WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 4, 1371-1379. Research Article ISSN 2277– 7105

NOVEL IMIDAZOLINONES DERIVATIVES WITH DIVERSE BIOLOGICAL ACTIVITIES

Noosrat Kortiwala, Jitesh Patel and Vikas A. Desai*

Department of Chemistry, B.K.M. Science College, Valsad, 396001, Gujarat, India.

Article Received on
06 Feb 2016,
Revised on 27 Feb 2016,
Accepted on 18 Mar 2016
DOI: 10.20959/wjpr20164-5962

***Correspondence for Author**
Vikas A. Desai
Department of Chemistry,
B.K.M. Science College,
Valsad, Gujarat, India

ABSTRACT

A series of imidazolinone were synthesized by reaction of 5-oxazolone derivatives with 1-[2-amino-1-(3-methoxyphenyl)ethyl]cyclohexanol. Oxazolone were synthesized by reaction of Hippuric acid and different substituted aromatic aldehyde i.p.o Sodium Acetate and Acetic anhydride. All the synthesized compounds have been characterized on the basis of elemental analysis, IR, 1H-NMR and they compounds have been screened for antibacterial and antifungal activity.

KEYWORDS: Imidazolinone, Oxazolone, Antibacterial, Antifungal.

INTRODUCTION

The synthesis of heterocyclic compounds has always drawn the attention of chemists over the years mainly because of their wide range of important biological properties. Imidazoline have been reported to possess different biological activities such as antimicrobial[1], anticancer[2], analgesic activity[3], anti-neoplastic activity[4], anticonvulsant[5], sedative and hypnotics[6], potent CNS depressant[7,8], antihistamine[9], anti-inflammatory[10,11], local anaesthetic[12], potent antiparkinsonian[13], Herbicidal[14], insecticidal[15], Antibacterial[16,17], Antifungal[18-21], Antihelmentic[22], HIV[23], antitubercular[24], antifilarial[25], antitumour[26], cardiovascular activity[27,28], anti- viral activity and anti- ulcer activity.

Imidazole forms a part of many important biological molecules. The most prevalent is the amino acid “histidine”, which has an “imidazole” side chain. Histidine is present in many proteins and enzymes and it forms an essential part in the structure and binding functions of haemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound.[29] The overall reactivity of imidazole is referred from sets of resonance structure in which then dipolar contributors have finite importance. These predict

electrophilic attack in imidazole at position 'N-3' or any ring carbon atom, a possible nucleophilic attack at C-2 or C-1and also the amphoteric nature of the molecule.[30]

In present claim, imidazoline have been synthesized by condensation of Azalactones. These azalactone derivatives are prepared by well known Erlenmeyer condensation of hippuric acid with different aromatic aldehydes in presence of sodium acetate and acetic anhydride.[31]

Azalactones form an intermediate stage for synthesizing Imidazolones. The reaction of Azlactones with different substituted aromatic amines have focused a great attention now a days for their wide range of pharmacological application and their biological activities.[32]

The structures of the various synthesized compounds were assigned on the basis of elemental analyses, IR and 1H NMR spectral data. The compounds of this series were also screened for antibacterial and antifungal activity. During this study, we observed that several compounds displayed promising antibacterial and antifungal activity. This article showed the biological significance of some of the most important imidazolone derivatives.

Experimental: All chemicals used in the synthesis of the titled compounds were of analytical grade. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was determined by thin layer chromatography (TLC) plates using Toluene-Ethyl Acetate (7.5: 2.5, 9:1) solutions. The spots were observed by exposure to iodine vapours or by UV light. The IR spectra were obtained on SHIMADZU, Model: FTIR 8400S With DRS. The 1H-NMR were recorded on a BRUKER NMR spectrometer (300 MHz) in DMSO. The results of particular Elemental analysis of all the compounds were in good agreement with the calculated values.

General procedure for the synthesis of 4- (substituted Phenyls)-1-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl)-2-phenyl-1H-imidazol-5(4H)-one

STEP – I: Preparation of 4-(substituted Phenyls)-2-phenyloxazol-5(4H)-one

A mixture of any substituted aldehyde (0.01 mol), hippuric acid (0.01 mol), acetic anhydride (0.04 mol) and sodium acetate (0.01 mol) in a round bottom flask (50 ml) was heated up to 100°C under constant stirring for the 2-3 hrs. Then cooled the flask at 50°C; added ethanol (10 ml) slowly and kept the mass at room temperature over night. After then the reaction mass is filtered followed by hot water washing and the solid product obtained is recrystallized from ethanol. Similarly remaining compounds were prepared by same method.

