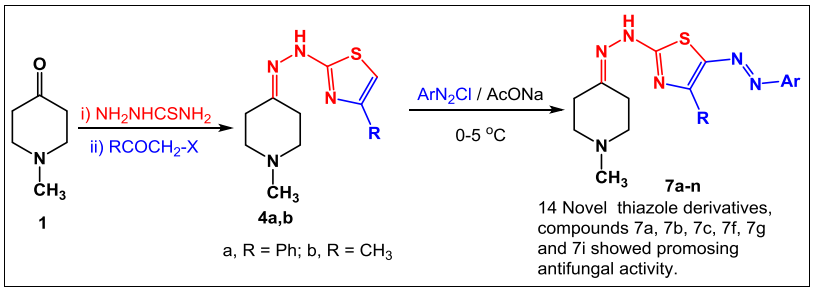
Salama A. Ouf,[a] Sobhi M. Gomha,[b]* Mohamed M. Ewies,[a] and Ihab A. A. Sharawy[a]

[a]Botany and Microbiology Department, Faculty of Science, Cairo University, Giza 12613, Egypt
[b]Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt
*E-mail: s.m.gomha@gmail.com
Received July 26, 2017
DOI 10.1002/jhet.3040
Published online 27 October 2017 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel arylazothiazole derivatives were synthesized in good yield via coupling of thiazole derivatives with arenediazonium chloride in ethanol in the presence of sodium acetate trihydrate at 0–5°C. The structures of the newly synthesized products were elucidated via elemental analysis, spectral data, and alternative routes whenever possible. Moreover, the antidermatophtic activity screening of the products was evaluated, and the results revealed that compounds **7a**, **7b**, **7c**, **7f**, **7g**, and **7i** showed broad potency and induced more inhibition against the tested fungi compared to fluconazole as antifungal standard drug.

J. Heterocyclic Chem., **55**, 258 (2018).

INTRODUCTION

One of the most important heterocyclic compounds is thiazole ring because of the wide range of biological activities [1–7]. Several marketing drugs for several diseases contain thiazole moiety such as sulfathiazole (antimicrobial drug), thiabenzadole (antifungal drug), ritonavir (antiretroviral), cefdinir (bacteriocidal antibiotic of the cephalosporin class of antibiotics), talipexole (treatment for Parkinson's disease), epothilones (cancer drugs), and simeprevir (a drug for the treatment and cure of hepatitis C) (Fig. 1).

Piperidin-4-one derivatives are widely prevalent in numerous alkaloids and synthetically derived compounds of biological importance due to their antibacterial, antifungal, analgesic, antipyretic, and antimycobacterial activities [8–11]. Antimicrobial screening studies pointed out that variously 2-[3-methyl-2,6-disubstituted piperidin-4-hydrazono]-1,3-thiazolidin-4-ones have promising activities against *Staphylococcus aureus*, Rhizopus sp., and *Klebsiella pneumoniae* and showed twofold improved potency than ciprofloxacin and amphotericin B reference drugs [12]

From the previous findings and as a part of an ongoing research program on synthesis of bioactive thiazoles [13–22], we are interested herein to synthesize a new series of 2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-4-substituted-5-(aryldiazenyl)thiazole derivatives to investigate their antidermatophtic activity.

RESULTS AND DISCUSSION

The aim of our research to synthesize new active thiazole derivatives can be achieved by synthesis of the starting thiosemicarbazone derivative **2** *via* the reaction of 1-methylpiperidin-4-one (**1**) with thiosemicarbazide under reflux in ethanol in the presence of HCl as acidic catalyst as depicted in Scheme 1. The structure of compound **2** was characterized using the spectral data and elemental analyses (see Experimental part).

Reaction of compound **2** with α-haloketones as phenacyl bromide **3a** and chloroacetone **3b** in dioxane in the presence of Et_3N afforded the thiazole derivatives **4a,b**, respectively, *via* the substitution reaction with elimination of HCl, followed by *in situ* cyclization with elimination of water molecule (Scheme 1).

The authentic sample of **4a** could be prepared through alternative synthetic procedure. Thus, 1-methylpiperidin-4-one (**1**) was reacted with 2-hydrazinyl-4-phenylthiazole (**5**) in refluxing ethanol to give thiazole derivative **4a** (Scheme 1).

Next, our study was extended to investigate the reactivity of compound **2** toward hydrazonoyl halides aiming to synthesize new heterocyclic compounds containing 1,3-thiazole ring. Thus, thiazole **4a,b** was react with benzenediazonium chloride in ethanol in the presence of sodium acetate trihydrate at 0–5°C to give one isolable product (as evidenced by TLC analysis of

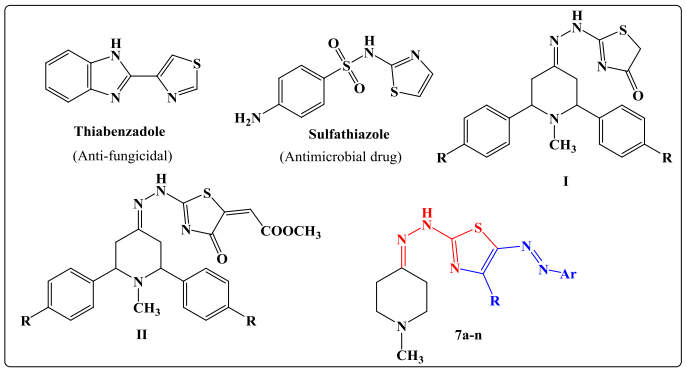
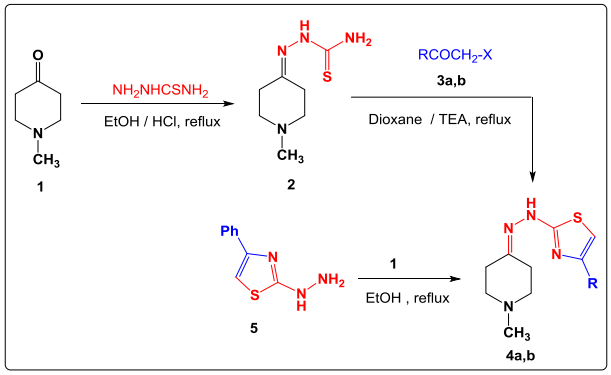


Figure 1. Structures of some thiazole-based antimicrobials and the targeted compounds **7a–n.** [Color figure can be viewed at wileyonlinelibrary.com]

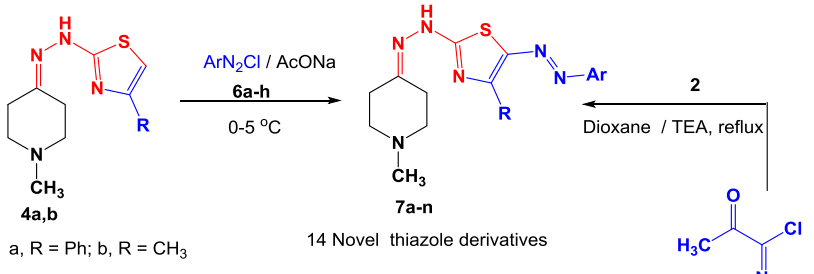
Scheme 1. Synthesis of thiazole derivatives **4a,b.** [Color figure can be viewed at wileyonlinelibrary.com]



the crude product), which were identified to be products **7** (Scheme 2). The structures of products **7** were elucidated by elemental and spectral (IR, ^{1}HNMR, mass) data. The IR spectra of products **7** showed in each case one stretching band at υ ~3430 cm^{-1} assigned to the NH group. ^{1}HNMR spectra of compounds **7** revealed in addition to the expected signals of the aromatic protons, and the protons of the 1-methylpiperidine and the R groups, a singlet signal at δ ~9.80 ppm assigned to the −NH proton. The mass spectra of all products **7** exhibited in each case, a molecular ion peak at the correct molecular weight for the respective compound (see Experimental).

The structures of products **7** were further confirmed by an alternative method. Thus, reaction of compound **2** with 2-oxo-*N*′-phenylpropanehydrazonoyl chloride (**8**) [23] in dioxane under reflux in the presence of triethylamine as basic catalyst, to give a product identical in all respects (IR, mp, and mixed mp.) with **7f**, which obtained from reaction of **4b** with benzene diazonium chloride **6a** (Scheme 2).

Scheme 2. Synthesis of arylazothiazole derivatives **7a–n.** [Color figure can be viewed at wileyonlinelibrary.com]



Cpd No.	R	Ar	Cpd No.	R	Ar
a	Ph	Ph	h	CH_3	2-$CH_3C_6H_4$
b	Ph	4-$CH_3C_6H_4$	i	CH_3	4-$CH_3OC_6H_4$
c	Ph	4-$CH_3OC_6H_4$	j	CH_3	4-ClC_6H_4
d	Ph	4-ClC_6H_4	k	CH_3	2-ClC_6H_4
e	Ph	4-$NO_2C_6H_4$	l	CH_3	3-ClC_6H_4
f	CH_3	Ph	m	CH_3	4-$NO_2C_6H_4$
g	CH_3	4-$CH_3C_6H_4$	n	CH_3	2,4-$(Cl)_2C_6H_3$

BIOLOGICAL ACTIVITY

***In vitro* evaluation of antifungal activity.** The synthesized compounds **7a–n** were screened for their *in vitro* antifungal activity against the skin infecting fungi, namely, *Candida albicans* (RCMB 05079, Ca), *Microsporum gypseum* (RCMB 09321, Mg), and *Trichophyton mentagrophytes* (RCMB 09285, Tm), using Fluconazole as standard drug to evaluate the potency of the tested compounds under the same conditions. The organisms were tested against the activity of solutions of concentrations (100 µg/mL) and using inhibition zone diameter in mm using a diffusion assay method.

The results depicted in Table 1 and Figure 2 revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested fungal strains.

