Synthesis and Antimicrobial Activity of 5-Imidazolinone Derivatives

N. C. DESAI*, A. M. BHAVSAR AND B. B. BALDANIYA
Medicinal Chemistry Division, University Department of Chemistry, Bhavnagar University, Bhavnagar-364 002, India

Several 4-arylidene-2-phenyl-1-(2,4,5-trichlorophenyl)-1H-imidazol-5(4H)-ones (4a-q), N-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-4-chlorobenzamides (5a-o) and N-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-2,4-dichlorobenzamides (6a-m) were prepared. All newly synthesized compounds have been tested for their antibacterial activity against gram (+)ve and gram (–)ve bacteria and also on different strains of fungi. Introduction of OH, OCH_3, NO_2, Cl and Br groups to the heterocyclic frame work enhanced antibacterial and antifungal activities.

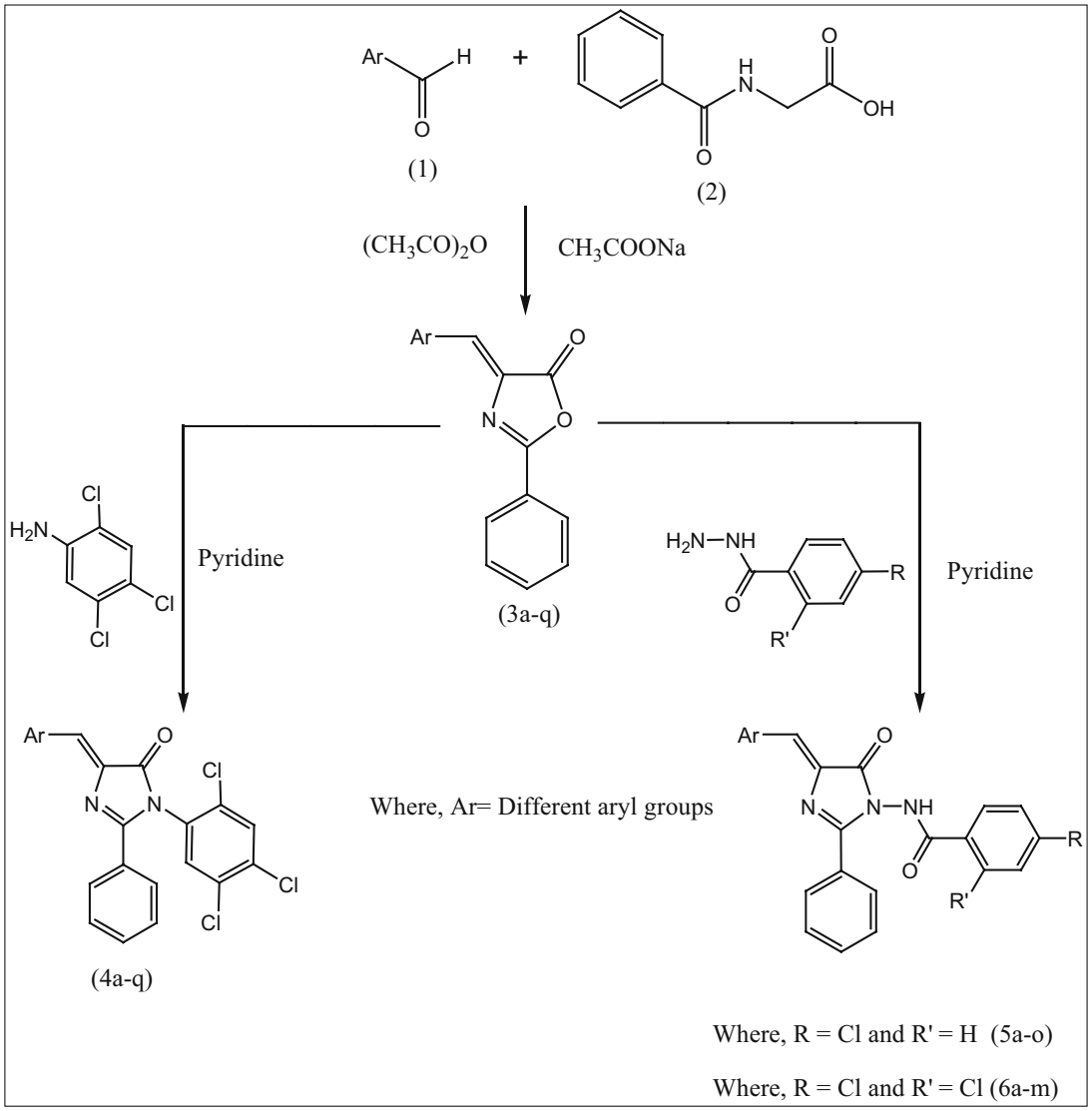
Key words: 5-Imidazolinone, antibacterial activity, antifungal activity

