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PYRIMIDINE: THE MOLECULE OF DIVERSE BIOLOGICAL AND MEDICINAL IMPORTANCE

Raghav Mishra* and Isha Tomar

College Of Pharmacy, Teerthankar Mahaveer University, Delhi Road, Moradabad, Uttar Pradesh, India

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Pyrimidine: medicinal importance

Correspondence to Author:

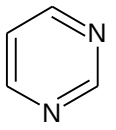
Raghav Mishra

College Of Pharmacy, Teerthankar Mahaveer University, Delhi Road, Moradabad, Uttar Pradesh, India

ABSTRACT

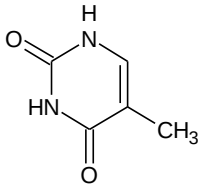
Pyrimidine nucleus is one of the most important heterocycles exhibiting remarkable pharmacological activities. The present review provides a broad view of the biological and medicinal activity possessed by compounds having pyrimidine nucleus.

INTRODUCTION: The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. The process of establishing a new drug is exceeding complex and involves talent of people from variety of disciplines [1]. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity [2]. Pyrimidine is a six membered cyclic compound containing 4 carbon and 2 nitrogen atoms and is pharmacologically inactive but its synthetic derivatives possess an important role in modern medicine.

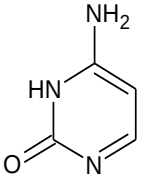


PYRIMIDINE

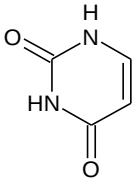
Biological Importance of Pyrimidine: In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one of the possible reasons for their activities [3].



THYMINE

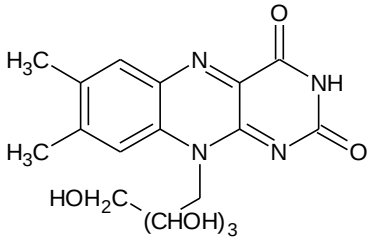


CYTOSINE

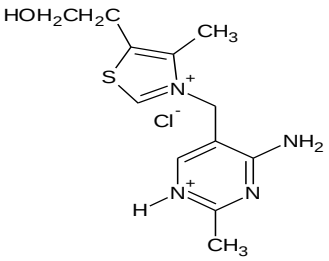


URACIL

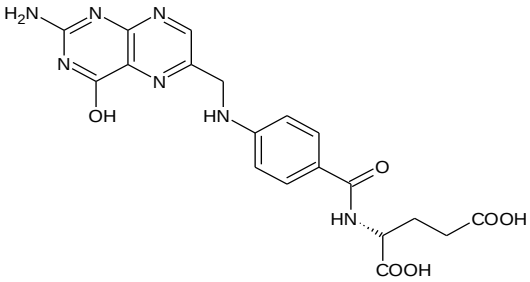
Vitamins are essential for body. Pyrimidine ring is found in vitamins like riboflavin, thiamine and folic acid [4].



RIBOFLAVIN

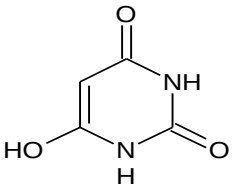


THIAMINE

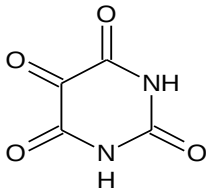


FOLIC ACID

Pyrimidine nucleus is also present in barbituric acid and its several derivatives e.g. Veranal) which are used as hypnotics [5].

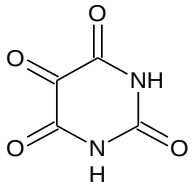


BARBITURIC ACID



VERANAL

In addition to this, pyrimidine nucleus is also found in alloxan, which is known for its diabetogenic action in a number of animals [6].

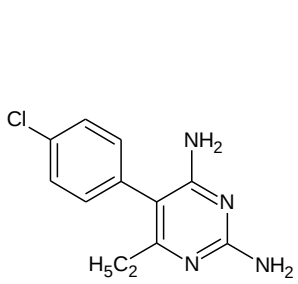


ALLOXAN

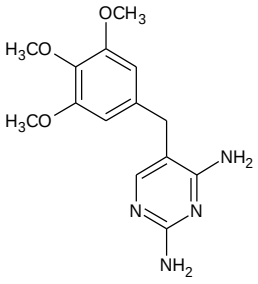
Medicinal Importance of Pyrimidine: In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. Many pyrimidine derivatives have been developed as chemotherapeutic agents and are widely used.

- **Antimicrobial Activity:** Microbes are causative agents for various types of disease like pneumonia, amoebiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. Various approaches were made to check the role of pyrimidine moiety as antimicrobial agent from the discovery of molecule to the present scenario.

Hitchings, in 1948, made an important observation that a large number of 2, 4 di amino pyrimidines and some 2- amino- 4 hydroxy pyrimidines are antagonists of folic acid [7]. These pyrimidines were than eventually proved as inhibitors of the enzyme dihydrofolate reductase (DHFR) [8]. Amongst the 2, 4-diaminopyrimidine drugs, pyrimethamine is a selective inhibitor of the DHFR of malarial plasmodia. Trimethoprim, an antibacterial drug is also a selective inhibitor and selectively inhibits bacterial DHFR [9].

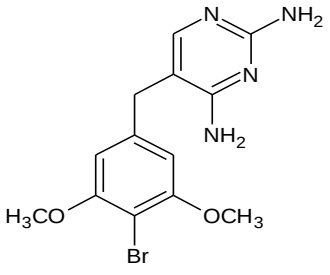


PYRIMETHAMINE



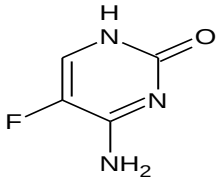
TRIMETHOPRIM

Brodimoprim, is also found to be an effective antibacterial compound[10].



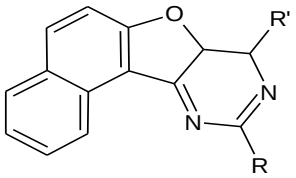
BRODIPRIM

Pyrimidine also shows antifungal properties. Flucytosine is a fluorinated pyrimidine used as nucleosidal anti fungal agent for the treatment of serious systemic infections caused by susceptible strains of candida and Cryptococcus [11].



