Supporting Information

Synthesis and Structure-Activity Relationships of Novel Antimalarial 5-Pyridinyl-4(*1H*)-Pyridones.

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Contents:

A) Determination of physicochemical parameters

%HSA (Percentage of Human Serum Albumin Binding)

The determination of compounds binding to human serum albumin (HAS) has been carried out by retention time measurements using immobilized HAS HPLC columns obtained from Chiral Technologies Ltd, France. The column dimensions were 50x3 mm.

The mobile phase was 50mM ammonium acetate buffer pH 7.4 and HPLC grade 2-propanol. HPLC Method : Flow rate 1.8 ml/min applying 2.5 min 2-propanol gradient up to 30%. From 2.5 min to 4.5 min the 2-propanol concentration in the mobile phase was kept at 30%. From 4.5 min to 4.6 min, the 2-propanol concentration was decreased to 0% and kept like that until the end of the gradient run which was 6 min. A calibration set of compounds have been analyzed first for which plasma protein binding data were available: Warfarin, Nizatidine, Bromazepam, Carbamazepine, Budesonide, Nicardipine, Indomethacine Piroxicam, Naproxen. The calculation of the HSA binding data expressed as %HSA has been carried out as described previously[30].

Chromatographic Hydrophobicity Index (CHIlogD)

The determination of compounds Chromatographic Hydrophobicity Index (CHI) at acidic, neutral and alkaline pHs has been accomplished by retention time measurements using Luna C18 columns obtained from Phenomenex**.** The column dimensions were 50 x 3 mm, particle size, 5um. Compounds analysed were dissolved in Acetonitrile (0.5mM) from a stock solution 10mM in DMSO. Mobile Phase A : 50mM Ammonium Acetate aqueous solution, pH adjusted to 7.4 and 10.5 by addition of concentrated ammonia solution and 0.01M concentrated phosphoric acid in water, pH 2. Mobile Phase B : Acetonitrile. HPLC Method: Flow rate: 1.0ml/min, Temperature: 30ºC. Gradient: 0 to 3.0 min 0 to 100% B solvent*;* 3.0 to 3.5 min. 100% B solvent (Acetonitrile);

3.5 to 3.7 min. from 100% B to 0% B. Total run time 5 min. Calibration set of compounds : Theophylline, Phenyltetrazole, Benzimidazole, Colchicine, Phenyltheophylline, Acetophenone, Indole, Propiophenone,Butyrophenone, Valerophenone. The calculation of the Chromatographic Hydrophobicity data expressed as CHIlogD has been carried out as described previously[31]

Solubility in biorelevant fluids FaSSIF and FeSSIF

Organic solvents of HPLC grade were used. Ultra pure water (Milli-Q grade) was used. Buffers were prepared with ultra pure water and filtered using 0.45µ nylon filters. The compositions of the media employed in this assay have been prepared according to reported procedures[32]. 1 mg of solid compound was weighted in one 4 mL glass vial and 2 mL of the corresponding medium freshly prepared (SGF, FaSSIF, FeSSIF or PBS) were added. All these samples were prepared by duplicate. The samples were stirred (rolling mixing) for 24 hr at room temperature. If required, additional solid compound (0.1 mg) was added to maintain excess of it (saturated solutions). After 24 hours, the samples were filtered (Millipore Milex filters nylon 0.45 □m) and the filtrates were analysed by LC-MS. The pH of the final solution in each sample was measured with a pH-meter (WTW pH330i and a pH-electrode Sentix 41). All filtered aliquots were analysed by LC-MS. Quantification of those samples was carried out against calibration curves obtained from 1 mg/mL DMSO (Aldrich *cat. ref.*: 27685-5) stock solutions, by dilution with the mobile phase used in the chromatography. Depending on the solubility range, U.V. (1 µg/mL to 100 µg/mL) or MS (1 µg/mL to 1 ng/mL) detector were used in the quantification. The analysis of all LC-MS data was performed with MassLynx 3.4 software and Analyst 1.4.2. Statistical and graphic analysis of data was performed using Microsoft Excel. The concentration (µM) and solubility (µg/ml) for each compound was calculated using the peak areas from the sample and those from the calibration curve.

B) *In vitro* antimalarial assay procedures

In vitro activity against P. falciparum

P. falciparum trains 3D7A (MRA-151) and FCR3-A (MRA-158) were obtained from the Malaria research and Reference Reagent Resource Centre (MR4). Chloroquine disphosphate was purchased from Sigma.

The assays were performed in 96 well flat bottom microplates.

1. Serial dilutions of the compounds (50 μL of a 5x solution/well) were dispensed in duplicate.

2. The inoculum was prepared as a suspension of parasitized red blood cells (PRBCs) at 2.5% of hematocrit and 0.5% of parasitemia (*P. falciparum* 3D7A strain) in complete medium without hypoxanthine.

3. [^{3}H]Hypoxanthine (Amersham Biosciences) was added at a concentration of 1 μCi/mL (0.25 μCi /well); 200 μL of the suspension was distributed, leading to a final volume of 250 μL, at 2% of hematocrit and 0.5% of parasitemia/well.

4. In each plate, 2 columns were reserved for control wells:

Columm 11: PRBCs with 0.2% DMSO.

Columm 12: A12-D12- Uninfected RBCs – blank control.

E12-G12- PRBCs without DMSO.

H12-Non-radioactive well. PRBCs with cold hypoxanthine.

For each assay, Chloroquine and Atovaquone were used as internal controls.

5. The plates were incubated for 48 h at 37 ºC under low oxygen atmosphere. At the end of the assay, a thin film was made with the non-radioactive sample (well H12) for a visual control of the development of the parasites. Incorporation was stopped by freezing the plates overnight at –80 ºC.

