Oxetanes in Drug Discovery

Key Points

- More metabolically stable and lipophilicity neutral
- Reducing the basicity of its adjacent nitrogen atom, thus possibly lowering the drug's overall lipophilicity

Overview

Oxetanes have been employed to improve drugs' physiochemical properties. Currently, over a dozen oxetane-containing drugs have progressed to different phases of clinical trials. Once one of them gains the FDA approval, the enthusiasm toward its utility in drug discovery will grow exponentially.

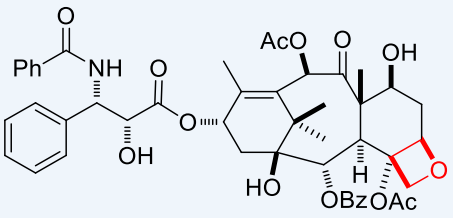
PharmaBlock

PharmaBlock has designed and synthesized over 957 oxetanes, and 174 oxetane products are currently in stock. A list of featured oxetane derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

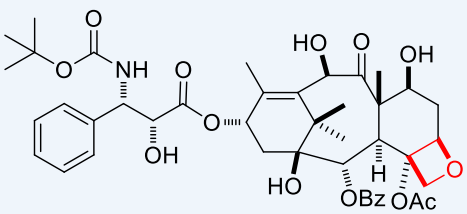
Oxetane adopts a rigid and slightly puckered (8.7°) conformation. As a bioisotere for dimethyl and carbonyl groups, oxetane is more metabolically stable and lipophilicity neutral.[1] Since oxetane is an electron-withdrawing group, it reduces the basicity of its adjacent nitrogen atom and the subtle modulation of the basicity may lower the drug's overall lipophilicity. The last two decades have seen a flurry of oxetane's utility in medicinal chemistry. Over a dozen oxetane-containing drugs have now progressed to different phases of clinical trials.

Oxetane-containing Drugs

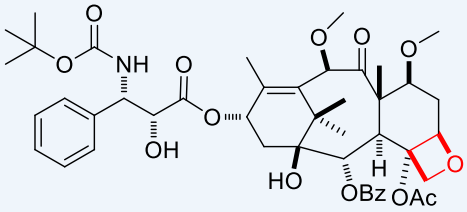
Three FDA-approved oxetane-containing drugs are taxol (**1**) and its two semisynthetic brethrens: Sanofi's docetaxel (Taxotere, **2**) and cabazitaxel (Jevtana, **3**), all chemotherapies for treating cancer. Their mechanism of action (MOA) is disrupting protein microtubule functions in the cell which pull apart the chromosomes before cell division (mitosis). Computational studies showed the oxetane moiety providing: a. Rigidification of the overall structure; and b. H-Bond acceptor for a threonine-OH group in binding pocket. Furthermore, any permutation of the oxetane ring such as replacing the oxygen atom with sulfur or nitrogen resulted in lower activities.



paclitaxel (Taxol, **1**)
BMS, 1993
Disrupt microtubules

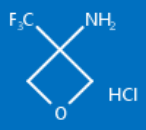


docetaxel (Taxotere, **2**)
Sanofi, 1995
Disrupt microtubule function



cabazitaxel (Jevtana, **3**)
Sanofi, 2010
Disrupt microtubule function

Featured Products



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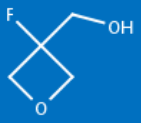

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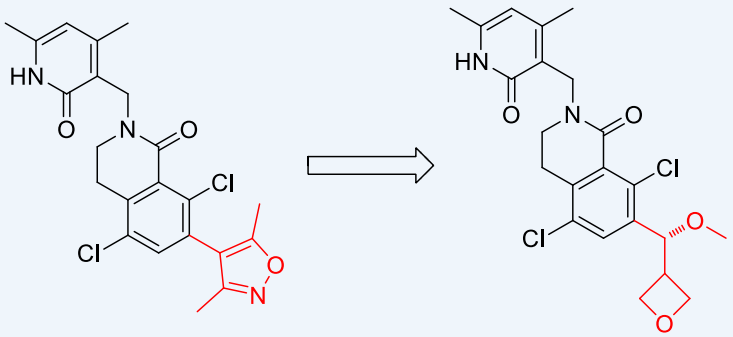
Oxetanes in Drug Discovery

Oxetanes are frequently utilized to improve drugs' physiochemical properties.

