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Pyrimidine and its Derivatives: An Important Pharmacological Activity of an Agent: A Review

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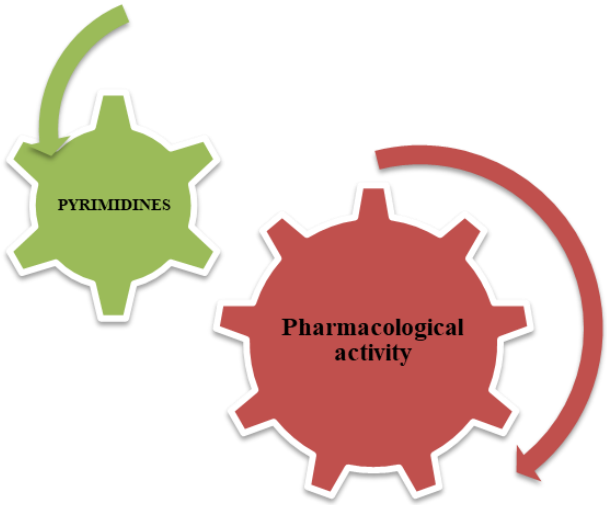
KEYWORDS
Pyrimidines, Pharmacological activity, Anti-HCV, Anti-HIV, Anti-HBV

ABSTRACT:
Pyrimidine and its derivatives as the pharmacophore exhibit broad spectrum pharmacological activities encompassing anti hypertensive activity, Antiproliferative activ Anti-HIV activity, Antiviral activity, Agonistic activity, Anti Parkinson's activity, Antagoni activity, Anti cancer activity, Anti-angiogenic and anti-HBV activity, Anti-HCV activity Antibacterial activity.



1. Introduction

The pyrimidine ring serves as a core nucleus in numerous synthetic compounds, including barbiturates and the HIV medication zidovudine, as well as many naturally occurring substances[1], such as the nucleotides thiamine and alloxan. Many helpful medications with a variety of biological functions also contain the pyrimidine ring[2]. The antimicrobial[3], analgesic, antiviral, antiinflammatory[4], anti-HIV[5], antitubercular[6], antitumor[7], antineoplastic[8], antimalarial[9], diuretic[10], and cardiovascular[11] properties of pyrimidine derivatives have been documented.

2. Pharmacological Activity

Pyrimidine and its derivatives have a wide range of pharmacological actions when used as a pharmacophore. Pyrimidine and its derivatives act as anti hypertensive activity, Antiproliferative activity, Anti-HIV activity, Antiviral activity, Agonistic activity, Anti Parkinson's activity, Antagonistic activity, Anti cancer activity, Anti-angiogenic and anti-HBV activity, Anti-HCV activity and Antibacterial activity. **Figure A.**

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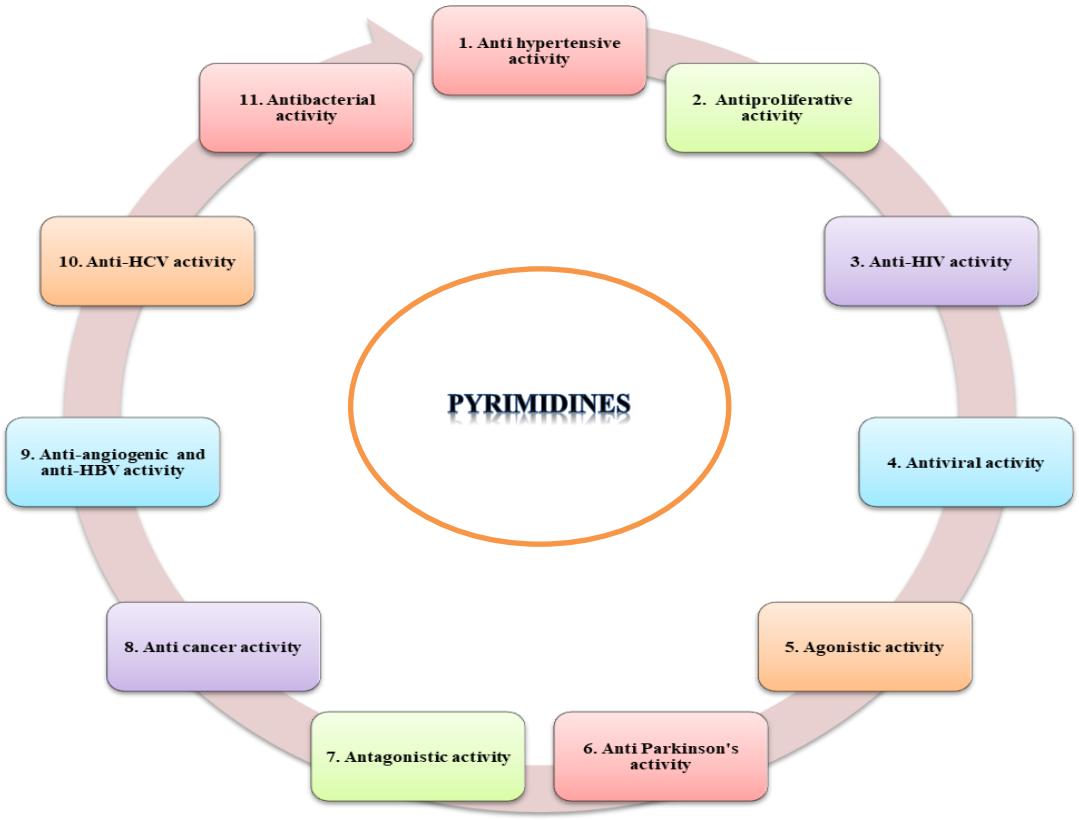

