Solid Phase Synthesis of Substituted 4-Amino-5-Hydroxy-2(5H)-furanones

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ABSTRACT A solid phase approach towards the synthesis of substituted 4-amino-5-hydroxy-2(5H)-furanones was developed and applied to the construction of a two dimensional library of ∇^2-butenolides. Four halogenated 5-hydroxy∇^2-butenolide building blocks **1A-1D** have been attached, via the 5-hydroxy group, to a scavenger isocyanate resin giving the resin bound carbamates **2A-2D.** Reacting each resin bound butenolide **2A-2D** individually with a total of 16 amines **a-p** furnished the 64 linked 4-amino-5-hydroxy-butenolides **3Aa-3Dp**. After the cleavage from the resin with TFA 48 different and individual 4-alkylamino-5-hydroxy-2(5H)-furanones **Aa-Cp** were obtained from a total library of 64 compounds, as building block **C** and **D** resulted in the same molecules.

KEYWORDS: Solid phase synthesis, resin bound methyl-isocyanate, carbamate linkage, hydroxy-∇^2 butenolides, 4-amino-5-hydroxy-2(5H)-furanones, vinylogue amides.

INTRODUCTION

The 5-hydroxy-2(5H)-furanone moiety is widespread in nature and also a substructure of the pyranofuranone key pharmacophore in the anti-infammtory agent Manoalide.[1] Other bis-heterocyclic furanones, like the biscyclic butenolide (pyrrolyl-furanone) shown in Fig 1, have been derived from that oxacyclic system.[2] Butenolides containing substituted o-chloro-benzylamine have been recently identified as antibiotic agents against the multiresistant *Staphillococcus aurus* [MRSA] in a combinatorial library of 3-, 4-, 5-substituted 2(5H)-furanones.[3] Narthogenine is another example of a 5-hydroxy-2(5H)-furanone with antibiotic properties and Basidalin represents an 4-amino-2(5H)-furanone which has shown anitumor activity.[4]

Solid phase chemistry is expected to speed up the discovery of new lead structures in the field of pharmaceutical research and agriculture by using high-throughput screening assays.[5] Often, these solid phase approaches[6] require protecting group chemistry, which is reported, for example, for the construction of 1,4-benzodiazepines[7] . By our approach, the resin acted as a protecting group, which was subsequently removed after the conversion into the desired 4-amino-2(5H)-furanone. Here, the protection of the 5-hydroxy group is essential, as in the presence of the free hydroxy-group, the aldehyde form of the muco halogen acids reacts differently and does <u>not</u> react in the desired IPSO substitution reaction.[8]

So called pseudoesters, which are chemically acetals, and pseudoanhydrides of the hydroxy form of muco halogen acids are easily synthesized from furanones[9] and these building blocks have recently been evaluated as cytotoxic agents.[4] A pseudo-carbamate/carbamate linkage was used by our approach to connect the 2(5H)-furanone template to the resin in the 5-position. The carbamate linkage, in general, has been widely used for the synthesis of various heterocyclic systems.[10]

Here, for the first time, a solid phase approach to the synthesis of 4-amino-5-hydroxy-2(5H)-furanones is reported, in which the substituents in the 3- and 4-positions of the butenolide scaffold, have been varied independently (Fig 1).

METHODS AND RESULTS

Synthesis of Building Blocks

Furfural, a versatile aromatic aldehyde, which is available from biomass, was used as the initial starting material in the construction of the required butenolide building blocks **1A-1D**. Furfural is the only aldehyde that can be synthesized from biomass as renewable resource. The husk and hulls (biomass) from crops like rice can be reacted with sulphuric acid to give furfural in one step. Mucochloric acid **1A** and mucobromic acid **1B** can be synthesized from furfural but they are also commercially available. 4-Chloro-5-hydroxy-furanone **1C** was prepared according to a modified method[11] (Fig 2), which

