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Steroid pathways as viable drug targets

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Steroid hormones are indispensable for normal development of all mammalian organisms. The formation of steroid hormones proceeds via the hypothalamic-pituitary-gonadal/adrenal axis. The biosynthesis of all steroid hormones begins with enzymatic side-chain cleavage of cholesterol to the progestins which subsequently progress via divergent routes to give mineralocorticoids, glucocorticoids and the sexual hormones. The major enzymes responsible for these biosynthetic transformations, include, cytochrome P450s (CYPs) oxygenases, hydroxysteroid dehydrogenases (HSDs), and reductases. These enzymes represent important targets for drug discovery and development for the treatments of hormone-dependent diseases. My talk will focus on the most extensively developed studies on the discovery and developments of small molecule inhibitors to target: [1] cytochrome P450 aromatase (CYP19), responsible for the conversion of androgens into estrogens and a target in the treatment of breast cancer; [2] cytochrome P450 17 α -hydroxylase/17,20-lyase (CYP17), a multifunctional enzyme that lies at the crossroads of androgen and corticoids biosynthesis and a target in the treatment of prostate cancer; and [3] 5 α -reductase (5-AR) responsible for the conversion of testosterone (T) to dihydrotestosterone (DHT) and a target for prostate cancer and benign prostatic hyperplasia (BPH). Specifically, I will highlight the discovery and development of US Food and Drug Administration (FDA) approved drugs for the treatment of breast and prostate cancer and also BPH; because resistance to most therapies is a major concern, I will also highlight a few promising inhibitors, including those developed in my laboratory, currently in advanced clinical trials in women and men with breast or prostate cancers.

Biography

Vincent C O Njar received his BSc (Hons.) from University of Ibadan, Nigeria in Chemistry in 1976, and his PhD from University College London, United Kingdom in Organic/Medicinal Chemistry in 1980 under the mentorship of Derek Banthorpe. His postdoctoral training with the late Eliahu Caspi was at the Worcester foundation for Experimental Biology, Shrewsbury, Mass. USA (1980-1982). He joined the faculty at University of Ibadan (UI) as Lecturer II in 1982 and was promoted through the ranks, and became Professor of Organic Chemistry in 1996. During his tenure at UI, he was a visiting Professor at several institutions in Europe and North America. He is currently Professor of Medicinal Chemistry and Pharmacology, Department of Pharmacology; Head, Medicinal Chemistry Group, Center for Biomolecular Therapeutics, University of Maryland School of Medicine, Baltimore, MD, USA. His long standing interest is in the rational design/synthesis, discovery and development of small molecules as anti-cancer agents. One of his inventions, VN/124-1 (now called TOK-001 or Galeterone) would soon enter Phase III clinical trials in men with castration resistant prostate cancer. He has published extensively in reputable medicinal chemistry, biology and cancer journals, holds several patents, and serves as reviewer for many journals, research grant awarding agencies and as Editorial Board Member of several journals.

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