INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

SYNTHESIS OF THE 2, 4, 6-TRISUBSTITUTED PYRIMIDINES AND SCREENING OF ANTI-BACTERIAL ACTIVITY

G Maggi Hepsiba*, N.Srinivasa Rao

Department of Pharmaceutical Chemistry, Vikas College of Pharmacy, Vissanapeta, Krishna Dist, Andhra Pradesh,India

ABSTRACT

Aim of the study is to synthesize some new 2, 4, 6-trisubstituted pyrimidines by conventional method. All the synthesized compounds were characterized by FT-IR and ^{1}H-NMR spectral studies and the structures were established. All the synthesized compounds were predicted for biological properties by using PASS computer programme and screened for Anti-Bacterial activity in *Staphylococcus aureus*&*E.coli*by using Ciprofloxacin as standard. From the results of Anti-bacterial activity, it was clear that the compounds SB-4, SB-5, SB-8 & SB-9 exhibit significant activity in comparison with that of standard. This may be due to the presence of electron donating groups like Nitro group at position -6 of the parent molecule.

Key Words: 2,4,6-Trisubstituted Pyrimidines, anti-bacterial activity

Author for correspondence:
G Maggi Hepsiba
Department of Pharmaceutical Chemistry, Vikas College of Pharmacy, Vissanapeta, Krishna Dist, Andhra Pradesh, India.
E mail: maggihepsiba@gmail.com,

INTRODUCTION

Literature survey revealed that the history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. After World War II, there was an enormous explosions research in the field of heterocycles. Heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry [1-5]. Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. Since in hetrocycles non-carbons usually are considered to replace carbon atoms, they are called hetero atoms. The heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyzed or depolymerized.[6] Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are in general, stable. Those with two hetero atoms are more likely to occur as reactive intermediates. Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely founded in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavonones as well as in haeme and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life. Heterocyclic

compounds include many of the biochemical material essential to life.

For example, nucleic acids, the chemical substance that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds, as are most hallucinogens. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics Heterocyclic compounds were classified into aliphatic and aromatic. The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thioethers, amides, etc. Their properties are particularly influenced by the presence of strain in the ring. The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties. Furthermore, these compounds also comply with the general rule proposed by Huckel. *This rule states that aromaticity is obtained in cyclic conjugated and planar systems containing* $(4n + 2)\ \pi$ *electrons*. The conjugated cyclic rings contain six π-electrons as in benzene, and this forms a conjugated molecular orbital system which is thermodynamically more stable than the non-cyclically conjugated system. This extra stabilization results in a diminished tendency of the molecule to react by addition but a larger tendency to react by substitution in which the aromatic ring remains intact. A large number of heterocyclic compounds are essential to life. Various compounds such as alkaloids, antibiotics, essential amino acids, the vitamins, haemoglobin, thehormones and a large number of synthetic drugs and dyes contain heterocyclicring systems. Heterocyclic series are also of great interest, becoming readable collections that allow an update of the literature in the field. Progress in heterocyclic chemistry describes mostly the advances in every relevant field of heterocyclic chemistry in a yearly volume.The series of monographs advances in heterocyclic chemistry, which consists of 101 volumes to date, covers in depth very different topics in the field.[7,8] Other recent monographs are of interest in various topics on the field, called Name Reactions in Heterocyclic Chemistry has been given by Li and the monograph Aromaticity in Heterocyclic .Compounds is also a good basic help for heterocyclic chemists, as is the Synthesis of Heterocycles via Multicomponent reactions . Other recent monographs have centered on synthesis techniques such as palladium chemistry, chemistry of heterocyclic carbene, or synthesis with microwave . In addition, a recent monograph on general heterocyclic chemistry emphasizes the importance of heterocyclic compounds in the field of medicinal chemistry and natural products .[9,10,11]

Several 2,4,6-tri substituted pyrimidine derivatives have found to exhibit interesting different biological activities including anti-neoplastic, anti-fungal, anti-bacterial, anti-viral, anthelmintic, liver disorders, vasodilators, respiratory tract infections, ear infections, peripheral infections, gastrointestinal infections, hyperuricemia, expectorant, mucolytic, urinary tract infections, hypnotic , sedative , anti-convulsant, parkinsonism, anti-tumour, male baldness, anti-inflamatory, long-standing insulin dependent diabetes mellitus, alcoholism, polyneuritis, beriberi, anxiolytic and anaesthetic activities. Some of the derivatives are exist in the market and several compounds are found in patented literature indicating that many of them are under goining trials for clinical activity. It is proved from the literature survey that substituted pyrimidines and its derivatives were found to possess important biological activities. Keeping this view, it was proposed to synthesize some new 2,4,6-trisubstituted pyrimidines by conventional method. Hence to attempt a very simple and facile procedures for the synthesis of the 2,4,6-trisubstituted pyrimidines.