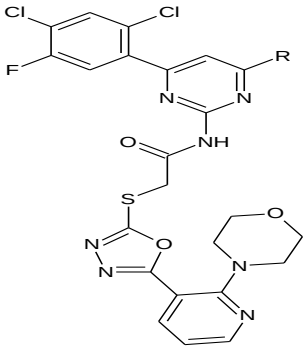
FLUCYTOSINE

Padamshari *et al.,* [12] synthesized Naptho [2, 1- b] furo [3, 2-a] pyrimidine which were useful in the preparation of pharmacologically active compound like anti-inflammatory, anti- antihelmintic and antimicrobial agents.



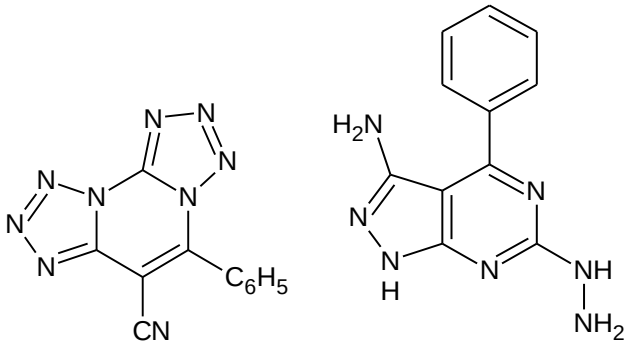
Where R= CH_3, C_6H_5; R'=OCH_3, OC_2H_5, NHC_2H_5, NHC_6H_5

Naik *et al.,* [13] synthesized 2-[{2 (Morpholino)-3-pyridinyl- 5- thio} - 2 oxoethyl oxadiazolyl]- amino- 4- (2, 4 dichloro- 5- fluorophenyl)- 6- (aryl) pyrimidines, which exhibit maximum zone of inhibition against *E.coli*, *S. aureus*, *S.typhii* and *B.subtilis*.

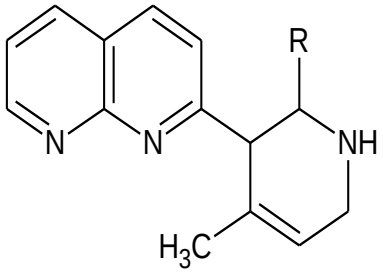


R= 4-$CH_3.C_6H_4$; 4-$Cl.C_6H_4$; 2, 4-$(Cl)_2.C_6H_3$; 4-$F.C_6H_4$; 3, 4, 5-$(OCH_3)_3.C_6H_2$

Aly *et al.,* [14] synthesized a series of 1- glycosyl thiopyrimidines, annulated pyrimidines derivatives, pyrazolo[3, 4-d] pyrimidines, ditetrazolo[1, 5- a, 1, 5'-c] pyrimidines thieno [2, 3-d] pyrimidines derivative. The antimicrobial were determined in vitro using cup plate and paper disc method.

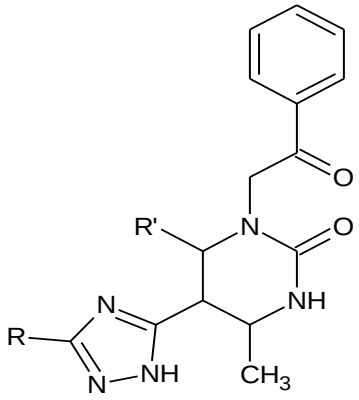


Mogilaiah *et al.,* [15] reported 1, 8 Napthopyridine derivatives which were tested for their antibacterial activity *in vitro* against *E. coli* and *B. subtilis* using filter paper disc technique.



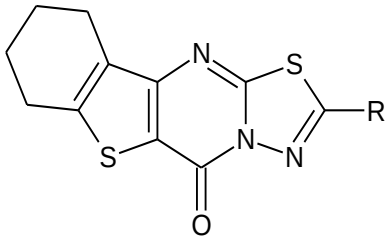
Where R= C_6H_5, p-$CH_3C_6H_5$, $CH_3OC_6H_4$, o-ClC_6H_4 p-ClC_6H_4, p-OHC_6H_4

Mishra *et al.,* [16] synthesized various derivatives of pyrimidines. The fungicidal activities of the compound were evaluated against *P. infestans* and *C. falcatum* by the usual agar plate method.



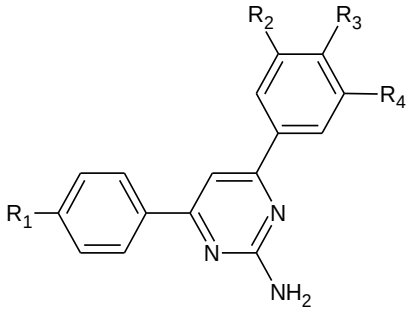
R= C_6H_5, p-ClC_6H_4, m-$NO_2C_6H_4$, p-$OCH_3C_6H_4$; R'= m-$NO_2C_6H_4$, p- $OCH_3C_6H_4$

V. Alagarsamy *et al.,* [17] synthesized some 2 substituted (1, 3, 4) thiadiazole(2, 3-b) tetrahydro-benzothieno [3, 2-e] pyrimidines and then screened them for anticancer, antibacterial and antifungal activities.



R= H, CH_3, $NHCH_3$, $(CH_2)_2CH_3$

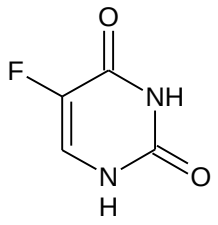
Rajesh Vyas *et al.,* [18] synthesized some 2 amino- 4, 6 diaryl substituted pyrimidines and than screened them for antibacterial and herbicidal activity.



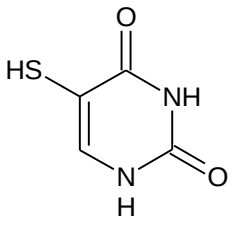
R_1= H, Cl, Br, OCH_3; R_2= OCH_3, H; R_3= OCH_3, N $(CH_3)_2$; R_4= OCH_3, H

In other words it can be stated that pyrimidine moiety serves as a royal warrior against almost all types of microbes.

- **Anticancer Activity:** The pyrimidine moiety with some substitution shows promising antitumor activity as there are large numbers of pyrimidine based antimetabolites. The structural modification may be on the pyrimidine ring or on the pendant sugar groups. Early metabolite prepared was 5-fluorouracil [19], a pyrimidine derivative followed by 5-Thiouracil which also exhibits some useful antineoplastic activities [20].

