Supplementary Materials

Protein	PDB code	Binding site	X	Y	Ζ	Native inhibitor
E protein	10KE	K site [33]	-14.0	78.6	43.6	FN5Y [27]
		Y site [27]	-19.5	60.5	59.5	
NS2B/3 protease	2FOM	Allosteric site [34]	-7.0	-9.7	9.0	Compound 9 [25]
NS5 MTase	5EHI	SAM site [28]	32.3	48.5	10.2	Sinefungin [28]
NS5 RdRp	3VWS	Active site [26]	20.0	60.1	16.0	NITD-107 [26]

Table S1 The grid box parameters for molecular docking using AutoDock VinaXB

Mass Spectrum List Report

Analysis Info

 Analysis Name
 D:\Data\Data Service\190401\T70_RC4_01_2444.d

 Method
 nv_pos_5min_profile_190214.m

 Sample Name
 T70

 Comment
 T70

Acquisition Date 4/1/2019 7:49:59 PM

Operator CU. Instrument / Ser# micrOTOF-Q II 10335





Figure S1. TH011 identification by (a) HR-ESI-MS. (b) ¹H NMR spectrum (Acetone-d₆, 400 MHz) (c)The ¹³C NMR spectrum (Acetone-d₆, 100 MHz).

Mass Spectrum List Report

Analysis Info

Acquisition Date 9/24/2018 1:20:00 PM

D:\Data\Data Service\180924_pos_T9.d Analysis Name NV_pos_0.3min_profile_1segment_lowNubulizerDrygas.m Method Sample Name 180924 pos T9 Comment

CU. Operator Instrument / Ser# micrOTOF-Q II 10335

Acquisition Parameter







Figure S2. TH002 identification by (a) HR-ESI-MS. (b) ¹H NMR spectrum (Acetone-d₆, 400 MHz) (c)The ¹³C NMR spectrum (Acetone-d₆, 100 MHz).

Mass Spectrum List Report

Analysis Info

Analysis Name D: Method nv Sample Name Te Comment

ime D:\Data\Data Service\190401\T61_RC3_01_2443.d nv_pos_5min_profile_190214.m me T61 Acquisition Date 4/1/2019 7:43:32 PM

Operator CU. Instrument / Ser# micrOTOF-Q II 10335







Figure S3. TH012 identification by (a) HR-ESI-MS. (b) ¹H NMR spectrum (Acetone-d₆, 400 MHz) (c)The ¹³C NMR spectrum (Acetone-d₆, 100 MHz).



Figure S4. TH018 identification by (a) ¹H NMR spectrum (Acetone-d₆, 400 MHz) (b)The ¹³C NMR spectrum (Acetone-d₆, 100 MHz).



Figure S5. Fusion inhibition assay; TH002 and TH011 (10 μ M) were incubated with the DENV2-infected cells for 2 days before addition of 0.5 M MES, pH 5.5. The 4G2 antibody was an inhibitor of DENV envelope fusion and was used as a control. Pos and Neg were abbreviated from positive (DENV) and negative (media-only) controls, respectively.

