Cyclohexanes in Drug Discovery

Key Points

- May function as a bioisostere for the *t*-butyl group for a deeper hydrophilic pocket on target protein.
- May offer better affinity.
- May offer more contact points with target protein.

Overview

The cyclohexyl fragment is a popular building in both natural and synthetic drugs, serving as either the core structure or as part of a peripheral side chain. The cyclohexyl group may function as a bioisostere for the *t*-butyl group for a deeper hydrophilic pocket on target protein. As a rigid version of floppy alkyl chain, the cyclohexyl replacement reduces entropy and may offer better affinity. As a bioisotere for the flat phenyl group, cyclohexyl substituent has the advantage of being three dimensional, which potentially offers more contact points with target protein. This concept has been proven in the discovery of venetoclax (Venclexta). In addition, the cyclohex*e*nyl motif is a metabolically more stable bioisostere for furanose and this concept has been demonstrated by the success of oseltamivir (Tamiflu).

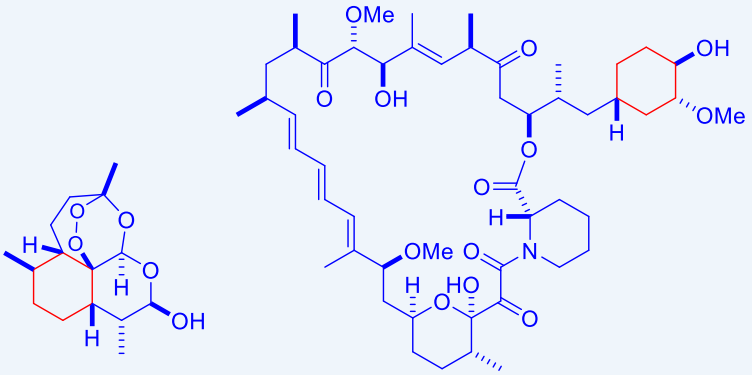
PharmaBlock

PharmaBlock designs and synthesizes over 2472 Cyclohexanes and 358 Cyclohexyl products are in stock. CLICK HERE to find detailed product information on webpage.

As a bioisotere for the *t*-butyl moiety, cyclohexyl fragment occupies more space, which could be beneficial when binding to a deeper lipophilic pocket on the target protein. On the other hand, as a bioisotere for the flat phenyl group, cyclohexyl substituent has the advantage of being three dimensional, which potentially offers more contact points with target protein.

Cyclohexane-containing Drugs

Many drugs isolated from Nature contain the cyclohexyl group either as the core structure such as in dihydroartemisinin (**1**) or on the side-chain such as in the case of sirolimus (rapamycin, Rapamune, **2**). Additional cyclohexane-containing drugs from Nature also include steroids, cocaine, FK506, lovastatin (Mevacor), simvastatin (Zocor), morphine and analogues, reserpine, streptomycin, taxol and its analogues.



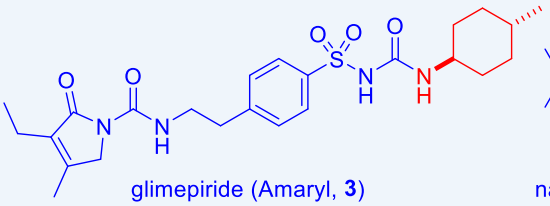
Here we focus our attention on synthetic cyclohexane-containing drugs, which encompass nearly all therapeutic areas. Glimepiride (Amaryl, **3**) is a sulfonylurea anti-diabetic. Nateglinide (Starlix, **4**), although not a sulfonylurea *per se*, is an antagonist of sulfonylurea receptor. Both are used to treat type II diabetes mellitus. In terms of CNS drugs, Wyeth's venlafaxine (Effexor, **5**) and its metabolite desvenlafaxine (Pristiq, **6**) are selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), whereas Pfizer's sertraline (Zoloft, **7**) is a selective serotonin reuptake inhibitor (SSRI).

PharmaBlock Products

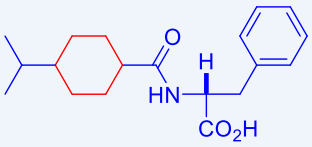
PBJL217

PBZ3534

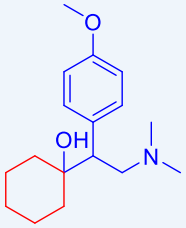
All three drugs **5**–**7** are antidepressants. The most recent entry to antidepressants is Janssen's esketamine (Spravato, **8**, as nasal spray), which modulates the glutamate/GABA neurotransmitter systems, for treatment-resistant depression (TRD). Parke–Davis' gabapentin (Neurontin, **9**) is a relatively older anticonvulsant (its mechanism of action is through inhibiting the α2-δ subunit of calcium channel), Xenoport and GSK co-developed its prodrug, gabapentin enacarbil (Horizant, **10**), which gained the FDA approval for marketing in 2011. Also in 2011, the FDA approved Dainippon's lurasidone (Latuda, **11**), which exhibits significant antagonist effects at the D_2, 5-HT_{2A}, 7-HT_7 receptors, for the treatment of schizophrenia.



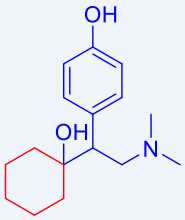
glimepiride (Amaryl, **3**)



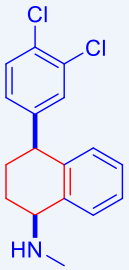
nateglinide (Starlix, **4**)



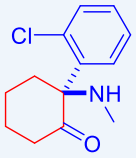
venlafaxine (Effexor, **5**)
Wyeth, 1993



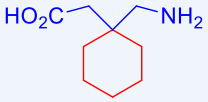
desvenlafaxine (Pristiq, **6**)
Wyeth, 2007



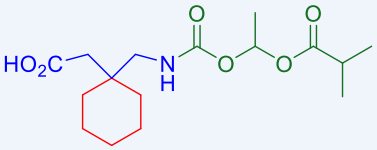
sertraline (Zoloft, **7**)
Pfizer, 1997



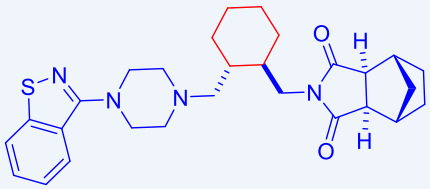
esketamine (Spravato, **8**)
Janssen, 2019