Figure A

2.1. Anti hypertensive activity:

Figure 1: Pyrimidine and its derivatives are widely known for a variety of actions, according to George *et al*[12]. A number of substituents that were added to the pyrimidine ring produced molecules with a range of activity. More powerful hypertensive and monoamine oxidase inhibitory effects are provided by the 3-amino-2-oxazolidine of 2-piperidino-3-formyl-4-oxo-4*H*-pyrido[1,2-a]pyrimidine **1** and its hexahydro derivatives **2**.

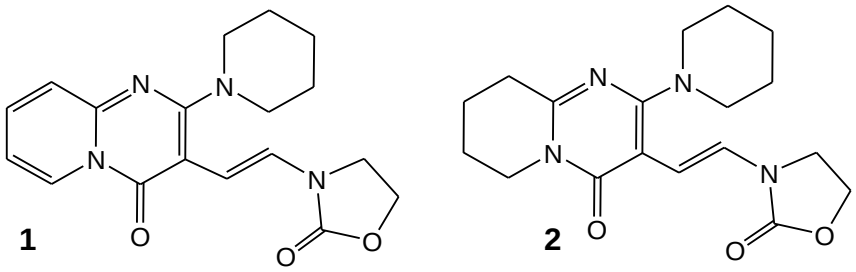

Figure 1

Figure 2: Tetsuo *et al*.[13] reported the synthesis of many 4-amino-2-(4-cinnamoyl- piperazino)-6,7-dimethoxyquinazoline derivatives and testing for their capacity to lower blood pressure in conscious, spontaneously hypertensive rats (SHR). A few of these substances, particularly substances **3-5**, demonstrated

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activity at oral dosages ranging from 0.3 to 10 mg/kg. Discussion is held over how the activity of the piperazine group's 4-substituents is affected. The compounds **3-5** demonstrated alpha-adrenoceptor blocking actions in isolated rat aortas and were efficacious in renal hypertensive rats at oral doses of 3 and 10 mg/kg.

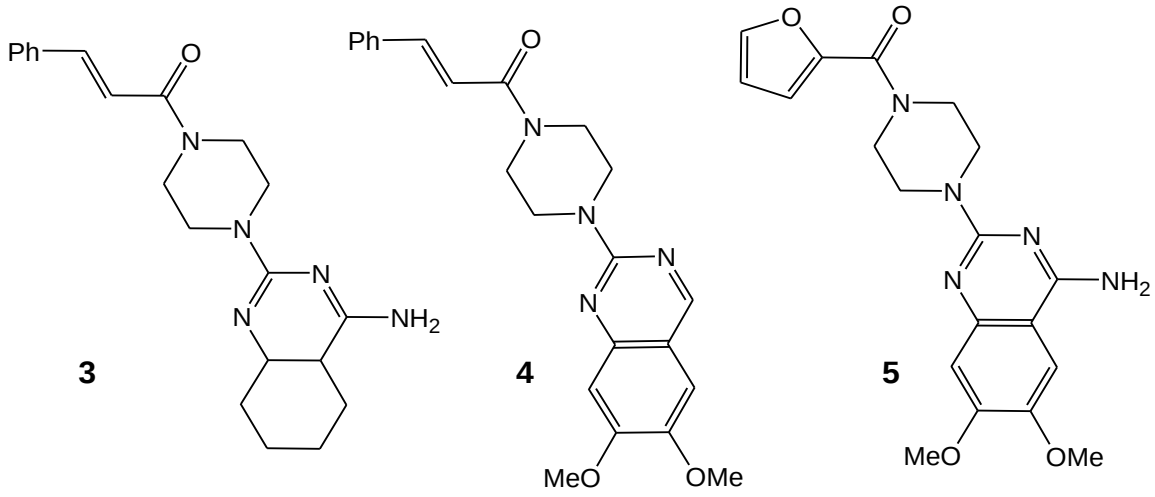

Figure 2

2.2. Antiproliferative activity:

Figure 3: A new series of diarylureas and amides with pyrrolo[2,3-d]pyrimidine scaffolds are synthesised and examined for their *in vitro* antiproliferative effects against the HS 27 fibroblast cell line and the A375 human melanoma cell line, as well as the impact of substituents on pyrrolo[2,3-d]pyrimidine. With the exception of N-acetyl derivatives, the newly synthesised substances typically exhibited higher or comparable efficacy against A375 to sorafenib. The compound **6** which include imidazole and morpholine moieties, respectively, displayed the most antiproliferative effect against A375 out of all of these derivatives[14].

