Heteroatom Chemistry
Volume 17, Number 4, 2006

Preparation, Antimicrobial Activity, and Toxicity of 2-Amino-4-arylthiazole Derivatives

Pedro Morales-Bonilla,[1] Andrea Pérez-Cardeña,[1] Esther Quintero-Mármol,[1] José Luis Arias-Téllez,[2] and Gonzalo J. Mena-Rejón[1]

[1]*Facultad de Química, Universidad Autónoma de Yucatán, 41 No. 421 Col. Industrial, C.P. 97150, Mérida, Yucatán, México*

[2]*Facultad de Estudios Superiores-Cuautitlán, Universidad Nacional Autónoma de México, Cuautitlán Izcalli, C.P. 54700, Estado de México, México*

Received 27 April 2005; revised 12 September 2005

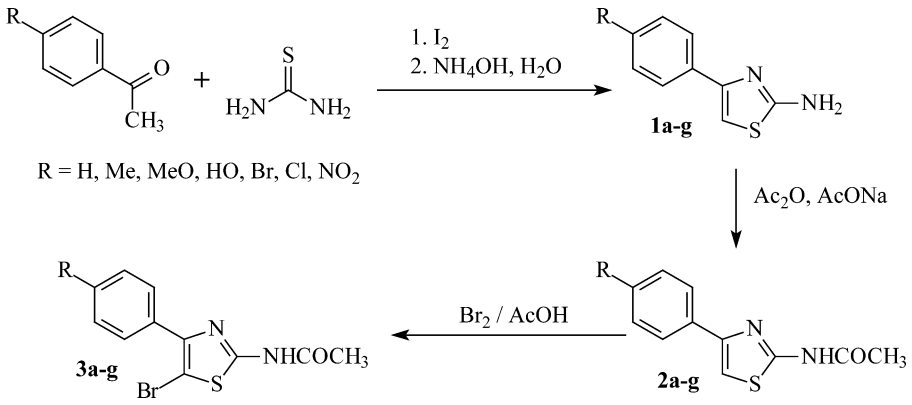
ABSTRACT: *Seven 2-amino-4-aryl-1,3-thiazoles (***1a–g***) and their corresponding 2-aminoacetyl (***2a–g***) and 2-aminoacetyl-5-bromo (***3a–g***) derivatives were synthesized and tested in vitro against 11 reference strains, three Gram-positive and four Gram-negative bacteria, two yeasts, and two moulds. Toxicity of the compounds was also evaluated using the brine shrimp test. Compounds* **1a, 1b, 1e–g**, *and* **3b** *showed moderate antimicrobial activity at different concentrations. The results indicated that acetylation of the amino group and bromination at position 5 of the thiazole moiety cause lost of activity. Compounds* **1a, 1e**, *and* **1f** *showed toxicity to brine shrimp nauplii below 10 ppm. Most other compounds showed moderate toxicity, LD_{50} above 100 ppm. Structures of all compounds were confirmed by NMR and MS data.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:254–260, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20182

Correspondence to: Gonzalo J. Mena-Rejón; e-mail: mrejon@tunku.uady.mx.

Contract grant sponsor: Facultad de Química de la Universidad Autónoma de Yucatán.
Contract grant number: RP-01-2001.