In general, the chemical structure of the whole molecule, comprising the nature of the heterocyclic system as well as the type of the substituted function present in the heterocyclic ring structure, has a pronounced effect on antifungal activity.

Most of the corresponding substituted analogues produced higher inhibitory effects against the tested fungal strains similar or superior to the reference drug fluconazole.

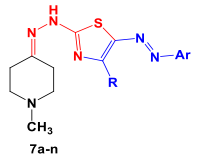
The results revealed that the descending order of activity of the newly synthesized compounds was as follows: for CA: **7a** > **7f**; for MG: **7i** > **7g** > **7a** > **7f**; for TM: **7a** > **7c** > **7f** > **7b.**

Examination of the SAR leads to the following conclusions.

- 4-Phenyl-substituted thiazoles have *in vitro* inhibitory activity more than 4-methyl-thiazoles: for CA: **7a** > **7f**, **7b** > **7g**, **7c** > **7i**, **7d** > **7j**; for MG: **7a** > **7f**, **7d** > **7j**, **7e** > **7m**; for TM: **7a** > **7f**, **7b** > **7g**, **7c** > **7i**, **7d** > **7j**, **7e** > **7m**.
- For CA and TM, on fixation the substituent at position 4 of the thiazole derivatives, the un-substituted thiazole derivatives have *in vitro* inhibitory activity more than the substituted thiazoles (**7a** and **7f** are the most active thiazoles).
- The introduction of a methoxy group or methyl group (electron-donating groups) at the 4-position of phenyl group at position 5 in the thiazole ring resulted in the increase of the activity. In contrast, introduction of chlorine atom or nitro group (electron-withdrawing groups) decreases the antifungal activity (for phenyl-thiazoles: **7b**, **7c** > **7d**, **7e** with all the tested fungal strains).
- Thiazoles with methoxy group or methyl group as electron-donating group on aryl moiety have promising antifungal activity while thiazoles with chlorine atom or nitro group as electron-withdrawing group on aryl moiety have low activity (for phenyl-thiazoles: **7b**, **7c** > **7d**, **7e** with all the tested fungal strains).
- For phenyl-thiazoles: the introduction of methyl group at the 4-position of phenyl group at position 5 in the

Table 1

Preliminary test for the fungitoxicity of synthesized thiazole derivatives (100 µg/mL) on diameter of inhibition zone of *Candida albicans*, *Trichophyton mentagrophytes*, and *Microsporum gypseum*.



7a-n

Thiazole derivatives	R	Ar	Inhibition zone (mm)		
			C. A	*M. G*	*T. M*
7a	Ph	Ph	4.32 ± 0.10	7.20 ± 0.10	7.58 ± 0.10
7b	Ph	4-$CH_3C_6H_4$	3.33 ± 0.12	5.79 ± 0.10	6.75 ± 0.10
7c	Ph	4-$CH_3OC_6H_4$	3.51 ± 0.12	5.94 ± 0.09	7.27 ± 0.15
7d	Ph	4-ClC_6H_4	2.55 ± 0.09	5.60 ± 0.10	5.33 ± 0.10
7e	Ph	4-$NO_2C_6H_4$	1.35 ± 0.09	5.30 ± 0.10	5.60 ± 0.09
7f	CH_3	Ph	4.02 ± 06	7.10 ± 0.09	6.85 ± 0.09
7g	CH_3	4-$CH_3C_6H_4$	2.35 ± 0.05	7.60 ± 0.09	4.20 ± 0.09
7h	CH_3	2-$CH_3C_6H_4$	1.80 ± 0.05	4.60 ± 0.09	3.83 ± 0.08
7i	CH_3	4-$CH_3OC_6H_4$	1.73 ± 0.06	7.68 ± 0.09	3.48 ± 0.08
7j	CH_3	4-ClC_6H_4	1.65 ± 0.05	5.33 ± 0.08	4.25 ± 0.08
7k	CH_3	2-ClC_6H_4	2.38 ± 0.09	5.60 ± 0.23	4.33 ± 1.24
7l	CH_3	3-ClC_6H_4	2.56 ± 0.05	5.85 ± 0.06	4.87 ± 0.09
7m	CH_3	4-$NO_2C_6H_4$	2.43 ± 0.06	4.68 ± 0.08	4.68 ± 0.08
7n	CH_3	2,4-$(Cl)_2C_6H_3$	2.37 ± 0.06	4.60 ± 0.09	4.10 ± 0.09
Fluconazole	–	–	3.83 ± 0.06	6.83 ± 0.06	6.17 ± 0.06

