MedChemica

CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Using Matched Molecular Pairs for CoreDesign®

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Agenda

- What are we trying to do?
- Introduce MMPs
- CoreDesign®
- Examples

What are we trying to do?

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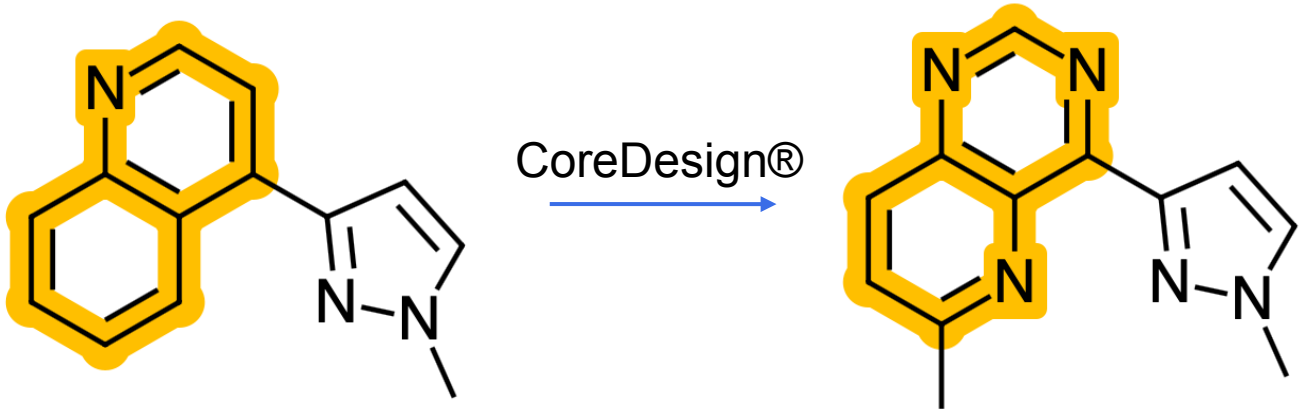
Idea generation for new core structures



CoreDesign Uses:

- Idea generator
- Scaffold hopping

Key Features:

- More **flexible** than RuleDesign as transformations do not have to be rules (i.e. can have one example)
- **Bibliography** of references provided to showcase the transformation (where available)

What is a core?

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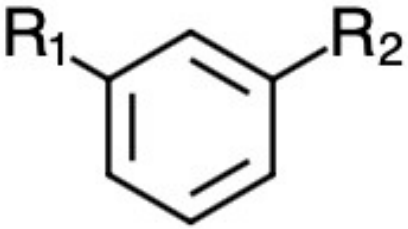
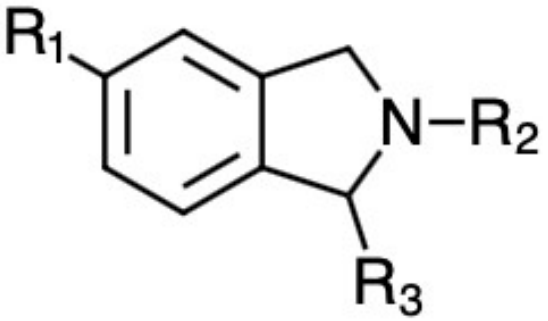
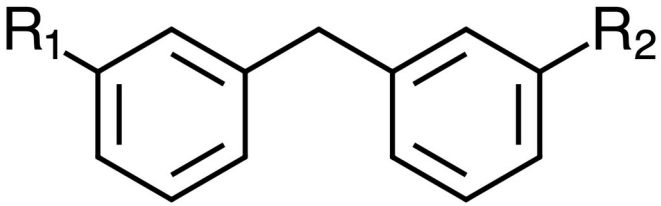
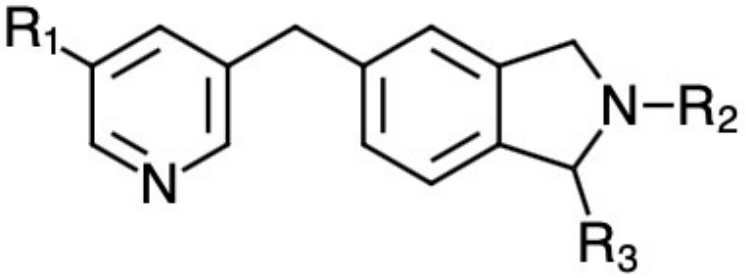
- A core of a molecule can be either a ring or ring system(s) that are connected via linker(s). Cores are therefore built of rings and linkers.









What are we trying to do?

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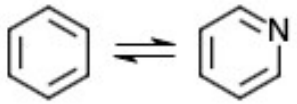
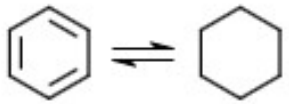
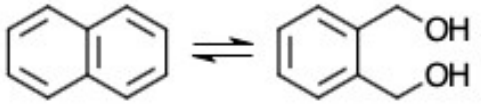
- Different Core Alterations
  - Or a combination of these

Changing an Atom(s)

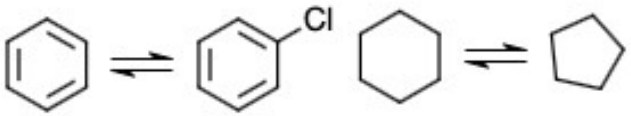


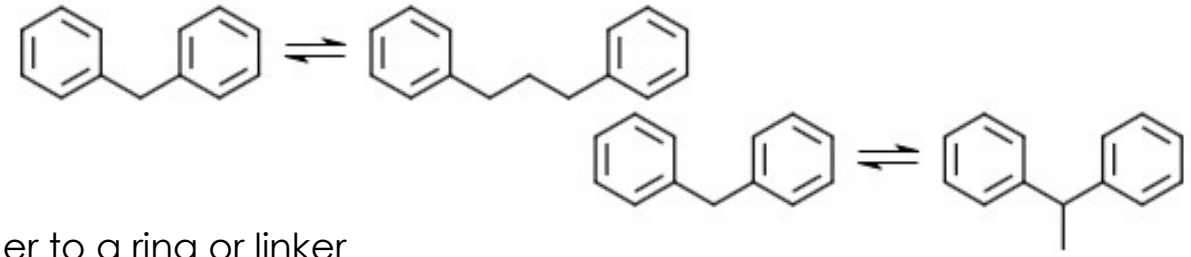
Changing or breaking a bond including changing the aromaticity of a ring



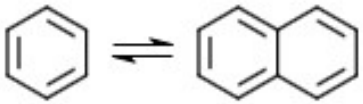


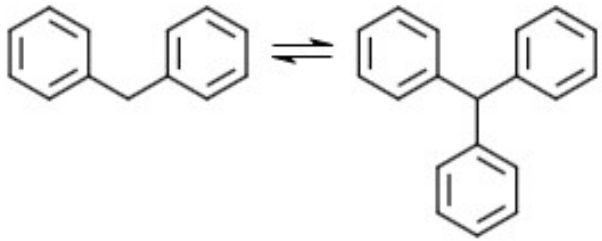
Adding or Removing an Atom(s) either to a ring or linker





Adding or Removing a Ring either to a ring or linker





Matched Molecular Pairs

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Matched Molecular Pairs

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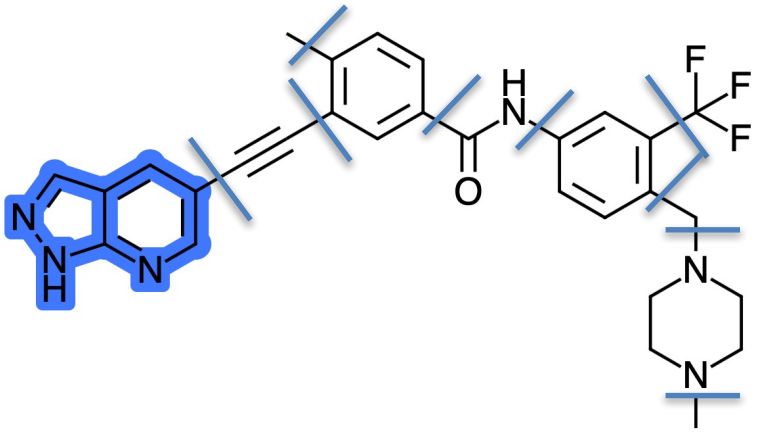
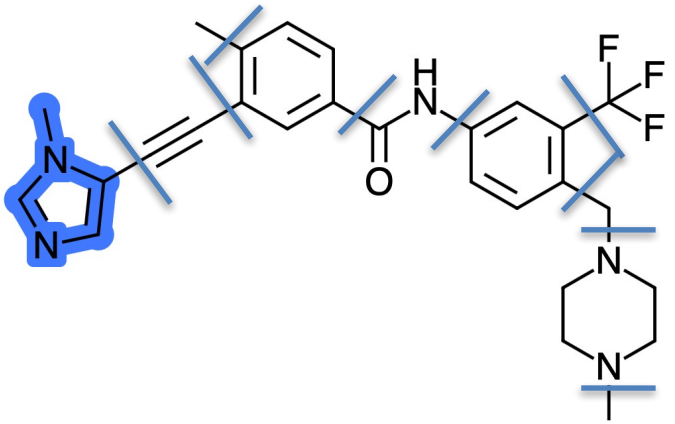
- Molecules that differ only by a well-defined structural chemical change are said to have a matched molecular pair
- Two methods of finding MMP
  - Fragment and Index Method



A - CHEMBL2316582



B - CHEMBL1784632

- Break all single rotatable bonds and groups on common 'core' parts
- Single, Double and Triple cuts combinations are made as standard
- Leads to many fragments from a single molecule
- …and the same pair paired by many combinations of core / frag

