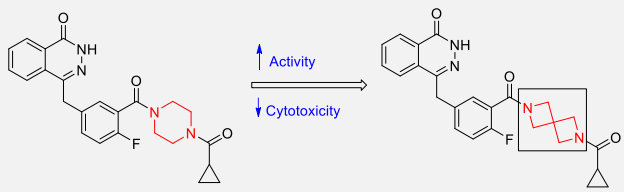
MEDCHEM HIGHLIGHTS

Enamine

Piperazine Bioisosteres for Drug Design

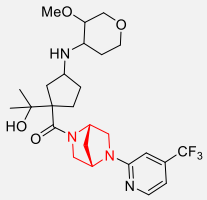
Introduction

More than 100 FDA-approved drugs contain the piperazine moiety.[1] Piperazine-based analogues may advantageously alter important pharmacokinetic properties when grafted onto molecular scaffolds.[2-5] In 2018, chemists showed that replacing a piperazine ring in the drug Olaparib with the spirodiamine analogue beneficially affected activity and reduced cytotoxicity of the parent compound.[6] Herein we have designed and synthesized a library of piperazine analogues for drug design.

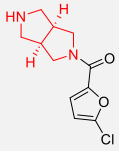


Olaparib (anti-cancer drug)
AstraZeneca and Merck & Co.

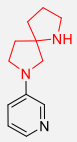
SpiroOlaparib



Chemokine receptor modulator
US 2011/0144129 A1
Pfizer

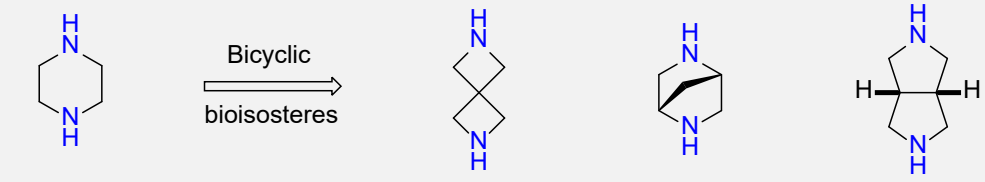


AZD1446 (Reached Phase II)
Nicotinic receptor agonist
AstraZeneca

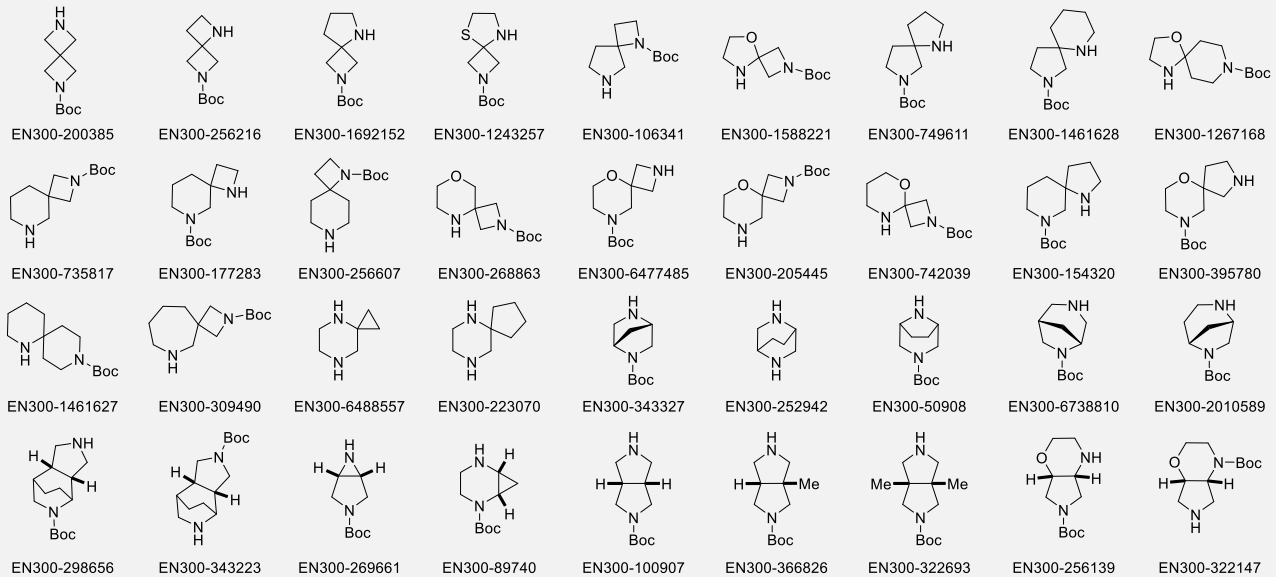


TC-2216 (Reached Phase I)
Nicotinic receptor agonist
Targacept

Design



We offer >100 unique piperazine analogues on a 5-50 g scale from stock.



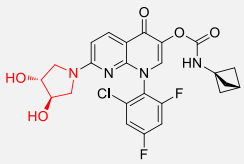
References

1. www.drugbank.ca
2. J. A. Burkhard et al. *ANIE.* **2010**, *49*, 3524.
3. B. Chalyk et al. *Chem. Eur. J.* **2017**, *23*, 16782.
4. B. Chalyk et al. *Eur. J. Org. Chem.* **2017**, *31*, 4530.
5. A. Kirichok et al. *Chem. Eur. J.* **2018**, *24*, 5444.
6. S. W. Reilly et al. *J. Med. Chem.* **2018**, *61*, 5367.

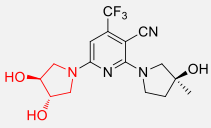
Sugar-like Building Blocks for Drug Design

Introduction

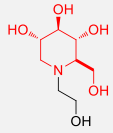
Saturated azaheterocycles are popular in modern drug discovery programs. More than 50 FDA-approved drugs containing a fragment of pyrrolidine and piperidine have appeared on the market.[1] Pyrrolidine/piperidine-based azasugars and their analogues are potent glycosidase inhibitors. These unique molecules promise a new generation of iminosugar-based medicines for a wide range of diseases.[2-5] For example, a bioactive azasugar includes the anti-diabetic drug *Glyset*. In this context, herein we have designed and synthesized a library of sugar-like derivatives for drug design.



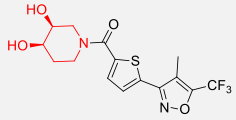
Allosteric modulator of the muscarinic M2 receptor
WO 2016/198342 A1
Bayer



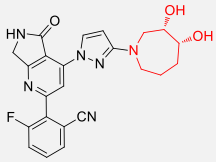
KHK inhibition
J. Med. Chem. **2017**, *60*, 7835.
Pfizer



Glyset
anti-diabetic drug
Pfizer

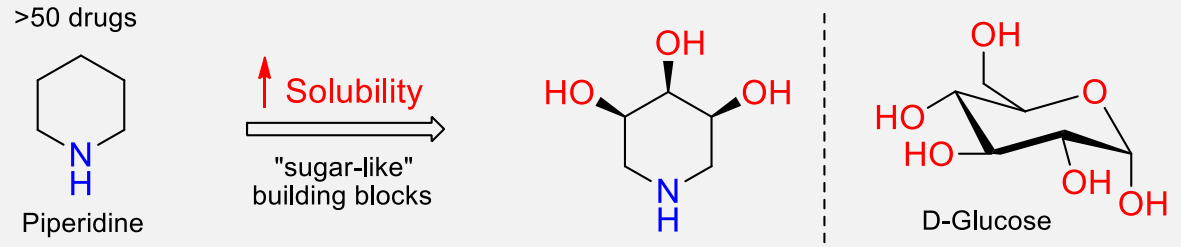


MAO-B inhibition
WO 2016/044635 A1
Dart NeuroScience

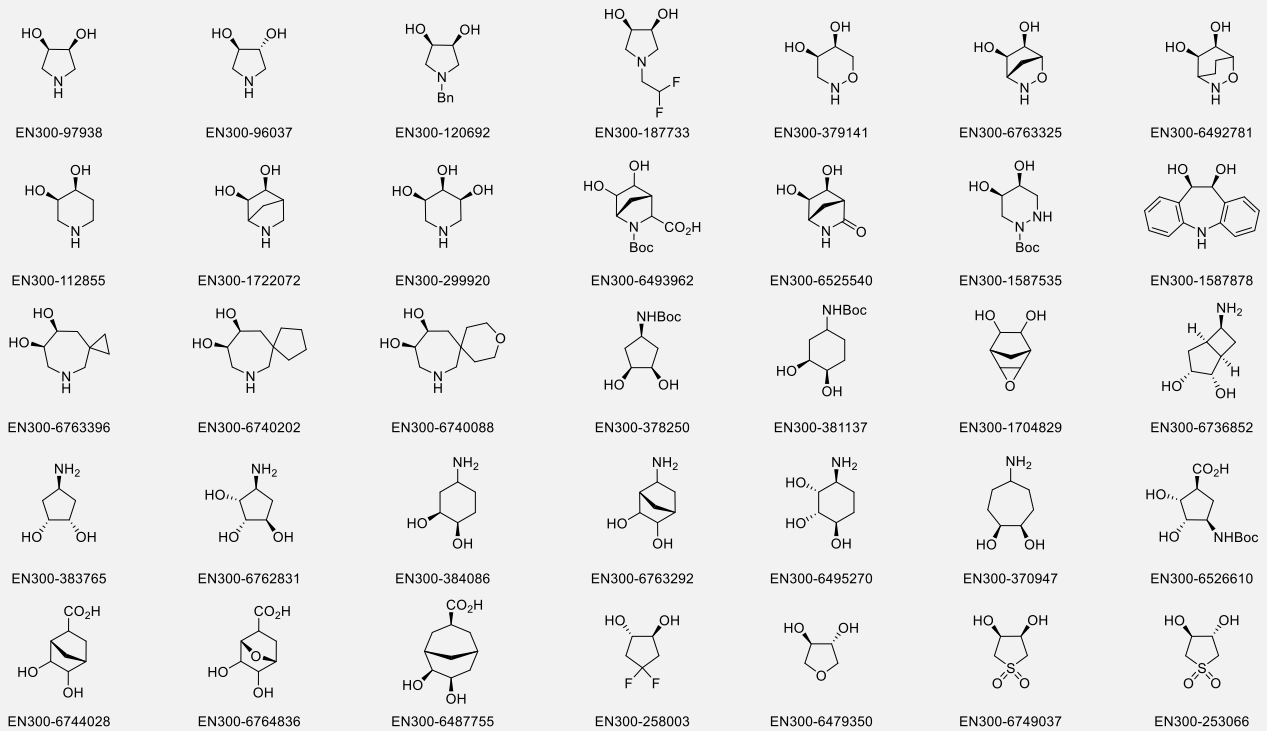


Tyk2 inhibition
WO 2017/040757 A1
Nimbus Therapeutics

Design



We offer >50 unique **sugar-like** derivatives on a 5-50 g scale in stock.



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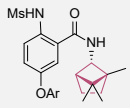
2. N. F. Bras et al. *Expert Opin. Ther. Patents* **2004**, *24*, 857.
3. V. R. Doddi et al. *Eur. J. Org. Chem.* **2007**, 5583.
4. Y. L. Merrer et al. *Bioorg. Med. Chem.* **1997**, *5*, 519.
5. P. Compain et al. *Iminosugars: From Synthesis to Therapeutic Applications*, John Wiley & Sons, **2008**.

Saturated Bioisosteres of *ortho-/meta*-substituted Benzenes

Introduction

The fragment of benzene comprises to the structure of more than 500 FDA-approved drugs.[1] In 2012, *Stepan* and coworkers showed that bicyclo[1.1.1]pentane skeleton could act as a saturated "*nonclassical phenyl ring bioisostere*".[2-6] Adding one carbon atom gives the closest homologue – bicyclo[2.1.1]hexane. The lack of the practical synthetic approaches restricts the common use of bicyclo[2.1.1]hexanes in chemistry. Herein we have designed and synthesized a library of saturated mimics of the *ortho*- and *meta*-benzene ring for drug design.



Precursor to anthelmintics
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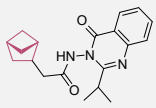
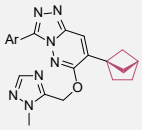
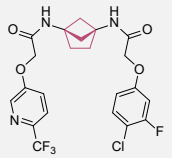
Novartis



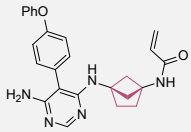
Potassium channel modulators
US 2012/122890
Abbott



Ligand for GABA receptors
US 2001/6303597
Merck



Modulator of the integrated stress pathway
WO 2017/193034
Calico



Inhibitor of Bruton's tyrosine kinase
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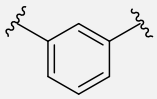
Merck

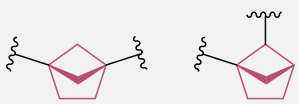
Design



meta-substituted Benzene

Escape from Flatland

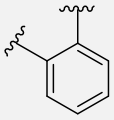
$F(sp^3)$-*rich*
>100 drugs



Mimics for *ortho-/meta*-substituted Benzenes

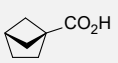
Escape from Flatland

$F(sp^3)$-*rich*
>100 drugs



ortho-substituted Benzene

We offer



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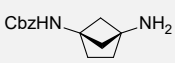

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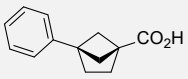

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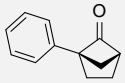

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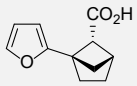

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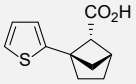

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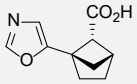

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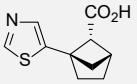

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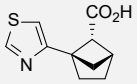

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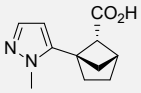

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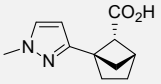

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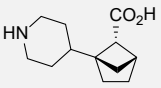

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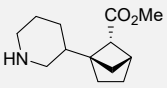

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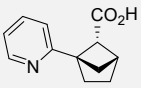

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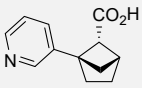

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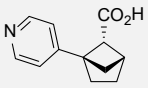

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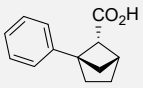

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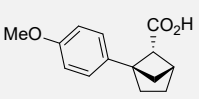

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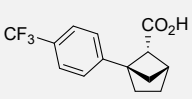

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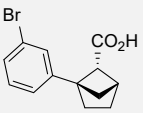

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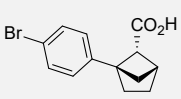

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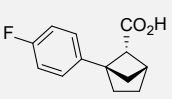

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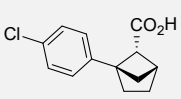

EN300-6479063

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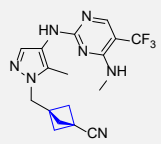
2. A. F. Stepan et al. *J. Med. Chem.* **2012**, *55*, 3414.
3. Y. L. Goh et al. *J. Am. Chem. Soc.* **2016**, *138*, 1698.
4. P. K. Mykhailiuk et al. *ANIE* **2006**, *45*, 5659.
5. S. O. Kokhan et al. *ANIE* **2016**, *55*, 14788.
6. S. O. Kokhan et al. *Eur. J. Org. Chem.* **2017**, *43*, 6455.