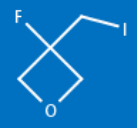
An oxetane fragment conferred a profound impact on Pfizer's zeste homolog 2 (EZH2) Inhibitors, especially their oral bioavailability while still maintaining the activity.[2] The initial lead compound bicyclic lactam **4** was active in both enzymatic (the Y641N mutant form of the enzyme) and cellular-based assays and displayed impressive tumor growth inhibition effects in Karpas-422 xenograft model. Regrettably, **4** was extensively metabolized (HLM Cl = 169 μL/min/mg in protein), had poor permeability in MDCK-LE assay, and low thermodynamic solubility due to its highly crystallinity (mp, 246 °C). One of the fundamental tactics to improve a drug's solubility is to break its aromaticity by adding more sp^3 carbons and oxetane fits the bill. After extensive optimization using ligand and property-based design strategies (especially lipophilic ligand efficiency, LipE), Pfizer arrived at the oxetane-containing PF-06821497 (**5**) where the aromatic dimethylisoxazole on **4** was replaced by all sp^3 centers. PF-06821497 (**5**) displayed the best combination of EZH2 inhibitory activity, LipE, *in vitro* metabolic stability, and permeability characteristics. More importantly, it had a drastically improved (150-fold) thermodynamic solubility over **4**. In comparison, the corresponding tetrahydrofuran analogues had similar potency as **4** but were less permeable. The corresponding tetrahydropyran analogues were more lipophilic, had lower kinetic solubility, and were relatively more labile in the *in vitro* metabolic stability assessments without any appreciable boost of potency. After thorough profiling PF-06821497 (**5**) in terms of PK/PD as a drug candidate, it has been advanced to clinical trials after it was shown to display robust tumor growth inhibition activity in mouse xenograft models along with strong associated pharmacodynamics effects such as reduction of H3K27me3 in tumors.[2]



lactam-isoxazole **4**
EZH2 Y641N K_i = 1.2 nM
HLM Cl 169 μL/min/mg protein
LipE = 5.8
Solubility = 2 μg/mL

PF-06821497 (**5**)
EZH2 Y641N K_i < 0.1 nM
HLM Cl 39 μL/min/mg protein
LipE = 8.3
Solubility = 315 μg/mL

Featured Products



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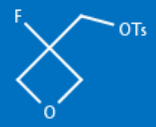

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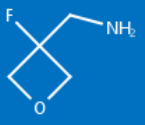

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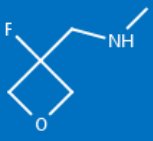
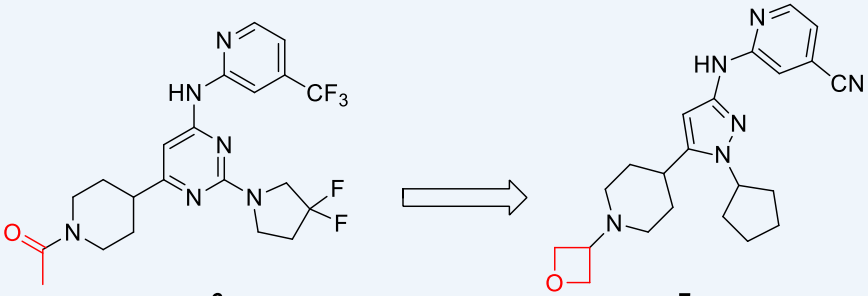