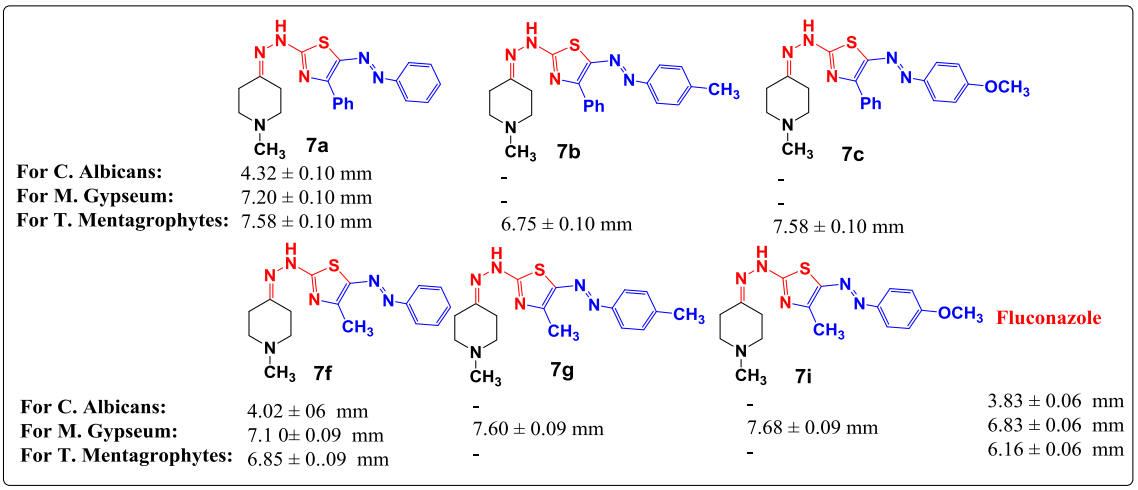


Figure 2. Structures of the most active 1-methylpiperidin-4-ylidene-hydrazinyl-5-(aryldiazenyl)thiazoles. [Color figure can be viewed at wileyonlinelibrary.com]

thiazole ring resulted in the increase of the activity than 2-position (**7g** > **7h**) with all the tested fungal strains. In contrast, introduction of chlorine atom at the 4-position of phenyl group at position 5 in the thiazole ring resulted in the decrease of the activity than 2-position than 3-po sition (**7j** > **7k** > **7l**) with all the tested fungal strains.

EXPERIMENTAL

All melting points were determined on an electrothermal Gallen kamp apparatus and are uncorrected. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}HNMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz) using TMS as an internal standard in dimethyl sulfoxide (DMSO)-d_6. The mass spectra were recorded on a GCMSQ1000-EX Shimadzu and GCMS 5988-A HP spectrometers, and the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt.

Synthesis of 2-(1-methylpiperidin-4-ylidene) hydrazinecarbothioamide (2). A mixture of 1-methylpiperidin-4-one (**1**) (1.13 g, 10 mmol) and thiosemicarbazide (0.91 g, 10 mmol) was dissolved in 40 mL of EtOH containing catalytic amounts of HCl that was refluxed for 6 h. The desired product was precipitated from reaction mixture, which was filtered, washed with EtOH, and recrystallized from dioxane to give the hydrazinecarbothioamide derivative **2** as yellowish-white solid (70%); mp 170–172°C (dioxane); IR (KBr): *v* 3421, 3250 (NH + NH_2), 3047, 2927 (CH), 1601 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.22–1.30 (m, 4H, $2CH_2$), 2.93–3.04 (m, 4H, $2CH_2$), 3.53 (s, 3H, NCH_3), 4.70 (brs, 2H, NH_2), 10.28 (brs, 1H, NH); MS *m/z* (%): 186 (M^+, 9), 134 (42), 117 (100), 75 (65), 61 (96). *Anal*. Calcd. for $C_7H_{14}N_4S$ (186.09): C, 45.13; H, 7.58; N, 30.08. Found: C, 45.32; H, 7.46; N, 30.01%.

Synthesis of thiazoles 4a,b. A mixture of an equimolecular amounts of 2-(1-methylpiperidin-4-ylidene)hydrazine carbothioamide (**2**) (1.86 g, 10 mmol) and phenacyl bromide (**3a**) or chloroacetone (**3b**) (10 mmol) in ethanol was refluxed for 4 h (monitored by TLC). After cooling, the reaction mixture was poured into ice/HCl and the precipitate formed was collected by filtration, dried and recrystallized from ethanol to give products **4a,b,** respectively.

2-(2-(1-Methylpiperidin-4-ylidene)hydrazinyl)-4-phenylthiazole (4a). Yellow solid (69%); mp 149–151°C (EtOH); IR (KBr): *v* 3431 (NH), 3029, 2936 (CH), 1599 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.24 (m, 4H, $2CH_2$), 2.92 (m, 4H, $2CH_2$), 3.52 (s, 3H, NCH_3), 6.95–7.32 (m, 5H, Ar-H), 7.66 (s, 1H, thiazole-H), 10.03 (s, 1H, NH); MS *m/z* (%): 286 (M^+, 8), 253 (60), 155 (38), 77 (100). *Anal*. Calcd. for $C_{15}H_{18}N_4S$ (286.13): C, 62.91; H, 6.33; N, 19.56. Found: C, 62.99; H, 6.30; N, 19.39%.

