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Synthesis and Antiviral Activity of Some 1*H*-Pyrrolo[3,2-b]pyridin-6-yl)acetic Acid Derivatives

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Pyrrolopyridine derivatives for the treatment of HIV1-infection were synthesized by 10 step reactions. Methyl 2-(3-bromo-7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-b]pyridin-6-yl)-2-(*tert*-butoxy)acetate converted efficiently into the corresponding 1*H*-pyrrolo[3,2-b]pyridin-6-yl)acetic acid derivatives by Suzuki coupling reaction. Present procedure provides short reaction times and good to excellent yields for a wide range of compounds, including pyrrolopyridine scaffolds. 7-Halogenated 1*H*-pyrrolo[3,2,b]pyridine acetic acid derivatives of final products showed good activity inthe HIV-1 IN inhibition test, while the other derivatives showed relatively low activity.

Keywords: Pyrrolopyridine, Suzuki coupling reaction, HIV-1, Integrase.

INTRODUCTION

HIV-1 integrase (IN) is essential for viral replication and it has become one of the most important therapeutic targets. Many integrase strand transfer inhibitors with different chemical scaffolds targeting the strand transfer reaction of HIV-1 IN have been developed [1-3].

The chemistry of pyridines and their derivatives has been studied for over a century because of their diverse biological activities and primarily, fused pyridines continue to attract considerable attention because of their great practical usefulness. Compounds containing a fused pyridine ring have significant biological activity and are of particular interest in cancer and virus research [4-6]. We report herein the synthesis of some new heterocyclic compounds containing pyridine moiety fused with pyrrole. In view of the biological importance of HIV-1 IN, we aimed to synthesize a series of 1*H*-pyrrolo[3,2-b]pyridine acetic acid (compound **12**).

EXPERIMENTAL

All the chemicals and reagents used in this study were of laboratory grade and purchased from Aldrich chemical company. Analytic thin-layer chromatography was performed on glass plates coated with silica gel (Silicycle, 60A pore size, 40-64 μm particle size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by ultraviolet light. Flash column chromatography was performed with silica gel (Merck, 60A pore size, 230-400 mesh). ^{1}H NMR spectra were recorded on a Bruker 300 MHz or 500 MHz spectrometer (Bruker Corporation Ltd., Germany) using $CDCl_3$ or methanol-d_4 as solvent with TMS as the internal standard. Chemical shift values are given in ppm. Both EI-MS spectra and high resolution mass spectra (HR-MS) were recorded on a JEOL JMS-700 double-focusing type mass spectrometer. LC-MS data were obtained on Waters Acquity UPLC H-Class/SQD2 system (ESI, 70 ev). Elementary analysis was performed on a Thermo Scientific FLASH EA-2000 organic elemental analyzer.

Following products were obtained from various reactions:

Ethyl 3-amino-1*H*-pyrrole-2-carboxylate (1): To a solution of isoxazole (30 g, 0.43 mol) in anhydrous ethanol (120 mL) was added drop-wise sodium ethoxide (21 %, in ethanol) (0.45 mol) at 0-5 °C. After stirring for 30 min, acetic acid (0.43 mol), diethyl amino malonate hydrochloride (0.30 mol), anhydrous sodium acetate (0.33 mol) were added. After stirring at room temperature for 18 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with chloroform (1.5 L) and water (500 mL), the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in anhydrous ethanol (450 mL), sodium ethoxide (21 %, in ethanol) (0.45 mol) was added drop-wise at 0-5 °C. The reaction mixture was warmed to room temperature slowly, stirred for 18 h, was quenched with acetic acid (0.45 mol) and basified with aq.

Na_2CO_3 pH range for 8. The mixture was extracted with chloroform (1 L) and washed water (500 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatograph (25 % ethyl acetate in hexane). Yield (20 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 6.71 (s, 1H), 5.75 (t, 1H, *J* = 2.8 Hz), 4.33 (m, 4H, *J* = 6.9 Hz), 1.37 (t, 3H, *J* = 7.0 Hz); EI-MS *m/z*: (M^++1) 154; Anal. calcd. (%) for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N18.17. Found (%): C, 54.78; H, 6.57; N, 16.88.

(E)-Ethyl 3-[(4-ethyoxy-4-oxobut-2-en-2-yl)amino]-1*H*-pyrrole-2-carboxylate (2): Compound **1** (12.8 g, 0.08 mmol) and (Z)-ethyl-3-ethoxy but-2-enoate (0.10 mol) were dissolved in toluene (250 mL). Then *p*-toluene sulfonic acid monohydrate (2.63 mmol) was added and the reaction mixture was allowed to reflux with stirring for 18 h. The crude products were purified by silica gel column chromatography (20 % ethyl acetate in hexane) to give compound **2**. Yield (34 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.28 (d, 1H, *J* = 1.1 Hz), 8.64 (d, 1H, *J* = 1.1 Hz), 6.81 (t, 1H, *J* = 3.1 Hz), 6.15 (t, 1H, *J* = 2.8 Hz), 4.71 (s, 1H), 4.43 (q, 2H, *J* = 7.0 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 2.22 (s, 3H), 1.40 (t, 3H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 7.0 Hz); EI-MS *m/z*: (M^++1) 266; Anal. calcd. (%) for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found (%): C, 59.00; H, 6.91; N, 10.43.

