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Anticancer chemotherapies targeting Wnt/β-catenin signaling pathway: a review on molecular insights

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Abstract

Background: The Wnt/β-catenin signaling pathway, a highly conserved signaling axis involved in diverse physiological processes such as proliferation, differentiation, apoptosis, migration, invasion, and homeostasis balance, has been implicated in human cancer development and progression. Notably, various cancer types, such as colorectal cancer, hepatocellular carcinoma, melanoma, thyroid cancer, desmoid tumors, ovarian tumors, and multiple myeloma, have demonstrated associations with specific Wnt-activating mutations, emphasizing the widespread influence of the Wnt pathway in diverse malignancies.

Objective: This review highlights the inhibitors targeting the Wnt ligand-receptor interface, focusing on their preclinical and clinical evaluations in various cancer types. Additionally, we explore small-molecule design strategies, focusing on inhibitors of β-catenin, GSK-3, and Porcupine.

Method: Conducted as a narrative review, we collected and analyzed relevant papers from PubMed/Google Scholar and clinical trials associated with Wnt pathway inhibitors from clinicaltrial.gov. A total of 61 papers and 24 clinical trials were reviewed, providing an overview of the molecular insights within the research landscape of this field.

Result: Dysregulated Wnt/β-catenin signaling is implicated in the progression of several solid tumors and hematological malignancies, highlighting the urgent need for targeted anticancer interventions. Our discussion on the inhibitors targeting the Wnt ligand-receptor interface highlights promising outcomes in both preclinical and clinical settings. This paper also presents the chemical structures of these compounds, detailing their interactions with key Wnt signaling components and their potential to disrupt aberrant signaling. The strategies for small-molecule design targeting the Wnt signal are discussed, highlighting inhibitors targeting β-catenin, GSK-3, and Porcupine. The complex chemical structures of these compounds are elucidated, showcasing their specific interactions with key components of the Wnt signaling pathway and their potential to disrupt aberrant Wnt signaling in diverse cancer types. The emerging directions and future prospects in Wnt pathway research demonstrate the importance of utilizing big data and artificial intelligence for drug development.

Conclusion: The review delves into the potential inhibition of the disheveled protein as a promising target for cancer therapy, proposing novel molecular design strategies based on recent discoveries.

Keywords*:* Wnt signaling pathway, β-catenin inhibitors, GSK-3 inhibitors, porcupine inhibitors, Disheveled protein inhibitors

1. Introduction

The Wnt/β-catenin signaling pathway, a crucial cascade in various physiological processes, is implicated in cancer development and progression. In particular, Wnt pathway

plays a critical role in cell proliferation, differentiation, apoptosis, migration, invasion, and maintenance of tissue homeostasis (Choi *et al*., 2020; Liu *et al.*, 2022; Salik *et al*., 2020; Soleas *et al.*, 2020). Increasing evidence suggests that dysregulated Wnt/β-catenin signaling contributes significantly to the development and progression of several solid tumors and hematological malignancies (Cao *et al*., 2018; Gajos-Michniewicz & Czyz, 2020; He & Tang, 2020; Zhang *et al*., 2018). This review focuses on the molecular aspects of the Wnt signaling pathway, its role in carcinogenesis, and the development of small-molecule drugs to target this pathway for anticancer therapies.

2. Method

This study employed a narrative review methodology, as previously described (Snyder, 2019). We collected and scrutinized relevant literature sourced from PubMed and Google Scholar indexed publications pertaining to the Wnt pathway, specifically focusing on small molecule inhibitors. Furthermore, clinical trials associated with these inhibitors were checked on clinicaltrial.gov. Our analysis incorporated 61 scientific articles and 24 clinical trials, providing an overview of the molecular insights within the research landscape of this field.

3. Result and discussion

3.1. Mutations activating the Wnt pathway drive cancer development and persistence

The Wnt pathway plays a critical role at various stages of tumor progression. Notably, mutations in the *APC* gene have been identified as a focal point, accounting for approximately 80% of colorectal cancers (Flanagan *et al*., 2019; Huong *et al*., 2018; Zhang *et al.*, 2018). Moreover, a multitude of cancer types exhibit Wnt-activating mutations, including hepatocellular carcinoma with *CTNNB1* and *AXIN1/2* mutations, and melanoma with the *BRAFV600E* mutation (Cao *et al.*, 2018; Ding *et al*., 2017; Zablocka *et al.*, 2022). Thyroid cancer, desmoid tumors, ovarian tumors, and multiple myeloma have all demonstrated associations with specific Wnt-activating mutations (Miyoshi *et al*., 1998; Sastre-Perona & Santisteban, 2012; Zyla *et al*., 2021). Understanding the role of Wnt-activating mutations is vital, as these mutations have been linked to resistance to anticancer drugs (Ha *et al.*, 2021; Tomar *et al.*, 2020). Furthermore, the Wnt/β-catenin signaling pathway interacts with several other cellular signaling cascades, such as EGFR, Hippo/YAP, NF-κB, Notch, Sonic Hedgehog, and the PI3K/Akt pathway, influencing critical molecular mechanisms in cancer development (Chen *et al*., 2012;