INTRODUCTION

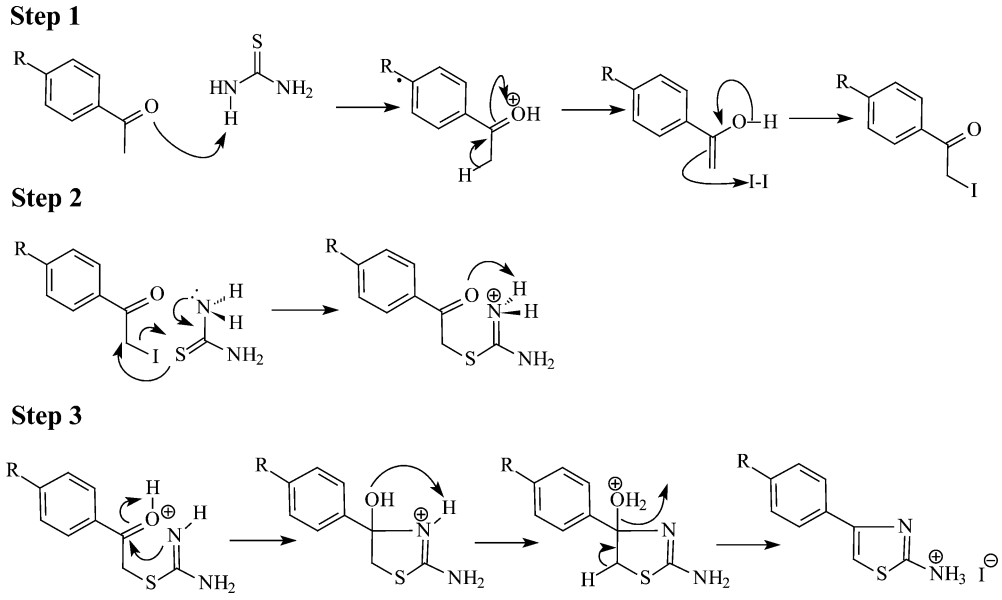
It is well known that the thiazole derivatives are important compounds due to their broad range of biological activities [1–3]. 2-Aminothiazoles as well as 2-amino-4-arylthiazoles and their derivatives have shown radioprotective [4,5], bactericidal, antifungal [6–8], antiviral [9,10], insecticidal [8], and anesthetic [11–13] activities. This type of compounds can be obtained using a solid phase reaction, which involves the cyclocondensation of *p*-substituted acetophenones and thiourea in the presence of iodine [14–16]. Other synthetic methods involve the use of ketones, *N*-bromosuccinimide, thiourea, and benzoyl peroxide [17], or bromination of ketones in the presence of $AlCl_3$ followed by cyclocondensation of the intermediate α-bromoketones with thiourea. As part of our search for antimicrobial heterocyclic compounds, we have undertaken the preparation of seven 2-amino-4-(*p*-substituted-phenyl)-1,3-thiazoles (**1a–g**) and their corresponding 2-aminoacetyl (**2a–g**) and 2-aminoacetyl-5-bromo (**3a–g**) derivatives, and evaluated their in vitro antimicrobial activity against bacteria, yeasts, and filamentous fungi. The toxicity of all prepared compounds was also tested using the *Artemia salina* test.



SCHEME 1 Synthesis of 2-acetamide-5-bromo-4(4-substituted-phenyl)-1,3-thiazoles.

RESULTS AND DISCUSSION

2-Acetamido-5-bromo-4-phenyl-1,3-thiazole (**3a**) and six *p*-substituted-phenyl derivatives (**3b–g**) were prepared from their corresponding 2-amino-4-phenyl-1,3-thiazole and 2-amino-4-(*p*-substituted-phenyl)-1,3-thiazoles (**1a–g**) (Scheme 1). Compounds **1a–g** were obtained by a Hantzch's modified method, a one-pot single-stage solid phase reaction [16]. The compound formation can be explained by a three-step mechanism. This process yields the 2-amino-4-(*p*-substituted-phenyl)-1,3-thiazoles derivatives as the hydroiodides, which are converted into the free bases when treated with aqueous alkaline solutions (Scheme 2). The reaction yields were clearly affected by the *p*-phenyl substituents. The general tendency observed indicated that the presence of electron-withdrawing groups or electron-donating groups decreases the reaction yield. Nevertheless, the chloro group was the exception giving the highest yield (Table 1). This behavior could be due to a selective action of the activating or deactivating groups over the steps of the Hantzch's reaction. It is possible that electron-withdrawing substituents increases the positive charge on carbonyl carbon by resonance effects, avoiding an efficient protonation of the carbonyl oxygen (step 1); while electron-donating substituents decrease the positive charge on the carbonyl carbon, thus making it less attractive to nucleophilic attack of the thiourea nitrogen (step 3). Acetylation of compounds **1a–g** with acetic



SCHEME 2 Mechanism of the Hantzch's reaction.

