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4-Pyridone derivatives as new inhibitors of bacterial enoyl-ACP reductase FabI

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Abstract—Bacterial FAS provides essential fatty acids for use in the assembly of key cellular components. Among them, FabI is an enoyl-ACP reductase which catalyzes the final and rate-limiting step of bacterial FAS. It is a potential target for selective antibacterial action, because it shows low overall sequence homology with mammalian enzymes. Until today, various compounds have been reported as inhibitors of bacterial FabI-inhibitory compounds. To discover novel small-molecular FabI inhibitors, we initially screened our compound library for inhibitory activity toward FabI of *Escherichia coli*. And discovered 4-pyridone derivatives as a lead compound. Structure optimization studies yielded 4-pyridone derivatives **7n** having strong FabI-inhibitory and antibacterial activities against *Staphylococcus aureus*. There have been no reports concerning 4-pyridone derivatives as FabI inhibitor.

1. Introduction

The emergence of bacterial resistance to most of the antibacterials currently in clinical use represents a major medical challenge.[1] In particular, the spread of multiresistant Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA)[2] and penicillin-resistant *Streptococcus pneumoniae* (PRSP),[3] during the last two decades is of major concern in chemotherapy, and consequently research to discover antibacterial agents with novel mechanisms of action is very important. However, very few novel classes of broad-spectrum antibacterial agents have been marketed since the mid-1970s.[4] In this regard, bacterial fatty acid biosynthesis (FAS) is an attractive target.[5] Bacterial FAS provides essential fatty acids for use in the assembly of key cellular components, such as the cell envelope, phospholipids, lipoproteins, lipopolysaccharides, and mycolic acids. FabI is an enoyl-ACP reductase which catalyzes the final and rate-limiting step of bacterial FAS.[6] It is a potential target for selective antibacterial action, because it shows low overall sequence homology with mammalian enzymes.

Various compounds, including isoniazid,[7] diazaborines,[8] triclosan,[9] indole naphthyridinones,[10] and thiopyridine,[11] have been reported as inhibitors of bacterial enoyl-ACP reductase, and a FabI-targeting approach to antibacterial drug therapy appears feasible (Fig. 1). To discover novel small-molecular FabI inhibitors, we initially screened our compound library for inhibitory activity toward FabI of *Escherichia coli*. Among the hits, compound **1** having 4-pyridone as the basic structure was selected as a lead compound (Fig. 2).

Structure optimization studies yielded 4-pyridone derivatives with strong FabI-inhibitory activity. We also found that compound **7n** showed good antibacterial activity against *S. aureus*. In this report, we present our investigation of a series of 4-pyridone derivatives as novel FabI inhibitors with potent antibacterial activity against *S. aureus*.

2. Chemistry

4-Pyridone derivatives substituted at the 3-position were prepared as outlined in Schemes 1 and 2. The benzyl-type derivatives were synthesized by method A in Scheme 1. Commercially available 4-methoxypyridine was treated with alkyl magnesium bromide and carbobenzyloxy chloride in THF at −78 °C to afford compound **3**. The reaction of **3** with aldehyde was carried

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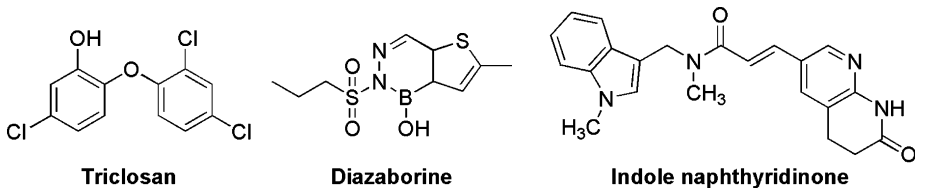


Figure 1. Structures of FabI inhibitors.

out in THF at −78 °C in the presence of a lithium hexamethyldisilazide and the corresponding aldol adduct **4** was obtained. The hydroxyl group of compound **4** was converted into the methanesulfonate **5** by treatment with methanesulfonyl chloride under ice cooling. Elimination of the methanesulfonyloxy group, followed by isomerization of the double bond with potassium *tert*-butoxide, yielded the desired 4(1*H*)-pyridone **6**. Alkylation of **6** with alkyl halide in the presence of sodium hydride afforded 1-alkyl 4-pyridone **7**.[12]

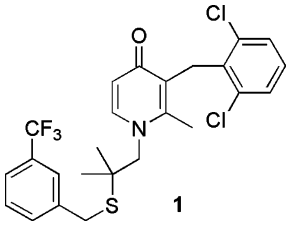
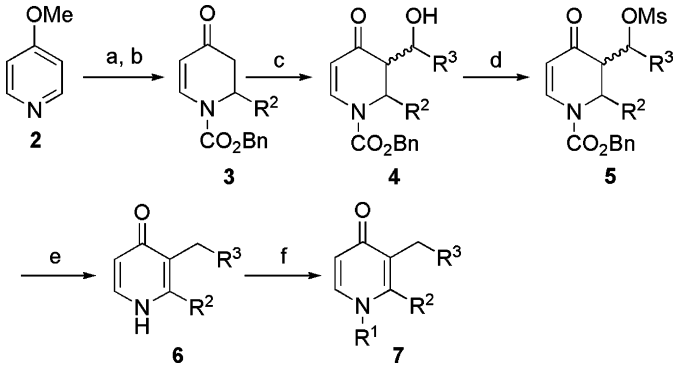
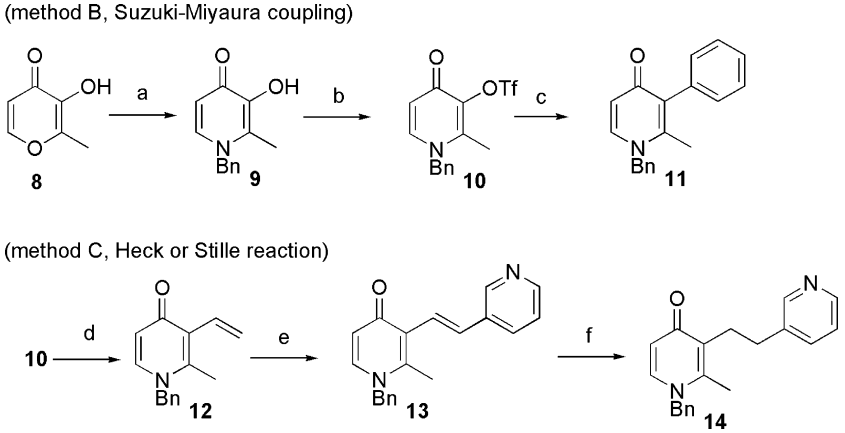


Figure 2. Our discovered FabI inhibitor.

