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A Study of New Chemical Entities for Infectious Disease Treatment

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Abstract – A number of infectious disease treatments are available today. However, infectious diseases still pose serious threats to patients because of the development of antibiotic resistance and the emergence of new infectious diseases. As on date, about 400 drugs including New Chemical Entities (NCEs), biologics, vaccines, new dosage forms and drug combinations are at different phases of their development against infectious diseases. Several antibiotics have been discovered following the discovery of penicillin. These antibiotics had been helpful in treatment of infectious diseases considered dread for centuries. The advent of multiple drug resistance in microbes has posed new challenge to researchers. The scientists are now evaluating alternatives for combating infectious diseases. This article provides preliminary information about New Chemical Entities (NCEs) for which New Drug Application (NDA) has been submitted by pharmaceutical companies to Food and Drug Administration (FDA) or which are in Phase III of their clinical trial. It would be interesting to see how many of New Chemical Entities (NCEs), among those discussed in this article, will see the face of the future.

Keywords: Infectious, Disease, Treatments, Development, Biologics, Vaccines, Drug, Information, Chemical Entities, etc.

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INTRODUCTION

Infectious diseases have been problematic and devastating to human lives since centuries. A large number of vaccines and infectious disease treatments are available today. However, infectious diseases still pose serious threats to patients because of the development of antibiotic resistance and the emergence of new infectious diseases, for example, since 1970s about 40 new infectious diseases have been discovered including swine flu, avian flu, MERS, and SARS. According to the literature, antibiotic resistant infections affect more than 2 million American people annually, cause about 23000 deaths annually, and account for $20 billion in direct health care costs annually. Therefore, continuous efforts are required to develop new drugs for the treatment of infectious diseases [1-4]. However, for pharmaceutical research companies, bringing new treatments for infectious diseases to the market is a challenging process because of the development of antibiotic resistance. Once a treatment has developed resistance to an infectious disease, medical practitioners start prescribing new treatments available in the market. This leads to financial loss to pharmaceutical research companies. Accordingly, on July 9, 2012, the Generating Antibiotic Incentives Now Act (GAIN Act) was signed into law by the President of U.S.A. as part of the U.S. Food and Drug Administration Safety and Innovation Act. The GAIN Act grants five years of exclusivity for those new antibiotics designated under the law as a “Qualified Infectious Disease Product (QIDP). The QIDP has been defined as an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections. During the exclusivity period antibiotics having QIDP designation can be sold without generic competition [5]. This period of exclusivity will increase the potential for profits from new antibiotics by giving pharmaceutical research companies more time to recoup their investment costs. Because of the implementation of GAIN Act, about 400 drugs including New Chemical Entities (NCEs), biologics, vaccines, new dosage forms and drug combinations, are in the development against, for example, bacterial infections, viral infections, fungal infections and parasitic infections [6-8]. These drugs are in different phases of clinical trials and for some of these drugs New Drug Application (NDA) has also been submitted by pharmaceutical companies to the U.S. Food and Drug Administration (FDA). The U.S. Food and Drug Administration (FDA) has also designated Fast Track status to many drugs which are in clinical trials. Fast Track designation is a process designed to expedite the development of new drugs and to get new drugs to the patient earlier [9]. This article provides preliminary information about New Chemical Entities (NCEs) for which New Drug Application (NDA) has been submitted by pharmaceutical companies to U.S. Food and Drug

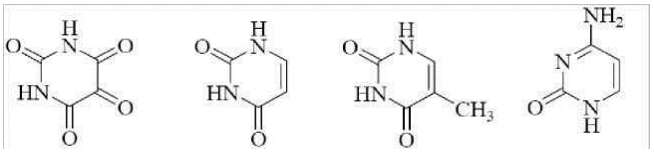
Administration or which are in Phase III of their clinical trial [10].

REVIEW OF LITERATURE:

ORGANIC AND RESTORATIVE CENTRALITY OF PYRIMIDINES AND OTHER RELATED HETEROCYCLIC PLATFORMS: Numerous heterocyclic structures have been recognized in different ways and they have indicated intense natural movement beginning from established vitamins to present day drugs/receptor based medication atoms [11]. A reasonable audit of these heterocyclic frameworks is said here in a brief way particularly identified with the ensuing sections on engineered perspectives.

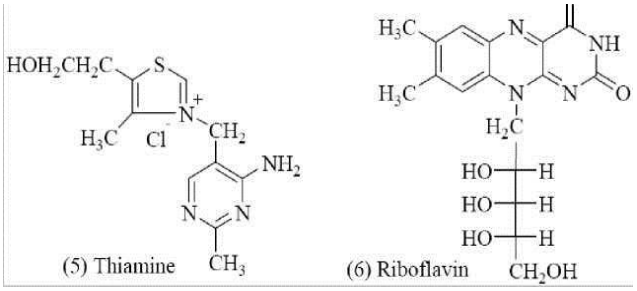
1. **Natural importance:** Pyrimidines have a long and recognized history reaching out from the times of their discovery as vital constituents of nucleic acids to their present use in the chemotherapy of AIDS [12].

