CHAPTER-6

3,5,6-Trisubstituted-
1,2,4-Triazines
6.1 Theoretical

1,2,4-Triazines are an important class of compounds, which act as anti-inflammatory\textsuperscript{1-3}, and antimalarial\textsuperscript{4} agents. Some of them are used as antibacterial\textsuperscript{5-7} and antidiabetics\textsuperscript{8}. 3-Sulfanilamido-5-dimethyllethyl-1,2,4-triazine is manufactured and used as a drug\textsuperscript{9}. 6-Azacytidine derivatives show antiviral effects on the adenovirus genome\textsuperscript{10}, whereas some triazinone derivatives are used as antiulcer agents\textsuperscript{11}. Fluorene containing substituted 3-thioxo-1,2,4-triazin-5-ones exhibit antihuman immune virus activity\textsuperscript{12}.

The 1,2,4-triazine moiety plays a vital role in many biological activities including antiviral\textsuperscript{13}, antihypertensive\textsuperscript{13,14}, blood-platelet aggregation inhibitory\textsuperscript{14,15}, analgesic\textsuperscript{16}, and antibacterial properties\textsuperscript{17,18} as well as some of new anti-HIV and anticancer agents\textsuperscript{19}.

Microwave assisted organic synthesis (MAOS) continues to affect synthetic chemistry significantly by enabling rapid, reproducible and scalable chemistry development\textsuperscript{20}. The use of microwave irradiation has been an established tool in organic synthesis for achieving better selectivity, rate enhancement and reduction of thermally degradative by products\textsuperscript{21,22}. However these procedures are practically limited as the solvents in microwave oven at elevated temperatures create high pressure, which may cause explosion. One of the advances to overcome this problem is the inorganic solid supported\textsuperscript{23,24} organic synthesis which attracted attention because of enhanced selectivity, milder reaction conditions and associated ease of manipulation. Moreover they also provide an opportunity to work with open vessels and enhanced possibility of upscaling the reactions on preparative scale\textsuperscript{25,26}.

Numerous reactions including condensations, cycloadditions, heterocycle formation, metal catalyzed cross coupling have been explored under microwave conditions, some of which have been applied to medicinal chemistry and total synthesis of natural products\textsuperscript{27}. 
Safieh et al.\textsuperscript{28} have described novel method for the synthesis of a new series of 5-substituted 1,3-dimethyl pyrazolo-[4,3-e][1,2,4]-triazines (v) (Scheme 6.1).

\begin{center}
\begin{tikzpicture}
  \node (i) at (0,0) {\includegraphics[width=0.2\textwidth]{Scheme6.1_i.png}};
  \node (ii) at (0,1.5) {\includegraphics[width=0.2\textwidth]{Scheme6.1_ii.png}};
  \node (iii) at (0,3) {\includegraphics[width=0.2\textwidth]{Scheme6.1_iii.png}};
  \node (iv) at (1.5,0) {\includegraphics[width=0.2\textwidth]{Scheme6.1_iv.png}};
  \node (v) at (1.5,1.5) {\includegraphics[width=0.2\textwidth]{Scheme6.1_v.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 6.1}

A number of 6-aryl and 3-substituted-6-aryl-1,2,4-triazines (ix) have been prepared by heating a mixture of \(\alpha\)-haloacetophenone (vi) and two equivalent of acid hydrazide (vii) in alcohol or acetic acid in presence of slight excess of NaOAc, KOAc or AgOAc for few minutes\textsuperscript{29} (Scheme 6.2).

\begin{center}
\begin{tikzpicture}
  \node (vi) at (0,0) {\includegraphics[width=0.2\textwidth]{Scheme6.2_vi.png}};
  \node (vii) at (0,1.5) {\includegraphics[width=0.2\textwidth]{Scheme6.2_vii.png}};
  \node (viii) at (1.5,0) {\includegraphics[width=0.2\textwidth]{Scheme6.2_viii.png}};
  \node (ix) at (1.5,1.5) {\includegraphics[width=0.2\textwidth]{Scheme6.2_ix.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 6.2}

Synthesis of thiadiazone and triazino [3,4-b] thiadiazine derivatives were reported by Nami et al.\textsuperscript{30} The addition of dimethyl acetylenedicarboxylate (DMAD)
to dithizon (x) afforded dimethyl-2-methoxycarbonylmethylene-4,8-diphenyl-1,2,4-triazino[3,4-b]-1,3,4-thiadiazin-3-one-6,7-dicarboxylate (xi) (Scheme 6.3).