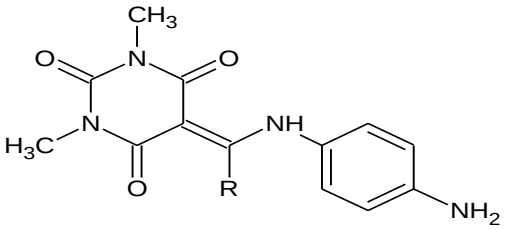


5- FLUOROURACIL



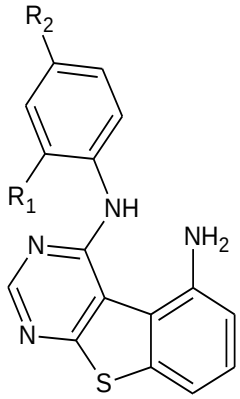
5- THIOURACIL

Palwinder Singh *et al.,* [21] reacted 5 benzoyl/ 5-carbaldehyde-/ 5- (3- phenyl acryloyl o- 6- hydroxy-1H- pyrimidine- 2, 4 diones with amines provided the corresponding enamines. The investigation for anticancer activity of molecule at 59 human tumor cell lines was done representing leukemia, melanoma and cancer of lung, colon, brain, ovary, breast as well as kidney.



R = H, CH=CH-Ph, Ph

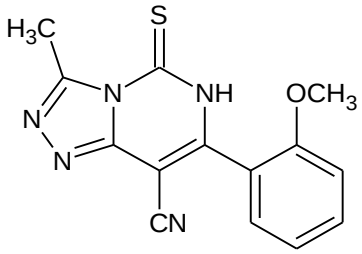
Stephane pedeboscq *et al.,* [22] synthesized 4-(2-Methylanilino) benzo[b] thieno [2, 3-d] pyrimidine (1) and 4-(2-Methoxyanilino) benzo [b] thieno[2, 3-d]pyrimidine (2) which showed a similar cytotoxicity to the standard anti-EGFR geftinib suggesting a blockade of the EGFR pathway by binding to the tyrosine kinase receptor.



R_1= CH_3 $R_{2=}$ H for (1)

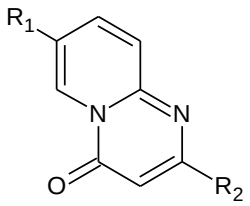
R_1= OCH_3 $R_{2=}$ H for (2)

Fathalla *et al.,* [23] synthesized a series of some new pyrimidine derivatives like 7-(2-methoxyphenyl)-3-methyl-5-thioxo-5, 6-dihydro[1, 2, 4]-triazolo[4, 3-c]pyrimidine-8-carbo-nitrile via reaction of ethyl cyanoacetate with thiourea and the appropriate aldehydes namely 2-methyl-benzaldehyde and 2-methoxy-benzaldehyde followed via reaction with different reagents. All structures were than screened for bacterial activity and anticancer activity.



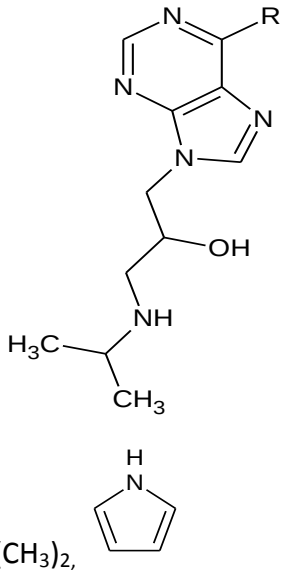
Organic compounds and their complex with various ligands have found many applications in biomedicine. Al Allaf *et al.,* [24] describe the preparation of R_2SnCl_2 complex of some 4 H-pyrido [1, 2-a] pyrimidin-4-one derivatives as donating

ligand having multiple donor sites and examine the cytotoxic activity of some of these complex against fine tumor cell lines.



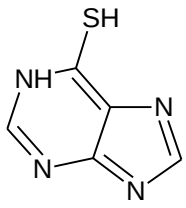
R_1 = H, 7-CH_3, 8-CH_3; R_2 = 2-CH_2Br, 3-CH_3COO

Silvana Raic-Malic *et al.,* [25] synthesized the novel purine and pyrimidine nucleoside analogues possessing a 2, 3-epoxypropyl, 2, 3-epoxypropyl ether, or 3-amino-2-hydroxypropyl moiety bonded at either N-9 of the C-6 substituted purine ring or N-1 and N-3 of the pyrimidine ring, and were evaluated for their antitumour and antiviral activities.

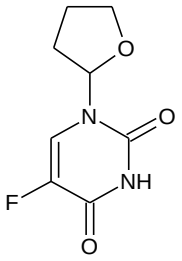


R= NH_2, $NHCH(CH_3)_2$,

Guanine nucleus containing antineoplastic compounds like mercaptopurine [26], tegafur [27] etc. were discovered after formulation of antimetabolite theory [28].

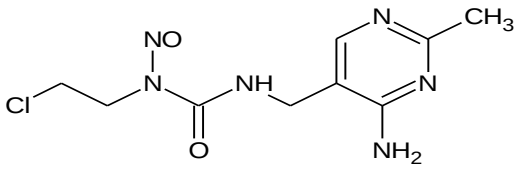


MERCAPTOPURINE

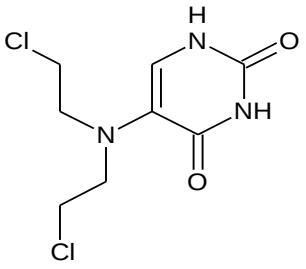


TEGAFUR

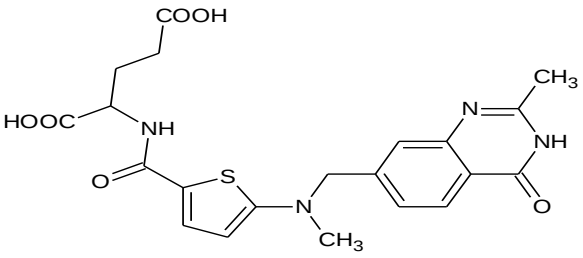
Recently, new compounds have been developed like nimustine [29], uramustine [30], raltitrexed [31] etc.



