Enamine

総集編！

Enamine社ホットトピック Building Blocks

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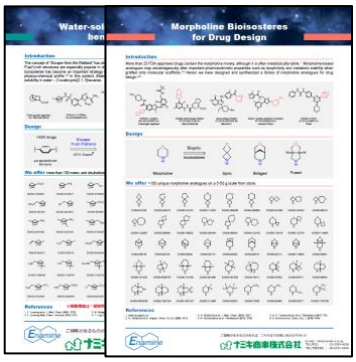

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ユニークなBuilding Blocksをぜひご活用下さい！

ナミキ商事株式会社

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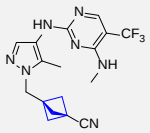
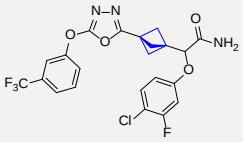
Saturated Bioisosteres of *para*-substituted Benzenes

Introduction

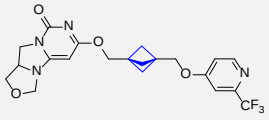
The residue of benzene comprises to the structure of more than 500 FDA-approved drugs.[1] In 2012, *Stepan* and coworkers showed that bicyclo[1.1.1]pentane skeleton could act as a saturated "*nonclassical phenyl ring bioisostere*" in the design of a γ-secretase inhibitor.[2] Since then, the core of bicyclo[1.1.1]pentane 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.



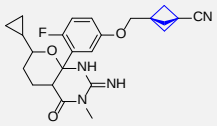
LRRK2 inhibitor
WO 2017/218843
Denali Therapeutics



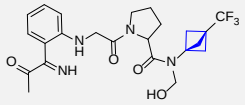
Integrated stress pathway modulator
WO 2017/193030
Calico Life Sciences



Inhibitor of Lp-PLA2 activity
WO 2016/011930
GlaxoSmithKline



BACE inhibitor
WO 2016/085780
Merck & Co.



Complement pathway modulator
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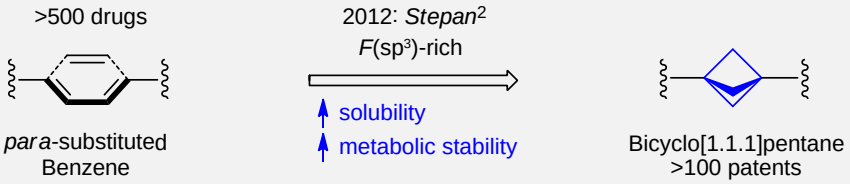
Design



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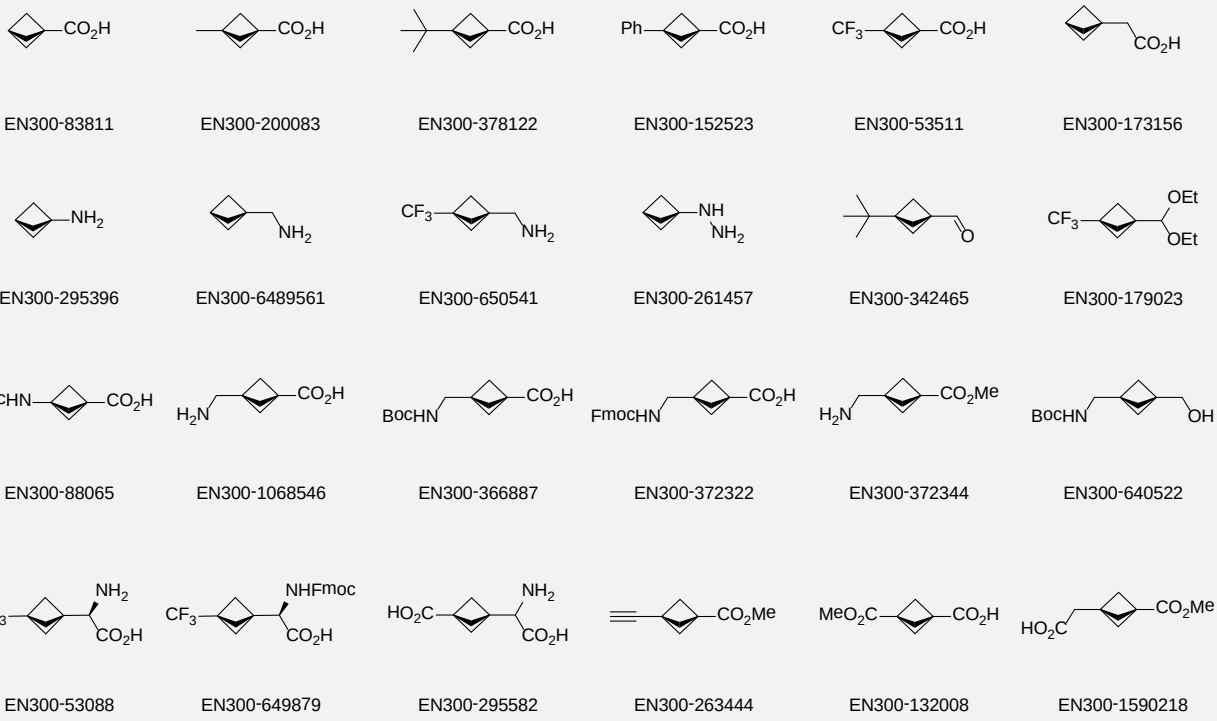

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EN300-53088 | EN300-649879 | EN300-295582 | EN300-263444 | EN300-132008 | EN300-1590218

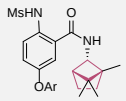
References

1. R. D. Taylor et al. *J. Med. Chem.* **2014**, *57*, 5845.
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. K. C. Nicolaou et al. *ChemMedChem* **2016**, *11*, 31.
7. N. D. Measom et al. *ACS Med. Chem. Lett.* **2017**, *8*, 43.
8. A. M. Dilmac et al. *ANIE* **2017**, *56*, 5684 .

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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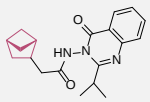
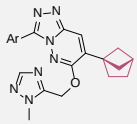
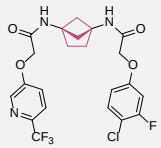


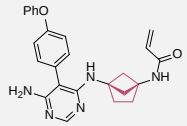
Potassium channel modulators
US 2012/122890
Abbott



Ligand for GABA receptors
US 2001/6303597
Merck

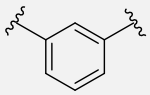


Modulator of the integrated stress pathway
WO 2017/193034
Calico



Inhibitor of Bruton's tyrosine kinase
WO 2012/170976
Merck

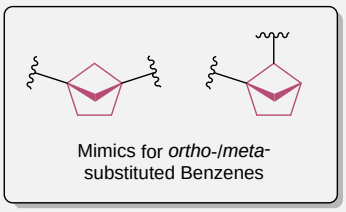
Design



meta-substituted Benzene

Escape from Flatland

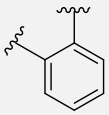
$F(sp^3)$-*rich*
>100 drugs



Mimics for *ortho-/meta*-substituted Benzenes

Escape from Flatland

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



ortho-substituted Benzene

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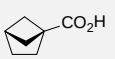

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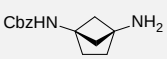

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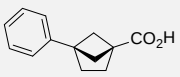

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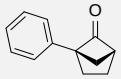

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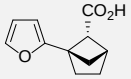

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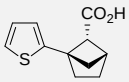

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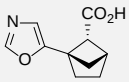

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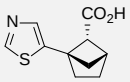

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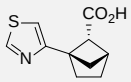

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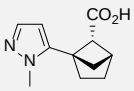

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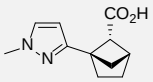

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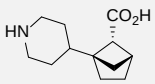

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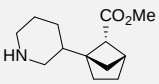

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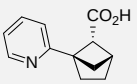

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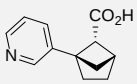

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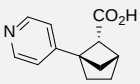

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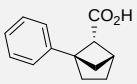

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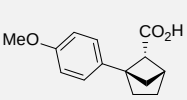

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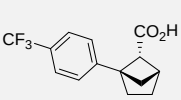

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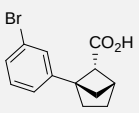

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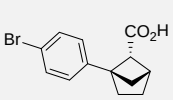

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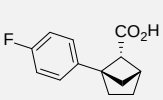

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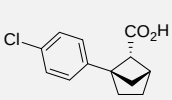


EN300-6479063

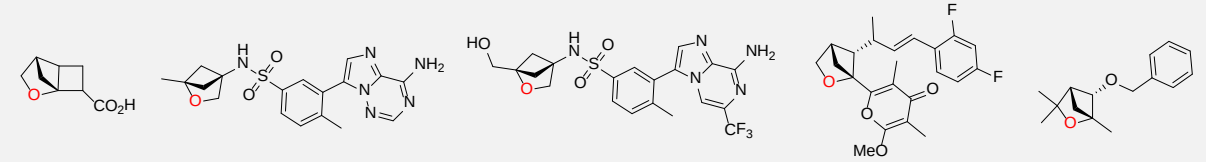
References

1. R. D. Taylor et al. *J. Med. Chem.* **2014**, *57*, 5845.
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.

Water-soluble non-classical benzene mimics

Introduction

The concept of "*Escape from the Flatland*" has already gained considerable attention in medicinal chemistry. Nowadays small F(sp^3)-rich structures are especially popular in drug discovery projects. In particular, replacing benzene rings with saturated bioisosteres has become an important strategy to obtain novel patent-free molecules with improved biological activity and physico-chemical profile.[1-6] In this context, *Enamine* offers a new generation of saturated benzene mimics with improved solubility in water – 2-oxabicyclo[2.1.1]hexanes.



Plant growth regulator
US 1987/467004 A

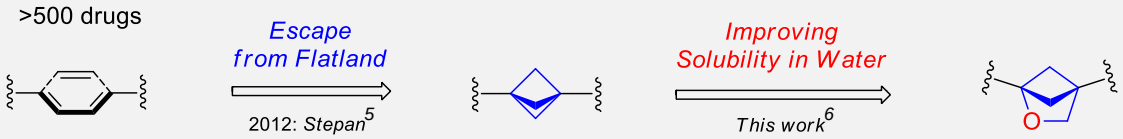
Inhibitor of PI3K-γ
US 2018/009816 A1

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:

EN300-1604607	EN300-6734977	EN300-6759622	EN300-2007648	EN300-254079	EN300-2496461	EN300-1703979
EN300-329106	EN300-2575407	EN300-380986	EN300-6489840	EN300-6736397	EN300-6474960	EN300-741774
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EN300-1698458	EN300-1725764	EN300-1725750	EN300-2008188	EN300-6736511	EN300-6473212	EN300-6764720
EN300-7432909	EN300-2008982	EN300-6503987	EN300-396744	EN300-1664176	EN300-6474965	EN300-6482097

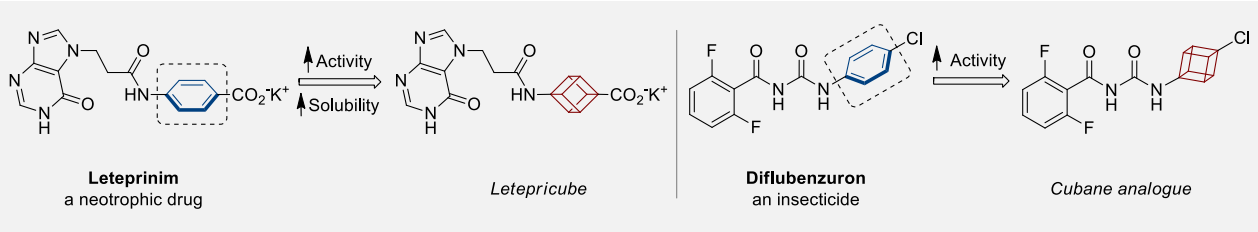
References

1. F. Lovering et al. *J. Med. Chem.* **2009**, 6752.
2. F. Lovering *Med. Chem. Commun.* **2013**, 515.
3. M. Westphal et al. *ChemMedChem.* **2015**, 461.
4. Y. Ling Goh et al. *Org. Lett.* **2014**, 1884.
5. A. Stepan et al. *J. Med. Chem.* **2012**, 3414.
6. V. Levterov et al. *ANIE*, **2020** (doi.org/10.1002/anie.202000548).

Cubanes for Medicinal Chemistry

Introduction

In 1992, Eaton predicted a high potential of cubane in a pharmaceutical research as a bioisoster of benzene, based on their similarity in size. In 2016, *Williams* and collaborators showed that replacing a benzene ring in the neurotropic compound *Leteprinim* with cubane beneficially affected activity and solubility of the parent compound. The cubane analogue significantly outperformed pesticide *Diflubenzuron*. Since then the cubane-containing building blocks have been playing an important role in medchem projects, as mimics for the *para*-substituted benzene ring. In this context, *Enamine* offers a library of cubane-containing building blocks for drug design.[1-6]



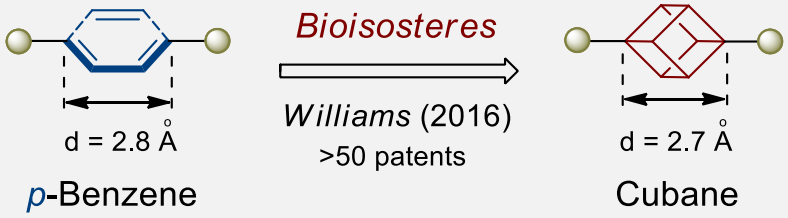
Leteprinim
a neotrophic drug

Letepricube

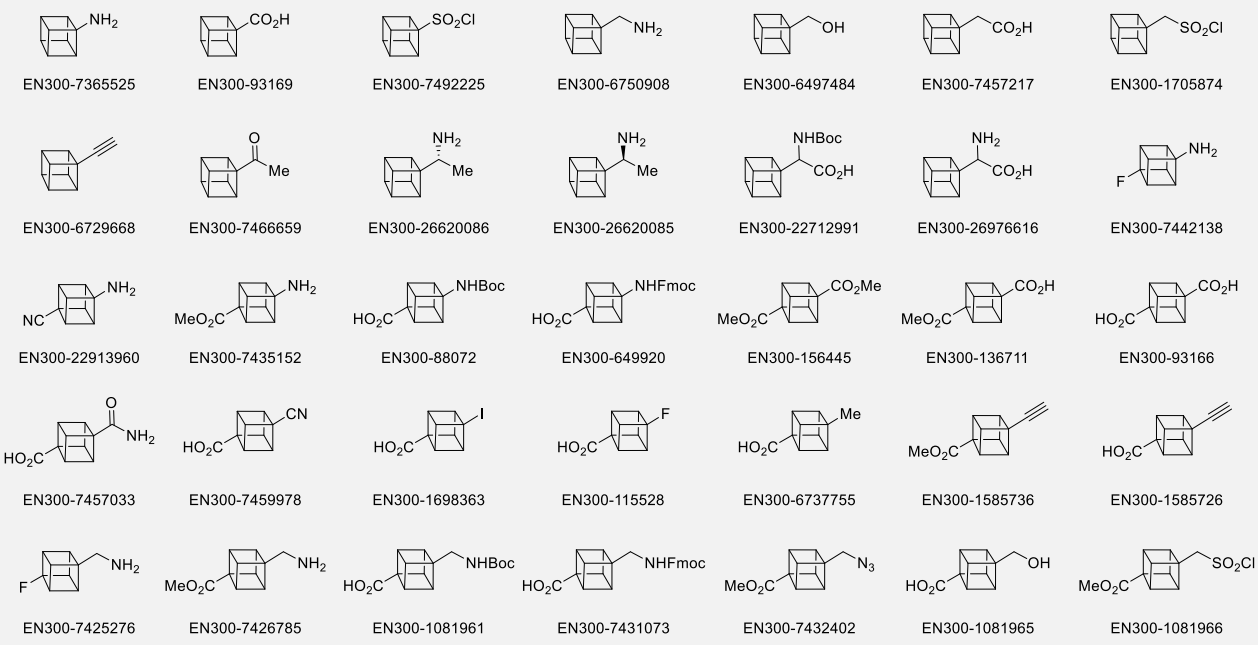
Diflubenzuron
an insecticide

Cubane analogue

Concept



We offer: cubane-containing building blocks from stock on a 5-10 g scale.



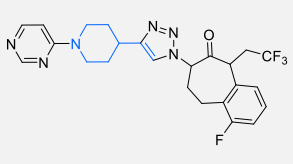
References

1. B. A. Chalmers et al. *Angew. Chem. Int. Ed.* **2016**, 3580.
2. J. Wlochal et al. *Synlett*, **2016**, 919.
3. J. Wlochal et al. *Org. Lett.* **2014**, 4094.
4. M. J. Falkiner et al. *Org. Process. Res. Dev.* **2013**, 1503.
5. P. K. Mykhailiuk. *Org. Biomol. Chem.* **2019**,*17*, 2839.
6. S. D. Houston. *Org. Biomol. Chem.* **2019**,*17*, 6790.

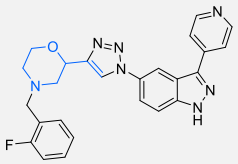
Alkyne-containing Linkers

Introduction

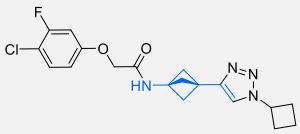
Acetylenes are used in the Huisgen azide-alkyne 1,3-dipolar cycloaddition reaction – “click chemistry”. 1,2,3-Triazole function formed by click reaction between an azide and alkyne bears a physicochemical resemblance to the amide bond. Using “click chemistry” one can efficiently connect complex molecules such as ligands and tool compounds.[1-6]



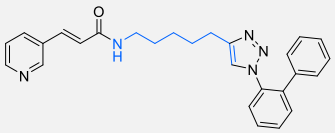
Treatment of Alzheimer's disease
WO2010/71741, A1
Merck & Co.



ERK-inhibitor
WO2012/58127, A2
Schering Corporation

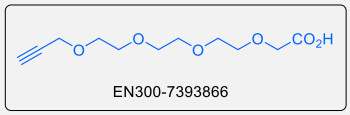


Treatment of neurodegenerative diseases
WO2019/32743, A1
Denali Therapeutics



NAMPT inhibitor
MedChem **2015**, *6*, 1891.

In this context, Enamine offers a library of unique functionalized alkynes that can be used as linker compounds, for example, in synthesis of PROTACs.



