



Bicyclo[3.1.0]hexanes in Drug Discovery

Overview

Key Points

- Conformationally constrained bioisostere of cyclohexane
- Confer tighter binding to the target protein
- Provide better selectivity, resulting in less off-target effects

Bicyclo[3.1.0]hexanes are conformationally restrained isosteres for cyclohexanes, but with no increase in molecular weight and only a modest elevation in lipophilicity. They may confer tighter binding to the target protein, more resistance to metabolism, and often provide better selectivity, resulting in less off-target effects.

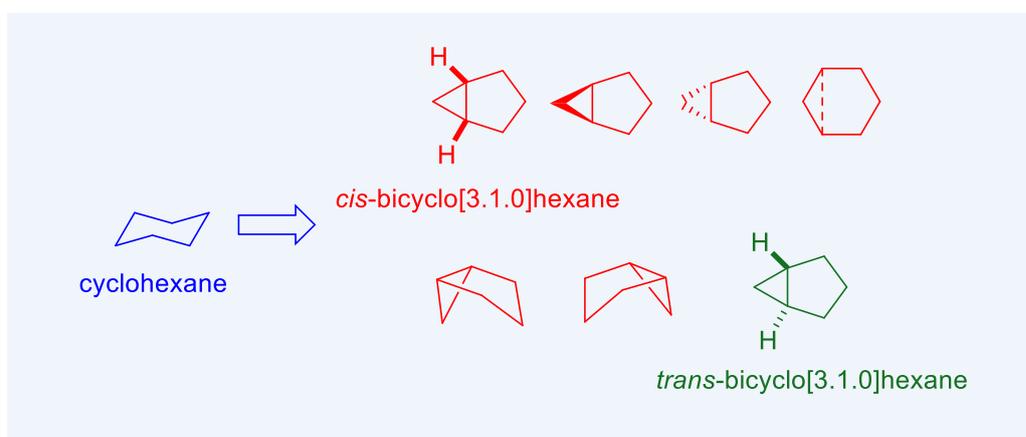
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PharmaBlock designs and synthesizes over 581 Bicyclo[3.1.0]hexanes and 141 Bicyclo[3.1.0]hexane products are in stock. [CLICK HERE](#) to find detailed product information on webpage.

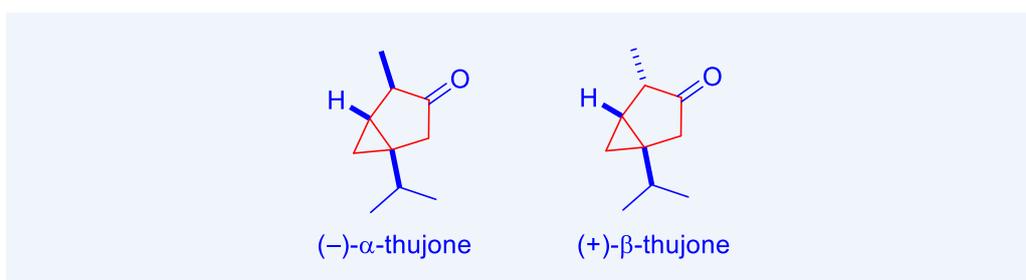


Bicyclo[3.1.0]hexane is a conformationally constrained bioisostere of cyclohexane. Although *trans*-bicyclo[3.1.0]hexane does exist, it is so rare that it has never been explored as a drug fragment. Therefore, we focus our attention solely on *cis*-bicyclo[3.1.0]hexanes.

Cyclohexane prefers to adopt the chair conformation, which is thermodynamically most stable. *cis*-Bicyclo[3.1.0]hexane, as a rigidified cyclohexane analog, adopts a *puckered* shape, which closely resembles a boat conformation of cyclohexane. Thus *cis*-bicyclo[3.1.0]hexane is like a perpetual boat, though a somewhat distorted boat.



Absinthe is a brilliantly green spirit made by adding green anise, grande wormwood, and Florence fennel to liquor. It contains several monoterpenoid thujanes as represented by (–)- α -thujone and (+)- β -thujone, both of which contain the *cis*-bicyclo[3.1.0]hexane core structure. However, thujones are not responsible for the green color.



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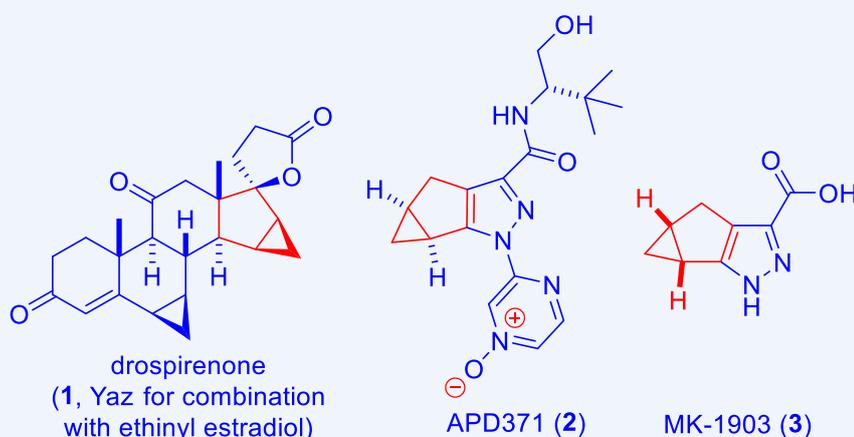
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Bicyclo[3.1.0]hexane-containing Drugs

