15 APIs of interest in COVID-19 treatment

Recently, there have been many reports of investigations into the repurposing of currently available drugs as effective treatments for the novel coronavirus disease COVID-19, with numerous clinical trials taking place.

To support these efforts, we have collected all approved API entries from Pharmaceutical Substances that have been considered in this context, and we would like to share these with you as freely available pdfs. This information includes established synthetic routes that are applied in industry for the preparation of these compounds.

Approved APIs investigated as potential COVID-19 treatments

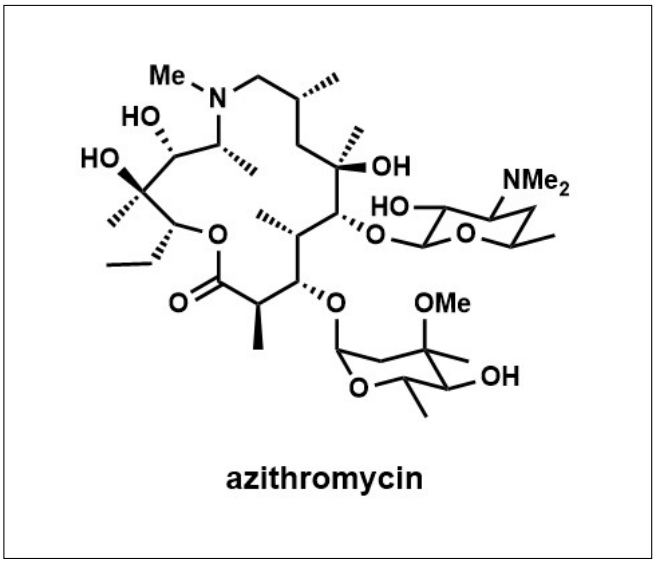
About Pharmaceutical Substances

Pharmaceutical Substances is designed to be a complete reference guide to every pharmaceutical compound of significance. It provides access to syntheses, patents and applications for a compendium of over 2,700 active pharmaceutical ingredients (APIs) of interest to the chemical and pharmaceutical industries. For more information click here.

Find more APIs on ps.thieme.com

Thieme

Azithromycin



azithromycin

Related reviews in Science of Synthesis

- 1,2-Diols
- Lactones
- Glycosyl Oxygen Compounds
- Reaction of Hydroxylamines with Alkylating Agents
- Reduction of Amine Oxides

Synonyms: Aritromicina

ATC: J01FA10; S01AA26

Use: macrolide antibiotic

Chemical name: [2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)]-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one

Formula: $C_{38}H_{72}N_2O_{12}$

MW: 749.00 g/mol

CAS-RN: 83905-01-5

InChI Key: MQTOSJVFKKJCRP-FHZDSTMTSA-N

InChI: InChI=1S/C38H72N2O12/c1-15-27-38(10,46)31(42)24(6)40(13)19-20(2)17-36(8,45)33(52-35-29(41)26(39(11)12)16-21(3)48-35)22(4)30(23(5)34(44)50-27)51-28-18-37(9,47-14)32(43)25(7)49-28/h20-33,35,41-43,45-46H,15-19H2,1-14H3/t20-,21?,22+,23-,24-,25?,26?,27-,28?,29?,30+,31-,32?,33-,35?,36-,37?,38-/m1/s1

LD50: 1200 mg/kg (M, i.p.); 825 mg/kg (M, i.p.); 3 g/kg (M, p.o.); >2 g/kg (R, p.o.)

Derivatives

monohydrochloride

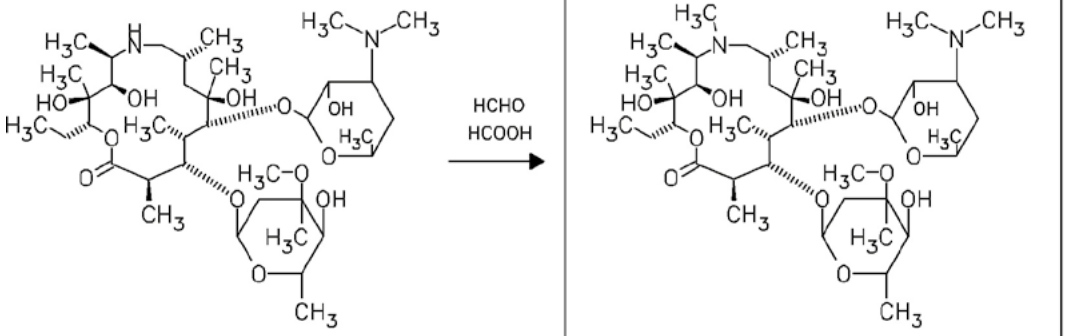
Formula: $C_{38}H_{72}N_2O_{12} \cdot HCl$

MW: 785.46 g/mol

CAS-RN: 90581-30-9

Synthesis Path

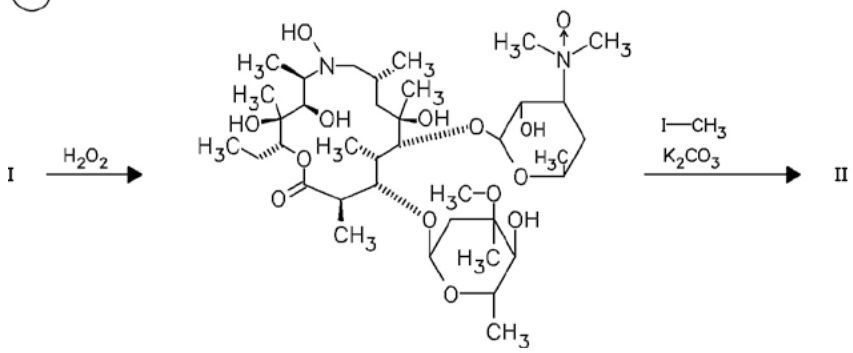
a

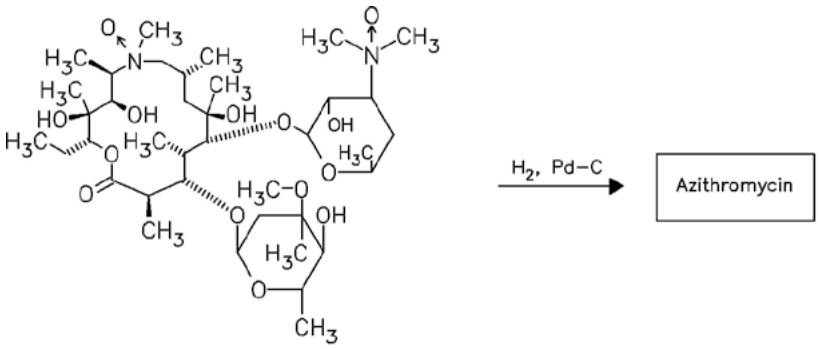


9-deoxo-9a-aza-9a-homoerythromycin A (I)
(from erythromycin A, q. v.)

Azithromycin

b





(II)

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
76801-85-9	$C_{37}H_{70}N_2O_{12}$	2-deoxo-9a-aza-9a-homoerythromycin A	1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-, [2R-(2R*,3S*,4R*,5R*,8R*,10R*,11R*,12S*,13S*,14R*)]-
90503-04-1	$C_{37}H_{70}N_2O_{14}$	[2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)]-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,6,10-tetrahydroxy-3,5,8,10,12,14-hexamethyl-13-[[3,4,6-trideoxy-3-(dimethyloxidoamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one	1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,6,10-tetrahydroxy-3,5,8,10,12,14-hexamethyl-13-[[3,4,6-trideoxy-3-(dimethyloxidoamino)-β-D-xylo-hexopyranosyl]oxy]-, [2R-(2R*,3S*,4R*,5R*,8R*,10R*,11R*,12S*,13S*,14R*)]-
90503-05-2	$C_{38}H_{72}N_2O_{14}$	[2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)]-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethyloxidoamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one 6-oxide	1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethyloxidoamino)-β-D-xylo-hexopyranosyl]oxy]-, 6-oxide, [2R-(2R*,3S*,4R*,5R*,8R*,10R*,11R*,12S*,13S*,14R*)]-
50-00-0	CH_2O	formaldehyde	Formaldehyde
74-88-4	CH_3I	methyl iodide	Methane, iodo-

Trade Names

Country	Trade Name	Vendor	Annotation
D	Ultreon	Pfizer	
	Zithromax	Pfizer Pharma/Gödecke/Parke-Davis	
	numerous generic preparations		
F	Azadose	Pfizer	
	Monodose	Pfizer	
	Zithromax	Pfizer	
GB	Zithromax	Pfizer	
I	Azitrocin	Bioindustria	
	Ribotrex	Pierre Fabre	
	Trocozina	Sigma-Tau	
	Zithromax	Pfizer	
J	Zithromac	Pfizer	
USA	Azasite	InSite Vision	
	Zithromax	Pfizer	as dihydrate

Formulations

cps. 100 mg, 250 mg; Gran. 10%; susp. 200 mg (as dihydrate); tabl. 250 mg

References

Djokic, S. et al.: J. Antibiot. (JANTAJ) **40**, 1006 (1987).

a DOS 3 140 449 (Pliva; appl. 12.10.1981; YU-prior. 6.3.1981).
US 4 517 359 (Pliva; 14.5.1985; appl. 22.9.1981; YU-prior. 6.3.1981).

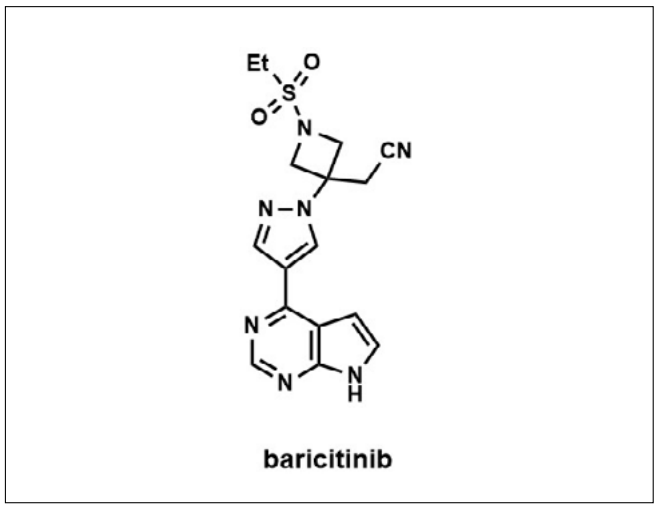
b EP 101 186 (Pliva; appl. 14.7.1983; USA-prior. 19.7.1982, 15.11.1982).
US 4 474 768 (Pfizer; 2.10.1984; prior. 19.7.1982, 15.11.1982).

educt by ring expansion of* erythromycin A oxime *by Beckmann rearrangement:
Djokic, S. et al.: J. Chem. Soc., Perkin Trans. 1 (JCPRB4) **1986**, 1881-1890.
Bright, G.M. et al.: J. Antibiot. (JANTAJ) **41**, 1029 (1988). US 4 328 334 (Pliva; 4.5.1982; YU-prior. 2.4.1979).

stable, non-hygroscopic dihydrate: EP 298 650 (Pfizer; appl. 28.6.1988).

medical use for treatment of protozoal infections:
US 4 963 531 (Pfizer; 16.10.1990; prior. 16.8.1988, 10.9.1987).

Baricitinib



baricitinib

Related reviews in Science of Synthesis

- Pyrimidines
- Pyrazoles
- Azetidines
- Alkanesulfonamides
- Nitriles
- Hetarylboron Cross-Coupling Reactions (Suzuki–Miyaura)

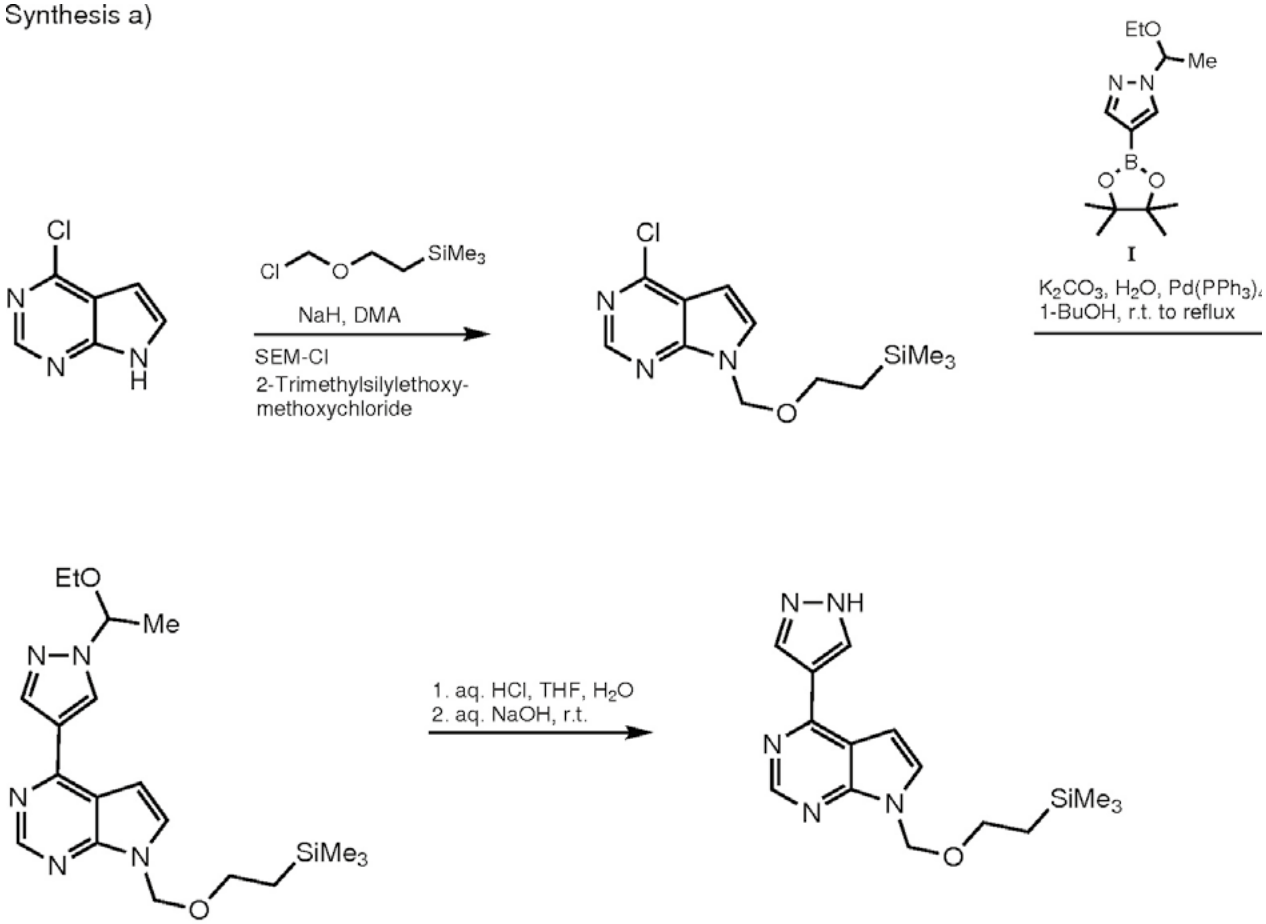
Synonyms: INCB-28050; LY-3009104
ATC: L04AA37
Use: rheumatoid arthritis, JAK inhibitor
Chemical name: 2-[1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl]acetonitrile
Formula: $C_{16}H_{17}N_7O_2S$
MW: 371.42 g/mol
CAS-RN: 1187594-09-7
InChI Key: XUZMWHLSFXCVMG-UHFFFAOYSA-N
InChI: InChI=1S/C16H17N7O2S/c1-2-26(24,25)22-9-16(10-22,4-5-17)23-8-12(7-21-23)14-13-3-6-18-15(13)20-11-19-14/h3,6-8,11H,2,4,9-10H2,1H3,(H,18,19,20)

Derivatives

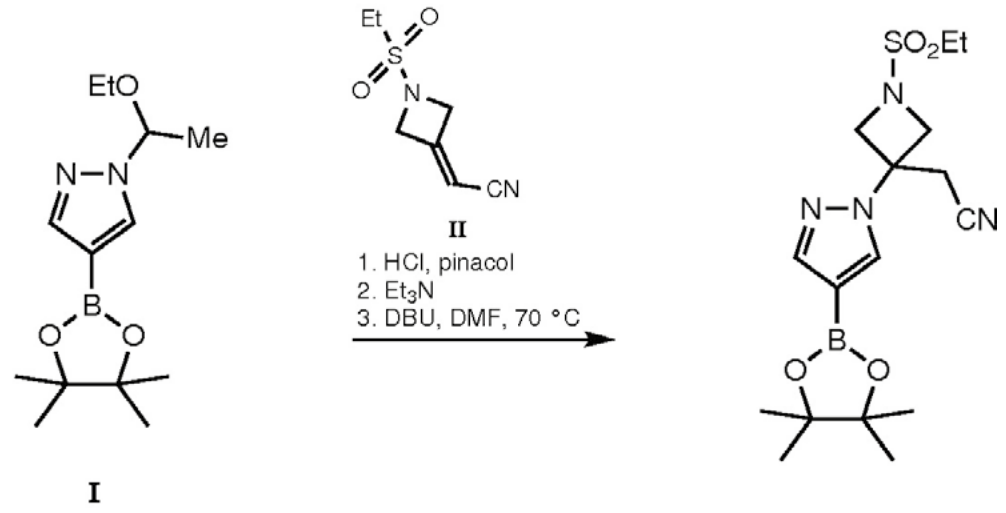
Phosphate
Formula: $C_{19}H_{17}N_7O_6PS$
MW: 469.41 g/mol
CAS-RN: 1187595-84-1

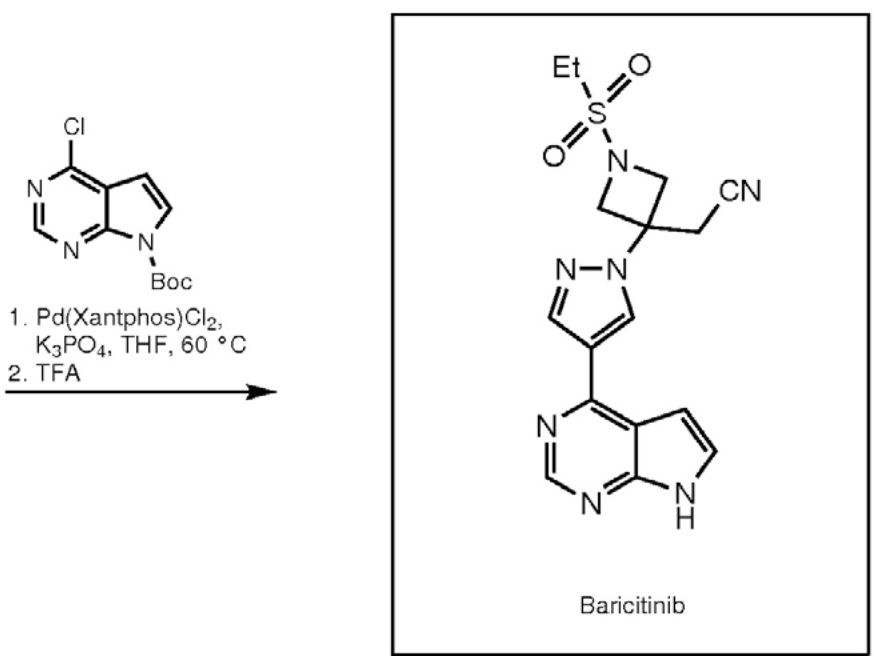
Synthesis Path

Synthesis a)

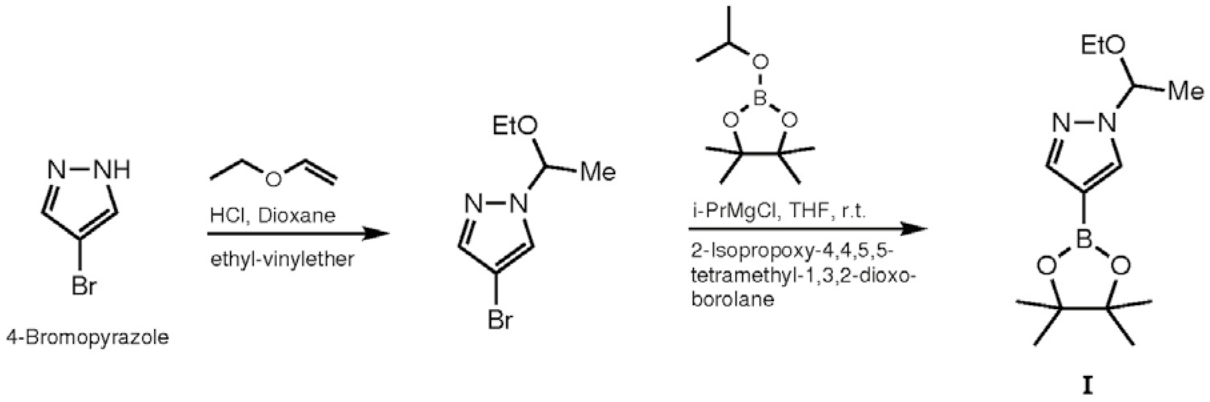


Synthesis b)





Preparation of 1-(1-Ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (I)

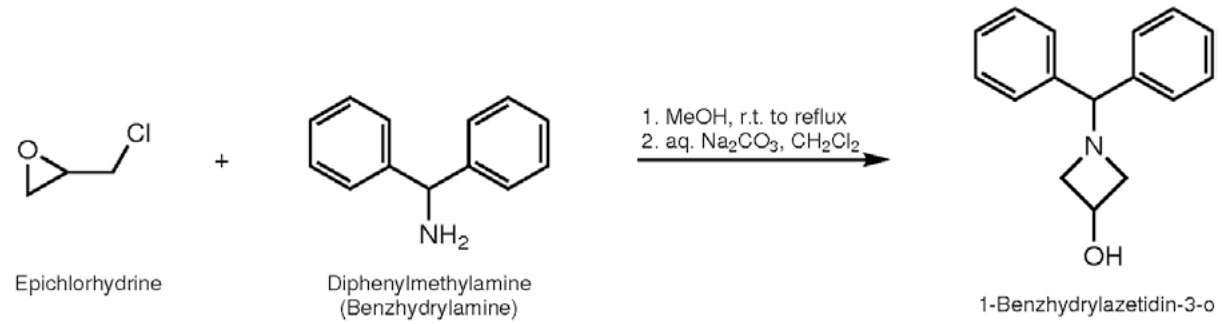


4-Bromopyrazole

I

1-(1-Ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (I)

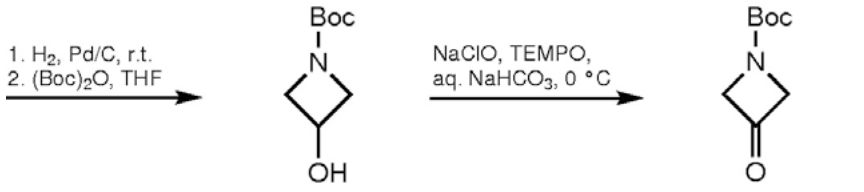
Preparation of 2-[1-(ethylsulfonyl)-3-azetidinylidene] acetonitrile (II)



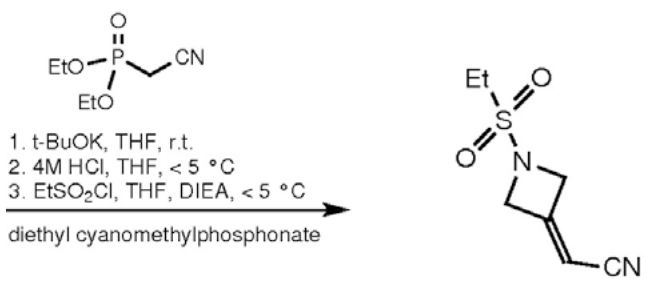
Epichlorhydrine

Diphenylmethylamine (Benzhydrylamine)

1-Benzhydrylazetidin-3-o



1-Boc-azetidin-3-one



II

2-[1-(ethylsulfonyl)-3-azetidinylidene] acetonitrile (II)

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name
76513-69-4	$C_6H_{15}ClOSi$	2-Trimethylsilylethoxy-methoxychloride
2075-45-8	$C_3H_3BrN_2$	4-Bromopyrazole
109-92-2	C_4H_8O	ethyl-vinylether
61676-62-8	$C_9H_{19}BO_3$	2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxo-borolane
1029716-44-6	$C_3H_{23}N_2O_3$	1-(1-Ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole
106-89-8	C_3H_5ClO	Epichlorhydrine
91-00-9	$C_{13}H_{13}N$	Diphenylmethylamine
18621-17-5	$C_{16}H_{13}NO$	1-Benzhydrylazetidin-3-ol
2537-48-6	$C_6H_{12}NO_3P$	diethyl cyanomethylphosphonate
1187595-85-2	$C_7H_{10}N_2O_2S$	2-[1-(ethylsulfonyl)-3-azetidinylidene] acetonitrile
398489-26-4	$C_8H_{13}NO_3$	1-Boc-azetidin-3-one

Trade Names

Country	Trade Name	Vendor
USA	Olumiant	Eli Lilly, *2016*
EU	Olumiant	Eli Lilly, *2016*

Formulations

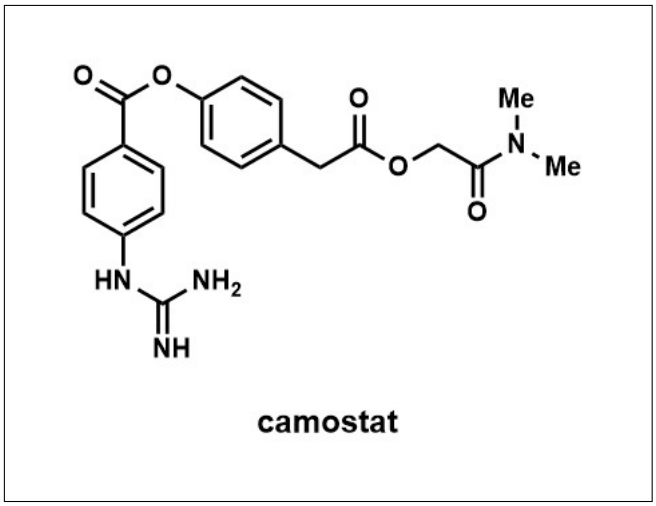
f.c. tablet 2 mg, 4 mg (as phosphate)

References

Jiaojiao, X. et al., *Journal of Chem. Research*, (2016) **40** (4), 205.
a WO 2009 114512 (Incyte; 17.09.2009; US-prior. 11.03.2008).
US 8 158 616 (Incyte; 17.04.2012; US-prior. 11.03.2008).
b WO 2016 205487 (Eli Lilly & Co.; 22.12.2016; US-prior. 19.06.2015).

