Research Article **CODEN: AJPAD7** **ISSN: 2321 - 0923**

Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry

Journal home page: www.ajpamc.com

https://doi.org/10.36673/AJPAMC.2022.v10.i01.A04

SYNTHESIS, CHARACTERIZATION, ANTI-MICROBIAL AND ANTIOXIDANT ACTIVITY OF NOVEL DIHYDROPYRIMIDINES

Chennu M.M. Prasada Rao*[1], Tanniru Rajeswari[1], Parmender, Kuldeep[1], Santosh Kumar Yadav[1]

[1*]Department of Pharmaceutical Chemistry, School of Pharmacy, Raffles University, Neemrana, Rajasthan, India.

ABSTRACT

The synthesis of dihydro pyrimidines were done using chalcone Derivatives with glacial acetic caid and sodium acetate to form the cyclic heterocyclic structure. The formed compounds were characterised by using IR, NMRspectroscopy. The anti-microbial activity was performed using diffusion method on the Gram positive and negative microorganisms. The antioxidant activity was performed using the DPPH method. The compound PR-06 shows better activity than other compounds due to presence of the electron withdrawing groups.

KEYWORDS

Pyrimidine derivatives, Urea, Antimicrobial activity, DPPH method and Antioxidant activity.

Author for Correspondence:

Chennu M.M, Prasada Rao,

Department of Pharmaceutical Chemistry,

School of Pharmacy, Raffles University,

Neemrana, Rajasthan, India.

Email: chennuprasad12@gmail.com

INTRODUCTION

Pyrimidines[1] 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[2,3]. Substituted purines and pyrimidines occur very widely in living organisms and were some of the first compounds studied by the organic chemists[4]. Pyrimidines are biologically very important Heterocycles and represent by far the most important of the di azine family with uracil[5-10] and thymine[10-19] being constituents of ribonucleic acid

(RNA) and deoxyribonucleic acid (DNA) and with cytosine[20]. In addition to this, various analogs of pyrimidines have been found to possesantibacterial[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[37].

EXPERIMENTAL WORK

MATERIAL 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[38]

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.

Biological evolution of compounds

The synthesised compounds evaluation was done for anti-microbial and antioxidant using the diffusion method and DPPH method respectively,

Antibacterial activity[39-45]

Antimicrobial activity was performed against the microorganisms using diffusion method. The testing was done using the concentration of 10, 20, 30µ g/ml using the DMSO as solvent. For testing both Gram +ve and -ve bacteria were used. The results were reported as Zone of inhibition as in mm.

Anti-oxidant activity evolution by DPPH radical scavenging method[45-50]

Equal volume of DPPH reagent with 100 microgram concentration in methanol was added to different concentration the synthesised compounds with concentration of 0-200 micro grams/ml kept dark place for 20 min. Take the reading at the absorbance of 517nM using UV spectrophotometer plot graph between the absorbance and concentration and calculate the percentage of scavenging by the following formula

DPPH scavenging effect (%) or Percent inhibition = Ao-A1/Ao×100

Spectral data of compounds

By performing the characterization on the all six compounds in the IR and NMR shoes the spectra on IR and NMR as follows

C= O str. at 1660.7Cm^{-1}, C=C.str. 1602.33Cm^{-1} and N-H str at 3366cm-1 and H^{1}NMR spectra shows c2 of imidazole at 7.05 and 1H d, c4 imidazole at 7.62. Based on the above spectral results conclude that the proper cyclisation and dihydropyrimidinone nucleus was formed.

DISCUSSION

The antimicrobial activity by diffusion method was found that compounds PR-06 shows better activity than other compounds due to presence of the electron with drawing groups make that compound more than the others.

