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Synthesis and Antimicrobial Activity of 1-Aryl-4-(arylimino)-6-iminohexahydro-1,3,5-triazine-2-thione Derivatives

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Abstract—A series of 6-imino-1-aryl-4-(arylimino)-1,3,5-triazinane-2-thione derivatives are synthesized by cyclization of 1-aryl-3-cyanoguanidine with aryl isothiocyante in the presence of sodium methoxide under MW irradiation. Structures of the synthesized compounds **3a–j** are elucidated from ^{1}H and ^{13}C NMR, MS, and IR, data. The synthesized compounds are evaluated for their antimicrobial activity against *B. subtilis, S. aureus, P. aeruginosa, and E. Coli*. Some compounds demonstrate promising activity against the tested strains.

Keywords: 1,3,5-triazinane-2-thione, isothiocyante, micro-wave irradiation, anti microbial activity

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INTRODUCTION

Among heterocyclic structures that compose significant building blocks for many functionalized molecules [1], 1,3,5-triazine derivatives represent an important class of compounds due to broad spectrum of their biological activities [2–6].

Several synthetic approaches to 6-imino-1-aryl-4-iminoaryl-1,3,5-triazine-2-thione derivatives were proposed. Kurzer and co-workers [7] synthesized triazines by reaction of substituted diguanides with isothiocyanate esters. Kaiser and co-workers [8] synthesized similar 1,3,5-triazines by reaction of thiocyanic acid with l-phenyl-3-cyano-guanidine. Rao et al. [9] used strong alkali to prepare 1-phenyl-4,6-diimino-2-thio-hexahydro-1,3,5-triazine from dicyan-amide and an appropriate isothiocyanate. However, some disadvantages of the above methods stimulated development of an efficient and environmentally benign protocol [10] for the synthesis of 1-phenyl-4,6-diimino-2-thio-hexahydro-1,3,5-triazine derivatives. MW promoted synthesis is one of such approaches [11, 12].

In view of the above and in continuation of our study of biologically active heterocyclic compounds, we report herein the MW assisted synthesis of 1-phenyl-4,6-diimino-2-thio-hexahydro-1,3,5-triazine derivatives for evaluation of their antimicrobial properties.

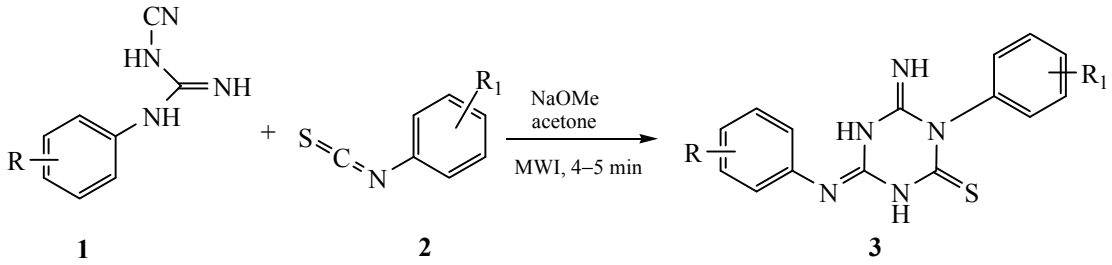
RESULTS AND DISCUSSION

The trial reaction of 1-aryl-3-cyano guanidine (1.0 mmol) with aryl isothiocyante (1.0 mmol) at 70–80°C gave the desired product in 38% yield along with the unreacted starting compounds, even after prolonged reaction time (24 h). The following application of MW irradiation at 50°C led to the higher yield (84%) of the process. Further optimization of the method indicated 80°C and MW irradiation to be the most efficient in the synthesis of compounds **3a**–**3j** (Scheme 1, Table 1).

Structures of thus synthesized compounds were characterized by ^{1}H and ^{13}C NMR, MS, and IR spectra. A possible pathway of the reaction is presented in Scheme 2. The initial attack of isothiocyanate by the imino group of cyanoguanidine results it formation of the intermediate **A**, cyclization of which leads to formation of the intermediate anion **B**. Its following protonation leads to the desired molecule **C**.

