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Original Article

Synthesis Characterization and Molinspiration Analysis, Anti-bacterial activity of Novel 2,4,6-tri Substituted Pyrimidines

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ABSTRACT

Background: Antibiotics are drugs used to prevent or treat bacterial infections. Globally this antibiotic resistance is rising in high levels and the emergence of new mechanisms to treat infectious diseases. This resistance can be reversed by resistance breakers or a more effective antibiotic against that organism. Antibiotics can save lives but their use contributes to resistant germs. This antibiotic resistance is accelerated when the presence of antibiotics pressure bacteria and fungi to adapt. The three mechanisms of antimicrobial resistance are enzymatic degradation of antibacterial drugs, altering bacterial proteins and changes in membrane permeability to antibiotics. There is a need to synthesise new drugs. Pyrimidines are the most important constituents of nucleic acids to present use in the chemotherapy of AIDS. **Methods:** Many researchers have attempted to determine the synthetic routes and various biological activities of these compounds. A Variety of 2,4,6-tri substituted Pyrimidines were synthesised by reacting Chalcones with Metformin as one of the guanidine moieties. **Results:** All the new compounds were characterised by IR, ^{1}H NMR and MASS Spectrometry. The newly prepared compounds were evaluated for their antibacterial action and some of the compounds have shown significant action when compared with Ciprofloxacin as standard in the concentration of 10µg/ml. **Conclusion:** Among five Synthesized compounds 3 and 4 exhibits significant activity in comparison with that of standard. This is due to the presence of electron-donating groups and predicted molecular descriptors and bioactivity scores using Molinspiration online software and compound 5 showed a good percentage of drug absorption in the gut.

Key words: Novel Pyrimidines, Chalcones, Guanidine Moiety, Antibacterial activity, Molinspiration.

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INTRODUCTION

Antibiotic resistance is one of the biggest obstacles to global health and development today. Antibiotic resistance will affect individuals of any age group in several countries.[1] Antibiotic resistance happens naturally, however misuse of antibiotics in humans and animals is fast. A growing variety of infections like respiratory illness, TB, gonorrhoea, and gastrointestinal disorder are getting more durable to treat because the antibiotics familiar to treating them decline effectively.[2-3] Antibiotic resistance ends up in longer hospital stays, higher medical prices and accumulated mortality. Antibiotic resistance is rising to hazardously high levels all told components of the planet. New resistance mechanisms fair measure rising and spreading globally, threatening our ability to treat common infectious diseases. A growing list of infections like respiratory illness, TB, blood disease, gonorrhoea, and foodborne diseases are getting more durable, and typically not possible, to treat as antibiotics resistant effectively without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.[4-5]

Synthesis of pyrimidines have been developed to improve and modify the Biginelli reaction using Microwave irradiation, Ultrasound irradiation, Direct condensation, Ionic liquids, Lewis and Protic acid promoters such as lanthanide triflate, H_3BO_3, silica chloride, HCOOH, $ZnCl_2$, DMF, Tf_2O, $Pd(PPh)_3Cl_2$ etc. 2,4,6-tri substituted Pyrimidine heterocyclic compounds containing nitrogen atoms in rings are highly reactive due to ring strain and in a generally stable, and are likely to occur as intermediate reactions. The heterocyclic compounds usually possess a stable ring structure since they do not readily hydrolyze or depolymerize. Heterocyclic compounds played a vital role in biological processes and are widespread as natural products.[6-7]

Chalcones or benzylidene acetophenone are α,β unsaturated ketones, it has 1,3 diaryl-1-one skeletal system, which was recognized as the main pharmacophore for. Chalcones and show potential activities against pathogens. The analogs have been reported to possess strong biological properties which have proved harmful to the growth of microbes, tubercle bacilli, malaria parasites and intestinal worms.[8-9]

The structure of the basic molecule of Chalcones consists of two phenyl rings and have one α,β unsaturated double bond. the Ring A must contain an electron-deficient moiety like ethyl, methyl and alkyl groups for better action. Ring B must have contained the hydrophobic (electron-withdrawing) groups like halogens, nitro, cyano for better action. Para position on ring B shows the best activity when compared to the ortho position of ring B. The electron-withdrawing groups like Cl, F, Br, CF_3 and NO_2 increased the penetration of molecules into the lipid membrane so that they increase the antioxidant activity by combining with the reactive oxygen species, which is generated by the different disease conditions.[10]