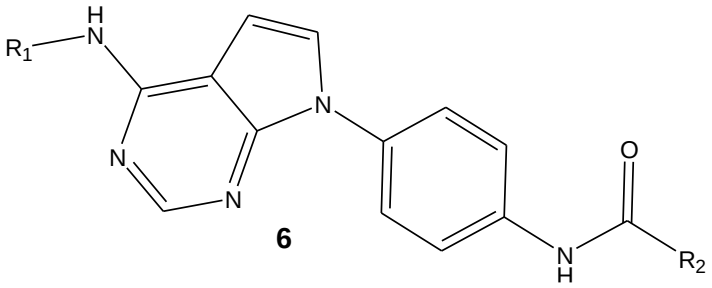

Figure 3

2.3. Anti-HIV activity:

Figure 4: The new anti-HIV-1 lead compound [1-[2',5'-bis-O-(tert-butyldimethylsilyl)-D-ribofuranosyl]thymine]3-spiro-5-(4-amino-1,2-oxathiole-2,2-dioxide) TSAO-T **7** and **8** was synthesised and evaluated as inhibitors of HIV-I and HIV-2 replication in cell cultures by Felix *et al.*[15]. Regarding their antiviral and/or cytotoxic activities, a number of substituted TSAO-thymine, TSAO-uracil, and TSAO-cytosine derivatives were discovered to be superior to their unsubstituted TSAO congeners.

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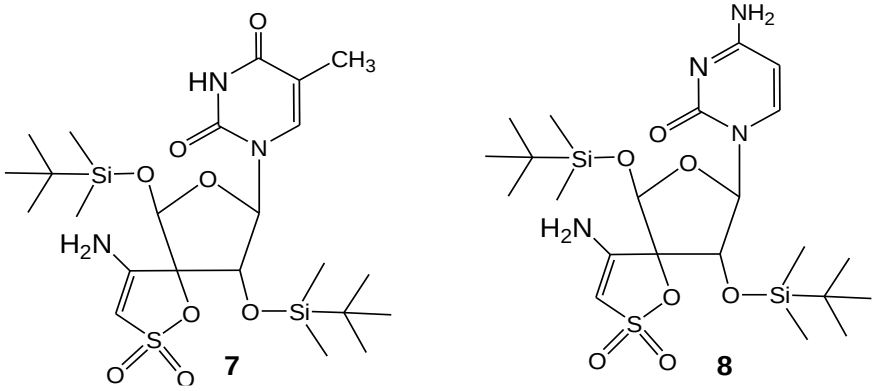

Figure 4

Figure 5: According to Venkat *et al.*[16], a group of 4-aminopyrimidines **9** and **10** were discovered to be new HIV inhibitors with an unidentified molecular target. To determine its SAR and the connection location for target recognition, structural alterations were made. Numerous analogues were discovered to have low-level HIV replication inhibitory action. A biotinated analogue was among several analogues with diverse possible linkers that showed great effectiveness and may be used to find new anti-HIV targets.

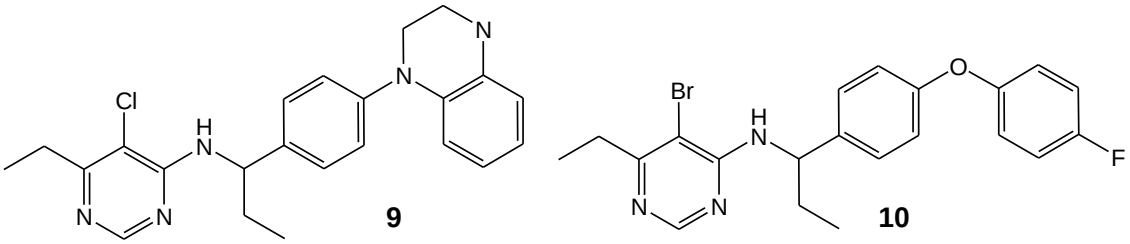

Figure 5

2.4. Antiviral activity:

Figure 6: Numerous 2-aminopyrimidine-nucleated phospheno derivatives have a wide range of antiviral activity. The corresponding cytosine derivative [(S)-HPMPC] **12** has selective activity against cytomegalovirus while a compound like (S)-9-[3-hydroxy-2-(phosphonomethoxy)-propyl]adenine [(S)-HPMPA] **11** exhibits a range of anti-DNA virus activity, including activity against herpes simplex virus types 1 and 2 (HSV-1,2). Similar to this, compound **13** exhibits strong anti-retroviral activity, including against HIV[17].

