Supplementary Materials

Antiviral activity of isoquinolone derivatives against influenza viruses and their cytotoxicity

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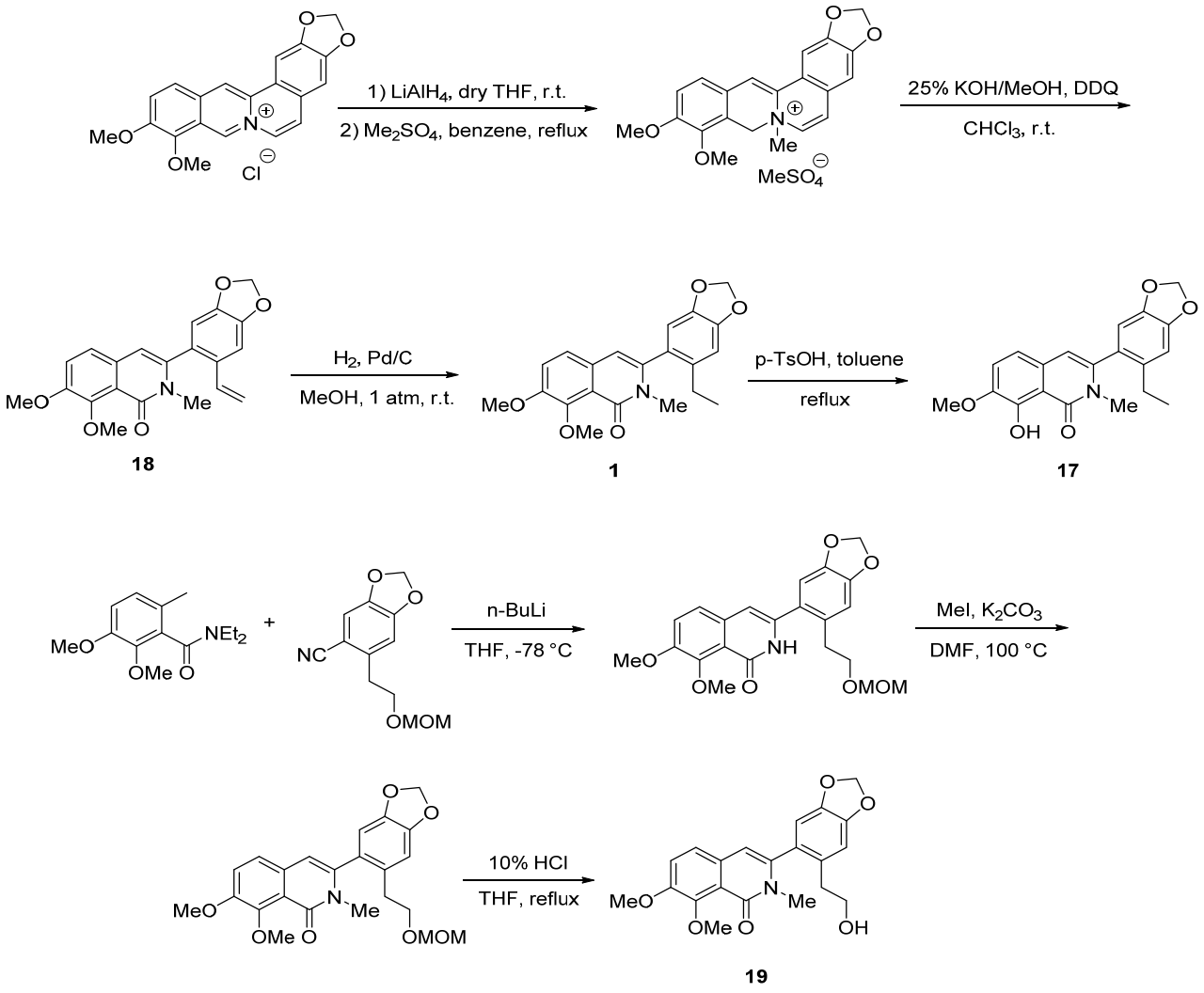
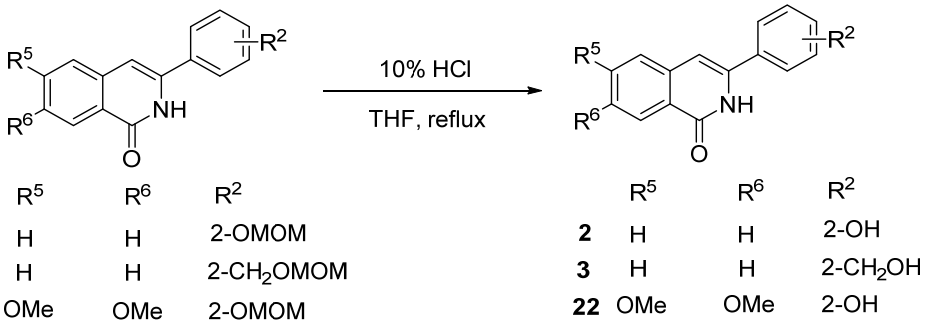
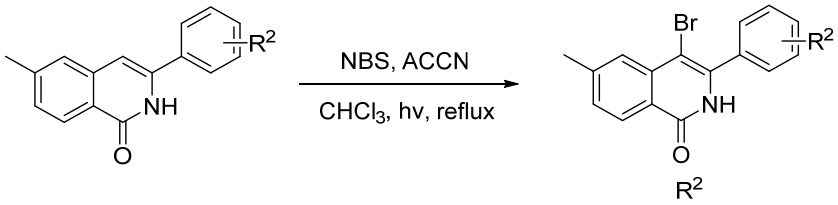


Supplementary Scheme S1. Synthesis of phenylisoquinolones **1** and **17-19** [1, 2].