Imidazolinone ring system is of biological and chemical interest since long. The imidazolinones[1] are associated with a wide range of therapeutic activities[2-7] such as anticonvulsant, sedative and hypnotic, potent CNS depressant, antihistamine, antifilarial, bactericidal, fungicidal, antiinflammatory, MAO inhibitory, antiparkinsonian, antihypertensive and anthelmintic. Recently some new imidazolinone derivatives have been reported as antiinflammatory, herbicidal and hypertensive activities. Some workers have recognized 5-imidazolone as having anticancer activity[8]. The therapeutic importance of the compounds inspired us to synthesize some potential imidazolinones[9-13].

Desai *et al.*[14] have synthesized 4-benzylidene-2-phenyloxazole-5-one based on the methods descried in the literature which is a special type of Perkin condensation in which reaction between aldehyde and benzoylglycine proceeds first followed by ring closer. It is observed that aldehyde condenses under the influence of a base with the reactive methylene group in the azalactone which is formed by the dehydration of benzoylglycine, when the latter reacts with Ac_2O in presence of sodium acetate. In view of these observations, we have synthesized imidazol-5-ones (Scheme I, Table 1).

Various 4-arylidene-2-phenyl-1-(2,4,5-trichlorophenyl)-1*H*-imidazol-5(4*H*)-ones (4a-q) were prepared by the reaction of 2,4,5-trichlorobenzenamine with 4-arylidene-2-phenyloxazol-5(4*H*)-ones (3a-q). *N*-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-4-chlorobenzamide (5a-o) were synthesized by the reaction of 4-chlorobenzohydrazide and

***Address for correspondence**
E-mail: dnisheeth@rediffmail.com



Scheme 1: Synthetic pathway for synthesis of 5-imidazolone derivatives

4-arylidene-2-phenyloxazol-5(4*H*)-ones (3a-q). *N*-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-2,4-dichlorobenzamides (6a-m) were obtained by the reaction of 2,4-dichlorobenzohydrazide with 4-arylidene-2-phenyloxazol-5(4*H*)-ones (3a-q).

Melting points were taken in open capillaries using paraffin bath and are uncorrected. IR spectra were recorded on FTIR-Perkin-Elmer spectrometer (V_{max} cm^{-1}); ^1H NMR spectra were recorded on Bruker Avance 300 FT-NMR spectrometer using $CDCl_3$ as a solvent and mass spectra carried out on JEOL SX 102/DA-600 mass spectrometer, respectively. All the compounds were analyzed for carbon, hydrogen and nitrogen and the results were within ±0.4% of theoretical values. Purity was checked by TLC using TLC aluminum sheets silica gel 60, supplied by E. Merck, Mumbai, India. The spots were located by keeping the plates in iodine vapor and 2,4,5-trichlorobenzenamine was supplied by S. D. Fine Chem Limited, Mumbai, India. 4-Chlorobenzohydrazide, 2,4-dichlorobenzo hydrazide and 4-arylidene-2-phenyloxazol-5(4*H*)-one (3a-q), were prepared as given in literature method[15-20].

