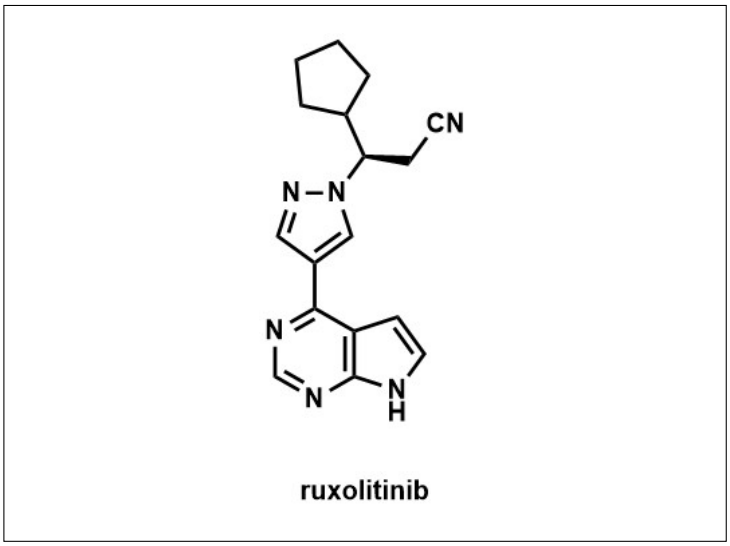
Ruxolitinib



ruxolitinib

Related reviews in Science of Synthesis

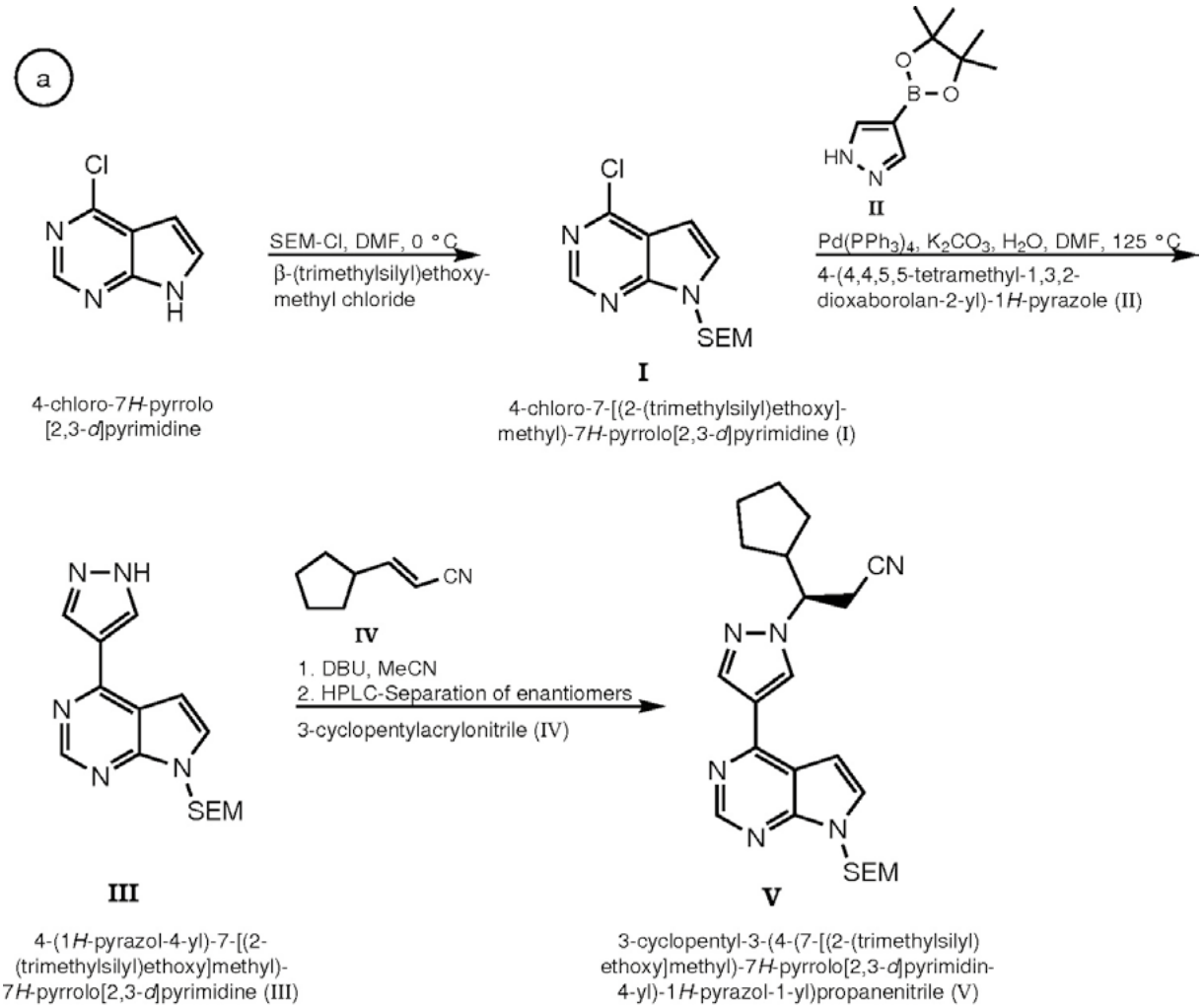
- Pyrazoles
- Pyrimidines
- Nitriles
- Hetarylboron Cross-Coupling Reactions
- Asymmetric aza-Michael Reaction