(E)-Ethyl 3-[(4-ethoxy-4-oxobut-2-en-2-yl)amino]-1-methyl-1*H*-pyrrole-2-carboxylate (3): In sequence, compound **2** (7.04 g, 0.026 mol), methyl iodide (0.029 mol), potassium hydroxide, pellets (0.06 mol) and tetra-*n*-butylammonium bromide (TBAB) (3 mmol) were dissolved in methylene chloride (160 mL). The reaction mixture was stirred for 18 h at room temperature. Next 2 N HCl solution was added (pH about 7-8) and then the resulting mixture was extracted with methylene chloride. We obtained pure compound **3** by silica gel column chromatography (20 % ethyl acetate in hexane). Yield (87 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.18 (s, 1H), 6.63 (d, 1H, *J* = 2.8 Hz), 6.00 (d, 1H, *J* = 2.9 Hz), 4.68 (s, 1H), 4.43 (q, 2H, *J* = 7.0 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 3.86 (s, 3H), 2.16 (s, 3H), 1.40 (t, 3H, *J* = 7.1 Hz), 1.28 (t, 3H, *J* = 7.1 Hz); EI-MS *m/z*: (M^++1) 280; Anal. calcd. (%) for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found (%): C, 60.24; H, 7.42; N, 10.01.

Ethyl-1,5-dimethyl-7-oxo-4,7-dihydro-1*H*-pyrrole-[3,2-*b*]pyridine-6-carboxylate (4): To the stirred mixture of compound **3** (5.5 g, 19.5 mmol) in anhydrous ethanol (115 mL) was added a solution of sodium ethoxide (21 %, in ethanol) (2.3 mol). After the reaction mixture was stirred and refluxed for 18 h, 2N-HCl solution was added (pH about 6). Water (80 mL) and methylene chloride (20 mL) were then added and the reaction mixture was stirred for an additional 1 h. A white precipitate formed and was filtered off and recrystallized from water/methylene chloride to produce compound **4**. Yield (75 %). ^{1}H NMR (500 MHz, CD_3OD-d4): δ 7.17 (d, 1H, *J* = 2.8 Hz), 6.18 (d, 1H, *J* = 2.9 Hz), 4.36 (q, 2H, *J* = 7.1 Hz), 4.11 (s, 3H), 2.43 (s, 3H), 1.39 (t, 3H, *J* = 7.2 Hz); EI-MS *m/z*: (M^++1) 234; Anal. calcd. (%) for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found (%): C, 61.41; H, 6.06; N, 11.81.

Ethyl 7-chloro-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-6-carboxylate (5): Compound **4** (2g, 8.54 mmol) was dissolved in phosphoryl chloride (0.43 mol) and the solution was stirred for 5 h at 60 °C. The solvent was removed from the reaction mixture. Water/methylene chloride was added and the layers were separated. The aqueous phase was extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure, yielding a residue which was purified by column chromatography (33.3 % ethyl acetate in hexane) to give compound **5**. Yield (50 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, 1H, *J* = 3.2 Hz), 6.61 (d, 1H, *J* = 3.2 Hz), 4.49 (q, 2H, *J* = 7.1 Hz), 4.12 (s, 3H), 2.64 (s, 3H), 1.45 (t, 3H, *J* = 7.2 Hz); EI-MS *m/z*: (M^++1) 252; Anal. calcd. (%) for $C_{12}H_{13}N_2O_2Cl$: C, 57.04; H, 5.19; N, 11.09. Found (%): C, 56.78; H, 5.18; N, 10.99.

(7-Chloro-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)methanol (6): To a solution of compound **5** (0.73 g, 2.87 mmol) in anhydrous methylene chloride (9 mL) cooled to -78 °C was added drop-wise 1 M DIBAL-H/toluene (8.61 mmol). The reaction mixture was allowed to slowly warm to -20 °C and stirred for 1 h. Water (0.5 mL) and 2 N NaOH solution (0.5 mL) were slowly added for a minute and then the reaction mixture was filtered over celite and washed with 50 % ethyl acetate in methanol. Pure compound **6** was provided by column chromatography (5 % methanol in methylene chloride). Yield (90 %). ^{1}H NMR (500 MHz, CD_3OD-d_4): δ 7.44 (d, 1H, *J* = 3.1 Hz), 6.50 (d, 1H, *J* = 3.1 Hz), 4.93 (s, 2H), 4.15 (s, 3H), 2.73 (s, 3H); EI-MS *m/z*: (M^++1) 210; Anal. calcd. (%) for $C_{10}H_{11}N_2OCl$: C, 57.01; H, 5.26; N, 13.30. Found (%): C, 56.58; H, 5.25; N, 13.15.

