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Novel synthetic approach to 2-(1′-hydroxyalkyl)- and 2-amido-3-hydroxypyridin-4-ones

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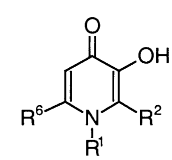
Abstract—Novel methods for the synthesis of high pFe^{3+} iron chelators, 2-(1′-hydroxyalkyl)- and 2-amido-3-hydroxypyridin-4-ones, have been developed. The products are obtained, via *N*-oxide intermediates, from either maltol or ethyl maltol.

1. Introduction

The 3-hydroxypyridin-4-ones form one of the main candidate groups for the development of orally active iron chelators,[1] in fact the 1,2-dimethyl derivative **1** (deferiprone) is already available for clinical use (marketed by Apotex Inc., Toronto, Canada as Ferriprox™).[2] Attempts have been made to improve the efficacy of these bidentate ligands[3,4] and recently we have established that the introduction of either a 1′-hydroxyalkyl group or an amido group at the 2-position of 3-hydroxypyridin-4-ones leads to a considerable enhancement of the iron(III) chelating ability monitored by the pFe^{3+} value.[4–6] The pFe^{3+} value, defined as the negative logarithm of the concentration of the free iron(III) in solution, is a more suitable comparator than the stability constant since it takes into account the effect of ligand basicity, denticity, degree of protonation and differences in metal–ligand stoichiometries.[2] Chelators with high pFe^{3+} values are predicted, not only to be able to scavenge iron more efficiently at low ligand concentrations, but also to dissociate less readily and therefore form lower amounts of partially co-ordinated complexes. Such iron complexes render the iron(III) cation surface accessible to oxygen and hydrogen peroxide and thereby susceptible to the possible generation of hydroxyl radicals.[1] With 3-hydroxypyridin-4-ones the increase of the pFe^{3+} value results from the lowering of pK_a values corresponding to both the 3- and 4-pyridinone oxygens. These differences are associated with the enhanced stability of the ionised species. Such stability may result from a combination of intramolecular hydrogen bonding between the 2-(1′-hydroxyalkyl) group (or 2-amido group) (**2**,**3**) and the adjacent 3-hydroxyl moiety, together with a powerful inductive effect.[5,6] Although such an effect lowers the overall stability constant (log β_3) as well as the affinity of the ligand for protons, these changes result in an increase in the binding of iron(III) over the pH range 5–8, as reflected in the increase of the pFe^{3+} value. A selection of these 'second generation' 3-hydroxypyridin-4-ones are under consideration for pre-clinical development and for this reason we are investigating synthetic methodology relating to these and related compounds. In the present paper we report a more convenient and economical method for the synthesis of 2-(1′-hydroxyalkyl)- and 2-amido-3-hydroxypyridin-4-ones.



(1) $R^1 = R^2 = CH_3$, $R^6 = H$

(2) $R^2 = CH(OH)R'$

(3) $R^2 = CONHR''$

2. Chemistry and discussion

Pyromeconic acid **4** and allomaltol **5**, the starting materials used in the existing methods (Scheme 1), are not commercially available and require multi-step syntheses.[4–6] In contrast, the method reported herein uses maltol **6a** and ethyl maltol **6b** as starting materials which are readily available.[7] The unsubstituted 2-position of both **4** and **5** can be functionalised by classical aldol condensation.[5] This furnishes the 2-(1′-hydroxyalkyl)-3-hydroxypyridin-4-ones and with further derivatisation the 2-amido-3-hydroxypyridin-4-ones (Scheme 1). In contrast, the 2-positions of

Keywords: iron chelators; 3-hydroxypyridin-4-one; pyridine *N*-oxide; pFe^{3+} value.

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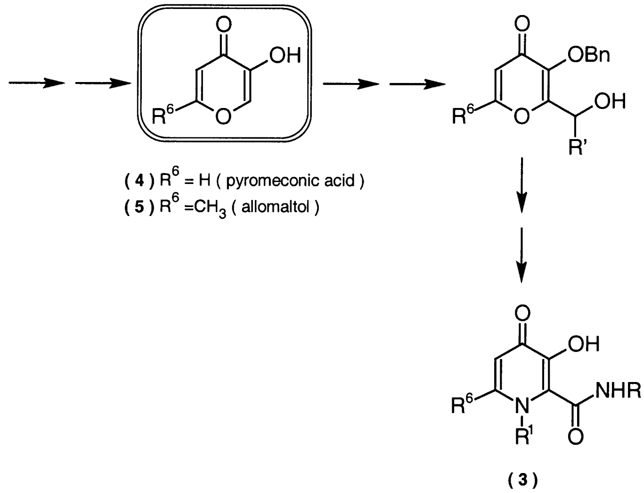
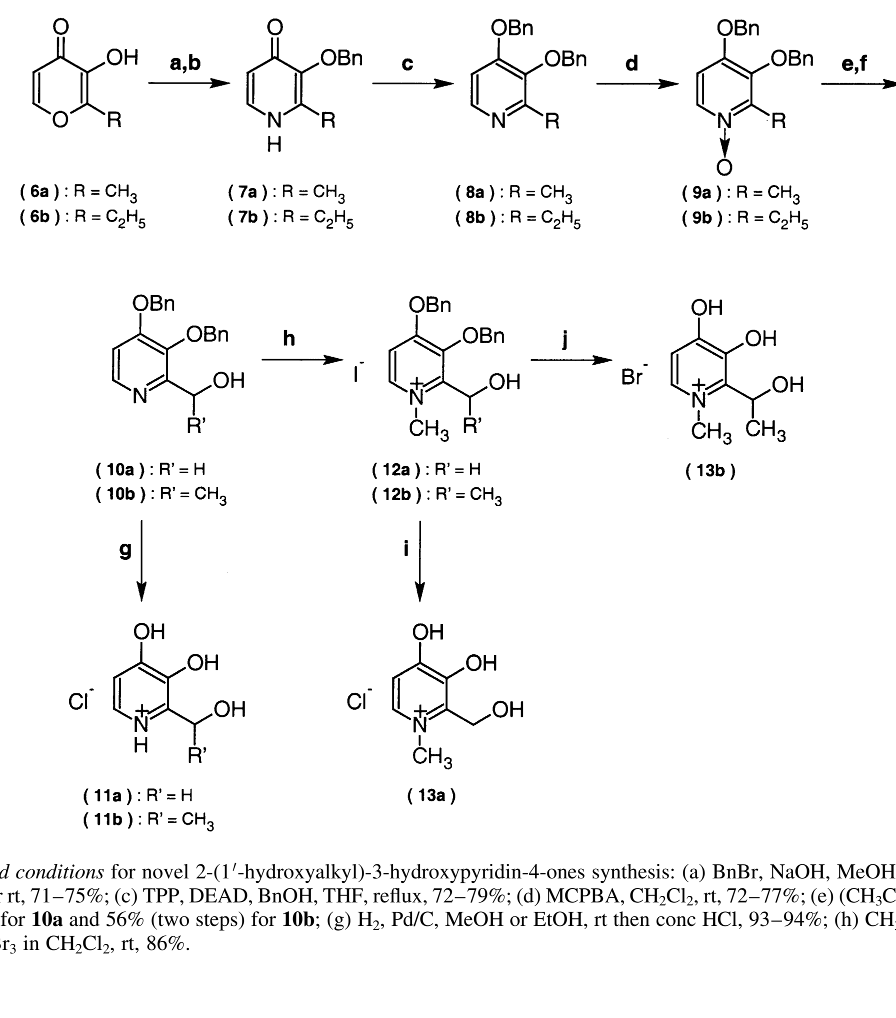


