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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME 3-ARYL-5-IMIDAZOLYL-2-PYRAZOLINES

MOHAMMAD ALI EBRAHIMZADEH*AND FERESHTEH POURMORAD

Pharmaceutical Sciences Research Center, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

M. A. Ebrahimzadeh, Department of Medicinal Chemistry, School of Pharmacy, Mazandaran University of Medical Sciences,

ABSTRACT

Pyrazolines are well known and important nitrogen containing five membered heterocyclic compounds. Considerable interest has been focused on the pyrazoline structure, which has been known to possess a broad spectrum of biological activities. Reaction of α,β-unsaturated aldehyde and/or ketones with hydrazines is one of the most popular method for the preparation of 2-pyrazolines. In this study a new series of 3-aryl-5-imidazolyl-2-pyrazolines have been synthesized and evaluated for their antibacterial and antifungal activities. Desired chalcones were prepared by condensing appropriate acetophenones with substituted imidazole-5-carboxaldehyde. Reaction of chalcones with phenyl hydrazine, hydrazine hydrate or thiosemicarbazide gave desirable pyrazolines. Compounds with thiosemicarbazide and para hydroxyl substitution showed potent antibacterial activity. This is consistent with the observation made earlier by other researchers. The compounds did not show any antifungal activity.

KEYWORDS: Antimicrobial activity, Chalcones, Imidazole, Pyrazoline.

INTRODUCTION

It is obvious that we are facing with an alarming increase in life threatening microbial infections especially in immuno-compromised individuals suffering from diseases such as AIDS and cancer. There is a great need for more potent and broad spectrum antimicrobial agents with reduced side effects. Combat against bacterial infections has resulted in the development of a wide variety of antibiotics. After years of misuse and overuse of antibiotics, bacteria are becoming antibiotic resistant, resulting in a potential global health crisis. There are some evidences that show antibacterial resistance is associated with an increase in mortality. Therefore, recent efforts have been directed toward exploring novel antibacterial agents (Ozdemir A et al. 2007). Apart from this, during the past 20 years an increase of invasive fungal infections has been observed, especially in immunosuppressed patients, which are now causes of morbidity and mortality. Autopsy data in fact indicate that more than half of the patients who die with malignancies are infected with Candida spp. and increasing numbers with other fungi. There are some different classes of antifungal agents. However, there is still a critical need for new antifungal agents to treat life threatening invasive mycoses (Ozdemir A et al. 2007). In order to overcome this drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. In drug designing programs an essential component of the search for new leads is the synthesis of molecules,

which are novel yet resemble known biologically active molecules by virtue of the presence of critical structural features. Compounds including a pyrazoline nucleus are known to possess several activities such as analgesic, anti-inflammatory and antibacterial (Acharya BN et al. 2010; Chandra T et al. 2010), tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive and antidepressant (Turan-Zitouni G et al. 2000; Amnerkar ND et al. 2010). Different derivatives of imidazolyl compounds combined with other heterocyclic rings have been prepared and evaluated for various activities such as antimicrobial, anti-inflammatory, and antitumor effects (Shafiee A et al. 1998; Ebrahimzadeh MA et al. 2004; Sadashiva MP et al. 2005; Demirayak S et al. 2010). Therefore, in this work we prepared a series of 3-aryl-5-imidazolyl-2-pyrazolines to investigate their antimicrobial properties.

MATERIALS AND METHODS

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide on a Nicolet 550-FT infrared spectrophotometer. The ^{1}H-NMR spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) were in *ppm* relative to internal tetramethysilane. Mass spectra were run on a Varian model MAT MS-311 spectrometer at 70 ev.

General procedures for synthesis of compounds (1-5)

Compounds 1-3, were prepared according to our reported procedure as seen in scheme 1 (Ebrahimzadehm MA et al. 2004a and 2004b). The chalcone, 1-Aryl-3-(1-methyl-2-methylthio-5-imidazolyl)-2-propen-1-one, **4**, was synthesized by condensing appropriate acetophenones with substituted imidazole-5- carboxaldehyde in basic media. Reaction of chalcones with phenyl hydrazine, hydrazine hydrate or thiosemicarbazide gave desirable pyrazolines, **5**, in good yield (Palaska E et al, 2001). Synthesis and identification of compounds are given below.

