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Synthesis of some 5-nitrofuran derivatives like as anti bacterial drugs in animals

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Abstract: Reaction of 5-nitrofuran-2-aldehyde **2** with 4-substituted-1,2-phenylendiamine **1a-b,** naphthalene-1,8-diamine **4** and 2-hydroxy aniline **6** in water in the present of ferric ammonium sulfate ($NH_4Fe(SO_4)_2$), obtained 6-substituted-2-(5-nitro-furan-2-yl)-1H-benzimidazole **3a-b,** 2-(5-nitro-furan-2-yl)-1H-perimidine **5** and 2-(5-nitro-furan-2-yl)-benzoxazole **7** respectively, in good yields. Reaction of 5-nitrofuran-2-aldehyde with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazol under reflux condition gave 4-amino-5-[N'-(5-nitro-furan-2-yl-methylene)-hydrazino]-4H-[1,2,4]triazole-3-thiol **9**. Compound **9** was reacted with terphthaluic acid and dimethyl acetylendicarboxylate (DMAD) to obtain Bis{6-yl-3-hydrazon-(2-yl-5-nitrofurfural)-1,2,4-triazol [3,4-b]1,3,4-thiadiazole}terphtaloyl **11** and 1,2,4-triazino[3,4-b]1,2,4-thiadiazine-7-one-3-hydrazon92-yl-5-nitrofurfural)6-exomethylenmethyl carboxylate **10** in good yields, respectively. The structures of these compounds were distinguished by ^{1}H NMR, ^{13}C NMR, IR, Mass spectra and microanalysis**.**

Keywords: 5-NitroFuran-2-aldehyde, Ferric ammonium sulfate, Dimethyl acetylendicarboxylate, 1,2,4-triazino[3,4-b] thiadiazine, Benzimidazole, Benzoxazole.

Introduction

Parasitic diseases in tropical and subtropical areas constitute a major health and economic problem. Chagas, disease, produced by several strains of Trypanosoma cruzi (T. Cruzi), affects approximately 24 million people from Southern California to Argentina and Chile [1]. Nifurtimox and benznidazole are currently used to treat this disease (Figure **1**) [2].

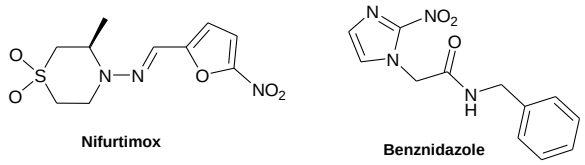

Figure 1: Parasitic diseases drugs.

A characteristic ESR signal corresponding to the nitro anion radical ($R\text{-}NO_2$) appears when nifurtimox is added to intact *T. Cruzi* cells [3]. This and other experiments [4-6] suggest that intracellular reduction of nifurtimox followed by redox cycling, yielding O_2 and H_2O_2, may be the major mode of action against *T. Cruzi*. However, the use of nifurtimox has the disadvantage of its side effects [7]. Nitro compounds, especially 5-nitrofuryl derivatives, have been documented to be of great value as antiparasitic drugs. Recently it was explored 5-nitro-2-furaldehyde derivatives to find new substances with fewer side effects than nifurtimox [8-12]. It was also carried out three-dimensional quantitative structure-activity relationship (3-D QSAR) studies on the *in vitro* and *in vivo* antiparasitic activities against *Trypanosoma cruzi* to establish the mode of action for this kind of semicarbazone derivatives [13, 14]. In general, the biological effects of nitroheterocyclic compounds, especially in *T. Cruzi*, involve redox cycling of these

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compounds and oxygen radical production, two processes in which the nitroanion radicals play an essential role [15]. Previously, it was reported studies on the antiprotozoal activities of 5- nitrofurfural and 5-nitrothiophene-2-carboxaldehyde derivatives, and it was showed that these compounds generate nitro anion radicals, characterized by ESR spectroscopy [16, 17]. Some of 5-nitro-2-furaldehyde derivatives have fewer side effects than nifurtimox.

Ferric Ammonium Sulfate, $NH_4Fe(SO_4)_2{\cdot}12H_2O$ ('FAS'), is a double salt in the class of aluns, which consists of compounds with the general formula AB $(SO_4)_2{\cdot}12H_2O$. It has been used in a wide area of applications, including adiabatic refrigeration equipment [18], biochemical analysis [19] and organic synthesis [20].

