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# Therapeutic potential of adenosine receptor modulators in cancer treatment

Prasenjit Maity, Swastika Ganguly and Pran Kishore Deb \*

All human cells contain the universal autocoid adenosine, which interacts with four types of G protein-coupled receptors (GPCRs), namely  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$  adenosine receptors (ARs). Among these receptors,  $A_{2A}$  and  $A_{2B}$  ARs activate adenylyl cyclase, while  $A_1$  and  $A_3$  ARs suppress the adenylyl cyclase activity. Adenosine-receptor interactions play a crucial role in cancer biology by modulating the immune microenvironment, which tumors exploit to create immunosuppression that promotes their growth and metastasis. When the  $A_{2A}$  AR is activated on natural killer (NK) cells and T cells, it reduces their ability to carry out cytotoxic functions. This activation also encourages the formation of immune-suppressing cell types, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), further weakening the immune response. Targeting adenosine receptors, particularly the  $A_{2A}$  subtype, represents a promising therapeutic strategy. By antagonizing these receptors, it may be possible to restore T cell function, helping the body to recognize and attack cancer cells more effectively. Despite recent advancements in the discovery of novel, targeted anticancer agents, these treatments have shown limited effectiveness against metastatic tumours, complicating cancer management. Moreover, developing adenosine receptor agonists or antagonists with high target selectivity and potency remains a significant challenge, as the widespread distribution of adenosine receptors throughout the body raises concerns about off-target effects and reduced therapeutic efficacy. In order to improve outcomes for patients with advanced cancer, researchers are actively investigating safer and more efficient

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Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi, 835215, Jharkhand, India. E-mail: [prankishore1@gmail.com](mailto:prankishore1@gmail.com); [prankishoredeb@bitmesra.ac.in](mailto:prankishoredeb@bitmesra.ac.in)



Prasenjit Maity

BPharm. and MPharm. degrees with first-class honours from the Bengal School of Technology, Chinsurah, Hooghly, West Bengal. His research interests focus on Computer-Aided Drug Design (CADD) and the discovery and development of novel chemical entities (NCEs) as adenosine receptor antagonists, as well as agents with anti-inflammatory and antibacterial potential.

Mr Prasenjit Maity is a PhD research scholar in Pharmaceutical Medicinal Chemistry at the Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology (BIT), Mesra, Ranchi, India. He is pursuing his doctoral studies under the supervision of Dr Pran Kishore Deb and the co-supervision of Dr Swastika Ganguly with the prestigious Institute Research Scholarship (IRS). Mr Maity earned his



Swastika Ganguly

infections. She has guided more than 30 MPharm. dissertations and 14 PhD scholars, with five currently under her mentorship. Dr Ganguly has over 130 publications, more than 60 conference presentations, and has served as the APTI Women's Forum East Zone Coordinator. She is a Chartered Chemist recognized by the Indian Institution of Chemists and currently serves as the Chancellor's nominee at Jadavpur University, Kolkata.

Dr Swastika Ganguly is a Professor in the Department of Pharmaceutical Sciences and Technology at BIT Mesra, Ranchi, and served as Head of the Department from 2021 to 2023. She completed her BPharm., MPharm., and PhD (CSIR-SRF) at BIT Mesra. With over 27 years of experience in teaching and research, her expertise lies in Computer-Aided Drug Design and the synthesis of drugs targeting HIV and associated



chemotherapy substitutes. However, drugs that activate  $A_3$  adenosine receptors and block  $A_{2A}$  receptors are being explored as a novel approach for cancer treatment. Monoclonal antibodies and small-molecule inhibitors targeting the CD39/CD73/ $A_{2A}$  AR axis are also being tested in clinical trials, both as standalone treatments and in combination with anti-PD-1/PD-L1 immunotherapies. This review primarily focuses on the signaling pathways and the therapeutic potential of various adenosine receptor agonists and antagonists across various cancer types, highlighting their ongoing evaluation in preclinical and clinical trials, both as monotherapies and in rational combination with immunotherapy, chemotherapy, or targeted therapies, potentially leading to the development of advanced treatments that could aid in tumor suppression.

## 1. Introduction

Adenosine is an endogenous purine nucleoside that comprises an adenine base linked to a sugar-containing ribose molecule *via* a  $\beta$ -N9-glycosidic bond, as depicted in Fig. 1.<sup>1</sup> It serves as an essential element in human biology.<sup>2</sup> Adenosine has been investigated for its potential role as a molecule with protective properties against cancer.<sup>3</sup> Adenosine is well known for being an important local regulator of tissue function, particularly in situations where cellular energy demand exceeds the available energy supply.<sup>4</sup> Adenosine is pivotal in maintaining cellular protection and modulating diverse physiological and pathological processes. In 1929, Drury and Szent-Gyorgyi elucidated adenosine's role as an extracellular signalling molecule, highlighting its broad impact on physiological functions.<sup>5</sup>

Adenosine exerts an important function in inhibiting the immune response against tumours by encouraging the growth of blood vessels (angiogenesis) and boosting the growth, progression, and mobility of tumour cells.<sup>6,7</sup> However, there is ongoing debate about how adenosine specifically affects the death of cancer cells through apoptosis.<sup>8</sup> As a result, ARs are considered promising targets for treating various medical conditions.<sup>9–13</sup> Adenosine plays a role in the body's immune suppression in tumors. Some studies have shown that blocking

adenosine or its receptors might lead to enhanced immunity against tumours, but it could also reduce the body's anti-tumour responses under certain conditions.<sup>13</sup>

Adenosine is a type of molecule derived from adenosine triphosphate (ATP) which is crucial for cellular energy. It serves as a significant regulator within the tumour microenvironment (TME). In conditions where there is low oxygen, limited blood flow, or inflammation, the level of adenosine increases in the region surrounding the tumour. This rise in adenosine can influence both the immune system's reactions and the tumor's growth dynamics.<sup>14,15</sup>

All four types of adenosine receptors have been identified as contributing to the progression of cancer.<sup>10</sup> Numerous drug candidates that affect adenosine receptors in the body, including agonists, antagonists, partial agonists, and allosteric modulators, have been recently discovered and patented, and many of them are currently undergoing clinical trials.<sup>14–23</sup>

Recently, a growing focus has been on understanding the role of adenosine receptors' impact on cancer, affecting tumour growth, spread, and the immune system's response. Investigating these roles is vital for developing new treatments to combat cancer effectively. This review is focused on possible treatment strategies emphasizing the role of adenosine and its receptors in cancer development.

## 2. Adenosine & adenosine receptors

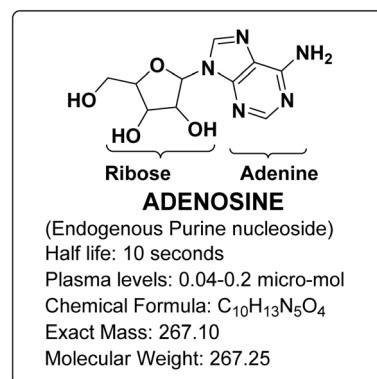
Adenosine is ubiquitous, released by nearly all cells, and produced in the extracellular environment through the breakdown of ATP by a cascade of ectoenzymes, including apyrase (CD39) and 5'-nucleotidase (CD73).<sup>24</sup> When adenosine levels



**Pran Kishore Deb**

*Dr Pran Kishore Deb is an Assistant Professor in the Department of Pharmaceutical Sciences and Technology at BIT Mesra, Ranchi, India. He earned his PhD in Pharmaceutical Medicinal Chemistry from the University Institute of Pharmaceutical Sciences (UIPS), Panjab University, Chandigarh, under the CSIR-SRF fellowship (New Delhi, India). His primary research interests include computer-aided drug design (CADD) and the development of novel chemical entities (NCEs) targeting adenosine receptors, COX-2, mosquito larvae, and tuberculosis. Dr Deb has published over 150 research articles and holds over 35 international patents. He has earned several national and international honors and has been consistently listed among the World's Top 2% Scientists by Stanford University, USA, for the past five years.*

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**Fig. 1** Structure of adenosine.





Table 1 The molecular features and functions of adenosine receptors in cells<sup>a</sup>

Receptors	Gene	Chromosomal location	Molecular weight (by amino acid sequence)/ length (residues)	Affinity for adenosine (nM)	G-protein coupling	Signalling system	Effects on ion channels	Distribution		
								High expression	Intermediate expression	Low expression
A <sub>1</sub> AR	ADO RA <sub>1</sub>	1q32.1	36 512/326	1–10	G <sub>i</sub> /G <sub>o</sub>	Block AC (↓cAMP), stimulate PLC (↑IP3/DAG), ↑PI3 kinase, ↑MAPK, ↑K <sup>+</sup> , Ca <sup>2+</sup>	↑K <sup>+</sup> & ↓Ca <sup>2+</sup>	CNS, spinal cord, adrenal gland, atria	Adipose tissue, liver, renal tissue & skeletal muscle	In the higher bronchi & pancreas
A <sub>2A</sub> AR	ADORA <sub>2A</sub>	22q11.2	44 707/412	30	G <sub>s</sub> /G <sub>oif</sub>	Stimulate AC (↑cAMP), ↑MAPK	Inhibit Ca <sup>2+</sup> channels	Lymphoid tissue (spleen, thymus, WBC & platelets)	Blood vessels, cardiac tissue, lung & peripheral nerve	Other regions of CNS
A <sub>2B</sub> AR	ADORA <sub>2B</sub>	17p11.2-12	36 333/332	1000	G <sub>s</sub> /G <sub>q</sub>	Stimulate AC (↑cAMP), activate PLC (↑IP3/DAG), ↑MAPK	Inhibit Ca <sup>2+</sup> channels	Intraperitoneal pouch (cecum), urinary bladder, and colon	Lungs, eye, must cell & blood vessel	Adipose tissue, CNS, kidney & adrenal gland
A <sub>3</sub> AR	ADORA <sub>3</sub>	1p13.2	36 185/318	100	G <sub>i</sub> /G <sub>q</sub>	Block AC (↓cAMP), activate PLC (↑IP3/DAG), ↑PI3 kinase, ↑MAPK		Testis & must cell	CNS (hippocampus and cerebellum)	Liver, lymphatic tissue, thyroid and adrenal gland

<sup>a</sup> AC (adenyl cyclase), PLC (phospholipase C), G<sub>i</sub>/G<sub>o</sub> (inhibitory G-proteins), DAG (diacylglycerol), IP3 (inositol triphosphate), G<sub>s</sub>/G<sub>oif</sub> (stimulatory G-proteins), cAMP (cyclic adenosine monophosphate), K<sup>+</sup> (potassium ion), Ca<sup>2+</sup> (calcium ion), WBCs (white blood cells), CNS (central nervous system), PI3K (phosphoinositide 3-kinase), ADORA (adenosine receptor A), nM (nanomolar), MAPK (mitogen-activated protein kinase).

become excessive, the body has mechanisms to reduce them. Adenosine kinase can convert adenosine back into adenosine monophosphate (AMP) through phosphorylation, and adenosine deaminase (ADA) can deaminate adenosine into inosine.<sup>16,17</sup> Both processes require sufficient oxygen to function effectively. However, these enzymes may not work efficiently in areas with low oxygen levels, such as in tumours affected by hypoxia. This can lead to the accumulation of adenosine in these regions, which can affect inflammation and contribute to tumour growth. Thus, the oxygen-dependent regulation of adenosine metabolism plays a crucial role in the tumour microenvironment.<sup>17</sup>

Elevated levels of CD73 have been noted in multiple cancer types, such as breast, colon, ovarian, melanoma, glioma, glioblastoma, leukemia, and bladder cancer.<sup>18</sup>

Adenosine, in turn, can act on immune cells and other cells in the tumour microenvironment, promoting immunosuppression and supporting tumour growth and metastasis. Therefore, CD73 expression in cancer cells is of interest as a potential target for therapeutic interventions to modulate the immune response against tumours.<sup>19,25,26</sup>

Adenosine is a potent compound that influences various cells and tissues, including platelets, coronary arteries, smooth muscle, cardiac muscle, and immune cells.<sup>27</sup> As an extracellular messenger, it plays a role in conditions such as neurodegenerative diseases, psychiatric disorders, heart issues, lung injuries, cancers, and eye diseases.<sup>28</sup>

Adenosine receptors, encoded by separate genes, belong to the G protein-coupled receptor (GPCR) family. These receptors are categorized as A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub> adenosine receptors (AR).<sup>29,30</sup> The ARs are found throughout the human body in various organs and tissues, where they play crucial roles in regulating essential physiological functions, as shown in Table 1.<sup>22,31–35</sup> Extracellular adenosine serves as a natural ligand for all these receptors. Each AR subtype exhibits unique binding affinities and is activated by adenosine in different ways, influencing diverse physiological processes.<sup>36,37</sup> This interaction pattern allows adenosine to regulate neurotransmission, immune responses, inflammation, and vascular function across different tissues and organ systems in the body.<sup>38</sup> The A<sub>1</sub> AR, A<sub>2A</sub> AR, and A<sub>3</sub> ARs have moderate to high affinities for adenosine, and they usually require 1–10 nM, 30 nM and 100 nM concentrations of adenosine, respectively, for their activation. The A<sub>2B</sub> AR, has the lowest affinity and requires a higher concentration of adenosine (approximately 1000 nM) for its activation.<sup>10,23,39</sup>

This similarity percentage gives us a rough estimate of how closely these receptors are related to each other; comparing the amino acid sequences of these receptors are roughly 49% of the residues in the A<sub>1</sub> receptor are identical to those in the A<sub>3</sub> receptor. Roughly 59% of the residues in the A<sub>2A</sub> receptor are identical to those in the A<sub>2B</sub> receptor.<sup>37,40</sup>

When adenosine binds to its receptors on the cell surface, it triggers a cascade of molecular events inside the cell. This includes activating MAPK (mitogen-activated protein kinase) proteins, which are enzymes that relay signals from the cell membrane to the nucleus. Once activated, MAPKs phosphorylate various target proteins involved in gene expression, cell

cycle progression, and differentiation pathways.<sup>41</sup> This pathway is essential for regulating fundamental cellular processes, including proliferation (cell division) and differentiation (maturation into specialized cell types). Various external signals can activate the MAPK pathway, with GPCRs playing a significant function in this process.<sup>42</sup>

AR, which is indeed a type of GPCR, regulates adenylyl cyclase (AC) activity by either stimulating or inhibiting it. When AC is inhibited, it reduces the amount of cAMP in the cell. This affects the activity of PKA, which in turn phosphorylates proteins involved in the MAPK and AKT signalling pathways.<sup>43,44</sup> The A<sub>2A</sub> and A<sub>2B</sub> receptors increase the activity of AC through the G<sub>s</sub> protein. The A<sub>2A</sub> receptor activates the G<sub>s</sub> protein, while the A<sub>2B</sub> receptor activates phospholipase C (PLC) through the G<sub>q</sub> protein. Which results in the formation of IP<sub>3</sub> (Inositol triphosphate) and DAG (Diacylglycerol).<sup>45,46</sup>

