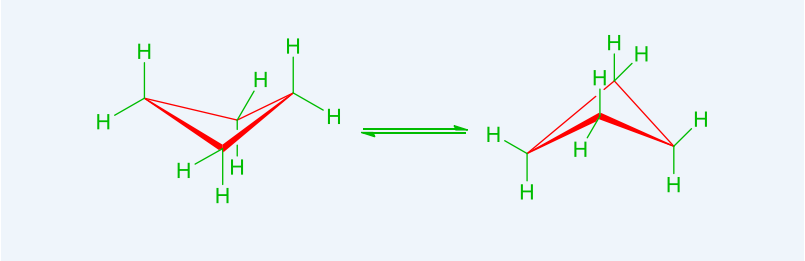
Cyclobutane Derivatives in Drug Discovery

Key Points

- Cyclobutane adopts a rigid puckered conformation
- Offering advantages on potency, selectivity and pharmacokinetic (PK) profile.

Overview

Unlike larger and conformationally flexible cycloalkanes, cyclobutane and cyclopropane have rigid conformations. Due to the ring strain, cyclobutane adopts a rigid puckered (~30°) conformation. This unique architecture bestowed certain cyclobutane-containing drugs with unique properties. When applied appropriately, cyclobutyl scaffolds may offer advantages on potency, selectivity and pharmacokinetic (PK) profile.



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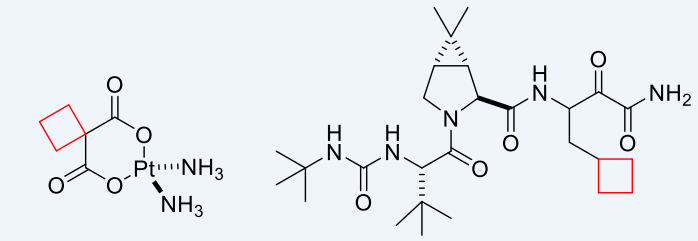
Cyclobutane-containing Drugs

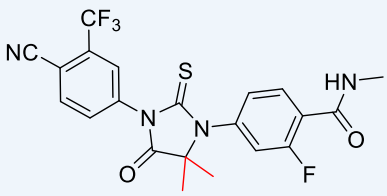
At least four cyclobutane-containing drugs are currently on the market. Chemotherapy carboplatin (Paraplatin, **1**) for treating ovarian cancer was prepared to lower the strong nephrotoxicity associated with cisplatin. By replacing cisplatin's two chlorine atoms with cyclobutane-1,1-dicarboxylic acid, carboplatin (**1**) has a much lower nephrotoxicity than cisplatin. On the other hand, Schering-Plough/Merck's hepatitis C virus (HCV) NS3/4A protease inhibitor boceprevir (Victrelis, **2**) also contains a cyclobutane group in its P_1 region. It is 3- and 19-fold more potent than the corresponding cyclopropyl and cyclopentyl analogues, respectively.[1]



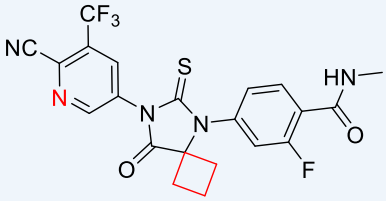
carboplatin (Paraplatin, **1**)
BMS, 1989
DNA intercalator
ovarian cancer

boceprevir (Victrelis, **2**)
Schering-Plough, 2011
HCV NS3/4A protease inhibitor

Androgen receptor (AR) antagonist apalutamide (Erleada, **4**) for treating castration-resistant prostate cancer (CRPC) has a spirocyclic cyclobutane scaffold. It is in the same series as enzalutamide (Xtandi, **3**) discovered by Jung's group at UCLA in the 2000s. The cyclobutyl- (**4**) and cyclopentyl-derivative have activities comparable to the dimethyl analogue although the corresponding six-, seven-, and eight-membered rings are slightly less active.[2] On a separate note, thiohydantoins are known structural alerts to cause toxicities. However, in this particular case for the particular indication (CRPC), both enzalutamide (**3**) and apalutamide (**4**) have sufficiently large enough therapeutic windows to pass FDA's stringent requirements on safety and efficacy. Being dogmatic about structural alerts would have missed these life-saving medicines!



