Xanthine: Synthetic Strategy And Biological Activity

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Abstract: Xanthine and its derivatives belong to the class of purine alkaloids. They are natural bases holding nitrogen atoms within the molecular structure, and they have an effective pharmacological alteration in both animals and human beings. Substituted xanthine, theophylline/caffeine being prototype, is one of the derivatives which have shown prominent binding to adenosine receptors as agonist or antagonist. Various mechanistic approaches are involved in exerting bronchospasmolytic, neuroprotective, hypoglycemic, MAO modulatory, along cardiac effects. Mostly, xanthine derivatives reduce inflammation and bronchospasm in asthmatic conditions. Other therapeutics effects are in the management of cancer, Alzheimer's disease, vasoconstriction, and also possess excellent central nervous system-penetration ability; thus, they can also be used as stimulants and anti-depressants. Their actions are relatively very weak, but their pharmacological effects are also associated with snarl-up adenosine-mediated functions. An assortment of the biological profile of the xanthine scaffold attracted many research groups over the years to explore this nucleus vividly. The present review is aimed to cover every aspect of the xanthine moiety reported in the earlier years. This review covers all the major biological roles and various synthetic strategies adopted to synthesize xanthine moiety and its derivatives.

Keywords: xanthines; adenosine antagonists; Alzheimer's; MAO-inhibitors; 1,3-dimethyl uracil.
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1. Introduction

Various widely known biologically active scaffolds are available with a varying range of diversity in their biological profile. They may be organic or inorganic, either containing carbon atoms or one or more atoms other than carbon. The nitrogen-containing compounds are gaining more attention in the present era because of their wide diversity in their biological activities [1].

Xanthines are usually the derivative of purine alkaloids containing a nitrogen atom at positions 1-, 3-, 7- and 9, along with a carbonyl group at positions 2- and 6. Among naturally occurring xanthines, caffeine was the one that was isolated from coffee in the year 1820. The seeds of Theobroma cocoa contain caffeine and theobromine, while tea is obtained from the leaves of Thea sinensis containing caffeine which was isolated and named as "thein" further called theophylline, a dimethylxanthine [2].

Recent studies on caffeine (first isolated in 1819 by Ferdinand Runge) showed that it is also associated with Parkinson's disease as a treatment and preventive measure. This neuroprotective effect of caffeine is linked to its binding to adenosine A2A receptors [3–8].
Theophylline is chemically related as a natural metabolite of xanthine (I) which further metabolizes to uric acid (II) on oxidation by the enzyme xanthine oxidase at position-8 (Figure 1) [9].

![Xanthine Oxidase](image)

**Figure 1.** Oxidation of xanthine to uric acid.

Thus, most research is based on synthesizing 8-substituted xanthine, and this scaffold is a key nucleus of many clinically available drugs. Pentoxifylline, a hemorheological agent, is a trisubstituted xanthine, while dimenhydrinate, an over-the-counter antiemetic, is 8-chloroxanthine. Similarly, other substituted xanthines are found to act as nonselective inhibitors of adenosine receptors, selective inhibitors of phosphodiesterase, as anti-inflammatory agents, and as monoamine oxidase-B (MAO-B) inhibitors in treating Parkinson's disease [10].

Xanthine and its derivative are less soluble than their parent compound purine because of the strong intramolecular bonds between N-H groups and strong inter-base hydrogen bonds and base stacking. The increasing number of methyl groups at various positions on the xanthine nucleus profoundly affects its solubility [11–13]. The present review emphasizes the various synthetic strategies available to date to synthesize 8-substituted xanthines along with the many biological activities associated with this nucleus with regards to its structure-activity relationship studies and the effect of increasing alkyl chain at positions 1- and 3- and the effect of various substituents at position-8 [14].

2. Materials and Methods

2.1. Synthetic Strategies.

The various ways to synthesize various xanthine derivatives include synthesis of a key compound, 1-mono- or 1, 3-disubstituted-6-aminouracils. The starting compound possesses considerable diuretic activity, synthesized by Traübe using the classical method and further modified by Baum.

The proposed method includes condensation of substituted urea (1) with cyanoacetic acid (2) in the presence of acetic anhydride to result in intermediate cyanoacetyl urea (3). The resultant syrupy-based compound 3 on treatment with an alkali affects ring closure to form 6-aminouracil (4) as depicted in Scheme 1.

![Scheme 1](image)

**Scheme 1.** Synthesis of 6-Aminouracil.
In the case of mono-substituted urea (R’=H), the condensation occurs at unsubstituted nitrogen atom leading to the synthesis of 1-substituted-6-aminouracil, while in the case of disubstituted urea, condensation occurs at either nitrogen atom but predominantly at the nitrogen to which a smaller substituent group is attached [15].

