4-[(*N*-Imidazol-2-ylmethyl)anilino]pyranopyridine Analogs as Novel Anti-Angiogenic Agents

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We attempted to replace a benzopyran ring of 4-[(*N*-imidazol-2-ylmethyl)-4-chloroanilino]benzopyran, previously discovered as anti-angiogenic agent with antitumor activity, with pyranopyridines. The [3,2-c]-, [3,2-b]-, [2,3-c]-, and [2,3-b]-pyranopyridines with *N*-(imidazol-2-ylmethyl)aniline moiety at the 4-position, were synthesized respectively, and evaluated for primary anti-angiogenic properties through primary cultured HUVEC tube formation assay. From this study, we found that the pyranopyridine ring, especially [3,2-b]- and [2,3-c]-isomer, can replace the benzopyran ring of the compound **1** and can be optimized through the introduction of substituents both on the pyranopyridine ring and the aniline moiety for the identification of a novel anti-angiogenic agent.

Key Words : Pyranopyridine, Angiogenesis, HUVEC tube formation

Introduction

Angiogenesis is a multistep process by which new capillaries sprout and grow from existing blood vessels.[1] Growing tumors require a vasculature to provide nutrients and remove waste product, as well as providing a conduit for the dispersal of metastases.[2,3] Then, angiogenesis is well recognized as an important mechanism governing tumor growth and metastases. Some degree of skepticism towards the potential of anti-angiogenic cancer therapy arose from disappointing results in early clinical trials, but new clinical data with recently developed agents have provided a proof of concept for this therapy.[4,5]

In a previous study, we found that 4-[(*N*-imidazol-2-ylmethyl)-4-chloroanilino]benzopyran compound **1** (Fig. 1) strongly inhibited HUVEC tube formation and significantly inhibited tumor growth by 52% on A549 (human non small cell lung carcinoma) in nude mice xenografts without any significant side effects by oral administration.[6] With the compound **1** in hand, we continuously attempted to optimize **1**, aiming at the identification of a novel structure showing anti-angiogenic properties. In this study, we synthesized a series of pyranopyridines bearing *N*-(imidazol-2-ylmethyl)-aniline moiety at the 4-position and evaluated their biological profiles to determine whether the pyranopyridine can replace the benzopyran ring of **1**, and to identify a novel anti-angiogenic agent.

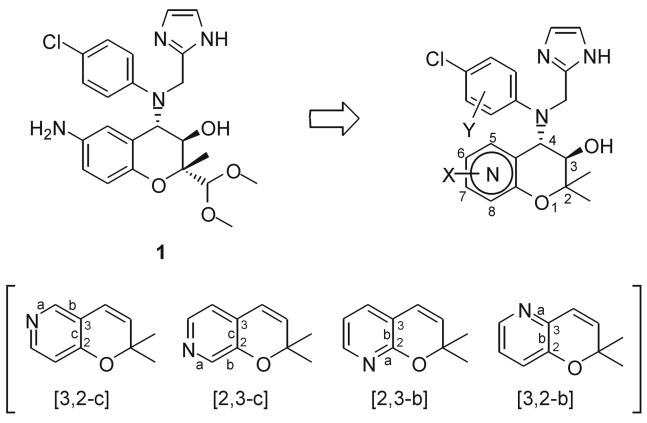
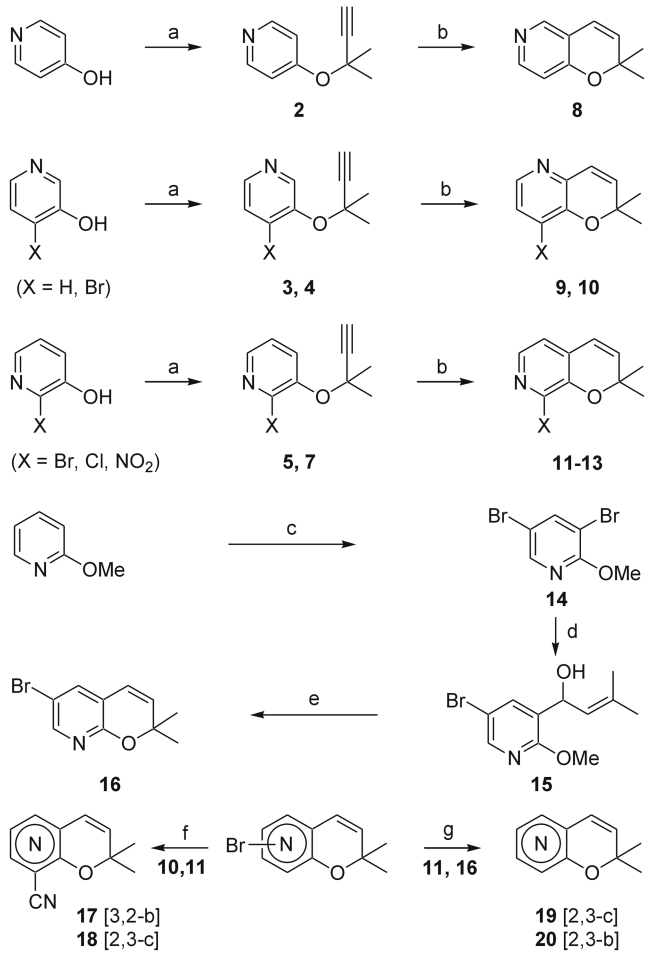


Figure 1

Chemistry

As the core intermediates to obtain 4-[(*N*-imidazol-2-ylmethyl)anilino]pyranopyridine derivatives, 4 types of 2,2-dimethyl-2*H*-1-pyranopyridines (**8**-**13**, **16**-**20**), [3,2-c], [3,2-b], [2,3-c], and [2,3-b], were prepared (Scheme 1).[7] To eliminate one of the chiral centers, we introduced dimethyl function at the 2-position instead of an acetal of **1**. Alkylation of 4-hydroxypyridine with 3-chloro-3-methyl-but-1-yne using phase transfer catalyst gave the propargyl ether **2**, and cyclisation of **2** through the Claisen rearrangement resulted in 2*H*-pyrano[3,2-c]pyridine **8** in overall 50% yield. It has been reported that the same procedure using 3-hydroxypyridine as a starting material exclusively gave one regioisomer, [3,2-b]- **9**, with less than 5% of [2,3-c]-isomer,[7] which was the same as our result. 8-Bromo [3,2-b]-compound **10** was also prepared by the same procedure from 4-bromo-3-hydroxypyridine obtained through a sequence of reactions;[8] *O*-protection of 3-hydroxypyridine with *N*,*N*-diethylcarbamoylchloride, selective bromination to the 4-position, and deprotection of carbamoyl group using NaOMe.[9] To obtain [2,3-c]-isomer, the 2-position blocked staring material such as 2-bromo-3-pyridinol was used. The alkylation and subsequent cyclisation provided the 8-bromo-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine **11**. Additionally, 8-chloro **12**, and 8-nitro **13** compounds were prepared. Because

