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Overcoming multifaceted challenges in cancer treatment: Targeting signal transduction pathways and tumor microenvironment for enhanced therapeutic efficacy

Abdul Majeed Ansari[1], Naresh Kumar Sharma[1], Kashinath Tripathi[2], Gautam Bhardwaj[3*], Ritu Chauhan[4*], Rajiv Kumar Tonk[3], Moyad Shahwan[5,6], Hardeep Singh Tuli[7], Abhishek Chauhan[8]

[1]Department of Chemistry, Government P.G. College, Bundi, India.
[2]Department of Chemistry, Udai Pratap College (An Autonomous College), Varanasi, India.
[3]Department of Pharmaceutical Chemistry, Pharmaceutical Sciences and Research University, New Delhi, India.
[4]Department of Biotechnology, Graphic Era (Deemed to be University), Dehradun, India.
[5]Department of Clinical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates.
[6]Centre of Medical and Bio-Allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates.
[7]Department of Bio-Sciences and Technology, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to Be University), Mullana, Ambala, India.
[8]Amity Institute of Environmental Toxicology Safety and Management, Amity University, Noida, India.

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ABSTRACT

Cancer, a leading global cause of mortality, persists despite extensive research. While progress, notably in protein kinase-modulating drugs, is evident, a definitive cure remains elusive due to multifaceted challenges. This article discusses diverse approaches in cancer treatment, recognizing its complexity. Key hurdles include cancer progression stages, the intricate tumor microenvironment, drug resistance, pharmacodynamics, tumor hypoxia, and compromised immunity. Signal transduction pathways are crucial in cancer progression and resistance, particularly in immune regulation, hypoxia response, and autophagy. Understanding and targeting these pathways are vital for developing novel therapies. By elucidating the interplay between immunity, signaling, and therapeutics, researchers seek to overcome treatment obstacles. A comprehensive approach offers hope for improved outcomes and breakthroughs in cancer management.

INTRODUCTION

The complexity of cancer has provided both researchers and healthcare professionals with a significant opportunity to advance understanding and treatment. Across various classifications, cancer remains a leading cause of death worldwide [1], despite the implementation of multiple therapeutic approaches. One of the most daunting challenges lies in the intricate etiology of cancer, particularly as it progresses to advanced stages. The widely accepted tumor node metastasis staging system underscores the complexity of cancer diagnosis and treatment planning. While early-stage tumors may be effectively managed through surgical interventions, the presence of metastasis necessitates a combination of adjuvant chemo radiation and surgical modalities. However, the success rates of these interventions remain dishearteningly low, largely due to the aggressive nature of metastatic cancer, which can infiltrate and affect multiple organs in various ways. Chemo radiation therapy, in NSCLC, paclitaxel in chemotherapy with radiation, and oxaliplatin in chemotherapy with radiation although integral to cancer treatment, often fall short of fully addressing

*Corresponding Author
Gautam Bhardwaj, Department of Pharmaceutical Chemistry, Pharmaceutical Sciences and Research University, New Delhi, India. E-mail: gbhardwaj @ gmail.com
Ritu Chauhan, Department of Biotechnology, Graphic Era (Deemed to be University), Dehradun, India. E-mail:rituachauhan25 @ gmail.com

metastatic cancer. Consequently, chemotherapy emerges as a cornerstone modality in the management of metastasized cancer. However, the emergence of chemotherapeutic drug resistance poses a significant hurdle to achieving successful treatment outcomes [2].

In recent years, the development of novel drug candidates utilizing sophisticated drug design approaches and considering explicit clinical parameters has shown promise. Despite these advancements, the persistence of chemotherapy resistance highlights the ongoing challenge of achieving a comprehensive cure for cancer. In navigating this landscape, it is crucial to delve deeper into the mechanisms driving cancer progression and treatment resistance. By embracing a multifaceted approach that combines innovative therapeutic modalities with a nuanced understanding of cancer biology, we can strive towards more effective treatment strategies and improved outcomes for patients battling this formidable disease.

Approaches on the robust basis of physiology *via* killing cancerous cells by oxidized free radicals and reactive oxygen species (ROS) in cells. The study revealed platinum class alkylating chemotherapeutic drug generated free radicals in cells that accept and transfer electrons oxygen and kill cancerous cells [1]. Cell organelle has a vital role involving mitochondria, endoplasmic reticulum, lysosomes, and Golgi bodies. Mitochondria and HIF have a strong interconnection in regulating cell death. Subdue mitochondrial function by HIF to participate in drug treatment failure [2].

The Otto Warburg illustrates damaged respiration and excessive fermentation in cells responsible for Cancer [3,4]. The D.N.A. of cell damage by ultra violet radiation. Carcinogens consequently defect in apoptosis liable for tumorigenesis [5]. Apoptosis of damaged D.N.A. control by (Ataxia telangiectasis mutated and RAD3 related) A.T.R./Chk-1 but mechanism not yet well established [6,7]. Evidently, upon D.N.A. damage by U.V. simultaneously activation of (Ataxia telangiectasis mutated) A.T.M./Chk-1 signaling pathway consequently down-regulates Smurf-1 and increases Rho-B consequently, apoptosis [8–10]. Failures are considered as an opportunity to be emphasized in this article. Multiple transduction pathways are to be found, analyzed, and then designed for chemotherapy. Among all other protein kinases, the most acceptable pathway is still a significant impediment in clinical oncology. Protein kinase involves receptor and non-receptor tyrosine kinase, Serine and threonine kinase, and other associated pathways. All signal transduction pathways majorly inhibit translation by altered transcription and replication whereas this perspective emphasizes hypoxia and immunotherapy. Another, parameter, tumor microenvironment (TME), was altered drug penetration due to adverse pharmacokinetic conditions consequently, promote tumor growth. Stromal cells in T.M.E. participate in uncontrolled proliferation, angiogenesis, and metastasis with drug impediments [11–18]. Tumor cells participate in hypoxia in the TME and its major impediment to cancer drugs [12]**.** Hypoxia participates by HIF-α and acidic TME. In hypoxic conditions, the fast proliferation of cancerous cells due to creates new angiogenic vasculature that contributes to delivering oxygenated blood [19,20]. The slowly proliferating cancer cells, under hypoxic conditions, escape from chemotherapy drugs, and these cancer cells ensure epithelial to mesenchymal transition. Some studies revealed in the acidic environment of cells lysosomes and endosomes in tumor cells support metastasis by activating protease [21,22]**.** The degradation of tumor cells in a neutral environment and simultaneously, improved by cytotoxic T lymphocyte, immunotherapy [23]. In the light of above point, hypoxia alters apoptosis cell death, autophagy to remove dead from cells, and immunotherapy to manage cancer.

Hypoxia bolstering ROS to induced cancer

During hypoxic conditions, ROS levels increased due to decreased oxygen utilization, the passage of electrons from the mitochondrial complex by the electron transport chain (ETC), and electron leak from the ETC, consequently overproduction of ROS. ROS destabilize genomic stability and disrupt the DNA repair pathways and simultaneously, ROS. cause mutation and promotion of cancer with multidrug resistance cells [24–27]. Hypoxic stress aids tumor resistance with immunosuppression by tumor-associated macrophages [28,29]. The drug does not diffuse into the cell in an acidic environment and simultaneously, genetic alteration in P53 due to Hypoxia, also known as ion trapping [30]. In hypoxic conditions, multidrug resistance has increased the activity of multidrug transporter p-glycoprotein (p-gp) and its expression with the mechanism of multidrug resistance expressed by the MDR1 gene. Simultaneously, in hypoxic conditions mRNA levels remain the same, and activity increases consequently, tumor progression increases [31–34]. Tumor cells in the human body then alter the metabolism of normal cells under hypoxic conditions and proliferate by capturing the host immune system, disrupting apoptosis [35,36] by Caspase-mediated selective cleavage off a subset of cellular polypeptides. Simultaneously, participating biochemical and morphological cell apoptosis [37]. DNA damage and microtubule disruption by intracellular caspase cascades accelerate by death receptor ligand system and cellular stress. DNA damage and microtubule disruption regulate B cell lymphoma-2(Bcl-2) family members have pro-apoptic and anti-apoptic class. Intracellular caspase cascade is regulated by the Bcl-2 family by cytochrome-c and other polypeptides [38,39].

Hypoxia modulation to manage Cancer

Hypoxia is to be considered as targeted for cancer therapy. Multiple ways to target hypoxic tumors are hypoxia-activated prodrug [40], hypoxia-inducible factor 1-alpha (HIF-1α) modulator, Prolyl 4-hydroxylase alpha-1 (P4HA1), Prolyl hydroxylase domain 2, Gene therapy, specific target pathways critical in hypoxia such as mTOR (mammalian target of rapamycin), unfolding protein response (UPR) pathways, Acid induced tumor. HIF-1α induced chemotherapeutic resistance in pancreatic cancer *via* up-regulation of cytidine triphosphate synthase and transketolase while using digoxigenin to halt HIF-1α induced translation. Consequently, encouraging results of gemcitabine in pancreatic Cancer [41–43].P4HA1 up regulated by HIF-1α in the TME of breast cancer. P4HA1 regulates cell metabolism and enhances tumors; thus, P4HA1 is a prominent

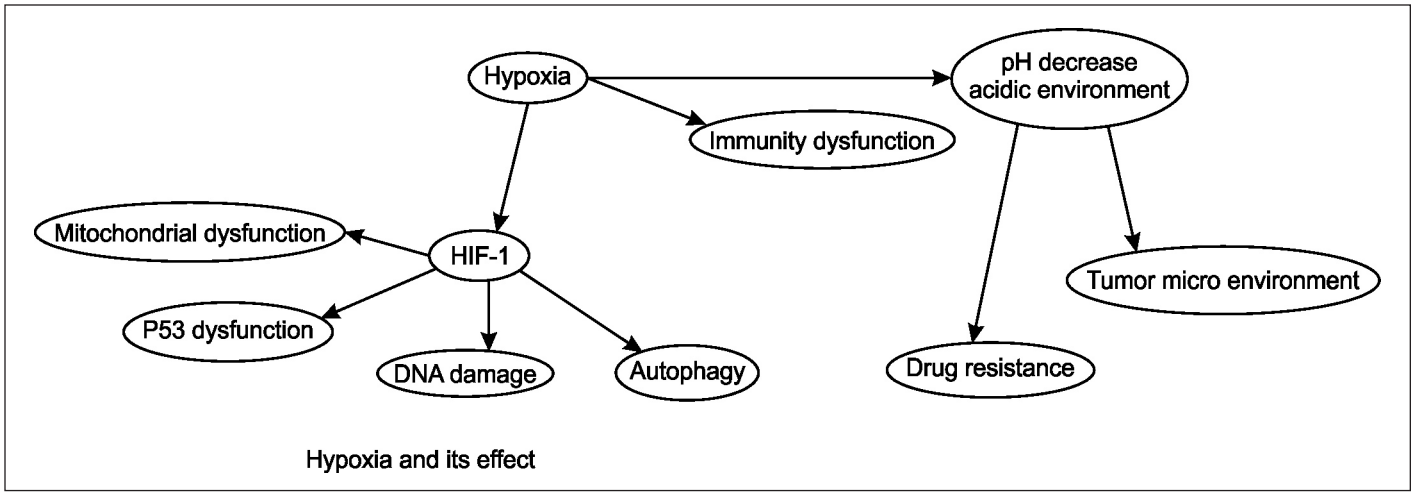


Figure 1. The figure depicts the effects of hypoxia on cellular and physiological processes. Hypoxia leads to the activation of HIF-1αsss, which results in mitochondrial dysfunction, p53 dysfunction, DNA damage, and autophagy. Additionally, hypoxia causes a decrease in pH, creating an acidic environment that contributes to immunity dysfunction, alteration of the **TME**, and increased drug resistance. This interplay highlights the critical role of hypoxia and HIF-1 in tumor progression and resistance to therapy.