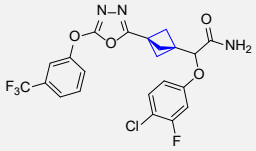
Saturated Bioisosteres of *para*-substituted Benzenes

Introduction

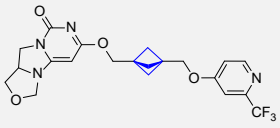
The residue of benzene comprises to the structure of more than 500 FDA-approved drugs.[1] In 2012, *Stepan* and coworkers showed that bicyclo[1.1.1]pentane skeleton could act as a saturated "*nonclassical phenyl ring bioisostere*" in the design of a γ-secretase inhibitor.[2] Since then, the core of bicyclo[1.1.1]pentane is often used in the design of analogues of natural compounds,[3] peptide studies,[4,5] medicinal chemistry,[6,7] and supramolecular chemistry.[8] Herein we have designed and synthesized a library of saturated mimics of the *para*-benzene ring for drug design.



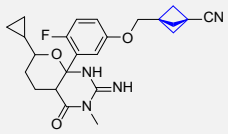
LRRK2 inhibitor
WO 2017/218843
Denali Therapeutics



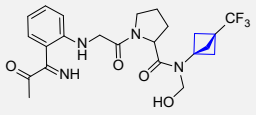
Integrated stress pathway modulator
WO 2017/193030
Calico Life Sciences



Inhibitor of Lp-PLA2 activity
WO 2016/011930
GlaxoSmithKline

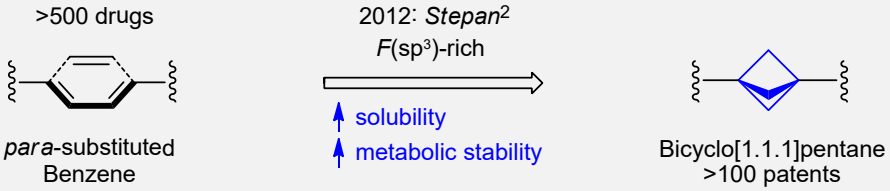


BACE inhibitor
WO 2016/085780
Merck & Co.

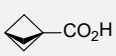


Complement pathway modulator
WO 2014/002054
Novartis

Design



We offer



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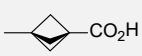

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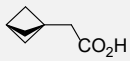

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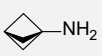

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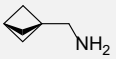

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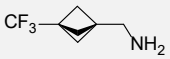

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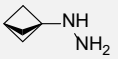

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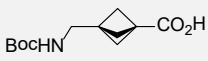

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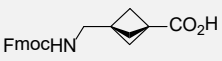

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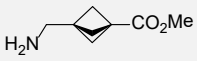

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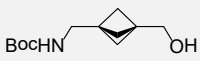

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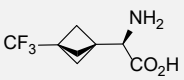

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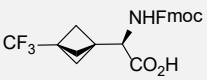

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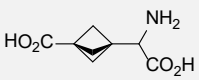

EN300-295582

EN300-263444

EN300-132008

EN300-1590218

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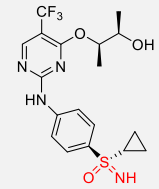
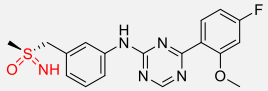
Sulfoximines for Drug Design

Introduction

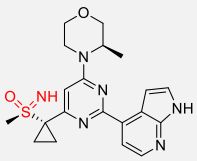
Incorporation of sulfoximine group into bioactive compounds often improves their ADME/Tox profile, and enhances potency. Moreover, the moiety of sulfoximine is chemically and metabolically stable. NH-sulfoximines can serve as the both hydrogen bond donors and acceptors at the same time.[1-6] Production and commercialization of the building blocks that already contain sulfoximine group allow significant accelerating discovery of drug candidates. Herein we have designed and synthesized a library of sulfoximines for drug design.



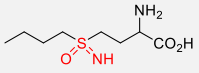
Roniciclib (BAY 1000394)
pan-CDK inhibitor
(Phase II)



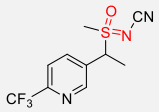
BAY 1143572
PTEFb Inhibitor
(Phase I)



AZD 6738
ATR Inhibitor
(Phase II)

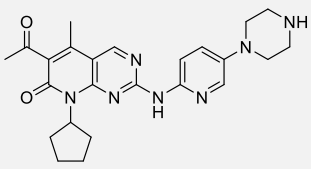


Buthionine sulphoximine
GCL inhibitor



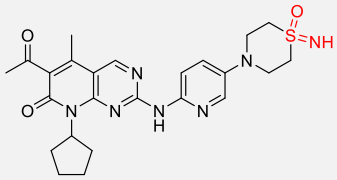
Sulfoxaflor
Insecticide

Design



Approved drug **Palbociclib**

activity
selectivity

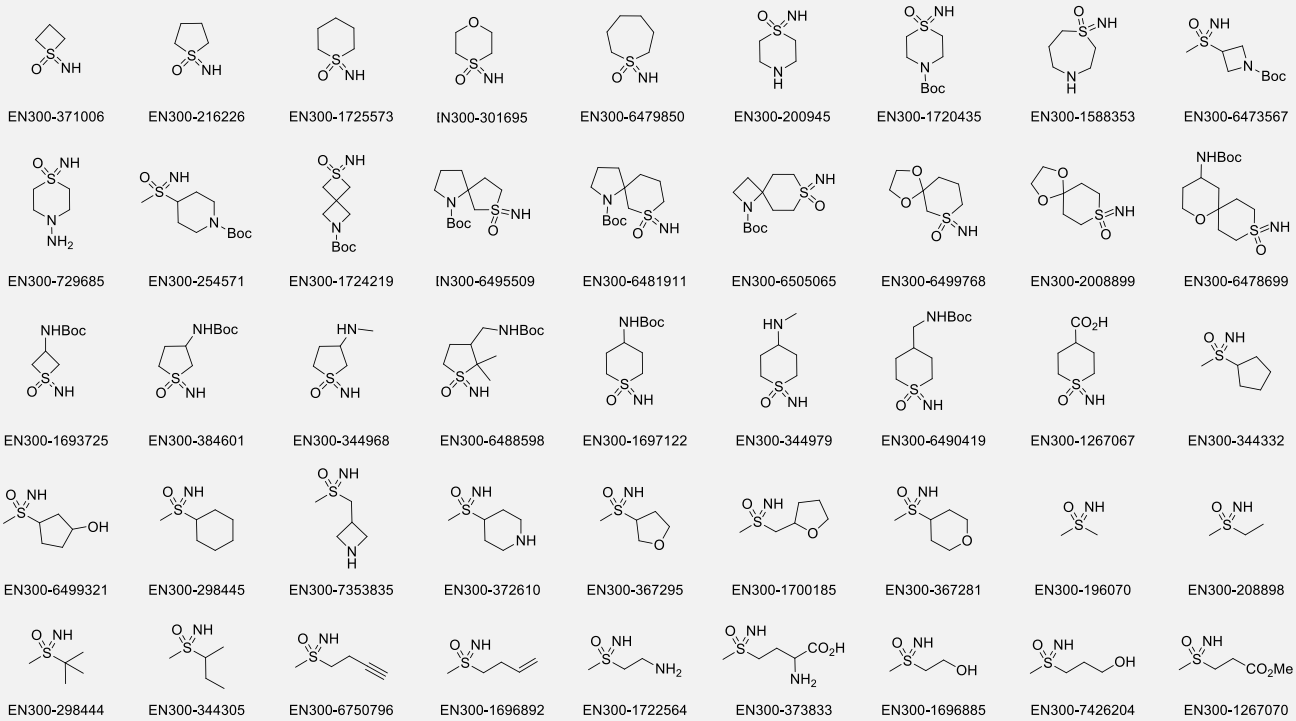


Sulfoximine analogue

Sulfoximine group:

- has high chemical and metabolical stability;
- increases aqueous solubility;
- serves as H-bond donor and acceptor.

We offer >100 unique sulfoximines on a 5-50 g scale from stock.



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EN300-298444 EN300-344305 EN300-6750796 EN300-1696892 EN300-1722564 EN300-373833 EN300-1696885 EN300-7426204 EN300-1267070

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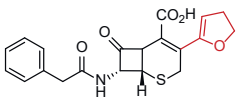
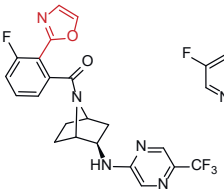
Stannanes for Drug Design

Introduction

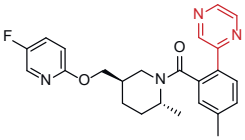
The Stille reaction has become one of the most powerful synthetic tools in organic chemistry. The Stille coupling as a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, has very few limitations on the R-groups. Today, the Stille reaction constitutes a reliable and often-used method for the construction of carbocyclic and heterocyclic rings. Stannanes are stable and allow to prepare alternatives to unstable boronic acids or to be used in click chemistry.



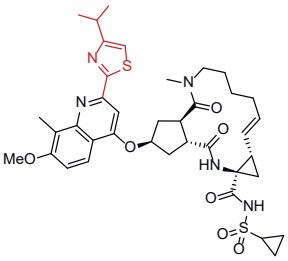
Antibacterial agent
US 1997/5635501
Pfizer



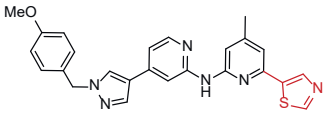
Modulator of orexin receptor
US 2016/46640
Johnson & Johnson



Antagonist of orexin receptor
WO 2008/147518
Merck & Co.

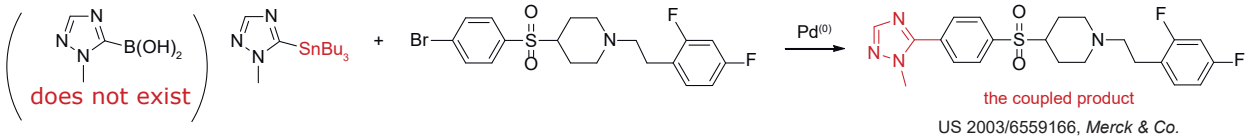


Simeprevir (TMC 435)
NS3/4A protein inhibitor
Janssen



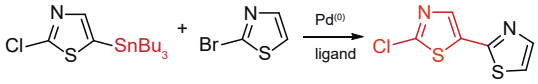
WO 2014/074422
Syk inhibitor
Merck & Co.

Advantages



US 2003/6559166, *Merck & Co.*

Reactivity

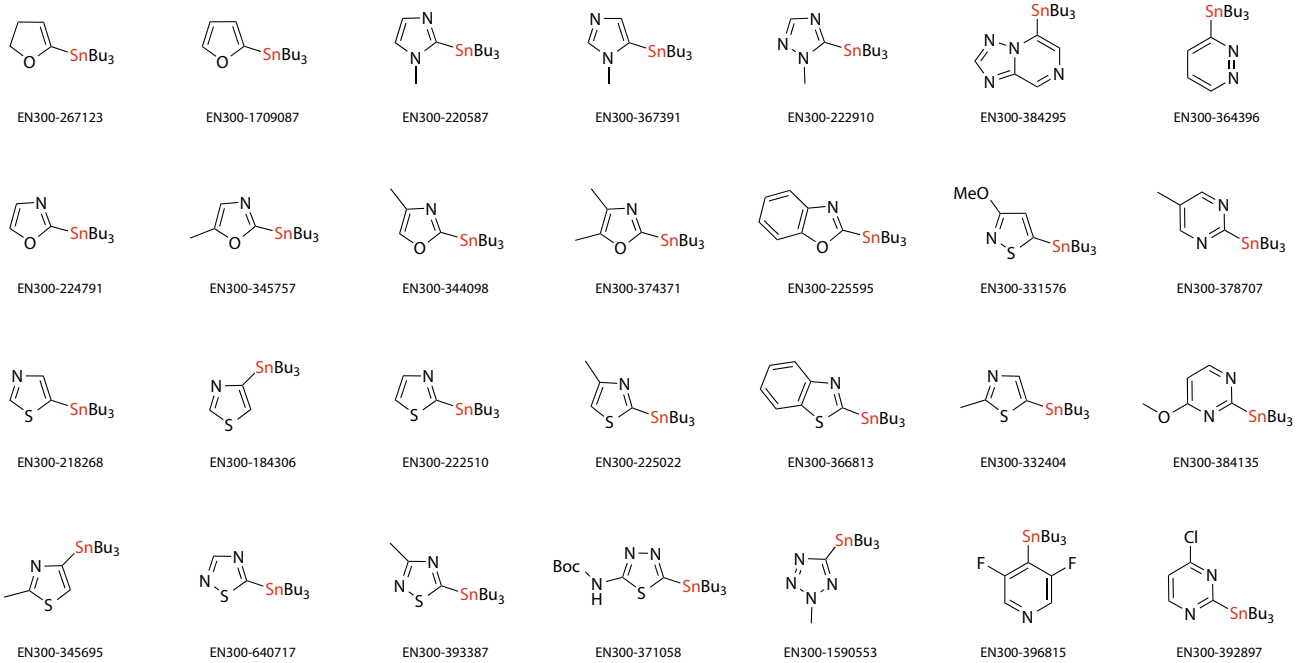


Synthesis of bithiazoles using Pd-catalyzed reactions in which Stille is superior to Negishi and Suzuki couplings.