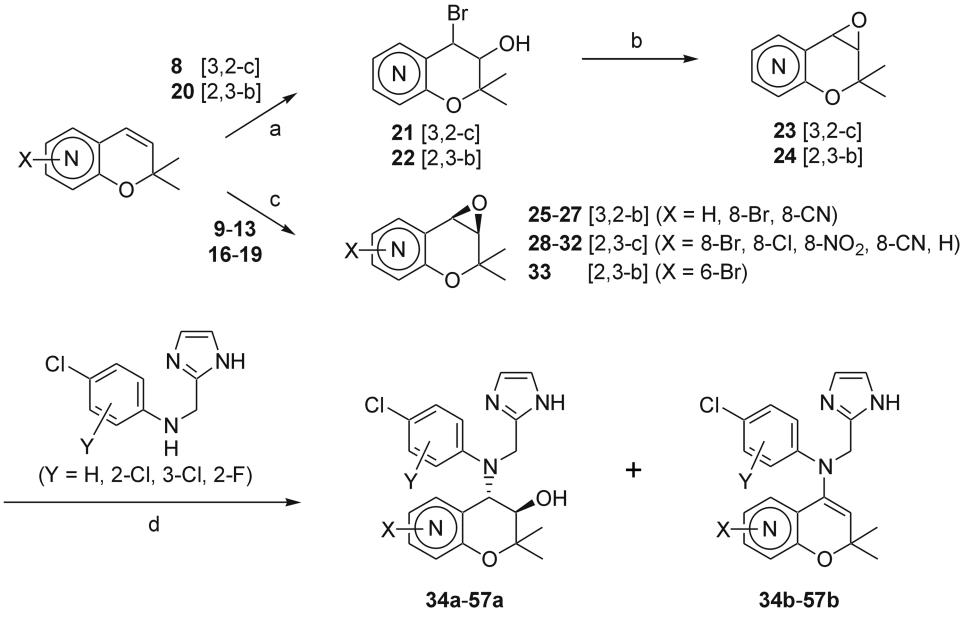


Scheme 1. Reagents and conditions: (a) 3-cloro-3-methylbut-1-yne, 40% benzyltrimethylammonium hydroxide, NaOH, CH_2Cl_2, rt; (b) *o*-dichlorobenzene, reflux; (c) NaOAc, Br_2, HOAc, rt ~80 °C; (d) *n*-BuLi, 3-methyl-2-butenal, ether/THF, −78 °C; (e) 48% HBr, HOAc, 100 °C; (f) CuCN, DMF, microwave, 200 °C; (g) *n*-BuLi, ether, −78 °C.

the treatment of 2-pyridinol with 3-chloro-3-methylbut-1-yne didn't give the desired *O*-alkylation product, alternative method was employed for the synthesis of the [2,3-b]-isomers. The reaction of 3,5-dibromo-2-methoxypyridine **14**[10] with *n*-BuLi and 3-methyl-2-butenal gave the allylic alcohol **15**, followed by the treatment with 48% HBr in acetic acid provided the pyrano[2,3-b]pyridine **16**. The bromine of pyranopyridines was further converted to nitrile via nucleophilic substitution with CuCN under microwave irradiation, or debrominated using *n*-BuLi.

For the preparation of optically pure compounds, an epoxidation using Jacobsen's catalyst (*R*,*R*) was attempted.[11] The enantioselective epoxidation of [3,2-b]- and [2,3-c]-isomers was smoothly proceeded (Scheme 2). However, the epoxidation of [3,2-c]- **8** and [2,3-b]-pyranopyridine **20** using Jacobsen's catalyst didn't yield the significant amount of product. Therefore, we prepared racemic epoxides *via* the bromohydrin intermediates. Unlike unsubstituted pyrano-[2,3-b]pyridine, 6-bromopyrano[2,3-b]pyridine **16** was reacted with Jacobsen's catalyst to afford an optically active epoxide.

While the compound **1** was prepared from the benzopyran epoxide by the treatment with *N*-(1*H*-imidazol-2-ylmethyl)-anilines in the presence of $CoCl_2$ in CH_3CN, pyranopyridine epoxide didn't react with anilines in that condition.[12,13] Through the several trials for the epoxide ring opening in various conditions, the method using NaH in DMSO was employed. Depending on the substituents at the pyrano-pyridine ring and *N*-(imidazol-2-ylmethyl)aniline or the amount of base and the reaction time, the dehydrated compounds **34b**-**57b** were obtained in various yields as well as **34a**-**57a** as represented in Table 1. Generally, the 2-substituted anilines seemed to yield dehydrated products **b** less than the other derivatives.

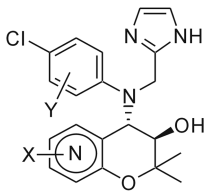


Scheme 2. Reagents and conditions: (a) NBS, DMSO, H_2O, rt; (b) KOH, ether/THF, rt; (c) Jacobsen's cat. (*R*,*R*), Na_2HPO_4, NaOCl, CH_2Cl_2, rt; (d) NaH, DMSO, rt.

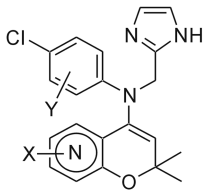
Results and Discussion

The inhibitory effect of the synthesized compounds on angiogenesis was measured by the vascular tube formation assay of HUVECs (human umbilical vein endothelial cells) at 50 μM concentration, which is one of the major angiogenic steps (Table 1). We used primary cultured cells within passage 5 on Matrigel. In previous study on the benzopyran analogs of **1**, *p*-chloro substituted anilines represented the most potent efficacy in HUVEC tube formation assay. Based on 4-chloro substituted aniline, we prepared 4-chloro, 2,4-dichloro, 3,4-dichloro, and 2-fluoro-4-chloroanilines to examine the effect of disubstitution. Primarily, we investigated the efficacy of unsubstituted compounds at the pyranopyridine ring. The [3,2-c]- **34a**-**37a** and [2,3-b]-isomers **54a**-**57a** didn't represent any significant efficacy in this experiment. The pyrano[3,2-b]pyridine **38a** showed a weak activity, and its dehydrated analog **38b** significantly inhibited HUVEC tube formation. However, 4-(2,4-dichloroanilino)pyrano[3,2-b]pyridines **39a**, **39b** didn't exhibit any efficacy. 8-Bromopyrano[3,2-b]pyridines **40**, **41** didn't enhance the potency of unsubsituted compounds **38**, **39**. Unsubstituted [2,3-c]-isomers **50a**, **51a** with 2,4-dichloro and 3,4-dichloro substitution showed weak activity, while its 4-chloroaniline and 2-fluoro-4-chloroaniline analogs, **49a**, **52a** didn't represent any efficacy. The 8-position of pyrano[2,3-c]pyridine was diversified with bromine, chlorine, nitrile, and nitro group, and their effect on tube formation was also determined. The bromine and chlorine substitution (**45a**, **46a**) seemed to enhance the potency. Especially 8-chloropryano[2,3-c]pyridine with 2,4-dichloroaniline **46a** completely inhibited HUVEC tube formation at 50 μM concentration. This preliminary study suggests the possibility that pyranopyridines, especially [3,2-b]- and [2,3-c]-isomers, can replace the benzopyran ring of the compound **1** and can be optimized through the introduction of substituents both on pyranopyridine ring and (*N*-imidazol-2-ylmethyl)aniline. We will more intensively diversify the structure of this pyranopyridine compounds for the study of structure-activity relationships as well as the identification of a novel anti-angiogenic agent. In addition, we will continuously study the physicochemical and biological profiles of **46a** as well as the compound **1**.

Table 1. Inhibitory Effects on HUVEC Tube Formation of Synthesized Pyranopyridines



34a-**57a**



34b-**57b**

Compds		X	Y	Yield (%)		Tube formation[a]	
				a	**b**	**a**	**b**
1						+++	
34[b]	[3,2-c]	H	H	37	6	+	na
35[b]	[3,2-c]	H	2-Cl	49	0	–	na
36[b]	[3,2-c]	H	3-Cl	36	3	–	na
37[b]	[3,2-c]	H	2-F	41	0	–	na
38	[3,2-b]	H	H	18	2	+	++
39	[3,2-b]	H	2-Cl	25	3	–	–
40	[3,2-b]	8-Br	H	21	2	+	–
41	[3,2-b]	8-Br	2-Cl	23	5	+	na
42	[3,2-b]	8-CN	2-Cl	30	0	na	na
43	[2,3-c]	8-Br	H	19	15	–	na
44	[2,3-c]	8-Br	2-Cl	23	9	+	+
45	[2,3-c]	8-Br	3-Cl	28	12	++	+
46	[2,3-c]	8-Cl	2-Cl	28	5	+++	+
47	[2,3-c]	8-NO_2	2-Cl	20	7	–	–
48	[2,3-c]	8-CN	2-Cl	22	6	–	na
49	[2,3-c]	H	H	33	22	–	na
50	[2,3-c]	H	2-Cl	28	7	+	na
51	[2,3-c]	H	3-Cl	28	15	+	na
52	[2,3-c]	H	2-F	32	14	–	na
53	[2,3-b]	6-Br	H	33	8	–	na
54[b]	[2,3-b]	H	H	24	4	–	na
55[b]	[2,3-b]	H	2-Cl	36	0	–	na
56[b]	[2,3-b]	H	3-Cl	31	26	–	na
57[b]	[2,3-b]	H	2-F	32	9	–	na

[a]–: control; +: inhibition; ++: significant inhibition; +++: tubes were not formed; na: not assayed; assayed at 50 μM concentration of each compound; [b]racemic mixture.

