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A REVIEW ON BIOLOGICAL IMPORTANCE OF PYRIMIDINE CONTAINS INDOLE DERIVATIVES

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ABSTRACT

Heterocyclic molecules are frequently found in nature and are attracting increased from organic and pharmaceutical chemists. Heterocyclic compounds are acquiring more importance in recent years because of their broad pharmacological activities. Nitrogen, sulphur or oxygen containing five or six membered heterocyclic compound has occupied enormous significance in the field of medicinal chemistry. Indole is a bicyclic heterocycle consisting of a six membered benzene ring fused to a five membered nitrogen containing pyrrole ring. Indoles are an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, but also because they have a wide range of biological activities. Hence, it is not surprising that indoles act as lead compounds and are key building blocks in numerous pharmaceuticals. Pyrimidine is the six membered heterocyclic organic colorless compound containing two nitrogen atoms at 1st and 3rd positions. Pyrimidines (1,3-diazines) and their fused analogues form a large group of heterocyclic compounds. Pyrimidine which is an integral part of DNA and RNA imparts diverse pharmacological properties. Pyrimidine contain Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including antihypertensive, antiproliferative, antiviral, antitumor, analgesic, anti-inflammatory, antimicrobial, antifungal activities, etc. Although pyrimidine contain indole moiety is very small but is fascinated by scientists because of the diverse biological activities. This review represents some synthesized pyrimidine contain indole derivatives and their pharmacological profiles which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines.

KEYWORDS: Pyrimidine, indole, antimicrobial, anticancer, antiiflammatory, antioxidant.

INTRODUCTION

Heterocycles constitute the largest classical divisions of organic compounds. Heterocycles are essential building blocks that are frequently used as a key structural unit in synthetic pharmaceuticals and agrochemicals. In the pharmaceutical industry, more than 95% of branded drugs contain at least one heterocyclic fragment. heterocycles remains the largest area of research in organic chemistry. Though millions of heterocyclic compounds are known, the synthesis has been continuing every day in search of some with special properties. Nitrogen, oxygen and sulphur are the most common heteroatoms. These compounds generally consist of small (3- and 4-membered) and common (5- to 7-membered) ring systems. A heterocyclic ring may comprise of three or more atoms which may be saturated or unsaturated. Also the ring may contain more than one hetero atom which may be similar or dissimilar. There are also heterocyclic compounds fused with other cyclic organic compounds which are commonly known as condensed heterocyclic compounds.

The chemical and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. Most of the known chemicals used in medicine are based on heterocyclic frameworks. Some of the common heterocyclic compounds used in the medicines include amino acids like proline, histidine and tryptophan, vitamins and coenzymes precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, B12 and E families of the vitamins.

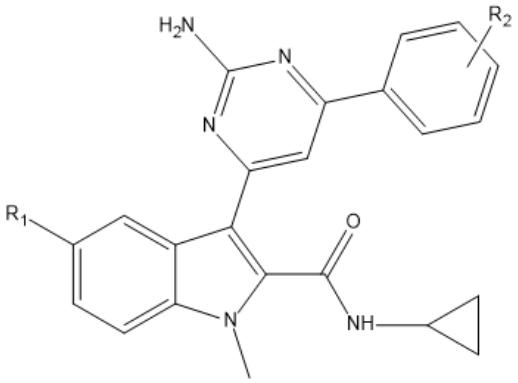
The name indole is portmanteau of the words indigo and oleum, since indole was first isolated by treatment of the indigo dye with oleum. Indole chemistry began with the study of the dye indigo. Indole is an aromatic heterocyclic nucleus. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen containing pyrrole ring through the 2- and 3-positions of the pyrrole nucleus. Indole is called as benzopyrrole. The indole ring is also found in many natural products such as the vinca alkaloids, fungal metabolites and marine natural products.1 Indole is a popular component of fragrances.2 Indoles are a pervasive class of compounds found in abundance in biologically active compounds such as pharmaceuticals, agrochemicals and alkaloids. Since the first synthesis of indole in 1866, a number of synthetic methods for the construction of the indole nucleus have been devised. Indole myriad derivatives have, therefore, captured the attention of organic synthetic chemists. Medicine and biochemistry are also interested in many aspects

of the indole chemistry. indole derivatives exhibit versatile pharmacological properties such as antifungal, antiiflammatory, analgesic, antitumor, anticonvulsant, antidepressant, antibacterial etc.

Pyrimidine is the six membered heterocyclic organic colorless compound containing two nitrogen atoms at 1st and 3rd positions. The name of the pyrimidine was frst applied by Pinner from the combination of two words pyridine and amidine). Pyrimidines(1,3-diazines) and their fused analogues form a large group of heterocyclic compounds. Pyrimidine which is an integral part of DNA and RNA imparts diverse pharmacological properties. The pyrimidine have been isolated from the nucleic acid hydrolyses and much weaker base than pyridine and soluble in water. Pyrimidine and its derivatives have been described with a wide range of biological potential i.e. anticancer, antiviral, antimicrobial, antiiflammatory, analgesic, antioxidant and antimalarial etc.