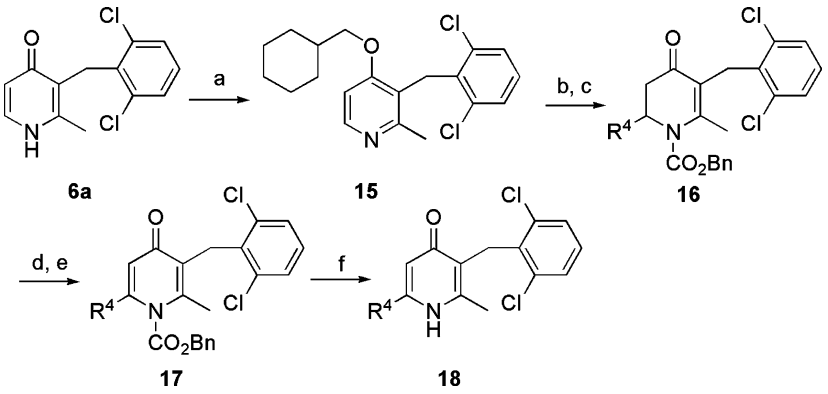
The biaryl-type derivative **11** was obtained starting from a commercially available natural product, maltol **8**, from which the triflate ester **10** was synthesized as a key intermediate. Compound **10** was coupled with phenylboronic acid (catalyzed by palladium) to give the desired biaryl-type product **11** (Scheme 2, method B). Compound **10** was coupled with tributylvinylstannane to give **12**. It was reacted with 3-bromopyridine in the



Scheme 1. Synthesis of compound **7** (method A). Reagents: (a) BnOCOCl, R^2MgBr, THF; (b) 3 N HCl; (c) R^3CHO, HMDSLi, THF; (d) MsCl, pyridine; (e) *t*-BuOK, THF (in the case of compound **7x** ($R^{3'}$ = *n*-Pr) and **7y** ($R^{3'}$ = cyclohexyl), DBU was used in stead of *t*-BuOK and then Pd/C, H_2, THF); (f) R^1X, NaH, THF.



Scheme 2. Synthesis of 4-pyridone derivatives. Reagents and conditions: (a) $BnNH_2$, $EtOH/H_2O$ (35%); (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, rt (74%); (c) phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 60 °C (20%); (d) tributylvinylstannane, $Pd(PPh_3)_4$, LiCl, 1,4-dioxane, reflux (61%); (e) 3-bromopyridine, $Pd_2(dba)_3$, *t*-Bu_3P, Cy_2NMe, 1,4-dioxane, reflux (32%); (f) Pd/C, H_2, CH_3OH, rt (51%).



Scheme 3. Synthesis of compound **19**. Reagents and conditions: (a) bromomethylcyclohexane, NaH, DMF; (b) BnOCOCl, R^4MgBr, THF; (c) 3 N HCl; (d) PhSeBr, HMDSLi, THF; (e) *m*-CPBA, CH_2Cl_2; (f) CH_3OH, reflux.

presence of palladium catalyst to give **13**. The double bond of compound **13** was reduced with palladium on activated carbon under a hydrogen atmosphere to give **14** (Scheme 2, method C).

The 4-pyridone derivatives substituted at the 6-position were prepared as outlined in Scheme 3. Alkylation of the pyridone **6a** with bromomethylcyclohexane in the presence of sodium hydride in DMF afforded the O-alkylated pyridine **15** as a major product. Addition of alkylmagnesium bromide to the 6-position of compound **15** in the presence of carbobenzoxy chloride afforded compound **16**. The dehydrogenation of **16** to **17** by introduction of a phenylselenyl group, followed by oxidation to a selenoxide with *m*-CPBA and eventual *syn*-elimination, proceeded well. Deprotection of the carbobenzoxy group gave the corresponding 4(1*H*)-pyridone **18**.

3. Biological methods

3.1. Preparation of His-tagged FabI

The *fabI* gene from *E. coli* DH5α was amplified by PCR and cloned into pBAD/Myc-His B vector (Invitrogen). The resulting plasmid was transformed into *E. coli* TOP10. The expression of FabI protein fused with a His-tag was induced with 0.2% arabinose. The cell pellets were resuspended in lysis buffer (5 mM Tris–HCl, pH 8.0, 0.3 M NaCl, containing 1 mg/ml of lysozyme) and lysed by sonication. Cell lysates were applied to a Ni–NTA agarose column (QIAGEN) and eluted with 250 mM imidazole. The solvent was exchanged to 20 mM Tris–HCl, pH 7.5, 10 mM EDTA, pH 8.0, 1 mM DTT by dialysis and the purified protein was stored at −80 °C until use.

3.2. Assay of FabI-inhibitory activity

Enzyme inhibition assays were carried out in half-area, 96-well microtiter plates. Compounds were evaluated in 100 μL assay mixtures containing 100 mM sodium phosphate (pH 7.4), 0.25 mM crotonoyl-CoA, 0.4 mM NADH, and 50 μg/mL of His-tagged *E. coli* FabI, prepared as described above. The consumption of NADH was monitored at room temperature for 10 min by following the change in absorbance at 340 nm. The concentration giving 50% reduction of the absorption was determined as the IC_{50}.

3.3. Antibacterial activity assay

Antibacterial activity was determined by the agar dilution method in Mueller–Hinton agar supplemented with 5% horse blood. *S. aureus* ATCC29213 was used as a test strain. Approximately 10^4 CFU per spot was inoculated onto agar plates containing twofold serial dilutions of compounds. After incubation at 35 °C for 20 h, the minimum inhibitory concentration (MIC) was determined as the lowest concentration of the test compound that prevented visible growth.

4. Results and discussion

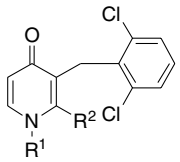
The synthesized compounds were evaluated for the FabI-inhibitory and antibacterial activities against *S. aureus*.

SAR of 1,2-substituted-3-(2,6-dichloro)benzyl-4-pyridone is shown in Table 1.

Lead compound **1** exhibited weak FabI-inhibitory activity of *E. coli* (IC_{50} = 1.9 μM). The compound **6a** (R^1 = H) showed significantly decreased both activities. These results indicate that some kind of functional group is essential to 1-position. Compound **7a**–**7c** having an alkyl group at 1-position showed good FabI-inhibitory activity compared with **6a**. In particular, compound **7b** (R^1 = *n*-Bu) exhibited a potent antibacterial activity. We speculate that the substituent R^1 may be directed toward the surface of the FabI enzyme in the binding mode. Therefore, compound **7c** having a long alkyl chain seems to be tolerant for FabI-inhibitory activity. However compound **7e** having a carboxyl group at the end of alkyl chain exhibited weak FabI-inhibitory activity.

Introduction of benzyl group into 1-position (**7g**) afforded good FabI-inhibitory and antibacterial activities. But introduction of various functional groups into the

Table 1. Antibacterial activities of FabI inhibitors: effect of variation of R^1 and R^2



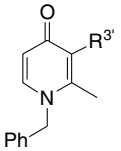
Compound[a]	R^1	R^2	IC_{50} (μM) for *Escherichia coli* FabI	MIC (μg/mL) for *Staphylococcus aureus* [b]
1	3-CF_3–$PhCH_2SC(CH_3)_2CH_2$	CH_3	1.9	64
6a	H	CH_3	120	>64
7a	CH_3	CH_3	11	>128
7b	*n*-Bu	CH_3	0.31	2
7c	$CH_3(CH_2)_9$	CH_3	0.22	32
7d	$HO(CH_2)_5$	CH_3	1.8	8
7e	$HO_2C(CH_2)_4$	CH_3	110	NT[c]
7f	Furan-2-yl-CH_2	CH_3	0.47	2
7g	$PhCH_2$	CH_3	0.30	0.5
7h	4-NO_2–$PhCH_2$	CH_3	1.8	16
7i	4-CO_2CH_3–$PhCH_2$	CH_3	0.30	>128
7j	4-CO_2H–$PhCH_2$	CH_3	22	>128
7k	4-NH_2–$PhCH_2$	CH_3	0.29	1
7l	4-$CONH_2$–$PhCH_2$	CH_3	2.5	32
7m	2,6-Dichloro-$PhCH_2$	CH_3	8.4	32
7n	Cyclohexyl-CH_2	CH_3	0.22	0.25
7o	$PhCH_2$	CH_3CH_2	0.78	8
7p	$PhCH_2$	$CH_3(CH_2)_3$	4.5	32
Triclosan			0.51	0.125

[a] Prepared by method A.
[b] *Staphylococcus aureus* ATCC29213.
[c] NT, not tested.

phenyl group (**7h**–**7m**) did not improve both activities. Replacement of benzyl group with cyclohexylmethyl group at 1-position (**7n**) improved FabI-inhibitory (0.22 μM) and antibacterial activities (0.25 μg/mL).

