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Review

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Methods for the synthesis of xanthine-derived polycyclic fused systems

Abstract: Xanthines are a widely known group of alkaloids, commonly used as bronchodilators and psycho and cardiac stimulants. Most of their actions are principally connected with either antagonism of adenosine receptors or phosphodiesterase inhibition; nevertheless, other profiles of their biological activity – antiviral, antitumor or anticancer – are also known. Here, we present a review of the main synthetic methods to obtain xanthine-derived heterocyclic fused systems. The five-, six- or seven-membered heterocyclic ring is attached to the purine-2,6-dione core with one or two bridgehead (ring junction) nitrogen atoms. The biological activity profile of the individual heterocyclic systems is mentioned.

Keywords: adenosine receptor; heterocyclic fused systems; phosphodiesterase; purine-2,6-dione; xanthine.

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Introduction

The pyrimidine and purine ring systems undoubtedly belong to the most ubiquitous heterocycles in nature, as they represent the main structure of many biologically significant compounds, including nucleosides and nucleotides. Among numerous important compounds based on the structure of the purine, there is a group of natural xanthines, including caffeine, theobromine and theophylline. Xanthine derivatives exhibit a variety of physiological effects, such as positive inotropic and chronotropic effects on the heart, decreased airway resistance in the lung and respiratory stimulation, as well as significant behavioral effects on measures of locomotor activity, schedule-controlled behavior, drug self-administration, and learning and memory [1–4]. The respiratory-stimulant effects of xanthines seem to be mainly linked to the inhibition of phosphodiesterases, enzymes responsible for the hydrolytic inactivation of cyclic AMP and cyclic GMP [1, 5]. By contrast, it is suggested that the psychostimulant and cardiac effects of xanthines are principally connected with the antagonism of adenosine receptors, located both in the heart and brain [1, 4].

In recent years, many studies have been conducted in the direction of the potential use of synthetic xanthine derivatives, including polycyclic fused ring systems, as potent antagonists at various adenosine receptor subtypes [1–3, 6–9]. Compounds with this profile have been suggested to be useful as neuroprotective agents in diseases such as stroke, traumatic brain injury, Alzheimer's disease, Parkinson's disease, Huntington's disease and multiple sclerosis [8–11], cardioprotective agents in myocardial ischemia [12], as well as potential treatment of schizophrenia, epilepsy [10] or asthma [5]. Xanthines have also been suggested to be useful in diseases with etiology independent of adenosine receptors and phosphodiesterases, showing confirmed antiviral [13], antitumor and antimicrobial activity [7, 14]. Some of pyrimido[2,1-*f*]theophylline derivatives show potent affinity towards the 5-HT_{1A} receptor [15].

Here, we review the main methods of the synthesis of xanthine-derived heterocyclic fused systems. The five-, six- or seven-membered heterocyclic unit is attached to the xanthine core with one or two bridgehead (ring junction) nitrogen atoms (with retention of the three-coordinate neutral character of N). For the purpose of this article, all described compounds were divided into six groups depending on the peripheral side of the parent xanthine component, identified by a letter locant according to IUPAC rules [16] (Figure 1).

Chemistry

Group A

Group A includes tricyclic structures with a five- or six-membered heterocyclic ring fused to the *a*-bond of the

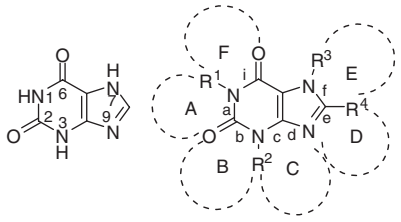


Figure 1 The structure of xanthine and its fused derivatives. Within the text R^1–R^4 are assigned to their position on the structure above, whereas the next substituents are numbered in the order of their appearance.

6-purinone system (Figure 1). Compounds of this series are classified to one of the following subgroups according to the structure and depending on the number and type of heteroatoms in the third ring:

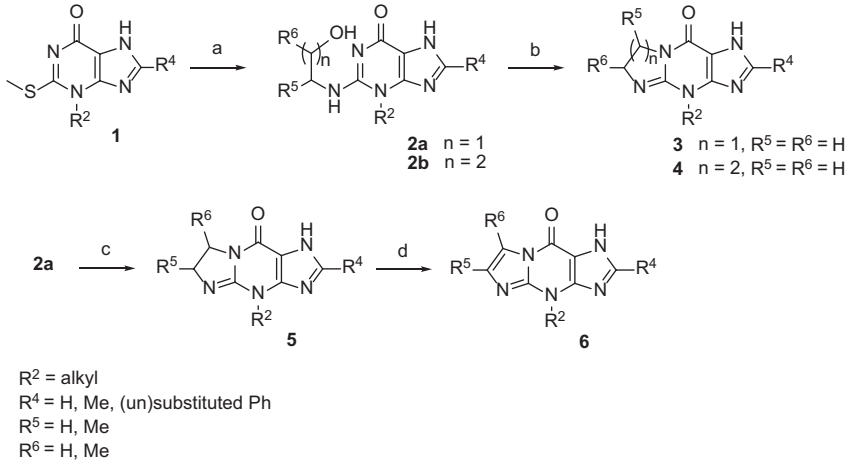
- imidazo[1,2-*a*]purinones and pyrimido[1,2-*a*]purinones,
- triazolo[1,5-*a*]purinones and triazolo[4,3-*a*]purinones,
- tetrazolo[1,5-*a*]purinones,
- oxazolo[3,2-*a*]purinones.

Imidazo[1,2-*a*]purinones and pyrimido[1,2-*a*]purinones One of the synthetic pathways leading to pyrimido or imidazo fused purinones is presented in Scheme 1. The starting material, 2-(methylthio)-1*H*-purin-6(7*H*)-one (**1**) is treated with aminoalcohol, (un)substituted 2-aminoethanol or 3-amino-1-propanol, affording the corresponding intermediates **2a** or **2b**. Cyclization of 2-aminoethanol derivatives **2a** is achieved by treatment with polyphosphoric acid (PPA) or phosphoryl chloride followed by oxidation of the resultant product **3** by manganese dioxide in the next step to give the desired 2-, 4-, 6- or 7-substituted 1*H*-imidazo[1,2-*a*]purin-9(4*H*)-ones **4** [17]. In the alternative method, thionyl chloride is used for cyclization of **2**, forming the final 6,7-dihydro-1*H*-imidazo[1,2-*a*]purin-9(4*H*)-ones **5** and 4,6,7,8-tetrahydro-pyrimido[1,2-*a*]purin-10(1*H*)-ones **6** [18].

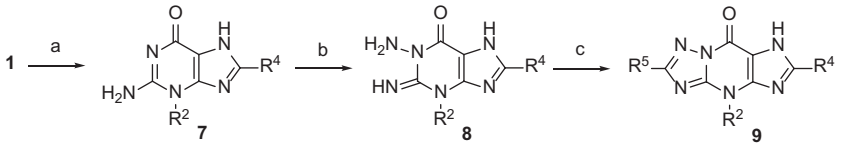
Xanthine derivatives with a structure based on the imidazo[1,2-*a*]purinone scaffold have been tested as inhibitors of phosphodiesterases, showing selective but moderate affinity towards phosphodiesterase 4 (PDE4) in the micromolar range [18].