Hu & Li, 2010; Krishnamurthy & Kurzrock, 2018; Liu *et al.*, 2020; Perry *et al*., 2020; Tomar *et al.*, 2020).

The interplay of the Wnt/β-catenin signaling pathway with diverse cellular cascades highlights its significant role in cancer development and persistence. The prevalence of diverse Wnt-activating mutations in various cancer types emphasizes the widespread influence of the Wnt pathway in malignancies (Parsons *et al*., 2021). These mutations are associated with the pathogenesis of numerous cancer types, suggesting the critical importance of comprehending the molecular mechanisms underlying Wnt-related oncogenesis. Furthermore, the correlation between Wnt-activating mutations and resistance to conventional anticancer therapies emphasizes the urgency for the development of targeted interventions aimed at disrupting aberrant Wnt signaling (Hinze *et al.*, 2020).

The schematic representation of the Wnt/β-catenin signaling pathway presented in **Figure 1** elucidates the core regulatory mechanisms involved in the pathway, providing valuable insights into the intricate molecular events contributing to Wnt signaling-mediated tumorigenesis (Wall *et al.*, 2021; Zhang *et al.*, 2018). The pivotal role of the Wnt/β-catenin signaling pathway in cancer biology, along with the development of small-molecule drugs targeting this pathway, offers promising avenues for the advancement of novel anticancer therapies. The crosstalk between the Wnt/β-catenin pathway and other pivotal cellular signaling cascades reflects the multifaceted nature of the molecular mechanisms driving cancer development, providing valuable prospects for future research and therapeutic exploration (Bisevac *et al*., 2023).

3.2. Strategies of small-molecule design targeting the Wnt signal

While currently no approved anticancer drug targeting the Wnt pathway exists, certain compounds have displayed potential in clinical trials, exhibiting promising toxicity profiles and favorable preclinical data. **Table 1** presents an overview of clinical trials investigating small-molecule inhibitors targeting the Wnt signaling pathway. These agents aim to modulate key components of the Wnt signaling pathway, including PORCN, β-catenin, and GSK-3, to disrupt aberrant Wnt signaling implicated in diverse cancer types. **Figure 2** outlines small-molecule agents designed to target specific components of the Wnt signaling pathway, representing potential candidates for the development of effective anticancer drugs. Each compound interacts with particular elements of the pathway, modulating their activity and ultimately

influencing cancer progression. These chemical agents demonstrate the complexities of the design and targeting strategies involved in the development of anticancer drugs focused on the Wnt signaling pathway, highlighting ongoing efforts to leverage the intricate molecular mechanisms of cancer development for the advancement of targeted therapies. However, these drug designs are also based on shared characteristics, grounded in specific chemical scaffolds. These shared features may serve as guiding principles for researchers to continue designing potentially effective Wnt signal inhibitors for cancer treatment. The subsequent content of the article delves deeper into notable drug design directions (Morris *et al*., 2022).

3.2.1. Targeting β-catenin

β-catenin, a central component of the Wnt pathway crucial for the regulation of gene expression (Krishnamurthy & Kurzrock, 2018), has garnered significant attention in the development of small-molecule inhibitors such as BC2059 (Tegavivint), E7386, SM08502, CWP232291, and PRI-724, intended to modulate β-catenin function across various cancer types, including desmoid tumors, colorectal neoplasms, pancreatic cancer, and multiple myeloma (Bisevac *et al*., 2023).

Compounds such as E7386, PRI-724, BC2059, and SM08502 (**Figure 2A**) are engineered to interact with β-catenin or its associated molecular partners, aiming to disrupt its signaling function and impede its oncogenic potential (Kahn, 2014). These compounds possess their chemical structures incorporating diverse functional groups that enable them to bind to specific regions of β-catenin, thereby modulating its activity and downstream signaling cascades (Wang *et al.*, 2020). While E7386 and PRI-724 were both designed on the scaffold of *pyrazino[2,1-c][1,2,4]triazine-4,7-dione*, the structural properties of E7386 reveal a complex configuration with multiple functional groups that may contribute to its specific binding and inhibitory effects on β-catenin (Yamada *et al*., 2021). In contrast, PRI-724 exhibits a distinctive structure, potentially contributing to its mechanism of action as a selective inhibitor of β-catenin-dependent transcription (Boone *et al*., 2016).

