Synthesis and anticancer activities of 5-halogeno pyrimidine

SOLID STATE MICROWAVE-ASSISTED SYNTHESIS AND ANTICANCER ACTIVITIES OF *N* -DERIVATIVES OF 5-HALOGENO SUBSTITUTED PYRIMIDINE 2, 4 DIONE

BY

TAHIRA SAGHIR

ABSTRACT

This study will report the synthesis of some substituted 5-halogenated pyrimidine 2, 4dione by conventional and solid state microwave assisted methods. Derivitization of 5-halogenated pyrimidine, 2, 4 dione give predominately N_1 and N_3 -subsituted compounds where R may be the alkyl , aryl, allyl, acyl, cyclohexenyleetc. 5-halogenated pyrimidine 2, 4 dione derivatives represent the new group of anticancer and antibacterial agents with potential for development of medicinal application. The application of solid state microwaves to organic synthesis is opening up new opportunities for the synthetic chemist by providing new routes. High consumption of chemicals for prolonged time has adverse effecton environment. This is the key reason to adopt solvent free condition i. e. eco-friendly microwave assisted solid state synthetic routes.

Introduction

Microwave irradiation has emerged as powerful tool for organic synthesis. In concern with a rapidly expanding applications base, microwave synthesis can be effectively applied to any type of chemistry resulting in faster reaction time from minutes to seconds and improved product yield.

The environmental protection has become a global concern and chemical industry is increasingly searching the ways of developing and applying more efficiently and environmentally begins strategies for future sustainable growth.

An important part of present effort towards eco friendly synthesis is aimed at reduction of use of solvents as in classical procedures. For this purpose in organic synthesis solid support has made a land mark as the reaction can be performed in dry media or solvent free conditions.

Further usage of solid support in conjunction with microwave leads to high yield remarkable reaction rate enhancement high catalytic activity with optimum utilization of energy. The solvent less approach provide an opportunity to conduct selective organic functional group transformation more efficiently and also allows the work to conductin open vessel thus avoiding the risk of high pressure development.

5-halogenated pyrimidine 2, 4dione is used as an anticancer agent. A major difference between cancer cells and normal cells are that the cancer cells divide much more rapidly. Rapidly dividing cells require a constant new supply of DNA is the nucleoside, deoxythimidine, which is synthesized in the cell by methylation of uridine. Flouro uracil is administrated to a cancer patient as part of chemotherapy. The body convert it in to flourouridinegreatly decreasing DNA synthesis.

A number of pyrimidine bases possess anti viral and anti cancer activities. In addition N_1 and N_3 -di substituted 5 halogenated pyrimidine2, 4dione also exhibit anticancer , antibacterial and anti fungalactivities.

Literature Review

Zeng and his coworkersstudied on activity and structure of co-relation which are useful to drug discovery. By modifying the nature and position of substituent or pyrimidine and theirderivatives, a change in biological activity is observed. The synthesis of organic compound and pharmacological evaluation of these compound have been described by them, they have synthesized large number of compound using different reaction condition i. e. liquid phase reaction and solid phase [1] .

Stefeny, PaulaM and their coworkers applied microwave assisted organic synthesis in many formats ranging from traditional solution phase to solvent free reactions [2] .

Verma and Rajender Singh made solvent free synthesis of heterocyclic compounds. They reported that microwave enhanced solvent free synthetic approach has many advantages. These advantages aresimplicity, manipulative ease of the operation and conservation of solvent . A variety of solid state reactions are described that occur rapidly at ambient pressure under solventless conditions and provide ready access to intermediates such as enamines and tosyloxyketones which can be transformed in situ to biologically significant heterocyclic compounds such as isoflav-3-enes, flavones, quinolones, 2-aroylbenzo[b]furans and thiazoles in one-pot

operation. Multicomponent reactions under these solvent-free conditions can be adapted for high speed parallel synthesis and are exemplified by assembly of dihydropyrimidine-2(1H)-ones (Biginelli reaction) and imidazo[1, 2-a]annulated pyridines, pyrazines and pyrimidines (Ugi reaction) which may have potential in building a library of such compounds [3] .

Verma et al. 2009 found that microwave enhanced solvent free synthatic approach has the

features: simplicity manipulative ease of the operation and conservation of solvents as the main advantage. This eco friendly approach is found as an application in facile organic functional group transformation is applied to rapid assembly of hetrocyclic compounds [4] .

Filler and Roberts postulated the importance of fluore containing compounds synthesis in bio and medicinal chemistry e. g. amino acid, anti canceragents, nucleosides, centeral nervous system agents and anesthetic agents [5] .

