
# Pyrrolidine Derivatives in Drug Discovery

## Key Points

- May offer enhanced aqueous solubility and other physiochemical properties

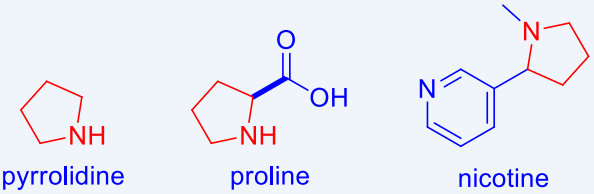
## Overview

Pyrrolidine motif on a drug may offer enhanced aqueous solubility and improve other physiochemical properties in addition to being part of the pharmacophore. The NH may serve as a hydrogen bond donor and, when its NH is masked, the N atom may serve as a hydrogen bond acceptor to its target protein. While pyrrolidine moiety appears frequently in drugs, it may have a potential liability of being bio-activated to the corresponding iminium ion and aminoaldehyde. These reactive metabolites have potential genotoxicity and mutagenicity. While this is not prevalent, it is always a good idea to be vigilant.

PharmaBlock

PharmaBlock designs and synthesizes over 3528 Pyrrolidines and 816 Pyrrolidine products are in stock. CLICK HERE to find detailed product information on webpage.

Pyrrolidine is a part of proline (Pro, P), a natural amino acid. Not surprisingly, pyrrolidine plays an important role in drug discovery. The NH group may serve as a hydrogen bond donor and, when its NH is masked as in the case for nicotine, the N atom may serve as a hydrogen bond acceptor to its target protein. Meanwhile, the pyrrolidine motif may offer enhanced aqueous solubility and other physiochemical properties in addition to being part of the pharmacophore.




**Pyrrolidine-containing Drugs**

More than two dozens of pyrrolidine-containing drugs are currently on the market. Hoechst's high-ceiling sulfonamide diuretic piretanide (Arelix, **1**) was one of the first *synthetic* pyrrolidine-containing drugs. This was partially because the synthetic methodology for installing the pyrrolidine ring to a benzene was not available until then. Angiotensin-converting enzyme (ACE) inhibitors are a class of antihypertensive drugs emerged after sulfonamide diuretics. The prototype was BMS's captopril (Capoten, **2**) approved in 1980 and its second-generation ACE inhibitor fosinopril (Fozitec, **3**) appeared on the market in 1991. To overcome captopril (**2**)'s trio of shortcomings (short half-life, rashes, and loss of taste perception), Merck took advantage of a previously unappreciated $S_1'$ hydrophobic pocket on the ACE protein and arrived at enalapril (Vasotec, **4**) and subsequently lisinopril (Zestril, **5**).

## PharmaBlock Products

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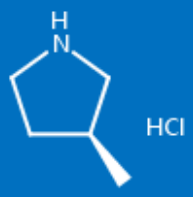


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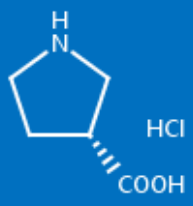


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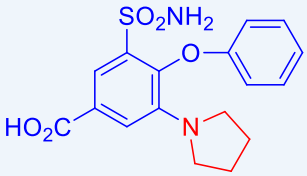
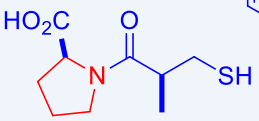
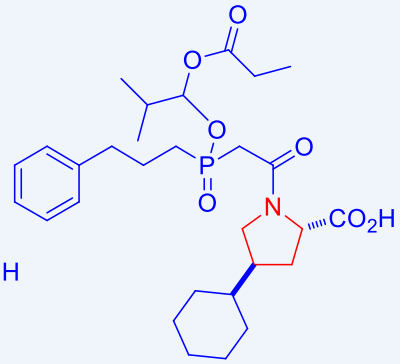


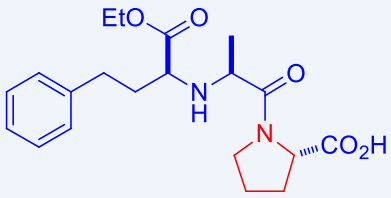

piretanide (Arelix, **1**)
Hoechst/Aventis, 1981
high-ceiling diuretic



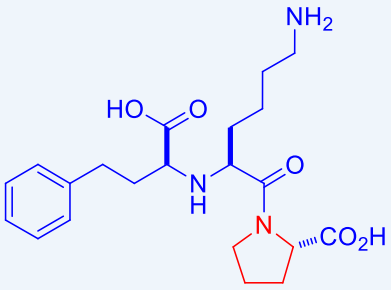

captopril (Capoten, **2**)
BMS, 1980
ACE inhibitor




fosinopril (Fozitec, **3**)
BMS, 1991
ACE inhibitor




enalapril (Vasotec, **4**)
Merck, 1984
ACE inhibitor




lisinopril (Zestril, **5**)
Merck, 1987
ACE inhibitor

In the realm of drugs to treat type II diabetes mellitus (T2DM), four of approximately 10 dipeptidyl peptidase-IV (DPP-4) inhibitors on the market contain the pyrrolidine fragment. They are Novartis' vildagliptin (Galvus, **6**), BMS' saxagliptin (Onglyza, **7**), Kenkyusho's anagliptin (Suiny, **8**), and Mitsubishi Tanabe's teneligliptin (Tenelia, **9**). The last two DPP-4 inhibitors **8** and **9** are only available in Japan. In term of mechanism of action (MOA), the nitrile group on compounds **6**–**8** forms a reversible covalent bond to $Ser_{630}$ in coordination with $Tyr_{547}$ in the $S_1$ pocket of the DPP-4 enzyme.

**PharmaBlock Products**

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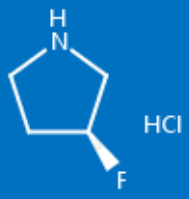

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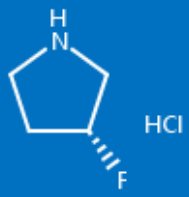

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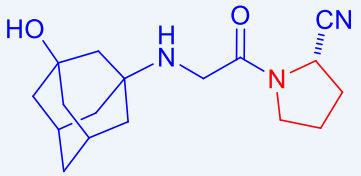
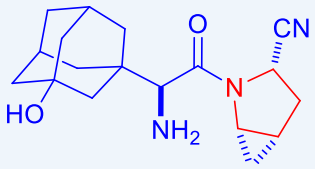
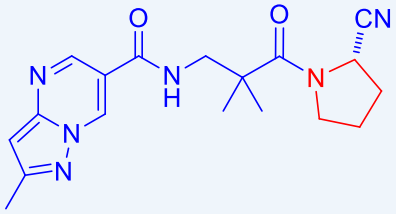


