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1 H-PURINE 2,6 DIONES : STRONG PHOSPHODIESTERASE INHIBITORS

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Abstract

Purine 2,6 diones is a versatile bioisostere having different pharmacological activities. It is a bicyclic, heterocyclic compound producing phosphodiesterase (PDE) inhibitory activity. PDE is an enzyme corresponding to catalyse the secondary messengers in asthma. In this article, we focused different derivatives of Purine 2,6 -diones which are having PDE inhibitory action and may be applied in the treatment of asthma.

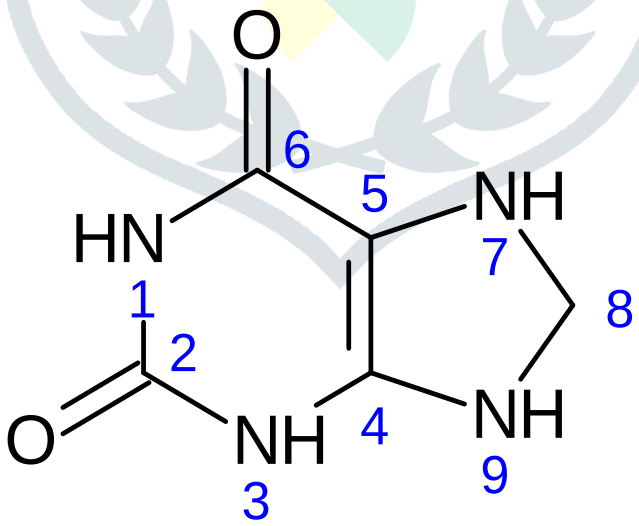
Keywords

Purine 2,6 diones, Cyclic GMP, Phosphodiesterase, Xanthine, Anti asthmatic activity

Introduction

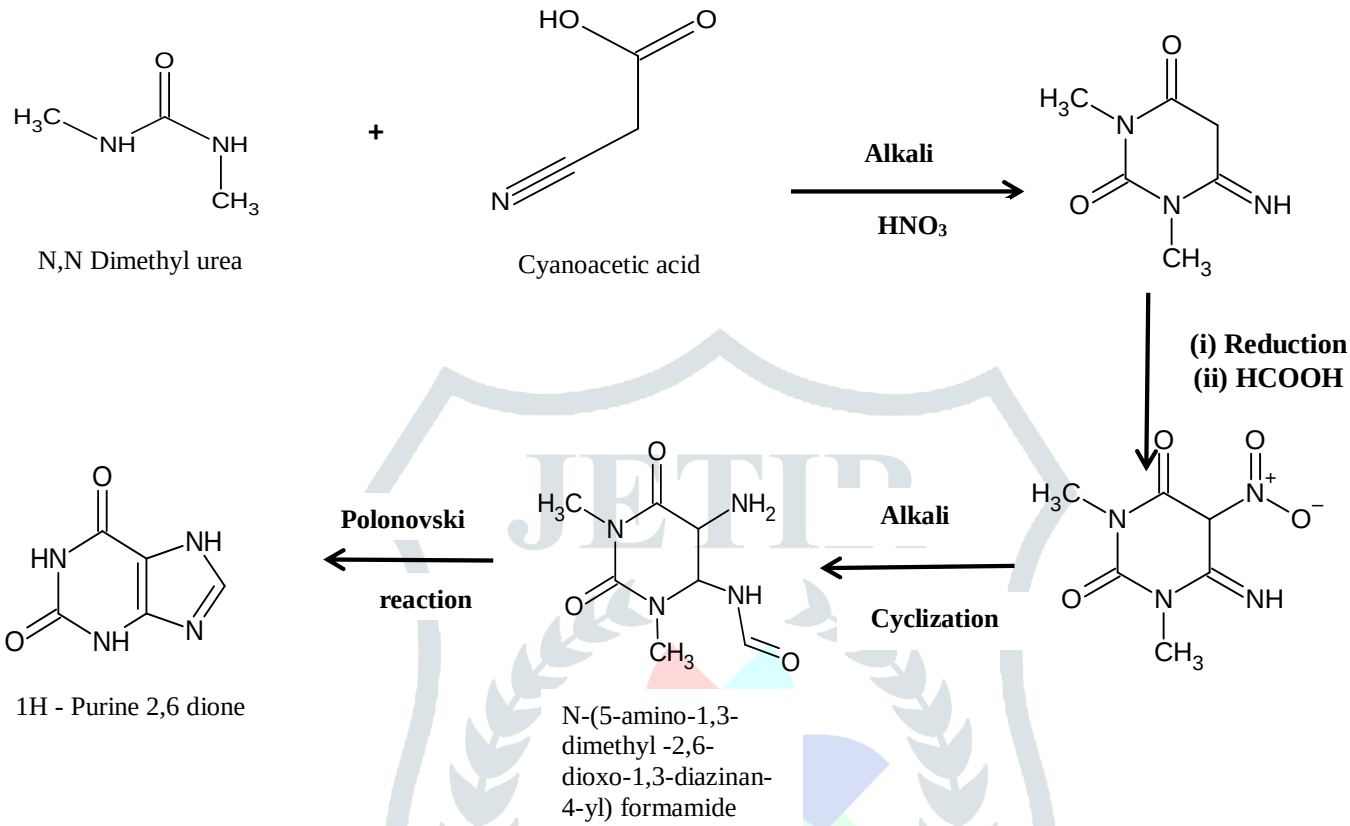
PDE are proteinaceous enzymes responsible for decreasing the cAMP and cGMP. By inhibiting, the PDE increases the cAMP and cGMP in the cell and thereby dilating the bronchi. Therefore, it has been used in the treatment of asthma.[15][16][20][26] Purine 2,6 diones are the heterocyclic compound, having N at positions 1, 3, 7 and 9 which directly contributes to various pharmacological actions of the molecule. The nucleus act as mild CNS stimulant, bronchodilator by inhibiting phosphodiesterase enzymes and non-selective adenosine receptor antagonist.

