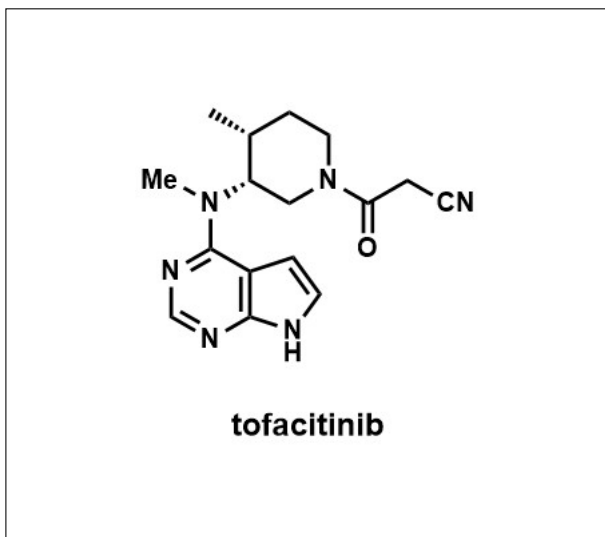


## Tofacitinib



### 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<sub>16</sub>H<sub>20</sub>N<sub>6</sub>O

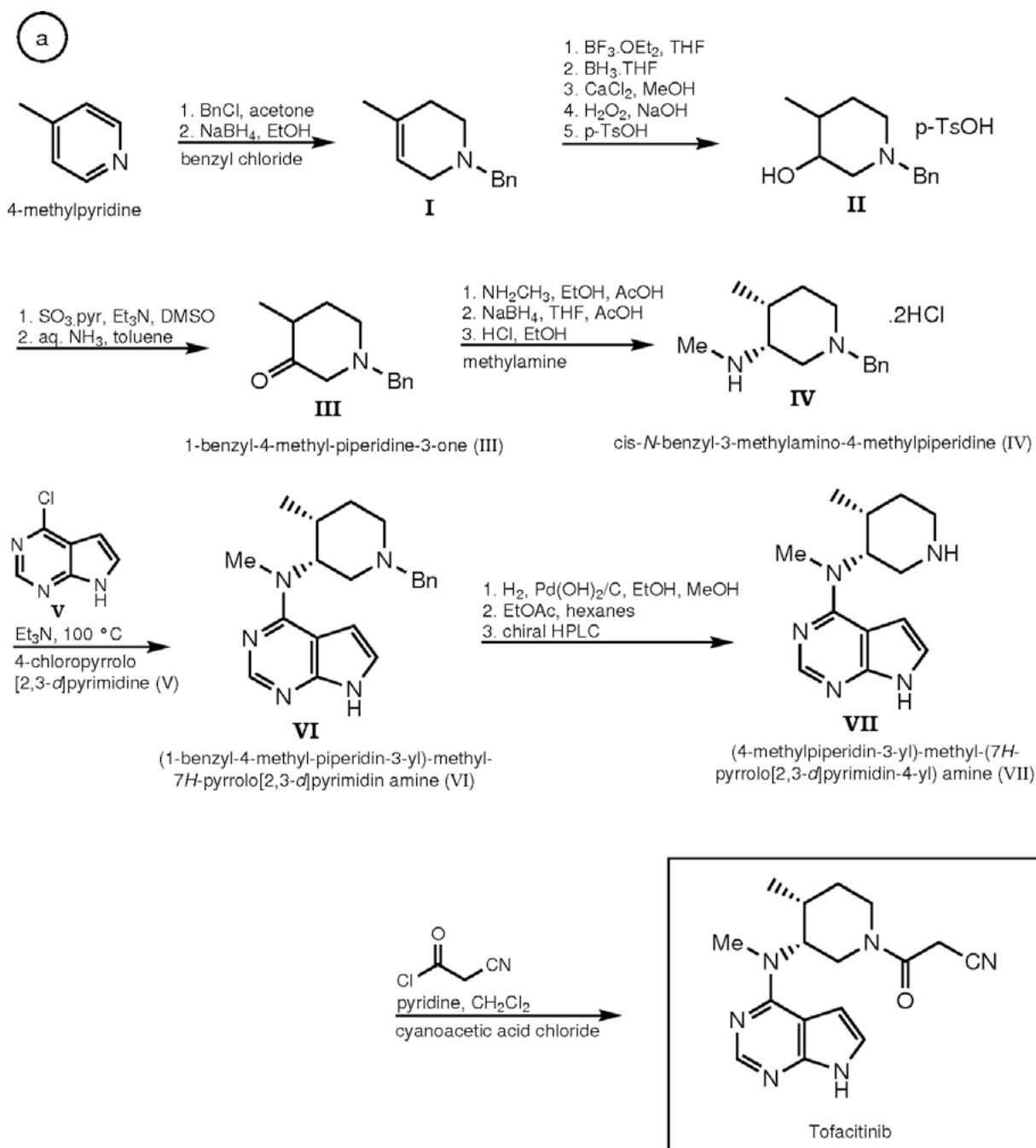
**MW:** 312.4 g/mol

**CAS-RN:** 477600-75-2

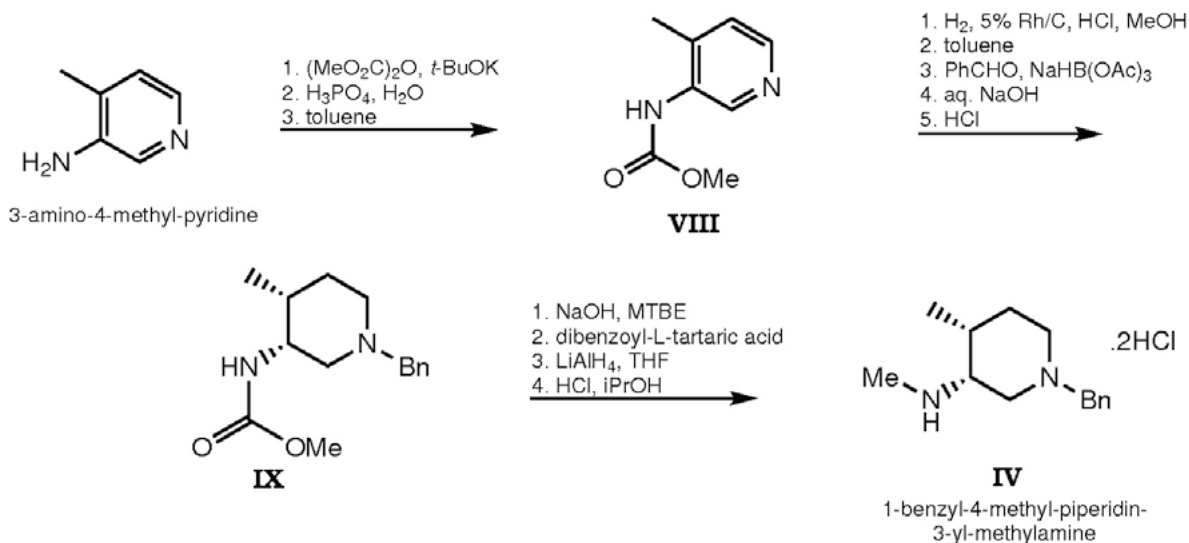
**InChI Key:** UJLAWZDWDVHWOW-YPMHNXCESA-N

