

Synthesis and Antimicrobial Evaluation of Certain Novel Thiazoles

Meesaraganda Sreedevi^{1*}, Aluru Raghavendra Guru Prasad², Yadati Narasimha Spoorthy¹, Lakshmana Rao Krishna Rao Ravindranath¹

¹ Sri Krishnadevaraya Univerisity, Anantapur, Andhra Pradesh, India.

² ICFAI Foundation for Higher Education, Hyderabad, Andhra Pradesh, India.

ARTICLE INFO

Article Type:

Research Article

Article History:

Received: 25 November 2012

Revised: 26 December 2012

Accepted: 27 December 2012

ePublished: 7 February 2013

Keywords:

Imidazole moiety

Thiazole moiety

Synthesis

Characterization

Antimicrobial activity

ABSTRACT

Purpose: This article makes an attempt to synthesize certain compounds containing thiazole and imidazole moieties and screen for the antimicrobial properties. **Methods:** The novel compounds synthesized were characterized by elemental analysis, IR and ¹HNMR spectral data. The antimicrobial activity of novel compounds was evaluated by cup plate method. **Results:** The compound *p-t* showed more antibacterial activity than that of the standard. *p-hp* and *p-as* showed considerable antibacterial activity. *p-t* demonstrated higher antifungal activity than that of the standard while *p-hp* and *p-as* showed considerable antifungal activity. **Conclusion:** The antimicrobial activity studies were conducted on certain selected bacteria and fungi. In each case antimicrobial activity of the compounds was compared with that of standards. *p-t*, *p-hp*, *p-np*, *p-cp*, *p-ts* and *p-as* showed considerable antimicrobial activity.

Introduction

The thiazole chemistry has been extensively developing because of their unique physiological properties. Thiazoles are stable, non-carcinogenic aromatic compounds with relatively small size. The reason being the susceptibility of reactive sites at 2-, 3- and 5-positions of the thiazole nucleus to biochemical attack during the metabolism involving reduction, hydrolysis, amination, decarboxylation of CO₂H group etc. Their wide variety of applications in medicinal chemistry has been encouraging and is reflected by the extensive literature available.¹⁻⁵ The potent medicinal significance of imidazoles is also well known.⁶⁻⁹ In continuation of our effort¹⁰ to incorporate multiple pharmacologically important moieties in a single entity, we herewith propose to synthesize novel compounds containing both imidazole and thiazole moieties.

Materials and Methods

The chemicals employed in the studies were of analytical reagent grade. Melting points were determined in open capillary tubes and were uncorrected. The infrared spectra were recorded on Perkin – Elmer KBr spectrometer. ν values were expressed in cm⁻¹. ¹HNMR spectra were recorded on JEOL MODEL GSX 270 FT NMR Spectrometer and NMR 200 MHz Supercon machine, using CDCl₃ and DMSO – d₆ as solvents and TMS as an internal standard. Chemical shifts were expressed as δ values (ppm).

Results and Discussion

Synthesis and characterization of (2-methyl-5-nitro-4-phenylazo-imidazol-1-yl)-acetic acid N-(4-phenyl-thiazol-2-yl)-hydrazides 3

Phenyl aryl bromides and 3-(4'-substituted phenyl)-4-bromo acetyl sydnones were synthesized by the procedures reported in the literature.¹⁰

A mixture of (2-methyl-5-nitro-4-phenyl azo-imidazole-1-yl)-acetic acid hydrazide 1 (0.01 mole), potassium thiocyanate (0.02 mole), concentrated hydrochloric acid (1 mL), ethyl alcohol (10 mL) and water (20 mL) were refluxed for 3 hours. The cooled solution was filtered, the precipitate was washed with water, dried and recrystallized from ethanol-DMF mixture to yield 2-methyl-5-nitro-4-phenyl azo-imidazole-1-yl)-acetic thiosemicarbazone 2. The structure of 2 was confirmed by IR and ¹HNMR spectral data.

Elemental analysis (Compound: Molecular Formula; Yield %; m.p (°C); found (calcd) %.)

