

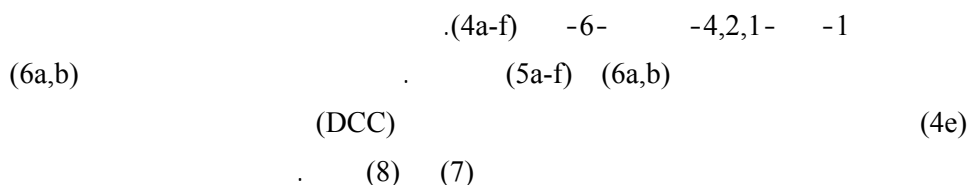
Potential RGD Mimetics by Incorporating Hydrazino Benzoic Acid with Nitroarginine 1,2,4-Triazin-6-one

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-4,2,1

RGD

-6-



Abstract

Nitrilimines (**2a-f**), 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-f**). Condensation of these compounds with para and ortho hydrazino benzoic acids gave the hydrazono derivatives (**5a-f**) and (**6a,b**) respectively. Attempts to cyclize compounds (**6a,b**) and (**4e**) using dicyclohexylcarbodiimide (DCC) or acetic anhydride to prepare fused heterobicyclic systems (**7**) and (**8**), respectively, were unsuccessful. The structures of compounds (**5a-f**, **6a,b**) were deduced from IR, MS, ¹H and ¹³C NMR spectral data.

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Introduction:

1,2,4-triazines are important pool for synthesis of a wide range of pharmacological and biological systems (Abdel-Rahman et al. 1999A). The chemistry of triazinone derivatives has been the subject of great interest in recent years due to the use of triazinone ring as the core structure in many heterocyclic compounds covering a wide range of pharmacological application (Farshori et al. 2011). 1,2,4-triazinone derivatives possess significant biological activities, such as antimicrobial, antibacterial, fungicide, pesticide, herbicide and crop protection (EI-Mariah et al., 2000, Abdel-Rahman et al. 2001A, Abdel-Rahman et al. 2001B). It has been also reported that certain 1,2,4-triazin-6-one possess antitumoral activity against ovarian cancer, leukemia, breast cancer and small and large lung cancer cells (El-Gendy et al. 2001, El-Gendy et al. 2003, Holla et al. 2002).

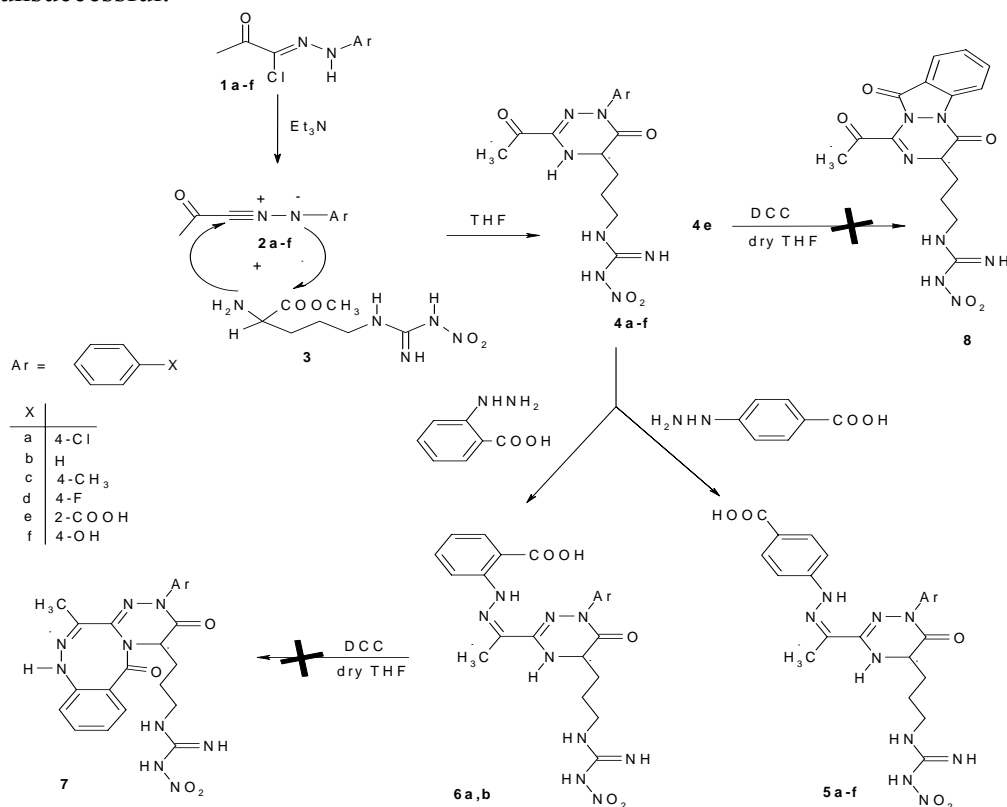
A facile preparation of 1,2,4-triazin-6-ones from the reaction of nitrilimines with α -amino esters was reported (El-Abadelah et al. 1991), as well as the reaction of nitrilimines with α -aminoacetonitrile (Hussein et al. 1994). Nitrilimines react with α -hydrazinoester to give 4-amino-1,2,4-triazin-6-ones (El-Abadelah et al. 1997). The cyclocondensation reactions of nitrilimines with 2-hydrazinoacetate represent a synthetic route for the preparation of 1,2,4-triazinone (Dalloul et al. 2008). In addition, the synthesis of 1,2,4-triazin-6-one containing nitroarginine have been reported (Abu Thaher et al. 2009).