A) ANTIBACTERIAL AND ANTICANCER ACTIVITY

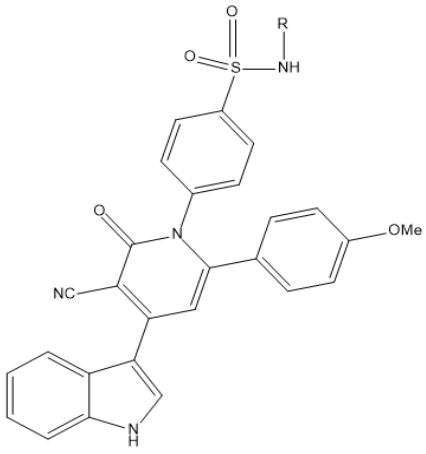
1. Nikhilagokhale A et al, reported the facile synthesis of new N-cyclopropyl-1-methyl-1H-indole-2-carboxamide derivatives bearing substituted 2-amino pyrimidine moiety at position-3 of the indole ring. All the intermediate and title compounds were characterized adeptly by 1H NMR, 13C NMR, ESI–MS and elemental analyses. All the compounds screened in-vitro at a concentration of 10 lg/disc for their antibacterial activity against two Gram-positive strains (Staphylococcus aureus and Bacillus subtilis) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). The antifungal evaluation was carried out against Candida albicans and Aspergillusniger at a concentration of 10 lg/disc. Standard antibacterial drug ciprofloxacin (10 lg/disc) and antifungal drug fluconazole (10 lg/disc). Compounds 1a, 1b and 1c inhibit significantly in the case of anti-microbial studies by disc diffusion method, compounds were evaluated for their ability to inhibit the growth of HepG2, MCF-7, HeLa and the non-tumourigenic Vero by MTT assay. Compounds 1d, 10e, 1f,1g, 1h, 1i, 1j and 1k which contain a chloro or fluoro substitution (R2) at either position-3 or 4 of the phenyl ring spectrum anti-tumour activity compared to o standard Doxorubicin.



1

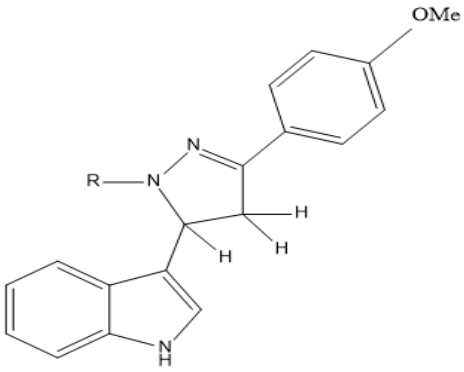
	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k
R_1=	H	F	F	H	H	H	H	H	F	F	F
R2=	4-Me	4-Br	3-F	4-F	4-Cl	3-F	Cl	4-F	4-Cl	3-F	3-Cl

2. Ekhlassnassar; Reported the Aldol condensation reaction between 3-indolaldehyde and 4-methoxyacetophenone gave a chalcone compound from which some pyrazoline, pyridine, and pyrimidine derivatives linked to indole moiety were obtained. Antiproliferative screening of synthesized Compounds were tested against a human breast carcinoma cell line (MCF7) and a human liver carcinoma cell line (HEPG2), using 5-Fluorouracil (5-Fluoro-1Hpyrimidine-2,4-dione) as a reference drug Compounds $2a_1$and $2a_2$ showed high activities. Antimicrobial screening of synthesized new compounds showed high or moderate bactericidal activity against Staphylococcus aureus and Pseudomonas aeroginosa compared to that of ciprofloxacin. Compounds 2b, 2c, 2e, $2a_3$, $2a_1$and $2a_2$ showed a good fungicidal activity, near to that of nystin, against Fusarium.



2a

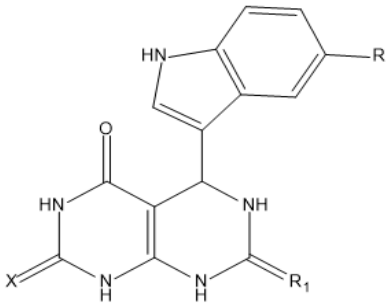
2a;	**a_1**	**a_2**	**a_3**
R;	**H**	**n-Pr**	**4-MeOC6H4**



2b

2b;R=H

3. Talavara Venkatesha et al,. Have been reported eco-friendly synthesis of indol-5,8-pyrimido[4,5 *d*]pyrimidine derivatives using CAN catalyst *via* Biginelli reaction The synthesized compounds were evaluated for *in vitro* antibacterial and anticancer activities. *in silico* molecular docking studies was also performed to predict the binding interactions of synthetic molecules with appropriate target molecules in connection to their antimicrobial and anti-cancer effects compounds 3a, 3b and 3c were found to have effective antibacterial activity against the tested pathogens, cytotoxicity studies of synthesized pyrimidine derivatives were found to be effective against K-562, HeLa, MCF-7 and Hepg-2 cancer cell lines.