2: C₁₃H₁₄N₈O₃S; 68; 230 °C; C 43.58(43.09), H 3.67(3.89), N 31.24(30.92), O 13.46(13.25), S 8.34(8.85).

IR spectral details

The IR (KBr) spectrum of 2 showed absorption bands around 3220 cm⁻¹ (NH-str), 2950 cm⁻¹ (CH, str), 1679 cm⁻¹ (C=O, str), 1540 cm⁻¹ (C=N, str), 1610 cm⁻¹ (N=N, str), 1500 cm⁻¹ (asymmetric stretching, Nitro group), 1329 cm⁻¹ (symmetric stretching, Nitro group).

*Corresponding author: Meesaraganda Sreedevi, Sri Krishnadevaraya Univerisity, Anantapur, Andhra Pradesh, India. Tel: 91 9440515447,

Email: sreedevisep@yahoo.in

Copyright © 2013 by Tabriz University of Medical Sciences

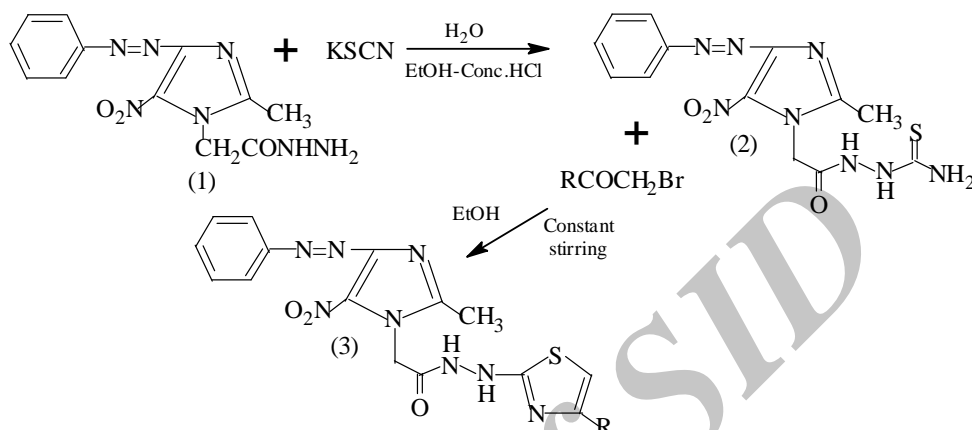
¹HNMR spectral details

The ¹HNMR (200MHz) spectrum of 2 was recorded in CDCl₃+DMSO-d₆. The signals were noticed at δ 2.29 (s, 3H, CH₃), δ 4.80 (s, 2H, N-CH₂-CO), δ 3.33 (s, 2H, NH₂), δ 9.40 (s, 2H, CO-NH-NH), δ 7.4 – 7.6 (m, 5H, Ar-H).

A mixture of (2-methyl 5-nitro-4-phenyl azoimidazole-1-yl)-acetyl thiosemicarbazone 2 (0.01 mole) in DMF (10 mL) and various bromoacetyl

derivatives (0.01 mol) in ethanol (10 mL) was stirred at room temperature for 2 hours. The solid separated was filtered, dried and recrystallized from ethanol-DMF mixture. The compounds synthesized 3 have been characterized by means of IR and ¹HNMR spectral data.

The reaction sequence leading to the formation of these compounds is outlined in Scheme 1.



Scheme 1. Synthesis and characterization of (2-methyl-5-nitro-4-phenylazoimidazole-1-yl)-acetic acid-N-(4-phenylthiazol-2-yl)hydrazide 3. [R = phenyl (phe), *p*-tolyl (*p*-t), *p*-anisyl (*p*-a), *p*-hydroxy phenyl (*p*-hp), *p*-nitro phenyl (*p*-np), *p*-chloro phenyl (*p*-cp), *p*-bromo phenyl (*p*-bp), *p*-phenyl sydnonyl (*p*-ps), *N*-*p*-tolyl sydnonyl (*p*-ts), *N*-*p*-anisyl sydnonyl (*p*-as)]