Only one bicyclo[3.1.0]hexane-containing drug is currently on the market: Schering AG's birth control drug drospirenone (**1**, brand name Yaz when combined with ethinyl estradiol). Structurally related to 17- α -spiro lactone, it is a progestin with anti-mineralocorticoid and anti-androgenic activity.¹

Several bicyclo[3.1.0]hexane-containing drugs have gone to clinical trials. One recent entry is Arena's cannabinoid receptor type 2 (CB₂) agonist APD371 (**2**) for treating chronic pain. Its bicyclo[3.1.0]hexane fragment is fused to a pyrazole ring.² Cannabinoid receptor is a G-protein coupled receptor (GPCR) with two isoforms, CB₁ and CB₂. The structure of APD371 (**2**) bears certain resemblance to Sanofi's rimonabant (Accomplia), an inverse agonist of CB₁, which was approved by the EMA in 2006 as an anorectic antiobesity drug, but was withdrawn worldwide in 2008 due to serious psychiatric side effects.

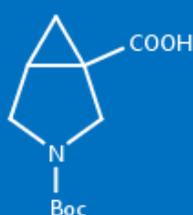
It seems that at some point Arena developed an infatuation toward the bicyclo[3.1.0]hexane building block. Similar to their CB₂ agonist APD371 (**2**), their potent GPR109a agonist MK-1903 (**3**), co-developed with Merck, also has its bicyclo[3.1.0]hexane fragment fused to a pyrazole ring. The drug has been in clinical trials for lowering free fatty acids in humans.³



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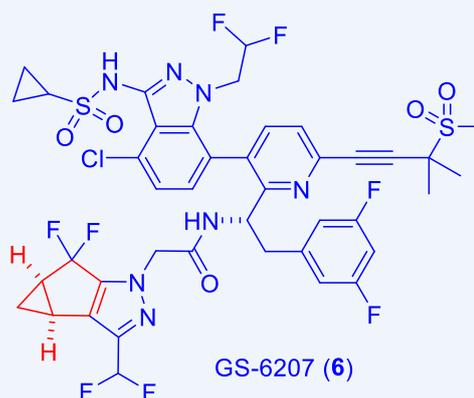
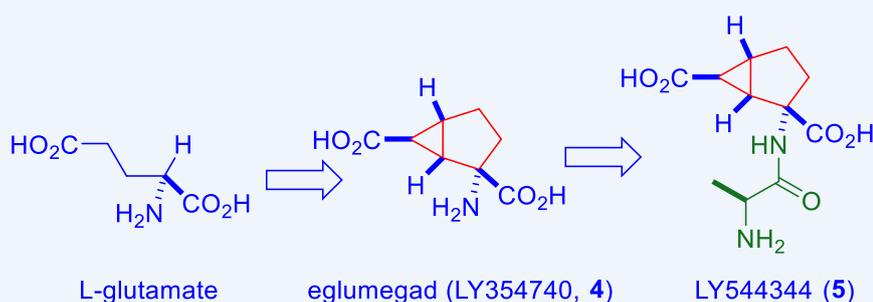
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Metabotropic glutamate receptor (mGluR) modulators, both agonists and antagonists, hold great promise in treating central nervous system (CNS) disorders such as psychosis and Parkinson's disease (PD). Lilly's eglumegad (LY354740, **4**) is a potent, selective, and orally active mGluR2/3 agonist that went to clinical trials for treating anxiety and drug addiction.⁴ With the bicyclo[3.1.0]hexane core structure, eglumegad (**4**) may be considered as a rigidified analog of L-glutamate. After eglumegad (**4**) was found to have low bioavailability (3–5%) in human, its alanine prodrug LY544344 (**5**) was prepared and found to have a 13-fold boost of oral bioavailability in human in comparison to its prototype eglumegad (**4**).⁵ The corresponding dipeptide prodrug was also synthesized and found to have an eight-fold increase of bioavailability in human relative to eglumegad (**4**).⁶ Elevation of bioavailability of the two prodrugs may be attributed to active transports of human amino acid transporters or human peptide transporters.

In terms of size, eglumegad (**4**) is a dwarf while Gilead's GS-6207 (GS-CA1, **6**) a giant. It is a highly potent, selective, and long-acting first-in-class small-molecule HIV-1 capsid inhibitor.⁷ With a molecular weight of 958, GS-6207 (**6**) is outside Lipinski's rule of five (Ro5) space, also known as beyond the rule of five (bRo5). It is not orally bioavailable, but is given as an injectable.



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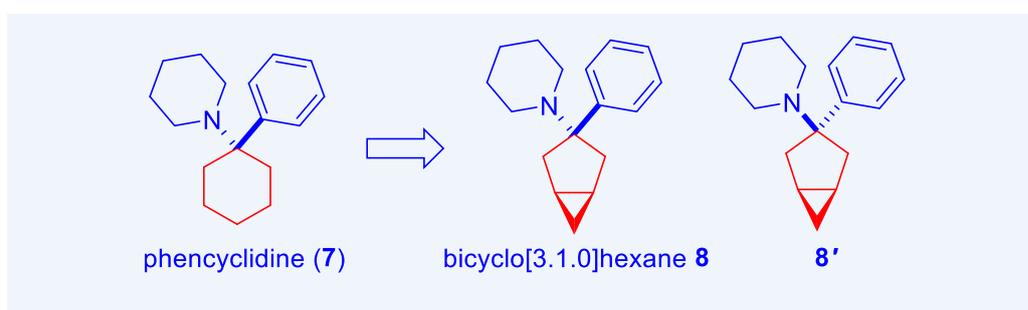
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Bicyclo[3.1.0]hexanes in Drug Discovery