4-Arylidene-2-phenyl-1-(2,4,5-trichlorophenyl)-1*H*-imidazol-5(4*H*)-one (4) were synthesized as follows; A mixture of 2,4,5-trichloroaniline (0.01 mol) and 4-(arylidene)-2-phenyloxazol-5(4*H*)-one**s** (0.01 mol) was placed in a round bottom flask and 10 ml of pyridine were added to it. The reaction mixture was refluxed on a sand bath for 6 h. (scheme I) and the mixture was poured into ice-cold water and then a required amount of conc. hydrochloric

acid was added to neutralize the reaction mixture. The progress of the reaction and the purity of compounds were routinely checked on TLC. The solid obtained was left overnight, filtered and washed with water. The product was dried and recrystallized from ethanol (99%). m.p.195° Yield 53% anal. found: C, 57.06; N, 5.98; calc for $C_{22}H_{12}Cl_4N_2O$: C, 57.17; N, 6.06%.

Compound 4f: IR (KBr): 3062 cm^{-1} (-C-H str., aromatic), 1643 cm^{-1} (>C=O str., cyclic ring), 1359 cm^{-1} (>C=N str., imidazol ring), 1284 cm^{-1} (-C-N tertiary amine), 1074 cm^{-1} (-C-Cl str., aromatic), 744 cm^{-1} (>C=CH medium), 704, 688, 613 cm^{-1} (trisubstituted aromatic). ^1H NMR ($CDCl_3$): δ7.2 (s, 1H, -CH), 7.26-8.54 (m, 11H, Ar-H, C=C-Ar) ppm. MS: m/z 461 with 62% relative intensity (base peak) & 462 with 47% relative intensity (M^+). Other compounds of the series were prepared by using a similar method and their physical data are recorded in Table 1.

N-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-4-chlorobenzamides (5)/ *N*-(4-