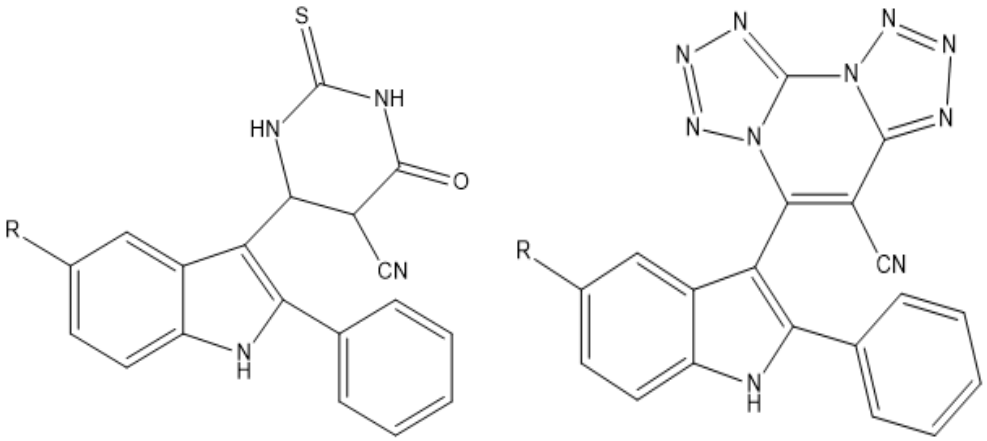
3

3a: X-S, R-F, R1-O, 3b: X-O, R-F, R1-O, 3c:X-O,R-F, R1-S.

B) ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY

4. Saundane anand raghunath et al, has been synthesized a new series of tetrahydropyrimidines, pyrazolo[3,4-d]pyrimidines, and ditetrazolo[1,5-a;10,50-c]pyrimidines using appropriate synthetic routes. The newly synthesized compounds have been tested for their antimicrobial and antioxidant activities against DPPH stable free radical. In the case of antibacterial activity compounds 4a, $4b_1$, and $4b_2$ exhibited the

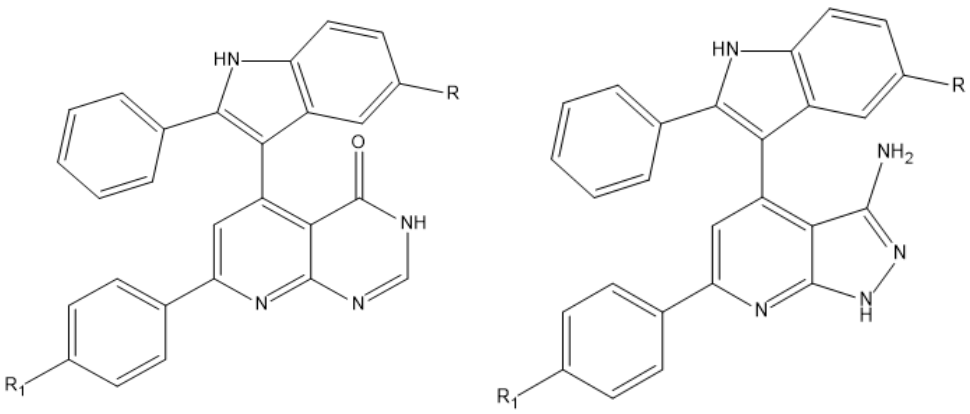
maximum zone of inhibition against Staphylococcus aureus. In case of antioxidant activities, compound 4a showed the highest DPPH radical scavenging acivity.



4a **4b**

4a:R;Cl, 4b$_1$: R;Cl, 4b$_2$:R;H

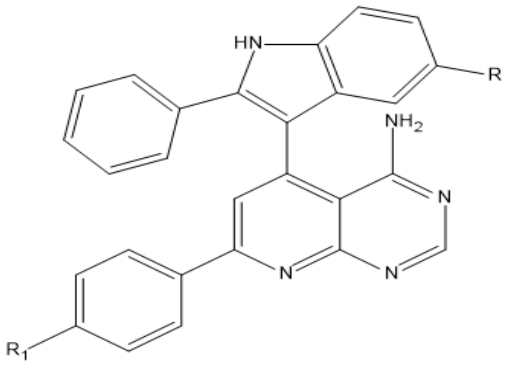
5. Anand R et al,. have been synthesized new indole analogues containing pyrido[2,3-d]pyrimidin-4-(3H)-ones (3a–i), pyrazolo[3,4-b]pyridin3-amines (4a–i) and pyrido[2,3-d]pyrimidin-4-amines. These newly synthesized compounds were screened for their antimicrobial and antioxidant activities. Compounds 5a$_1$, 5a$_4$, 5b$_2$, 5b$_3$, 5b$_4$, 5c$_1$, 5c$_2$ and 5c$_3$ exhibited good antibacterial and antifungal activities. The compounds 5a$_2$, 5a$_3$, 5a$_4$, 5b$_1$, 5b$_3$, 5b$_4$and 5c$_1$ exhibited good radical scavenging activity. Compounds 5a$_1$ exhibited good metal chelating activity.



