Phenyl and Biphenyl Molecular Metaphors in Drug Design

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Outline

- Background
  - - prevalence of rings in drugs
  - - marketed natural products with phenyl rings
- Compound attrition and molecular complexity
  - - higher Fsp^3 count associated with marketed drugs
- Inverse relationship between # of rings & drug developability
  - - phenyl rings believed to be the problem
- Phenyl ring replacements
  - - some geometrical properties
- Phenyl ring isosteres to solve developability problems
  - - parameter optimization
- Replacements for terminal phenyl rings
  - - select examples from the literature
- Replacements for scaffolding phenyl rings
  - - heterocycle pedigrees
  - - *para* topology
  - - *meta* topology
  - - *ortho* topology
- Conclusion

Journal of
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Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design

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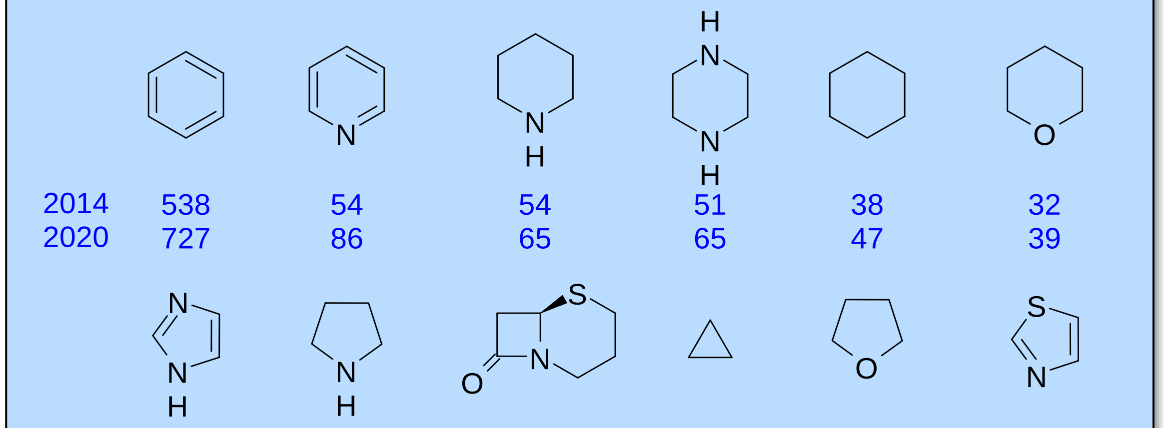
M.A.M. Subbaiah & N.A. Meanwell, *J. Med. Chem.,* 2021, **64**, 14046-141281

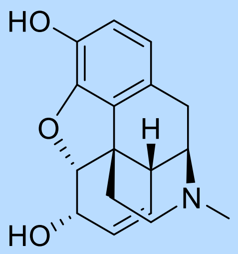
Phenyl Rings: Prevalence in Marketed Drugs

The 12 most prevalent rings in FDA-approved drugs 2014/2020

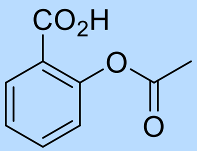


2014	538	54	54	51	38	32
2020	727	86	65	65	47	39
2014	30	29	29	28	29	30
2020	30	36	33	39	31	30

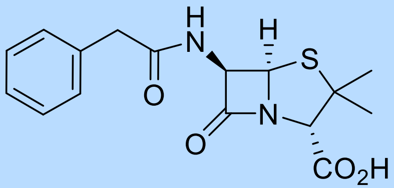
Phenyl rings represented in natural product drugs



morphine
commercialized in 1827



aspirin
commercialized in 1899

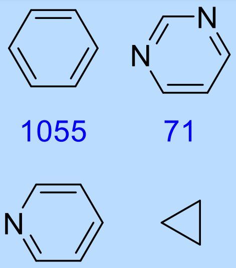


penicillin G
discovered in 1928
structure proposed in 1942
confirmed by X-ray in 1945
clincal use began in 1940s

FDA founded June 30th, 1906
(Federal Food & Drugs Act)

- 1175 FDA-approved drugs up to January 2014
  - 6 membered rings the most prevalent topology
    - 767 examples (65%); 1029 in 2020 dataset
- Benzene is the most common ring
  - 538 examples (46%); 727 in 2020
- Pyridine is the 2nd most prevalent ring
  - 54 examples (4.6%); 86 in 2020
  - similar prevalence to piperidine and piperazine
- Phenyl rings are common in Nature
  - component of morphine & aspirin
  - present in penicillin G

Marketed Ag. Chem. Products

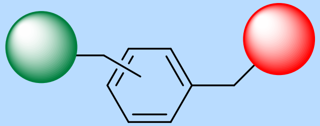


1055 71

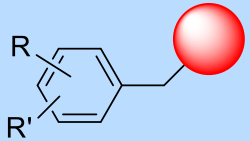
86 68

2019: 1737 total

- Ph rings deployed as scaffolds or pharmacophores
  - 200 years of synthetic organic chemistry
  - straightforward to decorate
  - no complications from chirality
- Scaffold effects
  - exit vectors confer versatility
  - allows for multiple combinations
- Pharmacophore
  - well-established substituent interrelationships
  - electronic, lipophilic effects of substituents
    - Hansch QSAR, Topliss tree, *p*Cl-phenyl



scaffold element

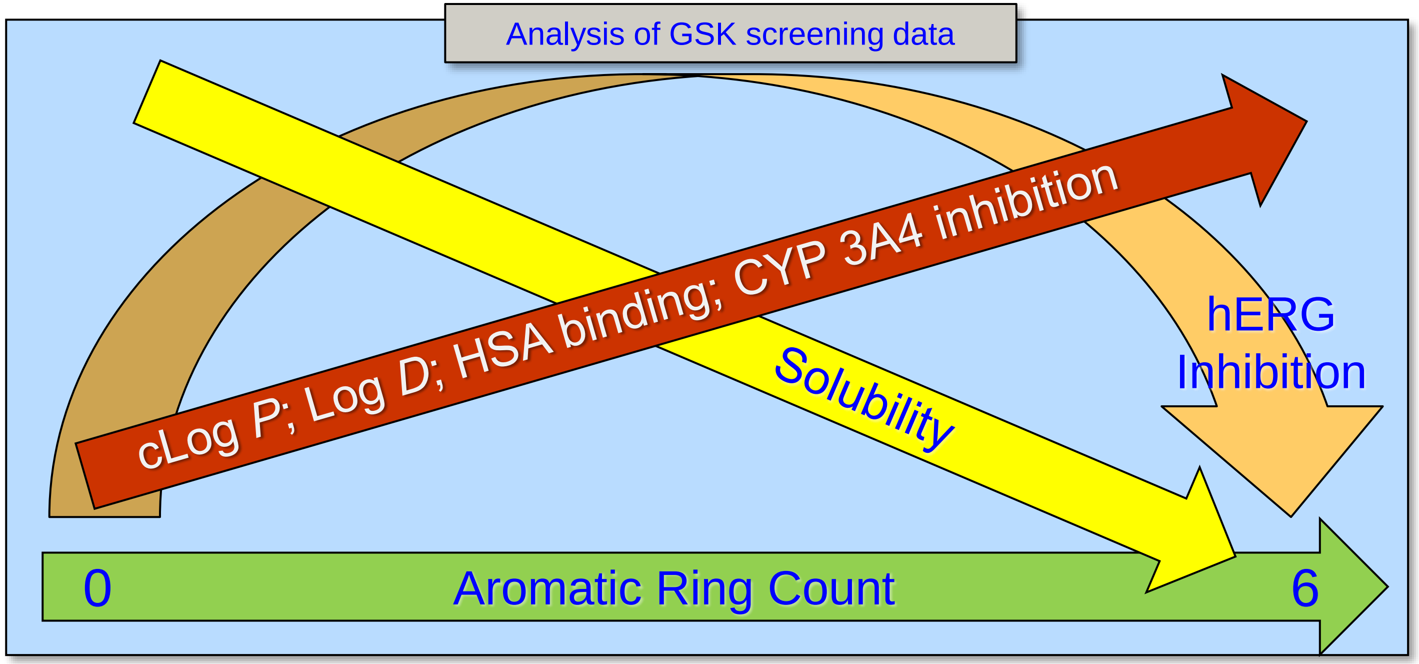


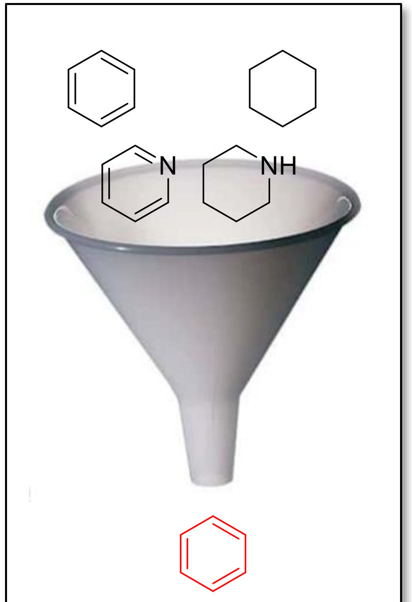
pharmacophore

R.D. Taylor *et al., J. Med. Chem.*, 2014, **57**, 5845-5859; *J. Med. Chem.*, 2022, **65**, 8699-8712; C. Hansch *et al., J. Med. Chem.*, 1973, **16**, 1207-1216
J.G. Topliss, *J. Med. Chem.*, 1977, **20**, 463-469; D.G. Brown *et al., J. Med. Chem.*, 2015, **58**, 2390-2405

Ring Count, Planarity & Developability

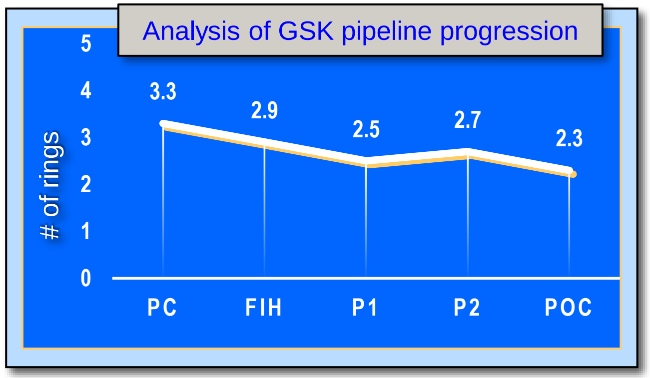
Analysis of GSK screening data

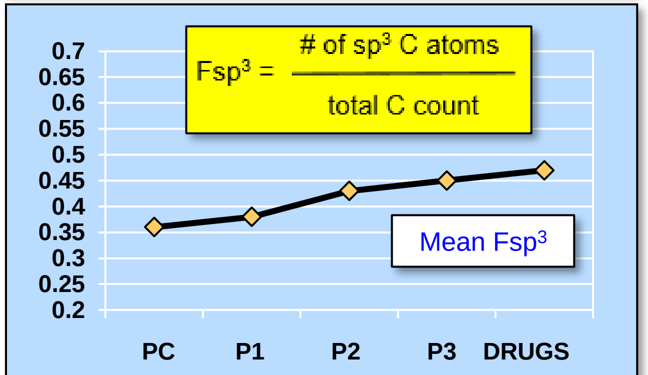




Phenyl rings underlie the property trends

Analysis of GSK pipeline progression





$$\mathrm{Fsp}^3 = \frac{\#\text{ of sp}^3\text{ C atoms}}{\text{total C count}}$$

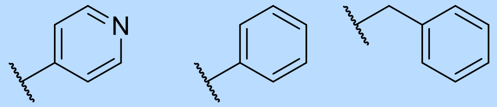
Analysis of the GVK BIO database

- ◆ cLog *P* & Log *D* increase, & solubility decreases with increasing aromatic ring count
  - HSA binding, CYP 3A4 inhibition ↑; hERG inhibition shows a hump function
- ◆ **Carboaromatic rings** determined to be the most problematic in promoting these trends
  - phenyl rings are often deployed indiscriminately: potency can be driven by entropic effects
- ◆ Ph ring should bring 460x ↑ in potency to maintain 0.3 $\mathrm{LLE_{AT}}$ value
  - a benzyl moiety requires ~900x ↑ in potency
- ◆ Mean $\mathrm{Fsp^3}$ count increases with development stage
  - attrition of planar aromatic compounds
- Property Forecast Index (PFI) predicts many developability challenges

$$\mathrm{PFI} = \text{Chrom Log } D_{\mathrm{pH7.4}} + \#\mathrm{Ar} \text{ or } \mathrm{iPFI} = \text{Chrom Log } P + \#\mathrm{Ar}$$

$$\mathrm{LE} = \frac{-\Delta G_{\mathrm{binding}}}{\mathrm{HAC}} = \frac{\mathrm{pIC}_{50}}{\mathrm{HAC} \times 0.74}$$

$$\mathrm{LLE_{AT}} = \frac{(\mathrm{p}K_i,\ \mathrm{p}K_d,\ \mathrm{pIC}_{50} - \mathrm{cLog}\ P)}{\mathrm{HAC} \times 0.74} + 0.11$$



LE	22x	22x	36x
$\mathrm{LLE_{AT}}$	30x	460x	~900x

Fold potency increase required to maintain LE & $\mathrm{LLE_{AT}}$ = 0.3 for aryl substituents

T.R. Ritchie *et al.*, *Drug Discov. Today*, 2009, **14**, 1011-1120; 2011, **16**, 164-171; *Med. Chem. Commun*, 2012, **3**, 1062-1069; F. Lovering *et al.*, *J. Med. Chem.*, 2009, **52**, 6752-6756; M.L. Verdonk & D.C. Rees, *ChemMedChem*, 2008, **3**, 1179-1180; P.N. Mortenson & C.W. Murray, *J. Comput. Aided Mol. Des.*, 2011, **25**, 663-667l; R.J. Young, *BMCL*, 2011, **21**, 6228-6235; *Topics Med. Chem.*, 2015, **9**, 1-68

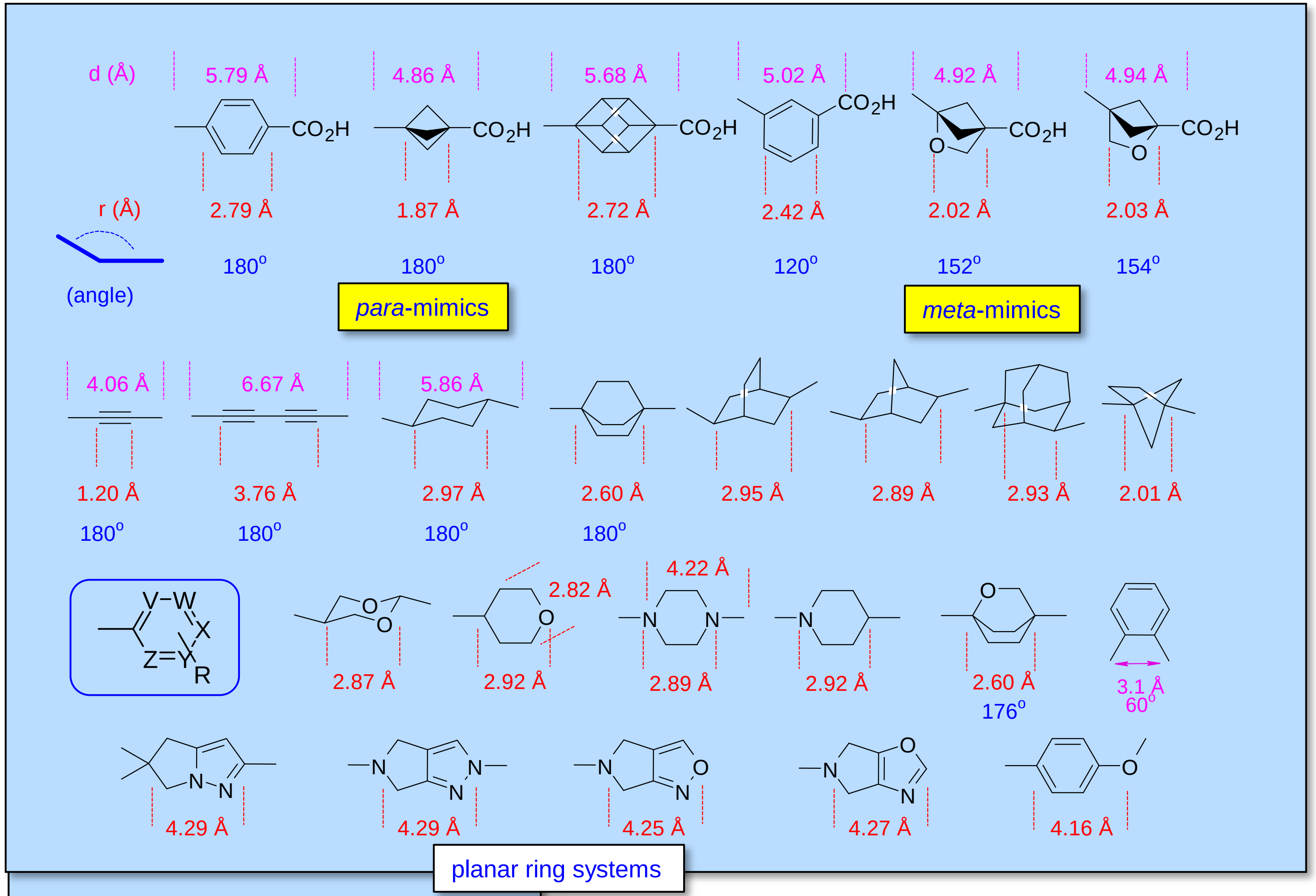
Phenyl Isosteres & Compound Optimization

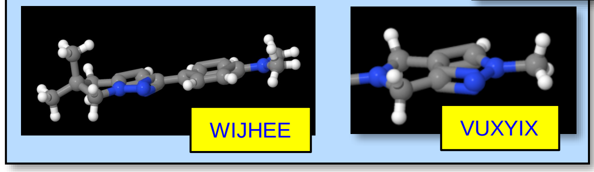
Property	Optimization Parameter
Molecular Properties	Shape & conformation of a molecule, aromatic ring count, Fsp^3 value, introduce a H-bond acceptor (HBA) or donor (HBD)
Physicochemical Parameters	Lipophilicity, basicity, modulating melting point, dissolution rate, aqueous solubility, membrane permeability
Pharmacological Parameters	*In vitro* biochemical potency, cellular potency, selectivity against target isoforms, genotype coverage, promiscuity, *in vivo* efficacy
ADME/PK Parameters	Metabolic stability, plasma exposure, volume of distribution, half-life, clearance, CYP450 inhibition, pregnane X receptor (PXR) liability, plasma protein binding, oral bioavailability
Safety and Toxicity Parameters	CYP450 time-dependent inhibition (TDI), reactive metabolite formation, hepatotoxicity, phototoxicity, phospholipidosis, mutagenicity, hERG inhibition & other CV liabilities, DNA binding
Other Parameters	Structural diversity, new bioisostere design

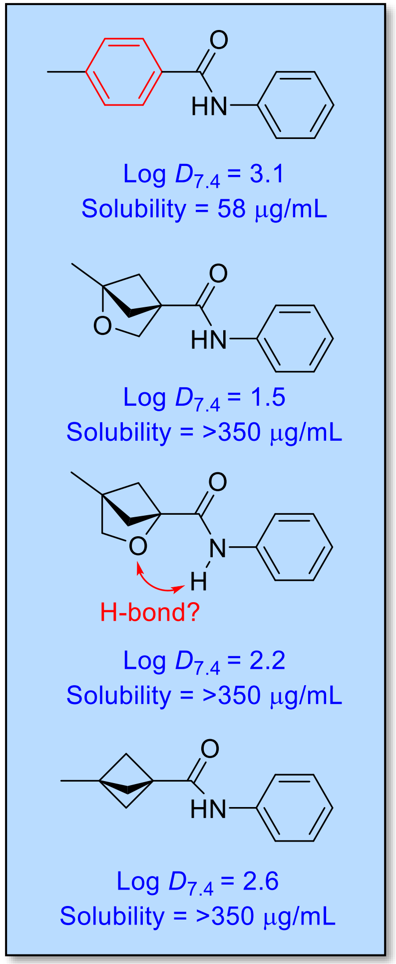
- ◆ Bioisosteres of phenyl rings have shown the potential to address a range of developability challenges
  - - improved solubility, metabolic stability; removal of toxicophores are common examples
- ◆ Effect of isosteric replacement on biological activity varies
  - - bioisosterism is contextual, dependent on the biochemical target & the role of the phenyl ring

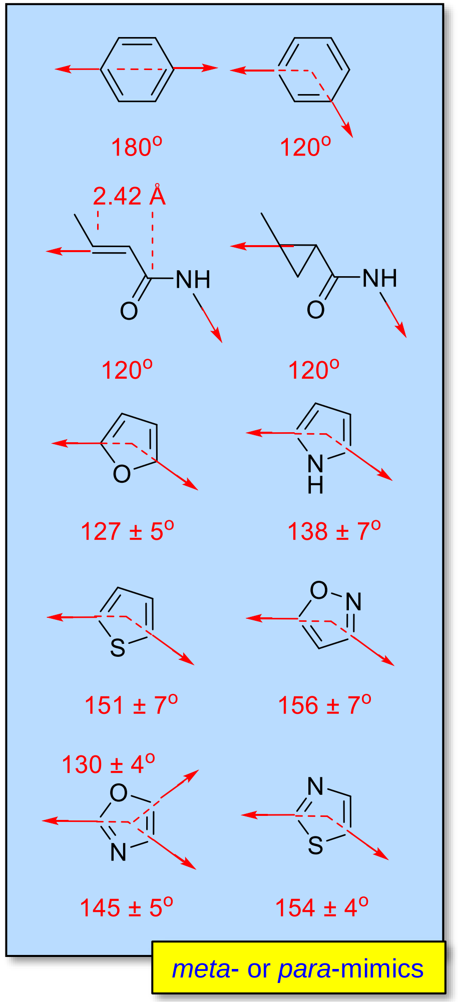
M.A.M. Subbaiah & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 14046-141281

Phenyl Mimic Vectors and Geometric Parameters







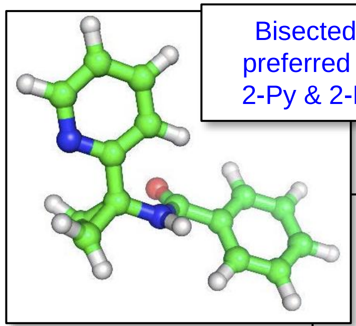


- ◆ Azines, other 6 membered rings, some bicycles are the most conservative isosteres
  - closely recapitulate exit vectors for *ortho*-, *meta*-, *para*-substitution
- ◆ Azoles, bicycles offer altered exit vectors that allow for flexibility
  - other ring systems offer unique vectors & properties

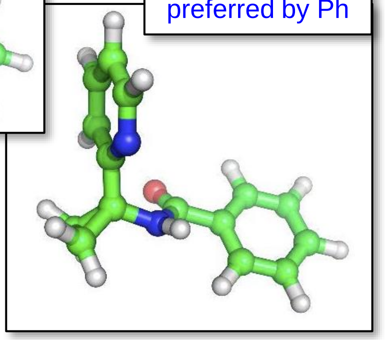
M.A.M. Subbaiah & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 14046-141281; V.V. Levterov *et al., Angew. Chem. Int. Ed.*, 2020, **59**, 7161-7167

Replacements for Terminal Phenyl Rings

Azines as Terminal Phenyl Replacements: HCV NS5B Inhibitors

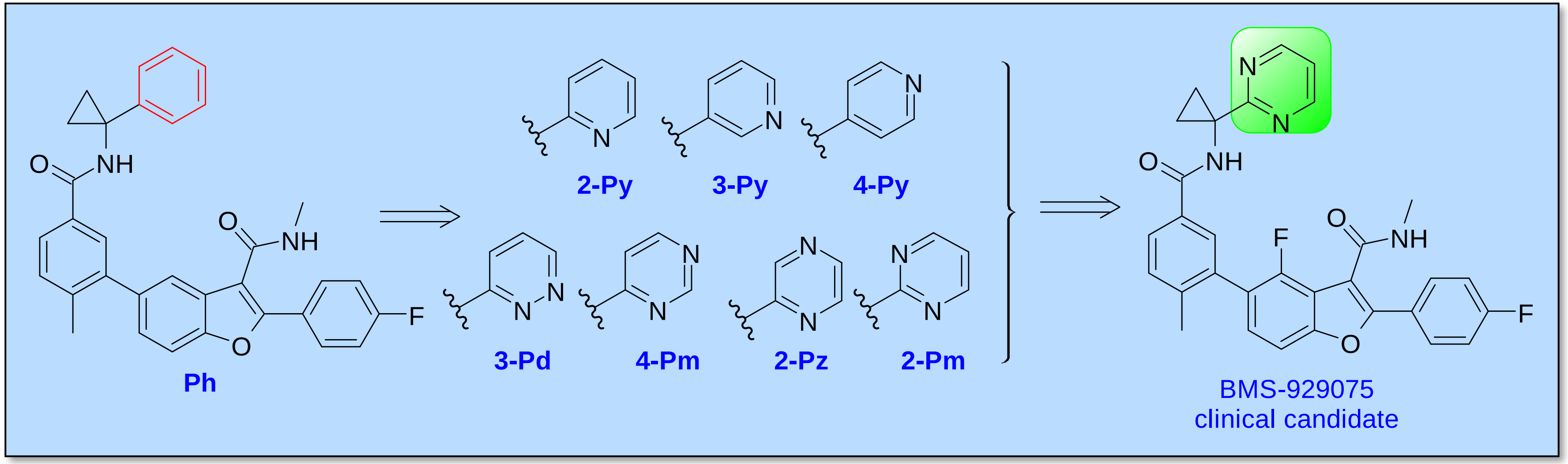


Bisected - preferred by 2-Py & 2-Pm



Perpendicular - preferred by Ph

CYP inh.
imidazole>Py
>Pd>Py,Pz



BMS-929075
clinical candidate

	Lead	Bioisosteric analogue							
	Ph	**2-Py**	**3-Py**	**4-Py**	**3-Pd**	**4-Pm**	**2-Pz**	**2-Pm**	**BMS-929075**
HCV replicon GT-1a/1b/1b C316N EC_{50} (nM)	2.1/1.3/35	2.8/1.9/55	17/2.2/193	8.3/0.83/63	17/2.9/139	13/1.9/109	15/2.6/308	2.3/1.0/51	9/4/18
cLog *P*	6.28	5.44	5.05	5.05	4.49	4.77	4.22	4.83	4.98
CYP 3A4 IC_{50} (μM)	2.1	4.1	0.063	0.073				11.4	>13
% remaining (HLM/RLM)	68/39	89/82	0.7/0.6	11/11			* $t_{1/2}$ (min)	>120*/86*	>120*/120*

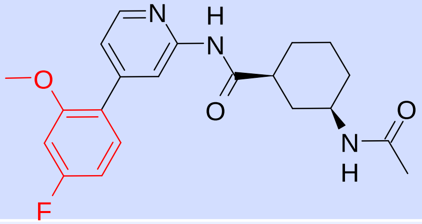
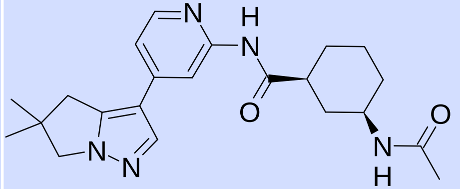
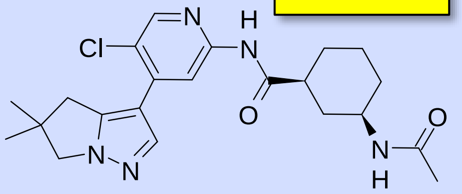
- ◆ Potent allosteric HCV NS5B inhibitors
  - - highly lipophilic, CYP 3A4 inhibition; moderate LM stability
- ◆ Systematically replaces terminal phenyl ring with azines
  - - all reduced cLog *P*; potency toward C316N mutant varied
  - - pyridines with exposed *N* associated with CYP 3A4 inhibition
  - - preferred conformation may reduce *N* exposure in 2-isomer

