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Synthesis and Antitumor Activity Evaluation of Some Schiff Bases Derived from 2-Aminothiazole Derivatives

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ABSTRACT: *A novel series of thiazolyl Schiff bases have been designed and synthesized. These new compounds were obtained by the reactions of 4-phenyl-5-(1H-1,2,4-triazol-1-yl) thiazol-2-amine and substituted aromatic aldehydes and were characterized on the basis of ^1H NMR and elemental analysis. The newly synthesized compounds were screened for their antitumor activity against human cancer cell lines, namely HL-60 (leukemia), BGC-823 (stomach), and HEP-2 (larynx cancer).* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:55–59, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20256

INTRODUCTION

In the past few years, we have been very much interested in the chemistry of thiazole derivatives[1,2]. They appear frequently in a variety of biological compounds, for example, thiamine (vitamin B1) [3,4]. Some synthetic thiazoles have also exhibited a range of biological activities, such as antitumor, antibiotic, antibacterial, antifungal, and anti-inflammatory activities [5–7].

Schiff bases have been widely used as ligands in the formation of transition metal complexes[8]. In addition, free Schiff bases have also been found to possess potent activities including antibacterial, antifungal, antiviral, and anti-inflammatory [9–13].

In our previous work, we synthesized a series of 2-aminothiazoles by incorporating the triazole moiety into 2-aminothiazole derivatives and investigated their crystal structure [1,2] and biological activities.

In this context, we designed and synthesized a range of Schiff bases, shown in Fig. 1, by combination of a novel series of 2-aminothiazole with an arylidene moiety bearing different substituents, and evaluated them for their antitumor activity in vitro with three human tumor cell lines.

RESULTS AND DISCUSSION

Chemistry

Schiff bases synthesized for this study are shown in Scheme 1. It was reported that reactions of simple 2-aminothiazole derivatives with aromatic aldehydes were carried out in boiling ethanol with a few drops of acetic acid or piperdine as a catalyst [14]. However, after incorporation of the triazole ring into the 5-position of 2-aminothiazole, nucleophilic addition of the NH_2 group to the carbonyl function of the

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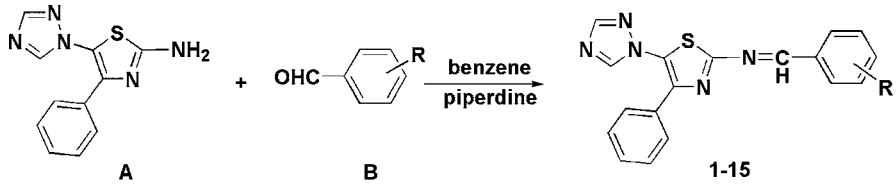
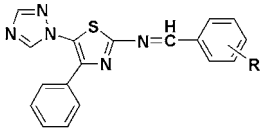


1 R=H(86.1%)
2 R=4-F(70.2%)
3 R=2-F(30.1%)
4 R=4-Cl(72.5%)
5 R=2-Cl(10.9%)
6 R=2, 6-Cl(68.8%)
7 R=2, 4-Cl(73.8%)
8 R=2-OCH_3(7.0%)
9 R=2-NO_2(18.6%)
10 R=3- NO_2(59.9%)
11 R=2, 4- NO_2(39.2%)
12 R=3, 4-CH_3(78.0%)
13 R=2, 4-CH_3(86.2%)
14 R=4-$N(C_2H_5)_2$(56.3%)
15 R= 3, 4-O-CH_2-O(45.8%)

SCHEME 1



1 R=H
2 R=4-F
3 R=2-F
4 R=4-Cl
5 R=2-Cl
6 R=2, 6-Cl
7 R=2, 4-Cl
8 R=2-OCH_3
9 R=2-NO_2
10 R=3- NO_2
11 R=2, 4- NO_2
12 R=3, 4-CH_3
13 R=2, 4-CH_3
14 R=4-$N(C_2H_5)_2$
15 R= 3, 4-O-CH_2-O