Preparation of I
Qiyan, L. et al., *Organic Letters*, (2009) **11**(9), 1999-2002.

Camostat



camostat

Related reviews in Science of Synthesis

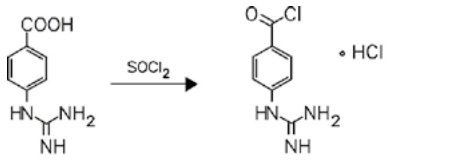
- Arenecarboxylic Acid Esters
- α-Heteroatom-Substituted Alkanamides
- Guanidines
- Carboxylic Acids to Acid Halides Using Thionyl Chloride

ATC: B02AB04
Use: trypsin inhibitor (for treatment of chronic pancreatitis)
Chemical name: 4-[[4-[(aminoiminomethyl)amino]benzoyl]oxy]benzeneacetic acid 2-(dimethylamino)-2-oxoethyl ester
Formula: $C_{20}H_{22}N_4O_5$
MW: 398.42 g/mol
CAS-RN: 59721-28-7
InChI Key: XASIMHXSUQUHLV-UHFFFAOYSA-N
InChI: InChI=1S/C20H22N4O5/c1-24(2)17(25)12-28-18(26)11-13-3-9-16(10-4-13)29-19(27)14-5-7-15(8-6-14)23-20(21)22/h3-10H,11-12H2,1-2H3,(H4,21,22,23)

Derivatives

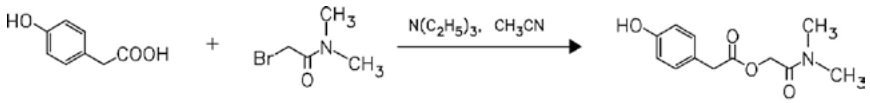
monomesylate
Formula: $C_{20}H_{22}N_4O_5 \cdot CH_4O_3S$
MW: 494.53 g/mol
CAS-RN: 59721-29-8
LD50: 200 mg/kg (M, i.v.); 3 g/kg (M, p.o.); 152 mg/kg (R, i.v.); 3 g/kg (R, p.o.)

Synthesis Path



4-guanidino-benzoic acid

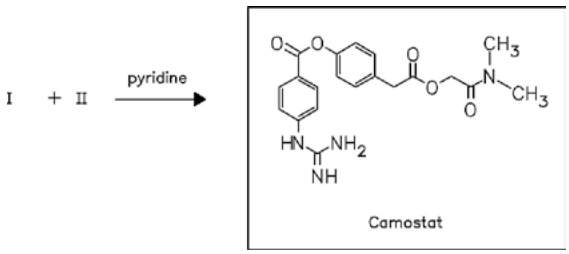
4-guanidinobenzoyl chloride hydrochloride (I)



(4-hydroxyphenyl)-acetic acid

2-bromo-N,N-dimethyl-acetamide

N,N-dimethylcarbamoylmethyl (4-hydroxyphenyl)acetate (II)



Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
5468-77-9	C_4H_8BrNO	2-bromo-*N*,*N*-dimethylacetamide	Acetamide, 2-bromo-N,N-dimethyl-
59721-16-3	$C_{12}H_{15}NO_4$	*N*,*N*-dimethylcarbamoylmethyl (4-hydroxyphenyl)acetate	Benzeneacetic acid, 4-hydroxy-, 2-(dimethylamino)-2-oxoethyl ester
16060-65-4	$C_8H_9N_3O_2$	4-guanidinobenzoic acid	Benzoic acid, 4-[(aminoiminomethyl)amino]-
7035-79-2	$C_8H_9Cl_2N_3O$	4-guanidinobenzoyl chloride hydrochloride	Benzoyl chloride, 4-[(aminoiminomethyl)amino]-, monohydrochloride
156-38-7	$C_8H_8O_3$	4-hydroxyphenylacetic acid	Benzeneacetic acid, 4-hydroxy-

Trade Names

Country	Trade Name	Vendor
J	Foipan	Ono

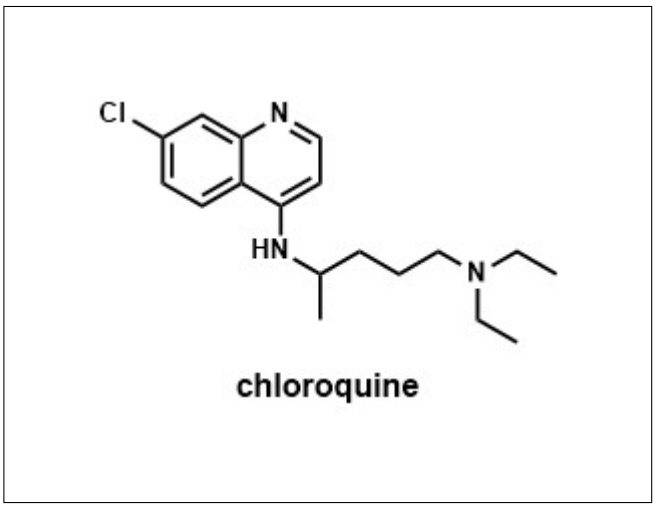
Formulations

gran. 200 mg; tabl. 100 mg

References

DOS 2 548 886 (Ono Pharmac.; appl. 31.10.1975; J-prior. 1.11.1974, 17.12.1974, 27.5.1975).
US 4 021 472 (Ono Pharmac.; 3.5.1977; J-prior. 1.11.1974, 17.12.1974, 27.5.1975).
GB 1 472 700 (Ono Pharmac.; appl. 23.10.1975; J-prior. 1.11.1974; 17.12.1974, 27.5.1975).
FR 2 289 181 (Ono Pharmac.; appl. 30.10.1975; J-prior. 1.11.1974, 17.12.1974, 27.5.1975).

Chloroquine



Related reviews in Science of Synthesis

- Quinolines
- Quinolinamines
- Reductive Amination of Carbonyl Compounds

ATC: P01BA01
Use: antirheumatic, antimalarial
Chemical name: *N*4-(7-chloro-4-quinolinyl)-*N*1,*N*1-diethyl-1,4-pentanediamine
Formula: $C_{18}H_{26}ClN_3$
MW: 319.88 g/mol
CAS-RN:54-05-7
InChI Key: WHTVZRBIWZFKQO-UHFFFAOYSA-N
InChI: InChI=1S/C18H26ClN3/c1-4-22(5-2)12-6-7-14(3)21-17-10-11-20-18-13-15(19)8-9-16(17)18/h8-11,13-14H,4-7,12H2,1-3H3,(H,20,21)
EINECS: 200-191-2
LD_{50}: 21.6 mg/kg (M, i.v.); 311 mg/kg (M, p.o.); 60 mg/kg (R, i.v.); 330 mg/kg (R, p.o.)

Derivatives

diphosphate
Formula: $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$
MW: 515.87 g/mol
CAS-RN: 50-63-5
EINECS: 200-055-2
LD_{50}: 500 mg/kg (M, p .o.)

sulfate (1:1)
Formula: $C_{18}H_{26}ClN_3 \cdot H_2SO_4$
MW: 417.96 g/mol
CAS-RN: 132-73-0
EINECS: 205-077-6

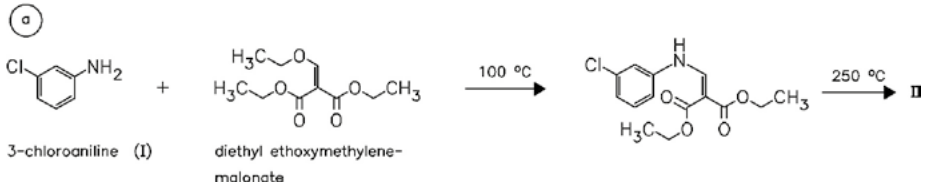
sulfate (1:1) monohydrate
Formula: $C_{18}H_{26}ClN_3 \cdot H_2O_4S \cdot H_2O$
MW: 435.97 g/mol
CAS-RN: 6823-83-2

dihydrochloride
Formula: $C_{18}H_{26}ClN_3 \cdot 2HCl$
MW: 392.80 g/mol
CAS-RN: 3545-67-3
EINECS: 222-592-1

2,5-dihydroxybenzoate
Formula: $C_{18}H_{26}ClN_3 \cdot xC_7H_6O_4$
MW: unspecified
CAS-RN: 16510-14-8
EINECS: 240-578-3

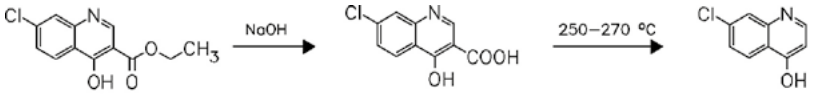
diorotate
Formula: $C_{18}H_{26}ClN_3 \cdot 2C_5H_4N_2O_4$
MW: 632.07 g/mol
CAS-RN: 16301-30-7
EINECS: 240-389-6
LD_{50}: 1130 mg/kg (M, p.o.)

starting products:
1. 4.7-Dichloroquinoline



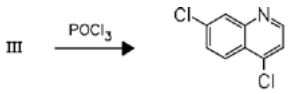
3-chloroaniline (I)

diethyl ethoxymethylene-malonate

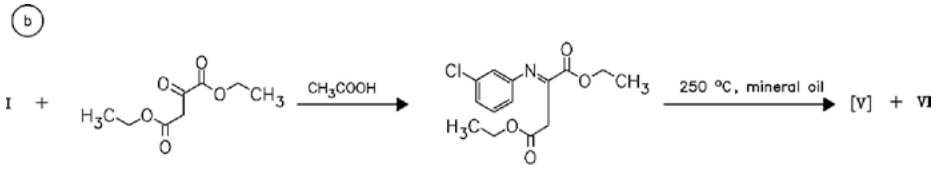


ethyl 7-chloro-4-hydroxy-3-quinoline-carboxylate (II)

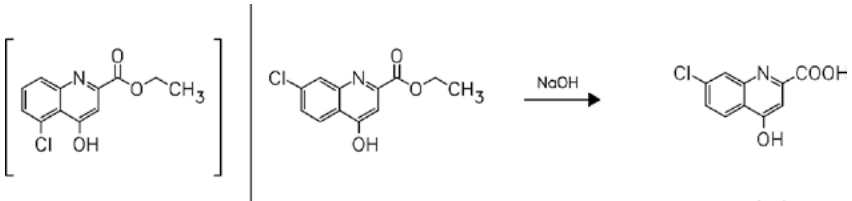
7-chloro-4-hydroxy-quinoline (III)



4,7-dichloro-quinoline (IV)



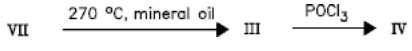
diethyl oxaloacetate



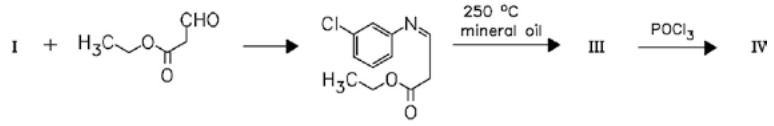
ethyl 5-chloro-4-hydroxy-2-quinoline-carboxylate (V) (removal by crystallization from acetic acid)

ethyl 7-chloro-4-hydroxy-2-quinoline-carboxylate (VI)

(VII)



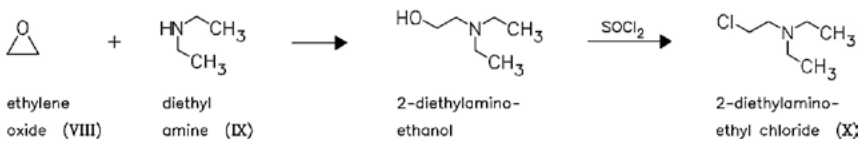
c



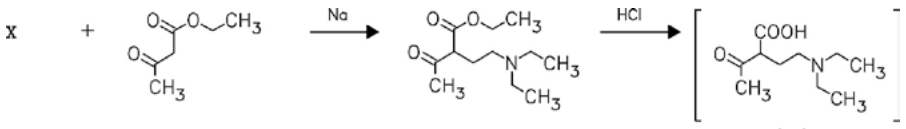
ethyl formyl-
acetate

2. Novoldiamine

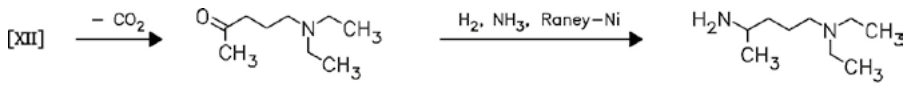
a



ethylene oxide (VIII) | diethyl amine (IX) | 2-diethylamino-ethanol | 2-diethylamino-ethyl chloride (X)

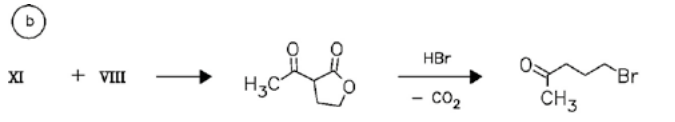


ethyl acetoacetate (XI) | (XII)

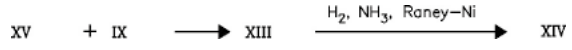


1-diethylamino-4-pentanone (XIII) | novoldiamine (XIV)

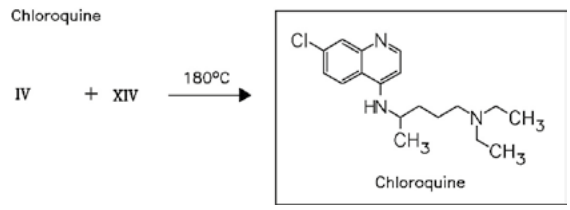
b



2-acetyl-butyrolactone | 1-bromo-4-pentanone (XV)



final product:
Chloroquine



Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
141-97-9	$C_6H_{10}O_3$	acetoacetic acid ethyl ester	Butanoic acid, 3-oxo-, ethyl ester
517-23-7	$C_6H_8O_3$	2-acetylbutyrolactone	2(3H)-Furanone, 3-acetyldihydro-
140-80-7	$C_9H_{22}N_2$	2-amino-5-diethylaminopentane	1,4-Pentanediamine, N1,N1-diethyl-
3884-71-7	C_5H_9BrO	1-bromo-4-pentanone	2-Pentanone, 5-bromo-
108-42-9	C_6H_6ClN	3-chloroaniline	Benzenamine, 3-chloro-
86-99-7	C_9H_6ClNO	7-chloro-4-hydroxyquinoline	4-Quinolinol, 7-chloro-
18000-24-3	$C_{10}H_6ClNO_3$	7-chloro-4-hydroxy-2-quinolinecarboxylic acid	2-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-
86-47-5	$C_{10}H_6ClNO_3$	7-chloro-4-hydroxy-3-quinolinecarboxylic acid	3-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-
3412-99-5	$C_{14}H_{16}ClNO_4$	[[(3-chlorophenyl)amino]methylene]propanedioic acid diethyl ester	Propanedioic acid, [[(3-chlorophenyl)amino]methylene]-, diethyl ester
	$C_{14}H_{16}ClNO_4$	α-[(2-chlorophenyl)imino]butanedioic acid diethyl ester	
82673-23-2	$C_{11}H_{12}ClNO_2$	3-[(3-chlorophenyl)imino]propanoic acid ethyl ester	
86-98-6	$C_9H_5Cl_2N$	4,7-dichloroquinoline	Quinoline, 4,7-dichloro-
109-89-7	$C_4H_{11}N$	diethylamine	Ethanamine, N-ethyl-
100-35-6	$C_6H_{14}ClN$	2-diethylaminoethyl chloride	Ethanamine, 2-chloro-N,N-diethyl-
105-14-6	$C_9H_{19}NO$	1-diethylamino-4-pentanone	2-Pentanone, 5-(diethylamino)-
87-13-8	$C_{10}H_{16}O_5$	diethyl ethoxymethylenemalonate	Propanedioic acid, (ethoxymethylene)-, diethyl ester
108-56-5	$C_8H_{12}O_5$	diethyl oxaloacetate	Butanedioic acid, oxo-, diethyl ester
108-01-0	$C_4H_{11}NO$	2-dimethylaminoethanol	Ethanol, 2-(dimethylamino)-
87-13-8	$C_{10}H_{16}O_5$	ethoxymethylenemalonic acid diethyl ester	Propanedioic acid, (ethoxymethylene)-, diethyl ester
141-97-9	$C_6H_{10}O_3$	ethyl acetoacetate	Butanoic acid, 3-oxo-, ethyl ester
21640-98-2	$C_{12}H_{10}ClNO_3$	ethyl 5-chloro-4-hydroxy-2-quinolinecarboxylate	2-Quinolinecarboxylic acid, 5-chloro-4-hydroxy-, ethyl ester
21640-97-1	$C_{12}H_{10}ClNO_3$	ethyl 7-chloro-4-hydroxy-2-quinolinecarboxylate	2-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-, ethyl ester
16600-22-9	$C_{12}H_{10}ClNO_3$	ethyl 7-chloro-4-hydroxy-3-quinolinecarboxylate	3-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-, ethyl ester
23999-02-2	$C_{12}H_{23}NO_3$	ethyl 2-(2-diethylaminoethyl)acetoacetate	Butanoic acid, 2-[2-(diethylamino)ethyl]-3-oxo-, ethyl ester
75-21-8	C_2H_4O	ethylene oxide	Oxirane
34780-29-5	$C_5H_8O_3$	ethyl formylacetate	Propanoic acid, 3-oxo-, ethyl ester
140-80-7	$C_9H_{22}N_2$	novoldiamine	1,4-Pentanediamine, N1,N1-diethyl-

Trade Names

Country	Trade Name	Vendor	Annotation
D	Resochin	Bayer Vital	
F	Nivaquine	Sanofi-Aventis	
	Savarine	AstraZeneca	
GB	Avloclor	AstraZeneca	
I	Clorochina	Formulario NazionaleBayer	
USA	Aralen	Sanofi	as hydrochloride
	Aralen	Sanofi	as phosphate

Formulations

amp. 250 mg/5 ml; syrup 15 mg; tabl. 50 mg, 155 mg, 300 mg (as phosphate)

References

Drake, N.L. et al.: J. Am. Chem. Soc. (JACSAT) 68, 1214 (1946).
1 a Price, C.C.; Roberts, R.M.: J. Am. Chem. Soc. (JACSAT) 68, 1204 (1946).
b Surrey, A.R.; Hammer, H.F.: J. Am. Chem. Soc. (JACSAT) 68, 113 (1946).
2 b Elderfield, R.C. et al.: J. Am. Chem. Soc. (JACSAT) 68, 1579 (1946).
US 2 233 970 (Winthrop; 1941; D-prior. 1937).
DRP 683 692 (I. G. Farben; appl. 1937).
DD 53 065 (S. Schwarz et al.; appl. 1966).
c US 2 478 125 (American Cyanamid; 1949; appl. 1944).
2 a DRP 486 079 (I. G. Farben; appl. 1924).

***alternative syntheses of* novoldiamine:**
US 2 365 825 (Monsanto; 1944; appl. 1942).
GB 1 157 637 (Sterling Drug; appl. 1966; USA-prior. 1965).

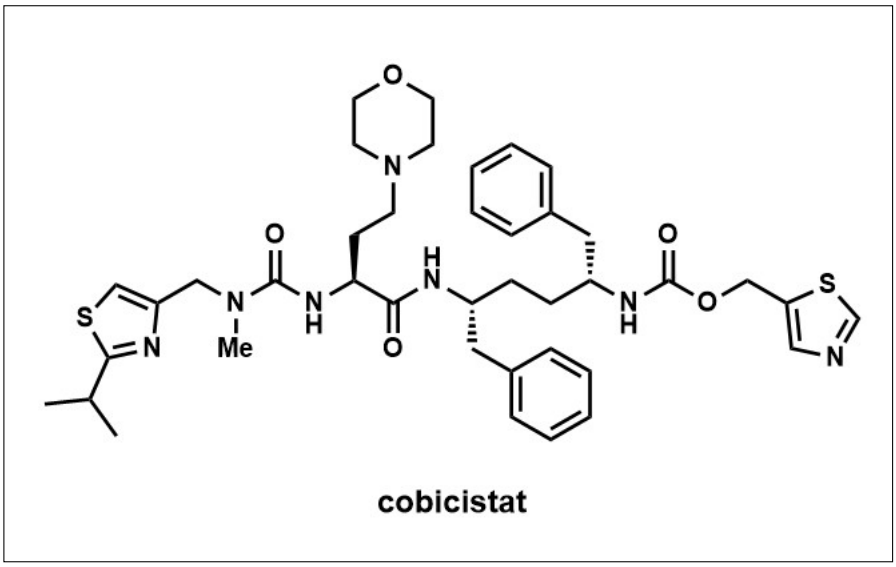
aminating hydrogenation of* novolketone, *continuous method:
DOS 2 923 472 (Bayer; appl. 9.6.1979).

alternative synthesis of* 4,7-dichloroquinoline *from* 3-chloroaniline *and acrylic acid ester:
FR 1 514 280 (Roussel-Uclaf; appl. 10.1.1967).
EP 56 765 (Rhône-Poulenc; appl. 15.1.1982; F-prior. 16.1.1981).

***alternative synthesis of* chloroquine *from* 7-chloro-4-oxo-1,2,3,4-tetrahydroquinoline *and* novoldiamine:**
EP 56 766 (Rhône-Poulenc; appl. 15.1.1982; F-prior. 16.1.1981).

***chlorination of* 7-chloro-4-hydroxyquinoline *with* benzotrichloride:**
DOS 3 112 415 (Dynamit Nobel; appl. 28.3.1981).

