



Scholars Research Library

Der Pharma Chemica, 2012, 4(6):2368-2372

(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis, characterization and antimicrobial potential study of substituted bis-[1,2,4]-dithiazolidine derivatives

Pradip P. Deohate

P. G. Department of Chemistry, Shri Radhakisan Laxminarayan Toshniwal College of Science, Akola-444001, India

ABSTRACT

A facile synthesis of pharmacologically important 4-{4-[4-(5-arylimino-3-phenylimino-[1,2,4]-dithiazolidin-4-yl)-3-nitro-benzyl]-2-nitro-phenyl}-5-arylimino-3-phenylimino-[1,2,4]-dithiazolidines have been achieved by the interaction of 1-{4-[4-(3-aryl thiocarbamido)-3-nitro-benzyl]-2-nitro-phenyl}-3-aryl thiocarbamides with N-phenyl-S-chloro isothiocarbamoyl chloride followed by the basification with dilute ammonium hydroxide solution. Initially 1-{4-[4-(3-aryl thiocarbamido)-3-nitro-benzyl]-2-nitro-phenyl}-3-aryl thiocarbamides were prepared by the interaction of different aryl isothiocyanates with 4,4'-methylene-bis-(2-nitro aniline). The latter was obtained by treating the mixture of 2-nitro aniline and concentrated hydrochloric acid with 3% aqueous formaldehyde followed by neutralization with sodium hydroxide. The structures of synthesized compounds have been established on the basis of chemical transformation, elemental analysis, equivalent weight determination and IR, ¹H-NMR spectral studies. The title compounds have been assayed for their biological activity against gram-positive as well as gram-negative microorganisms.

Keywords: Synthesis, characterization, antimicrobial potential, bis-[1,2,4]-dithiazolidines.

INTRODUCTION

Synthesis and biological evaluation of various pharmacologically important [1,2,4]-dithiazolidines have been reported earlier [1-7]. The literature has been enriched with progressive findings about the synthesis of [1,2,4]-dithiazolidines by using the reagent N-phenyl-S-chloro isothiocarbamoyl chloride and by oxidative cyclization using bromine and iodine [8-10]. [1,2,4]-dithiazolidines have been found to have potent anti-inflammatory and antitumor properties as they down regulate the NF-kB transcription factor [11]. Various substituted [1,2,4]-dithiazolidines are known for their medicinal activities particularly as antibacterial and antifungal agents [12-14].

In view of the utility of N-phenyl-S-chloro isothiocarbamoyl chloride in the synthesis of nitrogen and sulphur containing heterocyclic compounds and as a part of our research towards the development of efficient methodologies for the synthesis of heterocyclic compounds, we report herein the synthesis, characterization and antimicrobial potential study of substituted bis-[1,2,4]-dithiazolidine derivatives.

MATERIALS AND METHODS

The melting points of all synthesized compounds were recorded using the digital melting point apparatus (Veego,

VMP-D) and are uncorrected. Chemicals used were of AR grade. ¹H NMR spectra were recorded with TMS as internal standard using CDCl₃ and DMSO-*d*₆ as solvents. IR spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000-400 cm⁻¹ in nujol mull and as KBr pellete. Purity of the compounds was checked on silica gel-G plates by TLC.

The parent compound 4,4'-methylene-bis-(2-nitro aniline) (**1**) was prepared by dissolving 2-nitro aniline (0.01 mole) in distilled water (15 mL) and 36.5% hydrochloric acid (2.5 mL) at 50°C. The mixture was then treated with 3% aqueous formaldehyde (3.5 mL) at 20°C with stirring for 1 hr. and neutralized with 10% sodium hydroxide solution, yellow precipitate was obtained. It was washed with hot water and crystallized from acetic acid, (**1**) (80%), m.p. 208°C. (Found: C, 53.67; H, 4.02; N, 19.11. Calcd. for C₁₃H₁₂N₄O₄: C, 54.16; H, 4.16; N, 19.44%).

Synthesis of 1-{2-nitro-4-[3-nitro-4-(3-phenyl thiocarbamido)-benzyl]-phenyl}-3-phenyl thiocarbamide (**2a**).