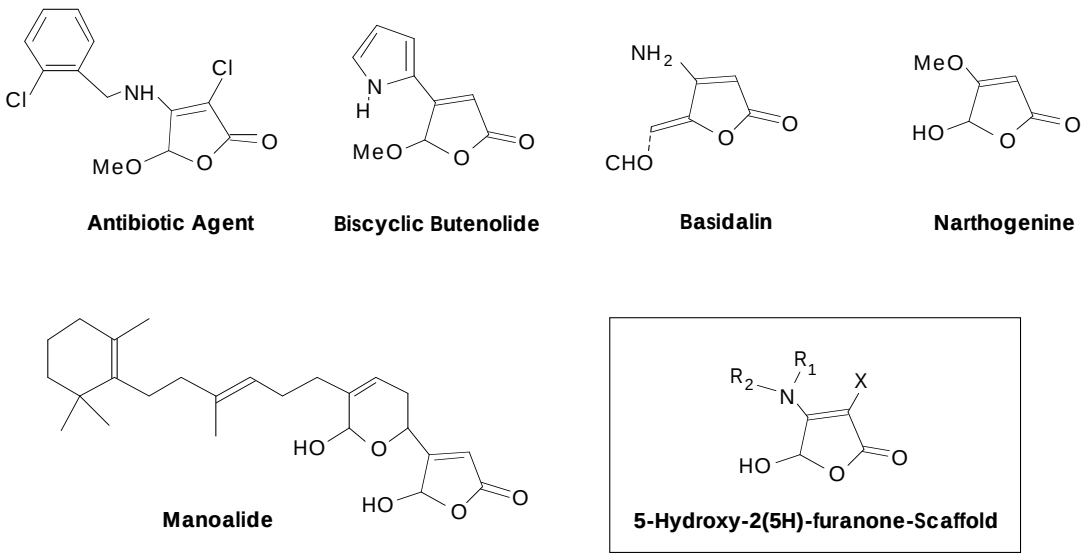


Fig 1. Overview of selected 2(5H)-furanones (—[2]-butenolides) and the butenolide scaffold with X and R_1, R_2 to be varied by the solid phase approach.