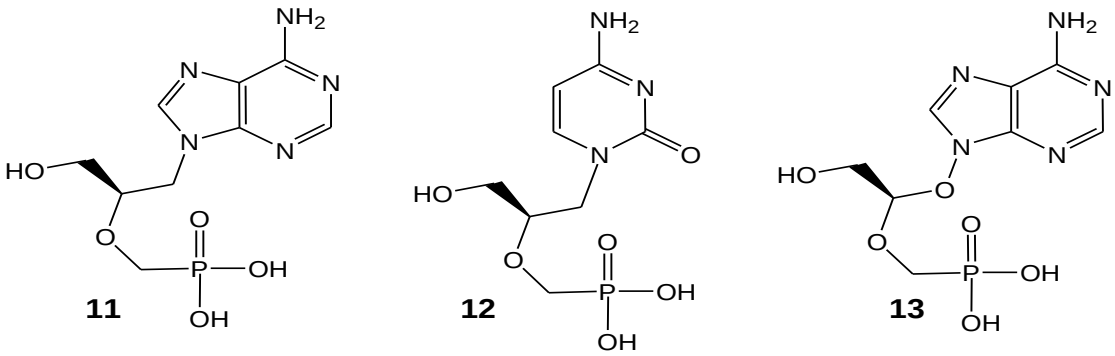

Figure 6

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Figure 7: According to Raymond *et al.*[18], since arabinosyl nucleosides have antiviral and/or cytostatic activity, the synthesis of the corresponding arabinonucleosides with an amino substituent in the 5th position in substitution of the 5-hydroxyl moiety **14** was undertaken to prepare more effective antiviral compounds.1-(5-amino-5-deoxy-D-erythro-pentofuranosyl)-5-iodouracil) A These 5-aminoarabinonucleoside analogues' impact on HSV-1, S-180, and L1210 cell cultures, as well as their capacity to prevent phosphorylation by their parent substances. The related halogen-containing analogues were discovered to show strong antiviral activity against HSV-1 as well as a notable cytostatic effect on S-180 and L1210 cells *in vitro*.

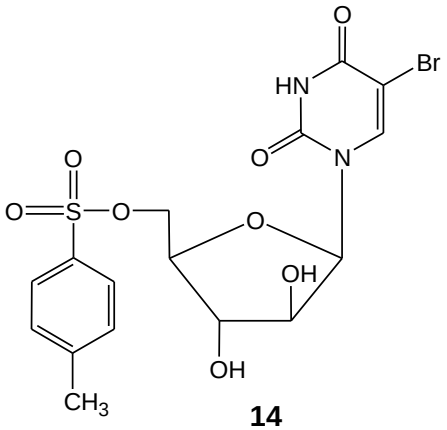

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Figure 7

2.5. Agonistic activity:

Figure 8: A number of novel, highly selective A1-AdoR agonists are reported by Elfatih *et al.*[19] a compound with a carboxylic acid functionality in the pyrazole ring's fourth position had a KiL value for the A1-AdoR of 1 nM and shown >5000-fold selectivity over the A3 and A2A-AdoRs. Additionally, compound **15**, which included a carboxamide functionality in the 4-position of the pyrazole ring, exhibited >600-fold selectivity for the A3 and A2A-AdoRs and subnanomolar affinity for the A1-AdoR (KiL = 0.6 nM).

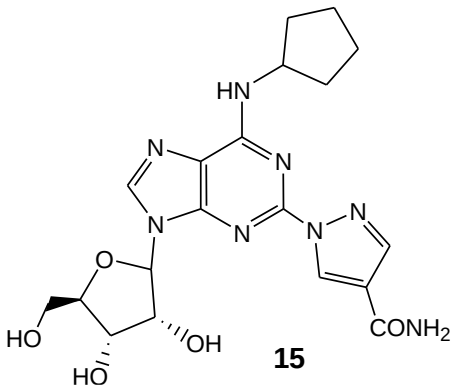

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Figure 8

2.6. Anti Parkinson's activity:

Figure 9: Parkinson's disease treatment holds out a lot of potential thanks to antagonists of the adenosine A2A receptor. Bernard *et al.*[20] discovered the powerful and selective (vs. A1) antagonist **16** which is orally active in the rat haloperidol-induced catalepsy paradigm and used the well-known pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine A2A antagonist as a starting point. They subsequently improved this lead to produce the methoxyethoxyethyl ether **17**, which has great *in vivo*

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activity, broad selectivity, and favourable pharmacokinetics.