6. After thawing the plates, the content of the wells was harvested on glass fibre filters (Wallac) with a semi-automated cell-harvester (Harvester 96, Tomtec). The filters were dried and treated with a Melt-on scintillator (Meltilex® A, PerkinElmer). Incorporation of radioactivity was measured with a β-counter (Wallac Microbeta, PerkinElmer). The assays were repeated at least three independent times.

C) *In vivo* efficacy assay procedures

Mice (CD1) were infected intravenously with $6.7x10^6$ *P. yoelii* 17X-parasitized erythrocytes. Drugs were formulated as suspensions in water 1% methylcellulose (Sigma) to form a fine suspension, which was kept at room temperature in the dark. The test compounds were administered one hour after infection (day 0) by oral route at 20 ml/Kg in 4 doses over 4 days (day 0 to day 3). Parasitaemia was measured on day 4 by flow cytometry using the nucleic acid dye YOYO-1 as described[40]. Parasitemias were fitted to a logistic equation and the therapeutic efficacy of compounds was expressed as the effective dose (mg/Kg) that reduces parasitemia by 50% or 90% with respect to vehicle treated groups (ED_{50} and ED_{90}, respectively).

D) PK experimental procedures

For pharmacokinetic studies, animals received 4(*1H*)-Pyridone derivatives by either bolus injection or orally by gavage. At selected time points, blood samples (25 µL) were obtained by tail puncture and mixed immediately with same volume (25 µL) of 0.1% saponin in distilled water for lysis. Protein precipitation process by liquid-liquid extraction was performed directly in a 96-well plate with filter system (MultiScreen Solvinert 0.45µm Hidrophobic PTFE; Millipore) by putting 10 µL of blood/saponin lysate sample per well, then adding 120 µL of suitable organic solvent as extractant, vortexing for 10 min. and finally filtrating with the help of a vacuum system. The filtrates were stored frozen at -70ºC until analysis by LC/MS/MS methods specifically devised for each compound. Concentration versus time data were analyzed by non-compartmental analysis (NCA) methods using WinNonlin® Professional Version 5.2 (Pharsight Corporation, Mountain View, California, USA). Additional statistical analysis of the data was performed when needed with GraphPad Prism® Version 5.01 (GraphPad Software Inc, San Diego California, USA).

E) Additional espectroscopical data

2,6-Dimethyl-6'-{[4-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (8)

^{1}H-NMR(δ, ppm, $CDCl_3$): 8.00(d, 1H); 7.65-7.53(m, 5H); 6.89(d, 1H); 6.20(s, 1H); 5.46(s, 2H); 2.29(s, 3H); 2.24(s, 3H).

2,6-Dimethyl-6'-{[3-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (9)

^{1}H-NMR(δ, ppm, $CDCl_3$): 8.02(d, 1H); 7.74(s, 1H); 7.63(m, 1H); 7.55-7.45(m, 3H); 6.90(d, 1H); 6.20(s, 1H); 5.45(s, 2H); 2.29(s, 3H); 2.24(s, 3H).

2,6-Dimethyl-6'-{[2-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (10)

^{1}H-NMR(δ, ppm, CD_3OD): 8.01(d, 1H); 7.76-7.71(m, 2H); 7.65-7.58(m, 2H); 7.52-7.47(m, 1H); 6.96(d,1H); 6.26(s, 1H); 5.58(s, 2H); 2.35(s, 3H); 2.26(s, 3H).

2,6-Dimethyl-6'-{[3,5-bis(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (11)

^{1}H-NMR(δ, ppm, CD_3OD): 8.07(bs, 2H); 8.00(d, 1H); 7.90(bs, 1H); 7.61(dd, 1H); 7.00(d, 1H); 6.26(s, 1H); 5.57(s, 2H); 2.35(s, 3H); 2.25(s, 3H).

6'-{[4-Fluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (12)

^{1}H-NMR(δ, ppm, $CDCl_3$): 8.01(d, 1H); 7.53(dd, 1H); 7.47-7.41(m, 2H); 7.10-7.02(m, 2H); 6.86(d, 1H); 6.20(s, 1H); 5.35(s, 2H); 2.29(s, 3H); 2.24(s, 3H).

6'-{[3,5-Difluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (13)

^{1}H-NMR(δ, ppm, CD_3OD): 8.00(d, 1H); 7.59(dd, 1H); 7.10-7.03(m, 2H); 6.97(d, 1H); 6.90-6.82(m, 1H); 6.26(s, 1H); 5.41(s, 2H); 2.35(s, 3H); 2.25(s, 3H).

2,6-Dimethyl-6'-{[4-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (15)

^{1}H-NMR(δ, ppm,$DMSO-d_6$): 11.15(bs, 1H); 7.93(s, 1H); 7.75-7.63(m, 4H); 7.54(d, 1H); 6.93(s, 1H); 5.92(s, 1H); 5,47(d, 2H); 2.18(s, 3H); 2.08(s, 3H).

2,6-Dimethyl-6'-{[3-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (16)

^{1}H-NMR(δ, ppm, CD_3OD): 7.98(d, 1H); 7.76(bs, 1H); 7.74-7.70(m, 1H); 7.60-7.53(m, 3H); 6.95(d, 1H); 6.27(s, 1H); 5.47(s, 2H); 2.34(s, 3H); 2.18(s, 3H).