Various 1, 3, 8-trisubstituted xanthines were reported by Erickson et al. (Scheme 2), starting with the nitrosation of 1,3-dialkyl-substituted-6-aminouracil (4) to give 6-amino-1,3-dialkyl-5-nitrosouracil (5) followed by catalytic hydrogenation to give 1,3-dialkyl-5,6-diaminouracil (6). The diamino uracil, a key compound, obtained was then converted to 1, 3, 8-trisubstituted xanthines by three different pathways that included condensation of diamino uracil with various aldehydes (7) to give imine (8) followed by oxidative cyclization with diethyl azodicarboxylate. Another method includes a reaction of 6 with carboxylic acid (9) to give amide (10) followed by cyclization with sodium hydroxide or direct melting of 6 and 9 to give amide (11) [16,17].

Another efficient one-pot method to synthesize xanthines was reported through direct coupling of carboxaldehyde with earlier available 5,6-diaminouracil (12) in the presence of mild conditions such as bromo dimethyl-sulfonium bromide (BDMS). In the presence of stoichiometric conditions, aldehydes on coupling with 12 gave high yields of xanthines (16) through an imine intermediate (14) or aminal form (15). The isolation of intermediates was unsuccessful except imine form, which was isolated at 10% buildup of bromo dimethyl-sulfonium bromide (BDMS) (Scheme 3) [18–23].
Another approach includes the reaction of appropriate diamino uracil (17) and substituted benzaldehydes (18) to give a benzylidene adduct (19) which resulted in the formation of the imidazole ring of xanthine core on oxidative closure. The substituted aldehydes were the product of the alkylation reaction of \( p \)-hydroxybenzaldehyde with iodoacetate. The oxidative ring closure was affected by heating with ferric chloride to afford resultant xanthines (20) (Scheme 4) [1].

The presence of solvent has a considerable effect at this step. In the presence of ethanol, considerable ethyl ester (21) will be formed, while in dimethylformamide (DMF), the carboxylic acid congener of xanthine (22) will be formed. The coupling of this acid congener with various amines presents a solubility problem, so \( N \)-hydroxysuccinimide ester (23) of 22 was prepared, which proved as an active form of the drug to be coupled with various amines.
in the presence of Dimethylformamide (DMF) to form amide derivatives of xanthine (24), while the ethyl ester (21) can also be aminolyzed directly to give amides (Scheme 5) [1].

Another coupling reaction between sulfophenylxanthines and amines resulted in sulfonamide derivatives of xanthines. The general 1, 3-dialkyl-8-phenylxanthines exhibit low solubility in water; thus, the introduction of the sulfonate group was done to increase the solubility followed by the synthesis of a series of sulfonamide derivatives.

The sulfonic acid (25) was first converted to its chloro sulfonyl derivative with thionyl chloride, chlorosulfonic acid, phosphorous oxychloride, or phosphorous pentachloride, followed by its treatment with an appropriate amine to give sulfonamide (26) but with poor yield (Scheme 6) [24].

Thus, the same method was used to determine whether nitro phenoxides are better-leaving groups than halogenides. The nitrophenoxysulfonyl benzene derivative of xanthine [25] which can be synthesized easily, crystalline, highly lipophilic, and stable, treated with various amines in dimethyl sulfoxide (DMSO) at room temperature for 30 min., along with heating at 150 °C for 3 hrs to obtain a good yield of sulfonamides 26-37 (Scheme 7).
Scheme 7. (c) primary or secondary amine, method A= DMSO, 150 °C, 3h; method B= DMSO, 150 °C, 5h; method C= DMSO, r.t., 72h, argon; method D= DMF, r.t., 48h, reflux, 1h.

Depending upon the substituent attached to the xanthine nucleus, different methods were applied to obtain sulfonamide derivatives in high yields, followed by their purification by column chromatography as given in Table 1 [26].

| Compound No. | R_1 | R_2 | R_3 | R_4 | % Yield |
|--------------|-----|-----|-----|-----|---------|
| 26           | Pr  | H   |     | H   | 51      |
| 27           | Pr  | H   | -CH_2CH_3Ph | H   | 88      |
| 28           | Pr  | H   | -CH_2CH_2OH | H   | 28      |
| 29           | Pr  | H   | -CH_2COOH | H   | 34      |
| 30           | Pr  | H   | Pr   | Pr  | 33      |
| 31           | Pr  | H   | Ph   | H   | 40      |
| 32           | Pr  | H   | -CH_2CH_2N(Bn)CH_2CH_2- | H   | 57      |
| 33           | Me  | Me  | Pr   | H   | 61      |
| 34           | Me  | Me  | -CH_2CH_2Ph | H   | 42      |
| 35           | Me  | Me  | Bu   | H   | 44      |
| 36           | Me  | Me  | -CH_2CH_2OH | H   | 51      |
| 37           | Me  | Me  | -CH_2COOH | H   | 28      |

A series of 8-(substituted-phenyl)-xanthines were synthesized by the reaction of 5,6-diamino-1,3-dimethyluracil (38) with various substituted aldehydes 39a-e, 42a-e, 45a-e to give...
corresponding Schiff bases/benzylidene derivatives 40a-e, 43a-e, 46a-e in methanol: glacial acetic acid (MeOH-AcOH) (4:1) at room temperature for 18 hours. The cyclization of these benzylidene derivatives in refluxing thionyl chloride for about 1 hour yielded the resultant xanthine derivatives 41a-e, 44a-e, and 47a-e.

