ISSN: 0974 - 7516 Volume 11 Issue 7

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 11(7), 2015 [267-272]

Antimicrobial studies of newly synthesized 1-[(4-methoxycinnamoyl) amino]-2-methyl-4-aryl methine-5-oxo-imidazolines

P.M.Chatrabhuji[1]*, A.P.Zala[2], N.K.Undavia[3]

[1]Department of Chemistry, Pramukh Swami Science & H. D. Patel Arts College, Kadi-382 715 Gujarat, (INDIA)

[2]Sir P.P.Institute of Science, Maharaja Krishnakumarsinhji Bhavnagar University Bhavnagar, (INDIA)

[3]Department of Chemistry, Bhavnagar University Bhavnagar, (INDIA)

ABSTRACT

Various 5-oxo-imidazolines derivatives of Cinnamic acid were prepared and evaluated for their in vitro antimicrobial activity against various strains of bacteria.Structures of the compounds synthesized were elucidated by spectral studies.

KEYWORDS

Pyridinylthiadiazole;
Triazolylthiadiazole;
Indolylthiadiazole;
Quinazolinonylthiadiazole.

INTRODUCTION

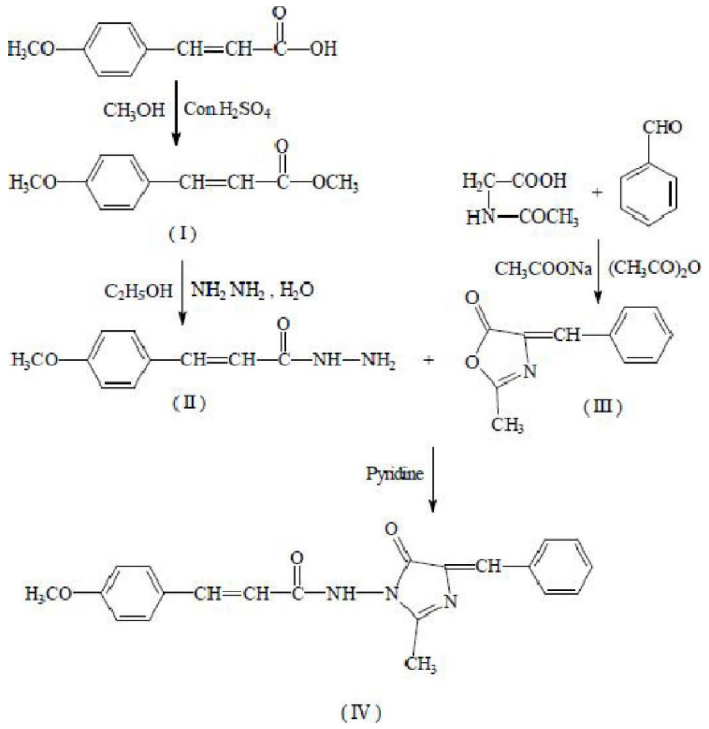
The synthesis of heterocyclic compounds has always drawn the attention of chemists over the years, mainly because of their important biological properties. As an important member of the five-membered ring heterocycles, imidazole moiety is present in a wide range of naturally occurring molecule. Compounds with imidazole moiety have many pharmaceutical activities. Diverse biological activities such as potent antibacterial activity, anti-inflammatory, anti-tubercular and antiviral activities have been found to be associated with 5-imidazolone derivatives. Imidazolinones has resulted in many potential drugs and are known to possess a broad biological spectrum such as Anticonvulsant[2–31] Potent CNS depressant[32–36] Sedative and hypnotic[37] Monoamino Oxidase (MAO) inhibitory[38-41] Antihypertensive[42-44] Insecticidal[45] Fungicidal[46-50] Antiparkinsonian[16, 51-54], cardiovascular agents[55-69].

Moreover, styryl moiety has shown antibacterial[70], anti-HIV and anticancer activities. These interesting biological activities have attracted our attention to the chemistry of nitrogen containing heterocycles. Hence it was thought of interest that 5-oxo-imidazolinones, if coupled to styryl moiety; the resulting compounds may possess significant biological potency.

