ISSN: 2395-0536 Impact Factor- 2.95*

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

SYNTHESIS OF PYRAMIDIN DERIVATIVES AND STUDY OF THEIR ANTI CANCER ACTIVITY

A.Lavanya, B.Raju, N.Srinivasa Rao

Department of Pharmaceutical Chemistry, Vikas College of Pharmacy, Vissanapet, Andhra Pradesh, India.

ABSTRACT

Synthesized compounds were characterized, screened for their anticancer, antimycobacterial, antibacterial and antifungal activities. It was found that pyramidins 1c and 2a, 4a and 6abd, and 10d, 11a and 12d exhibited excellent anticancer activity against Ehrlich ascites carcinoma. In case of antimycobacterial activity 2ac and 3cdf and 4b, 6b and 8c exhibited potent antimycobacterial activity.

Key Words: pyramidins , anticancer activity

Author for correspondence

A.Lavanya,
Department of Pharmaceutical Chemistry,
Vikas College of Pharmacy, Vissanapet,
Andhra Pradesh, India.
Email: lavanya.aakula96@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) π 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].

MATERIALS AND METHODS

Procedure for Synthesis of some 2,4,6 tri substituted pyrimidine derivatives [9, 10]

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. 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

In vitro cytotoxic activity

The EAC cells were collected, counted and adjusted to 106 cells/mL in normal saline. The drug dilutions were made with phosphate buffer saline and were further adjusted to concentrations ranging from 125-1000 μg/mL. The drug dilutions were then added to the EAC cells and incubated at 37 °C for 3 h. At the end of 3 h, the cell viability was determined by trypan blue exclusion method. Under identical conditions, standard anticancer agent vincristine was evaluated for its in vitro anticancer activity. The percentage cytotoxicitywas calculated using the formula,

Percentage cytotoxicity = 100 = TotalCells– Dead Cells Total Cells /Total Cellsx 100

The percentage cytotoxicity of furyl-quinazolin-4-ones, imidazolyl-quinazolin-4- ones, and pipierazinyl-quinazolin-4-ones are given in Table 5.1.2.1, Table 5.1.2.2, and Table 5.1.2.3 respectively.

Body weight analysis

After cancer cell inoculation, all the mice were weighed daily up to 11 days. Those compounds that had good in vitro anticancer activity, significantly opposed the average increase in the bodyweight ofthe carcinoma induced mice. The decrease in bodyweight of the test and standard group animals were compared with control group.

Determination of mean survival time (MST) and percentage increase in life span(%J ILS)

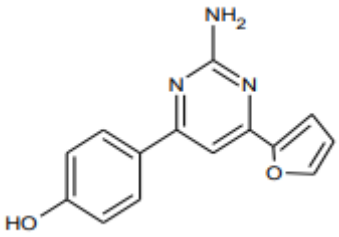
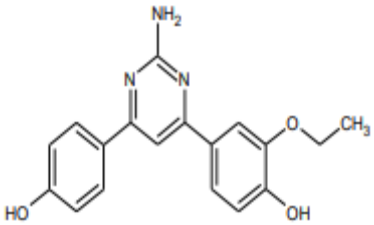
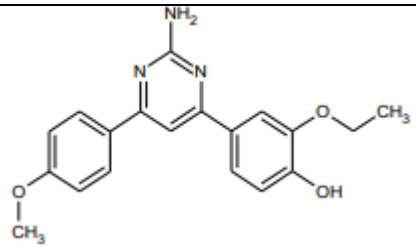
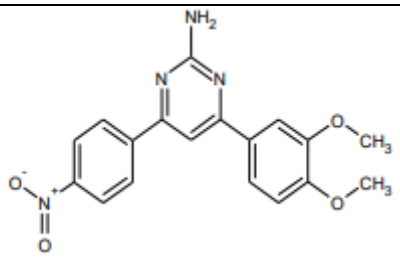
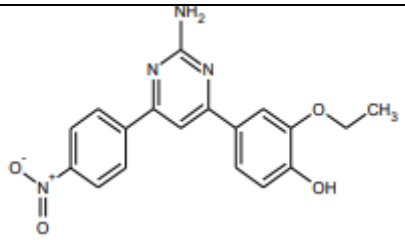
The survival times of EAC bearing mice were noted. The MST of the test and standard group animals were compared with control group. Student t test was performed to ascertain the significance of the exhibited activity.