4-Methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl) thiazole (4b). Yellow solid (66%); mp 182–184°C (EtOH); IR (KBr): *v* 3427 (NH), 3029, 2936 (CH), 1597 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28 (m, 4H, $2CH_2$), 2.92 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 7.62 (s, 1H, thiazole-H), 10.26 (s, 1H, NH); MS *m/z* (%): 224 (M^+, 14), 187 (100), 105 (69), 64 (83). *Anal*. Calcd. for $C_{10}H_{16}N_4S$ (224.11): C, 53.54; H, 7.19; N, 24.98. Found: C, 53.54; H, 7.19; N, 24.98%.

Alternate synthesis of 4a. A mixture of 1-methylpiperidin-4-one (**1**) (0.113 g, 1 mmol) and 2-hydrazinyl-4-phenylthiazole (**5**) (0.191 g, 1 mmol) in

ethanol (10 mL) was refluxed for 4 h. The formed precipitate after cooling was isolated by filtration, washed with methanol, dried and recrystallized from DMF to give product proved to be identical in all respects (mp, mixed mp and IR spectra) with compounds **4a**, which obtained from reaction of **2** with **3a.**

Coupling of thiazoles 4a,b with arenediazonium chlorides 6a–n. ***General procedure.*** To a solution of thiazole derivatives, **4a** or **4b** (1 mmol) in pyridine (10 mL) was added with the appropriate arenediazonium chloride solution [prepared as usual by diazotizing substituted aniline derivatives (1 mmol) in hydrochloric acid (1 mL, 6 M) with sodium nitrite (0.07 g, 1 mmol) in 10 mL of water], portionwise with stirring and cooling. After complete addition, the reaction mixture was left for 12 h in the refrigerator. The precipitate formed was collected by filtration, washed with water, dried and then recrystallized from DMF to give the respective products **7a–n**. The products **7a–n** together with their physical constants are listed in the following.

2-(2-(1-Methylpiperidin-4-ylidene)hydrazinyl)-4-phenyl-5-(phenyldiazenyl)thiazole (7a). Red solid (69%); mp 132–134°C (DMF); IR (KBr): *v* 3431 (NH), 3038, 2925 (CH), 1625 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.20 (m, 4H, $2CH_2$), 2.82 (m, 4H, $2CH_2$), 3.53 (s, 3H, NCH_3), 7.22–8.23 (m, 10H, Ar-H), 9.76 (brs, 1H, NH); MS *m*/*z* (%): 390 (M^+, 12), 350 (36), 279 (28), 134 (44), 77 (82), 59 (100). *Anal*. Calcd. for $C_{21}H_{22}N_6S$ (390.16): C, 64.59; H, 5.68; N, 21.52. Found: C, 64.47; H, 5.55; N, 21.38%.

2-(2-(1-Methylpiperidin-4-ylidene)hydrazinyl)-4-phenyl-5-(p-tolyldiazenyl)thiazole (7b). Red solid (69%); mp 125–127°C (EtOH); IR (KBr): *v* 3431 (NH), 3059, 2922(CH), 1614 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.23 (m, 4H, $2CH_2$), 2.35 (s, 3H, CH_3), 2.85 (m, 4H, $2CH_2$), 3.56 (s, 3H, NCH_3), 7.06–8.26 (m, 9H, Ar-H), 9.89 (br s, 1H, NH); MS *m*/*z* (%): 404 (M^+, 25), 305 (16), 189 (21), 117 (34), 87 (22), 59 (100). *Anal*. Calcd. for $C_{22}H_{24}N_6S$ (404.18): C, 65.32; H, 5.98; N, 20.77. Found: C, 65.47; H, 5.79; N, 20.58%.

5-((4-Methoxyphenyl)diazenyl)-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-4-phenylthiazole (7c). Red solid (66%); mp 174–176°C (DMF); IR (KBr): *v* 3422 (NH), 3048, 2926 (CH), 1621 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.23 (m, 4H, $2CH_2$), 2.80 (m, 4H, $2CH_2$), 3.56 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 7.08–8.25 (m, 9H, Ar-H), 9.78 (br s, 1H, NH); MS *m*/*z* (%): 420 (M^+, 31), 305 (10), 175 (21), 117 (35), 87 (20), 59 (100). *Anal*. Calcd. for $C_{22}H_{24}N_6OS$ (420.17): C, 62.83; H, 5.75; N, 19.98. Found: C, 62.64; H, 5.71; N, 19.74%.

5-((4-Chlorophenyl)diazenyl)-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-4-phenyl thiazole (7d). Red solid (69%); mp 160–162°C (DMF); IR (KBr): *v* 3431 (NH), 3040, 2924 (CH), 1617 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.24 (m, 4H, $2CH_2$), 2.83 (m, 4H, $2CH_2$), 3.57 (s, 3H, NCH_3), 7.20–8.24 (m, 9H, Ar-H), 9.83 (br s, 1H, NH); MS *m*/*z* (%): 426 (M^++2, 6), 424 (M^+, 20), 305 (16), 247 (12), 189 (15), 113 (40), 59 (100). *Anal*. Calcd. for $C_{21}H_{21}ClN_6S$ (424.12): C, 59.35; H, 4.98; N, 19.78. Found: C, 59.57; H, 4.91; N, 19.63%.