The starting molecule(4e) can be considered as peptide mimetic aggregation of Arg-Gly-Asp. Arg-Gly-Asp sequence(RGD) as well as its mimetics have been incorporated into drug candidates and used to prevent thrombosis (Elizabeth et al. 1996). The condensation of hydrazino benzoic acid with compounds (4) yield RGD mimetic (5, 6) (scheme 1). In addition, hydrazones possessing an azomethine proton (-NHN=CH-) constitute an important class of compounds for new drug development, therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities(Sevim et al. 2007). Consequently, the incorporation of azomethine group in compound 5 and 6 containing triazine moiety may enhance the activity of the target molecule. The new triazinone derivatives will be bioassayed and the results will be communicated separately.

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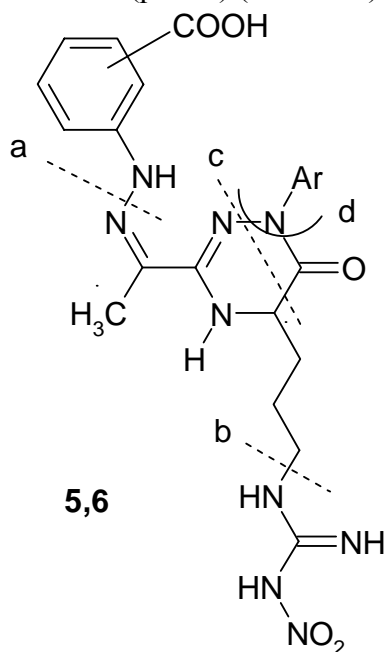
RESULTS AND DISCUSSION:

Nitrilimines (**2**), generated *in situ* from the respective hydrazoneyl 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 1,2,4-triazin-6-ones (**4**). Compounds (**4**) are achieved via a nucleophilic attack of the amino group of the nitroarginine (**3**) at nitrilimines followed by intracyclization. Condensation of compounds (**4**) with 4-hydrazinobenzoic acid and 2-hydrazino benzoic acid yielded the corresponding hydrazone derivatives (**5a-f**) and (**6a, b**), respectively, (scheme 1). Attempts to prepare fused heterobicyclic systems through cyclization of compounds (**6a, b**) and (**4e**) by using dicyclohexylcarbodiimide (DCC) in dry THF (ice bath), or refluxing in acetic anhydride to produce compounds (**7**) and (**8**), respectively, were unsuccessful.



