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Grewia asiatica (Phalsa) fruit juice catalysed synthesis of some biologically active dihydroprimidinone derivatives under microwave irradiation.

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Abstract

The dihydropyrimidinone derivatives were synthesized by Biginelli reaction employing equimolar amount of acetoacetic ester, urea and substituted aromatic aldehyde using grewia asiatica fruit juice as biocatalyst under microwave irradiation. The synthesized dihydropyrimidinones were evaluated for their antibacterial activity against S. aureus and E.coli, by cup-plate agar diffusion method.

Key words:- Grewia asiatica juice, dihydropyrimidinones, Biginelli reaction, microwave, S. aureus, E.Coli.

Introduction

Dihydropyrimidinones are N- Containing heterocyclic compounds. It contains pyrimidine nucleus which is building blocks of DNA and RNA. DNA contains pyrimidine bases like thymine and cytosine and RNA contains uracil and cytosine as the pyrimidine bases. Thus it shows that dihydropyrimidinones are very much important heterocyclic compounds in various field of pharmacology and medicinal chemistry.[1]

Dihydropyrimidin-2 (1H) – one derivatives act as antihypertensive and calcium channel blocker agent.[2] These derivatives exhibit antitumor[3] antibacterial[4], antiviral[5], anti-Alzheimer[6], analgesic[7], antioxidant[8] and anti-inflammatory[9] activities. Certain pyrimidione derivatives are potent inhibitor of cancer cell proliferation[10]. Previous workers employed various toxic catalysis such as BF_3, $FeCl_3$, $InCL_3$, $LaCl_3$, $LiClO_4$, $Mn(OAc)_3$, CAN etc and toxic solvent lie EtOH, CH_3CN, THF, etc for the synthesis of dihydropyrimidinones. To minimize toxicity of catalysts and solvents various ecofriendly methodologies were developed. The use of ionic solvents[11], aqueous medium[12], ultrasonication[13], microwave irradiation[14], grinding[15] and stirring at room temperature are very much ecofriendly benign techniques in the synthesis of dihydropyrimidinones.

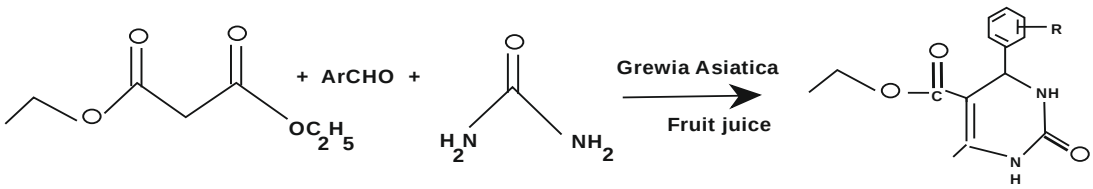
At present synthesis of dihydropyrimidinone by Biginelli reaction has been successfully developed in fruit juice medium under microwave irradiation, ultrasonication which are potential tool for green synthesis resulting higher yield of product in shorter time consuming lesser energy as compared to conventional methods.

G.M. Nazeruddin[13] et al. reported the U.S., assisted synthesis of dihydropyrimidinones using tamarind juice as biocatalyst. Tanay pramanic[14] et, al reported synthesis of dihydropyrimidinones using orange juice, lime juice and amla juice as biocatalysts under microwave irradiation.

Grape juice[15], crushed garlic clove[16], pine apple juice[17], Karvand juice[18], lemon juice[19] catalysed syntheses of dihydropyrimidinones have been reported by different workers. We have used grewia asiatica (Phalsa) fruit juice as biocatalyst to synthesize dihydropyrimidinone derivatives under microwave irradiation with the hope of achieving higher yield of products in shorter reaction time.

Present work

We have synthesized dihydropyrimidinone derivatives by Biginelli reaction employing equimolar amounts of ethylacetoacetate, urea and different aromatic aldehydes using biodegradable catalyst grewia asiatica fruit juice under microwave irradiation.



This fruit is easily available in the local markets in the month of may and june. Grewia asiatica (Phalsa) fruit juice contains minerals, carbohydrates, fibers, ascorbic acid, amino acids[18,20] like aspartic acid, glycene, threnone, tyrosine and glutamic acid[21]. Anthrocynine, flavonoid, tannin etc are also present in phalsa fruit. The colour of fresh juice is bright red (pH=3.99) but after 14 days storage juice turns brown in colour and pH[22] changes to 3.54. The 14 days old juice (pH=3.54) was used as biocatalyst in the synthesis.

Experimental

Chemicals and Methods

All the chemicals were managed from commercial sources and were used without further purification. The melting points of synthesized compounds, were determined in open capillary and are uncorrected. The IR spectra was recorded with a Perkin- Elmer FT-IR-100. Spectrophotometer in KBr discs and peaks are expressed in cm^{-1}. ^1H NMR spectra was recorded BRUKER-400 MHz. Spectrometer in DMSO-d_6 using TMS as standard and chemical shifts are given in δ units.

