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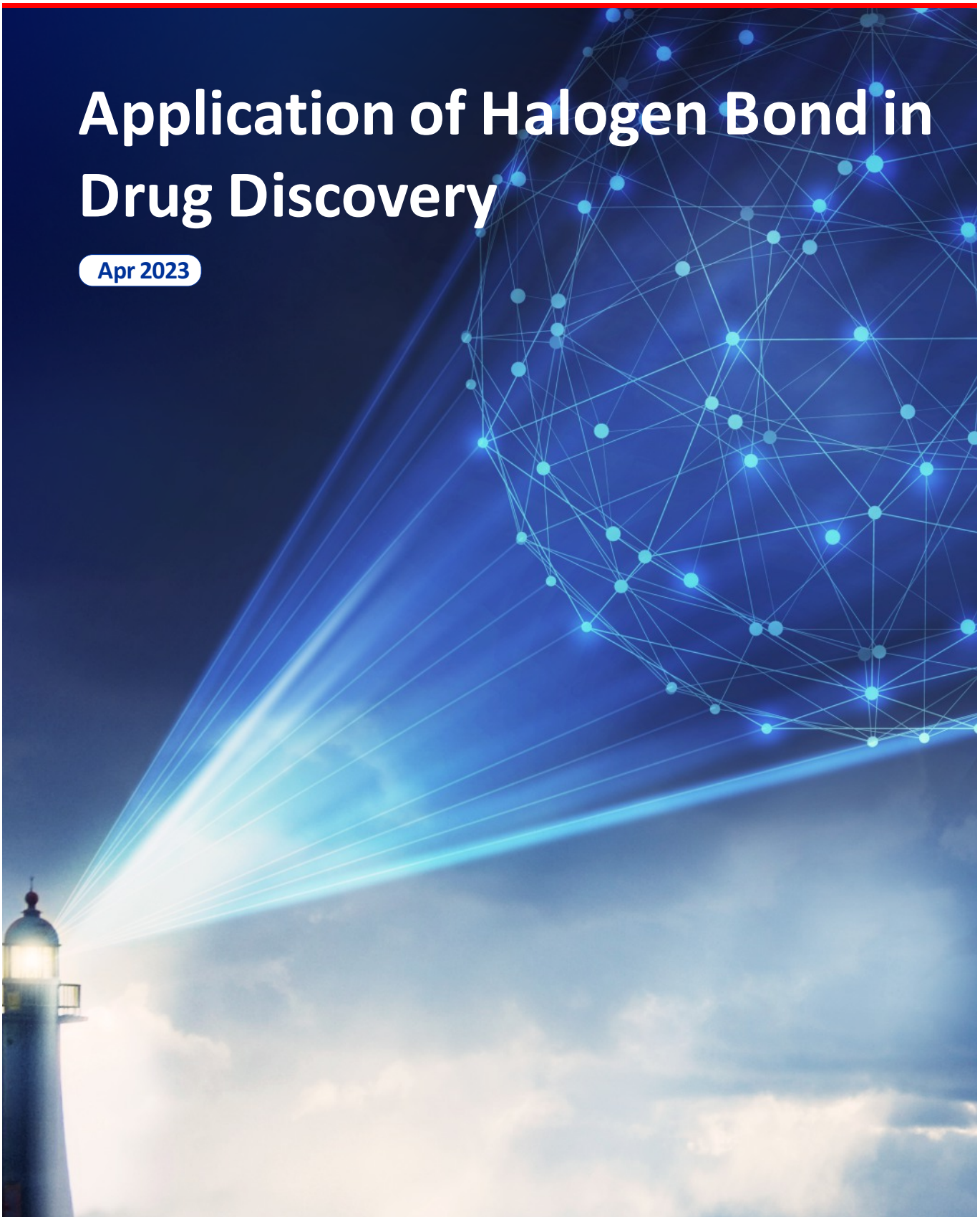
SCIENTIFIC INSIGHTS

Application of Halogen Bond in Drug Discovery

Apr 2023



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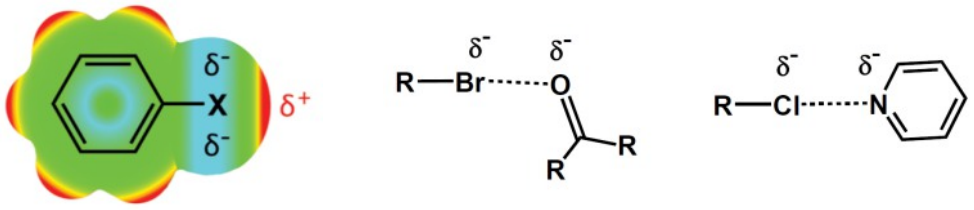
Introduction

