Applications of Non-Covalent Sulfur Interactions in Drug Design

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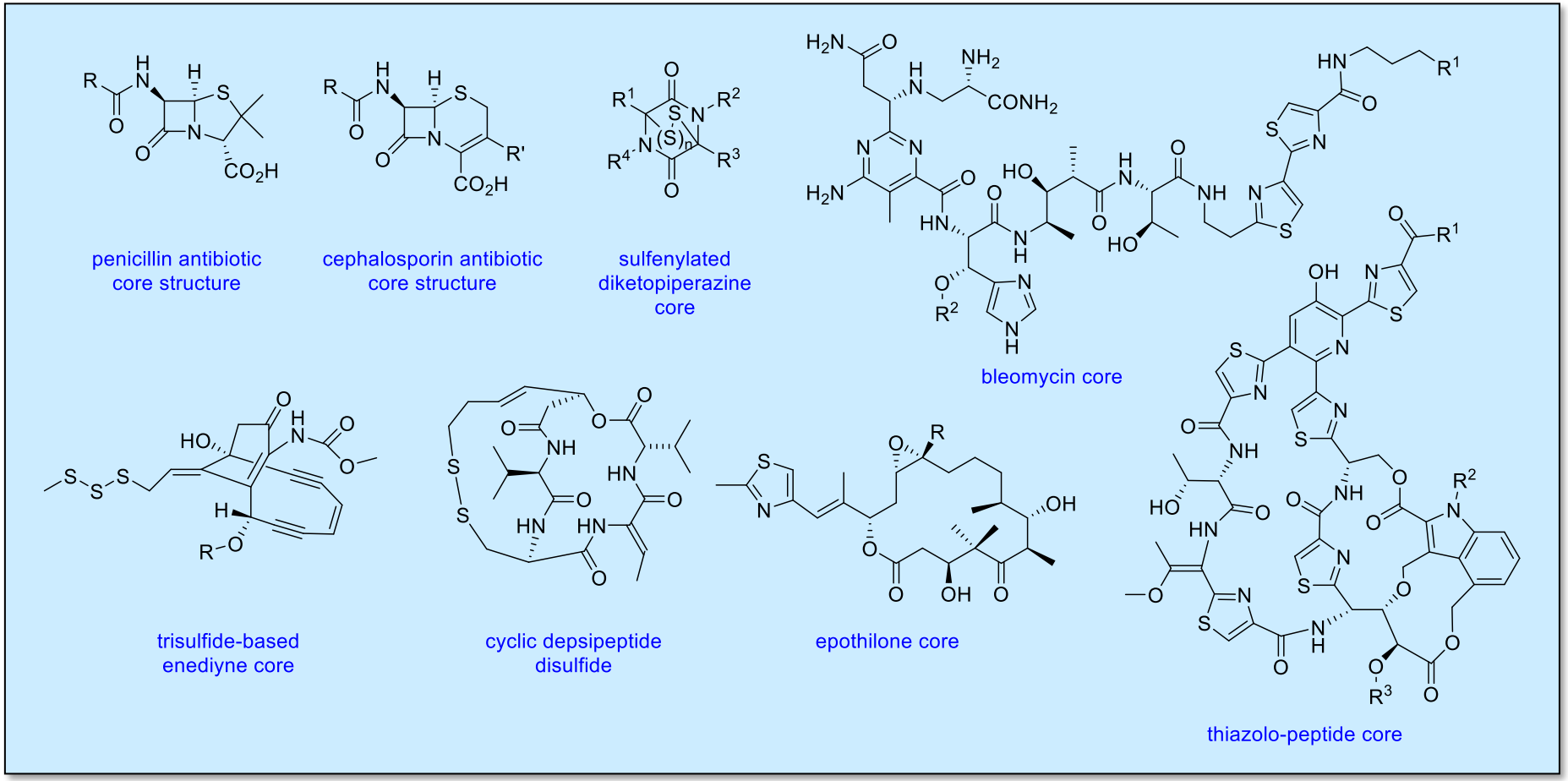
Outline

- Sulfur in natural products and drugs
- σ-Holes on sulfur
  - background, theory and occurrence
  - comparison with σ-holes on halogens
  - stereoelectronic implications for conformational control
- Applications of O to S interactions in drug design and synthesis
  - 1,4 O to S
  - 1,5 O to S
  - 1,6 O to S
- Applications of N to S interactions
  - 1,4 N to S
  - 1,5 N to S
  - 1,6 N to S
- Halogen to S interactions
  - F to S
  - Cl to S
- Intermolecular O to S interactions
  - emerging examples
- Conclusion

S can effectively mimic an OH or NH with the advantage of a reduced desolvation penalty – more lipophilic

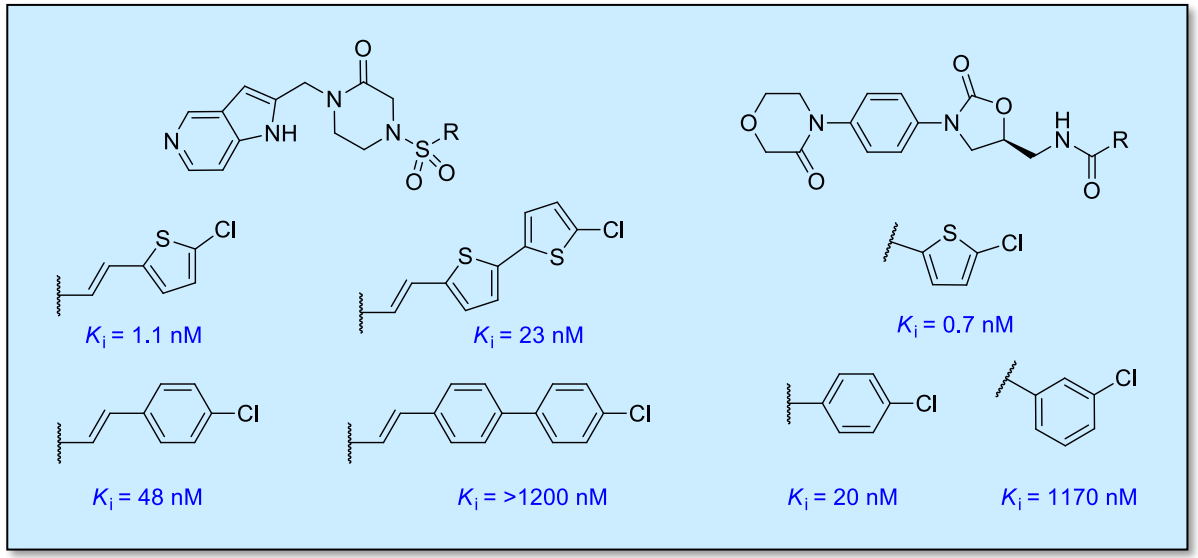
S can effectively mimic a Cl, Br or I Similarly lipophilic

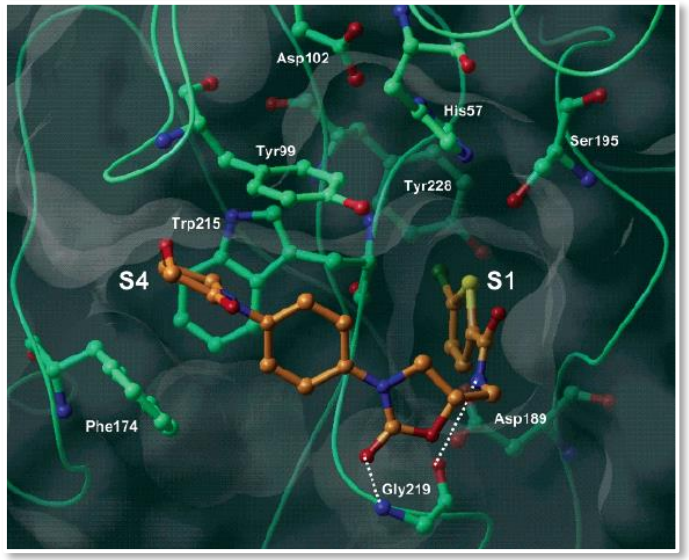
Sulfur in Natural Products



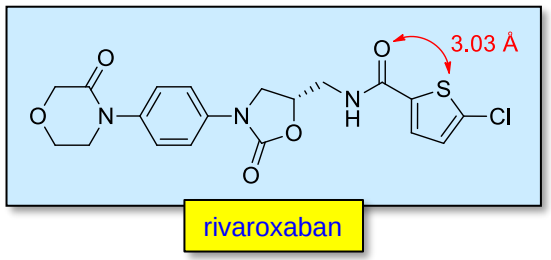
- Sulfur is an important element in multiple natural products
  - prevalent in approved drugs
  - not always electron-deficient

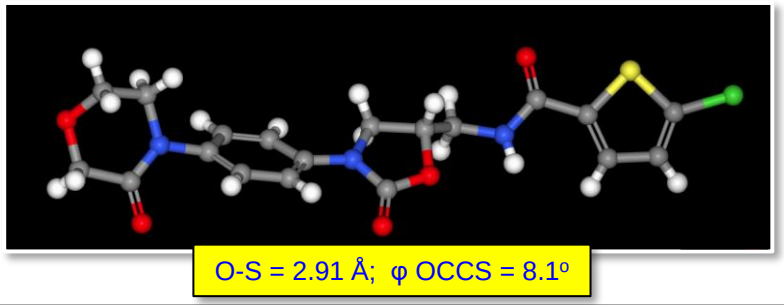
Thiophenes & Factor Xa Inhibition

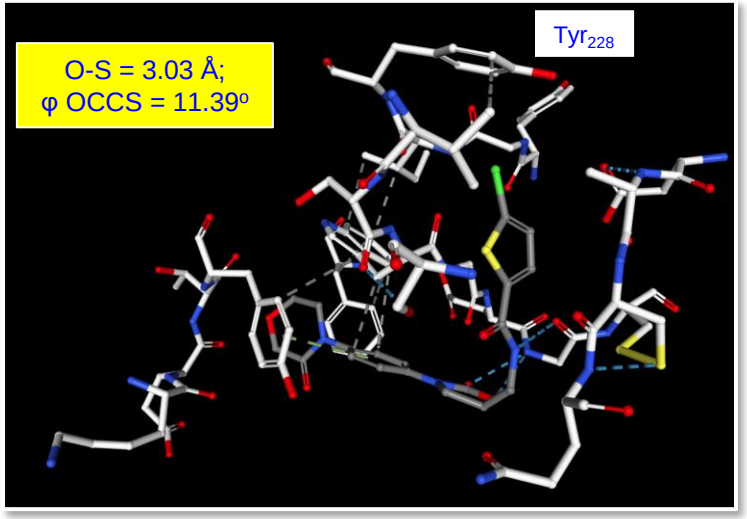




- Thiophene critical for potent FXa inhibition
  - Cl interacts with Tyr_{228} in S1 *via* a halogen bond
- Unique shape and vectors match FXa active site
  - critically important for expression of potent inhibition
  - intramolecular O to S interaction stabilizes thiophene geometry

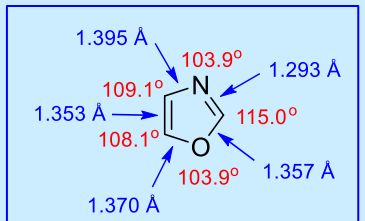


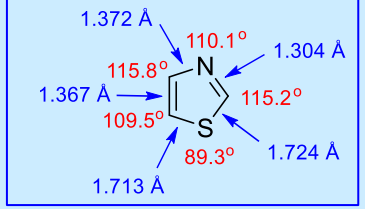


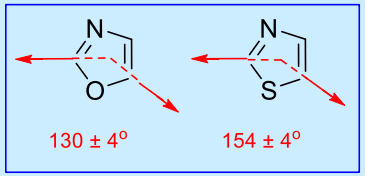


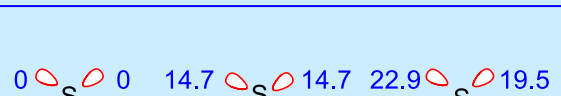
Y.M. Choi-Siedeski *et al., J. Med. Chem*., 2003, **46**, 681-684; S. Roehrig *et al., J. Med. Chem*., 2005, **48**, 5900-5908
J. Shen *et al*., *Acta Cryst.,* 2018, **E74**, 51-54; Y. Imai *et al., Protein Sci*., 2008, **17**, 1129-1137

Sulfur-Containing Heterocycles Have Unique Attributes

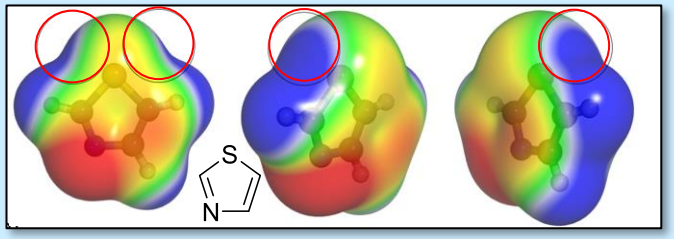




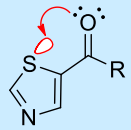




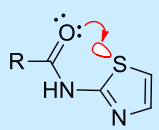
$V_{S,max}$ values: +ve electrostatic potentials



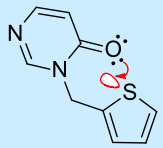
O to *S*



1,4-O to S interaction



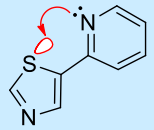
1,5- O to S interaction



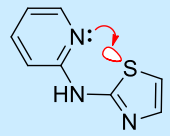
1,6- O to S interaction

X to *S*

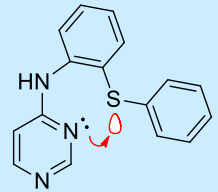
N to *S*



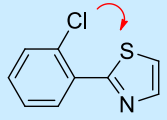
1,4-N to S interaction



1,5- N to S interaction



1,6- N to S interaction



	vdW radius	Σ X+S
S	1.80 Å	
O	1.52 Å	O + S: 3.32 Å
N	1.55 Å	N + S: 3.35 Å

interaction if proximity is < Σ of the vdW radii

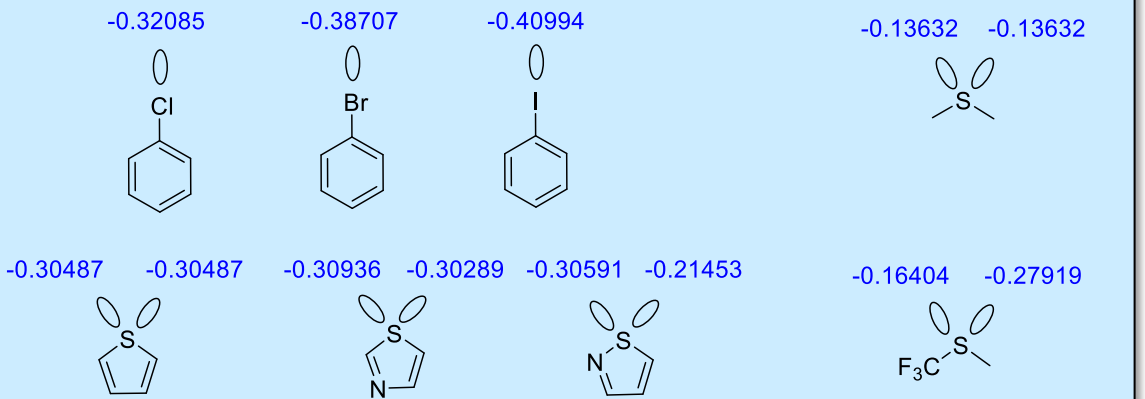
- S-containing azoles have altered geometries
  - 25% longer C-S bond lengths; bond angles smaller by 10-20°
- Electron-deficient *S* atoms possess area of positive electrostatic potential
  - corresponds to the C-S or N-S σ* orbital
  - modulated by electronics of substituents
- Interacts productively with electron-rich atoms – *O, N* or halogen
  - equivalent to a H-bond donor without the desolvation penalty
  - predominantly intramolecular due to geometrical constraints
    - plays a role in conformational constraint
- Can play a role in intermolecular interactions
  - examples beginning to be documented

1,4-interactions are generally considered to be electrostatic in nature

1,5- & 1,6- geometry allows orbital overlap

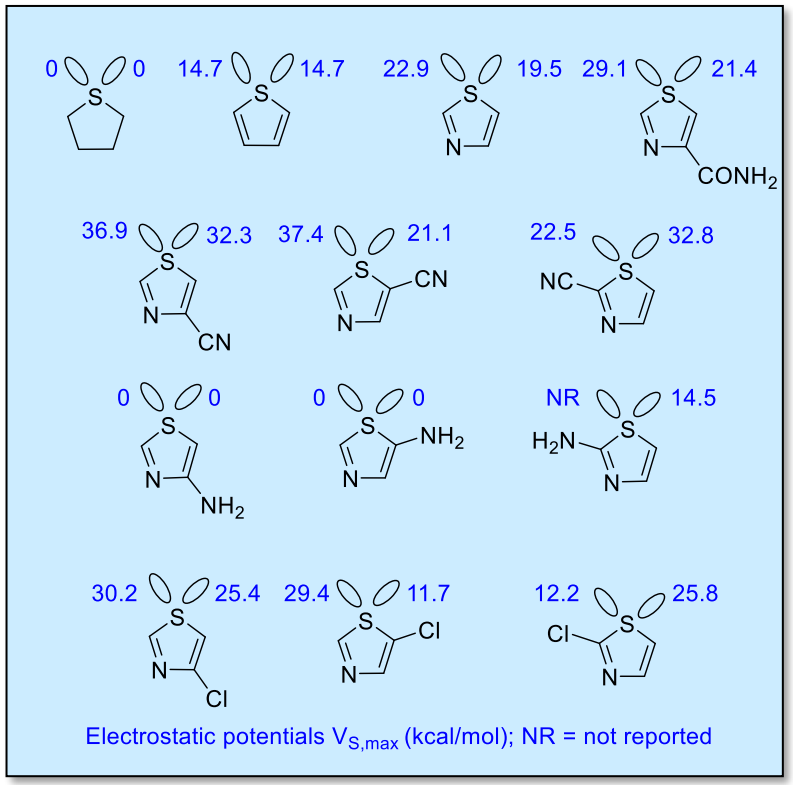
N.A. Meanwell *et al., J. Med. Chem.*, 2015, **58**, 4383-4438; N.A. Meanwell, *Adv. Het. Chem.*, 2017, **123**, 245-361
J.S. Murray *et al., Int. J. Quantum Chem.*, 2008, **108**, 2770-2781; T. Lu *et al., J. Chem. Inf. Model.* 2015, **55**, 2138−2153

σ Holes – Halogens & S Atoms

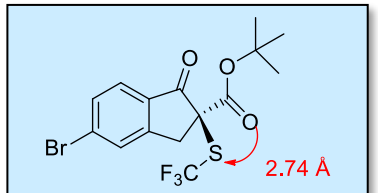


σ* non-bonded orbital energy levels in atomic units based on B3LYP/6-311G(d)

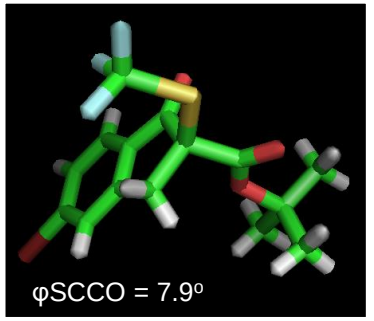
- S σ* orbital energy level comparable to PhCl
  - halogen geometry better disposed for intermolecular interactions
- Low lying σ* orbitals on electron-deficient S atoms
  - asymmetric σ* holes on S dependent on structure, substitution pattern
  - stereoelectronic effects: disposed for intramolecular interactions
- σ* orbital energy level can be modulated by substituent
  - EWGs increase size of electrostatic potential, reduce energy of σ*
  - EDGs reduce the energy of σ*: can abrogate the effect
- CF_3 reduces energy of σ* on sulfide S
  - close association in single crystal X-ray structure (1,4-interaction)
  - O to S = 2.74 Å; SCCO torsion angle = 7.9°