gabapentin (Neurontin, **9**)
Parke-Davis, 1993



gabapentin enacarbil
(Horizant, **10**)
Xenoport/GSK, 2011

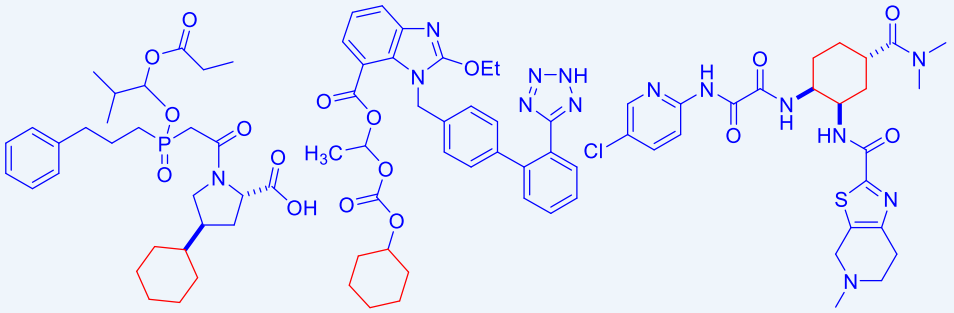


lurasidone (Latuda, **11**)
Dainippon, 2011
D_2, 5-HT_{2A}, 7-HT_7 antagonist

PharmaBlock Products

PBJL218

PBZ3148



fosinopril (Fozitec, **12**)
Squibb, 1991
ACE inhibitor

candesartan (Atacand, **13**)
AstraZeneca/Takeda, 1997
AT_1 antagonist

edoxaban (Savaysa, **14**)
Sankyo, 2011
FXa inhibitor

Several cyclohexane-containing cardiovascular drugs exist on the market. Squibb's ACE inhibitor fosinopril (Fozitec, **12**) is one and AstraZeneca's AT_1 receptor antagonist candesartan (Atacand, **13**) is another. For the latter drug, the cyclohexyl group is part of the pro-drug, which is hydrolyzed by esterases *in vivo*. Sankyo's factor Xa inhibitor edoxaban (Savaysa, **14**) has a tri-substituted cyclohexyl moiety as its core structure.

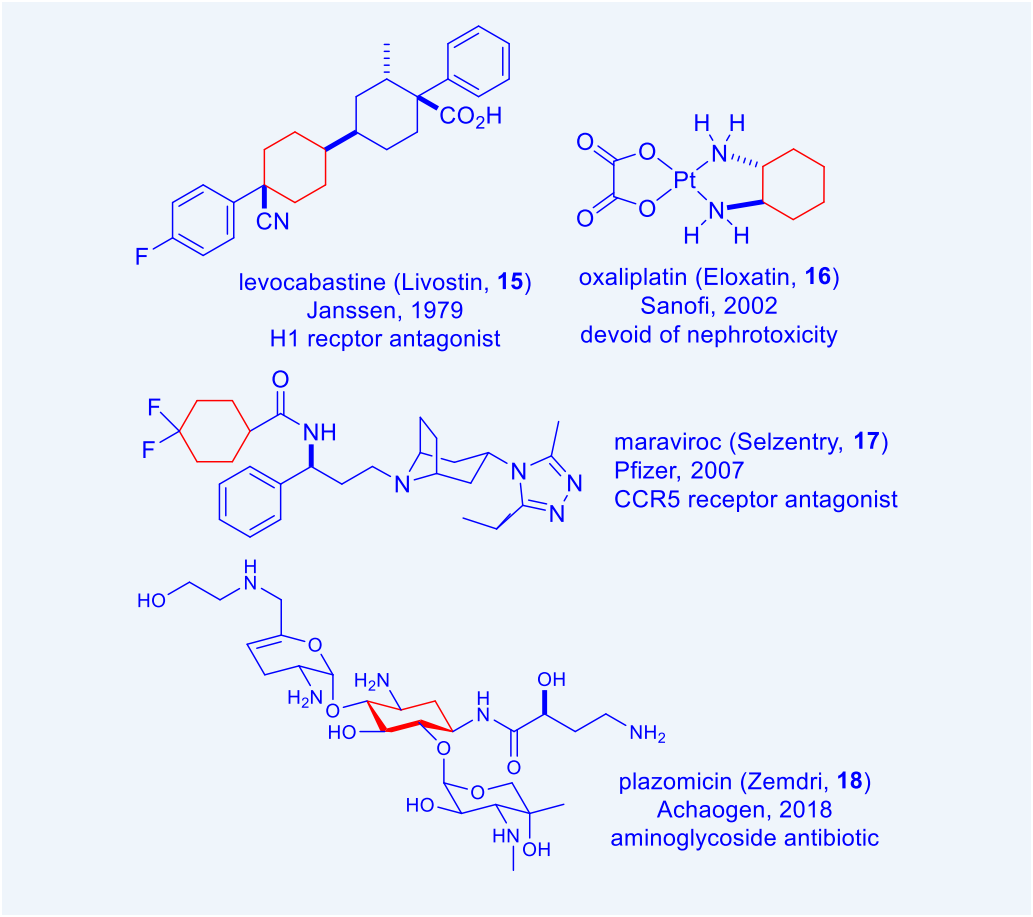
In 1979, Janssen's H_1 receptor antagonist levocabastine (Livostin, **15**), an antihistamine eye drop, garnered regulatory approval for treating eye allergies. As far as cyclohexane-containing anticancer drugs are concerned, while cisplatin is plagued by renal toxicity, its analogue oxaliplatin (Eloxatin, **16**) is devoid of nephrotoxicity. Evidently, replacing the two ammonia ligands with a *trans*-diaminocyclohexane is instrumental to the reduction of the drugs' kidney toxicity. In the field of antiviral drugs, Pfizer's CCR5 receptor antagonist maraviroc (Selzentry, **15**) has been on the market to treat HIV infection since 2007.

In 2018, the FDA approved Achaogen's aminoglycoside antibiotic plazomicin (Zemdri, **18**). Regrettably, the drug is a commercial flop and the company went bankrupt recently. Success in science does not always translate to financial success, unfortunately.

