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THIOPYRIMIDINE - AN OVERVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY

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ABSTRACT:

Thiopyrimidine derivatives have received the greatest attention, and several of its analogues are effective in treating a number of pathological disorders that are briefly covered in this article. The thiopyrimidine entity, which has interesting activities in the present article, focuses on synthesis and biological activity for various pathological conditions like Cancer, HIV, Tuberculosis, Convulsant etc. Many of its analogues are active against a variety of pathological conditions, and these are evaluated against varies elemental and mass spectral analysis which are briefly discussed in this article. Here, innovative, simple, conventional and microwave synthesis are all discussed simultaneously.

Keywords: Thiopyrimidines, Pathological disorders, Spectral analysis, Biological activity.

MEDICINAL CHEMISTRY/ HETEROCYCLIC CHEMISTRY:

The identification, synthesis, and development of new chemical entities that are appropriate for medical or pharmaceutical application are the focus of the field of medicinal chemistry, which lies at the nexus of chemistry and pharmacology. Organic chemistry, phytochemistry, pharmacology, toxicology, molecular biology, biochemistry, computational chemistry, physical chemistry, and statistics are just a few of the interdisciplinary fields that make up medicinal chemistry. As part of this, existing medications are also studied, as well as their pharmacological characteristics, toxic consequences, and quantitative structure-activity connections (QSARs).

Natural products and synthetic organic chemicals make up the majority of medicinal compounds used as medications. The majority of chemical compounds include heteroatoms like N, O, S, etc. These heterocycles are useful for altering the pharmacological activity as well as physical characteristics like solubility, polarity, bonding, and lipophilicity that lead to the optimization of the ADMET properties of drugs they can be either aliphatic heterocyclic compounds or aromatic heterocyclic compounds[(1)]. Some of the examples are given below in figure 1[(2)].

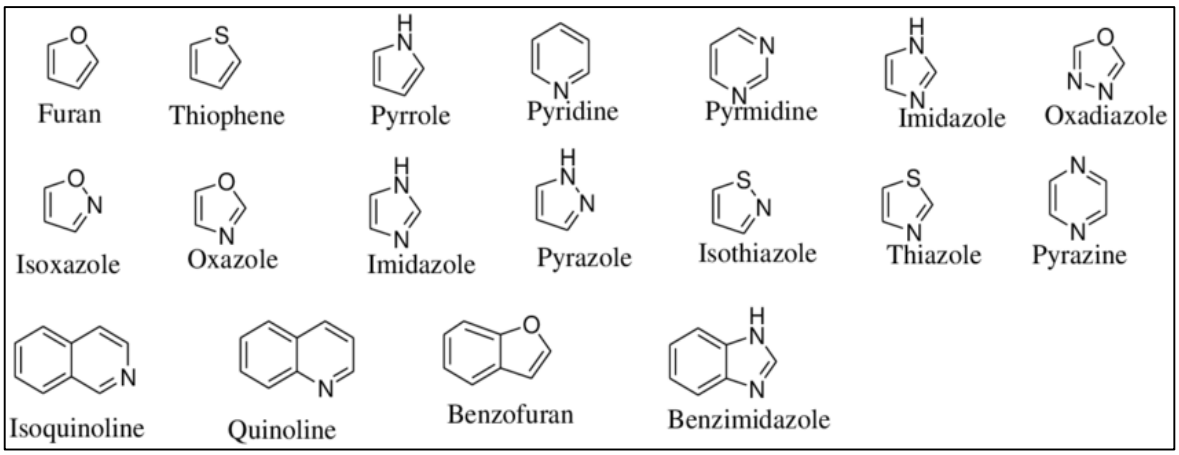


Figure -1[(2)]

THIOPYRIMIDINE:

