Research Article

Open Access

Dong-Mei Chen, Jia-Yan Liu, Ming Wei, Bing-Wei Wang, Ruo-Han Chu and Dong-Sheng Chen*

Synthesis of indazolo[5,4-*b*][1,6]naphthyridine and indazolo[6,7-*b*][1,6]naphthyridine derivatives

<https://doi.org/10.1515/hc-2019-0006>

Received October 08, 2018; accepted November 16, 2018.

Abstract: A simple method for the synthesis of the title compounds by an efficient *in-situ* reduction and cyclization reactions of aromatic aldehydes, *tert*-butyl 2,4-dioxopiperidine-1-carboxylate and 5-nitro-1*H*-indazole or 6-nitro-1*H*-indazole was developed.

Keywords: *in-situ* reduction, nitro compounds, indazolo[5,4-*b*][1,6]naphthyridine, indazolo[6,7-*b*][1,6]naphthyridine

Introduction

Naphthyridines are an important class of heterocycles due to their inherent biological activities [1-5]. Substituted indazoles are also pharmaceutically important [6]. Previously, we introduced a three-component reaction of 1*H*-indol-6-amine, aromatic aldehyde and cyclic 1,3-dicarbonyl compound under catalyst-free conditions [7-9]. Compared with amino compounds, nitro derivatives are more stable, easier to obtain, and they can be easily reduced to the amines [10, 11]. The reduction is often accomplished with the use of iron [Fe(0)]. This reagent is one of the most abundant, nontoxic, inexpensive and environmentally friendly transition metals [12-14]. In view of the importance of the previously detailed structures, in this report we describe synthesis of indazolo[5,4-*b*][1,6]naphthyridine and indazolo[6,7-*b*][1,6]naphthyridine derivatives starting from 5-nitro-1*H*-indazole or 6-nitro-1*H*-indazole using Fe(0) as a reducing agent via a one-pot multicomponent protocol [15-17].

Results and discussion

Initially, 4-chlorobenzaldehyde (**1a**), *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (**2**) and 6-nitro-1*H*-indazole (**3**) were allowed to react to optimize the reaction conditions (Scheme 1). When the reaction was performed in the presence of two equivalents of Fe(0), water (1 mL) and acetic acid (1 mL) in ethanol at 80°C, we were pleased to obtain the expected product **4a** in 58% yield. Then, the reaction was tested in ethanol under different ratios of **3** and Fe(0). With three equivalents of Fe(0), the yield was increased to 88%. The effects of the amounts of water and acetic acid were also evaluated. The best results were obtained in the presence of 1 mL of water and 1 mL of acetic acid using ethanol as solvent. Ethanol was the optimal solvent in comparison to tetrahydrofuran, methanol, dioxane and toluene. With the optimized reaction conditions in hand, other aromatic aldehydes **1b-j** were applied in this synthesis to furnish products **4a-j** in good yields (Scheme 1). It was found that under the optimized conditions the treatment of 5-nitro-1*H*-indazole (**5**), instead of the isomer **3**, with **1** and **2** furnished the expected products **6** (Scheme 2). The structures of all products were characterized by IR, NMR and HRMS spectral methods.

A possible mechanism is shown in Scheme 3 using substrate **3** as an example. First, the nitro compound **3** is reduced to 6-aminoindazole **A**. At the same time, the Knoevenagel product **B** is generated by the reaction of substrates **1** and **2**. Then, 6-aminoindazole **A** undergoes reaction with the intermediate product **B** to obtain the intermediate **C**. Then, intramolecular cyclization of **C** generates the intermediate product **D** which is the final precursor to the observed product **4**.

Conclusion

A simple and efficient method was developed for the synthesis of indazolo[5,4-*b*][1,6]naphthyridine and indazolo[6,7-*b*][1,6]naphthyridine derivatives directly

* Corresponding author: Dong-Sheng Chen, Kangda College of Nanjing Medical University, Lianyungang 222000, Jiangsu, People's Republic of China, e-mail: dschen@njmu.edu.cn

Dong-Mei Chen, Jia-Yan Liu, Ming Wei, Bing-Wei Wang and Ruo-Han Chu, Kangda College of Nanjing Medical University, Lianyungang 222000, Jiangsu, People's Republic of China

Scheme 1 Synthesis of indazolo[6,7-*b*][1,6]naphthyridine derivatives **4a-4j**. Scheme 2 Synthesis of indazolo[5,4-*b*][1,6]naphthyridine derivatives **6a-6j**.