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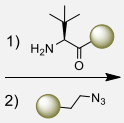
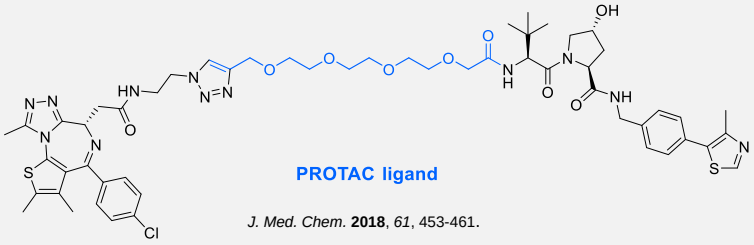
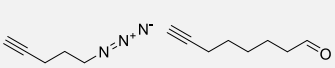




PROTAC ligand

J. Med. Chem. **2018**, *61*, 453-461.

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



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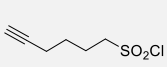

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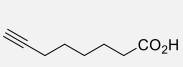

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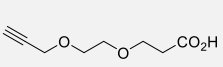

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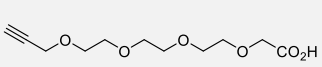

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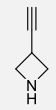

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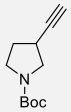

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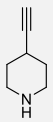

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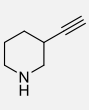

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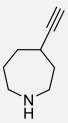

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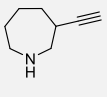

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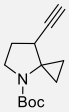

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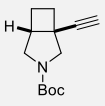

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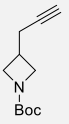

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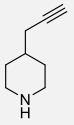

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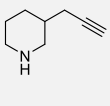

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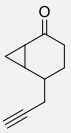

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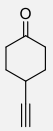

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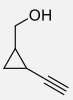

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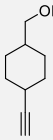

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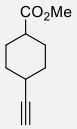

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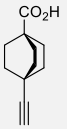

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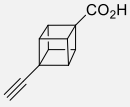

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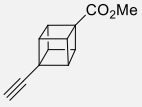

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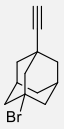


EN300-6734344

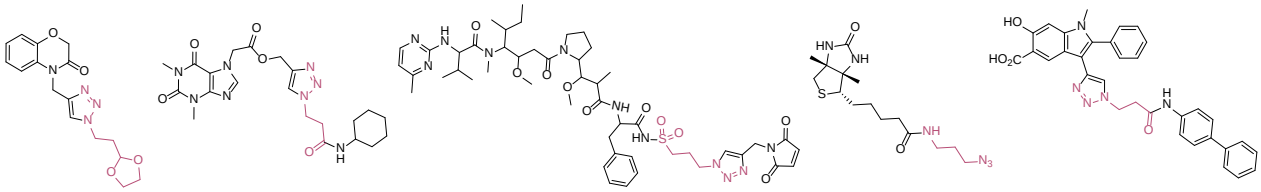
References

1. H. C. Kold et al. *Angew. Chem. Int. Ed.* **2001**, 2004.
2. L. H. Jones et al. *Angew. Chem. Int. Ed.* **2012**, 6320.
3. P. Thirumurugan et al. *Chem. Rev*. **2013**, 4905.
4. C. D. Hein et al. *Pharm Res*. **2008**, *10*, 2216.
5. N. M. Meghani et al. *Drug Discov. Today,* **2017**, *22*, 1604.
6. E. Kim et al. *Chem. Sci*. **2019**, *10*, 7835.

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

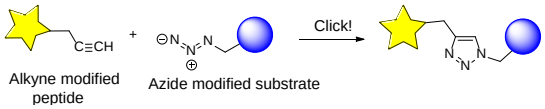
Labeling glycoconjugates
US 2012/0149887

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

Advantages

Aliphatic functionalized azides

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



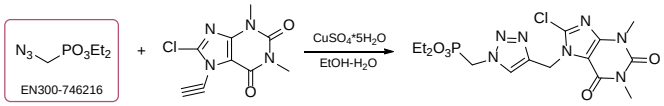
Alkyne modified peptide

Azide modified substrate

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

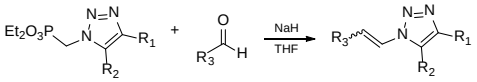
- The presence of the azide-group and a functional group allows the molecule to be modified before or after the click reaction.

Copper-mediated azide-alkyne conjugation



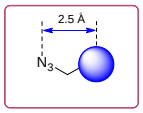
1,2,3-triazole linker

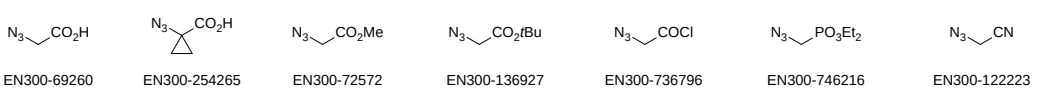
The Homer-Wadsworth-Emmons olefination of the triazoles



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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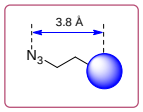

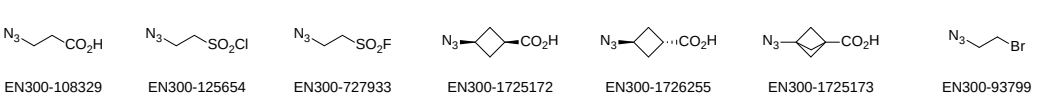

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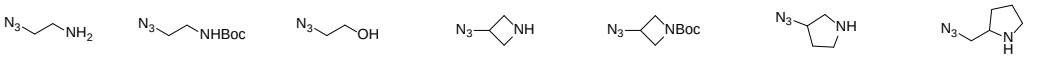

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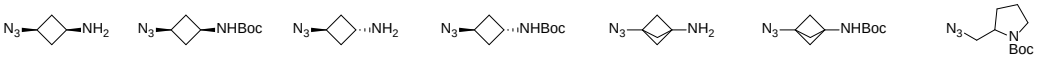

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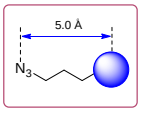

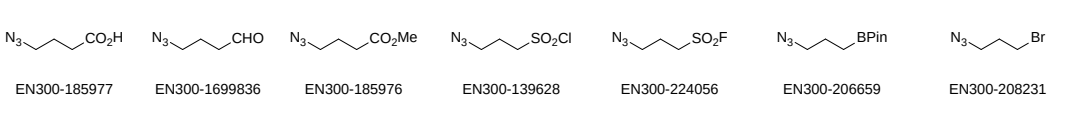

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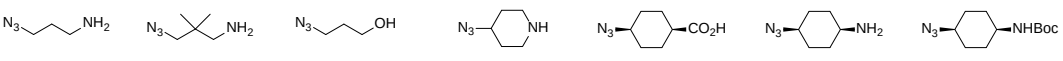

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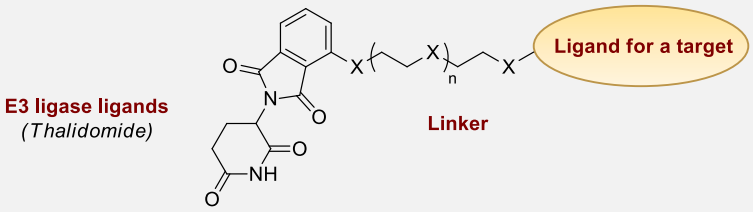
Building blocks and linkers for PROTAC synthesis

Introduction

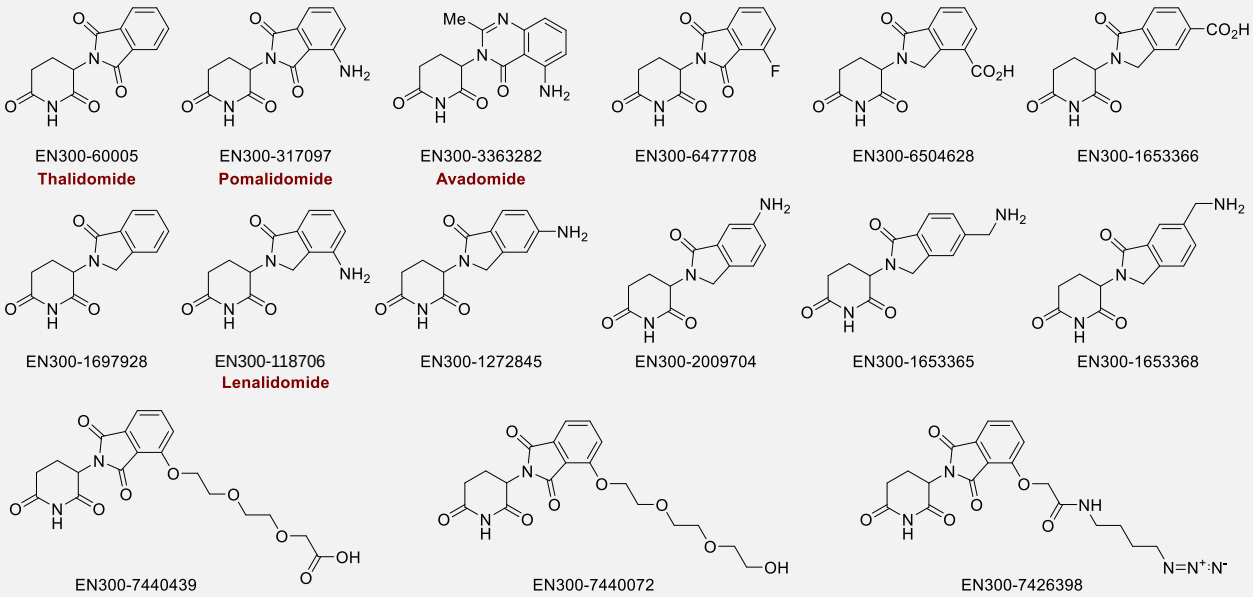
Proteolysis targeting chimeras (PROTACs) is the recently emerged field in drug discovery. This new approach works through the activation of the ubiquitin-proteasome system to remove disease-causing proteins. This new modality of therapeutic intervention requires new chemistry and new approaches to synthesize functional PROTAC molecules. Several recent papers of Oprea and Cravatt examined chemical space and ligandable proteome to evaluate a state of the targeted human genome. Herein we offer known and novel building blocks (E3 ligase ligands, ligands with linkers, linkers) for the synthesis of PROTACs.

PROTAC model:



Ligands for E3 ligases (Cereblon, VHL, MDM2 *etc*) from stock:

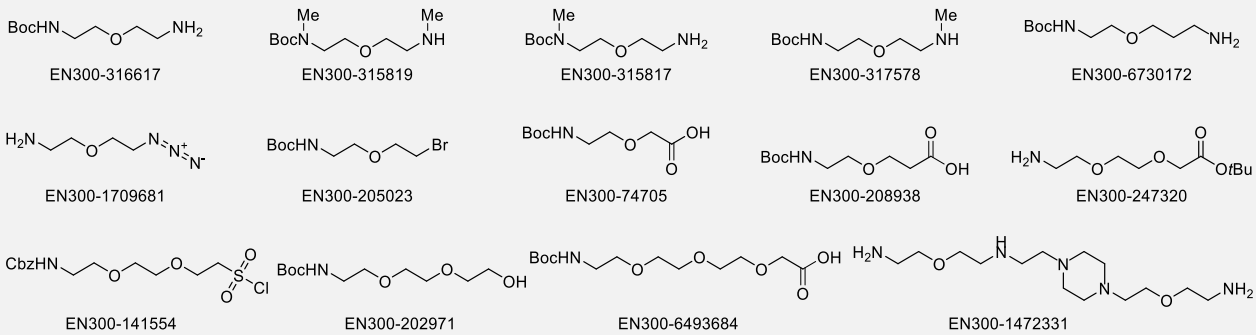
over 100 ligands:



EN300-60005 **Thalidomide**
EN300-317097 **Pomalidomide**
EN300-3363282 **Avadomide**
EN300-6477708
EN300-6504628
EN300-1653366
EN300-1697928
EN300-118706 **Lenalidomide**
EN300-1272845
EN300-2009704
EN300-1653365
EN300-1653368
EN300-7440439
EN300-7440072
EN300-7426398

PEG-linkers from stock:

over 50 linkers:

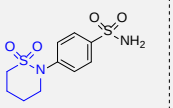


EN300-316617
EN300-315819
EN300-315817
EN300-317578
EN300-6730172
EN300-1709681
EN300-205023
EN300-74705
EN300-208938
EN300-247320
EN300-141554
EN300-202971
EN300-6493684
EN300-1472331

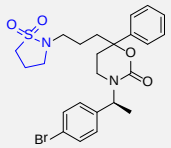
Cyclic Sulfonamides for Drug Design

Introduction

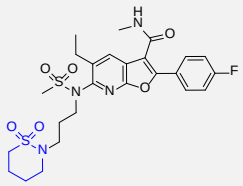
Sulfonamides are popular in drug discovery: more than 100 FDA-approved drugs on the market are sulfonamide-containing. Bioactive cyclic sulfonamides (sultams) include the anticonvulsant *Sultiame* (Bayer) and the anti-inflammatory drug *Piroxicam* (Pfizer).[1-5] Mostly, the *N*-aryl substituted sultams 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

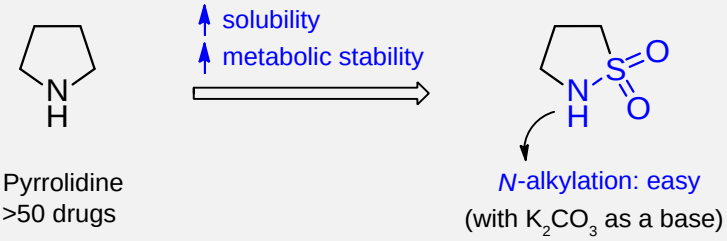


WO 2011/131709 A1
Novartis

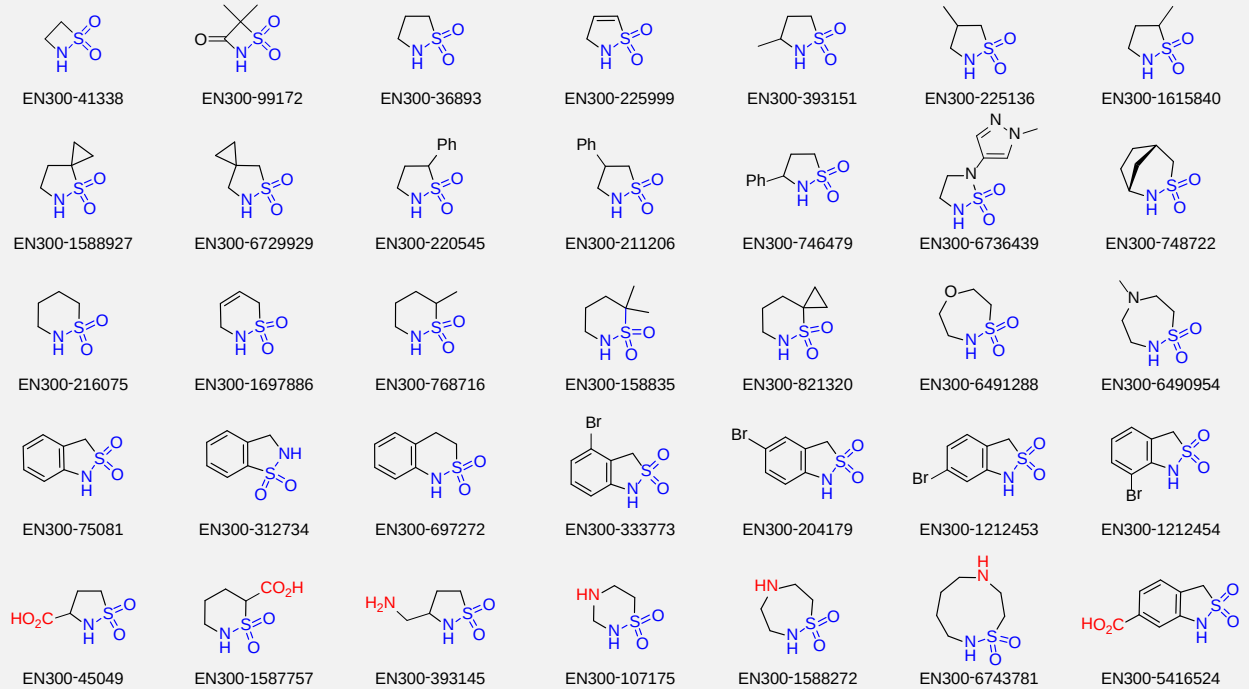
Sultam group:

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

Design



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



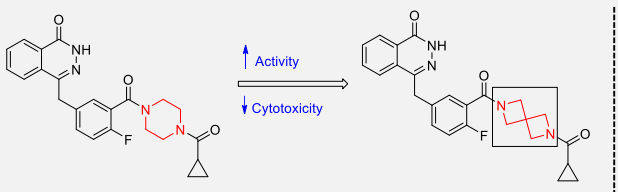
References

1. C. K. Jones et al. *J. Med. Chem.* **2011**, *54*, 7639.
2. A. Scozzafava et al. *Curr. Med. Chem.* **2003**, *10*, 925.
3. M. I. Page et al. *J. Phys. Org. Chem.* **2006**, *19*, 446.
4. M. Inagaki et al. *J. Med. Chem.* **2000**, *43*, 2040.
5. M. Jiménez-Hopkins et al. *Org Lett.* **2008**, *10*, 2223.

Piperazine Bioisosteres for Drug Design

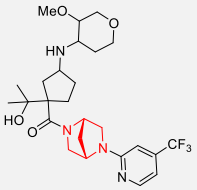
Introduction

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.

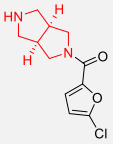


Olaparib (anti-cancer drug)
AstraZeneca and Merck & Co.

