CYTOTOXIC ACTIVITY AND CELL CYCLE DISTURBANCES INDUCED BY PYRIMIDOBENZIMIDAZOLES DERIVATIVES IN MCF-7 BREAST CANCER CELLS

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INTRODUCTION

The derivatives of pirimidobenzimidazoles (PBZ), analogous molecules of nitrogen bases present in DNA and RNA, seems to have potential antitumor activity. In the present study, we report the biologic evaluation and molecular mechanism of a series of PBZ against the growth of several human cancer cell lines.

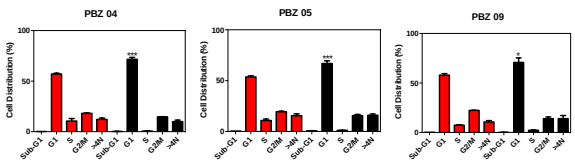
RESULTS

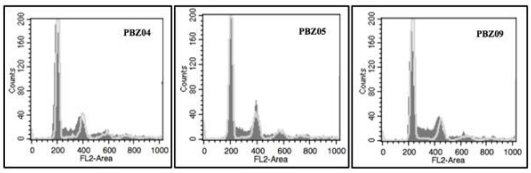
PBZ 04, 05 and 09 exerted the highest cytotoxicity against MCF-7 cells

Compounds	IC50 (μM)[a] Selectivity index (SI)[b]/superscript value						
	HEK-293T	MCF-7	HepG-2	T-24	HCT-116	HT-29	CACO-2
PBZ01	33.0	34.88[MR]	>50	>50	37.0[MR]	>50	>50
PBZ02	25.11	26.22[MR]	37.24[MR]	>50	>50	43.0[MR]	44.9[MR]
PBZ03	23.05	>50	19.0	22.09	42.44[MR]	>50	>50
PBZ04	28.75	15.41[TN]	17.67[TN]	6.90[TN]	20.25	>50	>50
PBZ05	27.86	19.52	>50	>50	22.66	>50	>50
PBZ06	31.99	42.66[MR]	>50	>50	>50	34.99[MR]	>50
PBZ09	21.21	8.11[TN]	14.62	23.88	>50	>50	>50
MXT[c]	3.88	0.87	3.5	2.50	0.61	0.88	2.4

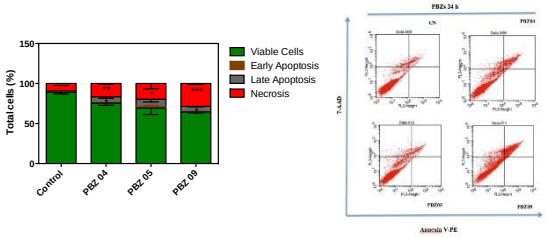
[a]Drug concentration required to inhibit the cell growth by 50% after 24 h of incubation. [b]Selectivity index (*in vitro*): IC50 in HEK293 cells/IC50 in tumoral cells. [c]Mitoxantrone (MXT) was used as positive control. MR: more resistant in tumoral cells.

After 24h of treatment, PBZs 4, 5 and 9 induce cell cycle arrest of MCF-7 cells in G1 fase.

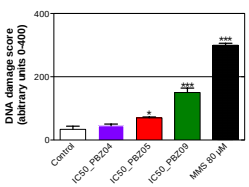




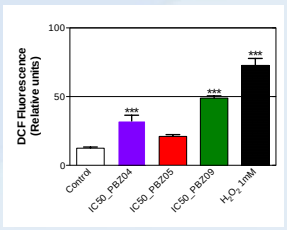
MCF-7 cells were induced to late apoptosis and necrosis after the treatment with PBZs 4, 5 and 9.

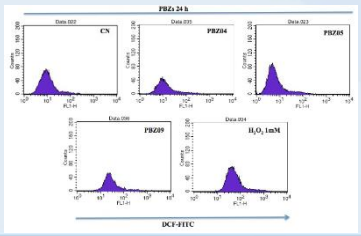


PBZ 4 does not generate DNA-strand breaks, while PBZ 5 and 9 induce signifcant DNA damage.

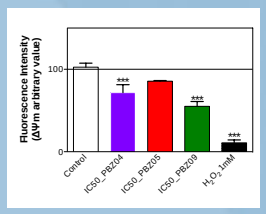


PBZ 4, 5 and 9 promotes DNA demage by ROS generation in MCF-7 cells.

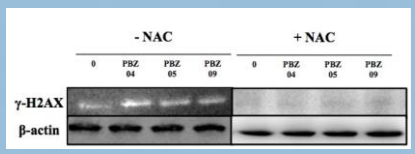




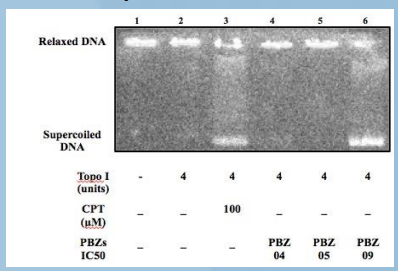
PBZ 4, 5 and 9 induce significant mitochondrial depolarization in MCF-7 cells.



γ-H2AX was induced after PBZ 04, 05 and 09 treatment and returned to the baseline levels of untreated cells after treatment with NAC.

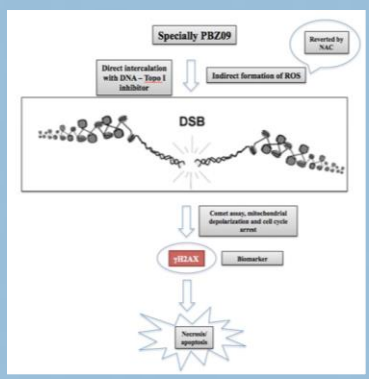


Relaxation of the plasmid was inhibited only by PBZ 9.



CONCLUSION

Among the 3 compounds studied, PBZ 09 seems to present the most promising antitumoral activity, especially against MCF-7 cells. Our results demonstrate that PBZ 09 interacts with Topo I enzyme, generates ROS leading to DNA damage, γ-H2AX induction, cell cycle arrest and cell death. Therefore, further studies with this small molecule are essential for its safety management in breast cancer therapy.



FINANCIAL SUPPORT

FAPERGS
CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES