



Cresset
BioMolecular Discovery Limited

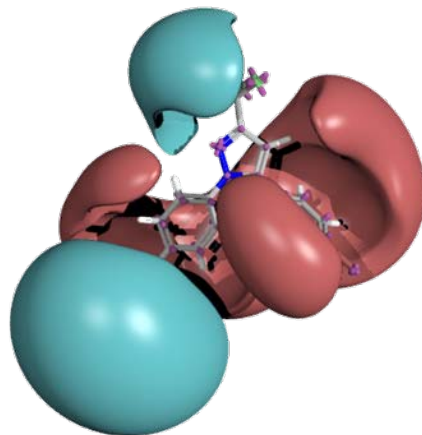
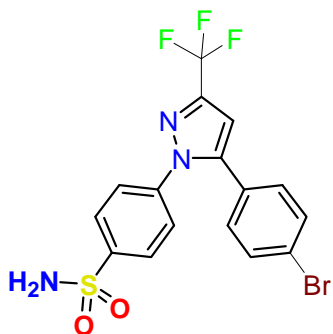


FieldStere

Bioisosteric replacement using Molecular
Fields

Molecular fields

- Look at electrostatic, hydrophobic and shape properties simultaneously (“protein’s view”)
 - Molecular Field Extrema (“Field Points”)



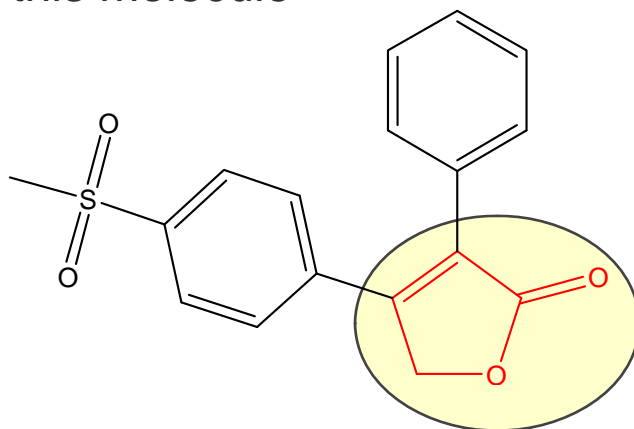
Red = Positive , Blue = Negative
Yellow = Shape, Orange = Hydrophobic

Applications

- Using fields we can align and score molecules in 3D
 - Virtual Screening
 - Molecular alignment
 - Pharmacophore hypothesis generation
- Extend this: can we focus on parts of existing molecules?

Bioisosteric replacement with Fields

Love this molecule

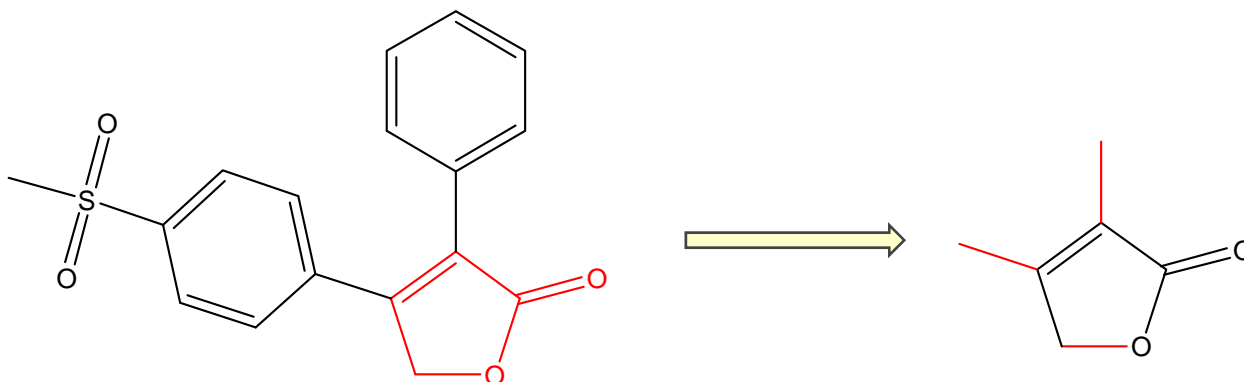


... but hate this bit

Can we use field similarity to find replacement fragments?

Search for fragments or molecules?

- Existing approaches have tended to focus on fragment space

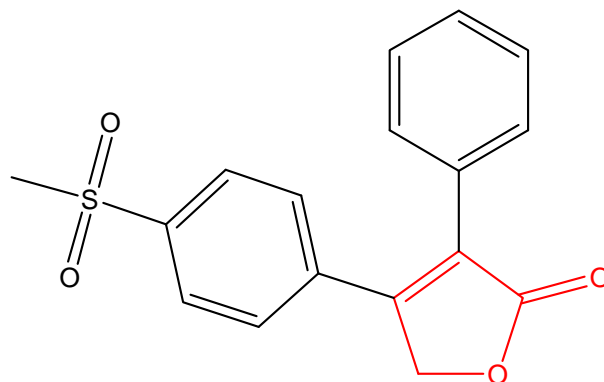


Search for fragments
that look like this

- Fields are **global** properties
- The properties of the fragment affect the rest of the molecule!

