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REVIEW ARTICLE

Significance The Biological Activity to Pyrimidine Analogues

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ABSTRACT

Heterocyclic organic compounds constitute an extremely important type of compounds. "In fact, this class contains more than 50% of all recognized organic compounds. Many known medicines, such as atropine, morphine, folic acid, vitamin B1, etc., are heterocyclic compounds and are used for treating wide range of diseases. Some synthetic drugs are classified as very potent heterocycles these are: barbiturates, flucytosine, pyrantal pamoate, antipyrine, and the HIV drug. One of the most the most important heterocycles compounds is the pyrimidine, which used to treat various illnesses such as cancer, Leukemia. pyrimidine also represents the backbone of RNA and DNA.

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PYRIMIDINES

Pyrimidine is the diazine compound which has an excessive attention. This heterocyclic structure is a numerous bioactive materials, pharmaceutical, and veterinary [1]. Its reactivity has been the subject of many synthetic and theoretical studies. Reviews were summarized periodically [2-13]. Essential facets of synthesis and transformation [14]. Pyrimidine can be prepared easily from barbituric acid, $C_4H_4N_2$. Pyrimidine is similar to pyridine and basically flat ring, but it is different from benzene, which has an irregular hexagon with 6 various bond lengths and 4 unalike bond angles (Fig. 1).

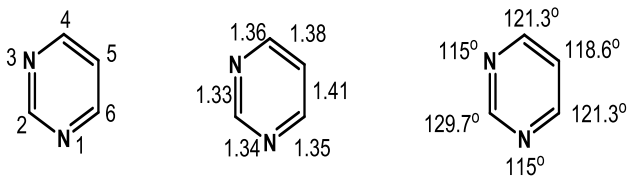


Fig. 1. Structure of Pyrimidine, Its Bond lenths, and Angles

The alloxan earliest pyrimidine derivative that isolated by oxidation of both uric and nitric acid [15]. The name of pyrimidine derived from two words (pyridine and amidine) and first used by Pinner [16], where the parent compound was first prepared by Gabriel and Colman [17].

Pyrimidines one of the six membered heterocyclic containing duple nitrogen atoms at site 1,3. It is isomeric and contains multiple pyrimidines (uracil, thymine, and cytosine) with other types of nucleic acid hydrolysis (Fig . 2). Of the two forms of DNA and RNA nucleic acid, cytosine is found in both DNA and RNA, while uracil is only present in RNA and thymine is only present in DNA [18].

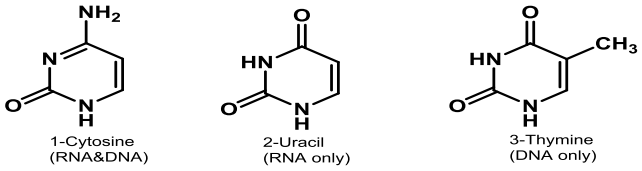


Fig. 2. Pyrimidine nucleobases

The pyrimidine ring is virtually flat, and its reactivity exhibited electrophilic and nucleophilic attacks. Electrophilic substances almost reacted with pyrimidines at the carbon number 5 positions, it can be simply nitrated, halogenated, sulfonated and joined with diazonium salt. Although carbon number 2, 4 and 6 positions of the pyrimidine are the better target for direct nucleophilic attack [19].

Lathyrine comprising of pyrimidine ring non-proteinogenic a--amino acid (tingitanine, 8), extracted from the Lathyrus tingotanus seed [20]. "Variolin B 9" is pyrimidine-based alkaloid that has an activity to viral and cytostatic (Fig. 3)[21]. Bleomycins A2 and B2 are Complex natural products that have antitumor activity, they are peptides linked to several heterocycles ring of pyrimidine[22].

