Turk J Chem
32 (2008) , 585 – 592.

Synthesis and Antifungal Activity of Some Novel N-(4-Phenyl-3-aroylthiazol-2(3H)-ylidene) Substituted Benzamides

Aamer SAEED[1,*], **Sabah ZAMAN**[1], **Maryam JAMIL**[2], **Bushra MIRZA**[2]
[1] *Department of Chemistry, Quaid-I-Azam University 45320, Islamabad-PAKISTAN*
e-mail: aamersaeed@yahoo.com
[2] *Department of Microbiology, Quaid-I-Azam University 45320, Islamabad-PAKISTAN*

Received 13.02.2008

Variously substituted N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene)benzamides (**2a-t**) were prepared by base-catalyzed cyclization of corresponding 1-aroyl-3-aryl thioureas with acetophenone in the presence of bromine. Some of the synthesized compounds were assayed in vitro for their antifungal activity and were found to exhibit low to moderate activity.

Key Words: N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene) substituted benzamides, antifungal.

Introduction

Thiazoline heterocycle is a commonly occurring substructure in organic chemistry, found in a variety of structurally and biologically interesting natural products such as mirabazoles, thingazole, and tantazoles, which display selective cytotoxicity against murine solid tumors and are potent and selective inhibitors of HIV-1.[1,2] More examples include apratoxins A-C possessing potent cytotoxic activity,[3,4] trunkamide A having marked antitumor activity,[5] and thiostrepton displaying antibiotic and antimalarial activities.[6] Synthetic thiazoline derivatives are useful medicaments showing antifungal,[7,8] anti-allergic,[9] anti-hypertensive,[10] anti-inflammatory,[11] antibacterial,[12] analgesic, anti-rheumatic, anti-pyretic, and anti-HIV[13] activities. Some fused thiazolines find applications in the treatment of allergies, hypertension, inflammation, schizophrenia, and bacterial and HIV infections.[14] 2-Thiazolylimino-5-arylidene-4-thiazolidinones show marked antimicrobial activity against bacteria, yeasts, and molds.[15] Bis(ethylenedithio) dithiadiazafulvenes[16] act as molecular conductors and their radical ion salts exhibit superconducting behavior. Some cyclic chiral oligothiazolines, having a wheel-like architecture containing a linear array of thiazoline rings, are well known supramolecules.[17] 2-(Tetrahydronaphthalen-1-yl)iminothiazolidine exhibits pronounced antidepressant activity,[18] and β-(hydroxyethyl) thiazolidines are effective antihypertensives.[19] 3-Substituted 2-(cyanoimino)thiazolidines can be used in agriculture due to their neonicotinoid insecticidal activity.[20]

*Corresponding author

3-Substituted thiazolidines show radioprotective properties against γ-radiations.[21]2-Imino-1,3-thiazolines derivatives have shown antifungal activity against the rice blast fungus *Pyricularia oryzae*[22] and thus can be used as fungicides. KHG22394, a 2-imino-1,3-thiazoline derivative, significantly inhibits melanin production in a dose-dependant manner, thus acting as a skin whitening agent,[23] and pifithrin-α is a reversible inhibitor of p53-mediated apoptosis and p53-dependent gene transcription.[24]

Taking into consideration the aforementioned biological and synthetic significance of 2-imino-1,3-thiazolines, we designed the synthesis of some new 1,3-thiazolines (Figure 1) having 3 points of structural diversity, i.e. a substituted *N*-aroyl group at C-2, a substituted *N*-aryl group at C-3, and a C-4 phenyl (which may be substituted), for systematic evaluation of biological activities and establishment of structure activity relationship (SAR) in depth. Herein, the synthesis and antifungal activity of some N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene) substituted benzamides are described.