Scheme 3 The proposed mechanism.

form nitro compounds by *in situ* reduction and cyclization reaction in Fe/H₂O medium.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellets. ¹H NMR (400 MHz) and ¹³C NMR (125 MHz) spectra were obtained in DMSO-*d*₆ with Me₄Si as internal standard using Bruker-400 and Bruker-500 spectrometers. ESI-HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General procedure for the synthesis of 4 and 6

A dry 25-mL round-bottom flask was charged with aromatic aldehyde **1** (1 mmol), *tert*-butyl 2,4-dioxopiperidine-1-carboxylate **2** (1.0 mmol), 6-nitro-1*H*-indazole **3** or 5-nitro-1*H*-indazole **5** (1.0 mmol), powdered iron (3 mmol), EtOH (5 mL), H₂O (1 mL), and AcOH (1 mL). The mixture was stirred at 80°C for 8–10 h until TLC analysis revealed that the reaction was completed and then treated with brine (10 mL). The mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined and washed thoroughly with brine, dried with Na₂SO₄, and filtered through Celite. Following removal of the solvent *in vacuo*, the residue was purified by crystallization from DMF to give the pure product **4** or **6**.

tert-Butyl 11-(4-chlorophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (**4a**)

Yield 88%; white powder; mp 240–241°C; IR: ν 3427, 3316, 2936, 1741, 1626, 1606, 1533, 1494, 1398, 1213, 1159, 1047, 949, 851, 774, 703 cm⁻¹; ¹H NMR: δ_H 12.90 (s, 1H, NH), 9.80 (s, 1H, NH), 7.94 (s, 1H, ArH), 7.53 (d, *J* = 8.4 Hz, 1H, ArH), 7.40 (d, *J* = 8.0 Hz, 2H, ArH), 7.23 (d, *J* = 8.0 Hz, 2H, ArH), 6.85 (d, *J* = 8.4 Hz, 1H, ArH), 5.56 (s, 1H, CH), 4.01–3.98 (m, 1H, CH₂), 3.50–3.44 (m, 1H, CH₂), 2.82–2.78 (m, 1H, CH₂), 2.66–2.62 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.1, 152.5, 148.6, 145.8, 138.5, 134.1, 134.0, 130.6, 129.3, 127.8, 119.9, 119.6, 111.3, 104.7, 100.0, 80.9, 42.1, 35.8, 27.7, 26.3. HRMS. Calcd for C₂₄H₂₂N₄O₃Cl, [M - H]⁻: *m/z* 449.1386. Found: *m/z* 449.1384.

tert-Butyl 11-(4-bromophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (**4b**)

Yield 90%; white powder; mp: 242–243°C; IR: ν 3310, 3061, 1735, 1633, 1599, 1536, 1494, 1387, 1285, 1154, 1061, 947, 830,

775, 702 cm⁻¹; ¹H NMR: δ_H 12.89 (s, 1H, NH), 9.79 (s, 1H, NH), 7.93 (s, 1H, ArH), 7.53 (d, *J* = 8.4 Hz, 1H, ArH), 7.37–7.33 (m, 4H, ArH), 6.84 (d, *J* = 8.0 Hz, 1H, ArH), 5.54 (s, 1H, CH), 4.01–3.98 (m, 1H, CH₂), 3.51–3.43 (m, 1H, CH₂), 2.82–2.75 (m, 1H, CH₂), 2.66–2.62 (m, 1H, CH₂), 1.43 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.6, 153.0, 149.1, 146.7, 139.0, 134.6, 134.5, 131.3, 130.3, 120.4, 120.1, 119.6, 111.8, 105.2, 100.5, 81.4, 42.6, 36.4, 28.3, 26.9. HRMS. Calcd for C₂₄H₂₂N₄O₃Br, [M - H]⁻: *m/z* 493.0881. Found: *m/z* 493.0885.

tert-Butyl 11-(4-fluorophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (**4c**)

Yield 81%; white powder; mp 243–244°C; IR: ν 3471, 3307, 2980, 1738, 1670, 1535, 1503, 1461, 1369, 1248, 1141, 1050, 946, 850, 743, 710 cm⁻¹; ¹H NMR: δ_H 12.88 (s, 1H, NH), 9.76 (s, 1H, NH), 7.93 (s, 1H, ArH), 7.52 (d, *J* = 8.0 Hz, 1H, ArH), 7.41–7.37 (m, 2H, ArH), 6.99–6.95 (m, 2H, ArH), 6.82 (d, *J* = 8.4 Hz, 1H, ArH), 5.54 (s, 1H, CH), 4.01–3.95 (m, 1H, CH₂), 3.48–3.40 (m, 1H, CH₂), 2.81–2.72 (m, 1H, CH₂), 2.66–2.59 (m, 1H, CH₂), 1.41 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.6, 161.1 (d, *J*_{F-C} = 192.4 Hz), 153.0, 149.0, 143.6, 139.1, 134.6, 134.4, 129.7 (d, *J*_{F-C} = 6.3 Hz), 120.4, 120.0, 115.0 (d, *J*_{F-C} = 16.7 Hz), 111.8, 105.6, 100.8, 81.3, 42.6, 36.1, 28.2, 26.9. HRMS. Calcd for C₂₄H₂₂N₄O₃F, [M - H]⁻: *m/z* 433.1681. Found: *m/z* 433.1680.

tert-Butyl 11-(4-nitrophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (**4d**)