MATERIALS AND METHODS (12-15)

Procedure for Synthesis of some 2,4,6 tri substituted pyrimidine derivatives can be followed by two steps (Fig-1). First step is synthesis of chalcone and the Second step is condensation of chalcone with compound containing guanidine moiety to obtain the final product.

Step-1

Aromatic Aldehyde and acetophenone(0.1M) was dissolved in rectified spirit containing beaker, equipped with magnetic stirrer. NaOH (20%) solution was added drop wise to the reaction mixture on vigorous stirring for 0.5 hrs. Then the solution

becomes turbid, the temperature should be maintained between20-25 . Stirr the mixture in cold water bath for 4-5 hrs on the magnetic stirrer. Reaction mixture was neutralized by 0.1-0.2 N HCl, then the product was precipitated, filter it. The obtained crude chalcone was collected, air dried and then recrystallised by using ethanol.

STEP-2

Equimolar quantities of formed chalcone and compound containing guanidine moiety in methanol was taken. Double the quantity of NaOH dissolved in water and added to the reaction mixture. Then reflux for 6 hrs, poured in water and recrystallised.

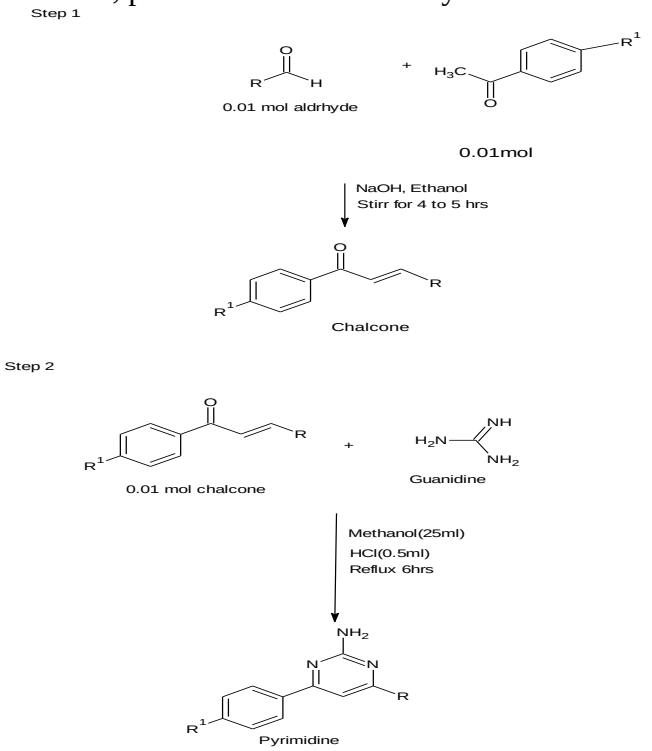

Fig-1 Synthetic scheme

***In-Silico* Methodology**

During the last three decades, new techniques and advancements have added layers of complexity to the research done in drug discovery, biotechnology and biomedical research. Many of these techniques are computational in nature, taking their particular disciplines,*In –silico,* i.e., to be executed with in the computer. Drug development techniquesrequires detailed information about the biological activity of the pharmacological compounds against selected targets. It is widely accepted that drug activity is obtained through the molecular binding of ligand to the receptor, which is commonly a protein. The application of computational methods to study the formation of intermolecular complexes has been the subject of intensive research during last two decades.[102]

Prediction of Activity Spectrum of Substances (PASS) *In-Silico* prediction of biological activity in relation to the chemical structure of a compound is now a commonly used technique in drug discovery and development. It is possible with computer program PASS, to predict the biological activity spectrum for a compound on the basis of its structural formula. It helps in finding most probable new leads with required activity spectra among the compounds from in-house and commercial data base. Novel pharmacological actions can be found for synthesized compounds on the basis of computer program PASS. Its application to the synthesized compounds was done in order to identify Prospective pharmacological properties that could be confirmed by experimental studies. PASS compares the structure of a new compound with structures of well-known biological activity substance and therefore it is possible to estimate if a new compound may have a particular effect. It operates with many thousands of substances from thetraining set, and provides more objective estimation. Structures of the title compounds were drawn through Chem Sketch software submitted to the PASS computer program and predicted the possible mechanism of action as well as biological activities. PASS is based on a robust analysis of structure-activity relationships in heterogeneous trainings set currently including about sixty thousand of biologically active compounds from different chemical series with about four thousand five hundred types of biological activity. Biological activity spectrum for a substance is a list of biological activity types for which the probability to be revealed (Pa) and the probability not to be revealed (Pi) are calculated. Pa and Pi values are independent and their values vary from 0.0001-1.000. It is reasonable that only those types of activities may be revealed by the compound, where Pa>Pi and so they are put in to the biological activity spectrum. If Pa>0.7, the compound is likely to