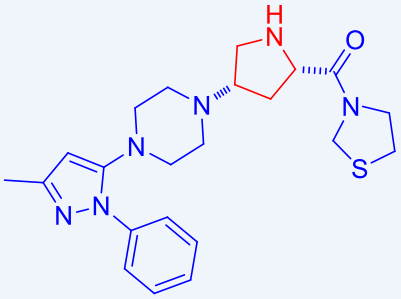
vildagliptin (Galvus, **6**)
Novartis, 2007
DPP-4 inhibitor



saxagliptin (Onglyza, **7**)
Bristol-Myers Squibb, 2009
DPP-4 inhibitor



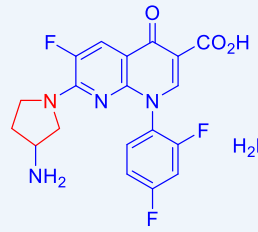
anagliptin (Suiny, **8**)
Sanwa Kagaku Kenkyusho, 2012
DPP-4 inhibitor



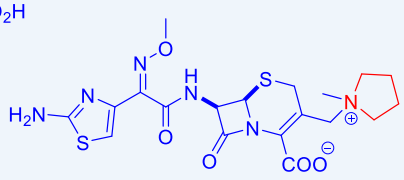
teneligliptin (Tenelia, **9**)
Mitsubishi Tanabe, 2012 (Japan)
DPP-4 inhibitor

As far as antibacterial medicines are concerned, the third generation quinolone tosufloxacin (Ozex, **10**) is only sold in Japan due to its controversial safety profile. Pyrrolidine-containing cefepime (Maxipime, **11**) is a fourth-generation cephalosporin antibiotic, which has a greater resistance to β-lactamases than third-generation cephalosporins.

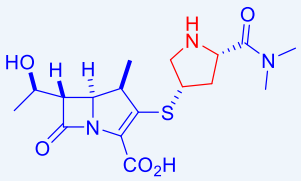
The first marketed carbapenem antibiotic in the US was imipenem (Primaxin), which does not contain a pyrrolidine. Rather, it has an amidine tail. Pyrrolidine-containing meropenem (Merrem, **12**) was the second. Incorporation of the hydrophobic pyrrolidinyl sidechain enhanced its potency against *P. aeruginosa* and other Gram-negative pathogens. Merck's ertapenem (Invanz, **13**) was the third marketed carbapenem and doripenem (Doribax, **14**), approved by the FDA in 2007, was the fourth.



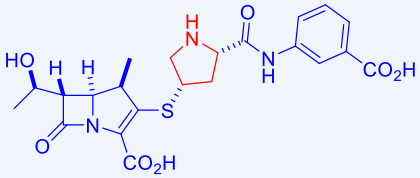
tosufloxacin (Ozex, **10**)
third generation
quinolone antibiotic



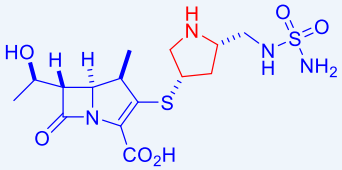
cefepime (Maxipime, **11**)
BMS, 1994
cephalosporin antibiotic



meropenem (Merrem, **12**)
AstraZeneca, 1996
carbapenem antibiotic



ertapenem (Invanz, **13**)
Merck, 2001
carbapenem antibiotic



doripenem (Doribax, **14**)
Shionogi, 2007
carbapenem antibiotic

With exception of the three MEK inhibitors, nearly all kinase inhibitors on the market are competitive inhibitors, occupying the adenine triphosphate (ATP) binding pocket. As a consequence, they possess a flat aromatic core structure, mimicking the adenine portion of ATP. However, flat aromatic compounds tend to be highly crystalline and have low aqueous solubility. Imatinib (Gleevec) has a piperazine group specifically installed to boost its solubility. For AstraZeneca/Acerta's covalent Bruton's tyrosine kinase (BTK) inhibitor acalabrutinib (Calquence, **15**), its ynamide "warhead" is attached to a pyrrolidinyl ring to improve its solubility.

Not all kinase inhibitors are cancer drugs. Abbvie's Janus kinase (JAK)1/2 inhibitor upadacitinib (Rinvoq, **16**) is approved for treating rheumatoid arthritis (RA). Its pyrrolidinyl fragment, albeit as a substituent of a urea, helps boosting the drug's solubility and improving other physiochemical properties.

**PharmaBlock Products**

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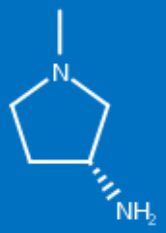

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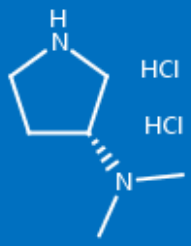

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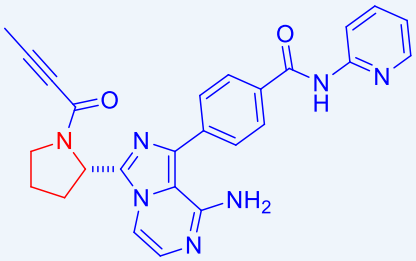
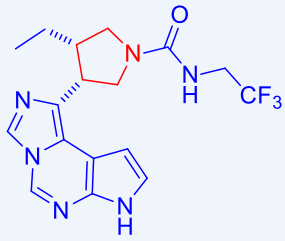
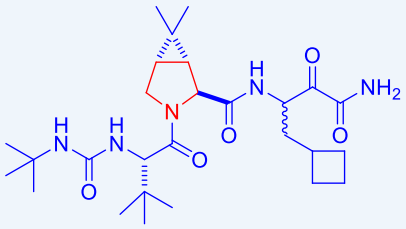


acalabrutinib (Calquence, **15**)
AZ/Acerta, 2017
BTK inhibitor

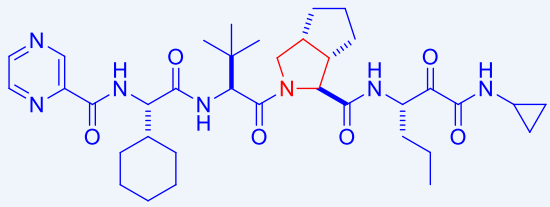


upadacitinib (Rinvoq, **16**)
Abbvie, 2019 (for RA)
JAK1/2 inhibitor

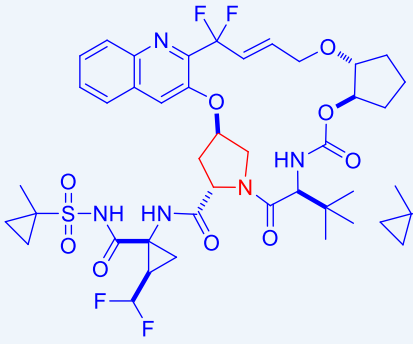
The most abundant pyrrolidine-containing drugs are found in the field of hepatitis C virus (HCV) drugs. HCV has a positive sense single-stranded RNA genome, which includes nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B. Schering–Plough/Merck's boceprevir (Victrelis, **17**) and Vertex's telaprevir (Incivek, **18**) are the first two NS3/4A serine protease inhibitors approved in 2011. Their keto-amide "warheads" form reversible covalent tetrahedral hemiacetal intermediates with the protein's serine$_{139}$ in concert with Asp$_{81}$. Both boceprevir (**17**) and telaprevir (**18**) have fused pyrrolidine backbones.