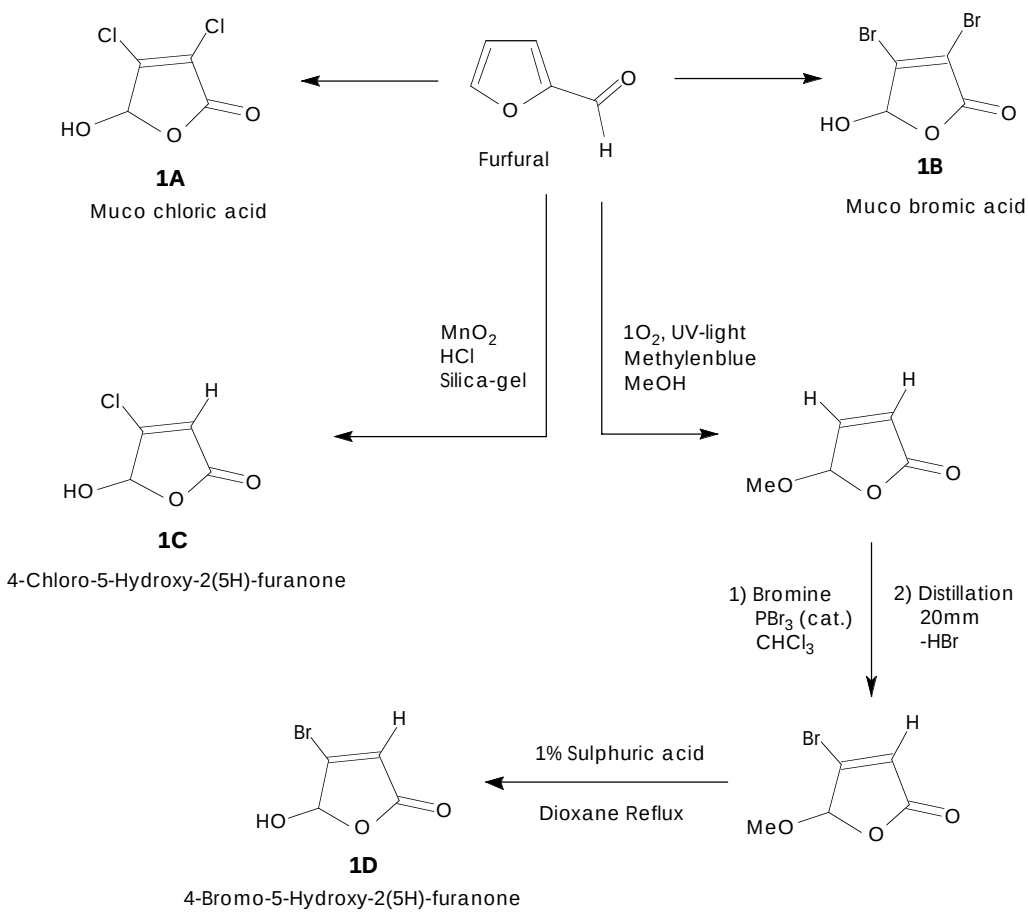
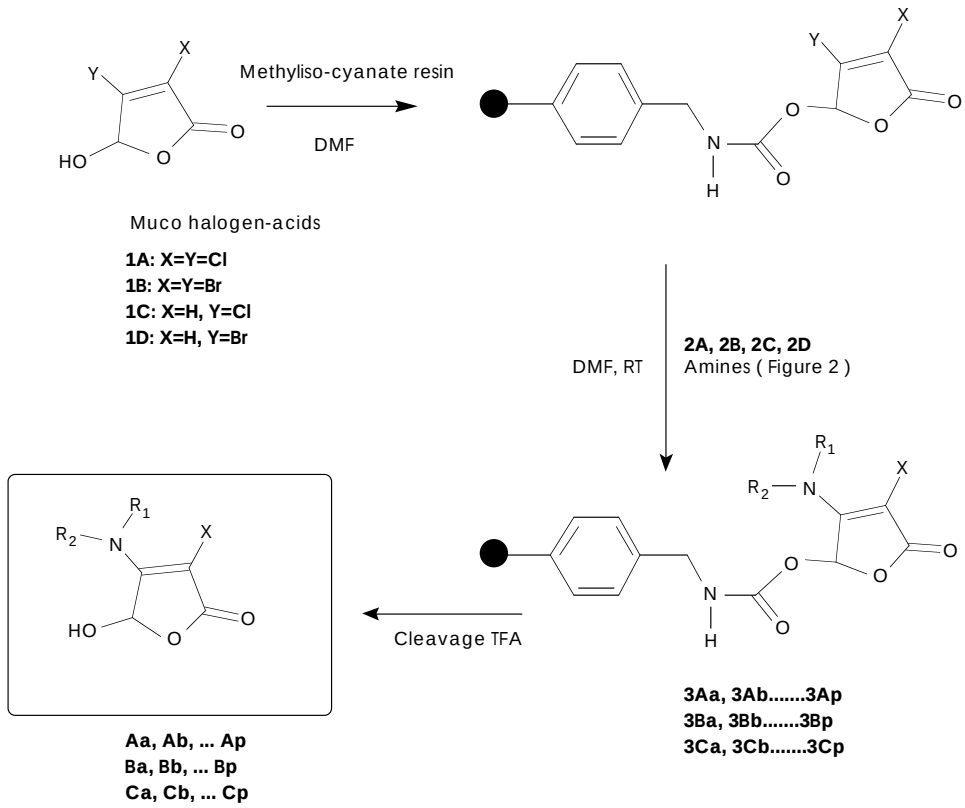


Fig 2. Synthesis of Butenolide Building Blocks.



Solid Phase Synthesis. Reaction Scheme 1.

was previously applied to the construction of a sub-library of 5-alkoxylated 3,4-dihalogenated-2(5H)-furanones[12]. For the synthesis of 1D, furfural was firstly converted with singlett oxygen and methylene blue as a sensitizer in methanol to 5-methoxy-2(5H)-furanone. Bromination of the 5-methoxy-2(5H)-furanone in chloroform with phosphorus-tribromide as a catalyst furnished the 3,4-dibromo-2(5H)-furanone. This intermediate was distilled under vacuum with the elimination of HBr gas to give the crystalline 4-bromo-5-methoxy-2(5H)-furanone, that can be stored in the freezer. For further reaction, the 4-bromo-5-methoxy-2(5H)-furanone was refluxed with 1% sulfuric acid in dioxane to furnish the desired 4-bromo-5-hydroxy-2(5H)-furanone 1D in good yield (Fig 2).