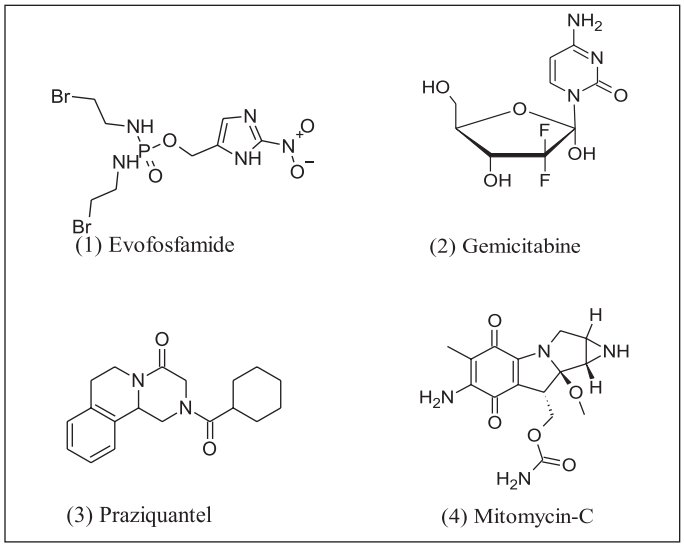


Figure 2. Hypoxic prodrugs.

target for breast cancer [41]. HIF-1α regulates the transcriptional regulation by gene TFP1 in breast cancer. Another prominent target of HIF-1α is prolyl hydroxylase domain 2 (PHD2) for breast cancer treatment. The hypoxia is further illustrated in Figure 1.

The hypoxic prodrug was activated by cellular reductase, re-oxidized into initial drug progenitors in anorexic cells, and then converted into a cytotoxic substance. Clinical trial phase-II results encourage hypoxic progenitor TH-302 with gemcitabine. Hypoxic agents as progenitors, also known as alkylating agents, are in Figure 2. TH-302 ((1) Evofosfamide) chemical class of alkylating agent and, in combination with (2) gemcitabine, synergistic action in pancreatic cancer [44]. Synergistic action of (3) praziquantel use as an adjunct therapy in bladder cancer with (4) Mitomycin-derived prodrug [45].

Autophagy and Cancer (Hypoxia by HIF-1α induction of autophagy)

Autophagy, a vital cellular process, is essential for maintaining cellular viability by removing misfolded proteins and dysfunctional organelles [46–52]. It is particularly crucial for cellular stress management and homeostasis, thereby inhibiting tumor formation. However, in the context of solid tumors, autophagy's role becomes complex and controversial as it aids tumor survival under hypoxic conditions [53]. Hypoxia, often found in solid tumors, induces autophagy through the HIF-1α pathway. This pathway activates autophagy-related proteins such as ULK-1, Atg13, and FIP200 through mTOR and LKB1-AMPK signaling [54].

Autophagy is classified into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy. In solid tumors, inhibiting autophagy has been shown to enhance chemotherapy effectiveness, highlighting its dual role in cancer therapy [55]. Hypoxia-induced autophagy occurs in tumor regions, where the UPR contributes to chemotherapy resistance. This resistance is mediated by the PERK-dependent transcriptional induction of microtubule-associated protein 1 light chain 3 and autophagy-related genes [55,55]. Furthermore, autophagy is associated with multidrug resistance due to the activation of ATP-binding cassette transporters. Therefore, understanding the balance between autophagy's protective roles and its support for tumor survival under hypoxia is crucial for developing effective cancer therapies.

m-TOR pathway

The elevated level of m-TORC1 was detected in rodents and human tumors. Further, confirmed in tumor-derived cell lines have knockdown of TSC1:TSC2 [56–67]. Cell growth is regulated by the mTOR pathway involved, specifically by m-TORC1 upregulating and downregulating the TSC1/TSC2 complex. Other factors regulate cell growth by activating the m-TOR pathway and rising level A.M.P. consequently activated

AMP kinase (AMPK) in multiple ways among one genotoxic stress by P-53 mediated activation. The mTORC1 activity is upregulated by growth factors through insulin or insulin-like growth factors, phosphoinositide-3' kinase, A.K.T. pathway, Wnt-GSK3 signaling pathway and ERK-RSK kinase cascade [68,69].

m TORC1 activity modulates in adverse conditions, nutrient limitation, Hypoxia, and DNA damage disrupt the cell cycle and P53 signal. m TORC1 activity upregulates and downregulates by TSC1:TSC2 complex *via* GAP (GTPase activating protein) by action of GTPase-Rheb that stimulates mTORC1. m TOR regulation involves specifically sestrin-2 due to a decrease in GTP level. TSC activity also regulated by other kinase AKT, ERK, RSK, AMPK [70,71].

In stressed conditions, P53 precisely targets gene p21waf to activate sestrin, which means sestrin-1(PA26) and sestrin-2(Hi95) dimer interact with TSC1:TSC2 (Hamartin:tuberin) complex and phosphorylation by AMP induced AMPK-α consequently autophosphorylation TSC1:TSC2 complex simultaneously GAP activity by Rap1 induced by TSC2 and another factor Guanidine exchange factor also participate support by transitional controlled tumor protein study in drosophila [72] and m-TOR inhibition [73]. In cancer conditions, G.A.P. mutates, mTORC1 activation, and cell growth. m TOR proteins are serine-threonine kinase that belongs to the family of the phosphoinositide 3 kinase-related kinase and occurs in eukaryotes. m TOR occurs in two complex forms: mTORC1 and mTORC2. mTORC1 evidently participates in cancer, neurodegeneration while mTORC2 function is still not fully understood [74–77]. The m-TOR activity is illustrated in Figure 3 [78].

m TORC1 modulation was TSC complex-dependent signaling. TSC suppresses tumor cells and downregulates by phosphorylation. m-TORC1 upregulates cell growth, but the mTOR pathway still needs further research. m-TOR inhibitors (5), (6), (7), and (8) are in Figure 4. TSC complex downregulates by phosphorylation among GSK-3β, energy stress, and hypoxia to AMP activates AMPK, and hypoxia to HIF1α activates REDD1. In contrast, on the other side, hypoxia-induced HIF1α inhibited by Von Hippel-Lindau tumor suppressor furthermore WNT pathway inhibits GSK-3β to phosphorylation [79–88].

Immunotherapy and Cancer

In cancer few decades, immunotherapy is illustrated in Figure 5 as one option to combat cancer [89–91]. Immunotherapy boosts immunity to kill cancer cells at checkpoints *via* checkpoint inhibitors, adoptive cell transfer, and vaccines. The increased immunity combat cancer cells *via* several checkpoint inhibitors among Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein 1 (PD-1) and other renowned checkpoint inhibitor monoclonal antibodies (mAB) with the disadvantage of administration schedule, time-consuming procedure and costly and toxic effects not to be altered by any way in comparison to small drug molecule. The small drug molecule can reach the target site in the TME and low immunogenicity [92]. Find out small molecules that work in the TMEt and modulate immune suppression *via* either activating innate immune response or adaptive immune signaling pathway to treat Cancer. Among adenosine receptor signaling at immune checkpoint prominent target. Adenosine $A_{2A}R$ and $A_{2B}R$ receptor antagonists were used for cancer management by immune-modulation. The human immune system combats pathogens by way of inflammatory response. Tumors hijack and take control of the immune system, grow, and then metastasize [93]. The immune checkpoint pathways PD1, CTLA-4, $A_{2A}R$,$A_{2B}R$, TIM-3(T cell immunoglobin and mucin domain-3) [94,95]. In normal physiological conditions, the level of adenosine is less than 1 µM [96] but observed adenosine levels (10 µM) in the TME and related pathological conditions are, as Cancer related fibroblasts, regulatory T cells, myeloid-derived suppressor cells (MDSCs), endothelial cells and T helper cells [97–103].

Upon binding adenosine to $A_{2A}R$ and $A_{2B}R$ to increase c AMP protein kinase, the signal is associated with the immune system and consequently, immunosuppressant in the TME. Increased intracellular c AMP level in T cells due to activation of $A_{2A}R$ and $A_{2B}R$ receptor consequently, decreased Tumor necrosis factor (TNFα), interleukin 2, and interferon Gamma, and compromised CD-8+ T cell infiltration [104–106]. Adenosine 2A receptor activation on regulatory T cells increases PD-1 and CTLA-4 expression, and macrophages promote tumor cell proliferation and increase immunosuppressant [107,108]. $A_{2B}R$ alters cell differentiation by the mononuclear-phagocyte system, consequently, cancer angiogenesis, tumor spread, and suppression of lymphocyte-mediated anti-tumor immunity [109]. Thus, Adenosine receptor antagonist, PD1, CTLA-4, a prominent oncotarget. Evidently, in some studies alone, $A_{2A}R$ antagonists were not encouraged as a result in CL8-1 melanoma cell line and RMA T cell lymphoma cell line exhibits dependent on CD8+ T cell activity but prominent observation metastasis decrease. The union of $A_{2A}R$ and $A_{2B}R$ antagonists with inhibition of PD-1 and CTLA-4 results in a prominent anticancer effect [110,111]. The $A_{2B}R$ inhibition has prominent anti-tumor effects in prostate cancer, slow growth of the bladder, and breast cancer with decreased cell proliferation. Furthermore, it decreases tumor growth and immune suppression due to MDSCs and inhibits vascular endothelial growth factor and angiogenesis [112–115].