Keeping in view of these varied pharmacological activities, we have planned to synthesize new 1-[(4 - methoxycinnamoyl) amino]-2-phenyl-4-aryl methine-5-oxo-imidazolines by condensing of 4 – methoxycinnamoyl hydrazine with arylidineoxazolones from hippuric acid and aromatic aldehydes in the presence of acetic anhydride and anhydrous zinc chloride[71].

The constitution of all the products has been characterized using elemental analyses, IR, 1HNMR and mass spectral study. All the compounds were screened for their *in vitro* antimicrobial activity against different strains of bacteria.

Full Paper



EXPERIMENTAL

All the melting points are determined in open capillary tubes and are uncorrected. Thin layer chromatography was used for monitoring the reaction and to check purity. IR spectra recorded on Bio-Rad FTS-40 spectrophotometer on KBr disc. 1H NMR spectra were recorded on amodelDPX-200 Brucker FT-NMR instrument using TMS as an internal standard, FAB mass spectra were recorded on JEOL SX 102/ DA 6000 spectrophotometer. All the compounds gave satisfactory elemental analyses.

Preparation of 1 - [(4 - methoxycinnamoyl) amino] - 2 - phenyl - 4 - benzylidine - 5 - oxo–imidazoline

Preparation of 4 – methoxycinnamoyl hydrazine (II):

Methyl-4 – methoxycinnamate (38.4 gm; 0.2 mole) was dissolved in ethanol (150 ml; 95%) with stirring. Hydrazine hydrate (40 ml; 80%) was added drop-wise and contents were refluxed on water-bath for ten hours. Excess of solvent and hydrazine hydrates were distilled off and reaction mixture was cooled to 4-5^{O}C. The separated product was filtered and washed with ice cold water and dried. Recrystallised from ethanol. *Yield: 29.5 gm,76.82% ; M.P. : 63^{O}C*

Preparation of 2 –phenyl -4– benzylidine – 5 – oxazolone (III)

Benzaldehyde (2.12 gm; 0.02 mole), acetyl glycine (2.34 gm; 0.02 mole), acetic anhydride (6.18 gm ; 0.06 mole) and anhydrous sodium acetate (1.64 gm; 0.02 mole) were mixed in a 250 ml R.B.F. The mixture was stirred on hot plate. After the liquification of mixture it was heated on water-bath for two hours. Then 100 ml of absolute alcohol was added to the contents of the flask and left overnight at room temperature. Crystallised product obtained was filtered and washed with cold absolute alcohol and then with boiling water, dried and recrytallised from benzene. *Yield: 3.0 gm; 80.21%; M.P: 150^{O}C*

Preparation of 1-[(4 - methoxycinnamoyl) amino] - 2 - methyl - 4 - benzylidine - 5 - oxo - imidazoline (IV)

A mixture of 4–methoxycinnamoyl hydrazine (1.92gm; 0.01mole) and 2- methyl - 4 - benzylidine - 5- oxazolone (1.87gm; 0.01mole) and pyridine (10 ml) was refluxed for 6 hours. After cooling solution was poured over crushed ice and acidified with dilute hydrochloric acid to remove pyridine. The solid obtained was filtered, washed with cold water and