Scheme 1: Synthesis of compounds 5 and 6

The structures of **(5a-f)** and **(6a, b)** have been established from: IR, mass spectra, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$, the IR spectra of compounds **(5a-f)** and **(6a, b)** in KBr revealed five bands in the region $3480 - 3300\text{ cm}^{-1}$ (one NH for triazinone, one NH for hydrazone and three NH's for nitroguanidine). Two strong absorption bands are also observed in the region $1710 - 1690\text{ cm}^{-1}$ (COOH) and about 1670 cm^{-1} (C=O triazinone). Three stretching bands of (three C=N) appeared around $1650 - 1620\text{ cm}^{-1}$ and a broad band in the region $3200 - 2500\text{ cm}^{-1}$ acidic OH. The structure of compounds **(5a-f)** and **(6a, b)** have been confirmed on the basis of mass spectral fragmentation pattern of these compounds: The presence of m/e 137 indicates the elimination of $[\text{HOOCPhH}_2\text{N}]^+$ (path a), the loss of nitroguanidine m/e 104 as $[\text{NO}_2\text{NHCNHH}_2\text{N}]^+$ (path b) and other important fragments are observed as $[\text{ArNCO}]^+$ (path c) and ArN^+ (path d) (scheme 2).



Scheme 3: Mass fragmentation pattern of compounds 5 and 6

The $^1\text{H-NMR}$ spectra of compounds **(5a-f)** and **(6a, b)** show all the required signals for the NHs, COOH, CH₃ and aromatic rings protons.

$^{13}\text{C-NMR}$ spectra of these compounds show the carbon of (C=N) of hydrazone around 149 ppm and the carbon of (COOH) around 167 ppm, the

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carbon of (C=O triazinone) around 163 ppm and the carbon of (C=NH) of nitroguanidine around 159 ppm.

Experimental

Melting points (uncorrected) were determined on Stuart melting point apparatus. IR spectra (in cm^{-1}) records as KBr discs on Perkin-Elmer 237 infrared spectrometer. Mass spectra were recorded on a Gas Chromatographic GCMS-QP10000 EX Shimadzu instrument at 70 eV. ^1H - 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).

The appropriate hydrazonoyl chlorides employed in this work were prepared as reported in the literature (El-Abadelah et al. 1988). Nitroarginine methyl ester hydrochloride (**3**) employed in this work was obtained by reaction of nitroarginine with thionyl chloride in methanol and 1,2,4-triazin-6-ones (**4a-f**) were obtained by following the literature procedure (Abu Thaher et al. 2009).

Synthesis of (5a-f) and (6a,b) :

4-hydrazinobenzoic acid or 2-hydrazinobenzoic acid, (15 mmol) were added to a solution of the appropriate 1,2,4-triazin-6-one (**4**) (10 mmol) in absolute ethanol (60 mL) with drops of glacial acetic acid. The stirred reaction mixture was refluxed for 2-3 hours. The solvent was then evaporated in vacuum and the residue product was collected and recrystallized from ethanol. The following compounds were obtained by this method:

1-(4-Chlorophenyl)-3-(4'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1*H*-1,2,4-triazin-6-one (5a)

Yield = 60%, m. p. = $267\text{-}269^\circ\text{C}$, IR (KBr): cm^{-1} 3473-3290 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1680 (COOH), 1660 (C=O triazinone), 1650 - 1610 (3 C=N). ^1H -NMR (DMSO-d_6): δ / ppm 1.62 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 2.10 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 3.12 (m, 2H, CH_2NH), 4.02 (m, 1H, H-5), 7.30 (s, 1H, NH overlapped), 7.54 -7.40 (m, 8H aromatic protons), 8.5-7.8 (3s, 3H, 3NH nitroguanidine), 9.94 (s, 1H, NH hydrazone), 12.2 (s, 1H, COOH). ^{13}C -NMR (DMSO-d_6): δ / ppm 11.15 ($\text{CH}_3\text{C}=\text{N}$), 24.5, 30.2 (CH_2)₂ and 40.6

(CH₂NH), 52.2 (C-5), 113.6, 121.9, 126.4, 128.7, 130.6, 131.4, 136.9, 140.3 (aromatic carbons), 145.9 (C-3), 148.9 (C=N hydrazone), 159.6 (C=N nitroguanidine), 163.0 (C=O triazinone), 168 (COOH). MS: m/z (C₂₂H₂₄CIN₉O₅) = 529/531 (M⁺), 153/155 [p-ClC₆H₄NCO]⁺, 137 [HOOCPhNH₂]⁺, 136 [HOOCPhNH]⁺, 125/127 [p-ClC₆H₄N]⁺, 111/113 [p-ClC₆H₄]⁺, 103 [NO₂NHCNHNH]⁺.

