Chemical Modifications of 1,2,5-Oxadiazole *N*-Oxide System Searching for Cytotoxic Selective Hypoxic Drugs

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Abstract: New analogues of 3-Formyl-4-phenyl-1,2,5-oxadiazole N-oxide **(1)** are prepared and evaluated as cytotoxic selective agents in hypoxia.

Introduction

As part of our research project on biorreducible drugs in hypoxia conditions, we have developed a series of compound derivatives of *N*-oxide of 1,2,5-oxadiazoles system. They were evaluated as cytotoxic agents against V79 cells in oxia and hypoxic conditions. None of them showed selectivity in hypoxic conditions, but the derivative **1** presented a good profile of Cytotoxicity (**Figure 1**). In order to gain insight the mechanism of action and to obtain a selective compound, we designed the following modifications.

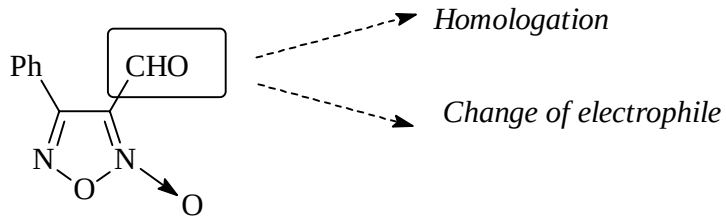

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Figure 1.

Experimental

Following, we showed the modifications outlined.

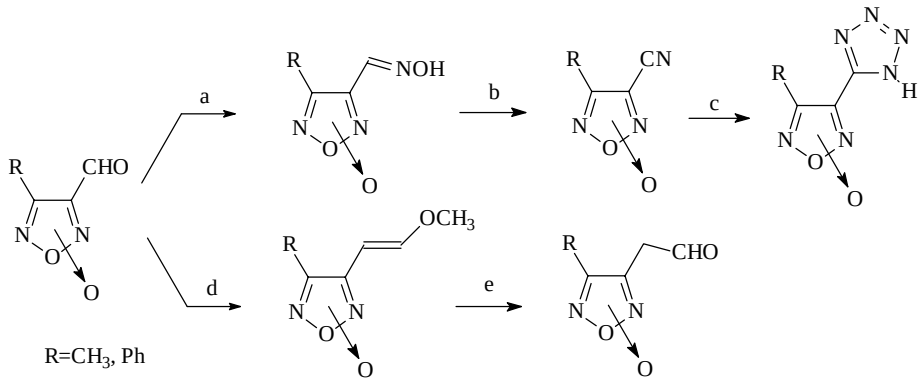

Figure 2. *Conditions:* (a) $NH_2OH.HCl$/*p*-TsOH/EtOH; (b) $SOCl_2$/DMF; (c) NaN_3/NH_4Cl/DMF; (d) $Ph_3P^+CH_2OCH_3\ Cl^-$; (e) H_3O^+.

All the products were characterized by ^1H RMN, ^{13}C RMN, (1D, 2D), EM, IR and in same cases elemental microanalysis. The cytotoxicity of the synthesized products was tested against V79 cells in oxia and hipoxia conditions at a concentration of 20 µM, following a protocol previously described [1].

Results and Discussion

All the synthetic procedures conducted to the products of interest with variable yields. As the drug-modulations previously described [2], the new ones may asseverate that the substituent at the 3 position of the 1,2,5-oxadiazol *N*-oxide plays an important role in the cytotoxic activity of this kind of compounds.

Acknowledgment: C.H.L.C.C., CYTED, PEDECIBA.

References and Notes

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2. Cerecetto, H.; González, M.; Risso, M.; Seoane, G.; Ezpeleta, O.; López de Cérain; Monge, A. *Derivados del Sistema N-Óxido de 1,2,5-oxadiazol como Agentes Citotóxicos Selectivos en Hypoxia. Fármaco-modulaciones y Estudio del Mecanismo de Acción*; VIII Congreso Argentino de Farmacia y Bioquímica Industrial, Buenos Aires, Argentina, junio-1999, 171.