TABLE 1 Characteristic Physical Data of 2-Amino-4(4-substituted-phenyl)-1,3-thiazoles and Derivatives

Compound	*Substituent*	*MP (°C)*	*Yield (%)*
1a	H	148–150	69.4
1b	Me	130–132	66.1
1c	MeO	200–203	36.1
1d	HO	175–177	40.0
1e	Br	227–230	55.0
1f	Cl	203–205	85.8
1g	NO_2	283–285	43.7
2a	H	208–210	88.8
2b	Me	204–206	81.0
2c	MeO	188–190	78.8
2d	HO	189–191	71.5
2e	Br	264–266	45.5
2f	Cl	233–235	52.4
2g	NO_2	–	75.0
3a	H	238–240	82.0
3b	Me	218–220	75.0
3c	MeO	242–244	83.6
3d	OH	210–212	88.0
3e	Br	228–230	60.5
3f	Cl	236–238	67.4
3g	NO_2	236–238	89.0

anhydride/sodium acetate gave the corresponding aminoacetyl derivatives **2a–g** in moderate to good yields depending of the *p*-phenyl substituent, with an opposite tendency compared with compounds **1a–g** (Table 1). The 5-bromo derivatives **3a–g** were easily obtained from the aminoacetyl derivatives **2a–g**, using bromine in acetic acid. The results indicate that the presence of the N-acetyl group is required for the bromination at 5-position.

The structures of the synthesized compounds and the general method are shown in Scheme 1. All compounds were identified by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The NMR assignments are based on HSQC and HMBC experiments (Tables 2 and 3). All data were in full agreement with the assigned structures. The chemical shifts of protons and carbons at 5-position are clearly affected by *p*-substituents in the phenyl group. The nitro group deshields the protons at positions 7 and 11, while the carbons at the same positions were not affected. The EIMS and IR data are shown in Tables 4 and 5.

All the compounds were tested against *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus. agalactiae* (Gram-positive bacteria), *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Shigella flexneri* serotype 4 (Gram-negative bacteria), *Candida albicans*, *Saccharomyces cerevisae* (yeasts), *Aspergillus niger*, and *Trichophyton mentagrophytes* (filamentous fungi). The 86% of the tested compounds were not active against bacteria; only three compounds showed activity against some bacteria. **1b** and **1f** exhibited a selective activity; **1b** was active against *K. pneumoniae*, while **1f** showed activity against *St. agalactiae*. Compound **1g** showed nonselective antibacterial activity and was active against all Gram-positive bacteria. Unfortunately, the minimum inhibitory concentrations (MICs) were very high in all cases, indicating a very slight antibacterial activity. On the other hand, five compounds (**1a, 1b, 1e, 1f, 3b**) showed moderate antifungal activity, **1b** and **1f** were active against *A. niger* and *T. mentagrophytes* below 500 μg/mL. 2-Amino-4-(*p*-chlorophenyl)-1,3-thiazole (**1f**) was the most active compound that inhibited growth of *T. mentagrophytes* at 100 μg/mL, followed by 2-amino-4-(*p*-methylphenyl)-1,3-thiazole (**1b**), which inhibited the fungus growth at 200 μg/mL. This is an important fact because *T. mentagrophytes*, a keratinophilic filamentous fungus, is the causal agent inducing dermatophytosis infections of hair, skin, and nails [18–22]. In addition, *Trichophyton* species may cause invasive infections in immune-compromised hosts [23]. In spite of the moderate activity of compounds **1b** and **1f**, it is remarkable because of the lack of effective antifungal drugs and the pathogenicity of this species.

All active compounds were 2-amino-4-(*p*-substituted-phenyl)-1,3-thiazoles, except **3b**. This result suggests that acetylation of the amino group or the bromination at 5-position has a negative effect on the antimicrobial activity.