We examined the effect of the R^2 side chain (compounds **7o** and **7p**), but the FabI-inhibitory and antibacterial activities were not improved. Therefore, we chose the methyl group as the preferred R^2 substituent.

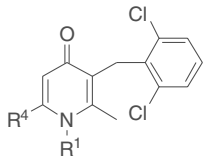
Table 2. Antibacterial activities of FabI inhibitors: effect of variation of $R^{3'}$



Compound	Method[a]	$R^{3'}$	IC_{50} (μM) for *Escherichia coli* FabI	MIC (μg/mL) for *Staphylococcus aureus*[b]
7q	A	$PhCH_2$	20	64
7r	A	2-Chloro-$PhCH_2$	4.2	64
7g	A	2,6-Dichloro-$PhCH_2$	0.30	0.5
7s	A	2,4-Dichloro-$PhCH_2$	2.0	32
7t	A	2,4,6-Trichloro-$PhCH_2$	1.5	8
7u	A	2-Chloro-6-fluoro-$PhCH_2$	0.39	2
7v	A	2,6-Difluoro-$PhCH_2$	2.7	4
7w	A	2,6-Dimethyl-$PhCH_2$	4.3	16
11	B	Ph	2.9	NT[c]
13	C	(*E*)-2-(Pyridin-2-yl)vinyl	>100	NT[c]
14	C	2-(Pyridin-2-yl)Et	>100	NT[c]
12	C	Vinyl	>100	NT[c]
7x	A	*n*-Bu	61	>128
7y	A	Cyclohexyl-CH_2	0.40	32

[a] Method of synthesis.
[b] *Staphylococcus aureus* ATCC29213.
[c] NT, not tested.

Table 3. Antibacterial activities of FabI inhibitors: effect of variation of R^4



Compound	R^1	R^4	IC_{50} (μM) for *Escherichia coli* FabI	MIC (μg/mL) for *Staphylococcus aureus*[a]
6a	H	H	120	>64
18a	CO_2CH_2Ph	*n*-Bu	0.38	8
18b	CO_2CH_2Ph	Cyclohexyl-CH_2	0.29	2

[a] *Staphylococcus aureus* ATCC29213.

SAR of 1-benzyl-2-methyl-3-subsutituted-4-pyridone is shown in Table 2. Compound **7q** having a non-substituted benzyl group as $R^{3'}$ showed drastically reduced FabI-inhibitory and antibacterial activities compared with **7g** ($R^{3'}$ = 2,6-dichlorobenzyl). Compounds **7r**–**7w** possessing various subsutituted benzyl group at 3-position showed reduced both activities compared with **7g**.

Compound **11** having a phenyl group as $R^{3'}$ showed moderate FabI-inhibitory activity. Replacement of benzyl group with cyclohexylmethyl group at 3-position (**7y**) improved FabI-inhibitory activity. However, compounds **13** ($R^{3'}$ = (*E*)-2-(pyridine-2-yl)vinyl) and **12** ($R^{3'}$ = vinyl) did not show FabI-inhibitory activity.

From these results, we concluded that the 2,6-dichlorobenzyl moiety was favorable for both FabI-inhibitory and antibacterial activities. We presumed that R^3 should be a lipophilic substituent which would conform to the substrate-binding site of FabI.

The effects of the 6-position derivatives on the FabI-inhibitory and antibacterial activities were examined (Table 3). Introduction of the substituent into 6-position (**18a**, **18b**) strengthened FabI-inhibitory activity and antibacterial activity compared with **6a**. Therefore, we presume that the substituents at 6-position act an important role for FabI-inhibitory activity and antibacterial activity similar to 1-substituents.

5. Conclusion

We discovered the 4-pyridone derivative **7n** as a novel inhibitor of bacterial enoyl-ACP reductase (FabI). Compound **7n** exhibited both strong FabI-inhibitory activity and good antibacterial activity. The present results support the idea that FabI is a valid antibacterial target, and that small-molecular FabI inhibitors are candidate drugs for the treatment of bacterial infections, and further suggest that the 4-pyridone structure represents a good lead structure. Further structural development studies are in progress.

6. Experimental

6.1. Chemistry

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were measured with a JASCO FT/IR-410 spectrometer. ^{1}H NMR (400 MHz) spectra were recorded on a JEOL lambda400 spectrometer. Chemical shifts were reported in δ value (ppm) with tetramethylsilane (TMS) as the internal standard (NMR peak designations: s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet; and br, broad peak). Mass spectra were recorded with a JEOL JMS-700 spectrometer. High-resolution mass spectra (HRMS) were obtained on a JMS-FABmate spectrometer. Column chromatography was performed with silicagel (Kanto Chemical: 60N spherical, neutral). All the reagents and solvents were from commercial suppliers and were used without further purification.

6.1.1. 1-Benzyloxycarbonyl-2,3-dihydro-2-methyl-4-pyridone (3a).[13]. To a solution of methylmagnesium bromide (178 mmol) and 4-methoxypyridine (16.1 g, 148 mmol) in THF (300 ml) at −25 °C was added benzyl chloroformate over a period of 30 min. The resulting mixture was stirred at −25 °C for 4 h and then poured into 3 N HCl (300 ml). After stirring for 10 min at room temperature, the mixture was extracted with ethyl acetate twice and the combined organic extract was washed with 5% $NaHCO_3$ aq, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [hexane/AcOEt (3:1)] to afford **3a** (34.1 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 6.8 Hz), 2.31 (1H, d, J = 16.6 Hz), 2.85 (1H, dd, J = 16.6, 6.8 Hz), 4.73 (1H, br), 5.22–5.40 (3H, m), 7.28–7.45 (5H, m), 7.74 (1H, d, J = 8.0 Hz); MS (FAB$^+$) *m*/*z* 246 (M+H)$^+$.

6.1.2. 1-Benzyloxycarbonyl-2,3-dihydro-2-ethyl-4-pyridone (3b). Yield (1.04 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.5 Hz), 1.59–1.77 (2H, m), 2.47 (1H, *d*, J = 16.8 Hz), 2.80 (1H, dd, J = 16.8, 6.6 Hz), 4.52 (1H, br), 5.27 (2H, s), 5.31 (1H, br), 7.28–7.45 (5H, m), 7.78 (1H, br); MS (FAB$^+$) *m*/*z* 260 (M+H)$^+$.

6.1.3. 1-Benzyloxycarbonyl-2-butyl-2,3-dihydro-4-pyridone (3c). Yield (5.57 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, br), 1.10–1.45 (4H, br), 1.55–1.74 (2H, m), 2.45 (1H, d, J = 16.6 Hz), 2.80 (1H, dd, J = 16.6, 6.6 Hz), 4.58 (1H, br), 5.21–5.40 (3H, m), 7.28–7.40 (5H, m), 7.76 (1H, br); MS (FAB$^+$) m/z 288 (M+H)$^+$.