Cobicistat



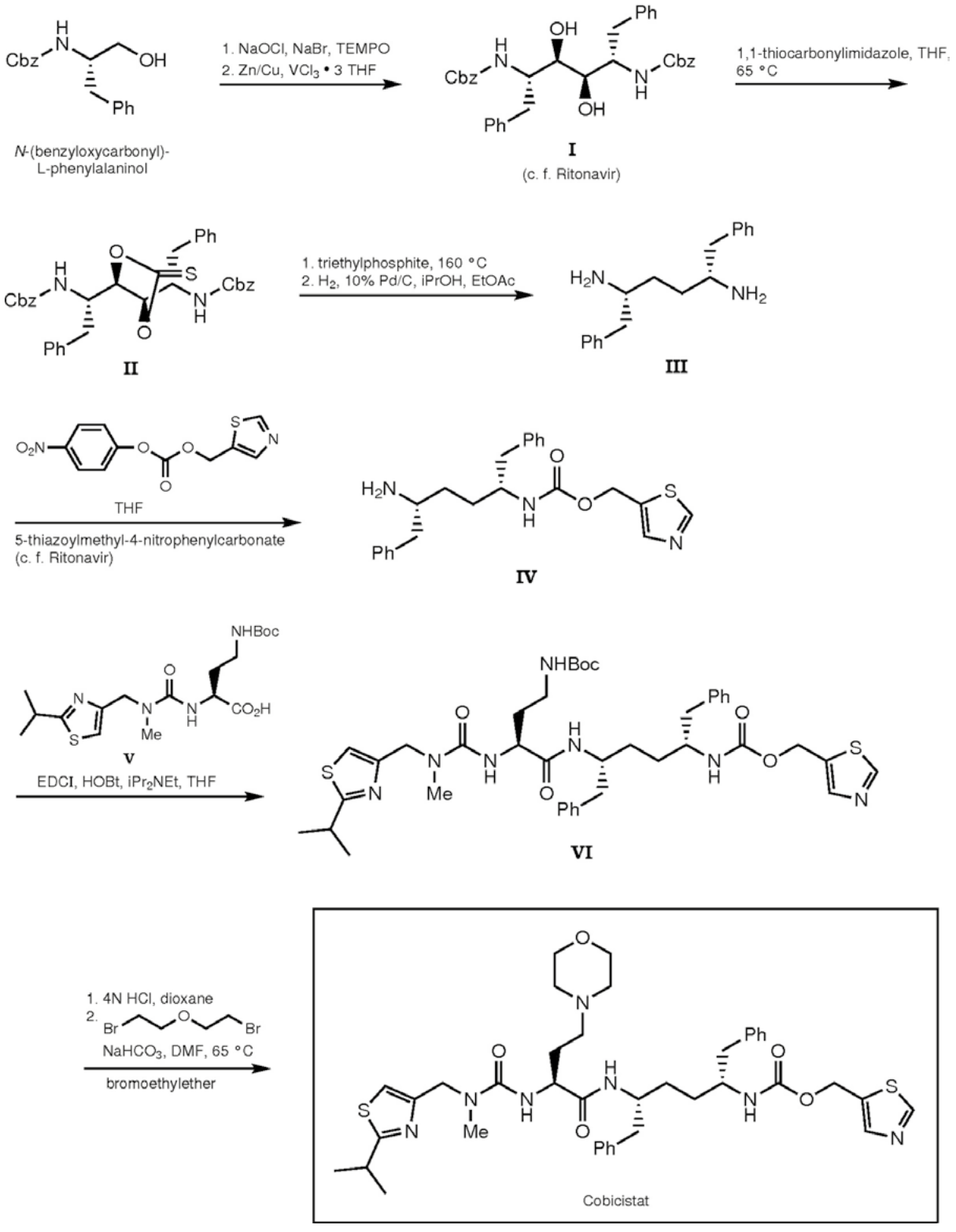
Related reviews in Science of Synthesis

- Thiazoles
- Amides
- Urea Derivatives
- Alkenes by Reductive Extrusion of 1,3-Dithiolane-2-thiones

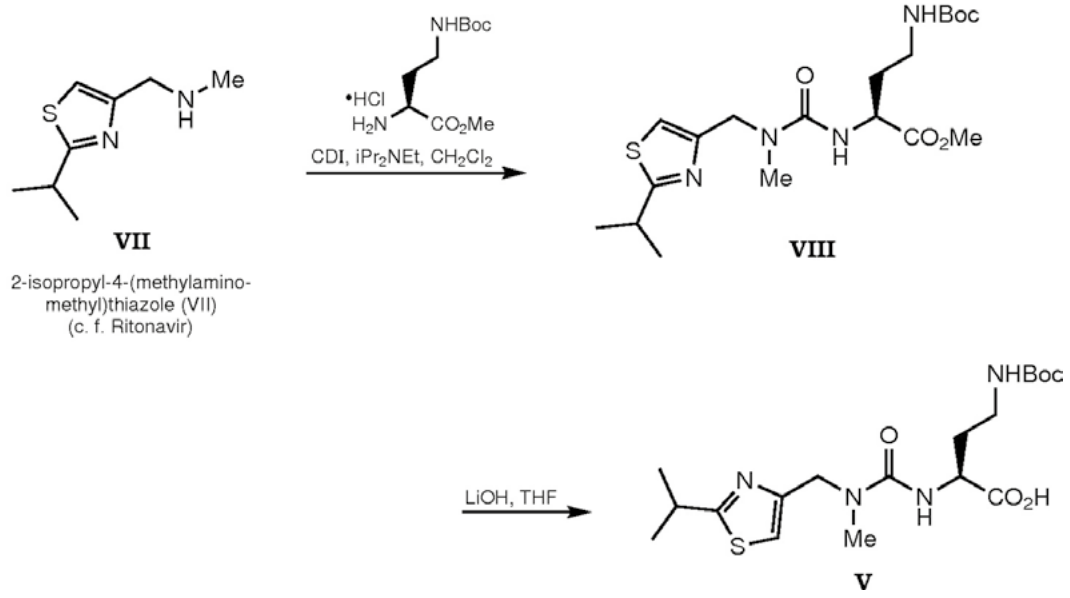
Synonyms: GS-9350
ATC: V03AX03
Use: anti-HIV; inhibitor of cytochrome P450
Chemical name: Thiazol-5-ylmethyl *N*-[1-benzyl-4-[[2-[[(2-isopropylthiazol-4-yl)methyl-methyl-carbamoyl]amino]-4-morpholinobutanoyl]amino]-5-phenyl-pentyl]carbamate
Formula: $C_{40}H_{53}N_7O_5S_2$
MW: 776.0 g/mol
CAS-RN: 1004316-88-4
InChI Key: ZCIGNRJZKPOIKD-CQXVEOKZSA-N
InChI: InChI=1S/C40H53N7O5S2/c1-29(2)38-43-34(27-53-38)25-46(3)39(49)45-36(16-17-47-18-20-51-21-19-47)37(48)42-32(22-30-10-6-4-7-11-30)14-15-33(23-31-12-8-5-9-13-31)44-40(50)52-26-35-24-41-28-54-35/h4-13,24,27-29,32-33,36H,14-23,25-26H2,1-3H3,(H,42,48)(H,44,50)(H,45,49)/t32-,33-,36+/m1/s1

Synthesis Path

a

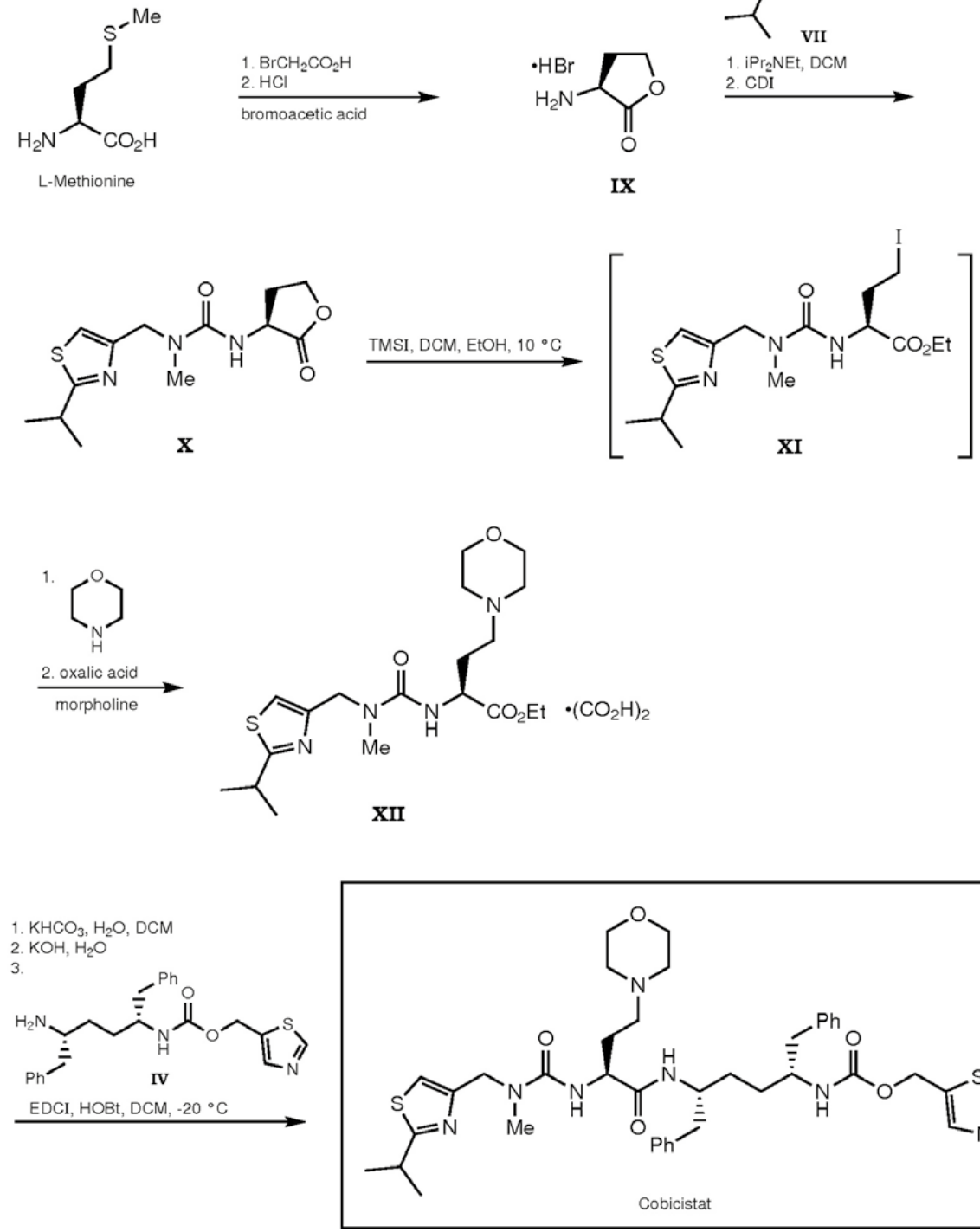


aa synthesis of V

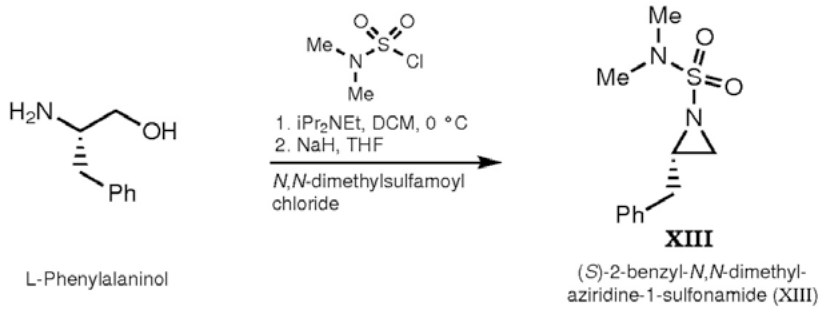


2-isopropyl-4-(methylamino-methyl)thiazole (VII) (c. f. Ritonavir)

b improved synthesis



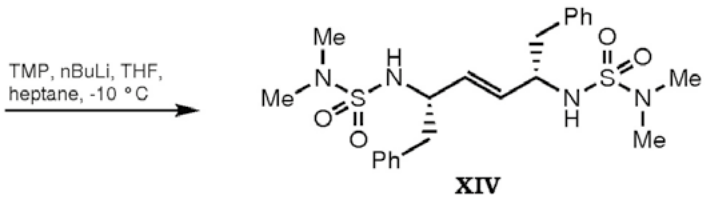
ba alternative synthesis of intermediate III



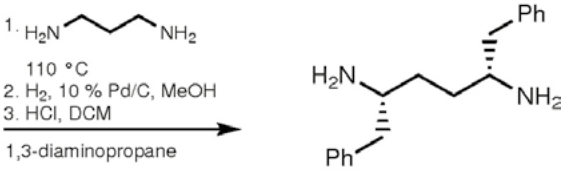
L-Phenylalaninol

XIII

(*S*)-2-benzyl-*N*,*N*-dimethyl-aziridine-1-sulfonamide (XIII)

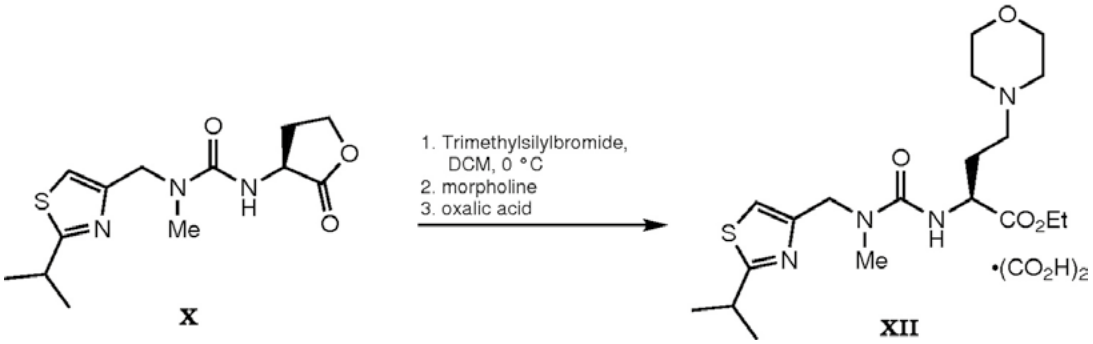


XIV



III

c alternative synthesis of XII



X

XII

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name
6372-14-1	$C_{17}H_{19}NO_3$	*N*-(benzyloxycarbonyl)-L-phenylalaninol
144163-97-3	$C_{11}H_8N_2O_5S$	5-thiazoylmethyl-4-nitrophenylcarbonate
154212-60-9	$C_8H_{14}N_2S$	2-isopropyl-4-(methylaminomethyl)thiazole
63-68-3	$C_8H_{14}N_2S$	L-Methionine
3182-95-4	$C_5H_{11}NO_2S$	L-Phenylalaninol
13360-57-1	$C_2H_6ClNO_2S$	*N*,*N*-dimethylsulfamoyl chloride
902146-43-4	$C_{11}H_{16}N_2O_2S$	(*S*)-2-benzyl-*N*,*N*-dimethylaziridine-1-sulfonamide

Trade Names

Country	Trade Name	Vendor	Annotation
USA	Tybost	Gilead Sciences, *2014*	
	Stribild	Gilead Sciences, *2012*	in combination with Elvitegravir, Emtricitabine and Tenofovir
EU	Tybost	Gilead Sciences, *2014*	
	Rezolsta	Jansen	in combination with Darunavir

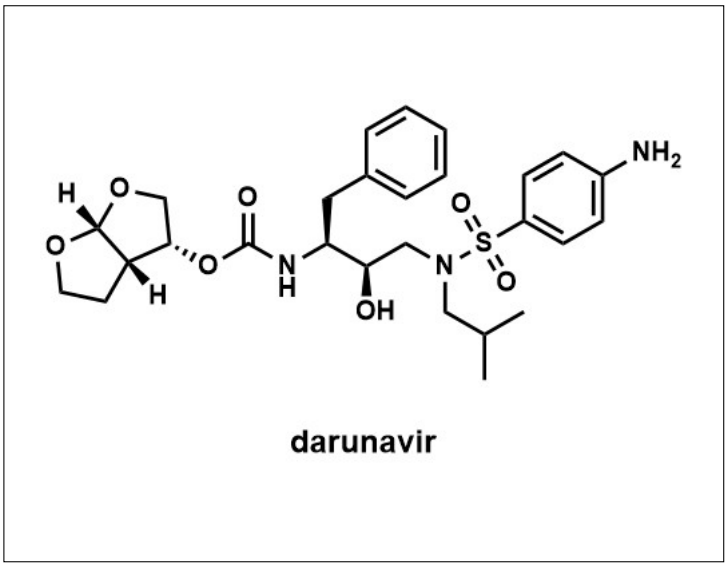
Formulations

tabs; 150 mg; tabs.; 150 mg fixed combination with 150 mg Elvitegravir, 200 mg Emtricitabine and 300 mg Tenofovir; tabs.; 150 mg in fixed combination with 800 mg Darunavir

References

b Xu, L. et al., *ACS Med. Chem. Lett.*, (2010) **1**, 209-213.
a US 8 148 374 (Gilead Sciences; 3.4.2012; appl. 22.2.2008; USA-prior. 23.2.2007).
US 8 497 396 (Gilead Sciences; 30.7.2013; appl. 1.4.2010; USA-prior. 3.4.2009).
c WO 2014 057498 (Mylan Labs.; 17.4.2014; appl. 7.10.2013; USA-prior. 8.10.2012).

Darunavir



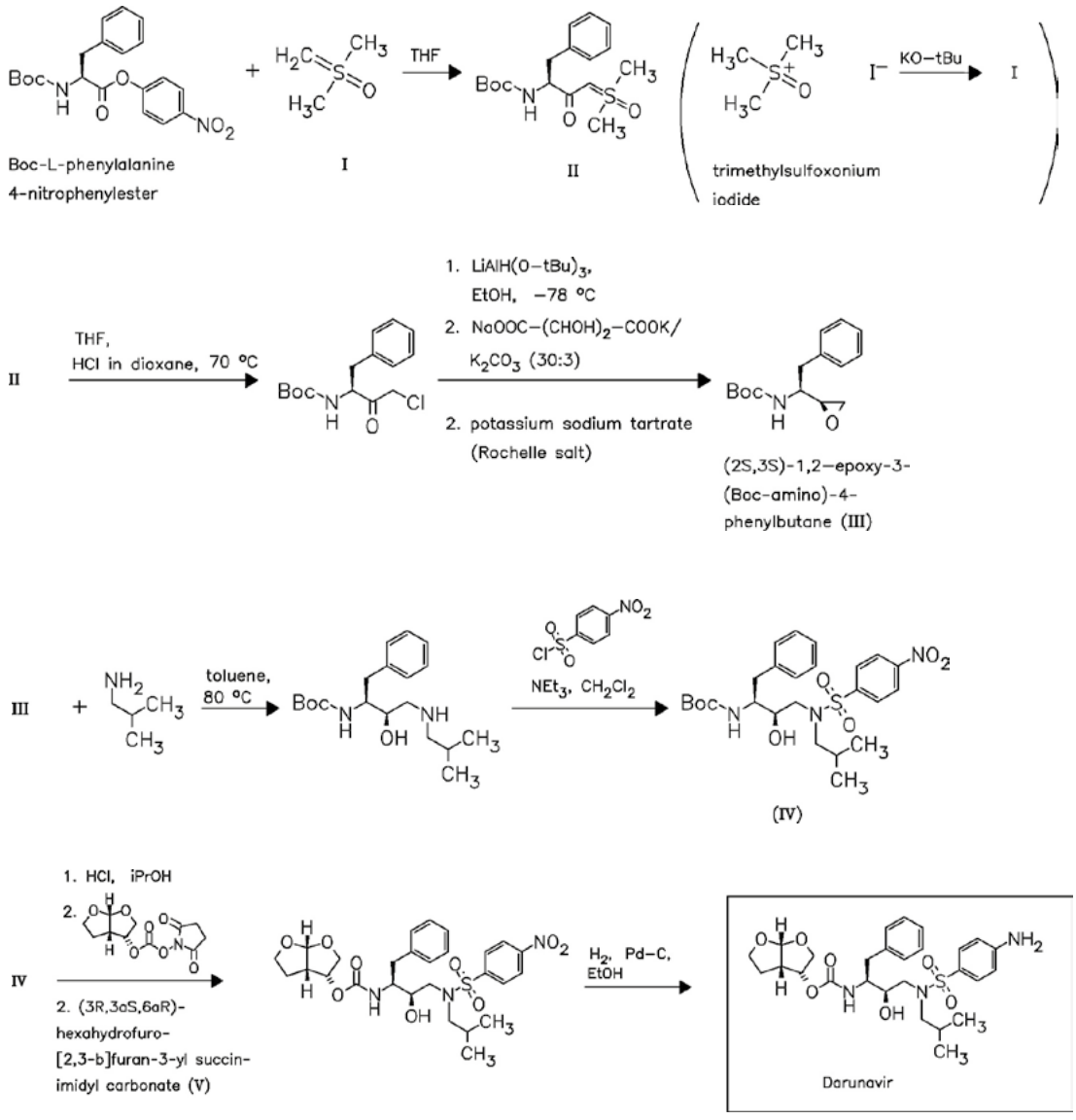
darunavir

Related reviews in Science of Synthesis

- β-Amino Alcohols
- Carbamic Acid Esters
- Arenesulfonamides
- Asymmetric Cross-Aldol Reaction for Key Intermediate

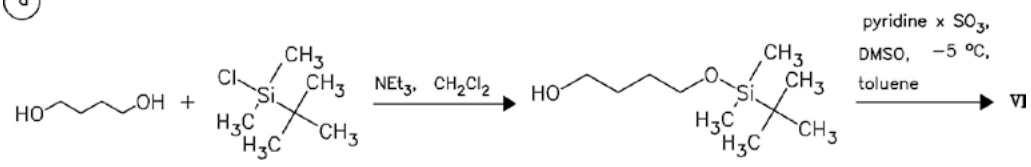
Synonyms: TMC-114, UIC-94017
ATC: J05AE10
Use: antiviral, HIV-protease inhibitor
Chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester
Formula: $C_{27}H_{37}N_3O_7S$
MW: 547.67 g/mol
CAS-RN: 206361-99-1
InChI Key: CJBJHOAVZSMMDJ-HEXNFIEUSA-N
InChI: InChI=1S/C27H37N3O7S/c1-18(2)15-30(38(33,34)21-10-8-20(28)9-11-21)16-24(31)23(14-19-6-4-3-5-7-19)29-27(32)37-25-17-36-26-22(25)12-13-35-26/h3-11,18,22-26,31H,12-17,28H2,1-2H3,(H,29,32)/t22-,23-,24+,25-,26+/m0/s1

Synthesis Path

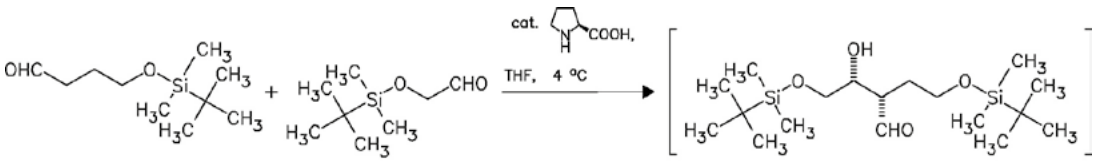


preparation of V

a



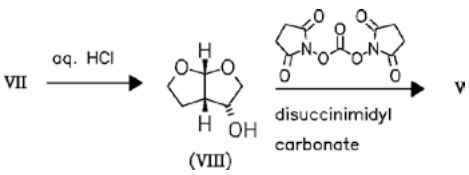
1,4-butanediol



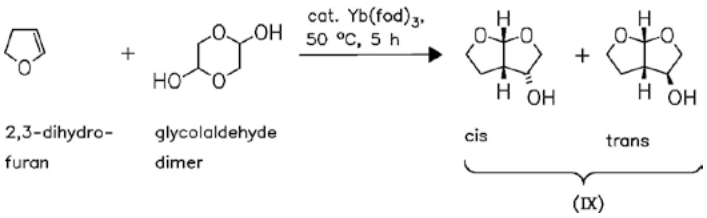
4-(tert-butyldimethylsilyloxy)-butyraldehyde (VI)

(tert-butyldimethylsilyloxy)-acetaldehyde

major diastereomer (VII)

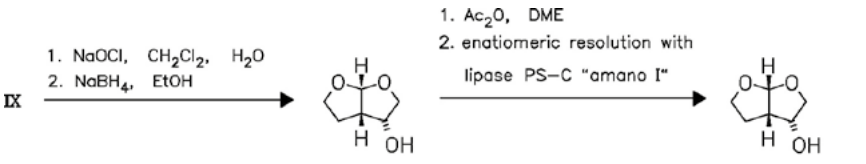


b Gilead's route



2,3-dihydro-furan

glycolaldehyde dimer



cis-rac

(3R,3aS,6aR)-hexahydrofuro-[2,3-b]furan-3-ol (VIII)

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
7535-56-0	$C_{20}H_{22}N_2O_6$	Boc-L-phenylalanine 4-nitrophenyl ester	
110-63-4	$C_4H_{10}O_2$	1,4-butanediol	1,4-Butanediol
18162-48-6	$C_6H_{15}ClSi$	*tert*-butyldimethylsilyl chloride	Silane, chloro(1,1-dimethylethyl)dimethyl-
102191-92-4	$C_8H_{18}OSi$	(*tert*-butyldimethylsilyloxy)acetaldehyde	
87184-81-4	$C_{10}H_{22}OSi$	4-(*tert*-butyldimethylsilyloxy)butyraldehyde	
160232-08-6	$C_{19}H_{32}N_2O_3$	*tert*-butyl [(1*S*,2*R*)-2-hydroxy-3-[(2-methylpropyl)amino]-1-(phenylmethyl)propyl]carbamate	Carbamic acid, [(1S,2R)-2-hydroxy-3-[(2-methylpropyl)amino]-1-(phenylmethyl)propyl]-, 1,1-dimethylethyl ester
191226-98-9	$C_{25}H_{35}N_3O_7S$	*tert*-butyl [(1*S*,2*R*)-2-hydroxy-3-[(2-methylpropyl)[(4-nitrophenyl)sulfonyl]amino]-1-(phenylmethyl)propyl]carbamate	Carbamic acid, [(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[(4-nitrophenyl)sulfonyl]amino]-1-(phenylmethyl)propyl]-, 1,1-dimethylethyl ester
74124-79-1	$C_9H_8N_2O_7$	1,1'-[carbonylbis(oxy)]bis[2,5-pyrrolidinedione]	
1191-99-7	C_4H_6O	2,3-dihydrofuran	Furan, 2,3-dihydro-
	$C_{17}H_{25}NO_4S$	[(3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-oxo-4-phenylbutylidene]dimethyloxosulfur(VI)	
102123-74-0	$C_{15}H_{20}ClNO_3$	1,1-dimethylethyl [(1*S*)-3-chloro-2-oxo-1-(phenylmethyl)propyl]carbamate	
87184-99-4	$C_{10}H_{24}OSi$	4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-butanol	
	$C_{15}H_{19}NO_3$	1,1-dimethylethyl [(1*S*)-1-[(1*S*)-oxiranyl]-2-phenylethyl]carbamate	
5367-24-8	C_3H_8OS	dimethylsulfoxonium methylide	
	$C_{11}H_{13}NO_7$	(2,5-dioxopyrrolidin-1-yl) [(3*R*,3a*R*,6a*R*)-hexahydrofuro[2,3-*b*]furan-2-yl] carbonate	
23147-58-2	$C_4H_8O_2$	glycolaldehyde dimer	
156928-09-5	$C_6H_{10}O_3$	(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol	
	$C_6H_{10}O_3$	*rel*-(3*R*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-3-ol	
	$C_6H_{10}O_3$	*rel*-(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol	
	$C_{27}H_{35}N_3O_9S$	(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl [(1*S*,2*R*)-2-hydroxy-3-[(2-methylpropyl)[(4-nitrophenyl)sulfonyl]amino]-1-(phenylmethyl)propyl]carbamate	
	$C_{18}H_{40}O_4Si_2$	(2*S*,3*R*)-3-hydroxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]butanal	
78-81-9	$C_4H_{11}N$	isobutylamine	1-Propanamine, 2-methyl-
98-74-8	$C_6H_4ClNO_4S$	4-nitrobenzenesulfonyl chloride	Benzenesulfonyl chloride, 4-nitro-
18162-48-6	$C_6H_{15}ClSi$	TBDMS chloride	Silane, chloro(1,1-dimethylethyl)dimethyl-
18162-48-6	$C_6H_{15}ClSi$	TBDMS-Cl	Silane, chloro(1,1-dimethylethyl)dimethyl-
1774-47-6	C_3H_9IOS	trimethylsulfoxonium iodide	Sulfoxonium, trimethyl-, iodide

Trade Names

Country	Trade Name	Vendor
D	Prezista	Janssen-Cilag, 2007
I	Prezista	Janssen-Cilag, 2007
USA	Prezista	Tibotec, 2006

Formulations

tabl. 75 mg, 300 mg, 400 mg, 600 mg

References

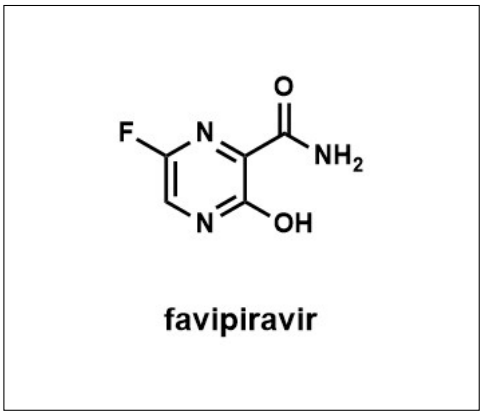
Ghosh, A. K. et al.: J. Org. Chem. (JOCEAH) **69**, 23, 7822 (2004).
Surleraux, D. L. N. G. et al.: J. Med. Chem. (JMCMAR) **48**, 1813 (2005).
Gosh, A. K. et al.: J. Med. Chem. (JMCMAR) **49**, 5252 (2006).
EP 17 255 566 (Tibotec; 14.7.2005; EP-prior. 23.12.2003).

