Int. J. New. Chem., 2025, Vol. 11, Issue 5, pp. 1036-1045.

International Journal of New Chemistry

Published online 2025 in http://www.ijnc.ir/.

Open Access

Print ISSN: 2645-7236

Online ISSN: 2383-188x

Review

A New Survey on the mTOR Inhibitors as Cancer Chemopreventive Agents

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Received: 2025-01-03 *Accepted: 2025-04-27* *Published: 2025-04-28*

ABSTRACT

The mammalian target of rapamycin (mTOR) pathway, which is critical for regulating cellular processes such as growth, metabolism, and survival, plays an important role in cancer development when dysregulated. mTOR inhibitors, notably rapamycin and its variants, have emerged as promising possibilities for cancer treatment and chemoprevention. This study focuses on the chemical characteristics of mTOR inhibitors and their potential utility in cancer chemoprevention. We investigate mTOR's function in cancer, assess the chemical structures of first- and second-generation mTOR inhibitors, describe their mode of action, and review preclinical and clinical data. In addition, we look at novel natural product-based inhibitors, dual inhibitors that target both PI3K and mTOR, and the hurdles of bringing these inhibitors to clinical usage.

Keywords: Mammalian Target of Rapamycin, mTOR, Cancer, Natural Product, Cancer Chemopreventive

Introduction

Cancer, humanity's largest cause of mortality, is frequently caused by the accumulation of genetic abnormalities and abnormal cellular communication. The mammalian target of rapamycin (mTOR) signaling pathway is a key player in the development of many malignancies (**Fig. 1)** [1].

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mTOR is a serine/threonine kinase that occurs in two different complexes: mTORC1 as well as mTORC2, both of which control essential cellular activities as growth, protein synthesis, autophagy, and metabolism. mTORC1 responds largely to food and growth factor availability, whereas mTORC2 regulates cell survival and cytoskeletal architecture [2]. Mutations in upstream regulators such as PTEN or TSC1/2 typically cause mTOR signaling dysregulation in a variety of malignancies, including breast, prostate, lung, and colon cancer [3].

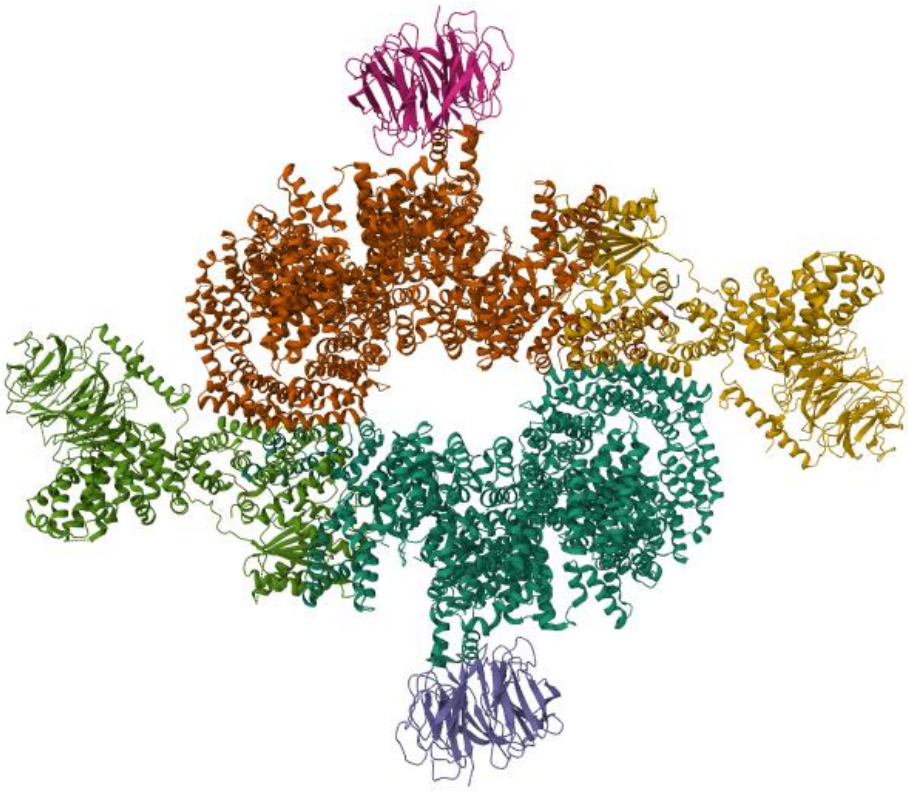

Figure 1. The three-dimensional structure of mTOR

Given its critical role in cellular proliferation and survival, mTOR has emerged as a key target for cancer treatment and chemoprevention. Chemoprevention is the use of natural or manmade medicines to prevent or postpone cancer progression. mTOR inhibitors, which were originally designed as cancer therapies, have showed promise in terms of lowering cancer incidence in high-risk groups. This study examines chemical-based methods to mTOR inhibition, concentrating on chemical characteristics, modes of action, and the inhibitors' potential as cancer chemopreventive drugs.

mTOR Signaling and Its Role in Tumorigenesis

The mTOR combines signals from growth factors, nutrition, and cellular energy state to govern activities such as cell growth, division, and survival. mTORC1 regulates protein synthesis by phosphorylating targets such S6 kinase (S6K1) and 4E-BP1, which are involved in mRNA translation. mTORC1 also suppresses autophagy, which helps cells recycle damaged organelles and proteins. mTORC2, on the other hand, controls cell survival by phosphorylating Akt, a kinase that prevents apoptosis [4]. The mTOR signaling dysregulation can be caused by a variety of mutations in upstream regulators, including PTEN loss of function, activation of the PI3K/Akt pathway, and TSC1/2 complex mutations [5]. These changes cause mTOR hyperactivation, which promotes uncontrolled cell proliferation, resistance to apoptosis, and enhanced angiogenesis, all of which are characteristic of cancer. In addition, feedback loops involving mTOR and other signaling pathways such as MAPK and PI3K contribute to cancer cells' resistance to targeted therapy. Animal studies have shown that inhibiting mTOR can reduce tumor development, making it a promising target for both therapeutic and preventative measures [6]. For example, mTOR inhibitors have been demonstrated to suppress tumor development in breast, colon, and prostate cancer models, indicating their potential for cancer prevention.

First-Generation mTOR Inhibitors: Rapalogs

Rapalogs, meaning first-generation mTOR inhibitors, comprise rapamycin, everolimus, temsirolimus, and ridaforolimus (**Fig. 2**). These inhibitors function by binding to the FKBP12 protein and creating a complex that allosterically inhibits mTORC1 [7]. While rapalogs have demonstrated success in the treatment of a variety of malignancies, including renal cell carcinoma and breast cancer, their potential as chemopreventive medicines is more intriguing due to their comparatively low side-effect profiles. However, rapalogs have limitations, most notably the inability to regulate mTORC2 [8]. This might cause compensatory activation of the Akt pathway, which may reduce the efficacy of these medications in certain situations. Despite this restriction, rapalogs have been thoroughly investigated for their potential in cancer chemoprevention [9]. Rapamycin, for example, has been demonstrated to lower tumor incidence in genetically predisposed mice models, such as those with PTEN deletion, which are particularly prone to tumor development [10]. Rapalogs are especially effective in preventing cancer in high-risk individuals

or those who have inherited abnormalities in tumor suppressor genes such as PTEN [11]. Their chemopreventive ability has also been studied in preclinical models of colon or skin cancer, wherein rapamycin inhibited the growth of adenomas and tumors [12].

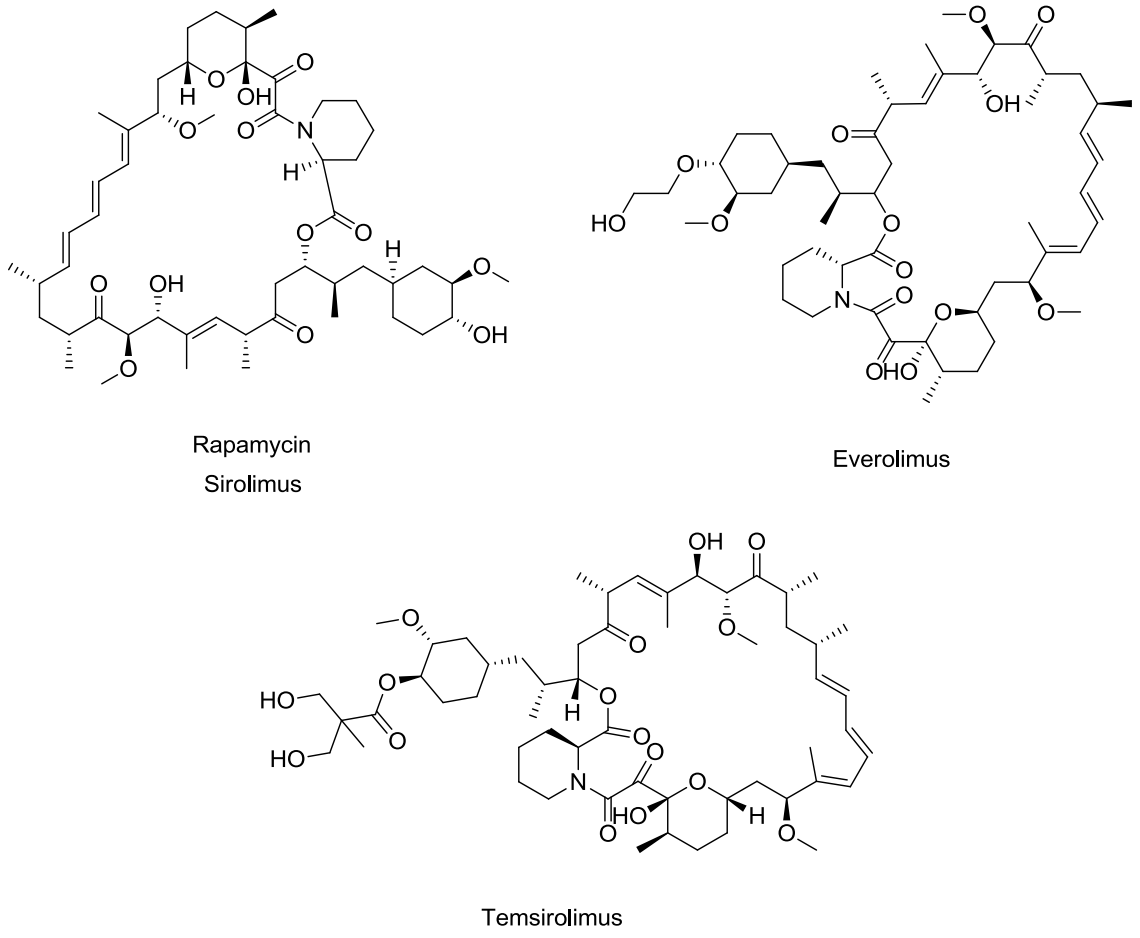

Figure 2. The first generation of mTOR inhibitors (Rapalogs).

Structure-Activity Relationship of mTOR Inhibitors

The structure-activity relationship (SAR) of mTOR inhibitors provides critical insights into how chemical modifications influence their binding affinity, selectivity, and therapeutic efficacy. The mTOR inhibitors can be broadly categorized into rapalogs (allosteric inhibitors), ATP-competitive inhibitors, and dual PI3K/mTOR inhibitors, each exhibiting distinct SAR characteristics [13].

Rapamycin and its analogs selectively inhibit mTORC1 by forming a complex with FKBP12, which then allosterically binds to the FKBP12-rapamycin binding (FRB) domain of mTOR [14]. The macrolide core (lactone ring) is essential for FKBP12 binding and subsequent inhibition of mTORC1. Modifications at the C-40 position (e.g., everolimus and temsirolimus) improve solubility and bioavailability while maintaining potency. Substitutions at C-43 or C-16 can influence stability and pharmacokinetics. Lack of direct inhibition of mTORC2 limits their efficacy in certain cancers, leading to resistance (**Fig. 3**).