Biological activity. The compounds **3a**–**3j** were screened in vitro for their antibacterial activity against Gram-positive *Bacillus subtilis* (ATCC 6633) and

Scheme 1. Synthesis of 6-imino-1-aryl-4-(arylimino)-1,3,5-triazinane-2-thione derivatives.



1 **2** **3**

Staphylococcus aureus (ATCC 6538) and Gram-negative *Escherichia coli* (ATCC 11229), and *P. aeruginosa* (ATCC 29213) bacteria. Agar well-diffusion method [13] was used to assay the antibacterial activity using chloramphenicol as a standard antibacterial drug (Table 2).

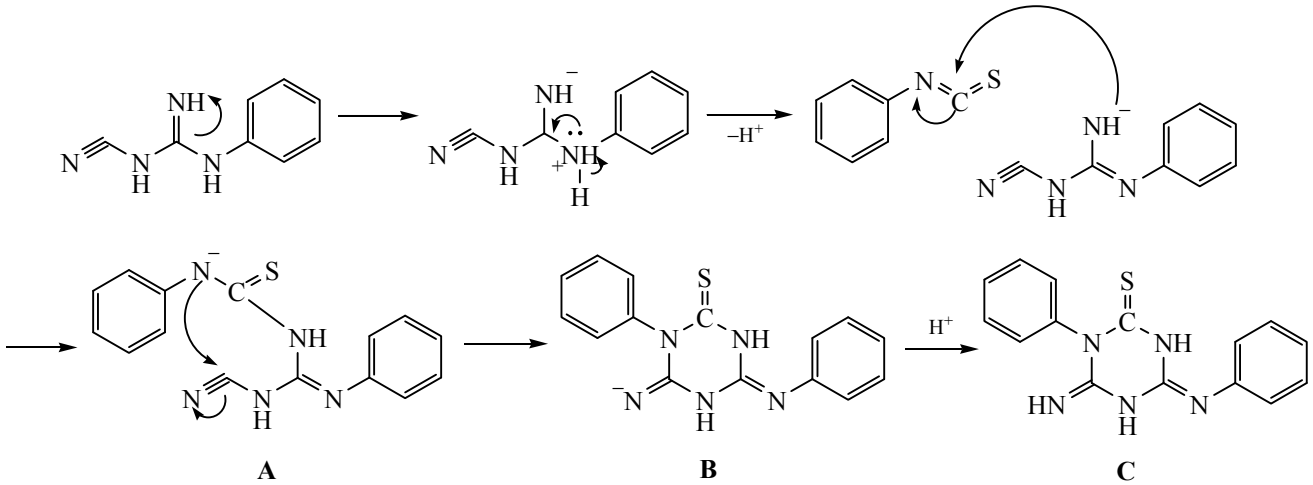
Among the synthesized compounds 2-trifluoro-methoxy-1,3,5-triazines **3i** and **3j** demonstrated potent activity against both Gram-positive bacterial strains. Compound **3c** exhibited moderate activity against Gram-positive *S. aureus* and Gram-negative *E. coli* bacterial strains. The compounds **3g** and **3d** demonstrated moderate activity against *S. aureus, B. subtilis, P. aeruginosa,* and *E. Coli*.

EXPERIMENTAL

All reagent grade chemicals were purchased from Sigma-Aldrich Chemicals Co. and Spectrochem Pvt. Ltd. and used without further purification. Solvents were dried according to standard methods. All reactions were monitored by TLC on Merck Kieselgel 60 (F524) and visualized under UV light and/or by spraying 5% solution of H_2SO_4 in ethanol followed by heating. Column chromatography was performed on Silica Gel 60 (60–120 mesh). Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded for KBr pellets on a JASCO FT-IR-4100 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL 400 MHz spectrometer in DMSO-d_6 using TMS as the internal standard. MS were measured on a SHIMADZU LC-2010EV spectrometer. Microwave reactions were carried out in a Milestone multi SYNTH series (ATC-FO 300) multimode microwave equipped with a twin magnetron (2x800 W, 2.45 GHz), a maximum delivered power 1,000 W (10 W increments pulsed irradiation).