Electrostatic potentials $V_{S,max}$ (kcal/mol); NR = not reported

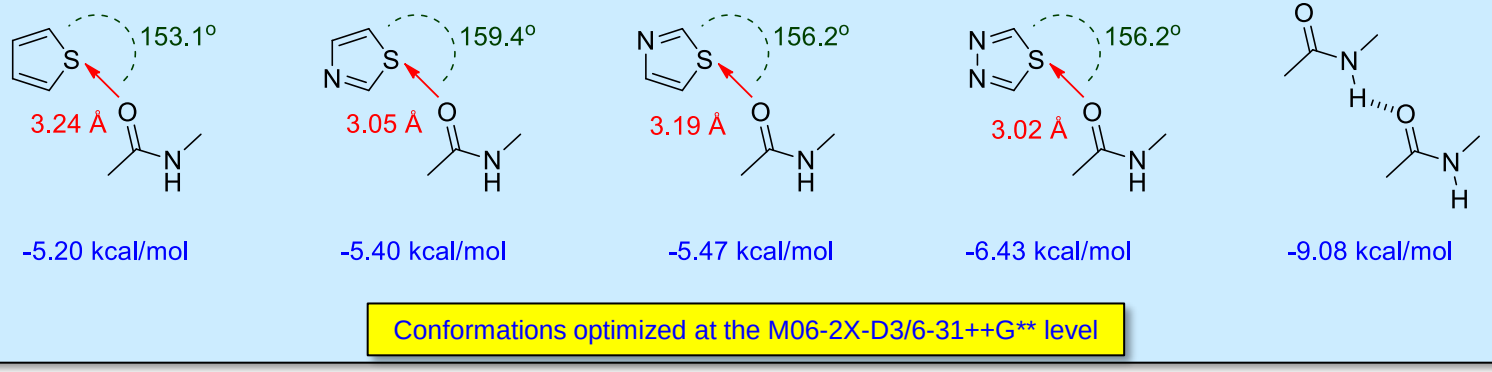


Σ O+S = 3.32 Å



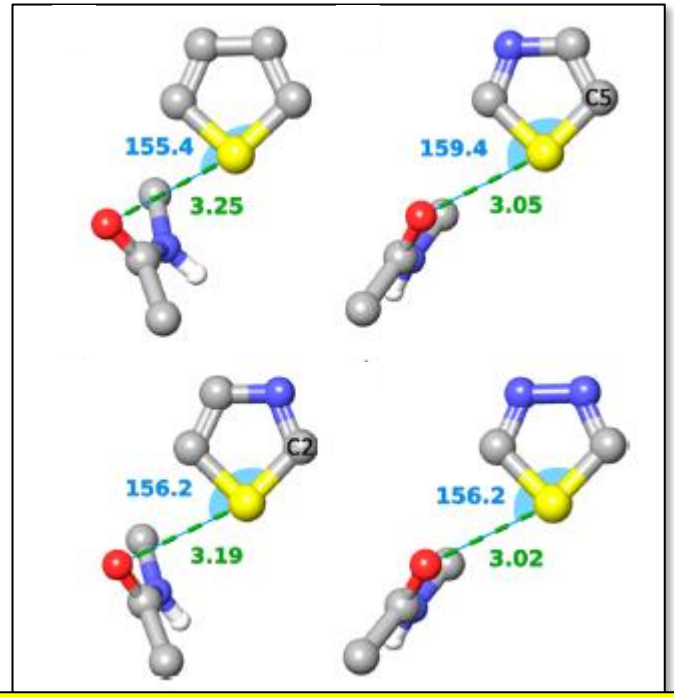
J.S. Murray *et al., Int. J. Quantum Chem.,* 2008, **108**, 2770-2781; N.A. Meanwell *et al., J. Med. Chem.,* 2015, **58**, 4383-4438
X. Wang *et al., Angew. Chem. Int. Ed.,* 2013, **52**, 12860-12864; T. Bootwicha *et al., Angew. Chem. Int. Ed.,* 2013, **52**, 12856-12859

σ Holes & O/S Bonding Interactions



-5.20 kcal/mol | -5.40 kcal/mol | -5.47 kcal/mol | -6.43 kcal/mol | -9.08 kcal/mol

Conformations optimized at the M06-2X-D3/6-31++G** level



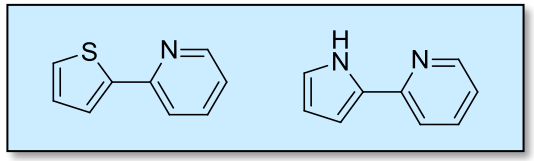
Note: for thiophene, discordance between Table & Figure

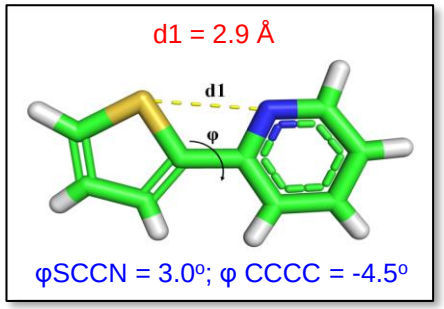
- H-bond strength is typically 5.25-7.20 kcal/mol
  - H_2O dimer = 5.7 kcal/mol
  - H_2O-NH_3 = 7.20 kcal/mol
- Thiophene-NMA
  - C-S = -5.20 kcal/mol; 3.24 Å
- Thiazole-NMA
  - C-C-S = -5.40 kcal/mol; 3.05 Å
  - N-C-S = -5.47 kcal/mol; 3.19 Å
- Thiadiazole-NMA
  - N-C-S = -6.43 kcal/mol; 3.02 Å
- NMA-NMA
  - H-bond = -9.08 kcal/mol

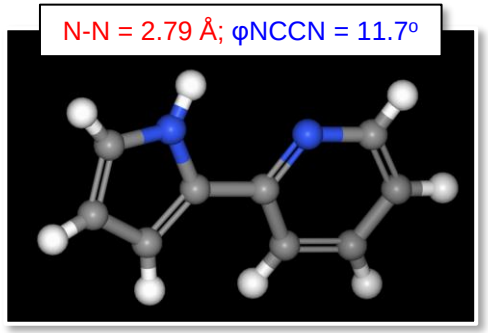
O-S interactions ~60-70% of energy of a H-bond

X. Zhang *et al., J. Chem. Inf. Model.,* 2015, **55**, 2138−2153

Sulfur Interactions and Conformation

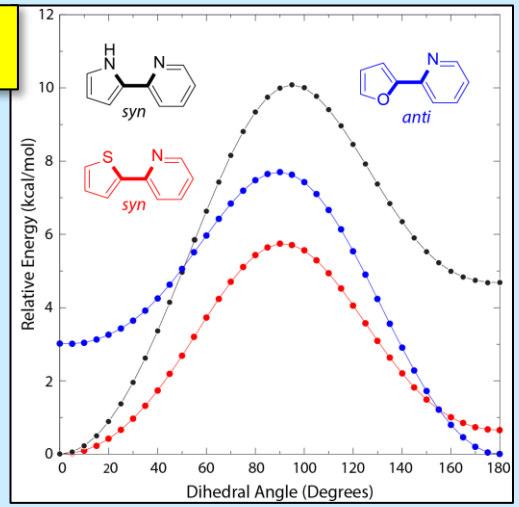


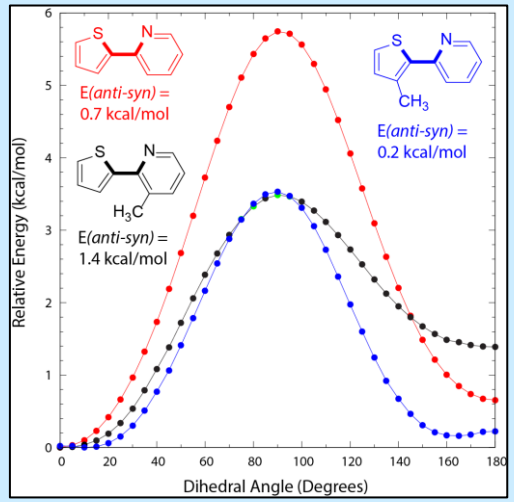


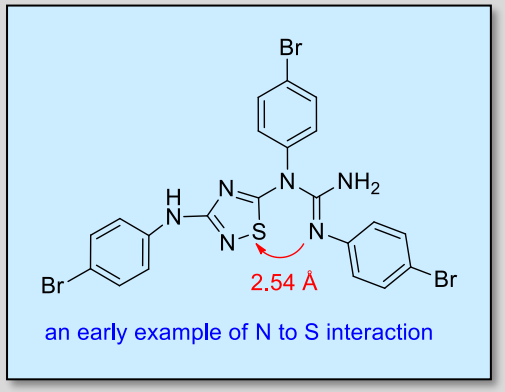


- 2-Thienyl pyridine
  - d1 = 2.9 Å; φSCCN = 3.0º; φ CCCC = -4.5º
  - N to S distance much < than Σ of vdW radii
  - favors a planar molecular topography
- *Syn* conformation of thienyl pyridine has lowest energy at 0º
  - similar to 2-pyrrolyl pyridine; furyl pyridine has lowest energy at 180º
- 3-Methyl pyridine has enhanced preference for *syn* form
  - CH_3 inductively donates electrons to strengthen N to S
  - overcomes allylic 1,3-strain
- Thiophene is an isostere of pyrrole in this context
  - S mimics the effect of N-H

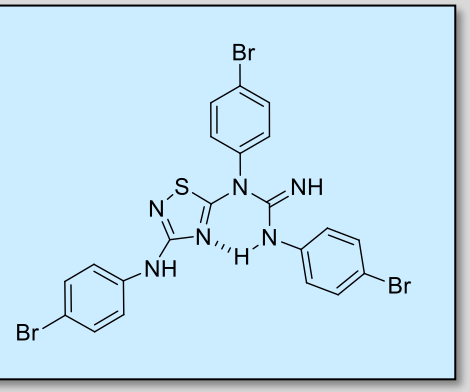
dipole effects with pyrrole?







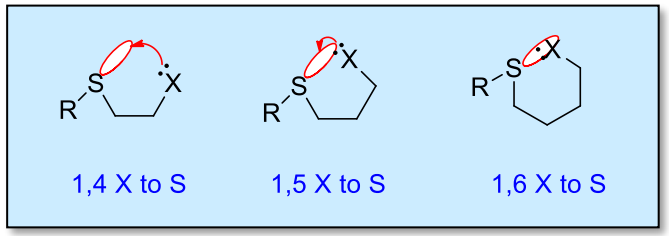
an early example of N to S interaction

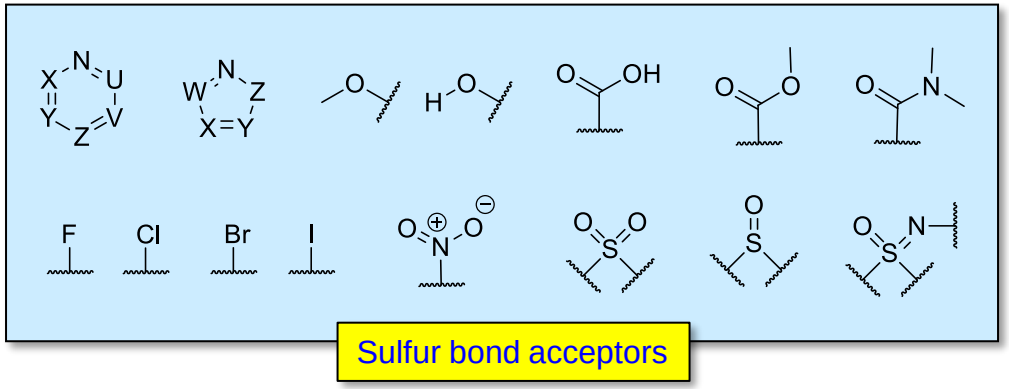


O-S interaction favored over H-bond

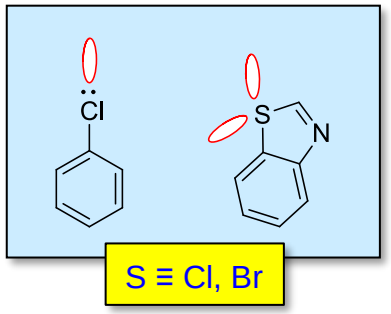
R. Ghosh *et al., Acta Cryst.,* 1993, **C49**, 1031-1032; K. Akiba *et al*., *Chem. Lett.,* 1976, 723-726; *Tetrahedron Lett.,* 1976, **17**, 3819-3820

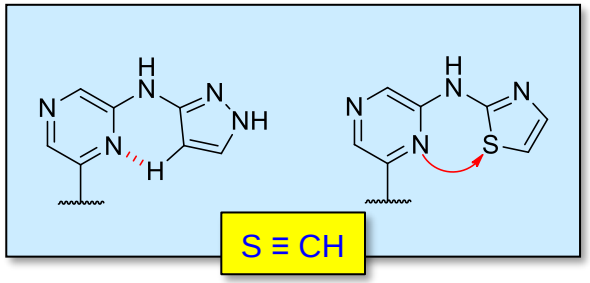
Sulfur Bond Acceptors & Bioisosteric Relationships

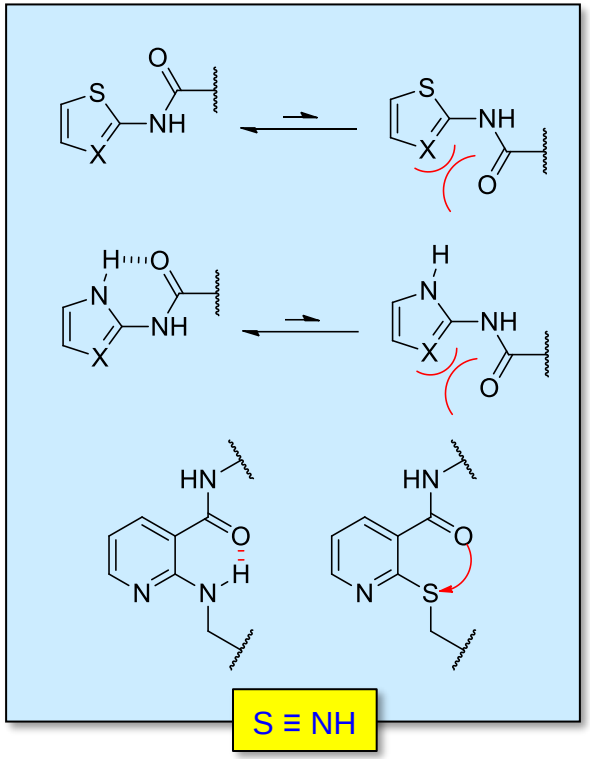


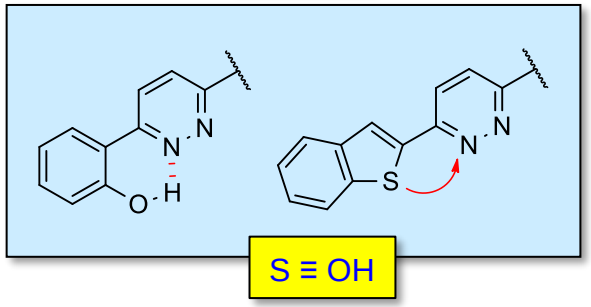


- Geometry of S σ* holes influences interaction with electron donor
  - 1,4 relationship relies upon an electrostatic interaction
  - 1,5- & 1,6- can avail of orbital overlap
- Atoms with lone pairs of electrons act as S bond acceptors
  - azine, azole N atoms, range of O atoms, & halogens
  - S atoms, π-systems
- Isosteric relationships
  - S ≡ N-H; S ≡ O-H; S ≡ C-H; S ≡ Cl





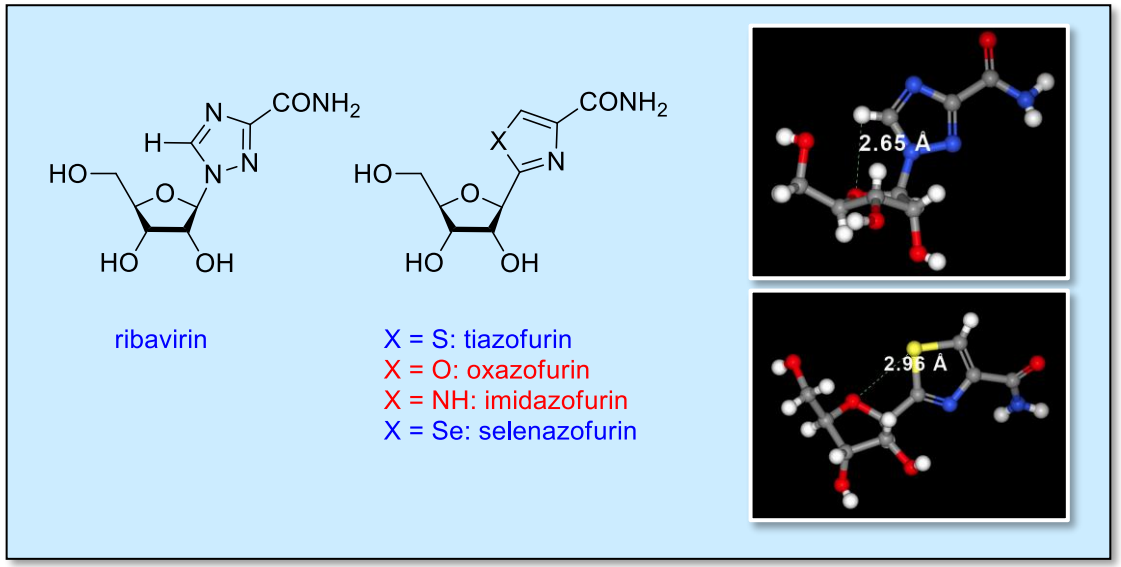




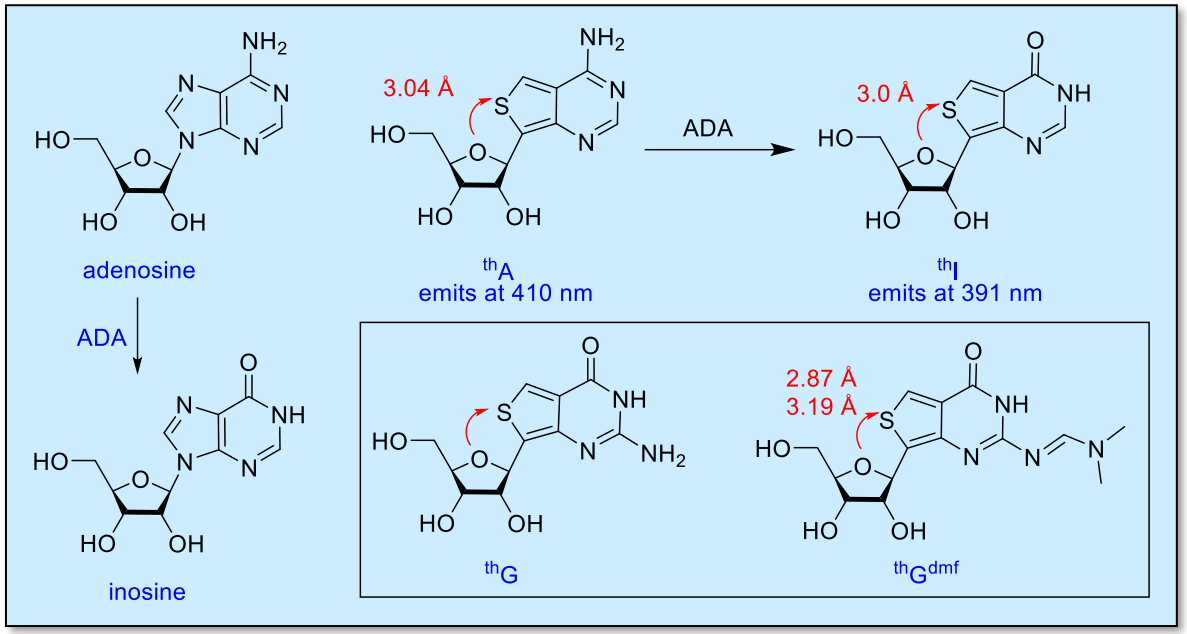
O to S Interactions

1,4 O to S Interactions

Nucleosides: Tiazofurin, Adenosine Deaminase Substrates

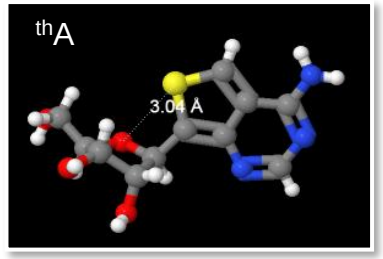


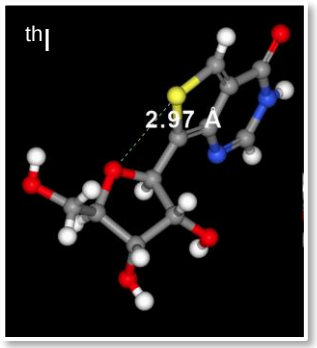
- Ribavirin is an IMPDH inhibitor after metabolism to NAD analogue
  - tiazofurin expresses similar biological activity
- X-rays of tiazofurin, 2-deoxy and the α-anomer all reveal close O/S contacts
  - O-S distances of 2.83-3.02 Å
  - interaction enhanced by the $CONH_2$ electron withdrawal
- Selenazafurin also active: O to Se interaction stabilizes active conformation
  - oxazofurin, imidazofurin not active
- Observations explained by conformational arguments
  - favorable O to S stabilizes conformation recognized by enzymes
  - C-H to O in ribavirin