Toxicity of the prepared compounds was evaluated using *Artemia salina* nauplii [24], and cytotoxicity was inferred based on the same brine shrimp lethality assay, which has been found to have a good relationship with antitumoral activity [25]. The results indicate that 71% of the synthesized thiazoles can be considered moderate-low toxic, since they show toxicity at concentrations above 100 ppm (Table 6). However, compounds **1a, 1e**, and **1f** showed toxicity below 10 ppm. Correlation of these results and those obtained in the antifungal test indicated that **1b** was the better antifungal compound of the synthesized thiazoles due to its moderate toxicity. Although the brine shrimp lethality bioassay is an excellent choice to elementary toxicity investigations, it is necessary the use of human line cells to evaluate the cytotoxicity of the synthesized compounds.

EXPERIMENTAL

Melting points were determined on an Electrothermal apparatus model IA9100 in open capillaries and are uncorrected. IR spectra (KBr disks) were recorded using a Nicolet Magna-550 FT

TABLE 2 ^{1}H NMR Data (400 MHz) in DMSO-d_6 of 2-Amino-4(4-substituted-phenyl)-1,3-thiazoles and Derivates

	H5	*H7, 11*	*H8, 10*	*H9*	*NH_2*	*NH*	*Me*	*MeO*	*OH*	*Ac*
1a	6.99	7.79 (d, 7.6)	7.36 (t, 7.2)	7.25 (t, 7.0)	7.04					
1b	6.90	7.67 (dd, 6.8, 1.2)	7.16 (d, 7.2)		7.01		2.35			
1c	6.85	7.71 (dd, 7.2, 1.3)	6.92 (dd, 7.5, 1.3)		6.98			3.76		
1d	6.71	7.59 (dd, 6.4, 2)	6.74 (dd, 6.4, 2.0)		6.95				9.50	
1e	7.07	7.74 (dd, 6.8, 2)	7.54 (dd, 6.8, 2.0)		7.07					
1f	7.05	7.79 (d, 8.4)	7.40 (d, 8.4)		7.08					
1g	7.36	8.21 (d, 8.4)	8.01 (d, 8.4)		7.18					
2a	7.54	7.81 (d, 8.0)	7.42 (t, 8.0)	7.34 (t, 8.0)		12.19				1.75
2b	7.53	7.80 (d, 7.8.0)	7.25 (d, 7.8)			12.26	2.34			2.19
2c	7.00	7.73 (d, 8.0)	6.94 (d, 8.0)			11.73		3.83		1.75
2d	7.29	7.67 (d, 8.2)	6.78 (d, 8.2)			12.15			9.62	2.13
2e	7.68	7.86 (d, 8.2)	7.65 (d, 8.2)			12.29				2.19
2f	7.64	7.89 (d, 8.0)	7.48 (d, 8.0)			12.26				2.16
2g	7.95	8.27 (d, 8.1)	8.14 (d, 8.1)			12.36				2.16
3a		7.83 (d, 8.0)	7.46 (t, 8.0)	7.39 (t, 8.0)		12.48				2.17
3b		7.72 (d, 4)	7.26 (d, 8.0)			12.46	2.28			2.32
3c		7.79 (d, 8.0)	7.01 (d, 8.0)			12.44		3.81		2.19
3d		7.92	7.28			12.55			10.50	2.19
3e		7.81 (d, 8.0)	7.69 (d, 8.0)			12.56				2.16
3f		7.87 (d, 8.3)	7.54 (d, 8.3)			12.55				2.16
3g		8.38 (d, 8.0)	8.18 (d, 8.0)			12.66				2.21

TABLE 3 ^{13}C NMR Data (100 MHz) in DMSO-d_6 of 2-Amino-4(4-substituted-phenyl)-1,3-thiazoles and Derivatives

