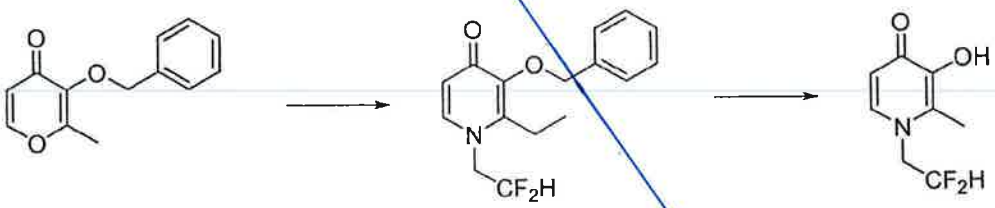
(a) In a similar manner as in example 1(a), 3-(benzyloxy)-2-ethyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (1.10 g) was prepared from 3-(benzyloxy)-2-ethyl-4*H*-pyran-4-one (1.20 g, 5.2 mmol) and 2,2,2,-trifluoroethylamine hydrochloride (3.57 g, 26.1 mmol) in pyridine (10 mL). Yield = 67%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 7.07 - 7.59 (m, 6H), 6.51 (d, *J* = 7.7 Hz, 1H), 5.20 (s, 2H), 4.38 (q, *J* = 7.7 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 2H) and 0.97 (t, *J* = 7.5 Hz, 3H); MS *m/z* 312 $[M+1]^+$.

(b) In a similar manner as described in example 1(b), 2-ethyl-3-hydroxy-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (0.30g) was prepared from 3-(benzyloxy)-2-ethyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (0.90g, 2.9 mmol) with 10% palladium on charcoal (wet, 90 mg) in methanol (5 mL) and ethanol (35 mL) under hydrogen at 15 psi for 1.5 hours. Yield = 47%; ^{1}H NMR (DMSO-D_6, 400MHz) δ (ppm): 7.58 (d, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 7.3 Hz, 1H), 4.92 (q, J=8.1, 2H), 2.72 (t, *J* = 7.5 Hz, 2H) and 1.20 (t, *J* = 7.5Hz, 3H); MS *m/z* 222 $[M+1]^+$.

Example 3

Preparation of 1-(2,2-difluoroethyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one

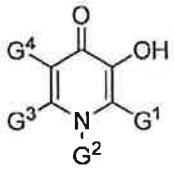


(a) Preparation of 3-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one.

3-(Benzyloxy)-2-methyl-4*H*-pyran-4-one (432 mg, 2.0 mmol) was mixed with 2,2-difluoroethylamine (655 mg, 8.0 mmol) and triethylamine hydrochloride (1.10 g, 8.0 mmol) in pyridine (6 mL) in a sealed vial. The reaction mixture was heated at 110 °C for overnight. The solid was filtered and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was mixed with water, and then extracted with ethyl acetate. The organic layer was washed with water and brine. The product was purified by column chromatography on silica gel with 5% methanol in ethyl acetate as eluant to give 3-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one (337 mg) as pale-yellow solid. Yield = 60%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 7.66 (d, *J* = 7.1 Hz, 1H), 7.16-7.55 (m, 5H),

mainteined in the presence of TET. Cytotoxic concentration (CC1) was defined as the lowest compound concentration resulting in viability significantly below 80%. CC2 is the lowest compound concentration resulting in viability significantly below 80% in cells expressing AP (i.e. cultured without tetracycline).

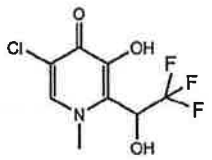
Chemical Structures of Compounds



Apo#	G^1	G^2	G^3	G^4
6994	H	CH_2CF_3	Me	H
6995	Me	CH_2CF_3	H	H
6998	$CH(CF_3)$-D-ala-NHMe	Me	H	H
7021	CH_2CF_3	Me	CH_2NMe_2	H
7022	$CH(OH)CF_3$	Me	CH_2NMe_2	H
7030	Et	CH_2CF_3	H	H
7032	$CH(OH)CF_3$	Me	CH_2-L-ala-OH	H
7033	$CH(OH)CF_3$	Me	CH_2-L-ala-NHMe	H
7035	$CH(OH)CF_3$	H	CH_2NMe_2	H
7038	$CH(OH)CF_3$	Me	Me	Cl
7040	CH_2CF_3	Me	Me	Cl
7041	$CH(NMe_2)CF_3$	Me	H	H
7053	Me	Me	H	$CH(NMe_2)CF_3$
7054	Me	Me	H	CH(piperidinyl)CF_3
7055	Me	Me	H	CH(imidazolyl)CF_3
7056	Me	Me	$CH(NHMe)CF_3$	H
7057	CH(propargylamino)CF_3	Me	H	H

a pink solid. Yield = 85%; ^{1}H-NMR (MeOD-D_4, 90 MHz) δ (ppm): 5.9 (q, J = 9.1 Hz, 1H), 4.01 (s, 3H) and 2.65 (s, 3H); MS-ESI m/z 272 $[M+1]^+$.

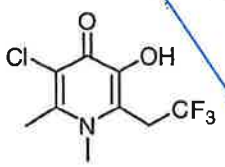
B. Preparation of 5-chloro-3-hydroxy-1-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one



In a similar manner, 5-chloro-3-hydroxy-1-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one (1.40 g) was prepared from 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (1.27 g, 8.0 mmol) and trifluoroacetaldehyde methyl hemiacetal (12.7 mL) in presence of potassium carbonate (0.22 g, 1.6 mmol). Yield = 68%; ^{1}H NMR (DMSO-D_6) δ (ppm): 8.10 (s, 1H), 5.80 (q, J = 8.7 Hz, 1H) and 3.88 (s, 3H); MS m/z 258 $[M+1]^+$.

Example 16

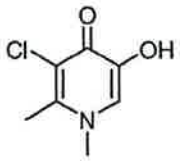
A. Preparation of 3-chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one.



3-Chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1H)-one (300 mg, 1.10 mmol) was suspended in 10 mL of acetonitrile and thionyl chloride (398 µL, 5.50 mmol) was added dropwise. The reaction was stirred at room temperature. After 2 hours, the reaction was concentrated. The crude was diluted with 10 mL of methanol and sodium borohydride (329 mg, 8.80 mmol) was added in small portions. After 15 hours, the reaction was filtered and the filtrate was concentrated in vacuo. The resulting solid was dissolved in methanol and ethyl acetate added, filtered and concentrated. The crude product was purified by column chromatography on silica gel using a mixture of 30% EtOAc in MeOH as eluant. Fractions rich in product were combined and evaporated to dryness. The residue product was recrystallised from methanol/ethyl acetate to give

3-(Benzyloxy)-5-chloro-1-methylpyridin-4(1*H*)-one (2.70 g, 10.8 mmol) was mixed in 6N HCl (15 mL) and ethanol (10 mL). After being refluxed for 2 hours, the reaction mixture was concentrated by rotary evaporator. The residue was mixed with water (5 mL) and basified to pH 8-9 with concentrated ammonia. An off-white precipitate came out, ant the mixture was again concentrated in vacuo to remove volatiles. The off-white solid was collected by suction filtration and dried to give 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (1.32 g). Yield = 76.6%; ^{1}H NMR (DMSO-D_6, 90 MHz) δ (ppm): 7.98 (s, 1H), 7.47 (s, 1H) and 3.67 (s, 3H).

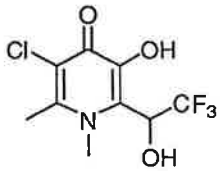
B. Preparation of 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one



In a similar manner, 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (600 mg), was prepared by refluxing a mixture of 5-(benzyloxy)-3-chloro-1,2-dimethylpyridin-4(1*H*)-one (2.00 g, 7.6 mmol) with 6N HCl (20 mL) and methanol (10 mL) at 100 °C for 2 hours. Yield = 46%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 8.08 (s, 1H) 4.08 (s, 3H) and 2.72 (s, 3H); MS *m/z* 174 $[M+1]^+$.

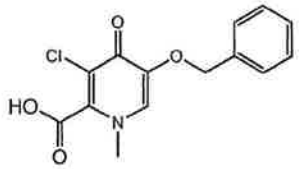
Example 15

A. Preparation of 3-chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one.



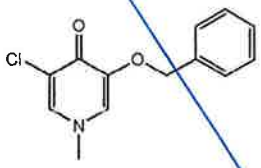
3-Chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (500 mg, 2.80 mmol) was suspended in trifluoroacetaldehyde methyl hemiacetal (3 mL). Potassium carbonate (119 mg, 0.86 mmol) was added and the mixture was heated to 120 °C. After 2.5 hours, the reaction mixture was allowed to cool to room temperature, then diluted with methanol and filtered. The filtrate was concentrated to dryness and diluted with acetone. The solution was filtered and the filtrate was concentrated to give 3-chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one (650 mg) as

E. Preparation of 5-(benzyloxy)-3-chloro-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid.



To a mixture of 5-(benzyloxy)-3-chloro-2-(hydroxymethyl)-1-methylpyridin-4(1*H*)-one (4.90 g, 17.5 mmol), TEMPO (120 mg, 0.77 mmol) and potassium bromide (120 mg, 1.00 mmol) in acetone (50 mL) and saturated sodium bicarbonate (40 mL) below 7 °C was added dropwise a 10-14% sodium hypochlorite (50 mL) solution during 30 minutes. After being stirred for 2 hours, the reaction mixture was diluted with water and adjusted to pH about 1.5 with 6N HCl. The solid was filtered and washed with water to give 5-(benzyloxy)-3-chloro-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid (2.89 g) as a white solid. Yield = 56%; ^{1}H NMR (DMSO-D_6, 90 MHz) δ (ppm): 7.79 (s, 1H), 7.16-7.62 (m, 5H), 5.03 (s, 2H) and 3.67 (s, 3H); MS *m/z* 294 $[M+1]^+$.

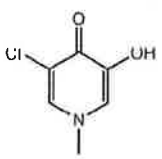
F. Preparation of 3-(benzyloxy)-5-chloro-1-methylpyridin-4(1*H*)-one.



5-(Benzyloxy)-3-chloro-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid (3.50 g, 11.9 mmol) was heated in DMF (10 mL) for one hour. The reaction mixture was concentrated by rotary evaporation and the residue was triturated with ethyl acetate/ether to give 3-(benzyloxy)-5-chloro-1-methylpyridin-4(1*H*)-one (2.80 g) as a pale brown solid. Yield = 94%; ^{1}H NMR (DMSO-D_6, 90 MHz) δ (ppm): 8.08 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.19-7.58 (m, 5H), 5.01 (s, 2H) and 3.67 (s, 3H).

Example 14

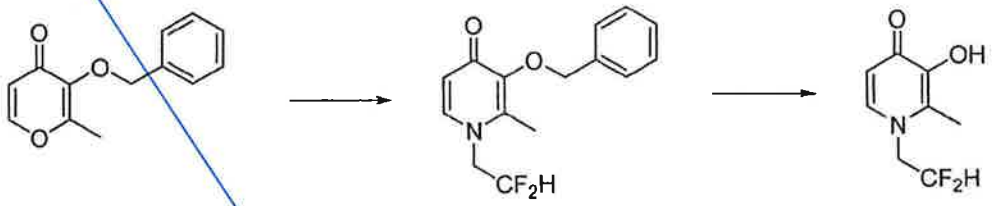
A. Preparation of 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one.



hydrochloride (24.5 g). Yield = 65%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 8.18 (s, 1H), 7.21 (s, 1H), 5.31 (q, *J* = 8.2 Hz, 2H) and 2.67 (s, 3H).

Example 5

Preparation of 1-(2,2-difluoroethyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one



(a) In a similar manner as described in example 4(a), 3-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one (2.20 g) was prepared from a mixture of 5-(benzyloxy)-2-methyl-4*H*-pyran-4-one (3.00 g, 13.8 mmol), difluoroethylamine (2.48 g, 55.2 mmol), triethylamine hydrochloride (5.58 g, 55.2 mmol) and pyridine (15 mL). Yield = 58%; ^{1}H NMR (90 MHz, MeOD-D_4) δ (ppm): 7.53 (s, 1H), 7.27-7.45 (m, 5H), 6.36 (s, 1H), 5.56-6.77 (tt, *J* = 54.9, 3.6 Hz, 1H), 5.04 (s, 2H), 4.24-4.60 (td, *J* = 14.9, 2.7, 2H) and 2.36 (s, 3H); MS *m/z* 280 $[M+1]^+$.

(b) In a similar manner as described in example 1(b), 1-(2,2-difluoroethyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (230 mg) was prepared from 3-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one (500 mg, 1.80 mmol) with 10% Pd/C (wet, 50 mg) in methanol (40 mL) under hydrogen at 15 psi pressure in a Parr apparatus for 27 minutes. Yield = 99%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 7.46 (s, 1H), 6.37 (s, 1H), 5.62-6.83 (tt, *J* = 54.9, 3.6 Hz, 1H), 4.26-4.60 (td, *J* = 15.3, 2.4Hz, 2H) and 2.38 (s, 3H); MS *m/z* 190 $[M+1]^+$.

filtrate was evaporated to give 3-hydroxy-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (0.78 g) as white solid. Yield = 95%; ^{1}H NMR (DMSO-D_6, 400MHz) δ (ppm) 7.60 (d, J = 7.1 Hz, 1H), 7.46 (s, 1H), 6.23 (d, J = 7.1 Hz, 1H) and 4.80 - 5.00 (m, 2H); MS *m/z* 194 $[M+1]^+$.

Example 7

Preparation of

3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one

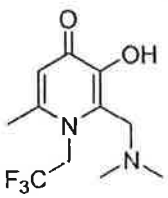


5-Hydroxy-2-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one hydrochloride (4.87 g. 20.0 mmol) was mixed with 37% formaldehyde (30 mL) and 6N sodium hydroxide (7 mL, 42.0 mmol). The reaction mixture was stirred at 39-42 °C for 11 hours, and then additional 37% formaldehyde (30 mL) was added. The reaction mixture was stirred at 37 °C for 12 hours and then left at room temperature for a further 12 hours. The solid was filtered and the filtrate was acidified to pH about 5 to 6. The solution was concentrated with silica gel and the product was purified by column chromatography with a gradient mixture of 5-10% methanol in ethyl acetate as eluant to give the title compound 3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (3.02 g) as pale-peach solid. Yield 63.5%; ^{1}H NMR (DMSO-D_6 + D_2O, 90 MHz) δ (ppm): 6.20 (s, 1H), 5.15 (q, J = 8.8 Hz, 2H), 4.33 - 4.92 (m, 2H) and 2.37 (s, 3H); MS *m/z* 238 $[M+1]^+$.