Synthesis of 1-aryl-4-(arylimino)-6-imino hexa-hydro-1, 3, 5-triazine-2-thione derivatives (3a–3j). A mixture of substituted aryl cyanoguanidine **1a**–**1d** (1.0 mmol) with aryl isothiocyanate (1.0 mmol) and sodium methoxide (1.0 mmol) in dry acetone (10 mol) was loaded in a quartz tube and inserted into a capped

Scheme 2. Possible pathway of the reaction.



A **B** **C**

Table 1. Synthesis of 1-aryl-4-(arylimino)-6-iminohexahydro-1,3,5-triazine-2-thione derivatives **3a**–**3j** under MW irradiation

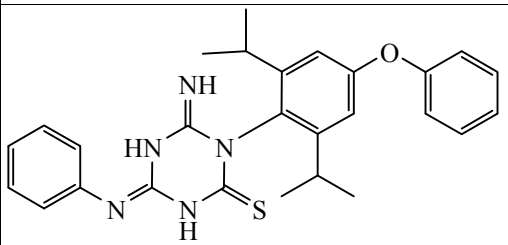
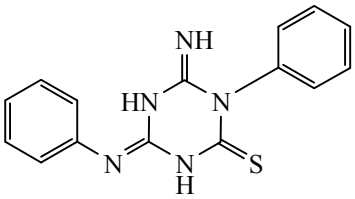
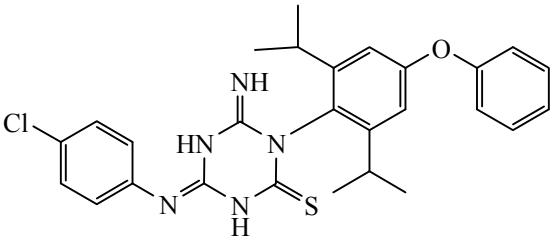
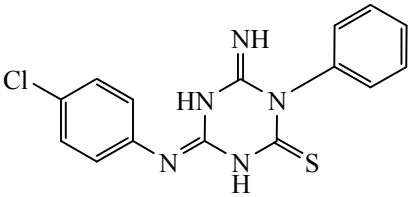
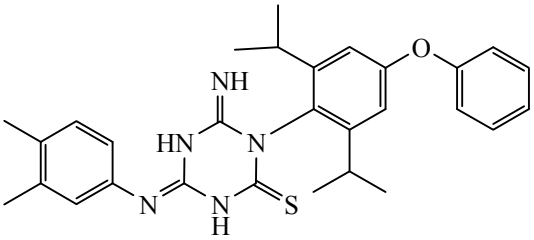
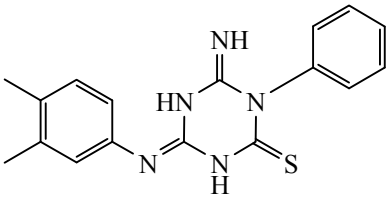
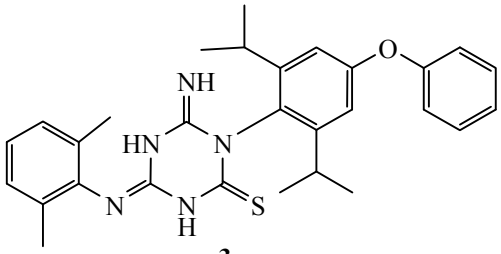
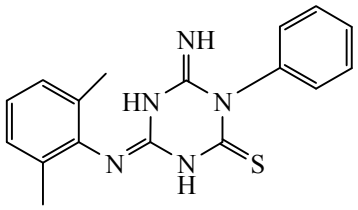
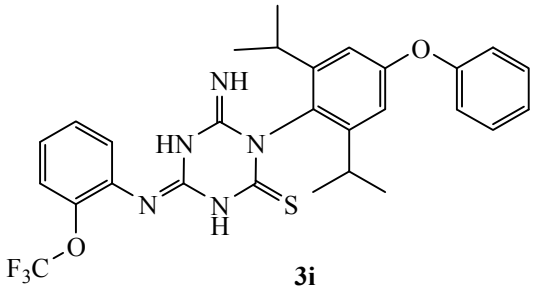
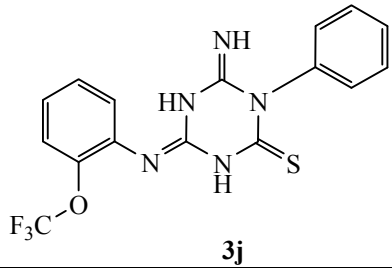
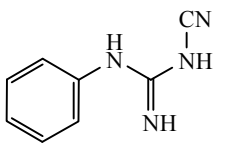
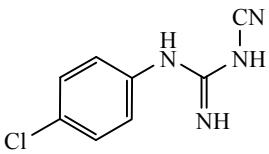
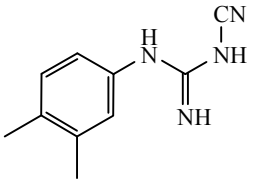
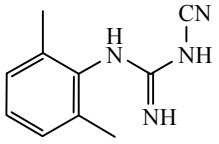
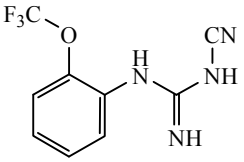
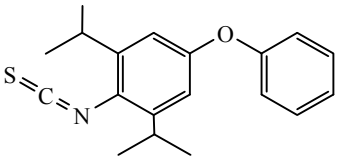
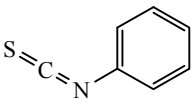
Substrate **1**[a]	Substrate **2**[b]	Product	Time, min	Yield[c], %
1a	**2a**	 **3a**	5.0	84
1a	**2b**	 **3b**	4.5	91
1b	**2a**	 **3c**	4.0	89
1b	**2b**	 **3d**	5.0	90
1c	**2a**	 **3e**	5.0	88
1c	**2b**	 **3f**	4.5	92

