

# Pyrrole indolin-2-One Based Kinase Inhibitor as Anti-Cancer Agents

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## Article Info

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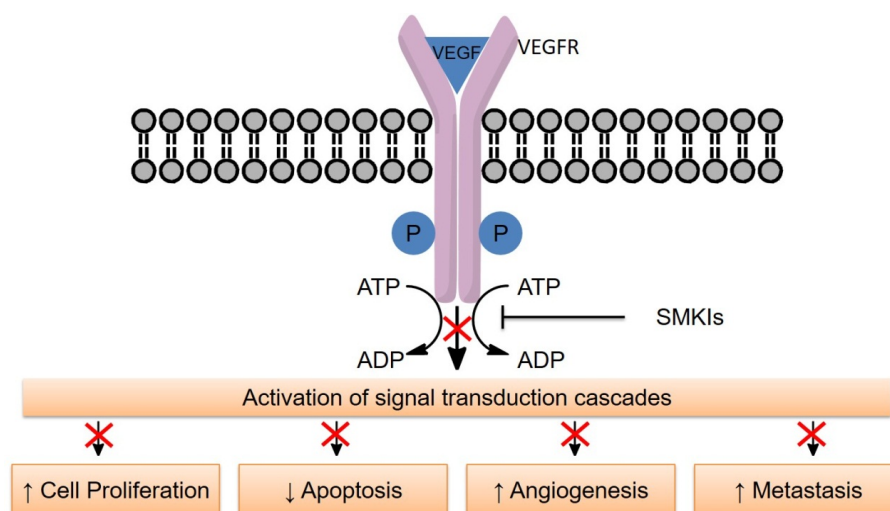
## ABSTRACT

Cancer cells are characterized by uncontrolled proliferation after escaping from inherent physiological constraints on growth and survival and by destructive invasion of the healthy surrounding tissues. Many kinases involved in signal transduction are overactive in malignant tumor cells. Thus, pharmacotherapeutic interventions targeting kinases responsible for signal transduction of cancer hallmarks have become promising in developing novel anticancer agents. Pyrrole indolin-2-one (or pyrrole oxindole, **1**), a lead scaffold of kinase inhibitors, is used for anti-angiogenesis via inhibiting vascular endothelial growth factor receptors (VEGFs) and platelet-derived growth factor receptors (PDGFRs). The kinase selectivity and inhibitory activity of pyrrole indolin-2-one **1** can be significantly influenced through structural modifications. This mini-review provides a detailed overview of structural modification of pyrrole indolin-2-one derivatives for the development of novel kinase inhibitors.

## Introduction

The activity of proteins or enzymes can be enhanced after phosphorylation by specific protein kinase. Protein phosphorylation is a fundamental mechanism of signal transduction used by all cells to regulate their protein properties in response to external or internal signals<sup>1</sup>. Phosphorylation and dephosphorylation regulates most cellular functions in both normal and abnormal cells<sup>2</sup>. For instance, kinase signal transduction is involved in many of cancer hallmarks such as stimulating cell proliferation, survival, and tumor induced angiogenesis, which is critical for supplying oxygen, nutrients, and paths of metastasis of tumor tissues<sup>3,4</sup>. Additionally, tumor-induced angiogenesis can be stimulated by many pro-angiogenesis growth factors, such as angiopoietin-2, epidermal growth factors (EGFs), fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs), and platelet-derived growth factors (PDGFs)<sup>5</sup>. Among them, VEGFs, PDGFs, and their receptor tyrosine kinases (RTKs) play key roles in tumor angiogenesis signal transduction<sup>6</sup>. Therefore, most small molecule kinase inhibitors (SMKIs) can inhibit cancer cell proliferation by inhibiting RTKs of VEGFs and PDGFs, can block the downstream signal pathways, such as proliferation, migration, and enhance cell survival of endothelial cells, fibroblast, and vascular smooth muscle cells (Figure 1)<sup>7-10</sup>. Recently, several small-molecule anti-angiogenesis agents targeting VEGFRs and PDGFRs have been developed and approved for clinical use.