Example 8

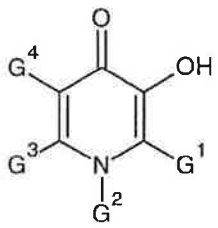
A. Preparation of

2-[(dimethylamino)methyl]-3-hydroxy-6-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one



What is claimed is:

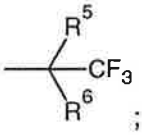
1. A compound of Formula I:



I

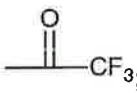
wherein

G^1 is H, C_1-C_4 alkyl, CH_2OH, $CH_2NR^1R^2$, $CH(R^4)CF_3$, $CH(R^7)CF_2H$, NR^1R^2, or



;

G^2 is H, C_1-C_4 alkyl, cyclopropyl or $(CH_2)_nCF_2R^3$;

G^3 is H, C_1-C_4 alkyl, CH_2OH, $CH_2NR^1R^2$, $CH(R^6)CF_3$, CH_2-A-OH, CH_2-A-NHR^9 or CH_2CF_3 or ; and

G^4 is H, C_1-C_4 alkyl, halo or $CH(R^8)CF_3$;

n is 1, 2 or 3;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholinyl, and piperidinyl;

R^3 is H or F;

R^4 and R^7 are independently selected from the group consisting of: H, OH, NR^1R^2, imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N phonylpiporazinyl, 2-pyridylpiporazinyl and -A-NH-R^{10}; and when R^4 or R^7 is imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl,

2-pyridylpiperazinyl or -A-NH-R^{10}, a point of attachment of R^4 or R^7 to the CH moiety of G^1 is an N atom of R^4 or R^7;

R^5 is C_1-C_4 alkyl;

R^6 is H or OH;

R^8 is selected from the group consisting of: NR^1R^2, imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl and -A-NH-R^{10}; and when R^8 is imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl or -A-NH-R^{10} a point of attachment of R^8 to the CH moiety of G^4 is an N atom of R^8;

R^9 and R^{10} are independently H or C_1-C_4 alkyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

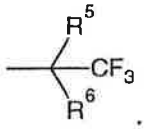
m is 1, 2 or 3; and

provided that:

at least one of G^1, G^2, G^3 and G^4 comprise at least one fluorine moiety;

when G^1 is $CH(R^4)CF_3$ and R^4 is H or OH, then either (i) G^3 is $CH_2NR^1R^2$, CH_2-A-OH, CH_2-A-NHR^9 or (ii) G^4 is halo or $CH(NR^1R^2)CF_3$; and

when G^3 is $CH(R^6)CF_3$, then G^1 is $CH_2NR^1R^2$, $CH(R^4)CF_3$, $CH(R^7)CF_2H$, NR^1R^2 or

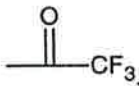


.

2. The compound of claim 1 wherein when G^1 is $CH(NR^1R^2)CF_3$, then G^3 and G^4 are independently H or C_1-C_4 alkyl, and G^2 is H, C_1-C_4 alkyl or cyclopropyl.

3. The compound of claim 1 or 2 wherein when G^2 is $(CH_2)_nCF_2R^3$, then G^1 and G^3 are independently H, C_1-C_4 alkyl, CH_2OH or $CH_2NR^1R^2$.

4. The compound of any one of claims 1 to 3 wherein when G^2 is H, then G^4 is H or C_1-C_4 alkyl.

5. The compound of any one of claims 1 to 4 wherein when G^3 is , then G^1 and G^4 are independently H or C_1-C_4 alkyl.

6. The compound of any one of claims 1 to 5 wherein when G^3 is CH_2CF_3, then G^1 is NR^1R^2.

7. The compound of any one of claims 1 to 6 wherein when G^1 is $CH_2NR^1R^2$, then G^2 is $(CH_2)_nCF_2R^3$.

8. The compound of any one of claims 1 to 7 wherein when G^1 is $CH(R^7)CF_2H$, then G^3 and G^4 are independently H or C_1-C_4 alkyl, and G^2 is C_1-C_4 alkyl or cyclopropyl.

9. The compound of any one of claims 1 to 8 wherein when G^1 is $CH(R^4)CF_3$, then G^2 is C_1-C_4 alkyl or cyclopropyl; provided that when R^4 is H or OH, then G^3 is $CH_2NR^1R^2$, CH_2-A-OH, CH_2-A-NHR^9.

10. The compound of any one of claims 1 to 9 wherein when G^1 is $CH(R^4)CF_3$ and R^4 is H or OH, then G^4 is halo.

11. The compound of any one of claims 1 to 10 wherein when G^1 or G^3 is CH_2OH, then G^2 is $(CH_2)_nCF_2R^3$.

12. The compound of any one of claims 1 to 11 wherein when G^1 is NR^1R^2, then G^3 is CH_2CF_3, G^4 is H or C_1-C_4 alkyl and G^2 is C_1-C_4 alkyl or cyclopropyl.

13. The compound of any one of claims 1 to 12 wherein when G^4 is $CH(R^8)CF_3$, then G^1 and G^3 are independently H or C_1-C_4 alkyl, and G^2 is hydrogen, C_1-C_4 alkyl or cyclopropyl.

14. The compound of any one of claims 1 to 13 wherein when G^3 is CH_2-A-OH or CH_2-A-NHR, then G^4 is H or C_1-C_4 alkyl, G^2 is C_1-C_4 alkyl or cyclopropyl and G^1 is $CH(R^4)CF_3$ where R^4 is H or OH.

15. The compound of any one of claims 1 to 14 wherein when G^3 is $CH_2NR^1R^2$, and G^2 is C_1-C_4 alkyl or cyclpropyl, then G^4 is H or C_1-C_4 alkyl, and G^1 is $CH(R^4)CF_3$ where R^4 is H or OH.

16. The compound of any one of claims 1 to 15 wherein when G^1 is $CH(R^4)CF_3$ and R^4 is H or OH, then either G^3 is $CH_2NR^1R^2$ or G^4 is halo.

17. The compound of any one of claims 1 to 16 wherein when G^3 is $CH(R^6)CF_3$, then G^1 is $CH_2NR^1R^2$ or NR^1R^2.

18. The compound of claim 1 wherein

G^1 is H, C_1-C_4 alkyl, $-CH_2OH$, or $-CH_2NR^1R^2$;

G^2 is $(CH_2)_n$-CF_2R^3;

G^3 is H, C_1-C_4 alkyl, $-CH_2OH$, or $-CH_2NR^1R^2$;

G^4 is H, C_1-C_4 alkyl, or halo;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

n is 1, 2 or 3; and

R^3 is H, or F.

19. The compound of claim 18 wherein n is 1.

20. The compound of claim 19 wherein G^4 is H.

21. The compound of claim 20 wherein R^3 is H.

22. The compound of claim 20 wherein R^3 is F.

23. The compound of claim 22 wherein G^1 is hydrogen, and G^3 is methyl.

24. The compound of claim 22 wherein G^1 is methyl, and G^3 is H.

25. The compound of claim 22 wherein G^1 is ethyl, and G^3 is H.

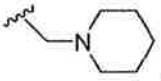
26. The compound of claim 22 wherein G^1 is H, and G^3 is H.

27. The compound of claim 22 wherein G^1 is $-CH_2OH$, and G^3 is H.

28. The compound of claim 22 wherein G^1 is $-CH_2NMe_2$, and G^3 is methyl.

29. The compound of claim 22 wherein G^1 is $-CH_2NMe_2$, and G^3 is H.

30. The compound of claim 22 wherein G^1 is $-CH_2OH$, and G^3 is methyl.

31. The compound of claim 22 wherein G^1 is , and G^3 is methyl.

32. The compound of claim 21 wherein G^1 is methyl and G^3 is H.

33. The compound of claim 21 wherein G^1 is H and G^3 is methyl.

34. The compound of claim 21 wherein G^1 is $-CH_2NMe_2$ and G^3 is methyl.

35. The compound of claim 1 wherein

G^1 is $-CH(R^4)CF_3$;

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, C_1-C_4 alkyl, CH_2-A-OH, CH_2-A-NHR^9, or $CH_2NR^1R^2$;

G^4 is H, C_1-C_4 alkyl, or halo;

R^4 is selected from the group consisting of: H, OH, NR^1R^2, imidazole, 1,2,4-triazole, piperazine, N-C_1-C_4 alkylpiperazine, N-benzylpiperazine, N-phenylpipreazine, 2-pyridylpiperazine, and -A-NH-R^{10}; and when R^4 is NR^1R^2, imidazole, 1,2,4-triazole, piperazine, N-C_1-C_4 alkylpiperazine, N-benzylpiperazine, N-phenylpipreazine, 2-pyridylpiperazine, or -A-NH-R^{10}, a point of attachment of R^4 to the –CH moiety of G^1 is an N-atom of R^4;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

m is 1, 2 or 3; and

R^9 and R^{10} are independently H, or C_1-C_4 alkyl.