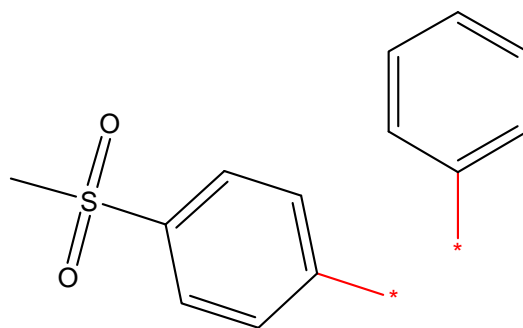
Our approach

Select a region to replace



Our approach

Generate attachment vectors



Our approach

Search database for matching fragments

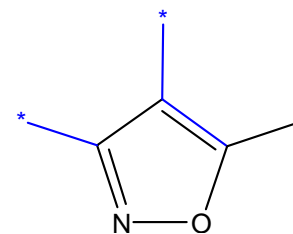
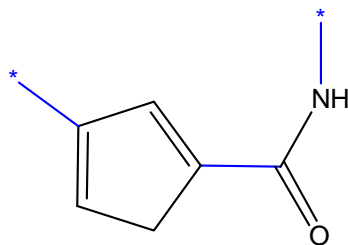
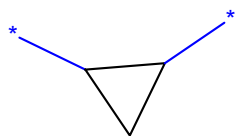


Match attachment points

Search database for matching fragments



Wrong angle

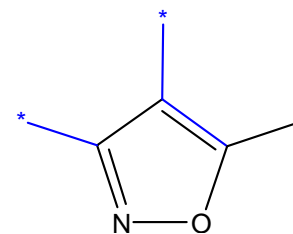
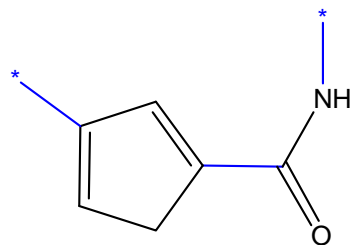


Match attachment points

Search database for matching fragments



Too far apart

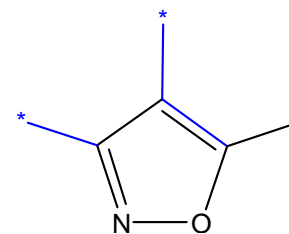


Match attachment points

Search database for matching fragments

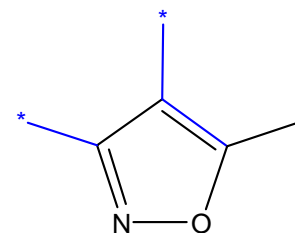
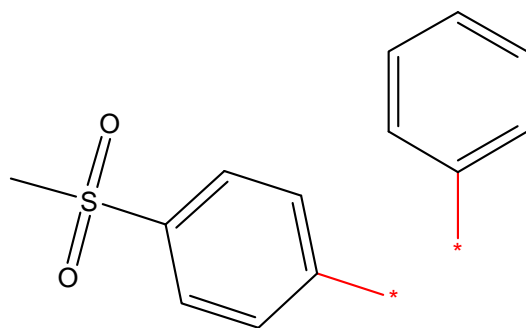


Good match



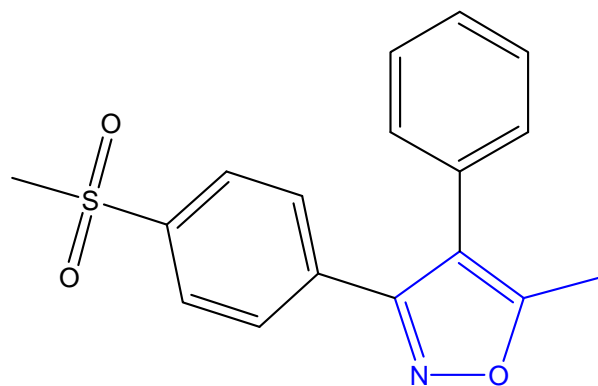
Work in product space

Merge fragment into target molecule



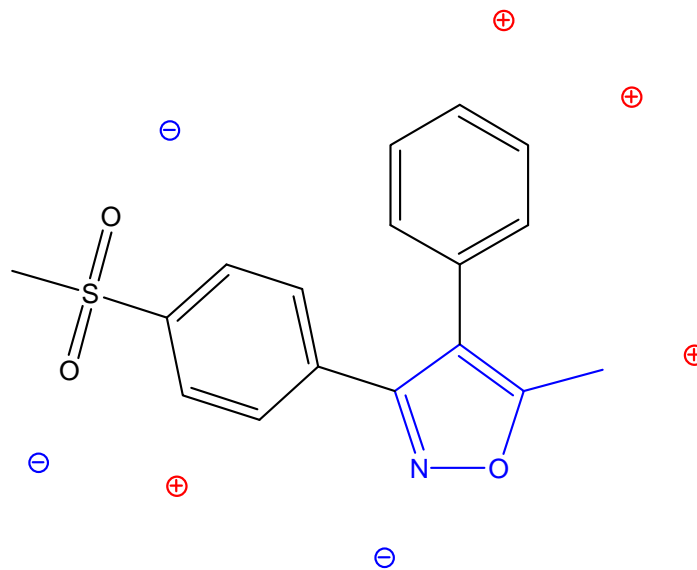
Work in product space

Merge fragment into target molecule



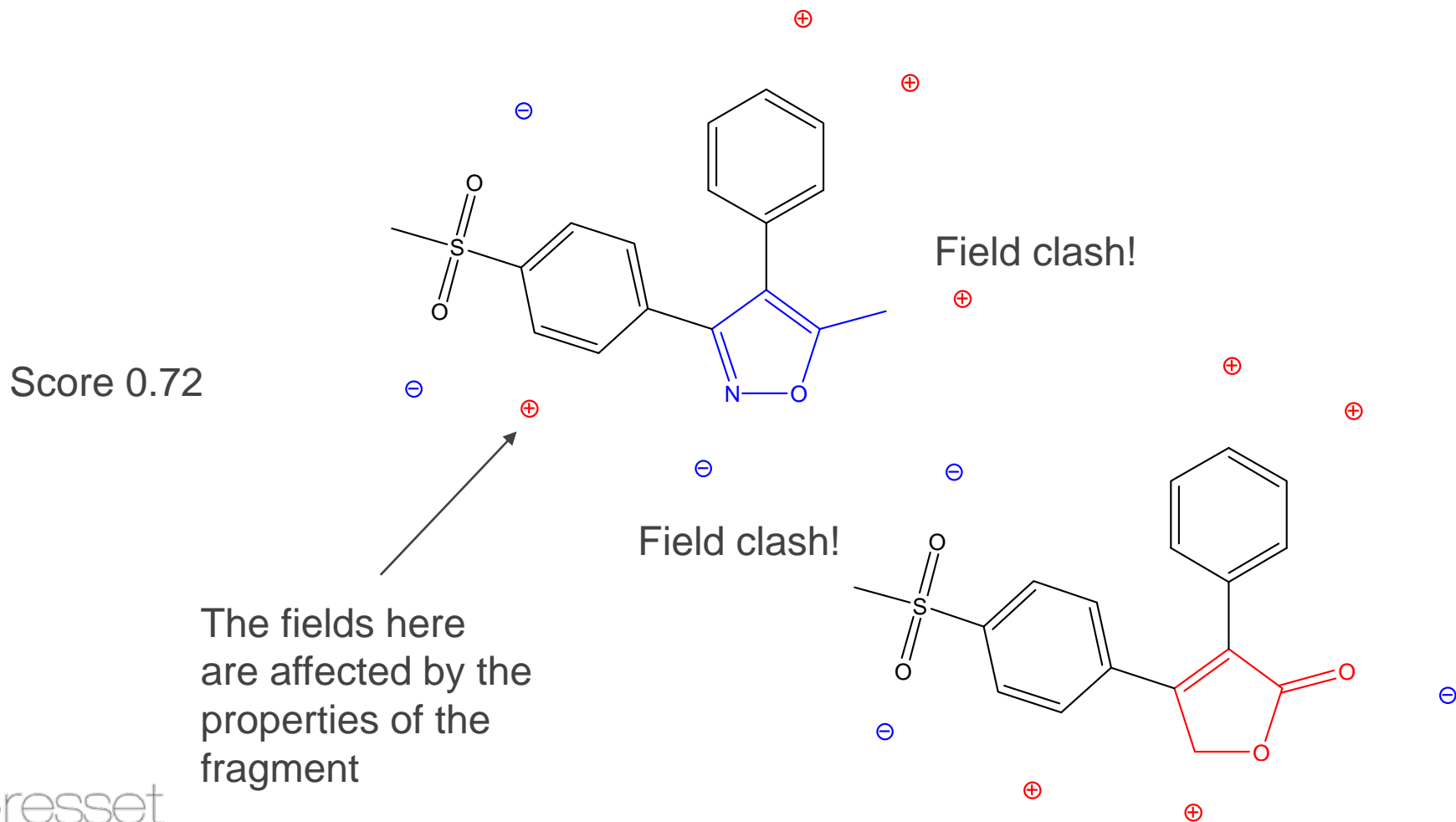
Work in product space

Calculate field points



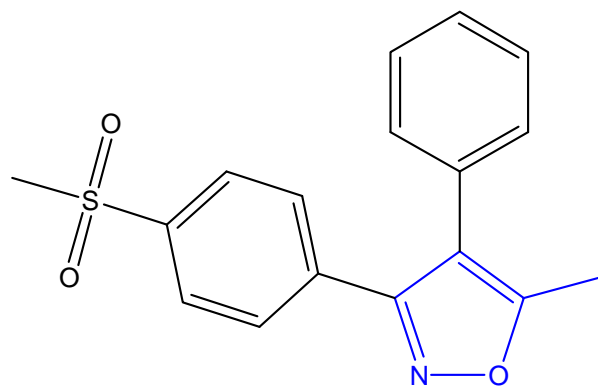
Score in product space

Score against original molecule



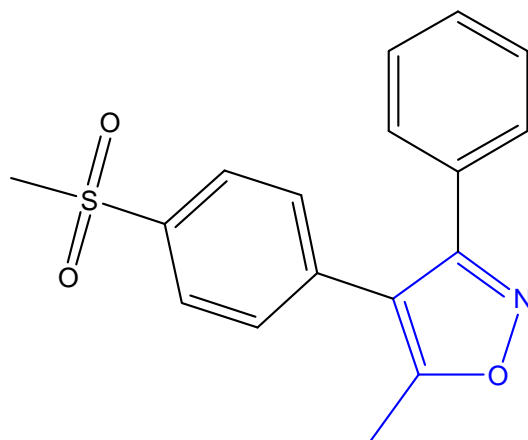
Multiple possibilities per fragment?

Try both ways...



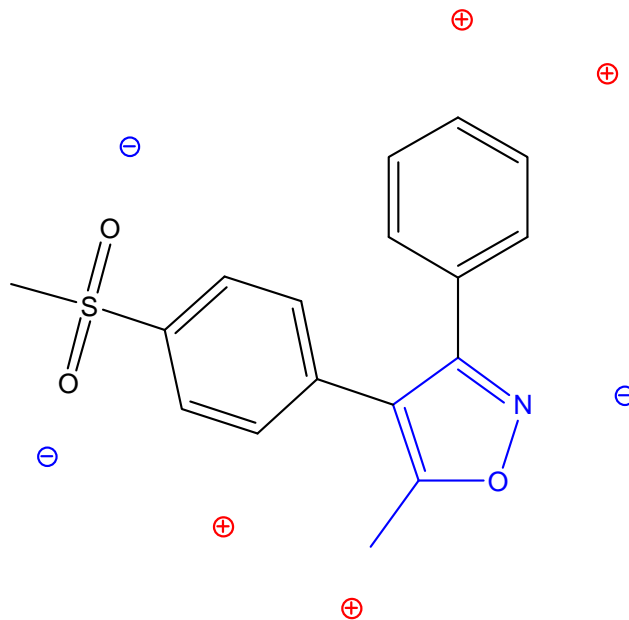
Multiple possibilities per fragment?

