Synthesis of Dihydro-1,2,4-Triazin-6-one Containing Nitroarginine Moiety

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Abstract: Nitrilimines (2), react with nitroarginine methyl ester (3) at room temperature, through cyclocondensation reaction, to give 1-aryl-3-substituted-1,2,4-triazin-6-ones (4a-k). The structure of these compounds was deduced from: elemental analysis, IR, mass spectra, $^1$H and $^{13}$C NMR.

Introduction

1,2,4-triazines are considered an important pool of intermediates for the synthesis of a wide range of pharmacological and biological systems [1]. A lot of information about the important methods of synthesis, the structure, physical / chemical reactivity of these compounds are described in the literature [1-4]. A common method for synthesis of 1,2,4-triazin-6-ones is the cyclization of $\alpha$-(acylamino) carboxyhydrazides [5,6], as well as from the reaction of nitrilimines with $\alpha$-aminoacetonitrile [7]. Nitrilimines have been reported to react with $\alpha$-hydrazinoester to give 1,2,4-triazin-6-ones [6]. It is known that the reaction of nitrile oxides with $\alpha$-amino esters gives 4,5-dihydro-1,2,4-oxadiazin-6-ones [8]. A facile preparation of 4,5-dihydro-1,2,4-triazin-6-(1H)-ones from the reaction of nitrilimines with $\alpha$-amino esters was reported [9]. However, attempts to anchor arginine moiety with 1,2,4-triazines were problematic and unproductive due to the presence of the guanidine group. The importance of the present work stems from the ability to solve this problem by protecting this active guanidine group using the nitro group. It was possible to prepare 1,2,4-triazin-6-one containing nitroarginine.
moiety as depicted in scheme 1. In addition, the target molecule could be considered as peptide mimetic aggregation of Arg-Gly-Asp. This Arg-Gly-Asp sequence (RGD) or its mimetics have been incorporated into drug candidates which were used to treat or prevent thrombosis [10]. The new triazinone derivatives will be bioassayed, and the results will be communicated separately.

RESULTS AND DISCUSSION

Nitrilimines (2), generated in situ from the respective hydrazonyl halides (1) in THF upon the addition of triethylamine, are found to react with nitroarginine methyl ester (3), in methanol as a solvent at room temperature, through cyclocondensation reaction, to give a series of 1,2,4-triazin-6-ones (4a-k) Scheme 1. The target compounds (4) are achieved via a nucleophilic attack of the amino group of the nitroarginine (3) to nitrilimines followed by intracyclization.
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The IR spectra of compounds (4) in KBr revealed four bands in the region 3450-3240 cm\(^{-1}\) for 1 NH (triazinone) and 3 NH (nitroguanidine). Two strong absorption bands are also observed in the regions 1705-1680 cm\(^{-1}\) (C=O acetyl or ester) and 1685-1630 cm\(^{-1}\) (C=O lactam). Two stretching bands (C=N) appeared in the region 1650-1590 cm\(^{-1}\). The \(^1\)H-NMR spectra of compounds (4) show a singlet for the CH\(_3\) of the acetyl group around 2.4 ppm (4a-i) and that of compounds containing ester group about 3.7 ppm (4j-k). The signals of –CH\(_2\) – CH\(_2\) – CH\(_2\) – protons appear between 3.1-1.4 ppm as multiplets and the NH proton for triazinone appear in the aromatic region between 7.5-7.0 ppm and 3 NH for nitroguanidine are observed between 8.8-7.5 ppm as singlets. The signals of the aromatic protons are observed between 7.5-6.8 ppm as a multiplet. The C5-H proton appears as a multiplet about 4.2 ppm. The \(^13\)C-NMR spectra of compounds (4) show the CH\(_3\) of the acetyl group around 24.8 ppm and that of compounds containing ester group about 59 ppm. The carbonyl carbon (C=O) of acetyl group appears about 193 ppm and that of compounds containing ester group around 156 ppm. The signal of C-5 carbon appears about 52.5 ppm and C-3 carbon around 145 ppm. The carbon of lactam (C=O) and the carbon (C=NH) of nitroguanidine appear around 160 and 162 ppm. The carbons of (CH\(_2\))\(_3\) appears around 20 ppm, 30 ppm, 40 ppm. The aromatic carbons appear between 143-115 ppm. It was reported that the main fragmentation modes of the closely related 3-aryl-4,5-dihydro-1,2,4-traizin-6-ones involving heteroring cleavage at the dotted lines are in agreement with our suggested structures (4a–k) [9, 11]. Fragmentation of compound (4a), as an example, at the dotted line a, in scheme 2, produces the ions with the masses (M\(^+\)) 173, and 222/224. Another fragmentation pattern, path b, gives the ion M\(^+\) = 153/155. Fragmentation patterns c, d occur to a much smaller extent and give the ions ArN\(^+\) 125/127 and Ar\(^+\) 111/113 respectively, (see scheme 2).
EXPERIMENTAL
Melting points were determined on Steuart melting point apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer in KBr discs. Mass spectra were recorded on a Gas Chromatographic GCMS qp 10000ex Schimadzu instrument at 70 eV. $^1$H
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and $^{13}$C-NMR were recorded on a Bruker AM 300 MHz NMR spectrometer using DMSO-$d_6$ as a solvent at 21 °C and TMS as an internal reference. Chemical shifts are expressed in δ (ppm) downfield from TMS and coupling constants are in Hertz (Hz). Elemental analysis were carried out at micro analytical laboratory, university of Cairo, Egypt.

The hydrazonoyl halides (1a–e, h) employed in this study, were prepared through coupling of the appropriate arenediazonium chloride with 3-chloro-2,4-pentanedione in aqueous pyridine solution, while (1j, k) were obtained by coupling of the diazonium salt with α-chloro-acetoacetate under the same conditions [10,11]. Other hydrazonoyl halides (1f–g, i) were prepared through coupling of the appropriate arenediazonium chloride with 2,4-pentanedione in sodium acetate / ethanol solution [12]. Nitroarginine methyl ester hydrochloride (3) employed in this work was obtained by reaction the appropriate nitroarginine with thionyl chloride in methanol following literature procedure [13].

Synthesis of 1,2,4-triazin-6-ones (4a-k)

General procedure: To a stirred solution of the particular nitroarginine methyl ester hydrochloride (0. 015 mol) in methanol (60 ml) was added a solution of the appropriate hydrazonyl halides (1) (0.01 mol) in tetrahydrofuran (100 ml) at room temperature. To the resulting reaction mixture, was added dropwise triethylamine (0.05 mol). Stirring of the reaction mixture was continued at room temperature overnight. The organic solvent was then removed under reduced pressure, and the residue washed with water. The residual crude product was then collected and recrystallized from aqueous ethanol or tetrahydrofuran / pet. ether (40- 60 °C). The residual crude product of compounds (4f), (4g) and (4i) containing COOH group at ortho or para position were dissolved in water and then drops of acetic acid were added until the solution becomes slightly acidic, a yellow precipitate was filtered and recrystallized from hot ethanol. The yields were in the range 25 -85%.

The following compounds were obtained by this method:

3-Acetyl-1-(4-chlorophenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4a)