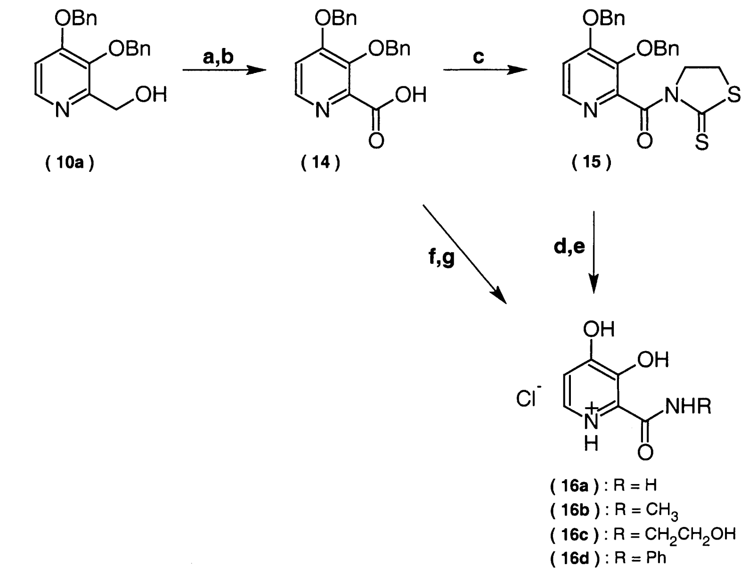
Scheme 1. Multi-step syntheses of 2-(1′-hydroxyalkyl)- and 2-amido-3-hydroxypyridin-4-ones.[3–5]

6a and **6b** both possess an alkyl group substituent which is not easy to selectively functionalise.

The novel synthetic route to 2-(1′-hydroxyalkyl)-3-hydroxypyridin-4-ones described in this paper (Scheme 2) starts with the protection of the 3-hydroxyl moieties of **6a** and **6b**, followed by conversion to pyridones **7a** and **7b** which are generally more resistant to extremes of pH.[8] At this stage some difficulties were encountered as the *NH*-containing pyridones can be alkylated on either the 4-oxygen or the 1-nitrogen, producing alkoxypyridines or *N*-alkylpyridones in proportions depending on the reaction conditions.[9] However, when the pyridin-4-one oxygen is protected as for instance as a *O*-trimethylsilyl ether, alkylation can occur selectively at the ring nitrogen.[10] This example prompted us to undertake a similar reaction with compounds **7a** and **7b**. When both the pyridone oxygens are protected, the ring nitrogens become electron rich. Silyl ethers were found to be inappropriate for use as protecting groups in multi-step syntheses as they are easily cleaved



Scheme 2. *Reagents and conditions* for novel 2-(1′-hydroxyalkyl)-3-hydroxypyridin-4-ones synthesis: (a) BnBr, NaOH, MeOH or EtOH, reflux, 80–81%; (b) NH_3, EtOH, reflux or rt, 71–75%; (c) TPP, DEAD, BnOH, THF, reflux, 72–79%; (d) MCPBA, CH_2Cl_2, rt, 72–77%; (e) $(CH_3CO)_2O$, reflux; (f) 2N NaOH, reflux, 81% (two steps) for **10a** and 56% (two steps) for **10b**; (g) H_2, Pd/C, MeOH or EtOH, rt then conc HCl, 93–94%; (h) CH_3I, rt, 74–82%; (i) 6N HCl, reflux, 83%; (j) 1 M BBr_3 in CH_2Cl_2, rt, 86%.



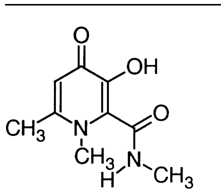
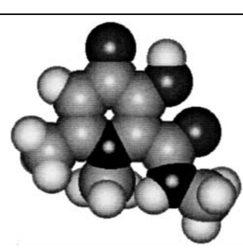
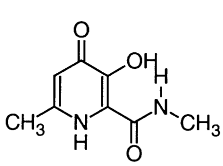
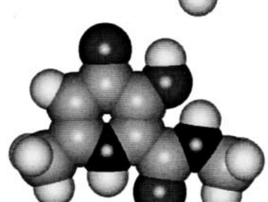
Scheme 3. *Reagents and conditions* for novel 2-amido-3-hydroxypyridin-4-ones synthesis: (a) DMSO, Py-SO_3, TEA, $CHCl_3$, rt, 62%; (b) $NaClO_2$, H_2NSO_3H, acetone:H_2O (1:1), rt, 77%; (c) DCCI, DMAP, 2-mercaptothiazoline, CH_2Cl_2, rt; (d) primary amines, rt, 44–48% (two steps); (eandg) H_2, Pd/C, MeOH or EtOH, rt, 87–91%; (f) PyBOP, TEA, $PhNH_2$, CH_2Cl_2, rt, 44%.

under basic conditions. For this reason benzyl ethers were adopted, their preparation being achieved via the Mitsunobu reaction[11] where only the phenol tautomers of the *N*-unsubstituted pyridones **7a** and **7b** reacted with benzyl alcohol and gave selectively the corresponding *O*-benzylated products **8a** and **8b**. The dibenzyl protected compounds were subjected to oxidation with *m*-chloroperoxybenzoic acid (MCPBA) to form the *N*-oxides **9a** and **9b**.[12]

In order to functionalise the 2-alkyl group, the *N*-oxide group was acetylated with acetic anhydride. The resulting intermediate undergoes an intramolecular rearrangement leading to the formation of an acetylated alcohol on the 2-alkyl group.[13–15] Subsequent saponification with sodium hydroxide gave the corresponding 2-(1′-hydroxyalkyl)-pyridines **10a** and **10b** which when subjected to *N*-methylation yielded the quaternary pyridinium salts **12a** and **12b**.