***preparation of* V:**

b Yu, R. H. et al.: Org. Process Res. Dev. (OPRDFK) **11**, 972 (2007).
Kesteleyn, B. R. R. et al.: Org. Lett. (ORLEF7) **7**, 5912 (2005).
Ghosh, A. K.; Li, J.; Perali, R. S.: Synthesis (SYNTBF) **18**, 3015 (2006).
Ghosh, A. K. et al.: Tetrahedron Lett. (TELEAY) **36**, 4, 505 (1995).

a WO 2 008 034 598 (DSM IP Asseto; 27.3.2008; EP-prior. 19.9.2006).
EP 1 999 133 (GILEAD Sciences; 11.8.2007; USA-prior. 29.3.2006).
US 7 468 448 (Sumitomo Chemical Comp.; 23.12.2008; J-prior. 22.7.2002).
US 6 919 465 (The Board of Trustees of the University of Illinois; 19.7.2005; USA-prior. 9.10.2002).
US 7 145 024 (SmithKline Beecham; USA-prior. 20.9.2001; 5.12.2006).

Favipiravir



favipiravir

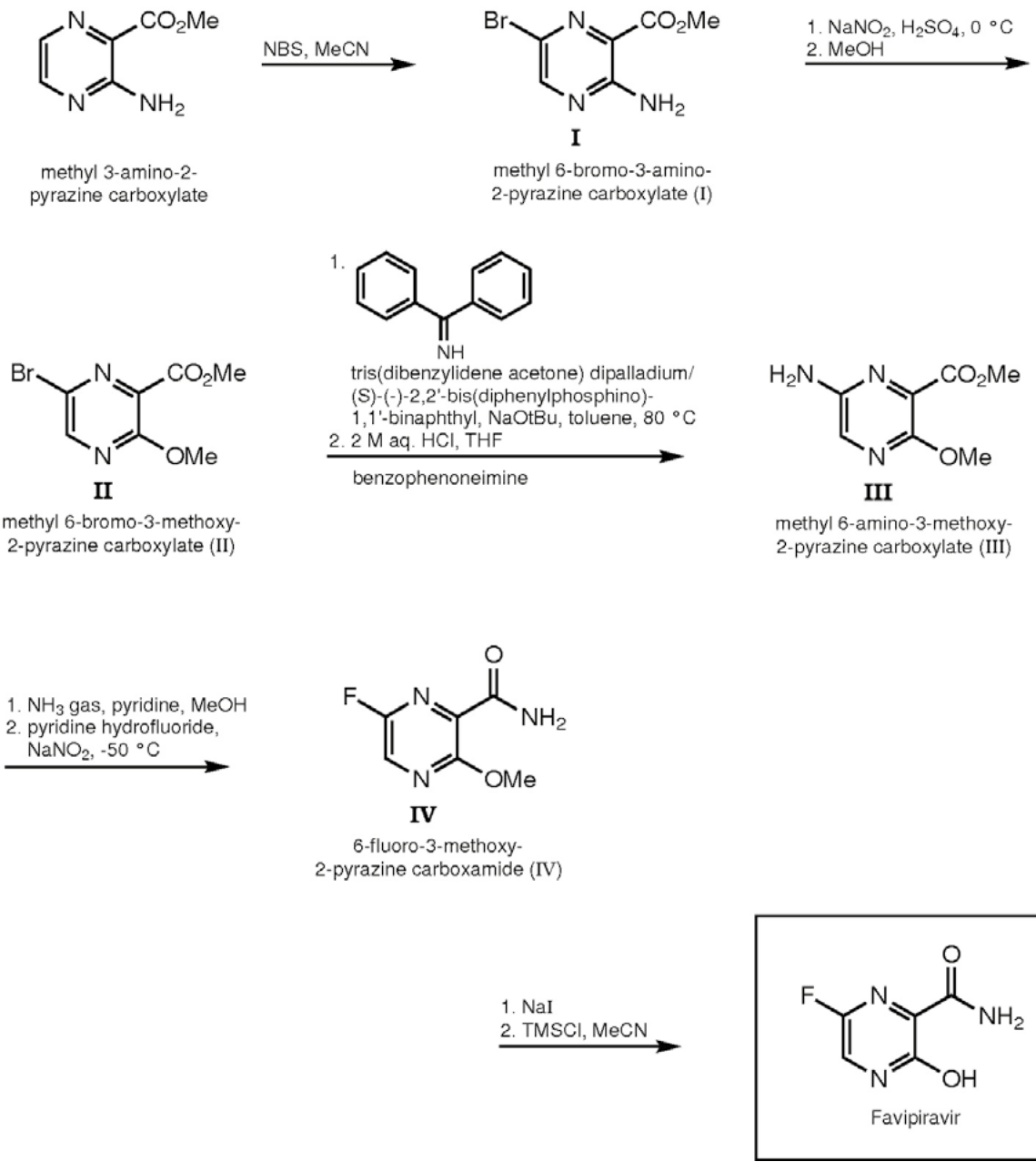
Related reviews in Science of Synthesis

- Pyrazines
- Amides
- Bromination of Pyrazinamines Using NBS
- Fluorination with Hydrogen Fluoride/Pyridine Mixtures

Synonyms: T-705
ATC: -
Use: antiviral; RNA Polymerase (NS5B) inhibitor; anti-Influenza
Chemical name: 5-Fluoro-2-oxo-1*H*-pyrazine-3-carboxamide
Formula: $C_5H_4FN_3O_2$
MW: 157.1 g/mol
CAS-RN: 259793-96-9
InChI Key: ZCGNOVWYSGBHAU-UHFFFAOYSA-N
InChI: InChI=1S/C5H4FN3O2/c6-2-1-8-5(11)3(9-2)4(7)10/h1H,(H2,7,10)(H,8,11)

Synthesis Path

a



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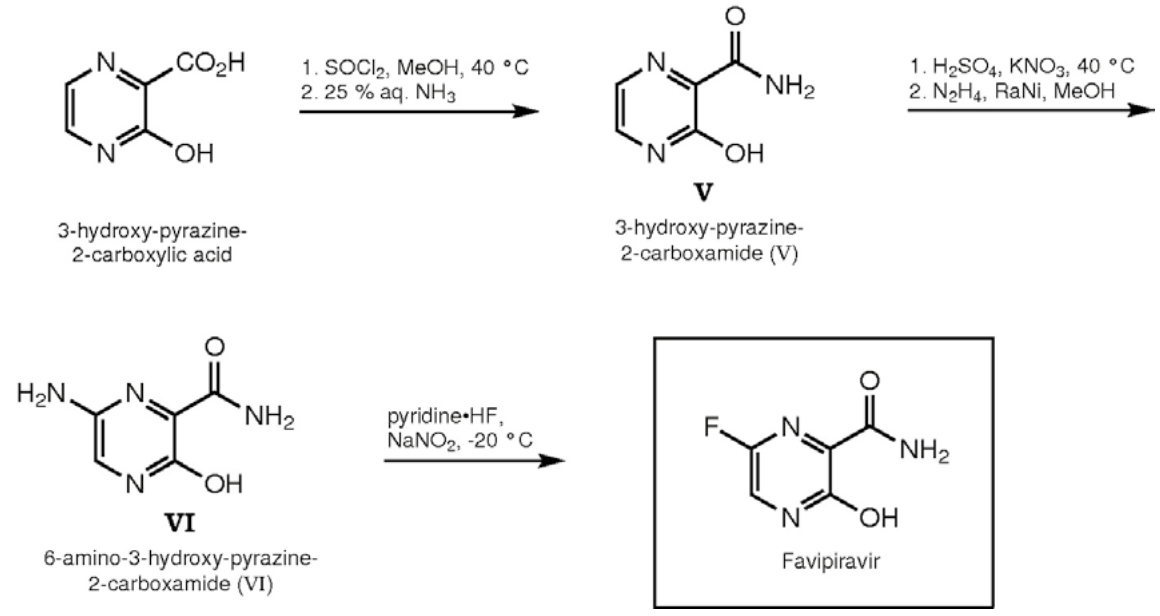


Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name
16298-03-6	$C_6H_7N_3O_2$	methyl 3-amino-2-pyrazine carboxylate
6966-01-4	$C_6H_6N_3O_2$	methyl 6-bromo-3-amino-2-pyrazine carboxylate
259794-06-4	$C_7H_7BrN_2O_3$	methyl 6-bromo-3-methoxy-2-pyrazine carboxylate
259794-07-5	$C_7H_9N_3O_3$	methyl 6-amino-3-methoxy-2-pyrazine carboxylate
259794-09-7	$C_6H_6FN_3O_2$	6-fluoro-3-methoxy-2-pyrazine carboxamide
20737-42-2	$C_5H_4N_2O_3$	3-hydroxy-pyrazine-2-carboxylic acid
55321-99-8	$C_5H_5N_3O_2$	3-hydroxy-pyrazine-2-carboxamide
1413942-41-2	$C_5H_6N_4O_2$	6-amino-3-hydroxy-pyrazine-2-carboxamide

Trade Names

Country	Trade Name	Vendor
J	AVIGAN	Toyama Chemical, *2014*

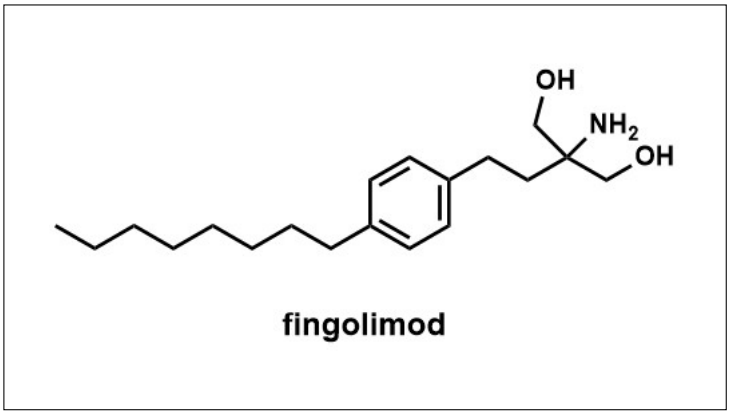
Formulations

tabs.; 200 mg

References

Furuta, Y. et al., *Antiviral Research*, (2009) **82**, 95-102.
b Shi, F. et al., *Drug Discoveries Therapeutics*, (2014) **8**(3), 117-120.
a EP 1 112 743 (Toyama Chemical; 4.7.2001; appl. 18.8.1999; JP-Prior. 20.8.1998).

Fingolimod



fingolimod

Related reviews in Science of Synthesis

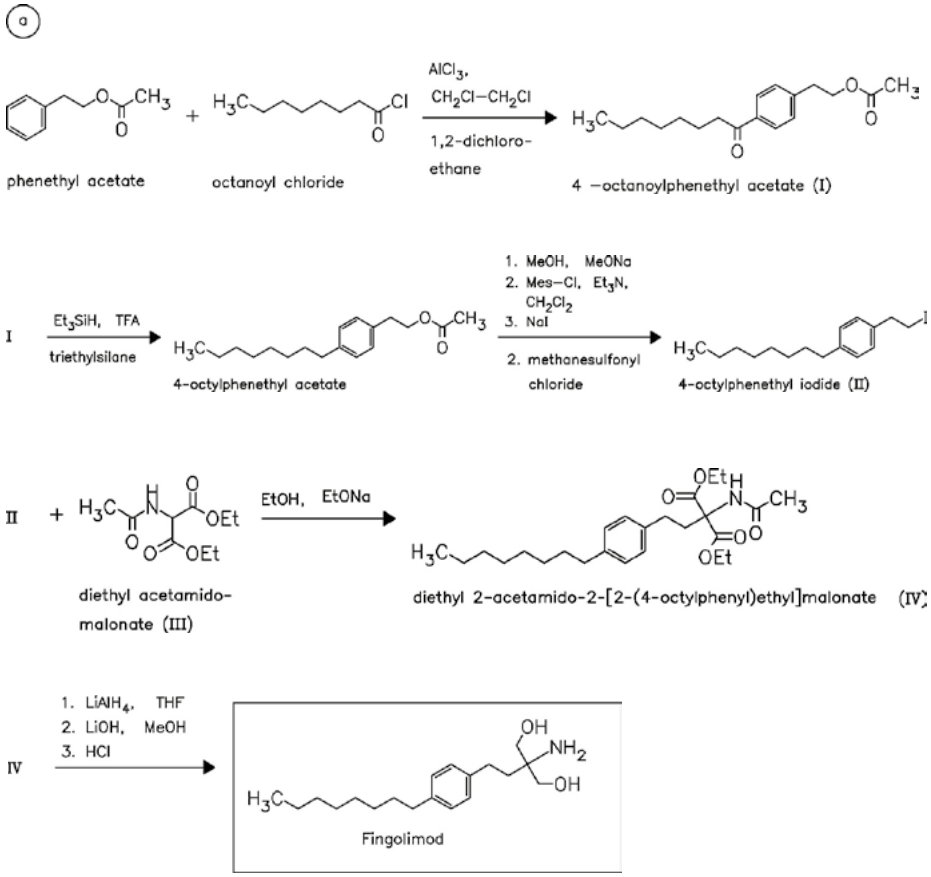
- β-Amino Alcohols
- 1,3-Diols
- Alkylarenes
- Friedel–Crafts Acylation
- Reduction of Aryl Alkyl Ketones Using Organosilanes
- Kumada Cross-Coupling Reactions

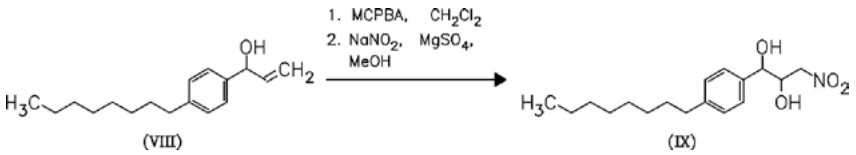
Synonyms: FTY-720
ATC: L04AA27
Use: Immunomodulator
Chemical name: 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol
Formula: $C_{19}H_{33}NO_2$
MW: 307.48 g/mol
CAS-RN: 162359-55-9
InChI Key: KKGQTZUTZRNORY-UHFFFAOYSA-N
InChI: InChI=1S/C19H33NO2/c1-2-3-4-5-6-7-8-17-9-11-18(12-10-17)13-14-19(20,15-21)16-22/h9-12,21-22H,2-8,13-16,20H2,1H3

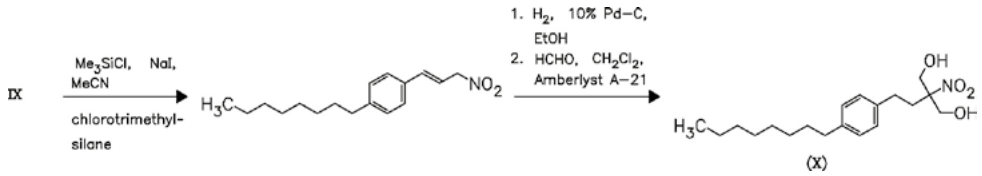
Derivatives

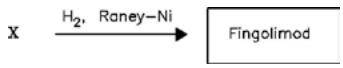
hydrochloride
Formula: $C_{19}H_{33}NO_2 \cdot HCl$
MW: 343.94 g/mol
CAS-RN: 162359-56-0

Synthesis Path

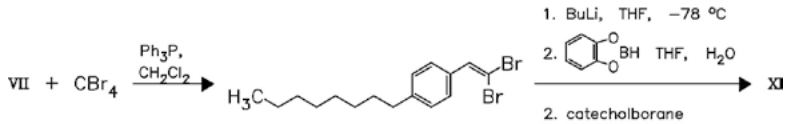


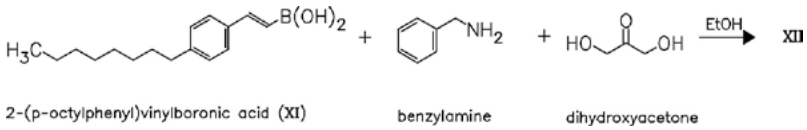




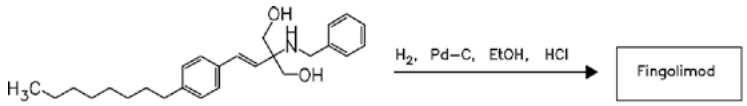


d



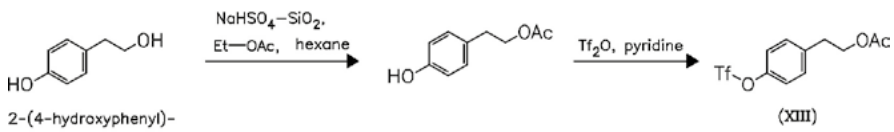


2-(p-octylphenyl)vinylboronic acid (XI) benzylamine dihydroxyacetone

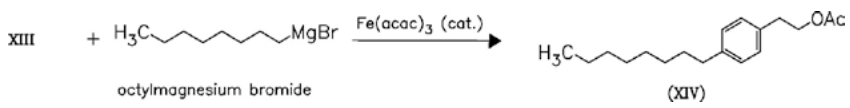


(E)-2-benzylamino-2-[2-(4-octylphenyl)-ethenyl]propane-1,3-diol (XII)

e



2-(4-hydroxyphenyl)-



octylmagnesium bromide

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
	$C_{11}H_{11}F_3O_5S$	4-[2-(acetyloxy)ethyl]phenyl trifluoromethanesulfonate	
100-46-9	C_7H_9N	benzylamine	Benzenemethanamine
	$C_{26}H_{39}NO_2$	(*E*)-2-benzylamino-2-[2-(4-octylphenyl)ethenyl]-propane-1,3-diol	
22118-09-8	C_2H_2BrClO	bromoacetyl chloride	Acetyl chloride, bromo-
	$C_{16}H_{23}BrO$	2-bromo-1-(4-octylphenyl)-1-ethanone	
104-88-1	C_7H_5ClO	4-chlorobenzaldehyde	Benzaldehyde, 4-chloro-
	$C_{16}H_{22}Br_2$	2-(2,2-dibromoethenyl)-4-octylbenzene	
1068-90-2	$C_9H_{15}NO_5$	diethyl acetamidomalonate	Propanedioic acid, (acetylamino)-, diethyl ester
	$C_{25}H_{39}NO_5$	diethyl (acetylamino)[2-(4-octylphenyl)ethyl]malonate	
	$C_{24}H_{37}NO_6$	diethyl 2-(acetylamino)-2-[4-(octylphenyl)-2-oxoethyl]propanedioate	
96-26-4	$C_3H_6O_3$	1,3-dihydroxyacetone	2-Propanone, 1,3-dihydroxy-
	$C_{17}H_{26}O$	α-ethenyl-4-octylbenzenemethanol	
141-78-6	$C_4H_8O_2$	ethyl acetate	Acetic acid ethyl ester
50-00-0	CH_2O	formaldehyde	Formaldehyde
58556-55-1	$C_{10}H_{12}O_3$	4-hydroxbenzenethanol α-acetate	
501-94-0	$C_8H_{10}O_2$	2-(4-hydroxyphenyl)ethanol	
374077-88-0	$C_{19}H_{31}NO_4$	2-nitro-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol	
374077-82-4	$C_{17}H_{27}NO_4$	3-nitro-1-(4-octylphenyl)-1,2-propanediol	
374077-86-8	$C_{17}H_{25}NO_2$	1-(3-nitro-1-propenyl)-4-octylbenzene	
111-64-8	$C_8H_{15}ClO$	octanoyl chloride	Octanoyl chloride
	$C_{18}H_{26}O_3$	4-octanoylphenethyl acetate	
49763-66-8	$C_{15}H_{22}O$	4-octylbenzaldehyde	
	$C_{18}H_{28}O_2$	4-octylbenzeneethanol acetate	
17049-49-9	$C_8H_{17}BrMg$	octylmagnesium bromide	
	$C_{18}H_{28}O_2$	4-octylphenethyl acetate	
	$C_{16}H_{25}I$	4-octylphenethyl iodide	
	$C_{16}H_{25}BO_2$	[2-(4-octylphenyl)ethenyl]boronic acid	
	$C_8H_{17}IZn$	octylzinc iodide	
103-45-7	$C_{10}H_{12}O_2$	phenethyl acetate	
2189-60-8	$C_{14}H_{22}$	phenylocatane	
558-13-4	CBr_4	tetrabromomethane	
3536-96-7	C_2H_3ClMg	vinylmagnesium chloride	Magnesium, chloroethenyl-

Trade Names

Country	Trade Name	Vendor
USA	Gilenia	Novartis, 2010

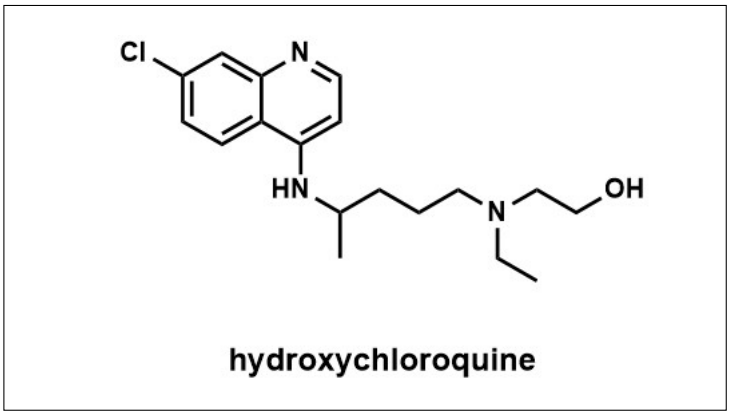
Formulations

cps. 0,5 mg

References

Adachi, K. et al.: Bioorg. Med. Chem. Lett. (BMCLE8) **5**, 847 (1995).
Adachi, K. et al.: Bioorg. Med. Chem. Lett. (BMCLE8) **5**, 853 (1995).
Kiuchi, M. et al.: J. Med. Chem. (JMCMAR) **43**, 2946-2961 (2000).
b Durand, P. et al.: Synthesis (SYNTBF) **4**, 505-506 (2000).
c Kalita, B. et al.: Synlett (SYNLES) **9**, 1411-1414 (2001).
d Sugiyama, S. et al.: Chem. Pharm. Bull. (CPBTAL) **53**, 100-102 (2005).
e Seidel, G. et al.: J. Org. Chem. (JOCEAH) **69**, 3950-3952 (2004).
a EP 0 627 406 (Yoshitomi Pharm.; 28.4.1994; appl. 18.10.1993; J-prior. 21.10.1992).
for chiral analogues see:
Hinterding, K. et al.: Tetrahedron Lett. (TELEAY) **43**. 8095-8097 (2002).
Zhu, R. et al.: J. Med. Chem. (JMCMAR) **50**, 6428-6435 (2007).
use of 1,3-propanediol derivatives:
US 6 486 209 (Novartis AG; 26.11.2002; appl. 3.7.2001; GB-prior. 19.11.1996).