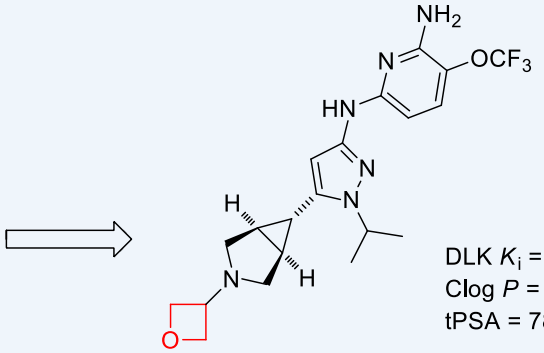
PBOX0007

Inhibitors of dual leucine zipper kinase (DLK, MAP3K12), prominent in the regulation of neuronal degradation, have potential as treatment of neurodegenerative diseases such as Alzheimer's disease (AD). Using an initial hit from high-throughput screening (HTS) as a starting point, Genentech arrived at a potent DLK inhibitor **6** (K_i = 33 nM). Since it was extensively metabolized, a scaffold-hopping campaign produced piperidine-oxetane **7**. Here, an oxetane was successfully used to reduce the basicity of piperidine to limit efflux, important for a brain penetrant, while maintaining good metabolic stability.[3] Further efforts to improve **7**'s potency, kinase selectivity, and drug-like properties befitting a brain-penetrant therapeutic delivered azabicyclo[3.1.0]-hexane pyrazole **8** (K_i = 3 nM). With a favorable *in vitro* safety properties and *in vivo* tolerability, and efficacy in animal models, DLK inhibitor **8** has been advanced to clinical trials.[4]



6
DLK K_i = 33 nM (LipE 2.9)
pJNK IC_{50} = 300 nM
Rat CLu = 4500 mL/min/kg

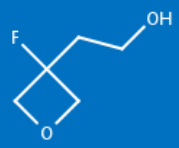
7
DLK K_i = 42 nM (LipE 3.7)
pJNK IC_{50} = 536 nM
Rat CLu = 327 mL/min/kg



8
DLK K_i = 3 nM (LipE 5.8)
Clog *P* = 2.8
tPSA = 78

Oxetan-3-ol has been evaluated as a bioisostere of carboxylic acid.[5] The acid functionality on the household analgesic ibuprofen (**9**, p*K*a = 4.64) is negatively ionized in physiological conditions that is responsible for an insufficient passive diffusion across biological membranes. In stark

Featured Products



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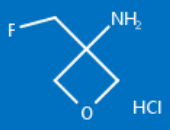

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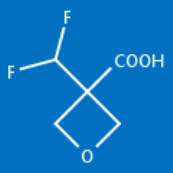
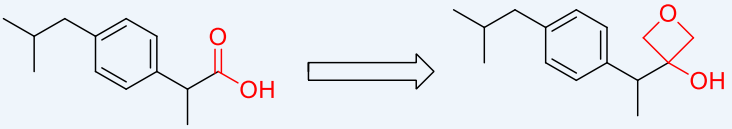


PBLL1823

PBLL1758

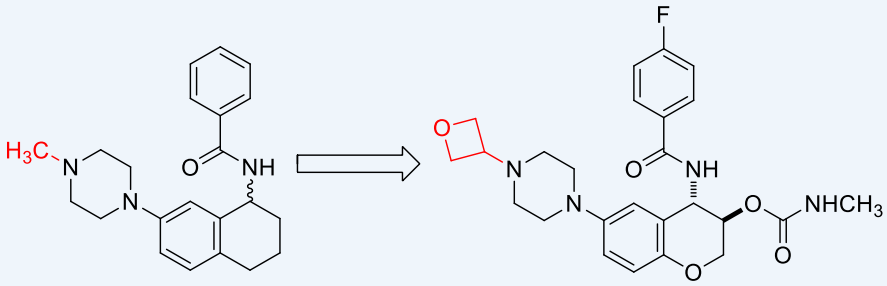
contrast, as an analogue of ibuprofen (**9**), oxetan-3-ol **10** is mostly neutral (p*K*a > 12) at physiological pH and comparatively more lipophilic and more permeable in comparison to ibuprofen (**9**). Given the relatively low acidity and high permeability, oxetan-3-ol **10** may be useful in the context of central nervous system (CNS) drug design. Moreover, oxetan-3-ol **10** also inhibits 5-lipoxygenase-derived leukotriene B_4 (LTB_4) while ibuprofen (**9**) is inactive against this target.[5]