[7-(4-Chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-b]pyridin-6-yl]methanol (7): Compound **6** (0.347g, 4.65 mmol), 4-chlorophenylboronic acid pinacol ester (6.05 mmol), *tetrakis*(triphenylphosphine) palladium(0) (1.40 mmol) and potassium carbonate (23.25 mmol) were dissolved in DMF. We performed nitrogen degassing of the reaction mixture and then stirred for 20 min. The reaction mixture was refluxed with stirring under nitrogen atmosphere for 18 h. The solution was then allowed to cool to room temperature, filtered over celite, washed with ethyl acetate and concentrated under reduced pressure. Then, DMF solvent was removed by high vacuum pump. We obtained pure compound **7** by silica gel column chromatography (only ethyl acetate). Yield (52 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, 2H, *J* = 7.8 Hz), 7.36 (d, 2H, *J* = 7.9 Hz), 7.15 (s, 1H), 6.66 (s, 1H), 4.54 (s, 2H), 3.17 (s, 3H), 2.83 (s, 3H); EI-MS *m/z*: (M^++1) 286; Anal. calcd. (%) for $C_{16}H_{15}N_2OCl$: C, 67.02; H, 5.27; N, 9.77. Found (%): C, 67.72; H, 5.54; N, 9.02.

7-(4-Chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-6-carbaldehyde (8): Compound **7** (0.74 mmol) and manganese(IV) oxide (29.6 mmol) were dissolved in methylene chloride (30 mL) and then the reaction mixture was refluxed, while stirring for 18h under nitrogen atmosphere. The reaction mixture was filtered over celite, washed with ethyl acetate and concentrated under reduced pressure. Pure compound **8** as a white sold was provided by silica gel column chromatography (33.3 % ethyl acetate in hexane). Yield (61 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.51 (m, 3H), 7.38 (m, 3H), 6.73 (d, 1H, *J* = 1.6 Hz), 3.24 (d, 3H, *J* = 18.3

Hz), 2.67 (d, 3H, *J* = 8.9 Hz); EI-MS *m/z*: (M^++1) 284; Anal. calcd. (%) for $C_{16}H_{13}N_2OCl$: C, 67.49; H, 4.60; N, 9.84. Found (%): C, 69.11; H, 4.73; N, 8.97.

Methyl 2-[7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo-[3,2-*b*]pyridin-6-yl]-2-hydroxyacetate (9): To the stirred mixture (ice bath) of compound **8** (0.34 g, 1.2 mmol) and zinc iodide (2.4 mmol) in dry methylene chloride (11 mL) was added drop-wise trimethylsilyl cyanide (4.8 mmol) over a period of 20 min. The reaction mixture was stirred for 1 h (ice bath) and then for a further 3 h at room temperature. The mixture was dissolved in methylene chloride (30 mL) and washed with water. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated to obtain a yellow solid crude product (2-(7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-b]pyridine-6-yl)-2-((trimethylsilyl)oxy)acetonitrile). To the crude product (0.46 g, 100 % yield on the assumption) in methanol (6.5 mL) was added sulfuric acid (1.3 mL). The reaction mixture was refluxed while stirring for 18 h. The reaction mixture was allowed to cool to room temperature, concentrated and then a saturated aqueous solution of sodium carbonate (pH about 7) was added. We performed extraction with ethyl acetate. The organic layer was dried over magnesium sulfate, the solvent evaporated under reduced pressure and the residue purified by chromatography (50 % ethyl acetate in hexane) to give compound **9**. Yield (58 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 5H), 6.56 (d, 1H, *J* = 5.4 Hz), 5.17 (s, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.62 (s, 3H); EI-MS *m/z*: (M^++1) 344; Anal. calcd. (%) for $C_{18}H_{17}N_2O_3Cl$: C, 62.70; H, 4.97; N, 8.12. Found (%): C, 61.02; H, 4.86; N, 7.60.

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate (10): To a solution of compound **9** (1.13 g, 2.92 mmol) in methylene chloride (33 mL) was added *tert*-butylacetate (65.2 mL) and then 70 % perchloric acid (14.6 mmol) in methylene chloride (1 mL) was added drop-wise for 0.5 h. The reaction mixture was stirred for 3 h at room temperature, then cooled to 10 °C and an aqueous solution of 20 % sodium carbonate added. The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure. Pure compound **10** was provided by silica gel column chromatography (50 % ethyl acetate in hexane) of the residue. Yield (47 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (m, 3H), 7.35 (dd, 1H, *J* = 9.65 Hz), 7.14 (d, 1H, *J* = 3.2 Hz), 6.68 (d, 1H, *J* = 3.2 Hz), 5.06 (s, 1H), 3.69 (s, 3H), 3.10 (s, 3H) 2.76 (s, 3H) 1.02 (s, 9H);); EI-MS *m/z*: (M^++1) 400; Anal. calcd. (%) for $C_{22}H_{26}N_2O_3Cl$: C, 65.91; H, 6.29; N, 6.99. Found (%): C, 65.78; H, 6.39; N, 6.78.