Conclusion

This report describes the synthesis of pyranopyridines with 4-(*N*-imidazol-2-ylmethyl)aniline moiety and the evaluation of their primary anti-angiogenic properties through the assay of HUVEC tube formation, aiming at the identification of a novel structure which can replace the benzopyran ring of 4-[(*N*-imidazol-2-ylmethyl)-4-chloro-anilino]benzopyran **1**, previously identified as an anti-angiogenic agent with an excellent anticancer efficacy. From this study we found that the pyranopyridine ring, especially [3,2-b]- and [2,3-c]-isomer, can replace the benzopyran ring of the compound **1** and can be optimized through the introduction of substituents both on pyranopyridine ring and *N*-(imidazol-2-ylmethyl)aniline. Among the newly designed and synthesized compounds, 8-chloropyrano[2,3-c]pyridine with 2,4-dichloroaniline **46a** exhibited the most potent inhibitory activity on HUVEC at 50 μM concentration. The compound **46a** will be further investigated using *in vivo* tumor models.

Experimental Section

Chemistry. Anhydrous solvents were dried by conventional methods. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) or on a Varian Gemini 200 (200 MHz) with TMS as

an internal standard. Chemical shifts are reported in δ(ppm). Mass spectra were obtained with a JEOL JMS-DX 303 instrument by using electron impact or chemical ionization techniques.

General procedure for the preparation of 2,2-dimethyl-2*H*-pyranopyridine (8-13). To a solution of hydroxypyridine (23 g, 240 mmol), a 40% solution of benzyltrimethylammonium hydroxide in CH_3OH (50.7 g, 120 mmol), and 3-chlroro-3-methyl-1-but-1-yne (37.4 g, 360 mmol) in CH_2Cl_2 (150 mL) was added 2.4 N NaOH (150 mL) with stirring. The mixture was continuously stirred at room temperature for 4 days. Layers were separated and an aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with 10% NaOH, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude propargyl ether (**2-7**), which was heated at reflux for an hour in *o*-dichlorobenzene under N_2 atmosphere. The solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 10 : 1~3 : 1) to afford 2,2-dimethyl-2H-pyranopyridine (**8-13**).

2,2-Dimethyl-2*H*-pyrano[3,2-c]pyridine (8). Starting from 4-hydroxypyridine (23.0 g, 0.24 mol), the compound **8** was obtained as a yellow oil (12.0 g, 50%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 6H), 5.65 (d, 1H, J = 9.9 Hz), 6.34 (d, 1H, J = 9.9 Hz), 6.66 (d, 1H, J = 5.5 Hz), 8.12 (s, 1H), 8.22 (d, 1H, J = 5.5 Hz); Ms 161 (M^+).

2,2-Dimethyl-2*H*-pyrano[3,2-b]pyridine (9). Starting from 3-hydroxypyridine (23.0 g, 0.24 mol), the compound **9** was obtained as a yellow oil (9.27 g, 24%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 6H), 5.88 (d, 1H, J = 9.9 Hz), 6.52 (d, 1H, J = 9.9 Hz), 7.02 (m, 2H), 8.05 (m, 1H); Ms 161 (M^+).

8-Bromo-2,2-dimethyl-2*H*-pyrano[3,2-b]pyridine (10). Starting from 4-bromo-3-pyridinol (1.17 g, 6.72 mmol), the compound **10** was obtained as a yellow oil (290 mg, 18%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 6H), 5.94 (d, 1H, J = 10.1 Hz), 6.49 (d, 1H, J = 10.1 Hz), 7.24 (d, 1H, J = 6.3 Hz), 7.86 (d, 1H, J = 6.3 Hz); Ms 240 (M^+).

8-Bromo-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (11). Starting from 2-bromo-3-pyridinol (5.09 g, 29.3 mmol), the compound **11** was obtained as a yellow oil (2.52 g, 36%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 6H), 5.88 (d, 1H, J = 9.8 Hz), 6.29 (d, 1H, J = 9.8 Hz), 6.84 (d, 1H, J = 4.7 Hz), 7.88 (d, 1H, J = 4.7 Hz); Ms 239 (M^+).

8-Chloro-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (12). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 6H), 5.89 (d, 1H, J = 9.9 Hz), 6.31 (d, 1H, J = 9.9 Hz), 6.84 (d, 1H, J = 4.8 Hz), 7.88 (d, 1H, J = 4.8 Hz); Ms 195 (M^+).

8-Nitro-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (13). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 6H), 6.04 (d, 1H, J = 9.9 Hz), 6.39 (d, 1H, J = 9.9 Hz), 7.14 (d, 1H, J = 4.5 Hz), 7.98 (d, 1H, J = 4.5 Hz); Ms 206 (M^+).

3,5-Dibromo-2-methoxypyridine (14). To a solution of 2-methoxypyridine (15.0 g, 0.13 mol) in acetic acid (67 mL) was added sodium acetate (22.15 g, 0.17 mol), and then Br_2 (24.3 mL, 0.45 mol) at 35 °C. The reaction mixture was heated at 80 °C for 6 h with stirring, then continuously stirred for 16 h at room temperature. The reaction was quenched with an addition of H_2O (90 mL). The mixture was extracted with CCl_4 (100 mL × 2). The organic layer was washed with 1 N NaOH and 1 N $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a white solid (25.5 g, 73%). The crude product was used for the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.92 (s, 1H), 8.13 (s, 1H); Ms 267 (M^+).

5-Bromo-α-(2-methyl-1-propenyl)-2-methoxy-3-pyridinemethanol (15). To a solution of the compound **14** (12.7 g, 47.5 mmol) in anhydrous ether (100 mL) was slowly added *n*-BuLi (1.6 M in hexane, 30 mL) at –65 °C under N_2 atmosphere, and the mixture was stirred for 30 min. To the mixture, a solution of 3-methyl-2-butenal (3.99 g, 57 mmol) in anhydrous THF (60 mL) was added dropwise *via* a dropping funnel, and continuously stirred at –70 °C for 30 min. The reaction was terminated by an addition of $NaHCO_3$ solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a white solid (6.5 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 6H), 2.35 (d, 1H, J = 4.0 Hz), 3.95 (s, 3H), 5.30 (d, 1H, J = 10.0 Hz), 5.50 (d, 1H, J = 10.0 Hz), 7.75 (d, 1H, J = 2.0 Hz), 8.10 (d, 1H, J = 2.0 Hz); Ms 271 (M^+).

6-Bromo-2,2-dimethyl-2*H*-pyrano[2,3-b]pyridine (16). To a stirred solution of the compound **15** (4.7 g, 17 mmol) in acetic acid (50 mL) was added 48% HBr (7 mL) at 100 °C under N_2 atmosphere. The reaction mixture was continuously stirred for 30 min at 100 °C, cooled to room temperature, and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate in pentane) to give a white solid (1.8 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 6H), 5.74 (d, 1H, J = 9.7 Hz), 6.25 (d, 1H, J = 9.7 Hz), 7.36 (d, 1H, J = 2.4 Hz), 8.05 (d, 1H, J = 2.4 Hz); Ms 239 (M^+).

