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Synthesis and antibacterial activities of 5-hydroxy-4-amino-2(5*H*)-furanones

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Abstract—Starting from the mucohalogen acids **1a** and **b** 5-hydroxy-2(5*H*)-furanones **2a**–**h** have been prepared and tested. These novel 4-amino-5-hydroxy 2(5*H*)-furananones have shown a broad antibiotic activity against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 in the micromolar range. A one step synthesis from mucohalogen acids towards the antibacterials **2a**–**h** was developed, in which the target was obtained from **1a** and **b** under reflux in toluene in presence of a catalytic amount of sulfuric acid. The derivatives **2b** and **c** displayed a MIC and MBC of 4/8 μg/ml, against *Staphylococcus aureus* with a selectivity towards the resistant strains.
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1. Introduction

Penicillin acid[1] and Basidalin[2] are butenolide natural products[3] exhibiting antitumour activity in the millimolar range. Butalactin is an antibiotic containing an epoxide side chain.[4] The novel aminofuranones represent bioisosteres of Narthogenin[5] in which the methoxy group was replaced by substituted amino groups.[6] Here, we wish to report our findings, on the synthesis of novel 4-amino-2(5*H*)-furanones and their in vitro evaluation (Fig. 1).

Protected mucohalogen acids were substituted in the 4-position to give 5-alkoxy aminofuranones.[7] Derived from a series of pseudoesters, 5-formamido-2(5*H*)-furanones[8] were evaluated as antineoplastic agents[9] and these intermediates may furnish under rearrangement the described antibacterials (Scheme 1).

2. Chemistry

Mucohalogen acids[10] such as the mucochloric acid **1a** and mucobromic acid **1b** are commercially available and are synthesised from furfural on a technical scale. Furfural itself is obtained by heating biomass with sulfuric acid. Our findings are particularly useful, as any chemical application of furfural present an important example of using a renewable resource from biomass.

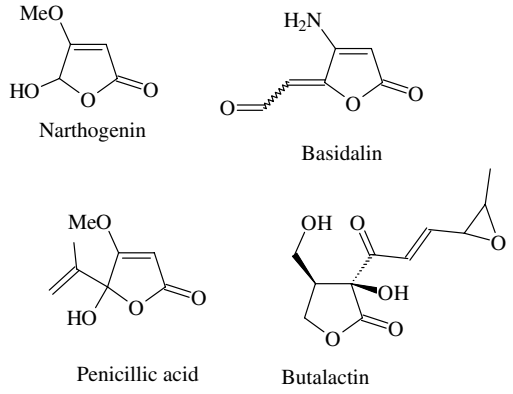

Figure 1. Overview of furanones with antibiotic activity.

Anilines were reacted with mucochloric acid to give various derivatives depending on the solvent system.[11]

Here, amides such as methylformamide, *t*-butylformamide, benzylformamide and formamide gave in a one-step synthesis the 5-hydroxyfuranones **2a**–**h** under reflux

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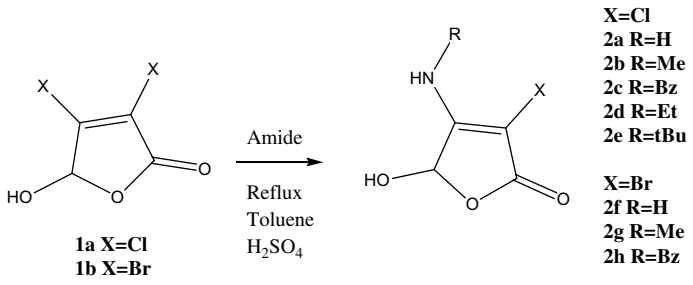

Scheme 1. Synthesis of 4-amino-5-hydroxy-2(5*H*)-furanones.

Table 1. Zone of inhibition

Code [yield]	Zone of inhibition (mm)		
	S. aureus	*E. coli*	*P. aeruginosa*
25% DMSO	0	0	0
Chloramphenicol 30 μg	0	15	0
Gentamycin 10 μg	31	25	0
2a [38%]	16	8	8
2b [74%]	10	11	8
2c [17%]	16	6	6
2g [53%]	16	9	7

conditions. The formamides were commercially available or could be synthesised from ethyl formate.[12] Selected formamides were refluxed in toluene with mucohalogen acids **1a** and **b** to furnish the furanones **2a**–**h** over night. No 5-formamido-intermediates[13] were detected under those conditions (Ref. 8). Yields vary and were high for the alkylformamides and low for the benzylformamides (Table 1). This applied to mucochloric acid **1a** and mucobromic acid **1b**.

3. Antibacterial activity

The initial test of the microbiological screening was the determination of the zone of inhibition on agar plates.

A solution of 25% of DMSO in water served as negative and 30 μg of chloramphenicol/10 μg of gentamycin per well as positive control testing the microorganism *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. A broad antibacterial activity was observed for the novel 4-amino-5-hydroxy-2(5*H*)-furanones. With 30 μg of the 2(5*H*)-furanone a zone of inhibition up to 16 mm was determined for the 4-amino-furanone **2a** against *S. aureus*.

The brominated derivative **2g**[14] has shown a good zone of inhibition for *S. aureus*, but displayed not a higher MIC than the parent compound **2b** and was supposed to be potentially toxic.

Following this initial screening, the MIC/MBC[15] were determined and the results are outlined in Table 2 for the chlorinated compounds **2a**–**c**.

A wide range of bacterials (Table 2) was selected for the determination of the minimum inhibitory concentration (MIC) and the minimum bacteriostatic concentration (MBC) using standard strains such as *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 25923 initially. *Acinetobacter* spp., *E. coli*, *Enterobacter* spp., *Klebsiella pneumoniae*, *P. aeruginosa* and *S. aureus* were tested as patient isolates, including the resistant strains E3, P12 and S2.