TABLE 1

Comp. No.	AR	Molecular Formula	M.W.	M.P. ^{O}C	% of Yield	% Of nitrogen	
						REQ.	Found
IVa	C_6H_5-	$C_{22}H_{20}N_2O_3$	360.41	103	77	7.77	7.72
IVb	4(CH_3)C_6H_4-	$C_{22}H_{22}N_2O_3$	374.43	83	75	7.48	7.43
IVc	4(NO_2)C_6H_4-	$C_{22}H_{19}N_3O_5$	405.40	76	60	10.36	10.30
IVd	3(NO_2)C_6H_4-	$C_{22}H_{19}N_3O_5$	405.40	78	77	10.36	10.30
IVe	4(Cl)C_6H_4-	$C_{22}H_{19}N_2O_3Cl$	394.85	83	73	7.09	7.04
IVf	4(OH)C_6H_4-	$C_{22}H_{20}N_2O_4$	376.41	88	65	7.44	7.41
IVg	2(OH)C_6H_4-	$C_{22}H_{20}N_2O_4$	376.41	86	74	7.44	7.40
IVh	4(OCH_3)C_6H_4-	$C_{22}H_{22}N_2O_4$	390.43	108	61	7.17	7.14
IVi	2,3(OCH_3)$_2C_6H_3$-	$C_{24}H_{24}N_2O_5$	420.46	60	65	6.66	6.60
IVj	3,4(OCH_3)$_2C_6H_3$-	$C_{24}H_{24}N_2O_5$	420.46	65	78	6.66	6.61
IVk	3,4,5(OCH_3)$_3C_6H_2$-	$C_{25}H_{26}N_2O_6$	450.49	76	76	6.22	6.18
IVl	4(OH),3(OCH_3)C_6H_3-	$C_{22}H_{22}N_2O_5$	406.43	79	78	6.89	6.86
IVm	5(Br),4(OH),3(OCH_3)C_6H_3-	$C_{22}H_{21}N_2O_5Br$	485.33	98	80	5.77	5.72
IVn	3,4,-O-(CH_2)-O-C_6H_3-	$C_{22}H_{20}N_2O_5$	404.42	87	67	6.92	6.86
IVo	C_6H_5-CH=CH-	$C_{24}H_{22}N_2O_3$	386.45	79	65	7.25	7.20

TABLE 2 :Antimicrobial activity of the compounds (IVa-o)

Comp. No.	AR	Zone of inhibition in mm.	
		E.coli	S.aureus
IVa	C_6H_5-	20	12
IVb	2(OH)C_6H_4-	21	12
IVc	3(OH)C_6H_4-	20	12
IVd	4(OH)C_6H_4-	18	15
IVe	2(OCH_3)C_6H_4-	17	17
IVf	3(OCH_3)C_6H_4-	21	17
IVg	4(OCH_3)C_6H_4-	20	12
IVh	2,3(OCH_3)$_2C_6H_3$-	18	12
IVi	2(Cl)C_6H_4-	17	14
IVj	4(Cl)C_6H_4-	12	18
IVk	4(NO_2)C_6H_4-	19	17
IVl	4(OH),3(OCH_3)C_6H_3-	21	20
IVm	3,4,5(OCH_3)$_3C_6H_2$-	17	17
IVn	3,4,-O-(CH_2)-O-C_6H_3-	17	12
IVo	C_6H_5-CH=CH-	18	21
	Chloramphenicol	23	27

dried. It wa s recrystallized from ethanol (95 %). *Yield: 2.6 gm ; 72.22 % ; M.P. : 76O C*

Similarly other 5-oxo-imidazolines were prepared. The physical data are recorded in TABLE-1.

Spectral studies of compound IVa

IR (KBr)

836 cm^{-1}, 892cm^{-1}, 1300 cm^{-1}, 1650 cm^{-1}, 2941 cm^{-1}, 3241 cm^{-1}

^{1}H NMR

7.4 δ-8.3 δ (9 H, Aromatic protons), 5.8 δ(1H, -CO – NH), 5.3 δ (1H, > C = CH -), 3.6 δ (3H, Ar – OCH3), 2.4 (3H, Ar–CH3), 2.3 δ (2H,-CH = CH -).

Antibacterial susceptibility testing[72]

The study has been conducted according to the method adopted by R.Cruickshank et al. Nutrient agar broth was melted in a water-bath and cooled to 45O c with gentle shaking before pouring on the sterilized petri dishes (25 ml in each petri dish). The poured material was allowed to set (1.5 hour) and thereafter the "cups" (10 mm diameter) were made by punching into the agar surface with a sterile cork borer and scooping out punched part of the agar. Into these cups were added 0.1 ml portions (100 ug) of the test compounds in DMF with the help of sterile syringe. The drug solution was allowed to diffuse into the medium for about one hour. The plates were incubated at 37O c for 48 hours and the width of growth inhibition zone noted. Chloramphenicol was used as standard drug and a solvent was also run to know the activity of the solvent.

RESULTSAND DISCUSSION:

Compounds (IVa-o) were screened for their in vitro antibacterial activity using cup-plate agar diffusion method[72] at a concentration of 40ug/ml using gram positive bacterial strains such as Staphylococcus and gram negative bacterial strain such as Escherichia coli. By visulizing the antimicrobial data, these compounds have no noteworthy activity as observed in TABLE-2. Only compounds (IVj) and(IVl) have goodactivityagainst S.aureus.,While compounds (IVb), (IVf), and (IVl) possess very good activity against E. coli.