### 3. Purpose, mode of action, storage, release, and synthesis of adenosine

Adenosine is not stored in vesicles but is continuously released in response to metabolic changes. It modulates neuronal activity both presynaptically and postsynaptically. After acting, adenosine is either internalized for recycling or metabolized within the cell.<sup>1,47</sup>

Adenosine is primarily produced extracellularly through the dephosphorylation of ATP, ADP, and AMP by two enzymes: CD39 (NTPDase 1), which converts ATP to ADP and AMP, and CD73 (5'-NT), which converts AMP to adenosine under stress (Fig. 2). Additionally, ecto-phosphodiesterase (ecto-PDE) enhances adenosine production by converting cAMP to AMP, further activating CD73.<sup>48,49</sup>

Once produced, adenosine is transported across the cell membrane by concentrative nucleoside transporters (CNTs) and equilibrative nucleoside transporters (ENTs).<sup>50,51</sup> Equilibrative nucleoside transporters (ENTs) are membrane proteins that regulate intracellular nucleoside levels by facilitating their passive, bidirectional transport across the cell membrane *via* facilitated diffusion. They allow adenosine and other nucleosides to move in response to concentration gradients, helping maintain extracellular adenosine levels without ATP or ionic gradients.<sup>52</sup>

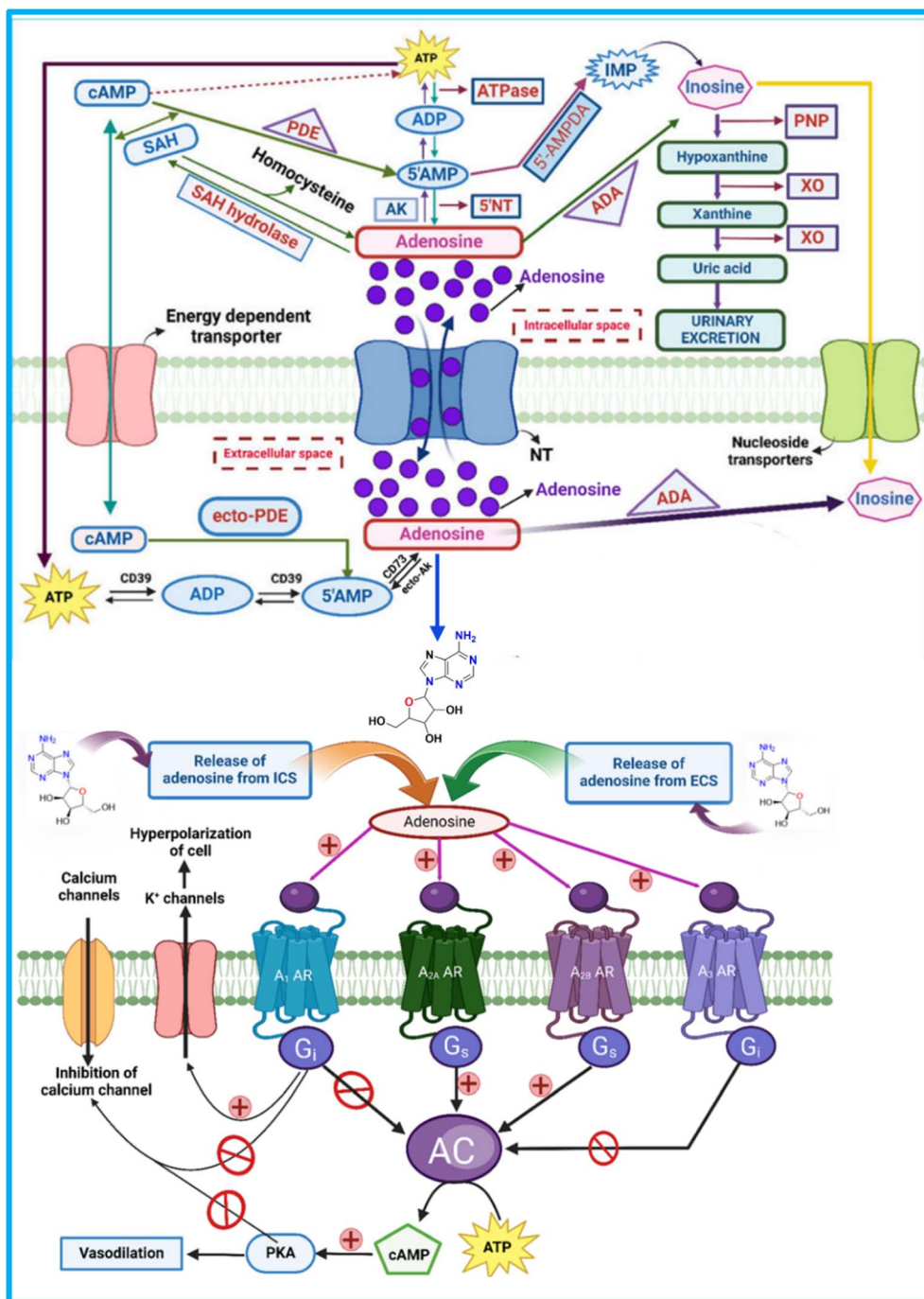
Inside the cell, adenosine undergoes key enzymatic transformations, including hydrolysis to form SAH by SAHH, phosphorylation to AMP by AK, and deamination to inosine by ADA. These processes are essential for regulating adenosine levels.<sup>10,53,54</sup> The ecto-ADA removes extracellular adenosine and transports it inside cells *via* ENTs.<sup>10,55–57</sup> Fig. 2 represents the synthesis, storage, release, and signalling pathways of adenosine through adenosine receptors.

### 4. Adenosine's mode of action on its receptor subtypes

The affinity of each adenosine receptor for adenosine determines its activation, triggering G-proteins that regulate







**Fig. 2** Synthesis, storage, release, and signalling pathways of adenosine through adenosine receptors. ATP – “Adenosine triphosphate”, CD73 – “Ecto-5'-nucleotidase” cAMP – “Cyclic adenosine monophosphate”, ADA – “Adenosine deaminase”, ADA – “Adenosine deaminase”, XO – “Xanthine oxidase”, CD39 – Ectonucleoside triphosphate diphosphohydrolase-1, PDE – “Phosphodiesterase”, SAH – “S-adenosyl-homocysteine”, 5-AMP – “5-Adenosine monophosphate”, PNP – “Purine nucleoside phosphorylase”, ADP – “Adenosine diphosphate”, 5NT – “5'-Nucleotidase”, ecto-AK – “Extracellular adenosine kinase”, A<sub>1</sub> AR – “A<sub>1</sub> adenosine receptor”, K<sup>+</sup> channel – “Potassium channels”, A<sub>2B</sub> AR – “A<sub>2B</sub> adenosine receptor”, cAMP – “cyclic adenosine monophosphate”, G<sub>i</sub> – “inhibitory G-proteins”, A<sub>2A</sub> AR – “A<sub>2A</sub> adenosine receptor”, AC – “Adenyl cyclase”, G<sub>s</sub> – “Stimulatory G-proteins”, PKA – “Protein kinase A” A<sub>3</sub> AR – “A<sub>3</sub> adenosine receptor”. The figure was created in BioRender. Deb, P. (2025).

enzymes like adenylate cyclase (AC) to produce cAMP and modulate ion channels, affecting ion flow across the membrane. This regulation is crucial for intracellular signal transduction. Activating the A<sub>1</sub> receptor by adenosine opens

K<sup>+</sup> channels, causing cell hyperpolarisation and inhibiting Ca<sup>2+</sup> channels (Fig. 2), reducing calcium entry. This leads to vasodilation, lowering blood pressure, and increasing blood flow.<sup>58</sup>



Adenosine receptor activation affects cellular signalling by modifying critical pathways like cAMP production, activating PKA, and MAPK signalling, which influence gene expression, cell proliferation, and survival.<sup>59–62</sup> The activation of the A<sub>1</sub> AR inhibits AC and reduces cAMP levels. This diminishes PKA activity and CREB-1 phosphorylation, both crucial for gene regulation.<sup>63,64</sup> A<sub>1</sub> AR also activates MAPKs, including JNK, ERK1/2, and p38, which influence tumor growth and gene expression.<sup>65–69</sup>

Activation of A<sub>2A</sub> AR triggers G<sub>s</sub> protein signalling, which increases cAMP production *via* AC activation. PKA is activated by elevated cAMP, which also affects phosphodiesterases (PDES), CREB, and signalling pathways that control cell survival and proliferation. PKA also phosphorylates DARPP-32, modulating various cellular processes.<sup>70,71</sup>

A<sub>2B</sub> AR directly affects essential proteins like p38 MAPK, ERK1/2, and JNK through its involvement in the MAPK signalling cascade. A<sub>2B</sub> receptor activation plays a significant role in cancer cell growth and tumour progression by modulating stress-activated protein kinases (SAPK) and other MAPK-related processes.<sup>72,73</sup>

Through G<sub>i</sub> protein signalling, A<sub>3</sub> AR activation decreases cAMP levels and reduces PKA activity. As a result, increased activation of GSK-3 $\beta$  leads to decreased  $\beta$ -catenin, cyclin D1, and c-MYC expression, which inhibit cell growth and proliferation. Additionally, A<sub>3</sub> AR suppresses NF- $\kappa$ B, which is involved in immune responses and inflammation.<sup>74</sup>

## 5. Role of adenosine and adenosine receptors on cancer

In cancer, the TME often exhibits higher levels of adenosine production, primarily due to reduced oxygen availability (hypoxia). Hypoxia promotes the breakdown of ATP, resulting in increased amounts of adenosine within the TME.<sup>75</sup> The secretion of adenosine during hypoxic conditions stimulates angiogenesis, which in turn promotes tumor growth. In solid tumors, hypoxia enhances the production of CD39 and CD73, enzymes that generate adenosine, supporting tumor survival.<sup>76,77</sup> Hypoxia activates transcription factors like HIF-1 $\alpha$ , which regulate these enzymes, maintaining adenosine production under low-oxygen conditions.<sup>78</sup> Elevated adenosine levels promote tumor growth, immune suppression, and angiogenesis by binding to A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub> receptors.<sup>79</sup>

Adenosine accumulation in tumor hypoxic regions impairs immune cells' ability to target and destroy cancer cells. While lymphokine-activated killer (LAK) cell therapy shows promise for cancers resistant to standard treatments, its effectiveness is limited in colon cancer due to the tumor's immune-suppressive environment.<sup>80,81</sup> Colon adenocarcinoma cells release a substance, distinct from TGF- $\beta$  or prostaglandins, that inhibits the activation of anti-CD3-activated killer cells, helping the tumor evade immune attacks.<sup>82</sup> In hypoxic tumor regions, adenosine accumulates and interacts with specific receptors on cytotoxic T cells, reducing their adhesion to cancer cells and impairing their activation.<sup>82–84</sup> This effect, mediated by the A<sub>3</sub>

AR, inhibits cytotoxic T-cell activation and function in mice,<sup>85</sup> contributing to immunosuppression and reduced efficacy of immunotherapy. Additionally, adenosine interferes with integrin  $\alpha$ 4 $\beta$ 7, further impairing T cell adhesion to tumor cells.<sup>86</sup>

While adenosine's impact on other angiogenic factors is debated, it is known to boost the synthesis of certain phospholipases and support endothelial cell migration, further facilitating tumor growth and spread.<sup>87,88</sup> Adenosine's capacity to stimulate the creation of PLCs and increase endothelial cell motility contributes to its involvement in promoting angiogenesis.<sup>89,90</sup>

## 6. A<sub>1</sub> adenosine receptors' role in cancer: molecular signaling pathways

The A<sub>1</sub> adenosine receptor (A<sub>1</sub> AR) plays several roles in cancer by influencing the TME. A<sub>1</sub> AR signalling also affects cellular migration and invasion, potentially impacting metastasis and therapeutic resistance.<sup>91</sup> Activation of the A<sub>1</sub> AR stimulates phospholipase C-beta (PLC- $\beta$ ), which hydrolyzes PIP<sub>2</sub> to produce IP<sub>3</sub> and DAG. IP<sub>3</sub> triggers calcium release from intracellular stores, activating calcium-dependent PKC and other calcium-binding proteins, impacting cellular functions.<sup>10,64,92</sup> A<sub>1</sub> AR activation also opens potassium channels, causing hyperpolarization and reducing cellular excitability, while inhibiting N-type and P/Q-type calcium channels (Fig. 3), further decreasing calcium influx and excitability in neurons and heart muscle.<sup>93,94</sup>

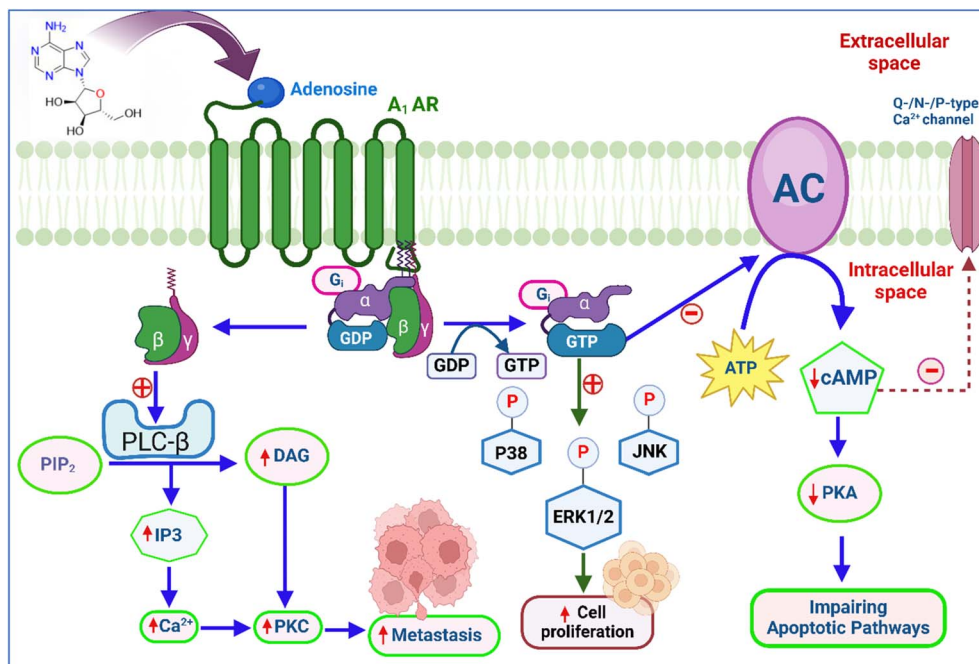
Overexpression of AC-3 increases molecules like matrix metalloproteinase 2 (MMP2), matrix metalloproteinase 9 (MMP9), and cAMP, promoting tumour growth.<sup>68,69</sup> Inhibition of AC-3 slows tumor progression, while AC-2 is a marker for poor colon cancer outcomes. A<sub>1</sub> receptor agonists reduce glioblastoma formation and microglial proliferation, and the absence of A<sub>1</sub> AR increases microglial density around tumors.<sup>95,96</sup>