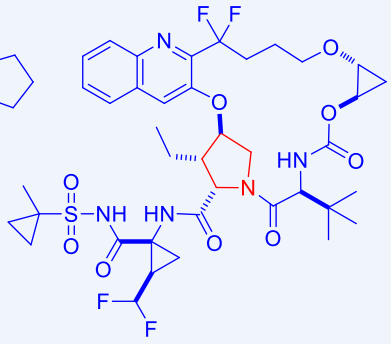
boceprevir (Victrelis, **17**)
Schering-Plough/Merck, 2011
HCV NS3/4A
Serine Protease Inhibitor



telaprevir (Incivek, **18**)
Vertex, 2011
HCV NS3/4A
Serine Protease Inhibitor

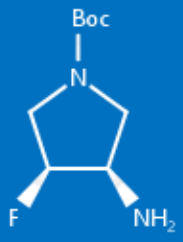


glecaprevir (Mavyret, **19**)
Gilead, 2017
HCV NS3/4A inhibitor



voxilaprevir (Vosevi, **20**)
Gilead, 2017
HCV NS3/4A inhibitor

**PharmaBlock Products**

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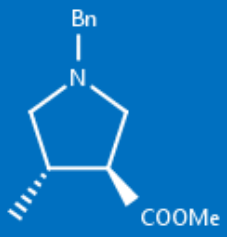
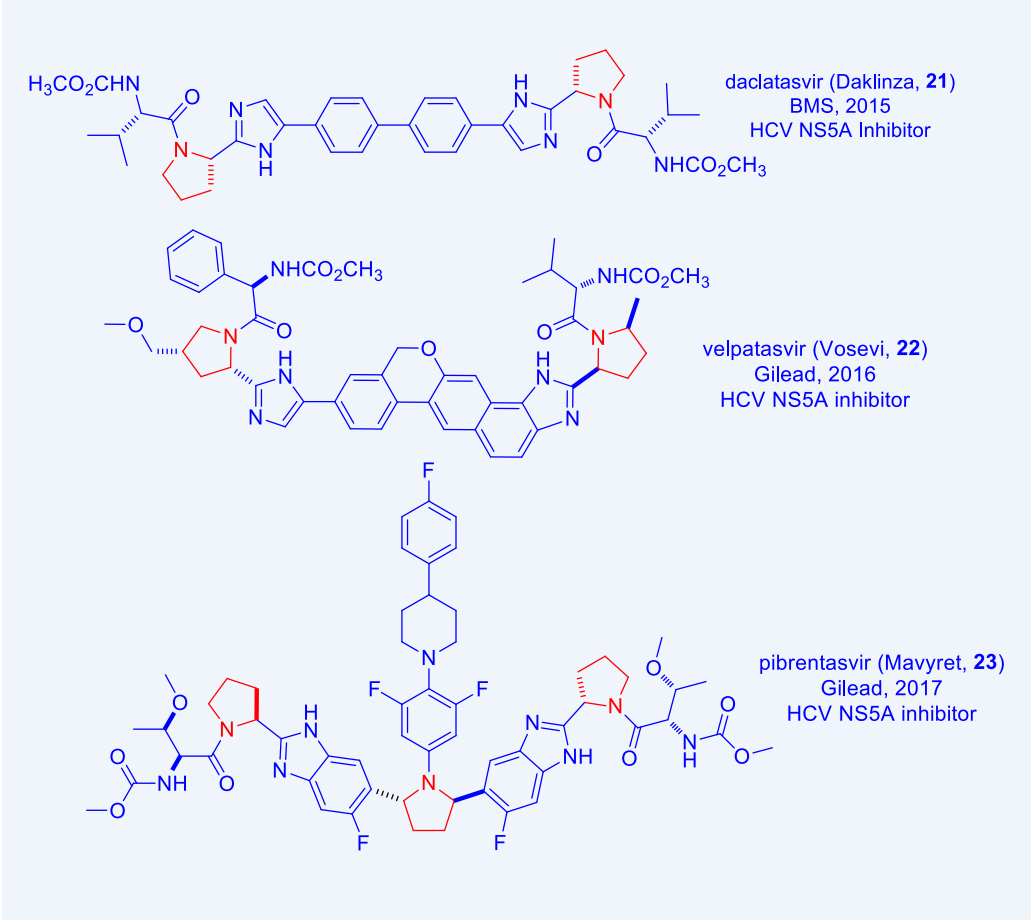



**PBLJ7457**

Four additional NS3/4A serine protease inhibitors gained the FDA approval: glecaprevir (Mavyret, **19**), voxilaprevir (Vosevi, **20**), paritaprevir, and simeprevir. The first two contain a pyrrolidine group.

Six HCV NS5A polymerase inhibitors daclatasvir (Daklinza, **21**), elbasvir, ledipasvir, ombitasvir, velpatasvir (Vosevi, **22**), and pibrentasvir (Mavyret, **23**) are currently on the market. The two NS5B polymerase inhibitors dasabuvir (Exviera) and sofosbuvir (Ribavirin), however, do not contain the pyrrolidine moiety.




Tracing their roots to procainamide, pyrrolidine-containing *o*-anisamides sultopiride (Barnetil, **24**, a sulfone), remoxipride (Roxiam, **25**), and sulpiride (dogmatil, **26**, a sulfonamide) have been used as treatments of psychosis. They are not remarkable drugs in terms of either efficacy or safety. But an important lesson may be learned here. Thanks to their intramolecular hydrogen bonds, all three very polar drugs can cross the cell membrane and blood-brain barrier (BBB) with ease.