**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

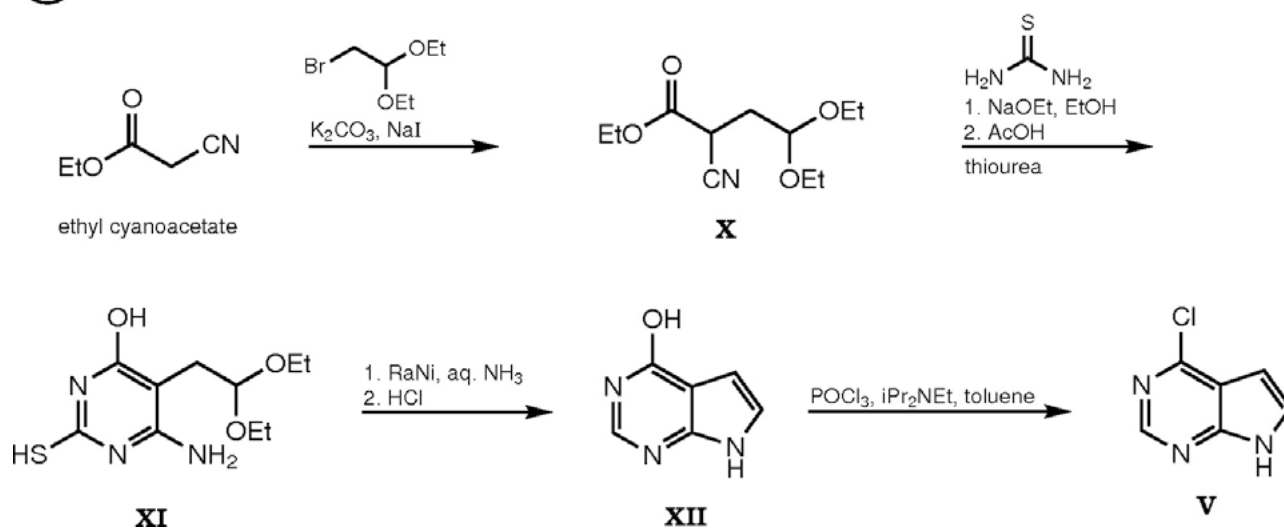
## Synthesis Path



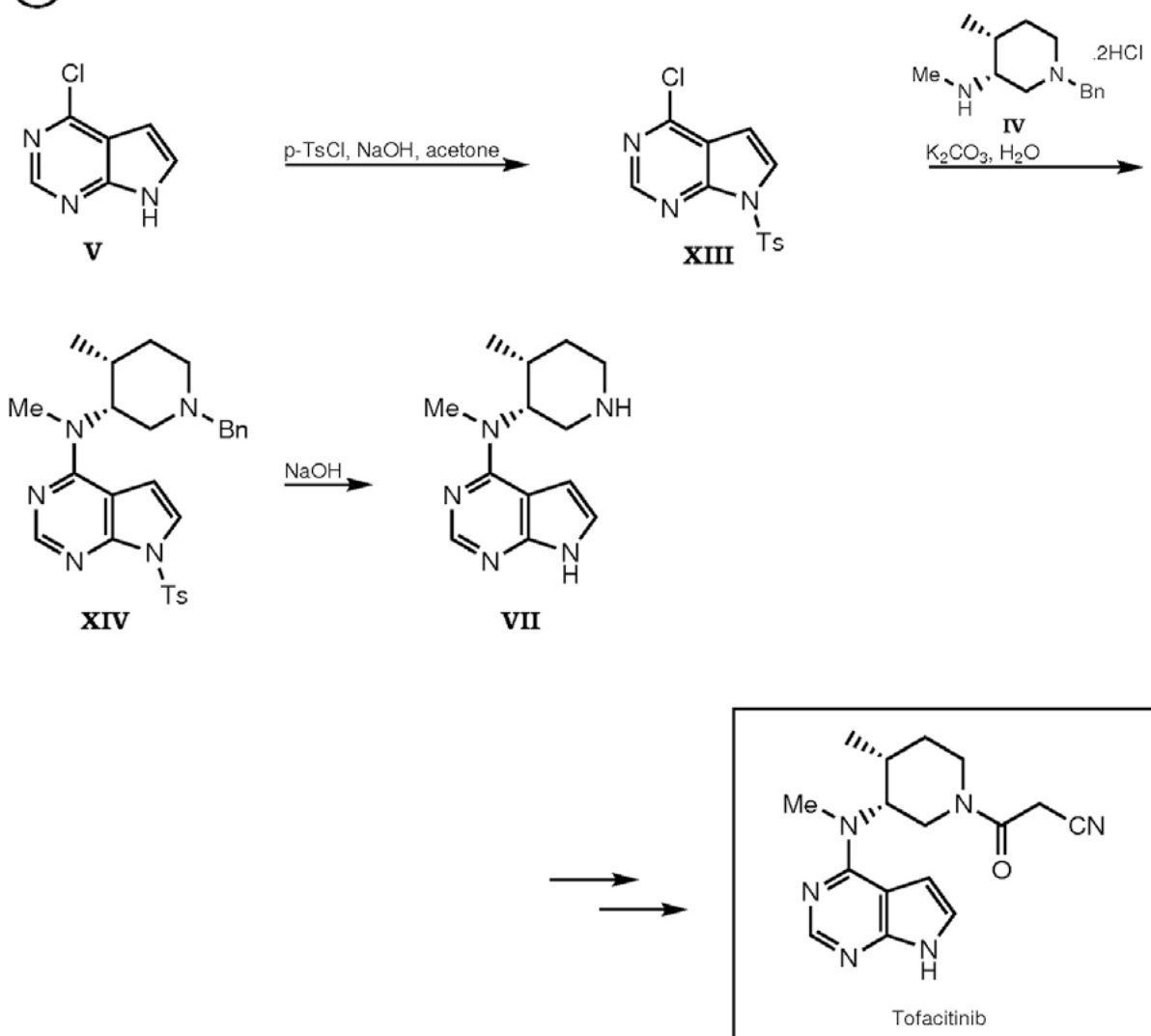
b) alternative route for *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine (IV):