General procedure for synthesis of compounds (11a-11c): To a solution of compound **10** (41 mg, 0.1 mmol) in dry tetrahydrofuran (THF) (0.8 mL) cooled to -78 °C was added, drop-wise over a period of 20 min under nitrogen atmosphere, a solution of N-bromosuccinimde (NBS) (to give compound **11a**), N-chlorosuccimide (NCS) (to give compound **11b**), or N-iodosuccimide (NIS) (to give compound **11c**) (0.1 mmol), as appropriate, dissolved in THF (0.6 mL). After complete addition, the reaction mixture was stirred for a further 1 h at the same temperature and then allowed to warm to room temperature and treated with sodium sulfite. The mixture was evaporated under reduced pressure. The crude products were purified by silica gel column chromatography (50 % ethyl acetate in hexane). Also the products obtained were found to be pure by TLC and NMR spectra.

Methyl 2-[3-bromo-7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]-2-(*tert*-butoxy)acetate (11a): Yield (99.9 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (m, 3H), 7.18 (s, 1H), 5.06 (s, 1H), 3.68 (s, 3H), 3.09 (s, 3H) 2.81 (s, 3H) 1.02 (s, 9H); EI-MS *m/z*: (M^++1) 478; Anal. calcd. (%) for $C_{22}H_{24}N_2O_3BrCl$: C, 55.07; H, 5.04; N, 5.84. Found (%): C, 56.76; H, 5.34; N, 5.66.

Methyl 2-(*tert*-butoxy)-2-[3-chloro-7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate (11b): Yield (71.3 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (m, 3H), 7.31 (d, 1H, *J* = 8.1 Hz), 7.13 (s, 1H), 5.06 (s, 1H), 3.69 (s, 3H), 3.08 (s, 3H) 2.81 (s, 3H) 1.02 (s, 9H); EI-MS *m/z*: (M^++1) 434; $C_{22}H_{24}N_2O_3Cl_2$: C, 60.70; H, 5.56; N, 6.43. Found (%): C, 60.77; H, 5.60; N, 6.41.

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-3-iodo-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate (11c): Yield (65.8 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (m, 5H), 5.06 (s, 1H), 3.68 (s, 3H), 3.11 (s, 3H) 2.82 (s, 3H) 1.01 (s, 9H); EI-MS *m/z*: (M^++1) 526; Anal. calcd. (%) for $C_{22}H_{24}N_2O_3ClI$: C, 50.16; H, 4.59; N, 5.32. Found (%): C, 51.24; H, 4.68; N, 5.29.

General procedure for Suzuki coupling of aryl compounds with aryl boronic acids (11d-11j): To the stirred mixture of compound **11a** and aryl boronic acid (Table-1, entry 1-7) in 1,2-dimethoxyethane and water was added sodium carbonate and Pd(dppf)Cl_2-DCM (1,1'-*bis*(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane adduct) under nitrogen atmosphere (at -78 °C). After complete addition, the reaction mixture was stirred for 5 h (reflux). The mixture was cooled, filtered over celite and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (10 % ethyl acetate in hexane). We obtained various compounds (**11d-11j**).

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-1,5-dimethyl-3-phenyl-1*H*-pyrrolo[3,2-b]pyridin-6-yl]acetate (11d): Yield (99.9 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, 2H), 7.42 (m, 8H), 5.09 (s, 1H), 3.69 (s, 3H), 3.15 (s, 3H) 2.85 (s, 3H) 1.04 (s, 9H); HRMS (EI) calcd. (%) for $C_{28}H_{29}N_2O_3Cl$ (M^++1): 476.1867. Found (%) 476.1866.

Methyl 2-(*tert*-butoxy)-2-[3-(3-chlorophenyl)-7-(4-chlorophenyl]-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)acetate (11e): Yield (53.3 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.45 (m, 5H), 7.25 (s, 1H), 6.79 (s, 1H), 5.08 (s, 1H), 3.69 (s, 3H), 3.12 (s, 3H), 2.82 (s, 3H) 1.03 (s, 9H); HRMS (EI) calcd. (%) for $C_{28}H_{29}N_2O_3Cl_2$ (M^++1): 510.1477. Found (%) 510.1475.