3-(p– Chlorophenyl)-5-(1-methyl-2-methylthio-5-imidazolyl) 2-pyrazoline (**5a**)

The Chalcone (10 mmol) was dissolved in ethanol (10 ml) and refluxed with hydrazine hydrate (0.5 ml) overnight. The reaction mixture was cooled and poured onto crushed ice. The precipitate was collected by filtration and recrystallized from a mixture of dichloromethane and ethanol.
^{1}H-NMR($CDCl_3$): δ(ppm) 9.80(s, 1H, NH, exchangeable with D_2O), 6.85-7.53 (m, 4H, Phenyl), 6.85 (s,1H, H_4-imidazole), 5.20-5.23 (dd, 1H, H_x), 3.70 (s, 3H, NCH_3), 3.60-3.65 (dd, 1H, H_b), 3.08-3.12 (dd, 1H, H_a), 2.53 (s, 3H, SCH_3), IR (KBr): ν (cm^{-1}) 3416 (N-H), 3180 (H_4-imidazole), 1681 (C=N), 1593 (C=C aromatic), 1375 (CH_3), 852 (para substituted).

3-(p-Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-2-pyrazoline (**5b**)
5b was prepared in a similar way as **5a**.
Mass: m/z (%), 286 (10), 285 (66), 178 (31), 227 (48), 155(34), 128(89), 122(100), 113(26).
^{1}H-NMR(DMSO-d_6): δ; 10.1(s, 1H, OH), 7.9-6.7(m,5H, Ar), 6.9(s, 1H, H_4-imidazole), 3.66 (m, 4H, NCH_3, H_b), 4.45(dd, 1H, H_x), 3.80(s, 1H, NCH_3), 3.66(s, 1H, H_a), 2.61 ppm (s, 3H, SCH_3).

1.4. 3-(o–Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-2-pyrazoline (**5c**)
5c was prepared in a similar way as **5a**.
^{1}H-NMR($CDCl_3$): δ(ppm): 7.96-7.45(*m,* 4H, phenyl), 7.59 (*s*, 1H, NH, exchangeable with D_2O), 6.96 (*s*, 1H, imidazole-H_4), 5.25 (*dd*, 1H, pyrazoline-H_5(H_x)), 3.68 (*s*, 3H, NCH_3), 3.60 (*dd*, 1H, pyrazoline-H_4(H_a)), 2.60 (*dd*, 1H, pyrazoline-H_4(H_b)) and 2.55 (s, 3H, SCH_3) ppm.

3-(Phenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-2-pyrazoline (**5d**)
5d was prepared in a similar way as **5a**.
^{1}H-NMR ($CDCl_3$): δ (ppm) 7.70-7.26 (m, 5H, Phenyl), 6.98(s, 1H, H_4-imidazole), 5.20-4.90 (dd, 1H, H_x,), 3.59 (s, 3H, NCH_3), 3.32 (dd, 1H, H_b, Jxb=12.8), 3. (dd, 1H, H_a, Jxa=14.4), 2.60 (s, 3H, SCH_3). IR (KBr disc): ν, 1510 (aromatic), 2900, 2820, 1450 cm^{-1} (aliphatic).

3-(p–Chlorophenyl)-5-[1-(p–Chlorophenyl) -2-methylthio-5-imidazolyl]2-pyrazoline (**5e**)
5e was prepared in a similar way as **5a.**

^{1}H-NMR: ($CDCl_3$, 80MHz): δ (ppm) 7.30-7.60 (m, 8H, phenyl) , 6.98 (s, 1H, Imidazole- H_4), 5.9 (dd, J=4.8Hz, 1H, pyrazole, H_5 (Hx)) , 3.55 (dd, 1H, pyrazole, H_4 (Ha) , 3.1 (dd, 1H, pyrazole , H_4 (H_b) , 2.53 (s, 3H, SCH_3).

3-(p–Chloroyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-phenyl-2-pyrazoline (**6a**)
A mixture of chalcone (10 mmol), phenylhydrazine (10 mmol) was refluxed in glacial acetic acid (10 ml) for 24 hrs. The mixture was poured into ice-water. The precipitate was filtered off and extracted from ethyl acetate. The product was purified by a mixture of ethanol and acetone.
Mass: m/z (%) 382(M^+ 12), 298(18), 255(10), 150(55), 108(100), ^{1}H-NMR (DMSO-d_6): δ; 8.02-7.51(m, 9H, phenyl), 6.84 (s, 1H, imidazole-H_4), 5.30(dd, 1H, H_x), 3.83(s, 3H, NCH_3), 3.55(dd, 2H, H_a & H_b) and 2.52(s, 3H, SCH_3) ppm.