Pyrrole indolin-2-one **1** is known to be a critical structures in some inhibitors of receptor tyrosine kinases (RTKs). Semaxanib (SU5416, **2**), a derivative of pyrrole indolin-2-one **1**, was the first example of these tested clinically as a potent RTK inhibitor of VEGFRs



**Figure 1:** Small molecule kinase inhibitors (SMKIs) inhibit the proliferation of cancer cells by blocking the downstream signal pathways.

and PDGFRs for anti-angiogenesis, although not licensed for use<sup>11</sup>. Among the most potent anti-angiogenesis and anti-cancer agents is sunitinib (**3**), which is produced by structural modification of semaxanib and approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) in 2006<sup>11</sup>. Sunitinib was the first cancer drug simultaneously approved for two different indications. In 2011, sunitinib was approved by the FDA for treating patients with progressive neuroendocrine cancerous tumors located in the pancreas that cannot be removed by surgery or that have metastasized<sup>11</sup>. Sunitinib inhibits cellular signaling by specifically targeting multiple kinases, including VEGFRs, PDGFRs, aurora kinases (A, B and C), RET, Flt-3, Yes, Src, CSF-1R, and c-Kit<sup>12-17</sup>.

The ATP-binding site of the RTK can be divided into six regions: adenine pocket, specific pocket, hydrophobic pocket I, hydrophobic pocket II, ribose binding region, and phosphate binding region<sup>18</sup>. Since the ATP-binding sites of RTKs are highly conserved, most SMKIs targeting the ATP-binding site show a broad kinase inhibitory activity. Therefore, structural modification of small molecule RKTs has become a very important strategy for improving the selectivity and activity of kinase inhibition<sup>19</sup>. Structure-activity relationships (SARs) of the pyrrole indolin-2-one derivatives have been comprehensively investigated in previous works<sup>20-31</sup>. Both the crystal data and molecular modeling data demonstrate that the C(3') amino tail of pyrrole indolin-2-one derivatives is exposed to the solvent region of the ATP-binding sites<sup>24,28-30,32,33</sup> and has a critical influence on the solubility of the pyrrole indolin-2-one derivatives<sup>33,34</sup>. Additionally, the C(3') amino tail can be further modified to target the pyrrole indolin-2-ones to some specific cell, organelle, or protein, such as mitochondria<sup>35-38</sup>. The oxindole moiety (herein oxindole