In brain tumors, hypoxic conditions within the TME cause adenosine levels to rise.<sup>97</sup> This elevated adenosine activates the A<sub>1</sub> AR in microglia, the brain's immune cells.<sup>98</sup> Once A<sub>1</sub> AR is activated, microglia become less effective at targeting and destroying cancer cells. This reduction in immune activity allows tumours to grow and spread more easily.<sup>99</sup>

The A<sub>1</sub> AR and other adenosine receptors significantly aid tumor growth by promoting angiogenesis and forming new blood vessels. Tumors, especially in low-oxygen conditions, release high levels of adenosine which stimulates the production of vascular endothelial growth factor (VEGF) by interacting with A<sub>1</sub> AR and other receptors on surrounding cells.<sup>100</sup> VEGF then prompts endothelial cells to grow and form new blood vessels, which extend into the tumor, enhancing its blood supply, resulting in increased supply of nutrients and oxygen facilitating the tumor's growth and spread to other parts of the body.<sup>100,101</sup>

Blocking or modifying A<sub>1</sub> AR function can counteract this suppression, enhancing the immune response and improving tumor control. This approach can be used alongside existing

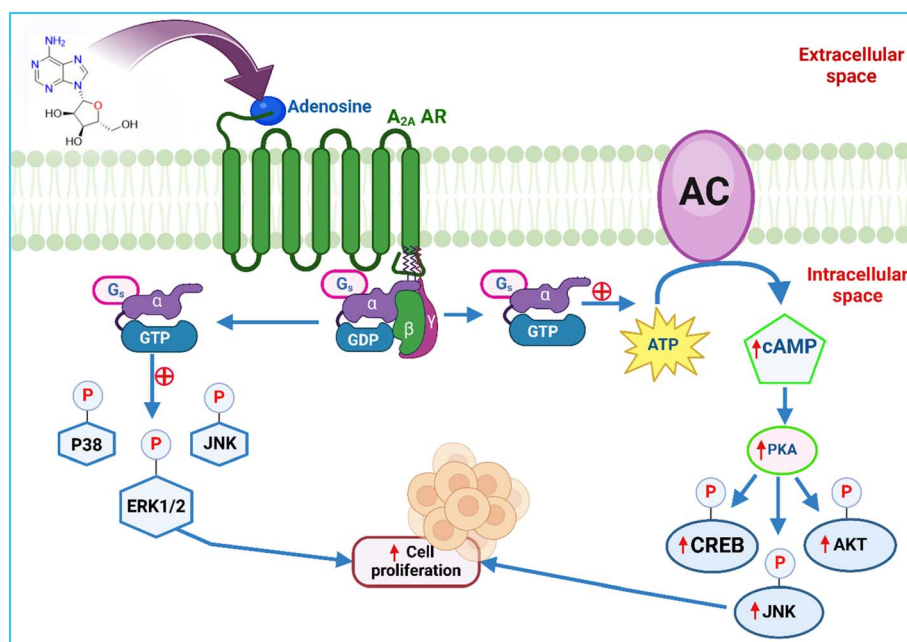




**Fig. 3**  $A_1$  adenosine receptors' role in cancer: molecular signaling pathways. GTP – "Guanosine triphosphate", PKC – "Protein kinase C", PKA – "Protein kinase A", DAG – "Diacylglycerol", GDP – "Guanosine diphosphate", ERK1/2 – "Extracellular signal-regulated kinases", ATP – "Adenosine triphosphate", PIP2 – "Phosphatidylinositol 4,5-bisphosphate", and IP3 – "Inositol trisphosphate", cAMP – "Cyclic adenosine monophosphate" NK – "c-Jun N-terminal kinases". The figure was created in BioRender. Deb, P. (2025).

therapies, such as chemotherapy, radiation, or immunotherapy, to overcome resistance and improve patient outcomes. By addressing specific mechanisms of immune suppression, targeting  $A_1$  AR offers a promising strategy to enhance cancer treatment and survival rates.<sup>102–104</sup>

However, adenosine can also promote microglial proliferation through the combined action of  $A_1$  and  $A_2$ ARs. While  $A_1$  ARs are often linked with suppressing immune responses, their interaction with  $A_2$  ARs can have different effects. Specifically, when adenosine activates both  $A_1$  and  $A_2$  ARs, it can stimulate



**Fig. 4**  $A_{2A}$  adenosine receptors' role in cancer: molecular signaling pathways. GTP – "Guanosine triphosphate", CREB – "cAMP-response element binding protein", JNK – "c-Jun N-terminal kinases", ERK1/2 – "Extracellular signal-regulated kinases", ATP – "Adenosine triphosphate", AKT – "Protein kinase B", GDP – "Guanosine diphosphate", and cAMP – "Cyclic adenosine monophosphate". The figure was created in BioRender. Deb, P. (2025).





the growth of microglia, which may alter the TME in ways that facilitate tumor growth and progression.<sup>103</sup> A separate study found that blocking  $A_1$  AR prevented cell death caused by adenosine, while activating  $A_1$  AR led to the death of human colorectal carcinoma (CW2) cells. These findings imply that  $A_1$  AR contributes to the tumor-inhibitory properties of adenosine, suggesting that activation of this receptor may cause cancer cells to undergo apoptosis.<sup>105</sup> The role of  $A_1$  AR in cancer was confirmed through studies where  $A_1$  AR levels were reduced in breast glands<sup>106</sup> and kidney cancers.<sup>107</sup> This was achieved using RNA interference and the  $A_1$  AR blocker DPCPX. Reducing  $A_1$  AR not only triggered cell death (apoptosis) in breast cancer cells but also slowed down tumour growth. Additionally, it caused cancer cells to stop progressing through the cell cycle at the  $G_2/M$  phase and reduce the number of cells in the S phase, which is crucial for cell division.<sup>106,108</sup>

## 7. $A_{2A}$ adenosine receptors' role in cancer: molecular signaling pathways

$A_{2A}$  AR receptors play a key role in several cancer processes, including rapid cell proliferation, angiogenesis, immune escape, and metastasis.<sup>109,110</sup> Thus, the increased presence of  $A_{2A}$  ARs enhances the cancer's ability to grow and metastasize uncontrollably (Fig. 4).<sup>110</sup>

Alternatively, the overexpression of  $A_{2A}$  ARs can also affect how immune cells, such as T cells, recognize and target cancer cells. Elevated levels of  $A_{2A}$  ARs can impair T cells' ability to effectively identify and attack tumour cells, as adenosine

signalling through these receptors inhibits T cell activation and functionality,<sup>111–113</sup> leading to suppression of immune cells, which in turn causes increased hypoxia within the tumour cells.<sup>114</sup> Under hypoxic conditions, adenosine levels increase in the tumor microenvironment (TME), leading to immune suppression. When adenosine accumulates in the TME, it binds to the  $A_{2A}$  AR, and inhibits the immune system. This binding particularly impairs the function of tumor-reactive immune cells, such as T cells and natural killer (NK) cells<sup>115,116</sup>

## 8. $A_{2B}$ adenosine receptors' role in cancer: molecular signalling pathways

Chinese hamster ovary (CHO) cells that produce recombinant human  $A_{2B}$  AR have been the primary and original demonstration source for classical  $A_{2B}$  AR signalling.<sup>117–119</sup> Like the  $A_{2A}$  receptor, the  $A_{2B}$  AR is coupled with the  $G_s$  protein, which is crucial for intracellular signalling.<sup>120</sup> Adenosine activates PKA (Fig. 5) by binding to  $A_{2B}$  AR, which phosphorylates target proteins and also recruits effectors like Epac (exchange protein directly activated by cAMP).<sup>120–122</sup> This Epac impacts the proliferation of umbilical vein endothelial cells and triggers the expression of early genes, ultimately reducing smooth muscle cell growth in human coronary arteries.<sup>123–125</sup> Additionally,  $A_{2B}$  AR is coupled with  $G_q$  proteins, which activate PLC that converts a molecule called PI2 into two important products: DAG and IP3. IP3 releases calcium ions within the cell, while DAG activates PKC.<sup>126,127</sup> According to recent studies, activating  $A_{2B}$  AR reduces the activity of signalling molecules that are usually

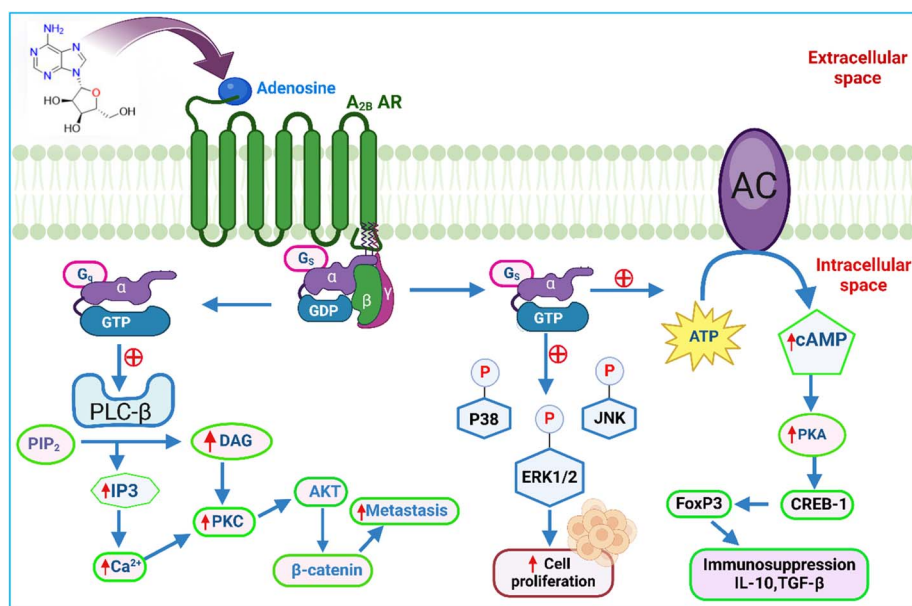


Fig. 5  $A_{2B}$  adenosine receptors' role in cancer: molecular signalling pathways. ATP – "Adenosine triphosphate", CREB – "cAMP-response element binding protein", PKC – "Protein kinase C", IP3 – "Inositol trisphosphate", GDP – "Guanosine diphosphate", PLC- $\beta$  – "phospholipase C- $\beta$ ", IL-10 – "Interleukin 10", AKT – "Protein kinase B", ERK1/2 – "Extracellular signal-regulated kinases", cAMP – "Cyclic adenosine monophosphate", FoxP3 – "Forkhead box P3", DAG – "Diacylglycerol", PKA – "Protein kinase A", GTP – "Guanosine triphosphate", JNK – "c-Jun N-terminal kinases", PIP2 – "Phosphatidylinositol 4,5-bisphosphate" and TGF- $\beta$  "Transforming growth factor  $\beta$ ". The figure was created in Bio-Render. Deb, P. (2025).





activated by the RANKL protein, such as p38, NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells), ERK1/2 (extracellular signal-regulated kinases 1 and 2), and p38. These signalling pathways collectively support tumour development and growth.<sup>128</sup> Many studies have highlighted the importance of A<sub>2B</sub> AR signalling in various disorders, including atherosclerosis,<sup>129,130</sup> neurological inflammation,<sup>131,132</sup> inflammatory bowel disease,<sup>133</sup> ischemic heart preconditioning<sup>134</sup> and the prevention of cardiovascular fibrosis. Overexpression of A<sub>2B</sub> receptors is also linked to renal disorders.<sup>135</sup>

Wei *et al.* discovered that the A<sub>2B</sub> AR is the most highly expressed adenosine receptor in human prostate cancer cell lines. According to their findings, TNF $\alpha$  and chemotherapy-induced cell death are lessened when the A<sub>2B</sub> receptor is activated.<sup>136</sup> J. Linden and colleagues showed the selective antagonist ATL801 to block the A<sub>2B</sub> receptor, which prevents the development of 4T1 mammary carcinoma and MB49 urinary bladder tumours *in vivo*.<sup>137</sup>

## 9. A<sub>3</sub> adenosine receptors' role in cancer: molecular signalling pathways

The A<sub>3</sub> AR is linked to G<sub>q</sub> proteins that activate phospholipase C- $\beta$  (PLC- $\beta$ ), producing IP<sub>3</sub>, which further increases intracellular calcium and activates PKC (Fig. 6).<sup>10,138,139</sup>

In normal tissue, A<sub>3</sub> AR expression is minimal, but in tumour cells, it is markedly elevated;<sup>140</sup> as a result, it can be regarded as a possible tumour marker. A<sub>3</sub> AR levels are elevated in colorectal cancer and other malignant tumours, including pancreatic carcinoma, small-cell lung cancer, breast cancer, and

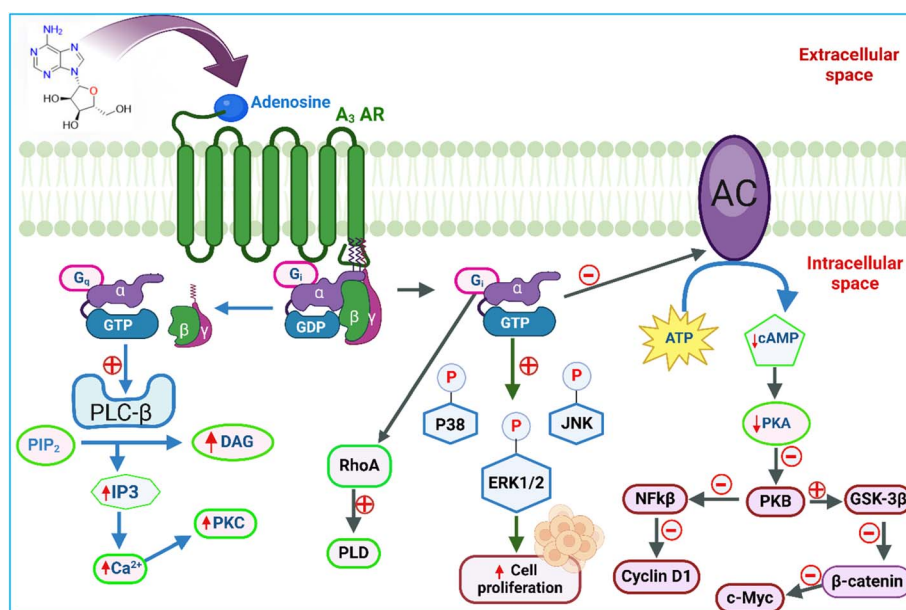
melanoma, and are associated with disease progression.<sup>141–144</sup> According to reports, human melanoma cells that express A<sub>3</sub> AR signalling exhibit pro-survival effects.<sup>145</sup> Glycogen synthase kinase (GSK)-3 $\beta$ , an enzyme essential for  $\beta$ -catenin phosphorylation, regulates this pathway, increasing tumour cell development.<sup>146</sup> The expression of genes crucial for advancing the cell cycle, such as cyclin D1 and c-myc, is encouraged by phosphorylated  $\beta$ -catenin.<sup>147</sup>

Chromosome 1 at location p13.3 in humans contains the gene that codes for the A<sub>3</sub> AR.<sup>148</sup> A<sub>3</sub> AR's overexpression in various tumour cells and tissues suggests that it may be useful as a therapeutic target and a cancer marker.<sup>38,143</sup>

## 10. Potential use of adenosine receptor ligands in cancer treatment

Selective modulators of adenosine receptors provide promising strategies for cancer treatment by directly inhibiting tumour growth or modifying the tumour microenvironment to enhance anti-tumour immune responses. These modulators target specific adenosine receptors: A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>, each playing distinct roles in cancer progression (Table 2). Their effects and mechanisms in cancer treatment are actively being explored, and future research will likely continue to refine these pathways for more targeted and effective therapies. Below is an elaboration on the selective modulators for each receptor type, their effects, and mechanisms in cancer treatment.

