DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW ANALOGUES OF BISACODYL *N*-OXIDES TYPE AS POTENTIAL ANTI-INFLAMMATORY AGENTS

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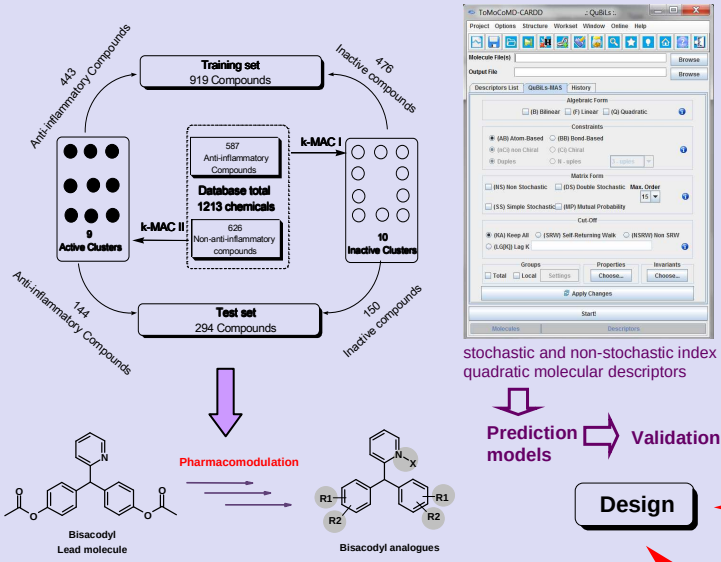
Bisacodyl: old drug, new use

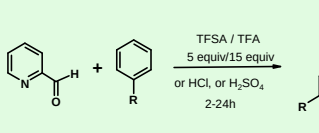
The identification of bisacodyl as a potential anti-inflammatory molecule was carried out using the *TOMOCOMD-CARDD* method (**TO**pological **MO**lecular **COM**putational **D**esing **C**omputer-**A**ided-**R**ational-**D**rug **D**esign) and linear discriminant analysis (LDA).[1]



Analogues *N*-oxides type

Synthesis of symmetric triarylmethanes structurally related to bisacodyl [2]

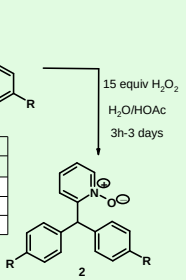
Step 1 Hydroxyalkylation of Friedel-Crafts

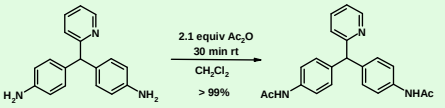


R	Catalyst	T(°C)	Yield (%) of 1	
			p,p	*o,p*
F	TFSA /TFA	rt	78	4
Cl	TFSA / TFA	rt	72	16
Br	TFSA / TFA	50	50	13
I	TFSA / TFA	rt	37	8

R	Catalyst	T(°C)	Yield (%) of 1	
			p,p	*o,p*
Me	H_2SO_4	rt	30	34
t-Bu	H_2SO_4	rt	60	0
NH_2	HCl	150	63	0

Step 2 Oxidation

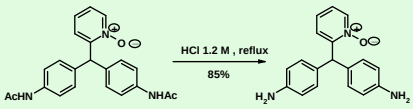




R	Yield (%) of 2
F	80
Cl	93
Br	70
I	40 (1)

R	Yield (%) of 2
Me	69
t-Bu	98
$OCOCH_3$	12
NHAc	45
NH_2	0

The *N*-oxide derivatives of Bisacodyl were easily prepared in good yields using a low-cost synthetic procedure.



(1) 25 equiv of H_2O_2 were used

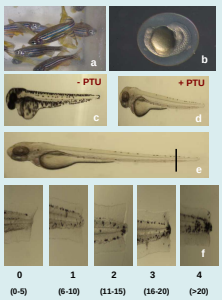
Synthesis

Bisacodyl: an anti-inflammatory drug?