6.1.4. 1-Benzyloxycarbonyl-3-[(2,6-dichlorophenyl)(hydroxy)-methyl]-2,3-dihydro-2-methyl-4-pyridone (4a). To a solution of **3a** (5.0 g, 20.4 mmol) in THF (60 ml) at −78 °C was added 1 M lithium bis(trimethylsilyl)amide in THF (22.4 ml). The resulting mixture was stirred at 0 °C for 30 min and cooled to −78 °C. To this solution was added 2,6-dichlorobenzaldehyde (4.64 g, 26.5 mmol). The resulting solution was stirred at −78 °C for 1 h, then poured into saturated NH_4Cl aq (200 ml). The mixture was extracted with ethyl acetate twice and the combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [hexane/AcOEt (3:1)] to afford **4a** (8.4 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 6.8 Hz), 3.12 (1H, d, J = 9.0 Hz), 3.17–3.30 (1H, br), 3.90–4.15 (1H, br), 5.10–5.63 (4H, m), 7.05–7.50 (8H, br), 7.70–8.00 (1H, br); MS (FAB$^+$) m/z 420 (M+H)$^+$.

6.1.5. 1-Benzyloxycarbonyl-3-[(2,6-dichlorophenyl)(methylsulfonyloxy)methyl]-2,3-dihydro-2-methyl-4-pyridone (5a). To a solution of **4a** (1.61 g, 3.83 mmol) in pyridine (10 ml) at 0 °C was added mesyl chloride (0.445 ml, 5.75 mmol). The resulting mixture was stirred at room temperature for 3 h, then poured into water (150 ml). The mixture was extracted with ethyl acetate (150 ml) and the organic extract was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [hexane/AcOEt (3:1)] to afford **5a** (1.79 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, J = 6.8 Hz), 2.89 (3H, s), 3.40–3.61 (1H, br), 3.91–4.15 (1H, br), 5.02–5.59 (3H, m), 6.40 (1H, d, J = 10.7 Hz), 7.05–7.52 (8H, br), 7.80–8.05 (1H, br); MS (FAB$^+$) m/z 498 (M+H)$^+$.

6.1.6. 3-(2,6-Dichlorobenzyl)-2-methyl-4-pyridone (6a). To a solution of **a** (1.00 g, 2.01 mmol) in THF (35 ml) was added potassium *tert*-butoxide (1.13 g 10.0 mmol). The resulting solution was stirred at room temperature for 10 min, then poured into 5% NH_4Cl aq (100 ml). The mixture was extracted with chloroform/*i*-propanol (5:1, 100 ml) twice and the combined organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (9:1)] to afford **6a** (469 mg, 87%). IR (KBr) 3333, 1624, 1503, 1159, 842, 768, 543 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (3H, s), 4.24 (2H, s), 6.23 (1H, d, J = 7.1 Hz), 7.05 (1H, t, J = 8.1 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.26 (1H, br). ^{13}C NMR (100 MHz, CD_3OD) δ 17.5, 28.0, 115.3, 126.4, 129.3, 129.7, 137.2, 137.57, 137.63, 147.2, 180.4; HRMS (FAB$^+$) m/z: calcd for $C_{13}H_{12}Cl_2NO$ (M+H)$^+$: 268.0296, found: 268.0294.

The following compounds (**6b–6k**) were prepared from **3a** or **3b** or **3c** and appropriate aldehydes by a similar procedure to that described for **4a**, **5a**, and **6a**.

6.1.7. 3-Benzyl-2-methyl-4-pyridone (6b). Yield (110 mg, 27%, 3 steps). IR (KBr) 3331, 1623, 1498, 1168, 841, 724, 549 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (3H, s), 3.91 (2H, s), 6.27 (1H, d, J = 7.1 Hz), 7.06–7.22 (6H, m), 12.4 (1H, br). ^{13}C NMR (100 MHz, CD_3OD) δ 17.5, 31.1, 115.9, 127.0, 128.3, 129.2, 129.4, 137.7, 141.3, 148.3, 180.6; HRMS (FAB$^+$) m/z: calcd for $C_{13}H_{14}NO$ (M+H)$^+$: 200.1075, found: 200.1074.

6.1.8. 3-(2-Chlorobenzyl)-2-methyl-4-pyridone (6c). Yield (185 mg, 37%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (3H, s), 3.92 (2H, s), 6.30 (1H, d, J = 7.1 Hz), 6.80 (2H, dd, J = 5.6, 4.1 Hz), 7.01–7.09 (2H, m), 7.23 (1H, d, J = 7.1 Hz), 7.26–7.29 (1H, m); MS (FAB$^+$) m/z 234 (M+H)$^+$.

6.1.9. 3-(2,4-Dichlorobenzyl)-2-methyl-4-pyridone (6d). Yield (224 mg, 17%, 3 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 2.22 (3H, s), 3.96 (2H, s), 6.43 (1H, d, J = 7.3 Hz), 6.85 (1H, d, J = 8.5 Hz), 7.16 (1H, dd, J = 8.5, 2.2 Hz), 7.67 (1H, d, J = 7.3 Hz); MS (FAB$^+$) m/z 268 (M+H)$^+$.

6.1.10. 2-Methyl-3-(2,4,6-trichlorobenzyl)-4-pyridone (6e). Yield (684 mg, 57%, 3 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (3H, s), 4.07 (2H, s), 6.01 (1H, d, J = 7.1 Hz), 7.39–7.56 (3H, m); MS (FAB$^+$) m/z 302 (M+H)$^+$.

6.1.11. 3-(2-Chloro-6-fluorobenzyl)-2-methyl-4-pyridone (6f). Yield (131 mg, 19%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (3H, s), 4.06 (2H, s), 6.23 (1H, d, J = 7.1 Hz), 6.79–6.87 (1H, m), 6.99–7.11 (1H, m), 7.30 (1H, d, J = 7.1 Hz); MS (FAB$^+$) m/z 252 (M+H)$^+$.

6.1.12. 3-(2,6-Difluorobenzyl)-2-methyl-4-pyridone (6g). Yield (240 mg, 9%, 3 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 2.30 (3H, s), 3.95 (2H, s), 6.34 (1H, d, J = 7.1 Hz), 6.81–6.91 (2H, m), 7.15–7.24 (1H, m), 7.57 (1H, d, J = 7.1 Hz); MS (FAB$^+$) m/z 236 (M+H)$^+$.

6.1.13. 3-(2,6-Dimethylbenzyl)-2-methyl-4-pyridone (6h). Yield (171 mg, 37%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (3H, s), 2.20 (6H, s), 4.00 (2H, s), 6.28 (1H, d, J = 7.1 Hz), 6.88–7.00 (3H, m), 7.37 (1H, d, J = 7.1 Hz); MS (FAB$^+$) m/z 228 (M+H)$^+$.

6.1.14. 3-(2,6-Dichlorobenzyl)-2-ethyl-4-pyridone (6i). Yield (61.1 mg, 23%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, t, J = 7.6 Hz), 2.49 (2H, q, J = 7.6 Hz), 4.30 (2H, s), 6.33 (1H, d, J = 7.1 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.33 (2H, d, J = 7.8 Hz), 7.59 (1H, d, J = 7.1 Hz); MS (FAB$^+$) m/z 282 (M+H)$^+$.

6.1.15. 2-Butyl-3-(2,6-dichlorobenzyl)-4-pyridone (6j). Yield (92 mg, 50%, 3 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 0.76 (3H, t, J = 7.1 Hz), 1.03–1.39 (4H, m), 2.53 (2H, br), 4.29 (2H, s), 6.27 (1H, d, J = 7.1 Hz),

7.05 (1H, t, J = 7.8 Hz), 7.21–7.26 (2H, m), 7.45 (1H, d, J = 7.1 Hz); MS (FAB^+) m/z 310 $(M+H)^+$.