Cleavage of the protected *NH*-pyridones was undertaken by hydrogenolysis in order to prepare the 2-(1′-hydroxyalkyl)-3-hydroxypyridin-4-ones **11a** and **11b**. However, hydrogenolysis was unsuccessful when performed with the protected *N*-alkyl derivatives, as the quaternary pyridinium salts apparently poison the palladium/carbon catalyst. Consequently compound **12a** was subjected to acidic reflux in order to give **13a**. The secondary alcohol function of **12b** was found to be susceptible to dehydration under these conditions. Thus debenzylation catalysed by boron

Table 1. Comparison of physicochemical properties and energy minimised structures between compound **3a** and **3b**

Structure	Energy minimised conformer[a]	pK_a	Affinity constants for Fe(III)[b]				pFe^{3+c}	$D_{7.4}$[d] (n=5)
			log K_1	log K_2	log K_3	log β_3		
 (3a)		2.77, 8.44 (spectrophotometric) 2.75, 8.47 (potentiometric)	13.41	11.47	9.43	34.31	21.7	0.04±0.01
 (3b)		2.32, 6.66 (spectrophotometric) 2.29, 6.68 (potentiometric)	14.50	10.49	7.47	32.46	22.8	0.17±0.01

[a] Space filling model (H=white; C=light grey; N=black; O=dark grey).
[b] The cumulative stability constant (β_3) obtained by summation of the three stepwise equilibrium constants (K_1, K_2 and K_3).
[c] $pFe^{3+}=-\log [Fe^{3+}]$ when $[ligand]_{total}=10^{-5}$ M. and $[Fe^{3+}]_{total}=10^{-6}$ M. at pH 7.45.
[d] $D_{7.4}$=distribution coefficient (n-octanol/ water) at pH 7.4.

tribromide in dichloromethane[16] was established as the method of choice for compound **12b**.

The synthetic pathway for the 2-amido-3-hydroxypyridin-4-ones is summarised in Scheme 3. Direct conversion of the primary alcohol of **10a** to a carboxylic acid was initially attempted using Jones reagent, however, extensive decomposition occurred, resulting in poor yields. Thus the intermediate aldehyde was isolated before further oxidation to the carboxylic acid **14** was attempted. Activation of **14** was achieved prior to reaction with various aliphatic primary amines using previously established conditions.[6] This method was found to be less efficient with aromatic amines. For such reactions an alternative method was introduced using benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP®) as a coupling reagent (Scheme 3).

In contrast to the 2-(1′-hydroxyalkyl)-pyridines, *N*-alkylation of the 2-amidopyridines could not be achieved due to a strong inductive effect of the 2-amido substituent. However, studies have demonstrated that when there is no *N*-alkyl substitution in the ring (compound **3b**), the pK_a values are significantly lower than that of the *N*-methyl analogue **3a** (Table 1). This difference is due to two main factors, firstly the positive inductive effect of the alkyl group and secondly the existence of coplanar intramolecular hydrogen bonding between the amide *NH* and the 3-hydroxyl group of compound **3b**. The intramolecular hydrogen bonding in compound **3a** is not so well favoured as appreciable steric repulsion exists between the 1-methyl group and the amide oxygen atom. The smaller bulk of the 1-hydrogen in compound **3b** permits the alternative orientation of the amide function, such that coplanar intramolecular hydrogen bonding is possible (Table 1). The enhanced hydrophobicity of compound **3b** (Table 1) confirms the existence of efficient intramolecular hydrogen bonding which reduces the ability of the compound to interact with water. Because of the enhanced affinity for iron(III) of the *NH*-containing pyridinones no further attempts were made to achieve *N*-alkylation of these derivatives.

3. Experimental

3.1. General chemistry procedure

Melting points were determined using an Electrothermal IA 9100 Digital Melting Point Apparatus and are uncorrected. IR spectra were performed on a Perkin-Elmer 1605 FTIR Spectrophotometer and ^{1}H NMR spectra were recorded on a Perkin–Elmer (60 MHz) or Bruker (400 MHz) spectrometers. Chemical shifts (δ) are reported in ppm downfield from the internal standard tetramethylsilane (TMS). Mass spectra (FAB) analyses were carried out by Mass Spectrometry Facility, Department of Pharmaceutical and Biological Chemistry, The School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX. The samples were dissolved in either 3-nitrobenzylalcohol or a mixture of thioglycerol, glycerol and trifluoroacetic acid matrix. Elemental analyses were performed by Microanalytical Laboratories, Department of Chemistry, The University of Manchester, Manchester M13 9PL. Column chromatography was performed on silica gel 220–440 mesh (Fluka).

3.1.1. 2-Methyl-3-benzyloxypyran-4(1*H*)-one. To a solution of maltol (**6a**) (100 g, 0.794 mol) in methanol (100 mL) was added sodium hydroxide (34.9 g, 0.873 mol, 1.1 equiv.) in water (80 mL). The reaction mixture was heated to reflux before benzyl bromide (104 mL, 0.873 mol, 1.1 equiv.) was slowly introduced into the flask and the mixture was left to reflux overnight. After the solvent was removed, the residue was taken into water (200 mL) and dichloromethane (400 mL). The aqueous fraction was discarded and the organic fraction washed with sodium hydroxide (5%, 3×200 mL) followed by water (2×200 mL). The combined fractions were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Recrystallisation from diethyl ether afforded off-white crystals (136.3 g, 80%): mp 54–56°C (Lit. 17 value 53–55°C); δ_H (60 MHz, $CDCl_3$) 2.07 (3H, s, *Me*), 5.04 (2H, s, CH_2Ph), 6.19 (1H, d, *J*=6.0 Hz, 5-*H*), 7.22 (5H, s, CH_2*Ph*), 7.45 (1H, d, *J*=6.0 Hz, 6-*H*).

3.1.2. 2-Ethyl-3-benzyloxypyran-4(1*H*)-one. The same procedure as described for 2-methyl-3-benzyloxypyran-4(1*H*)-one was used with ethyl maltol (**6b**) (200 g, 1.43 mol) in ethanol (150 mL). Recrystallisation from chloroform/petroleum spirit afforded light yellow crystals (265.0 g, 81%): mp 34–35°C (Lit. 17 value 33–34°C); δ_H (60 MHz, $CDCl_3$) 0.94 (3H, t, *J*=7.8 Hz, CH_2*Me*), 2.43 (2H, q, *J*=7.8 Hz, CH_2Me), 5.03 (2H, s, CH_2Ph), 6.18 (1H, d, *J*=6.0 Hz, 5-*H*), 7.20 (5H, s, CH_2*Ph*), 7.46 (1H, d, *J*=6.0 Hz, 6-*H*).

3.1.3. 2-Methyl-3-benzyloxypyridin-4(1*H*)-one (7a). To a solution of 2-methyl-3-benzyloxypyran-4(1*H*)-one (26.5 g, 0.123 mol) in ethanol (50 mL) was added ammonia solution (100 mL) and refluxed overnight. The solvent was removed under reduced pressure, then taken into water (200 mL) and adjusted to pH 1 with concentrated hydrochloric acid. The aqueous mixture was washed with ethyl acetate (3×150 mL) and the pH was adjusted to pH 10 with sodium hydroxide (2 M.). The aqueous phase was extracted with chloroform (3×200 mL), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Recrystallisation from methanol/diethyl ether gave brown cubic crystals (19.9 g, 75%): mp 162–164°C (Lit. 18 value 162–163°C); δ_H (60 MHz, $CDCl_3$) 2.14 (3H, s, *Me*), 4.92 (2H, s, CH_2Ph), 6.25 (1H, d, *J*=6.0 Hz, 5-*H*), 7.18 (5H, s, CH_2*Ph*), 6.8–7.5 (1H, buried d, 6-*H*).