- thA designed as adenosine deaminase (ADA) substrate
  - thA emits at 410 nm while thI emits at 391 nm
- Single crystal X-rays revealed close O to S contacts
  - stabilizes conformation preferred by adenosine
  - recognized by deaminase

Impact
Conformational preorganization for molecular recognition

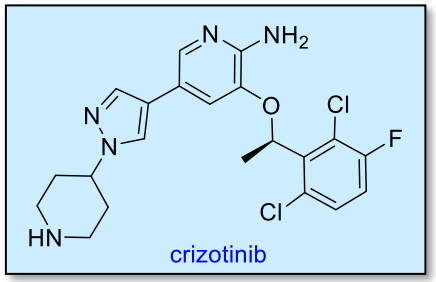


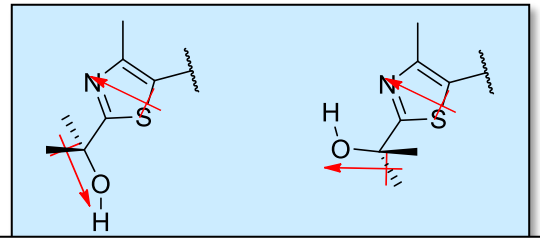


Σ O + S: 3.32 Å

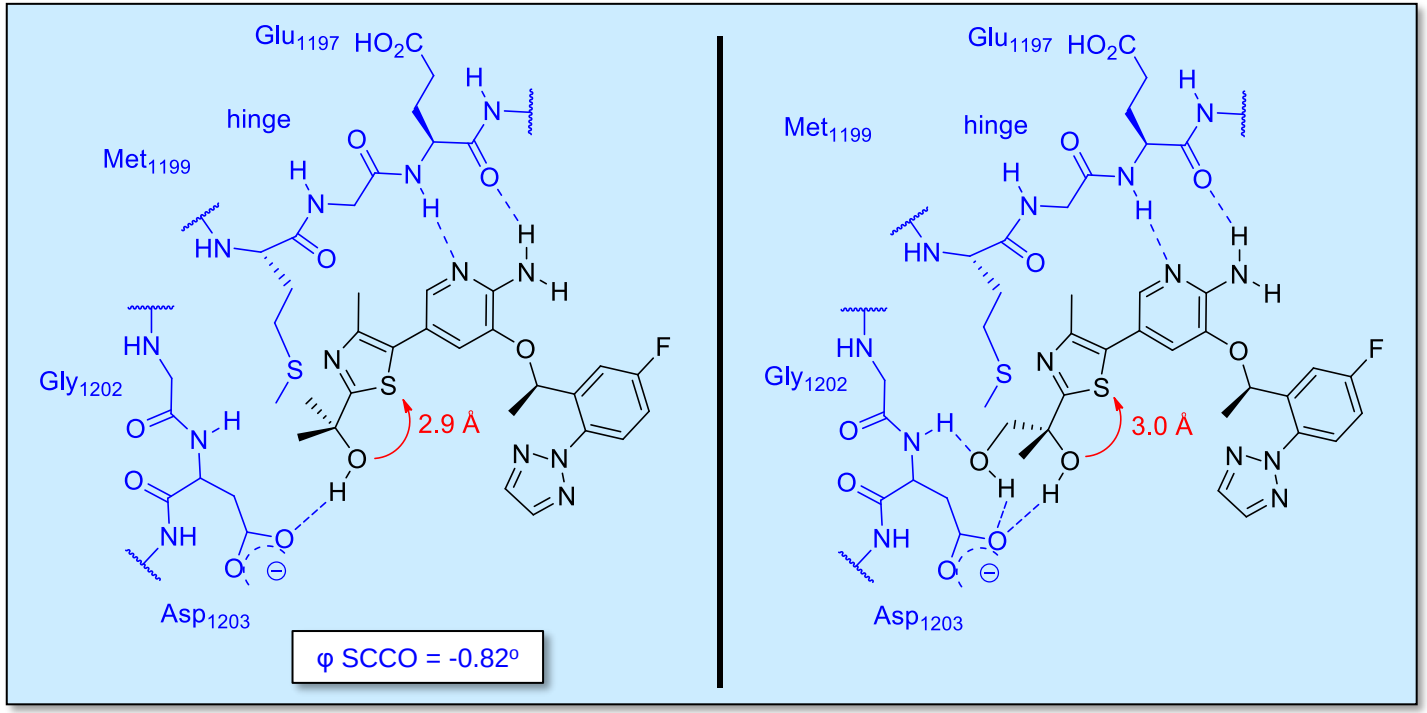
B.M. Goldstein *et al., JACS,* 1983, **105**, 7416-7422; *J. Med. Chem.*, 1988, **31**, 1026-1031*; Advan. Enzyme Regul.*, 2000, **40**, 405-426
Y. Tor *et al., J. Am. Chem. Soc.,* 2011, **133**, 14912-14915; *Angew. Chem. Int. Ed.*, 2013, **52**, 14026-14030

Optimization of Alk Inhibition by Crizotinib





O/S & dipole effects overcome intramolecular H-bond?



- Crizotinib designed as a c-Met inhibitor
  - effects in non-small cell lung cancer mediated by Alk
- Optimization of potency towards Alk focused on the pyrazole moiety
  - enhance WT & resistant mutant L1196M Alk potency; engage Asp_{1203} *via* H-bonds
- Mono OH & diols made to establish H-bond network with kinase
  - close contact between O & S stabilizes planar topography
  - dipole-dipole interactions may play a role in topology
- Alcohol engages Asp_{1203}; diol establishes 2 H-bonds
  - alcohol: K_i = 0.4 nM; cell EC_{50} = 27 nM
  - diol: K_i = 0.2 nM; cell EC_{50} = 6.6 nM

Alk = anaplastic lymphoma kinase

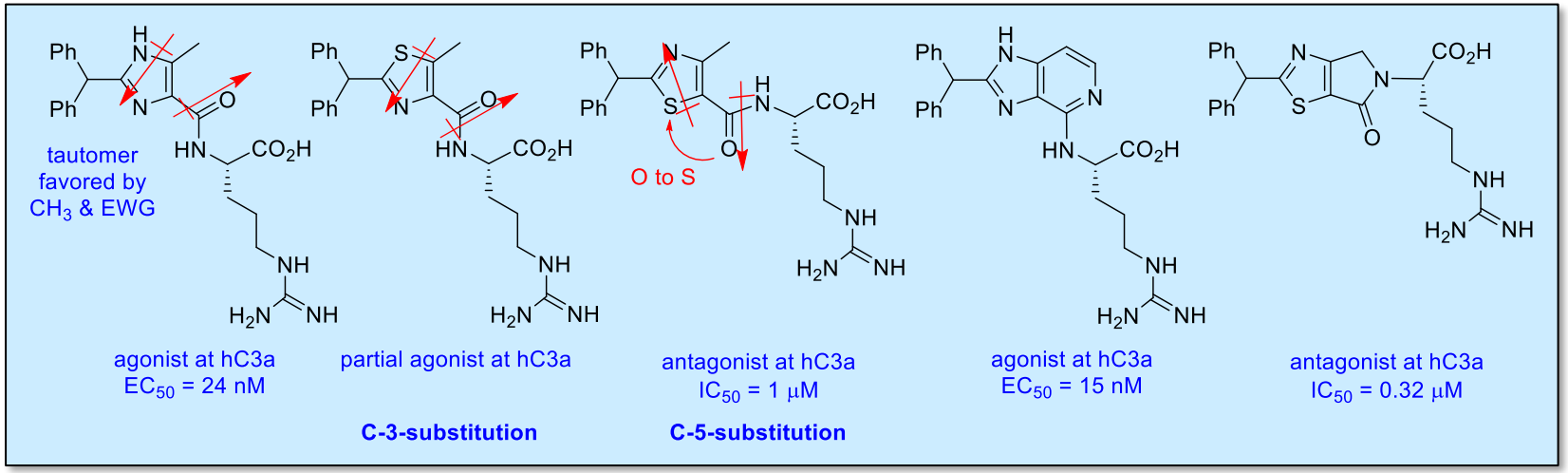
Impact
Conformational preorganization for molecular recognition
H-bond assistance

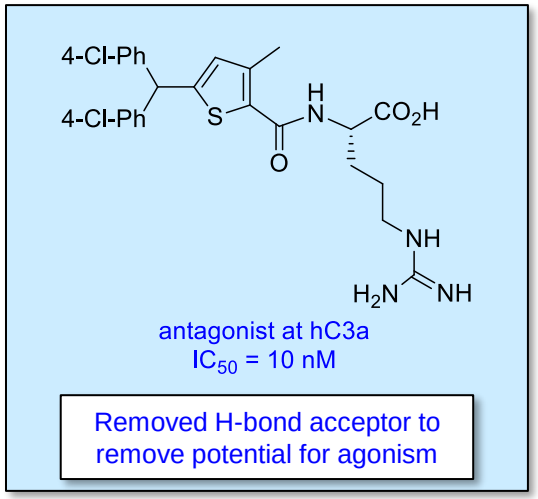
Origin
1,4- O/S & dipole-dipole effects

Σ O + S: 3.32 Å

Q. Huang *et al.*, *J. Med. Chem.*, 2014, **57**, 1170-1187

Dipole & O/S Interactions in C3a Ligands





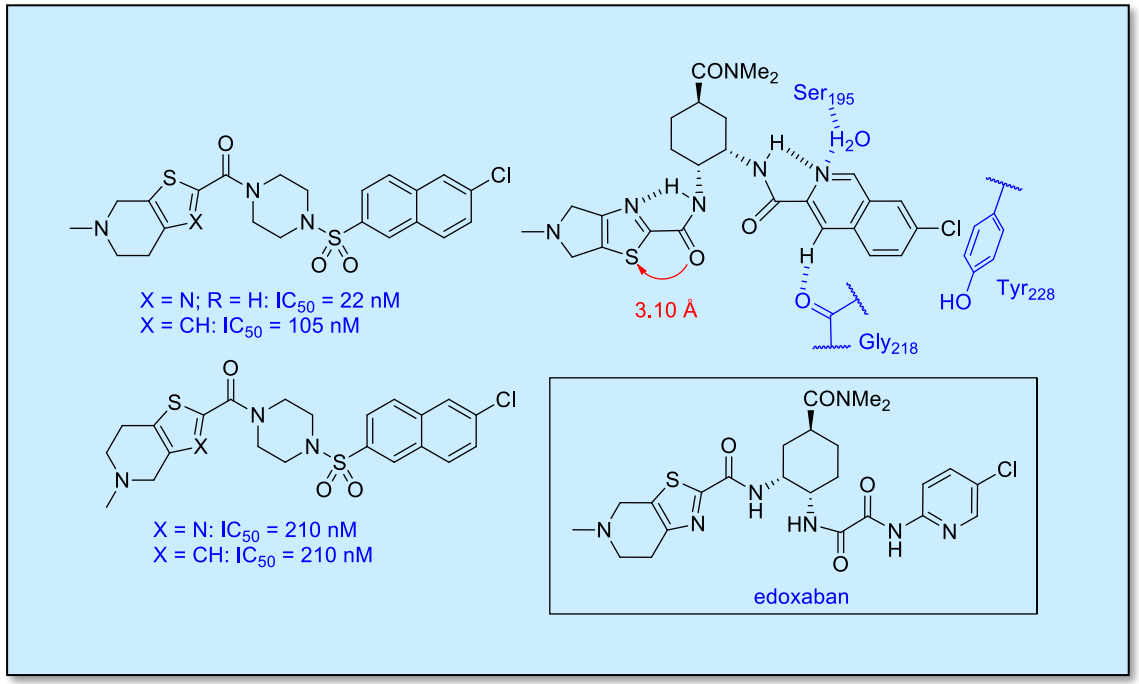
- Complement C3a: a pro-inflammatory 77 AA helical protein that binds to GPCR C3aR
  - stimulates chemotaxis of immune cells to sites of infection
  - intracellular Ca^{2+} mobilization releases bactericidal agent & inflammatory cytokines
- Imidazole is a potent agonist
  - partially mimicked by a C3-thiazole homologue
  - isomeric C5-thiazole is an antagonist: *S* and *N* switched topologically
- Rationalized by topological preferences
  - C=O & ring dipoles align to minimize electrostatic repulsion:
    - controls C=O geometry
  - dipole interactions reversed in topologically isomeric thiazole
    - also stabilized by 1,4-*O* to *S* interaction
- Activity-topology relationship confirmed with locked analogues
  - activity of fused ring isosteres consistent with hypothesis

Impact
Conformational preorganization for molecular recognition

Origin
1,4- O/S interaction
Dipole-dipole effects
Intramolecular H-bond

R.C. Reid *et al., J. Am. Chem. Soc.*, 2014, **136**, 11914-11917; *J. Med. Chem.,* 2020, **63**, 529−541
For a discussion of imidazole tautomerism see: R. Ganellin, *J. Med. Chem.*, 1981, **24**, 913-920

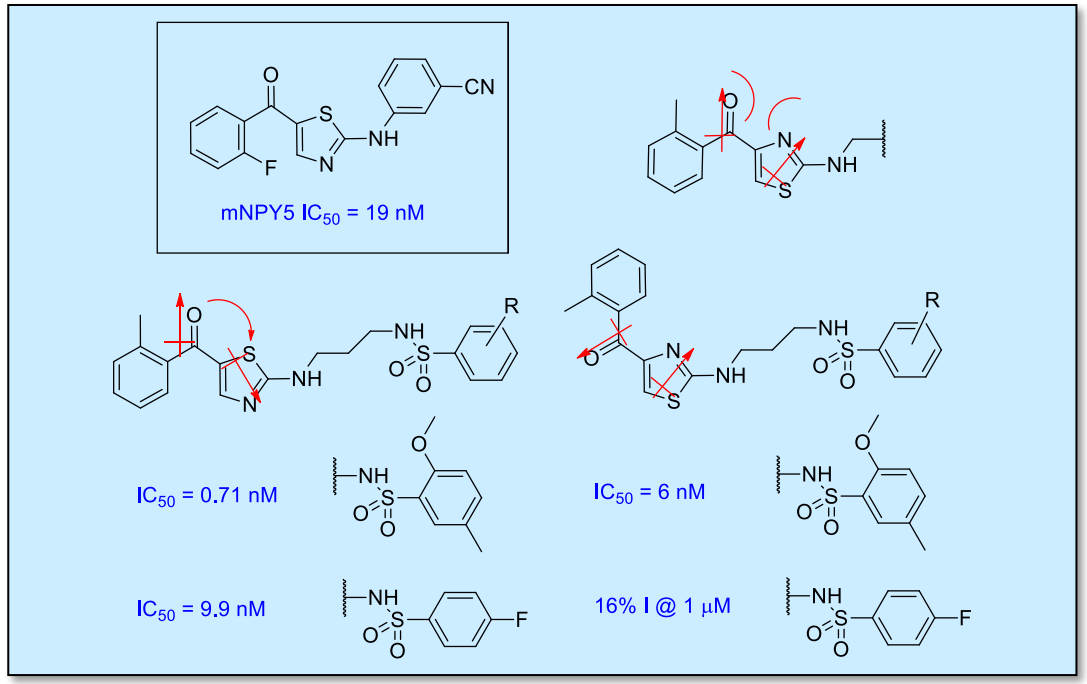
1,4 C=O to S in FXa Inhibitors & NPY5 Antagonists



- Potency of FXa inhibitors sensitive to piperidine amine topology
  - amide/thiazole conformation stabilized by O to S/unfavorable O to N
  - amide/thiophene modulated by favorable O to S
- N-Me alignment important to avoid steric clash with enzyme
  - lower penalty for thiophene to adopt alternate conformation

Impact
Conformational preorganization for molecular recognition

Origin
1,4- O/S interaction
Dipole-dipole effects
Intramolecular H-bond



- Potent thiazole-based mouse NPY5 antagonist
  - optimized by extending 2-substituent
- Isomeric thiazole ≥10-fold weaker
  - attributed to inherent conformational preferences
- Active compounds stabilized by favorable O to S & dipole/dipole effects
  - alternate thiazole adopts different conformation
  - reduces unfavorable O to N and dipole-dipole interactions

Impact
Conformational preorganization for molecular recognition

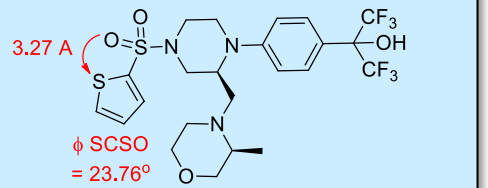
Origin
1,4- O/S interaction
Dipole-dipole effects

Σ O + S: 3.32 Å

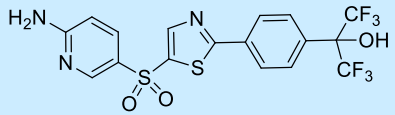
S. Komoriya *et al., J. Med. Chem*., 2004, **47**, 5167-5182; *Bioorg. Med. Chem.,* 2006, **14**, 1309-1330; 2009, **17**, 1193-1206
W. Guba, M. Nettekoven *et al., Bioorg. Med. Chem. Lett*. 2005, **15**, 1599-1603; 3446-3449; *ChemMedChem* 2006, **1**, 45-48