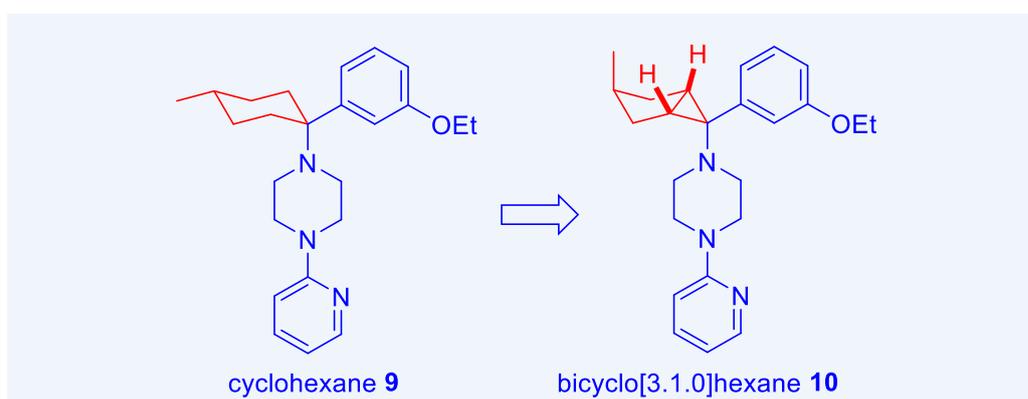
a. *Bicyclo[3.1.0]hexanes as Bioisosteres of Cyclohexanes*

Bicyclo[3.1.0]hexanes are frequently employed as isosteres of cyclohexanes.

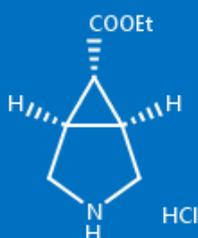
As early as in 1988, an attempt was made to replace phencyclidine (PCP, **7**)'s cyclohexane fragment with conformationally restrained bicyclo[3.1.0]-hexane analogs. The resulting bicyclo[3.1.0]hexane **8** and its diastereomer **8'** were equipotent in binding affinity for the PCP receptor, but were only one seventh as potent as PCP (**7**).⁸



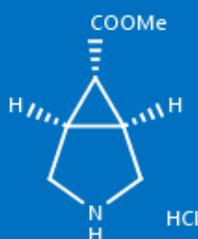
There are five neuropeptide Y (NPY) receptors (Y1–Y5). A selective NPY1 antagonist, cyclohexanyl-piperazine **9**, was discovered as a potential therapeutic intervention of obesity. It was noted that the comparatively flexible cyclohexyl ring may contribute to reduced potency and a more constrained analog may offer tighter binding to the receptor. Indeed, the corresponding bicyclo[3.1.0]hexanyl-piperazine **10** was proven to be potent ($IC_{50} = 62$ nM) and displayed excellent oral bioavailability in rat ($\%F_{po} = 80$) as well as good brain penetration (B/P ratio = 0.61).⁹



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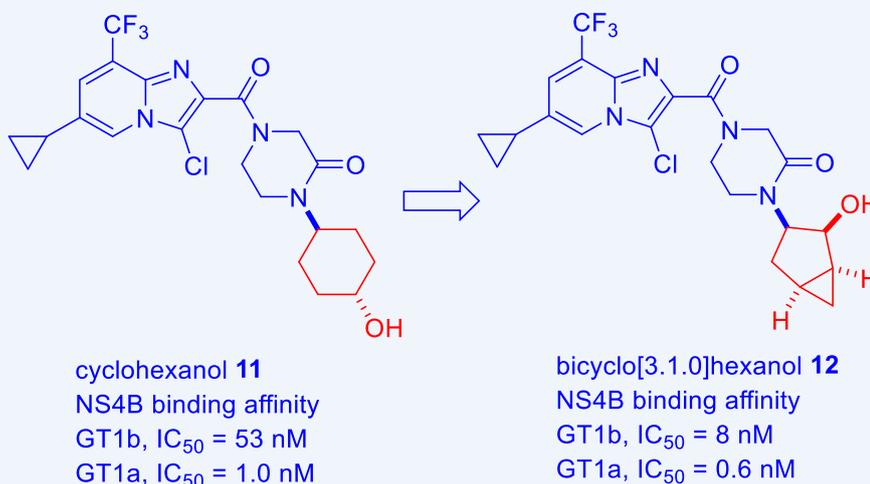
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GSK discovered a series of imidazo[1,2-*a*]pyridine hepatitis C virus non-structural protein 4B (HCV NS4B) inhibitors as potential treatments of HCV infection. Cyclohexanol **11** was tested with high binding affinity (low nanomolar) for both HCV genotype 1b and 1a replicons. However, escalating oral doses of **11** in rats failed to achieve the higher plasma drug exposure required for preliminary safety studies. Furthermore, *in vitro* resistance passaging experiments employing wild-type HCV replicons revealed that single-point mutation within the NS4B protein rendered the virus partially resistant to **11**.¹⁰

Significant improvements were realized with isosteric modifications in the amide (tail) portion of the series. Bridging the terminal cyclohexyl substituent to form a bicyclo[3.1.0]hexane ring afforded bicyclo[3.1.0]hexanol **12** with $IC_{50} < 1$ nM in the replicon assays. It possessed an improved antiviral profile with no increase in molecular weight and only a modest elevation in lipophilicity. It was also demonstrated that bicyclo[3.1.0]hexanol **12** can inhibit viral replication *in vivo*. This successful proof-of-concept (PoC) study suggests that drugs targeting NS4B may represent a viable treatment option for curing HCV infection.¹⁰



Gilead's oseltamivir (Tamiflu) is the ethyl ester prodrug of GS-4071 (**13**), a viral neuroaminase (sialidases) inhibitor to treat influenza A. The mechanism of action (MoA) for both oseltamivir and GS-4071 (**13**) is functioning as transition state mimetics. The choice of using cyclohexene was wise since it provided better oral bioavailability. Scaffold hopping to cyclopentane core structure was also successful, leading to the discovery of peramivir (Rapivab by BioCryst).