8-Cyano-2,2-dimethyl-2*H*-pyrano[3,2-b]pyridine (17). To a stirred solution of the compound **10** (280 mg, 1.16 mmol) in DMF (3 mL) was added CuCN (135 mg, 1.52 mmol). The reaction mixture was stirred at 100 °C for 15 min with microwave irradiation. After completion of the reaction, 2 N HCl was added to the mixture, and which was extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give a yellow oil (115 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 6H), 6.05 (d, 1H, J = 10.3 Hz), 6.55 (d, 1H, J = 10.3 Hz), 7.20 (d, 1H, J = 5.0 Hz), 8.12 (d, 1H, J = 5.0 Hz); Ms 186 (M^+).

8-Cyano-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (18). The compound **18** (242 mg, 58%) was obtained as a pale

brown solid by the same procedure to prepare the compound **17** except using the compound **11** (538 mg, 2.24 mmol) as a starting material. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (s, 3H), 5.99 (d, 1H, J = 10.0 Hz), 6.34 (d, 1H, J = 10.0 Hz), 7.05 (d, 1H, J = 4.2 Hz), 8.16 (d, 1H, J = 4.2 Hz); Ms 186 (M^+).

2,2-Dimethyl-2*H*-pyrano[2,3-c]pyridine (19). To a stirred solution of the compound **11** (2.4 g, 10 mmol) in anhydrous ether (50 mL) was added *n*-BuLi (1.6 M in hexane, 6.9 mL) dropwise at –78 °C with stirring under N_2 atmosphere, and the mixture was continuously stirred at –78 °C for 2 h. The reaction was terminated by an addition of H_2O, which was extracted with ether. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give an oil (1.4 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 6H), 5.84 (d, 1H, J = 9.8 Hz), 6.31 (d, 1H, J = 9.8 Hz), 6.87 (d, 1H, J = 4.7 Hz), 8.10 (d, 1H, J = 4.7 Hz), 8.12 (s, 1H); Ms 161 (M^+).

2,2-Dimethyl-2*H*-pyrano[2,3-b]pyridine (20). The compound **20** (700 mg, 98%) was obtained as a yellow oil by the same procedure to prepare the compound **19** except using the compound **16** (1.06 g, 4.4 mmol) as a starting material. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 3H), 5.67 (d, 1H, J = 9.9 Hz), 6.29 (d, 1H, J = 9.9 Hz), 6.80 (dd, 1H, J = 4.9, 7.2 Hz), 8.16 (dd, 1H, J = 1.8, 7.2 Hz), 8.01 (dd, 1H, J = 1.8, 4.9 Hz); Ms 161 (M^+).

***trans*-4-Bromo-3-hydroxy-3,4-dihydro-2,2-dimethyl-2*H*-pyrano[3,2-c]pyridine (21).** To a solution of the compound **8** (1.0 g, 6.2 mmol) in DMSO (50 mL) and H_2O (15 mL) was added *N*-bromosuccinimide (2.2 g, 12.4 mmol). The mixture was stirred at room temperature for 3 h, and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give a pale yellow solid (544 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.63 (s, 3H), 4.15 (d, 1H, J = 9.0 Hz), 4.98 (d, 1H, J = 9.0 Hz), 6.74 (d, 1H, J = 5.7 Hz), 8.29 (d, 1H, J = 5.7 Hz), 8.63 (s, 1H); Ms 257 (M^+).

***trans*-4-Bromo-3-hydroxy-3,4-dihydro-2,2-dimethyl-2*H*-pyrano[2,3-b]pyridine (22).** The compound **22** (1.26 g, 80%) was obtained as a pale yellow solid by the same procedure to prepare the compound **21** except using the compound **20** (986 mg, 6.12 mmol) as a starting material. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.65 (s, 3H), 4.17 (d, 1H, J = 9.6 Hz), 4.97 (d, 1H, J = 9.6 Hz), 6.97 (dd, 1H, J = 4.8, 7.7 Hz), 7.92 (dd, 1H, J = 1.8, 7.5 Hz), 8.13 (dd, 1H, J = 1.8, 4.8 Hz); Ms 257 (M^+).

3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[3,2-c]-pyridine (23). To a solution of the compound **22** (1.5 g, 5.81 mmol) in ether (290 mL) was added KOH (326 mg, 5.81 mmol), and then the mixture was stirred at room temperature for 4 days. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a yellow oil (840 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.59 (s, 3H), 3.56 (d, 1H, J = 4.2 Hz), 3.97 (d, 1H, J = 4.2 Hz), 6.71 (d, 1H, J = 5.4 Hz), 8.38 (d, 1H, J = 5.4 Hz), 8.49 (s, 1H); Ms 177 (M^+).

3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[2,3-b]-pyridine (24). The compound **24** (1.04 g, 73%) was obtained as a yellow oil by the same procedure to prepare the compound **23** except using the compound **22** (1.0 g, 3.87 mmol) as a starting material. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.64 (s, 3H), 3.55 (d, 1H, J = 4.4 Hz), 3.94 (d, 1H, J = 4.4 Hz), 6.92 (dd, 1H, J = 7.7, 11.1 Hz), 7.71 (dd, 1H, J = 3.0, 11.1 Hz), 8.21 (dd, 1H, J = 3.0, 7.7 Hz); Ms 177 (M^+).

General procedure for the synthesis of epoxides (25-33). To a solution of olefin (500 mg, 3.10 mmol) and Jacobsen's reagent (*R,R*, 98.6 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added a mixture of 0.55 M NaOCl (22 mL) and 0.05 M Na_2HPO_4 (9 mL) dropwise at 0 °C. After vigorous stirring at room temperature overnight, the reaction mixture was passed through a pad of Celite, and washed with CH_2Cl_2 and H_2O, 3-4 times. The filtrate was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

(3*R*,4*R*)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano [3,2-b]pyridine (25). The compound **25** (307 mg, 56%) was obtained from the olefin compound **9** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.59 (s, 3H), 3.57 (d, 1H, J = 4.3 Hz), 4.12 (d, 1H, J = 4.3 Hz), 7.18 (m, 2H), 8.16 (d, 1H, J = 4.6 Hz); Ms 177 (M^+).

(3*R*,4*R*)-8-Bromo-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[3,2-b]pyridine (26). The compound **26** (1.06 g, 83%) was obtained from the olefin compound **10** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.67 (s, 3H), 3.61 (d, 1H, J = 4.2 Hz), 4.10 (d, 1H, J = 4.2 Hz), 7.45 (d, 1H, J = 5.1 Hz), 8.97 (d, 1H, J = 5.1 Hz); Ms 240 (M^+).

(3*R*,4*R*)-8-Cyano-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[3,2-b]pyridine (27). The compound **27** was obtained from the olefin compound **17** in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.69 (s, 3H), 3.65 (d, 1H, J = 4.5 Hz), 4.16 (d, 1H, J = 4.5 Hz), 7.40 (d, 1H, J = 4.8 Hz), 8.22 (d, 1H, J = 4.8 Hz); Ms 202 (M^+).

(3*R*,4*R*)-8-Bromo-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[2,3-c]pyridine (28). The compound **28** (850 mg, 80%) was obtained from the olefin compound **11** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.67 (s, 3H), 3.57 (d, 1H, J = 4.5 Hz), 3.87 (d, 1H, J = 4.5 Hz), 7.27 (d, 1H, J = 4.5 Hz), 7.98 (d, 1H, J = 4.5 Hz); Ms 255 (M^+).

(3*R*,4*R*)-8-Chloro-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[2,3-c]pyridine (29). The compound **29** was obtained from the compound **12** in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.67 (s, 3H), 3.57 (d, 1H, J = 4.2 Hz), 3.89 (d, 1H, J = 4.2 Hz), 7.25 (d, 1H, J = 4.8 Hz), 7.99 (d, 1H, J = 4.8 Hz); Ms 211 (M^+).