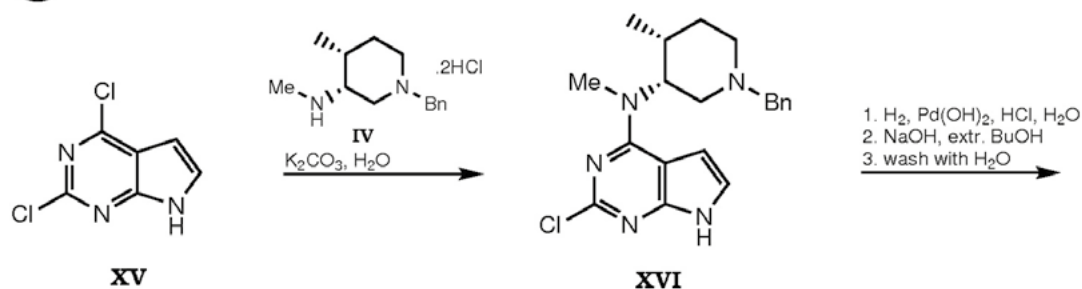
c) synthesis of starting material V:



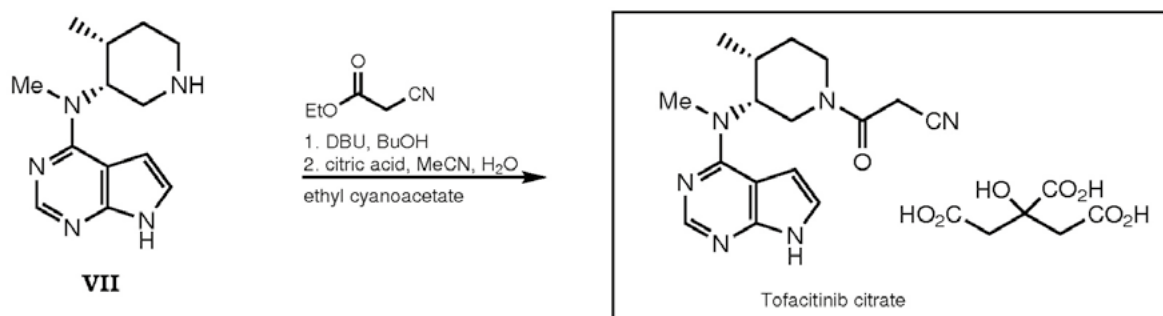
d optimized process:



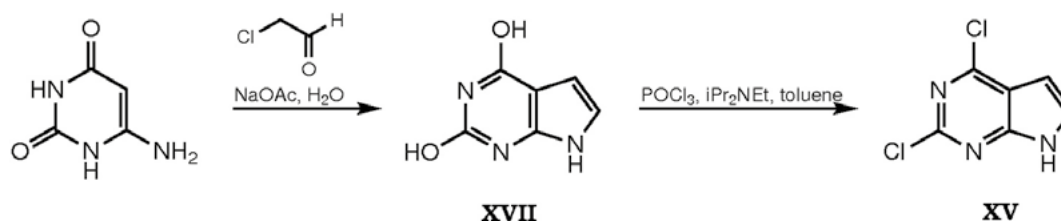
e) robust process for the manufacture of Tofacitinib citrate:



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 <sub>6</sub> H <sub>7</sub> N	4-methylpyridine	
34737-89-8	C <sub>10</sub> H <sub>19</sub> NO	1-benzyl-4-methyl-piperidine-3-one	
1062580-52-2	C <sub>11</sub> H <sub>24</sub> N <sub>2</sub>	cis-N-benzyl-3-methylamino-4-methylpiperidine	
3680-69-1	C <sub>6</sub> H <sub>4</sub> ClN <sub>3</sub>	4-chloropyrrolo[2,3-d]pyrimidine	
1206825-40-2	C <sub>17</sub> H <sub>27</sub> N <sub>5</sub>	(1-benzyl-4-methyl-piperidin-3-yl)-methyl-7H-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 <sub>13</sub> H <sub>19</sub> N <sub>5</sub>	methyl-(4-piperidin-3-yl)-(7H-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 <sub>3</sub> H <sub>2</sub> ClNO	cyanoacetic acid chloride	
3430-27-1	C <sub>6</sub> H <sub>8</sub> N <sub>2</sub>	3-amino-4-methyl-pyridine	
105-56-6	C <sub>5</sub> H <sub>7</sub> NO <sub>2</sub>	ethyl cyanoacetate	
62-56-6	CH <sub>4</sub> N <sub>2</sub> S	thiourea	
90213-66-4	C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub> N <sub>3</sub>	2,4-dichloropyrrolopyrimidine	

## Trade Names

Country	Trade Name	Vendor
USA	Xeljanz	Pfizer, 2012

## Formulations

tabs., 5 mg as citrate

## References

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 Ripin, D. H. B. et al., *Org. Process Res. Dev.*, (2003) **7**, 115-120.  
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 US 7 265 221 (Pfizer; 4.9.2007; appl. 23.6.2006; USA-prior. 10.12.1999).  
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 US 7 301 023 (Pfizer; 17.4.2003; appl. 23.5.2002; USA-prior. 6.12.2001).  
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 Maricán, A. et al., *THL*, (2013) **54**(37), 5096-5098.  
**novel crystalline compound:**  
 US 6 965 027 (Pfizer; 10.7.2003; appl. 4.12.2001; USA-prior. 6.12.2001).  
**crystalline and non-crystalline forms of Tofacitinib and pharmaceutical compositions:**  
 US 2012 137111 (Pfizer; 11.10.2012; appl. 29.3.2012; USA-prior. 8.4.2011).  
**processes for preparing salts:**  
 US 2012 135338 (Teva; 4.10.2012; appl. 28.3.2012; USA-prior. 28.3.2011).  
**combinations with kinase inhibitor:**  
 US 2009 0156602 (Novartis; 18.6.2009; appl. 22.11.2005; USA-prior. 24.11.2004).  
**pharmaceutical compositions:**  
 US 2012 195933 (Stefan, R. et al.; 2.8.2012; appl. 27.1.2012; USA-prior. 27.1.2011).  
**tofacitinib salts:**  
 WO 2013 090490 (Ratiopharm/Teva; 20.6.2013; appl. 13.12.2012; USA-prior. 15.12.2011).