Properties

- readily prepared, purified and stored;
- tolerate a wide variety of functional groups;
- require mild reaction conditions;
- not sensitive to moisture or oxygen;
- allow to prepare alternative compounds to unstable boronic acids

Our offer



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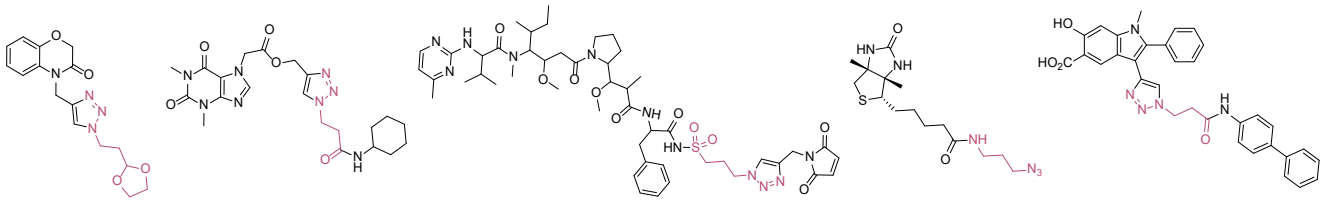
Azide-linkers for Drug Design

Introduction

Organic azides became enormously popular for their participation in the Cu(I)-catalyzed Huisgen azide-alkyne 1,3-dipolar cycloaddition reaction – “click chemistry”. 1,2,3-triazole function formed by click reaction between an azide and alkyne bears a physicochemical resemblance to the amide bond. Besides, “click chemistry” involves functionalities that can be introduced in small molecules and into specific locations in biomolecules. “Click chemistry” continues to gain popularity and is used in a variety of research fields with significant contributions to the fields of bioconjugation and drug discovery.



Treatment of HCC
Eur. J. Med. Chem. **2017**, *132*, 90.

Anticancer agent
MedChemComm, **2017**, 176.

Treatment of cell proliferative disorders
WO 2015/189791

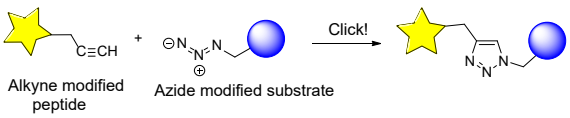
Labeling glycoconjugates
US 2012/0149887

Tyrosine phosphatase inhibitor
J. Med. Chem. **2010**, *53*, 2482.

Advantages

Aliphatic functionalized azides

- Wide in scope.
- Form stable products.
- Give very high yields.



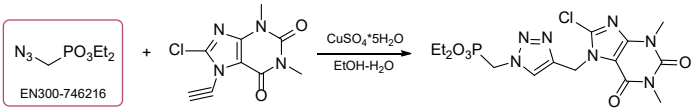
Alkyne modified peptide

Azide modified substrate

Figure 1. Click reaction forming a triazole link in peptide.

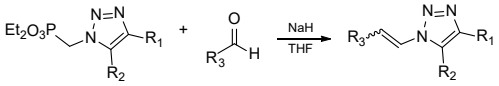
- The presence of the azide-group and a functional group allows the molecule to be modified before or after the click reaction.

Copper-mediated azide-alkyne conjugation



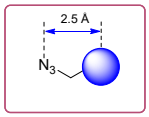
1,2,3-triazole linker

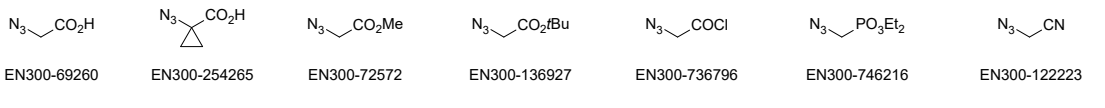
The Homer-Wadsworth-Emmons olefination of the triazoles



We offer

Over 100 different building blocks in multi gram amounts in stock. We also have designed a library azide-containing building blocks for drug discovery programs. These molecules can be synthesized upon request within 4-6 weeks.





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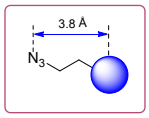

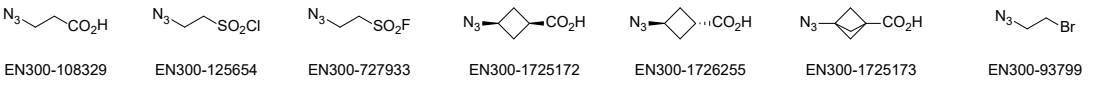

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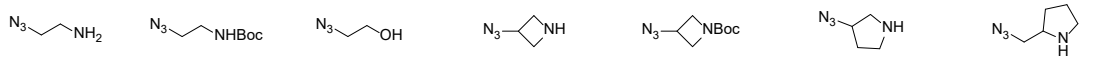

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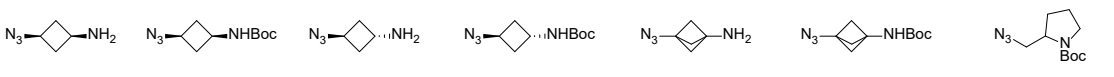

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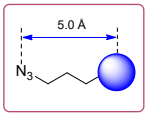

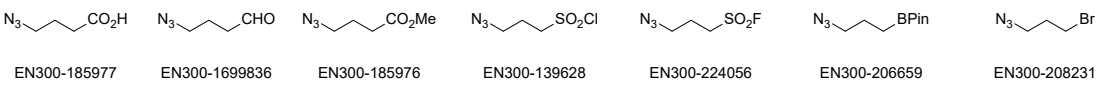

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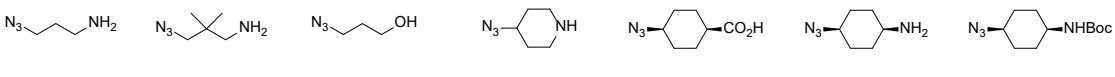

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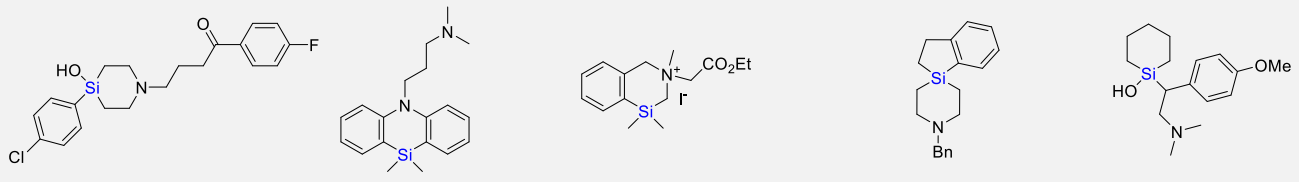
Silicon-Containing Building Blocks for Drug Design

Introduction

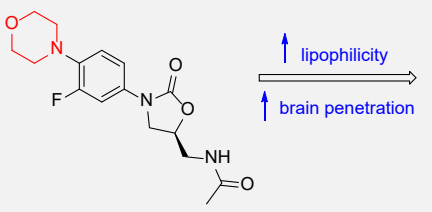
Silicon-containing compounds have been largely ignored in drug design until recently.[1] Silicon can be considered a bioisostere of carbon and hence offers an innovative avenue in drug discovery. For example, C/Si exchange in drug-like scaffolds provides an exciting approach in medicinal chemistry to improve ADME/Tox profile and to enhance potency of the biologically active compounds (Figure 1).[2-6] Herein we have designed and synthesized a library of silicon-containing building blocks for drug design.



Sila-haloperidol | Sila-dimetracrine | Sila-analogue of tetrahydroisoquinoline | Spirocyclic σ-receptor ligand | Sila-venlafaxine

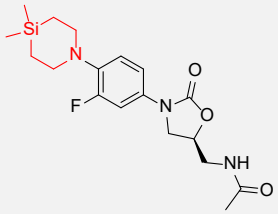
Figure 1. Examples of silicon-containing molecules of medicinal interest.

Design



Linezolid
(marketed antibiotic)

lipophilicity
brain penetration



Siliconized linezolid

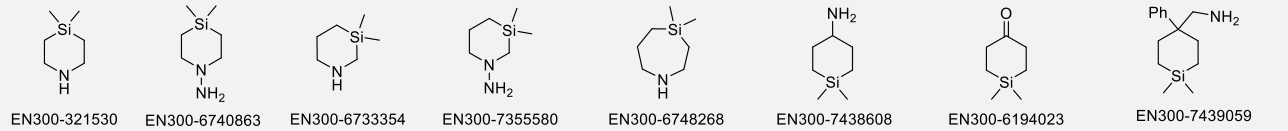
Advantages of "Silicon Switch":

- Larger C–Si bond length (C–C = 1.54 Å, C–Si = 1.87 Å) → changes in the interactions with specific proteins.
- Increase in lipophilicity → improved cell penetration and selectivity.
- Difference in bonding preferences: Si prefers higher coordination numbers → access to compounds for which corresponding carbon analogs are not available.

We offer

Over 15 unique silicon-containing building blocks on a 1-30 g scale from stock. We also have designed a library of silicon-containing building blocks for drug discovery programs. These molecules can be synthesized upon request within 4-6 weeks.

Compounds from Stock:



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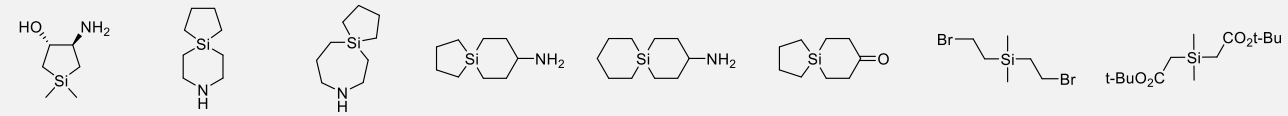
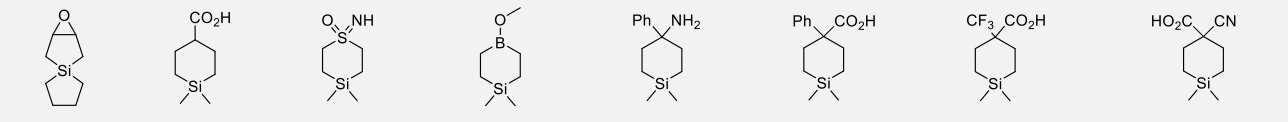


EN300-7354885 | EN300-6491014 | EN300-7426333 | EN300-6740317 | EN300-6745717 | EN300-6746677 | EN300-320867 | EN300-266027

Feasible Compounds:



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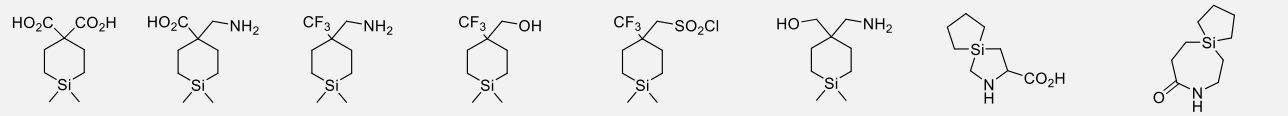

EN300-7444602 | EN300-6738097 | EN300-7444603 | EN300-7444604 | EN300-7444605 | EN300-7443172 | EN300-718566 | EN300-7354798

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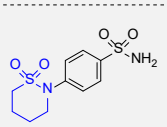
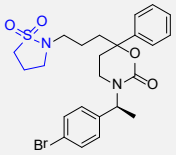
Cyclic Sulfonamides for Drug Design

Introduction

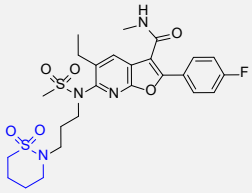
Sulfonamides are popular in drug discovery: more than 100 FDA-approved drugs on the market are sulfonamide-containing. Bioactive cyclic sulfonamides (sultams) include the anticonvulsant *Sultiame* (Bayer) and the anti-inflammatory drug *Piroxicam* (Pfizer).[1-5] Mostly, the *N*-aryl substituted sultams are synthesized from the corresponding anilines. Herein, we present a library of aliphatic sultams that can be easily alkylated at the *N*-atom. These compounds can be considered as water-soluble mimics of common cyclic amines – pyrrolidines, piperidines, *etc*.



Sultiame
anticonvulsant drug
Bayer



US 2011/9402 A1
Boehringer Ingelheim

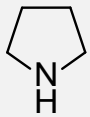


WO 2011/131709 A1
Novartis

Sultam group:

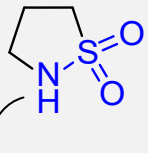
- easy *N*-alkylation (with K_2CO_3 as a base);
- metabolically stable;
- water soluble.

