Paths of analysis*

Analysis 9

Synthia

March 3, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: FGI, FGI with protections

Max. paths returned: 5

Max. iterations: 300

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1000 $/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 10

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Reaction scoring formula: TUNNEL_COEF*FGI_COEF*STEP*20+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,SMALLER^ 1.5

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

FGI Coeff: 0

JSON Parameters: {}

2 Paths

3 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

2.1 Path 1

Score: 1000319.07

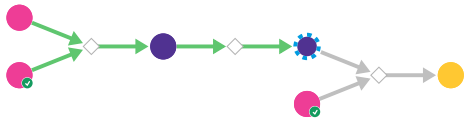
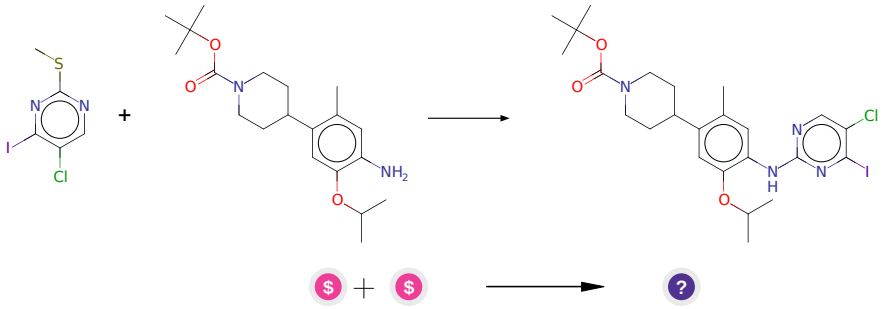


Figure 1: Outline of path 1

2.1.1 Substiution of 2-thiomethylpyrimidines with amines



Substrates:

1. tert-Butyl 4-(4-amino-5-isopropoxy-2-methylphenyl)piperidine-1-carboxylate - *Combi-Blocks*
2. 5-Chloro-4-iodo-2-(methylthio)pyrimidine - *available at Sigma-Aldrich*

Products:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCN(C(=O)OC(C)(C)C)CC1

Typical conditions: K2CO3.DMF

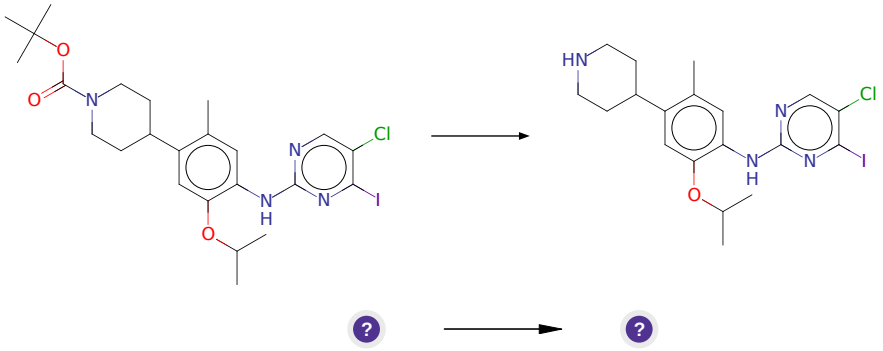
Protections: none

Yield: good

Reference: *10.1021/jm980222w* AND *10.1016/j.cclet.2014.10.007* AND *10.1002/jhet.5570280520* AND *10.1080/00397910701396930*

Retrosynthesis ID: 14935

2.1.2 Boc removal



Substrates:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCN(C(=O)OC(C)(C)C)CC1

Products:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCNCC1

Typical conditions: TFA.DCM or HCl.EtOH

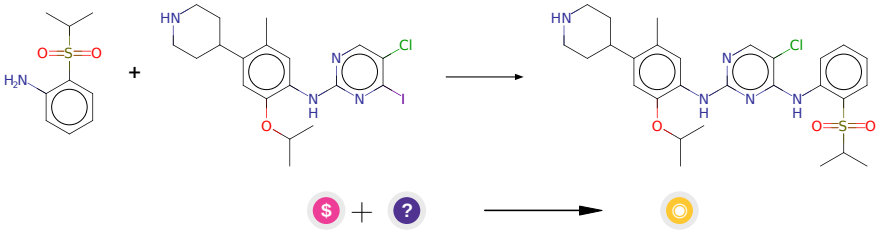
Protections: none

Yield: good

Reference: *10.1021/jm070794t* and *10.1021/jm020598g* and *10.1021/acs.oprd.5b00144* and *10.1016/j.bmc.2003.08.022*