3.2.2. Targeting GSK-3

Another set of chemical agents depicted in Figure 2B focuses on targeting GSK-3, a key downstream component of the Wnt pathway, is also under investigation. LY2090314 (Bisevac *et al*., 2023) and 9-ING-4 (Coats *et al.*, 2023) are specifically designed to inhibit GSK-3 activity, thereby interfering with the phosphorylation of downstream substrates and affecting various cellular processes linked to cancer development and progression (Beurel *et al*., 2015). The

intricate chemical structures of these compounds reflect the precise targeting of GSK-3 and the intricate balance required to modulate its activity for therapeutic benefit in the context of cancer treatment. Small-molecule inhibitors like 9-ING-41 and LY2090314 are being evaluated in refractory cancers, myelofibrosis, and leukemia, aiming to regulate the activity of GSK-3 and modulate the downstream effects of the Wnt signaling pathway (Beurel *et al*., 2015). The diverse agents and the range of cancer types being targeted in these clinical trials suggest the importance of the Wnt signaling pathway in cancer biology and the potential of these small-molecule inhibitors in developing innovative and effective cancer therapies (Beurel *et al*., 2015; Coats *et al*., 2023). The outcomes of these ongoing trials are anticipated to provide valuable insights into the clinical efficacy and safety profiles of these agents, facilitating the development of targeted therapies for various types of cancer (Beurel *et al.*, 2015).

3.2.3. Targeting Porcupine

Porcupine (PORCN), an enzyme belonging to the membrane-bound O-acyltransferase (MBOAT) family, plays a vital role in the secretion of Wnt ligands. Several inhibitors targeting PORCN aim to hinder the process of Wnt protein palmitoylation within the endoplasmic reticulum, specifically diminishing the capacity for Wnt ligand secretion, while leaving the secretion of other types of ligands unaffected (Madan & Virshup, 2015). Hence, Porcupine is considered a highly specific target for Wnt-driven cancers. Furthermore, the compounds identified as PORCN inhibitors, including WNT974 (NCT01351103, 2023), RXC004 (Phillips *et al*., 2022), and CGX-1321 (Wall *et al*., 2021), represent a class of chemical agents targeting the Wnt signaling pathway (Figure 3C). These inhibitors act by blocking the function of PORCN, a crucial enzyme involved in the secretion and processing of Wnt ligands (Madan & Virshup, 2015). By inhibiting PORCN activity, these compounds disrupt the Wnt ligand secretion and consequent activation of the Wnt signaling cascade, thus interfering with the proliferation and progression of various cancers (Proffitt *et al*., 2013).

3.3. Emerging directions and future prospects

Recent trends in drug development emphasize the utilization of big data and artificial intelligence trained on extensive biological data (Fang *et al*., 2023). The growing availability of biomedical data, supported by scientific advancements, has greatly facilitated cancer drug research by predefining molecular targets. From these targets, it is possible to design small-molecule drugs or biopharmaceuticals to intervene at the target level, regulating signals at the

cellular and molecular levels. Consequently, based on combination therapies and precision medicine treatments, therapeutic protocols can be developed. The design and synthesis of an organic chemical with various advantages are based on supportive theoretical foundations such as pharmacophore and bioisosterism. In silico tools also play a significant role in the design of small-molecule drugs. Within the scope of this article, we delve into the emerging direction of inhibiting the Disheveled protein, as recent discoveries have highlighted its significant potential as a target, marking its critical role and considerable potential (Nardella *et al*., 2021).

In Figure 3, a schematic summary of the Disheveled protein mechanism in the context of Wnt signal interaction is proposed (Sharma *et al*., 2018). Notably, several protein domains have been clearly identified for their ability to interact with signals, suggesting the design of small molecules to inhibit Wnt based on this molecular mechanism. Of particular interest are the DIX, PZD, and DEF domains, all found to play a role in intermolecular interactions, connecting Wnt signals within the cell. In recent studies, the PZD domain has been recognized as a potential binding site for new Wnt signal inhibitors (Grandy *et al*., 2009; Kamdem *et al.*, 2021).The structure of the PZD domain is depicted in Figure 4, based on X-ray scattering methods, with clearly defined spatial arrangements conducive to in silico studies and proposals for the design of small molecules aimed at high-affinity binding to the PZD domain to inhibit Wnt signaling (Kamdem *et al*., 2021). Several proposed compounds have been studied and described in Figure 5, such as NSC668036 (a small peptide) KY-02327, KY-0206 (aromatic-based scaffold design) (Kim *et al*., 2016), and a series of molecules synthesized on the scaffold of 2-(hydrosulfonylamino) benzoic acid (Kamdem *et al*., 2021). The diversity of molecules shows that the development of Wnt signaling inhibitors along these lines of research has been attracting interest. However, there are still no PZD domain inhibitors that have been successfully tested in clinical research, so there are still many knowledge gaps in this direction of drug development that need to be explored.

Other targets and approaches for inhibiting Wnt signaling are diverse and abundant, creating opportunities for the development of cancer drugs based on this mechanism (Flanagan *et al*., 2022). Additionally, the identification and validation of reliable biomarkers associated with Wnt pathway activation and treatment response will facilitate the monitoring of treatment efficacy and the prediction of patient outcomes. However, within the limits of this article, only a few aspects of small-molecule drug development have been discussed. Deeper

discussions on other related mechanisms are necessary for further research, depending on the researchers' chosen directions in drug development, including drug repurposing, polypharmacology deployment, drug combinations, and proposals in preclinical models. This includes the development of more accurate animal models and sophisticated *in vitro* systems, which are crucial for the effective evaluation of Wnt-targeted therapies.

4. Conclusion

In conclusion, our review draw attention to the significance of developing small molecule drugs targeting the Wnt signaling pathway for effective cancer therapy. While several inhibitors have shown promise in disrupting tumor cell development, further exploration is needed. We advocate for continued research into the structural properties of these compounds and the potential for combining them to enhance their effectiveness and safety in cancer treatment.

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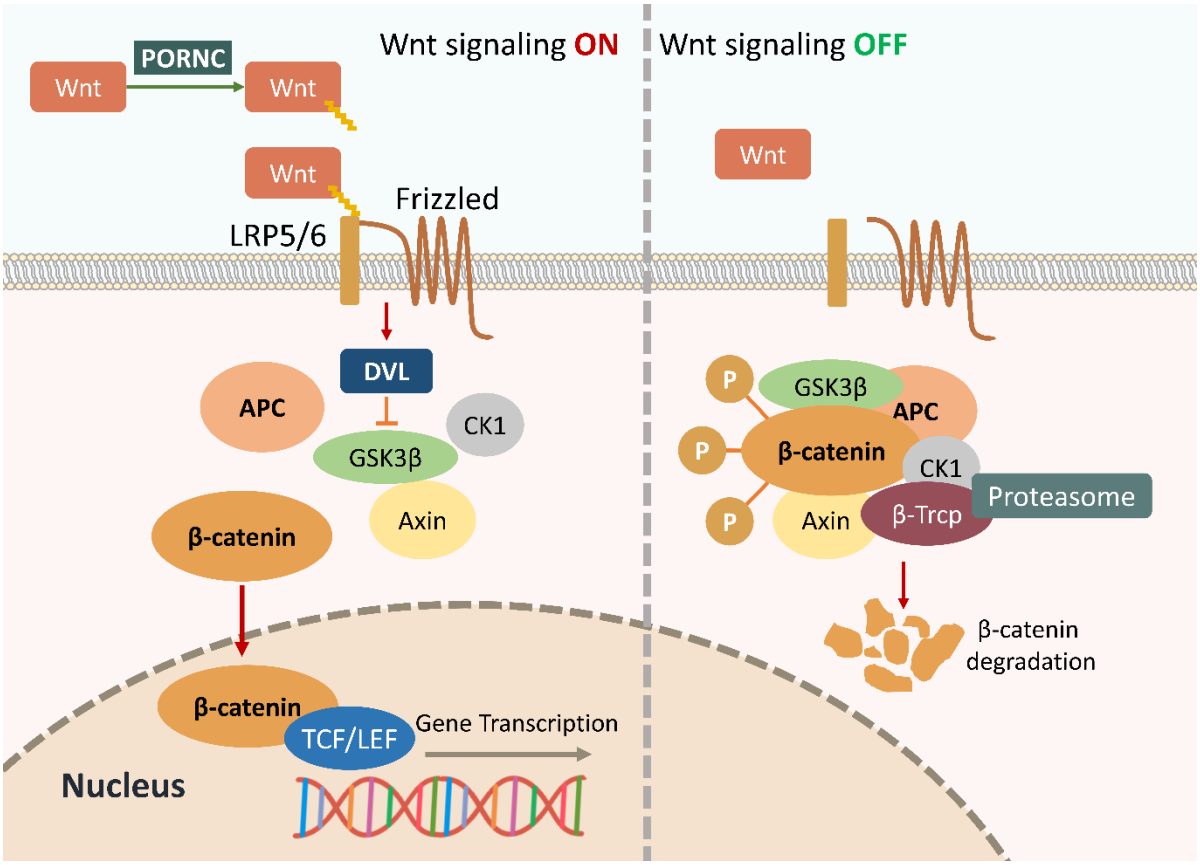