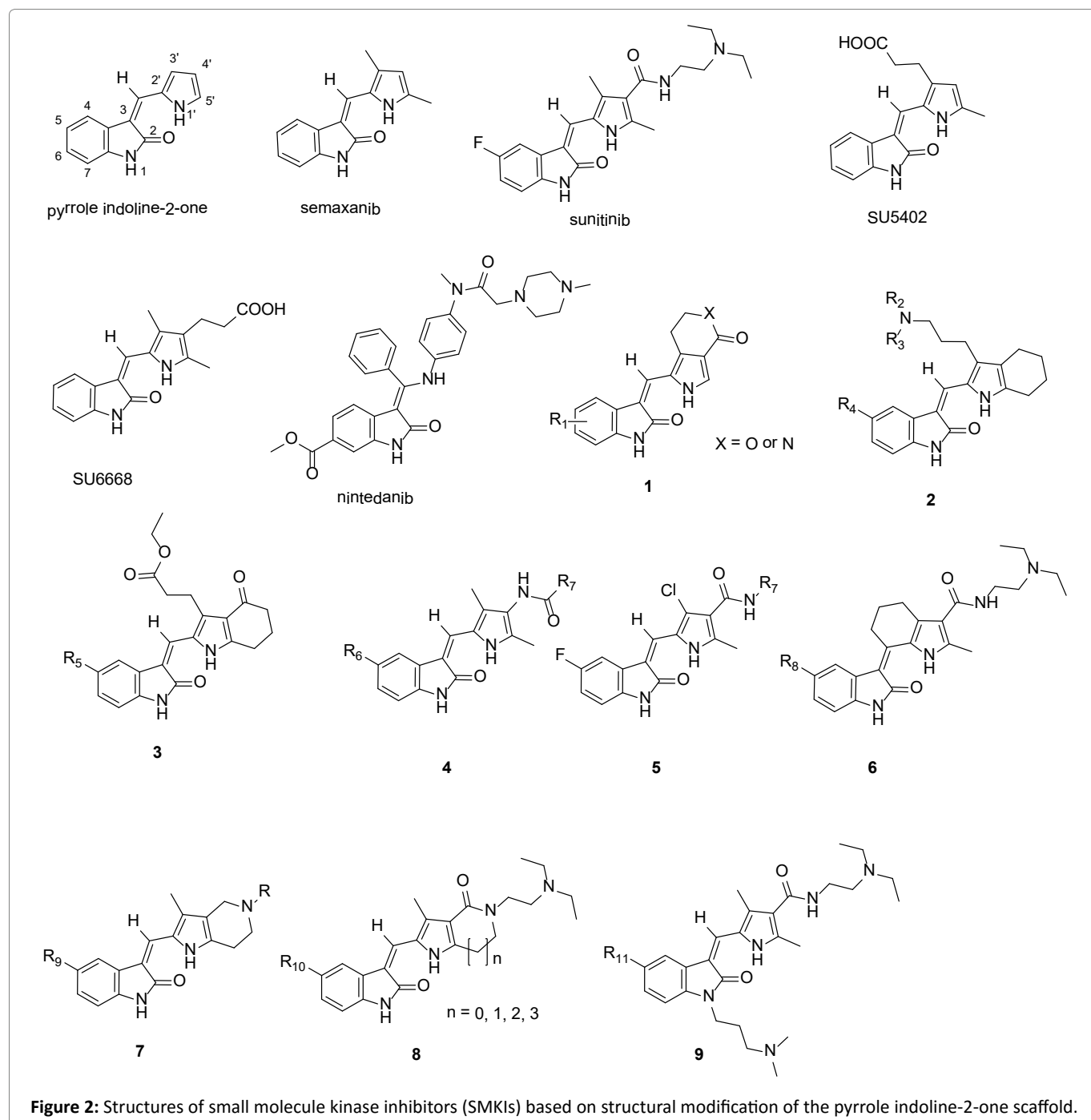
means the C(2) of indole is oxidized), which is the key fragment in the binding affinity of kinases and pyrrole indolin-2-ones, occupies the adenine pocket, forming two hydrogen bonds with kinases<sup>4,22,30,39</sup>. Finally, appropriate substitutions of the oxindole moiety can enhance affinity by increasing kinase interactions<sup>4</sup>.

This mini-review provides an overview of the development of SMKIs based on structural modification of the pyrrole indolin-2-one scaffold **1** (Figure 2).

### Modification of Pyrrole Moiety

The pyrrole moiety of the pyrrole indolin-2-one scaffold **1** binds to the hydrophobic pocket I of the ATP-binding site of kinases, which is also known as the selective pocket<sup>18,40</sup>. Modification of the pyrrole moiety of the pyrrole indolin-2-ones, therefore, can positively affect kinase inhibition selectivity. First, lactamization or lactonization of C(3') and C(4') of the pyrrole of pyrrole indolin-2-ones produced compounds **5** and were found to change the selectivity of cyclin-dependent kinases (CDK)<sup>31</sup>. Compared to semaxanib (SU5416, **2**) and SU5402 (**4**), the tetrahydroindole-containing **6** have stronger Src inhibiting effects and a broad range of VEGFR-2 and PDGFR $\beta$  inhibiting effects. Obviously, the scaffold of compounds **6** is a possible structure unit in the determination of the activity and selectivity of Src inhibition<sup>17</sup>.