Pinocembrin (Th	1022)			
₩ @ @	<i>/</i> /////		Water Solubility	
	LIPO	Log S (ESOL) 📀	-3.64	
		Solubility	5.81e-02 mg/ml ; 2.27e-04 mol/l	
OH D	FLEX	Class 🧐	Soluble	
		Log S (Ali) 📀	-3.94	
ſ ſ Ì Ì		Solubility	2.93e-02 mg/ml ; 1.14e-04 mol/l	
HO	\sim	Class 🤒	Soluble	
		Log S (SILICOS-IT) 😣	-4.00	
	POLAR	Solubility	2.58e-02 mg/ml ; 1.01e-04 mol/l	
		Class 🧐	Soluble	
	INSOLU	GL absorption 😣	High	
SMILES Oc1cc2OC(CC(=0	D)c2c(c1)O)c1ccccc1	BBB permeant ()	Yes	
Ph	ysicochemical Properties	P-gp substrate ⁽²⁾	No	
Formula	C15H12O4	CYP1A2 inhibitor 😣	Yes	
Molecular weight	256.25 g/mol	CYP2C19 inhibitor ⁽⁹⁾	Yes	
Num. neavy atoms	19	CYP2C9 inhibitor 🥹	No	
Fraction Csp3	0.13	CYP2D6 inhibitor 🗐	No	
Num. rotatable bonds	1	CYP3A4 Inhibitor	NO	
Num. H-bond acceptors	4	Log Ap (skin permeation)	-5.82 CTT/S	
Num. H-bond donors	2	Lininski 🖗	Yes: 0 violation	
Molar Refractivity	69.55	Ghose 9	Yes	
IPSA 🥑	66.76 A ²	Veber 🛞	Yes	
Log P-+ (il OGP) 🤫	2 11	Egan 🛞	Yes	
$\log P$ (XLOGP3)	2.89	Muegge 🥹	Yes	
	2.00	Bioavailability Score 🥺	0.55	
$\log P_{0/W}$ (WLOGP)	2.40	DAINO O	Medicinal Chemistry	
	1.27	PAINS U	0 alert	
Log P _{o/w} (SILICOS-IT)	2.55		Yes	
Consensus Log Po/w	2.26	Synthetic accessibility 0	2.96	
Chrysin				
Chrysin			Water Solubility	
Chrysin tt ⊕ ₽	LIPO	Log <i>S</i> (ESOL) 📀	Water Solubility -4.19	
Chrysin tt © 🔗	LIPO	Log <i>S</i> (ESOL) Solubility	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l	
Chrysin tt	LIPO FLEX SIZE	Log S (ESOL) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble	
Chrysin tt ③ 🏈	FLEX SIZE	Log S (ESOL) Solubility Class Log S (Ali) S	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69	3
Chrysin tt ③ 🏈	FLEX SIZE	Log S (ESOL) Solubility Class Log S (Ali) Solubility	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l	
Chrysin tt ③	FLEX SIZE	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble	(
Chrysin tt ③	FLEX SIZE	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT)	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98	
Chrysin tt ③	FLEX INSATU	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l	
Chrysin tt ③	FLEX INSATU	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble	3
Chrysin tt ③ 🏈	FLEX INSATU INSATU	Log S (ESOL) Solubility Class Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics Hich	
Chrysin H I I I I I I I I I I I I I I I I I I I	FLEX FLEX INSATU INSATU INSOLU POLAR POLAR	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Gl absorption BBB permeant	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes	
Chrysin H I I I I I I I I I I I I I I I I I I I	FLEX FLEX FLEX NINATU NINATU NINATU FULX	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Gl absorption BBB permeant P-gp substrate	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No	
Chrysin H I I I I I I I I I I I I I I I I I I I	FLEX FLEX INSATU INSATU INSATU INSOLU POLAR POLAR C(cc2=O)c1ccccc1 ysicochemical Properties C15H10O4	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Gl absorption BBB permeant P-gp substrate CYP1A2 inhibitor	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes	
Chrysin H I I I I I I I I I I I I I I I I I I I	FLEX FLEX INSATU INSATU INSATU INSOLU POLAR POLAR C15H1004 254.24 g/mol	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-05 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No	
Chrysin H I I I I I I I I I I I I I I I I I I I	FLEX FLEX INSATU INSATU INSOLU POLAR POLAR POLAR POLAR C15H1004 254.24 g/mol 19	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No No	
Chrysin H O O OH O HO OH OH OH OH	FLEX FLEX FLEX FUEX FUEX FUEX FUEX FOLA	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No No No No No	
Chrysin Provide the second state of the secon	FLEX FLEX FLEX FLEX FUEX FOLA	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No No Yes	