3-(p–Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-phenyl-2-pyrazoline (**6b**)
6b was synthesized according the method described for **6a**.
Mass: m/z (%), 316 (7), 302 (16), 229 (77), 212 (100), 154(78), 121(67), ^{1}H-NMR (DMSO-d_6): δ; 9.3(s, 1H, OH), 7.7-6.5(m, 10H, Ar), 3.9(dd, 1H, H_x), 3.8(s, 3H, NCH_3), 3.1(m, 2H, H_a & H_b), 2.55(s, 3H, SCH_3) ppm

3-(o–Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-phenyl-2-pyrazoline (**6c**)
6c was synthesized according the method described for **6a**.
^{1}H-NMR ($CDCl_3$): δ(ppm) 6.73-7.51 (m, 9H, Phenyl), 6.73(s, 1H, H_4-imidazole), 5.34-5.37 (dd, 1H, H_x), 3.98 (s, 3H, NCH_3), 3.90-3.95 (dd, 1H, H_b), 3.34-3.38 (dd, 1H, H_a), 2.66 (s, 3H, SCH_3)
IR (KBr): ν(cm^{-1}) 3413 (O-H), 3061 (C-H_4-imidazole), 1637 (C=N), 1617,1597 (C=C aromatic), 1384 (CH_3), 818,752,692 (ortho substituted).

3-(o–Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-phenyl-2-pyrazoline (**6d**)
6d was synthesized according the method described for **6a**.
^{1}H-NMR ($CDCl_3$): δ(ppm) 7.67-7.20 (m, 10H, Phenyl), 6.80(s, 1H, H_4-imidazole), 5.28 (dd, 1H, H_x), 3.77 (s, 3H, NCH_3), 3.38 (m, 1H, H_b & H_a), 2.60 (s, 3H, SCH_3), IR (KBr): ν, 1550, 1495, 750, 700 (aromatic), 2900, 2820, 1400 cm^{-1} (aliphatic).

3-(p–Chlorophenyl)-5-[1-(p–Chlorophenyl)-2-methylthio-5-imidazolyl]-1-phenyl-2-pyrazoline (**6e**). **6e** was synthesized according the method described for **6a**.
^{1}H-NMR: ($CDCl_3$, 80MHz): δ (ppm) 6.8-7.3 (m, 14H, phenyl, H_4 Imidazole), 5.3 (dd, pyrazoline-H_5), 3.6 (dd, 1H, pyrazoline (Ha), H_4) , 3.1 (dd, 1H, pyrazoline, H_4, (H_b)), 2.52 (s,3H, SCH_3), Mass: m/z (%), 479 (M^+, 9), 333 (16), 125 (100), 77 (60).

3-(p-Chlorophenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-thiocarbamoyl-2-pyrazoline (**7a**)
A mixture of chalcone (10 mmol), thiosemicarbazide (10 mmol) and NaOH (25 mmol) was refluxed in ethanol (25 ml) for 24 hrs. The mixture was poured into ice- water. The precipitate was filtered off and extracted from ethyl acetate. Crystallization was carried out by a mixture of ethanol and acetone.
^{1}H-NMR($CDCl_3$): δ(ppm) 11.28 (br.s, 2H, NH_2), 7.15-8.06 (m, 4H, Phenyl), 7.35 (s, 1H, H_4-imidazole), 5.78-5.81 (dd, 1H, H_x), 3.78 (s, 3H, NCH_3), 3.56-3.61 (dd, 1H, H_b), 2.66-2.70 (dd, 1H, H_a), 2.59 (s, 3H, SCH_3), IR (KBr): ν (cm^{-1}) 3421 (NH_2), 3131 (H_4-imidazole), 1609, 1593 (C=C aromatic), 1355 (CH_3), 832 (para substituted).