Yield = 75%, M. P. = 168-170 °C, IR (KBr): cm$^{-1}$ 3450-3280 (4NH bands), 1701 (acetyl), 1682 (C=O lactam), 1645 and 1613 (C=N nitroguanidine and C=N triazinone). $^1$H NMR (DMSO-$d_6$): δ / ppm 1.5 (m, 2H, CH$_2$), 1.7 (m, 2H, CH$_2$), 2.3 (s, 3H, CH$_3$CO), 3.1 (m, 2H, CH$_2$), 4.1 (m, 1H, CH), 7.5 - 7.4 (m, 5H, 1NH + 4H aromatic protons underneath), 7.7 (br.s, 2H, 2NH), 8.5 (br.s, 1H, 1NH). $^{13}$C NMR (DMSO-$d_6$): 24.8 (CH$_3$CO), 20.0, 30.7, 40.7 (CH$_2$)$_3$, 52.9 (C-5), 126.6, 128.6, 131.0, 140.1, 143.2 (aromatic carbons + C-

3-Acetyl-1-phenyl-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4b)
Yield = 85%, M. P. = 153-155 ºC, IR (KBr): cm⁻¹ 3400-3306 (4NH bands), 1698 (acetyl), 1681 (C=O lactam), 1645 and 1594 (C=N nitroguanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.6 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.4 (s, 3H, CH₃CO), 3.4 (m, 2H, CH₂), 4.1 (m, 1H, CH), 7.5-7.0 (m, 6H, 1NH + 5H aromatic protons underneath), 7.7 (br.s, 2H, 2NH), 8.5 (br.s, 1H, 1NH). ¹³C NMR (DMSO-d₆): δ/ppm 25.83 (CH₃CO), 18.0, 30.7, 40.64 (CH₂), 52.7 (C-5), 115.3, 123.1, 129.8, 137.0 (aromatic carbons) 143.0(C-3), 159.7 (C=N nitroguanidine), 162.8 (C=O lactam), 188 (CH₃CO) MS: m/z 361 (M⁺), 188 [CH₃COC=NN (CO)-p-ClC₆H₄]+, 119 [C₆H₄NCO]+, 91 [C₆H₅N]+, 77 (base beak) [C₆H₅]+. Elemental analysis: M.wt. 361, M.F. C₁₅H₁₉ClN₇O₄, calcd.(%): C 49.86, H 4.5, N 27.13, found (%): C 49.23, H 4.42, N 26.63.

3-Acetyl-1-(4-fluorophenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-ones (4c)
Yield=76%, M. P.=149-150 ºC, IR (KBr): cm⁻¹ 3450-3270 (4NH bands), 1704 (acetyl), 1679 (C=O lactam), 1645 and 1594 (C=N nitroguanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.6 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.3 (s, 3H, CH₃CO), 3.4 (m, 2H, CH₂), 4.1 (m, 1H, CH), 7.5-7.0 (m, 5H, 1NH + 4H aromatic protons underneath), 8.5 - 7.7 (m, 3H, 3NH nitroguanidine). ¹³C NMR (DMSO-d₆): δ/ppm 24.68 (CH₃CO), 23.77, 30.74, 40.73 (CH₂), 52.9 (C-5), 115.82, 127.38, 137.50, 138.0 (aromatic carbons), 143.1 (C-3), 159.62 (C=N nitroguanidine), 162.12 (C=O lactam), 193 (CH₃CO). MS: m/z 379 (M⁺), 206 [CH₂COC=NN (CO)-p-FC₆H₄]+, 137 [p-FC₆H₄NCO]+, 109 [C₆H₄FN]⁺, 95 ( base beak) [p-FC₆H₄]+. Elemental analysis: M.wt.= 379, M.F. C₁₅H₁₈FN₇O₄, calcd. (%): C 47.46, H 4.5, N 27.13, found (%): C 47.85, H 4.53, N 25.75.

