Adding Reactions into the Chemistry Commons, Retrosynthetic Analoging, and Reaction Enumeration

Acrylamide Reaction
By Maksim DuNova

Chemistry Commons

The goal of Chemistry Commons is to make an interactive space for chemists to facilitate collaboration on reaction curation and to share their own reactions for the purpose of exploring chemical space!

Chemistry Commons   Reactions Synthons   Login/Register ▾

Welcome to Chemistry Commons!

The Chemistry Commons is an effort to facilitate the connections between synthetic organic chemists biologists seeking new reagents for biology as well as medicinal chemists and computational chemists.

The Chemistry Commons is a platform for sharing chemistry. Synthetic organic chemists looking to make their chemistry available to explore. Chemists use the chemistry commons to articulate and enumerate libraries of accessible compounds. With our assistance, libraries in 2D and 3D are prepared and made available. Medicinal chemists and biologists seeking new chemistry for their biological targets use our tools to search, download, and dock these libraries. Compounds are prioritized for synthesis, and an agreement is made between the synthetic chemist and the biology lab testing the compounds. Ideally, compounds are produced, tested, and, ideally, some compounds will work.

Reaction Database

Synthon Database

Synthons

Show entries

10

Search

Synthon ID	Synthon Name	SMARTS
1	Acetylenes__AlkyneCH	C#[CH]
		Picture created by the SMARTSviewer [https://smarts.plus/].
2	Acid__Aromatic_Acid	[OD1]C(=O)c1ccccc1

Reaction Details

ACETYLATION

Reaction Details

Reaction ID	CC-1
Reaction Description	Amide: amine + acid anhydride
Reaction SMARTS	[#6:1][NH:2][#6:3].[C:4][C:5](=O)OC(=O)C>>[#6:1][N:2]([#6:3])[#6:5](=O)[#6:4]
SMARTS Description	

Synthons

Anhydrides__Acyclic_Anhydrides

Inclusion Smarts

[#6]-C(=O)!@-O-C(-[#6])=O   Arthor

Exclusion Smarts

C=[NH]

[SiH,SiH2,SiH3,SiH4,PH,PH2,PH3,SH,SH2,BH,BH2,BH3,BH4]

[N;$([NH,NH2]);!$(NC=[C,N,O,P,S])!$(N=[C,N,O,S])!$(N[P,S])!$(N#[C])]

[S,P](=[O,N])[F,Cl]

[OH,SH,S-,O-]

[Si,P,S,B][Cl,F,Br,I]

How to add a Reaction into the Chemistry Commons.

How to add a Reaction into the Chemistry Commons.

Sort By Tag ▾   20 ▾   Per Page

search   +

« ‹ 1 2 3 4 5 › »

Rxn ID	Short Name	Product: Reagents	Rxn SMARTS	Act
CC-1	Acetylation	Amide: amine + acid anhydride	[C:1][NH:2][C:3].[C:4][C:5](=O)OC(=O)C>>[C:1][N:2]([C:3])[C:5](=O)[C:4]	👁
CC-2.11	Suzuki-Cl-CA-1	Biaryl (Suzuki): aryl boronic acid + aryl halide; one or both components contain carboxylic group in a side chain.	[c:1]B(O)O.[c:2][Cl]>>[c:1]-[c:2]	👁
CC-2.12	Suzuki-Cl-CA-2	Biaryl (Suzuki): aryl boronic acid + aryl halide; one or both components contain carboxylic group in a side chain.	[c:1]B(O)O.[c:2][Cl]>>[c:1]-[c:2]	👁
CC-2.13	Suzuki-Cl-CA-3	Biaryl (Suzuki): aryl boronic acid + aryl halide; one or both components contain carboxylic group in a side chain.	[c:1]B(O)O.[c:2][Cl]>>[c:1]-[c:2]	👁
CC-2.21	Suzuki-Br-CA-1	Biaryl (Suzuki): aryl boronic acid + aryl halide; one or both components contain carboxylic group in a side chain.	[c:1]B(O)O.[c:2][Br]>>[c:1]-[c:2]	👁
CC-2.22	Suzuki-Br-CA-2	Biaryl (Suzuki): aryl boronic acid + aryl halide; one or both components contain carboxylic group in a side chain.	[c:1]B(O)O.[c:2][Br]>>[c:1]-[c:2]	👁

Enter in Reaction Details and Submit!
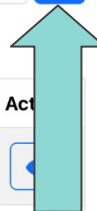
Enter in Reaction Details and Submit!