36. The compound of claim 35 wherein G^2 is C_1-C_4 alkyl, or cyclopropyl; G^3 is H, or C_1-C_4 alkyl; and R^4 is selected from the group consisting of: NR^1R^2, imidazole, 1,2,4-triazole, piperazine, N-C_1-C_4 alkylpiperazine, N-benzylpiperazine, N-phenylpiperazine, 2-pyridylpiperazine and –A-NH-R^{10}.

37. The compound of claim 36 wherein G^2 is methyl.

38. The compound of claim 37 wherein G^3 is H and G^4 is H.

39. The compound of claim 38 R^4 is NR^1R^2.

40. The compound of claim 38 wherein R^4 is A-NHR^{10}; A is D-alanyl; and R^{10} is methyl.

41. The compound of claim 39 wherein R^1 is methyl and R^2 is methyl.

42. The compound of claim 39 wherein R^1 is methyl and R^2 is propargyl.

43. The compound of claim 39 wherein R^1 is H and R^2 is cyclopropyl.

44. The compound of claim 39 wherein R^1 is H and R^2 is allyl.

45. The compound of claim 39 wherein NR^1R^2 is piperidinyl.

46. The compound of claim 39 wherein NR^1R^2 is N-methylpiperazinyl.

47. The compound of claim 35 wherein G^3 is CH_2-A-OH, CH_2-A-NHR^9, or $CH_2NR^1R^2$; G^4 is H, or C_1-C_4 aklyl; and R^4 is H, or OH.

48. The compound of claim 47 wherein G^2 is methyl.

49. The compound of claim 48 wherein G^4 is H.

50. The compound of claim 49 wherein G^3 is $CH_2NR^1R^2$; R^1 is methyl; R^2 is methyl; and R^4 is H.

51. The compound of claim 49 wherein G^3 is $CH_2NR^1R_2$; R^1 is methyl; R^2 is methyl; and R^4 is OH.

52. The compound of claim 49 wherein G^3 is CH_2-A-OH; A is L-alanyl; and R^4 is OH.

53. The compound of claim 49 wherein G^3 is CH_2-A-NHR^9; A is L-alanyl; R^9 is methyl; and R^4 is OH.

54. The compound of claim 35 wherein G^3 is H or C_1-C_4 alkyl; and G^4 is halo.

55. The compound of claim 54 wherein G^2 is methyl.

56. The compound of claim 55 wherein G^4 is chloro.

57. The compound of claim 56 wherein G^3 is methyl; and R^4 is OH.

58. The compound of claim 56 wherein G^3 is methyl; and R^4 is H.

59. The compound of claim 56 wherein G^3 is methyl; R^4 is NR^1R^2; R^1 is methyl; and R^2 is methyl.

60. The compound of claim 56 wherein G^3 is H; R^4 is NR^1R^2; R^1 is methyl; and R^2 is methyl.

61. The compound of claim 56 wherein G^3 is H; R^4 is NR^1R^2; and NR^1R^2 is piperidinyl.

62. The compound of claim 56 wherein G^3 is H; and R^4 is H.

63. The compound of claim 1 wherein

G^1 is H, or C_1-C_4 alkyl;

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, or C_1-C_4 alkyl;

G^4 is $-CH(CF_3)(R^8)$;

R^8 is selected from the group consisting of: NR^1R^2, imidazole, 1,2,4-triazole, piperazine, N-C_1-C_4 alkylpiperazine, N-benzylpiperazine, N-phenylpipreazine, 2-pyridylpiperazine, and -A-NH-R^{10}; a point of attachment of R^8 to the –CH moiety of G^1 is an N-atom of R^8;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

m is 1, 2 or 3; and

R^{10} is H, or C_1-C_4 alkyl.

64. The compound of claim 63 wherein G^3 is H.

65. The compound of claim 64 wherein G^1 is methyl.

66. The compound of claim 65 wherein G^2 is H; R^8 is -A-NH-R^{10}; A is L-alanyl; and R^{10} is methyl.

67. The compound of claim 65 wherein G^2 is methyl; R^8 is NR^1R^2; R^1 is methyl and R^2 is methyl.

68. The compound of claim 65 wherein G^2 is methyl; R^8 is NR^1R^2; R^1 is H and R^2 is methyl.

69. The compound of claim 65 wherein G^2 is methyl; R^8 is NR^1R^2; and NR^1R^2 is piperidinyl.

70. The compound of claim 65 wherein G^2 is methyl; R^8 is NR^1R^2; and NR^1R^2 is imidazolyl.

71. The compound of claim 65 wherein G^2 is methyl; R^8 is NR^1R^2; and NR^1R^2 is N-methylpiperazinyl.

72. The compound of claim 1 wherein

G^1 is $CH_2NR^1R^2$, or NR^1R^2;

G^2 is C_1-C_4 alkyl, or cyclopropyl;

G^3 is $-CH(CF_3)(R^6)$;

G^4 is H, or C_1-C_4 alkyl;

R^6 is H, or OH; and

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl.

73. The compound of claim 72 wherein G^4 is H.

74. The compound of claim 73 wherein G^2 is methyl.

75. The compound of claim 74 wherein G^1 is NR^1R^2; R^1 is methyl; R^2 is methyl; and R^6 is H.

76. The compound of claim 74 wherein G^1 is $CH_2NR^1R^2$; R^1 is methyl; R^2 is methyl; and R^6 is OH.

77. The compound of claim 1 wherein

G^1 is $-CH(CF_2H)(R^7)$;

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, or C_1-C_4 alkyl;

G^4 is H, or C_1-C_4 alkyl;

R^7 is selected from the group consisting of: H, OH, NR^1R^2, imidazolyl, 1,2,4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl, and -CH_2-A-NH-R^{10}; and when R^7 is NR^1R^2, imidazolyl, 1,2,4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl or -CH_2-A-NH-R^{10}, a point of attachment of R^7 to the –CH moiety of G^1 is an N-atom of R^7;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

m is 1, 2 or 3; and

R^{10} is H, C_1-C_4 alkyl.

78. The compound of claim 73 wherein G^2 is methyl, G^3 is H, G^4 is H, and R^7 is OH.

79. The compound of claim 73 wherein G^2 is methyl, G^3 is H, G^4 is H, and R^7 is H.

80. The compound of claim 1 wherein

G^1 is $C(R^5)(R^6)(CF_3)$

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, or C_1-C_4 alkyl; and

G^4 is H, or C_1-C_4 alkyl.

81. The compound of claim 80 wherein G^2 is methyl; G^3 is H; G^4 is H; R^5 is methyl; and R^6 is H or OH.

82. The compound of claim 81 wherein R^6 is OH.

83. Use of a compound of any one of claims 1 to 82 for treatment of a medical condition related to a toxic concentration of iron.

84. Use of a compound of any one of claims 1 to 82 for preparation of a medicament for treatment of a medical condition related to a toxic concentration of iron.

85. The use of claim 83 or 84 wherein the medical condition related to a toxic concentration of iron is selected from the group consisting of: cancer, pulmonary disease, progressive kidney disease and Frederich's Ataxia.

86. A method of medical treatment comprising administering a therapeutically effective amount of a compound of any one of claims 1 to 82 to a subject having or suspected of having a medical condition related to a toxic concentration of iron.

