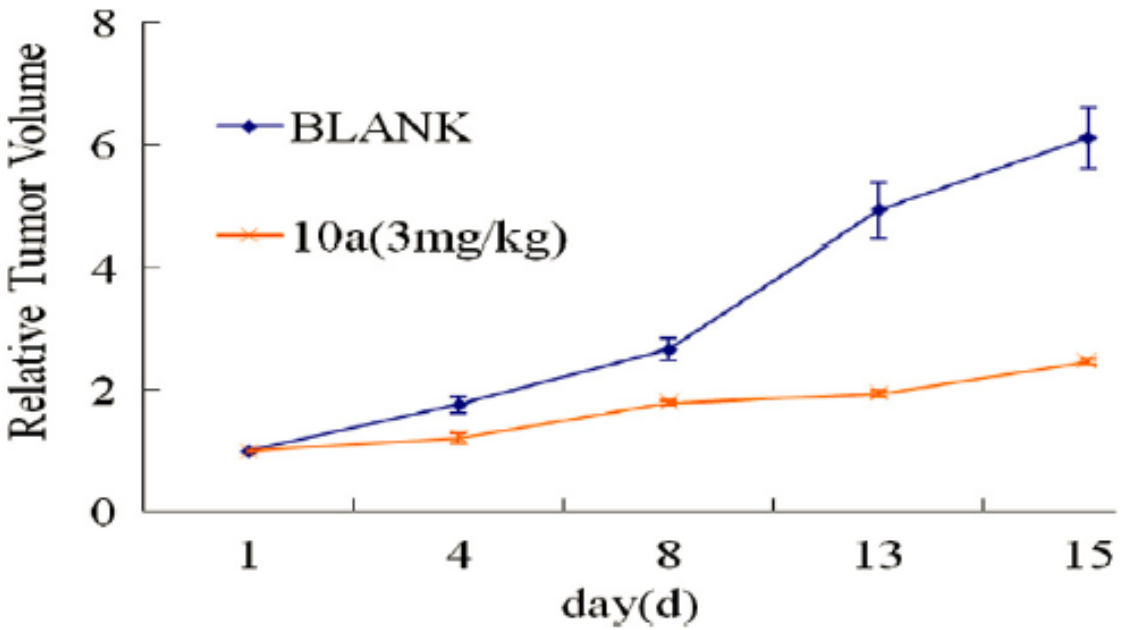
7a
MEK1 IC50 = 12.3 nM
Colo-205 IC50 = 108 nM



10a
MEK1 IC50 = 1.6 nM
Colo-205 IC50 =2.0 nM

PK and In vivo efficacy of 10a

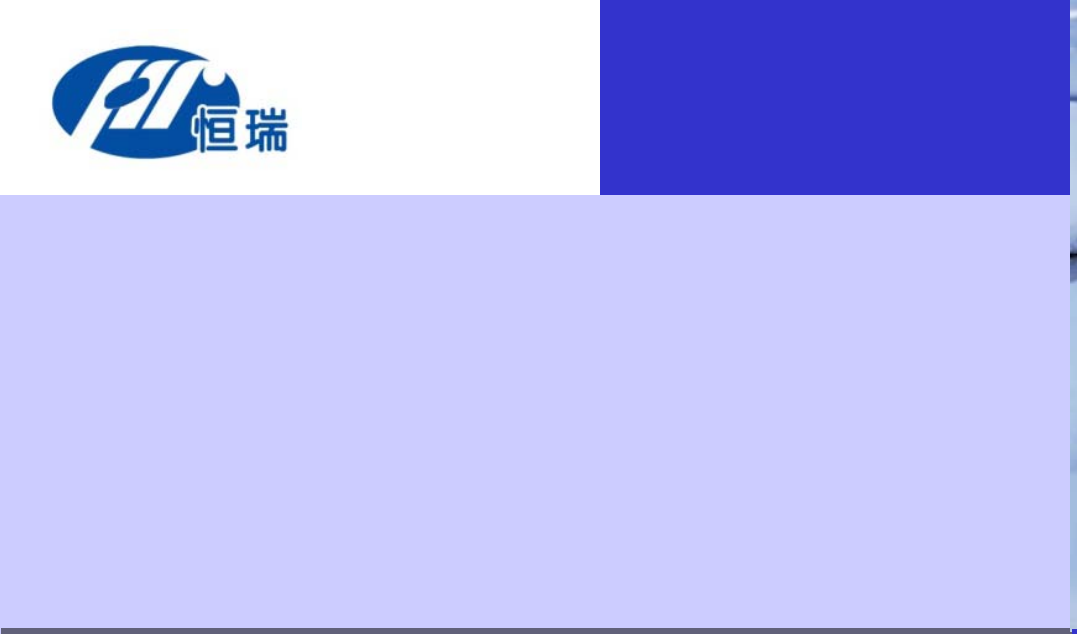
Species	Dose (mg/kg)	C_{max} (ng/ml)	AUC (ng h/ml)	$T_{1/2}$ (h)	*F*%
Rat	5.0, PO	1080 ± 271	4886 ± 1236	5.56 ± 1.65	—
Dog	1.0, PO	117 ± 44	510 ± 154	4.88 ± 2.26	43
	1.0, IV	—	1188 ± 213	3.11 ± 0.35	



恒瑞医药在研产品管线 (Clinical Pipeline)

- > 10 novel small molecules and biologics in the clinical pipeline

恒瑞



谢谢

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