Alloxan (1) is known for its diabetogenic activity in various creatures. Uracil (2), thymine (3) and cytosine (4) are the three critical constituents of nucleic acids.

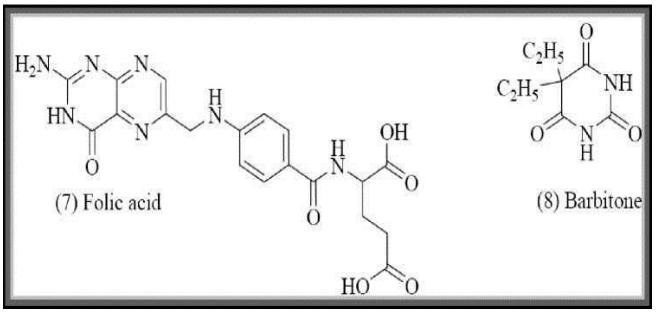


(1) Alloxan (2) Uracil (3) Thymine (4) Cytosine

The pyrimidine ring is found in vitamins like thiamine (5), riboflavin (6) and folic acid (7). Barbitone (8), the first barbiturate hypnotic, sedative and anticonvulsant are pyrimidine derivatives.



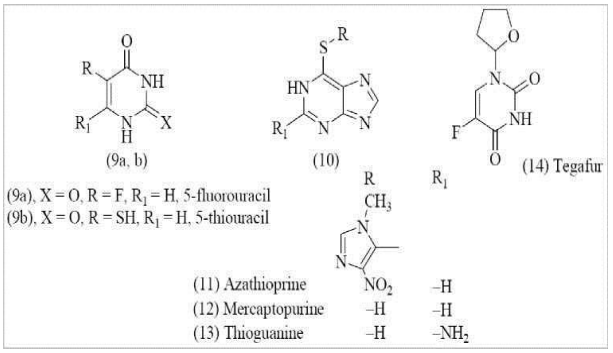
(5) Thiamine (6) Riboflavin



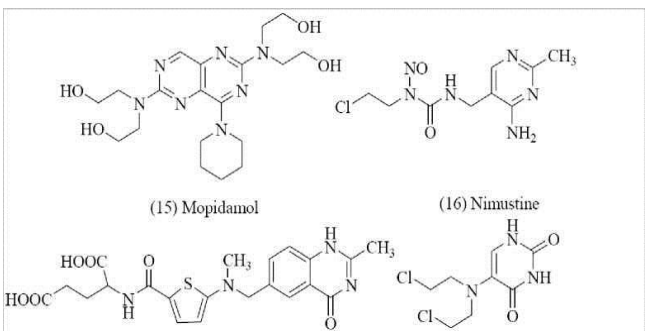
(7) Folic acid (8) Barbitone

2. **Medicinal Significance**: Amid the most recent two decades, a few pyrimidines subordinates have been produced as chemotherapeutic operators and have discovered wide clinical applications.

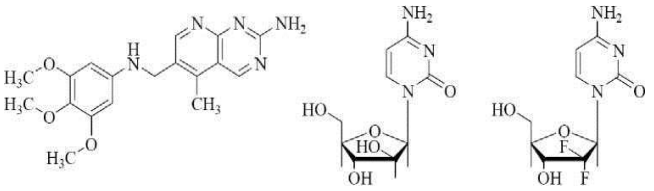
Antineoplastic /anticancer specialists: There are a substantial number of pyrimidine-based against metabolites. As a rule, they are fundamentally identified with the endogenous substrates that they irritate. The auxiliary adjustment might be on the pyrimidine ring or on the pendant sugar gatherings. One of the early metabolites arranged was 5-fluorouracil (5-FU, 9a) , a pyrimidines subsidiary. 5-Thiouracil (9b) likewise shows some helpful antineoplastic exercises [186]. The antineoplastic mixes having the guanine core (10) like azathioprine (11), mercaptopurine (12), thioguanine (13), tegafur (14), and so on were found after definition of the antimetabolite hypothesis by Woods and Fildes in 1940. These medications keep the usage of typical cell metabolites.



There are many more in recent times, like mopidamol (15) , nimustine (16) , raltitrexed (17), uramustine (18) and trimetrixate (19) . 1-5- DArabinosylcytosine (Ara-C, 20) is also an example of a pyrimidine antimetabolite in which the sugar is arabinose having a beta configuration. It is mainly used as an anticancer agent and also exhibits significant therapeutic effects in patients with herpes virus infections and herpes encephalitis. Gemcitabine (21), a pyrimidine antimetabolite, shows excellent antitumour activity against murine solid tumours [198].