Commons   Reactions   Synthons   Tutorials   Maksim

Register Reaction

Reaction Name*

Acrylamide-UM-Primary

Reaction Description

Enter Reaction Description

Reaction SMARTS*

[#6:1]-[ND1:2]>>[#6:1]-[ND2:2]-[C](=[O])-[C]=[C]

SMARTS Description/References

Enter SMARTS

Add Reaction Tag

1-reagent ✕   Covalent ✕

Synthons ⊕

Synthon 1

Synthon Name*

Primary Amine for Acrylamide

InSMARTS*

[#6]-[ND1]

ExSMARTS*

[#6]-[ND2]-C=[O,S]
[SH]
[Or3] Peroxide
[$(*-[NX2-]-[NX2+]#[NX1]),$(*-[NX2]=[NX2+]=[NX1-])]
[$([NX1-]=[NX2+]=[NX1-]),$([NX1]#[NX2+]-[NX1-2])]

Submit Reaction and Synthons

First Step is to learn SMARTS Resources

- [Smarts Plus](#)
- [Daylight SMARTS](#)

    These are useful resources in helping learn the syntax of SMARTS, visualize SMARTS, as well as seeing if the SMARTS patterns are valid or not
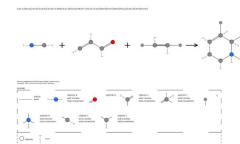
First Step is to learn SMARTS Resources

- [BBFilter module on tldr.docking.org](http://tldr.docking.org)

  This is a module on from our own tool that helps verify your inclusion and exclusion SMARTS

Transforming the Reaction into SMARTS

- Figure out the reaction that you want to transform into SMARTS!
- This is 1 Component Reaction used to transform molecules into covalent ready ones for computational purposes!
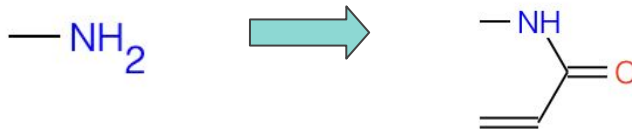
Transforming the Reaction into SMARTS: Finding the SMILES of each Reactant

- First step is to figure out the SMILES of the reactant(s) and product
- You can do this simply by drawing the molecule in our tool <u>Arthor</u> and copying the SMILES output by the drawing tool
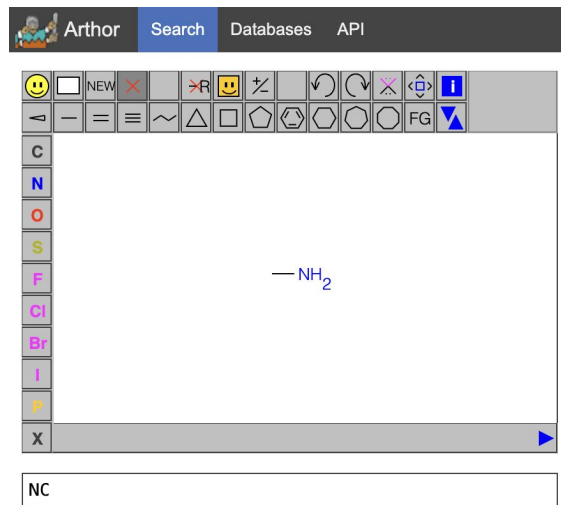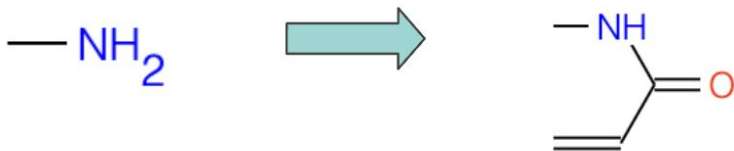
Transforming the Reaction into SMARTS: R Group SMARTS