2-(2-(1-Methylpiperidin-4-ylidene)hydrazinyl)-5-((4-nitrophenyl)diazenyl)-4-phenylthiazole (7e). Brown solid (70%); mp 128–230°C (EtOH); IR (KBr): *v* 3431 (NH), 3062, 2924 (CH), 1593 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.25 (m, 4H, $2CH_2$), 2.85 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 7.18–8.29 (m, 9H, Ar-H), 9.70 (br s, 1H, NH); MS *m*/*z* (%): 435 (M^+, 36), 305 (16), 189 (26), 117 (29), 87 (22), 59 (100). *Anal*. Calcd. for $C_{21}H_{21}N_7O_2S$ (435.15): C, 57.92; H, 4.86; N, 22.51. Found: C, 57.75; H, 4.69; N, 22.36%.

4-Methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-5-(phenyldiazenyl)thiazole (7f). Red solid (66%); mp 180–182°C (DMF); IR (KBr): *v* 3427 (NH), 3025, 2921(CH), 1597 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.21 (d, 4H, $2CH_2$), 2.44 (s, 3H, CH_3), 2.67 (d, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 7.05–8.21 (m, 5H, Ar-H), 11.16 (br s, 1H, NH); MS *m*/*z* (%): 328 (M^+, 11), 227 (51), 117 (38), 59 (100). *Anal*. Calcd. for $C_{16}H_{20}N_6S$ (328.15): C, 58.51; H, 6.14; N, 25.59. Found: C, 58.69; H, 6.02; N, 25.47%.

4-Methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-5-(p-tolyldiazenyl)thiazole (7g). Red solid (68%); mp 167–169°C (DMF); IR (KBr): *v* 3434 (NH), 3029, 2921(CH), 1617 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.19 (m, 4H, $2CH_2$), 2.24 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.60 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 6.89–7.92 (m, 4H, Ar-H), 10.04 (br s, 1H, NH); MS *m*/*z* (%): 342 (38), 247 (40), 117 (35), 59 (100). *Anal*. Calcd. for $C_{17}H_{22}N_6S$ (342.16): C, 59.62; H, 6.48; N, 24.54. Found: C, 59.79; H, 6.35; N, 24.46%.

4-Methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-5-(o-tolyldiazenyl)thiazole (7h). Red solid (68%); mp 160–162°C (DMF); IR (KBr): *v* 3428 (NH), 3029, 2965 (CH), 1627 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.18 (m, 4H, $2CH_2$), 2.27 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.97 (m, 4H, $2CH_2$), 3.55 (s, 3H, NCH_3), 6.89–7.92 (m, 4H, Ar-H), 10.95 (br s, 1H, NH); MS *m*/*z* (%): 342 (41), 247 (30), 117 (69), 87 (52), 59 (100). *Anal*. Calcd. for $C_{17}H_{22}N_6S$ (342.16): C, 59.62; H, 6.48; N, 24.54. Found: C, 59.72; H, 6.41; N, 24.32%.

5-((4-Methoxyphenyl)diazenyl)-4-methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)thiazole (7i). Red solid (66%); mp 185–187°C (DMF); IR (KBr): *v* 3422 (NH), 3033, 2960 (CH), 1617 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.15 (m, 4H, $2CH_2$), 2.47 (s, 3H, CH_3), 3.02 (m, 4H, $2CH_2$), 3.67 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.89–7.92 (m, 4H, Ar-H), 10.04 (brs, 1H, NH); MS *m*/*z* (%): 358 (20), 297 (36), 251 (46), 113 (40), 59 (100). *Anal*. Calcd. for $C_{17}H_{22}N_6OS$ (358.16): C, 56.96; H, 6.19; N, 23.44. Found: C, 56.74; H, 6.04; N, 23.30%.

5-((4-Chlorophenyl)diazenyl)-4-methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)thiazole (7j). Red solid (68%); mp 218–220°C (DMF); IR (KBr): *v* 3424 (NH), 3027, 2929 (CH), 1623 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.19 (m, 4H, $2CH_2$), 2.37 (s, 3H, CH_3), 3.01 (m, 4H, $2CH_2$), 3.60 (s, 3H, NCH_3), 7.11–7.76 (m, 4H, Ar-H), 10.22 (br s, 1H, NH); MS *m*/*z* (%): 364 (M^++2, 4), 362 (M^++2, 11), 247 (20), 297 (30), 189 (38), 117 (62), 59 (100). *Anal*. Calcd. for $C_{16}H_{19}ClN_6S$ (362.11): C, 52.96; H, 5.28; N, 23.16. Found: C, 52.96; H, 5.28; N, 23.16%.