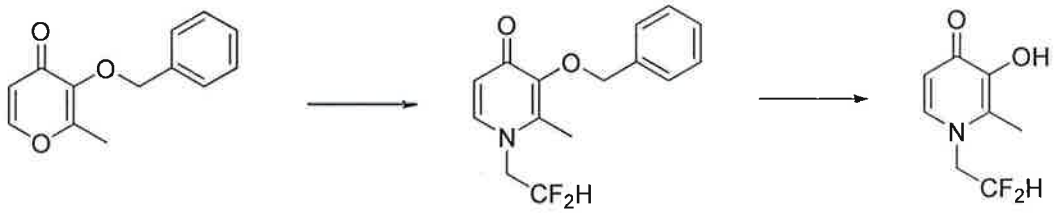
87. The method of claim 86 wherein the medical condition related to a toxic concentration of iron is selected from the group consisting of: cancer, pulmonary disease, progressive kidney disease and Frederich's Ataxia.

(a) In a similar manner as in example 1(a), 3-(benzyloxy)-2-ethyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (1.10 g) was prepared from 3-(benzyloxy)-2-ethyl-4*H*-pyran-4-one (1.20 g, 5.2 mmol) and 2,2,2,-trifluoroethylamine hydrochloride (3.57 g, 26.1 mmol) in pyridine (10 mL). Yield = 67%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 7.07 - 7.59 (m, 6H), 6.51 (d, *J* = 7.7 Hz, 1H), 5.20 (s, 2H), 4.38 (q, *J* = 7.7 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 2H) and 0.97 (t, *J* = 7.5 Hz, 3H); MS *m/z* 312 $[M+1]^+$.

(b) In a similar manner as described in example 1(b), 2-ethyl-3-hydroxy-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (0.30g) was prepared from 3-(benzyloxy)-2-ethyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (0.90g, 2.9 mmol) with 10% palladium on charcoal (wet, 90 mg) in methanol (5 mL) and ethanol (35 mL) under hydrogen at 15 psi for 1.5 hours. Yield = 47%; ^{1}H NMR (DMSO-D_6, 400MHz) δ (ppm): 7.58 (d, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 7.3 Hz, 1H), 4.92 (q, J=8.1, 2H), 2.72 (t, *J* = 7.5 Hz, 2H) and 1.20 (t, *J* = 7.5Hz, 3H); MS *m/z* 222 $[M+1]^+$.

Example 3

Preparation of 1-(2,2-difluoroethyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one



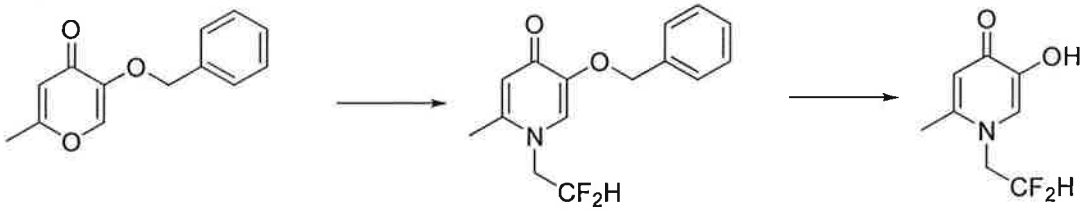
(a) Preparation of 3-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one.

3-(Benzyloxy)-2-methyl-4*H*-pyran-4-one (432 mg, 2.0 mmol) was mixed with 2,2-difluoroethylamine (655 mg, 8.0 mmol) and triethylamine hydrochloride (1.10 g, 8.0 mmol) in pyridine (6 mL) in a sealed vial. The reaction mixture was heated at 110 °C for overnight. The solid was filtered and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was mixed with water, and then extracted with ethyl acetate. The organic layer was washed with water and brine. The product was purified by column chromatography on silica gel with 5% methanol in ethyl acetate as eluant to give 3-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one (337 mg) as pale-yellow solid. Yield = 60%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 7.66 (d, *J* = 7.1 Hz, 1H), 7.16-7.55 (m, 5H),

hydrochloride (24.5 g). Yield = 65%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 8.18 (s, 1H), 7.21 (s, 1H), 5.31 (q, *J* = 8.2 Hz, 2H) and 2.67 (s, 3H).

Example 5

Preparation of 1-(2,2-difluoroethyl)-5-hydroxy-2-methylpyridin-4(1*H*)-one



(a) In a similar manner as described in example 4(a), 5-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one (2.20 g) was prepared from a mixture of 5-(benzyloxy)-2-methyl-4*H*-pyran-4-one (3.00 g, 13.8 mmol), difluoroethylamine (2.48 g, 55.2 mmol), triethylamine hydrochloride (5.58 g, 55.2 mmol) and pyridine (15 mL). Yield = 58%; ^{1}H NMR (90 MHz, MeOD-D_4) δ (ppm): 7.53 (s, 1H), 7.27-7.45 (m, 5H), 6.36 (s, 1H), 5.56-6.77 (tt, *J* = 54.9, 3.6 Hz, 1H), 5.04 (s, 2H), 4.24-4.60 (td, *J* = 14.9, 2.7, 2H) and 2.36 (s, 3H); MS *m/z* 280 $[M+1]^+$.

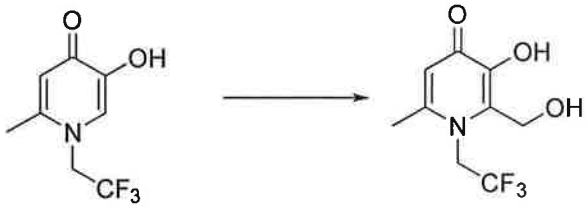
(b) In a similar manner as described in example 1(b), 1-(2,2-difluoroethyl)-5-hydroxy-2-methylpyridin-4(1*H*)-one (230 mg) was prepared from 5-(benzyloxy)-1-(2,2-difluoroethyl)-2-methylpyridin-4(1*H*)-one (500 mg, 1.80 mmol) with 10% Pd/C (wet, 50 mg) in methanol (40 mL) under hydrogen at 15 psi pressure in a Parr apparatus for 27 minutes. Yield = 99%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 7.46 (s, 1H), 6.37 (s, 1H), 5.62-6.83 (tt, *J* = 54.9, 3.6 Hz, 1H), 4.26-4.60 (td, *J* = 15.3, 2.4Hz, 2H) and 2.38 (s, 3H); MS *m/z* 190 $[M+1]^+$.

filtrate was evaporated to give 3-hydroxy-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (0.78 g) as white solid. Yield = 95%; ^{1}H NMR (DMSO-D_6, 400MHz) δ (ppm) 7.60 (d, *J* = 7.1 Hz, 1H), 7.46 (s, 1H), 6.23 (d, *J* = 7.1 Hz, 1H) and 4.80 - 5.00 (m, 2H); MS *m/z* 194 $[M+1]^+$.

Example 7

Preparation of

3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one



5-Hydroxy-2-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one hydrochloride (4.87 g. 20.0 mmol) was mixed with 37% formaldehyde (30 mL) and 6N sodium hydroxide (7 mL, 42.0 mmol). The reaction mixture was stirred at 39-42 °C for 11 hours, and then additional 37% formaldehyde (30 mL) was added. The reaction mixture was stirred at 37 °C for 12 hours and then left at room temperature for a further 12 hours. The solid was filtered and the filtrate was acidified to pH about 5 to 6. The solution was concentrated with silica gel and the product was purified by column chromatography with a gradient mixture of 5-10% methanol in ethyl acetate as eluant to give the title compound 3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one (3.02 g) as pale-peach solid. Yield 63.5%; ^{1}H NMR (DMSO-D_6 + D_2O, 90 MHz) δ (ppm): 6.20 (s, 1H), 5.15 (q, *J* = 8.8 Hz, 2H), 4.33 - 4.92 (m, 2H) and 2.37 (s, 3H); MS *m/z* 238 $[M+1]^+$.