1-Phenyl-3-(4'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1*H*-1,2,4-triazin-6-one (5b)

Yield = 75%, m. p. = 247-248°C, IR (KBr): cm⁻¹ 3380-3230 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1708 (COOH), 1667 (C=O triazinone), 1650 - 1610 (3 C=N). ¹H-NMR (DMSO-d₆): δ / ppm 1.63 (m, 2H, CH₂), 1.70 (m, 2H, CH₂), 2.11 (s, 3H, CH₃C=N), 3.13 (m, 2H, CH₂NH), 4.05 (m, 1H, H-5), 7.22 (s, 1H, NH overlapped), 7.53 - 7.41 (m, 9H aromatic protons), 8.47-7.78 (3s, 3H, 3NH nitroguanidine), 9.95 (s, 1H, NH hydrazone), 12.3 (s, 1H, COOH). ¹³C NMR (DMSO-d₆): δ / ppm 11.3 (CH₃C=N), 24.4, 30.5 (CH₂)₂ and 40.8 (CH₂NH), 53.4 (C-5), 113.2, 122.1, 124.9, 126.5, 128.8, 131.1, 137.2, 141.8 (aromatic carbons), 145.6 (C-3), 149.0 (C=N hydrazone), 159.1 (C=N nitroguanidine), 162.8 (C=O triazinone), 167.8 (COOH). MS: m/z (C₂₂H₂₅N₉O₅) = 495 (M⁺), 137 [HOOCPhNH₂]⁺, 136 [HOOCPhNH]⁺, 119 [C₆H₅NCO]⁺, 104 [NO₂NHCNHNH₂]⁺, 103 [NO₂NHCNHNH]⁺, 91 [C₆H₅N]⁺.

1-(4-Methylphenyl)-3-(4'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1*H*-1,2,4-triazin-6-one (5c)

Yield = 63%, m. p. = 253-254°C, IR (KBr): cm⁻¹ 3381-3240 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1709 (COOH), 1664 (C=O triazinone), 1640 - 1597 (3 C=N). ¹H-NMR (DMSO-d₆): δ / ppm 1.70 (m, 2H, CH₂), 2.11 (m, 2H, CH₂), 2.30 (s, 3H, ArCH₃), 2.51 (s, 3H, CH₃C=N), 3.23 (m, 2H, CH₂NH), 4.1 (m, 1H, H-5), 7.36 (s, 1H, NH overlapped), 7.4 - 7.2 (m, 8H aromatic protons), 8.55-7.83 (3s, 3H, 3NH nitroguanidine), 9.98 (s, 1H, NH hydrazone), 12.34 (s, 1H, COOH). ¹³C-NMR (DMSO-d₆): δ / ppm 11.5 (CH₃C=N), 22.4, 30.8 (CH₂)₂ and 40.5 (CH₂NH), 30.5 (ArCH₃), 52.4 (C-5), 115.7, 121.2, 126.6, 128.4, 131.7, 136.4, 137.3, 138.9 (aromatic carbons), 143.0 (C-3), 149.0

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(C=N hydrazone), 159.7 (C=N nitroguanidine), 162.8 (C=O triazinone), 167.1 (COOH). MS: m/z ($C_{23}H_{27}N_9O_5$) = 509 (M^+), 137 [$HOOCPhNH_2$] $^+$, 136 [$HOOCPhNH$] $^+$, 133 [$p-CH_3C_6H_4NCO$] $^+$, 119 [C_6H_5NCO] $^+$, 105 [$p-CH_3C_6H_4N$] $^+$, 104 [$NO_2NHCNHNH_2$] $^+$, 92 [C_6H_5NH] $^+$.

1-(4-Fluorophenyl)-3-(4'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1*H*-1,2,4-triazin-6-one (5d)