Adenosine antagonist for cancer immunotherapy

Adenosine 2A receptors have significance in cancer immunotherapy such as pyrazole and pyrimidine core. That article emphasizes anti-tumor effects concerning immunity. Natural and synthetic analogs as Adenosine receptor antagonists are Xanthine and analogue, Pyrimidine analogue, Azolopyrimidine analogues, Triazolo pyrimidine analogues, 2-oxothiazole analogue, Pyrazole and Benzothiazole analogue, Benzimidazole, Benzothiazole, Quinoxalines, Amino Pyrimidines, Triazine isomers, Pyrazole linked heterocyclics and miscellaneous as illustrated in Table 1.

Xanthine and its analogue

Xanthine and semi-synthetic analogues are illustrated in Figure 6. (9) Caffeine is a non-specific naturally occurring

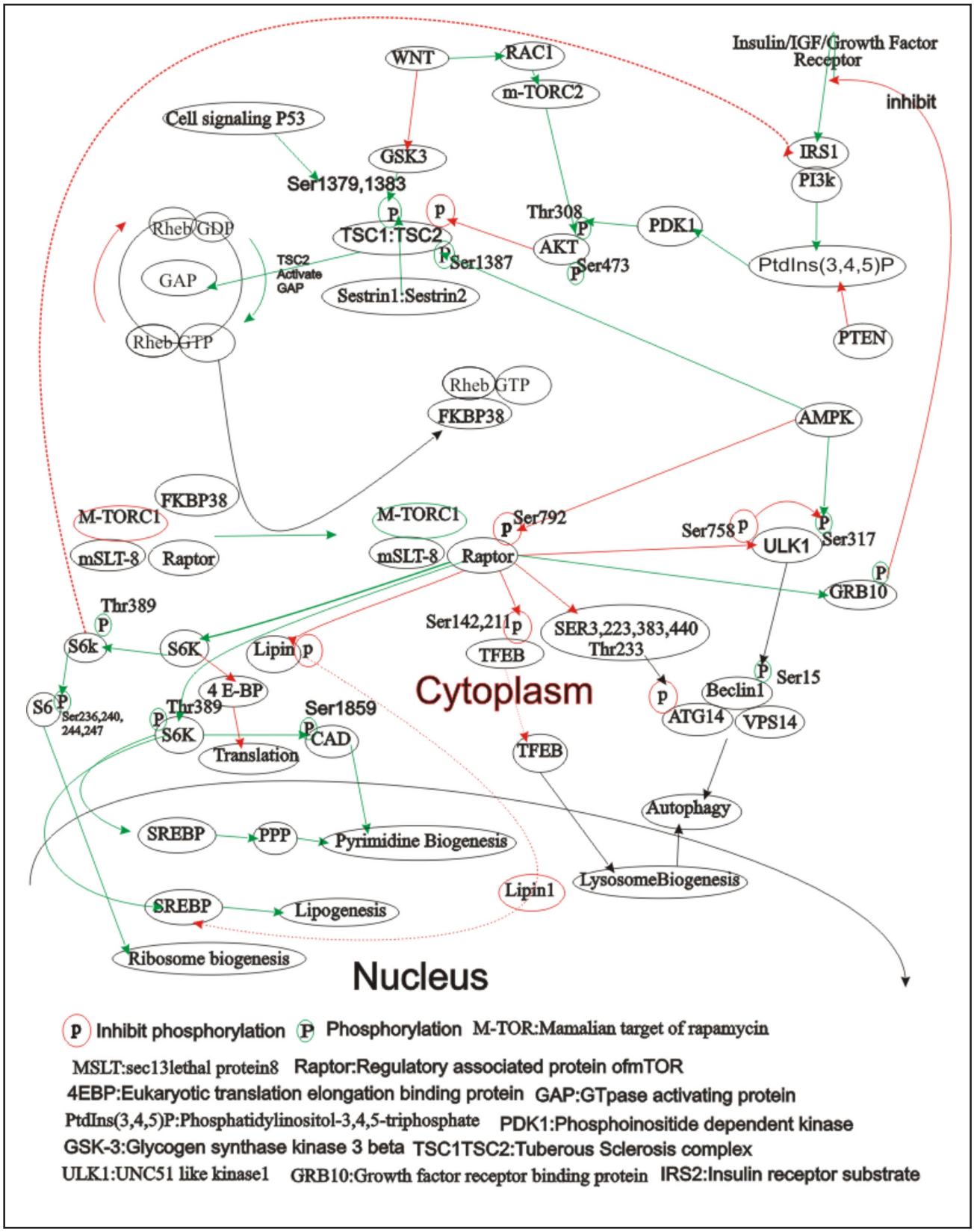


Figure 3. The figure illustrates the complex signaling pathways involving the mammalian target of rapamycin (mTOR), focusing on its two complexes: mTORC1 and mTORC2. mTORC1 is regulated by nutrients, growth factors, and energy status, promoting protein synthesis, lipogenesis, and ribosome biogenesis while inhibiting autophagy. Key regulators include Rheb-GTP, FKBP38, TSC1/TSC2, PI3K, AKT, and AMPK. mTORC2 mainly regulates cytoskeletal organization and cell survival through AKT, SGK, and PKC. The figure also highlights the downstream effects of mTOR activation, such as translation promotion via S6K and 4EBP1, and autophagy regulation through ULK1 and Beclin1. This interplay underscores the importance of mTOR in cellular growth, metabolism, and survival, pointing to potential therapeutic targets for diseases like cancer.

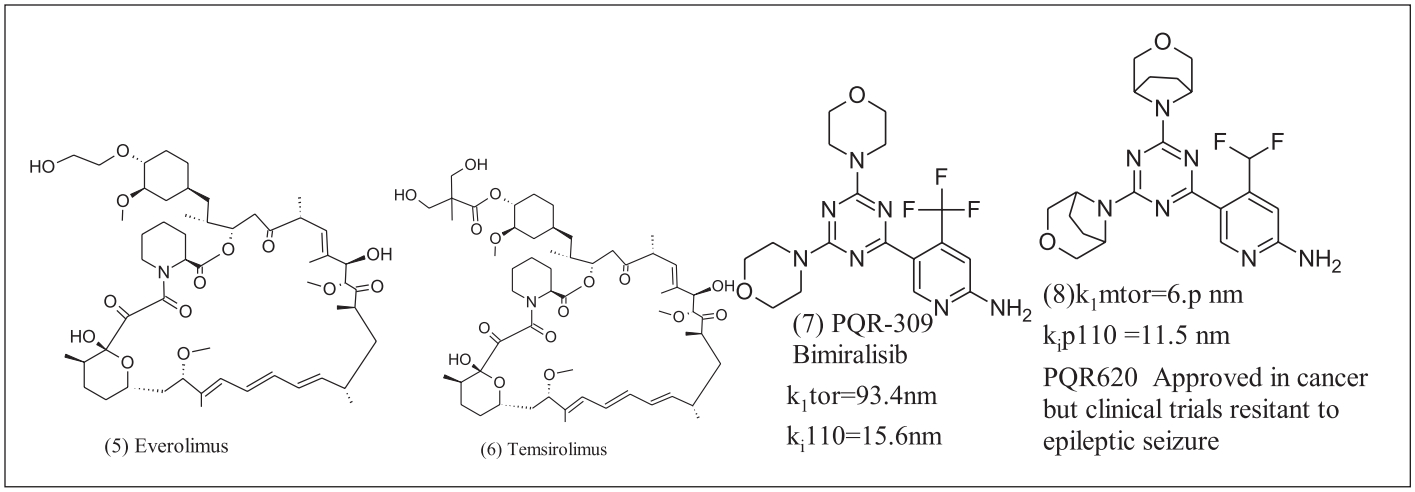


Figure 4. mTOR modulator.

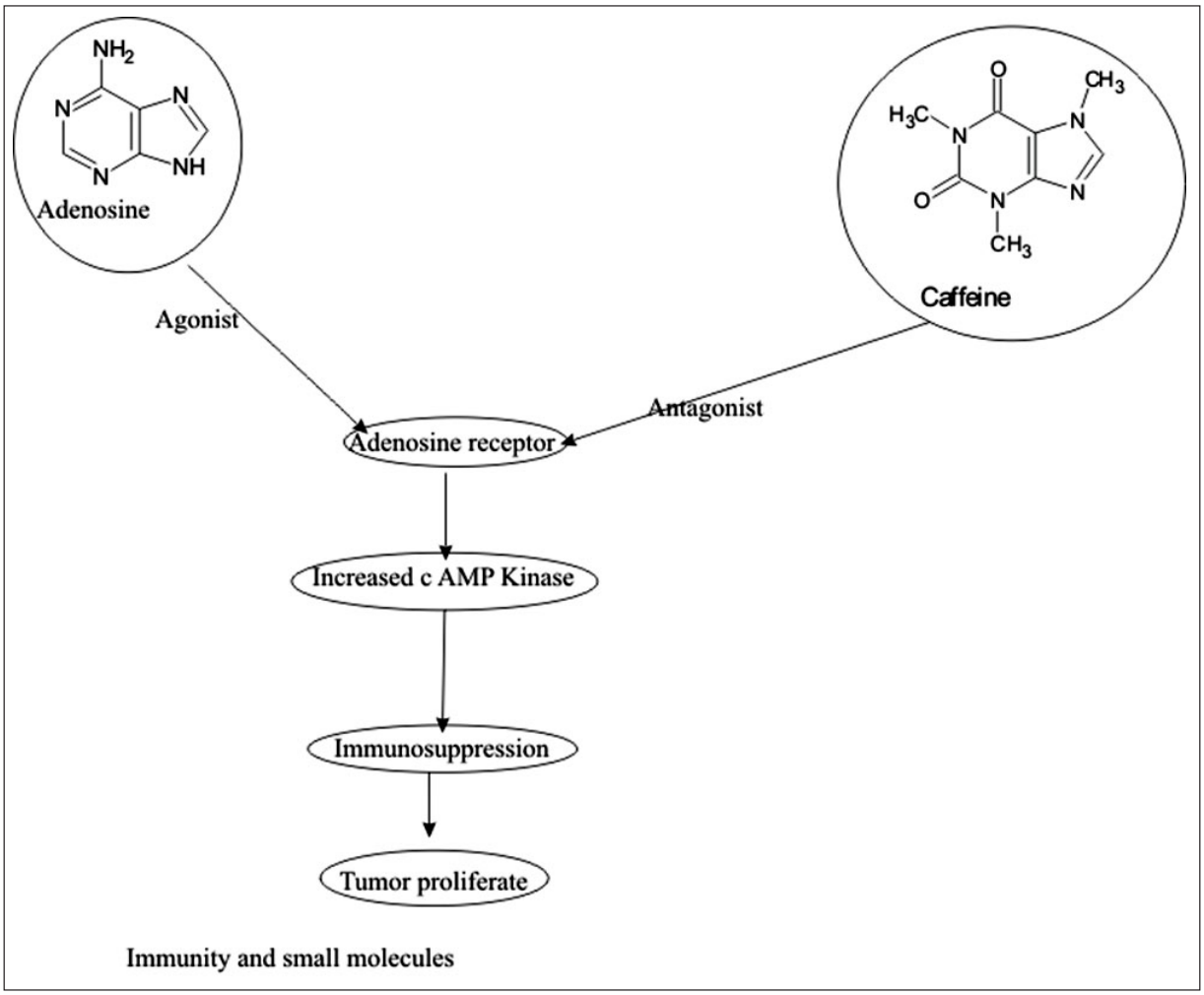


Figure 5. The diagram illustrates the interaction between adenosine and caffeine with the adenosine receptor. Adenosine acts as an agonist, binding to the adenosine receptor, leading to an increase in cAMP kinase activity. This cascade results in immunosuppression and the promotion of tumor proliferation. Conversely, caffeine functions as an antagonist to the adenosine receptor, potentially disrupting this pathway. The overall theme is the impact of small molecules on immunity and cellular processes.