The aldehydes 39a-e, 42a-e, 45a-e prepared by reaction of vanillin, isovanillin, and 3-hydroxybenzaldehyde with the hydrochlorides of dialkylaminoethyl chloride such as β-dimethylaminoethylchloride, β-diethylaminoethylchloride, 1-(2-chloroethyl)-piperidine, 4-(2-chloroethyl)-morpholine, and 1-(2-chloroethyl)-pyrrolidine in the presence of potassium carbonate (anhydrous) in refluxing ethyl methyl ketone (Scheme 8-10) [27].

![Scheme 9. Synthetic route to compounds 44 (a-e). Reagents and conditions (a) MeOH/CH₃COOH, r.t., 18h; (b) SOCl₂, reflux, 30-40 min., NH₄OH.](https://biointerfaceresearch.com/)

On changing positions of alkyl aminoalkoxy side chain and -OCH₃ group arrangement on the 8-phenyl ring, there is a significant change in the properties of various xanthine derivatives towards adenosine receptor subtypes binding, and this change depends on the type of substituents attached. The mono-substituted xanthine derivatives 47 (a-e), containing only one polar side chain at position-3 of the 8-phenyl group, displayed a potent affinity for A₁ and A₂A receptor subtypes adenosine. The presence of a –OCH₃ substituent ortho to a polar side chain at 3- or 4-position of phenyl ring resulted in increased selectivity for A₂ over A₁ receptors. A polar side chain at 3-position of the 8-phenyl ring without a –OCH₃ group resulted in almost equal selectivity for both subtypes. It can be established that appropriate selection and placement of aryl substituents may lead to the synthesis of potent and selective xanthine-based adenosine receptor antagonists.
Scheme 10. Synthetic route to compounds 47 (a-e). Reagents and conditions (a) MeOH/CH₃COOH, r.t., 18h; (b) SOCl₂, reflux, 30-40 min., NH₄OH.

Scheme 11. Synthetic route to 8-(p-substitutedphenyl)-xanthine derivatives. Reagents and conditions (a) MeOH/CH₃COOH, r.t., 18h; (b) SOCl₂, reflux.
In continuation to above, the impact of substituting polar dialkylaminoethoxy substituent at the para position of the 8-phenyl ring of xanthine on adenosine receptor binding affinity and selectivity was studied. Also, the introduction of a methylene spacer between the aromatic unit and the C8 of the xanthine nucleus was studied to determine its effect on biological activity. The 5, 6-diamino-1, 3-dimethyluracil (38) was treated with substituted aldehydes 48a-g to afford benzylidene adducts 49a-g in the presence of methanol and MeOH/AcOH (4:1) at room temperature for 18 hours. These adducts were refluxed in thionyl chloride for 1 hour to afford oxidative cyclization, resulting in the formation of targeted xanthines (50a-g) (Scheme 11) [28,29].

The imidazole-derived xanthines were also reported to possess adenosine binding affinity and antihistaminic properties too. The effect was studied by thermally fusing chloroalkoxy derivative of xanthine, 50f with powdered imidazole to afford corresponding congener 51 (Scheme 12), which was the potent compound for A\textsubscript{2A} adenosine receptor [30,31].

Yan et al. reported a process for the synthesis of a sulfonic acid-nitrophenyl ester of xanthines starting from the chlorination of potassium salt of p-sulfobenzoic acid (52) at low temperature with the help of chlorosulfonic acid to give sulfonyl chloride (53), which was further converted to either meta-(54) or para-(nitrophenoxysulfonyl)-benzoic acid (55) under Schotten-Baumann conditions [32].

The condensation of 54 and 55 with 5,6-diaminouracil using EDC as a condensing agent resulted in 6-amino-5-\{4-[\textit{m}-nitrophenoxy]-sulfonyl\}-benzamido\}-uracil derivatives 56a-e and 6-amino-5-\{4-[\textit{p}-nitrophenoxy]-sulfonyl\}-benzamido\}-uracil derivatives 57a-e. The heating of these compounds with polyphosphoric acid trimethylsilyl ester (PPSE) at 170°C
for 2 hours resulted in the synthesis of the corresponding meta- 58a-e and para-nitrophenylsulfonyl phenyl xanthine derivatives 59a-e (Scheme 13, Table 2) [25,32–36].