STEP – II: Preparation of 4-(substituted Phenyls)-1-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-2-phenyl-1H-imidazol-5(4H)-one

A mixture of 4-(substituted Phenyls)-2-phenyloxazol-5(4H)-one (0.01 Mol) and 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (0.01 Mol) was taken in pyridine (20 ml), heated the reaction mass for 15 h at reflux temperature. After completion of reaction, excess pyridine was distilled under vacuum and poured it into crushed ice containing concentrated HCl. Product was filtered and recrystalised from ethanol. Similarly remaining compounds were prepared by same method.

1-1b: 4-(3,4-dihydroxy-5-nitrobenzylidene)-1-(2-(1-hydroxycyclohexyl) -2-(4-methoxyphenyl) ethyl)-2-phenyl-1H-imidazol-5(4H)-one

Brown solid, M.P. 118-120 °C, yield: 60%; IR (KBr) ν cm-1: 1650 (C=O), 1030(C-N), 1516 (C=C), 1605(C=N).

1H NMR (DMSO): δ 6.20(s, 1H, -CH=), δ 3.80(s, $-OCH_3$), δ 2.77(s, 1H, -CH<), δ 3.85(d, 2H, $-CH_2$), δ 6.55-7.70 (m, 13H, Ar-H), δ 1.20-1.59 (m, 10H, Cyclohexane); *m/z*: 555.66(M+1).

Elemental analyses of $C_{31}H_{31}N_3O_7$; M. WT: 557.59.
Calculated: C-66.77; H-5.06; N-7.53; found C-66.75; H-5.02; N-7.50.

1-2b: 4-(4-(dimethylamino)benzylidene)-1-(2-(1-hydroxycyclohexyl) -2-(4-methoxyphenyl) ethyl)-2-phenyl-1H-imidazol-5(4H)-one

Brown solid, M.P. 201-203 °C, yield:55%; IR (KBr) ν cm-1: 1654(C=O), 1034(C-N), 1512 (C=C), 1609(C=N).

1H NMR (DMSO): δ 6.59(s, 1H, -CH=), δ 3.72(s, $-OCH_3$), δ 2.69(s, 1H, -CH<), δ 3.82(d, 2H, $-CH_2$), δ 6.79-7.89 (m, 13H, Ar-H), δ 1.27-1.73 (m, 10H, Cyclohexane); *m/z*: 509.58(M+1).

Elemental analyses of $C_{31}H_{32}N_2O_4$; M.WT:496.59.
Calculated: C- 75.68; H-7.12; N-8.02; found C-75.66; H-7.10; N-8.00.

1-3b: 1-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-4-(4-methylbenzylidene)-2-phenyl-1H-imidazol-5(4H)-one

Brown solid, M.P. 201-203 °C, yield:55%; IR (KBr) ν cm-1: 1655(C=O), 1033(C-N), 1510 (C=C), 1600(C=N).

1H NMR (DMSO): δ 6.15(s, 1H, -CH=), δ 3.70(s, $-OCH_3$), δ 2.80(s, 1H, -CH<), δ 3.91(d, 2H, $-CH_2$), δ 6.66-7.50 (m, 13H, Ar-H), δ 1.20-1.82 (m, 10H, Cyclohexane); *m/z*: 493.08(M+1).

Elemental analyses of $C_{32}H_{34}N_2O_3$; M.WT:494.62
Calculated: C-77.70; H-6.92; N-5.66; found C-77.68; H-6.90; N-5.64.

1-4b: 4-benzylidene-1-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-2-phenyl-1H-imidazol-5(4H)-one

Brown solid, M.P. 106-108 °C, yield:80%; IR (KBr) ν cm-1: 1649(C=O), 1029(C-N), 1511 (C=C), 1606(C=N).

1H NMR (DMSO): δ 6.55(s, 1H, -CH=), δ 3.65(s, $-OCH_3$), δ 2.42(s, 1H, -CH<), δ 3.88(d, 2H, $-CH_2$), δ 6.50-7.60 (m, 13H, Ar-H), δ 1.28-1.69 (m, 10H, Cyclohexane); *m/z*: 509.58(M+1).