Try both ways...



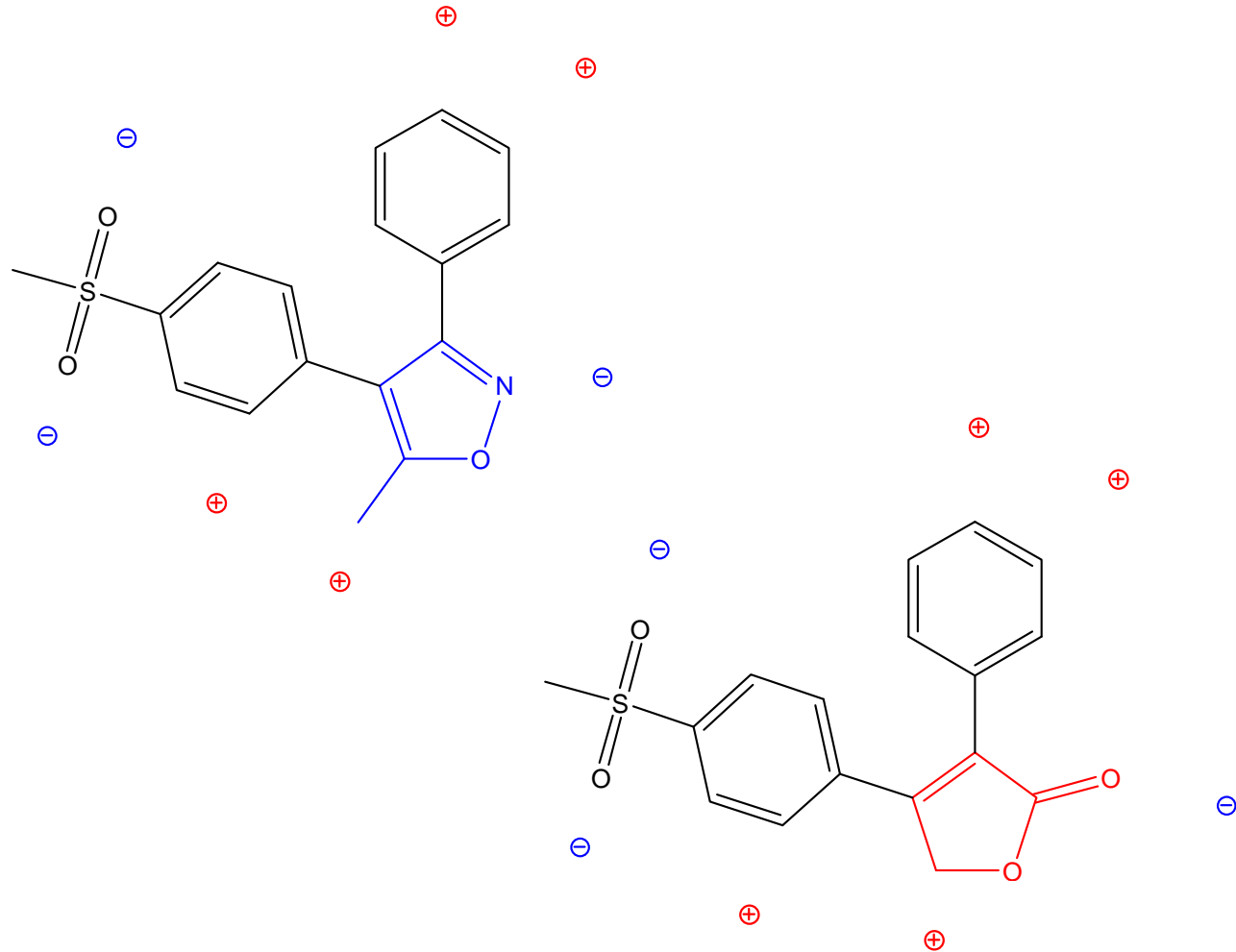
Multiple possibilities per fragment

Add fields



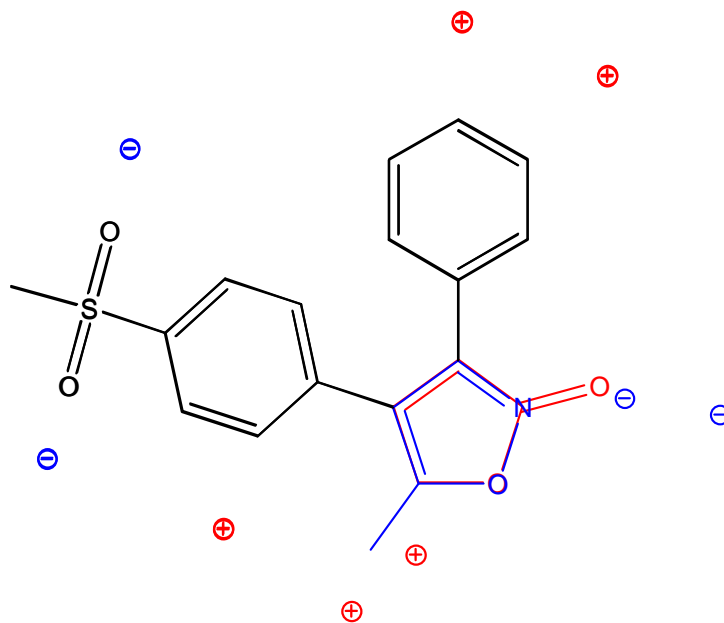
Multiple possibilities per fragment

Score against original molecule



Multiple possibilities per fragment

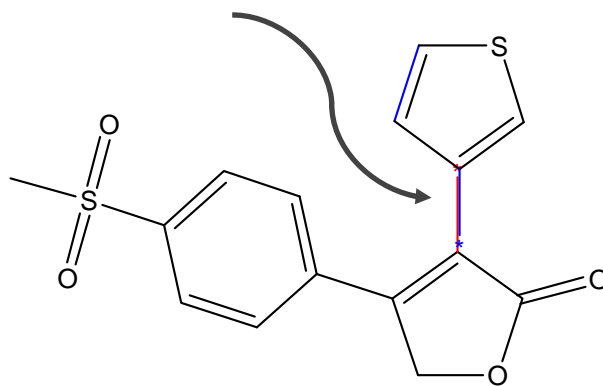
Score against original molecule



Score 0.88

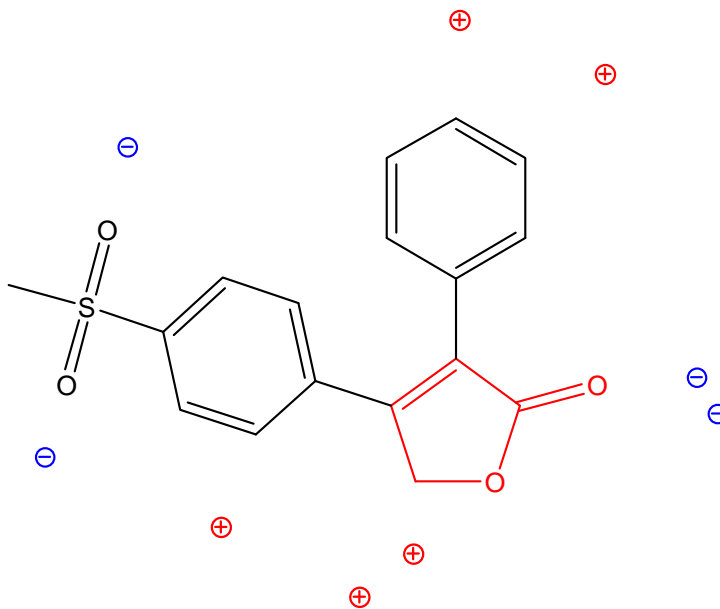
Single attachment points

For single attachment points we rotate to find the best position