The above anti oxidant activity of synthesized compounds was evolved using DPPH assay method. In the compounds PR-02 shows inhibition at 92.44 ± 0.18, 175.41±0.33, 194.44±0.32, 345.66±0.54, 477.84±0.45 at concentration of 5, 10, 20, 40, 60µg/ml respectively than other compounds, and the latter compounds PR-01, PR-05, PR-03 shows activity. Here compound PR-05 shows less activity than other compounds at concentration of 100, 200, 300, 400, 500µg/ml. The compound PR-06 potency was compare with the standard compounds ascorbic acid at similar concentration of test compounds.

Table No.1: List of aldehydes

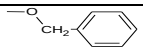
S.No	Chalcone	Radicals				
		R_2	R_3	R_4	R_5	R_6
1	PR-01	-O-H	-H	-O-H	-H	$-O-CH_3$
2	PR-02	-H	$-O-CH_3$	-O-H	-O-H	-H
3	PR-03	$--O-CH_3$	-H	$-S-CH_3$	-H	-H
4	PR-04	$-O-CH_3$	-H	$-CF_3$	-H	-H
5	PR-05	-H	-H		-H	-H
6	PR-06	$-CF_3$	-H	$-O-CH_3$	-H	-H

Table No.2: Physical data for the synthesised compounds

S.No	Compound	Molecular formula	Molecular Weight	M.P (^OC)	% Yield
1	PR 01	$C_{16}H_{14}N_2O_4$	298.2	175-177	86
2	PR 02	$C_{17}H_{16}N_2O_4$	312.3	185-186	87
3	PR 03	$C_{18}H_{18}N_2O_2S$	326.4	156-158	82
4	PR 04	$C_{18}H_{15}F_2N_2O_2$	348.3	178-179	75
5	PR 05	$C_{23}H_{20}N_2O_2$	35604	182-183	76
6	PR 06	$C_{18}H_{15}F_3N_2O_2$	348.3	176-177	74

Table No.3: Elemental compositions

S.No	Compound		C	H	N	O	S	Cl	F
1	PR 01	%Calculated	64.22	4.56	13.78	15.75	-	-	-
		%Found	63.33	4.57	13.70	15.72	-	-	-
2	PR 02	%Calculated	65.38	5.16	8.97	20.14	-	-	-
		%Found	65.10	5.10	8.77	19.97	-	-	
3	PR 03	%Calculated	66.23	5.56	8.58	9.80	9.82	-	-
		%Found	66.12	5.45	8.48	9.75		-	-
4	PR 04	%Calculated	62.07	4.34	8.04	9.19		-	16.36
		%Found	61.90	4.25	8.01	9.11	-	-	16.26
5	PR 05	%Calculated	77.51	5.66	7.86	8.98	-	-	-
		%Found	77.49	5.59	7.76	8.92	-	-	-
6	PR 06	%Calculated	62.50	3.93	14.58	4.16	-	-	14.83
		%Found	62.51	3.91	14.60	4.19	-	-	14.85

Anti bacterial evolution

Table No.4: Anti microbial results

S.No		Concentration (µg/ml)	*B.subtilis*	*S.aureus*	*E.coli*	*P.vulgaris*
		Zone of inhibition (mm)				
1	PR-01	10	15	16	12	13
		20	18	17	16	17
		30	22	23	23	22
2	PR-02	10	18	17	16	15
		20	20	19	17	19
		30	24	25	25	24
3	PR-03	10	7	7	8	7

		20	9	10	13	11
		30	13	11	15	14
4	PR-04	10	23	23	21	22
		20	25	26	25	24
		30	28	29	33	31
5	PR-05	10	10	10	10	9
		20	14	14	15	14
		30	17	16	18	19
6	PR-06	10	24	25	24	26
		20	26	28	26	27
		30	30	30	34	34
7	Standard (streptomycin)	10	26	28	28	28
		20	28	30	32	34
		30	32	36	38	36
8	Control (DMSO)	10	-	-	-	-
		20	-	-	-	-
		30	-	-	-	-