2,6-Dimethyl-6'-{[2-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (17)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.16(bs, 1H); 7.94(d, 1H); 7.80-7.69(m, 3H); 7.60-7.53(m, 2H); 6.90(d, 1H); 5.92(s, 1H); 5.51(s, 2H); 2.18(s, 3H); 2.09(s, 3H).

2,6-Dimethyl-6'-{[3,5-bis(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (18)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.17(bs, 1H); 8.18(s, 2H); 8.07(s, 1H); 7.95(d, 1H); 7.57(dd, 1H); 6.96(d, 1H); 5.92(s, 1H); 5.54(s, 2H); 2.18(s, 3H); 2.08(s, 3H).

6'-{[4-Fluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (19)

^{1}H-NMR(δ, ppm, CD_3OD): 7.97(d, 1H); 7.55(dd, 1H); 7.50-7.46(m, 2H); 7.11-7.05(m, 2H); 6.90(d, 1H); 6.27(s, 1H); 5.35(s, 2H); 2.34(s, 3H); 2.19(s, 3H).

6'-{[3,5-Difluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (20)

^{1}H-NMR(δ, ppm, CD_3OD): 7.96(d, 1H); 7.57(dd, 1H); 7.10-7.03(m, 2H); 6.95(d, 1H); 6.89-6.82(m, 1H); 6.27(s, 1H); 5.41(s, 2H); 2.34(s, 3H); 2.19(s, 3H).

5-Bromo-2,6-dimethyl-6'-{[4-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (22)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.68(bs, 1H); 7.96(bs, 1H); 7.76-7.65(m, 4H); 7.58(d, 1H); 6.94(d, 1H); 5.47(s, 2H); 2.41(s, 3H); 2.10(s, 3H); [ES MS] m/z 454 (MH^+), 452(MH^-)

5-Bromo-2,6-dimethyl-6'-{[3-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (23)

^{1}H-NMR(δ, ppm, $CDCl_3$): 7.93(d, 1H); 7.70(s, 1H); 7.60(m, 1H); 7.57-7.43(m, 3H); 6.83(d, 1H); 5.38(s, 2H); 2.40(s, 3H); 2.08(s, 3H); [ES MS] m/z 454 (MH^+), 452(MH^-)

5-Bromo-2,6-dimethyl-6'-{[2-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (24)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.68(bs, 1H); 7.96(bs, 1H); 7.80-7.71(m, 3H); 7.60-7.55(m, 2H); 6.92(d, 1H); 5.52(s, 2H); 2.42(s, 3H); 2.11(s, 3H); [ES MS] m/z 454 (MH^+), 452(MH^-)

5-Bromo-2,6-dimethyl-6'-{[3,5-bis(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (25)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.70(bs, 1H); 8.18(s, 2H); 8.07(s, 1H); 7.98(d, 1H); 7.59(d, 1H); 6.98(d, 1H); 5.55(s, 2H); 2.41(s, 3H); 2.10(s, 3H); [ES MS] m/z 522 (MH^+)

5-Bromo-6'-{[4-fluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (26)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.68(bs, 1H); 7.97(s, 1H); 7.57-7.49(m, 3H); 7.23-7.17(m, 2H); 6.87(d, 1H); 5.34(s, 2H); 2.41(s, 3H); 2.10(s, 3H); [ES MS] m/z 404 (MH+)

5-Bromo-6'-{[3,5-difluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (27)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.69(bs, 1H); 7.96(d, 1H); 7.58(d, 1H); 7.19-7.14(m, 3H); 6.95(d, 1H); 5.39(s, 2H); 2.41(s, 3H); 2.10(s, 3H); [ES MS] m/z 422 (MH^+)

5-Chloro-2,6-dimethyl-6'-{[4-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (29)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.65(bs, 1H); 7.96(s, 1H); 7.76-7.66(m, 4H); 7.58(d, 1H); 6.93(d, 1H); 5.47(s, 2H); 2.37(s, 3H); 2.11(s, 3H); [ES MS] m/z 409 (MH^+)

5-Chloro-2,6-dimethyl-6'-{[3-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (30)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.64(bs, 1H); 7.96(d, 1H); 7.82(s, 1H); 7.77(m, 1H); 7.70-7.55(m, 3H); 6.93(d, 1H); 5.46(s, 2H); 2.36(s, 3H); 2.09(s, 3H); [ES MS] m/z 407(MH^-)

5-Chloro-2,6-dimethyl-6'-{[2-(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (31)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.64(bs, 1H); 7.96(s, 1H); 7.80-7.72(m, 3H); 7.60-7.54(m, 2H); 6.93(d, 1H); 5.52(s, 2H); 2.37(s, 3H); 2.11(s, 3H); [ES MS] m/z 409 (MH^+)

5-Chloro-2,6-dimethyl-6'-{[3,5-bis(trifluoromethyl)benzyl]oxy}-3,3'-bipyridin-4(1*H*)-one (32)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.66(bs, 1H); 8.18(s, 2H); 8.07(s, 1H); 7.98(d, 1H); 7.59(d, 1H); 6.98(d, 1H); 5.55(s, 2H); 2.37(s, 3H); 2.10(s, 3H); [ES MS] m/z 477 (MH^+),

5-Chloro-6'-{[4-fluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (33)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.65(bs, 1H); 7.97(s, 1H); 7.57-7.50(m, 3H); 7.23-7.17(m, 2H); 6.89(d, 1H); 5.34(s, 2H); 2.37(s, 3H); 2.11(s, 3H); [ES MS] m/z 359 (MH^+)

5-Chloro-6'-{[3,5-difluorobenzyl]oxy}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (34)

^{1}H-NMR(δ, ppm, DMSO-d_6): 11.63(bs, 1H); 7.96(s, 1H); 7.58(d, 1H); 7.21-7.14(m, 3H); 6.94(d, 1H); 5.38(s, 2H); 2.37(s, 3H); 2.10(s, 3H); [ES MS] m/z 377 (MH^+), 375 (MH^-)

3-(6-{[2,4-Difluorophenyl]ethynyl}-3-pyridinyl)-2,6-dimethyl-4*H*-pyran-4-one (43)

^{1}H-NMR(δ, ppm, CD_3OD): 8.46(bs,1H); 7.82-7.64 (m, 3H); 7.16-7.02(m, 2H); 6.30(s, 1H); 2.37(s,3H); 2.29(s, 3H).