S Interactions in GK-GKRP Disruptors

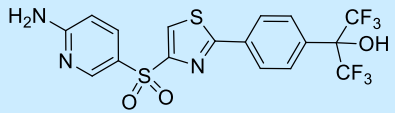
AlphaScreen IC_{50} = 1.42 μM
rGK translocation EC_{50} = 3.64 μM



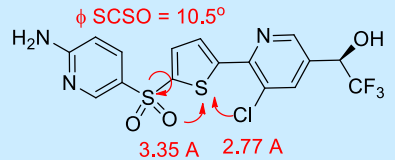
AlphaScreen IC_{50} = 0.021 μM
rGK translocation EC_{50} = 0.082 μM



AlphaScreen IC_{50} = 0.53 μM

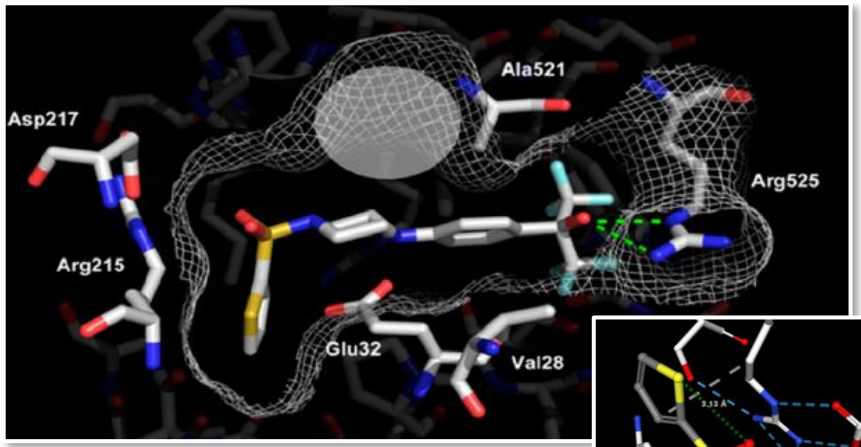


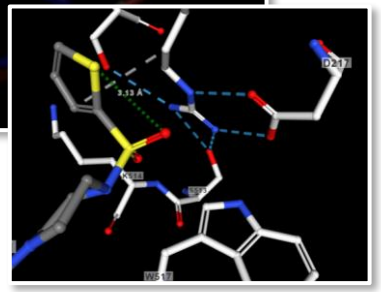
AlphaScreen IC_{50} >33 μM



AlphaScreen IC_{50} = 0.129 μM
rGK translocation EC_{50} = NT

Cl-S dominates over N-S



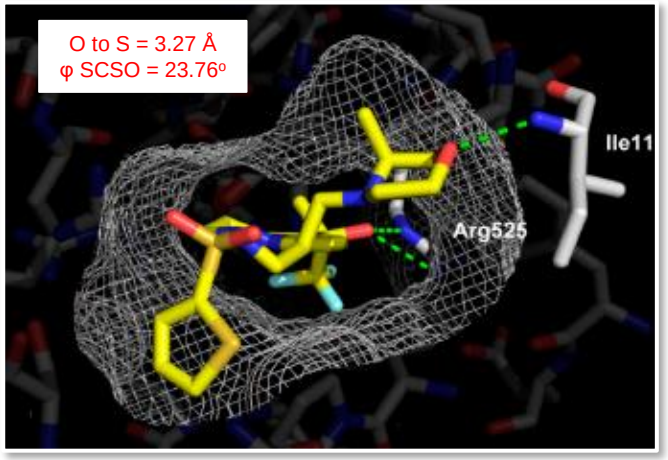


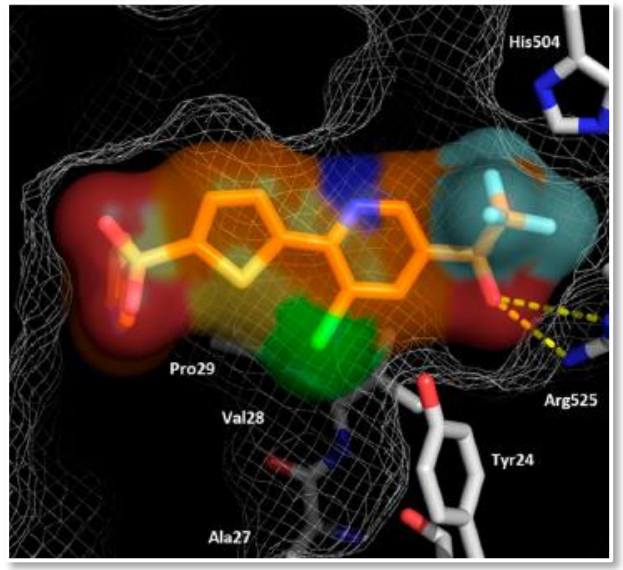
Impact
Conformational preorganization for molecular recognition

Origin
1,4- O/S; 1,5- Cl/S

- GK- GKRP interaction inhibitors
  - enhances GK levels & modulates glucose
- Screening lead as 2-SO_2 thiophene
  - close O/S interaction stabilizes conformation
  - maintained in optimized homologue
- Second class of GK- GKRP interaction inhibitors
  - thiazole topology critical: 60x Δ
  - O/S & Cl/S interactions stabilize conformation
  - Cl/S dominates over N/S

GK: glucose kinase GKRP: glucokinase regulatory protein

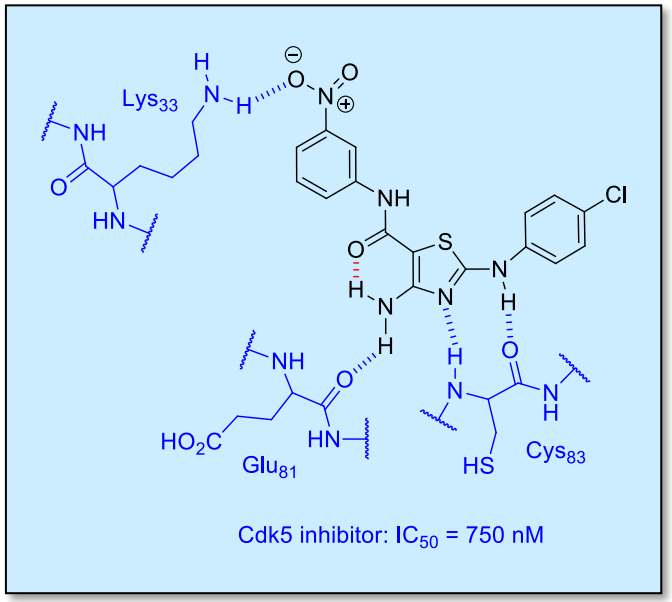


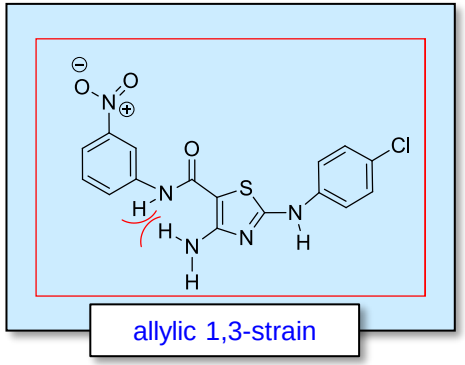


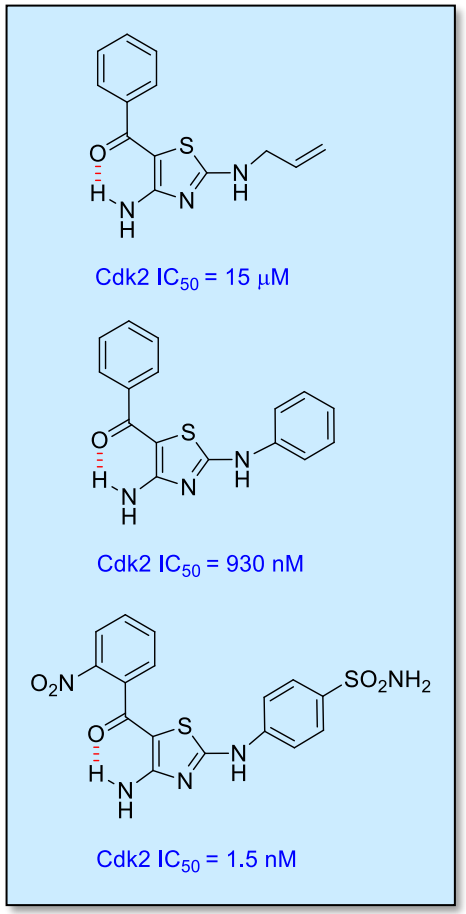
Σ O + S: 3.32 Å

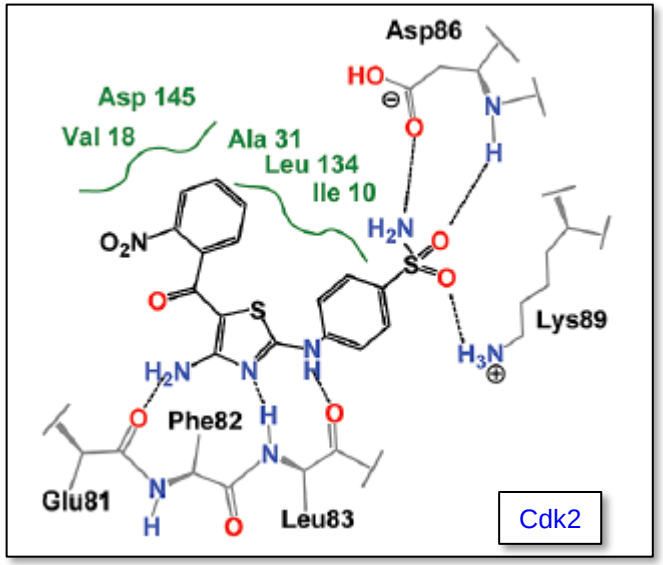
K.S. Ashton *et al., J. Med. Chem.*, 2014, **57**, 309-324; N.A. Tamayo *et al., J. Med. Chem.*, 2015, **58**, 4462-4482

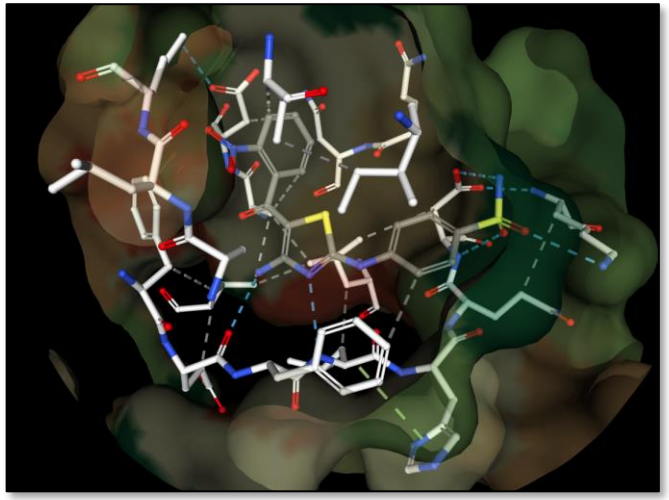
Cdk Inhibitors: H-Bonding Dominates











- Amide C=O/NH intra-molecular H-bond forms a pseudo ring
  - C=O interacts with proximal NH
  - projects NO_2-Ph ring toward Lys_{33}
- Electron-donating substituents reduce electrostatic potential of C-Sσ*
  - productive O-S interaction would create allylic-1,3-strain
- Ketone-based series adopted similar topology
  - SO_2NH_2 engaged in 3 H-bonding interactions
  - significantly (600x) improved potency

Impact
Conformational preorganization for molecular recognition

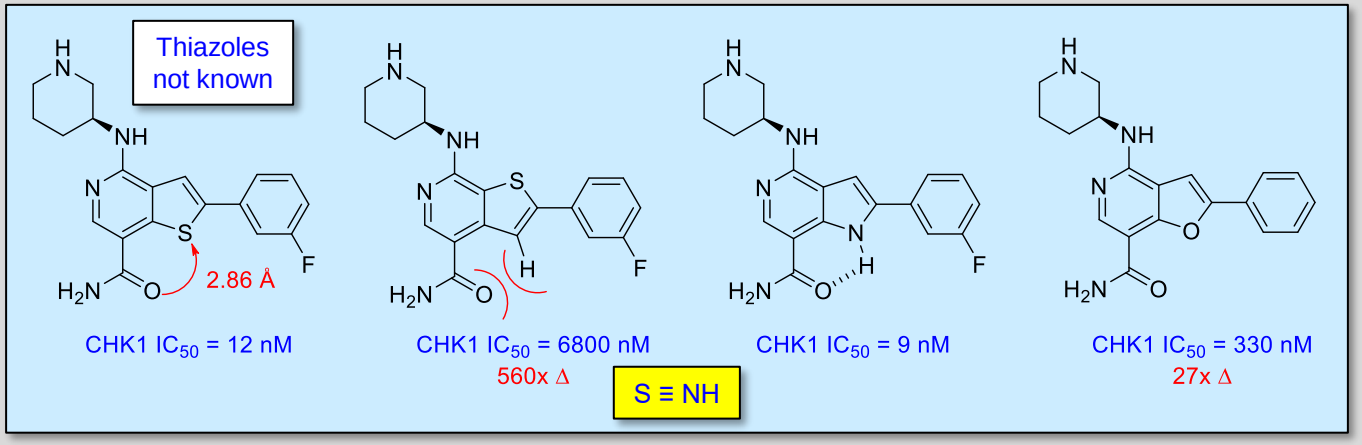
Origin
Intramolecular H-bond
Reduced Sσ* effect due to substation pattern

J.K. Laha *et al.*, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2098-2101; J.S. Ahn *et al.*, *Chem. Biol.*, 2005, **12**, 811-823; E. Schonbrunn *et al.*, *J. Med. Chem.*, 2013, **56**, 3768-3782

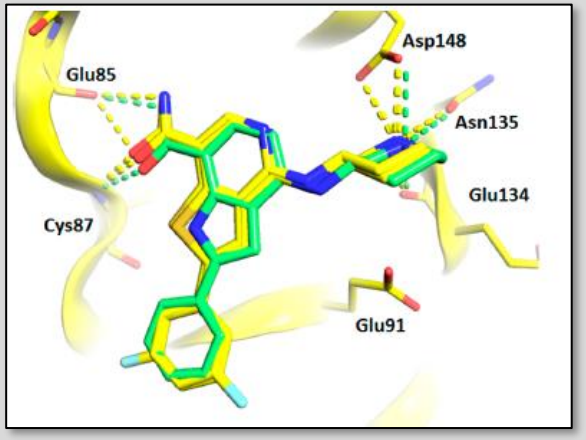
1,5 O to S Interactions

O to S in CHK1 & VEGFR Inhibitors

1,5- *O* to *S*



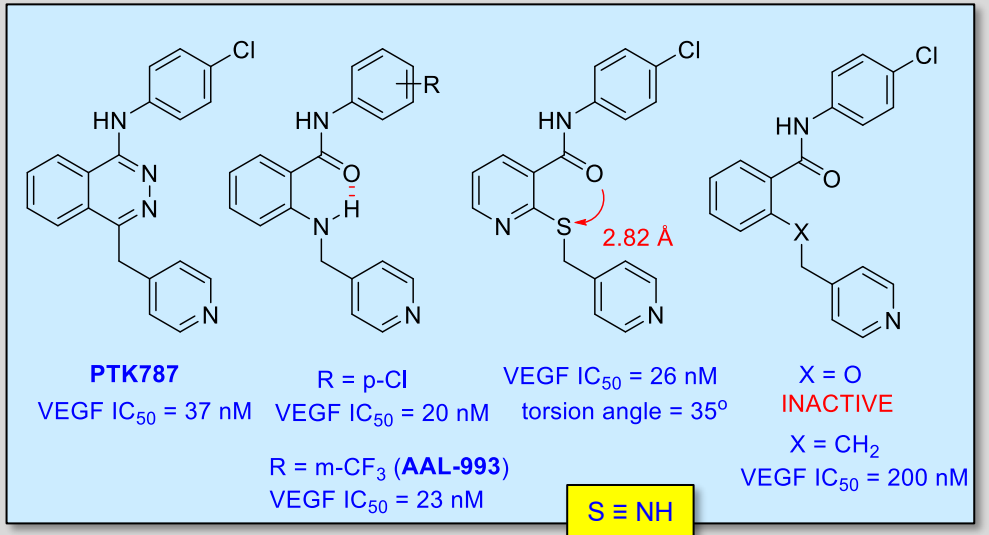
- Thiophene topology critical for potency
  - **560-fold** difference in enzyme inhibition
- Stabilizing *O* to *S* interaction in active isomer
  - close *O* to *S* contact seen in X-ray: 2.86 Å
  - favors a planar topography
  - 1º amide is the hinge binding element
- Topological isomer introduces allylic 1,3-strain
  - H/C=O interaction sterically distorts planarity
  - amide *O* and NHs poorly aligned for CHK1
- Indole N-H designed to mimic *O* to *S* interaction
  - potency similar: N-H ≡ S
  - furan is **27-33x less potent**



Impact
Conformational preorganization for molecular recognition

Origin
1,5- O/S interaction

- PTK787: potent lead VEGF kinase inhibitor
- Intramolecular H-bond mimics pyridazine ring
  - H-bond stabilizes planar conformation
- Thioether retains potency
  - O inactive, CH_2 weak
- S *ortho* to electron withdrawing C=N moiety
  - strengthens O to S interaction
  - O to S contact orients pyridylmethyl
  - preserves planarity

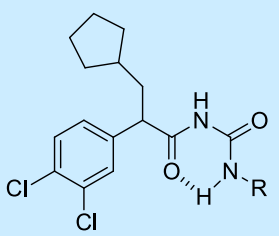


Excellent examples of N-H/S bioisosterism

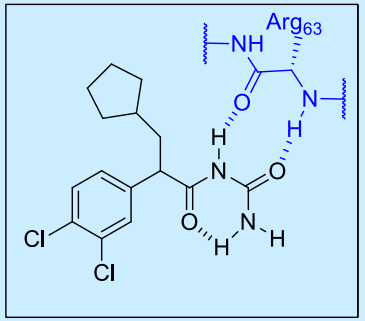
Σ O + S: 3.32 Å

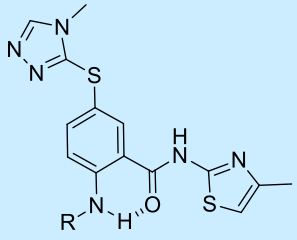
B. Yang *et al., J. Med. Chem*., 2018, **61**, 1061-1073; see L. Zhao *et al., Bioorg. Med. Chem. Lett*., 2010, **20**, 7216-7221 for a closely related series
T. Honda *et al., Bioorg. Med. Chem. Lett*., 2008, **18**, 2939-2943; 2010, **20**, 7234-7238; 2011, **21**, 1232-1235

