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Der ChemicaSinica, 2015, 6(5):122-125

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis,characterization and antimicrobial activity of 3-(substitutedpiperazin)acetyimidazolidine-2,4-diones

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ABSTRACT

5,5-disubstituted imidazolidine-2,4-dione derivatives possess a variety of biochemical and medicinal properties. Due to these vast pharmacological applications of these derivatives, fifteen new compounds were synthesized via the famous Bucherer-Bergreaction followed chloroacetylation and the reactions with substituted piperazins. The final products were characterized and evaluated for their antimicrobial activities. The results showed the moderate bioactivity in some compounds.

Keywords: Imidazolidinediones, Hydentoin, Piperazin

INTRODUCTION

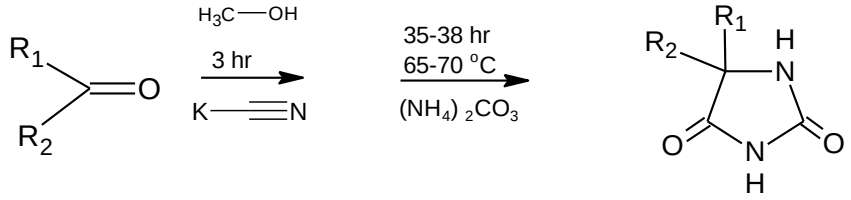
Over the last few decades, there has been progressive interest found in the synthesis and characterization of Imidazolidinediones derivatives as an important class of heterocyclic molecules. They are well known as Hydantoin derivatives. These molecules are useful as the anticonvulsants in the treatment of epilepsy and other diseases too. These derivatives have not only been used in medicinal chemistry as anti-HSV, antidiabetic, but also used as fungicides and herbicides in agrochemical research [1-4].These hydantoins are also called phenytoins are used for the treatment of different types of convulsions and seizures.Due to the great importance of these compounds, we have decided to synthesize some active substituted imidazolidinedione derivatives. From the literature review we found that there several methods for the preparation of hydantoin derivatives [5-10]. Among these methods we used the Bucherer-Berg reaction for the synthesis of the intermediate compounds. The paper describes the synthesis, characterization and activity of the products.

MATERIALS AND METHODS

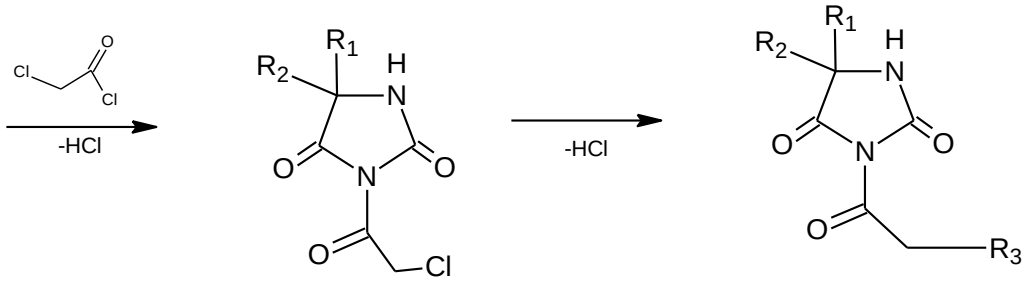
All reagents and chemicals were of analytical reagent grade, they were used without further purification. The melting points were determined in open capillary tubes on SUNBIM apparatus and are uncorrected. IR spectra were recorded on Bruker ALPHA FTIRspectrophotometer in KBr pellets. The H-NMR spectra were recorded on Bruker Avance II spectrometer in d-DMSO. Chemical shifts relative to TMS used as internal standard were obtained in d unit.The FTIR spectral analysis was carried out at Department of Chemical Engineering, VGEC, Chandkheda.The antimicrobial tests were performed at microlab Surat.

General Experimental Procedure:
According to Bucherer-Berg reaction, (Scheme-1) three different ketones(0.05mol) were added in 50 % of Ethanol with KCN(0.1 mol) and stirred for 3 hours at 30-35^{o}C temperature. Than it was added Ammonium bicarbonate (0.3 mol) and refluxed for 35 to 38 hours at 70-75^{o} C.These ketones were treated with chloroacetyle chloride at 0-5^{o}C.

These products were then allowed to react with five different substituted piparazines. Thus we obtained fifteen new molecules. The reaction completion was checked by thin layer chromatography for each step.



