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Preparation and Biological Screening of Novel Heterocyclic Compounds

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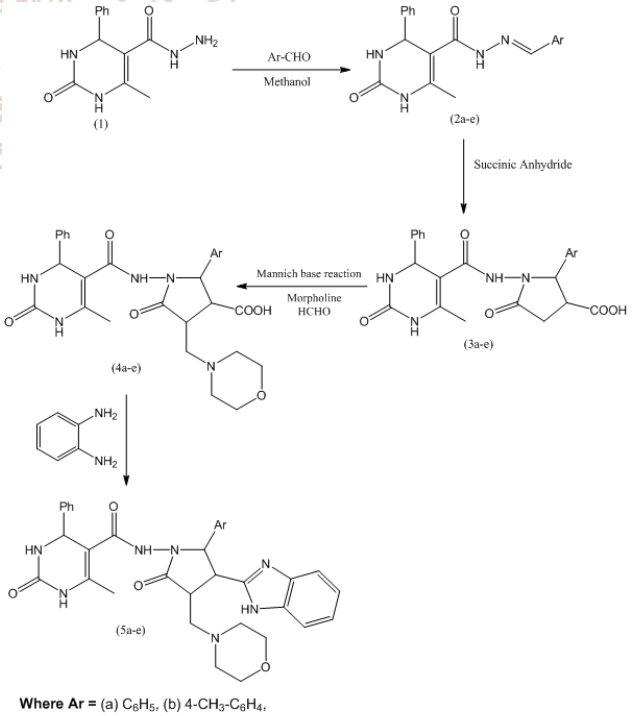
ABSTRACT

The Pyrimidone derivatives say, N'-arylidine-6-methyl-2-oxo-4-phenyl-1,2,3, 4-tetrahydropyrimidonecarbohydrazides (2a-e) were synthesized by condensation of Benzaldehyde derivatives with 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidone carbohydrazides (1) in good yield. The so called hydrazone were cyclocondensed with succinic anhydride to afford 1-[6-methyl-2-oxo-4-phenyl-1,2,3, 4-tetrahydropyrimidone-5-carboxamido)-5-oxo-2-aryl pyrrolidine-3-carboxylic acid (3a-e). These (3a-e) on Mannich reaction with formaldehyde and morpholine offered 2-aryl-1-(6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamido)-4-(morpholinomethyl)-5-oxopyrrolidine-3-carboxylic acid (4a-e). Further (4a-e) on condensation with 1, 2-benzenediamine yield N-(3-(1H-benzo[d]imidazol-2-yl)-2-aryl-4-(morpholinomethyl)-5-oxopyrro lidin-1-yl)-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (5a-e). Their structures were confirmed by elemental contents and spectral features. The antimicrobial activities of all three series have also been evaluated. The whole synthetic route is shown below.

KEYWORDS: *Schiff base, pyrrolidine, Spectral study, antibacterial and antifungal activities.*

INTRODUCTION

Hydrazones and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [1-10]. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the other compounds says, pyrimidone and their condensed products play a vital role in medicinal chemistry [11-13]. 2-pyrrolidine and its arylidene compounds give good pharmacological properties [14-19]. Hence, it was thought of interest to merge both of pyrrolidine and pyrimidone moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of pyrimidone containing pyrrolidine moiety. Hence the current communication covers the study of 1-(6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbox amido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (3a-e) followed by Mannich reaction products (4a-e) and imidazolyl derivatives (5a-e). The whole route of synthesis is given in scheme-1.



Scheme-1

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. 6-methyl-2-oxo-4-phenyl - 1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide was prepared by reported method.[20]

Preparation of N'-arylidene-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (2a-e):– An equimolecular mixture of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (1) (0.01mole) and the aromatic aldehydes [a-e] in ethanol (15ml) was refluxed on a water bath for 2-2.5 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation of 1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (3a-e):- A mixture of N'-arylidene-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbo hydrazide (2a-e) (0.01 mole) and Succinic anhydride (0.01mole) in p-Xylene (50ml) was refluxed for 5-7 hrs. The reaction mixture was allowed to stand for 2 days, the solid was filtered. The product thus formed was recrystallized from ethanol to give 1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (3a-e). The yields, melting points and other characterization data of these compounds are given in Table -2.

Preparation of 2-aryl-1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-4-(morpholinomethyl)-5-oxopyrrolidine-3-carboxylic acid (4a-e)[21]:- The above1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (3a-e) derivatives were reacted with morpholine and 37% w/w formalin at stoichiametric ratio in 1,4-dioxane under refluxed condition for 3hrs.The products were checked by TLC. The yields, melting points and other characterization data of these compounds are given in Table -3.