Design

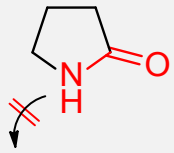


Pyrrolidine
>50 drugs

solubility
metabolic stability

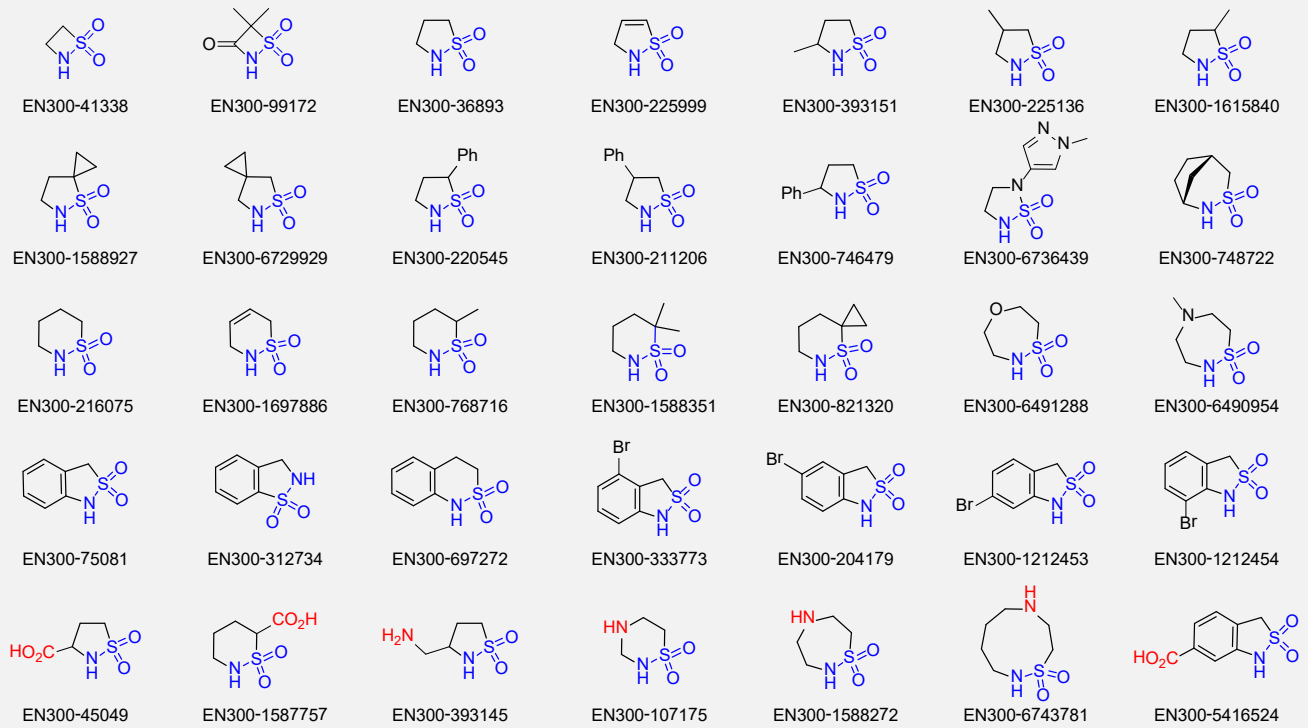


N-alkylation: easy
(with K_2CO_3 as a base)



N-alkylation: difficult

We offer >50 unique sultams on 5-50 g scale in stock.



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EN300-75081 EN300-312734 EN300-697272 EN300-333773 EN300-204179 EN300-1212453 EN300-1212454
EN300-45049 EN300-1587757 EN300-393145 EN300-107175 EN300-1588272 EN300-6743781 EN300-5416524

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Cubanes for Drug Design

Introduction

In 2016, chemists showed that replacing a benzene ring in the neurotropic compound Leteprinim with a skeleton of cubane beneficially affected activity and water solubility of the parent compound (Figure 1).[1] Since then the cubane-containing building blocks are gaining high popularity in drug discovery projects, as mimics for the benzene ring (Figure 2).[2,3]

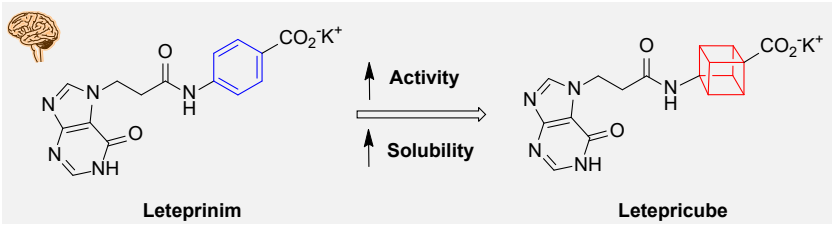


Figure 1. Modification and improvement of activity of Leteprinim drug.

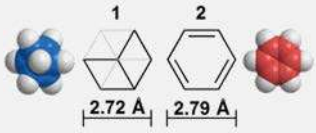
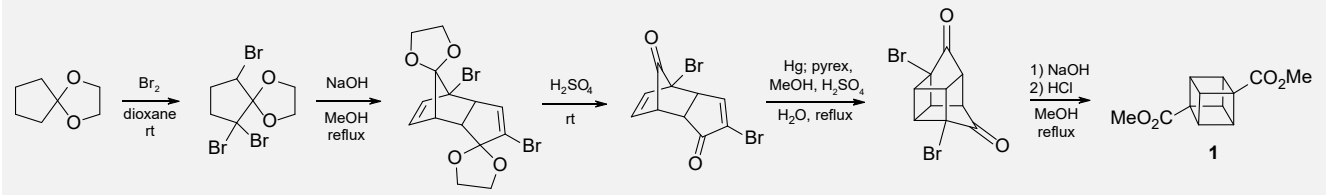


Figure 2. Comparison of 2- and 3-dimensional body views of cubane and benzene.

Synthesis

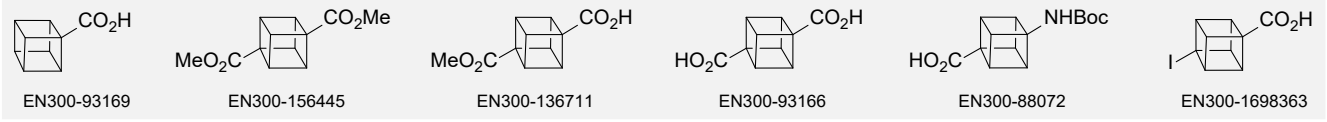
Herein, we synthesized cubane-1,4-diester **1** in 100 g scale following the literature protocol,[4] and used it for the synthesis of diverse cubane-containing building blocks (Schemes 1).



Scheme 1. Literature synthesis of cubane-containing compound 1.[4]

Our offer

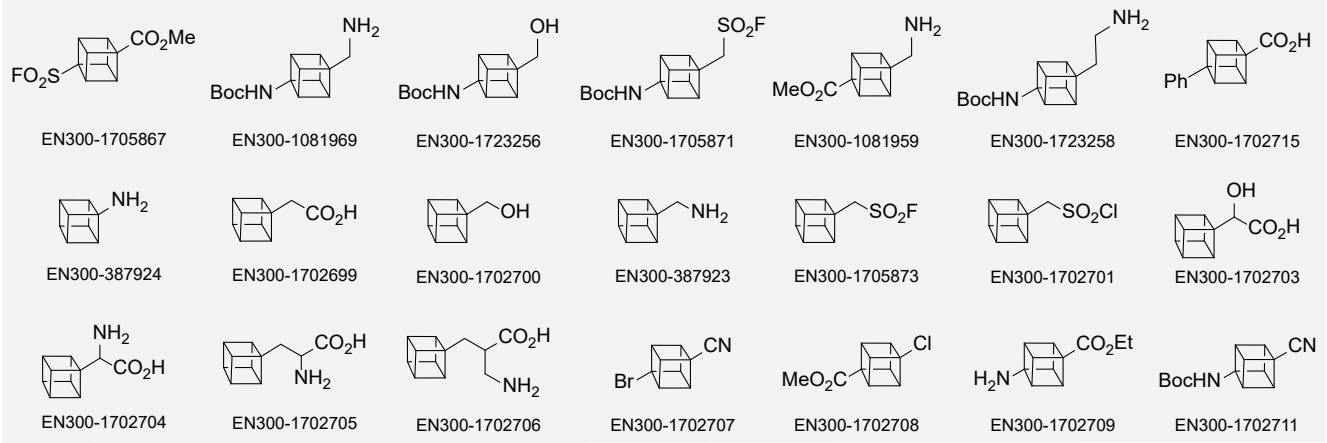
Currently, we have synthesized 6 cubane-containing building blocks, that are available in our EnamineStore on a gram scale.



EN300-93169 | EN300-156445 | EN300-136711 | EN300-93166 | EN300-88072 | EN300-1698363

Pre-order

We also have designed a library of cubane-containing building blocks for drug discovery programs. These molecules can be synthesized upon request within 4-6 weeks.



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EN300-387924 | EN300-1702699 | EN300-1702700 | EN300-387923 | EN300-1705873 | EN300-1702701 | EN300-1702703

EN300-1702704 | EN300-1702705 | EN300-1702706 | EN300-1702707 | EN300-1702708 | EN300-1702709 | EN300-1702711

References

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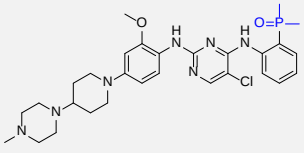
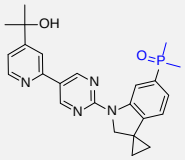
P(O)Me$_2$-containing Building Blocks for Drug Design

Introduction

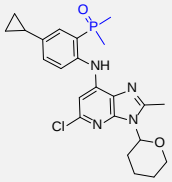
Phosphine oxides belong to a chemical class seldom employed in drug design. However, the FDA-approval of *Brigatinib* drug (ARIAD Pharm.) in 2017 may further inspire application of this unique functional group in medicinal chemistry. The highly ionic P=O bond imparts a number of important drug-like properties, including decreased lipophilicity, increased aqueous solubility, H-bond acceptor ability, and high metabolic stability.[1-3] Herein we have designed and synthesized a library of phosphine oxide derivatives for drug design.



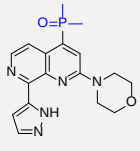
Anti-cancer drug **Brigatinib** (Alunbrig)
ARIAD Pharm.
2016



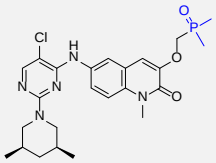
Phoshodiesterase inhibitor
WO2017/108203, A1
Grünenthal GmbH



TYK2 inhibitor
WO2018/075937, A1
Nimbus Lakshmi

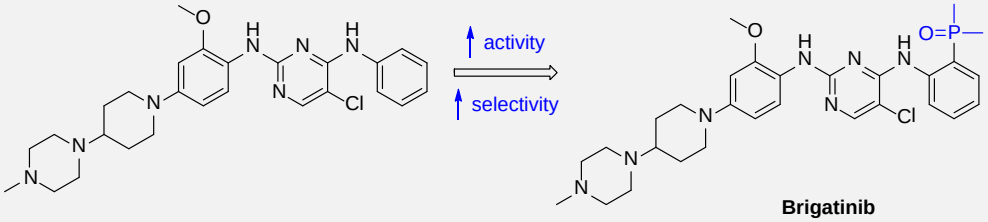


ATR kinase inhibitor
WO2018/153969, A1
Bayer Pharm.



BCL6 inhibitor
WO2018/108704, A1
Boehringer Ingelheim

Discovery of *Brigatinib*

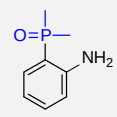


Brigatinib

P(O)Me$_2$-group:

- chemically stable;
- metabolically stable;
- H-bond acceptor;
- increases solubility;
- decreases lipophilicity.

We offer >30 unique P(O)Me$_2$-containing derivatives on a 5-50 g scale from our stock.



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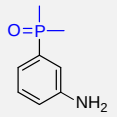

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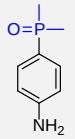

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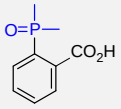

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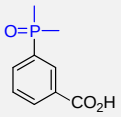

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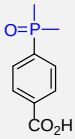

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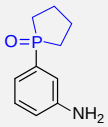

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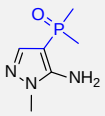

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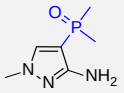

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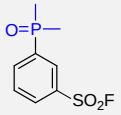

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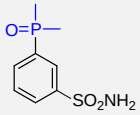

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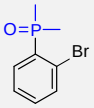

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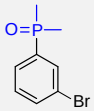

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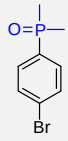
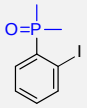


EN300-174270



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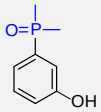

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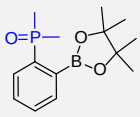

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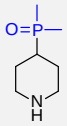

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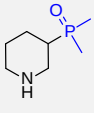

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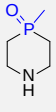

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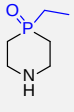

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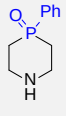

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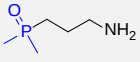

EN300-6497225

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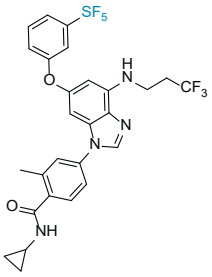
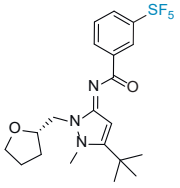
1. W.-S. Huang et al. *J. Med. Chem.* **2016**, *59*, 4948.
2. A. A. Kamel. *International Journal of Chemical and Biomedical Science*, **2015**, *1*, 56.
3. V. Iaroshenko. *Organophosphorus Chemistry: From Molecules to Applications*, John Wiley & Sons, **2019**, 568.

SF_5-Building Blocks

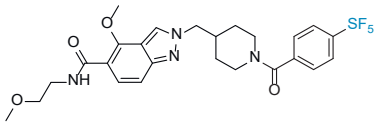
The organic chemistry of the pentafluorosulfanyl group (SF_5) has been developing since 1950's. As the SF_5 group is larger and more lipophilic than the CF_3 one, it is often considered as a "super-trifluoromethyl group". Over the past decade, the SF_5-containing aromatic compounds have found great practical application in medicinal chemistry.



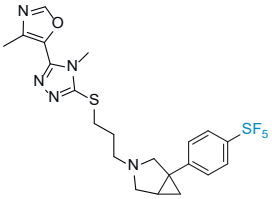
Inhibitor of Mps-1
WO 2012/130905
Bayer



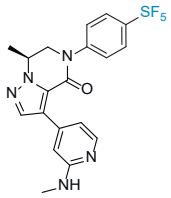
Inhibitor of CB2
WO 2009/105306
Abbott



Antagonist of EP2 receptor
US 2016/89364
Bayer



Modulator of DRD3
WO 2006/108700
GlaxoSmithKline



Antagonist of GRM2
WO 2016/87489
Janssen

	NO_2 CO_2H	SF_5 CO_2H	CF_3 CO_2H	SCF_3 CO_2H	OCF_3 CO_2H	F CO_2H
pKa $EtOH/H_2O$ 50:50	4.60	**4.82**	5.11	5.15	5.16	5.28

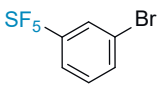
Lipophilicity (π) of substituent X

X	SCF_3	**SF_5**	OCF_3	CF_3	F	H
π_p	1.44	**1.23**	1.04	0.88	0.14	0

Properties

- One of the most electron-withdrawing groups
- high chemical and thermal stability
- high lipophilicity

Our offer: >30 SF_5-buiding blocks in gram amounts in stock. Custom synthesis of further analogues and compound libraries



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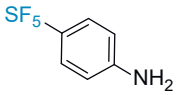

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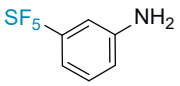

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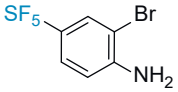

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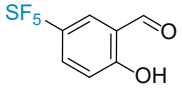

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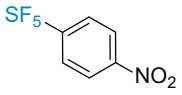

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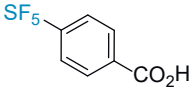

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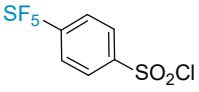

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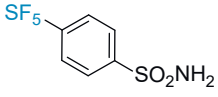

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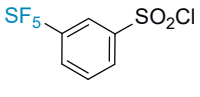

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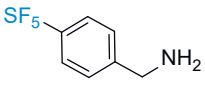

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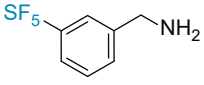

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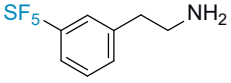

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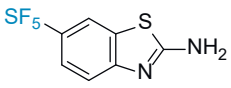

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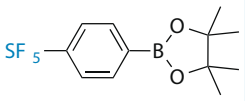

EN300-1704475

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[2] S. Altomonte *et al. J. Fluor. Chem.* **2012**, 57.
[3] P. Kirsch. *Modern Fluoroorganic Chemistry.* **2004**, 146.