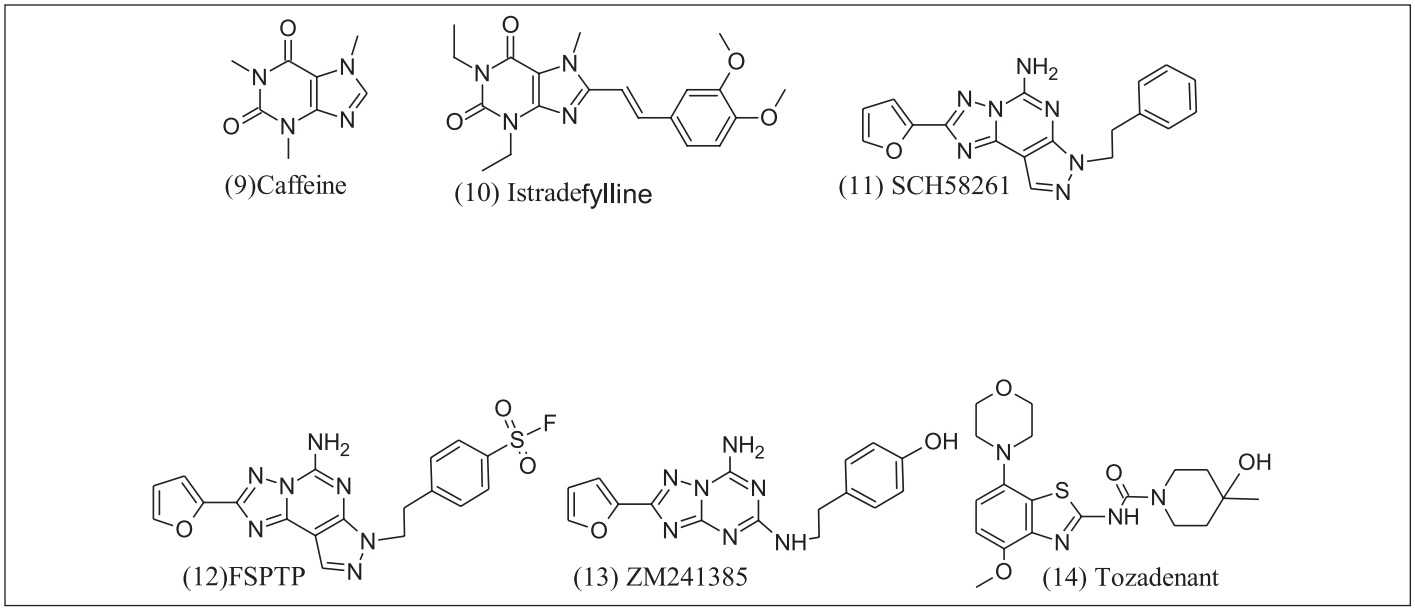


Figure 6. Xanthine and Pyrazolo triazole pyrimidine inhibitor.

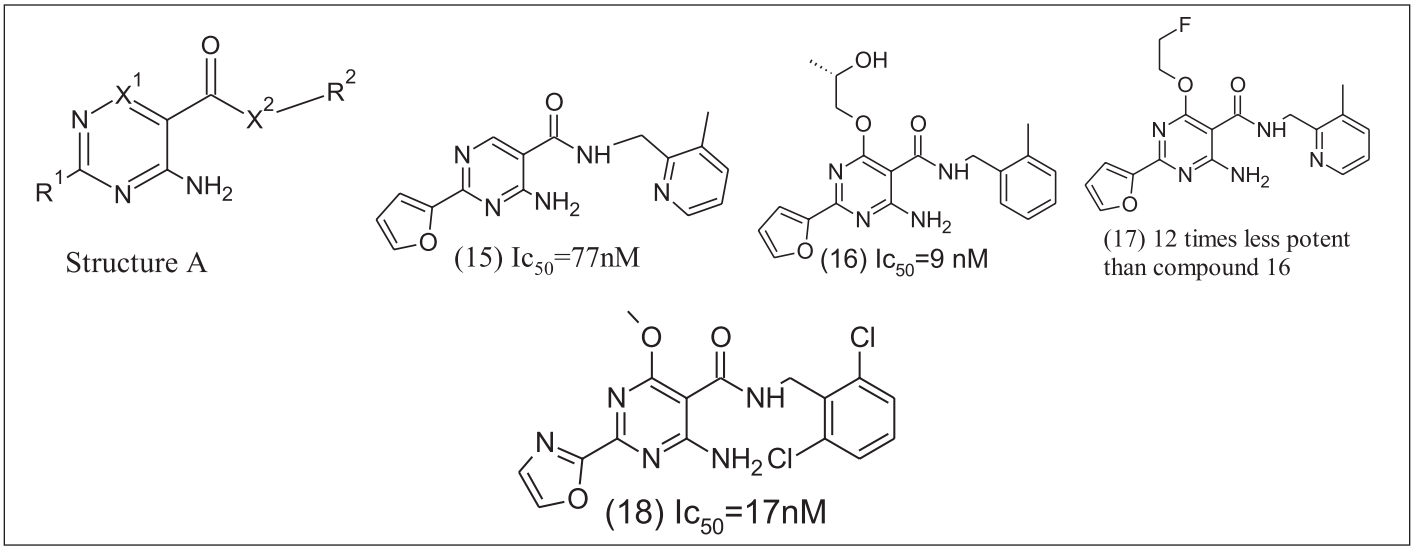
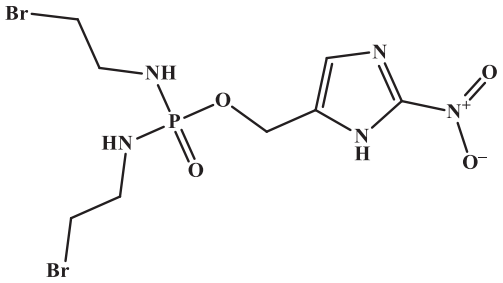
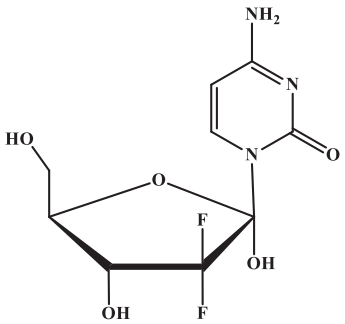
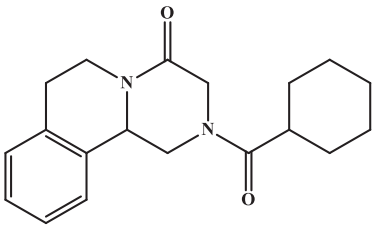
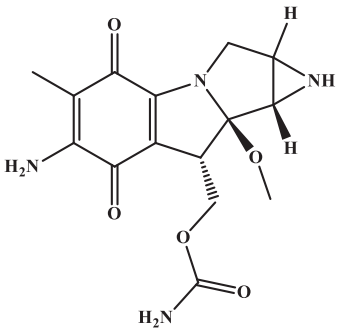
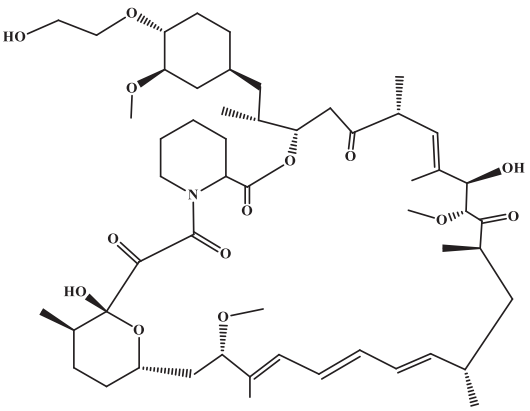


Figure 7. Pyrimidine inhibitors.

adenosine receptor antagonist (10) Istradefylline, a semi-synthetic xanthine analogue, have adenosine antagonist action and was initially designed to treat Parkinsonism, but (10) has revealed good result in Cancer [116] thus, as an option to repurpose for Cancer. Xanthine analogues have poor water solubility. Pyrazolo triazole Pyrimidine analogue non-xanthine adenosine 2A receptor antagonists are SCH58261, FSTP, ZM241385, and Tozadenant [117,118] (11). SCH58261 revealed the slowdown of metastasis in breast cancer by CD73 endogenously, and melanomas activate Nk cells (12). FSTP irreversible type antagonist and low efficacy due to impaired CD+ T cell differentiation and accumulation [119], (13) ZM241385 has poor solubility but inhibits lung cancer tumor metastasis [110], (14) Tozadenant enters clinical trial phase-3, but adverse events and scientists were further studies but encouraging results in breast cancer in combination with PD-1 inhibitors and mAB [105].

Pyrimidine analoguesAdoRx therapeutics design and patented pyrimidine derivatives are illustrated in Figure 7 as potent $A_{2A}R$ and $A_{2B}R$ antagonists. The 2-amino pyrimidine core chemical structure of the antagonist is A at R^1 position furan ring and at X-R^2 position aryl methylamine. These analogue (15), (16), (17), and (18) exhibit responses in lipopolysaccharide mediate TNFα release NECA reversal assay.

Table 1. Synthetic analogues for cancer.

