Xanthine and its derivatives are considered a pharmacologically potential moiety that manifests immense biological activities. Owing to this much diversity in the biological field, this scaffold has fascinated the attention of many researchers around the globe to scrutinize its basic structure chemically as well as biologically. In recent years, xanthine derivatives have been used therapeutically in different pathological conditions due to their presence in day-to-day life. Herein, we review the recent progress in the synthesis of xanthine and its derivatives. Some of the widely used synthetic strategies such as (a) Traube’s synthesis, (b) one-pot synthesis, (c) xanthine-anneleated synthesis, and (d) miscellaneous synthesis were compiled in this review paper. The results obtained from this review paper highlight the significance of various xanthine derivatives as possible leads to the development of new drugs. The data compiled in this review paper could help the medicinal chemist in designing new active compounds from the modification of the already existing compounds in the search for novel drug leads. This report concludes that the various synthetic procedures exemplified in this review paper may serve as a support system for the designing of new molecules with a xanthine scaffold. Thus, we hope that this molecule may serve as the prototype in order to find out more active xanthine derivatives.

1. Introduction

Xanthine or 3,7-dihydropurine-2,6-dione (see Figure 1), a unique heterocycle is a purine base containing nitrogen as a central atom and composed of a pyrimidine ring fused with an imidazole ring.

It is an essential core element of diverse natural products because their structural fragments are found in various natural and synthetic medicinally active compounds [1]. The versatility of the xanthine moiety displays that it is the essential part of several medicinal agents and some of its derivatives have shown innumerable physiological and pharmacological activities viz. respiratory tract, heart, smooth muscle cells, CNS (central nervous system), kidney, and stomach [2]. In brief, the objective of such studies is to expose the drug-like properties of xanthine and its derivatives in order to build prospects for harnessing the full potential of this scaffold.

Xanthine scaffold has fascinated the attention of researchers in health sciences due to its remarkable properties either chemical or physical [3]. Over the last two decades, the compound and its derivatives have gained considerable interest [4]. The xanthine scaffold can also act as a basic framework for numerous pharmacologically active scaffolds [5]. Several patent applications were also filed for xanthine derivatives as mentioned in (see Table 1), which displays the therapeutic effectiveness of this scaffold.

Owing to the importance of xanthine moiety in medicinal chemistry and its broad range of biological activity [22]. This review article primarily focuses on the updated knowledge of synthetic methods used to access xanthine scaffolds. In the present work, we have compiled the recent literature that belongs to the synthetic strategies of these derivatives.

2. Search Strategy

The data has been compiled from the year 2010 to 13 July 2022. We performed an electronic search to find out the existing literature on xanthine derivatives. For this purpose, the compiled data has been searched from different search engines and databases such as Science Direct, Google
A series of 8-substituted xanthines by using 1,3-dimethyl and 1, 3-diethyl 5, 6-diaminouracils (31) as starting compounds was reported. The uracil was treated with desired carboxylic acid (32) to yield intermediate amides. Furthermore, the amide was reacted with NaOH (sodium hydroxide) to yield 1-, 3-, 7-trisubstituted xanthines (33). The obtained compound was further treated with an excess of iodomethane or iodoethane to yield 1-, 3-, 7-, 8-substituted xanthines (34) [25] (Scheme 3).

Novel 8-(p-substituted) xanthine derivatives were designed, synthesized, and reported. The synthesis was done by using 5, 6-diamino-1, 3-dimethyluracil (35). The treatment of uracil with aldehydes (36) yields the corresponding Schiff base (37), and further ring closure afforded the desired xanthine derivatives (38) [26] (Scheme 5).

The synthesis of 1, 3, 7, 8-substituted xanthine derivatives was reported. The synthesis was done by reacting 1,3-dialkyl-5, 6-diaminouracil (39) with that of substituted phenoxy acetic acid (40) and EDAC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide). In the next step, the obtained intermediate amide was treated with aq. NaOH to yield the desired xanthine analog (41, 42) [27] (Scheme 6).

1-, 3-, 8-substituted xanthines were synthesized from 1,3-dipropyl-5, 6-diaminouracil (43). The uracil was reacted with corresponding carboxylic acid (44) in presence of EDCI [1-ethyl-3-(3-dimethylaminopropyl) carbodiimide] to yield the benzylidene derivative (45), and further ring closure was achieved with NaOH to give 8-substituted xanthines (46-49) [28] (Scheme 7).