Yield 84%; yellow powder; mp 235–236°C; IR: ν 3310, 3217, 2977, 1737, 1665, 1638, 1540, 1509, 1393, 1214, 1138, 1049, 943, 852, 781, 710 cm⁻¹; ¹H NMR: δ_H 12.97 (s, 1H, NH), 9.90 (s, 1H, NH), 8.07 (d, *J* = 8.8 Hz, 2H, ArH), 7.95 (s, 1H, ArH), 7.64 (d, *J* = 8.4 Hz, 2H, ArH), 7.57 (d, *J* = 8.4 Hz, 1H, ArH), 6.88 (d, *J* = 8.8 Hz, 1H, ArH), 5.72 (s, 1H, CH), 4.01–3.96 (m, 1H, CH₂), 3.53–3.42 (m, 1H, CH₂), 2.85–2.76 (m, 1H, CH₂), 2.70–2.62 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.5, 154.5, 152.9, 149.5, 146.3, 139.1, 134.8, 134.6, 129.2, 123.8, 120.54, 120.46, 111.9, 104.3, 99.9, 81.4, 42.5, 37.1, 28.2, 26.9. HRMS. Calcd for C₂₄H₂₂N₅O₅, [M - H]⁻: *m/z* 460.1626. Found: *m/z* 460.1635.

tert-Butyl 11-(3-chlorophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (**4e**)

Yield 84%; white powder; mp: 227–228°C; IR: ν 3450, 3291, 2977, 1738, 1667, 1626, 1536, 1496, 1446, 1369, 1212, 1138, 1048, 949, 850, 776, 731 cm⁻¹; ¹H NMR: δ_H 12.93 (s, 1H, NH),

9.83 (s, 1H, NH), 7.94 (s, 1H, ArH), 7.56-7.52 (m, 2H, ArH), 7.27 (d, $J = 7.6$ Hz, 1H, ArH), 7.22-7.18 (m, 1H, ArH), 7.14-7.11 (m, 1H, ArH), 6.86 (d, $J = 8.8$ Hz, 1H, ArH), 5.55 (s, 1H, CH), 4.02-3.97 (m, 1H, CH₂), 3.51-3.44 (m, 1H, CH₂), 2.83-2.76 (m, 1H, CH₂), 2.70-2.64 (m, 1H, CH₂), 1.43 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.6, 152.9, 149.6, 149.2, 139.0, 134.7, 134.5, 133.0, 130.4, 127.8, 126.7, 126.5, 120.4, 120.2, 111.8, 105.0, 100.3, 81.4, 42.6, 36.7, 28.3, 26.8. HRMS. Calcd for C₂₄H₂₂N₄O₃Cl, [M - H]⁻: m/z 449.1386. Found: m/z 449.1404.

***tert*-Butyl 11-(3-bromophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (4f)**

Yield 83%; white powder; mp: 229-230°C; IR: ν 3450, 3279, 2972, 1745, 1625, 1537, 1498, 1467, 1367, 1216, 1158, 1049, 945, 815, 775, 712 cm⁻¹; ¹H NMR: δ_H 12.94 (s, 1H, NH), 9.83 (s, 1H, NH), 7.94 (s, 1H, ArH), 7.66 (s, 1H, ArH), 7.54 (d, $J = 8.4$ Hz, 1H, ArH), 7.32-7.25 (m, 2H, ArH), 7.17-7.12 (m, 1H, ArH), 6.86 (d, $J = 8.4$ Hz, 1H, ArH), 5.54 (s, 1H, CH), 4.02-3.90 (m, 1H, CH₂), 3.51-3.43 (m, 1H, CH₂), 2.83-2.76 (m, 1H, CH₂), 2.70-2.65 (m, 1H, CH₂), 1.43 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.5, 152.9, 149.9, 149.2, 139.0, 134.7, 134.5, 130.8, 130.7, 129.4, 127.1, 121.8, 120.4, 120.2, 111.8, 105.0, 100.4, 81.4, 42.6, 36.8, 28.3, 26.8. HRMS. Calcd for C₂₄H₂₂N₄O₃Br, [M - H]⁻: m/z 493.0881. Found: m/z 493.0893.

***tert*-Butyl 11-(3,4-dichlorophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (4g)**

Yield 89%; white powder; mp: 250-251°C; IR: ν 3301, 2978, 1737, 1630, 1601, 1540, 1496, 1392, 1285, 1215, 1155, 1049, 975, 871, 774, 701 cm⁻¹; ¹H NMR: δ_H 12.94 (s, 1H, NH), 9.86 (s, 1H, NH), 7.96 (s, 1H, ArH), 7.71 (d, $J = 8.4$ Hz, 1H, ArH), 7.56 (d, $J = 8.8$ Hz, 1H, ArH), 7.44 (d, $J = 8.4$ Hz, 1H, ArH), 7.25 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H, ArH), 6.86 (d, $J = 8.4$ Hz, 1H, ArH), 5.55 (s, 1H, CH), 4.01-3.95 (m, 1H, CH₂), 3.54-3.45 (m, 1H, CH₂), 2.82-2.74 (m, 1H, CH₂), 2.70-2.63 (m, 1H, CH₂), 1.43 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.5, 152.9, 149.3, 148.1, 139.0, 134.7, 134.5, 130.9, 130.8, 129.9, 129.1, 128.4, 120.4, 111.8, 104.5, 100.0, 81.4, 42.6, 36.4, 28.2, 26.8. HRMS. Calcd for C₂₄H₂₁N₄O₃Cl₂, [M - H]⁻: m/z 483.0996. Found: m/z 483.0994.