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-1,5-dimethyl-3-{3-(trifluoromethyl)phenyl}-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate (11f): Yield (67.9 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 9H), 5.08 (s, 1H), 3.68 (s, 3H), 3.14 (s, 3H), 2.81 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{29}H_{28}ClF_3N_2O_3$ (M^++1): 544.1741. Found (%) 544.1740.

TABLE-1
SUZUKI COUPLING OF ARYL COMPOUNDS WITH ARYL BORONIC ACIDS

Entry	Aryl boronic acid	Time (h)	Coupling product (**11**)	Yield (%)
1	Phenylboronic acid	5	**11d**	99.9
2	3-Chlorophenylboronic acid	5	**11e**	53.3
3	3-(Trifluoromethyl)phenylboronic acid	5	**11f**	67.9
4	3-Biphenylboronic acid	5	**11g**	37.0
5	3-Fluorobiphenylboronic acid	5	**11h**	47.5
6	3-Furanylboronic acid	5	**11i**	21.5
7	3-Methoxy-phenylboronic acid	5	**11j**	17.4

Methyl 2-(3-([1,1'-biphenyl]-3-yl)-7-(4-chlorophenyl)-1,5-dimethyl)-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)-2-(*tert*-butoxy)acetate (11g): Yield (37 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (m, 14H), 5.07 (s, 1H), 3.68 (s, 3H), 3.14 (s, 3H), 2.81 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{34}H_{33}N_2O_3Cl$ (M^++1): 552.2180. Found (%) 552.2178.

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-3-(2-fluoro-[1,1'-biphenyl]-4-yl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate (11h): Yield (47.5 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (m, 13H), 5.07 (s, 1H), 3.68 (s, 3H), 3.14 (s, 3H), 2.83 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{34}H_{32}N_2O_3ClF$ (M^++1): 570.2085. Found (%) 570.2084.

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-3-(furan-3-yl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate (11i): Yield (21.5 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.45 (m, 5H), 7.25 (s, 1H), 6.79 (s, 1H), 5.08 (s, 1H), 3.69 (s, 3H), 3.12 (s, 3H), 2.82 (s, 3H) 1.03 (s, 9H); HRMS (EI) calcd. (%) for $C_{26}H_{27}ClN_2O_4$ (M^++1): 466.1659. Found (%) 466.1658.

Methyl 2-(*tert*-butoxy)-2-[7-(4-chlorophenyl)-3-(3-methoxyphenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetate. (11j): Yield (17.4 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (m, 9H), 5.09 (s, 1H), 3.92 (s, 3H), 3.69 (s, 3H), 2.83 (s, 3H) 1.04 (s, 9H); HRMS (EI) calcd. (%) for $C_{29}H_{31}N_2O_4Cl$ (M^++1): 506.1972. Found (%) 506.1971.

General procedure for preparation of compounds (11a-j to 12a-j): Compound **11** (0.013 mmol) was dissolved in THF (2 mmol) and then 4 N NaOH in methanol solution (1 mmol) was added. After complete addition, the reaction mixture was stirred for 4 h at room temperature and an aqueous solution of 2 N HCl added. The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water, dried magnesium sulfate and concentrated under reduced pressure. Pure compound **12** was provided by silica gel column chromatography (5 % methanol in methylene chloride) of the residue.

2-[3-Bromo-7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]-2-(*tert*-butoxy)acetic acid (12a): Yield 79.9 (%). ^{1}H NMR (500 MHz, CD_3OD-d4): δ 7.58 (m, 5H), 5.11 (s, 1H), 3.16 (s, 3H), 2.77 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{21}H_{22}N_2O_3BrCl$ (M^++1): 464.0502. Found (%) 464.0472.

2-(*tert*-Butoxy)-2-[3-chloro-7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12b): Yield 81.8 (%). ^{1}H NMR (500 MHz, CD_3OD-d4): δ 7.67 (m, 5H), 5.11 (s, 1H), 3.15 (s, 3H), 2.77 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{21}H_{22}N_2O_3Cl_2$ (M^++1): 420.1007. Found (%) 420.1006.

2-(*tert*-Butoxy)-2-[7-(4-chlorophenyl)-3-iodo-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12c): Yield 69.9 (%). ^{1}H NMR (500 MHz, CD_3OD-d4): δ 7.54 (m, 5H), 5.11 (s, 1H), 3.17 (s, 3H), 2.78 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{21}H_{22}N_2O_3ClI$ (M^++1): 512.0354. Found (%) 512.0347.

2-(*tert*-Butoxy)-2-[7-(4-chlorophenyl)-1,5-dimethyl-3-phenyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12d): Yield (83.5 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (m, 10H), 4.99 (s, 1H), 3.09 (s, 3H) 2.68 (s, 3H) 0.91 (s, 9H); HRMS (EI) calcd. (%) for $C_{27}H_{27}N_2O_3Cl$ (M^++1): 462.1710. Found (%) 462.1709.