3-(p-Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-thiocarbamoyl-2-pyrazoline (**7b**). **7b** was synthesized according the method described for **7a**.
Mass: m/z (%); 293(12), 229(25), 212(34), 154(58), 141(100), 113(43), IR (KBr disc): 3480(OH), 3420-3270 (NH), 3096 (imidazole-H_4), 1632(C = N), 1612, 1544, 1516(C = C), 1282 (C = S), 802 cm^{-1}

3-(o-Hydroxyphenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-thiocarbamoyl-2-pyrazoline (**7c**). **7c** was synthesized according the method described for **7a**.
Mass: m/z (%) 347 (M^+ 100), 331(18), 181(55), ^{1}H-NMR($CDCl_3$): δ (ppm) 9.82(brs, 2H, NH_2), 8.13-7.50 (m, 4H, Phenyl), 6.97 (s, 1H, imidazole-H_4), 6.08 (dd, 1H, H_x), 4.14 (dd, 1H, pyrazoline-H_b)

3.84(s, 3H, NCH_3), 3.68(dd, 1H, pyrazoline-H_a) and 2.68 (s, 3H, SCH_3)

3-(Phenyl)-5-(1-methyl-2-methylthio-5-imidazolyl)-1-thiocarbamoyl-2-pyrazoline (**7d**)
7d was synthesized according the method described for **7a**.
^{1}H-NMR($CDCl_3$): δ(ppm) 7.37-7.26 (d, 5H, Phenyl), 6.86 (s, 1H, H_4-imidazole), 5.28 (dd, 1H, H_x), 3.44 (s, 3H, NCH_3), 3.17 (m, 2H, H_b & H_a), 2.07 (s, 3H, SCH_3), IR (KBr): ν, 1610, 1550, 1475, 810 (aromatic), 2900, 1400 cm^{-1} (aliphatic).

3-(p-Chlorophenyl)-5-[1-(p- chlorophenyl)- 2-methylthio-5-imidazolyl]-1-thiocarbamoyl-2-pyrazoline (**7e**). **7e** was synthesized according the method described for **7a**.
^{1}H-NMR: ($CDCl_3$, 80MHz): δ (ppm)7.30-7.60 (m, 8H, phenyl) , 6.98 (s, 1H , Imidazole- H_4) , 5.9 (dd, 1H, pyrazole, H_5 (Hx)) , 3.55 (dd, 1H, pyrazole, H_4 (Ha) , 3.1 (dd, 1H, pyrazole , H_4 (H_b) , 2.53 (s, 3H, SCH_3), Mass: m/z (%) 462 (M^+, 4), 277 (100) , 262 (131) , 111 (14).

Antimicrobial Activity
Biological activity of the series **5, 6** and **7** were screened for their antibacterial activity by disk-diffusion technique against *Klebsiella pnemoniae, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes and Candida albicans*, at 100µg/ml. The inhibited zone diameters (mm) were measured and compared to gentamicin as a standard compound. The minimal inhibitory concentration (MIC) values of the strongly active compounds were also determined using agar dilution method according to The National Committee for Clinical Laboratory Standards (NCCLS).

RESULTS AND DISCUSSION

Pyrazolines are well known and important nitrogen containing five membered heterocyclic compounds. Considerable interest has been focused on the pyrazoline structure, which has been known to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive, and antidepressant activities (Rajendra Prasad Y et al. 2005). After the pioneer work of Fischer and Knovenagal in the late nineteenth century, the reaction of a,β-unsaturated aldehyde and ketones with hydrazines became one of the most popular method for the preparation of 2-pyrazolines (Girisha KS et al. 2010). In view of these observations and in continuation of our search for biologically active pyrazole derivatives (Ebrahimzadeh MA et al. 2004a), we herein report the synthesis and antimicrobial activity of a series of 3-Aryl-5-Imidazolyl-2-Pyrazolines. In the present work, 15 new compounds were synthesized. The structures of all compounds were confirmed by FT-IR, ^{1}H-NMR and Mass spectra. IR spectra of the compounds showed C=N and C=C stretching bands at 1637 cm^{-1} and 1597 cm^{-1}, respectively. The CH protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 3.17-3. 81 ppm (Ha), 3.12-4.14 ppm (Hb). The CH (Hx) proton appeared as a doublet of doublets at δ 5.18-6.74 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring (JAB = 17.07, JAX= 6.30, JBX= 11.05 Hz). The protons belonging to the aromatic ring and phenyl substituent were observed at expected chemical shift and integral values. The 4-H proton of imidazole was observed as a singlet between δ 6.8-7.3 ppm. A careful analysis of the antimicrobial activity data of the compounds suggested that o-hydroxyl and p-hydroxy derivatives of compounds in series 5 were comparatively more active in the screening, with respect to their hydrophobic analogs. Derivatives 6b, 6c and 6d with the same functional groups exhibited potent antibacterial properties. It seems the existence of thiosemicarbazide enhanced antibacterial activity in compounds 7c and 7d compared to other analogs (Table 1). This is consistent with the observation made earlier by other researchers. The results of Rajendra Prasad (Rajendra Prasad Y et al. 2005) revealed that the compounds possessing electron-releasing groups such as dimethylamino, methoxy, and hydroxyl substituents, on both the aromatic rings at positions 3 and 5 of pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the phenyl rings. According to the results of Turan-Zitouni′s report (Turan-Zitouni G et al. 2000), an increase in the hypotensive activity