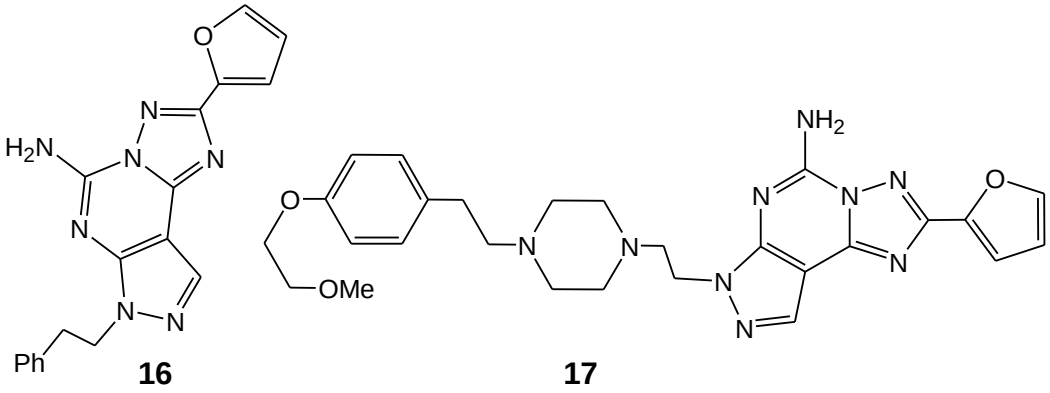

Figure 9

2.7. Antagonistic activity:

Figure 10: According to Laurent *et al.*[21], the 4,6-diaminopyrimidine scaffold of 3-substituted azetidinyl substituents **18** improved the PDE_4 inhibitory effects. In lung inflammatory models, preliminary *in vivo* activity is reported. According to Laurent *et al.*[22], the first effective dual M3 antagonists and PDE4 inhibitors were discovered by SAR centred around 4,6-diaminopyrimidine derivatives. The discovery of **19**, which has the most intriguing profile on both targets, was made possible by a variety of chemical modifications made to that scaffold.

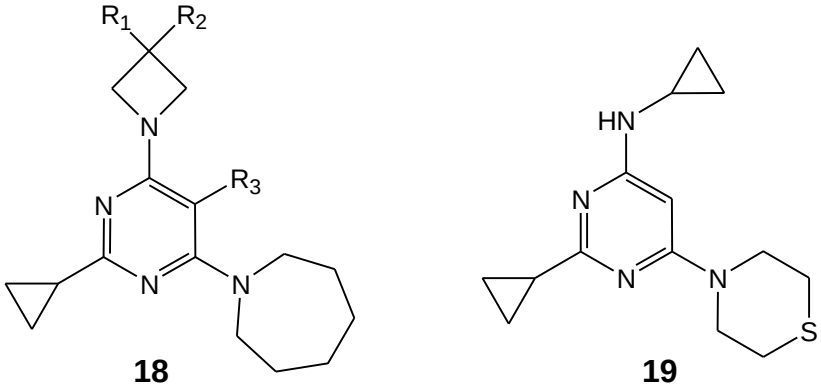

Figure 10

Figure 11: Numerous new pyrimido[5,4-b]indole and [1]benzothieno[3,2-d]pyrimidine derivatives **20** were synthesised and tested for their ability to bind to and function at various subtypes of the 1-adrenergic receptor. They exhibited powerful 1-AR antagonistic behaviour. Some of them demonstrated extremely high affinity for the 1D-AR subtype in binding studies[23]. The new class of selective and highly-affine 1-adrenoceptor (1-AR) ligands was identified by Valeria *et al* [24]. A few synthetic compounds, including **21**, exhibited affinity for 1-ARs in the nanomolar range and significant selectivity for 5-HT1A and dopaminergic D1 and D2 receptors. Functional tests on a few variants revealed antagonistic characteristics.

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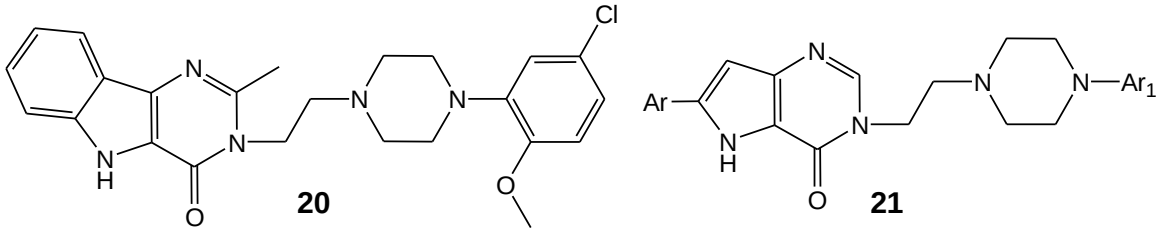

Figure 11

Figure 12: The ability of a number of compounds with an unsaturated side chain at position 6 of the core pyrimidine and structural similarities to bosentan to inhibit the ETA and ETB receptor has been investigated by Martin *et al*[25]. The 2-butyne-1,4-diol linker with a pyridyl carbamoyl moiety was added, and the result was *in vitro* highly effective endothelin receptor antagonists. In *in vivo* model studies using salt-sensitive, hypertensive Dahl rats, the propargyl derivative **22** substantially lowered blood pressure. Numerous 4-heterocyclic biphenylsulfonamide derivatives have been synthesized, by Natesan *et al*.[26], and they have been described as powerful and selective endothelin A (ETA) receptor antagonists. The pyrimidine derivative **23**, which is roughly similar to 1, is the analogue that is most effective (Ki=0.9 nM) and selective for the ETA receptor.