**Table 2.** Various substituents on nitrophenyl ester prodrugs of p-sulphonylphenyl xanthine derivatives.

| Compound No. | R$_1$   | R$_2$   | Nitro |
|--------------|---------|---------|-------|
| 58a          | Methyl  | Methyl  | m-    |
| 58b          | Propyl  | Propyl  | m-    |
| 58c          | Methyl  | H       | m-    |
| 58d          | Propyl  | H       | m-    |
| 58e          | Butyl   | H       | m-    |
| 59a          | Methyl  | Methyl  | p-    |
| 59b          | Propyl  | Propyl  | p-    |
| 59c          | Methyl  | H       | p-    |
| 59d          | Propyl  | H       | p-    |
| 59e          | Butyl   | H       | p-    |

Furthermore, a series of 8-heterocycle-substituted xanthines has been described. The several heterocycles introduced were pyrazole, isoxazole, pyridine, and pyridazine at 8-position of the xanthine nucleus, and different spacers such as substituted acetamide, oxyacetamide, and urea moieties were introduced. Various different groups were also introduced at 3- or 4- positions of the phenylacetamide moiety.

Scheme 14. Reagents: (1) Methanol, EDCI, 4-5 h; (2) Methanol, NaOH, 2.5 N, 70 °C, 12 h.

The reaction of 1, 3-disubstituted-5, 6-diaminouracil with pyrazole carboxylic acid (60, 61) and phenyl carboxylic acid (62) in methanol using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI) as a condensing agent then ring closure at 70 °C in the presence of sodium hydroxide yielded 8-aminopyrazolo- and 8-aminophenylxanthines 63a, 64b, 65b and 66b (Scheme 14) [37] [16,37].

Furthermore, 9-deazaxanthine (9-dAXs) (1,3-dialkyl-8-substituted-1H-pyrrolo [3,2-d] pyrimidine-2,4-(3H, 5H)-diones) derivatives were synthesized by the reaction of 1,3-dialkyl-6-methyl-5-nitopyrimidine-2,4-(1H,3H)-dione (67) with appropriate benzaldehydes (68) and piperidine in dry dioxane under argon atmosphere and refluxed for 5-70 h to give nitrostyryl derivatives (69). These 6-styryluracils were cyclized to their corresponding 9-dAXs (70) and to their equivalent 9-halogen derivatives (71) containing an oxyacetic acid or ester group on the para position of the 8-phenyl ring (Scheme 15) [38–41].
Scheme 15. Reagents (a) Dioxane/piperidine/reflux; (b) P(OEt)$_3$, reflux; (c) Na$_2$S$_2$O$_4$/HCOOH, reflux; (d) SO$_2$Cl$_2$ or Br$_2$/AcOH.

Balo et al. reported the synthesis of novel 1- and 8-substituted-3-furfuryl xanthines as described in Scheme 16. The condensation of 1-furfuryl urea with cyanoacetic acid [42] gave uracil (72), which was further alkylated directly by using 15% aqueous sodium hydroxide (NaOH) or with appropriate alkyl halide [43] or by refluxing with ammonium sulfate in hexamethyldisilazane (HMDS) and then the addition of iodine and appropriate halide [44,45] to give 1,3-disubstituted-6-aminouracil (73). The nitrosation of 73a-l with sodium acetate in acetic acid followed by reduction with sodium dithionite gave diaminouracils 75a-l. The condensation of these diaminouracils with a different carboxylic acid in the presence of diisopropylcarbodiimide (DIC) in methanol and then cyclization with 2.5N NaOH in methanol under reflux afforded targeted xanthines 76 (a-aa) Table 3 [46].

Scheme 16. Reagents and conditions: (i) KOCN, H$_2$SO$_4$; (ii) NCCH$_2$COOH; (iii) (a) RX, NaOH, EtOH; (b) (NH$_4$)$_2$SO$_4$, HMDS, I$_2$, RX, Na$_2$S$_2$O$_3$, H$_2$O; (iv) NaN$_2$, AcOH; (v) Na$_2$S$_2$O$_3$, NH$_2$OH; (vi) (a) R$_2$COOH, DIC, MeOH, rt, 0.5h; (b) 2.5N NaOH, MeOH, reflux, 10min.-1h.
Table 3. Various substituents of 1- and 8-substituted-3-furfuryl xanthines 76(a-aa).

| S. No. | Compound | \(R_1\) | \(R_2\) |
|--------|----------|---------|---------|
| 1      | 76a      | Methyl  | Furan-2-yl |
| 2      | 76b      | Ethyl   | Phenyl   |
| 3      | 76c      | Ethyl   | Furan-2-yl |
| 4      | 76d      | Ethyl   | Thiphen-2-yl |
| 5      | 76e      | Propyl  | Phenyl   |
| 6      | 76f      | Propyl  | Furan-2-yl |
| 7      | 76g      | Propyl  | Thiphen-2-yl |
| 8      | 76h      | Isobutyl| Phenyl   |
| 9      | 76i      | Isobutyl| Thiphen-2-yl |
| 10     | 76j      | Pentyl  | Phenyl   |
| 11     | 76k      | Pentyl  | Thiphen-2-yl |
| 12     | 76l      | Cyclopropylmethyl| Thiphen-2-yl |
| 13     | 76m      | Cyclopropylmethyl| 2,6-Difluorophenyl |
| 14     | 76n      | Prop-2-ynyl| Thiphen-2-yl |
| 15     | 76o      | Prop-2-ynyl| 2,6-Difluorophenyl |
| 16     | 76p      | Allyl   | Thiphen-2-yl |
| 17     | 76q      | Allyl   | 2,6-Difluorophenyl |
| 18     | 76r      | 2-Methoxyethyl| Phenyl |
| 19     | 76s      | 2-Methoxyethyl| Thiphen-2-yl |
| 20     | 76t      | 2-Methoxyethyl| 2,6-Difluorophenyl |
| 21     | 76u      | 2-Ethoxyethyl| Phenyl |
| 22     | 76v      | 2-Ethoxyethyl| Thiphen-2-yl |
| 23     | 76w      | 2-(Methylthio)ethyl| Thiphen-2-yl |
| 24     | 76x      | 2-(Methylthio)ethyl| 2,6-Difluorophenyl |
| 25     | 76y      | 2-(Ethylthio)ethyl| Phenyl |
| 26     | 76z      | 2-(Ethylthio)ethyl| Furan-2-yl |
| 27     | 76aa     | 2-(Ethylthio)ethyl| Thiphen-2-yl |

