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Non-canonical Modulators of Nuclear Receptors

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Abstract

Like G protein–coupled receptors (GPCRs) and protein kinases, nuclear receptors (NRs) are a rich source of pharmaceutical targets. Over 80 NR-targeting drugs have been approved for 18 NRs. The focus of drug discovery in NRs has hitherto been on identifying ligands that bind to the canonical ligand binding pockets of the C-terminal ligand binding domains (LBD). Due to the development of drug resistance and selectivity concerns, there has been considerable interest in exploring other, non-canonical ligand binding sites. Unfortunately, the potencies of compounds binding at other sites have generally not been sufficient for clinical development. However, the situation has changed dramatically over the last three years, as compounds with sufficient potency have been reported for several NR targets. Here we review recent developments in this area from a medicinal chemistry point of view in the hope of stimulating further interest in this area of research.

Keywords: Allosteric, non-canonical, nuclear receptor, agonist, antagonist, drug discovery

Introduction

The human nuclear receptor (NR) superfamily consists of 48 members. These ligand-regulated transcription factors bind small molecules such as steroid and thyroid hormones, vitamins, and fatty acids and their derivatives, regulating growth, development and metabolic homeostasis.[1] Endogenous ligands have been identified for approximately half of the NRs. The NRs for which an endogenous ligand has yet to be elucidated are often referred to as orphan receptors. As the ligands for orphan receptors are subsequently discovered, these NRs become potential therapeutic targets. One recent example is the retinoic acid receptor (RAR)-related orphan nuclear receptor gamma t (RORγt), an emerging target for autoimmune and inflammatory diseases.[2] NRs are a rich source of pharmaceutical targets[3] and over 80 NR-targeting drugs have been approved for 18 NRs.[4]

Even though NRs are involved in diverse physiological processes, nearly all NRs share a similar modular structure that consists of an N-terminal domain, a central DNA-binding domain (DBD), a hinge region, a ligand binding domain (LBD), and a highly variable C-terminal domain. A typical LBD (e.g., Figure 1) contains 12 α helices (H1-H12) arranged around a central hydrophobic pocket (the ligand binding pocket (LBP)), which is shaped mainly by amino acid sidechains of helices 3, 7, and 10.[5] The sizes of the hydrophobic pockets vary considerably from nearly zero, where the pocket is filled by the receptor's own hydrophobic sidechains, to 1600 $Å^3$.[6] The shapes and sizes of the LBPs are highly inducible. The most dynamic part of the LBD is helix 12 (H12) which can undergo considerable shifts in position upon ligand binding. In structures of apo receptors, H12 can display various poses ranging from