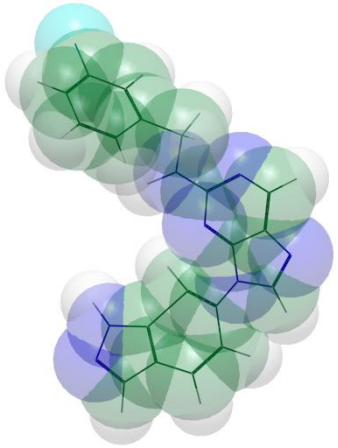

DCAM Pharma Inc.

Drug hunts with sparkV10: Case studies from the literature and current campaigns to develop immunokinase inhibitors

Field Based Chemistry 2013

Non-Confidential

aajami@dcampharma.com

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History: Ajami + DCAM

- Founder / CSO – biotech start-ups
  - Kor, Tracer Technologies, Phenome Sciences, Raymar, Xanthus, Antisoma/AIID
- Corporate and consulting projects
  - 1 NDA (after big pharma failure)
  - 4 Phase 3
  - 6 Phase 2
  - 14 Phase 1 (5 Investigator trials)
- M&A, IP and venture due diligence
- IP-to-IND problem solver

aajami@dcampharma.com

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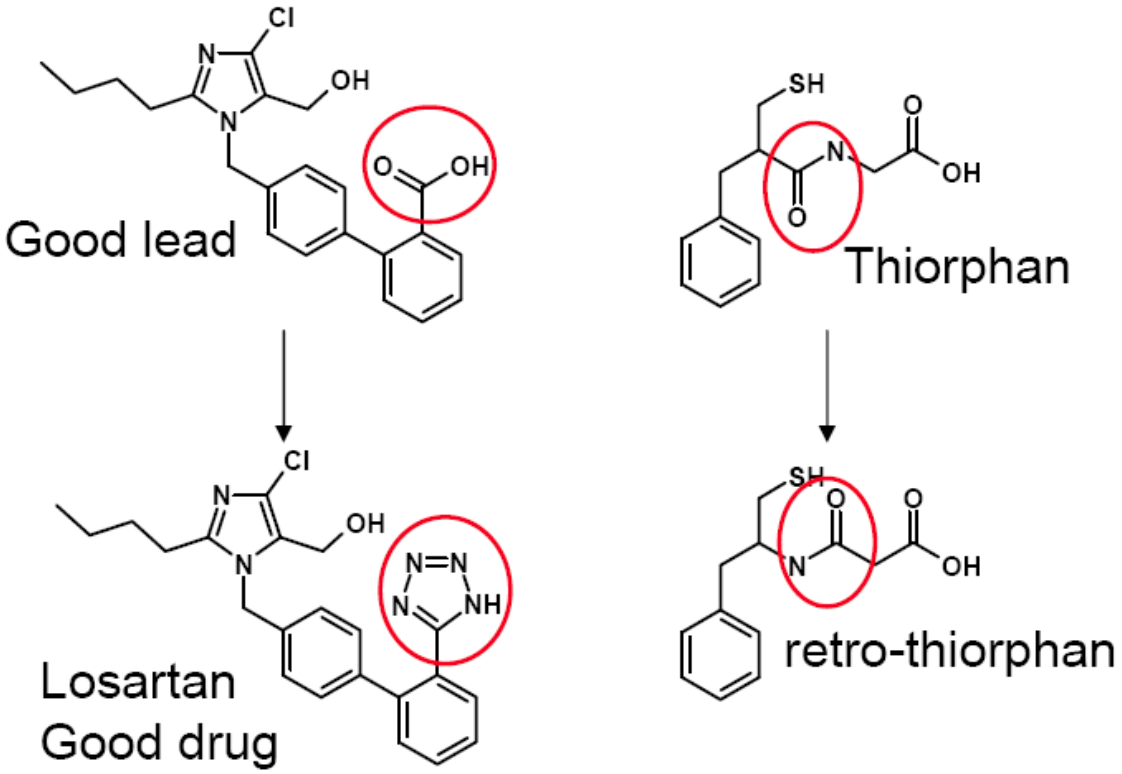
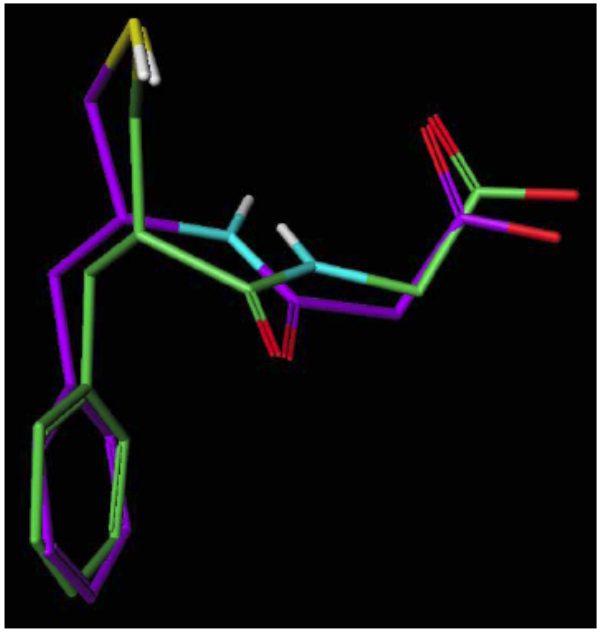
Bioisosteres: a definition

"Substituents imparting similar biological properties on a compound"