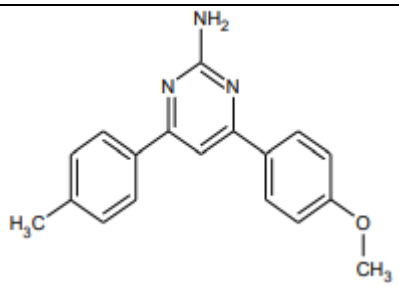
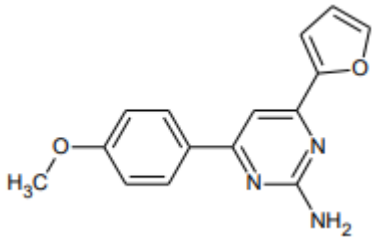
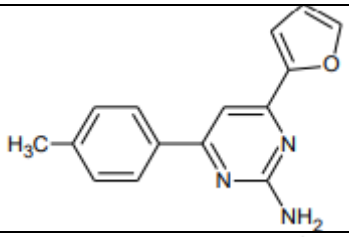
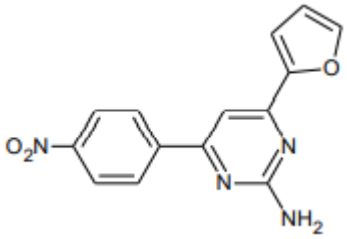
% ILS = MST of treated group – MST of control group / MST of control group x 100

RESULTS AND DISCUSSION

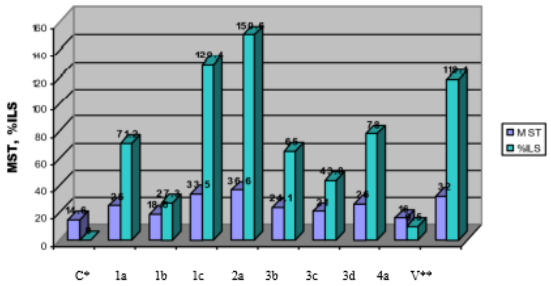
Synthesis was carried out by above procedure and synthesized compounds were characterized by IR, NMR and mass (Table-1)

Table-1 Structures and IUPAC Nomenclature of Some Derived Pyrimidines

COMPOUND CODE	STRUCTURE	IUPAC NAME
SB-1		4-[2-amino-6-(furan-2-yl)pyrimidin-4-yl]phenol
SB-2		4-[2-amino-6-(4-hydroxyphenyl)pyrimidin-4- yl]-2-ethoxyphenol
SB-3		4-[2-amino-6-(4-methoxyphenyl)pyrimidin-4- yl]-2-ethoxyphenol
SB-4		4-(3,4-dimethoxyphenyl)-6- (4-nitrophenyl)pyrimidin-2-amine
SB-5		4-[2-amino-6-(4-nitrophenyl)pyrimidin-4-yl]- 2-ethoxyphenol

SB-6		4-(4-methoxyphenyl)-6-(4-methylphenyl)pyrimidin-2- amine
SB-7		4-(furan-2-yl)-6-(4-methoxy phenyl)pyrimidin-2-amine
SB-8		4-(furan-2-yl)-6-(4-methylphenyl)pyrimidin-2-amine
SB-9		4-(furan-2-yl)-6-(4-nitrophenyl)pyrimidin-2-amine