Hydroxychloroquine



hydroxychloroquine

Related reviews in Science of Synthesis

- β-Amino Alcohols
- Quinolines
- Quinolinamines
- Reductive Amination of Carbonyl Compounds

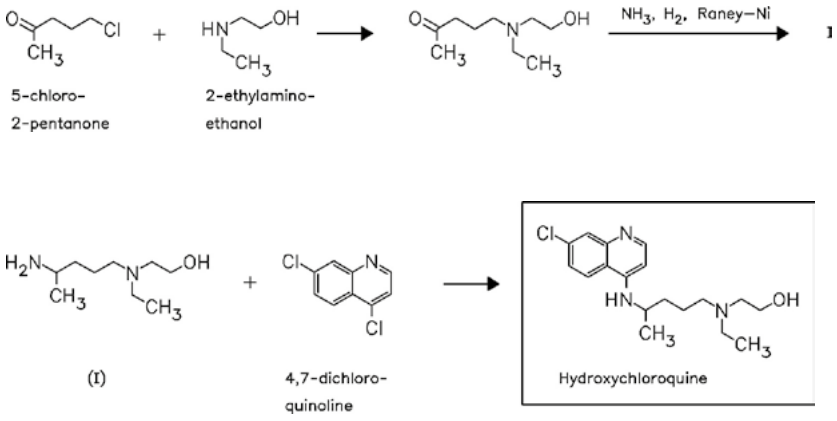
ATC: P01BA02
Use: antirheumatic, antimalarial
Chemical name: 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol
Formula: $C_{18}H_{26}ClN_3O$
MW: 335.88 g/mol
CAS-RN: 118-42-3
InChI Key: XXSMGPRMXLTPCZ-UHFFFAOYSA-N
InChI: InChI=1S/C18H26ClN3O/c1-3-22(11-12-23)10-4-5-14(2)21-17-8-9-20-18-13-15(19)6-7-16(17)18/h6-9,13-14,23H,3-5,10-12H2,1-2H3,(H,20,21)
EINECS: 204-249-8
LD50: 1240 mg/kg (M, p.o.)

Derivatives

sulfate (1:1)
Formula: $C_{18}H_{26}ClN_3O \cdot H_2SO_4$
MW: 433.96 g/mol
CAS-RN: 747-36-4
EINECS: 212-019-3

phosphate (1:2)
Formula: $C_{18}H_{26}ClN_3O \cdot 2H_3PO_4$
MW: 531.87 g/mol
CAS-RN: 6168-85-0

Synthesis Path



Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
69559-11-1	$C_9H_{22}N_2O$	2-[(4-aminopentyl)ethylamino]ethanol	Ethanol, 2-[(4-aminopentyl)ethylamino]-
5891-21-4	C_5H_9ClO	5-chloro-2-pentanone	2-Pentanone, 5-chloro-
86-98-6	$C_9H_5Cl_2N$	4,7-dichloroquinoline	Quinoline, 4,7-dichloro-
110-73-6	$C_4H_{11}NO$	2-(ethylamino)ethanol	Ethanol, 2-(ethylamino)-
74509-79-8	$C_9H_{19}NO_2$	5-[ethyl(2-hydroxyethyl)amino]-2-pentanone	2-Pentanone, 5-[ethyl(2-hydroxyethyl)amino]-

Trade Names

Country	Trade Name	Vendor	Anno-tation
D	Quensyl	Sanofi-Aventis	
F	Plaquenil	Sanofi-Aventis	
GB	Plaquenil	Sanofi-Aventis	
I	Plaquenil	Sanofi-Aventis	
USA	Hydroxychloroquine	MylanWatson	

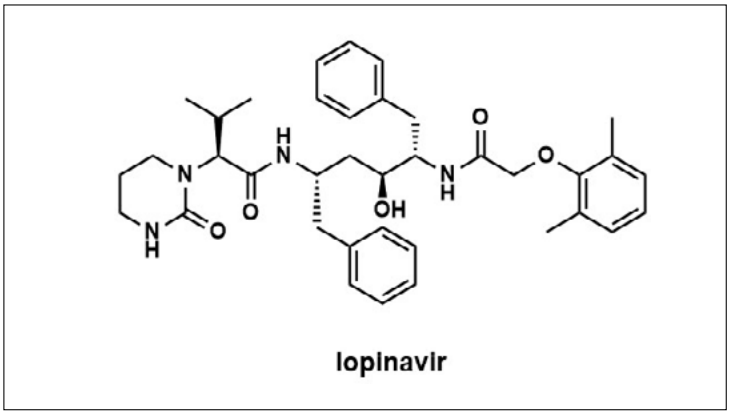
Formulations

drg. 200 mg (as hydrochloride)

References

US 2 546 658 (Sterling Drug; 1951; prior. 1949).

Lopinavir

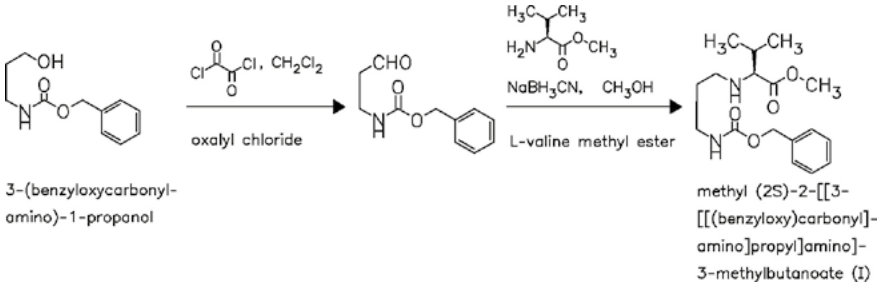


Related reviews in Science of Synthesis

- β-Amino Alcohols
- Urea Derivatives
- Reductive Amination Using Sodium Cyanoborohydride

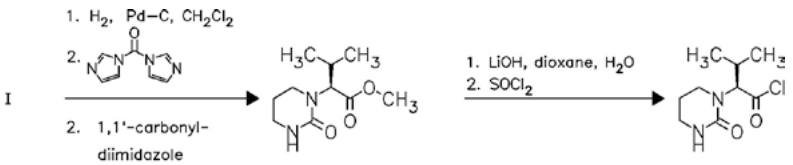
Synonyms: A-157378.0, ABT-378, Amviran, RS-346
ATC: J05AE06
Use: antiviral, AIDS therapeutic, HIV-1-protease inhibitor
Chemical name: (α*S*)-*N*-[(1*S*,3*S*,4*S*)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2*H*)-pyrimidineacetamide
Formula: $C_{37}H_{48}N_4O_5$
MW: 628.81 g/mol
CAS-RN: 192725-17-0
InChI Key: KJHKTHWMRKYKJE-SUGCFTRWSA-N
InChI: InChI=1S/C37H48N4O5/c1-25(2)34(41-20-12-19-38-37(41)45)36(44)39-30(21-28-15-7-5-8-16-28)23-32(42)31(22-29-17-9-6-10-18-29)40-33(43)24-46-35-26(3)13-11-14-27(35)4/h5-11,13-18,25,30-32,34,42H,12,19-24H2,1-4H3,(H,38,45)(H,39,44)(H,40,43)/t30-,31-,32-,34-/m0/s1

Synthesis Path

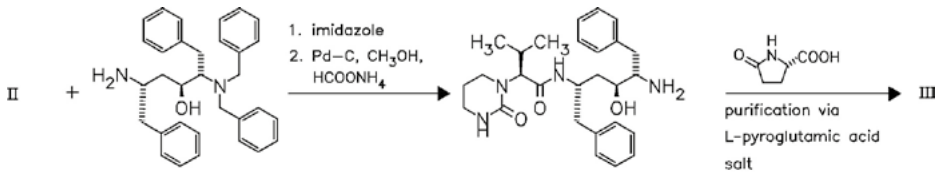


3-(benzyloxycarbonyl-amino)-1-propanol

methyl (2S)-2-[[3-[[(benzyloxy)carbonyl]-amino]propyl]amino]-3-methylbutanoate (I)

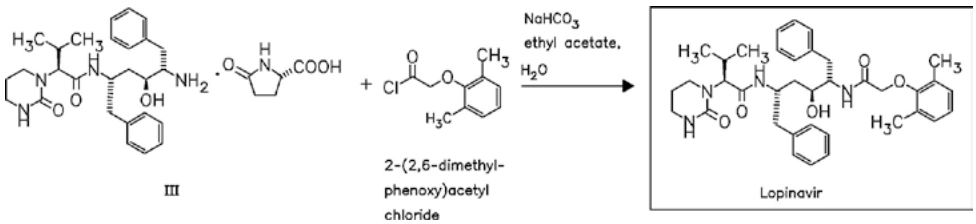


methyl (2S)-3-methyl-2-[2-oxotetrahydro-1(2H)-pyrimidinyl]-butanoate

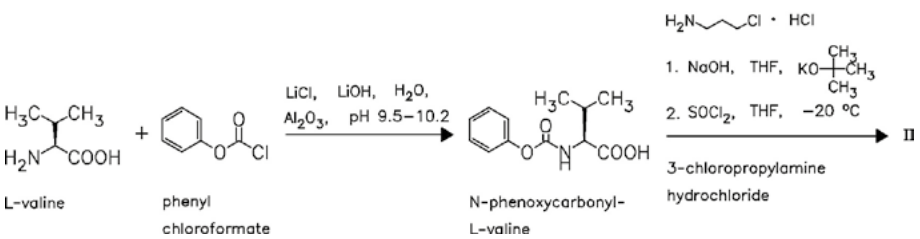


(2S,3S,5S)-5-amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (cf. ritonavir synthesis)

(2S)-N-[(1S,3S,4S)-4-amino-1-benzyl-3-hydroxy-5-phenylpentyl]-3-methyl-2-[2-oxotetrahydro-1(2H)-pyrimidinyl]-butanamide



alternative synthesis of II



L-valine

phenyl chloroformate

N-phenoxycarbonyl-L-valine

3-chloropropylamine hydrochloride

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
192726-05-9	$C_{27}H_{38}N_4O_3$	(2*S*)-*N*-[(1*S*,3*S*,4*S*)-4-amino-1-benzyl-3-hydroxy-5-phenylpentyl]-3-methyl-2-[2-oxotetrahydro-1(2*H*)-pyrimidinyl]butanamide	1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-amino-3-hydroxy-5-phenyl-1-(phenylmethyl) pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)-
156732-15-9	$C_{32}H_{36}N_2O$	(2*S*,3*S*,5*S*)-5-amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane	Benzenebutanol, γ-amino-α-[1-[bis(phenylmethyl)amino]-2-phenylethyl]-, [αS-[αR*(R*),γR*]]-
34637-22-4	$C_{11}H_{15}NO_3$	3-(benzyloxycarbonylamino)-1-propanol	Carbamic acid, (3-hydroxypropyl)-, phenylmethyl ester
6276-54-6	$C_3H_9Cl_2N$	3-chloropropylamine hydrochloride	1-Propanamine, 3-chloro-, hydrochloride
20143-48-0	$C_{10}H_{11}ClO_2$	2-(2,6-dimethylphenoxy)acetyl chloride	Acetyl chloride, (2,6-dimethylphenoxy)-
192725-83-0	$C_{17}H_{26}N_2O_4$	methyl (2*S*)-2-[[3-[[(benzyloxy)carbonyl]amino]propyl]amino]-3-methylbutanoate	L-Valine, N-[3-[[(phenylmethoxy)carbonyl]amino]propyl]-, methyl ester
192725-85-2	$C_{10}H_{18}N_2O_3$	methyl (2*S*)-3-methyl-2-[2-oxotetrahydro-1(2*H*)-pyrimidinyl]butanoate	1(2H)-Pyrimidineacetic acid, tetrahydro-α-(1-methylethyl)-2-oxo-, methyl ester, (αS)-
192726-06-0	$C_{32}H_{45}N_5O_6$	5-oxo-L-proline compd. with (α*S*)-*N*-[(1*S*,3*S*,4*S*)-4-amino-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl] tetrahydro-α-(1-methylethyl)-2-oxo-1(2*H*)pyrimidineacetamide (1:1)	L-Proline, 5-oxo-, compd. with (αS)-N-[(1S,3S,4S)-4-amino-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl] tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (1:1)
65564-05-8	$C_{11}H_{13}NO_3$	(3-oxopropyl)carbamic acid phenylmethyl ester	Carbamic acid, (3-oxopropyl)-, phenylmethyl ester
126147-70-4	$C_{12}H_{15}NO_4$	*N*-phenoxycarbonyl-L-valine	L-Valine, N-(phenoxycarbonyl)-
1885-14-9	$C_7H_5ClO_2$	phenyl chloroformate	Carbonochloridic acid, phenyl ester
98-79-3	$C_5H_7NO_3$	L-pyroglutamic acid	L-Proline, 5-oxo-
192800-77-4	$C_9H_{15}ClN_2O_2$	(α*S*)-tetrahydro-α-(1-methylethyl)-2-oxo-1(2*H*)-pyrimidineacetyl chloride	1(2H)-Pyrimidineacetyl chloride, tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)-
72-18-4	$C_5H_{11}NO_2$	L-valine	
4070-48-8	$C_6H_{13}NO_2$	L-valine methyl ester	

Trade Names

Country	Trade Name	Vendor	Annotation
D	Kaletra	Abbott	comb. with ritonavir
F	Kaletra	Abbott	
GB	Kaletra	Abbott	
I	Kaletra	Abbott	
J	Kaletra	Abbott	comb. with ritonavir
USA	Kaletra	Abbott	comb. with ritonavir

Formulations

oral sol. 80 mg/ml Lopinavir and 20 mg/ml Ritonavir; soft-gelatin cps. 133.3 mg Lopinavir and 33.3 mg Ritonavir

References

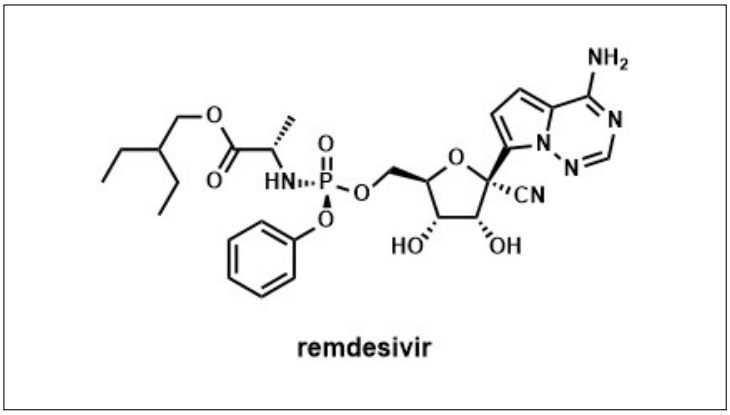
Stoner, E.J. et al.: Org. Process Res. Dev. (OPRDFK) **3** (2), 145 (1999).
US 5 914 332 (Abbott; 22.6.1999; appl. 21.11.1996; USA-prior. 13.12.1995).
US 5 635 523 (Abbott; 3.6.1997; appl. 6.4.1995; USA-prior. 23.5.1989, 8.9.1989, 22.12.1989, 9.5.1990, 20.11.1990, 15.8.1991, 23.10.1991, 29.12.1992, 2.12.1993).
US 5 541 206 (Abbott; 30.7.1996; appl. 25.4.1995; USA-prior. 23.5.1989, 8.9.1989, 22.12.1989, 9.5.1990, 20.11.1990, 15.8.1991, 23.10.1991, 29.12.1992, 2.12.1993).
US 5 674 882 (Abbott; 7.10.1997; appl. 29.3.1995; USA-prior. 23.5.1989, 8.9.1989, 22.12.1989, 9.5.1990, 20.11.1990, 15.8.1991, 23.10.1991, 29.12.1992, 2.12.1993).
US 5 886 036 (Abbott; 23.3.1999; appl. 20.3.1997; USA-prior. 29.12.1992, 2.12.1993, 28.3.1995).
US 5 846 987 (Abbott; 8.12.1998; appl. 20.3.1997; USA-prior. 29.12.1992, 2.12.1993, 6.4.1995).
US 5 648 497 (Abbott; 15.7.1997; appl. 24.3.1995; USA-prior. 23.5.1989, 8.9.1989, 22.12.1989, 9.5.1990, 20.11.1990, 15.8.1991, 23.10.1991, 14.9.1993, 23.8.1994).
WO 9 721 683 (Abbott; appl. 6.12.1996; USA-prior. 13.12.1995).
WO 9 721 685 (Abbott; appl. 6.12.1996; USA-prior. 13.12.1995).

***alternative synthesis of I*:**
Stoner, E.J. et al.: Org. Process Res. Dev. (OPRDFK) **4** (4), 264 (2000).
Chang, S.-J.; Stuk, T.L.: Synth. Commun. (SYNCAV) **30** (5), 955-961 (2000).

***solid dispersions*:**
WO 2 001 034 119 (Abbott; appl. 10.11.2000; USA-prior. 12.11.1999).

***liquid compositions*:**
US 6 232 333 (Abbott; appl. 7.11.1997; 15.5.2001).

Remdesivir



remdesivir

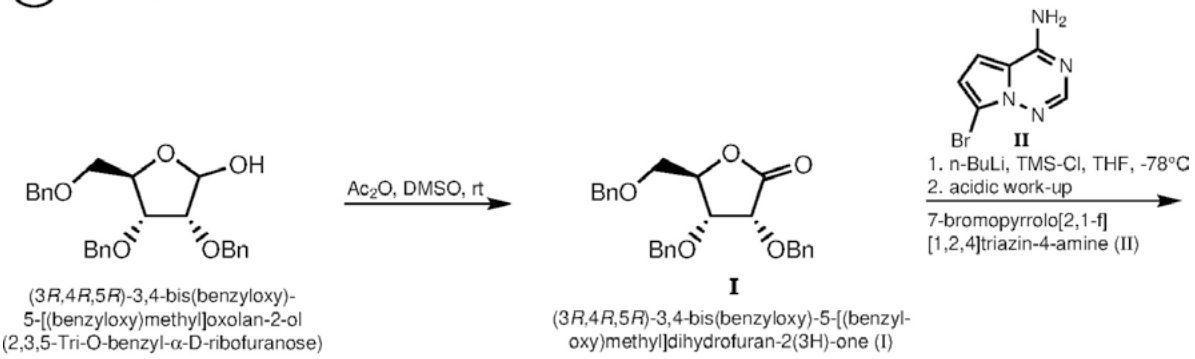
Related reviews in Science of Synthesis

- 1,2,4-Triazines
- 1,2-Diols
- Nitriles

Synonyms: GS-5734; prodrug of GS-441524
ATC: -
Use antiviral: RNA polymerase inhibitor against Ebola and Corona virus
Chem. Name: (S)-2-Ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl]-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)phenoxy)phosphoryl)amino) propanoate
Formula: $C_{27}H_{35}N_6O_8P$
MW: 602.59 g/mol
CAS-RN: 1809249-37-3

Synthesis Path

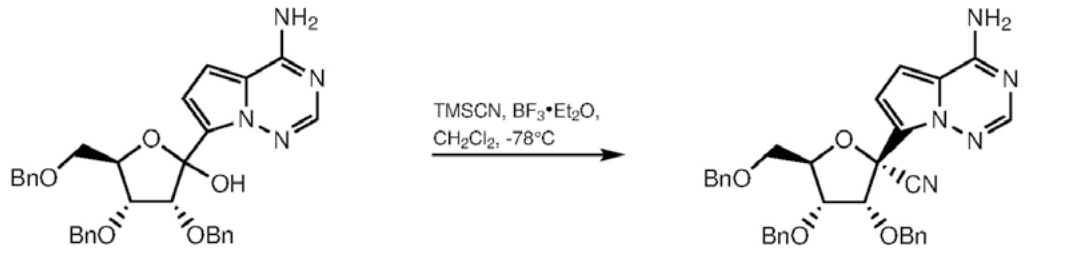
a First generation synthesis:



(3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]oxolan-2-ol (2,3,5-Tri-O-benzyl-α-D-ribofuranose)

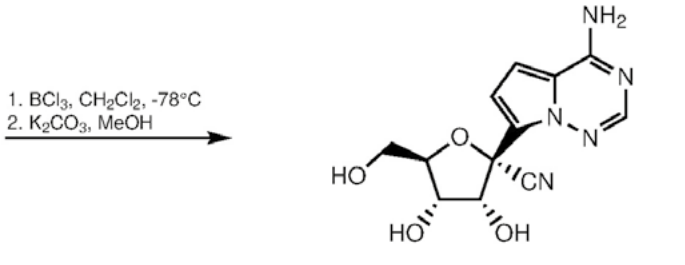
I

(3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]dihydrofuran-2(3H)-one (I)

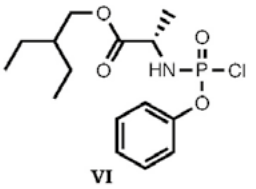


(3*R*,4*R*,5*R*)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]tetrahydrofuran-2-ol (III)

(2*R*,3*R*,4*R*,5*R*)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]tetrahydrofuran-2-carbonitrile (IV)

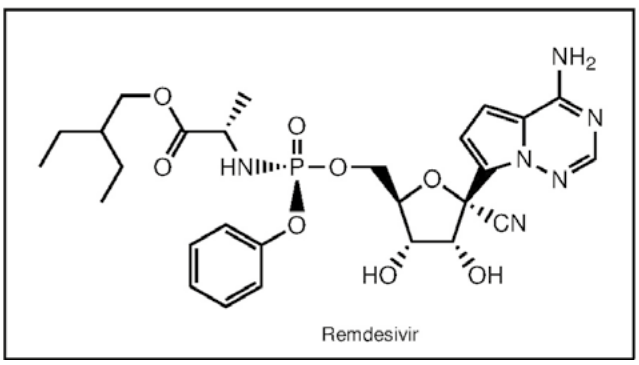


(2*R*,3*R*,4*S*,5*R*)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (V)



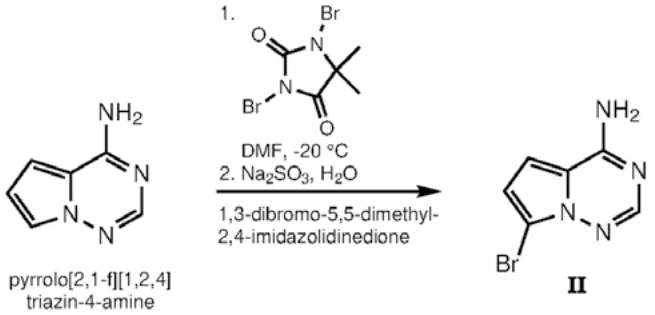
1. NMI, $OP(OMe)_3$
2. chiral HPLC

methyl imidazole, trimethyl phosphate, (2*S*)-2-ethylbutyl 2-(chloro-(phenoxy)phosphorylamino)-propanoate (VI)