Analogues name	Structure	Class	Reference
(1) Evofosfamide		Alkylating agent	[45]
(2) Gemicitabine		Alkylating agent	[45]
(3) Praziquantel		Alkylating agent	[45]
(4) Mitomycin-C		Alkylating agent	[45]
(5) Everolimus		mTOR	[79–88]

(*Continued*)

Table 1. (*Continued*)

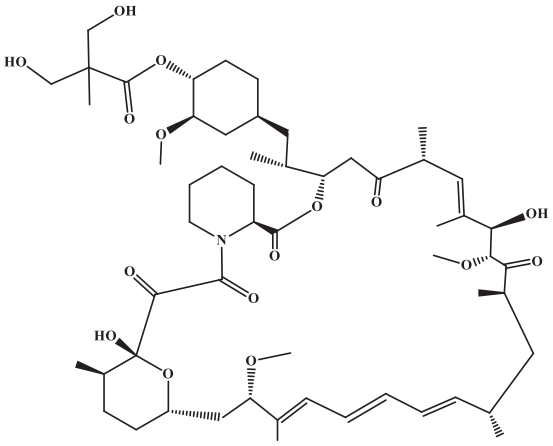
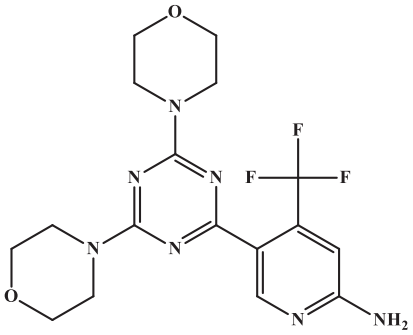
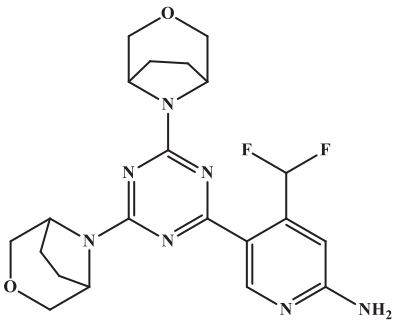
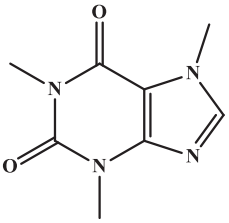
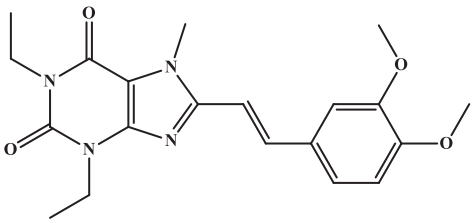
Analogues name	Structure	Class	Reference
(6) Temsirolimus		mTOR	[79–88]
(7) PQR-309 Bimiralisib $k_i$tor = 93.4 nm k_i110 = 15.6 nm		mTOR	[79–88]
(8) $k_i$mtor = 6.p nm k_ip110 = 11.5 nm PQR620 approved in cancer but clinical trials resistant to epileptic seizure		mTOR	[79–88]
(9) Caffeine		Xanthine analogue	[117–119]
(10) Istradefylline		Xanthine analogue	[117–119]

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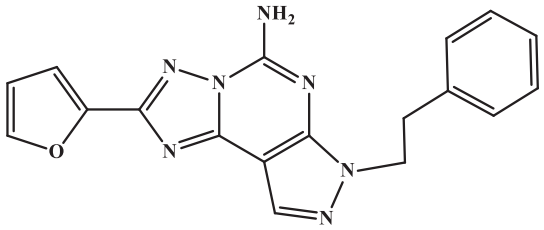
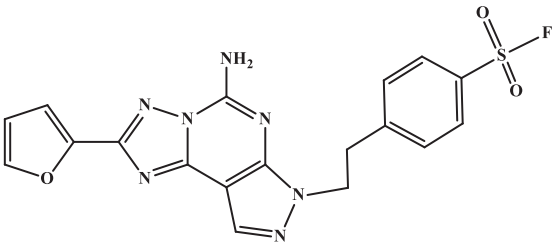
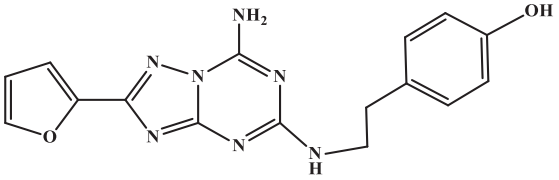
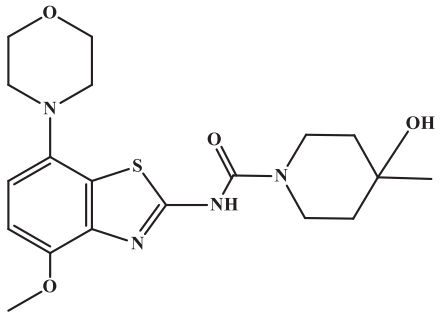
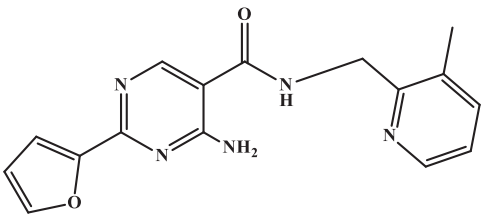
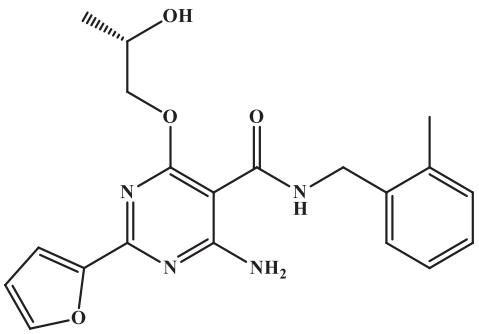
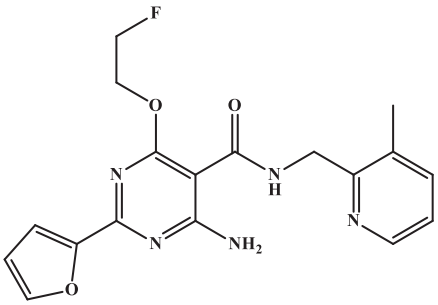
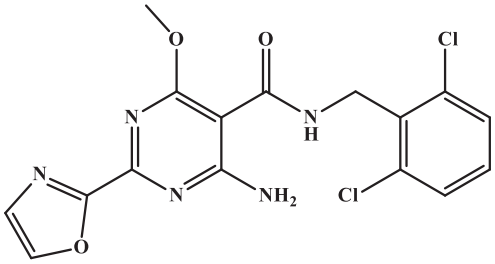
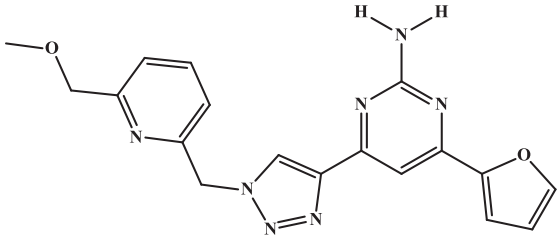
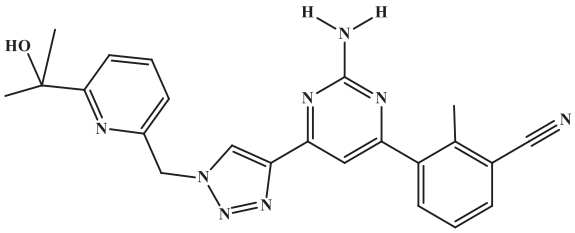
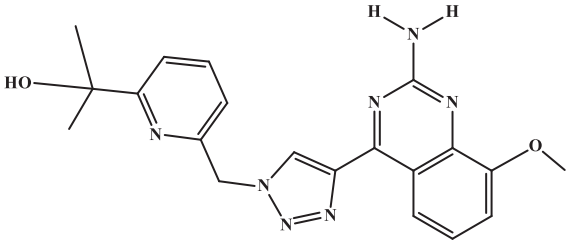
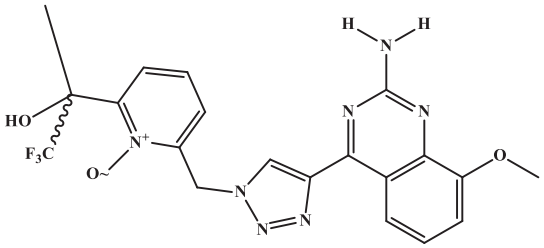
Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(11) SCH58261		Xanthine analogue	[117–119]
(12) FSPTP		Xanthine analogue	[117–119]
(13) ZM241385		Xanthine analogue	[117–119]
(14) Tozadenant		Xanthine analogue	[117–119]
(15) IC_{50} = 77 nM		Pyrimidine inhibitors	
(16) IC_{50} = 9 nM		Pyrimidine inhibitors	

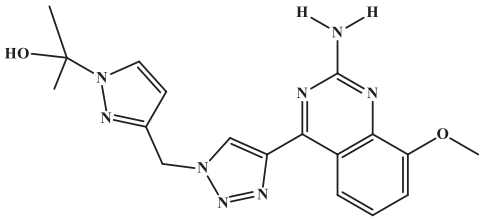
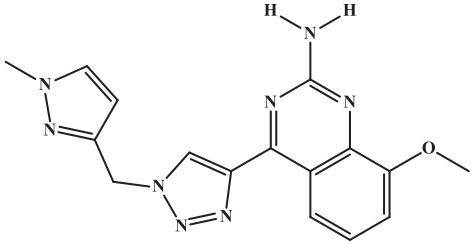
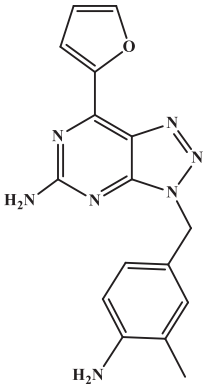
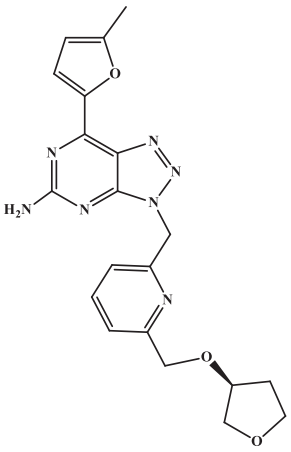
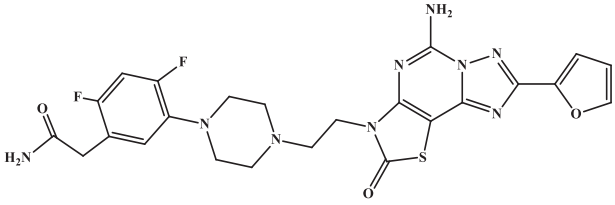
(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(17) 12 times less potent than compound 16		Pyrimidine inhibitors	
(18) IC_{50} = 17 nM		Pyrimidine inhibitors	
(19) IC_{50} > 100		Azolo pyrimidine	[120–122]
(20) AB928		Azolo pyrimidine	[120–122]
(21)		Azolo pyrimidine	[120–122]
(22)		Azolo pyrimidine	[120–122]