Anti-inflammatory activity

The anti-inflammatory activity of bisacodyl was biologically confirmed by different models of inflammation

Lipopolysaccharide-induced leukocyte migration assay in zebrafish larvae



$$\%\text{ leukocyte migration (\%LM)} = \%LM_t / LM_c \times 100$$

	leukocyte migration (%)			MTC (µM)
	10 µM	30 µM	100 µM	
Bisacodyl	44,33	11,29	T	30
Indomethacin	19,67	15,46	13,43	>100

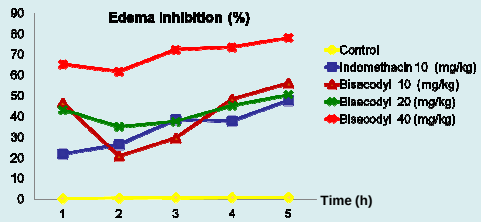
MTC: maximum tolerated concentration T: toxic

LM_t : number of leukocytes in the treated groups
LM_c : number of leukocytes in the control group

a. zebrafish adult; **b.** transgenic embryos (line fli-1:EGPF); **c.** larvae 4dpf without PTU; **d.** larvae 4dpf with PTU used for the treated and control groups; **e.** transection of the tail and then incubation with lypopolysaccharide (LPS) 7h at 28 ºC; **f.** chemical staining with 4-chloro-1-naphthol then analysis of leukocyte migration using an optical microscope.

Carrageenan-induced paw edema test in rats

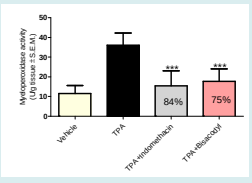
The anti-inflammatory activity assessed by the percentage inhibition of edema. Edema was expressed as the increase in paw volume due to carrageenan injection, and edema inhibition was expressed as the reduction in volume with respect to the control group.



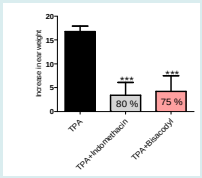
a. adult male rats « WISTAR »; **b.** intraperitoneal administration; **c.** edema induced on the right hind paw by subplantar injection of carrageenan (1% w/v in saline, 0.1 ml); **d.** The evolution of the edema was determined at 1 h, 2 h, 3 h, 4 h and 5 h, with measurement of the final volume of the paw using a plethysmometer (Ugo Basile)

Determination of topical anti-inflammatory activity in mouse ear edema

Effects of Bisacodyl on changes in MPO activity in 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema.



Inhibitory effects of Bisacodyl on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema.

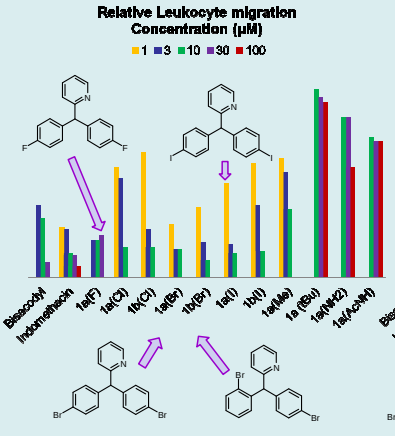


The anti-inflammatory activity of Bisacodyl is comparable to that of Indomethacin.

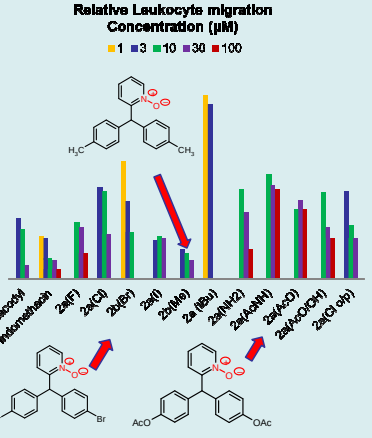
Analogues *N*-oxides type of bisacodyl: potential anti-inflammatory drugs

A selected set of analogues has been biologically investigated by anti-inflammatory assay in zebrafish

Pyridine derivatives



Pyridine oxide derivatives



Some novel compounds showed a low toxicity and an anti-inflammatory activity comparable to indomethacin in the zebrafish assay.

1) Y. Marrero Ponce, D. Siveiro Mota, *et al.* Discovery of novel anti-inflammatory drug-like compounds by aligning *in silico* and *in vivo* screening. *Eur. J. Med. Chem.* 46, 5736-5753, **2011**; **2)** M. Sylla, Y. Marrero, D. Siveiro *et al. in preparation for publication,* **2012.**

This study provides interesting new scaffolds to obtain promising anti-inflammatory agents for future preclinical development.