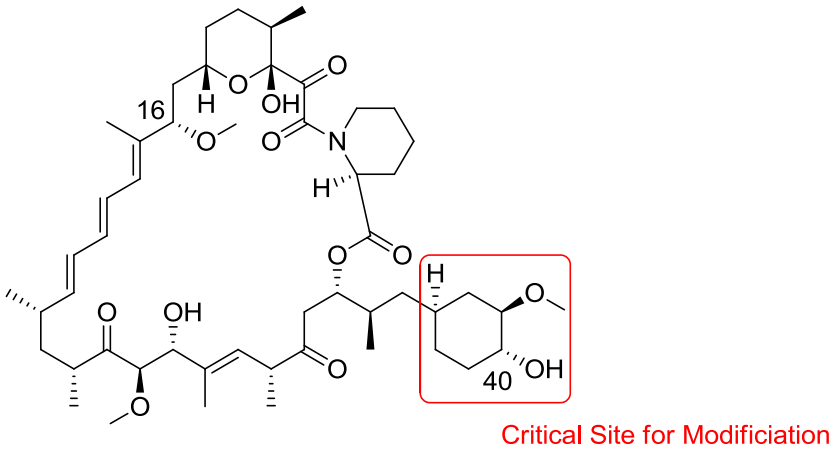

Figure 3. Summarized SAR of Rapalogs.

Second-Generation mTOR Inhibitors

To address the limitations of rapalogs, second-generation mTOR inhibitors have been created. These inhibitors, including MLN0128 and AZD8055 (**Fig. 4**), are ATP-competitive and directly target the mTOR kinase domain, inhibiting either mTORC1 and mTORC2. By inhibiting both complexes, these inhibitors prevent the stimulation of downstream signaling pathways, including Akt, that is frequently linked to resistance to mTORC1 inhibition.

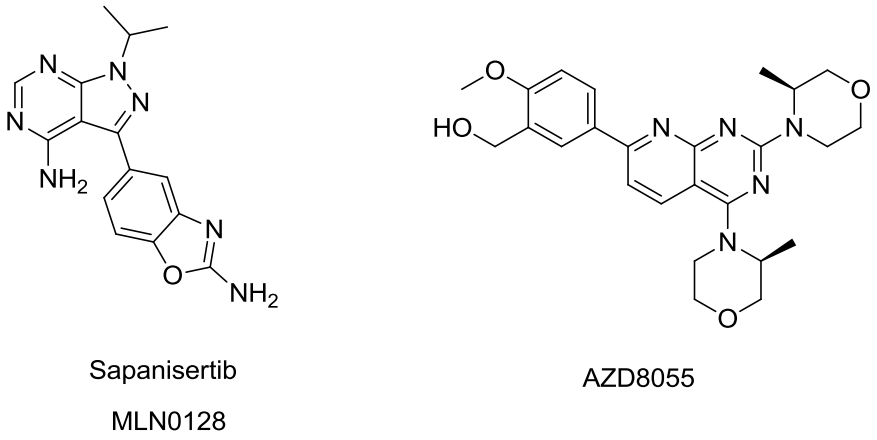

Figure 4. The second generation of mTOR inhibitors.

The second generation mTOR inhibitors have outperformed rapalogs in preclinical studies. For example, MLN0128 shows excellent anticancer activity in breast cancer models, but AZD8055 has showed promise in the treatment of colorectal and pancreatic malignancies. These inhibitors have also been tested in clinical studies, with some demonstrating good pharmacokinetics and tolerability. However, toxicity remains a worry, as inhibiting mTORC2 can affect critical cellular functions such as immunological function and glucose metabolism. The discovery of second-generation inhibitors marks a significant advance in cancer chemoprevention. Yet, like rapalogs, these medications are still in the early phases of clinical development, and their long-term safety and efficacy must be assessed.

Dual PI3K/mTOR Inhibitors

Considering the strong link between the PI3K/Akt along with mTOR signaling pathways, dual inhibitors targeting both PI3K and mTOR have been designed to block several areas of oncogenic signaling at the same time. Dual PI3K/mTOR inhibitors, including BEZ235 and GDC-0980 (**Fig. 5**), are intended to block both PI3K and mTOR kinases, inhibiting the activation of Akt as well as mTOR signaling.