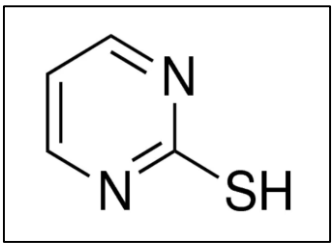


Figure-2

An aromatic heterocyclic organic compound resembling pyrimidine is thiopyrimidine. It has two nitrogen atoms in the ring, and a Sulphur or thio group in the second position. It was discovered that the 2-thiopyrimidine moiety played a deciding role in the biological activity. Similar to a vitamin thiamine, pyrimidine and its derivatives have been discovered to have a variety of pharmacological effects, including antiviral, anticancer, antifungal, antimalarial, anti-convulsant, hypnotic and sedative actions. Six-membered rings with nitrogen and Sulphur make up thiopyrimidines. They generate a lot of interest because they offer a significant class of both natural and non-natural products a lot of which exhibit important pharmacological and clinical applications.

In the 19th century, thiopyrimidines were first studied. The addition of a thio group, on the other hand, may be thought of as a less well-known method of chemical modification. It offers more chances for continued functionalization and the capacity to control the oxidative processes in the organism. Since pyrimidine derivatives and their condensed analogues with an exocyclic Sulphur atom at position 2 of the pyrimidine ring are biologically active compounds, the present review is focused on gathering and analyzing literature data regarding the methods of synthesis and studies of their biological properties.

Many times, the only way to create these heterocyclic systems is by directly interacting different 2-halo derivatives with chemicals that contain Sulphur. However, there exist techniques where 2-thioxopyrimidines and their condensed analogues are formed based on the [3+3], [4+2], or [5+1] the domino reactions and heterocyclization reactions that are the focus of this review [(3)].

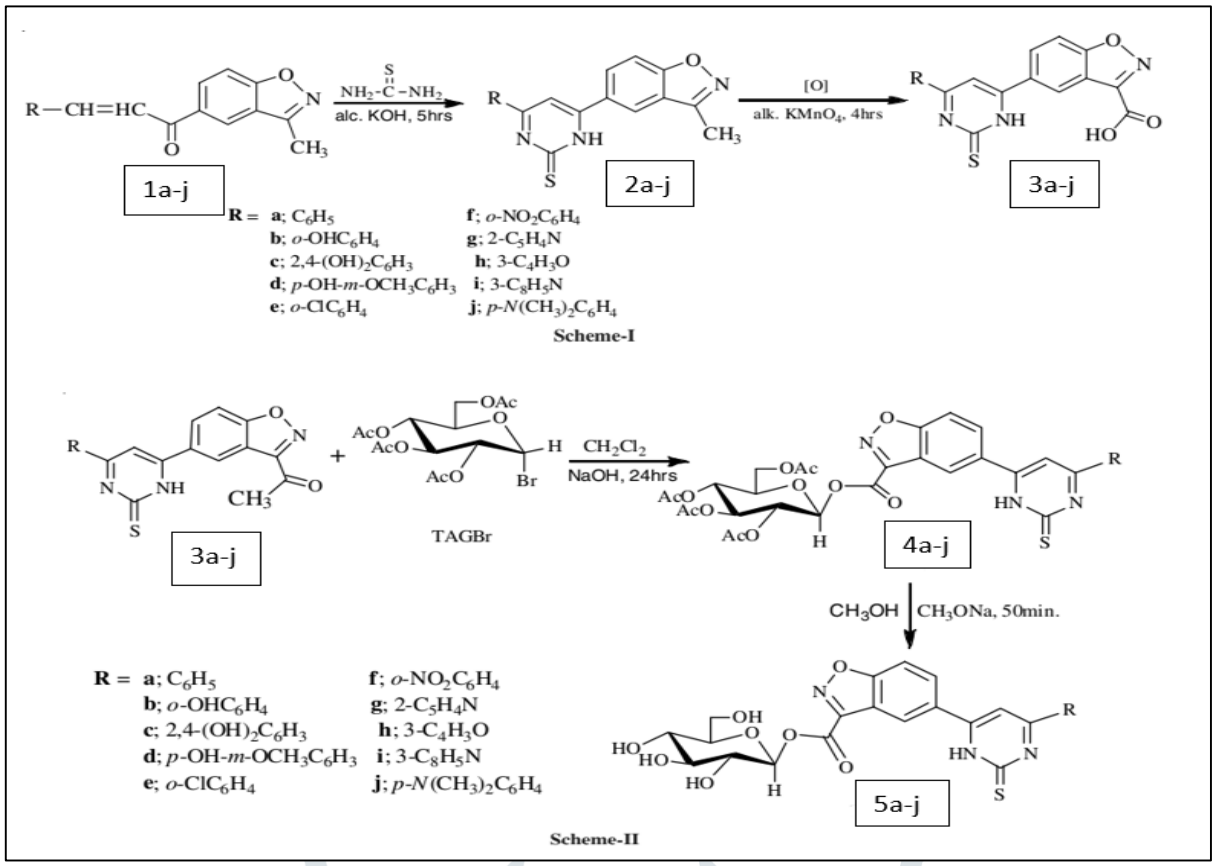
GENERAL SYNTHESIS:

NOVEL AND FACILE SYNTHESIS:

Numerous thiopyrimidines have been produced using a quick and effective approach, and they exhibit strong anti-inflammatory, analgesic, protein kinase, and inhibitory properties. Due to the biological and chemotherapeutic importance of its derivatives, organic chemists have been drawn to them. Related fused heterocycles are significant classes of heterocyclic compounds that exhibit a wide range of biological importance, including anticancer, antiviral, antibacterial, antioxidant, anxiolytic, antidepressant, and analgesic properties.

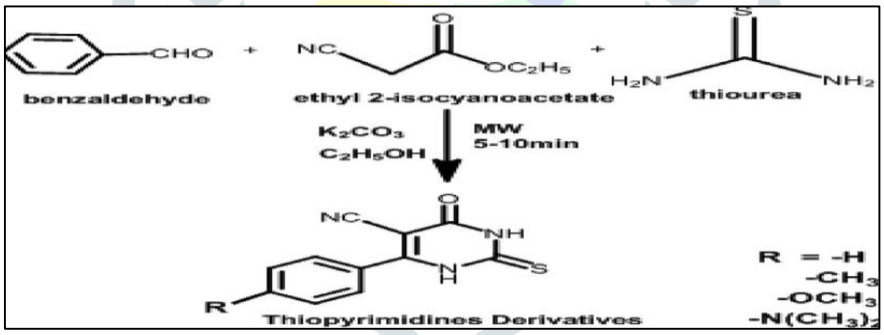
Glucosides are often optically active and water-soluble substances. O-Glucosides are the acetals of alcohols or phenols and are found in a wide variety of plants and animals in the natural world. O-glucosides primary purpose is to act as the pharmacophoric group's handle so that target cells can recognize the structure. The synthesis of a number of new pyrazoles, carboxylic acid, and chalcone derivatives with an O-glucoside moiety was described. Thiopyrimidine nuclei, renowned for having a variety of physiological actions, play a significant role in this regard. This inspired to create several thiopyrimidine derivatives, which we describe in this study together with their physicochemical characterization and investigation of their possible biological activity.

After being refluxed for five hours, a mixture of 1a-j, thiourea, ethyl alcohol, and KOH produces 2a-j; subsequent alkalization with $Kmno_4$ creates 3a-j; and the presence of CH_2Cl_2 in TAGBr produces 4a-j and 5a-j compounds in presence of CH_2Cl_2, NaOH for 24hrs as shown in scheme-I & scheme-II. The elements of all the produced compounds were examined using FT-IR, ^1H NMR, elemental analysis (C, H, and N), and mass spectral data. By using the cup-plate method, the majority of the produced compounds had been tested for their antibacterial and antifungal properties. The current method has a number of benefits, including quicker reaction times, cleaner reactions, good yields, inexpensive reagent, and gentle reaction conditions [(4)].