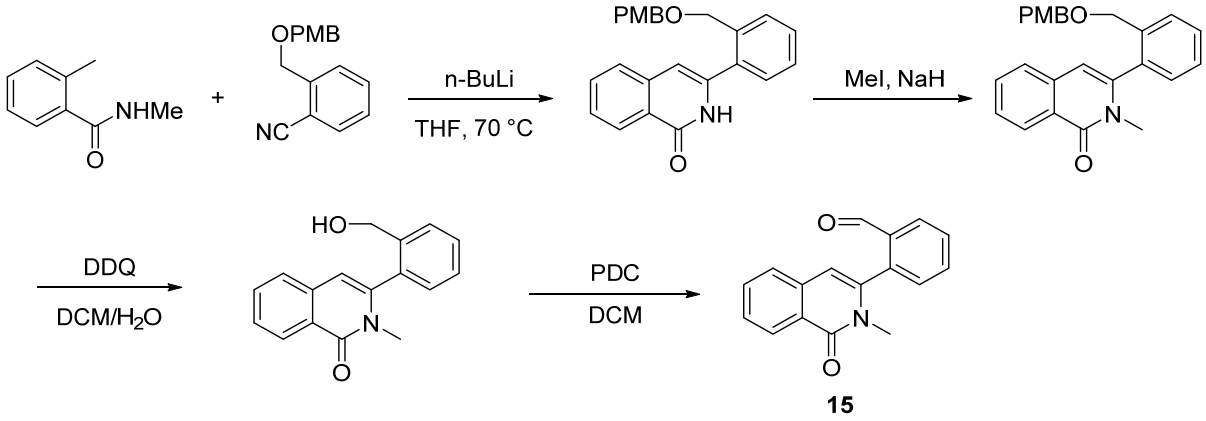


R^5	R^6	R^2
H	H	2-OMOM
H	H	2-CH_2OMOM
OMe	OMe	2-OMOM

	R^5	R^6	R^2
2	H	H	2-OH
3	H	H	2-CH_2OH
22	OMe	OMe	2-OH



13: 3',4'-$(OMe)_2$
14: 2',6'-Me_2



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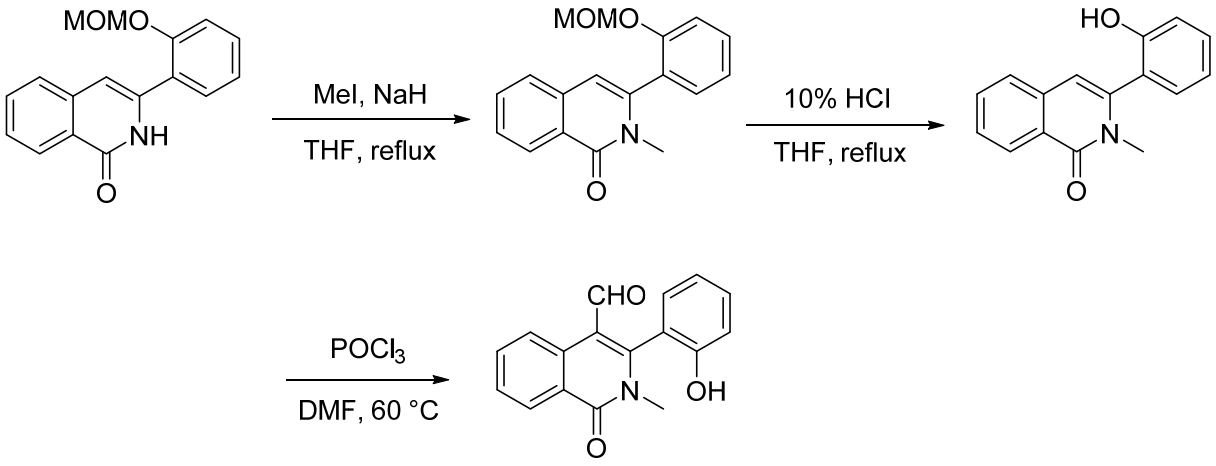
Supplementary Scheme S2. Synthesis of phenylisoquinolones **2**, **3**, **13**-**15** and **22** [3-6].



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Supplementary Scheme S3. Synthesis of phenylisoquinolone **16** [7].