	C2	*C4*	*C5*	*C6*	*C7, 11*	*C8, 10*	*C9*	*Me*	*MeO*	*Ac*
1a	169.1	150.8	102.4	135.8	126.5	129.4	128.1			
1b	168.2	149.9	100.6	132.3	125.5	129.0	136.4	20.8		
1c	169.1	150.7	100.3	128.8	127.8	114.8	159.5		56.0	
1d	168.4	150.3	99.0	126.6	127.2	115.5	157.0			
1e	168.4	148.7	102.5	134.1	127.6	131.4	120.2			
1f	168.4	148.6	102.4	131.6	127.3	128.5	133.7			
1g	168.9	148.0	106.9	141.0	124.3	126.5	146.2			
2a	159.8	149.6	108.0	134.4	126.4	129.1	128.5			22.8
2b	158.8	149.8	108.0	132.7	126.6	130.3	138.1	21.8		23.5
2c	159.8	149.4	106.3	127.4	127.3	114.4	158.1		55.5	22.7
2d	158.0	149.3	105.3	126.0	127.4	115.7	157.5			22.8
2e	158.7	148.1	109.3	134.1	128.2	132.3	121.4			23.1
2f	159.0	148.4	109.4	133.1	128.2	129.5	134.1			23.3
2g	158.8	146.8	112.6	140.5	124.5	126.7	146.6			22.7
3a	157.2	146.0	97.2	134.2	128.2	128.7	128.7			22.5
3b	157.1	146.0	96.5	138.2	128.1	129.2	130.6	21.1		22.8
3c	159.4	146.0	95.6	126.9	129.6	114.1	157.0		55.5	22.8
3d	158.1	146.4	95.2	122.5	129.9	115.6	157.8			22.9
3e	158.0	145.4	98.3	133.3	130.7	132.2	122.5			23.0
3f	158.1	145.4	98.5	133.0	129.5	130.6	134.0			23.2
3g	158.0	147.3	100.3	139.9	124.4	129.5	144.2			22.8

spectrophotometer. A Bruker Avance 400 Ultrashield spectrometer, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C with XWINMR software package, was used for NMR experiments measured in DMSO-d_6 with TMS as internal reference, chemical shifts are recorded in δ values. EIMS were obtained on a Hewlett–Packard 5892 mass spectrometer using a Hewlett–Packard 5970 series II gas chromatograph as injection system, equipped with an Ultra II (5% diphenyl–95% dimethylsiloxane) fused-silica column (25 m × 0.2 mm i.d.; 0.33 μm film).

*2-Amino-4-phenyl-1,3-thiazole (**1a**) and Derivatives (**1b–g**) (General Procedure)*

Thiourea (0.98 g, 12.9 mmol) and I_2 (3.28 g, 12.9 mmol) were triturated and mixed with acetophenone (1.03 g, 8.6 mmol). The mixture was

TABLE 4 Mass Spectrometric Data of 2-Amino-4(4-substituted-phenyl)-1,3-thiazoles and Derivatives

	EIMS (70 eV) m/z
1a	176 $[M]^+$; 134, 104, 89, 77, 63, 51
1b	190 $[M]^+$; 147, 118, 91, 77, 63, 51
1c	206 $[M]^+$; 191, 164, 149, 134, 121, 77, 63
1d	192 $[M]^+$; 150, 121, 105, 93, 77
1e	264 $[M]^+$; 212, 182, 175, 148, 133, 120, 102, 89, 75, 63
1f	210 $[M]^+$; 168, 133, 102, 89, 63
1g	221 $[M]^+$; 191, 175, 149, 121, 89, 63
2a	218 $[M]^+$; 176, 134, 104, 89, 77, 43
2b	232 $[M]^+$; 190, 148, 118, 91, 65, 43
2c	248 $[M]^+$; 206, 191, 164, 149, 121, 77, 43
2d	234 $[M]^+$; 192, 150, 121, 93, 77, 65, 43
2e	306$[M]^+$; 254, 212, 182, 174, 133, 120, 89, 75, 43
2f	252 $[M]^+$; 210 (PB), 168, 133, 89, 43
2g	263$[M]^+$; 221, 191, 175, 146, 121, 103, 89, 43
3a	306$[M]^+$; 254, 212, 174, 146, 133, 103, 89, 77, 43
3b	320 $[M]^+$; 268, 226, 188, 147, 103, 91, 77, 43
3c	336 $[M]^+$; 284, 269, 227, 204, 175, 163, 134, 120, 89, 63, 43
3d	322 $[M]^+$; 192, 150, 121, 93, 77, 65, 43
3e	394 $[M]^+$; 332, 252, 211, 182, 174, 146, 132, 102, 93, 75, 43
3f	340 $[M]^+$; 288, 252, 208, 167, 137, 123, 102, 71, 43
3g	351 $[M]^+$; 299, 269, 253, 219, 178, 146, 132, 120, 102, 43