Anti oxidant activity

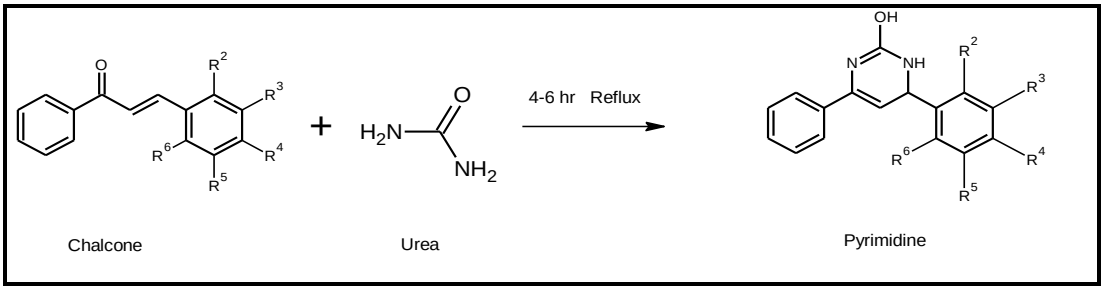
Table No.5: Anti oxidant results

S.No	Compound	Concentration (µM)	DPPH Screening (µM)
1	PR-01	5	59.92 ± 0.22
		10	122.31±0.34
		20	146.55±0.22
		40	269.72±0.52
		60	380.44±0.44
2	PR-02	5	53.66 ± 0.18
		10	102.31±0.33
		20	144.35±0.32
		40	259.11±0.54
		60	379.74±0.45
3	PR-03	5	71.63 ± 0.18
		10	142.31±0.33
		20	174.45±0.32
		40	221.41±0.54
		60	411.24±0.45
4	PR-04	5	83.66 ± 0.18
		10	166.41±0.33
		20	185.65±0.32
		40	311.41±0.54
		60	458.44±0.45
5	PR-05	5	66.63 ± 0.18
		10	128.11±0.33
		20	166.4±0.32
		40	268.41±0.54

		60	400.24±0.45
6	PR-06	5	92.44 ± 0.18
		10	175.41±0.33
		20	194.44±0.32
		40	345.66±0.54
		60	477.84±0.45
11	Ascorbic acid	5	48.63 ± 0.18
		10	98.31±0.33
		20	140.25±0.32
		40	210.41±0.54
		60	310.24±0.45

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

Chemical reaction



CONCLUSION

Based the results conclude that the compound PR-06 is the best compound than other compounds due to shows better activity the other compounds for antimicrobial and anti-oxidant activity.

ACKNOWLEDGEMENT

The authors thankful to Dr. Justice Meena V. Gomber, Management of Raffles University for providing necessary facilities and support to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Brown D J. Comprehensive heterocyclic chemistry, *Pergamon Press, Oxford, UK,* 14, 1984.
2. Elderfield R C. Heterocyclic compounds, *John Wiley and Sons, New York, USA,* 6, 1957.
3. Bruice P Y. Organic chemistry, *Pearson Education, Singapore,* 3rd Edition, 2007.
4. Schweizer H P. Triclosan: A widely used biocide and its link to antibiotics, *FEMS Microbiology Letters*, 202(1), 2001, 1-7.
5. Levy S B. Antibiotic and antiseptic resistance: impact on public health, *Pediatric Infectious Disease Journal,* 19(10), 2000, S120–S122.
6. Levy S B. Active efflux, a common mechanism for biocide and antibiotic resistance, *Journal of Applied Microbiology,* 92(1), 2002, 65S-71S.
7. Poole K. Mechanisms of bacterial biocide and antibiotic resistance, *Journal of Applied Microbiology*, 92(1), 2002, 55S-64S.
8. Hassan M, Van Der Lelie D, Springael D, Romling U, Ahmed N, Mergeay M. Identification of a gene cluster, CZR, involved in cadmium and zinc resistance in Pseudomonas aeruginosa, *Gene,* 238(2), 1999, 417-425.
9. Porter E A. Diazines and benzodiazines, *Pregamon Press, Elsevier Science BV, Amsterdam, The Netherlands,* 14, 1979.