Another efficient method for synthesizing 8-substituted xanthines includes the reaction of 5, 6-diaminouracils, and carboxaldehyde using bromo dimethylsulfonium bromide (BDMS) [18,47]. The coupling of diamino uracil to methyl-2-formylbenzoate under BDMS gave xanthine benzoate (77) after filtration. The methylation of xanthine and saponification of benzoate yielded methylxanthine benzoic acid (79) (Scheme 17) [48].

Another method for synthesizing xanthines is synthesizing 1-substituted uracil derivatives 80a-b, according to Papesch and Schröder [49]. From 80a-b, xanthines were obtained by different pathways. One method was their conversion to nitroso uracils 81a-b. The reaction of 81b with a mixture of benzylamine hydrochloride at high temperature yielded the xanthine derivative 83d. Another method includes the reduction of nitrosouracils to

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diaminouracils 82a-b by sodium dithionite. Being unstable due to oxidative dimerization in the presence of oxygen, they were used further without any purification [50]. The diaminouracil 82a was reacted with triethyl orthoformate to yield another xanthine derivative 83b (Scheme 18) [51].

Scheme 18. Reagents (i) NaNO₂, H₂O/CH₃COOH, (ii) Na₂S₂O₄, H₂O/NH₃, (iii) C₆H₅CH₂NH₂.HCl, C₆H₅CH₂NH₂, 3h, 170 °C; (iv) (C₂H₅O)₃CH, 12h, heat.

Scheme 19. Solid-phase synthesis of fully substituted xanthine.
A solid-phase technology was also employed to synthesize fully substituted xanthine derivatives. The reaction included coupling bromoacetic acid to the free amino function of the solid support (84). Through the nitrogen atom, 1-alkyl-4-chlorouracil (85) was attached to the solid phase by the method of alkylation to form an intermediate 86. The chlorine atom of resin-bound uracil intermediate was replaced by 1° benzylamines to give 4-benzylaminouracil (87). The solid support bound 87 was treated with isopentyl nitrite in acetic acid to form a nitroso compound that undergoes immediate ring closure to form a xanthine derivative (88). The progress at each step was monitored by the cleavage of the reaction product from the solid phase and its analysis by UV spectroscopy. The alkylation of 88 in the presence of excess alkylation agent and triethylamine gave fully substituted xanthine 89. The solid support was finally cleaved by the action of trifluoroacetic acid resulting in final fully substituted xanthines (90). The cleavage procedure included treating resin twice with 95% trifluoroacetic acid and washing with 95% trifluoroacetic acid, dichloromethane, and trifluoroethanol. The combined solvents were removed over KOH in an evacuated desiccator. Residues were lyophilized twice from dilute acetic acid and purified directly by HPLC (Scheme 19) [52–55].

2.1. Biological profile

The xanthine nucleus possesses numerous properties biologically. Xanthines are used widely as anti-asthmatics, adenosine receptor antagonists, and monoamine oxidase-B (MAO-B) inhibitors in treating neurodegenerative disorders in the treatment of type-2 diabetes and many more conditions. Some of the xanthine nuclei drugs are already available in the market, while some are under different phases of clinical trials, as presented in Table 4 [56].