A new reaction for the synthesis of tetrahydropyrazino [2,1f] purinediones was reported. The 5,6-diaminouracil (50) was treated with glycolic acid at 100°C, ring closure was achieved with NaOH solution to give 8-hydroxyxanthine (51). Subsequent alkylation (52) at position-7 in the presence of DIPEA (N, N-diisopropylethylamine). In the end, the obtained compound (53) was treated with various amines (54) resulting in xanthine derivatives (55) [29] (Scheme 8).

8-(2-nitroaryl) xanthines were synthesized from dimethyl urea (56), cyanoacetic acid, and acetic anhydride. The nitrosation (57) and reduction of 6-aminouracil (58) was achieved resulting in 5, 6-diaminouracil (59), which on further treatment with a corresponding aldehyde (60) yielded benzylidene derivative (61). These derivatives were further cyclized by refluxing in thionyl chloride to give the required xanthines (62). All the synthesized compounds were further biologically evaluated for adenosine receptor subtypes [30] (Scheme 9).
| S. No. | Patent application number | Year of filing | Applicant name | Patent office | Compound | Category |
|--------|--------------------------|---------------|---------------|---------------|-----------|----------|
| 1      | AU 200521 958-B2 [6]     | 2005          | Boehringer Ingelheim International GmbH | Australian | ![Chemical structure](image1) | DPP-IV inhibitor |
|        |                          |               |               |               | 8-(3-Amino-piperidin-1-yl)-xanthine | |
| 2      | CA 02873524 [7]          | 2007          | Boehringer Ingelheim International GmbH | Canadian   | ![Chemical structure](image2) | DPP-IV inhibitor |
|        |                          |               |               |               | 1-[(4-methyl-quinazolin-2-yl)methyl]-3-7-(2-butyn-1-yl)-8-(3-(R)-aminopiperidin-1-yl)xanthine | |
| 3      | EP 2058311A2 [8]         | 2003          | Boehringer Ingelheim International GmbH and Co. | European | ![Chemical structure](image3) | DPP-IV inhibitor |
|        |                          |               |               |               | 8-{3-amino-piperidin-1-yl}-xanthine | |
| 4      | DE 6020050 00 986T2 [9]  | 2005          | Loreal Paris  | Deutsches patent under Markenamt | —         | Obesity |
| 5      | EP 1368349 B1 [10]       | 2002          | Boehringer Ingelheim International GmbH and Co. | European | ![Chemical structure](image4) | DPP-IV |
|        |                          |               |               |               | Xanthine derivative | |
| 6      | EP 1515972 B1 [11]       | 2003          | F.Hoffman-La Roche AG 4070 Basel (CH) | European | ![Chemical structure](image5) | Type-II diabetes |
|        |                          |               |               |               | Amide substituted xanthine derivative | |
| 7      | EP 1599477 B1 [12]       | 2004          | F.Hoffman-La Roche AG 4070 Basel (CH) | European | ![Chemical structure](image6) | PEPCK inhibitors |
|        |                          |               |               |               | Sulphonamide substituted xanthine Derivative | |
| S. No. | Patent application number | Year of filing | Applicant name | Patent office | Compound | Category |
|-------|---------------------------|----------------|----------------|---------------|----------|----------|
| 8     | EP 1689748 B1 [13]       | 2004           | Boehringer Ingelheim International GmbH | European | ![Compound 6](image) | Diabetes |
|       |                           |                |                |               | 8-(piperazine-1-yl) and 8-(1, 4 diazepam-1-yl)-xanthine |          |
| 9     | ES 2401128 T3 [14]       | 2006           | GlaxoSmithKline LLC | Spain | ![Compound 7](image) | Agonist of HM74 A |
|       |                           |                |                |               | Xanthine derivative |          |
| 10    | US 7696212 B2 [15]       | 2010           | Boehringer Ingelheim International GmbH and Co. KG | United States | ![Compound 8](image) | DPP-IV inhibitor |
|       |                           |                |                |               | Xanthine derivative |          |
| 11    | US 7838529 B2 [16]       | 2010           | Boehringer Ingelheim International GmbH, Ingelheim am Rhein (DE) | United States | ![Compound 9](image) | Type-2 diabetes mellitus, antiobesity. |
|       |                           |                |                |               | Xanthine derivative |          |
| 12    | US 7879864 B2 [17]       | 2011           | Sanofi-Aventis Deutschland GmbH, Frankfurt am main (DE) | United States | ![Compound 10](image) | DPP-IV inhibitor |
|       |                           |                |                |               | 8-amino alkoxy: xanthine |          |
| 13    | US 9221821 B2 [18]       | 2015           | Forest Laboratories Holdings Limited, Hamilton (BM) | United States | ![Compound 11](image) | 1, 3-Substituted aminouracils and xanthine derivatives |
A novel series of 1-,3-,7-triethyl substituted xanthine derivatives were reported. The 5,6-diamino-1,3-dialkyluracil (63) was used as the starting material. The starting material was treated with commercially available carboxylic acid (64) to give 1,3-dialkyl-6-amino-5-carboxamidouracil (65) intermediate, subsequent cyclisation of this derivative yield corresponding xanthine derivatives (66,67) [31] (Scheme 10).