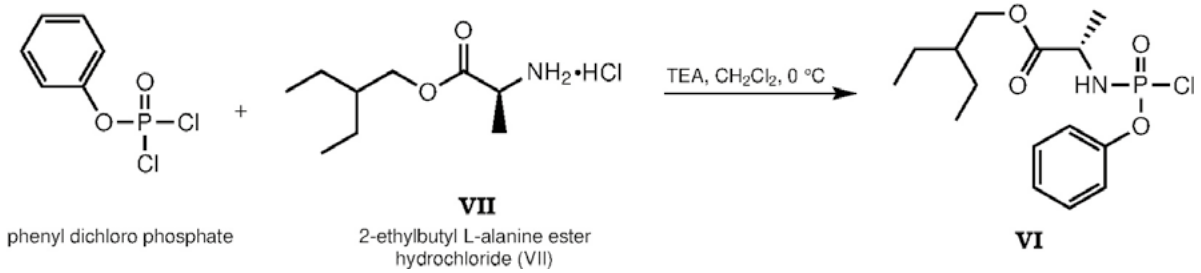


Remdesivir

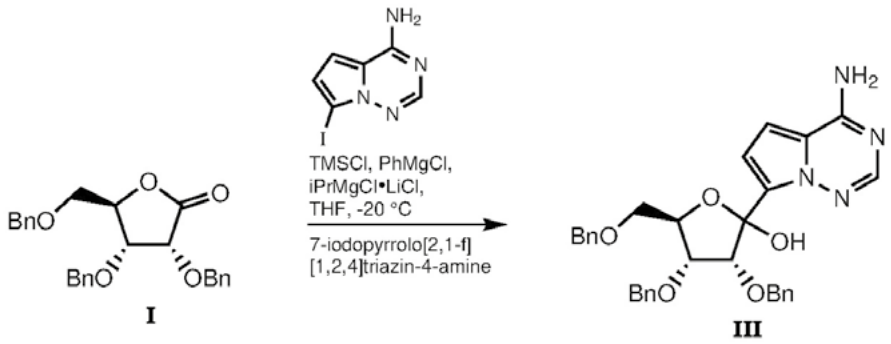
ab Synthesis of II:

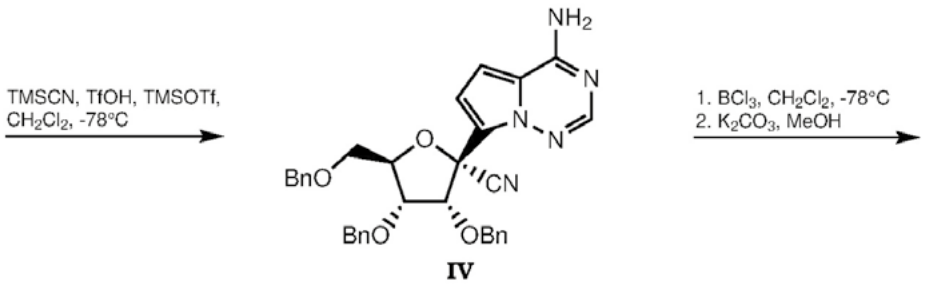


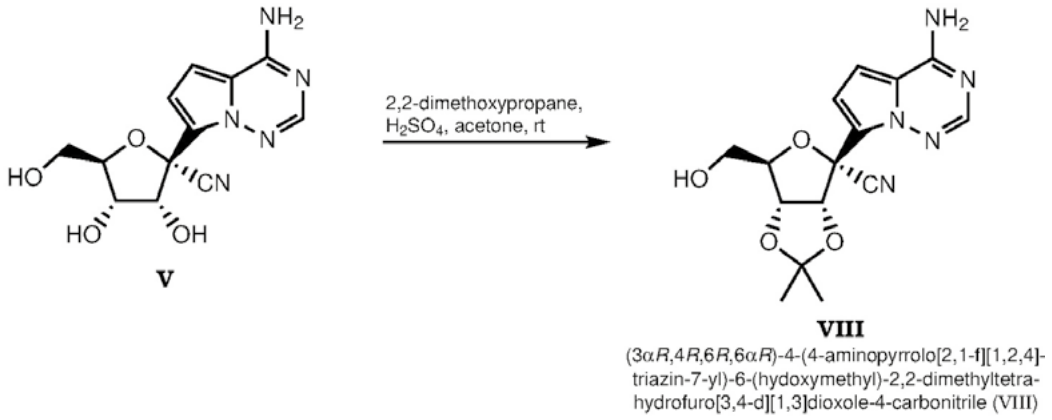
ac Synthesis of VI:

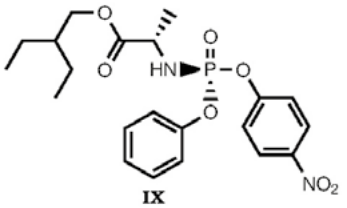


b Second generation synthesis:



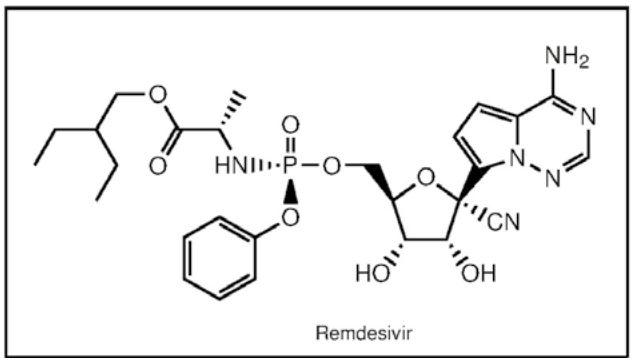






1. $MgCl_2$, DIPEA, MeCN, 50 °C
2. 37% HCl, THF, rt

2-ethylbutyl ((*S*)-(4-nitro-phenoxy)
(phenoxy)phosphoryl)-
L-alaninate (IX)



Trade Names

Country	Trade Name	Vendor	Annotation
USA			On 1 May 2020 FDA granted Gilead Sciences an Emergency Use Authorization of remdesivir to be distributed and used by licensed health care providers to treat hospitalized patients with severe COVID-19.

Formulations

vial, powder for concentrate for solution for infusion 100 mg

References

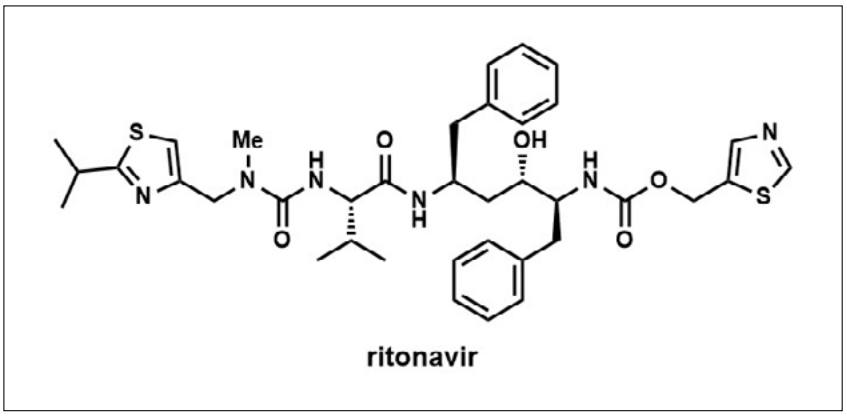
Warren, T.K. et al., Nature, (2016) 531 (7594), 381-385.
Grein, J. et al., NEJM April 10, 2020; doi 10.1056/NEJMoa 2007016.
Avataneo, V. et al., J. Antimicrob. Chemother, May 3, 2020; doi 10.1093/jac/dkaa 152.
a+b) Siegel, D. et al., J. Med. Chem., (2017) 60, 1648-1661.
US 9 724 360 (Gilead Sciences; 8.8.2017; appl. 29.10.2015; USA-prior. 29.10.2014).

Methods for treating arenaviridae and coronaviridae virus infections:
US 2017 0071964 (Gilead Sciences; 16.3.2017; appl. 16.9.2016; USA-prior. 16.9.2015).

Crystalline forms:
US 2018 346504 (Gilead Sciences; 6.12.2018; appl. 27.4.2018; USA-prior. 1.5.2017).

Compositions comprising an RNA polymerase inhibitor:
US 2019 083525 (Gilead Sciences; 21.3.2019; appl. 10.7.2018; USA-prior. 11.7.2017).

Ritonavir



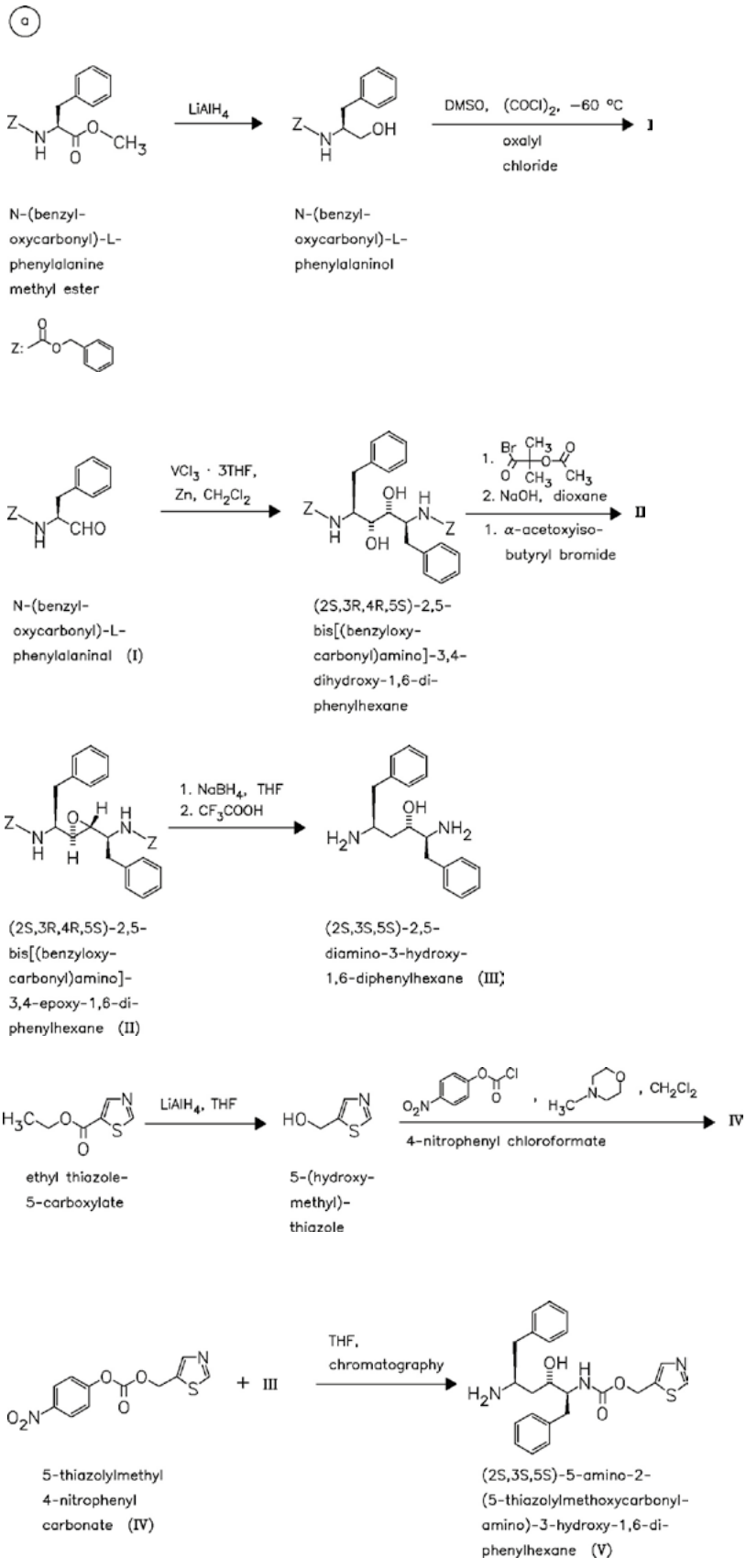
ritonavir

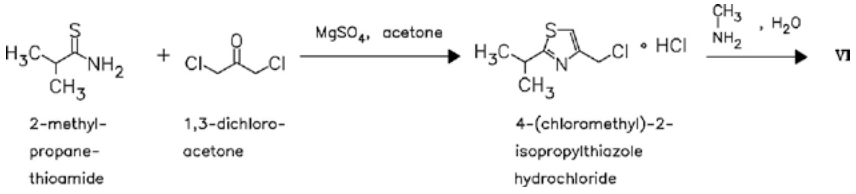
Related reviews in Science of Synthesis

- Urea Derivatives
- Thiazoles
- Carbamic Acid Esters

Synonyms: A-84538, ABT-538
ATC: J05AE03
Use: AIDS therapeutic, antiviral, HIV-1-protease inhibitor
Chemical name: [5*S*-(5*R**,8*R**,10*R**,11*R**)]-10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester
Formula: $C_{37}H_{48}N_6O_5S_2$
MW: 720.96 g/mol
CAS-RN: 155213-67-5
InChI Key: NCDNCNXCDXHOMX-XGKFQTDJSA-N
InChI: InChI=1S/C37H48N6O5S2/c1-24(2)33(42-36(46)43(5)20-29-22-49-35(40-29)25(3)4)34(45)39-28(16-26-12-8-6-9-13-26)18-32(44)31(17-27-14-10-7-11-15-27)41-37(47)48-21-30-19-38-23-50-30/h6-15,19,22-25,28,31-33,44H,16-18,20-21H2,1-5H3,(H,39,45)(H,41,47)(H,42,46)/t28-,31-,32-,33-/m0/s1

Synthesis Path

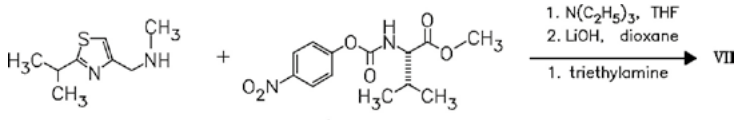




2-methyl-propane-thioamide

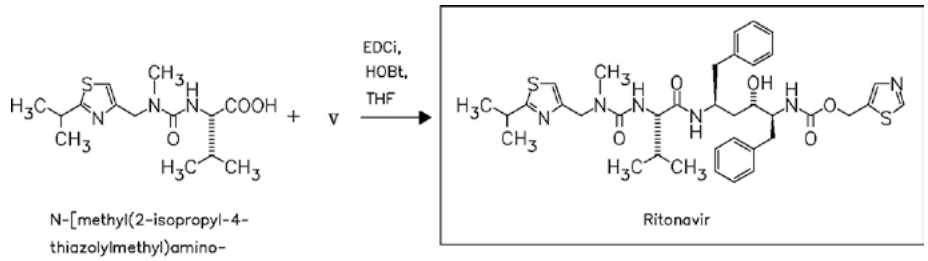
1,3-dichloro-acetone

4-(chloromethyl)-2-isopropylthiazole hydrochloride

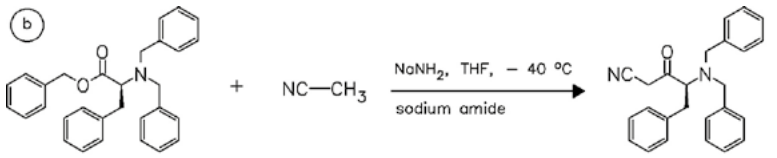


2-isopropyl-4-(methylamino-methyl)thiazole (VI)

N-(4-nitrophenyloxy-carbonyl)-L-valine methyl ester

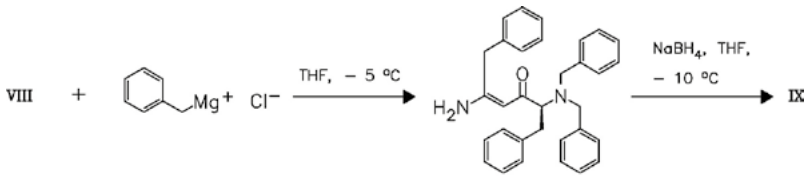


N-[methyl(2-isopropyl-4-thiazolylmethyl)amino-carbonyl]-L-valine (VII)



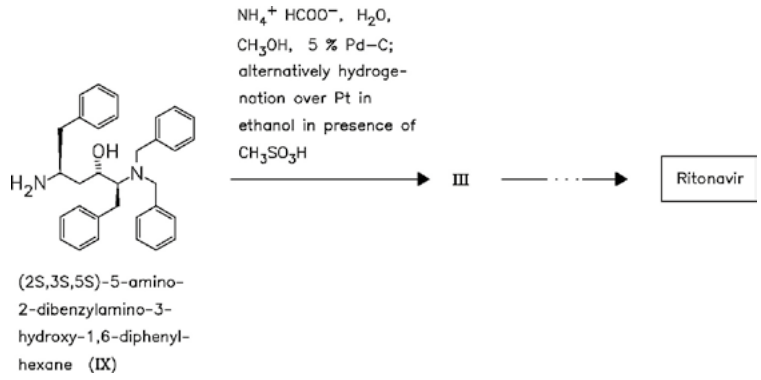
N,N-dibenzyl-L-phenylalanine benzyl ester

4(S)-dibenzylamino-3-oxo-5-phenyl-pentanenitrile (VIII)

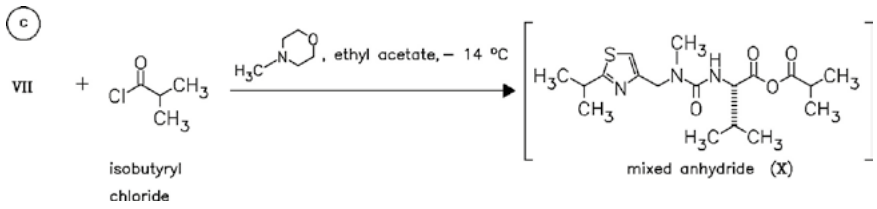


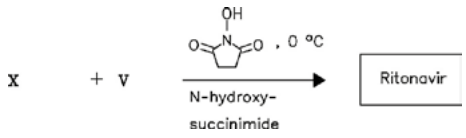
benzylmagnesium chloride

2-amino-5(S)-di-benzylamino-4-oxo-1,6-diphenyl-2-hexene



(2S,3S,5S)-5-amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (IX)





Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
75-05-8	C_2H_3N	acetonitrile	Acetonitrile
156732-15-9	$C_{32}H_{36}N_2O$	(2*S*,3*S*,5*S*)-5-amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane	Benzenebutanol, γ-amino-α-[1-[bis(phenylmethyl)amino]-2-phenylethyl]-, [αS-[αR*(R*),γR*]]-
156732-13-7	$C_{32}H_{32}N_2O$	2-amino-5(*S*)-dibenzylamino-4-oxo-1,6-diphenyl-2-hexene	4-Hexen-3-one, 5-amino-2-[bis(phenylmethyl)amino]-1,6-diphenyl-, (S)-
144164-11-4	$C_{23}H_{27}N_3O_3S$	(2*S*,3*S*,5*S*)-5-amino-2-(5-thiazolylmethoxycarbonylamino)-3-hydroxy-1,6-diphenylhexane	Carbamic acid, [4-amino-2-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]-, 5-thiazolylmethyl ester, [1S-(1R*,2R*,4R*)]-
6921-34-2	C_7H_7ClMg	benzylmagnesium chloride	Magnesium, chloro(phenylmethyl)-
59830-60-3	$C_{17}H_{17}NO_3$	*N*-(benzyloxycarbonyl)-L-phenylalaninal	
35909-92-3	$C_{18}H_{19}NO_4$	*N*-(benzyloxycarbonyl)-L-phenylalanine methyl ester	
6372-14-1	$C_{17}H_{19}NO_3$	*N*-(benzyloxycarbonyl)-L-phenylalaninol	
137649-69-5	$C_{34}H_{36}N_2O_6$	(2*S*,3*R*,4*R*,5*S*)-2,5-bis[(benzyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane	
162849-92-5	$C_{34}H_{34}N_2O_5$	(2*S*,3*R*,4*R*,5*S*)-2,5-bis[(benzyloxycarbonyl)amino]-3,4-epoxy-1,6-diphenylhexane	
65386-28-9	$C_7H_{11}Cl_2NS$	4-(chloromethyl)-2-isopropylthiazole hydrochloride	Thiazole, 4-(chloromethyl)-2-(1-methylethyl)-, hydrochloride
144163-44-0	$C_{18}H_{24}N_2O$	(2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane	Benzenebutanol, γ-amino-α-(1-amino-2-phenylethyl)-, [αS-[αR*(R*),γR*]]-
156732-12-6	$C_{25}H_{24}N_2O$	4(*S*)-dibenzylamino-3-oxo-5-phenylpentanenitrile	Benzenepentanenitrile, γ-[bis(phenylmethyl)amino]-β-oxo-, (S)-
111138-83-1	$C_{30}H_{29}NO_2$	*N*,*N*-dibenzyl-L-phenylalanine benzyl ester	L-Phenylalanine, N,N-bis(phenylmethyl)-, phenylmethyl ester
534-07-6	$C_3H_4Cl_2O$	1,3-dichloroacetone	2-Propanone, 1,3-dichloro-
32955-22-9	$C_6H_7NO_2S$	ethyl thiazole-5-carboxylate	5-Thiazolecarboxylic acid, ethyl ester
38585-74-9	C_4H_5NOS	5-(hydroxymethyl)thiazole	5-Thiazolemethanol
6066-82-6	$C_4H_5NO_3$	*N*-hydroxysuccinimide	2,5-Pyrrolidinedione, 1-hydroxy-
79-30-1	C_4H_7ClO	isobutyryl chloride	Propanoyl chloride, 2-methyl-
154212-60-9	$C_8H_{14}N_2S$	2-isopropyl-4-(methylaminomethyl)thiazole	4-Thiazolemethanamine, N-methyl-2-(1-methylethyl)-
74-89-5	CH_5N	methylamine	Methanamine
154212-61-0	$C_{14}H_{23}N_3O_3S$	*N*-[methyl(2-isopropyl-4-thiazolylmethyl)aminocarbonyl]-L-valine	L-Valine, N-[[methyl[[2-(1-methylethyl)-4-thiazolyl]methyl]amino]carbonyl]-
13515-65-6	C_4H_9NS	2-methylpropanethioamide	Propanethioamide, 2-methyl-
162537-10-2	$C_{13}H_{16}N_2O_6$	*N*-[(4-nitrophenoxy)carbonyl]-L-valine methyl ester	L-Valine, N-[(4-nitrophenoxy)carbonyl]-, methyl ester
7693-46-1	$C_7H_4ClNO_4$	4-nitrophenyl chloroformate	Carbonochloridic acid, 4-nitrophenyl ester
79-37-8	$C_2Cl_2O_2$	oxalyl chloride	Ethanedioyl dichloride
144163-97-3	$C_{11}H_8N_2O_5S$	5-thiazolylmethyl 4-nitrophenyl carbonate	Carbonic acid, 4-nitrophenyl 5-thiazolylmethyl ester

Trade Names

Country	Trade Name	Vendor	Annotation
D	Kaletra	Abbott	comb.
	Norvir	Abbott	
F	Kaletra	Abbott	
	Norvir	Boehringer Ingelheim	
GB	Norvir	Abbott	
I	Kaletra	Abbott	comb.
	Norvir	Abbott	
J	Norvir	Dainabott-Dainippon	
USA	Kaletra	Abbott	comb.
	Norvir	Abbott	

Formulations

cps. 100 mg wfm; sol. 600 mg/7.5 ml, 8%

References

Kempf, D.J. et al.: J. Med. Chem. (JMCMAR) **41**, 602 (1998).
a ,**b** US 5 635 523 (Abbott; 3.6.1997; appl. 6.4.1995; USA-prior. 23.5.1989, 8.9.1989, 22.12.1989, 9.5.1990, 20.11.1990, 15.8.1991, 23.10.1991, 29.12.1992, 2.12.1993).
WO 9 414 436 (Abbott Labs.; appl. 16.12.1993; USA-prior. 29.12.1992, 2.12.1993).
b WO 9 511 224 (Abbott Labs.; appl. 26.9.1994; USA-prior. 22.10.1993, 27.7.1994).
WO 9 604 232 (Abbott Labs.; appl. 17.7.1995; USA-prior. 29.7.1994).
c US 5 567 823 (Abbott Labs; 22.10.1996; appl. 6.6.1995; USA-prior. 6.6.1995).

polymorphs:
Chemburkar, S.R. et al.: Org. Process Res. Dev. (OPRDFK) **4,** 43 (2000).

pharmaceutical composition in alcoholic/organic solvent:
WO 9 507 696 (Abbott Labs.; appl. 30.4.1994; USA-prior. 13.9.1993, 28.1.1994, 15.8.1994).
WO 9 520 384 (Abbott Labs.; appl. 3.1.1995; USA-prior. 29.7.1994, 28.1.1994, 12.5.1995).

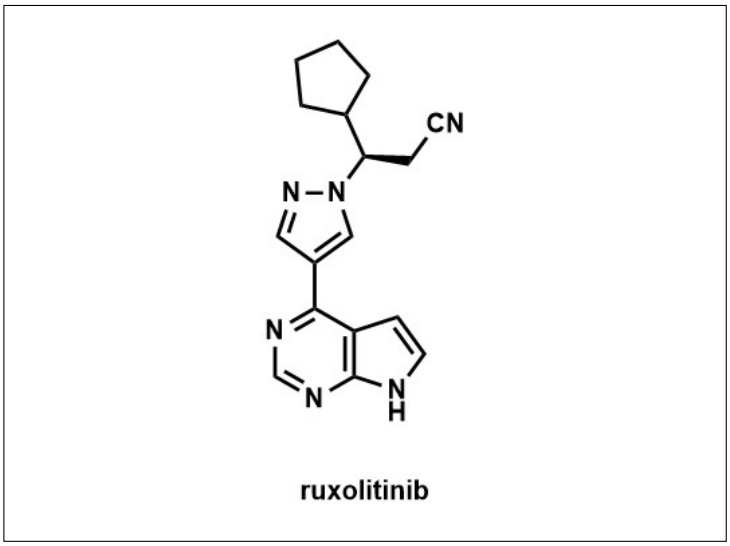
use for treating HIV:
WO 9 701 349 (Abbott Labs.; appl. 28.6.1996; USA-prior. 15.9.1995, 29.6.1995).