Chrysin H O O OH O HO OH OH OH OC OC OC Coloc(O)c2c(c1)c Ph Formula Molecular weight Num. heavy atoms Fraction Csp3 Num. rotatable bonds Num. rotatable bonds Num. H-bond acceptors	FLEX FLEX FLEX FLEX FUEX FUEX FOLA	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class GI absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C9 inhibitor CYP3A4 inh	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No Yes Yes -5.35 cm/s	
Chrysin Provide the second se	FLEX FLEX FLEX FLEX FUEX FOLA	Log S (ESOL) Solubility Class Solubility Class Log S (Ali) Solubility Class Class Gl absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C9 inhibitor CYP3A4 inhibitor Log K _p (skin permeation)	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No No Yes Yes -5.35 cm/s Druglikeness Yes: 0 violation	
Chrysin To Chrysin To Chrysin	FLEX FLEX FLEX FLEX FOLAR	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Gl absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C19 inhibitor CYP3A4 inhibitor CYP3	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No Yes -5.35 cm/s Druglikeness Yes; 0 violation Yes	
Chrysin If O O OH O U U OH O OH OH O OH O O O O O O O O O O O O O	FLEX FLEX FLEX FLEX FUNCUU FOLAR	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Gl absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C19 inhibitor C	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No Yes -5.35 cm/s Druglikeness Yes	
Chrysin H O O OH O H O Chrysin H O Chrysin	FLEX FLEX FLEX FUEX FOLAR	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Gl absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP3A4 inhibitor Log K _p (skin permeation) Lipinski Ghose Veber Egan	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No Yes -5.35 cm/s Druglikeness Yes Yes </td <td></td>	
Chrysin H O OH OH OH OH OH OH OH OH OH O	FLEX FLEX FLEX FUEX FOLAR	Log S (ESOL) Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Class GI absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2C19 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP2D6 inhibitor CYP3A4 inhibitor Log K _p (skin permeation) Lipinski Ghose Veber Egan Muegge	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes No Yes -5.35 cm/s Druglikeness Yes Yes </td <td></td>	
Chrysin H O O OH O OH O OH O OH O OH O OH OH OH OH OH OH OH OH OH O	FLEX FLEX FLEX FUEX	Log S (ESOL) Solubility Class Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes Solution Yes Yes () violation Yes	
Chrysin If O O OH O OH O OH O OH O OH O OH O OH O OH OH OH OH OH OH OH OH OH O	FLEX FLEX FLEX FUEX	Log S (ESOL) Solubility Class Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes Solution Yes Yes () violation Yes	
Chrysin	FLEX FLEX FLEX FUEX FUEX FOLAR POLAR	Log S (ESOL) Solubility Class Solubility Class Log S (Ali) Solubility Class	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes So Yes So Yes	
Chrysin	FLEX FLEX FLEX FUEX FUEX FUEX FOLAR P	Log S (ESOL) Solubility Class Solubility Class Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class Class Gl absorption BBB permeant P-gp substrate CYP1A2 inhibitor CYP2C9 inhibitor CYP2C9 inhibitor CYP2C9 inhibitor CYP2C9 inhibitor CYP2C9 inhibitor CYP2C9 inhibitor CYP2C9 inhibitor CYP2A4 inhibitor CYP2A6 inhibitor CYP2A6 inhibitor CYP2A6 inhibitor CYP2A6 inhibitor CYP2A6 inhibitor CYP3A4 inhibitor CYP3A4 inhibitor Eggan Muegge Bioavailability Score PAINS Brenk Leadlikeness	Water Solubility -4.19 1.64e-02 mg/ml ; 6.44e-05 mol/l Moderately soluble -4.69 5.22e-03 mg/ml ; 2.05e-05 mol/l Moderately soluble -4.98 2.64e-03 mg/ml ; 1.04e-05 mol/l Moderately soluble Pharmacokinetics High Yes No Yes So Yes	

Figure S6. Solubility comparison of pinocembrin (TH022) and chrysin.