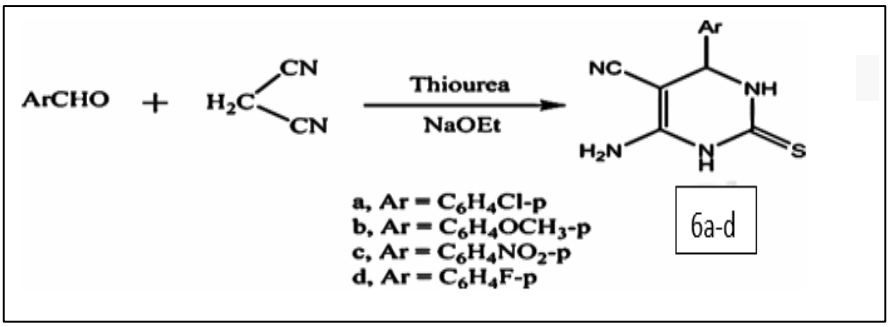
Microwave synthesis:

- Thiopyrimidine derivatives are produced by microwave synthesis of benzaldehyde, ethyl-2- isocynoacetate, and thiourea in the presence of K_2CO_3 and C_2H_5OH for 5–10 minutes, reaction is represented in scheme III [5]



Scheme III

- Thiopyrimidine derivative (6a-d) is produced when an aldehyde and cyanide moiety are combined with thiourea and sodium ethoxide is shown in scheme IV[6].



Scheme IV

SYNTHESIS AND BIOLOGICAL ACTIVITY OF THIOPYRIMIDINE DERIVATIVES:

ANTICANCER ACTIVITY:

- Cancer is one of the most common causes of death worldwide. Stomach, breast, prostatic, lung, and colon cancer have the greatest mortality rates from cancer. breast cancer is the most typical cancer among women. It accounts for 16% of all cancers in women and 18.2% of all cancer-related deaths in both men and women.

  Signal transducer and activator of transcription protein family is a crucial signalling intermediate in cancer cells, including leukaemia, breast, and colon cancer cells. Overactivation of STAT, which activates receptor tyrosine kinase, results in tumorigenesis. Inhibiting STAT3 and STAT5a causes tumour cells to undergo apoptosis. One of the most significant classes of pyrimidines are 2-thiopyrimidines (2-TPs), also known as 2-mercaptopyrimidines. Their numerous uses in the creation of antitubercular, anti-inflammatory, and cardiotonic medicines draw the attention of biochemists.

  Additionally, 2-TPs had their anticancer activities assessed. According to reports, they have strong anticancer activity against leukaemia, colon, and breast cell lines. Chalcone and thiourea react to produce derivatives of 2-thiopyrimidines/2-mercaptopyrimidine. They work by blocking STAT3 and STAT5a, which have an anti-cancer effect on human lung and breast cancer. Novel 2-TP/chalcone hybrids figure 3 compound were created with the intention of serving as anticancer medications. Utilizing several spectroscopic methods, they were synthesised and identified. It has shown increased anti-cancer activity and reference drug used here is erlotinib and cis platin[7].