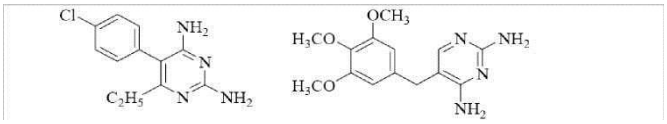


(17) Raltitrexed (18) Uramustine

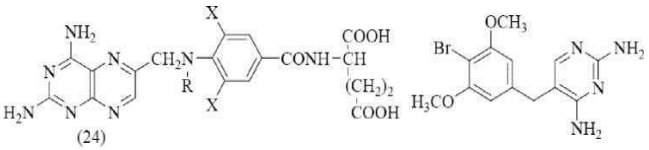


(19) Trimetrexate glucuronate (20) Ara-C (-1) Gemcitabine

Antifolates, Antibacterial, & Antiprotozoals



(22) Pyrimethamine (23) Trimethoprim



(24)

Brodimoprim

R = CHj. X = H: Methotrexate

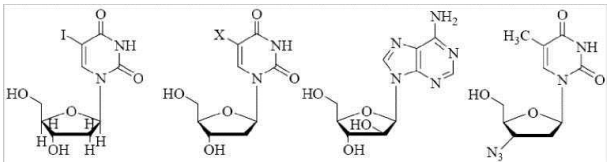
R = X = H: Aminopterin

R - CHj. X = Cl: 3 ' ,5'-di ch 1 o 10 metliot rex a te

In 1948, Hitchings made an important observation that a large number of 2,4- diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid [200]. Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates. It was eventually proved that these pyrimidines are inhibitors of the enzyme dihydrofolate reductase (DHFR). Notable amongst the 2,4-diaminopyrimidine drugs are pyrimethamine (22), a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim (23), an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non-selective DHFR inhibitors, methotrexate (24a) and aminopterin (24b), both used in cancer chemotherapy [203]. 3',5'-dichloromethotrexate (24c), which is less toxic and more readily metabolized than methotrexate, has recently been introduced for anticancer therapy [204]. Brodimoprim (25) is also found to be an effective antibacterial compound.

ANTIVIRALS & ANTI-AIDS

Recently, pyrimidine derivatives have generated widespread interest due to their antiviral properties. 5-Iododeoxyuridine (31) is an antiviral agent of high selectivity.



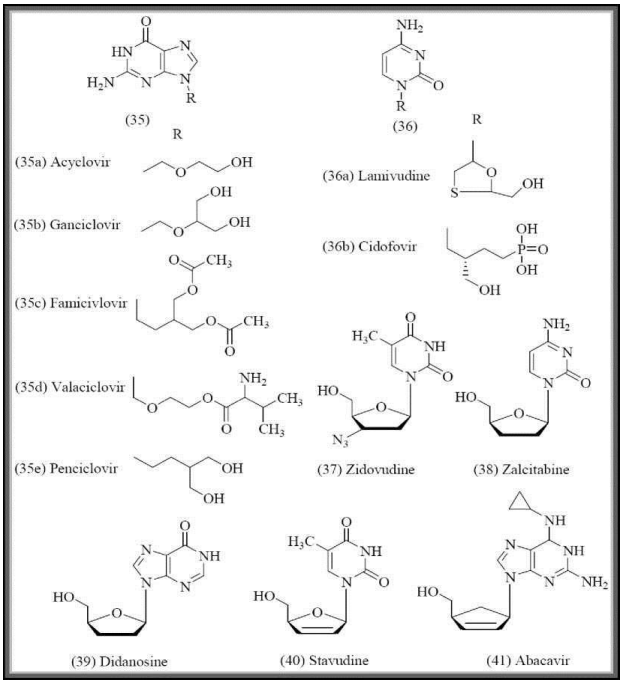
(31) 5-Ioclodeoxyuridilie (32) (33) Ara-A (34) Retrovir

X = I, 5-iodo-2'-deoxyuridine

X = CF_3. 5-trifluromethyl-2'-deoxyuridine

IDU (5-iodo-2'-deoxyuridine) (32a) has been extensively utilized for viral infections. 5-Trifluromethyl-2'-deoxyuridine (F3 TDR, 32b) has been found useful against infections resistant to IDU therapy. Ara-A, 9-5-D-arabinofuranosyl adenine (33), a relatively new antiviral drug, is effective against herpes infections of eye, brain and skin. It is especially effective against IDU-resistant herpes virus.