Triazolo[1,5-*a*]purinones and triazolo[4,3-*a*]purinones The first group of synthetic methods leading to triazolo[1,5-*a*]purin-9-ones **9** is based on the addition of the third heterocyclic ring to the existing purinone structure (Scheme 2). The nucleophilic substitution of 2-methylthio fragment of the starting purinone 1 with an amine group results in the guanine derivative **7**, which is then allowed to react with hydroxylamine-*O*-sulfonic acid (HAOS) in sodium hydroxide. Cyclization of the obtained compound **8** is achieved by treatment with either ortho ester or with aldehyde and diethyl azodicarboxylate (DEAD) in DMF to yield the corresponding 1*H*-[1,2,4]triazolo[1,5-*a*]purin-9(4*H*)-ones **9** [17].

Another method of synthesis of **9** is based on the cyclocondensation of the obtained triazolo[1,5-*a*]pyrimidin-7-one system (Scheme 3) [19]. The reaction between aminoguanidine **10** and carboxylic acid gives 5-amino-1,2,4-triazole **11**, which is then treated with alkyl cyanoacetate to afford a bicyclic structure of 5-amino-[1,2,4]triazolo[1,5-*a*]pyrimidin-7(4*H*)-one **12**. Electrophilic substitution of **12** with sodium nitrite, followed by reduction of the 6-nitroso group using $Na_2S_2O_4$ (or a similar reducing agent) and then acylation with appropriate carboxylic acid results in the formation of the key 5-amino bicyclic intermediate **13**. Cyclization of this compound with sodium hydroxide gives the target triazolopurinone **9**.

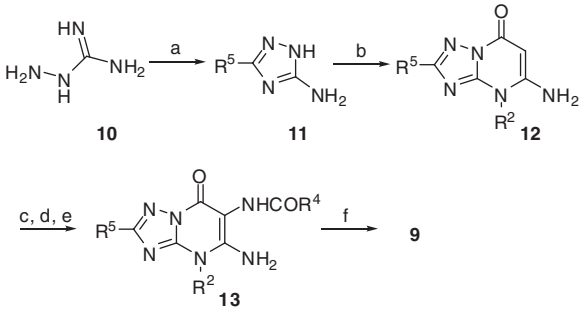


Scheme 1 Reagents: (a) $H_2NCH(R^5)CH(R^6)OH$, 2-amino-1-ethanol/3-amino-1-propanol, (b) $SOCl_2$, (c) PPA or POCl, (d) MnO_2.



R^2 = Me
R^4 = H, Me
R^5 = H, Me, Ph

Scheme 2 Reagents: (a) NH_3, (b) HAOS, NaOH, (c) $R^5C(OEt)_3$ or R^5CHO, DEAD, DMF.

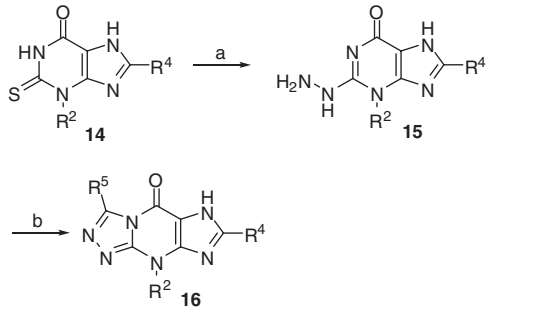


R^2 = alkyl, benzyl
R^4 = alkyl, aryl, heteroaryl, heterocycloalkyl
R^5 = alkyl, aryl, heteroaryl, heterocycloalkyl

Scheme 3 Reagents: (a) R^5COOH, (b) alkyl cyanoacetate, (c) $NaNO_2$, H^+, (d) $Na_2S_2O_4$, NH_3 aq., (e) R^4COOH, (F) NaOH.

Screening tests in the group of triazolopurinone derivatives **9**, conducted to find selectivity for adenosine receptors, have pointed to a few strong antagonists with nanomolar affinity to human A_1 receptors with over 300-fold greater selectivity for A_1 than A_{2A} receptors [19].

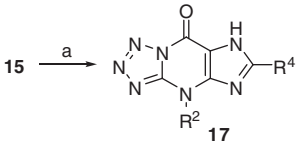
The synthesis of another series of triazolo fused derivatives, triazolo[4,3-*a*]purin-5-ones **16**, starts from 2-thioxanthines (Scheme 4) [20, 21]. Treatment of **14** with 50% aqueous hydrazine affords the 2-hydrazinylpurine-6-ones **15**, which are then allowed to react with appropriate ortho esters giving the substituted 6,9-dihydro-5*H*-[1,2,4]triazolo[4,3-*a*]purin-5-ones **16**.



R^2 = alkyl
R^4 = alkyl, aryl, halogen, heterocycloalkyl, heteroaryl,
R^5 = acyl, alkyl, amine, aryl, heterocycloalkyl, heteroaryl, thioacyl

Scheme 4 Reagents: (a) NH_2NH_2, H_2O, (b) $R^5C(OC_2H_5)_3$.

Tetrazolo[1,5-*a*]purinones The convenient starting material for the synthesis of tetrazolo[1,5-*a*]purinones is hydrazino-substituted derivative **15** (Scheme 5). Treatment of 2-hydrazinopurin-6-ones with nitrous acid affords 4,7-dihydro-1*H*-tetrazolo[1,5-*a*]purin-8(2*H*)-ones **17** [20, 21].



R^2 = alkyl
R^4 = alkyl, halogen

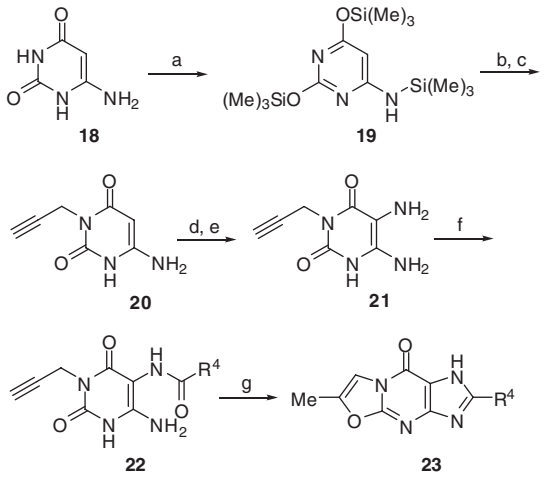
Scheme 5 Reagents: (a) $NaNO_2$, HCl, H_2O.

Oxazolo[3,2-*a*]purinones In the first step of synthesis of oxazolo[3,2-*a*]purin-9-one derivatives, 6-aminouracil (**18**) is silylated with hexamethyldisilazane (HMDS) (Scheme 6). Subsequent reaction with propargyl bromide, catalyzed by iodine, yields 3-propargyl-6-aminouracil (**20**), which is nitrosated at the 5-position by treatment with nitrous acid followed by reduction of the intermediate nitroso compound to the 5,6-diaminouracil derivative **21** [22]. The reaction with carboxylic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) gives compound **22**, which in the next step is treated with polyphosphoric acid trimethylsilyl ester (PPSE) to obtain the final oxazolo[3,2-*a*]purin-9(1*H*)-ones **23** [23].

