Spirooxetanes in Drug Discovery

Key Points

- Combine the characteristics of both oxetanes and spirocycles.
- Offer enhanced aqueous solubility
- More extensive interactions with target proteins and more favorable physiochemical properties

Overview

Spirooxetanes combine the characteristics of both oxetanes and spirocycles. The oxygen atom on the oxetane may serve as a hydrogen bond acceptor, interacting with the target protein. The oxetane motif on a drug may also offer enhanced aqueous solubility and other physiochemical properties. Meanwhile, spirooxetanes, like most spirocycles, are bestowed with a trio of advantages: (a) More extensive interactions with target proteins; (b) more favorable physiochemical properties; and (c) potential novel intellectual properties.

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Spirocyclic oxetanes (spirooxetanes) combine characteristics of both oxetanes and spirocycles. As a bioisostere for dimethyl 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.

Spirocyclization provides rigidification of floppy molecules. Spirooxetanes[2] may be considered bioisosteres of oxetanes with a three-dimensional (3-D) geometry. Like most 3-D structures, spirooxetanes have a trio of advantages: (a) More extensive interactions with target proteins; (b) More favorable physio-chemical properties; and (c) Potential novel intellectual properties (IP).

With regard to bicyclic spirooxetanes, the other ring may be fused to oxetane at either the α- or β-position of the oxygen atom. The majority examples in the literature are the β-fused spirooxetanes.

Spirooxetanes in Drug Discovery

Only one spirooxetane-containing drug AZD1979 (**10**), a melanin-concentrating hormone receptor 1 (MCHr1) antagonist, has advanced to clinical trials for the treatment of diabetes (*vide infra*).

Pharmasset/Gilead's mega-blockbuster drug sofosbuvir (Sovaldi, **2**) is a phosphoramidate prodrug of ribonucleoside (ProTide) PSI-6130 (**1**).[3] As a hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase (RdRp)

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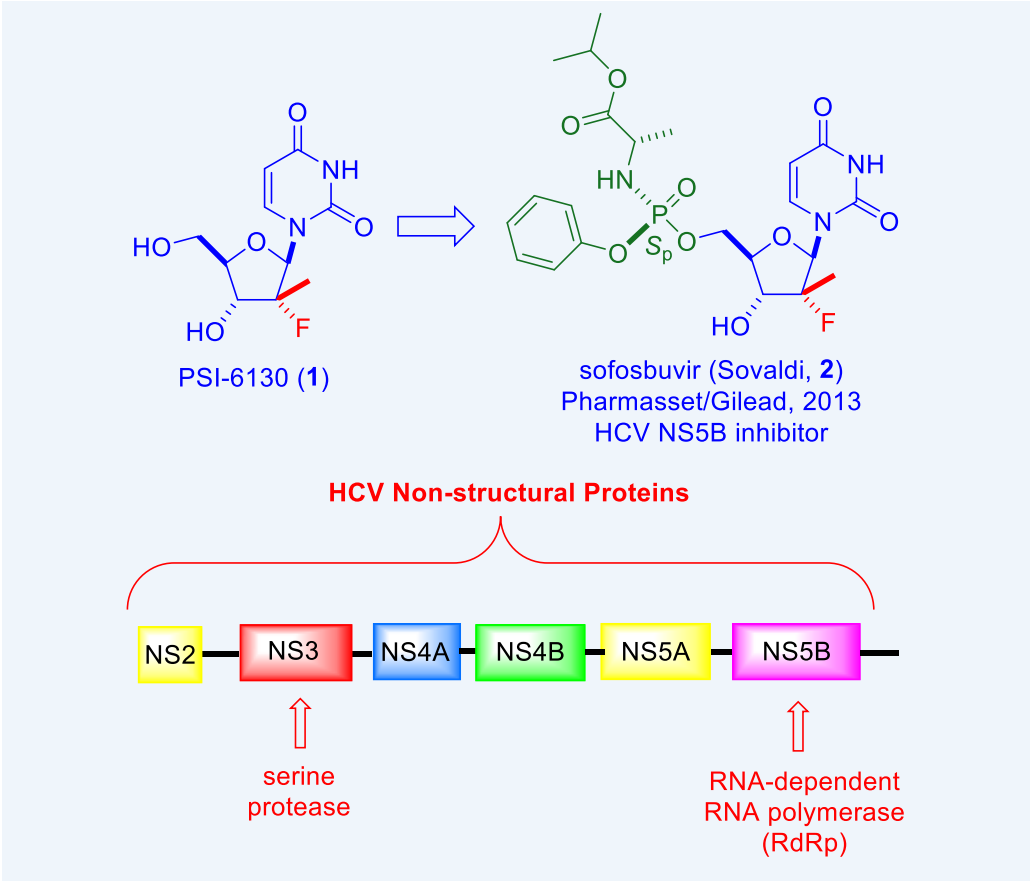
inhibitor, sofosbuvir (**2**) has contributed significantly to the cure of HCV as either a monotherapy or as an ingredient of combination drugs.