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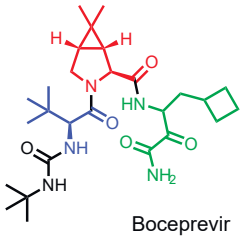
Amino acids are a privileged class of building blocks in drug design. Synthesis of new unusual amino acids has always been in focus of Enamine's research since its foundation 26 years ago. We are proud to offer the world's largest collection of unnatural amino acids from our stock and offer our skills and expertise in synthesis of custom compounds or compound libraries.



Boceprevir
antiviral drug

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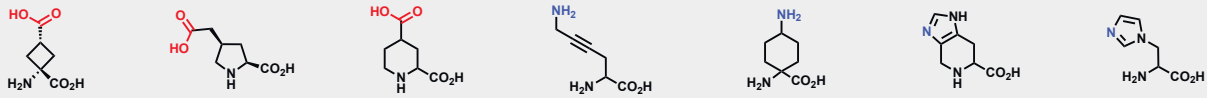
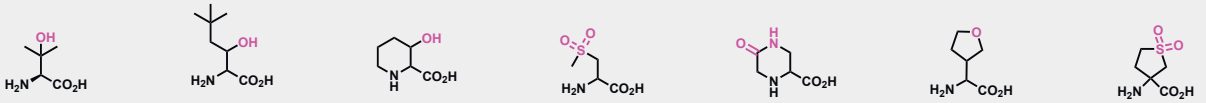
- Focus on DNA-encoded library synthesis: supply of Fmoc-derivatives in µmol amounts
- Custom synthesis of amino acids, their derivatives, and compound libraries

Amino acids with charged side chains



EN300-63952 EN300-762992 EN300-148730 EN300-150853 EN300-149315 EN300-762993 EN300-156012

Amino acids with polar and hydrophilic side chains



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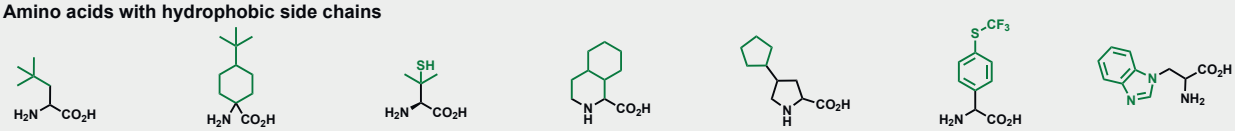
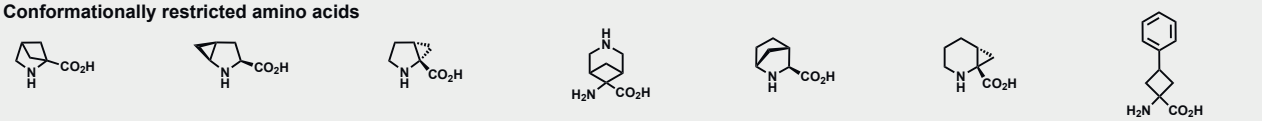
Amino acids with hydrophobic side chains



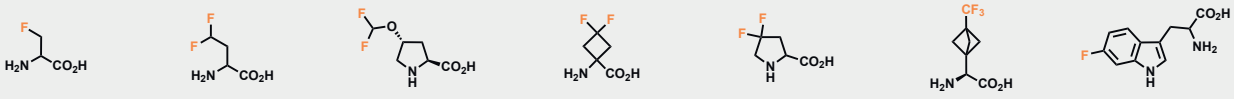
EN300-114441 EN300-58167 EN300-34663 EN300-762994 EN300-344208 EN300-182109 EN300-178651

Conformationally restricted amino acids



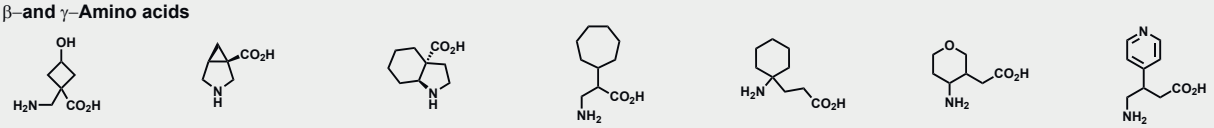
EN300-28750 EN300-30421 EN300-58616 EN300-762995 EN300-33992 EN300-762996 EN300-89725

Fluorinated amino acids



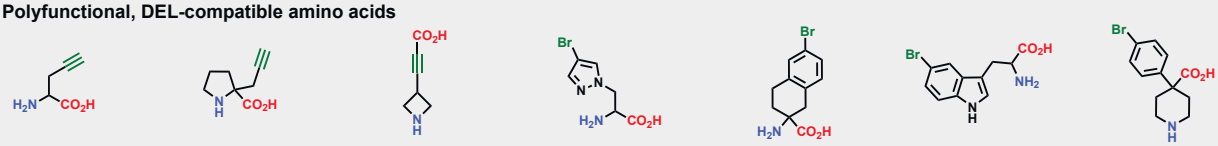
EN300-93448 EN300-65367 EN300-762997 EN300-89720 EN300-89756 EN300-53088 EN300-99675

β–and γ–Amino acids



EN300-302182 EN300-762998 EN300-762999 EN300-686983 EN300-198745 EN300-746143 EN300-717434

Polyfunctional, DEL-compatible amino acids



EN300-66130 EN300-763005 EN300-332806 EN300-132362 EN300-150920 EN300-85120 EN300-716305

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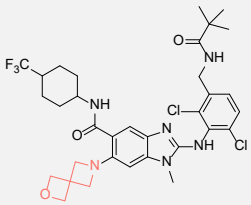
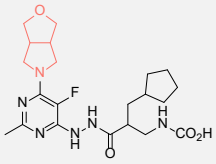
Morpholine Bioisosteres for Drug Design

Introduction

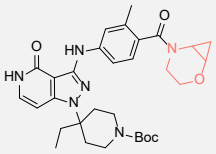
More than 20 FDA-approved drugs contain the morpholine moiety, although it is often metabolically labile.[1] Morpholine-based analogues may advantageously alter important pharmacokinetic properties such as lipophilicity and metabolic stability when grafted onto molecular scaffolds.[2,3] Herein we have designed and synthesized a library of morpholine analogues for drug design.[4-6]



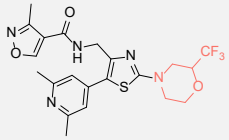
mPGES-1 inhibitor
WO 2012/076673 A1
Boehringer Ingelheim



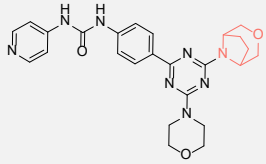
Peptide deformylase inhibitor
EP 2015/2217226 B1
GlaxoSmithKline



Janus kinase inhibitor
US 2018/10072025 B2
Merck&Co.

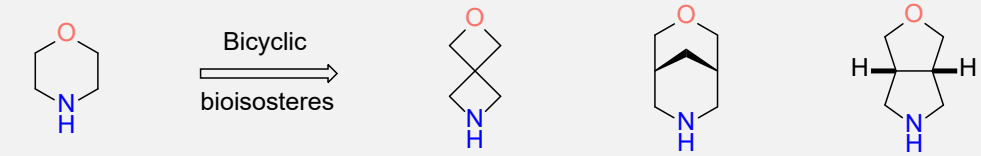


Alpha 7 positive allosteric modulator
EP 2015/2504333 B1
Janssen Pharm.



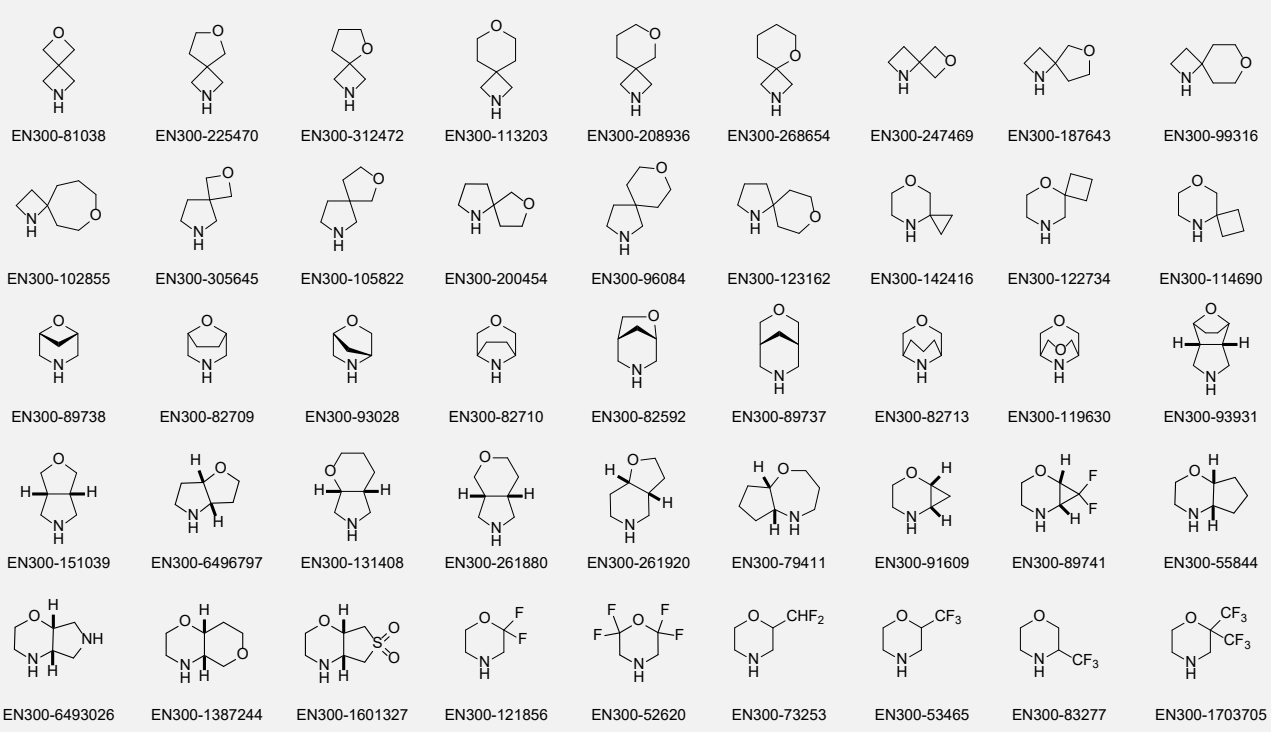
Inhibitor of PI3K
US 2013/109670 A1
Pfizer

Design



Morpholine | Spiro | Bridged | Fused

We offer >100 unique morpholine analogues on a 5-50 g scale from stock.

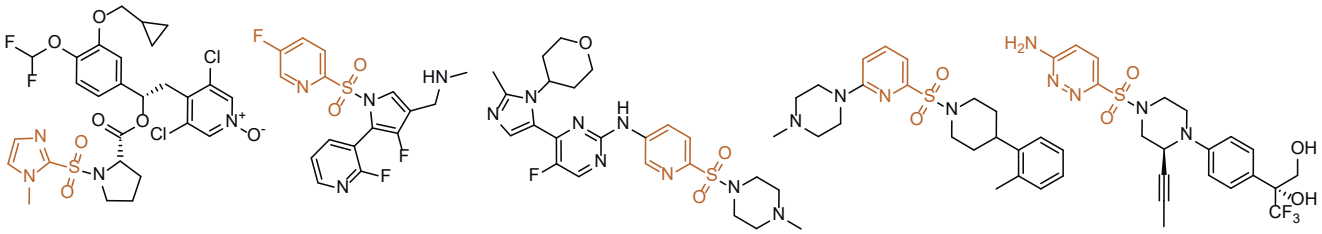


References

1. www.drugbank.ca
2. G. Wuitschik et al. *Angew. Chem. Int. Ed.* **2008**, 4512.
3. G. Wuitschik et al. *J. Med. Chem.* **2010**, 3227.
4. A. Shcherbatiuk et al. *Tetrahedron* **2013**, 3746.
5. A. D. Tereshchenko et al. *Tetrahedron* **2017**, 750.
6. A. Kirichok et al. *Chem. Eur. J.* **2018**, 5444.

Sulfonyl fluorides (-SO_2F): more options for drug design

Sulfonyl chlorides (-SO_2Cl) are widely used in medicinal chemistry and agrochemistry as precursors to pharmacologically important sulfonamides. Many sulfonyl chlorides with heteroaromatic substituents, however, are unstable due to SO_2 extrusion. More stable sulfonyl fluorides (-SO_2F) in many cases are the only option to synthesize the desired sulfonamides. They are less reactive, so that they might even have a free aliphatic amino groups in their structure. Besides unique monofunctional sulfonyl fluorides, *Enamine* offers a wide array of scaffolds and linker compounds.