2-(*tert*-Butoxy)-2-[3-(3-chlorophenyl)-7-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12e): Yield (64.8 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 9H), 5.17 (s, 1H), 3.15 (s, 3H), 2.79 (s, 3H) 1.05 (s, 9H); HRMS (EI) calcd. (%) for $C_{27}H_{26}N_2O_3Cl_2$ (M^++1): 496.1320. Found (%) 496.1322.

2-(*tert*-Butoxy)-2-[7-(4-chlorophenyl)-1,5-dimethyl-3-{3-(trifluoromethyl)phenyl}-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12f): Yield (60.5 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (m, 9H), 5.17 (s, 1H), 3.17 (s, 3H), 2.79 (s, 3H) 1.05 (s, 9H); HRMS (EI) calcd. (%) for $C_{28}H_{26}N_2O_3ClF_3$ (M^++1): 530.1584. Found (%) 530.1583.

2-(3-([1,1'-Biphenyl]-3-yl)-7-(4-chlorophenyl)-1,5-dimethyl)-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)-2-(*tert*-butoxy)-acetic acid (12g): Yield (96.6 %). ^{1}H NMR (300 MHz, methnaol-d_4): δ 7.63 (m, 14H), 5.09 (s, 1H), 3.21 (s, 3H), 2.86 (s, 3H) 0.96 (s, 9H); HRMS (EI) calcd. (%) for $C_{33}H_{31}N_2O_3Cl$ (M^++1): 538.2023. Found (%) 538.1993.

2-(*tert*-Butoxy)-2-[7-(4-chlorophenyl)-3-(2-fluoro-[1,1'-biphenyl]-4-yl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]-pyridin-6-yl]acetic acid (12h): Yield (64.9 %). ^{1}H NMR (500 MHz, methnaol-d_4): δ 7.72 (m, 13H), 5.13 (s, 1H), 3.21 (s, 3H), 2.82 (s, 3H) 1.04 (s, 9H); HRMS (EI) calcd. (%) for $C_{33}H_{30}N_2O_3ClF$ (M^++1): 556.1929. Found (%) 556.1931.

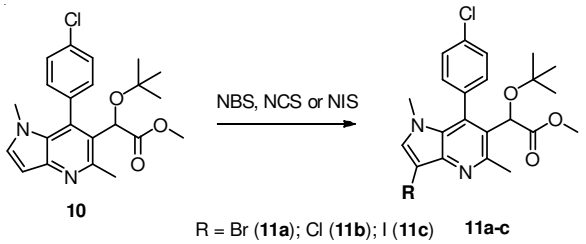
2-(*tert*-Butoxy)-2-[7-(4-chlorophenyl)-3-(furan-3-yl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12i): Yield (53.3 %). ^{1}H NMR (500 MHz, methnaol-d_4): δ 8.23 (s, 1H), 7.59 (m, 6H), 6.84 (s, 1H), 5.11 (s, 1H), 3.17 (s, 3H), 2.79 (s, 3H) 1.02 (s, 9H); HRMS (EI) calcd. (%) for $C_{25}H_{25}N_2O_4Cl$ (M^++1): 452.1503. Found (%) 452.1506.

2-(*tert*-Butoxy)-2-[7-(4-chlorophenyl)-3-(3-methoxy-phenyl)-1,5-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl]acetic acid (12j): Yield (75.6 %)**.** ^{1}H NMR (500 MHz, methnaol-d_4): δ 7.61 (m, 5H), 7.32 (t, 1H, J = 15.85 Hz), 6.84 (dd, 1H, J = 10.35 Hz), 5.11 (s, 1H), 3.88 (s, 3H), 3.20 (s, 3H) 2.80 (s, 3H) 1.03 (s, 9H); HRMS (EI) calcd. (%) for $C_{28}H_{29}ClN_2O_4$ (M^++1): 492.1816. Found (%) 492.1814.