Sugiyama, H, etal. explained 5 iodo uracil containing DNA-zalpha complex showed photo reactivity. For the high tendency binding it was observed that NH_2 terminusZ-alpha and double strained RNA was very profound respectively. In the absence the incidence of Z-alpha, to relate the structure of Z-DNA induced by Zalpha, were perceived in comparison to that with high salt concentration, than the hydroxylated product was meritoriously produced in it specified by Z-alpha. [6]

Zhan, etal. have made the solvent and catalyst-free synthesis of dihydropyrimidione in one pot conditions under focused microwave irradiation in 2008. [7]

Andre Loupy has defined microwave chemistry as “ the science of applying microwave irradiation to chemical reaction’’ [8] . In literature we found that initiallyRichard Gedye and coworkers have described the use of microwave irradiation for organic synthesis. After Richard then number of other scientist in the field of organic chemistry reported in detail about various organic reactions which were performed by using this technology. Various reactions in literatureinclude Alkylation, Esterification, Sponification, Condensation , Oxidation. Reduction. Cycloaddition, Rearrangments, N-acylations, and Olefination. [9]

Kidwai and Rastogi reported an eco friendly approach for the synthesis of 2 substituted-4-6-diarylpyrimidines using inorganic solid supports for its catalytic roleas well as energy transfer medium is described. The methodology eliminates the usage of solvents during reaction. Microwave assisted basic alumina catalysed reaction is the best as a catalysis as well as reaction time and yield. [10]

Gedye and Langahave talked about specific microwave effects. [11]

Loupy and coworkershave published a number of rewiews on solvent-free reactions. [12]

Kamal Alannan have reported that substituted uracils especially at 5-position play a key role in many metabolic processes. Uracil reacts with halogens such as, chlorine, Bromine. Iodine&florine to give haogen substituted compounds. From the literature it was found that the halogen substituted uracils are important anticancer drugs. [13]

Zhang and zhou reported the major advantage of solvent-free, for the green synthesis derivatives of heterocyclic compounds. The major advantages of this method are simple experimental and work-up procedures, solvent-free reaction conditions, small amount of catalyst and short reaction time, high yield, and utilization of an inexpensive and reusable catalyst [14]

Zhao and co-workers reported the advances in the research of pyrimidine derivatives as antitumor drug according to their action on targets. [15]

Chowdhury and shanker describe the recent development in solvent-free multi component reactions which was the perfect synergy for eco-compatible organic synthesis. The eco-friendly solvent free approach opens up numerous possibilities for conducting rapid organic sunthesis. [16]

Khosrou and Ali reported the cytotoxicity of synthesized dinitrophenyl derivatives of 5-fluorouracil under hypotoxic conditions on HT-29 cell line under both aerobic and hypotoxic conditions. [17]

Objectives

Solid state microwaves assisted organic synthesis have an impact on drug discovery. The discovery of compounds with improved biological properties can be made more efficient by using new techniques.

The objectives of the present research will be:

1. Synthesis of new bio active compounds.
2. Method development for synthesis of new bioactive compounds.
3. Characterization of all synthesized compounds.
4. Pharmacological evaluation.

Plan of work

1. Synthesis of 5 -halogen substituted pyrimidine 2, 4 dione.
2. Synthesis of N-derivatives of 5-halogeno substituted pyrmindine-2, 4-dione.
3. Structure elucidation will be carried out by

a. UV/VIS spectroscopy

b. FTIRspectroscopy

c. NMR

d. Mass spectrometry

4. Pharmacological evaluation(anticanceractivities)of synthesized compounds.

METHODOLOGY

Microwave- assisted synthesis has been applied in many formats ranging from traditional solution phase to solid phase and solvent free reactions. By using dry conditions, the hazards of volatile organic solvents in microwave oven can be eliminated. The solid state synthesis of N-derivatives of 5-halogen substituted of pyrimidine 2, 4 dione is of great interest in present research.

PLACE OF WORK

1. Lahore College For Women University, Lahore.

2. University of Veterinary and Animal Sciences Lahore.

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References

1. Zeng , *J . pharma, Res* . 16, 304-309, 1999.

2. Stafani, H. A; Gatti, P. M, *Synth. commun* . 30, 2165-2173, 2000.

3. Varma, R. S., *JournalofHetrocycle. Chem* . 36, 1565-1571, 1999.

4. Verma, R. S., *Journal of Heterocyclic Chemistry , 36* (6), 1565 – 1571, 2009.

5. Filler, *ACS. Symp. Ser,* 60, 616, 3793, 2000.

6. Oyoshi, T.; Sugiyama, H. *Journal of Nucleic Acids Research* , (1), 123-4, 2001.

7. Zhan, H. W; Wang, J. X. *Journal ofChin. Chem,* Lett. 19, 1183-1185, 2008.

8. Loupy, *Micro wave in Organic synthesis* , Willey-VCH, Weinhein, 2006.

9. Gedye, N; Smith F. E, *Can J. Chem* . 66, 17, 1887.

10. Kidwai, S. Rastogi, *Bul and KoreanChen. Soc.* , 24, 11- 1575, 2003.

11. Lang, F *. org. synth.* , 4, 373-386, 1997.

12. Loupy, A. *Synthesis* 1998.

13. Kamal, A; Venka, P, *J. Chem, soc., Daton Trans* , 3381-339, 2002.

14. Zhang, Y; Zhou, Z, *Organic chemistry international* , 1, 194784-5, 2012

15. Zhao, P; You W, *Acta pharmacentica sinica* , 47(5): 580-7, 2012

16. Choudhury, S; Shankar, M, *RSC Adv* . 2, 4547-4592, 2012

17. Khosrou, Ali , *ISI journal of Bio Chemistry and molecular Biology* . 27/59, 176/290, 2013