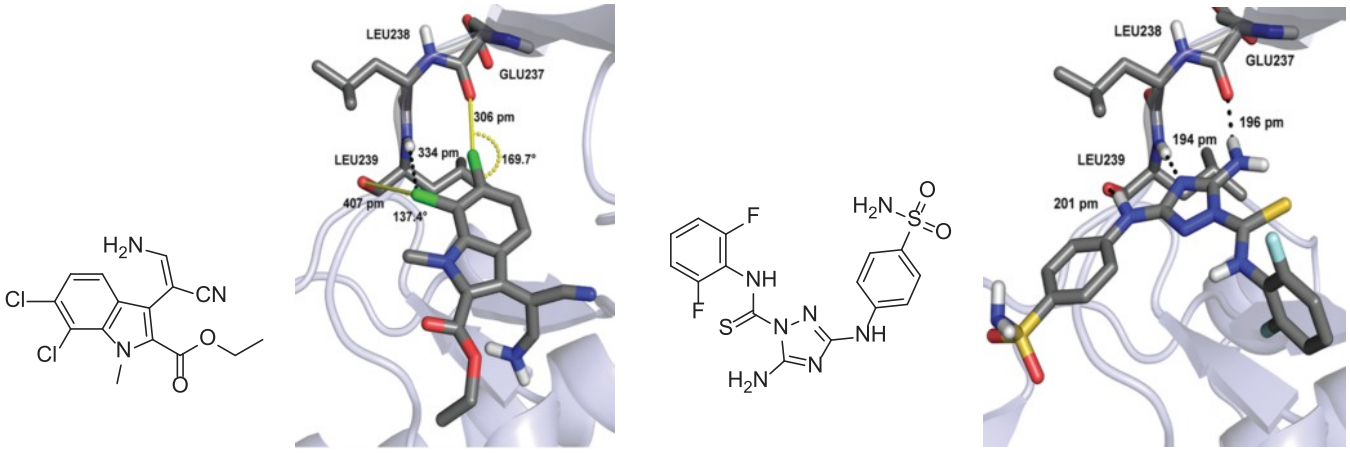
Halogen bond (XB) is a highly directional and specific interaction driven by the σ-hole, a positively charged region on the hind side of X along the R−X bond axis that is caused by an anisotropy of electron density on the halogen (**Figure 1a**) [1]. Halogen bond is formed between a covalently bonded halogen atom (XB donor) and a nucleophile (i.e., Lewis base; XB acceptor) (**Figure 1b**). In general, heavy halogens, such as -Cl, -Br and -I, can form halogen bonds while fluorine cannot[2].



a b

Figure 1: 1a) The anisotropy of the electron density on the Halogen. The positive surface potential (including the σ-hole on the halogen) is colored in red, and the negative surface potential is colored in light blue. 1b) Typical Halogen bonds: one covalently bonded halogen atom and a nucleophile. R-X... acceptor angle is close to 180°.

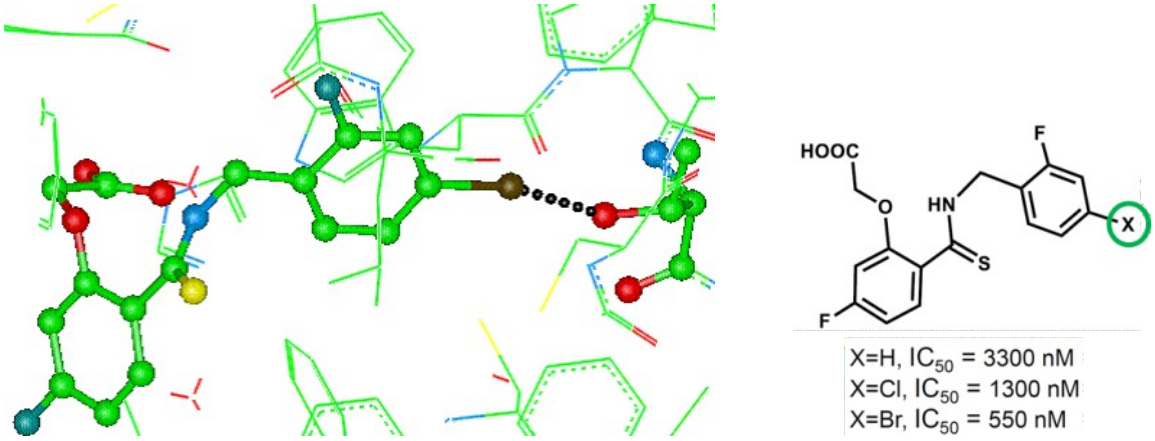
In protein−ligand environments, halogen bonds can be formed between a halogenated ligand and any accessible Lewis base in the binding pocket, such as the backbone carbonyl oxygen, hydroxyls in serine, threonine, and tyrosine, carboxylate groups in aspartate and glutamate, sulfur in cysteine and methionine, nitrogen in histidine, and the π surface of phenylalanine, tyrosine, histidine, and tryptophan[1]. One typical example is halogen atoms getting involved in the hinge region binding instead of the canonical hinge binders (**Figure 2**) [1].