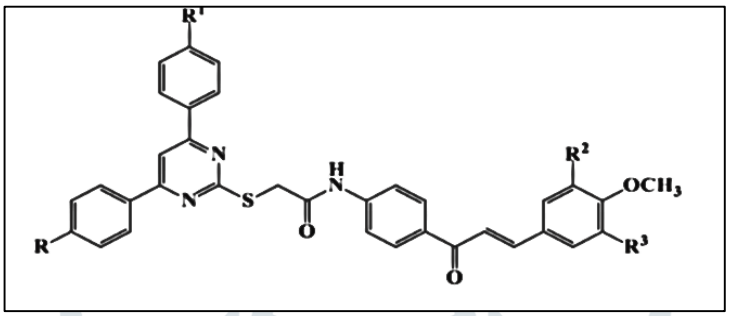


Figure 3

R-OCH_3,Cl R²-H,OCH_2

R^1-CH_3,NO_2,OCH_2CH_2Cl R^3-H,OCH_2

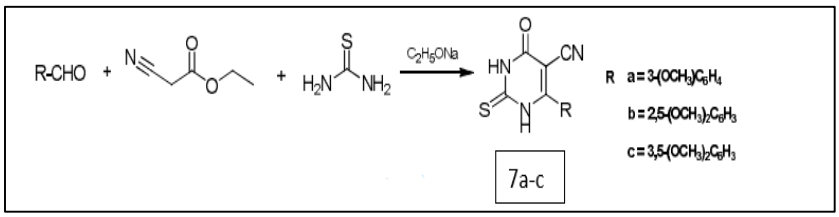
- DNA synthesis and cell division are the main targets of conventional anti-cancer medications such alkylating agents, antimetabolites, topoisomerase inhibitors, and anti-microtubule medicines. Even though these medications are effective, their inability to distinguish between tumor cells and normal cells frequently results in serious side effects that restrict their use, such as bone marrow suppression and cardiac, hepatic, and renal toxicities.

  Thiouracil derivatives have received a lot of attention recently for their anti-tumor potential. The thiouracil carbonitrile ring system has also played a significant role in the design and synthesis of new chemotherapeutic drugs with outstanding anticancer and antibacterial activity, according to a literature review. It has also been acknowledged that one promising target for therapeutic development is the suppression of folate-dependent enzymes such thymidylate synthase, which catalysis the reductive methylation of deoxy uridylate (DUMP) to thymidylate (DTMP). This effort attempts to design and synthesis a new series of thiouracil carbonitrile derivatives as anticipated anti-cancer medicines based on all of these discoveries. HepG2 was used to test some of the novel compounds' cytotoxic properties.

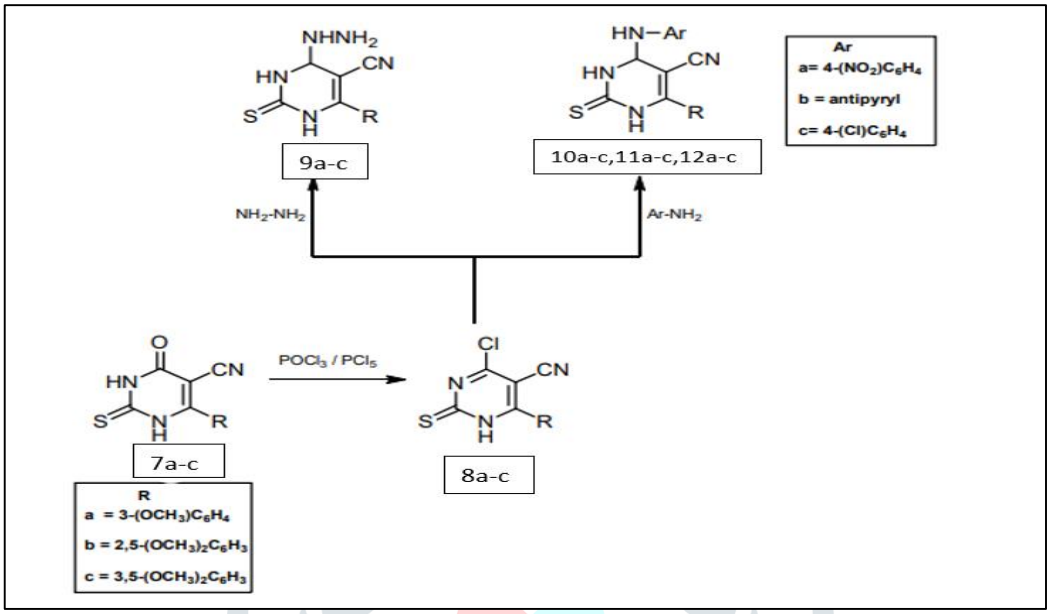
  Thiourea and ethyl cyanoacetate were combined with the proper aldehydes, such as 3-methoxy benzaldehyde, 2,5-dimethoxy benzaldehyde and 3,5-dimethoxy benzaldehyde, to create the necessary building block 6-substituted-4-oxo-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carbonitriles 7a-c as shown in scheme V. phosphorous pentachloride and phosphorous oxychloride have been used to make this reaction, resulting in 4-chloro-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile 8a-c.