3-Acetyl-1-(4-hydroxyphenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-ones (4d)
Yield=60%, M. P.=273-275 ºC, IR (KBr): cm⁻¹ 3450-3270 (4NH bands), 3300-2500 (abroad OH), 1682 (acetyl), 1640 (C=O lactam), 1618 and 1596 (C=N nitroguanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.5 (m, 2H, CH₂), 1.6 (m, 2H, CH₂), 2.3 (s, 3H, CH₃CO), 3.1 (m, 2H, CH₂), 4.1 (m, 1H, CH), 7.4-6.9 (m, 5H, 1NH + 4H aromatic protons underneath),
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8.3-7.6 (s, 3H, 3NH nitroguanidine), 14.5 (ArOH). $^{13}$C NMR (DMSO-d$_6$): $\delta$ / ppm 26.8 (CH$_3$CO), 22.0, 31.5, 40.5 (CH$_2$)$_3$, 52.9 (C-5), 116.1, 123.5, 134.1, 141.1 (aromatic carbons), 143.3 (C-3), 159.4 (C=N nitroguanidine), 162.2 (C=O lactam), 196 (CH$_3$CO). MS: m/z 377 (M$^+$), 204 [CH$_3$COC=NN (CO)-p-OHC$_6$H$_4$]+, 135 [p-OHC$_6$H$_4$NCO]$^+$, 108 (base beak) [p-OHC$_6$H$_4$NH]$^+$, 93 [p-OHC$_6$H$_4$]. M.wt.= 377, M. F. C$_{16}$H$_{16}$N$_7$O$_5$.

3-Acetyl-1-(4-methylphenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4e)

Yield=84%, M. P.= 202-204 ºC, IR (KBr): cm$^{-1}$ 3439-3282 (4NH bands), 1700 (acetyl), 681 (C=O lactam), 1648 and 1610 (C=N triazinone). $^1$H NMR (DMSO-d$_6$): $\delta$ / ppm 1.5 (m, 2H, CH$_2$), 1.7 (m, 2H, CH$_2$), 2.3 (s, 3H, ArCH$_3$), 2.3 (s, 3H,CH$_3$CO), 3.1 (m, 2H, CH$_2$), 4.1 (m, 1H, CH), 7.6-7.16 (m, 6H, 1NH + 5H aromatic protons underneath), 7.8 (br.s, 2H, 2NH), 8.5 (br.s, 1H, 1NH).$^{13}$C NMR (DMSO-d$_6$): $\delta$/ppm 26.8 (CH$_3$CO), 22.0, 30.8 (ArCH$_3$), 22.0, 30.6, 40.7 (CH$_2$)$_3$, 52.4 (C- 5), 125.2, 129.5, 136.4, 139 (aromatic carbons), 143 (C-3), 159.8 (C=N nitroguanidine), 162.8 (C=O lactam), 193 (CH$_3$CO). MS: m/z 375 (M$^+$), 202 (base beak), [CH$_3$COC=N(CO)-p-CH$_3$C$_6$H$_4$]+, 133 [p-CH$_3$C$_6$H$_4$NCO]$^+$, 105 [p-CH$_3$C$_6$H$_4$NH]$^+$, 91 [p-CH$_3$C$_6$H$_4$]. Elemental analysis: M.wt.= 375, M.F. C$_{16}$H$_{21}$N$_7$O$_4$, calcd.(%): C 49.49, H 4.78, N 25.85, found (%): C 49.68, H 4.53, N 25.75.

3-Acetyl-1-(4-carboxyphenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4f)