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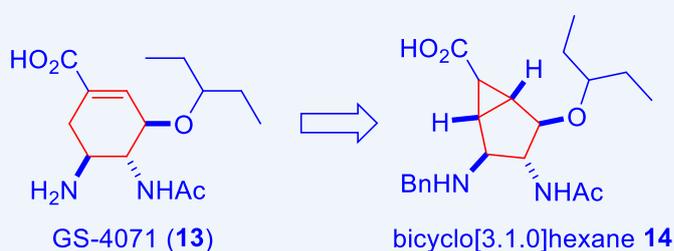


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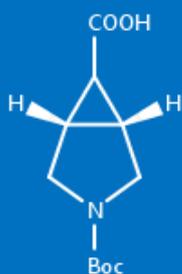
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Another scaffold hopping from GS-4071 (**13**) led to a novel class of derivatives based on bicyclo[3.1.0]hexane core structure, proposed as mimics of sialic acid in a distorted boat conformation that is on the catalytic pathway of neuraminidases. As represented by bicyclo[3.1.0]hexane **14**, they demonstrated micromolar inhibition against both group-1 (H5N1) and group-2 (H9N2) influenza neuroaminase subtypes, indicating good affinity for the α - and β -sialic acid mimics and 150-cavity-targeted derivatives. These results provide a validation of a bicyclo[3.1.0]hexane scaffold as a mimic of a distorted sialic acid bound in the neuraminidase active site during catalysis.¹¹



Diglyceride acyltransferase (DGAT) catalyzes the formation of triglycerides from diacylglycerol and acyl-CoA. DGAT1 inhibitors have potential for the treatment of obesity. Merck's benzimidazole-based DGAT1 inhibitor **15** containing a cyclohexane carboxylic acid moiety demonstrated excellent potency inhibiting human DGAT1 enzyme. It was also selective against the A2A receptor and ACAT1. However, *in vivo*, cyclohexane **15** suffered from isomerization at the α -position of the carboxylic acid group, generating active metabolites, which exhibit DGAT1 inhibition comparable to the corresponding parent compound. *The likelihood of generating an active metabolite in human therefore hampered the advancement of compound 15.* Replacing the cyclohexane moiety with its isostere bicyclo[3.1.0]hexane led to compound **16**, which maintained *in vitro* and *in vivo* inhibition against human DGAT1 enzyme. In contrast to the prototype cyclohexane **15**, bicyclo[3.1.0]hexane **16** did not undergo isomerization during *in vitro* hepatocyte incubation study or *in vivo* mouse study.¹²

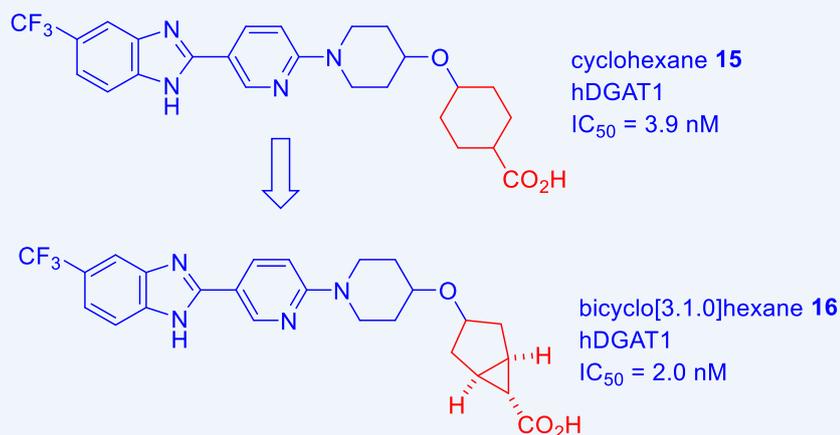
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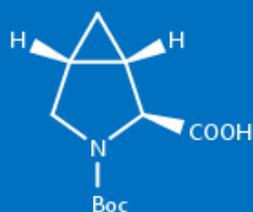


b. Utility of Bicyclo[3.1.0]hexanes in Medicinal Chemistry

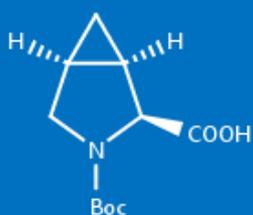
For decades, Jacobson and coworkers at NIH have focused on replacing the ribose core structure of nucleosides and nucleotides with the bicyclo[3.1.0]-hexane core structure in their drug discovery efforts. By applying structure-based functional group manipulations, rigidified adenosine derivatives (also known as *methanocarba nucleosides*) can be repurposed to satisfy pharmacophoric requirements of various GPCRs (adenosine, P2, and 5HT_{2B} serotonin receptors), ion channels, enzymes (kinases and polymerases) and transporters (dopamine transporter), initially detected as off-target activities.¹³