  Afterwards, this reacts with hydrazine hydrate to produce 9a-c and combines with primary amines to produce 10a-c, 11, and 12 shown in scheme VI. Because of the structural resemblance to 5-FU, which was used as the standard reference drug, compound 10a proved particularly effective against cancer (3-times more potent). All docking studies were performed using 'Internal Coordinate Mechanics [Molsoft ICM 3.5-0a][8]

Scheme-V



Scheme-VI



Therefore, mentioned information leads to a conclusion that novel thiopyrimidine derivatives exert anticancer activity similar to that of 5-FU by inhibiting the enzyme ***thymidylate synthase***[8].

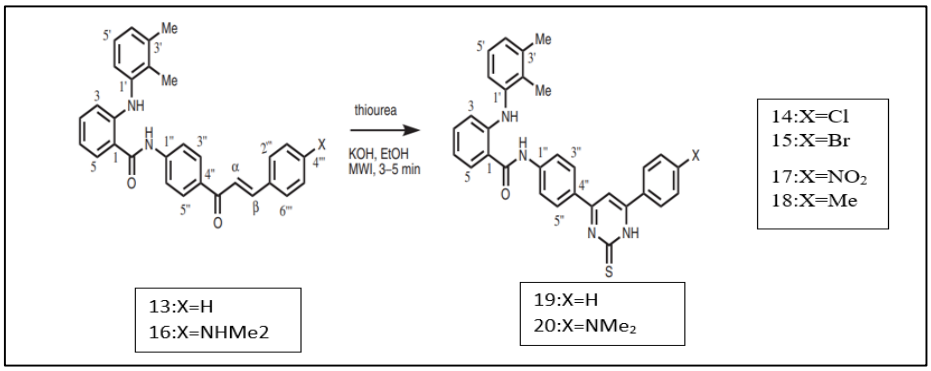
ANTI-HIV & ANTI-LEUKEMIC ACTIVITY:

The well-known intermediates for the synthesis of numerous heterocyclic compounds are chalcones. It has been discovered that the biological activity of chalcones is caused by the presence of a reactive alpha, beta-unsaturated keto group. For the treatment of HIV infection, a variety of therapeutic methods have been employed.

Due to their distinct antiviral efficacy, high specificity, and minimal toxicity, non-nucleoside reverse transcriptase inhibitors have cemented a significant and crucial place in the treatment of HIV. In view of the significance of chalcones, which yield thiopyrimidine derivatives that exhibit anti-HIV and anti-cancer activity, we present the synthesis, anti-HIV activity, and cytotoxicity of novel chalcone analogues derived from mefenamic acid.

The chalcones 13 and 16 are the building blocks for the development of new thiopyrimidine derivatives with the intention of comparing their anti-HIV activity and cytotoxicity against human lymphocyte MT-4 cells to that of the chalcone analogues 13 to 18 in these tests. Thus, after purification and neutralization with HCl, the treatment of 13 and 16 with thiourea in 20 % NaOH and EtOH under microwave irradiation (400 W, 180°C) for 3-6 min provided the thiopyrimidine derivatives 19 and 20 in 65 % and 60 % yield, respectively.

Thiopyrimidine analogues 19 and 20 were produced by treating 13 and 16 with thiourea in a basic media, respectively as shown in scheme VII. The newly created substances were in MT-4 cells tested for against HIV-1 and HIV-2. Compounds 14 and 16 demonstrated for cytotoxicity values of 2.17 and 2.06 μm, respectively, against mock-infected MT-4 cells (C type adult T leukaemia cells), which considered to be promising antileukemic agents. Structures are determined under IR, H and ^{13}C NMR[9].