PharmaBlock Products

PBJL100441

PBZ3146

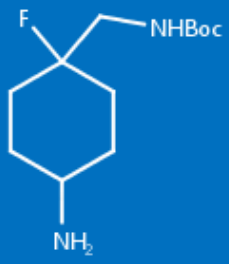


Cyclohexanes in Drug Discovery

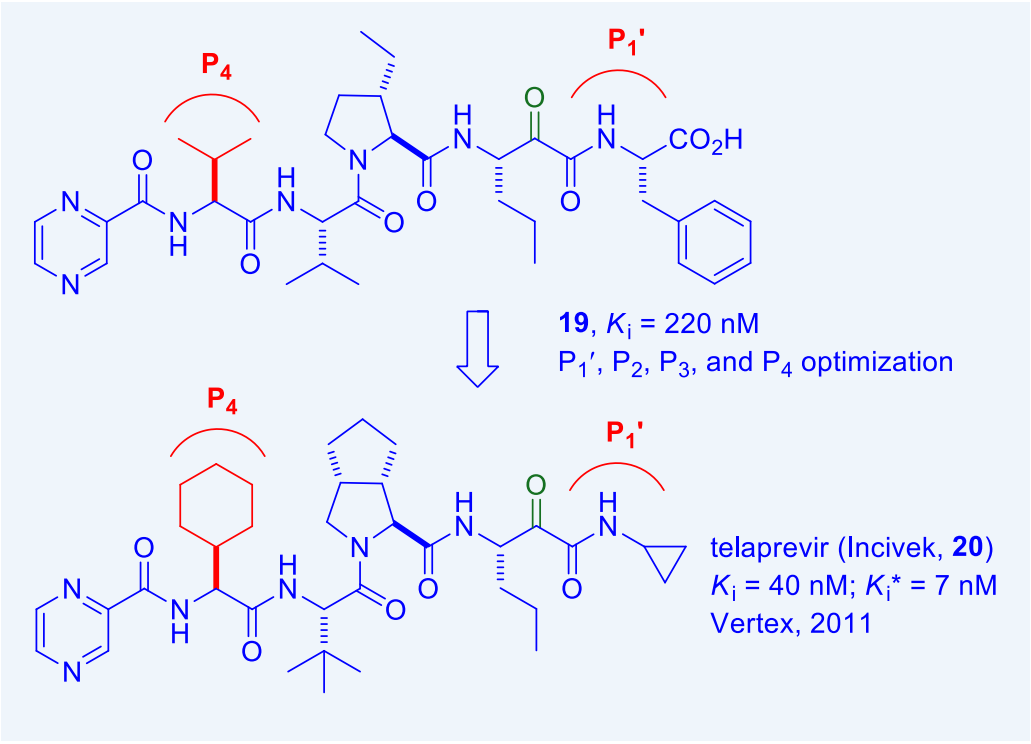
The bioisosterism between the cyclohexyl and the *t*-butyl group is amply demonstrated during the structure–activity relationship (SAR) investigations for the two marketed hepatitis C virus (HCV) non-structural protein (NS)3/4A inhibitors telaprevir (Incivek, **20**) and boceprevir (Victrelis, **21**). Both are serine protease reversible covalent inhibitors. Aided by structure-based drug design (SBDD), Vertex arrived at hexapeptide **19** with a K_i value of 200 nM. Extensive SAR efforts led to truncation of the P_1' amide. More relevantly, the P_4 position on **19** was an isopropyl fragment (not a *t*-butyl group *per se*, but a close analogue). Evidently, the corresponding S_4 pocket on the NS3/4A serine protease protein was deeper. As a consequence, employing a cyclohexyl substituent enhanced the hydrophobic binding, which eventually led to the discovery of a potent and bioavailable covalent telaprevir (Incivek, **20**) on top of P_2 and P_3 optimization.[1] That was a significant achievement of medicinal chemistry considering "Trying to land an inhibitor in the HCV protease target binding site was like trying to land a plane on a piece of pizza — it's flat and greasy and there's nothing to hang onto".[2]

PharmaBlock Products

PBJL219



PBJL221

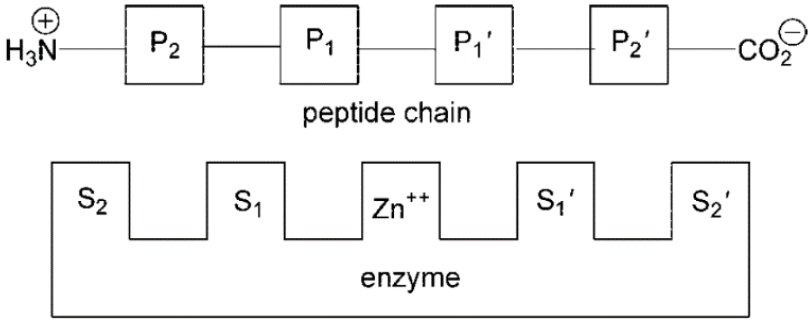


While veteran drug hunters know intimately the nomenclature of binding pockets of proteases, it might be useful to show the definition here for our novice colleagues. As shown in the scheme below, the active catalytic site serves as the reference point: the catalytic zinc in the scheme for angiotensin converting enzyme (ACE). But the NS3/4A serine protease protein's catalytic serine residue (Ser139) is the reference point, which attacks the ketoamide "warhead" and causes cleavage of the substrate. Binding pockets on the right of the catalytic site are known as prime pockets (S_1', S_2', and S_3', etc.) and binding pockets on the left of the catalytic site are known as non-prime pockets (S_1, S_2, and S_3, etc.). Correspondingly, substituents on the endogenous ligands that occupy the prime pockets are known as prime substituents (P_1', P_2', and P_3', etc.) and substituents that occupy the non-prime pockets are known as non-prime substituents (P_1, P_2, and P_3, etc.).

PharmaBlock Products

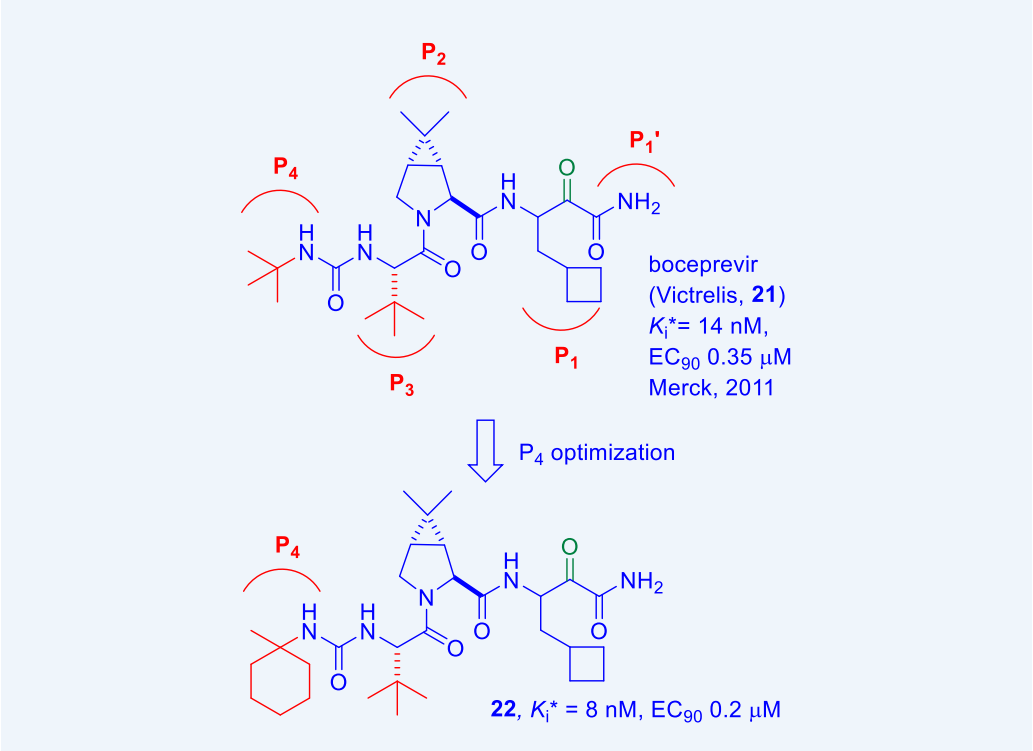
PBJL220

PBJL232



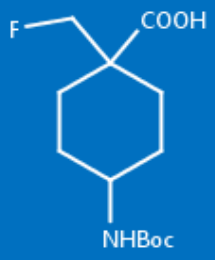
Definition of binding pockets and endogenous ligand for protease (ACE)

To improve upon boceprevir (Victrelis, **21**), Schering–Plough carried out additional SAR to develop more potent inhibitors with improved PK profile, particularly in monkeys, to target a once daily compound. Changing the P_4 group from *t*-butylurea to cyclohexylmethylurea gave rise to compound **22** with higher potency in both an enzyme assay (K_i*) and a cell-based assay (EC_{90}).[3] These efforts eventually led to the marketing of narlaprevir (Arlansa, **61**), a *t*-butylsulfonyl analogue of **22**.