5a **5b**

R:5a1;Cl,5a2;CH3,5a3;H,5a4;Cl **R:5b1;Cl,5b2;h,5b3;CH3,5b4;H**

R1:5a1;Cl,5a2;Cl,5a3;Cl,5a4;H **R1:5b1;Cl,5b2;Cl,5b3;H,5b4;H**

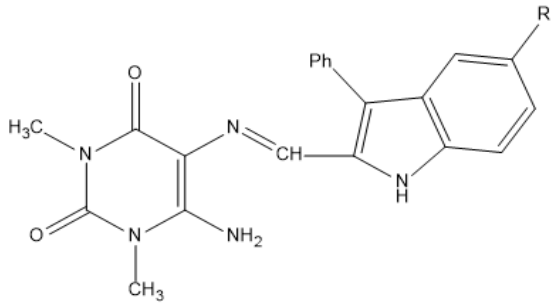


5c

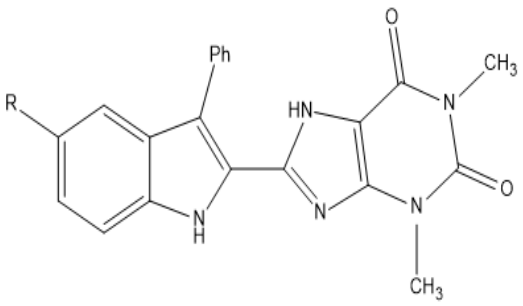
R:5c$_1$;Cl,5c$_2$;H,5c$_3$;H

R1:5c$_1$;Cl,5c$_2$;Cl,5c$_3$;CH3

6. Vaijnath verma A et al,. Have been reported a novel series of required intermediate 5-((5-substituted3-phenyl 1*H*-indol-2-yl) methyleneamino)-6- amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones (3a-c) was prepared on condensation 5,6-diamino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1) with various 5- substituted 3-phenyl-1*H*-indole-2-carbaldehyde (2a-c) gave the respective Schiff bases, which on cyclization with thionly chloride afforded targeted compound 8-(5-substituted 3-phenyl-1*H*- indol-2-yl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (4a-c). These newly synthesized compounds were screened for their antimicrobial and antioxidant activities, Compounds 6a$_3$, 6b$_1$ and 6b$_3$ exhibited promising antimicrobial activity. Compounds 6a$_1$, 6b$_2$, 6b$_1$ and 6b$_2$ showed potency of antioxidant ac*tivity*.



6a



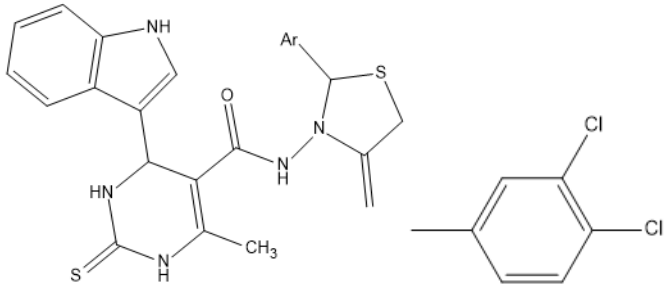
6b

R=6a$_1$;6b$_1$=Cl, 6a$_2$;6b$_2$=CH3,6a$_3$;6b$_3$=OCH3

C) ANTIPROLIFERATIVE ACTIVITY

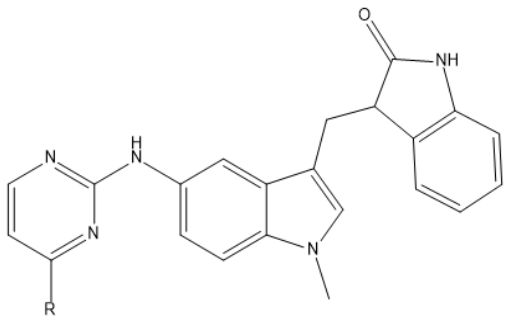
7. Naglaa M et al, have been synthesized series of novel indolyl-pyrimidine hybrids and evaluated in vitro and in vivo for their antitumor activity. The in vitro antiproliferative activity of all compounds was obtained against MCF-7, HepG2, and HCT-116 cancer cell

lines, as well as against WI38 normal cells using the resazurin assay. The most potent antiproliferative compound in this study was compound 7 in vitro against MCF-7, HepG2 and HCT-116 with IC50 = 5.1 ± 1.14, 5.02 ± 1.19 and 6.6 ± 1.40 µM. Comparable to the standard treatment (5-FU and erlotinib). The presence of electron withdrawal group such as Cl atoms was found to be a potential reason for such activity.



7

8. Santoshkumar prajapatia et al,. Have been synthesized a series of oxindole linked indolyl-pyrimidine derivatives and characterized by IR, 1H NMR, 13C NMR and Mass spectral analysis. All the newly synthesized target compounds were assessed against PA-1 (ovarian), U-87MG (glioblastoma), LnCaP (prostate), and MCF-7 (Breast) cancer cell lines for their cytotoxic potential, with majority of them showing inhibitory activity at low micro-molar concentrations. Significantly, compound 8 was found to be most potent with an IC50 value of (2.43±0.29 µM) on PA-1 cells.