Table 2. MIC and MBC

Organism	MIC/MBC[a] (μg/ml)		
	2a	**2b**	**2c**
E. coli ATCC 25922[b]	(64/128)	(16/32)	(8/16)
P. aeruginosa ATCC 27853[b]	(32/64)	(16/32)	(32/64)
S. aureus ATCC 25923[b]	(16/32)	(8/16)	(4/8)
Acinetobacter spp.[c]	A1 (16/32)	A1 (8/16)	A1 (4/8)
	A2 (32/64)	A2 (64/64)	A2 (8/16)
E. coli[c]	E1 (32/64)	E1 (32/32)	E1 (16/16)
	E3 (64/128)	E3 (64/64)	E3 (16/32)
Enterobacter spp[c]	En1 (64/64)	En1 (32/64)	En1 (8/16)
	En3 (64/64)	En3 (32/32)	En3 (16/32)
K. pneumoniae[c]	K1 (32/64)	K1 (16/32)	K1 (32/32)
	K2 (128/128)	K2 (32/64)	K2 (16/32)
P. aeruginosa[c]	P7 (32/64)	P7 (32/64)	P7 (32/32)
	P12 (64/128)	P12 (32/64)	P12 (16/32)
S. aureus[c]	S1 (16/16)	S1 (16/32)	S1 (16/32)
	S2 (4/8)	S2 (4/8)	S2 (32/32)

E3, P12, S2 resistant strains.
[a] The first value in bracket represents the MIC and the second is the MBC.
[b] Standard strains.
[c] Patient isolates.

The template **2a** occurred a broad antibacterial activity and the replacement of the H of the furanone template **2a** by simple alkyl groups, increased the antibacterial activity, as seen for the selected N-methyl derivative **2b**. An 8-fold lower MIC of the benzyl derivative **2c** compared with **2a** was found for *E. coli* and a 4-fold better antibacterial activity for *S. aureus*. Generally, the introduction of the methyl- and benzyl-groups enhanced the antibiotic activity. Unfortunately, the benzyl derivatives **2c** and **h** were obtained in low yields by direct conversion of mucochloric acid.

Interestingly, **2b**[16] had a 4-fold lower MIC in patient isolates for the antibiotic resistant strain S2 than the corresponding non-resistant isolate S1. These compounds may represent a new class of antibacterial agents, acting by a new biological mechanism.

4. Conclusion

The described chemical method opened a new access towards 5-hydroxy-2(5*H*)-furanones,[17] which were usually prepared from the parent furan by singlet oxygen oxygenation. The synthesis and evaluation of a series of 2(5*H*)-furanones led to the discovery[18] of a novel class of antibiotics. The lead structure has shown a broad anti-microbiological profile and a full SAR optimisation is currently ongoing.

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14. Analytical data for 3-bromo-5-hydroxy-4-methylamino-2(5*H*)-furanone **2g**:
    Yield: 53 %. MW: 207.23. IR (KBr-disc) max: 3380, 2924, 1755, 1716, 1628, 1452, 1172 cm^{-1}. MS (APCI+): 223 (M + H + MeOH), 191 *m/z*. ^{1}H NMR ($CDCl_3$) 300 K: 7.12 (br s, 1H, OH), 6.76 (br s, 1H, NH) 3.10 (s, 3H, $-CH_3$) ppm. ^{13}C NMR ($CDCl_3$) 300 K: 165.20 (C2), 141.73 (C4), 126.00 (C3), 99.21 (C5), 24.54 (Me) ppm.
15. *Inoculum preparation*
    The bacteria were streaked on a nutrient agar plate to obtain a freshly isolated colony subsequently incubated overnight at 37 °C. Four to five isolated colonies were added into Mueller Hinton broth (MHB) solution, incubated for 4 h at 37 °C. The turbidity was adjusted to the McFarland tube and the solution was diluted with MHB to 1:200. Antibacterial dilution tested: The test solution was diluted with dimethyl sulfoxide (DMSO) and MHB in the ratio of 1:4 to get a final concentration of 512 g/ml. MHB (50 μl) was added to each of twelve wells except the first well. Dilutions were made, mixed and the solutions were then incubated overnight at 37 °C. The MIC, the lowest concentration, which showed a clear solution, was examined for each compound. In order to determine the MBC, a loopful of each clear well was streaked onto a nutrient containing agar plate, which was subsequently incubated overnight at 37 °C. The MBC was then determined as the lowest concentration, which has shown no visible colony for each chemical.
16. Compound **2b**: 3-chloro-5-hydroxy-4-methylamino-2(5*H*)-furanone
    Dry mucochloric acid (15.0 g, 88.8 mmol) and N-methylformamide (9.46 g, 180 mmol) were refluxed in toluene (100 ml) with 1% of conc. H_2SO_4. After 8h the mixture was evaporated off to a third of the volume and silicagel was added until a brown powder was obtained. The mixture was extracted ether/petrolether (solid extraction) and the solvent was evaporated off to give the target compound as white solid (mp: 121 °C).
    Yield: 74%. MW: 162.54. IR (KBr-disc) max: 3267, 2983, 2844, 1779, 1782, 1637, 1243, 1169, 950 cm^{-1}. MS (APCI+): 178 (M + H + MeOH), 146 *m/z*. ^{1}H NMR ($CDCl_3$) 300 K: 7.10 + 6.75 (br s, 2H, NH, OH) 5.95 (s, 1H, C5H), 3.15 (s, 3H, $-CH_3$) ppm. ^{13}C NMR ($CDCl_3$) 300 K: 168.21 (C2), 146.73 (C4), 122.23 (C3), 95.21 (C5), 26.68 (Me) ppm.
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