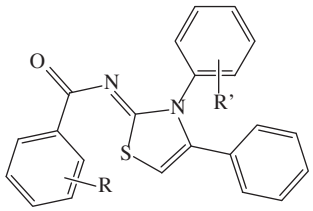


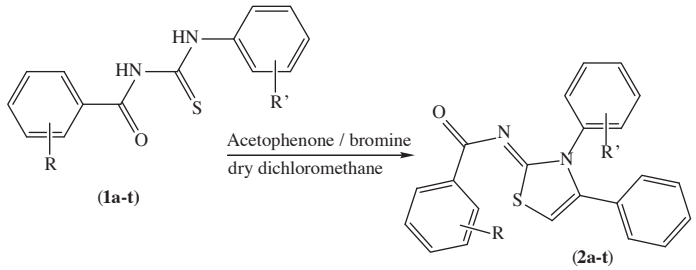
Figure 1. N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene)benzamides.

Results and Discussion

1-(Substituted benzoyl)-3-aryl thioureas (**1a-t**) were prepared according to the published procedure involving treatment of aroyl chloride with potassium thiocyanate in acetone followed by reaction with suitably substituted anilines.[25] A typical 1-aroyl-thiourea showed absorptions at 3351 and 3200 cm^{-1} for free and associated NH, at 1660 for carbonyl, and at 1230 cm^{-1} for thiocarbonyl groups in IR spectra and singlets at δ 9.0 and 12 for HN(1) and HN(3) and peaks at 170 and 179 for carbonyl and thiocarbonyl were observed in ^{1}H- and ^{13}C-NMR spectra respectively. The cyclocondensation of 1-aroyl-3-arylthioureas with acetophenone was achieved in the presence of bromine and base. Thus triethyl amine was added to a solution of 1-aroyl-3-arylthioureas in dry dichloromethane, followed by the treatment with a mixture of acetophenone and bromine under an inert atmosphere to afford N-(4-phenyl-3-aroylthiazol-2(3*H*)-ylidene) substituted benzamides. The absence of N-H peaks at 3200-3400 cm^{-1}, slight shifting of C=O absorptions to 1630-1675 cm^{-1}, and appearance of characteristic C=N at 1450-1495 cm^{-1} were observed in the IR spectra. ^{1}H-NMR spectra showed the disappearance of N-H peaks and emergence of a 1H characteristic singlet at δ 6.5-6.9 due to C=C-H of the thiazoline ring. In ^{13}C-NMR the characteristic peak for olefinic carbon at δ 107.2-107.9 confirmed the formation of benzamides.

Although the same mesomeric anionic thiourea intermediate may furnish either imino-1,3-thiazolines (*S*-cyclization products) or isomeric imidazole-2-thiones (*N*-cyclization products), we have already unequivocally demonstrated,[26] and this was also shown later by another research group,[27] that under these conditions the thermodynamically stable imino-1,3-thiazolines are the exclusive products, in contrast to some other reports.[28,29]

In the mass spectra of these substituted benzamides the base peak originates from the aroyl cation. The mass fragmentation patterns of N-(3-(3-chlorobenzoyl)-4-phenylthiazol-2(3H)-ylidene)-3-methylbenzamide (**2c**) show the base peak at m/z 119; other important peaks include those at m/z 313, 277, 91, and 65 (Figure 2).



Scheme. Synthesis of N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene)benzamides.