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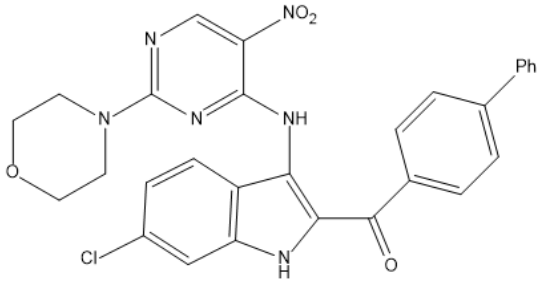
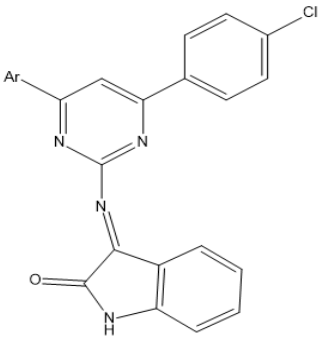
9. Peng-Cheng Diao et al,. a series of novel indole-pyrimidine hybrids possessing morpholine or thiomorpholine moiety were synthesized *via* an efficient one-pot multistep synthetic method. The 175 antiproliferative activities of the synthesized compounds were evaluated *in vitro* against HeLa, MDA-MB-231, MCF-7, and HCT116 cell lines. The IC50 values of the most promising compound 9 were 0.29, 4.04, and 9.48 µM against

MCF-7, HeLa, and HCT116 cell lines, respectively, which was 48.0, 4.9, and 1.8 folds more active than the lead 180 compound 1. the compound 9 also exhibited the most potent anti-tubulin activity showing 42% inhibition at 10 μM.



9

10. Anna PratimaNikalje et al,. Have been reported ultrasound-mediated greener synthesis of 11 novel 3-(4-(4-chlorophenyl)-6-(substituted phenyl/heteryl)pyrimidin-2-ylimino)indolin-2-one derivatives. The synthesized derivatives were evaluated for their in vitro anticancer activity against a panel of selected human cancer cell lines of breast (MCF-7), cervix (HeLa), prostate (PC-3) and lung (A-549). Among the tested compounds, 10 exhibited most promising in vitro anticancer activity against HeLa, PC-3 and A-549 with GI50 value 15.38, 19.67 and 4.37 μM, respectively. The compounds were also screened for induction of apoptosis and morphological changes in cancer cells at their GI50 concentration. Computational molecular docking study highlight and supports the experimental results for in vitro anticancer activity.



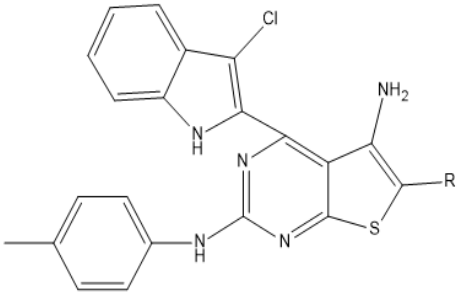
10

Ar=4-chlorophenyl

D) ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY

11. Mostafa sayed et al,. Have been synthesized new heterocyclic compounds containing indolylthienopyrimidine and their structures were confirmed using elemental and

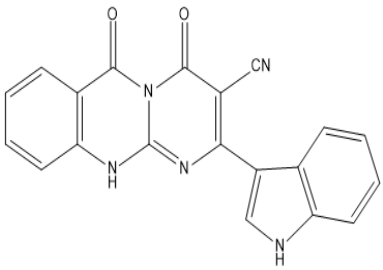
spectral analyses. some selected compounds display "aggregation-induced emission" (AIE) activity with high fluorescence efficiency in the solid state (ex. 21.4%).The agar well-diffusion method was used to screen all the new synthesized compounds in vitro as antimicrobial materials against some strains of bacteria and fungi. Compounds were compared with clotrimazole as an antifungal reference and ofloxacin, imipenem, and clindamycin as standards for the antibacterial tests The structure activity studies confirmed that the indolylpyrimidiothienopyrimidine moiety has an important effect on the antimicrobial activity. It was also observed that the presence of electron withdrawing groups in the phenyl ring is more favorable to get higher antimicrobial activity



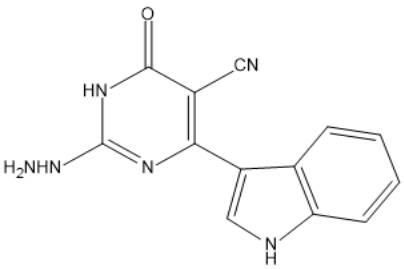
11

11a: R=CONH2, 11b: R=COOEt, 11c:R=COCH3, 11d:R=COPh, 11e:R=ClC6H4-NHCOCH2Cl

12. Mohamed M S et al,. Have been synthesized a series of new indolyl-pyrimidine-5-Carbonitriles, structure of the synthesized compounds was confirmed by means of their IR,1H-NMR spectral data and elemental analysis. synthesized compounds are evaluated for their antibacterial and antifungal activity, comparison with penicillin and fluconazole as standard. compounds 2-(1H-indol-3-yl)-4, 6-dioxo-6, 11-dihydro-4H-pyrimido [2, 1 b]quinazoline-3-carbonitrile (12a) and 2-hydrazino-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (12b) showed high antibacterial acivity.

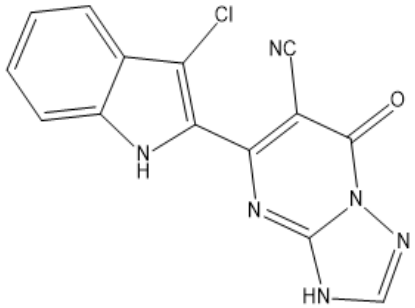


12a



12b

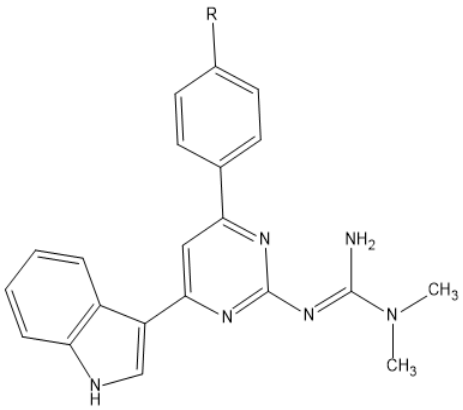
13. Mostafa sayed et al,. have been reported synthesis, characterization, and antimicrobial activities of some new indole bearing thiazolo[3,2-a] pyrimidine, trizolo[4,3-a]pyrimidine, and pyrimido[2,1-c]triazine derivatives. The starting compound 3-chloro-1H-indole-2-carbaldehyde was used to synthesize the target compounds. Compound 13 was found to be the most active compounds against all species of fungi and bacteria.