A mixture of 4,4'-methylene-bis-(2-nitro aniline) (**1**) (0.01 mole) and phenyl isothiocyanate (0.02 mole) in chloroform (15 mL) was refluxed for 1.5 hr. Then chloroform was distilled off, a solid mass was obtained. It was washed with petroleum ether (60-80°C) and crystallized from ethanol to yield 1-{2-nitro-4-[3-nitro-4-(3-phenyl thiocarbamido)-benzyl]-phenyl}-3-phenyl thiocarbamide (**2a**), (75%), m.p. 56°C. (Found: N, 14.63; S, 11.23. Calcd. for C₂₇H₂₂N₆O₄S₂: N, 15.05; S, 11.46%); ν_{\max} 3448, 3378 (NH), 1618 (C=N), 1521 (N=O), 1310 (C-N), 1234 cm⁻¹ (C=S); δ (CDCl₃+DMSO-*d*₆) 6.58-7.24 (16H, m, Ar-H), 4.52 (4H, s, NH), 2.69 (2H, s, CH₂) [15,16]. This reaction was extended to synthesize other compounds (**2b-g**): (**2b**) (75%), m.p. 69°C (Found: N, 14.12; S, 10.83. Calcd. for C₂₉H₂₆N₆O₄S₂: N, 14.33; S, 10.92); (**2c**) (70%), m.p. 84°C (Found: N, 14.29; S, 10.88. Calcd. for C₂₉H₂₆N₆O₄S₂: N, 14.33; S, 10.92); (**2d**) (78%), m.p. 60°C (Found: N, 14.37; S, 10.96. Calcd. for C₂₉H₂₆N₆O₄S₂: N, 14.33; S, 10.92); (**2e**) (72%), m.p. 91°C (Found: N, 13.32; S, 10.09. Calcd. for C₂₇H₂₀N₆O₄S₂Cl₂: N, 13.39; S, 10.20%); (**2f**) (68%), m.p. 64°C (Found: N, 13.24; S, 10.17. Calcd. for C₂₇H₂₀N₆O₄S₂Cl₂: N, 13.39; S, 10.20%); (**2g**) (70%), m.p. 78°C (Found: N, 13.40; S, 10.13. Calcd. for C₂₇H₂₀N₆O₄S₂Cl₂: N, 13.39; S, 10.20%).

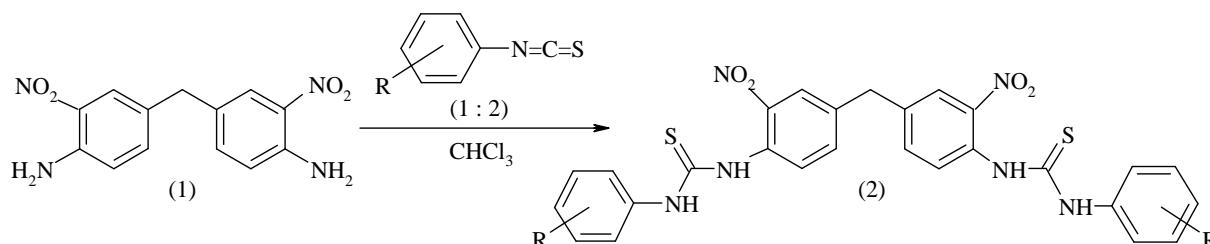
Synthesis of 4-{4-[4-(3,5-bis-phenylimino-[1,2,4]-dithiazolidin-4-yl)-3-nitro-benzyl]-2-nitro-phenyl}-3,5-bis-phenylimino-[1,2,4]-dithiazolidine (**3a**).