enzalutamide (Xtandi, **3**)
Medivation/Astellas, 2012
androgen receptor antagonist



apalutamide (Erleada, **4**)
Janssen, 2018
androgen receptor antagonist

Featured Products

PB01374

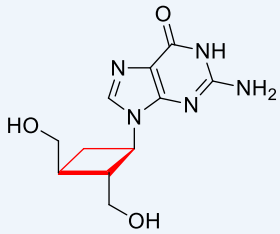
PBLG1180

PB01366

PBN20120281-1

Agios' ivosidenib (Tibsovo, **16**, *vide supra*), a first-in-class IDH1 inhibitor containing a difluorcyclobutylamine substituent, was approved by the FDA in July 2018 for the treatment of IDH1-mutant cancers.[8]

Unlike the conformationally flexible tetrahydrofuran ring found in natural nucleosides, the conformationally more rigid 4-membered cyclobutane ring on BMS's lobucavir (**5**) favors a single puckered conformation. It is active against human immunodeficiency virus-1 (HIV-1), hepatitis B virus (HBV), and herpesviruses, suggesting that scaffold conformational flexibility is not essential for antiviral activity and that a rigid scaffold can be compatible with the inhibition of viral replication.[3] Although the phase III clinical trials for lobucavir (**5**) were discontinued in 1999 due to safety concerns, it paved the road for the discovery of BMS's entecavir (Baraclude) as an effective treatment for hepatitis B.



lobucavir (**5**)
RNA-directed DNA polymerase inhibitors

Cyclobutanes in Drug Discovery

Cyclobutane motif has been employed to improve a drug's potency, selectivity, and pharmacokinetic profile.

Triazole **6** as a tankyrase (TNKS) inhibitor had a poor PK in rats. A structure-guided hybridization approach gave a new series combining triazole **6** and benzimidazolone **7**. Here the *trans*-cyclobutyl linker displayed superior affinity compared to a cyclohexyl and phenyl linker. The resulting hybrid cyclobutane **8** showed favorable activity, selectivity and *in vitro* ADME profile. Moreover, it was shown to be efficacious in xenograft models.[4]

Featured Products

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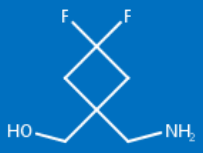
PBLJ2811

PB05328



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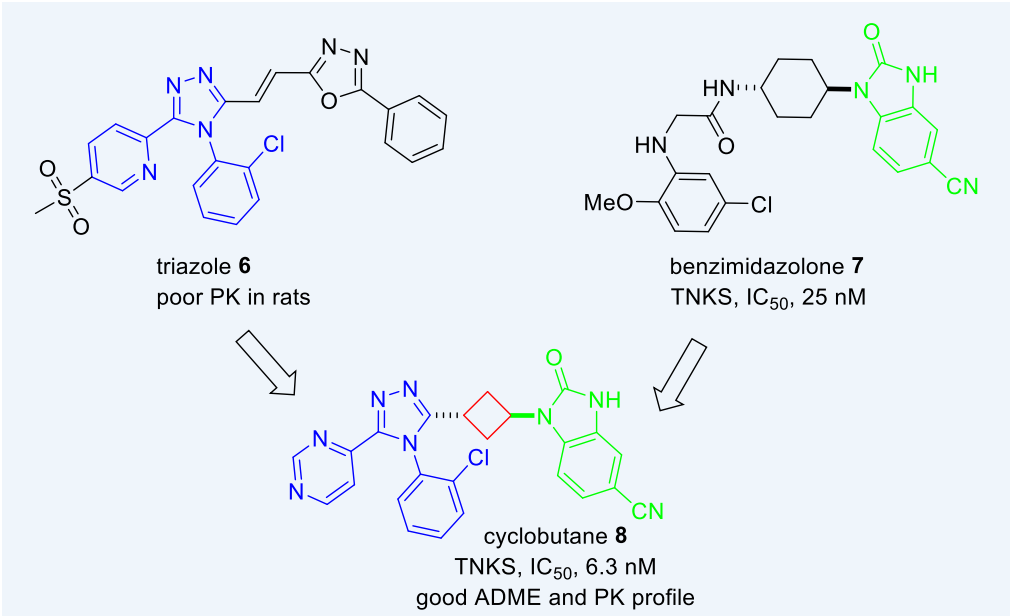
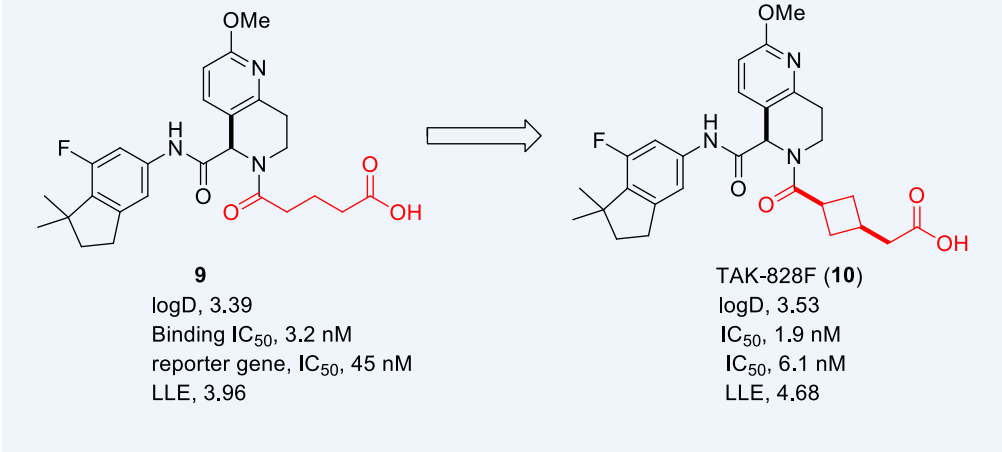