Solid phase chemistry

The scavenger resin was purchased from Novabiochem, UK and contained 1.6 mmol/g of the resin bound methyl-isocyanate. It was reacted with a 10% solution of the pseudo-hydroxy group of the mucohalogen acids[13] 1A and 1B, 4-chloro-5-hydroxy-2(5H)-furanone (1C) and 4-bromo-hydroxy-2(5H)-furanone (1D) in DMF / DCM at 50°C over night to give the carbamate-linked butenolides 2A - 2D (Scheme 1). The coupling process was repeated for the chlorinated furanone 1C. After the reaction had gone to completion, the resin bound butenolides 2A - 2D were washed with DMF, DCM and DMF (3 times). Each of the resin bound butenolides, 2A, 2B, 2C and 2D, was placed in 16 peptide flasks and was subsequently converted into the desired amides 3Aa, 3Ab... 3Ap ..... 3Da, 3Db... 3Dp by using the amines a-p in DMF at 35°C over a period of 2 days. The desired substituted 5-hydroxy-4-amino-furanones Aa, Ab... Ap; Ba... Bp; Ca... Cp and Da... Dp (Fig 3) were obtained after cleavage with TFA at ambient temperature.[14] The TFA was evaporated off at ambient temperature in a constant steam of argon.

Using the four reactive butenolide building blocks 1A, 1B, 1C and 1D with 16 diverse amines in a combinatorial manner, a library of 64 individual compounds was afforded in total. Only 48 different chemical structures were obtained in this library, as building block C and D gave the same molecules.

The reaction products formed of the 4-chloro-5-hydroxy-2(5H)-furanone 1C and the secondary