5-((2-Chlorophenyl)diazenyl)-4-methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)thiazole (7k). Red solid (66%); mp 187–189°C (EtOH); IR (KBr): *v* 3430 (NH), 2927 (CH), 1594 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.19 (m, 4H, $2CH_2$), 2.41 (s, 3H, CH_3), 3.03 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 7.06–7.78 (m, 4H, Ar-H), 10.20 (br s, 1H, NH); MS *m*/*z* (%): 364 (M^++2, 29), 362 (M^++2, 90), 329 (28), 189 (30), 117 (55), 59 (100). *Anal*. Calcd. for $C_{16}H_{19}ClN_6S$ (362.11): C, 52.96; H, 5.28; N, 23.16. Found: C, 52.91; H, 5.15; N, 23.02%.

5-((3-Chlorophenyl)diazenyl)-4-methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)thiazole (7l). Red solid (66%); mp 170–172°C (DMF); IR (KBr): *v* 3425 (NH), 2970, 2927 (CH), 1592 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.18 (m, 4H, $2CH_2$), 2.42 (s, 3H, CH_3), 3.05 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 6.93–7.76 (m, 4H, Ar-H), 10.73 (br s, 1H, NH); MS *m*/*z* (%): 364 (M^++2, 17), 362 (M^++2, 49), 247 (31), 117 (40), 59 (100). *Anal*. Calcd. for $C_{16}H_{19}ClN_6S$ (362.11): C, 52.96; H, 5.28; N, 23.16. Found: C, 52.69; H, 5.15; N, 23.04%.

4-Methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)-5-((4-nitrophenyl)diazenyl)thiazole (7m). Brown solid (66%); mp 210–212°C (EtOH); IR (KBr): *v* 3430 (NH), 2925 (CH), 1595 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.19 (m, 4H, $2CH_2$), 2.45 (s, 3H, CH_3), 3.04 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 7.10–8.18 (m, 4H, Ar-H), 10.43 (br s, 1H, NH); MS *m*/*z* (%): 373 (M^+, 28), 317 (80), 247 (24), 117 (39), 59 (100). *Anal*. Calcd. for $C_{16}H_{19}N_7O_2S$ (373.13): C, 51.46; H, 5.13; N, 26.26. Found: C, 51.59; H, 5.01; N, 26.15%.

5-((2,4-Dichlorophenyl)diazenyl)-4-methyl-2-(2-(1-methylpiperidin-4-ylidene)hydrazinyl)thiazole (7n). Brown solid (71%); mp 247–249°C (DMF); IR (KBr): *v* 3433 (NH), 2975, 2938 (CH), 1592 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.19 (m, 4H, $2CH_2$), 2.46 (s, 3H, CH_3), 3.02 (m, 4H, $2CH_2$), 3.54 (s, 3H, NCH_3), 7.76 (m, 3H, Ar-H), 10.37 (br s, 1H, NH); MS *m*/*z* (%): 369 (M^+, 18), 247 (40), 113 (36), 59 (100). *Anal*. Calcd. for $C_{16}H_{18}Cl_2N_6S$ (396.07): C, 48.37; H, 4.57; N, 21.15. Found: C, 48.25; H, 4.50; N, 21.26%.

Alternate synthesis of 7f. A mixture of 2-(1-methylpiperidin-4-ylidene) hydrazinecarbothioamide (**2**) (0.186 g, 1 mmol) and 2-oxo-*N*′-phenylpropane hydrazonoyl chloride (**8**) (0.196 g, 1 mmol) in dioxane (30 mL) containing triethylamine (0.1 g, 1 mmol) was refluxed for 8 h. The formed precipitate after cooling was isolated by filtration, washed with methanol, dried and recrystallized from DMF to give product proved to be identical in all respects (mp, mixed mp and IR spectra) with compounds **7a**, which obtained from reaction of **4b** with **6a**.

IN VITRO EVALUATION OF ANTIFUNGAL ACTIVITY

Test fungi. Three skin infecting fungi, namely, *C. albicans*, *Microsporum gypseum*, and *Trichophyton mentagrophytes*, were used in this study. *C. albicans* was obtained from the department of microbiology, faculty of medicine, Cairo University, and was originally isolated from oral cavity of patient attending the university hospital. The other fungi were obtained from culture collection of the second author and were originally isolated from the dermatology clinics at Kasr Elainy, hospitals. The fungi were stored in Sabouraud dextrose (SD) broth (Oxoid) with 20% glycerol at 28°C and propagated on potato dextrose agar (Oxoid) plates incubated at 28°C before each test. The inocula were prepared from 7-day-old cultures.