Chalcones are prepared by Claisen-Schmidt condensation of aromatic aldehydes with aliphatic or aromatic ketones in presence of aqueous alkali or acid-base catalyst or biosynthetically Chalcones are prepared by enzymes like Chalcones synthase (present in plants), Chalcones isomerase etc.[11-13] The cyclo condensation of Chalcones with guanidine hydrochloride resulted in the formation of novel amino pyrimidines. The main thing in this method of condensation require harsh conditions and the advantage of Chalcone require cheap or easily accessible materials.[14]

METHODS

The material used for synthesis are ketones like p-hydroxy acetophenone, p-methoxy acetophenone, p-nitro acetophenone and p-methyl acetophenone. Aldehydes like vanillin, veratraldehyde, 4-Anisal dehyde. All the chemicals were purchased from SD FINE chemicals company, Hyderabad, India. All others chemicals used are AR grade. Melting points were tested using a one-end-open capillary tube. The synthesized compounds were exposed to TLC on silica gel G plates. IR spectra (KBr) were recorded on a SHIMADZU-FTIR 4000 spectrophotometer. ^{1}H-NMR spectra were taken instrument like BRUKER AV-III 500MHZ FT-NMR spectrophotometer (Chemical shifts in δ ppm) using TMS(tetramethylsilane) as an internal standard. Mass spectra were obtained on the JEOL GC MATE GC-Mass spectrophotometer at 70ev using the direct insertion probe method.

Step 1: Synthesis of Chalcones

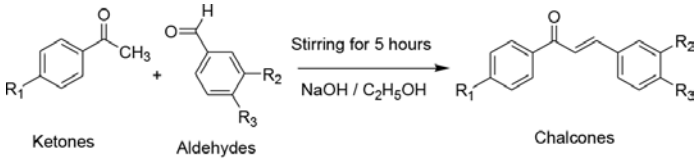
To Equimolar quantities of aromatic aldehydes, aromatic ketones (0.1M) in rectified spirit were added and equipped with a magnetic stirrer. Then the reaction mixture was alkaline by a solution of 20% NaOH was added dropwise to the reaction mixture on vigorous stirring for 0.5hrs. Then the solution became turbid and the temperature was maintained at 25°C and stirred the mixture for 5hr. The reaction mixture was neutralized by adding 0.2N HCl, then the resulting precipitated Chalcone was removed by vacuum and the residue was air-dried and then recrystallised with ethanol.

Step 2: Synthesis of Pyrimidines

Equimolar quantities of formed Chalcones and compound containing guanidine moiety (metformin) in methanol was taken, to that double, the quantity of alkaline solution was added to the reaction mixture and condensed for 6hr, the formed final product was poured in water and recrystallized

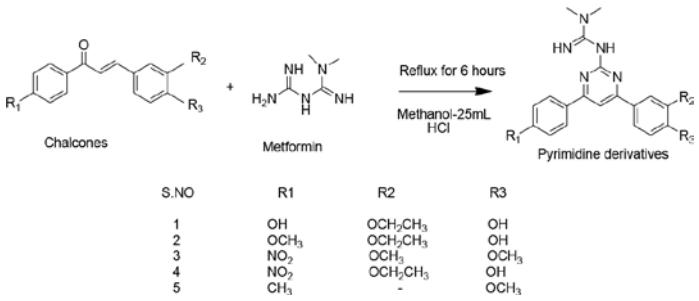
Spectral data

3-(4-(3-ethoxy-4-hydroxyphenyl)-6-(4-hydroxyphenyl)pyrimidine-2-yl)-1,1-dimethylguanidine (1):R$_f$ value 0.92,**IR (KBr):** 3458 (N-H str), 1694 (C=N str), 1451 (aromatic - OH), 864 (C-H aromatic) **^{1}H NMR** (500 MH$_Z$ MeOH) 3.0-3.5 (s, 3-^{1}H methyl), 3.5-4.0 (m,2-^{1}H methoxy), 5.5-6.5 (s, 1-^{1}H imine), 6.5-8.5 (m,15-^{1}H aromatic), 9.5-10.0 (s, 3-^{1}H 2^0-NH) Formula: $C_{21}H_{23}N_5O_3$, C-64.11, H-5.89, N-17.80, O-12.20, **Mass** (m/z) 392.54



	R1	R2	R3
1	OH	OCH_2CH_3	OH
2	OCH_3	OCH_2CH_3	OH
3	NO_2	OCH_3	OCH_3
4	NO_2	OCH_2CH_3	OH
5	CH_3	--	OCH_3

Scheme 1: synthetic route.



