Anti-*Helicobacter pylori* Activity of New Synthetic Fenitoin Derivatives

Geisa Helmold Aspesi[a]*, Ana Lúcia Alves de Arruda[a] and Carlos Kleber Z. Andrade[b]

[a] *Departamento de Ciências Biológicas e da Saúde, Universidade Católica Dom Bosco (UCDB), Avenida Tamandaré 6000, Jardim Seminário, C. P. 79117-900, Campo Grande, MS, Brasil.*

[b] *Laboratório de Química Metodológica e Orgânica Sintética - LaQMOS - Instituto de Química, Universidade de Brasília, Campus Darcy Ribeiro, Asa Norte, C. P. 70910-970 Brasília, DF, Brasil.*

**ghaspesi@gmail.com*

Keywords: Synthesis, Fenitoin, Helicobacter pylori

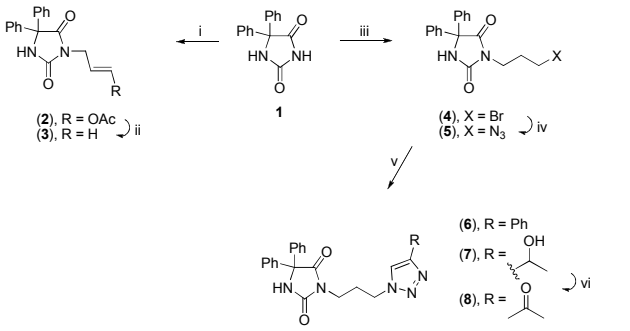
INTRODUCTION

Many hidantoin derivatives have pharmacological activities (anticonvulsant[1], antifungic[2], antibacterial[2] and antiparasitic[2]), related to the substituent in positions 3 or 5 of the imidazolidinic-like ring.

In this work, several 3-substituted imidazolidinic-like compounds were synthesized from fenitoin, aiming at potential new drugs presenting more selectivity, security, less toxicity and lower cost on the treatment of ulcer, caused by *Helicobacter pylori*.

RESULTS AND DISCUSSION

Synthetic fenitoin **1**, after being converted to the *N*-alkylated compound **2** (29%), from (*Z*)-4-chloro-2-butenyl acetate[3] and DBU in CH_2Cl_2, afforded by subsequent hydrolysis in aqueous HCl,[3] the respective alcohol **3** in 68% yield (**Scheme 1**). On another route, fenitoin **1** was *N*-alkylated with 1,3-dibromo-propane[4] and the resulting halogenated intermediate **4** (69%), after treatment with sodium azide, yielded the corresponding azide **5** (92%). Using Click chemistry,[5] the triazol rings **6** and **7** were obtained in 83% and 38% yield, respectively. The allylic alcohol in **7** was oxidized with manganese dioxide[6] to give the corresponding ketone **8** (92%).



Reagents and conditions: i) 2 $AcOCH_2CH{=}CHCH_2Cl$, DBU, CH_2Cl_2, reflux, 24h
ii) HCl, EtOH, reflux, 24 h
iii) $BrCH_2CH_2CH_2Br$, DBU, CH_2Cl_2, reflux, 3 h
iv) 3 NaN_3, EtOH/H_2O 20%, reflux
v) PhCCH or $CH_3CH(OH)CCH$, $CuSO_4.5H_2O$, Na ascorbate, MW, 3 min
vi) MnO_2, CH_2Cl_2, r.t., 24 h

Scheme 1. New derivatives of hydantoin synthesis

The activity against *Helicobacter pylori (ATTC)* was evaluated by disc diffusion assay[7]. Sterile 0,6 mm diameter filter paper discs were impregnated with 20 µL of the samples (100 mg/mL) and placed in Müller Hinton agar. Commercially discs with amoxicillin and DMSO were used as positive and negative controls, respectively. The discs with the samples, positive and negative controls, were distributed by Petri plates and incubated at 37 ºC for 24 h. The results, illustrated in Table 1, were recorded by measuring the growth inhibition zones surrounding the disc. All tests were carried out in triplicate.

Table 1. Evaluation of Anti-*Helicobacter pylori* activity of fenitoin derivatives and standard controls

S	2	3	4	5	6	7	8	PC	C-
IZ	8,3	8,0	8,0	9,0	8,0	7,6	8,6	16,0	-

*S: Samples; IZ: Inhibition zone diameter (mm); PC: Positive control; C-: Negative control (DMSO)

CONCLUSION

All compounds tested were active against *Helicobacter pylori* indicating that these new derivatives are promising drugs and shall be more carefully studied.

ACKNOWLEDGEMENTS

CNPq, IQ-UnB and Universidade Católica Dom Bosco - UCDB, MS.

REFERENCES

[1] Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G. *Goodman: & Gilman – As Bases Farmacológicas da Terapêutica*, 9ª ed. McGraw-Hill: México, **1996**.

[2] Oliveira, S. M.; Silva, J. B. P.; Hernandes, M. Z.; Lima, M. C. A.; Galdino, S. L.; Pitta, I. R.; *Quím. Nova* **2008**, *31*, 614.

[3] Aspesi, G. H. Síntese de derivados barbituratos e tiobarbituratos de tamanho médio e macrocíclico via translactonização interna. PhD thesis, Universidade de Brasília – UnB, 2006, pp 356.

[4] Peng, G. W.; Marquez, V. E.; Driscoll, J. S. *J. Med. Chem.* **1975**, *18*, 846.

[5] Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

[6] Aoyama, T.; Sonoda, N.; Yamauchi, K. T.; Anzai, M.; Ando, A.; Shioiri, T.; *Synlett* **1998**, 35.

[7] Bauer, H.; Paronetto, F; Burns, W.; Einheber, A.; *J. Exp. Med.* **1966**, *123*, 1013.