6.1.16. 3-Butyl-2-methyl-4-pyridone (6k). To a solution of 1-benzyloxycarbonyl-3-[1-(methylsulfonyloxy)butyl]-2,3-dihydro-2-methyl-4-pyridone (prepared in the same manner as **4a** and **5a** (112 mg, 0.354 mmol) in THF (2 ml) was added DBU (0.079 ml, 0.531 mmol)). The resulting solution was stirred at room temperature overnight, then diluted with ethyl acetate and washed with 5% $NaHCO_3$ aq and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [hexane/AcOEt (4:1)] to afford1-benzyloxycarbonyl-3-butylidene-2,3-dihidro-2-methyl-4-pyridone (90 mg, 85%, E: Z = 2:8). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–1.00 (3H, m), 122–1.36 (3H, m), 1.37–1.57 (4H, m), 2.02–2.28 (1.6H, br), 4.78–5.06 (0.2H, br), 5.20–5.65 (3.8H, br), 5.78–5.95 (0.2H, br), 6.69 (0.8H, t, J = 6.7 Hz), 7.32–7.45 (5H, br), 7.50–7.80 (1H, br); HRMS (FAB+) m/z: calcd for $C_{18}H_{22}NO_3$ (M+H)+: 300.1600, found: 300.1596.

To a solution of afford1-benzyloxycarbonyl-3-butylidene-2,3-dihidro-2-methyl-4-pyridone(64 mg, 0.214 mmol) in methanol (1 ml) was added 10% Pd/C (15 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 10 min, filtered through Celite, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (9:1)] to afford **6l** (33 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.1 Hz), 1.28–1.50 (4H, m), 2.39 (3H, s), 2.53 (2H, t, J = 7.8 Hz), 6.28 (1H, d, J = 6.8 Hz), 7.43 (1H, d, J = 6.8 Hz), 13.1 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.2, 23.0, 25.3, 30.8, 114.3, 128.5, 136.0, 145.5, 178.6; HRMS (FAB^+) m/z: calcd for $C_{10}H_{16}NO$ $(M+H)^+$: 166.1232, found: 166.1236.

6.1.17. 3-Cyclohexylmethyl-2-methyl-4-pyridone (6l). The title compound was prepared from **3a** by means of a similar procedure to that described for **6k**, (59 mg, 57%, 4 steps). ^1H NMR (400 MHz, $CDCl_3$) δ 0.85–1.01 (2H, br), 1.05–1.20 (3H, br), 1.45–1.68 (6H, br), 2.25 (3H, s), 2.32 (2H, d, J = 7.1 Hz), 6.23 (1H, d, J = 7.1 Hz), 7.46 (1H, d, J = 7.1 Hz); MS (FAB^+) m/z 206 $(M+H)^+$.

6.1.18. 1-Benzyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (7g). To a solution of **6a** (100 mg, 0.373 mmol) in THF (3 ml) were added sodium hydride (19.4 mg, 0.485 mmol as a 60% dispersion in mineral oil) and benzyl bromide (0.0577 ml, 0.485 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with ethyl acetate and washed with 5% NaCl aq. The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (20:1)] to afford **7g** (123 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (3H, s), 4.36 (2H, s), 5.01 (2H, s), 6.38 (1H, d, J = 7.6 Hz), 6.96–7.06 (3H, m), 7.21–7.39 (6H, m); HRMS (FAB^+) m/z: calcd for $C_{20}H_{18}Cl_2NO$ $(M+H)^+$: 358.0765, found: 358.0775.

The following compounds (**7a**–**7d**, **7f**–**7j**, **7m**–**7w**, and **7x**–**7y**) were similarly obtained.

6.1.19. 3-(2,6-Dichlorobenzyl)-1,2-dimethyl-4-pyridone (7a). Yield (45 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (3H, s), 3.53 (3H, s), 4.37 (2H, s), 6.30 (1H, d, J = 7.6 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.21 (1H, d, J = 7.6 Hz), 7.25 (2H, d, J = 8.0 Hz); MS (FAB^+) m/z 282 $(M+H)^+$.

6.1.20. 1-Butyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (7b). Yield (49 mg, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.6 Hz), 1.34 (2H, tq, J = 7.6 Hz), 1.58–1.74 (2H, m), 2.09 (3H, s), 3.74 (2H, t, J = 7.6 Hz), 4.36 (2H, s), 6.31 (1H, d, J = 7.6 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.21 (1H, d, J = 7.6 Hz), 7.25 (2H, d, J = 8.0 Hz); MS (FAB^+) m/z 324 $(M+H)^+$.

6.1.21. 1-Decyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (7c). Yield (49 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.25 (14H, br), 1.68 (2H, br), 2.08 (3H, s), 3.73 (2H, t, J = 7.6 Hz), 4.37 (2H, s), 6.31 (1H, d, J = 7.6 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.21 (2H, d, J = 7.6 Hz), 7.26 (2H, d, J = 8.0 Hz); MS (FAB^+) m/z 408 $(M+H)^+$.

6.1.22. 3-(2,6-Dichlorobenzyl)-1-(5-hydroxypentyl)-2-methyl-4-pyridone (7d). Yield (89 mg, 21%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.35–1.47 (2H, m), 1.50–1.81 (4H, m), 2.10 (3H, s), 3.65 (2H, t, J = 6.2 Hz), 3.77 (2H, t, J = 7.5 Hz), 4.35 (2H, s), 6.31 (1H, d, J = 7.3 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.20–7.26 (2H, m); MS (FAB^+) m/z 354 $(M+H)^+$.

6.1.23. 3-(2,6-Dichlorobenzyl)-1-furfuryl-2-methyl-4-pyridone (7f). Yield (61 mg, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s), 4.35 (2H, s), 4.90 (2H, s), 6.15–6.21 (1H, m), 6.29–6.39 (2H, m), 7.05 (1H, t, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.31 (1H, d, J = 7.6 Hz), 7.37–7.43 (1H, m); HRMS (FAB^+) m/z: calcd for $C_{18}H_{16}Cl_2NO_2$ $(M+H)^+$: 348.0558, found: 348.0561.

6.1.24. 3-(2,6-Dichlorobenzyl)-1-(4-nitrobenzyl)-2-methyl-4- pyridone (7h). Yield (16 mg, 86%). ^1H NMR (400 MHz, CD_3OD) δ 1.96 (3H, s), 4.37 (2H, s), 5.11 (2H, s), 6.41 (1H, d, J = 7.6 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.16 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.30 (1H, d, J = 7.6 Hz), 8.23 (2H, d, J = 8.8 Hz); MS (FAB^+) m/z 403 $(M+H)^+$.

6.1.25. Methyl 4-[3-(2,6-dichlorobenzyl)-2-methyl-4-pyridon-1-yl]methylbenzoate (7i). Yield (294 mg, 40%). ^1H NMR (400 MHz, CD_3OD) δ 2.29 (3H, s), 3.90 (3H, s), 4.43 (2H, s), 5.61 (2H, s), 6.88 (1H, d, J = 7.2 Hz), 7.15–7.22 (3H, m), 7.34 (2H, d, J = 7.8 Hz), 8.03 (2H, d, J = 7.8 Hz), 8.30 (1H, d, J = 7.2 Hz); MS (FAB^+) m/z 416 $(M+H)^+$.