a b

Figure 2: 2a) Kinase Hinge binding through two chlorine atoms with the with backbone carbonyl oxygens; 2b) Kinase Canonical Hinge binding by Hydrogen bonds.

Halogen bond has attracted a lot of attention in drug discovery for hit-to-lead-to-candidate optimization aiming at improving drug-target binding affinity over the past twenty years. The improvement of potency ranges from several folds (**Figure 3a**) [3] to many folds (**Figure 3b**) [4].



a b

Figure 3. Halogen bond can increase the potency several folds

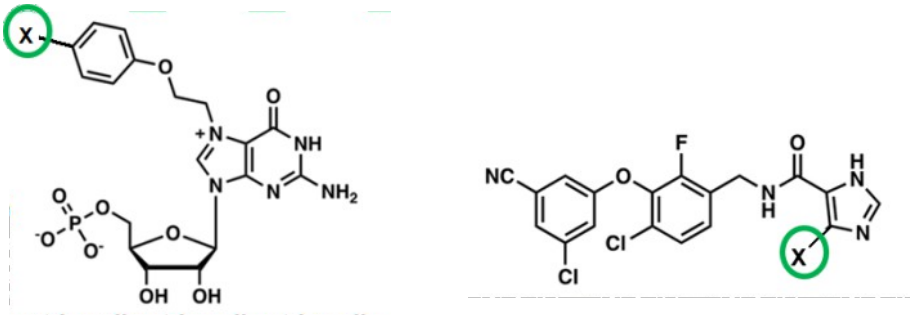
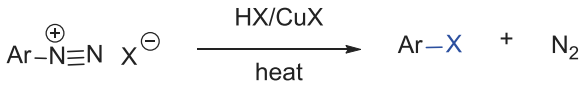


Figure 4. Halogen bond can increase the potency many folds

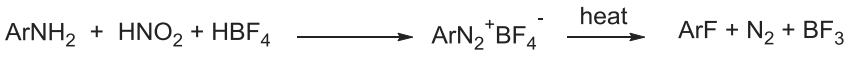
Synthesis of Aryl Halides

1) Substitution of diazonium groups in aromatic compounds by halo.

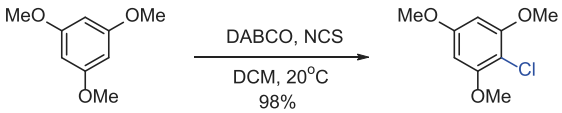


Substitution of diazonium groups in aromatic compounds by halo or cyano groups in the presence of cuprous salts (Sandmeyer reaction), copper powder and hydrochloric or hydrobromic acid (Gattermann reaction) or cupric salts (Körner-Contardi reaction).

Formation of diazonium fluoroborates by diazotization of aromatic amines in the presence of fluoroborates, followed by their thermal decomposition to aryl fluorides (Balz-Schiemann reaction):

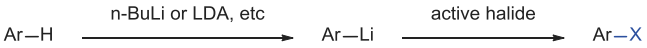


2) Electrophilic addition of aromatic compounds

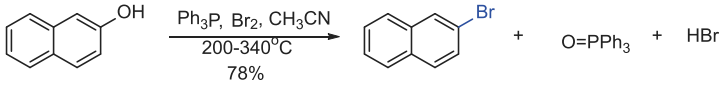


RSC Advances, 2022, 12, 7115 - 7119

3) Reaction of aryl lithium and active halide (Br2, CBr4, 1,2-dibromotetrafluoroethane, I2, hexachloroethane, NFSI, etc).

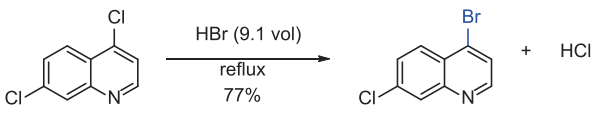


4) Bromination of phenols



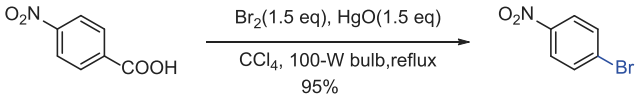
Organic Syntheses, Coll. 1973,5,142 ; 1969,49, 6

5) Halogen exchange reaction



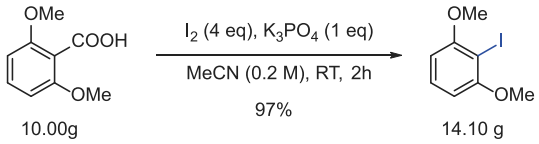
Journal of the American Chemical Society, 1959, 81, 3984-9

6) Photoassisted Cristol-Firth-Hunsdiecker reaction

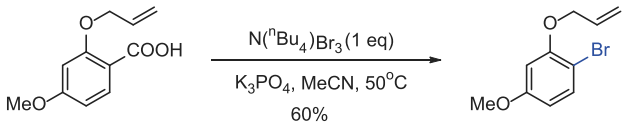


Journal of Organic Chemistry, 1979, 44, 3405-6

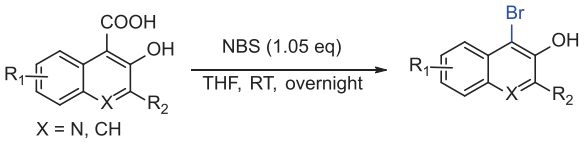
7) Decarboxylation halogenation



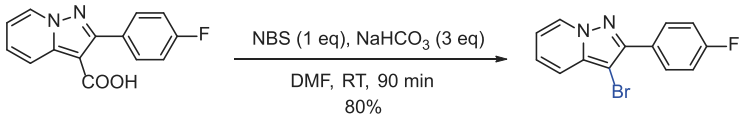
J. Am. Chem. Soc. 2017, 139, 11527−11536



J. Name., 2013, 00, 1-3

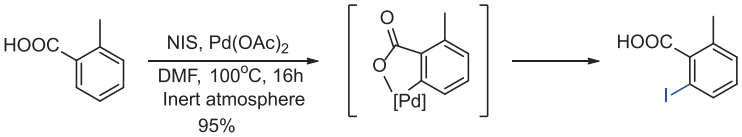


J. Org. Chem. 2009, 74, 8874–8877



Organic Letters, 2005,7, 4753-4756

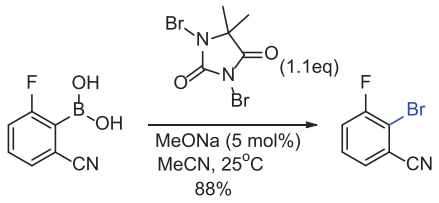
8) Ortho-iodination reaction of benzoic acid derivatives via directed ortho-palladation followed by metal–iodine exchange



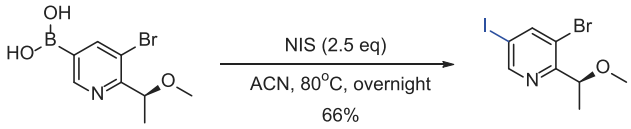
US2013/5705

Chemistry - A European Journal, 2009, 15, .5956 - 5968

9) Halodeboronation of aryl boronic acids



J. Org. Chem. 2004, 69, 566-569



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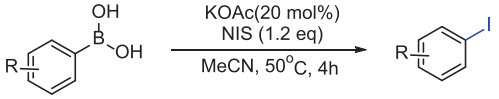
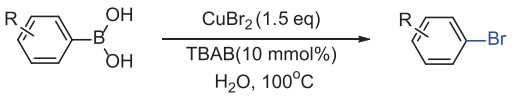


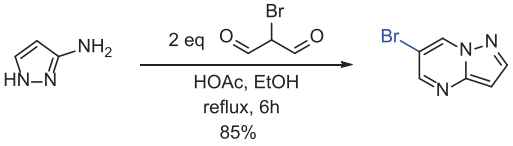
Organic Letters,2019, 21, 2488-2492



- Ligand-free and base-free
- functional group tolerable
- Gram-scale reaction

Tetrahedron Letters, 2021, 64, 152738

10) Using aliphatic brominated compounds as starting materials



Bioorganic & Medicinal Chemistry, 2021, 52, 116522

Building Blocks Containing Halogen Bonds

PharmaBlock has conducted a systematic study of clinical and preclinical drug molecules, and our chemists continue to pay attention to the latest research, design and synthesize a large number of halogenated organic compounds , which can be used to explore structure-activity relationship (SAR) and structure-property relationship (SPR). We offer more than 10000 unique heterocyclic building blocks, ranging from grams to kilograms, most of which are in stock (**Figure 5**).