of the substituted pyrazolines has been observed when a hydroxyl or a methoxy group introduces in phenyl substitution. Substitution of methoxy group in 2, 3 or 4 position of phenyl in 5-phenyl pyrazolines was reported to be the most active antimalarial compound in its series (Acharya BN et al. 2010). 5c and 7c showed the least MIC. Generally, the existence of hydroxyl and thiosemicarbazide has been involved in increasing the antibacterial activity. The compounds did not show any antifungal activity.

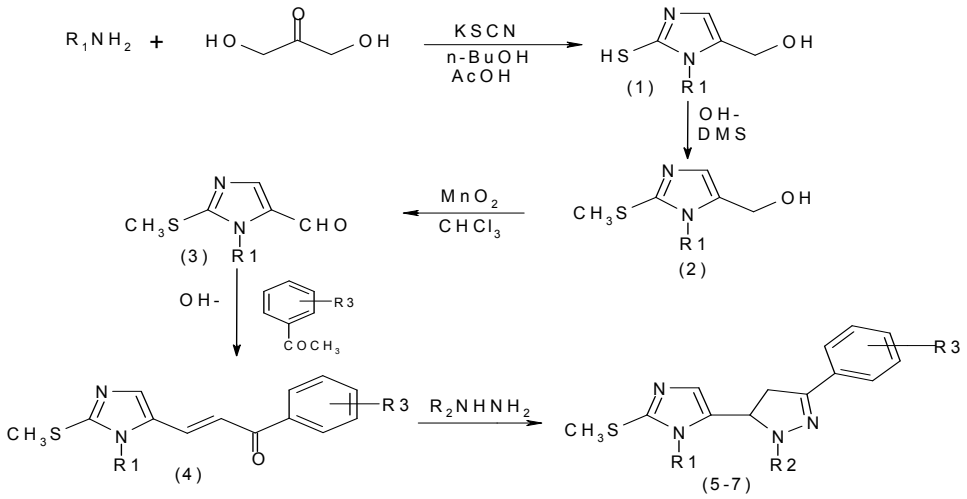
Table 1

Different functional group, physical and antimicrobial data of the synthesized compounds

Compound	R_1	R_2	R_3	m.p.	Yield (%)	*K. pnemoniae*	*S. aureus*
5a	CH_3	H	4-Cl	108-110	30	6	6
6a	CH_3	Ph	4-Cl	127-128	50	6	6
7a	CH_3	$-CSNH_2$	4-Cl	130-132	42	6	6
5b	CH_3	H	4-OH	232-234	32	6	24
6b	CH_3	Ph	4-OH	252-253	52	28	6
7b	CH_3	$-CSNH_2$	4-OH	240-242	46	6	6
5c	CH_3	H	2-OH	166-167	42	32	6
6c	CH_3	Ph	2-OH	220-222	50	6	25
7c	CH_3	$-CSNH_2$	2-OH	177-178	61	32	6
5d	CH_3	H	H	159-160	39	6	6
6d	CH_3	Ph	H	123-125	20	6	28
7d	CH_3	$-CSNH_2$	H	235-237	27	6	26
5e	4-Cl-Ph	H	4-Cl	188-189	30	6	6
6e	4-Cl-Ph	Ph	4-Cl	154-156	35	6	6
7e	4-Cl-Ph	$-CSNH_2$	4-Cl	248-249	56	6	6
Gentamicin						32	30

Scheme1

Synthetic routs of compounds 5-7. For R_1, R_2 and R_3 see Table 1.



CONFLICT OF INTEREST

Conflict of interest declared none.

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