1,5-O to S in Glucokinase Activators & Aurora Kinase Inhibitors

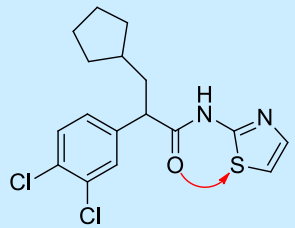


R = H: $SC_{1.5}$ = 4.4 μM
R = CH_3: $SC_{1.5}$ = 1 μM

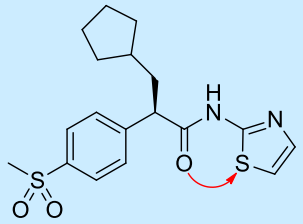




R = H: EC_{50} = 0.42 μM
R = CH_3: EC_{50} = 1.1 μM

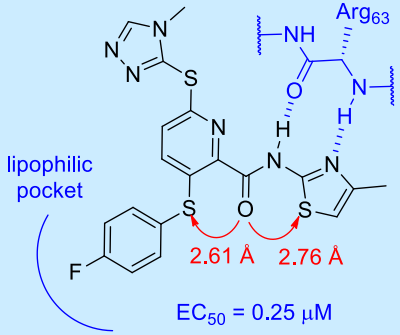


$SC_{1.5}$ = 0.94 μM



$SC_{1.5}$ = 0.24 μM

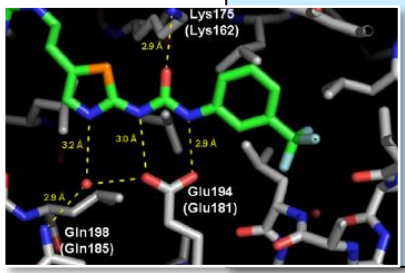
clinical candidate

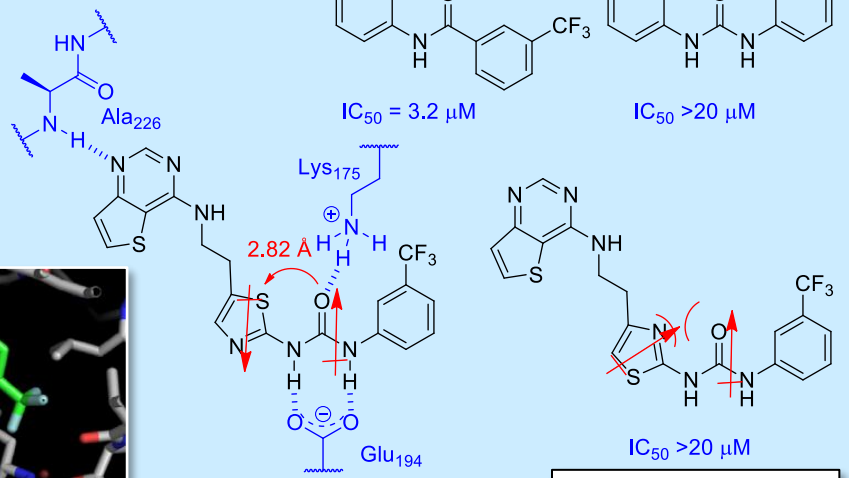


EC_{50} = 0.25 μM

Impact
Conformational preorganization for molecular recognition

Origin
1,5- O/S interaction
Dipole-dipole alignment





IC_{50} = 3.2 μM

IC_{50} >20 μM

IC_{50} = 22 nM

IC_{50} >20 μM

1,000x ↓ than isomer

S ≡ NH

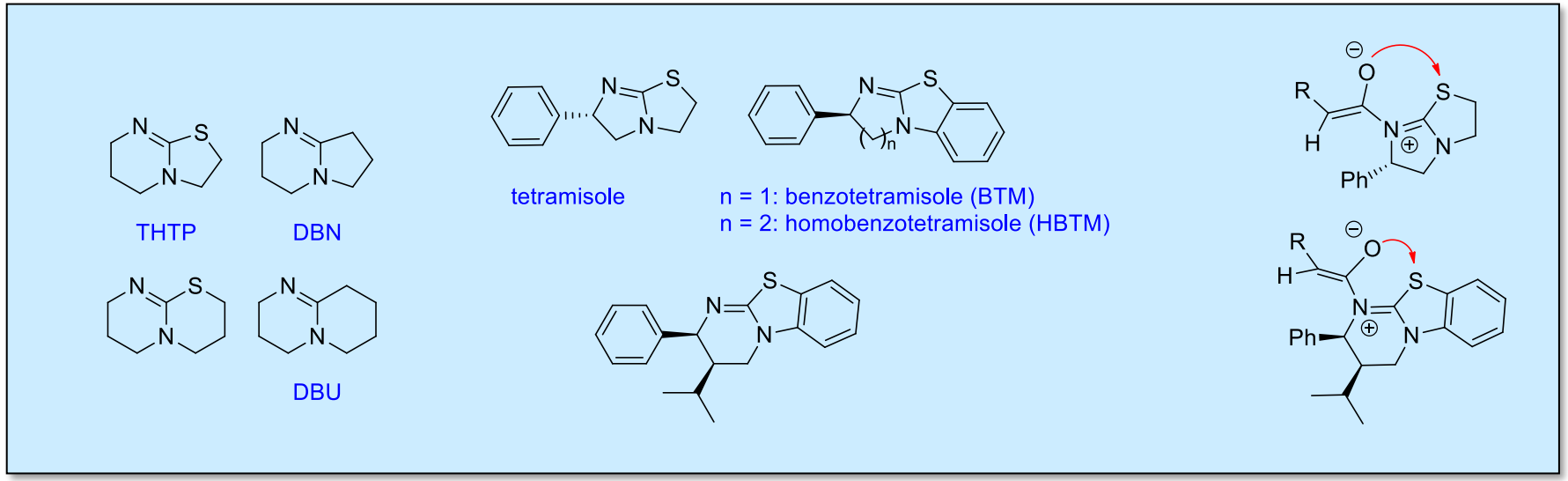
- Allosteric glucokinase activators
  - bind 20 Å from glucose binding site
- Acyl urea lead stabilized by intramolecular H-bond: X-ray cocrystal
- 2-Aminothiazole an effective mimic: $MeSO_2$ a clinical candidate
  - close O to S contact seen in X-ray, preserves H-bonds to Arg_{63}
- NH to C=O H-bond replaced by O to S in 2nd series
  - orients F-Ph into a lipophilic pocket that opens up

- 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
  - dipoles aligned in optimal topology

Σ O + S: 3.32 Å

N.E. Haynes *et al., J. Med. Chem.*, 2010, **53**, 3618-3625; Z.S. Cheruvallath *et al.*, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2166-2171
T. Nishimura *et al., Bioorg. Med. Chem. Lett.*, 2009, **19**, 1357-1360; 2009, **19**, 2718-2712; J.D. Oslob *et al., Bioorg. Med. Chem. Lett.,* 2008, **18**, 4880-4884

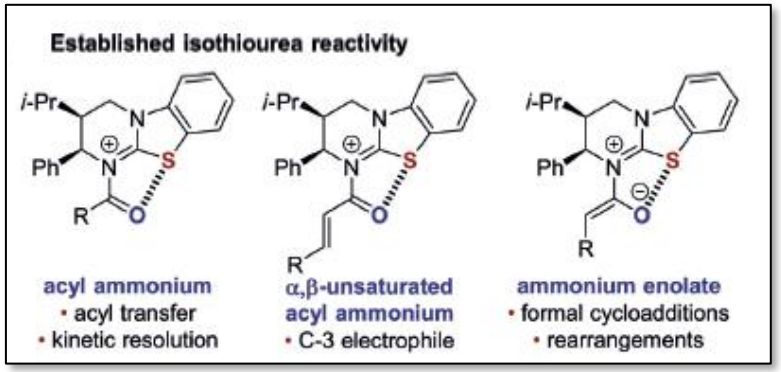
1,5 O to S in Organic Synthesis



Impact
Conformational preorganization for asymmetric induction

Origin
1,5- O/S interaction in transition state

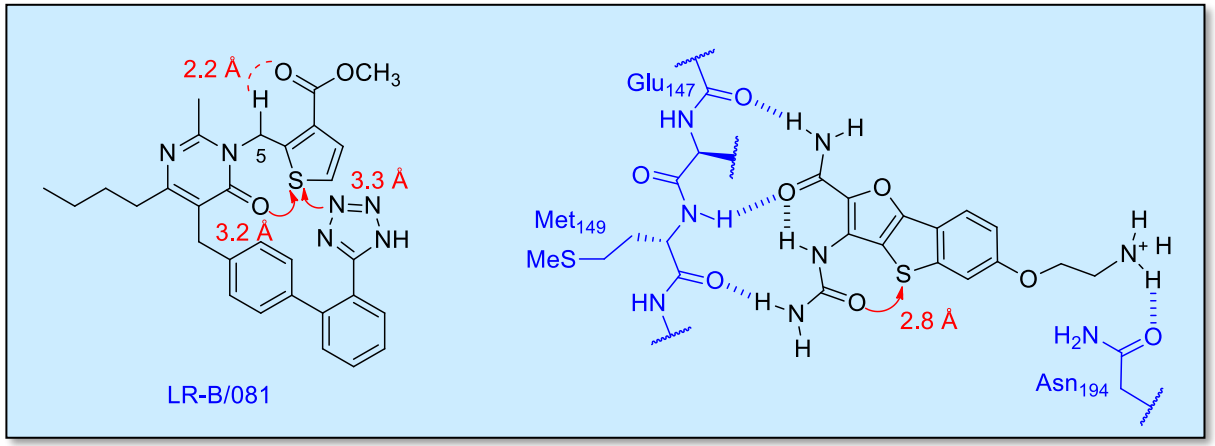
- Isothiourea-catalyzed reactions of enolates
- THTP a superior catalyst to DBN
  - ascribed to transition state stabilization by THTP
- Fusing aryl ring afforded more active catalysts due to π-π interactions in TS
  - tetramisole to benzotetramisole
- Process rendered asymmetric by introducing chirality to amidine ring
- O to S in TS thought to pre-organize enolate
  - allows pendent Ph to direct asymmetric alkylation

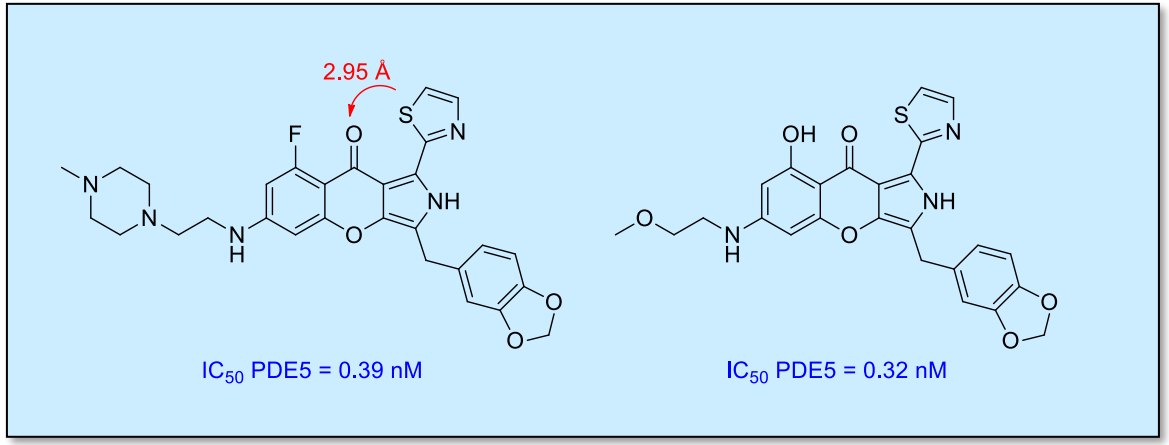


V.B. Birman *et al., Org. Lett*., 2007, **9**, 37-40; 2006, **8**, 1351-1354; *JACS*, 2006, **128**, 6536-6537; *Org. Lett*., 2006, **8**, 4859-4861; 2007, **9**, 3237-3240; 2008, **10**, 1115-1118; 2010, **12**, 892-895
J. Merad *et al., Eur. J. Org. Chem*., 2016, 5589-5610; V.B. Birman, *Aldrichimica Acta* 2016, **49**, 23-33; A.D. Smith *et al., Angew. Chem. Int. Ed*., 2020, **59**, 3705-3710

1,6 O to S Interactions

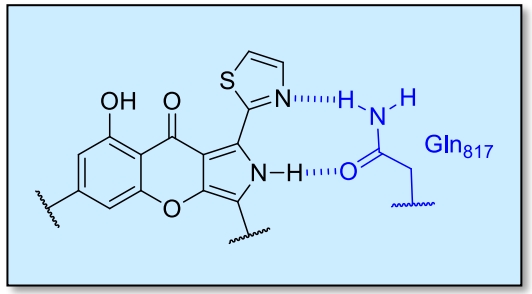
1,6 O to S in AII and JNK Kinase





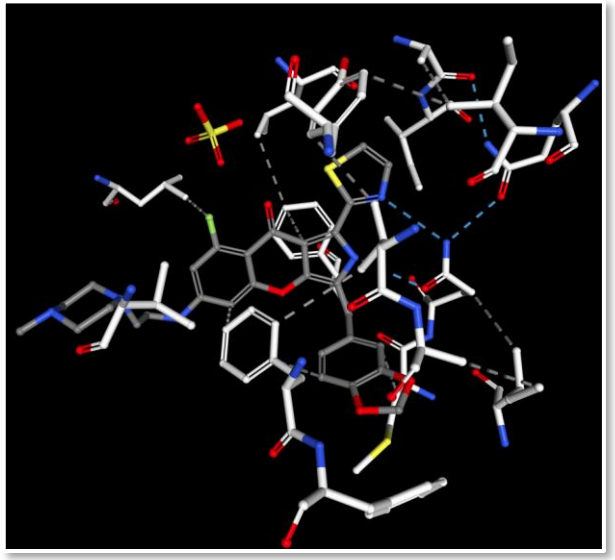
- 1,6 O to S interactions not well documented
- O to S in LR-B/081 measured as 3.20 Å in single crystal X-ray
  - just less than the 3.32 Å sum of vdW radii
  - close association between S and tetrazole N: 3.30 Å (3.35 Å is vdW sum)
  - ester O close to C-5 H: vdW radii sum = 2.72 Å
- IKKβ inhibitor (IC_{50} = 45 nM) in complex with JNK3 kinase
  - close 1,6-O to S contact of 2.8 Å observed
- Alternate heterocycles gave 3-4-fold lower potency
  - may play a role in modulating conformation
- PDE5 inhibitors originated from thiophene-based lead
  - thiazole designed to engage in H-bonding interaction with enzyme

Σ O + S: 3.32 Å



Impact
Conformational preorganization for molecular recognition

Origin
1,6- O/S interaction

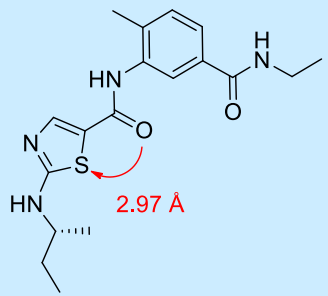


A. Salimbeni *et al., J. Med. Chem.,* 1995, **38**, 4806-4820; R. Destor *et al., Acta Crystallogr. Sect. C,* 1995, **51**, 1383-1385; *Chem. Eur. J.* 2005, **11**, 4621-4634; 2007, **13**, 6942-6956
H. Sugiyama *et al.*, *Chem. Pharm. Bull.*, 2007, **55**, 613-624; H.B. Luo *et al., J. Med. Chem.*, 2017, *60*, 6622-6637; 2018, **61**, 8468-8473

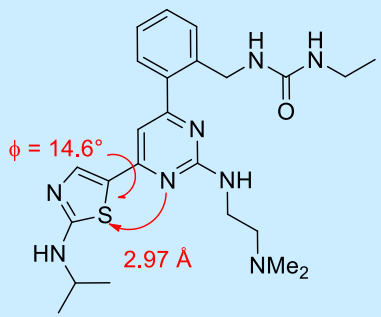
N to S Interactions

1,4 N to S Interactions

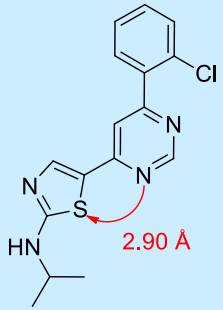
1,4 N to S in p38α MAP Kinase Inhibitors



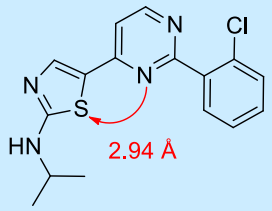
p38α IC_{50} = 3.5 nM



p38α IC_{50} = 2 nM



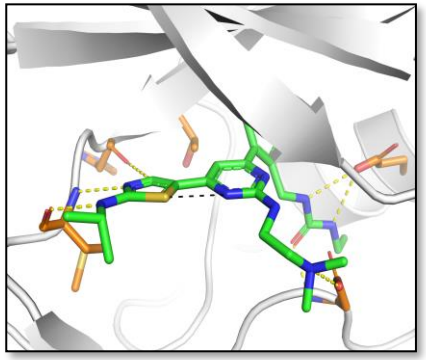
p38α IC_{50} = 46 nM



p38α IC_{50} = 223 nM

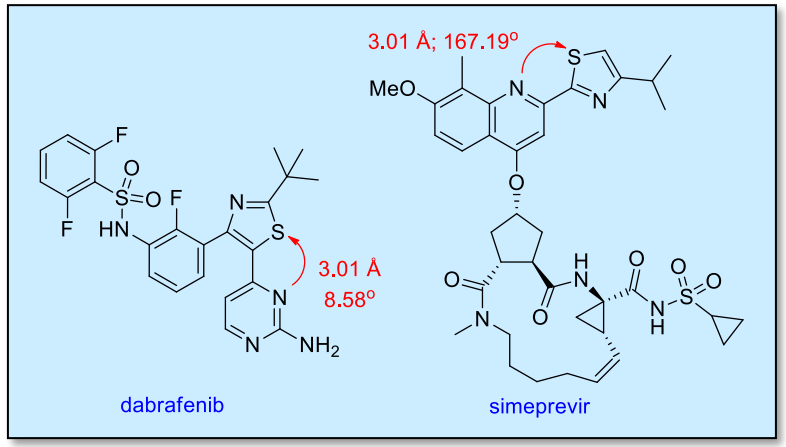
Matched molecular pair

- p38α MAP kinase inhibitor
  - 1,4-O to S to stabilizes planar conformation
- Pyrimidine designed to mimic planar topography
  - confirmed by X-ray cocrystal
- Role of the 1,4 N to S shown by pyrimidine isomers
  - vector disposition of 2-Cl-Ph moiety important for potency
- 2-Subtituted pyrimidine stabilized in wrong topology
  - 5x difference in potency



Σ N + S: 3.35 Å

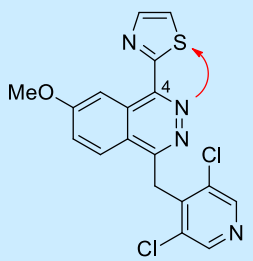
- PDE IV inhibitors
  - potency related to planarity at C-4
  - 2 C-H to N interactions stabilize planar array conformation of triazole in single crystal X-ray
  - thiazole can readily adopt coplanar arrangement



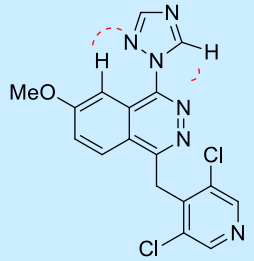
dabrafenib

simeprevir

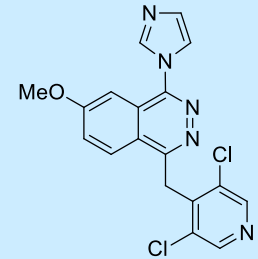
- Dabrafenib: B-Raf V600E kinase inhibitor
  - N to S stabilizes planar conformation
- N to S stabilizes conformation of simeprevir
  - observed in cocrystal with HCV NS3