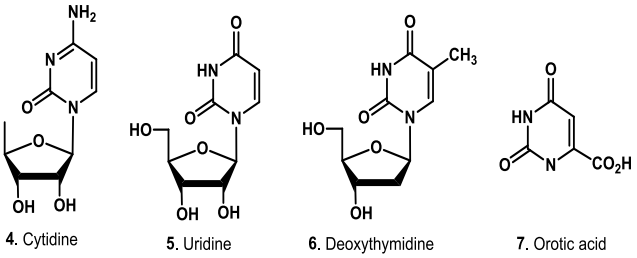


Fig. 3. Pyrimidine-Based Nucleosides and Orotic acid

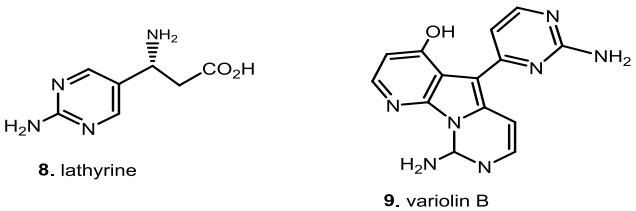


Fig. 4. Naturally Occuring Pyrimidine Lathyrine and Variolin B

Thiamine, **10** (B12) biosynthesis by different microorganisms addition to plants, the structure was explained ten years later after isolated in 1926, (Fig. 4) [23-25]. Furthermore, some antibiotics that contain pyrimidines such as bacimethrine **11** (Fig. 5) is isolated from *Bacillus megaterium* in 1961 that have bioactive to yeasts and bacteria[26,27].

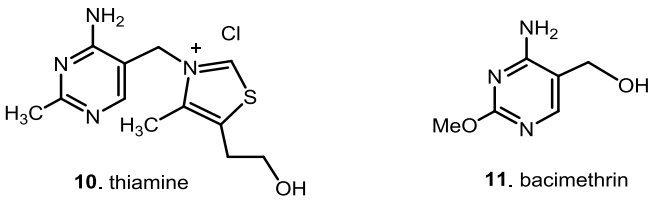


Fig. 5. Thiamine and its Natural Antagonist Bacimethrin

Medicinal Significance of Pyrimidines

The derivatives of Pyrimidine and Pyrimidine have potential bioactivities including antimicrobial and anticancer. This broad spectrum of targets due to the synthetic flexibility of pyrimidine, which has acceptable to the generation of a huge number of derivatives structure including analogues of the aryl ring , and/or derivatization of the pyrimidine nitrogen and 2,4,5,6 carbon sites. The medicinal properties of pyrimidines were reviewed by Jians *et al.* [28] in 2006 with more than 90 references while the biological importance of pyrimidines were reported by Arikkat *et al.* [29] and Mishra and Tomar[30].

Pyrimidine's biological activities suggest the maneuverability and flexibility of the medicinal chemist's continued interest in the pyrimidine skeleton in medicinal chemistry and drug development that is an active and critical field of heterocyclic chemistry research, which has found wide clinical applications. Figure 6 summarizes the medicinal significance of pyrimidines, in general.

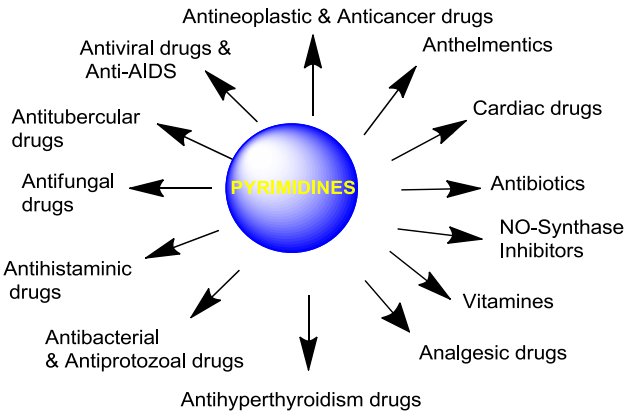


Fig. 6. Medicinal Significance of Pyimidines

Antineoplastics and anticancer agents

Present large number of antimetabolites pyrimidine-based. The first metabolites made is 5-fluorouracil [22,31,32] (5-FU, **12**), a pyrimidine derivative, which is clinically established anticancer drug for breast tumors treatment and tumor of colon and ovary[22]. *In vivo*, 5-fluorouracil also used as an anticancer drug when activated to 5-fluorodeoxyuridine [22]. Cytosine arabinoside known as (Cytarabin, **14**) is a antineoplastic agent [22]. 5-Thiouracil

15 also exhibits some useful antineoplastic activities[33] (Fig. 7).