Yield=52%, M. P.= 238-240 ºC, IR (KBr): cm$^{-1}$ 3405-3243 (4NH bands), 3300-2500 (abroad OH), 1710 (COOH), 1693 (acetyl), 1637 C=O lactam), 1610 and 1591 (C=N triazinone). $^1$H NMR (DMSO-d$_6$): $\delta$/ppm 1.5 (m, 2H, CH$_2$), 1.7 (m, 2H, CH$_2$), 2.4 (s, 3H, CH$_3$CO), 3.1 (m, 2H, CH$_2$), 4.1 (m, 1H, CH), 7.7-7.4 (m, 5H, 1NH + 4H aromatic protons underneath), 8.4-7.9 (s, 3H, 3NH nitroguanidine), 12.5 (ArCOOH). $^{13}$C NMR (DMSO-d$_6$): $\delta$/ppm 24.7 (CH$_3$CO), 23.8, 30.7, 40.3 (CH$_2$)$_3$, 52.0 (C- 5), 124.3, 128.8, 138.1, 143.3 (aromatic carbons), 144.6 (C-3), 159.7 (C=N nitroguanidine), 162.5 (C=O lactam), 167 (ArCOOH), 193 (CH$_3$CO). MS: m/z 405 (M$^+$), 232 [CH$_3$COC=NN(CO)-p-COOHC$_6$H$_4$]+, 163 [p-COOHC$_6$H$_4$NCO]$^+$, 120 (base beak) [p-COOHC$_6$H$_4$NH]$^+$, 107 [p-COOHC$_6$H$_4$]. Elemental analysis: M.wt. = 405, M.F. C$_{16}$H$_{19}$N$_7$O$_6$, calcd.(%): C 47.41, H 4.72, N 24.19, found(%): C 47.08, H 4.33, N 23.65.
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3-Acetyl-1-(4-carboxymethylphenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4g)
Yield=43%, M. P.=223-225 ºC, IR (KBr): cm⁻¹ 3405-3243 (4NH bands), 3300-2500 (abroad OH), 1710 (COOH), 1693 (acyetyl), 1637 (C=O lactam), 1610 and 1592 (C=N nitroguanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.5 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.4 (s, 3H, CH₃CO), 2.7 (s, 2H, CH₂COOH), 3.1 (m, 2H, CH₂), 4.1 (m, 1H, CH), 7.7-7.5 (m, 5H, 1NH + 4H aromatic protons underneath), 8.5-7.9 (s, 3H, 3NH nitroguanidine), 12.5 (ArCOOH). ¹³C NMR (DMSO-d₆): δ/ppm 23.7 (CH₃CO), 22.7, 30.8, 40.3 (CH₂), 42.4 (CH₃COOH), 52.2 (C-5), 123.3, 128.9, 139.2, 142 (aromatic carbons), 143.8 (C-3), 159.9 (C=N nitroguanidine), 162.5 (C=O lactam), 167 (ArCH₂COOH), 193 (CH₃CO). MS: m/z 419 (M⁺), 246 [CH₃COC=NN(CO)-p-(CH₂COOH)C₆H₄]⁺, 177 [C₆H₄CH₂COOHNC]⁺, 149 [p-(CH₂COOH)C₆H₄N]⁺, 135 [p-CH₂COOH₆H₄]⁺, 59 [p-CH₂COOH]⁺. M. wt.= 419, M.F. C₁₇H₂₁N₇O₆.

3-Acetyl-1-(4-acetylphenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4h)
Yield=50%, M. P.=252-253 ºC, IR (KBr): cm⁻¹ 4110-3278 (4NH bands), 1698 and 1682 (two groups of acetyl), 1665 (C=O lactam), 1620 and 1597 (C=N nitroguanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.5 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.3 (s, 3H, CH₃CO), 2.4 (s, 3H, p-CH₃CO), 3.1 (m, 2H, CH₂), 4.1 (m, 1H, CH), 7.6-7.1 (m, 5H, 1NH + 4H aromatic protons underneath), 8.5-7.8 (s, 3H, 3NH nitroguanidine). ¹³C NMR (DMSO-d₆): δ/ppm 24.5 (CH₃CO), 26.6 (p-CH₃CO), 21.4, 30.4, 40.4 (CH₂), 52.8 (C-5), 123.7, 128.5, 137.3, 141.5 (aromatic carbons), 143.2 (C-3), 159.7 (C=N nitroguanidine), 162.7 (C=O lactam), 192.1 (p-CH₃CO), 193.4 (CH₃CO), M. wt.= 403, M.F. C₁₇H₂₁N₇O₆.