TABLE 1: PHYSICAL CONSTANTS AND ELEMENTAL ANALYSIS OF 5-IMIDAZOLNES4a-q, 5a-o AND 6a-m

Sr No	Ar-	Molecular Formula	M.P.	Yield (%)	Elemental Analysis			
					% Carbon		% Nitrogen	
					Cal.	Found	Cal.	Found
4a	C_6H_5	$C_{22}H_{13}Cl_3N_2O$	173	65	61.78	61.69	6.55	6.41
4b	2-OH-C_6H_4	$C_{22}H_{13}Cl_3N_2O_2$	170	60	59.55	59.47	6.31	6.25
4c	4-OCH_3-C_6H_4	$C_{23}H_{15}Cl_3N_2O_2$	160	55	60.35	60.28	6.12	6.03
4d	3-Cl-C_6H_4	$C_{22}H_{12}Cl_4N_2O$	185	54	57.17	57.06	6.06	6.01
4e	3-OCH_3-C_6H_4	$C_{23}H_{15}Cl_3N_2O_2$	190	50	60.35	60.21	6.12	6.03
4f	2-Cl-C_6H_4	$C_{22}H_{12}Cl_4N_2O$	195	53	57.17	57.06	6.06	5.98
4g	4-Cl-C_6H_4	$C_{22}H_{12}Cl_4N_2O$	210	54	57.17	57.05	6.06	6.01
4h	2-NO_2-C_6H_4	$C_{22}H_{12}Cl_3N_3O_3$	180	57	55.90	55.79	8.89	8.80
4i	3-NO_2-C_6H_4	$C_{22}H_{12}Cl_3N_3O_3$	230	55	55.90	55.74	8.89	8.78
4j	3-OCH_3-4-OH-C_6H_3	$C_{23}H_{15}Cl_3N_2O_3$	170	65	58.31	58.21	5.91	5.70
4k	5-Br-3OCH_3-4-OH-C_6H_2	$C_{23}H_{14}BrCl_3N_2O_3$	235	68	49.99	49.85	5.07	4.98
4l	4-OH-C_6H_4	$C_{22}H_{13}Cl_3N_2O_2$	145	57	59.55	59.36	6.31	6.21
4m	5-Br-2OH-C_6H_3	$C_{22}H_{12}BrCl_3N_2O_2$	175	50	50.56	50.45	5.36	5.22
4n	3-OC_6H_5-C_6H_4	$C_{28}H_{17}Cl_3N_2O_2$	160	48	64.70	64.64	5.39	5.34
4o	2,4,5 $(OCH_3)_3$-C_6H_2	$C_{25}H_{19}Cl_3N_2O_4$	198	45	57.99	57.90	5.41	5.33
4p	3,4,5 $(OCH_3)_3$-C_6H_2	$C_{25}H_{19}Cl_3N_2O_4$	185	45	57.99	57.89	5.41	5.35
4q	3-OH-C_6H_4	$C_{22}H_{13}Cl_3N_2O_2$	165	58	59.55	57.47	6.31	6.26
5a	C_6H_5	$C_{23}H_{16}ClN_3O_2$	233	60	68.74	68.62	10.46	10.35
5b	2-OH-C_6H_4	$C_{23}H_{16}ClN_3O_3$	235	65	66.11	66.05	10.06	9.97
5c	3-Cl-C_6H_4	$C_{23}H_{15}Cl_2N_3O_2$	237	66	63.32	63.20	9.63	9.51
5d	3-OCH_3-C_6H_4	$C_{24}H_{18}ClN_3O_3$	246	55	66.75	66.66	9.37	9.29
5e	2-Cl-C_6H_4	$C_{23}H_{15}Cl_2N_3O_2$	212	62	63.32	63.19	9.63	9.51
5f	4-Cl-C_6H_4	$C_{23}H_{15}Cl_2N_3O_2$	214	64	63.32	63.23	9.63	9.54
5g	2-NO_2-C_6H_4	$C_{23}H_{15}ClN_4O_4$	248	50	61.82	61.73	12.54	12.45
5h	3-NO_2-C_6H_4	$C_{23}H_{15}ClN_4O_4$	223	56	61.82	61.69	12.54	12.47
5i	3-OCH_3-4-OH-C_6H_3	$C_{24}H_{18}ClN_3O_4$	226	45	64.36	64.25	9.38	9.25
5j	4-OH-C_6H_4	$C_{23}H_{16}ClN_3O_3$	231	47	66.11	66.01	10.06	9.98
5k	3-OC_6H_5-C_6H_4	$C_{29}H_{20}ClN_3O_3$	186	48	70.52	70.40	8.51	8.39
5l	2,4,5 $(OCH_3)_3$-C_6H_2	$C_{26}H_{22}ClN_3O_5$	245	46	63.48	63.40	8.54	8.47
5m	3,4,5 $(OCH_3)_3$-C_6H_2	$C_{26}H_{22}ClN_3O_5$	210	50	63.48	63.41	8.54	8.45
5n	3-OH-C_6H_4	$C_{23}H_{16}ClN_3O_3$	182	57	66.11	66.02	10.06	9.98
5o	4-N(C_2H_5)2-2-OH-C_6H_3	$C_{27}H_{25}ClN_4O_3$	176	43	66.21	66.21	11.46	11.40
6a	2-OH-C_6H_4	$C_{23}H_{15}Cl_2N_3O_3$	175	60	61.08	61.01	9.29	9.93
6b	3-Cl-C_6H_4	$C_{23}H_{14}Cl_3N_3O_2$	208	58	58.68	58.61	8.39	8.88
6c	3-OCH_3-C_6H_4	$C_{24}H_{17}Cl_2N_3O_3$	202	55	61.82	61.70	9.01	5.90
6d	2-Cl-C_6H_4	$C_{23}H_{14}Cl_3N_3O_2$	205	56	58.68	58.58	8.93	8.85
6e	4-Cl-C_6H_4	$C_{23}H_{14}Cl_3N_3O_2$	244	55	58.68	58.59	8.93	8.87
6f	2-NO_2-C_6H_4	$C_{23}H_{14}Cl_2N_4O_4$	216	58	57.40	57.31	11.64	11.55
6g	3-NO_2-C_6H_4	$C_{23}H_{14}Cl_2N_4O_4$	233	60	57.40	57.32	11.64	11.56
6h	3-OCH_3-4-OH-C_6H_3	$C_{24}H_{17}Cl_2N_3O_4$	237	48	59.77	59.65	8.74	8.65
6i	4-OH-C_6H_4	$C_{23}H_{15}Cl_2N_3O_3$	236	45	61.08	61.01	9.29	9.22
6 j	3-OC_6H_5-C_6H_4	$C_{29}H_{19}Cl_2N_3O_3$	224	48	65.92	65.80	7.95	7.81
6k	2,4,5 $(OCH_3)_3$-C_6H_2	$C_{26}H_{21}Cl_2N_3O_5$	238	43	59.33	59.27	7.98	7.90
6l	3,4,5 $(OCH_3)_3$-C_6H_2	$C_{26}H_{21}Cl_2N_3O_5$	212	45	59.33	59.26	7.98	7.88
6m	3-OH-C_6H_4	$C_{23}H_{14}Cl_2N_3O_3$	190	48	61.08	61.01	9.29	9.20

benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-2,4-dichlorobenzamides (6) were prepared using the following procedure; A mixture of 4-chlorobenzohydrazide/ 2,4-dichlorobenzohydrazide (0.01 mol) and 4-(arylidene)-2-phenyloxazol-5(4*H*)-ones (0.01 mol) was placed in a round bottom flask and 10 ml of pyridine was added to this mixture. The reaction mixture was refluxed on a sand bath for 6 h (Scheme I). The mixture was poured into ice-cold water and then required amount of con. hydrochloric acid was added to neutralize the reaction mixture. The solid obtained was left overnight, filtered and washed with water. The product was dried and recrystallized from ethanol (99%).

Compound 5f: IR (KBr): 3249 cm^{-1} (medium –CONH-), 3033 cm^{-1} (-C-H str., aromatic), 1656 cm^{-1} (>C=O str., cyclic ring), 1625 cm^{-1} (>C=N str., imidazol ring), 1490 cm^{-1} (>NH weak), 1299 cm^{-1} (-C-N tertiary amine), 1095 cm^{-1} (-C-Cl str., aromatic), 754 cm^{-1} (>C=CH medium), 707 cm^{-1} (monosubstituted aromatic). ^1H NMR ($CDCl_3$): δ7.28 (s, 1H, -CH), 7.26-8.54 (m, 13H, Ar-H, -C=C-Ar), 10.02 (s, 1H, -NH-CO-) ppm. MS: m/z 436 with 45% relative intensity (base peak) & 437 with 32% relative intensity (M^+).

Compound 6e: IR (KBr): 3213 cm^{-1} (medium, –CONH-), 2993 cm^{-1} (-C-H str., aromatic), 1662 cm^{-1} (>C=O str., cyclic ring), 1635 cm^{-1} (>C=N str., imidazol ring), 1473 cm^{-1} (>NH weak), 1305 cm^{-1} (-C-N tertiary amine), 1109 cm^{-1} (-C-Cl str., aromatic), 925 cm^{-1} (>C=CH medium), 825, 713 cm^{-1} (disubstituted aromatic), 707 cm^{-1} (monosubstituted aromatic). ^1H NMR ($CDCl_3$): δ7.2 (s, 1H ,-CH), 7.32-8.05 (m, 12H, Ar-H,C=C-Ar), 10.02 (s,1H, -NH-CO-) ppm. MS: m/z 471 with 79% relative intensity (base peak) and 472 with 51% relative intensity (M^+). Other compounds of the series were prepared by using a similar method and their physical data are recorded in Table 1.

Antibacterial activity was carried out by broth dilution method[21]. The strains used for the activity were procured from Institute of Microbial Technology, Chandigarh. The compounds 4a-q, 5a-o and 6a-m were screened for their antibacterial activity against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Staphylococcous pyogenes* at concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/ml respectively (Table 2). Same compounds were tested for antifungal activity against *C. albicans, A. niger* and *A. clavatus* at concentrations of 1000, 500, 200, and 100 µg/ml respectively (Table 2). The results are recorded in the form of primary and secondary screening.