Matched Molecular Pairs

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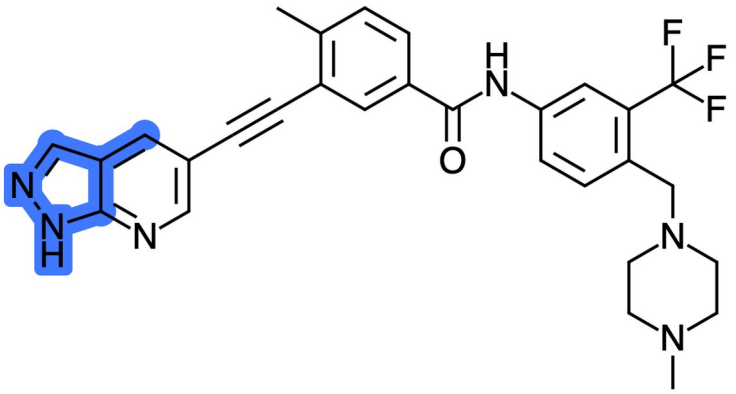
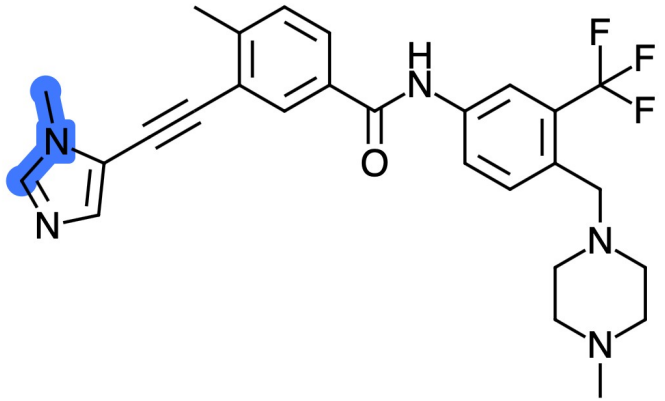
- Molecules that differ only by a well-defined structural chemical change are said to have a matched molecular pair
- Two methods of finding MMP
  - Fragment and Index Method
  - Maximum Common Substructure Method



A - CHEMBL2316582



B - CHEMBL1784632

- Structures matched by overlapping of the matching heavy atom
- Semantically the same matched pair as F/I but syntactically different in that 'points of modification' **are not** the same
- Encoding of the resultant transformation can be different

Matched Molecular Pairs As SMIRKS

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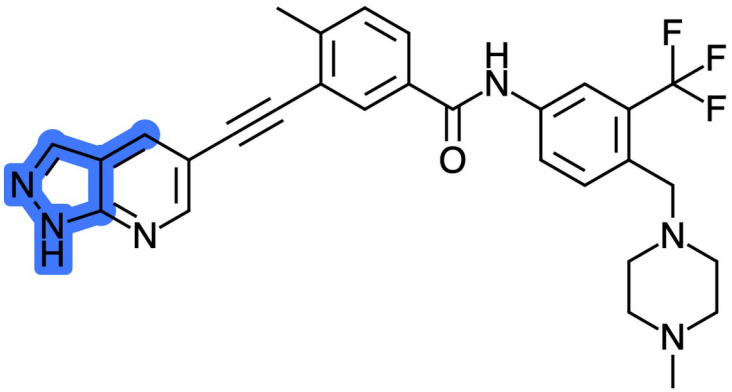

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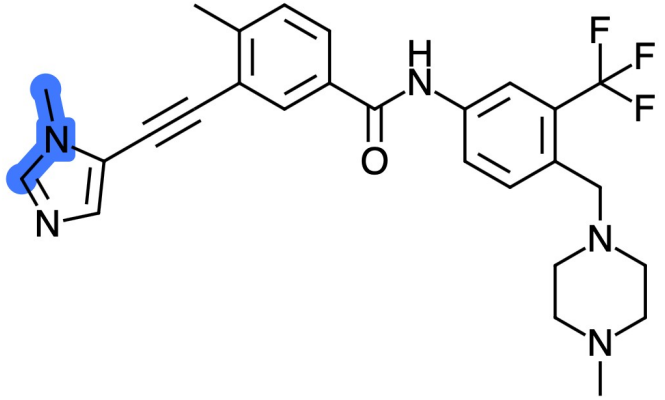

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- MMP encoded as SMIRKS
  - [c][c]1[c][n][n][c]1 >> [c][n][C]
  - Along with delta values of properties

A $\xrightarrow{\Delta\ -2.721}$ B

smirk.RunReactants((mol,))

Environment Size

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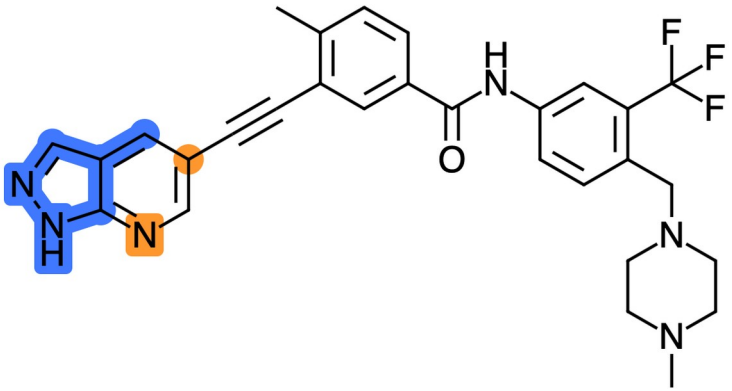
- Capture the environment around a transformation – up to 4 atoms



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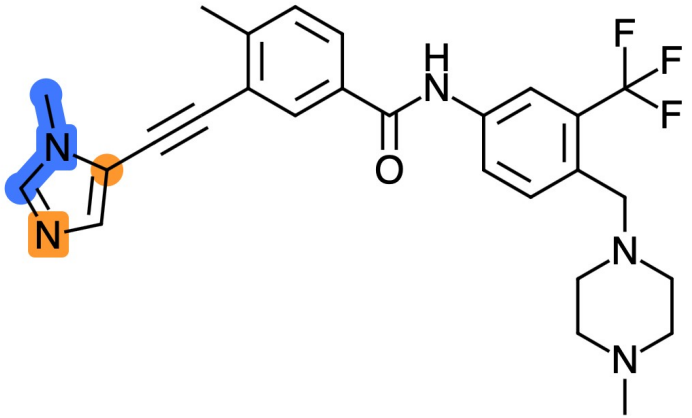

B - CHEMBL1784632

- Environment size 1: [c][c][c]1[c][n][n][c]1[n] >> [c][n]([c][n])[C]

Environment Size

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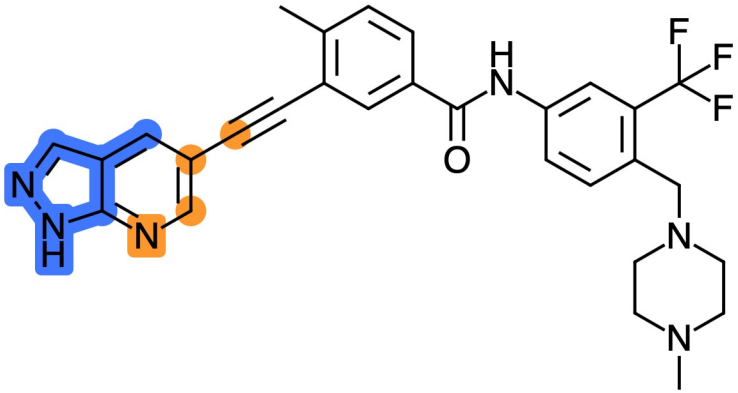
- Capture the environment around a transformation – up to 4 atoms



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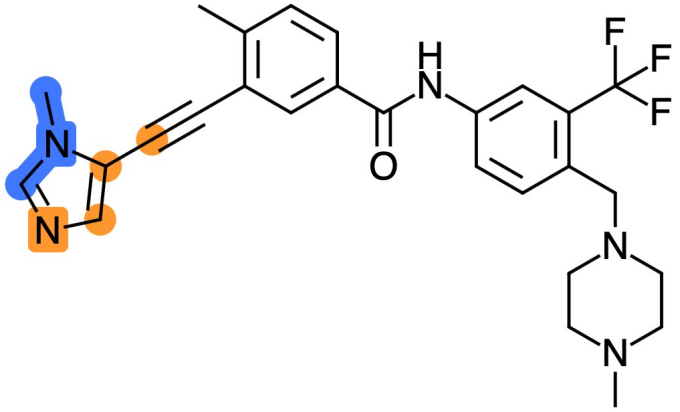

B - CHEMBL1784632

- Environment size 1: [c][c][c]1[c][n][n][c]1[n] >> [c][n]([c][n])[C]
- Environment size 2: [C][c]1[c][c]2[c][n][n][c]2[n][c]1 >> [C][c]1[c][n][c][n]1[C]

Environment Size

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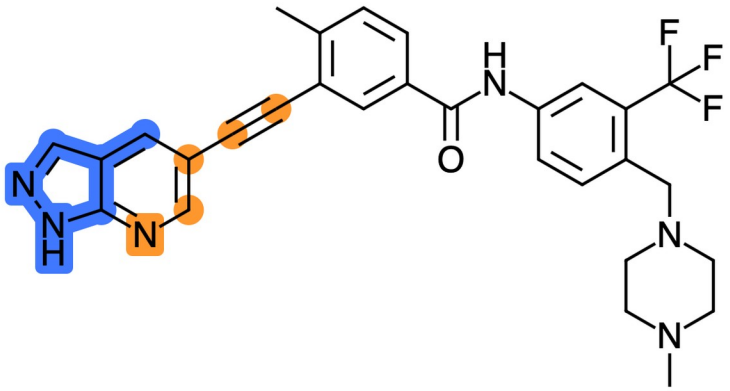
- Capture the environment around a transformation – up to 4 atoms



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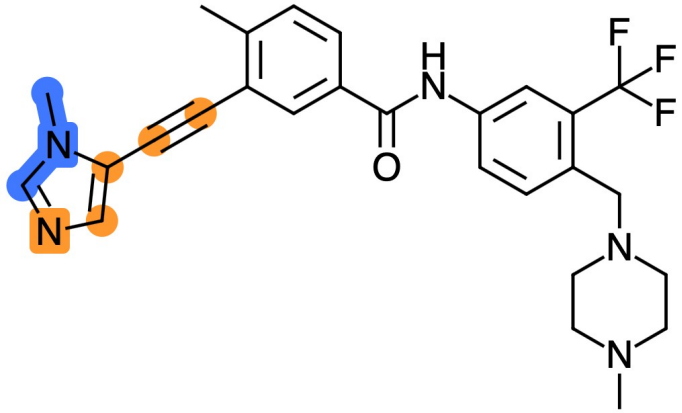

B - CHEMBL1784632

- Environment size 1: [c][c][c]1[c][n][n][c]1[n] >> [c][n]([c][n])[C]
- Environment size 2: [C][c]1[c][c]2[c][n][n][c]2[n][c]1 >> [C][c]1[c][n][c][n]1[C]
- Environment size 3: [C]#[C][c]1[c][c]2[c][n][n][c]2[n][c]1 >> [C]#[C][c]1[c][n][c][n]1[C]

Environment Size

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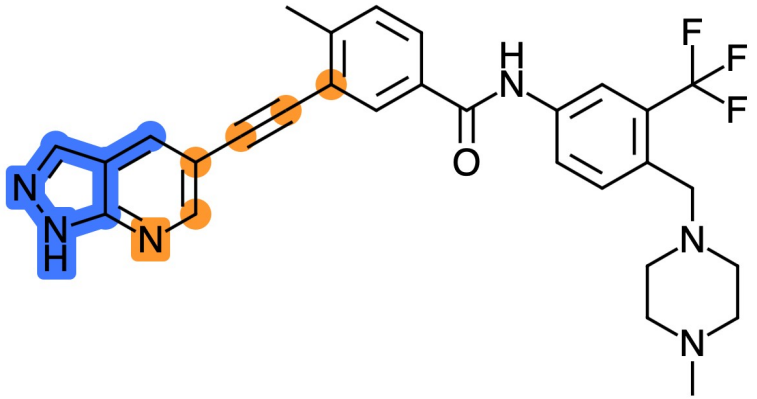
- Capture the environment around a transformation – up to 4 atoms



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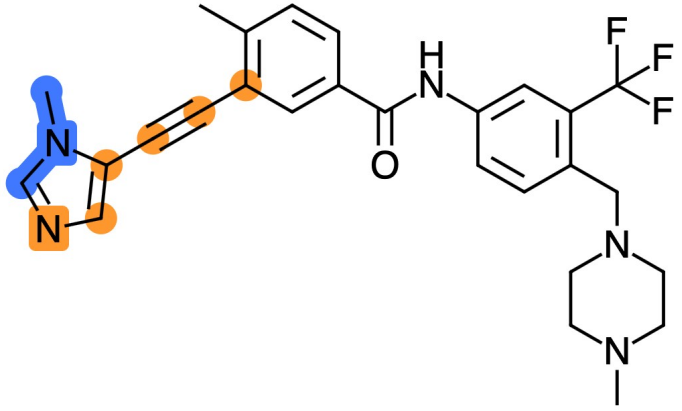

B - CHEMBL1784632

- Environment size 1: [c][c][c]1[c][n][n][c]1[n] >> [c][n]([c][n])[C]
- Environment size 2: [C][c]1[c][c]2[c][n][n][c]2[n][c]1 >> [C][c]1[c][n][c][n]1[C]
- Environment size 3: [C]#[C][c]1[c][c]2[c][n][n][c]2[n][c]1 >> [C]#[C][c]1[c][n][c][n]1[C]
- Environment size 4: [c][C]#[C][c]1[c][c]2[c][n][n][c]2[n][c]1 >> [c][C]#[C][c]1[c][n][c][n]1[C]

RuleDesign®

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- A rule requires 6 or more MMPs with 95% confidence [1]
- RuleDesign® applies rules to improve a property of interest to provide new molecule suggestions

- RuleDesign gives ideas and a new direction **based upon rules**
- CoreDesign gives new ideas based upon any previously seen examples – *with references*

1. Leach et al. *J. Chem. Inf. Model.* **2017**, **57**, 2424 - 2436

CoreDesign® Key Differences

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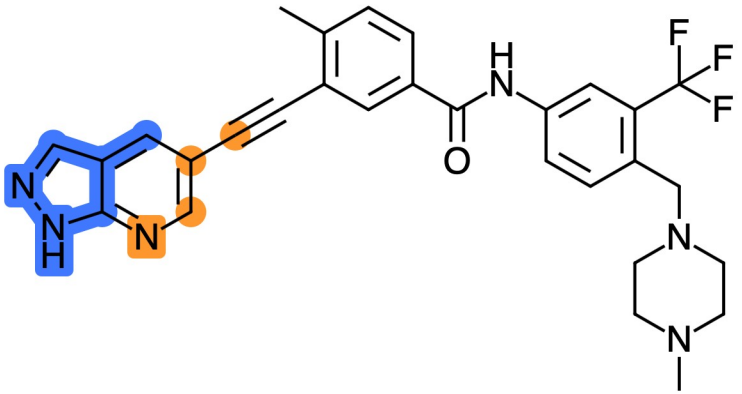
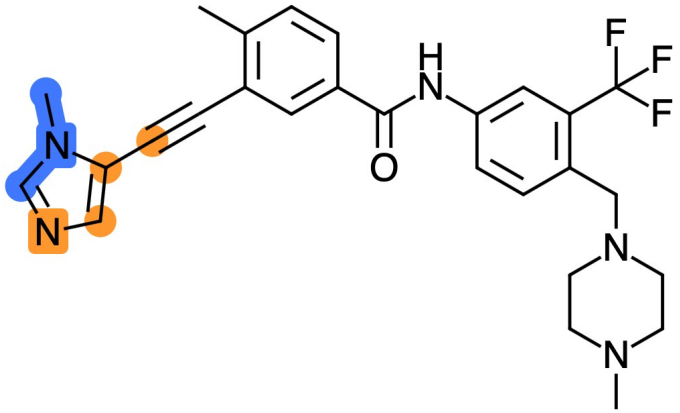
- Apply any MMPs that are within the database with environment size 1 or 2
- Property value is not of interest



A - CHEMBL2316582

Δ -2 21



B - CHEMBL1784632

- MMP env size 1
- MMP env size 2
- ~~MMP env size 3~~
- ~~MMP env size 4~~

Rinkers

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- Cores are built up of rings and linkers (or a combination)
- These are known as our **rinker** transformations

- A rinker transformation can be associated to a bibliography as long as the transformation has previously been seen within the same journal article

- Therefore, we can create a biology along with our CoreDesign suggestions

* Rinker != Riniker *

Rinkers

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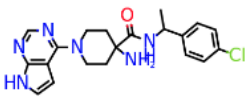
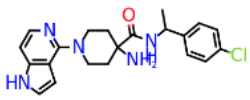
Results viewer



CHEMBL2325997



1c566a39-3936-4691-a20b-4235c6413910_4

Properties

References

Compound A	Compound B	Journal	Title	DOI
CHEMBL4468832	CHEMBL4526935	J. Med. Chem.	Synthesis and Antichlamydial Activity of Molecules Based on Dysregulators of Cylindrical Proteases.	10.1021/acs.jmedchem.0c00371
CHEMBL4649394	CHEMBL4632548	J. Med. Chem.	Treating Cancer by Spindle Assembly Checkpoint Abrogation: Discovery of Two Clinical Candidates, BAY 1161909 and BAY 1217389, Targeting MPS1 Kinase.	10.1021/acs.jmedchem.9b02035
			2-Aminomethylene-5-	

* Rinker != Riniker *

CoreDesign®

How it works...

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Performing CoreDesign Transformation

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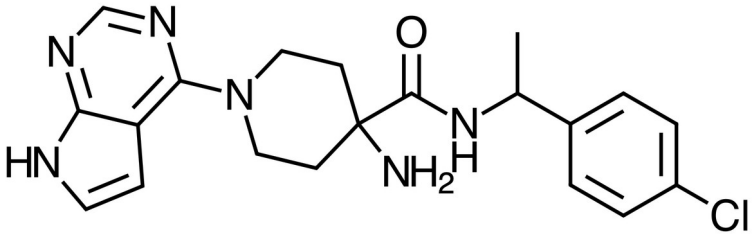
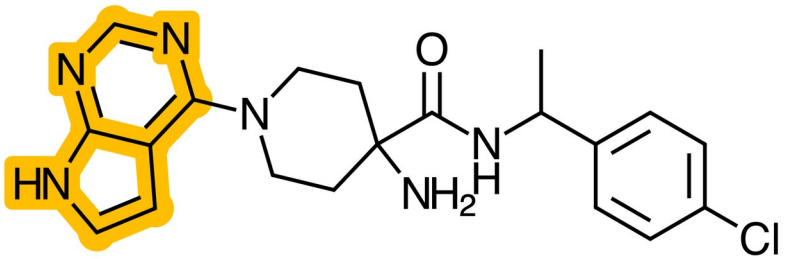


Input Molecule



With a defined core

Apply CoreDesign Transformations

Products

Performing CoreDesign Transformation

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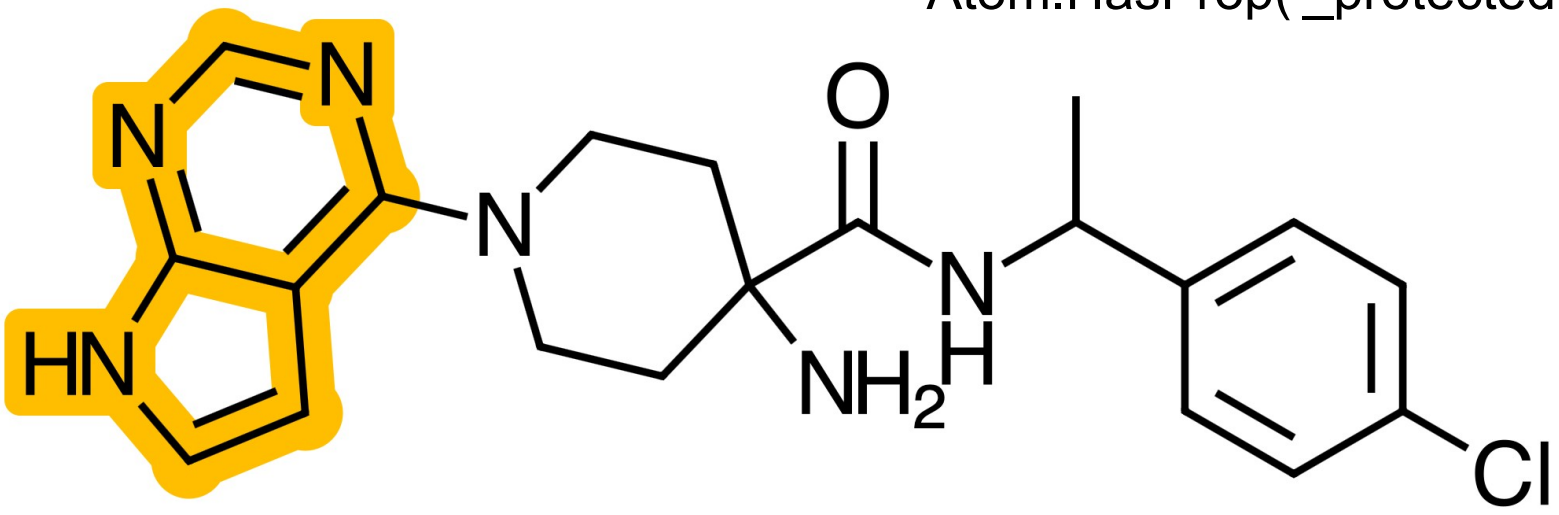
- Need to let the mol object know what is the core and what isn't
- Protect atoms that are not part of the core

Atom.HasProp('_protected', '1')



Atom.HasProp('core', '1')