PDE IV IC_{50} = 14 nM



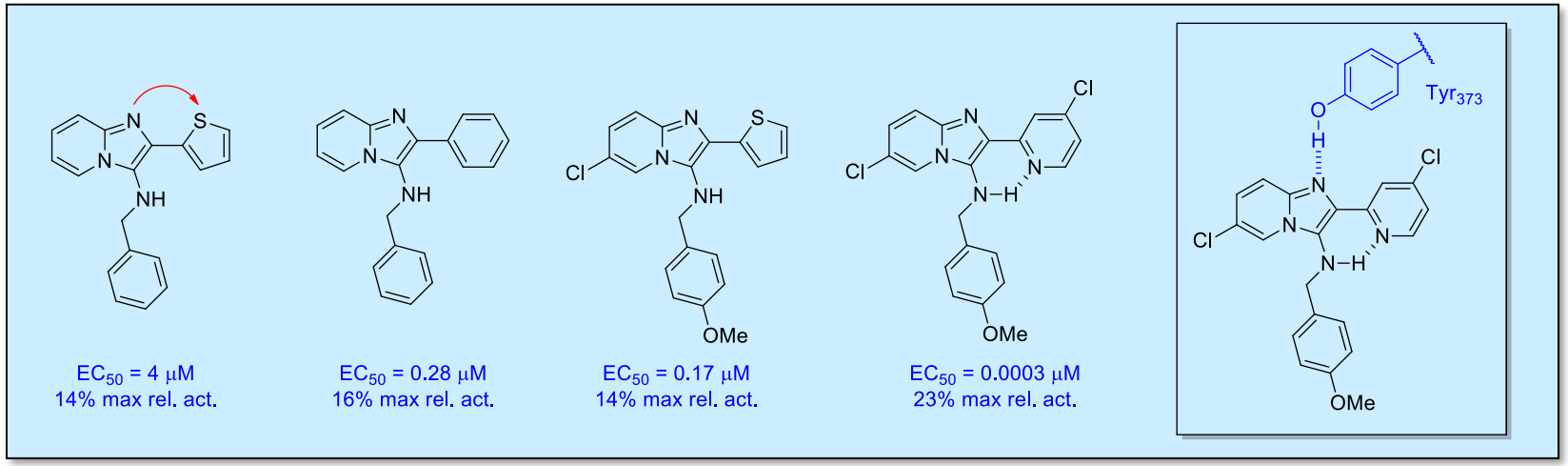
PDE IV IC_{50} = 241 nM



PDE IV 17% Inh. @100 nM

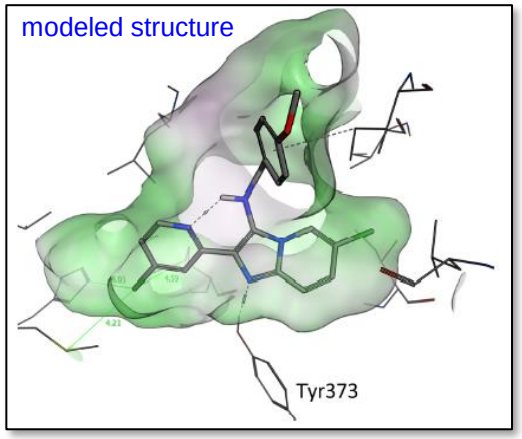
S. Lin *et al., Bioorg. Med. Chem. Lett.,* 2010, **20**, 5864-5868; J. Hynes *et al*., *Bioorg. Med. Chem. Lett*., 2008, **18**, 1762-1767; T.R. Rheault, *et al., ACS Med. Chem. Lett*., 2013, **4**, 358-362; T. Haack *et al*., *Bioorg. Med. Chem.,* 2005, **13**, 4425-4433; M.D. Cummings *et al., Angew. Chem. Int. Ed.,* 2010, **49**, 1652-1655

Intramolecular 1,4-N/S Reduces Potency



1,4- N/S

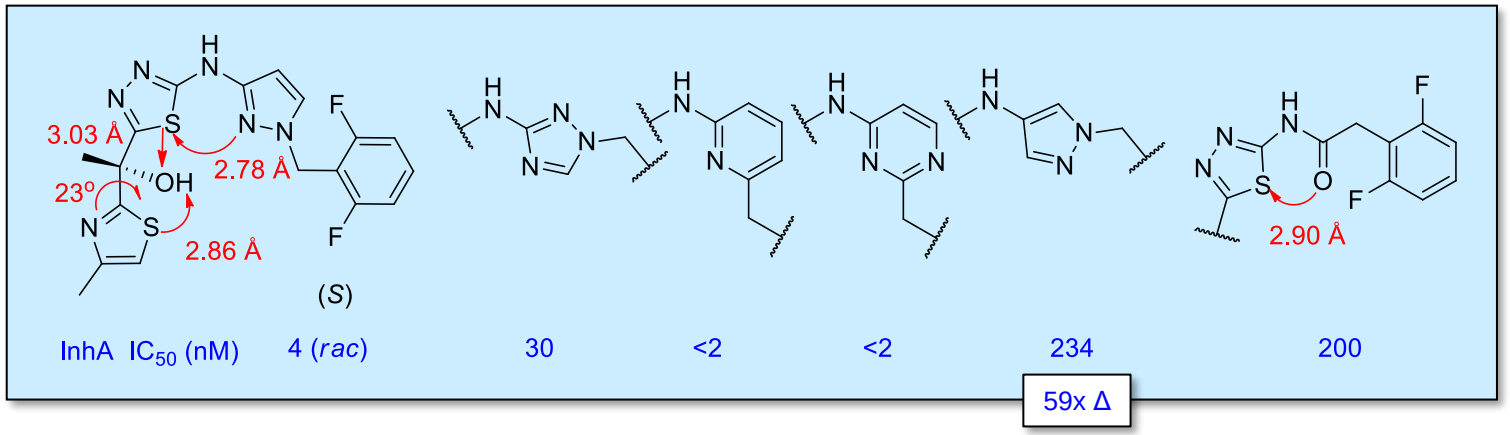
- Non-steroidal farnesoid X receptor (FXR) modulators
  - potential therapy for NASH & other liver diseases
- Thienyl derivative a modestly potent lead
  - phenyl homologue 14-fold more potent
- Modeling suggested H-bond interaction with protein
  - OH of Tyr_{373} donates to imidazole N
  - intramolecular N/S interaction proposed to abrogate
- Pyridyl homologue highly potent: EC_{50} = 300 pM
  - intramolecular H-bond stabilizes planar, bound conformation

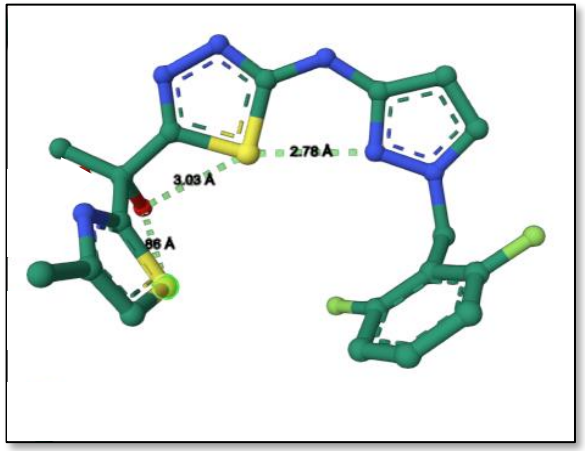


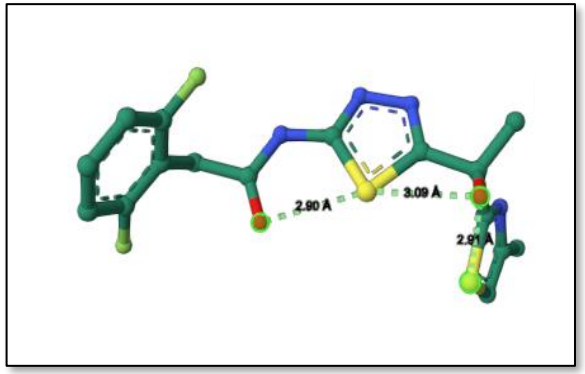
D. Flesch *et al., J. Med. Chem.*, 2017, **60**, 7199–7205

1,5 N to S Interactions

N to S & O to S in *M.tb* InhA Inhibitors







- Inhibitors of *M.tb* enoyl-acyl carrier protein reductase (InhA)
- X-ray cocrystal shows close pyrazole N to thiadiazole S
  - favors coplanar topography
- Thiadiazole N & NH engage NH and C=O of Met_{98}
  - project diF-Ph into hydrophobic pocket
- Close contacts between hydroxy O & thiazole S atoms
  - 2.86 Å with φ = 23°, 3.03 Å
  - topography reflects favorable dipole alignments
- Inhibition maintained by heterocycles that allow N to S interaction
  - isomeric pyrazole 59-fold weaker
- Amide analogue 50-fold less potent
  - close O to S (2.90 Å, φ = 5.2°) organizes thiadiazole amide appropriately
  - amide projects diF-Ph poorly for interaction with InhA

Impact
Conformational preorganization for molecular recognition

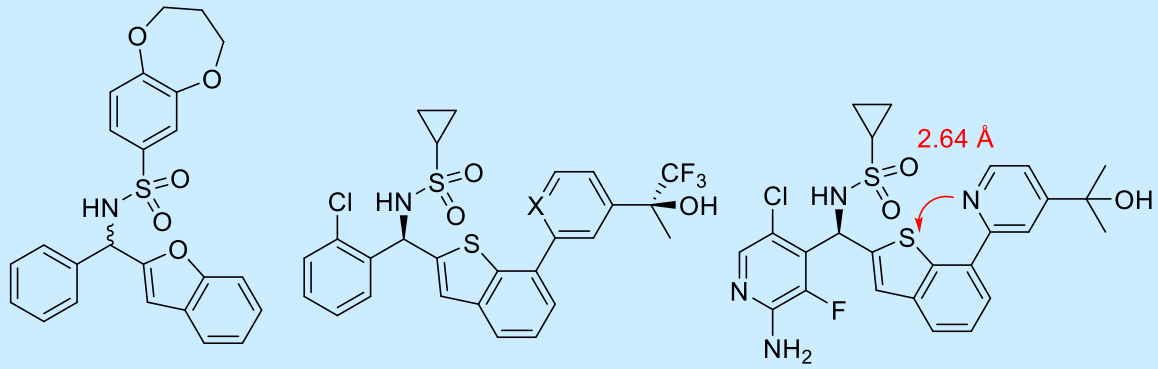
Origin
1,5- N/S interaction
1,4-O/S interactions
Dipole-dipole alignment

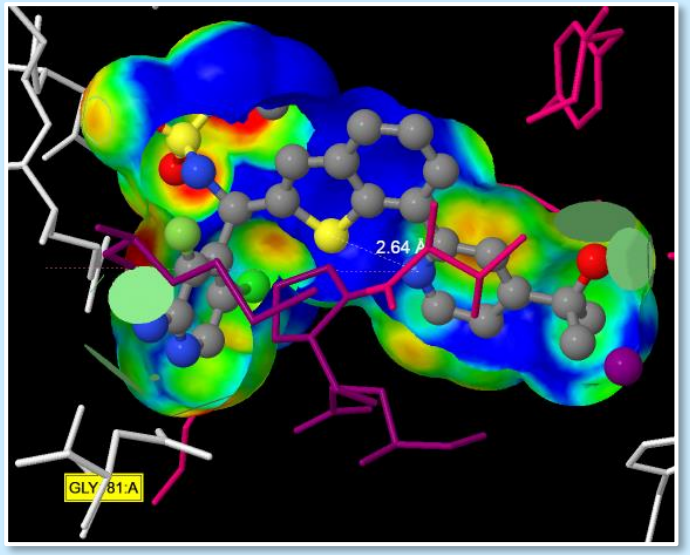
Σ N + S: 3.35 Å

Σ O + S: 3.32 Å

P.S. Shirude *et al., J. Med. Chem.,* 2013, **56**, 8533-8542

N to S in Glucokinase-Glucokinase Regulatory Protein Disruptors





- Inhibitors of glucokinase-glucokinase regulatory protein binding interaction
  - GKRP regulates cellular location of GK
- Lead identified by HTS
  - modest potency, binds to an allosteric site on GKRP
  - benzothiophene more potent: IC_{50} = 0.017 μM
- X-ray cocrystal suggested adding an ortho phenyl ring to the benzothiophene
  - establish contact with Arg_{525} *via* OH but would require coplanar topography
- Exploited an N to S interaction to favor planar conformation
  - confirmed by X-ray cocrystal of optimized compound: 2.64 Å (Σ vdW = 3.35 Å)
- Note: SO_2 moiety projects away from thienyl S atom

Proactive use of N-S to control conformation

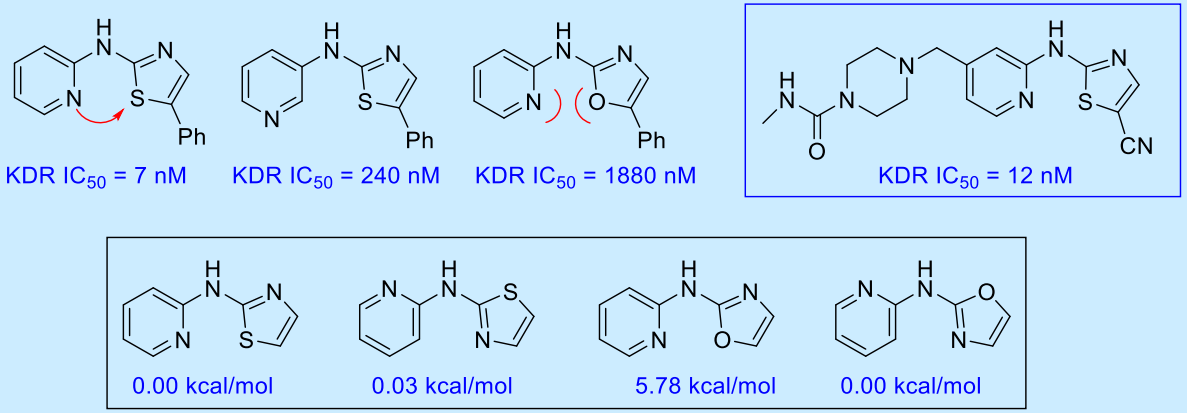
Impact
Conformational preorganization for molecular recognition

Origin
1,5- N/S interaction

Σ N + S: 3.35 Å

L.D. Pennington, M.D. Bartberger *et al., J. Med. Chem.*, 2015, **58**, 9663-9679

KDR & Chk1 Inhibitors



- Potent checkpoint kinase 1 (Chk1) inhibitors
  - X-ray cocrystal reveals close N to S contacts
  - stabilize bound conformation
  - promote topology that allows thiazole N & NH to engage Chk1
- Exhibit slow dissociation rates
  - ethylene diamine moiety enhances potency
  - engages in 3 H-bonds

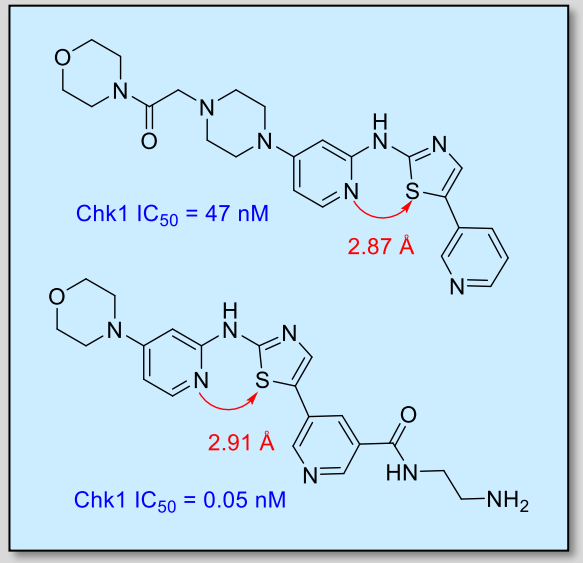
- Structurally simple KDR inhibitors with profound SAR
  - pyridine isomer, oxazole substantially less active
- Analyzed computationally based on preferred conformation
  - most potent compound coplanar stabilized by N to S
- Oxazole destabilized by unfavorable O to N
  - prefers alternate conformer of pyridine
- Optimized analogue active in vivo
  - electron withdrawing CN enhances N to S

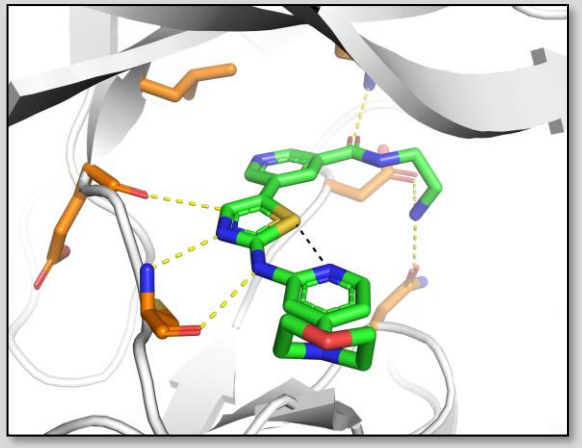
KDR = kinase insert domain receptor

Impact
Conformational preorganization for molecular recognition

Origin
1,5- N/S interaction

Σ N + S: 3.35 Å

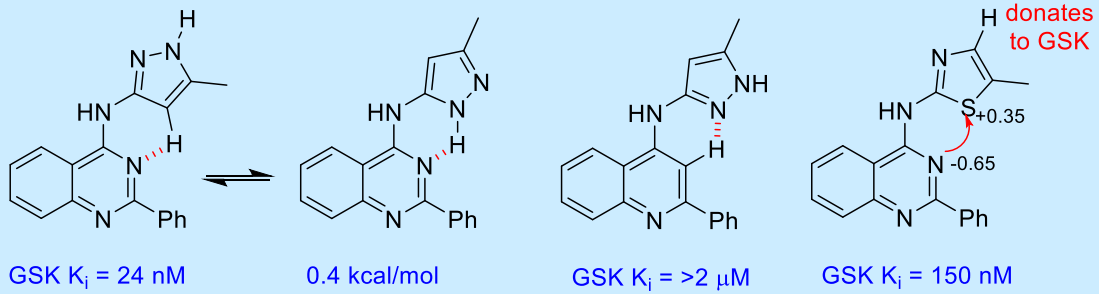




Intramolecular 1,5 N to S interaction, d1 = 2.91 Å, φ1 = 0.7°, φ2 = -7.1°. Only gatekeeper residue Leu_{84} and residues forming direct H-bonds to ligand are shown.