James Mills & Carolyn Barker
Pfizer GRD, Sandwich, UK

Computational goals & resources

- Replace scaffold, fragment or decoration
  - With(out) SAR training sets or docking models
- Dedicated software suites
  - Cresset/sparkV10, Accelrys (BIOSTER)
- Small molecule discovery suites
  - Schrödinger, Chem. Computing Group, Tripos
  - Web portals (NCGC, QID; click2drug.org)
  - Customized tactics (Meanwell, J. Med. Chem. 54:2529, 2011; J. Chem. Inf. Model.)
- Databases
  - Integrity, PubChem, chEMBL → Dx/ABLE

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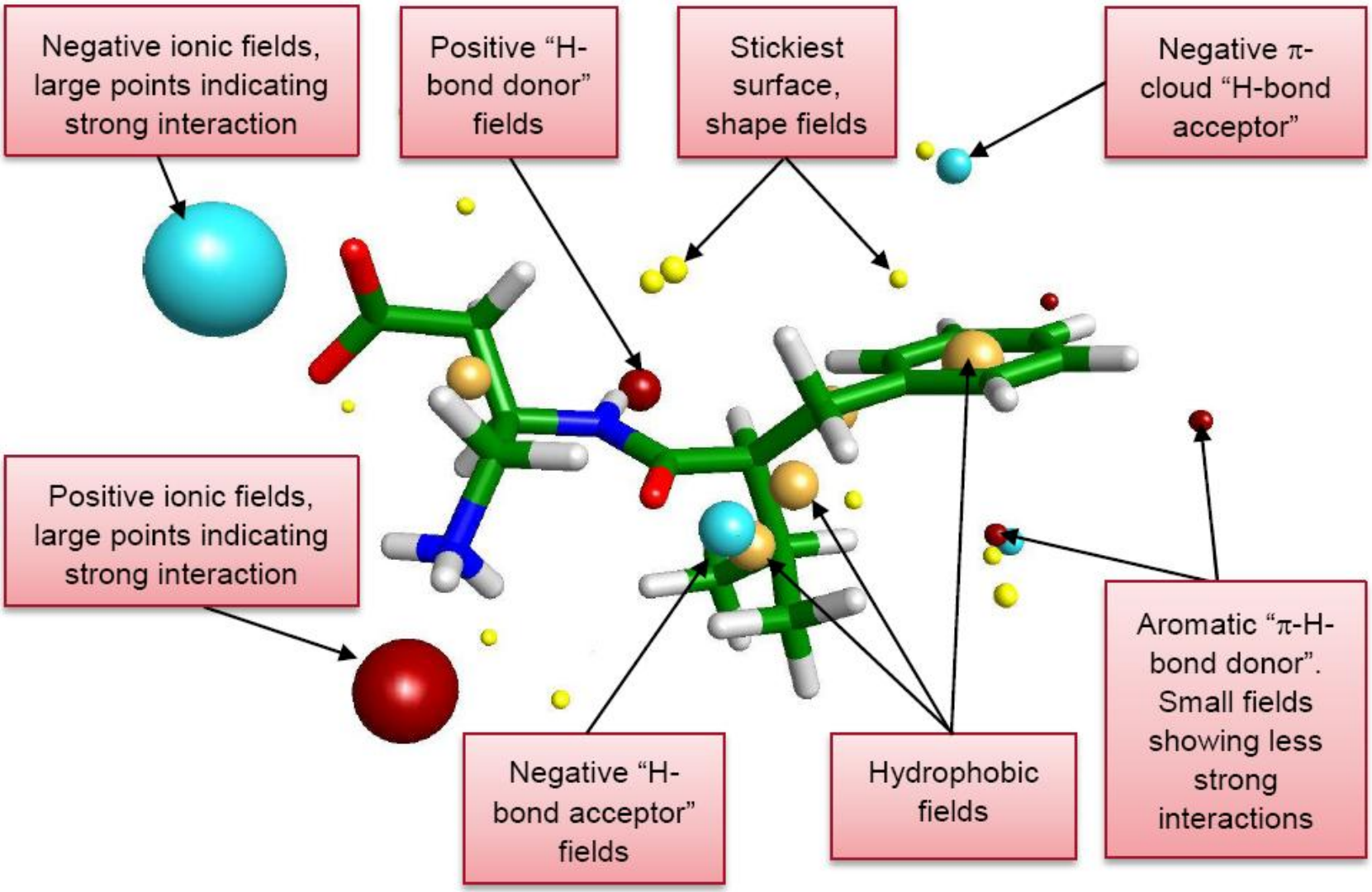
sparkV10: “Field Point” technology



Interpretation of a field point pattern. The size of the point indicates the potential strength of the interaction

From 08/30/2012 manual

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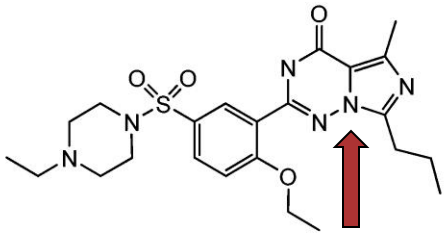
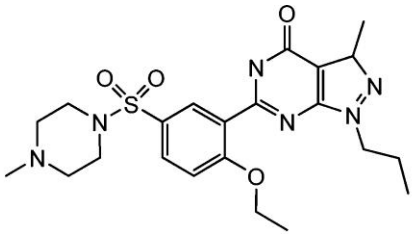
Case study (1): PDE5 inhibitors

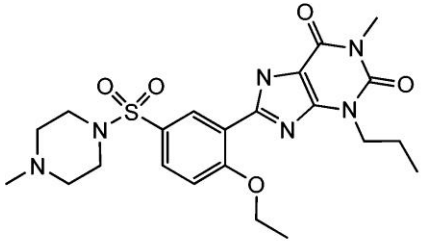
- Would bioisosteric replacement in sildenafil have predicted vardenafil & *vice versa*?