ACKNOWLEDGEMENTS

The authors are thankful to Head of the Department, Department of Chemistry, Bhavnagar University, Bhavnagar, Pramukh Swami Science & H. D. Patel Arts College, Kadi for providing research facility and CSMCRI Bhavnagar for providing instrumental facilities.

REFERENCES

[1] S.W. Fox; "Chemistry of the biologically important Imidazoles", Chem.Rev., **32**, 479 **(1943)**.
[2] R.Filler, H.Nover; J.Org.Chem.; **35**, 663 **(1970)**.
[3] A.Mustufa, A.H.E.Harhash; J.Org.Chem., **21**, 575 **(1956)**.
[4] Satya, Prakash et al.; J.Ind.Chem.Soc., **43**, 651 **(1966)**.
[5] A.F.M.Fahmy; M.O.A.Okabi; Indian J.Chem.; **10**, 961 –964 **(1972)**.
[6] Abdel, Hamid, Harhash, Kassab, Elbanani; Indian J.Chem., **9**, 789-793 **(1971)**; Chem.Abstr.; **78**, 129700 f **(1971)**.
[7] Heinrich, Wille; Ann., **436**, 229–262 **(1924)**; Chem.Abstr., **18**, 2130 **(1924)**.
[8] Isidor, Greenwald; J.Am.Chem.Soc., **47**, 1443 **(1925)**; Chem.Abstr.; **19**,1853 **(1925)**.
[9] G.M.Devasia; Tetrahedron Lett., 571, **(1976)**.
[10] Isidor, Greenwald, Joseph, Gross; J.Biol.Chem.; **59**, 601 **(1924)**; Chem.Abstr.; **18**, 2130 **(1924)**.
[11] CH.Granacher, M.Mahter, Helv.Chim.Acta.; **10**, 818-826 **(1927)**; Chem.Abstr.; **21**, 1813 **(1927)**.
[12] CH.Granacher, G.Gulbas, Helv.Chim.Acta.; **10**, 818-826 **(1927)**; Chem.Abstr.; **22**, 781 **(1928)**.
[13] C.Manich, Kollasch; Ann., **453**, 177-190 **(1927)**.
[14] Chinmai, Verma; Ph.D.Thesis, A.P.S.University, Rewa, **(1987)**.
[15] Jolly; Ph.D.Thesis, A.P.S.University, Rewa, **(1977)**.
[16] S.S.Tiwari, R.K.Satasangi; J.Ind.Chem.Soc., **56**, 627 **(1979)**.
[17] V.K.Srivastava et al.; J.Ind.Chem.Soc., **56**, 1024 **(1979)**; Chem.Abstr., **93**, 46521 u **(1980)**.
[18] Plochi; Ber., **16**, 2815 **(1883)**.
[19] Erlenmeyer; Stadline; Ann., **387**, 271 **(1904)**.
[20] Rebuffat; Ghazz.Chim.Ital., **19**, 55 **(1889)**.
[21] P.Shanthanrao, R.V.Venkataratnam; Indian J.Chem., **33B**, 984-985 **(1994)**.
[22] Upadhyay, Paresh, Pandya, Ajay, Parekh, Hansa; J.Ind.Chem.Soc., **68(5)**, 296–298 **(1991)**; Chem.Abstr., **116**, 157647 f **(1992)**.
[23] Amir, Mohammed, Singh, Era; Acta.Pharm., **42(9)**, 133-137 **(1992)**; Chem.Abstr., **118**, 6904 z **(1993)**.
[24] K.C.Pandya; P.N.Kurien, V.R.Surange; J.Ind.Chem.Soc., **11**, 823 **(1934)**.
[25] S.C.Ghosal; J.Ind.Chem.Soc., **3**, 105, **(1926)**.
[26] R.Duschinsky; U.S.Appl., **2**, 707, 186; Chem.Abstr., **50**, 5766 I (**1956)**.
[27] A.Sudhir, P.C.Dandiya; Indian Pharmacol.Soc., **(1977)**.
[28] F.Godeproi, Brik, J.Reatge; J.Med.Chem., **15**, 336 **(1972)**.
[29] P.S.Upadhyay, S.N.Joshi, A.J.Baxi, A.R.Parikh; J.Ind.Chem.Soc., **68**, 364 **(1991)**; Chem.Abstr., **116**,

