Androgen receptor is a master regulator of prostate cancer (PCa), and therefore a pivotal drug target for the treatment of PCa including its castration-resistance form (CRPC). The development of acquired resistance is a major challenge in the use of current antiandrogens. The recent advancements in inhibiting AR activity with small molecules specifically designed to target areas distinct from the receptor’s androgen binding site are carefully discussed.

Our new classes of AR inhibitors of AF2 and BF3 functional sites and DBD domains designed using cheminformatics techniques are promising to circumvent various AR-dependent resistance mechanisms.