Review Article

COMPARATIVE STUDY OF MICROWAVE AND CONVENTIONAL SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PYRIMIDINES: A REVIEW

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ABSTRACT

Pyrimidine derivatives play a vital role in many biological processes. Pyrimidine ring system is being present in nucleic acids, several vitamins, coenzymes, uric acid and some marine microorganisms (e.g. Sponge). The nitrogen heterocycles in general and pyrimidines in particular are found in several biologically active natural products and depict considerable therapeutic potential. Chalcone derivatives have been prepared by condensation of various substituted aryl aldehydes and acetophenone in alkaline ethanol, while pyrimidine-2-one derivatives have been prepared by the combination of chalcones and urea under conventional and ultrasonic conditions. The compound substituted ethyl-1,2,3,6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenyl-1-(4,6-diphenyl-1Himidazolyl-2-yl)pyrimidine-5-carboxylates have been synthesized by condensing substituted Benzil and enthyl-1-formyl-1,2,3,6-tetrahydro-4-methyl-6-phenyl-2-oxo/thioxo-pyrimidine-5-carboxylates in the presence of ammonium acetate were dissolved in glacial acetic. The quinolinylpyrimidine derivatives were prepared by the condensation of quinolinyl chalcones with urea (or thiourea) under basic conditions by using both conventional and microwave heating. A beneficial ultrasound effect was observed and high yields of the products were obtained. Characterization and structural elucidation of the products have been done on the basis of chemical, analytical and spectral analysis. The newly prepared pyrimidine derivatives were screened for antimicrobial activities.

Keywords: Pyrimidine derivatives, Chalcone derivatives, Quinolinylpyrimidine, Antimicrobial, Biginelli compounds, chemotherapeutic agents.

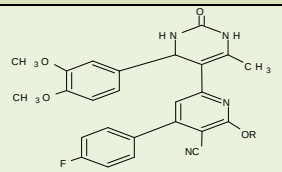
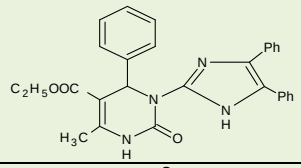
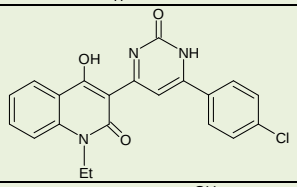
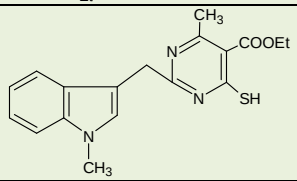
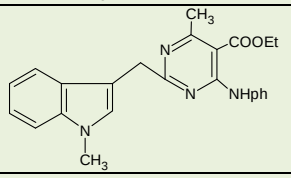
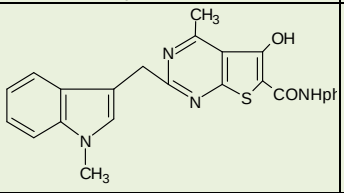
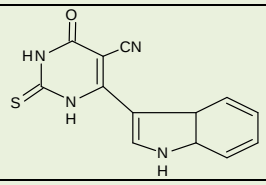
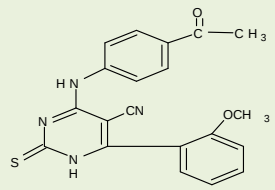
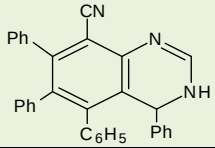
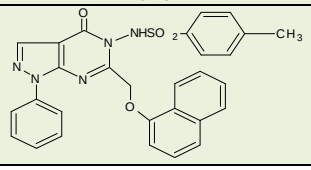
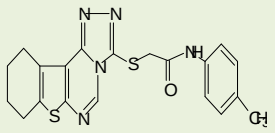
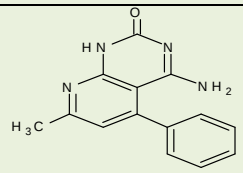
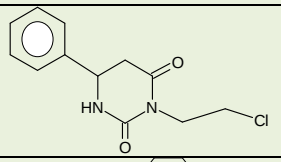
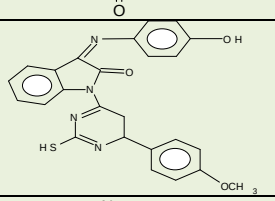
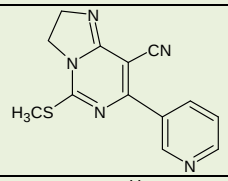
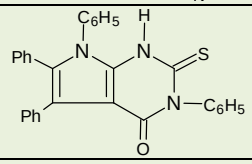
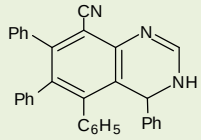
INTRODUCTION

Heterocyclic rings have played an important role in medicinal chemistry, serving as key templates central to the development of numerous important therapeutic agents[1]. Chalcone derivatives are important starting materials for the synthesis of different classes of heterocyclic compounds such as pyrazolines, thiophenes and pyrimidines, etc. most of these compounds are highly bioactive and are widely used in pharmaceutics[2].