Many studies have been conducted on the structure–activity relationship (SAR) of adenosine derivatives as agonists of the AR. Adenosine and xanthosine, two purine nucleoside



**Fig. 6** A<sub>3</sub> adenosine receptors' role in cancer: molecular signaling pathways. ERK1/2 – “Extracellular signal-regulated kinases”, ATP – “Adenosine triphosphate”, PKA – “protein kinase A”, PIP2 – “Phosphatidylinositol 4,5-bisphosphate”, FoxP3 – “Forkhead box P3”, GSK-3 $\beta$  – “Glycogen synthase kinase-3 $\beta$ ”, IP3 – “Inositol trisphosphate”, cAMP – “Cyclic adenosine monophosphate”, JNK – “c-Jun N-terminal kinases”, DAG – “Diacylglycerol”, PKC – “Protein kinase C”, PKB – “Protein kinase B”, RhoA – “Ras homolog family member A” and NF $\kappa$ B – “Nuclear factor kappa-light-chain-enhancer of activated B cells”. The figure was created in BioRender. Deb, P. (2025).



**Table 2** Some selective modulators for various types of adenosine receptors, along with their effects and mechanisms of action in cancer treatment

S. No.	Name of the compounds	Agonist/ antagonist	Target receptor subtype	Transduction mechanism	Description role
1	CHA	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Binds to A <sub>1</sub> AR and activates it; this activation leads to decreased AC and decreased cAMP in the cell
2	CPA	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Activated G <sub>i</sub> proteins inhibit AC activity, decreasing the production of cAMP from ATP. Lower cAMP levels result in reduced activation of PKA and downstream signaling pathways
3	CCPA	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	cAMP levels can lead to decreased activation of protein kinase A (PKA), which promotes cell growth and proliferation
4	S-ENBA	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	cAMP levels due to A <sub>1</sub> AR activation can lead to decreased activation of protein kinase A (PKA)
5	5'-Cl-ENBA	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Can reduce PKA activity, potentially inhibiting the proliferation of cancer cells
6	Sele-denoson or DTI 0009	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Lowering AC level
7	GR79236X	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Decrease the cAMP level
8	Tiazofurin	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Inhibit inosine monophosphate dehydrogenase (IMP dehydrogenase) activity so, it can decrease the levels of downstream purine nucleotides, which can impact cell proliferation, especially in rapidly dividing cells such as cancer cells
9	Cyclosaligenyl-tiazofurin monophosphate	Agonist	A <sub>1</sub> receptor	AC ↓ PLC ↑	Reduction in cAMP levels may affect downstream effectors, such as protein kinase A (PKA), which can influence cell growth
10	1,3-Dipropyl-8-cyclopentylxanthine	Antagonist	A <sub>1</sub> receptor	AC ↑	The inhibitory effect that adenosine has on adenylate cyclase, increased adenylate cyclase activity and higher levels of cAMP within the cell
11	HENECA	Agonist	A <sub>2A</sub> receptor	AC ↑	Activating A <sub>2A</sub> receptors may influence the immune response within the tumor microenvironment
12	CGS15943	Antagonist	A <sub>2A</sub> receptor	AC ↓	Binding to the A <sub>1</sub> receptor usually results in reduced cyclic AMP (cAMP) levels due to inhibition of adenylate cyclase
13	ZM241385	Antagonist	A <sub>2A</sub> receptor	AC ↓	Antagonising A <sub>2A</sub> adenosine receptors, leading to decreased cAMP production
14	SCH58261	Antagonist	A <sub>2A</sub> receptor	AC ↓	Promote T cell function and enhance anti-tumour immune responses
15	SCH-442416	Antagonist	A <sub>2A</sub> receptor	AC ↓	Blocking the A <sub>2A</sub> receptor
16	SYN115 (tozadenant)	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibition of the A <sub>2A</sub> receptor can disrupt pathways that allow cancer cells to evade immune surveillance, potentially leading to reduced tumor growth
17	TP455	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibition of A <sub>2A</sub> receptors can lead to increased activation and proliferation of T cells
18	CPI-444	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibits the A <sub>2A</sub> adenosine receptor
19	PBF-509	Antagonist	A <sub>2A</sub> receptor	AC ↓	The antagonism of A <sub>2A</sub> receptors may also help inhibit pathways that contribute to tumor cell survival and proliferation
20	AZD4635	Antagonist	A <sub>2A</sub> receptor	AC ↓	Blocking the A <sub>2A</sub> receptor
21	TT-10	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibits the A <sub>2A</sub> adenosine receptor
22	Preladenant	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibits the A <sub>2A</sub> receptor
23	Etrumadenant (AB928)	Antagonist	A <sub>2A</sub> receptor	AC ↓	Blocking A <sub>2A</sub> receptors helps to counteract the immunosuppressive effects of adenosine
24	Inupadenant	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibits the A <sub>2A</sub> AR
25	ANR 94	Antagonist	A <sub>2A</sub> receptor	AC ↓	Selectively inhibits the A <sub>2A</sub> receptor
26	CPI-444 analog	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibition of A <sub>2A</sub> receptors
27	Istradefylline	Antagonist	A <sub>2A</sub> receptor	AC ↓	Inhibition of A <sub>2A</sub> receptors
28	PSB1115	Antagonist	A <sub>2B</sub> receptor	AC ↑	Inhibit A <sub>2B</sub> receptor
29	PSB603	Antagonist	A <sub>2B</sub> receptor	AC ↑	Blocked A <sub>2B</sub> receptor
30	ATL801 (30)	Antagonist	A <sub>2B</sub> receptor	AC ↑	A <sub>2B</sub> receptor blocked
31	AB928	Antagonist	A <sub>2B</sub> receptor	AC ↑	A <sub>2B</sub> receptor inhibitor
32	Piclidenoson (IB-MECA)	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	Boost the activity of regulatory T cells (Tregs), thereby increasing immunosuppression within the TME



Table 2 (Contd.)

S. No.	Name of the compounds	Agonist/ antagonist	Target receptor subtype	Transduction mechanism	Description role
33	Namodenoson (Cl-IB-MECA)	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	Promoting anti-tumor immunity by reducing inflammation while also potentially inducing apoptosis in tumor cells
34	Thio-Cl-IB-MECA	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	Thio-Cl-IB-MECA binds to the A <sub>3</sub> adenosine receptor. Upon activation, the A <sub>3</sub> receptor inhibits adenylate cyclase, leading to decreased levels of cAMP in the cell
35	Cordycepin	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	A <sub>3</sub> receptor activation
36	N <sup>6</sup> -(2-Isopentenyl) adenosine	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	Activation of A <sub>3</sub> receptors lead to the inhibition of cell proliferation
37	Resveratrol-3-O-D-glucuronide	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	A <sub>3</sub> receptor activation
38	Resveratrol 4'-O-D-glucuronide	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	A <sub>3</sub> receptor activation
39	Linagliptin	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	A <sub>3</sub> receptor activation
40	Oxidative degradation product of linagliptin	Agonist	A <sub>3</sub> receptor	AC ↓ PLC ↑	A <sub>3</sub> receptor activation
41	MRS 1523	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
42	Truncated thio-Cl-IB-MECA	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
43	N <sup>6</sup> -(2,2-Diphenylethyl)-2-phenylethynylAdo	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
44	[1,2,4]-Triazolo[1,5-c]pyrimidines	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
45	MRS 1097	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
46	MRS 1067	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
47	MRS 1220	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor
48	MRS 1191	Antagonist	A <sub>3</sub> receptor	AC ↑	Inhibit A <sub>3</sub> receptor

derivatives, constitute the basis for the majority of known AR agonists. Many agonists that target distinct AR subtypes have been developed due to modifications to the physiological agonist adenosine. Adenosine's affinity for adenosine receptors is increased by adding nitrogen atoms at positions 3 and 7.<sup>149</sup> Mono-substitution of the N<sup>6</sup> position (exocyclic amino group) of adenosine with a large, non-polar (hydrophobic) group enhances the molecule's ability to preferentially bind to the A<sub>1</sub> and A<sub>3</sub> AR subtypes.<sup>33,149</sup> The existence of a hydrogen atom at position N<sup>6</sup> is critical for agonist activation because it creates hydrogen bonds with the receptor.<sup>150</sup> For tiny halogen atoms or

bigger substituents, modifications to adenine at the C<sub>2</sub> position are generally well tolerated.<sup>151</sup> Strong and focused agonistic action at ARs is produced by substitutions at the 5'-position, which are often well tolerated and require the presence of a ribose sugar moiety. In the adenosine structure, the 2'- and 3'-hydroxyl (OH) groups of the ribose moiety are essential for agonist activity at adenosine receptors (Fig. 7).

Structure-activity relationship (SAR) studies at adenosine receptors show that xanthines with strong inhibitory activity were consistently alkylated at the 1-position, where substituting hydrogen with a methyl group enhanced potency by

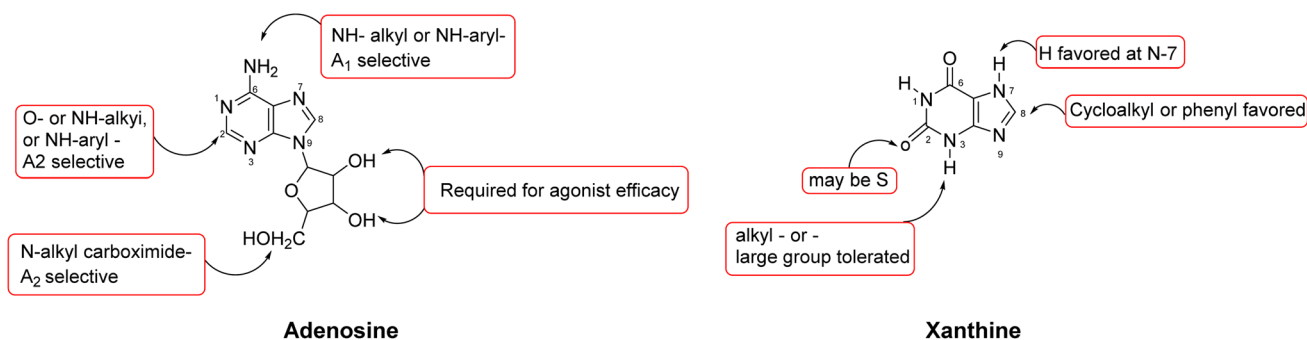


Fig. 7 Impact of structural modifications of adenosine and xanthine derivatives on adenosine receptor binding.



approximately 20-fold. Modifications at the 3-position were not essential for high activity. Substitution at the 7- and 8-position might slightly increase or decrease the potency, while substitutions at the 7-position are typically considered unfavourable. However, certain alkyl modifications at these positions can selectively boost affinity for the  $A_2$  receptor subtype.<sup>152</sup>

### 10.1 The $A_1$ receptor agonists

The selectivity towards  $A_1$  AR was found to be increased mainly upon the introduction of a larger cycloalkyl group at the  $N^6$ -position of the agonists like CHA ( $N^6$ -cyclohexyladenosine) (1) and CPA ( $N^6$ -cyclopentyladenosine) (2), being 400- and 800-fold selective.<sup>153</sup> Combined substitutions at the  $N^6$ - and 2-positions have yielded 2-chloro-CPA (CCPA) (3), which is 1500-fold  $A_1$ -selective, and helpful in wide pharmaceutical applications.<sup>33,149–151,154,155</sup>

Mice deficient in  $A_1$  AR and their wild-type littermates responded differently to injections of GL261 glioblastoma tumour cells and treatment with adenosine and  $N^6$ -cyclopentyladenosine (CPA), where CPA significantly reduced the growth of the tumour. Remarkably, research revealed that in brain slices taken from  $A_1$  AR-deficient mice, neither adenosine nor CPA ( $N^6$ -cyclopentyladenosine) had any impact on tumour formation. These results suggest that CPA and adenosine influence tumour size reduction by selectively interacting with  $A_1$  ARs on microglial cells.<sup>96</sup>

Like numerous other  $N^6$ -substituted adenosine analogues, both CPA and CCPA derivatives show notable affinity for the  $A_3$  AR as well. In contrast to  $A_1$  AR, CCPA has been identified as an antagonist at the human  $A_3$  AR, with a  $K_i$  value of 35 nM.<sup>156</sup>  $N^6$ -Bicycloalkyladenosine is even more  $A_1$ -selective, with S-ENBA (4), showing 4700-fold selectivity for the  $A_1$  receptor.<sup>157–159</sup> Among the most selective  $A_1$  AR agonists, 5'-Cl-ENBA (5) demonstrates exceptionally high affinity and selectivity for the  $A_1$  AR compared to other AR subtypes.<sup>160,161</sup> Through the activation of  $A_1$  AR,  $N^6$ -cyclopentyl-NECA, often referred to as seledenoson or DTI 0009 (6), exhibited the strongest negative dromotropic impact ( $A_1$  AR).<sup>162</sup> Seledenoson has been tested in phase 2 clinical trials to determine its efficacy in treating atrial fibrillation *via* oral and intravenous (IV) routes.<sup>163</sup> In addition the other  $A_1$ -selective adenosine derivatives, including GR79236, clinical investigations have examined the possible use of  $N^6$ -[(1*S*, *trans*)-2-hydroxy-cyclopentyl] adenosine (GR79236X) (7), a hydroxylated derivative of CPA, in the treatment of myocardial ischemia, diabetes, and pain.<sup>33</sup>

Tiazofurin (8) is a C-nucleoside that inhibits inosine monophosphate dehydrogenase (IMPDH) and has demonstrated anticancer efficacy in clinical settings. Tiazofurin adenine dinucleotide, produced when metabolized, inhibits the IMPDH enzyme, stopping nucleotide synthesis and inhibiting the growth of cancerous cells.<sup>108</sup> A new tiazofurin pronucleotide called cyclosaligenyl-tiazofurin monophosphate (9) is a selective

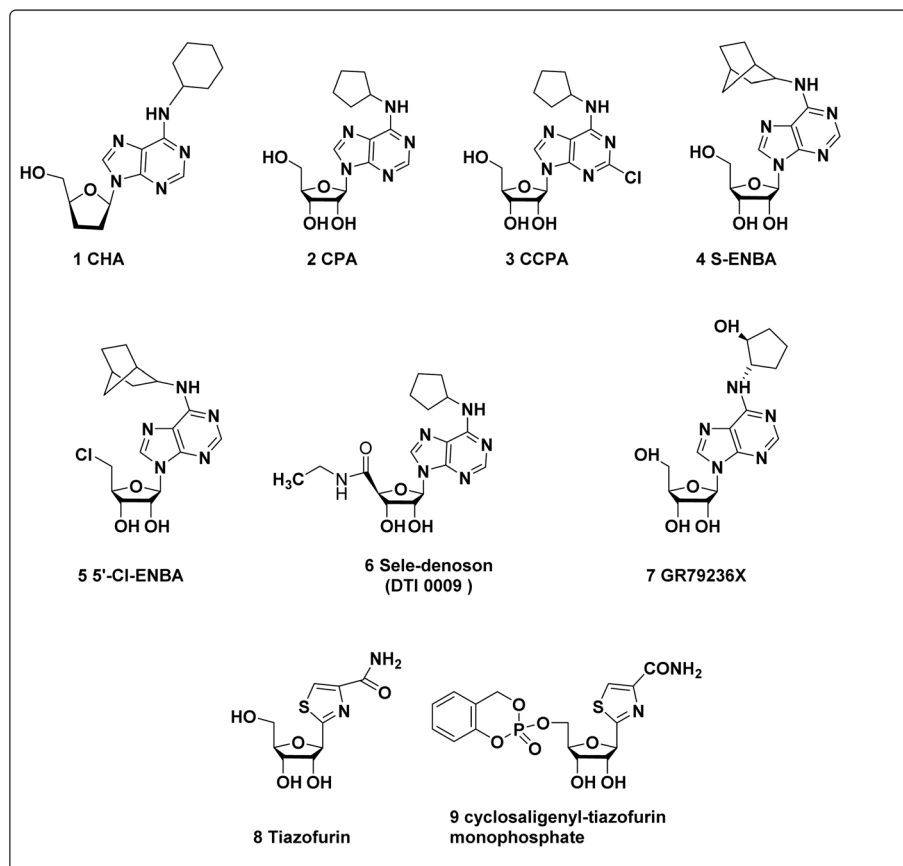


Fig. 8 Potential  $A_1$  adenosine receptor agonists exhibiting promising anticancer properties.