- ◆ Pyrimidine optimal azine in this series
  - - reduced CYP 3A4 inhibition
  - - improved HLM/RLM stability
- ◆ CYP 3A4 inhibition not an issue with F-homologue
  - - BMS-929075 advanced into clinical trials
  - - doses of ≥25 mg gave 10x EC_{50} vs C316N mutant C_{24}

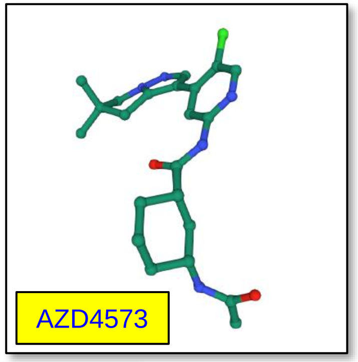
Impact
↓ cLog *P*
↓ CYP450 inhibition
↑ metabolic stability

K.-S. Yeung *et al., J. Med. Chem.*, 2017, **60**, 4369-4385. See also L.D. Pennington *et al., J. Med. Chem.*, 2017, **60**, 3552-3579; *J. Med. Chem.*, 2020, **63**, 8956-8976; A.G. Leach *et al.*, *JCIM*, 2011, **51**, 1048-1063

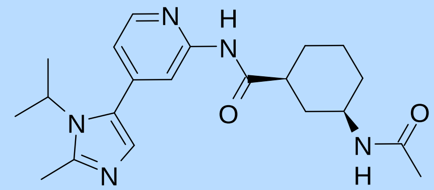
Terminal Phenyl Replacements in CDK9 Inhibitors

	Lead	Bioisosteric analogue	
cis-cyclohexane is a phenyl replacement			AZD4573 
CDK9 IC_{50}	29 nM	29 nM	4 nM
pSer2 cell IC_{50}	130 nM	150 nM	13.4 nM
Log $D_{7.4}$	3.0	2.8	3.8
Sol. (µM)	33	970	150
Rat hepatocytes Cl_{int} (µL/min/10^6 cells)	58	45	73
HLM Cl_{int} (µL/min/mg)	12	<3	50

Impact
↑ biochemical & cell potency;
↑ solubility



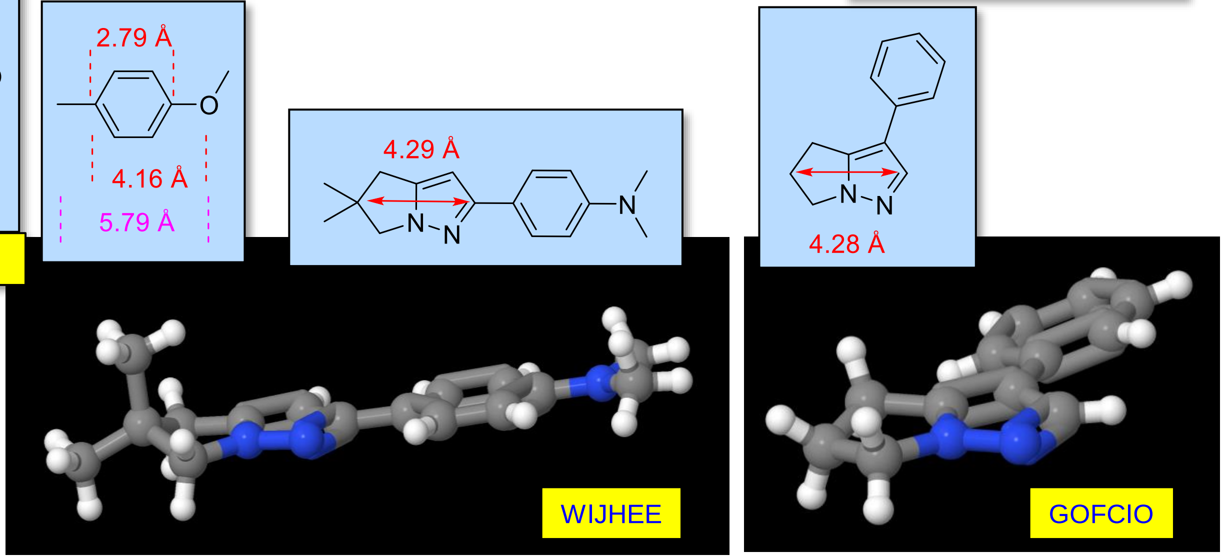
- ◆ CDK9 inhibitor for hematological malignancies
  - IV administration & short $t_{1/2}$ to mitigate tox.
  - poor solubility of lead precluded IV dosing
- ◆ Replaced phenyl ring with azole isosteres
  - a substituted imidazole improved solubility
    - but …. potency reduced 10x
- ◆ Fused pyrazole offered potency & solubility
  - presents a relatively planar topography
  - 1.5 Å longer than a phenyl ring; comparable to anisole
- ◆ Cl enhances potency, reduces metabolic stability in HLM
  - modulates conformation; increases lipophilicity (π = 0.71)
  - fused ring is the site of metabolism
    - hydroxylation of CH_2 adjacent to N
- ◆ AZD4573 currently in clinical trials for hematological malignancies



IC_{50} = 380 nM

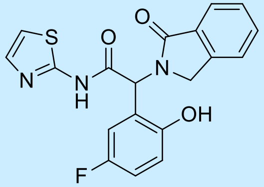
Soly. = 660 µM

substituted azoles less potent

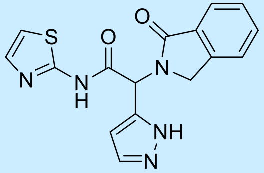


B. Barlaam *et al.*, *J. Med. Chem.*, 2020, **63**, 15564-15590

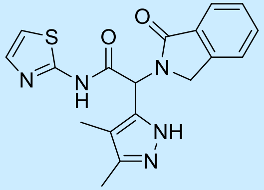
Terminal Phenyl (Phenol) Replacement in EGFR



pEGFR (LRTMCS) IC_{50} = 6 nM



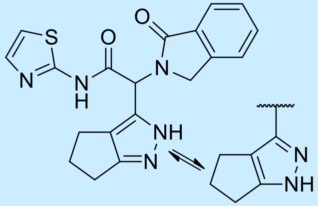
pEGFR (LRTMCS) IC_{50} = 1100 nM



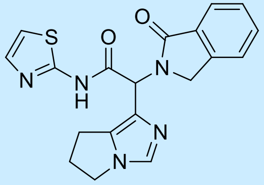
pEGFR (LRTMCS) IC_{50} >10,000 nM

1 CH_2

435x

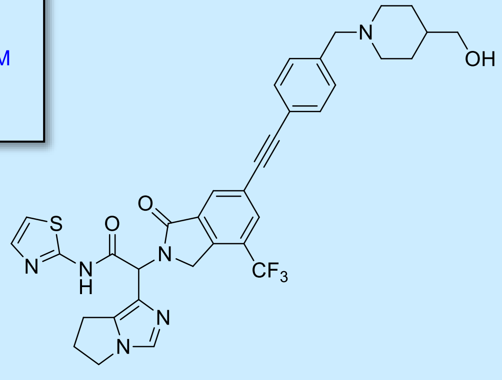


pEGFR (LRTMCS) IC_{50} = 51 nM



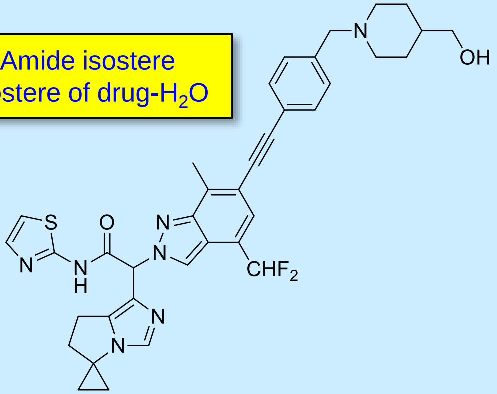
pEGFR (LRTMCS) IC_{50} = 16 nM

LRTMCS = L858R/T790M/C797S



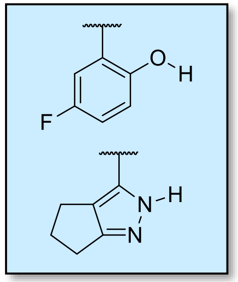
pEGFR (LRTMCS) IC_{50} = 3 nM

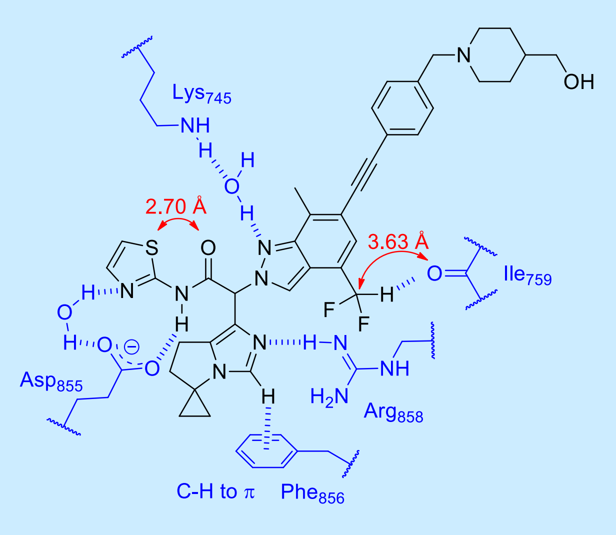
Amide isostere
Isostere of drug-H_2O



pEGFR (LRTMCS) IC_{50} = 2 nM

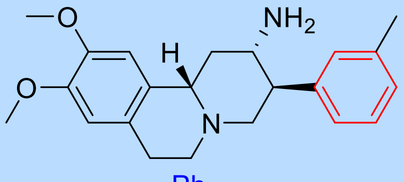
- Sought allosteric Type III inhibitors of EGFR kinase
  - 4th generation inhibitor
  - to overcome resistance to Type I & Type II inhibitors
- EGFR activating L858R mutation
  - 90% of patients with NSCLC
- Osimertinib is a 3rd generation inhibitor
  - C797S mutation abrogates Michael addition
- Pyrazole to replace PhOH
  - preserves H-bond donor: poorly active
- Added CH_3's to expand size
  - even weaker potency
- Incorporated into cyclopentane
  - to avoid steric interaction with amide
    - amide engages Asp_{855}
  - 435x enhanced potency
    - pyrazole tautomerism allows Phe_{856} π interaction
- Evolution to pyrrolo[1,2-*c*]imidazole
  - C-H bond donor



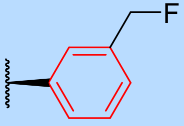


G. Jaeschke *et al., J. Med. Chem.*, 2022, **65**, 13052-13073

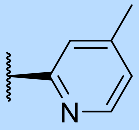
Terminal Phenyl Mimics in DPP4 Inhibitors & GR Agonists



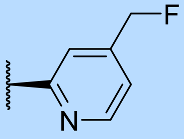
Ph



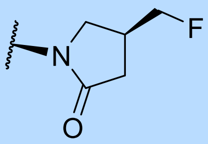
FCH$_2$-Ph



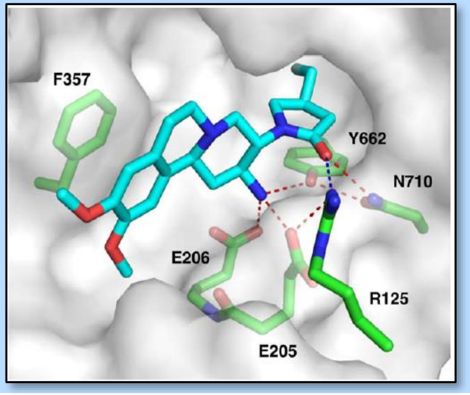
CH$_3$-Py



FCH$_2$-Py



carmegliptin



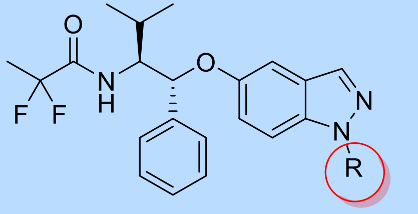
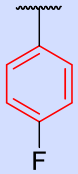
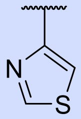
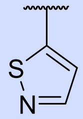
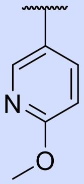
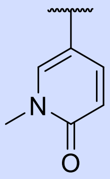
	Lead		Bioisosteric analogue		
	Ph	FCH$_2$-Ph	CH$_3$-Py	FCH$_2$-Py	carmegliptin
DPP-IV IC$_{50}$ (nM)	4.6	0.5	19	1.2	6.8
Log $D_{7.4}$	1.3	1.6	0.3	0.1	0.5
In vitro PL* (µM)	2.5	NT	15	NT	>20

*Lowest concentration at which phospholipidosis is induced in cultured fibroblasts; NT = not tested

Impact
↓ brain penetration
↓ potential for phospholipidosis
↓ lipophilicity

- ◆ Glucocorticoid receptor (NHR) allosteric agonist
    - treatment of inflammatory diseases
    - rheumatoid arthritis, respiratory tract disorders
- ◆ Sought partial agonists to avoid side effects
    - based on experience with SERMs
- ◆ Poor intrinsic aqueous solubility
    - indazole *N*-F-phenyl replacements explored
    - sought to reduce cLog *P*, enhance solubility
- ◆ Isothiazole & 2-MeO-pyridine reduced potency
    - cell effects poor
- ◆ *N*-Me pyridone optimal
    - potent partial agonist
    - solubility improved100x over MeO-pyridine
    - cLog *P* reduced by 2.3 units from F-Ph
- ◆ AZD9567 in clinical trials: QD drug
    - improved profile compared to prednisolone

- ◆ Potent DDP4 inhibitor
    - treatment of diabetes
- ◆ Phenyl lead subject to high clearance in rats
    - high V_d & undesirable CNS penetrance
    - amphipathic compound: phospholipidosis *in vitro*
- ◆ CH_3 to F-CH_2 enhanced potency 10x
    - F-CH_2-Py +ve in an Ames assay
- ◆ Sought to replace the aromatic ring
    - pyrrolidinone gave carmegliptin
    - C=O: Asn$_{710}$ NH$_2$, Arg$_{125}$ dual H-bond interactions

	Lead	Bioisosteric analogue			AZD9567
					
GR IC$_{50}$ (nM)	<14	52	NT	57	3.8
Cell TR EC$_{50}$ (nM)/% eff.	<0.34/92	3.3/71	39/31	40% at 1 µM	7/87
Solubility (µM)	<0.08	5.8	0.96	<0.5	55
cLog *P*	6.7	5.1	5.4	6.0	4.4

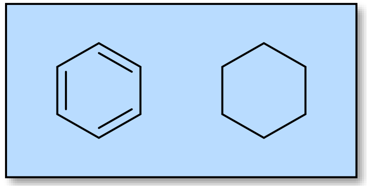
Impact
↓ lipophilicity
↑ solubility
↑ potency

Pyridone
↑ potency 15x
↑ cell >200x
↑ soly. >100x
↓ cLog *P* 1.6

M. Boehringer *et al.*, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1106-1108; P. Mattei *et al.*, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1109-1113; L. Ripa *et al.*, *J. Med. Chem.*, 2018, **61**, 1785-1799

Cyclohexyl as a Terminal Phenyl Bioisostere

- **Phenyl rings** prevalent in drug design
  - frequently associated with π-π stacking interactions
- Matched pairs analysis: compared phenyl with cyclohexane
  - sampled the Merck, Amgen and BindingDB databases
    - 11021, 1341 and 2468 matched pairs, respectively
- For 36-45%, potency within 2-fold
  - for 25-39%, Ph ≥2-fold more potent
  - for 25-30%, cyclohexyl ≥2-fold more potent
- Examined examples in each category
  - only where X-ray cocrystal data available
  - phenyl & cyclohexyl can engage in similar types of stacking interactions
  - challenges a long-held assumption
- Replacing a phenyl with cyclohexyl will increase Fsp^3
  - but…. also increases Log *P* by ~0.5 units
  - other adjustments may be required



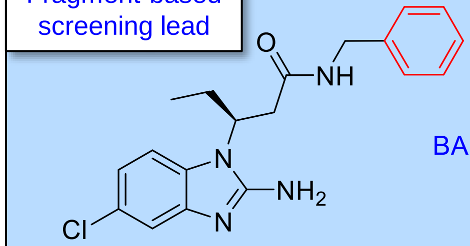
cyclohexyl acceptable
~70% of the time

$$Fsp^3 = \frac{\text{\# of } sp^3 \text{ C atoms}}{\text{total C count}}$$

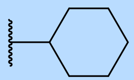
Impact
10x ↑ potency
↑ Fsp^3 content
↑ LLE despite ↑ cLog *P*

Top: Ph & Cy π stack
Middle: Cy 30x Ph
Bottom: Ph 30x Cy

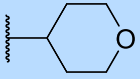
Fragment-based screening lead



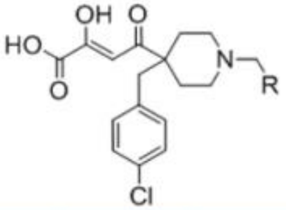
BACE1 IC_{50} = 72 μM
LE = 0.24
cLog *P* = 3.9
LLE = 0.24



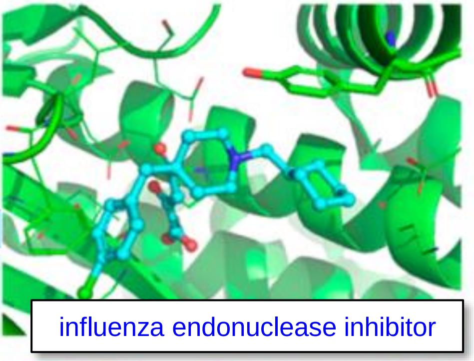
BACE1 IC_{50} = 7 μM
LE = 0.29
cLog *P* = 4.7
LLE = 0.83



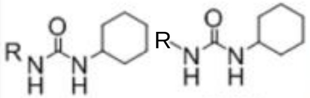
BACE1 IC_{50} >1,000 μM



	R	K_i (μM)
C1	Phenyl	0.090
C2	Cyclohexyl	0.084

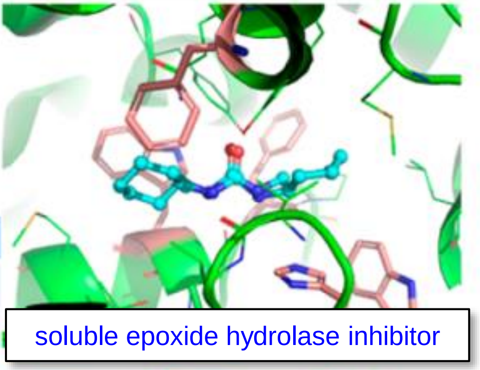


influenza endonuclease inhibitor

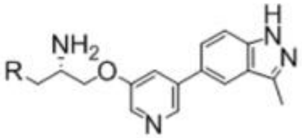


5AKZ

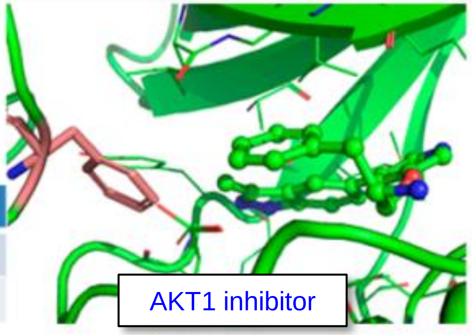
	R	IC_{50} (μM)
C7	Phenyl	0.760
C8	Cyclohexyl	0.025



soluble epoxide hydrolase inhibitor



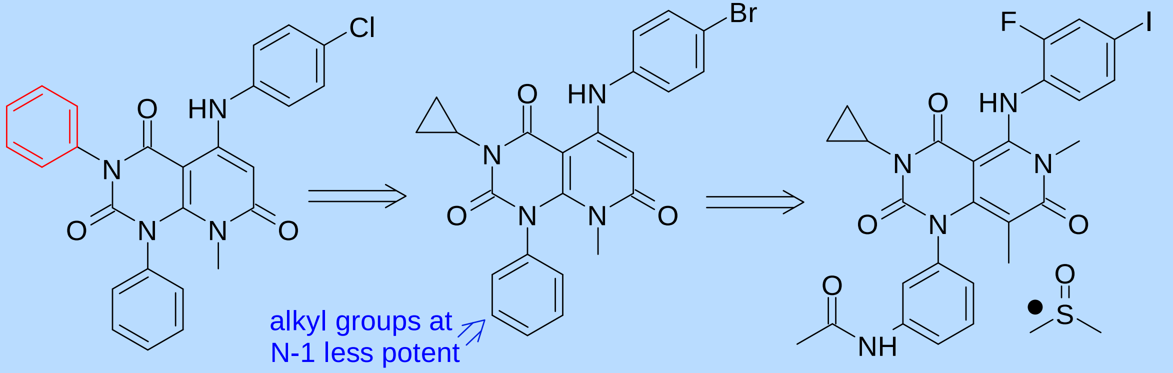
	R	K_i (μM)
C13	Phenyl	0.011
C14	Cyclohexyl	0.386



AKT1 inhibitor

H. Gunaydin & M.D. Bartberger, *ACS Med. Chem. Lett.*, 2016, **7**, 341-344; J. Madden *et al.*, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5329-5333

Cyclopropyl as Terminal Phenyl Mimic: MEK, BACE-1 Inhibitors

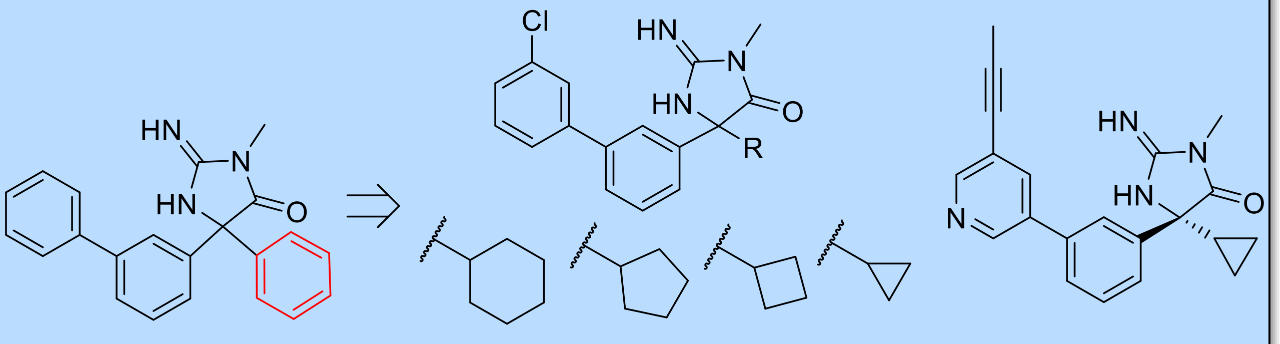


alkyl groups at N-1 less potent

HTS hit

lead compound

GSK1120212/JTP-74057
trametinib
(approved by FDA 2013)



lead

Fsp^3 = 0.09

C_6 C_5 C_4 C_3

optimized lead (OL)

Fsp^3 = 0.29

	Hit	Lead	Trametinib
ACHN cell IC_{50} (nM)	4800	1270	9.8
HT-29 cell IC_{50} (nM)	990	100	0.57
cLog *P*	6.3	5.0	5.0

Impact
↑ cell potency
↓ hydrophobicity

	Lead	Bioisosteric analogue				
	Ph	**C_6**	**C_5**	**C_4**	**C_3**	**OL**
BACE1 K_i (nM)	3300	470	470	110	47	5.4
Aβ40 IC_{50} (μM)		11	6.9	2.8	1.9	0.082
cLog *P*		5.4	4.9	4.3	3.8	2.4

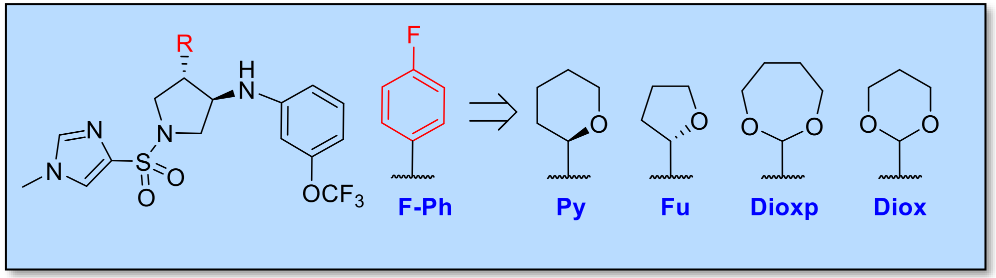
Impact
↑ biochemical potency
↓ cLog *P*
↑ Fsp^3

- MEK inhibitor with high cLog *P*
    - systematic study of the 3 aryl rings
    - cyclopropyl at imide *N* offered improved cell-based potency
    - alkyl groups at *N*-1 reduced potency
- Further modification gave trametinib
    - high melting polymorph formed
        - gave solubility/dissolution-limited absorption
    - DMSO solvate conferred targeted pharmaceutical properties
    - approved by FDA in 2013 for V600E mutated metastatic melanoma

- BACE1 inhibitors
    - all 4 cycloalkyl analogues offered improved enzyme & cell potency
    - additional optimization of *m*-Cl-phenyl ring gave optimized lead

H. Abe *et al.*, *ACS Med. Chem. Lett.*, 2011, **2**, 320-324; J.N. Cumming *et al.*, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2444-2449

Oxygenated Heterocycles as Terminal Phenyl Mimics



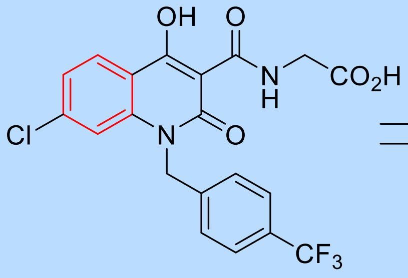
	Lead	Bioisosteric analogue			
	F-Ph	**Py**	**Fu**	**Dioxp**	**Diox**
hGlyT1 K_i (nM)	4	3	24	2	2
Efflux ratio	0.7	0.8	ND	0.9	1.1
Free B/P ratio in rat	1.3	1.0	ND	0.5	0.4
LM $Cl_{int,u}$ (L/hr/kg)					
human	227	23	17	19	6
rat	328	41	36	30	8
cLog *P*	4	2.4	2	0.6	0

Impact
↓ lipophilicity
↓ intrinsic clearance in RLM & HLM

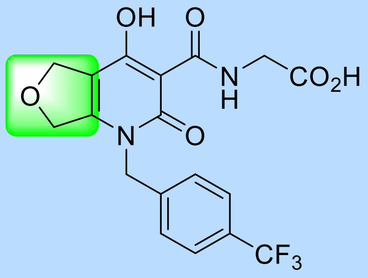
- Glycine transporter (GlyT1) inhibitors
  - phenyl lead had high clearance in HLM & RLM; rats
- Dioxane substituted effectively for Ph
  - ↓ Log *P;* ↓ clearance in HLM & RLM
  - orally bioavailable in rat: F = 35%
  - ↓ efflux ratio compared to several analogues studied
  - reasonable CNS penetrance maintained
- Dioxane incubated at pH = 1 in aqueous solution
  - stable for several days

Impact
↓ cLog *P*
↑ liver selectivity

- Prolyl hydroxylase (PHD) inhibitors
  - ↓ cLog *P*
  - ↓ permeability
  - uptake by OATP
    - liver selective



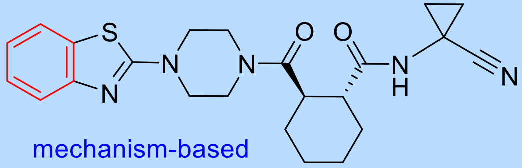
systemically active lead inhibitor of hypoxia-inducible factor prolyl hydroxylase



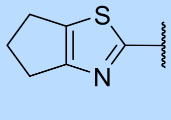
liver-selective analogue targets OATP

	Lead	Bioisostere
PHD1/2/3 EC_{50} (nM)	3.2/4.8/16	3.6/4.9/8.2
cLog *P*	2.3	1.0
P_{app} (*10^{-6} cm/s)	16	4.2
Liver/plasma ratio	3.6	16

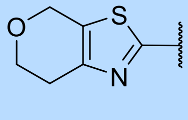
Impact
↓ lipophilicity;
↑ solubility;
↓ hERG liability