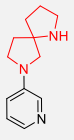
SpiroOlaparib



Chemokine receptor modulator
US 2011/0144129 A1
Pfizer

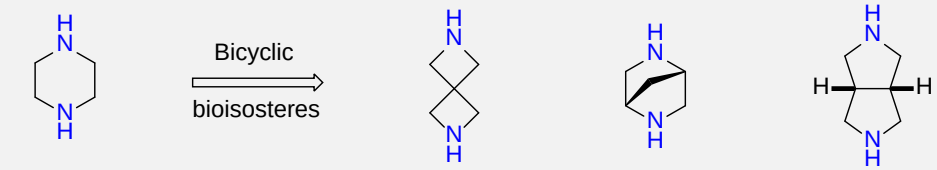


AZD1446 (Reached Phase II)
Nicotinic receptor agonist
AstraZeneca

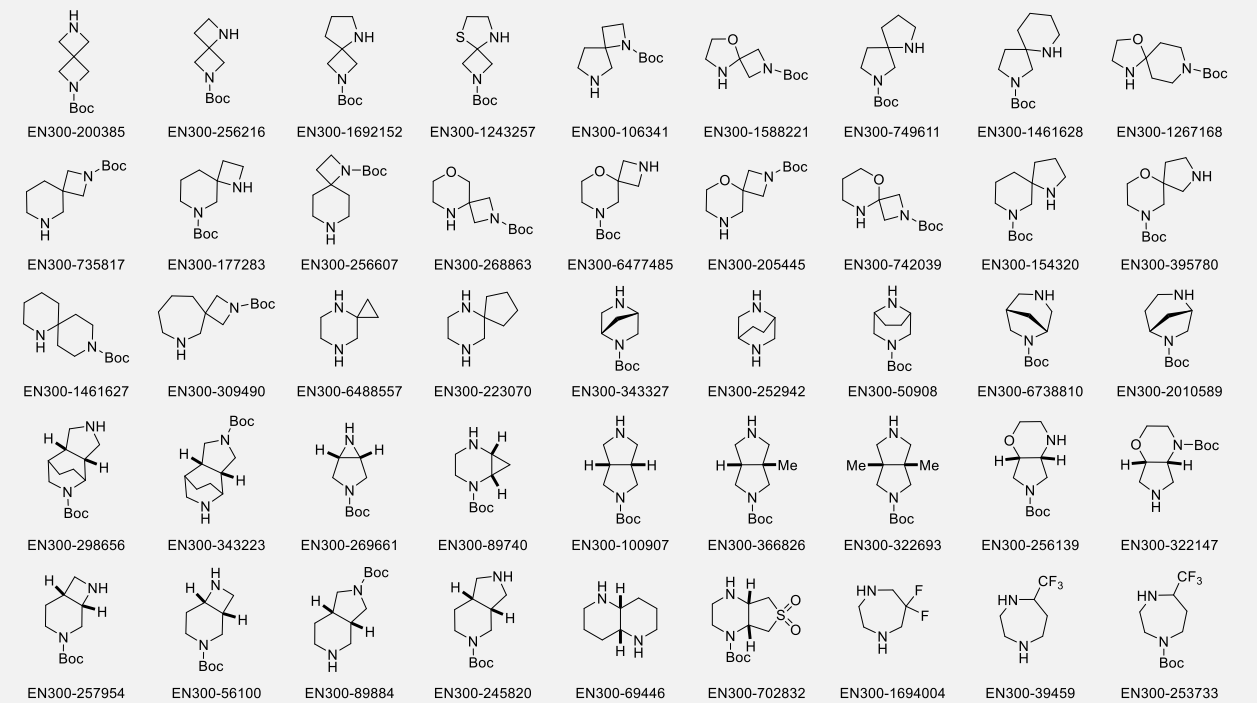


TC-2216 (Reached Phase I)
Nicotinic receptor agonist
Targacept

Design



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



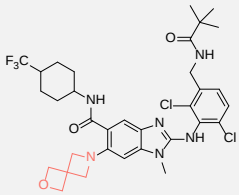
References

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.

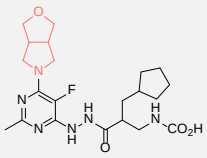
Morpholine Bioisosteres for Drug Design

Introduction

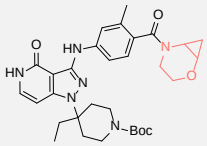
More than 20 FDA-approved drugs contain the morpholine moiety, although it is often metabolically labile.[1] Morpholine-based analogues may advantageously alter important pharmacokinetic properties such as lipophilicity and metabolic stability when grafted onto molecular scaffolds.[2,3] Herein we have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



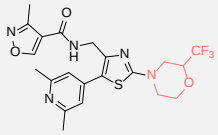
mPGES-1 inhibitor
WO 2012/076673 A1
Boehringer Ingelheim



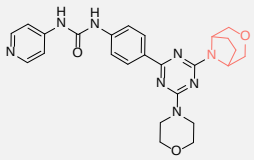
Peptide deformylase inhibitor
EP 2015/2217226 B1
GlaxoSmithKline



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

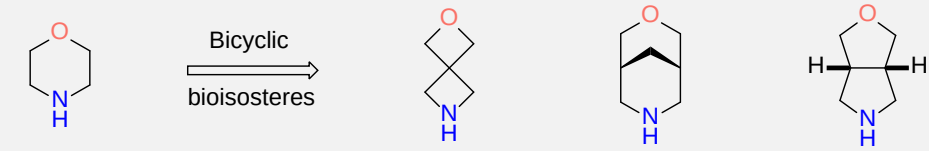


Alpha 7 positive allosteric modulator
EP 2015/2504333 B1
Janssen Pharm.

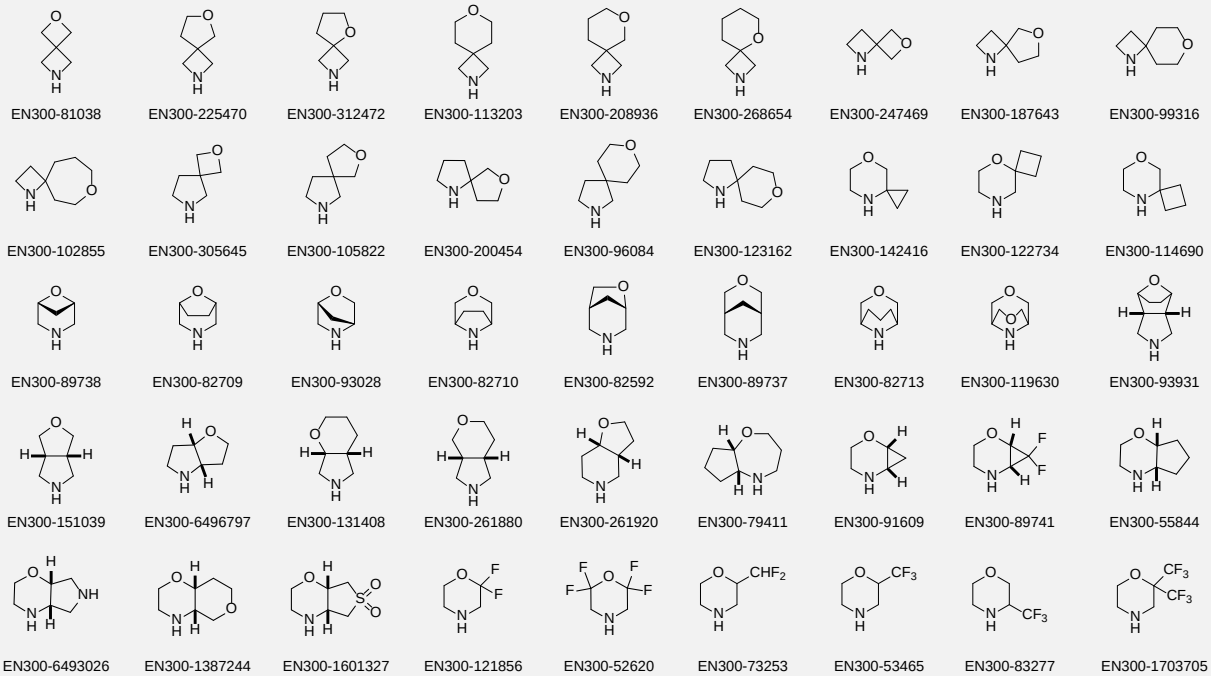


Inhibitor of PI3K
US 2013/109670 A1
Pfizer

Design



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



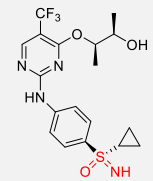
References

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.

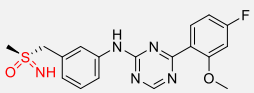
Sulfoximines for Drug Design

Introduction

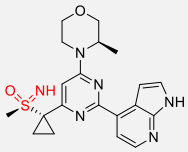
Incorporation of sulfoximine group into bioactive compounds often improves their ADME/Tox profile, and enhances potency. Moreover, the moiety of sulfoximine is chemically and metabolically stable. NH-sulfoximines can serve as the both hydrogen bond donors and acceptors at the same time.[1-6] Production 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.



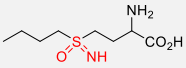
Roniciclib (BAY 1000394)
pan-CDK inhibitor
(Phase II)



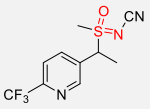
BAY 1143572
PTEFb Inhibitor
(Phase I)



AZD 6738
ATR Inhibitor
(Phase II)

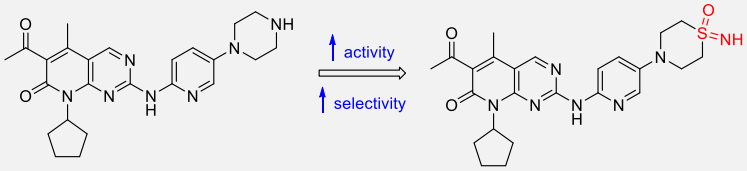


Buthionine sulphoximine
GCL inhibitor



Sulfoxaflor
Insecticide

Design



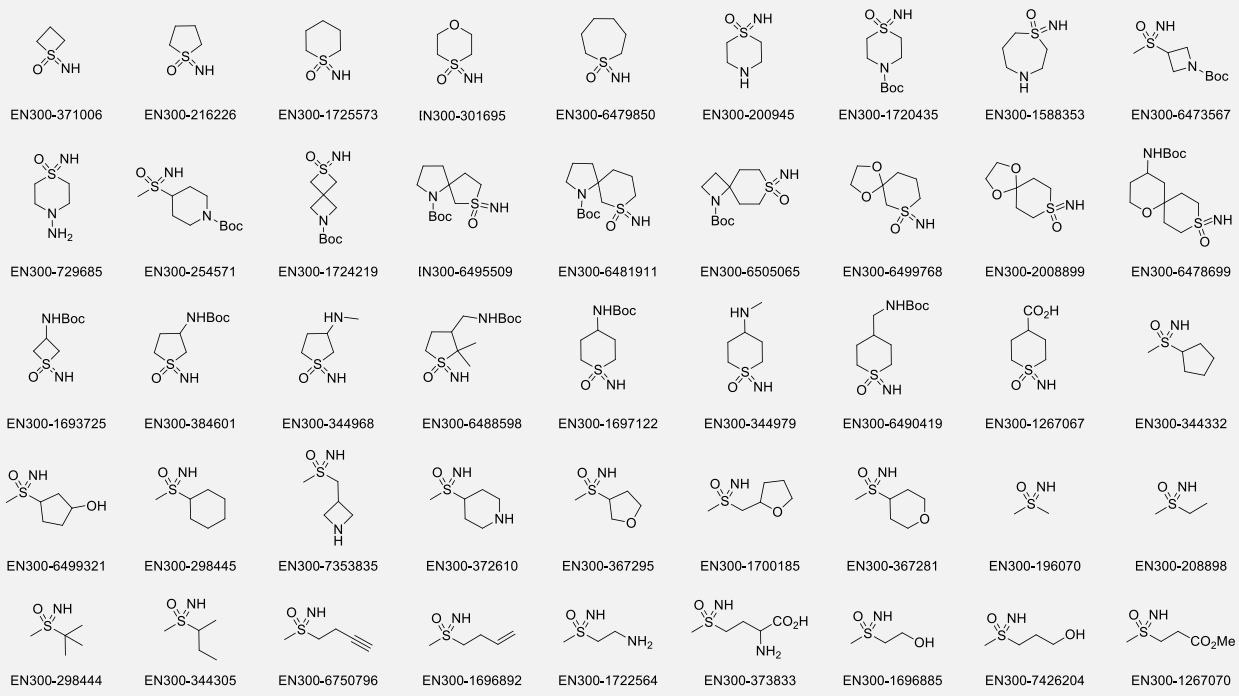
Approved drug **Palbociclib**

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.



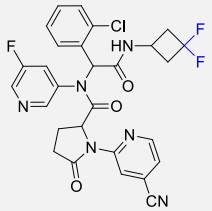
References

1. J. A. Sirvent et al. *ChemMedChem*. **2017**, 487.
2. M. Frings et al. *Eur. J. Med. Chem.* **2017**, 225.
3. U. Lücking. *Angew. Chem. Int. Ed.* **2013**, 9399.
4. S. Park et al. *Bioorg. Med. Chem. Lett.* **2011**, 4888.
5. J. A. Bull et al. *Synlett* **2017**, *28*, 2525.
6. D. P.Walker et al. *Bioorg. Med. Chem. Lett.* **2009**, 3253.

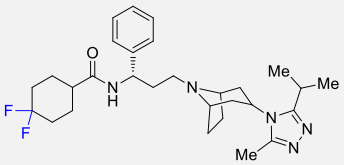
gem-Difluorinated Amines for Drug Design

Introduction

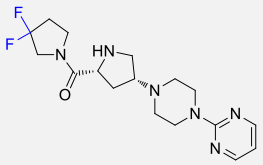
Fluorinated derivatives play an important role in medicinal chemistry. The selective incorporation of a fluoroalkyl group into bioactive compounds often affects their binding affinity, metabolic stability, lipophilicity, membrane permeability and bioactivity. *gem*-Difluoromethylene group (CF_2) is a valuable fluorinated motif that is present in pharmaceuticals and biologically active compounds. In particular, *gem*-CF_2 group improves ADME- and PK-properties.[1-6] In this context, *Enamine* offers a library of unique difluoro-substituted cyclic amines for drug design.



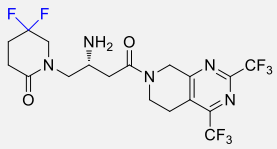
Ivosidenib
Anticancer drug
Agios Pharmaceuticals



Maraviroc
Antiretroviral drug
Pfizer

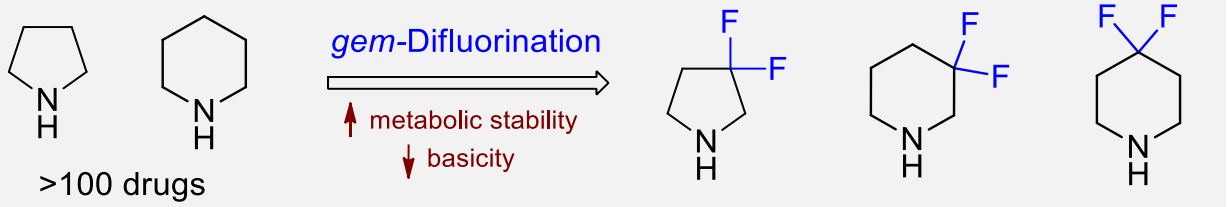


Gosogliptin
Anti-diabetic drug
Pfizer

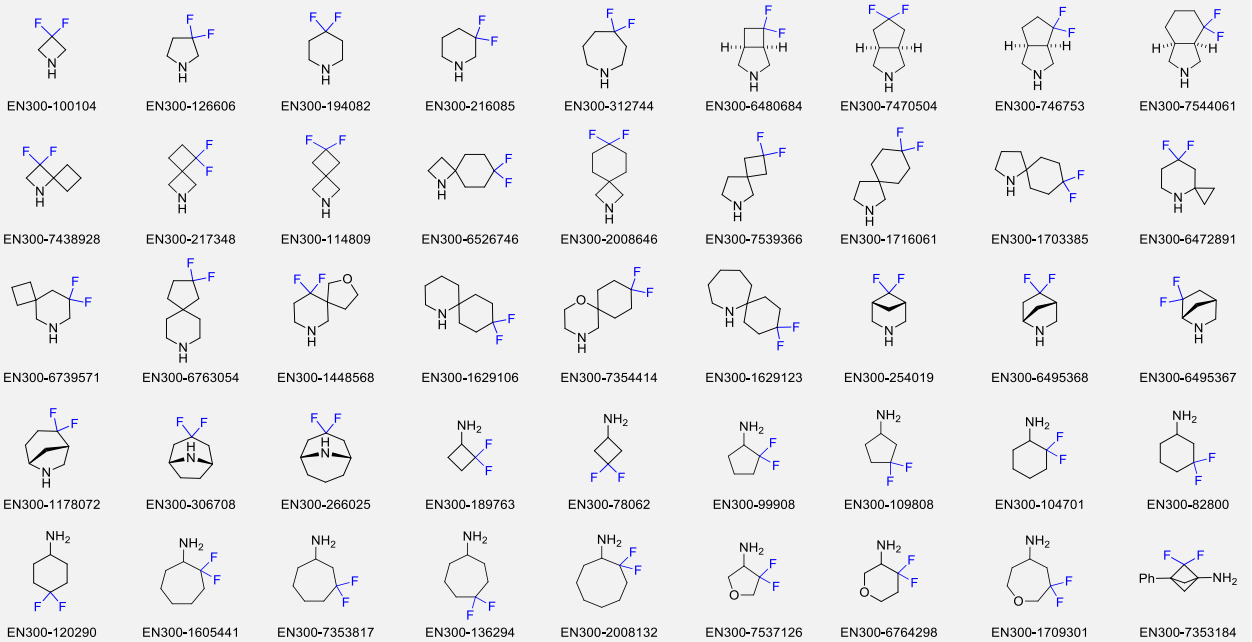


Gemigliptin
Anti-diabetic drug
LG Life Sciences

Concept



We offer: >100 *gem*-difluorinated amines on gram-scale from stock.



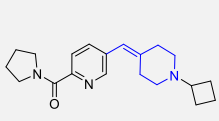
References

1. E. P. Gillis et al. *J. Med. Chem.* **2015**, *58, 21*, 8315.
2. X. Ma et al. *Org. Lett.* **2019**, *21, 18,* 7199.
3. R. M. Bychek et al. *J. Org. Chem.* **2019**, *84, 23,* 15106.
4. S. Purser et al. *Chem. Soc. Rev.* **2008**, *37*, 320.
5. Z. Feng et al. *Acc. Chem. Res.* **2018**, *51*, 2264.
6. Y.-L. Liu et al. *Asian J. Org. Chem.* **2013**, *2*, 194.

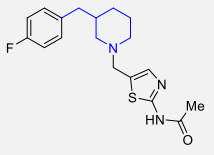
Functionalized Vinyl Boronates for C-C couplings

Introduction

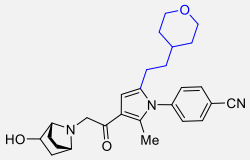
The Suzuki–Miyaura cross-coupling of boronic acid derivatives is one of the most used reactions in organic and medicinal chemist's toolbox. The rapid advancement of this method resulted in its efficient application for the late-stage modification of biologically active substrates and construction of combinatorial libraries. One of the recent trends in the field of organoboron reagents is related to the shift from aromatic compounds towards cyclic sp^3-enriched structures, which comply with criteria of lead-oriented synthesis.[1-6] In this context, *Enamine* offers a library of alkenylboronic esters for metal-mediated couplings.



