STUDY OF ISOSTERIC SUBSTITUTION OF THE 1,4-BENZODIOXANE OXYGEN ATOMS IN BENZAMIDES FTSZ INHIBITORS.

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FtsZ & STATE OF THE ART

Antibiotic resistance is rising to dangerously high levels in all parts of the world. Thence there is the urgent need of efficient antibiotics with innovative mechanisms of action. An interesting promising target is the cell division process, together with its essential proteins. [1]

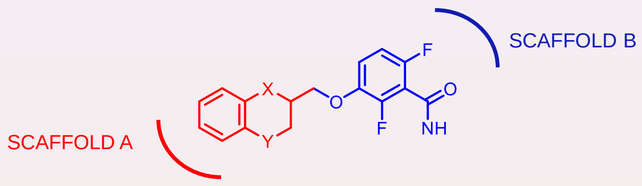
Among them **FtsZ** plays a crucial role; [2] it is:

- A self-assembling GTPase;
- A β-tubulin homologue;
- Widely conserved among bacteria;
- Able to polymerize forming the Z-ring, a membrane-associated structure recruiting a protein complex that enables cell constriction, formation of the mesosome and of the two daughter cells. [3]

Starting from **3-MBA**, which proved to modestly interfere with the GTPasic activity of FtsZ, and from its more potent analogs **PC190723** and **DFNB**, [4-6] we recently prepared a series of benzodioxanes,[7-9] linked by a methylenoxy bridge to a 2,6-difluorobenzamide (Compounds I-III). They have interesting antimicrobial activity vs *S. aureus* (*Sa*), *E. faecalis* and *M. tuberculosis*. Here we report our recent updates on the SAR of these bactericides.

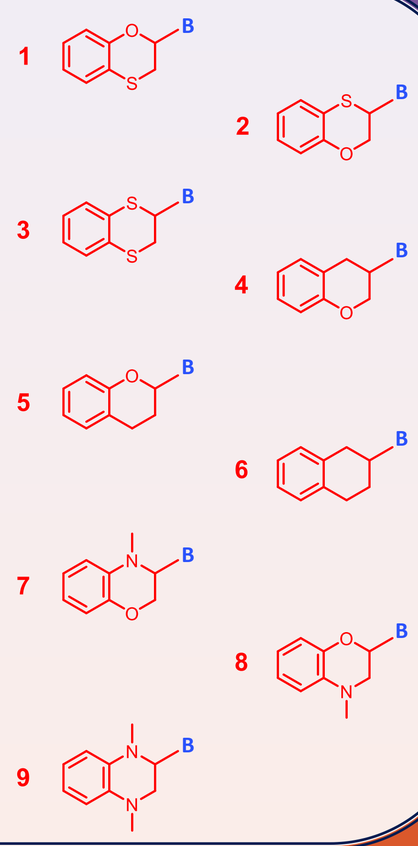
SAR STUDY

The SAR study started considering the mandatory features pointed out in our previous results; specifically the **maintenance of the primary amide**, as well of a **defined distance** between **Scaffold A** and **Scaffold B**.