**PharmaBlock Products**

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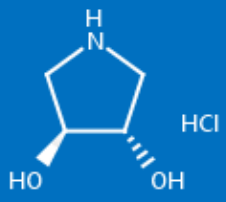


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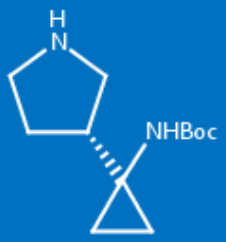
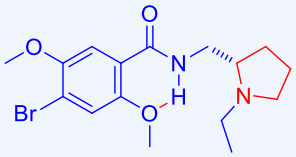
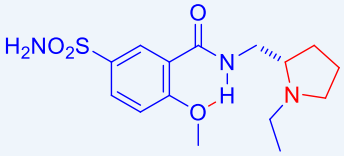



**PB94805**


sultopiride (Barnetil, **24**)
Sanofi-Aventis, 1976
atypical antipsychotic




remoxipride (Roxiam, **25**)
Astra-Zeneca, 1990
typical antipsychotic




sulpiride (dogmatil, **26**)
Sanofi, 1993
atypical antipsychotic

## Pyrrolidines in Drug Discovery

Pyrrolidine motif has been employed to improve a drug's potency, selectivity, and pharmacokinetic profile.

As a natural amino acid, proline is ubiquitous as a building block in enzymes, receptors, ion channels, and endogenous ligands. Not surprisingly, some drugs derived from nature contain the proline moiety as well.

In the early 1970s, Squibb isolated teprotide (**27**, a nonapeptide: 9 amino acids) by degrading dried extract of the venom of the poisonous Brazilian pit viper, *Bothrops jararaca*. It was shown to reduce blood pressure in healthy volunteers and confirmed that it was a selective ACE inhibitor in humans. Cushman and Ondetti at Squibb truncated teprotide (**27**) and obtained succinoyl-1-proline **28** with an $IC_{50}$ value 330 nM for ACE inhibition. The activity of **28** demonstrated that a small molecular weight drug could be a potent inhibitor of ACE by occupying only a small fraction of the extended active site cavities because the chemistry of peptide bond hydrolysis is typically dependent on a small number of critical amino acids (sometimes merely a triad of amino acids). Compound **28** was chosen as the starting point because the C-terminal amino acid occurs at the free C-terminus of all the naturally occurring peptidic inhibitors.

**PharmaBlock Products**

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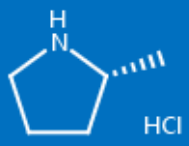

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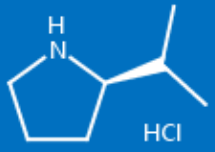
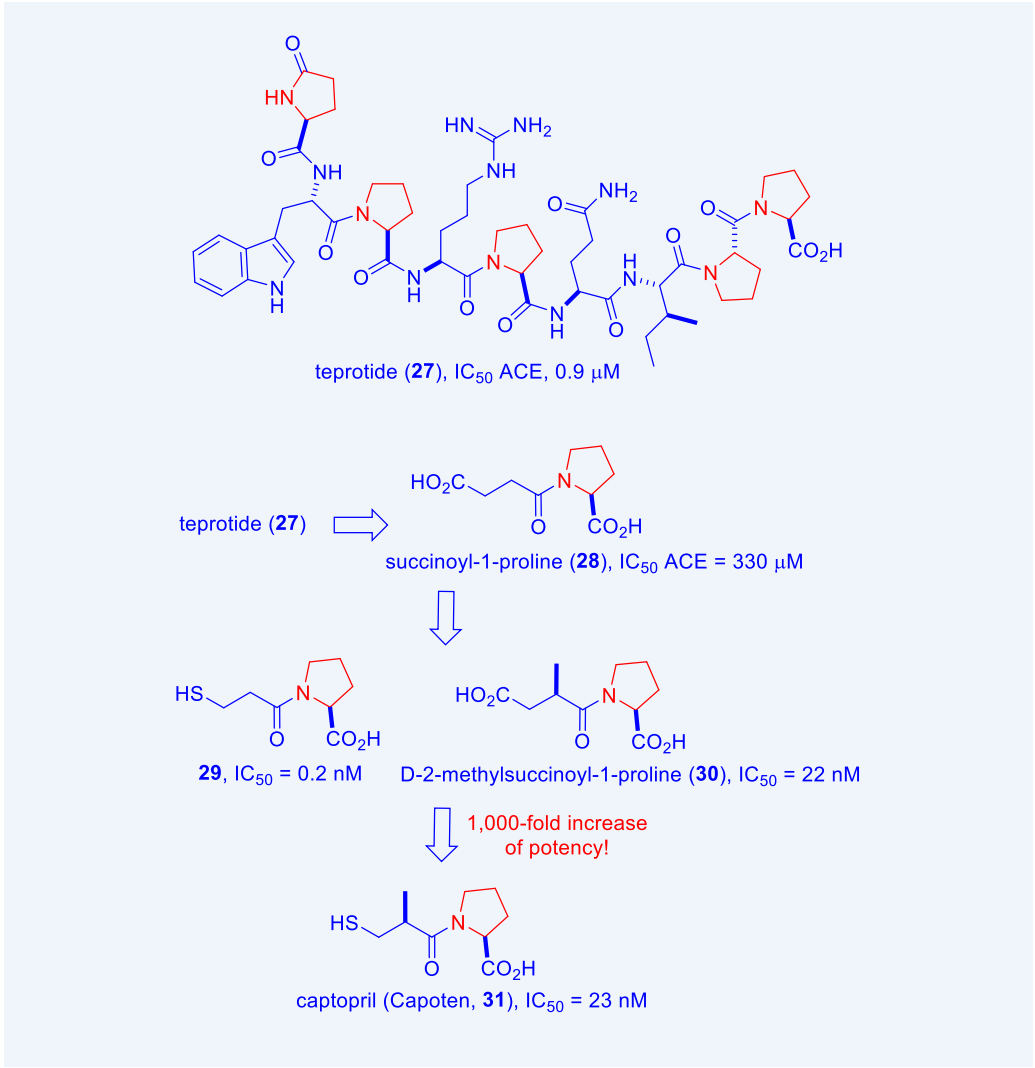


**PBLJ3281-1**

Later on, two important observations were made stemming from succinoyl-1-proline **28**. (a) A moderate boost of activity (1.6-fold) was observed when the carboxylic acid was replaced with a sulfhydryl as in **29**. (b) A significant increase of the binding activity was obtained when an extra methyl group was installed at the α-position of the amide bond, giving rise to D-(*R*)-2-methylsuccinoyl-1-proline (**30**) with an $IC_{50}$ of 22 nM. Interestingly, the L-(*S*)-enantiomer of **30** was found to be much less active. A breakthrough came when both features of **29** and **30** were incorporate into one molecule (**31**). Thus, they replaced the carboxylate group with a sulfhydryl (–SH) and installed an additional methyl group to achieve a 1,000-fold improvement in potency for ACE inhibition. The drug became the first oral ACE inhibitor, captopril (Capoten, **31**), which was approved by the FDA in 1978 and significantly contributed to the management of hypertension and hypertension-related target-organ damage. Squibb arrived at captopril (**31**) from only 60 compounds logically synthesized and tested.[1]