Figure 1. Schematic representation of the Wnt/β-catenin pathway in activated and inhibited status. Adapted from (Alharbi *et al.*, 2022; Zhang *et al.*, 2021) under Creative Commons Attribution License, created with Microsoft PowerPoint 2016.

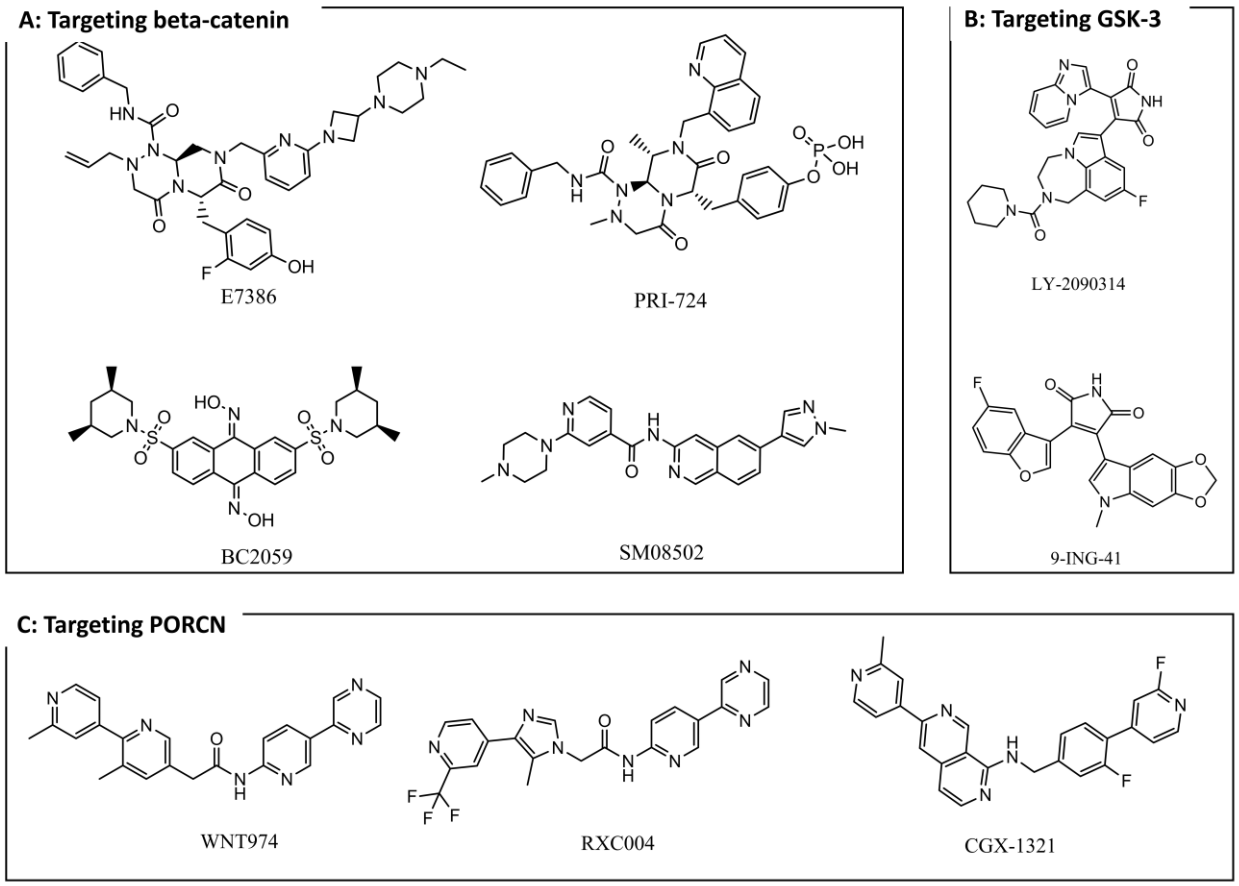

Figure 2. Small molecules used in clinical trials targeting WNT signaling pathway. Chemical structure of small molecules targeting: (A) beta-catenin, (B) GSK-3, (C) PORCN.