Retrosynthesis ID: 10025810

2.1.3 Amination of aryl iodides



Substrates:

1. 1-Amino-2-(isopropylsulphonyl)benzene - *available at Sigma-Aldrich*
2. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCNCC1

Products:

1. LDK378 - *Combi-Blocks*

Typical conditions: [Pd] or CuI.base.solvent

Protections:

Functional group SMARTS	Classification	Protecting groups
[CX4,c][NH][CX4,c]	amines	t-Butyl Carbamate
		N-Acetyl
		N-Trifluoroacetyl
		N-Benzyl
		N-Benzoyl
		N-Triphenylmethyl

Yield: good

Reference: *10.1016/j.tet.2013.02.040* and *10.1021/ic200966f* (SI) and *10.1021/jo034994y*

Retrosynthesis ID: 1230

2.2 Path 2

Score: `1250345.43`

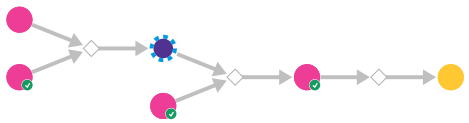
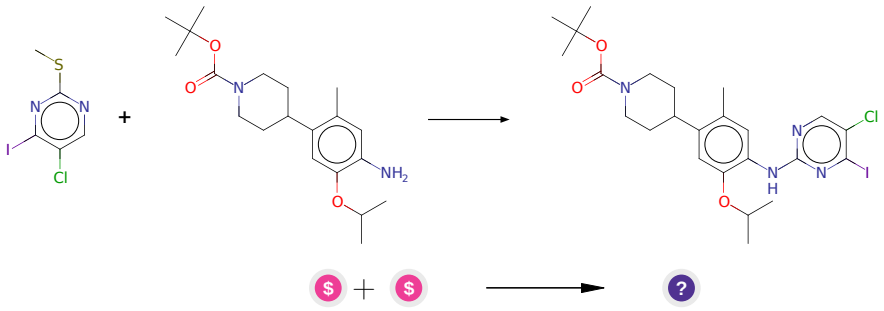


Figure 2: Outline of path 2

2.2.1 Substiution of 2-thiomethylpyrimidines with amines



Substrates:

1. tert-Butyl 4-(4-amino-5-isopropoxy-2-methylphenyl)piperidine-1-carboxylate - *Combi-Blocks*
2. 5-Chloro-4-iodo-2-(methylthio)pyrimidine - *available at Sigma-Aldrich*

Products:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCN(C(=O)OC(C)(C)C)CC1

Typical conditions: K2CO3.DMF

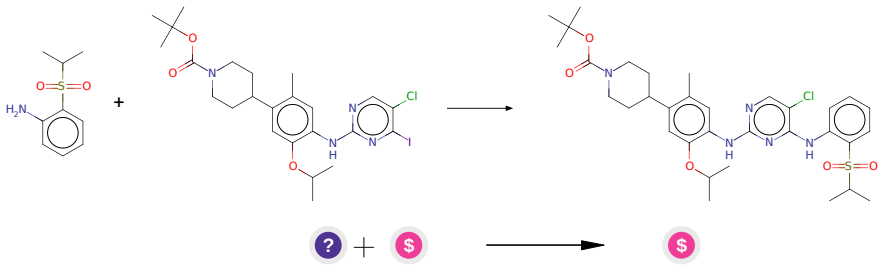
Protections: none

Yield: good

Reference: *10.1021/jm980222w* AND *10.1016/j.cclet.2014.10.007* AND *10.1002/jhet.5570280520* AND *10.1080/00397910701396930*

Retrosynthesis ID: 14935

2.2.2 Amination of aryl iodides



Substrates:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCN(C(=O)OC(C)(C)C)CC1
2. 1-Amino-2-(isopropylsulphonyl)benzene - *available at Sigma-Aldrich*

Products:

1. 4-[4-[[5-Chloro-4-[[2-[(propan-2-yl)sulfonyl]phenyl]amino]pyrimidin-2-yl]amino]-5-isopropoxy-2-methylphenyl]piperidine-1-carboxylic acid tert-butyl ester - *available at Sigma-Aldrich*