The compound 1-{2-nitro-4-[3-nitro-4-(3-phenyl thiocarbamido)-benzyl]-phenyl}-3-phenyl thiocarbamide (**2a**) (0.01 mole) was suspended in chloroform (15 mL). To this a solution of *N*-phenyl-*S*-chloro isothiocarbamoyl chloride (0.02 mole) in chloroform was added. The reaction mixture was refluxed on water bath for 2 hr. The evolution of hydrogen chloride gas was observed. Then chloroform was distilled off, a sticky mass was obtained. It was repeatedly washed with petroleum ether (60-80°C) followed by the addition of ethanol. It was acidic to litmus and on determination of equivalent weight found be 4-[4-[4-(3,5-bis-phenylimino-[1,2,4]-dithiazolidin-4-yl)-3-nitro-benzyl]-2-nitro-phenyl]-3,5-bis-phenylimino-[1,2,4]-dithiazolidine dihydrochloride, m.p. 78°C. It on basification with dilute ammonium hydroxide solution afforded a free base. It was crystallized from ethanol and identified as 4-[4-[4-(3,5-bis-phenylimino-[1,2,4]-dithiazolidin-4-yl)-3-nitro-benzyl]-2-nitro-phenyl]-3,5-bis-phenylimino-[1,2,4]-dithiazolidine (**3a**) (73%), m.p. 170°C. (Found: C, 58.88; H, 3.32; N, 12.79; S, 15.38. Calcd. for C₄₁H₂₈N₈O₄S₄: C, 59.70; H, 3.39; N, 13.59; S, 15.53%); ν_{\max} 1629 (C=N), 1500 (N=O), 1346 (C-N), 740 (C-S), 414 cm⁻¹ (C-S); δ (CDCl₃+DMSO-*d*₆) 6.57-8.22 (26H, m, Ar-H), 2.53 (2H, s, CH₂). This reaction was extended to synthesize other compounds (**3b-g**): (**3b**) (72%), m.p. 165°C (Found: C, 59.11; H, 3.14; N, 13.21; S, 14.89. Calcd. for C₄₃H₃₂N₈O₄S₄: C, 60.56; H, 3.75; N, 13.14; S, 15.02%); ν_{\max} 1342 (C=N), 1512 (N=O), 1326 (C-N), 726 (C-S), 422 cm⁻¹ (C-S); δ (CDCl₃+DMSO-*d*₆) 6.72-8.04 (24H, m, Ar-H), 2.61 (2H, s, CH₂), 2.31 (6H, s, Ar-CH₃); (**3c**) (80%), m.p. 217°C (Found: C, 60.87; H, 3.70; N, 13.18; S, 14.75. Calcd. for C₄₃H₃₂N₈O₄S₄: C, 60.56; H, 3.75; N, 13.14; S, 15.02%); (**3d**) (82%), m.p. 160°C (Found: C, 60.21; H, 3.66; N, 12.98; S, 15.00. Calcd. for C₄₃H₃₂N₈O₄S₄: C, 60.56; H, 3.75; N, 13.14; S, 15.02%); (**3e**) (78%), m.p. 133°C (Found: C, 54.63; H, 2.82; N, 12.58; S, 14.02. Calcd. for C₄₁H₂₆N₈O₄S₄Cl₂: C, 55.09; H, 2.91; N, 12.54; S, 14.33%); (**3f**) (75%), m.p. 154°C (Found: C, 55.13; H, 2.99; N, 12.45; S, 14.21. Calcd. for C₄₁H₂₆N₈O₄S₄Cl₂: C, 55.09; H, 2.91; N, 12.54; S, 14.33%); (**3g**) (75%), m.p. 110°C (Found: C, 55.03; H, 2.89; N, 12.22; S, 14.28. Calcd. for C₄₁H₂₆N₈O₄S₄Cl₂: C, 55.09; H, 2.91; N, 12.54; S, 14.33%).

RESULTS AND DISCUSSION

The parent compound 4,4'-methylene-bis-(2-nitro aniline) (**1**) was prepared by dissolving 2-nitro aniline (0.01 mole) in distilled water (15 mL) and 36.5% hydrochloric acid (2.5 mL) at 50°C. The mixture was then treated with 3% aqueous formaldehyde (3.5 mL) at 20°C with stirring for 1 hr. and neutralized with 10% sodium hydroxide. It was transformed into 1-{4-[4-(3-aryl thiocarbamido)-3-nitro-benzyl]-2-nitro-phenyl}-3-aryl thiocarbamides (**2a-g**) by