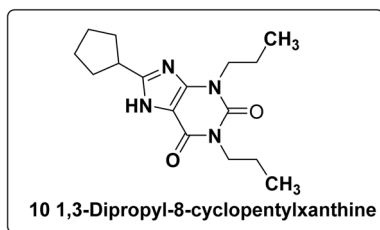


Fig. 9 Potential A<sub>1</sub> adenosine receptor antagonist exhibiting promising anticancer properties.

agonist of the A<sub>1</sub> AR. Its binding affinity is comparable to that of tiazofurin, suggesting a similar mechanism of action at this receptor subtype. Additionally, it exhibits significant efficacy against the K-562 cell line, which is a model for human chronic myelogenous leukaemia (*in vitro*). Structural representations of interesting A<sub>1</sub> AR agonists with anti-cancer activity are shown in Fig. 8.

### 10.2 The A<sub>1</sub> receptor antagonists

The A<sub>1</sub> AR antagonist has diverse effects on different forms of cancer and may help in preventing the development of specific cancer types. Recent investigations have employed quantitative real-time PCR and western blotting analysis to ascertain the function of A<sub>1</sub> AR in kidney cancer in 786-O & ACHN cell lines. In addition, investigations on anticancer research have shown that 1,3-dipropyl-8-cyclopentylxanthine (**10**), an A<sub>1</sub> AR antagonist (Fig. 9), efficiently decreases the formation of tumours *in vivo* and the proliferation of RCC cells *in vitro*. Compound **10** also inhibited the migration of RCC cells; however, the selective A<sub>1</sub> agonist N<sup>6</sup>-cyclopentyladenosine (CPA) increased the migration of RCC cells. Furthermore, the xanthine derivative **10** produced an arrest in the S-phase of the cell cycle and increased apoptosis in 786-O and ACHN cells.<sup>108</sup>

### 10.3 The A<sub>2A</sub> receptor selective agonists

With A-375 cells, the anticancer effects were studied using a particular A<sub>2A</sub> agonist, (2*S*,3*R*,5*R*)-HENECA (2-hexynyl-NECA) (**11**) as shown in Fig. 10, which demonstrated consistent, modest effects in inhibiting cell proliferation and lowering cytotoxicity in A-375 cell lines.<sup>106,164</sup> Compound **11** causes concentration-dependent cell death, with peak effects being shown at 100 nM. Higher concentrations, however, resulted in a decrease in its effectiveness.

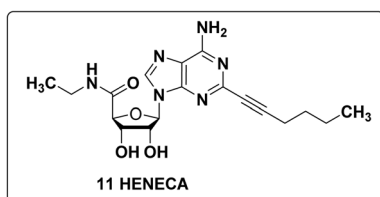


Fig. 10 Potential A<sub>2A</sub> adenosine receptor agonist exhibiting promising anticancer properties.

### 10.4 The A<sub>2A</sub> receptor-selective antagonists

Hypoxic solid tumours are known to include an increased amount of adenosine, which hinders the capacity of cytolytic T lymphocytes that are essential to identify cancer cells as targets.<sup>112,165</sup> It has been discovered that the activation of A<sub>2A</sub> AR stimulates angiogenesis and boosts the growth of melanoma and mammary cells. These findings emphasise the significance of developing A<sub>2A</sub> AR antagonists for the treatment of cancer.<sup>166,167</sup> Examples of A<sub>2A</sub> AR antagonists with anticancer effects are shown in Fig. 11.

The effects of adding styryl groups to xanthines at the 8-position have been brought to light by recent developments in search of A<sub>2A</sub> AR antagonists. This has increased the A<sub>2A</sub> AR selectivity.<sup>168–170</sup>

However, replacing the xanthine core with various heterocyclic ring systems has resulted in exceptionally high affinity and selectivity for the A<sub>2A</sub> AR. An early example of a heterocyclic structure proposed as an A<sub>2A</sub> AR antagonist was triazoloquinazoline (CGS15943) (**12**), which was later found to exhibit only modest selectivity. Subsequent modifications, such as adding a third ring or altering the nitrogen arrangement within the heterocyclic system, significantly enhanced A<sub>2A</sub> AR selectivity.<sup>5,171</sup> Triazoloquinazoline CGS15943 (**12**), an early example of a heterocyclic antagonist, was discovered to have only moderate selectivity, contrary to initial predictions.

Selectivity for the A<sub>2A</sub> AR was markedly increased by further modifications to the triazoloquinazoline, with adjustments to the nitrogen arrangement within the heterocyclic structure leading to the development of a compound with improved potency, triazolotriazine ZM241385 (**13**).<sup>172</sup>

ZM241385 “(4-(2-((7-amino-2-(furan-2-yl)-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-yl)amino)ethyl)phenol)” is an A<sub>2A</sub> AR antagonist that enhances the ability of antitumor T lymphocytes to suppress tumour growth, eradicate cancer, and prevent the production of new blood vessels. Compound **13** stimulated the development of anti-CL8-1 CD8<sup>+</sup> T cells and markedly slowed the growth of CL8-1 tumours in wild-type mice. When this antagonist (compound **13**) is used in conjunction with anti-CD8<sup>+</sup> T cells in adoptive immunotherapy models, tumour growth is successfully prevented; however, the antagonist by itself does not have the same impact.<sup>170</sup> In melanoma-bearing mice, the efficacy of compound **13**, was investigated in combination with an anti-CTLA4 monoclonal antibody.<sup>173</sup> Tumor growth was significantly inhibited in mice receiving just compound **13** treatment. In contrast to either the control group or treatment with compound **13** alone, the combination therapy led to a more noticeable delay in the progression of the tumor. There is a theory that this enhanced effect is linked to a decrease in regulatory T cells (TREGs) and an increase in CD8-positive (CD8<sup>+</sup>) T lymphocyte infiltration within the tumor tissue. In cutaneous melanoma tissue, treatment with the compound **13** alone resulted in increased infiltration of CD8<sup>+</sup> T cells and a decrease in regulatory T cells (TREGs).<sup>168</sup>

Interestingly, the pyrazolotriazolopyrimidine group plays a significant role in improving A<sub>2A</sub> AR selectivity. In SCH58261 (**14**), the xanthine core is also modified, but it includes



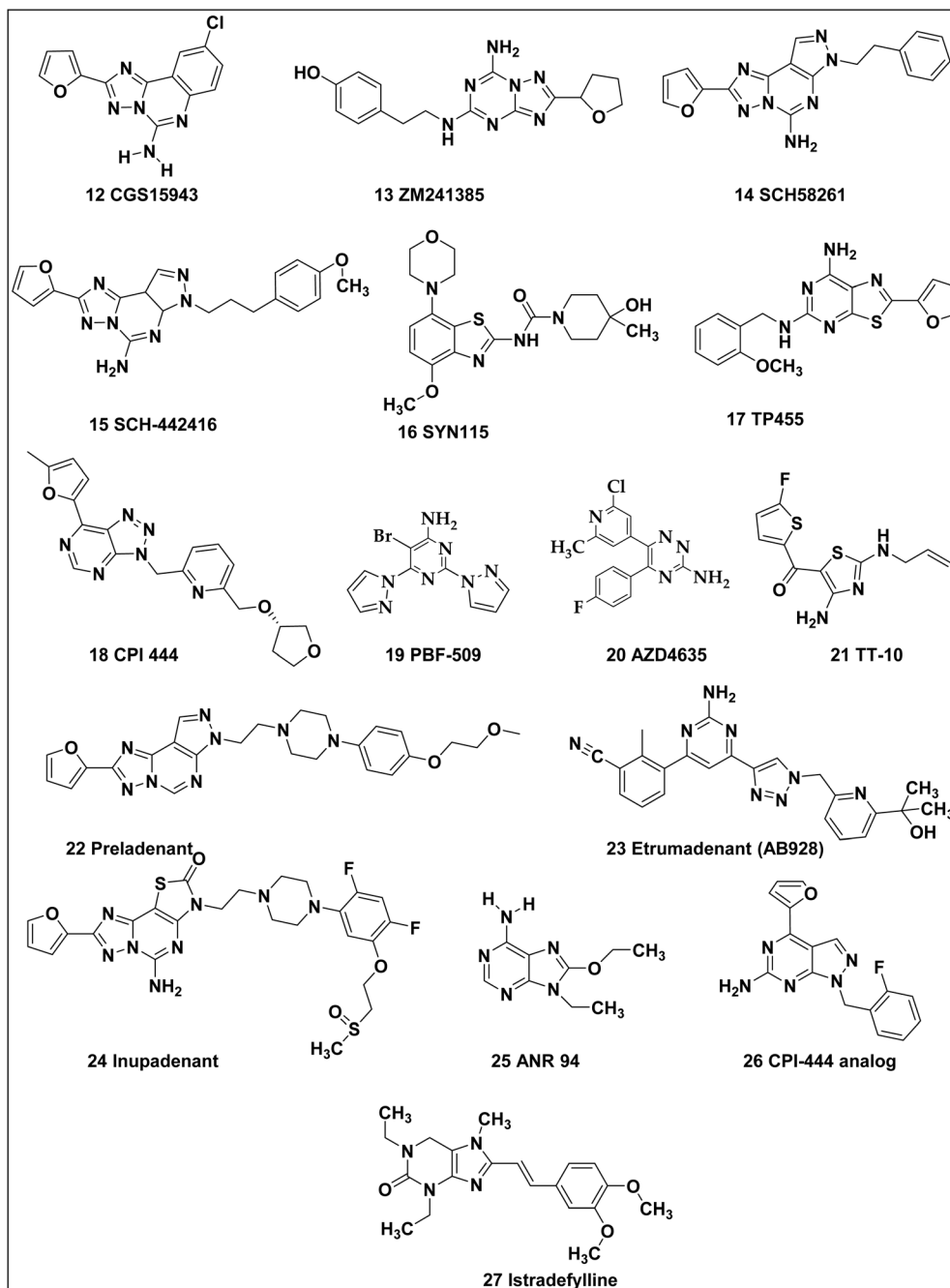


Fig. 11 Potential  $A_{2A}$  adenosine receptor antagonists exhibiting promising anticancer properties.

additional aromatic and heteroatom-containing groups. SCH58261 (**14**) “2-(furan-2-yl)-7-phenethyl-7*H*-pyrazolo[4,3-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine” is an  $A_{2A}$  receptor blocker that has been studied for its potential to prevent metastasis using the 4T1.2 cancer model, a highly aggressive metastatic mammary gland tumor cell line.<sup>174</sup> Research has demonstrated that by blocking the  $A_{2A}$  AR, the triazolo-pyrimidine derivative **14** dramatically reduces cancer cell proliferation in B16F10 CD73<sup>+</sup> malignancies. Additionally, compared to the control group, therapy with the  $A_{2A}$  antagonist **14** resulted in a significant reduction in the metastasis of 4T1.2

tumors. Moreover,  $A_{2A}$ –/– animals showed significant defence against B16-F10 CD73<sup>+</sup> tumor cell metastasis.<sup>175</sup> In non- $A_{2A}$ –/– animals, the  $A_{2A}$  antagonist **14** likewise showed decreased efficacy, demonstrating the drug’s specificity for the  $A_{2A}$  receptor.<sup>175,176</sup> In animal models of skin and breast tumor, compound **14** was also demonstrated to improve survival and lessen the stress caused by metastatic cancer when given in combination with an anti-PD-1 monoclonal antibody.<sup>176</sup>

Incorporating pyrazole and triazole rings into the structure of SCH442416 (**15**) enhances its binding affinity by altering the electronic properties of the xanthine core. These modifications

improve interactions with the  $A_{2A}$  receptor.<sup>29</sup> Specifically, the addition of an  $N'$ -substituted pyrazolotriazopyrimidine group refines the molecule's conformation, increasing  $A_{2A}$  receptor selectivity while reducing affinity for other adenosine receptor subtypes. As a result, SCH442416 exhibits high affinity for the  $A_{2A}$  receptor ( $hA_{2A}$   $K_i$  = 1.1 nM) and significantly lower affinity for the  $A_1$  receptor ( $hA_1$   $K_i$  = 549 nM), establishing it as a widely used reference antagonist for  $A_{2A}$  receptor studies.<sup>177</sup>

In a follow-up investigation, researchers evaluated the benzothiazole derivative SYN115 (tozadenant) (**16**) for its potential to act as an antagonist of the  $A_{2A}$  AR. The study focused on how this property could enhance the anticancer effects of an anti-PD-1 monoclonal antibody, which is used in cancer immunotherapy. By blocking the  $A_{2A}$  receptor, SYN115 may help improve immunological reaction to malignancies, thereby possibly increasing the effectiveness of the anti-PD-1 treatment in combating cancer. It was demonstrated that the  $A_{2A}$  receptor blocker **16** significantly increased the anticancer efficacy of the anti-PD-1 antibody, with results comparable to compound **15**.<sup>70</sup>

The role of  $A_{2A}$  AR in a number of human cancers, such as rat MRMT-1 breast cancer, A-375 melanoma, and A-549 lung cancer, has been extensively studied. Special attention has been paid to the signaling pathways involved and the outcomes of a novel  $A_{2A}$  receptor antagonist, TP455 (**17**) (2-(furan-2-yl)- $N$ 5-(2-methoxybenzyl)thiazolo[5,4- $d$ ]pyrimidine-5,7-diamine), as well as the actions of this antagonist.<sup>178</sup>