| S. No. | Compound | Description |
|-------|----------|-------------|
| 1.    | GW493838 | • A1 receptor agonist  
       |          | • Discontinued at Phase IIb-III of clinical trials |
| 2.    | Regadenoson | • A2 receptor agonist  
         |          | • Completed Phase IIb-III of clinical trials |
| S. No. | Compound | Description |
|--------|----------|-------------|
| 3.     | ![Apadenoson](image) | - A2 receptor agonist  
- Completed Phase IIb-III of clinical trials |
| 4.     | ![CF101](image) | - A3 receptor agonist  
- Completed Phase IIb-III of clinical trials |
| 5.     | ![CF102](image) | - A3 receptor agonist  
- In Phase IIb-III of clinical trials |
| 6.     | ![Tonapofylline BG9928](image) | - A1 receptor antagonist  
- Discontinued at Phase IIb-III of clinical trials |
| 7.     | ![Istradefylline KW6002](image) | - A2A receptor antagonist  
- In Phase IIb-III of clinical trials |
| S. No. | Compound | Description |
|--------|----------|-------------|
| 8.     | ![Dimenhydrinate](dimenhydrinate.png) | • An OTC antiemetic used for motion sickness  
        • Combination of 8-chlorotheophylline and diphenhydramine |
| 9.     | ![IBMX](ibmx.png) | • Competitive nonselective phosphodiesterase inhibitor  
        • Nonselective adenosine receptor antagonist |
| 10.    | ![DMPX](dmpx.png) | • Possess affinity towards A2-adenosine receptors |
| 11.    | ![Theo 24](theo_24.png) | • Also known as theochron, Elixophyllin and Uniphyl  
        • Inhibitor of Phosphodiesterase enzyme  
        • Useful in Acute bronchospasm |
| 12.    | ![Dilor](dilor.png) | • Also known as Lufyllin  
        • Inhibitor of Phosphodiesterase enzyme  
        • Useful in renal impairment |

2.3. **Antibacterial agents.**

A series of 8-(substituted)-aryloxycaffeine were evaluated for their *in vitro* antibacterial activity compared to *Staphylococcus aureus* (KCTC 1916), *Salmonella enteritidis* (KCTC 12021), *Salmonella typhimurium* (KCTC 2515), and *Bacillus subtilis* (ATCC 6633). Among the series, the 8-(5-chloropyridin-3-yl oxy)-1, 3, 7-trimethyl-1H-purine-2, 6(3H,7H)-dione (91) displayed strong inhibitory activity (MIC= 15.6 µg/ml) against gram-negative (-) bacteria *Salmonella enteritidis*. The other three derivatives, 92-94, also showed excellent inhibitory activity with a value of 31.2 µg/ml against gram-negative (-) bacteria *Salmonella enteritidis* and gram-positive (+) bacteria *Bacillus subtilis* (Figure 2) [57].
2.4. DNA topoisomerase II inhibitors.

Topo II inhibitory activity of 8-(substituted)-aryloxy-caffeine was calculated by assessing the recreation of supercoiled pBR322 plasmid DNA. Among all the caffeine derivatives, 1,3,7-trimethyl-8-(quinolin-8- yloxy)-1H-purine-2,6(3H,7H)-dione (95) was the highly active inhibitor showing 28.42% and 48.92% inhibition as compared to 42.82% and 66.87% of etoposide at 20µM and 100µM concentration [58].

2.5. Analgesics.

The analgesic effect of a series of 8-(substituted)-aryloxy-caffeine derivatives was studied by their effect on motor activity in mice, their general behavior, and their effect on thermal pain. The phenoxy (96) and pyridine (97) substituted derivatives showed an increase in locomotion percentage, while methylpyridine (98) and trifluoromethylpyridine (99) substituted derivatives showed analgesic activity without any central stimulation (Figure 3) [59].

2.6. Monoamine oxidase-B (MAO-B) inhibitors.

MAO-B oxidizes dopamine in the brain. For each mole of dopamine oxidized, one mole of hydrogen peroxide (H₂O₂) is produced, which interacts with free ions to form highly reactive...
hydroxyl radicals resulting in age-related neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [59]. Thus MAO-B inhibitors are useful in treating neurodegenerative disease [60,61]. (E)-8-(3-chlorostyryl) caffeine (CSC, 100) found to be the promising agent with a good affinity for adenosine A<sub>2A</sub> receptor subtype and also MAO-B inhibitory potency. The further modifications of caffeinyl core of CSC and bioisosteric replacement of purine nitrogen atom at 9-position resulted in 9-deazaxanthines acting as both A<sub>2A</sub> antagonists and MAO-B inhibitors. The p-chlorostyryl derivative (101) of 9-deazaxanthine and benzyloxy (102) or phenylalkynyl (103) substituents replaced at 8-styryl portion of 100 resulted in compounds showing remarkable MAO-B inhibitory potency even higher than CSC [62]. Also, a series of (E,E)-8-(4-phenylbutadien-1-yl)caffeine analogs (104-107) were found as potent inhibitors of MAO-B (Figure 4) [63].

![Chemical Structures](https://biointerfaceresearch.com/)

**Figure 4.** Xanthine nucleus contains compounds as MAO-B inhibitors.

### 2.7. Anti-Parkinson's agents.

Various A<sub>2A</sub> antagonists found to be useful in treating the symptoms of Parkinson’s disease which lead to discovery of CSC [64], istradefylline (KW6002, 108) [65–67], KF-17837 (109) [68–70], DMPX (110) [71], DPMTX (111) [72], MSX-2 (112) [73–76], SCH 58261 (113) [77–79], ZM241385 (114) [80,81], CGS 15943 (115) [82] and ST1535 (116) [83–92]. They found to improve motor impairment and reduced “off” time when co-administered with levodopa (Figure 5) [93].