M.T. Bilodeau *et al., Bioorg. Med. Chem. Lett.*, 2004, **14**, 2941–2945; *J. Med. Chem.*, 2004, **47**, 6363-6372; V.Y. Dudkin *et al., Bioorg. Med. Chem. Lett.*, 2012, **22**, 2609-2612

N to S in GSK and JAK2 Inhibitors



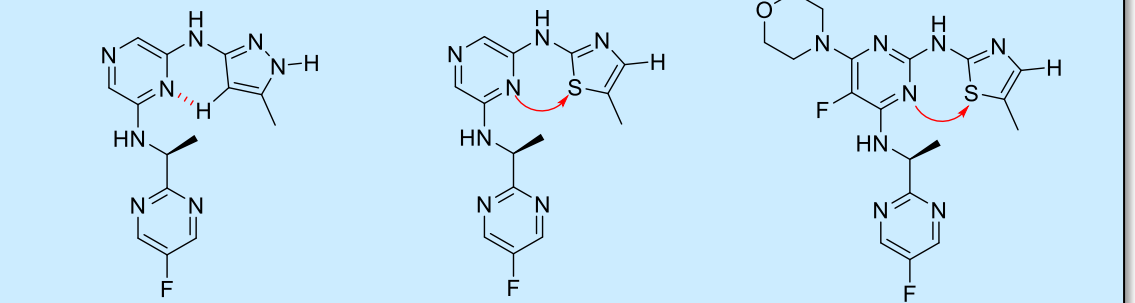
GSK K_i = 24 nM

0.4 kcal/mol higher energy Me in wrong place

GSK K_i = >2 μM Me in wrong place

GSK K_i = 150 nM

- N to S in GSK and JAK2 inhibitors
  - N to S mimics N to NH



JAK2 IC_{50} = <3 nM (*Km* ATP) = 3 nM (5 mM ATP)

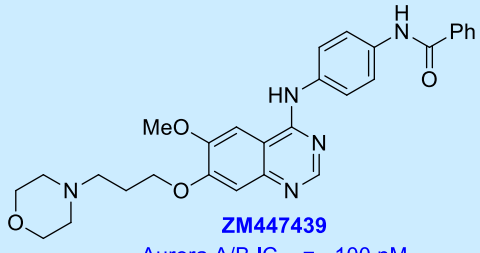
JAK2 IC_{50} = 4 nM (*Km* ATP) = 49 nM (5 mM ATP) GI_{50} = ~0.37 μM

JAK2 IC_{50} = 20 nM (5 mM ATP) GI_{50} = 30 nM

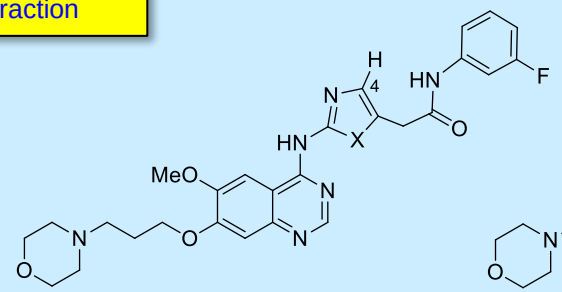
Impact
Conformational preorganization for molecular recognition

Origin
1,5- N/S interaction

S ≡ NH
S ≡ CH

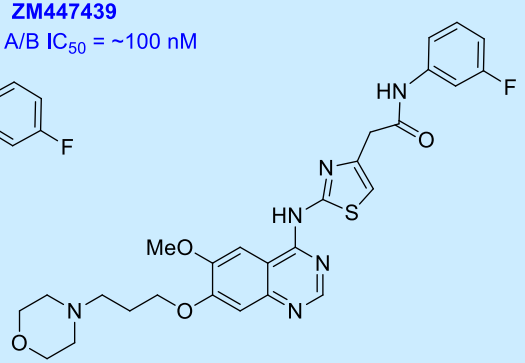


ZM447439
Aurora A/B IC_{50} = ~100 nM



X = S, Aurora A/B IC_{50} = <1 nM
SW620 cell IC_{50} = <1 nM

X = O, Aurora A/B IC_{50} = 470/340 nM
SW620 cell IC_{50} = 1 μM



Aurora A/B IC_{50} = 0.578/0.012 nM
SW620 cell IC_{50} = 0.2 μM

- ZM447439 a lead aurora kinase inhibitor
  - thiazole analogue 100-fold more potent
- Planar conformation with close N to S
  - favored by 17.2 kcal/mole over alternate
  - projects F-Ph into hydrophobic selectivity pocket
- Oxazole analogue >300-fold less potent
  - not planar: torsion angle = 28°
- C-4-substituted isomer >500-fold weaker vs Aurora A; 12x vs Aurora B
  - F-Ph not projected correctly

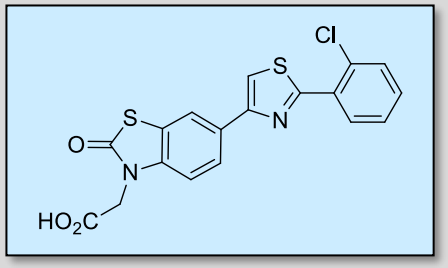
A.C. Pierce *et al., J. Med. Chem.,* 2005, **48**, 1278-1281; S.M. Ioannidis *et al., Bioorg. Med. Chem. Lett.,* 2010, **20**, 1669-1673; F.H. Jung *et al., J. Med. Chem.,* 2006, **49**, 955-970

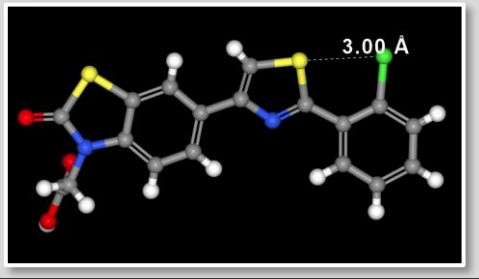
Halogen to S Interactions

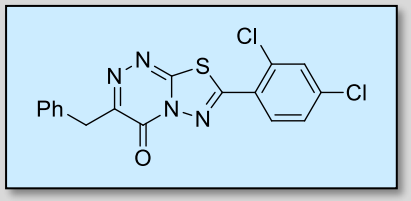
Intramolecular Cl/S & Cl/F Interactions

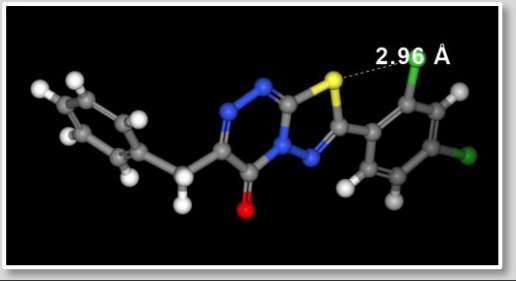
- Halogen-sulfur interactions can be seen in small molecule single crystal X-ray structures
  - both F & Cl engage
- Not always observed
  - crystal packing forces?

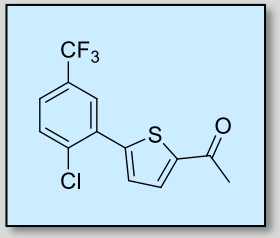
Σ S + Cl = 3.55 Å
Σ S + F = 3.27 Å



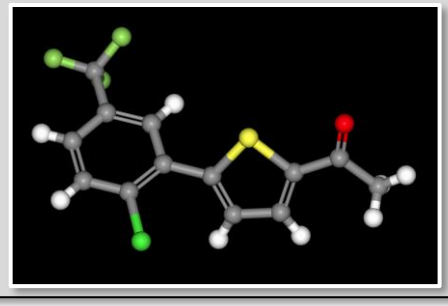


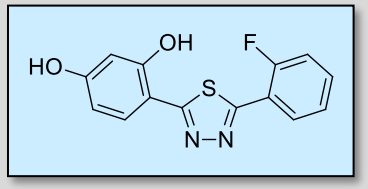


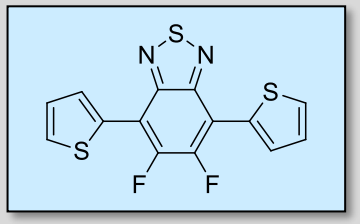




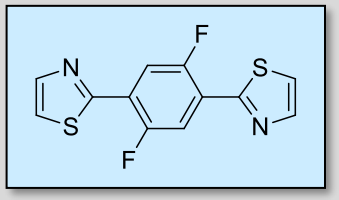
S/Cl not favored; O/S is

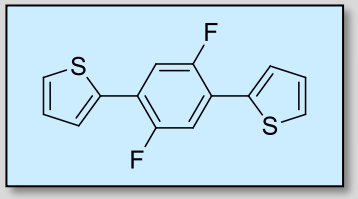




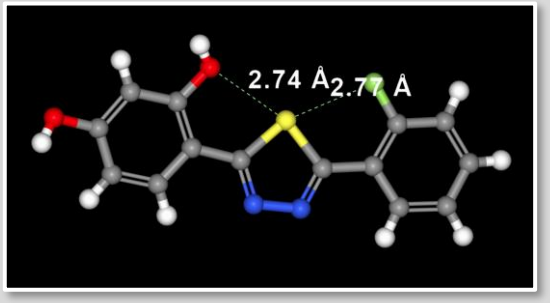


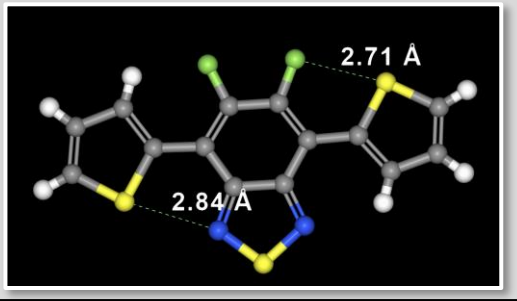
S/F favored on 1 side; N/S on other

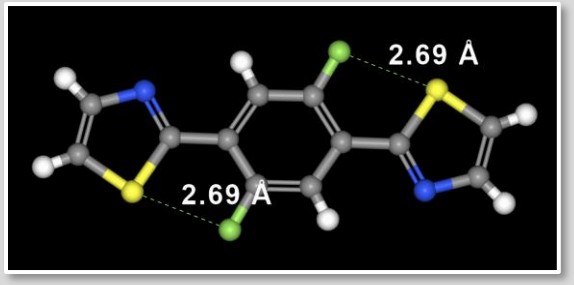


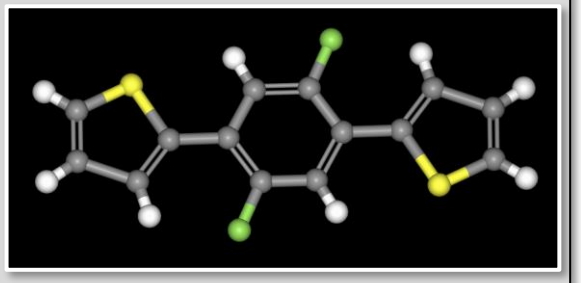


S/F not favored





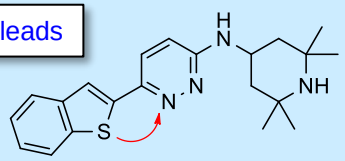




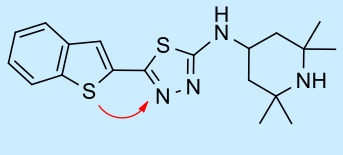
A.A. Hoser *et al., Cryst. Growth Des*., 2018, **18**, 3851-3862; C.B. Nielsen *et al., J. Org. Chem*., 2015, **80**, 5045-5048; M. Barlóg *et al., Org. Chem. Front*., 2019, **6**, 780-790

Pyridazine, Thiadiazole & Intramolecular Interactions

leads



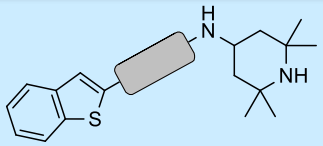
EC_{50} = 0.6 μM
SMN protein: 2.5x increase

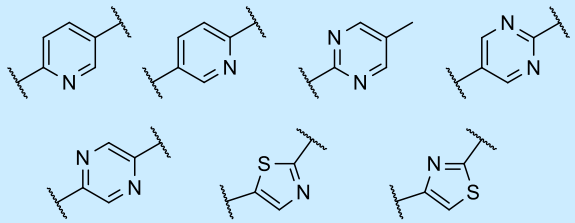


EC_{50} = 0.02-0.1 μM

Pyridazine & thiadiazole uniquely active

SAR





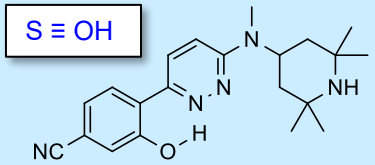
EC_{50} >10 μM

EC_{50} = 4.47 μM
SMN protein: 1.7x increase

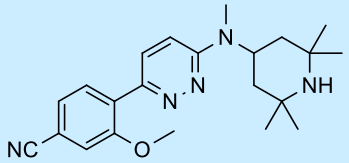
EC_{50} = 0.53 μM
SMN protein: 2.8x increase

N-S favors planarity; augmented by Cl to S interaction

S ≡ OH

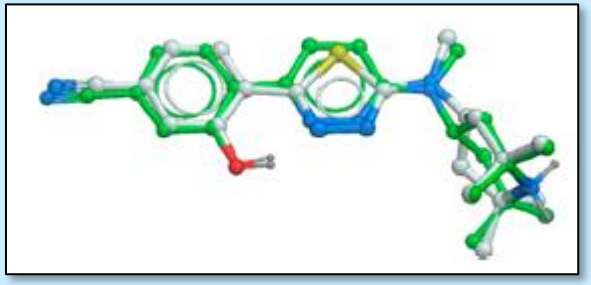


EC_{50} = 0.031 μM
SMN protein: 3.1x increase

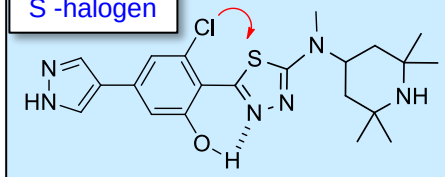


EC_{50} = 1.69 μM
SMN protein: 2.3x increase

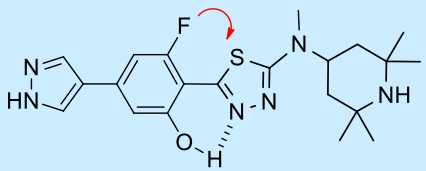
Planarity important – intramolecular H-bond
Confirmed by single crystal X-ray structures



S -halogen



EC_{50} = 0.003 μM
SMN protein: 2.5x increase

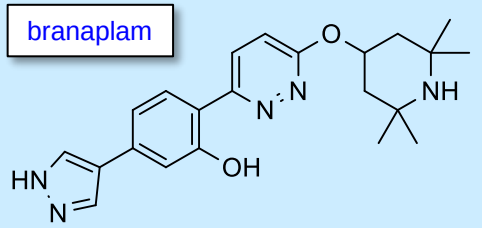


EC_{50} = 0.006 μM
SMN protein: 2.6x increase

Intramolecular H-bond; halogen to S interaction

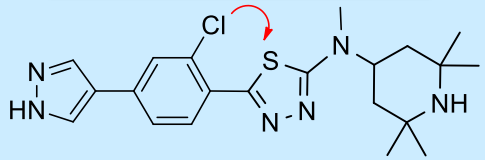
◆ SMN2 splicing modulators

branaplam

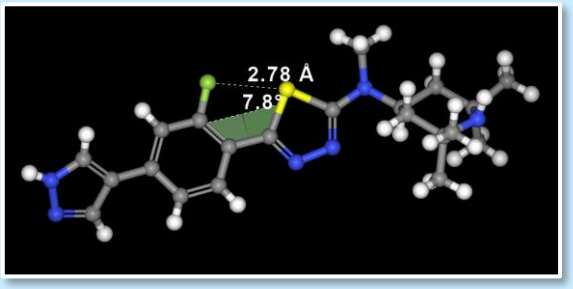


EC_{50} = 0.02 μM
SMN protein: 3.6x increase

X-ray shows Cl & S proximity



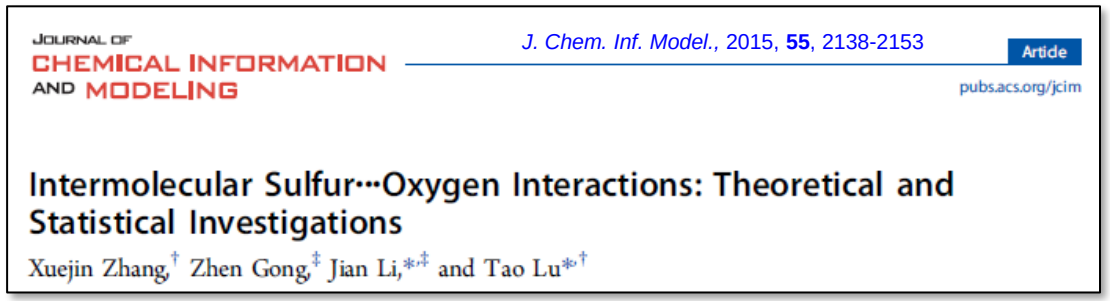
EC_{50} = 0.034 μM
SMN protein: 2.5x increase

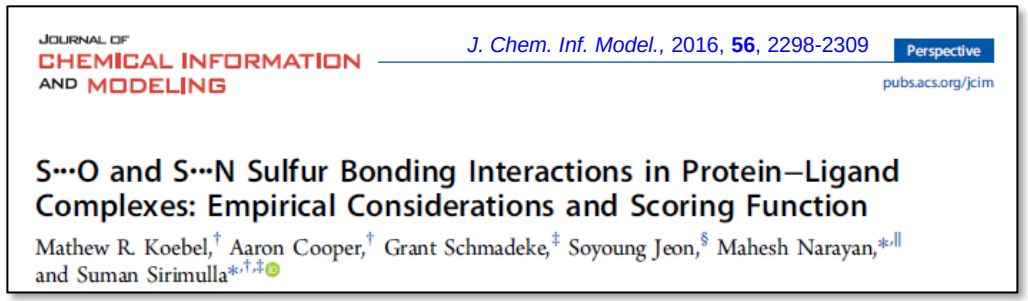


vdW radius S = 1.8 Å; Cl = 1.75 Å Σ = 3.55 Å

A.T. Cheung *et al., J. Med. Chem.*, 2018, **61**, 11021-11036; J. Axford *et al., J. Med. Chem.*, 2021, **64**, 4744-4761

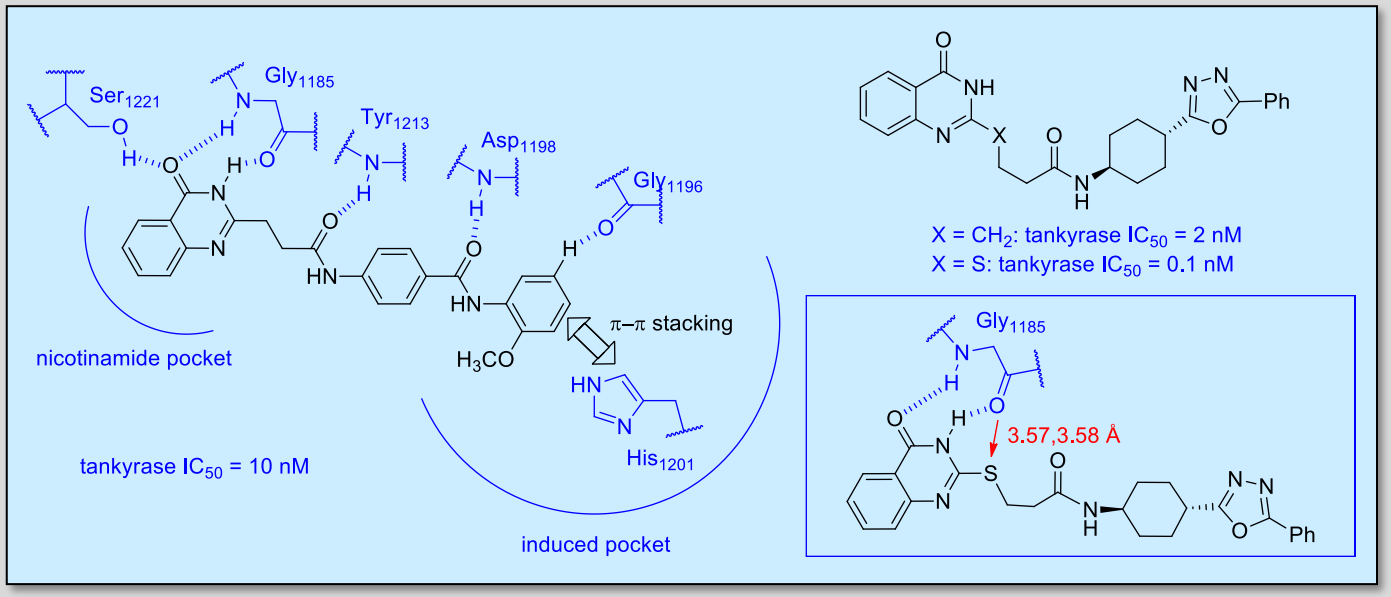
Intermolecular O to S Interactions



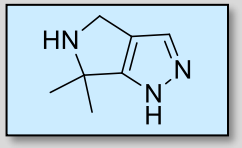


X. Zhang *et al., J. Chem. Inf. Model.,* 2015, **55**, 2138-2153; M.R. Koebel *et al., J. Chem. Inf. Model.,* 2016, **56**, 2298-2309