Elemental analysis (Compound: R; Molecular Formula; Yield %; m.p (°C); found (calcd) %.)

phe: phenyl; C₂₁H₁₈N₈O₃S; 66; 258; C 54.54(54.44), H 3.92(3.72), N 24.23(23.73), O 10.60 (10.39), S 6.47 (6.93).

p-t: *p*-tolyl; C₂₂H₂₀N₈O₃S; 45; 202; C 55.45(54.98), H 4.23(4.01), N 23.52(23.14), O 10.82 (10.08), S 6.57 (6.72).

p-a: *p*-anisyl; C₂₂H₂₀N₈O₄S; 54; 221; C 53.65(53.24), H 4.09(3.98), N 22.75(22.27), O 13.68 (13.01), S 6.89 (6.54).

p-hp: *p*-hydroxyphenyl; C₂₁H₁₈N₈O₄S; 50; 195; C 52.71(52.34), H 3.79(3.54), N 23.42(22.96), O 13.68 (13.39), S 6.49 (6.69).

p-np: *p*-nitro phenyl; C₂₁H₁₇N₉O₅S; 64; 232; C 49.70(49.27), H 3.38(3.16), N 24.84(24.40), O 16.47(15.78), S 6.21(6.31).

p-cp: *p*-chloro phenyl; C₂₁H₁₇ClN₈O₃S; 58; 193; C 50.76(50.31), H 3.45(3.23), N 22.55(22.10), O 10.65(10.22), S 6.21(82), Cl 7.99(7.55).

p-bp: *p*-bromo phenyl; C₂₁H₁₇BrN₈O₃S; 56; 204; C 46.59(46.13), H 3.17(2.95), N 20.70(20.31), O 9.24(8.87), S 6.31(5.92), Br 14.99(14.77).

p-ps: *p*-phenyl sydnonyl; C₂₃H₂₀N₁₀O₅S; 52; 197; C 50.36(49.84), H 3.68(3.43), N 25.53(25.06), O 00.00 (14.60), S 00.00 (5.84).

p-ts: *N*-*p*-tolyl sydnonyl; C₂₄H₂₂N₁₀O₅S; 57; 182; C 51.24(50.81), H 3.94(3.71), N 24.90(24.49), O 14.89(14.23), S 5.12(5.69).

p-as: *N*-*p*-anisyl sydnonyl; C₂₄H₂₂N₁₀O₆S; 43; 191; C 49.82 (49.45), H 3.83(3.69), N 24.21(23.78), O 17.21(16.61), S 5.12 (5.54).

IR spectral details

The IR (KBr) spectrum of (2-methyl-5-nitro-4-phenylazoimidazole-1-yl) - acetic acid-N-(4-phenylthiazol-2-yl)hydrazide (phe) exhibited absorption bands at 3210 cm⁻¹ (C = O str), 1526 cm⁻¹ (C = N str). The data is given below.

IR spectral data (ν in cm⁻¹):

phe: NH 3210, CH 2942, C=O 1672, C=N 1526, N=N

1612, N=O $\begin{bmatrix} 1500 \\ 1325 \end{bmatrix}$.

p-hp: NH 3230, CH 2956, C=O 1687, C=N 1546, N=N

1612, N=O $\begin{bmatrix} 1500 \\ 1329 \end{bmatrix}$.

p-np: NH 3240, CH 2960, C=O 1700, C=N 1540, N=N

1612, N=O $\begin{bmatrix} 1500 \\ 1325 \end{bmatrix}$.

p-cp: NH 3202, CH 2940, C=O 1667, C=N 1528, N=N

1612, N=O $\begin{bmatrix} 1500 \\ 1327 \end{bmatrix}$.

p-ps: NH 3256, CH 2921, C=O 1669, C=N 1539, N=N

1612, N=O $\begin{bmatrix} 1500 \\ 1325 \end{bmatrix}$, sydnone C=O str 1719.