NIMUSTINE



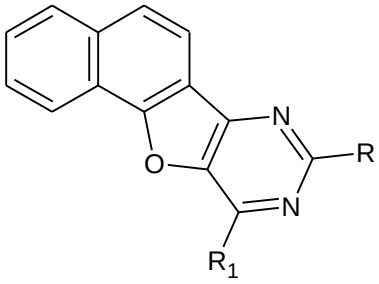
URAMUSTINE



RALTITREXED

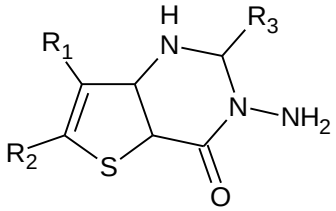
- **Anti-inflammatory Activity:** Pyrimidine has a remarkable pharmacological efficiency and therefore an intensive research has been focused on anti-inflammatory activity of pyrimidine nucleus. Recently two PCT international applications have been filed for 2-thiopyrimidine derivatives possessing potent activity against inflammation and immune disorders [32].

Naphtho [2, 1- b] furo [3, 2- d] pyrimidine was reported by Padama shale *et al.,* [33]. Carrageen induced rat paw edema method was employed for evaluating the anti- inflammatory activity. The compounds were given at a dose of 80 mg/kg body weight in albino rats weighing between 150 and 200 g. The edema was produced by injecting carrageenan solution at the left hind paw.



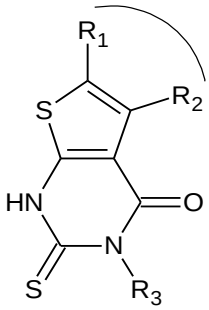
R= CH_3, C_6H_5; R_1= OCH_3, OC_2H_5, NHC_2H_5, NHC_6H_5

Marylene Favre *et al.,* [34] synthesized some substituted thieno pyrimidines-4-one and screened then for analgesic and anti-inflammatory activity.



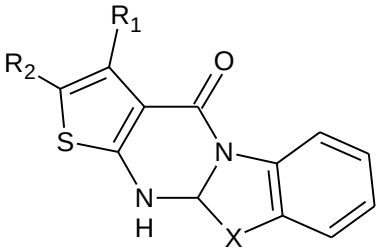
R_1, R_2= -$(CH_2)_3$, -$(CH_2)_5$, -$(CH_2)_4$; R_3= CH_3

A Cannito *et al.,* [35] synthesized some 3-substituted thienopyrimidin- 4- one- 2- thiones and then screened them for analgesic and anti-inflammatory activity.



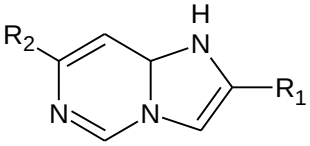
R_1, R_2= -$(CH_2)_3$, -$(CH_2)_4$

F. Russo *et al.,* [36] synthesized new thienopyrimido benzothiazole and thieno pyrimidobenzo oxazoles and then screened them for analgesic and anti-inflammatory activity.



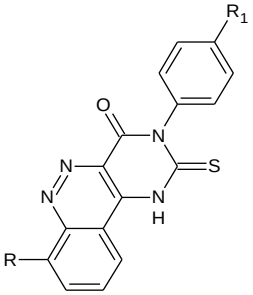
X= O, S; R_1= CH_3, H; R_2= CH_3, H, C_6H_5

Cenicola *et al*., [37] evaluated some imidazolo [1, 2-c] pyrimidines for anti-inflammatory, analgesic and antipyretic activities. Anti-inflammatory activity was studied by carrageenan- induced paw oedema in rats and fund to show activity comparable to indomethacin.



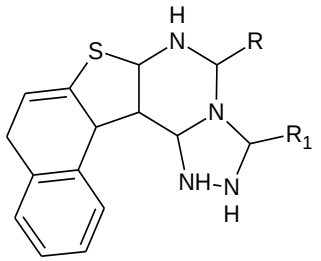
R_1= Cl, OCH_3, CH_3; R_2= COOH, CH_2COOH

Nargund *et al.,* [38] reported the synthesis of few substituted 2-mercapto-3-(N-alkyl) pyrimido [5, 4-c] cinnolin- 4- (3H)- ones and screened them for anti-inflammatory and antimicrobial activities. The anti-inflammatory activity was done by carrageenan induced paw oedema method.

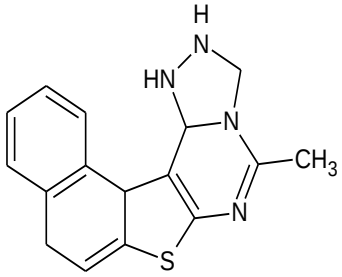


R= H, CH_3; R_1= H, o-CH_3, p-CH_3, p-Cl

Thieno tetrazolopyrimidines and thieno triazolo pyrimidine derivatives prepared by Rashand *et al.,* [39] compounds were tested as potent at anti-inflammatory agent and derivatives showed patent activity in Carrageenan test.



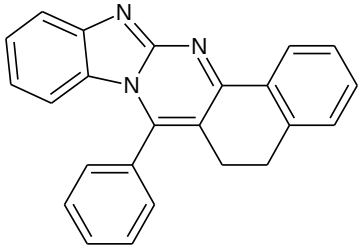
Thienotriazolo pyrimidine derivative; (R=H, CH_3; R_1= H, CH_3)



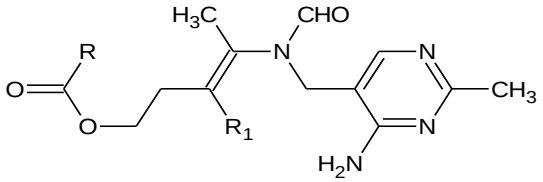
THIENOTRIAZOLOPYRIMIDINE

Antidiabetic Activity: Lee *et al.,* [40] synthesized some novel pyrimidines derivative having thiazolidinedione. These compounds were evaluated for their glucose and lipid lowering activity using pioglitazone and rosiglitazone as reference compound.

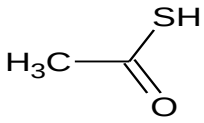
Desenko *et al.,* [41] synthesized azolopyrimidine derivatives and compounds were evaluated for hypoglycemic activity.

