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Design, Synthesis, and Antiproliferative Evaluation of Novel

Longifolene-derived Tetraline Pyrimidine Derivatives with

Fluorescence Property

Qing-Min Li, Gui-Shan Lin, * Wen-Gui Duan,* Yu-Cheng Cui, Fu-Hou Lei, and

Fang-Yao Li

* Corresponding Author. Gui-Shan Lin and Wen-Gui Duan

E-mail address: Guishan Lin, gslin@gxu.edu.cn; Wengui Duan, wgduan@gxu.edu.cn.

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1. General experimental information

FT-IR, ¹H NMR, ¹³C NMR, ESI-MS, and elemental analysis were employed to characterize the structure of the target compounds, and the characterization data were included in Supporting Information. FT-IR spectra were recorded by a Nicolet iS50 FT-IR spectrometer using KBr pellets. ¹H and ¹³C NMR spectra were recorded in a CDCl₃ using a Bruker AVANCE AV-600 spectrometer and TMS as an internal standard. The mass spectra were obtained from the TSQ Quantum Access MAX HPLC-MS instrument. The elemental analyses were tested on PerkinElmer 2400II Elemental Analyzer. Fluorescence spectra were obtained by Hitachi F4700 fluorescence spectrophotometer. The UV-vis absorption spectra were estimated on the UV-1800 ultraviolet-visible spectrophotometer. The melting points of the target compounds were measured on a Hanon MP420 automatic melting point apparatus. XO-SM50 program-controlled ultrasonic-microwave reaction system. Longifolene (GC purity 85%) (1) was provided by Wuzhou Pine Chemicals Co., Ltd., Wuzhou, China. All the other reagents were purchased from commercial suppliers and used without further purification.

2. Synthetic Route of Target Compounds 5a-5r



5a: R= *o*-F; 5b: R= *m*-F; 5c: R= *p*-F; 5d: R= *o*-Cl; 5e: R= *m*-Cl; 5f: R= *p*-Cl; 5g: R= *o*-Br; 5h: R= *m*-Br; 5i: R= *p*-Br; 5j: R= *m*-CN; 5k: R= *p*-CN; 5l: R= *o*-CH₃; 5m: R= *p*-CH₃; 5n: R= *m*-OCH₃; 5o: R= *p*-OCH₃; 5p: R= *m*-CF₃; 5q: R= *p*-OCF₃; 5r: R= H;

Scheme 1. Synthetic Route of Target Compounds 5a-5r

3. IR, NMR and MS data for compound 4 and 5

Compoud **4a**: Yellow liquid; yield 85.6%; IR (KBr) v_{max} 3065 (Ar-H), 2961, 2929, 2871 (C-H), 1671 (C=O), 1602 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.09$ (d, J = 8.1 Hz, 1H), 7.92 (s, 1H), 7.37 – 7.32 (m, 1H), 7.28 (ddd, J = 13.5, 5.6, 2.6 Hz, 1H), 7.25 (d, J = 1.5 Hz, 1H), 7.20 (dd, J = 8.1, 1.6 Hz, 1H), 7.14 (td, J = 7.5, 0.8 Hz, 1H), 7.06 (t, J = 9.1 Hz, 1H), 2.94 (hept, J = 6.9 Hz, 1H), 2.84 (s, 1H), 1.29 (s, 3H), 1.26 (d, J = 7.0 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 186.67$, 161.25, 159.59, 154.98, 151.58, 136.17, 130.34, 130.32, 129.99, 129.94, 129.66, 129.64, 129.62, 128.60, 124.63, 123.63, 123.60, 122.47, 115.55, 115.41, 41.87, 34.75, 34.39, 29.64, 23.42; ESI-MS m/z 323.12 [M+H]+. Anal. Calcd. For C₂₂H₂₃FO: C, 81.95; H, 7.19. Found: C, 81.93; H, 7.21.

Compoud **4b**: Yellow liquid; yield 80.3%; IR (KBr) v_{max} 3063 (Ar-H), 2961, 2928 (C-H), 1670 (C=O), 1604 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.08$ (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.33 (td, J = 7.9, 6.2 Hz, 1H), 7.26 (d, J = 1.2 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.11 (d, J = 9.7 Hz, 1H), 6.99 (td, J = 8.4, 2.2 Hz, 1H), 2.99 – 2.91 (m, 2H), 1.31 (s, 3H), 1.26 (d, J = 7.0 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 186.88$, 163.17, 161.54, 154.99, 151.35, 137.90, 137.85, 135.29, 135.11, 129.76, 129.71, 129.69, 128.62, 125.31, 125.30, 124.67, 122.40, 116.05, 115.90, 115.01, 114.87, 41.48, 34.71, 34.40, 29.71, 23.43; ESI-MS m/z 323.12 [M+H]⁺. Anal. Calcd. For C₂₂H₂₃FO: C, 81.95; H, 7.19. Found: C, 81.96; H, 7.20.