13

E) ***ANTIMICROBIAL AND ANTIDIABETIC ACTIVITY***

14. Veerasamy Ramya et al,. Have been synthesized a novel series of (E)-2-(4- (1H-indol-3-yl)-6-p-substituted phenylpyrimidin-2-yl)dimethylguanidine derivatives, evaluate their molecular docking studies, antimicrobial, and anti-diabetic activities. compound 14a exhibits excellent CDOCKER energy (− 11.36 kcal/mol), The entire compounds confirm very good antimicrobial activity towards the tested microorganisms. In the in vitro anti-diabetic studies, compounds (14a, 14b, and 14c) confirm higher alpha-amylase and alpha-glucosidase inhibition activity In the in vivo anti-diabetic activities, the synthesized compounds (10 mg/kg, p.o.) show considerable fasting blood glucose level when compared to metformin hydrochloride as a reference.

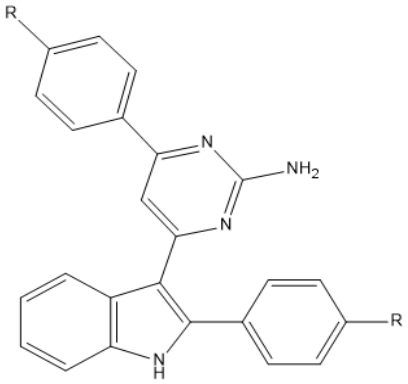


14

14a R=H, 14b R=OCH3, 14c R=Br

F) ANALGESIC, INFLAMATORY AND ULCEROGENIC ACTIVTY

15. Rajashree chavan S et al,. reported synthesis of Various derivatives of 3-(2-aminopyrimidin-4-yl) indoles viz. 4-(4-substitutedphenyl)-6-(2-(4- substitutedphenyl)-1H-indol-3-yl) pyrimidin-2-amine were synthesized by cyclization of (3-(4-substitutedphenyl)-1-(2-(4-substitutedphenyl)-1H-indol-3-yl) prop-2-en-1-one) of indole with guanidine hydrochloride in the presence of sodium isopropoxide. Their structures were confirmed by FTIR, 1H NMR and elemental analysis. All the compounds were investigated for their analgesic, inflammatory and ulcerogenic activities. comparable to that of the reference standard, indomethacin. Compounds 15a and 15b showed 87.4 and 88.2 % inhibition of paw edema, 78.5 and 76.6 % protection against acetic acid-induced writhings and 0.89 and 1.12 of severity index, respectively, compared to 92.7 %, 82.8 %and 2.2, respectively, for indomethacin.

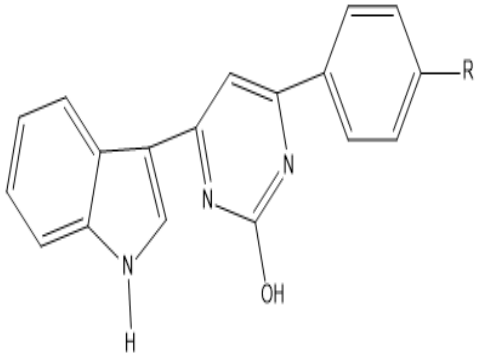


15

15a: R;Cl, R';OH, 15b: R; Cl, R'; NH2

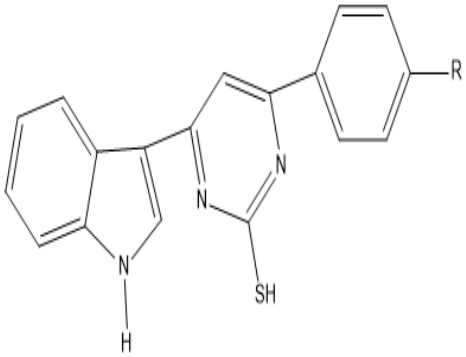
G) ANTIINFLAMMATORY, ANTIOXIDANT AND ANTIBACTERIAL ACTIVTY

16. Panda S S et al,. reported A number of chalcones were synthesized by reacting indole-3-aldehyde, prepared by Vilsemeir Haack reaction with 4-substituted acetophenone in NaOH solution in ethanol. These chalcones were immediately reacted with urea, thiourea and guanidine hydrochloride in presence of concentrated hydrochloric acid as reagent to obtain the corresponding hydroxy, thio and amino pyrimidines. products were screened for antiiflammatory, antioxidant and antibacterial activity. compounds $16a_2$, $16b_1$and $16c_1$ have shown better antiiflammatory activity than the standard drug, ibuprofen. Compounds $16a_1$, $16a_2$, $16a_3$, $16b_1$, $16b_2$, $16c_2$ and $16c_3$ have exhibited good antioxidant activity which is comparable with standard drug, ascorbic acid. antibacterial activity towards different strains of *Staphylococcus aureus, Bacillus subtilis Pseudomonas aeruginosa*and *Escherichiacoli.*