### 2.8. Bronchodilators.

Various 8-aryl or 8-cycloaryl substituted xanthines were found to be potent bronchodilators on isolated guinea-pig tracheal strips, which were precontracted by acetylcholine or histamine. 8-[1-(4-benzoylphenyl) ethyl]-1,3-dimethyl-3,7-dihydropurin-2,6-dione (117) has some inhibitory effect on acetylcholine-induced precontractions as that of theophylline. The substitution of furan ring at 8-position of xanthine also gave compounds with significant inhibitory activity on the tracheal strips precontracted by histamine (118, 119). The substitution with morpholino- (120), piperidine- (121), and pyrimidine- (122) moieties also
showed the considerable effect as bronchodilators. The compound 123 also had a similar effect as 121 (Figure 6) [94].

Figure 5. Xanthine nucleus containing compounds as Antiparkinson's agents.

Figure 6. Xanthine nucleus contains compounds as bronchodilators.

2.9. *Dipeptidyl peptidase (DPP-4) inhibitors.*

DPP-4 inhibitors degrade various neuropeptides, peptide hormones, and cytokines such as glucagon-like peptides (GLP-1) and GIP. GLP-1 inhibits glucagon release from pancreatic α cells, reduces food intake, and retards gastric emptying. The inhibition of DPP-4 will improve glucose homeostasis. A novel, potent and selective DPP-4 inhibitor originated from the class of xanthine (BI1356, 124). Another 7-,8-substituted xanthine derivative (125) was discovered through high-throughput screening. Various other xanthine derivatives also showed considerable DPP-4 inhibitory activity against human DPP-4 derived preparation from Caco-2
cells. The replacement of piperazine at C-8 for 3-aminopiperidine in 126 resulted in a tremendous increase in potency. The optimization at N-7 resulted in more potent compounds (127, 128), while further substitution at N-1(129) in the case of 127 resulted in an additional increase in potency whose (S)-configuration was twice as potent as (R)-configuration (Figure 7) [10].

![Chemical structures](124-129)

**Figure 7.** Xanthine nucleus contains compounds as DPP-4 inhibitors.

2.10. Kinase inhibitors.

Xanthine analogs were also identified as potent kinase inhibitors against PI3Ks and also found to inhibit the proliferation in T47D tumor cells. Additionally, xanthine-based kinase inhibitors also showed significant fluorescence emission in a concentration-dependent response. The group was the first to disclose the importance of xanthine scaffolds as fluorophores. 8-acetamido substituted xanthine (130) showed the potent antiproliferative effect on tumor cells against MTT assay. Another xanthine derivative, 131, was also found to show an inhibitory effect on various kinases (Figure 8) [95–97].

![Chemical structures](130-131)

**Figure 8.** Xanthine nucleus contains compounds as Kinase inhibitors.

2.11. Antiviral agents.

Various antiviral agents are derivatives of uracil, a key compound for the synthesis of xanthine derivatives, such as zidovudine (AZT, 132) [98], stavudine (Zerit, 133) [99], abacavir (Ziagen, 134 [100] and 1-((2-hydroxyethoxy)methyl)-6-(phenylthio)thymine (HEPT,135) [101–103] and its derivatives. The xanthine derivative, i.e., Acyclovir (136), is also used clinically as an antiviral agent. The antiviral property is associated with either inhibiting the reverse transcription process of the virus replication or through DNA chain termination of viral DNA by being incorporated in the viral DNA chain (Figure 9) [104–106].
2.12. Adenosine receptor antagonists.

Adenosine plays an important role in asthma by activating A2B adenosine receptors on mast cells and bronchial smooth muscle cells, thus enhancing the degranulation of mast cells and releasing inflammatory cytokines. The antagonist of A2B adenosine receptors plays an important role as antiasthmatics. Various 1-,3- and 8-substituted xanthines possess affinity and selectivity for adenosine receptor subtypes (A1, A2A, A2B, and A3) [107–109]. Several 3-furyl-7-methylxanthine derivatives showed a high affinity towards human A2B receptors. 1-ethyl-3-((furan-2-yl) methyl)-7-methyl-8-((thiophen-2-yl) methyl)-IH-purine-2, 6-(3H,7H)-dione (137) was found to be most active with a \( K_i \) value of 7.4 nm for hA2B receptors among this series [46]. MRS-1754 (138) and CVT-5440 (\( K_i = 50 \) nm, 139) were also discovered as high-affinity A2B adenosine receptor antagonists with good selectivity [110]. Jacobson and co-workers reported a useful radioligand \([3^H]ZM241385\) (140) and XAC (141) for the study of the A2B adenosine receptor subtype [111–113].