Typical conditions: [Pd] or CuI.base.solvent

Protections:

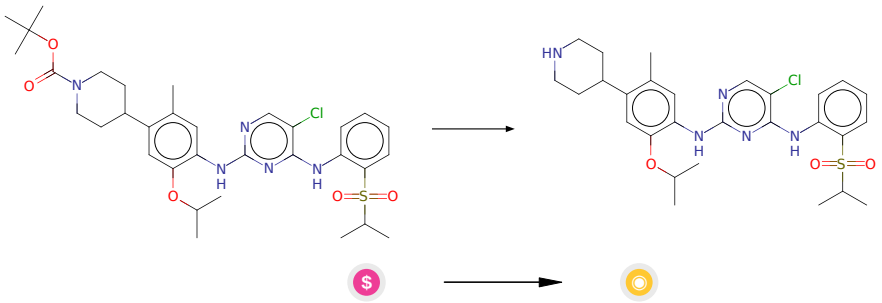
Functional group SMARTS	Classification	Protecting groups
[CX4,c][NH][CX4,c]	amines	t-Butyl Carbamate N-Acetyl N-Trifluoroacetyl N-Benzyl N-Benzoyl N-Triphenylmethyl

Yield: good

Reference: *10.1016/j.tet.2013.02.040* and *10.1021/ic200966f* (SI) and *10.1021/jo034994y*

Retrosynthesis ID: 1230

2.2.3 Boc removal



Substrates:

1. 4-[4-[[5-Chloro-4-[[2-[(propan-2-yl)sulfonyl]phenyl]amino]pyrimidin-2-yl]amino]-5-isopropoxy-2-methylphenyl]piperidine-1-carboxylic acid tert-butyl ester - *available at Sigma-Aldrich*

Products:

1. LDK378 - *Combi-Blocks*

Typical conditions: TFA.DCM or HCl.EtOH

Protections: none

Yield: good

Reference: *10.1021/jm070794t* and *10.1021/jm020598g* and *10.1021/acs.oprd.5b00144* and *10.1016/j.bmc.2003.08.022*

Retrosynthesis ID: 10025810

2.3 Path 3

Score: `1250414.60`

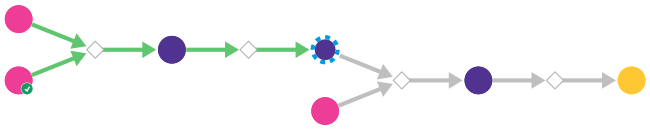
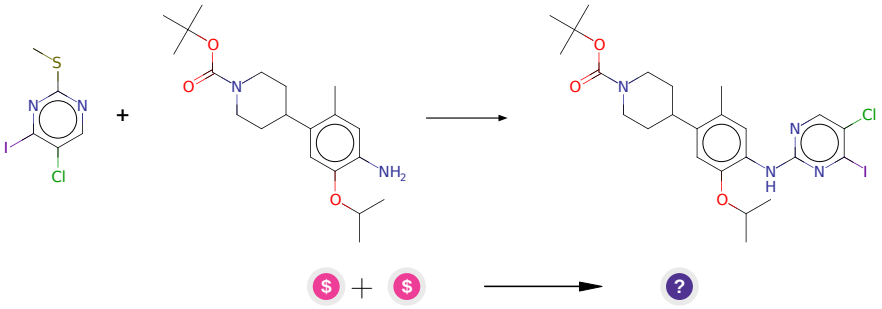


Figure 3: Outline of path 3

2.3.1 Substiution of 2-thiomethylpyrimidines with amines



Substrates:

1. tert-Butyl 4-(4-amino-5-isopropoxy-2-methylphenyl)piperidine-1-carboxylate - *Combi-Blocks*
2. 5-Chloro-4-iodo-2-(methylthio)pyrimidine - *available at Sigma-Aldrich*

Products:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCN(C(=O)OC(C)(C)C)CC1