Table 1. (Contd.)

Substrate **1**[a]	Substrate **2**[b]	Product	Time, min	Yield[c], %
1d	**2a**	 **3g**	5.0	88
1d	**2b**	 **3h**	4.5	92
1e	**2a**	 **3i**	5.0	84
1e	**2b**	 **3j**	4.5	91

[a]  (**1a**),  (**1b**),  (**1c**),  (**1d**),  (**1e**).

[b]  (**2a**),  (**2b**).

[c] Isolated yield.

Table 2. Antibacterial activity data for the synthesized 1,3,5-triazine derivatives **3a**–**3j**

Compound	Gram-positive strains		Gram-negative strains	
	Bacillus subtilis	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*
3a	11.0	10.0	17.0	18.0
3b	11.0	11.0	16.0	15.0
3c	15.0	16.0	15.0	17.0
3d	16.0	15.0	11.0	12.0
3e	11.0	10.0	11.0	10.0
3f	10.0	11.0	14.0	13.0
3g	17.0	16.0	18.0	19.0
3h	11.0	10.0	13.0	11.0
3i	18.0	19.5	14.0	13.0
3j	21.0	20.0	18.0	21.0
Chloramphenicol	25.0	24.0	22.0	20.0

teflon vial and MW irradiated at 80°C for 4–5 min. After completion of the reaction (as indicated by TLC), 5% of methanol in dichloromethane (100 mL) and water (25 mL) were added. The organic layer was dried over sodium sulfate and concentrated in vacuum. The crude product was purified by making slurry with dichloromethane (25 mL) and ethyl acetate (25 mL). Upon filtration the corresponding titled compound **3a**–**3j** was isolated as off white solid.