3.1.4. 2-Ethyl-3-benzyloxypyridin-4(1*H*)-one (7b). To a solution of 2-ethyl-3-benzyloxypyran-4(1*H*)-one (55 g, 0.239 mol) in ethanol (100 mL) was added ammonia solution (200 mL) and left to stir at room temperature for 7 days. The product was filtered and washed with diethyl ether. The filtrate was evaporated under reduced pressure then crystallised from methanol/diethyl ether to yield off-white needle crystals (39.0 g, 71%): mp 179–181°C (Lit. 17 value 168–169°C); δ_H (60 MHz, $CDCl_3$) 1.14 (3H, t, *J*=7.8 Hz, CH_2*Me*), 2.63 (2H, q, *J*=7.8 Hz, CH_2Me), 5.08 (2H, s, CH_2Ph), 6.30 (1H, d, *J*=7.0 Hz, 5-*H*), 7.25 (5H, s, CH_2*Ph*), 7.38 (1H, d, *J*=7.0 Hz, 6-*H*).

3.1.5. 2-Methyl-3,4-dibenzyloxypyridine (8a). Triphenyl phosphine (TPP) (29.3 g, 111.6 mmol, 1.2 equiv.) was slowly added to a solution of 2-methyl-3-benzyloxypyridin-4(1*H*)-one (**7a**) (20 g, 93 mmol) in dry tetrahydrofuran (150 mL) which was cooled to 20°C. Benzyl alcohol (10.6 mL, 102.3 mmol, 1.1 equiv.) was later introduced dropwise followed by diethylazodicarboxylate (DEAD) (17.6 mL, 111.6 mmol, 1.2 equiv.) in the same manner. After refluxing the reaction mixture overnight, the solvent was removed under reduced pressure and the residue was extracted with water (200 mL). The mixture was adjusted to pH 1 with concentrated hydrochloric acid before washing with diethyl ether (4×200 mL). The pH of the aqueous fraction was increased to 8 with sodium hydroxide (2 M.), followed by extraction with ethyl acetate (4×200 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a white solid (22.4 g, 79%). Recrystallisation from chloroform/petroleum spirit gave white crystals: mp 85–87°C; ν_{max} (KBr) 3264 (ring C–H), 1589, 1498, 1485 and 1449 (ring C═C), 1218 and 1066 (C–O–C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, *Me*), 5.00 (2H, s, 3-OCH_2Ph), 5.16 (2H, s, 4-OCH_2Ph), 6.78 (1H, d, *J*=5.6 Hz, 5-*H*), 7.31–7.44 (10H, m, 3-OCH$_2$*Ph* and 4-OCH$_2$*Ph*), 8.12 (1H, d, *J*=5.6 Hz, 6-*H*); *m*/*z* (FAB) 306 $[(M+H)^+]$; HRMS (FAB): $[(M+H)^+]$, found 306.1504. $C_{20}H_{20}O_2N$ requires 306.1494.

3.1.6. 2-Ethyl-3,4-dibenzyloxypyridine (8b). The same procedure as described for **8a** was used with 2-ethyl-3-benzyloxypyridin-4(1*H*)-one (**7b**) (20.3 g, 88.8 mmol). After recrystallisation from chloroform/petroleum spirit, off-white crystals were obtained (20.5 g, 72%): mp 154–156°C; ν_{max} (KBr) 3347 (ring C–H), 1498, 1488, 1465 and 1447 1449 (ring C═C), 1253 and 1096 (C–O–C) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.14 (3H, t, *J*=7.8 Hz, CH$_2$*Me*), 2.72 (2H, q, *J*=7.8 Hz, CH_2Me), 4.85 (2H, s, 3-OCH_2Ph), 4.94 (2H, s, 4-OCH_2Ph), 6.55 (1H, d, *J*=6.0 Hz, 5-*H*), 7.20 (10H, s, 3-OCH$_2$*Ph* and 4-OCH$_2$*Ph*), 8.00 (1H, d, *J*=6.0 Hz, 6-*H*); *m*/*z* (FAB) 320 $[(M+H)^+]$; HRMS (FAB): $[(M+H)^+]$, found 320.1639. $C_{21}H_{22}O_2N$ requires 320.1651.

3.1.7. 2-Methyl-3,4-dibenzyloxypyridine *N*-oxide (9a). A solution of *m*-chloroperoxybenzoic acid (MCPBA) (24 g, 80.9 mmol, 1.1 equiv.) in dichloromethane (100 mL) was prepared and cooled to 0°C. A solution of 2-methyl-3,4-dibenzyloxypyridine (**8a**) (22.4 g, 73.5 mmol) in dichloromethane (100 mL) was added slowly. The reaction mixture was left to stir at room temperature for 3 h prior to addition of dichloromethane (200 mL) to increase the volume. The solution was washed with sodium carbonate (5%, 3×200 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give yellow oil. Crystallisation in the form of white fluffy powder resulted subsequent to the addition of diethyl ether (18.1 g, 77%): mp 127–129°C; ν_{max} (KBr) 3245 (ring C–H), 3041 and 2991 (aliphatic C–H), 1533 (ring C═C), 1240 and 1068 (C–O–C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s, *Me*), 5.00 (2H, s, 3-OCH_2Ph), 5.16 (2H, s, 4-OCH_2Ph), 6.78 (1H, d, *J*=7.3 Hz, 5-*H*), 7.31–7.45 (10H, m, 3-OCH$_2$*Ph* and 4-OCH$_2$*Ph*), 8.12 (1H, d, *J*=7.3 Hz, 6-*H*); *m*/*z* (FAB) 322 $[(M+H)^+]$; HRMS (FAB): $[(M+H)^+]$, found 322.1442. $C_{20}H_{20}O_3N$ requires 322.1443.

3.1.8. 2-Ethyl-3,4-dibenzyloxypyridine *N*-oxide (9b). 2-Ethyl-3,4-dibenzyloxypyridine (**8b**) (11.3 g, 35.5 mmol) was treated as **9a** and produced a white fluffy powder (8.5 g, 72%): mp 97–99°C; ν_{max} (KBr) 3250 (ring C–H), 3040 and 2991 (aliphatic C–H), 1616 and 1531 (ring C═C), 1253 and 1067 (C–O–C) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.20 (3H, t, *J*=7.2 Hz, CH$_2$*Me*), 2.96 (2H, q, *J*=7.2 Hz, CH_2Me), 5.02 (2H, s, 3-OCH_2Ph), 5.11 (2H, s, 4-OCH_2Ph), 6.67 (1H, d, *J*=7.2 Hz, 5-*H*), 7.30 (5H, s, 3-OCH$_2$*Ph*), 7.37 (5H, s, 4-OCH$_2$*Ph*), 7.96 (1H, d, *J*=7.2 Hz, 6-*H*); *m*/*z* (FAB) 336 $[(M+H)^+]$; HRMS (FAB): $[(M+H)^+]$, found 336.1604. $C_{21}H_{22}O_3N$ requires 336.1600.