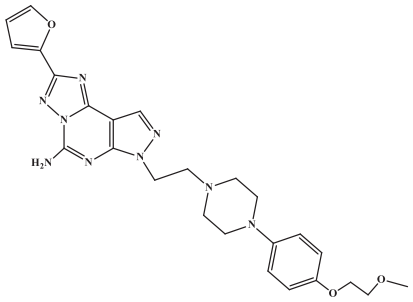
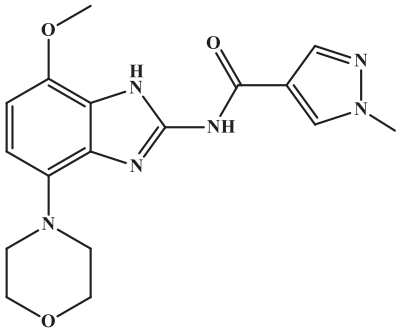
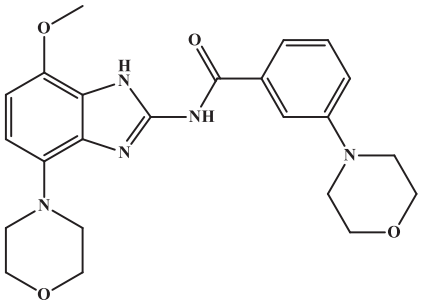
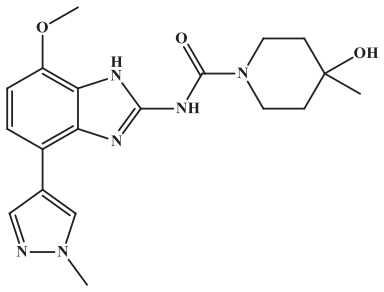
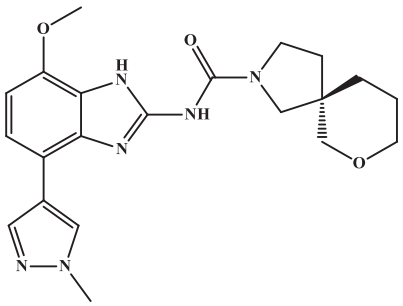
(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(23)		Azolo pyrimidine	[120–122]
(24)		Azolo pyrimidine analogue	[120–122]
(25) Vipadenant		Triazolo pyrimidine analogue	
(26) Ciforadenant		Triazolo pyrimidine analogue	
(27A) E-1		Oxothiazole analogue	

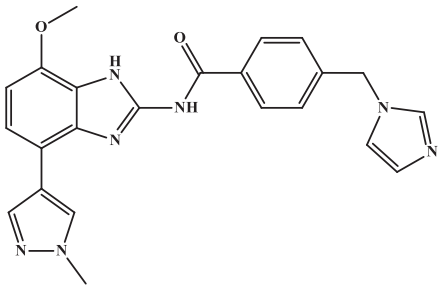
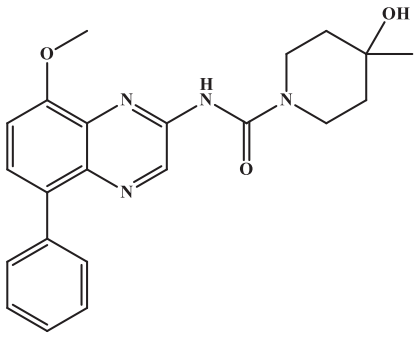
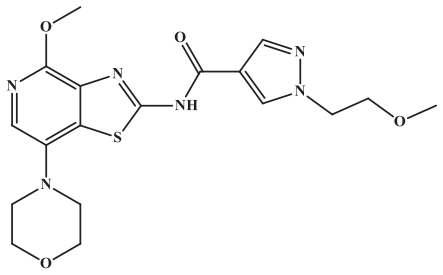
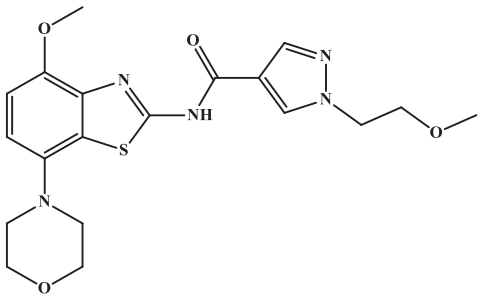
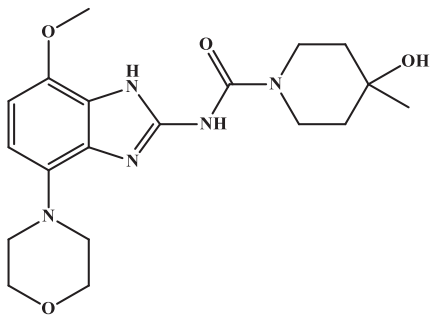
(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(28) Preladenant		Quinazoline analogue	
(29)		Quinazoline analogue	[123]
(30)		Quinazoline analogue	[123]
(31)		Quinazoline analogue	[123]
(32)		Quinazoline analogue	[123]

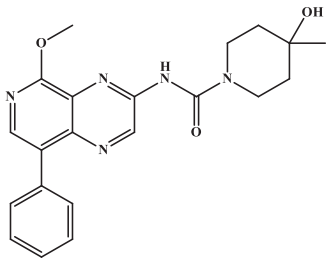
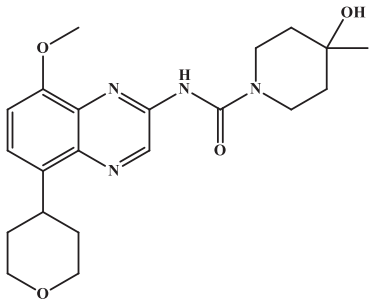
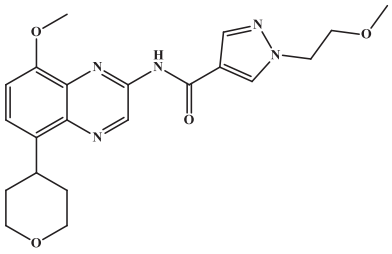
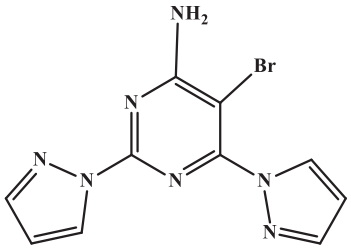
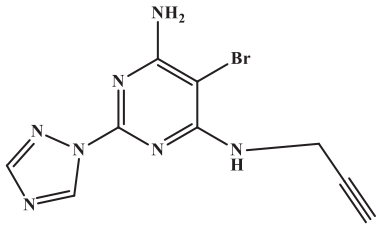
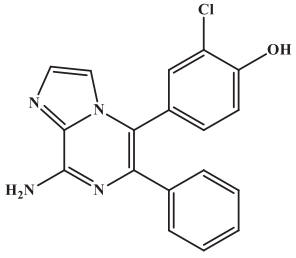
(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(33)		Quinazoline analogue	[123]
(34)		Quinazoline analogue	[123]
(35)		Quinazoline analogue	[123]
(36)		Quinazoline analogue	[123]
(37)		Quinazoline analogue	[123]

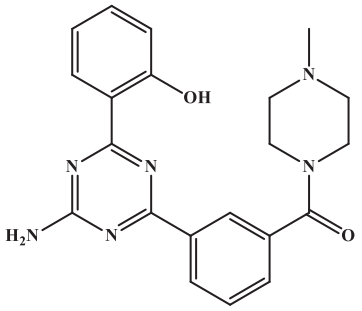
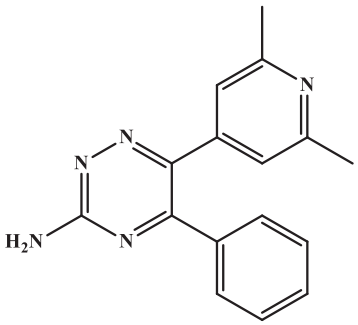
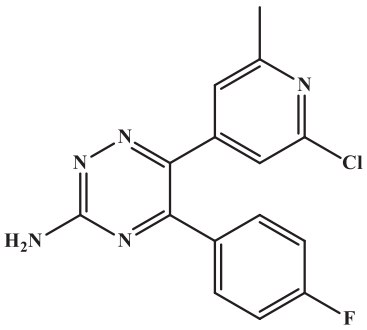
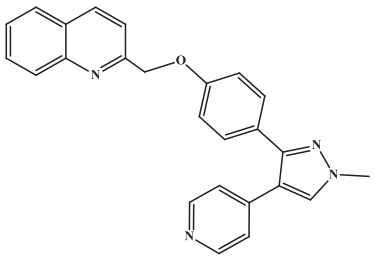
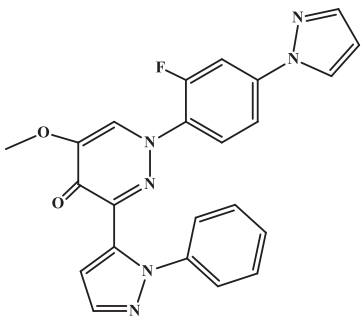
(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(38)		Quinazoline analogue	[123]
(39)		Quinazoline analogue	[123]
(40)		Quinazoline analogue	[123]
(41) Taminadentant (PBF509)		Imidazo [1,2-α] pyrazin-8-amine	
(42) PBF-999		Imidazo [1,2-α] pyrazin-8-amine	
(43)		Amino pyrimidine	

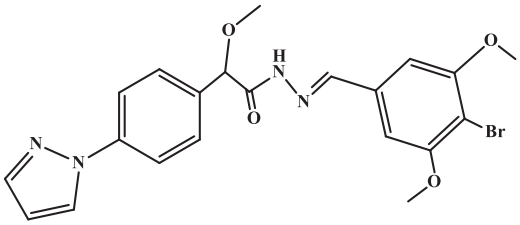
(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(44)		Triazine Analogue	[123]
(45)		Triazine Analogue	[123]
(46) AZD4635		Triazine Analogue	[123]
(47) PF 02545920 IC_{50} = 0.37 nM (PDE10A)		Pyrazole analogue	[123]
(48) TAK063 IC_{50} = 0.3 nM (PDE10A)		Pyrazole analogue	[123]

(*Continued*)

Table 1. (*Continued*)

Analogues name	Structure	Class	Reference
(49) OMS 824 IC_{50} (PDE10A) not disclosed		Pyrazole analogue	[123]