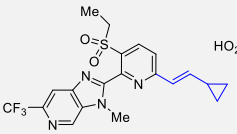
Treatment of histamine H3 related disorders
WO 2013/27001 A1
Takeda Pharm.



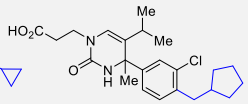
Treatment of neurodegenerative diseases
WO 2019/178191 A1
Biogen



Treatment of a dysfunction in proteostasis
WO 2020/006296 A1
Proteostasis Therapeutics

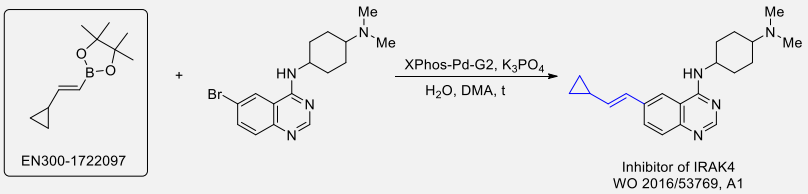


Crop protection
US 2018/16273 A1
Bayer CropScience



Inhibitor of RORγ
US 2016/194290 A1
Japan Tobacco

Case studies

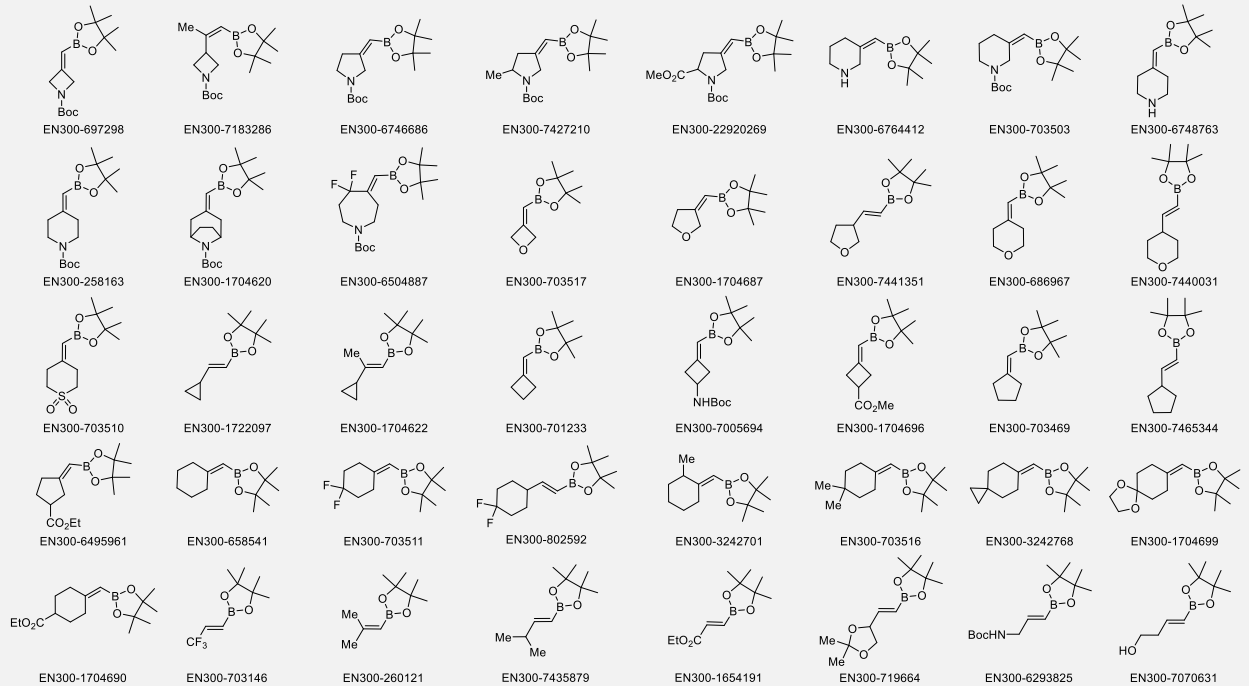


Inhibitor of IRAK4
WO 2016/53769, A1
Merck & Co.

Unique properties:

- sp^3-enriched structures;
- stable in the air;
- easy to store;
- fast formation of a new C-C bond;
- allow further modification.

We offer: more than 50 of vinyl boronates from stock on a 5-10 g scale.



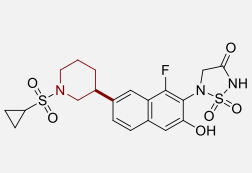
References

1. M. Kovalenko et al. *Eur. J. Org. Chem.* **2019**, 5624.
2. D. G. Brown et al. *J. Med. Chem.* **2016**, *59*, 4443.
3. S. D. Roughley et al. *J. Med. Chem.* **2011**, *54*, 3451.
4. P. Schäfer et al. *Nat. Commun.* **2018**, *9*, 16216.
5. P. S. Campbell et al. *Chem. Commun.* **2018**, *54*, 46.
6. A. Nadin et al. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114.

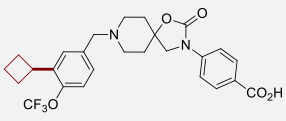
Aliphatic Trifluoroborates (-BF_3) for C-C couplings

Introduction

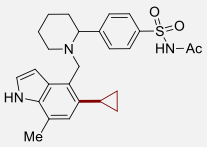
Saturated organotrifluoroborates are crystalline bench stable solids used in the standard and photoredox-accelerated Suzuki-Miyaura reaction as well as other transition-metal-catalyzed cross-couplings. One of the recent trends in the field of organoboron reagents is related to the shift from aromatic compounds towards cyclic F(sp^3)-enriched structures, which comply with criteria of lead-oriented synthesis. Increasing the number of C(sp^3)-hybridized carbons is a way to make a compound more drug-like.[1-6] In this context, *Enamine* offers a library of saturated organotrifluoroborates for metal-mediated couplings.



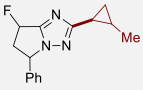
Inhibitor of PTPN2
WO2019/246513, A1
Calico Life Sciences



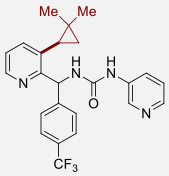
Antagonist of SSTR5
WO2012/24183, A1
Merck & Co.



Inhibitor of Factor B
WO2015/9616, A1
Novartis

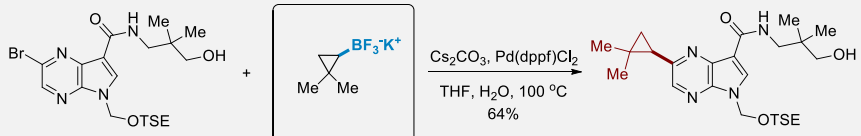


Inhibitor of RIP1
WO2019/72942, A1
Hoffmann-La Roche



Antagonist of TRPM8
WO2012/177896, A1
Amgen

Case studies



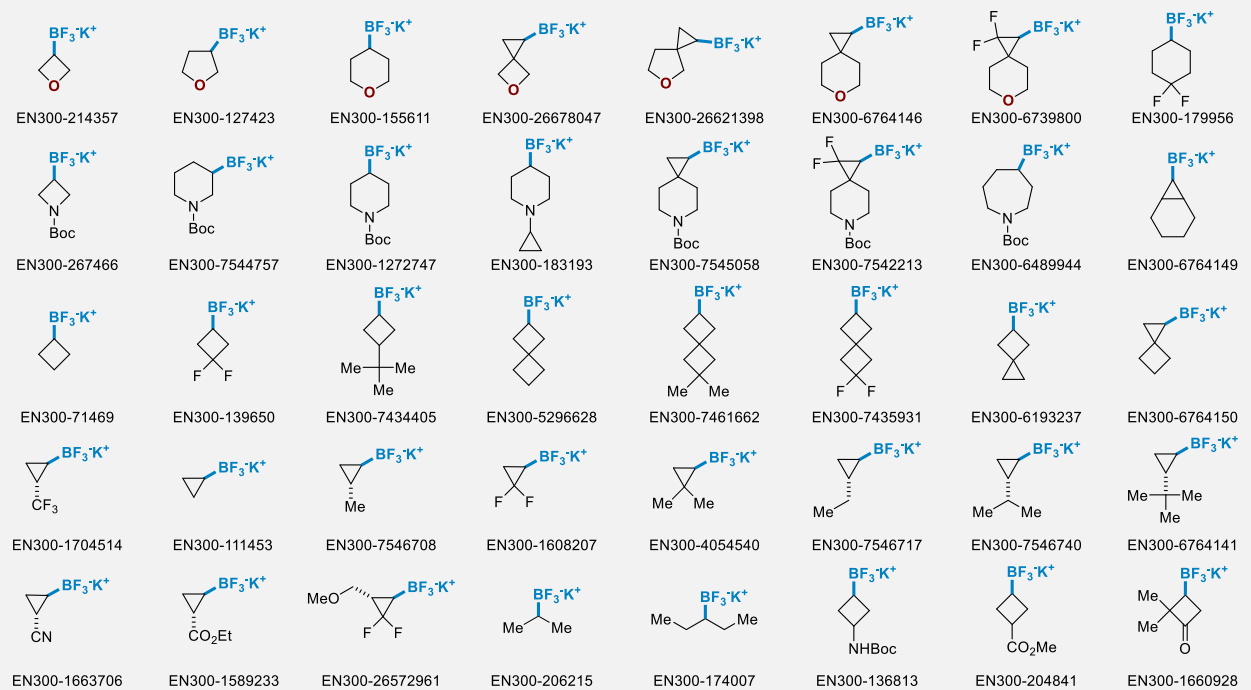
EN300-4054540

Precursor to JAK and SYK inhibitors
WO2011/144585, A1
Hoffmann-La Roche

Unique properties:

- crystalline solids;
- stable on air;
- easy to store;
- F(sp^3)-enriched structures;
- allow further modification.

We offer: >50 of aliphatic trifluoroborates from stock on a 5-10 g scale.



EN300-214357, EN300-127423, EN300-155611, EN300-26678047, EN300-26621398, EN300-6764146, EN300-6739800, EN300-179956
EN300-267466, EN300-7544757, EN300-1272747, EN300-183193, EN300-7545058, EN300-7542213, EN300-6489944, EN300-6764149
EN300-71469, EN300-139650, EN300-7434405, EN300-5296628, EN300-7461662, EN300-7435931, EN300-6193237, EN300-6764150
EN300-1704514, EN300-111453, EN300-7546708, EN300-1608207, EN300-4054540, EN300-7546717, EN300-7546740, EN300-6764141
EN300-1663706, EN300-1589233, EN300-26572961, EN300-206215, EN300-174007, EN300-136813, EN300-204841, EN300-1660928

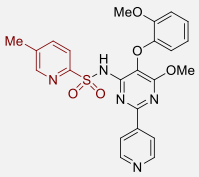
References

1. A. W. Dombrowski et al. *ACS Med. Chem. Lett.* **2020**, *11*, 597.
2. G. A. Molander et al. *Curr. Opin. Drug Discov. Devel.* **2009**, 811.
3. O. Hryshchuk et al. *Eur. J. Org. Chem.* **2020**, 2217.
4. J. Yi et al. *Org. Lett.* **2019**, *21*, 4853.
5. S. Darses et al. *Eur. J. Org. Chem.* **2003**, *22*, 4313.
6. O. V. Hryschuk et al. *Adv. Synth. Catal.* **2019**, 5428.

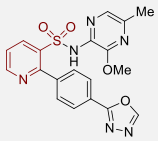
Heterocyclic Sulfonyl Fluorides for Pd-Catalyzed C–C Coupling Reactions

Introduction

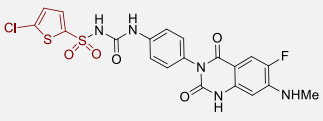
Hetaryl bromides and iodides bearing SO_2F group are versatile substrates for metal catalyzed crosscoupling reactions. Due to the high energy of the S–F bond, sulfonyl fluorides are stable toward hydrolysis, metal catalysis, or reductive reaction conditions.On the other hand, they undergo selective nucleophilic substitution at the sulfur(VI) electrophilic center under controllable reaction conditions.[1-5] Herein we have designed and synthesized a library of bifunctional building blocks for drug design.



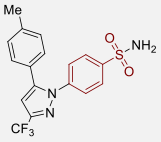
Avosentan (reached phase **III**)
Overt diabetic nephropathy
Novartis



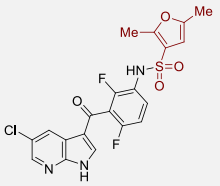
Zibotentan (reached phase **III**)
Anti-cancer drug candidate
AstraZeneca



Elinogrel (reached phase **II**)
Antiplatelet drug candidate
Portola Pharmaceuticals

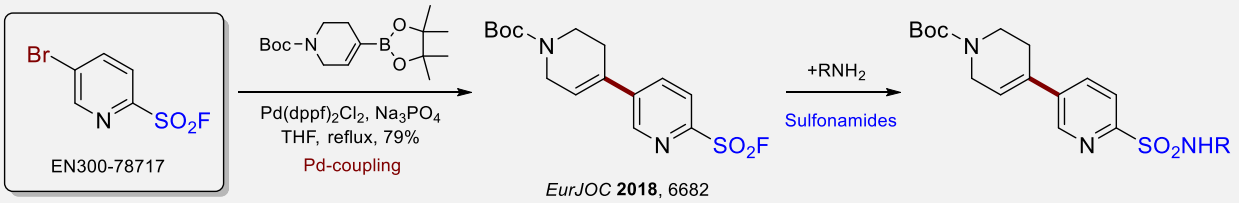


Celecoxib
anti-inflammatory drug
Pfizer



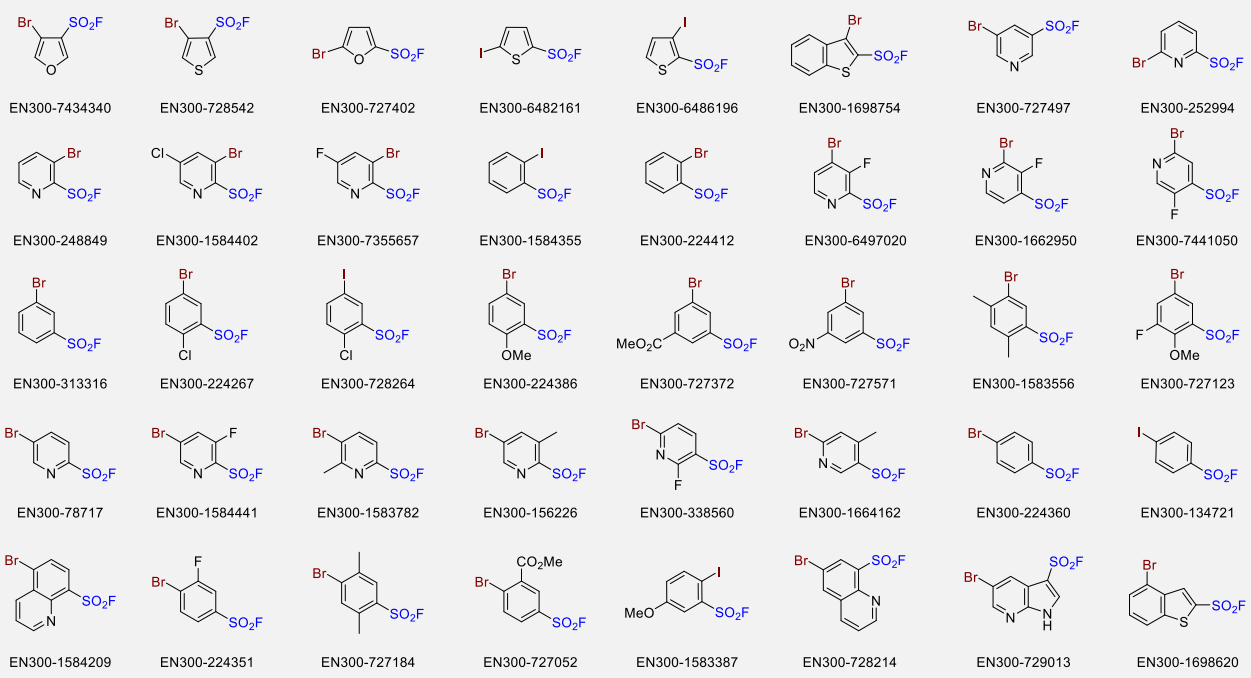
Protein kinase inhibitor
WO 2007/002325 A1
Plexxikon

Design



EurJOC **2018**, 6682

We offer



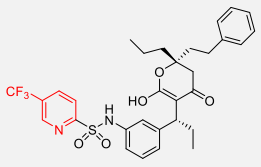
References

1. A. Y. Cherepakha et al. *Eur. J. Org. Chem.* **2018**, *47*, 6682.
2. Y. L. Hsu et al. *Tetrahedron* **2016**, *72*, 58.
3. S. A. Zhersh et al. *Chem. Eur. J.* **2018**, *24*, 8343.
4. P. K. Chinthakindi et al. *Eur. J. Org. Chem.* **2018**, 3648.
5. P. K. Chinthakindi et al. *J. Org. Chem.* **2016**, *81*, 2618.

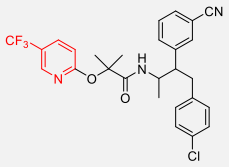
Analogues of CF_3-Pyridine for Drug Design

Introduction

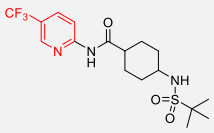
More than 100 FDA-approved drugs contain pyridine ring and another 100 have been in clinical trials.[1] Examples containing CF_3-pyridine moiety include the antiviral drug *Tipranavir* and drug candidates *Taranabant, Velneperit, SB-705498*. Besides, CF_3-pyridine containing compounds have been playing a fundamental 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.



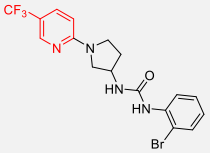
Tipranavir
Drug for treatment of HIV infection
Boehringer Ingelheim



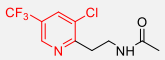
Taranabant (Reached Phase III)
Treatment for obesity
Merck & Co.



