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RECENT INNOVATIONS IN BIOLOGICAL ACTIVITIES OF XANTHINE AND ITS DERIVATIVES: A REVIEW

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Xanthine and its derivatives are considered pharmacologically important entities exhibiting considerable biological activities. Due to the significant diversity within the biological field, this scaffold has captivated the interest of several researchers worldwide to examine its fundamental structure from both a physiological and a chemical perspective. Xanthine derivatives have recently been utilized therapeutically in several clinical situations owing to their widespread availability in daily life. These derivatives are mostly recognized for their varied pharmacological applications, including adenosine receptor antagonism, phosphodiesterase inhibition and exhibiting antitumor, anti-inflammatory, antibacterial, antiviral, antioxidant and antidiabetic activities. Chemical synthesis enhances the diversity of xanthine-based derivatization. This review highlights the significance of xanthine derivatives as potential candidates for novel medication development. Consequently, we anticipate that these compounds may function as a template for discovering other active xanthine derivatives. Furthermore, the progress and deep investigations of xanthine derivatives will open the door towards discovery of new drug candidates have diversity of biological activities.

Keywords: Xanthines, biological activities, antitumor, Drug candidates.

INTRODUCTION

Xanthines are derivatives of purine alkaloids that possess a nitrogen atom at the 1-, 3-, 7-, and 9- positions, as well as a carbonyl group at the 2- and 6- positions. The German chemist Emil Fischer first discovered xanthine 1 (1*H*-purine-2,6(3*H*,7*H*)-diones) in 1889, and the term 'xanthine' was subsequently introduced in 1899[1]. Furthermore, xanthine is a precursor to uric acid and a critical component of the metabolism of nucleotides and nucleic acids[2]. Consequently, xanthine is structurally similar to purines, the building blocks of RNA and DNA. Xanthine is a promising therapeutic molecule due to its structural similarity to two major purine derivatives, adenine and guanine[3]. Xanthine affords the highest potential for substitutes, five categories of mono substitutions (1-, 3-, 7-, 8-, and 9-), eight for di-substitutions (1,3-, 1,7-, 1,8-, 1,9-, 3,7-, 3,8-, 3,9-, and 7,8-), and three for tri-substitutions (1,3,7-, 1,3,8-, and 1,3,9-) and also tetra-substitutions have been synthesized[4-10]. While most substitutions are easily accessible, replacement at the N9 position is challenging due to its low nucleophilicity, necessitating specific conditions for electrophilic attack[4]. Bioactive xanthine derivatives have been the subject of multiple reports. These compounds

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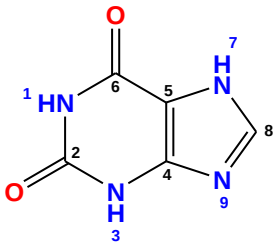
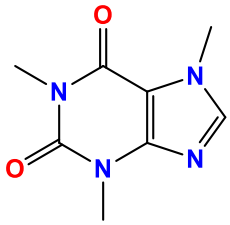
have been made available through the transmethylation process in plants, the biotransformation process in bacteria, fungi, and enzymes and also the chemical synthesis[11&12].

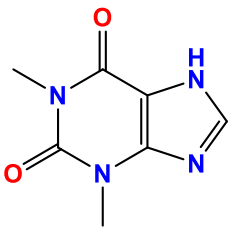


Xanthine
1

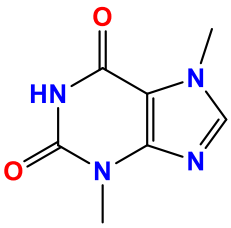
Purine-based nitrogenous compounds, such as caffeine **2** (1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione), theophylline **3** (1,3-dimethy-l,3,7-dihydro-1*H*-purine-2,6-dione), and theobromine **4** (3,7-dimethyl-3,7-dihydro-1*H*- purine-2,6-dione), are natural xanthine derivatives that possess distinct medicinal properties utilized in various applications. They are typically called methyl xanthine derivatives, which are generated by both plants and animals[13&14].



Caffeine
2



Theophylline
3



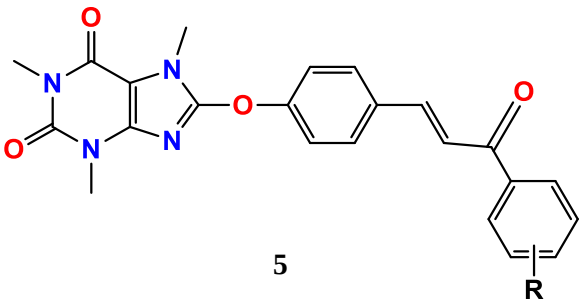
Theobromine
4

Because of strong intramolecular interactions between N-H groups, base stacking, and inter-base hydrogen bonding, xanthine and its derivatives are less soluble than purine, the molecule from which they are derived. As the number of methyl groups at different places increases, the xanthine nucleus becomes more and more insoluble[15]. The adaptability of the xanthine moiety implies that it is a critical component of various medicinal agents. Numerous derivatives present a variety of physiological and pharmacological activities in various body organs, including the respiratory tract, heart, central nervous system, kidneys, liver, and stomach. The primary emphasis of this review article is the most recent data regarding the diverse biological activities of xanthine scaffolds.

Therapeutic avenues of xanthine derivatives

1- Anticancer

Soltani *et al.* designed and synthesized 8-caffeinyl chalcone hybrid conjugates, which were evaluated for their anticancer activities. Compounds **5** and **6** comprise 8-caffeinyl and chalcone frameworks including various substituents. When tested *in-vitro* against breast cancer MCF-7 and melanoma A-375 cell lines, the anticancer efficacy of the produced compounds showed significant activity in comparison to methotrexate[16].



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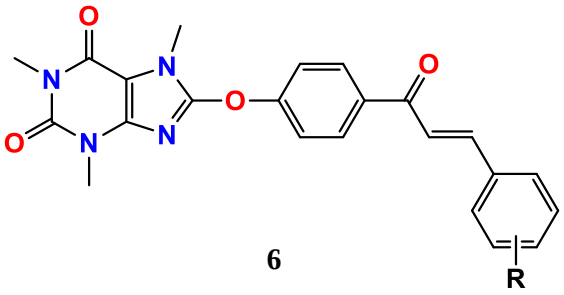
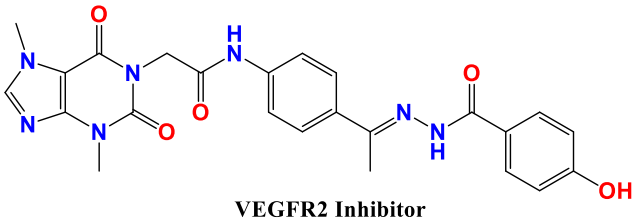


6

Researches provide that Vascular endothelial growth factor receptor-2 (VEGFR-2) receptors are markedly more prevalent in cancer cells compared to normal cells, offering a viable avenue for the development of therapeutics that can selectively target tumor angiogenesis while protecting normal cells[17]. A series of theobromine derivatives was developed by Eissa *et al.* utilizing the fundamental pharmacophoric characteristics of VEGFR-2 inhibitors. Compound 7 showed the

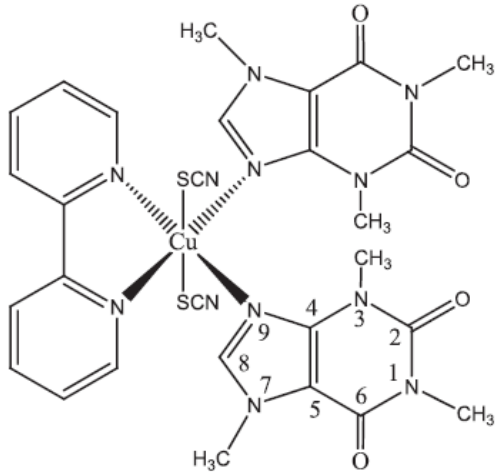
most cytotoxic effects against MCF-7 and HepG2 with an IC_{50} value of 0.42 µM and 0.22 µM, respectively. The IC_{50} value of compound **7** (0.067 µM) was compared to sorafenib (IC_{50}= 0.056 µM) to evaluate its effectiveness for VEGFR-2 inhibition[18].