ibuprofen (**9**)
p*K*a = 4.64
PGE_2/D_2 IC_{50} = 0.6 μM
LTB_4 IC_{50} > 100 μM

oxetan-3-ol **10**
p*K*a > 12
PGE_2/D_2 IC_{50} = 34.1 μM
LTB_4 IC_{50} = 8.4 μM

As a cathepsin S inhibitor, Lilly's lead tetrahydronaphthalene **11** was not very potent (IC_{50} = 4 μM). Extensive structure-activity relationship (SAR) campaign was exercised to optimize the lead compound. A key aspect of this modification process was replacing the *N*-methyl group on **11**'s piperazine with an *N*-oxetanyl unit to modulate the basicity of the nitrogen atom and to lower the overall lipophilicity. This modification, along with others, led to the development of clinical candidate LY3000328 (**12**) for the treatment of abdominal aortic aneurysm (AAA).[6]

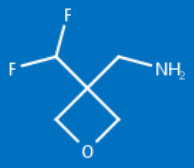


11
hCat S IC_{50} = 4,000 nM
mCat S IC_{50} = 3,930 nM

LY3000328 (**12**)
hCat S IC_{50} = 7.7 nM
mCat S IC_{50} = 1.7 nM

Trifluoromethyl oxetane may serve as a less lipophilic bioisostere of the *tert*-butyl group. AstraZeneca's G-protein coupled receptor 119 (GPR119) agonist **13** as a potential diabetes treatment, although potent, suffered from poor aqueous solubility (24 μM). After extensive experimentations,

Featured Products



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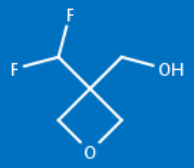

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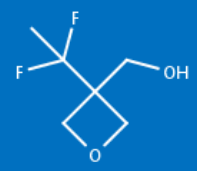

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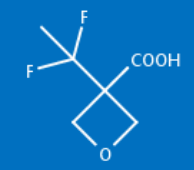
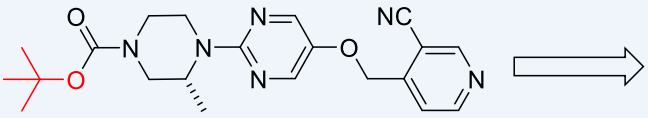
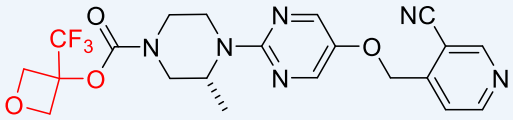


PBLL1822

trifluoromethyl oxetane derivative **14** had a desirable aqueous solubility of 116 μM and was found to be the best combination of potency boost and metabolic stability. While the corresponding ethyl and isopropyl-oxetane derivatives proved unstable in human liver microsomes (HLM), no metabolism of the trifluoromethyl oxetane was detected. Similarly, the ring expanded homologue of **14**, trifluoromethyl terahydrofuran, had a similar potency, higher lipophilicity, which resulted in lower solubility, higher clearance in HLM, and an erosion of ligand-lipophilicity efficiency (LLE = pEC_{50} – log *D*).[7]