Pyrimidine derivatives have found application in a wide range of medicinal chemistry because of their diverse biological activities, such as anti allergic[3], antitumor[3], antipyretic[3] anti-inflammatory[3], antiparasitic[4], anti fungal[5], antimalarial[5], antibacterial[5], antimycotic[5], anticancer[6], antimicrobial[1], anti HSV[7], anti-convulsion[7] and anti-viral[7] also these compounds are considered to be important for synthetic drugs (e.g. Barbituric acid derivatives)[8], chemotherapeutic agents (e.g. Sulfadiazine)[8] and agricultural chemicals. During a screening effort for antiviral agents, we found that multi functionalized tetrahydropyrimidines derivatives bearing bulky C-2 alkyl substituents depict cytostatic activity and inhibit proliferation of murine leukemia, murine mammary carcinoma, human T-lymphocyte and human cervix carcinoma cells[9], 3, 4-Dihydropyrimidin-2-(1H)-ones (DHPMs) and their appropriately functionalized derivatives have interesting pharmacological profiles[10]. These are potent antihypertensive agents, mitotic kinesin inhibitors, a1a-adrenergic receptor antagonists, or hepatitis B virus replication inhibitors and depict a variety of other biological effects. Although a large number of DHPM derivatives have been prepared in a single-pot Biginelli multi component reaction[10] (MCR) and its variants[10], very useful and convincing structural variability of these interesting heterocycles have been achieved through chemical functionalization of all the six positions around the DHPM core[10]. The 4-aryl-1, 2, 3, 4-tetrahydropyrimidines has been given the name Biginelli compounds. The main interest in Biginelli compounds, however, is due to the strong antihypertensive activity exhibited by certain derivatives[8].

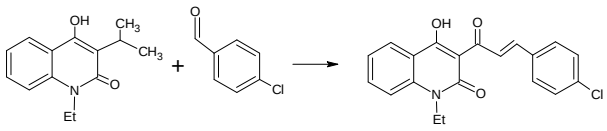
Pyrimidines and fused pyrimidines, being an integral part of DNA and RNA, play an essential role in several biological processes and have considerable pharmacological importance, particularly, the pyrimidine ring can be found in nucleoside, antibiotics, Cardiovascular as well as agrochemical and veterinarian products. Pyrimidines present an interesting group of compounds many of which possess wide-spread pharmacological properties such as antidepressant, anticon-vulsant activities. Heterocyclic compounds have received considerable attention owing to their variety of biological activities, especially as inhibitors of PDE5 extracted from human platelets, HIV-1 reverse transcriptase, human EPK2. Also heterocyclic nitrogen compounds are indispensable structural units for medicinal chemists and used as antibiotics, anthelmintics. anti-depressant and anti-inflammatory[11].

Table 1: Pharmacological activities of Pyrimidines

Ref. no.	Structure	Pharmacological Activity
8		Antimicrobial activity
12		Antifungal and Antibacterial activity
2		Antibacterial activity
11		Analgesic activity
11		Anti-inflammatory activity
11		Anti-parkinsonism activity
13		Antibacterial and Antibacterial activity
14		Antimicrobial activity
15		Antibacterial and antifungal activity
16		Antimicrobial activity
17		Antimicrobial activity
18		Anti-inflammatory activity
19		Antibacterial and Antifungal activity
20		Antioxidant and Antibacterial activity
21		Antileishmanial activity
22		Antibacterial and Antifungal activity
23		Antibacterial and Antifungal activity

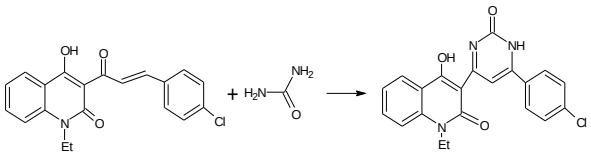
PREPARATION METHODS

The chalcones were prepared by the Claisen Schmidt condensation using both conventional as well as ultrasonic assisted methods (Scheme I) [3].