Tetrahydronaphthyridine **9** is a novel inverse agonist for retinoic acid-related receptor γt (RORγt). Changing the flexible *n*-butanoic acid on **9** to a rigid *cis*-cyclobutane acetic acid on **10** led to an improvement of *in vitro* potency through reduction of the entropy loss of the carboxylic acid group, which occurs through interaction with amino acid residues in the binding site. Indeed, the resultant TAK-828F (**10**) demonstrated potent RORγt inverse agonistic activity, excellent selectivity against other ROR isoforms and nuclear receptors, and a good pharmacokinetic profile. After testing efficacious in animal models, TAK-828F (**10**) is now in clinical trials for the treatment of Th17-driven autoimmune disease.[5]



Featured Products

PB01367

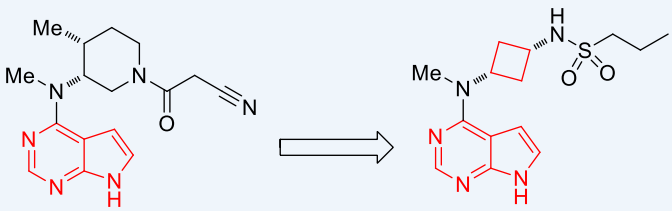
PB01369-01

PBZQ0001

PBN20121017

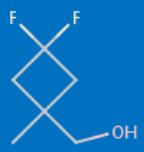
The rigidity offered by the cyclobutane may be useful in improving drug selectivity.

Janus kinases (JAKs) are intracellular tyrosine kinases that mediate the signaling of numerous cytokines and growth factors involved in the regulation of immunity, inflammation, and hematopoiesis. There are four members of the Janus kinase family: JAK1, JAK2, JAK3, and TYK2. Marketed as a treatment of rheumatoid arthritis (RA) since 2012, Pfizer's tofacitinib (Xeljanz, **11**) is a JAK1/JAK3 inhibitor with moderate activity on JAK2. In an pursuit a selective JAK1 inhibitor, Pfizer prepared the corresponding sulfonamides bearing a *cis*-1,3-cyclobutane diamine linker that conferred both excellent potency and excellent selectivity within the JAK family. In particular, PF-04965842 (**12**) has a 28-fold selectivity for JAK1/JAK2. After demonstrating efficacy in a rat adjuvant-induced arthritis (rAIA) model, PF-04965842 (**12**) was nominated as a clinical candidate for the treatment of JAK1-mediated autoimmune diseases.[6]



Indazole **13** with the methylsulfonamide appendage was found to be a highly selective β_3-adrenergic receptor (β_3-AR) agonist, but it was metabolically unstable because of high clearance. Exchanging the methylsulfonamide to the corresponding cyclobutylsulfonamide and an additional of isopropyl/methyl switch at the right portion of the molecules provided indazole **14**. It was not only highly potent and selective as a β_3-AR agonist, it also had a desirable metabolic stability and was orally available. Cyclobutylsulfonamide **14** showed dose-dependent β_3-AR-mediated responses in marmoset urinary bladder smooth muscle. It may serve as a candidate drug for the treatment of overactive bladder without off-target-based cardiovascular side effects.[7]