RESULTS AND DISCUSSION

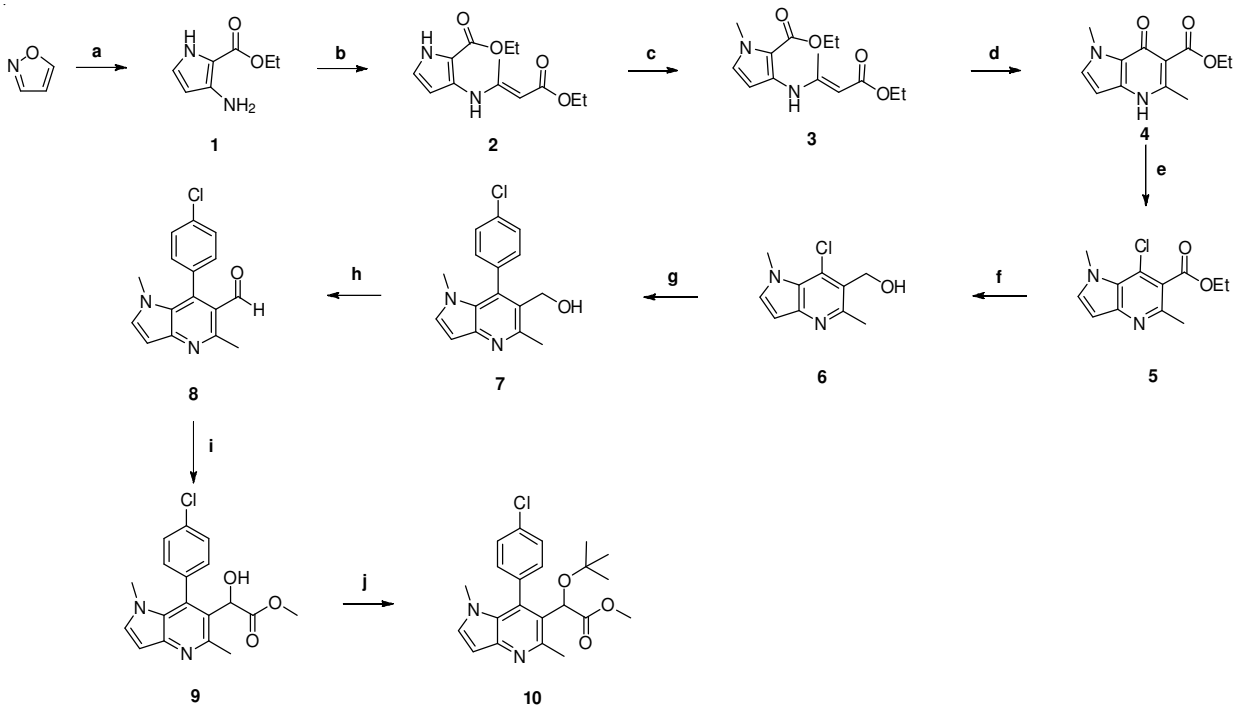
We synthesized new scaffolds of pyrrolo-pyridine derivatives based on a chemical structure study about HIV-activity [7-9]. This class of compounds is reported to show activities of the HIV1 virus [10-18]. A multistep synthesis was required for preparing the pyrrolo-pyridine derivative **10** (**Scheme-I**). Ethyl 3-amino-1*H*-pyrrole-2-carboxylate (**1**) was prepared as reported in the literature [19]. Treatment of compound **1** with (Z)-ethyl-3-ethoxybut-2-enoate and *p*-toluenesulfonic acid monohydrate yielded compound **2**, which in turn was allowed to substitute at the N-position of the pyrrole to give compound **3** [20]. It is subjected to cyclization to give compound **4** [21], which existed as a mixture of keto and enol forms, chlorination (to give **5**) and the DIBAL reduction reaction were performed in sequence, which resulted in the preparation of compound **6**. In order to prepare compound **7**, a chloro-phenyl group was attached to compound **6** *via* the Suzuki coupling reaction. We obtained compound **8** by oxidation and then compound **8** was treated with TMS-CN and methanol in the presence of acidic conditions as a one-pot reaction to give compound **9**. After completing the reaction for compound **9**, we studied the O-*t*-butylation of compound **9** because the mechanism of the O-*t*-butylation reaction has several problems. First, compound **9** was not completely dissolved in *tert*-butyl acetate. Second, we should slowly add chloric acid because of the probability of self-assembly between reagents (side products). We attempted to dilute chloric acid by using methylene chloride and also the reactant was dissolved in methylene chloride and *tert*-butyl acetate. A method was discovered for the preparation of compound **10** when we repeated a procedure reported in the literature [22,23].

Compound **11** was prepared by two processes as follows: halides were attached to **10** (**Scheme-II**) and aromatic moieties were coupled with **11a** *via* the Suzuki coupling reaction (**Scheme-III**). Compound **11a** was prepared by NBS (N-bromosuccinimide). A similar result was produced using NCS (N-chlorosuccinimide) (to give **11b**) and NIS (N-iodosuccinimide) (to give **11c**). For the reaction condition of **11a** with aryl boronic acid, refer to the literature (Table-1) [24,25]. The coupling reaction of **11a** was conducted in a mixture of DMF and water and gave byproducts. The solvent was changed to DME, but there was no improvement. We used mild reaction conditions because the reaction temperature was lower than with DMF. DME was finally shown to be suitable for the task. Compound **11a** was reacted with different arylboronic acids under the same conditions to afford compounds **11d-j** with yields of 17.4 to 99 % (Table-1). The method for coupling with aryl boronic acid was different from that required for alkylboronic acid. The target compounds **12a-j** were finally obtained by the same method (**Scheme-IV**, Table-2).