2,6-Dimethyl-3-(6-{[3-(trifluoromethyl)phenyl]ethynyl}-3-pyridinyl)-4*H*-pyran-4-one (44)

^{1}H-NMR(δ, ppm, CD_3OD): 8.48(m,1H); 7.92-7.73(m, 3H); 7.67-7.52(m, 3H); 6.30(s, 1H); 2.37(s, 3H); 2.29(s, 3H)

6'-{[2,4-diifluorophenyl]ethynyl}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (46)

^{1}H-NMR(δ, ppm, CD_3OD): 8.44(m,1H); 7.79-7.65 (m, 3H); 7.12-7.05(m, 2H); 6.30(s, 1H); 2.36(s, 3H); 2.23(s, 3H)

5-Chloro-6'-{[2,4-difluorophenyl]ethynyl}-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (49)

^{1}H-NMR(δ, ppm, CD_3OD): 8.45(m,1H); 7.80-7.68 (m, 3H); 7.10(m, 2H); 2.51(s, 3H); 2.23(m, 3H)

[ES MS] m/z 371 (MH^+)

2,6-Dimethyl-3-(6-{2-[3-(trifluoromethyl)phenyl]ethyl}-3-pyridinyl)-4*H*-pyran-4-one (51)

^{1}H-NMR(δ, ppm, CD_3OD): 8.35(m,1H); 7.67.7.54(m, 3H); 7.46(m, 2H); 7.31(d, 1H); 6.27(bs, 1H); 3,14(s, 4H); 2.36(s, 3H); 2.23(s, 3H)

2,6-Dimethyl-6'-{2-[3-(trifluoromethyl)phenyl]ethyl}-3,3'-bipyridin-4(1*H*)-one (53)

^{1}H-NMR(δ, ppm, CD_3OD): 8.32(d,1H); 7.59(dd, 1H); 7.47(m, 4H); 7.30(d, 1H); 6.28(s, 1H); 3,14(s, 4H); 2.35(s, 3H); 2.16(s, 3H)

5-Chloro-2,6-dimethyl-6'-{2-[3-(trifluoromethyl)phenyl]ethyl}-3,3'-bipyridin-4(1*H*)-one (55)

^{1}H-NMR(δ, ppm, CD_3OD): 8.33(m,1H); 7.60(dd, 1H); 7.47(m, 4H); 7.30(d, 1H); 3.14(s, 4H); 2.50(s,3H); 2.17(s,3H); [ES MS] m/z 407 (MH+)

2,6-Dimethyl-3-(6-{4-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl)-4H-pyran-4-one (57).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.58 (m, 1H), 8.13(bd, 2H); 7.84-7.72 (m, 4H), 6.25 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H).

2,6-Dimethyl-3-(6-{3-[trifluoromethyl]phenyl}-3-pyridinyl)-4H-pyran-4-one (58).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.57 (d, 1H), 8.30 (s, 1H), 8.19 (d, 1H), 7.85-7.75 (m, 2H), 7.70-7.58 (m, 2H), 6.24 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

2,6-Dimethyl-3-(6-{2-[trifluoromethyl]phenyl}-3-pyridinyl)-4H-pyran-4-one (59).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.49 (bs, 1H), 7.77-7.47 (m, 6H), 6.24 (s, 1H), 2.31 (s, 3H), 2.27 (s, 3H).

3-(6-{4-Chlorophenyl}-3-pyridinyl)-2,6-dimethyl-4H-pyran-4-one (60).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.58 (s, 1H), 7.74-7.34 (m, 6H), 6.24 (s, 1H), 2.32 (s, 3H), 2.28 (s, 3H).

3-(6-{3-Chlorophenyl}-3-pyridinyl)-2,6-dimethyl-4H-pyran-4-one (61).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.55 (bs, 1H), 8.03 (bs, 1H), 7.90-7.86 (m, 1H), 7.77-7.75 (m, 2H), 7.42-7.39 (m, 2H), 6.24 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

3-(6-{2-Chlorophenyl}-3-pyridinyl)-2,6-dimethyl-4H-pyran-4-one (62).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.58 (s, 1H), 7.74-7.34 (m, 6H), 6.24 (s, 1H), 2.32 (s, 3H), 2.23 (s, 3H).

2,6-dimethyl-3-(6-phenyl-3-pyridinyl)-4H-pyran-4-one (63).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.57 (s, 1H), 7.98 (d, 2H, J= 8.5Hz), 7.81 (m, 2H), 7.48 (d, 2H, J= 8.5Hz), 6.24 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H).

3-(6-{4-Fluorophenyl}-3-pyridinyl)-2,6-dimethyl-4H-pyran-4-one (64).

^{1}H-NMR (δ, ppm, CD_3OD): 8.48 (d, 1H), 8.07-8.02 (m, 2H), 7.91 (d, 1H), 7.78 (dd, 1H), 7.25-7.20 (m, 2H), 6.30 (s, 1H), 2.38 (s, 3H), 2.30 (s, 3H).