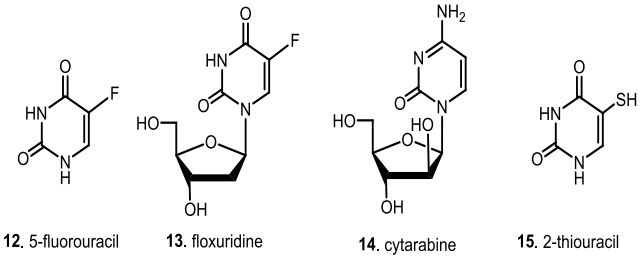


Fig. 7 Structures of Pyrimidine-Based Antimycotic and Antitumor Drugs

Some nucleobases and nucleosides of pyrimidine were modified for therapy of cancer (Fig. 8), such as gemcitabine **16**, [22,34], capecitabine **17** [35,36], tegafur **18** [37] and eniluracil **19** [38] which exhibited an excellent antitumor activity against solid tumors.

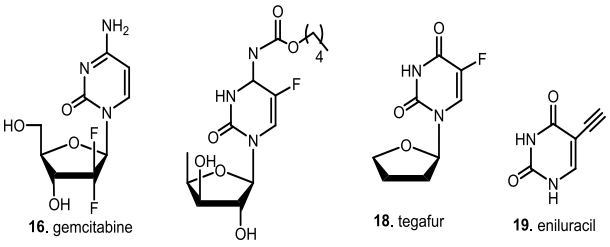


Fig. 8. Novel Pyrimidine-Based Cytostatics

Tyrosine kinase inhibitor imatinib mesylate (Gleevec, 20) is the novel agent of Leukemia treatment, comprises a 4-pyridyl-substituted pyrimidine-2-amine compound as the aromatic component (Fig. 9) [39].

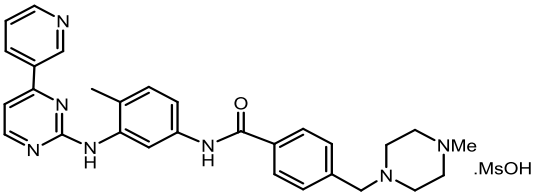


Fig. 9. Chemical Structure of Tyrosine kinase Inhibitor (**Gleevec**, **20**)

The antineoplastic [40] having guanine nucleus **21** *e.g.*: azathioprine **22** [41], mercaptopurine **23** [42], thioguanine **24** [43] were revealed after Woods and Fildes's theory are formulated of the antimetabolite in 1940. These medicines avoid normal cellular metabolites to utilized [40] (Fig. 10).

Fig. 10. Guanine Analogues as Antineoplastic drugs

Other compounds, such as mopidamol **25** [44], nimustine **26** [45], raltirexed **27** [46], uramustine **28** [47] and trimetrixate **29** [48] (Fig. 11) showed anticancer activity.