(3*R*,4*R*)-8-Nitro-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[2,3-c]pyridine (30). The compound **30** was

obtained from the olefin compound **13** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.65 (s, 3H), 3.63 (d, 1H, *J* = 4.2 Hz), 4.00 (d, 1H, *J* = 4.2 Hz), 7.58 (d, 1H, *J* = 4.5 Hz), 8.08 (d, 1H, *J* = 4.5 Hz); Ms 222 (M^+).

(3*R*,4*R*)-8-Cyano-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[2,3-c]pyridine (31). The compound **31** was obtained from the olefin compound **18** in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.68 (s, 3H), 3.62 (d, 1H, *J* = 4.2 Hz), 3.94 (d, 1H, *J* = 4.2 Hz), 7.51 (d, 1H, *J* = 4.8 Hz), 8.22 (d, 1H, *J* = 4.8 Hz); Ms 211 (M^+).

(3*R*,4*R*)-3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano [2,3-c]pyridine (32). The compound **32** was obtained from the olefin compound **19** in 50% yield as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.59 (s, 3H), 3.55 (d, 1H, *J* = 4.4 Hz), 3.87 (d, 1H, *J* = 4.4 Hz), 7.29 (d, 1H, *J* = 4.6 Hz), 8.19 (d, 1H, *J* = 4.6 Hz); Ms 177 (M^+).

(3*R*,4*R*)-6-Bromo-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-pyrano[2,3-b]pyridine (33). The compound **33** was obtained from the olefin compound **16** in 75% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.64 (s, 3H), 3.54 (d, 1H, *J* = 4.2 Hz), 3.90 (d, 1H, *J* = 4.2 Hz), 7.81 (d, 1H, *J* = 2.4 Hz), 8.25 (d, 1H, *J* = 2.4 Hz); Ms 255 (M^+).

General procedure for the synthesis of (34-57). To a solution of an appropriately substituted *N*-(1*H*-imidazol-2-ylmethyl)aniline (218 mg, 0.90 mmol) in DMSO was added NaH (60% in oil, 32 mg, 0.8 mmol), and the mixture was stirred at room temperature for 10 min, followed by slow addition of a solution of an epoxide (200 mg, 1.12 mmol) in DMSO (1 mL). The reaction mixture was continuously stirred at room temperature for 8 h, and the reaction was terminated by an addition of H_2O, which was extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-c]pyridine (34a). The compound **34a** was obtained from the compound **23** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 37% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.55 (s, 3H), 3.97 (d, 1H, *J* = 10.1 Hz), 4.48 (d, 1H, *J* = 15.0 Hz), 4.78 (d, 1H, *J* = 15.0 Hz), 5.65 (d, 1H, *J* = 10.1 Hz), 6.73 (d, 2H, *J* = 8.7 Hz), 6.87 (s, 1H), 6.88 (d, 1H, *J* = 5.8 Hz), 7.00 (s, 1H), 7.10 (d, 2H, *J* = 8.7 Hz), 7.62 (s, 1H), 8.19 (d, 1H, *J* = 5.8 Hz); Ms 384 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[3,2-c]pyridine (34b). The compound **34b** was obtained from the compound **23** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 6% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (s, 6H), 4.23 (s, 2H), 5.90 (s, 1H), 6.41 (d, 1H, *J* = 5.1 Hz), 6.47 (dd, 2H, *J* = 1.9, 6.8 Hz), 6.94 (d, 1H, *J* = 1.2 Hz), 7.07 (dd, 2H, *J* = 1.9, 6.8 Hz), 7.16 (d, 1H, *J* = 1.2 Hz), 8.10 (d, 1H, *J* = 5.1 Hz), 8.27 (s, 1H); Ms 366 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-c]pyridine (35a). The compound **35a** was obtained from the compound **23** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 49% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.58 (s, 3H), 3.83 (d, 1H, *J* = 9.4 Hz), 4.44 (d, 1H, *J* = 13.8 Hz), 4.64 (d, 1H, *J* = 13.8 Hz), 5.07 (s, 1H), 5.32 (d, 1H, *J* = 9.4 Hz), 6.50 (s, 1H), 6.73 (m, 3H), 7.08 (d, 1H, *J* = 6.7 Hz), 7.23 (d, 1H, *J* = 1.9 Hz), 7.76 (s, 1H), 8.25 (d, 1H, *J*= 5.6 Hz); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-c]pyridine (36a). The compound **36a** was obtained from the compound **23** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 36% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.60 (s, 3H), 3.77 (d, 1H, *J* = 9.1 Hz), 4.32 (d, 1H, *J* = 13.2 Hz), 4.56 (d, 1H, *J* = 13.2 Hz), 5.27 (d, 1H, *J* = 9.1 Hz), 5.38 (s, 1H), 6.47°¡6.78 (m, 5H), 7.14 (d, 1H, *J* = 8.6 Hz), 7.65 (s, 1H), 8.23 (d, 1H, *J* = 5.6 Hz); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-2,2-dimethyl-2*H*-pyrano[3,2-c]pyridine (36b). The compound **36b** was obtained from the compound **23** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 3% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 6H), 4.22 (d, 2H, *J* = 3.0 Hz), 4.44 (s, 1H), 5.73 (s, 1H), 6.42 (dd, 1H, *J* = 2.7, 8.7Hz), 6.60 (d, 1H, *J* = 2.7 Hz), 6.81 (d, 1H, *J* = 5.4 Hz), 7.01 (s, 1H), 7.16 (d, 1H, *J* = 8.7 Hz), 7.17 (s, 1H), 7.71 (s, 1H), 8.36 (d, 1H, *J* = 5.4 Hz); Ms 400 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2-fluoro-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-c]pyridine (37a). The compound **37a** was obtained from the compound **23** and *N*-(1*H*-imidazol-2-ylmethyl)-2-fluoro-4-chloroaniline in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.59 (s, 3H), 3.85 (d, 1H, *J* = 9.5 Hz), 4.31 (d, 1H, *J* = 12.7 Hz), 4.65 (d, 1H, *J* = 12.7 Hz), 4.87 (s, 1H) 5.37 (d, 1H, *J* = 9.5 Hz), 6.54 (s, 1H), 6.77 (m, 2H), 6.79 (d, 1H, *J* = 5.7 Hz), 6.98 (d, 2H, *J* = 9.6 Hz), 7.81 (s, 1H), 8.29 (d, 1H, *J* = 5.7 Hz); Ms 402 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-b]pyridine (38a). The compound **38a** was obtained from the compound **25** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 18% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (s, 3H), 1.45 (s, 3H), 4.04 (dd, 1H, *J* = 5.6, 9.8 Hz), 4.35 (d, 1H, *J* = 14.5 Hz), 4.42 (d, 1H, *J* = 14.5 Hz), 5.34 (d, 1H, *J* = 9.8 Hz), 6.03 (d, 1H, *J* = 5.6 Hz), 6.1 (s, 1H), 6.74 (d, 2H, *J* = 8.4 Hz), 6.79 (s, 1H), 6.91 (s, 1H), 7.11 (d, 2H, *J* = 8.4 Hz), 7.27 (m, 2H), 8.09 (d, 1H, *J* = 3.9 Hz); Ms 384 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[3,2-b]pyridine (38b). The compound **38b** was obtained from the compound **25** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 2% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 6H), 4.23 (s, 2H), 4.41 (s, 1H), 5.90 (s, 1.0 Hz), 6.44 (m, 2H), 7.11 (m, 6H), 8.09 (m, 1H); Ms 366 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [3,2-b]pyridine (39a). The compound **39a** was obtained