3-(6-{2-Fluorophenyl}-3-pyridinyl)-2,6-dimethyl-4H-pyran-4-one (65).

^{1}H-NMR (δ, ppm, CD_3OD): 8.53 (d, 1H), 7.91-7.80 (m, 4H), 7.35-7.21 (m, 2H), 6.30 (s, 1H), 2.38 (s, 3H), 2.31 (s, 3H).

3-{6-[3-(hydroxymethyl)phenyl]-3-pyridinyl}-2,6-dimethyl-4H-pyran-4-one (66).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.57 (d, 1H, J= 2.2 Hz), 8.03-7.98 (m, 2H), 7.79 (d, 1H, J= 8.4Hz), 7.72 (dd, 1H, J= 2.2, 8.4 Hz), 7.48 (d, 2H, J= 8.1Hz), 6.23 (s, 1H), 4.77 (d, 2H, J= 5.8Hz), 2.31 (s, 3H), 2.29 (s, 3H).

4-[5-(2,6-dimethyl-4-oxo-4*H*-pyran-3-yl)-2-pyridinyl]benzonitrile (67).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.58 (d, 1H), 8.16-8.11 (m, 2H), 7.85-7.75 (m, 4H), 6.24 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

2,6-dimethyl-3-{6-[4-(methylsulfonyl)phenyl]-3-pyridinyl}-4H-pyran-4-one (68).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.60 (d, 1H), 8.24-8.20 (m, 2H), 8.08-8.04 (m, 2H), 7.86 (d, 1H, J= 7.7 Hz), 7.86 (dd, 1H, J= 2.0, 7.7 Hz), 6.25 (s, 1H), 3.10 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H).

2,6-Dimethyl-3-(6-{2,4-[bistrifluoromethyl]phenyl}-3-pyridinyl)-4H-pyran-4-one (69).

^{1}H-NMR (δ, ppm, CD_3OD): 8.54 (d, 1H), 8.12 (s, 1H), 8.08 (d, 1H), 7.88 (dd, 1H), 7.80 (d, 1H), 7.67-7.61 (m, 1H), 6.30 (s, 1H), 2.39 (s, 3H), 2.31 (s, 3H).

2,6-Dimethyl-3-(6-{3,5-[bistrifluoromethyl]phenyl}-3-pyridinyl)-4H-pyran-4-one (70).

^{1}H-NMR (δ, ppm, CD_3OD): 8.67 (s, 1H), 8.61 (d, 1H), 8.16 (d, 1H), 8.05 (s, 1H), 7.90 (dd, 1H), 6.30 (s, 1H), 2.39 (s, 3H), 2.32 (s, 3H).

3-[6-(4-hydroxyphenyl)-3-pyridinyl]-2,6-dimethyl-4H-pyran-4-one (71).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.60-8.55 (m, 1H), 7.78-7.70 (m, 2H), 7.67-7.63 (m, 1H), 7.51-7.46 (m, 1H), 7.41-7.30 (m, 2H), 6.24 (s, 1H), 2.32 (s, 3H), 2.31 (s, 3H).

4-[5-(2,6-dimethyl-4-oxo-4H-pyran-3-yl)-2-pyridinyl]benzaldehyde (72).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.60-8.54 (m, 1H), 8.11 (d, 2H, J= 7.9 Hz), 7.87-7.39 (m, 6H), 6.72 (t, 3H), 6.24 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H).

2,6-dimethyl-3-(6-{3-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl)-4H-pyran-4-one (73).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.56 (s, 1H), 7.95 (bs, 1H), 7.92-7.91 (m, 2H), 7.78-7.76 (m, 2H), 7.29 (bs, 1H), 6.24 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

2,6-Dimethyl-3-(6-{2-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl)-4H-pyran-4-one (74).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.59 (bs, 1H), 7.89-7.86 (m, 1H), 7.74-7.72 (m, 2H), 7.46-7.37 (m, 3H), 6.24 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

2,6-dimethyl-3-{6-[4-(methyloxy)phenyl]-3-pyridinyl}-4H-pyran-4-one (75).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.50 (m, 1H); 8.01-7.93 (m, 2H), 7.75-7.65 (m, 2H); 7.04-6.97 (m, 2H), 6.23 (s,1H), 3.87 (s, 3H), 2.31(s, 3H), 2.28(s, 3H); [ES MS] m/z 308 (MH+).

3-{6-[2-chloro-4-(trifluoromethyl)phenyl]-3-pyridinyl}-2,6-dimethyl-4H-pyran-4-one (76).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.60 (m, 1H); 7.81 (m, 5H), 6.25 (s,1H), 2.33(s, 3H), 2.31(s, 3H).

3-{6-[2-chloro-5-(trifluoromethyl)phenyl]-3-pyridinyl}-2,6-dimethyl-4H-pyran-4-one (77).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.61 (m, 1H); 7.96 (m,1H), 7.81-7.65 (m, 2H), 7.65-7.56 (m, 2H), 6.25 (s,1H), 2.33(s, 3H), 2.31(s, 3H).

3-{6-[2-fluoro-4-(trifluoromethyl)phenyl]-3-pyridinyl}-2,6-dimethyl-4H-pyran-4-one (78).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.62 (m, 1H); 8.19 (t, 1H, J= 8.0 Hz), 7.75 (dd,1H, J= 2.2, 8.5 Hz), 7.72-7.63 (m, 2H), 7.58-7.42 (m, 2H), 6.24 (s,1H), 2.33(s, 3H), 2.30(s, 3H).