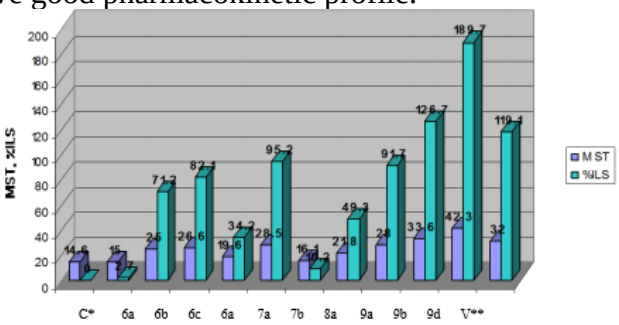
In vivo cytotoxicity and in vitro anticancer activity studies indicated that compounds 1c and 2a exhibited the highest degree of anticancer activity than standard vincristine. Compounds 1a and 3b-d had moderate anticancer activity. Other compounds had no significant anticancer activity (Fig-1). Structure activity relationship (SAR) studies of the synthesized compounds for anticancer activity indicates that compound 1c (%ILS, 129.45) increases the percentage increase in life span (%ILS) as compared to compound 1a (%ILS, 71.23). Interestingly compound 2a (%ILS, 150.68) is found to be more beneficial than 3d (%ILS, 78.08) and 2d (%ILS, not determined as its in vitro activity was negligible) respectively. Compounds 1ac, 2a, and 3b-d proves more effective than 3f (%ILS, 9.58) and 2f (%ILS, not determined as its in vitro activity was negligible)



*** = Control, ** = Vincristine**

Fig-1 Anticancer activity of piperidines derivatives from 1a to 4a

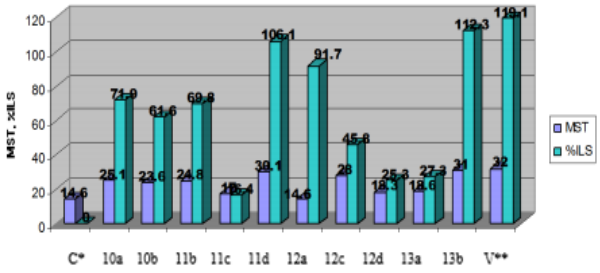
In vivo and in vitro anticancer activity studies indicated that compounds 9b and 9d exhibited the highest degree of anticancer activity than standard vincristine. Compound 7a, 6bc, 8a, and 9a had moderate anticancer activity. Other compounds had no significant anticancer activity (Fig-2). Structure activity studies of the title compounds for anticancer activity suggest that compounds 9d (%ILS, 189.72), 9b (%ILS, 126.71), 7a (%ILS, 95.2) increases the percentage increase in life span (%ILS) as compared to compound 8a (%ILS, 49.31). Compound 9b (%ILS, 126.71) is more active than compound 9a (%ILS, 91.78). Compounds 9a (%ILS, 91.78), 7a (%ILS, 95.2) are more active than 6a (%ILS, 2.73). Compound 8a had good in vitro activity but failed to show good in vivo activity indicating that the compound 8a may not have good pharmacokinetic profile.



*** = Control, ** = Vincristine**

Fig-2 Anticancer activity of piperidines derivatives from 6a to 9d

In vitro and in vivo anticancer activity studies prompted compounds 11d, 12a, and 15d as most potent compounds among the series as their activities are comparable to standard vincristine. Compounds 10b, 11b and 12c had moderate anticancer activity. Compounds 12d, 13d, and 14b showed less activity among the series(Fig-3). Structure activity relationship studies suggests that compounds 13d (%ILS, 112.32) and 11d (%ILS, 106.16) are more active than 13a (%ILS, 27.39) and 11a (%ILS was not determined as its in vitro activity was negligible) respectively. Compounds 11b (%ILS, 69.86) and 10b (%ILS, 71.91)) are more active than 11a and 10a; %ILS was not determined as their in vitro activity was negligible. Compund 11b (%ILS, 69.86) is less active than 10b (%ILS, 71.91). Compounds 10d, 11d, 12d, and 13d are not having significant activity except compound 10d (%ILS, 61.46) which is moderately active. Compound 12a (%ILS, 91.78)) favors anticancer compound 11a (%ILS was not determined as its in vitro activity wasnegligible)).



