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Microwave-Assisted Synthesis and Antifungal Activity of Some New 1*H*-1,2,4-Triazole Derivatives*

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Abstract—A number of 3-aryl-4-arylmethylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were synthesized by reaction of the corresponding aromatic aldehydes with 4-amino-3-aryl-1*H*-1,2,4-triazol-5-ones in anhydrous ethanol under microwave irradiation. The newly synthesized 1*H*-1,2,4-triazole derivatives were tested for antimicrobial activity. They showed no antibacterial activity but slight mycostatic activity against some *Candida* species.

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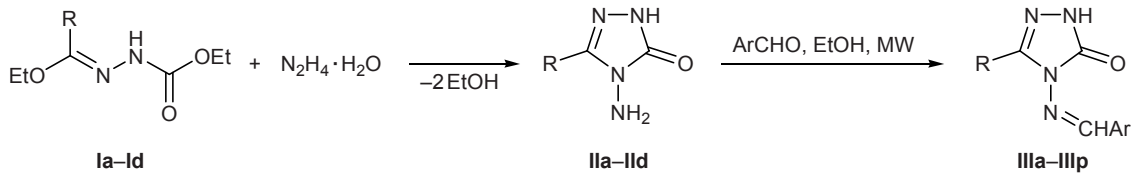
The use of microwave energy to enhance organic reactions has recently attracted chemists' attention [1]. Microwave-assisted syntheses ensure higher reaction rates, improved yields, and easy experimental manipulations [2–4]. Therefore, interest in microwave-assisted organic syntheses has grown tremendously [5–10]. Since 2001, the number of publications related to microwave-assisted organic synthesis (MAOS) has increased to such a level that it might be assumed that in a few years most chemists will probably use microwave energy to perform chemical reactions on a laboratory scale.

It is known that microwave irradiation not only considerably reduces reaction times but also minimizes side processes, increases the yields, and improves reproducibility. Many academic and industrial research groups are already using MAOS as a technology for rapid reaction optimization, for efficient synthesis of new chemical products, and for discovering and probing new chemical reactivity [11–14].

1,2,4-Triazole derivatives are interesting compounds due to their application and biological activity, including antibacterial, antifungal, and tuberculostatic action [15–22].

In the present paper we describe the reaction of 3-aryl-4-amino-4,5-dihydro-1*H*-1,2,4-triazole-5-ones **II** [23] with aromatic aldehydes under microwave irradiation, which leads to the formation of the corresponding 3-aryl-4-arylmethylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **III** (Scheme 1). The reactions

Scheme 1.



Ia–Id **IIa–IId** **IIIa–IIIp**

I, **II**, R = 2-$ClC_6H_4CH_2$ (**a**), 3-$ClC_6H_4CH_2$ (**b**), 2-$MeC_6H_4CH_2$ (**c**), 3-$MeC_6H_4CH_2$ (**d**); **III**, R = 2-$ClC_6H_4CH_2$, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-*t*-BuC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 3-BrC_6H_4 (**e**), 3,4-$(MeO)_2C_6H_3$ (**f**), 3,4,5-$(MeO)_3C_6H_2$ (**g**); R = 3-$ClC_6H_4CH_2$, Ar = Ph (**h**), 4-MeC_6H_4 (**i**), 4-*t*-BuC_6H_4 (**j**), 4-ClC_6H_4 (**k**), 3-BrC_6H_4 (**l**), 3,4-$(MeO)_2C_6H_3$ (**m**), 3,4,5-$(MeO)_3C_6H_2$ (**n**); R = 2-$MeC_6H_4CH_2$, Ar = Ph (**o**); R = 3-$MeC_6H_4CH_2$, Ar = Ph (**p**).

* The text was submitted by the authors in English.

were carried out using anhydrous ethanol as solvent. The reaction time was as short as 5 min, and the products (compounds **IIIa**–**IIIp**) were isolated in up to 96% yield. The product structure was confirmed by the IR and ^{1}H NMR spectra and elemental analyses.

Newly synthesized compounds **IIIa**–**IIIp** were tested for antimicrobial activity against the following bacterial strains: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923, and *Bacillus subtilis* ATCC 6633; in addition, their activity against four yeast strains, *Candida albicans* ATCC 60193, *Candida parapsilosis* ATCC 22019, *Candida kefyr* ATCC 46764, and *Candida glabrata* ATCC 66032, was examined.

No antibacterial activity of 1,2,4-triazole derivatives **IIIa**–**IIIp** toward the above bacterial strains was found, while all these compounds showed antifungal activity in yeasts of the *Candida* family (see table). Inhibition of yeast growth on Sabouraud dextrose agar plates indicated that compounds **IIIa**–**IIIp** exhibit mycostatic activity (the corresponding data are not given here). The inhibition zone diameters determined by the agar well diffusion method and minimal inhibitory concentrations determined by the broth microdilution technique are collected in table.