Some purine nucleosides are equally noteworthy. Retrovir (AZT-16, 34) is a potent inhibitor of the *in vivo* replication and cytopathic effects of HIV and has been recently approved for use against AIDS and severe ARC [212]. At present, Acyclovir (35a) is the only remedy for genital herpes. The oral formulation of Acyclovir is effective against both first and second degree recurrence genital herpes with minimal side effects. Ganciclovir (35b) has shown good *in vivo* activity against HCV1&2.



A few individuals from a progression of non-cyclic nucleosides, which contain a melded pyrimidine ring (fundamentally purine), are observed to be successful antivirals. Famiciclovir (35c) and valaciclovir (35d) are drugs utilized for a few DNA infections; including HSV composes 1 and 2, Varicella-zoster infection and Epstein-Barr infection. Penciclovir (35e) is helpful for topical treatment of intermittent herpes, Libialis. Cidofovir (36b), an antimetabolite for deoxycytosine triphosphate is utilized for the treatment of cytomegalovirus (CMV) in AIDS patients. Lamivudine (36a) is a powerful against

AIDS medicate when utilized as a part of blend with zidovudine (37) [216]. Zidovudine is a simple of thymidine in which the azido gathering is substituted at the 3-position of the dideoxyribose moiety. It is dynamic against RNA tumor infections (retroviruses) that are the causative specialists of AIDS and Immune system microorganism leukemia. It is utilized as a part of AIDS and AIDS related complex (Circular segment) to control pioneering contaminations by raising outright CD4+ lymphocyte tallies. Additionally, zalcitabine (38) is another valuable elective medication to zidovudine. It is given in blend with zidovudine, when CD4+ cell check falls beneath 300 cells/mm3. Didanosine (39) is a purine dideoxynucleoside, which is a simple of inosine. Didanosine represses HIV RT and applies a virustatic impact on the retroviruses. Joined with zidovudine, antiretroviral action of didanosine is expanded. Stavudine (40) is a pyrimidine nucleoside simple that has huge action against HIV-1 after intracellular change of the medication to a D4T-triphosphate. It is more powerful than zidovudine or didenosine for treatment in patients for deferring the movement of HIV contamination. It is prescribed for patients with cutting edge HIV contamination. Abacavir sulfate (41) was endorsed in 1998 as a NRTI (Nucleoside Turn around Transcriptase Inhibitor) to be utilized as a part of blend with different medications for the treatment of HIV and AIDS. The significant utilization of abacavir has all the earmarks of being in blend with different NRTIs.

CONCLUSION:

Infectious diseases cannot be eradicated completely. However, the efforts made by pharmaceutical research companies will help medical practitioners to combat infectious diseases. U.S. Food and Drug Administration (FDA) has also taken initiative to encourage pharmaceutical research companies to develop drugs for infectious diseases by providing Fast Track status and / or Qualified Infectious Disease Product (QIDP) status to the drugs which are under development. Therefore, it is expected that the process of development of drugs and / or New Chemical Entities (NCEs) for infectious diseases would be expedited. It would also be interesting to see how many of New Chemical Entities (NCEs), among those discussed in this article, will see the face of the future.

REFERENCES:

American Medical Association, Tavaborole, In: Statement on a Nonproprietary Name Adopted by the United States Adopted Names Council, AMA, Chicago, 2011, 1 (http://www.ama-assn.org/resources/doc/usan/tavaborole.pdf).

American Medical Association, Tedizolid Phosphate, In: Statement on a Nonproprietary Name Adopted by the United States Adopted Names Council, AMA, Chicago, 2010, 1 (http://www.ama-assn.org/resources/doc/usan/tedizolid-phosphate.pdf).

Anderson VR, Keating GM, Drugs, 2008, 68, 639.

Baldoni D, Furustrand UT, Aeppli S, Angevaare E, Oliva A, Haschke M, Zimmerli W, Trampuz A, Int J Antimicrob Agents, 2013, 42, 220.

Barak O, Loo DS, Curr Opin Investig Drugs, 2007, 8, 662.

Debaditya D, Paul MT, Purvi M, Edward F, Philippe P, Clin Infect Dis,2014, 58, S51.

Gupta AK, Simpson FC, Expert Opin Invest Drugs, 2014, 23, 97.

Malabarba A, Goldstein BP, J Antimicrob Chemother, 2005, 55(Suppl. 2), ii15.

Moellering RC Jr,ClinInfectDis, 2014, 58, S1.

Osborne R, BioWorld Today, 2013, 24, 1.

Pharmaceutical Research and Manufacturers of America, Infectious Diseases: A Report on Diseases Caused by Bacteria, Viruses, Fungi and Parasites, In: Medicines in Development, PhRMA, Washington DC, 2013, 1 (http://www.healthhiv.org/modules/info/files/files_529f8c1217798.pdf).

World Health Organization, Miltefosine, In: WHO Technical Report Series 965, WHO, Geneva, 2012, 63

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