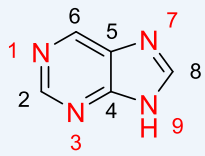
# Utility of Deazapurines in Drug Discovery

### Key Points

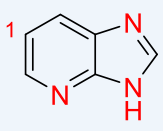
- 7-deazapurine
- 9-deazapurine
- 1-deazapurine & 3-deazapurine

## Overview

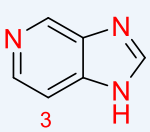
Deazapurines are *bona fide* bioisosteres for purines and exist in several marketed drugs. This article describes four deazapurines including 1-deazapurine, 3-deazapurine, 7-deazapurine, and 9-deazapurine.



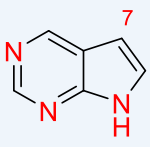

purine



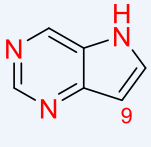

1-deazapurine




3-deazapurine




7-deazapurine



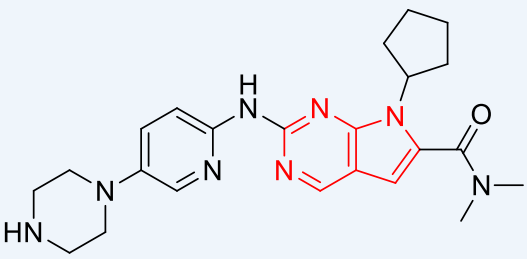

9-deazapurine

PharmaBlock

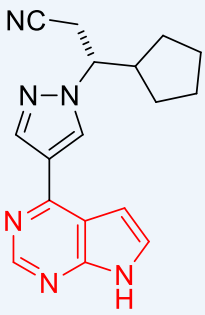
## Deazapurines in Drug Discovery

PharmaBlock designs and synthesizes over 610 deazapurines, and 200 deazapurine products are in stock. A list of featured deazapurine derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

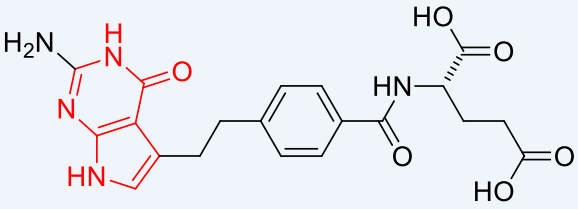
Novartis' ribociclib (Kisqali, **1**), approved by the FDA in 2017 for treating breast cancer, is a cyclin-dependent kinase (CDK) 4/6 inhibitor. Incyte's ruxolitinib (Jakafi, **2**), a Janus kinase (JAK) 1/2 inhibitor, was approved in 2011 for the treatment of bone marrow cancer. Lilly's pemetrexed (Alimta, **3**), a folate analogue metabolic inhibitor initially discovered by Ed Taylor, was approved in 2004 for treating pleural mesothelioma. BioCryst's fododesine (Mundesine, **4**), a transition-state analogue of purine nucleoside phosphorylase, won the FDA approval in 2017 for treating leukemia. **Notably, the four representative deazapurine-containing drugs on the market are all 7-deazapurines.**



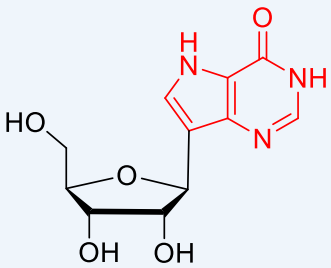
ribociclib (Kisqali, **1**)
Novartis, 2017
CDK4/6 inhibitor



ruxolitinib (Jakafi, **2**)
Incyte, 2011
bone marrow cancer



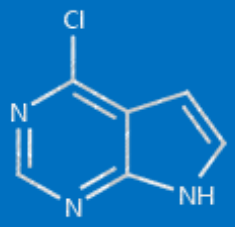
pemetrexed (Alimta, **3**)
Lilly, 2004
folate analogue metabolic inhibitor
for pleural mesothelioma