Reveal its activity in experiments, but in this case, the chance of being the analogue of the known pharmaceutical agent is high. If 0.5<Pa>0.7, the compound is likely to reveal this activity in experiments, but this is less and the compound is not so similar to the known pharmaceutical agent. If Pa<0.5, the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confrimed in the experiment, the compound might be a new chemical entity.

RESULTS AND DISCUSSION

A facile method has been devised to synthesize the title compounds where the pharmacophores amino groupat 2nd position in the pyrimidine nucleus. The methods include mild conditions and the yields were satisfactory.

Table-1 Datas of synthesized compounds

S.no	Compound	Molecular formula	Molecular weight	Composition	Percentage yield	R_f value	Melting point (°C)
1	SB-1	$C_{14}H_{11}N_3O_2$	253.25	C(66.40%) H(4.38%) N(16.59%) O(12.63%)	71	0.676	270
2	SB-2	$C_{18}H_{17}N_3O_3$	323.34	C(66.86%) H(5.30%) N(13.00%) O(14.84%)	68	0.803	262
3	SB-3	$C_{19}H_{19}N_3O_3$	337.37	C(67.64%) H(5.68%) N(12.46%) O(14.23%)	68	0.816	286
4	SB-4	$C_{18}H_{16}N_4O_4$	352.34	C(61.36%) H(4.58%) N(15.90%) O(18.16%)	69	0.796	254
5	SB-5	$C_{18}H_{16}N_4O_4$	352.34	C(61.36%) H(4.58%) N(15.90%) O(18.16%)	66	0.786	260
6	SB-6	$C_{18}H_{17}N_3O$	291.34	C(74.20%) H(5.88%) N(14.42%) O(5.49%)	65	0.696	246
7	SB-7	$C_{15}H_{13}N_3O_2$	267.28	C(67.40%) H(4.90%) N(15.72%) O(11.97%)	58	0.712	218
8	SB-8	$C_{15}H_{13}N_3O$	251.28	C(71.70%) H(5.21%) N(16.72%) O(6.37%)	56	0.724	184
9	SB-9	$C_{14}H_{10}N_4O_3$	282.25	C(59.57%) H(3.57%) N(19.85%) O(17.01%)	68	0.623	236

The course of the proposed reaction was confirmed by TLC. All the synthesized compounds were characterized by FT-IR and ^{1}H-NMR spectral studies and the structures were established.

All the synthesized compounds were predicted for biological properties by using PASS computer programme and screened for Anti-Bacterial activity in *Staphylococcus aureus*&*E.coli*by using Ciprofloxacin as standard(Table-2 and fig-2 and 3).

Table -2 Comparision of antibacterial activity with standard

S.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
SB-1	2	7	11	17	9	16	19	22
SB-2	4	6	9	11	7	10	13	15
SB-3	3	4	6	11	7	11	15	17
SB-4	9	11	17	22	12	18	24	26
SB-5	5	8	13	19	11	18	22	23
SB-6	2	5	9	16	8	12	15	18
SB-7	4	6	8	12	10	11	15	19
SB-8	6	7	9	14	11	13	16	22
SB-9	7	9	10	16	10	14	18	20
STD	Ciprofloxacin sensitive at 10 µg/ml for *E.coli* is 32mm and *Staphylococcus aureus* is 27mm.							

