Since the ATP-binding site is highly conserved, most small molecule kinase inhibitors have various kinase inhibiting activities. Therefore, two or more kinase targets can be simutaneously inhibited by the same molecule, i.e., multitarget kinase inhibitor. However, varied kinase inhibitory activity also leads to toxicities or side effects, such as hypertension and cardiotoxicity[45]. Thus, improving the inhibitory selectivity and/or reducing toxicities of theraputic tagets should be priortized when developing SMKIs. Data recently reported in the literature indicate that kinase inhibitory selectivity is closely related to the structural modification in the pyrrole moiety in this scaffold. Recent research shows that replacing the pyrrole moiety into other aromatic rings also influences kinase inhibitory selectivity. For instance, nintedanib (**13**) received FDA approval for use in targeting VEGFR, FGFR, and PDGFR in the treatment of non-small-cell lung cancer (NSCLC) in 2014[46].

Structural Modification of Oxindole Moiety

The oxindole moiety of pyrrole indolin-2-ones can provide two hydrogen bonds, which are critical for the binding of pyrrole indolin-2-ones to the ATP-binding site of the kinases, i.e., VEGFR-2, FGFR-1, and PDK-1[4,22,23,28-31,39,42,47]. The C(5) and C(6) positions of the pyrrole indolin-2-ons are considered as one of most effective positions for interaction with the ATP-binding site[20-30,48]. Since substitutions on C(5) and C(6) could substantially affect ligand protein binding affinity, these sites of the oxindole moiety are the most commonly selected for structural modification.

Modification on N(1)

Prodrugs of semaxanib (**2**) and sunitinib (**3**) are usually generated by linking squalene to their N(1) positions[49]. The squalenoyl prodrugs can form nanoparticles and can be activated by changing pH in the body[49]. Another example of the sunitinib prodrug is *N*-hydroxylmethylsunitinib (AST-004), which is activated via hydrolysis catalyzed with esterase[50]. This prodrug can also reduce the toxicity of sunitinib (**3**)[50]. Introducing a 3-dimethylaminopropyl to N(1) of the pyrrole indolin-2-ones led to the discovery of compounds **14** which display various anti-tumor activities[51].

Modification on C(5) and C(6)

Replacement on C(5)-halogen is the most common modification of the oxindole moiety of the pyrrole indolin-2-one derivatives, which have excellent overall inhibiting activities against VEGFR-2 and PDGFRβ[22,28,33,34,42-44,52]. The C(5)-halides form hydrophobic interaction between the ligand and the hydrophobic pocket II of the ATP-binding site. However, bioisosteric replacement of C(5)-halogens with C(5)-CF_3 does not improve inhibition activity against VEGFR-2 and PDGFRβ[39,41]. Linking the alkyl groups or aromatic rings with sulfonamides, amides, or a urea bond to C(5) or C(6) is very common in the modification on the oxindole moiety[18,21,23,27-29,42]. The products provide the best possible activity by enabling additional hydrogen bonding interactions. Alkyl or aromatic groups might also enable further hydrophobic interactions with the hydrophobic pocket II of the ATP binding site. The effect of a methoxy group at C(5) of the oxindole moity on kinase inhibitory activity and selectivity is highly dependent on the C(3) substituents of indolin-2-one[23,47,52]. Introducing a -OH or a -SH to the C(5) position of the oxindole moity of the five-membered heterocycle fused pyrrole indolin-2-ones significantly improves inhibitory activity against VEGFR-2 and PDGFRβ[28].

The pyrrole indolin-2-one derivatives can be turned into irreversible kinase inhibitors by introducing a chloromethylketone, a chloroacetamide, or other Michael acceptors to generate Nek2 selective inhibitors[24].

In summary, pyrrole indolin-2-one analogues are most promising in kinase inhibitor development. Among the structural modifications, pyrrole indolin-2-ones with substitution of halides on C(5), such as sunitinib (**3**), approved by the FDA, and famitinib (n = 1, R_{11}: -F in **12**), tested in phase III clinical trial for colorectal cancer treatment, possess superior inhibitory activity against VEGFR-2 and PDGFRβ[53]. Apart from C(5)-halide substituents, the kinase selectivity and activity of other C(5) or C(6) substituted (e.g., -OMe, -OH, COOMe, -SH) pyrrole indolin-2-ones depend on the modification of the pyrrole moiety. It is noted, however, that some adverse reactions, such as hypertension and cardiotoxicity, were still observed in clinical trials[45]. To improve the safety and promote the quality of life of patients, further investigation for novel compounds with better activity/selectivity and lower toxicity is needed.

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