![Scheme 6.3](image)

Ali\textsuperscript{31} has synthesized 4-(4-\{[(6-Chloro-4-oxo-4H-chromen-3-yl)methylene]amino\}phenyl)-5,6-dihydro-5-phenyl-3-thioxo-1,2,4-triazine and 4-(4-\{[(6-Chloro-4-oxo-4H-chromen-3-yl)methylene]-amino\}phenyl)-2,5-dihydro-5,6-diphenyl-3-thioxo-1,2,4-triazine (xiii) as potential antifungal agents (Scheme 6.4).

![Scheme 6.4](image)

Heravi \textit{et al.}\textsuperscript{32} have reported the synthesis of [1,3,4]thiadiazolo [2,3-c][1,2,4]triazin-4-ones (xv) using sulfuric acid supported onto silica gel in solventless system (Scheme 6.5).

![Scheme 6.5](image)
Broadening the scope of 1,2,4-triazine synthesis by the application of microwave technology Zhao et al. have developed the rapid synthesis of diverse 3,5,6-trisubstituted-1,2,4-triazines (xviii) in excellent yield and purity, including many previously unknown 3-heterocyclic-1,2,4-triazines (Scheme 6.6).

\[
\begin{align*}
\text{(xvi)} & \quad + \quad \text{(xvii)} \quad \xrightarrow{\text{NH}_2\text{Ac (10 equiv.)}, \text{AcOH}} \quad \text{(xviii)} \\
\end{align*}
\]

**Scheme 6.6**

4-Amino-6-(tert-butyl)-3-methylthio-4,5-dihydro-1,2,4-triazin-5-one (xix) was used in nucleophilic substitution reaction with carboxylic acid hydrazides (Scheme 6.7).

\[
\begin{align*}
\text{(xix)} & \quad \xrightarrow{\text{H}_2\text{NNOC-}} \quad \text{(xx)} \\
\end{align*}
\]

**Scheme 6.7**

In a one pot microwave reaction, an acyl hydrazide-tethered indole underwent a 3-component condensation to form a triazine (xxiii), followed by an inverse-electron demand Diels-Alder reaction and subsequent chelotropic expulsion of nitrogen to deliver novel, unnatural β-carboline alkaloids (xxiv) in good isolated yields (Scheme 6.8).
Scheme 6.8
6.2 Microwave Assisted Efficient One-pot Synthesis of 3,5,6-Trisubstituted-1,2,4-triazines from Fatty Acid Hydrazides Under Solvent-Free Conditions and their Antimicrobial Activity*

1,2,4-Triazines are a representative class of heterocyclic compounds with a wide variety of interesting properties which are used in medicine and agriculture. It has been associated with diverse pharmacological activities such as hypertension and inhibition of platelets, antileukemic, anti-inflammatory and potent neuroprotective agents. The 1,2,4-triazine moiety is a structural element in antimalarial, anticancer, antifungal, anticonvulsant, antibacterial and antiviral compounds. Certain compounds containing 1,2,4-triazines nucleus have been reported to possess pesticidal, neuropharmacological, analgesic and antidepressant properties. Also some 1,2,4-triazine derivatives are used for the determination of metal ions and as dyes. The N-methyl derivatives of 1,2,4-triazines are the naturally occurring antibiotics fervenulin (planomycin), toxoflavin (xanthothricin) and neomycin.

In view of above mentioned pharmacological importance of heterocycles and our ongoing efforts to synthesize heterocycles from fatty acids we now describe a expeditious ecofriendly solvent free microwave accelerated solid state approach for the rapid synthesis of 3,5,6-trisubstituted-1,2,4-triazines from saturated and olefinic fatty acid hydrazides wherein several disadvantages such as long reaction time and tedious work up has overcome.