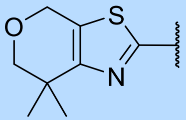
mechanism-based cathepsin K inhibitor



Cyp



Py



DiMePy

- Cat K
  - ↓ Log *D;* ↑ LLE
  - ↑ solubility
  - ↓ hERG inhibition

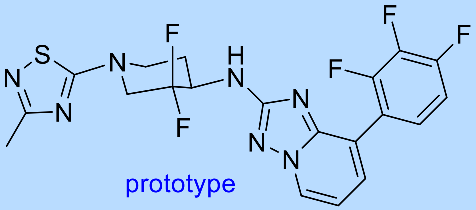
	Lead	Bioisosteric analogue		
	Ph	**Cyp**	**Py**	**DiMePy**
Cat K pIC_{50} (nM)	8.0	7.9	7.6	7.9
Log $D_{7.4}$ (LLE)	2.6 (5.4)	>3.0 <4.9)	1.4 (6.2)	2.4 (5.5)
hERG pIC_{50}	5.1		<4.0	<4.0
Sol. at pH 7.4 (μM)	1000	-	>3600	1700
HLM (μL/min/kg)	<2.0	11	<2.4	33

Y. Wang *et al., J. Med. Chem.,* 2018, **61**, 7486-7502; P. Liu *et al., ACS Med. Chem. Lett.,* 2018, **9**, 1193-1198; A.G. Dossetter *et al., Bioorg. Med. Chem. Lett.,* 2012, **22**, 5563-5568
Y.-J. Wu & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 9786-9874

Terminal Phenyl Mimics: γ-Secretase & PKC-θ Inhibitors

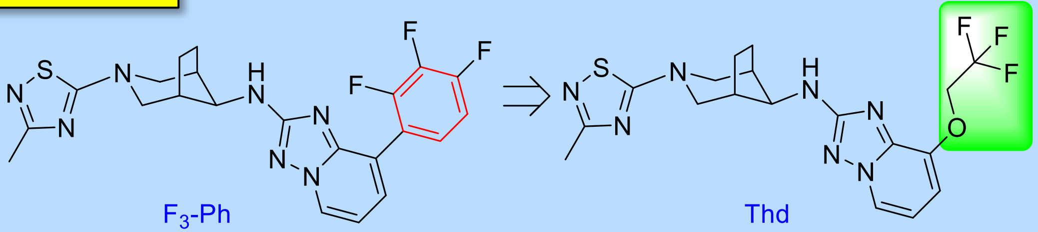
γ-Secretase Modulators

note: the piperidine & bicyclic piperidine are phenyl replacements



prototype

prototype associated with phototoxicity risk



F_3-Ph

Thd

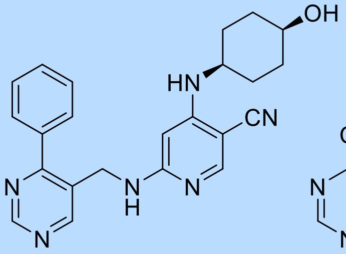
	Lead	Bioisostere
	F_3-Ph	**Thd**
h IC_{50} Aβ42 total/free (nM)	4.5/1	21/12
Mouse IC_{50} total/free (nM)	4/0.9	9/5
in vivo remaining %Aβ42 @ 1/3/10 mg/kg PO	56/27/22	59/33/15
Log *D*	4.14	3.17
Solubility (μg/mL)	3	198
PPB f.u. (h/m) (%)	0.4/0.3	2.8/10.1
IC_{50} UVA (μM)	1.67	443
Cl heps (h/m): (μL/min/Mcells)	6.6/5.4	1.3/1.4
hERG IC_{50} (μM)	<2	>10

Impact

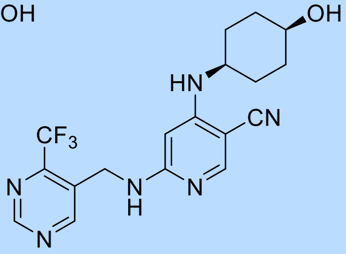
↓ phototoxicity risk
↓ lipophilicity
↑ solubility
↓ plasma protein binding
↓ protein covalent binding
↓ hERG inhibition

- γ-Secretase modulators: phototoxicity issue
  - CF_3-phenyl moiety replaced by a CF_3-CH_2-O
  - ↓ Log *D*, ↑ solubility; ↓ phototoxicity, PCB, hERG risks

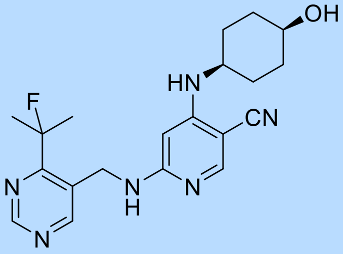
PKC-θ Inhibitors



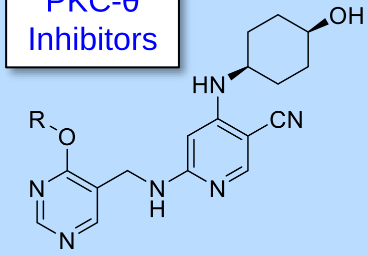
IC_{50} = 90 nM



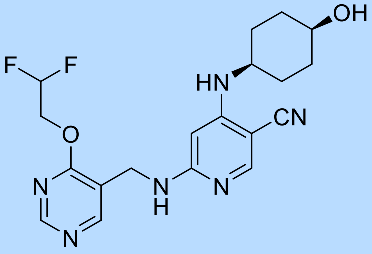
IC_{50} = 450 nM



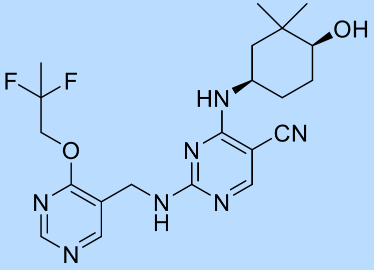
IC_{50} = 32 nM



R = CH_3: IC_{50} = 800 nM
R = tBu: IC_{50} = 200 nM



IC_{50} = 90 nM



IC_{50} = 8 nM

CC90005

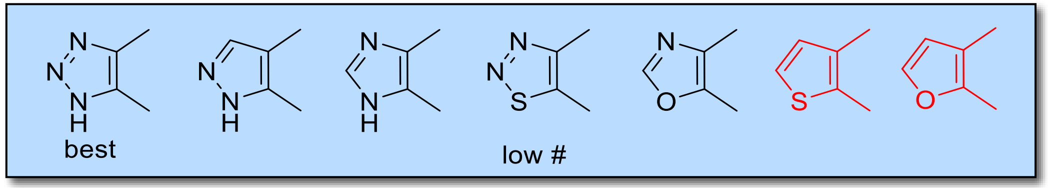
- PKC-θ inhibitors
  - CF_3, OCH_3, O-tBu poor substitutes for phenyl
  - $CF(CH_3)_2$ 3-fold more potent than Ph
- O-CH_2-CHF_2 exhibits comparable potency to phenyl
  - potency enhanced 10x by methylation
- CC90005 selected for clinical evaluation
  - highly selective over PKC-δ and 456 other kinases

R.M. Rodríguez Sarmiento *et al., J. Med. Chem.*, 2020, **63**, 8534-8553; D.S. Mortensen *et al., J. Med. Chem.*, 2021, **64**, 11886-11903

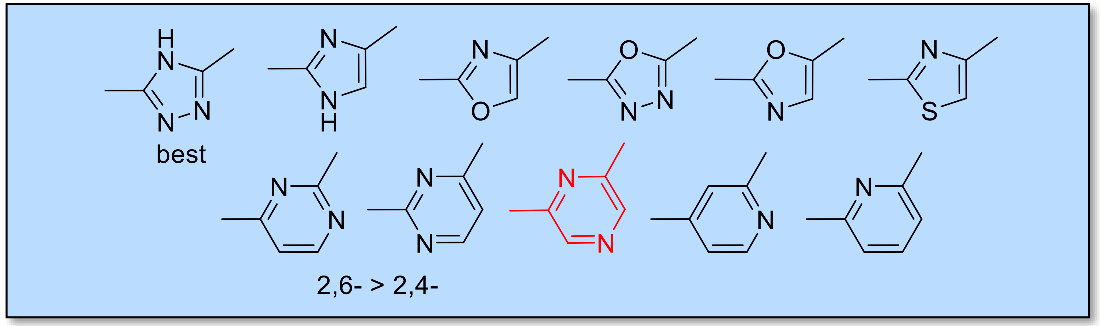
Replacements for Phenyl Ring Scaffolds

Heterocycles as Phenyl Mimics: Metabolic Stability

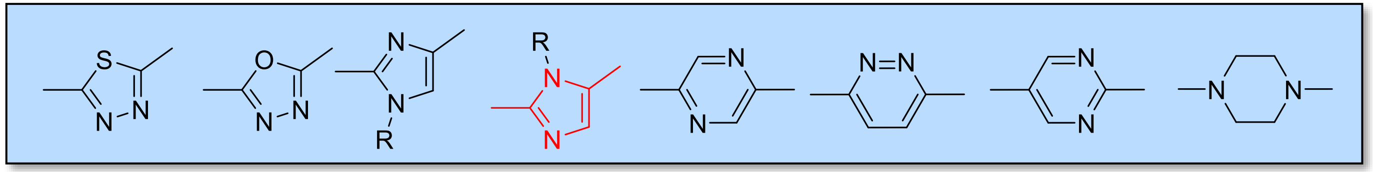
- Heterocycle replacements for a phenyl ring with higher metabolic stability
  - molecular matched pairs analysis
  - 2323 pairs evaluated with 1,2-, 1,3- & 1,4-topologies examined
  - piperazine the sole saturated ring examined in 1,4 relationship
- 1,2-topology: furan, thiophene performed poorly; pyrrole a neutral transform



- 1,3-topology: 5-membered heterocycles generally performed well
  - (3,5)-1*H*-1,2,4,-triazole & (2,4)-1*H*-imidazole best; (3,5)-pyrazine poor



- 1,4-topology: 2,5-dipyrazine the best azine; pyridazine & piperazine good
  - (2,5)-1*H*-imidazole poor



1,2-	Mean Δ*
(4,5)-1*H*-triazole	0.97
(4,5)-1*H*-pyrazole	0.73
(4,5)-1*H*-imidazole	0.65
(4,5)-1,2,3-thiadiazole	0.64
2,3-furan	-0.07
2,3-1*H*-pyrrole	-0.01
2,3-thiophene	-0.12
(2,3)-pyrazine	0.35
(4,5)-pyrimidine	0.33
(2,3)-pyridine	0.20
(3,4)-pyridine	0.15

1,4-	Mean Δ*
(2,5)-1,3,4-thiadiazole	0.65
(2,4)-1*H*-imidazole	0.64
(2,5)-1,3,4-oxadiazole	0.45
(2,5)-1*H*-imidazole	-0.33
(2,5)-pyrazine	0.46
(3,6)-pyridazine	0.25
(2,5)-pyrimidine	0.19
(2,5)-pyridine	0.11
N,*N*-piperazine	0.30

1,3-	Mean Δ*
(3,5)-1*H*-1,2,4-triazole	0.91
(2,4)-1*H*-imidazole	0.87
(2,4)-oxazole	0.80
(2,5)-1,3,4-oxadiazole	0.62
(2,5)-oxazole	0.59
(3,5)-isoxazole	0.47
(3,5)-1,2,4-oxadiazole	0.39
(2,5)-oxazole	0.12
(2,4)-thiazole	0.04
(2,6)-pyrimidine	0.43
(2,4)-pyrimidine	0.10
(2,4)-pyridine	0.23
(2,6)-pyridine	0.17
(3,5)-pyridine	0.14
(3,5)-pyrazine	-0.19

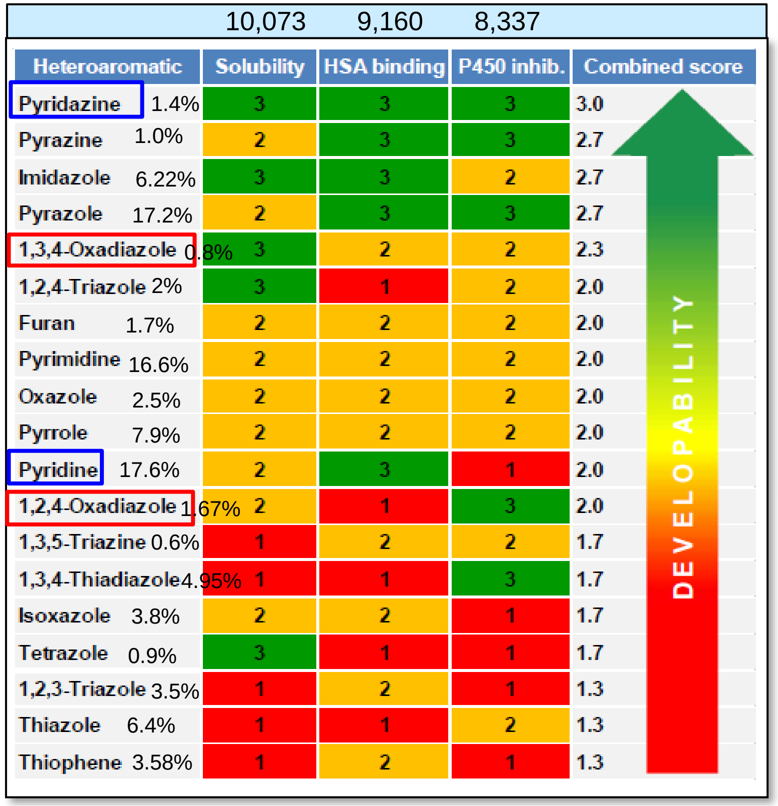
*Mean(Δ(log$_{10}$ Mean Cl$_{\text{ints}}$ for transform))

A.G. Dossetter *et al.*, *Med. Chem. Commun.*, 2012, **3**, 1164-1169

See also T.R. Ritchie & S.J.F. Macdonald, *Eur. J. Med. Chem.*, 2016, **124**, 1057-1068 for ADME & terminal phenyl replacements; G. Chang *et al., Bioorg. Med. Chem.*, 2017, **25**, 381-388

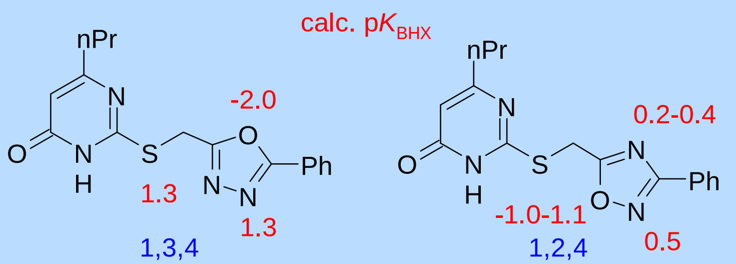
Heterocycles Have Different Pedigrees

- ◆ Heterocycles are a mainstay of drug design
    - - 5- & 6-membered rings common scaffolds
    - - can address a range of problems
- ◆ Key properties:
    - - can be basic: pyridine, imidazole, triazole,
    - - H-bond acceptor
    - - H-bond donor: N-H, O-H, C-H
    - - electron withdrawing properties, dipoles
- ◆ Heterocycle properties readily modulated
    - - effect of substituents on heterocycle
    - - reciprocal effects on substituent
- ◆ Heterocycle identity will modulate effects
    - - impact on geometry, conformation & potency
- ◆ Silhouettes similar (distorted by presence of S)
    - - but…. properties can be very different
        - - electronic
        - - physicochemical
        - - biological
        - - developability
    - - 1,3,4-oxadiazoles vs 1,2,4-isomers
    - - pyridazines vs pyridines



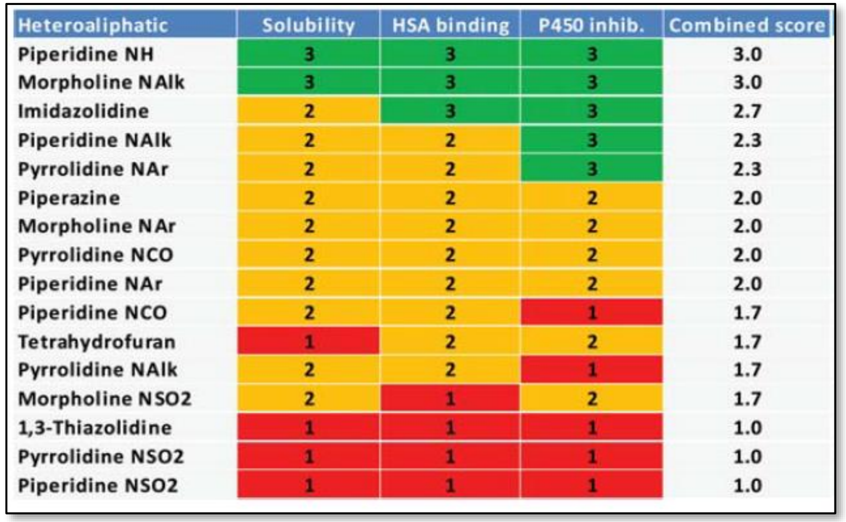
	10,073	9,160	8,337	
Heteroaromatic	**Solubility**	**HSA binding**	**P450 inhib.**	**Combined score**
Pyridazine 1.4%	3	3	3	3.0
Pyrazine 1.0%	2	3	3	2.7
Imidazole 6.22%	3	3	2	2.7
Pyrazole 17.2%	2	3	3	2.7
1,3,4-Oxadiazole 0.8%	3	2	2	2.3
1,2,4-Triazole 2%	3	1	2	2.0
Furan 1.7%	2	2	2	2.0
Pyrimidine 16.6%	2	2	2	2.0
Oxazole 2.5%	2	2	2	2.0
Pyrrole 7.9%	2	2	2	2.0
Pyridine 17.6%	2	3	1	2.0
1,2,4-Oxadiazole 1.67%	2	1	3	2.0
1,3,5-Triazine 0.6%	1	2	2	1.7
1,3,4-Thiadiazole 4.95%	1	1	3	1.7
Isoxazole 3.8%	2	2	1	1.7
Tetrazole 0.9%	3	1	1	1.7
1,2,3-Triazole 3.5%	1	2	1	1.3
Thiazole 6.4%	1	1	2	1.3
Thiophene 3.58%	1	2	1	1.3

% of 10,073



1,3,4
Log D = 2.2
Sol. = 81 μM
stronger calcd. dipole: 3.37 *D*
stronger H-bond accpetor

1,2,4
Log D = 3.1
Sol. = 5 μM
calcd. dipole: 1.48 *D*



Heteroaliphatic	Solubility	HSA binding	P450 inhib.	Combined score
Piperidine NH	3	3	3	3.0
Morpholine NAlk	3	3	3	3.0
Imidazolidine	2	3	3	2.7
Piperidine NAlk	2	2	3	2.3
Pyrrolidine NAr	2	2	3	2.3
Piperazine	2	2	2	2.0
Morpholine NAr	2	2	2	2.0
Pyrrolidine NCO	2	2	2	2.0
Piperidine NAr	2	2	2	2.0
Piperidine NCO	2	2	1	1.7
Tetrahydrofuran	1	2	2	1.7
Pyrrolidine NAlk	2	2	1	1.7
Morpholine NSO2	2	1	2	1.7
1,3-Thiazolidine	1	1	1	1.0
Pyrrolidine NSO2	1	1	1	1.0
Piperidine NSO2	1	1	1	1.0

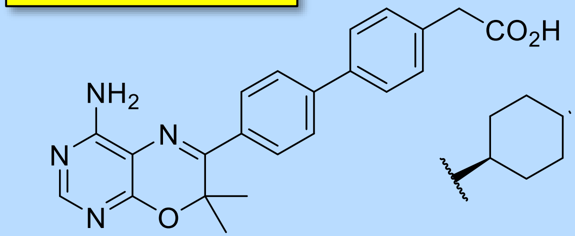
T.R. Ritchie *et al*., *Drug Discov. Today*, 2009, **14**, 1011-1120; 2011, **16**, 164-171; *Med. Chem. Commun*, 2012, **3**, 1062-1069
J. Boström *et al., J. Med. Chem.*, 2012, **55**, 1817-1830; C. Wermuth, *Med. Chem. Commun*, 2011, **2**, 935-941; N.A, Meanwell, *Med. Chem, Res*., 2023, *in press*

para-Substituted Phenyl Mimetics

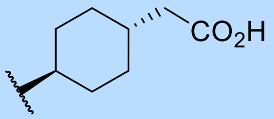
Phenyl Mimics: Cyclohexanes & Bicyclo[2.2.2]octanes

Impact
↑ cellular activity

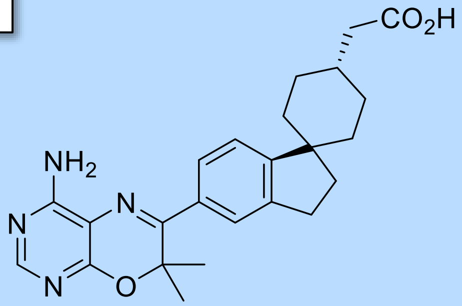
Amgen



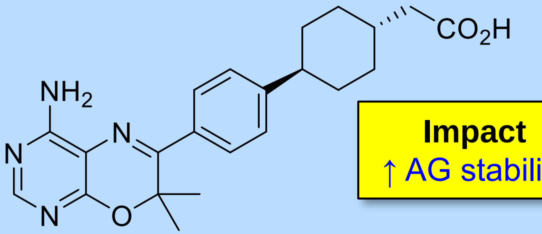
hDGAT-1 IC_{50} = 6 nM
DGAT-1 cellular EC_{50} >3 μM



hDGAT-1 IC_{50} = 6 nM
DGAT-1 cellular EC_{50} = 40 nM

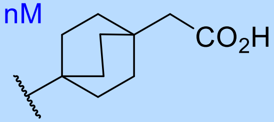


hDGAT-1 IC_{50} = 4 nM
DGAT-1 cellular EC_{50} = 3 nM
clinical candidate



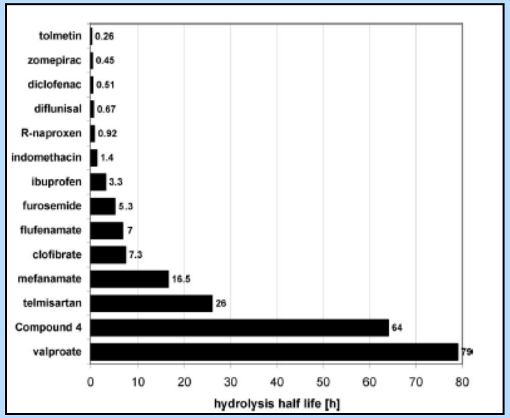
hDGAT-1 IC_{50} = 15 nM

Impact
↑ AG stability



hDGAT-1 IC_{50} = 15 nM

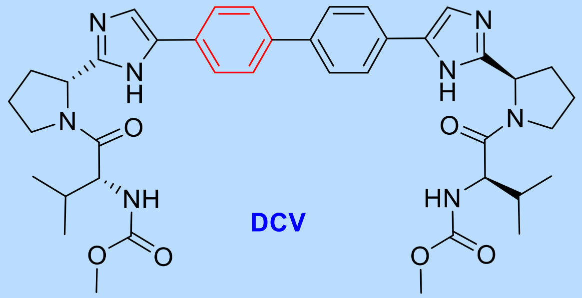
Astra-Zeneca



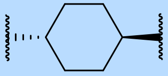
Hydrolysis $t_{1/2}$ at 37^{o}C in phosphate buffer at pH = 7.4

- ◆ Amgen hDGAT inhibitors: phenyl lead potent *in vitro*
  - poor activity in cell-based assay
  - cyclohexyl offers equivalent biochemical potency
    - much enhanced cell-based potency
- ◆ AZ DGAT-1 inhibitors: *trans*-cyclohexane potent *in vitro*
  - blocks triglyceride synthesis and storage
- ◆ Acyl glucuronide the 1^{o} metabolite
  - added bulk to cyclohexane to increase stability of the AG
  - $t_{1/2}$ = 64 h in phosphate buffer: <15% rearrangement over 80 h
- ◆ HCV NS5A inhibitors
  - cyclohexyl & BCO analogues of daclatasvir: 6-15x less potent
  - see improved solubility properties, higher %F in rats

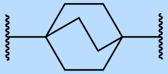
Impact
↑ solubility



DCV



Cy



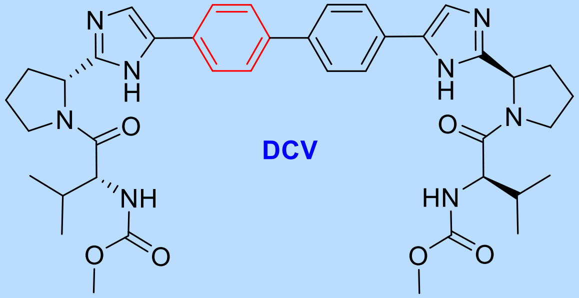
BCO

	Lead	Isostere	
	DCV	**Cy**	**BCO**
HCV GT-1a EC_{50} (nM)	0.14	2.0	1.4
HCV GT-1b EC_{50} (nM)	0.023	0.05	0.06
Sol. pH 7.4 (μg/mL)	6.8	66.3	45
F (rats) (* = BMS lit.)	(50%)*	44%	124%

A.M. Birch *et al*., *J. Med. Chem.,* 2009, **52**, 1558-1568; B.M. Fox *et* al., *J. Med. Chem.*, 2014, **57**, 3464−3483; M. Zhong *et al*., *Bioorg. Med. Chem. Lett*., 2014, **24**, 5731-5737

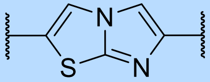
para-Phenyl Replacements in HCV NS5A Inhibitors

Impact
structural novelty

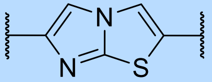


DCV

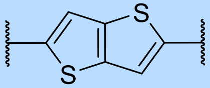
GT-1a EC_{50} = 50 pM
GT-1b EC_{50} = 9 pM



GT-1b EC_{50} <1 nM

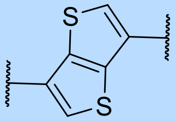


GT-1b EC_{50} <1 nM

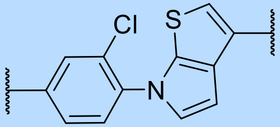


GT-1b EC_{50} <1 nM

GT-1b EC_{50} <1 nM

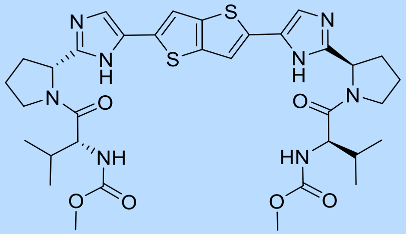


GT-1a, 1b, 2a, 4a EC_{50} <100 pM
GT-3a EC_{50} = 100 pM to 1 nM

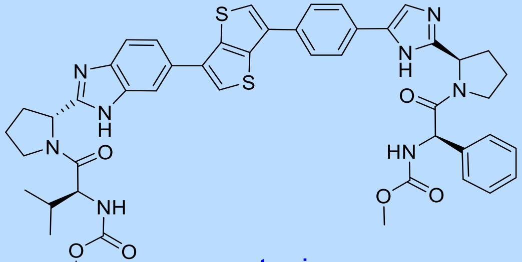


GT-1b EC_{50} <1 nM

- ◆ Inhibitors of HCV NS5A replication complex
  - daclatasvir (DCV) the prototype
  - biphenyl moiety is a scaffold that projects the Pro-Val termini
- ◆ Replacements for the biphenyl a fertile area of research endeavor
  - these fused fully aromatic systems are planar with defined vectors
  - examined as phenyl replacements in complementary topologies
- ◆ Provided highly potent antiviral agents
  - less effective as a biphenyl replacement
  - too short: inadequate pharmacophore separation
- ◆ Pyrrolidino-azoles offer similar planar topography & vectors
  - have been deployed as bioisosteres of piperazines
  - distance closer to that of a 4-substituted piperidine/piperazine or aryl ring

