wjpmr, 2018,4(4), 174 -180

SJIF Impact Factor: 4.639

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVOLUTION OF 4,6-DIPHENYL-1,6-DIHYDROPYRIMIDIN-2-OL DERIVATIVES

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Article Received on 07/02/2018 **Article Revised on 28/02/2018** **Article Accepted on 21/03/2018**

ABSTRACT

The pyrimidine derivatives were synthesized from chalcone as intermediate compound .the chalcones were reacted with urea in presence of glacilal cetic acid and sodim acetate to form cyclic compound pyrimidine-2-ol derivatives and the structures were confirmed by spectral evidence. The compounds were tested for anti microbial activity and antioxidant activity using diffusion method by measuring the Zone of the inhibition in mm and DPPH measuring by measuring the percentage of inhibition. In these test compounds, PR-06 shows maximum anti bacterial activity than compare with other compounds, with Bacillus substilis zone of inhibition 24,26,30 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, Staphylococcus aureus zone of inhibition 25,28,30 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, with Pseudomonas vulgaris zone of inhibition 26,27,34 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, with Escherichia coli the zone of inhibition 24,26,34 mm at 50 µg/ml,100 µg/ml, 150 µg/ml compare with the standard streptomycin. In case of anti oxidant activity the compound PR-02 shows inhibition at 54.63 ± 0.18, 101.31±0.33, 145.25±0.32, 260.41±0.54, 380.24±0.45 at concentration of 100, 200, 300,400, 500 µg/ml respectively compare with the standard ascorbic acid.

KEYWORDS: Pyrimidine-2- ol derivatives, urea, anti microbial, anti oxidant, DPPH reagent.

INTRODUCTION

Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics.[1,2] Hence, they have attracted considerable attention in the design of biologically active molecules[3,4] and advanced organic chemistry.[5,6] Also in the family of heterocyclic compounds nitrogen containing Heterocyclic compounds are an important in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes.[7] However, the current review intends to focus on the significance of Pyrimidines class of antimicrobial agents along with clinical andin vitro applications of pyrimidine derivatives to facilitate the development of more potent as well as effective antimicrobial agents.

Pyrimidines[10] are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and non natural products, many of which exhibit useful biological activities and clinical applications.[11,12] Substituted purines and pyrimidines occur very widely in living organisms and were some of the first compounds studied by the organic chemists.[13] Pyrimidines are biologically very important Heterocycles and represent by far the most important of the di azine family with uracil[14] and thymine[15] being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine.[16] In addition to this, pyrimidines skeleton is also present in many natural products such as vitamin B1 (thiamine) and many synthetic compounds, such as barbituric acid[17] and Veranal[18] which are used as hypnotics.[19] The Pyrimidines represent one of the most active classes of compounds possessing wide spectrum of biological activities like significantin vitroactivity against unrelated DNA and RNA, viruses including polioherpes viruses, diuretic, antitumour, anti-HIV, and cardiovascular.[20] The literature survey indicated that a wide range of pharmacological activities are exhibited by the compounds encompassing pyrimidines nucleus. In addition to this, various analogs of pyrimidines have been found to posses antibacterial,[21] antifungal,[22] antileishmanial,[23] anti-inflammatory,[24] analgesic,[25] antihypertensive,[26] antipyretic,[27] antiviral,[28] antidiabetic,[29] antiallerggic,[30] anticonvulsant,[31] antioxidant,[32] antihistaminic,[33] herbicidal,[34] and anticancer activities[35] and many of Pyrimidines derivatives are reported to possess potential central

nervous system (CNS) depressant properties[36] and also act as calcium channel blockers.[36]