Antagonist of V1B
WO 2014/140186
AbbVie

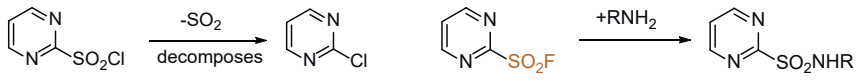
Modulator of RORγt
WO 2015/111870
Johnson & Johnson

Inhibitor of BUB1
WO 2013/50438
Bayer

Inhibitor of ALK
WO 2013/132376
Pfizer

Inhibitor of MKNK2
WO 2015/74986
Bayer

Properties of sulfonyl fluorides

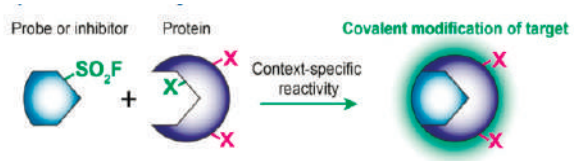


Unstable

Stable

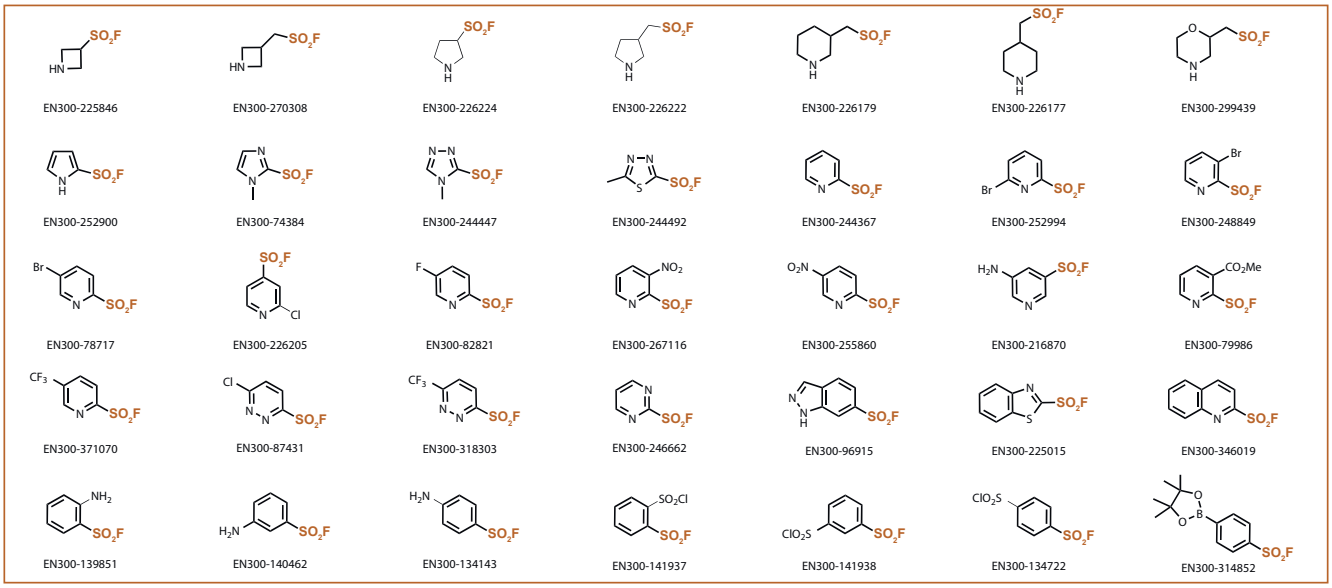
- stable to moisture
- improved selectivity
- orthogonal reactivity to many other functional groups

-SO_2F probes in chemical biology



The **SO_2F** group covalently binds to the residues of serine, threonine, tyrosine, lysine, cysteine, and histidine in proteins. Sulfonyl fluorides are widely used as chemical probes and covalent protein inhibitors.

Our offer: >200 Sulfonyl fluorides (-SO_2F) in gram amounts in stock
Custom synthesis of further analogues and compound libraries



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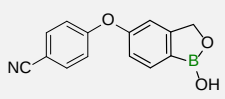
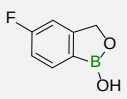
Benzoxaboroles for Drug Design

Introduction

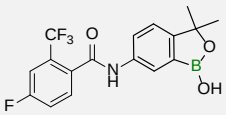
Benzoxaborole is a versatile boron-heterocyclic scaffold which has found in the last 10 years a broad spectrum of applications in medicinal chemistry. The use of benzoxaborole moiety in the design of compounds led to the discovery of new classes of anti-bacterial, anti-fungal, anti-protozoal, anti-viral and as anti-inflammatory agents with interesting drug development perspectives. Two benzoxaborole derivatives are already clinically used for the treatment of onychomycosis (*Tavaborole*) and atopic dermatitis (*Crisaborole*), with several others in various phases of clinical trials[1-9].



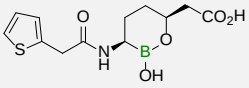
Crisaborole (Eucrisa)
treatment of psoriasis and eczema
Anacor Pharm. 2016



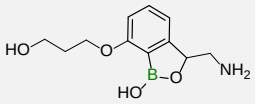
Tavaborole (Kerydin)
antifungal drug
Novartis, 2014



SCYX-7158
antiprotozoal drug (reached Phase III)
Anacor Pharm. 2009

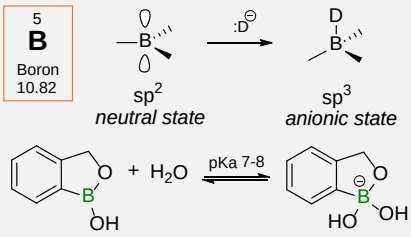


Vaborbactam
component of antibactrial drug Vabomere
Rempex Pharm. 2017



Epetraborole
antibacterial (reached Phase II)
Anacor Pharm. 2009

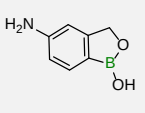
Advantages



Properties of benzoxaboroles:

- Low biotoxicity.
- Good solubility in water.
- They can coordinate to O and N.
- Ability to interfere protein synthesis.
- Covalent bonding- and nonbonding interactions with protein targets.

We offer



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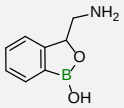

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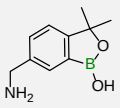

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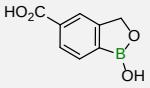

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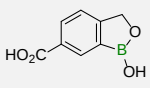

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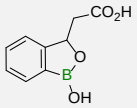

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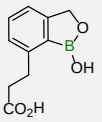

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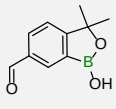

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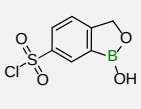

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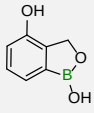

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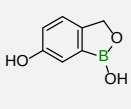

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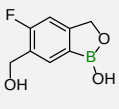

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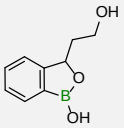

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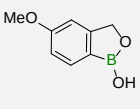

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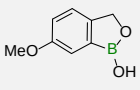

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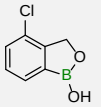

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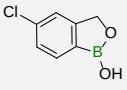

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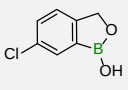

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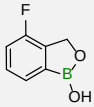

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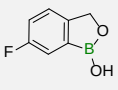

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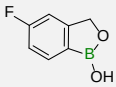

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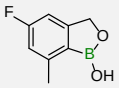

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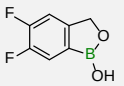

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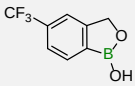

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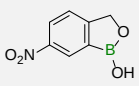

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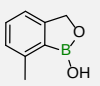

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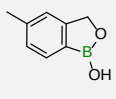

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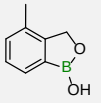

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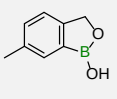

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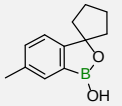

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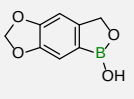

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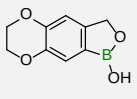

EN300-262861

EN300-262839

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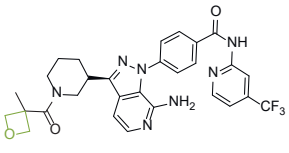
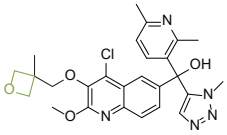
Oxetanes

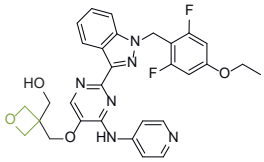
For more than 130 years since the first preparation by Reboul, oxetanes have largely remained neglected in medicinal chemistry. The unit of oxetane can trigger profound changes in aqueous solubility, lipophilicity, metabolic stability, and conformational preference when replacing the commonly employed functionalities such as gem-dimethyl or carbonyl groups. Of particular interest are the oxetanes substituted at the 3-position, since they remain none-chiral. At the moment, oxetane-containing building blocks flourish in medicinal chemistry and drug discovery.



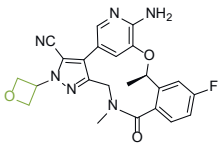
Antagonist of V1B
WO 2014/140186
AbbVie



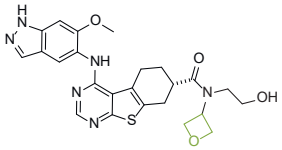
Modulator of RORγt
WO 2015/111870
Johnson & Johnson



Inhibitor of BUB1
WO 2013/50438
Bayer



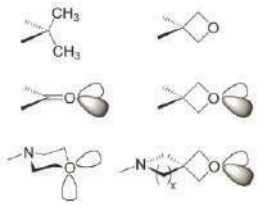
Inhibitor of ALK
WO 2013/132376
Pfizer



Inhibitor of MKNK2
WO 2015/74986
Bayer

Properties of Oxetanes

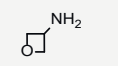
- high chemical stability;
- high aqueous solubility;
- low lipophilicity;
- high metabolic stability;
- hydrogen-bond acceptor ability.



Application of Oxetanes

- less lipophilic and more metabolically stable than a *gem*-dimethyl group;
- replacement for a metabolically and chemically labile carbonyl group;
- metabolically-robust analogue of morpholine.

Our offer: >200 oxetane-containing building blocks on gram scale in stock.



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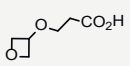

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EN300-217002

EN300-76721

EN300-105937

EN300-102401

EN300-182561

EN300-185704

EN300-247220

EN300-249834

EN300-317771

EN300-105692

EN300-105482

EN300-104496

EN300-102347

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EN300-248257

EN300-89755

EN300-247469

EN300-113883

EN300-199738

EN300-217771

EN300-366278

EN300-249022

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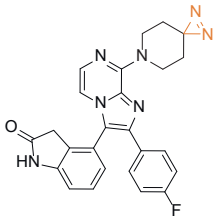
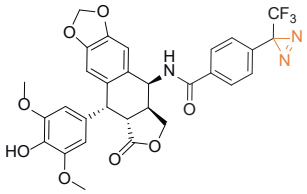
[1] G. Wuitschik *et al. J. Med. Chem.* **2010**, 3227.
[2] J.A. Burkhard *et al. Angew. Chem. Int. Ed.* **2010**, 9052
[3] G. Wuitschik *et al. Angew. Chem. Int. Ed.* **2008**, 4512.
[4] G. Wuitschik *et al. Angew. Chem. Int. Ed.* **2006**, 7736.

Diazirines

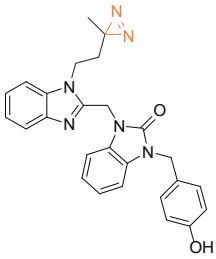
Diazirine is a smallest heterocycle that is stable in the dark, but forms reactive carbene upon irradiation with light. Its introduction into the structures of biologically active compounds accompanying with only minor change in MW (plus only 2 nitrogen atoms!) has proven to provide efficient tools to study interactions with biological targets including their isolation and identification. Given the success and progress in the field of activity-based protein profiling, the use of diazirine photolabeling will most likely continue to rise and it is important to have a commercial access to diverse diazirine-containing building blocks.



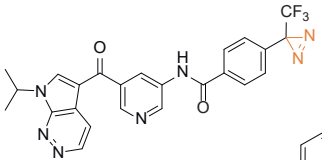
Antagonist of GRIA1
WO 2016/176457
Janssen Pharm.



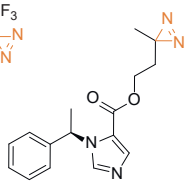
Analog of etoposide
Bioorg. Med. Chem.
2010, 830.



Inhibitor of RSV
Bioorg. Med. Chem.
2004, 1133.



Inhibitor of TrkA
US 2012/258950
Pfizer

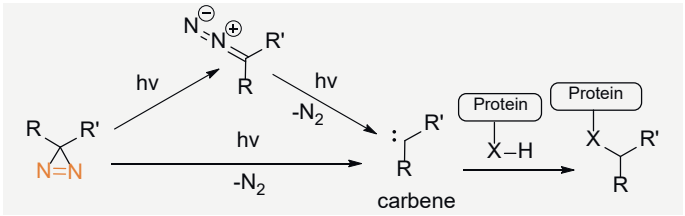


Blocker of nAChRs
Mol. Pharmacol.
2009, 1084.

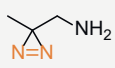
Properties

- smallest photoreactive group
- excitation at 355 nm
- high chemical stability

Upon irradiation of a ligand-target complex, a diazirine-containing ligand generates a reactive carbene that covalently binds the ligand to the target.



Our offer: >30 building blocks from stock.
Custom synthesis of the diazirine building blocks and diazirine-containing ligands.



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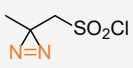

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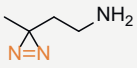

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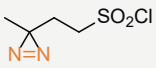

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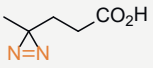

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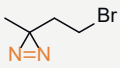

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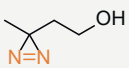

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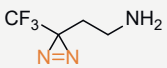

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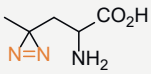

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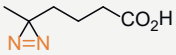

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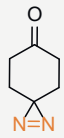

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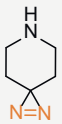

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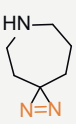

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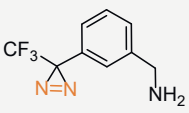

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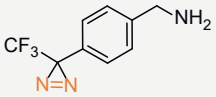

EN300-315165

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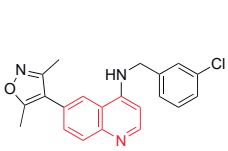
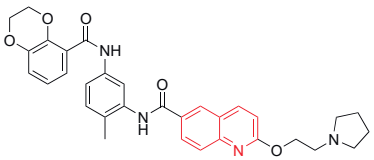
[1] L. Dubinsky *et al. Bioorg. Med. Chem.* **2012**, 554.
[2] N. Burkard *et al. Eur. J. Org. Chem.* **2010**, 2176.
[3] A. Blencowe *et al. Soft Matter.* **2005**, 178.
[4] Hatanaka *et al. Curr. Top. Med. Chem.* **2002**, 271.