*Research paper entitled "Microwave assisted efficient one-pot synthesis of 3,5,6-trisubstituted-1,2,4-triazines from fatty acid hydrazides under solvent-free conditions and their antimicrobial activity" is published. (A. Rauf, S. Sharma, S. Gangal, ARKIVOC 2007 (xvi) 137-147).
6.3 Results and discussion

Considering that MW irradiations using commercial domestic ovens have been used to accelerate organic reactions, the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction times and better yields, we became interested to synthesize heterocycles from fatty acids under microwave irradiations. We now report the synthesis of 3,5,6-trisubstituted-1,2,4-triazine 3a-1 by condensation of 1,2-diketone 2a-b with various saturated and olefinic (internal and terminal) fatty acids hydrazides 1a-f under MW and solvent free conditions in short time (Scheme 6.9).

As can been seen from Table 6.1 and Table 6.2 the scope of the reaction using saturated, olefinic (internal and terminal) and hydroxy fatty acid hydrazides was found to be good.
The yield of 3,5,6-trisubstituted-1,2,4-triazine did not depend on the length of chain of fatty acid hydrazide and was found to be appreciable (Table 6.2). In order to determine the optimum conditions for the synthesis of triazines in faster and efficient way, molar ratios of reagents and the irradiation time and power level of microwave set-up was investigated. After some experimentation, we found a set of conditions that generally provides products in good yield. The optimum conditions employed are that the molar ratio of fatty acid hydrazides and 1,2-diketone is 1:1 and irradiation time and power level of microwave set up are 10-15 minutes, 60 and 100% power.
Table 6.2 *Optimization for the reaction of fatty acid hydrazides with 1,2-diketones under microwave irradiation*

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>Ratio 1/2</th>
<th>Microwave Equipment</th>
<th>Power (%)</th>
<th>Time (minutes)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<tr>
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<td>1a</td>
<td>2a</td>
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<td>7</td>
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<td>92</td>
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<tr>
<td>2</td>
<td>1b</td>
<td>2a</td>
<td>1:1</td>
<td>Multimode</td>
<td>60</td>
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</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2a</td>
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<td>60</td>
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<td>3c</td>
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<td>Multimode</td>
<td>100</td>
<td>12</td>
<td>3l</td>
<td>88</td>
</tr>
</tbody>
</table>

(a) All reactions were carried out using fatty acid hydrazides (1 eq) with respect to 1,3-diketone under microwave irradiation.

(b) Microwave equipment multimode was used.

(c) Full power is 1.35 kHz.

(d) Monitored by TLC.

(e) All yields refer to isolated products and the products were characterized by IR, $^1$H NMR, $^{13}$C NMR, MS and elemental analysis.

$^1$H NMR spectrum of 3-(heptadec-8-enyl)-5,6-dimethyl-1,2,4-triazine 3d showed characteristic signal of triplet for two hydrogens at δ 2.77 for methylene protons alpha to triazine ring and multiplet of two hydrogens at 1.63 for $-CH_2\_\_β$ to ring. The structure of 3d was further supported by its mass spectral studies, which showed molecular ion peak at m/z 345 consistent with its molecular formula C$_{15}$H$_{25}$N$_3$. Base peak appears at m/z 108. Detailed spectra of titled compounds are given in the experimental section.

To check the biological activity of the compounds, the series of the compounds (3a-l) were screened for the antimicrobial activity against bacteria (e.g. *Escherichia*...
coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhimurium), fungus (Penicillium sp, Helminthosporum oryzae, Aspergillus niger) and Candida albicans. The results are shown in Table 6.3 and Table 6.4. The compounds showed good activity against *H. oryzae*, *S. aureus*, *E. coli* and better results were obtained against *C. albicans*, Penicillium, *A. niger*. The moderate activity of compounds was observed against *S. typhimurium* and *B. subtilis*.