***combination with* lamivudine:**
WO 9 626 734 (Glaxo; appl. 22.2.1996; GB-prior. 25.2.1995).

combination of HIV protease inhibitors:
WO 9 604 913 (Merck & Co.; appl. 7.8.1995; USA-prior. 20.7.1995, 11.8.1994, 14.11.1994).
EP 691 345 (Bristol-Myers Squibb; appl. 5.7.1995; USA-prior. 17.5.1995, 5.7.1994, 31.7.1987).

pharmaceutical composition with improved oral bioavailability:
WO 9 509 614 (Abbott Labs.; appl. 9.9.1994; USA-prior. 31.8.1994).

Ruxolitinib



ruxolitinib

Related reviews in Science of Synthesis

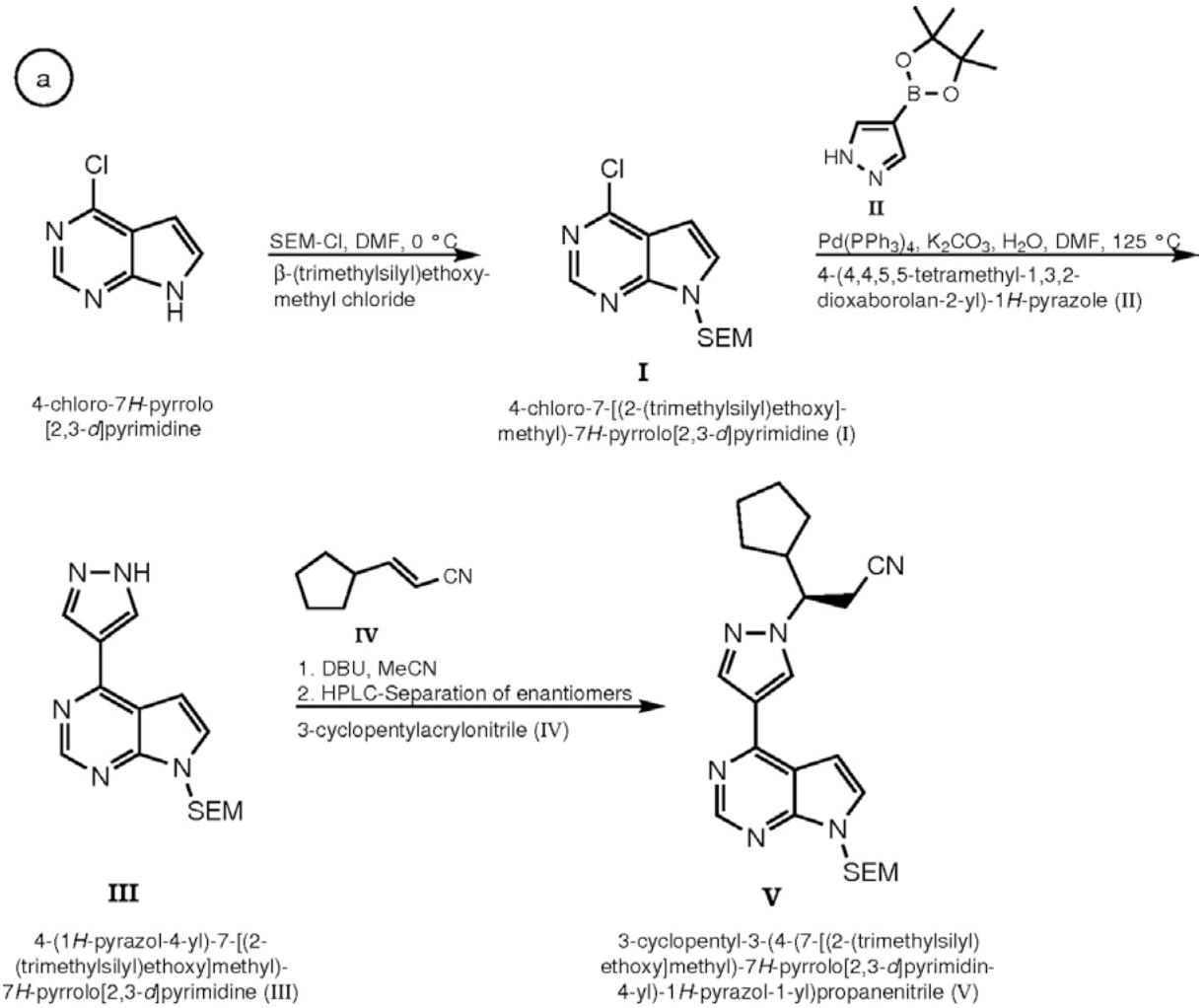
- Pyrazoles
- Pyrimidines
- Nitriles
- Hetarylboron Cross-Coupling Reactions
- Asymmetric aza-Michael Reaction

Synonyms: INCB018424
ATC: L01XE18
Use: anticancer, Janus kinase inhibitior, treatment of bone marrow cancer
Chemical name:(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile
Formula: $C_{17}H_{18}N_6$
MW: 306.4 g/mol
CAS-RN: 941678-49-5
InChI Key: HFNKQEVNSGCOJV-OAHLLOKOSA-N
InChI: InChI=1S/C17H18N6/c18-7-5-15(12-3-1-2-4-12)23-10-13(9-22-23)16-14-6-8-19-17(14)21-11-20-16/h6,8-12,15H,1-5H2,(H,19,20,21)/t15-/m1/s1

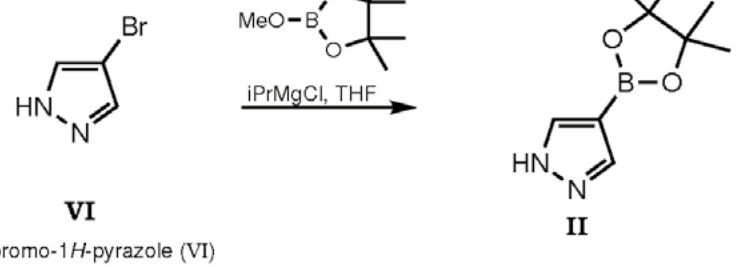
Derivatives

base
Formula: $C_{17}H_{18}N_6$
MW: 306.4 g/mol
CAS-RN: 941678-49-5
phosphate
Formula: $C_{17}H_{21}N_6O_4P$
MW: 404.4 g/mol
CAS-RN: 1092939-17-7

Synthesis Path



aa synthesis of II:

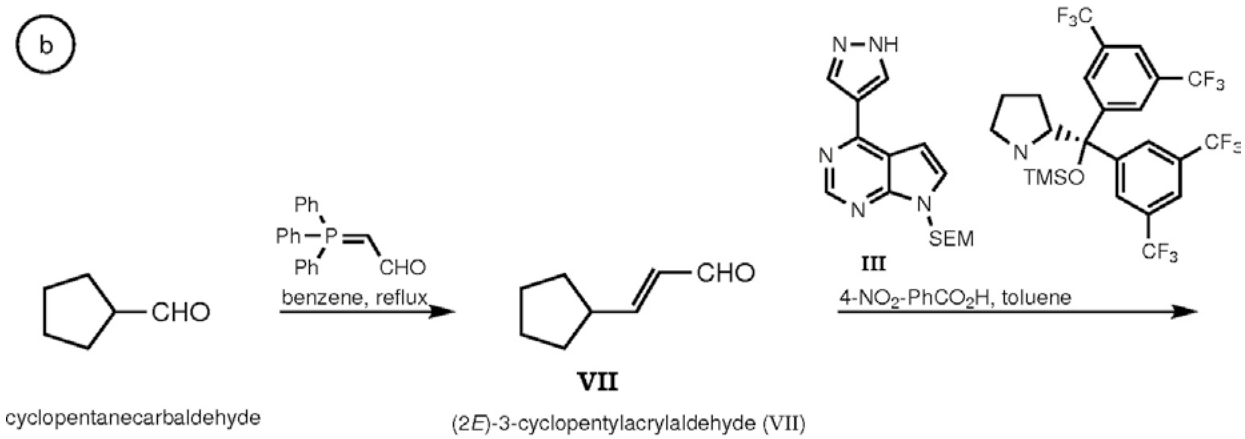


VI

4-bromo-1*H*-pyrazole (VI)

II

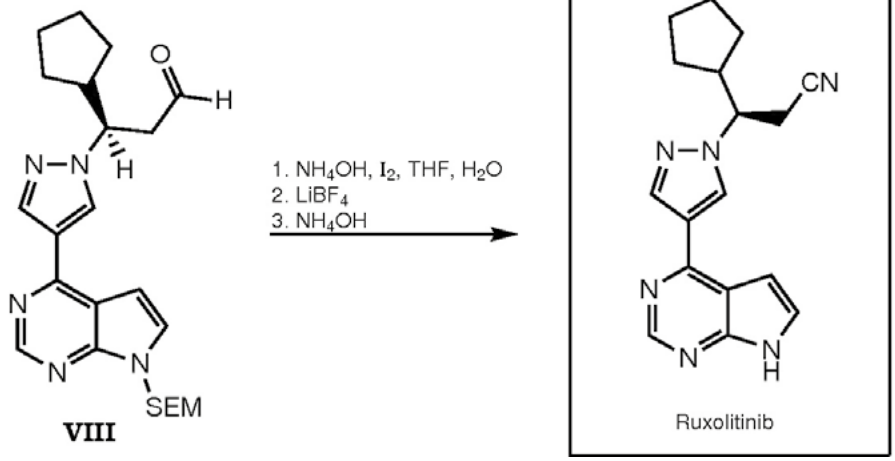
b



cyclopentanecarbaldehyde

VII

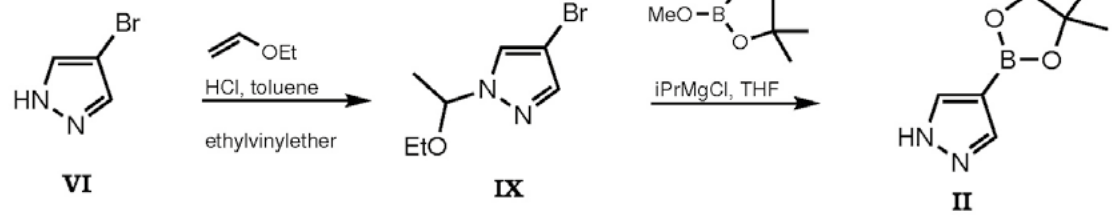
(2*E*)-3-cyclopentylacrylaldehyde (VII)



VIII

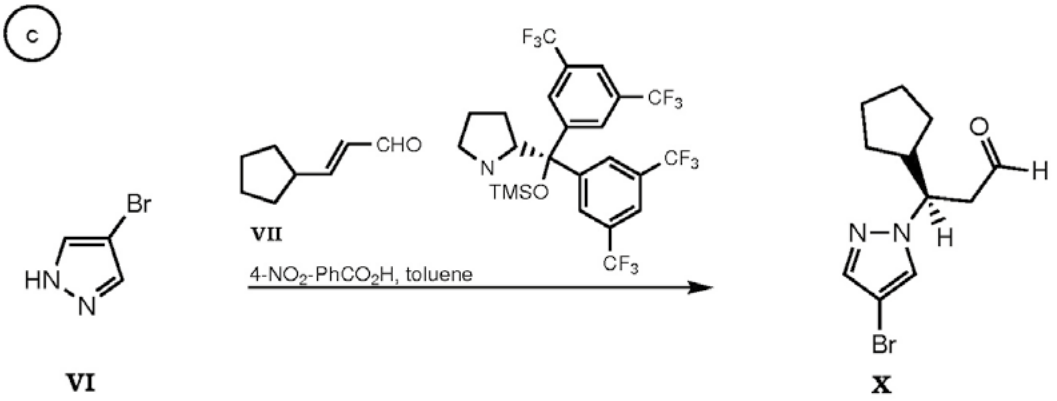
Ruxolitinib

ba alternativ synthesis of II:

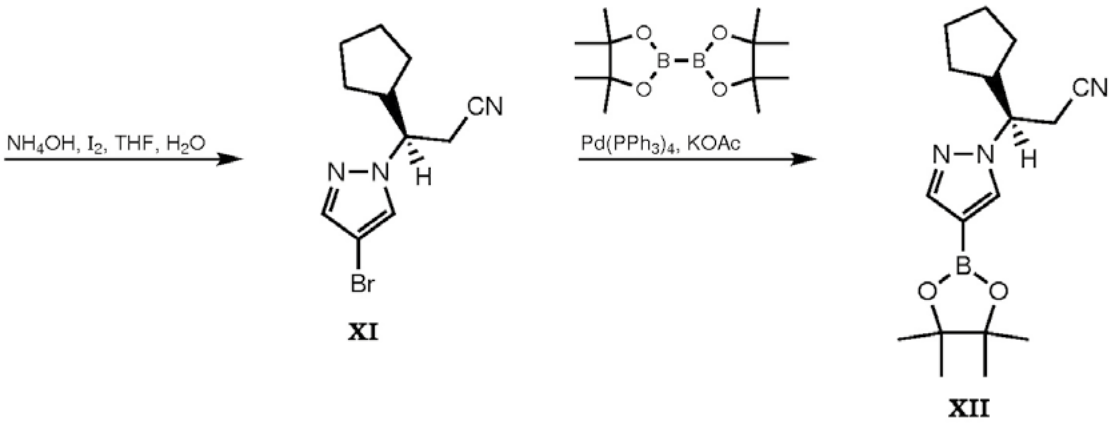


VI IX II

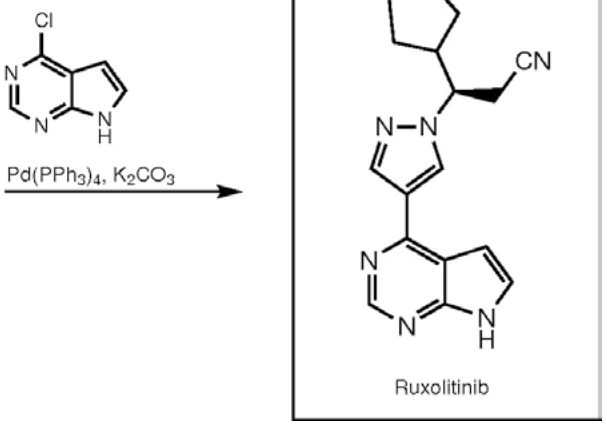
c



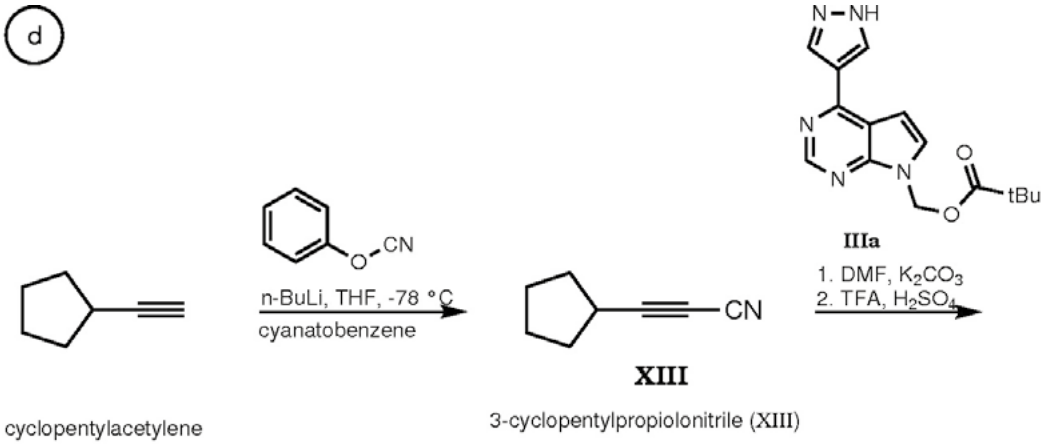
VI VII X



XI XII



d

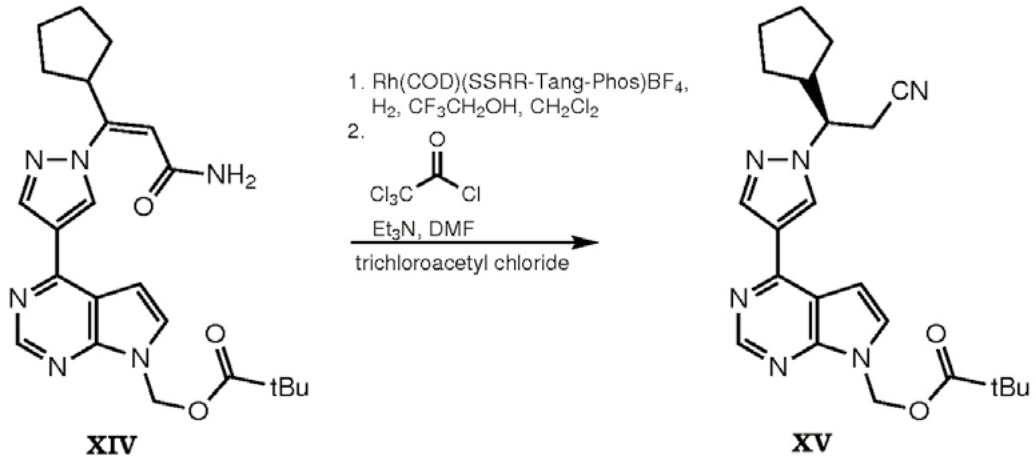


cyclopentylacetylene

IIIa

XIII

3-cyclopentylpropiolonitrile (XIII)

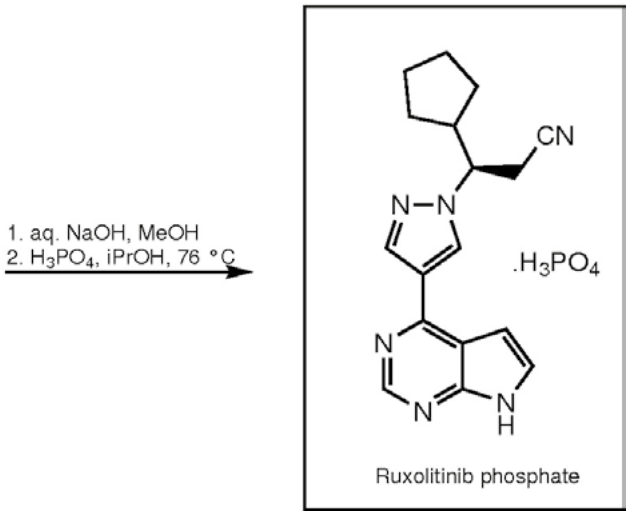


XIV

(*Z*)-(4-(1-(3-amino-1-cyclopentyl-3-oxoprop-1-enyl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (XIV)

XV

(*R*)-(4-(1-(2-cyano-1-cyclopentylethyl)-1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl pivalate (XV)



Ruxolitinib phosphate

Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
3680-69-1	$C_6H_4ClN_3$	4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine	
941685-26-3	$C_{13}H_{19}ClN_2OSi$	4-chloro-7-[(2-(trimethylsilyl)ethoxy]-methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	7H-Pyrrolo[2,3-d]pyrimidine, 4-chloro-7-[[2-(trimethylsilyl)ethoxy]methyl]-
29410-08-4	$C_9H_{15}N_2O_2$	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole	
941685-27-4	$C_{15}H_{21}N_5OSi$	4-(1*H*-pyrazol-4-yl)-7-[(2-(trimethylsilyl) ethoxy]methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	7H-Pyrrolo[2,3-d]pyrimidine, 4-(1H-pyrazol-4-yl)-7-[[2-(trimethylsilyl)ethoxy]methyl]-
	$C_8H_{11}N$	3-cyclopentylacrylonitrile	
941685-40-1	$C_{23}H_{32}N_6OSi$	3-cyclopentyl-3-(4-(7-[(2-(trimethylsilyl) ethoxy]methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)propanenitrile	1H-Pyrazole-1-propanenitrile, .beta.-cyclopentyl-4-[7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-, (.beta.R)-
2075-45-8	$C_3H_3BrN_2$	4-bromo-1*H*-pyrazole	
118235-51-1	$C_8H_{12}O$	(2*E*)-3-cyclopentylacrylaldehyde	2-Propenal, 3-cyclopentyl-, (2E)-
930-51-8	C_7H_{10}	cyclopentylacetylene	
591769-05-0	C_8H_9N	3-cyclopentylpropiolonitrile	
1236033-18-3	$C_{24}H_{30}N_6O_2$	(*Z*)-(4-(1-(3-amino-1-cyclopentyl-3-oxoprop-1-enyl)-1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)methyl pivalate	Propanoic acid, 2,2-dimethyl-, [4-[1-[(1Z)-3-amino-1-cyclopentyl-3-oxo-1-propen-1-yl]-1H-pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl ester
1146629-80-2	$C_{23}H_{28}N_6O_2$	(*R*)-(4-(1-(2-cyano-1-cyclopentylethyl)-1*H*-pyrazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl) methyl pivalate	Propanoic acid, 2,2-dimethyl-, [4-[1-[(1R)-2-cyano-1-cyclopentylethyl]-1H-pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]methyl ester

Trade Names

Country	Trade Name	Vendor
USA	Jakafi	Incyte Pharms.; Novartis, *2011*
EU	Jakavi	Novartis, *2012*

Formulations

tabs. oral; 5, 10, 15, 20 and 25 mg

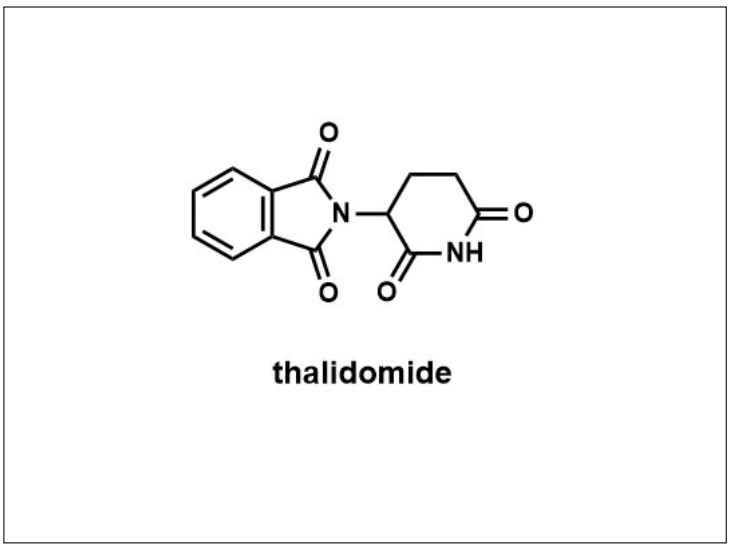
References

Mesa, R. A. et al., *Nature Reviews Drug Discovery*, (2012) **11**(2), 103-104.
b,c Lin, Q. et al., *Org. Letters*, (2009) **11**(9), 1999-2002.
a US 7 598 257 (Incyte Corp.; 14.6.2007; appl. 12.12.2006; USA-prior. 13.12.2005).
US 8 415 362 (Incyte Corp.; 9.4.2013; appl. 12.6.2008; USA-prior. 13.12.2005).
d US 2010 0190981 (Incyte Corp.; 29.7.2010; appl. 14.1.2010; USA-prior. 15.1.2009).

salts of the JAK-inhibitor Ruxolitinib:
US 2008 312259 (Incyte Corp.; 18.12.2008; appl. 12.6.2008; USA-prior. 13.6.2007).

metabolites:
US 2008 0312258 (Incyte Corp.; 18.12.2008; appl. 12.6.2008; USA-prior. 13.6.2007).