Scheme-VII

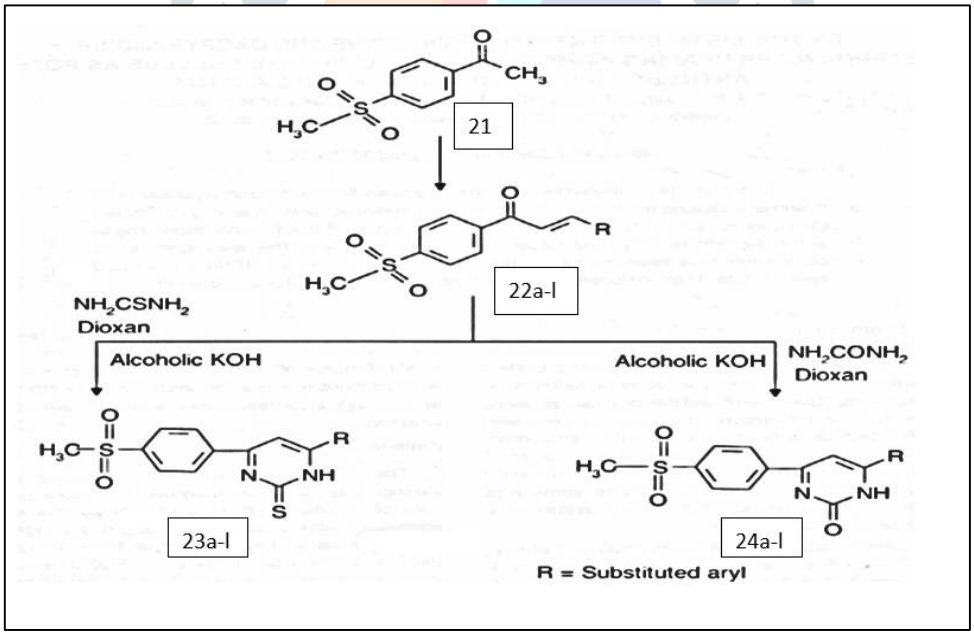
ANTI-TUBERCULAR AND ANTI-MICROBIAL ACTIVITY:

By undergoing evaluation, it was shown that thiopyrimidine nucleus displayed numerous biological activities like anti-HIV, antibacterial, anti-tubercular etc... Chalcones are the primary intermediates for the production of many heterocyclic chemicals. Condensation of 21 with aromatic aldehydes gives 22a-l this on reaction with thiourea affords 23a-l and on reaction with urea yields 24a-l as shown in scheme VIII .

On primary screening of compounds for anti-tubercular activity against mycobacterium tuberculosis by using medium ALAMAR radiometric method and the data was compared against standard drug rifampicin it showed 98% inhibition.

Anti-microbial activity was assayed by using cup-plate agar diffusion method by measuring the zone of inhibition in mm. bacterial strains such as bacillus, E.coli and obtained data was compared against standard drugs like penicillin, Griseofulvin , ampicillin, amoxicillin etc.….

Carlo Erba's EA 1108 elemental analyser was used for elemental analyses. KBR disc was used to record IR spectra using an FTIR 8400 spectrophotometer. Thin layer chromatography was used to verify the purity of the molecule after 1H NMR spectra were obtained using a Bruker Avance II 400 Spectrometer, mass spectra were computed using a GCMS-QP2010 mass spectrometer[10].