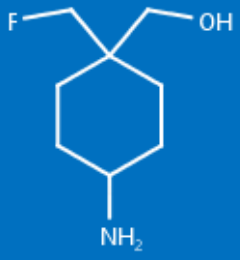


Since aripiprazole (Abilify, **23**) as a D_2 partial agonist is probably the most successful antipsychotic, many "me-too" drugs have stemmed from it. Rigidifying aripiprazole (**23**)'s floppy linear linker into a cyclohexyl ring led to the discovery of cariprazine (Vraylar, **24**), which is a D_3 (rD_3 K_i = 0.71 nM) selective partial agonist and is 13-fold more selective against the D_2 receptor (rD_2 K_i = 9.3 nM) in a rat dopamine receptor assay.[4]

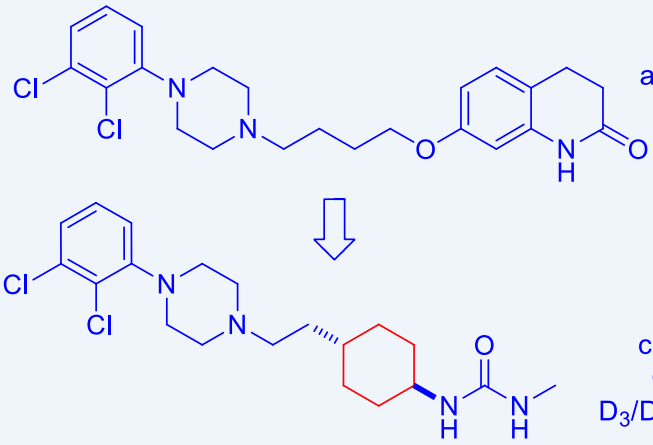
PharmaBlock Products



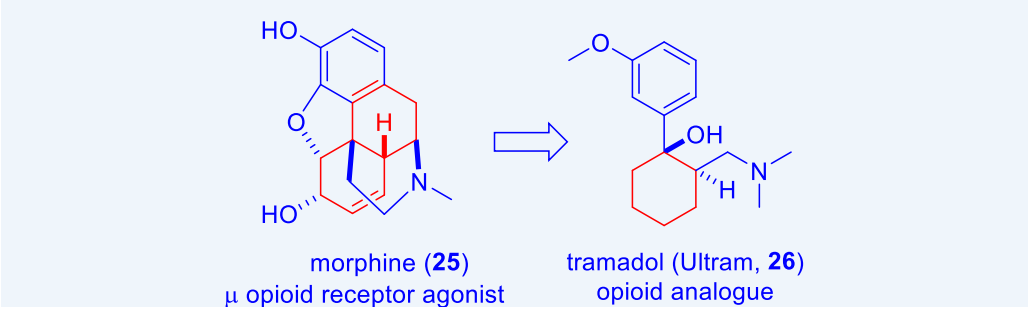
PBJL234



PBJL236

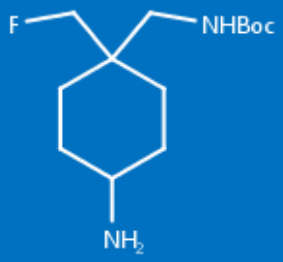


Truncation of the structure of morphine (**25**), a μ opioid receptor agonist, resulted in the discovery of a new pain medicine tramadol (Ultram, **26**) as an opioid analogue.[5] It is evident that the cyclohexyl core structure is part of the crucial pharmacophore.

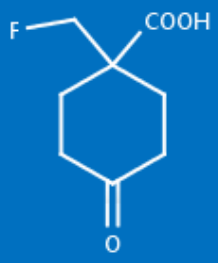


The cyclohexene ring has been employed as a bioisostere of a furanose ring since its conformational behabior is similar to that of a saturated five-membered ring and it may offer more metabolic stability.[6] The genesis of oseltamivir (Tamiflu, **28**) is a case in point. Gilead wisely chose the cyclohexene ring to replace the tetrahydropyranyl core structure on zanamivir (Relenza, **27**). Zanamivir (**27**) is so polar that it does not cross cell membrane thus has to be given via inhalation. The cyclohexene ring was expected to be chemically and enzymatically stable, to be suited for chemical modifications, and, more importantly, to be suitable bioisostere of the proposed oxonium cation in the transition state of sialic acid cleavage by neuraminidase.[7] Indeed, oseltamivir (Tamiflu, **28**) is orally bioavailable with a bioavailability of 75% and a half-life of 6–10 h.

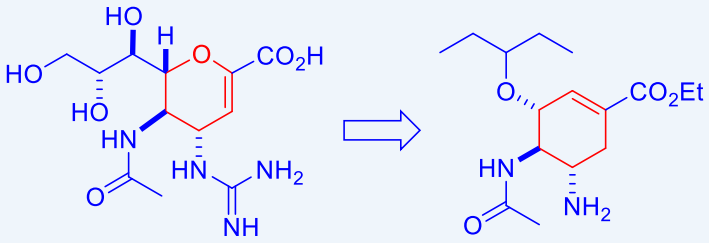
PharmaBlock Products



PBJL237

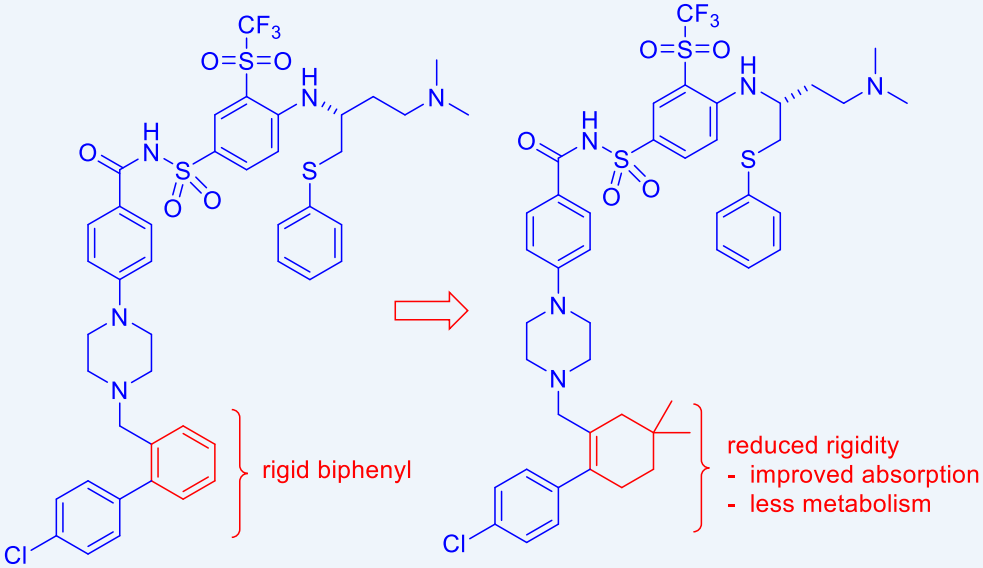


PBJL231



zanamivir (Relenza, **27**) oseltamivir (Tamiflu, **28**)

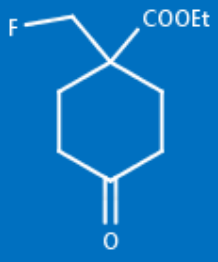
In the same vein, *en route* to the discovery of its ground-breaking B-cell lymphoma-2 (BCL-2) inhibitor venetoclax (Venclexta, **31**) via fragment-based drug discovery (FBDD), Abbvie arrived at compound **29** with a rigid biphenyl structure. Switching one of the phenyl ring to cyclohexene provided an opportunity to make ring modifications that were fundamentally different from those that were made to the aromatic ring in its place. Simply bulking up the ring by adding alkyl groups produced the dimethylcyclohexene **30**, which had still higher plasma levels, and also appeared to improve tissue/plasma distributions in various pharmacokinetic models.[8] Addition of the dimethyl group was a great idea since it eliminates the metabolic liability associated with simple cyclohexenes, which are prone to be oxidized to the corresponding aromatic phenyl analogue.