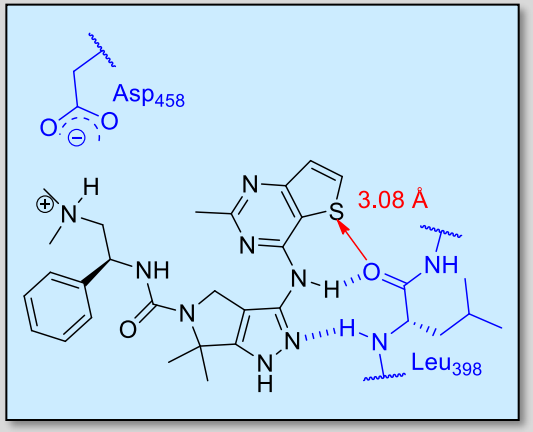
Intermolecular O/S in Tankyrase & p21 Kinase Inhibitors

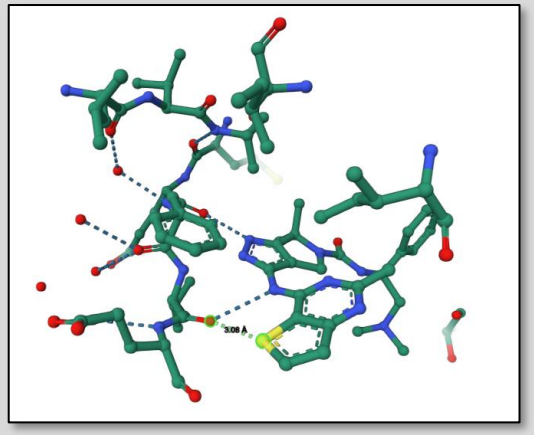


- Potent tankyrase inhibitor based on ethylene linker element
- Thioether 20-fold more potent than matched CH_2 analogue
- S atom is close to O of Gly_{1185}
  - just beyond vdW radii
  - provides better alignment of S atom with side chain of Phe_{1208}
- Effect transmitted to the oxadiazole moiety
  - exhibits optimal H-bond interactions



Interesting planar hinge binding motif



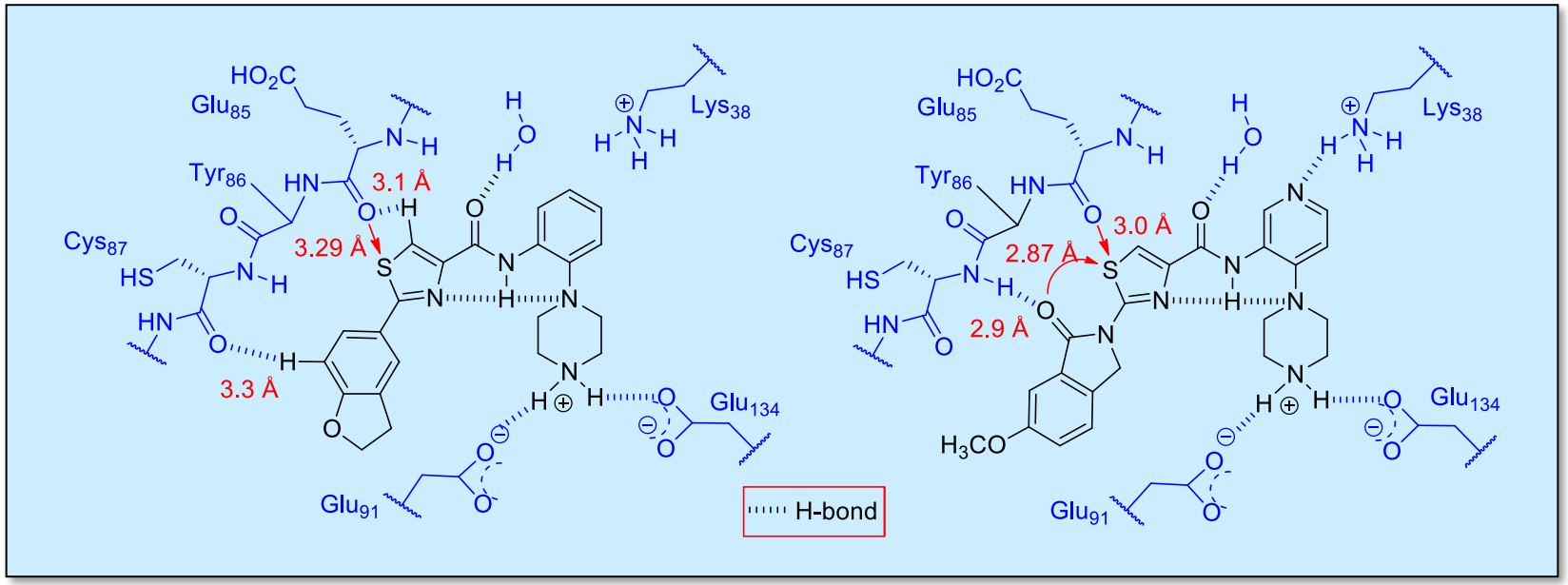


- p21-activated kinase-4 (PAK4) inhibitor
  - oncology target
- PF-3758309 identified as a potnt PAK inhibitor
  - used SBDD from multiple distinct series
  - ATP-competitive inhibitor of PAK4
  - K_i = 18.7 nM; K_d = 2.7 nM (by ITC)
- X-ray cocrystal structure revealed key contacts at the hinge
  - N-H to Leu_{398} H-bond
  - H-bond from Leu_{398} NH to pyrazole N atom
- Close interaction between Leu_{398} O & thienyl S
  - 3.08 Å: <vdW radii

Σ O + S: 3.32 Å

Z. Hua *et al., J. Med. Chem.,* 2013, **56**, 10003-10015; B.W. Murray *et al., PNAS*, 2010, **107**, 9446-9451

Intermolecular O/S in CHK1 Kinase Inhibitors



- Lead CHK1 kinase inhibitor: IC_{50} = 75 nM
  - affinity selection MS-based automated ligand identification system screen (ALIS)
- X-Ray cocrystal structure highlighted key interactions
  - weak H-bonds to hinge backbone
    - benzofuran C-H to Cys_{87} O
    - thiazole C-H to Glu_{85} O
  - Glu_{55} C=O close to S of thiazole: slightly less than vdW radii
- Isoindolinone: IC_{50} = 1 nM
  - H-bonds with isoindolinone C=O & pyridine N increase potency
  - close O/S interaction stabilizes bound conformation: 3.0 Å distance

Σ O + S: 3.32 Å

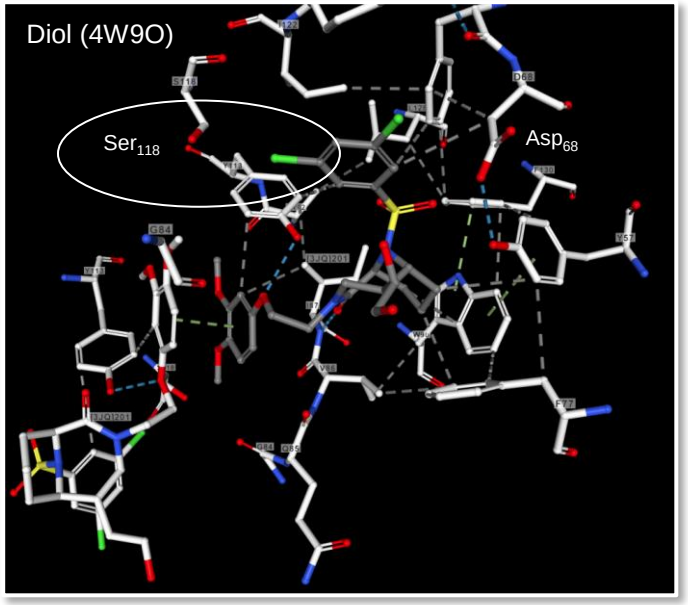
G.W. Shipps, Jr. *et al., ACS Med. Chem. Lett.*, 2012, **3**, 123-128; *Bioorg. Med. Chem. Lett.,* 2013, **23**, 2590–2594

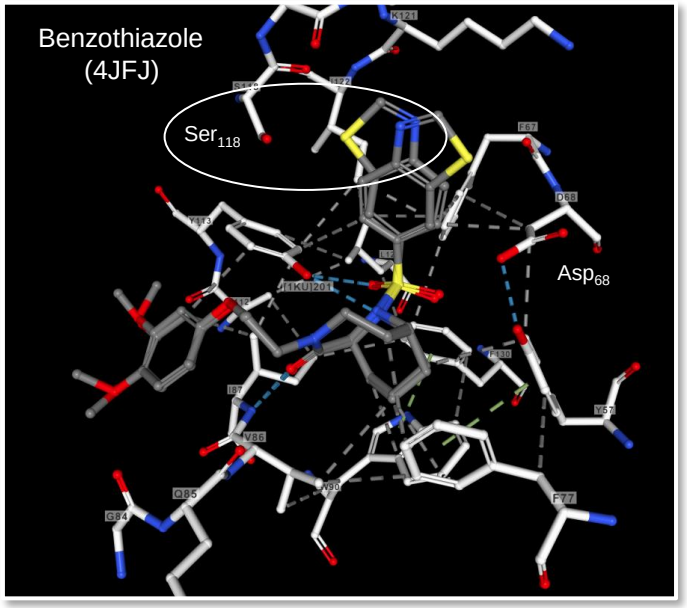
Ph-Cl & Benzothiazole Bioisosterism in FKBP Proteins

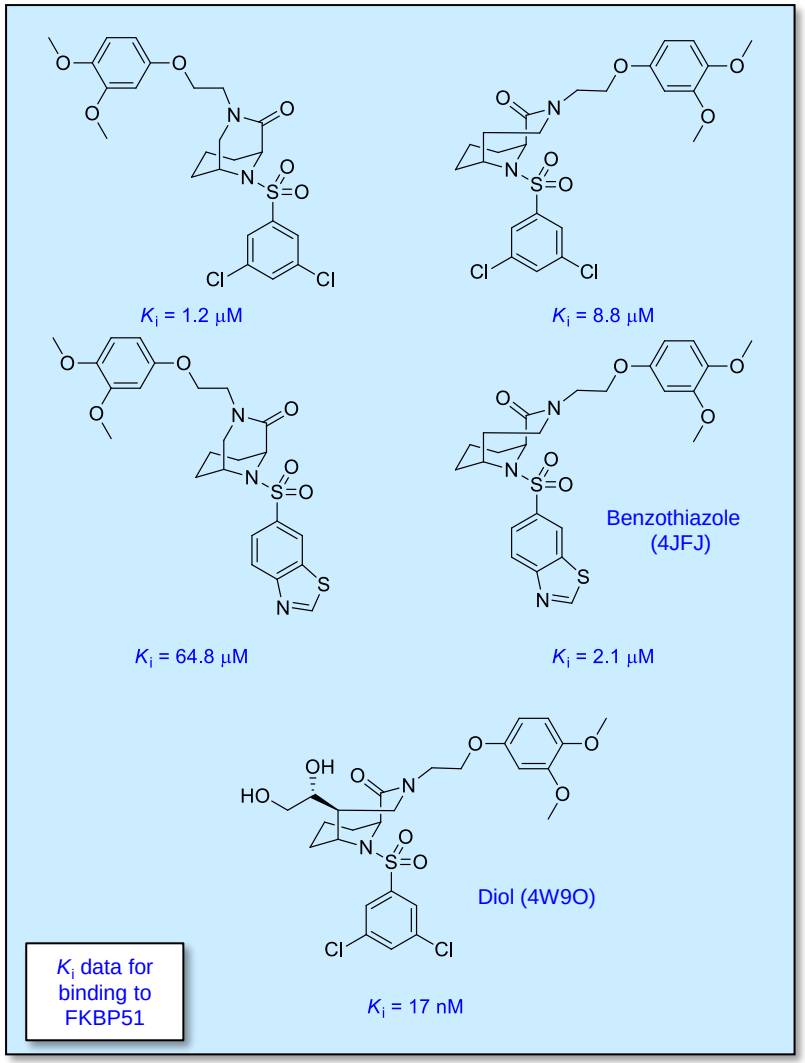
- Chlorine makes halogen bond to Ser_{118}
  - Cl-O distance is 3.10 Å
  - 2nd Cl not projecting toward Asp_{68}
- For benzothiazole, 2 rotamers are observed in the cocrystal structure
  - in 1 rotamer, S engages with Ser_{118}: O-S = 2.73 Å
  - in 2nd rotamer, S reaches out to Asp_{68}: O-S = 3.9 Å
- An interesting example of chlorophenyl/benzisothiazole bioisosterism

FK506-Binding Protein 51

Σ 1.80 + 1.52 = 3.32 Å



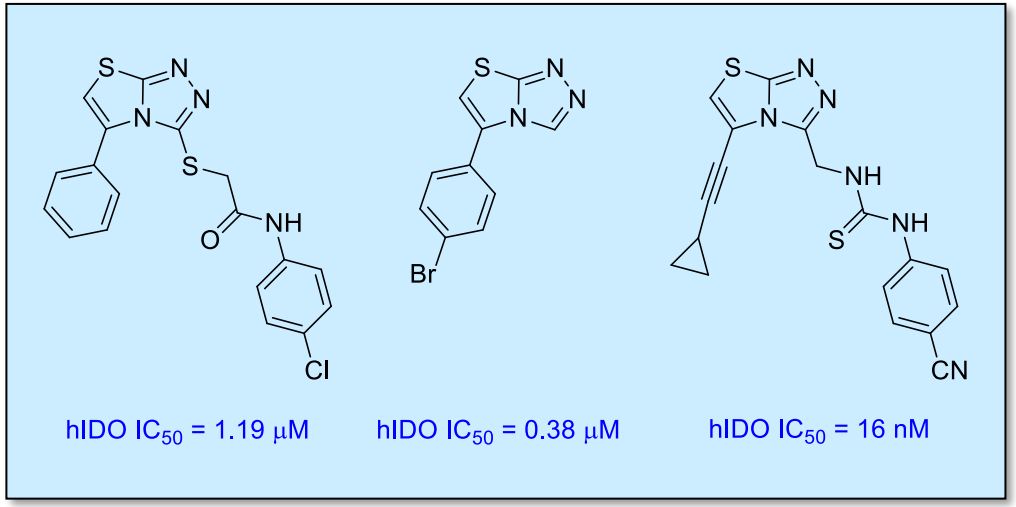


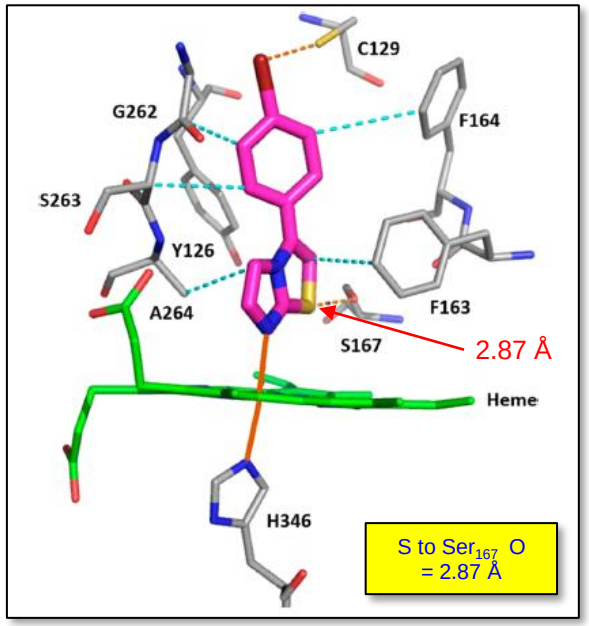


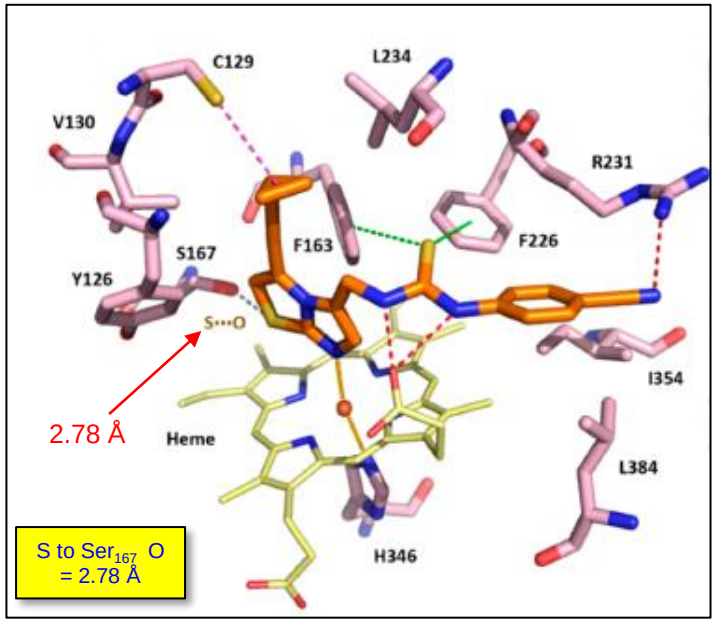
Σ O + S: 3.32 Å

F. Hausch *et al., J. Med. Chem.,* 2013, **56**, 3922-3935; *Angew. Chem. Int. Ed. Engl.*, 2015, **54**, 345-348

IDO Inhibitors







- Indoleamine 2,3-dioxygenase (IDO1) inhibitor
  - catalyzes the first step in the kynurenine pathway
    - degradation of Trp
- IDO1 overexpressed in tumor cells
  - therapeutic target for combination with IO therapy
- HTS screening lead wit modest potency
  - optimization enhanced potency by 75x
- X-ray cocrystal structure revealed N coordination to heme Fe atom
  - close interaction between S and Ser_{167} O atom: 2.87 Å; ∠ C-S-O = 172°
  - heterocyclic core π-stacking with Phe_{163}
  - halogen bond between Cys_{129} S & Br: 3.2 Å; ∠ C-S-Br = 162°

- Thiourea of most potent derivative
  - interaction between S & Ser_{167} O atom maintained:
    - d = 2.78 Å
  - C=S engaged with Phe_{163} & Phe_{226}:
    - d = 5.2 Å & 5.3 Å (<6 Å productive)

Σ O + S: 3.32 Å

Y.-H. Peng *et al., J. Med. Chem.,* 2020, **63**, 1642-1659

Conclusion

Conclusion

- σ-Holes on sulfur offer opportunity for interaction with electron donors
  - O (OH, ether, C=O) and N (heterocycle) most common donors
  - analogous to halogen bonding
    - intramolecular interaction favored by geometry of σ* bonds
- Frequently contribute to drug design
  - not always appreciated
  - examples of a priori application emerging
  - stabilizes active conformations
- Can exert a profound effect on SAR
  - incorrect deployment can lead to reduced potency
  - can favor inactive conformation
- Intermolecular interactions beginning to be document
  - restricted to date to O to S: only histidine available for N to S

Acknowledgments

Brett R. Beno

Kap-Sun Yeung

Michael D. Bartberger (Amgen)

Lewis D. Pennington (Amgen)