Preparation of Grewia asiatica (Phalsa) fruit juice

Matured phalsa fruits were purchased from Varanasi fruit market, 250 gm of phasla fruit was well washed with running tap water. It was grinded in mixer machine. The pulp was squeezed with muslin cloth. The liquid obtained was filtered with whatman-I filter paper to get bright red colour juice (pH= 3.9). The juice was stored for 14 days at room temperature. The colour of juice[22] changes to brown and pH changes to 3.54. The 14 days old juice was used as catalyst in the synthesis.

We have concluded that after optimization of catalyst concentration (ml) for the reaction (R=p-OCH_3, R^1= OEt) the use of 8ml juice result maximum yield (86 %) of product after 12 minutes of microwave irradiation.

General method for the synthesis

The aromatic aldehyde (30 m mole), ethylacetoacetate (30 m mole), urea (30 m mole) and phalsa juice (8ml) were taken in a 100ml conical flask. It was kept inside domestic microwave at 180 W and irradiated. The reaction mixture was stirred at room temperature after every 4 minutes of irradiation. Reaction progress was checked by TLC. After completion of reaction (checked by TLC), the reaction mixture was cooled to room temperature. The solid product obtained after cooling, was filtered and recrystallized from ethanol to get pure DHPM.

The physical data of the products are listed in Table-1 and spectral studies data are listed in Table-2.

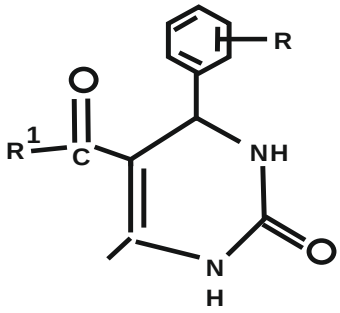
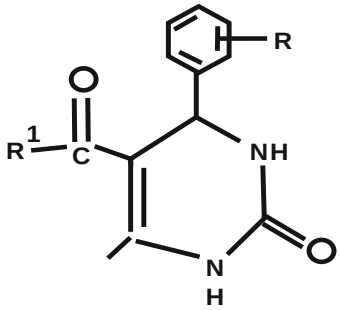


Table-1 The physical data of dihydropyrimidinone derivatives

S. No.	R	R^1	Yield %	Time in min	M.P. (°c) Observed	M.P. (°c) Repeated
1	4-OMe	OEt	86	12	200	199-201[23]
2	2-OH	OEt	82	11	201	201-202[24]
3	4-OH	OEt	87	12	224	226-228[24]
4	H	OEt	88	14	211	209-210[25]

5	4-Cl	OEt	90	12	212	212-214[26]
6	3-NO_2	OEt	91	11	228	230[27]
7	4-CH_3	OEt	76	14	214	215-216[28]
8	2-NO_2	OEt	90	11	207	208[24]
9	4-OCH_3	OMe	87	12	190	190-193[29]
10	4-NO_2	OMe	91	10	232	233-236[29]

Table:-2 Spectral studies of dihydropyrimidinone derivatives



S. NO.	Compound Name	IR cm^{-1}	NMR (DMSO-D6) δ (ppm)
1	Ethyl-4-(4-Me-thoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3242, 3223, 2929, 2833, 1706, 1652, 1516, 1458, 1280, 1185, 790	1.14 (t, 3H, -OCH_2 -CH_3), 2.25 (S, 3H, -CH_3), 3.74 (S, 3H, Ar-OCH_3) 4.02 (q 2H, -OCH_2 -CH_3), 5.15 (S, 1H, CH), 6.8-7.2 (m, 4H, Ar-H), 7.62 (S, 1H, NH), 9.10 (S, 1H, NH)
2	Ethyl-4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3350, 3244, 3113, 3040, 1720, 1645, 1487, 1460, 1230, 1090, 762	1.05 (t, 3H, -OCH_2 –CH_3), 2.23 (S, 3H, -CH_3), 4.03 (q, 2H, -OCH_2 CH_3), 5.21 (S, 1H, CH), 7.11-7.31(m,

			4H, ArH), 7.60 (S, 1H, -NH), 9.12 (S, 1H, NH), 9.10 (S, 1H, -OH)
3	Ethyl-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3348, 3244, 3110, 3040, 1360, 1720, 1640, 1445, 1460, 1240, 1085, 762	1.14 (t, 3H, -OCH_2, CH_3), 2,21 (S, 3H, CH_3), 4.02 (q, 2H, -OCH_2-CH_3), 5.20 (S, 1H, CH), 7.15-7.31 (m, 4H, ArH), 7.62 (S, 1H,NH), 9.22 (S, 1H, NH), 9.18 (S, 1H, -OH)
4	Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3242, 3113, 1724, 2958, 1625, 1649, 1487, 1321, 1090, 785	1.17 (t, 3H, -OCH_2, CH_3), 2,27 (S, 3H, CH_3), 4.02 (q, 2H, -OCH_2-CH_3), 5.20 (S, 1H, CH), 7.18-7.31 (m, 5H,ArH),7.28 (S, 1H,NH), 9.28 (S, 1H, NH)
5	Ethyl-4-(4-chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3242, 3113, 2929, 1724, 1650, 1575 1487, 1325, 1280, 1035, 861	1.14 (t, 3H, -OCH_2 CH_3), 2,26 (S, 3H, CH_3), 4.02 (q, 2H, -OCH_2 CH_3), 5.18 (S, 1H, CH), 7.25-7.50 (m, 4H, ArH), 7.65 (S, 1H, NH), 9.10 (S, 1H, NH)
6	Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxol-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3350, 3244, 3117, 2983, 1720,1642, 15391489, 1375, 1090, 770	1.14 (t, 3H, -OCH_2CH_3), 2,27 (S, 3H, CH_3), 4.03 (q, 2H, -OCH_2 CH_3), 5.18 (S, 1H, CH), 7.48-8.17 (m, 4H, ArH), 7.64 (S, 1H,NH), 9.18 (S, 1H, NH)
7	Ethyl-4-(4-Methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3325, 3152, 1691, 1655, 1562, 1232 1058, 783,	1.12 (t, 3H, -OCH_2 CH_3), 2,24 (S, 3H, CH_3), 4.02 (q, 2H, -OCH_2 CH_3), 5.20 (S, 1H, CH), 7.24 (m, 4H, ArH), 7.75 (S, 1H, NH), 9.08 (S, 1H, NH)