Featured Products



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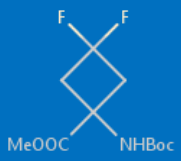

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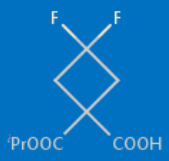

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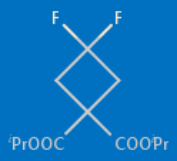

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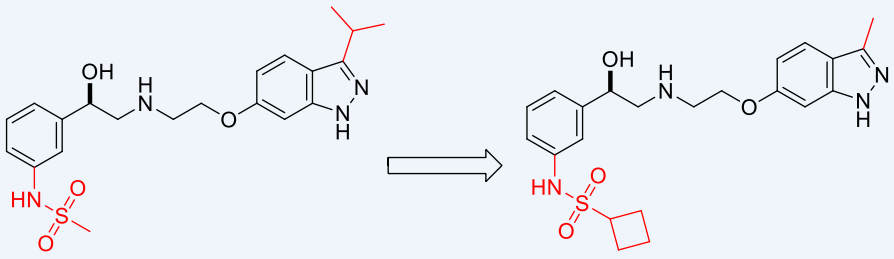
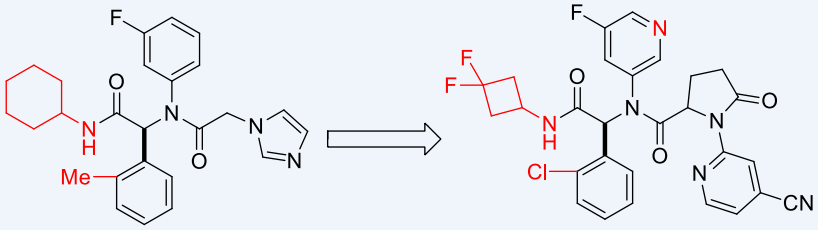


13
β_3-AR EC_{50} = 13 nM
poor metabolic stability
poor pharmacokijnetics
(C_{max} and AUC)

14
β_3-AR EC_{50} = 18 nM
improved metabolic stability
orally abailable
no cardiovascular side effects

Point mutations in isocitrate dehydrogenase (IDH) 1 and 2 are found in multiple tumors, including glioma, cholangiocarcinoma, chondrosarcoma, and acute myeloid leukemia (AML). FDA's 2017 approval of Agios/Celgene's mIDH2 Inhibitor enasidenib (Idhifa) for treating relapsed/refractory AML fueled much enthusiasm for this novel cancer target. Agios's IDH*1* inhibitor AGI-5198 (**15**) inhibited both biochemical and cellular production of oncometabolite D-2-hydroxyglutatrate (2-HG) and was efficacious *in vivo* in xenograft model. But its poor pharmaceutical properties precluded its use in clinical studies. The major culprits included metabolic instability of the cyclohexane and the imidazole moieties. One key strategy to decrease metabolic clearance was replacing cyclohexyl amine with difluorocycbutanyl amine, which brought the metabolic stability into the medium clearance range. Additional optimizations led to ivosidenib (Tibsovo, **16**), which is potent, selective, and, more importantly, metabolically stable. It is a first-in-class IDH*1* inhibitor now approved by the FDA in July 2018 for the treatment of IDH1-mutant cancers.[8] Agios' enasidenib and ivosidenib represent a novel class of cancer therapy based on cellular differentiation.