EXPERIMENTAL WORK

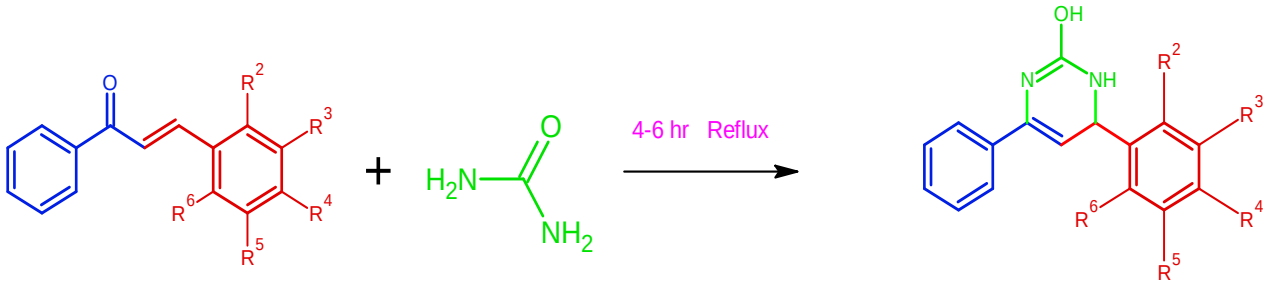
MATERIALS AND METHODS

(2*E*)-1,3-diphenylprop-2-en-1-one,Urea, sodium acetate, glacial acetic acid conc. HCl, DMSO, DPPH reagent .all the reagents were purchased analytical grade. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General method of preparation[4]

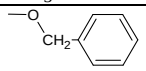
A mixture of (2*E*)-1-phenyl]-3-phenylprop-2-en-1-one (0.001moles) and urea -(0.001moles) were dissolved in sodium acetate in glacial acetic acid (20ml) reflux it for 6hr.afetr that add the solution to the cooling water . The mixture was kept for 24hours and it was acidified with 1:1 HCl and water, then it was filtered through vacuum by washing with water.

Chemical reaction



Chalcone Urea Pyrimidine

Table 1: List of aldehydes.

Chalcone	Radicals				
	R_2	R_3	R_4	R_5	R_6
PR-01	-O-CH_3	-H	-O-CH_3	-H	-O-CH_3
PR-02	-H	-O-CH_3	-O-CH_3	-O-CH_3	-H
PR-03	-H	-H	-S-CH_3	-H	-H
PR-04	-H	-H	-CF_3	-H	-H
PR-05	-H	-H		-H	-H
PR-06	-CF_3	-H	-H	-H	-H

Biological evolution of compounds

Based on the literature, chalcones were reported to possess antimicrobial activity, anti oxidant, anti inflammatory, analgesic, anti cancerous, etc. Therefore the present work performs the anti microbial, anti oxidant activities.

Antibacterial activity[38-39]

The antibacterial activity was tested by determining inhibitory concentration by diffusion disc technique. The bacterial strains were obtained from National Chemical Laboratories (NCL), Pune and Microbial Type Culture Collection (MTCC), Chandigarh. The strains used for the present study were Staphylococcus aureus (MTCC 737) Bacillus subtilis (MTCC 441), Escherichia coli (MTCC 1687), P.vulgaris MTCC 1771.

Procedure

The antimicrobial activity of the compounds was assessed by disc diffusion method Nutrient agar medium was prepared and sterilized by an autoclave. In an aseptic room, they were poured into a petridishes to a uniform depth of 4 mm and then allowed to solidify at room temperature. After solidification, the test organisms, Staphylococcus aureus, Bacillus subtilis, Escherichia coli and P. vulgaris were spread over the media with the help of a sterile swab socked in bacterium and is used for antibacterial study. The synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) to produce a concentration of 500 µg/disc, 1 mg/disc and used for the study. Streptomycin 5 µg/disc was used as the standard. Then the sterile filter paper discs (6mm) having a capacity to hold 10 µl of solution were immersed in definite concentration of compounds and placed over the solidified agar in such a way that there is no overlapping of the zone of inhibition. Plates were kept at room temperature for half an hour for the diffusion of the sample into the agar media. The organism inoculated petridishes were incubated at 37°C for 24 hours. After the incubation period is over, the zone of inhibition

produced by the samples and standard were measured. All tests were performed in triplicate.

Anti oxidant activity evolution by DPPH radical scavenging method[40-43]

DPPH is a stable free radical that can accept anelectron or hydrogen radical to become a stable diamagnetic molecule. Due to its oddelectron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron donating molecules (reducing agents or antioxidants). When electrons become paired off, bleaching of the DPPH solution is the result. This results in the formation of the colourless 2,2'-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in absorbance at 517 nm.