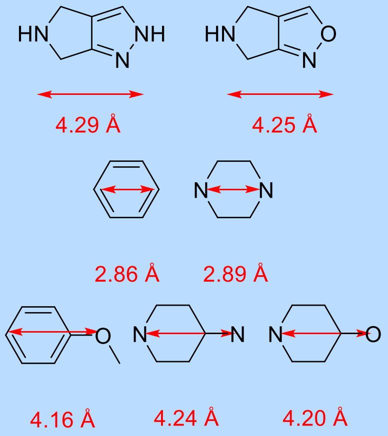


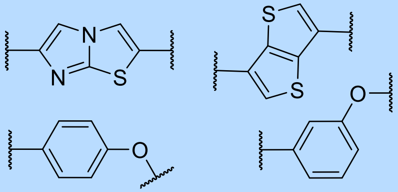
GT-1b EC_{50} <100 pM
GT-1a EC_{50} = 10-100 nM



samatasvir
GT-1a, 1b, 2a, 3a, 4a, 5a EC_{50} = 2-24 pM

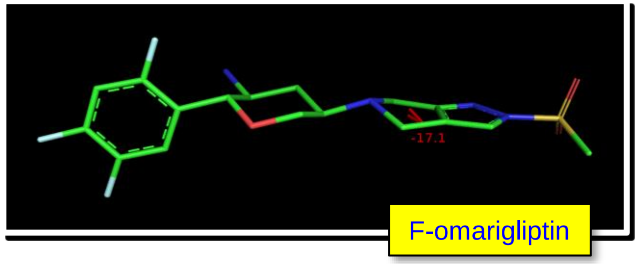
samatasvir advanced to clinic



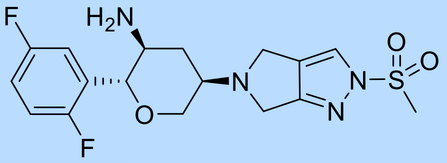


p-phenoxy mimic

m-phenoxy mimic



F-omarigliptin



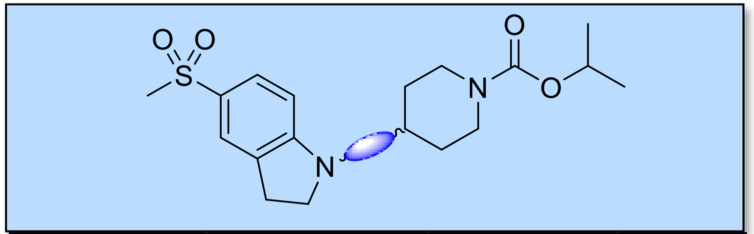
QW approved in Japan

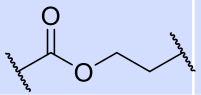
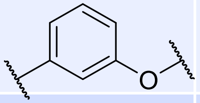
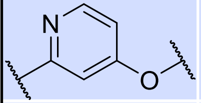
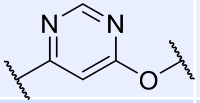
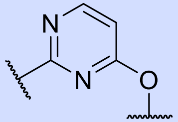
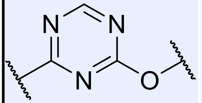
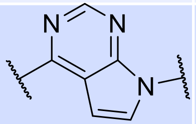
omarigliptin

piperazine isostere

B.C. Dousson *et al*., WO 2021/075615 A1; WO 2012/135581 A1; J.P. Bilello *et al*., *Antimicrob. Agents Chemother*., 2014, **58**, 4431-4442
N.A. Meanwell & R. Sistla, *Adv. Het. Chem*. 2020, **134**, 31-100; Piperazine isostere: V.J. Santora *et al., J. Med. Chem*. 2018, **61**, 6018-6033

Heterocycle Linkers in GPR119 Agonists

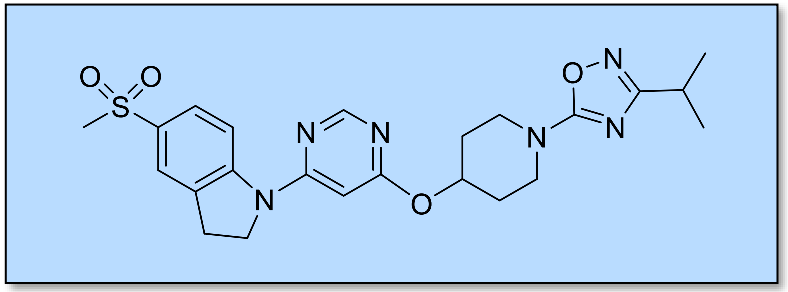


Linker	EC$_{50}$ (nM)	Log $D_{7.4}$	LLE
	68	3.1	4.1
	490	3.5	2.8
	87	3.0	4.1
	17	3.1	4.7
	520x 8,800	3.5	1.6
	520	2.6	3.7
	16 (t-Boc deriv)	3.2	4.6

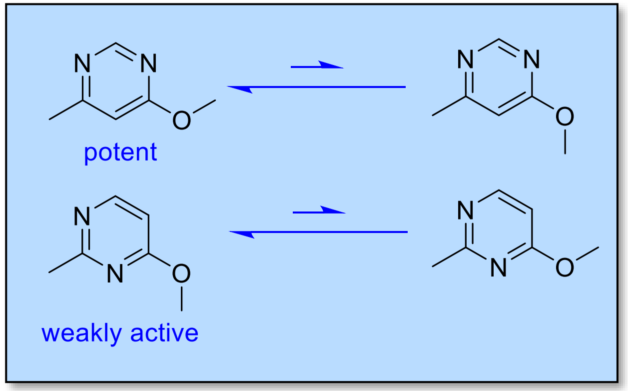
- ◆ GPR119 agonists
  - - increases cAMP in pancreatic β-cells
    - - stimulates insulin release
- ◆ Linker variation examined
  - - acyclic & cyclic moieties explored
- ◆ Carbamate potent
  - - C=O suggested to act as a HBA
  - - SAR indicated preference for a planar linker
- ◆ Phenyl spacer 7-fold weaker than carbamate
  - - 2-fold more potent than simple C4 alkyl chain
  - - provided insight into preferred topology

Impact
↑ potency; ↓ lipophilicity; ↑ LLE

- ◆ Pyridine & 4,6-pyrimidine enhanced potency
  - - *N* atoms mimic C=O as HBA
- ◆ 2,4-Pyrimidine isomer 520x weaker
  - - explained by conformational preferences
- ◆ Triazine 30x weaker than pyrimidine
  - - conflicted topology?
- ◆ Pyrrolo[2,3-*d*]pyrimidine ≡ to pyrimidine
  - - recapitulates preferred vector
  - - confirms topological arguments



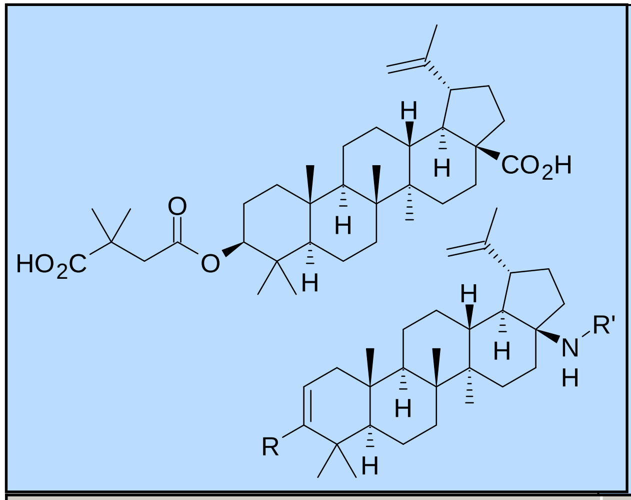
Optimal analogue
Active *in vivo* in glucose tolerance tests:
Lowered plasma glucose excursion
Reduced glucose-dependent insulin secretion

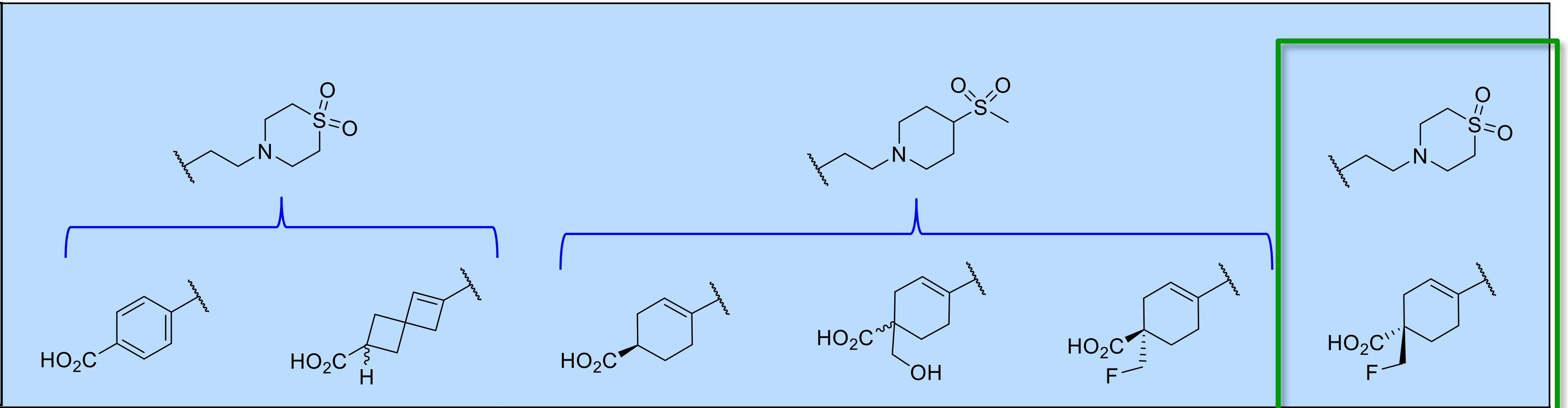


preferred conformational topologies

K. Sato *et al., Bioorg. Med. Chem.*, 2014, **22**, 1649-1666; C.D. Blundell *et al., Prog. Med. Chem.*, 2016, **55**, 45-147; R.-J. Chien and E.J. Corey, *Org. Lett.*, 2010, **12**, 132-135

p-Phenyl Mimics in HIV-1 Maturation Inhibitors





WT/ΔV370 EC_{50} (nM)	2/13	1.5/2	1/4	1/1	2/8	2/5
WT (HSA) EC_{50} (nM)	10	7	7	13	15	13
V362I/V370A EC_{50} (nM)	🟥	48	10	1	-	2
T332S/V362I/prR41G EC_{50} (nM)	🟥	365	21	1	7	7
Glucuronide reactivity			reactive	non-reactive	non-reactive	non-reactive
Rat PK PO AUC (nM*h)	13,743	12,614	8,594	2,396	25,250	7,368
Hepatotoxicity					🟥	

Fipravirimat

- Mix and match best C-3 and C-17 amines substituents
  - C-3 α-fluoromethyl cyclohexene & C-17 *endo*- and *exo*-cyclic sulfones have best profiles

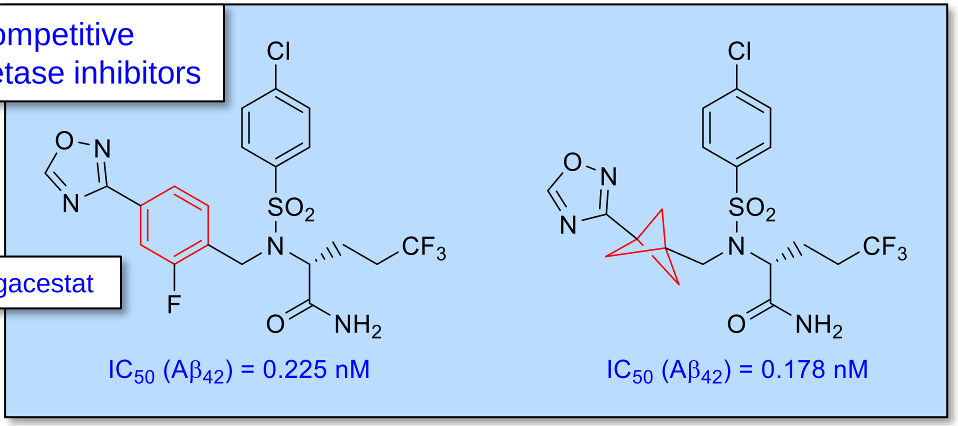
Fipravirimat (GSK3640254) presented the best combination of virology, safety and PK profiles

Impact
improved virological profile

J.J. Swidorski *et al., Bioorg. Med. Chem. Lett.*, 2021, **36**, 127823; A. Regueiro-Ren *et al., J. Med Chem.*, 2022, **65**, 11927-11948

Bicycles as *para*-Substituted Phenyl Mimics in γ-Secretase Inhibitors

Competitive γ-secretase inhibitors



avegacestat

IC_{50} ($A\beta_{42}$) = 0.225 nM

IC_{50} ($A\beta_{42}$) = 0.178 nM

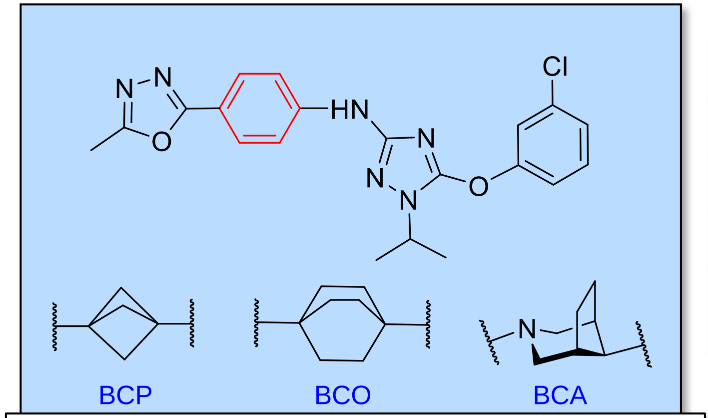
- Bicyclopentanes as phenyl mimics pioneered by Pellicciari in 1990s
- Examined in γ-secretase inhibitors: fully preserves potency
  - mimicry confirmed by single crystal X-ray structures
- Lipophilicity reduced
  - solubility & metabolic stability in HLM improved
  - membrane permeability enhanced

	Solubility (μM)		Perm 10^{-6} cm/s
	Kinetic	Therm	
Ph	0.60	1.70	5.52
	216	19.7	19.3

Impact
↑ solubility;
↑ membrane permeability

All efficiency metrics improved

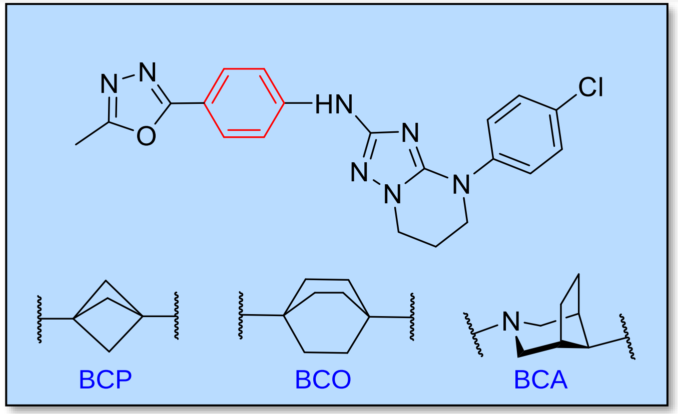
	pIC_{50}	Elog*D*	LE	LLE	LLE_{AT}	LELP	Ar-sp^3	Fsp^3
Ph	-9.65	4.70	0.28	4.76	0.30	16.6	12	0.25
	-9.75	3.80	0.30	6.55	0.39	12.5	1	0.52



Allosteric γ-secretase inhibitors (modulators)

	Lead	Analogue		
	Ph	BCP	BCO	BCA
EC_{50} (nM)	510	214	118	42
Log *D*	>4	4.1	4.1	3.6
Solubility (μg/mL)	<0.1	88	15	104

Impact
↓ Log *P*
↑ solubility



	Lead	Analogue		
	Ph	BCP	BCO	BCA
EC_{50} (nM)	95	777	114	34
Log *D*	3.2	2.4	3.1	2.7
Solubility (μg/mL)	<0.1	167	132	233

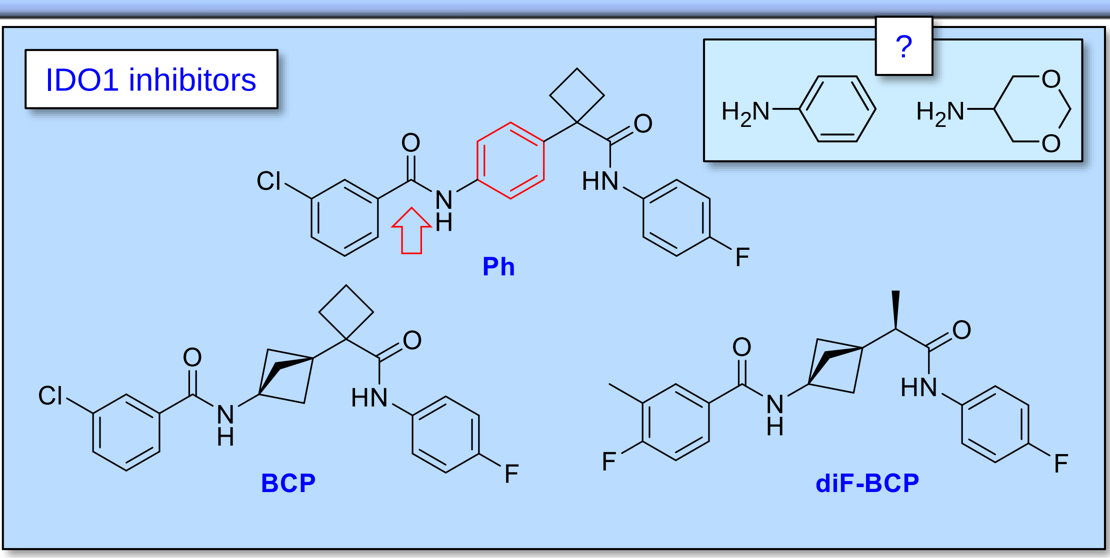
BCA>BCO>BCP

- Allosteric modulators of γ-secretase
  - several series based on aniline substituent variation
- Effect of sp^3-based phenyl mimics on potency context-dependent
  - bicyclic amine performs optimally in both series: BCA>BCO>BCP
  - solubility uniformly enhanced by all phenyl mimics

R. Pellicciari *et al.*, *J. Med. Chem.*, 1996, **39**, 2874-2876; *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1569-1574; *Bioorg. Med. Chem.*, 2001, **9**, 221-227
A.F. Stepan *et al.*, *J. Med. Chem.*, 2012, **55**, 3414-3424; H. Ratni *et al., RSC Med. Chem.*, 2021, **12**, 758-766

Aniline Isosteres in IDO1 and MDM2/p53 Inhibitors

IDO1 inhibitors

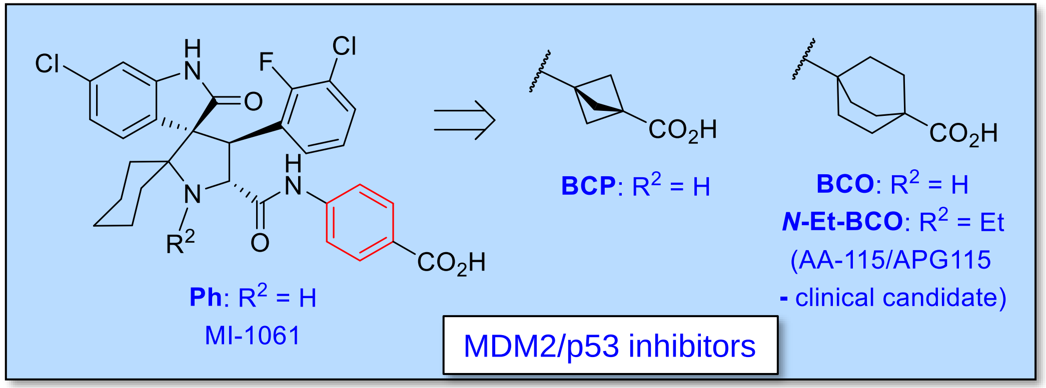


	Lead	Bioisosteric analogue	
	Ph	**BCP**	**diF-BCP**
HeLa EC_{50} (nM)	1.7	5.2	1.9
hWB EC_{50} (nM)	30	ND	36
ALog *P*	5.3	4.1	3.3
Rat hepatocyte Cl_{int} (mL/min/kg)	1935		195
Rat *in vivo* Cl_u (mL/min/kg)	4371		37

Impact
↑ metabolic stability
↓ amide hydrolysis to mitigate aniline release
↓ lipophilicity

- ◆ IDO1 inhibitor discovered by an affinity MS screen
  - poor metabolic stability *in vitro* & *in vivo* in rat
  - mCl-benzamide cleavage to release aniline major pathway
- ◆ BCP an excellent phenyl bioisostere from X-ray cocrystals
  - improved PK properties: F = 83%, 79% in rat, dog

- ◆ Inhibitor of MDM2/p53 association
  - BCP performed poorly in cell-based assay
  - BCO comparable to phenyl prototype
  - active *in vivo* in SJSA-1 xenograft model
- ◆ Alrizomadlin (AA-115/APG115) advanced into clinical trials
  - orphan drug status for malignant melanoma, retinoblastoma, soft tissue sarcoma on July 14th, 2021



Ph: R^2 = H
MI-1061

BCP: R^2 = H

BCO: R^2 = H
***N*-Et-BCO**: R^2 = Et
(AA-115/APG115
- clinical candidate)

MDM2/p53 inhibitors

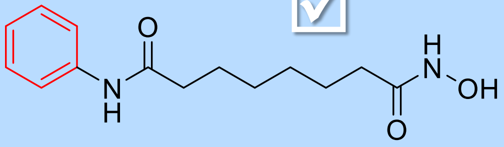
	Lead	Bioisosteric analogue		
	Ph	**BCP**	**BCO**	**N-Et-BCO**
MDM2 IC_{50} (nM)	4.4	6.4	3.7	3.8
SJSA-1 EC_{50} (nM)	100	542	89	60
rat F (25 mg/kg PO)	31.5	NT	35.0	40.3
antitumor efficacy (% regression)	86%	NT	0%	100%

MDM2 = Murine Double Minute 2

Impact
↑ oral PK
no potential for aniline release

Q. Pu *et al., ACS Med. Chem. Lett.*, 2020, **11**, 1548-1554; A. Aguilar *et al., J. Med. Chem.*, 2014, **57**, 10486-10498; *J. Med. Chem.*, 2017, **60**, 2819-2839

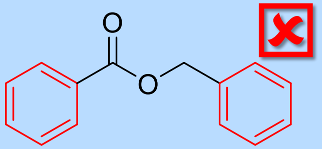
Cubane as a *para*-Phenyl Mimic: Terminal & Scaffold



☑

vorinostat (SAHA)

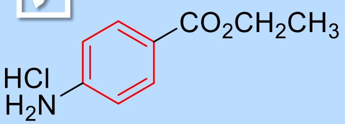
HDAC inhibitor
epigenetic modulator, cancer



☒

benzyl benzoate

scabies & lice

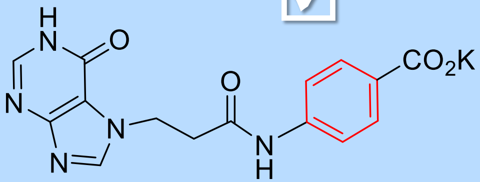


☑

benzocaine

local anesthetic

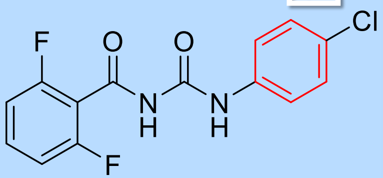
☑



leteprinim

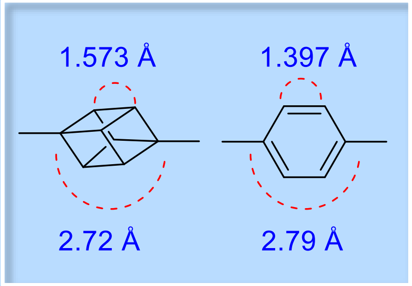
nerve growth stimulant

☑

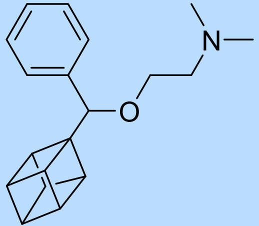


diflubenzuron

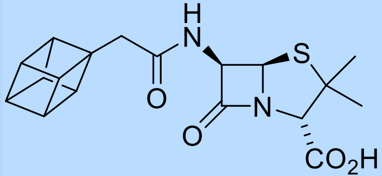
insecticide



diphenhydramine: antihistamine

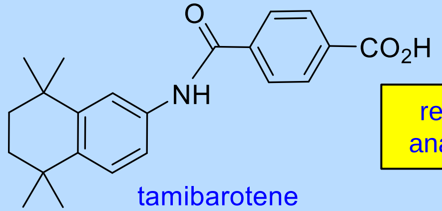


unstable,
accelerated by H^+



unstable
could not isolate

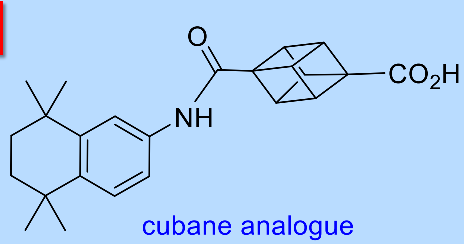
penicillin G: antibiotic



retinoid analogue

tamibarotene

☒

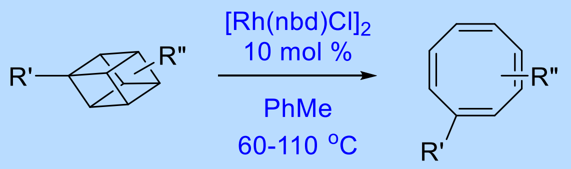


cubane analogue

(µM)	MCF7	MM96L	HT-29	HeLa	Log *P*
Ph	<0.5	25	41	48	3.49
CUB	30	70	251	107	2.99

- ◆ C-H bond dissociation energy of cubane = 104 kcal/mol: due to high s character
- ◆ SAHA analogue ≡ potency as inhibitor of tumor cell growth
- ◆ Cubane analogue of leteprinim more effective at promoting neurite outgrowth
- ◆ Benzocaine and cubacaine similarly potent at blocking nociception in rat
- ◆ Cubane analogue of diflubezuron a more effective insecticide: attributed to increased metabolic stability
- ◆ All 3 analogues of benzyl benzoate poorer at killing scabies mite
- ◆ Cubane a poor replacement for terephthalic acid in the retinoid analogue tamibarotene; lowered Log *P*
- ◆ Several cubane analogues of drug molecules proved to be unstable e.g. diphenhydramine
- ◆ Cubanes and bicycloalkanes offer enhanced solubility and reduced non-specific binding compared to a phenyl

- ◆ Postulated as a potential benzene mimic by Eaton in 1992
- ◆ Validated by Williams in 2016 (*ACIE* 2016, **31**, 1421)
- ◆ Additional limitations: Williams 2019 (*OBC* 2019, **17**, 6790)
  - advanced COT as potential phenyl mimics

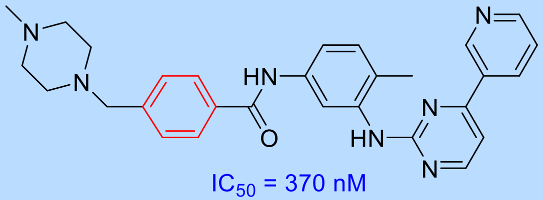


P.E. Eaton, *ACIE*, 1992, **31**, 1421-1436; C.M. Williams *et al. ACIE*, 2016, **55**, 3580-3585; *Org. Biomol. Chem.*, 2019, **17**, 6790-6798; *Chem. Eur. J.*, 2019, **25**, 2729-2734
Y.P. Auberson *et al.*, *ChemMedChem*, 2017, **12**, 590-598; D.W.C. Macmillan *et al.*, *Nature*, 2023, DOI:10.1038/s41586-023-06021-8

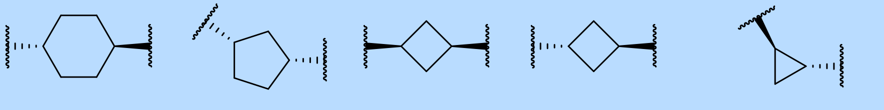
para-Substituted Phenyl Rings can be Critical Scaffolding Elements