*** = Control, ** = Vincristine**

Fig-3 Anticancer activity of piperidines derivatives from 10a to 13b

CONCLUSION

A new approach for developing substituted pyramidins as chemotherapeutic agent has been adopted. Synthesis of the pyramidinsring structure, its molecular modifications by attaching different pharmacophoric groups of existing bioactive agents to the pyramidinsring system has been done. Synthesized compounds were characterized, screened for their anticancer, antimycobacterial, antibacterial and antifungal activities. It was found that pyramidins 1c and 2a, 4a and 6abd, and 10d, 11a and 12d exhibited excellent anticancer activity against Ehrlich ascites

carcinoma. In case of antimycobacterial activity 2ac and 3cdf and 4b, 6b and 8c exhibited potent antimycobacterial activity. Hence it is concluded that these drugs can be developed into clinically useful agents for their anticancer and antimycobacterial activity. In case of antibacterial and antifungal activity, even though some of the substituted pyramidins showed significant activity but to a lesser degree compared to the standard drug used, their efficacy is not enough to develop them into clinically useful agents. Hence necessary structural modifications have to be made to improve the potency of these compounds so as to develop them into clinically useful anticancer and antifungal agents.

REFERENCES

1. Adcock H. Pharmageddon: is it too late to tackle growing resistance to antiinfectives. *Pharmaceutical Journal*. 2002, 269:599-600.
2. Agarwala SS, Kirkwood JM. Temozolomide, a novel alkylating agent with activity in the central nervous system, may improve the treatment of advanced metastatic melanoma. *The Oncologist*. 2000, 5:144-151.
3. Alagarsamy V, Revathi R, Meena S, Ramaseshu KV, Rajasekaran S, De-Clercq E. Anti-HIV, antibacterial and antifungal activities of some 2,3-disubstituted quinazolin-4-(3H)-ones. *Indian Journal of Pharmaceutical Sciences*. 2004, 4:459- 462.
4. Alksnis E, Korneeva D, Lukevics E. Adenine and uracil derivatives with antitubercular activity. *Chemistry of Heterocyclic Compounds*. 2001, 37:743-746.
5. Al-Rashood ST, Aboldahab IA, Nagi MN, Abouzeid LA, Abdel-Aziz AAM, Abdelhamide SG, Youssef KM, Al-Obaida AM, El-Subbagha HI. Synthesis, dihydrofolatereductase inhibition, antitumor testing, and molecular modeling study of some new 4(3H)-quinazolinone analogs. *Bioorganic and Medicinal Chemistry*. 2006, 14:8608- 8621.
6. Anand N, Remers WA. *Synthetic antibacterial agents*. In: Burger's medicinal chemistry and drug discovery: Chemotherapeutic agents. 6th ed., (Abraham DJ, eds.) New Jersey: John Wiley & Sons, Inc; 2003. p. 538-606.
7. Anand RM, Sumathi K, Sharma SV, Murugan V. 3-D QSAR CoMFA study of nitrogen mustards possessing new chemical entities as possible anticancer agents. *Indian Journal of Pharmaceutical Sciences*. 2006, 68:323-326.
8. Andriole VT. *In current clinical topics in infectious diseases*. (Remington J, Swartz M. eds.). Malden; 1998. Vol. 18, p 19-36.
9. Bansal RK. *Heterocyclic chemistry*. 4th ed., New Delhi: New Age International (P) Limited; 2005.
10. Bartroli J, Turmo E, Alguero M, Boncompte E, Vericat ML, Conte L, Ramis J, Merlos M, Garcia-Rafanell J, Forn J. New azole antifungals: . synthesis and antifungal activity of 3-substituted-4(3H)-quinazolinones. *Journal of Medicinal Chemistry*. 1998, 41:1869-1882.