Scheme 2: Synthetic route.

3-(4-(3-ethoxy-4-hydroxyphenyl)-6-(4-methoxyphenyl)pyrimidine-2-yl)-1,1-dimethylguanidine (2):R$_f$ value 0.95,**IR (KBr):** 3425 (1^0 amine), 3818 (aromatic-OH), 1638 (C=N), 1184 (C-N aromatic) ^{1}H NMR (500 MH$_Z$ MeOH) 3.0-3.5 (s, 7-^{1}H methyl), 3.5-4.0 (m,4-^{1}H methoxy), 5.5-6.5 (s, 3-^{1}H imine), 6.5-8.5 (m,4-^{1}H aromatic), 9.5-10.0 (s, 5-^{1}H 2^0-NH) Formula:$C_{22}H_{25}N_5O_3$, C-64.85, H-6.81, N-17.19, O-11.78, Mass (m/z) 407.27

3-(4-(3,4-dimethoxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)-1,1-dimethylguanidine (3):R$_f$value 0.88,**IR (KBr):** 3472 (1^0 amine str), 1527 (C=C str), 1431 (aromatic-NO_2), 1319 (2^0 amine), 1261 (C-N aromatic) ^{1}H NMR: (500 MH$_Z$ MeOH) 3.0-3.5 (s, 4-^{1}H methyl), 3.5-4.0 (m,2-^{1}H methoxy), 5.5-6.5 (s, 3-^{1}H imine), 6.5-8.5 (m,15-^{1}H aromatic), 9.5-10.0 (s, 1-^{1}H 2^0-NH) Formula:$C_{21}H_{22}N_6O_4$, C-59.71, H-5.25, N-19.89, O-15.15, Mass (m/z) 421.66.

3-(4-(3-ethoxy-4-hydroxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)-1,1-dimethylguanidine (4): R$_f$ value 0.82, **IR (KBr):** 3333 (1^0 amine str), 1574 (C=C str), 1527 (aromatic-NO_2), 1400 (aromatic-OH), 1346 (2^0 amine) ^{1}H NMR (500 MH$_Z$ MeOH) 3.0-3.5 (s, 4-^{1}H methyl), 3.5-4.0 (m,4-^{1}H methoxy), 5.5-6.5 (s, 1-^{1}H imine), 6.5-8.5 (m,6-^{1}H aromatic), 9.5-10.0 (s, 5-^{1}H 2^0-NH) Formula: $C_{21}H_{22}N_6O_4$, C-59.71, H-5.25, N-19.89, O-15.15,Mass (m/z) 421.66

3-(4-(4-methoxyphenyl)-6-(4-methylphenyl)pyrimidin-2-yl)-1,1-dimethylguanidine (5): R$_f$ value 0.71, **IR (KBr):** 3380 (1^0 amine str), 1798 (C=N str), 1618 (aromatic-CH_3), 1423 (aromatic-OH) ^{1}H NMR (500 MH$_Z$ MeOH) 3.0-3.5 (s, 4-^{1}H methyl), 3.5-4.0 (m,5-^{1}H methoxy), 5.5-6.5 (s, 2-^{1}H imine), 6.5-8.5 (m,6-^{1}H aromatic), 9.5-10.0 (s, 5-^{1}H 2^0-NH) Formula: $C_{21}H_{23}N_5O$, C-69.78, H-6.41, N-19.38, O-4.43, Mass (m/z) 361.28.

Molinspiration Analysis

In Molinspiration Log p measures the totality of fragment-based aids and correction factors. This method processes all organic and organometallic molecules. Topological polar surface area(TPSA) is the sum of fragment contributions, O and N centred polar fragments are considered. It is a good descriptor containing drug absorption plus intestinal absorption, bioavailability, and blood-brain barrier penetration. Molecular volume is based on group contributions. mostly drug-like molecules. Several bonds are rotatable, it is a measure of molecular flexibility. it is a fine descriptor of the oral bioavailability of drugs. Rotatable bond is distinct for any single non-ring bond, limited to a non-terminal heavy atom. The Lipinski rule of five affirms, that most drug-like molecules have log P ≤ than or equal to 5, molecular weight ≤ than or equivalent to 500, number of hydrogen bond acceptors ≤ than or equivalent to 10 and number of hydrogen bond donors less than or equal to 5. Molecules crossing more than one of these rules may have encountered the problems of bioavailability. The rule is known as the Lipinski Rule of five. Molinspiration software is written in java software, it is a molecular properties computation toolkit, Molinspiration is applied in the process of a large number of molecules

Table 1: Molinspiration molecular descriptors prediction.