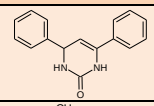
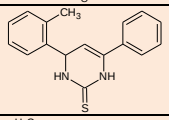
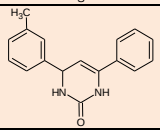
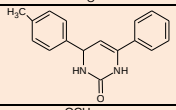
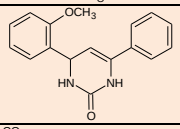
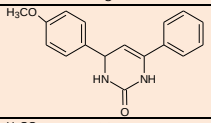
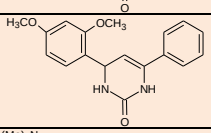
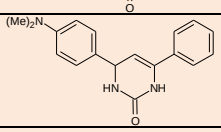
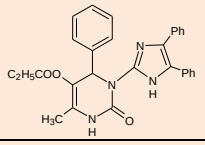
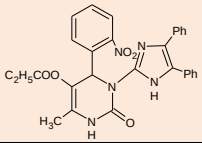
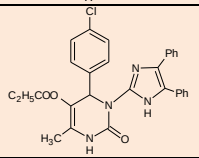
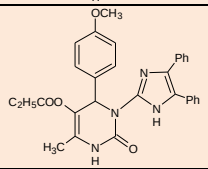
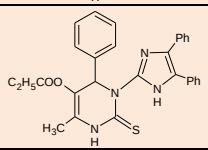
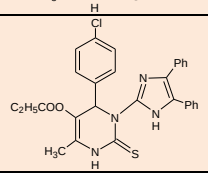
Scheme I

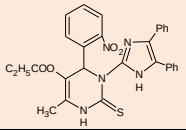
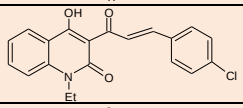
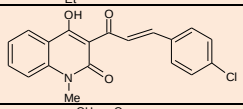
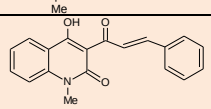
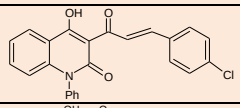
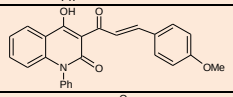
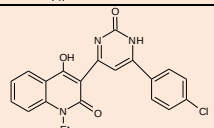
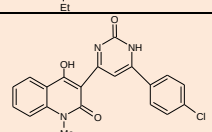
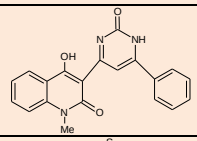
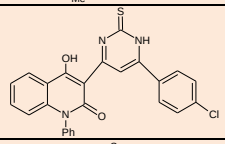
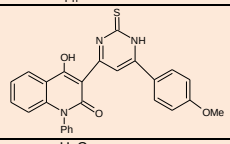
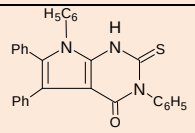
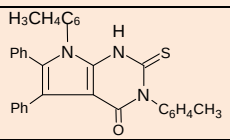
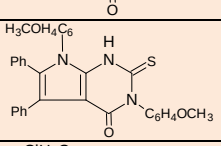
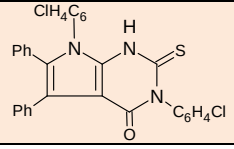
A series of quinolinylpyrimidine derivatives have been prepared by using both conventional and microwave induced heating. The compounds were prepared by the condensation of quinolinyl chalcones with urea (or thiourea) in basic media under prolonged refluxing conditions or under microwave irradiations (Scheme II)[3].

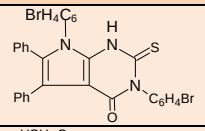
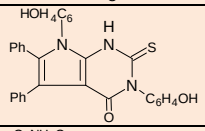
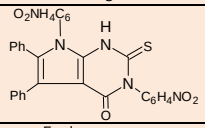
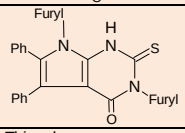
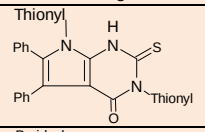
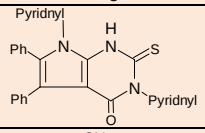
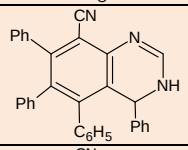
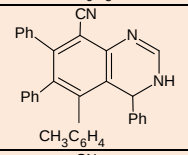
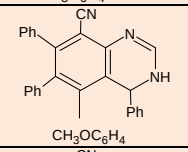
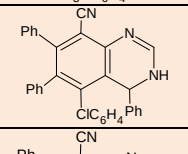
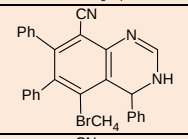
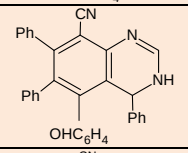
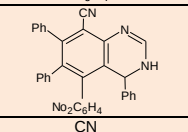
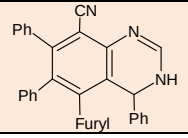