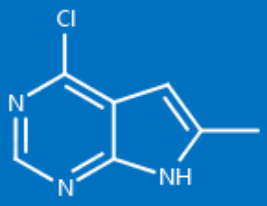
fododesine (Mundesine, **4**)
BioCryst Pharmaceuticals, 2017
transition-state analog inhibitor
of purine nucleoside phosphorylase

## 7-Deazapurines

**Bulk Products Supplied by PharmaBlock**



**PB00031**



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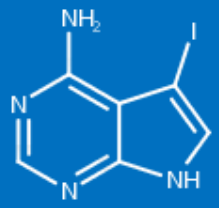
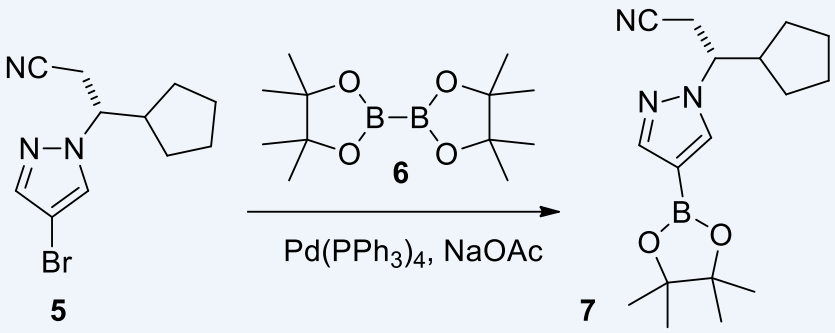
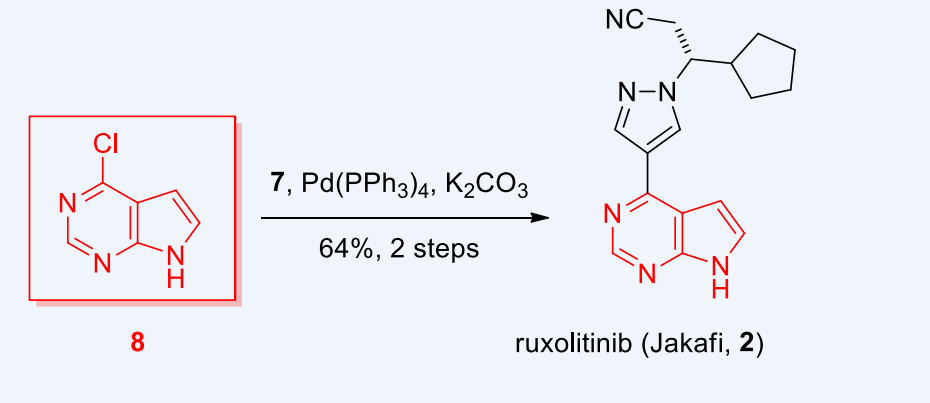


**PBN20120170**

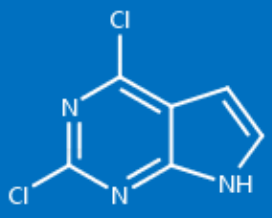
One of Incyte's syntheses of ruxolitinib (Jakafi, **2**) employed 6-chloro-7-deazapurine (**8**, PharmaBlock product, **PB00031**) as a starting material. As shown below, (*R*)-4-bromopyrazole (**5**) underwent a Suzuki–Miyaura coupling with bis (pinacolato) diboron (**6**) to produce pyrazole-boronate (**7**) *in situ*. Subsequently, pyrazole-boronate **7**, in turn, underwent another Suzuki coupling with 6-chloro-7-deazapurine (**8**) to deliver ruxolitinib (Jakafi, **2**) in 64% yield for two steps.[1]




**Many 7-deazapurines have found utility in drug discovery as purine's isosteres.** 7-Deazapurine (pyrrolo[2,3-d]pyrimidine) nucleosides are important analogues of biogenic purine nucleosides with diverse biological activities. Replacement of the N7 atom with a carbon atom makes the five-membered ring more electron-rich and brings a possibility of attaching additional substituents at the C7 position. This often leads to derivatives with increased base-pairing in DNA or RNA or better binding to enzymes.[2] **Not surprisingly, many 7-deazapurine derivatives found utility as antiviral and anticancer drugs.**