S.No	Mi Logp	TPSA	n atoms	MW	n ON	n OHNH	n viol	n rotb	Volume	%ABS
1	3.11	114.59	29	393.44	8	4	0	7	357.54	69.4
2	3.64	103.60	30	407.47	8	3	0	8	375.06	73.2
3	3.48	129.19	31	422.44	10	2	0	8	373.58	64.4
4	3.54	140.19	31	422.44	10	3	0	8	372.85	60.6
5	4.38	74.14	27	361.44	6	2	0	6	341.26	83.4

Table 2: Molinspiration bioactivity scores prediction.

S.No	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	0.17	-0.03	0.10	-0.14	-0.19	-0.02
2	0.12	-0.09	0.05	-0.20	-0.22	-0.07
3	0.01	-0.12	-0.03	-0.34	-0.29	-0.14
4	0.01	-0.10	-0.05	-0.26	-0.31	-0.13
5	0.14	-0.14	0.02	-0.29	-0.20	-0.12

in batch mode and can process data of about 10000 molecules per 60sec, it is way in through web interface directly on the internet.[15-17]

Evaluation of antibacterial activity

Strains of bacteria used Gram-Positive bacteria: *Streptococcus aureus*, Gram-negative bacteria: *Escherichia coli*, Standard drug used: Ciprofloxacin

Procedure

Clean and sterilized Petri plates were taken, nutrient agar media was prepared according to the following formula given Peptone 0.5g, Yeast extract 0.3gms, NaCl 0.5gms, Nutrient agar 2gms, Distilled water 100mL. The nutrient agar media was sterilized from the autoclave and was poured into different bacterial culture Petri plates mixed well and solidified the culture medium. The solidified Petri plates were subjected to 37°C for 24hr in an incubator. After 24hr the bacterial culture was developed. The sterilized Whatman filter paper discs were soaked in different test samples as well as standard and dried for 15-20 min. The dried filter paper discs were placed on the surface of the culture media. The standard antibiotic disc was used as a reference. Again the Petri plates were undergo incubation at 37°C for 24hr. The diameter of the zone of inhibition was measured and was recorded in millimetres.[18-21]

RESULTS

The results describe that compounds show the log p-values and all compounds show TPSA less than 150A^0 indicating a good drug permeability in the plasma membrane. Percentage absorption (%ABS) should be in the range of 60.6- 83.4% signifying good absorption in the intestine shown in Table 1.

Formula for calculation of percentage absorption:

%ABS $= 109 - 0.345 \times TPSA$

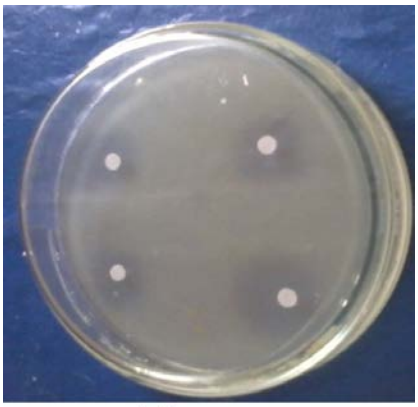
Bioactivity scores calculation

Compounds 1-5 are active as G-protein coupled receptor (GPCR) ligands. and compounds 1,2,5 are active at kinase inhibitor. For organic compounds, the probability is, that if bioactivity scores are greater than 0, then it is active. If the score is between -5 and 0 then moderately active, If the score is less than -5 then inactive. All compounds are moderately active at ion channel modulator, nuclear receptor ligand, protease inhibitor, enzyme inhibitor. Shown in Table 2.

Anti microbial activity of 3rd compound

E.coli

Figure 1: 3rd compound activity with Escherichia coli



Staphylococcus aureus

Figure 2: 3rd compound activity with Streptococcus aureus.