Filtering Molecules…

Do not allow core substituents
Linker length range

Number of Core Substituents

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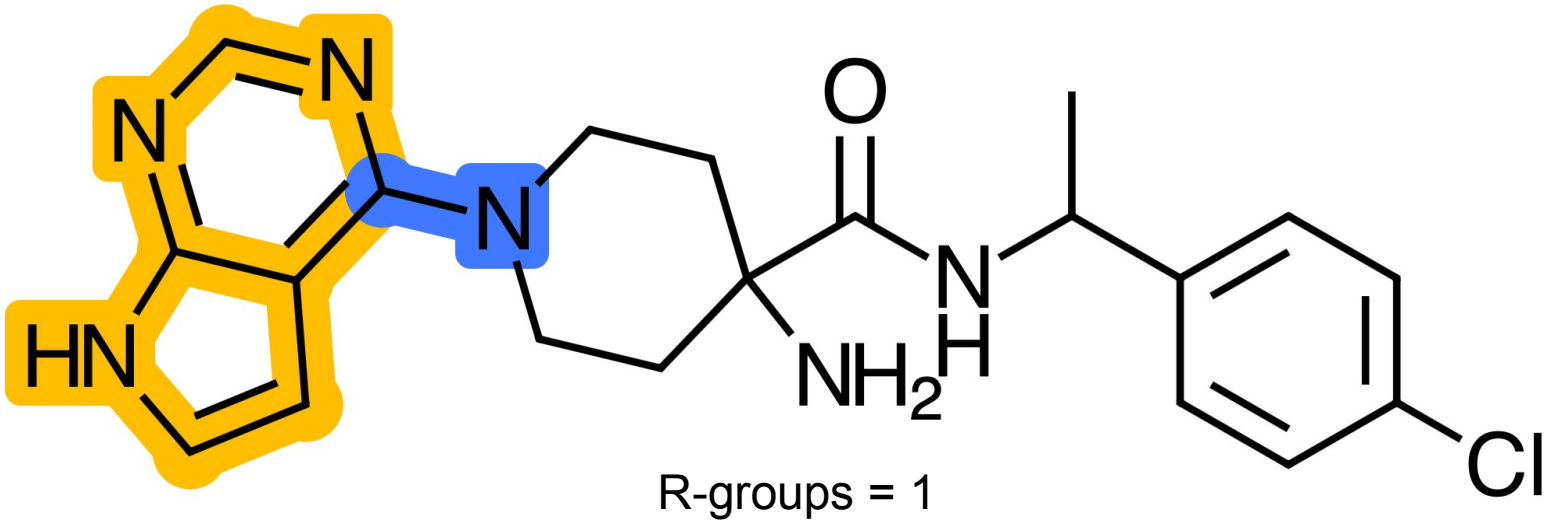
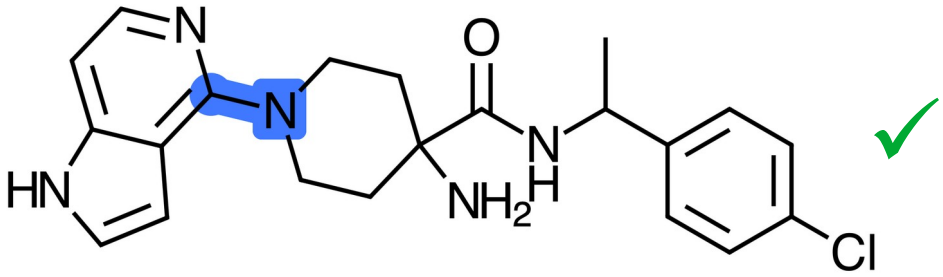
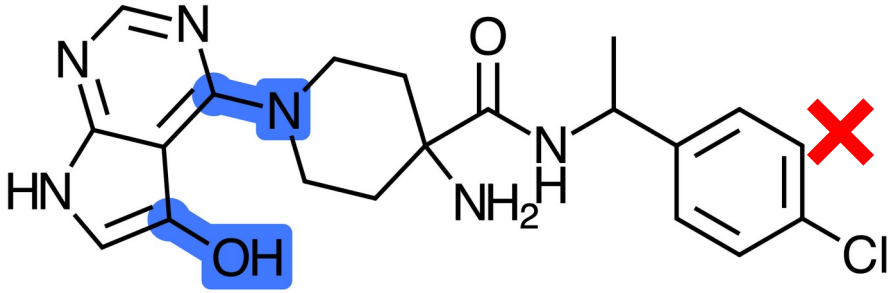
- Calculate the number of core substituents and compare



R-groups = 1





Linker Length

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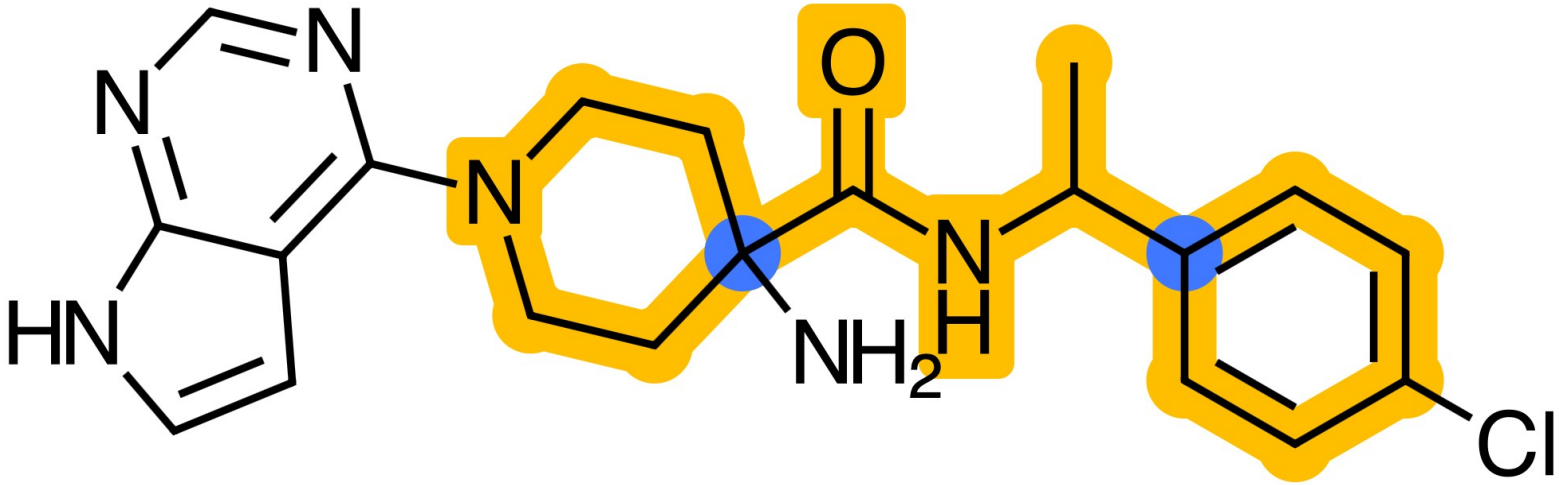
- Set a range the linker length can change by (if linker present)



Linker Length

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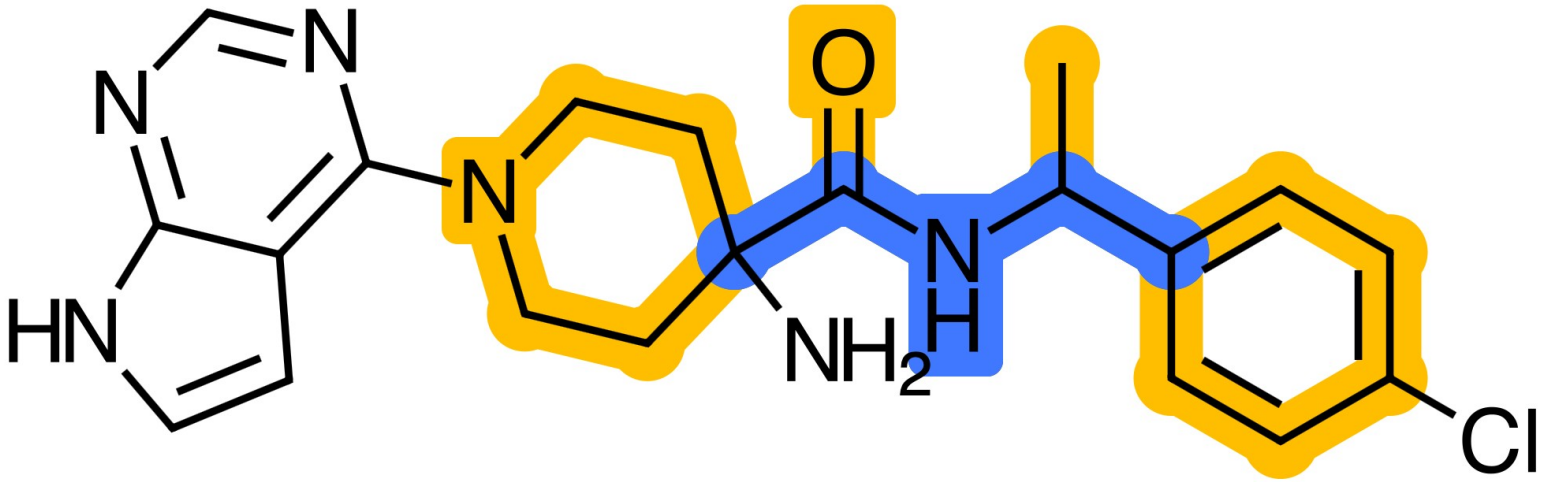