Scheme-VIII

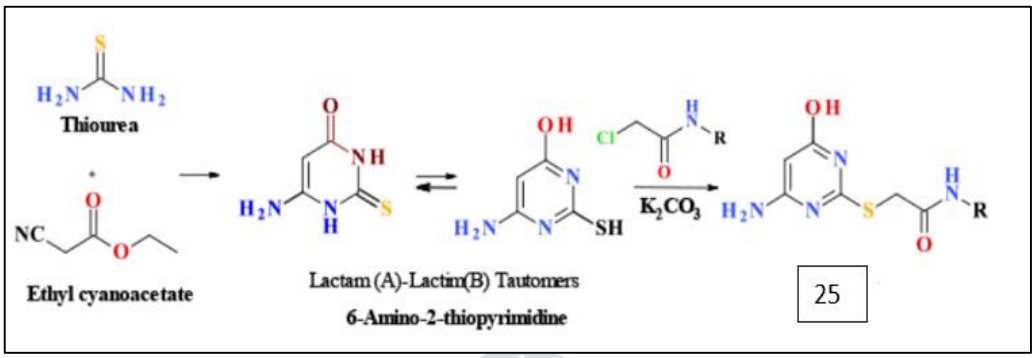
ANTI-CONVULSANT ACTIVITY

The offered research's objective was to specifically synthesis derivatives of the anticonvulsant drug (4-amino-6-hydroxy-pyrimidin-2-yl)thio-N-acetamides. The ADMET approach and docking study were used to examine the perspective of the search for anticonvulsants.

The initial 6-amino-2-thiopyrimidine was produced by the interaction of thiourea with ethyl cyanoacetate in the presence of sodium ethoxide. By alkylating 6-amino-2-thiopyrimidine with the appropriate 2-chloroacetamides in a DMFA environment with potassium carbonate present, the desired thioacetamide derivatives (25) were created as shown in scheme IX.

LS/MS, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis were used to determine the structure of the produced compounds. On a model of rat seizures brought on by pentylenetetrazole, anticonvulsant activity was investigated. 2-((4-amino-6-hydroxypyrimidin-2-yl) thio)- N-(3-methylphenyl) acetamide was identified as the lead substance.

The above-mentioned substance has demonstrated its capacity to increase latency period, decrease seizure frequency and intensity, and prevent fatality. There are some characteristics that correlate between structure and anticonvulsant action. The results of the molecular docking analysis revealed the lead compound's affinity for the GABAA, GABAAT, Carbonic Anhydrase II, and NMDA receptors as well as a potential mechanism of action for its anticonvulsant effects [(11)].



Scheme IX

CONCLUSION:

The most widely investigated thiopyrimidine derivatives and its analogues are efficacious against a variety of clinical diseases, which are briefly discussed in this article. The focus of the current article is on the synthesis and biological activity of thiopyrimidine and its derivatives. Current article focuses on synthesis and biological activity for different pathological conditions like cancer, leukemia, HIV, tuberculosis, microbial infections, convulsant etc.

Novel and facile synthetic procedures are designed using a variety of compounds, including thiourea and ethyl alcohol followed by alkylation, this current novel approach has a variety of advantages, such as faster reaction times, cleaner reactions, good yields, affordable reagent, and mild reaction conditions and they are examined using elemental and spectral analysis. thiourea and aldehyde ethyl cyanoacetate react and produce thiopyrimidine derivatives that showed inhibitory activity against STAT3 and STAT5a and resulted in an anti-cancer effect, as well as thiourea and chalcone react and produce thiopyrimidine derivatives by undergoing reaction with various compounds that were 3 times more potent than 5-FU by inhibiting thymidylate synthesis.

Anti-HIV activity was tested against MT-4 which showed prominent activity against HIV. Anti-tubercular activity was tested against Mycobacterium tuberculosis. Bacillus and E. coli bacterial strains and the data acquired were compared to common antibiotics including penicillin, Griseofulvin, ampicillin, and amoxicillin, among others and the data was compared against rifampicin, anti-convulsant activity was tested by reacting thiourea and ethyl cyanoacetate and producing thiopyrimidine that showed affinity for GABA, and carbonic anhydrase that showed promising activity. Hence this proves that thiopyrimidine and its derivatives have vital role as medication for many pathological disorders or active against various pharmacological disorders.

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