1062211y **(1991)**.
[30] D.Mukherji, S.R.Nautiyi, C.R.Prasad; Indian Drugs, **18**, 125 **(1981)**.
[31] V.K.Pandey, H.C.Lohani; Curr.Sci., **57**, 460 **(1982)**; Chem.Abstr., **98**, 53766j **(1983)**.
[32] T.C.Chadha, H.S.Mahal, K.Venkataramman; J.Chem.Soc., 1459 **(1933)**.
[33] W.B.Wright, H.J.Brabander, R.A.Hardy, A.C.Osterberg; J.Med.Chem., **9**, 852 **(1966)**; Chem.Abstr., **66**, 1469 g **(1967)**.
[34] W.B.Wright, H.J.Brabander; J.Org.Chem., **26**, 4051 **(1961)**.
[35] L.P.Kyrides, F.B.Zienty, G.W.Steahly, H.L.Morill; J.Org.Chem., **12**, 577 **(1947)**.
[36] R.Agarwal, C.Chaudhary, V.S.Mishra; Indian J.Chem., **22B**, 308 **(1983)**; Chem.Abstr., **99**, 88128 a **(1983)**.
[37] M.W.Goldberg; H.H.lehr, U.S.P., **2**, 602, 086 **(1952)**; Chem.Abstr., **47**, 6987 d **(1953)**.
[38] C.Dwived i, R.D.Halbison, B.Ali, S.S.Parmar; J.Pharm.Sci., **63**, 1124 **(1974)**.
[39] M.Verma, A.K.Chaturvedi, A.Chaudhari, S.S.Parmar; J.Pharm.Sci., **63**, 1740-1744 **(1974)**.
[40] B.R.Pandey, K.Raman, J.P.Bharthwal, K.R.Bhargava, S.S.Parmar; Proc.Dec.Confr.Indian Pharmacol.Soc. **(1977)**.
[41] Z.N.Nazarova; Zhur.Obshchei.Khim, **24**, 575-578 **(1954)**; Chem.Abstr., **68**, 67430 n **(1968)**.
[42] P.A.Van, Zwieten; KlinWochenschr., **46(2)**, 77-80 **(1968)**; Chem.Abstr., **68**, 67430 n **(1968)**.
[43] Karjalainen et al.; Eur.Pat.Appl., E.P., **58**, 047; Chem.Abstr., **98**, 16692 m **(1983)**.
[44] Misra, Upma, A.K.Pathak, D.C.Tiwari; Indian Drugs, **27(12)**, 607-609 **(1990)**; Chem.Abstr., **114**, 81702 c **(1991)**.
[45] S.A.Agripat, Nath.Appl., **6**, 611, 087 **(1967)**; Chem.Abstr., **68**, 29699 z **(1968)**.
[46] C.V.Reddy et al.; Indian J.Chem., **28B(12)**, 1096-1098 **(1989)**.
[47] Michal B.Gravestock, John F.Ryley; "Antifungal Chemotherapy in annual reports in Medicinal Chemistry", **19**, 127 **(1984)**.
[48] W.Draber, K.H.Buechel; Ger.Offe n.1, **940**, 627 **(1971)**; Chem.Abstr., **74**, 125697 s **(1971)**.
[49] L.G.Copping, R.J.Birchmore, K.P.Wright, D.H.Godson; Pestic.Sci., **15**, 280-284 **(1980)**; Chem.Abstr., **101**, 85536 f **(1984)**.
[50] Marie-Pascale; PCT.Inst.Appl., WO, **96**, 03, 044; Chem.Abstr., **124**, 335656 e **(1996)**.
[51] P.Kumar, C.Nath, K.Shanker, Pharmazie; **40-H 4**, 267 **(1985)**.
[52] P.Kumar, C.Nath, J.C.Agarwal, K.P.Bhargava, K.Shanker; Indian J.Chem., **22B**, 955 **(1983)**.
[53] V.K.Shrivastava, G.Palit, K.Shanker; Pharmazie, 183 **(1975)**.
[54] P.K.Naithani, V.K.Shrivastava, J.P.Barthwal, A.K.Saxena, T.A.Gupta, K.Shanker; Indian J.Chem., **28B**, 990-992 **(1989)**.
[55] Ahcene B, Xavier R and Boutonnat J, Chalcones derivatives actingas cell cycle blockers: potential anticancer drugs? Curr.DrugTargets, **10(4)**, 363-371 **(2009)**.