Compoud **4c**: White solid; yield 90.5%; m.p 102.5-114.2 °C; IR (KBr) v_{max} 3063, 3039 (Ar-H), 2959, 2928, 2868 (C-H), 1659 (C=O), 1610 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.09$ (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.46 – 7.39 (m, 1H), 7.28 – 7.21

(m, 1H), 7.15 – 7.07 (m, 1H), 3.01 – 2.93 (m, 2H), 1.34 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.48$, 163.32, 161.67, 155.18, 151.51, 135.96, 134.09, 131.98, 131.96, 131.64, 131.58, 130.00, 128.79, 124.87, 122.57, 115.55, 115.41, 41.73, 34.92, 34.64, 29.95, 23.67; ESI-MS m/z 323.12 [M+H]⁺. Anal. Calcd. For C₂₂H₂₃FO: C, 81.95; H, 7.19. Found: C, 81.94; H, 7.22.

Compoud **4d**: Yellow liquid, yield 80.0%; IR (KBr) v_{max} 3059 (Ar-H), 2960, 2926 (C-H), 1671 (C=O), 1603 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.13$ (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.46 – 7.41 (m, 1H), 7.34 – 7.22 (m, 2H), 3.03 – 2.91 (m, 1H), 2.81 (s, 1H), 1.31 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.26$, 155.25, 151.77, 135.91, 134.59, 134.50, 134.09, 130.20, 129.73, 129.53, 129.32, 128.71, 126.26, 124.81, 122.71, 41.75, 35.06, 34.55, 29.74, 23.58; ESI-MS m/z 323.12 [M+H]⁺. Anal. Calcd. For C₂₂H₂₃ClO: C, 77.98; H, 6.84. Found: C, 77.99; H, 6.82.

Compoud **4e**: Yellow liquid; yield 88.3%; IR (KBr) v_{max} 3061 (Ar-H), 2960, 2930 (C-H), 1664 (C=O), 1607 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.09$ (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.41 (s, 1H), 7.37 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 3.02 – 2.93 (m, 2H), 1.34 (s, 3H), 1.30 (d, J = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 187.29, 155.32, 151.61, 137.74, 135.45, 135.39, 134.28, 129.82, 129.65, 129.40, 128.82, 128.28, 127.78, 124.92, 122.63, 41.68, 35.00, 34.63, 29.95, 23.65; ESI-MS m/z 323.12 [M+H]⁺. Anal. Calcd. For C₂₂H₂₃ClO: C, 77.98; H, 6.84. Found: C, 77.95; H, 6.85.

Compoud **4f**: Yellow solid; yield 84.5%; m.p 98.7-101.6 °C; IR (KBr) v_{max} 3033 (Ar-H), 2959, 2928, 2870 (C-H), 1659 (C=O), 1605 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.08$ (d, J = 7.9 Hz, 1H), 7.87 (s, 1H), 7.41 – 7.35 (m, 2H), 7.27 – 7.22 (m, 1H), 2.99 (dt, J = 13.8, 6.9 Hz, 1H), 2.94 (d, J = 1.8 Hz, 1H), 1.33 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.41$, 155.28, 151.56, 135.74, 134.82, 134.36, 134.23, 131.02, 129.93, 128.83, 128.66, 124.92, 122.62, 41.80, 34.98, 34.66, 29.97, 23.68; ESI-MS m/z 323.12 [M+H]⁺. Anal. Calcd. For C₂₂H₂₃ClO: C, 77.98; H, 6.84. Found: C, 77.98; H, 6.86.

Compoud **4i**: Yellow solid; yield 89.6%; m.p 125.6-126.5 °C; IR (KBr) v_{max} 3061, 3026 (Ar-H), 2958, 2935, 2863 (C-H), 1662 (C=O), 1607 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.08$ (d, J = 7.9 Hz, 1H), 7.84 (s, 1H), 7.57 – 7.52 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.27 – 7.22 (m, 1H), 3.01 – 2.95 (m, 1H), 2.94 (t, J = 5.2 Hz, 1H), 1.33 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.40$, 155.30, 151.56, 135.75, 134.92, 134.81, 131.62, 131.26, 129.91, 128.83, 124.93, 122.62, 122.51, 41.80, 34.98, 34.66, 29.97, 23.68.