VEGFR2 Inhibitor

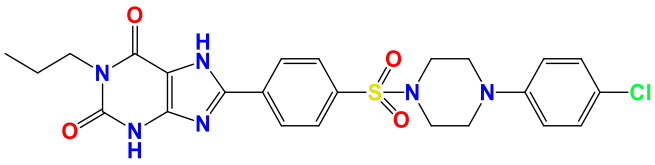
7

Kisku *et al*. have synthesized a mixed-ligand complex of copper (II) incorporating bipyridine, caffeine, and thiocyanate **8**. The complex, referred to as Complex A, incorporates caffeine as the secondary ligand, exhibiting a metal to ligand ratio of 1:1:2:2, represented by the chemical formula [Cu(byp)(Caf)2(SCN)2]. Complex A has demonstrated potential superoxide dismutase-like activity as an effective antioxidant, exhibiting *in-vitro* antibacterial efficacy and anti-cancer action against colorectal adenocarcinoma (Caco-2) and breast cancer (Mcf-7) cell lines[19].



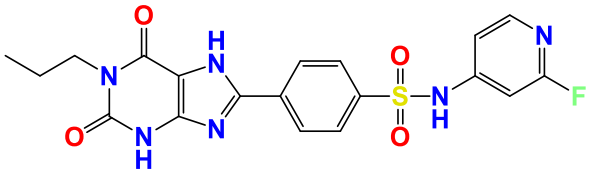
8

The G protein-coupled adenosine A2B receptor is implicated in numerous pathological processes associated with elevated adenosine levels observed in inflammation, hypoxia, and malignancy[20]. Thus, the adenosine A2B receptor is highlighted as a novel target for cancer treatment and noninvasive molecular imaging *via* positron emission tomography (PET). For the purpose of imaging the adenosine A2B receptor in brain tumors, the xanthine derivative PSB-603 **9** was selected as the lead molecule to create a radiotracer tagged with the PET radionuclide fluorine-18[21&22]. Initial biodistribution experiments in mice indicated minimal brain uptake of **9**, prompting structural alterations to enhance its physicochemical qualities for improved blood–brain barrier penetration so Lindemann *et al.* synthesized two new fluorinated xanthine derivatives. Both compounds **10** and **11** exhibited a strong affinity for the adenosine A2B receptor (Ki for **10** is 9.97 ± 0.86 nM; Ki for **11** is 12.3 ± 3.6 nM) with modest selectivity relative to other adenosine receptor subtypes[23].

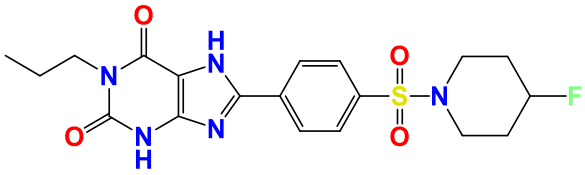


PSB-603

9

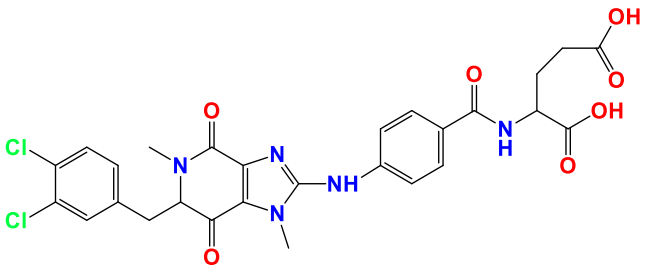


10



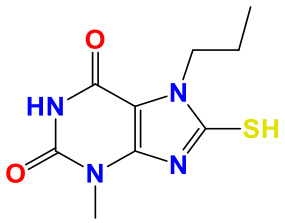
11

Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) is crucial in one-carbon metabolism. The MTHFD2 gene is a viable target for cancer therapy because it is elevated in numerous tumors but expressed at low or undetectable levels in normal proliferating cells[24]. Lee *et al.* conducted a study that demonstrated the ability of the xanthine derivative **12** to allosterically bind to MTHFD2 and coexist with the substrate analogue. Kinetic analysis revealed the uncompetitive inhibition of MTHFD2 by **12**[25].

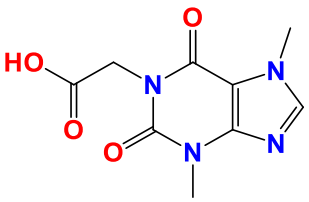


12

The initial histone demethylase to be identified was histone lysine specific demethylase 1 (LSD1, also known as KDM1A) in 2004[26]. LSD1 plays a role in regulating and sustaining normal physiological processes[27] and the progression of various disease conditions, including cancers (AML, SCLC, etc.)[28] and neurodegenerative disorders[29]. Consequently, LSD1 has emerged as a critical epigenetic target for the treatment of diseases. For the first time, Ma *et al.* documented the ligand-based design of fragment-like xanthine derivatives as inhibitors of LSD1. Having obtained the key intermediates **13** and **14**, they continued to synthesize a targeted library of xanthine derivatives by modifying the substituents at positions 1 or 8 of the core scaffold. Compound **13** was the most effective one, it demonstrated an appropriate fragment-like nature and satisfactory pharmacological inhibition of LSD1 (IC_{50} = 6.45 Mm), making it as a suitable template for the generation of novel LSD1 inhibitors[30].

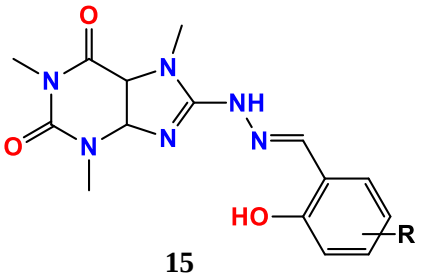


13



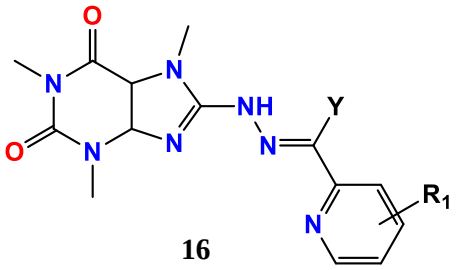
14

Kaplanek *et al*. have developed a series of innovative anticancer agents that are derived from caffeine–hydrazones that contain either a 2-hydroxyaryl- or 2-N-heteroaryl moiety **15** and **16**. The results showed that several derivatives exhibited a high selectivity index toward T-lymphoblastic leukemia cells and exhibited significant anticancer activity. Generally, hydrazones containing a 2-N-heteroaryl group have greater activity and selectivity compared to those with a 2-hydroxyaryl group. The evaluated substances exhibited dose-dependent suppression of both RNA and DNA production[31].