Procedure

Equal volumes of 100 µM 2,2'-diphenyl-1-picrylhydrazyl (DPPH) in methanol was added to different concentrations of test compounds (0 – 200 µM/ml) in methanol, mixed well and kept in dark for 20 min. The absorbance at 517 nm was measured using the spectrophotometer UV-1650, Shimadzu.[6] Plotting the percentage DPPH• scavenging against concentration gave the standard curve and the percentage scavenging was calculated from the following equation:

DPPH scavenging effect (%) or Percent inhibition =

$$Ao-A1/Ao\times100$$

Where A0 was the Absorbance of control

A1 was the Absorbance in presence of test or standard sample.

Table 2: Physical data of synthesised compounds.

Compound Code	Molecular Formula	Mol. Wt	M.P (^{O}C)	% Yield
PR 01	$C_{22}H_{22}N_4O_4$	406.4	186-188	85
PR 02	$C_{22}H_{22}N_4O_4$	406.4	184-185	84
PR 03	$C_{20}H_{18}N_4OS$	362.4	178-179	81
PR 04	$C_{20}H_{15}F_3N_4O$	384.3	175-176	79
PR 05	$C_{26}H_{22}N_4O_2$	422.4	172-173	78
PR 06	$C_{20}H_{15}F_3N_4O$	384.3	165-167	75

Table 3: Elemental Compositions.

Compound		C	H	N	O	S	Cl	F
PR 01	%Calculated	65.01	5.46	13.78	15.75	-	-	-
	%Found	65.33	5.50	13.70	15.72	-	-	-
PR 02	%Calculated	65.01	5.46	13.78	15.75	-	-	-
	%Found	65.20	5.48	13.70	15.73	-	-	
PR 03	%Calculated	66.28	5.01	15.46	4.41	8.85	-	-
	%Found	66.26	5.30	15.48	4.50	8.87	-	-
PR 04	%Calculated	62.50	3.93	14.58	4.16	-	-	14.83
	%Found	62.54	3.90	14.60	4.14	-	-	14.84
PR 05	%Calculated	73.92	5.25	13.26	7.57	-	-	-
	%Found	73.90	5.27	13.28	7.56	-	-	-
PR 06	%Calculated	62.50	3.93	14.58	4.16	-	-	14.83
	%Found	62.51	3.91	14.60	4.19	-	-	14.85

Table 4: Spectral data of compounds.