from the compound **25** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 25% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09 (s, 3H) 1.28 (s, 3H), 3.88 (d, 1H, J = 9.9 Hz), 4.17 (d, 1H, J = 14.5 Hz), 4.35 (d, 1H, J = 14.5 Hz), 5.22 (d, 1H, J = 9.9 Hz), 5.79 (d, 1H, J = 5.5 Hz), 5.89 (s, 1H), 6.64 (s, 1H), 6.84 (m, 2H), 7.06 (m, 3H), 7.20 (d, 1H, J = 2.1 Hz), 7.89 (d, 1H, J = 4.0 Hz); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-2,2-dimethyl-2*H*-pyrano[3,2-b]pyridine (39b). The compound **39b** was obtained from the compound **25** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 3% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 6H), 4.36 (d, 2H, J = 5.4 Hz), 4.77 (s, 1H), 5.87 (s, 1H), 6.58 (d, 1H, J = 8.7 Hz), 6.97 (d, 1H, J = 1.1 Hz), 7.03 (dd, 1H, J = 2.3, 8.7 Hz), 7.15 (m, 4H), 8.08 (dd, 1H, J = 2.3, 3.7 Hz); Ms 400 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-8-bromo-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [3,2-b]pyridine (40a). The compound **40a** was obtained from the compound **26** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 21% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (s, 3H), 1.50 (s, 3H), 4.02 (d, 1H, J = 9.9 Hz), 4.35 (d, 1H, J = 13.5 Hz), 4.44 (d, 1H, J = 13.5 Hz), 5.40 (d, 1H, J = 9.9 Hz), 6.12 (bs, 2H), 6.74 (d, 2H, J = 8.2 Hz), 6.78 (s, 1H), 7.10 (d, 2H, J = 8.2 Hz), 7.61 (d, 2H, J = 5.0 Hz), 7.93 (d, 1H, J = 5.0 Hz); Ms 464 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-8-bromo-2,2-dimethyl-2*H*-pyrano[3,2-b]pyridine (40b). The compound **40b** was obtained from the compound **26** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 2% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 6H), 4.23 (s, 2H), 5.98 (s, 1H), 6.37 (d, 1H, J = 4.8 Hz), 6.45 (m, 2H), 7.21 (m, 4H), 7.81 (d, 1H, J = 4.8 Hz); Ms 446 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmtehyl)-2,4-dichloroanilino]-8-bromo-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-b]pyridine (41a). The compound **41a** was obtained from the compound **26** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 23% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.67 (s, 3H), 4.08 (d, 1H, J = 9.7 Hz), 4.35 (d, 1H, J = 15.0 Hz), 4.42 (d, 1H, J = 15.0 Hz), 5.32 (d, 1H, J = 9.7 Hz), 6.53 (m, 2H), 6.75 (s, 1H), 7.07 (dd, 1H, J = 2.3, 8.6 Hz), 7.21 (d, 1H, J = 2.3 Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.91 (d, 1H, J = 5.0 Hz); Ms 498 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-bromo-2,2-dimethyl-3-2*H*-pyrano[3,2-b]pyridine (41b). The compound **41b** was obtained from the compound **26** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 5% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 6H), 4.36 (d, 2H, J = 4.2Hz), 4.72 (s, 1H), 5.94 (s, 1H), 6.55 (d, 1H, J = 8.7 Hz), 6.95 (s, 1H), 7.02 (dd, 1H, J = 2.4, 8.7 Hz), 7.14 (s, 1H), 7.19 (d, 1H, J = 2.4 Hz), 7.37 (d, 1H, J = 5.1 Hz), 7.86 (d, 1H, J = 5.1 Hz); Ms 480 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[3,2-b]pyridine (42a). The compound **42a** was obtained from the compound **27** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 30% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 1.39 (s, 3H), 1.63 (s, 3H), 4.22 (d, 1H, J = 10.1 Hz), 4.61 (m, 2H), 5.62 (d, 1H, J = 10.1 Hz), 6.90 (d, 1H, J = 8.7 Hz), 6.96 (d, 2H, J = 3.2 Hz), 7.12 (dd, 1H, J = 2.3, 8.7 Hz), 7.25 (d, 1H, J = 2.3 Hz), 7.56 (d, 1H, J = 4.8 Hz), 8.19 (d, 1H, J = 4.8 Hz); Ms 443 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-8-bromo-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [2,3-c]pyridine (43a). The compound **43a** was obtained from the compound **28** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 19% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 1.32 (s, 3H), 1.60 (s, 3H), 4.01 (d, 1H, J = 9.8 Hz), 4.48 (d, 1H, J = 14.6 Hz), 4.75 (d, 1H, J = 14.6 Hz), 5.63 (d, 1H, J = 9.8 Hz), 6.52 (d, 1H, J = 5.0 Hz), 6.74 (d, 2H, J = 7.9 Hz), 6.86 (s, 1H), 6.99 (s, 1H), 7.10 (d, 2H, J = 8.6 Hz), 7.71 (d, 1H, J = 5.0 Hz); Ms 464 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-8-bromo-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (43b). The compound **43b** was obtained from the compound **28** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 15% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 6H), 4.23 (s, 2H), 5.95 (s, 1H), 6.35 (d, 1H, J = 4.8 Hz), 6.47 (d, 2H, J = 8.7 Hz), 6.92 (s, 1H), 7.08 (d, 2H, J = 8.7 Hz), 7.16 (s, 1H), 7.86 (d, 1H, J = 4.8 Hz); Ms 446 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-bromo-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [2,3-c]pyridine (44a). The compound **44a** was obtained from the compound **28** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 23% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (s, 3H) 1.50 (s, 3H), 4.02 (d, 1H, J = 10.0 Hz), 4.49 (d, 1H, J = 12.6 Hz), 4.70 (d, 1H, J = 12.6 Hz), 5.52 (d, 1H, J = 10.0 Hz), 6.06 (d, 1H, J = 6.0 Hz), 6.26 (s, 1H), 6.41 (d, 1H, J = 4.8 Hz), 6.89 (s, 1H), 7.06 (s, 1H), 7.11 (d, 1H, J = 7.1 Hz), 7.23 (d, 1H, J = 7.1 Hz), 7.37 (s, 1H), 7.76 (d, 1H, J = 4.8 Hz); Ms 498 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-bromo-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (44b). The compound **44b** was obtained from the compound **28** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 9% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 6H), 4.35 (d, 2H, J = 5.1Hz), 4.67 (s, 1H), 5.96 (s, 1H), 6.24 (d, 1H, J = 4.8 Hz), 6.63 (d, 1H, J = 8.8 Hz), 6.93 (d, 1H, J = 1.2 Hz), 7.06 (dd, 1H, J =2.3, 8.8 Hz) 7.17 (d, 1H, J = 1.2 Hz), 7.19 (d, 1H, J = 2.3 Hz), 7.80 (d, 1H, J = 4.8 Hz); Ms 480 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-8-bromo-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (45a). The compound **45a** was obtained from the compound **28** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 28% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.27 (s, 3H) 1.50 (s, 3H), 3.99 (d, 1H, J = 9.8 Hz), 4.36 (d, 1H, J = 15.7 Hz), 3.61 (d, 1H, J = 15.7 Hz), 5.36 (d, 1H, J = 9.8 Hz), 6.11 (s, 1H), 6.44 (d, 1H, J = 4.8 Hz), 6.69 (s, 1H), 6.70 (d, 1H, J = 8.7 Hz), 6.88 (s, 1H), 7.03 (d, 2H, J = 18.4 Hz), 7.28 (d, 1H, J = 8.7 Hz), 7.78 (d, 1H, J = 4.8 Hz); Ms 498 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmehyl)-3,4-dichloroanilino]-8-bromo-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (45b). The compound **45b** was obtained from the compound **28** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 12% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ1.58 (s, 6H), 4.20 (d, 2H, *J* = 5.4 Hz), 4.36 (s, 1H), 5.96 (s, 1H), 6.35 (d, 1H, *J* = 4.8 Hz), 6.40 (dd, 1H, *J* = 2.7, 8.7 Hz), 6.60 (d, 1H, *J* = 2.7 Hz), 6.94 (d, 1H, *J* = 1.2 Hz), 7.13 (d, 1H, *J* = 8.7 Hz), 7.16 (d, 1H, *J* = 1.2 Hz), 7.89 (d, 1H, *J* = 4.8 Hz); Ms 480 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (46a). The compound **46a** was obtained from the compound **29** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 28% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ1.31 (s, 3H), 1.50 (s, 3H), 4.04 (d, 1H, *J* = 9.7 Hz), 4.49 (d, 1H, *J* = 14.3 Hz), 4.70 (d, 1H, *J* = 14.3 Hz), 5.52 (d, 1H, *J* = 9.7 Hz), 6.07 (d, 1H, *J* = 5.5 Hz), 6.27 (s, 1H), 6.40 (d, 1H, *J* = 4.8 Hz), 6.89 (s, 1H), 7.05 (s, 1H), 7.11 (d, 1H, *J* = 8.3 Hz), 7.23 (d, 1H, *J* = 8.3 Hz), 7.36 (s, 1H), 7.77 (d, 1H, *J* = 4.8 Hz); Ms 452 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-chloro-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (46b). The compound **46b** was obtained from the compound **29** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 5% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ1.60 (s, 6H), 4.44 (d, 2H, *J* = 4.5 Hz), 5.79 (s, 1H), 6.25 (d, 1H, *J* = 4.8 Hz), 6.45 (s, 1H), 6.81 (d, 1H, *J* = 8.8 Hz), 7.10 (s, 1H), 7.17 (dd, 1H, *J* = 2.5, 8.8 Hz), 7.32 (d, 2H, *J* = 2.5 Hz), 7.80 (d, 1H, *J* = 4.8 Hz); Ms 434 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-nitro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (47a). The compound **47a** was obtained from the compound **30** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 20% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ1.36 (s, 3H), 1.47 (s, 3H), 4.05 (d, 1H, *J* = 9.9 Hz), 4.51 (d, 1H, *J* = 14.9 Hz), 4.67 (d, 1H, *J* = 14.9 Hz), 5.61 (d, 1H, *J* = 9.9 Hz), 6.19 (d, 1H, *J* = 6.0 Hz), 6.28 (s, 1H), 6.77 (d, 1H, *J* = 4.4 Hz), 6.92 (s, 1H), 7.11 (d, 1H, *J* = 8.8 Hz), 7.16 (s, 1H), 7.24 (d, 1H, *J* = 8.8 Hz), 7.37 (s, 1H), 7.92 (d, 1H, *J* = 4.4 Hz); Ms 463 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmehyl)-2,4-dichloroanilino]-8-nito-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (47b). The compound **47b** was obtained from the compound **30** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 7% yield. ^{1}H NMR (300 MHz, CD_3OD): δ1.42 (s, 6H), 4.31 (s, 2H), 4.41 (s, 1H), 6.18 (d, 1H, *J* = 4.8 Hz), 6.20 (s, 1H), 6.44 (d, 1H, *J* = 8.7 Hz), 6.86 (dd, 1H, *J* = 2.4, 8.7 Hz), 6.92 (d, 1H, *J* = 2.4 Hz), 6.96 (d, 1H, *J* = 1.1 Hz), 7.03 (d, 1H, *J* = 1.1 Hz), 7.48 (d, 1H, *J* = 4.8 Hz); Ms 446 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (48a). The compound **48a** was obtained from the compound **31** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 22% yield. ^{1}H NMR (300 MHz, CD_3OD): δ1.30 (s, 3H), 1.52 (s, 3H), 3.95 (d, 1H, *J* = 10.1 Hz), 4.52 (d, 1H, *J* = 14.9 Hz), 4.67 (d, 1H, 14.9 Hz), 5.62 (d, 1H, *J* = 10.1 Hz), 6.55 (d, 1H, *J* = 4.4 Hz), 6.86 (m, 3H), 7.05 (d, 1H, *J* = 7.7 Hz), 7.14 (s, 1H), 7.91 (d, 1H, *J* = 4.4 Hz); Ms 443 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-8-cyano-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (48b). The compound **48b** was obtained from the compound **31** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 6% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.58 (s, 6H), 4.36 (s, 2H), 4.41 (s, 1H, *J* = 5.2 Hz), 4.52 (s, 1H), 5.98 (s, 1H), 6.33 (d, 1H, *J* = 4.8 Hz), 6.58-7.16 (m, 5H), 8.07 (d, 1H, *J* = 4.8 Hz); Ms 425 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (49a). The compound **49a** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 33% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.60 (s, 3H), 3.91 (d, 1H, *J* = 9.4 Hz), 4.41 (d, 1H, *J* = 14.6 Hz), 4.59 (d, 1H, *J* = 14.6 Hz), 5.29 (d, 1H, *J* = 9.4 Hz), 6.52°¦6.85 (m, 5H), 7.14 (d, 2H, *J* = 8.5 Hz), 8.06 (d, 1H, *J* = 5.1 Hz), 8.27 (s, 1H); Ms 384 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (49b). The compound **49b** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 22% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.55 (s, 6H), 4.23 (s, 2H), 5.90 (s, 1H), 6.41 (d, 1H, *J* = 5.1 Hz), 6.47 (dd, 2H, *J* = 1.9, 6.8 Hz), 6.94 (d, 1H, *J* = 1.2 Hz), 7.07 (dd, 2H, *J* = 1.9, 6.8 Hz), 7.16 (d, 1H, *J* = 1.2 Hz), 8.10 (d, 1H, *J* = 5.1 Hz), 8.27 (s, 1H); Ms 366 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (50a). The compound **50a** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 28% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.30 (s, 3H), 1.60 (s, 3H), 3.89 (d, 1H, *J* = 9.6 Hz), 4.52 (d, 1H, *J* = 14.7 Hz), 4.67 (d, 1H, *J* = 14.7 Hz), 4.99 (s, 1H), 5.32 (d, 1H, *J* = 9.6 Hz), 6.50 (d, 2H, *J* = 4.6 Hz), 6.76 (d, 1H, *J* = 9.0 Hz), 6.84 (s, 1H), 7.11 (d, 1H, *J* = 9.0 Hz), 7.26 (s, 1H), 8.04 (d, 1H, *J* = 4.6 Hz), 8.26 (s, 1H); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (50b). The compound **50b** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 7% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.55 (s, 6H), 4.35 (d, 2H, *J* = 5.4Hz), 4.71 (s, 1H), 5.91 (s, 1H), 6.31 (d, 1H, *J* = 4.8 Hz), 6.63 (d, 1H, *J* = 8.7 Hz), 6.94 (s, 1H), 7.05 (dd, 1H, *J* = 2.2, 8.7 Hz), 7.17 (s, 1H), 7.19 (d, 1H, *J* = 2.2 Hz), 8.05 (d, 1H, *J* = 4.8 Hz), 8.26 (s, 1H); Ms 400 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-c]pyridine (51a). The compound **51a** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 28% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.32 (s, 3H), 1.63 (s, 3H), 3.89 (d, 1H, *J* = 9.6 Hz), 4.32 (d, 1H, *J* = 14.1 Hz), 4.52 (d, 1H, *J* = 14.1 Hz), 5.03 (s, 1H), 5.24 (d, 1H, *J* = 9.6 Hz), 6.45-6.71 (m, 5H), 7.16 (d, 1H, *J* = 8.7 Hz), 8.02 (d, 1H, *J* = 4.8 Hz); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (51b). The compound **51b** was obtained from the compound **32** and *N*-(1*H*-