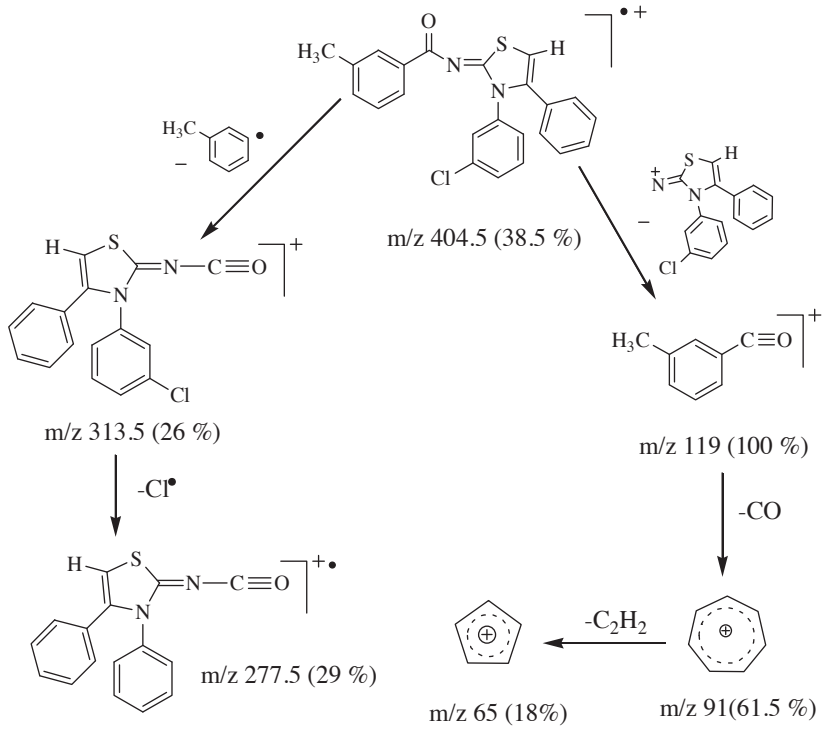


Figure 2. The mass fragmentation pattern of N-(3-(3-chlorobenzoyl)-4-phenyl thiazol-2(3H)-ylidene)-3-methylbenzamide (**2c**).

Primary bioassay screening provides the first indication of bioactivities and helps in the selection of lead compounds for secondary screening for detailed pharmacological evaluation. Some of the benzamides were checked for their antifungal activity against 5 fungal strains: *Aspergillus flavus*, *A. nigar*, *A. fumigatus*, *Fusarium solani*, and *Mucor* species. The antifungal activity was carried out in DMSO using the agar tube dilution method. Growth in the media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control.

$$\text{Percentage inhibition of fungal growth} = 100 - \frac{\text{Linear growth in test tube (mm)}}{\text{Linear growth in control (mm)}} \times 100$$

Table 1. Physicochemical, spectral, and elemental data of benzanilides (**2a-t**).