In the A_1 and A_{2A} adenosine receptor binding studies at rat brain membranes, oxazolo[3,2-*a*]purinones showed antagonism against adenosine receptors with selectivity over 26-fold greater for A_1 than A_{2A}; however, their affinity was demonstrated only in the micromolar range [23].

Group B

This group contains tricyclic and tetracyclic fused systems created by the attachment of an additional ring(s) to the 6-purinone core, using carbon *C*2 and nitrogen *N*3 atoms as ring junctions (group B, Figure 1). Compounds in this group belong to one of the following three classes according to their structure:



Scheme 6 Reagents: (a) HMDS, $(NH_4)_2SO_4$, (b) $CHCCH_2Br$, I_2, (c) $NaHCO_3$ aq., (d) $NaNO_2$, H^+, (e) $Na_2S_2O_4$, NH_3 aq., (f) R^4COOH, EDC, (g) PPSE.

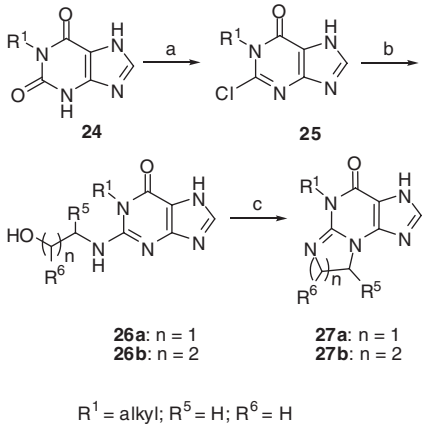
- imidazo[2,1-*b*]purinones and pyrimido[2,1-*b*]purinones,
- tetracyclic imidazo[2,1-*b*]purinones,
- triazolo[5,1-*b*]purinones.

Imidazo[2,1-*b*]purinones and pyrimido[2,1-*b*]purinones A general approach to the synthesis of the imidazo and pyrimido[2,1-*b*]purinones is presented in Scheme 7. The starting material, 1-substituted xanthine **24**, is treated with phosphoryl chloride to form the chloropurinone **25**, which is then allowed to react with an appropriate (un)substituted aminoalcohol to give the corresponding intermediates 2-(hydroxyalkylamino)purinones **26a**, **26b**. The final 7,8-dihydro-3*H*-imidazo[2,1-*b*]purin-4(5*H*)-one **27a** and 5,7,8,9-tetrahydropyrimido[2,1-*b*]purin-4(3*H*)-one **27b** are obtained by cyclocondensation of **26a** and **26b** by means of thionyl chloride [18, 24].

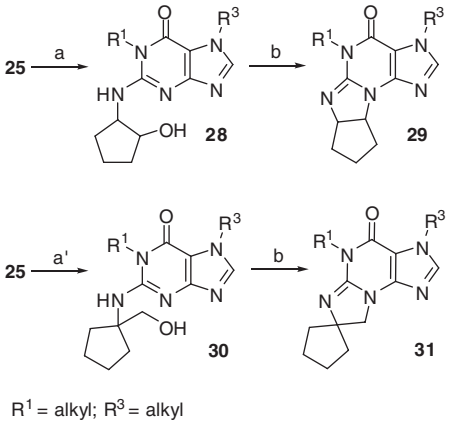
Tetracyclic imidazo[2,1-*b*]purinones An interesting example of application of the method discussed above is the preparation of tetracyclic purinone derivatives including spiro compounds (Scheme 8) [25–27]. To add the third and the fourth ring, 2-chloropurinone **25** is treated with 2-aminocyclopentanol or 1-amino-1-cyclopentanemethanol in *N*,*N*-diisopropylethylamine (DIPEA) and *N*-methyl-2-pyrrolidinone (NMP) to yield structures **28** and **30**. Cyclization in both pathways is conducted by the use of thionyl chloride leading to final hexahydrocyclopenta[*d*]imidazo[2,1-*b*]- and 5′,8′-dihydrospirocyclopentane-1,7′-imidazo[2,1-*b*]purinones **29** and **31**, respectively.

Xanthine derivatives with a structure based on the imidazo[2,1-*b*]- or pyrimido[2,1-*b*]purinone scaffold have been tested as inhibitors of phosphodiesterases [18] and showed selective micromolar affinity towards PDE4. Some of them exhibit single digit nanomolar potency and isozyme selectivity to PDE5, which is greater than those for the approved drugs sildenafil, vardenafil and tadalafil [28]. Tetracyclic purinones show selective, high-binding affinity towards PDE1 in the nanomolar range [25].

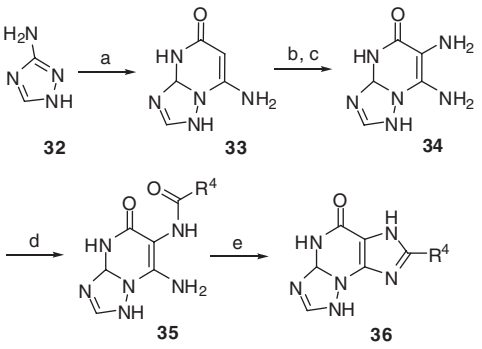
Triazolo[5,1-*b*]purinones To obtain triazolo[5,1-*b*]purinone derivatives, 3-amino-1,2,4-triazole (**32**) is first reacted with ethyl cyanoacetate (Scheme 9). The resultant 7-amino[1,2,4]triazolo[1,5-*a*]pyrimidinone (**33**) is in the next step nitrosated by treatment with isoamyl nitrite and the intermediate nitroso compound is then reduced to the diamino pyrimidinone intermediate **34**. Acylation of **34** with carboxylic acid chloride followed by cyclization of the resultant compound **35** with sodium and calcium



Scheme 7 Reagents: (a) $POCl_3$, (b) (un)substituted 2-amino-1-ethanol/3-amino-1-propanol, pyridine, (c) $SOCl_2$, CH_2Cl_2.



Scheme 8 Reagents: (a) 2-amino-cyclopentanol, DIPEA, NMP, (b) $SOCl_2$, (a′) 1-amino-1-cyclopentanemethanol, DIPEA, NMP.



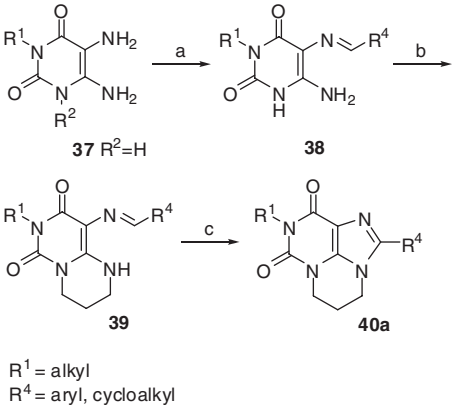
Scheme 9 Reagents: (a) ethyl cyanoacetate, (b) isoamyl nitrite, (c) $Na_2S_2O_4$, NH_3 aq., (d) R^4COCl, (e) NaOH, $Ca(OH)_2$.

hydroxide gives target 3a,4-dihydro-1*H*-[1,2,4]triazolo[5,1-*b*]purin-5(6*H*)-ones **36** [29].

Purinone derivatives with a structure of **36** have been tested as antagonists of adenosine receptors, showing selective high affinity towards human A_1 receptors and A_3 receptors in the nanomolar range [29].