AGI-5198 (**15**)
enzyme IC_{50}, 70 nM
cellular IC_{50}, 497 nM
E_h 0.93

ivosidenib (Tibsovo, **16**)
12 nM
8 nM
0.15

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- 20000+ supplied within two weeks
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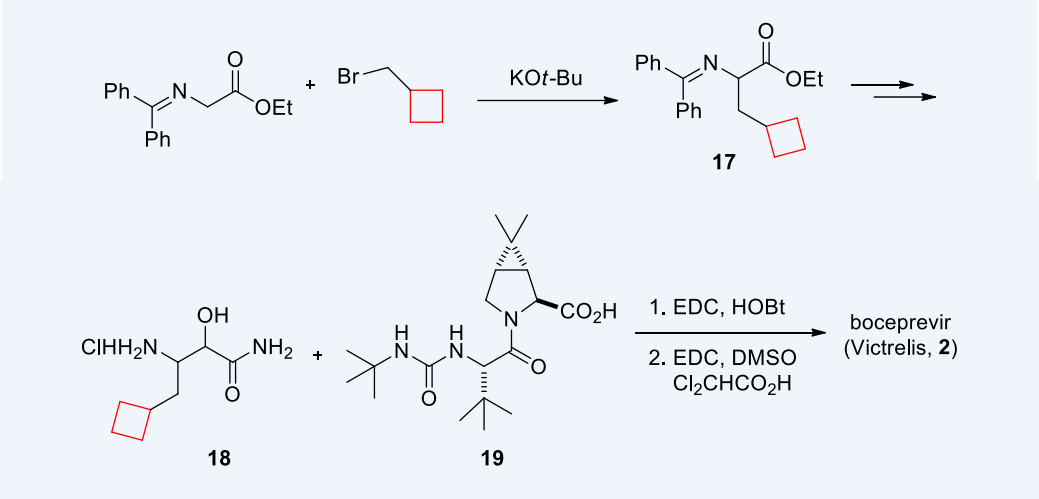
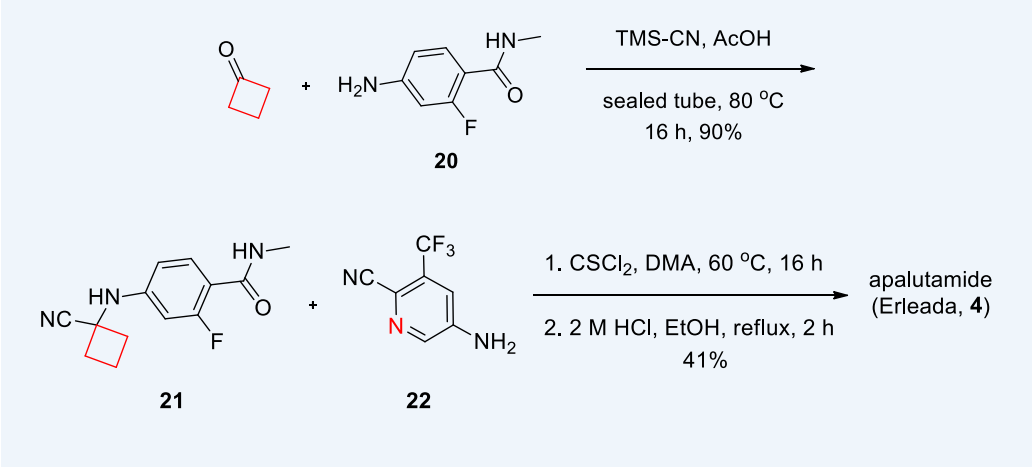
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance

Synthesis of Some Cyclobutane-containing Drugs

The cyclobutylmethyl fragment on Schering–Plough/Merck's boceprevir (Victrelis, **2**) was incorporated from cyclobutylmethyl bromide. Therefore, alkylation of glycine ethyl ester with cyclobutylmethyl bromide was aided by KO*t*-Bu to produce adduct **17**. Eight additional steps converted **17** to the desired P_1 intermediate **18**. Amide formation from amine **18** and P_2–P_3 intermediate as acid **19** was followed by the Moffatt oxidation of the alcohol to ketone to deliver boceprevir (**2**).[1]



In a synthesis of apalutamide (Erleada, **4**), cyclobutanone was employed as the building block to install the spirocyclic cyclobutane motif. A Stecker reaction between cyclobutanone and aniline **20** in the presence of TMS-CN in acetic acid provided cyclobutyl nitrile **21**. Cyclization of **21** with aniline **22** and thiophosgene followed by acidification afforded apalutamide (**4**).[9]