FIGURE 1 The structures of title compounds.

aromatic aldehyde becomes difficult. We optimized the reaction conditions by the use of anhydrous benzene as solvent, a few drops of piperidine as a catalyst, and molecular sieves (4 Å) to remove the water produced by the condensation. Under these conditions, the products were obtained in satisfactory yields. At the end of the reactions (monitored by TLC), solvent was evaporated under reduced pressure and the crude products were filtered. The products were still impure even after numerous recrystallizations as unreacted 4-phenyl-5-(1*H*-1,2,4-triazol-1-yl)-2-aminothiazole (**A**) was more easily crystallized from the solvents. Only compound **15** could be obtained by recrystallization from ethanol. Product separation was effected by silica gel column chromatography using petroleum ether and ethyl acetate (3:1, v/v) as eluent. The Schiff bases formed crystals with different shades of yellow due to the presence of chromophoric groups (C=N) in the molecules.

The yields data show that the reactions of compound **A** with 4-substituted aldehydes get higher yields than those with 2-substituted aldehydes. It may be a steric effect that makes the nucleophilic addition of the NH_2 group to the carbonyl function difficult. In addition, compounds **3, 5**, and **9**, where the phenyl rings carry 2-fluoro, 2-chloro, and 2-nitro substituents, decomposed easily in solution. It may be substituent on 2-position of the phenyl ring that affects the stability of the double bond.

All product structures have been confirmed by elemental analyses and ^{1}H NMR spectroscopy. The presence of CH=N protons was confirmed by ^{1}H NMR spectra in all of the aldimines by observing one-proton singlets at δ 8.61–9.73. Two-proton doublets at δ 8.098.21 were assigned as the triazole group NH. Signals corresponding to aromatic protons were observed in the region of δ 6.68–8.97.

Biological Activity

All compounds were screened for their antitumor activity in vitro against HL-60 (leukemia) by the MTT method and BGC-823 (stomach cancer) and Hep-2 (larynx cancer) by the SRB method at the concentration of 10 μM. The results are presented in Table 1.

Among the compounds tested, compounds **7, 10**, and **11**, where the phenyl ring bears 2,4-dichloro,

TABLE 1 Inhibitory Ratios of the Title Compounds Against Several Tumor Cell Lines

	Percentage of Inhibition		(%, 10 μ*mol/L*)
Compd	*HL-60*	*BGC-823*	*Hep-2*
1	19.6	7.7	18.35
2	7.92	29.56	35.75
3	8.83	14.98	13.94
4	10.94	16.17	20.19
5	8.68	23.82	34.78
6	28.13	63.54	68.59
7	43.41	95.00	84.95
8	0.68	−3.46	−6.19
9	55.67	74.67	73.05
10	55.34	87.43	84.98
11	91.97	98.49	91.16
12	19.52	27.81	36.39
13	18.59	16.71	22.14
14	9.69	28.77	37.52
15	9.92	23.52	21.75

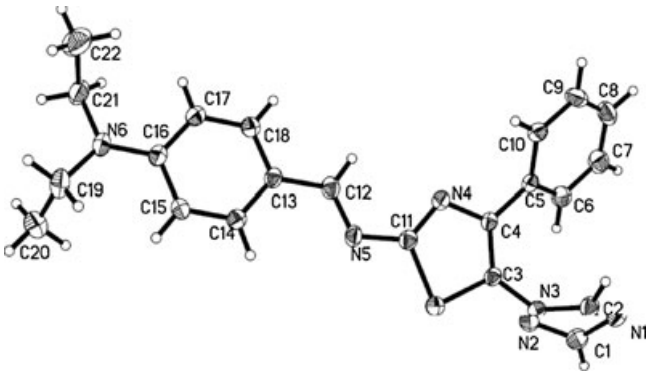


FIGURE 2 Molecular structure and crystallographic numbering scheme for compound 14.