Experimental data of newly synthesized compounds

*3-(4-Chlorophenyl)-5-(dimethylamino)isoquinolin-1(2H)-one (**07**)*

The procedures described for **06** were used with 2.5 M *n*-BuLi in hexane (7.8 mL, 19.6 mmol), 3-(dimethylamino)-N,N-diethyl-2-methylbenzamide (2 g, 9.8 mmol), 4-chlorobenzonitrile (1.7 g, 11.8 mmol) and dry THF to obtain **07** (640 mg, 21%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.5 (s, 1H), 8.00–7.50 (m, 7H), 6.92 (s, 1H), 2.78 (s, 6H).

*3-(4-Bromophenyl)-5-(dimethylamino)isoquinolin-1(2H)-one (**08**)*

The procedures described for **06** were used with 2.5 M *n*-BuLi in hexane (7.7 mL, 19.5 mmol), 3-(dimethylamino)-N,N-diethyl-2-methylbenzamide (2 g, 9.74 mmol), 4-bromobenzonitrile (2.2 g, 11.7 mmol) and dry THF to obtain **08** (725 mg, 21%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.87 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.79–7.25 (m, 6H), 7.16 (s, 1H), 2.86 (s, 6H).

*5-(Dimethylamino)-3-(4-methoxyphenyl)isoquinolin-1(2H)-one (**09**)*

The procedures described for **06** were used with 2.5 M *n*-BuLi in hexane (7.8 mL, 19.4 mmol), 3-(dimethylamino)-N,N-diethyl-2-methylbenzamide (2.0 g, 9.7 mmol), 4-methoxybenzonitrile (1.6 g, 11.7 mmol) and dry THF to obtain **09** (640 mg, 22%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.30 (s, 1H), 8.03 (d, J = 7.0Hz, 1H), 7.95–7.2 (m, 6H), 7.0 (s, 1H), 3.88 (s, 3H), 2.85 (s, 6H).

*3-(3-Methoxyphenyl)-5-methylisoquinolin-1(2H)-one (**10**)*

The procedures described for **06** were used with *N*,*N*-diethyl-2,3-dimethylbenzamide (1.02 g, 5 mmol), 3-methoxybenzonitrile (832 mg, 6.25 mmol), 2.5 M *n*-BuLi in hexane (5 mL, 12 mmol) and dry THF to obtain **10** (1 g, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.42 (s, 1H), 8.28 (d, *J* = 8.0, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.45–7.41 (m, 1H), 7.39–7.31 (m, 3H), 7.03–7.00 (m, 1H), 6.89 (s, 1H), 3.92 (s, 3H), 2.59 (s, 3H).

*6,7-Dimethoxy-3-phenylisoquinolin-1(2H)-one (**21**)*

The procedures described for **06** were used with 3-(dimethylamino)-N,N-diethyl-2-methylbenzamide (1 g, 3.98 mmol), benzonitrile (468 mg, 4.53 mmol), 2.5 M *n*-BuLi in hexane (3.2 mL, 7.96 mmol) and dry THF to obtain **21** (98 mg, 8%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.06 (s, 1H), 7.78 (s, 1H), 7.65–7.62 (m, 2H), 7.53–7.43 (m, 3H), 6.97 (s, 1H), 6.71 (s, 1H), 4.03 (s, 3H), 4.02 (s, 3H).