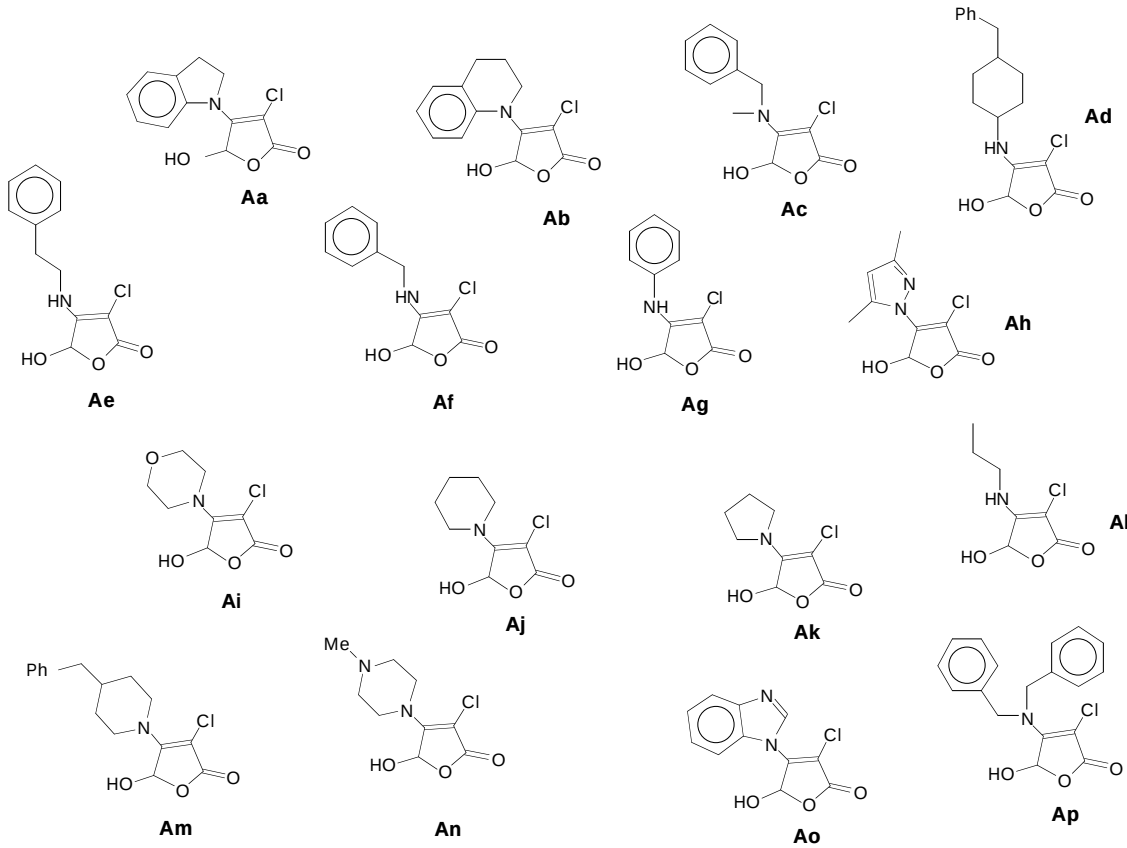


Fig 3. Selected 5-hydroxy-4-amino-2(5H)-furanones Aa-Ap.

amines a, b, c, i, j, k, and m showed a single (M+1) peak in APCI (Atmospheric Pressure Chemical Ionization) mass spectroscopy. Others compounds of this series were contaminated with by-products.

The series based on mucochloric acid 1A, whose reactivity was enhanced by a second chlorine in the 3-position compared to 1C, reacted very well to give products in excellent purity, and all structures of that series are outlined in Figure 2. The yields obtained were generally above 90%.

Mucobromic acid 1B as a building block is too reactive, as higher peaks can be seen in the APCI mass spectra's, which correspond to 4-5-bis substituted 2(5H)-furanones.

The 4-bromo-5-hydroxy furanone 1D, which is less reactive than 1B, is the preferred building block towards the synthesis of 4-amino-5-hydroxy-2(5H)-furanones. However, the synthesis of the required butenolide starting material 1D requires more steps than the construction of 1C, which can be more easily prepared from furfural in only a single synthetic step.

The target molecules of the 4-amino-3-chloro-2(5H)-furanone and 4-amino-2(5H)-furanone series (Aa - Ap & Da - Dp) have been isolated by chromatography and were fully characterized by APCI mass spectroscopy, FT-IR, ^{1}H- and ^{13}C-resonance spectroscopy. Selected spectroscopic data are outlined in the Notes and References section.

Discussion

For the first time, a solid phase approach towards the synthesis of 4-amino-5-hydroxy-2(5H)-furanones is reported. The key synthetic step is the reaction of an isocyanate scavenger resin, which formed a carbamate linkage to the 5-position of the 2(5H)-furanone scaffold with subsequent IPSO substitution in the 4-position. These novel, potentially bioactive substituted 4-amino-5-hydroxy-2(5H)-furanones are currently been evaluated in a high throughput-screening assay in order to discover new lead structures in the field of pharmaceuticals or agrochemicals.

Furfural has been used previously for the construction of antibiotics[15] and anti-depressants.[16] In the search for new applications of this renewable

chemical resource, a use in plant protection would be particular useful, as furfural itself is synthesized from crops with sulfuric acid. This new solid phase approach, which provides exciting 5-hydroxy-butenolides, is a first step in the discovery of new applications of ∇^2-butenolides from biomass, a renewable resource.

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Notes and References

4-N-Morpholino-5-hydroxyfuran-2(5H)-one **Di** : ^{13}C-NMR (D_6-DMSO) : d = 47.36 (CH_2, C-1), 65.78 (CH_2, C-2), 81.49 (CH, C-5), 93.02 (CH, C-3), 167.77 (C, C-4), 171.99 (C, C-2); ^{1}H-NMR (250 MHz, D_6-DMSO) : d = 3.23-3.43 (m, 4 H, H-1), 3.64 (m, 4 H, H-2), 4.72 (s, 1 H, H-5), 6.03 (s, 1 H, H-3), 7.72 (bs, 1 H, OH); IR ($CHCl_3$): n = 3232 bm, 2968 m, 2928 m, 2860 m, 1732 vs, 1620 vs, 1448 m, 1344 m, 1308 m, 1264 m, 1244 m, 1168 m, 1116 vs, 992 m, 908 m, 864 m cm^{-1}; MS (APCI+) m/z : 186 (M+1)