Chemically, it is a xanthine base containing pyrimidine ring fused with imidazole ring. Purines are the basic nucleus of various antiasthmatic drug such as theophylline and aminophylline. [1] [2]



Synthesis

N,N dimethyl urea is treated with cyanoacetic acid in presence of nitric acid in alkaline medium. The intermediate so formed undergoes reduction with formic acid and cyclisation to form a complex structure N-(5-amino-1,3- dimethyl -2,6-dioxo-1,3-diazinan-4-yl) formamide. This is then subjected to demethylation through Polonovkski reaction and forms 1H - Purine 2,6 dione.



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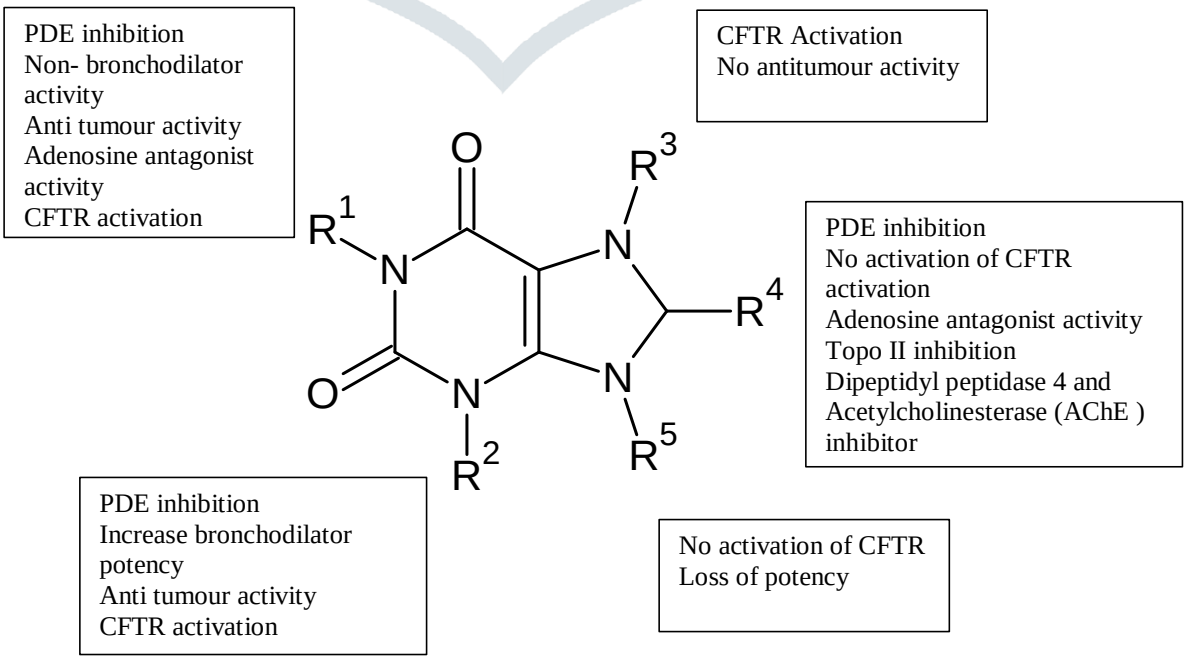
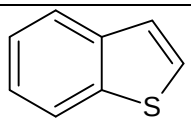
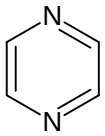
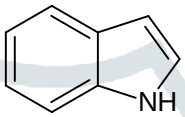
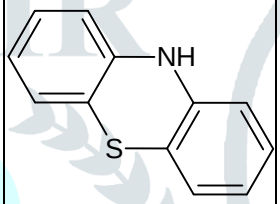
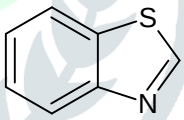
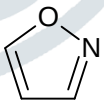
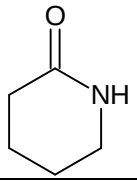
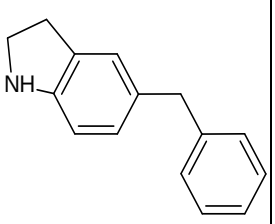
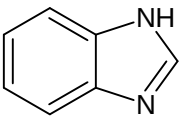
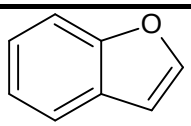
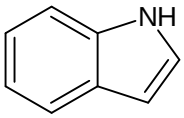
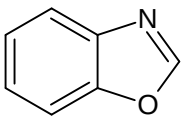
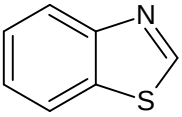
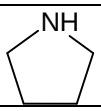
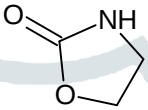
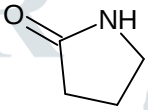
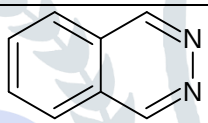
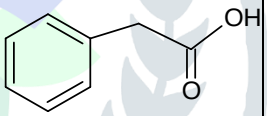
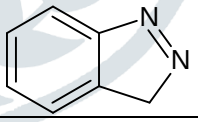
The structural activity relationship of Purine 2,6 diones is depicted below. Substituition at N1 position can lead to PDE inhibition, adenosine antagonist activity. Substituition at N^1, N^2 and N^3 shows CFTR activation while no CFTR activation is shown for substituition in N^5. There is complete loss of potency in substituition at N^5. [4]