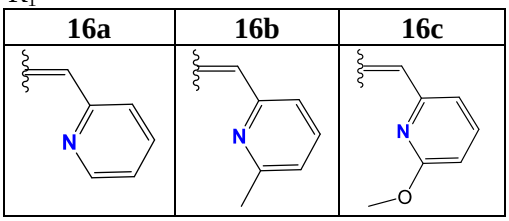
15

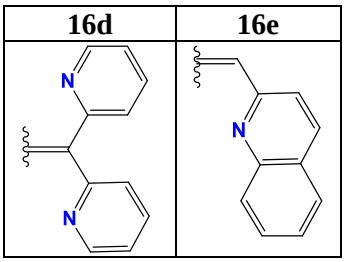
R= H, *m*-CH_3, *m*-OCH_3, *m*-OH, *P*-OCH_3, *P*-OH, *P*-NEt_2, 5-CH_3, 5-OCH_3, 5-OH, 5-Cl, 5-Br, 5- t-Bu, 5-NO_2, 3,5-dibromo, 3,5-dichloro, 3,5-di t-Bu



16

Y, R_1=





2- Dental disorders

Toothpaste containing theobromine **4** is potentially useful for demineralizing white spot lesions and preventing early enamel lesions due to its additional effects of raising salivary PH and lowering Streptococcus mutans levels[32]. It can also increase the surface hardness of teeth[33].

3- Neurodegenerative disorders

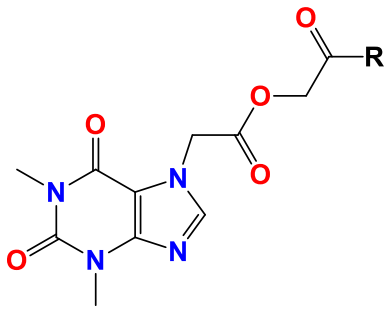
Cognitive function

Better cognitive function performance and a protective effect are linked to a higher intake of caffeine **2** and theobromine **4**. In addition,

the concurrent consumption of both substances exhibits a synergistic effect in the prevention of cognitive impairment when contrasted with the ingestion of caffeine or theobromine alone[34].

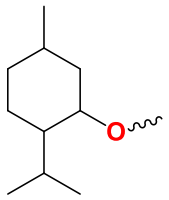
Alzheimer's Disease

Elgazar *et al.* studied the conjugation of theophylline with several naturally derived compounds menthol, thymol, eugenol, and vanillin **17(a-d)** via Steglich esterification, aiming to develop novel hybrids exhibiting dual activity against cholinergic and inflammatory pathways as possible therapeutic treatments for Alzheimer's disease (AD)[35].

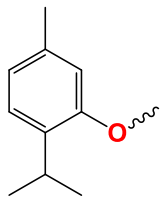


17

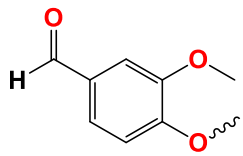
R=



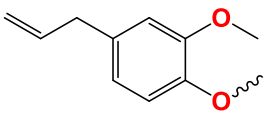
Menthol
17a



Thymol
17b



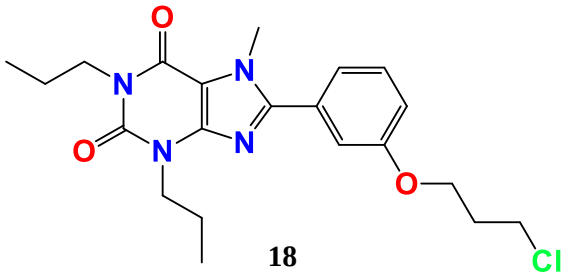
Vaniilin
17c



Eugenol
17d

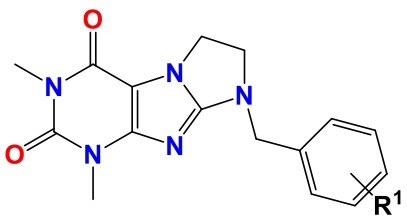
Parkinson's Disease (PD)

The antagonistic interactions between dopamine and A2A adenosine receptors are the foundation for the development of adenosine receptor (AR) antagonists as potential drug candidates for Parkinson's disease[36]. Rohilla *et al.* created a set of powerful and selective AR ligands based on 1, 3, 7, 8-tetrasubstituted xanthine for the treatment of Parkinson's disease. The most potent compound in the series, 1,3-Dipropylxanthine **18**, possesses a methyl substituent at the N-7 position and demonstrates the highest affinity (A2A, Ki=0.108 Mm). However, the incorporation of a propargyl group at the 7-position of the xanthine nucleus appears to be the most suitable substitution to enhance selectivity towards the A2A subtype while maintaining reasonable potency. The antiparkinsonian efficacy has been assessed using perphenazine-induced catatonia in rats[37].



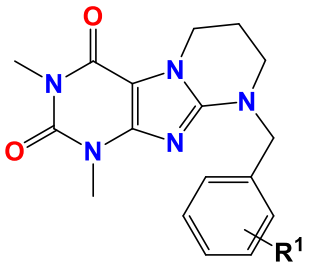
18

Studies have suggested that the neurodegenerative process is accelerated by elevated monoamine oxidase B (MAO-B) levels in the ageing brain. This is due to the formation of potentially neurotoxic by-products, including hydrogen peroxide and dopaldehyde, as a consequence of the enzyme's catalytic function. These reactive chemicals may induce neuronal death through the oxidizing nucleic acids or proteins, resulting in oxidative damage via Fenton's reaction, which generates hydroxyl radicals[38]. N9-benzyl-substituted imidazo- **19**, pyrimido- **20**, and 1,3-diazepino[2,1-*f]* purinediones **21** were synthesized by Załuski *et al.* as dual-target ligands, exhibiting antagonistic activity against A2A adenosine receptors (AR) and inhibition of (MAO-B). Derivatives of these ligands were subjected to biological evaluation in radioligand binding assays at adrenergic receptor subtypes and for their ability to inhibit MAOB[39].



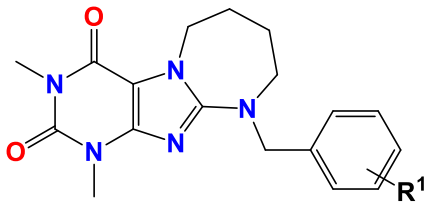
Imidazo-[2,1-f]purinedione

19



Pyrimido-[2,1-f]purinedione

20



1,3-diazepino-[2,1-f]purinedione

21

4- Respiratory disorders

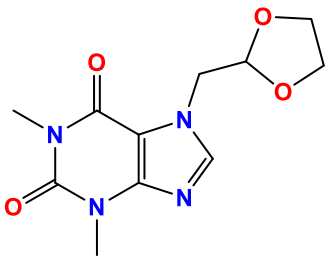
Apnea

Caffeine **2** is employed therapeutically to alleviate headache pain in adults, as a stimulant to prevent lethargy and fatigue, and to treat neonatal apnea. Currently, caffeine citrate is one of the most frequently prescribed medications in neonatal units for apnea of prematurity. It is the preferred drug among all methylxanthines due to its efficiency, enhanced tolerance, and broader therapeutic spectrum. The respiratory center is stimulated by caffeine, which increases its sensitivity to hypercapnia. Consequently, the average respiratory rate elevates, pulmonary blood flow is augmented, carbon dioxide sensitivity is boosted, and diaphragmatic function along with breathing patterns are optimized[40].