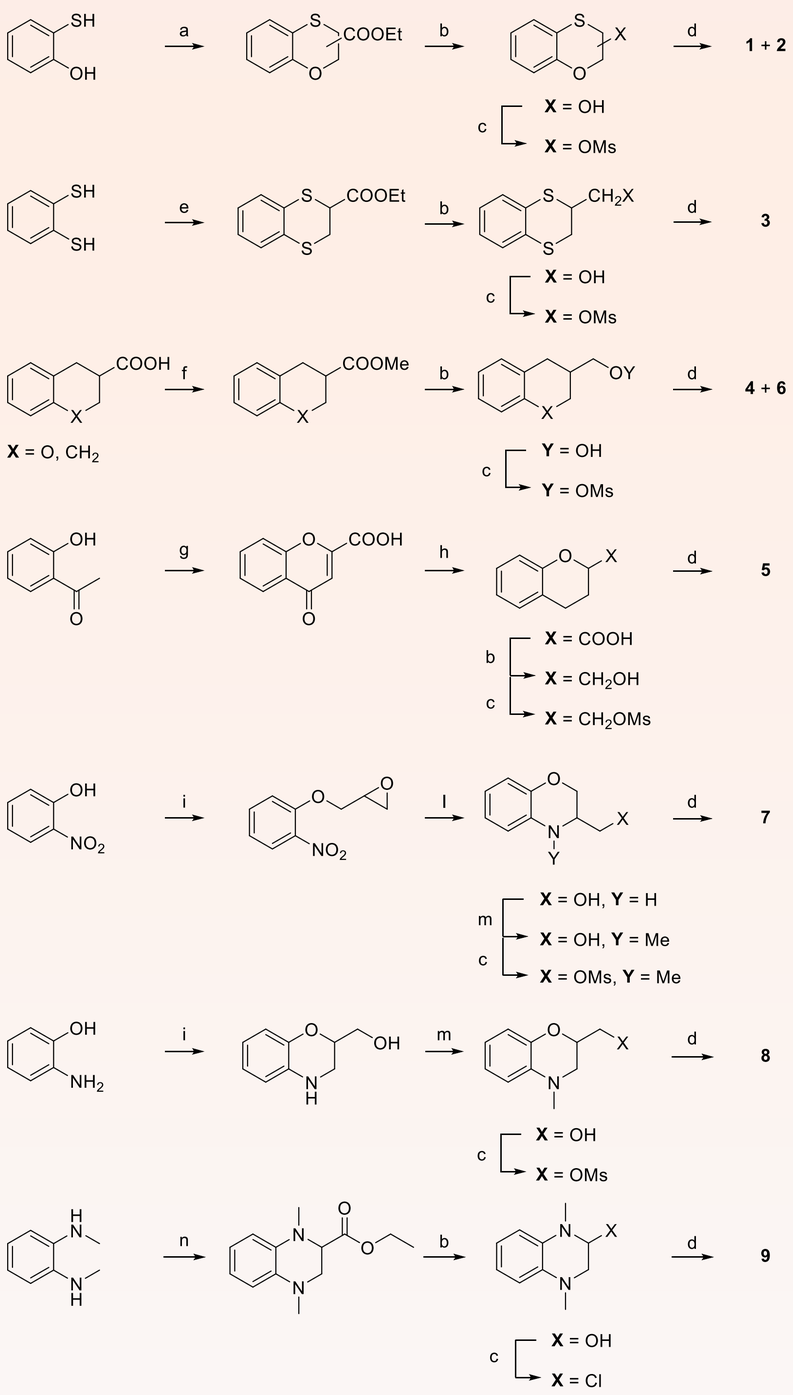


Specifically, we designed **Compounds 1-9** reported here aside, modifying the Scaffold A of **I**, **substituting the benzodioxane O(1) and/or O(4) with:**

- **Sulfur**, an interesting heteroatom with peculiar lipophilicity, HBA potency and steric hindrance (**Compounds 1-3**);
- **Carbon**, in order to evaluate the importance of the HBA property of both Oxygen atoms (**Compounds 4-6**);
- **Tertiary Nitrogen**, keeping the HBA nature while slightly increasing the steric hindrance of the substituent. (**Compounds 7-9**).



CHEMISTRY



Reagents and Solvents: a) Ethyl 2,3-dibromopropionate, TEA, ACN/H_2O 1:1, RT; b) $LiAlH_4$, THF, RT; c) MsCl, TEA, DCM, RT; d) 2,6-difuoro-3-hydroxybenzamide, K_2CO_3, 80°C e) Ethyl 2,3-dibromopropionate, TEA, DMF, 60°C; f) MeOH, H_2SO_4, reflux; g) Diethyl oxalate, EtONa, EtOH, reflux; h) H_2, Pd/C, AcOH; i) Epichlorohydrin, aq. NaOH, RT; l) Fe, AcOH, MeOH, RT; m) MeI, K_2CO_3, DMF, RT; n) Ethyl 2,3-dibromopropionate, TEA, Toluene, 80°C.

BIOLOGICAL EVALUATION

Compounds **1-9** and **I**, **III** and **DNFB** as references, were tested on Gram positive *S. aureus*, both methicillin-sensitive (**MSSA**) and methicillin-resistant (**MRSA**) strains. The most promising derivatives were also assessed for their cytotoxicity in human **MRC-5 cells**; all the results are shown below.

Compound	MSSA ATCC 29213			MRSA ATCC 43300			MRC-5
	MIC (μg/mL)	MBC (μg/mL)	TI	MIC (μg/mL)	MBC (μg/mL)	TI	TD 90 (μg/mL)
DNFB	1	1	>200	1	1	/	>200
I	5	80	n.d.	3.1	6.3	/	n.d.
III	0.6	0.6	>1280	n.d	n.d.	/	>800
1	1	1	>800	1	1	>800	>800
2	20	20	10	20	20	10	200 ± 4.3
3	5	10	20	5	10	20	200 ± 23.2
4	100	100	/	100	100	/	/
5	5	5	ongoing	5	5	ongoing	ongoing
6	>100	>100	/	>100	>100	/	/
7	100	100	/	100	100	/	/
8	100	100	/	10	20	/	/
9	>100	>100	/	>100	>100	/	/

DISCUSSION

- Promising MICs and MBCs of **1** and **3** points out a productive **substitution of benzodioxane O(4) with Sulfur**;
- The differences in antimicrobial activities strengthened the **importance of keeping benzodioxane O(1)** to allow a strong target interaction;
- The loss of antibacterial activity of **7, 8** and **9** indicates how the **steric hindrance in both positions** of the benzodioxane ring is **poorly tolerated**;
- Considering the impressive bactericidal potency of **1**, compared to its reference compound **I**, **Sulfur** could be an **effective bioisoster** of the **benzodioxane O(4).**

REFERENCES

[1] *Nature Reviews Drug Discovery* **2008**, 7, 324-338; **[2]** *Journal of Molecular Biology* **2004**, *342*, 953–970; **[3]** *Nature Reviews Molecular Cell Biology* **2005**, *6*, 862-872; **[4]** *Science* **2008**, *321*, 1673-1675; **[5]** *BMCL* **2009**, *19*, 524-527; **[6]** *BMCL* **2014**, *24*, 353-359; **[7]** *EJMC* **2015**, *89*, 252-265; **[8]** *EJMC* **2016**, *120*, 227-243; **[9]** *ChemMedChem* **2017**, *12*, 1303 –1318; **[10]** *Journal of Biological Chemistry* **2010**, *285*, 14239–14246; **[11]** *Journal of Biological Chemistry* **2005**, *280*, 39709–39715.