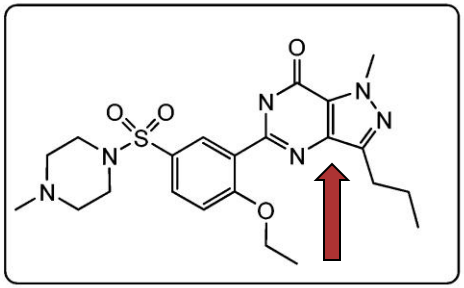
224785-90-4
Vardenafil



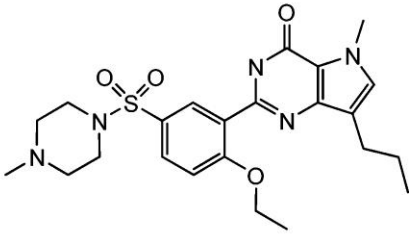
264919-66-6



251472-88-5



139755-83-2
Sildenafil



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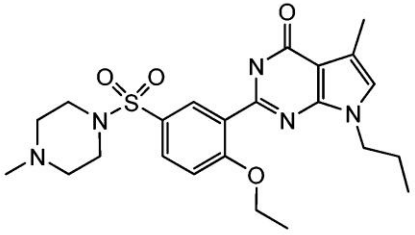
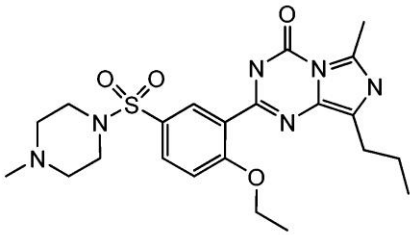


804519-75-3



346604-72-6

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sparkV10 results: maximal "tweaks"

- 1100 analogs (similarity p > 95%)
  - 38 best "actives" by IC/EC_{50} (Integrity+Dx/ABLE)
- Use "trimmed" structure + binding model info
  - select field points, bond types & hetero atoms
- Output = 400 molecules – rank top 40

SEARCH Template	Actives	Sildenafil	Vardenafil
Fused pyrazole ring	22	20	18
Phenylsulfonyl ring	7	5	4
Sulfonamide	9	6	6
All (including S & V)	**38**	**31 (BIF)** **27 (S)**	**28 (BIF)** **23 (S)**

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Case study (2): phenol replacement

- Matches to the data underlying BIOSTER from 57 studies

Acta Pharmaceutica Hungarica 73. 163–169. 2003.

Fragmentum-alapú hatóanyagtervezés a bioizosztéria alkalmazásával
Esettanulmány: a fenolcsoport analogonjai a Bioster adatbázisban

UJVÁRY ISTVÁN[1], GYŐRFFY WERNER[2] ÉS LOPATA ANTAL[2]

[1]MTA Kémiai Kutatóközpont Kémiai Intézet, Budapest, Pf. 17 – 1525
[2]CheMicro Kft., Budapest, Károly körút 1. – 1075

Summary

Ujváry, I., Győrffy, W., and Lopata, A.: ***Fragment-based drug design using bioisosterism. A case study of analogues of the phenol group in the Bioster database***

This case study examined various structural features of the 55 bioisosteric fragments of the phenol group registered in version 2002.1 of the Bioster database. The size, calculated lipophilicity and H-bond donor or acceptor character of the fragments were found to vary on a fairly wide scale. In most cases, molecular modelling calculations indicated similarities in the electrostatic potential maps of the fragments.

Összefoglalás

Esettanulmányunkban a Bioster adatbázis 2002.1 verziójában szereplő, a fenolcsoporttal bioizosztérnek tekinthető 55 fragmentum néhány szerkezeti jellemzőjét vizsgáltuk. Megállapítottuk, hogy a változatos szerkezetű fragmentumok mérete, számolt lipofilitása és H-kötés donor ill. akceptor jellege széles skálán mozog. A fragmentumok molekulamodellezéssel számított elektrosztatikus potenciáltérképe a legtöbb esetben hasonlónak mutatkozott.

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sparkV10 results: no “tweaks”

- Use pathfinder molecule as template
- Allow all substitutions for the phenolic ring
  - user choice for anchor points to other fragments
- Output = 200 molecules – rank top 20 by BIF

Published Actives (upper quartile)	% Actives predicted
Dopamine (ant)agonists	90
Receptor (ant)agonists	84
Adrenergic drugs	82
Steroids	78
Hydroxylase substrates	72