**Table 1: Continued.**

| S. No. | Patent application number | Year of filing | Applicant name | Patent office | Compound | Category |
|-------|---------------------------|----------------|----------------|---------------|----------|----------|
| 14    | US 10202383 B2 [19]       | 2019           | Boehringer Ingelheim International GmbH, Ingelheim am Rhein (DE) | United States | ![image](image1) | DPP-IV |
| 15    | US 10214530 B2 [20]       | 2019           | Max-Delbruck-Centrum Fur Molekulare Medizin, Berlin (De), Forschungs-Verbund-Berlin-E. V., Berlin (De) | United States | ![image](image2) | Serotonin based disease |
| 16    | US 201111 8464 [21]       | 2009           | Ing-Jun Chen Linya District (TW) | United States | ![image](image3) | Halogenated xanthine derivative |

**Scheme 1:** Synthetic procedure for substituted xanthines by Traube’s method.
Reagents and conditions: (i) (a) HMDS, (NH₄)₂SO₄, reflux, 2 h, (b) R₁X, toluene, reflux, 90 min, (c) Na₂S₂O₃, H₂O, rt; (ii) NaNO₂, 50% aq AcOH, 80°C, 45 min; (iii) Na₂S₂O₄, 35% aq NH₄OH, 60°C, 1 h; (iv) R₃CO₂H, DIC, MeOH, rt, 1 h; (v) R₂X, K₂CO₃, DMF, 50°C, 48 h; (vi) NaOH, MeOH, reflux, 2 h; (vii) CH₃I, K₂CO₃, DMF, 100°C, 5 h.

Scheme 2: Synthesis of 1-,3-,8-trisubstituted 1H-purine-2,6(3H,9H)-diones.

Reagents and conditions: i) EDAC, dioxane: H₂O (1:1); (ii) NaOH (aq), reflux (iii) CH₃I or C₂H₅I, K₂CO₃, DMF, ethanol or acetone.

Scheme 3: Synthesis of 8-cyclopentyloxyphenyl xanthine derivatives.

Scheme 4: Synthetic pathway to xanthine derivatives.

Scheme 5: Synthesis of 8-(p-substituted) xanthine derivatives.
8-phenyl-1,3-dimethylxanthine derivatives were synthesized and reported. In this synthesis 5,6-diaminouracil (68) was used as the key intermediate. The intermediate was treated with a different substituted aldehyde (69) and methanol: acetic acid (4:1) results in the formation of benzylidene derivative (70), which further gets cyclized to form xanthine carboxylate ester (71), which on treatment with substituted amines at 80–100°C to yield (72-75) [32] (Scheme 11).

The fast, efficient synthesis of 6-Amino-5-carboxamidouracils as the predecessor for the 8-substituted xanthines was reported. In Procedure A: the 5,6-diaminouracils (76) were condensed with aldehydes, results in imine formation (77), following oxidative cyclisation resulted in 8-substituted xanthine derivatives (78), which is the most common route of xanthine synthesis. In Procedure B, the uracil (76) derivative was treated with carboxylic acid (80) and EDAC-HCl (1-ethyl-3-(3-dimethylaminopropyl)) carbodiimide hydrochloride (79) which lead to the formation of xanthine derivative (78). In Procedure-C, the 5,6-diaminouracils (76) were made to react with carboxylic acid but prior to this reaction the activation of the carboxylic acid to form carboxylic acid chloride was done, further leading to the formation of 6-amino-5-carboxamidouracil derivative (77) and then subsequent ring closure yield 8-substituted xanthines (73) [33] (Scheme 12).