3-nitro, and 2,4-dinitro substituents, showed good antitumor activity against HL-60, BGC-823, and Hep-2, especially **11** whose inhibition ratios on HL-60, BGC-823, and Hep-2 were 91.97%, 98.49%, and 91.16%, respectively. The obtained results indicate **7, 10**, and **11** to be good candidates for further studies in vitro against a broad panel of human cell lines, with an aim to select the most active compounds for further preclinical in vivo studies.

Crystal Structure

Single crystals of compound **14** were obtained from ethanol. The molecular structure is shown in Fig. 2. Selected bond lengths and angles are given in Table 2. The torsion angle C11–N5–C12–C13 is 177.7°. It shows that the substituted phenyl and the thiazole rings are in a transconfiguration.

EXPERIMENTAL

Melting points (°C) were determined with X-4 digital melting point apparatus and are uncorrected. Elemental analyses of new compounds were performed in the Central Analytical Laboratory of Nankai University, China, on an elemental Vario EL for C, H, and N. The experimental values for C, H, and N were always ±0.4% of the theoretical value.

^{1}H NMR spectra in *d*-$CHCl_3$ solutions were recorded on a Bruker AC 300. Chemical shifts are reported as δ (ppm) relative to TMS as an internal standard. Reaction progress was monitored by thin-layer chromatography with F_{254} silica gel precoated sheets using petroleum ether/ethyl acetate (v/v 3:1).

TABLE 2 Selected Bond Distances and Bond Angles of Compound **14**

Bond	*Distance (Å)*	*Bond*	*Angles (°)*
S(1)–C(3)	1.719	C(3)–S(1)–C(11)	88.17
S(1)–C(11)	1.738	C(2)–N(1)–C(1)	101.58
N(1)–C(2)	1.312	C(1)–N(2)–N(3)	101.45
N(1)–C(1)	1.355	C(2)–N(3)–N(2)	109.08
N(2)–N(3)	1.368	C(11)–N(4)–C(4)	111.22
N(3)–C(3)	1.415	C(11)–N(5)–C(12)	117.26
N(4)–C(4)	1.382	N(5)–C(12)–C(13)	123.3
C(4)–C(5)	1.478	N(4)–C(11)–S(1)	115.10
N(5)–C(11)	1.389	N(5)–C(11)–S(1)	116.20
N(5)–C(12)	1.287	C(3)–C(4)–C(5)	127.39
C(12)–C(13)	1.437	N(2)–N(3)–C(3)	120.87

*N-Benzylidene-4-phenyl-5-(1H-1, 2,4-traizol-1-yl) thiazol-2-amine (**1**)*

To a mixture of 4-phenyl-5-(1*H*-1,2,4-traizol-1-yl)-2-aminothiazole (0.49 g, 2 mmol) and benzaldehyde (0.21 g, 2 mmol) in anhydrous benzene, three drops of piperidine were added, then refluxed for 8 h (monitored by TLC). Solvent was evaporated under reduced pressure after being cooled; the product was isolated by a silica gel column chromatogram using petroleum ether and ethyl acetate (3:1, v/v) as eluent. The product was obtained by evaporating the solvents under reduced pressure, with a yield of 0.57 g (86.1%); mp 129–130°C; ^{1}H NMR: δ 9.11 (s, 1H, CH=N), 8.18 (s, 1H, TrH), 8.11 (s, 1H, TrH), 8.00–8.02 (d, 2H, arom), 7.48–7.60 (m, 3H, arom), 7.33–7.43 (m, 5H, arom). Anal. Calcd for $C_{18}H_{13}N_5S$: C, 65.24; H, 3.95; N, 21.13; Found: C, 65.25; H, 4.09; N, 21.20.

*N-(4-Fluorobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**2**)*

This compound was obtained by using 4-fluorobenzaldehyde in a yield of 0.49 g (70.2%); mp 130–132°C; 1H NMR: δ 9.10 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.12 (s, 1H, TrH), 8.01–8.06 (m, 2H, arom), 7.35–7.40 (m, 5H, arom), 7.21–7.24 (m, 2H, arom). Anal. Calcd for $C_{18}H_{12}FN_5S$: C, 61.88; H, 3.46; N, 20.04; Found: C, 61.97; H, 3.46; N, 20.04.