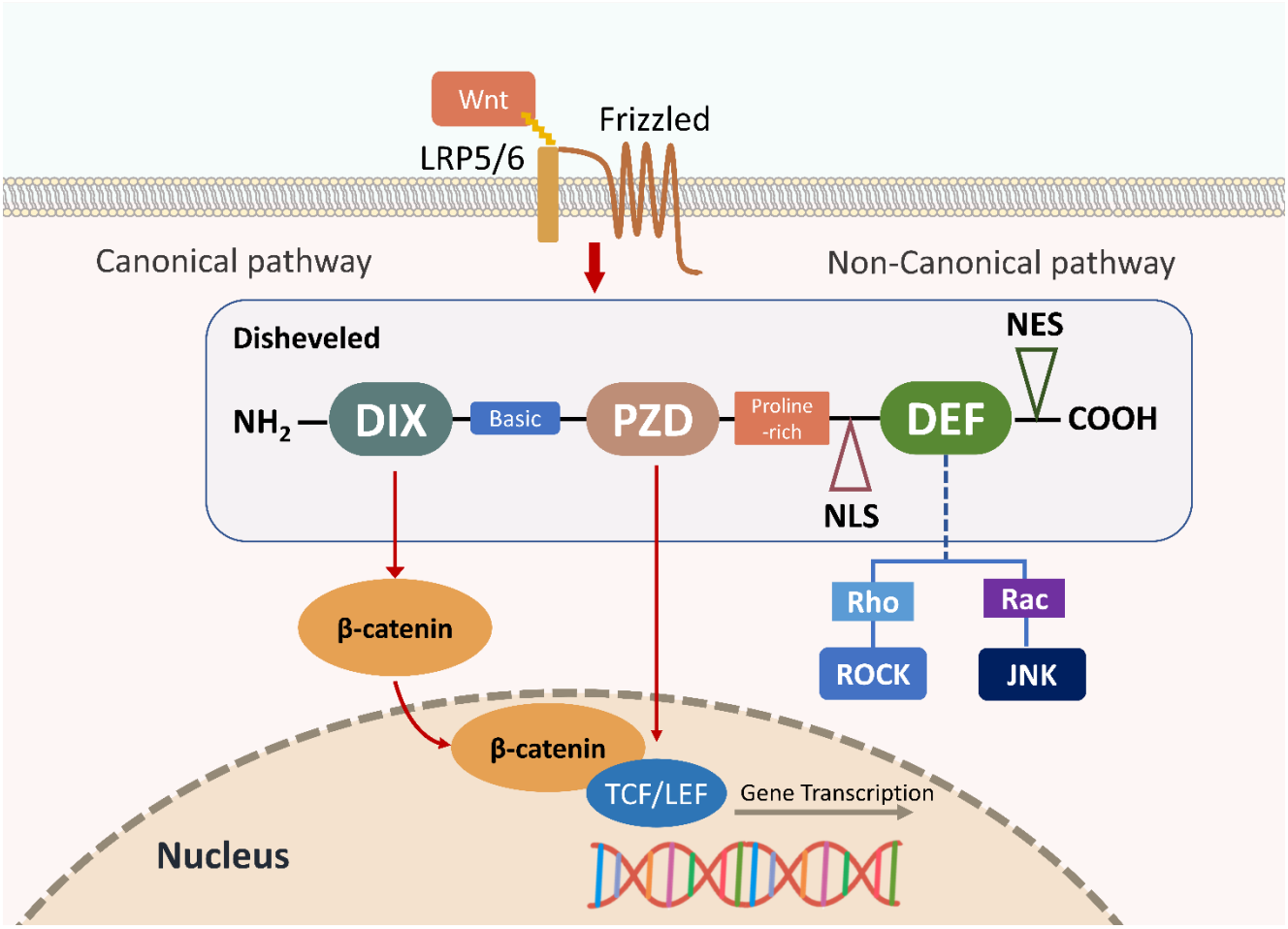

Figure 3: schematic summary of the Disheveled protein mechanism in the context of Wnt signal interaction. Adapted from (Alharbi *et al.*, 2022; Zhang *et al.*, 2021) under Creative Commons Attribution License, created with Microsoft PowerPoint 2016.