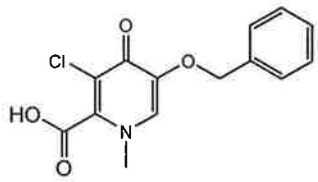
Example 8

A. Preparation of

2-[(dimethylamino)methyl]-3-hydroxy-6-methyl-1-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one

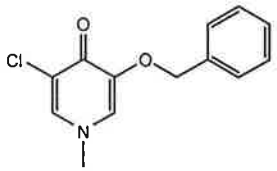


E. Preparation of 5-(benzyloxy)-3-chloro-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid.



To a mixture of 5-(benzyloxy)-3-chloro-2-(hydroxymethyl)-1-methylpyridin-4(1*H*)-one (4.90 g, 17.5 mmol), TEMPO (120 mg, 0.77 mmol) and potassium bromide (120 mg, 1.00 mmol) in acetone (50 mL) and saturated sodium bicarbonate (40 mL) below 7 ^{o}C was added dropwise a 10-14% sodium hypochlorite (50 mL) solution during 30 minutes. After being stirred for 2 hours, the reaction mixture was diluted with water and adjusted to pH about 1.5 with 6N HCl. The solid was filtered and washed with water to give 5-(benzyloxy)-3-chloro-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid (2.89 g) as a white solid. Yield = 56%; ^{1}H NMR (DMSO-D_6, 90 MHz) δ (ppm): 7.79 (s, 1H), 7.16-7.62 (m, 5H), 5.03 (s, 2H) and 3.67 (s, 3H); MS *m/z* 294 $[M+1]^{+}$.

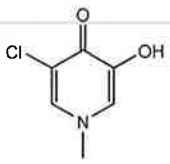
F. Preparation of 3-(benzyloxy)-5-chloro-1-methylpyridin-4(1*H*)-one.



5-(Benzyloxy)-3-chloro-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid (3.50 g, 11.9 mmol) was heated in DMF (10 mL) for one hour. The reaction mixture was concentrated by rotary evaporation and the residue was triturated with ethyl acetate/ether to give 3-(benzyloxy)-5-chloro-1-methylpyridin-4(1*H*)-one (2.80 g) as a pale brown solid. Yield = 94%; ^{1}H NMR (DMSO-D_6, 90 MHz) δ (ppm): 8.08 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.19-7.58 (m, 5H), 5.01 (s, 2H) and 3.67 (s, 3H).

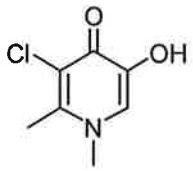
Example 14

A. Preparation of 3-chloro-5-hydroxy-1-methylpyridin-4(1*H*)-one.



3-(Benzyloxy)-5-chloro-1-methylpyridin-4(1*H*)-one (2.70 g, 10.8 mmol) was mixed in 6N HCl (15 mL) and ethanol (10 mL). After being refluxed for 2 hours, the reaction mixture was concentrated by rotary evaporator. The residue was mixed with water (5 mL) and basified to pH 8-9 with concentrated ammonia. An off-white precipitate came out, ant the mixture was again concentrated in vacuo to remove volatiles. The off-white solid was collected by suction filtration and dried to give 3-chloro-5-hydroxy-1-methylpyridin-4(1*H*)-one (1.32 g). Yield = 76.6%; ^{1}H NMR (DMSO-D_6, 90 MHz) δ (ppm): 7.98 (s, 1H), 7.47 (s, 1H) and 3.67 (s, 3H).

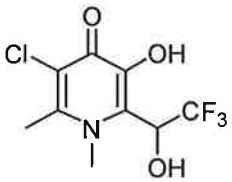
B. Preparation of 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one



In a similar manner, 3-chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (600 mg), was prepared by refluxing a mixture of 5-(benzyloxy)-3-chloro-1,2-dimethylpyridin-4(1*H*)-one (2.00 g, 7.6 mmol) with 6N HCl (20 mL) and methanol (10 mL) at 100 °C for 2 hours. Yield = 46%; ^{1}H NMR (MeOD-D_4, 90 MHz) δ (ppm): 8.08 (s, 1H) 4.08 (s, 3H) and 2.72 (s, 3H); MS *m/z* 174 $[M+1]^+$.

Example 15

A. Preparation of 3-chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one.



3-Chloro-5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (500 mg, 2.80 mmol) was suspended in trifluoroacetaldehyde methyl hemiacetal (3 mL). Potassium carbonate (119 mg, 0.86 mmol) was added and the mixture was heated to 120 °C. After 2.5 hours, the reaction mixture was allowed to cool to room temperature, then diluted with methanol and filtered. The filtrate was concentrated to dryness and diluted with acetone. The solution was filtered and the filtrate was concentrated to give 3-chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one (650 mg) as

a pink solid. Yield = 85%; ^{1}H-NMR (MeOD-D_4, 90 MHz) δ (ppm): 5.9 (q, J = 9.1 Hz, 1H), 4.01 (s, 3H) and 2.65 (s, 3H); MS-ESI *m/z* 272 $[M+1]^+$.

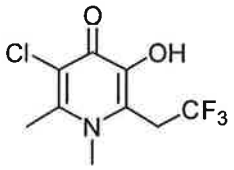
B. Preparation of
5-chloro-3-hydroxy-1-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one



In a similar manner, 5-chloro-3-hydroxy-1-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1*H*)-one (1.40 g) was prepared from 3-chloro-5-hydroxy-1-methylpyridin-4(1*H*)-one (1.27 g, 8.0 mmol) and trifluoroacetaldehyde methyl hemiacetal (12.7 mL) in presence of potassium carbonate (0.22 g, 1.6 mmol). Yield = 68%; ^{1}H NMR (DMSO-D_6) δ (ppm): 8.10 (s, 1H), 5.80 (q, J = 8.7 Hz, 1H) and 3.88 (s, 3H); MS *m/z* 258 $[M+1]^+$.

Example 16

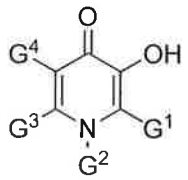
A. Preparation of
3-chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoroethyl)pyridin-4(1*H*)-one.



3-Chloro-5-hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-4(1H)-one (300 mg, 1.10 mmol) was suspended in 10 mL of acetonitrile and thionyl chloride (398 µL, 5.50 mmol) was added dropwise. The reaction was stirred at room temperature. After 2 hours, the reaction was concentrated. The crude was diluted with 10 mL of methanol and sodium borohydride (329 mg, 8.80 mmol) was added in small portions. After 15 hours, the reaction was filtered and the filtrate was concentrated in vacuo. The resulting solid was dissolved in methanol and ethyl acetate added, filtered and concentrated. The crude product was purified by column chromatography on silica gel using a mixture of 30% EtOAc in MeOH as eluant. Fractions rich in product were combined and evaporated to dryness. The residue product was recrystallised from methanol/ethyl acetate to give

maintained in the presence of TET. Cytotoxic concentration (CC1) was defined as the lowest compound concentration resulting in viability significantly below 80%. CC2 is the lowest compound concentration resulting in viability significantly below 80% in cells expressing AP (i.e. cultured without tetracycline).