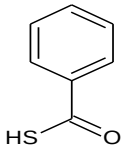


Analgesic Activity: New forms of thiamine are lipid-soluble like acetiamine, bentiamine [42] etc., having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus.

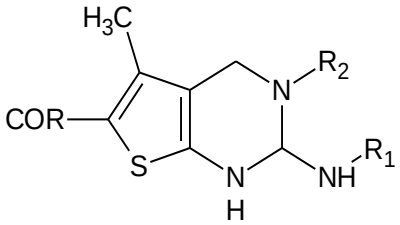


R R_1

Acetiamine $-CH_2$ 

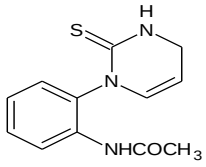
Bentiamine C_6H_5 

Ishwaarsinh S. Rathod *et al.,* [43] synthesized substituted thieno [2, 3-d] pyrimidine- 4(3H)-ones and then screened them for analgesic activity.

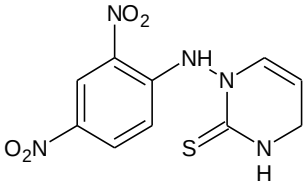


R= $-CH_3$,-NHPh; R_1= R_2= Ph, o-Anisyl

Sondhi *et al.,* [44] have reported anti-inflammatory and analgesic activity of synthesized pyrimidine derivatives (1 and 2).

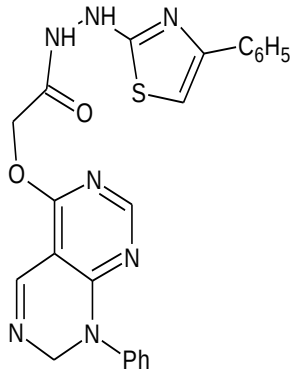


(1)

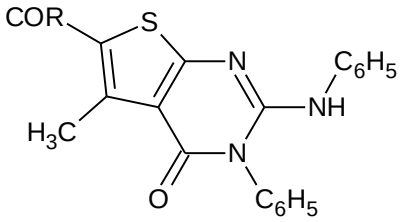


(2)

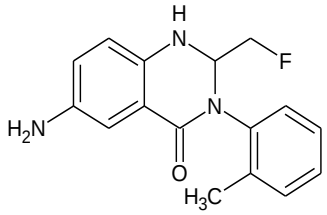
Vijay Raj *et al.,* [45] synthesized some new 2-[c]-phenyl- 1H- pyrazolo [3, 4- d] pyrimidin- 4- yl) acetohydrazide derivative have been prepared and screened for their analgesic activity by acetic acid induced writhing test using standard drug diclofenac sodium.



Rathod *et al.,* [46] synthesized 2- aryl amino- 3- aryl- 5- methyl- 6- (substituted) thione [2, 3- d] pyrimidin- 4 (3H)- ones. All the synthesized compounds were screened for the analgesic activity by tail flick method on albino rats and by writhing method on albino mice.

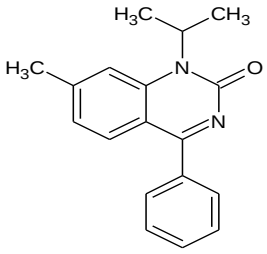


Afloqualone [47] has been evaluated as a successful anti-inflammatory agent with lower back pain patients.



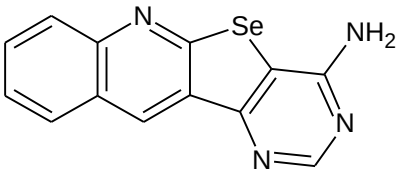
AFLOQUALONE

A condensed pyrimidin-2-one derivative, proquazone [48], has been reported to exhibit good NSAID potential.

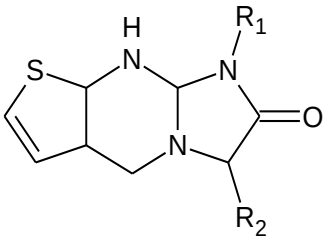


PROQUAZONE

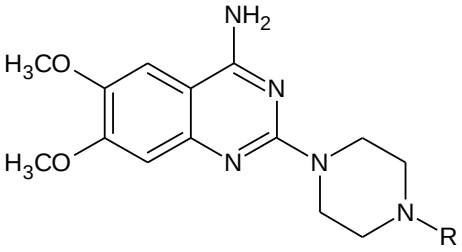
- **Platelet Aggregation Inhibition Activity:** Nandeeshaiah *et al.,* [49] reported the synthesis of which showed the blood platelet disaggregating property.

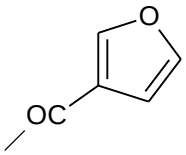


Fumiyoshi Ishikawa, *et al.,* [50] synthesized cyclic Guanides (Imido [1, 2-a] thienopyrimidin-2-one derivatives and then screened them for blood platelet aggregation inhibitors.



- **Antihypertensive Activity:** Many pyrimidine ring containing drugs have exhibited antihypertensive activity. A quinozoline derivative, prazosin, is a selective *α*1-adrenergic antagonist [51]. Its related analogues bunazosin [52], trimazosin [53] and terazosin [54] are potent antihypertensive agents.

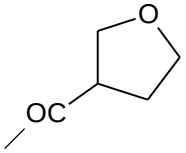




R= for Prazocin

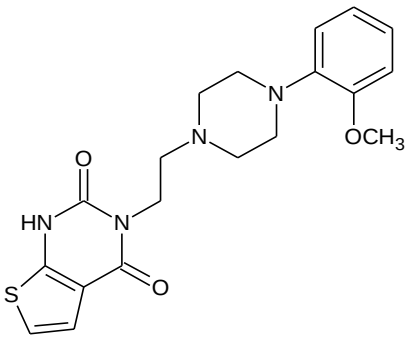
R= -$COOCH_2COH(CH_3)_2$ for Bunazosin

R= -$COCH_2CH_2\ CH_3$ for Trimazosin

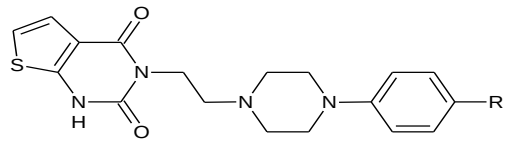


R= for Terazosin

Mery. B. Press *et al.,* [55] synthesized furo [3, 4-d] pyrimidines-2, 4- dione derivatives, analogues of thienopyrimidines-2, 4-diones and then screened them for antihypertensive activity.