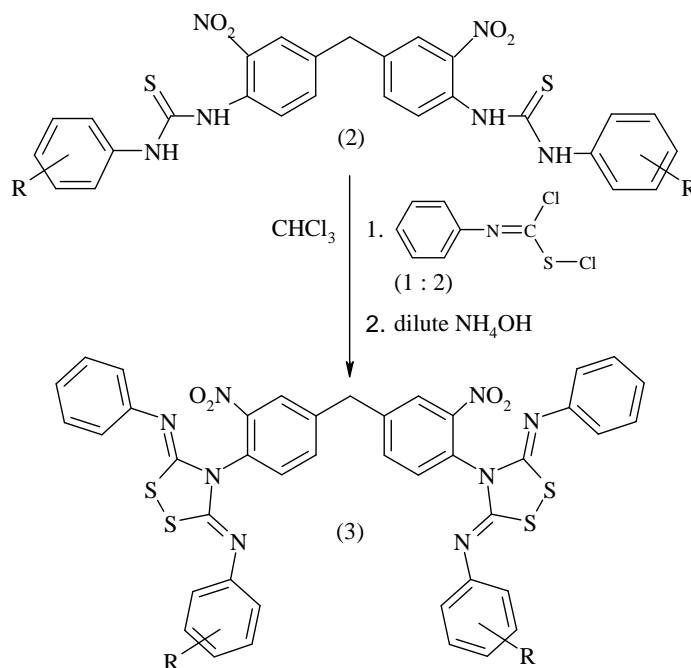
condensing it with different aryl isothiocyanates (0.02 mole) in refluxing chloroform medium for 1.5 hr. (Scheme 1).



Where, 2a-g : R = H, 2-CH₃, 3-CH₃, 4-CH₃, 2-Cl, 3-Cl, 4-Cl

(Scheme 1)

The compounds (2a-g) were then reacted with N-phenyl-S-chloro isothiocarbamoyl chloride (0.02 mole) in boiling chloroform medium over a water bath for 2 hr. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. Cooling the reaction mixture and distilling off chloroform afforded sticky masses, which on washing with petroleum ether gave granular solids. These were acidic to litmus and on titrimetric analysis identified as 4-{4-[4-(5-arylimino-3-phenylimino-[1,2,4]-dithiazolidin-4-yl)-3-nitro-benzyl]-2-nitro-phenyl}-5-arylimino-3-phenylimino-[1,2,4]-dithiazolidine dihydrochlorides. These on basification with dilute ammonium hydroxide solution afforded free bases (3a-g) (Scheme 2).



Where, 2,3a-g : R = H, 2-CH₃, 3-CH₃, 4-CH₃, 2-Cl, 3-Cl, 4-Cl

(Scheme 2)

Antimicrobial activity

The synthesized compounds (3a-g) were screened for their antibacterial activity using cup plate diffusion method [17,18]. The bacterial organisms used included both gram-positive as well as gram-negative strains like *E. coli*, *S. aureus*, *S. typhi* and *B. subtilis*. Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU ml⁻¹ and each well (diameter 10 mm) was loaded with 0.1 ml of test compound solution (1000 µg ml⁻¹) in DMF, so that concentration of each test compound was 100 µg ml⁻¹. The zones of inhibition were recorded after incubation for 24 hr. at 37°C, using Vernier caliper. Inhibition zone record of the compounds clearly indicated that (3b), (3c), (3e) and

(3f) were highly active against *E. coli*, *S. typhi* and moderately active against *B. subtilis*. Majority of the compounds were found inactive against *S. aureus* (Table 1).

To determine minimum inhibitory concentration (MIC), the serial dilution technique [19]—was followed using nutrient broth medium. The MIC values of compounds (3b) and (3e) were determined against *S. typhi*, which were found to be 60 and 65 $\mu\text{g ml}^{-1}$ respectively.

Screening of these compounds (3a-g) having the concentration 1%, for antifungal activity using paper disc method [20] showed that (3b) and (3e) were highly active against *A. niger*, whereas other compounds showed low to moderate activity. The zones of inhibition were recorded after incubation for 48 hr. at 37°C (Table 1).

Table 1 - Antibacterial and antifungal activity of compounds 3a-g.