**Table 6.3 In vitro antibacterial activity of 3,5,6-trisubstituted-1,2,4-triazines**

<table>
<thead>
<tr>
<th>S. No.</th>
<th><em>E. coli</em></th>
<th><em>B. subtilis</em></th>
<th><em>S. aureus</em></th>
<th><em>S. typhimurium</em></th>
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<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>3b</td>
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<td>+</td>
</tr>
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<td>3g</td>
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<td>+</td>
</tr>
<tr>
<td>3h</td>
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<td>+</td>
</tr>
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<td>Control DMF</td>
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<tr>
<td>Chloroamphenicol</td>
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</tbody>
</table>

Zone of diameter of growth inhibition: <10 mm (-), 10-12 mm (+), 13-15 mm (++), 16-20 mm (+++).

**Table 6.4 In vitro antifungal activity of 3,5,6-trisubstituted-1,2,4-triazines**

<table>
<thead>
<tr>
<th>S. No.</th>
<th><em>C. albicans</em></th>
<th>Penicillium sp</th>
<th><em>A. niger</em></th>
<th><em>H. oryzae</em></th>
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</thead>
<tbody>
<tr>
<td>3a</td>
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<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
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<td>+++</td>
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<td>3j</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>3k</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<td>3l</td>
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<td>++</td>
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<td>Nystatin</td>
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</tbody>
</table>

Zone of diameter of growth inhibition: <10 mm (-), 10-12 mm (+), 13-15 mm (++), 16-20 mm (+++).
6.4 Experimental

The sources of all the fatty acids and instrumentation details are the same as given in Chapter 1 (page 38). The microwave irradiations were carried out using an unmodified domestic oven (LG, Model MC-808WAR, 1.35 KW, 2450MHz).

General procedure for the synthesis of 3,5,6-trisubstituted-1,2,4-triazines (3a-l)

The hydrazides of corresponding fatty acids were prepared as reported earlier in Chapter 2 (page 38)\(^\text{58}\). A mixture of fatty acid hydrazide 1a-f (2mmol), diketone 2a-b (2mmol) and silica gel was ground with a pestle, NH\(_4\)OAc and Et\(_3\)N were added in catalytic amount and the prepared mixture was introduced into microwave irradiation in open pyrex beaker for appropriate time (Table 6.2). After complete conversion as indicated by TLC, the mixture was extracted with petroleum ether and washed with water. Then the solvent was extracted in vacuum and the product was purified by column chromatography (Hexane:EtOAc, v:v) 3a, (99:1); 3b, (99:1); 3c, (99:1), 3d, (98:2); 3e, (98:2); 3f, (98:2); 3g, (99:1); 3h, (99:1); 3i, (99:1); 3j, (98:2); 3k, (97:3); 3l, (97:3).

Antibacterial Activity

The newly synthesized compounds were screened in vitro against an assortment of \textit{S. aureus} MSSA 22, \textit{B. subtilis} ATCC 6051, \textit{E. coli} K12 and \textit{S. typhimurium} MTCC 98. Screening results are summarized in Table 6.3. All the synthesized compounds were dissolved in DMF. The antibacterial activity of test compounds and standard chloramphenicol was done by filter paper disc method\(^\text{57}\). Media with DMF was set up as control.

Antifungal Activity

The standard agar disc diffusion method\(^\text{57}\) was performed to evaluate the antifungal property of the test compounds and standard nystatin. The newly synthesized compounds were screened for \textit{A. niger} (lab isolate), \textit{C. albicans} IOA-109, \textit{Penicillium}...
3,5,6-Trisubstituted-1,2,4-triazines

sp. (lab isolate) and H. oryzae (2537 ICAR, Jaipur). The synthesized compounds were dissolved in DMF. Media with DMF was set up as control.

**Spectroscopic data**

*3-Pentadecyl-5,6-dimethyl-1,2,4-triazine (3a)*

**IR** (KBr): 2930, 2859, 1594, 778 cm⁻¹.

**¹H NMR** (400 MHz, CDCl₃): δ 2.88 (t, 2H, J= 6.84 Hz, -CH₂ α to ring), 2.35 (m, 6H, ring CH₃), 1.62 (m, 2H, -CH₂ β to ring), 1.28 (br.s, 24H, chain CH₂), 0.88 (3H, dist.t, CH₃).