The most recent example of methanocarba nucleosides is MRS7334 (**18**) as a highly potent and selective A₃ adenosine receptor (A₃AR) agonist. In comparison to its corresponding ribose **17**, the bicyclo[3.1.0]hexane-containing **18** has a *K_i* value of 280 picomolar in the hA₃AR assay, an eight-fold boost of the binding affinity. MRS7334 (**18**) is also significantly more selective against hA₁AR (*K_i* = 33 nM), a 40,000-fold selectivity. Furthermore, methanocarba nucleoside **18** also displayed a favorable pharmacokinetics profile, as well as off-target activity profile against 240 GPCRs and 466 kinases. Despite added synthetic difficulty, the (N)-methanocarba modification has distinct advantages for A₃AR, which have translational potential for chronic disease treatment.¹⁴

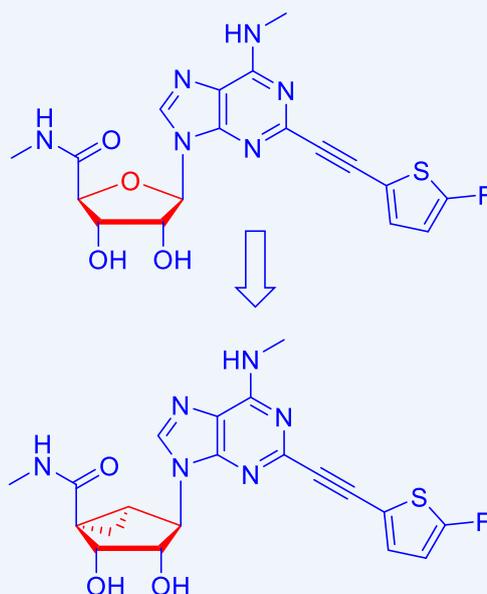
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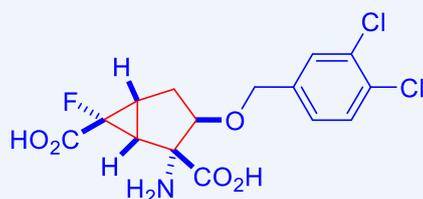
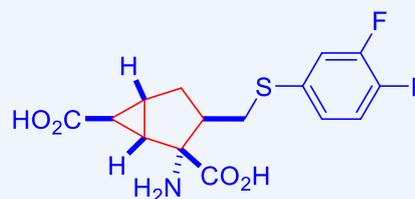
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ribose **17**
 K_i (hA₃AR) = 2,300 pM
 Selectivity vs. hA₁AR
 ~ 20

MRS7334 (**18**)
 K_i (hA₃AR) = 280 pM
 Selectivity vs. hA₁AR
 ~ 40,000

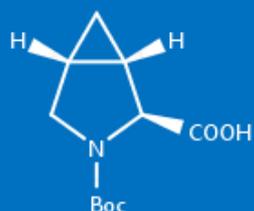
Lilly brought several bicyclo[3.1.0]hexane-containing mGluR2/3 agonists, such as eglumegad (**4**) and LY544344 (**5**), to clinical trials. Meanwhile, Lilly has pursued mGluR2/3 antagonists with rigor during the last decade. Inspired by Taisho's MGS0039 (**19**),¹⁵ an mGluR2/3 antagonist that showed antidepressant and anxiolytic effects in behavioral models in rats, Lilly discovered LY3020371 (**20**) as a potent, selective, and maximally efficacious mGluR2/3 antagonist. LY3020371 (**20**) also demonstrated *in vivo* activity with an antidepressant-like signature in the mouse forced-swim test (mFST) assay when brain levels of this compound exceeded the cellular mGlu₂ IC₅₀ value.¹⁶

MGS0039 (**19**)LY3020371 (**20**)

Sheng et al. at Gilead discovered a bicyclo[3.1.0]hexane-containing drug GS-9451 (**21**) as an acid inhibitor of the HCV NS3/4A protease.¹⁷

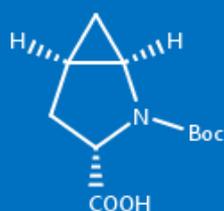
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Absolute

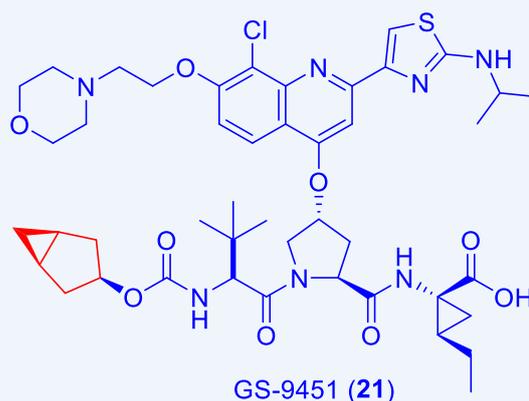


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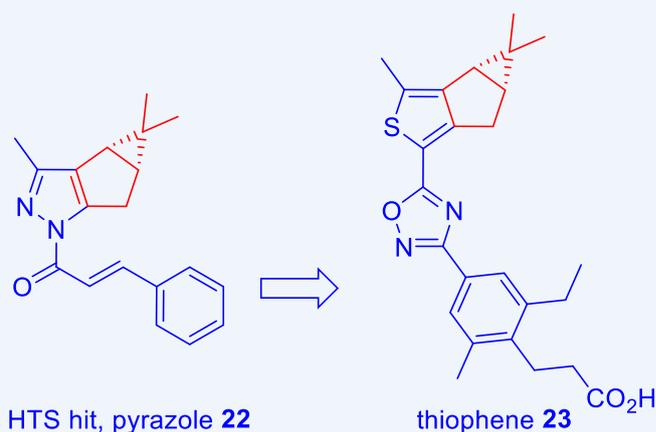
Absolute