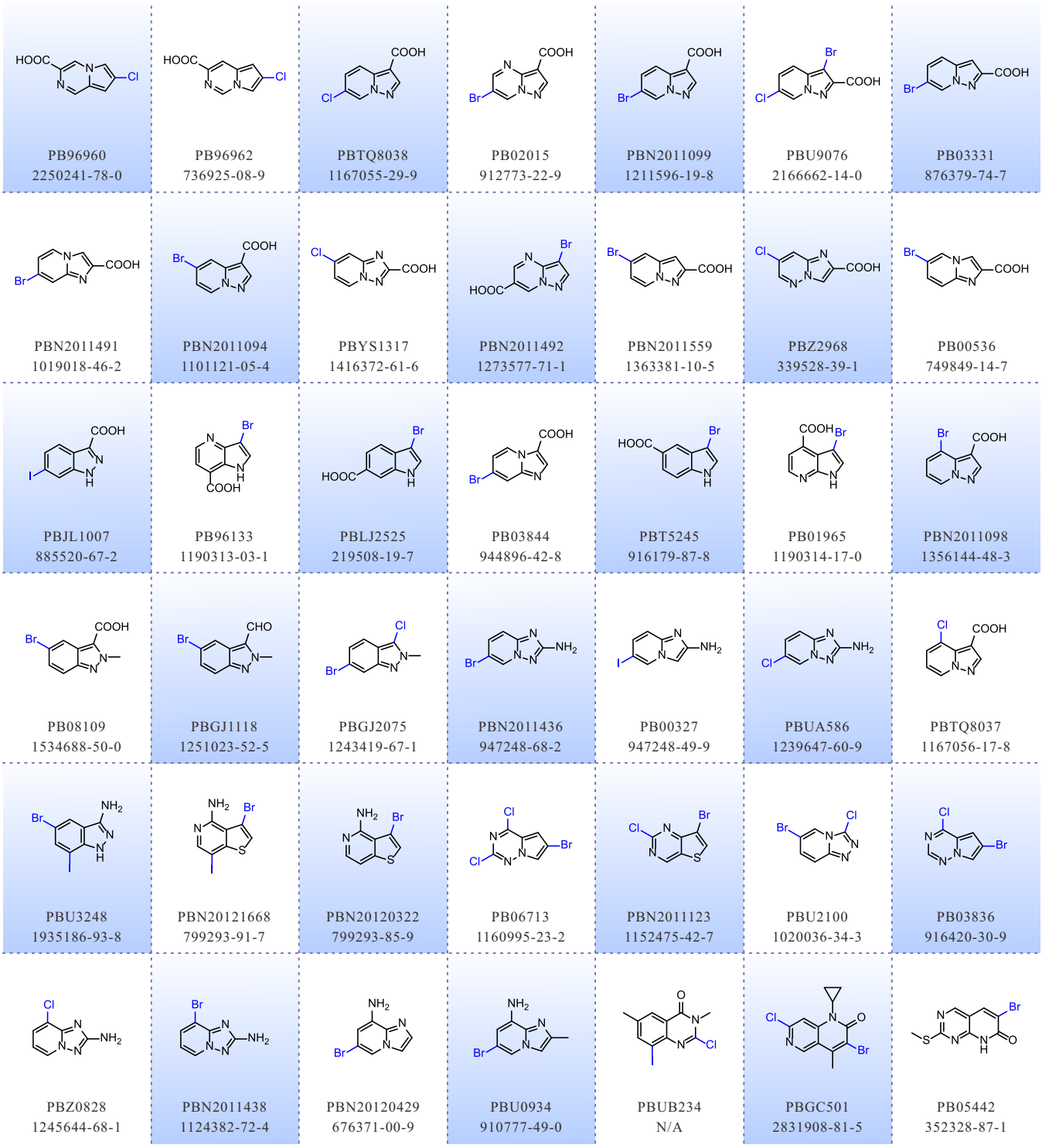


Figure 5. Representative building blocks containing halogen bonds at PharmaBlock

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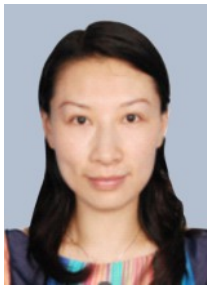

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