**Bulk Products Supplied by PharmaBlock**



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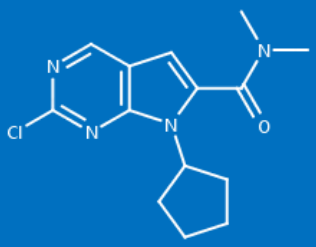

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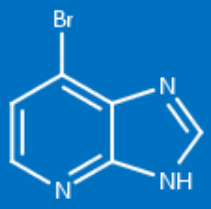

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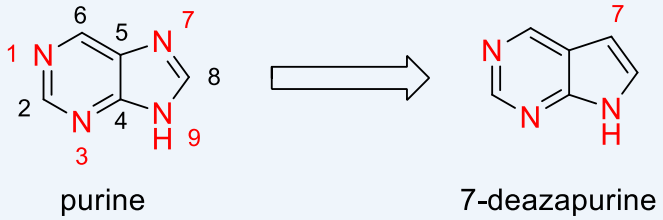
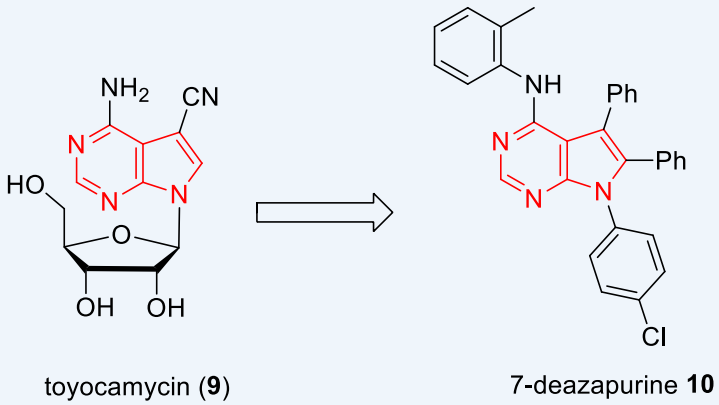
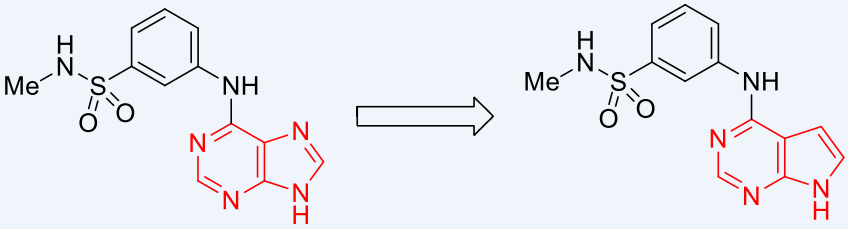



7-Deazapurine (**10**) was derived using naturally-occurring toyocamycin (**9**) as a starting point in an effort to search for non-nucleoside hepatitis C virus (HCV) NS5B polymerase inhibitors. The non-toxic doses of 7-deazapurine (**10**) on Huh 7.5 cell line was determined and its antiviral activity against HCVcc genotype was examined. The percent of reduction for the non-toxic dose of **10** was 90%.[3]




**A hit-to-lead (H2L) exercise led to 7-deazapurines as potent, selective, and orally bioavailable TNNI3K inhibitors.** From GSK's screening effort, purine **11** was identified as a good hit as a type I inhibitor of troponin I-interacting kinase (TNNI3K). But it was only moderately potent and had an extremely poor aqueous solubility. An X-ray structure of hit **11** bound to the ATP-binding site of TNNI3K confirmed its type I binding mode and was used to rationalize the structure–activity relationship (SAR). Identification of the 7-deazapurine heterocycle as a superior template (vs. purine) and its elaboration by introduction of $C_4$-benzenesulfonamide and 7-deazapurine substituents produced compounds with substantial improvements in potency and general kinase selectivity. 7-Deazapurine **12** has increased aqueous solubility (50 μM) and offers an improved rat pharmacokinetics profile (Cl = 68 mL/min/kg, F = 34%, >10-fold increase in poDNAUC, DNAUC, dose-normalized area under the curve). It has properties suitable