TABLE 5 Infrared Spectroscopic Data of 2-Amino-4(4-substituted-phenyl)-1,3-thiazoles and Derivatives

	IR (KBr) ν_{max} *(cm*$^{-1}$*)*
1a	3436, 3254, 3157, 3157, 3115, 1599, 1518, 1331, 715
1b	3401, 3291, 3180, 3120, 1626, 1518, 1335, 821
1c	3441, 3274, 3168, 3118, 1626, 1538, 1494, 1331, 1250, 1177, 1033, 836
1d	3490, 3381, 3128, 1600, 1511, 1331, 1273, 1178, 841
1e	3446, 3361, 3118, 1622, 1532, 1348, 827, 650
1f	3441, 3363, 3122, 1622, 1532, 1348, 827, 732
1g	3403, 3309, 3156, 1642, 1597, 1534, 1507, 1328, 847
2a	3158, 3071, 1639, 1580, 1540, 1301, 711
2b	3172, 3065, 1643, 1580, 1309, 812
2c	3164, 3063, 1642, 1575, 1304, 825
2d	3188, 3068, 1671, 1475, 1300, 752
2e	3175, 3070, 1644, 1557, 1305, 831
2f	3175, 3070, 1644, 1557, 1305, 831
2g	3164, 3071, 1642, 1576, 1526, 1340, 855
3a	3172, 3065, 1648, 1560, 1298, 771, 693
3b	3171, 3067, 2993, 1645, 1550, 1300, 995, 803
3c	3407, 3149, 2963, 1639, 1555, 1302, 831, 756
3d	3189, 1671, 1551, 1455, 1295, 1238, 752
3e	3163, 3063, 2988, 1643, 1550, 1467, 1308, 990, 819
3f	3173, 3072, 2996, 1644, 1552, 1460, 981, 825
3g	3179, 3078, 3005, 2925, 1658, 1552, 1506, 1336, 1283, 704

heated at 150°C on a sand bath for 2 h. The obtained solid was triturated with Et_2O, filtered, and washed with the same solvent to remove the unreacted acetophenone. The crude product was dissolved in hot water, and the thiazole was precipitated by the addition of NH_4OH and was separated by filtration. The obtained solid was purified by crystallization from a mixture of EtOH:H_2O (1:4).

*2-Acetamide-4-phenyl-1,3-thiazole (***2a***) and Derivatives (***2b–g***) (General Procedure)*

Equimolar amounts of 2-amino-4-phenyl-1,3-thiazole (1 g, 5.68 mmol) and sodium acetate were dissolved in acetic anhydride (7 mL). The reaction mixture was refluxed for 1 h. Then, 20 mL of cold water was slowly added with vigorous stirring. The

TABLE 6 Minimum Inhibitory Concentration (mg/mL) Against Microorganisms and Toxicity Against *Artemia salina* of 2-Amino-4(4-substituted-phenyl)-1,3-thiazoles Synthesized

	Sa	*Bs*	*Sta*	*Ec*	*Pa*	*Kp*	*Sf*	*Ca*	*Sc*	*An*	*Tm*	LD_{50}
1a									6.25		3.13	3
1b						1.56		0.78	3.13	0.40	0.20	223
1e									6.25		0.79	7
1f			3.13						1.56	0.40	0.10	3
1g	6.25	3.13	6.25			6.25						36
3b								6.25			12.5	215

Sa, *Staphylococcus aureus*; Bs, *Bacillus subtilis*; Sta, *Streptococcus agalactiae*; Ec, *Escherichia coli*; Kp, *Pseudomonas aeruginosa*; Kp, *Klebsiella pneumoniae*; Sf, *Shigella flexneri* serotype 4; Ca, *Candida albicans*; Sc, *Saccharomyces cerevisae*; An, *Aspergillus niger*; Tm, *Trichophyton mentagrophytes*; LD_{50}, lethal dose in ppm for 50% of the brine shrimp.

product was precipitated by addition of NH_4OH and separated by filtration. The crude product was dried and crystallized from a mixture of EtOH:H_2O (1:4).