In some cases, replacing phenyl rings has been unsuccessful

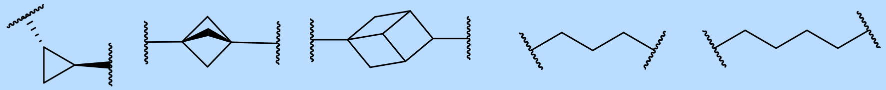
imatinib analogues



IC_{50} = 370 nM
Sol. = 30.7 µM at pH = 7.4

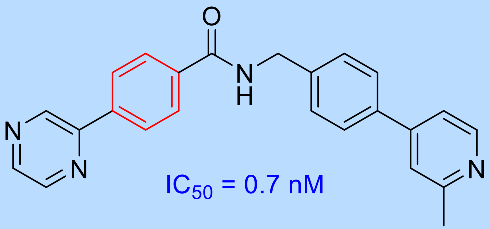


Sol. = 56 µM
Sol. = 885 µM
Sol. = 2000 µM
Sol. = 3720 µM

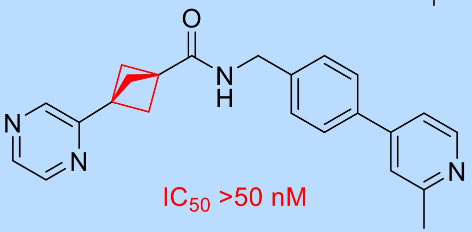


Sol. = 2680 µM
Sol. = 356 µM

all IC_{50} >1 µM



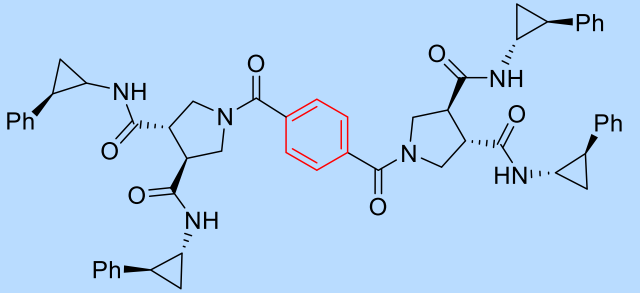
IC_{50} = 0.7 nM



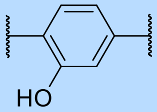
IC_{50} >50 nM

Wnt pathway inhibitor
BCP analogue inactive in a cell-based Wnt reporter assay

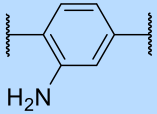
diprovicim analogues



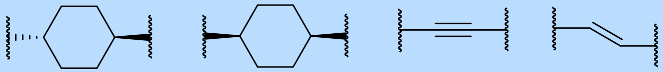
EC_{50} (THP-1) = 0.11 nM



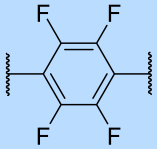
EC_{50} = 0.2 nM



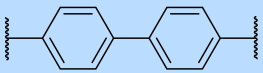
EC_{50} = 1 nM



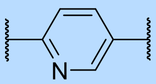
EC_{50} >5000 nM



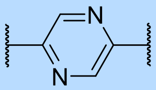
EC_{50} = 110 nM



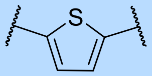
EC_{50} = 90 nM



EC_{50} = 4 nM



EC_{50} = 130 nM



EC_{50} = 350 nM

◆ Imatinib (Gleevec®) analogues
  - none of 11 phenyl replacements effective: IC_{50} >1 µM & 40 kinases
  - cubane analogue exhibited detectable effect in cell-based assay

◆ X-ray data suggest improper alignment of key interactions
  - disruption of piperazine *N* atom which engages Ile_{360}

◆ All isosteres tested showed enhanced aqueous solubility
  - all demonstrated lower cLog $D_{7.4}$ values

◆ Diprovicims discovered as TLR-1/2 agonists by phenotypic screening
  - stimulation of TNF-α production in human THP-1 macrophages
  - promote TLR1/2 association

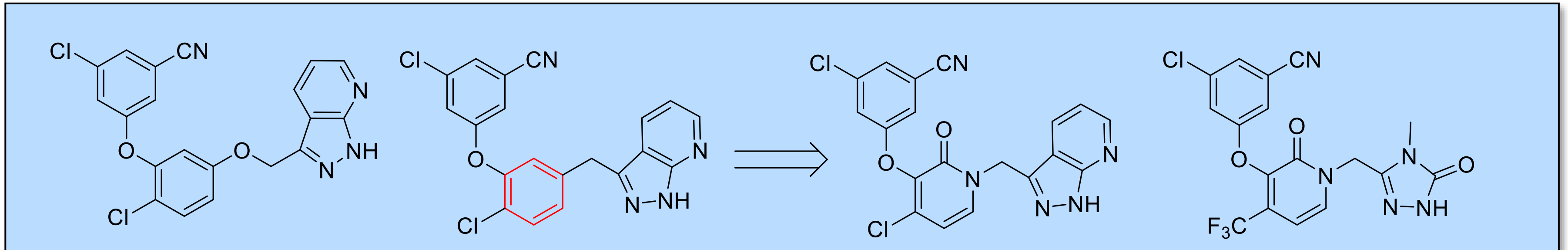
◆ Activity highly sensitive to the identity of the amide terminus
  - 4-F-phenethyl active but phenethyl not

◆ Core terephthalic acid scaffold also a critical scaffolding element
  - all replacements studied eroded potency

K.C. Nicolaou, A Stepan *et al.*, *ChemMedChem*, 2016, **11**, 31-37; N.T. Thirumoorthi *et al.*, *Org. Biomol. Chem.*, 2016, **14**, 9485-9489; D.L. Boger *et al.*, *JACS*, 2018, **140**, 14440−14454

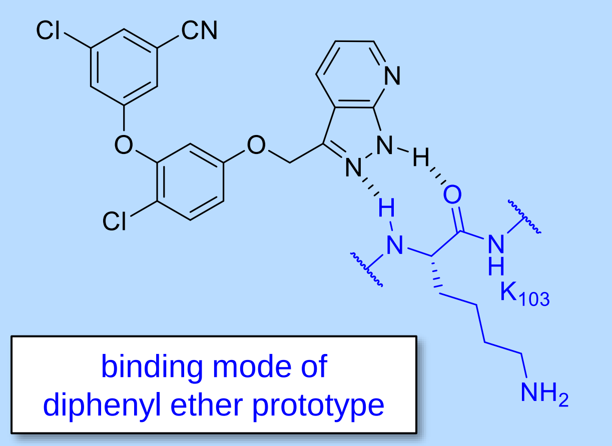
meta-Substituted Phenyl Mimetics

Pyridones as *meta*-Phenyl Mimics in HIV NNRTIs - Doravirine



Ph **MK-6186** **Py** **MK-1439**

doraviring

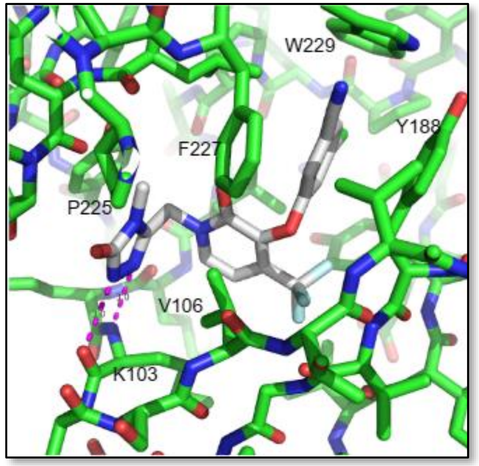


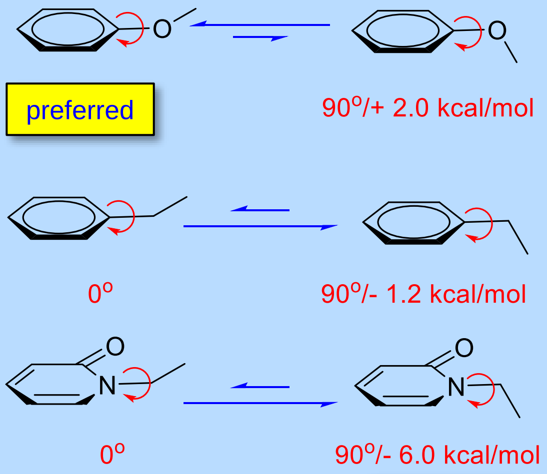
binding mode of
diphenyl ether prototype

	Virus	Lead		Bioisosteric analogue	
		Ph	**MK-6186**	**Py**	**MK-1439**
HIV-1 inhibition CIC_{95} (nM)	WT	10	22	12	19
	K103N	15	211	20	42
	Y181C	22	NT	70	25

Impact
recapitulating preferred conformation to maintain potency;
↑ PK;
↑ solubility

- Lead HIV-1 NNRTI: azaindazole engages K_{103} in a dual H-bonding interaction
- OCH_2 linker to CH_2 preserved activity toward WT, mutants in enzyme assay
  - but … activity of MK-6186 toward the K103N mutant in cell culture lower
- Sought replacements for phenyl ring (benzyl) to enhance potency & PK
  - modeling indicated importance of orthogonal conformation of Ar-CH_2
- *N*-alkyl pyridones offered targeted polarity
  - modeled conformational landscape: strong preference for orthogonality
  - non-bonded interactions between C=O & *N*-substituent
  - mimicked conformation preferred by Ph-CH_2CH_3
- Triazolone enhanced solubility from 1 μM to 45 μM
  - improved pharmaceutical properties & PK profile
  - doravirine approved by the FDA in August, 2018

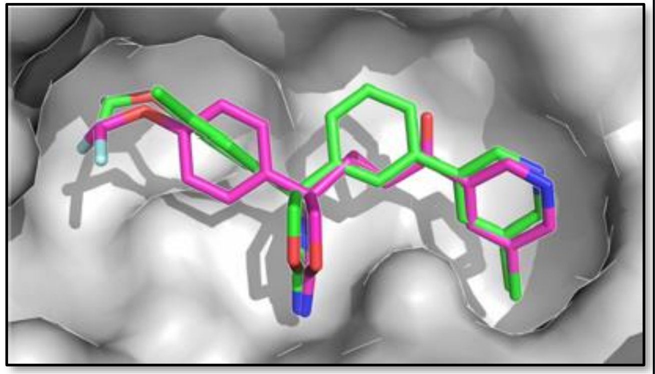




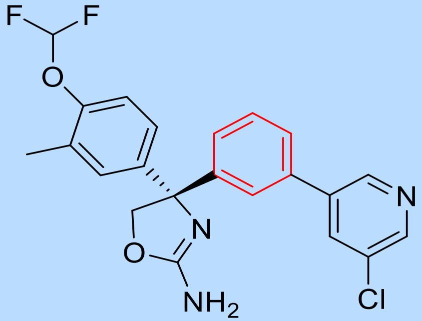
2-pyridone geometry mimics phenyl-alkyl

R. Gomez *et al.*, *J. Med. Chem.*, 2011, **54**, 7920-7933; *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7344-7350; B. Côté *et al.*, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 917-922
Y. Zhang & A. Pike, *Bioorg. Med. Chem. Lett.*, 2021, **38**, 127849

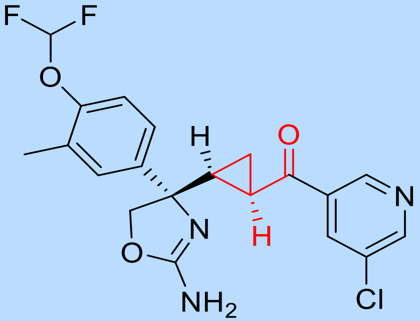
meta-Substituted Phenyl Mimics in BACE-1 Inhibitors



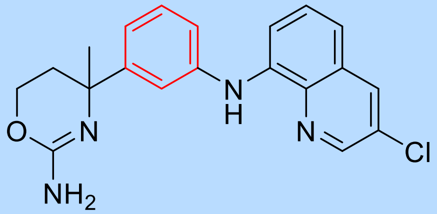
pyridyl-phenyl series



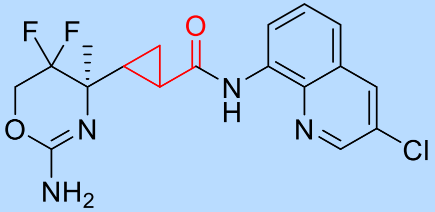
BACE1 IC_{50} (cell) = 145 nM
Log $D_{(pH7.4)}$ = 4.0
$Soly_{(pH6.5)}$ = <1 μg/mL



BACE1 IC_{50} (cell) = 87 nM
Log $D_{(pH7.4)}$ = 3.1
$Soly_{(pH6.5)}$ = 109 μg/mL



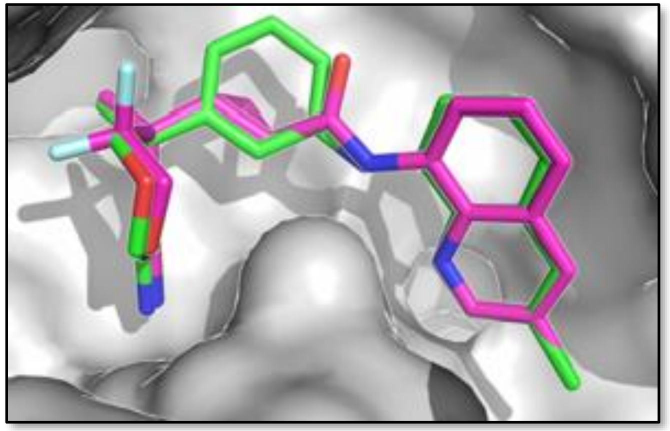
BACE1 IC_{50} (cell) = 250 nM
$Soly_{(pH6.5)}$ = <1 μg/mL



BACE1 IC_{50} (cell) = 420 nM
$Soly_{(pH6.5)}$ = 64 μg/mL

	Phenyl	cPr
IC_{50}	145 nM	87 nM
pIC_{50}	6.84	7.1
LE	0.32	0.34
LLE	2.8	4.0
LLE_{AT}	0.24	0.30
LELP	12.5	9.0
Fsp^3	0.18	0.35

- BACE1 inhibitors with poor solubility
- Searched CSD for *meta*-phenyl vector mimetics
  - - *trans* cyclopropyl dihedral angle exit vectors differ by only 2.6°
  - - an almost perfect superimposition
- *trans*-Cyclopropyl introduced to BACE1 inhibitor
  - - potency preserved, Log *D* reduced by 0.9 unit
  - - solubility increased by >100-fold
- Extended to a *meta*-aniline-based series
  - - not a precisely matched molecual pair
  - - activity maintained; aq. solubility improved >60-fold
  - - mimicry confirmed by X-ray cocrystal comparison

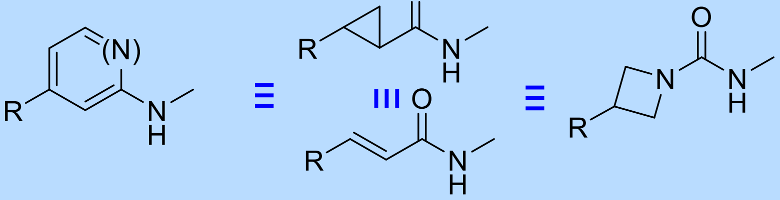


Impact
↑ solubility
↓ Log *D*
↑ efficiency metrics

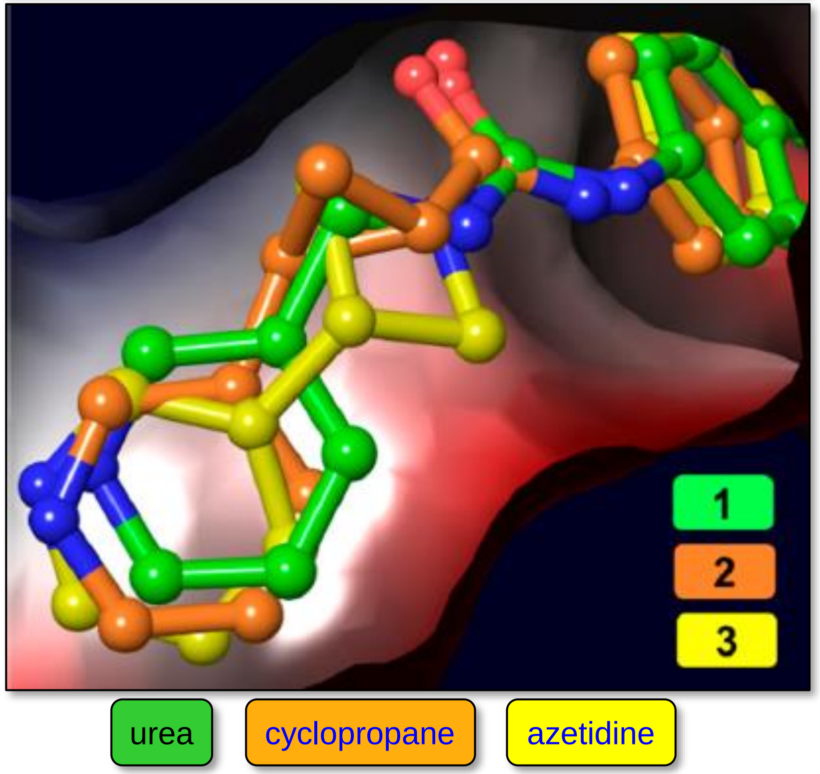
M. Stahl *et al*., *J. Med. Chem.*, 2016, **59**, 4087-4102

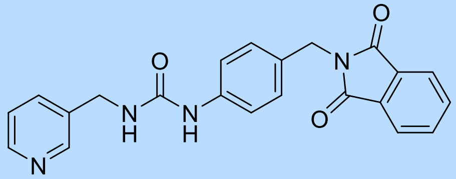
meta-Substituted Phenyl Mimic – Speculative Extension

Premise:

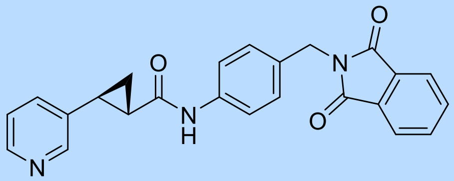


e.g. HCV NS5B,
LFA-1/ICAM-1 inhibitors

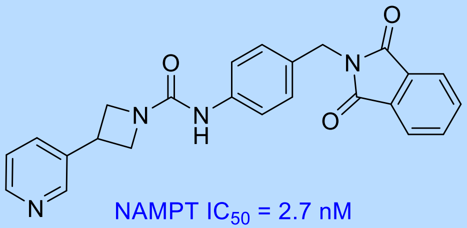




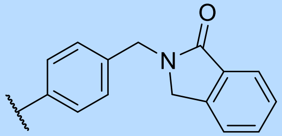
NAMPT IC_{50} = 3.1 nM
A2780 CTG IC_{50} = 100 nM

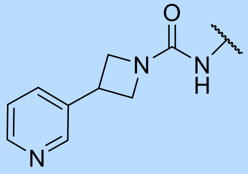


NAMPT IC_{50} <1 nM
A2780 CTG IC_{50} = 27 nM

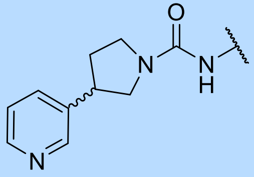


NAMPT IC_{50} = 2.7 nM
A2780 CTG IC_{50} = 5 nM

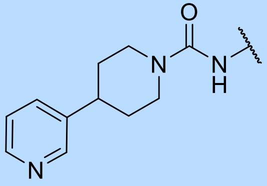




A2780 CTG IC_{50} = 0.6 nM



A2780 CTG
IC_{50} = 1030; >2500 nM



A2780 CTG
IC_{50} = 1030 nM

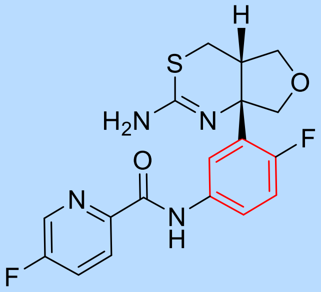
- NAMPT inhibitor from a phenotypic screen
  - inhibitor of NAD^+ synthesis in salvage pathway
- Urea CH_2-*N* morphed into a cyclopropane moiety
  - full preservation of activity
- Explored variants that installed urea *N* atom into a ring
  - azetidine conceived & modeled: a potent inhibitor
  - X-ray cocrystal structures of each revealed good overlap
- Ring homologues considerably less active
  - ≥ 350-fold less potent
- Cell activity is a function of ribophosphorylation of the pyridine *N* atom
  - metabolized to a more potent inhibitor

$$\text{NAM} + \text{PRPP} \xrightarrow{\text{NAMPT}} \text{NMN} \xrightarrow{\text{NMNAT}} \text{NAD}^+$$

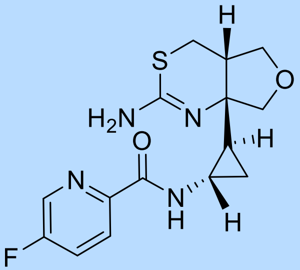
NAMPT = nicotinamide
phosphoribosyltransferase

R.G. Gentles *et al., J. Med. Chem*., 2014, **57**, 1855−1879; G. Liu *et al., J. Med. Chem.,* 2000, **43**, 4025-4040
G.C. Tron *et al., J. Med. Chem*. 2013, **56**, 6279-6296 (Perspective); D.S. Palacios *et al*., *ACS Med. Chem. Lett.*, 2017, **10**, 1524-1529

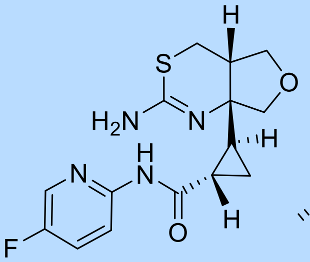
meta-Phenyl Mimics in BACE1, Aurora Kinase Inhibitors



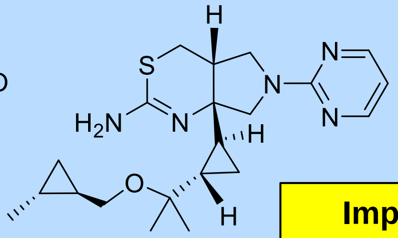
LY28886721
(clinical candidate)



cyclopropyl analogue



reverse amide



optimized lead

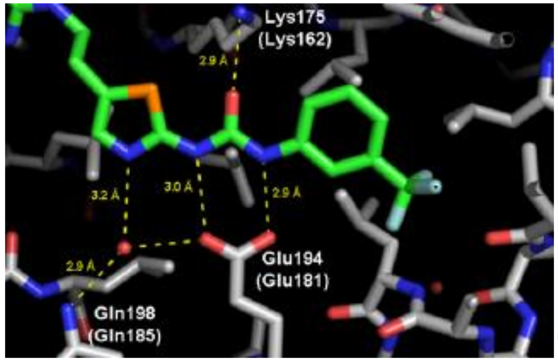
Impact
↓ lipophilicity
↓ PSA ↑ Fsp^3

	Lead	Bioisosteric analogue		
	LY	**CyPr**	**Rev Am**	**OL**
BACE1 IC_{50} (µM)	0.02	>100	92.4	0.01
PSA (Å^2)	90	90	90	77
cLog *P*	2.5	0.49	1.1	3.0

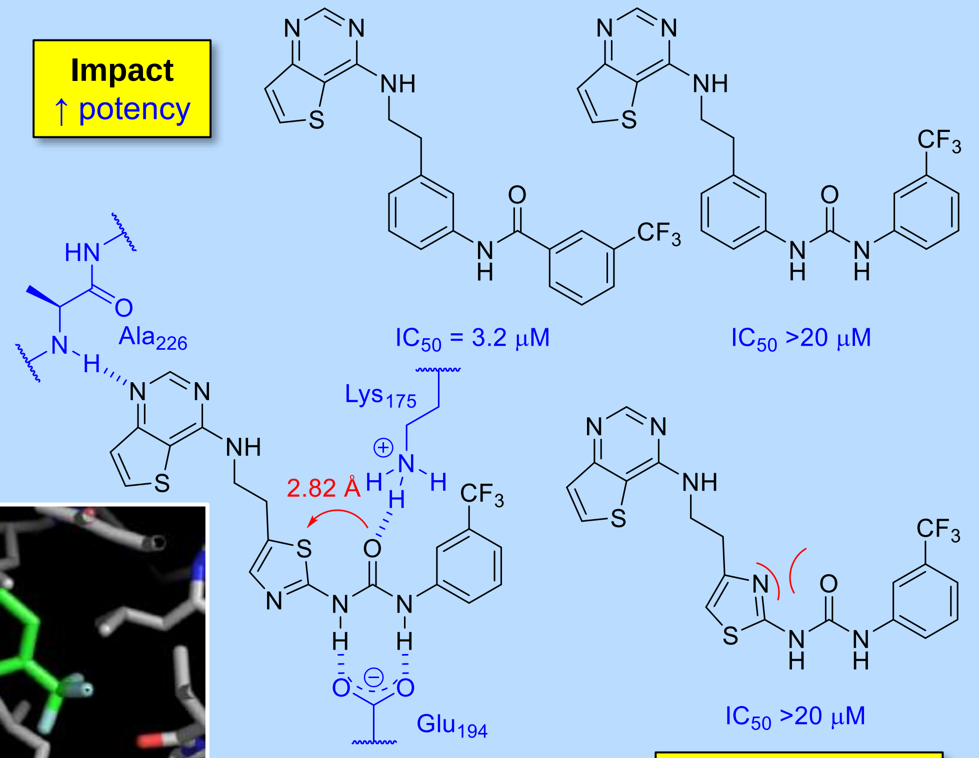
◆ LY28886721 advanced to clinical trials
  - robust reduction of CSF Aβ levels in Phase 1
  - 1st BACE1 inhibitor to advance to Phase 2

◆ Cyclopropyl explored as a replacement for *meta*-phenyl
  - altered vectors provided more opportunity for optimization

◆ Amides poorly potent
  - ether offered improved potency
    - inspired by serendipitous (unknown) element in X-ray
  - membrane permeability enhanced & P-gp efflux reduced



Impact
↑ potency



IC_{50} = 3.2 µM

IC_{50} >20 µM

IC_{50} >20 µM

IC_{50} = 22 nM

1,000x ↓ than isomer

◆ Aurora A kinase inhibitor: modestly potent amide; urea poor
  - thieno-pyrimidine binds to N-H of the hinge Ala$_{226}$

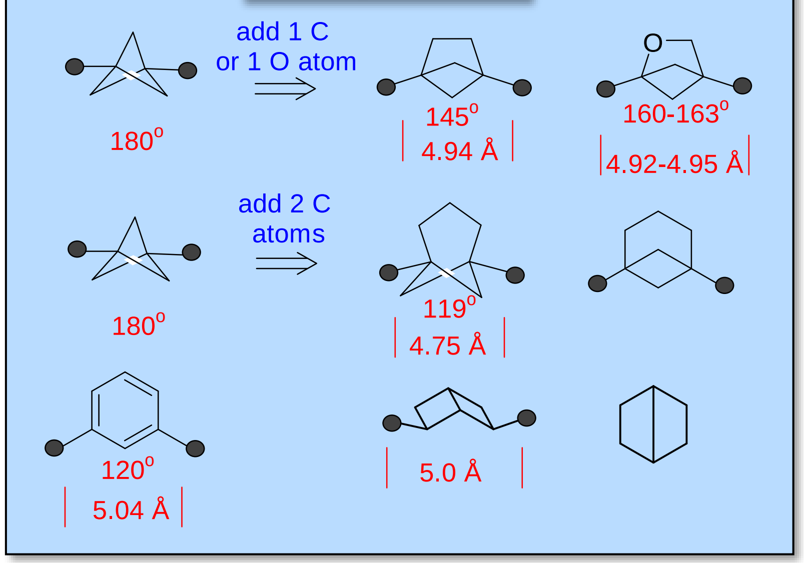
◆ Linker ring critical: thiazole >1,000-fold more potent than Ph

◆ Topology of thiazole critical: correctly orients thieno-pyrimidine
  - O to S stabilizes bound conformation in cocrystal

