Synthesis and antitumor activity of novel Schiff bases derived from 6-hydroxy-1,3-benzoxathiol-2-one

Eliza de L. Chazin (PG)[1,*], Paola de S. Sanches (IC)[1], Walcimar T. Vellasco Júnior (PG)[1,2], Claudia R. B. Gomes (PQ)[2], Raquel C. Montenegro (PQ)[3], Thatyana R. A. Vasconcelos (PQ)[1]

1- Universidade Federal Fluminense, IQ/PPGQ, Outeiro de S. João Batista, s/n, Centro, Niterói, 24020-141, RJ, Brazil.
2- *FIOCRUZ/Farmanguinhos,Sizenando Nabuco 100, Manguinhos, Rio de Janeiro, 21041-250, RJ, Brazil.*
3- *Universidade Federal do Pará, Av. Augusto Corrêa 01, Guamá, 66075-110, Belém, PA, Brazil.*

**elizachazin@gmail.com*

Keywords: 1,3-benzoxathiol-2-one; Schiff bases; antitumor.

INTRODUCTION

Heterocycles comprise a class of compounds that draw synthetic interest due to their occurrence on natural products and pharmacologically active substances.[1] Among them, 1,3-benzoxathiol-2-ones and its derivatives are important pharmacophores that exhibit antibacterial, antimycotic, antioxidant, antitumor, and anti-inflammatory activities.[2] Schiff bases have also been found to possess interesting and diversified biological properties such as antibacterial, antitumor and antioxidant.[3]

In this context, we have proposed to synthesize novel Schiff bases **4** containing the 1,3-benzoxathiol-2-one moiety with potential antitumor activity (**Figure 1**).

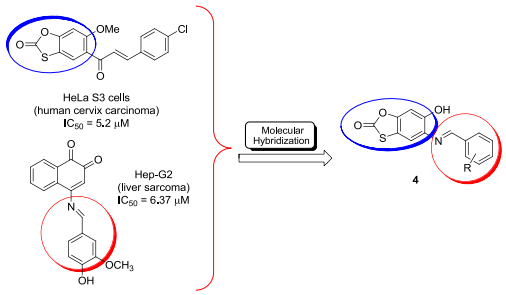
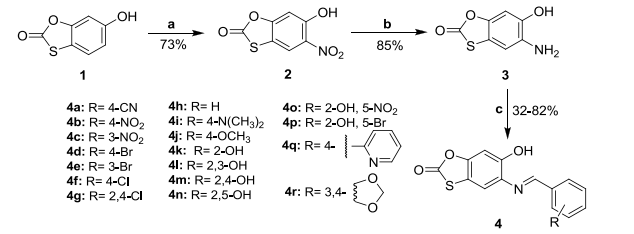


Figure 1. Design of the novel Schiff bases.

RESULTS AND DISCUSSION

The first step of the synthesis consisted in the selective nitration at position 5 of thioxolone (**1**) using HNO_3 65% and CH_2Cl_2 as solvent. In a subsequent step, the nitro derivative (**2**) was submitted to a catalytic hydrogenation with Pd/C 10% leading to the unpublished key intermediate (**3**). Further reactions between **3** and different benzaldehydes and heteroaromatic aldehydes in ethanol at room temperature resulted in the formation of the novel Schiff bases **4** (**Scheme 1**). All structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and ESI-MS spectra.

The cytotoxic potential of the new substances was evaluated against three different cancer cell lines: ACP-03 (gastric), SKMEL-19 (melanoma) and HCT-116 (colon).The significant results are in **Table 1**. None of the compounds was capable to cause hemolysis in mouse erythrocytes.



a: HNO_3 65%, CH_2Cl_2, r.t., 2h; **b:** H_2/Pd/C 10%, EtOH, 7 bar, 50°C, 10-12h; **c:** ArCHO, EtOH, r.t., 0,5-8h.

Scheme 1. Synthetic route for the novel Schiff bases.

Table 1. Antitumor activities of **4b**, **4m**, **4n** and **4o**.

Comp.	Cell line	IC_{50} (μM)	Comp.	Cell line	IC_{50} (μM)
4b	ACP-03*	4.82	**4n**	SKMEL-19**	5.57
4m	SKMEL-19**	9.37	**4o**	SKMEL-19**	2.79

Reference drug: doxorrubicin *IC_{50} = 0.27 μM; **IC_{50} = 0.04 μM.

CONCLUSION

Eighteen novel Schiff bases bearing the 1,3-benzoxathiol-2-one core were synthesized through a simple and reproductive methodology in good yields. Compounds **4b**, **4m**, **4n** and **4o** showed good antitumor activity.

ACKNOWLEDGEMENTS

UFF, CAPES, FAPERJ, Farmanguinhos/FIOCRUZ, CNPq, UFPA.

REFERENCES

[1] Katritzky, A.R. *Tetrahedron*, **1995**, *52* (9), xiii.
[2] Vellasco Júnior, W. T.; Gomes, C.R.B.; Vasconcelos, T.R.A. *Mini-Rev. Org. Chem.* **2011**, *8*, 103-109.
[3] Anand, P.; Patil, V.M.; Sharma, V.K.; Khosa, R.L.; Masand, N. Int *J. Drug. Des. Discov.* **2012**, *3*, **85**1-868.