*N-(2-Fluorobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**3**)*

This compound was obtained by using 2-fluorobenzaldehyde in a yield of 0.21 g (30.1%); mp 143–144°C; 1H NMR: δ 9.43 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.24 (t, 1H, TrH), 8.24–8.29 (t, 1H, arom), 7.53–7.61 (q, 1H, arom), 7.34–7.41 (m, 6H, arom), 7.15–7.21 (m, 1H, arom). Anal. Calcd for $C_{18}H_{12}FN_5S$: C, 61.88; H, 3.46; N, 20.04; Found: C, 61.73; H, 3.46; N, 20.17.

*N-(4-Chlorobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**4**)*

This compound was obtained by using 4-chlorobenzaldehyde in a yield of 0.53 g (72.5%); mp 144–145°C; 1H NMR: δ 9.10 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.11 (s, 1H, TrH), 7.94–7.97 (d, 2H, arom), 7.48–7.51 (d, 2H, arom), 7.29–7.42 (m, 5H, arom). Anal. Calcd for $C_{18}H_{12}ClN_5S$: C, 59.09; H, 3.28; N, 19.15; Found: C, 58.90; H, 3.11; N, 19.40.

*N-(2-Chlorobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**5**)*

This compound was obtained by using 2-chlorobenzaldehyde in a yield of 0.08 g (10.9%); mp 124–126°C; 1H NMR: δ 9.56 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.12 (s, 1H, TrH), 8.34–8.34 (d, 1H, arom), 8.20–8.13 (s, 1H, arom), 7.49–7.50 (m, 2H, arom), 7.35–7.43 (m, 6H, arom). Anal. Calcd for $C_{18}H_{12}ClN_5S$: C, 59.09; H, 3.28; N, 19.15; Found: C, 58.99; H, 3.30; N, 19.13.

*N-(2,6-Dichlorobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**6**)*

This compound was obtained by using 2, 6-dichlorobenzaldehyde in a yield of 0.55 g (68.8%); mp 143–145°C; 1H NMR: δ 9.48 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.12 (s, 1H, TrH), 7.31–7.45 (m, 9H, arom). Anal. Calcd for $C_{18}H_{11}Cl_2N_5S$: C, 54.10; H, 2.77; N, 17.50; Found: C, 54.19; H, 2.79; N, 17.31.

*N-(2,4-Dichlorobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**7**)*

This compound was obtained by using 2,4-dichlorobenzaldehyde in a yield of 0.59 g (73.8%); mp 165–167°C; 1H NMR: δ 9.48 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.12 (s, 1H, TrH), 8.26–8.29 (d, 1H, arom), 7.46–7.49 (m, 1H, arom), 7.27–7.42 (m, 6H, arom). Anal. Calcd for $C_{18}H_{11}Cl_2N_5S$ C, 54.10; H, 2.77; N, 17.50; Found: C, 53.99; H, 2.89; N, 17.47.

*N-(2-Methoxylbenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**8**)*

This compound was obtained by using 2-methoxylbenzaldehyde in a yield of 0.05 g (7.0%); mp 116–118°C; 1H NMR: δ 9.49 (s, 1H, CH=N), 8.19 (s, 1H, TrH), 8.12 (s, 1H, TrH), 8.24–8.27 (d, 1H, arom), 7.41–7.43 (t, 1H, arom), 6.99 (m, 2H, arom), 3.94 (s, 3H, arom). Anal. Calcd for $C_{19}H_{15}N_5OS$: C, 63.14; H, 4.18; N, 19.38; Found: C, 62.76; H, 4.59; N, 19.79.