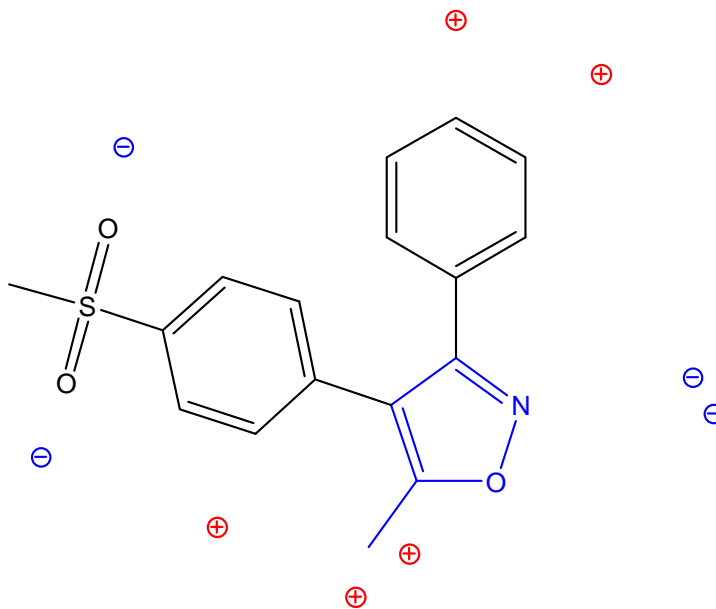
Speed issues

- Calculating field patterns is expensive (10-100 ms)
- Tiered approach
 - Stage 1
 - Use field point positions of target and fragment



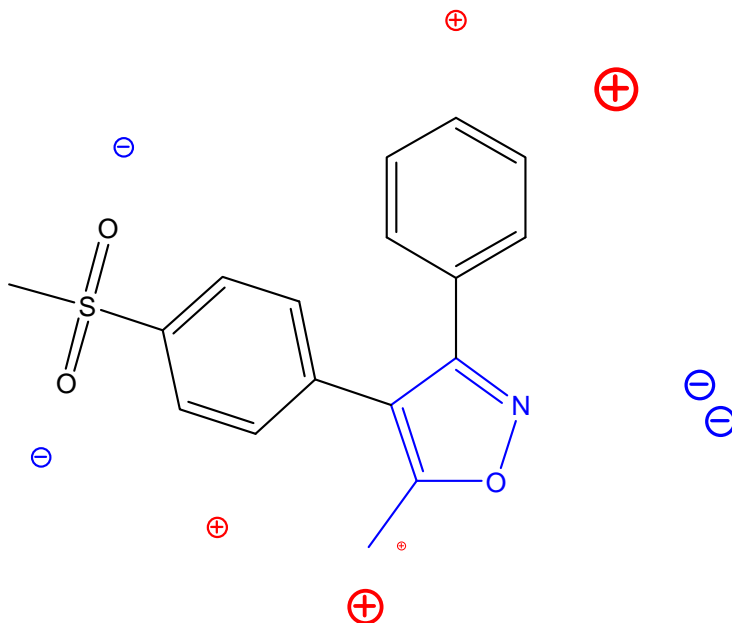
Speed issues

- Calculating field patterns is expensive (10-100 ms)
- Tiered approach
 - Stage 1
 - Use field point positions of target and fragment
 - Update field point sizes based on true field