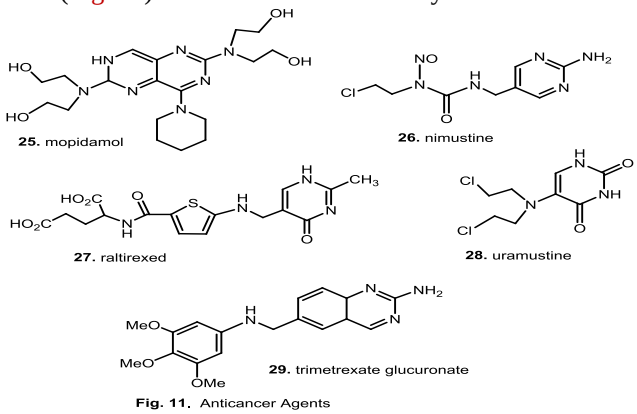


Fig. 11. Anticancer Agents

In 1999, Prof. Mayer of Konstanz University, Germany [49], discovered *monastrol*, (**30**), which inhibits the Kinesin Eg5, a motor protein that is important for spindle bipolarity. Drugs inhibit kinesins were developed as anti-cancer with hope to inhibit propagation of cancer cells (Fig. 12). Also, Xie *et al.* [50] synthesized novel 2,4,5- derivatives of pyrimidine **31** and **32**, then assessed *in-vitro* against human carcinoma of hepatocellular BEL-74502 cell proliferation. manycompounds have strong anticancer activity with an IC_{50} less than 0.10 μM (Fig. 12). Pease and co-workers [51,52] used a high-throughout screening campaign to identify 4,6-bis-anilino pyrimidines **33** and **34** as inhibitors of the cyclin-dependent kinase (CDK4) for treatment of cancer. (Fig. 13).

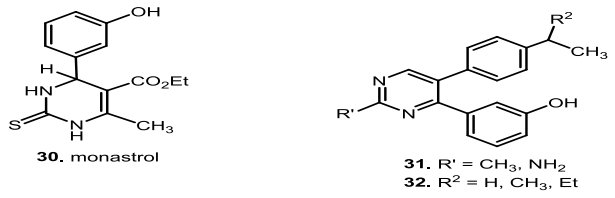


Fig. 12 pyrimidine derivatives for treatment of cancer

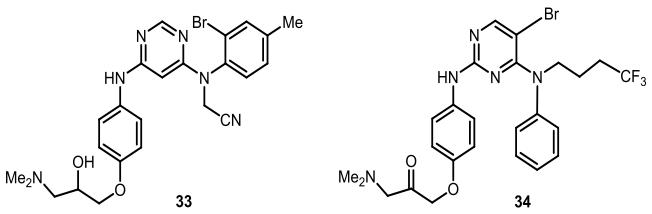


Fig. 13

Several pyrimidine derivatives *e.g.* derivatives of hydrazine-pyrimidine-5-carbonitrile **35** exhibited significant antitumor activity which showed inhibitory effects on growth of a different type of cancer cell lines commonly cases at 10^{-7} M concentrations [53]. Moreover, 2,4-diamino-6-(5-chloro-2-methylphenyl)-N^4-(4-trifluoromethyl) phenyl) pyrimidnes **36** were evaluated as blocked proliferation of tumour cell lines *in vivo*, especially duodenum cancer (DU145, IC_{50} = 0.23 μM [54] (Fig. 14).

Pyrimidine bridged thiadiazole derivatives, 5-benzyl-3-(((4,6-dimethylpyrimidine-2-yl)thio)methyl)-2,3-disubstituted-pyrimidin)1,3,4-thiadiazole **37** (Fig. 16), were synthesized by Azam *et al.* [55]. These pyrimidines exhibited significant antitumor activity against human breast cancer MCF 7 cell line.

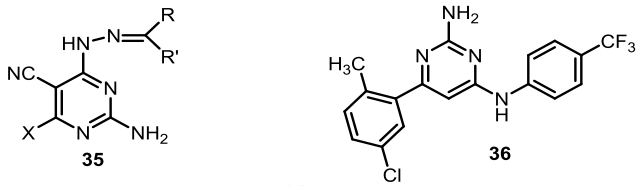


Fig. 14

Three tetralin-6-yl pyrimidines **38** and **39,** which were synthesized by Amin and *et al.* [56], were found active against liver cancer cell (Hep G2) with IC_{50} = 8.66 and 7.11 μg/mL, respectively (Fig. 15).

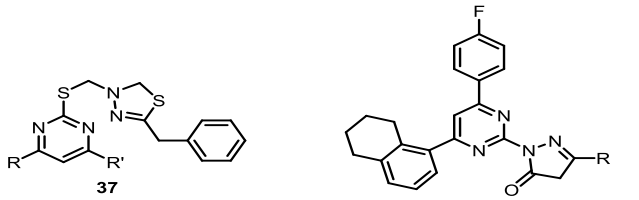
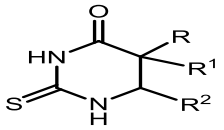


Fig. 15

Hyperthyroidism Drugs

2-Thiouracil **40** and its alkyl analogue, propylthiouracil **41** are active drugs towards hyperthyroidism. with minimum side effects the Thiobarbital **42** is used as a drug for hyperthyroidism [57] (Fig. 16).