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

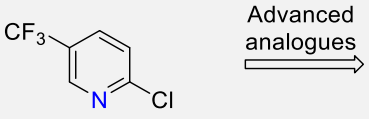


SB-705498 (Reached Phase II)
Treatment of rhinitis and chronic cough
GlaxoSmithKline



Fluopyram
Fungicide, inhibitor of SDH
Bayer CropScience

Design



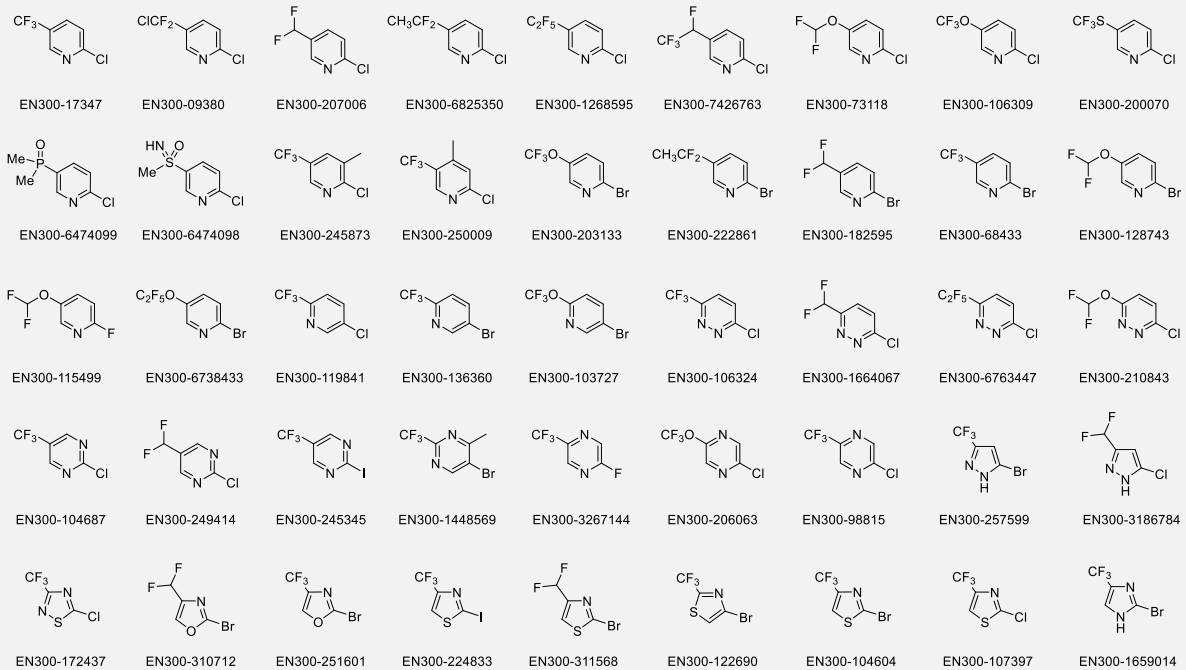
A popular building block in agro and drug design

EN300-207006

EN300-6474098

EN300-6474099

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



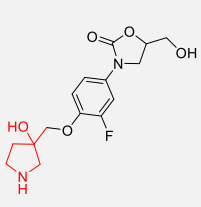
References

1. www.ebi.ac.uk/chembl
2. A.-Y. Guan et al. *Bioorg. Med. Chem.* **2016**, *24*, 342.
3. *Bioactive Heterocyclic Compound Classes: Agrochemicals, Wiley-VCH*, **2012**, 209-223.
4. *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Academic Press, **2019**, 181-211.

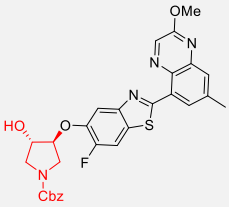
Epoxides for Drug Design

Introduction

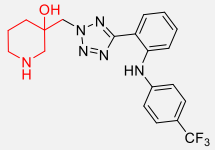
Epoxides are important heterocyclic units found in various naturally occurring molecules, some with potential bioactivities. At least fourteen drugs on the market are epoxide-containing.[1] In addition, epoxides are valuable building blocks in medicinal chemistry. They react with nucleophiles in a ring-opening 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.



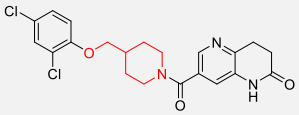
Antibacterial agent
US 2009/247578, A1
Actelion Pharm.



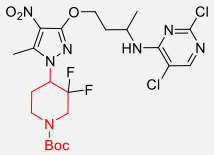
Precursor to PAR4 inhibitor
WO 2018/13770, A1
Bristol-Myers Squibb



Treatment of cancer
WO 2018/204532, A1
Vivace Therapeutics

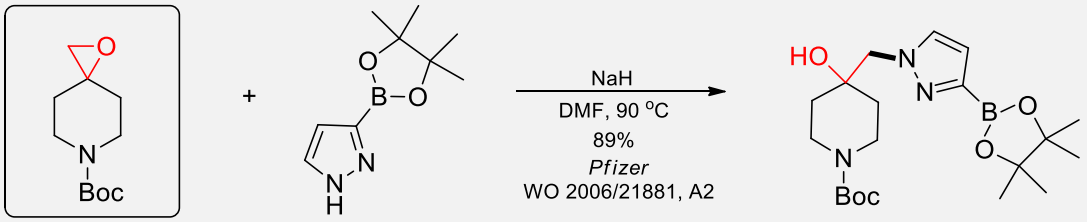


MAGL inhibitor
EP/3279191, 2018, A1
Takeda Pharm.

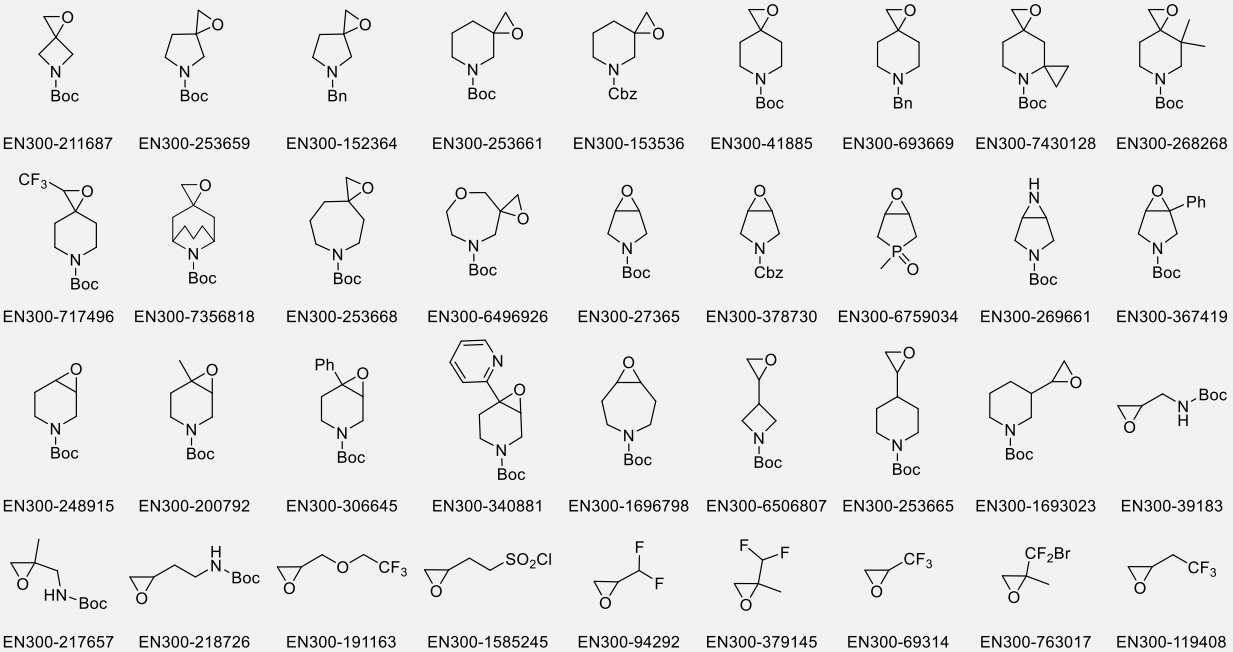


Precursor to LRRK2 inhibitor
WO 2019/12093, A1
GlaxoSmithKline

Design



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



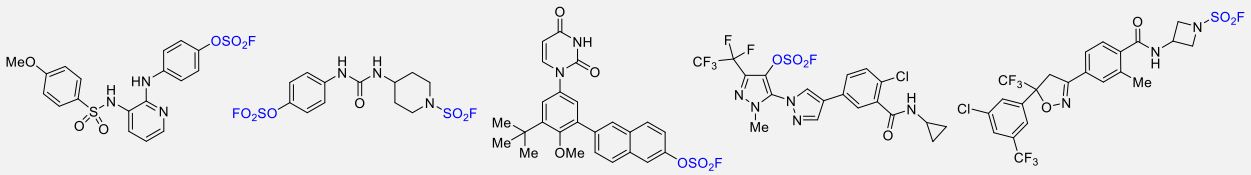
References

1. www.ebi.ac.uk/chembl.
2. E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421.
3. T. B. Hughes et al. *ACS Cent Sci.* **2015**, *4*, 168.
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.

Fluorosulfates and Sulfamoyl Fluorides for Drug Design

Introduction

Aryl fluorosulfates and sulfamoyl fluorides are widely used in chemical biology, medicinal chemistry and agrochemistry. The former exhibit chemoselective reactivity with the side chains of tyrosine, lysine, serine and histidine in the proteins, and can be used to target non-enzymes as well as enzymes. Depending on the nature of the substituent, the -OSO_2F unit can be a good leaving group or a robust connector. The fluorosulfates are quite stable toward hydrolysis under neutral or acidic conditions. The *N*-disubstituted sulfamoyl fluorides are stable toward hydrolysis under basic condition, inert toward a wide range of nucleophiles and dramatically more robust than analogous chlorides.[1-6] In this context, *Enamine* offers a library of unique aryl fluorosulfates and sulfamoyl fluorides for drug design.



Antimitotic agent for treating cancers
US 2019/0167604 A1
Scripps Research Institute

sEH inhibitor
WO 2015/188060 A1
Scripps Research Institute

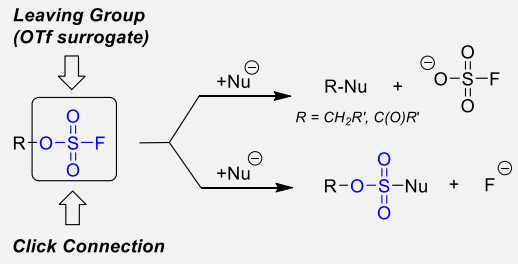
Preparation of antiviral compounds
WO 2014/031791 A1
AbbVie

Crop protection
WO 2017/140771 A1
Syngenta

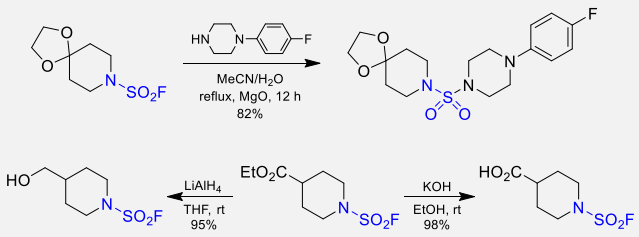
Crop protection
WO 2018/114791 A1
Syngenta

Properties of $ROSO_2F$ and R_2NSO_2F

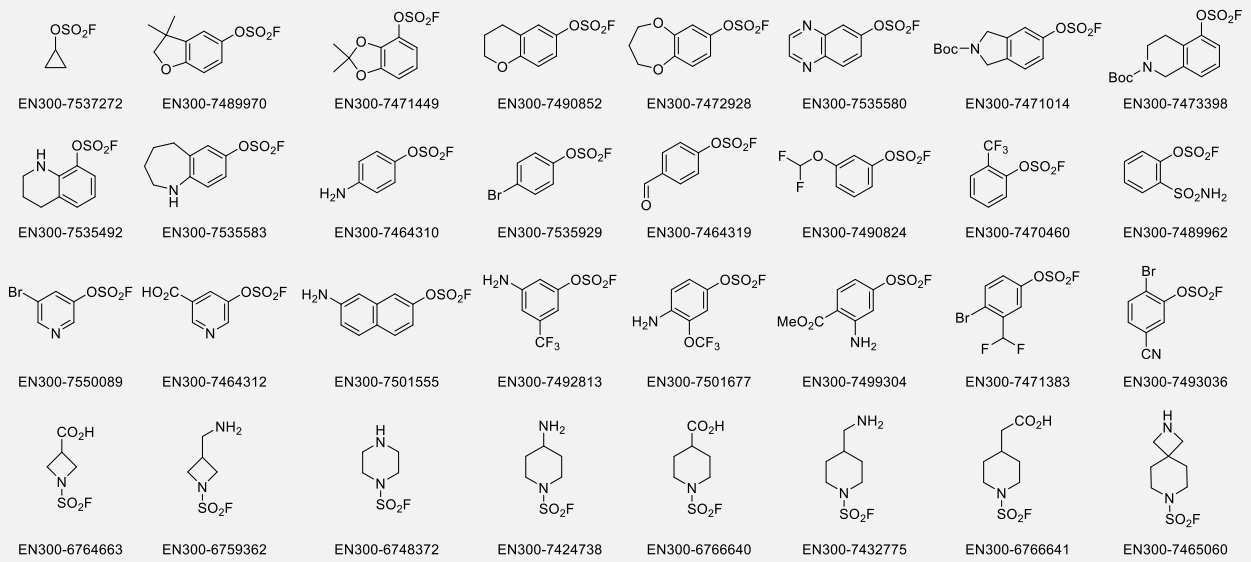
Dual reactivity of fluorosulfates



Reactivity and stability of the sulfamoyl fluorides



We offer: >100 unique fluorosulfates and sulfamoyl fluorides in gram amounts in stock.



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EN300-7535492 | EN300-7535583 | EN300-7464310 | EN300-7535929 | EN300-7464319 | EN300-7490824 | EN300-7470460 | EN300-7489962

EN300-7550089 | EN300-7464312 | EN300-7501555 | EN300-7492813 | EN300-7501677 | EN300-7499304 | EN300-7471383 | EN300-7493036

EN300-6764663 | EN300-6759362 | EN300-6748372 | EN300-7424738 | EN300-6766640 | EN300-7432775 | EN300-6766641 | EN300-7465060

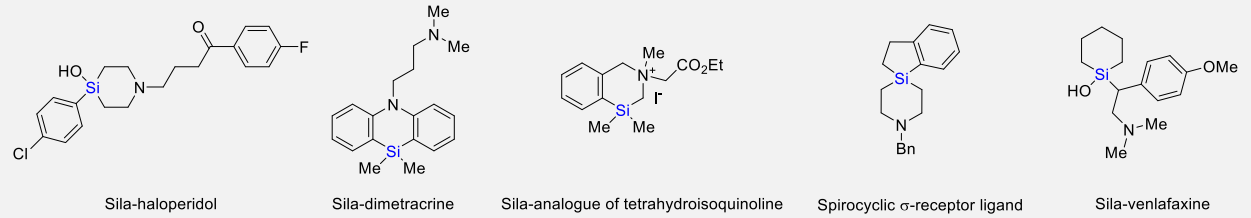
References

1. J. Dong et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 9430.
2. H. Zhou et al. *Org. Lett.* **2018**, *20*, 812.
3. D. E. Mortenson et al. *J. Am. Chem. Soc.* **2018**, *140*, 200.
4. W. Chen et al. *J. Am. Chem. Soc.* **2016**, *138*, 7353.
5. L. H. Jones. *ACS Med Chem Lett.* **2018**, *9*, 584.
6. W. Chen et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 1835.

Silicon-Containing Building Blocks for Drug Design

Introduction

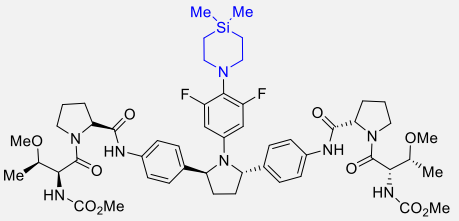
Silicon-containing compounds have been largely ignored in drug design until recently.[1] Silicon can be considered a bioisostere of carbon and hence offers an innovative avenue in drug discovery. For example, C/Si exchange in drug-like scaffolds provides an exciting approach in medicinal chemistry to 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



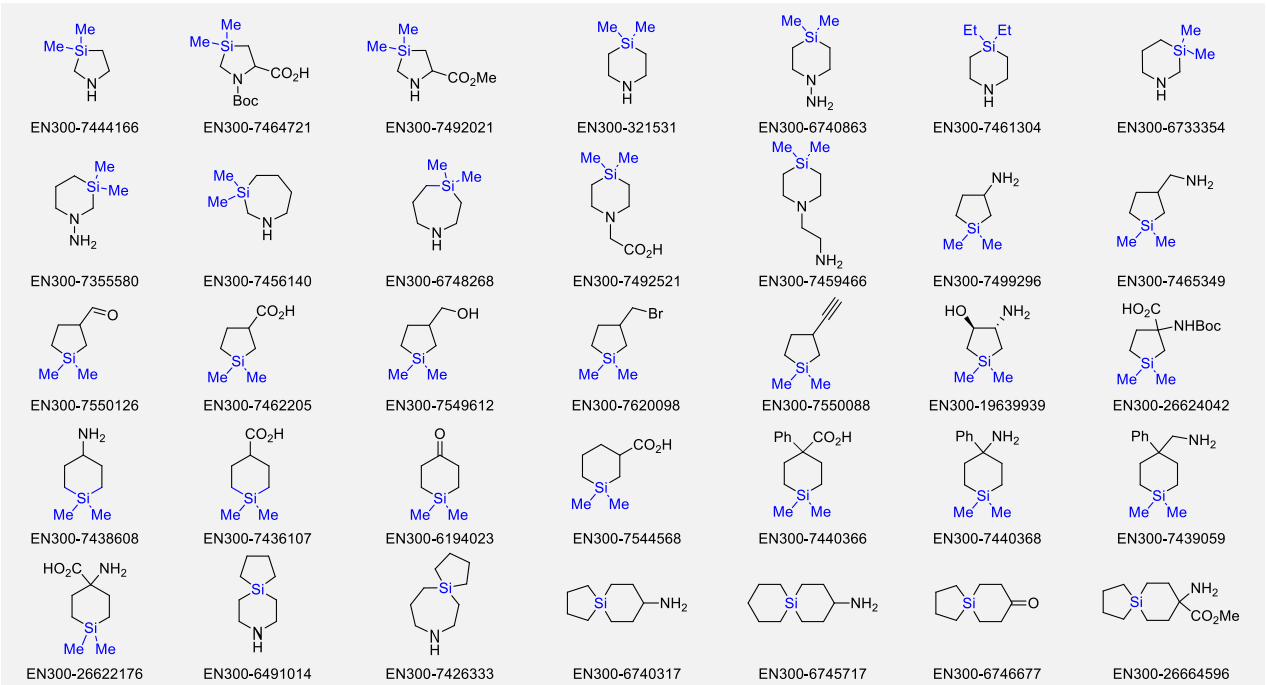
- Silicon-containing NS5A inhibitor;
- Pan-genotypic activity against GT1-6 HCV;
- Improved activity against GT6a HCV;
- High liver distribution.