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

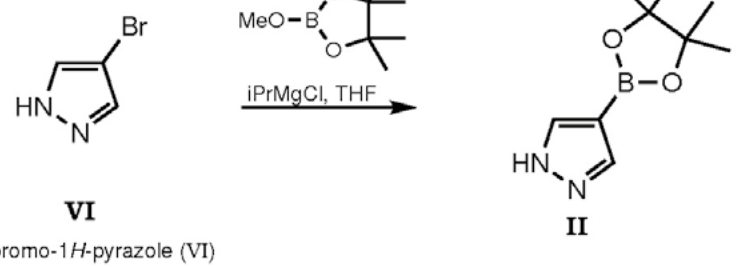
Derivatives

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:

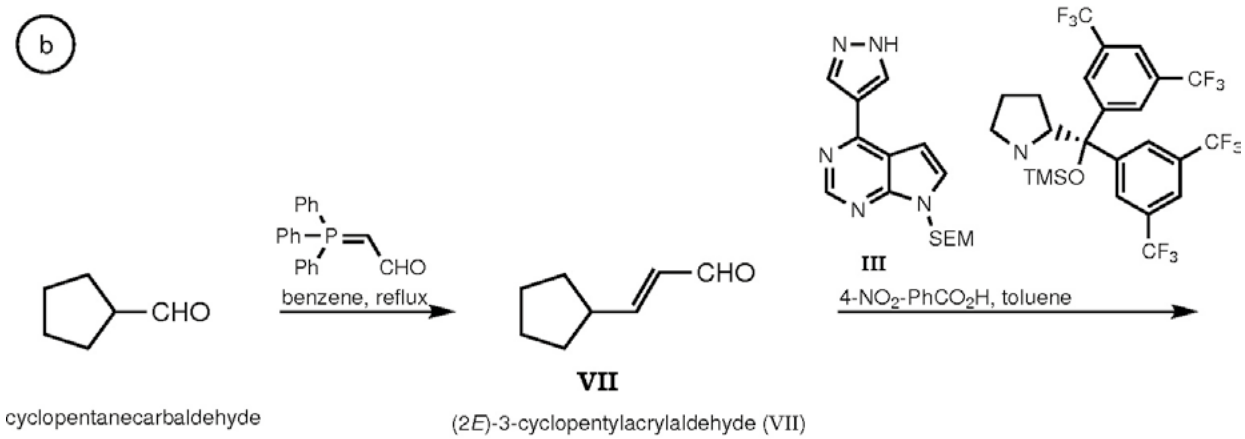


VI

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

II

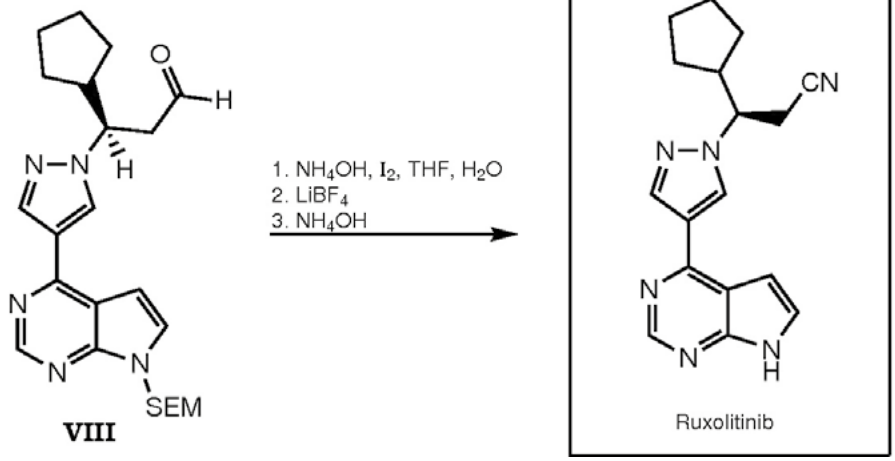
b



cyclopentanecarbaldehyde

VII

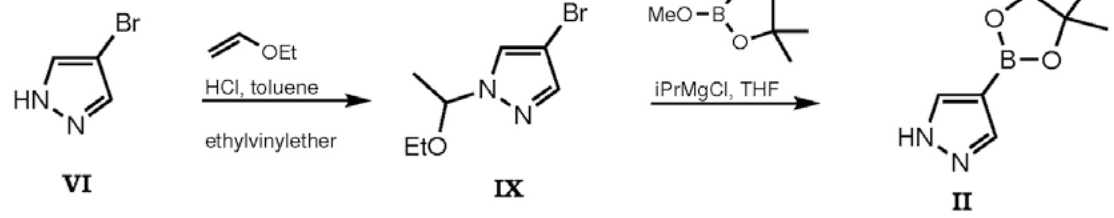
(2*E*)-3-cyclopentylacrylaldehyde (VII)



VIII

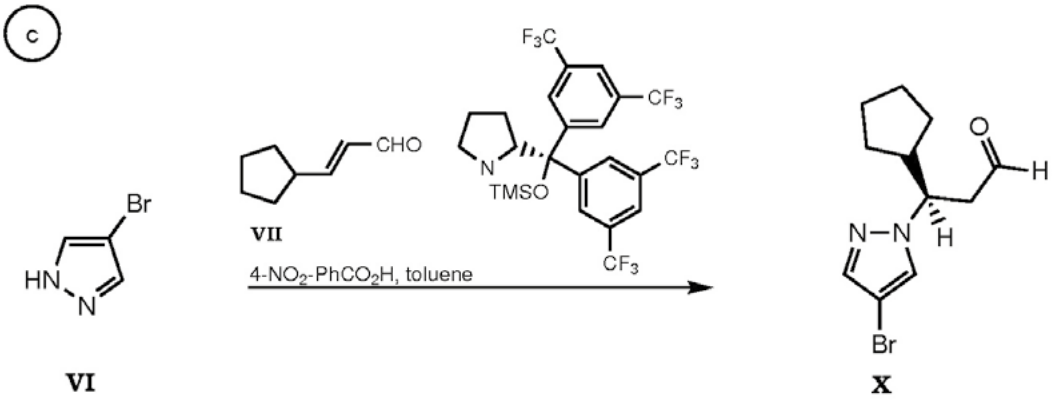
Ruxolitinib

ba alternativ synthesis of II:

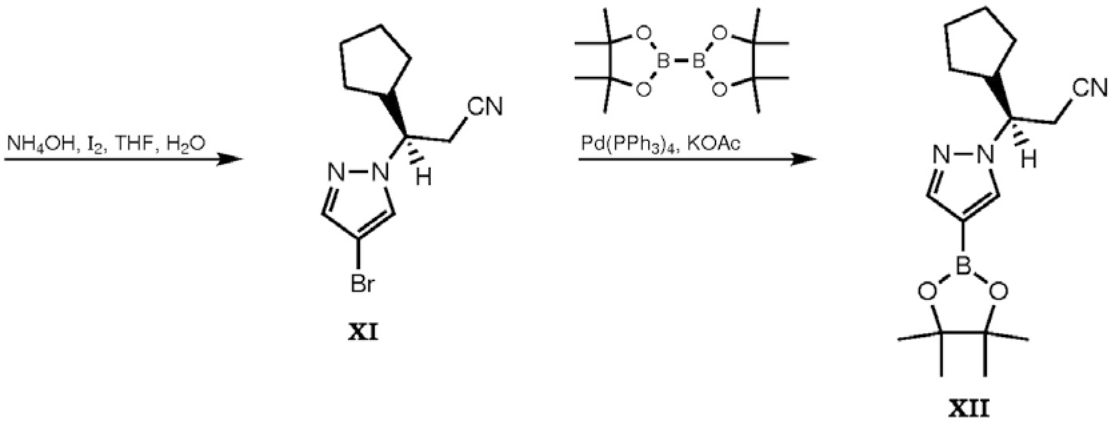


VI IX II

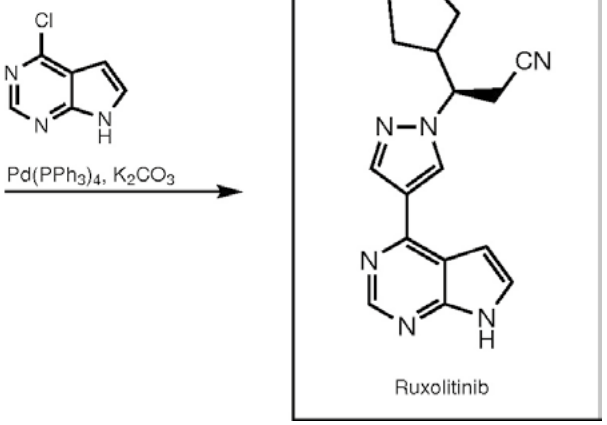
c



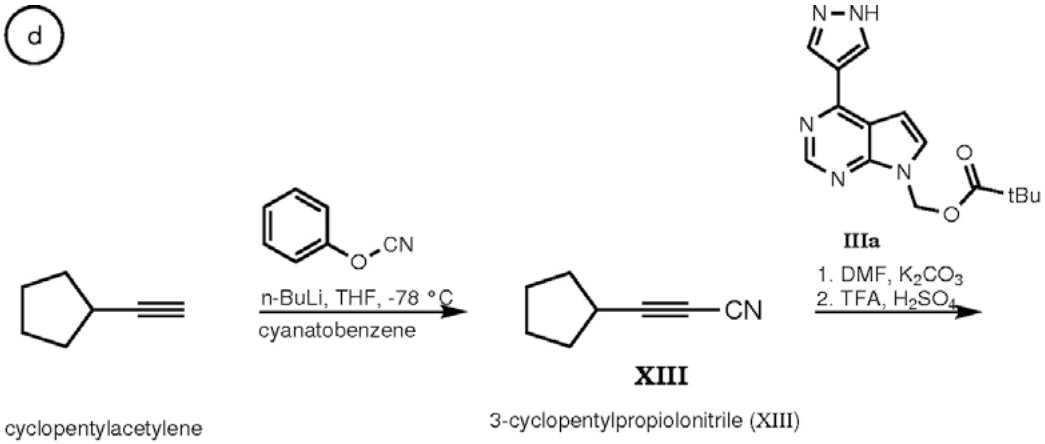
VI VII X



XI XII



d

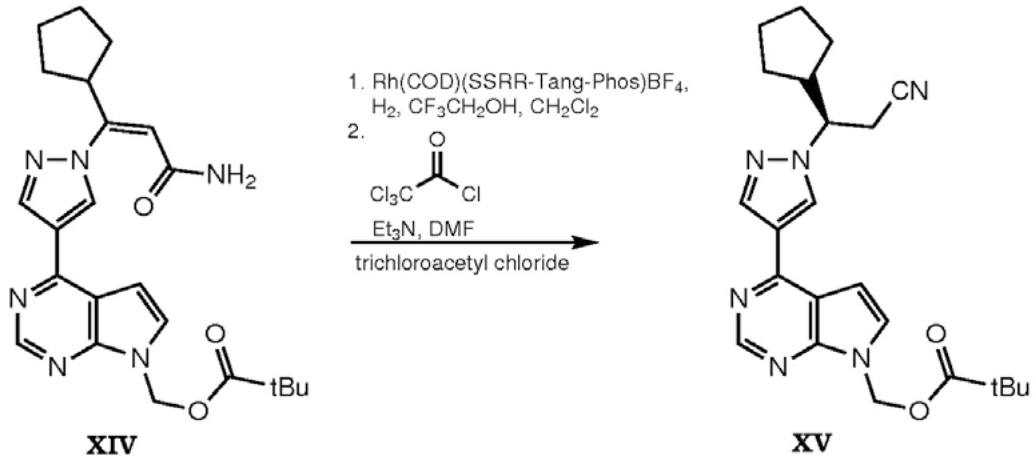


cyclopentylacetylene

IIIa

XIII

3-cyclopentylpropiolonitrile (XIII)

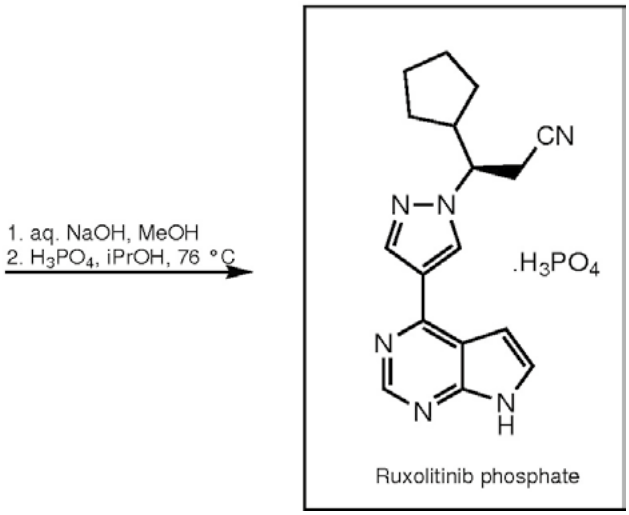


XIV

(*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).