X_1 , X_2 and X_3



X_4 , X_5 and X_6

Where,

R_1= -CH_3 : R_2= -CH_3, -C_2H_5, -Ph : R_3= Substituted piperazines

Scheme:1:Synthesis path

RESULTS AND DISCUSSION

The synthesis of imidazolidinedione derivatives with the prperazines A(11-15), A(21-25) and A(31-35) was accomplished. The main three intermediates X_1, X_2 and X_3(Scheme-1)weresynthesizedaccordingtoBucherer-Berg reaction method followed by condensation reaction with chloroacetyl chloride. To get good yield the last step was carried out at 0-5^{o}C. Than these intermediates were merged with five different piperaziens viz. N-methylpiperazine, N-ethylpiperazine, N-phenylpiperazine, N-(2,3-dichlorophenyl)piperazine and N-(2,5-dichlorophenyl)piperazine the yields of the products were reasonably good to better. All the compounds were purified by column chromatography and checked for M.P. The results of physical and analytical tests are given in Table-1.

Spectral Analysis:

5,5-dimethyl-3-[(4-methylpiperazin-1-yl)acetyl]imidazolidine-2,4-dione(A11): IR (KBr, cm^{-1}): 3278(NH), 1769, 1718, 1710(c=o), 1422, 1401(-CH_3, -CH_2), 1055, 1042; **^{1}H NMR** (400 MHz, DMSO-d_6): δ ppm = 1.20-1.28(s, 6H), 2.41-2.46(s, 3H), 3.09-3.33(m, 8H) 4.10-4.15(s, 2H), 8.40(s, br, 1H).,

5,5-dimethyl-3-[(4-ethylpiperazin-1-yl)acetyl]imidazolidine-2,4-dione (A12):IR (KBr, cm^{-1}): 3291(NH), 1751, 1731, 1719(c=o), 1461, 1436, 1408(-CH_3, -CH_2), 1045, 1021; **^{1}H NMR** (400 MHz, DMSO-d_6): δ ppm = 1.08-1.19(s, 6H), 3.07-3.26(t, 3H), 3.49-3.73(m, 8H) 4.10-4.15(s, 2H), 5.15-5.27(q, 2H), 9.08(s, br, 1H).

5-ethyl-3-[(4-ethylpiperazin-1-yl)acetyl]-5-methylimidazolidine-2,4-dione (A22): IR (KBr, cm^{-1}): 3331(NH), 1747, 1730, 1719(c=o), 1449, 1421, 1412(-CH_3, -CH_2), 145, 1072; **^{1}H NMR** (400 MHz, DMSO-d_6): δ ppm = 1.19-1.24(s, 3H), 1.32-1.38(t, 3H), 2.02-2.28(t, 3H), 3.29-3.44(m, 8H) 4.30-4.36(s, 2H), 4.89-4.95(q, 2H), 5.44-5.49(q, 2H),9.77(s, br, 1H).

3-{[4-(2,5-dichlorophenyl)piperazin-1-yl]acetyl}-5-ethyl-5-phenylimidazolidine-2,4-dione (A35): IR (KBr, cm^{-1}): 3340(NH), 1769, 1718, 1709(c=o), 1520(c=c Ar),1422, 1401(-CH_3, -CH_2), 11014, 1042, 834; **^{1}H NMR** (400 MHz, DMSO-d_6): δ ppm = 1.56(s, 3H), 2.79-3.07(m, 8H), 3.53(s, 2H), 7.10(s, 1H Ar), 7.44 (s, 1H Ar), 7.50-7.56(m, 5H Ar), 7.30 (s, 1H Ar), 9.56(s, br, 1H).