29, $AUC_{0-8\ h}$ = 0.87 μg/mL
F%, 8.7
EC_{50} = 39 nM,
H146 SCLC cells, 10% srum
AUC/EC_{50} = 19

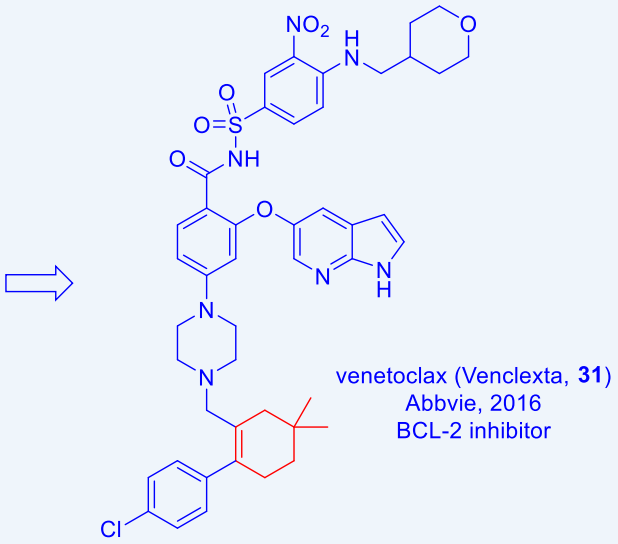
30, $AUC_{0-8\ h}$ = 2.9 μg/mL
F%, 14
EC_{50} = 28 nM,
H146 SCLC cells, 10% srum
AUC/EC_{50} = 104

PharmaBlock Products



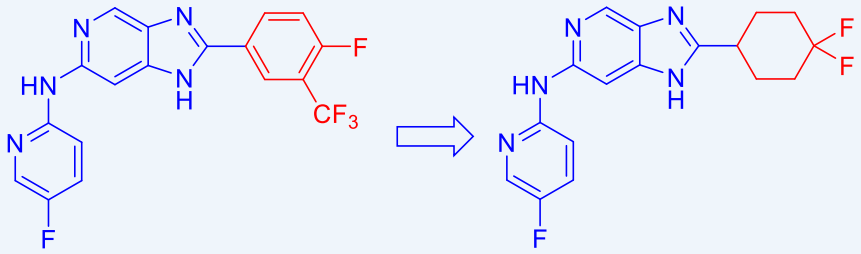
PBS63459

PBSQA149



venetoclax (Venclexta, **31**)
Abbvie, 2016
BCL-2 inhibitor

The cyclohexyl fragment helps breaking the crystal lattices and boosts aqueous solubility in imidazopyridine antimalarial drugs. Compound **32** as an NF54 inhibitor was rather potent (IC_{50}, 18 nM) but suffered poor aqueous solubility. Replacing the 1-fluoro-2-(trifluoromethyl)phenyl group with a 1,1-difluorocyclohexyl substituent gave rise to compound **33**, which was 3.8-fold less potent than **32** but enjoyed greatly improved aqueous solubility at both pH2 and pH6.5, respectively.[9]



32
aq. solubility at pH2, 13 μM
aq. solubility at pH6.5, < 5 μM

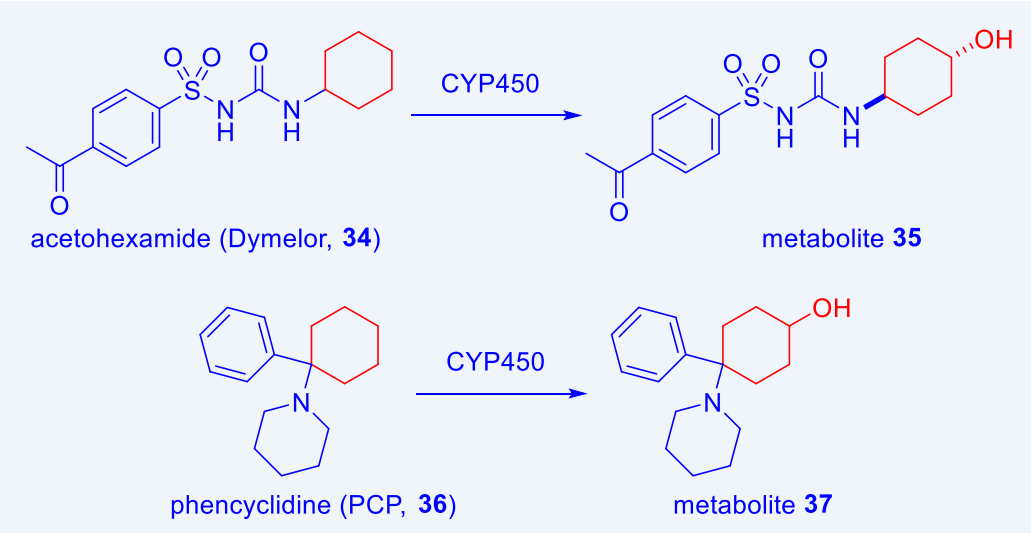
33
aq. solubility at pH2, 200 μM
aq. solubility at pH6.5, 170 μM

PharmaBlock Products

PBJL224

PBJL226

Being greasy, the cyclohexyl motif is prone to CYP450 oxidation to the corresponding cyclohexanol. For instance, one of the major metabolites of sulfonylurea drug acetohexamide (Dymelor, **34**, for the treatment of type II diabetes mellitus) is *para*-hydroxylhexyl derivative **35**. Another key metabolite of acetohexamide (**34**) is the secondary alcohol from reduction of the acetyl group by carbonyl reductase.[10] In a similar manner, phencyclidine (PCP, **36**) is metabolized to the corresponding *para*-hydroxyhexyl derivative **37**.[11]

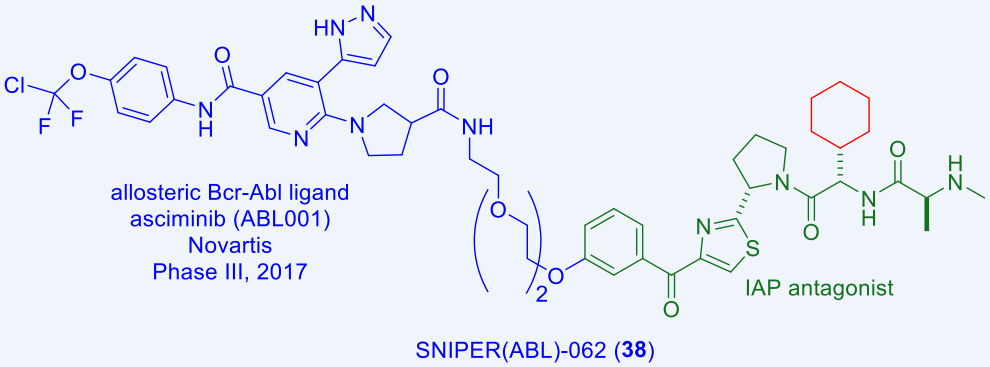


Proteolysis targeting chimera (PROTAC) as a drug discovery approach has gained much momentum lately since Arvinas' androgen receptor protein degrader ARV-110 advanced to phase I clinical trials in 2019. A similar technique, Specific and Non-genetic IAP-dependent Protein Eraser (SNIPER), employs small molecule ligands for E3 ubiquitin ligases cIAP1 (cellular inhibitor of apoptosis protein), which contains a cyclohexyl substituent. For instance, SNIPER(ABL)-062 (**38**) showed binding affinities against ABL1, cIAP1/2, and XIAP and induced potent Bcr-Abl protein degradation.[12] Asciminib is the first allosteric kinase inhibitor in clinical trials.