*N-(2-Nitrobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**9**)*

This compound was obtained by using 2-nitrobenzaldehyde in a yield of 0.14 g (18.6%); mp 159–162°C; 1H NMR: δ 9.63 (s, 1H, CH=N), 8.20 (s, 1H, TrH), 8.14 (s, 1H, TrH), 8.39–8.42 (d, 1H, arom), 7.72–7.81 (m, 2H, arom), 7.28–7.43 (m, 6H, arom). Anal. Calcd for $C_{18}H_{12}N_6O_2S$: C, 57.44; H, 3.21; N, 22.33; Found: C, 57.05; H, 3.42; N, 22.57.

*N-(3-Nitrobenzylidene)-4-phenyl-5-(1H-1,2,4-traizol-1-yl) thiazol-2-amine (**10**)*

This compound was obtained by using 3-nitrobenzaldehyde in a yield of 0.45 g (59.9%); mp 116–119°C; 1H NMR: δ 9.27(s, 1H, CH=N), 8.20 (s, 1H, TrH), 8.14 (s, 1H, TrH), 8.85–8.87 (t, 1H, arom), 8.40–8.43 (d, 1H, arom), 8.32–8.35 (d, 1H, arom), 7.70–7.75 (t, 1H, arom), 7.35–7.42 (d, 1H, arom). Anal. Calcd for $C_{18}H_{12}N_6O_2S$: C, 57.44; H, 3.21; N, 22.33; Found: C, 57.31; H, 3.14; N, 22.11.

*N-(2,4-Dinitrobenzylidene)-4-phenyl-5-(1H-1,2, 4-traizol-1-yl)thiazol-2-amine (**11**)*

This compound was obtained by using 2,4-dinitrobenzaldehyde in a yield of 0.33 g (39.2%); mp 194–195°C; 1H NMR: δ 9.73 (s, 1H, CH=N), 8.21 (s, 1H, TrH), 8.14 (s, 1H, TrH), 8.96–8.97 (d, 1H, arom), 7.39–7.41 (m, 5H, arom). Anal. Calcd for $C_{18}H_{11}N_7O_4S$: C, 51.30; H, 2.63; N, 23.27; Found: C, 51.11; H, 2.58; N, 23.01.

*N-(3, 4-dimethylbenzylidene)-4-phenyl-5-(1H-1, 2, 4-traizol-1-yl)thiazol-2- amine (**12**)*

This compound was obtained by using 3,4-dimethylbenzaldehyde in a yield of 0.56 g (78.0%); mp 172–175°C; 1H NMR: δ 9.73 (s, 1H, CH=N), 8.21 (s, 1H, TrH), 8.14 (s, 1H, TrH), 8.96–8.97 (d, 1H, arom), 7.39–7.41 (m, 5H, arom). Anal. Calcd for $C_{20}H_{17}N_5S$: C, 66.83; H, 4.77; N, 19.48; Found: C, 66.29; H, 4.43; N, 19.75.

*N-(2,4-Dimethylbenzylidene)-4-phenyl-5-(1H-1, 2, 4-traizol-1-yl) thiazol-2-amine (**13**)*

This compound was obtained by using 2,4-dimethylbenzaldehyde in a yield of 0.62 g (86.2%); mp 126–128°C; 1H NMR: δ 9.34 (s, 1H, CH=N), 8.18 (s, 1H, TrH), 8.11 (s, 1H, TrH), 7.28–7.43 (m, 6H, arom), 7.09–7.16 (m, 2H, arom), 2.39 (s, 3h, CH_3), 2.62 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{17}N_5S$: C,

66.83; H, 4.77; N, 19.48; Found: C, 66.75; H, 4.78; N, 19.21.

*N-(4-(N,N-Diethylamino)benzylidene)-4-phenyl-5-(1H-1,2,4-triazol-1-yl) thiazol-2-amine (**14**)*

This compound was obtained by using 4-(*N, N*-diethylamino) benzaldehyde in a yield of 0.42 g (56.3%); mp 159–161°C; 1H NMR: δ 8.81(s, 1H, CH=N), 8.17 (s, 1H, TrH), 8.09 (s, 1H, TrH), 7.83–7.86 (d, 2H, arom), 7.39–7.42 (m, 2H, arom), 7.30–7.33 (m, 3H, arom), 6.69–6.72 (d, 2H, arom), 3.42–3.49 (q, 4H, CH_2), 1.21–1.26 (t, 3H, CH_3). Anal. Calcd for $C_{22}H_{22}N_6S$: C, 65.65; H, 5.51; N, 20.88; Found: C, 65.75; H, 5.30; N, 19.91.