In view of the above facts and as a part of an ongoing investigation into biologically more active and less toxic substances, our current interest is focused on the synthesis of a series of new 5-nitrofuran derivatives.

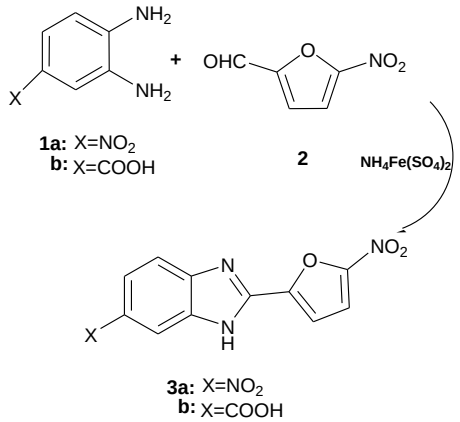
Results and discussion

Reaction of 4-substituted-1,2-phenylendiamine **1a-b** with 5-nitrofuran-2-aldehyde **2** in water in the presence of ferric ammonium sulfate ($NH_4Fe(SO_4)_2$), obtained 6-substituted-2-(5-nitro-furan-2-yl)-1H- benzimidazole **3a-b** in good yields. The structure of these compounds was deduced by IR, ^{1}H-NMR, Mass spectra and elemental analysis. The spectral data are in good agreement with the structures.

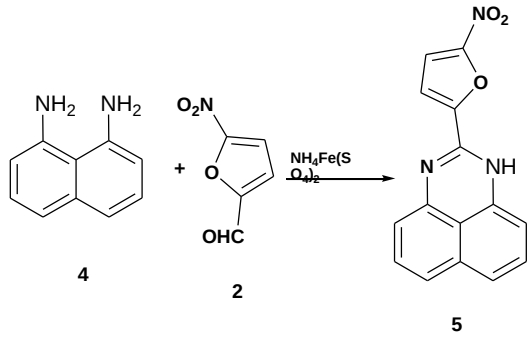
The reaction proceeds through a nucleophilic attack of N-1 of the 4-substituted-1,2-phenylendiamine on the carbonyl carbon and then oxidation of carbonyl carbon and $NH_4Fe(SO_4)_2$, following by further nucleophilic attack of the N-2 to the carbonyl carbon and subsequent dehydration of the cyclized intermediate to give **3** (Scheme **1-3**).

The synthesis of 2-(5-nitro-furan-2-yl)-1H-perimidine **5** can be achieved by the reaction of naphthalene-1,8-diamine **4** with compound **2** in water in the present of $NH_4Fe(SO_4)_2$ under reflux condition. The reaction took place the same as compound **3**. The structure of this compound was determined by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra and microanalysis. The mass spectrum of **5** (which showed a peak at m/z 279 (7%) that is characteristic for the molecular Ion) are in agreement with the molecular formula of $C_{15}H_9N_3O_3$.

The ^{1}H-NMR spectra of **5** showed one NH exchangeable proton at δ 9.21 ppm. In ^{13}C-NMR spectrum of **5** showed ten signals for heterocyclic ring and aromatic rings carbon atoms, CH=C, CH=CH, C=C and C=N.



Scheme 1: Synthesis of 6-substituted-2-(5-nitro-furan-2-yl)-1H- benzimidazole **3a-b.**

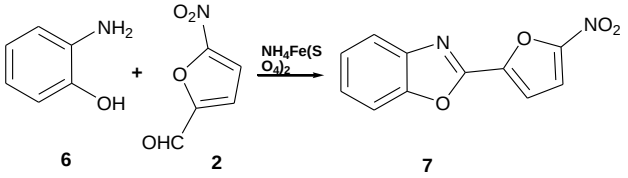


Scheme 2: Synthesis of 2-(5-nitro-furan-2-yl)-1H-perimidine **5.**

Reaction of 2-hydroxy aniline **6** with compound **2** afforded 2-(5-nitro-furan-2-yl)-benzoxazole **7**. The structure of this compound was determined by NMR, IR, Mass spectra and microanalysis. The mass spectrum of this compound displayed a molecular Ion peak at appropriate *m/z* 230**.** The ^{1}H-NMR spectrum of compound **7** didn't show any exchangeable proton. The IR spectrum of the reaction product **7** showed NO_2 group stretching at 1375 and 1535 cm^{-1}. Microanalysis is in good agreement with the formula of $C_{11}H_6N_2O_4$.