3.1.9. 2-Acetoxymethyl-3,4-dibenzyloxypyridine. Acetic anhydride (100 mL) was added into a flask which contain 2-methyl-3,4-dibenzyloxypyridine *N*-oxide (**9a**) (5.1 g, 17.8 mmol) and the reaction mixture was heated to 130°C for 1 h. The solvent was removed under reduced pressure and the residue dissolved in water (200 mL). The pH of the solution was adjusted to 8 with sodium hydroxide (2 M.) and was then extracted with dichloromethane (3×200 mL). The organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield brown oil. Treatment with decolourising charcoal yielded yellow oil: δ_H (60 MHz, $CDCl_3$) 1.93 (3H, s, OCO*Me*), 4.92 (2H, s, 3-OCH_2Ph), 4.95 (2H, s, 4-OCH_2Ph), 5.05 (2H, s, CH_2OCOMe), 6.65 (1H, d, *J*=6.0 Hz, 5-*H*), 7.14 (5H, s, 3-OCH$_2$*Ph*), 7.20 (5H, s, 4-OCH$_2$*Ph*), 8.02 (1H, d, *J*=6.0 Hz, 6-*H*).

3.1.10. 2-(1′-Acetoxyethyl)-3,4-dibenzyloxypyridine. The same procedure as described for 2-acetoxymethyl-3,4-dibenzyloxypyridine was used with 2-ethyl-3,4-dibenzyloxypyridine *N*-oxide (**9b**) to yield brown oil: ν_{max} (Neat) 3031 (ring C–H), 1732 (ester C═O), 1581 (ring C═C), 1245 and 1027 (C–O–C) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.20 (3H, d, *J*=6.6 Hz, CH*Me*), 1.65 (3H, s, OCO*Me*), 4.60 (2H, s, 3-OCH_2Ph), 4.75 (2H, s, 4-OCH_2Ph), 5.98 (1H, q, *J*=6.6 Hz, C*H*Me), 6.33 (1H, d, *J*=6.0 Hz, 5-*H*), 6.92 (10H, s, 3-OCH$_2$*Ph* and 4-OCH$_2$*Ph*), 7.80 (1H, d, *J*=6.0 Hz, 6-*H*).

3.1.11. 2-Hydroxymethyl-3,4-dibenzyloxypyridine (10a). To a solution of 2-acetoxymethyl-3,4-dibenzyloxypyridine (8.3 g, 22.8 mmol) in ethanol (30 mL), sodium hydroxide (2 M., 50 mL) was added and the reaction mixture refluxed for 2 h. The product was extracted with dichloromethane (4×200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give an off-white solid (81% overall yield in two steps). Recrystallisation from diethyl ether/petroleum spirit gave an off-white fluffy powder: mp 83–85°C; ν_{max} (KBr) 3165 (br, O–H), 2954 (aliphatic C–H), 1595 (ring C═C), 1301 and 1035 (C–O–C) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 3.69 (1H, s, CH$_2$O*H*), 4.61 (2H, s, CH_2OH), 5.00 (2H, s, 3-OCH_2Ph), 5.14 (2H, s, 4-OCH_2Ph), 6.80 (1H, d, *J*=6.0 Hz, 5-*H*), 7.28 (5H, s, 3-OCH$_2$*Ph*), 7.36 (5H, s, 4-OCH$_2$*Ph*), 8.10 (1H, d, *J*=6.0 Hz, 6-*H*); *m*/*z* (FAB) 322 $[(M+H)^+]$; HRMS (FAB): $[(M+H)^+]$, found 322.1455. $C_{20}H_{20}O_3N$ requires 322.1443.

3.1.12. 2-(1′-Hydroxyethyl)-3,4-dibenzyloxypyridine (10b). The same procedure as reported with **10a** was used with 2-(1′-acetoxyethyl)-3,4-dibenzyloxypyridine. Purification on a silica gel column (eluant: methanol/chloroform; 10:90 v/v) followed by recrystallisation from chloroform/petroleum spirit yielded white flake crystals (56% overall yield in two steps): mp 70–72°C; ν_{max} (KBr) 3332 (br, O–H), 2968 (aliphatic C–H), 1586 (ring C=C), 1297 and 1019 (C–O–C) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.38 (3H, d, *J*=6.6 Hz, CH*Me*), 3.80–4.50 (1H, br, CHO*H*), 4.95 (2H, s, 3-OCH_2Ph), 4.85–5.25 (1H, buried q, C*H*Me), 5.04 (2H, s, 4-OCH_2Ph), 6.69 (1H, d, *J*=5.4 Hz, 5-*H*), 7.21 (5H, s, 3-OCH$_2$*Ph*), 7.25 (5H, s, 4-OCH$_2$*Ph*), 8.02 (1H, d, *J*=5.4 Hz, 6-*H*); *m*/*z* (FAB) 336 [$(M+H)^+$]; HRMS (FAB): [$(M+H)^+$], found 336.1604. $C_{21}H_{22}O_3N$ requires 336.1600.

3.1.13. 1-Methyl-2-hydroxymethyl-3,4-dibenzyloxypyridinium iodide (12a). Methyl iodide (20 mL) was added to 2-hydroxymethyl-3,4-dibenzyloxypyridine (**10a**) (3.1 g, 9.6 mmol) and the reaction mixture was stirred at room temperature overnight. The product was obtained by filtration of the suspension, washed with diethyl ether, and isolated as light yellow flake crystals (3.6 g, 82%): mp 127–129°C; ν_{max} (KBr) 3261 (br, O–H), 3055 and 3030 (aliphatic C–H), 1508 (ring C=C), 1258 and 1011 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 3.00–3.50 (1H, br, CH$_2$O*H*), 4.18 (3H, s, N*Me*), 4.68 (2H, s, CH_2OH), 4.98 (2H, s, 3-OCH_2Ph), 5.45 (2H, s, 4-OCH_2Ph), 7.24 (5H, s, 3-OCH$_2$*Ph*), 7.35 (5H, s, 4-OCH$_2$*Ph*), 7.76 (1H, d, *J*=7.2 Hz, 5-*H*), 8.70 (1H, d, *J*=7.2 Hz, 6-*H*); *m*/*z* (FAB) 336 [$(M-I)^+$]; HRMS (FAB): [$(M-I)^+$], found 336.1604. $C_{21}H_{22}O_3N$ requires 336.1600.