L.L. Winneroski *et al.*, *Bioorg. Med. Chem.*, 2020, **28**, 115194; J.D. Oslob *et al.*, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4880-4884

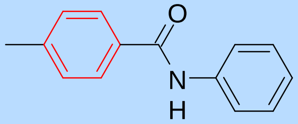
Bicyclic Systems as *meta*-Phenyl Mimics

BCP ring expansions



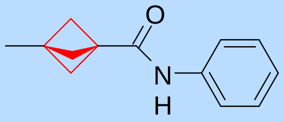
Value has not been established in the context of biologically active compounds

2-Oxabicyclo[2.1.1]hexanes



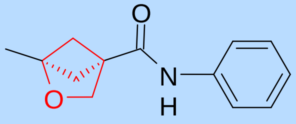
Log $D_{7.4}$ = 3.1

Solubility = 58 μg/mL



Log $D_{7.4}$ = 2.6

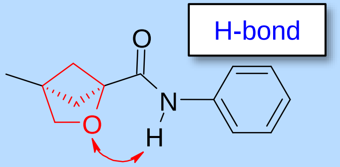
Solubility = >350 μg/mL



Log $D_{7.4}$ = 1.5

Solubility = >350 μg/mL

H-bond

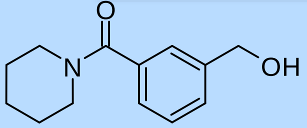


Log $D_{7.4}$ = 2.2

Solubility = >350 μg/mL

Log *P* decreased; Permeability improved

Ladderanes (bicyclo[2.2.0]hexanes)

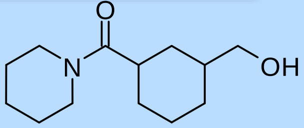


Soly. = >0.2 mM

rat $\mathrm{Cl_{int}}$ <10 mL/min

$\mathrm{P_{app}}$ = 32 x 10^{-6} cm/s

Log *P* = 0.41

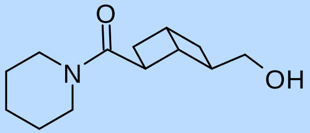


Soly. = >0.2 mM

rat $\mathrm{Cl_{int}}$ = 15 mL/min

$\mathrm{P_{app}}$ = 29 x 10^{-6} cm/s

Log *P* = 0.74



Soly. = 0.2 mM

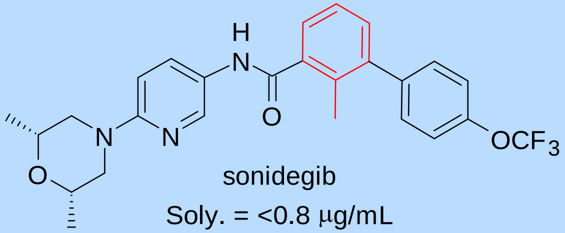
rat $\mathrm{Cl_{int}}$ <10 mL/min

$\mathrm{P_{app}}$ = 4 x 10^{-6} cm/s

Log *P* = 0.95

Log *P* increased; Permeability reduced

Bicyclo[2.2.2]hexanes (BCHeps)



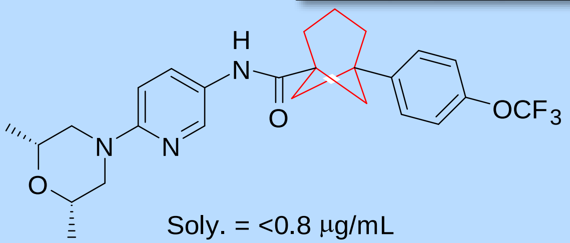
sonidegib

Soly. = <0.8 μg/mL

HLM $\mathrm{Cl_{int}}$ = 20 mL/min/mg

Caco $\mathrm{P_{app}}$ = 0.6/0.7 x 10^{-6} cm/s

cLog *P* = 6.8

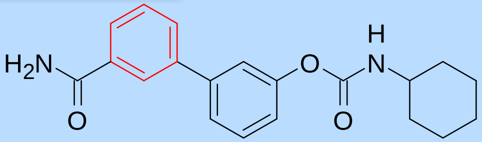


Soly. = <0.8 μg/mL

HLM $\mathrm{Cl_{int}}$ = 18 mL/min/mg

Caco $\mathrm{P_{app}}$ = 3.7/2.7 x 10^{-6} cm/s

cLog *P* = 6.2



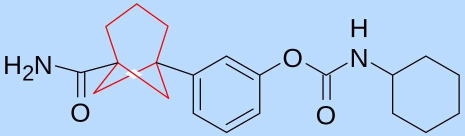
URB597

Soly. = <0.5 μg/mL

HLM $\mathrm{Cl_{int}}$ = 54 mL/min/mg

Caco $\mathrm{P_{app}}$ = 16.7/11.1 x 10^{-6} cm/s

cLog *P* = 3.8



Soly. = <0.6 μg/mL

HLM $\mathrm{Cl_{int}}$ = 17 mL/min/mg

Caco $\mathrm{P_{app}}$ = 15.3/24.4/11.1 x 10^{-6} cm/s

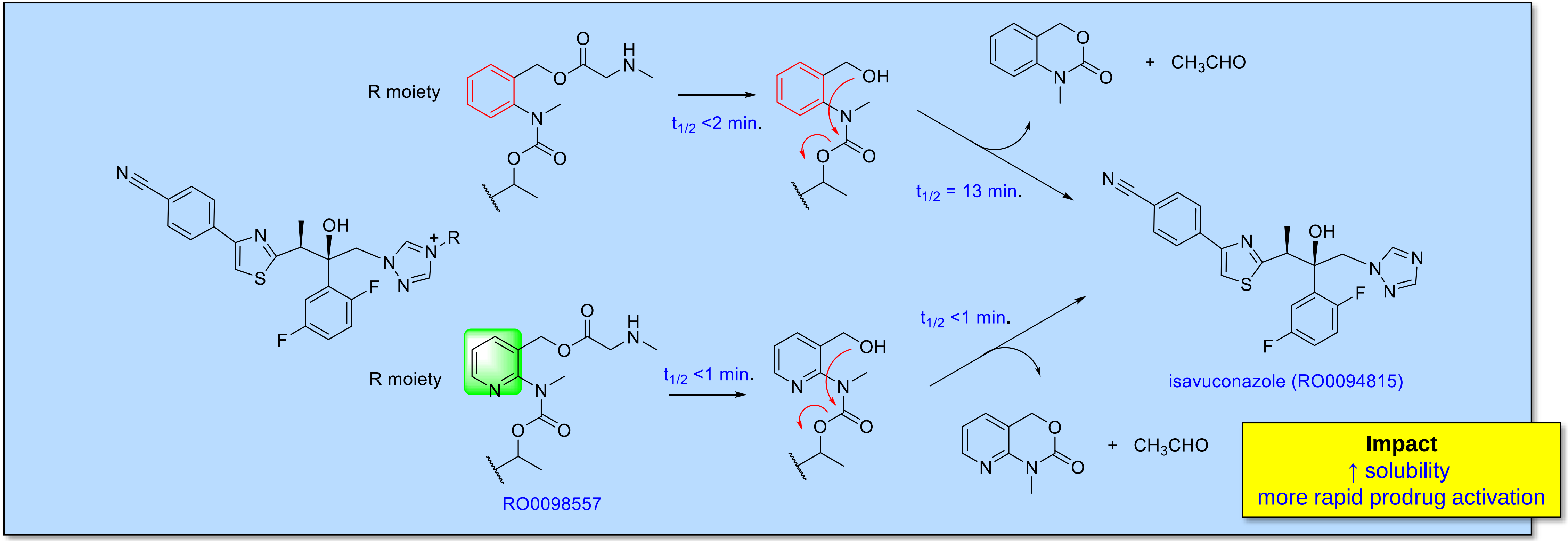
cLog *P* = 3.7

Largely a neutral molecular edit

A. Denisenko *et al., Angew. Chem. Int. Ed*. 2020, **59**, 20515 -20521; E.A. Anderson *et al*., *Nature*, 2022, **611**, 721-726;
J. Waser *et al., ChemRxiv*., 2023, DOI:10.26434/chemrxiv-2023-s8j30; P. Li *et al., JACS*, 2023, DOI: 0.1021/jacs.2c13740; K.M. Brown *et al*., *Nat. Commun*., 2022, **13**, 6056

ortho-Substituted Phenyl Mimetics

ortho-Phenyl Mimic in a Self-Immolating Prodrug Moiety



RO0098557

isavuconazole (RO0094815)

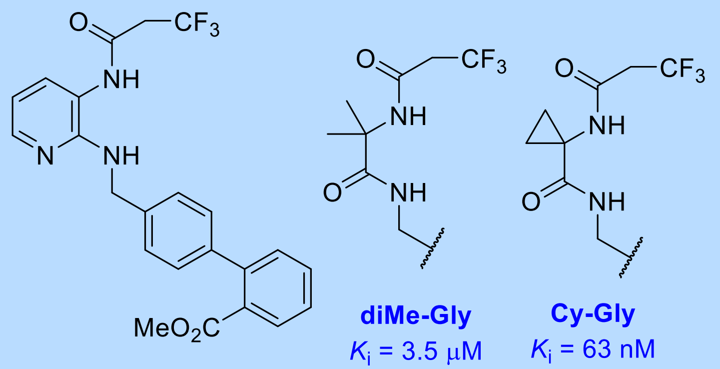
Impact
↑ solubility
more rapid prodrug activation

- ◆ Isavuconazole
  - azole antifungal agent approved by FDA & EMA in 2015
- ◆ Prodrug to Increase aqueous solubility for IV administration
  - pyridine offered superior release performance
    - 20x rate of cyclization
    - conformational and/or electronic effects
  - an isostere rather than a bioisostere

	Lead	Isostere
	Phenyl	**Pyridyl**
Solubility	1 mg/mL	>100 mg/mL
Prodrug $t_{1/2}$ in rat plasma	<2 min.	<1 min.
Alcohol $t_{1/2}$ in rat plasma	13 min.	<1 min. (undetected)

J. Ohwada *et al.*, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 191-196

ortho-Substituted Benzene (Pyridine) Isostere



pyridine
K_i = 11.8 nM

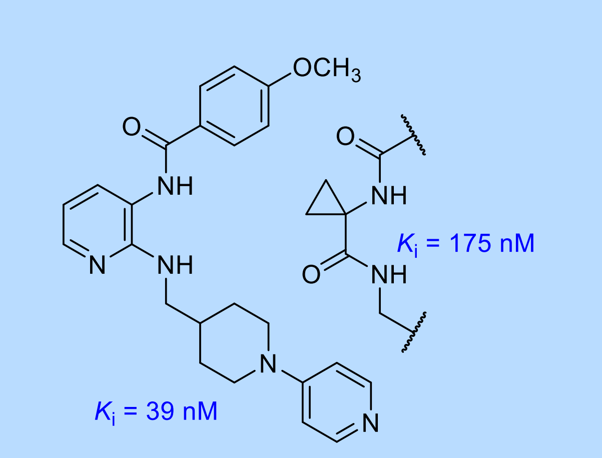
diMe-Gly
K_i = 3.5 µM

Cy-Gly
K_i = 63 nM

Bradykinin B1 antagonists

	Lead	Analogue	
	pyridine	**diMe-Gly**	**Cy-Gly**
hBK B_1 K_i (µM)	0.012	3.45	0.063
Rat PK			
F (%)	9	35	26
$t_{1/2}$ (h)	0.15	6.6	9.5
Cl (mL/min/kg)	35	4.2	9.3

Impact
↑ metabolic stability
mitigated bioactivation & GSH adduct formation
↑ oral bioavailability

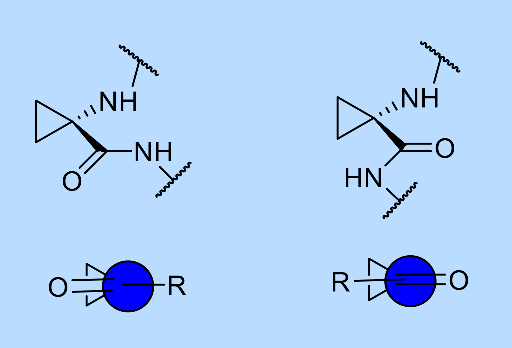


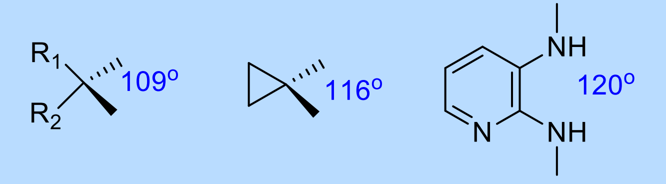
K_i = 39 nM

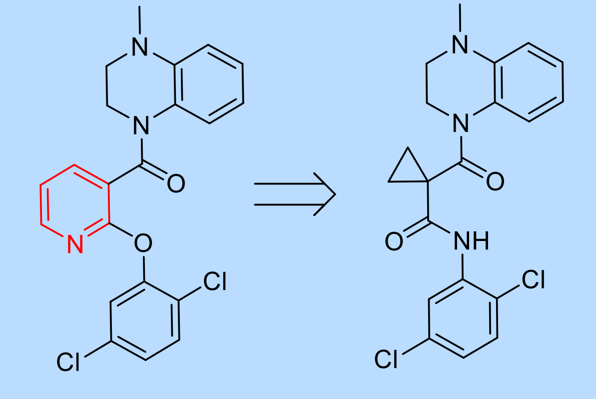
K_i = 175 nM

FXa inhibitors

- ◆ Bradykinin B1 antagonist
  - saw metabolic activation of pyridine ring
- ◆ Reduced pharmacophore to a simple N-CH_2-CH_2-N moiety
  - rebuilt to potent inhibitors
- ◆ Cyclopropyl analogue with improved potency
  - di-CH_3 substantially less potent
- ◆ Attributed to π-π hyperconjugation between ΔC-C bonds & C=O
  - cyclopropyl C-C bonds have increased p-character
  - optimal at 0º and 180º
  - exerts conformational bias
- ◆ Bond angles enforced by cyclopropyl closer to 120º in pyridine
- ◆ Saw improved PK in rats with transforms
- ◆ Isostere demonstrated to be applicable to FXa inhibitors
  - similar motif exploited in the design of TGR5 agonists







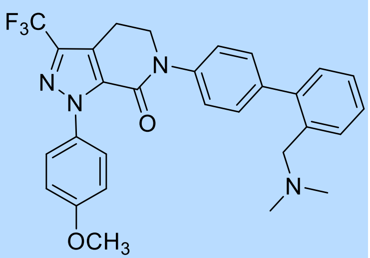
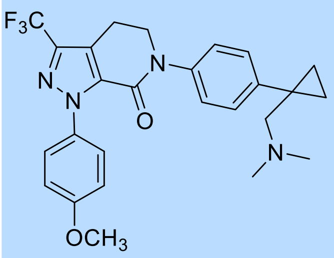
EC_{50} = 6.1 nM

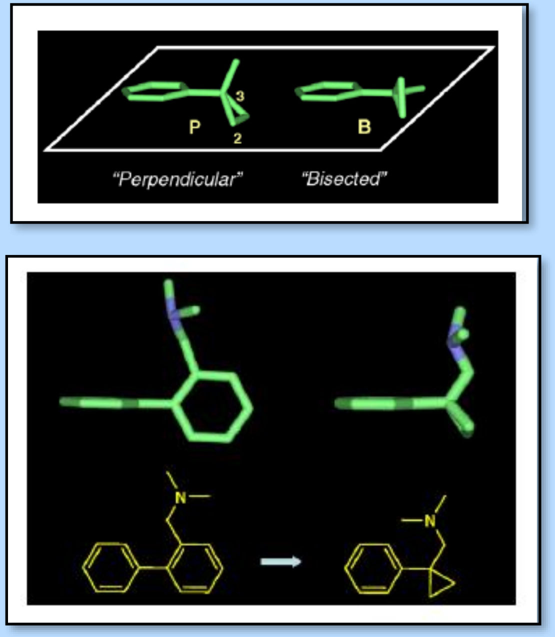
EC_{50} = 5.1 nM

TGR5 agonists

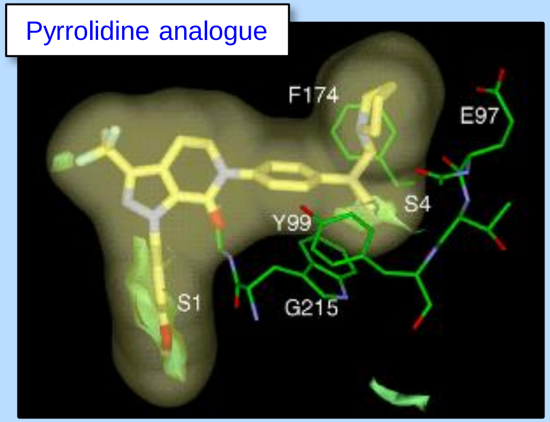
S.D. Kuduk *et al*., *J. Med. Chem.*, 2004, **47**, 6439-6442 ; C. Tang *et al.*,*Chem. Res. Toxicol.*, 2005, **18**, 934-945
M.S. Wood *et al.*, *J. Med. Chem.*, 2006, **49**, 1231-1234; K.H. Min *et al.*, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4271-4275

ortho-Substituted Phenyl Mimics in Factor Xa Inhibitors

Impact ↑ potency ↑ cell activity ↓ MW ↓ Log *P*		
FXa K_i	0.3 nM	0.035 nM
PT EC_{2x}	8 μM	.18 μM
cLog *P*	6.73	5.99
MW	520.5	484.2
HAC	38	35
LE	0.35	0.42
LLE (pIC_{50} - cLog *P*)	4.50	7.11
LLE_{AT}	0.27	0.39
LELP	14.3	8.0
Fsp^3	0.24	0.38
$Ar\text{-}sp^3$	16	7
PFI: Log $D_{pH7.4}$ + #Ar	9.02	6.35



Pyrrolidine analogue



$$Fsp^3 = \frac{\text{\# of } sp^3 \text{ C atoms}}{\text{total C count}}$$

$$LELP = \frac{\text{cLog } P}{LE}$$

$$LE = \frac{pIC_{50} \times 1.37}{HAC}$$

kcal/mol/heavy atom

- ◆ α-Substituted cyclopropane favors perpendicular conformation
  - \- CH_3 favors perpendicular orientation by 0.7 kcal/mol
- ◆ Potency increased 10x: consistent across a series of analogues
  - \- anticoagulant activity improved ~4-fold across the series
  - \- LE, LLE, LLE_{AT} and Fsp^3 increased
  - \- LELP, $Ar\text{-}sp^3$ decreased
- ◆ X-ray co-crystal of analogue with FXa
  - \- confirmed perpendicular conformation
  - \- improved hydrophobic interactions of dialkyl amine explains potency

$$LLE_{AT} = \frac{LLE}{HAC \times 0.74} + 0.11 = \frac{(pK_i, pK_D, pIC_{50}) - \text{cLog } P)}{HAC \times 0.74} + 0.11$$

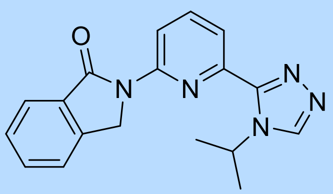
kcal/mol per non-H atom

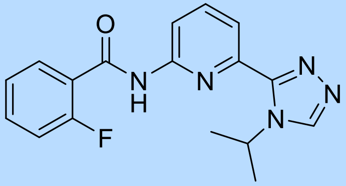
HLM $t_{1/2}$ = 110 min.
Caco-2 P_{app} = 8.5 x 10^{-6} cm/s
F (dog) = 53%

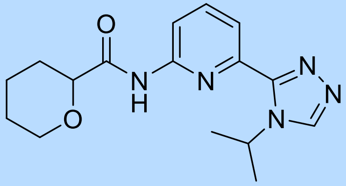
PFI = property forecast index

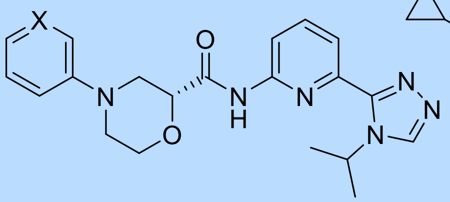
J.X. Qiao *et al.*, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4118-4123

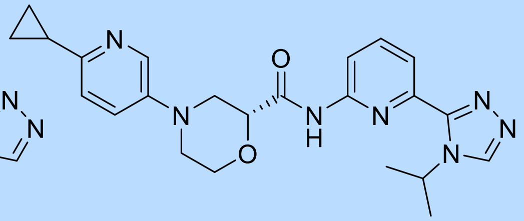
Pyran as *Ortho*-Fluoro Phenyl Replacement in ASK1


ASK1 IC$_{50}$ = 14 nM
LE = 0.45; LLE = 5.9

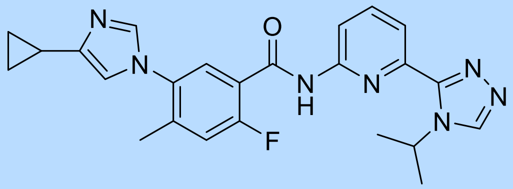

ASK1 IC$_{50}$ = 100 nM
cLog *D* = 1.7
LE = 0.4; LLE = 5.3


ASK1 IC$_{50}$ = 270 nM
cLog *D* = 2.0
LE = 0.39; LLE = 4.6

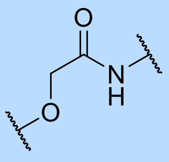

X = CH: ASK1 IC$_{50}$ = 130 nM
cLog *D* = 2.3; LLE = 4.2
X = N: ASK1 IC$_{50}$ = 31 nM
cLog *D* = 1.1; LLE = 6.0

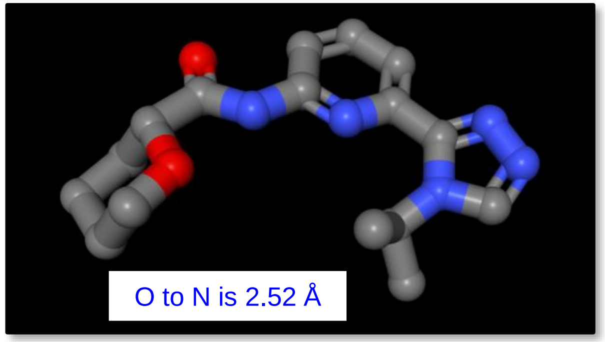

ASK1 IC$_{50}$ = 17 nM
cLog *D* = 2.1
LLE = 5.4

Impact
improved selectivity


selonsertib
ASK1 IC$_{50}$ = 3 nM
LE = 0.35; LLE = 5.8

- ◆ Apoptosis signal-regulating kinase-1 (ASK1 or MAP3K5) inhibitors
  - activated by extracellular signals: cytokines, ER stressors, reactive oxygen species
  - phosphorylates MAP kinase effectors MKK3/6 & MKK4/7 leading to activation of p38 & JNK pathways
  - immunology target but is involved in cardiac ischemia pathophysiology; maybe involved in NAFLD & NASH
- ◆ Potent isoindolone lead from a Takeda article with cocrystal structure data
  - amide C=O engages Val$_{757}$ NH of the hinge
- ◆ iPr-triazole a critical pharmacophore element
  - focused on modification of the isoindolone while retaining planarity
- ◆ THP offered reasonable potency – good LE & LLE values
  - cocrystal structure confirmed similar binding mode to lead; O & NH coplanar
  - MAP kinase screening (12 enzymes) indicated enhanced selectivity over the lead
- ◆ Switch to a morpholine provided a vector to project toward Gly$_{759}$
  - guided by model of selonsertib where imidazole π stacks over the amide
- ◆ Substituted pyridine optimal in resolved form; highly selective for ASK1 vs 350 kinases
  - poor PK prevented advancement

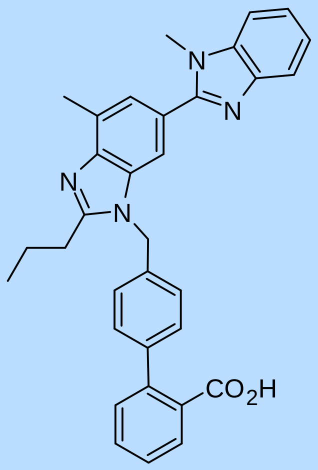

known intramolecular H-bonded motif


O to N is 2.52 Å

- ◆ Analyzed the PDB
  - saturated amides rare in 5,490 kinase inhibitors
  - typical phenyl rings & homologues (>99%)
- ◆ Unusual 2-F-phenyl replacement
  - 2-F-phenyl is a common motif in kinase inhibitors

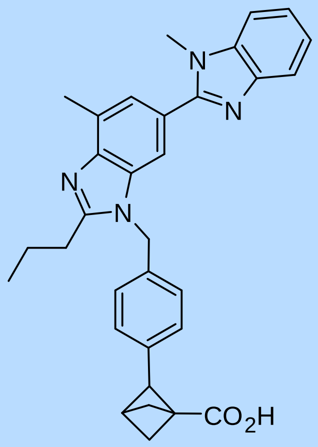
S.V. Bigi-Botterilla *et al., Bioorg. Med. Chem. Lett.*, 2020, **30**, 127405; M. Lanier *et al., ACS Med. Chem. Lett.*, 2017, **8**, 316−320

[1.1.1]-BCPs as *ortho*-Substituted Phenyl Mimics

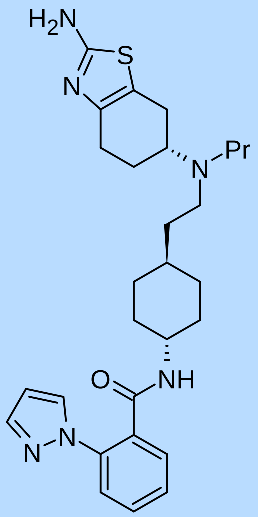


hAT$_1$ IC$_{50}$ = 1.0 nM
Soly. pH7 = 20 mg/mL

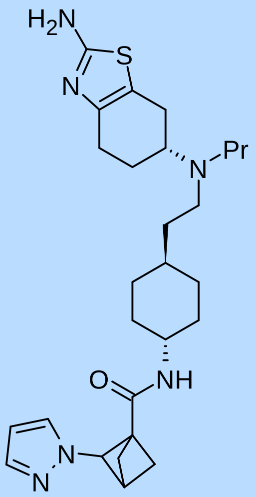
telmisartan



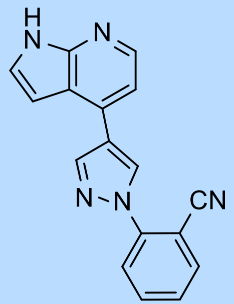
hAT$_1$ IC$_{50}$ = 4.3 nM (+)
Soly. pH7 = 131 ng/mL
hAT$_1$ IC$_{50}$ = 5.9 nM (-)
Soly. pH7 = 147 mg/mL



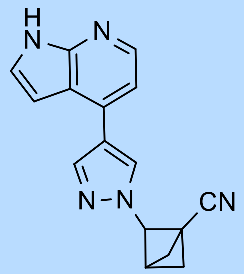
D$_3$ agonism <3 nM
Soly. pH7 = 157 ng/mL



D$_3$ agonism: <3 nM (+)
Soly. pH7 = 154 ng/mL
D$_3$ agonism: <3 nM (-)
Soly. pH7 = 159 ng/mL



JAK1 IC$_{50}$ = 192 nM
JAK2 IC$_{50}$ = 18.4 nM
JAK3 IC$_{50}$ = 176 nM
Soly. pH7 = 75 mg/mL