The aromatic [6]and heterocyclic[2][3][5][6][8][9][10][12][13][16][17][18][19][21][22][23][24][25] compounds having anti-asthmatic actions can be linked to the N7 position of 1H-Purine 2,6 diones to exhibit the drug action.

Findings

Sl.No.	Code	Derivative	Substituition site	Structure	Smiles Notation
1.	D1	Benzothiophene	N7		c1cccc2sccc12
2.	D2	Pyrazine	N7		c1cnccn1
3.	D3	7- Azaindole	N7		c1cccc2[NH]ccc12
4.	D4	Phenothiazine	N7		c1ccc2Sc3ccccc3Nc2c1
5.	D5	Piperidine	N7		C1CCCCN1
6.	D6	Benzothiazole	N7		c1cccc2scnc12
7.	D7	Isooxazole	N7		c1ccno1
8.	D8	Piperidone	N7		O=C1CCCCN1
9.	D9	Benzyl indole	N7		c1c(ccc2NCCc12)Cc1ccccc1
10.	D10	Benzimidazole	N7		c1cccc2[NH]cnc12

11.	D11	Benzofuran	N7		c1cccc2occc12
12.	D12	Indole	N7		c1cccc2[NH]ccc12
13.	D13	Benzoxazole	N7		c1cccc2ocnc12
14.	D14	Benzothiazole	N7		c1cccc2scnc12
15.	D15	Pyrrolidine	N7		C1CCCN1
16.	D16	Oxazolidinone	N7		O=C1NCCO1
17.	D17	Oxopyrrolidine	N7		O=C1CCCN1
18.	D18	Phthalzine	N7		c1cccc2cnncc12
19.	D19	Phenylacetic acid	N7		OC(=O)Cc1ccccc1
20.	D20	Indazole	N7		c1cccc2N=NCc12

Future perspectives

From this review, the different heterocyclic and aromatic compounds substituted to the 7th position N of the Purine 2,6 diones[1]having promising phosphodiesterase inhibitor activity. Compounds such as theophylline[2], aminophylline[28] containing the same nucleus have already found to have anti-asthmatic actions. [7][16]Hence they may be nominated as a good lead in the anti-asthmatic category.

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