Elemental analyses of $C_{31}H_{32}N_2O_3$; M.WT: 480.59.
Calculated: C-77.46; H-6.71; N-5.83; found C-77.44; H-6.70; N-5.80.

1-9b: 1-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-4-(4-methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one

Brown solid, M.P. 205-207°C, yield: 85%; IR (KBr) ν cm-1: 1654(C=O), 1034(C-N), 1512 (C=C), 1609(C=N).

1H NMR (DMSO): δ 6.59(s, 1H, -CH=), δ 3.72(s, $-OCH_3$), δ 2.69(s, 1H, -CH<), δ 3.82(d, 2H, $-CH_2$), δ 6.79-7.89 (m, 13H, Ar-H), δ 1.27-1.73 (m, 10H, Cyclohexane); *m/z*: 509.58(M+1).

Elemental analyses of $C_{32}H_{34}N_2O_4$; M.WT:510.62.
Calculated: C-75.27; H-6.71; N-5.49; found C- 75.25; H-6.70; N-5.47.

3. RESULTS AND DISCUSSION

The Imidazolones are synthesised from Azalactones containing different Aryl Aldehydes. When Azalactone was treated with in Pyridine, Imidazolones are formed. All the synthesized compounds are confirmed from their characteristic IR, 1H NMR spectroscopic data and elemental analysis as described above. The structures of the synthesized compounds (1-(1-10) b) were supported by spectral analysis. In IR spectra -C=O of Imidazolone was observed at 1649-1655 cm^{-1}. Another C-N stretching found at 1029-1234 cm^{-1}, C=C at 1510-1516cm^{-1} and C=N stretching observed at 1600-1609cm^{-1}. The 1H-NMR signals of Aromatic Hydrogens were observed at 6.50-7.89 and -OCH_3 in the ring. From the above spectral discussions, the structure of Imidazolone in synthesised compounds is confirmed.

Table 1

Series 2 - Antibacterial Activity Table					
Sr.No.	**R**	**Minimal Inhibition Concentration**			
		Gram negative		**Gram positive**	
		E.COLI	**K. Pneumoniae**	**S. Aureus**	**S. Pyogenus**
		MTCC 443	**MTCC 109**	**MTCC 96**	**MTCC 442**
1b	3,4-dihydroxy-5-nitrovanillin	100	125	200	100
2b	4-hydroxy benzaldehyde	200	250	500	200
3b	4-methyl benzaldehyde	250	200	250	500
4b	Benzaldehyde	200	100	250	250
5b	2-chlorobenzaldehydel	200	500	100	125
6b	2-flourobenzaldehyde	250	200	125	62.5
7b	4-Hydroxy-3-methoxybenzaldehyde	62.5	100	200	125
8b	4-Hydroxy-3-methoxy-5-nitrobenzaldehyde	100	125	62.5	100
9b	4-methoxy benzaldehyde	500	500	200	250
10b	2,3-dimethyl-4-amino benzaldehyde	100	125	500	100
STANDARD DRUGS		**MICROGRAMME/ML**			
1.	GENTAMYCIN	0.05	1	0.25	0.5
2.	AMPICILLIN	100	--	250	100
3.	CHLORAMPHENICOL	50	50	50	50
4.	CIPROFLOXACIN	25	25	50	50
5.	NORFLOXACIN	10	10	10	10

Antimicrobial activity

All compounds given in Table-1 were tested in vitro for their antimicrobial activity. The products are screened for their antimicrobial activity using Broth dilution method by measuring the Minimum inhibition concentration (MIC) of compounds 1b (1-10) against

gram positive strains of S. aureus and S. pyogenus and gram negative strains of E-coli and K. Pneumoniae bacteria.

