ELSEVIER

Il Farmaco 57 (2002) 569–572

IL FARMACO

www.elsevier.com/locate/farmac

Synthesis and antimicrobial activity of some pyridinyliminothiazoline derivatives

G. Turan-Zitouni*, D.M. Sıvacı, Z.A. Kaplancıklı, A. Özdemir

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Anadolu, 26470 Eskişehir, Turkey

Received 24 January 2002; accepted 27 January 2002

Abstract

The synthesis of some pyridinyliminothiazoline derivatives starting from *N*-pyridine-*N*′-phenyl thiourea and α-halogenoacetophenones is described. The chemical structures of the compounds were elucidated. The prepared compounds were tested for antimicrobial activity.

Keywords: Pyridinyliminothiazoline; Antimicrobial activity

1. Introduction

Thiazoline derivatives present some interesting biological activities. Among them the most important effects are; anticonvulsant [1,2], convulsant [2], local anesthesic [3], fungicide [4], bactericide [5,6], herbicide [6], insecticide [7], antituberculostatic [8], cardiotonic [9], acaricid [6,7], antiulcer [10] and antineoplastic [11] activities.

Some pyridine derivatives have been reported to possess analgesic [12], antibacterial [13], antituberculostatic [14], uriner antiseptic [15], anesthesic [16], Vit B_6 [17], analeptic [18] activities.

Therefore, we aimed the synthesis of new pyridinyliminothiazoline derivatives.

2. Chemistry

In this work; *N*-pyridinyl-*N*′-phenyl thioureas (**1**) were prepared for the first time in accordance with the method described in literature [19].

The reaction of thiourea (**1** or **3**) with α-halogenoacetophenone gave the pyridinyliminothiazoline derivatives (**2a**–**g**, **4**) (Scheme 1).

Analytical and spectral data (IR, ^{1}H NMR, MS-(FAB$^+$)) confirmed the structure of all compounds.

3. Experimental

3.1. Chemistry

M.p.s were determined by using a Gallenkamp apparatus. Spectroscopic data were recorded by the following instruments. IR: Shimadzu 435 spectrophotometer; ^{1}H NMR: Bruker 400 MHz spectrometer; MS: VG Quattro mass spectrometer.

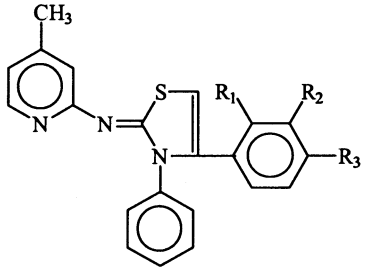
3.1.1. General procedure for the synthesis of the compounds

*3.1.1.1. Preparation of N-(4-methyl-2-pyridinyl)-N′-phenyl thiourea derivatives (**1**) and N-(3-pyridinylmethyl)-N′-phenyl thiourea (**3**).* A mixture of aminopyridine (0.1 mol) and phenylisothiocyanate (0.1 mol) in EtOH was refluxed for 2 h. The solid separated upon cooling was filtered, dried and recrystallized.

*3.1.1.2. Preparation of pyridinyliminothiazoline derivatives (**2a**–**g**, **4**).* Thiourea (**1** or **3**) (0.001 mol) and appropriate α-halogenoacetophenone (0.001 mol) in absolute EtOH was refluxed for 4–5 h. The solid separated was filtered and recrystallized (Table 1).

* Corresponding author
E-mail address: gzitouni@anadolu.edu.tr (G. Turan-Zitouni).