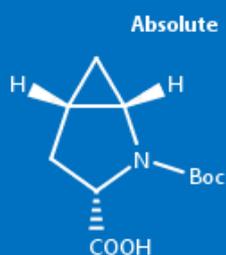
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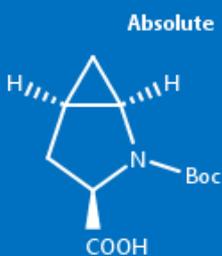
Sphingosine-1-phosphate receptor 1 (S1P₁) is a GPCR. S1P₁ signaling has been associated with the regulation of lymphocyte maturation, migration and trafficking. S1P₁ receptor agonists, on the other hand, showed potential as treatment of cardiovascular diseases. From high throughput screening (HTS), Actelion found a hit: bicyclo[3.1.0]hexane-fused pyrazole **22**. Through scaffold hopping, thiophene **23** was obtained as an optimized S1P₁ receptor agonist with an EC₅₀ of 7 nM and was selective against S1P₃ receptor (EC₅₀ = 2,880 nM). It also had favorable pharmacokinetic properties in rat and dog, distributed well into brain tissue, and efficiently and dose-dependently reduced the blood lymphocyte count in the rat. Thiophene **23** affected the heart rate during the wake phase of animals only, but showed no effect on mean arterial blood pressure.¹⁸



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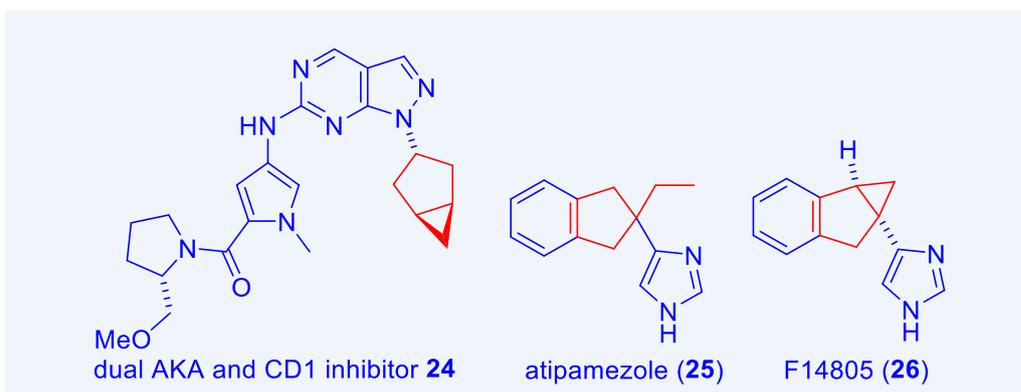


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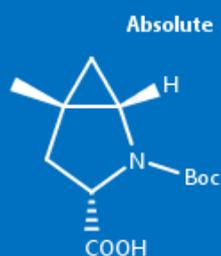
Additional bicyclo[3.1.0]hexane-containing drugs also include Biogen's dual inhibitor **24** of Aurora kinase A (AKA) and cyclin dependent kinase 1 (CDK1).¹⁹ Rigid analogs, including bicyclo[3.1.0]hexane-containing F14805 (**26**), of the α 2-andrenergic blocker atipamezole (**25**) showed that small changes could have big sequences in terms of their pharmacology.²⁰



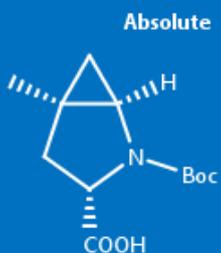
Synthesis of Some Bicyclo[3.1.0]hexane-containing Drugs

Synthesis of AstraZeneca's CB₂ agonist APD371 (**2**) began with an intramolecular cyclopropanation of (S)-2-(but-3-en-1-yl)oxirane (**27**) catalyzed by lithium tetramethylpiperidine (LTMP) to prepare bicyclo[3.1.0]hexanol **28**.²¹ 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO)-catalyzed bleach oxidation converted alcohol **28** to the corresponding ketone **29**. Acylation of ketone **29** with diethyl oxalate was followed by condensation with 2-hydrazinylpyrazine to assemble tricyclic pyrazinyl-pyrazole ester **30**. Hydrolysis of the ethyl ester using LiOH was followed by selective oxidation employing *m*-CPBA to form N-oxide acid **31**. Eventually, HATU-mediated amide formation by coupling acid **31** with amino alcohol **32** then delivered APD371 (**2**).²