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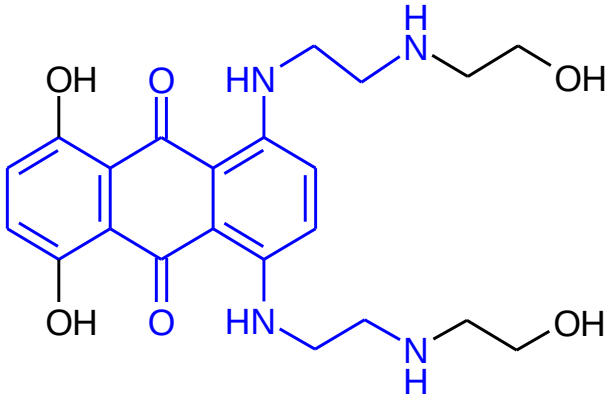
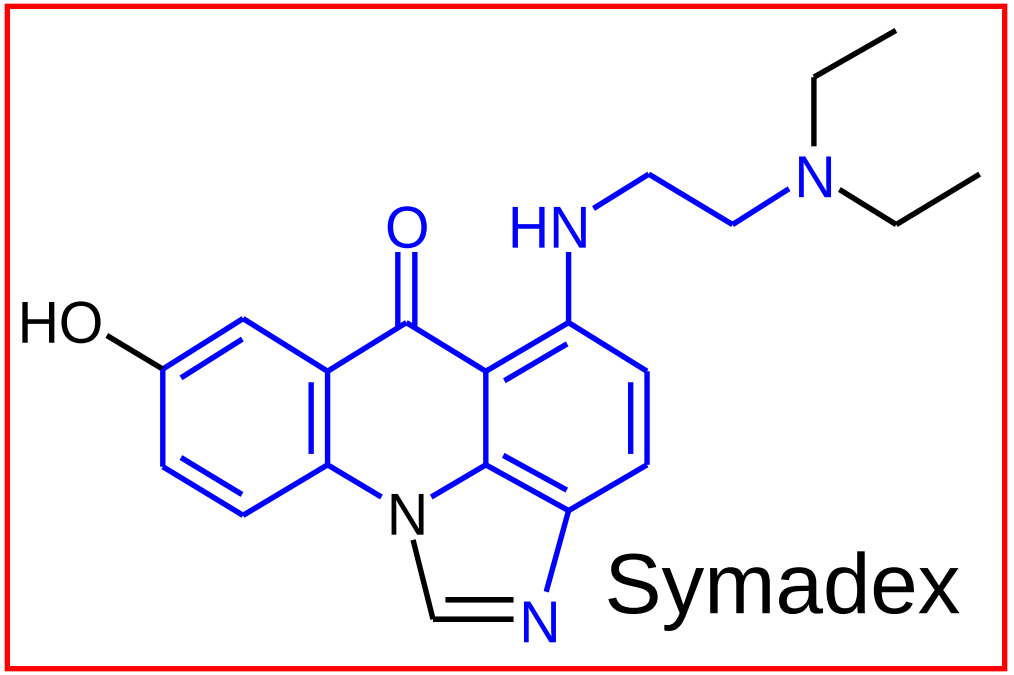
Pathfinder molecule: Symadex

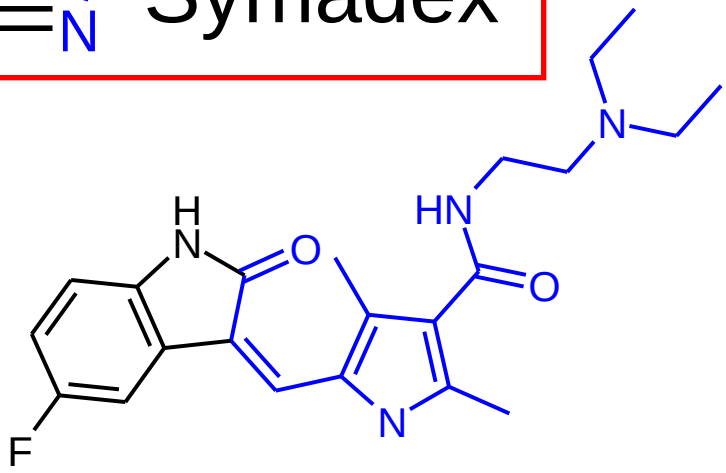


Anthracenedione



Symadex

Heterocyclic RTKi



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Medicinal chemistry strategy

- Drug design via bioisosteric optimization
  - *In silico* verification with RTK binding model
- Model used to select preferred scaffolds
- Added decorations to create focused library
- Key discovery objectives
  - Maintain RTKi Group III specificity
  - Eliminate cytotoxicity and mutagenicity
  - Optimize for favorable ADME/Tox
- Synthesize & test top scoring leads