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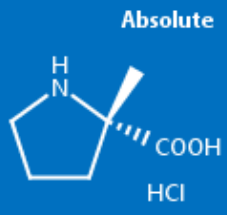


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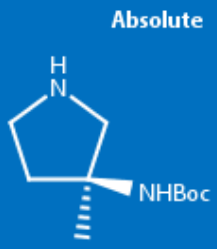
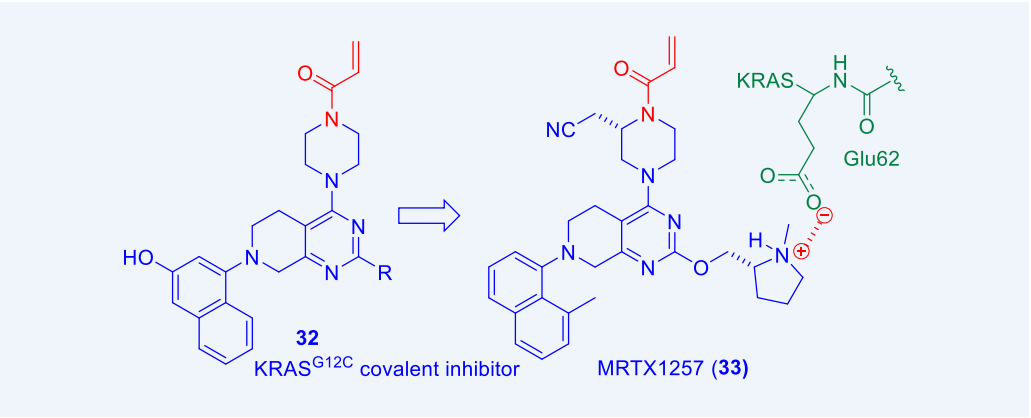


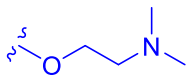
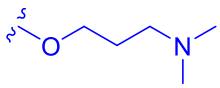
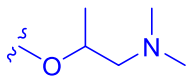
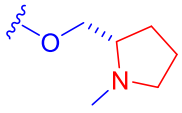
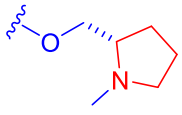

**PBXA3216**

*KRAS p.G12C* mutation is prevalent among the top most deadly cancer types in the United States: it has a causal role in 14% of lung adenocarcinomas (non-small cell lung cancer, NSCLC) and 5% of colorectal adenocarcinomas (colorectal cancer, CRC). A breakthrough came in 2013 when Shokat et al. at UCSF reported identification of compounds that covalently bound to a previously unappreciated pocket near the KRAS Switch-II effector region. The compounds form an irreversibly covalent bond to the mutant cysteine-12, locking the protein in its inactive GDP-bound state. Targeting the Switch-II binding site was a clear advance in the field.[2]

Building upon Shokat's ground-breaking discovery, Mirati and Array BioPharma pursued their own $KRAS^{G12C}$ inhibitors. Initial screening of "warheads" and SAR investigations led their discovery of compound **32a**. Its percent of control modification (POC Mod.) value was low (8%), indicating a low percentage of protein and adduct formation. This was reflected by a weaker potency in cellular assay using an H358 $KRAS^{G12C}$-driven cell line ($IC_{50}$, 7.6 μM). They hypothesized that substitution at the C-2 position of the pyrimidine ring would afford access to the carboxylate of $Glu_{62}$ on the $KRAS^{G12C}$ enzyme. The potential ionic interactions (salt bridge) with $Glu_{62}$ were tested with compounds **32b** and **32c** by varying the chain length to place a basic amine near the carboxylate. Both of these compounds were more active in the protein modification assay under the 15 min/3 μM conditions. The rigidified α-methyl analog **32d** showed a further increase in cell potency but only the (*R*)-enantiomer was seen in the cocrystal structure with $KRAS^{G12C}$. On the basis of this X-ray structure and the observed amine interactions with $Glu_{62}$ and $His_{95}$, Mirati designed compound **32e** with the aim of eliminating one rotatable bond and introducing more hydrophobic contacts with $His_{95}$. Docking studies of compound **32e** suggested that the pyrrolidine ring amine would make the same salt bridge interaction with $Glu_{62}$ and cation–π interaction with $His_{95}$. Furthermore, B-subunit of crystal structure with **32e** has pyrrolidine interacting with $Asp_{92}$ via a salt bridge and a water-mediated hydrogen bond.

Indeed, compound **32e** with the *N*-methyl pyrrolidine C-2 amine substituent displayed a dramatic boost in biochemical and cellular potency (cell $IC_{50}$ = 0.070 μM) and protein modification (POC = 84%). This potency increase was attributed to the aforementioned interactions and removal of one rotatable bond.[3] Additional efforts eventually led to orally bioavailable $KRAS^{G12C}$ covalent inhibitor MRTX1257 (**33**). Its close analog MRTX849 is currently undergoing phase I clinical trials in 2019.




| | R = | POC Mod. (15 min/3 μM) | H358 $IC_{50}$ (μM) |
|---|---|---|---|
| **32a** |  | 8% | 7.6 |
| **32b** |  | 52% | 1.9 |
| **32c** |  | 22% | 1.5 |
| **32d** |  | 21% | 0.54 |
| **32e** |  | 84% | 0.070 |
| **33** |  | 59% | 0.0009! |

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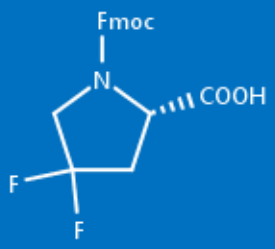
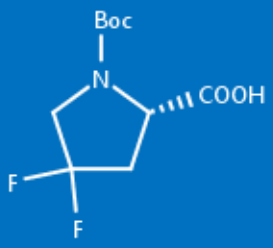
Absolute