6.1.26. 1,3-Bis(2,6-dichlorobenzyl)-2-methyl-4-pyridone (7m). Yield (57 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 4.41 (2H, s), 5.20 (2H, s), 6.22 (1H, d, J = 7.8 Hz), 6.86 (1H, d, J = 7.8 Hz),

7.06 (1H, t, J = 8.3 Hz), 7.24–7.29 (2H, br), 7.30–7.47 (1H, m), 7.42 (2H, d, J = 8.3 Hz); MS (FAB^+) m/z 426 $(M+H)^+$.

6.1.27. 1-Cyclohexylmethyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (7n). Yield (30 mg, 44%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.85–1.00 (2H, m), 1.08–1.28 (3H, m), 1.50–1.82 (6H, m), 2.08 (3H, s), 3.58 (2H, d, J = 7.1 Hz), 4.37 (2H, s), 6.29 (1H, d, J = 7.6 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.16 (1H, d, J = 7.6 Hz), 7.25 (2H, d, J = 8.0 Hz); HRMS (FAB^+) m/z: calcd for $C_{20}H_{24}Cl_2NO$ $(M+H)^+$: 364.1235, found: 364.1230.

6.1.28. 1-Benzyl-3-(2,6-dichlorobenzyl)-2-ethyl-4-pyridone (7o). Yield (13 mg, 49%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.6 Hz), 2.48 (2H, q, J = 7.6 Hz), 4.39 (2H, s), 5.02 (2H, s), 6.37 (1H, d, J = 7.5 Hz), 6.97 (2H, d, J = 7.1 Hz), 7.03 (1H, t, J = 8.0 Hz), 7.24–7.38 (6H, m); MS (FAB^+) m/z 372 $(M+H)^+$.

6.1.29. 1-Benzyl-2-butyl-3-(2,6-dichlorobenzyl)-4-pyridone (7p). Yield (21 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H, t, J = 7.3 Hz), 0.96–1.22 (4H, m), 2.40 (2H, br), 4.39 (2H, s), 4.99 (2H, s), 6.36 (1H, d, J = 7.5 Hz), 6.98 (2H, d, J = 7.1 Hz), 7.05 (1H, t, J = 7.8 Hz), 7.24–7.45 (6H, m); MS (FAB^+) m/z 400 $(M+H)^+$.

6.1.30. 1,3-Dibenzyl-2-methyl-4-pyridone (7q). Yield (58 mg, 50%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s), 4.03 (2H, s), 5.03 (2H, s), 6.48 (1H, d, J = 7.3 Hz), 7.02 (2H, d, J = 6.8 Hz), 7.10–7.16 (1H, m), 7.18–7.23 (4H, m), 7.32–7.41 (4H, m); MS (FAB^+) m/z 290 $(M+H)^+$.

6.1.31. 1-Benzyl-3-(2-chlorobenzyl)-2-methyl-4-pyridone (7r). Yield (20 mg, 33%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.95 (2H, s), 5.09 (2H, s), 6.49 (1H, d, J = 7.5 Hz), 6.90–6.17 (5H, m), 7.27–7.95 (5H, m); MS (FAB^+) m/z 324 $(M+H)^+$.

6.1.32. 1-Benzyl-3-(2,4-dichlorobenzyl)-2-methyl-4-pyridone (7s). Yield (39 mg, 45%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 4.06 (2H, s), 5.06 (2H, s), 6.49 (1H, d, J = 7.6 Hz), 6.94 (1H, d, J = 8.3 Hz), 7.02 (2H, d, J = 6.8 Hz), 7.06 (1H, dd, J = 8.3, 2.2 Hz), 7.31–7.43 (5H, m); MS (FAB^+) m/z 358 $(M+H)^+$.

6.1.33. 1-Benzyl-2-methyl-3-(2,4,6-trichlorobenzyl)-4-pyridone (7t). Yield (50 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (3H, s), 4.38 (2H, s), 5.03 (2H, s), 6.38 (1H, d, J = 7.6 Hz), 6.98 (2H, d, J = 7.3 Hz), 7.17–7.25 (2H, m), 7.29–7.41 (4H, m); MS (FAB^+) m/z 392 $(M+H)^+$.

6.1.34. 1-Benzyl-3-(2-chloro-6-fluorobenzyl)-2-methyl-4-pyridone (7u). Yield (103 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (3H, s), 4.20 (2H, s), 5.02 (2H,s), 6.40 (1H, d, J = 7.3 Hz), 6.84–6.92 (1H, m), 6.99 (2H, d, J = 6.8 Hz), 7.02–7.14 (2H, m), 7.28–7.39 (4H, m); HRMS (FAB^+) m/z: calcd for $C_{20}H_{18}ClFNO$ $(M+H)^+$: 342.1061, found: 362.1067.

6.1.35. 1-Benzyl-3-(2,6-difluorobenzyl)-2-methyl-4-pyridone (7v). Yield (37 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, s), 2.50 (2H, s), 5.02 (2H, s), 6.40 (1H, d, J = 7.6 Hz), 6.74–6.82 (2H, m), 6.97–7.02 (2H, m), 7.04–7.13 (1H, m), 7.28–7.39 (4H, m); HRMS (FAB^+) m/z: calcd for $C_{20}H_{18}F_2NO$ $(M+H)^+$: 326.1356, found: 326.1362.

6.1.36. 1-Benzyl-3-(2,6-dimethylbenzyl)-2-methyl-4-pyridone (7w). Yield (35 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, s), 2.23 (6H, s), 4.14 (2H, s), 4.97 (2H, s), 6.44 (1H, d, J = 7.3 Hz), 6.89–7.02 (5H, m), 7.28–7.48 (4H, m); MS (FAB^+) m/z 318 $(M+H)^+$.

6.1.37. 1-Benzyl-3-butyl-2-methyl-4-pyridone (7x). Yield (5.0 mg, 44%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.1 Hz), 1.24 (4H, br), 2.22 (3H, s), 2.59 (2H, t, J = 7.3 Hz), 5.05 (2H, s), 6.37 (1H, d, J = 7.6 Hz), 7.02 (2H, d, J = 7.6 Hz), 7.26–7.43 (4H, m); MS (FAB^+) m/z 256 $(M+H)^+$.

6.1.38. 3-Cyclohexylmethyl-1-benzyl-2-methyl-4-pyridone (7y). Yield (13.5 mg, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.95–1.25 (5H, m), 1.45–1.78 (6H, m), 2.21 (3H, s), 2.49 (2H, d, J = 7.3 Hz), 5.05 (2H, s), 6.36 (1H, d, J = 7.5 Hz), 7.01 (2H, d, J = 7.1 Hz), 7.27–7.40 (4 H, m); MS (FAB^+) m/z 296 $(M+H)^+$.

6.1.39. 5-[3-(2,6-Dichlorobenzyl)-2-methyl-4-pyridon-1-yl]pentanoic acid (7e). To a solution of **7d** (10.9 mg, 0.031 mmol) in acetone (0.11 ml) at 0 °C was added an aqueous solution of chromium(VI) oxide and sulfuric acid (2.2 mg 0.022 mmol). The mixture was stirred at room temperature for 70 min, then methanol (0.1 ml) was added. The mixture was diluted with ethyl acetate and washed with brine. The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC [$CHCl_3$/MeOH (8:1)] to give **7e** (2.5 mg, 25%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–1.80 (6H, m), 2.13 (3H, s), 3.83 (2H, br), 4.36 (2H, br), 6.52 (1H, d, J = 7.5 Hz), 7.06 (1H, t, J = 8.1 Hz), 7.22–7.26 (2H, m), 7.35 (1H, d, J = 7.5 Hz); MS (FAB^+) m/z 368 $(M+H)^+$.