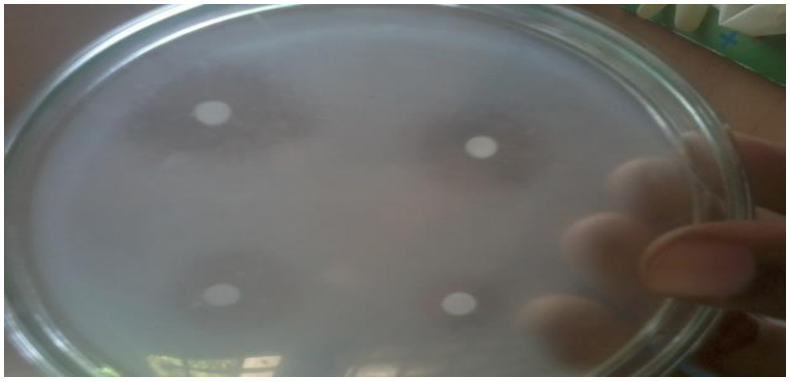

Fig-2 anti microbial activity of SB-4 compound on *E.Coli*

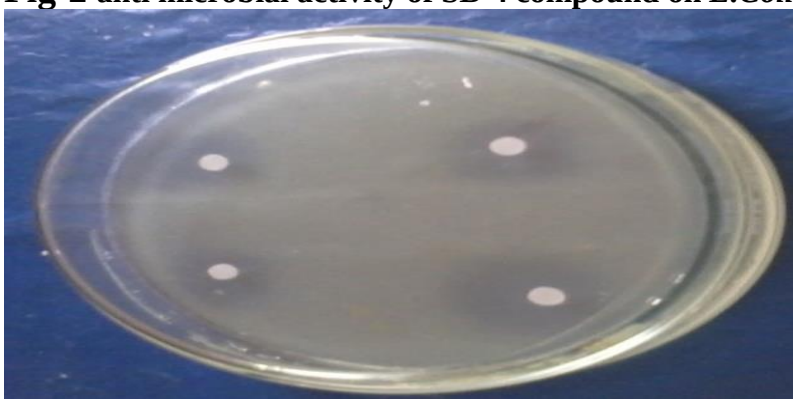

Fig-3 anti microbial activity of SB-4 compound on *Staphylococcus aureus*

From the results of Anti-bacterial activity, it was clear that the compounds SB-4, SB-5, SB-8 & SB-9 exhibit significant activity in comparison with that of standard. This may be due to the presence of electron donating groups like Nitro group at position -6 of the parent molecule.

CONCLUSION

All the titled compounds were synthesized, characterized and screened for their anti-bacterial activity.The results of Anti-bacterial activity revealed that all the titled compounds exhibit significant activity. The compounds SB-4, SB-5, SB-8 & SB-9 exhibit significant activity in comparison with that of standard. This may be due to the presence of electron donating groups like Nitro group at position -6 of the parent molecule. Further studies involves QSAR modeling and Docking studies of titled compounds.

REFERENCES

1. Gribble G.W. and Joule J. Progress in Heterocyclic Chemistry, Elsevier, Amsterdam., 2009.
2. Katrizky A.R. , Advances in Heterocyclic Chemistry, Elsevier , Amsterdam., 2010.
3. Li J.J. , Name Reactions in Heterocyclic Chemistry, John Wiley & Sons , *Inc.*,2004.
4. Krygowski T.M. and Cyranski M.K. , Aromaticity in Heterocyclic Compounds (Topics in Heterocyclic Compounds).,2009.
5. Orru R.V.A., Ruijter E. and Maes B.U.W. , Synthesis of Heterocycles via Multicomponent Reactions I (Topics in Heterocyclic Chemistry)., 2010.
6. Li J.J. and Gribble G.W. , Palladium in Heterocyclic Chemistry. A Guide for the Synthetic Chemist., 2006,2nd edn.
7. Nolan S.P. N-Heterocyclic Carbenes in Synthesis.2006.
8. Kuhl O. ,Functionalised N-Heterocyclic Carbene Complexes , John Wiley & Sons , *Ltd.*,2010.
9. McGuinnessD.Heterocyclic CarbeneComplexes,Reaction Chemistry and Catalytic Application.,2009.
10. Vander Eycken E. and Kappe C.O., Microwave-Assisted Synthesis of Heterocycles(Topics in Heterocyclic Chemistry).,2006.
11. Quin L.D. and Tyrell J.,Fundamentals of Heterocyclic Chemistry, Importance in Natural and in the Synthesis of Pharmaceuticals, John Wiley & Sons, Inc.,2010
12. TheivendrenPanneerSelvam ,CaiadoRicha James, PhadteVijaysarathyDniandev, SilveiraKarynValzita. A mini review of pyrimidine and fused pyrimidine marketed Drugs. *Research in Pharmacy.*, 2012, 01-09.
13. Stuart AL, Ayisi NK, Tourigny G, Gupta VS. Antiviral activity, antimetabolite activity and cyctotoxicity of 3-substituted deoxypyrimidine nucleosides. *J Pharma Sci.*, 1985, 246-249.
14. Nicolaou K.C, Montagnon T, Molecules that Changed the world.,*Wiley-VCH*,2008.
15. Baxendale I.R., Hayward J.J, Ley S.V, TranmerG.k , *ChemMedChem.*,2007,768-788.