Group C

Pyrimido[1,2,3-*cd*]purinediones and diazepino[1,2,3-*cd*]purinediones This group collects together compounds with an additional six- or seven-membered heterocyclic ring created partially by bonds *c* and *d* of the 2,6-purinedione core, with *N*3 and *N*9 atoms at ring junctions (Figure 1). One of the synthetic methods leading to this type of structures is presented in Scheme 10. The starting material, 5,6-diamino-3-substituted uracil **37**, is treated with an appropriate aldehyde, and the resultant intermediate **38** is then converted to the pyrimido[1,6-*a*]



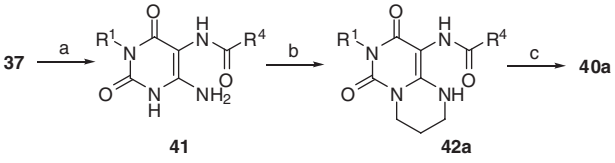
Scheme 10 Reagents: (a) R^2CHO, (b) DMF, K_2CO_3, $Br(CH_2)_3Br$, (c) $SOCl_2$.

pyrimidine-6,8-dione derivative **39** by reaction with 1,3-dibromopropane. The final ring closure is achieved oxidatively with thionyl chloride as reagent and solvent, to give 5,6-dihydropyrimido[1,2,3-*cd*]purine-8,10(4*H*,9*H*)-dione **40a** [30].

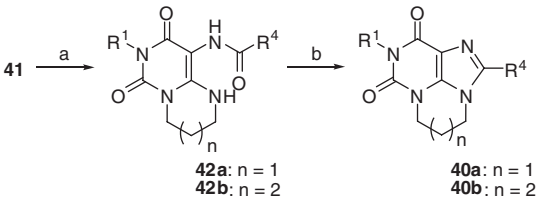
An alternative procedure for preparation of tricyclic compounds **40a** has been explored (Scheme 11). The 5,6-diaminouracil derivative **37** is reacted with carboxylic acid and the product **41** is then converted to the bicyclic compound **42a** by reaction with 1,3-dibromopropane, in analogy to the preparation of the amide derivatives **39**. The final ring formation is achieved by the reaction with hexamethyldisilazane to form the target 5,6-dihydropyrimido[1,2,3-*cd*]purine-8,10(4*H*,9*H*)-dione **40a** [30].

For formation of the final ring a microwave oven can be used as well (Scheme 12); this modification has been described for preparation of both pyrimido[1,2,3-*cd*]- and diazepino[1,2,3-*cd*]purinediones [31]. 6-Aminouracil derivative **41** is treated with α,ω-dibromoalkane (1,3-dibromopropane or 1,4-dibromobutane) affording intermediates **42a** or **42b**, respectively. Compounds **42a** and **42b** are cyclized by treatment with HMDS in the microwave oven, which yields the respective 5,6-dihydropyrimido[1,2,3-*cd*]purine-8,10(4*H*,9*H*)-dione **40a** and 6,7-dihydro-4*H*-[1,3]diazepino[1,2,3-*cd*]purine-9,11(5*H*,10*H*)-dione **40b**.

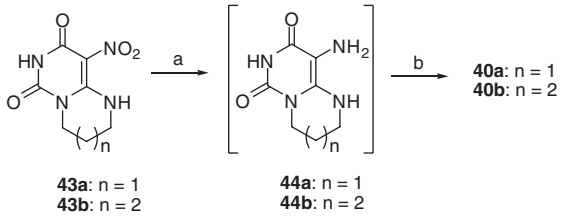
Another short, two-step method leading to pyrimido or diazepino fused purinediones is presented in Scheme 13. The starting nitropyrimidines **43a** or **43b** are



Scheme 11 Reagents: (a) R^4COOH, (b) DMF, K_2CO_3, $Br(CH_2)_3Br$, (c) HMDS.



Scheme 12 Reagents: (a) DMF, K_2CO_3, $Br(CH_2)_nBr$, (b) HMDS, THF, MW.



Scheme 13 Reagents: (a) Pd/C, H_2/H_2O, (b) $HC(OEt)_3$.

hydrogenated over palladium on carbon and the obtained diamines **44a**, **44b** are then treated with ethyl orthoformate to form the corresponding condensed compounds **40a** or **40b**, respectively [18].

Preliminary radioligand binding studies have indicated that the substituted pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones exhibit high, nanomolar concentration affinity and selectivity for the A_1 adenosine receptor [32]. These compounds have also been tested as inhibitors of phosphodiesterases, but showed no activity against PDE1, PDE3 and PDE4 [18].

Group D

Group D contains tricyclic structures with a five- or six-membered heterocyclic ring fused through the adjacent *C*8 and *N*9 atoms of the 2,6-purinedione core (Figure 1). Depending on the attached ring, such compounds are divided into two groups:

- triazolo[3,4-*e*]purinediones,
- triazino[3,4-*e*]purinetriones.

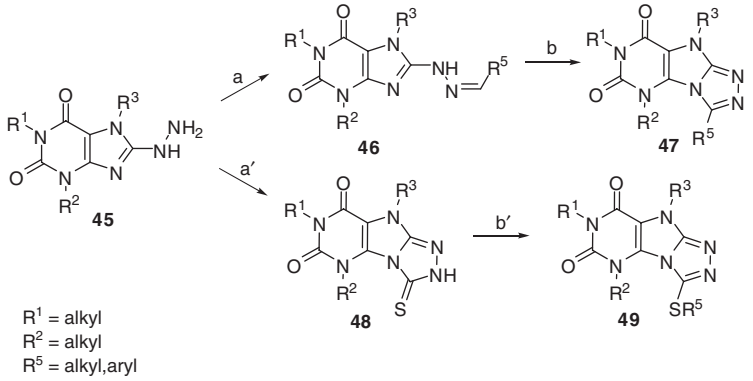
Triazolo[3,4-*e*]purinediones The general methods of the synthesis of triazolo[3,4-*e*]purinediones are presented in Scheme 14. A convenient starting material in both pathways is substituted 8-hydrazinoxanthine **45.** Condensation of **45** with appropriate aldehydes in boiling ethanol yields the 8-(arylidenehydrazino)purinediones **46**, that are cyclized using bromine in the presence of anhydrous sodium carbonate, giving the final 5*H*-[1,2,4]triazolo[3,4-*e*]purine-6,8(7*H*,9*H*)-diones **47**. By contrast, refluxing **45** with carbon disulfide in the presence of sodium hydroxide leads to a tricyclic xanthine derivative with a thioxo substituent at the third ring. Alkylation of **48** with different alkyl halides gives the corresponding 3-alkylthio- or 3-arylthio-5*H*-[1,2,4]triazolo[3,4-*e*]purine-6,8(7*H*,9*H*)-diones **49** [14].

Triazino[3,4-*e*]purinetriones The target tricyclic triazino[3,4-*e*]purine-4,7,9-triones are prepared following the synthetic pathways depicted in Scheme 15. In first step, the 8-aminoxanthine derivative **50** is converted into diazonium salt, which is then treated with an alkyl cyanide in dry pyridine to give 8-substituted 2,6-purinediones **52**. Heating **52** in ethanol under reflux results in intramolecular cyclocondensation and leads to 4-imino-6,8-dihydro-[1,2,4]triazino[3,4-*e*]purine-7,9(1*H*,4*H*)-dione (**53**), which is subsequently hydrolyzed by treatment with hydrochloric acid to afford [1,2,4]triazino[3,4-*e*]purine-4,7,9(1*H*,6*H*,8*H*)-triones **54** [14].