Compd.	R	R'	mp (°C)	IR (ν/cm^{-1})	^{1}H- and ^{13}C-NMR spectral data (δ ppm)	(% Calcd.) C, H, N, S (% found) (C, H, N, S)
2a	2-Me	2-MeO	205	1633 (C=O), 1561 (Ar-C=C), 1466 (C=N), 1267 (C-S), 1158 (C-N)	^{1}H-NMR: 6.98 (*s*, CH=C), 7.12-8.43 (*m*, 13H, Ar-H), 3.65 (*s*, OCH_3), 2.47 (*s*, CH_3). ^{13}C-NMR: 21.51, 55.68, 107.79, 126.49, 126.75, 128.0, 128.63, 128.71, 128.84, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.3, 137.66, 138.59, 169.54, 174.60.	71.98; 5.03; 6.99; 8.01 (70.66; 5.11; 7.21; 8.11)
2b	″	3-Me	185	1645 (C=O), 1557 (Ar-C=C), 1456 (C=N), 1248 (C-S), 1159 (C-N)	^{1}H-NMR: 6.44 (*s*, CH=C), 7.14-8.25 (*m*, 13H, Ar-H), 2.46 (*s*, CH_3), 2.42 (*s*, CH_3).^{13}C-NMR: 21.40, 21.37, 107.71, 126.50, 126.75, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.0, 130.18, 132.51, 134.30, 136.3, 137.68, 138.59, 169.58, 174.61.	74.97; 5.24; 7.29; 8.34. (74.55; 5.30; 7.68; 8.26)
2c	″	2-Cl	165	1657 (C=O), 1589 (Ar-C), 1474 (C=N), 1298 (C-S), 1157 (C-N)	^{1}H-NMR: 6.48 (*s*, CH=C), 7.24-8.04 (*m*, 13H, Ar-H), 2.37 (*s*, CH_3).^{13}C-NMR: 21.44, 107.76, 126.51, 126.75, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.3, 137.66, 138.59, 169.56, 174.66.	68.22; 4.23; 6.92; 7.92 (68.01; 4.33; 7.21; 7.90)
2d	″	3-Cl	182	1654 (C=O), 1589 (Ar-C), 1455 (C=N), 1279 (C-S), 1161 (C-N)	^{1}H-NMR: 6.46 (*s*, CH=C), 6.98-8.11 (*m*, 13H, Ar-H), 2.51 (*s*, CH_3).^{13}C-NMR: 21.39, 107.71, 126.51, 128.0, 128.21, 128.51, 129.40, 130.14, 131.5, 132.54, 134.30, 134.5, 137.0, 138.47, 170.2, 174.51.	68.22;4.23; 6.92; 7.92 (68.13; 4.20; 7.13; 7.89).
2e	3-Me	2-Me	172	1634 (C=O), 1598 (Ar-C), 1476 (C=N), 1266 (C-S), 1140 (C-N)	^{1}H-NMR: 6.74 (*s*, CH=C), 7.05-8.13 (*m*, 13H, Ar-H), 2.58 (*s*, CH_3), 2.44 (*s*, CH_3).^{13}C-NMR: 21.39, 21.31, 107.71, 126.56, 126.75, 128.0, 128.63, 128.77, 128.89, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.38, 137.66, 138.59, 169.58, 174.70.	74.97; 5.24; 7.29; 8.34 (74.29; 5.35; 7.59; 8.29)
2f	″	3-Me	192	1644 (C=O), 1595 (Ar-C), 1458 (C=N), 1263 (C-S), 1138 (C-N)	^{1}H-NMR: 6.84 (*s*, CH=C), 7.00-8.23 (*m*, 13H, Ar-H), 2.65 (*s*, CH_3), 2.55 (*s*, CH_3). ^{13}C-NMR: 21.51, 21.49, 107.73, 126.51, 126.75, 128.20, 128.63, 128.77, 128.08, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.32, 137.66, 138.59, 169.60, 174.76.	74.97; 5.24; 7.29; 8.34 (74.54; 5.21; 7.51; 8.25)
2g	″	3-Cl	187	1646 (C=O), 1569 (Ar-C), 1489 (C=N), 1265 (C-S), 1157 (C-N)	^{1}H-NMR: 6.73 (*s*, CH=C), 7.15-7.99 (*m*, 13H, Ar-H), 2.38 (*s*, CH_3). ^{13}C-NMR: 21.44, 107.76, 126.51, 126.75, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.3, 137.66, 138.59, 169.56, 174.66.	68.22; H 4.23; 6.92; 7.92 (68.08; 4.30; 7.29; 7.81)
2h	″	4-Br	150	1695 (C=O), 1561 (Ar-C), 1449 (C=N), 1234 (C-S), 1159 (C-N)	^{1}H-NMR: 6.71 (*s*, CH=C), 7.12-8.00 (*m*, 13H, Ar-H), 2.39 (*s*, CH_3). ^{13}C-NMR: 21.65, 107.67, 121.95, 122.36, 128.62, 128.82, 128.89, 129.02, 129.40, 130.17, 130.33, 131.99, 133.87, 136.87, 137.63, 138.53, 142.13, 169.57, 174.67.	61.48; 3.81; 6.23; 7.14 (61.19; 3.49; 6.99; 7.20)
2i	″	2-MeO	167	1666 (C=O), 1544 (Ar-C), 1472 (C=N), 1275 (C-S), 1146 (C-N)	^{1}H-NMR: 6.67 (*s*, CH=C), 6.89-7.99 (*m*, 13H, Ar-H), 3.62 (*s*, OCH_3), 2.40 (*s*, CH_3). ^{13}C-NMR: δ 21.34, 56.08, 107.69, 126.51, 126.75, 128.09, 128.63, 128.77, 128.76, 129.06, 129.12, 129.67, 130.09, 130.21, 132.54, 134.30, 136.51, 137.66, 138.59, 169.56, 174.66.	71.98; 5.03; 6.99; 8.01 (70.65; 5.20; 7.35 8.09)

Table 1. Contunied.