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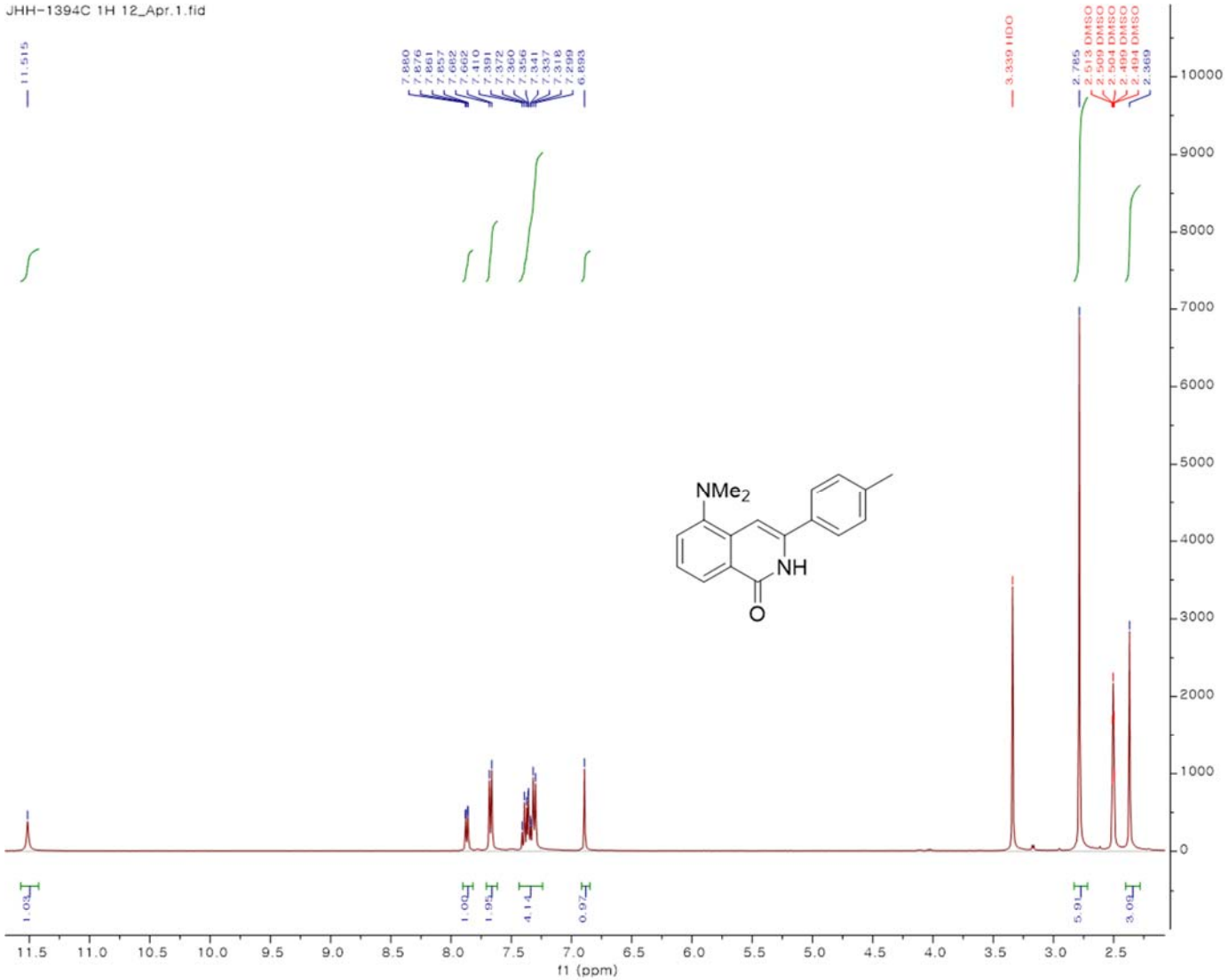
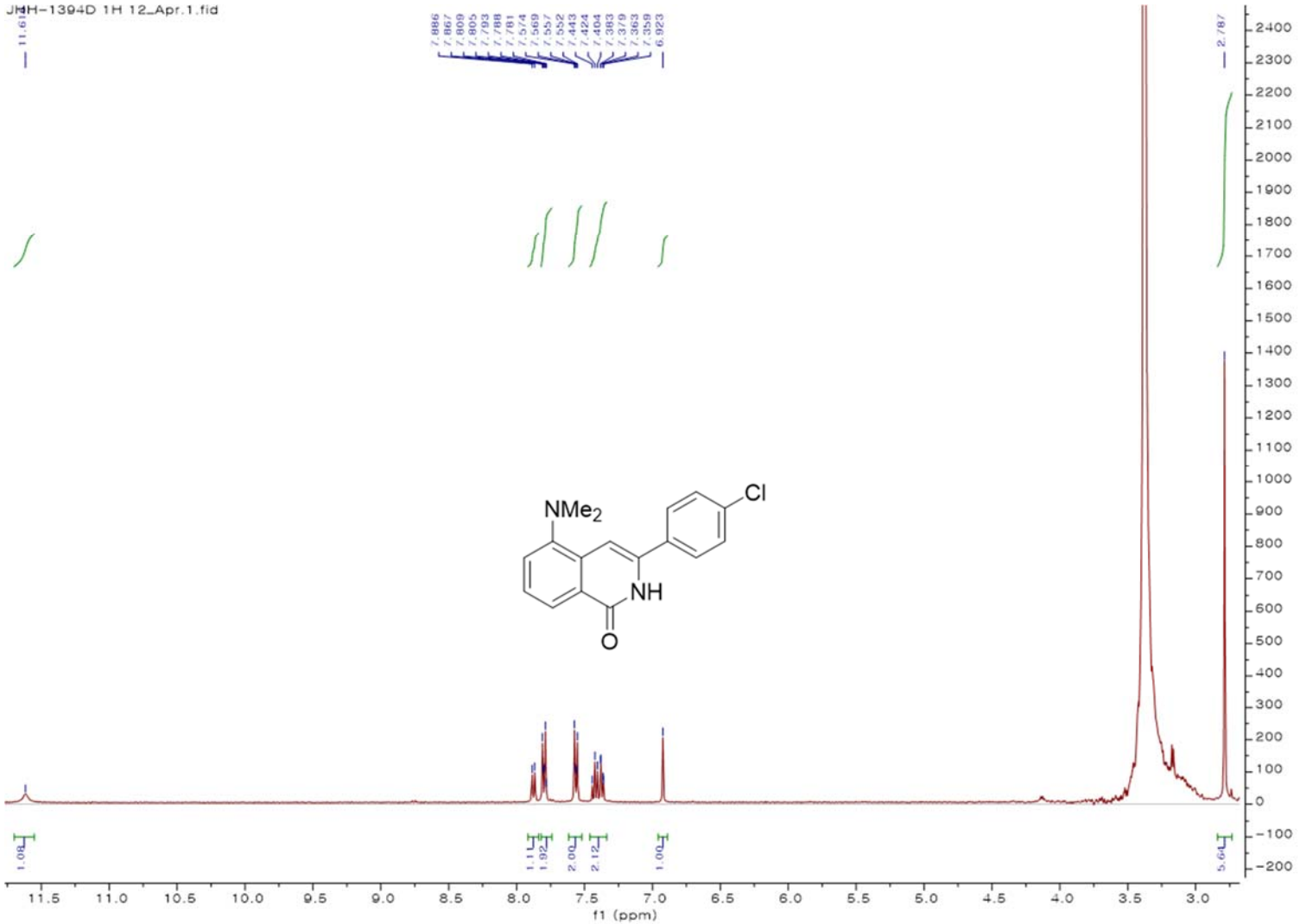
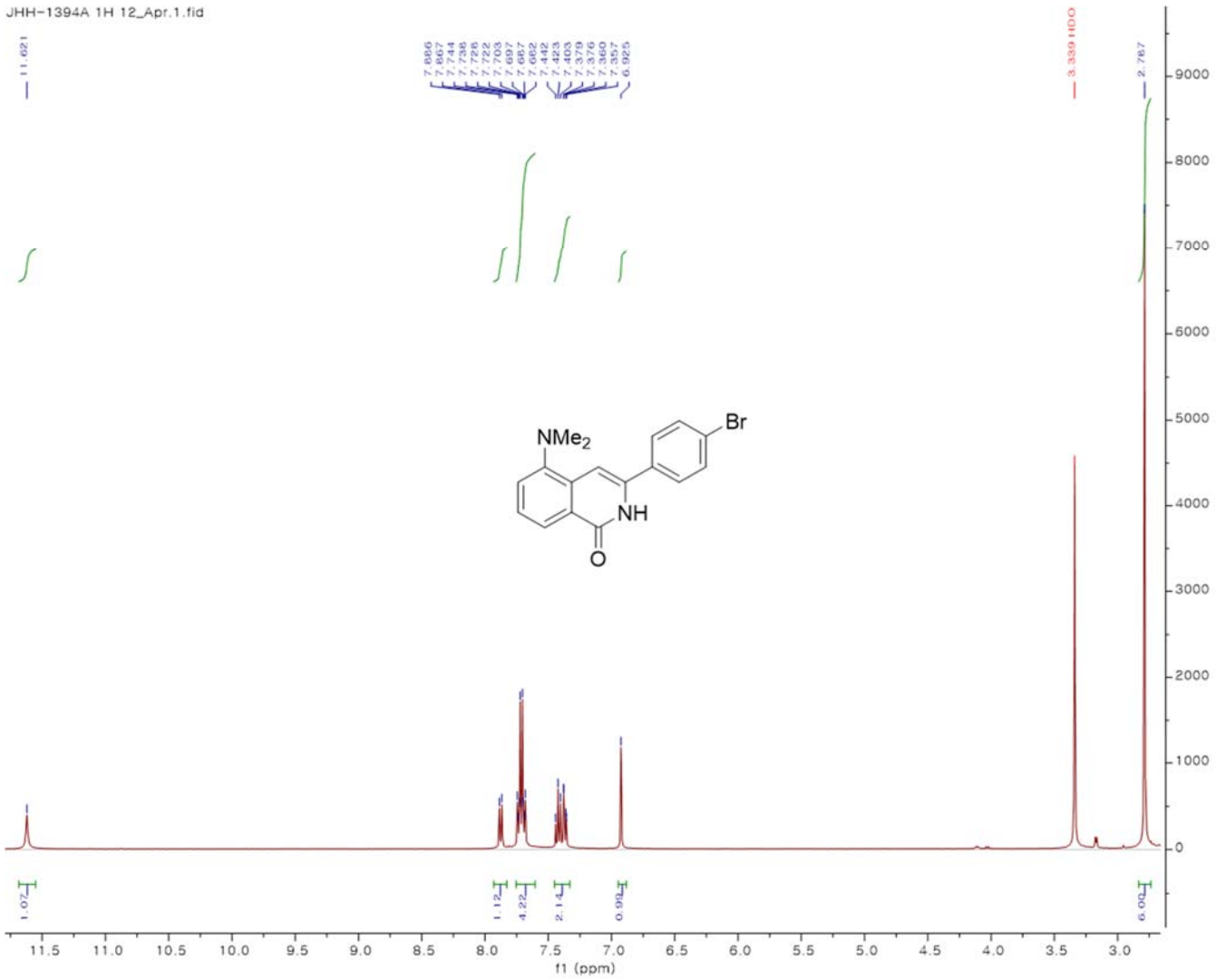


