

Building Blocks

Robust Solutions for Critical Issues
in Medicinal Chemistry

Polarized C-H as Nonconventional Hydrogen Bond Donor

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Canonical hydrogen bond donors, N-H and O-H, play key roles in interactions between molecules and proteins and exist in substantial drug and clinical candidate molecules, especially in kinase inhibitors which have a N-H forming a hydrogen bond with hinge region. Issues associated with canonical hydrogen bond donors are their potentially negative influences in aqueous solubility, permeability, glucosidation metabolism, etc. In order to circumvent this, C-H in heteroaromatic rings containing nitrogen is often used as nonconventional hydrogen bond donors due to the increased acidity of the involved C-H hydrogen. For example, C-H in pyrazine was found to form nonconventional hydrogen bonds with protein backbone and –COOH residues (**Figure 7**).^[1]

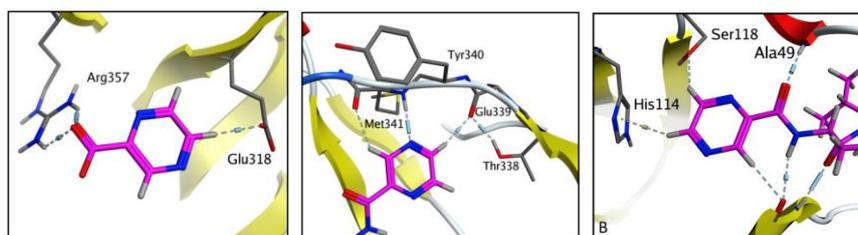


Figure 7. C-H in pyrazine ring as nonconventional hydrogen bond donors (PDB code: 4NNI, 3U4W respectively)

In order to discover BBB-penetrant LRRK2 inhibitors, replacement of indazole N1-H in compound **24** with imidazo[1,5-a]pyridine core C-H in compound **25** and “reverse indazole” C3-H in compound **26** was explored.^[2] Despite the anticipated loss in potency, significantly reduced P-gp efflux was observed for compound **26**, positively differentiating this core. Further optimization of compound **26** afforded highly potent, selective and BBB-penetrant LRRK2 inhibitors. A nonconventional hydrogen bond between C3-H in indazole with backbone C=O of LRRK2 Glu85 was demonstrated in an X-ray structure of one of LRRK2 inhibitors bound to LRRK2 (**Figure 8**).

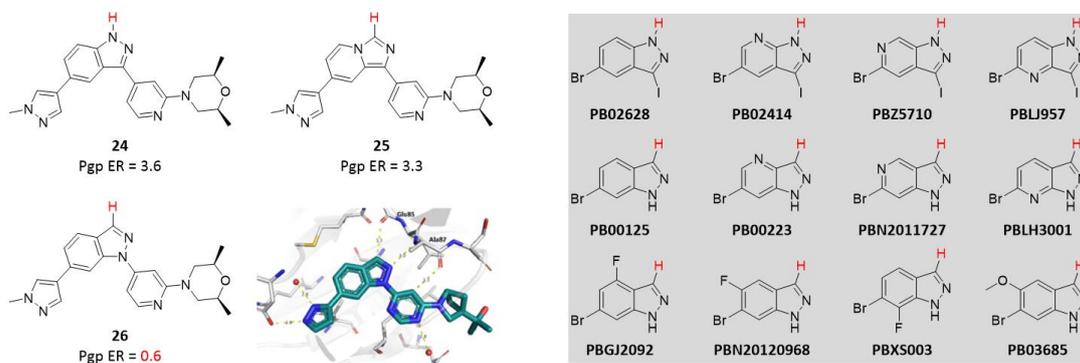


Figure 8. C3-H in “reverse indazole” was used as a nonconventional hydrogen bond donor. (PDB code: 8E80)

Polarization of the aryl C-H to increase the hydrogen bonding potential was believed to be necessary to bring about sufficient TYK2 activity and two point binding. With this strategy in mind, several [5,6]-fused heteroaromatic systems, including imidazopyridine scaffold in compound **27**, [1,2,4]triazole[1,5]pyridine scaffold in compound **28**, [1,2,4]triazole[4,3]pyridine scaffold in compound **29** and pyrazole[1,5]pyrazine scaffold in compound **30**, were designed and evaluated (**Figure 9**).^[3] Among of the above scaffolds, pyrazole[1,5]pyrazine scaffold was of particular interest due to the calculated increased polarization of the C-H for hydrogen bond donor properties. Consistent with calculation result, pyrazole[1,5]pyrazine analog **30** was found to be a potent TYK2 enzyme inhibitor at 10 nM. An X-ray crystal structure of compound **30** bound to TYK2 confirmed the

expected binding mode with polarized C7-H engaged in an interaction with the backbone C=O of TYK2 Val981. As proved by this case study, pyrazole[1,5]pyrazine scaffold could be potentially used as kinase hinge binding motif for discovery of kinase inhibitors, especially for that requiring BBB-penetration.

