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Pyranopyrimidine: A promising scaffold with various biological activities

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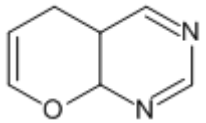
ABSTRACT
Heterocyclic compounds are one of the most important molecules in the synthesis of pharmacologically active compounds. One of the most promising heterocycles among all is the pyranopyrimidine scaffold, that has been found in both natural and synthetic sources. It has been confirmed to possess a range of biological activity, including anti-HIV, anti-tubercular, anti-HBV, anti-dyslipidemic, anti-platelet, anti-inflammatory, antioxidant, and antibacterial properties.The objective of this review is to highlight significant pyranopyrimidine analogues with a range of biological activity.

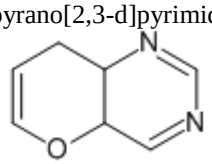
Keywords: Pyranopyrimidine, antimicrobial activity, docking, Staphylococcus aureus, Klebsiella pneumonia and Bacilluscereus

I. INTRODUCTION

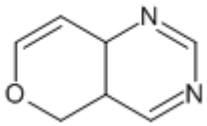
Pyridopyrimidines are a class of heterocyclic compounds comprising a pyrimidine ring with two nitrogen atoms at "1,3- positions" fused to a pyran ring with one oxygen atom. Various isomers are found for this class of compounds, it includes 5H-pyrano[2,3-d]pyrimidines, 8H-pyrano [3,2-d]pyrimidines, 8H-pyrano[3,4-d]pyrimidines, and 5H-pyrano[4,3-d]pyrimidines without a conceivable location of a nitrogen atom at the ring junction.



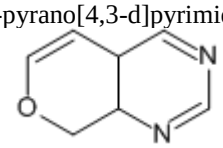
5H-pyrano[2,3-d]pyrimidines



8H-pyrano [3,2-d]pyrimidines



5H-pyrano[4,3-d]pyrimidines



8H-pyrano[3,4-d]pyrimidines
Isomeric structures of pyranopyrimidine

The common approach for the synthesis of heterocycles with pyrano[2,3-d]pyrimidine nucleus generally involves multicomponent reactions of barbituric acid, malononitrile, and aryl aldehydes in the presence of a base. [1-3]

Pyranopyrimidine heterocycles have significant and confidential biological and physiological potency since this class of compounds demonstrated antibacterial, antitumor, antimicrobial, anti-inflammatory, antioxidant, antidiabetic, tyrosine phosphatase inhibitors, antitubercular, antihypertensive, antimalarial, antiviral,anticancer,and cardiotonic agents.The pyranopyrimidine moiety is also synthesized by the eco-friendly method using one- pot three- component condensation reaction that is carried out by the reaction of p- chlorobenzaldehyde, thiobarbituric acid, and malononitrile in the presence of the catalytic amount of (Fe_3O_4, ZnO, Mn_3O_4) nanoparticles.[4]This review will elucidate various biological aspects of pyranopyrimidines and possible targets and mechanisms underlying its inhibitory effects.

Biological activity

Antitubercular activity

Nimesh R. Kamdar et.al[5], synthesized pyranopyrimidine derivatives and evaluated for their in vitro antitubercular activity against Mycobacterium tuberculosis H37Rv [ATCC-27294]. The antitubercular activity study revealed

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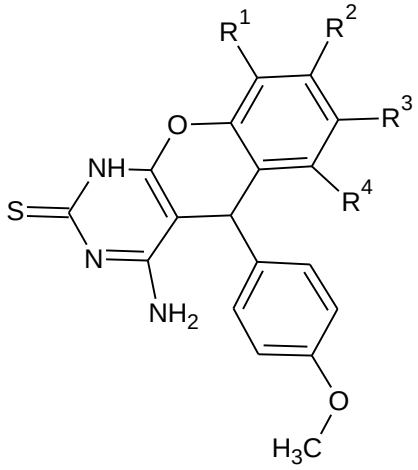
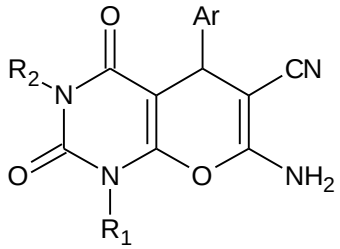
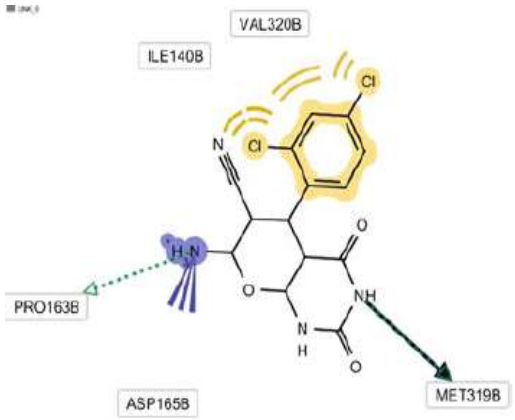
that all the tested compounds showed good to moderate antitubercular activities against Mycobacterium tuberculosis H37Rv.