The immune-activating and anti-tumor properties of ( $S$ )-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5- $d$ ]pyrimidin-5-amine, CPI-444 (**18**), either alone or in combination with anti-PD-1/PD-L1 monoclonal antibodies, have been evaluated *in vitro* using activated primary human T cells. The results showed that pyrimidine derivative **18** completely inhibited the production of intracellular cAMP when the cells were incubated with 5'- $N$ -ethylcarboxamidoadenosine (NECA), a stable adenosine analog. Activated T lymphocytes produce less IL-2 and IFN- $\gamma$  when the  $A_{2A}$  AR agonist prevents fast TCR-mediated ERK phosphorylation. On the other hand, T cell signalling and function were restored when antagonist **17** blocked the  $A_{2A}$  AR. Efficacy of the compound **18** has been examined using CT26 and MC38 syngeneic animal tumor models. The absence of fresh tumour development in cured animals when re-challenged with MC38 cells indicates that antagonist **18** produced systemic anti-cancer immunological memory. Molecule **17**, in conjunction with an anti-PD-L1 monoclonal antibody in the MC38 model, led to a synergistic decrease in tumour development and total tumour eradication in 9 out of 10 treated mice. In the CT26 model, antagonist **17** and anti-PD-1 monoclonal antibody also showed synergistic effects; the combination dramatically reduced tumour development and increased survival over antagonist **17** treatment alone.<sup>179,180</sup>

The  $A_{2A}$  AR-mediated immunological checkpoint is activated when adenosine levels rise in the tumour microenvironment, suppressing anti-tumour responses. Enhancing anti-tumour T cell function may be possible by focusing on this immunological checkpoint. PBF-509 (5-bromo-2,6-di(1H-pyrazol-1-yl)pyrimidin-4-amine) (**19**) is a novel  $A_{2A}$  AR antagonist that has

been developed as a possible treatment for non-small cell pulmonary carcinoma in this regard.<sup>181</sup> According to research, PBF-509 has strong selectivity for the  $A_{2A}$  AR. PBF-509 therapy decreased lung metastases in a mouse model compared to the control group. Additionally, among recently extracted tumor-infiltrating lymphocytes from lung cancer patients, investigations showed varied expression of the  $A_{2A}$  receptor in CD8<sup>+</sup> cells and enhanced expression in CD4<sup>+</sup> cells. Additionally, when PBF-509 was administered in conjunction with anti-PD-1 or anti-PD-L1 therapy, human tumor-infiltrating lymphocytes showed enhanced reactivity, according to *in vitro* investigations.<sup>182</sup> These results imply that blocking the  $A_{2A}$  AR may open up new avenues for the development of creative immunotherapeutic approaches to treat non-small-cell lung cancer.<sup>183</sup>

The use of  $A_{2A}$  AR antagonists in the treatment of cancer, either as monotherapy or in addition to different immunotherapies, is now being investigated in a number of clinical trials, which is relevant.<sup>91,184</sup> A number of  $A_{2A}$  AR antagonists are currently being evaluated in clinical settings including AZD4635 (**20**). In TT-10 (**21**), [4-amino-2-(prop-2-enylamino)-1,3-thiazol-5-yl]-(5-fluorothiophen-2-yl)methanone is an immunomodulatory drug that is being developed by Portage Biotech for oral administration. TT-10 exhibited a higher level of tumor growth suppression in preclinical investigations employing the 4T1 syngeneic mouse model of breast cancer than both the vehicle control and anti-PD-1 treatment groups. TT-10 therapy also resulted in a notable decrease in myeloid-derived suppressor cell (MDSC) numbers.<sup>185,186</sup> The adenosine pathway is a target for cancer immunotherapy, and 2020 saw the publication of the first clinical data supporting this theory. In this trial, 68 patients with renal cell carcinoma were treated with either ciferadenant alone or with atezolizumab (PD-L1 inhibitor). Many of these patients had tumors that were primarily PD-L1-negative and were resistant to or refractory to anti-PD-1/PD-L1 antibodies. The research emphasized that in patients with resistant renal cell carcinoma, anti-PD-L1 combination therapy, and monotherapy both had antitumor efficaciousness. Compared to combination therapy, which had a median progression-free survival of 5.8 months, monotherapy had a median survival of 4.1 months. Furthermore, overall survival rates for monotherapy at 16 months and combination therapy at 25 months were higher than 69% and 90%, respectively.  $A_{2A}$  AR antagonists' efficacy in immunotherapy for various cancer types has also been shown in additional trials. The research emphasized that in patients with resistant renal cell carcinoma, anti-PD-L1 combination therapy and monotherapy both had antitumor efficaciousness. In comparison to combination therapy, which had a median progression-free survival of 5.8 months, monotherapy had a median survival of 4.1 months.  $A_{2A}$  AR antagonists' efficacy in immunotherapy for a range of cancer types has also been shown in additional trials.<sup>187–189</sup>

A recent Phase Ib/II trial (NCT03099161) evaluated the safety of Preladenant (**22**), both standalone and in combination with the anti-PD-1 drug Pembrolizumab, in patients with advanced cancers.<sup>190</sup> However, the results have not yet been released.

In a Phase 1 open-label, multicenter trial, patients with advanced solid tumors will receive continuous oral



administration of AZD4635 (**20**) for evaluation.<sup>103,104</sup> Determining the maximal safe dosage of AZD4635 in conjunction with the anti-PD-L1 medication Durvalumab (NCT02740985) is the main goal of the trial.<sup>191</sup> In patients with non-small cell lung cancer (NSCLC), this A<sub>2A</sub> antagonist will also be evaluated for safety, tolerability, and anticancer effectiveness in combination with the anti-CD73 medication MEDI9497 and the EGFR inhibitor osimertinib (NCT03381274).<sup>183</sup>

There are several other high-affinity and selective adenosine A<sub>2A</sub> receptor inhibitors that have been discovered with potential clinical applications. These include Etrumadenant (AB928) (**23**), Inupadenant (**24**), ANR 94 (**25**), CPI-444 analogue (**26**). A<sub>2A</sub> AR selectivity has been achieved by altering xanthines at the 8-position with alkenes, especially styryl groups. One of the earliest recognised A<sub>2A</sub> AR antagonists was 8-styryl-xanthine, istradefylline (**27**) (KW6002).<sup>183,192,193</sup> The US-FDA has approved istradefylline for the treatment of Parkinson's disease.<sup>194</sup> This milestone, coupled with advancing insights into the role of adenosine (ADO) in cancer biology, is anticipated to accelerate the development of ADO receptor ligands as promising anti-cancer agents or as adjunct therapy to existing treatments.

### 10.5 The A<sub>2B</sub> receptor selective antagonists

The release of angiogenic factors from vascular smooth muscle, endothelial cells, and host immune cells is thought to be facilitated by the stimulation of the A<sub>2B</sub> AR, which in turn aids in the formation of tumors.<sup>145,195</sup> Conversely, blocking the A<sub>2B</sub> AR increases the activation of dendritic cells (DC) and thus increases the synthesis of CXCL10 (C-X-C pattern chemokine 10) which is induced by IFN- $\gamma$ . This chemokine contributes to the activation of lymphocytes and the induction of an angiostatic response in malignancies.<sup>196</sup> Antitumor actions of several synthetic A<sub>2B</sub> adenosine receptor antagonists have shown promise, as illustrated in Fig. 12.

Specific modifications of the xanthine core at the 8-position with aryl groups have been shown to confer selectivity for the

A<sub>2B</sub> AR. In PSB-1115 (**28**), modification of the xanthine core with an aryl group at the 8-position enhances receptor selectivity. Studies have demonstrated that melanoma growth can be effectively slowed by selectively inhibiting the A<sub>2B</sub> AR with the antagonist "PSB1115 (4-(2,6-dioxo-1-propyl-3,7-dihydropurin-8-yl)benzenesulfonic acid)" (**28**). To do this, antitumor immune responses are reactivated, and the growth of myeloid-derived suppressor cells (MDSCs) within tumors is suppressed.<sup>197</sup>

Furthermore, studies have shown that employing the antagonist **28** targets the A<sub>2B</sub> AR, which is known to play a role in suppressing the immune response within tumors. By inhibiting this receptor, the immune system can become more effective against the cancer, leading to a significant reduction in tumor growth. Compound **28**, derived from xanthine, is effective in diminishing specific immune cell populations associated with tumors (*Gr-1*<sup>+</sup>*CD11b*<sup>+</sup> cells) in melanoma. Additionally, it decreases the production of key regulatory molecules, such as interleukin-10 (IL-10) and monocyte chemoattractant protein 1 (MCP-1) that can suppress immune responses, potentially enhancing the body's ability to fight the tumor. The T cells that release cytokines like those produced by T helper 1 (Th1) cells are linked to these effects, and there are higher numbers of CD8<sup>+</sup> T cells and natural killer T (NKT) cells within tumours. These outcomes imply that the ability of the A<sub>2B</sub> AR antagonist **28** to minimise the infiltration of MDSCs (myeloid-derived suppressor cells) in tumours and to strengthen the anti-cancer T cell response is related to its efficacy. Furthermore, the xanthine derivative **28** has been found to drastically reduce the metastasis of B16F10 CD73<sup>+</sup> malignancies by blocking the A<sub>2B</sub> AR.<sup>198</sup>

"PSB603 (8-(4-(4-chlorophenyl)piperazine-1-sulfonyl)phenyl)-1-propylxanthine" (**29**), a recognized A<sub>2B</sub> receptor antagonist, exhibits particularly high affinity and selectivity for the A<sub>2B</sub> receptor, not only in humans but also in rodents. PSB-1115 also offers high water solubility, making it suitable for *in vivo* studies; however, its A<sub>2B</sub> receptor affinity and selectivity are lower than other A<sub>2B</sub> antagonists.<sup>199</sup> PSB603 is being

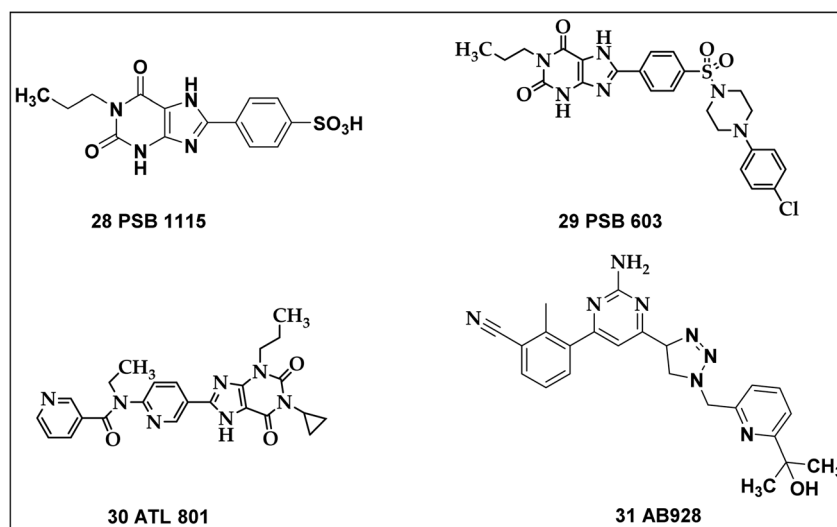


Fig. 12 Potential A<sub>2B</sub> adenosine receptor antagonists exhibiting promising anticancer properties.



investigated in C57BL/6 mice bearing B16 melanoma to see how it affects tumour progression. The *in vivo* observations revealed a significant decrease in tumour volume, postponed tumour growth, and decreased metastasis, associated with a decrease in the regulatory T-cell population in mice. This antagonist increases CD4<sup>+</sup> helper T cell and CD8<sup>+</sup> cytotoxic T cell populations, which improves anti-tumor immunity in tumor-bearing animals. As a result, inhibiting the A<sub>2B</sub> receptor increases the quantity of helper and cytotoxic T cells, that are necessary for the development of cancer immunity.<sup>137,176</sup>

ATL801 (30), an A<sub>2B</sub> receptor antagonist, has been demonstrated to successfully block the growth of 4T1 mammary carcinoma and MB49 urinary bladder cancer in syngeneic animal models. It also stops breast cancer cells from metastasizing. When administered intravenously, compound 30 can elicit adaptive immunological responses in a way that is dependent on CXCR3, most likely *via* indirectly increasing the activity of dendritic cells (DCs). This process prevents the growth of tumors and helps offset the immunosuppressive effects of adenosine. These results imply that stimulating T cell activation and inhibiting formation of new blood vessel in solid tumors may be accomplished by selectively blocking the A<sub>2B</sub> adenosine receptor.<sup>200</sup>

Lastly, it is noteworthy that a number of antagonists are presently being studied in clinical studies for different types of cancer. Notably, AB928 (31), a dual A<sub>2A</sub>/A<sub>2B</sub> antagonist, is currently being investigated in patients with breast tumor, non-

small-cell pulmonary carcinoma, and ovarian carcinoma after demonstrating encouraging findings in a Phase I clinical trial.<sup>137,201</sup>

## 10.6 The A<sub>3</sub> receptor selective agonists

The possibility of A<sub>3</sub> receptors as a therapeutic target for the treatment of cancer is highlighted by their overexpression in malignant and inflammatory cells.<sup>202</sup> Various potential A<sub>3</sub> receptor agonists are illustrated in Fig. 13. Interestingly, the effects of these agonists on tumor cell proliferation differ from those on normal cell growth. Most of the A<sub>3</sub> AR agonists developed to date are based on the nucleoside structure of the endogenous ligand, adenosine. The most effective enhancements in A<sub>3</sub> AR potency and selectivity have been achieved through substitutions at the N<sup>6</sup>-, C<sub>2</sub>-, and 5'-positions, or through strategic combinations of these modifications.