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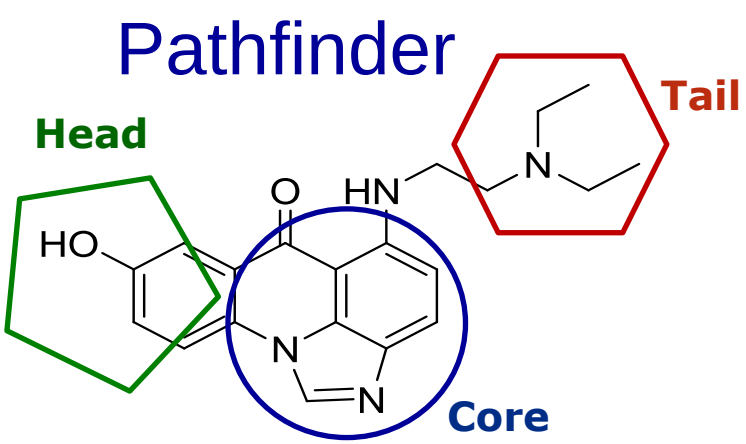
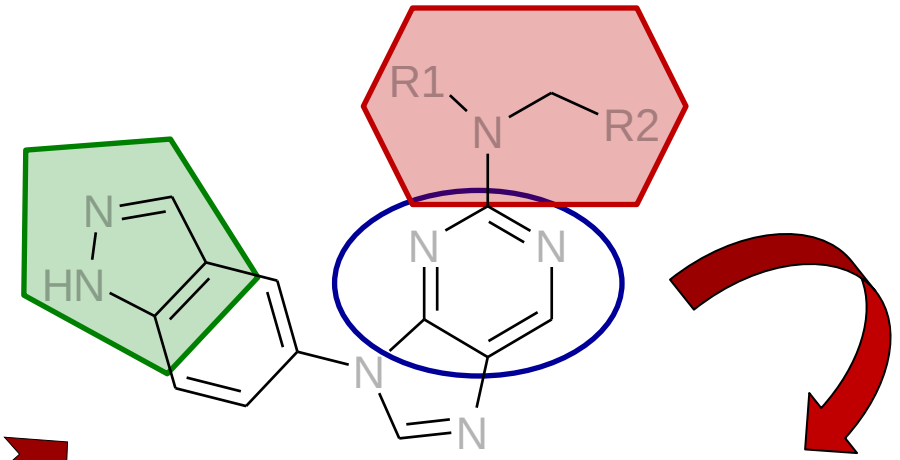
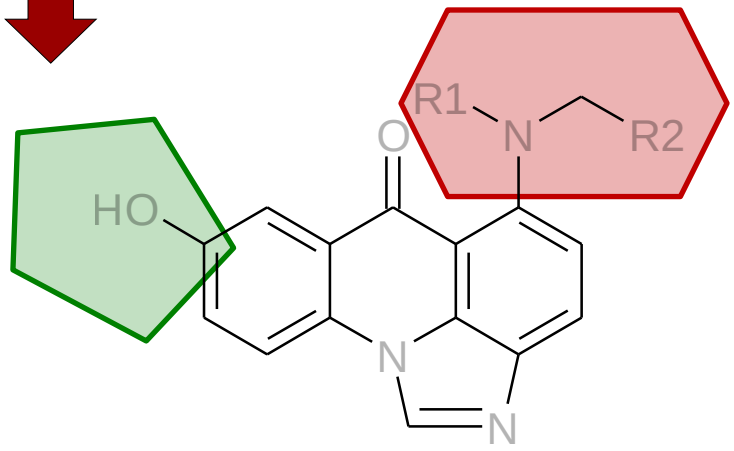
Bioisosteric optimization