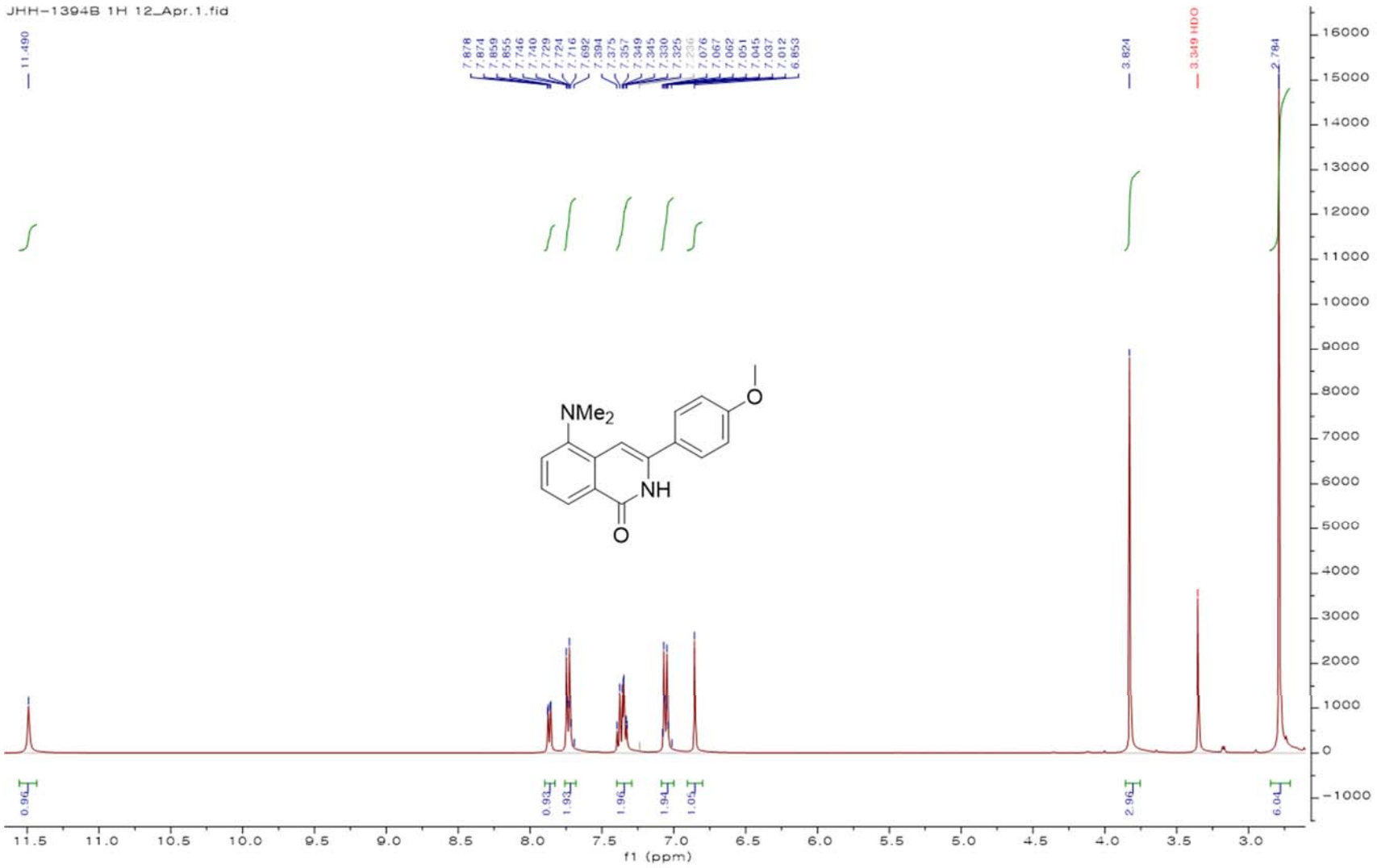
Supplementary Figure S1. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of **7**.