10. Kappe O. 100 years of the biginellidihydropyrimidine synthesis, *Tetrahedron,* 49(32), 1993, 6937-6963.
11. Sharma P, Rane N, Gurram V K. Synthesis and QSAR studies of pyrimido[4, 5-d]pyrimidine-2, 5-dione derivatives as potential antimicrobial agents, *Bioorganic and Medicinal Chemistry Letters,* 14(16), 2004, 4185-4190.
12. Ito S, Masuda K, Kusano S *et al*. Pyrimidine derivative, process for preparing same and agricultural or horticultural fungicidal composition containing same, *U.S. Patent 4,* 988, 704, 1991.
13. Ram V J, Haque N, Guru P Y. Chemotherapeutic agents XXV: Synthesis and leishmanicidal activity of carbazolylpyrimidines, *European Journal of Medicinal Chemistry,* 27(8), 1992, 851-855.
14. Amir M, Javed S A, Kumar H. Pyrimidine as anti-inflammatory agent: A review, *Indian Journal of Pharmaceutical Sciences,* 69(3), 2007, 337-343.
15. Vega S, Alonso J, Diaz J A, Junquera F. Synthesis of 3-substituted-4-phenyl-2-thioxo-1, 2, 3, 4, 5, 6, 7, 8-octahydrobenzo[4, 5] thieno [2, 3-d] pyrimidines, *Journal of Heterocyclic Chemistry,* 27(2), 1990, 269-273.
16. Hannah D R, Stevens M F G. Structural studies on bioactive compounds-part 38.1: reactions of 5-aminoimidazole-4-carboxamide: Synthesis of imidazo [1, 5-a] quinazoline-3-carboxamides, *Journal of Chemical Research,* 2003(7), 2003, 398-401.
17. Smith P A S, Kan R O. Cyclization of isothiocyanates as a route to phthalic and homophthalic acid derivatives, *Journal of Organic Chemistry,* 29(8), 1964, 2261-2265.
18. Balzarini J, McGuigan C. Bicyclic pyrimidine nucleoside analogues (BCNAs) as highly selective and potent inhibitors of varicella-zoster virus replication, *Jour of Anti Chem,* 50(1), 2002, 5-9.
19. Lee H W, Bok Y K, Joong B A *et al*. Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione, *European Journal of Medicinal Chemistry,* 40(9), 2005, 862-874.
20. Juby P F, Hudyma T W, Brown M, Essery J M, Partyka R. A. Antiallergy agents. 1. 1, 6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acids and esters, *Journal of Medicinal Chemistry,* 22(3), 1979, 263-269.
21. Gupta K, Sanjay, Kayath H P, Singh A, Sharma G, Mishra K C. Anticonvulsant activity of pyrimidine thiols, *Indian Journal of Pharmacology,* 26(3), 1994, 227-228.
22. Abu-Hashem A, Youssef M M, Hussein H A R. Synthesis, antioxidant, antituomer activities of some new thiazolopyrimidines, pyrrolothiazolopyrimidines and triazolopyrrolothiazolopyrimidines derivatives, *Journal of the Chinese Chemical Society,* 58(1), 2011, 41-48.
23. Rahaman S A, Pasad Y R, Kumar P, Kumar B. Synthesis and anti-histaminic activity of some novel pyrimidines, *Saudi Pharmaceutical Journal,* 17(3), 2009, 255-258.
24. Nezu Y, Miyazaki M, Sugiyama K. Kajiwara I. Dimethoxypyrimidine as novel herbicides-part1: Synthesis and herbicidal activity of dimethoxyphenoxyphenoxypyrimidines and analogues, *Pesticide Science,* 47(2), 1996, 103-113.
25. Coe J W, Fliri A F J, Kaneko T, Larson E R. Pyrimidine derivatives enhancing antitumour activity, *U.S. Patent 5,* 491, 234, 1996.
26. Rodrigues L S, Rosa J M, Gadotti V M *et al*. Antidepressant-like and antinociceptive-like actions of 4-(4′-chlorophenyl)-6-(4″-methylphenyl)-2-hydrazinepyrimidine Mannich base in mice, *Pharmacology Biochemistry and Behavior,* 82(1), 2005, 156-162.
27. Kumar B. Kaur, Kaur J, Parmar A, Anand R D, Kumar H. Thermal/microwave assisted synthesis of substituted tetrahydropyrimidines as potent calcium channel blockers, *Indian*