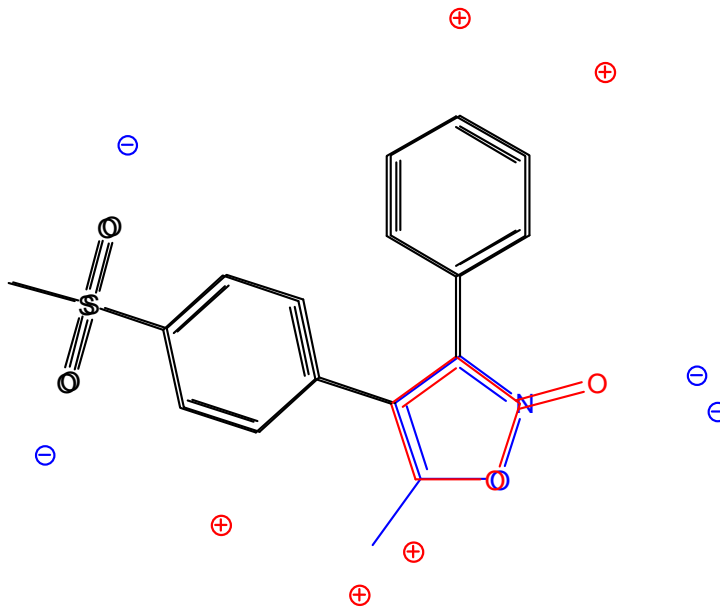
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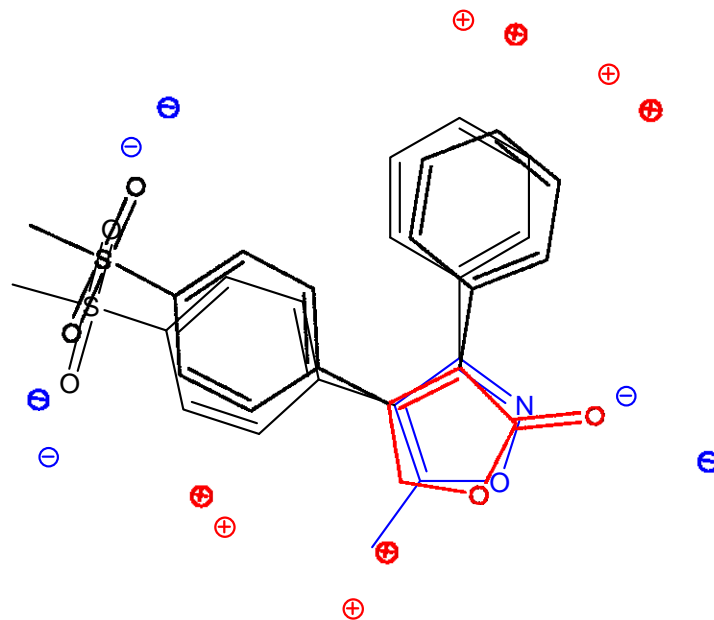
Speed issues

- Calculating field patterns is expensive (10-100 ms)
- Tiered approach
 - Stage 1
 - Use field point positions of target and fragment
 - Update field point sizes based on true field
 - Score in fixed alignment



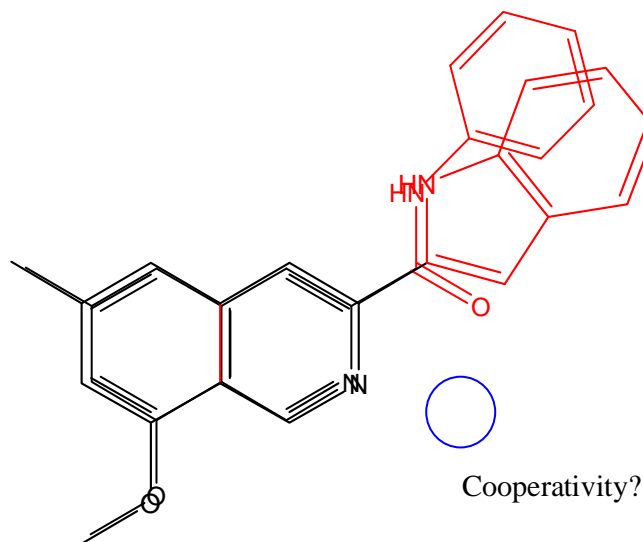
Speed issues

- Calculating field patterns is expensive (10-100 ms)
- Tiered approach
 - Stage 1
 - Use field point positions of target and fragment
 - Update field point sizes based on true field
 - Score in fixed alignment
 - Stage 2
 - Minimise
 - Generate true field
 - Optimise alignment



Advantages

- Scoring is whole-molecule
- Allows for electronic influence of fragment on the rest of the molecule and vice versa.
- Will allow partial replacement of rings, etc
- Allows for cooperativity of the fragment's fields with those of the retained part