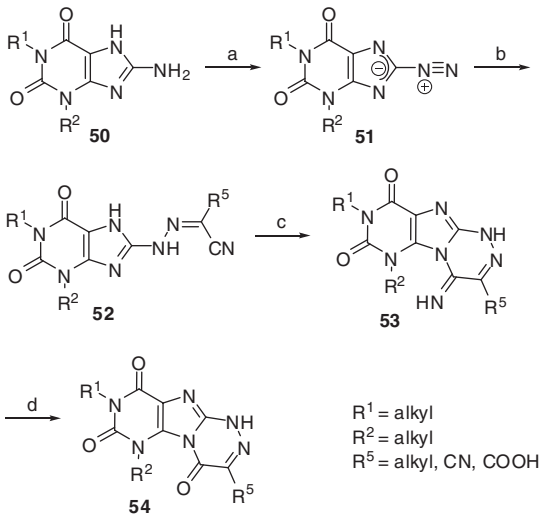
Compounds fused with a triazine or triazole ring to the *e*-bond of the 2,6-purinedione system (**47–49**, **53**, **54**) have been tested to determine their potential antitumor activity. Among this series, only 4-imino-6,8-dihydro-[1,2,4]triazino[3,4-*e*]purine-7,9(1*H*,4*H*)-diones **53** show promising activity against the breast MCF-7 cell line, reducing the growth of breast cell line to <32% [14].

Group E

This group comprises tricyclic compounds with an additional five-, six- or seven- membered ring fused to the *f*-bond of the 2,6-purinedione system (Figure 1). Compounds of this series are classified to one of the following



Scheme 14 Reagents: (a) R^5CHO, EtOH, T, (b) Br_2, Na_2CO_3, (a′) CS_2, NaOH, (b′) R^5X, K_2CO_3.

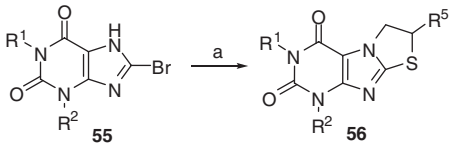


Scheme 15 Reagents: (a) $NaNO_2$, HCl, (b) $CH_2(R^5)CN$, pyridine, (c) EtOH, T, (d) HCl.

subgroups according to the number and type of heteroatoms in the third ring:

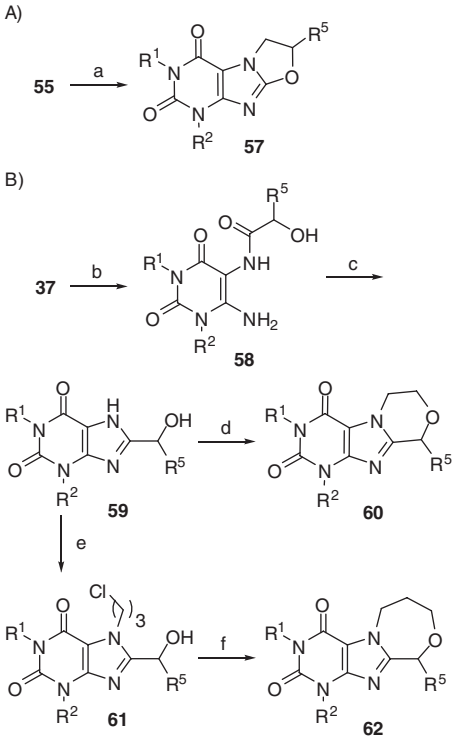
- thiazolo[3,2-*f*]purinediones,
- oxazolo[3,2-*f*]purinediones, oxazino[4,3-*f*]purinediones and oxazepino[4,3-*f*]purinediones,
- pyrrolo[1,2-*f*]purinediones and pyrido[1,2-*f*]purinediones,
- imidazo[1,2-*f*]purinediones, pyrimido[1,2-*f*]purinediones and diazepino[1,2-*f*]purinediones,
- imidazo[1,2-*f*]purinetriones and pyrimido[1,2-*f*]purinetriones,
- pyrazino[1,2-*f*]purinediones,
- triazolo[4,3-*f*]purinediones.

Thiazolo[3,2-*f*]purinediones The general synthetic pathway leading to thiazolo[3,2-*f*]purinedione derivatives is presented in Scheme 16. In this short, one-step method the starting material, the 1,3-substituted 8-bromoxanthine **55**, is treated with 2-(un)substituted thiirane under basic conditions, giving the final 6,7-dihydrothiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione **56** [33].



Scheme 16 Reagents: (a) 2-(un)substituted thiirane, KOH.

Oxazolo[3,2-*f*]purinediones, oxazino[4,3-*f*]purinediones and oxazepino[4,3-*f*]purinediones Convenient methods for synthesis of 1,3-dialkylxanthine derivatives with fused oxazole, oxazine and oxazepine rings are presented in Scheme 17. Target 6,7-dihydrooxazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-diones **57** are prepared by the reaction of 8-bromopurinedione **55** with oxiranes in pyridine (Scheme 17A) [34, 35]. The starting material for the syntheses of oxazino[4,3-*f*]purinediones **60** and oxazepino[4,3-*f*]purinediones **62** is 8-hydroxyalkyl-substituted xanthine **59**, obtained by melting of 5,6-diaminouracil **37** with a hydroxy acid followed by dehydration of the resulting 6-amino-5-(hydroxyacetamido)uracil (**58**) in an alkaline medium (Scheme 17B) [35]. The intermediate product **59** is cyclized in a catalytic two-phase reaction with 1,2-dibromoethane in the presence of K_2CO_3 and benzyltriethylammonium chloride (TEBA) as a phase-transfer catalyst to form the final 6,7-dihydro-1*H*-[1,4]oxazino[4,3-*f*]purine-2,4(3*H*,9*H*)-dione **60**. By contrast, cyclization of **59** to the final, oxazepine ring-containing derivative **62** requires a two-step reaction. First, 7-(3-chloropropyl)-8-hydroxyalkyl-substituted purinedione **61** is obtained by reaction of **59** with 1-bromo-3-chloropropane under the catalytic



Scheme 17 Reagents: (a) 2-(un)substituted oxirane, pyridine, (b) $R^5CH(OH)COOH$, T, (c) NaOH, (d) $Br(CH_2)_2Br$, K_2CO_3, TEBA, (e) $Br(CH_2)_3Cl$, K_2CO_3, TEBA, (f) KOH.