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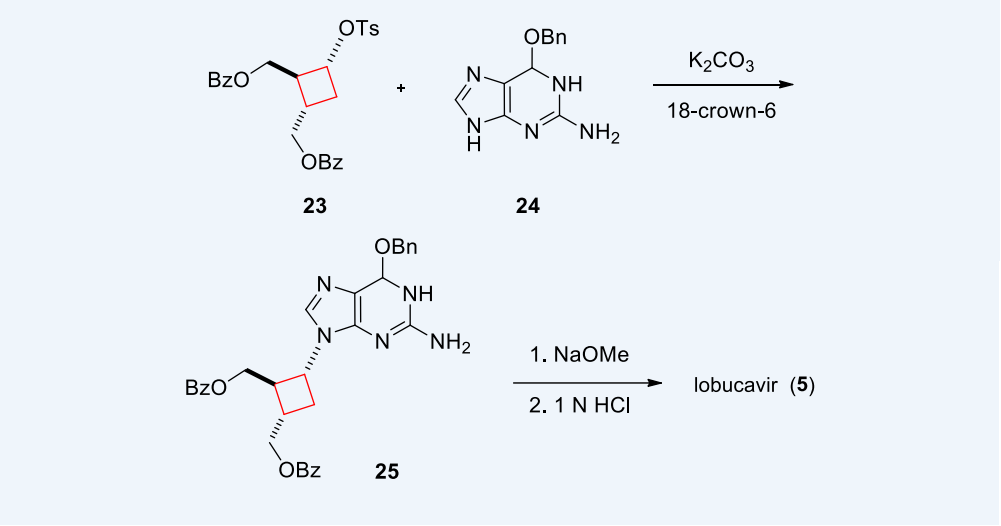
Finally, BMS' synthesis of lobucavir (**5**) relied on a key S_N2 displacement of cyclobutyl tosylate **23**. Thus, the coupling between **23** and 2-amino-6-(benzyloxy)purine (**24**) assembled adduct **25**. Global removal of the three protective groups revealed the desired lobucavir (**5**).[10]



In conclusion, the conformational rigidity has bestowed the cyclobutane derivatives with unique properties. When applied appropriately, cyclobutyl scaffolds may offer advantages on potency, selectivity and pharmacokinetic profile.

References

1. Chen, K. X.; Njoroge, F. G. In *Antiviral Drugs: From Basic Discovery Through Clinical Trials,* Kazmierski, W. M., ed., Wiley: Hoboken, NJ, **2011,** pp 296–335.
2. Jung, M. E.; Ouk, S.; Yoo, D.; Sawyers, C. L.; Chen, C.; Tran, C.; Wongvipat, J. *J. Med. Chem.* **2010,** *53,* 2779–2796.
3. Wilber, R.; Kreter, B.; Bifano, M.; Danetz, S.; Lehman-McKeeman, L.; Tenney, D. J.; Meanwell, N.; Zahler, R.; Brett-Smith, H. In *Antiviral Drugs: From Basic Discovery Through Clinical Trials,* Kazmierski, W. M., ed., Wiley: Hoboken, NJ, **2011,** pp 401–416.
4. Anumala, U. R.; Waaler, J.; Nkizinkiko, Y.; Ignatev, A.; Lazarow, K.; Lindemann, P.; Olsen, P. A.; Murthy, S.; Obaji, E.; Majouga, A. G.; et al. *J. Med. Chem.* **2017,** *60,* 10013–10025.
5. Kono, M.; Ochida, A.; Oda, T.; Imada, T.; Banno, Y.; Taya, N.; Masada, S.; Kawamoto, T.; Yonemori, K.; Nara, Y.; et al. *J. Med. Chem.* **2018,** *61,* 2973–2988.
6. Vazquez, M. L.; Kaila, N.; Strohbach, J. W.; Trzupek, J. D.; Brown, M. F.; Flanagan, M. E.; Mitton-Fry, M. J.; Johnson, T. A.; TenBrink, R. E.; Arnold, E. P.; et al. *J. Med. Chem.* **2018,** *61,* 1130–1152.
7. Wada, Y.; Nakano, S.; Morimoto, A.; Kasahara, K.-i.; Hayashi, T.; Takada, Y.; Suzuki, H.; Niwa-Sakai, M.; Ohashi, S.; Mori, M.; et al. *J. Med. Chem.* **2017,** *60,* 3252–3265.
8. Popovici-Muller, J.; Lemieux, R. M.; Artin, E.; Saunders, J.O.; Salituro, F. G.; Travins, J.; Cianchetta, G.; Cai, Z.; Zhou, D.; Cui, D.; et al. *ACS Med. Chem. Lett.* **2018,** *9,* 300–305.
9. Pang, X.; Wang, Y.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2017,** *27*, 2803–2806.
10. Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; et al. *J. Med. Chem.* **1991,** *34,* 1415–1421.