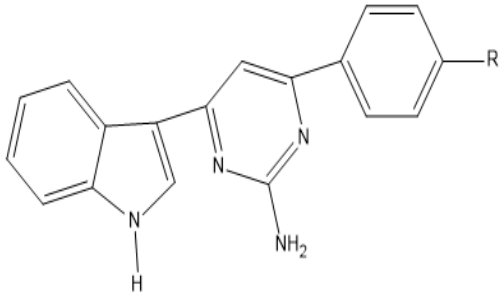
16a

16a$_1$=NH2(P), 16a$_2$=F(P), 16a$_3$=OCH3(P)



16

16b$_1$=NH2(P), 16b$_2$=OCH3(P)

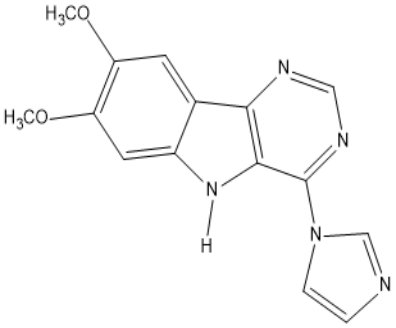


16c

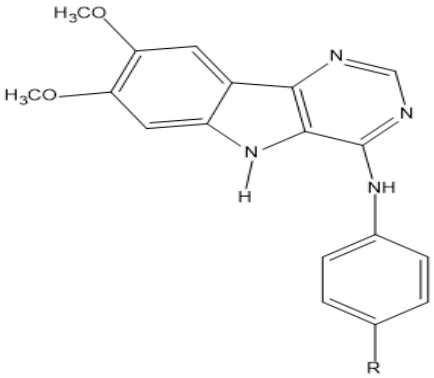
16c$_1$=Br(P), 16c$_2$=OH(O,P), 16c$_3$=OCH3(P)

H) ANTIHYPERTENSIVE ACTIVITY

17. Antonio mongea et al,. have been synthesized a series of 4-amino-7,8-dimethoxy-5H-pyrimido[5,4-b]indole derivatives, These compounds resemble carbazeram and other pyridazino compounds with activity in the cardiovascular system. Some of these new compounds possess inotropic activity, with a complementary effect on the inhibition of different CGI-PDE. The most active compounds 17a, 17b, and 17c also possess activity as vasodilators, Some of these new compounds inhibit blood platelet aggregation induced by ADP and AA and are active as inhibitors of human platelet PDEs. The inhibitory capacity of phosphodiesterase was determined by studying the activity shown by the compounds onCGI-PDE isolated through DEAE-Sepharose ionic exchange chromatography.

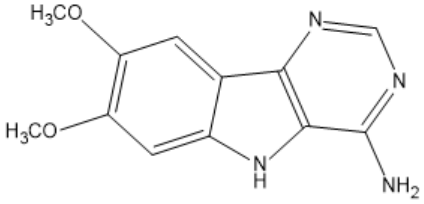


17a



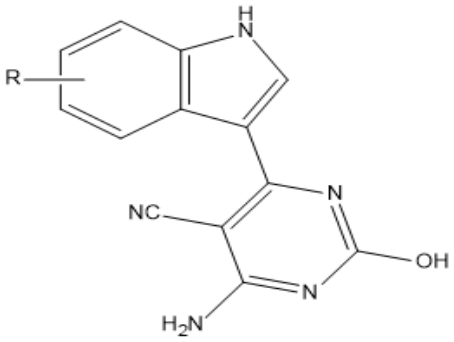
17b

R=nC4H9



17c

18. Radhika bhat et al,. Have been reported synthesis of new indol(1*H*-3-yl) pyrimidine derivatives using various substituted indole-3-carbaldehydes, urea and malononitrile in the presence of ammonium chloride. The resulting compounds were characterized using analytical and spectroscopic methods. The molecular docking study exhibits that among the synthesized compounds, 18(a-c) have great binding ability toward B-DNA. The binding efficiencies of compounds 4(c-e) with CT-DNA were evaluated via UV-visible absorption spectral and viscosity studies. The findings establish that the compounds firmly bind through an intercalative mode to CT-DNA and provide a unique pattern of DNA binding. The photo-induced cleavage indicates that the compounds have UV-visible photo nuclease properties toward plasmid DNA as revealed by agarose gel electrophoresis approach.



18

18a=5-Cl, 18b=6-Br, 18c=4-NO2

CONCLUSION

Indole and pyrimidine are a unique template that is associated with several biological activities. Due to the diverse and versatile biological properties of pyrimidine contain indole derivatives, they are of great interest to the research community. In particular, their physiological, bacteriostatic, antitumor, antioxidant and antiiflammatory activities makes these compounds attractive candidates not only for the microbe borne diseases but also for the several other conditions like Alzheimer's disease and others where oxidative stress and inflammation is involved. This review has presented comprehensive details of pyrimidine contain indole analogues, potent compounds reported for particular biological activity. More research must be carried out to evaluate the therapeutic efficacy of pyrimidine contain indole derivatives for many other untreatable diseases like AIDS, hepatitis and cancer.