PharmaBlock Products

PBJL227

PBJL230



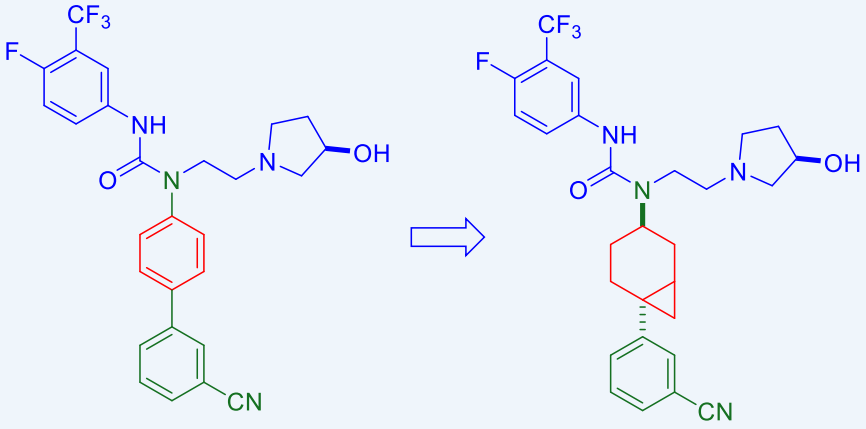
SNIPER(ABL)-062 (**38**)

Schering–Plough employed bicycle[4.1.0]heptanes as phenyl isosteres for their melanin-concentrating hormone (MCH) receptors antagonists, which have potential as treatment of obesity. Compound **39** was a potent MCH-R1 antagonist which exhibited oral efficacy in chronic (28 days) rodent models, reducing cumulative food intake and body weight gain relative to vehicle controls. Unfortunately, the biphenyl amine moiety (in green and red) was a very potent mutagenic agent as indicated by its strong positive result in an Ames test. Although the biphenylamine itself was not formed *in vivo*, it was deemed unsuitable for development because of the potential risk of exposure to such a highly mutagenic precursor. Replacing the middle phenyl ring with pyrazine, pyrimidine and saturated derivatives such as piperidines, their MCH-R1 activities were drastically reduced. While the cyclohexenyl replacement was extremely active (K_i = 3 nM), the cyclohexenyl fragment has a dual liability of intrinsic metabolic instability associated with the styrene and its potential for generating a biphenylamine via aromatization. Further exploration to discover more stable analogues led to cyclopropanation of the double bond to form a bicyclo[4.1.0]alkyl group achieved this goal. The bicyclo[4.1.0]heptanyl analogue **40** had a comparable binding affinity and similar efficacy in obese animal models and it was devoid of the mutagenicity issue associated with biphenylamine derivatives.[13]

PharmaBlock Products

PBJL228

PBJL223

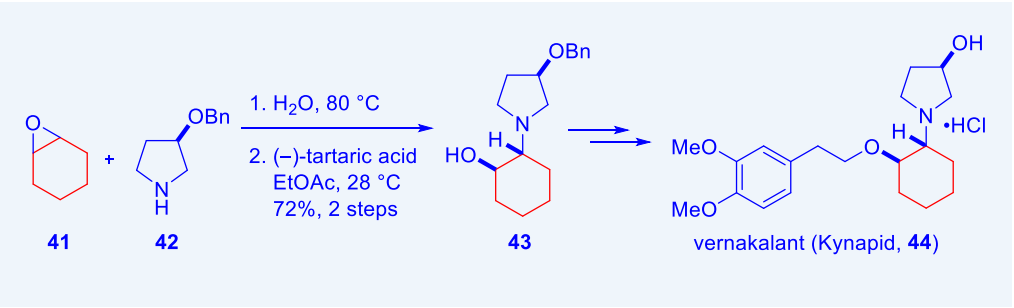


39
MCH-R1 K_i = 2 nM
diet-induced obese (DIO)
at 6 h = 17% @30 mg/kg

40
12 nM
DIO =
16%

Synthesis of Some Cyclohexane-containing Drugs

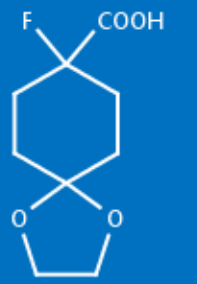
Merck's vernakalant (Kynapid, **44**) is an atrial potassium channel blocker. In one of the synthetic routes leading to vernakalant (**44**), racemic cyclohexyl epoxide (**41**) was opened with protected prolinol **42** as the nucleophile in hot water. The resulting mixture of diastereomers were separated by classical resolution of the corresponding tartrate salt to afford *cis*-isomer **43**. Subsequent ether formation from **43** was followed by de-benzylation to deliver the desired active pharmaceutical ingredient (API) **44**.[14]



41 **42** **43** vernakalant (Kynapid, **44**)

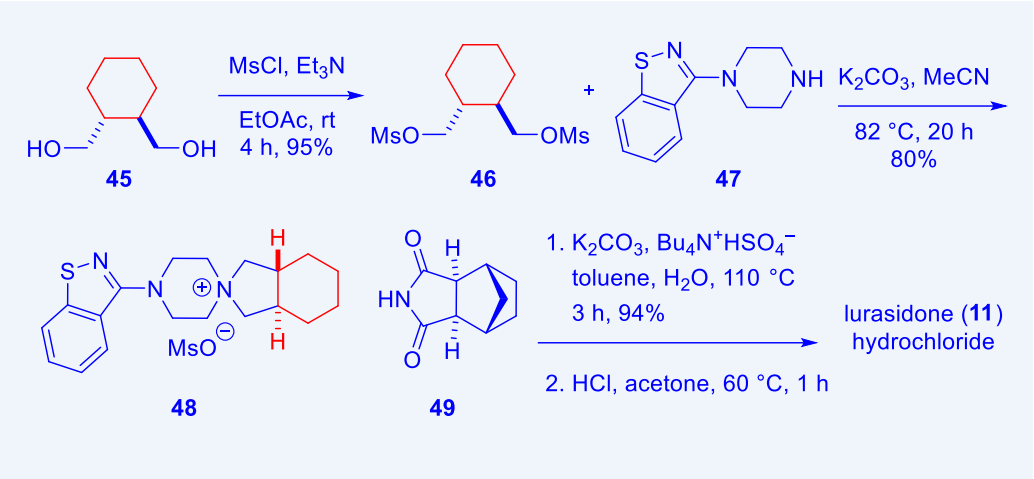
PharmaBlock Products

PBJL222



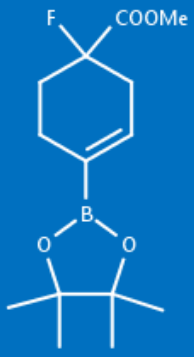
PBLJ00046

Dainippon's preparation of lurasidone (Latuda, **11**) commenced with mesylation of commercially available diol **45** to give bis-mesylate **46**. Condensation of bis-electrophile **46** with aryl-piperizine **47** offered dialkylation product as ammonium salt **48**. Since **48** is such a reactive intermediate, its S_N2 reaction with succinimide **49** readily took place to deliver lurasidone (**11**), which was conveniently converted to lurasidone hydrochloride as the API.[15]

