Castrate resistant prostate cancer (CRPC) is the fatal form of prostate cancer. CRPC is accompanied by a rising prostatic specific antigen (PSA) despite castrate levels of circulating androgens and suggests that the tumor makes its own androgens from adrenal precursors. The clinical success of abiraterone acetate (a CYP17A1 inhibitor) in the treatment of CRPC supports this concept. Type 5 17b-hydroxysteroid dehydrogenase [aldo-keto reductase 1C3 (AKR1C3)] acts downstream from CYP17A1, and all pathways to the potent androgen 5a-dihydrotestosterone (DHT) proceed through AKR1C3. In the “classical pathway”, AKR1C3 catalyzes the conversion of 4-androstene-3,17-dione (4-AD) to testosterone, in the “alternative pathway” AKR1C3 catalyzes the conversion of 5a-androstane-3,17-dione to DHT, and in the “backdoor pathway” AKR1C3 catalyzes the conversion of androsterone to 3a-androstanediol. AKR1C3 is one of the most overexpressed steroidogenic genes in CRPC and is upregulated by ADT. To target AKR1C3 in CRPC we have developed three major classes of inhibitors based on nonsteroidal anti-inflammatory drug analogs: [Class 1] N-phenylamino-benzoates based on flufenamic acid; [Class 2] N-naphthyl-amino benzoates; and [Class 3] indomethacin analogs. In each class, compounds exist that have nanomolar potency for AKR1C3, do not inhibit the related AKR1C1, AKR1C2, and AKR1C4 isoforms, do not inhibit COX-1 or COX-2 (the NSAID target), and block AKR1C3 mediated T production and 4-AD mediated PSA production in LNCaP-AKR1C3 cells. Compounds in class 2 also acted as androgen receptor antagonists and caused AR degradation in the presence and absence of DHT. The optimization of these inhibitors exploits newly solved crystal structures of AKR1C3 in complex with a compound from each inhibitor class. Each class of inhibitor exhibits a unique binding pose in which different sub-pockets of AKR1C3 are occupied. These inhibitors may lead to agents that can be used in the neoadjuvant setting, may be superior to abiraterone and may surmount abiraterone resistance [Supported by 1R01CA90744].