The synthesized compounds found to be active in the primary screening were further tested in a second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 100, 50, 25 µg/ml concentrations. Ten microlitres suspensions from each well were further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MBC/MFC for each drug. The highest dilution showing at least 99% inhibition was taken as MBC/MFC. The result

TABLE 2: ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF THE SYNTHESIZED COMPOUNDS*

Sr. No.	Minimal bactericidal concentration (MBC) in µg/ml				Minimal fungicidal concentration (MFC) in µg/ml		
	E. coli MTCC-443	*P. aeruginosa* MTCC-1688	*S. aureus* MTCC-96	*S. pyogenus* MTCC-442	*C. albicans* MTCC-227	*A. niger* MTCC-282	*A. clavatus* MTCC-1323
4a	25	-	-	-	-	-	-
4b	25	50	-	-	-	-	-
4f	100	-	-	-	100	100	100
4i	25	-	-	-	-	-	-
4j	25	-	-	-	-	-	-
4k	50	100	50	-	-	-	-
4q	50	100	-	-	-	-	-
5b	-	-	-	-	100	100	100
5e	50	50	-	-	-	-	-
6f	100	-	-	-	100	100	100
6j	-	-	-	-	-	-	100
6l	-	-	-	-	100	-	100
6m	-	-	-	-	100	-	-

Gentamycin is used as standard for antibacterial activity which showed (0.05, 0.25, 0.5 and 1 µg/ml) MBC against *E. coli*, *S. aureus*, *S. pyogenus* and *P. aeruginosa* respectively. K nystatin was used as the standard for antifungal activity which showed 100 µg/ml MFC against fungi, used for the antifungal activity. *All the compounds were tested for the antibacterial and antifungal activities but data of active compounds have been reported as present protocol

of this test is affected by the size of the inoculums. The test mixture should contain 10^8 organisms/ml. For antibacterial activity, in present protocol 50 µg/ml is considered as active as compared to the standard drug gentamycin. For antifungal activity, 100 µg/ml is considered as active as compared to standard nystatin. Compounds 4a, 4b, 4i, 4j, 4k, 4q and 5e are active on *E. coli* where as 4b and 5e are active on *P. aeruginosa*. Compound 4k is active on *S. aureus* and 6m is also active on *S. pyogens*. Compounds 4f, 5b, 6f, 6l, and 6m are active on fungi strains. On the basis of biological activity results, it may be concluded that the introduction of OH, OCH_3, NO_2, Cl and Br groups to the heterocyclic frame work enhanced antibacterial and antifungal activities.

ACKNOWLEDGEMENTS

The Authors are thankful to the Bhavnagar University for providing research facilities. Authors are also thankful to director, FSL Gandhinagar for the spectral data.