3.1.14. 1-Methyl-2-(1′-hydroxyethyl)-3,4-dibenzyloxypyridinium iodide (12b). The same procedure as described for **12a** was used with 2-(1′-hydroxyethyl)-3,4-dibenzyloxypyridine (**10b**) (2.5 g, 70.4 mmol). The product was isolated after filtration as yellow flake crystals (2.6 g, 74%): mp 116–118°C; ν_{max} (KBr) 3270 (br, O–H), 3034 (ring C–H), 2983 and 2938 (aliphatic C–H), 1623, 1500 and 1453 (ring C=C), 1253 and 1043 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 1.30 (3H, d, CH*Me*), 4.20 (3H, s, N*Me*), 4.90 (2H, s, 3-OCH_2Ph), 5.40 (2H, s, 4-OCH_2Ph), 5.15–5.70 (1H, buried s, CHO*H*), 5.87 (1H, q, C*H*Me), 7.11 (5H, s, 3-OCH$_2$*Ph*), 7.23 (5H, s, 4-OCH$_2$*Ph*), 7.68 (1H, d, *J*=6.6 Hz, 5-*H*), 8.57 (1H, d, *J*=6.6 Hz, 6-*H*); *m*/*z* (FAB) 350 [$(M-I)^+$]; HRMS (FAB): [$(M-I)^+$], found 350.1766. $C_{22}H_{24}O_3N$ requires 350.1756.

3.1.15. 1-Methyl-2-hydroxymethyl-3-hydroxypyridin-4(1*H*)-one hydrochloride (13a). 1-Methyl-2-hydroxymethyl-3,4-dibenzyloxypyridinium iodide (**12a**) (3.2 g, 6.9 mmol) was dissolved in hydrochloric acid (6 M., 50 mL) and refluxed for 6 h. The reaction mixture was concentrated under reduced pressure to produce a crude solid (1.1 g. 83%). Methanol was added and evaporated twice to remove iodine. Recrystallisation from methanol/acidic diethyl ether (prepared by bubbling hydrogen chloride gas into diethyl ether) yielded light yellow needle crystals: mp 157–159°C (Lit. 5 mp 157–159°C); [Found: C, 43.9; H, 5.4; N, 7.3. $C_7H_{10}ClNO_3$ requires C, 43.88; H, 5.26; N, 7.31%]; δ_H (60 MHz, DMSO-d_6) 4.06 (3H, s, N*Me*), 4.64 (2H, s, CH_2OH), 7.25 (1H, d, *J*=6.6 Hz, 5-*H*), 8.17 (1H, d, *J*=6.6 Hz, 6-*H*), 8.40–9.80 (3H, br, O*H*); *m*/*z* (FAB) 156 [$(M-Cl)^+$]; HRMS (FAB): [$(M-Cl)^+$], found 156.0655. $C_7H_{10}O_3N$ requires 156.0661.

3.1.16. 1-Methyl-2-(1′-hydroxyethyl)-3-hydroxypyridin-4(1*H*)-one hydrobromide (13b). 1-Methyl-2-(1′-hydroxyethyl)-3,4-dibenzyloxypyridinium iodide (**12b**) (2.4 g, 5 mmol) was weighed in a 100 mL round bottom flask which was then sealed and flushed with nitrogen. After the flask was cooled to 0°C, boron tribromide (1 M in dichloromethane, 4 equiv.) was slowly added and the reaction mixture was allowed to stir at room temperature for 3 h. The excess boron tribromide was eliminated at the end of the reaction by the addition of some methanol and left to stir for another 0.5 h. The mixture was concentrated under reduced pressure to yield a white solid (1.1 g, 86%). Recrystallisation from methanol/diethyl ether afforded a yellow powder: mp 141–143°C; [Found: C, 38.62; H, 5.01; N, 5.50; Br, 32.39. $C_8H_{12}BrNO_3$ requires C, 38.42; H, 4.84; N, 5.60; Br, 31.95%]; ν_{max} (KBr) 3229 (br, O–H, intermolecular hydrogen bonding), 2927 (br, O–H, intramolecular hydrogen bonding) 1589, 1531, 1501 and 1457 (ring C=C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 1.45 (3H, d, *J*=6.6 Hz, CH*Me*), 4.16 (3H, s, NMe), 5.48, (1H, q, *J*=6.6 Hz, C*H*Me), 7.10 (1H, d, *J*=6.6 Hz, 5-*H*), 8.15 (1H, d, *J*=6.6 Hz, 6-*H*), 8.00–9.80 (3H, br, O*H*); *m*/*z* (FAB) 170 [$(M-Br)^+$].

3.1.17. 2-Formyl-3,4-dibenzyloxypyridine. To a solution of 2-hydroxymethyl-3,4-dibenzyloxypyridine (**10a**) (5.7 g, 17.6 mmol) in chloroform (100 mL), was added dimethyl sulfoxide (DMSO) (27 mL) and triethylamine (TEA) (14.7 mL, 105.8 mmol, 6 equiv.). The reaction mixture was then cooled in an ice-bath followed by the slow addition of sulfur trioxide pyridine complex (14 g, 88.2 mmol, 5 equiv.). The mixture was allowed to thaw at room temperature and left to stir overnight. Water (2×100 mL) was used to wash the organic fraction, which was subsequently dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The dark green residue obtained was loaded on to a silica gel column (eluant: chloroform: methanol/ethyl acetate; 45:5:50 v/v) to yield an off-white solid (3.5 g, 62%). Recrystallisation from chloroform/petroleum spirit yielded off-white fluffy crystals: mp 103–104°C; ν_{max} (KBr) 3065 and 3031 (ring C–H), 2858 (aldehyde C–H), 1709 (aldehyde C=O), 1573 (ring C=C), 1251 and 1043 (C–O–C) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 5.12 (4H, s, 3-O*CH*$_2$Ph and 4-O*CH*$_2$Ph), 6.95 (1H, d, *J*=6.0 Hz, 5-*H*), 7.24 (5H, s, 3-OCH$_2$*Ph*), 7.34 (5H, s, 4-OCH$_2$*Ph*), 8.26 (1H, d, *J*=6.0 Hz, 6-*H*), 10.12 (1H, s, C*H*O); *m*/*z* (FAB) 320 [$(M+H)^+$]; HRMS (FAB): [$(M+H)^+$], found 320.1267. $C_{20}H_{18}O_3N$ requires 320.1287.

3.1.18. 2-Carboxy-3,4-dibenzyloxypyridine (14). 2-Formyl-3,4-dibenzyloxypyridine (11.6 g, 36.5 mmol) was dissolved in acetone (100 mL) and water (100 mL). To this solution was added sulfamic acid (5.0 g, 51.0 mmol, 1.4 equiv.) and sodium chlorite (80%, 4.5 g, 40.1 mmol, 1.1 equiv.) and stirred at room temperature for 3 h. in an open flask. Removal of acetone in vacuo yielded crude product as a precipitate in the remaining aqueous solution. This was collected, washed with acetone and dried to yield off-white powder (8.2 g, 77%): mp 120°C (dec.); ν_{max} (KBr) 3033 (br, O–H), 1707 (br, acid C═O), 1607 and 1499 (ring C═C), 1223 and 1026 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 4.91 (2H, s, 3-OCH_2Ph), 5.22 (2H, s, 4-OCH_2Ph), 7.16 (5H, s, 3-OCH$_2$*Ph*), 7.28 (5H, s, 4-OCH$_2$*Ph*), 6.80–7.60 (1H, buried d, 5-*H*), 7.60–8.00 (1H, br, COO*H*), 8.20 (1H, d, *J*=6.0 Hz, 6-*H*); *m/z* (FAB) 336 [(M+H)$^+$]; HRMS (FAB): [(M+H)$^+$], found 336.1232. $C_{20}H_{18}O_4N$ requires 336.1236.