1-(2,6-Diisopropyl-4-phenoxyphenyl)-6-imino-4-(phenylimino)-1,3,5-triazinane-2-thione (3a). mp 270–275°C. IR spectrum, ν, cm^{-1}: 3425, 3285, 1626, 1599, 1489, 1372, 1268, 1089, 999, 866, 693. ^{1}H NMR spectrum, δ, ppm: 1.11 d (J = 6.8 Hz, 6H), 1.15 d (J = 6.8 Hz, 6H), 2.52–2.60 m (2H), 6.73 s (1H, NH), 6.88 s (2H, C_6H_5), 7.04 t (J = 7.6 Hz, 1H, C_6H_5), 7.13–7.18 m (3H, C_6H_5), 7.30 t (2H, J =7.6 Hz, C_6H_5), 7.41–7.45 m (2H, C_6H_5), 7.79 d (J = 7.6 Hz, 2H, C_6H_5), 8.31 s (1H, NH), 10.10 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 23.6, 23.7, 28.5, 114.8, 118.4, 120.5, 122.9, 123.4, 128.1, 128.4, 129.9, 139.1, 147.1, 156.4, 157.2, 157.9, 158.2, 183.4. ESI-MS: 472.26 $[M + H]^+$. Calculated for $C_{27}H_{30}N_5OS$.

6-Imino-1-phenyl-4-(phenylimino)-1,3,5-triazinane-2-thione (3b). mp 264–267°C. IR spectrum, ν, cm^{-1}: 3625, 3613, 2966, 2868, 1955, 1894, 1787, 1694, 1519, 1384, 1238, 1075, 947, 809, 662, 486. ^{1}H NMR spectrum, δ, ppm: 6.38 s (1H, NH), 7.03 t (J =7.6 Hz, 1H, C_6H_5), 7.27–7.33 m (4H, C_6H_5), 7.42–7.53 m (3H, C_6H_5), 7.79 d (J = 7.2 Hz, 2H, C_6H_5), 8.20 s (1H, NH), 10.10 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 30.7, 120.4, 121.2, 122.8, 128.6, 128.8, 138.2, 139.2, 157.5, 158.1, 183.2. ESI-MS: 296.04 $[M + H]^+$. Calculated for $C_{15}H_{14}N_5S$.

4-[(3-Chlorophenyl)imino]-1-(2,6-diisopropyl-4-phenoxyphenyl)-6-imino-1,3,5-triazinane-2-thione (3c). mp 283–284°C. IR spectrum, ν, cm^{-1}: 3644, 3625, 3429, 3310, 3212, 2932, 2354, 1983, 1865, 1745, 1602, 1386, 1255, 1092, 967, 770, 622, 439. ^{1}H NMR spectrum, δ, ppm: 1.11 d (J = 6.8 Hz, 6H), 1.15 d (J = 6.8 Hz, 6H), 2.59–2.52 m (2H), 6.79 s (1H, NH), 6.89 s (2H, C_6H_5), 7.13–7.18 m (3H, C_6H_5), 7.33–7.35 m (2H, C_6H_5), 7.41–7.45 m (2H, C_6H_5), 7.84 d (J = 8.4 Hz, 2H, C_6H_5), 8.37 s (1H, NH), 10.25 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 29.7, 34.6, 120.8, 124.5, 127.9, 129.4, 132.6, 134.0, 134.3, 136.0, 144.3, 153.2, 16.5, 163.3, 164.0, 164.2, 189.6. ESI-MS: 506.25 $[M + H]^+$. Calculated for $C_{27}H_{29}ClN_5OS$.

4-[(3-Chlorophenyl)imino]-6-imino-1-phenyl-1,3,5-triazinane-2-thione (3d). mp 220–223°C. IR spectrum, ν, cm^{-1}: 3694, 3583, 3460, 3322, 2959, 2629, 2319, 1987, 1864, 1788, 1516, 1327, 1168, 994, 755, 575, 442. ^{1}H NMR spectrum, δ, ppm: 6.40 s (1H, NH), 7.00–7.20 m (3H, C_6H_5), 7.25–7.50 m (5H, C_6H_5), 7.80–7.91 m (1H, C_6H_5), 8.25 s (1H, NH), 10.17 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 121.0,

122.3, 123.3, 126.9, 128.8, 129.0, 129.1, 129.4, 130.4, 131.3, 138.7, 138.9, 139.7, 158.0, 158.6. ESI-MS: 330.06 $[M + H]^+$. Calculated for $C_{15}H_{13}ClN_5OS$.