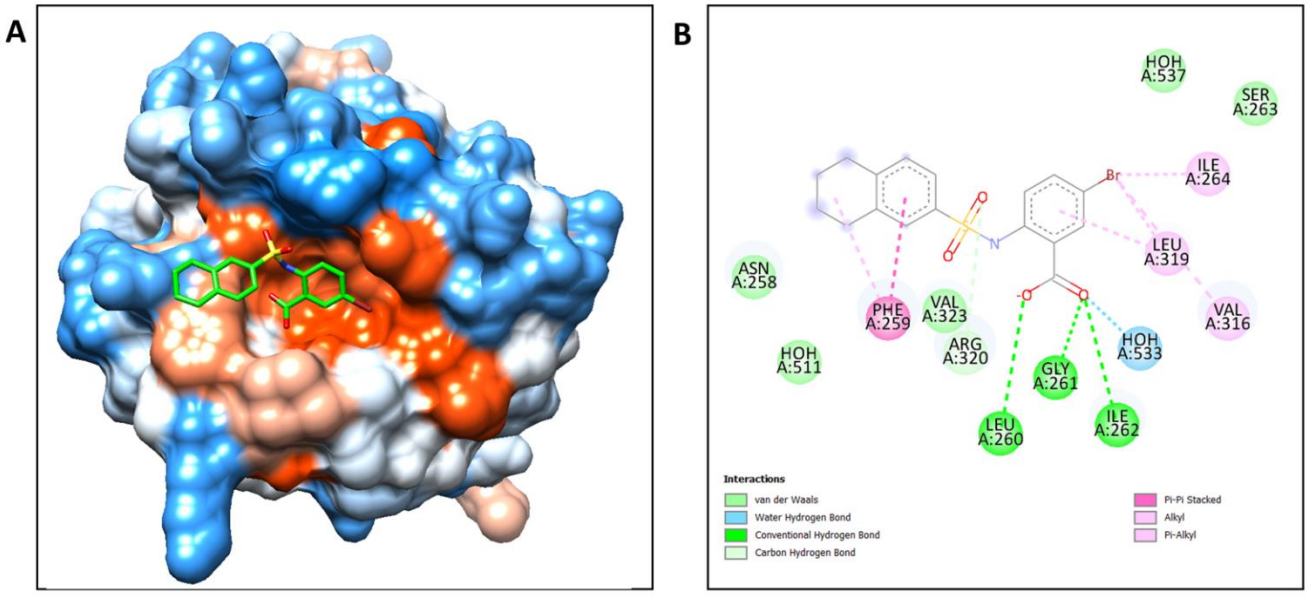

Figure 4: An example of Disheveled protein inhibitor, bound at PZD domain. A: Three-dimensional model in hydrophobicity view of the binding site of Disheveled PZD domain. B: Two-dimensional intermolecular interactions between ligand and aminoacid residues at binding site of PZD domain.