Potent and selective A<sub>3</sub> AR agonists were developed by combining N<sup>6</sup>-substitution with a 5'-uronamide group. The first A<sub>3</sub> AR-selective compounds featured a 5'-N-alkyluronamide moiety paired with an N<sup>6</sup>-benzyl group. A key representative of this series, N<sup>6</sup>-(3-iodobenzyl)adenosine-5'-N-methyluronamide (IB-MECA; 32), also known as piclidenoson was discovered in 1994.<sup>203,204</sup>

Extensive studies have explored the effects of various substitution patterns at the N<sup>6</sup>- and C<sub>2</sub>-positions of the adenine core in 5'-N-alkylcarbamoyl-adenosine derivatives. Introducing small functional groups, such as halogens, methylamino, or

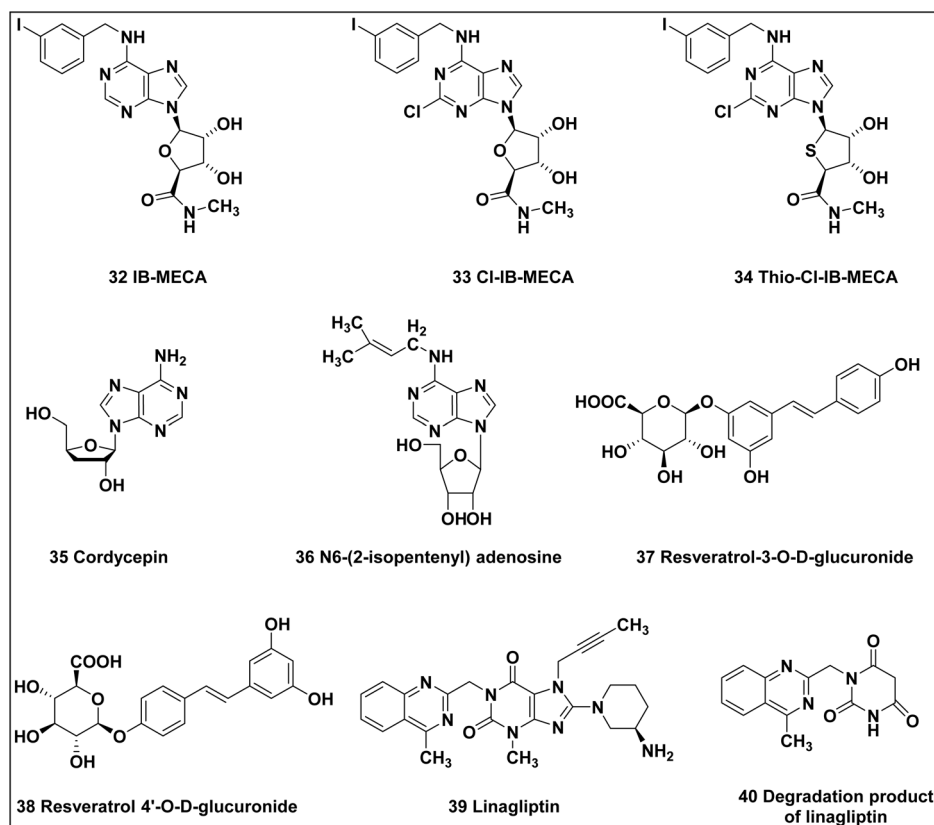


Fig. 13 Potential A<sub>3</sub> adenosine receptor agonists exhibiting promising anticancer properties.



thiomethyl, at the  $C_2$ -position of IB-MECA has enhanced both affinity and selectivity for the  $A_3$  adenosine receptor ( $A_3AR$ ). This led to the development of  $C_2$ -chloro- $N^6$ -(3-iodobenzyl)-5'- $N$ -methylcarboxamido-adenosine (Cl-IB-MECA), a highly selective  $A_3AR$  agonist now considered the prototypical ligand for this receptor subtype. Cl-IB-MECA exhibits very high affinity towards rat  $A_3AR$  ( $K_i = 0.33$  nM), compared to the rat  $A_1$  and  $A_{2A}$  receptors with  $K_i$  820 nM and 470 nM, respectively.<sup>205</sup> Both the  $A_3$  receptor agonists piclidenoson (IB-MECA; **32**) and namodenoson (Cl-IB-MECA; **33**), have a noteworthy effect even at low doses on the proliferation of tumor cells.<sup>139,206</sup>

When combined with 5-fluorouracil, compound **32** demonstrates more effective growth inhibition of HCT-116 human colon carcinoma cells compared to the use of 5-fluorouracil alone.<sup>207</sup> Studies looking into the effects of this ligand on cells expressing estrogen receptor  $\alpha$  ( $ER\alpha$ ) have discovered that derivative **33** quickly lowers the levels of  $ER\alpha$  at both the mRNA and protein levels. Different kinds of breast cancer cells may experience apoptosis as a result of this action, which hinders cell proliferation.<sup>208,209</sup>

The synthetic  $A_3AR$  agonist **32**, even at low nanomolar concentrations, can inhibit the growth of HCT-116 human colon carcinoma cells. Moreover, the agonist **32** has a synergistic anticancer action when coupled with 5-FU. Additionally, it reduces the myelotoxicity brought on by 5-FU, preserving normal neutrophil and white blood cell numbers. These results show that in mice with colon cancer, the  $A_3AR$  agonist **32** provides systemic anticancer, antimetastatic, and myeloprotective effects. It may also function as an adjuvant therapy to increase the efficiency of chemotherapy and lessen myelotoxicity.<sup>210</sup>

The chloro-substituted adenosine derivative **33** showed a dose-dependent reduction of Hep-3B cell proliferation at dosages of 1 and 10 nM in a xenograft animal model employing Hep-3B hepatocellular carcinoma (HCC) cells. Compound **33** effectively reduces HCC tumor growth *in vivo*, as evidenced by the differences in tumor size between the compound-treated and vehicle-treated groups after 45 days of tumor inoculation. The leading cause of this effect is the elevated production of apoptotic proteins, which are activated by the compound **33**, including FasR, caspase-8, Bax, Bad, cytochrome-*c*, and caspase-3.<sup>211</sup>

It has been demonstrated that micromolar doses of the  $A_3AR$  agonist 2-chloro- $N^6$ -(3-iodobenzyl)-5'- $N$ -methylcarbamoyl-4'-thioadenosine, a sulfur-containing analogue of Cl-IB-MECA,<sup>212</sup> often referred to as LJ-529 or thio-Cl-IB-MECA (**34**), cause anti-leukemic actions in HL-60 human leukemia cell cultures. Studies on poly(ADP-ribose) polymerase (PARP) cleavage and DNA fragmentation support the apoptotic explanation for this impact.<sup>213</sup> In a different investigation, it was discovered that agonist **34** inhibited the growth of breast cancer cells' tumors *in vivo* and their *in vitro* proliferation by causing apoptosis and interfering with the Wnt signaling pathway. The thioadenosine derivative **34** has been connected to the down-regulation of c-ErbB2, a critical marker for the prognosis and treatment of breast cancer, as well as the molecular mechanisms behind these effects. In both *in vitro* and *in vivo* experiments, this down-

regulation is seen in SK-BR-3 breast cancer cells, suggesting that the molecule may be useful in the treatment of breast cancer.<sup>214</sup> Interestingly, by acting on  $A_3AR$ , the herbal compound cordycepin (3'-deoxyadenosine) (**35**) that is extracted from the parasitic fungus *Cordyceps sinensis*, which is utilized in traditional Chinese medicine, inhibits the growth of tumor cells.<sup>215</sup> At micromolar concentrations, this molecule significantly inhibited the growth of murine B16-BL6 melanoma and Lewis lung carcinoma (LCC) tumor cells. Aqueous extracts from *Cordyceps sinensis* have been investigated recently for their potential anticancer and antimetastatic effects *in vitro* using mouse melanoma B16 and LLC cells as models. These extracts showed direct cytotoxic effects at 10 and 30  $\mu\text{g mL}^{-1}$ , respectively. Furthermore, an *in vivo* investigation employing oral cordycepin (**35**) in B16-BL6 cell tumor-bearing C57BL/6Cr mice demonstrated a decrease in the main tumor weight without resulting in a reduction in body weight or systemic toxicity. With little side effects, cordycepin seems to be a potential treatment for melanoma.<sup>216</sup>

Comparable antiproliferative effects to Cl-IB-MECA (**33**) were shown by the naturally occurring anticancer nucleoside  $N^6$ -(2-isopentenyl) adenosine (**36**), which shows strong affinity and selectivity for  $A_3AR$  in human and rat tumor cell lines LNCaP and N1S1.<sup>217</sup>

It has been demonstrated that the resveratrol glucuronides like resveratrol-3-*O*- $\beta$ -glucuronide (**37**) and resveratrol 4'-*O*- $\beta$ -glucuronide (**38**), with  $IC_{50}$  values ranging from 9.8 to 31  $\mu\text{M}$ , suppress the development of colon cancer cells Caco-2, HCT-116, and CCL-228. In CCL-228 and Caco-2 cells, these glucuronides similarly caused a G1 phase arrest.<sup>218</sup> However, the adenosine  $A_3$  receptor antagonist MRS1191 (**48**), which reversed the growth inhibition caused by these two compounds, provided direct proof that the biological activity of these drugs is mediated through  $A_3AR$ . Further evidence that  $A_3AR$  is involved in this process comes from the G1 phase arrest and cyclin D1 depletion mechanisms used to suppress cell proliferation.<sup>170,219</sup>

The compound 3,7-dihydro-1*H*-purine-2,6-dione, known as linagliptin (**39**), is an FDA-certified anti-hyperglycemic medication used primarily to manage type 2 diabetes. The principal oxidative degradation product of linagliptin (**40**) is a pyrimidine derivative. Both compounds, **39** and **40**, have been assessed due to their capacity to harm cells,  $A_3AR$  binding compatibility, cAMP levels, and apoptosis-inducing capabilities. They demonstrated inhibitory effects against hepatocellular carcinoma cell lines, inducing apoptosis at the G2/M phase, increasing caspase-3 levels, and causing suppression of the  $A_3AR$  gene and protein expression, which was followed by an enhancement in cAMP levels. Linagliptin's quantitative *in vitro* binding affinity for  $A_3AR$  displays a blocking characteristic with a 37.7 nM  $K_i$  value.<sup>220</sup>

### 10.7 The $A_3$ receptor selective antagonists

$A_3AR$  antagonists have garnered attention due to their potential as cancer therapeutics and are frequently linked to anti-inflammatory properties.<sup>221,222</sup>



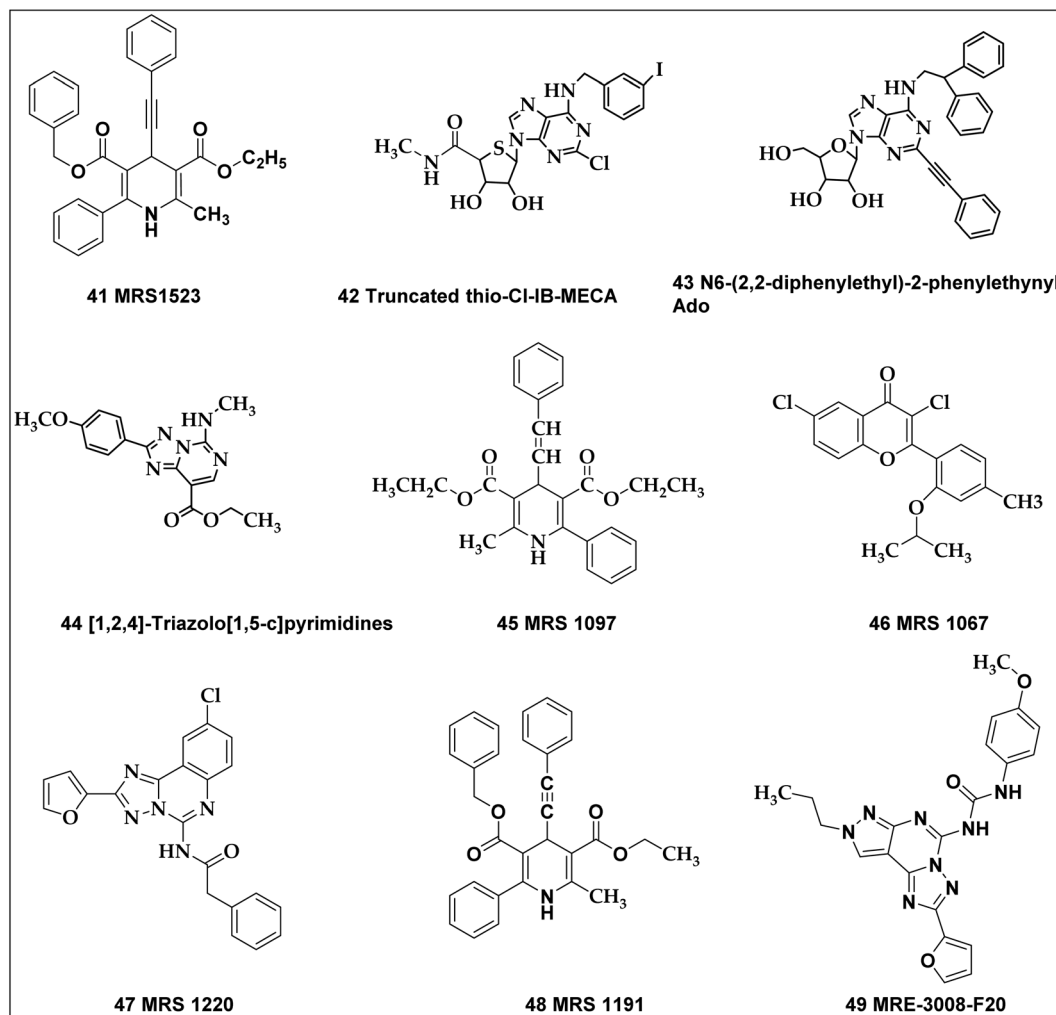


Fig. 14 Potential A<sub>3</sub> adenosine receptor antagonists exhibiting promising anticancer properties.