Heterocyclic scaffolds

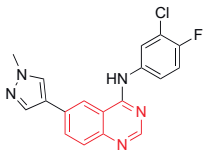
Unsaturated heterocycles are popular in bioactive compounds and drugs. Herein, we offer a library of heterocycles with two halogen atoms bearing different activity. They can be used for the stepwise nucleophilic substitution followed by a metal-mediated cross-coupling to produce the functionalized products.



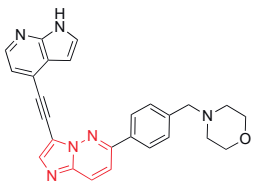
Inhibitor of bromodomain-containing proteins
WO 2017/91661



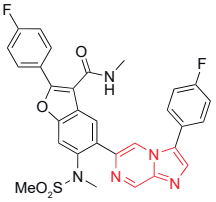
Detection of inhibitors of the HSF1 stress pathway
J. Med. Chem. **2017**, *60*, 180



Inhibitory activity against EGFR and SK-BR-3 cell line
Eur. J. Med. Chem. **2016**, *118*, 276



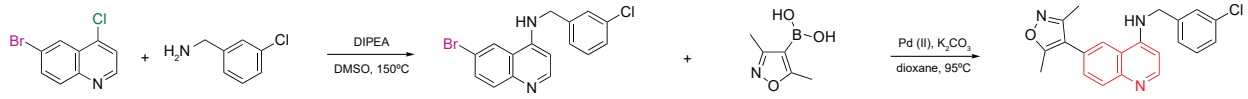
Inhibitor of the MAP kinase
WO 2015/050505



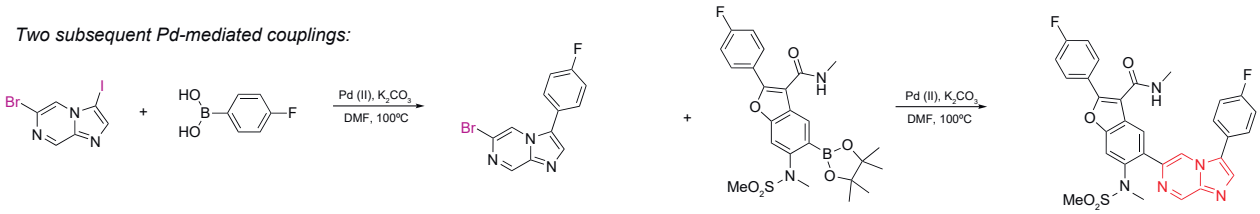
Inhibitor of HCV NS5B polymerase activity
WO 2013/34048

Synthesis of bioactive compounds

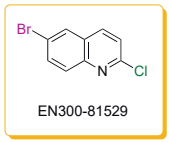
Nucleophilic substitution and Pd-mediated coupling:



Two subsequent Pd-mediated couplings:



Our offer: over 100 different bicyclic heterocycles with two different halogens on a gram scale in stock.



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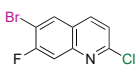

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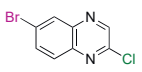

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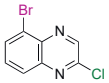

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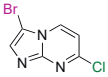

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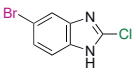

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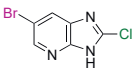

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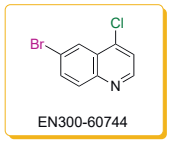

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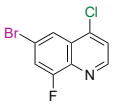

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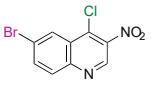

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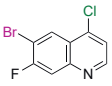

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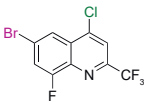

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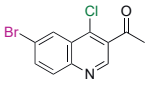

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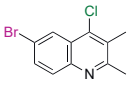

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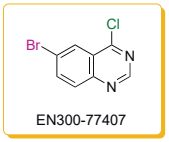

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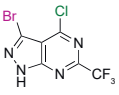

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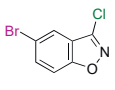

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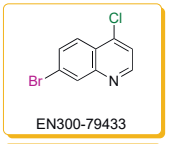

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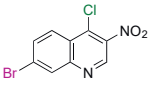

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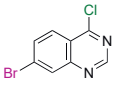

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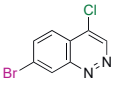

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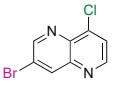

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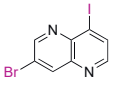

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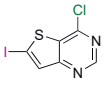

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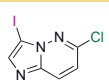

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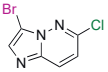
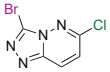


EN300-117363



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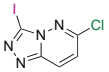

EN300-268640

EN300-1654630

EN300-412396

EN300-805039

EN300-262727

EN300-262215

EN300-172628

EN300-243666

EN300-262529

EN300-366554

EN300-258713

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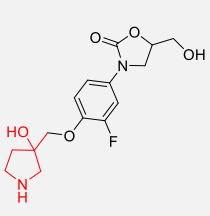
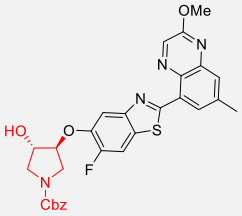
Epoxides for Drug Design

Introduction

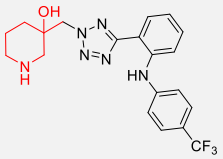
Epoxides are important heterocyclic units found in various naturally occurring molecules, some with potential bioactivities. At least fourteen drugs on the market are epoxide-containing.[1] In addition, epoxides are valuable building blocks in medicinal chemistry. They react with nucleophiles in a ring-opening process to form new C-C, C-O and C-N bonds.[2-5] Herein we have designed and synthesized a library of small heteroaliphatic epoxides for drug design.



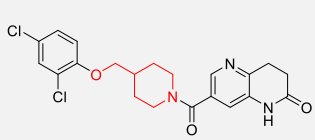
Antibacterial agent
US 2009/247578, A1
Actelion Pharm.



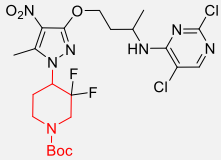
Precursor to PAR4 inhibitor
WO 2018/13770, A1
Bristol-Myers Squibb



Treatment of cancer
WO 2018/204532, A1
Vivace Therapeutics

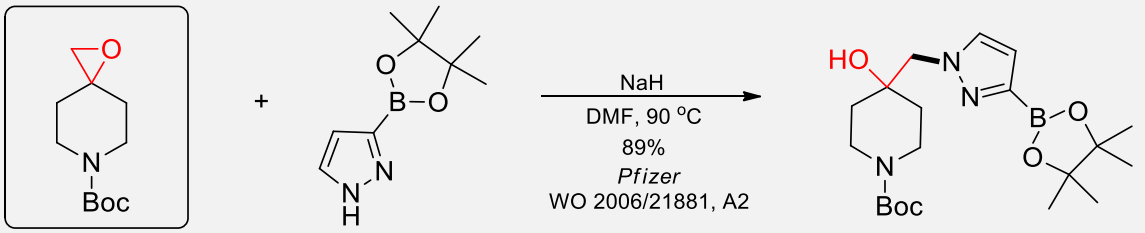


MAGL inhibitor
EP/3279191, 2018, A1
Takeda Pharm.

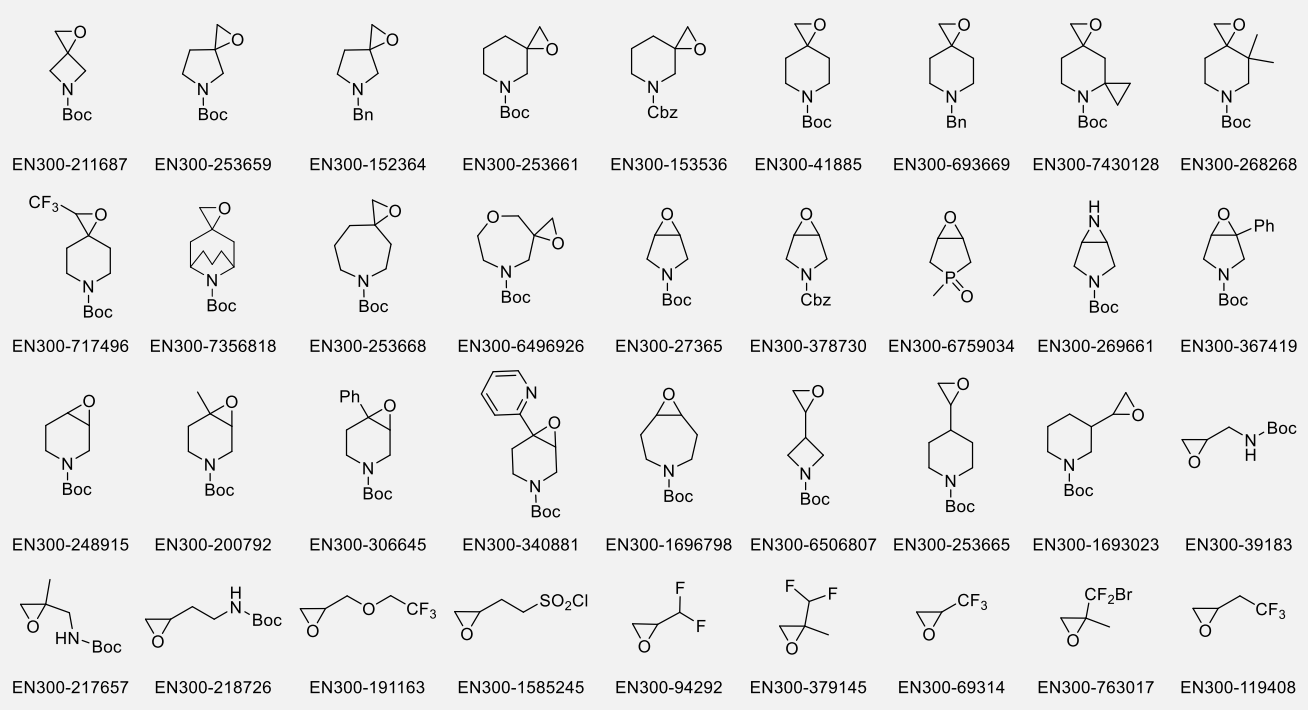


Precursor to LRRK2 inhibitor
WO 2019/12093, A1
GlaxoSmithKline

Design



We offer >100 unique epoxides on a 5-50 g scale from stock.



EN300-211687 EN300-253659 EN300-152364 EN300-253661 EN300-153536 EN300-41885 EN300-693669 EN300-7430128 EN300-268268

EN300-717496 EN300-7356818 EN300-253668 EN300-6496926 EN300-27365 EN300-378730 EN300-6759034 EN300-269661 EN300-367419

EN300-248915 EN300-200792 EN300-306645 EN300-340881 EN300-1696798 EN300-6506807 EN300-253665 EN300-1693023 EN300-39183

EN300-217657 EN300-218726 EN300-191163 EN300-1585245 EN300-94292 EN300-379145 EN300-69314 EN300-763017 EN300-119408

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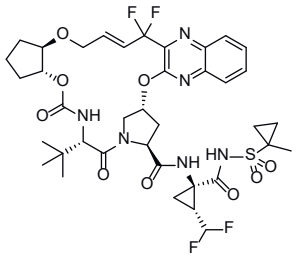
4. D. M. Hodgson et al. *Tetrahedron*, **1996**, *52*, 14361.
5. G. Dake. *Comprehensive Heterocyclic Chemistry III, 1.03 Oxiranes and Oxirenes: Monocyclic*, **2008**, p. 173.

Macrocycles

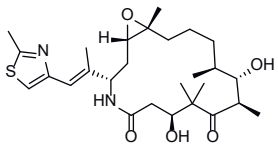
Macrocyclic motifs are commonly found in natural products and also interesting for Drug Discovery especially in efforts to tackle “difficult” targets with extended binding sites. The size and complexity of macrocyclic compounds make possible to ensure numerous and spatially distributed binding interactions, thereby increasing both binding affinity and selectivity. Macrocylic structure often provides necessary balance between degree of structural preorganisation (that may reduce the entropy cost of receptor binding as compared to linear analogues) and sufficient flexibility (comparing to common rigid (poly)cyclic cores) that can facilitate interactions with diverse dynamic protein targets. In addition often macrocycles have favorable ADME- and PK-properties. In spite of such attractiveness for medicinal chemistry the chemical space of macrocycles is still poorly investigated.