Compd.	R	R'	mp (°C)	IR (ν/cm^{-1})	^{1}H- and ^{13}C-NMR spectral data (δ ppm)	(% Calcd.) C, H, N, S (% found) (C, H, N, S)
2j	″	2-NO_2	170	1645 (C=O), 1561 (Ar-C=C), 1459 (C=N), 1264 (C-S), 1154 (C-N)	^{1}H-NMR: 6.77 (*s*, 1H, CH=C), 7.11-8.20 (*m*, 13H, $2C_6H_4$, C_6H_5), 2.45 (*s*, 3H, CH_3); ^{13}C-NMR: 21.34, 107.71, 126.51, 126.75, 128.09, 128.63, 128.77, 129.12, 129.63, 130.09, 130.21, 132.54, 134.09, 136.51, 137.66, 138.42, 169.51, 174.83	66.49; 4.12; 10.11; 7.72 (65.89; 4.26; 10.67; 7.84)
2k	″	3-NO_2	191	1654 (C=O), 1567 (Ar), 1466 (C=N), 1285 (C-S), 1155 (C-N)	^{1}H-NMR: 6.58 (*s*, 1H, CH=C), 7.12-8.24 (*m*, 13H, $2C_6H_4$, C_6H_5), 2.45 (*s*, 3H, CH_3). ^{13}C-NMR: 21.53, 107.79, 126.51, 126.75, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 135.39, 137.66, 138.60, 169.76, 174.78.	66.49; 4.12; 10.11; 7.72 (66.01; 4.19; 10.50;7.80)
2l	4-Me	H	168	1634 (C=O), 1607 (Ar), 1459 (C=N), 1256 (C-S), 1155 (C-N)	^{1}H-NMR: 6.62 (*s*, CH=C), 7.14-8.11 (*m*, 14H, Ar-H), 2.45 (*s*, CH_3). ^{13}C-NMR: δ 21.44, 107.76, 126.51, 126.75, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.3, 137.66, 138.59, 169.56, 174.66.	74.57; 4.90; 7.96; 8.66 (74.14; 4.82; 8.21; 8.61)
2m	″	4-Br	204	1648 (C=O), 1598 (Ar), 1461 (C=N), 1258 (C-S), 1154 (C-N)	^{1}H-NMR: 6.68 (*s*, CH=C), 7.35-8.03 (*m*, 13H, Ar-H), 2.40 (*s*, CH_3). ^{13}C-NMR: δ 21.65, 107.67, 121.95, 122.36, 128.62, 128.82, 128.89, 129.02, 129.40, 130.17, 130.33, 131.99, 133.87, 136.87, 137.63, 138.53, 142.13, 169.57, 174.67.	61.48; 3.81; 6.23; 7.14 (61.06; 3.51; 6.52; 7.16)
2n	″	2-Me	159	1643 (C=O), 1590 (Ar), 1451 (C=N), 1260 (C-S), 1156 (C-N)	^{1}H-NMR: 6.06 (*s*, CH=C), 7.10-8.13 (*m*, 13H, Ar-H), 2.47 (*s*, CH_3), 2.42 (*s*, CH_3).	74.97; 5.24; 7.29; 8.34 (74.61; 5.29; 7.64; 8.28)