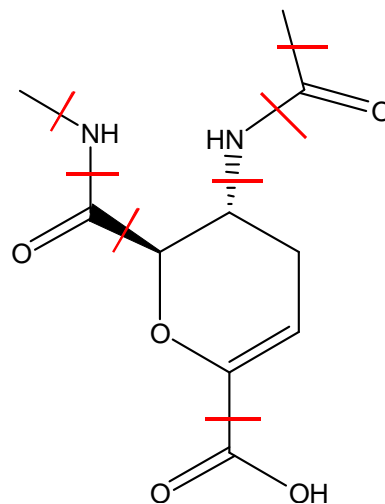


Scoring options

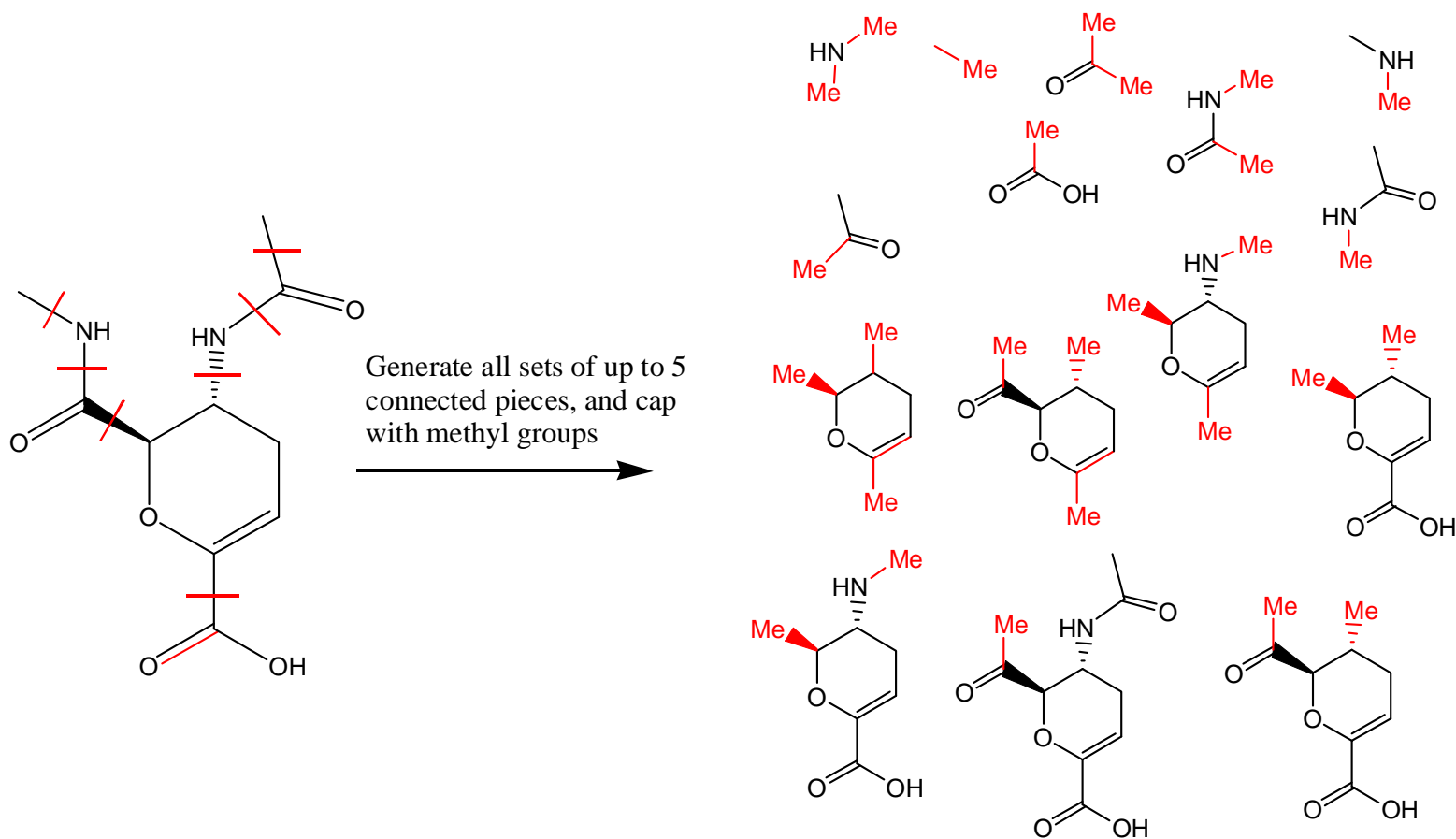
- Score on shape, fields, or mixture
- Field constraints to fine-tune scoring
- Filtering
 - Fragment properties
 - Contains S, contains a ring, no toxophores, etc
 - Number of heavy atoms, MW
 - Attachment point properties
 - Must attach through a sp³ nitrogen

Where do you get fragments from?

- Fragment existing molecules
- RECAP rules and the like a bit too restrictive
- Fragment at
 - Heteroatoms
 - C=O and C=S
 - Bonds to rings
 - Not NO₂, COOH, etc
- Generate all sets of connected pieces
 - Subject to MW, NH, and rotatable bond limits



Fragmentation example



Conformation hunt done on all fragments

Fragments

- Commercial compounds
- Split by frequency
 - V. Common (~25K)
 - Common (~75K)
 - Less Common (~100K)
 - Rare (1&2) (~450K)
- Frequency roughly correlates with synthesisability(?)

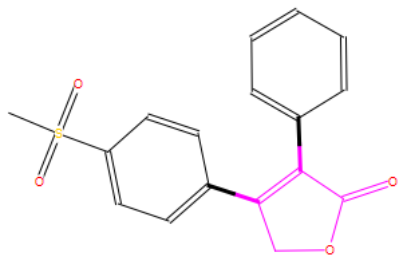
Application – LI/LO– COX-2

FieldStere - rofecoxib

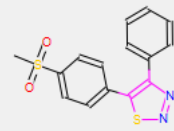
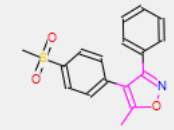
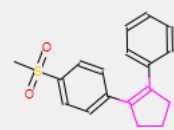
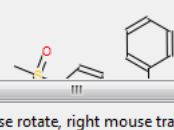
File Edit View Display Run Help