- After you figure out the SMILES of each component, now specify the R-group bond order/connections using SMARTS notation if this is required for your reaction
- Example: C=C -> [CX4]=C-[CX4]
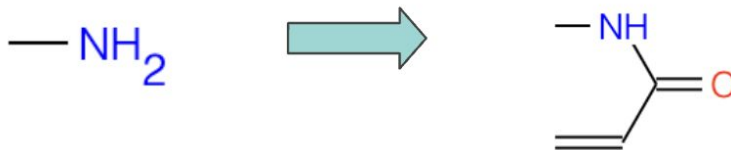
Transforming the Reaction into SMARTS: Daylight Resource

- Again Daylight SMARTS is a good resource if you need to learn SMARTS notation

SMARTS Atomic Primitives

| Symbol	Symbol name	Atomic property requirements	Default
*	wildcard	any atom	(no default)
a	aromatic	aromatic	(no default)
A	aliphatic	aliphatic	(no default)
D<n>	degree	<n> explicit connections	exactly one
H<n>	total-H-count	<n> attached hydrogens	exactly one[1]
h<n>	implicit-H-count	<n> implicit hydrogens	at least one
R<n>	ring membership	in <n> SSSR rings	any ring atom
r<n>	ring size	in smallest SSSR ring of size <n>	any ring atom[2]
v<n>	valence	total bond order <n>	exactly one[2]
X<n>	connectivity	<n> total connections	exactly one[2]
x<n>	ring connectivity	<n> total ring connections	at least one[2]
- <n>	negative charge	-<n> charge	-1 charge (-- is -2, etc)
+<n>	positive charge	+<n> formal charge	+1 charge (++ is +2, etc)
#n	atomic number	atomic number <n>	(no default)[2]
@	chirality	anticlockwise	anticlockwise, default class[2]
@@	chirality	clockwise	clockwise, default class[2]
@<c><n>	chirality	chiral class <c> chirality <n>	(nodefault)
@<c><n>?	chiral or unspec	chirality <c><n> or unspecified	(no default)
<n>	atomic mass	explicit atomic mass	unspecified mass

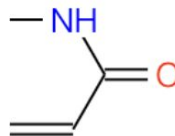# Transforming the Reaction into SMARTS: Inclusion SMARTS

- At the step you should have the some simplified SMARTS of each component

1.Primary Amine
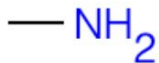
2.Acrylamide Product
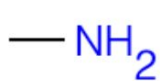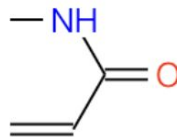
[#6]-[N]

[#6]-[N]-[C](=[O])-[C]=[C]

Transforming the Reaction into SMARTS: Bond SMARTS

- Save the SMARTS from the previous step as these will be our inclusion SMARTS
- Next step is to specify bonds!
- Only need 1 change on both sides, since the only bond that is specified(primary) and changes bond order is the amine

[#6]-[ND1]   [#6]-[ND2]-[C](=[O])-[C]=[C]

Transforming the Reaction into SMARTS: Mapping Atoms

- Next is to **Map** the atoms in the reactants into the product
- Only two atoms you need to specify in this reaction
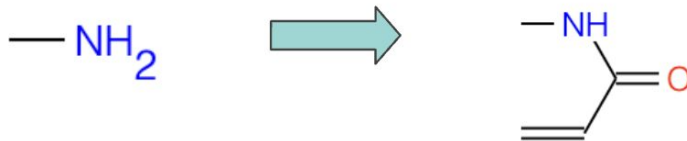
[#6:1]-[ND1:2]   [#6:1]-[ND2:2]-[C](=[O])-[C]=[C]
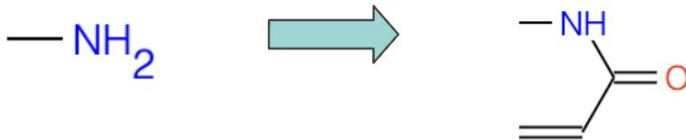
Transforming the Reaction into SMARTS: Combining it all together

- Now these parts can be all put together to get your reaction SMARTS!