***tert*-Butyl 11-(2-chlorophenyl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (4h)**

Yield 86%; white powder; mp: 280-281°C; IR: ν 3414, 3319, 3101, 2974, 1745, 1627, 1531, 1494, 1469, 1398, 1321, 1210, 1141, 1048, 943, 872, 782, 704 cm⁻¹; ¹H NMR: δ_H 11.97 (s,

1H, NH), 9.89 (s, 1H, NH), 7.90 (s, 1H, ArH), 7.86 (d, $J = 7.6$ Hz, 1H, ArH), 7.50 (d, $J = 8.4$ Hz, 1H, ArH), 7.24-7.19 (m, 2H, ArH), 7.13-7.09 (m, 1H, ArH), 6.77 (d, $J = 8.4$ Hz, 1H, ArH), 5.80 (s, 1H, CH), 4.01-3.96 (m, 1H, CH₂), 3.45-3.37 (m, 1H, CH₂), 2.80-2.71 (m, 1H, CH₂), 2.59-2.48 (m, 1H, CH₂), 1.40 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.3, 152.8, 149.7, 142.2, 139.4, 135.3, 134.9, 133.6, 132.8, 130.5, 128.5, 127.0, 120.44, 120.37, 111.7, 103.4, 98.1, 81.3, 42.6, 38.1, 28.3, 26.9. HRMS. Calcd for C₂₄H₂₂N₄O₃Cl, [M - H]⁻: m/z 449.1386. Found: m/z 449.1386.

***tert*-Butyl 10-oxo-11-(thiophen-2-yl)-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (4i)**

Yield 89%; white powder; mp > 300°C; IR: ν 3203, 3079, 2975, 1699, 1651, 1604, 1545, 1504, 1453, 1388, 1324, 1216, 1156, 970, 850, 767, 710 cm⁻¹; ¹H NMR: δ_H 13.08 (s, 1H, NH), 9.88 (s, 1H, NH), 7.97 (s, 1H, ArH), 7.54 (d, $J = 8.4$ Hz, 1H, ArH), 7.17-7.15 (m, 1H, ArH), 6.97 (d, $J = 3.2$ Hz, 1H, ArH), 6.83-6.78 (m, 2H, ArH), 5.94 (s, 1H, CH), 4.08-4.03 (m, 1H, CH₂), 3.49-3.41 (m, 1H, CH₂), 2.86-2.76 (m, 1H, CH₂), 2.67-2.62 (m, 1H, CH₂), 1.44 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.6, 153.0, 151.5, 148.9, 139.0, 134.5, 134.3, 126.8, 124.3, 123.8, 120.4, 120.1, 111.7, 105.2, 100.4, 81.4, 42.6, 32.0, 28.3, 26.9. HRMS. Calcd for C₂₂H₂₁N₄O₃S, [M - H]⁻: m/z 421.1340. Found: m/z 421.1331.

***tert*-Butyl 11-(benzo[*d*][1,3]dioxol-5-yl)-10-oxo-7,8,10,11-tetrahydro-1*H*-indazolo [6,7-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (4j)**

Yield 87%; white powder; mp 247-248°C; IR: ν 3296, 3224, 2971, 1710, 1673, 1625, 1538, 1503, 1443, 1327, 1287, 1166, 1049, 946, 811, 776, 703 cm⁻¹; ¹H NMR: δ_H 12.86 (s, 1H, NH), 9.74 (s, 1H, NH), 7.93 (s, 1H, ArH), 7.51 (d, $J = 8.4$ Hz, 1H, ArH), 6.98 (s, 1H, ArH), 6.89-6.78 (m, 2H, ArH), 6.70 (d, $J = 7.2$ Hz, 1H, ArH), 5.88 (d, $J = 7.2$ Hz, 2H, CH₂), 5.46 (s, 1H, CH), 4.01-3.98 (m, 1H, CH₂), 3.50-3.44 (m, 1H, CH₂), 2.81-2.78 (m, 1H, CH₂), 2.67-2.63 (m, 1H, CH₂), 1.43 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.6, 153.0, 148.7, 147.3, 145.9, 141.7, 139.1, 134.5, 134.3, 120.9, 120.3, 119.8, 111.8, 108.7, 108.2, 106.0, 101.1, 101.0, 81.3, 42.6, 36.5, 28.3, 26.9. HRMS. Calcd for C₂₅H₂₃N₄O₅, [M - H]⁻: m/z 459.1674. Found: m/z 459.1667.