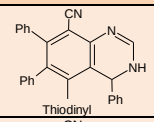
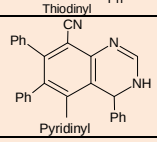
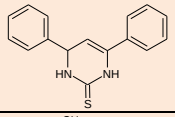
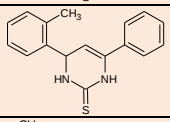
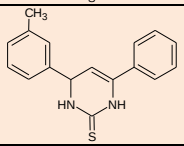
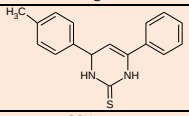
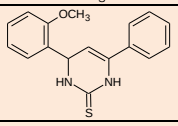
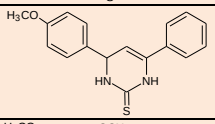
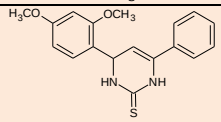
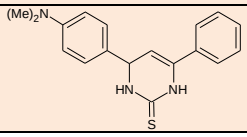
Scheme II

Table 2: Comparison between microwave-assisted and conventional method of synthesis in terms of yield and time

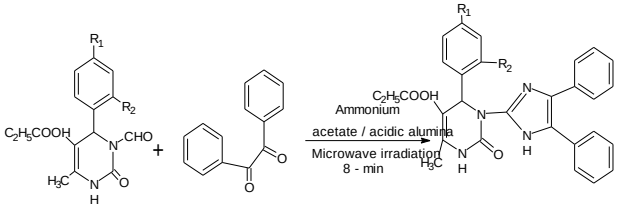
Structure	Microwave Irradiation		Conventional Heating		Ref. No.
	Time (min)	Yield (%)	Time (hr.)	Yield (%)	
	24	82	6.5	65	3
	22	78	6	55	3
	21	80	6	54	3
	24	76	6	58	3
	28	78	5.5	60	3
	25	75	5.5	61	3
	22	73	5	65	3
	29	75	5.5	55	3
	8	79	12	64	3
	8	78	12	64	3
	8	69	12	62	3
	8	72	12	65	3
	8	78	12	65	3
	8	75	12	63	3

Structure	Microwave Irradiation		Conventional Heating		Ref. No.
	Time (min)	Yield (%)	Time (hr.)	Yield (%)	
	8	67	12	60	3
	85	65	6	27	3
	80	72	6	26	3
	85	74	6	38	3
	90	75	6	36	3
	85	65	6	28	3
	4.5	85	10	40	3
	4.5	82	10	39	3
	4.0	80	8	38	3
	4.0	82	8	38	3
	4.5	85	8	45	3
	9	80	12	62	23
	8.5	87	11	65	23
	8.0	91	11	68	23
	8.0	90	11.5	65	23

Structure	Microwave Irradiation		Conventional Heating		Ref. No.
	Time (min)	Yield (%)	Time (hr.)	Yield (%)	
	8.5	85	12	67	23
	9.0	82	12	60	23
	8.0	87	12	70	23
	9	86	11	67	23
	8.5	92	11.5	72	23
	9.0	80	12	60	23
	5	75	7	53	24
	4.5	78	6.5	54	24
	4	81	6.5	57	24
	4	87	6	65	24
	4.5	82	6.5	60	24
	5	73	7	52	24
	4.5	85	6.5	63	24
	4	79	6	56	24