[#6]-[ND1] >> [#6]-[ND2]-[C](=[O])-[C]=[C]

Transforming the Reaction into SMARTS: Filtering the Reagents

- Now it's time to think about what should and should not be allowed for each reactant
- These will be our Inclusion/Exclusion SMARTS

Transforming the Reaction into SMARTS: Inclusion/Exclusion SMARTS

- Inclusion SMARTS were already made earlier though making the reaction SMARTS!
- As for Exclusion SMARTS it can be and string of molecules that should not work as a reactant. Example: Anything with SiO in it
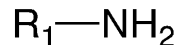
$R_1\!-\!NH_2$

Transforming the Reaction into SMARTS: Testing Inclusion/Exclusion SMARTS

- You can use the bbfilter module in TLDR to test Inclusion/Exclusion SMARTS to see if you get sensible molecules or if you're filtering too many!

Enumeration and Debugging!

- Once you feel more or less confidant with your Reaction and Inclusion/Exclusion SMARTS it is time to run some Enumeration to test your SMARTS!

```
-bash-4.1$ ls
bb50      chbrbb1123        Filtered  NirMADE        scripts
BU        chbrbb1223        innovabb  otavabb        sialbb
chbr      ChemistryCommons  junk      README         sialbb1123
chbrbb    emolbb            MADE      REAL_Space_22Q3_29B  Test
-bash-4.1$ cd bb50
-bash-4.1$ ls
CC-10      CC-122.22  CC-140    CC-36.2  CC-4.4   CC-69.2  CC-80.2  CC-93.3
CC-108     CC-122.23  CC-142    CC-39.1  CC-53    CC-69.3  CC-92.1  CC-94.1
CC-122.11  CC-122.31  CC-142.1  CC-39.2  CC-68.1  CC-70.1  CC-92.2  CC-94.2
CC-122.12  CC-122.32  CC-143    CC-4.1   CC-68.2  CC-70.2  CC-92.3  CC-94.3
CC-122.13  CC-122.33  CC-148    CC-4.2   CC-68.3  CC-70.3  CC-93.1
CC-122.21  CC-138     CC-36.1   CC-4.3   CC-69.1  CC-80.1  CC-93.2
-bash-4.1$
```

Exporting Chemistry Commons Reaction

-Once you have made your reaction on Chemistry commons it's time to export your JSON containing the reaction into the command line!

```
-bash-4.1$ cd /nfs/exj/Fe/scripts/common_db/
-bash-4.1$ ls
export    export_cc.bash    log
-bash-4.1$ bash export_cc.bash
```

Finding Reaction and Synthon JSONs

-Once run the export script you can find the Reactions.json and Synthons.json in the export directory

```
-bash-4.1$ cd export
-bash-4.1$ ls
commons_20231002.sql   commons_20231208.sql   commons_20231216.sql
commons_20231009.sql   commons_20231209.sql   commons_20231217.sql
commons_20231017.sql   commons_20231210.sql   commons_20231218.sql
commons_20231031.sql   commons_20231211.sql   commons_20231219.sql
commons_20231115.sql   commons_20231212.sql   Reactions.json
commons_20231204.sql   commons_20231213.sql   Synthons.json
commons_20231206.sql   commons_20231214.sql
commons_20231207.sql   commons_20231215.sql
```