Table 2

SERIES 2 - ANTIFUNGAL ACTIVITY TABLE				
Sr.No.	**R**	**MINIMAL FUNGICIDAL CONCENTRATION**		
		C.ALBICANS	**A.NIGER**	**A.CLAVATUS**
		MTCC 227	**MTCC 282**	**MTCC 1323**
1b	3,4-dihydroxy-5-nitro vanillin	500	>1000	500
2b	4-hydroxy benzaldehyde	1000	500	>1000
3b	4-methyl benzaldehyde	1000	>1000	>1000
4b	Benzaldehyde	250	500	500
5b	2-chlorobenzaldehydel	250	>1000	>1000
6b	2-flourobenzaldehyde	250	500	>1000
7b	Vanillin	500	1000	1000
8b	5-Nitrovanillin	100	500	>1000
9b	4-methoxy benzaldehyde	250	500	500
10b	2,3-dimethyl-4-amino benzaldehyde	500	500	500
STANDARD DRUGS		**MICROGRAMME/ML**		
1.	NYSTATIN	100	100	100
2.	GRESEOFULVIN	500	100	100

From the antibacterial results of the series presented, compound 9b showed high activity and 2b,5b and 6b showed good activity against gram positive organisms whereas compounds 2b and 3b showed good activity against gram negative organisms. Rest of compounds showed good to moderate activity.

Gentamycin, Ampiciline, Chloramphenicol, Ciprofloxacin and Norfloxacin are used as the standard antibacterial drugs.

All the synthesized compounds have been screened against fungal strains C. albicans, A.clavatus and A. niger. Compounds 3b and 7b are the most active against both the fungal species. Remaining compounds showed the moderate activity. Nystatin and Greseofulvin are used as the standard antifungal drugs.

CONCLUSIONS

In order to find novel and potent Antibacterials, the best way is to overcome bacterial resistance to the maximum extent. So a series of substituted Imidazoline were designed to study the its biological activities. On basis of the inhibition values of these compounds, it can be concluded that compounds which substituted with chloro, methoxy, hydroxyl, methyl and

dimethyl amino in imidazolinone skeleton furnishes active antimicrobial activity, however, best antimicrobial activity can be obtained with methoxy, chloro and hydroxy substitution. Thus, it appears that most potential antimicrobial activity of compound can be achieved with appropriate combination of heterocyclic moiety substitution with various active functional groups as above.

ACKNOWLEDGEMENT

The authors are thankful to the Professor and Head, Department of Chemistry and Librarian B.K.M. Science College, Valsad for laboratory facilities and library Facilities, Aarti Group of Industries for NMR, Mass facilities, Shree Dhanvantary Pharmaceutical Analysis & Research Centre for IR facility and Microcare Laboratory Surat for antimicrobial activity.

REFERENCES

1. Adel A.H. Abdel-Rahman, Shafei Donia, Ashraf Wasfy, Aly Abd El-maboud Aly, A.Y. E;-Gazzar. Antimicrobial activity of newly synthesized imidazolones, their oxadiazolyl and acyclic C-nucleosides, Der Pharma Chemica, 2013; 5(1): 196-204.
2. Sampath Saravanan, Perumal Senthamil Selvan, Natesan Gopal, Jayanta Kumar Gupta and Biplap De. Synthesis and Antibacterial Activity of Some Imidazole-5-(4H)one Derivatives, Archiv der Pharmazie, 2005; 338(10): 488–492.
3. Flora Ferrari, Simonetta Fiorentino, Laura Mennuni, Paolo Garofalo, Ornella Letari, Stefano Mandelli, Antonio Giordani, Marco Lanza, and Gianfranco Caselli. Analgesic efficacy of CR4056, a novel imidazoline-2 receptor ligand, in rat models of inflammatory and neuropathic pain, J Pain Res., 2011; 4: 111–125.
4. Johnson R.A., Huong S.M., Huang E.S. Inhibitory effect of 4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole on HCMV DNA replication and permissive infection, Anti viral research, 1999; 41(3): 101-111.
5. P.Shanmugasundaram, B.Vijayakumar, G.Devadass, A.Appi Reddy and M.Vijey Aanandhi. Synthesis And Biological Activity Of Noval Imidazoline Derivatives, Rasayan J. Chem, 2009; 2(4): 890-894, ISSN: 0974-1496.
6. M. W. Goldberg & H. H. Lehr. Chem. Abstr., 1953; 47: 6987d.
7. Shradha Sinha, Shailja Pandey, Ridam Misra. Journal Of International Academic Research For Multidisciplinary, 2016; 4(1): ISSN: 2320-5083.
8. W. B. Wright, H. J. Brabander, R. A. Hardy and A. C. Osterberg. J. Med. Chem., 9, 852; Chem. Abstr., 1966; 66, 1463g.