Preparation of N-(3-(1H-benzo [d]imidazol-2-yl)-2-aryl-4-(morpholinomethyl)-5-oxopyrrolidin-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (5a-e)[22]:-

A mixture of o-Phenylenediamine and 2-aryl-1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-4-(morpholinomethyl)-5-oxopyrrolidine-3-carboxylic acid (4a-e) was refluxed thermally. The reaction mixture was cooled and sodium hydroxide solution was added and then the crude product,N-(3-(1H-benzo[d]imidazol-2-yl)-2-aryl-4-(morpholinomethyl)-5-oxopyrrolidin-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (5a-e) was washed with ice cold water and dissolved in boiling water for recrystallization, filtered and dried. The yields, melting points and other characterization data of these compounds are given in Table -4.

RESULTS AND DISCUSSION

It was observed that 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding N'-arylidene-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo hydrazide (2a-e). The structures of (2a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at 1630-1660cm^{-1} (C=N), 3030-3085cm^{-1} (C-H of Ar), 2815-2850cm^{-1} (CH_3), 1720cm^{-1} (CO), 3260cm^{-1} (-NH), 735cm^{-1} (C-Cl), 590cm^{-1} (C-Br), 1235cm^{-1} (OCH_3). ^{1}H NMR :7.30 –8.10(10H,m,Ar-H), 8.43-8.80(1H,s, N=CH), 5.63(1H,s,-CH), 6.10-7.92(3H,s,-NH), 2.30(3H,s,CH_3), 2b; 2.1(3H,s,CH_3), 2e; 3.90(3H,s,OCH_3). The C, H, N analysis data of all compounds are presented in Table-1.

The structures assigned to 1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (3a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1720cm^{-1}(C=O of pyrrolidine ring), 3040-3058cm^{-1}(C-H of Ar), 1660-1670cm^{-1} (-CO), 2815-2850cm^{-1} (CH_3), 3260cm^{-1} (-NH), 735cm^{-1} (C-Cl), 590cm^{-1} (C-Br), 1235cm^{-1} (OCH_3) for (3a-e) compound. ^{1}H NMR: 7.30 – 8.10(10H, m, Ar-H), 4.72(1H,s,C_2H of the ring), 3.45 (1H,t,C_3H), 2.82-2.58(2H,d,C_4H), 12.96 (1H,s,-COOH), 5.63(1H,s,-CH), 6.10-7.92 (3H,s,-NH), 2.30(3H,s,CH_3), 3b; 2.1 (3H,s,CH_3), 3e; 3.90 (3H,s,OCH_3). The C, H, N analysis data of all compounds are presented in Table-2.

Table:-1 Analytical Data and Elemental Analysis of Compounds (2a-e)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{19}H_{18}N_4O_2$ (334)	84	240-241	68.2	68.25	5.4	5.43	16.7	16.76
2b	$C_{20}H_{20}N_4O_2$ (348)	80	243-244	68.9	68.95	5.7	5.79	16.0	16.08
2c	$C_{19}H_{17}N_4O_2Cl$ (368)	82	240-242	61.8	61.87	4.6	4.65	15.1	15.19
2d	$C_{19}H_{18}N_4O_2Br$ (412)	83	245-247	55.2	55.22	4.1	4.15	13.5	13.56
2e	$C_{19}H_{18}N_4O_2$ (364)	86	248-249	65.9	65.92	5.5	5.53	15.3	15.38

* Uncorrected LC-MS data 2a-351,2d-429

Table:-2 Analytical Data and Elemental Analysis of Compounds (3a-e)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{23}H_{22}N_4O_5$ (434)	64	225-226	63.5	63.59	5.0	5.10	12.8	12.90
3b	$C_{24}H_{24}N_4O_5$ (448)	68	214-216	64.2	64.28	5.3	5.39	12.4	12.49
3c	$C_{23}H_{21}ClN_4O_5$ (468)	70	212-213	58.9	58.91	4.5	4.51	11.9	11.95
3d	$C_{23}H_{21}BrN_4O_5$ (512)	72	218-219	53.8	53.81	4.1	4.12	10.9	10.91
3e	$C_{24}H_{24}N_4O_6S$ (464)	67	223-225	62.0	62.06	5.2	5.21	12.0	12.06

* Uncorrected LC-MS data 3b-462,3e-480

The structures assigned to 2-aryl-1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamido)-4-(morpholino methyl)-5-oxopyrrolidine-3-carboxylic acid (4a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1720cm^{-1}(C=O of pyrrolidine ring), 3040-3058 cm^{-1}(C-H of Ar), 1660-1670cm^{-1} (-CO), 2815-2850cm^{-1} (CH_3,CH_2), 3260cm^{-1} (-NH), 735cm^{-1} (C-Cl), 590cm^{-1} (C-Br), 1235cm^{-1} (OCH_3) for (4a-e) compound. ^{1}H NMR: 7.30 – 8.10(10H, m, Ar-H), 4.72(1H,s,C_2H of the ring), 3.45(1H,t,C_3H), 2.82(1H,s,C_4H), 2.75-2.52(2H,d,CH_2), 3.66-2.70(8H,t,CH_2), 12.96(1H,s)(COOH), 5.63(1H,s,-CH), 6.10-7.92(3H,s,-NH), 2.30(3H,s,CH_3), 4b; 2.1 (3H,s,CH_3), 4e; 3.90 (3H,s,OCH_3). The C, H, N analysis data of all compounds are presented in Table-3.