*2-Acetamide-5-bromo-4-phenyl-1,3-thiazole (**3a**) and Derivatives (**3b–g**) (General Procedure)*

Bromine (2 mL, 4.0 mmol) dissolved in acetic acid (10 mL) was slowly dropped to a cold solution (10°C) of 2-acetamide-4-phenyl-1,3-thiazole (8.72 g, 4.0 mmol) in acetic acid (10 mL). The mixture reaction was kept on stirring until white solid precipitated. The product was separated by filtration, dried, and crystallized from a mixture of EtOH:H_2O (1:3).

Brine Shrimp Lethality Assay

Dry cysts, purchased from San Francisco Bay Brand Co., were washed for 30 min with an aqueous bleach solution (50%), rinsed thoroughly with water, and then were incubated in a hatcher at 28–30°C with strong aeration, under a continuous light regime. Approximately 12 h after hatching, the phototropic nauplii were collected with a pipette from the lighted side and concentrated in a 20 mL vial. Each test consisted of exposing groups of 10 nauplii aged 12 h (in instar II/III) to each synthesized compound. Each test was performed in triplicate. Each compound was tested at 10, 100, and 1000 ppm. The concentrations were obtained by transferring 5, 50, and 500 μL from a stock solution (1% in DMSO) to 10 mL vials and filtered, and sterilized seawater was added to get a final volume of 5 mL. The number of survivors was counted, and the LD_{50} was calculated. Larvae were considered dead if they did not exhibit any internal or external movement during 10 s of observation under stereoscopic microscope.

Antimicrobial Assays

Synthesized compounds were screened, using the disk-diffusion method, against *S. aureus* (4012), *B. subtilis* (465), *St. agalactiae* (4768), *E. coli* (128), *P. aeruginosa* (260), *Klebsiella pneumoniae* (4209), *Shigella flexneri* serotype 4 (9748), *Candida albicans* (752), *Saccharomyces cerevisae* (287), *Aspergillus niger* (16888), and *Trichophyton mentagrophytes* (4807); all of them were purchased from the American Type Culture Collection. Diluted bacterial culture (1.5×10^8 UFC/mL) was spread on a sterile Muller–Hinton agar plates. 6-mm Diameter disks were impregnated with 5 μL of 2% (w/v) of a chloroform solution of each synthesized compound, after that the disks were placed on the plates. The plates were incubated for 24 h at 37°C under aerobic conditions. The inhibition zone diameter around each disk was measured and recorded. Amikacin (0.03 mg/mL), nystatin (50 IU/mL), and itraconazole (0.025 mg/mL) were used as positive control for bacteria, yeast, and fungi, respectively; chloroform was used as negative control. All determinations were performed in triplicate.

Determination of Minimum Inhibitory Concentration (MIC)

MIC values were determined by a microdilution technique in 96-well cell culture plates [26]. Each active compound was dissolved in DMSO to give a concentration of 400 mg/mL. Twofold serial dilutions were made in broth over a range to give final concentrations of 200 mg–100 μg/mL. In each microplate well, 50 μL of a bacterial suspension (1.5×10^8 UFC/mL) was added to 50 μL of serial dilutions. The plates were incubated at 37°C for 24 h after to indicate bacterial growth, 50 μL *p*-iodonitrotetrazolium violet dissolved in water was added to the microplate wells and incubated at 37°C for 10–30 min. The MIC was defined as the lowest concentration at which no bacterial growth was observed. All determinations were performed in triplicate.