Yield = 68%, m. p. = 259-260°C, IR (KBr): cm^{-1} 3454-3297 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1705 (COOH), 1663 (C=O triazinone), 1641 - 1598 (3 C=N). 1H -NMR (DMSO- d_6): δ / ppm 1.56 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 2.11 (s, 3H, $CH_3C=N$), 3.12 (m, 2H, CH_2NH), 4.09 (m, 1H, H-5), 7.32 (s, 1H, NH overlapped), 7.51 - 7.20 (m, 8H aromatic protons), 8.50-7.72 (3s, 3H, 3NH nitroguanidine), 9.91 (s, 1H, NH hydrazone), 12.25 (s, 1H, COOH). ^{13}C NMR (DMSO- d_6): δ / ppm 11.2 ($CH_3C=N$), 23.8, 30.7 (CH_2) $_2$ and 40.7 (CH_2NH), 52.9 (C-5), 115.8, 121.6, 127.7, 129.9, 136.6, 137.4, 138.9, 141.2 (aromatic carbons), 143.2 (C-3), 148.3 (C=N hydrazone), 159.6 (C=N nitroguanidine), 162.1 (C=O triazinone), 167.3 (COOH). MS: m/z ($C_{22}H_{24}FN_9O_5$) = 513 (M^+), 137 [$HOOCPhNH_2$] $^+$, 136 [$HOOCPhNH$] $^+$, 137 [$p-FC_6H_4NCO$] $^+$, 109 [$p-FC_6H_4N$] $^+$, 104 [$NO_2NHCNHNH_2$] $^+$, 92 [C_6H_5NH] $^+$.

1-(4-Carboxyphenyl)-3-(4'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1*H*-1,2,4-triazin-6-one (5e)

Yield = 83%, M. P. = 273-274°C, IR (KBr): cm^{-1} 3380-3245 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1709, 1705 (2COOH), 1662 (C=O triazinone), 1650 - 1615 (3 C=N). 1H -NMR (DMSO- d_6): δ / ppm 1.45 (m, 2H, CH_2), 1.68 (m, 2H, CH_2), 2.15 (s, 3H, $CH_3C=N$), 3.10 (m, 2H, CH_2NH), 4.11 (m, 1H, H-5), 7.5 (s, 1H, NH overlapped), 7.8 - 7.4 (m, 8H aromatic protons), 8.45-7.72 (s, 3H, 3NH nitroguanidine), 9.96 (s, 1H, NH hydrazone), 12.51 (s, 1H, COOH), 12.52 (s, 1H, COOH). ^{13}C NMR (DMSO- d_6): δ / ppm 11.4 ($CH_3C=N$), 24.3, 30.4 (CH_2) $_2$ and 40.7 (CH_2NH), 53.5 (C-5), 113.3, 122.2, 123.7, 128.1, 130.0, 131.3, 136.9, 145.2 (aromatic carbons), 146.9 (C-3), 150.0 (C=N)

hydrazone), 159.72 (C=N nitroguanidine), 163.29 (C=O triazinone), 167.2 (COOH), 167.8 (COOH). MS: m/z (C₂₃H₂₅N₉O₇) = 539 (M⁺), 163 [p-COOHC₆H₄NCO]⁺, 137 [HOOCPhNH₂]⁺, 136 [HOOCPhNH]⁺, 135 [p-COOHC₆H₄N]⁺, 121[p-COOHC₆H₄]⁺, 104 [NO₂NHCNHNH₂]⁺, 103 [NO₂NHCNHNH]⁺, 92 [C₆H₅NH]⁺.

1-(4-Hydroxyphenyl)-3-(4'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1H-1,2,4-triazin-6-one (5f)

Yield = 82%, M. P. = 250-251°C, IR (KBr): cm⁻¹ 3400-3250 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1708 (COOH), 1670 (C=O triazinone), 1650 - 1610 (3 C=N). ¹H-NMR (DMSO-d₆): δ / ppm 1.60 (m, 2H, CH₂), 1.7 (m, 2H, CH₂), 2.1 (s, 3H, CH₃C=N), 3.12 (m, 2H, CH₂NH), 4.04 (m, 1H, H-5), 7.30 (s, 1H, NH, overlapped), 7.53 - 7.46 (m, 8H aromatic protons), 8.45-7.79 (3s, 3H, 3NH nitroguanidine), 9.93 (s, 1H, NH hydrazone), 12.4 (s, 1H, COOH), 14.3 (s, 1H, ArOH). ¹³C NMR (DMSO-d₆): δ / ppm 11.9 (CH₃C=N), 26.8, 30.5 (CH₂)₂ and 40.2 (CH₂NH), 53.4 (C-5), 116.1, 116.2, 124.8, 125.5, 130.8, 132.5, 137.2, 141.7 (aromatic carbons), 145.6 (C-3), 149.0 (C=N hydrazone), 157.0 (C=N nitroguanidine), 161.0 (C=O triazinone), 167.7 (COOH). MS: m/z (C₂₂H₂₅N₉O₆) = 511 (M⁺), 137[HOOCPhNH₂]⁺, 136[HOOCPhNH]⁺, 135 [p-OHC₆H₄NCO]⁺, 107 [p-OHC₆H₄N]⁺, 104 [NO₂NHCNHNH₂]⁺, 103 [NO₂NHCNHNH]⁺, 92 [C₆H₅NH]⁺.