¹HNMR spectral details

The ¹HNMR (200MHz) spectrum of (2-methyl-5-nitro-4-phenylazo-imidazol-1-yl) – acetic acid N-(4-phenylthiazol-2-yl)-hydrazide (phe) in CDCl₃ + DMSO-d₆ showed signals at δ2.30 (s, 3H, CH₃), δ7.1 (s, 1H, ArNH), δ6.5 – 6.70 (m, 5H, Ar-H), δ 7.12 – 7.36 (m, 5H, Ar-H), δ 9.2 (s, 1H, N-NH). The data is given below.

¹HNMR spectral data (δ ppm): phe: 2.30 (s, 3H, CH₃), 4.65 (s, 2H, N-CH₂-CO), 10.40 (s, 1H, CO - NH), 9.70 (s, 2H, NH-N-NH), 7.23 (s, 1H, thiazole-4H), 6.9 – 7.1 (m, 5H, Ar-H), 7.2 – 7.3 (m, 5H, Ar-H).

p-hp: 2.25 (s, 3H, CH₃), 7.90 (s, 1H, imidazole – 4H), 4.66 (s, 2H, N-CH₂-CO), 10.45 (s, 1H, CO-NH), 8.9 (s, 2H, NH – NH), 7.3 (s, 1H, thiazole – 4H), 6.9 – 7.10 (m, 5H, Ar – H), 7.3 (d, 2H, Ar – H), 7.4 (d, 2H, Ar – H), 4.3 (s, 1H, OH).

p-np: 2.30 (s, 3H, CH₃), 4.70 (s, 2H, N – CH₂ – CO), 10.35 (s, 1H, CO – NH), 9.8 (s, 2H, N – NH), 7.23 (s, 1H, thiazole – 4H), 6.9 – 7.1 (m, 5H, Ar – H), 7.3 (d, 2H, Ar – H), 7.45 (d, 2H, Ar – H).

p-cp: 2.38 (s, 3H, CH₃), 4.95 (s, 2H, NCH₂CO), 7.49 (d, 2H, *o*-protons of *p*-chlorophenyl), 7.70 (d, 2H, *m*-protons of *p*-chlorophenyl), 7.27 (s, 1H, thiazole – 4H), 9.69 (s, H, NH), 10.71 (s, H, CONH), 6.8-7.1 (m, 5H, Ar – H).

p-ps: 2.27 (s, 3H, CH₃), 4.66 (s, 2H, N-CH₂-CO), 7.61 – 7.81 (m, 5H, Ar – H), 7.26 (s, 1H, thiazole – 4H), 7.98 (s, 1H, imidazole – 4H), 9.85 (s, 1H, NH), 10.48 (s, 1H, CONH), 6.8 – 7.1 (m, 5H, Ar – H).

p-ts: 2.11 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 4.66 (s, 2H, N-CH₂-CO), 10.38 (s, 1H, CO-NH), 9.75 (s, 1H, N-NH) 7.25 (s, 1H, thiazole-4H), 6.8-7.1 (m, 5H, Ar-H), 7.2 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H), 7.94 (s, 1H, imidazole-4H).

Antibacterial Activity Studies

The antibacterial activity of the newly synthesized compounds was assessed by cup-plate method.¹¹

The newly synthesized thiazole derivatives 3 were screened for antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Staphylococcus aureus*. Among the compounds tested, the compound *p*-t showed more antibacterial activity than that of the standard. *p*-hp and *p*-as showed considerable antibacterial activity. The antifungal activity studies were carried out against *Candida albicans*, *Aspergillus flavus*, *Aspergillus fumigates* and *Trichophyton rubrum*. Among the compounds tested, *p*-t showed higher activity than that of the standard while *p*-hp and *p*-as showed considerable antifungal activity. The results are present in Table 1.

Table 1. *Details of antimicrobial studies of novel thiazoles 3.