ACKNOWLEDGMENTS

The authors wish to thank Durcy Ruiz-Ciau and Gumersindo Mirón-López for GC–MS and IR technical assistance, respectively. The authors are grateful to Dr. Leovigildo Quijano for the critical review and the document translation.

REFERENCES

[1] Liu, H.; Li, Z.; Anthonsen, T. Molecules 2000, 5, 1055–1061.
[2] Kearney, P. C.; Fernandez, N.; Flygare, J. A. J Org Chem 1998, 63, 196–200.
[3] Zav'yalov, S. I.; Dorofeeva, O. V.; Rumyantseva, E. E.; Kulikova, L. B.; Ezhova, G. I.; Kravchenko, N. E.; Zavozin, A. G. Pharm Chem J 2001, 35(2), 96–98.
[4] Rasina, L. N.; Chupakhin, O. N. Radioekologiya 1999, 39 (2/3), 223–226.
[5] Rasina, L. N.; Chupakhin, O. N.; Chibiryak, M. V. Radiobiologiya 1990, 30(2), 162–165.
[6] Hassan, H. M.; Kora, F. A.; El-Haddad, A. F.; El-Naggar, A. M.; Abdel-Kader, M. Acta Pharm (Zagreb, Croatia) 1997, 47(3), 159–166.
[7] Panhekar, D. Y.; Ghiya, B. J. Indian J Heterocycl Chem 1995, 5(2), 159–160.
[8] Trivedi, V.; Rao, J. T. J Inst Chem (India) 1997, 69(3), 75–77.
[9] Flygare, J. A.; Jaen, J. C.; Kearney, P. C.; Medina, J. C.; Sivaraja, M. (Tularik Inc., USA); PCT Int Appl, 1999; p. 70.
[10] Simoneau, B. Chimia 1999, 53(6), 297–298.
[11] Chiba, A.; Chichibu, S. Comp Biochem Physiol, Part C: Toxicol Pharmacol 1992, 102(3), 433–437.
[12] Bizhev, A.; Boyadzhiev, N.; Natova, L. Farmatsiya (Sofia, Bulgaria) 1987, 37(5), 14–21.
[13] Sekizawa, Y.; Itoh, O. Nippon Suisan Gakkaishi 1977, 43(9), 1133–1138.
[14] Dodson, R. M.; Carroll King, L. J Am Chem Soc 1945, 67, 2242–2243.
[15] Carroll King, L.; Hlavek, R. J. J Am Chem Soc 1950, 72, 3722–3725.
[16] Naoto, I.; Masumi, N.; Hiroshi, A. Japanese Patent 60056970A, 1985.
[17] Dahiya, R.; Pujari, H. K. Indian J Chem 1986, 25B, 9, 966.
[18] Aly, R.; Hay, R. J.; Del Palacio, A.; Galimberti, R. Med Mycol 2000, 38, 183–188.
[19] Aman, S.; Haroon, T. S.; Hussain, I.; Bokhari, M. A.; Khurshid, K. Med Mycol 2001, 39, 177–180.
[20] Evans, E. G. V. J Am Acad Dermatol 1998, 38, 32–36.
[21] Roldan, Y. B.; Mata-Essayag, R.; Hartung, C. Mycoses 2000, 43, 181–183.
[22] Sabota, J.; Brodell, R.; Rutecki, G. W.; Hoppes, W. L. Clin Infect Dis 1996, 23, 1308–1310.
[23] Squeo, R. F.; Beer, R.; Silvers, D.; Weitzman, I.; Grossman, M. J Am Acad Dermatol 1998, 39, 379–380.
[24] Carballo, J. L.; Hernández-Inda, Z.; Pérez, P.; García-Grávalos, M. D. BMC Biotechnol 2002, 2, 17.
[25] Solis, P. N.; Wright, C. W.; Anderson, M. M.; Gupta, M. P.; Phillipson, J. D. Planta Med 1993, 59, 250–252.
[26] Eloff, J. N. Planta Med 1998, 64, 711–713.