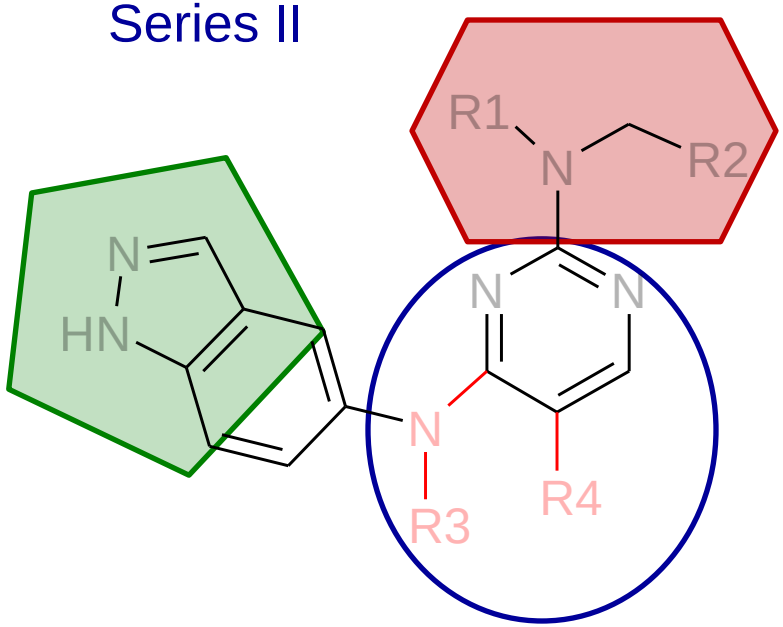
Pathfinder





Series II





Series III

Series Ia - R1 = Me, R2=H

Series Ib – R1 = H, R2 = Phenyl

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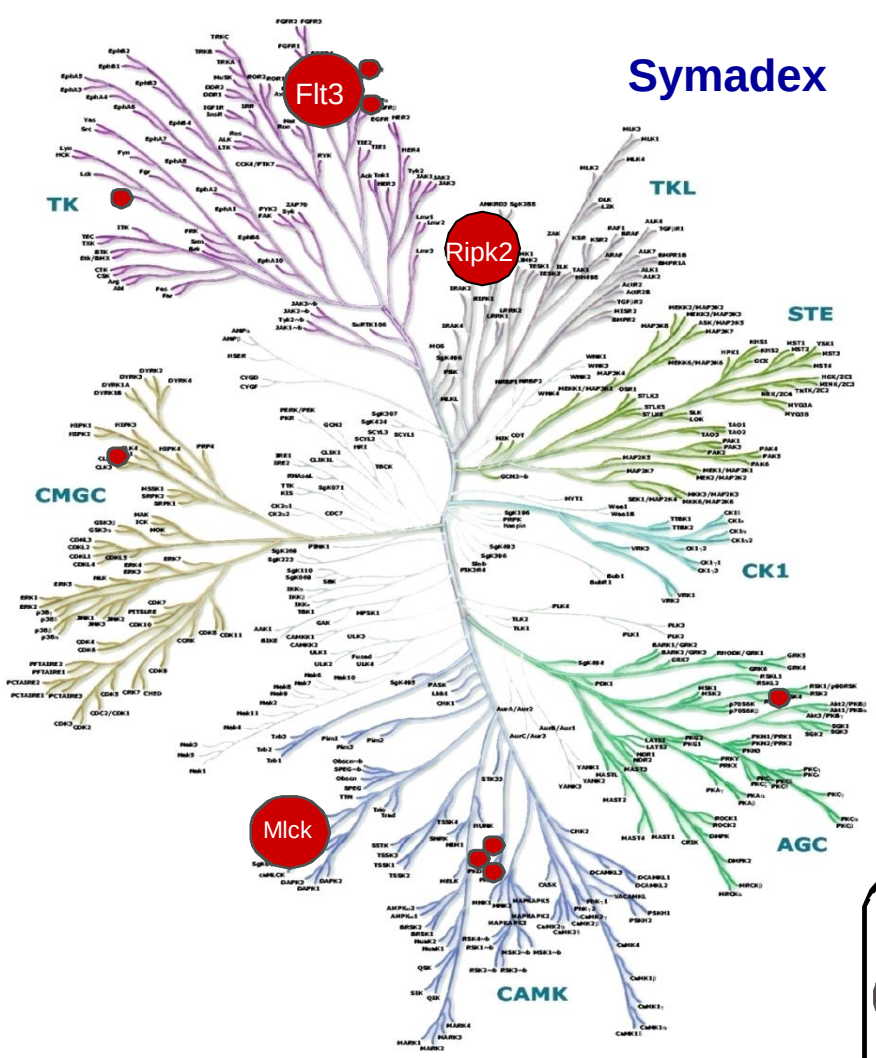
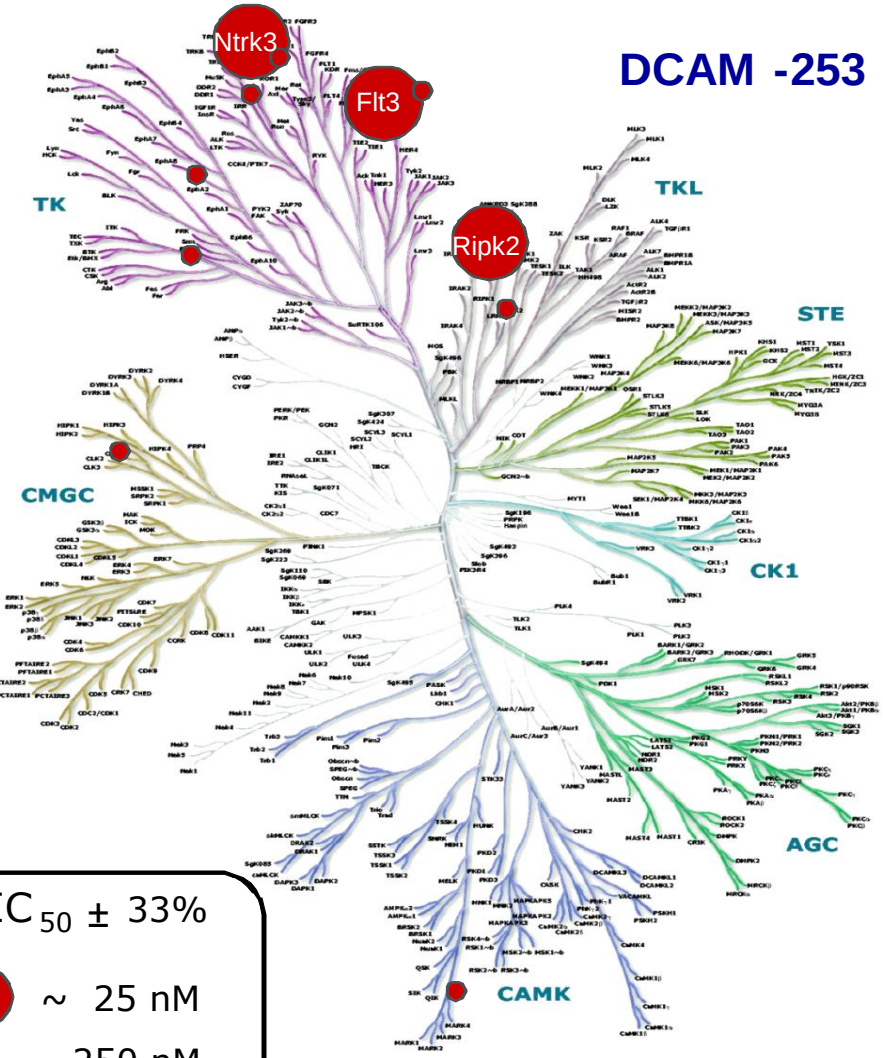
Pathfinder compared to lead DCAM





IC_{50} ± 33%

~ 25 nM

~250 nM

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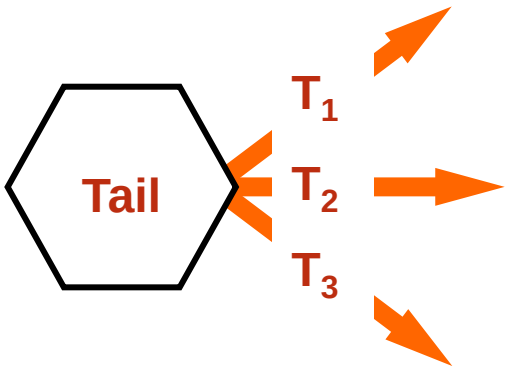
DCAM status & sparkV10 predictions

- 430 compounds synthesized (Series II)
  - 301 testable molecules
- 150 hits with selective RTKi activity
  - 40 leads with activity ≥ pathfinder molecule
  - 25 qualified leads (ADME/T and safety screen)
- sparkV10 retrospective predictions (BIF 0.9+)
  - Series Ia,b as templates + docking "field points"
  - Predicted indazole/isoindazole "heads" on 1st try
  - Predicted 25/40 leads, 17/25 qualified leads; 6/8 finalists; identified 50 additional NCEs

Kinase inhibition profiles for Series II



Type T_1: Aliphatic or aralkyl on Core I
DCAM **253**, 365, 395
Flt3, Ntrk, Ripk2