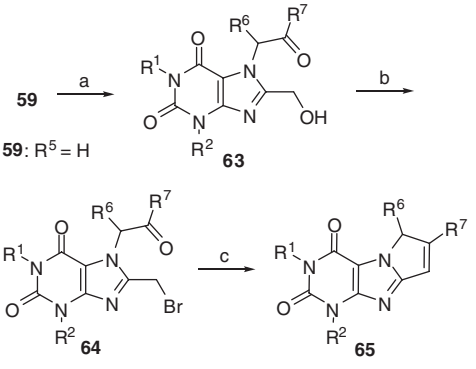
two-phase conditions mentioned above. The ring closure condensation is then carried out in an alcoholic solution of KOH, yielding 6,7,8,10-tetrahydro-[1,4]oxazepino[4,3-*f*] purine-2,4(1*H*,3*H*)-dione **62.**

Tricyclic oxazolo[2,3-*f*]purinediones with a structure of **57** are adenosine receptor ligands with moderate affinity mostly exhibiting selectivity for A_{2A} versus A_1 receptors. The most potent A_{2A} ligands demonstrate a K_i value of 0.998 μM towards rat A_{2A} receptors [34].

Pyrrolo[1,2-*f*]- and pyrido[1,2-*f*]purinediones The synthesis of 1*H*-pyrrolo[1,2-*f*]purine-2,4(3*H*,6*H*)-diones **65** requires the conversion of compounds **59** (Scheme 18) into 8-bromomethyl-7-oxoalkylxanthines **64** through intermediary of **63**. To obtain the pyrrole fused xanthines **65**, the reaction of **64** with triphenylphosphine and subsequent intramolecular Wittig cyclization of the obtained phosphonium salt in the presence of sodium methoxide are used [36].

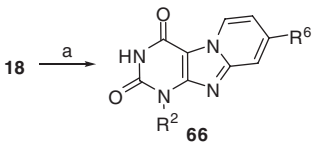
The pyrido[1,2-*f*]purine-2,4(1*H*,3*H*)-dione derivatives **66** are synthesized in a short, two-step one-pot reaction, presented in Scheme 19 [37]. The synthetic procedure includes the treatment of the 6-aminouracil derivative **18** with *N*-bromosuccinimide (NBS) in acetonitrile to generate the intermediate 5,5-dibromo-6-imino derivative, not isolated but treated *in situ* with various 4-substituted pyridines to afford the target compounds **66.**

Compounds including the pyrrole or pyridine ring fused to the *f*-bond of the 2,6-purinedione system have been evaluated in radioligand binding assays to determine their affinities for human A_1, A_{2A} and A_3 adenosine receptors. Both types of xanthine derivatives are active towards the adenosine A_3 receptor subtype with K_i values in the low nanomolar concentration range of 3.5–200 nM [36, 37].



R^1 = alkyl; R^2 = benzyl; R^6 = alkyl
R^7 = alkyl, aryl, cycloalkyl

Scheme 18 Reagents: (a) α-halo-ketone, K_2CO_3, DMF, (b) PBr_3, benzene, (c) 1. PPh_3, benzene, 2. CH_3ONa.



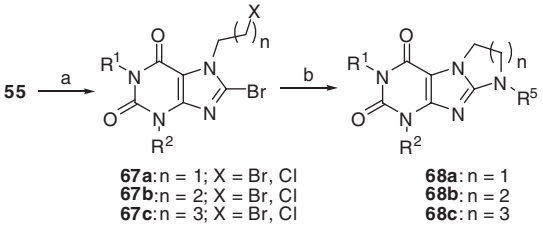
R^2 = benzyl; R^6 = alkyl, aryl, OMe

Scheme 19 Reagents: (a) NBS, CH_3CN, 4-substituted pyridine.

Imidazo[1,2-*f*]purinediones, pyrimido[1,2-*f*]purinediones and diazepino[1,2-*f*]purinediones The synthesis of tricyclic systems containing perhydroimidazole, pyrimidine or diazepine ring fused to 2,6-purinedione core with *C*8 and *N*7 atoms as ring junctions can be accomplished as shown in Scheme 20. The starting 1,3-substituted-8-bromoxanthine **55** is treated with α,ω-dibromoalkane giving intermediate 7-(ω-bromoalkyl) purinediones **67a–c**. The final cyclization is achieved by refluxing **67a–c** with appropriate amines, which leads to 7,8-dihydro-1*H*-imidazo[1,2-*f*]purine-2,4(3*H*,6*H*)-diones **68a**, 6,7,8,9-tetrahydropyrimido[1,2-*f*]purine-2,4 (1*H*,3*H*)-diones **68b** and 7,8,9,10-tetrahydro-1*H*-[1,3]diazepino[1,2-*f*] purine-2,4(3*H*,6*H*)-diones **68c** [38–41].

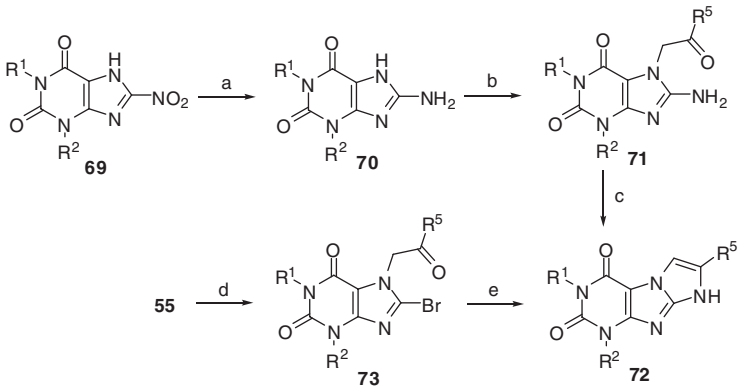
The obtained compounds have been evaluated for their affinity to rat adenosine A_1 and A_{2A} receptors. Selected compounds were additionally investigated for affinity to the human A_1, A_{2A}, A_{2B} and A_3 receptor subtypes. The results of the radioligand binding assays at adenosine A_1 and A_{2A} receptors show that the compounds bind to the adenosine A_{2A} receptor at micromolar or submicromolar concentrations; a fused pyrimidine ring was beneficial for A_{2A} affinity. The most potent A_{2A} ligands demonstrated K_i values of 0.31 mM towards human A_{2A} and 0.33 mM towards rat A_{2A} receptors [38–41].

Another group of synthetic methods leading to tricyclic imidazo fused xanthines is presented in Scheme 21. The first step of synthesis leading to 1*H*-imidazo[1,2-*f*]purine-2,4(3*H*,8*H*)-dione derivatives **72** starts from 1,3-dialkyl-8-nitroxanthine **69**, which is reduced by treatment with



R^1 = alkyl; R^2 = alkyl
R^5 = alkyl, aryl, cycloalkyl, cycloalkanol, halogenoaryl

Scheme 20 Reagents: (a) $Br(CH_2)_{n+1}X$, TEBA, K_2CO_3, acetone, (b) RNH_2, T.



R^1 = alkyl; R^2 = benzyl; R^5 = alkyl, aryl

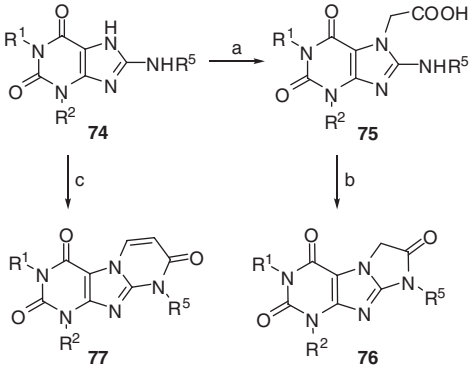
Scheme 21 Reagents: (a) NH_2NH_2, Pd/C, CH_3OH, (b) α-halogeno-ketone, K_2CO_3, DMF, (c) CH_3COOH, (d) α-Br-acetoketone, K_2CO_3, DMF, (e) NH_3, EtOH.

hydrazine and 10% Pd/C in methanol to furnish intermediates **70**. Compounds **70** are then alkylated at *N*7-position by treatment with α-bromoketone to obtain 8-amino-7-oxoalkylxanthines **71**. The imidazole ring closure is performed by refluxing **71** in acetic acid to yield the final tricycles **72** [42]. An alternative group of methods begins with alkylation of 1,3-dialkyl-8-bromoxanthine **55** at *N*7-position in a manner indicated above, followed by cyclization into 1*H*-imidazo[1,2-*f*]purine-2,4(3*H*,8*H*)-diones **72** by reaction with liquid ammonia [42].