Reaction of 5-nitrofuran-2-aldehyde with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazol under reflux condition gave 4-amino-5-[N'-(5-nitro-furan-2-yl-methylene)-hydrazino]-4H-[1,2,4]triazole-3-thiol **9**. Compound **9** was reacted with terphthaluic acid and dimethyl acetylendicarboxylate (DMAD) to obtain Bis{6-yl-3- hydrazon- (2-yl-5-nitro furfural)-1,2,4-triazol [3,4-b]1,3,4-thiadiazole}terphtaloyl **11** and 1,2,4- triazino [3,4-b]1,2,4- thiadiazine-7-one-3-hydrazon(2-yl-5-nitrofurfural)6-exomethylenmethyl carboxylate **10** in good yields, respectively. The

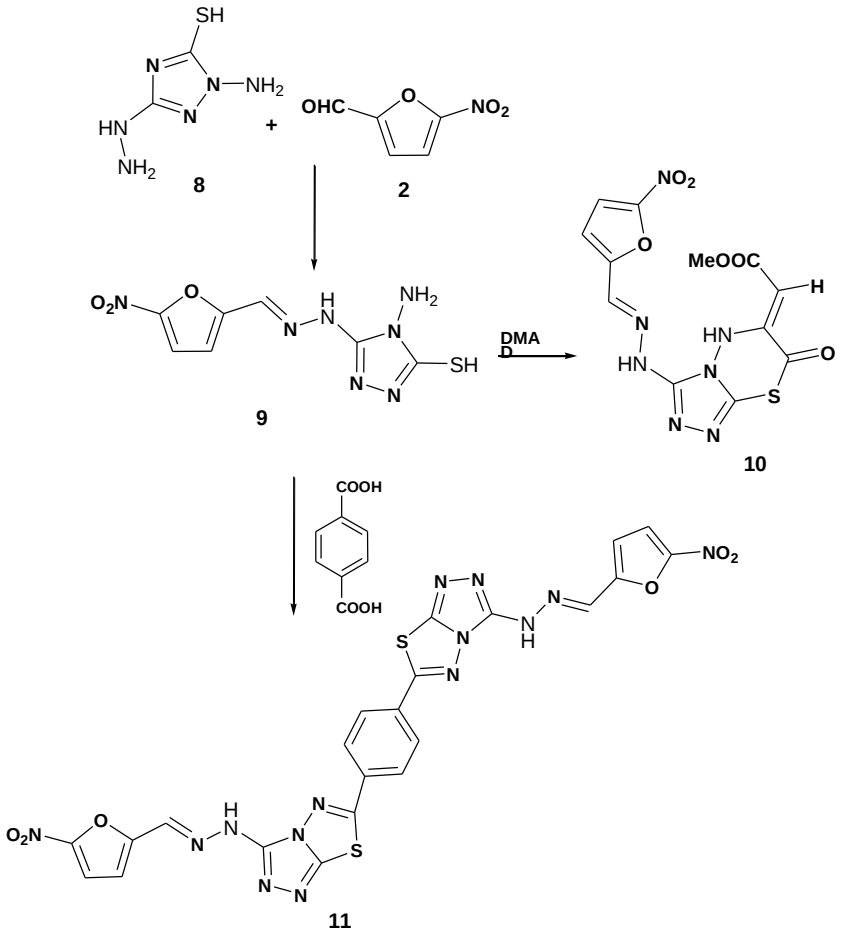
structures of these compounds were distinguished by ^{1}H NMR, ^{13}C NMR, IR, Mass spectra and microanalysis**.**



6 2 7

Scheme 3: Synthesis of 2-(5-nitro-furan-2-yl)-benzoxazole **7**.

For preparation of compound **10**, the reactions took place with the addition of SH and NH_2 groups of the compound **9** to acetylene bond and C=O groups of DMAD by Michael type addition and OMe elimination. TLC and the NMR spectrum of compound **10** showed that only a single, pure compound was present. The mass spectrum of **10** (which showed a peak at m/z 379 (12%) that is characteristic for the molecular Ion) are in agreement with the molecular formula of $C_{12}H_9N_7O_6S$. The ^{1}H-NMR spectra of **11** showed two exchangeable protons (NH protons). The IR spectrum of **11** showed NO_2 group stretching at 1350 and 1565 cm^{-1}, NH groups stretching at 3124 and 3363cm^{-1}.