2o	″	2-MeO	206	1652 (C=O), 1597 (Ar), 1461 (C=N), 1249 (C-S), 1157 (C-N)	^{1}H-NMR: 6.16 (*s*, CH=C), 7.11-8.25 (*m*, 13H, Ar-H), 3.57 (*s*, OCH_3), 2.46 (*s*, CH_3).	71.98; 5.03; 6.99; 8.01 (71.21; 5.12; 7.08; 8.10)
2p	H	H	210	1633 (C=O), 1531 (Ar), 1450 (C=N), 1275 (C-S), 1158 (C-N)	^{1}H-NMR: 6.71 (*s*, CH=C), 7.00-8.21 (*m*, 15H, Ar-H).^{13}C-NMR: δ 107.6, 128.1, 128.5, 128.6, 128.9, 129.0, 129.4, 130.7, 131.6, 136.8, 137.7, 139.2, 170.0, 174.7.	74.13; 4.52; 7.86; 9.00 (74.01; 4.477.99; 8.78)
2q	2-Br	2,4-DiCl	181	1649 (C=O), 1542 (Ar), 1454 (C=N), 1256 (C-S), 1150 (C-N)	^{1}H-NMR: 6.76 (*s*, CH=C), 7.17-7.85 (*m*, 12H, Ar-H). ^{13}C-NMR: 107.8, 122.3, 128.0, 128.6, 128.8, 129.0, 129.1, 129.7, 130.5, 132.6, 134.4, 137.6, 139.0, 139.4, 170.1, 173.2.	52.40; 2.60; 5.56; 6.36 (52.15; 2.54; 5.83; 6.21)
2r	2-Cl	2-Me O	165	1640 (C=O), 1529 (Ar), 1453 (C=), 1278 (C-S), 1153 (C-N)	^{1}H-NMR: 6.72 (*s*, CH=C), 6.85-7.89 (*m*, 13H, Ar-H), 3.57 (*s*, OCH_3). ^{13}C-NMR: 21.49, 55.98, 107.71, 126.51, 126.75, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.09, 132.54, 134.30, 136.3, 137.66, 138.61, 169.67, 174.69.	65.63; 4.07; 6.66; 7.62 (65.17; 4.01; 6.97; 7.51)
2s	3-Cl	H	202	1653 (C=O), 1526 (Ar), 1451 (C=), 1265 (C-S), 1151 (C-N)	^{1}H-NMR: 6.76 (*s*, CH=C), 7.13-8.09 (*m*, 14H, Ar-H). ^{13}C-NMR: 107.70, 126.57, 126.71, 128.0, 128.63, 128.77, 128.88, 129.06, 129.12, 129.67, 130.09, 130.18, 132.54, 134.30, 136.31, 137.66, 138.53, 169.59, 174.79.	67.60; 3.87; 7.17; 8.2 (67.14; 3.76; 7.48; 8.04)
2t	H	1-naphthyl	194	1655 (C=O), 1560 (Ar), 1457 (C=), 1255 (C-S), 1154 (C-N)	^{1}H-NMR: 6.84 (*s*, CH=C), 7.08-7.99 (*m*, 17H, Ar-H). ^{13}C-NMR: 107.22, 122.98, 125.10, 126.57, 126.90, 127.38, 127.79, 128.22, 128.39, 128.48, 128.93, 129.23, 129.66, 130.14, 130.39, 131.36, 134.02, 134.58, 136.60, 169.97, 174.69.	76.82; 4.46; 6.89; 7.8 (75.30; 4.49; 7.08; 7.46)