Chem.GetShortestPath(mol, atom1, atom2) = 5

Linker Length

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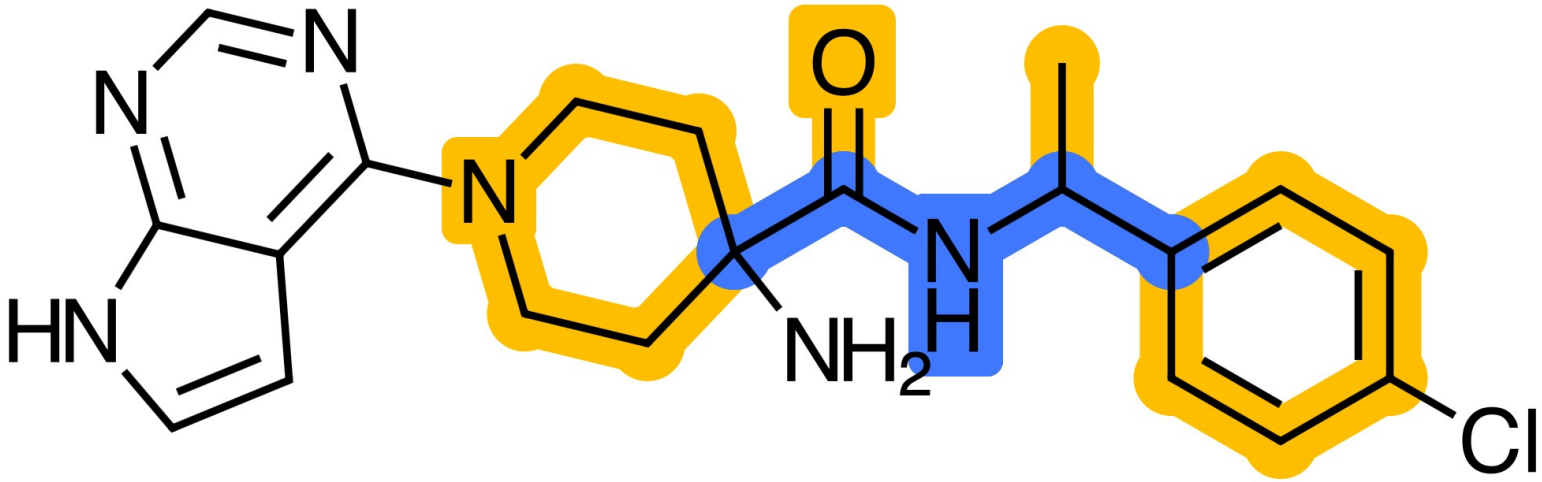
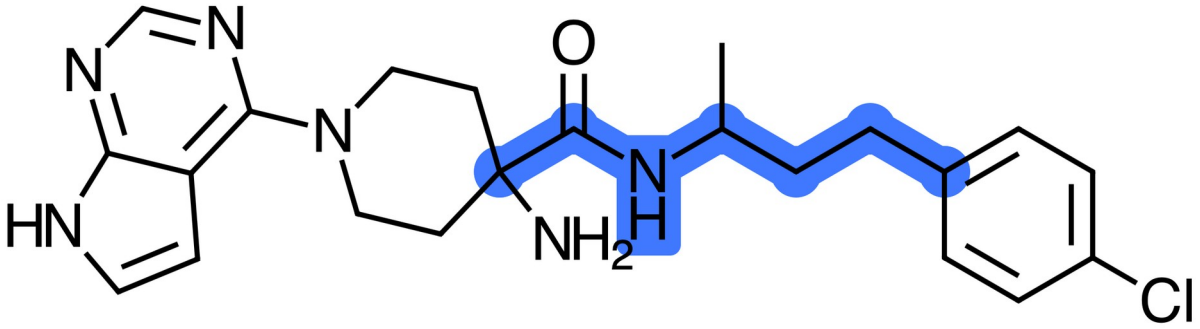
- Set a range the linker length can change by (if linker present)



Chem.GetShortestPath(mol, atom1, atom2) = 5



= 7

Δ=+2

PROTACs Examples

What is a PROTAC?

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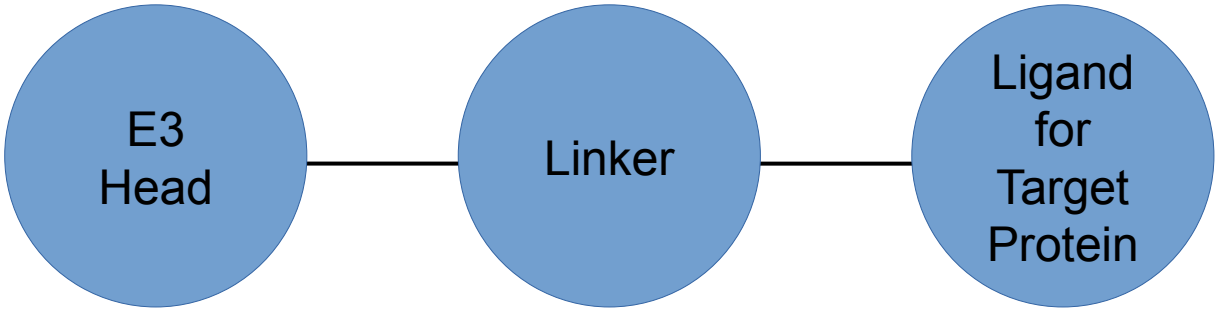
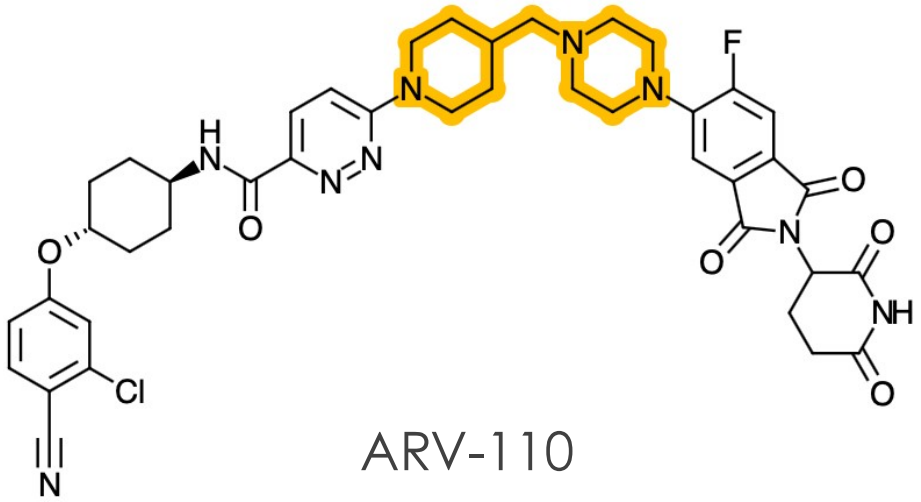
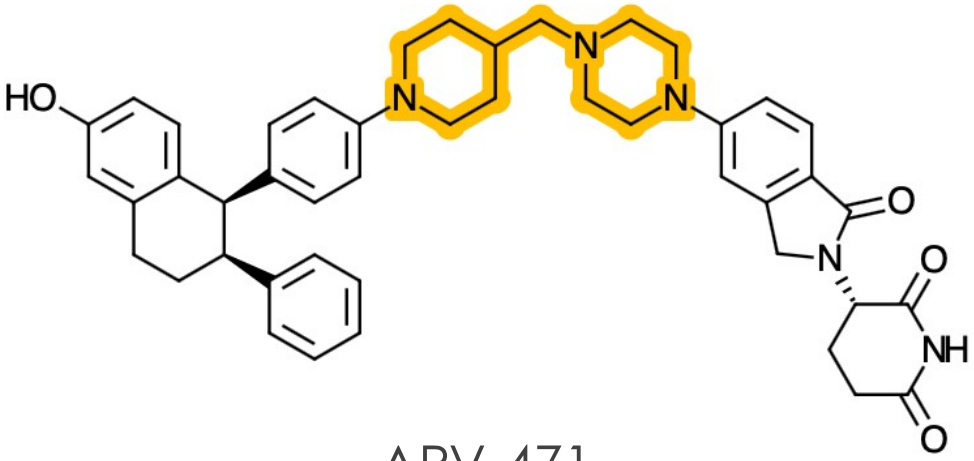
- Built from three components:



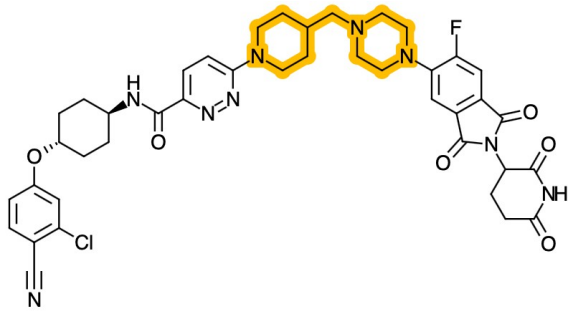
- A **Pro**teolysis **Ta**rgeting **C**himera
- Used to remove a selected protein from cells
- Changing the linker (& linker length) is a known problem as other two building blocks are specific for binding

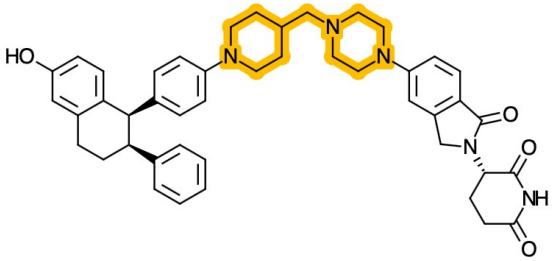


ARV-110

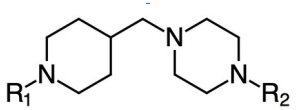


ARV-471

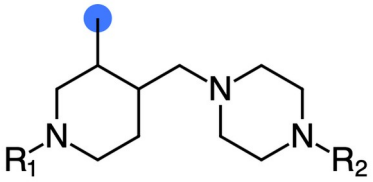


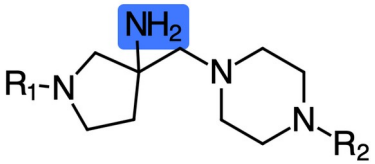


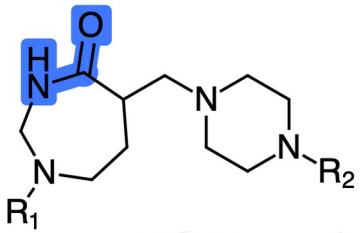
Linker length range -2 to +2

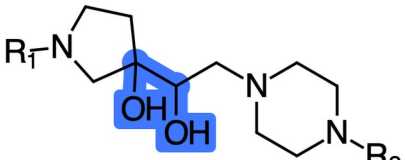


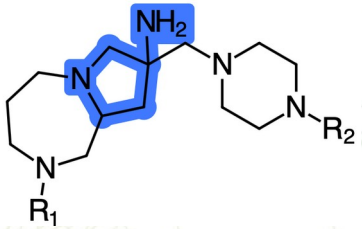
Allow new core substituents
Suggestions = 8,186

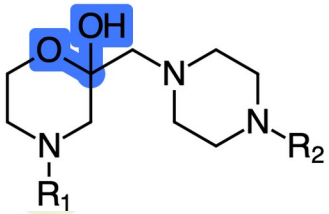




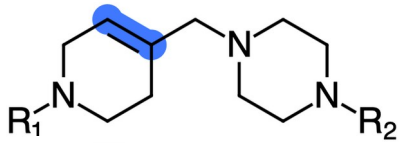


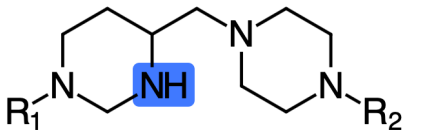


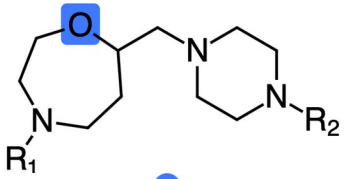


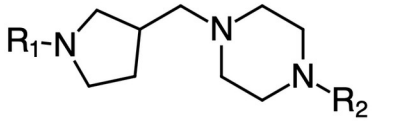


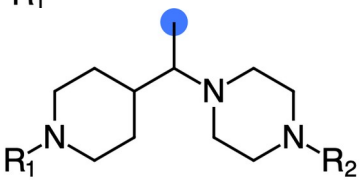
Do not allow new core substituents
Suggestions = 3,214