Scheme 4: Synthesis of 1,2,4-triazino[3,4-b]1,2,4-thiadiazine-7-one-3-hydrazon92-yl-5-nitrofurfural)6-exomethylenmethyl carboxylate **10** and bis{6-yl-3-hydrazon-(2-yl-5-nitrofurfural)-1,2,4-triazol [3,4-b]1,3,4-thiadiazole}terphtaloyl **11.**

Conclusion

In summary, the presented reactions carried the advantage of being performed under mild conditions and good yields. These compounds could be interesting in pharmacology and biology.

Experimental

All of the chemical materials and solvents were purchased from Merck Chemical Company. The melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (the samples as KBr disks for the range 4000–400 cm^{-1}). The ^{1}H and

^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H, 400 MHz; ^{13}C, 75.469 MHz) using TMS as an internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The C, H, and N analyses were performed by the microanalytical service of the NIOC Research Institute of Petroleum Industry.

General methods for synthesis of compound 3, 5, 7:

Mixture of starting materials (10 mmol) and ferric ammonium sulfat (10 mmol, 5 g) in water (40 mL) was reacted under reflux condition. After 2 hours, a solution of ferric ammonium sulfate (20 mmol, 10 g) in water (50 mL) was added to the mixture of reaction. The reaction continued for 4 hours, the progress of the reaction was monitored by TLC, using ethyl acetate: n-hexane (1:1). The mixture of the reaction was cold; the precipitate was filtered, washed with water, dried and recrystallized by ethanol.

6-Nitro-2-(5-nitro-furan-2-yl)-1H-benzimidazole 3a:

Yellow powder; Mp 126-127°C; Yield 56%; IR (KBr) *ν* : 1375, 1504 (NO_2), 1604 (C=N), 3294 cm^{-1} (NH); ^{1}H-NMR 400 MHz (d_6-DMSO) *δ*: 7.66 (m, 1H, CH_{Ar}), 8.10 (m, 1H, CH_{Ar}), 8.18 (m, 1H, CH_{Ar}), 8.48 (d, 1H, *J*=12, CH_{Ar}), 8.53 (d, 1H, *J*=12, CH_{Ar}), 12.71 (br, 1H, NH). MS: m/z 274 (M+); Anal. Calcd. for $C_{11}H_6N_4O_5$: C, 48.19; H, 2.21; N, 20.43. Found: C, 48.08; H, 2.35; N, 20.18.

2-(5-Nitro-furan-2-yl)-3H-benzimidazole-5-carboxylic acid 3b:

Yellow powder; Mp 184-186°C; Yield 59%; IR (KBr) *ν:* 1620 (C=C), 1681 (C=O), 2400-3200 (COOH), 3322 cm^{-1} (NH); ^{1}H-NMR 400 MHz (d_6-DMSO) *δ*: 7.39 (s, 1H, CH_{Ar}), 7.61 (d, 1H, CH_{Ar}, *J*= 10.7), 7.65 (d, 1H, CH_{Ar}, *J*= 10.7), 7.88 (d, 1H, CH_{Ar}, *J*= 8.5), 8.01 (d, 1H, CH_{Ar}, *J*= 8.5), 10.65 (br, 1H, NH), 12.75 (br, 1H, COOH). MS: m/z 273 (M+). Anal. Calcd. for $C_{12}H_7N_3O_5$: C, 52.76; H, 2.58; N, 15.38. Found: C, 51.91; H, 2.75; N, 15.71.

2-(5-Nitro-furan-2-yl)-1H-perimidine 5:

Yellow powder; Mp 206-207°C; Yield 68%; IR (KBr) *ν:* 1496, 1531 (C=N), 1596 (C=C), 3255 cm^{-1} (NH); ^{1}H-NMR 400 MHz (d_6-DMSO) δ: 6.82 (s, 1H, CH_{Ar}), 6.92-6.97 (m, 3H, CH_{Ar}), 7.49 (t, 1H, CH_{Ar}, *J*= 3.9), 8.06 (s, 1H, CH_{Ar}), 8.20 (d,1H, $CH_{Ar,}$ *J*= 11.2), 8.24 (s,1H, CH_{Ar}), 9.21 (s, 1H, NH). ^{13}C-NMR: δ (d_6-DMSO), 119.47, 127.96, 128.15, 128.87, 128.93, 130.10, 134.73, 143.54, 154.06, 156.87. MS: m/z 279 (M+). Anal. calcd. for $C_{15}H_9N_3O_3$: C, 64.52; H, 3.25; N, 15.05. Found: C, 65.01; H, 3.12; N, 14.88.