for use in *in vitro* and *in vivo* experiments aimed at elucidating the role of TNNI3K in cardiac biology and serve as leads for developing novel heart failure medicines.[4]



hit **11**
TNNI3K $IC_{50}$ = 500 nM
calcd p*K*a $BH^+$ = 3.2
insoluble in IV dosing vehicle
poDNAUC = 0.0 h-kg/L
> 10X selectivity against
96% (195/203) of kinome
B-Raf V600E $IC_{50}$ = 32 nM

lead **12**
TNNI3K $IC_{50}$ = 80 nM
calcd p*K*a $BH^+$ = 5.2
Cl = 68 mL/min/kg, F = 34%
poDNAUC = 0.08 h-kg/L
> 10X selectivity against
97% (180/185) of kinome
B-Raf V600E $IC_{50}$ = 50 nM

## 9-Deazapurines

A class of 9-deazapurines have been synthesized and investigated for their inhibitory power against three ATP-binding cassette (ABC) transport proteins such as P-gp, MRP1, and BCRP.

P-gp (permeability glycoprotein) is the most prevalent drug efflux transporter. In addition, multidrug resistance-associated protein 1 (MRP1) and breast cancer resistance protein (BCRP) also contribute to multidrug resistance. The development of potent and selective inhibitors of one of the three transport proteins was the focus of medicinal chemistry in the last four decades, but triple inhibitors are rare. Systemic SAR effort led to such a 9-deazapurine (7*H*-pyrrolo [3,2-*d*]pyrimidine) triple inhibitor (**13**), which was active in a very low micromolar concentration range against all three transporters and restored sensitivity toward related cells. More important, it was a non-competitive inhibitor of calcein AM (P-gp), daunorbicin (MRP1), and pheophorbide A (BCRP) transport.[5]

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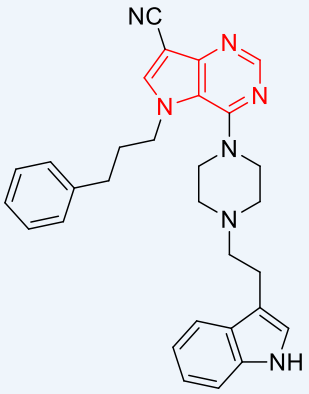



Pgp (calcein AM) $IC_{50}$, 1.46 μM

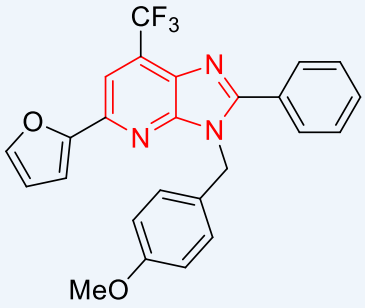
MRP1 (daunorbicin) $IC_{50}$, 0.50 μM

BCRP (pheophorbide A) $IC_{50}$, 1.69 μM

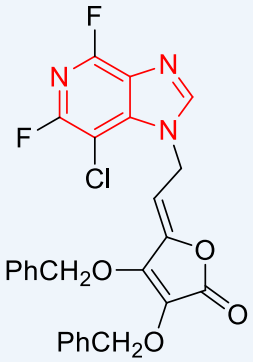
9-deazapurine triple inhibitor **13**

## 1-Deazapurines & 3-Deazapurines

Whereas 7-deazapurines occupy the most prominent position as purine isosteres, *1-deazapurines* (3*H*-imidazo[4,5-*b*]pyridines) and *3-deazapurines* (1*H*-imidazo[4,5-*c*]pyridines) also found applications in medicinal chemistry. For instance, 1-deazapurine **14** was found to be a potent compound against carbonic anhydrase-II, α-glucosidase, and β-glucuronidase.[6] Meanwhile, a novel halogenated 3-deazapurine derivative of ascorbic acid **15** showed both antitumor and antiviral activities.[7]




1-deazapurine **14**




3-deazapurine **15**

## Summary

In conclusion, deazapurines have been extensively employed as purine's bioisosteres. **Although 7-deazapurines are most frequently encountered including four drugs 1–4 on the market, 1-deazapurines, 3-deazapurines, and 9-deazapurines all found utility in discovering new drugs.**

## References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