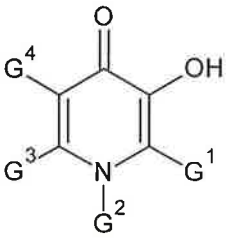
Chemical Structures of Compounds



Apo#	G^1	G^2	G^3	G^4
6994	H	CH_2CF_3	Me	H
6995	Me	CH_2CF_3	H	H
6998	$CH(CF_3)$-D-ala-NHMe	Me	H	H
7021	CH_2CF_3	Me	CH_2NMe_2	H
7022	$CH(OH)CF_3$	Me	CH_2NMe_2	H
7030	Et	CH_2CF_3	H	H
7032	$CH(OH)CF_3$	Me	CH_2-L-ala-OH	H
7033	$CH(OH)CF_3$	Me	CH_2-L-ala-NHMe	H
7035	$CH(OH)CF_3$	H	CH_2NMe_2	H
7038	$CH(OH)CF_3$	Me	Me	Cl
7040	CH_2CF_3	Me	Me	Cl
7041	$CH(NMe_2)CF_3$	Me	H	H
7053	Me	Me	H	$CH(NMe_2)CF_3$
7054	Me	Me	H	CH(piperidinyl)CF_3
7055	Me	Me	H	CH(imidazolyl)CF_3
7056	Me	Me	H	$CH(NHMe)CF_3$
7057	CH(propargylamino)CF_3	Me	H	H

Claims:

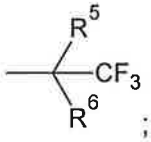
1. A compound of Formula I:



I

wherein

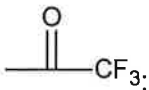
G^1 is H, C_1-C_4 alkyl, CH_2OH, $CH_2NR^1R^2$, $CH(R^4)CF_3$, $CH(R^7)CF_2H$, NR^1R^2, or



;

G^2 is H, C_1-C_4 alkyl, cyclopropyl or $(CH_2)_nCF_2R^3$;

G^3 is H, C_1-C_4 alkyl, CH_2OH, $CH_2NR^1R^2$, $CH(R^6)CF_3$, CH_2-A-OH, CH_2-A-NHR^9 or



; and

G^4 is H, C_1-C_4 alkyl, halo or $CH(R^8)CF_3$;

n is 1, 2 or 3;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholinyl, and piperidinyl;

R^3 is H or F;

R^4 and R^7 are independently selected from the group consisting of: H, OH, NR^1R^2, imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl and -A-NH-R^{10}; and when R^4 or R^7 is imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl or -A-NH-R^{10}, a point of attachment of R^4 or R^7 to the CH moiety of G^1 is an N atom of R^4 or R^7;

R^5 is C_1-C_4 alkyl;

R^6 is H or OH;

R^8 is selected from the group consisting of: NR^1R^2, imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl and -A-NH-R^{10}; and when R^8 is imidazolyl, 1-2-4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl or -A-NH-R^{10} a point of attachment of R^8 to the CH moiety of G^4 is an N atom of R^8;

R^9 and R^{10} are independently H or C_1-C_4 alkyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

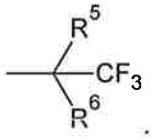
m is 1, 2 or 3; and

provided that:

at least one of G^1, G^2, G^3 and G^4 comprise at least one fluorine moiety;

when G^1 is $CH(R^4)CF_3$ and R^4 is H or OH, then either (i) G^3 is $CH_2NR^1R^2$, CH_2-A-OH, CH_2-A-NHR^9 or (ii) G^4 is halo or $CH(NR^1R^2)CF_3$; and

when G^3 is $CH(R^6)CF_3$, then G^1 is $CH_2NR^1R^2$, $CH(R^4)CF_3$, $CH(R^7)CF_2H$, NR^1R^2 or



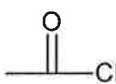
2. The compound of claim 1 wherein when G^1 is $CH(NR^1R^2)CF_3$, then G^3 and G^4 are independently H or C_1-C_4 alkyl, and G^2 is H, C_1-C_4 alkyl or cyclopropyl.

3. The compound of claim 1 or 2 wherein:

a) when G^2 is $(CH_2)_nCF_2R^3$, then G^1 and G^3 are independently H, C_1-C_4 alkyl, CH_2OH or $CH_2NR^1R^2$; or

b) when G^2 is H, then G^4 is H or C_1-C_4 alkyl.

4. The compound of any one of claims 1 to 3 wherein:

a) when G^3 is 

, then G^1 and G^4 are independently H or C_1-C_4 alkyl; or

b) when G^3 is $CH(R^6)CF_3$ and R^6 is H, then G^1 is NR^1R^2.

5. The compound of any one of claims 1 to 4 wherein:

a) when G^1 is $CH_2NR^1R^2$, then G^2 is $(CH_2)_nCF_2R^3$; or

b) when G^1 is $CH(R^7)CF_2H$, then G^3 and G^4 are independently H or C_1-C_4 alkyl, and G^2 is C_1-C_4 alkyl or cyclopropyl; or

c) when G^1 is $CH(R^4)CF_3$, then G^2 is C_1-C_4 alkyl or cyclopropyl; provided that when R^4 is H or OH, then G^3 is $CH_2NR^1R^2$, CH_2-A-OH, CH_2-A-NHR^9; or

d) when G^1 is $CH(R^4)CF_3$ and R^4 is H or OH, then G^4 is halo; or

e) when G^1 or G^3 is CH_2OH, then G^2 is $(CH_2)_nCF_2R^3$; or

f) when G^1 is NR^1R^2, then G^3 is $CH(R^6)CF_3$ and R^6 is H, G^4 is H or C_1-C_4 alkyl and G^2 is C_1-C_4 alkyl or cyclopropyl.

6. The compound of any one of claims 1 to 5 wherein when G^4 is $CH(R^8)CF_3$, then G^1 and G^3 are independently H or C_1-C_4 alkyl, and G^2 is hydrogen, C_1-C_4 alkyl or cyclopropyl.

7. The compound of any one of claims 1 to 6 wherein:

a) when G^3 is CH_2-A-OH or CH_2-A-NHR^9, then G^4 is H or C_1-C_4 alkyl, G^2 is C_1-C_4 alkyl or cyclopropyl and G^1 is $CH(R^4)CF_3$ where R^4 is H or OH; or

b) when G^3 is $CH_2NR^1R^2$, and G^2 is C_1-C_4 alkyl or cyclpropyl, then G^4 is H or C_1-C_4 alkyl, and G^1 is $CH(R^4)CF_3$ where R^4 is H or OH.

8. The compound of any one of claims 1 to 7 wherein when G^1 is $CH(R^4)CF_3$ and R^4 is H or OH, then either G^3 is $CH_2NR^1R^2$ or G^4 is halo.

9. The compound of any one of claims 1 to 8 wherein when G^3 is $CH(R^6)CF_3$, then G^1 is $CH_2NR^1R^2$ or NR^1R^2.

10. The compound of claim 1 wherein

G^1 is H, C_1-C_4 alkyl, -CH_2OH, or -$CH_2NR^1R^2$;

G^2 is $(CH_2)_n$-CF_2R^3;

G^3 is H, C_1-C_4 alkyl, -CH_2OH, or -$CH_2NR^1R^2$;

G^4 is H, C_1-C_4 alkyl, or halo;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

n is 1, 2 or 3; and

R^3 is H, or F.

11. The compound of claim 10 wherein n is 1.

12. The compound of claim 11 wherein G^4 is H.

13. The compound of claim 12 wherein R^3 is H.

14. The compound of claim 12 wherein R^3 is F.

15. The compound of claim 14 wherein:

a) G^1 is hydrogen, and G^3 is methyl; or

b) G^1 is methyl, and G^3 is H; or

c) G^1 is ethyl, and G^3 is H; or

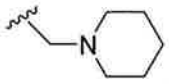
d) G^1 is H, and G^3 is H; or

e) G^1 is $-CH_2OH$, and G^3 is H; or

f) G^1 is $-CH_2NMe_2$, and G^3 is methyl; or

g) G^1 is $-CH_2NMe_2$, and G^3 is H; or

h) G^1 is $-CH_2OH$, and G^3 is methyl; or

i) G^1 is , and G^3 is methyl.

16. The compound of claim 13 wherein:

a) G^1 is methyl and G^3 is H; or

b) G^1 is H and G^3 is methyl; or

c) G^1 is $-CH_2NMe_2$ and G^3 is methyl.

17. The compound of claim 1 wherein

G^1 is $-CH(R^4)CF_3$;

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, C_1-C_4 alkyl, CH_2-A-OH, CH_2-A-NHR^9, or $CH_2NR^1R^2$;

G^4 is H, C_1-C_4 alkyl, or halo; and

R^4 is selected from the group consisting of: H, OH, NR^1R^2, imidazolyl, 1,2,4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl and -A-NH-R^{10}; and when R^4 is imidazolyl, 1,2,4-triazolyl, piperazinyl,

N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl or -A-NH-R^{10}, a point of attachment of R^4 to the CH moiety of G^1 is an N atom of R^4;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

m is 1, 2 or 3; and

R^9 and R^{10} are independently H, or C_1-C_4 alkyl.