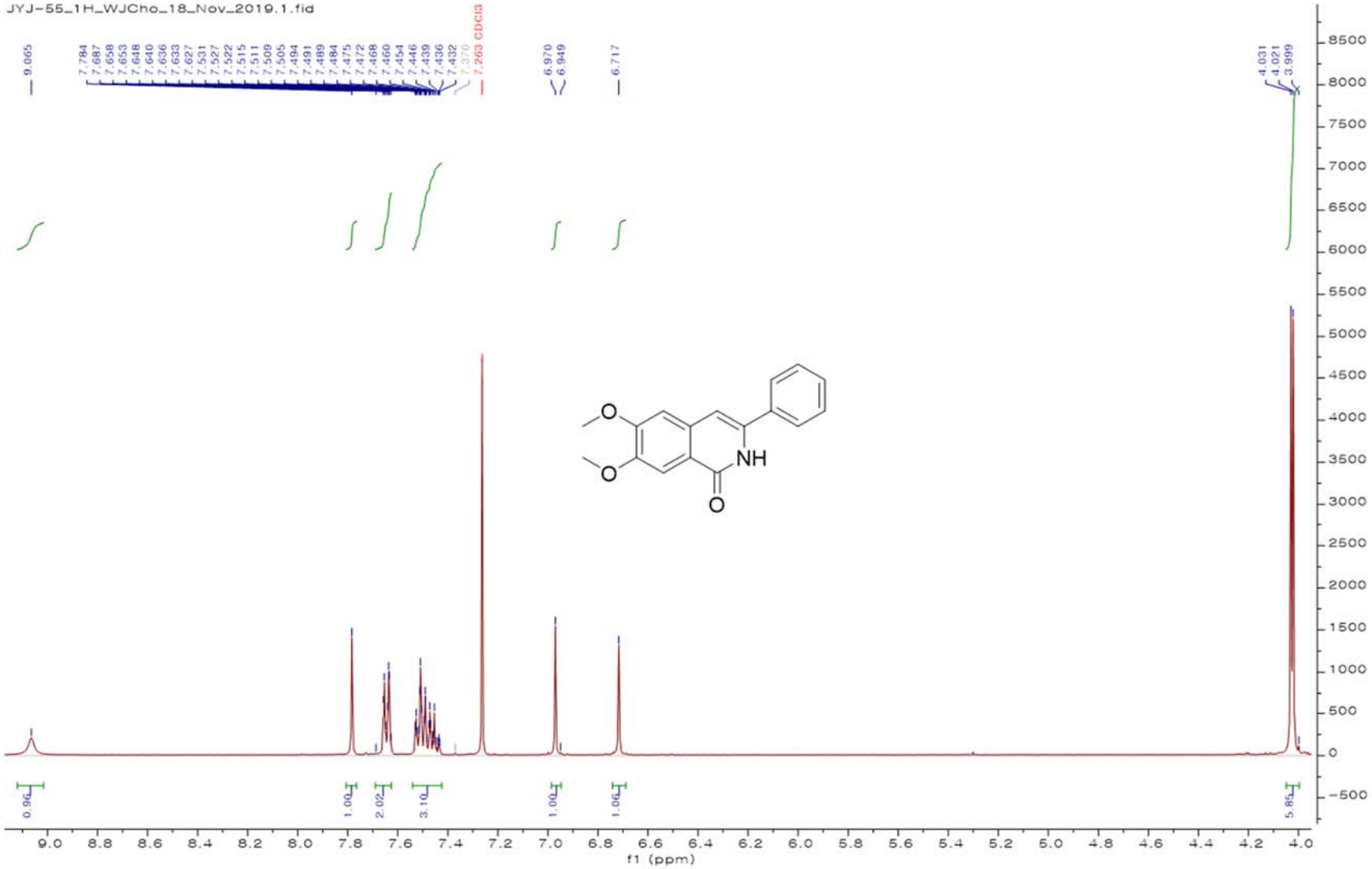
Supplementary Figure S2. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of 8.