EXPERIMENTAL

The melting points were determined in open capillaries on an oil-heated Büchi melting point apparatus and are uncorrected. The IR spectra were recorded in KBr pellets on a Perkin–Elmer 1600 FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured on a Varian 200 spectrometer using DMSO-d_6 as solvent and TMS as internal standard. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer; the experimental values were in agreement (±0.4%) with the calculated ones. Initial aromatic aldehydes were commercial products (Aldrich).

4-Arylmethylideneamino-3-(R-benzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones IIIa–IIIp (*general procedure***).** A solution of 0.01 mol of aminotriazole **IIa**–**IId** and 0.01 mol of the corresponding aromatic aldehyde in 10 ml of anhydrous ethanol was irradiated for 5 min in a microwave oven at a power of 350 W. The

Antimicrobial activity of compounds **IIIa**–**IIIp**[a]

Compound no.	*Candida albicans*		*Candida glabrata*		*Candida parapsilosis*		*Candida kefyr*	
	ZD	MIC	ZD	MIC	ZD	MIC	ZD	MIC
IIIa	12	0.25	9	0.5	13	0.25	13	0.125
IIIb	12	0.25	10	0.25	13	0.25	13	0.125
IIIc	13	0.25	10	0.25	13	0.125	13	0.125
IIId	13	0.25	9	0.25	13	0.125	14	0.125
IIIe	11	0.25	9	0.25	11	0.25	12	0.25
IIIf	11	0.5	8	0.5	12	0.25	12	0.25
IIIg	13	0.125	9	0.125	13	0.125	14	0.125
IIIh	10	0.5	8	0.5	10	0.25	12	0.25
IIIi	12	0.25	9	0.25	12	0.25	13	0.125
IIIj	11	0.5	8	0.5	12	0.25	12	0.25
IIIk	13	0.25	10	0.25	14	0.125	14	0.125
IIIl	12	0.5	9	0.5	11	0.25	12	0.125
IIIm	11	0.5	8	0.5	12	0.25	12	0.25
IIIn	13	0.25	9	0.25	13	0.125	14	0.125
IIIo	12	0.125	10	0.25	12	0.125	12	0.125
IIIp	12	0.125	10	0.25	12	0.125	13	0.125
Fluconazole	18	0.25	16	1	20	0.25	22	0.125

[a] ZD stands for zone diameter (mm), and MIC, for minimal inhibitory concentration (mg/ml).

solid material thus obtained was recrystallized from appropriate solvent.

4-Benzylideneamino-3-(2-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIa). Yield 29%, mp 180–181°C. IR spectrum, ν, cm^{-1}: 743, 1574–1586, 1707, 3367. ^1H NMR spectrum, δ, ppm: 3.92 s (2H, CH_2), 7.04–7.73 m (9H, H_{arom}), 10.01 s (1H, CH), 11.84 s (1H, NH). Found, %: C 61.34; H 4.10; N 17.95. $C_{16}H_{13}ClN_4O$. Calculated, %: C 61.44; H 4.19; N 17.91.

3-(2-Chlorobenzyl)-4-(4-methylbenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIb). Yield: 86%, mp 204–205°C. IR spectrum, ν, cm^{-1}: 749, 820, 1548–1603, 1714, 3388. ^1H NMR spectrum, δ, ppm: 2.19 s (3H, CH_3), 3.87 s (2H, CH_2), 7.11–7.84 m (8H, H_{arom}), 10.15 s (1H, CH), 11.35 s (1H, NH). Found, %: C 62.39; H 4.59; N 17.17. $C_{17}H_{15}ClN_4O$. Calculated, %: C 62.48; H 4.63; N 17.15.

4-(4-*tert*-Butylbenzylideneamino)-3-(2-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIc). Yield 65%, mp 167–168°C. IR spectrum, ν, cm^{-1}: 775, 835, 1535, 1621, 1723, 3343. ^1H NMR spectrum, δ, ppm: 2.21 s (9H, CH_3), 3.92 s (2H, CH_2), 7.03–7.73 m (8H, H_{arom}), 9.95 s (1H, CH), 11.12 s (1H, NH). Found, %: C 65.18; H 5.69; N 15.18. $C_{20}H_{21}ClN_4O$. Calculated, %: C 65.12; H 5.74; N 15.19.

3-(2-Chlorobenzyl)-4-(4-chlorobenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIId). Yield 69%, mp 210–211°C. IR spectrum, ν, cm^{-1}: 744, 821, 1589, 1624, 1697, 3374. ^1H NMR spectrum, δ, ppm: 4.05 s (2H, CH_2), 6.98–7.67 m (8H, H_{arom}), 10.21 s (1H, CH), 11.43 s (1H, NH). Found, %: C 55.25; H 3.46; N 16.22. $C_{16}H_{12}Cl_2N_4O$. Calculated, %: C 55.35; H 3.48; N 16.14.