Urease inhibitory activity

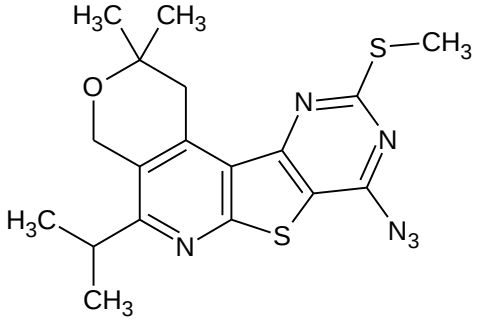
Ghodsi Mohammadi Ziarani et.al[6], reported the nano catalysed synthesis of pyrano[2,3-d]pyrimidine diones derivatives from the reaction of barbituric acid, malononitrile and various aromatic aldehydes using SBA-Pr-SO_3H as a nano catalyst. Computational studies were carried out using the Autodock tool with H. pylori urease (pdb ID: 3LA4) as the binding enzyme. Urease activity for the synthesized compounds were reported by rapid phenol red urease test.

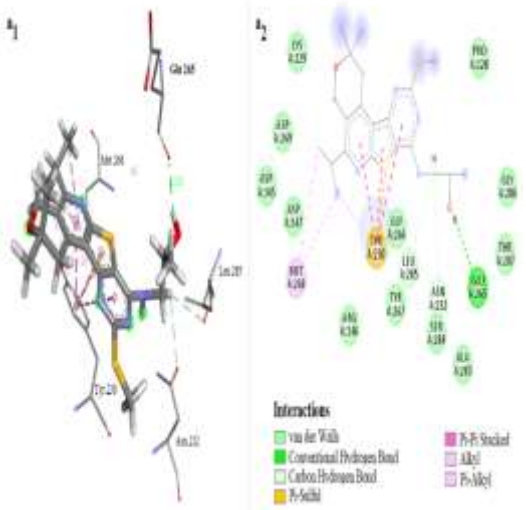




Antimicrobial activity

Samvel N. Sirakanyan et.al [7] reported the synthesis ofpyrano[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-d]pyrimidine. The possible antimicrobial activity of newly synthesized compounds against some gram-positive and gram-negative bacilli strains has been evaluated. The biological tests evidenced that some of them showed promising antimicrobial activity. Based upon the docking studies performed, the designed compounds were predicted as DnaG (PDB code: 1DDE) inhibitors.





Docked conformation of the most active compound

Suresh Maddila et.al, [8]proposed a series of novel pyrano[2,3-d]-pyrimidine beared 1,2,3-triazoles using $CuSO_4$ and sodium ascorbate as a catalyst via cycloaddition of alknyl pyranopyrim-iodinone with various substituted aryl azides. The antimicrobial activity of the synthesized molecules was screened in vitro bacterial strains against Escherichia coli, Klebsiella pneumonia, Bacillus subtilis , and Staphylococcus aureus by disc diffusion method and the fungal strains against Candida albicans and Aspergillus flavus by agar

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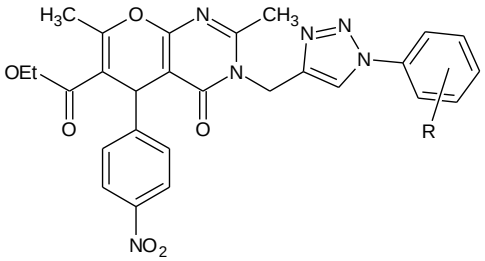
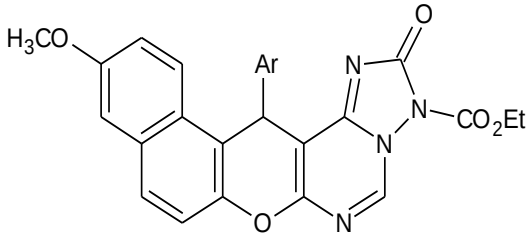
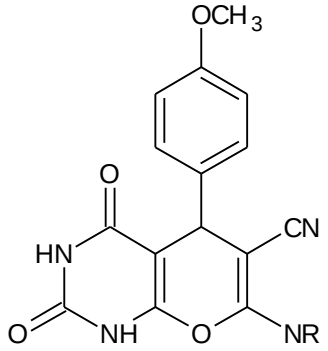
diffusion method. Two molecules exhibited the excellent activity in all the tested cell lines, which have electron withdrawing groups (fluoro) on the 1,2,3-triazolo phenyl ring linked pyranopyrimidine moiety. The molecules revealed good antimicrobial activity against all screened cell lines.