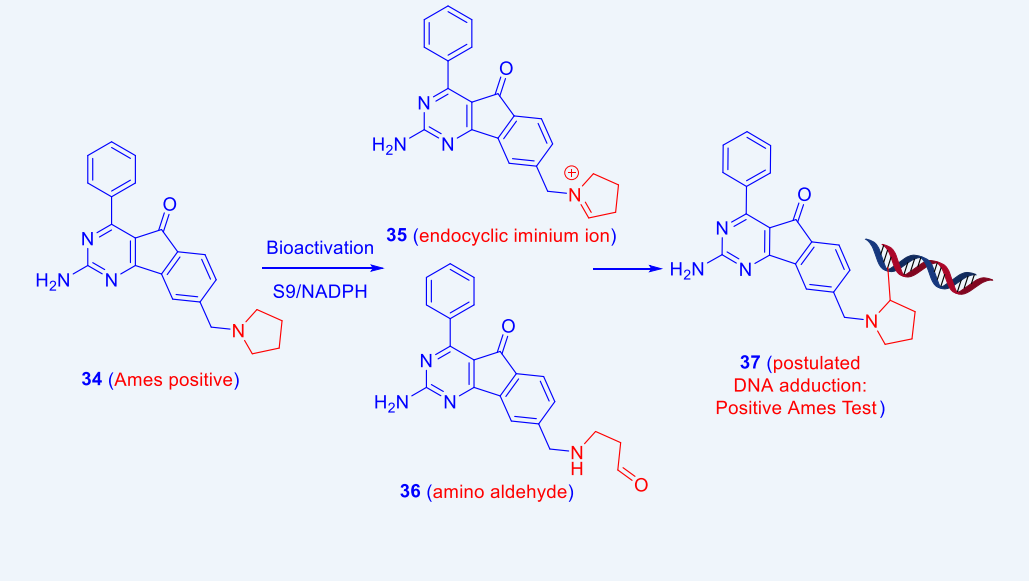

**PB93968**

Absolute



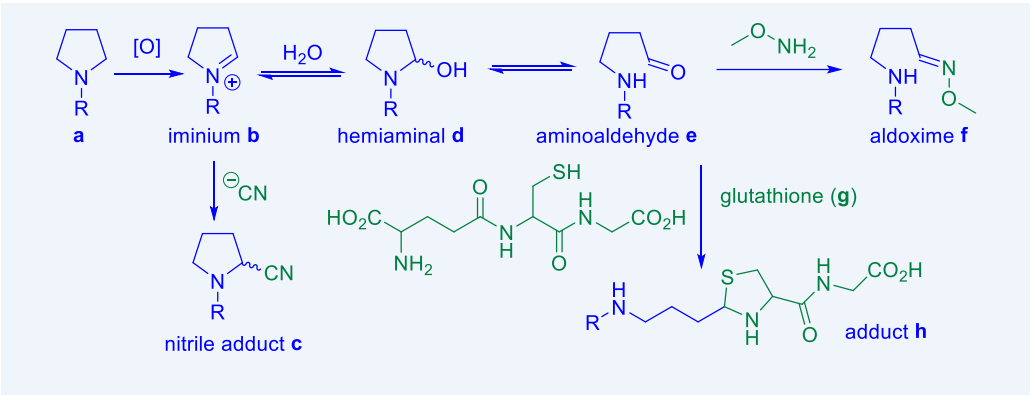

**PBN20120406**

There is a potential liability associated with pyrrolidine-containing drugs since pyrrolidine may be oxidized by CYP450 enzymes to reactive metabolites that form “hard” electrophiles with endogenous proteins. For instance, pyrrolidine-substituted arylindenopyrimidine **34** as a potent and selective dual adenosine A (2A)/A1 antagonist was determined to be genotoxic in both the bacterial *Salmonella* Ames reverse mutation and mouse lymphoma L5178Y assays (in an Aroclor 1254-induced rat liver S9/NADPH-dependent fashion).[4] It was proposed and experimentally confirmed that endocyclic iminium ion **35** and amino aldehyde **36** were the reactive metabolites after bio-activation by CYP450 enzymes. In addition to genotoxicity, it was concluded that **34** also had the potential to be mutagenic in human based on observing the endocyclic iminium ion following incubation with a human liver S9 preparation and the commensurate detection of DNA adducts **37**. It was suggested and experimentally confirmed that the corresponding dimethyl-substituted pyrrolidine and pyridine analogues were devoid of genotoxicity since those two fragments minimized their bioactivation to the corresponding iminium ion as a reactive intermediate.[4]



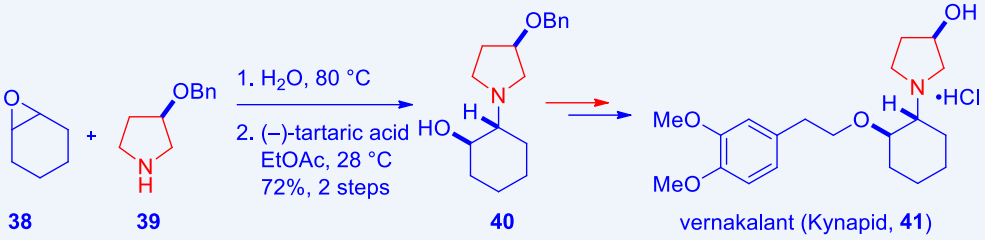
In fact, compound **34**'s genotoxicity is not unique. Cases linking the generation of iminium ion metabolites with protein covalent binding have been reported with xenobiotics such as phencyclidine (contains a piperidine ring) and nicotine (contains a pyrrolidine ring).[5]

Kalgutkar summarized the metabolic pathway of cyclic amines such as pyrrolidines and piperidines. As shown beneath, a cyclic amine as generically represented by pyrrolidine **a** is oxidized to iminium **b** by CYP450 enzymes. If cyanide was added to the experiment, monocyano adduct **c** would be obtained although addition of two cyanide groups was also possible to give the bis-cyano adduct. Under *in vivo* conditions, water addition to iminium **b** would give rise to hemiaminal **d**, which could be subsequently hydrolyzed to aminoaldehyde **e**. Again, if methoxyamine was added to the experiment, aldoxime **f** would be obtained. Otherwise, aminoaldehyde **e** would be captured by endogenous glutathione (**g**) to offer adduct **h**.[6]