It is evident from Table 2 that, in general, benzamides show low to moderate antifungal activity compared with terbinafine, which shows 100% inhibition in each case. Compounds with 3-methyl substituent at aroyl ring are somewhat more active as compared to those with 2-methyl and 4-methyl substituents. Those with a nitro or halo group in the aryl ring are more active. Compound **2e**, with no substitution at the aroyl ring and bearing a naphthyl group at C-3, is exceptionally active against 3 of the tested fungal strains.

Table 2. Growth effect % inhibition.

	R	**R'**	A. flavus	F. solani	Mucor sp.	A. niger	A. fumigatus
2a	2-Me	2-MeO	24.60	27.14	12.00	17.00	21.50
2b	2-Me	3-Me	25.47	29.31	11.00	15.00	23.70
2c	2-Me	2-Cl	31.64	37.42	21.00	18.00	21.70
2f	3-Me	3-Me	34.61	47.14	10.00	15.00	23.50
2g	3-Me	3-Cl	26.90	30.00	15.00	11.50	12.70
2h	3-Me	4-Br	34.61	31.42	22.50	14.50	26.70
2k	3-Me	2-NO_2	42.30	47.14	32.50	33.50	23.50
2n	4-Me	2-Me	26.23	28.00	15.00	11.30	19.40
2m	4-Me	4-Br	37.91	36.00	38.00	10.30	27.30
2o	4-Me	2-MeO	39.23	20.00	10.00	10.30	20.30
2q	2-Br	2,4-DiCl	38.46	30.00	27.50	15.60	10.80
2r	2-Cl	2-MeO	34.61	28.57	5.00	10.00	17.00
2s	3-Cl	H	42.30	32.85	20.00	13.00	12.70
2t	H	1-Naph-thyl	26.90	50.00	5.00	40.50	58.59
LLNC		-	65.00	35.00	100	90	78
Terbinafine	100	100	100	100	100	100	100

LLNC: Linear length in negative control

Criteria for significance:

Below 40% inhibition = Low activity 40%-60% Inhibition = Moderate activity

60%-70% Inhibition = Good activity 70% Inhibition = Significant activity

Experimental

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^{1}H-NMR spectra were determined as $CDCl_3$ solutions at 300 and 100 MHz on a Bruker AM-300 spectrophotometer. FT-IR spectra were recorded using an FTS 3000 MX spectrophotometer and elemental analyses with a LECO-183 CHNS analyzer. FT-IR spectra were recorded using an FTS 3000 MX spectrophotometer. Acetone and dichloromethane were dried according to standard procedures and distilled before use. All compounds were purified by thick layer chromatography using silica gel from Merck.

Antifungal screening

The antifungal activity was carried out in DMSO using the agar tube dilution method. Sabouraud dextrose agar (Merck) was prepared by dissolving 6.5 g/100 mL in distilled water and pH was adjusted at 5.6. The

contents were dissolved and dispensed as 4 mL volume into screw capped tubes and were autoclaved at 121 °C for 21 min. The tubes were allowed to cool to 50 °C and non-solidified SDA was loaded with 66.6 μL of compound by pipette from the stock solution. This gave the final concentration of 200 μg/mL of the pure compound in media. The tubes were then allowed to solidify in slanting position at room temperature. Tubes were prepared in triplicate for each fungus species. The tubes containing solidified media and test compound were inoculated with 4 mm diameter pieces of inocula, taken from a 7-day-old culture of fungus. Other media supplemented with DMSO and terbinafine were used as negative and positive control respectively. All experiments were done in 3 replicates. The tubes were incubated at 28 °C for 7 days. Cultures were examined twice weekly during the incubation. Growth in the media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control.

Synthesis of N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene substituted benzamides (2a–2t)

Triethylamine (1 mmol) was added to a stirred solution of 1-aroyl-3-arylthiourea (1 mmol) in dry dichloromethane (20 mL), followed by drop-wise addition of a solution of bromine (1 mmol) in acetophenone (1 mmol) under nitrogen. The reaction mixture was stirred for 1-2 h and progress of the reaction was monitored by thin layer chromatography (hexane:ethyl acetate 4:1). After the reaction was complete, the mixture was filtered; the filtrate was concentrated to afford N-(4-phenyl-3-aroylthiazol-2(3H)-ylidene) substituted benzamides, which were purified by recrystallization from 95% ethanol.