1-(4-Chlorophenyl)-3-(2'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1H-1,2,4-triazin-6-one (6a)

Yield = 80%, m. p. = 240-242°C, IR (KBr): cm⁻¹ 3469-3292 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1685 (COOH), 1660 (C=O triazinone), 1635 - 1594 (3 C=N). ¹H-NMR (DMSO-d₆): δ / ppm 1.62 (m, 2H, CH₂), 1.99 (m, 2H, CH₂), 2.29 (s, 3H, CH₃C=N), 3.15 (m, 2H, CH₂NH), 4.02 (m, 1H, H-5), 7.34 (s, 1H, NH, overlapped), 7.58 - 7.41 (m, 8H aromatic protons), 8.55-7.78 (3s, 3H, 3NH nitroguanidine), 9.96 (s, 1H, NH hydrazone), 12.41 (s, 1H, COOH). ¹³C-NMR (DMSO-d₆): δ / ppm 11.3 (CH₃C=N), 21.9, 30.3 (CH₂)₂ and 40.7 (CH₂NH), 53.3 (C-5), 113.1, 121.9, 124.8, 125.2, 129.2, 131.3, 137.1, 139.3

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(aromatic carbons), 145.1 (C-3), 148.1 (C=N hydrazone), 159.7 (C=N nitroguanidine), 162.6 (C=O triazinone), 167.8 (COOH). MS: m/z ($C_{22}H_{24}ClN_9O_5$) = 529/531 (M^+), 153/155 [$p\text{-ClC}_6\text{H}_4\text{NCO}$] $^+$, 137 [HOOCPhNH_2] $^+$, 136 [HOOCPhNH] $^+$, 125/127 [$p\text{-ClC}_6\text{H}_4\text{N}$] $^+$, 103 [$\text{NO}_2\text{NHCNHNH}$] $^+$.

1-Phenyl-3-(2'-carboxyphenylhydrazinoacetyl)-4,5-dihydro-5-[1'-nitroguanidine-3'-propyl]-1*H*-1,2,4-triazin-6-one (6b)

Yield = 78%, m. p. = 225-227°C, IR (KBr): cm^{-1} 3370-3243 (three NH nitroguanidine, one NH triazinone and one NH hydrazone), 3300-2500 (broad OH), 1706 (COOH), 1665 (C=O triazinone), 1642 - 1600 (3 C=N). $^1\text{H-NMR}$ (DMSO- d_6): δ / ppm 1.56 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.11 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 3.13 (m, 2H, CH_2NH), 4.1 (m, 1H, H-5), 7.20 (s, 1H, NH, overlapped), 7.31 - 7.01 (m, 9H aromatic protons), 8.86-7.47 (3s, 3H, 3NH nitroguanidine), 9.95 (s, 1H, NH hydrazone), 11.9 (s, 1H, COOH). $^{13}\text{C-NMR}$ (DMSO- d_6): δ / ppm 12.6 ($\text{CH}_3\text{C}=\text{N}$), 24.6, 30.5 (CH_2) $_2$ and 40.4 (CH_2NH), 53.4 (C-5), 113.6, 118.9, 121.2, 124.8, 129.7, 131.2, 135.1, 140.1 (aromatic carbons), 146.1 (C-3), 147.2 (C=N hydrazone), 159.7 (C=N nitroguanidine), 162.2 (C=O triazinone), 169.91 (COOH). MS: m/z ($C_{22}H_{25}N_9O_5$) = 495 (M^+), 137 [HOOCPhNH_2] $^+$, 136 [HOOCPhNH] $^+$, 119 [$\text{C}_6\text{H}_5\text{NCO}$] $^+$, 104 [$\text{NO}_2\text{NHCNHNH}_2$] $^+$, 103 [$\text{NO}_2\text{NHCNHNH}$] $^+$, 91 [$\text{C}_6\text{H}_5\text{N}$] $^+$.

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