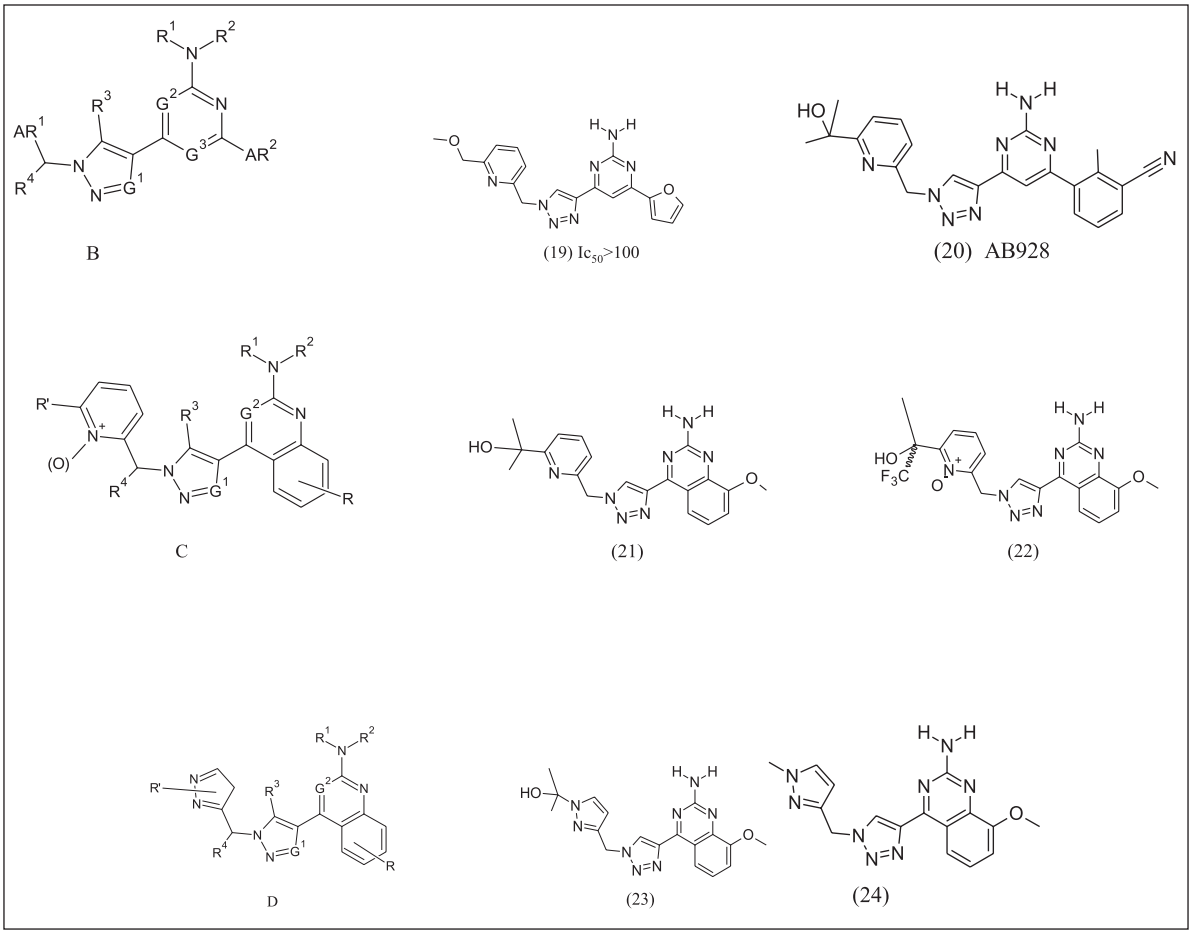


Figure 8. Azolo pyrimidine analogues.

Figure 9. Triazolo pyrimidine analogues.

Azolopyrimidine analogues

Arcus bioscience design and patented azolopyrimidine *illustrated in* Figure 8 to target Cancer [120] as an adenosine antagonist. In structure B at R^4 position, substitution with methyl group activity decreases compared to hydrogen. Compound (19) exhibits A_{2A} receptor antagonist activity in CHO-TREx cAMP assay. Compound (20) have methyl benzonitrile and dose 100 mg/kg, po, b.i.d alone [121] or in combination with anti-PD-1 (5 mg/kg) or doxorubicin(6 mg/kg), consequently anti-tumor effects on B16-F-10 melanoma [122]. Arcus further two patents, one on quinazoline pyridine as compound C and

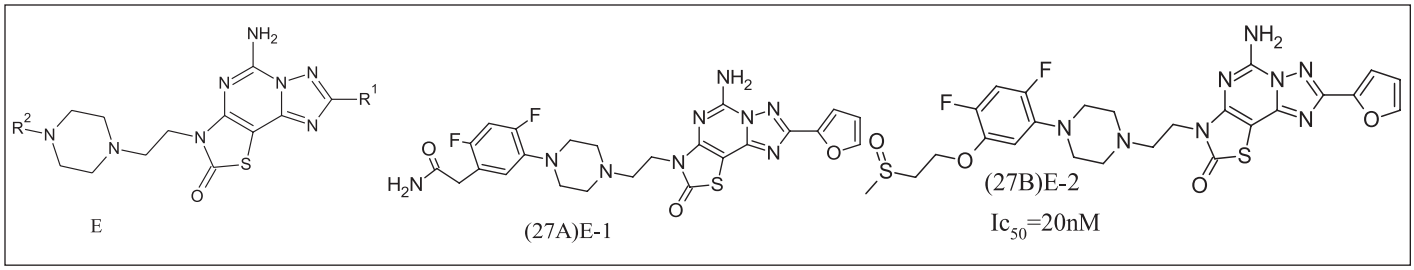


Figure 10. Oxothiazole analogue.

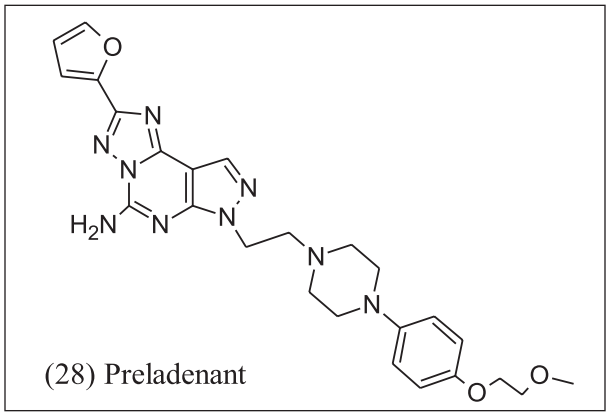


Figure 11. Pyrazole analogue.

its analogues (21), (22). Another quinazoline pyrazole core compound D and its analogue (23), (24). These compounds exhibit antagonist activity as $A_{2A}R$ and $A_{2B}R$

Triazolo pyrimidine analogues

Bristol-Myers Squibb research and design *illustrated in* Figure 9 (25) Vipadenant and (26) Ciforadenant have [1,2,3] triazolo[5,4-*d*] pyrimidine core was first introduced for Parkinsonism. It revealed the selectivity towards $A_{2A}R$, but it was discontinued due to failure in the phase-2 clinical trial in preclinical cancer immunology research and observed an othosteric binding site. Ciforadenant potently inhibits c AMP in HEK-293 cells at Ic_{50}=17nM and primary human T cells at IC_{50}=70 nM. Ciforadenant suppresses p CREB and restores PERK levels in human cells.

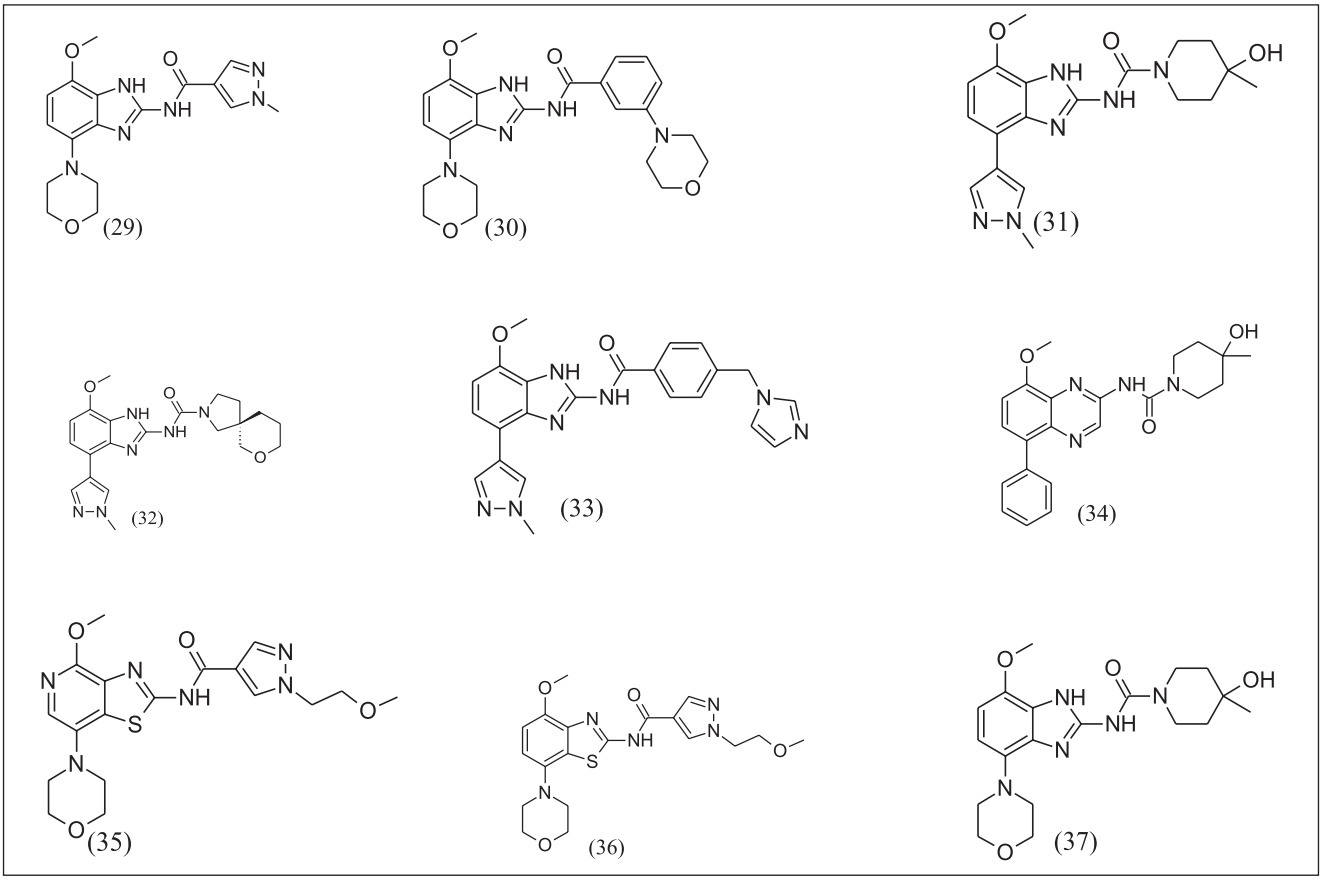


Figure 12. Benzimidazole and isosteric replacement analogues.