4-(3-Bromobenzylideneamino)-3-(2-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIe). Yield 48%, mp 191–192°C. IR spectrum, ν, cm^{-1}: 743, 766, 1587, 1609, 1705, 3369. ^1H NMR spectrum, δ, ppm: 4.22 s (2H, CH_2), 7.20–7.88 m (8H, H_{arom}), 9.15 s (1H, CH), 11.02 s (1H, NH). Found, %: C 49.12; H 3.01; N 14.29. $C_{16}H_{12}BrClN_4O$. Calculated, %: C 49.07; H 3.09; N 14.31.

3-(2-Chlorobenzyl)-4-(3,4-dimethoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIf). Yield 96%, mp 247–248°C. IR spectrum, ν, cm^{-1}: 762, 1565, 1622, 1717, 3343. ^1H NMR spectrum, δ, ppm: 2.85 s (3H, CH_3), 2.92 s (3H, CH_3), 3.86 s (2H, CH_2), 6.80–7.45 m (7H, H_{arom}), 10.09 s (1H, CH), 11.32 s (1H, NH). Found, %: C 57.98; H 4.67; N 14.94. $C_{18}H_{17}ClN_4O_3$. Calculated, %: C 57.99; H 4.60; N 15.03.

3-(2-Chlorobenzyl)-4-(3,4,5-trimethoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIg). Yield 80%, mp 196–197°C. IR spectrum, ν, cm^{-1}: 755, 1576, 1628, 1722, 3315. ^1H NMR spectrum, δ, ppm: 2.81 s (3H, CH_3), 2.85 s (3H, CH_3), 2.95 s (3H, CH_3), 3.99 s (2H, CH_2), 6.76–7.76 m (6H, H_{arom}), 9.97 s (1H, CH), 11.13 s (1H, NH). Found, %: C 56.62; H 4.64; N 13.90. $C_{19}H_{19}ClN_4O_4$. Calculated, %: C 56.65; H 4.75; N 13.91.

4-Benzylideneamino-3-(3-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIh). Yield: 30%, mp 207–209°C. IR spectrum, ν, cm^{-1}: 741, 1582, 1598, 1702, 3354. ^1H NMR spectrum, δ, ppm: 3.87 s (2H, CH_2), 7.13–7.78 m (9H, H_{arom}), 10.13 s (1H, CH), 11.42 s (1H, NH). Found, %: C 61.47; H 4.21; N 17.89. $C_{16}H_{13}ClN_4O$. Calculated, %: C 61.44; H 4.19; N 17.91.

3-(3-Chlorobenzyl)-4-(4-methylbenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIi). Yield 92%, mp 203–204°C. IR spectrum, ν, cm^{-1}: 764, 855, 1533, 1622, 1714, 3353. ^1H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 3.96 s (2H, CH_2), 7.01–7.75 m (8H, H_{arom}), 10.09 s (1H, CH), 11.22 s (1H, NH). Found, %: C 62.39; H 4.66; N 17.22. $C_{17}H_{15}ClN_4O$. Calculated, %: C 62.48; H 4.63; N 17.15.

4-(4-*tert*-Butylbenzylideneamino)-3-(3-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIj). Yield 54%, mp 167–168°C. IR spectrum, ν, cm^{-1}: 738, 802, 1566, 1651, 1716, 3318. ^1H NMR spectrum, δ, ppm: 2.33 s (9H, CH_3), 3.87 s (2H, CH_2), 7.05–7.76 m (8H, H_{arom}), 9.98 s (1H, CH), 11.10 s (1H, NH). Found, %: C 65.06; H 5.70; N 15.14. $C_{20}H_{21}ClN_4O$. Calculated, %: C 65.12; H 5.74; N 15.19.

3-(3-Chlorobenzyl)-4-(4-chlorobenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIk). Yield: 37%, mp 147–148°C. IR spectrum, ν, cm^{-1}: 742, 821, 1516, 1593, 1711, 3309. ^1H NMR spectrum, δ, ppm: 3.88 s (2H, CH_2), 6.99–7.75 m (8H, H_{arom}), 10.19 s (1H, CH), 11.65 s (1H, NH). Found, %: C 55.33; H 3.55; N 16.14. $C_{16}H_{12}Cl_2N_4O$. Calculated, %: C 55.35; H 3.48; N 16.14.

4-(3-Bromobenzylideneamino)-3-(3-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIl). Yield 34%, mp 137–138°C. IR spectrum, ν, cm^{-1}: 797, 819, 1515, 1593, 1713, 3309. ^1H NMR spectrum, δ, ppm: 4.10 s (2H, CH_2), 7.03–7.76 m (8H, H_{arom}), 10.03 s (1H, CH), 11.20 s (1H, NH). Found, %: C 49.01; H 3.13; N 14.34. $C_{16}H_{12}BrClN_4O$. Calculated, %: C 49.07; H 3.09; N 14.31.