6.1.40. 4-[3-(2,6-Dichlorobenzyl)-2-methyl-4-pyridone-1-yl]methylbenzoic acid (7j). To a solution of **7i** (100 mg, 0.240 mmol) in 1,4-dioxane (1 ml) was added 1 N NaOH (1 ml). The mixture was stirred at room temperature for 30 min. The solution was acidified with 1 N HCl, extracted with chloroform/*i*-propanol (5:1) three times, and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to give **7j** (75.1 mg, 78%). ^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (3H, s), 4.30 (2H, s), 5.76 (2H, s), 7.14 (1H, d, J = 7.2 Hz), 7.18 (2H, d, J = 8.3 Hz), 7.26 (1H, t, J = 8.3 Hz), 7.41 (2H, d, J = 7.8 Hz), 7.94 (2H, d, J = 7.8 Hz), 8.57 (1H, d, J = 7.2 Hz); MS (FAB^+) m/z 402 $(M+H)^+$.

6.1.41. 1-(4-Aminobenzyl)-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (7k). To a solution of **7h** (348 mg, 0.348 mmol) in methanol (3 ml) was added 10% Pd/C (35 mg). The mixture was stirred under a hydrogen

atmosphere at room temperature for 1 h, filtered through Celite, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (30:1)] to give **7k** (85 mg, 26%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s), 3.76 (2H, br), 4.35 (2H, s), 4.88 (2H, s), 6.35 (1H, d, J = 7.6 Hz), 6.64 (2H, d, J = 8.3 Hz), 6.78 (2H, d, J = 8.3 Hz), 7.03 (1H, t, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.32 (2H, d, J = 7.6 Hz); MS (FAB^+) m/z 373 $(M+H)^+$.

6.1.42. 4-[3-(2,6-Dichlorobenzyl)-2-methyl-4-pyridon-1-yl]methylbenzamide (7l). A solution of **7i** (50 mg, 0.120 mmol) in 7 M NH_3 in methanol (4 ml) was sealed and stirred at 60 °C for 3 h. The mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (30:1)] to give **7l** (20 mg, 42%). ^1H NMR (400 MHz, CD_3OD) δ 2.02 (3H, s), 4.35 (2H, s), 5.32 (2H, s), 6.44 (1H, d, J = 7.4 Hz), 7.08–7.16 (3H, m), 7.29 (2H, d, J = 8.0 Hz), 7.81 (1H, d, J = 7.4 Hz), 7.86 (2H, d, J = 8.3 Hz); MS (FAB^+) m/z 401 $(M+H)^+$.

6.1.43. 1-Benzyl-3-hydroxy-2-methyl-4-pyridone (9). To a solution of maltol (25 g, 198 mmol) in EtOH/H_2O (3:1, 100 ml) at room temperature was added benzylamine (108 ml, 991 mmol). The mixture was stirred overnight at 50 °C. The mixture was concentrated in vacuo, neutralized with 1 N HCl, and then extracted with $CHCl_3$. The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crystals were collected by filtration and washed with ethyl acetate to afford **9** (15.5 g, 36%); mp 195–198 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 5.13 (2H, s), 6.45 (1H, d, J = 7.3 Hz), 7.02 (2H, d, J = 6.8 Hz), 7.27–7.42 (4H, m); MS (FAB^+) m/z 216 $(M+H)^+$.

6.1.44. 1-Benzyl-2-methyl-4-pyridon-3-yl trifluoromethanesulfonate (10). To a solution of **9** (1.0 g, 4.65 mmol) in CH_2Cl_2 (20 ml) at 0 °C were added 2,6-lutidine (0.813 ml, 6.98 mmol) and trifluoromethanesulfonic anhydride (0.616 ml, 5.11 mmol). The mixture was stirred at 0 °C for 2 h, then diluted with $CHCl_3$ and washed with 5% NaCl aq. The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (30:1)] to afford **10** (1.20 g, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s), 5.10 (2H, s), 6.56 (1H, d, J = 7.8 Hz), 7.06 (2H, d, J = 6.8 Hz), 7.34–7.48 (4H, m); MS (FAB^+) m/z 348 $(M+H)^+$.

6.1.45. 1-Benzyl-2-methyl-3-phenyl-4-pyridone (11). To a solution of **10** (50 mg, 0.144 mmol) in 1,4-dioxane (1 ml) were added potassium carbonate (39.8 mg, 0.288 mmol), tetrakis(triphenylphosphine)palladium (16.6 mg, 10 mol%), and phenylboronic acid (26.3 mg, 0.216 mmol). The mixture was stirred overnight at 60 °C, then concentrated in vacuo. The resulting residue was purified by preparative TLC [$CHCl_3$/MeOH (9:1)] to give **11** (8 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 5.09 (2H, s), 6.51 (1H, d, J = 7.6 Hz), 7.10 (2H, d, J = 7.3 Hz), 7.18–7.46 (9H, m); HRMS (FAB^+) m/z: calcd for $C_{19}H_{18}NO$ $(M+H)^+$: 276.1388, found: 276.1387.

6.1.46. 1-Benzyl-2-methyl-3-vinyl-4-pyridone (12). To a solution of **10** (300 mg, 0.864 mmol) in 1,4-dioxane (4 ml) were added lithium chloride (73.2 mg, 1.73 mmol), tetrakis(triphenylphosphine)palladium (99.8 mg, 10 mol%), and tributyl(vinyl)tin (0.327 ml, 1.12 mmol). The mixture was stirred under reflux for 3 h then cooled and diluted with $CHCl_3$. The mixture was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [AcOEt/MeOH (20:1)] to afford **12** (118 mg, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H,s), 5.08 (2H, s), 5.57 (1H, dd, J = 11.7, 2.2 Hz), 5.75 (1H, dd, J = 17.8, 2.2 Hz), 6.44 (1H, d, J = 7.3 Hz), 6.67 (1H, dd, J = 17.8, 11.7 Hz), 7.05 (2H, d, J = 7.1 Hz), 7.24–7.43 (4H, m); MS (FAB^+) m/z 226 $(M+H)^+$.

6.1.47. (*E*)-1-Benzyl-2-methyl-3-[2-(pyridin-3-yl)vinyl]-4-pyridone (13). To a solution of **12** (30 mg, 0.133 mmol) in 1,4-dioxane (1 ml) were added 3-bromopyridine (31.6 mg, 0.200 mmol), dicyclohexylmethylamine (0.057 ml, 0.266 mmol), tris(dibenzylideneacetone)dipalladium (18.3 mg, 15 mol%), and tri-*tert*-butylphosphine (0.011 ml, 30 mol%). The mixture was stirred overnight at room temperature, then concentrated in vacuo. The residue was purified by preparative TLC [$CHCl_3$/MeOH (9:1)] to give **13** (13 mg, 32%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 5.12 (2H, s), 6.46 (1H, d, J = 7.6 Hz), 7.07 (2H, d, J = 7.8 Hz), 7.10 (1H, d, J = 16.3 Hz), 7.22–7.30 (1H, m), 7.31–7.46 (4H, m), 7.64 (1H, d, J = 16.3 Hz), 7.81 (1H, d, J = 8.0 Hz), 8.45 (1H, d, J = 4.6 Hz), 8.69 (1H, s); MS (FAB^+) m/z 303 $(M+H)^+$.