The fact that both PSI-6130 (**1**) and sofosbuvir (**2**) possess a tertiary 2′-carbon on the ribose ring suggests that sufficient space exists within the NS5B active-site to accommodate an additional atom especially if it resides within a constrained ring system. Pharmasset was inspired to explore novel 2′-spirocyclic ethers and this exercise led to the discovery of 2′-spirooxetanyl-nucleoside **3**, which was moderately active *in vitro* with an HCV replicon EC_{50} value of 56.6 μM and minimal cytotoxicity with a CC_{50} >100 μM. As in case of sofosbuvir (**2**), the corresponding phosphoramidate prodrug **4** was ten-fold more potent anti-HCV activity *in vitro* with an EC_{50} value of 16.7 μM and an excellent resistance profile.[4] As a side, *in vitro* activity for both drugs **3** and **4** are measured by the active 2′-deoxy-2′-spirooxetane uridine triphosphate (TP) **6** (*vide infra*).

Great minds think the same. Janssen came up exactly the same 2′-deoxy-2′-spirooxetane ribonucleoside **3** as a novel inhibitor of HCV NS5B polymerase.[5] Extensive prodrug exploration led to the discovery of NJ-

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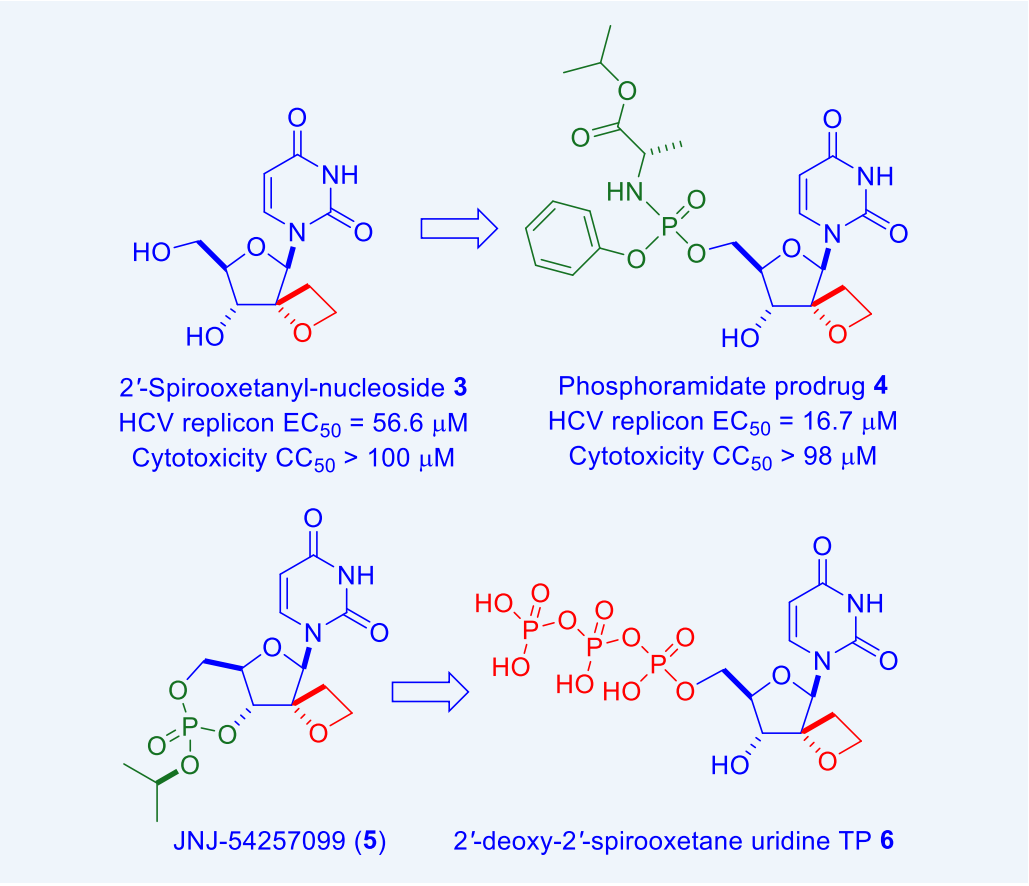
54257099 (**5**), a 3′,5′-cyclic phosphate ester prodrug.[6] The *in vitro* anti-HCV activities of NJ-54257099 (**5**) is not given here because it is inactive *in vitro*. Compounds **3**, **4**, and **5** may be considered prodrugs of 2′-deoxy-2′-spirooxetane uridine TP **6**, which is the *bona fide* actual active drug.