Typical conditions: K2CO3.DMF

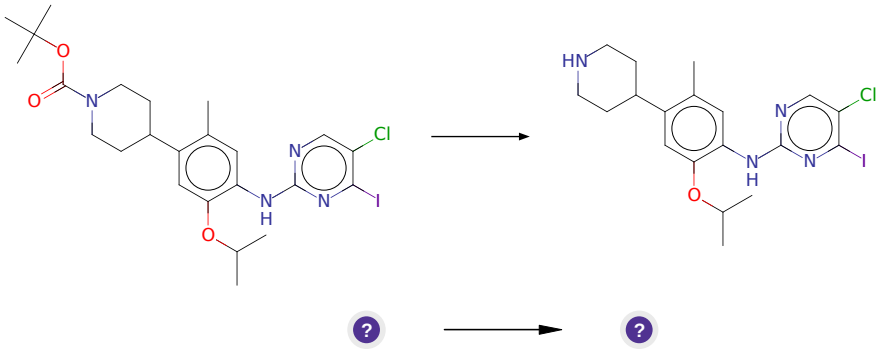
Protections: none

Yield: good

Reference: *10.1021/jm980222w* AND *10.1016/j.cclet.2014.10.007* AND *10.1002/jhet.5570280520* AND *10.1080/00397910701396930*

Retrosynthesis ID: 14935

2.3.2 Boc removal



Substrates:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCN(C(=O)OC(C)(C)C)CC1

Products:

1. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCNCC1

Typical conditions: TFA.DCM or HCl.EtOH

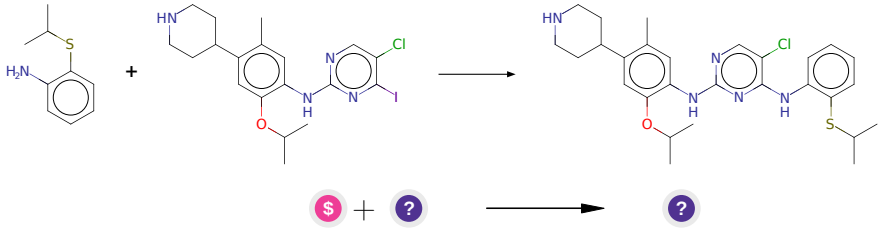
Protections: none

Yield: good

Reference: *10.1021/jm070794t* and *10.1021/jm020598g* and *10.1021/acs.oprd.5b00144* and *10.1016/j.bmc.2003.08.022*

Retrosynthesis ID: 10025810

2.3.3 Amination of aryl iodides



Substrates:

1. 2-(Isopropylthio)aniline - *Combi-Blocks*
2. Cc1cc(Nc2ncc(Cl)c(I)n2)c(OC(C)C)cc1C1CCNCC1

Products:

1. Cc1cc(Nc2ncc(Cl)c(Nc3ccccc3SC(C)C)n2)c(OC(C)C)cc1C1CCNCC1

Typical conditions: [Pd] or CuI.base.solvent

Protections:

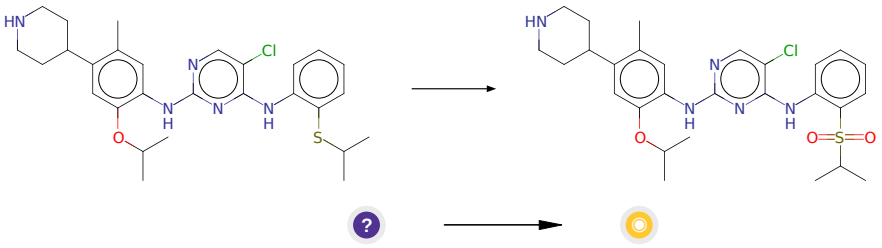
Functional group SMARTS	Classification	Protecting groups
[CX4,c][NH][CX4,c]	amines	t-Butyl Carbamate N-Acetyl N-Trifluoroacetyl N-Benzyl N-Benzoyl N-Triphenylmethyl

Yield: good

Reference: *10.1016/j.tet.2013.02.040* and *10.1021/ic200966f* (SI) and *10.1021/jo034994y*

Retrosynthesis ID: 1230

2.3.4 Nb carbide cat. oxidation of sulfides to sulfones



Substrates:

1. Cc1cc(Nc2ncc(Cl)c(Nc3ccccc3SC(C)C)n2)c(OC(C)C)cc1C1CCNCC1

Products:

1. LDK378 - *Combi-Blocks*

Typical conditions: NbMe.H2O2.EtOH.60C

Protections: none

Yield: good

Reference: DOI: *10.1055/s-0029-1219947*

Retrosynthesis ID: 10681