**¹³C NMR** (100 MHz, CDCl₃): 178.71, 176.77, 174.62, 34.62, 33.99, 31.64, 29.32, 28.01, 25.47, 23.42, 14.17.

**MS** (m/z, %): (M+1)⁺ 320 (12), M⁺ 319 (42), 150 (18), 136 (20), 122 (55), 108 (100).

**Anal: Calcd.** for C₂₀H₃₇N₃: C, 75.23; H, 11.59; N, 13.16. Found: C, 75.16; H, 11.60; N, 13.20%.

*3-Heptadecyl-5,6-dimethyl-1,2,4-triazine (3b)*

**IR** (KBr): 2930, 2860, 1590, 770 cm⁻¹.

**¹H NMR** (400 MHz, CDCl₃): δ 2.80 (t, 2H, J= 6.80 Hz, -CH₂ α to ring), 2.35 (m, 6H, ring CH₃), 1.63 (m, 2H, -CH₂ β to ring), 1.28 (28H, br.s, chain CH₂), 0.88 (3H, dist.t, CH₃).

**¹³C NMR** (100 MHz, CDCl₃): 180.10, 179.41, 177.09, 34.09, 31.95, 29.42, 24.71, 22.72, 14.15.

**MS** (m/z, %): (M+1)⁺ 348 (10), M⁺ 347 (32), 330 (66), 232 (36), 122 (48), 108 (100).

**Anal: Calcd.** for C₂₂H₄₁N₃: C, 76.08; H, 12.10; N, 11.81. Found: C, 76.11; H, 12.13; N, 11.89%.
3-(Dec-9-enyl)-5,6-dimethyl-1,2,4-triazine (3c)

**IR** (KBr): 2928, 2866, 1580, 775 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.82 (1H, tdd, $J_{H-H_2} = 6.6$ Hz, $J_{H-H_2} = 10.2$ Hz, $J_{H-H_x} = 17.1$ Hz, CH$_2$=CH-), 5.02 (1H, dd, $J_{H-H} = 10.2$ Hz, $J_{H-H_x} = 1.2$ Hz, H$_2$C=CH-), 4.90 (1H, dd, $J_{H-H} = 17.1$ Hz, $J_{H-H_x} = 1.2$ Hz, H$_2$C=CH-), 5.02 (1H, dd, $J_{H-H} = 6.6$ Hz, $J_{H-H_x} = 10.2$ Hz, $J_{H-H_x} = 1.2$ Hz, CH$_2$=CH-), 1.63 (m, 2H, CH$_2$ CH=CH-), 1.29 (br.s, 10H, chain CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): 180.64, 179.76, 178.45, 139.19, 114.22, 34.02, 29.15, 24.72.

**MS** (m/z, %): (M+1)$^+$ 248 (15), M$^+$ 247 (35), 220 (24), 139 (74), 108 (100).

**Anal:** Calcd. for C$_{15}$H$_{25}$N$_3$: C, 72.87; H, 10.12; N, 17.00. Found: C, 72.99; H, 10.16; N, 17.12 %

3-(Heptadec-8-enyl)-5,6-dimethyl-1,2,4-triazine (3d)

**IR** (KBr): 2930, 2856, 1585, 775 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.35 (m, 2H, -CH=CH-), 2.77 (t, 2H, $J = 6.52$ Hz, -CH$_2$ CH=CH-), 2.34 (m, 6H, ring CH$_3$), 2.03 (m, 4H, -CH$_2$-CH=CH-CH$_2$-), 1.63 (m, 2H, -CH$_2$ CH=CH-), 1.30 (br.s, 18H, chain CH$_2$), 0.88 (3H, dist.t, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$): 179.76, 176.77, 174.37, 130.01, 129.72, 44.37, 34.00, 31.64, 29.39, 27.13, 25.54, 24.74, 14.17.