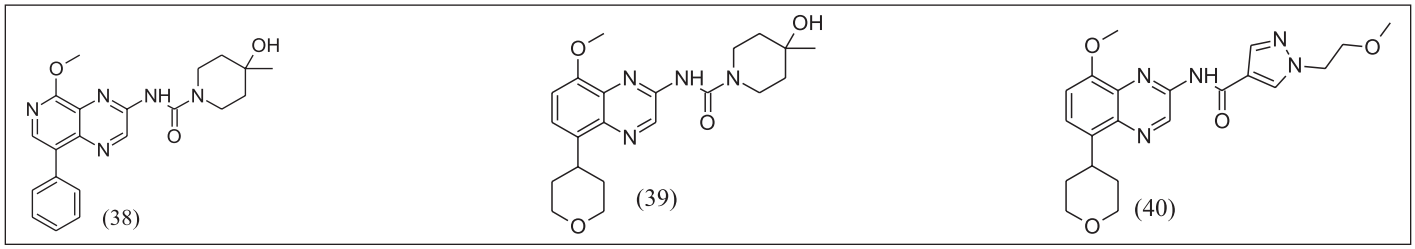


Figure 13. Quinazoline analogue.

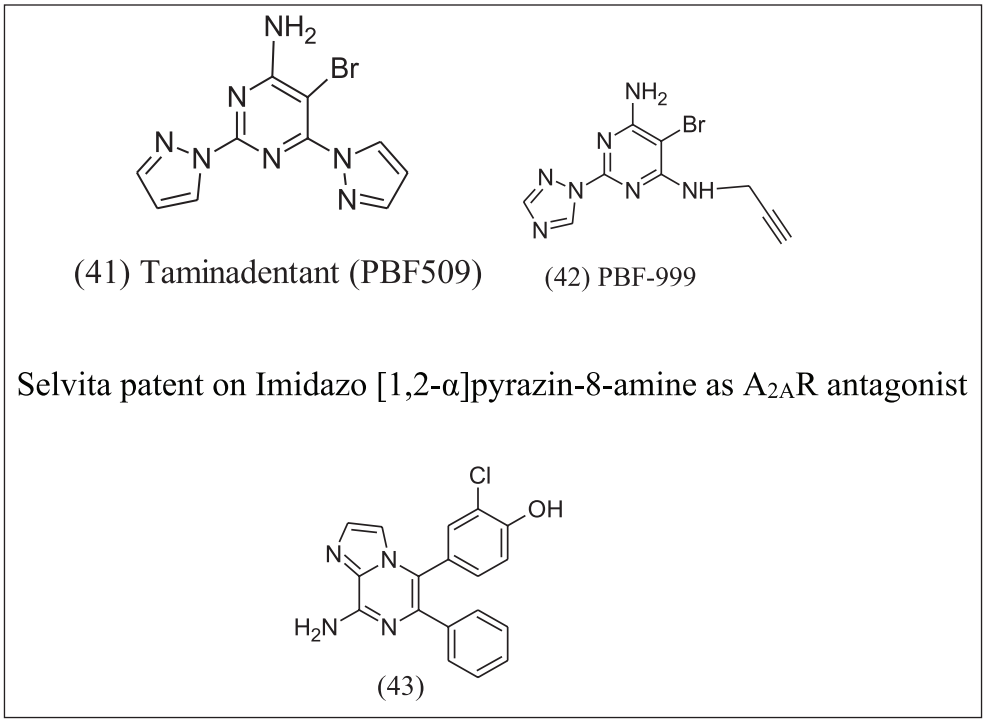


Figure 14. Amino pyrimidine analogue.

2-Oxothiazole analoguei

TEAOS research group developed 2-Oxothiazole, *illustrated in* Figure 10, as an $A_{2A}R$ antagonist to target Parkinsonism's disease, but due to a high adenosine environment, it does not exhibit antagonistic activity. The high dose required for inhibition within the tumor for cancer management [95]. E core was introduced as cAMP inhibition. It also inhibited CREB phosphorylation as a consequence of $A_{2A}R$ antagonism. 2-Oxothiazole and its analogues (27A, 27B).

Pyrazole and Benzothiazole analogue

Further researchers from Merck introduce pyrazolo [4,3-e]-1,2,4-triazolo-[1,5-c] pyrimidine analogue illustrated in Figure 11. (28) Preladenant was introduced for Parkinsonism but terminated in phase-3 consequences of failure in efficacy as compared to placebo. The Preladenant result of the phase-1 clinical trial of (NCT0399161) in advanced solid tumor but data did not support at the endpoint thus terminated. Merck has patented three Benzothiazole compounds (14) Tozadenant where nitrogen atom introduced to improve pharmacokinetic properties.

Benzimidazole (Bioisostere replacement of sulphur with nitrogen)

Benzimidazole and its analogue illustrated in Figure 12 have (29), (30), (31), (32), (33), and (34) $A_{2A}R$ antagonist effects. Benzimidazole analogues (35), (36), and (37) have the isosteric replacement of sulphur with nitrogen as a consequence of a half-life increase. The half-life of benzimidazole analogues further increased with aryl amide replacement. Consequently, the Benzimidazole morpholino group was replaced with heteroaryl, improving pharmacokinetic properties and these compounds as $A_{2A}R$ inhibitors. These compounds control the secretion of cytokine that is suppressed by adenosine. These compounds have IC_{50} = 100–1,000 nM range.

Quinoxalines analogue

Quinoxalines from Benzothiazole illustrated in Figure 13 (38), (39), and (40) retained adenosine antagonistic activity and a half-life of more than 2 hours. In Quinoxalines, the analogue aryl group was replaced with tetrahydropyran, consequently decreasing half-life, and the urea side chain was replaced with aryl amide, consequently poor pharmacokinetic properties.

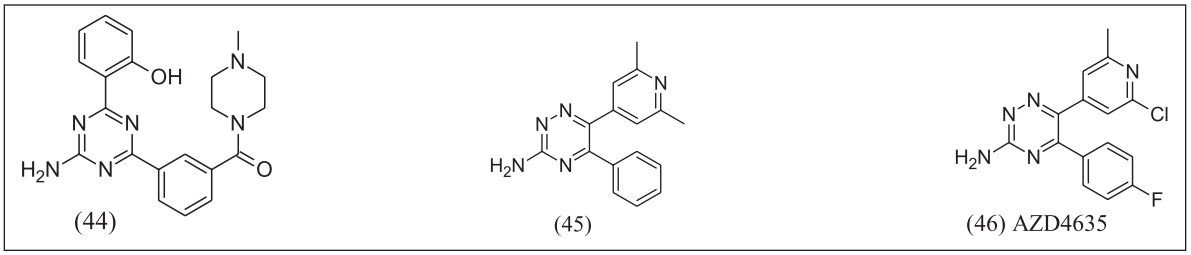


Figure 15. Triazine analogue.

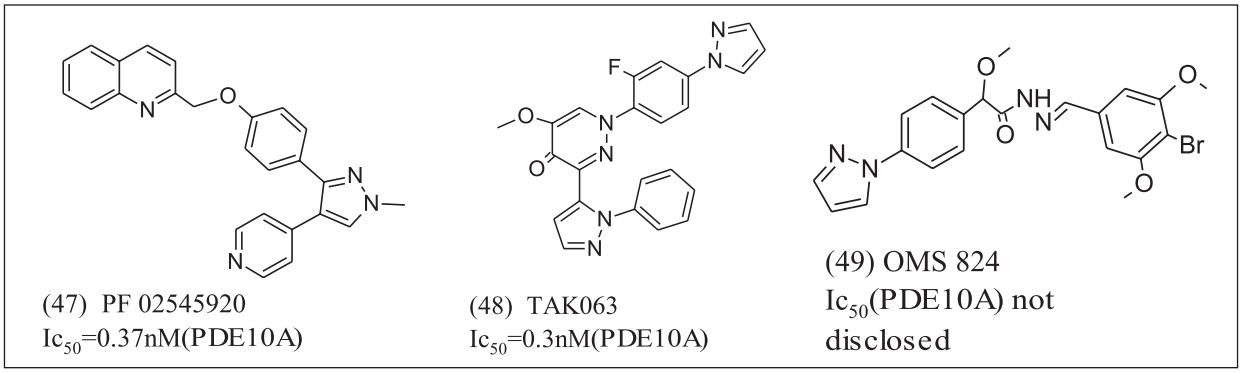


Figure 16. Pyrazole heterocycles.

Amino pyrimidines

2,6-Bis(heteroaryl)-4-amino-pyrimidines design illustrated in Figure 14 and introduces Novartis/Palobiopharma as an $A_{2A}R$ antagonist. The potency of the compound increased by introducing an electron-withdrawing group at position 5 of the pyrimidine ring. (41) Taminadentant (PBF-509) exhibit 25 times more potent antagonism as compared to bis(hetroaryl)-4-amino pyrimidine $A_{2A}R$ antagonist. (42), (43) Chloro / cyano substitution at fifth position and pyrrolidyl/ethylthiol/ trifluoroethoxyl at the sixth position of the bis(heteroaryl)-4-Amino pyrimidine for its antagonist response and it is important for binding to receptor. Furthermore, PBF-509 exhibits a decreased tumor burden in mice with B16-CD73+ tumors. PBF-509 with PD-L1 maintains immune response in tumor-infiltrating lymphocytes in non-small cell lung cancer cases. PBF-509 produced a synergistic anti-tumor effect with immunotherapeutic agents.

Triazine isomers

AstraZeneca, by using computational techniques to design, illustrates in Figure 15 1,3,5-triazines isomers and 1,2,4 triazines isomers as $A_{2A}R$ antagonists that access ribose pocket (44), (45), (46). AZD4635 was designed by using an SBDD strategy with PDB:6GT3 and decreased tumor growth (50 mg/kg,po,b.i.d) with anti-PDL1 [123].

Pyrazole linked heterocyclics as a phosphodiesterase inhibitor

Overexpression of PDE-10A was observed in Cancer then, specifically, PDE-10A inhibitors illustrated in Figure 16 (47), (48), (49).

CONCLUSION

In cancer life-threatening conditions chemotherapy failure and drug resistance are major emerging areas for researchers. Hypoxia and associated conditions, tumor micro environment, ROS, and immunosuppressant condition. Adenosine receptor and hypoxia significance emphasize above and management of cancer by modulation of pathway mTOR and in immunity by CTLA 4, PD1 Benzothiazole, quinazoline, and pyrimidine analogue have prominent inhibitory responses in adenosine sites. Alkylating agents exhibit prominent effects in hypoxic tumors and drug response. Thus, design Nitrogen-containing heterocyclic, Benzothiazole, quinazoline pyrimidine analogue have both alkylating and adenosine inhibitory action.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

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