imidazol-2-ylmethyl)-3,4-dichloroaniline in 15% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.57 (s, 6H), 4.21 (d, 2H, J = 5.1 Hz), 4.42 (s, 1H), 5.91 (s, 1H), 6.49 (m, 2H), 6.59 (d, 1H, J = 2.7 Hz), 6.95 (d, 1H, J = 1.1 Hz), 7.15 (m, 2H), 8.14 (d, 1H, J = 6.1 Hz), 8.28 (s, 1H); Ms 400 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2-fluoro-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [2,3-c]pyridine (52a). The compound **52a** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-2-fluoro-4-chloroaniline in 32% yield. . ^{1}H NMR (300 MHz, $CDCl_3$): δ1.30 (s, 3H) 1.61 (s, 3H), 3.88 (d, 1H, J = 9.4 Hz), 4.42 (d, 1H, J = 14.3 Hz), 4.65 (d, 1H, J = 14.3 Hz), 4.81 (s, 1H), 5.32 (d, 1H, J = 9.4 Hz), 6.49 (s, 1H), 6.55 (d, 1H, J = 4.9 Hz), 6.77 (s, 2H), 6.98 (d, 2H, J = 10.1 Hz), 8.05 (d, 1H, J = 14.9 Hz), 8.25 (s, 1H); Ms 402 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2-fluoro-4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-c]pyridine (52b). The compound **52b** was obtained from the compound **32** and *N*-(1*H*-imidazol-2-ylmethyl)-2-fluoro-4-chloroaniline in 14% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.55 (s, 6H) 4.31 (d, 2H, J = 4.4 Hz), 4.34 (s, 1H), 5.90 (s, 1H), 6.35 (d, 1H, J = 4.8 Hz), 6.63 (d, 1H, J = 8.7 Hz), 6.91 (m, 3H), 7.15 (s, 1H), 8.07 (d, 1H, J = 4.8 Hz), 8.26 (s, 1H); Ms 384 (M^+).