4-N-Piperidino-5-hydroxyfuran-2(5H)-one **Dj**: ^{13}C-NMR ($CDCl_3$): 15.25 (CH_2, C-3), 23.84 (CH_2, C-4), 25.47 (CH_2, C-5), 48.85 (CH_2, C-2), 65.86 (CH_2, C-6), 80.17 (CH, C-5) 94.58 (CH, C-3) 168.18 (C, C-4) 174.66 (C, C-2); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.64 (m, 6 H, H-3, H-4 & H-5), 3.25 – 3.51 (m, 4 H, H-2 & H-6), 4.51 (s, 1 H, H-5), 5.62 (bs, 1H, OH) 6.06 (s, 1 H, H-3); IR ($CHCl_3$): 3244 bm, 3000 m, 2944 s, 2860 m, 1750 m, 1724 vs, 1616 vs, 1452 m, 1340 m, 1312 m, 1244 m, 1180 s, 1120 s, 1024 m, 992 m, 944 m, 896 w, 852 m, cm^{-1}; MS (APCI+) m/z: 186 (M+1).

4-N-Methyl-N-piperazino-5-hydroxyfuran-2(5H)-one **Dn**: ^{13}C-NMR (D_6-DMSO): 45.83 (CH_3, NMe), 46.91 (CH_2, C-2 & C-5), 54.00 (CH_2, C-2 & C-6), 81.17 (CH, C-5), 93.04 (CH, C-3), 167.70 (C, C-4) 172.12 (C, C-2); ^{1}H-NMR (250 MHz, D_6-DMSO): 2.18 (s, 3H, NMe), 2.33 (t, J = 4.98Hz, 4H, H-2 & H-3), 3.1- 3.60 (m, 4 H, H-1 & H-4), 4.66 (s, 1 H, H-5), 5.99 (s, 1 H, H-3), 7.88 (bs, 1 H, OH); IR (KBr): 3428 bw, 3112 w, 2948 w, 1796 w, 1728 vs, 1628 vs, 1456 m, 1304 s, 1176 s, 1116 m, 1000 m, 952 m, 896 w, 776 m, cm^{-1}; MS (APCI+) m/z: 199 (M+1).

4-Benzylamino-5-hydroxyfuran-2(5H)-one **Df:** ^{13}C-NMR (D_6-Acetone): 49.99 (CH_2, CH_2Ph), 81.57 (CH, C-5), 94.82 (CH, C-3), 128.09 (CH, Ph), 128.23 (CH, Ph), 129.29 (CH, Ph), 128.55 (C, Ph), 168.27 (C, C-4) 172.54 (C, C-2); ^{1}H-NMR (250 MHz, D_6-Acetone): 4.40 (d, J = 5.70 Hz, 2H, CH_2Ph), 4.54 (s, 1H, H-5), 5.93 (s, 1H, H-3), 6.74 (bs, 1 H, NH), 7.12 (bs, 1 H, OH) 7.23 – 7.43 (m, 5H, Ph); IR (KBr): 3484 w, 3380 m, 3060 w, 2924 w, 2860 w, 1755 w, 1716 s, 1628 vs, 1536 w, 1452 m, 1332 w, 1280 w, 1172 m, 1128 m, 960 w, 780 w, 756 w, 696 w, cm^{-1}; MS (APCI+) m/z: 206 (M+1).

4-N-Pyrrolidino-5-hydroxyfuran-2(5H)-one **Dk:** ^{13}C-NMR (CD_3OD): 25.65 (CH_2, C-3), 26.81 (CH_2, C-4), 48.93 (CH_2, C-2), 50.69 (CH_2, C-5), 80.47 (CH, C-5), 95.63 (CH, C-5) 167.95 (C, C-4) 176.64 (C, C-2); ^{1}H-NMR (250 MHz, CD_3OD): 1.99 (m, 4 H, H-3 & H-4), 3.24 – 3.32 (m, 4 H, H-2 & H-5), 4.44 (s, 1 H, H-5), 6.03 (s, 1 H, H-3); IR (KBr): 3152 bm, 2980 w, 2952 m, 2924 m, 2868 m, 1692 vs, 1648 vs, 1628 vs, 1420 vs, 1420 m, 1332 s, 1192 s, 1124 s, 984 m, 944 s, 768 cm^{-1}; MS (APCI+) m/z: 170 (M+1).

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