0014-827X/02/$ - see front matter
PII: S0014-827X(02)01250-8

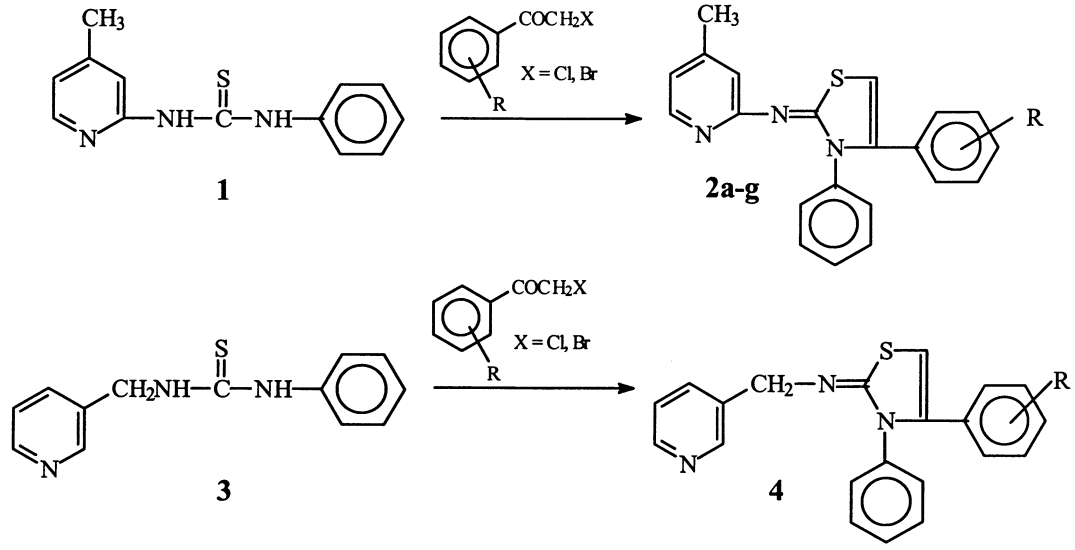


2a: IR (KBr) ν_{maks} (cm^{-1}): 1637 (C=N), 1592 (C=C aromatic). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.4 (3H, s, CH_3), 7.0–7.6 (13H, m, aromatic protons), 8.2 (1H, s, thiazoline 5-H). MS (ES^+): m/z: 344.2 [$M+1$].

2b: IR (KBr) ν_{maks} (cm^{-1}): 1625 (C=N), 1587 (C=C aromatic). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.3 (3H, s, CH_3), 6.8–8.0 (12H, m, aromatic protons), 8.2 (1H, s, thiazoline 5-H). MS (ES^+): m/z: 423 [$M+1$].

2c: IR (KBr) ν_{maks} (cm^{-1}): 1635 (C=N), 1587 (C=C aromatic) ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.4 (3H, s, CH_3), 3.7 (3H, s, OCH_3), 6.8 (2H, d ($J=8.7$ Hz), phenyl-2′-H, 6′-H), 7.1 (2H, d, $J=8.65$ Hz, phenyl 3′-H, 5′-H), 7.1–7.5 (8H, m, aromatic protons), 8.3 (1H, s, thiazoline 5-H). MS (ES^+): m/z: 374 [$M+1$].

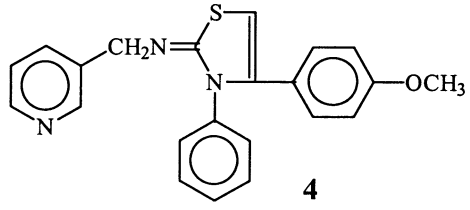
2d: IR (KBr) ν_{maks} (cm^{-1}): 1625 (C=N), 1587 (C=C aromatic). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.4 (3H, s, CH_3), 7.2 (2H, d, $J=6.77$ Hz, phenyl 2′-H, 6′-H), 7.5 (2H, d ($J=6.79$ Hz), phenyl 3′-H, 5′-H), 7.0–7.6 (8H, m, aromatic protons), 8.2 (1H, s, thiazoline 5-H). MS (ES^+): m/z: 378.2 [$M+1$].



Scheme 1.

Table 1

Comp.	R_1	R_2	R_3	M.p. (°C)	Yield (%)	Molecular formula
2a	H	H	H	298	85	$C_{21}H_{17}N_3S$
2b	Br	H	H	142	78	$C_{21}H_{16}BrN_3S$
2c	H	H	OCH_3	220	83	$C_{22}H_{19}N_3OS$
2d	H	H	Cl	210	81	$C_{21}H_{16}ClN_3S$
2e	H	Cl	Cl	197	83	$C_{21}H_{15}Cl_2N_3S$
2f	OH	H	H	162	79	$C_{21}H_{17}N_3OS$
2g	CH_3	H	OH	227	88	$C_{22}H_{19}N_3OS$