40. R = R^1 = R^2 = H, X = S; 2-thiouracil
41. R = R^1 = H, R^2 = C_3H_7, X = S; propylthiouracil
42 R = R^1 = C_2H_5, R^2 = O, X = S; thiobarbital

Fig. 16.

Antifolates, antibacterial and antiprotozoal agents

Hitchings made a notable discovery in 1948, a huge number of 2,4 diamino-pyrimidines and several 2-amino-4-hydroxy-pyrimidines are folic acid antagonists [58]. A significant number of 2,4-diaminopyrimidines were synthesized as antifolates since then [59,60]. Pyrimethamine is among the 2,4-diaminopyrimidine medications **43**, an antimalarial drug, trimethoprim **44** [20], an antibacterial drug, methotrexate **45** and aminopterin **46**, both used in cancer chemotherapy [57]. Brodimoprim **47** is also found to be an effective antibacterial agent [61] (Fig. 17).

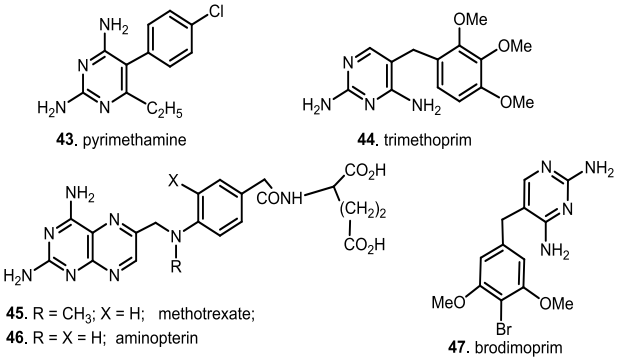


Fig. 17. Antibacterial and Antifolate Drugs

Antifungal effects were also demonstrated by Pyrimidine. Flucytosine 48 is a fluorinated pyrimidine used for treatment severe systemic infections of *candida* and *cryptococcus* as a nucleoside antifungal agent and antimycotic agent [62] (Fig. 18).

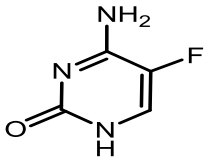


Fig. 18. Antifungal drug 'flucytosine' **48**

Antihelminitic and anti-inflammatory agents

Pyrantel pamoate **49** was identified as an antihelminitic agent for the treatment of roundworm and pinworm infestation by Hunziker [63]; while Basararaja *et al* synthesized naptho-pyrimidine analogues **50** [64] as anti-inflammatory, antiantihelmintic and antimicrobial agents (Fig. 19).

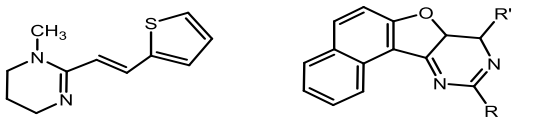


Fig. 19. Antihelminitic and antiinflammatory agents

Antiviral and anti-HIV agents

Because of their antiviral properties pyrimidine derivatives have created widespread interest recently. Due to its chemotherapeutic value against HIV, many powerful 6-alkylsulfanyl or sulfonyl-5-nitro-uracil families attract considerable interest. 1-[(2-hydroxy)ethyl]-6-(phenylthio)thymine (51) (HEPT) were synthesized by Miyasaki *et al.* [65,66] as a potent anti-HIV agent, whereas the HEPT analogues 52-54 were reported by Balazarini *et al.* [67] to be remained active against the majority of viruses containing including the HIV (Fig. 20).