**MS** (m/z, %): (M+1)$^+$ 346 (23), M$^+$ 345 (75), 330 (63), 232 (46), 122 (29), 108 (100).

**Anal:** Calcd. for C$_{22}$H$_{39}$N$_3$: C, 76.52; H, 11.30; N, 12.17. Found: C, 76.50; H, 11.33; N, 12.19 %

3-(8Z, 11R)-11-Hydroxyheptadec-8-enyl)-5,6-dimethyl-1,2,4-triazine (3e)

**IR** (KBr): 2940, 2866, 1580, 778 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.38 (m, 2H, -CH=CH-), 3.64 (m, 1H, -CHOH), 2.88 (t, 2H, $J = 6.82$ Hz, -CH$_2$ CH=CH-), 2.30 (m, 1H, -CHOH), 2.21 (m, 6H, ring CH$_3$),
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$2.03 \text{ (m, 4H, -CH}_2\text{-CH=CH-CH}_2\text{), 1.54 \text{ (m, 2H, -CH}_2\text{ β to ring), 1.37 \text{ (br.s, 18H, chain CH}_2\text{), 0.88 \text{ (3H, dist.t, CH}_3\text{).}}$ 

$^{13}C \text{ NMR (100 MHz, CDCl}_3\text{): 178.73, 177.0, 175.02, 127.98, 127.83, 77.67, 37.05, 34.63, 32.41, 29.16, 24.29, 14.15.}$

$MS \text{ (m/z, %): (M+1)^+ 362 (12), M^+ 361 (24), 276 (82), 136 (78), 122 (64), 108 (108).}$

$\text{Anal: Calcd. for C}_{22}\text{H}_{39}\text{N}_3\text{O: C, 73.13; H, 11.63; N, 10.80. Found: C, 73.11; H, 11.70; N, 10.89%}.$

3-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-5,6-dimethyl-1,2,4-triazine (3f)

$IR \text{ (KBr): 2930, 2859, 1594, 778 cm}^{-1}.$

$^{1}H \text{ NMR (400 MHz, CDCl}_3\text{): 8 5.38 \text{ (m, 2H, -CH=CH-), 3.64 \text{ (m, 1H, -CHOH), 2.83}}$

$\text{ (t, 2H, J = 6.82 Hz, -CH}_2\text{ α to ring), 2.24 \text{ (m, 6H, ring CH}_3\text{), 2.31 \text{ (m, 1H, -CHOH),}}$

$2.04 \text{ (m, 4H, -CH}_2\text{-CH=CH-CH}_2\text{-), 1.63 \text{ (m, 2H, -CH}_2\text{ β to ring), 1.36 \text{ (br.s, 18H, chain CH}_2\text{), 0.88 \text{ (3H, dist.t, CH}_3\text{).}}}$

$^{13}C \text{ NMR (100 MHz, CDCl}_3\text{): 178.71, 176.77, 174.62, 130.04, 129.67, 127.86, 71.67, 37.06, 34.60, 33.98, 31.64, 29.28, 24.29, 14.50.}$

$MS \text{ (m/z, %): (M+1)^+ 362 (14), M^+ 361 (78), 236 (32), 136 (62), 122 (18), 108 (100).}$

$\text{Anal: Calcd. for C}_{22}\text{H}_{39}\text{N}_3\text{O: C, 73.13; H, 11.63; N, 10.80. Found: C, 73.19; H, 11.80; N, 10.99%}.$

3-Pentadecyl-5,6-diphenyl-1,2,4-triazine (3g)

$IR \text{ (KBr): 2930, 1590, 2860, 770 cm}^{-1}.$

$^{1}H \text{ NMR (300 MHz, CDCl}_3\text{): 8 7.53-7.26 \text{ (m, 10 H, Ar-H), 2.52 \text{ (t, 2H, J = 7.2Hz,}}$

$-CH}_2\text{ α to ring), 1.96 \text{ (m, 2H, -CH}_2\text{ β to ring), 1.47 \text{ (br.s, 18H, chain CH}_2\text{), 0.88 \text{ (3H, dist.t, CH}_3\text{).}}}$

$^{13}C \text{ NMR (100 MHz, CDCl}_3\text{): 180.33, 179.76, 178.45, 134.94, 133.04, 129.51, 34.15, 31.98, 29.45, 23.74, 14.17.}$

$MS \text{ (m/z, %): (M+1)^+ 444 (9), M^+ 443 (12), 428 (82), 260 (80), 246 (34), 232 (100).}$
**3,5,6-Trisubstituted-1,2,4-triazines**

**Anal: Calcd.** for C\textsubscript{30}H\textsubscript{41}N\textsubscript{3}: C, 81.26; H, 9.25; N, 9.48. Found: C, 81.30; H, 11.70; N, 9.09%.