***tert*-Butyl 11-(4-chlorophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6a)**

Yield 87%; white powder; mp 221-222°C; IR: ν 3297, 3079, 2977, 2933, 2885, 1719, 1681, 1605, 1543, 1492, 1401, 1369, 1331, 1253, 1213, 1142, 1092, 1049, 949, 846, 805, 775, 703 cm⁻¹; ¹H NMR: δ_H 13.01 (s, 1H, NH), 9.67 (s, 1H, NH), 8.01

(s, 1H, ArH), 7.37-7.34 (m, 3H, ArH), 7.23 (d, $J = 8.4$ Hz, 2H, ArH), 7.07 (d, $J = 8.4$ Hz, 1H, ArH), 5.52 (s, 1H, CH), 4.02-3.96 (m, 1H, CH₂), 3.60-3.50 (m, 1H, CH₂), 2.82-2.75 (m, 1H, CH₂), 2.64-2.59 (m, 1H, CH₂), 1.41 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.7, 153.1, 148.9, 147.2, 137.9, 132.1, 130.9, 130.0, 129.3, 128.4, 122.1, 117.2, 114.3, 110.0, 99.1, 81.3, 42.6, 39.0, 28.3, 27.0. HRMS. Calcd for C₂₄H₂₂N₄O₃Cl, [M - H]⁺: m/z 449.1386. Found: m/z 449.1384.

***tert*-Butyl 11-(4-bromophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6b)**

Yield 90%; white powder; mp 223-225°C; IR: ν 3296, 3077, 2977, 2933, 2885, 1719, 1680, 1605, 1543, 1492, 1401, 1369, 1331, 1254, 1212, 1142, 1049, 949, 845, 804, 775, 738, 714 cm⁻¹; ¹H NMR: δ_H 12.97 (s, 1H, NH), 9.63 (s, 1H, NH), 7.98 (s, 1H, ArH), 7.35-7.32 (m, 3H, ArH), 7.28 (d, $J = 8.4$ Hz, 2H, ArH), 7.05 (d, $J = 8.8$ Hz, 1H, ArH), 5.49 (s, 1H, CH), 4.00-3.95 (m, 1H, CH₂), 3.46-3.39 (m, 1H, CH₂), 2.80-2.74 (m, 1H, CH₂), 2.62-2.58 (m, 1H, CH₂), 1.39 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.7, 153.1, 148.9, 147.7, 137.9, 132.1, 131.3, 130.4, 129.3, 122.1, 119.4, 117.2, 114.2, 110.0, 99.1, 81.3, 42.6, 39.1, 28.3, 27.0. HRMS. Calcd for C₂₄H₂₂N₄O₃Br [M - H]⁺: m/z 493.0881. Found: m/z 493.0873.

***tert*-Butyl 11-(3-chlorophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6c)**

Yield 86%; white powder; mp 287-288°C; IR: ν 3278, 3085, 2978, 2934, 2886, 1720, 1682, 1609, 1546, 1492, 1402, 1370, 1329, 1251, 1212, 1140, 1049, 947, 894, 841, 808, 777, 732 cm⁻¹; ¹H NMR: δ_H 13.02 (s, 1H, NH), 9.68 (s, 1H, NH), 8.06 (s, 1H, ArH), 7.37 (d, $J = 8.0$ Hz, 2H, ArH), 7.30 (d, $J = 7.6$ Hz, 1H, ArH), 7.23-7.19 (m, 1H, ArH), 7.13-7.07 (m, 2H, ArH), 5.55 (s, 1H, CH), 4.01-3.98 (m, 1H, CH₂), 3.49-3.44 (m, 1H, CH₂), 2.81-2.78 (m, 1H, CH₂), 2.68-2.63 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.7, 153.0, 150.7, 149.1, 137.9, 133.2, 132.2, 130.3, 129.3, 127.8, 126.9, 126.3, 122.1, 117.2, 114.0, 110.1, 99.0, 81.3, 42.6, 39.3, 28.3, 26.9. HRMS. Calcd for C₂₄H₂₂N₄O₃, [M - H]⁺: m/z 449.1386. Found: m/z 449.1387.

***tert*-Butyl 11-(3-bromophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6d)**

Yield 84%; white powder; mp 285-286°C; IR: ν 3291, 3085, 2977, 2934, 2886, 1721, 1681, 1609, 1545, 1494, 1401, 1369, 1328, 1251, 1211, 1159, 1139, 1049, 947, 892, 840, 808, 776, 711 cm⁻¹; ¹H NMR: δ_H 13.01 (s, 1H, NH), 9.67 (s, 1H, NH), 8.05

(s, 1H, ArH), 7.51-7.50 (m, 1H, ArH), 7.38-7.33 (m, 2H, ArH), 7.25 (d, $J = 8.0$ Hz, 1H, ArH), 7.17-7.13 (m, 1H, ArH), 7.09 (d, $J = 8.8$ Hz, 1H, ArH), 5.54 (s, 1H, CH), 4.02-3.97 (m, 1H, CH₂), 3.50-3.46 (m, 1H, CH₂), 2.82-2.78 (m, 1H, CH₂), 2.68-2.64 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.7, 153.0, 150.9, 149.1, 137.9, 132.2, 130.69, 130.67, 129.3, 129.2, 127.3, 122.1, 121.9, 117.2, 114.0, 110.1, 99.0, 81.3, 42.6, 39.3, 28.3, 26.9. HRMS. Calcd for C₂₄H₂₂N₄O₃Br, [M - H]⁺: m/z 493.0881. Found: m/z 493.0876.