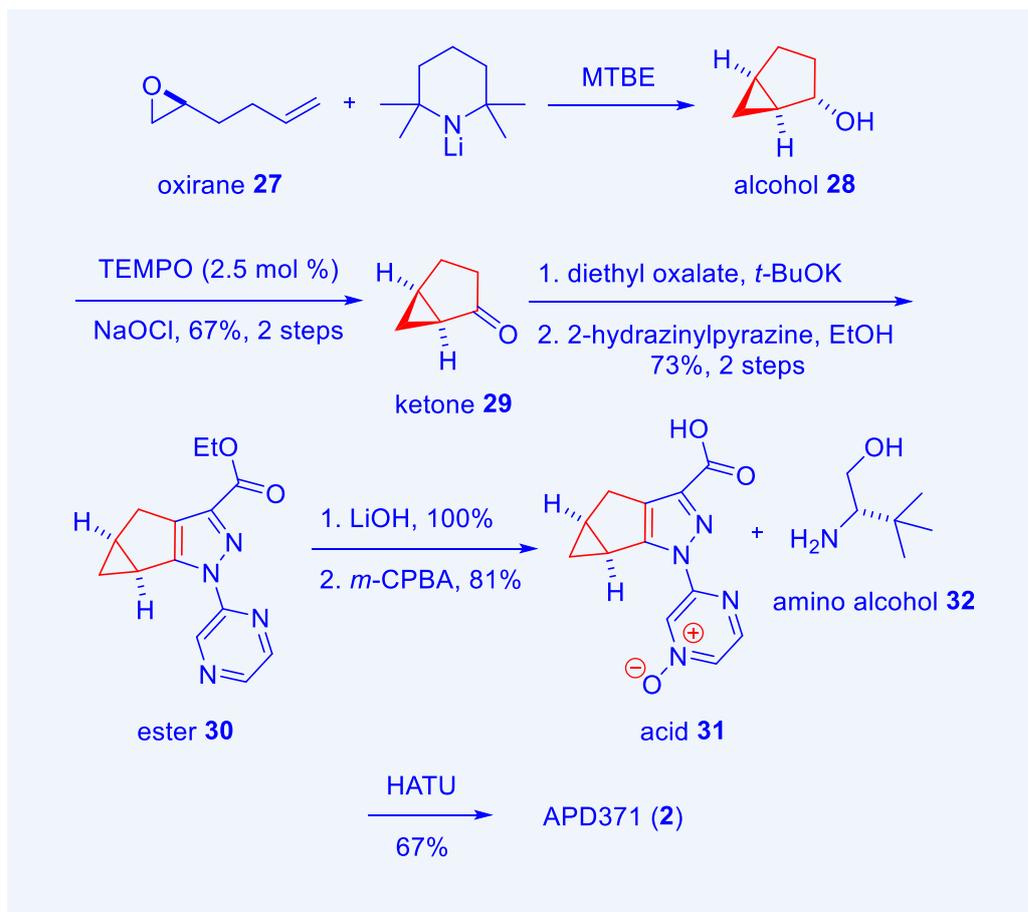
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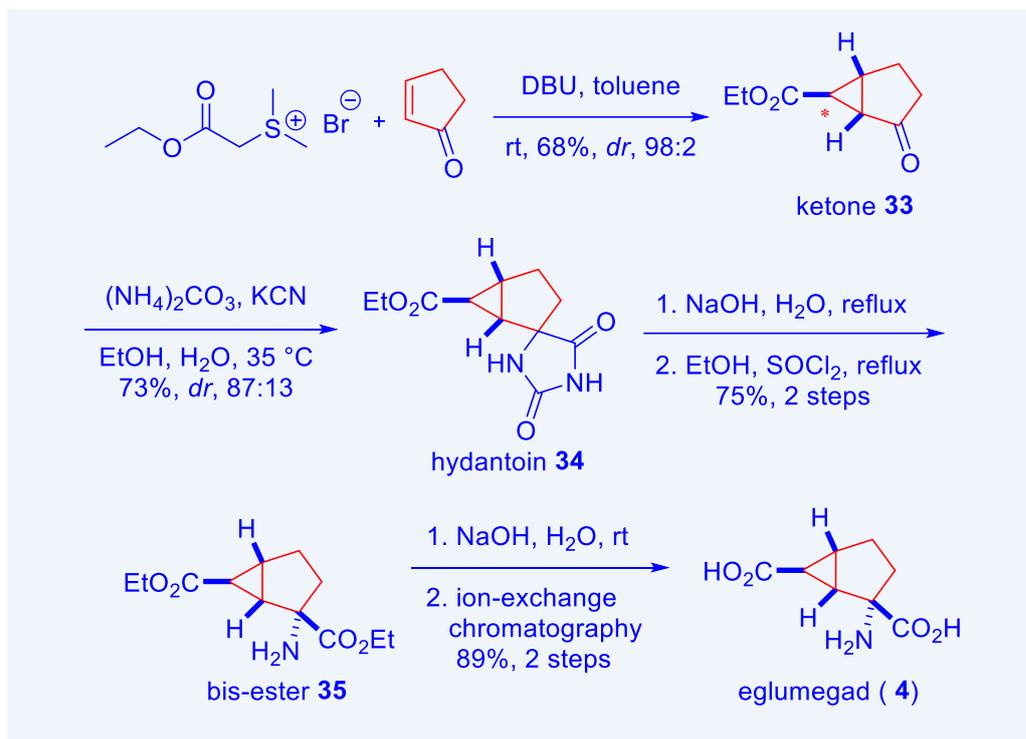
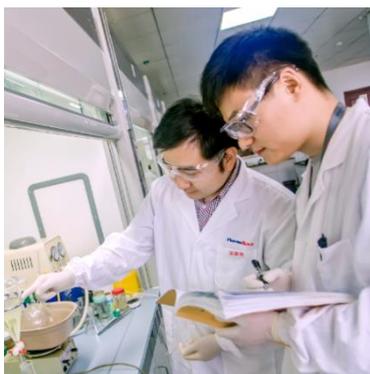
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Lilly's synthesis of their mGluR2/3 agonist eglumegad (**4**) commenced with a Corey–Chaykovsky carboxycyclopropanation of 2-cyclopentenone with ethyl (dimethylsulfonium)acetate bromide (EDSA) to prepare the bicyclo[3.1.0]-hexane-ketone **33** with excellent diastereoselectivity under optimized conditions. It was then subjected to hydantoin formation under Bucherer–Bergs conditions, yielding **34** as a mixture of two inseparable diastereomers. Exhaustive hydrolysis of hydantoin **34** was followed by esterification to afford bis-ester **35**, which was again hydrolyzed to deliver pure eglumegad (**4**) after ion-exchange chromatography.⁴