Asthma

For moderate to severe reversible bronchospasm, the xanthine medications, particularly theophylline, are considered the best bronchodilators. In addition, they enhance diaphragmatic contractility, which in turn improves respiratory exchange[41]. Theophylline **2** has been associated with undesirable symptoms such as nausea, vomiting, tachycardia, sleeplessness, and a limited therapeutic index. Therefore, the pursuit of novel chemicals that possess both antibacterial and anti-asthmatic properties remains a valuable objective and a formidable task for both medicinal chemists and physicians[42].

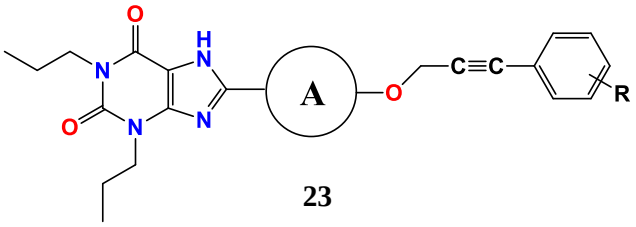
Doxofylline's **22** mechanisms of action diverge from those of theophylline and PDE4 inhibitors, as it does not substantially engage with any adenosine receptors or known phosphodiesterase (PDE) isoforms, with the exception of PDE2A. The presence of the dioxalane moiety at position 7, along with its unique pharmacological profile, distinguishes doxofylline from theophylline. The meta-analysis findings suggest the use of doxofylline for treating chronic obstructive respiratory diseases, demonstrating its superiority over theophylline due to a more superior effectiveness and safety profile[43]. Doxofylline diminishes the incidence of asthma episodes and lessens the reliance on salbutamol in asthmatic patients. It is equally efficacious as theophylline in enhancing Forced Expiratory Volume 1 (FEV1)[44].



Doxofylline

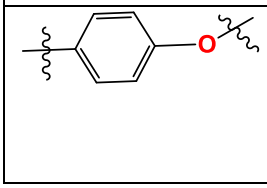
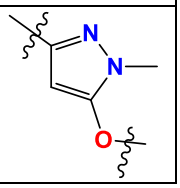
22

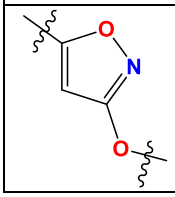
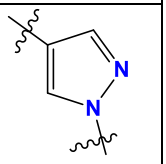
The aim of the research conducted by Basu *et al*. was to identify and create powerful and selective A2B adenosine receptor antagonists with favorable aqueous solubility and enhanced *in-vivo* half-life. They tested the effects of 2-propynylated C8-aryl or heteroaryl substitutions on the xanthine chemotype. The intermediates 8-phenyl-, 8-isoxazolyl-, 8-(1*H*-pyrazol-3)-, and 8-(1*H*-pyrazol-4-yl)-1,3-dipropyl xanthines **23 (a-d)** were synthesized. They observed that **23a** was better tolerated at C8. In order to improve the potency, selectivity, and solubility of A2B AR, substitutions on the terminal phenyl group were investigated. Generally, meta-substituted phenyl compounds had stronger A2B selectivity than para-substituted analogs[45].



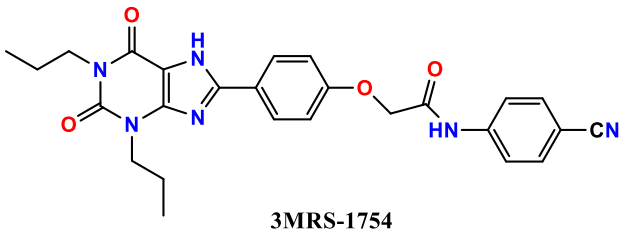
23

A=

23a	23b
	

23c	23d
	

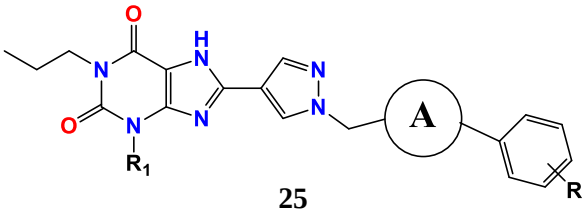
To develop powerful and selective A2B adenosine antagonists with enhanced pharmacokinetic features, Basu *et al.* initially investigated a more restricted variant of MRS-1754 **24**.



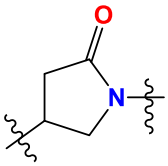
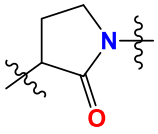
3MRS-1754

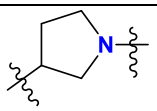
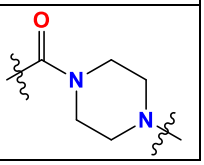
24

To enhance metabolic stability, various changes of the linker have been made, substituting the amide linker with alternative phenyl or other heteroaryl groups between the C8 position of the xanthine head group and the terminal phenyl ring. The *m*-CF_3 of the piperazinyl xanthine derivative **25d** (Ki = 1.5 nM) and the *P*-CF_3 derivative of the Pyrrolidinyl xanthine derivative **25a** (Ki = 1 nM) had the highest binding affinities. It was showed that they have high selectivity for A2B-AR as well. The *m*-CF_3 of **25d** alleviated airway inflammation in the *in-vivo* asthma model generated by ovalbumin in mice[46].

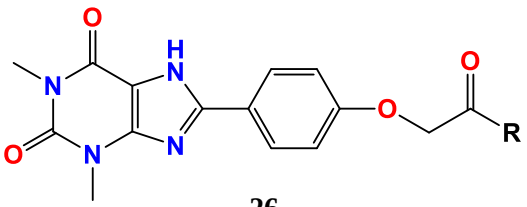


25

25a	25b
	

25c	25d
	

Yadav *et al.* have developed a series of selective molecules for adenosine A2A receptors, consisting of carboxylate amides derived from 8-phenyl-1,3-dimethylxanthine **26**–**29**. These derivatives were assessed for their bronchospasmolytic properties against histamine aerosol-induced bronchospasm in guinea pigs. They exhibited moderate to high affinities for various adenosine receptors based on radioligand binding assays. The diethylaminoethylamino moiety of the xanthine derivative **26** was the most potent A2A adenosine receptor ligand (Ki = 0.06 µM)[47].



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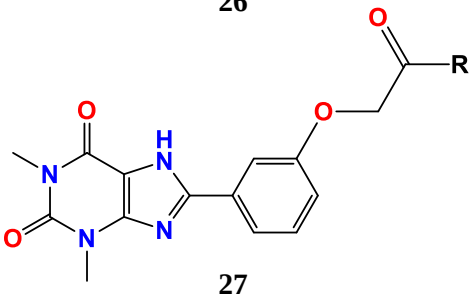
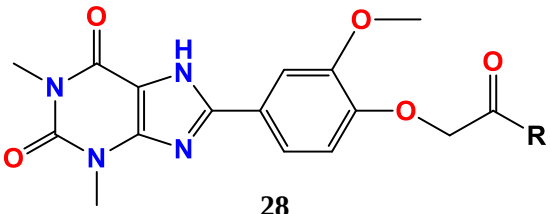


27

R= diethylaminoethylamino, dimethylamino-ethylamino, imidazole, morpholine, pyrrolidine, azepine, piperidine and piperazine.