***tert*-Butyl 11-(3,4-dichlorophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6e)**

Yield 89%; white powder; mp 256-257°C; IR: ν 3297, 3080, 2978, 2934, 2886, 1720, 1680, 1606, 1544, 1493, 1467, 1401, 1370, 1329, 1253, 1213, 1143, 1049, 1031, 947, 889, 840, 805, 776, 700 cm⁻¹; ¹H NMR: δ_H 13.02 (s, 1H, NH), 9.69 (s, 1H, NH), 8.07 (s, 1H, ArH), 7.60 (d, $J = 2.0$ Hz, 1H, ArH), 7.43 (d, $J = 8.4$ Hz, 1H, ArH), 7.38 (d, $J = 8.4$ Hz, 1H, ArH), 7.29 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H, ArH), 7.09 (d, $J = 8.4$ Hz, 1H, ArH), 5.58 (s, 1H, CH), 4.02-3.96 (m, 1H, CH₂), 3.52-3.45 (m, 1H, CH₂), 2.82-2.76 (m, 1H, CH₂), 2.68-2.62 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.7, 153.0, 149.20, 149.17, 137.9, 132.1, 131.0, 130.7, 129.9, 129.3, 128.9, 128.6, 122.0, 117.2, 113.6, 110.3, 98.7, 81.3, 42.6, 38.9, 28.3, 26.9. HRMS. Calcd for C₂₄H₂₁N₄O₃Cl₂, [M - H]⁺: m/z 483.0996. Found: m/z 483.0992.

***tert*-Butyl 11-(2-chlorophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6f)**

Yield 85%; white powder; mp 226-227°C; IR: ν 3270, 3076, 2972, 2935, 2888, 1719, 1622, 1601, 1543, 1491, 1388, 1336, 1251, 1211, 1142, 1049, 943, 894, 851, 807, 779, 759, 742, 705 cm⁻¹; ¹H NMR: δ_H 13.03 (s, 1H, NH), 9.70 (s, 1H, NH), 7.95 (s, 1H, ArH), 7.41 (d, $J = 7.2$ Hz, 1H, ArH), 7.36 (d, $J = 8.8$ Hz, 1H, ArH), 7.29 (d, $J = 7.6$ Hz, 1H, ArH), 7.18-7.15 (m, 1H, ArH), 7.10-7.06 (m, 2H, ArH), 5.89 (s, 1H, CH), 4.00-3.97 (m, 1H, CH₂), 3.46-3.44 (m, 1H, CH₂), 2.81-2.77 (m, 1H, CH₂), 2.64-2.60 (m, 1H, CH₂), 1.41 (s, 9H, 3CH₃); ¹³C NMR: δ_c 164.4, 152.8, 149.1, 145.8, 137.8, 132.0, 131.9, 131.4, 129.6, 129.4, 128.1, 127.9, 122.3, 117.4, 113.9, 110.2, 99.0, 81.2, 42.6, 37.4, 28.3, 27.0. HRMS. Calcd for C₂₄H₂₂N₄O₃Cl, [M - H]⁺: m/z 449.1386. Found: m/z 449.1391.

***tert*-Butyl 11-(2-bromophenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6g)**

Yield 83%; white powder; mp 225-227°C; IR: ν 3317, 3070, 2969, 2934, 2886, 1720, 1623, 1602, 1542, 1490, 1474, 1398,

1369, 1331, 1250, 1210, 1141, 1048, 942, 892, 851, 808, 781, 738, 710 cm⁻¹; ¹H NMR: δ_H 13.01 (s, 1H, NH), 9.68 (s, 1H, NH), 8.04 (s, 1H, ArH), 7.46 (d, *J* = 7.6 Hz, 1H, ArH), 7.39-7.35 (m, 2H, ArH), 7.22-7.19 (m, 1H, ArH), 7.07 (d, *J* = 8.8 Hz, 1H, ArH), 7.02-6.98 (m, 1H, ArH), 5.86 (s, 1H, CH), 4.01-3.95 (m, 1H, CH₂), 3.48-3.41 (m, 1H, CH₂), 2.81-2.76 (m, 1H, CH₂), 2.65-2.59 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.4, 152.7, 149.0, 147.6, 137.8, 132.7, 132.3, 132.2, 129.5, 128.5, 128.3, 122.3, 122.1, 117.4, 114.1, 110.2, 99.4, 81.2, 42.6, 39.5, 28.3, 27.0. HRMS. Calcd for C₂₄H₂₂N₄O₃Br, [M - H]⁺: *m/z* 493.0881. Found: *m/z* 493.0876.