3-Heptadecyl-5,6-diphenyl-1,2,4-triazine (3h)

**IR** (KBr): 2930, 2859, 1594, 778 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.53-7.26 (m, 10 H, Ar-H), 2.52 (t, 2H, J = 6.9Hz, -CH\textsubscript{2} α to ring), 1.96 (m, 2H, -CH\textsubscript{2} β to ring), 1.47 (br.s, 28H, chain CH\textsubscript{2}), 0.88 (3H, dist.t, CH\textsubscript{3}).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 180.10, 179.76, 173.83, 134.92, 133.01, 129.49, 34.09, 31.95, 29.42, 23.71, 14.15.

**MS** (m/z, %): (M+1)^+ 470 (12), M^+ 471 (28), 456 (39), 260 (44), 246 (26), 232 (100).

**Anal: Calcd.** for C\textsubscript{32}H\textsubscript{45}N\textsubscript{3}: C, 81.52; H, 9.55; N, 8.91. Found: C, 81.30; H, 9.66; N, 8.70%.

3-(Dec-9-enyl)-5,6-diphenyl-1,2,4-triazine (3i)

**IR** (KBr): 2933, 2856, 1580, 776 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 8.03-7.25 (m, 10 H, Ar-H), 5.82 (1H, tdd, J\textsubscript{H-H} = 6.6 Hz, J\textsubscript{H-H} = 10.2 Hz, J\textsubscript{H-H} = 17.1 Hz, CH\textsubscript{2}=CH-), 5.02 (1H, dd, J\textsubscript{H-H} = 10.2 Hz, J\textsubscript{H-H} = 1.2 Hz, H\textsubscript{2}C=CH-), 4.90 (1H, dd, J\textsubscript{H-H} = 17.1 Hz, J\textsubscript{H-H} = 1.2 Hz, H\textsubscript{2}C=CH-), 2.81 (t, 2H, J = 7.6Hz, -CH\textsubscript{2} α to ring), 2.02 (m, 2H, -CH\textsubscript{2}-CH=CH\textsubscript{2}), 1.68 (m, 2H, -CH\textsubscript{2} β to ring), 1.29 (br.s, 10H, chain CH\textsubscript{2}).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 178.71, 176.77, 174.62, 130.56, 130.47, 128.78, 34.62, 33.99, 31.64, 28.88, 24.30.

**MS** (m/z, %): (M+1)^+ 374 (13), M^+ 373 (35), 346 (66), 260 (70), 246 (82), 232 (100).

**Anal: Calcd.** for C\textsubscript{25}H\textsubscript{29}N\textsubscript{3}: C, 80.42; H, 8.31; N, 11.26. Found: C, 80.36; H, 8.39; N, 11.22%.
3-(Heptadec-8-enyl)-5,6-diphenyl-1,2,4-triazine (3j)

**IR** (KBr): 2933, 2855, 1580, 770 cm⁻¹.

\(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 7.85-7.33 (m, 10 H, Ar-H), 5.35 (m, 2H, -CH=CH-), 2.79 (t, 2H, \(J = 7.2\) Hz, -CH₂ α to ring), 2.02 (m, 4H, -CH₂-CH=CH-CH₂-), 1.73 (m, 2H, -CH₂ β to ring), 1.26 (br.s, 20H, chain CH₂), 0.88 (3H, dist.t, CH₃).

\(^13\)C NMR (100 MHz, CDCl₃): 180.33, 178.95, 176.77, 134.94, 133.04, 129.51, 34.15, 31.98, 29.45, 23.74, 14.17.