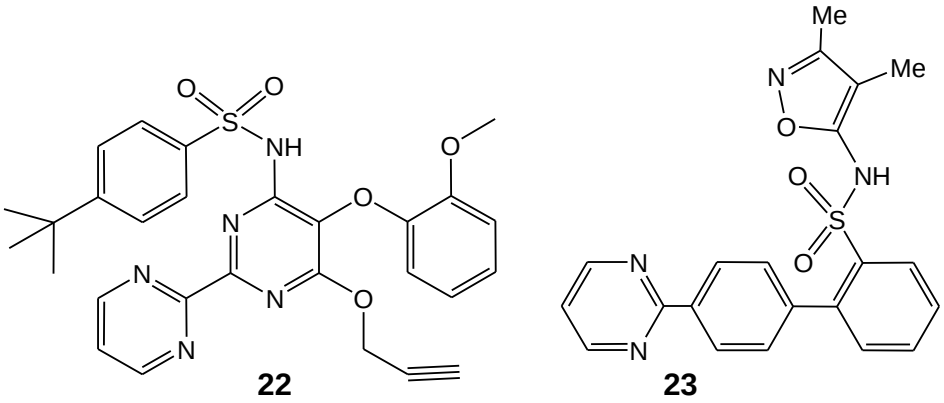

Figure 12

Figure 13: Each of a series of powerful ETA antagonists showed a very high affinity for the ETA receptor in porcine aortic membrane, ranging from IC_{50} 0.001 nM to 0.0039 nM. Hiroshi *et al*.[27] **24** modified the structure of the pyrimidine nucleus of each of these antagonists at the 2-position to improve water solubility and study structure activity relationships. The affinity changed when aryl, heteroaryl, alkyl, amino, alkoxy, or alkylthio groups were added to the 2-position. While showing better water solubility, derivatives containing hydrophilic groups at the 2-position tended to have lower ETA receptor affinities.

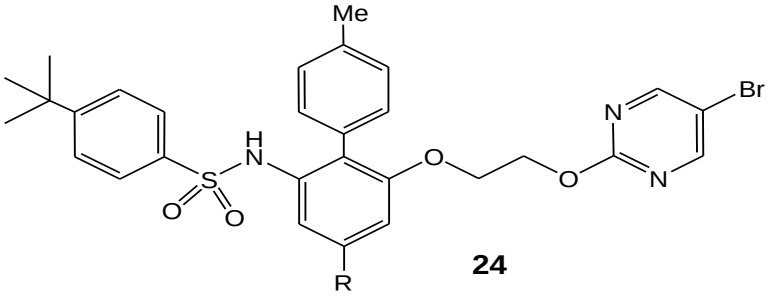

Figure 13

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Figure 14: For a number of pyrimidine and pyridine based VLA-4 antagonists, John *et al.*[28] published the SAR analyses to optimise both potency and rate of elimination in the rat, and described a number of pyridinyl and pyrimidyl analogues, including **25**, that prevent VLA-4 integrin from interacting with VCAM-1. To find PKC-theta specific inhibitors, an uHTS campaign was run. 2,4-diamino-5-nitropyrimidines **26** were shown to be potent and selective PKC-theta inhibitors after the hit set underwent first triage based on selectivity and historical analysis. A homology model and preliminary SAR are shown to show the necessity of an appropriate 4-diamino substituent along with a 2-arylalkylamino substituent for obtaining selectivity over a variety of kinases. On a few compounds, further hit to lead profiling is offered [29].

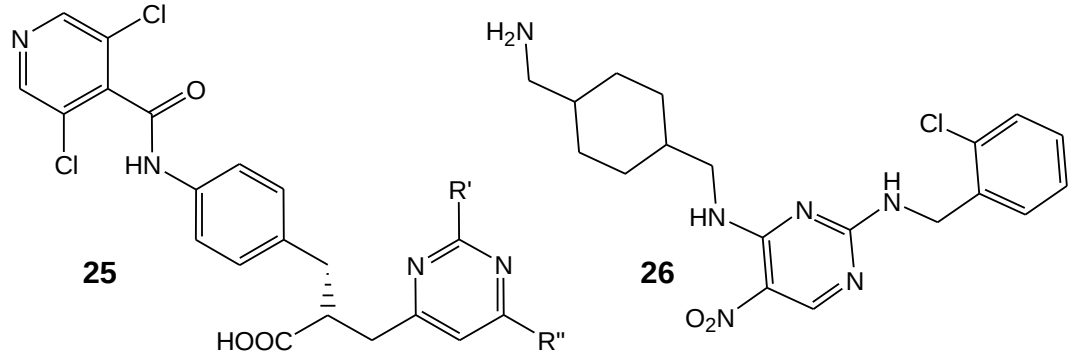

Figure 14

2.8. Anti cancer activity:

Figure 15: Sesquiterpene lactones exhibit a broad range of biological activities, including cytotoxic, anti-inflammatory, and antiviral action. Two of them, **27** and **28**, were shown to have antitumoral activity in HeLa, C-33, CALO, INBL, VIPA, SW480, SW620, MCF-7, and CHO cancer cell lines by Quintero *et al.*[30], who also described the effects of seven modified sesquiterpene lactones on the proliferation of various cancer cell lines. Compounds **27** and **28** demonstrated cytotoxic action (IC50) by preventing C-thymidine from incorporating into DNA. According to these studies, derivatives ought to prevent cancer cell lines from reproducing DNA.