REFERENCES

1. Duschinsky R. Imidazolone derivatives. US patent. 1995:US2707186.
2. Luigi A, Alfonso M, Pierluigi R, Afro G, Enzo Z, Nicola DT, *et al*. Derivatives of imidazoles. III. Synthesis and pharmacological activities of nitrile, amides, and carboxylic acid derivatives of imidazo[1,2-a] pyridine. J Med Chem 1969;12:122-6.
3. Godefroi EF, Platje JTJ. DL- l-(alpha-methylbenzyl)-2-methylimidazole-5-carboxylate esters. Synthesis and pharmacological properties. J Med Chem 1972;15:336.
4. Upadhyay PS, Joshi HD, Baxi AJ, Parikh AR. Synthesis and pharmacological evaluation of some new imidazolinones as anticonvusants. Indian J Heterocyc Chem 1991;1:71.
5. Harfenist M, Soroko EF, Mckenzie GM, 2-(Alkoxyaryl)-2-imidazoline monoamine oxidase inhibitors with antidepressant activity. J Med Chem 1978;21:405.
6. Mukerji D, Nautiyal SR, Prasad CR. Synthesis of some new 1-(2'-methoxy-4'-nitrophenyl)-2-methyl-4-substituted benzylidine-5-imidazolones as CNS depression compounds. Indian Drugs 1981;18:125.
7. Meenakshi S, Reena K, Renu S, Dixit KS, Nath C, Barthwal JP. Synthesis, anticonvusant and enzyme inhibitory activities of some indolyl-1,3,4-thiadiazoles. Indian J Chem 1990;29(B):85.
8. Solankee A, Kapadiya K, Thakor I, Patel J, Lad S. Synthesis and antimicrobial activity of 1-(4'-Trifluoromethylphenyl)-2-phenyl-4-(benzylidene/substituted benzylidene/2'-furylidene /2'-thienylidene)-imidazolin-5-ones. Asian J Chem 2004;16:917.
9. Naithani DK, Srivastava VK, Barthwal JP, Saxena AK, Gupta TK, Shanker K. Synthesis and antiparkinsonian activity of newer imidazolones. Indian J Chem 1989;28(B):990.
10. Desai NC, Dave D, Shah MD, Vyas GD. Synthesis and antibacterial activity of some novel 4-oxo-1,3-thiazolidines, 2-oxoazetidines and 5-oxoimidazolines. Indian J Chem 2000;39(B):277-82.
11. Tripathy PK. Microwave assisted one pot synthesis of (z)-1,2-disubstituted-4-arylmethylene-2 imidazolin-5-ones using solid support under solvent free condition. Indian J Heterocycl Chem 2004;14: 77-8.
12. Hirpara KV, Patel SP, Parikh KA, Bhimani AS, Parekh HH. Preparation, characterisation and antimicrobial activities of some novel nitriles and imidazolines. J Sci Islam Rep Iran 2004;15:135.
13. Rama Sharma, GVS, Reddy VM. Synthesis of 1,2 disubstituted-4-[(chromon-3-yl) methylene]imidazolin-5(4H)-ones as potential pharmacological agents. Indian J Heterocycl Chem 1993;3:111-6.
14. Shah MD, Desai NC, Awasthi KK, Saxena AK. Synthesis and QSAR studies of 5-imidazolinone derivatives as potential antibacterial agents. Indian J Chem 2001;40(B):201
15. Shah HP, Shah BR, Bhatt JJ, Deasi NC, Trivedi PB, Undavia NK. Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles as potential antimicrobial, anticancer and anti-HIV agents. Indian J Chem 1998;37(B):180.
16. Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR. Vogel's text book of practical organic chemistry. 5th Ed. London: Pearson Education; 2004. p. 1156.
17. Monk KA, Dusan S, Mohan RS. Bismuth (III) acetate: A new catalyst for preparation of azalactones via the Erlenmeyer synthesis. Synth Comm 2000;30:3167-70.
18. Imtiaz HM, Vinaykumar. Synthesis of 2-(2-benzothiazolyl/benzoxazolylthio)-N-[4,5-dihydro-4-((substitutedphenyl)methylene)-5-oxo-2-phenyl/methyl-1H-imidazole-1-l]acetamides as possible anthelmintics. Indian J Chem 1992;31(B):285-88.
19. Shah BR, Bhatt JJ, Patel HH, Undavia NK, Trivedi PB, Desai NC. Synthesis of 2,3-disubstituted-3,1-quinazolin-4(4H)-ones as potential anticancer and anti-HIV agents. Indian J Chem 1995;34(B):201.
20. Bhatt KN, Dave AM, Desai NC, Undavia NK, Trivedi PB. Studies on synthesis and antimicrobial evaluation of some new thiophenol derivatives. J Indian Chem Soc 1992;69:785.
21. National Committee for Clinical Laboratory Standard. Reference method for broth dilution antifungal susceptibility testing of yeasts Approved standard M27A. 1997; NCCLS, Wayne, PA

Accepted 14 February 2009
Revised 27 August 2008
Received 7 April 2008
Indian J. Pharm. Sci., 2009, 71 (1): 90-94