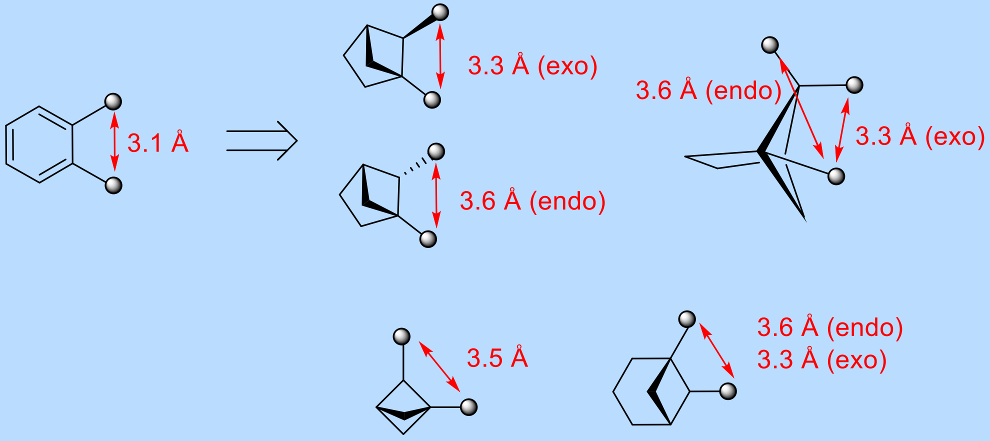
JAK1 IC$_{50}$ = (+) 134 nM/(-) 98.6 nM
JAK2 IC$_{50}$ = (+) 53.6 nM/(-) 49.3 nM
JAK3 IC$_{50}$ = (+) 116 nM/(-) 160 nM
Soly. pH7 = (+) 27 mg/mL/(-) 38 mg/mL

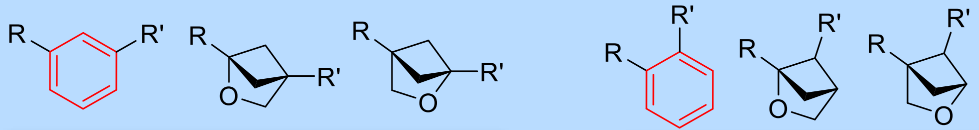
- Syntheses of 1,2-disubtituted [1.1.1]-BCPs developed
  - explored as *ortho*-substituted phenyl mimics
  - produces a mixture of enantiomers
- Examined in context of AT$_1$ antagonist, D$_3$ agonist, JAK2 inhibitor
  - activity preserved in AT$_1$ antagonist, D$_3$ agonist setting
  - JAK2 inhibitor 3-fold less potent with similar selectivity
- Solubility enhanced (AT$_1$) or preserved (D$_3$, JAK), dependent on context
  - lipophilicity preserved or reduced
  - clearance reduced in JAK inhibitors; increased in D$_3$ agonists

Impact
potency maintained
reduced sp^2 content
most properties preserved

D.W.C. MacMillan *et al., JACS,* 2023, **145**, 3092-3100; see also P.S. Baran, M.R. Collins *et al., PNAS,* 2021, **118**, e2108881118

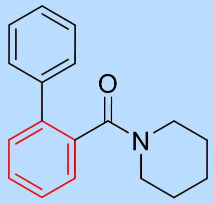
Bicyclo[2.1.1]hexanes as *ortho*-Phenyl Mimics



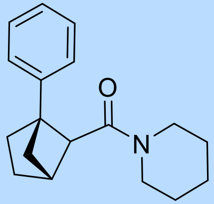


meta-mimics: methodology developed

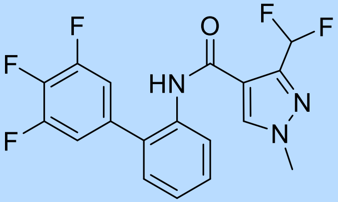
ortho-mimics: not described



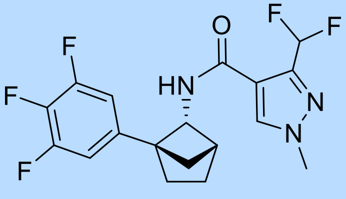
Sol. pH$_{7.4}$ = 397 μM
Log $D_{7.4}$ = 3.5



Sol. pH$_{7.4}$ = 492 μM
Log $D_{7.4}$ = 3.7

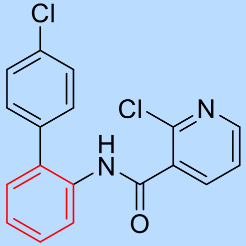


fluxapyroxad
(fungicide)

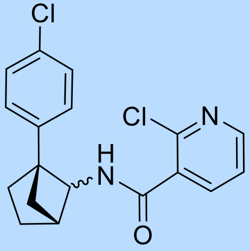


fluxapyroxad analogue

similar inhibition of growth of *Fusarium oxysporum* Schltdl

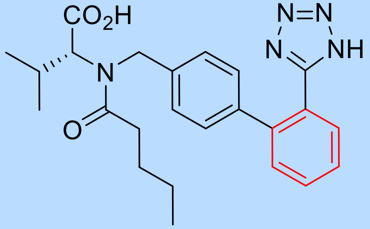


boscalid
(fungicide)

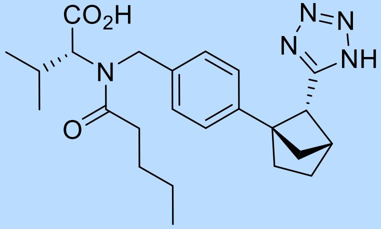


racemic boscalid analogue

similar inhibition of growth of *Fusarium oxysporum* Schltdl



valsartan
(angiotenisin II antagonist
anti-hypertensive drug)



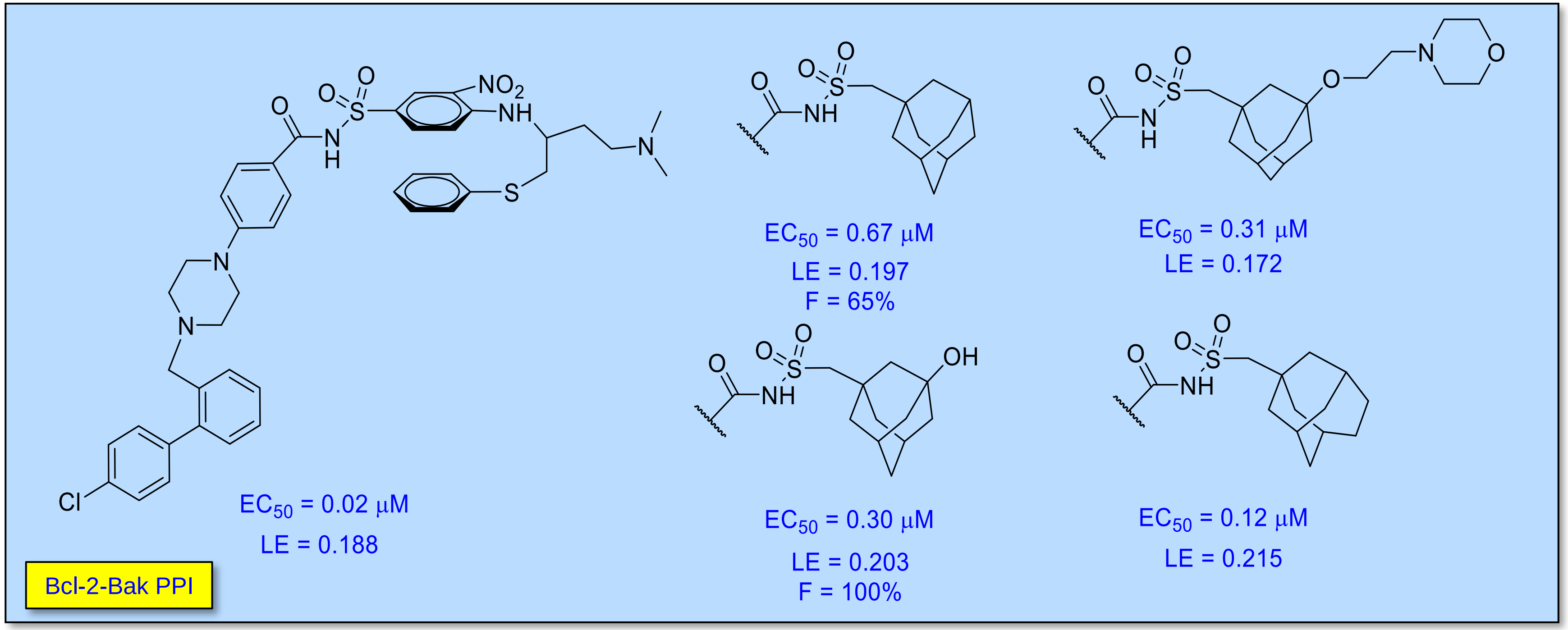
valsartan analogue

- Bicyclo[2.1.1]hexane
  - 1 C homologue of bicyclo[1.1.1]pentane; C analogue of oxabicyclo[2.1.1]hexane
- Bond distances slightly longer than benzene
  - comparable to BCP
- Solubility of test compound improved by 33%
  - comparable Log $D_{7.4}$
- Installed as *ortho-phenyl* replacement in 2 fungicides, valsartan
  - fungicide analogues demonstrated comparable biological activity to prototype

Impact
↓ sp^2 content
↑ solubility

A. Denisenko *et al., Angew. Chem. Int. Ed*. 2020, **59**, 20515 -20521; V.V. Levterov *et al., Angew. Chem. Int. Ed*. 2020, **59**, 7161-7167

Shape Isosteres: Adamantane & π-π Interacting Aryl Rings



EC$_{50}$ = 0.02 μM
LE = 0.188

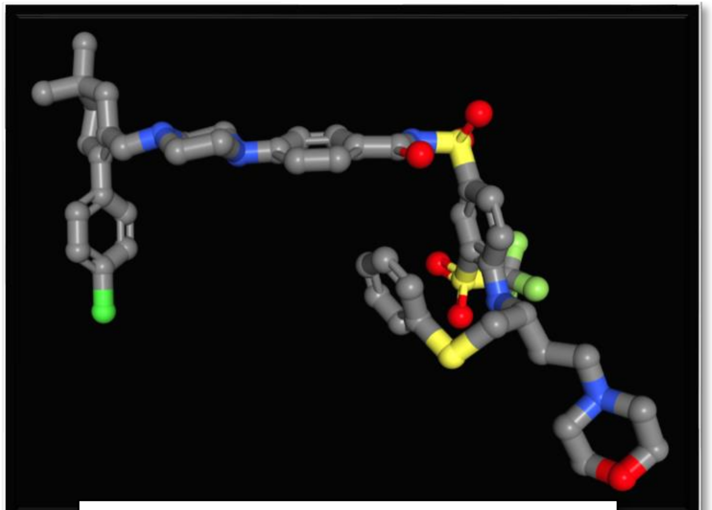
EC$_{50}$ = 0.67 μM
LE = 0.197
F = 65%

EC$_{50}$ = 0.31 μM
LE = 0.172

EC$_{50}$ = 0.30 μM
LE = 0.203
F = 100%

EC$_{50}$ = 0.12 μM
LE = 0.215

Bcl-2-Bak PPI



Structure abstracted from cocrystal

Impact
reduced sp^2 content

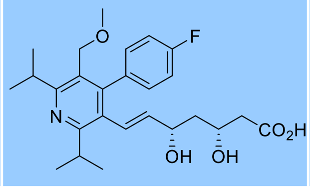
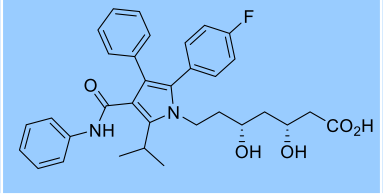
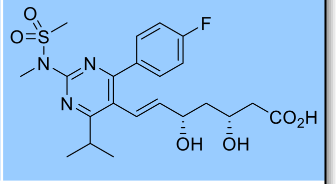
- ◆ ABT-737 a Bcl-2-Bak protein-protein inhibitor
  - X-ray cocrystal structure revealed that SPh folds back to π-π stack with NO$_2$-aryl
- ◆ Rigid tricyclics postulated as potential mimics
  - reduced lipophilicity & rotatable bond count
  - potential thermodynamic advantage with pre-organization
- ◆ Potency of simple CH$_2$-adamantyl 33x lower; CH$_2$-homoadamantyl 6x lower
  - X-ray indicates loss of H-bond from SO$_2$ to backbone NH of Gly$_{104}$
  - ligand efficiency improved for 3 simple compounds
- ◆ CH$_2$-adamantyl:
  - cLog P = 9.5, F = 66% in rat; OH: cLog P = 6.4, F = 100%

$$LE = \frac{pIC_{50} \times 1.37}{HAC}$$

kcal/mol/heavy atom

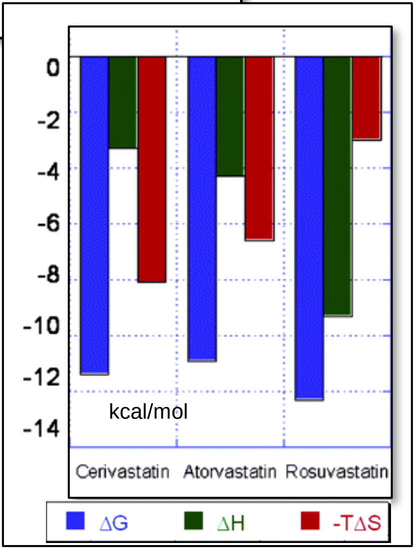
N. Yusuff *et al.*, *ACS Med. Chem. Lett.*, 2012, **3**, 579-583

Caveat Emptor

	Cerivastatin 	Atorvastatin 	Rosuvastatin 
HMG-CoA K_i	5.7 nM	14 nM	2.3 nM
Log D_{pH7}	0.40	1.08	-1.91
Log P	3.18	3.85	0.89
Mol. formula	$C_{26}H_{34}FNO_5$	$C_{33}H_{35}FN_2O_5$	$C_{22}H_{28}FN_3O_6S$
MW	459.5	558.6	481.5
HBA	6	7	9
HBD	3	4	3
∑HBA + HBD	9	11	12
RB	13	14	12
PSA	99.9 Å^2	112 Å^2	149 Å^2
Fsp^3	0.46	0.27	0.41
Ar-sp^3	0	14	3
# of rings	2	4	2
PFI/iPFI	2.4/5.18	5.08/7.85	-0.09/2.89
$\Delta G/\Delta H/-T\Delta S$ (kcal/mol)	-11.4/-3.3/-8.1	-10.9/-4.3/-6.6	-12.3/-9.3/-3.0

- Cerivastatin launched in June 1997
  - most potent statin *in vivo*, high %F
  - low clinical dose of 0.2-0.8 mg
- 2 Aromatic rings; high Fsp^3 value; very low Ar-sp^3; lowest MW
  - thermodynamic signature similar to atorvastatin
    - relies more on entropy than enthalpy
    - rosuvastatin is only statin with high Δ*H* dependence
- Appears to be a well-designed compound
  - low dose, high %F
  - mixed excretion *via* kidney & bile
- High rate of fatal rhabdomyolysis
  - ~800x atorvastatin; 50x the 0.19 average for all statins
    - more than 100 fatalities
  - exacerbated by concomitant gemfibrozil use
    - withdrawn worldwide August 2001

	Cerivostatin	Atorvastatin
Dose (mg)	0.2-0.8 mg	10-80 mg
C_{max} (mg/mL)	27-66 (0.2 mg)	2 (40 mg)
PB	>99%	80-90%
$t_{1/2}$ (h)	2.1-3.1	15-30
urine/fecal	30/70	2/70
rhabdomyolysis	3.16 per 10^6 R_x	0.04 per 10^6 R_x



PFI = Log $D_{pH7.4}$ + #Ar; iPFI = Log P + #Ar

T. Campbell & E. Freire, *Biochemistry* 2005, **44**, 11741-11748
M.H. Davidson, *Exp. Opin. Drug Saf.*, 2002, **1**, 207-212; M. Evans & A. Rees, *Drug Safety*, 2002, **25**, 649-663

Conclusion

Conclusion

◆ The presence of planar ring systems have been implicated in drug attrition
  - confer less than optimal physicochemical properties

◆ Phenyl rings the most problematic
  - seem to negatively affect solubility more than anticipated by Log *P* value

◆ The (ab)use of phenyl rings may have been driven by ready synthetic access
  - planar topography reduces complexity

◆ The introduction of phenyl ring can often be associated with increased potency
  - underlying effect may be entropic rather than enthalpic: use LLE to assess quality

◆ Bioisosteres of phenyl rings have been and continue to be explored extensively
  - demonstrated capacity to solve a range of developability challenges
  - low solubility, aniline release, PK, high protein binding, hERG inhibition, phospholipidosis, phototoxicity

◆ Significant progress made over the last decade in developing synthetic access to complex sp^3-rich ring systems
  - bicyclo[1.1.1]pentanes, cubanes prominent examples
  - oxa-substituted homologues attracting attention

◆ Effective mimics of *ortho*-, *meta*-, & *para*-substituted benzene scaffolds have been developed
  - bioisosteric effect is highly dependent on context
  - tailor/optimize an isostere to specific application

◆ In some examples, phenyl rings have been difficult to replace
  - stimulus for new bioisostere design: many opportunities remain

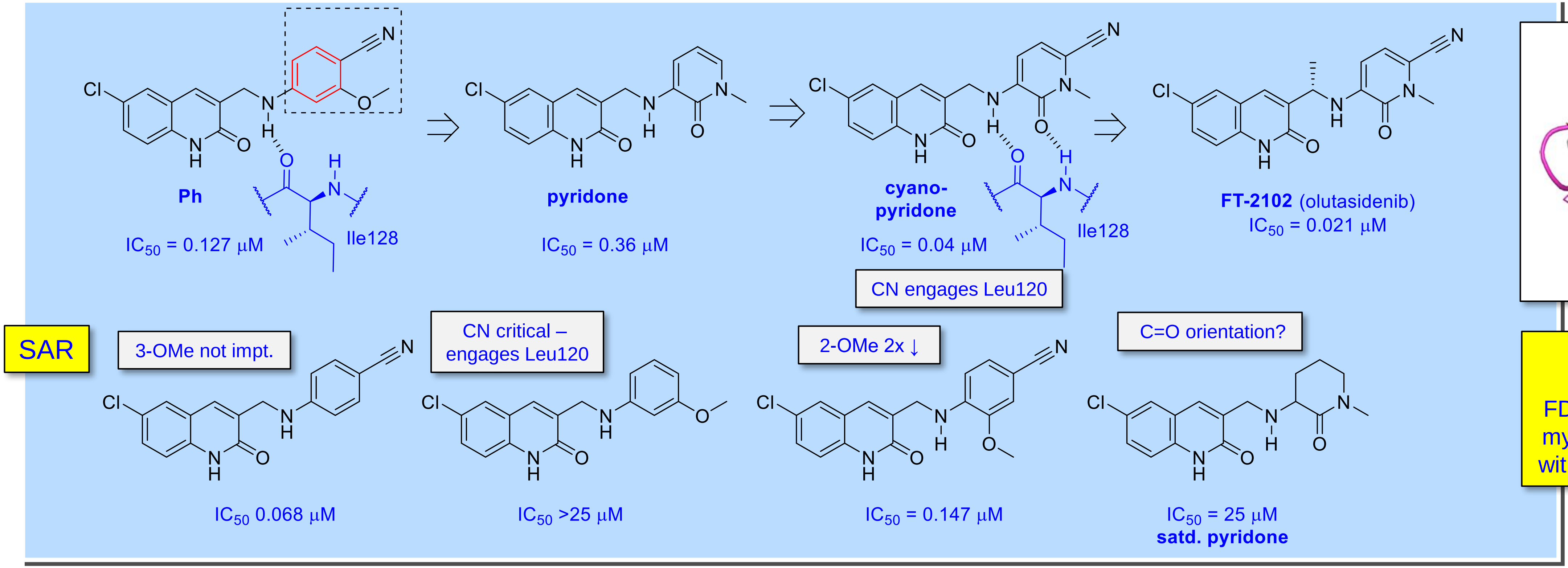
Acknowledgement

Murugaiah A.M. Subbaiah

Biocon Bristol Myers Squibb Research and Development Centre, Bangalore, India

M.A.M. Subbaiah & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 14046-141281

Pyridone to Replace a Terminal Phenyl Ring in IDH1 R132H Inhibitors



Ph

IC_{50} = 0.127 µM

Ile128

pyridone

IC_{50} = 0.36 µM

cyano-pyridone

IC_{50} = 0.04 µM

Ile128

CN engages Leu120

FT-2102 (olutasidenib)

IC_{50} = 0.021 µM

SAR

3-OMe not impt.

IC_{50} 0.068 µM

CN critical – engages Leu120

IC_{50} >25 µM

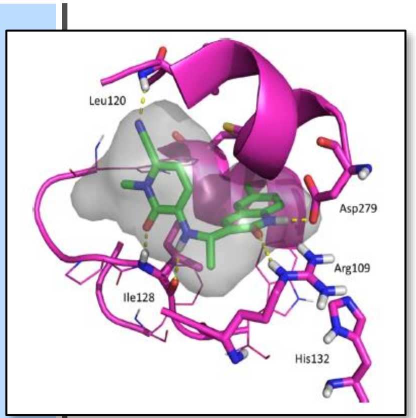
2-OMe 2x ↓

IC_{50} = 0.147 µM

C=O orientation?

IC_{50} = 25 µM

satd. pyridone



Olutasidenib
Dec 2022:
FDA approved for acute myeloid leukemia (AML) with IDHR132H mutation

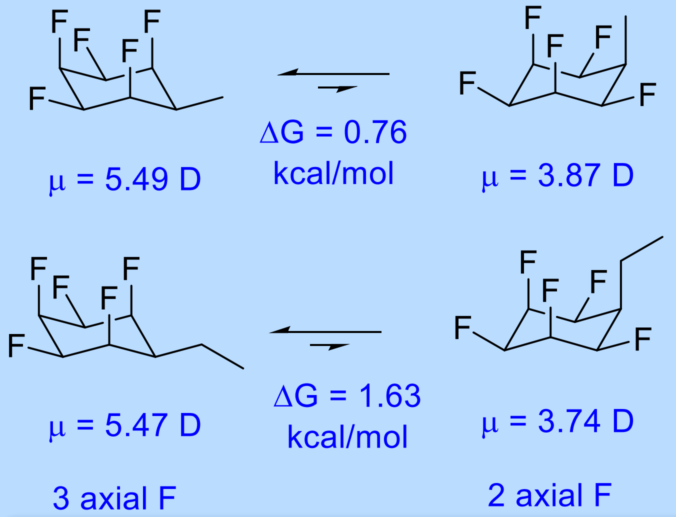
- Isocitrate dehydrogenase (IDH) inhibitor for glioblastoma
  - modest potency; poor solubility
  - poor oral exposure
  - modest CNS penetrance
- Cocrystal structure guided design toward olutasidenib
  - pyridone C=O engages Ile N-H
  - potency, solubility; met. stab. enhanced
  - brain:plasma ratio = 0.24

	Lead	Bioisosteric analogue			
	Ph	pyridone	satd. pyridone	cyano-pyridone	FT-2102
IDH1-R132H IC_{50} (µM)	0.127	0.36	25	0.0403	0.0212
MLM	42	26	83	73	92
HLM (% left at 30 min.)	81	90	99	99	100
Solubility (µM)	0.43	54	94	0.295	34.5

Impact
improved potency; increased metabolic stability; enhanced solubility; reduced lipophilicity

J. Lin *et al., J. Med. Chem.*, 2019, **62**, 6575-7596; J.A. Cavella *et al., J. Med. Chem.*, 2020, **63**, 1612-1623; Y. Zhang & A. Pike, *Bioorg. Med. Chem. Lett.*, 2021, **38**, 127849

All-*cis*-Poly-fluoro Cyclohexane Derivatives



μ = 5.49 D

ΔG = 0.76 kcal/mol

μ = 3.87 D

μ = 5.47 D

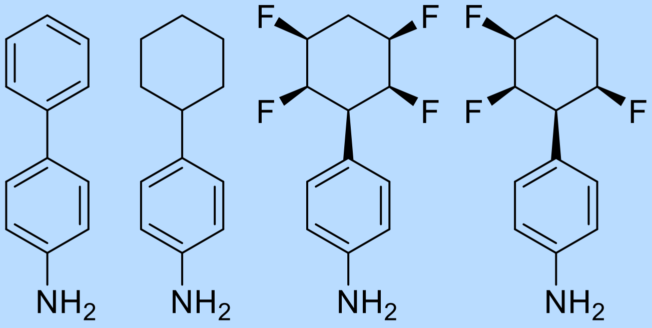
ΔG = 1.63 kcal/mol

μ = 3.74 D

3 axial F

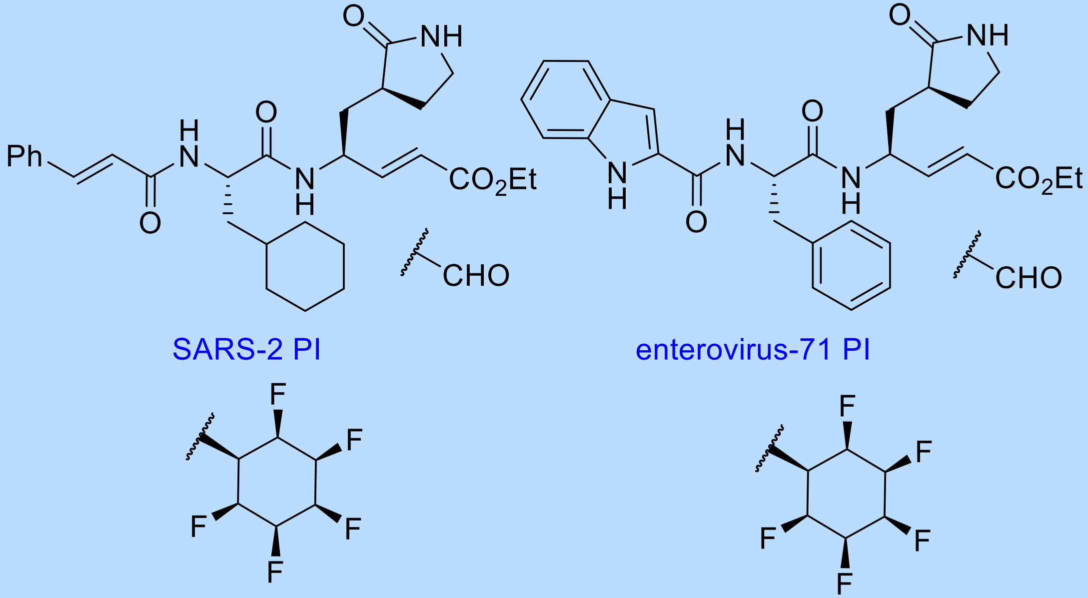
2 axial F

MO6L-D3/aug-cc-pVTZ level calculations - gas phase



Log *P*

2.80	3.65	1.03	1.02

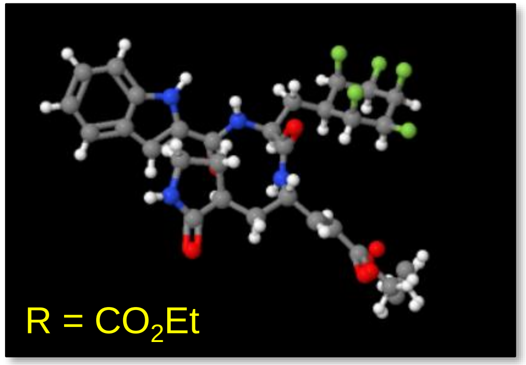


SARS-2 PI

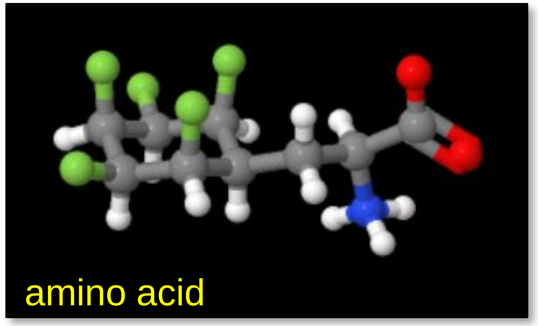
enterovirus-71 PI

R = CO_2Et: Log *P* = 1.41
R = CHO: Log *P* = 0.82

R = CO_2Et: Log *P* = 1.49
R = CHO: Log *P* = 0.69

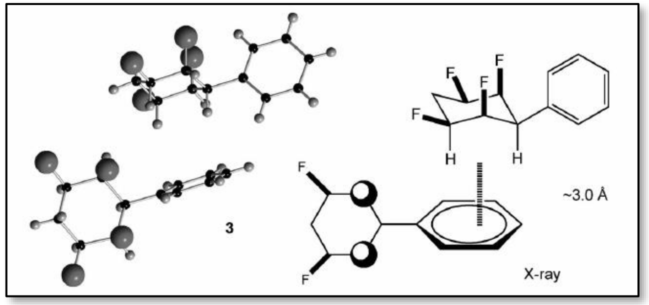


R = CO_2Et



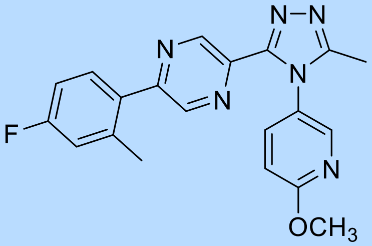
amino acid

- *cis*-Fluorocyclohexanes present large dipole moments
  - C-H and C-F face opposite directions
  - polarization facilitates C-H to π interactions
- Equatorial disposition of alkyl substituent favored
  - despite being associated with a higher dipole moment
- Log *P* of tetra-F reduced by 2.5 from cyclohexane
  - Log *P* value reduced by 1.75 compared to phenyl
- Incorporated penta-F cyclohexane into peptide-based viral cysteine protease inhibitors
  - none were active towards Zika or SARS-CoV-2 viruses in cell culture