3-{6-[2-fluoro-5-(trifluoromethyl)phenyl]-3-pyridinyl}-2,6-dimethyl-4H-pyran-4-one (79).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.61 (dd, 1H, J= 0.9, 2.3 Hz), 8.39 (dd, 1H, J= 2.3, 7.2 Hz), 7.90 (m, 1H, J= 0.9, 2.3, 8.2 Hz), 7.76 (dd, 1H, J= 2.3, 8.2 Hz), 7.69-7.62 (m, 1H), 7.34-7.28 (m, 1H), 6.24 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H).

2,6-Dimethyl-6'-{4-[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1H)-one (83).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.27 (bs, 1H), 8.52 (bs, 1H), 8.32 (d, 2H), 8.06 (d, 1H), 7.85 (d, 2H), 7.76 (d, 1H), 5.98 (s,1H), 2.21 (s, 3H), 2.15 (s, 3H).

2,6-Dimethyl-6'-{3-[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1H)-one (84).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.25 (s, 1H), 8.51 (d, 1H), 8.45 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.81-7.71 (m, 3H), 5.98 (s,1H), 2.21 (s, 3H), 2.14 (s, 3H).

2,6-Dimethyl-6'-{2-[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1H)-one (85).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.25 (s, 1H), 8.43 (d, 1H), 7.87-7.47 (m, 6H), 5.98 (s,1H), 2.21 (s, 3H), 2.13 (s, 3H).

6'-(4-Chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (86).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.24 (s, 1H), 8.46 (s, 1H), 8.13 (d, 2H), 7.97 (d, 1H), 7.71 (dd, 1H), 7.54 (d, 2H), 5.96(s,1H), 2.21 (s, 3H), 2.13 (s, 3H).

6'-(3-Chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (87).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.25 (s,1H), 8.48 (s, 1H), 8.15-8.01 (m, 3H), 7.72 (dd, 1H), 7.53-7.50 (m, 2H), 5.97 (s, 1H), 2.21 (s, 3H), 2.14 (s, 3H).

6'-(2-Chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (88).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.26 (s, 1H), 8.48 (s, 1H), 7.74-7.45 (m, 6H), 5.98 (s, 1H), 2.21 (s, 3H), 2.15 (s, 3H).

2,6-dimethyl-6'-phenyl-3,3'-bipyridin-4(1H)-one (89).

^{1}H-NMR (δ, ppm,, DMSO-d_6): 11.23 (s, 1H), 8.45 (m, 1H), 8.14-8.07 (m, 2H), 7.95 (d, 1H, J= 8.4 Hz), 7.69 (dd, 1H, J= 2.5, 8.4 Hz), 7.53-7.39 (m, 3H), 5.78 (s, 1H), 2.21 (s, 3H), 2.14 (s, 3H).

6'-(4-Fluorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (90).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.23 (s, 1H), 8.44 (d, 1H), 8.18-8.13 (m, 2H), 7.94 (d, 1H), 7.69 (dd, 1H), 7.34-7.28 (m, 2H), 5.96 (s, 1H), 2.21 (s, 3H), 2.13 (s, 3H).

6'-(2-Fluorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (91).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.20 (s, 1H), 8.50 (d, 1H), 7.97 (dd, 1H), 7.79 (dd, 1H), 7.72 (dd, 1H), 7.52-7.44 (m, 1H), 7.37-7.31 (m, 2H), 5.98 (s,1H), 2.21 (s, 3H), 2.14 (s, 3H).

6'-[3-(hydroxymethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (92).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.23 (s, 1H), 8.44 (d, 1H), 8.06 (d, 2H, J=8.3Hz), 7.92 (d, 1H, J=8.2Hz), 7.67 (dd, 1H, J= 2.1, 8.2Hz), 7.42 (d, 1H, J= 8.3Hz), 5.96 (s,1H), 5.24 (t, 1H, J= 5.6Hz), 4.55 (d, 2H, J= 5.6Hz), 2.21 (s, 3H), 2.14 (s, 3H).

4-(2',6'-dimethyl-4'-oxo-1',4'-dihydro-3,3'-bipyridin-6-yl)benzonitrile (93).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.26 (s, 1H), 8.53 (d, 1H), 8.31 (d, 2H, J= 8.4 Hz), 8.12-8.06 (m, 1H), 7.99-7.94 (m, 2H), 7.81-7.74 (m, 1H), 5.97 (s,1H), 2.21 (s, 3H), 2.14 (s, 3H).

2,6-dimethyl-6'-[4-(methylsulfonyl)phenyl]-3,3'-bipyridin-4(1H)-one (94).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.27 (s, 1H), 8.53 (d, 1H), 8.40-8.35 (m, 2H), 8.12-7.99 (m, 3H), 7.78 (dd, 1H, J= 2.2, 8.1 Hz), 5.98 (s,1H), 3.27(s, 3H), 2.21 (s, 3H), 2.15 (s, 3H).

2,6-Dimethyl-6'-{2,4-bis[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1H)-one (95).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.28 (s, 1H), 8.48 (d, 1H), 8.17 (bs, 2H), 7.85 (d, 1H), 7.78 (dd, 1H), 7.57 (d, 1H), 5.99 (s,1H), 2.22 (s, 3H), 2.14 (s, 3H).

2,6-Dimethyl-6'-{3,5-bis[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1H)-one (96).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.28 (s, 1H), 8.77 (s, 2H), 8.55 (d, 1H), 8.30 (d, 1H), 8.17 (s, 1H), 7.81 (dd, 1H), 5.98 (s, 1H), 2.22 (s, 3H), 2.15 (s, 3H).

