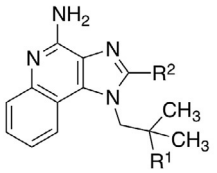
3.3 TOLL-LIKE AND NOD2 RECEPTORS

Nucleotide-binding and leucine rich repeat domain-containing proteins (NLR) are central to the formation of many inflammasome complexes. Toll-like receptors (TLRs) are transmembrane glycoproteins with an extracellular domain (ectodomain) that contains leucine-rich repeats responsible for mediating ligand recognition; a single transmembrane helix; and an intracellular Toll-like/IL-1 receptor domain responsible for downstream signaling.

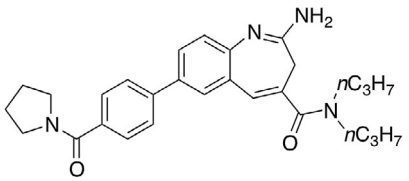
TLRs have a key role in host defense against pathogens by recognizing a variety of pathogen-associated molecular patterns. They are closely connected to inflammatory responses and are involved in the initiation of both innate and adaptive immune responses. Because functional TLRs are expressed not only on immune cells but also on cancer cells, they have a role in cancer by regulating cell proliferation and survival. TRL ligands have been described[58] as a "double-edged sword" in cancer because, on the one hand, uncontrolled TLR signaling creates a microenvironment that allows tumor cells to evade the immune response and proliferate, but on the other hand, TLRs can induce an antitumor immune response.

Some imidazoquinolines, such as imiquimod (R-837) and resiquimod (R-848), have been identified as agonists of TLRs, especially TLR-7, with subsequent secretion of cytokines, particularly IFN-α, IL-6, and TNF-α. Topical imiquimod (Zyclara®, Aldara®) is used to treat genital warts and certain skin cancers such as basal cell carcinoma, Bowen's disease, superficial squamous cell carcinoma, superficial malignant melanomas, and actinic keratosis, generally following surgery. Resiquimod is also used for the treatment of several types of skin lesions.

Motolimod is an agonist of TLR-8 that is able to activate myeloid DCs, monocytes, and natural killer cells, resulting in the liberation of mediators that integrate the innate and adaptive antitumor responses to a number of cancers. As a consequence, the combination of motolimod (VTX-2337) with small-molecule chemotherapeutic agents or mAbs increases their antitumor response. Phase II trials of some such combinations in solid tumors, including ovarian and head and neck cancer, are in progress.[59] In 2014, the FDA granted fast track designation to the motolimod-pegylated liposomal doxorubicin combination for the treatment of women with relapsed ovarian cancer after platinum-based chemotherapy.



Imiquimod $R^1 = R^2 = H$
Resequimod $R^1 = CH_2OH$; $R^2 = CH_2OEt$



Motilimod

Besides TLRs, the intracellular receptor of innate immunity NOD2 (nucleotide-binding oligomerization domain-containing protein 2) is another interesting immunity-related target. Although the molecular mechanisms underlying this signal transduction pathway remain largely unknown,[60] its activation by muramyl dipeptide (MDP), a peptidoglycan constituent of both Gram-positive and Gram-negative bacteria, stimulates an immune reaction mediated by monocytes and macrophages. Mifamurtide (liposomal muramyl tripeptide phosphatidyl ethanolamine, MTP-PE, Mepact®), a derivative of MDP, has similar effects, stimulating an immune reaction against cancer cells[61] with the advantage of having a longer half-life in plasma. Encapsulated into liposomes, where due to its phospholipid nature is