*N-((Benzo[d][1,3]dioxol-5-yl)methylene)-4-phenyl-5-(1H-1,2,4-triazol-1-yl) thiazol-2-amine (**15**)*

To a mixture of 4-phenyl-5-(1*H*-1,2,4-traizol-1-yl)-2-aminothiazole (0.49 g, 2 mmol) and piperonal (0.30 g, 2 mmol) in anhydrous benzene, three drops of piperidine were added, then refluxed for 8 h (monitored by TLC). The solvent was evaporated under reduced pressure after being cooled; the crude product was filtered and recrystallized from ethanol to give a yield of 0.36 g (45.8%); mp 172–173°C; 1H NMR: δ 8.96 (s, 1H, CH=N), 8.18 (s, 1H, TrH), 8.11 (s, 1H, TrH), 7.43 (d, 1H, arom), 7.33–7.41 (m, 6H, arom), 6.08 (s, 2H, CH_2). Anal. Calcd for $C_{20}H_{15}N_5O_2S$: C, 60.79; H, 3.49; N, 18.66; Found: C, 60.65; H, 3.46; N, 18.44.

REFERENCES

[1] Shao, L.; Hu, Y.; Zhou, X.; Zhang, Q.; Fang, J. X. Acta Crystallogr, Sect. E 2005, m1269.
[2] Shao, L.; Jin, Z.; Liu, J. B.; Zhou, X.; Zhang, Q.; Hu, Y.; Fang, J. X. Acta Crystallogr, Sect. E 2004, o2517.
[3] Holla, B. S.; Malini, K. V.; Rao, B. A.; Sarojini, B. K.; Kumari, N. S. Eur J Med Chem 2003, 38, 313.
[4] Kimiaki, I. J. Heterocyclic Chem 2004, 41, 723.
[5] Michael, J. G.; Tachel, M. L.; Susan, L. M.; John, H. B.; Milton, L. B. Bioorg Med Chem 2004, 12, 1029.
[6] Robert, A. F. Clin Microbiol Rev 1988, 1, 187.
[7] Jung, K. Y.; Kim, S. K.; Gao, Z. G.; Ariel, S. G.; Neli, M.; Denneth, A. J.; Kim, Y. C. Bioorg Med Chem 2004, 12, 613.
[8] Aysegul, G.; Mehmet, T.; Havva, D.; Wheatley, R. A. Inorg Chim Acta 2005, 358, 1785.
[9] Mustafa, Y.; Hüseyin, Ü.; Başaran, D.; Diğdem, E.; Nazan, O.; Ahmet, E.; Tahsin N. D. J Mol Struct 2005, 738, 253.
[10] Hüseyin, Ü.; Mustafa, Y.; Başaran, D.; Özen, Ö.; Engin, K.; Tahsin, N. D. J Mol Struct 2005, 737, 159.
[11] İlkay, K.; Küçükgüzel, Ş. G.; Sevim, R.; Gülten, Ö.; Osman, Ö.; Ibrahim, B.; Tuncay, A.; James, P. S. Il Farmaco 2004, 59, 893.
[12] Athina, G.; Dimitra, H. L.; Maria, A. Il Farmaco 2003, 58, 489.
[13] Cardile, V.; Panico, A. M.; Geronikaki, A.; Gentile, B.; Ronsisvalle, G. Il Farmaco 2002, 57, 1009.
[14] Paola, V.; Athina, G.; Mattero, I.; Bernadetta, B.; Graziella, P.; Carla A. C.; Paolo, L. C. Bioorg Med Chem 2003, 11, 4785.