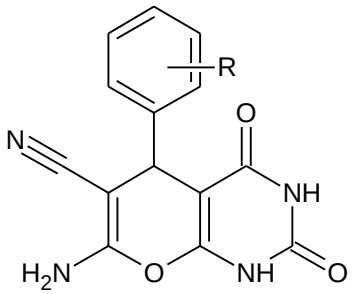
Fathy A. Eid et.al,[9]developed novel naphtho[2,1-b]pyrano[2,3-d]pyrimidines, pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines and their coumarin-3-yl derivatives. The study revealed that substitution at the 2-position of pyrano[3,2-e][1,2,4]- triazolo[1,5-c]pyrimidine with coumarin-3-yl and/or benzocoumarin-3-yl moieties caused a pronounced increase in their activities. Antimicrobial activity was increased by fusing the triazolopyrimidine nucleus with the pyrane ring.

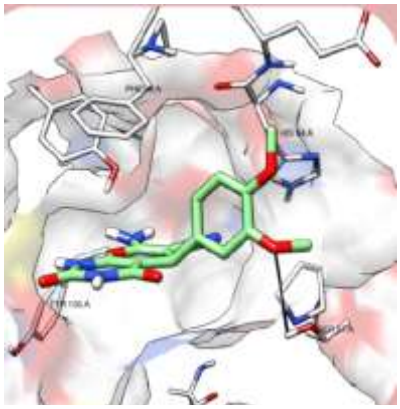


Nour E.A. Abd El-Sattar et.al,[10] synthesized Pyrano[2,3-d]pyrimidine derivatives seized by treating cyclic compounds containing active methylene group with aldehyde and malononitrile in butanol. The synthesized compounds have shown good antimicrobial activity against different microbial strains such as B. subtilis, S. aureus and E. coli. The antimicrobial activities were examined against gram positive bacteria, gram negative bacteria.



Ajmal R. Bhat et.al,[11]proposed the synthesized pyrano[2,3-d]pyrimidine derivatives with hydroxyl, methoxy, bromine, nitrile and nitro substituents. The synthesized compounds exerted different influence on its antimicrobial activity against some Gram-positive and Gram-negative bacteria such as Pseudomonas aureus, E. coli, Staphylococcus aureus, Klebsiella pneumonia and Bacilluscereus. Docking studies were performed by Glide software. The compound with 3,4-OCH_3group showed better glide score.





Anticancer

Sridevi Gorle et.al,[12]designed pyrazole connected pyrano[2,3-d]-pyrimidin-5(2H)-one derivatives and screened for their cytotoxicity against four human cancer cell lines like MCF-7 (breast), HeLa (cervical), CaCo2 (colorectal) and HepG2 (liver) by MTT assay.

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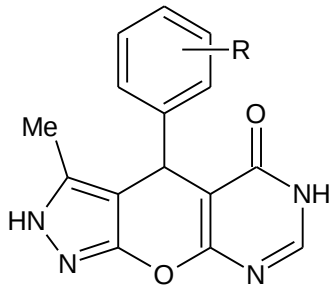
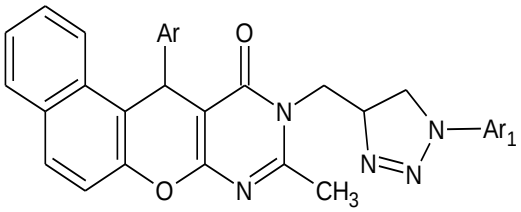


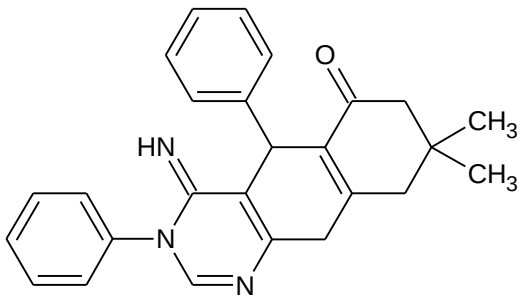
Anticholinesterase activity

Maher Cherif et.al,[13]synthesized pyranopyrimidinone moiety under microwave assisted condition. Molecular docking studies were carried out using AutoDock Vina Software for BuChE (PDB: 1P0I). The compounds showed the highest inhibitory activity against P. syringae pv syringae.



Antityrosinase activity

Meriem Debbabi et.al,[14]proposed the synthesis of novel pyranopyrimidines via the cyclo-condensation reaction of α-functionalized imino-ether. Most of the synthesized compounds showed antityrosinase activity. Docking studies were performed using 2Y9X.



II. CONCLUSION

The present review summarizes the literature reports of the pyranopyrimidinone moiety containing molecules with different biological perspectives based on the analysis of the relationship between structure and its activity. Since now, researchers have been attracted toward designing more potent pyranopyrimidinone derivatives and attention has been increasingly given to the synthesis of pyranopyrimidinone derivatives as a source of novel therapeutics. The present review is expected to provide rational of the pyranopyrimidinone derived compounds to a drug designers and medicinal chemists for a comprehensive and target-based information for the development of clinically accessible medications.

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