Compound	IR, NMR data
PR-01	C=O,str. – 1660.76cm^{-1} ;C=C, str. – 1602.33cm^{-1}, N-H stretching :3365.01 cm^{-1}, C-H stretching: 3105 cm^{-1},C-H stretching:3048.5 cm^{-1}, C-H stretching: 2936.16 cm^{-1}, C-C stretching:1583.83 cm^{-1},C-N stretching: 1461.77cm^{-1} C-N stretching: 1371.05 cm^{-1}, C-N stretching:1318.09 cm^{-1} :(H^{1} NMR(CHCl3):7.05 (1H, s, C-2 of imidazole), 7.58 (1H, d, C-4 of imidazole), 7.44-7.89 (6H, m, Ar-H), 7.59 (1H, d, α-H), 8.06 (1H, d, β-H), 3.83 (9H, s, 3-OCH_3)
PR-02	C=O,str. – 1661.12cm-1,C=C str. – 1588.75cm-1 C-O str. – 828.23cm-1; N-H stretching : 3364.71 cm^{-1}, C-H stretching:3364 cm^{-1} C-H stretching: 3119.04 cm^{-1}, C-H stretching: 2937.74 cm^{-1} C-C stretching: 2834.04 cm^{-1},C-N stretching: 1587.08 cm^{-1},C-N stretching: 1486.59 cm^{-1},C-N stretching: 1420.91 cm^{-1}:H^{1} NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.44-7.89 (6H, m, Ar-H), 7.59 (1H, d, α-H), 8.06 (1H, d, β-H), 3.83 (9H, s, 3-OCH_3)
PR-03	C=O: str. – 1657.87cm-1 C=C str. – 1600.46 cm-1 C-S str. – 1333.18 cm-1; N-H stretching :3404 cm^{-1}, C-H stretching: 3144.43 cm^{-1} C-H stretching :3051.37 cm^{-1}, C-H stretching:2926.41 cm^{-1}, C-C stretching:1588.82 cm^{-1},C-N stretching: 1491.32 cm^{-1},C-N stretching: 1491.32 cm^{-1},C-N stretching:1426.08 cm^{-1} H^{1} NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.44-7.89 (8H, m, Ar-H), 7.59 (1H, d, α-H), 8.06 (1H, d, β-H), -CH_3), 2.53 (3H, s, -CH_3)
PR-04	C=O,str. – 1661.12cm-1,C=C str. – 1588.75cm-1 C-O str. – 828.23cm-1; N-H stretching : 3379.04 cm^{-1}, C-H stretching:2971.04 cm^{-1} C-H stretching : 2922.0 cm^{-1}, C-H stretching: 2866.04 cm^{-1} C-C stretching: 1603.2 cm^{-1},C-N stretching: 1455.99 cm^{-1},C-N stretching: 1325.03 cm^{-1} : H^{1} NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.44-7.89 (8H, m, Ar-H), 7.59 (1H, d, α-H), 8.06 (1H, d, β-H)
PR-05	C=O: str. – 1657.87cm-1 C=C str. – 1600.46 cm-1 C-O str. – 1333.18 cm-1; N-H stretching : 3330.60 cm^{-1}, C-H stretching: 3115.98 cm^{-1} C-H stretching: 3034 cm^{-1}, C-H stretching: 2931.65 cm^{-1} C-C stretching: 1595.88 cm^{-1},C-N stretching: 1451.59 cm^{-1},C-N stretching: 1422.70 cm^{-1},C-N stretching: 1347.88 cm^{-1}, H^{1} NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.38-7.89 (13H, m, Ar-H), 7.59 (1H, d, α-H), 8.06 (1H, d, β-H), 3.83 (2H, s, -OCH_2-)
PR-06	C=O: str.- 1649.38cm-1 C=C str. – 1598.05cm-1 C-O str.- 1376.52cm-1; N-H stretching :3368.84 cm^{-1}, C-H stretching: 2971.98 cm^{-1} C-H stretching: 2834.04 cm^{-1}, C-H stretching: 11587.08 cm^{-1},C-C stretching: 1486.59 cm^{-1},C-N stretching: 1420.91 cm^{-1},C-N stretching: 1370.02 cm^{-1},C-N stretching:1326.02 cm^{-1}, H^{1} NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.31-7.89 (8H, m, Ar-H), 7.42 (1H, d, α-H), 8.33 (1H, d, β-H)

Anti bacterial evolution

Table 5: Anti microbial results.

	Concentration (µg/ml)	*B.subtilis*	*S.aureus*	*E.coli*	*P.vulgaris*
	Zone of inhibition (mm)				
PR-01	50	15	16	12	13
	100	18	17	16	17
	150	22	23	23	22
PR-02	50	18	17	16	15
	100	20	19	17	19
	150	24	25	25	24
PR-03	50	7	7	8	7
	100	9	10	13	11
	150	13	11	15	14
PR-04	50	23	23	21	22
	100	25	26	25	24
	150	28	29	33	31
PR-05	50	10	10	10	9
	100	14	14	15	14
	150	17	16	18	19
PR-06	50	24	25	24	26
	100	26	28	26	27
	150	30	30	34	34
Standard (streptomycin)	50	26	28	28	28
	100	28	30	32	34
	150	32	36	38	36
Control (DMSO)	50	-	-	-	-
	100	-	-	-	-
	150	-	-	-	-

Anti oxidant activity

Table 6: Anti oxidant results.

