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The development of anti-androgens with a new mechanism of action for treatment of resistant prostate cancer

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The Androgen Receptor (AR) is one of the most validated therapeutic targets in Prostate Cancer (PCa). Conventional anti-androgens lose effectiveness as cancer therapeutics because anti-androgen resistance usually develops after long term treatment. The challenge is that the current therapeutics should bind to the same site of the AR (hormone binding pocket) and act via the same mode, to which the receptor has already developed effective resistance mechanisms. Hence, there is a pressing need for novel therapeutics that inhibit the AR through novel, alternative modes of action. Recent studies have identified a novel binding pocket on the surface of AR called Binding Function 3 (BF3) that is important for the AR transcriptional activity. In order to identify compounds that specifically bind to BF3 site and inhibit the AR, we conducted a systematic *in silico* screen (that included large-scale docking, in-site rescoring, and consensus voting procedures) followed by experimental validation of the identified hit molecules. As a result, we have discovered a novel chemical series of indoles as lead BF3 inhibitors. One of the most potent inhibitors identified, VPC-13566, demonstrated an IC50 of 0.20 μ M in AR eGFP transcriptional assay. Confirming it as a true BF3 binder, VPC-13566 neither displaced the co-activator from an alternative co-activator binding site, activation function 2 site, nor androgen from the hormone binding pocket. Additionally, the Biolayer Interferometry assay detected direct reversible interactions between the AR ligand binding domain and the inhibitor. VPC-13163 demonstrated strong anti-proliferative activity against LNCaP and Enzalutamide-resistant prostate cancer cell lines (MR49F) whereas it did not affect the growth of AR independent PC3 cell line. It also inhibits Prostate Specific Antigen (PSA) in both LNCaP and MR49F and reduces expression of AR target genes, PSA and TMPRSS2. These findings suggest that VPC-13566 exhibits AR BF3 specific mechanism of action. Furthermore, VPC-13566 reduces AR-dependent growth of xenograft tumors *in vivo*. Based on these outcomes, it can be anticipated that such drug prototypes will lay a foundation for the development of alternative or supplementary small-molecule therapies capable of combating PCa even in its drug resistant forms. Because the emergence of castration resistance is the lethal end stage of the disease, we anticipate that the proposed research will eventually have a substantial impact on patient survival.

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Application of quantitative microbiological risk assessment in the field of pharmaceutical environmental monitoring

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Quantitative Microbiological Risk Assessment (QMRA) is a valuable tool that has been used in the field of food industry and drinking water evaluation. This technique could be applied in the assessment of potential risk that may arise from the contamination of the medicinal products from manufacturing environment including pharmaceutical water on the final consumer. Another simple technique that can be used by the health care professionals was developed by using Quantitative Risk Index (QRI). This index was developed based on combination of factors that contribute to the final microbiological safety level of the drug. As the risk value increases the possibility of hazard delivered to the patient increases. The risk takes into account the infectivity of microorganisms for specific patient condition by certain route, their abundance in environment, manufacturing processes that are hostile to the viability of microbes, antimicrobial power of the product including water activity, the volume or batch size of the dedicated drug, the maximum single dose that can be delivered to the patient and the general trend of microbial count. The newly applied risk showed primarily agreement with QMRA in the ranking of risks that is associated with specific bacteria under study. However, the expanding gap between the continually increasing number of objectionable microbes and the lack of the exact data about infective dose for human by specific route of each objectionable bug is rising and requires an extensive care by healthcare scientists to understand the risk associated with each microorganisms and not only the common pathogens.

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