3.1.19. *N*-(3,4-Dibenzyloxypyridine-2-carbonyl)-1,3-thiazolidine-2-thione (15). Dicyclohexylcarbodiimide (DCCI) (2.9 g, 14.2 mmol, 1.1 equiv.) was added into a solution of 2-carboxy-3,4-dibenzyloxypyridine (**14**) (4.3 g, 12.9 mmol) in dichloromethane (100 mL) followed by an addition of 2-mercaptothiazoline (1.7 g, 14.2 mmol, 1.1 equiv.) and a catalytic amount of dimethylaminopyridine (DMAP) (50 mg). The reaction mixture was stirred overnight at room temperature then placed in an ice bath for 1 h. The white precipitate of dicyclohexylurea (DCU) was filtered, discarded and the filtrate volume was increased to 200 mL with dichloromethane. The organic layer was washed with sodium hydroxide (0.1 M., 3×150 mL), water (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield a bright yellow oil.

3.1.20. 3,4-Dibenzyloxypyridine-2-carboxy-(*N*-phenyl)-amide hydrochloride. To a solution of 2-carboxy-3,4-dibenzyloxypyridine (**14**) (3 g, 9 mmol) in dichloromethane (100 mL), benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP®) (5.2 g, 10 mmol, 1.1 equiv.) was added, followed by the addition of triethylamine (2.5 mL, 17.9 mmol, 2 equiv.) and phenylamine (0.8 mL, 9 mmol, 1 equiv.), respectively. The reaction mixture was left to stir at room temperature overnight before it was washed with citric acid (5%, 100 mL), sodium bicarbonate (5%, 100 mL) and finally water (100 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Further purification on a silica gel column (eluant: methanol/chloroform; 10:90 v/v) furnished a white solid, which was taken into ethanol, adjusted to pH 1 with concentrated hydrochloric acid. The solvent was removed again in vacuo to give a white solid. Recrystallisation from chloroform/petroleum spirit afforded a white fluffy powder (1.5 g, 44%): mp 220°C (dec.); ν_{max} (KBr) 3015 (br, amide N–H), 1647 (amide C═O), 1599, 1541, 1497 and 1446 (ring C═C), 1244 and 1018 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 5.01 (2H, s, 3-OCH_2Ph), 5.33 (2H, s, 4-OCH_2Ph), 6.70–7.70 (17H, m, 3-OCH$_2$*Ph* and 4-OCH$_2$*Ph* and CONH*Ph* and 5-*H* and 6-*H*), 8.20–8.55 (1H, br, CON*H*Ph); *m/z* (FAB) 411 [(M−Cl)$^+$]; HRMS (FAB): [(M−Cl)$^+$], found 411.1690. $C_{26}H_{23}O_3N_2$ requires 411.1709.

3.2. General procedure for the preparation of 2-amido derivatives of 3,4-dibenzyloxypyridines

A solution of primary amine (2 equiv.) in either methanol or tetrahydrofuran or neat was added into a flask containing *N*-(3,4-dibenzyloxypyridine-2-carbonyl)-1,3-thiazolidine-2-thione (**15**) (as crude 1 equiv.). The reaction mixture was allowed to stir overnight at room temperature before the solvent was removed under reduced pressure. The residue was purified on a silica gel column (eluant: methanol/chloroform; 10:90 v/v) to obtain the product, which was taken up with ethanol and adjusted to pH 1 with concentrated hydrochloric acid. Recrystallisation from methanol/diethyl ether occurred when the solvent was removed in vacuo.

3.2.1. 3,4-Dibenzyloxypyridine-2-carboxyamide hydrochloride. Ammonia (1 M. in methanol) yielded a pinkish-white powder after recrystallisation (45% overall yield in two steps): mp 113–114°C; ν_{max} (KBr) 3463 and 3419 (1°amide N–H), 3061 and 3030 (ring C–H), 1687 (amide C═O), 1609, 1524 and 1499 (ring C═C), 1221 and 1046 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 5.00 (2H, s, 3-OCH_2Ph), 5.34 (2H, s, 4-OCH_2Ph), 7.15 (5H, s, 3-OCH$_2$*Ph*), 7.28 (5H, s, 4-OCH$_2$*Ph*), 7.60 (1H, d, *J*=6.0 Hz, 5-*H*), 7.85–8.25 (2H, br, CONH_2), 8.35 (1H, d, *J*=6.0 Hz, 6-*H*); *m/z* (FAB) 335 [(M−Cl)$^+$]; HRMS (FAB): [(M−Cl)$^+$], found 335.1370. $C_{20}H_{19}O_3N_2$ requires 335.1396.

3.2.2. 3,4-Dibenzyloxypyridine-2-carboxy-(*N*-methyl)-amide hydrochloride. Methylamine (1 M in tetrahydrofuran) yielded a pinkish-white fluffy powder after recrystallisation (48% overall yield in two steps): mp 164–166°C; ν_{max} (KBr) 3436 (amide N–H), 3031 (ring C–H), 1683 (amide C═O), 1571 (ring C═C), 1263 and 1026 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 2.83 (3H, d, *J*=5.4 Hz, CONH*Me*), 5.20 (2H, s, 3-OCH_2Ph), 5.47 (2H, s, 4-OCH_2Ph), 7.23 (5H, s, 3-OCH$_2$*Ph*), 7.38 (5H, s, 4-OCH$_2$*Ph*), 7.75 (1H, d, *J*=6.6 Hz, 5-*H*), 8.44 (1H, d, *J*=6.6 Hz, 6-*H*), 9.10 (1H, q, *J*=5.4 Hz, CON*H*Me); *m/z* (FAB) 349 [(M−Cl)$^+$]; HRMS (FAB): [(M−Cl)$^+$], found 349.1559. $C_{21}H_{21}O_3N_2$ requires 349.1552.

3.2.3. 3,4-Dibenzyloxypyridine-2-carboxy-(*N*-hydroxyethyl)-amide hydrochloride. Neat ethanolamine yielded a white fluffy powder after recrystallisation (44% overall yield in two steps): mp 127–129°C; ν_{max} (KBr) 3354 (amide N–H), 3281 (O–H intermolecular hydrogen bonding), 3065 (ring C–H), 1668 (amide C═O), 1603, 1547 and 1514 (ring C═C), 1217 and 1071 (C–O–C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 3.00–3.60 (4H, m, CONHCH_2CH_2OH), 4.97 (2H, s, 3-OCH_2Ph), 5.32 (2H, s, 4-OCH_2Ph), 6.50–7.00 (1H, br, CH$_2$CH$_2$O*H*), 7.14 (5H, s, 3-OCH$_2$*Ph*), 7.28 (5H, s, 4-OCH$_2$*Ph*), 7.56 (1H, d, *J*=6.0 Hz, 5-*H*), 8.35 (1H, d, *J*=6.0 Hz, 6-*H*), 8.48–8.90 (1H, br, CON*H*); *m/z* (FAB) 379 [(M−Cl)$^+$]; HRMS (FAB): [(M−Cl)$^+$], found 379.1660. $C_{22}H_{23}O_4N_2$ requires 379.1658.