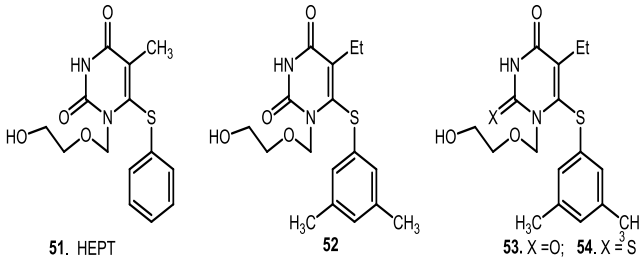


Fig. 20. Anti-HIV agents

A sequence of 5-nitro and 5-amino-6-arylsulfanyl-1-propyl-pyrimidine-2-4-diones 55 and 6-arylsulfanyl-1,3-dimethyl 56 and 2-amino 57 analogs have been synthesized by Al-Masoudi and co-workers [68] in order to produce new anti-HIV agents (Fig. 21).

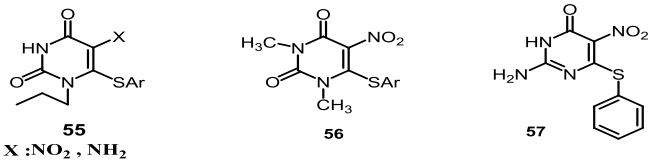


Fig. 21

The synthesis of various replaced 1,2,4-triazolo thymidines **58** and study of their anti-HIV activity (Fig. 22) were described by Al-Masoudi *et al.* [69] in their efforts to search for new potent and less toxic anti-HIV agents, have.

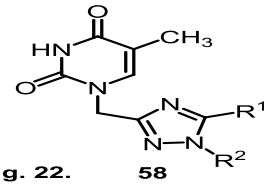


Fig. 22. **58**

Several members of a sequence of acyclic nucleosides containing a pyrimidine ring are considered to be effective antivirals, such as famicivlovir 59, valacyclovir 60 are drugs used for various DNA viruses, such as herpes simplex (HSV 1 and 2), varicella-zoster virus and Epstein-Bar virus [70].

Acyclovir **62** was used as a drug of choince for therapy of herpes simplex, while Penciclovir **61** was used for treatment of herpes simplex [71]. Meanwhile, Cidofovir **64** [72] was used for treatment of cytomegalovirus (CMV) in AIDS patient. Limivudine **63** [73] and abacavir sulfate **65** [74] were used as the nucleoside reverse transcriptase inhibitors for therapy of AIDS which were approved in 1998 (Fig. 23).

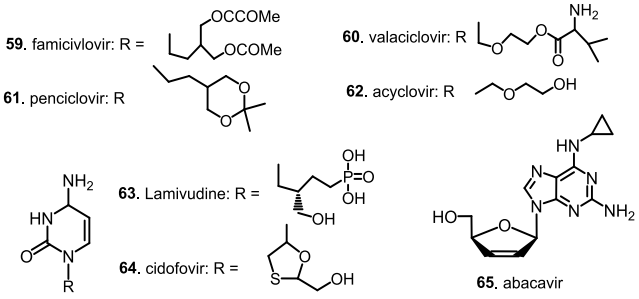


Fig. 23 Antiviral drugs

Antihypertenssive drugs

Several drugs containing pyrimidine rings demonstrated antihypertensive activity. Prazosin **66** is a selective α_1-adrenergic antagonist [75,76] while their analogues bunazosin **67** [77], terazosin **68** [78] and trimazosin **69** [79] are potent antihypertensive agents (Fig. 24).

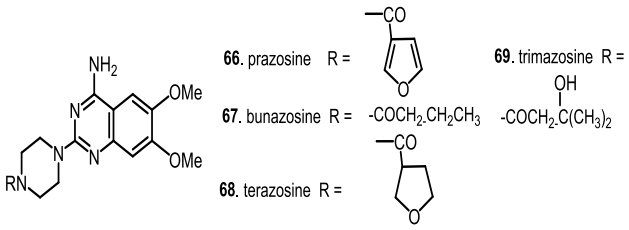


Fig. 24. Antihypertensive drugs

Antituberculosis drugs

Strepromyces capreolus produce Capreomycine **70s** is a second-line bacteriostatic antituberculin medication containing backbone pyrimidine [80,81] (Fig. 25).