The synthesis of 1,3-disubstituted-8-styrylxanthines under chemo and regioselective conditions was reported. The synthesis was achieved by using 6-aminouracil (83) as the starting material. The 6-aminouracil was alkylated at 3-position to form 6-amino-3-propyluracil (84), which undergo nitrosation (85) and reduction to yield 5,6-diamino-3-
propyl uracil (86). The obtained compound was condensed with EDCI and cinnamic acid to form 6-amino-3-propyl-5-styrylcarboxamide (87,88) and finally, cyclisation was achieved by using alkali to form the resultant xanthine derivative (89). All the synthesized compounds have shown good activity for both A1 and A2A adenosine receptors [34] (Scheme 13).

3.2. Xanthine-Annealed Synthesis. In xanthine-annealed synthesis, the upgradation of one more ring starting from the bicyclic xanthine scaffold produces several biologically important compounds with modified physiochemical properties. Though, xanthine-annealed synthesis is tedious but not widely used for the synthesis of xanthine derivatives. In this context, the synthesis of tetrahydropyrimido [2,1-f]...
purinediones by using a convergent approach was reported. The commercially available amines (91) were treated with 8-bromo-7-(3-chloropropyl)-1,3-dialkylxanthine (90) in presence of a base in DMF (dimethyl formamide) to form the substituted xanthine derivatives (92) [35] (Scheme 14).

Another contribution to this study is based on the synthesis of 8-Benzyl-substituted tetrahydropyrazino[2,1-f]purinediones was reported. The 1,3-dimethyl-8-hydroxymethylxanthine (93) was used as the starting material in this study. Primarily, position-7 of xanthine was alkylated...
Scheme 12: Synthesis of 8-substituted xanthine derivatives.

Scheme 13: 1,3-disubstituted 8-styrylxanthines.

Reagents: i. HMDS, (NH₄)₂SO₄, n-Pr-I, ii. NaNO₂, AcOH, iii. Na₂S₂O₄, NH₄OH, iv. C₉H₈O₂, CH₃OH, v. R-X, DMF, K₂CO₃, vi. KOH, CH₃OH.
with 1,2 dibromoethane. The hydroxy group present at the 8-position was then converted into the corresponding bromide to form the resulting purinedione derivative (95) which was further treated with different substituted benzylamines to afford the tetrahydropyrazino derivative (96) [36] (Scheme 15).

Another series based on xanthine annealed synthesis was reported. The N-9 benzyl substituted purinediones were synthesized from theophylline (97), which was oxidatively brominated to give the compound (98). Subsequently, 8-bromotheophylline has been alkylated at the N-7 position to obtain an 8-bromo-7-alkyltheophylline derivative (99).
Finally, condensation with appropriate amine leads to tricyclic xanthines (100) [37] (Scheme 16).

Moreover, 8-Substituted 1,3-dimethyltetrahydropyrazino [2,1-f] purinedione derivatives were reported as multitargeted drugs. Initially, the compound (101) was converted to the corresponding bromide to get compound (102). Furthermore, the compound was treated with appropriate amine (103) to afford tetrahydropyrazino derivatives (104) [38] (Scheme 17).

3.3. One-Pot Method. According to the emerging importance of xanthine and its derivatives. The development of a novel method for access to xanthine scaffold in less time, without using toxic chemicals, and improvement in yield is still in great demand. In this study, numerous functionalized xanthines were synthesized with better yield, without the use of toxic reagents, and in lower time. Based on the aforementioned information, a one-pot synthesis of xanthine was reported. The 5,6-diaminouracil (105) was chosen as the substrate. The substrate was refluxed with acetic anhydride in acetic acid to obtain compound (106) and heating of substrate with malononitrile gave compound (107) in good yield [39] (Scheme 18).

In addition, the synthesis of some 8-alkylmercaptocaffeine derivatives has been reported via a one-pot three-component reaction. The treatment of thiourea (109) with alkylbromide (108) and 8-bromocaffeine (110) yielded 8-alkylmercaptocaffeine derivative (111) in excellent yield [40] (Scheme 19).

Another one-pot synthesis of 8-xanthine derivatives was reported. The synthesis was done by treatment of 5,6-diaminouracil (112) with a simple aldehyde to form a xanthine derivative (113,114) through an imine intermediate (115). Furthermore, cyclisation of the intermediate yield xanthine derivative (116). All the synthesized compounds were observed for A2A adenosine receptor antagonist [41] (Scheme 20).