1*H*-Imidazo[1,2-*f*]purine-2,4(3*H*,8*H*)-dione derivatives have been examined as antagonists of adenosine receptors and showed selective high nanomolar affinity towards human A_3 receptors [43]. Compounds with this structure have also been tested as ligands of 5-HT_{1A}, 5-HT_{2A} and D_2 receptors showing selective, potent affinity to 5-HT_{1A} receptor with a K_i value of the nanomolar range [15].

Imidazo[1,2-*f*]purinetriones and pyrimido[1,2-*f*]purinetriones The first step in the synthesis of 1*H*-imidazo[1,2-*f*]purine-2,4,7(3*H*,6*H*,8*H*)-triones **76** is *N*7-alkylation of 8-(un)substituted amino xanthine **74** with 2-bromoacetic acid in anhydrous DMF (Scheme 22). Intramolecular condensation of 2-(8-amino-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetic acid **75** is carried out by refluxing in acetic anhydride [43]. The second series, pyrimido[1,2-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-triones **77**, can be obtained directly in the reaction of **74** with ethyl 2,3-dibromopropanoate, as a result of one-step substitution and cyclocondensation [44].

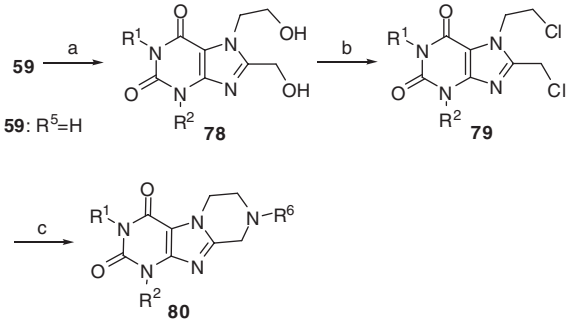
Pyrazino[1,2-*f*]purinediones In the synthesis of target pyrazino[1,2-*f*]purinedione derivatives, 1,3-dialkyl-8-hydroxymethylxanthine **59** is first *N*-alkylated by



R^1 = alkyl; R^2 = alkyl; R^5 = alkyl

Scheme 22 Reagents: (a) $CH_2(Br)COOH$, DMF, (b) $(CH_3CO)_2O$, (c) $BrCH_2CH(Br)COOEt$.

2-chloroethanol (Scheme 23). The product, dihydroxy compound **78**, is subsequently chlorinated by treatment with thionyl chloride, which leads to 7-(2-chloroethyl)-8-(chloromethyl)purinedione 7**9**. The



R^1 = alkyl; R^2 = alkyl; R^6 = alkyl, aryl, cycloalkyl

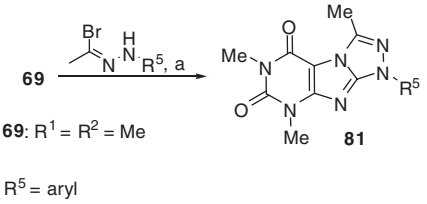
Scheme 23 Reagents: (a) $ClCH_2CH_2OH$, (b) $SOCl_2$, (c) H_2NR^6, T.

final cyclocondensation of **79** is achieved by refluxing with an appropriate amine, resulting in final 6,7,8,9-tetrahydropyrazino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione **80** [45].

Xanthine derivatives with a structure based on the tetrahydropyrazino[1,2-*f*]purinedione core have been tested as antagonists of adenosine receptors, showing micromolar affinity and selectivity for the A_1 adenosine receptor [45].

Triazolo[4,3-*f*]purinediones 3-Methyl-1*H*-[1,2,4]triazolo[4,3-*f*]purine-5,7(6*H*,8*H*)-dione derivatives **81** can be prepared by a cycloaddition reaction between a 1,3-dialkyl-8-nitroxanthine derivative and the *N*-(2-bromo-4-substituted)acetohydrazonoyl bromide (Scheme 24) [46].

All compounds **81** are completely inactive at all four adenosine receptor subtypes independently of their substitution pattern [46].



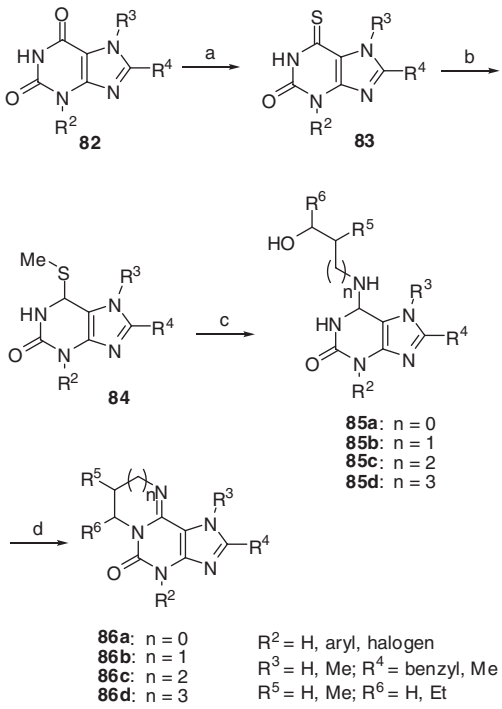
Scheme 24 Reagents: (a) Et_3N, dioxane.

Group F

The last group contains compounds with an additional five-, six-, seven- or eight-membered heterocyclic unit fused to the *i*-bond of the 2-purinone system (Figure 1). Compounds of this series are collected into one of the following subgroups:

- imidazo[1,2-*i*]purinones, pyrimido[1,2-*i*]purinones, diazepino[1,2-*i*]purinones and diazocino[1,2-*i*]purinones,
- tetrazolo[1,5-*i*]purinones.