18. The compound of claim 17 wherein G^2 is C_1-C_4 alkyl, or cyclopropyl; G^3 is H, or C_1-C_4 alkyl; and R^4 is selected from the group consisting of: NR^1R^2, imidazole, 1,2,4-triazole, piperazine, N-C_1-C_4 alkylpiperazine, N-benzylpiperazine, N-phenylpiperazine, 2-pyridylpiperazine and -A-NH-R^{10}.

19. The compound of claim 18 wherein G^2 is methyl.

20. The compound of claim 19 wherein G^3 is H and G^4 is H.

21. The compound of claim 20 wherein R^4 is NR^1R^2.

22. The compound of claim 20 wherein R^4 is A-NHR^{10}; A is D-alanyl; and R^{10} is methyl.

23. The compound of claim 21 wherein:

a) R^1 is methyl and R^2 is methyl; or

b) R^1 is methyl and R^2 is propargyl; or

c) R^1 is H and R^2 is cyclopropyl; or

d) R^1 is H and R^2 is allyl; or

e) NR^1R^2 is piperidinyl; or

f) NR^1R^2 is N-methylpiperazinyl.

24. The compound of claim 17 wherein G^3 is CH_2-A-OH, CH_2-A-NHR^9, or $CH_2NR^1R^2$; G^4 is H, or C_1-C_4 alkyl; and R^4 is H, or OH.

25. The compound of claim 24 wherein G^2 is methyl.

26. The compound of claim 25 wherein G^4 is H.

27. The compound of claim 26 wherein:

a) G^3 is $CH_2NR^1R^2$; R^1 is methyl; R^2 is methyl; and R^4 is H; or

b) G^3 is $CH_2NR^1R^2$; R^1 is methyl; R^2 is methyl; and R^4 is OH; or

c) G^3 is CH_2-A-OH; A is L-alanyl; and R^4 is OH; or

d) G^3 is CH_2-A-NHR^9; A is L-alanyl; R^9 is methyl; and R^4 is OH.

28. The compound of claim 17 wherein G^3 is H or C_1-C_4 alkyl; and G^4 is halo.

29. The compound of claim 28 wherein G^2 is methyl.

30. The compound of claim 29 wherein G^4 is chloro.

31. The compound of claim 30 wherein:

a) G^3 is methyl; and R^4 is OH; or

b) G^3 is methyl; and R^4 is H; or

c) G^3 is methyl; R^4 is NR^1R^2; R^1 is methyl; and R^2 is methyl; or

d) G^3 is H; R^4 is NR^1R^2; R^1 is methyl; and R^2 is methyl; or

e) G^3 is H; R^4 is NR^1R^2; and NR^1R^2 is piperidinyl; or

f) G^3 is H; and R^4 is H.

32. The compound of claim 1 wherein

G^1 is H, or C_1-C_4 alkyl;

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, or C_1-C_4 alkyl;

G^4 is $-CH(CF_3)(R^8)$;

R^8 is selected from the group consisting of: NR^1R^2, imidazole, 1,2,4-triazole, piperazine, N-C_1-C_4 alkylpiperazine, N-benzylpiperazine, N-phenylpiperazine, 2-pyridylpiperazine, and -A-NH-R^{10}; a point of attachment of R^8 to the –CH moiety of G^1 is an N-atom of R^8;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

A is -NH-$(CH_2)_m$-CO- or an alpha amino acid residue;

m is 1, 2 or 3; and

R^{10} is H, or C_1-C_4 alkyl.

33. The compound of claim 32 wherein G^3 is H.

34. The compound of claim 33 wherein G^1 is methyl.

35. The compound of claim 34 wherein:

a) G^2 is H; R^8 is -A-NH-R^{10}; A is L-alanyl; and R^{10} is methyl; or

b) G^2 is methyl; R^8 is NR^1R^2; R^1 is methyl and R^2 is methyl; or

c) G^2 is methyl; R^8 is NR^1R^2; R^1 is H and R^2 is methyl; or

d) G^2 is methyl; R^8 is NR^1R^2; and NR^1R^2 is piperidinyl; or

e) G^2 is methyl; R^8 is NR^1R^2; and NR^1R^2 is imidazolyl; or

f) G^2 is methyl; R^8 is NR^1R^2; and NR^1R^2 is N-methylpiperazinyl.

36. The compound of claim 1 wherein

G^1 is $CH_2NR^1R^2$, or NR^1R^2;

G^2 is C_1-C_4 alkyl, or cyclopropyl;

G^3 is $-CH(CF_3)(R^6)$;

G^4 is H, or C_1-C_4 alkyl;

R^6 is H, or OH; and

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl.

37. The compound of claim 36 wherein G^4 is H.

38. The compound of claim 37 wherein G^2 is methyl.

39. The compound of claim 38 wherein:

a) G^1 is NR^1R^2; R^1 is methyl; R^2 is methyl; and R^6 is H; or

b) G^1 is $CH_2NR^1R^2$; R^1 is methyl; R^2 is methyl; and R^6 is OH.

40. The compound of claim 1 wherein

G^1 is $-CH(CF_2H)(R^7)$;

G^2 is H, C_1-C_4 alkyl, or cyclopropyl;

G^3 is H, or C_1-C_4 alkyl;

G^4 is H, or C_1-C_4 alkyl;

R^7 is selected from the group consisting of: H, OH, NR^1R^2, imidazolyl, 1,2,4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl, and $-CH_2$-A-NH-R^{10}; and when R^7 is NR^1R^2, imidazolyl, 1,2,4-triazolyl, piperazinyl, N-C_1-C_4 alkylpiperazinyl, N-benzylpiperazinyl, N-phenylpiperazinyl, 2-pyridylpiperazinyl or $-CH_2$-A-NH-R^{10}, a point of attachment of R^7 to the –CH moiety of G^1 is an N-atom of R^7;

R^1 and R^2 are either (a) two independent groups or (b) together form a single ring group including the N to which they are bonded;

R^1 and R^2, when independent groups, are independently selected from the group consisting of: H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, allyl, and propargyl;

R^1 and R^2, when together form a single ring group including the N to which they are bonded, are selected from the group consisting of: piperazinyl, N-(C_1-C_4 alkyl)-substituted piperazinyl, morpholino, and piperidinyl;

A is $-NH-(CH_2)_m-CO-$ or an alpha amino acid residue;

m is 1, 2 or 3; and

R^{10} is H, C_1-C_4 alkyl.

41. The compound of claim 40 wherein:

a) G^2 is methyl, G^3 is H, G^4 is H, and R^7 is OH; or

b) G^2 is methyl, G^3 is H, G^4 is H, and R^7 is H.

42. The compound of claim 1 wherein
G^1 is $C(R^5)(R^6)(CF_3)$
G^2 is H, C_1-C_4 alkyl, or cyclopropyl;
G^3 is H, or C_1-C_4 alkyl; and
G^4 is H, or C_1-C_4 alkyl.

43. The compound of claim 42 wherein G^2 is methyl; G^3 is H; G^4 is H; R^5 is methyl; and R^6 is H or OH.

44. The compound of claim 43 wherein R^6 is OH.

45. A compound of any one of claims 1 to 44 for use in treating a medical condition related to a toxic concentration of iron.

46. Use of a compound of any one of claims 1 to 44 for preparation of a medicament for treatment of a medical condition related to a toxic concentration of iron.

47. The compound of claim 45 or the use of claim 46 wherein the medical condition related to a toxic concentration of iron is selected from the group consisting of: cancer, pulmonary disease, progressive kidney disease and Frederich's Ataxia.