**MS** (m/z, %): (M+1)⁺ 470 (8), M⁺ 469 (48), 356 (15), 260 (38), 246 (23), 232 (100).

**Anal: Calcd.** for C\(_{32}\)H\(_{43}\)N\(_3\): C, 81.87; H, 9.16; N, 8.95. Found: C, 81.36; H, 9.39; N, 8.82%.

3-[\((8Z,11R)-11\)-Hydroxyheptadec-8-enyl]-5,6-diphenyl-1,2,4-triazine (3k)

**IR** (KBr): 2930, 2850, 1585, 776 cm⁻¹.

\(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 8.03-7.21 (m, 10 H, Ar-H), 5.36 (m, 2H, -CH=CH-), 3.89 (m, IH, -CHOH), 2.61 (t, 2H, \(J = 7.5\) Hz, -CH₂ α to ring), 2.27 (m, 1H, -CHOH), 2.04 (m, 4H, -CH₂-CH=CH-CH₂-), 1.51 (m, 2H, -CH₂ β to ring), 1.25 (br.s, 18H, chain CH₂), 0.86 (3H, dist.t, CH₃).

\(^13\)C NMR (100 MHz, CDCl₃): 178.71, 177.09, 175.09, 130.56, 130.47, 128.78, 71.67, 37.06, 34.30, 31.64, 28.88, 24.30, 14.15.

**MS** (m/z, %): (M+1)⁺ 486 (22), M⁺ 485 (38), 400 (28), 260 (44), 246 (23), 232 (100).

**Anal: Calcd.** for C\(_{32}\)H\(_{43}\)N\(_3\)O: C, 79.17; H, 8.86; N, 8.65. Found: C, 79.20; H, 8.89; N, 8.60%.

3-[\((8R,11Z)-8\)-Hydroxyheptadec-11-enyl]-5,6-diphenyl-1,2,4-triazine (3l)

**IR** (KBr): 2940, 2866, 1585, 778 cm⁻¹.

\(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 7.35-7.00 (m, 10 H, Ar-H), 5.46 (m, 2H, -CH=CH-), 3.91 (m, 1H, -CHOH), 2.54 (t, 2H, \(J = 7.5\) Hz, -CH₂ α to ring), 2.36 (m, 1H, -CHOH), 2.02 (m, 4H, -CH₂-CH=CH-CH₂-), 1.73 (m, 2H, -CH₂ β to ring), 1.38 (br.s, 18H, chain CH₂), 0.88 (3H, dist.t, CH₃).
$^{13}$C NMR (100 MHz, CDCl$_3$): 178.71, 176.77, 174.62, 130.56, 130.47, 128.78, 71.67, 37.06, 34.60, 33.96, 31.68, 28.90, 24.29, 14.50.

**MS** (m/z, %): (M+1)$^+$ 486 (24), M$^+$ 485 (34), 360 (56), 260 (67), 246 (82), 232 (100).

**Anal. Calcd.** for C$_{32}$H$_{43}$N$_3$O: C, 79.17; H, 8.86; N, 8.65. **Found:** C, 79.16; H, 8.90; N, 8.59 %.
6.5 References


3. W. B. Lacefield, *French Demande*, 2, 243, 479; (Cl. A61K31/S3) (**1977**).


5. I. Saikawa, Y. Suzuki, T. Osada, Japanese Patent, 7026, 294; (Cl. 16E475) (**1970**).

6. I. Saikawa, T. Osada, Japanese Patent, 7026, 109; (Cl. 16E475) (**1970**).


8. I. Saikawa, T. Maeda, Japanese Patent, 7026, 106; (Cl. 16E475) (**1970**).

9. S. Kono, S. Zoga, T. Komaki, Japanese Patent, 6720, 313; (Cl. 16E475) (**1968**).


11. K. Hirai, H. Sugimoto, T. Mizushima, Japanese Patent, 61, 134; (Cl.CO7D401/1z) (**1986**).


3,5,6-Trisubstituted-1,2,4-triazines