Aliphatic in Core II
DCAM 379, 381
Flt3

Type T_2: Aralkyl on Core II
(DCAM 378, 389, 408, 449)
Flt3, Musk, Ros1

Type T_3: Aryl on Core II
(DCAM 422, 430)
Flt3, Csf-1r, Epha, Flt4, Kdr, Stk16

- Core I = indazolyl-benzimidazole
- Core II = isoindazolyl-benzimidazole

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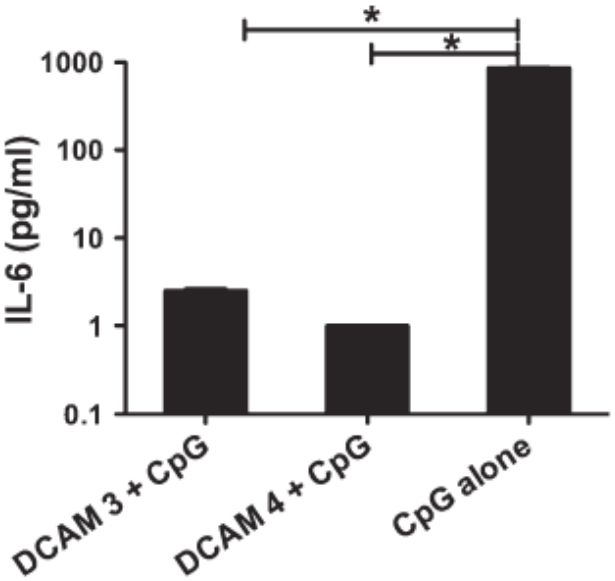
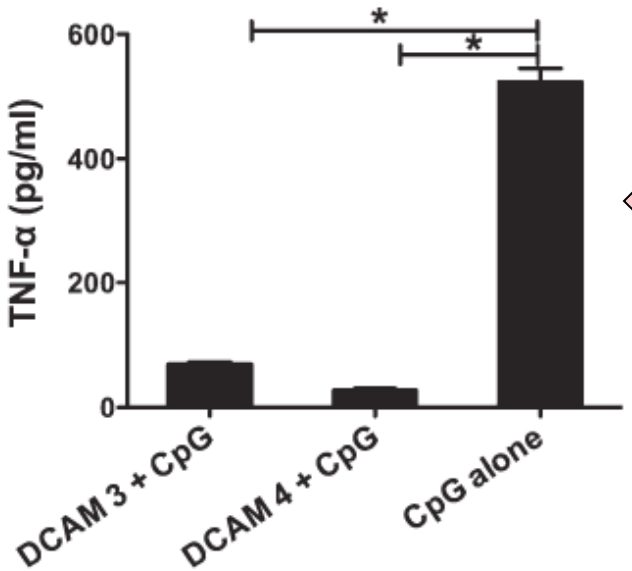
Target diversity (20-200 nM IC_{50} hits)

Csf-1r	Macrophage and dendritic cell stimulating factor receptor
Epha1	Ephrin receptor; cell migration/invasion control
Flt3	Dendritic cell, macrophage and monocyte growth factor
Flt4	Lymphatic endothelial growth regulator
KDR	Vascular endothelial growth regulator
Musk	Agrin receptor; neurite growth stop signal
Ntrk3	Neuroinflammation and neurite growth modulator
➔ **Ripk2**	NF-κB pathway and inflammasome regulator
Ros1	Oncogenic fusion kinase in brain, lung and hepatobiliary cancers
Stk16	Transcriptional factor in TGF-β pathway