M.P.(°C): 118
Yield(%): 80
Mol. Formula: $C_{22}H_{19}N_3OS$

Table 2
Antimicrobial activities of the compounds

Microorganizm	Strain	4	2a	2c	2d	2e	Control comp. 1	Control comp. 2
Escherichia coli	ATCC 25922	31.25	62.5	62.5	31.25	31.25	62.5	
Staphylococcus aureus	ATCC 6538	62.5	62.5	31.25	31.25	62.5	7.81	
Pseudomonas aeruginosa	ATCC 27853	62.5	125	125	250	62.5	250	
Entereobacter aerogenes	NRRL 3567	250	125	62.5	31.25	31.25	62.5	
Proteus vulgaris	NRRL 123	31.25	62.5	31.25	250	31.25	31.25	
Salmonella typhimurium	NRRL 4420	125	62.5	125	250	31.25	62.5	
Candida albicans	O.G.Ü. Tıp	15.62	62.5	31.25	31.25	15.62		125

*MIC (μg/ml); Control comp. 1, chloramphenicole; Control comp. 2, ketoconazole

2e: IR (KBr) ν_{maks} (cm^{-1}): 1631 (C=N), 1565 (C=C aromatic). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.4 (3H, s, CH_3), 7.0–7.6 (11H, m, aromatic protons), 8.2 (1H, s, thiazoline 5-H). MS (ES^+): m/z: 412.2 [$M+1$].

2f: IR (KBr) ν_{maks} (cm^{-1}): 1635 (C=N), 1585 (C=C aromatic), 3490 (O–H). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.3 (3H, s, CH_3), 6.8–8.1 (12H, m, aromatic protons), 8.2 (1H, s, thiazoline 5-H), 11.3 (1H, s, OH). MS (ES^+): m/z: 360 [$M+1$].

2g: IR (KBr) ν_{maks} (cm^{-1}): 1638 (C=N), 1585 (C=C aromatic), 3472 (O–H). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.1 (3H, s, CH_3), 2.3 (3H, s, CH_3), 6.9–8.0 (11H, m, aromatic protons), 8.2 (1H, s, thiazoline 5-H), 11.5 (1H, s, OH). MS (ES^+): m/z: 374 [$M+1$].

4: IR (KBr) ν_{maks} (cm^{-1}): 1642 (C=N), 1556 (C=C aromatic). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 3.3 (3H, s, OCH_3), 4.8 (2H, s, CH_2), 7.1–8.6 (13H, m, aromatic protons), 8.3 (1H, s, thiazoline 5-H). MS (ES^+): m/z: 374 [$M+1$].

3.2. Biological assay

Antibacterial activities of compounds were determined using the tube dilution technique [20]. MIC values were calculated as μg/ml (Table 2). Standard bacteria strain used were: *Esherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 27853), *Proteus vulgaris* (NRRL B-123), *Enterobacter aerogenes* (NRRL 3567), *Salmonella typhimurium* (NRRL B-4420) and *Candida albicans* (University of Osmangazi, Faculty of Medicine, Eskişehir).

4. Results and discussion

Scheme 1 illustrated the way used for the preparation of target compounds. As a starting material, aminopyridine and phenylisothiocyanates were used to produce thiazolines.

The structure of the compounds was elucidated by IR, ^1H NMR, MASS spectral data and elemental analysis.

IR spectra of all compounds C=N and C=C bands were observed at about 1635 and 1580 cm^{-1}, respectively.

In the NMR spectra of 3-methyliminopyridine derivatives the protons at methylene group resonated as a singlet of 4.8 ppm, while the aromatic protons signal appeared as multipled at 7.1–8.6 ppm.

In the NMR spectra of Pyridin-2-imino derivatives the protons of methyl group in the pyridine were observed at 2.3–2.4 ppm.

The proton of Thiazoline (C_5) was observed at 8.2–8.3 ppm.

An important antifungal activity was observed only for compounds **2e** (15.62 μg/ml) and **4** (15.62 μg/ml) against *C. albicans*. The other compounds showed MIC values >100 μg/ml against all the tested microbial strains.