Fusing the pyrrole moiety with 4'-oxo-4',5',6',7'-tetrahydroindole and introducing a carboxyethyl group to the side chain attached on C(3') obtains compounds **7**, which increase inhibitory activities of Aurora A and Aurora B<sup>41</sup>. Changing the carboxamide bond of sunitinib (**3**) through bioisosterism (amide-acyl bond) resulted in compounds **8** which exhibit a great enhancement in FLT3 and VEGFR-2 selectivity<sup>42,43</sup>. Changing the C(3')-methyl of sunitinib



(3) into chloride (e.g., 9) increases antitumor activities and reduces cardiotoxicity<sup>33</sup>. Compared to sunitinib (3), further modification by fusing a six-membered ring to the pyrrole ring led to the discovery of compounds 10, which show similar inhibitory activity against PDGFR $\beta$  but more potent to VEGFR-2 and c-Kit<sup>30</sup>. Fusing the pyrrole moiety of semaxanib (2) with a 1,4,6,7-tetrahydro-pyrrolo[3,2-c]pyridine results in compounds 11, which have various inhibitory activities in VEGFR-2, ALK, PDGFR $\alpha$ , and RET, and specifically selective to LRRK2 inhibition<sup>23</sup>.

Additionally, fusing the pyrrole moiety with five-, six-,

seven-, eight-membered heterocycle (e.g., 12) specifically increases the kinase inhibitory activity and selectivity<sup>28,29,44</sup>. Interestingly, the smaller heterocycles (five- or six-membered heterocycle) fused pyrrole indolin-2-ones show much better VEGFR and PDGFR $\beta$  inhibitory activity<sup>27,28,43</sup>. Compared to sunitinib (3), the five- and six-membered heterocycle fused pyrrole indolin-2-ones demonstrate better inhibiting activity against both VEGFR-2 and PDGFR $\beta$ <sup>28,29,44</sup>. Among them, famitinib (n = 1, R<sub>11</sub>: -F in 12) showed significantly improved progression free survival (PFS) in patients with advanced colorectal cancer in phase IIb study, while its toxicity was manageable<sup>45</sup>.

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 simultaneously 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<sup>45</sup>. Thus, improving the inhibitory selectivity and/or reducing toxicities of therapeutic targets should be prioritized 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<sup>46</sup>.

### 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<sup>4,22,23,28-31,39,42,47</sup>. The C(5) and C(6) positions of the pyrrole indolin-2-ones are considered as one of most effective positions for interaction with the ATP-binding site<sup>20-30,48</sup>. 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<sup>49</sup>. The squalenoyl prodrugs can form nanoparticles and can be activated by changing pH in the body<sup>49</sup>. Another example of the sunitinib prodrug is *N*-hydroxylmethylsunitinib (AST-004), which is activated via hydrolysis catalyzed with esterase<sup>50</sup>. This prodrug can also reduce the toxicity of sunitinib (**3**)<sup>50</sup>. 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<sup>51</sup>.

### 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 PDGFR $\beta$ <sup>22,28,33,34,42-44,52</sup>. 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<sub>3</sub> does not improve inhibition activity against VEGFR-2 and PDGFR $\beta$ <sup>39,41</sup>. 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<sup>18,21,23,27-29,42</sup>. 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 moiety on kinase inhibitory activity and selectivity is highly dependent on the C(3) substituents of indolin-2-one<sup>23,47,52</sup>. Introducing a -OH or a -SH to the C(5) position of the oxindole moiety of the five-membered heterocycle fused pyrrole indolin-2-ones significantly improves inhibitory activity against VEGFR-2 and PDGFR $\beta$ <sup>28</sup>.

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<sup>24</sup>.

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<sub>11</sub>: -F in **12**), tested in phase III clinical trial for colorectal cancer treatment, possess superior inhibitory activity against VEGFR-2 and PDGFR $\beta$ <sup>53</sup>. 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<sup>45</sup>. 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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