Imidazo[1,2-*i*]purinones, pyrimido[1,2-*i*]purinones, diazepino[1,2-*i*]purinones and diazocino[1,2-*i*]purinones The first group of synthetic methods leading to purinone derivatives with an additional five-, six-, seven-, or eight-membered ring containing two atoms of nitrogen is presented in Scheme 25. In the first step, 3,7-substituted purinones **82** are treated with phosphorus pentasulfide to give the required 6-thioxanthine **83**. The subsequent reaction with methyl iodide in the presence of sodium

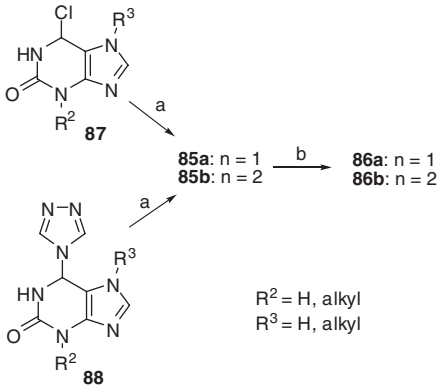


Scheme 25 Reagents: (a) P_2S_5, pyridine, (b) CH_3I, NaOH/EtOH, (c) 2-amino-butan/propan-1-ol, DMSO, (d) $SOCl_2$.

hydroxide gives *S*-methyl derivatives, which are allowed to react with an appropriate aminoalcohol leading to intermediate products **85a–d**. Final cyclization is performed by treatment with thionyl chloride, which gives the final 7,8-dihydro-1*H*-imidazo[1,2-*i*]purin-5(4*H*)-ones **86a**, 4,7,8,9-tetrahydropyrimido[1,2-*i*]purin-5(1*H*)-ones **86b**, 7,8,9,10-tetrahydro-1*H*-[1,3]diazepino[1,2-*i*]purin-5(4*H*)-ones **86c** or 4,7,8,9,10,11-hexahydro-[1,3]diazocino[1,2-*i*]purin-5(1*H*)-ones **86d** [47].

An alternative method of synthesis of imidazo[1,2-*i*]- and pyrimido[1,2-*i*]purin-5-ones **86a**,**b** is based on the reaction between either 6-chloro-3,7-disubstituted purinone **87** or 6-triazolo-3,7-disubstituted purinone **88** and an appropriate aminoalcohol (Scheme 26). The products **85** are then treated with methanesulfonyl chloride (MSCl), which results in intramolecular cyclocondensation and gives final compounds **86a** or **86b**, differing in the size of the fused ring [18].

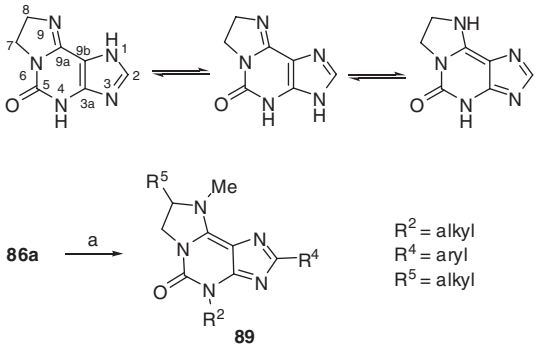
Screening tests of diazolo[1,2-*i*]purinone derivatives have been conducted to find selective agents for phosphodiesterases and adenosine receptors. Imidazo[1,2-*i*]purinones show antagonism against A_1 adenosine receptors (K_i = 7.4 nM) with selectivity >100-fold for A_1 than that for A_{2A} and 100-fold greater than that for A_3 adenosine receptors [47–49]. Some of these antagonists exhibit a K_i value of 2.3 nM at human A_3 adenosine receptors and are several



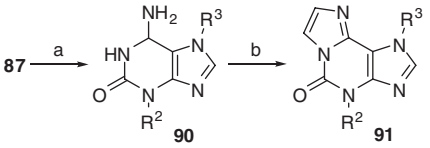
Scheme 26 Reagents: (a) 2-amino-butan/propan-1-ol, pyridine, (b) MSCl, Et_3N, DMF.

hundred-fold selective versus A_1, A_{2A} and A_{2B} adenosine receptors [6, 49, 50]. Compounds from this group have also demonstrated inhibition towards PDE4 enzymes in the nanomolar concentration range and lacked certain adverse reactions of xanthine derivatives and known PDE4 inhibitors [51, 52]. Pyrimido[1,2-*i*]purinones exhibit micromolar affinity towards A_1 and A_{2A} adenosine receptors [47] and to PDE4 enzyme in the micromolar concentration range [51]. Diazepino[1,2-*i*]- and diazocino[1,2-*i*]purinones have demonstrated similar, micromolar affinity and selectivity towards A_1 and A_{2A} adenosine receptors [47].

Another short, one-step method leading to condensed imidazo[1,2-*i*]purinones is based on the methylation of **86a**. Taking into account the tautomeric balance and possible structures of **86a**, substitution with an alkyl group (CH_3-) can occur at the *N*1, *N*3 and *N*9 positions, depending on the reaction conditions and the presence of other groups in the structure. Methylation of 2-unsubstituted imidazo[1,2-*i*]purinones has been reported to yield *N*1-methylated products [52], whereas a phenyl group present at position 2 affects the *N*1/*N*9 substitution ratio [49]. After reaction optimization, the substitution



Scheme 27 Reagents: (a) MeI, NaH, DMF.



Scheme 28 Reagents: (a) NH_3 aq., (b) $ClCH_2CHO$.

exclusively at *N*9-position has been achieved, using methyl iodide and sodium hydride in dry dimethylformamide to yield the final 9-methyl-8,9-dihydro-4*H*-imidazo[1,2-*i*]purin-5(7*H*)-ones **89** (Scheme 27) [49].

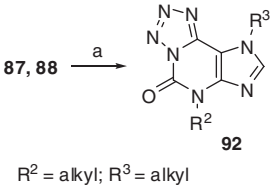
Compounds from this group have been tested as ligands of adenosine receptors and demonstrated selectivity and moderate affinity for the A_1 adenosine receptor. Several compounds show antagonism towards the A_1 adenosine receptor with a K_i value of approximately 395 nM [49].

The synthesis of the other series of imidazo[1,2-*i*]purinones derivatives starts from 6-chloroxanthine **87** (Scheme 28). Treatment of **87** with aqueous ammonia affords the 6-aminoxanthine **90**, which is then reacted with 2-chloroacetaldehyde giving the substituted 1*H*-imidazo[1,2-*i*]purin-5(4*H*)-one **91** [53].

Imidazopurin-2-ones with the structure **91** were tested as inhibitors of phosphodiesterases and demonstrated selective inhibitory activity for the PDE4 in the micromolar concentration range [53].

Tetrazolo[1,5-*i*]purinones The synthesis of tetrazolpurinones **92** can start from either 6-chloro- or 6-triazolo-3,7-disubstituted purinones (Scheme 29), the convenient starting compounds also used in the synthesis of diazolo[1,2-*i*]purinones described above (Scheme 28). Treatment of **87** or **88** with sodium azide leads to the closure to the tetrazole ring, yielding the target 6,9-dihydro-5*H*-tetrazolo[1,5-*i*]purin-5-one (**92**) [53].

Xanthine derivatives with a structure based on the tetrazolo[1,5-*i*]purin-5-one scaffold that have been tested as inhibitors of phosphodiesterases exhibit selectivity and micromolar affinity towards PDE4 [53].



Scheme 29 Reagents: (a) NaN_3.

Conclusion

By synthetic modification of the 2,6-purinedione core various tri- or tetracyclic fused systems can be obtained. An additional ring, usually a nitrogen-based heterocycle such as five-membered (imidazole, triazole, tetrazole) or six-membered moiety (pyrimidine, pyrazine, triazine) is built into the structure, using nitrogen atoms as ring junctions. Derivatives of oxygen- and sulfur-based heterocycles as well as seven-membered rings can also be obtained. Compounds with such structures often show activity either as adenosine receptor antagonists or phosphodiesterase inhibitors.

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