Supplementary Figure S3. [1]H NMR (400 MHz, DMSO-d6) spectrum of **9**.

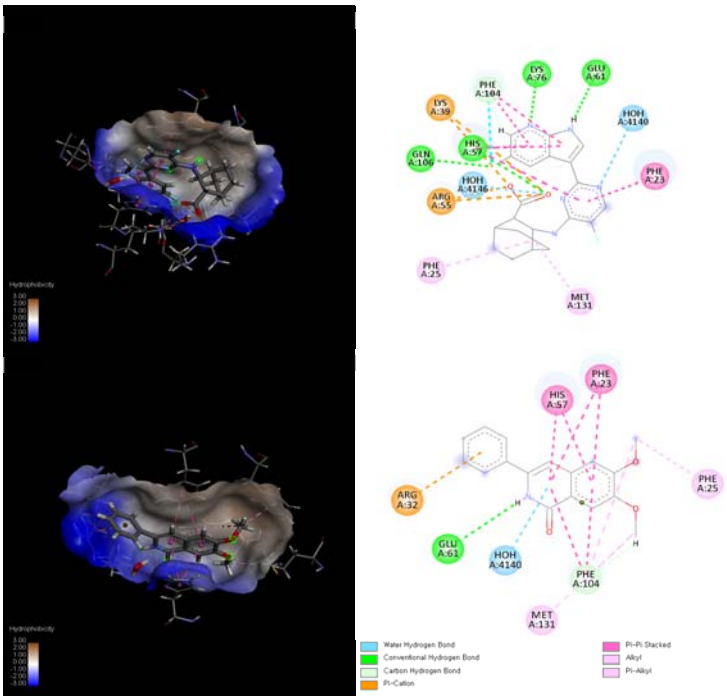


Supplementary Figure S4. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of **10**.