Compound	Antibacterial activity (diameter of zone inhibition in mm)				Antifungal activity (diameter of zone inhibition in mm)			
	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Klebsiella pneumonia</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i>	<i>Aspergillus flavus</i>	<i>Aspergillus fumigatus</i>	<i>Trichophyton rubrum</i>
<i>p</i> -t	23	25	25	26	22	26	24	22
<i>p</i> -hp	14	17	19	16	15	16	20	18
<i>p</i> -np	---	---	---	---	10	---	---	---
<i>p</i> -cp	---	14	---	---	---	12	---	09
<i>p</i> -ts	---	14	---	---	---	14	---	---
<i>p</i> -as	12	16	15	14	13	08	11	11
Ciprofloxacin (Std)	20	22	22	20	---	---	---	---
Ciclopiroxolamine (Std)	---	---	---	---	20	22	22	20
Solvent control (DMF)	---	---	---	---	---	---	---	---

*'---' indicates that the compound is inactive.

Conclusion

The newly synthesized compounds containing thiazole and imidazole moieties 3 were characterized by elemental analysis and spectral analysis. The antimicrobial activity all compounds were evaluated and reported. Among the compounds tested, *p*-np, *p*-cp and *p*-ts showed antibacterial activity against certain microorganism only whereas *p*-t, *p*-hp and *p*-as showed considerable antibacterial activity against all the bacteria and fungi tested.

Conflict of Interest

The authors report no conflicts of interest in this work.

References

- Luzina EL, Popov AV. Synthesis and anticancer activity of N-bis(trifluoromethyl)alkyl-N'-thiazolyl and N-bis(trifluoromethyl)alkyl-N'-benzothiazolyl ureas. *Eur J Med Chem* 2009;44(12):4944-53.
- Wagle D, Vasan S, Egan JJ, inventors; Alteon Inc., assignee. Thiazole, imidazole and oxazole compounds and treatments of disorders associated with protein aging. USA patent 6960605. 2005 Nov 1.
- Bharti SK, Nath G, Tilak R, Singh SK. Synthesis, anti-bacterial and anti-fungal activities of some

- novel schiff bases containing 2,4-disubstituted thiazole ring. *Eur J Med Chem* 2010;45(2):651-60.
- Rawal RK, Tripathi R, Katti SB, Pannecouque C, De Clercq E. Design, synthesis, and evaluation of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones as anti-HIV agents. *Bioorg Med Chem* 2007;15(4):1725-31.
 - Dawane BS, Konda SG, Mandawad GG, Shaikh BM. Poly(ethylene glycol) (PEG-400) as an alternative reaction solvent for the synthesis of some new 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl)-2-pyrazolines and their in vitro antimicrobial evaluation. *Eur J Med Chem* 2010;45(1):387-92.
 - Sharma D, Narasimhan B, Kumar P, Judge V, Narang R, De Clercq E, et al. Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives. *Eur J Med Chem* 2009;44(6):2347-53.
 - Krimer MZ, Makaev FZ, Styngach EP, Koretskii AG, Pogrebnoi SI, Kochug AI. Synthesis of substituted 2-amino-1-arylidenaminoimidazoles and 1-arylidenaminoimidazo[1,2-a]imidazoles. *Chem Heterocycl Compd* 1996; 32(9):1035-9.
 - Li WT, Hwang DR, Song JS, Chen CP, Chuu JJ, Hu CB, et al. Synthesis and biological activities of 2-amino-1-arylidenamino imidazoles as orally active anticancer agents. *J Med Chem* 2010;53(6):2409-17.
 - Ganguly S, Vithlani VV, Kesharwani AK, Kuhu R, Baskar L, Mitramazumder P, et al. Synthesis, antibacterial and potential anti-HIV activity of some novel imidazole analogs. *Acta Pharm* 2011;61(2):187-201.
 - Reddy MD, Guru Prasad AR, Spoorthy Y, Ravindranath L. Synthesis, characterization and antimicrobial activity of certain novel aryl hydrazone pyrazoline-5-ones containing thiazole moiety. *Adv Pharm Bull* 2013;3(1): 153-9.
 - Seelay HW, Van Demark PJ. *Microbes in Action, A laboratory Manual in Microbiology*. 2nd ed. Bombay: D.B. Taraporewala Sons and Co; 1975.