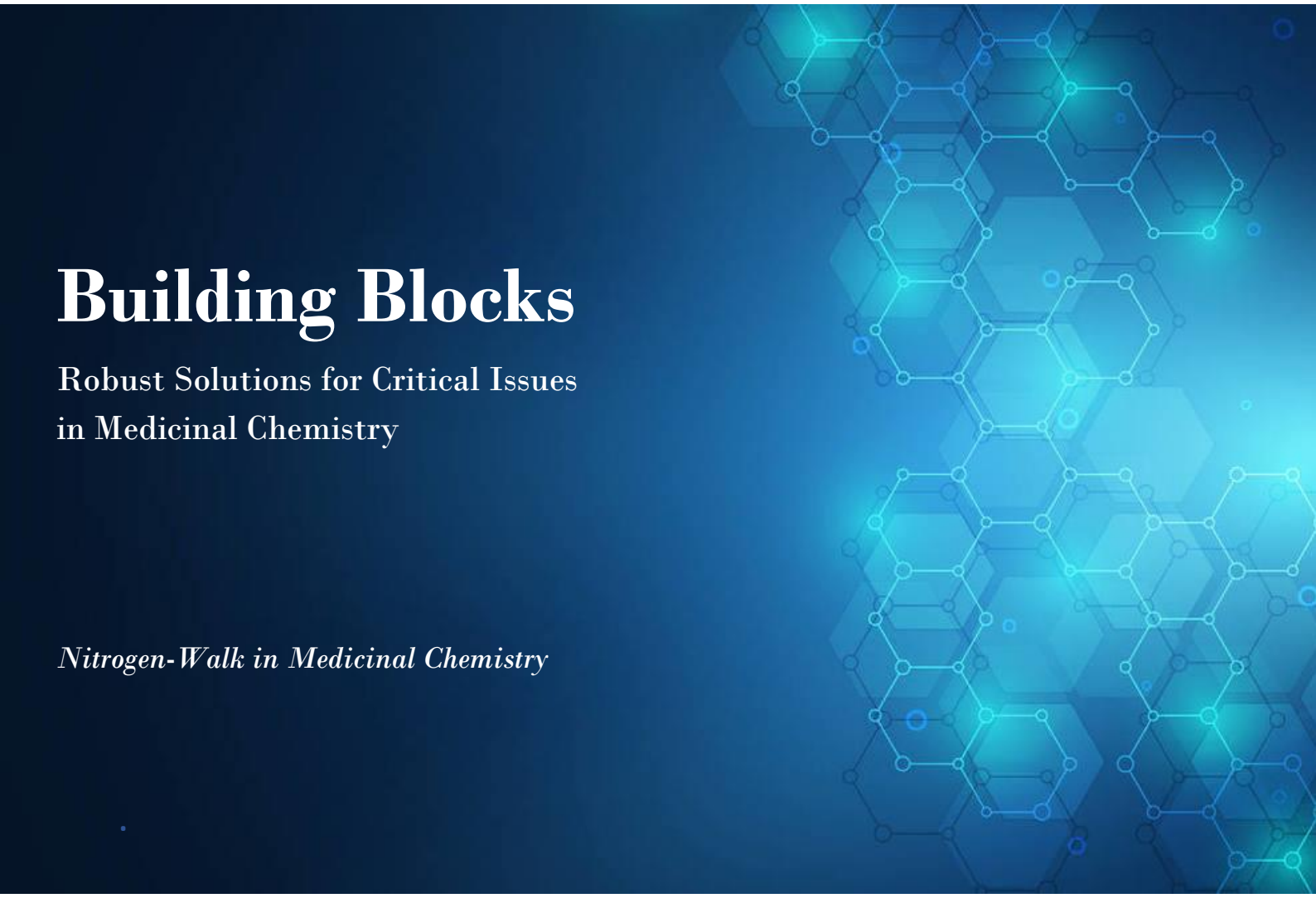

Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Nitrogen-Walk in Medicinal Chemistry

Nitrogen-Walk in Medicinal Chemistry

The replacement of a CH group with a N atom in aromatic and heteroaromatic ring systems can have many important effects on molecular and physicochemical properties and intra- and intermolecular interactions that can translate to improved pharmacological profiles. [1] Therefore, nitrogen-walk approach has been reported as a successful strategy to optimize biological activity, metabolic stability, and overall physicochemical properties. [2]

Nitrogen-walk on azaindole rings in compound **13**, **14**, **15** and **16** significantly impacted both potency and water solubility. Nitrogen at 7-postion of compound **16** afforded balance between potency and water solubility (Figure 4). [2] In the right of **Figure 4** are systematically designed azaindole building blocks bearing various functional groups for coupling reactions, supporting quick SAR and SPR explorations in medicinal chemistry campaign.

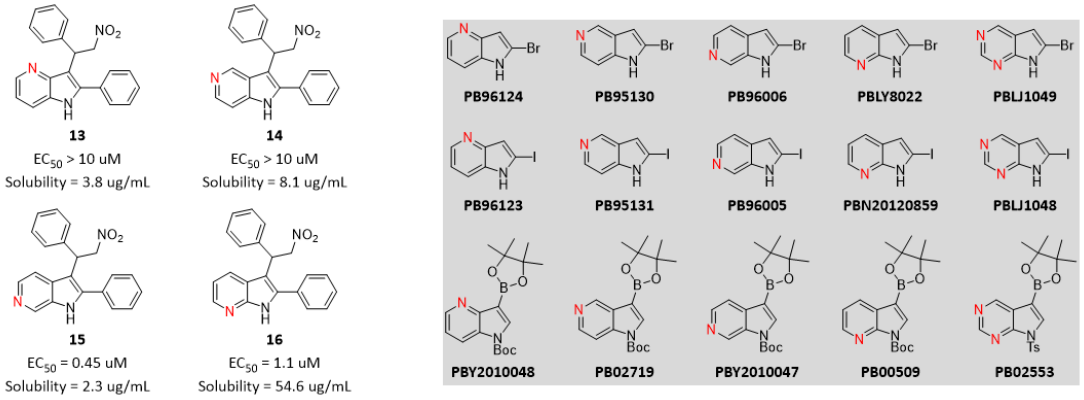

Figure 4. Nitrogen-walk on azaindole rings significantly impacted potency and solubility.

Nitrogen-walk from pyrazolo[4,3-b]pyridine **17** to pyrazolo[3,4-c]pyridine **18** yielded no significant increase in ALK2 inhibition. It was interesting additional nitrogen atom provided compound **19** with > 10-fold improved potency (**Figure 5**). [3] Dihalo- building blocks are the key starting materials for quick synthesis and evaluation of designed molecules.

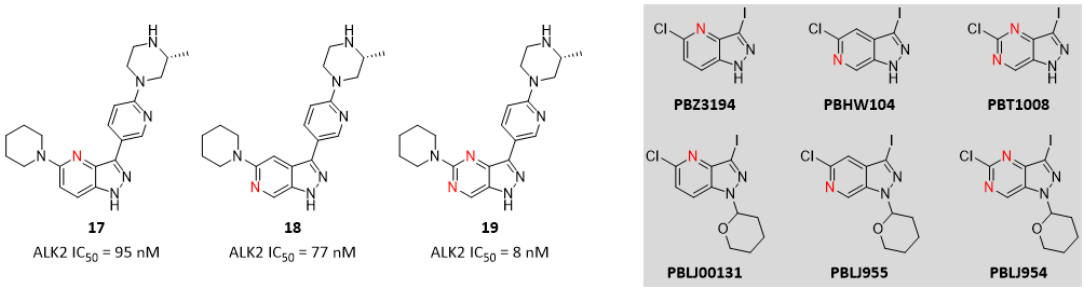

Figure 5. Nitrogen-walk on azaindazole rings impacted ALK2 inhibition.

Nitrogen-walk on pyridine rings in compound **20**, **21**, **22** and **23** gave extremely interesting results. Two nitrogen atoms in compound **20** and **23** are both ortho- to pyrazole ring, but **23** was proved inactive while **20** demonstrated high potency. Compound **21** with a meta- nitrogen and compound **22** with a para- nitrogen increased solubility dramatically while keeping high potency comparing to compound **20**. It was suggested that the polarity of ortho- nitrogen atom in compound **20** is somehow masked, possibly by an interaction with the lactam ring protons (**Figure 6**). [4]

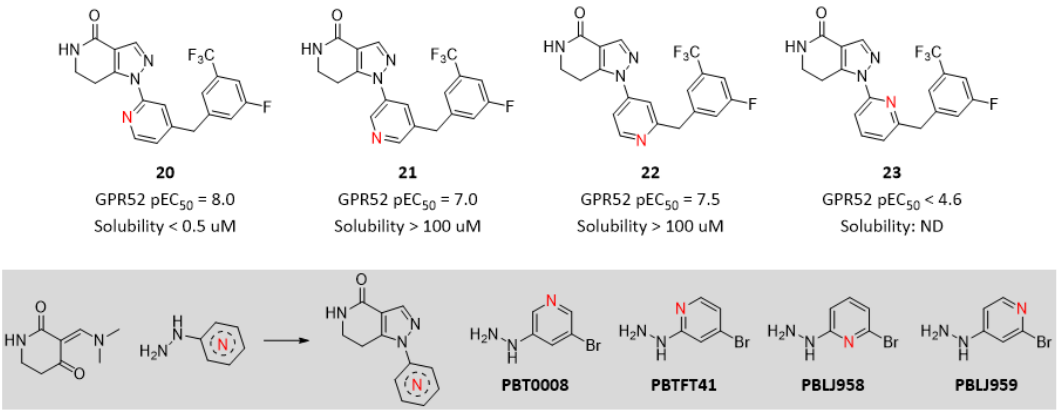

Figure 6. Nitrogen-walk on pyridine ring dramatically impacted potency and solubility.

References

[1] Lewis D. Pennington; *et al.* The necessary nitrogen atom: a versatile high-impact design element for multiparameter optimization. *J. Med. Chem.* **2017**, *60*, 3552-3579.

[2] Sumanta Garai; *et al.* Application of fluorine- and nitrogen-walk approaches: defining the structural and functional diversity of 2-phenylindole class of Cannabinoid 1 receptor positive allosteric modulators. *J. Med. Chem.* **2020**, *63*, 542-568.

[3] Minh H. Nguyen; et al. Discovery of novel pyrazolopyrimidines as potent, selective, and orally bioavailable inhibitors of ALK2. *ACS Med. Chem. Lett.* **2022**, *13*, 1159-1164.

[4] Simon Poulter; et al. The identification of GPR52 agonist HTL0041178, a potential therapy for schizophrenia and related psychiatric disorder. *J. Med. Chem.* **2023**, doi:10.1021/acsmedchemlett.3c00052.

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