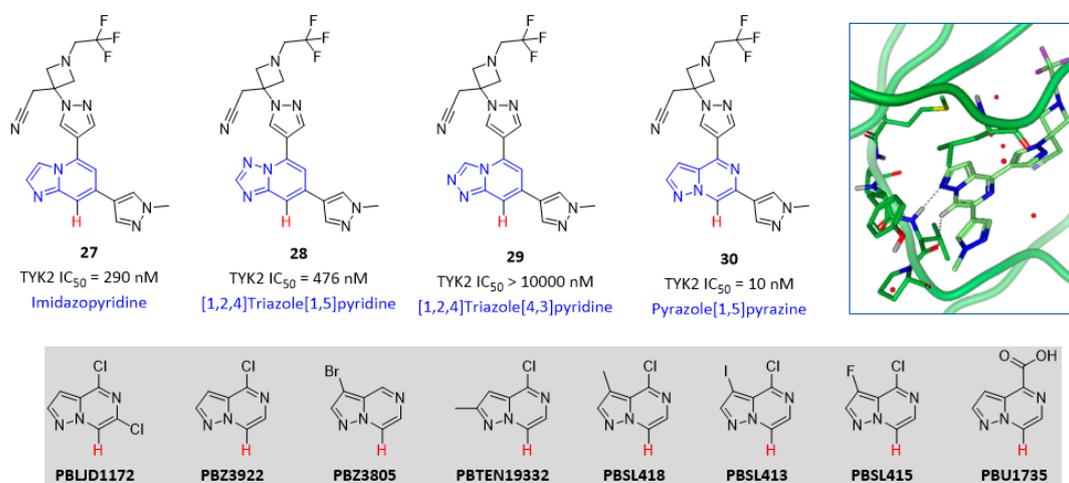


Figure 9. C7-H of pyrazole[1,5]pyrazine was used as a nonconventional hydrogen bond donor. (PDB code: 6X8F)

To better understand the origin of the increased potency and subtype selectivity of CK1 δ inhibitor **31**, an X-ray structure of compound **31** bound to CK1 δ was obtained. It was found that polarized C-H of lactam motif formed a nonconventional hydrogen bond with the backbone C=O of Leu85. Meanwhile, polarized C-H of pyridine formed an additional nonconventional hydrogen bond with the backbone C=O of Glu83 (Figure 10).^[4] Scaffold 6,7-dihydropyrrolo[3,4-b]pyridine-5-one could be utilized in the discovery of inhibitors of more kinases, since it potentially affords three hydrogen bonds with kinase hinge region.

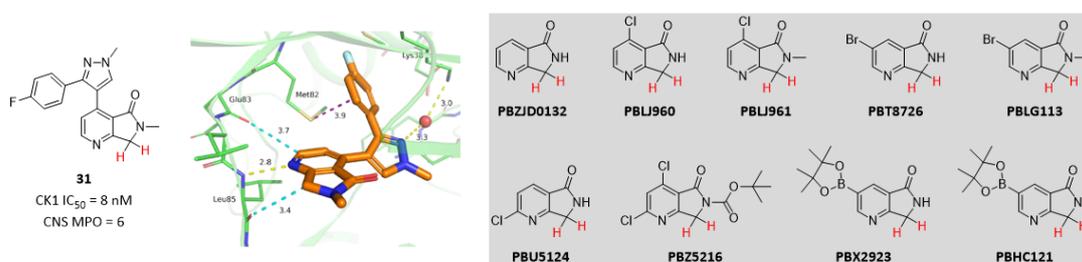


Figure 10. 6,7-Dihydropyrrolo[3,4-b]pyridine-5-one scaffold formed two nonconventional hydrogen bonds with CK1 δ hinge region. (PDB code: 5W4W)

References

- [1] Martin Juhas; *et al.* Molecular interactions of pyrazine-based compounds to proteins. *J. Med. Chem.* **2020**, *63*, 8901-8916.
- [2] David A. Candito; *et al.* Discovery and optimization of potent, selective, and brain-penetrant 1-heteroaryl-1H-indazole LRRK2 kinase inhibitors for the treatment of Parkinson's disease. *J. Med. Chem.* **2022**, *65*, 16801-16817.
- [3] Brian S. Gerstenberger; *et al.* Discovery of tyrosine kinase 2 (TYK2) inhibitor (PF-06826647) for the treatment of autoimmune diseases. *J. Med. Chem.* **2020**, *63*, 13561-13577.

[4] Travis T. Wager; *et al.* Identification and profiling of a selective and brain penetrant radioligand for in vivo target occupancy measurement of Casein kinase (CK1) inhibitors. *ACS Chem. Neurosci.* **2017**, *8*, 1995-2004.

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