2,6-dimethyl-6'-{4-[(2,2,2-trifluoroethyl)oxy]phenyl}-3,3'-bipyridin-4(1*H*)-one (97).

^{1}H-NMR (δ, ppm, $CDCl_3$): 8.53 (s, 1H), 7.96 (d, 2H, J= 8.2 Hz), 7.79-7.70 (m, 2H), 7.45 (d, 2H, J= 8.2 Hz), 6.23 (s, 1H), 2.31 (s, 3H), 2.28 (s, 3H).

6'-[4-(difluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (98).

^{1}H-NMR (δ, ppm, CD_3OD): 8.51 (s, 1H), 8.18-8.10 (m, 2H), 8.03-7.96 (m, 1H), 7.85-7.78 (m, 1H), 7.72-7.68 (m, 2H), 6.84 (t, 2H), 6.31 (s, 1H), 2.37 (s, 3H), 2.25 (s, 3H).

2,6-dimethyl-6'-{3-[(trifluoromethyl)oxy]phenyl}-3,3'-bipyridin-4(1*H*)-one (99).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.26 (bs, 1H), 8.49 (s, 1H), 8.14 (d, 1H), 8.08-8.03 (m, 2H), 7.74 (dd, 1H), 7.66-7.61 (m, 1H), 7.42 (d, 1H), 5.97 (s,1H), 2.21 (s, 3H), 2.14 (s, 3H).

2,6-Dimethyl-6'-{2-[(trifluoromethyl)oxy]phenyl}-3,3'-bipyridin-4(1H)-one (100).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.26 (s, 1H), 8.50 (s, 1H), 7.86-7.45 (m, 6H), 5.98 (s, 1H), 2.21 (s, 3H), 2.13 (s, 3H).

2,6-dimethyl-6'-[4-(methyloxy)phenyl]-3,3'-bipyridin-4(1H)-one (101).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.28-11.13 (bs, 1H); 8.40 (m, 1H), 8.09-8.03 (m, 2H), 7.90-7.84 (m, 1H), 7.66-7.61 (m, 1H), 7.07-7.01 (m, 2H), 5.95 (s,1H), 3.81 (s, 3H), 2.21(s, 3H), 2.13(s, 3H); [ES MS] m/z 307 (MH+)

6'-[2-chloro-4-(trifluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (102).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.27 (s, 1H), 8.53 (m, 1H), 8.01 (m, 1H), 7.85 (m, 2H), 7.76 (m, 2H), 5.99 (s,1H), 2.22(s, 3H), 2.15(s, 3H).

6'-[2-chloro-5-(trifluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (103).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.27 (bs, 1H), 8.53 (m, 1H), 7.96 (m, 1H), 7.88-7.74 (m, 4H), 5.99 (s,1H), 2.22(s, 3H), 2.15(s, 3H). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.24 (bs, 1H), 8.57 (m, 1H), 8.20 (t, 1H, J= 7.6 Hz), 7.91-7.68 (m, 4H), 5.98 (s,1H), 2.22 (s, 3H), 2.15(s, 3H).

6'-[2-fluoro-4-(trifluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (104).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.24 (bs, 1H), 8.57 (m, 1H), 8.20 (t, 1H, J= 7.6 Hz), 7.91-7.70 (m, 4H), 5.98 (s,1H), 2.22 (s, 3H), 2.15(s, 3H).

6'-[2-fluoro-5-(trifluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (105).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.27 (s, 1H), 8.60-8.53 (m, 1H), 8.38-8.31 (m, 1H), 7.94-7.85 (m, 2H), 7.79 (dd, 1H, J= 2.2, 8.0 Hz), 7.67-7.57 (m, 1H), 5.98 (s, 1H), 2.21 (s, 3H), 2.15 (s, 3H).

5-Bromo-2,6-dimethyl-6'-{3-[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1*H*)-one (107).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.75 (s, 1H), 8.53 (d, 1H), 8.46 (s, 1H), 8.42 (d, 1H), 8.14 (d, 1H), 7.82-7.72 (m, 3H), 2.44 (s, 3H), 2.16 (s, 3H); [ES MS] m/z 421 (MH-).

5-Bromo-6'-(4-chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (108).

^{1}H-NMR (δ, ppm, DMSO-d_6): 8.48 (s, 1H), 8.15 (d, 2H), 8.01 (d, 1H), 7.74 (dd, 1H), 7.55 (d, 2H), 2.44 (s, 3H), 2.15 (s, 3H); [ES MS] m/z 389 (MH+).

5-Bromo-6'-(2-chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (109).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.78 (s, 1H), 8.50 (s, 1H), 7.77-7.69 (m, 2H), 7.66-7.57 (m, 2H), 7.48-7.45 (m, 2H), 2.44 (s, 3H), 2.16 (s, 3H); [ES MS] m/z 389 (MH+).

5-Bromo-6'-(4-fluorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (110).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.76 (s, 1H), 8.47 (m, 1H), 8.17 (m, 2H), 7.97 (d, 1H), 7.72 (dd, 1H), 7.35-7.29 (m, 2H), 2.44 (s, 3H), 2.15 (s, 3H); [ES MS] m/z 371 (MH-).

5-Bromo-6'-(2-fluorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (111).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.77 (s, 1H), 8.52 (d, 1H), 7.98 (td, 1H), 7.82 (dd, 1H), 7.75 (dd, 1H), 7.53-7.45 (m, 1H), 7.38-7.31 (m, 2H), 2.44 (s, 3H), 2.16 (s, 3H); [ES MS] m/z 373 (MH+).