Checkpoint kinase 1 (CHK1) plays a key role in the DNA damage response, facilitating cell-cycle arrest to provide sufficient time for lesion repair. This leads to the hypothesis that inhibition of ChK1 might enhance the effectiveness of DNA-damaging therapies in the treatment of cancer. Many Genentech's 1,7-diazacarbazole ChK1 inhibitors, such as piperidine **7**, suffer from lack of selectivity against acetylcholine esterase (AChE) and are unsuitable for development. Efforts to mitigate AChE activity led to the discovery of spirooxetane **8** as a selective, orally bioavailable ChK1 inhibitor offering excellent *in vitro* potency with significantly reduced AChE activity.[7]

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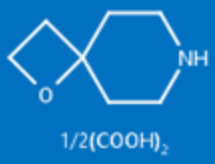

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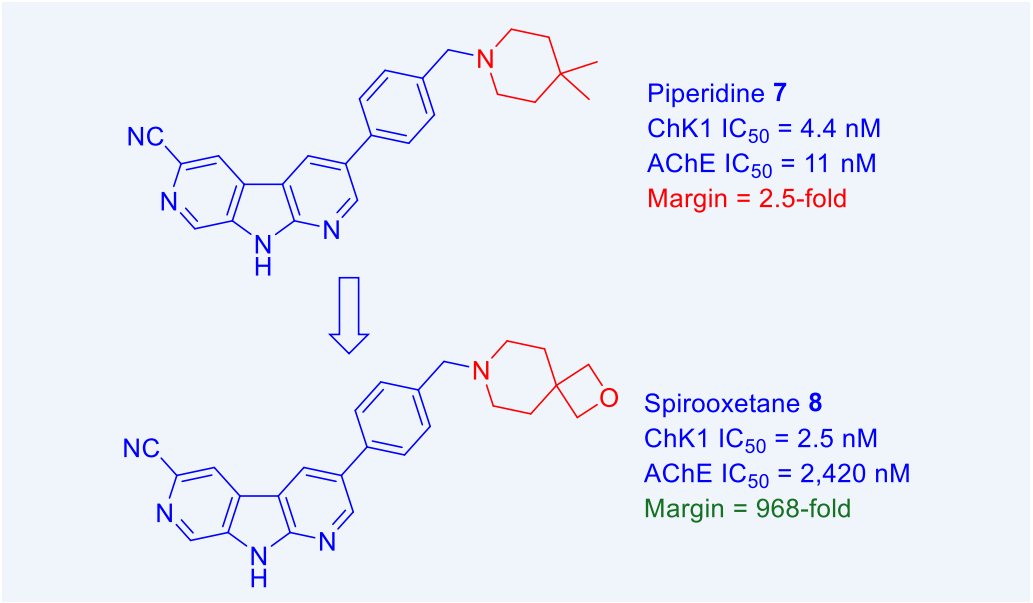
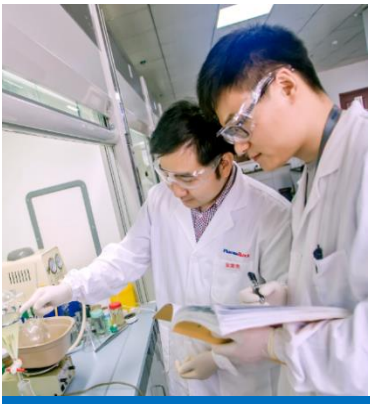


Melanin concentrating hormone receptor 1 (MCHr1) antagonists have been explored for weight control. AstraZeneca discovered a series of oxadiazole-containing compounds as represented by morpholine **9**. Their SAR efforts culminated in clinical candidate AZD1979 (**10**) with a novel peripheral spirooxetane moiety. Its peripheral spirooxetane (2-oxa-6-azaspiro[3.3]heptane) spirocycle is an isostere for morpholine. It displayed appropriate lipophilicity for a CNS indication, showed excellent permeability with no efflux, and possessed good off-target selectivity, including human ether-a-go-go (hERG) potassium channel activity. Preclinical good-laboratory practice (GLP) toxicology and safety pharmacology studies were without findings and AZD1979 **10** was taken into clinical trials for the treatment of diabetes.[8]

Not all spirooxetane isosteres work like a charm.