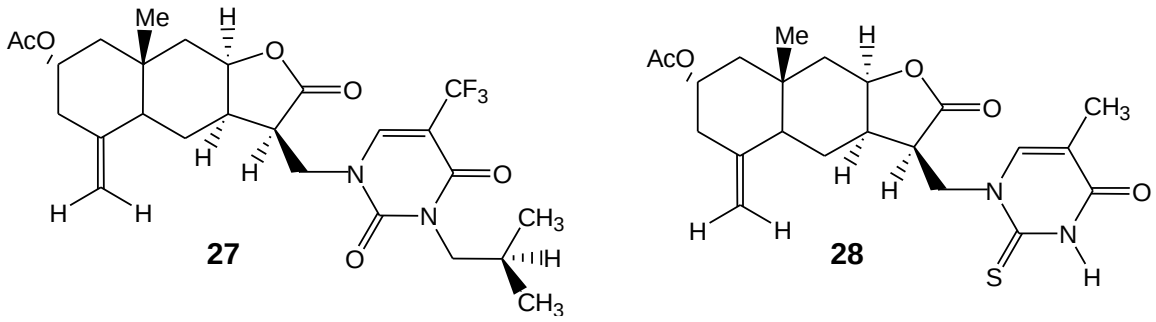

Figure 15

Figure 16: The design and synthesis of a novel class of pyrimidinyl group-containing ureas was described by Chuanfei et al.[31] and several human cancer cell lines were potentially lethal by some of the synthesised compounds **29**. They can infer from the structure-activity connections that the biological activities of these compounds depend on the presence of a sulphide bridge between the phenyl and pyrimidinyl rings.

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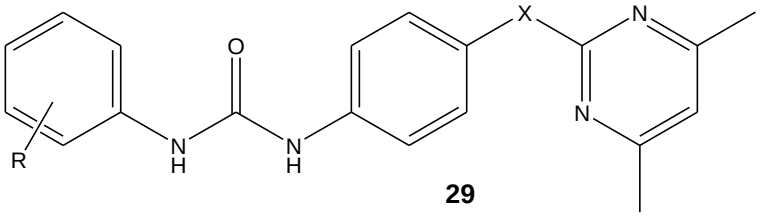

Figure 16

2.9. Anti-angiogenic and anti-HBV activity:

Figure 17: Yasushi *et al.*[32] discovered 4-amino-5-(4-((2-fluoro-5-(trifluoromethyl)phenyl)-aminocarbonylamino)phenyl)furo[2,3-*d*] pyrimidine **30** possessing strong inhibitory activity at both the enzyme and cellular level against VEGFR2 and Tie-2 during our effort to develop dual VEGFR2 and Tie-2 inhibitors as anti-angiogenic agents for When administered orally, compound **30** showed significant tumour growth reduction and anti-angiogenic efficacy in a mouse HT-29 xenograft model. It also showed substantial pharmacokinetic exposure. Similarly, several dioxolane pyrimidine nucleosides have been synthesised, and their anti-HBV activities have been assessed in 2.2.15 cells, in order to examine the correlations between structure and activity. According to the study [33], 5-fluoro-cytosine derivatives **31** had the strongest anti-HBV activity.

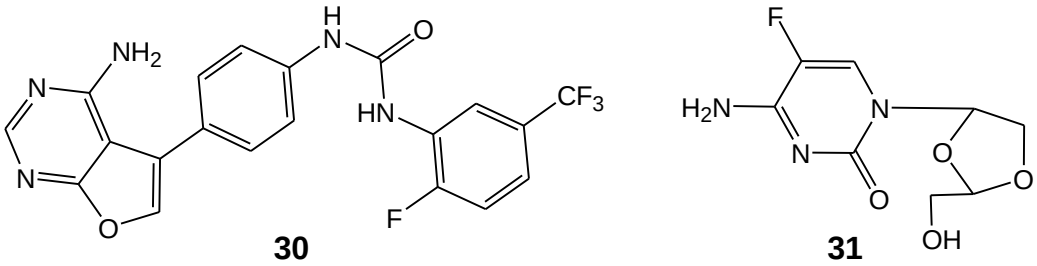

Figure 17

2.10. Anti-HCV activity:

Figure 18: A synthetic method that allowed for the inclusion of a 5R-methyl substituent from starting materials that were readily accessible in the market was used to create a series of optically pure 1,3-dioxolane nucleoside mimics. The purine derivative was changed out for the pyrrolo[2,3-d]pyrimidine heterocycle. Under solid-liquid phase transfer conditions, the pyrrolo[2,3-d]pyrimidine and the dioxolane were combined **32** and **33**. Anne *et al.*[34] A cell-based subgenomic replicon assay was used to evaluate the capacity to prevent HCV RNA replication. None of the substances mentioned showed any discernible anti-HCV action.