8	Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxol-1,2,3,4-tetrahydrophyrimidine-5-carboxylate	3230, 3109, 2977, 1701, 1641, 1591 1520, 1230, 1060, 770	1.09 (t, 3H, -OCH_2 CH_3), 2,25 (S, 3H, CH_3), 3.98 (q, 2H, -OCH_2-CH_3), 5.27 (S, 1H, CH), 7.50-8.16 (m, 4H, ArH), 7.68 (S, 1H, NH), 9.27 (S, 1H, NH)
9	5-(methoxy-corbonyl)-4-(4-methoxy phenyl)-6-methyl-3,4 dihhydrophyrimidine-2 (1H)-one	3460, 3242, 3150, 1721, 1655, 1637, 1230, 1070	2.24 (S, 3H, CH_3), 3,92 (S, 3H, Ar-OCH_3), 3.65 (S, 3H, -$COOCH_3$), 5.22 (S, 1H, CH), 6.58-7.70 (m, 4H, ArH), 7.62 (S, 1H, NH), 9.15 (S, 1H, NH)
10	5-(methoxy-corbonyl)-4-(4-nitro phenyl)-6-methyl-3,4 dihydrophyrimidine-2 (1H)-one	3470, 3232, 3148, 1724, 1631, 1637, 1540, 1485	2.21 (S, 3H, CH_3), 3,70 (S, 3H, -$COOCH_3$), 5.25 (S, 1H, CH), 7.45-8.16 (m, 4H, ArH), 7.44 (S, 1H, NH), 9.05 (S, 1H, NH)

Evaluation of antibacterial activity

The synthesized compounds were evaluated for antibacterial activity by cup-plate agar diffusion method[30]**,** against S. aureus (Gram (+) bacteria) and E.coli (Gram (-) bacteria). The standard antibiotic levofloxacin was also tested under similar condition, with a view to compare the results. The antibacterial activity of each compound was evaluated at 100µg/ml and 10µg/ml concentration. The zone of inhibitions of bacterial growth was measured in mm.

Table-3 Number of replicaties in each case=3

Compound	**Zone of inhibition (mm)**	
	S. Aureus (Gram (+ve))	**E.coli (Gram (-ve))**
	Concentration used	**Concentration used**

	100µg/ml	10µg/ml	100µg/ml	10µg/ml
1	18	12	16	10
2	16	10	15	12
3	15	9	14	8
4	12	8	11	8
5	21	12	20	11
6	22	13	21	12
7	11	9	10	8
8	20	12	19	10
9	15	20	14	9
10	18	14	17	12
Levofloxin	34	25	24	20

Result and Discussion

The synthesis of dihydropyrimidione derivatives has been carried out via Biginelli reaction using ethylacetoacetate, substituted aromatic aldehydes and urea under microwave irradiation. The results have been listed in Table. The reaction is ecofriendly completed in shorter time using biodegradable Grewia asiatica fruit juice as natural catalyst under microwave irradiation which is a green efficient source of energy and thus higher yield of products is obtained. We can see that the aryl ring containing electron attractive substituent becomes deactivated and carbonyl carbon of aryl aldehydes is easily attacked by nucleophile making the reaction easy and producing higher yield of product in

lesser time. The screening results of antibacterial activity, show that all the synthesized compounds are more active toward S. Aureus (Gram positive bacteria) as compared to E. Coli (Gram negative bacteria). Further compound 1,5,6,8,10 are more active at both the concentration against both bacteria as compared to other compounds. This shows that presence of electron acttracting and polar groups at aromatic nucleus enhance the activity. Further it is clear that the antibacterial activity decreases on dilution.

Conclusion

We conclude that this eco-friendly and simple process for the synthesis of dihydroprimidinones using Grewia asiatica (Phalsa) fruit juice as biocatalyst under microwave irradiation is an advantageous method. This developed method is environment benign and follow all the principles of green chemistry, producing good yield of product in shorter reaction time.

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