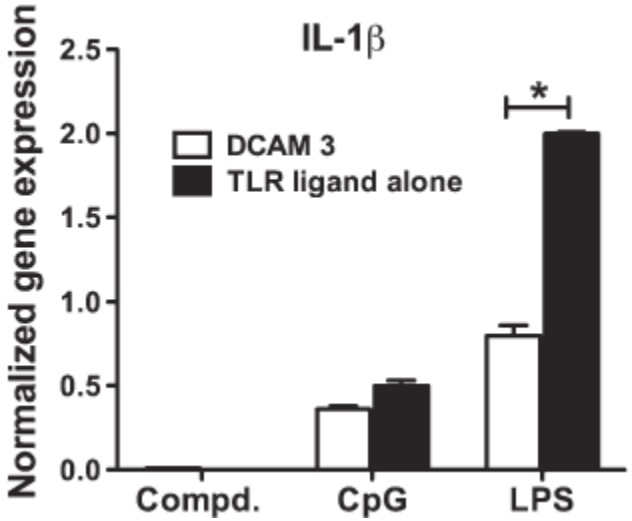
Unique opportunity to modulate NF-κB

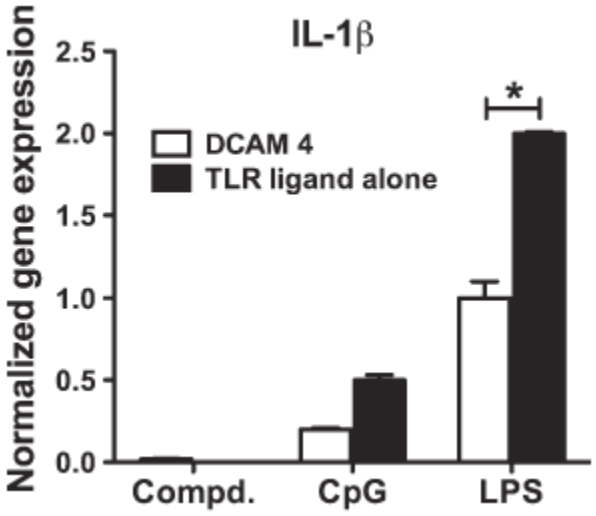




NF-κB

TLR9 mediated production in marrow-derived macrophages





NF-κB

TLR4 mediated production in marrow-derived macrophages

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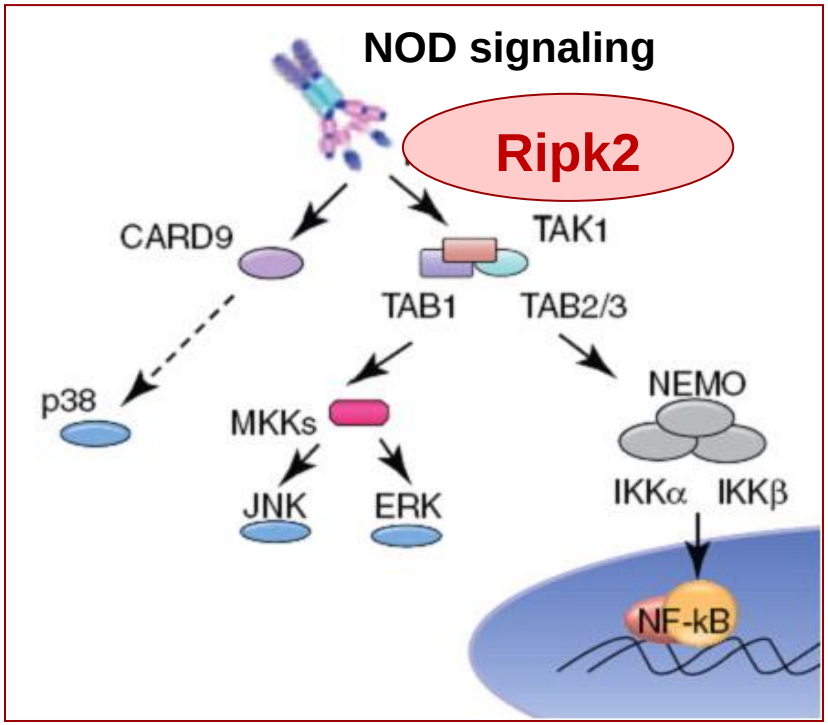
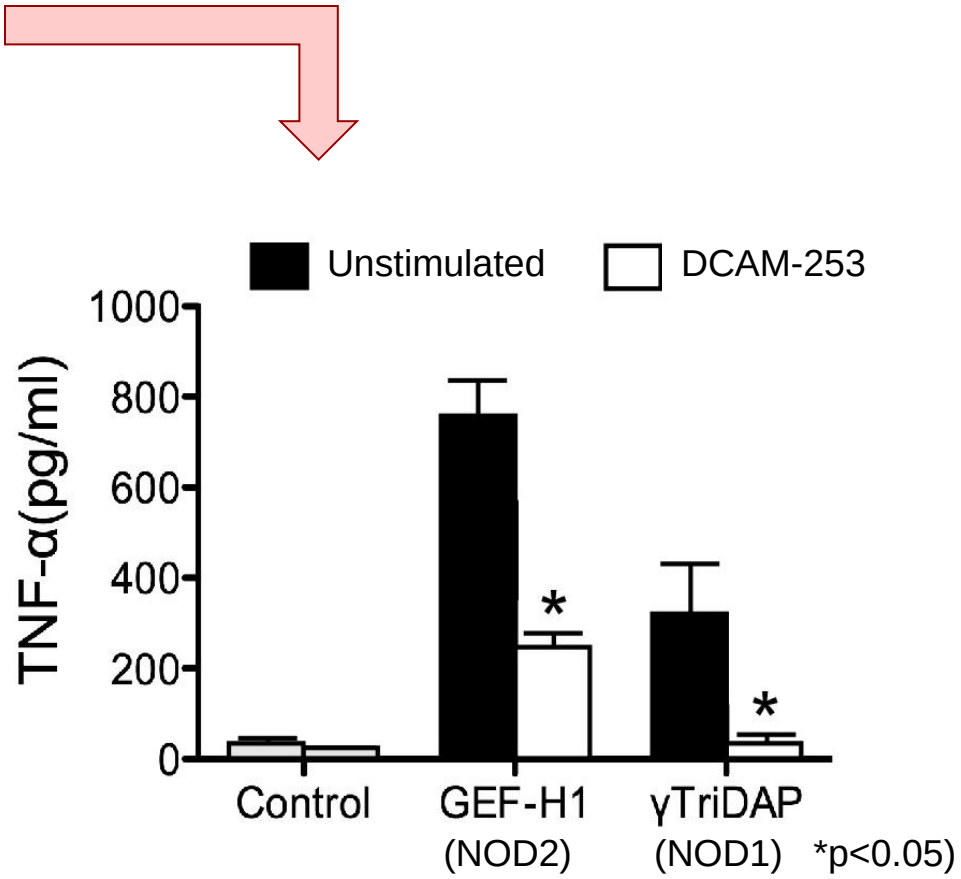
Block NF-κB activation via Ripk2





DCAM-253 decreased TNF-α production induced by GEF-H1 (NOD2) or TriDAP (NOD1) activation in HEK 293 cells.

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DCAMs in perspective

- Optimized via bioisosteric replacement
- Predicted by sparkV10 + additional NCEs
- Major underserved disease target – Ripk2
  - Relevant to autoimmune and cancer therapies
- Potential alternative to anti-TNF biologics
  - Small molecule, orally bioavailable, disease modifying agents
- Extensible platform for immunokinase inhibitors