MRS1523 (41), a pyridine derivative, is currently the most commonly used selective antagonist for the rat A<sub>3</sub> AR. However, its reported affinity and selectivity show some variability across different studies.<sup>223,224</sup> The reported  $K_i$  values of MRS1523 for the A<sub>3</sub> adenosine receptor are 43.9 nM in humans, 349 nM in mice, and 216 nM in rats.<sup>225</sup>

The antagonistic action of truncated thio-Cl-IB-MECA (42) (Fig. 14) on A<sub>3</sub> AR is responsible for the inhibition of T24 human urinary bladder carcinoma cells, resulting in sub-G1 cell cycle arrest and early and late-stage cell death.<sup>203,226</sup>

N<sup>6</sup>-(2,2-Diphenylethyl)-2-phenylethynylAdo (43) in particular showed the most efficacy, indicating that it has the potential to be a strong anticancer drug. The cytostatic effects seen with the A<sub>3</sub> receptor blocker Cl-IB-MECA and antagonists 46 and other related compounds highlight the fact that various cellular pathways contribute to the impact of these ligands against tumors, in addition to A<sub>3</sub> AR activity, which is not the only factor responsible for the anticancer consequences.<sup>226</sup>

Several "[1,2,4]-triazolo[1,5-c]pyrimidines" (44) demonstrated a strong tumor-suppressive effect on human cancer cell lines HCT16 and THP1. Compound 44 (Fig. 14), in particular,

showed notable efficacy against both cell lines. To further investigate its anticancer properties, the researchers assessed its ability to penetrate the phospholipid bilayer of the cell membrane. The compound can enter cells and interact with possible target molecules, according to the Parallel Artificial Membrane Permeability Assay (PAMPA) results, which supports the theory of an as-yet-undefined mechanism.<sup>227</sup>

Adenosine compounds that jointly oppose A<sub>3</sub> & A<sub>2A</sub> ARs and have cancer immunotherapeutic efficacy are highlighted in a recent study. As mentioned earlier, these compounds suppress the immunological checkpoint activity mediated by A<sub>2A</sub> AR in addition to targeting the anticancer signaling pathway triggered by A<sub>3</sub> AR inhibition. This reduces aberrant immune responses.<sup>228</sup>

MRS 1097 (45), MRS 1067 (46), MRS 1220 (47), & MRS 1191 (48), in contrast to focusing on a specific second messenger pathway, act as antagonists of the stimulation of [<sup>35</sup>S]GTPγS binding produced by agonists, according to a separate study. MRS 1220 and MRS 1191, with  $K_B$  values of 1.7 nM and 92 nM, respectively, demonstrated strong selectivity for the human A<sub>3</sub> AR over the human A<sub>1</sub> AR in mediating effects on adenylate



**Table 3** List of adenosine receptor modulators currently in clinical trials for treating various cancers, based on data available from Clinical-Trials.gov (<https://clinicaltrials.gov/>)

Compounds	Clinical trial identifier	Phase	Pharmaceutical sponsor	Patients	Description
<b>A<sub>2A</sub> receptor antagonists</b>					
Ciforadenant (CPI-444)	NCT02655822	I/Ib	Corvus pharmaceuticals, Inc	Carcinoma of the renal cells and mCRPC	A selective A <sub>2A</sub> AR antagonist that binds to the A <sub>2A</sub> AR with a K <sub>i</sub> value of 3.54 nM and exhibits over 50 times greater selectivity for A <sub>2A</sub> receptors compared to other adenosine receptor subtypes <sup>232</sup>
	NCT04280328	Ib		Relapsed multiple myeloma	
	NCT03454451	I		Healthy subjects	
	NCT03237988	I	Hoffmann-La Roche MD Anderson Cancer Center	Non-small cell lung cancer	
	NCT03337698	Ib/II		Advanced renal cell carcinoma	
Taminadenant (PBF-509/NIR 178)	NCT05501054	Ib/II	Novartis Pharmaceuticals II	Advanced renal cell carcinoma	A <sub>2A</sub> AR antagonist <sup>185</sup>
	NCT03207867	II <sup>a</sup>		NSCLC, carcinoma of the renal cells, pancreatic cancer, head and neck cancer, urothelial cancer, diffused large B cell lymphoma, TNBC, microsatellite stable colon cancer, melanoma, and mCRPC	
	NCT03549000	I/Ib <sup>a</sup>		NSCLC, TNBC, pancreatic ductal adenocarcinoma, colorectal cancer	
	NCT04895748	I/Ib		microsatellite stable, ovarian cancer, carcinoma of the renal cells, and mCRPC	
	NCT02403193	I/II		Renal cell cancer	
Preladenant	NCT03099161	Ib/II <sup>a</sup>	Palobiofarma SL/ Novartis Pharmaceuticals	Advanced solid tumours	Strong and competitive adenosine A <sub>2A</sub> AR antagonist <sup>233</sup>
ILB-2109	NCT05278546	Ia	Innolake Biopharm	Advanced solid tumours	A <sub>2A</sub> AR antagonist
AZD	NCT05955105	Ia/Ib	AstraZeneca	Advanced solid malignancies, colorectal carcinoma, mCRPC, and NSCLC	Oral A <sub>2A</sub> AR antagonist (K <sub>i</sub> value of 1.7 nM) binds to the human A <sub>2A</sub> receptor and has about 30 times the selectivity for A <sub>2A</sub> receptors over other adenosine receptor subtypes <sup>234</sup>
	NCT04089553			Prostate cancer and mCRPC	
	NCT03980821			Advanced solid malignancies	
	NCT04495179			Progressive mCRPC	
	NCT03381274			Advanced epidermal growth factor receptor mutant NSCLC	
Inupadenant (EOS-100850/ EOS-850)	NCT05060432	I/II	iTeosTherapeutics	Advanced solid tumors	Inupadenant is a highly selective oral A <sub>2A</sub> AR antagonist that is blood–brain barrier insensitive <sup>235</sup>
	NCT05403385	II		Advanced or metastatic non-small cell lung cancer	
	NCT05117177	I		Advanced lung non-small cell carcinoma	
TT-10	NCT04969315	I/II	Portage Biotech	NSCLC, mCRPC, renal cell cancer, and head and neck cancer	Potent and selective antagonists of A <sub>2A</sub> AR <sup>185,236</sup>
<b>Antagonists of both A<sub>2A</sub> and A<sub>2B</sub> receptors</b>					
Etrumadenant (AB928)	NCT03720678	I/Ib	Arcus Biosciences	Gastroesophageal cancer and colorectal cancer	A <sub>2A</sub> AR and A <sub>2B</sub> AR have K <sub>d</sub> values of 1.4 nM and 2 nM, respectively, for this new dual-active A <sub>2A</sub> /A <sub>2B</sub> AR antagonist <sup>201</sup>
	NCT04381832	Ib/II		mCRPC	
	NCT04892875	Ib	Vanderbilt-Ingram Cancer Center	Locally advanced head and neck cancers	
	NCT05024097	I/II		Rectal cancer	
	NCT05886634	II	Weill Medical College of Cornell University Memorial Sloan Kettering Cancer Center	Advanced dedifferentiated liposarcoma	





Table 3 (Contd.)

Compounds	Clinical trial identifier	Phase	Pharmaceutical sponsor	Patients	Description
M1069	NCT04660812	Ib/II	Arcus Biosciences	Metastatic colorectal cancer	A <sub>2A</sub> /A <sub>2B</sub> AR antagonist
	NCT05177770	II	Surface oncology	mCRPC	
	NCT05198349	I <sup>a</sup>	EMD Serono Research & Development Institute	Locally advanced unresectable solid tumors	
A <sub>3</sub> receptor agonists					
Namodenoson/ Cl-IB-MECA	NCT00790218	I-II	Can-Fite BioPharma	Hepatocellular carcinoma	Only an A <sub>3</sub> AR agonist with such high affinity has been found to date
	NCT02128958	II	Ltd	Hepatocellular carcinoma	
<sup>a</sup> Study terminated.					

<sup>a</sup> Study terminated.

cyclase.<sup>229</sup> These agents demonstrated high selectivity in blocking the inhibitory effects of AC mediated by human A<sub>3</sub> receptors compared to those mediated by human A<sub>1</sub> receptors.

Saturation binding experiments with the radiolabeled agonist [<sup>125</sup>I]AB-MECA (N<sup>6</sup>-(4-amino-3-iodobenzyl)adenosine-5'-N-methyluronamide) at cloned human brain A<sub>3</sub> AR produced in HEK-293 cells demonstrated the competitiveness of MRS 1220, MRS 1191, and MRS 1067. Functional tests, such as agonist-induced suppression of AC and activation of [<sup>35</sup>S]GTPγS binding to related G-proteins, were used to validate their antagonistic characteristics. When it came to their actions on AC, MRS 1220 and MRS 1191, whose *K<sub>B</sub>* values were 1.7 nM and 92 nM, respectively, showed strong selectivity for human A<sub>3</sub> receptors as opposed to human A<sub>1</sub> receptors. Additionally, MRS 1220 has shown effectiveness at reversing the A<sub>3</sub> agonist-induced reduction of tumour necrosis factor-α (TNF-α) production in the human macrophage U-937 cell line.<sup>193</sup>

Research has explored the pre- or co-administration of pharmaceutical formulations containing high-affinity adenosine A<sub>3</sub> AR antagonists like the triazine derivative MRE-3008-F20 (49), to enhance the effectiveness of chemotherapy. This includes treatments in combination with taxanes (paclitaxel), vinca alkaloids (vincristine), camptothecins (irinotecan), or antibacterial agents (doxorubicin).<sup>230</sup>

## 11. Clinical trials updates on adenosine receptors' modulators

Adenosine receptor antagonists are in clinical trials to investigate the treatment of various cancers. These agents block adenosine signalling to overcome tumour-induced immune suppression and boost anti-tumour immunity. Table 3 summarises key modulators under investigation, including their targets, cancer types, and combination strategies.<sup>185,231</sup>

## 12 Summary and future perspectives

AR activation affects immune suppression, angiogenesis, development of tumours, cell proliferation, and metastasis, all of which are essential to the progression of cancer. In the TME,

extracellular adenosine concentration is much higher than normal. This elevated level stimulates adenosine receptors, which then trigger various biological responses that can inhibit cancer cell growth and enhance the immune system's ability to target tumors. The existing literature on AR subtypes indicates that each subtype is significantly involved in cancer, supported by findings from both *in vitro* and *in vivo* research. Because of this, all four AR subtypes are thought to be viable targets for the development of innovative therapeutic approaches in the treatment of cancer. Clinical trials focusing on Parkinson's disease have assessed the safety of A<sub>2A</sub> AR antagonists. The role of A<sub>2B</sub> ARs in tumors is not fully understood. While these receptors may aid in tumour growth by releasing substances that encourage the formation of angiogenesis, they might also send signaling that blocks the growth of cancer cells. Their feasibility as therapeutic targets in the therapy of cancer is complicated by this contradiction. Medications that target A<sub>2B</sub> adenosine receptors (ARs) by either activating or inhibiting them have proven to be more effective in treating cancer. Meanwhile, synthetic drugs that activate A<sub>3</sub> ARs have been effective in slowing down cancer cell growth and promoting programmed apoptosis on various types of cancer. This effectiveness has been validated through laboratory studies and experiments on animals, highlighting the potential of these receptors as therapeutic targets in cancer treatment. Specifically, activating the A<sub>3</sub> receptor or blocking the A<sub>1</sub>, A<sub>2A</sub>, and A<sub>2B</sub> receptors could help shift the tumor environment from one that supports cancer growth to one that inhibits it, enhancing the body's ability to fight cancer. In this regard, numerous modulators targeting adenosine receptors (A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>), including preladenant, tozadenant, CPI444, NIR 178, PBF-509, M1069, Inupadenant, and Cl-IB-MECA, are in advanced clinical stages. However, many have failed for various reasons,<sup>185</sup> including unsatisfactory pharmacokinetic properties. Moreover, developing adenosine receptor agonists or antagonists with high target selectivity and potency remains a significant challenge due to the body's widespread presence of adenosine receptors,<sup>31</sup> raising concerns about off-target effects and limited efficacy. Moreover, data on the long-term impact of AR blockade, including tumour resistance and compensatory



GPCR signalling, remain unclear. Even clinical-stage compounds often lack complete optimisation for durable and selective anti-tumour activity. These gaps emphasise the need for improved mechanistic understanding and more targeted drug development strategies.<sup>22</sup>

Synthetic agonist activation of the A<sub>3</sub> AR decreases cell proliferation and enhances apoptosis in a range of cancer cells, as demonstrated by both *in vitro* and *in vivo* models. These agonists have already been shown in preclinical and Phase I/II trials to be safe and generally well-tolerated in human patients. However, a couple of studies revealed that A<sub>3</sub> AR antagonists may also be a viable therapeutic approach for cancer by preventing hypoxia-induced rises in HIF-1 $\alpha$  and decreasing angiogenesis and cell invasion in the tumor micro-environment. The A<sub>2A</sub> receptor activation contributes to immune system suppression in the tumour microenvironment (TME) *via* cAMP signalling, making it easier for cancer to evade the immune system. Interestingly, the enzyme that changes AMP into adenosine, CD39 and CD73 are highly expressed in various TME cell types and contribute to this immune suppressive effect. Recent studies have identified CD39, CD73, and A<sub>2A</sub> AR as promising targets for boosting antitumor immunity. Monoclonal antibodies and small-molecule inhibitors targeting the CD39/CD73/A<sub>2A</sub> AR axis are currently being tested in clinical trials, both as standalone treatments and in combination with anti-PD-1/PD-L1 immunotherapies.<sup>237</sup>

Results indicate that the antitumor immune response is enhanced when these antibodies are combined with A<sub>2A</sub> AR antagonists, potentially providing an impactful therapeutic strategy for cancer treatment.<sup>170,185</sup>

Clinical trials involving A<sub>2A</sub> antagonists and A<sub>3</sub> agonists will also take some time to conclude which therapy approach is more promising for cancer. The two receptors do have different biological effects: A<sub>2A</sub> receptor signalling decreases immune cell antitumor activity, whereas A<sub>3</sub> receptor signalling enhances immune function while inhibiting tumour growth. Thus, drugs that activate A<sub>3</sub> adenosine receptors and block A<sub>2A</sub> receptors are being explored as a novel approach for cancer treatment. This strategy aims to enhance the body's anti-tumour response by leveraging the beneficial effects of A<sub>3</sub> receptor activation while reducing the tumour-supportive signals associated with A<sub>2A</sub> receptor activation. As a result, this combination could potentially improve therapeutic outcomes for cancer patients. However, they are still in the early stages of development and must overcome several critical challenges, including stability, bioavailability, toxicity, and safety profile studies.<sup>238</sup>

## Abbreviations

5-AMP	5-Adenosine monophosphate
A <sub>1</sub> AR	A <sub>1</sub> adenosine receptor
A <sub>2A</sub> AR	A <sub>2A</sub> adenosine receptor
A <sub>2B</sub> AR	A <sub>2B</sub> adenosine receptor
A <sub>3</sub> AR	A <sub>3</sub> adenosine receptor
AC	Adenylate cyclase
ADA	Adenosine deaminase

ADP	Adenosine diphosphate
AK	Adenosine kinase
AK-T cell	Activated T cell
AMP	Adenosine monophosphate
ARs	Adenosine receptors
ATP	Adenosine triphosphate
Ca <sup>2+</sup>	Calcium channels
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CNTs	Concentrative nucleoside transporters
CPA	Cyclopentyl adenosine
CREB	Camp-response element binding protein
CTLs	Cytotoxic T lymphocytes
DAG	Diacylglycerol
ecto-PDE	Ecto-phosphodiesterase
ENTs	Equilibrative nucleoside transporters
ERK1/2	Extracellular signal-regulated kinases
FoxP3	Forkhead box P3
GDP	Guanosine diphosphate
GFR	Glomerular filtration rate
G <sub>i</sub> /G <sub>o</sub>	Inhibitory G-proteins
GPCRs	G protein-coupled receptors
G <sub>s</sub>	Stimulatory G-proteins
G <sub>s</sub> /G <sub>olf</sub>	Stimulatory G-proteins
GSK-3 $\beta$	Glycogen synthase kinase -3 $\beta$
GTP	Guanosine triphosphate
IMPDH	Inosine monophosphate dehydrogenase
IP3	Inositol triphosphate
JNK	C-Jun N-terminal kinases
K <sup>+</sup>	Potassium channels
LAK Cell	Lymphokine-activated killer cells
MAPKs	Mitogen-activated protein kinase
MMP2	Matrix metalloproteinase 2
NK	Natural killer
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PGs	Prostaglandins
PIP2	Phosphatidylinositol 4,5-bisphosphate
PKA	Protein kinase A
PLC	Phospholipase C
PLC- $\beta$	Phospholipase C-beta
PNP	Purine nucleoside phosphorylase
RhoA	Ras homolog family member A
ROS	Reactive oxygen species
SAH	S-Adenosyl-homocysteine
SAHH	S-Adenosyl-homocysteine hydrolase
SAMe	S-Adenosylmethionine
TGF- $\beta$	Transforming growth factor-beta
TME	Tumor microenvironment
VEGFs	Vascular endothelial growth factors

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.



## Conflicts of interest

The authors declare no conflicts of interest.

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