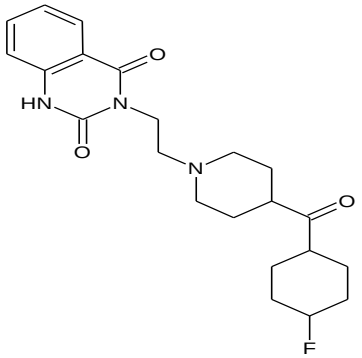


Russell *et al.,* [56] synthesized thienopyrimidine diones derivatives and then screened them for antihypertensive agent.

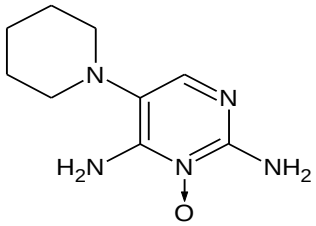


R= 2-OCH_3, 3-OCH_3, H

Ketanserin [57] has a similar effect and is an antagonist of both *α*1-adrenergic and serotonin-S2 receptors. A triaminopyrimidine derivative, minoxidil, whose mechanism of action and therapeutic action are similar to prazosin, has been introduced in therapy for its side effects, in the treatment of alopecia, male baldness etc., [58].

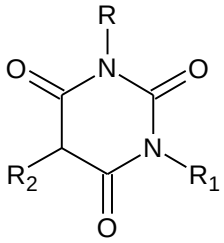


KETANSERIN

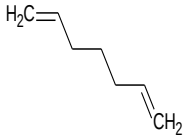


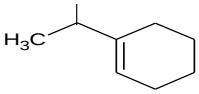
MINOXIDIL

- **CNS Activity:** Agents involved in this category include sedatives, hypnotic, anticonvulsants, anxiolytic agents, pyrimidine anaesthetics etc. Large variety of barbiturates are used as CNS active agents and are classified as short, intermediate and long acting depending upon duration of action [59].

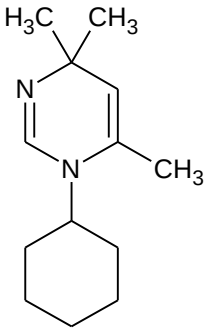


R R_1 R_2

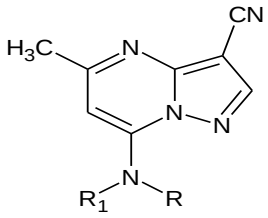
Allobarbital H H 

Hexobarbital H $-CH_3$ 

Gupta *et al.,* [60] synthesized a series of nitrophenyl 4, 4, 6 trimethyl, 1 H, 4H pyrimidine 2 thiols (NPTP) and tested their anticonvulsant activity in mice against maximal electro shock and metrazol (MET) induced convulsions.



Song Qing WANG *et al.,* [61] reported the synthesis of twelve new 5-methyl-7-substituted pyrazolo [1, 5-a] pyrimidine-3-carbonitrile derivatives by using simple starting materials such as propane dinitrile and triethyl orthoformate and were screened for hypnotic activity.

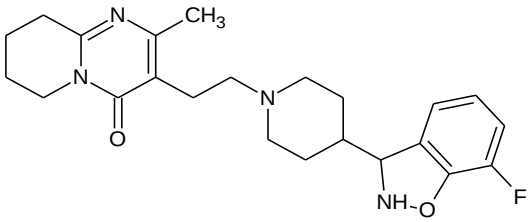


R= H, R'= Allyl

R= H, R'= CH_2Ph

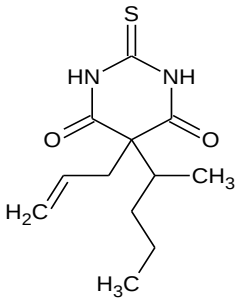
R= R'= CH_2Ph

Risoperidone is an antipsychotic drug, which is a structural hybrid of butyrophenone and can be used as anxiolytic, antidepressant and antiparkinsonian drug [62].



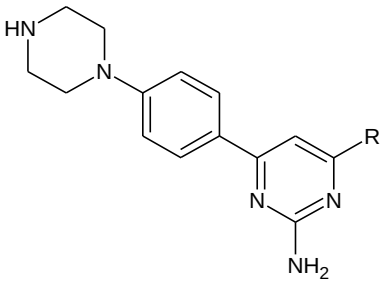
RISOPERIDONE

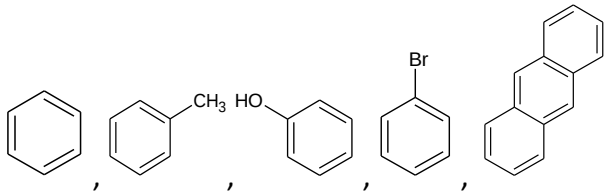
A pyrimidine analogue, thimylal is a short acting general anaesthetic drug [63].



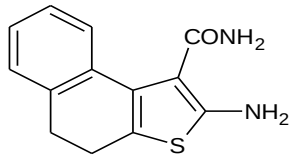
THIMYLAL

- **Miscellaneous Activity:** Rahaman *et al.,* [64] synthesized novel pyrimidines by the condensation of chalcones of 4'-piperazine acetophenone with guanidine HCl. The recorded % of histamine inhibition showed significant antihistaminic activity when compared to the reference antihistaminic drug mepiramine.

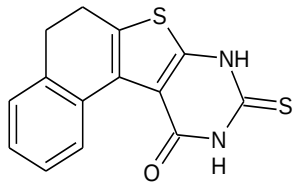


R= 

Aymn E. Rashad *et al.,* [65] synthesized several derivative (1, 2) containing dihydronaphtho-, naphtho[2, 1-b] thiophene- and thieno [2, 3-d] pyrimidine ring systems starting from 2-amino-4,5 dihydronaphtho [2, 1-b] thiophene-1 carbonitrile and were tested for antiviral activity against H5N1 virus.