tert-Butyl 11-(3-methoxyphenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6*h*)

Yield 86%; white powder; mp 281-283°C; IR: ν 3303, 3078, 2972, 2888, 1717, 1679, 1606, 1543, 1492, 1476, 1399, 1369, 1335, 1262, 1148, 1049, 949, 843, 807, 769, 735, 710 cm⁻¹; ¹H NMR: δ_H 11.76 (s, 1H, NH), 9.94 (s, 1H, NH), 7.94 (s, 1H, ArH), 7.86 (dd, *J* = 8.0 Hz, *J'* = 1.2 Hz, 1H, ArH), 7.53 (d, *J* = 8.4 Hz, 1H, ArH), 7.43-7.42 (m, 1H, ArH), 7.31-7.28 (m, 1H, ArH), 7.08-7.04 (m, 1H, ArH), 6.79 (d, *J* = 8.8 Hz, 1H, ArH), 5.82 (s, 1H, CH), 4.04-3.98 (m, 1H, CH₂), 3.67 (s, 3H, CH₃O), 3.48-3.41 (m, 1H, CH₂), 2.83-2.76 (m, 1H, CH₂), 2.62-2.56 (m, 1H, CH₂), 1.41 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.7, 159.5, 153.1, 149.8, 148.8, 137.9, 132.3, 129.4, 129.3, 122.2, 120.6, 117.1, 114.8, 114.5, 111.0, 109.7, 99.3, 81.2, 55.3, 42.6, 39.4, 28.3, 27.0. HRMS. Calcd for C₂₅H₂₅N₄O₄, [M - H]⁺: *m/z* 445.1881. Found: *m/z* 445.1877.

tert-Butyl 11-(3,5-dimethoxyphenyl)-10-oxo-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6*i*)

Yield 87%; white powder; mp 284-286°C; IR: ν 3307, 3082, 2976, 2887, 1792, 1660, 1610, 1546, 1497, 1464, 1398, 1368, 1250, 1211, 1143, 1052, 949, 934, 850, 817, 779, 731 cm⁻¹; ¹H NMR: δ_H 12.97 (s, 1H, NH), 9.59 (s, 1H, NH), 8.11 (s, 1H, ArH), 7.34 (d, *J* = 8.8 Hz, 1H, ArH), 7.06 (d, *J* = 8.4 Hz, 1H, ArH), 6.49-6.48 (m, 2H, ArH), 6.22 (s, 1H, ArH), 5.45 (s, 1H, CH), 4.03-4.00 (m, 1H, CH₂), 3.65 (s, 6H, 2CH₃O), 3.50-3.43 (m, 1H, CH₂), 2.82-2.77 (m, 1H, CH₂), 2.67-2.62 (m, 1H, CH₂), 1.43 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.8, 160.6, 153.1, 150.6, 148.8, 137.9, 132.4, 129.3, 122.2, 117.2, 114.8, 109.7, 106.8, 99.3, 97.4, 81.3, 55.4, 42.7, 39.4, 28.2, 27.0. HRMS. Calcd for C₂₆H₂₇N₄O₅, [M - H]⁺: *m/z* 475.1987. Found: *m/z* 475.1990.

tert-Butyl 10-oxo-11-phenyl-7,8,10,11-tetrahydro-3*H*-indazolo [5,4-*b*][1,6]naphthyridine-9(6*H*)-carboxylate (6*j*)

Yield 85%; white powder; mp 292-294°C; IR: ν 3296, 3080, 2974, 2889, 1719, 1604, 1543, 1493, 1400, 1370, 1254, 1212,

1158, 1049, 947, 845, 808, 783, 759, 709 cm⁻¹; ¹H NMR: δ_H 12.96 (s, 1H, NH), 9.61 (s, 1H, NH), 8.02 (s, 1H, ArH), 7.36-7.32 (m, 3H, ArH), 7.19-7.15 (m, 2H, ArH), 7.08-7.02 (m, 2H, ArH), 5.51 (s, 1H, CH), 4.03-3.99 (m, 1H, CH₂), 3.48-3.41 (m, 1H, CH₂), 2.83-2.73 (m, 1H, CH₂), 2.66-2.61 (m, 1H, CH₂), 1.42 (s, 9H, 3CH₃); ¹³C NMR: δ_C 164.7, 153.1, 148.8, 148.4, 137.9, 132.2, 129.2, 128.4, 128.1, 126.3, 122.2, 117.1, 114.9, 109.7, 99.4, 81.2, 42.6, 39.5, 28.3, 27.0. HRMS. Calcd for C₂₄H₂₃N₄O₃, [M - H]⁺: *m/z* 415.1776. Found: *m/z* 415.1769.