Thalidomide



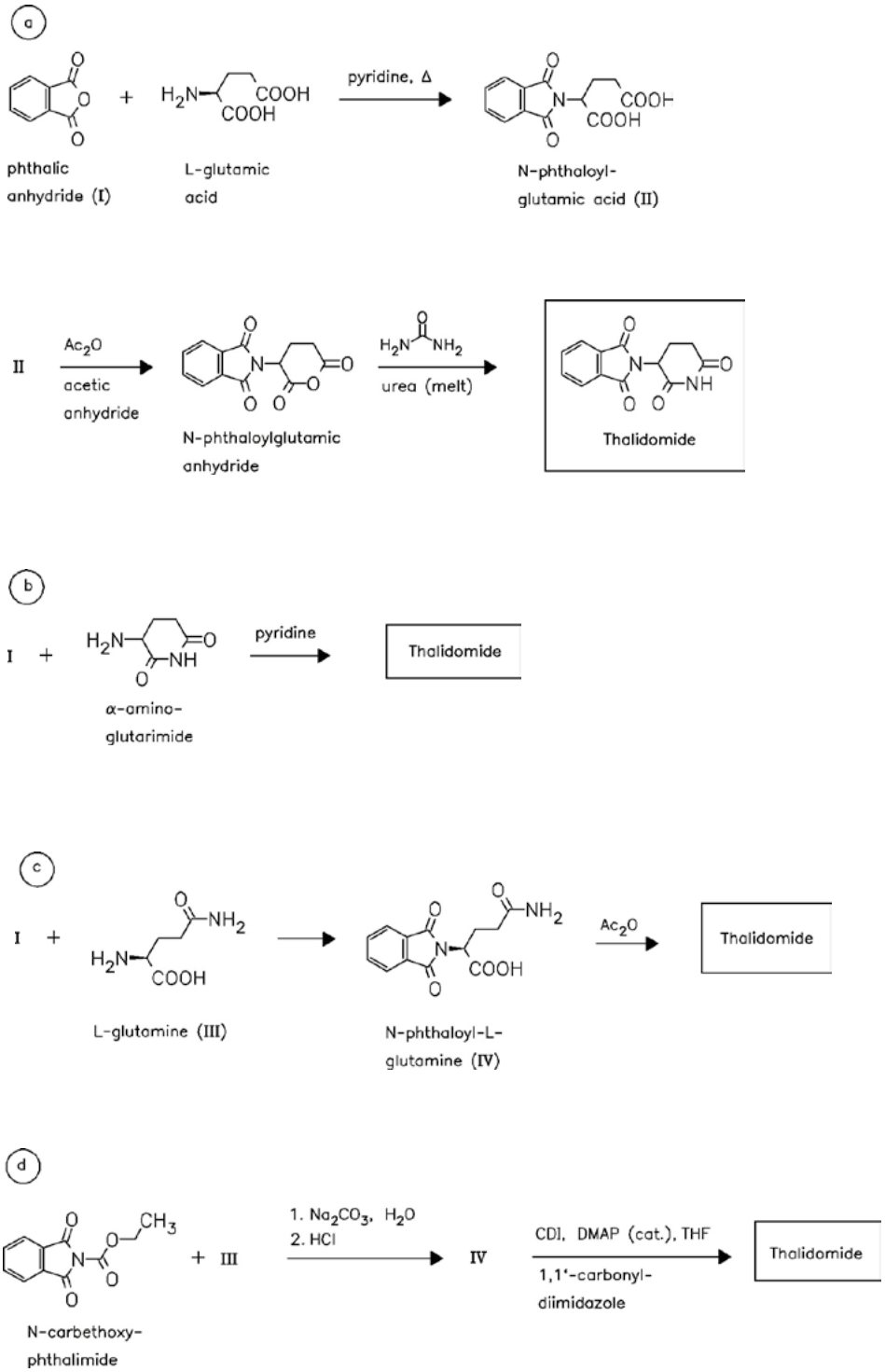
thalidomide

Related review in Science of Synthesis

- Imides (Diacylamines)

Synonyms: K-17, NSC-66847
ATC: L04AX02
Use: anti-inflammatory, immunomodulator, blocker of TNF-production, sedative, treatment of erythema nodosum leprosum
Chemical name: 2-(2,6-Dioxo-3-piperidinyl)-1*H*-isoindole-1,3(2*H*)-dione
Formula: $C_{13}H_{10}N_2O_4$
MW: 258.23 g/mol
CAS-RN: 50-35-1
InChI Key: UEJJHQNACJXSKW-UHFFFAOYSA-N
InChI: InChI=1S/C13H10N2O4/c16-10-6-5-9(11(17)14-10)15-12(18)7-3-1-2-4-8(7)13(15)19/h1-4,9H,5-6H2,(H,14,16,17)
EINECS: 200-031-1
LD_{50}: >5000 mg/kg (M, p. o.)

Synthesis Path



Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
108-24-7	$C_4H_6O_3$	acetic anhydride	Acetic acid, anhydride
2353-44-8	$C_5H_8N_2O_2$	α-aminoglutarimide	2,6-Piperidinedione, 3-amino-
22509-74-6	$C_{11}H_9NO_4$	*N*-carbethoxyphthalimide	2H-Isoindole-2-carboxylic acid, 1,3-dihydro-1,3-dioxo-, ethyl ester
22509-74-6	$C_{11}H_9NO_4$	*N*-ethoxycarbonylphthalimide	2H-Isoindole-2-carboxylic acid, 1,3-dihydro-1,3-dioxo-, ethyl ester
56-86-0	$C_5H_9NO_4$	L-glutamic acid	L-Glutamic acid
56-85-9	$C_5H_{10}N_2O_3$	L-glutamine	L-Glutamine
85-44-9	$C_8H_4O_3$	phthalic anhydride	1,3-Isobenzofurandione
6349-98-0	$C_{13}H_{11}NO_6$	*N*-phthaloylglutamic acid	Pentanedioic acid, 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-
3343-28-0	$C_{13}H_9NO_5$	*N*-phthaloylglutamic anhydride	1H-Isoindole-1,3(2H)-dione, 2-(tetrahydro-2,6-dioxo-2H-pyran-3-yl)-
3343-29-1	$C_{13}H_{12}N_2O_5$	*N*-phthaloyl-L-glutamine	2H-Isoindole-2-acetic acid, α-(3-amino-3-oxopropyl)-1,3-dihydro-1,3-dioxo-, (αS)-
57-13-6	CH_4N_2O	urea	Urea

Trade Names

Country	Trade Name	Vendor
USA	Thalomid	Celgene, 1998

Formulations

cps. 50 mg

References

Kunz, W. et al.: Arzneim.-Forsch. (ARZNAD) **6**, 426-430 (1956).
c King, F.E. et al.: J. Chem. Soc. (JCSOA9) **1957**, 873-880.
d Muller, G.W. et al.: Org. Process Res. Dev. (OPRDFK) **3**, 139-140 (1999).
a GB 768 821 (Chemie Grünenthal; 20.2.1957).
b JP 5 071 (Dainippon; 13.5.1960).

microwave promoted synthesis:
Seijas, J.A. et al.: Synthesis (SYNTBF) **7**, 999 (2001).

intravenous administration form for treatment of immunologic diseases:
EP 908 176 (Grünenthal; appl. 18.9.1998; D-prior. 6.10.1997).

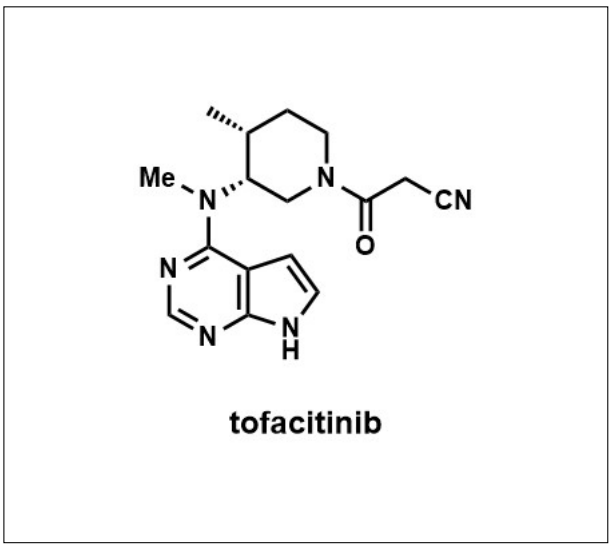
pharmaceutical comp. for the treatment of melanomas:
US 5 731 325 (Andrulis Pharm.; 24.3.1998; USA-prior. 6.6.1995).

use for treating neurocognitive disorders:
WO 9 517 154 (Andrulis Pharm.; appl. 22.12.1994; USA-prior. 23.12.1993).

treatment of rheumatoid arthritis:
WO 9 504 533 (Andrulis Pharm.; appl. 3.8.1994; USA-prior. 4.8.1993).

***controlling abnormal concentration of* TNF-α:**
WO 9 214 455 (Rockefeller Univ.; appl. 14.2.1992; USA-prior. 14.2.1991).

Tofacitinib



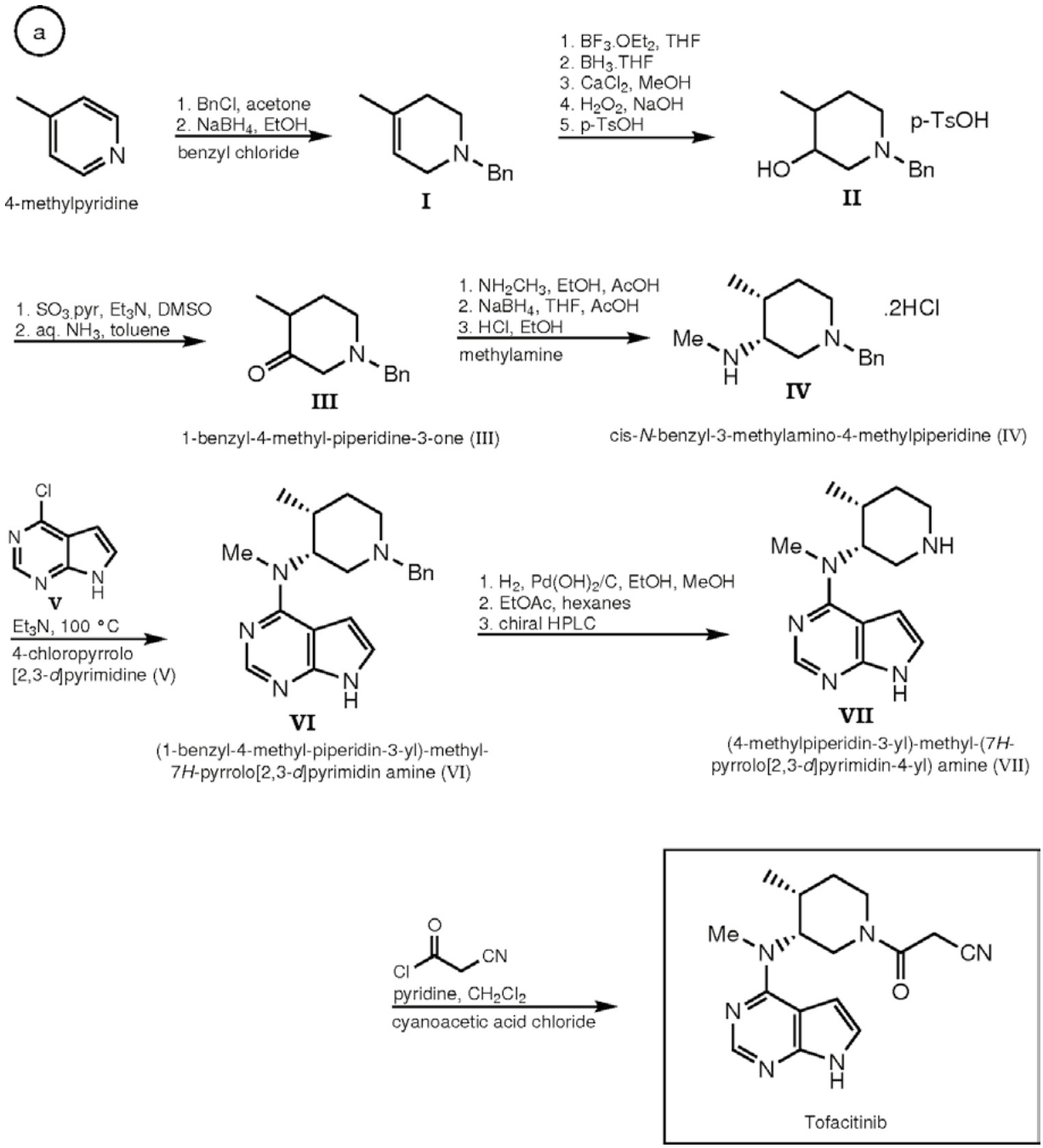
tofacitinib

Related reviews in Science of Synthesis

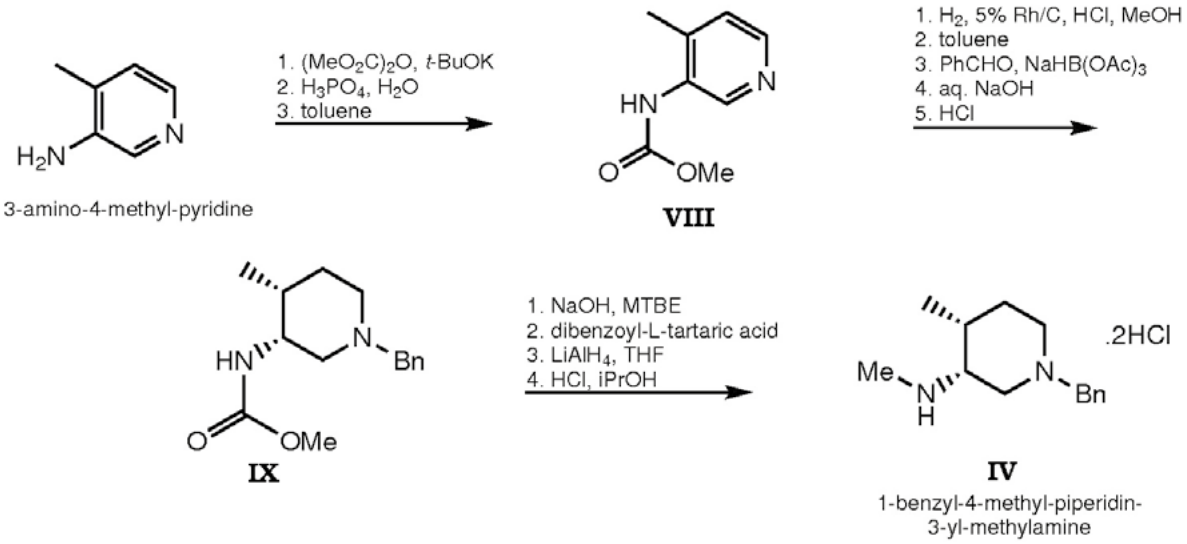
- Pyrimidines
- Nitriles
- Reaction of Cyanoacetates with Amidine Derivatives

Synonyms: CP-690550; Tasocitinib
ATC: L04AA29
Use: immunosuppressive, treatment of rheumatoid arthritis, Janus kinase 3 inhibitor
Chemical name: 3-[(3*R*,4*R*)-4-methyl-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino] piperidin-1-yl]-3-oxopropanenitrile
Formula: $C_{16}H_{20}N_6O$
MW: 312.4 g/mol
CAS-RN: 477600-75-2
InChI Key: UJLAWZDWDVHWOW-YPMHNXCESA-N
InChI: InChI=1S/C16H20N6O/c1-11-5-8-22(14(23)3-6-17)9-13(11)21(2)16-12-4-7-18-15(12)19-10-20-16/h4,7,10-11,13H,3,5,8-9H2,1-2H3,(H,18,19,20)/t11-,13+/m1/s1

Synthesis Path



b alternative route for cis-*N*-benzyl-3-methylamino-4-methylpiperidine (IV):



3-amino-4-methyl-pyridine

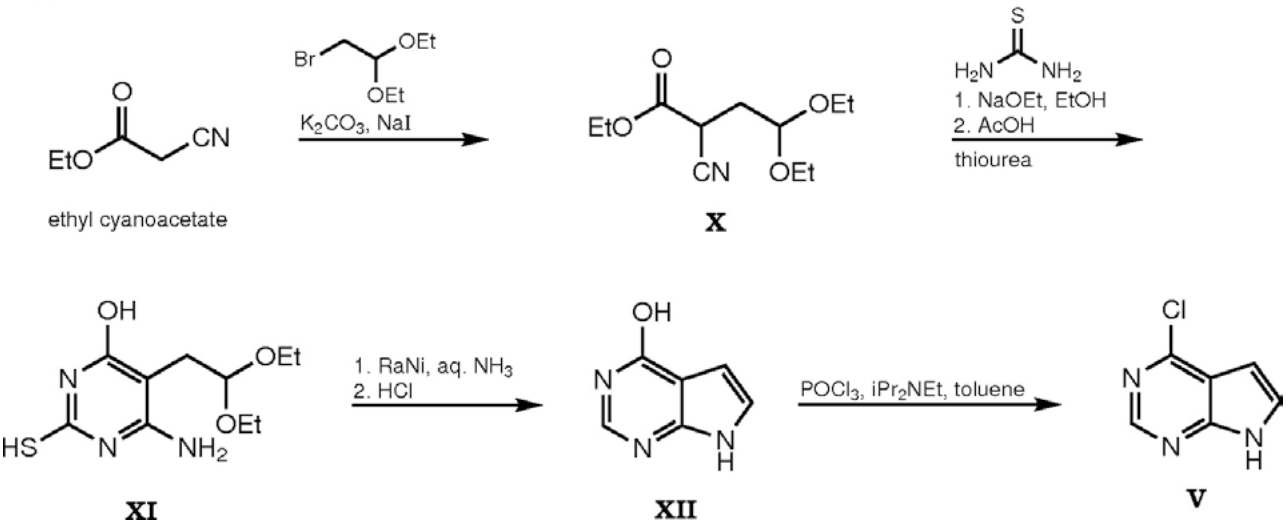
VIII

IX

IV

1-benzyl-4-methyl-piperidin-3-yl-methylamine

c synthesis of starting material V:



ethyl cyanoacetate

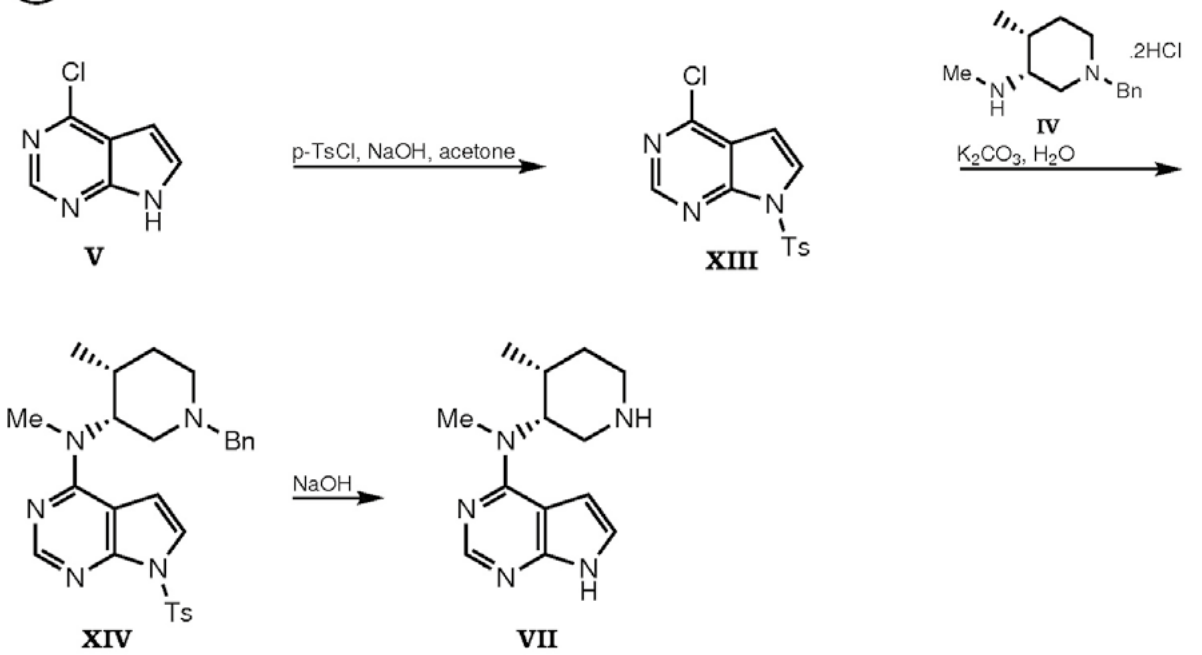
X

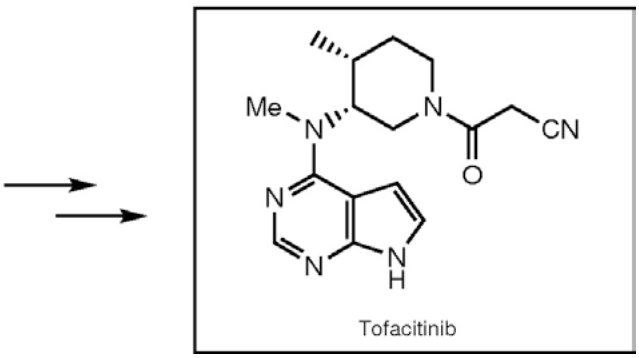
XI

XII

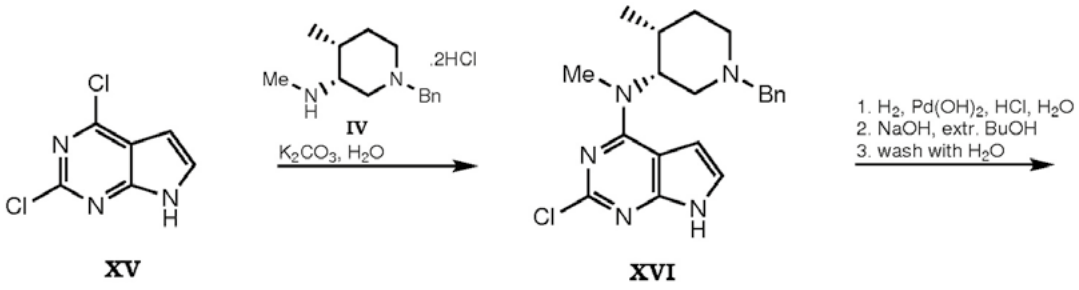
V

(d) optimized process:

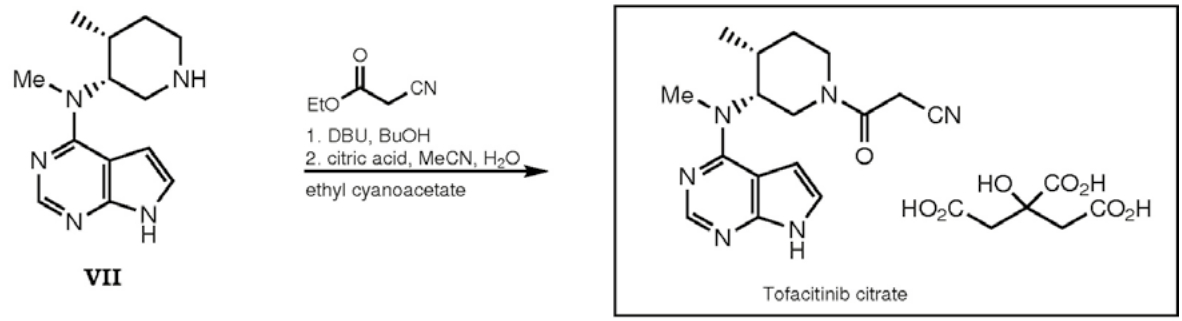




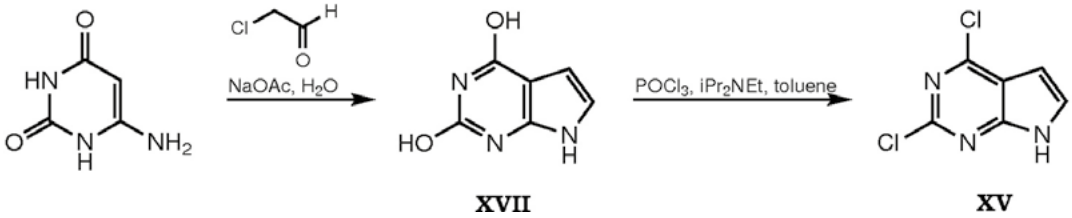
(e) robust process for the manufacture of Tofacitinib citrate:



2,4-dichloropyrrolopyrimidine (XV)



(f) synthesis of building block XV:



Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
108-89-4	C_6H_7N	4-methylpyridine	
34737-89-8	$C_{10}H_{19}NO$	1-benzyl-4-methyl-piperidine-3-one	
1062580-52-2	$C_{11}H_{24}N_2$	*cis*-*N*-benzyl-3-methylamino-4-methylpiperidine	
3680-69-1	$C_6H_4ClN_3$	4-chloropyrrolo[2,3-*d*]pyrimidine	
1206825-40-2	$C_{17}H_{27}N_5$	(1-benzyl-4-methyl-piperidin-3-yl)-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin amine	7H-Pyrrolo[2,3-d]pyrimidin-4-amine, N-methyl-N-[(3R,4R)-4-methyl-1-(phenylmethyl)-3-piperidinyl]-, rel-
1206825-36-6	$C_{13}H_{19}N_5$	methyl-(4-piperidin-3-yl)-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl) amine	7H-Pyrrolo[2,3-d]pyrimidin-4-amine, N-methyl-N-[(3R,4R)-4-methyl-3-piperidinyl]-, rel-
16130-58-8	C_3H_2ClNO	cyanoacetic acid chloride	
3430-27-1	$C_6H_8N_2$	3-amino-4-methyl-pyridine	
105-56-6	$C_5H_7NO_2$	ethyl cyanoacetate	
62-56-6	CH_4N_2S	thiourea	
90213-66-4	$C_6H_3Cl_2N_3$	2,4-dichloropyrrolopyrimidine	

Trade Names

Country	Trade Name	Vendor
USA	Xeljanz	Pfizer, *2012*

Formulations

tabs., 5 mg as citrate

References

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