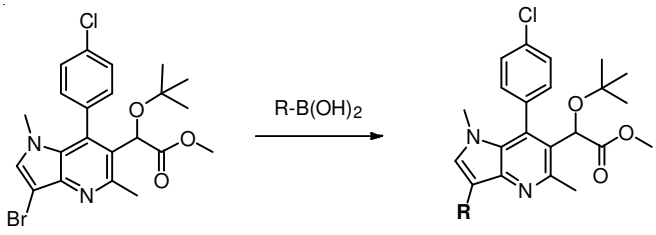
Conditions: **11a:** NBS, THF, -78 °C, 1 h, 99 %; **11b:** NCS, THF, -78 °C, 1 h, 71 %; **11c:** NIS, THF, -78 °C, 1 h, 66 %; NBS = N-borosuccinimide, NCS = N-chlorosuccimide; NIS = iodosuccimide

Scheme-II: Synthesis of pyrrolo-pyridine derivatives **11a-c**



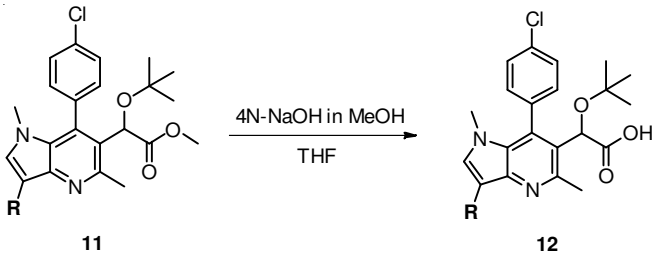
Conditions: (a) (1) NaOEt, AcOH, diethyl aminomalonate-HCl, NaOAc, EtOH, rt, 18h; (2) NaOEt, EtOH, rt, 18h, 20% (two steps); (b) (Z)-ehtyl-3-ethoxybut-2-enoate, p-TsOH-H_2O, toluene, reflux, 18h, 34%; (c) MeI, KOH, TBAB, CH_2Cl_2, rt, 18h, 87%; (d) NaOEt, EtOH, reflux, 18h, 75%; (e) $POCl_3$, 60°C, 5h, 50%; (f) dry CH_2Cl_2, DIBAL/toluene, -78°C, 1h, 90%; (g) 4-chlorophenylboronic acid pinacol ester, $[Pd(PPh_3)_4]$, K_2CO_3, DMF, reflux, 18h, 52%; (h) MnO_2, CH_2Cl_2, reflux, 18h, 61%; (i) (1) dry CH_2Cl_2, TMS-CN, ZnI_2, 0°C (1h) to rt (3h); (2) H_2SO_4, MeOH, reflux, 18h, 58% (two steps); (j) t-BuOAc, perchloric acid, CH_2Cl_2, rt, 3 h, 47 %; NaOEt= sodium ethoxide, p-TsOH = para-toluenesulfonic acid, DIBAL = diisobutylaluminum hydride, TMSCN = trimethylsilyl cyanide, t-BuOAc = tert - butylacetate.

Scheme-I: Synthesis of new scaffold of pyrrolo-pyridine derivatives (**10**)



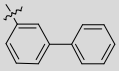
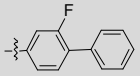
Conditions: $Pd(dppf)Cl_2$-DCM, Na_2CO_3, DMF, H_2O, reflux, 5 h

Scheme-III: Synthesis of pyrrolo-pyridine derivatives **11d-j**



Scheme-IV: Synthesis of final products **12a-j**

TABLE-2
ANTIVIRAL EVALUATION

Product No.	R groups	Yield (%)	Antiviral activity (EC_{50}) (μM)
12a	Br	79.9	5.02
12b	Cl	81.8	5.03
12c	I	69.9	5.07
12d		83.5	9.22
12e		64.8	12.86
12f		60.5	9.55
12g		96.6	10.31
12h		64.9	9.57
12i		53.3	7.98
12j		75.6	–
Raltegravir			0.0063
AZT			0.0063

Antiviral evaluation: In order to examine the HIV-1 inhibition effects of the prepared compounds, an *in vitro* test for HIV-1 inhibition effects was carried out as follows according to a known method [26]. MT-4 cells were used as host cells and the degree to which the prepared compounds inhibited the cytotoxicity of the virus-infected MT-4 cells was investigated. First, MT-4 cells were diffused at a concentration of 1×10^4 cell/well to a culture medium and HIV-1 was inoculated so that the concentration was 500 TCI_{50} (concentration at which 50 % of the cell is infected)/well. Immediately after the inoculation, the cell dispersion was transferred in aliquots of 100 μL each to a flat microtiter plate in which a sample of a prepared compound was placed. The sample was incubated for approximately 4 to 5 days at 17 °C and the virus suppression effect was determined using an MTT method. The HIV-1 inhibition test was performed for compounds **12a-j** by the above method with azidothymidine (AZT) and raltegravir as references. The results show that compounds **12a-c** have moderate activity against HIV-1 and compounds **12d-j** have lower activity (Table-2).

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