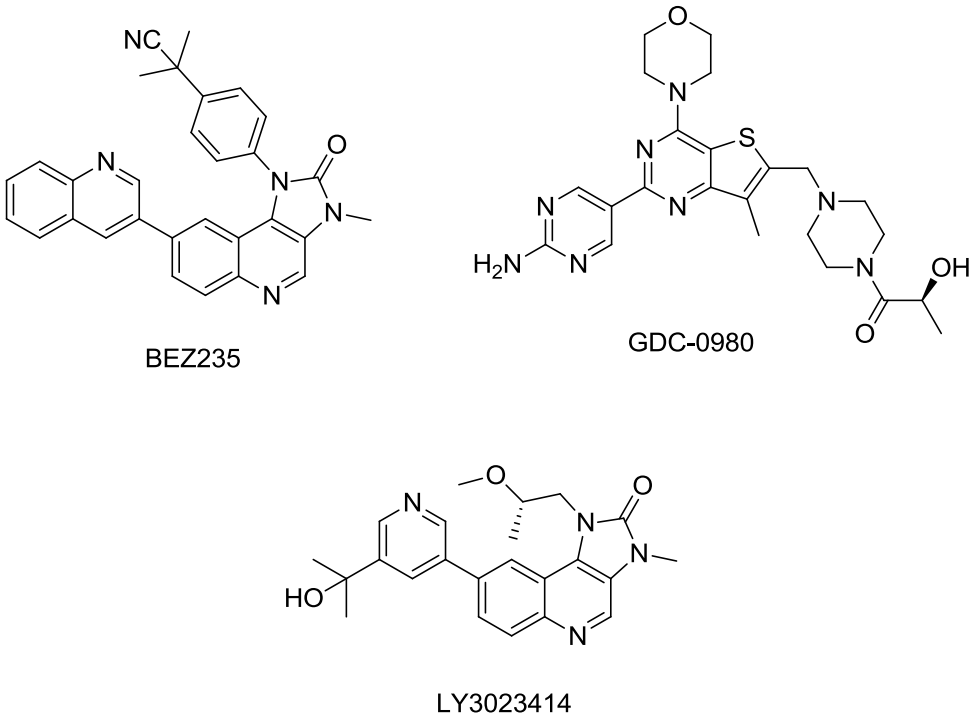

Figure 5. Dual PI3K/mTOR Inhibitors

Preclinical investigations using these inhibitors have yielded encouraging outcomes, notably in lung and colon cancer models. BEZ235, for example, has been demonstrated to inhibit tumor development and spread in colorectal cancer models [15]. Furthermore, dual inhibitors have the capacity to circumvent Akt feedback activation, as seen with rapalogs and second-generation mTOR inhibitors. However, dual inhibitors provide complications, notably in terms of toxicity. Inhibition of PI3K can disrupt normal physiological activities such as insulin signaling and glucose metabolism, potentially resulting in hyperglycemia and weight loss. Despite these obstacles, dual PI3K/mTOR inhibitors are attractive cancer chemoprevention agents, especially in malignancies characterized by abnormal PI3K/Akt/mTOR signaling [15].

Natural Product-Based mTOR Inhibitors

Natural substances have been utilized as a source of bioactive chemicals with medicinal use. Several natural substances have been found as mTOR inhibitors, providing an alternate strategy for cancer chemoprevention. Curcumin, resveratrol, plus epigallocatechin gallate (**Fig. 6**) are among the most promising naturally occurring mTOR inhibitors [16-18]. Curcumin, a polyphenol produced from turmeric, has been demonstrated to inhibit mTORC1 as well as promote autophagy in cancer cells.