2-(5-Nitro-furan-2-yl)-benzoxazole 7:

Yellow brown powder; Mp 236-237°C; Yield 64%; IR (KBr) *ν:* 1375, 1535 (NO_2), 1589 cm^{-1} (C=N); ^{1}H-NMR 400 MHz (d_6-DMSO) δ: 6.76 (d.d, 2H, CH_{Ar}, *J*=3.6, 11.3), 6.91 (d, 1H, CH_{Ar}, *J*=3.6), 7.34 (d, 1H, CH_{Ar}, *J*=9.7), 8.23 (d, 1H, CH_{Ar}, *J*=11.3), 8.48 (d, 1H, CH_{Ar}, *J*=9.7). MS: m/z (%) 230 (M+). Anal. Calcd. for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.63; N, 12.17. Found: C, 57.72; H, 2.95; N, 12.68.

4-amino-5-[N'-(5- nitro- furan-2-yl- methylene)-hydrazino]-4H-[1,2,4]triazole-3-thiol 9:

5-Nitrofuran-2-aldehyde (10 mmol, 1.4 g) was reacted with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazol (10 mmol, 1.5g) in ethanol 50% (20 ml) under reflux condition for 30 min. the progress of the reaction was monitored by TLC, using ethyl acetate. The mixture of the reaction was cold; the precipitate was filtered and dried. Orange powder; Mp 258-259°C; Yield 86%; IR (KBr) *ν:* 1388, 1573 (NO_2), 1596 (C=N), 1651 (C=C), 3147 (NH_2), 3217 cm^{-1} (NH); ^{1}H-NMR 400 MHz (d_6-DMSO) δ: 3.61 (s, 3H, OCH3), 4.60 (s, 2H, CH2), 6.54-7.50 (m, 6H, aromatic).

1,2,4-triazino [3,4-b]1,2,4- thiadiazine-7- one-3-hydrazon-2-yl-5-nitrofurfural)6-exomethylenmethyl carboxylate 10:

Compound **9** (10 mmol, 3 g) was reacted with DMAD (10 mmol, 1.42 g) in methanol (20 mL) under reflux condition for 30 min. The progress of the reaction was monitored by TLC, using ethylacetate: n-hexan (1:1). The mixture of the reaction was cold; the precipitate was filtered, dried and recrystallized by methanol. Orange powder; Mp 156-157°C; yield 86%; IR (KBr) *ν:* 1340, 1518 (NO_2), 1555 (C=N), 1606 (C=C), 1700 (C=O), 3164 (NH), 3243 cm^{-1} (NH); ^{1}H-NMR 400 MHz (d_6-DMSO) *δ*: 3.82(s, 3H, OCH3),8.26 (d, 1H, CH_{Ar}, *J*= 12.3), 8.33 (d, 1H, CH_{Ar}, *J*= 12.3), 8.70 (s, 1H, NH). ^{13}C-NMR: δ (d_6-DMSO), 51.53, 116.47, 116.72, 125.66, 139.19, 140.99, 142.92, 145.06, 145.66, 156.38, 164.41, 169.01. MS: m/z 379 (M+). Anal. Calcd. for $C_{12}H_9N_7O_6S$: C, 38.00; H, 2.39; N, 25.85. Found: C, 39.41; H, 2.15; N, 25.78.

Bis {6-yl-3-hydrazon-(2-yl-5-nitrofurfural)-1,2,4-triazol[3,4-b]1,3,4-thiadiazole}terphtaloyl 11:

Compound **9** (20 mmol, 5 g) and terphthaluic acid (10 mmol, 1.7 g) were added in solution of HCl 2N (20 mL) and ethanol 96% (20 mL). The mixture was

reacted under reflux condition 3 hours. The progress of the reaction was monitored by TLC, using ethyl acetate. The mixture of the reaction was cold; the precipitate was filtered, dried and recrystallized by ethanol. Yellow Orange powder; Mp > 300ºC; Yield 61%; IR (KBr) *v:* 1350, 1565 (NO_2), 1589 (C=C), 1632 (C=N), 3124 (NH), 3363 cm^{-1} (NH); ^{1}H-NMR 400 MHz (d_6-DMSO) δ: 6.74 (s, 1H, N=CH), 7.74 (s, 2H, CH_{Ar}), 8.01 (d, 1H, CH_{Ar}, *J*=10.5), 8.34 (d, 1H, CH_{Ar}, *J*=10.5), 13.11 (s, 1H, NH).