3-Acetyl-1-(2-carboxyphenyl)-4,5-dihydro-5-[3-nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4i)
Yield=60%, M. P.=225-227 ºC, IR (KBr): cm⁻¹ 3434-3250 (4NH bands), 3300-2500 (abroad OH), 1712 (COOH), 1691 (acyetyl), 1640 (C=O lactam), 1617, 1590 (C=N nitroguanidine and triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.5 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.4 (s, 3H, CH₃CO), 3.1 (m, 2H, CH₂), 4.2 (m, 1H, CH), 7.6-7.4 (m, 5H, 1NH + 4H aromatic protons underneath), 8.5-7.9 (s, 3H, 3NH nitroguanidine), 12.4 (ArCOOH). ¹³C NMR (DMSO-d₆): δ/ppm 24.5 (CH₃CO), 24.7, 30.7, 40.3 (CH₂), 52.3 (C-5), 124.3, 128.6, 138.6, 142.6 (aromatic carbons), 144.9 (C-3), 159.8 (C=N nitroguanidine), 162.6 (C=O lactam), 167 (ArCOOH), 193.2 (CH₃CO). MS: m/z 405 (M⁺), 232 [CH₃COC=NN(CO)-o-COOHC₆H₄]⁺, 163 [o-
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1-(4-Chlorophenyl)-3-methylcarboxylate-4,5-dihydro-5-[3 nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4j)
Yield=32%, M. P.=153-155 ºC, IR (KBr): cm⁻¹ 3452-3281 (4NH bands), 1711 (ester), 1684 (C=O lactam), 1644 and 1611 (C=N nitro-guanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.5 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 3.1 (m, 2H, CH₂), 3.7 (s, 3H, CH₃OCO), 4.1 (m, 1H, CH), 7.6-7.3 (m, 5H, 1NH + 4H aromatic protons underneath) 8.6-7.8 (s, 3H, 3NH nitroguanidine). ¹³C NMR (DMSO-d₆): δ/ppm 21.1, 30.6, 40.3 (CH₂), 52.9 (C- 5), 59.3 (CH₃OCO), 125.7, 128.9, 132.4, 140.4 (aromatic carbons), 143.7 (C-3), 156.4 (CH₃O), 160 (C=N nitroguanidine), 162 (C=O lactam). MS: m/z 411/413 (M⁺), 222/224 [CH₃COC=NN(CO)-p-ClC₆H₄]⁺, m/e 153/155 [p-ClC₆H₄NCO]⁺, 111/113 [p-ClC₆H₄]⁺. M. wt.= 411/413, M.F. C₁₅H₁₈N₇O₅.

1-(4-Acetylphenyl)-3-methylcarboxylate-4,5-dihydro-5-[3 nitroguanidineprop-1-yl]-1,2,4-triazin-6-one (4k)
Yield=25%, M. P.=202-204 ºC, IR (KBr): cm⁻¹ 3440-3240 (4NH bands), 1706 (ester), 1680 (acetyl), 1665 (C=O lactam), 1630 and 1592 (C=N nitroguanidine and C=N triazinone). ¹H NMR (DMSO-d₆): δ / ppm 1.5 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.4 (s, 3H, p-CH₃CO), 3.1 (m, 2H,CH₂), 3.7 (s, 3H, CH₃OCO), 4.1 (m, 1H, CH), 7.6-7.2 (m, 5H, 1NH + 4H aromatic protons underneath) 8.6-7.9 (s, 3H, 3NH nitroguanidine). ¹³C NMR (DMSO-d₆): δ/ppm 24.3 (p-CH₃CO), 22.45, 30.41, 40.3 (CH₂), 58.4 (CH₃OCO), 124.9, 129.32, 138.3, 140.6 (aromatic carbons), 143.3 (C-3), 156.4 (CH₃O), 159.9 (C=N nitroguanidine), 162.5 (C=O lactam). M.wt.= 419, M.F. C₁₅H₂₁N₇O₆.

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References