3-(3-Chlorobenzyl)-4-(3,4-dimethoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIm). Yield 85%, mp 241–242°C. IR spectrum, ν, cm^{-1}: 765, 1562, 1625, 1708, 3323. ^1H NMR spectrum, δ, ppm: 2.84 s (3H, CH_3), 2.90 s (3H, CH_3), 3.91 s (2H, CH_2), 6.83–7.53 m (7H, H_{arom}), 10.05 s (1H, CH), 11.24 s (1H, NH). Found, %: C 58.06; H 4.55; N 15.09. $C_{18}H_{17}ClN_4O_3$. Calculated, %: C 57.99; H 4.60; N 15.03.

3-(3-Chlorobenzyl)-4-(3,4,5-trimethoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIn). Yield 79%, mp 195–196°C. IR spectrum, ν, cm^{-1}: 790, 1567, 1629, 1718, 3319. ^1H NMR spectrum, δ, ppm: 2.80 s (3H, CH_3), 2.87 s (3H, CH_3), 2.91 s (3H, CH_3), 4.04 s (2H, CH_2), 6.76–7.71 m (6H, H_{arom}), 10.07 s (1H, CH), 11.18 s (1H, NH). Found, %: C 56.66; H 4.80; N 13.93. $C_{19}H_{19}ClN_4O_4$. Calculated, %: C 56.65; H 4.75; N 13.91.

4-Benzylideneamino-3-(2-methylbenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIo). Yield 96%, mp 168–169°C. IR spectrum, ν, cm^{-1}: 726, 1566, 1586, 1708, 3171. ^1H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 4.04 s (2H, CH_2), 7.10–7.80 m (9H, H_{arom}), 9.70 s (1H, CH), 11.97 s (1H, NH). Found, %: C 69.81; H 5.50; N 19.15. $C_{17}H_{16}N_4O$. Calculated, %: C 69.85; H 5.52; N 19.16.

4-Benzylideneamino-3-(3-methylbenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (IIIp). Yield 83%, mp 131–132°C. IR spectrum, ν, cm^{-1}: 817, 1555, 1590, 1712, 3177. ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 4.00 s (2H, CH_2), 7.00–7.79 m (9H, H_{arom}), 9.69 s (1H, CH), 11.87 s (1H, NH). Found, %: C 69.86; H 5.59; N 19.16. $C_{17}H_{16}N_4O$. Calculated, %: C 69.85; H 5.52; N 19.16.

Agar well diffusion assay was performed as described in [24]. Compound **IIIa–IIIp** and fluconazole (as control) were weighed and dissolved in dimethyl sulfoxide (DMSO) to prepare a stock solution with a concentration of 4 mg/ml. Microbial suspensions of the strains prepared in phosphate buffer saline (PBS) at a concentration of about 1.5×10^8 organism/ml using McFarland 0.5 turbidity tube were flood-inoculated onto surface of Mueller-Hinton or Sabouraud dextrose agar plates. Wells, 6 mm in diameter, were cut off from the agar using sterile glass pipettes attached to a vacuum pump, and 0.1 ml of a stock solution of compound **IIIa–IIIp** was introduced into the well (0.4 mg per well). On the next day, plates were examined for growth inhibition zone.

Determination of minimal inhibitory concentration. Minimal inhibitory concentrations (MIC) were determined by the broth microdilution method described in [25]. Mueller-Hinton broth (MHB) for bacteria or YEPD broth (1% of yeast extract, 2% of peptone, and 2% of dextrose) for yeasts, 100 μl, was introduced into wells on microplates. A solution of compound **IIIa–IIIp** (4 mg/ml), 100 μl, was introduced into the first well of a row of plates and was sequentially diluted. Microbial suspensions prepared in MHB or YEPD broth at a concentration of about 1.5×10^6 organism/ml were added to each well to attain final concentrations of compound **IIIa–IIIp** and fluconazole of 1, 0.5, 0.25, 0.125, 0.062, 0.031, 0.016, 0.008, 0.004, 0.002, 0.001, and 0.0005 mg/ml. The plates were incubated for 16–18 h at 37°C, and minimal inhibitory concentrations were determined as the lowest concentration of compound **IIIa–IIIp** at which no visible growth was observed.

Dimethyl sulfoxide was used as solvent, and Ampicillin and Fluconazole, as controls. All tests were repeated at least twice. The standard strains were obtained from and the tests were performed at the Biotest Laboratory, Department of Microbiology and Clinical Microbiology, School of Medicine, Karadeniz Technical University (Turkey).

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