S. No.	Compound	Concentration (µM)	DPPH Screening (µM)
1	PR-01	100	60.63 ± 0.18
		200	121.31±0.33
		300	155.25±0.32
		400	270.41±0.54
		500	390.24±0.45
2	PR-02	100	54.63 ± 0.18
		200	101.31±0.33
		300	145.25±0.32
		400	260.41±0.54
		500	380.24±0.45
3	PR-03	100	70.63 ± 0.18
		200	141.31±0.33
		300	172.25±0.32
		400	220.41±0.54
		500	410.24±0.45
4	PR-04	100	84.63 ± 0.18
		200	164.31±0.33
		300	189.25±0.32
		400	310.41±0.54
		500	455.24±0.45
5	PR-05	100	65.63 ± 0.18
		200	131.31±0.33
		300	165.25±0.32
		400	270.41±0.54
		500	400.24±0.45
6	PR-06	100	91.63 ± 0.18
		200	179.31±0.33
		300	194.25±0.32
		400	356.41±0.54
		500	470.24±0.45
11	Ascorbic acid	100	48.63 ± 0.18
		200	98.31±0.33
		300	140.25±0.32
		400	210.41±0.54
		500	310.24±0.45

Each value is expressed as mean ± SD of three replicates, NA- No Activity.

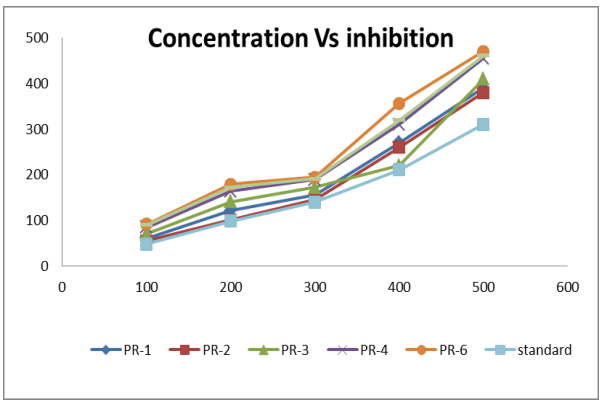


Fig: Concentration Vs Inhibition.

DISCUSSION

The above synthesized compounds anti microbial evolution were performed by using Diffusion method by the calculation of Zone of inhibition against the test organisms, the compounds shows that compound PR-06 shows maximum activity than compare with other compounds, with Bacillus substilis zone of inhibition 24,26,30 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, Staphylococcus aureus zone of inhibition 25,28,30 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, with Pseudomonas vulgaris zone of inhibition 26,27,34 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, with Escherichia coli the zone of inhibition 24,26,34 mm at 50 µg/ml,100 µg/ml, 150 µg/ml. the compound PY-04 shows activity against with Bacillus substilis zone of inhibition 23,25,28 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, Staphylococcus aureus zone of inhibition 23,26,29 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, with Pseudomonas vulgaris zone of inhibition 22,24,31 mm at 50 µg/ml,100 µg/ml, 150 µg/ml, with Escherichia coli the zone of inhibition 21,25,33 mm at 50 µg/ml,100 µg/ml, 150 µg/ml.

The above anti oxidant activity of synthesized compounds were evolved using DPPH assay method. In the compounds PR-02 shows inhibition at 54.63 ± 0.18, 101.31±0.33, 145.25±0.32, 260.41±0.54, 380.24±0.45 at concentration of 100, 200, 300,400, 500 µg/ml respectively than other compounds,and the latter compounds PR-01, PR-05,PR-03 shows activity .here compound PR-06 shows less activity than other compounds at concentration of 100, 200, 300,400, 500 µg/ml. the compound PR-02 potency was compare with the standard compounds ascorbic acid at similar concentration of test compounds.

CONCLUSION

The above results we concluding the compound PR-06 was showing the better anti microbial activity against both gram positive and gram negative the organism. The reason is due that compound contain more electron with drawing group than that of other compounds. In case of anti oxidant compound PR-02 shows better anti oxidant than other compounds due to less electron releasing tendency of the molecules. We concluding the compound PR-06 is may be best fit molecule against microbes, PR-02 having best anti-oxidant activity.

ACKNOWLEDGMENT

The author thankful to Principal, Management of DCRM College of Pharmacy, for provide all the facilities and supports for accomplishment and completion of this research work.

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