Table-1: Physical and analytical data for the synthesized compounds

Comp. M.F.	R_1	R_2	R_3	M.P	Yield %	Elemental Analysis Cal & Found (%)		
						C	H	N
A11 ($C_{12}H_{20}N_4O_3$)	$-CH_3$	$-CH_3$	$-C_5H_{11}N_2$	97°C	55	53.72 53.73	07.51 07.49	17.89 17.87
A12 ($C_{13}H_{22}N_4O_3$)	$-CH_3$	$-CH_3$	$-C_6H_{13}N_2$	110°C	69	55.30 55.31	07.85 07.84	19.84 19.83
A13 ($C_{17}H_{22}N_4O_3$)	$-CH_3$	$-CH_3$	$-C_{10}H_{13}N_2$	137°C	61	61.80 61.81	06.71 06.69	16.96 16.95
A14 ($C_{17}H_{20}Cl_2N_4O_3$)	$-CH_3$	$-CH_3$	$-C_{10}H_{11}Cl_2N_2$	137°C	71	51.14 51.12	05.05 05.04	17.76 17.78
A15 ($C_{17}H_{20}Cl_2N_4O_3$)	$-CH_3$	$-CH_3$	$-C_{10}H_{11}Cl_2N_2$	156°C	72	51.14 51.13	05.05 05.06	17.76 17.75
A21 ($C_{13}H_{22}N_4O_3$)	$-CH_3$	$-C_2H_5$	$-C_5H_{11}N_2$	103°C	57	55.30 55.28	07.85 07.85	19.84 19.83
A22 ($C_{14}H_{24}N_4O_3$)	$-CH_3$	$-C_2H_5$	$-C_6H_{13}N_2$	116°C	71	56.74 56.75	08.16 08.17	16.20 16.22
A23 ($C_{18}H_{24}N_4O_3$)	$-CH_3$	$-C_2H_5$	$-C_{10}H_{13}N_2$	127°C	68	62.77 62.76	07.02 07.04	16.27 16.29
A24 ($C_{18}H_{22}Cl_2N_4O_3$)	$-CH_3$	$-C_2H_5$	$-C_{10}H_{11}Cl_2N_2$	133°C	75	52.31 52.31	05.37 05.38	17.16 17.17
A25 ($C_{18}H_{22}Cl_2N_4O_3$)	$-CH_3$	$-C_2H_5$	$-C_{10}H_{11}Cl_2N_2$	186°C	76	52.31 52.30	05.37 05.38	17.16 17.18
A31 ($C_{17}H_{22}N_4O_3$)	$-CH_3$	$-C_6H_5$	$-C_5H_{11}N_2$	93°C	52	61.80 61.79	06.71 06.71	16.96 16.95
A32 ($C_{22}H_{24}N_4O_3$)	$-CH_3$	$-C_6H_5$	$-C_6H_{13}N_2$	117°C	64	62.77 62.75	07.02 07.02	16.27 16.26
A33 ($C_{12}H_{20}N_4O_3$)	$-CH_3$	$-C_6H_5$	$-C_{10}H_{13}N_2$	129°C	66	67.33 67.31	06.16 06.17	14.28 14.30
A34 ($C_{22}H_{22}Cl_2N_4O_3$)	$-CH_3$	$-C_6H_5$	$-C_{10}H_{11}Cl_2N_2$	143°C	75	57.28 57.26	04.81 04.82	12.14 12.13
A35 ($C_{22}H_{22}Cl_2N_4O_3$)	$-CH_3$	$-C_6H_5$	$-C_{10}H_{11}Cl_2N_2$	171°C	77	57.28 57.28	04.81 04.80	12.14 12.15

Antimicrobial Studies:

All the newly synthesized imidazolidine-2, 4-diones were screened for their antimicrobial (antibacterial and antifungal) activities. For antibacterial studies microorganisms employed were *P.aeruginosa*, *E. coli*, *B. subtilis* and *S. aureus*, for antifungal *P. piricola*, *A. niger* and *F. oxysporum* were used as microorganisms. Both antimicrobial studies were assessed by zone inhibition (mm) method. The results are given in Table-2.

Table-2: Antimicrobial activities of the synthesized compounds

Compounds and Standards	Bacterial Culture				Fungal Culture		
	P. aeruginosa	*E. coli*	*B. subtilis*	*S. aureus*	*P. piricola*	*A. niger*	*F. oxysporum*
A11	21	18	24	17	12	14	15
A12	17	14	19	15	17	16	14
A13	13	14	13	14	18	13	18
A14	19	18	21	18	16	14	17
A15	21	23	26	19	18	17	15
A21	19	17	18	14	15	19	16
A22	14	15	14	13	17	16	15
A23	16	15	18	17	18	19	18
A24	22	20	21	17	21	21	28
A25	21	19	22	19	17	17	18
A31	12	13	12	14	15	12	13
A32	15	12	14	14	12	14	13
A33	20	19	22	18	16	17	19
A34	21	22	26	22	17	18	18
A35	23	21	24	21	18	15	16
Ciprofloxacin	21	24	27	23	-	-	-
Fluconazole	-	-	-	-	21	23	19

The results show that all the compounds exhibited potent to moderate inhibitory activities against bacterial and fungal organisms. Especially the compounds A12, A22, A31 and A32 exhibited good results against the above bacterial organisms at lower concentration when compared with other compounds. The three compounds A11, A31 and A32 exhibited good results against fungal organisms.

CONCLUSION

In conclusion, a series of new imidazoline 2,4-diones derivatives of piperazine was accomplished with reasonably good yields. In the development of the target molecules, the substituted piperazines were effectively coupled with hydantoin good yields. The antimicrobial activities of the titled compounds were evaluated. The compounds A31 (5-methyl-3-[(4-methylpiperazin-1-yl)acetyl]-5-phenylimidazolidine-2,4-dione)and A32 (3-[(4-ethylpiperazin-1-yl)acetyl]-5-methyl-5-phenylimidazolidine-2,4-dione) were found to be promising antibacterial compounds with good activity.

Acknowledgement
Authors want to express their sincere appreciation to all the staff members of Chemical Engineering Department of Government Engineering College, Valsad for their helps and moral supports in this work. We are especially thankful to our Head of Department of Chemistry at B. K. M. Science College, and Principal GEC, Valsad for inspiring us. We heartily thankful to all the friends at different laboratories who helped us for the analysis work.

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