The synthesized compounds were screened for their *in vitro* antifungal activity against the skin infecting fungi using a diffusion assay method. The Sabouraud agar medium (dextrose 4%, peptone 1%, and agar 1.5%) was used for determining antifungal activity of the synthesized compounds. The medium was prepared and sterilized in an autoclave for 15 min at 15 psi. Then, it was aseptically transferred into sterilized Petri plates. After duration of 2 h, the fungal suspensions were adjusted to the turbidity of 1.5×10^5 CFU/mL with a sterile saline solution (0.85% NaCl) and were separately inoculated on the surface of Petri plates. Following this, the cups of approximately 6 mm in diameter were made in the Sabouraud agar medium using sterilized cup borer under aseptic conditions. Then 0.1 mL of each standard and test compounds (100 μg/mL) prepared by dissolving in 30% DMSO was added into cups. Following addition of solutions, the inoculated plates were incubated for 48 h in the case of *C. albicans* and for 72 h for the other two fungi at a temperature of 28 ± 2°C, and then, growth and zones of inhibition (in mm) were recorded. Negative controls were prepared using the same solvents employed to dissolve the tested compounds, and fluconazole (Sigma, Steinheim, Germany) was used as positive controls or reference standard drugs for comparing the sensitivity of tested fungi. Clear inhibition zones around discs indicated the presence of antimicrobial

activity. For optimal fidelity of results, each assay was repeated three times [24].

CONCLUSION

In the present paper, a simple and convenient method was developed for the synthesis of new ethylidenehy drazonothiazoles incorporating 1-methylpiperidine moiety. All the newly synthesized compounds were screened for their antifungal activity. The results indicated that six compounds exhibited high to moderate antidermatophtic activities compared with the reference drug used in the investigation.

REFERENCES AND NOTES

[1] Yadlapalli, R. K.; Chourasia, O. P.; Jogi, M. P.; Podile, A. R.; Perali, R. S. Med Chem Res 2013, 22, 2975.

[2] Gomha, S. M.; Khalil, K. D.; Abdel-aziz, H. M.; Abdalla, M. M. Heterocycles 2015, 91, 1763.

[3] Banothu, J.; Vaarla, K.; Bavantula, R.; Crooks, P. A. Chin Chem Lett 2014, 25, 172.

[4] Zablotskaya, A.; Segal, I.; Geronikaki, A.; Eremkina, T.; Belyakov, S.; Petrova, M.; Shestakova, I.; Zvejniece, L.; Nikolajeva, V. Eur J Med Chem 2013, 70, 846.

[5] Glotova, T. E.; Dvorko, M. Y.; Albanov, A. I.; Kazheva, O. N.; Shilov, G. V.; D'yachenko, O. A. Russ J Org Chem 2008, 44, 1532.

[6] Gouda, M. A.; Berghot, M. A.; Abd El-Ghani, G. E.; Khalil, A. M. Eur J Med Chem 2010, 45, 1338.

[7] Milinkevich, K. A.; Ye, L.; Kurth, M. J. J Comb Chem 2008, 10, 521.

[8] Grishina, G. V.; Gaidarova, E. L.; Zefirov, N. S. Chem Heterocycl Compd 1994, 30, 1401.

[9] Wang, C.-L.; Wuorola, M. A. Org Prep Proced Int 1992, 24, 585.

[10] Aridoss, G.; Balasubramanian, S.; Parthiban, P.; Kabilan, S. Spectrochim Acta Part A 2007, 68, 1153.

[11] Parthiban, P.; Ramachandran, R.; Aridoss, G.; Kabilan, S. Magn Reson Chem 2008, 46, 780.

[12] Aridoss, G.; Amirthaganesan, S.; Kim, M. S.; Kim, J. T.; Jeong, Y. T. Eur J Med Chem 2009, 44, 4199.

[13] Lv, P. C.; Wang, K. R.; Yang, Y.; Mao, W. J.; Chen, J.; Xiong, J.; Zhu, H. L. Bioorg Med Chem Lett 2009, 19, 6750.

[14] Gomha, S. M.; Edrees, M. M.; Altalbawy, F. M. A. Int J Mol Sci 2016, 17, 1499.

[15] Sayed, A. R.; Gomha, S. M.; Farghaly, T. A. J Heterocyclic Chem 2016, 53, 255.

[16] Gomha, S. M.; Salah, T. A.; Hassaneen, H. M. E.; Abdel-aziz, H.; Khedr, M. A. Molecules 2016, 21, 1.

[17] Gomha, S. M.; Khalil, K. D.; El-Zanate, A. M.; Riyadh, S. M. Heterocycles 2013, 87, 1109.

[18] Gomha, S. M.; Badrey, M. G.; Arafa, W. A. A. Heterocycles 2016, 92, 1450.

[19] Abdelhamid, A. O.; Gomha, S. M.; Abdelriheem, N. A.; Kandeel, S. M. Molecules 2016, 21, 929.

[20] Farghaly, T. A.; Gomha, S. M.; Sayed, A. R.; Khedr, M. A. Curr Org Synth 2016, 13, 445.

[21] Abdalla, M. A.; Gomha, S. M.; Abdelaziz, M.; Serag, N. Turk J Chem 2016, 40, 441.

[22] Dawood, K. M.; Gomha, S. M. J Heterocycl Chem 2015 52, 1400.

[23] Shawali, A. S.; Gomha, S. M. Adv SynthCatal 2000, 342, 599.

[24] Mosmann, T. J Immunol Methods 1983, 65, 55.