Features of Macrocycles

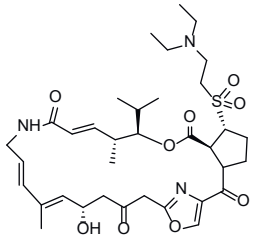
- Possibility to go beyond "Ro5"
- "Friendly" ADME and PK
- Complexity / 3D-shape
- Novelty
- **Balance between conformational confinement and flexibility**



Glecaprevir
Abbvie, anti-HCV



Ixabepilone
BMS, chemotherapy

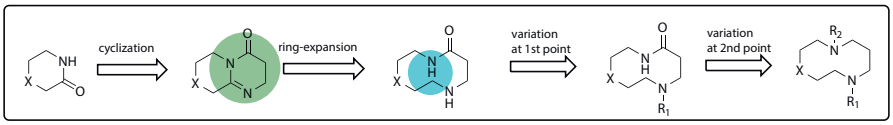


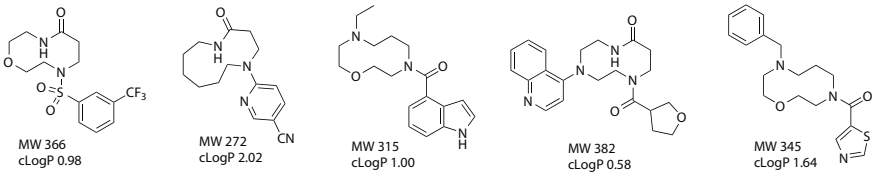
Dalfopristin
Sanofi, antibiotic

Enamine's offer

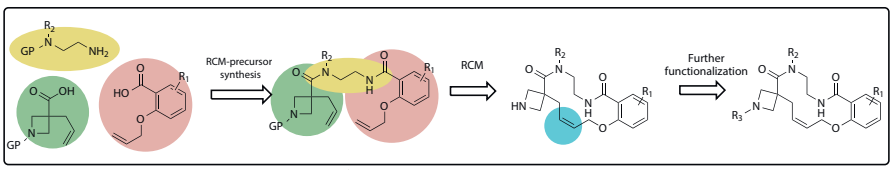
- **Libraries of drug-like compounds with medium sized and macrocyclic cores**
- **MedChem-friendly compounds** *(pass common MedChem filters including PAINS)*
- **Validated macrocyclization chemistry** *(RCM, click, ring-expansion, macrolacton/lactamization, etc.)*
- **Validated scaffolds** *(>10 key intermediates available in 1-5 g)*
- **Decoration with diverse Enamine building blocks (150,000 in stock)**
- **Rapid library synthesis** *(3 weeks for parallel synthesis of up to 200 cmpds from available scaffold)*

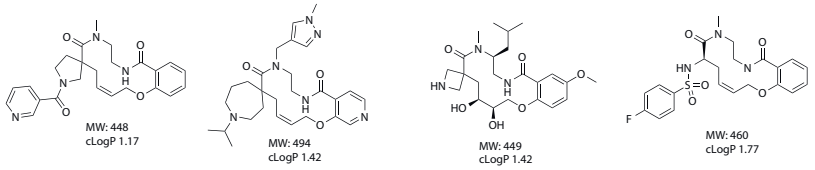
Ring-expansion to build a 10-membered diamino scaffold





Ring Closing Metathesis (RCM) in synthesis of new macrocyclic scaffolds at Enamine





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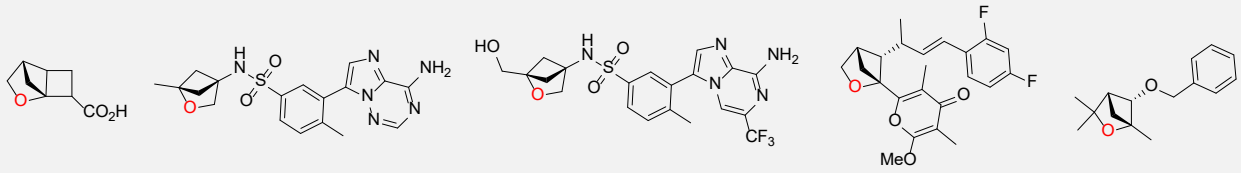
[2] D. Sun *et al. Molecules.* **2013**, 18.
[3] F Giordanetto *et al. J. Med. Chem.* **2014**, 278
[4] E. Marsault *J. Med. Chem.*, **2011**, 1961

Saturated Bioisosteres of Benzene with Improved Solubility

Introduction

"Escape the Flatland" concept has already gained considerable attention in medicinal chemistry.[1,2] Scientists are looking more and more now for 3D-shaped saturated building blocks.[3-7] In this context, conformationally rigid bicyclic tetrahydrofurans are intrinsically promising for drug discovery. In continuation of our ongoing program towards novel building blocks for drug discovery,[8-11] herein we have designed and synthesized a library of saturated mimics of the benzene ring with improved solubility in water.[12]



Plant growth regulator
US 1987/467004 A

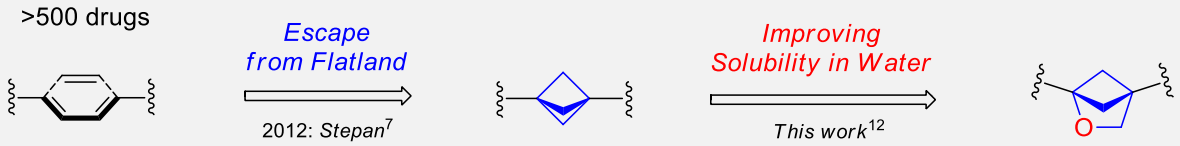
Inhibitor of PI3K-γ
US 2018/009816 A1

Inhibitor of PI3K-γ
US 2018/009816 A1

Antiviral agent
WO 2016/162405 A1

Inhibitor of histone diacetylase
US 2018/0099977 A1

Design

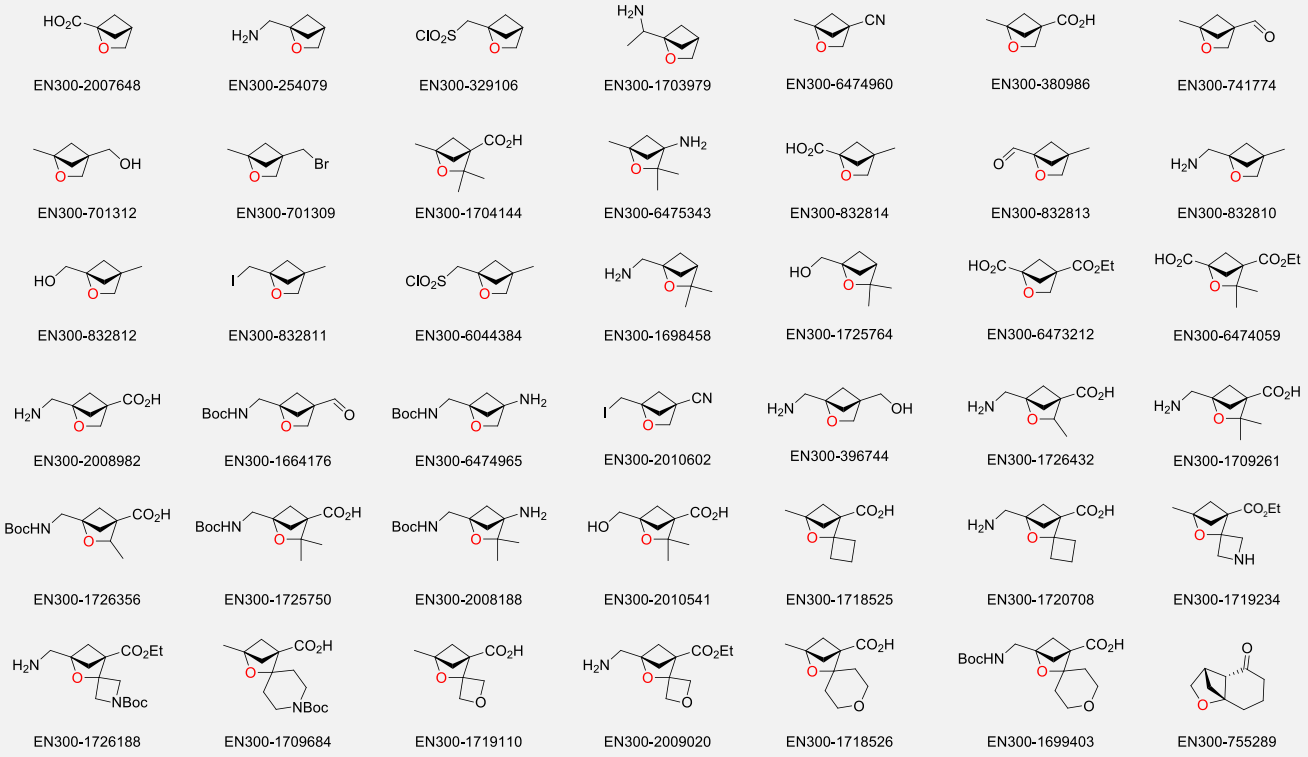


para-substituted Benzene

Bicyclo[1.1.1]pentane
>100 patents

Mimic for *meta*-/*para*-substituted Benzenes

We offer more than 100 *mono*- and *di*substituted benzene mimics with improved water solubility from stock on a 5-10 g scale:



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2. F. Lovering *Med. Chem. Commun.* **2013**, 515.
3. J. Wlochal et al. *Org. Lett.* **2014**, 4094.
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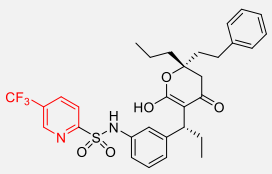
8. A. Kirichok et al. *ANIE* **2017**, 8865.
9. A. Kirichok et al. *Chem. Eur. J.* **2018**, 5444.
10. T. Druzhenko et al. *J. Org. Chem.* **2018**, 1394.
11. V. Levchenko et al. *J. Org. Chem.* **2018**, 3265.
12. V. Levterov et al. *manuscript under preparation*.

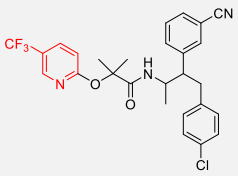
Analogues of CF_3-Pyridine for Drug Design

Introduction

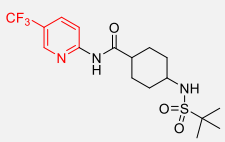
More than 100 FDA-approved drugs contain the pyridine moiety and the same amount was in clinical trials.[1] Examples containing CF_3-pyridine moiety include the antiviral drug *Tipranavir* and drug candidates *Taranabant, Velneperit, SB-705498*. Besides, CF3-pyridine containing compounds have been playing a crucial role in agrochemistry.[2,3] The introduction of fluorine-containing group alters important pharmacokinetic properties of molecular scaffolds.[4] Herein we have designed and synthesized a library of CF_3-substituted pyridine analogues for drug design and agrochemistry.



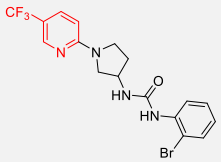
Tipranavir
Drug for treatment of HIV infection
Boehringer Ingelheim



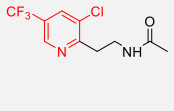
Taranabant (Reached Phase III)
Treatment for obesity
Merck & Co.



Velneperit (Reached Phase II)
Treatment for obesity
Shionogi & Co.

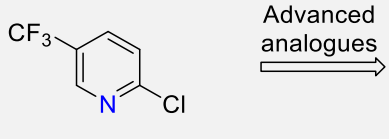


SB-705498 (Reached Phase II)
Treatment of rhinitis and chronic cough
GlaxoSmithKline



Fluopyram
Fungicide, inhibitor of SDH
Bayer CropScience

Design



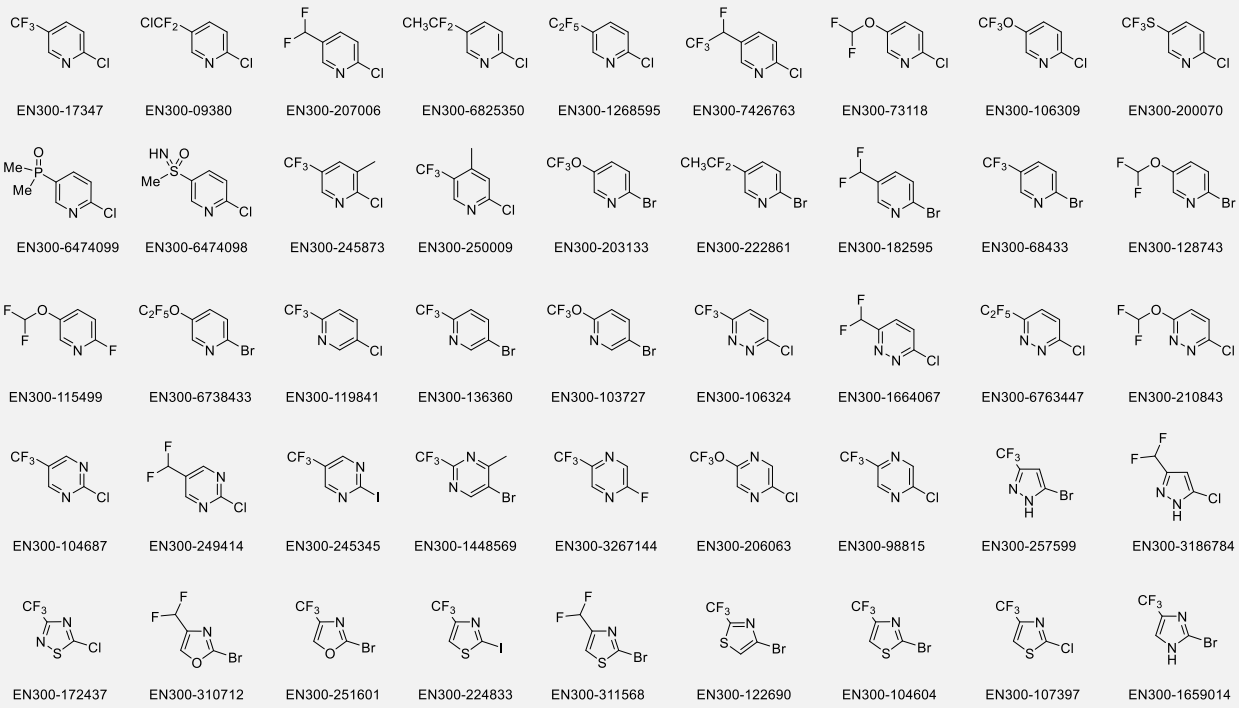
A popular building block in agro and drug design

EN300-207006

EN300-6474098

EN300-6474099

We offer >100 unique CF_3-pyridine analogues on a 5-50 g scale from stock



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EN300-6474099 EN300-6474098 EN300-245873 EN300-250009 EN300-203133 EN300-222861 EN300-182595 EN300-68433 EN300-128743

EN300-115499 EN300-6738433 EN300-119841 EN300-136360 EN300-103727 EN300-106324 EN300-1664067 EN300-6763447 EN300-210843

EN300-104687 EN300-249414 EN300-245345 EN300-1448569 EN300-3267144 EN300-206063 EN300-98815 EN300-257599 EN300-3186784

EN300-172437 EN300-310712 EN300-251601 EN300-224833 EN300-311568 EN300-122690 EN300-104604 EN300-107397 EN300-1659014

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