[56] N.J.Lawrence, A.T.McGown; The chemistry and biology of antimitotic chalcones and related enone systems, Curr.Pharm.Des., **11**, 1679-1693 **(2005)**.
[57] D.I.Batovska, I.T.Todorova; Trends in utilization of the pharmacological potential of chalcones, Curr.Clin.Pharmacol., **5(1)**, 1-29 **(2010)**.
[58] S.Ducki; Antimitotic chalcones and related compounds as inhibitors of tubulin assembly, Anticancer Agents Med.Chem., **9(3)**, 336-47 **(2009)**.
[59] L.Ni, C.Q.Meng, A.S.James; Recent advances in therapeutic chalcones, Expert Opin.Ther.Pat., **14(12)**, 1669-1691 **(2004)**.
[60] Z.Nowakowska; A review of anti-infective and anti-inflammatory chalcones, Eur.J.Med.Chem., **42(2)**, 125-137 **(2007)**.
[61] C.Kontogiorgis, M.Mantzanidou, D.Hadjipavlou-Litina; Chalcones and their potential role in inflammation, Mini-Rev.Med.Chem., **19(12)**, 1224-1242 **(2008)**.
[62] J.B.Harborne, C.A.Williams; Advances in flavonoid research since 1992, Phytochemistry, **55(6)**, 481-504 **(2000)**.
[63] M.H.E.Oak, J.Bedoui, V.B.Schini-Kerth; Antiangiogenic properties of natural polyphenols from red wine and green tea, J.Nutr.Biochem., **16**, 1-8 **(2005)**.
[64] A.T.Dinkova-Kostova, C.Abeygunawardana, P.Talalay; Chemoprotective properties of phenyl propenoidschemoprotective properties of phenylpropenoids, bis(benzylidene)cycloalkanones and related michael reaction acceptors: Correlation of potencies asphase 2 enzyme inducers and radical scavengers, J.Med.Chem., **41**, 5287-5296 **(1998)**.
[65] J.R.Dimmock, D.W.Elias, N.M.Kandepu; Bioactivities of chalcones, Curr.Med.Chem., **6(12)**, 1125-1149 **(1999)**.
[66] Y.Inamori, K.Baba, H.Tsujibo, M.Taniguchi, K.Nakata, M.Kozawa; Antibacterial activity of two

chalcones, xanthoangelol and 4-hydroxyderricin, isolated from the root of Angelica keiskeiKOIDZUMI, Chem.Pharm.Bull., **39(6)**, 1604-1605 **(1991)**.

[67] S.Gafner,J.Wolfender, S.Mavi, K.Hostettmann; Antifungal and antibacterial chalcones from Myricaserrata, Planta Med., **62(1)**, 67-69 **(1996)**.

[68] S.F.Nielsen, T.Boesen, M.Larsen, K.Schønning, H.Kromann; Antibacterial chalcones- bioisosteric replacement of the 4-hydroxygroup, Bioorg.Med.Chem., **12(11)**, 3047-3054 **(2004)**.

[69] Vikas Sharma, Vipin Kumar, Pradeep Kumar; Heterocyclic Chalcone Analogues as potential anticancer agents, Anti Cancer Agents in Medicinal Chemistry, **13**, 422-432 **(2013)**.

[70] N.G.Buu.Hoi, Comt.Rend.Soc.Biol.; **146**, 354 **(1952)**.

[71] S.J.Selle; "Fundamental principles of bacteriology", McGraw Hill, New Delhi, **(1967)**

[72] A.R.Surrey; J.Am.Chem.Soc., **69**, 2911 **(1947)**.