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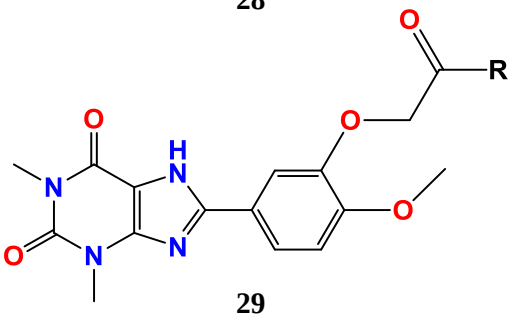
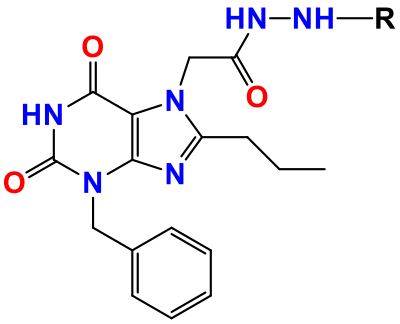


29

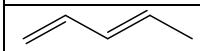
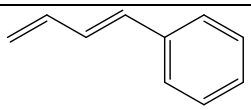
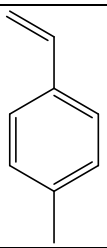
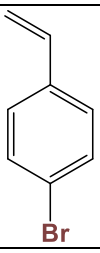
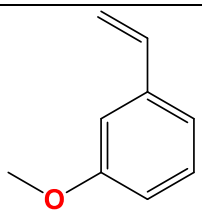
R = diethylaminoethylamino, dimethylamino-ethylamino, imidazole, morpholine, pyrrolidine, azepine, piperidine and piperazine.

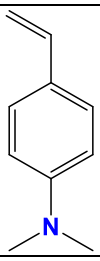
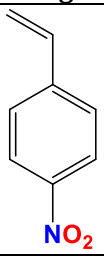
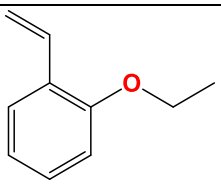
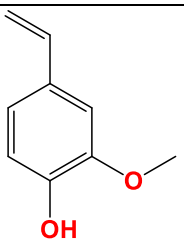
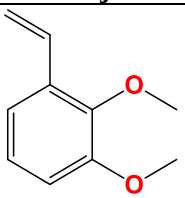
5- Cardiovascular disorders

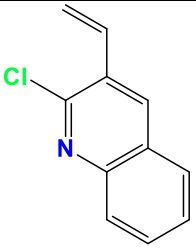
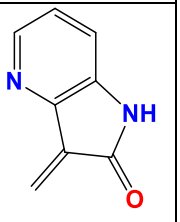
Aleksandrova *et al.* have synthesized acetohydrazide derivative **30(a-l)** of xanthine, and found that they exhibit excellent Diuretic activity[48].



30

R	30b	30c	30d	30e
				

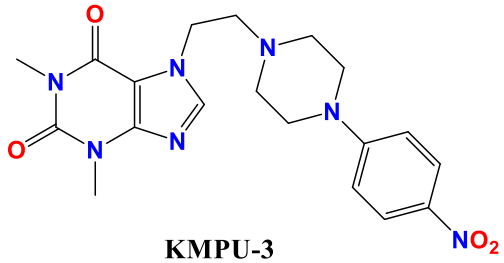
30f	30g	30h	30i	30j
				

30k	30l
	

Permanent pacing has been the primary treatment for painful Left Bundle Branch Block LBBB for many years, while the use of beta-blockers or ivabradine in medical therapy for the purpose of regulating sinus nodes was significantly correlated with reduced success rates. Amir *et al.* proved that oral theophylline was effective for severe LBBB[49].

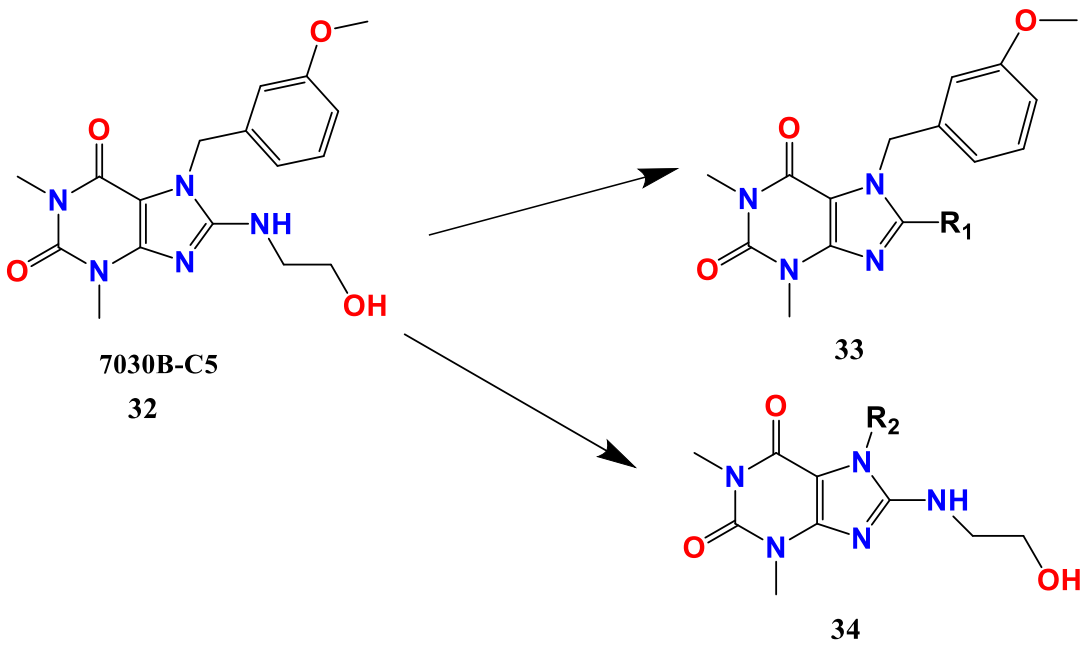
Liu *et al.* developed a strong phosphodiesterase (PDE) inhibitor by combining theophylline with piperazine, referred to as KMPU-3 **31**. It increases cardiac output, demonstrates cardioprotective properties and reduces Myocardial Infarction. The study examined the therapeutic efficacy of **31** and found that it elevates left ventricular systolic blood pressure (LVSP) and atrial inotropy and enhances the hypoperfused myocardium compared to other PDE inhibitors[50].

The development of small compounds that do not contain statins to treat hypercholesterolemia is still an ongoing challenge. Many studies have focused on the inhibition of Proprotein convertase subtilisin/kexin type 9 (PCSK9) for treatment of **Atherosclerosis**[51]. Following in the lead of the PCSK9 inhibitor 7030B-C5 **32**, Qiao *et al.* synthesized 45 variations of **32** and evaluated their capacity to inhibit PCSK9. Structural modifications have been done at N7 and C8 **33, 34**. In the *in-vitro* assay, some of them markedly diminished the PCSK9 protein concentration and increased low density lipoprotein receptor (LDLR) protein level. Furthermore, they facilitated the elimination of LDL cholesterol (LDL-C) in HepG2 cells more effectively than **32**[52].