1-(2,6-Diisopropyl-4-phenoxyphenyl)-4-[(3,4-dimethylphenyl)imino]-6-imino-1,3,5-triazinane-2-thione (3e). mp 269–270°C. IR spectrum, ν, cm^{-1}: 3656, 3594, 3582, 3208, 2867, 2354, 2088, 1713, 1488, 1295, 1105, 1009, 872, 737, 515, 405. ^1H NMR spectrum, δ, ppm: 1.11 d (J = 7.0 Hz, 6H), 1.15 d (J = 6.5 Hz, 6H), 2.55–2.59 m (2H), 6.66 s (1H, NH), 6.88 s (2H, C_6H_5), 7.04 d (J = 8.0 Hz, 1H, C_6H_5), 7.13–7.24 m (3H, C_6H_5), 7.58–7.61 m (1H, C_6H_5), 8.26 s (1H, NH), 9.94 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.7, 19.6, 23.6, 23.7, 28.5, 114.6, 118.0, 118.4, 121.6, 123.3, 128.1, 129.3, 129.9, 130.6, 136.2, 136.7, 147.2, 156.4, 157.2, 157.8, 158.1, 183.2. ESI-MS: 500.91 $[M + H]^+$. Calculated for $C_{29}H_{34}N_5OS$.

4-[(3,4-Dimethylphenyl)imino]-6-imino-1-phenyl-1,3,5-triazinane-2-thione (3f). mp 206–210°C. IR spectrum, ν, cm^{-1}: 3665, 3643, 3456, 3332, 2921, 1942, 1715, 1452, 1264, 1107, 966, 756, 609, 444, 401. ^1H NMR spectrum, δ, ppm: 2.17 s (3H), 2.20 s (3H), 6.38 s (1H, NH), 7.02–7.04 (m, 1H, C_6H_5), 7.26–7.30 (m, 2H, C_6H_5), 7.42–7.57 m (4H, C_6H_5), 7.79 d (J = 7.5 Hz, 1H, C_6H_5), 8.19 s (1H, NH), 9.94 s (1H, NH). ESI-MS: 324.65 $[M + H]^+$. Calculated for $C_{17}H_{18}N_5S$.

1-(2,6-Diisopropyl-4-phenoxyphenyl)-4-[(2,6-dimethylphenyl)imino]-6-imino-1,3,5-triazinane-2-thione (3g). mp 263–265°C. IR spectrum, ν, cm^{-1}: 3576, 3414, 3303, 3167, 3074, 2670, 2085, 1841, 1585, 1332, 1162, 1030, 879, 718, 579, 499, 427. ^1H NMR spectrum, δ, ppm: 1.07-1.17 m (12H), 2.19–2.23 m (6H), 2.53–2.57 m (2H), 6.41 s (1H, NH), 6.87 s (2H, C_6H_5), 7.11–7.16 m (6H, C_6H_5), 7.38–7.43 m (2H, C_6H_5), 8.00 s (1H, NH), 9.29 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.1, 18.2, 23.5, 23.6, 28.5, 114.7, 115.0, 118.1, 118.3, 123.1, 126.6, 127.7, 127.8, 129.8, 129.9, 135.1, 135.7, 147.1, 147.2, 156.7, 156.9, 157.9, 159.3, 183.3. ESI-MS: 500.91 $[M + H]^+$. Calculated for $C_{29}H_{34}N_5OS$.