Compoud **4k**: White solid; yield 82.3%; m.p 135.6-136.4 °C; IR (KBr) v_{max} 2959, 2939, 2871 (C-H), 2222 (C=N), 1664 (C=O), 1610 (C=C); ¹H NMR (600 MHz, CDCl₃) δ 8.08 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.27 – 7.23 (m, 1H), 3.01 – 2.95 (m, 1H), 2.92 (d, J = 1.8 Hz, 1H), 1.33 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 187.03, 155.66, 151.57, 140.65, 136.93, 134.60, 132.16, 130.10, 129.63, 128.93, 125.09, 122.72, 118.62, 111.65, 41.83, 35.09, 34.68, 30.00, 23.65.

Compoud **4m**: White solid; yield 82.9%; m.p 150.6-151.7 °C; IR (KBr) v_{max} 3023 (Ar-H), 2959, 2924, 2868 (C-H), 1658 (C=O), 1608 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.08$ (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.28 – 7.20 (m, 2H), 3.02 – 2.93 (m, 2H), 2.40 (s, 2H), 1.33 (s, 3H), 1.30 (d, J = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.74$, 155.01, 151.60, 138.55, 137.33, 133.48, 133.08, 130.19, 129.90, 129.13, 128.77, 124.81, 122.53, 41.85, 34.91, 34.65, 29.96, 23.70, 21.38.

Compoud **4n**: Yellow solid; yield 86.7%; m.p 95.3-96.7 °C; IR (KBr) v_{max} 3063 (Ar-H), 2960, 2933, 2869 (C-H), 1667 (C=O), 1602 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.08$ (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.04 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.90 (dd, J = 8.2, 2.2 Hz, 1H), 3.84 (s, 3H), 3.04 – 2.89 (m, 3H), 1.33 (s, 6H), 1.29 (d, J = 6.9 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.63$, 159.43, 155.12, 151.68, 137.27, 137.01, 134.48, 130.04, 129.36, 128.78, 124.82, 122.58, 122.13, 115.27, 113.80, 55.21, 41.77, 34.93, 34.63, 29.94, 23.67. ESI-MS m/z 335.12 [M+H]⁺. Anal. Calcd. For C₂₃H₂₆O₂: C, 82.60; H, 7.84. Found: C, 82.61; H, 7.83.

Compoud **40**: White solid; yield 92.5%; m.p 118.6-119.5 °C; IR (KBr) v_{max} 3063, 3001 (Ar-H), 2958, 2929 (C-H), 1656 (C=O), 1604 (C=C); ¹H NMR (600 MHz, CDCl₃): $\delta = 8.08$ (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.27 – 7.21 (m, 2H), 6.96 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H), 3.12 – 2.92 (m, 3H), 1.34 (s, 6H), 1.29 (d, J = 6.9 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃): $\delta = 187.63$, 159.78, 154.87, 151.42, 137.09, 132.33, 131.62, 130.25, 128.70, 128.44, 124.74, 122.45, 113.87,

55.24, 41.87, 34.81, 34.61, 29.96, 23.68; ESI-MS m/z 335.12 $\rm [M+H]^+.$ Anal. Calcd. For $C_{23}H_{26}O_2$: C, 82.60; H, 7.84. Found: C, 82.62; H, 7.80.

Table 1 The part result of molecular docking-based virtual screening for the designed compounds in descending order by D_score and PMF_score based on the crystal structure of the survivin / Smac / DIABLO complex.

0	🔆 Spreadsheet												
		Name	Structure	1: Total_Score	2: Crash	3: Polar	4: D_score	5: PMF_score	6: G_score	7: ChemScore	8: CSCORE		
1		м9_000		2.6669	-0.5276	0	-73.422	-22.133	-133.9694	-11.4982	0		
2		M78_000	N O Br	2.3537	-0.9733	0.001	-81.3984	-23.3449	-145.9704	-13.8312	1		
3		M10_000		2.775	-1.0637	0.0007	-77.4465	-25.5063	-144.3601	-12.5208	3		
4		M28_000		4.4502	-0.5834	0.0007	-88.4459	-26.0985	-152.3659	-11.5425	3		
5		NSC80467_000	- b - b - b - b - b - b - b - b - b - b	3.2742	-0.9636	2.4322	-90.1598	-26.2117	-130.0601	-17.7099	3		
6		M6_000		2.4948	-0.5151	0	-73.7993	-29.12	-123.2901	-10.5428	2		
7		M14_000		1.1493	-0.8791	0	-80.1796	-29.3566	-134.7637	-17.991	2		