KMPU-3

31



7030B-C5

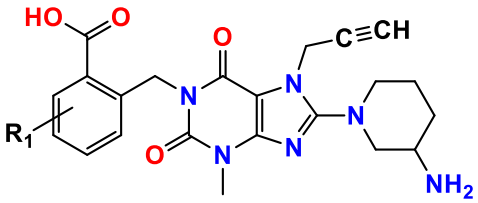
32

33

34

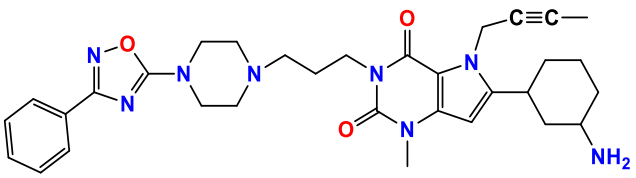
6- Antidiabetic

Rapid synthesis of xanthine derivatives containing benzoic acid moieties was done by li *et al*. The 5-Cl derivative of the hit compound **35** (IC_{50} = 0.1 nM) for dipeptidyl peptidase-4 (DPP-4) exhibited a 22-fold increase in inhibitory potency relative to the lead compound uracil, and it is 45 times more effective than alogliptin. This was followed by the identification of five DPP-4 inhibitors centered around benzoic acid moieties, which exhibited remarkable selectivity against different DPP-4 homologues and a low picomolar potency range (IC_{50}< 1 nM)[53].



35

G-protein-coupled receptor 119 (GPR119) has emerged as a prominent target for the treatment of type 2 diabetes mellitus (T2DM). GPR119 agonists facilitate a distinctive dual increase in both insulin and GLP-1, subsequently leading to a decrease in blood glucose levels[54]. Li *et al.* presented the synthesis, SARs, and (ADME/T) of HBK001 **36** and its derivatives. All drugs had significant DPP-4 inhibitory actions, but **36** exhibiting superior DPP-4 inhibition and GPR119 agonistic activity. The HCl derivative of it (IC_{50} = 4.9 mM) is more soluble and permeable than its free base resulting in better absorption and efficacy in reducing the blood glucose level *in-vivo*[55].



HBK001

36

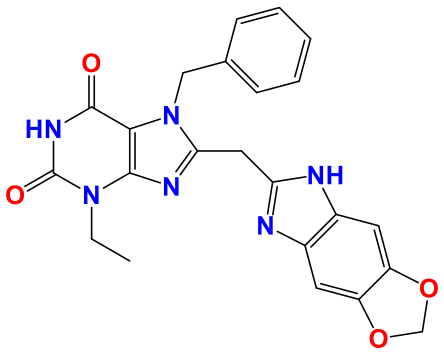
7- Kidney disorders

The structural properties of theobromine **4** enable it to prevent crystallization of uric acid, especially when urine concentration is more than 15 mg/L[56]. Furthermore, solubility of water can be increased by combining theobromine with uric acid, and this will promote the evacuation of kidney stones via urine. Hernandez *et al.* performed a double-blind and randomized research with several patients suffering from uric acid nephrolithiasis. The research demonstrated that the risk of uric acid crystallization was reduced following therapy with theobromine combined with citrate salts compared to treatment with citrate salts alone[57].

8- Obesity and fatty liver disease

Wei *et al.* tested the effects of theobromine on a NAFLD mice model, revealing its capacity to hinder the phosphorylation of mammalian targets of rapamycin (mTOR) and modulate hepatic lipid metabolism. This resulted in decreasing body weight and liver weight, and enhancing the liver morphology[58]. Theobromine's ability to inhibit phosphodiesterase-4 can lead to an increase in adipocyte cAMP levels, facilitating lipolysis and thermogenesis in brown adipocytes[59]. Sugimoto *et al*. proved that the phosphorylation levels of Akt and mTOR proteins in the livers and brains of rats substantially decreased after administration of oral theobromine for 30 days[60].

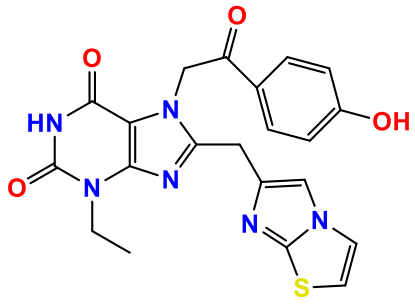
Tryptophan hydroxylases facilitate the initial and rate-limiting phase in serotonin production[61]. Research utilizing genetically modified mice models by El-Merahbi *et al.* has demonstrated that the imbalance of serotonin levels peripherally leads to metabolic and inflammatory diseases[62]. Consequently, Tryptophan hydroxylase 1 TPH1 has emerged as a therapeutic target for metabolic disorders, including obesity and fatty liver disease. Specker *et al*. have synthesized a series of xanthine derivatives to act as TPH1 inhibitors. A xanthine scaffold **37** with IC_{50} = 0.36+ 0.09 µM was the most effective one. It can be readily modified, facilitating the synthesis of a variety of analogs by permitting alterations at several sites, involving the N1, N3, and N7 locations, along with the C2, C6, and C8 positions[63].



Xanthine-benzimidazole TPH1 inhibitor

37

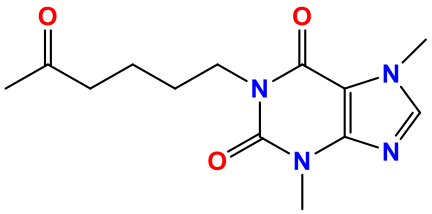
Then Yoon *et al.* have designed other derivatives acting as TPH1 inhibitors. Compound **38** exhibited promising *in-vitro* efficacy and stability in hepatic microsomes among the synthesized compounds. Docking experiments indicated that compound **38** (IC_{50} = 110.1 nM) exhibited superior binding to TPH1 through critical intermolecular interactions including the xanthine scaffold, imidazo-thiazolyl ring, and hydroxyphenyl moiety[64].



38

9- Inflammatory bowel syndrome

Chitinase 3-like 1 (CHI3L1) is a glycoprotein that may causes inflammation, cancer and apoptosis[65]. Lee *et al.* previously showed that CHI3L1 can promote bacterial invasion on intestinal epithelial cells (IECs) as it increases activation of AKT protein in IECs. Their study has indicated that the primary constituents of family 18 chitinases, CHI3L1 and acidic mammalian chitinase, are integral to the pathophysiology of inflammatory bowel disease (IBD) and various inflammatory conditions. High-throughput screening data indicate that these xanthine derivatives, caffeine **2**, theophylline **3**, and pentoxifylline **39** exhibit competitive inhibition of fungal family 18 chitinase compared to allosamidin by interacting with tryptophan residues in the protein's active site with IC_{50} values (126, 1500, 469 µmol/L) respectively[66].



Pentoxifylline

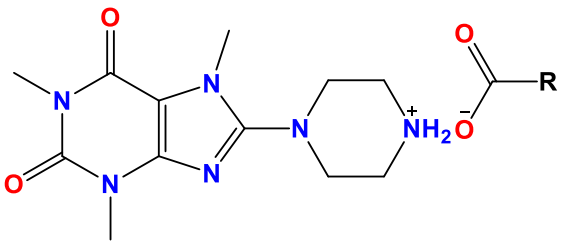
39

10- Dermatological diseases

Pentoxifylline **39** is an efficacious therapeutic agent with established and potential use in several dermatological disorders. It is used by dermatologists as a primary treatment and as an adjunctive therapy, offering an alternative to other treatment choices while decreasing the adverse effects associated with other drugs, including corticosteroids[67]. **39** has been approved for the management of claudication symptoms. It has been utilized in several dermatological conditions, including vasculopathic and granulomatous disorders because of its anti-inflammatory properties[68].