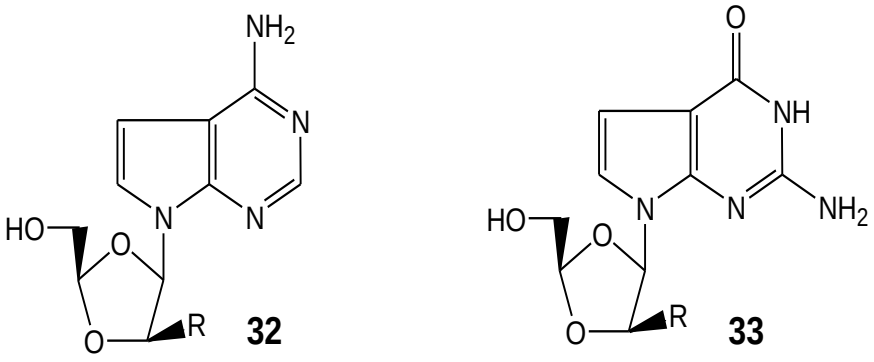

Figure 18

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2.11. Antibacterial activity:

Figure 19: According to Barbara *et al.*[35], with activity at least equal to that of trimethoprim, a group of 2,4-diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines (**34**-**36**) have been prepared. These compounds share structural similarities with trimethoprim and are good inhibitors of bacterial dihydrofolate reductase. The rigid aromatic series produced the greatest amount of inhibition, whereas the tetrahydroquinoline derivatives produced more specificity. This had a clear connection to compounds of 4-methyl-8-methoxy. Selectivity may be impacted by the spatial interactions surrounding N-1 and protonation at this location. These substances also exhibited good in vitro broad range antibacterial activity.

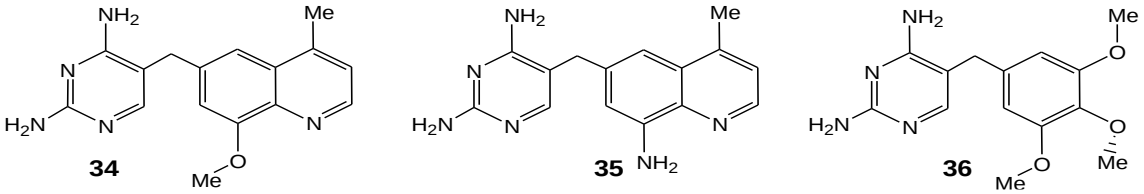

Figure 19

Figure 20: A new series of 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone **38(a-i)** were synthesized by the reaction of 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone **37(a-i)** with 4-morpholinecarboximidamide. According to Nagaraj *et al.*[36] The compounds **38(a-i)**were evaluated for their antibacterial activity against Gram-positive bacteria viz. B. subtilis, B.sphaericus and S. aureus and Gram-negative bacteria viz. P. aeruginosa, K. aerogenes and C.violaceum and also screened for their antifungal activity against four fungal organisms viz. C.Albicans, A. Fumigatus, T. rubrum and T.Mentagrophytes. Compounds 38b, 38f and 38h showed higher activity towards the Gram-positive bacterial strains. Compounds 38d and 38g showed good inhibition towards B. subtilis and S. aureus.The compounds 38e, 38h and 38i showed highestactivity against all the fungal strains used.

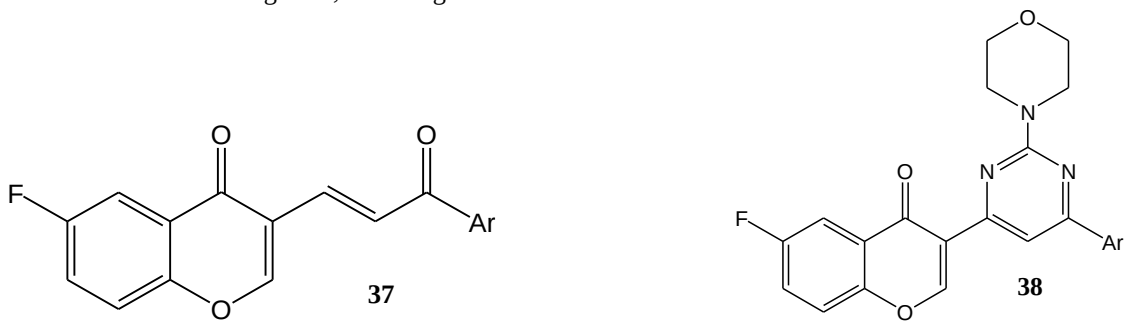

Figure 20

3. Conclusion

This review outlined the pyrimidine and their derivatives served as a resource for both basic and applied research on the subject.

4. Conflicts of interest

There are no conflicts to declare.

5. Acknowledgements

The author is thankful to the head, Department of Chemistry, Telangana University, Nizamabad, Telangana, India, for support and facilities provided.

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