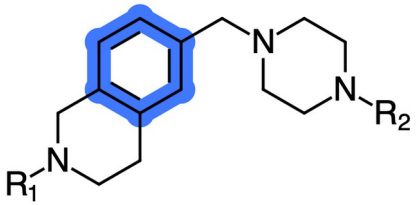


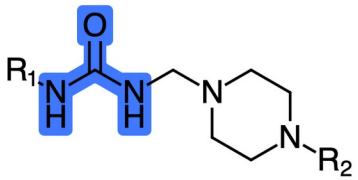


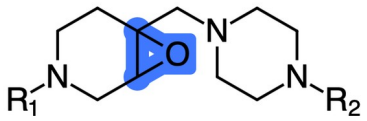












Focussing Suggestions

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Two issues remain in focusing suggestions:

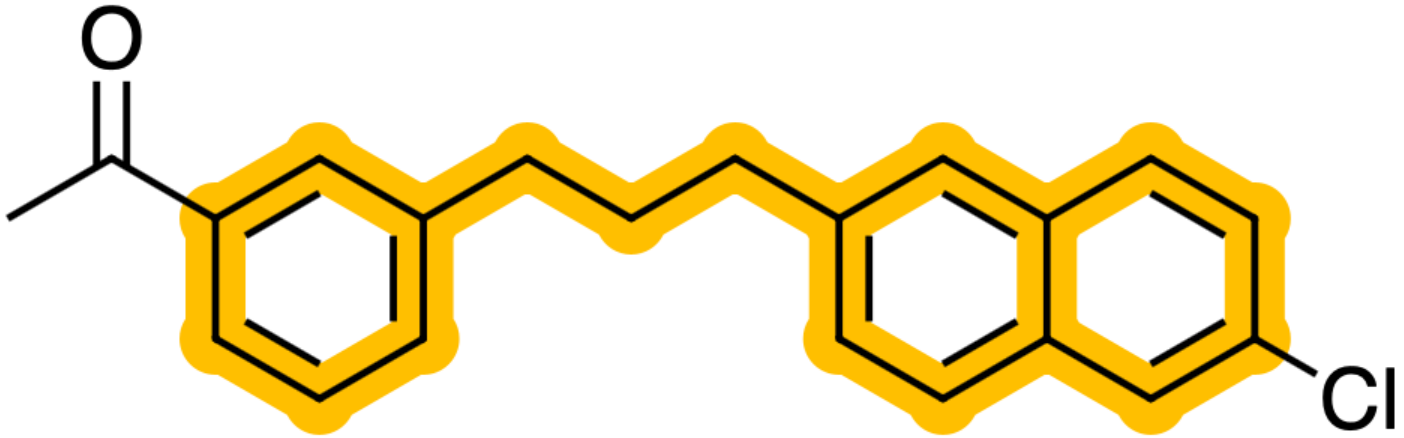
  Will the core or linker change maintain potency?

  - Filter by preferred vectors, overall shape, docking?

  What effect does the replacement have on ADMET properties?

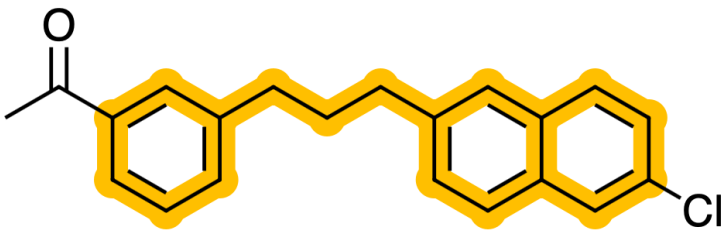
  - Particularly in large molecules: on permeability?
    - Understand change in HBD/A, tPSA?

Million Pound Question...
Ask the audience...



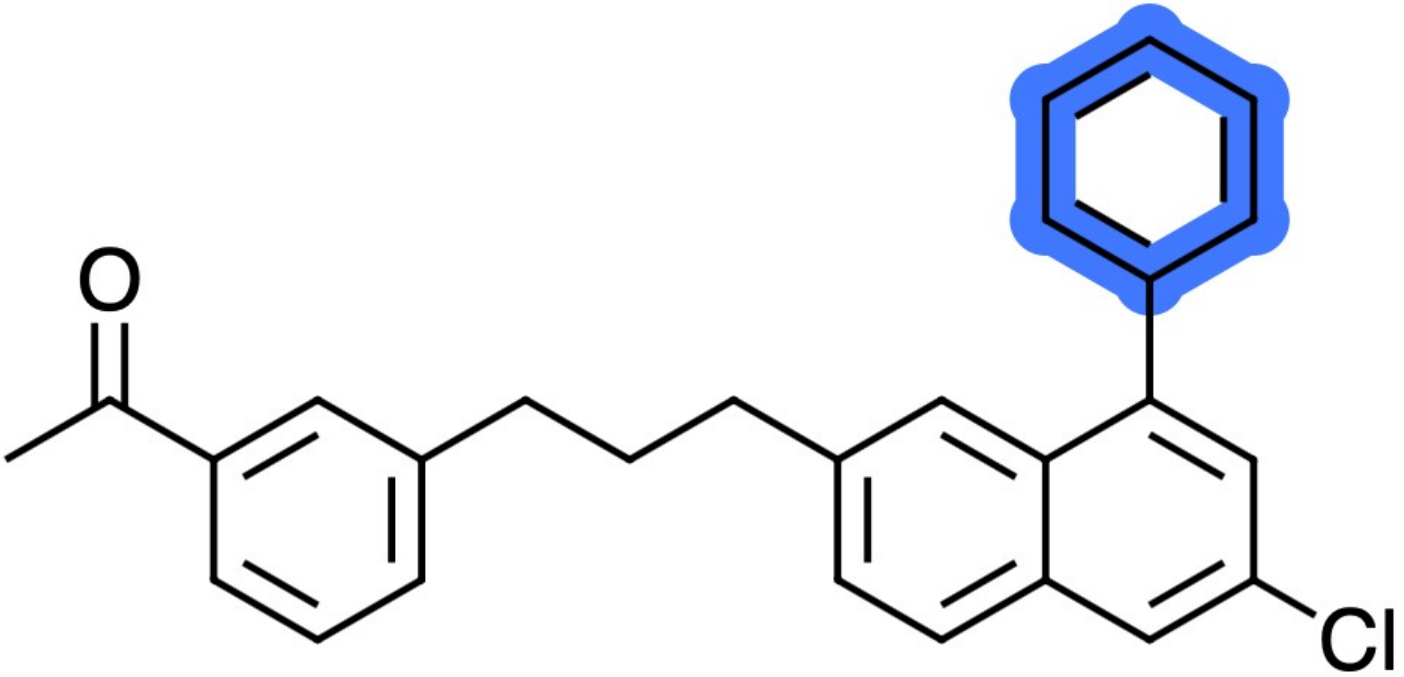
- Do not allow new core substituents
- Linker length range -2 to +2

- 8 examples



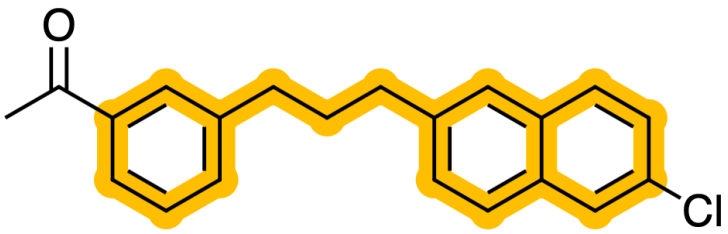
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2



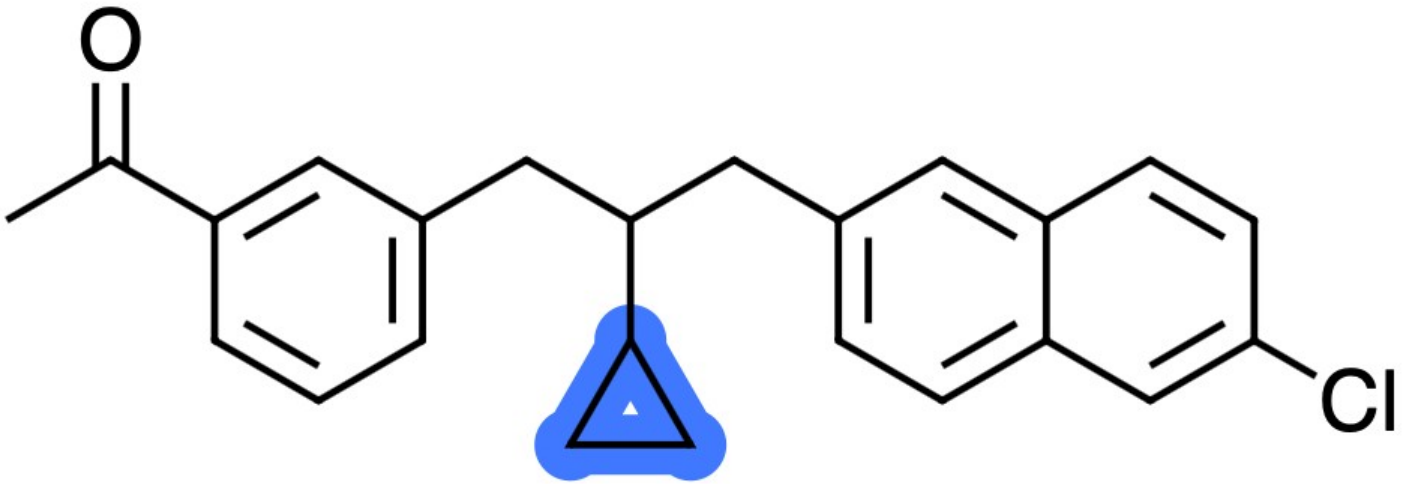
- We believe this is adding a new core substituent