J. Med. Chem. **2020**, *63*, *10*, 5312.

Advantages of "Silicon Switch":

- Bond length C–C = 1.54 Å, C–Si = 1.87 Å → changes in the interactions with specific proteins;
- Increase in lipophilicity;
- Si prefers higher coordination numbers → access to compounds for which corresponding carbon analogs are not available.

We offer more than 30 of silicon-containing building blocks from stock on a 5-10 g scale.

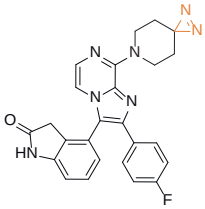


References

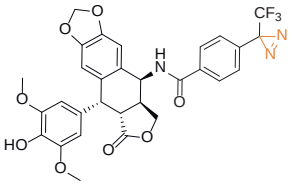
1. S. J. Barraza et al. *J. Am. Chem. Soc.* **2018**, *140*, 6668.
2. R. Ramesh et al. *J. Med. Chem.* **2018**, *61*, 3779.
3. S. Fujii et al. *Future Med. Chem.* **2017**, *9*, 485.
4. J. S. Mills et al. *Expert Opin. Investig. Drugs.* **2004**, *13*, 1149.
5. A. K. Franz et al. *J. Med. Chem.* **2013**, *56*, 388.
6. B. Liu et al. *J. Med. Chem.* **2020**, *63*, *10*, 5312.

DIAZIRINES

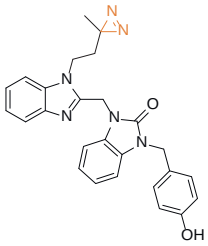
Diazirine is a smallest heterocycle that is stable in the dark, but forms reactive carbene upon irradiation with light. Its introduction into the structures of biologically active compounds accompanying with only minor change in MW (plus only 2 nitrogen atoms!) has proven to provide efficient tools to 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.



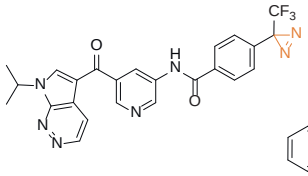
Antagonist of GRIA1
WO 2016/176457
Janssen Pharm.



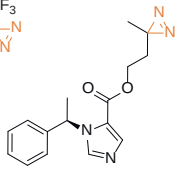
Analog of etoposide
Bioorg. Med. Chem.
2010, 830.



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



Inhibitor of TrkA
US 2012/258950
Pfizer

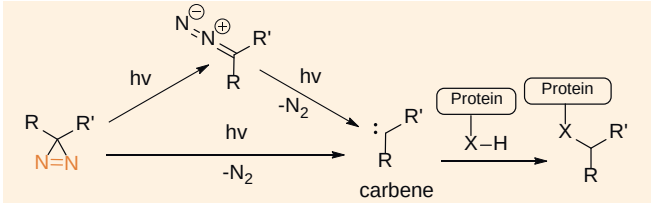


Blocker of nAChRs
Mol. Pharmacol.
2009, 1084.

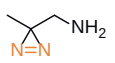
Properties

- 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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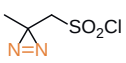

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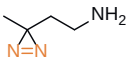

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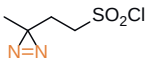

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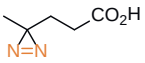
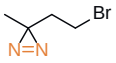
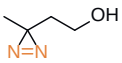


EN300-97492



EN300-138815



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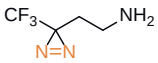

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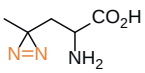

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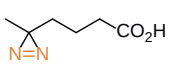

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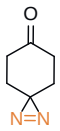

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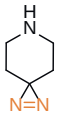

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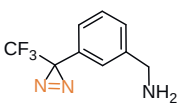
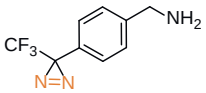
EN300-223410



EN300-311025



EN300-315165

References

[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.

Structurally optimized tetrazines for rapid biological labeling

Introduction

Bioorthogonal chemical reactions are closely associated with the characteristics of “click” chemistry, occurring with high selectivity and fast reaction kinetics in vivo.[1,2] Consequently, these reactions found use as multipurpose tools for chemical biology. The Inverse-electron-Demand Diels–Alder **(iEDDA)** reaction between tetrazines and strained alkenes is fairly new ligation reaction, which displays **rates 3-7 orders of magnitude faster** than many bioorthogonal reactions.[3] High reaction rates, biocompatibility, together with the ability of tetrazines to quench fluorescence of some fluorophores, widely used for fluorescent labeling, and recover it after **iEDDA** reaction **(Figure 1)** make tetrazine derivatives unique and versatile tools for bioortogonal chemistry. **Figure 2** is showcasing possible approach to modification of commonly used fluorophore as fluoresceine **(A)** with tetrazines[4] and application of tetrazine derivatives in DNA encoded libraries technologies (DELT), as the core scaffolds **(B)**.[5]

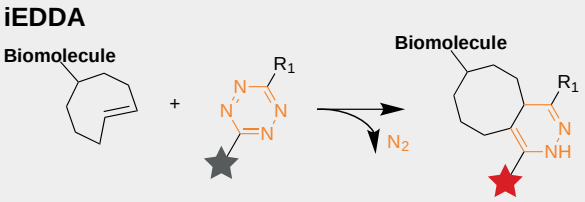


Figure 1. General scheme of **IeDDA** ligation.

Application

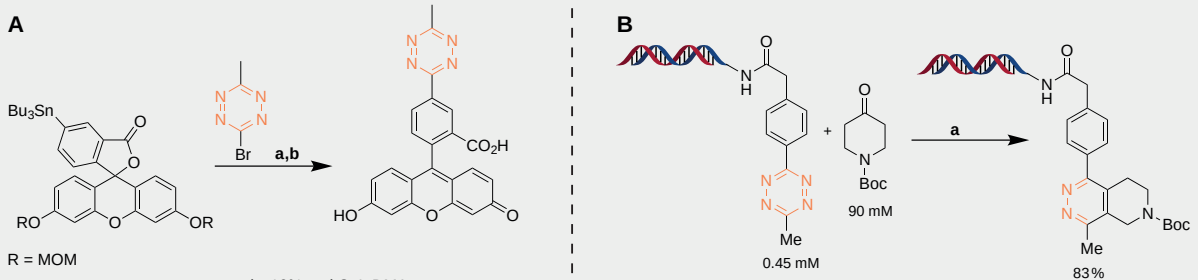
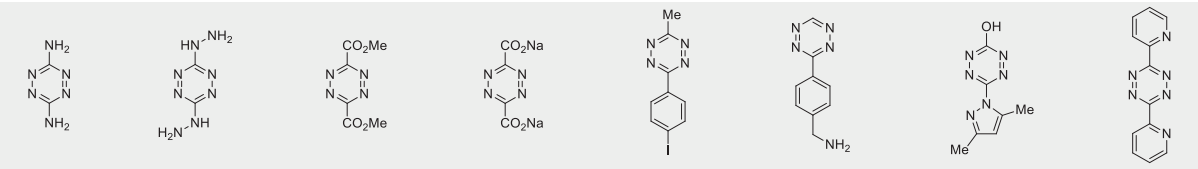


Figure 2. Tetrazine ligation of fluoresceine (**A**)[4] and use of tetrazine core in DELT-compatible reaction (**B**).[5]

We offer

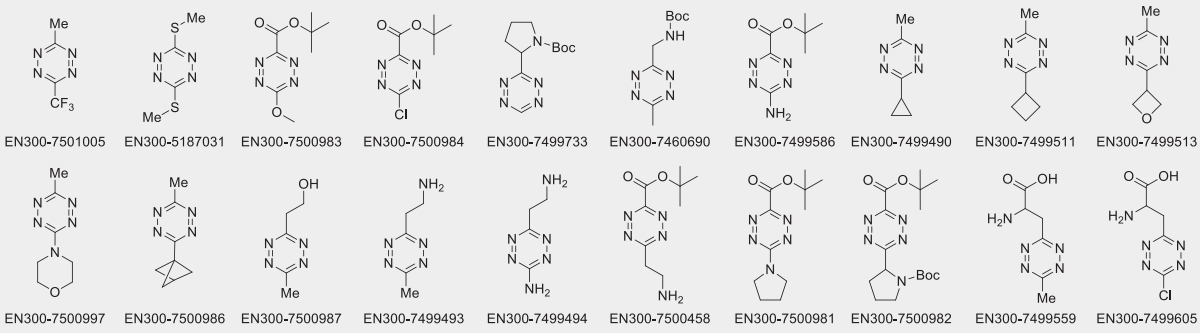
Currently, we have synthesized 8 tetrazine-containing building blocks, that are available in our store on a gram scale.



EN300-1726171 | EN300-6474737 | EN300-211397 | EN300-7544060 | EN300-1692436 | EN300-189526 | EN300-7460477 | EN300-1485623

Pre-order

We also have designed a library of tetrazine-containing building blocks. These molecules can be synthesized upon request.



EN300-7501005 | EN300-5187031 | EN300-7500983 | EN300-7500984 | EN300-7499733 | EN300-7460690 | EN300-7499586 | EN300-7499490 | EN300-7499511 | EN300-7499513

EN300-7500997 | EN300-7500986 | EN300-7500987 | EN300-7499493 | EN300-7499494 | EN300-7500458 | EN300-7500981 | EN300-7500982 | EN300-7499559 | EN300-7499605

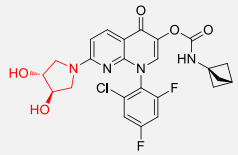
References

1. L. Carroll et al. *Org. Biomol. Chem.* **2013**, 11, 5772.
2. M. F. Debets et al. *Org. Biomol. Chem*. **2013**, 11, 6439.
3. H. L. Evans et al. *Chem. Commun.* **2014**, 50, 9557.
4. A. Wieczorek et al. *Chem. Sci.* **2017**, 8, 1506.
5. H. Li et al. *Org. Lett.* **2018**, *20* , 22, 7186.

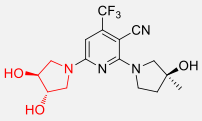
Sugar-like Building Blocks for Drug Design

Introduction

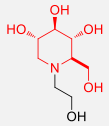
Saturated azaheterocycles are popular in modern drug discovery programs. More than 50 FDA-approved drugs containing a fragment of pyrrolidine and piperidine have appeared on the market.[1] Pyrrolidine/piperidine-based azasugars and their analogues are potent glycosidase inhibitors. These unique molecules 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.



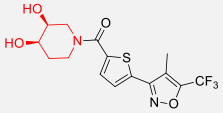
Allosteric modulator of the muscarinic M2 receptor
WO 2016/198342 A1
Bayer



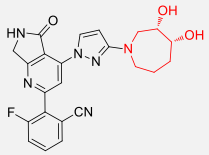
KHK inhibition
J. Med. Chem. **2017**, *60*, 7835.
Pfizer



Glyset
anti-diabetic drug
Pfizer

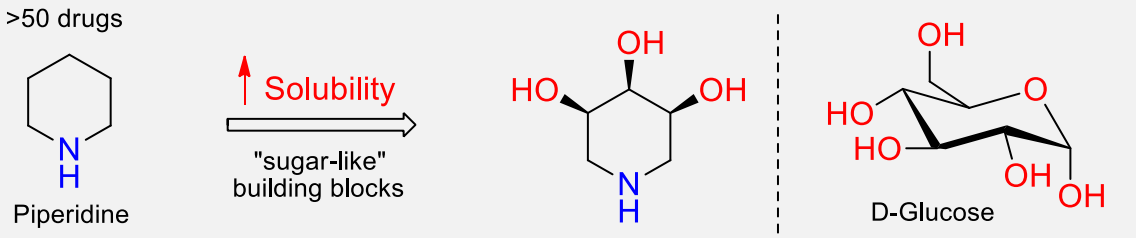


MAO-B inhibition
WO 2016/044635 A1
Dart NeuroScience

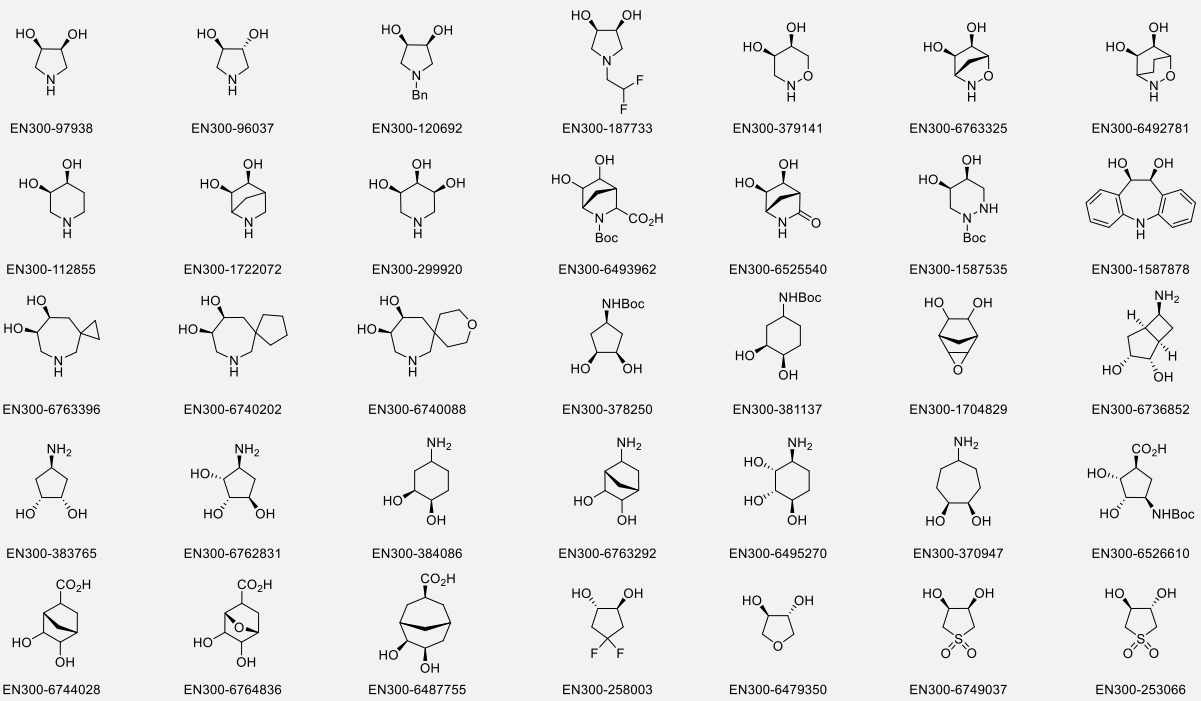


Tyk2 inhibition
WO 2017/040757 A1
Nimbus Therapeutics

Design



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



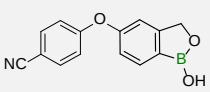
References

1. www.drugbank.ca
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**.

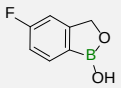
Benzoxaboroles for Drug Design

Introduction

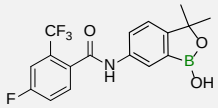
Benzoxaborole is a versatile boron-heterocyclic scaffold which has found in the last 10 years a broad spectrum of applications in medicinal chemistry. The use of benzoxaborole moiety in the design of compounds led to the discovery of new classes of anti-bacterial, anti-fungal, anti-protozoal, anti-viral 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].



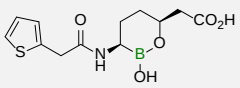
Crisaborole (Eucrisa)
treatment of psoriasis and eczema
Anacor Pharm. 2016



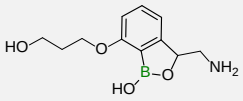
Tavaborole (Kerydin)
antifungal drug
Novartis, 2014



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

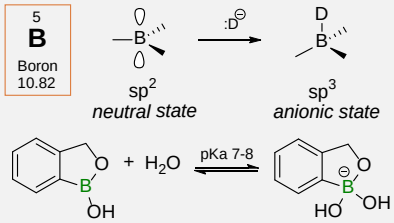


Vaborbactam
component of antibactrial drug Vabomere
Rempex Pharm. 2017



Epetraborole
antibacterial (reached Phase II)
Anacor Pharm. 2009

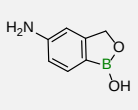
Advantages



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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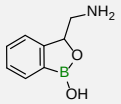

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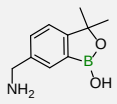

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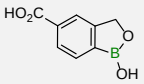
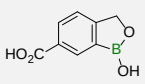
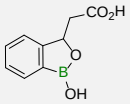


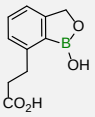
EN300-189558



EN300-189555



EN300-189015



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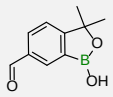

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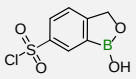

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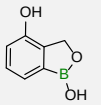

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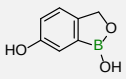

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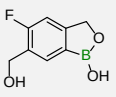

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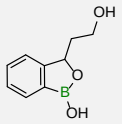

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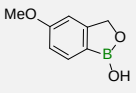

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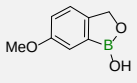

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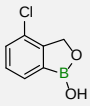

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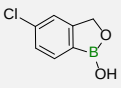

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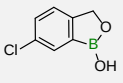

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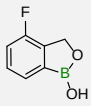

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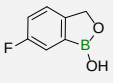

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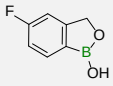

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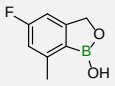

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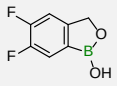

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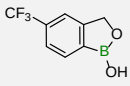

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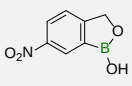

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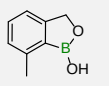

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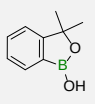

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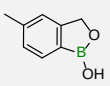

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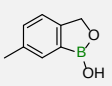

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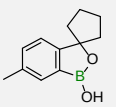

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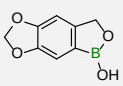

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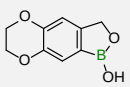


EN300-262861

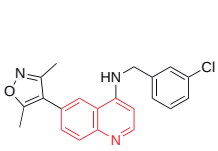
EN300-262839

References

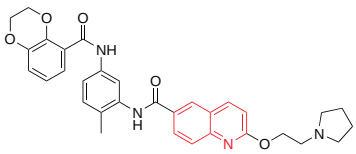
1. S. J. Baker et al. *Chem. Soc. Rev.* **2011**, 4279.
2. F. L. Rock et al. *Science* **2007**, 1759.
3. T. Akama et al. *Bioorg. Med. Chem. Lett.* **2009**, 2129.
4. X. Li et al. *Bioorganic Med. Chem. Lett.* **2010**, 3550.
5. V. Hernandez *et al. Antimicrob. Agents Chemother.* **2013,** *1394.*
6. D. B. Diaz et al. *Nat. Chem.* **2017**, 731.
7. V. M. Dembitsky et al. *Chem. Rev.* **2011**, 209.
8. A. Nocentini et al. *Expert Opin. Ther. Pat.* **2018**, 493.
9. Y. K. Zhang et al. *Bioorg. Med. Chem. Lett.* **2011**, 644.