3.4. Miscellaneous Synthesis. Xanthines can also be used as a starting material for the large-scale manufacture of xanthine derivatives. Mainly the alteration at 1-, 3-, 7- and 8- in the
xanthine scaffold results in derivatives with numerous pharmacological activities. To discover numerous roles of xanthes, the examination of various methods used for the synthesis became an emerging topic of research. In this context, a novel series of 1,2,3-triazole-based xanthes were designed and synthesized. The compound (117) was treated with bromine to form an intermediate (118). The intermediate was then allowed to react with 1-bromo-2-butyne gave compound (119), subsequent interaction of this compound with propargyl bromide gave another purine intermediate (120) which on treatment with morpholine gave morpholinodione intermediate (121). Lastly, the

**Scheme 21:** Synthesis of 1,2,3-triazole-based xanthes.

i) chloroacetic acid, chloroacetamide or propyl chloroacetate, NaHCO₃ and DMF, reflux. ii) NaOH, H₂O, reflux, iii) propanol, dioxane, H₂SO₄, reflux.

**Scheme 22:** Synthesis of 3-benzyl-8-propylanthinyl-7-acetic acid, its ester, and amide.
Scheme 23: Schematic synthesis of xanthine derivatives.

Table 2: Reported potent compounds of xanthines and their targets.

| S. No. | Substituted xanthine derivative | Disease target | Potent compounds reported |
|--------|--------------------------------|---------------|--------------------------|
| 1      | 1,3,8- and 1,3,7,8-substituted xanthines derivatives [23] | A2B and A1 adenosine receptors | Compound 14q |
| 2      | 8(cyclopentyloxy) phenylxanthines derivatives [24] | A1 and A2 adenosine receptors | Compound 6a, Compound 12 |
| S. No. | Substituted xanthine derivative                                                                 | Disease target                                               | Potent compounds reported |
|-------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------|
| 3     | 8-(phenoxymethyl) xanthine and 8-(3-phenylpropyl) xanthine derivatives [25]                      | A2A adenosine receptor antagonistic properties               | ![Compound 6f](image)     |
| 4     | 8-(p-substituted-phenyl/benzyl) xanthines derivatives [26]                                       | A2A adenosine receptor                                       | ![Compound 4f](image)     |
| 5     | 1,3-diethyl-7-methyl-8-(phenoxymethyl)-xanthine and 1,3,7-trimethyl-8-(phenoxymethyl)-xanthine derivatives [27] | A1 and A2A adenosine receptor antagonists                    | ![Compound 4b](image)     |
| 6     | 8-(1-prop-2-ynyl-1H-pyrazol-4-yl)-xanthine derivatives [28]                                      | A2B adenosine receptor antagonists                           | ![Compound 36](image)     |
| S. No. | Substituted xanthine derivative | Disease target | Potent compounds reported |
|-------|--------------------------------|----------------|--------------------------|
| 7     | Tetrahydropyrazino-annelated theophylline derivatives [29] | Multi-targeted drugs with adenosine receptor (A1, A2A) and MAO-B antagonistic activity. | ![Image](image1.png) ![Image](image2.png) ![Image](image3.png) ![Image](image4.png) ![Image](image5.png) |
| 8     | 8-(2-nitroaryl) xanthines [30] | Human A2A adenosine receptor | ![Image](image6.png) | Compound 9e |
| S. No. | Substituted xanthine derivative                                                                 | Disease target               | Potent compounds reported |
|-------|------------------------------------------------------------------------------------------------|----------------------------|---------------------------|
| 9     | 8-(3-phenylpropyl) xanthines 8-(2-phenylethyl) xanthines and 8-(phenoxyethyl) xanthines [31]    | Adenosine A1 receptors      | ![Compound 3d](image)     |
|       |                                                                                                |                             | ![Compound 4d](image)     |
|       |                                                                                                |                             | ![Compound 5d](image)     |
| 10    | Carboxylate amides of 8-phenyl-1,3-dimethylxanthine [32]                                       | Adenosine A2A receptors     | ![Compound 13b](image)    |
|       |                                                                                                |                             | ![Compound 16a](image)    |
|       |                                                                                                |                             | ![Compound 16d](image)    |
| No. | Substituted xanthine derivative | Disease target | Potent compounds reported |
|-----|---------------------------------|----------------|--------------------------|
| 11  | 6-amino-5-carboxamidouracils [33] | —              | ![Chemical Structure](image1) |
| 12  | 1,3-substituted 8-styrylxanthines [34] | A1 and A2A adenosine receptors antagonist | ![Chemical Structure](image2) |
| 13  | Tetrahydropyrimido[2,1-f] purinediones derivatives [35] | A2B adenosine receptor antagonists | ![Chemical Structure](image3) |
| S. No. | Substituted xanthine derivative | Disease target | Potent compounds reported |
|-------|--------------------------------|----------------|---------------------------|
| 14    | 8-benzyltetrahydropyrazino [2,1-f] purinediones derivatives [36] | Dual-target-directed A1/A2A adenosine receptor antagonists | ![Compound 72](image1) |
|       |                                |                | ![Compound 36](image2)    |
| 15    | 1,3-dialkyl-substituted tetrahydropyrimido [1,2-f]purine-2,4-diones [37] | Human A2A adenosine receptor antagonists | ![Compound 9u](image3) |
|       |                                |                | ![Compound 10d](image4)   |
| 16    | 8-benzyl-substituted tetrahydropyrazino [2,1-f] purinediones [38] | Dual A1/A2A adenosine receptor antagonists | ![Compound 41](image5) |
|       |                                |                | ![Compound 57](image6)    |
| S. No. | Substituted xanthine derivative | Disease target | Potent compounds reported |
|-------|--------------------------------|----------------|--------------------------|
| 17    | Xanthine derivatives [39]      | Antimicrobial and antioxidant activities | ![Chemical Structure of Xanthine Derivatives](image1) |
| 18    | 8-alkylmercaptocaffeine derivatives [40] | — | ![Chemical Structure of 8-Alkylmercaptocaffeine Derivatives](image2) |
| 19    | 8-substituted xanthine derivatives [41] | A2A adenosine receptor antagonists | ![Chemical Structure of 8-Substituted Xanthine Derivatives](image3) |
| S. No. | Substituted xanthine derivative | Disease target | Potent compounds reported |
|-------|---------------------------------|----------------|----------------------------|
| 20    | 1,2,3-triazole-based xanthine derivatives [42] | Dipeptidyl peptidase-4 inhibitors | ![Image](7b) |
| 21    | 3-benzyl-8-propylxanthinyl-7-acetic acid [43] | — | ![Image](6e) |
addition of the 1,3-dipolar cycle of terminal alkyne gave the corresponding 1,2,3-triazoles (122,123) in good yield [42] (Scheme 21).