Baraldi et al. synthesized a series of 8-heterocyclic xanthine derivatives, among which MRE2028F20 (142), MRE2029F20 (143), and MRE2030F20 (144) showed high affinity at A2B receptor subtypes and very good selectivity vs. other adenosine receptors (Figure 10) [37]. A2A adenosine receptors antagonists are also a major target for CNS drug delivery due to their interactions with D2 receptors. The lead compounds as A2A antagonists have been discovered as a clinical candidate for Parkinson’s disease-bearing a xanthine skeleton [18,114–116]. Bansal et al. also reported a series of 8-(substituted-phenyl)-xanthines possessing binding affinity towards adenosine A2Areceptors. Among the disubstituted vanilloid, series compounds with methoxy group ortho to polar substituents at the 4th position of phenyl ring (145-147) possess a good binding affinity for A2A receptors. While in isovanilloid series, 1,3-dimethyl-8-[4-methoxy-3-(2-morpholin-4-yloxy) phenylxanthine (148) found as most potent and active at A2A receptors (\( K_i = 100 \) nm) [27]. In the case of mono-substituted xanthines, compounds with diethylaminoethoxy substituent (149) emerged as the most potent towards A2A receptors. In this series, chloropropoxy phenyl substituted (150, \( K_i = 45 \) nm) and cyclopentyloxy derivative of 8-substituted xanthine (151, \( K_i = 72 \) nm) also exhibited remarkable affinity and selectivity towards A2A receptors (Figure 11) [30,117].
Figure 10. Xanthine nucleus containing compounds as A_{2B} adenosine receptor antagonist.

Figure 11. Xanthine nucleus contains compounds as A_{2A} adenosine receptor antagonists.
A series of 1,3,7-Triethylsubstituted xanthines were found to possess antagonistic properties at adenosine A1 receptors, thus having the therapeutic potential to treat complex neurological disorders like Alzheimer's disease and Parkinson's disease. Among the series of substituted xanthines, 1,3,7-Triethyl-8-(3-phenylpropyl) xanthine (152), 1,3,7-Triethyl-8-(2-phenylethyl) xanthine (153) and 1, 3, 7-Triethyl-8-(phenoxyethyl) xanthine (154) found to be potent and displayed the highest affinity against adenosine A1 receptors in GTP shift assays performed with either rat cortical or whole-brain membranes expressing adenosine A1 receptors (Figure 12) [118, 119].

![Figure 12. Xanthine nucleus contains compounds as A1 adenosine receptor antagonists.](152) (153) (154)

The various other xanthines usually used to treat asthma as given by WHO list of International Nonproprietary Names (INNs) are given in Table 5 [120].

| S. No. | Drug                | Comments                                                   |
|-------|---------------------|------------------------------------------------------------|
| 1     | Albifylline         | 1-(5-Hydroxy-5-methylhexyl)-3-methylxanthine               |
| 2     | Aminophylline       | A mixture of theophylline with ethylenediamine in a ratio of about 85:15, to increase the solubility of the xanthine, the ethylenediamine may cause hypersensitivity reactions |
| 3     | Bamifylline         | 8-Benzyl-7-[2-(N-ethyl-N-2-hydroxyethylamino)ethyl]theophylline--line |
| 4     | Caffeine            | Methyltheobromine                                         |
| 5     | Choline theophylline| Choline salt of theophylline                               |
| 6     | Diprophylline       | 7-(2,3-Dihydroxypropyl)1,3-dimethylxanthine                |
| 7     | Doxofylline         | (1,3-Dioxolan-2-ylmethyl)theophylline                     |
| 8     | Enprofylline        | 3,7-Dihydro-3-propylxanthine                              |
| 9     | Etofylline          | 7-(2-Hydroxyethyl)-1,3-dimethylxanthine                    |
| 10    | Heptaminol acephyllate | A salt of theophylline-7-y1 acetic acid                  |
| 11    | Proxyphylline       | 7-(2-Hydroxypropyl)-1,3-dimethylxanthine                   |
| 12    | Pyridophylline      | 2-(theophylline-7-y1)ethyl sulfate                         |
| 13    | Theobromine         | 3,7-Dimethylxanthine                                      |
| 14    | Theophylline        | 1,3-Dimethylxanthine                                      |

In addition, the COVID-19 pandemic presents an unprecedented challenge to identify effective drugs for the treatment. Pentoxifylline, a xanthine derivative, is a well-known anti-inflammatory and anti-oxidative molecule which may be beneficial for better clinical outcomes in COVID-19 patients. Along with the significant evidence and high safety profiles, xanthines offer a glimpse of considerations for future use as a potential adjuvant to COVID-19 treatment. However, additional clinical studies are required to confirm this speculation [121].

3. Conclusions

The importance, potency, and binding affinity of the substituted xanthine nucleus have been presented in this review. Xanthine and its derivatives are nowadays further explored for neurodegenerative disorders, mainly Parkinson's disease. The xanthines' 1-, 3- and 8-positions can be explored highly with different substitutions varying from increasing alkyl chain to aromatic or cyclic heteroaromatics to get potent and selective compounds. The 7th position of
the nucleus has also been considered for various biological targets. The xanthine nucleus possesses large diversity biologically, as clear from the literature cited in this review. Yet, there are areas and more biological targets to be explored in the direction of xanthine and its derivatives to get the most active and potent compounds.

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Conflict of interest

The authors declare no conflict of interest.

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