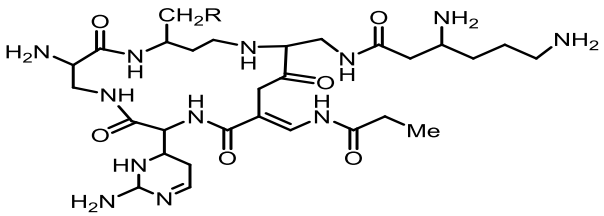


Fig. 25. Capreomycine **70**

Antibiotics

There are few examples of antibiotics containing pyrimidine. Bacimethrin 11, is active towards many staphylococcal infections [27,82], is the easiest of all. furthermore other Gram-negative and Gram-positive bacteria, Gourgetin 71, a cytosine derivative, is an active mycobacterium [83]. A Cytocine derivatives such as amicetin 72 and plicacetin are more active against rapid acid and Gram-positive bacteria [27] (Fig. 26).

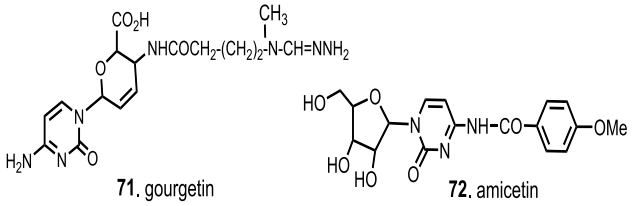


Fig. 26. Some antibiotics containing pyrimidine scaffold

Sulfa drugs compounds

pyrimidine derivatives of Sulfa, specifically sulfadiazine, sulfamerazine and sulfadimine, are preferable to other sulfonamides which used for many severe urinary tract inflammation, meningitis and pencillin allergic patients [84]. Sulfadoxine **73** [85], sulfisomidine **74** [86], sulfadiazine **75** [84], sulfamerazine **76** [84], sulfadimidine **77** [84] and sulfamethomidine **78** [87], carrying the pyrimidine backbone are considered the most potent drugs against several diseases (Fig. 27).

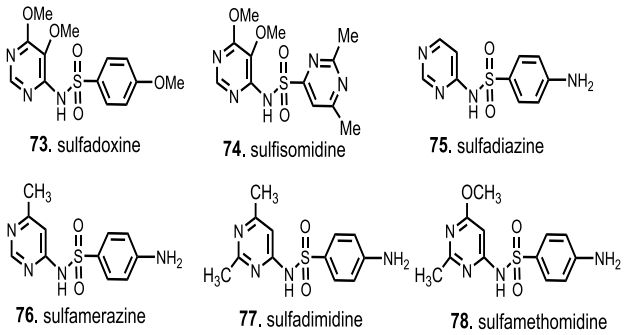


Fig. 27. Some sulfa drugs carrying pyrimidine backbone

Neurotoxines

Terodotoxin (tarichatoxin; 79) [88] is strong neurotoxins known to the non-proteins. It exists in the liver and the Japanese puffer fish or salamander ovarians (Taricha torosa) (Fig. 28). The structure is built upon a skeleton of 2-iminooctahydro-1H-quinazoline. In 1972, a complete synthesis of 79 was identified by Kishi *et al.* [89].

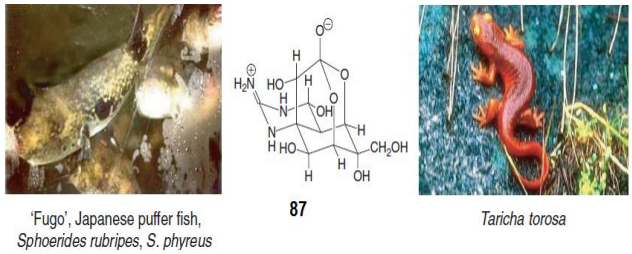


Fig. 28. **Neurotoxine 'Terodotoxin having pyrimidine scaffold' 79**

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