References

1. Parsons Jr.; R. L.; Heathcock, C. H. *Tetrahedron Lett.,* **1994**, *35*, 1379-.
2. Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.*, **1994**, *35*, 5705.
3. Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.*, **2001**, *123*, 5418.
4. Luesch, H.; Yoshida, Y.; Moore, R. E.; Paul, V. J. *Bioorg. Med. Chem.*, **2002** *10*, 1973.
5. Bowden B. F.; Garcia, G. D. (WO9739025A1, October 23, 1997); *Chem. Abstr.*, **1997**, *127*, 290919m.
6. Anderson, B.; Hodgkin, D. C.; Viswamitra, M. A. *Nature*, **1970**, *225*, 233.
7. McConkey, G. A.; Rogers, M. J.; McCutchan, T. F. *J. Biol. Chem.*, **1997**, *272*, 2046-
8. Quiroga; Hernandez, P.; Insuassty, B. R.; Abonia, R.; Cobo, J.; Sanchez, A.; Nogueras, M.; Low, J. N. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 555.
9. Hutchinson, I; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; M. F. G. Stevens*, J. Med. Chem.,* **2002**, *45*, 744.
10. Hargrave, D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.*, **1983**, *26*, 1158.
11. Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem.*, **1992**, *35*, 2562.
12. Sharma, K.; Sawnhney, S. N.; Gupta, A.; Singh, G. B.; Bani, S. *Indian J. Chem.*, **1998**, *37B*, 376-.
13. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 1601.

14. Naidu, B. N.; Sorenson, M. E.; Zhang, Y.; Kim, O. K.; Matiskella, J. D.; Wichtowski, J. A.; Connolly, T. P.; Li, W.; Lam, K. S.; Bronson, J. J.; Pucci, M. J.; Clark, J. M.; Ueda, Y. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 5573.
15. Vicini, P.; Geronikaki, A.; Anastasia, K.; Incertia, M.; Zania, F. *Bioorg. Med. Chem.*, **2006**, *14*, 3859.
16. Eid, S.; Guerro, M.; Lorcy, D. *J. Tetrahedron Lett.*, **47**, 8333.
17. Seenisamy, J.; Bashyam, S.; Gokhale, V.; Vankayalapati, H.; Sun, D.; Siddiqui-Jain, A.; Streiner, N.; Shin-Yan, K.; White, E.; Wilson, W. D.; Hurley, L. H. *J. Am. Chem. Soc.*, **2005**, *127*, 2944.
18. Shukla, U. P.; Singh, R.; Khanna, J. M.; Saxene, A. K.; Singh, H. K.; Sur, R. N.; Dhawan, B. N.; Anand, N. Coll. *Czech. Chem. Commun.*, **1992**, *57*, 415.
19. Xie, M.; Zhong, A.; Zhang, X. *Yaoxue Xuebao,* **1983**, *18*, 147. *Chem.*, **1980**, *23*, 773-.
20. Zhang, A.; Kayser, H.; Maienfisch, P.; Casida, J. E. *J. Neurochem.*, **2000**, *75*, 1294.
21. Hosseinimehr, S. J.; Shafiee, A.; Mozdarani, H.; Akhlagpour, S. *J. Radiat. Res.*, **2001**, *42*, 401.
22. Bae, S.; Hahnand, H. –G.; Nam, K. D. *J. Comb. Chem.*, **2005**, *7*, 7.
23. Kim, D.-S.; Jeong, Y. –M.; Park, I. –K.; Hahn, H. –G.; Lee, H. –K. *Biol. Pharm. Bull.*, **2007**, *30*, 180.
24. Saeed, A.; Parvez. M.; *Cent. Eur. J. Chem.*, **2005**, *3*, 780.
25. Pietrancosta, N.; Moumen, A.; Dono, R.; Lingor, P.; Planchamp, V.; Lamballe, F.; Bahr, M.; Jean-L Kraus, Maina, F.; *J. Med. Chem.* **2006,** *49,* 3645-3652.
26. Saeed, A.; Parvez, M.; *J. Heterocycl. Chem.,* **2006,** *43***,** 1027-1030.
27. Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397
28. Zeng, R.-S.; Zou, J.-P.; Zhi, S.-J.; Chen, J.; Shen, Q. *Org. Lett.* **2003**, *5*, 1657.
29. Wang, X.-C.; Wang, F.; Quan, Z. J.; Wang, M.-G.; Li, Z. *J. Chem. Res.* **2005**, 689.