Journal of Chemistry B, 41(7), 2002, 1526-1530.

28. Udaya Kumar R, Hazeena Begum V. Antimicrobial studies of some selected medicinal plants, *Anc Sci Life,* 21(4), 2002, 230-239.
29. Prasada Rao M M, Rahaman S A, Rajendra Prasad Y. Design and Synthesis of 1-(3', 5'-bis trifluoromethyl phenyl)-3-(substituted phenyl)-2-propene-1-one as potent anti fungal and antibacterial agents, *Der Pharma Chemica,* 4(5), 2012, 1997-2002.
30. Rao C P, Rahaman S A, Prasad Y R, Reddy P G. RP-HPLC method of simultaneous estimation of amlodipine besylate and metoprolol in combined dosage form, *International Journal of Pharmaceutical Research and Development,* 2(9), 2010, 69-76.
31. Rao C M, Konda R, Rao R N, Ramanjeneeyulu S, Reddy P G. Estimation of nevirapine anhydrous bulk formulation by using IR, RP-HPLC, GC methods, *Research Journal of Pharmacy and Technology,* 3(4), 2010, 1088-1092.
32. Rao C M, Rahaman S A, Prasad Y R, Rao G E. Design and synthesis of 1-(3', 5'-bis trifluoromethyl phenyl)-3-(substituted phenyl)-2-propene-1-one as potent antifungal and antibacterial agents, *Der Pharma Chemica,* 4(5), 2012, 1997-2002.
33. Rao C M, Rehaman S A, Yejella R P. Synthesis of novel 1-(2, 4′-difluorophenyl)-3-(4 ″-aryl)-2-propen-1-ones and their pharmacological activities, *World Journal of Pharmacy and Pharmaceutical Sciences (WJPPS),* 3(11), 2014, 576-586.
34. Rao C M, Dhachinamoorthi D, Mounika M, Pavani M, Shireennaaz S, Reddy C S, Annapurna M. Synthesis, characterization and anti microbial activity of novel chalcones and its di hydro pyrimidinenones, *International Journal of Life Science and Pharma Research,* 5(3), 2015, P13-16.
35. Madhuri M, Deepthi B, Vinatha V, Chmm P R. Analgesic activity of aqueous and alcohol root extracts of shoots of Dendrophthoe falcate, *International Journal of Research in Phytochemistry and Pharmacology,* 3(1), 2013, 54-56.
36. Junapudi S, Krishna J Y, Chari P V, Rao G E, M M C, Rao P. Evaluation of Antiarthritic Activity of Ethanolic Extract of Tephrosia purpurea (Linn.), *Inventi Rapid: Ethnopharmacology,* 2013(4), 2013, 1-4.
37. Rao C M, Yejella R P, Rehman R S, Basha S H. Molecular docking based screening of novel designed chalcone series of compounds for their anti-cancer activity targeting EGFR kinase domain, *Bioinformation,* 11(7), 2015, 322-329.
38. Chennu M M, Abdul R S, Yejella R P. Molecular docking based screening of G6PS with 1, 5 Benzothiazepine derivates for a potential inhibitor, *Bioinformation,* 11(12), 2015, 525-528.
39. Rao C M, Rehaman S A, Yejella R P. Molecular modelling and docking based studies of novel chalcone skeleton based compounds on glucosamine-6-phosphate synthase enzyme, *International Journal of Pharmaceutical Sciences and Research,* 7(5), 2016, 1956-1966.
40. Rao C H, Prasada M M. Novel series of 1, 5 Benzothiazepine skeleton based compounds as anti-cancer agents–In silico and MTT assay-based study, *Journal of Peer Scientist,* 1(2), 2018, e1000008.
41. Rao C M, Rajewsari T. Review on biological nitrogen fixation (BNF) in soil management, *International Journal of Pharmaceutics and Drug Analysis,* 7(8), 2019, 46-50.
42. Rao C M, Narapusetty Naidu J P, Rao K P, Ranjith K, Shobha S, Chowdary B S, Siddiraju S. Molecular docking and dynamic simulations of benzimidazoles with beta-tubulins, *Bioinformation,* 17(3), 2021, 404-412.
43. Sakthi Periasamy, Uma Jegadeesan, Kiruthika Sundaramoorthi, Tanniru Rajeswari, Venkata Naga Baji Tokala, Sumanta Bhattacharya, Sivachitra Muthusamy, Martin Sankoh,