9. Ronnie R. Grenshaw and Luke George M. Chem. Abstr., 1983; 98: 16649p.
10. Kalpana Pande, Reena Kalsi, T. N. Bhalla and P. Barthwal. Pharmazie, 1987; 42(4): 269; Chem. Abstr., 107, 89489q.
11. El-Araby, Omar A, Hassanein, El-Helby, Abdel-Rahman. Design, synthesis and in vivo anti-inflammatory activities of 2,4-diaryl-5-4H-imidazolone derivative, Molecules, Oct 18, 2012; 17(10): 12262-75.
12. U. Niedballa & J. Boettcher. Chem. Abstr., 1981; 94, 15732c.
13. P. Kumar, C. Nath, J. C. Agarwal, K. P. Bargawa and K. Shanker. (1983). Indian J. Chem., 22B, 955.
14. Imai Testsuya. Chem. Abstr., 1988; 101: 90933n.
15. S. R. Agripat. Chem. Abstr., 1968; 68: 29699z.
16. V. M. Rao & V. M. Reddy. J. Indian Chem. Soc., 1984; 61, 89.
17. H. A. Allimony, H. A. Saad & F. A. A. El-Meriah. Indian J. Chem., 1999; 38B, 445.
18. C. V. Reddy, K. Sastry, Shrinivasa Rao, K. Rastogi, M. L. Jain and G. S. Reddy. Indian J. Chem., 1989; 28B, 1096.
19. W. Draber & K. H. Buechel. Chem. Abstr., 1971; 74: 125697s.
20. A.F. Pozharskii. (1997). An introduction to heterocyclic chemistry and biochemistry and the role of heterocycles in science, technology, medicine and agriculture, Heterocycles in life and society, ISBN 0-471-96034-9.
21. Brewer M.D., Dorgan R.J., Manger B.R., Mamalis P., Webster R.A. Isothiourea derivatives of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole with broad-spectrum anthelmintic activity, J. Med. Chem., Oct 30, 1987; (10): 1848-53.
22. Dutta S. Synthesis and anthelmintic activity of some novel 2-substituted-4,5-diphenyl imidazoles, Acta Pharm., June, 2010; 60(2): 229-35.
23. B. R. Shah, J. T. Bhatt, H. H. Patel and N. K. Undavia. (1995). Indian J. Chem., 34, 201.
24. Dharti G. Joshi, Haresh B. Oza and H. Parekh. Synthesis Of Some Novel 1,3,4-Oxadlazoles And 5-Oxo-Imidazolines As Potent Biologically Active Agents, Heterocyclic Communications., 1997; 3(2): 169.
25. R. P. Srivastava, S. K. Singh and S. Sharma. (1991). Indian J. Chem., 30B, 859.
26. N.I Korotkikh, G.A.Losev, V.F. Lipnitskii, S.G. Kalistratov, A.S. Sokolova, O.P. Shvaika. Synthesis and antitumor activity of epoxy heterocyclic compounds, Pharmaceutical Chemistry Journal 2005; 27(1): 67-71.
27. Robertson D.W., Beedle E.E., Krushinski J.H., Pollock G.D., Willson H., Wyssvl J.S., Hayes. Structure-activity relationships of arylimidazopyridine cardiotonics: discovery and

inotropic activity of 2-[2-methoxy-4-(methylsulfinyl)phenyl]-1H-imidazo[4,5-c]pyridine, J. Med. Chem., 1985; 28(6): 717-27.

28. Erhardt P.W., Hagdon A.A., Davey D., Pease C.A., Venepalli, Griffin C.W., Gomez R.P., Wiggins J.R., Ingebretsen W.R., Pang D. J. Med. Chem., 1989; 32(6): 1173-6.
29. Bhatnagar A., Sharma P. K.2, Kumar N. A Review on "Imidazoles": Their Chemistry and Pharmacological Potentials International Journal of PharmTech Research, CODEN (USA): IJPRIF ISSN: 0974-4304. Jan-Mar, 2011; 3(1): 268-282.
30. Kartaraski. Comp. Hetro, Chem., 1984; 5: 345-498.
31. Brian S. Furniss, Antony J. Hannaford, Peter W.G. Smith, Austin R. Tatchell. Vogel's Text Book of Practical Organic Chemistry, Fifth Edition, 1994; 747.
32. Noosrat Kortiwala, Jitesh Patel & Vikas A. Desai. Imidazolone And ItsVarious Biological Activities - A Review, Journal of Chemistry and Chemical Sciences, 2016; 6(1): 25-32.