Leucine-rich repeat kinase 2 (LRRK2) inhibitors are potentially useful in the treatment of Parkinson's disease (PD). From high throughput screen (HTS) and lead optimization, Pfizer arrived at morpholine **11** (PF-06447475) as a highly potent (LRRRK2 enzymatic assay: IC_{50} = 3 nM), selective, brain penetrant, and *in vivo* active LRRK2 inhibitor. Attempt to replace the morpholino group with the 2-oxa-6-azaspiro[3.3]heptane isostere led to spirooxetane **12**, which was virtually inactive toward LRRK2, regrettably.[9]



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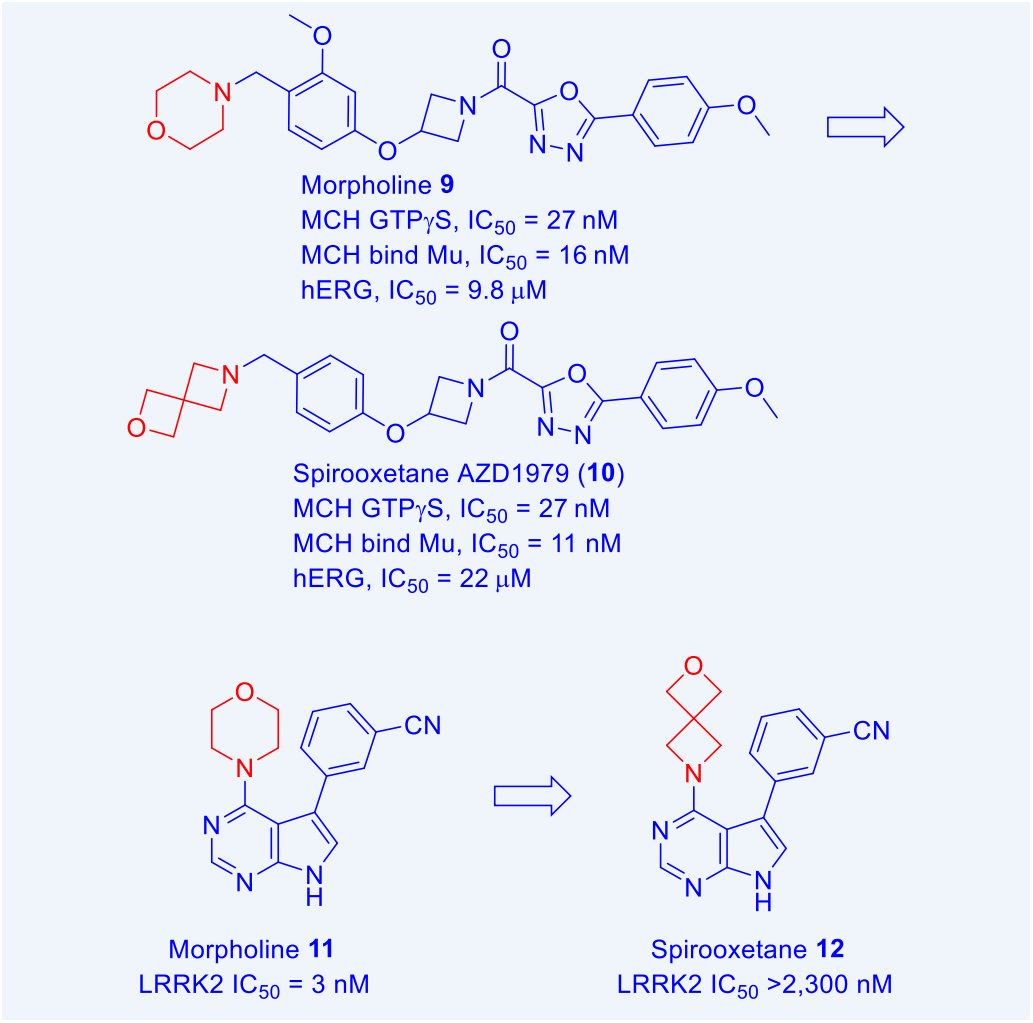

Synthesis of Some Spirooxetane-containing Drugs

Unlike most privileged building blocks, synthetic methodology developments for making spirooxetanes[2,10–17] are ahead of utility in medicinal chemistry. In other words, many spirooxetanes have been made, yet are waiting for applications in drug discovery.