5. The copies of IR, NMR and MS spectra for compounds 4 and 5



Figure 1. IR spectrum of compound 4a



Figure 2. ¹H NMR spectrum of compound 4a







Figure 4. MS spectrum of compound 4a



Figure 5. IR spectrum of compound 4b



Figure 6. ¹H NMR spectrum of compound 4b



Figure 7. ¹³C NMR spectrum of compound 4b



Figure 8. MS spectrum of compound 4b





Figure 10. ¹H NMR spectrum of compound 4c



Figure 11. ¹³C NMR spectrum of compound 4c



Figure 12. MS spectrum of compound 4c



Figure 13. IR spectrum of compound 4d



Figure 14. ¹H NMR spectrum of compound 4d







Figure 16. MS spectrum of compound 4d



Figure 17. IR spectrum of compound 4e



Figure 18. ¹H NMR spectrum of compound 4e



Figure 19. ¹³C NMR spectrum of compound 4e



Figure 20. IR spectrum of compound 4f







Figure 22. ¹³C NMR spectrum of compound 4f

Figure 24. IR spectrum of compound 4i

Figure 26. ¹³C NMR spectrum of compound 4i

Figure 27. IR spectrum of compound 4k

Figure 28. ¹H NMR spectrum of compound 4k

Figure 29. ¹³C NMR spectrum of compound 4k

Figure 30. IR spectrum of compound 4m

Figure 31. ¹H NMR spectrum of compound 4m

Figure 32. ¹³C NMR spectrum of compound 4m

Figure 34. ¹H NMR spectrum of compound 4n

Figure 35. ¹³C NMR spectrum of compound 4n

Figure 36. MS spectrum of compound 4n

Figure 37. IR spectrum of compound 40

Figure 38. ¹H NMR spectrum of compound 40

Figure 40. MS spectrum of compound 40

Figure 42. ¹H NMR spectrum of compound 5a

Figure 43. ¹³C NMR spectrum of compound 5a

Figure 44. MS spectrum of compound 5a

Figure 46. ¹H NMR spectrum of compound 5b

Figure 47. ¹³C NMR spectrum of compound 5b

Figure 48. MS spectrum of compound 5b

Figure 49. IR spectrum of compound 5c

Figure 50. ¹H NMR spectrum of compound 5c

Figure 51. ¹³C NMR spectrum of compound 5c

Figure 52. MS spectrum of compound 5c

Figure 54. ¹H NMR spectrum of compound 5d

Figure 55. ¹³C NMR spectrum of compound 5d

Figure 56. MS spectrum of compound 5d

Figure 58. ¹H NMR spectrum of compound 5e

Figure 60. MS spectrum of compound 5e

Figure 62. ¹H NMR spectrum of compound 5f

Figure 63. ¹³C NMR spectrum of compound 5f

Figure 64. MS spectrum of compound 5f

Figure 66. ¹H NMR spectrum of compound 5g

Figure 67. ¹³C NMR spectrum of compound 5g

Figure 69. IR spectrum of compound 5h

Figure 70. ¹H NMR spectrum of compound 5h

Figure 71. ¹³C NMR spectrum of compound 5h

Figure 72. MS spectrum of compound 5h

Figure 74. ¹H NMR spectrum of compound 5i

Figure 75. ¹³C NMR spectrum of compound 5i

Figure 76. MS spectrum of compound 5i

Figure 78. ¹H NMR spectrum of compound 5j

Figure 79. ¹³C NMR spectrum of compound 5j

Figure 80. MS spectrum of compound 5j

Figure 82. ¹H NMR spectrum of compound 5k

Figure 84. MS spectrum of compound 5k

Figure 86. ¹H NMR spectrum of compound 51

Figure 87. ¹³C NMR spectrum of compound 51

Figure 88. MS spectrum of compound 51

Figure 90. ¹H NMR spectrum of compound 5m

Figure 91. ¹³C NMR spectrum of compound 5m

Figure 92. MS spectrum of compound 5m

Figure 93. IR spectrum of compound 5n

Figure 94. ¹H NMR spectrum of compound 5n

Figure 95. ¹³C NMR spectrum of compound 5n

Figure 96. MS spectrum of compound 5n

Figure 97. IR spectrum of compound 50

Figure 98. ¹H NMR spectrum of compound 50

Figure 99. ¹³C NMR spectrum of compound 50

Figure 100. MS spectrum of compound 50

Figure 102. ¹H NMR spectrum of compound 5p

Figure 103. ¹³C NMR spectrum of compound 5p

Figure 104. MS spectrum of compound 5p

Figure 106. ¹H NMR spectrum of compound 5q

Figure 107. ¹³C NMR spectrum of compound 5r

Figure 108. MS spectrum of compound 5q

Figure 110. ¹H NMR spectrum of compound 5r

Figure 111. ¹³C NMR spectrum of compound 5r

Figure 112. MS spectrum of compound 5r