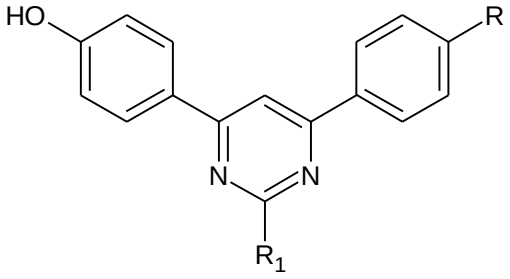


(1)

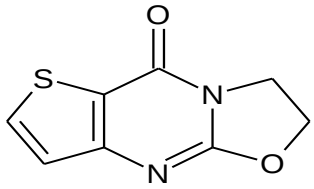


(2)

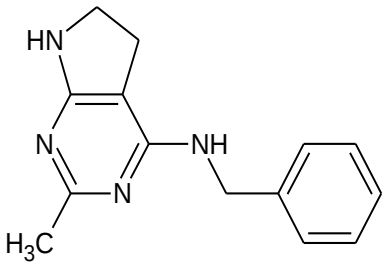
A small library of 20 tri-substituted pyrimidines was synthesized by Anu *et al.,* [66] evaluated for their *in vitro* anti-malarial and anti-tubercular activities. Out of the total screened compound, 16 compounds have shown in-vitro anti-malarial activity against *Plasmodium falciparum* in the range of 0.25- 2µg/ml and 8 compounds have shown anti- tubercular activity against Mycobacterium tuberculosis at a concentration of 12.5 µg/ml.



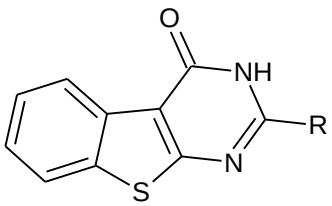
Sugiyama *et al.,* [67] synthesized condensed thieno pyrimidines (2, 3- dihydro- 5H- oxazolo thieno pyrimidine) derivatives and then they are screened for gastric antisecretory activity.



Erric A. Meade *et al.,* [68] synthesized analogues of 4-benzylamino-2, 7-H-pyrrolo [2, 3-d] pyrimidines and then screened them for their anxiolytic activity.



Chamanlal J. Shishoo *et al.,* [69] synthesized 2-substituted thieno [3, 2-d] pyrimidin-4(3H)-one and screened for QSAR relationship of antihyperlipaemic.



R= CH_3, CH_2Cl, $CHCl_2$

Apart from these activities, pyrimidines also possess diuretic, antianthelmentic and calcium channel blocking activity [70].

CONCLUSION: Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A vast literature has been accumulated over the years and chemistry of pyrimidines continues to be a blossoming field. The biological profiles of this new generation of pyrimidine represent much progress with regard to the older compounds.

REFERENCE:

1. Delgado JN and Remers WA; Wilson and Giswold's-Textbook of Organic Chemistry Medicinal and Pharmaceutical Chemistry; 10th ed. Philadelphia: Lippincott Raven; 1998.
2. Miller D; Remington- The Science and Practice of Pharmacy; 19th ed. Pennsylvania: MACK Publishing Company; 1995; 425.
3. Amir M, Javed SA and Kumar H; Indian J. Pharm. Sciences; 2007; 69(3); 337-343.
4. Cox RA; Quart. Rev.; 1968; 22; 499.
5. Jain MK, Sharnevas SC; Organic Chem.; 2008; 3; 997-999.
6. Eussell JA; Annu. Rev. Biochem.; 1945; 14; 309.
7. Hitchings GH, Elion GB, Wanderers H and Falco EA; J. Biol. Chem.; 1948; 174; 765.
8. Futterman S; J. Biol. Chem.; 1957, 228; 1031.
9. Cheng CC and Roth B; In Progress in Medicinal Chem. (eds Ellis GP and West GB), Butterworths London; 1982; 19; 267.
10. Kompis I and Wick A; Helv. Chim. Acta; 1977; 60; 3025.
11. Polak A. and Scholer HJ; Chemotherapy; 1975; 21; 113.
12. Padamshari B, Vaidya VP and Vijayayakumar ML; Indian J. Hetero. Chem.; 2002; 12; 89-94.
13. Naik TA and Chikhalia KH; E-Journal of Chem.; 2007; 4(1); 60-66.
14. Aly and AA, Chinese J. of Chem.; 2005; 23; 211-217.
15. Mogilaiah K and Sudhakar GR; Indian J. Hetero. Chem.; 2003; 42B; 636-640.
16. Mishra A and Singh DV; Indian J. Hetero. Chem.; 2004; 14; 43-46.
17. Alagarsamy V, Pathak US, Rajasolomon V, Meena S, Ramseshu KV, Rajesh R; Indian J. Hetero. Chem.; 2004; 13; 347.
18. Vyas R, Udaibhan Gahlot S, Verma BL, Indian J. Hetero. Chem; 2003; 13; 115.
19. Callery P and Gannett P; Cancer and Cancer Chemotherapy: In Foye's Principles of Medicinal Chemistry (eds Williams DA and Lemke TL), Lippincott Williams and Wilkins, Philadelphia; 2002; 934–935.
20. Al Safarjalani ON, Zhou XJ, Ras RH, Shi J, Schinazi RF, Naguib FN and El KouniMH; Cancer Chemotherapy Pharmacology; 2005; 55; 541–551.
21. Singh P, Kaur J and Paul K, Indian J. Chem.; 2008; 47B; 291-296.
22. Pedeboscq S, Gravier D, Casadebaig F, Hou G, Gissot A, Giorgi FD, Ichas F, Cambar J, Pometan J; Eur. J. Med. Chem.; 2010(45); 2473-2479.
23. Fathalla OA, Zeid IF, Haiba ME, Soliman AM, Abd- Elmoez and El- Serwy WS; World J. Chem.; 2009; 4 (2); 127-132.
24. Talal A, Allaf KA andRedna I; Applied Organo-metallic Chem.; 1996; 10; 47.
25. Malic S, Grdisab M, Pavelicb K, Mintasa M; Eur. J. Med. Chem.; 1999; 34; 405−413.
26. Burchenal JH et al; Blood; 1953; 8; 965.
27. Giller SA, Zhuk RA and Lidak MIU, Dokl. Akad. Nauk; SSR; 1967; 176; 332.
28. Remers WA; Antineoplastic Agents: In Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry (eds Delgado JN and Remers WA); Lippincott Williams and Wilkins, Philadelphia; 1998; 366–368.
29. Weller M, Muller B, Koch R, Bamberg M and Krauseneck P; J. Clin. Oncol. 2003; 21; 3276–3284.
30. Kennedy BJ, Torkelson JL and Torlakovic E; Cancer; 1999; 85; 2265–2272.
31. Horton TM et al; Clin. Cancer Res.; 2005; 11; 1884–1889.
32. Belema M, Bunker A, Nguyen V, Beaulieu F, Ouellet C, Marinier A, Roy S, Yung X, Zhang Y, Martel and Zuci C; PCT Int. Appl. WO 2003084, Through Chem. Abstr.; 2003; 139; 337987x.
33. Padmashali B, Vaidya VP and Vijaya Kumar ML, Indian J. Hetero. Chem.; 2002; 12; 89-94.
34. Marylenefavre, Cuong Luu Duu, Francios Huguet, Chantal Gaultier; J. Med. Chem.; 1998; 23; 453.
35. Cannito A, Perrissin M, Luu-Duc C, Huguet F, Gaultier C, Narcisse G; Eur. J. Med. Chem.; 1990; 25; 635.
36. Russo F, Romeo G, Caruso A, Cutuli V, Amore D and Santagati NA; Eur. J. Med. Chem.; 1999; 29; 569.
37. Cenicola, Donnoli D, Stella L, Paola CD, Constantino M, Anignente E, Arena F, Luraschi E and Saturnino C, Pharmacology Res.; 1990; 22; 80.
38. Nargund LVG, Badiger VV and Yarnal SM; J. Pharm. Sci.; 1992; 81; 365.
39. Rashand AE, Heikal OA and Abdul Megeig FME, Heteroatom Chemistry; 2005; 16; 226-234.
40. Lee HW and Kim BY; Euro. J. Med. Chem.; 2005; 4; 662.
41. Desenko SM, Lipsum VV and Gorbenko NI, J. Pharm. Chem.; 1995; 29; 265.
42. Gauthier B; Ann. Pharm. Fr; 1963; 21; 655.
43. Ishwaarsinh Rathod S, Ajay Pillai S and Vikas Shirsath S; Indian J. Heterocyclic Chem.; 2000; 10; 93.
44. Sondhi SM, Verma RP; Indian Drugs; 1999; 36(1); 50.
45. Vijaya Raj KK, Naryana B and Ashalatha BV; J. Pharmacology and Toxicology; 2006; 6; 559.
46. Rathod IS, Pillai AS and Shirsath VS; Indian J. Heterocyclic Chem.; 2000; 10; 93.