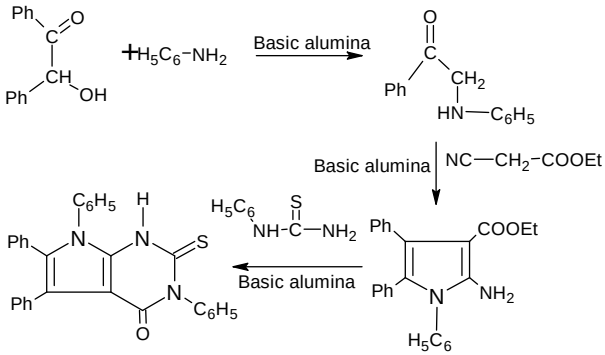
Structure	Microwave Irradiation		Conventional Heating		Ref. No.
	Time (min)	Yield (%)	Time (hr.)	Yield (%)	
 Thiodinyl	4	81	6	58	24
 Pyridinyl	4.5	76	7	56	24
	20	82	5.5	65	24
	22	78	6	55	24
	22	80	6	54	24
	24	76	5.5	58	24
	26	78	6	60	24
	24	75	6	61	24
	25	73	6.5	65	24
	29	75	5.5	55	24

Benzil (2.5m mole; 5.25g), ethyl-1-formyl-1, 2, 3, 6-tetrahydro-4-methy-6-phenyl-2-thioxopyrimidine-5-carboxylate and ammonium acetate were dissolved in glacial acetic acid. The reaction mixture was subjected to microwave irradiation to procedure substituted ethyl 1, 2, 3, 6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenyl-1- (4, 5-diphenyl-1-H-imidazol-2-yl) pyrimidine-5-carboxylate (scheme III)[3].



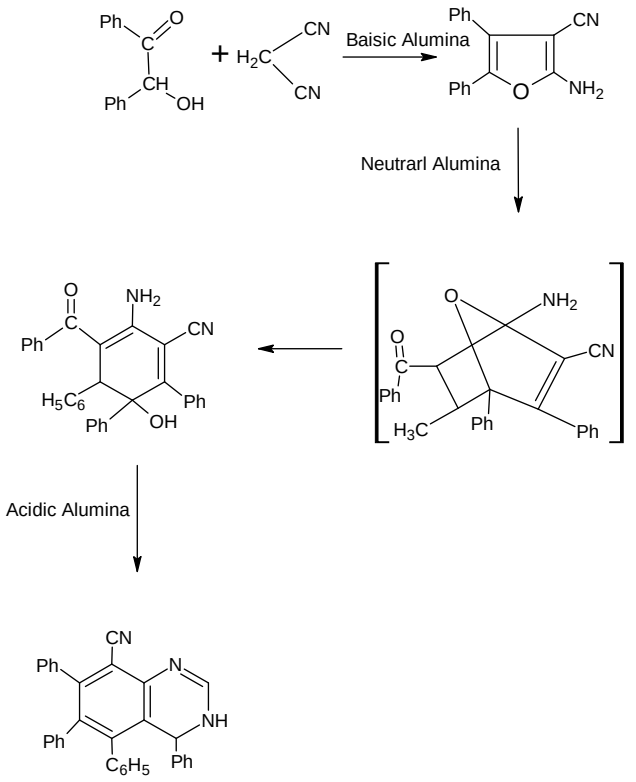
Scheme III

The procedures for the Synthesis of 2-amino-3-ethylcarboxylate-4, 5-diphenylpyrroles were followed as: 2-amino-2-phenylacetophenones and cyano-ethyl acetate were dissolved in 10 ml of EtOH and the resulting solution was adsorbed over 20g basic alumina or montmorillonite. The beaker containing reaction mixture was then kept in microwave oven in an alumina bath and irradiated for 6-7 minutes intermittently. Furthermore, synthesis of 2-thioxo-3, 7-disubstituted-5, 6-diphenyl-pyrrolo [2, 3-d] pyrimidin-4(1H)-ones was carried out using conventional and microwave methods (Scheme IV)[23].



Scheme IV

To produce 3, 4-dihydrobenzo 2, 3-d pyrimidines in dry media under microwave irradiations by the cyclization of 1, 3-cyclohexadiene derivatives with formamide under acidic conditions (Scheme V)[24].



Scheme V

CONCLUSION

Pyrimidine and pyrimidine derivatives have proved for many years to have significant therapeutic potential. They come from a wide variety of natural sources and new pyrimidine derivatives are being discovered or synthesized on a regular basis. It is evident from the research described that pyrimidine and pyrimidine derivatives are a plentiful source of potential drugs candidate in relation to its safety and efficacy. New pyrimidine derivatives have been synthesized using conventional and microwave heating methodology and characterized. The advantages in the use of microwave methodology are shorter reaction times, higher yields and simplified work up procedures for the point of purification of the prepared compound. The combination of solvent free reaction condition and microwave irradiation leads to significantly reduced reaction times, enhanced conversions and sometime higher selectivity with several advantages for the eco-friendly approach, termed as “Green Chemistry”.

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