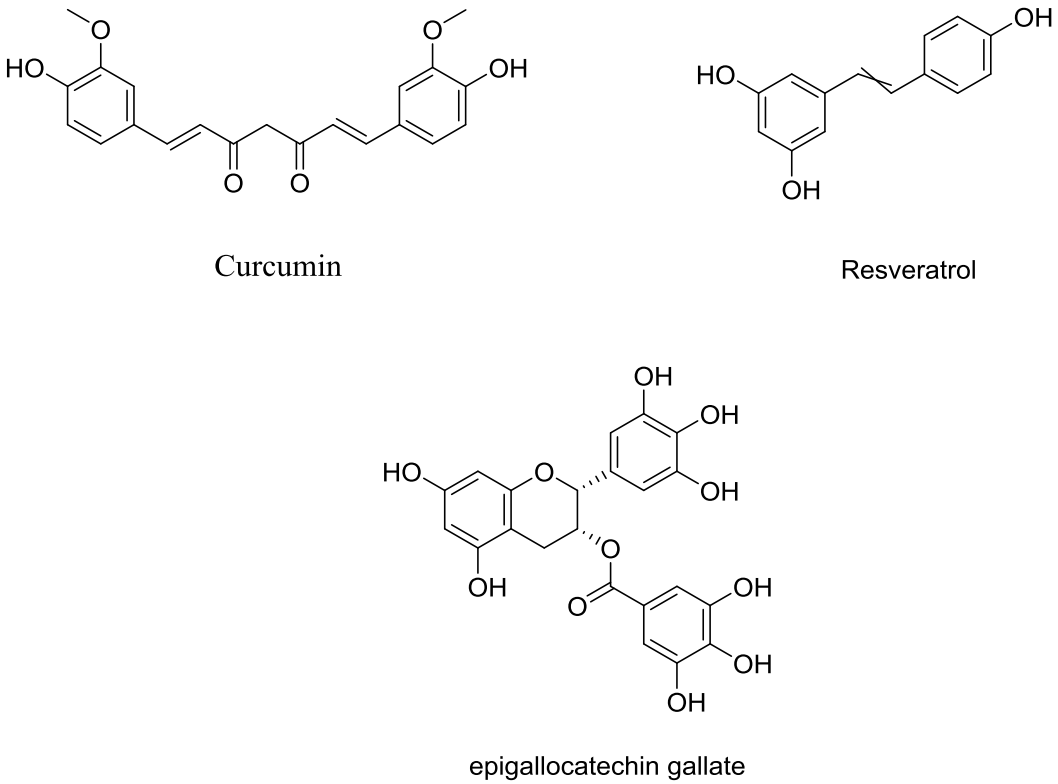

Figure 6. Natural Product-Based mTOR Inhibitors.

It also stimulates the AMPK pathway, hence inhibiting mTORC1. Curcumin has been shown in preclinical research to inhibit tumor development in colorectal and breast cancer models. Resveratrol, present in grapes and red wine, inhibits mTORC1 by activating AMPK and suppressing the PI3K/Akt pathway. It has been demonstrated to inhibit the development of prostate

and colon cancer cells in vitro and in vivo. Epigallocatechin gallate (EGCG), a key component of green tea, has been demonstrated to inhibit mTORC1 and lower cell proliferation in breast and prostate cancer models [17]. It also has antioxidant qualities, which may help with its chemopreventive benefits. Despite their promising potential, natural mTOR inhibitors frequently confront issues with absorption. Novel medication delivery technologies, such as nanoparticles and liposomes, are under investigation to improve their efficacy.

Challenges and Limitations

While mTOR inhibitors show great potential as cancer chemopreventive medicines, various difficulties must be overcome before they can be extensively employed in clinical settings. Toxicology is one of the most significant issues. Chronic mTOR inhibition can cause immunological suppression, hyperglycemia, and dyslipidemia. These adverse effects may restrict the long-term effectiveness of mTOR inhibitors in healthy people. The other obstacle is resistance. Tumor cells may acquire resistance to mTOR inhibitors by activating other pathways, such as MAPK signaling. Combining mTOR inhibitors with additional targeted medicines might help overcome this resistance. Furthermore, credible indicators for identifying which patients may benefit from mTOR-based chemoprevention are yet insufficient. Identifying these indicators will be critical to tailoring therapy and improving results. Finally, we want precise and comprehensive clinical translations. Preclinical studies provide a significant amount of data for mTOR inhibitors' chemopreventive effects. More clinical trials are required to determine the safety and effectiveness of these medicines in people.

Conclusion

Inhibitors of mTOR are a potential class of cancer chemopreventive medicines because they can disrupt critical pathways involved in tumor genesis and advancement. A wide range of mTOR inhibitors are being studied for potential use in cancer prevention, including rapalogs, second-generation ATP-competitive inhibitors, and natural product-based medicines. Despite problems such as toxicity, resistance, and clinical translation, current research is helping to improve these molecules for usage in high-risk patients. As our understanding of mTOR signaling and cancer biology advances, mTOR inhibitors might play a critical role in lowering the worldwide cancer burden.

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