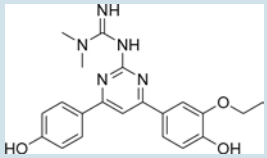
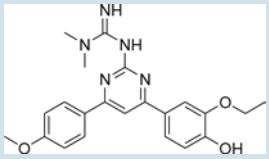
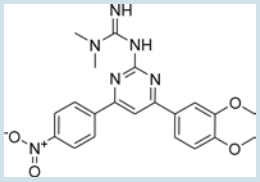
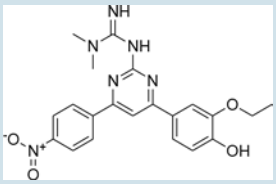
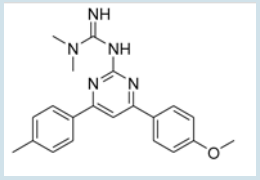
Anti-bacterial activity

All newly synthesised compounds were subjected for their antibacterial action against gram-positive *streptococcus aureus* and gram-negative *Escherichia coli* by taking ciprofloxacin as standard. Among five compounds synthesized only 3, 4 compounds showed better activity by agar diffusion disc variant technique.[22-24] Antimicrobial activity of 3rd compound shown in Figure 1 and Figure 2.

DISCUSSION

A facile method has been devised to synthesize the title compounds where the pharmacophore N, N-dimethyl guanidine at 2nd position, methoxy, the ethoxy group at 4th position and methyl, hydroxyl, nitro, methoxy

Table 3: Structures of compounds.

Sl. NO	Structure
1	
2	
3	
4	
5	

groups at 6th position are incorporated in the pyrimidine nucleus.[25-27] The methods include mild conditions and the yields were satisfactory and the chemical structures are given in Table 3. The different chalcones obtained on the reaction of ketones like p-hydroxy acetophenone, p-methoxy acetophenone, p-nitro acetophenone and p-methyl acetophenone. Aldehydes like vanillin, veratraldehyde, 4-Anisal dehyde. These different chalcones react with metformin to form pyrimidine derivatives.[28-29] This is shown in synthetic schemes. Total 5 compounds were synthesized and Spectral characterization like IR, proton NMR, MASS and underwent antibacterial activity using gram-positive organisms like *Staphylococcus aureus* and gram-negative organisms like *Escherichia coli* and finally estimating the bacterial growth and finding the zone of inhibition.[30] All structures are drawn using ChemDraw software and observed structures in Table 3. Molinspiration parameters like molecular formula, molecular weight and log *P* values, TPSA, no of violations, no of rotatable bonds, volume were given. predicted the bioactive scores of compounds and are active for G-protein coupled receptors and compounds 1,2,5 are active for kinase inhibitors and all compounds are moderately active or inactive for other enzymes. Calculated the percentage absorption from the intestine using the formula by taking values of topological surface area. Compound 5 showed the highest percentage absorption whereas other compounds have shown significant values. Even though the activities are less than standard, compounds 3 and 4 show antibacterial action and are sensitive to staphylococcus and *E. coli* by using agar disc diffusion technique. All the antibacterial results are good and compared with the ciprofloxacin drug and the concentrations taken are 10,30,40,50µg/ml shown in Table 4.

Table 4: Anti-bacterial activity of synthesized compounds.

Sl. No.	*Staphylococcus aureus* (Gram +ve)				*E. coli* (Gram -ve)			
	10µg/ml	30µg/ml	40µg/ml	50µg/ml	10µg/ml	30µg/ml	40µg/ml	50µg/ml
1	R	2	5	9	7	10	13	15
2	1	4	6	11	7	11	15	17
3	9	11	17	22	12	18	24	26
4	5	8	13	19	11	18	22	23
5	2	5	9	16	8	12	15	18
Standard	Ciprofloxacin sensitive at 10 µg/ml for *E.coli* is 32mm and *Staphylococcus aureus* is 27mm.							

CONCLUSION

All the titled compounds were synthesized, characterized and screened for their antibacterial activity. The results of Anti-bacterial activity revealed that all the titled compounds exhibited significant activity. Compounds 3 and 4 exhibit equipotent activity in comparison with that of standard. This may be due to the presence of electron-donating groups like the Nitro group at 6th position of the parent molecule. All compound's Molinspiration properties were predicted and calculated the percentage absorption in the gut. Compound 5 shows good absorption in the intestine. This reveals that compounds show significant activity and are future antibacterial agents, further synthetic work can be extended.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IR: Infrared spectroscopy, **^{1}H NMR:** Proton nuclear magnetic resonance; **MS:** Mass spectrometry; **TB:** Tuberculosis; **TLC:** Thin layer chromatography.

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