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Hu and Luo at BMS began synthesis of their selective NPY1 receptor antagonist bicyclo[3.1.0]hexanyl piperazine **10** with condensation of 4-methyl-cyclohexanone with N-benzylpiperazine to produce enamine **36**. Chlorination of enamine **36** with NCS at $-50\text{ }^\circ\text{C}$ to room temperature afforded chloroenamine **37**. After filtration of the by-product succinamide, the crude chloroenamine **37** in ether was exposed to the freshly prepared Grignard reagent to assemble the key bicyclo[3.1.0]hexane **38** in a total 82% yield for the last three steps. Palladium-catalyzed debenzoylation was followed by an $\text{S}_{\text{N}}\text{Ar}$ replacement reaction with an α -bromopyridine to deliver bicyclo[3.1.0]hexanyl piperazine **10**.⁹

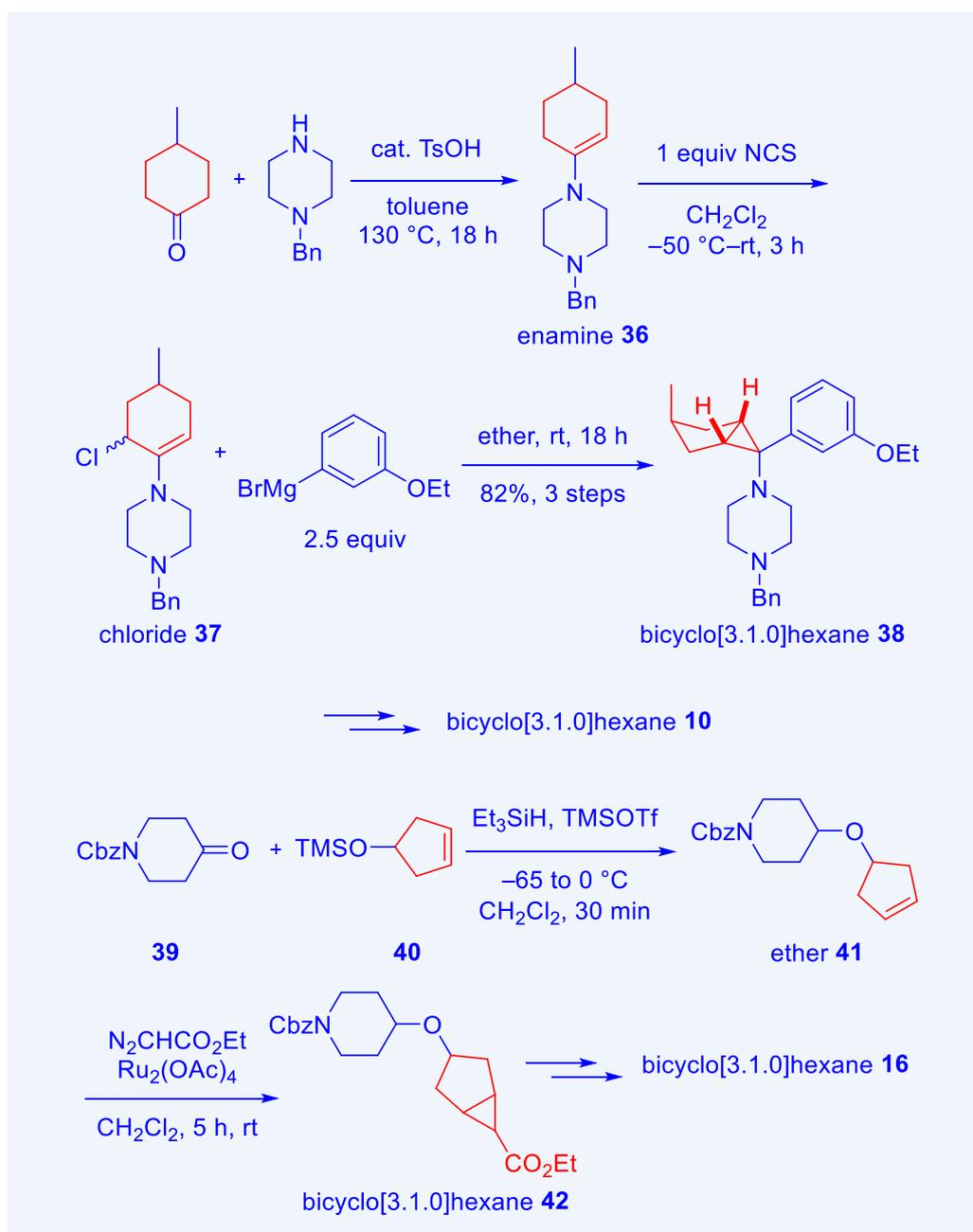
To make Merck's benzimidazole-based DGAT1 inhibitor **16**, reductive etherification of benzyl 4-oxopiperidine-1-carboxylate (**39**) with cyclopent-3-en-1-ol **40** assembled ether **41**.²² Rh(II)-catalyzed cyclopropanation of the double bond on alkene **41** furnished the key bicyclo[3.1.0]hexane **42** as a mixture of four diastereomers. After chiral supercritical fluid chromatography (SFC) separation, additional transformations led to the synthesis of bicyclo[3.1.0]hexane **16**.¹²



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To conclude, bicyclo[3.1.0]hexanes are conformationally restrained isosteres for cyclohexanes, but with no increase in molecular weight and only a modest elevation in lipophilicity. They may confer tighter binding to the target protein, more resistance to metabolism, and often provide better selectivity, resulting in less off-target effects.

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