3.3. General procedure for the preparation of 2-(1′-hydroxyalkyl) and 2-amido derivatives of 3-hydroxypyridin-4-ones

2-Amido or 2-(1′-hydroxyalkyl) derivatives of 3,4-dibenzyloxypyridines in either methanol or ethanol were subjected to hydrogenolysis in the presence of 5% Pd/C (10% w/w of the compound) as a catalyst for 3 h. The catalysts were removed by filtration and the filtrates acidified to pH 1 with concentrated hydrochloric acid. After the removal of solvents in vacuo, the residues were crystallised from methanol/ diethyl ether.

3.3.1. 2-Hydroxymethyl-3-hydroxypyridin-4(1*H*)-one hydrochloride (11a). 93% as a white powder, mp 170°C (dec.); [Found: C, 40.9; H, 4.7; N, 7.9. $C_6H_8ClNO_3$ requires C, 40.67; H, 4.55; N, 7.91%]; ν_{max} (KBr) 3356 (br, O–H, intermolecular hydrogen bonding), 3090 (br, O–H, intramolecular hydrogen bonding), 2952 (ring C–H), 1562 and 1500 (ring C=C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 4.53 (2H, s, CH_2OH), 4.70–6.10 (3H, br, O*H*), 7.24 (1H, d, *J*=6.6 Hz, 5-*H*), 7.93 (1H, d, *J*=6.6 Hz, 6-*H*); *m*/*z* (FAB) 142 $[(M-Cl)^+]$.

3.3.2. 2-(1′-Hydroxyethyl)-3-hydroxypyridin-4(1*H*)-one hydrochloride (11b). 94% as white needle crystals, mp 190°C (dec.); [Found: C, 43.9; H, 5.4; N, 7.2. $C_7H_{10}ClNO_3$ requires C, 43.88; H, 5.26; N, 7.31%]; ν_{max} (KBr) 3356 (O–H, intermolecular hydrogen bonding), 3080 (br, O–H, intramolecular hydrogen bonding), 2959 (ring C–H), 1565 and 1500 (ring C=C) cm^{-1}; δ_H (60 MHz, DMSO-d_6) 1.35 (3H, d, *J*=6.6 Hz, CH*Me*), 5.07 (1H, q, *J*=6.6 Hz, C*H*Me), 7.27 (1H, d, *J*=6.6 Hz, 5-*H*), 7.90 (1H, d, *J*=6.6 Hz, 6-*H*), 8.00–10.10 (3H, br, O*H*); *m*/*z* (FAB) 156 $[(M-Cl)^+]$.

3.3.3. 3-Hydroxypyridin-4(1*H*)-one-2-carboxyamide hydrochloride (16a). 91% as off-white crystals, mp 240°C (dec.); [Found: C, 34.5; H, 4.2; N, 13.2. $C_6H_7ClN_2O_3.H_2O$ requires C, 34.62; H, 4.33; N, 13.46%]; ν_{max} (KBr) 3406 and 3310 (1°amide N–H), 2920 (br, O–H), 1679 (amide C=O), 1587, 1543, 1507 and 1436 (ring C=C) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.50 (1H, d, *J*=6.3 Hz, 5-*H*), 8.13 (1H, d, *J*=6.3 Hz, 6-*H*), 8.27 (2H, s, O*H*), 8.61 (2H, s, CONH_2); *m*/*z* (FAB) 155 $[(M-Cl)^+]$; HRMS (FAB): $[(M-Cl)^+]$, found 155.0461. $C_6H_7O_3N_2$ requires 155.0457.

3.3.4. 3-Hydroxypyridin-4(1*H*)-one-2-carboxy-(*N*-methyl)-amide hydrochloride (16b). 88% as white powder, mp 236°C (dec.); [Found: C, 40.9; H, 4.6; N, 13.5. $C_7H_9ClN_2O_3$ requires C, 41.09; H, 4.43; N, 13.69%]; ν_{max} (KBr) 3074 (br, amide N–H), 2908 (br, O–H), 1655 (amide C=O), 1581, 1538 and 1501 (ring C=C) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.92 (3H, d, *J*=4.7 Hz, CONH*Me*), 5.60–6.30 (2H, br, O*H*), 7.49 (1H, d, *J*=6.3 Hz, 5-*H*), 8.11 (1H, d, *J*=6.3 Hz, 6-*H*), 8.82 (1H, q, *J*=4.7 Hz, CON*H*Me); *m*/*z* (FAB) 169 $[(M-Cl)^+]$.

3.3.5. 3-Hydroxypyridin-4(1*H*)-one-2-carboxy-(*N*-hydroxyethyl)-amide hydrochloride (16c). 87% as off-white powder, mp 201–203°C; [Found: C, 41.1; H, 4.5; N, 11.9. $C_8H_{11}ClN_2O_4$ requires C, 40.95; H, 4.73; N, 11.94%]; ν_{max} (KBr) 3425 (amide N–H), 3109 (br, O–H), 1671 (amide C=O), 1595, 1544 and 1498 (ring C=C) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.45–3.50 (2H, m, CONH$CH_2$$CH_2$OH), 3.56–3.59 (2H, m, CONH$CH_2$$CH_2$OH), 7.49 (1H, d, *J*=6.3 Hz, 5-*H*), 8.12 (1H, d, *J*=6.3 Hz, 6-*H*), 8.89 (1H, t, *J*=5.5 Hz, CON*H*CH_2CH_2OH)), 9.10–10.40 (3H, br, O*H*); *m*/*z* (FAB) 199 $[(M-Cl)^+]$.

3.3.6. 3-Hydroxypyridin-4(1*H*)-one-2-carboxy-(*N*-phenyl)-amide hydrochloride (16d). 90% as off-white crystals, mp 280°C (dec.); [Found: C, 54.2; H, 4.3; N, 10.6. $C_{12}H_{11}ClN_2O_3$ requires C, 54.13; H, 4.17; N, 10.53%]; ν_{max} (KBr) 3325 (O–H), 3119 (br, amide N–H), 1669 (amide C=O), 1598, 1560 and 1503 (ring C=C) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.80–6.70 (2H, br, O*H*), 7.16–7.74 (6H, m, CONH*Ph* and 5-*H*), 8.03 (1H, d, *J*=6.2 Hz, 6-*H*), 11.37 (1H, s, CON*H*Ph); *m*/*z* (FAB) 231 $[(M-Cl)^+]$; HRMS (FAB): $[(M-Cl)^+]$, found 231.0764. $C_{12}H_{11}O_3N_2$ requires 231.0770.

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