(3*R*,4*S*)-4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-6-bromo-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [2,3-b]pyridine (53a). The compound **53a** was obtained from the compound **33** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 33% yield. ^{1}H NMR (300 MHz, CD_3OD): δ1.32 (s, 3H), 1.60 (s, 3H), 4.01 (d, 1H, J = 9.8 Hz), 4.48 (d, 1H, J = 14.6 Hz), 4.75 (d, 1H, J = 14.6 Hz), 5.63 (d, 1H, J = 9.8 Hz), 6.52 (d, 1H, J = 5.0 Hz), 6.74 (d, 2H, J = 7.9 Hz), 6.86 (s, 1H), 6.99 (s, 1H), 7.10 (d, 2H, J = 8.6 Hz), 7.71 (d, 1H, J = 5.0 Hz); Ms 464 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-6-bromo-2,2-dimethyl-2*H*-pyrano[2,3-b]pyridine (53b). The compound **53b** was obtained from the compound **33** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 8% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.60 (s, 6H), 4.23 (s, 2H), 5.95 (s, 1H), 6.35 (d, 1H, J = 4.8 Hz), 6.47 (d, 2H, J = 8.7 Hz), 6.92 (s, 1H), 7.08 (d, 2H, J = 8.7 Hz), 7.16 (s, 1H), 7.86 (d, 1H, J = 4.8 Hz); Ms 446 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-b]pyridine (54a). The compound **54a** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 24% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.35 (s, 3H), 1.63 (s, 3H), 3.91 (d, 1H, J = 9.6 Hz), 4.35 (d, 1H, J = 14.1 Hz), 4.59 (d, 1H, J = 14.1 Hz), 5.33 (d, 1H, J = 9.6 Hz), 6.50 (s, 1H), 6.62 (d, 2H, J = 8.7 Hz), 6.76 (s, 1H), 6.84 (m, 1H), 7.01 (d, 1H, J = 7.2 Hz), 7.11 (d, 2H, J = 8.7 Hz), 8.16 (d, 1H, J = 3.3 Hz); Ms 384 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-b]pyridine (54b). The compound **54b** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-4-chloroaniline in 4% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.61 (s, 6H), 4.25 (s, 2H), 5.82 (s, 1H), 6.42 (d, 1H, J = 4.8 Hz), 6.98-7.18 (m, 5H), 8.10 (d, 1H, J = 4.8 Hz); Ms 366 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-b]pyridine (55a). The compound **55a** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-2,4-dichloroaniline in 36% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.36 (s, 3H), 1.63 (s, 3H), 3.91 (d, 1H, J = 9.4 Hz), 4.34 (d, 1H, J = 14.2 Hz), 4.69 (d, 1H, J = 14.2 Hz), 5.06 (s, 1H), 5.35 (d, 1H, J = 9.4 Hz), 6.47 (s, 1H), 6.73 (dd, 2H, J = 4.4, 8.5 Hz), 6.82 (dd, 1H, J = 4.6, 7.3 Hz), 6.96 (d, 1H, J = 7.3 Hz), 7.10 (d, 1H, J = 8.5 Hz), 7.24 (m, 1H), 8.15 (d, 1H, J = 4.4 Hz); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano[2,3-b]pyridine (56a). The compound **56a** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 31% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.37 (s, 3H), 1.64 (s, 3H), 3.95 (d, 1H, J = 9.4 Hz), 4.39 (d, 1H, J = 13.2 Hz), 4.55 (d, 1H, J = 13.2 Hz), 4.91 (s, 1H), 5.30 (d, 1H, J = 9.4 Hz), 6.53-6.91 (m, 5H), 7.06 (d, 1H, J = 7.8 Hz), 7.20 (d, 1H, J = 9.0 Hz), 8.21 (d, 1H, J = 3.6 Hz); Ms 418 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-3,4-dichloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-b]pyridine (56b). The compound **56b** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-3,4-dichloroaniline in 26% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.64 (s, 6H), 4.21 (d, 2H, J = 5.4 Hz), 4.43 (s, 1H), 5.79 (s, 1H), 6.40 (dd, 1H, J = 2.7, 8.7 Hz), 6.59 (d, 1H, J = 2.7 Hz), 6.80 (d, 2H, J = 3.4 Hz), 6.95 (s, 1H), 7.13 (d, 1H, J = 8.7 Hz), 7.16 (s, 1H), 8.15 (dd, 1H, J = 3.4, 3.4 Hz); Ms 400 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2-fluoro-4-chloroanilino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-pyrano [2,3-b] pyridine (57a). The compound **57a** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-2-fluoro-4-chloroaniline in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.62 (s, 3H), 3.91 (d, 1H, J = 9.4 Hz), 4.37 (d, 1H, J = 11.5 Hz), 4.63 (d, 1H, J = 11.5 Hz), 4.91 (s, 1H), 5.63 (d, 1H, J = 9.4 Hz), 6.47 (s, 1H), 6.72-7.01 (m, 6H), 8.14 (d, 1H, J = 3.5 Hz); Ms 402 (M^+).

4-[*N*-(1*H*-Imidazol-2-ylmethyl)-2-fluoro-4-chloroanilino]-2,2-dimethyl-2*H*-pyrano[2,3-b]pyridine (57b). The compound **57b** was obtained from the compound **24** and *N*-(1*H*-imidazol-2-ylmethyl)-2-fluoro-4-chloroaniline in 9% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.61 (s, 6H), 4.31 (d, 2H, J = 5.0 Hz), 4.40 (s, 1H), 5.79 (s, 1H), 6.62 (dd, 1H, J = 8.6, 9.4 Hz), 6.71-6.94 (m, 5H), 7.15 (s, 1H), 8.12 (dd, 1H, J = 2.3, 4.4 Hz); Ms 384 (M^+).

Biology. HUVECs (Human umbilical vein endothelial cells) were isolated from human umbilical vein, and cultured. HUVECs within passage 5 from confluent cultures were detached, and plated onto a layer of a bFGF (basic fibroblast growth factor)-reduced and polymerized Matrigel. Matrigel cultures were incubated with or without the compound, and the change of cell morphology was captured through a phase contrast microscope and photographed. The effects on tube formation of the compounds were compared with the vehicle treated control, then confirmed their *in vitro* anti-angiogenic effect indirectly.

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