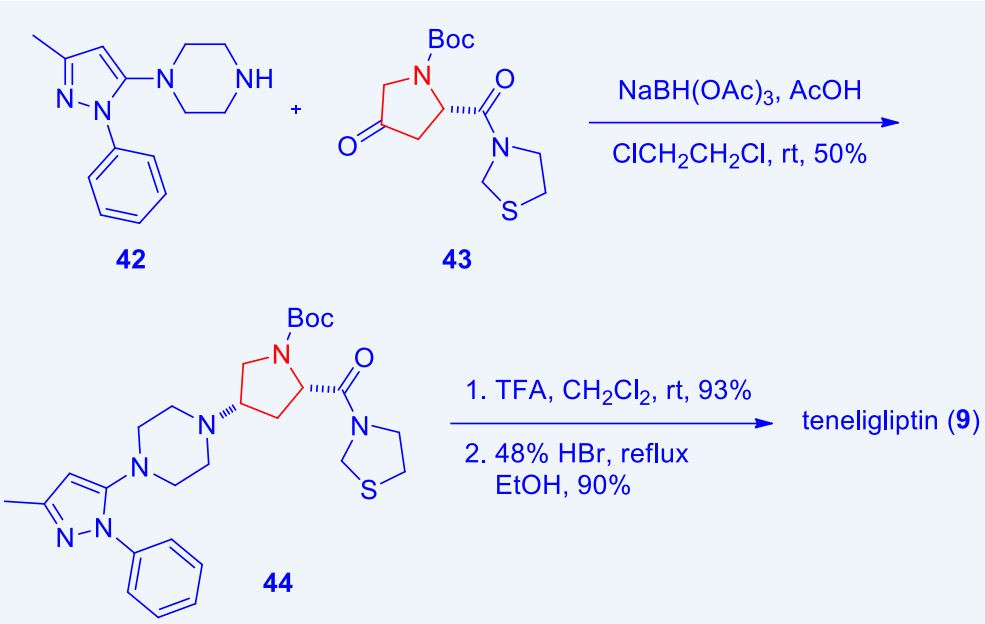



## Synthesis of Some Pyrrolidine-containing Drugs

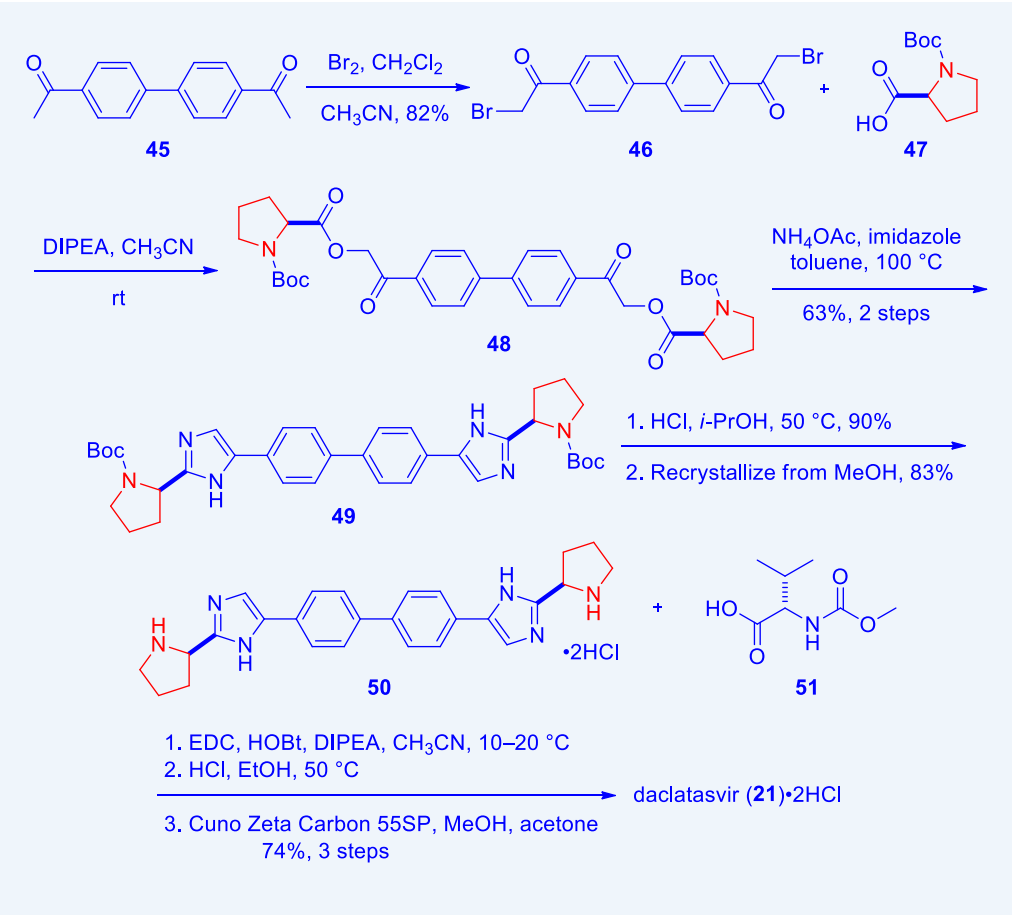
Merck's vernakalant (Kynapid, **41**) is an atrial potassium channel blocker. In one of the synthetic routes leading to vernakalant (**41**), racemic cyclohexyl epoxide (**38**) was opened with protected prolinol **39** as the nucleophile in hot water. The resulting mixture of diastereomers were separated by classical resolution of the corresponding tartrate salt to afford *cis*-isomer **40**. Subsequent ether formation from **40** was followed by debenzylation to deliver the desired active pharmaceutical ingredient (API) **41**.[7]




The only reported synthetic approach of DPP-4 inhibitor teneligliptin (**9**) resorted reductive amination of piperazine **42** and pyrrolidinone **43** to assemble adduct **44**. Deprotection of the Boc group and HBr salt formation then gave rise to teneligliptin (**9**).[8]




Synthesis of BMS' HCV NS5A replication complex inhibitor daclatasvir (**21**) commenced with bromination of bis-ketone **45** to make bis-bromide **46**. $S_N2$ displacement of the two bromide leaving groups on **46** by *N*-Boc-L-proline (**47**) assembled bis-ester **48**, which was transformed to bis-imidazole **49** by condensation of **48** with ammonium acetate. The two NH groups on the pyrrolidine rings were exposed by treating **49** with HCl and the resultant "naked" bis-pyrrolidine **50** was coupled with *N*-(methoxycarbonyl)-L-valine (**51**) to produce daclatasvir (**21**). The final API was prepared as its di-hydrochloride salt after purification with 3M's Cuno Zeta Carbon™ 55SP.[9]




Gilead's synthesis of pibrentasvir (**23**) employed an interesting Buchwald amidation. Thus, bis-phenyl chloride **52** was coupled with Boc-proline-amide **53** to assemble bis-amide **54** in 54% yield using $Pd_2(dba)_3$ as the catalyst, Xantphos as the ligand, and $Cs_2CO_3$ as the base.[10]

Not all pyrrolidine building blocks are commercially available. For more complicated pyrrolidines with many substitutions, they have to be prepared from commercially available starting materials. For instance, both pyrrolidine fragments on Gilead's HCV NS5A polymerase inhibitor velpatasvir (**22**) had to be "pre-fabricated".