11- Analgesic activity

Salts can be produced from compounds featuring a carboxyl group. 8-Piperazinylcaffeine (8-PC) carboxylate ionic liquids were synthesized by Soltani *et al.* by reacting 8-PC with several carboxylic acids **40**, including some notable NSAIDs, such as aspirin, mefenamic acid, ibuprofen, naproxen, and salicylic acid. These derivatives were employed to produce the respective salts. The formalin assay was used to assess the analgesic properties. The test results indicated that the combination between 8-PC and NSAID salts demonstrated significant analgesic efficacy in comparison to the Na salt of ibuprofen, a reference medication[69].

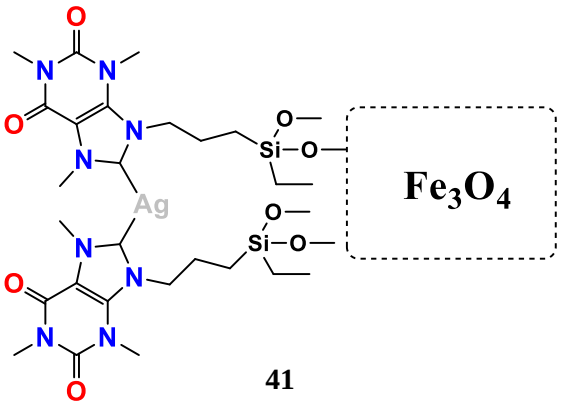


40

12- Antibacterial

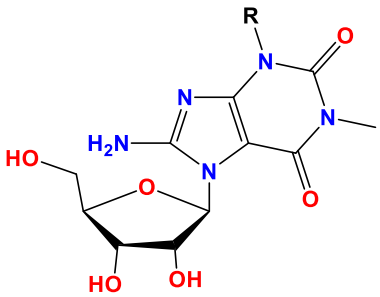
The salts of the previously mentioned compound **40** were evaluated *in-vitro* against *Escherichia coli*, as well as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The findings indicated that the salt of salicylic acid derivative showed considerable antibacterial efficacy relative to acrinol, especially against *Pseudomonas aeruginosa*[69].

Staphylococcus aureus, *Bacillus cereus*, and *Escherichia coli* were the microorganisms that were used to test the efficacy of complex **41** as an antibacterial agent by Gajare *et al*. The inclusion of silver in complex **41** is essential for antibacterial efficacy. The results demonstrated that it had superior antibacterial activity against both Gram-positive and Gram-negative bacterial strains in comparison to other complexes without silver[70].



41

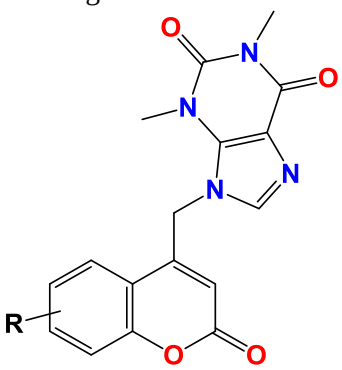
The formation of xanthine nucleosides **42** was studied by Mohamed *et al.* through the reaction of xanthine derivatives with l-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose. The majority of the compounds were evaluated *in-vitro* against two bacterial species, *Staphylococcus aureus* and *Escherichia coli* using ampicillin as a reference[71].



42

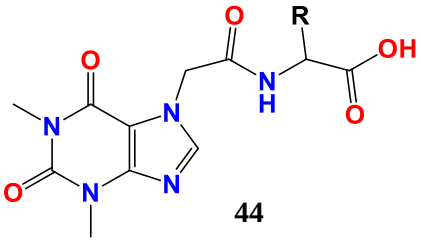
There has been an increase in tuberculosis-related deaths even when potent anti-TB medications like rifampicin and isoniazid are readily available. Consequently, Multi-drug-resistant (MDR) Mycobacterium tuberculosis strains provide a significant challenge to immunocompromised patients, making the discovery of new pharmacological agents an urgently required[72].

Mangasuli *et al.* have synthesized a number of coumarin-theophylline hybrids **43** and tested their antitubercular activity against Mycobacterium TB *H37Rv in-vitro*. The methyl substitution at the C-6 position of the coumarin moiety exhibited remarkable activity with a minimum inhibitory concentration (MIC) of 0.12 mg/mL[73].



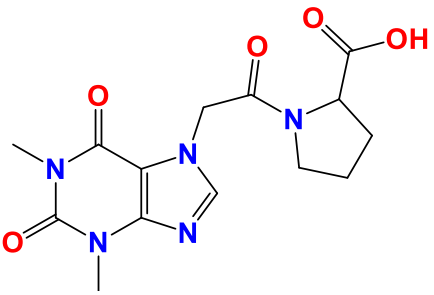
43

Voynikov *et al.* proposed that incorporating amino acids into the xanthine scaffold may represent a promising class of anti-mycobacterial agents. These hybrids were produced by combining theophylline-7-acetic acid with hydrochlorides of amino acid methyl ester. The sequential hydrolysis of amido-esters yielded the corresponding amido-acids **44(a-g)** and **45**. The synthesized compounds demonstrated remarkable efficacy against Mycobacterium TB *in-vitro* ranging from 10 to 25 times greater than ethambutol. The activity fluctuated based on the amino acid fragments, demonstrating exceptional values with MICs ranging from 0.46 to 0.26 µM[74].



44

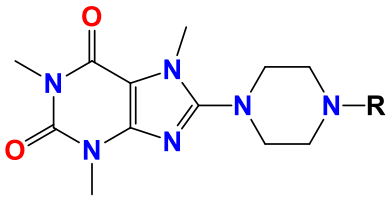
R= H, Me, i Pr, i Bu, 2-CH_2-indole, $CH_2CH_2COOCH_3$, $CH_2CH_2SCH_3$



45

13- Antiprotozoal

Some caffeine hybrid compounds have been tested for their efficacy against leishmaniasis by Rad *et al*. The three main structural components of these compounds are caffeinyl, piperazinyl, and N-alkyl/aryl moieties. The synthesis involved the bromination of caffeine with N-bromo-succinimide NBS to get 8-bromocaffeine. Then, 8-piperazinyl caffeine was formed through a substitution nucleophilic reaction with piperazine. The *in-vitro* evaluation of heptyl, octyl and decyl derivatives on Leishmania promastigotes has revealed that they exhibited exceptional leishmanicidal activity, compared to the reference drugs metronidazole and miltefosine, with IC_{50} values of 84 µM, 94 µM, and 89 µM, respectively[75].