Janssen employed D-ribose as the starting material to prepare 2′-spirooxetanyl-nucleoside **3**. It took five steps to manipulate D-ribose to compound **13**, which was protected as the glycosylation substrate **14**. With the aid of $SnCl_4$, coupling between **14** and persilylated uracil **15** gave uridine derivative **16** stereoselectively. After removal of the benzoate protective group, the resulting alcohol **17** was subjected to an oxidation and then reduction sequence, giving rise to diol **18**. The primary alcohol

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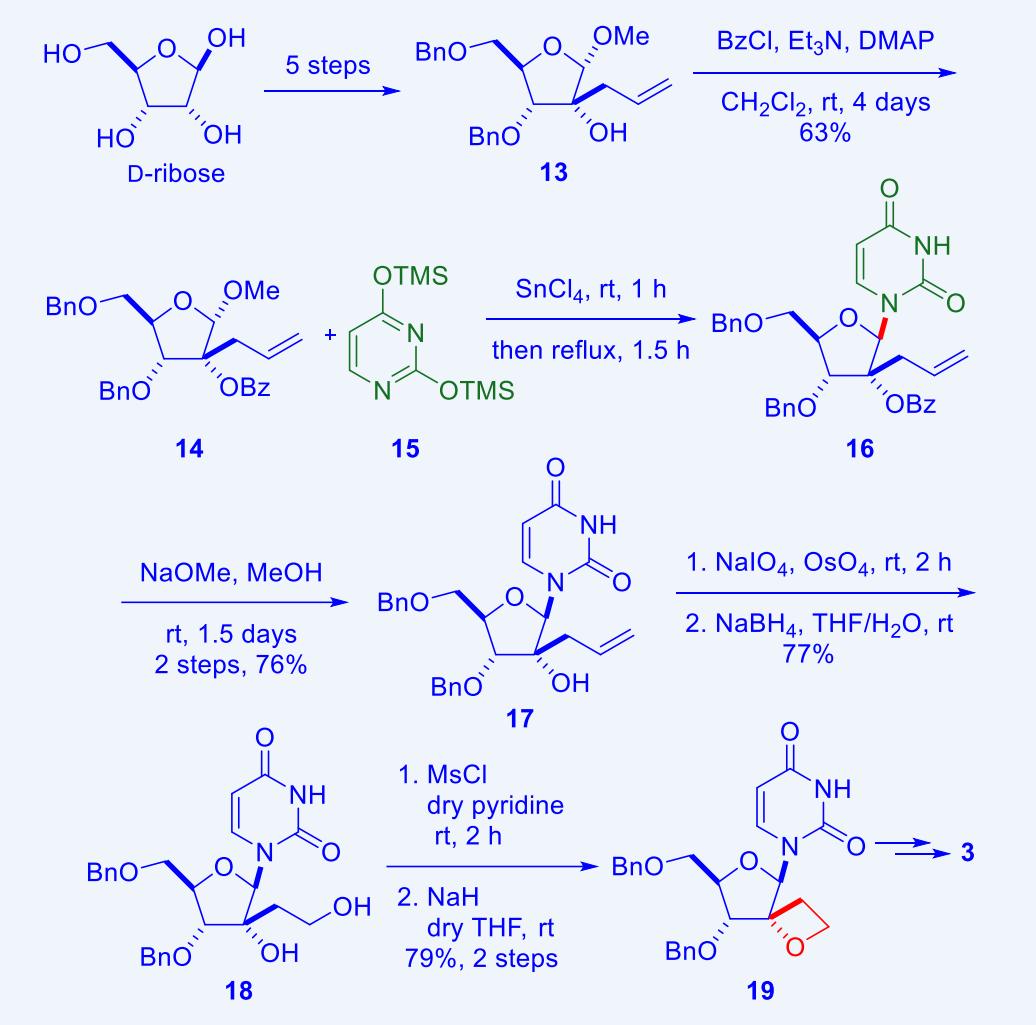
was selectively mesylated and the resulting mesylate was subjected to a sodium hydride-mediated cyclization to offer oxetane **19**. An additional four steps of functional group transformations the delivered 2′-spirooxetanyl-nucleoside **3**.[5]



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