References

[1] N. Ergenç, G. Çapan, Synthesis and anticonvulsant activity of new 4-thiazolidone and 4-thiazoline derivatives, Farmaco 49 (1994) 449–451.
[2] E. Goeres, A. Faehndrich, Convulsive and anticonvulsive action of aliphatic and alicyclic sulfonamides, Med. Ger. 20 (1968) 641–653.
[3] M. Engelmann, Synthesis of some 4-thiazolines from unsymmetrical thioureas and their fungicidal avtivity, US 2,027,030, January 7.
[4] B.C. Dash, B.B. Nandi, Synthesis of thiazoline compounds and the use of their mercurated derivatives as fungicides and bactericides, Nippon Noyaku Gakkaishi 3 (1978) 427–431.
[5] G.N. Mahapatra, Synthesis of thiazoline compounds and the use of their mercurated derivatives as fungicides and bactericides, J. Proc. Inst. Chemists (India) 31 (1959) 113–117.
[6] CIBA Ltd. Şti., Thiazolines., Belg. 627278, July 18, 1963; Swiss Appl. January 9, 1962, 33 pp.
[7] N.N. Mel'nikov, A.F. Grapov, Insecticide and acaricide, USSR 524339 (Cl A01N9/36), 05 May 1978, Appl. 2,087,260, 25 December 1974. From Otkrytiya, Izobret, Prom. Obraztsy, Tovarnye Znaki 55 17 (1978) 183–185.
[8] R.H. Mizzoni, P.C. Eisman, Some thiazolines and thiazolidinones with antituberculous activity, J. Am. Chem. Soc. 80 (1958) 3471–3475 Ciba Pharm. Products, Inc, Summit, NJ.
[9] A. Andreani, M. Rambaldi, Substituted 6-phenylimidazo[2,1-*b*]-thiazoles and thiazolines as potential cardiotonic agents, Eur. J. Med. Chem. —Chim. Ther. 19 (1984) 219–222.

[10] Y. Kiyotani, T. Yamaguchi, Preparation of thiazoles as antiulcer agents and liver-disease therapeutics, Jpn. Kokai Tokkyo Koho JP 63,203,672 [88,203,672] (Cl. C07D277/04). 23 August 1988, Appl. 87/35,705, 20 February 1987, 45 pp.
[11] M. Sakuta, T. Yoneda, M. Nishimura, Potent antitumor agents with low toxicity, Jpn. Kokai Tokkyo Koho JP 05 58,894 [93 58,894] (Cl. A61K31/425). 09 March 1993, Appl. 91/215,448, 27 August 1991; 26 pp.
[12] D.R. Jasinski, W.R. Martin, Dependence-producing properties of GPA-1657, profadol and propiram in man, Clin. Pharmacol. Ther. 12 (1971) 613–649.
[13] D. Liebermann, M. Moyeux, N. Rist, Preparation of new thioamides of pyridine with antitubercular activty, Compt. Rend. 242 (1956) 2409–2412.
[14] E.M. Bavin, B. James, E. Kay, The antibacterial activty of Mycobacterium tuberculosis of *o*-hydroxybenzalisonicotinoylhydrazone, J. Pharm. Pharmacol. 7 (1955) 1032–1037.
[15] M. Dohrn, P. Diedrich, Therapeutic azo derivatives of the heterocyclic series, June 7, See Ger. 543,288 (CA: 26, 2470).
[16] A.R. Johnston, The toxic effects of amines, J. Infectious Dis. 42 (1928) 473–484.
[17] E.T. Stiller, J.C. Keresztesy, The structure of Vitamin B_6, J. Am. Chem. Soc. 61 (1939) 1237–1239.
[18] C.H. Browning, J. Cohen, B.S. Ellingworth, Antiseptic action of the styrylpyridines and styrylquinolines, Br. Med. J. II (1923) 326–329.
[19] G. Vasilev, P. Ionova, Synthesis, and herbicidal and growth regulating activity of some *N*-alkyl- and *N′*-pyridylthioureas, Fiziol. Rast. (Sofia) 10 (1984) 40–49.
[20] E.W. Koneman, S.D. Allen, W.M. Janda, W.C. Winn, Color Atlas and Textbook of Diagnostic Microbiology, Lippincott-Raven Pub, Philadelphia, 1997, pp. 785–856.