REFERENCE

1. Gokhale N, Dalimba U, Kumsi M. Facile synthesis of indole-pyrimidine hybrids and evaluation of their anticancer and antimicrobial activity. Journal of Saudi Chemical Society, Nov 1, 2017; 21(7): 761-75.
2. Nassar E. Synthesis, (in vitro) antitumor and antimicrobial activity of some pyrazoline, pyridine, and pyrimidine derivatives linked to indole moiety. J. Am. Sci., 2010; 6(8): 463-71.
3. Venkatesh T, Bodke YD, SJ AR. Facile CAN catalyzed one pot synthesis of novel indol-5, 8-pyrimido [4, 5-d] pyrimidine derivatives and their pharmacological study. Chemical Data Collections, Feb 1, 2020; 25: 100335.
4. Raghunath SA, Manjunatha Y, Rayappa K. Synthesis, antimicrobial, and antioxidant activities of some new indole analogues containing pyrimidine and fused pyrimidine systems. Medicinal Chemistry Research, Nov., 2012; 21(11): 3809-17.
5. Saundane AR, Vijaykumar K, Vaijinath AV, Walmik P. Synthesis, antimicrobial and antioxidant activities of some new indole derivatives containing pyridopyrimidine and pyrazolopyridine moieties. Medicinal Chemistry Research, Feb, 2013; 22(2): 806-17.
6. Verma VA. Synthesis and biological evaluation of some novel indolyl-pyrimidine derivatives. International Journal of Recent Scientific Research Research, Mar., 2015; 6(03): 3120-24.
7. Ahmed NM, Youns MM, Soltan MK, Said AM. Design, synthesis, molecular modeling and antitumor evaluation of novel indolyl-pyrimidine derivatives with EGFR inhibitory activity. Molecules, Jan, 2021; 26(7): 1838.

8. Prajapti SK, Nagarsenkar A, Guggilapu SD, Gupta KK, Allakonda L, Jeengar MK, Naidu VG, Babu BN. Synthesis and biological evaluation of oxindole linked indolyl-pyrimidine derivatives as potential cytotoxic agents. Bioorganic & medicinal chemistry letters, Jul 1, 2016; 26(13): 3024-8.
9. Diao PC, Li Q, Hu MJ, Ma YF, You WW, Hong KH, Zhao PL. Synthesis and biological evaluation of novel indole-pyrimidine hybrids bearing morpholine and thiomorpholine moieties. European journal of medicinal chemistry, Jul 7, 2017; 134: 110-8.
10. Nikalje AP, Tiwari SV, Sangshetti JN, Damale MD. Ultrasound-mediated synthesis, biological evaluation, docking and in vivo acute oral toxicity study of novel indolin-2-one coupled pyrimidine derivatives. Research on Chemical Intermediates, May, 2018; 44(5): 3031-59.
11. Sayed M, Younis O, Hassanien R, Ahmed M, Mohammed AA, Kamal AM, Tsutsumi O. Design and synthesis of novel indole derivatives with aggregation-induced emission and antimicrobial activity. Journal of Photochemistry and Photobiology A: Chemistry, Oct 1, 2019; 383: 111969.
12. Mohamed MS, Awad SM, Ahmed NM. Synthesis and antimicrobial activities of new indolyl-pyrimidine derivatives. J Appl Pharm Sci., 2011; 1(05): 76-80.
13. Sayed M, Kamal El-Dean AM, Ahmed M, Hassanien R. Design, synthesis, and characterization of novel pyrimidines bearing indole as antimicrobial agents. Journal of the Chinese Chemical Society, Feb., 2019; 66(2): 218-25.
14. Ramya V, Vembu S, Ariharasivakumar G, Gopalakrishnan M. Synthesis, Characterisation, Molecular Docking, Anti-microbial and Anti-diabetic Screening of Substituted 4-indolylphenyl-6-arylpyrimidine-2-imine Derivatives. Drug research, Sep., 2017; 67(09): 515-26.
15. Chavan RS, More HN, Bhosale AV. Synthesis, characterization and evaluation of analgesic and anti-inflammatory activities of some novel indoles. Tropical Journal of Pharmaceutical Research, 2011; 10(4): 463-73.
16. Panda SS, Chowdary PV. Synthesis of novel indolyl-pyrimidine antiiflammatory, antioxidant and antibacterial agents. Indian journal of pharmaceutical sciences, Mar., 2008; 70(2): 208.
17. Monge A, Martínez-Crespo FJ, Villanueva MA, Font M, Santiago E, Mart JJ, de Irujo Í, Alberdi E, López-Unzu MJ, Cenarruzabeitia E, Castiella E. New 4-Amino-7,

8-dimethoxy-5h-pyrimido [5, 4-b] indole Derivatives: Synthesis and Studies as Inhibitors of Phosphodiesterases. Archiv der Pharmazie, 1993; 326(11): 879-85.

18. Bhat R, Begum NS. Synthesis, characterization and molecular docking studies of new indol (1 H-3-yl) pyrimidine derivatives: Insights into their role in DNA interaction. Nucleosides, Nucleotides & Nucleic Acids, Apr 29, 2021; 1-6.