Picking library to Enumerate

- From experience it's best to pick a larger library to Enumerate to make sure there are enough molecules in the database, such as **bb50**.
- However, if you need quick results I recommend **Sialbb**.

```
-bash-4.1$ cd /nfs/exj/Fe/Filtered/
-bash-4.1$ ls
bb50     emolbb    innovabb   otavabb-v              sialbb
chbrbb   indexed   MADE       REAL_Space_22Q3_29B    Test
-bash-4.1$
```

Filtering Synthons

- Go into the library of your choosing and run the filtering command below for each synthon

```
[-bash-4.1$ cd sialbb/
[-bash-4.1$ ls
sialbb_synthon_100_ReagentsForOlefination-Wittig
sialbb_synthon_101_ReagentsForOlefination-HornerWadsworthEmmonsReagents
sialbb_synthon_102_SecondaryAmines-SecAminesAliphaticPolycyclic
sialbb_synthon_103_SecondaryAmines-secHet-Anilines
sialbb_synthon_104_SecondaryAmines-Cyc-Aliphatic
sialbb_synthon_105_SecondaryAmines-Cyc-Benzylic
sialbb_synthon_106_SecondaryAmines-SecAminesAliphaticFluorinated
sialbb_synthon_107_SecondaryAmines-diArylAmines
sialbb_synthon_108_SecondaryAmines-Cyc-Het-benzylic
sialbb_synthon_109_SecondaryAmines-Cyc-Anilines
sialbb_synthon_10_Anhydrides-AcyclicAnhydrides
```

```
sialbb_synthon_9_Acylhalides-N-Acylhalides
-bash-4.1$ bash /nfs/exj/Fe/scripts/bb_wrapper.bash /nfs/exj/Fe/Filtered/indexed
/<catalog>/<catalog>.smi <id> /nfs/exj/Fe/scripts/common_db/export/Synthons.json
```

Enumeration: Part 1 of 3

1. First step is to source the environment:

```
-bash-4.1$ source /nfs/home/ak87/exa/UCSF/SynthI/BESPOKE/arthor-env/bin/activate
```

2. Next step is to go into Library Enumeration Directory or create your own!

```
(arthor-env) -bash-4.1$ cd /nfs/exj/Fe
(arthor-env) -bash-4.1$ ls
bb50      chbrbb1123          Filtered   NirMADE        scripts
BU        chbrbb1223          innovabb   otavabb        sialbb
chbr      ChemistryCommons    junk       README         sialbb1123
chbrbb    emolbb              MADE       REAL_Space_22Q3_29B  Test
(arthor-env) -bash-4.1$ cd sialbb
(arthor-env) -bash-4.1$ ls
CC-10      CC-122.22  CC-140   CC-4.1   CC-68.2  CC-70.2  CC-92.3  CC-94.3
CC-108     CC-122.23  CC-143   CC-4.2   CC-68.3  CC-70.3  CC-93.1
CC-122.11  CC-122.31  CC-36.1  CC-4.3   CC-69.1  CC-80.1  CC-93.2
CC-122.12  CC-122.32  CC-36.2  CC-4.4   CC-69.2  CC-80.2  CC-93.3
CC-122.13  CC-122.33  CC-39.1  CC-53    CC-69.3  CC-92.1  CC-94.1
```

Enumeration: Part 2 of 3

- Inside create a directory using the following Syntax: mkdir **CC-<Reaction ID>**
- Go inside the directory and run the first enumeration script:

```
(arthor-env) -bash-4.1$ python3 /nfs/exj/Fe/scripts/Enumeratorsplit.py -i <Synthonfile1> <Synthon
file2> -r CC-<Reaction ID> -o <library> -e /mnt/nfs/exj/Fe/Filtered/Test/EXAMPLE_Library_Enumerat
ion_File_hg2_noProtected_logP350_HAC35_RotB7_V3_A-AK1.json -a /nfs/exj/Fe/scripts/common_db/expor
t/Reactions.json
```