Compounds	Antibacterial activity				Antifungal activity
	<i>E. coli</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>B. subtilis</i>	<i>A. niger</i>
					(Conc. 1%)
3a	+	+	-	+	-
3b	+++	-	+++	++	+++
3c	+++	-	+++	++	++
3d	+	-	++	+	+
3e	+++	+	+++	++	+++
3f	+++	+	+++	++	+
3g	++	-	+	-	++

(-) : Inactive (12 mm and less)

(++) : Moderately active (17-20 mm)

(+) : Weakly active (13-16 mm)

(+++): Highly active (21 mm and above)

CONCLUSION

In present work, synthesis of 4-{4-[4-(5-arylimino-3-phenylimino-[1,2,4]-dithiazolidin-4-yl)-3-nitro-benzyl]-2-nitro-phenyl}-5-arylimino-3-phenylimino-[1,2,4]-dithiazolidines (3a-g) have been reported. The methods applied for the syntheses are quite simple, efficient and completed within a short period of time with high percent yield. Antimicrobial potential study of these compounds revealed that, most of the compounds have better antibacterial and antifungal activities.

Acknowledgement

Thanks are due to Director, R.S.I.C., Central Drug Research Institute, Chandigarh and Lucknow for providing analytical and spectral data. Author is thankful to Mr. Umer S. Khan and Vaishali R. Patil for their generous help during the work and also to Dr. V. D. Nanoty, Principal, Shri Radhakisan Laxminarayan Toshniwal College of Science, Akola for providing necessary facilities.

REFERENCES

- [1] R. M. Kharate, P. P. Deohate, B. N. Berad, *Int. J. Chem. Sci.*, **2009**, 7, 2843.
- [2] P. T. Agrawal, S. P. Deshmukh, *J. Indian Chem. Soc.*, **2009**, 86, 645.
- [3] R. Sing, V. K. Verma, *Indian J. Chem.*, **1977**, 15(B), 192.
- [4] B. N. Singh, *Acta Ciencia Indica (Chem.)*, **1998**, 24C, 113.
- [5] P. K. Singh, *Indian J. Hetero. Chem.*, **2001**, 10, 311.
- [6] A. V. Yadgire, D. L. Barate, S. P. Deshmukh, *Rasayan J. Chem.*, **2011**, 4(4), 780.
- [7] S. M. Thorat, J. P. Dhumale, S. P. Deshmukh, *Indian J. Hetero. Chem.*, **2011**, 20, 277.
- [8] P. P. Deohate, J. P. Deohate, B. N. Berad, *Asian J. Chem.*, **2004**, 16(1), 255.
- [9] M. G. Dhonde, D. V. Tale, S. P. Deshmukh, *Indian J. Chem.*, **2006**, 45(B), 829.
- [10] A. J. Barany, R. P. Hammer, R. B. Merrifield, G. Barany, *J. Am. Chem. Soc.*, **2005**, 127, 508.
- [11] P. Manna, R. Singh, K. K. Narang, S. K. Manna, *Indian J. Chem.*, **2005**, 44B, 1880.

- [12] M. K. Burghate, B. N. Berad, *Asian J. Chem.*, **2007**, 19(5), 3601.
- [13] P. P. Deohate, B. N. Berad, *Chemistry: An Indian J.*, **2006**, 1(6), 447.
- [14] P. T. Agrawal, S. P. Deshmukh, *Int. J. Chem. Sci.*, **2010**, 8(2), 969.
- [15] N. B. Colthup, L. H. Dally, S. E. Wiberly, *Introduction to Infrared and Raman Spectroscopy*, Academic Press, New York, **1964**.
- [16] R. M. Silverstein, G. C. Bassler, T. C. Morrill, *Spectrometric Identification of organic compounds*, 4th Edn., John Wiley & Sons, New York, **1981**.
- [17] A. L. Barry, *The Antimicrobial Susceptibility Test; Principle and Practices*, Illus Lea & Fibiger, Philadelphia, Pa, USA, 180.
- [18] F. Cavanagh, *Analytical Microbiology*, Academic Press, New York, **1963**, 126.
- [19] C. Nishina, N. Enoki, S. Tawata, A. Mori, K. Kobayashi, Fukushima, *Agric. Bio. Chem.*, **1987**, 51, 139.
- [20] R. Ananthanarayan, G. K. Jagram Pancka, *Text Book of Microbiology*, 4th Edn., Orient Longmans, **1990**.