Table:-3 Analytical Data and Elemental Analysis of Compounds (4a-e)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{28}H_{31}N_5O_6$ (533)	71	232-233	63.0	63.03	5.8	5.86	13.1	13.13
4b	$C_{29}H_{33}N_5O_6$ (547)	74	236-237	63.6	63.61	6.0	6.07	12.7	12.79
4c	$C_{28}H_{30}N_5O_6Cl$ (567)	69	241-243	59.21	59.21	5.3	5.32	12.3	12.33
4d	$C_{28}H_{30}N_5O_6Br$ (611)	73	234-235	54.9	54.91	4.9	4.94	11.4	11.43
4e	$C_{29}H_{33}N_5O_7S$ (563)	76	237-238	61.7	61.80	5.8	5.90	12.4	12.43

* Uncorrected LC-MS data 4a-549,4c-583

The structures assigned to N-(3-(1H-benzo[d]imidazol-2-yl)-2-aryl-4-(morpholinomethyl)-5-oxopyrrolidin-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (5a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at1720cm^{-1}(C=O of pyrrolidine ring), 3040-3058cm^{-1}(C-H, of Ar), 1660-1670cm^{-1}(-CO), 3430cm^{-1} (NH), 2815-2850cm^{-1} (CH_3,CH_2), 3260cm^{-1}(-NH), 735cm^{-1}(C-Cl), 590cm^{-1}(C-Br), 1235 cm^{-1} (OCH_3) for (5a-e) compound. ^{1}H NMR: 7.30–8.10(14H,m,Ar-H), 4.72(1H,s,C_2H of the ring), 3.45(1H,t, C_3H), 2.82(1H,s,C_4H), 2.75-2.52(2H,d,CH_2), 3.66-2.70(8H,t,CH_2), 5.63(1H,s,-CH), 5.80-7.92(4H,s,-NH), 2.30(3H,s,CH_3) 5b; 2.1 (3H,s,CH_3), 5e; 3.90 (3H,s,OCH_3). The C, H, N analysis data of all compounds are presented in Table-4.

Table:-4 Analytical Data and Elemental Analysis of Compounds (5a-e)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
5a	$C_{34}H_{35}N_7O_4$ (605)	70	241-243	67.4	67.42	5.8	5.82	16.1	16.19
5b	$C_{35}H_{37}N_7O_4$ (619)	73	255-256	67.8	67.83	6.0	6.02	15.8	15.82
5c	$C_{34}H_{34}N_7O_4Cl$ (639)	76	263-265	63.7	63.79	5.3	5.35	15.3	15.32
5d	$C_{34}H_{34}N_7O_4Br$ (683)	77	259-260	59.6	59.65	4.9	5.01	14.3	14.32
5e	$C_{35}H_{37}N_7O_5$ (635)	72	267-268	66.1	66.13	5.8	5.87	15.4	15.42

* Uncorrected LC-MS data 5b-638,5d-698

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. LC-MS data of selected compounds shows the molecular ion peak, which is consistent with their corresponds molecular weight.

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 3c, 3e, 4c, 4e, 5c and 5e were found more toxic for microbes. Other compounds found to be less or moderate active Tables -5.

Table:-3 Antibacterial Activity of Compounds (3a-e), (4a-e) and (5a-e)

Compounds	Gram +Ve		Gram –Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
3a	55	49	62	57
3b	54	54	60	70
3c	57	63	71	59
3d	52	52	62	54
3e	58	60	74	74
4a	57	53	64	59
4b	56	58	62	72
4c	59	67	73	61
4d	54	56	63	56
4e	59	64	76	75
5a	60	54	67	61
5b	59	59	65	74
5c	62	69	76	63
5d	57	57	65	58
5e	63	66	78	76

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum*, *Fusarium oxyporium*. The antifungal activities of all the compounds (3a-e),(4a-e) and(5a-e) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120°C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where,

X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (3a-e),(4a-e) and (5a-e) is shown in Tables-6.

Table:-6 Antifungal Activity of Compounds (3a-e), (4a-e) and (5a-e)

Compounds	Zone of Inhibition at 1000 ppm (%)				
	Botrydepladia Thiobromine	Rhizopus Nigricum	Aspergillus Niger	Nigrospora Sp.	Fusarium oxyporium
3a	61	62	58	56	66
3b	59	59	55	60	62
3c	73	67	62	72	69
3d	65	58	59	58	63
3e	70	71	64	65	67
4a	63	64	64	59	67
4b	75	78	74	73	63
4c	76	79	76	76	70
4d	68	72	72	73	65
4e	74	77	79	75	69
5a	64	64	64	59	68
5b	76	78	75	75	65
5c	78	80	77	78	71
5d	69	73	74	74	66
5e	76	79	81	77	70

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