Enumeration: Part 3 of 3

- Now after first script is finished running run the final script

```
(arthor-env) -bash-4.1$ python3 /nfs/exj/Fe/scripts/Enumeratorcombine.py -i <pairing file> -r CC-
<Reaction ID> -o <library> -e /mnt/nfs/exj/Fe/Filtered/Test/EXAMPLE_Library_Enumeration_File_hg2_
noProtected_logP350_HAC35_RotB7_V3_A-AK1.json -a /nfs/exj/Fe/scripts/common_db/export/Reactions.j
son
```

Analog By Building Block Tool or AB3

-Retrosynthesis is the process of taking a molecule and breaking it apart into building blocks

-We can use this concept to access a new area of purchasable chemical space!

ZINC450573233 a hit for the σ2 receptor

ZINC450573233
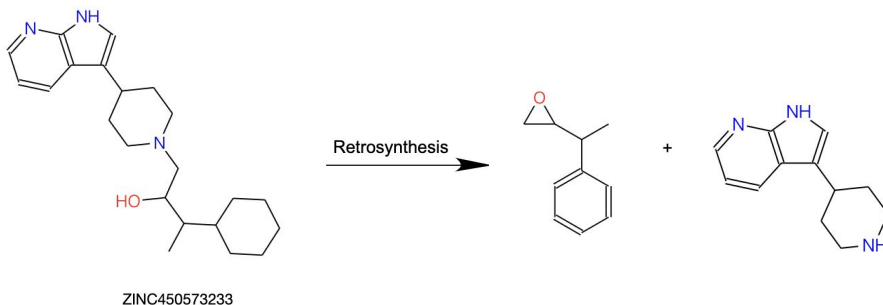
Retrosynthesis

Analog By Building Block Tool or AB3

1. Use a sturdy retrosynthetic reaction to break down a molecule into building blocks
2. Find purchasable analogs of the building blocks by doing a similarity search
3. The respective building blocks can now be recombined with a forward reaction to find a final analog of the starting molecule

ZINC450573233 a hit for the σ2 receptor

ZINC450573233

Retrosynthesis

Alon A, Lyu J, Braz JM, Tummino TA, Craik V, O'Meara MJ, Webb CM, Radchenko DS, Moroz YS, Huang XP, Liu Y, Roth BL, Irwin JJ, Basbaum AI, Shoichet BK, Kruse AC. Structures of the σ receptor enable docking for bioactive ligand discovery. Nature. 2021 Dec;600(7890):759-764. doi: 10.1038/s41586-021-04175-x. Epub 2021 Dec 8. PMID: 34880501; PMCID: PMC8867396.

Interface

JSME Molecular Editor by Peter Ertl and Bruno Bienfait

SMILES

TC

0.35

Submit   Test Gleevec

-Draw your molecule of interest or just put in the SMILES in the input box

Interface

-Draw your molecule of interest or just put in the SMILES in the input box

-Set your TC value and hit submit!

SMILES

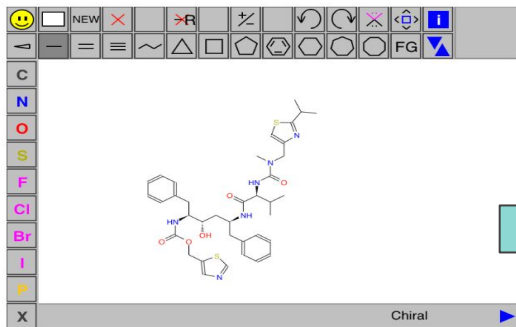CC(C)c4nc(CN(C)C(=O)N[C@@H](C(C)C)C(=O)N[C@