Acknowledgements: We are grateful to the Natural Science Foundation for Colleges and Universities of Jiangsu Province (18KJB150024), Science Research and Development Foundation of Nanjing Medical University (2017NJMU227), Science Research and Development Foundation of the Kangda College of Nanjing Medical University (KD201822NYDKJ03, KD2017KYJJYB003, KD2017KYJJYB004) and a Qing Lan Project for financial support.

References

- [1] Srivastava, S. K.; Jaggi, M.; Singh, A. T.; Madan, A.; Rani, N.; Vishnoi, M.; Agarwal, S. K.; Mukherjee, R.; Burman, A. C. Anticancer and anti-inflammatory activities of 1, 8-naphthyridine-3-carboxamide derivatives. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6660-6664.
- [2] Tsuzuki, Y.; Tomita, K.; Sato, Y.; Kashimoto, S.; Chiba, K. Synthesis and structure-activity relationships of 3-substituted 1, 4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines as novel antitumor agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3189-3193.
- [3] Huang, X. G.; Zhang, A. Q.; Chen, D. L.; Jia, Z. H.; Li, X. S. 4-Substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine: Novel C7 moieties of fluoroquinolones as antibacterial agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2859-2863.
- [4] Johns, B. A.; Weatherhead, J. G.; Allen, S. H.; Thompson, J. B.; Garvey, E. P.; Foster, S. A.; Jeffrey, J. L.; Miller, W. H. The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: Establishing the pharmacophore. *Med. Chem. Lett.* **2009**, *19*, 1802-1806.
- [5] Li, Y. W.; Liang, J.; Siu, T.; Hu, E.; Rossi, M. A.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Robinson, R. G.; Leander, K.; Huber, H. E.; Mittal, S.; Cosford, N.; Prasit, P. Allosteric inhibitors of Akt1 and Akt2: discovery of [1,2,4]triazolo[3, 4-*f*] [1,6] naphthyridines with potent and balanced activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 834-836.
- [6] Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. Synthesis of indazole motifs and their medicinal importance: An overview. *Eur. J. Med. Chem.* **2015**, *90*, 707.
- [7] Lu, W. Q.; Zhuang, R.; Chen, D. S.; Wang, X. S. An efficient synthesis of polycyclic heterocycles containing pyrazolo[3,4-*f*] quinoline or benzo[*h*]indazolo[6,7-*b*][1,6]naphthyridine under catalyst-free conditions. *Polycycl. Aromat. Comp.* **2014**, *34*, 606-619.

- [8] Zhang, M. M.; Chen, D. S.; Wang, X. S. A three-component domino reaction for efficient synthesis of functionalized pyrazolo[3,4-*f*]quinolines under catalyst-free conditions. *Res. Chem. Intermed.* **2015**, *41*, 6339-6350.
- [9] Chen, D. S.; Zhou, Y. J.; Li, Y. L.; Yao, C. S.; Wang, X. S. Combinatorial synthesis of pyrazoloquinoline and pyrazoloacridine derivatives with high regioselectivity. *Comb. Chem. High. T. Scr.* **2013**, *16*, 550-561.
- [10] Bellamy, F. D.; Ou, K. Selective reduction of aromatic nitro compounds with stannous chloride in non acidic and non aqueous medium. *Tetrahedron Lett.* **1984**, *25*, 839-842.
- [11] Corma, A.; Concepción, P.; Serna, P. A different reaction pathway for the reduction of aromatic nitro compounds on gold catalysts. *Angew. Chemie* **2007**, *119*, 7404-7407.
- [12] Damavandi, S.; Sandaroos, R. Solvent-free one pot synthesis of indenoquinolinones catalyzed by iron(III) triflate. *Heterocycl. Commun.* **2011**, *17*, 121-124.
- [13] Zhang, F. F.; Gao, Q.; Zhao, J. X.; Ge, M.; Bai, Y. J. Design and synthesis of a novel rhodamine-based chemosensor and recognition study to Fe³⁺. *Heterocycl. Commun.* **2016**, *22*, 37-42.
- [14] Bauer, I.; Knölker, H. J. Iron catalysis in organic synthesis. *Chem. Rev.* **2015**, *115*, 3170-3387.
- [15] Javahershenas, R.; Khalafy, J. A new synthesis of pyrrolo [3,2-*d*] pyrimidine derivatives by a one-pot, three-component reaction in the presence of L-proline as an organocatalyst. *Heterocycl. Commun.* **2018**, *24*, 37-41.
- [16] Ebrahimlo, A. R. M. Efficient three-component synthesis of 5-(6-hydroxy-2, 4-dioxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl)-5, 12-dihydrobenzo [*b*] pyrimido [5, 4-*g*][1,8] naphthyridine-2,4(1*H*,3*H*)- dione. *Heterocycl. Commun.* **2018**, *24*, 75-77.
- [17] Gao, Q.; Hao, W. J.; Liu, F.; Tu, S. J.; Wang, S. L.; Li, G. G.; Jiang, B. Unexpected isocyanide-based three-component bicyclization for the stereoselective synthesis of densely functionalized pyrano [3,4-*c*]pyrroles. *Chem. Commun.* **2016**, *52*, 900-903.