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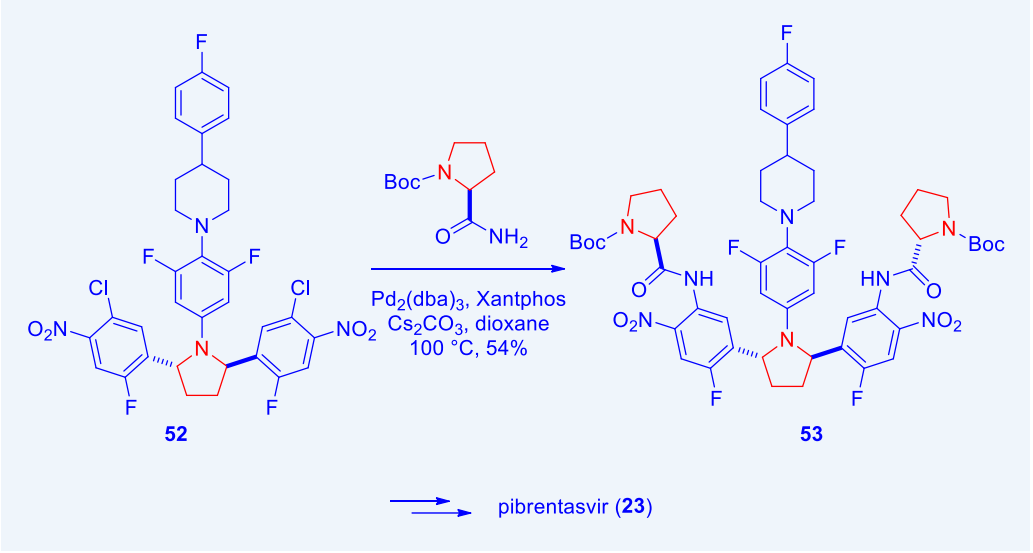
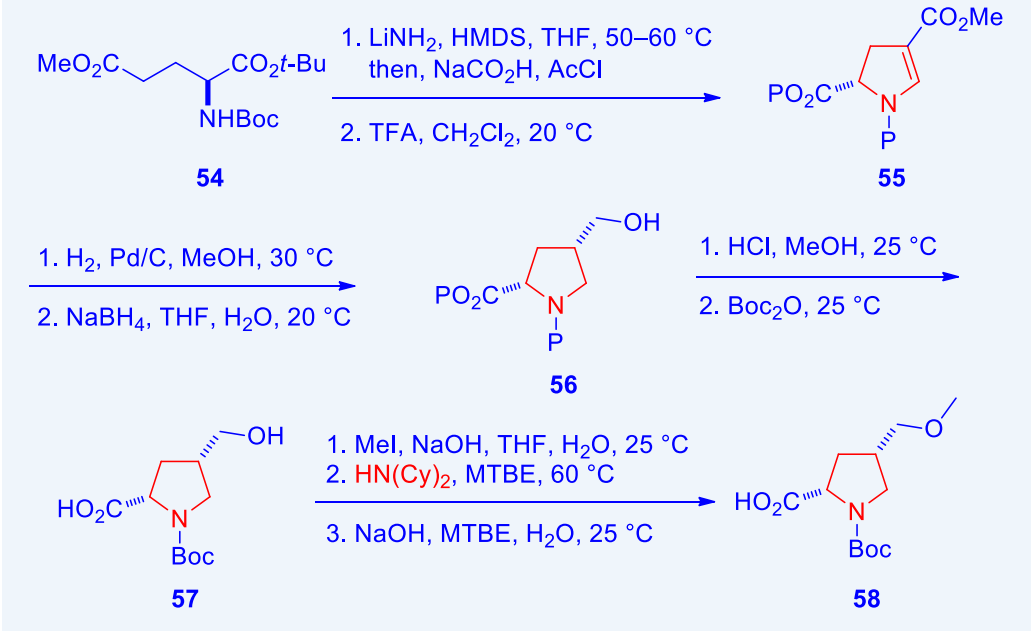



For preparation of pyrrolidine **58**, Gilead used glutamate **54** as the starting material. An intramolecular condensation of **54** was facilitated by NaHMDS and further *careful* exposure to TFA afforded dihydropyrrole **55** (there was some ambiguity on the patent with regard to the survival of the two *t*-butyl groups).[11a,b] Double reduction of **55** produced pyrrolidine alcohol **56**. After removal of both Boc and *t*-butyl ester on **56**, Boc was put back on to prepare **57**. Methylation of **57** was followed by salt formation with dicyclohexylamine [$HN(Cy)_2$, a common, useful tactic to purify carboxylic acids because dicyclohexylamine tends to form crystalline salts with acids], which allowed isolation of the desired *cis*-isomer. A subsequent "salt break" then delivered pyrrolidine **58**.[11]



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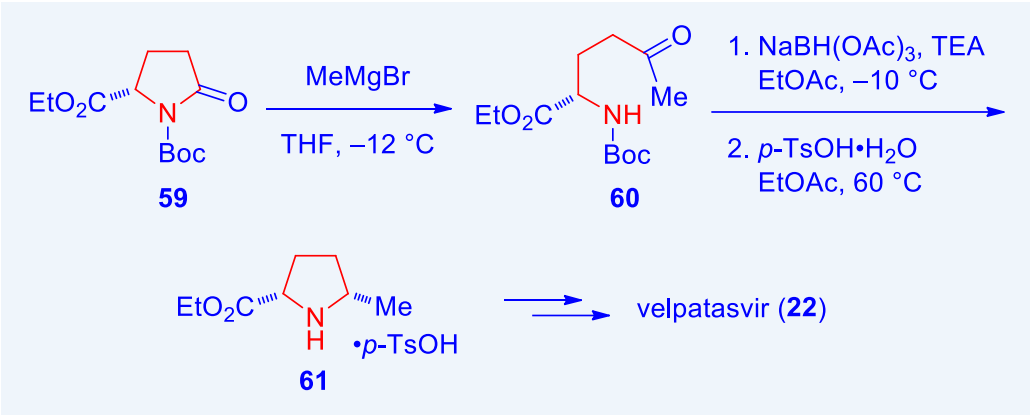
The other pyrrolidine fragment **61** was prepared from pyrrolidinone **59**, which was treated with methyl Grignard reagent to give ketone **60**. A one-pot Boc deprotection and subsequent ring-closing reductive amination assembled pyrrolidine fragment **61**. Installation of pyrrolidines **58** and **61** onto the corer structure was followed by further manipulations to deliver velpatasvir (**22**).[11]




In summary, pyrrolidine motif on a drug may offer enhanced aqueous solubility and improve other physiochemical properties in addition to being part of the pharmacophore. The NH may serve as a hydrogen bond donor and, when its NH is masked, the N atom may serve as a hydrogen bond acceptor to its target protein. While pyrrolidine moiety appears frequently in drugs, it may have a potential liability of being bioactivated to the corresponding iminium ion and aminoaldehyde. These reactive metabolites have potential genotoxicity and mutagenicity. While this is not prevalent, it is always a good idea to be vigilant.

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