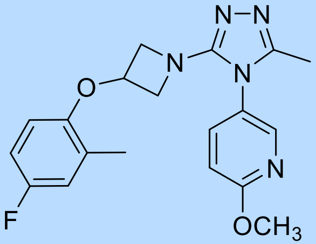


D. O'Hagan *et al.*, *Chem. Sci.*, 2021, **12**, 9712-9719; *Chem. Eur. J.*, 2021, **27**, 16000–16005

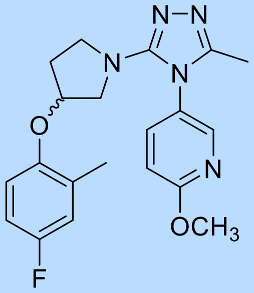
2,5-Di-Substituted Pyrazine Mimetics in Oxytocin Antagonists



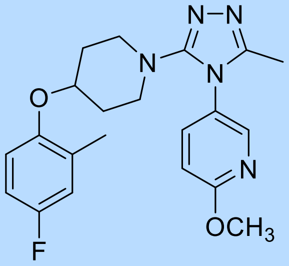
OT K_i = 6 nM
cLog P = 2.6
aq. sol. = 6 µg/mL



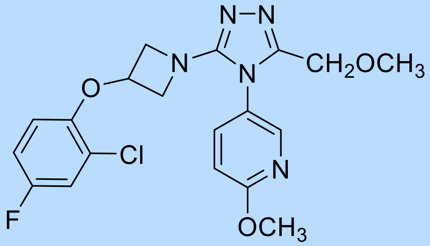
OT K_i = 17.5 nM
cLog P = 3.26



OT K_i = 17.9 nM
cLog P = 3.2



OT K_i = 4.2 nM
cLog P = 3.7



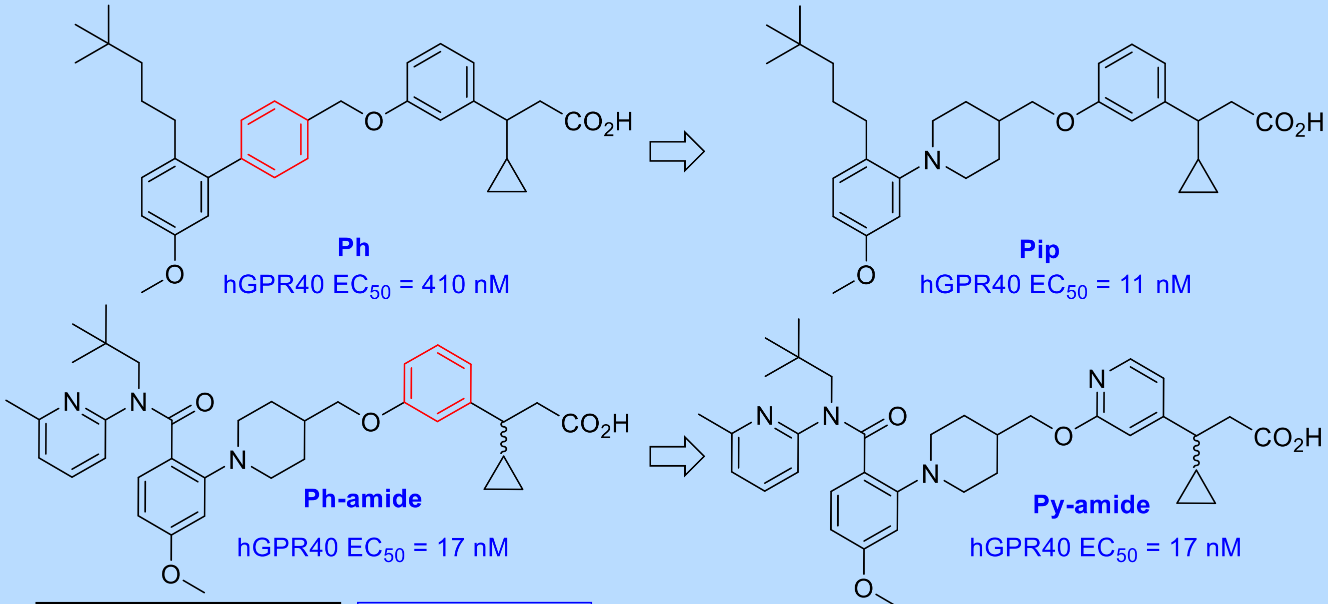
OT K_i = 9.5 nM
cLog P = 3.24
aq. sol. = 59 µg/mL
HLM Cl 10 µL/min/mg

- Oxytocin mimic with poor aqueous solubility
  - 4 planar aromatic systems
  - modest cLog *P* value
- Strategy: modify pseudo-biphenyl moiety to address solubility
  - saturated compounds typically exhibit enhanced solubility
- Azetidine, pyrrolidine, piperidine ethers modeled
  - exhibited good structural overlap with phenyl
  - all 3 structural motifs provided potently active compounds
  - modest increase in cLog *P*
- Excellent potency achieved with azetidine & additional structural variation
  - aqueous solubility improved by10-fold over prototype
  - cLog *P* maintained with final structural modifications

Impact
enhanced solubility
despite increased Log *P*

A. Brown *et al*., *Bioorg. Med. Chem. Lett*., 2010, **20**, 516-520

Phenyl Mimics at 2 Sites in GPR40 Agonists

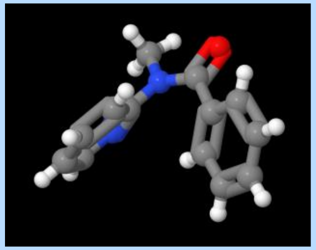


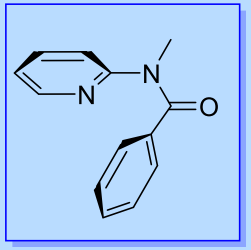
Ph
hGPR40 EC$_{50}$ = 410 nM

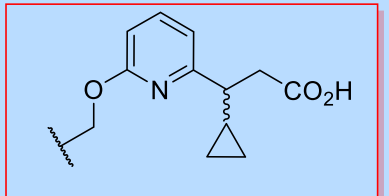
Pip
hGPR40 EC$_{50}$ = 11 nM

Ph-amide
hGPR40 EC$_{50}$ = 17 nM

Py-amide
hGPR40 EC$_{50}$ = 17 nM







hGPR40 = 39% at 10 μM

◆ Highly lipophilic GPR40 agonist
  - fatty acid receptor

◆ Replaced inner phenyl of biphenyl with a piperidine
  - potency enhanced ~40-fold; full agonism retained
  - cLog *P* fell by ~ 1 unit

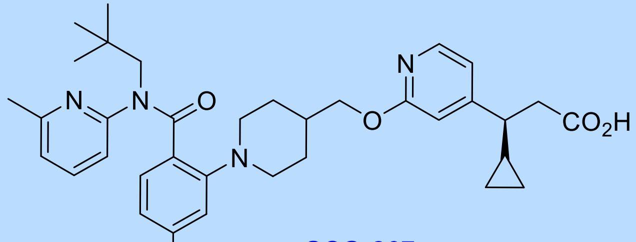
◆ *N*-Pyridylbenzamide element introduced
  - preserves potency/efficacy
  - prefers an L-shaped conformation
  - orients neopentyl substituent toward a lipophilic pocket

◆ Phenoxy moiety replaced by a pyridyl ether
  - potency & efficacy fully preserved
  - further reduction in cLog *P*
  - topological isomer significantly less potent
    - can be explained by conformational preference
    - depicted topology seen in X-ray structures

◆ SCO-267: resolved (*S*)-isomer is the eutomer
  - 7-fold more potent than the (*R*)-isomer (84 nM/109%)
  - advanced into clinical trials

	Lead	Bioisosteric analogue			
	Ph	**Pip**	**Ph-amide**	**Py-amide**	**SCO-267**
hGPR40 EC$_{50}$ (nM)	410	11	17	17	12
E$_{max}$ (%)	105	106	109	112	108
cLog *P*	9.35	8.4	6.4	5.8	5.8

Impact
↑ potency
↓ aromatic content
↓ lipophilicity

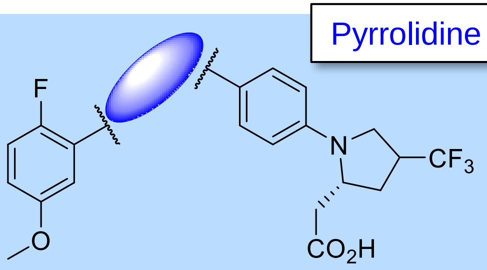


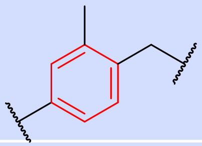
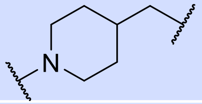
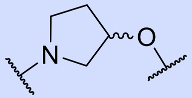
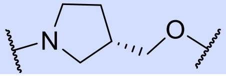
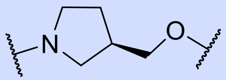
SCO-267
hGPR40 EC$_{50}$ = 12 nM

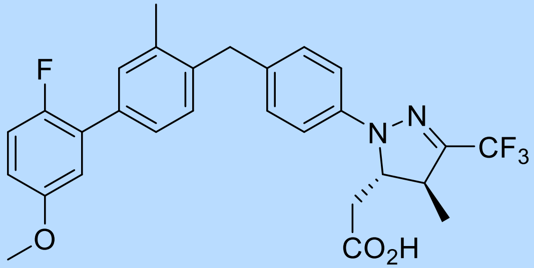
H. Furukawa *et al., J. Med. Chem.*, 2020, **63**, 10352-10379; R.-J. Chien & E.J. Corey, *Org. Lett.*, 2010, **12**, 132-135

Piperidine as Phenyl Mimic in GPR40 Agonists

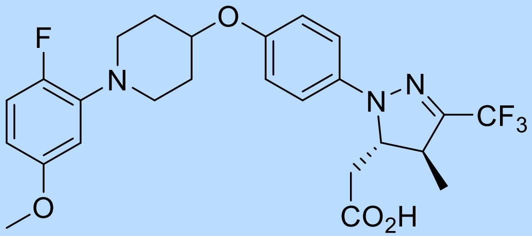
Pyrrolidine series



	FLIPR hGPR40 EC$_{50}$ (nM)	cLog *P*
	210	7
	530	5.73
	210	4.55
	2,830	4.48
	5,360	
	940	4.60
	630	



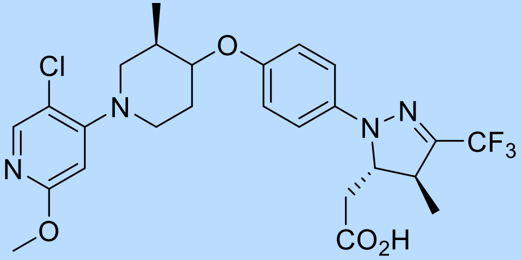
hGPR40 EC_{50} = 33 nM
mGPR40 EC_{50} = 31 nM
PPARγ EC_{50} = 2.6 μM
cLog *P* = 7.7



hGPR40 EC_{50} = 110 nM
mGPR40 EC_{50} = 70 nM
PPARγ EC_{50} = 2.6 μM
cLog *P* = 5.39

Impact
lower Log *P*;
reduced promiscuity

Dihydropyrazole series

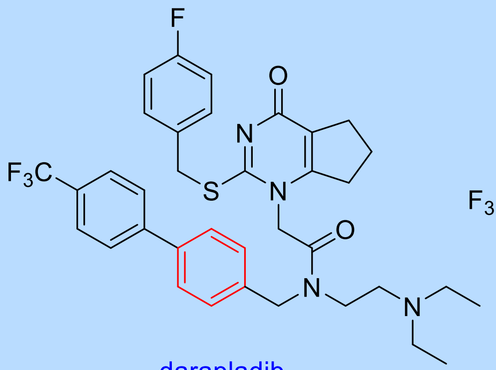


hGPR40 EC_{50} = 70 nM
mGPR40 EC_{50} = 63 nM
PPARγ EC_{50} >47 μM
cLog *P* = 5.9
measured Log $D_{6.5}$ = 4.6

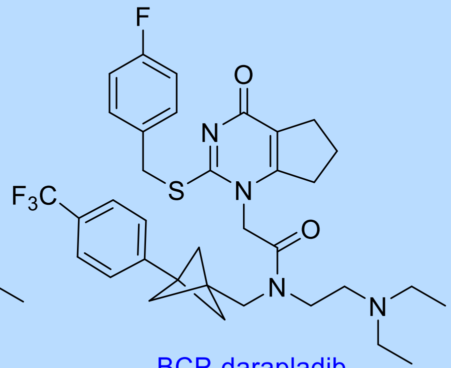
- GPR40 agonists
  - promote glucose-stimulated insulin release
- Saw cardiac (HR, BP) side effects & PPARγ agonism
  - high cLog *P* hypothesized as source of promiscuity
- Sought to lower cLog *P* and increase sp^3 content
  - replaced central phenyl ring with aza heterocycles
- Piperidine offered best *in vitro* performance
  - activity 2.5-3.0 x lower, cLog *P* fell by 1.3-2.5 units
  - saw GSH adducts with anisole moiety
- Optimized by O, CH_3 on piperidine in pyrazole series
  - pyridine ring introduced to reduce GSH adducts

J. Shi *et al.*, *J. Med. Chem.*, 2018, **61**, 681-694

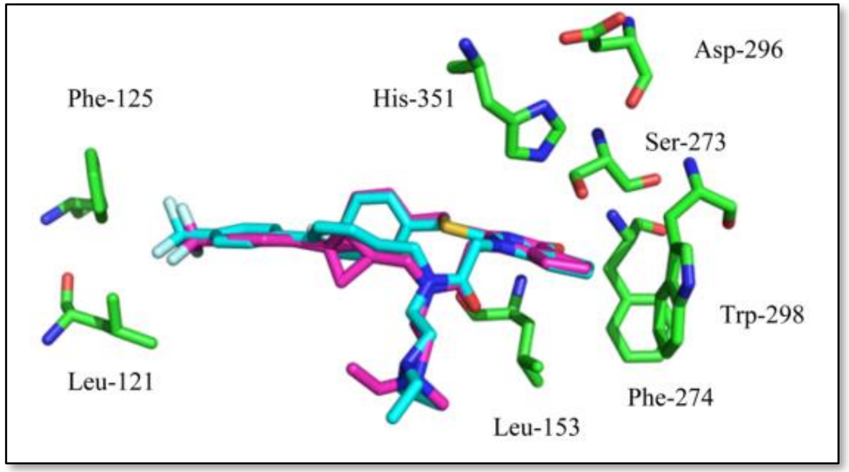
Bicyclopentane (BCP) as a Phenyl Mimic – LpPLA$_2$

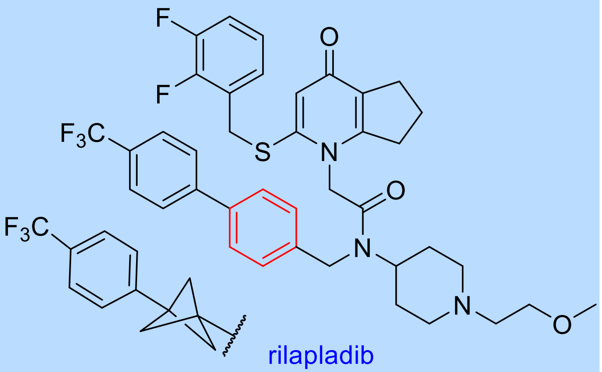


darapladib



BCP-darapladib





rilapladib

- ◆ Darapladib is a lipoprotein-associated PLA$_2$ (LpPLA$_2$) inhibitor
  - - binds to active site of LpPLA$_2$
  - - evaluated clinically as a therapy for atherosclerosis
- ◆ Has sub-optimal physicochemical properties
  - - ChromLog$D_{7.4}$ = 6.3; m/e = 667
- ◆ BCP analogue exhibited similar potency
  - - bioisosterism confirmed by X-ray cocrystal structures
- ◆ Solubility & permeability improved
  - - but: ChromLog$D_{7.4}$ increased & PFI was not altered
  - - low Cl in human liver microsomes in both series
- ◆ Properties mimicked by the BCP analogue of rilapladib

darapladib	Phenyl	BCP
pIC$_{50}$	10.2	9.4
Kinetic sol. (µM)	8	74
FASSIF sol. (µg/mL)	399	>1000
Membrane perm. (nm/s)	230	705
ChromLog $D_{7.4}$	6.3	7.0
PFI	10.3	10.0

rilapladib	Phenyl	BCP
pIC$_{50}$	9.6	NT
Kin sol. (µM)	<1	32
FASSIF sol. (µg/mL)	203	635
ChromLog $D_{7.4}$	6.74	7.06
PFI	11.74	11.06

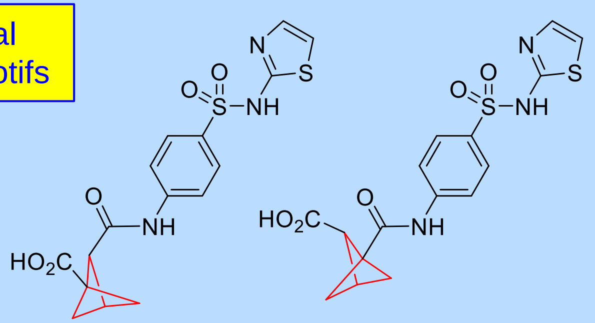
PFI = Log D_{pH7} + #Ar

Impact
increased solubility
enhanced membrane permeability
modest reduction in PFI

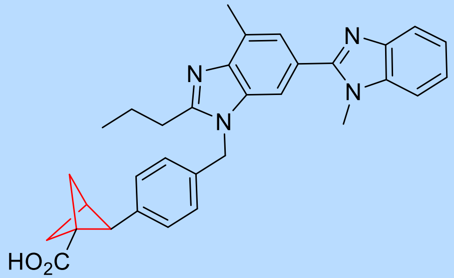
D.J. Hirst *et al.*, *ACS Med. Chem. Lett.*, 2017, **8**, 43-48

[1.1.1]-BCPs as *ortho*- or *meta*-Substituted Phenyl Mimics

Terminal phenyl motifs

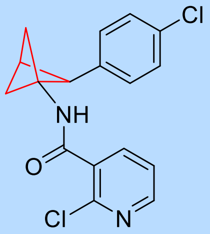


phthaylylsulfathiazole analogues

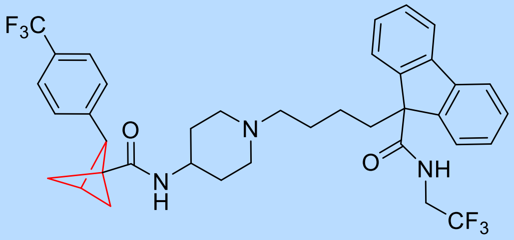


telmisartan analogue

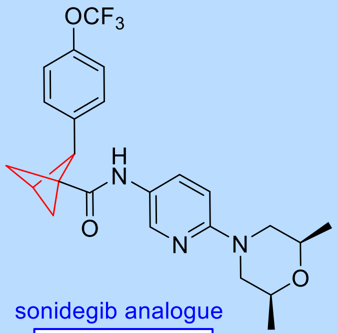
Biphenyl motifs



boscalid analogue



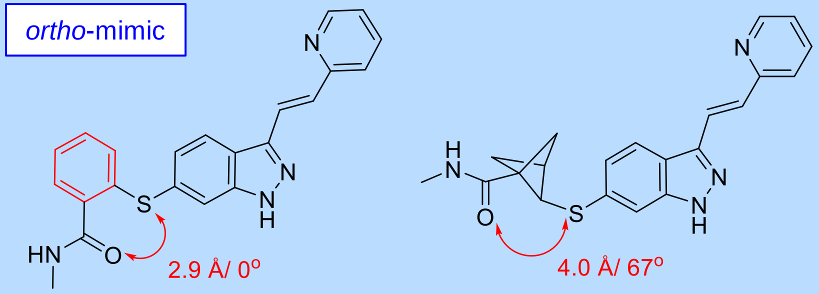
lomitapide analogue



sonidegib analogue

meta-mimic

ortho-mimic



axitinib	(+)-(*R*)-isomer	(-)-(*S*)-isomer
KDR IC_{50} = 1.6 nM	KDR IC_{50} = 1150 nM	KDR IC_{50} = 433 nM
Log *D* = 3.6	Log *D* = 3.6	Log *D* = 3.5
Sol. <1.6 μM	Sol. = 107.9 μM	Sol.125 μM
Perm. 35.4	Perm. 7.5	Perm. 2.8
hHepatocyte 21.4 μL/min	hHepatocyte 38.6 μL/min	hHepatocyte 34.0 μL/min

- Syntheses of 1,2-disubtituted [1.1.1]-BCPs developed
  - explored as *ortho*-and *meta*-substituted phenyl mimics
- No biological evaluations conducted
  - solubility typically enhanced by the transform
- Log *D*, membrane permeability & metabolic stability evaluated
  - effects varied

- Axitinib: VEGF kinase inhibitor
  - benzamide ring replaced with a [1.1.1]-BCP
  - potency declined by 270-718-fold
- X-ray cocrystal structure
  - O to S interaction (2.9 Å) favors planar conformation: 0°
  - both the NH & C=O of amide of axitinib engage the kinase
- [1.1.1]-BCP modeling
  - distance between O and S is 4.0 Å; torsion angle = 67°
  - disruption of key contacts between inhibitor & kinase
- Solubility enhanced with no change in Log *D*
  - other developability parameters less favorable

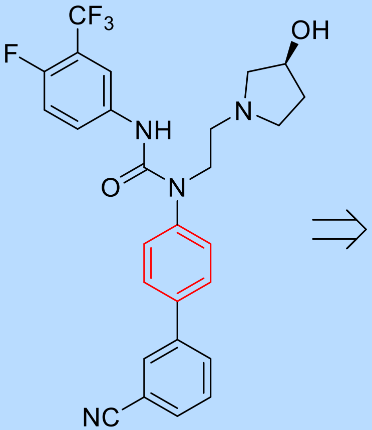
P.S. Baran, M.R. Collins *et al.*, *PNAS,* 2021, **118**, e2108881118

Melanin Concentrating Hormone Receptor (MCHR1) Antagonists

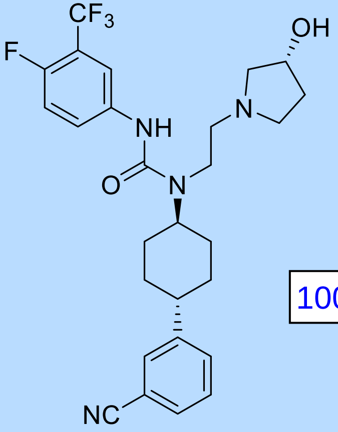
- Melanin Concentrating Hormone (MCH) regulates food intake
  - MCHR1 antagonists have potential as a therapy for obesity
- Potent biphenyl-based lead inhibitor identified
  - evidence for the release of the biphenyl aniline *in vivo*
  - tested positive in an Ames mutagenicity assay
- Explored a range of 6 membered rings as potential replacements
  - pyrazine, pyrimidine, piperidine all much less potent
- *trans*-Cyclohexyl analogue 150x ↓ potency to 297 nM
  - *cis*-isomer 10x weaker: K_i = 3,465 nM
- Cyclohexene (styrene) potent; 100x cyclohexane
  - 2 H atom difference from cyclohexane
  - concern for oxidation to phenyl *in vivo*
- Cyclopropanation blocked the potential for oxidation
  - all 4 possible isomers evaluated
    - all were potent antagonists
  - illustrates the complexity of using saturated phenyl isosteres

	Lead	Bioisosteric analogue					
	Ph	**Cy**	**Sty**	**A**	**B**	**C**	**D**
MCHR1 K_i (nM)	2	297	3	8.6	15	8.9	11.4
Rat PK AUC (h.ng/mL)				1924	2685	2183	2980
Mouse ex vivo binding (% at 6 h)				62	73	49	58
24 h DIO mouse assay at 6 h				16%	21%	1%	6%

DIO mouse: diet-induced obese mouse
% inh. of cumulative food intake at 30 mpk

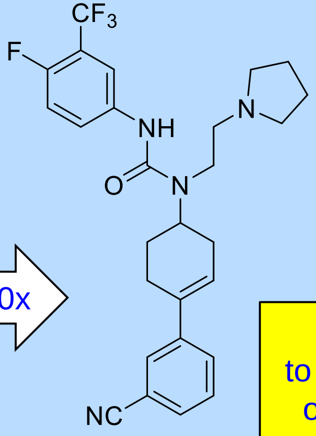


Ph
K_i = 2 nM

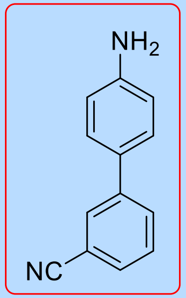


Cy
K_i = 297 nM

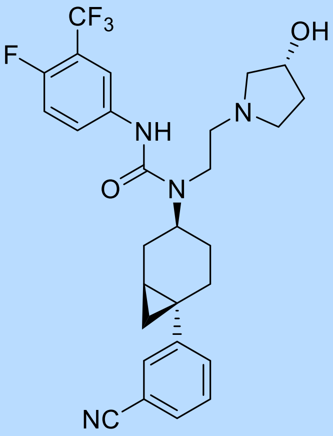
100x



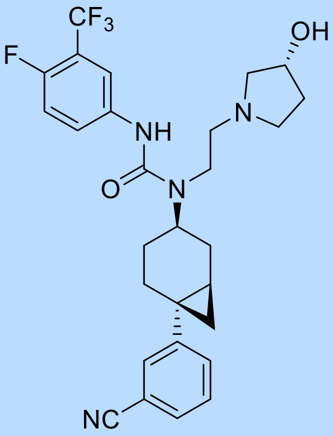
Sty
K_i = 3 nM



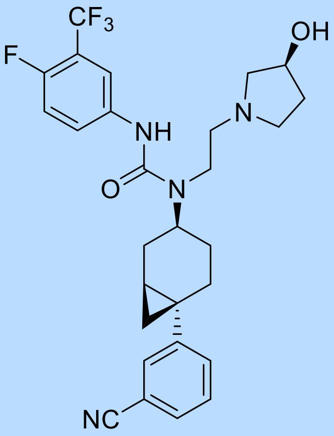
Impact
to eliminate release of an aniline as a potential mutagenic liability



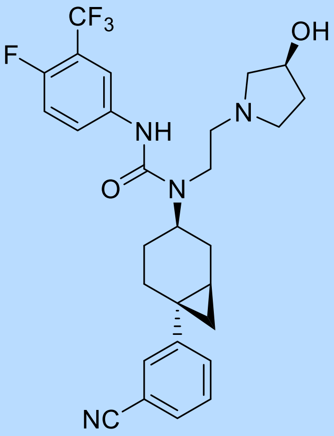
A
K_i = 8.6 nM



B
K_i = 15 nM



C
K_i = 8.9 nM



D
K_i = 11.4 nM

Superior *in vivo* performance

R. Xu *et al.*, *Bioorg. Med. Chem.*, 2006, **14**, 3285-3299