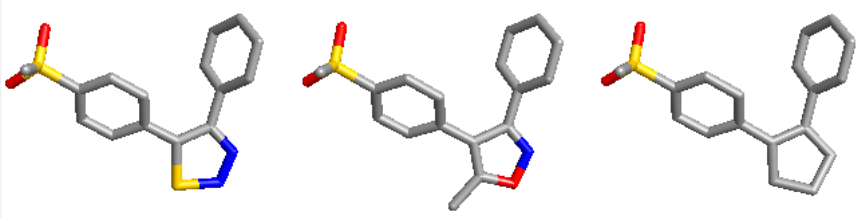
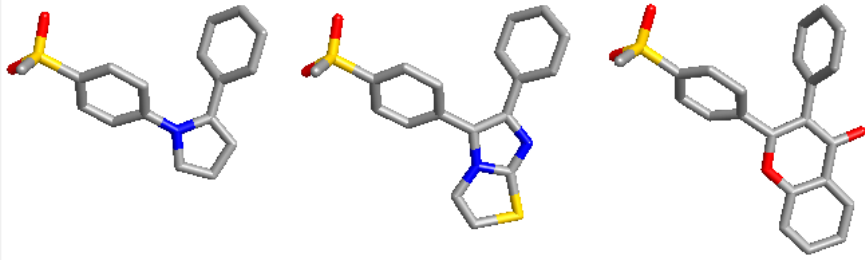
All Results

Target



Results

| Structure | Score | MW | Title |
|---|-------|--------|-------------------|
|  | 0.920 | 316.39 | Fm-c(sn1)c(Fm)n1 |
|  | 0.881 | 313.37 | Fm-c(n01)c(Fm)c1C |
|  | 0.867 | 298.39 | FmC(=C(Fm)C1)CC1 |
|  | 0.837 | 297.37 | Fm-n(c(Fm)c1)cc1 |

Molecule 1 of 1000. 6 favourites marked.
FmN(C(Fm)=NC=IO)C(=O)C1

Left mouse rotate, right mouse translate, middle mouse/wheel/Alt-left mouse scales. Keys + and - also scale.

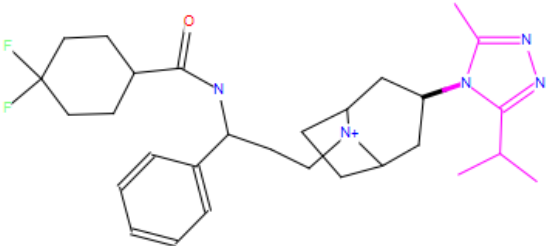
Application – LO - CCR5

FieldStere - CCR5_LO

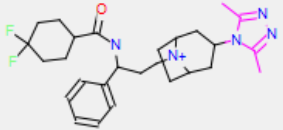
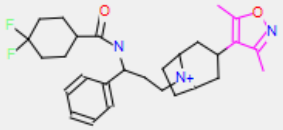
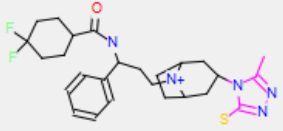
File Edit View Display Run Help

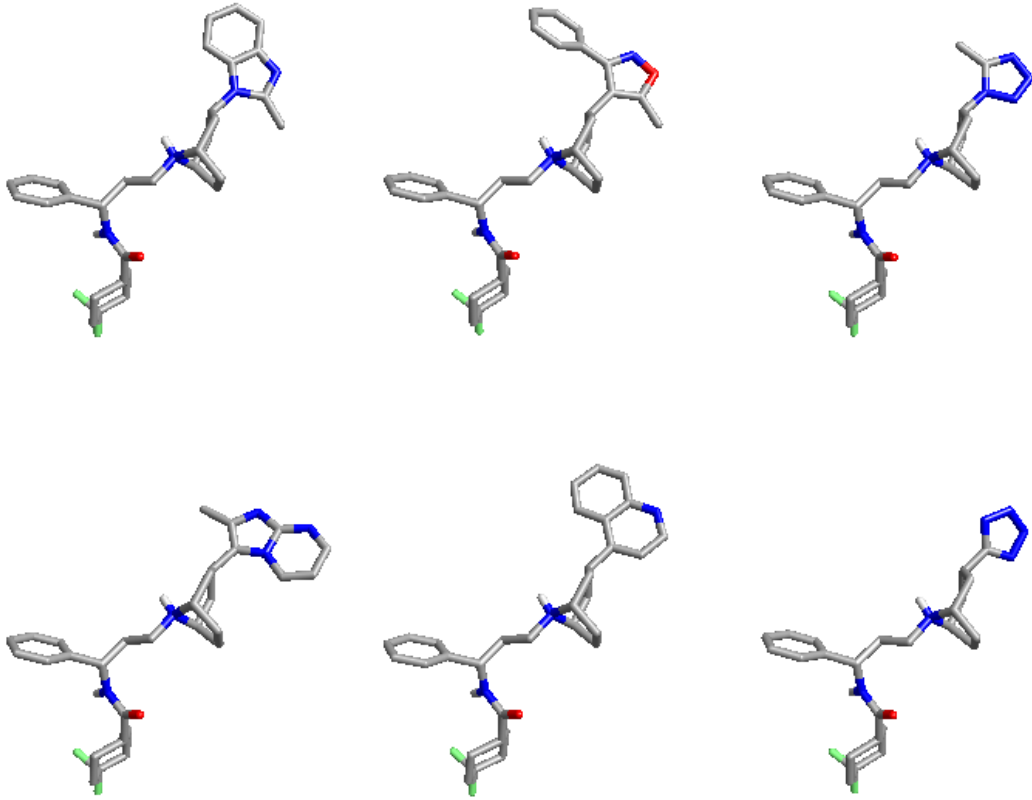
All Results

Target



Results

| N | Structure | Title |
|---|---|--------------------|
| 1 |  | Fm-n(c(n1)C)c(n1)C |
| 2 |  | Fm-c(c(o1)C)c(n1)C |
| 3 |  | Fm-n(c(S)n1)c(n1)C |



Molecule 22 of 1000. 6 favourites marked.
Fm-c(c(o1)C)c(n1)-c(ccc2)cc2

FieldStere





Cresset
BioMolecular Discovery Limited



FieldStere

Bioisosteric replacement using Molecular
Fields

Frequency vs # attachment points