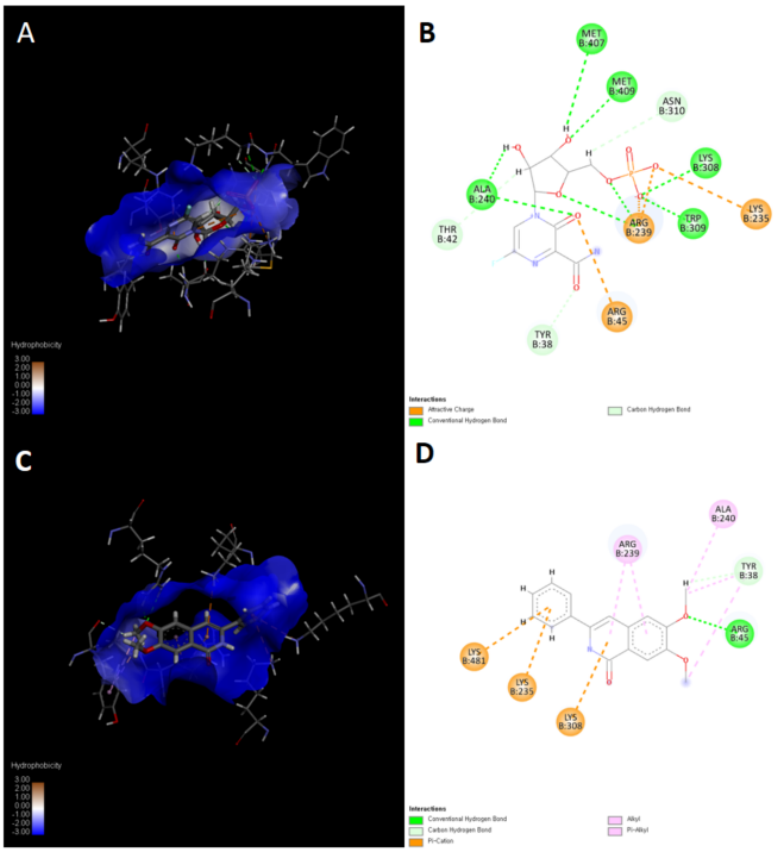


Supplementary Figure S5. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of 21.

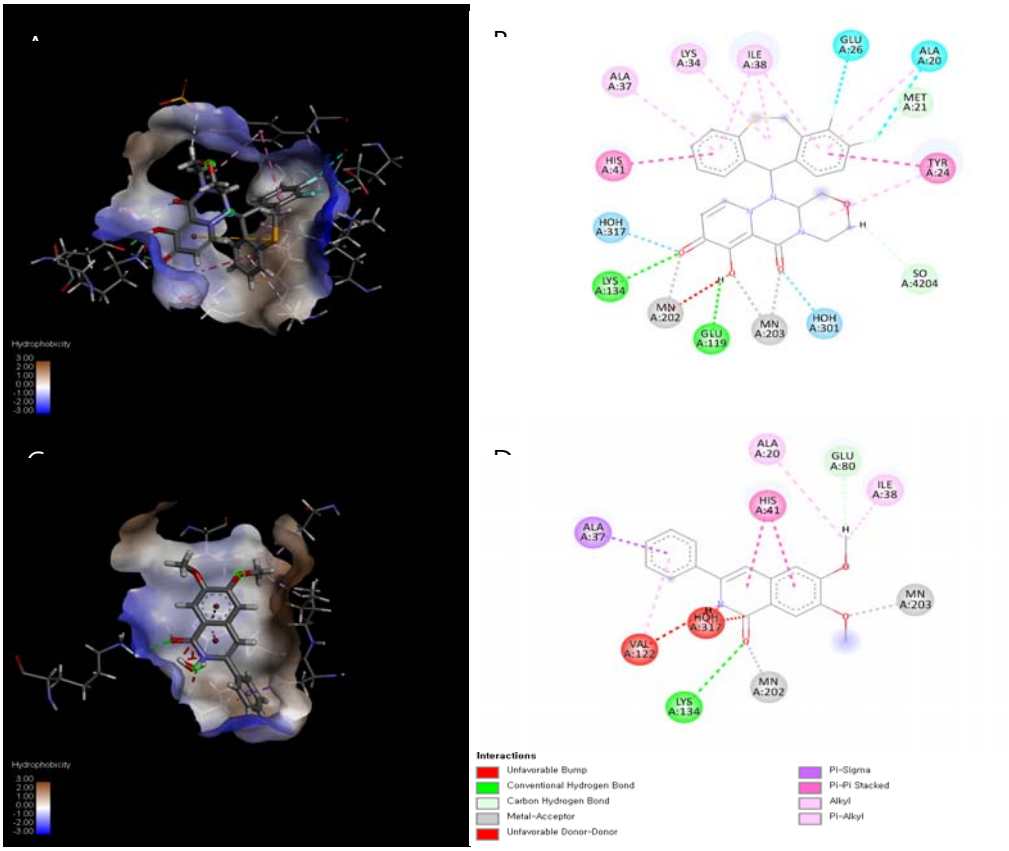
Docking Study. The software used for all docking studies was Flare versioned 3.0.0. The known x-ray 3D crystal structure of PB1 with T705, PB2 with VX-787, and PA with Baloxavir coded 4KN6, 4P1U, and 7K0W were retrieved from Protein Data Bank via software built-in function. The chemical structures of to-be-docked compound **21** were drawn by using the sketch molecule function and then minimized to their lowest energy states. For each protein, the binding site was defined based on its co-ligand. The preparation of protein was executed and the docking procedure of each inhibitor together with **21** using slow and accurate mode with 20 poses tested was carried out. After checking each poses, only the best and reasonable pose was analyzed in each case. The visualization of each results was performed in Dicovery Studio Visualizer and 2D figure was generated using its build-in fucntion.



Supplementary Figure S6. Docking pattern comparison of VX787 (A and B) and compound **21** (C and D) to PB2 (PDB ID: 4P1U).



Supplementary Figure S7. Docking pattern comparison of T705 (A and B) and compound **21** (C and D) to PB1 (PDB ID: 4WSB).



Supplementary Figure S8. Docking pattern comparison of Baloxavir (A and B) and compound **21** (C and D) to PA (PDB ID: 7K0W).