Heterocyclic scaffolds

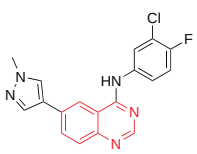
Unsaturated heterocycles are popular in bioactive compounds and drugs. Herein, we offer a library of heterocycles with two halogen atoms bearing different activity. They can be used for the stepwise nucleophilic substitution followed by a metal-mediated cross-coupling to produce the functionalized products.



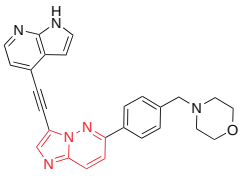
Inhibitor of bromodomain-containing proteins
WO 2017/91661



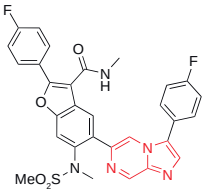
Detection of inhibitors of the HSF1 stress pathway
J. Med. Chem. **2017**, *60*, 180



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



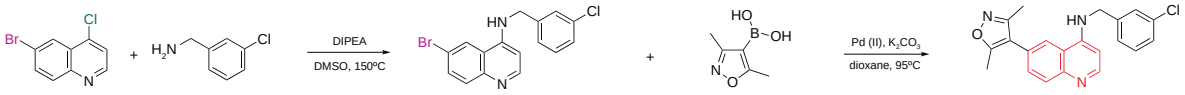
Inhibitor of the MAP kinase
WO 2015/050505



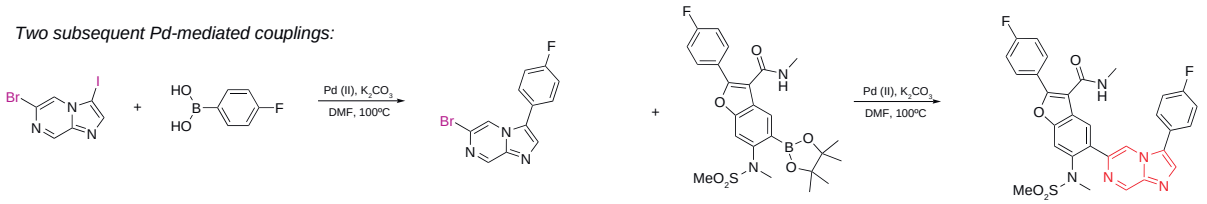
Inhibitor of HCV NS5B polymerase activity
WO 2013/34048

Synthesis of bioactive compounds

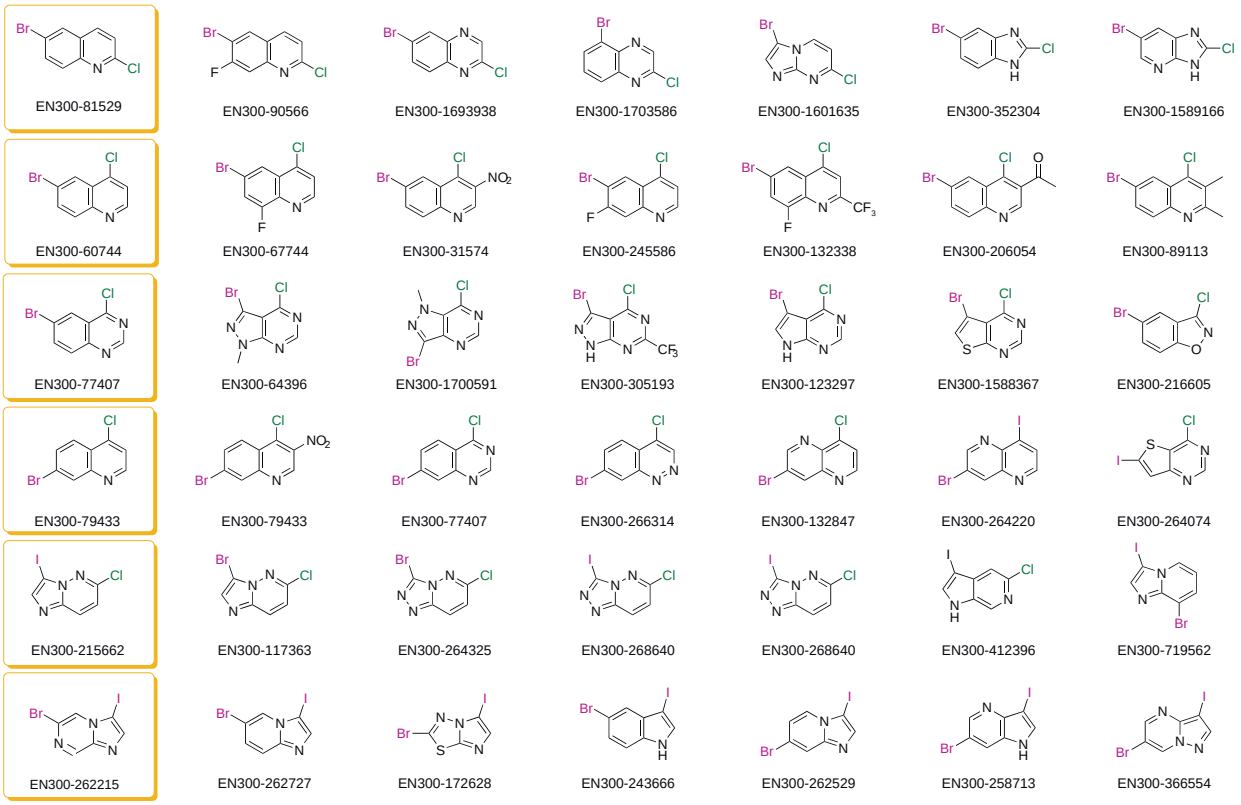
Nucleophilic substitution and Pd-mediated coupling:



Two subsequent Pd-mediated couplings:

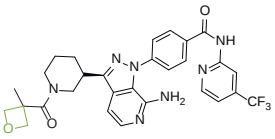


Our offer: over 100 different bicyclic heterocycles with two different halogens on a gram scale in stock.

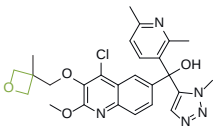


OXETANES

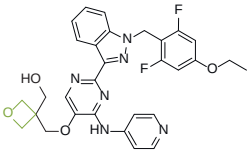
For more than 130 years since the first preparation by Reboul, oxetanes have largely remained neglected in medicinal chemistry. The unit of oxetane can trigger profound changes in aqueous solubility, lipophilicity, metabolic stability, and conformational preference when replacing the commonly employed 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.



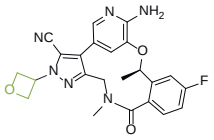
Antagonist of V1B
WO 2014/140186
AbbVie



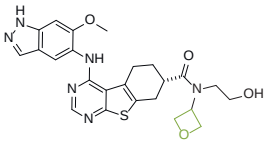
Modulator of RORγt
WO 2015/111870
Johnson & Johnson



Inhibitor of BUB1
WO 2013/50438
Bayer



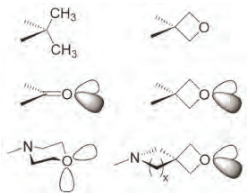
Inhibitor of ALK
WO 2013/132376
Pfizer



Inhibitor of MKNK2
WO 2015/74986
Bayer

Properties of Oxetanes

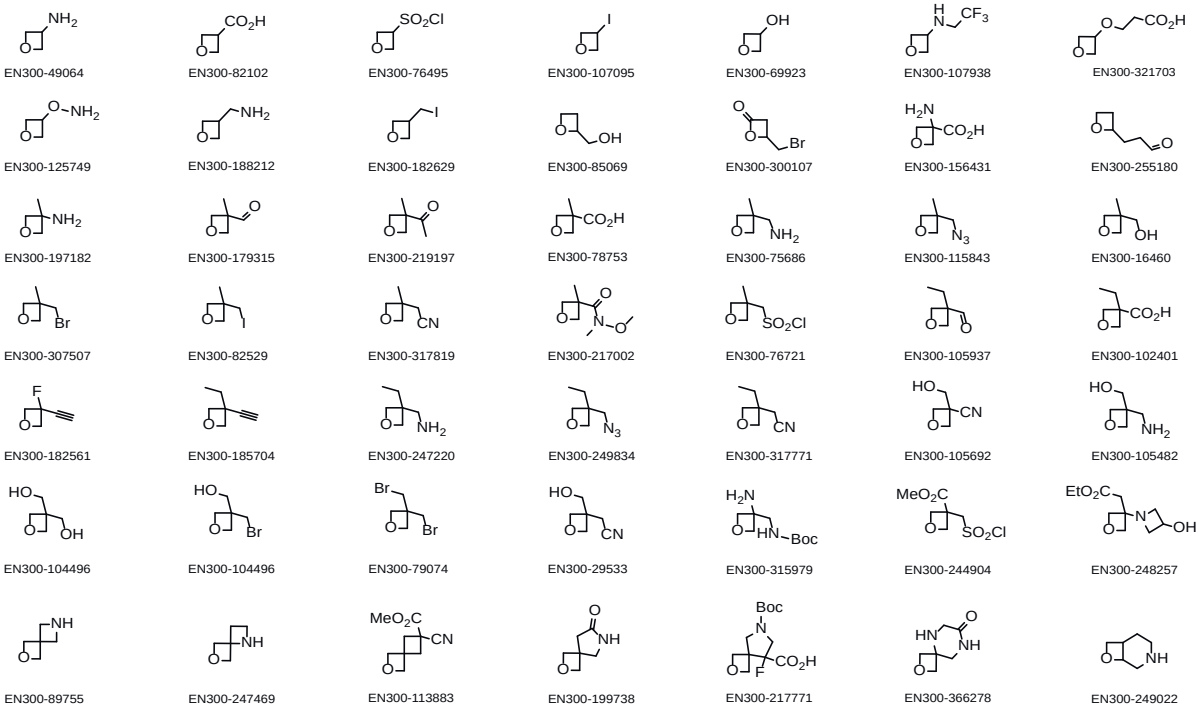
- high chemical stability;
- high aqueous solubility;
- low lipophilicity;
- high metabolic stability;
- hydrogen-bond acceptor ability.



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.



References

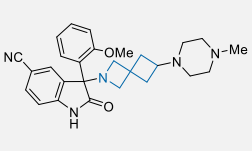
[1] G. Wuitschik *et al. J. Med. Chem.* **2010**, 3227.
[2] J.A. Burkhard *et al. Angew. Chem. Int. Ed.* **2010**, 9052
[3] G. Wuitschik *et al. Angew. Chem. Int. Ed.* **2008**, 4512.
[4] G. Wuitschik *et al. Angew. Chem. Int. Ed.* **2006**, 7736.

Unique 3D-shaped Spirocycles to Explore Novel Chemical Space

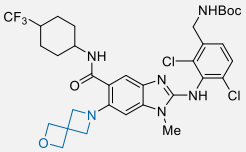
Introduction

Conformational rigidification of flexible compounds by introducing a ring is a popular strategy in drug design. The resulting cyclic analogues usually have a reduced conformational entropy penalty upon binding to a protein target. A conformational restriction can also be imposed by introduction of a spirocyclic ring. Spirocyclic systems are 3D-shaped, in strict contrast to flatten benzene compounds.[1-6] It is especially true for polycyclic compounds. In this context, *Enamine* offers a library of innovative three-cyclic scaffolds for drug design.

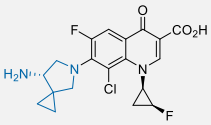
Unique Spirocycles in drug discovery



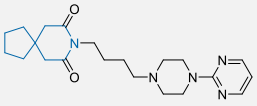
Antivasopressin agent
US2015/344489
AbbVie



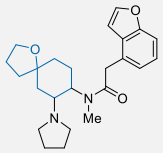
mPGES-1 inhibitor
WO 2012/076673 A1
Boehringer Ingelheim



Sitafloxacin
Fluoroquinolone antibiotic
Daiichi Sankyo Co.

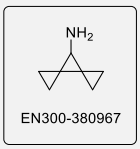


Buspirone
Treatment of anxiety disorders
Mead Johnson

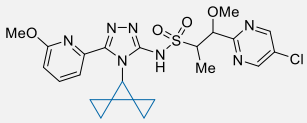


Enadoline
Highly selective k-opioid agonist

Case studies



EN300-380967

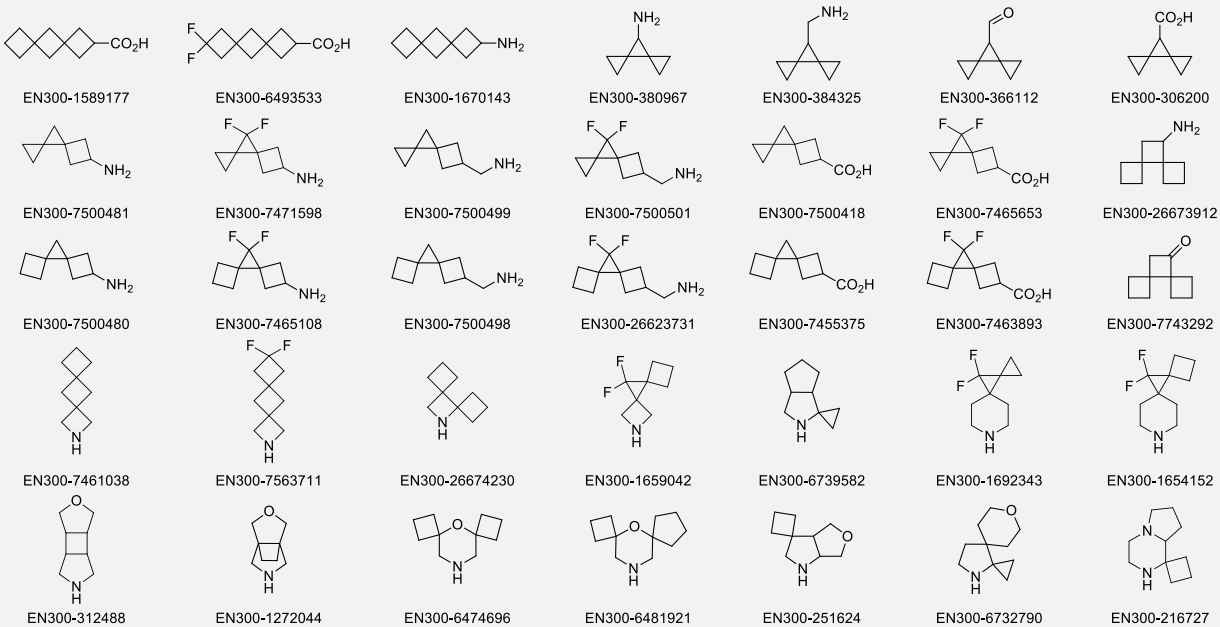


Agonist of the APJ receptor
WO2018/93580, 2018, A1
Amgen Inc.

Unique properties:

- 3D-shaped;
- Fsp^3-rich;
- conformationally restricted;
- functionalization of pharmacophores;
- entry into novel chemical space.

We offer: more than 50 of three-cyclic building blocks from stock on a 5-10 g scale



EN300-1589177, EN300-6493533, EN300-1670143, EN300-380967, EN300-384325, EN300-366112, EN300-306200
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EN300-312488, EN300-1272044, EN300-6474696, EN300-6481921, EN300-251624, EN300-6732790, EN300-216727

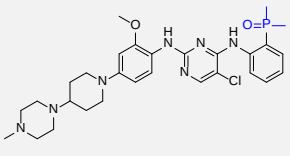
References

1. Y. Zheng et al. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673.
2. Y. Skalenko et al. *J. Org. Chem.* **2018**, *83*, 6275.
3. R. Bychek et al. *Chem. Eur. J.* **2018**, *24*, 12291.
4. A. Kirichok et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 8865.
5. P. Nosik et al. *Adv. Synth. Catal.* **2017**, *359*, 3126.
6. Y. M. Sokolenko et al. *J. Org. Chem.* **2019**, *84*, 13908.

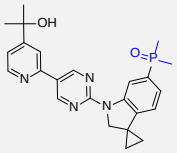
P(O)Me$_2$-containing Building Blocks for Drug Design

Introduction

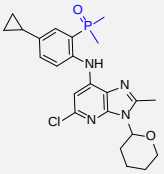
Phosphine oxides belong to a chemical class seldom employed in drug design. However, the FDA-approval of *Brigatinib* drug (ARIAD Pharm.) in 2017 may further inspire application of this unique functional group in medicinal chemistry. The highly ionic P=O bond imparts a number of important drug-like properties, 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.



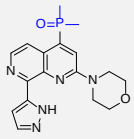
Anti-cancer drug **Brigatinib** (Alunbrig)
ARIAD Pharm.
2016



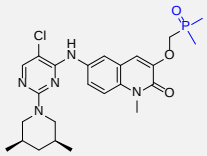
Phoshodiesterase inhibitor
WO2017/108203, A1
Grünenthal GmbH



TYK2 inhibitor
WO2018/075937, A1
Nimbus Lakshmi

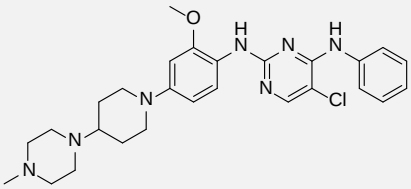


ATR kinase inhibitor
WO2018/153969, A1
Bayer Pharm.