Acknowledgment

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References

[1] WHO expert committee. Control of Chagas disease. WHO technical report series **2002**, 905.
[2] Cerecetto, H.; Gonzglez, M. *Curr. Topics Med. Chem*. **2002**, 2, 1185.
[3] Docampo, R.; Stoppani, A. O. M. *Medicina*. **1980**, 40, 10.
[4] Docampo, R.; Moreno, S. N. J. Free radical intermediates in the trypanocidal action of drugs and phagocytic cells. Free radicals in Biology (Edited by W.A. Pryor). Academic Press, New York. **1984**, VI, 243-288.
[5] Docampo, R.; Moreno, S. N. J. Free radical intermediates in the trypanocidal action of drugs and phagocytic cells. Oxygen radicals in Chemistry and Biology (Edited by W. Bors), **1984**, 749-752.
[6] Docampo, R.; Moreno, S. N. J.; Stoppani, A. O. M.; Leon, W.; Cruz, F. S.; Villalta, F.; Muniz, R. P. A. *Biochem. Pharmacol*. **1981**, 30, 1947.
[7] Tracy, J. M.; Webster, L. T. Drugs used in the chemotherapy of protozoal infections: amebiasis, trichomoniasis, trypanosomiasis, leishmaniasis, and other protozoal infections. In: Goodman and Gilman's "The pharmacological basis of therapeutics". Hardman J. G; Limbird, L. E.; Gilman, A. G. (editors) 10th edition. Mc Graw- Hill. New York. **2001**, 1097-1113.
[8] Cerecetto, H.; Mester, B.; Onetto, S.; Seoane, G.; Gonzلlez, M.; Zinola, Z. *Farmaco*, **1992**, 47, 1207.
[9] Cerecetto, H.; Di Maio, R.; Ibarruri, G.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Paulino, M,; *Farmaco*. **1988**, 53, 89.
[10] Di Maio, R.; Cerecetto, H.; Seoane, G.; Ochoa. C.; Argn, V. J.; Pérez, E.; Gomez, A.; Muelas, S.; Martdnez, A. R.; Arzneimittel, F. *Drug Res*. **1999**, 49, 759.
[11] Cerecetto, H.; Di Maio, R.; Gonzglez, M.; Risso, M.; Sagrera, G.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Basombrdo, M. A.; Stoppani, A. O. M.; Paulino, M.; Olea-Azar, C. *Eur. J. Med. Chem*. **2000**, 35, 343.
[12] Muelas, S.; Di Maio, R.; Cerecetto, H.; Seoane, G.; Ochoa, C.; Escario, J. A.; Gomez-Barrio, A. *Folia Parasit*. **2001**, 48, 105.
[13] Martdnez-Merino, V.; Cerecetto, H. *Bioorg. Med. Chem*. **2001**, 9, 1025.
[14] Paulino, M.; Iribarne, F.; Hansz, M.; Vega, M.; Seoane, G.; Cerecetto, H.; Di Maio, R.; Caracelli, I.; Zukerman-Schpector, J.; Olea, C.; Stoppani, A. O. M.; Tapia, O. *J. Mol. Struct. Theochem*. **2002**, 584, 95.
[15] Goijman, S. G.; Stoppani, A. O. M. Oxygen radical and macro molecule turnover in Trypanosoma Cruzi, Oxidative Damage and Related Enzymes (Eds. G. Rotilio and J.V. Bannister) Harwood Academic Publishers, London, New York. **1984**, 216-221.
[16] Olea-Azar, C.; Atria, A. M.; Mendizgbal, F.; Di Maio, R.; Seoane, G.; Cerecetto, H. *Spectroscopy Lett*. **1998**, 31, 99.
[17] Olea-Azar, C.; Atria, A. M.; Di Maio, R.; Seoane, G.; Cerecetto, H. *Spectroscopy Lett*. **1998**, 31, 849.
[18] Wilson, G. W.; Timbie, P. T. *Cryogenics*, **1999**, 39, 319.
[19] Whitehorn, J. C. *Journal of Biological Chemistry*, **1921**, 45, 449.
[20] Shanxin, Yu.; et al. *Gen. Rev.* **2005**, 17, 27.