47. Tani J; J. Med. Chem.; 1979; 22; 95.
48. Clissold SP and Beresford R; Drugs; 1984; 33; 478–502.
49. Nandeeshwariah SK and Sarvottam Ambekar, Indian J. Chem.; 1998; 37B; 995.
50. Fumiyoshi Ishikawa, Akira Kosasayama, Hitoshi Yamaguchi, Yoshifumi Watanabe, Juji Saegusa, Seiichi Shibamura, Kyoko Sakuma, Shinichiro Ashida and Yasushi Abiko; J. Med. Chem.; 1981; 24; 376.
51. Pfizer; US Patent; 3 511 836; 1970.
52. Hara H, Ichikawa M, Oku H, Shimazawa M and Araie M; Cardiovasc. Drug Rev.; 2005; 23; 43–56.
53. Meredith PA, Scott PJ, Kelman AW, Hughes DM and Reid JL; Am. J. Ther.; 1995; 2; 541–545.
54. Honkanen E, Pipuri A, Kairisalo P, Nore P, Karppaness H and Paakari I; J. Med. Chem.; 1983; 26; 143.
55. Mery Press B, James Mc Nally J, Joan Keisher A, Steve Offord J, Laurence Katz B, Robert Falotico and Alfonso Tobaia J; Eur. J. Med. Chem.; 1989; 24; 627.
56. Ronald Russell K, Jeffery Press B, Richard Rampulla A, James Mcnally J, Robert Falotico, Joan Keiser A, David Bright A and Alfonso Tobia; J. Med. Chem.; 1988; 31; 1786.
57. Ganzevoort W, Rep A, Bonsel G.J, De Vries JI and Wolf H; Hypertension; 2004; 22; 1235–1242.
58. Wong WM; Ann. Pharmacotherapy; 1994; 28; 290–291.
59. Daniels TC and Jorgensen EC; Central nervous system depressants-In Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry(ed. Doerge RF); J. B. Lippincott, Philadelphia; 1982; 33.
60. Gupta AK, Sanjay, Kayath HP, Ajit Singh, Geeta Sharma, Mishra KC; Indian J. Pharmacology; 1994; 26: 227 – 228.
61. Song Qing WANG; Lin FANG; Xiu Jie LIU; Kang ZHAO; Chinese Chemical Letters; 2004; 15(8); 885-888.
62. Howard HR and Seeger TF; Annu. Rep. Med. Chem.; 1993; 28; 39.
63. Abott; US Patent; 2153729; 1934.
64. Rahaman SA, Rajendra Pasad Y, Phani Kumar and Bharath Kumar; Saudi Pharmaceutical J.; 2009; 17(3); 259-264.
65. Rashad AE, Ahmed H. Shamroukh, Randa E. Abdel-Megeid, Ahmed M. Kandeil, Ahmed Mostafa, Rabeh Elshesheny, Mohamed A. Ali, Klaus Banert; Euro. J. Med. Chem.; 2010.
66. Agrawal A, Srivastava K and Puri SK; Bio. Org, and Med. Chem Lett.; 2005; 15; 5218.
67. Sugiyama M., Sakamoto T., Tabata K. and Fuumi H.; Chem. Pharm. Bull.; 1989; 37(10); 2717.
68. Erric Meade A, Marcos Sznaidman, Gerald Pollard T, Lilia Beauchamp M, James Howard L and Geraid Pollard T; Eur. J. Med .Chem. 1998; 33; 363.
69. Chamanlal Shishoo J, Kishore Jain S, Ishwarsinh Rathod S, Bipin Thakkar J, Samir Brahmbhatt B, Thakorbhai, Ramkrishna Bangaru and Ramesh Goyal K; 1996; Drug Res.; 46(1); Nr.3.
70. Jain KS, Chitre TS, Miniyar PB, Kathiravan MK, Bendre VS, Veer VS, Shahane SR and Shishoo CJ; Current Science; 2006; 90(6).

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