Manoj Kumar Nellore. Comparative Analysis of Synthesis and Characterization of Silver Nanoparticles Extracted Using Leaf, Flower, and Bark of Hibiscus rosasinensis and Examine Its Antimicrobicidal Activity, *Jour of Nano,* 2022, Article ID: 8123854, 2022, 10.

44. Chennu M. M. Prasada Rao, Jahnavi, Kishore. Synthesis and antimicrobial activity of some novel chalcones of acetophenone and benzaldehyde derivatives, *IJPI'S Journal of Medicinal Chemistry,* 1(6), 2011, 1-6.
45. Chennu M. M. Prasada Rao, Rahaman S A, Rajendra Prasad Yejella. Synthesis, characterization and anti-bacterial and cytotoxic studies of novel chalcones from 2, 4 di fluoro acetophenone, *Journal of Applied Chemistry,* 3(6), 2015, 1-8.
46. Chennu M. M. Prasada Rao, Rahaman S A, Rajendra Prasad Yejella. Synthesis, characterization and anti-bacterial and cytotoxic studies of novel 1, 5 benzothiazepines from chalcones of 2, 4 difluoro acetophenone, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 4(4), 2016, 128-139.
47. Chennu M. M. Prasada Rao, Rahaman S A, Rajendra Prasad Yejella. Synthesis, characterization and anti-bacterial and cytotoxic Studies of novel 1, 5 benzothiazepines from chalcones of 1-(2, 4-Difluorophenyl) ethanone precursor, *Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry,* 4(4), 2016, 175-186.
48. Chennu M. M. Prasada Rao, Nikitha V, Datta Tejaswi N. *In vitro* anthelmintic activity of novel mannich bases, *European Journal of Pharmaceutical and Medical Research,* 5(4), 2018, 579-582.
49. Chennu M. M. Prasada Rao, Jala Lakshmi A, Grace Mani Y, Santhi Sudha B. *In vitro* anthelmintic activity of novel benzimidazole derivatives from o-phenylene diamine, *World Journal of Pharmaceutical and Medical Research,* 4(4), 2018, 245-248.
50. Chennu M. M. Prasada Rao, Ranganayakulu Y, Vasu Babu A. Synthesis, characterization anti-oxidant activity of novel 1, 5 benzothiazepines from chalcones of 1-(2, 4-difluorophenyl) ethanone precursor, *WJPLS,* 3(4), 2017, 300-305.

Please cite this article in press as: Chennu M. M Prasada Rao. Synthesis, characterization, anti-microbial and antioxidant activity of novel dihydropyrimidines, *Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry,* 10(1), 2022, 21-28.