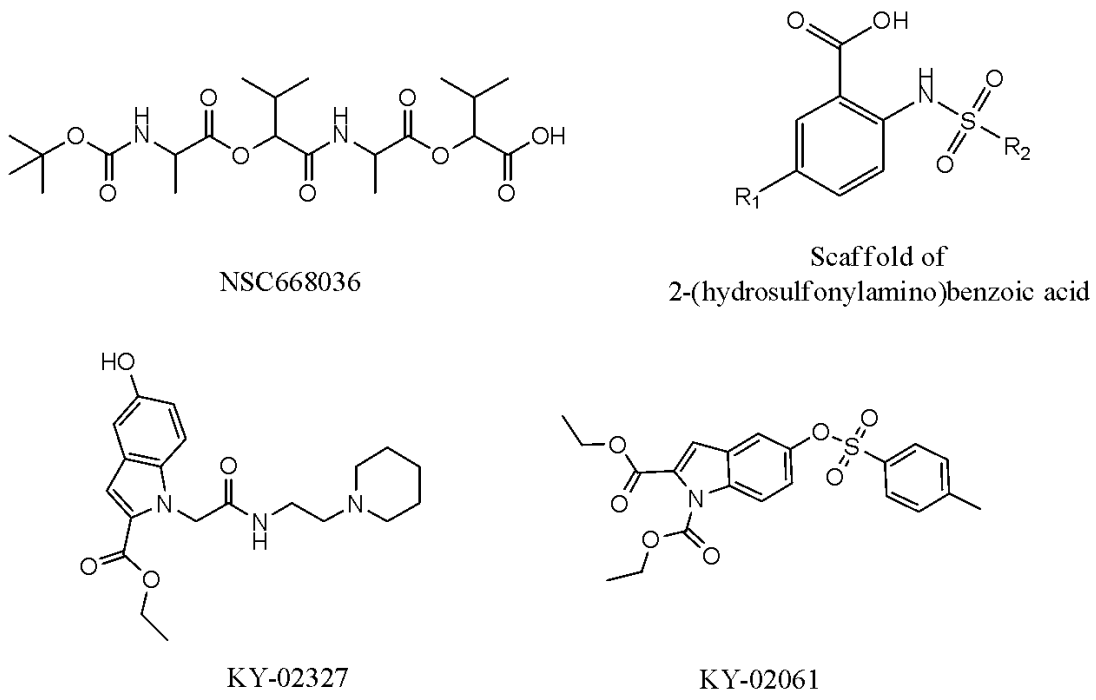

Figure 5: Small-molecules developed as Disheveled PZD domain inhibitors

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Table 1: Clinical trials of small-molecules targeting wnt signaling pathway for anticancer activities

Agent name	Target or action	Cancer type	Phase	References
WNT974	PORCN inhibitor	Various types of cancer	I	(NCT01351103, 2023; Rodon *et al*., 2021)
WNT974	PORCN inhibitor	Metastatic colorectal cancer	II	(NCT02278133, 2017; Tabernero *et al*., 2023)
RXC004	PORCN inhibitor	Solid tumor	I	(Cook *et al*., 2021; NCT03447470, 2023)
XNW7201	PORCN inhibitor	Advanced solid tumors	I	(NCT03901950, 2023)
BC2059 (Tegavivint)	β-Catenin	Desmoid tumor	I	(Cranmer *et al*., 2022; NCT03459469, 2023)
E7386	β-Catenin	Colorectal neoplasms	I	(Kondo *et al*., 2023; NCT03833700, 2023)
E7386	β-Catenin	Advanced neoplasms	I	(NCT03264664, 2023)
E7386	β-Catenin	Hepatic neoplasms	I	(Ikeda *et al*., 2023; NCT04008797, 2023)
9-ING-41	GSK-3 inhibitor	Refractory cancer, pediatric cancer and neuroblastoma	I	(DeNardo *et al*., 2022; NCT04239092, 2023)
9-ING-41	GSK-3 inhibitor	Myelofibrosis	II	(NCT04218071, 2023)
9-ING-41	GSK-3 inhibitor	Various type of cancer	I, II	(Mahalingam *et al*., 2022; NCT03678883, 2023)
ETC-1922159	PORCN inhibitor	Solid tumor	I	(NCT02521844, 2023; Tan *et al*., 2023)
CGX1321	PORCN inhibitor	Solid tumors and gastrointestinal cancer	I	(Giannakis *et al*., 2023; NCT02675946, 2022)
CGX1321	PORCN inhibitor	Various types of gastrointestinal cancer	I	(Giannakis *et al*., 2023; NCT03507998, 2020)
SM08502	β-Catenin controlled gene expression inhibitor	Solid tumors	I	(NCT03355066, 2022; Tam *et al*., 2020)
CWP232291	β-Catenin	Acute myeloid leukemia	I, II	(Cortes *et al*., 2015; NCT03055286, 2021)
CWP232291	β-Catenin	Multiple myeloma	I	(NCT02426723, 2019; Yoon *et al*., 2017)
CWP232291	β-Catenin	Acute myeloid leukemia, chronic myelomonocytic leukemia, myelodysplastic syndrome and myelofibrosis	I	(Cortes *et al*., 2015; Rodon *et al*., 2021)
LY2090314	GSK-3	Advanced cancer	I	(Gray *et al*., 2015; NCT01287520, 2019)
LY2090314	GSK-3	Pancreatic cancer	I, II	(NCT01632306, 2012)
LY2090314	GSK-3	Leukemia	II	(NCT01214603, 2018; Rizzieri *et al*., 2016)
PRI-724	β-Catenin	Pancreatic cancer	I	(Ko *et al*., 2016; NCT01764477, 2017)
PRI-724	β-Catenin	Acute myeloid leukemia and chronic myeloid leukemia	I, II	(NCT01606579, 2017)
PRI-724	β-Catenin	Colorectal cancer	II	(NCT02413853, 2017)
PRI-724	β-Catenin	Advanced solid tumors	I	(El-Khoueiry *et al*., 2013; NCT01302405, 2017)