X



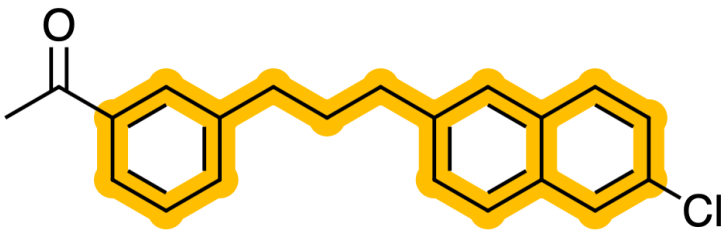
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2



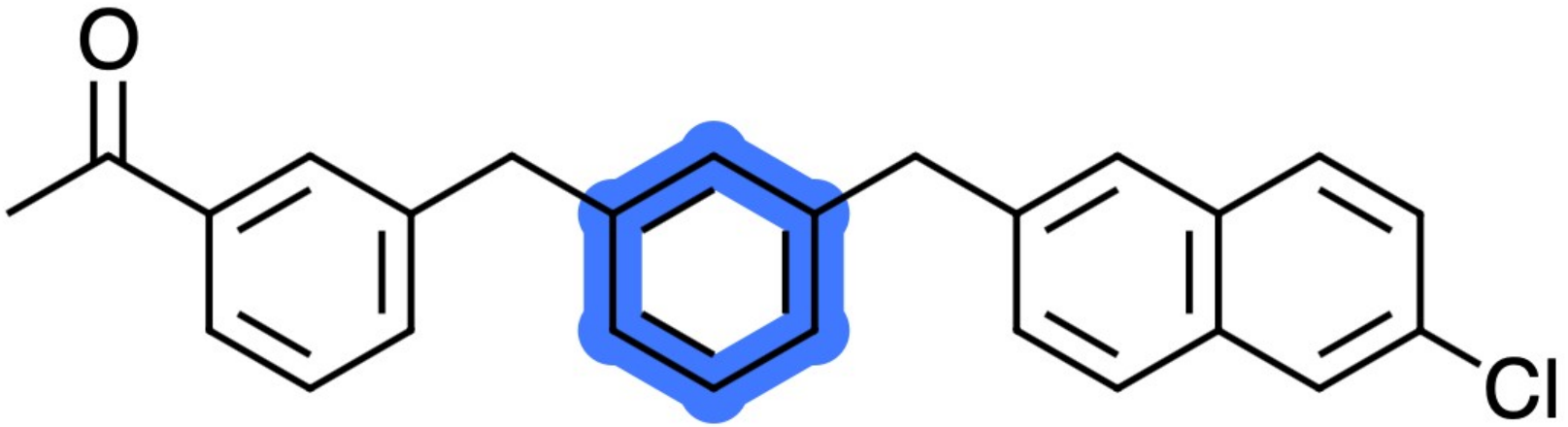
- We believe this is adding a new core substituent

X

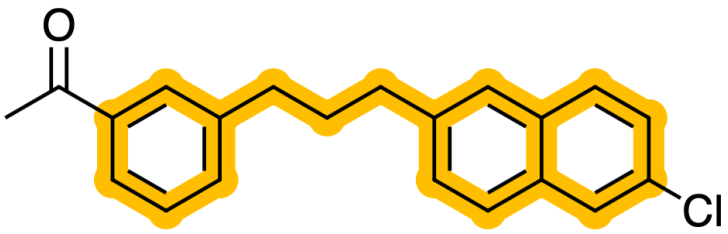


MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2

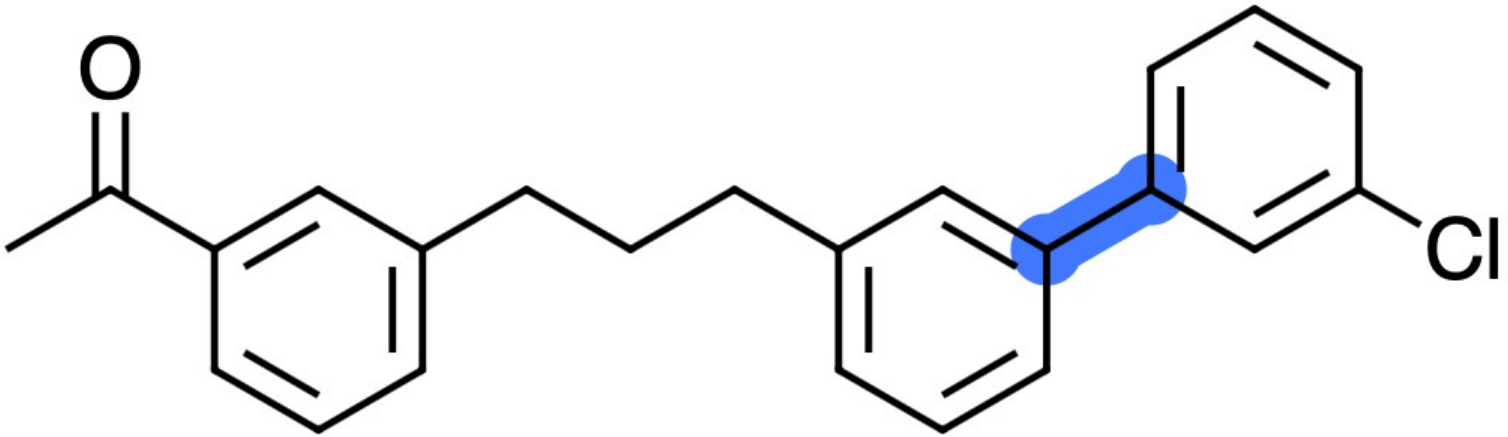


- We do not believe this is adding a new core substituent ✓

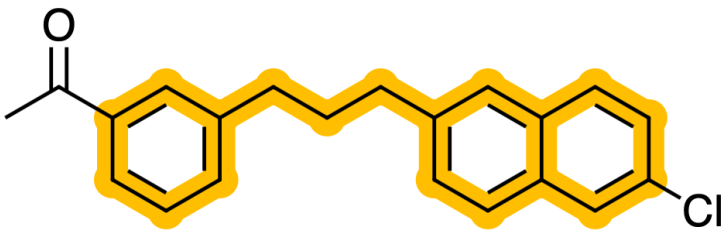


MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2

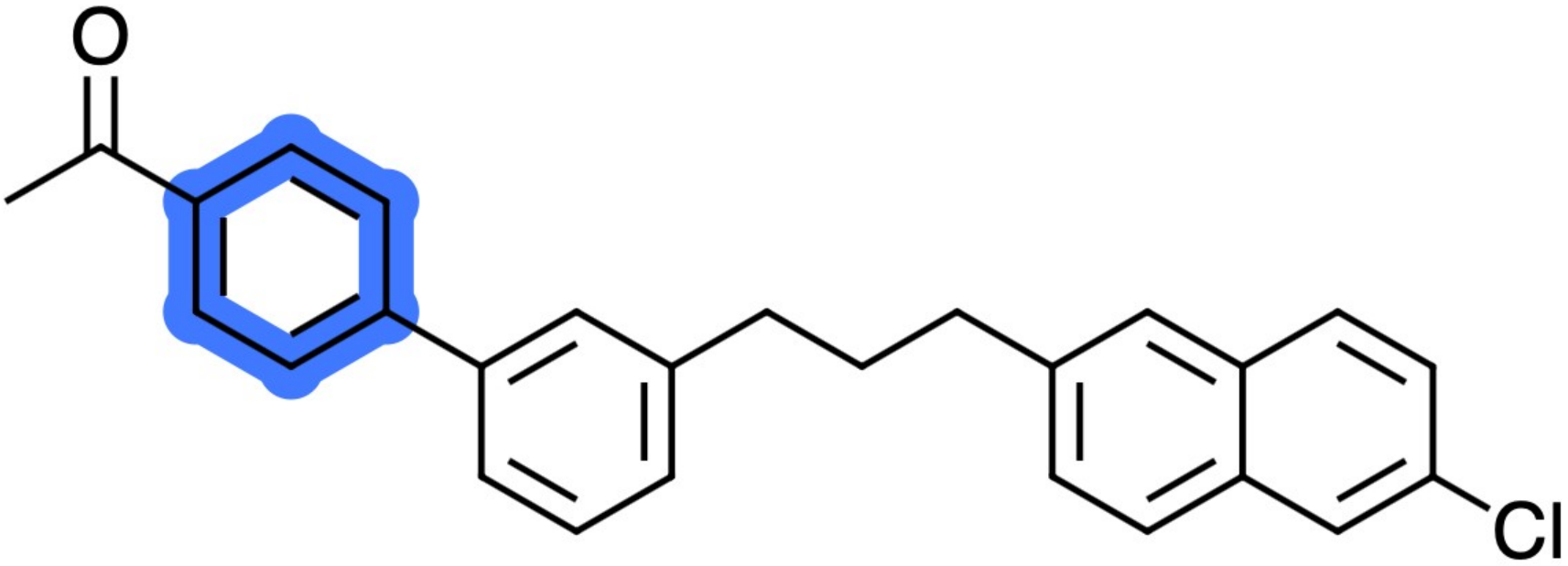


- We do not believe this is adding a new core substituent

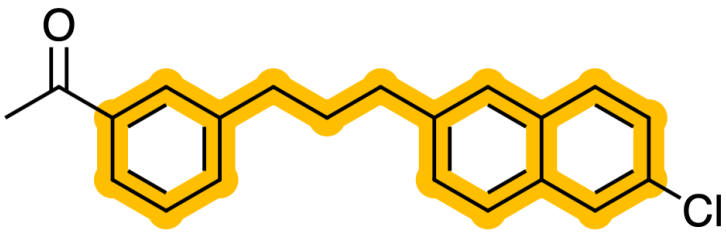


MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2

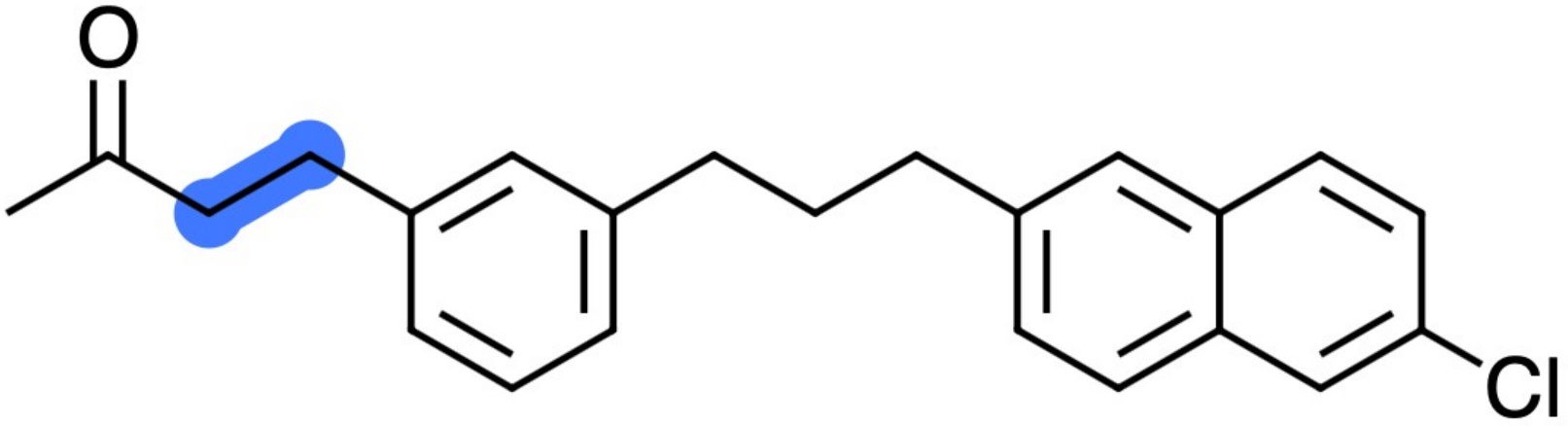


- We do not believe this is adding a new core substituent
- Linker length change is +2