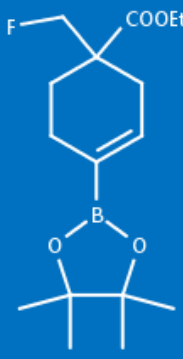


Production of Sankyo's FXa inhibitor edoxaban (Savaysa, **14**) began with cyclohexyl epoxide **50** as the starting material. Regio-specific S_N2 reaction with sodium azide gave the corresponding hydroxyazide intermediate, which was converted to alcohol **51** via palladium-catalyzed hydrogenation in the presence of Boc_2O. Mesylation of **51** and another S_N2 reaction with sodium azide produced azide **52**, which underwent another palladium-catalyzed hydrogenation and protection sequence to offer, this time, Cbz carbamate-protected amine **53**. Saponification of the ester group on **53** produced the acid, which was coupled with dimethylamine-HCl salt to form amide **54**. Removal of the Cbz protection and reaction of the exposed primary amine with oxalic acid gave rise to oxalate salt **55**, which was eventually transformed to the API edoxaban (Savaysa, **14**) after 5 additional steps.[16]

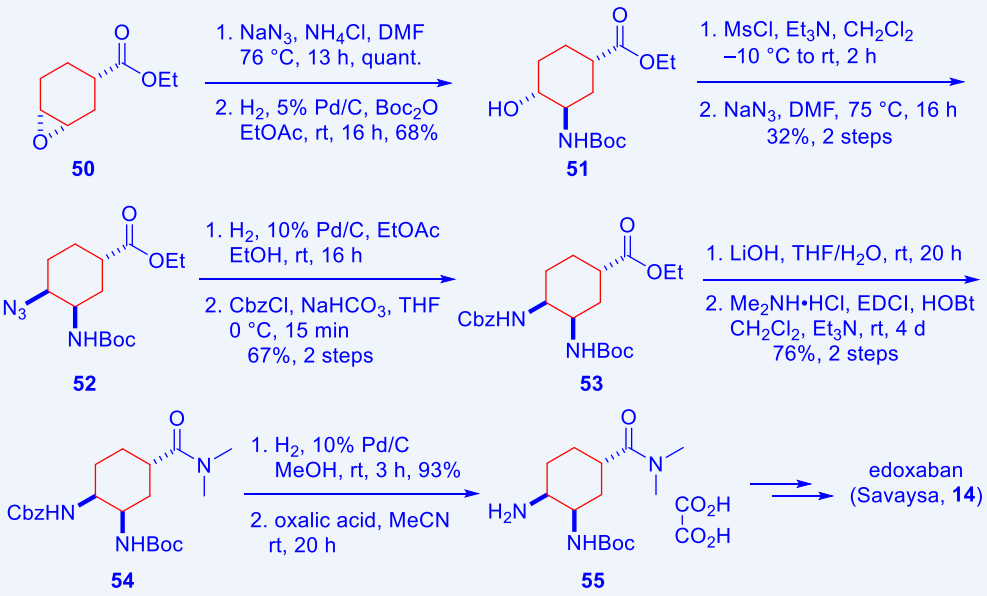
PharmaBlock Products



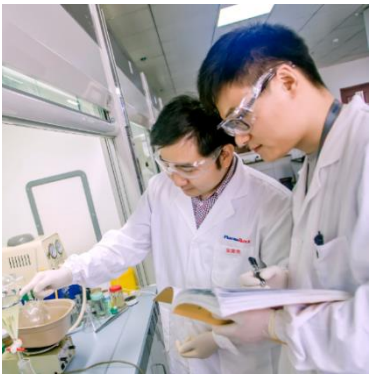
PB92896



PBS63460

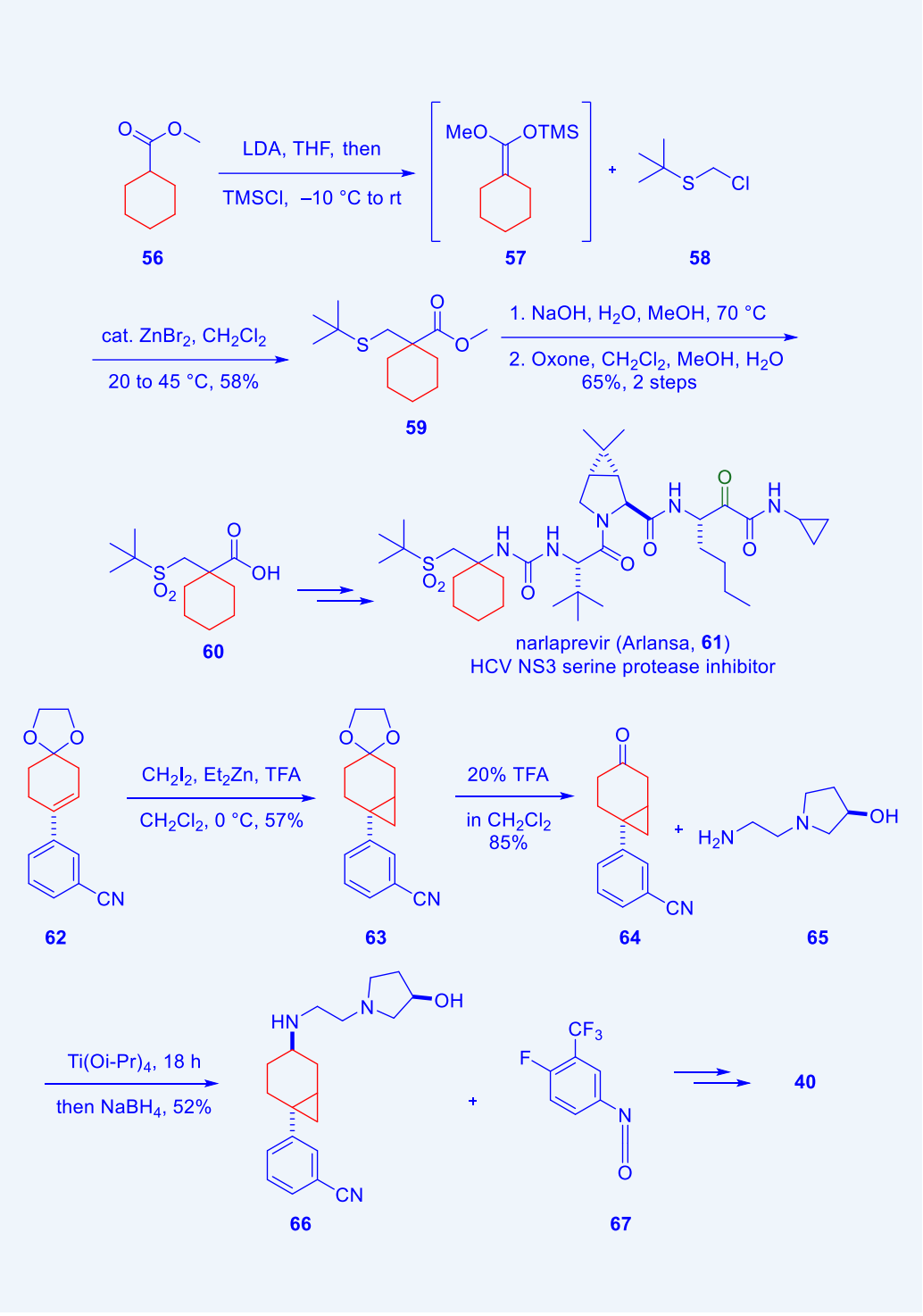


Methyl cyclohexylcarboxylate (**56**) was employed as the starting material for the synthesis of HCV NS3 serine protease inhibitor narlaprevir (Arlansa, **61**). Silyl enol ether **57** was generated *in situ* by treating **54** with freshly prepared LDA followed by quenching with TMSCl. It was immediately treated chloride **58** under Lewis acid catalysis to assemble adduct **59**. Subsequently, the ester on **59** was hydrolyzed to the corresponding acid and the sulfide was oxidized by Oxone to the corresponding sulfone **60**. Coupling of the key cyclohexyl intermediate **60** with three amino acid fragments delivered narlaprevir (**61**) in another additional 6 steps.[17]



PharmaBlock is recognized for its outstanding capability in the design, synthesis, production and commercialization of novel building blocks for use throughout the drug R&D process.

- 80,000+ building blocks
- 16,000+ in stock in both USA and China
- 20,000+ supplied within two weeks
- 1,000+ SAR tool kits
- Novel building blocks designed upon daily monitoring on recent researches and patents
- Keep optimizing cost effective route for better price and sustainable supply
- Fast delivery of custom synthesis
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance



Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel (PA): 1-877 878 5226
Tel (CA): 1-267 649 7271
Email: salesusa@pharmablock.com

Schering–Plough's synthesis of the bicyclo[4.1.0]heptanyl analogue **40** involved a modified Simmons–Smith reaction. Thus, cyclopropanation of cyclohexene **62** was achieved by treating **62** with CH_2I_2 and Et_2Zn in the presence of TFA to give bicyclo[4.1.0]heptanyl **63**. After removal of the ketal protection, the resulting ketone **64** underwent a reductive amination with amine **65** to afford adduct **66**. To avoid direct ketone reduction by $NaBH_4$, the imine intermediate was pre-formed with the aid of $Ti(O\textit{i}\text{-}Pr)_4$ before adding $NaBH_4$. Coupling between **66** with isocynate **67** then delivered the final product **40** after chiral separation.[13]