6.1.48. 1-Benzyl-2-methyl-3-[2-(pyridin-3-yl)ethyl]-4-pyridone (14). To a solution of **13** (5 mg, 0.016 mmol) in MeOH (0.5 ml) was added 10% Pd/C (1 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 3 h, then filtered through Celite and concentrated in vacuo. The residue was purified by preparative TLC [$CHCl_3$/MeOH (9:1)] to give **14** (2.5 mg, 51%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s), 2.80–2.94 (4H, m), 4.99 (2H, s), 6.42 (1H, d, J = 7.6 Hz), 6.97 (2H, d, J = 7.3 Hz), 7.12 (1H, dd, J = 7.8, 4.7 Hz), 7.30–7.43 (4H, m), 7.50 (1H, d, J = 7.8 Hz), 8.36–8.43 (2H, m); MS (FAB^+) m/z 305 $(M+H)^+$.

6.1.49. 4-Cyclohexylmethoxy-3-(2,6-dichlorobenzyl)-2-methylpyridine (15). To a solution of **6a** (150 mg, 0.559 mmol) in DMF (3 ml) were added sodium hydride (29 mg 0.727 mmol as a 60% dispersion in mineral oil) and cyclohexylmethyl bromide (128 mg, 0.727 mmol). The mixture was stirred at 50 °C for 6 h, then diluted with ethyl acetate and washed with 5% NaCl aq. The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (30:1)] to afford **15** (146 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.79–0.93 (2H, m), 1.06–1.30 (4H, m), 1.51–1.77 (5H, m), 2.48 (3H, s), 3.65 (2H, d, J = 6.1 Hz), 6.58 (1H, d, J = 5.6 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.25 (2H, d, J = 8.0 Hz), 8.23 (1H, d, J = 5.6 Hz); MS (FAB^+) m/z 364 $(M+H)^+$.

6.1.50. 1-Benzyloxycarbonyl-6-butyl-3-(2,6-dichlorobenzyl)-5,6-dihydro-2-methyl-4-pyridone (16a). To a solution of **15** (100 mg, 0.279 mmol) in THF (2 ml) at 0 °C were added butylmagnesium bromide (0.335 mmol as a 0.9 M THF solution) and benzylchloroformate (0.0397 ml, 0.279 mmol). The solution was stirred for 3 h at room temperature, then poured into 3 N HCl (15 ml) and stirred at room temperature for 1 h. The mixture was extracted with ethyl acetate, and the extract was washed with 5% $NaHCO_3$ aq, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel [hexane/AcOEt (5:1)] to afford **16a** (72 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 6.8 Hz), 1.10–1.32 (4H, m), 1.39–1.52 (1H, m), 1.73–1.89 (1H, m), 2.12 (3H, s), 2.36 (1H, dd, J = 17.3, 1.4 Hz), 2.81 (1H, dd, J = 17.3, 6.1 Hz), 3.93 (1H, d, J = 15.9 Hz), 4.03 (1H, d, J = 15.9 Hz), 4.77–4.86 (1H, m), 5.20 (2H, s), 7.07 (1H, t, J = 8.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.30–7.41 (5H, m); MS (FAB$^+$) m/z 460 (M+H)$^+$.

6.1.51. 1-Benzyloxycarbonyl-6-cyclohexylmethyl-3-(2,6-dichlorobenzyl)-5,6-dihydro-2-methyl-4-pyridone (16b). The title compound was prepared from **15** by means of a similar procedure to that described for **16b** (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76–0.94 (2H, m), 1.05–1.23 (4H, m), 1.24–1.37 (1H, m), 1.49–1.84 (6H, m), 2.11 (3H, s), 2.32 (1H, dd, J = 17.3, 1.4 Hz), 2.81 (1H, dd, J = 17.3, 6.1 Hz), 3.92 (1H, d, J = 15.8 Hz), 4.03 (1H, d, J = 15.8 Hz), 4.76–4.84 (1H, m), 5.17–5.23 (2H, m), 7.06 (1H, t, J = 8.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.30–7.41 (5H, m); MS (FAB$^+$)m/z 500 (M+H)$^+$.

6.1.52. 1-Benzyloxycarbonyl-6-butyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (17a). To a solution of **16a** (56 mg, 0.122 mmol) in THF (1 ml) at −78 °C was added 1 M lithium hexamethyldisilazide in THF (0.134 mmol). The mixture was stirred at 0 °C for 30 min, then cooled to −78 °C. To the resulting mixture was added phenylselenyl bromide (37 mg, 0.158 mmol), and the whole was stirred at −78 °C for 1 h, then poured into 1 N HCl. The mixture was extracted with ethyl acetate and washed with brine and 5% $NaHCO_3$ aq. The organic phase was dried over Na_2SO_4, filtered, concentrated in vacuo, and dissolved in CH_2Cl_2 (1 ml). To this solution was added *m*-chloroperbenzoic acid (17.8 mg, 0.129 mmol). The mixture was stirred at room temperature for 1 h and purified by preparative TLC [$CHCl_3$/MeOH (9:1)] to give **17a** (22 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 7.3 Hz), 1.26 (2H, tq, J = 7.3 Hz), 1.47 (2H, m), 1.95 (3H, s), 2.29 (2H, t, J = 7.5 Hz), 4.26 (2H, s), 5.36 (2H, s), 6.13 (1H, s), 7.06 (1H, t, J = 8.0 Hz), 7.22–7.27 (2H, m), 7.42 (5H, br); MS (FAB$^+$) m/z 458 (M+H)$^+$.

6.1.53. 1-Benzyloxycarbonyl-6-cyclohexylmethyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (17b). The title compound was prepared from **16b** by means of a similar procedure to that described for **17b** (31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64–0.84 (2H, m), 1.00–1.18 (3H, m), 1.31–1.70 (6H, m), 1.95 (3H, s), 2.17 (2H, d, J = 7.3 Hz), 4.27 (2H, s), 5.35 (2H, s), 6.10 (1H, s), 7.05 (1H, t, J = 8.0 Hz), 7.25 (2H, d, J = 8.0 Hz), 7.38–7.47 (5H, m); MS (FAB$^+$) m/z 498 (M+H)$^+$.

6.1.54. 6-Butyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (18a). A solution of **17a** (19 mg, 0.041 mmol) in methanol (3 ml) was refluxed for 15 h. The mixture was concentrated in vacuo and resulting residue was purified by column chromatography on silica gel [$CHCl_3$/MeOH (20:1)] to give **18a** (10 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.3 Hz), 1.26 (2H, tq, J = 7.3 Hz), 1.55 (2H, m), 2.08 (3H, s), 2.44 (2H, t, J = 7.6 Hz), 4.21 (2H, s), 6.06 (1H, s), 7.00 (1H, t, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 11.26 (1H, br); HRMS (FAB$^+$) m/z: calcd for $C_{17}H_{20}Cl_2NO$ (M+H)$^+$: 324.0922, found: 324.0927.

6.1.55. 6-Cyclohexylmethyl-3-(2,6-dichlorobenzyl)-2-methyl-4-pyridone (18b). The title compound was prepared from **17b** by means of a similar procedure to that described for **18b** (46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.96 (2H, m), 1.07–1.28 (3H, m), 1.48–1.74 (6H, m), 2.03 (3H, s), 2.29 (2H, d, J = 7.3 Hz), 4.25 (2H, s), 6.09 (1H, s), 7.04 (1H, t, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 8.70 (1H, br); HRMS (FAB$^+$) m/z: calcd for $C_{20}H_{24}Cl_2NO$ (M+H)$^+$: 364.1235, found: 364.1227.

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