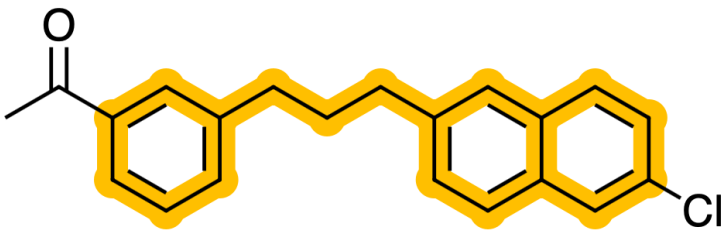
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2



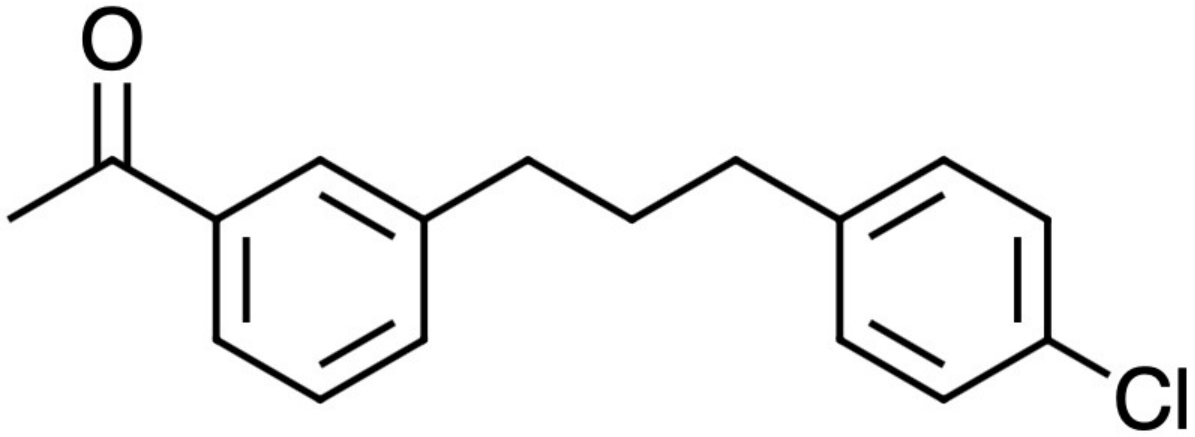
- We do not believe this is adding a new core substituent
- However, the linker length change is +4

X

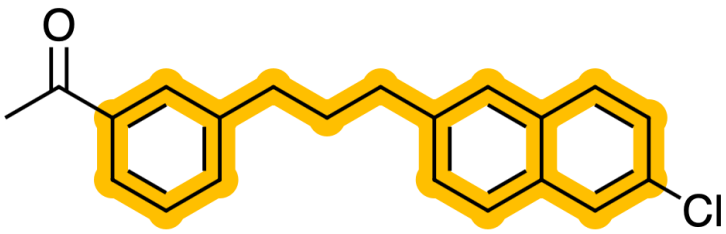


MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2

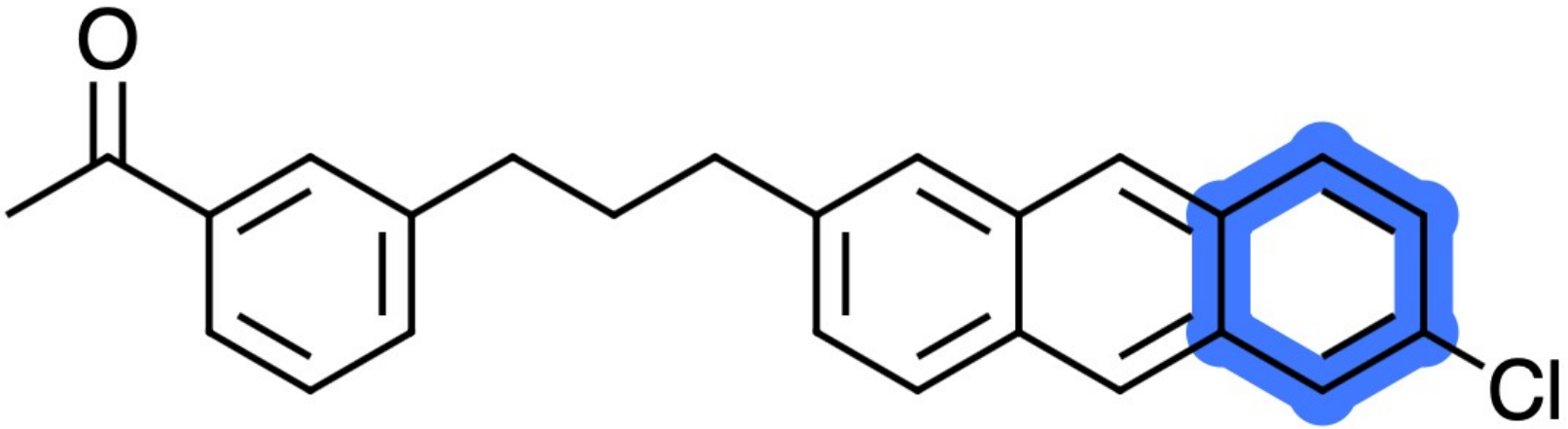


- We do not believe this is adding a new core substituent



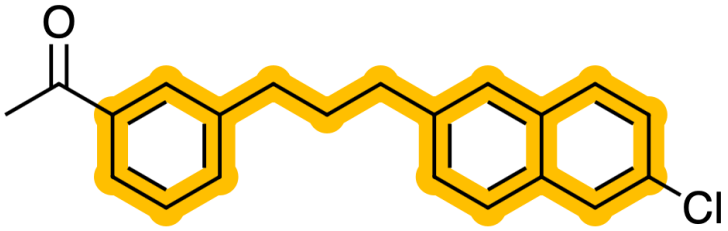
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Do not allow new core substituents
- Linker length range -2 to +2



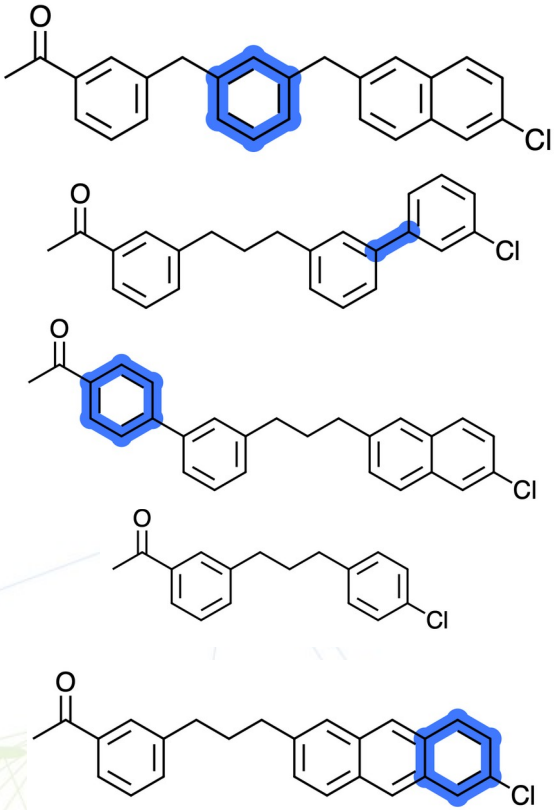
- We do not believe this is adding a new core substituent ✓

Summary

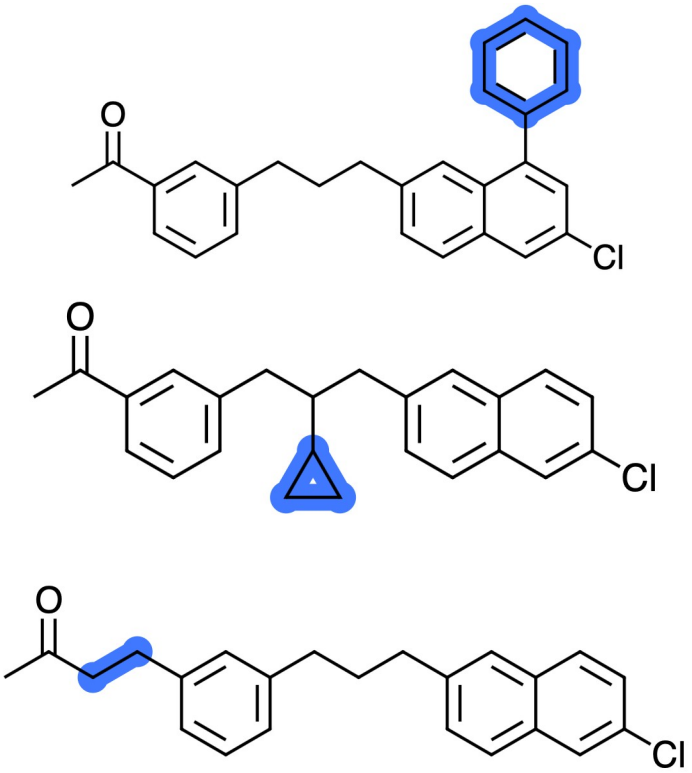


- Do not allow new core substituents
- Linker length range -2 to +2

Results Allowed



Results Not Allowed



Thank you for taking part

Conclusions

- MMPs can be used for CoreDesign
  - We can guide the user to iterate in the bibliography where previously seen examples with the same transformation can be reviewed
- Two new filters have been created
- RDKit can be used to achieve this
  - Setting atoms as '_protected' helps to optimise
  - Exploits the GetShortestPath function

Thank you for listening