To conclude, the cyclohexyl fragment is a popular building in both natural and synthetic drugs, serving as either the core structure or as part of a peripheral side chain. The cyclohexyl group may function as a bioisostere for the *t*-butyl group for a deeper hydrophilic pocket on target protein. As a rigid version of floppy alkyl chain, the cyclohexyl replacement reduces entropy and may offer better affinity. As a bioisotere for the flat phenyl group, cyclohexyl substituent has the advantage of being three dimensional, which potentially offers more contact points with target protein. This concept has been proven in the discovery of venetoclax (Venclexta). In addition, the cyclohexenyl motif is a metabolically more stable bioisostere for furanose and this concept has been demonstrated by the success of oseltamivir (Tamiflu).

References

1. Lin, C.; Kwong, A. D.; Perni, R. B. *Infect. Disord. Drug Targets* **2006**, *6*, 3–16.
2. Kwong, A. D.; Kauffman, R. S.; Hurter, P.; Mueller, P. *Nat. Biotechnol.* **2011**, *29*, 993–1003.
3. Bennett, F.; Huang, Y.; Hendrata, S.; Lovey, R.; Bogen, S. L.; Pan, W.; Guo, Z.; Prongay, A.; Chen, K. X.; Arasappan, A.; et al. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 2617–2621.
4. Ágai-Csongor, E.; Domány, G.; Nógrádi, K.; Galambos, J.; Vágó, I.; Keserü, G. M.; Greiner, I.; Laszlovszky, I.; Gere, A.; Schmidt, E.; et al. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 3437–3440.
5. Bravo, L.; Berrocoso, E.; Mico, J. A. *Exp. Opin. Drug Discov.* **2017,** *12*, 1281–1291.
6. Herdewijn, P.; De Clercq, E. D. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 1591–1597.
7. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; et al. *J. Am. Chem. Soc.* **1997,** *119*, 681–690.
8. Park, C.-M.; Bruncko, M.; Adickes, J.; Bauch, J.; Ding, H.; Kunzer, A.; Marsh, K. C.; Nimmer, P.; Shoemaker, A. R.; Song, X.; et al. *J. Med. Chem*. **2008,** *51*, 6902–6915.
9. Le Manach, C.; Paquet, T.; Wicht, K.; Nchinda, A. T.; Brunschwig, C.; Njoroge, M.; Gibhard, L.; Taylor, D.; Lawrence, N.; Wittlin, S.; et al. *J. Med. Chem*. **2018,** *61*, 9371–9385.
10. Kishimoto, M.; Kawamori, R.; Kamada, T.; Inaba, T. *Drug Metab. Dispos.* **1994,** *22*, 367–370.
11. Carroll, F. I.; Brine, G. A.; Boldt, K. G.; Cone, E. J.; Yousefnejad, D.; Vaupel, D. B.; Buchwald, W. F. *J. Med. Chem.* **1981,** *24*, 1047–1051.
12. Shimokawa, K.; Shibata, N.; Sameshima, T.; Miyamoto, N.; Ujikawa, O.; Nara, H.; Ohoka, N.; Hattori, T.; Cho, N.; Naito, M. *ACS Med. Chem. Lett*. **2017,** *8*, 1042–1047.
13. (a) Xu, Ru.; Li, S.; Paruchova, J.; McBriar, M. D.; Guzik, H.; Palani, A.; Clader, J. W.; Cox, K.; Greenlee, W. J.; Hawes, B. E.; et al. *Bioorg. Med. Chem.* **2006,** *14*, 3285–3299. (b) Su, J.; McKittrick, B. A.; Tang, H.; Burnett, D. A.; Clader, J. W.; Greenlee, W. J.; Hawes, B. E.; O'Neill, K.; Spar, B.; Weig, B.; et al. *Bioorg. Med. Chem.* **2007,** *15*, 5369–5385.
14. Chuo, D. T. H.; Jung, G; Plouvier, B.; Yee, J. G. K. WO 2006138673 A2 2006.
15. Ae, N.; Fijiwasa, Y. US 20110263847 A1 2011.
16. (a) Kawanami, K. WO 2010104106 A1, 2010; (b) Kawanami, K. WO 20122017932 A1, 2012.
17. Arasappan, A.; Bennett, F.; Bogen, S. L.; Venkatraman, S.; Blackman, M.; Chen, K. X.; Hendrata, S.; Huang, Y.; Huelgas, R. M.; Nair, L.; et al. *ACS Med. Chem. Lett.* **2010,** *1*, 64–69.