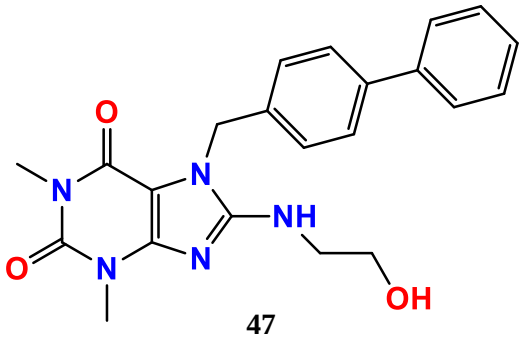


46

14- In COVID 19 therapy

The COVID-19 pandemic presents an exceptional difficulty in identifying viable therapeutic agents. Numerous clinical trials using various drugs have failed to cure COVID-19. COVID-19 causes severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure due to increased inflammation, oxidative stress, and cytokine storms from an overactive immune response[76].

A number of derivatives were synthesized and optimized using extensive SAR studies by Chen *et al*. Compound **47** demonstrated enhanced efficacy against multiple coronavirus microorganisms, such as HCoV-229E, HCoV-OC43, and SARS-CoV-2. Subsequent tests revealed that **47** affected the post-entry stages of viral replication and exhibited a distinct antiviral mechanism, unlike the therapeutically approved drugs nirmatrelvir and molnupiravir[77].



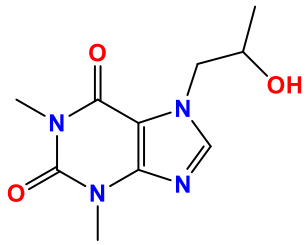
47

Pentoxifylline **39** relieves acute respiratory distress syndrome (ARDS) symptoms, while caffeine **2** has been used clinically for decades to improve respiratory function. **39**, an anti-inflammatory and antioxidant compound, inhibits TNF-α and other inflammatory cytokines in lung diseases, potentially improving clinical outcomes in patients suffering from COVID-19. It improves blood circulation, and tissue oxygenation, whereas **2** relieves asthma, pulmonary hypertension, and discomfort. There is plenty of evidence that pentoxifylline and caffeine fight viruses. With their strong safety profiles, pentoxifylline and caffeine are promising COVID-19 therapy adjuncts[78].

15- Antifungal

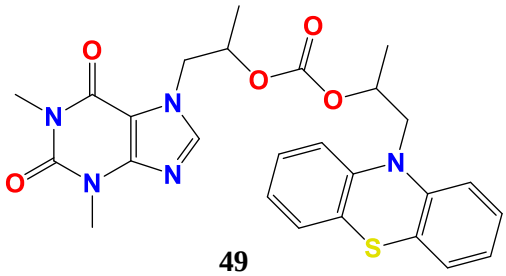
Candida albicans is the most prevalent opportunistic pathogen that causes fungal infections in immunocompromised individuals. The efficacy of antifungal therapies is diminished as a result of antimycotic resistance, which results in an increased mortality rate and economic costs in hospitals[79]. One rationale for selecting Proxyphylline **48** as a lead compound for synthesizing potential physiologically active compounds is its distinctive physicochemical properties, which contribute to its high solubility, permeability, and bioavailability. **48** with phenothiazine and polybrominated benzimidazole **49, 50** exhibited selective fungicidal activity against candida albicans but not against normal mammalian cells. These derivatives are considered dual antifungal-

anticancer agents because Borowieckia *et al.* have shown that they have exhibited moderate anticancer activity against human breast cancer and human T-cell leukemia[80].



Proxyphylline

48



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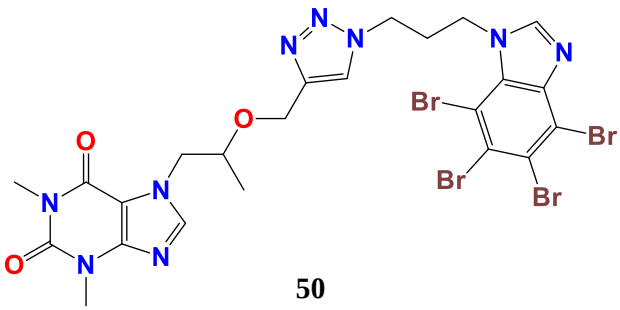

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Conclusion

This review highlights the significance, efficacy, and binding affinity of the substituted xanthine nucleus. The 1-, 3-, 7- and 8-positions of xanthines can be extensively investigated by various replacements, ranging from elongated alkyl chains to aromatic or cyclic heteroaromatics, to yield selective and powerful molecules. The xanthine nucleus exhibits significant biological variety, as evidenced by the literature referenced in this study. However, there remain additional regions and biological targets to investigate concerning xanthine and its derivatives to identify the most potent and effective molecules.

LIST OF ABBREVIATIONS

Abbreviation	Refers to
ARDS	Acute respiratory distress syndrome
AR	Adenosine receptor
A2A	Adenosine receptor subtype A
A2B	Adenosine receptor subtype B
AD	Alzheimer's disease
CHI3L1	Chitinase 3-like 1
DPP-4	Dipeptidyl peptidase-4
FEV1	Forced Expiratory Volume 1
GPR119	G-protein-coupled receptor 119
IBD	Inflammatory bowel disease
IECs	Intestinal epithelial cells
LBBB	Left Bundle Branch Block
LDLR	Low density lipoprotein receptor
LVSP	Left ventricular systolic blood pressure
LSD1	Lysine specific demethylase 1
MAO-B	Monoamine oxidase B
MDR	Multi-drug-resistant
MIC	Minimum inhibitory concentration
MTHFD2	Methylenetetrahydrofolate dehydrogenase 2
NBS	N-Bromosuccinimide
8-PC	8-Piperazinylcaffeine
PCSK9	Proprotein convertase subtilisin/ kexin type 9
PD	Parkinson's Disease
PDE	Phosphodiesterase
PET	Positron emission tomography
T2DM	Type 2 diabetes mellitus
TH1	Tryptophan hydroxylase 1
VEGFR-2	Vascular endothelial growth factor receptor-2

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الابتكارات الحديثة في الأنشطة البيولوجية للزانثين ومشتقاته: بحث مرجعي

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تعتبر الزانثين ومشتقاتها من الكيانات المهمة دوائيًا والتي تظهر أنشطة بيولوجية كبيرة. ونظرًا للتنوع الكبير في المجال البيولوجي ، فقد استحوذ هذا الهيكل على اهتمام العديد من الباحثين في جميع أنحاء العالم لفحص بنيته الأساسية من منظور فسيولوجي وكيميائي. وقد تم استخدام مشتقات الزانثين مؤخرًا علاجيًا في العديد من المواقف السريرية نظرًا لتوافرها على نطاق واسع في الحياة اليومية. تُعرف هذه المشتقات في الغالب بتطبيقاتها الدوائية المتنوعة ، بما في ذلك تثبيط مستقبلات الأدينوزين ، وتثبيط الفسفوديستيراز وإظهار أنشطة مضادة للأورام ومضادة للالتهابات ومضادة للبكتيريا ومضادة للفيروسات ومضادة للأكسدة ومضادة لمرض السكري. يعزز التخليق الكيميائي تنوع المشتقات القائمة على الزانثين. تسلط هذه المراجعة الضوء على أهمية مشتقات الزانثين كمرشحين محتملين لتطوير أدوية جديدة. وبالتالي ، نتوقع أن تعمل هذه المركبات كقالب لاكتشاف مشتقات زانثين نشطة أخرى. علاوة على ذلك ، فإن التقدم والتحققات العميقة لمشتقات الزانثين سوف تفتح الباب نحو اكتشاف مرشحين جدد للأدوية لديهم تنوع في الأنشطة البيولوجية.