4-[(2,6-Dimethylphenyl)imino]-6-imino-1-phenyl-1,3,5-triazinane-2-thione (3h). mp 246-248°C. IR spectrum, ν, cm^{-1}: 3583, 3501, 3303, 3158, 3008, 2674, 2327, 1970, 1841, 1558, 1154, 1001, 837, 661, 471, 424, 411. ^1H NMR spectrum, δ, ppm: 2.19 s (3H), 2.22 s (3H), 6.10 s (1H, NH), 7.08–7.10 (m, 3H, C_6H_5), 7.22–7.25 (m, 2H, C_6H_5), 7.38–7.48 m (3H, C_6H_5), 8.00 s (1H, NH), 9.30 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.3, 25.2, 126.4, 126.6, 127.6, 127.7, 128.7, 129.7, 135.2, 135.3, 135.8, 138.3, 138.4, 157.1, 157.6, 158.6, 159.4, 183.2, 184.4. ESI-MS: 324.68 $[M + H]^+$. Calculated for $C_{17}H_{18}N_5S$.

1-(2,6-Diisopropyl-4-phenoxyphenyl)-6-imino-4-{[2-(trifluoromethoxy)phenyl]imino}-1,3,5-triazinane-2-thione (3i). mp 254–256°C. IR spectrum, ν, cm^{-1}: 3594, 3437, 3216, 3080, 2929, 2422, 2083, 1895, 1715, 1554, 1370, 1212, 1045, 883, 753, 648, 521, 407. ^1H NMR spectrum, δ, ppm: 1.09 d (J = 6.5 Hz, 6H), 1.14 d (J = 6.5 Hz, 6H), 2.19–2.23 m (6H), 2.52–2.57 m (2H), 6.13 s (1H, NH), 6.87 s (2H, C_6H_5), 7.12–7.16 m (3H, C_6H_5), 7.30–7.33 m (1H, C_6H_5), 7.38–7.43 m (4H, C_6H_5), 7.75 d (J = 7.5 Hz, 1H, C_6H_5), 8.08 s (1H, NH), 9.56 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.0, 20.5, 20.6, 20.7, 23.6, 24.7, 26.3, 28.5, 34.1, 54.8, 59.7, 114.9, 118.3, 120.7, 121.1, 123.2, 126.4, 127.2, 128.0, 128.1, 129.9, 130.6, 142.5, 147.1, 156.5, 157.1, 157.9, 159.1, 184.2. ESI-MS: 556.85 $[M + H]^+$. Calculated for $C_{28}H_{29}F_3N_5O_2S$.

6-Imino-1-phenyl-4-{[2-(trifluoromethoxy)phenyl]-imino}-1,3,5-triazinane-2-thione (3j). mp 233– 235°C. IR spectrum, ν, cm^{-1}: 3592, 3426, 3371, 3167, 2886, 2329, 1955, 1808, 1654, 1338, 1182, 1049, 955, 775, 628, 498, 407. ^1H NMR spectrum, δ, ppm: 6.32 s (1H, NH), 7.04–7.30 m (3H, C_6H_5), 7.38–7.44 (m, 3H, C_6H_5), 7.50 t (J = 7.0 Hz, 2H, C_6H_5), 7.80 d (J = 7.5 Hz, 1H, C_6H_5), 8.02 s (1H, NH), 9.60 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.1, 117.0, 119.1, 121.1, 126.2, 127.3, 127.8, 128.1, 128.6, 128.9, 129.8, 130.8, 138.2, 142.1, 157.6, 159.0, 172.2, 184.1. ESI-MS: 380.59 $[M + H]^+$. Calculated for $C_{16}H_{13}F_3N_5OS$.

CONCLUSIONS

A mild and highly efficient protocol for the synthesis of 1-aryl-4-(arylimino)-6-iminohexahydro-1,3,5-triazine-2-thione derivatives under MW irradiation is developed. The method is characterized by short reaction time and high yields. The synthesized 1,3,5-triazine derivatives **3a**–**3j** are evaluated for their antimicrobial activity. Among these **3i** and **3j** demonstrate very good antibacterial activity. The other products show moderate microbial activity against the tested organisms.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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