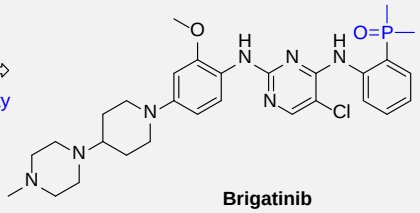


BCL6 inhibitor
WO2018/108704, A1
Boehringer Ingelheim

Discovery of *Brigatinib*



activity
selectivity

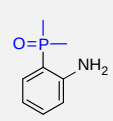


Brigatinib

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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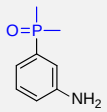

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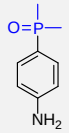

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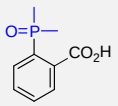

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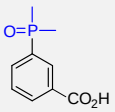

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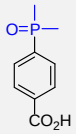

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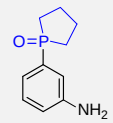

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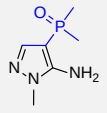

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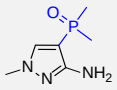

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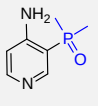

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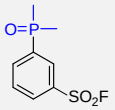

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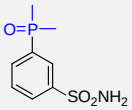

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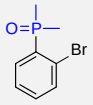

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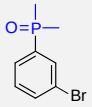

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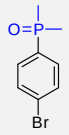

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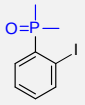

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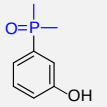

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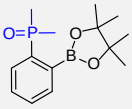

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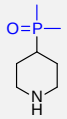

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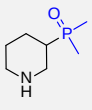

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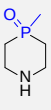

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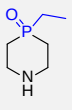

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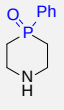

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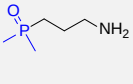

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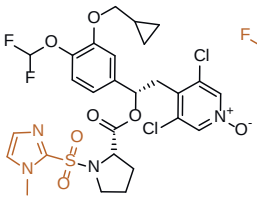
References

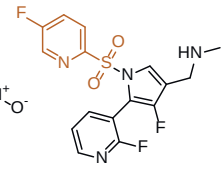
1. W.-S. Huang et al. *J. Med. Chem.* **2016**, *59*, 4948.
2. A. A. Kamel. *International Journal of Chemical and Biomedical Science*, **2015**, *1*, 56.
3. V. Iaroshenko. *Organophosphorus Chemistry: From Molecules to Applications*, John Wiley & Sons, **2019**, 568.

SULFONYL FLUORIDES (-SO_2F): MORE OPTIONS FOR DRUG DESIGN

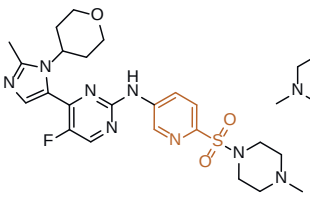
Sulfonyl chlorides (-SO_2Cl) are widely used in medicinal chemistry and agrochemistry as precursors to pharmacologically important sulfonamides. Many sulfonyl chlorides with heteroaromatic substituents, however, are unstable due to SO_2 extrusion. More stable sulfonyl fluorides (- SO_2F) in many cases 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.



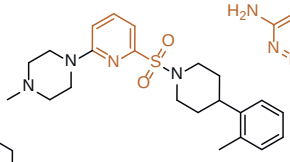
Antagonist of V1B
WO 2014/140186
AbbVie



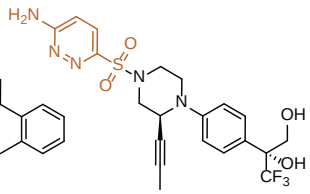
Modulator of RORγt
WO 2015/111870
Johnson & Johnson



Inhibitor of BUB1
WO 2013/50438
Bayer

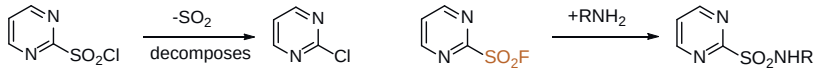


Inhibitor of ALK
WO 2013/132376
Pfizer



Inhibitor of MKNK2
WO 2015/74986
Bayer

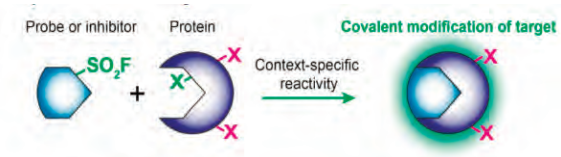
Properties of sulfonyl fluorides



Unstable **Stable**

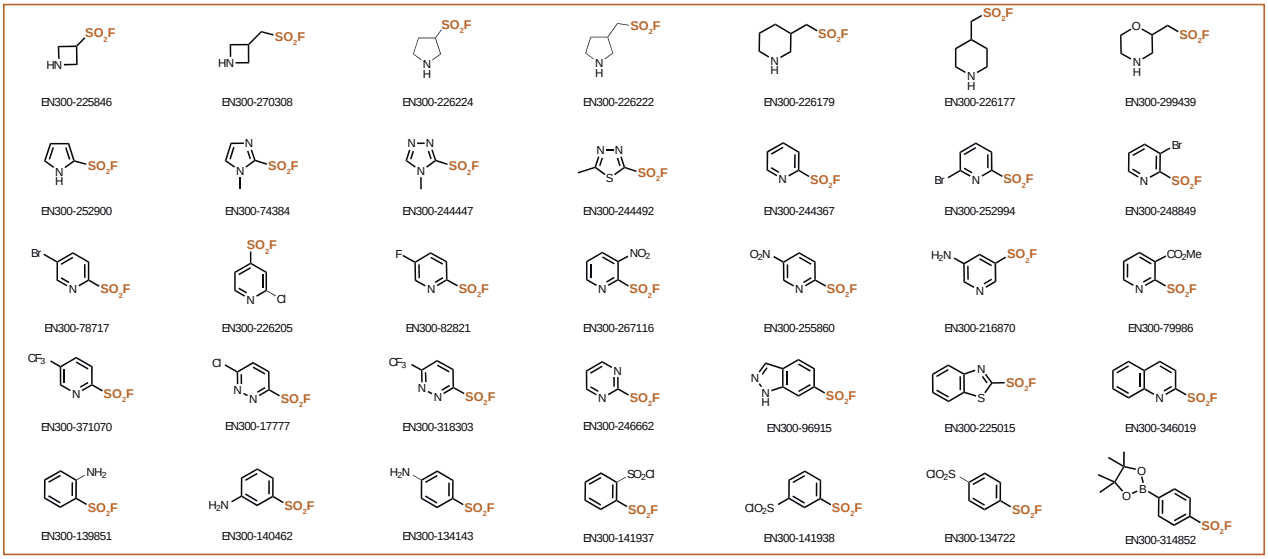
- stable to moisture
- improved selectivity
- orthogonal reactivity to many other functional groups

-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

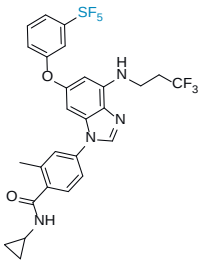


References

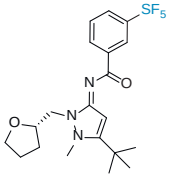
[1] A. Narayanana *et al. Chem. Sci.* **2015**, 2650.
[2] J. Dong *et al. Angew. Chem. Int. Ed.* **2014**, 9430.
[3] A. Garcia-Rubia *et al. Angew. Chem. Int. Ed.* **2011**, 10927.
[4] S. W. Wright *et al. J. Org. Chem.* **2006**, 1080.
[5] S. Caddick *et al. Org. Lett.* **2002**, 2549.

SF_5-BUILDING BLOCKS

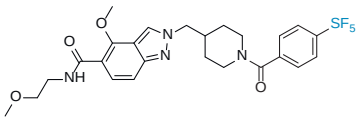
The organic chemistry of the pentafluorosulfanyl group (SF_5) has been developing since 1950's. As the SF_5 group is larger and more lipophilic than the CF_3 one, it is often considered as a "super-trifluoromethyl group". Over the past decade, the SF_5-containing aromatic compounds have found great practical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



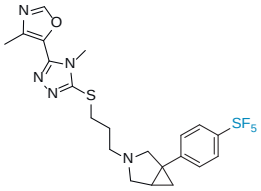
Inhibitor of Mps-1
WO 2012/130905
Bayer



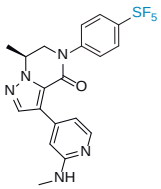
Inhibitor of CB2
WO 2009/105306
Abbott



Antagonist of EP2 receptor
US 2016/89364
Bayer



Modulator of DRD3
WO 2006/108700
GlaxoSmithKline



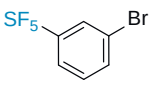
Antagonist of GRM2
WO 2016/87489
Janssen

	NO_2	SF_5	CF_3	SCF_3	OCF_3	F
	CO_2H	CO_2H	CO_2H	CO_2H	CO_2H	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

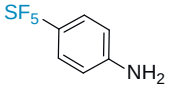
Properties

- 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



EN300-29892



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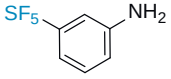

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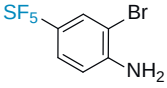

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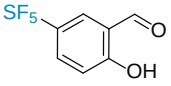

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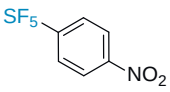

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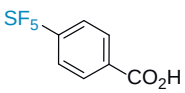

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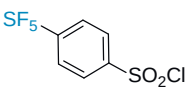

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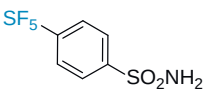

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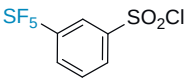

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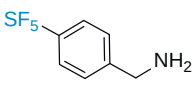

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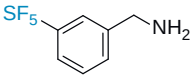

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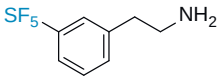

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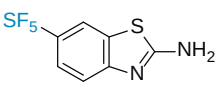

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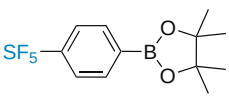


EN300-1704475

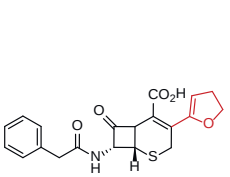
References

[1] R. Paul *et al. Chem. Rev.* **2015**, 1130.
[2] S. Altomonte *et al. J. Fluor. Chem.* **2012**, 57.
[3] P. Kirsch. *Modern Fluoroorganic Chemistry.* **2004**, 146.

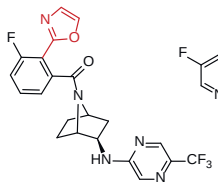
Stannanes for Drug Design

Introduction

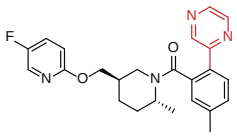
The Stille reaction has become one of the most powerful synthetic tools in organic chemistry. The Stille coupling as a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, has very few limitations on the R-groups. Today, the Stille reaction constitutes a reliable and often-used 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.



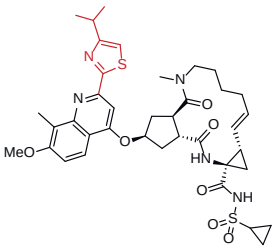
Antibacterial agent
US 1997/5635501
Pfizer



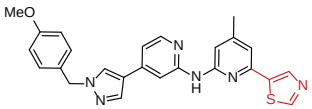
Modulator of orexin receptor
US 2016/46640
Johnson & Johnson



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

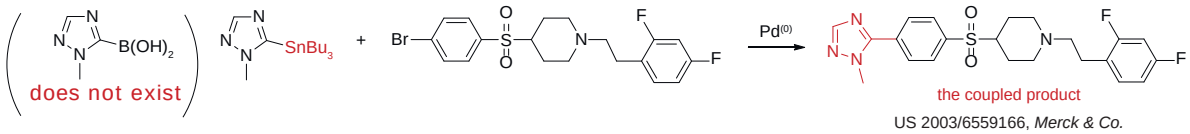


Simeprevir (TMC 435)
NS3/4A protein inhibitor
Janssen



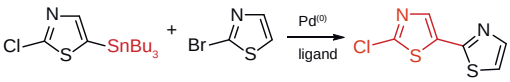
WO 2014/074422
Syk inhibitor
Merck & Co.

Advantages



US 2003/6559166, *Merck & Co.*

Reactivity

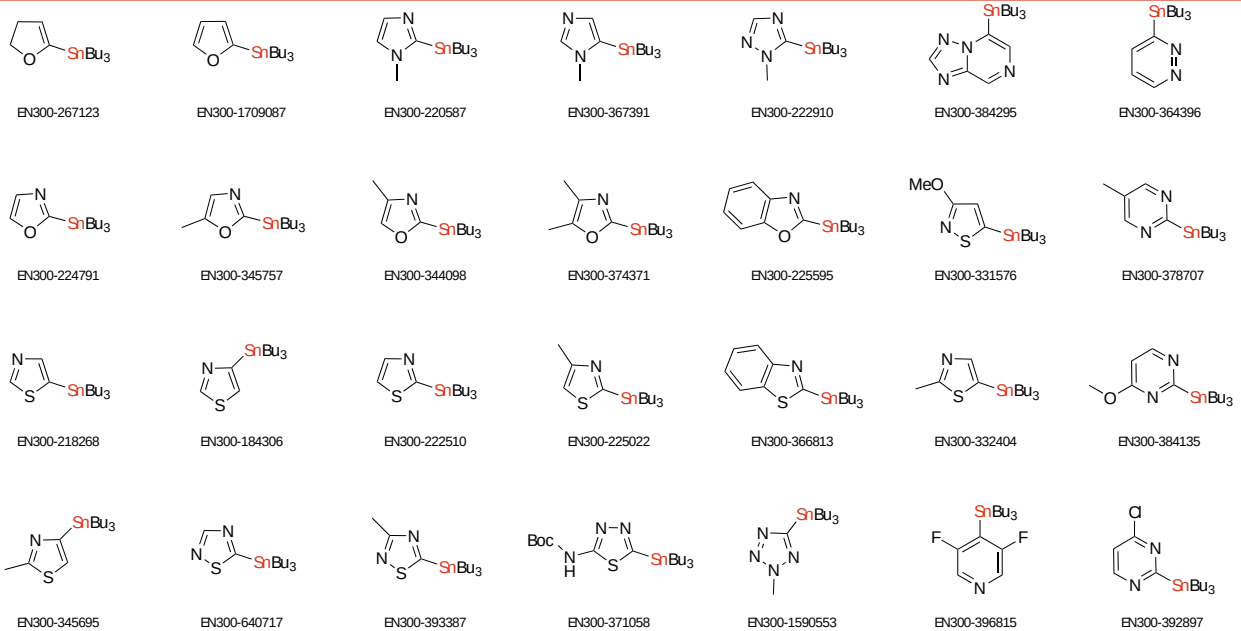


Synthesis of bithiazoles using Pd-catalyzed reactions in which Stille is superior to Negishi and Suzuki couplings.

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

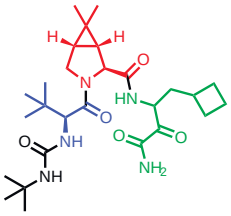


References

1 C. Cordovilla, *ACS Catal.* **2015**, 3040.
2 M. M. Heravi *et al. Tetrahedron.* **2014**, 7.
3 K. C. Nicolaou *et al. Angew. Chem. Int. Ed.* **2005**, 4442.
4 O. Krebs *et al. Org. Lett.* **2005**, 1063.

UNNATURAL AMINO ACIDS

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.



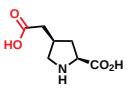
Boceprevir
antiviral drug

Our offer:

- Over **3,000 amino acids in stock on a gram scale**, racemic mixtures and pure enantiomers
- Over 1,000,000 synthetically accessible REAL amino acids, lead time 5-6 weeks, feasibility 75%
- 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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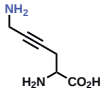
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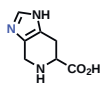
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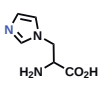
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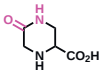
Amino acids with polar and hydrophilic side chains


EN300-703157


EN300-222053


EN300-134916


EN300-217200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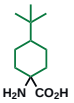
EN300-88021


EN300-205771

Amino acids with hydrophobic side chains


EN300-114441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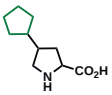
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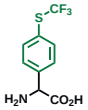
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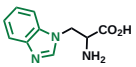
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Conformationally restricted amino acids


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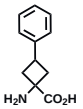
EN300-30421


EN300-58616


EN300-762995


EN300-33992


EN300-762996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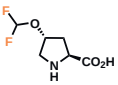
Fluorinated amino acids


EN300-93448


EN300-65367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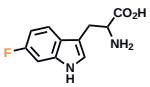
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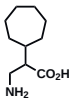
β–and γ–Amino acids


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

ACD,SciFinderにない構造が見つかります!!

Enamine Virtual Building Blocksのご案内

こんな時はご利用をご検討ください!!

◆希望の試薬の購入先が見つからない
◆条件に合うユニークな構造を提案してほしい

“2,000万構造 x 合成率80%”

依頼合成より手軽にユニークな試薬を入手してみませんか？

Enamine社のVirtual Building Blocksとは…

合成実績はないものの、**実現性の高い構造**として**世界最大規模のサプライヤー**である**Enamine社**が**カタログ化**した化合物群です。(BBV-というコードの品目が該当品です)

平均単価：10万円/1g、平均納期：5-6週間

【信頼できる合成力】

合成を行うのは**世界最大規模の化合物サプライヤー**であるEnamine社。
豊富な実績と高い技術力に基づいて行われる合成の**成功率は80%以上**を誇ります。

【依頼合成よりも手頃な費用】

予め自社に出発物質や設備が整っていることに加え、合成後、余分にできた化合物を在庫品として自社で販売するルートが確立しているため**費用が安価に抑えられます**。また、合成失敗や遅延により**キャンセルとなった場合の費用は一切発生しません**。

【安心のサポート力】

ご希望に応じた**簡易レポートの提供**に加え、提供後の問題発生や合成失敗時の**代替品提案**についても**総代理店であるナミキ商事が徹底したサポート**を行います。

お問い合わせフロー

Step①

弊社窓口へご希望の条件をメール

ナミキ商事

オススメPoint・・・
合成率80%で実現性が高い
ユニークな化合物を調査しお手頃価格でご提案

Step②

約2～5営業日で結果をご案内!!
(御見積書・メール)

お見積に際して料金は発生しません

Point・・・
ご注文後、合成失敗によりキャンセルとなった場合の費用は一切発生しません

Step③

合成完了後に通常試薬同様に納品

ナミキ商事

Point・・・
合成の進捗レポートや総代理店である弊社だからこその充実したサポート

弊社が提供するオンライン検索ツール「ChemCupid」上でも検索が可能です。
https://www.namiki-s.co.jp/compound/chemcupid/

ChemCupid®

ナミキ商事株式会社
E-mail：info@namiki-s.co.jp
TEL(本社)　：　03-3354-4026
TEL(大阪支店)　：　06-6231-5444