TC

0.35
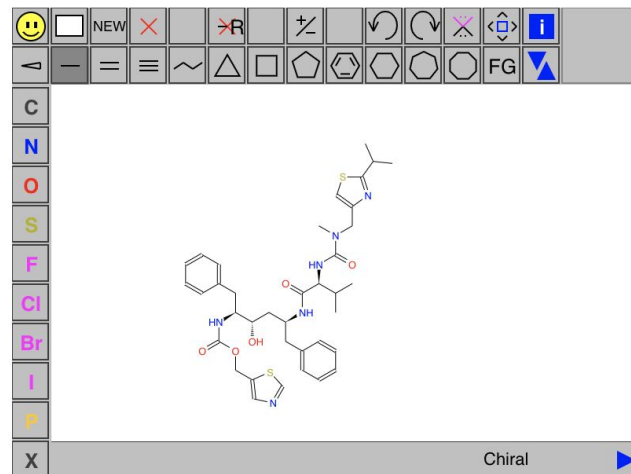
Submit   Test Gleevec

Ritonavir a new FDA approved drug to treat HIV/AIDS
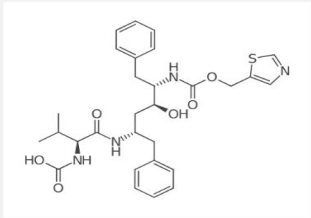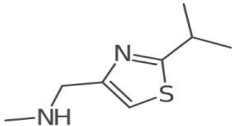
Home   Reactions   Contact

SMILES

CC(C)c4nc(CN(C)C(=O)N[C@@H](C(C)C)C(=O)N[C@

TC   0.35

Submit   Test Gleevec

Rxn/Rxn ID	BBs:16	BB SMILES	Analogs
AMIDE CC-4			
		CC(C)[C@H](NC(=O)O)C(=O)N[C@@H](Cc1ccccc1)C[C@H](O)[C@H](Cc1ccccc1)NC(=O)OCc1cncs1	Analogs
		CNCc1csc(C(C)C)n1	Analogs

Home   Reactions   Contact

Retrosynthesis results on the right
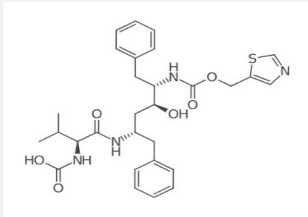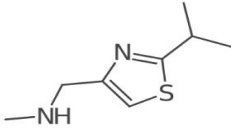
Rxn/Rxn ID	BBs:16		BB SMILES	Analogs
AMIDE CC-4				
			CC(C)[C@H](NC(=O)O)C(=O)N[C@@H](Cc1ccccc1)C[C@H](O)[C@H](Cc1ccccc1)NC(=O)OCc1cncs1	Analogs
			CNCc1csc(C(C)C)n1	Analogs

SMILES

CC(C)c4nc(CN(C)C(=O)N[C@@H](C(C)C)C(=O)N[C@

TC

0.35

Submit   Test Gleevec

AB3
Home Reactions Contact

Each retrosynthesis has atleast two results

SMILES

`CC(C)c4nc(CN(C)C(=O)N[C@@H](C(C)C)C(=O)N[C@`

TC 0.35

Submit Test Gleevec

Rxn/Rxn ID	BBs:16	BB SMILES	Analogs
AMIDE CC-4			
		CC(C)[C@H](NC(=O)O)C(=O)N[C@@H](Cc1ccccc1)C[C@H](O)[C@H](Cc1ccccc1)NC(=O)OCc1cncs1	Analogs
		CNCc1csc(C(C)C)n1	Analogs

Press Analogs to View

Purchasable Analogs of BB

Home   Reactions   Contact

SMILES

CC(C)c4nc(CN(C)C(=O)N[C@@H](C(C)C)C(=O)N[C@

TC   0.35

Submit   Test Gleevec

Rxn/Rxn ID	BBs:16	BB SMILES	Analogs
AMIDE CC-4			
		CC(C)[C@H](NC(=O)O)C(=O)N[C@@H](Cc1ccccc1)C[C@H](O)[C@H](Cc1ccccc1)NC(=O)OCc1cncs1	Analogs
		CNCc1csc(C(C)C)n1	Analogs