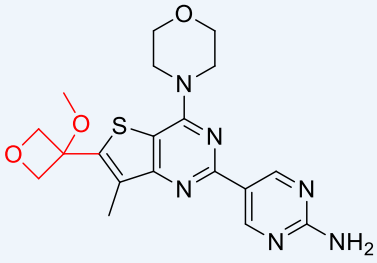


13
aqueous solubility, 24 μM
Log $D_{7.4}$ = 3.3
mp = 91–93 °C

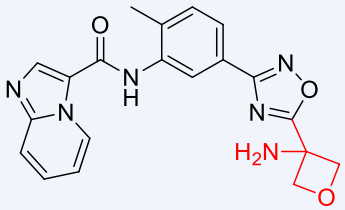


14
aqueous solubility, 110 μM
Log $D_{7.4}$ = 2.5
mp = 53–55 °C

Not all oxetane moieties on drugs are in the simplest form as on **10** and **12**. More substituted oxetanes have made their way to be parts of drugs. For instance, Genentech's phosphatidylinositol 3-kinase (PI3K) inhibitor **15** contains a 3-methoxy-oxetane, which is helpful to boost brain penetration.[8] A C-kit kinase inhibitor **16** possesses a 3-amino-oxetane motif.[9] Merck's tyrosine kinase MET inhibitor **17** has a 3-fluorooxetane fragment[10] and AstraZeneca's melanin-concentrating hormone receptor 1 (MCHr1) antagonist AZD1979 (**18**) is appended with a spirocyclic azetidine-oxetane substituent, which imparts favorable physiochemical properties.[11]



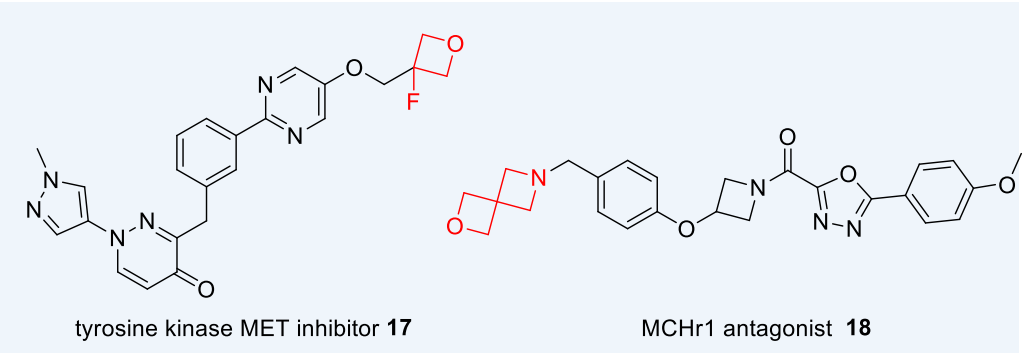
PI3K inhibitor **15**



C-kit kinase inhibitor **16**

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

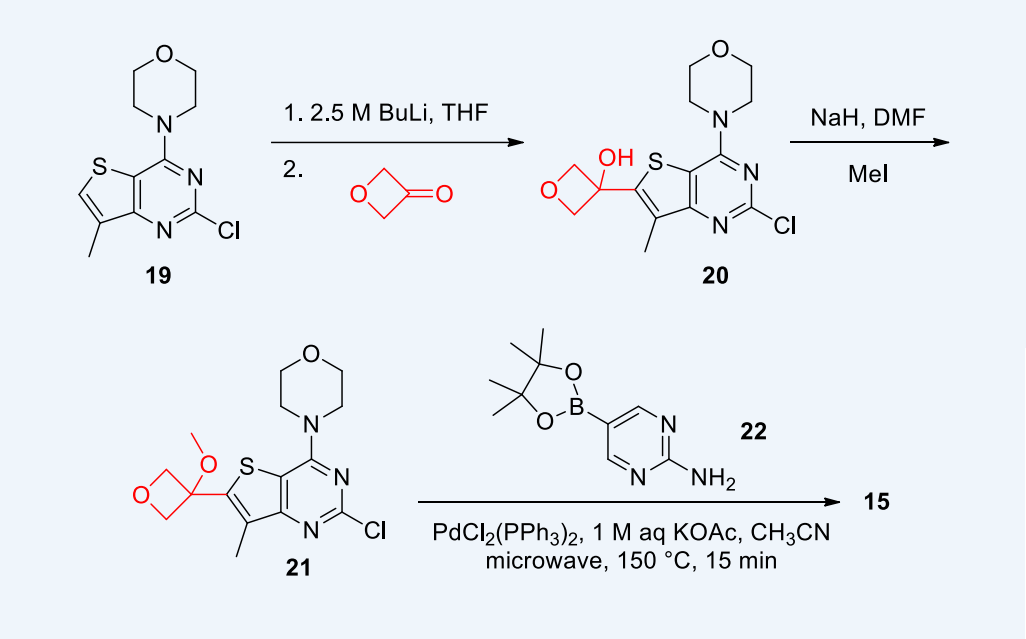
- 80000+ building blocks
- 10000+ in stock in both USA and China
- 20000+ supplied within two weeks
- 1000+ SAR tool kits
- Novel building blocks designed upon daily monitoring on recent researches and patents
- Keep optimizing cost effective route for better price and sustainable supply
- Fast delivery of custom synthesis
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance



tyrosine kinase MET inhibitor **17** MCHr1 antagonist **18**

Synthesis of Some Oxetane-containing Drugs

Genentech's synthesis of its PI3K inhibitor **15** installed the 3-methoxy-oxetane group using oxetanone as the starting material. Thus, lithiation of the thiophene moiety on morpholinopyrimidine **19** was followed by addition of oxetanone to give rise to 3-oxetanol **20**. Methylation of **20** was straightforward to afford 3-methoxy-oxetane **21** and a subsequent Suzuki coupling with 2-aminopyrimidine-5-boronic acid pinacol ester (**22**) assembled the desired **15**.[8]

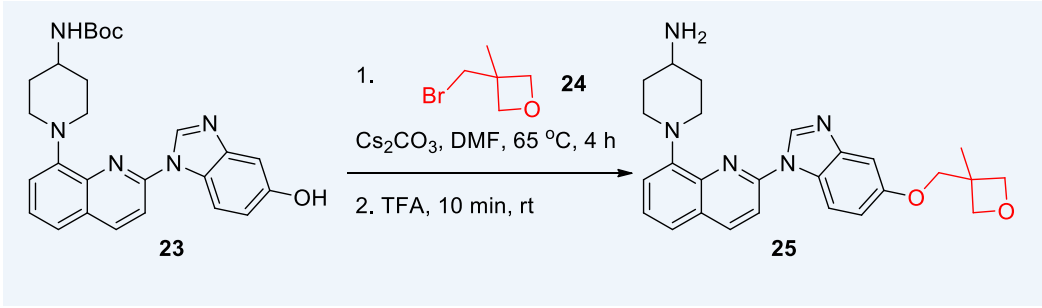


Synthesis of Pfizer's crenolanib (**25**), an inhibitor of FMS-like tyrosine kinase 3 (FLT3) and platelet-derived growth factor receptor-α/β (PDGFRα/β), was also uneventful. A simple S_N2 reaction between the advanced intermediate phenol **23** and 3-(bromomethyl)-3-methyloxetane (**24**) prepared crenolanib (**25**) after acidic removal of the Boc protection.[12]

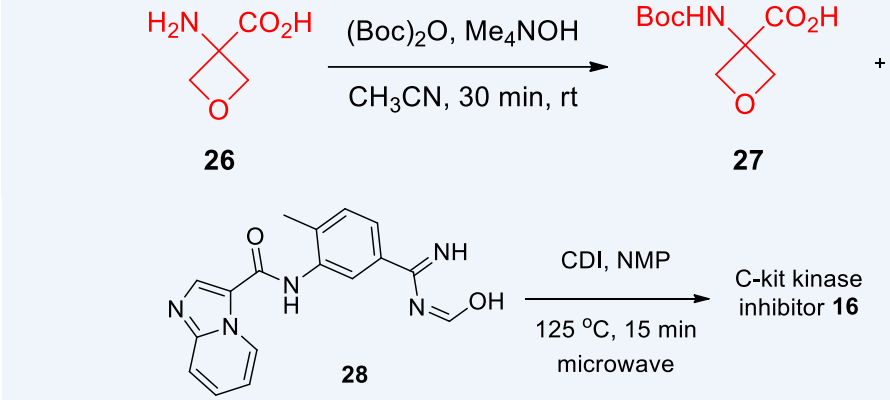
Contact Us

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

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



A synthesis of C-kit kinase inhibitor **16** employed 3-aminooxetane-3-carboxylic acid (**26**) as the source of its 3-amino-oxetane motif. After protection of **26** with Boc, the resultant **27** was then condensed with intermediate **28** to produce **16** after acidic removal of the Boc protection.[9]



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