3-benzyl-8-propylxanthinyl-7-acetic acid and its derivatives were designed, synthesized, and reported. The compound (124) was taken as a lead compound. The lead compound was treated with chloroacetic acid, chloroacetamide, or propyl chloroacetate to form the target xanthine derivatives (125-127) [43] (Scheme 22).

Theophylline (128), 8-bromotheophylline (129), and theobromine (130) were reacted with various 2/3-chloro-N-phenylacetamides or their propanamide analogs to obtain the resultant xanthine derivatives (131-133). The synthesized compounds were biologically assessed for in vitro bronchodilator activity [44] (Scheme 23).

### 4. Reported Potent Compounds of Xanthines and Their Targets

Natural and synthetic compounds consisting of xanthine scaffold showed a variety of pharmacological activities. A large number of biologically active compounds were obtained by incorporating different substituents at different places in this ring [22]. A number of reported potent compounds of xanthines along with the therapeutic disease target are discussed (Table 2).

### 5. Conclusion

Our prime aim in writing this review paper is that the content presented in this review paper will be beneficial to the field and will provide great help to those researchers working on this scaffold. This review article provides a summary overview of the synthesis of xanthine structures. The development of novel, selective and efficient methods for the formation of xanthine ring starting from commercially available substrates is a pivotal target in the current organic synthesis. In this regard, the synthesis of xanthine derivatives by traube’s method is the most used approach. However, other approaches were also found attractive to researchers. The various synthetic procedures exemplified in this review paper may serve as a support system for the designing of new molecules with xanthine scaffold. We hope that the data compiled in this review paper could help the medicinal chemist in designing new active compounds from the modification of the already existing compounds in the search for novel drug leads.

### Abbreviations

| Abbreviation | Description                      |
|--------------|----------------------------------|
| DMF:         | Dimethylformamide                |
| SAR:         | Structural activity relationship  |
| A₁, A₂A, A₂B, A₃: | Adenosine receptor subtypes      |
Conflicts of Interest

The authors declare that they have no conflicts of interest that could appear to influence the work reported in this review article.

Acknowledgments

The authors are grateful to the Honorable Vice-Chancellor, Banasthali Vidyapith, Rajasthan, for providing essential facilities.

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