5-bromo-6'-[3-(hydroxymethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (112).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.79 (s, 1H), 8.48 (d, 1H, J= 2.3 Hz), 8.09 (d, 2H, J= 8.4 Hz), 7.97 (d, 1H, J= 8.2 Hz), 7.72 (dd, 1H, J= 2.3, J= 8.2 Hz), 7.45 (d, 2H, J= 8.4 Hz), 4.57 (s, 2H), 2.45 (s, 3H), 2.17 (s, 3H); [ES MS] m/z 384 (MH-).

4-(5'-bromo-2',6'-dimethyl-4'-oxo-1',4'-dihydro-3,3'-bipyridin-6-yl)benzonitrile (113).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.78 (s, 1H), 8.55 (d, 1H, J= 2.3 Hz), 8.36-8.30 (m, 2H), 8.13 (d, 1H, J= 8.2 Hz), 7.99-7.94 (m, 2H), 7.80 (dd, 2H, J= 2.3, 8.2 Hz), 4.57 (s, 2H), 2.44 (s, 3H), 2.16 (s, 3H); [ES MS] m/z 381 (MH+).

5-bromo-2,6-dimethyl-6'-[4-(methylsulfonyl)phenyl]-3,3'-bipyridin-4(1H)-one (114).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.80 (s, 1H), 8.56 (d, 1H, J= 2.2 Hz), 8.39 (d, 2H, J= 8.4 Hz), 8.13 (d, 1H, J= 8.2 Hz), 8.04 (d, 2H, J= 8.4 Hz), 7.81 (dd, 1H, J= 2.2, J= 8.4 Hz), 3.27 (s, 3H), 2.44 (s, 3H), 2.17 (s, 3H); [ES MS] m/z 434 (MH+).

5-Bromo-2,6-dimethyl-6'-{2,4-bis[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1H)-one (115).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.80 (s, 1H), 8.50 (d, 1H), 8.19 (bs, 2H), 7.86 (d, 1H), 7.81 (dd, 1H), 7.60 (d, 1H), 2.45 (s, 3H), 2.15 (s, 3H); [ES MS] m/z 489 (MH-).

5-Chloro-2,6-dimethyl-6'-{2-[(trifluoromethyl)oxy]phenyl}-3,3'-bipyridin-4(1*H*)-one (117).

^{1}H-NMR (δ, ppm, DMSO-d_6): 8.47 (s, 1H), 7.88-7.85 (m, 1H), 7.69-7.49 (m, 5H), 2.22 (s, 3H), 2.00 (s, 3H); [ES MS] m/z 395 (MH+).

5-Chloro-2,6-dimethyl-6'-{4-[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1*H*)-one (118).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.85(bs, 1H); 8.54 (m, 1H), 8.33 (d, 2H), 8.09(d, 1H), 7.86(d, 2H); 7.78(m, 1H); 2.39 (s, 3H), 2.15 (s, 3H); [ES MS] m/z 379 (MH+).

5-Chloro-2,6-dimethyl-6'-{3-[trifluoromethyl]phenyl}-3,3'-bipyridin-4(1*H*)-one (119).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.77(bs, 1H); 8.53 (m, 1H), 8.46-8.41 (m, 2H), 8.14(d, 1H), 7.82-7.72(m, 3H); 2.40 (s, 3H), 2.16 (s, 3H); [ES MS] m/z 377 (MH-).

5-Chloro-6'-(3-chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (120).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.74 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 8.06-8.00 (m, 2H), 7.71 (dd, 1H), 7.51-7.44 (m, 2H), 2.36 (s, 3H), 2.12 (s, 3H); [ES MS] m/z 345 (MH+).

5-Chloro-6'-(3-chlorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (121).

^{1}H-NMR (δ, ppm, DMSO-d_6): 8.44 (s, 1H), 7.68-7.55 (m, 4H), 7.45-7.41 (m, 2H), 2.21 (s, 3H), 2.00 (s, 3H); [ES MS] m/z 343 (MH-)

5-Chloro-6'-(4-fluorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (122).

^{1}H-NMR (δ, ppm, DMSO-d_6): 12-10(bs, 1H); 8.45 (d, 1H), 8.15(m, 2H); 7.95 (d, 1H); 7.70(dd, 1H); 7.31(m, 2H); 2.36 (s, 3H), 2.12 (s, 3H); [ES MS] m/z 327 (MH-).

5-Chloro-6'-(2-fluorophenyl)-2,6-dimethyl-3,3'-bipyridin-4(1*H*)-one (123).

^{1}H-NMR (δ, ppm, DMSO-d_6): 12-11(bs, 1H); 8.52 (m, 1H), 7.98 (m, 1H); 7.77(m, 2H); 7.47(m, 1H); 7.34(m, 2H); 2.37(s, 3H), 2.13(s, 3H); [ES MS] m/z 329 (MH+).

5-chloro-6'-[2-chloro-4-(trifluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (124).

^{1}H-NMR (δ, ppm, DMSO-d_6): 8.50 (m, 1H), 7.98 (m, 1H); 7.85 (m, 2H); 7.70(m, 2H); 2.21(s, 3H), 2.01(s, 3H); [ES MS] m/z 413 (MH+).

5-chloro-6'-[2-fluoro-4-(trifluoromethyl)phenyl]-2,6-dimethyl-3,3'-bipyridin-4(1H)-one (125).

^{1}H-NMR (δ, ppm, DMSO-d_6): 11.90-11.60(bs, 1H); 8.59 (m, 1H); 8.21 (m, 1H), 7.85 (m, 4H); 7.73 (m, 1H); 2.40(s, 3H), 2.17(s, 3H); [ES MS] m/z 397 (MH+)