**Supplementary Table 1.** A summary of compounds tested *in vitro* and *in vivo* with inhibition potential for ZIKV. [N.D. = not determined; EC50= half maximal effective concentration; IC50= half maximal inhibitory concentration]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **Cell line (anti-ZIKV activity of compound, ZIKV strain)** | ***in vivo* model (dose of compound; ZIKV strain)** | **Mechanistic insight**  | **Description of compound** | **Ref.** |
| Amodiaquine dihydrochloride dihydrate (AQ) | hNPCs (IC50: 2.81 µM, MR766), hPSC-derived forebrain organoids (15 µM, suppresses MR766 infection) | SCID-Beige mice (40 mg/kg/day; MR766) |  N.D. | FDA approved drug  | (1)  |
| Hippeastrine hydrobromide (HH) | hNPCs (IC50: 3.62 µM, MR766), hPSC-derived forebrain organoids (25 µM, suppresses MR766 infection)  | SCID-Beige mice (100 and 200 mg/kg/day for MR766; 100 mg/kg/day for FSS13025). |  N.D. | FDA approved drug  | (1)  |
| Methylene blue | A549 (EC50: 0.2 µM, MR766; EC50: 0.87 µM, PRVABC59; EC50: 0.14 µM, FSS13025; EC50: 0.087 µM, MeX I-44; EC50: 0.14 µM, BeH819015), 3D mini-brain organoids (1.5 µM completely protected from PRVABC59) | IfnαβR−/− mice (100 mg/kg/day; PRVABC59) | Inhibit viral entry to host cell. Disrupts the interaction between NS2B and NS3 protease. Inhibitor of NS2B-NS3 protease (*in vitro*). | FDA approved drug  | (2)  |
| Temoporfin | A549 (EC50: 0.024 µM, PRVABC59), Vero (EC50: 0.1 µg/ml, GZ01/2016), HPECs (0.01-3 µM, PRVABC59), hNPCs (0.01-3 µM, PRVABC59), h-iPSC line HDF9 (0.04-3 µM, PRVABC59) | Balb/C mice (0.02 mg/mice/day; GZ01/2016), A129 mice (1mg/kg/day; GZ01/2016)  | Disrupts the interaction between NS2B and NS3 protease. Inhibitor of NS2B-NS3 protease (*in vitro* & *in silico*). | FDA approved drug  | (3)  |
| Methacycline | NSCs (IC50: 7.3 µM, French Polynesian\_2013) | C57BL/6 mice (10 mg/kg/day; Brazil\_2015) | Inhibitor of NS2B-NS3 protease (*in vitro* & *in silico*). Reduces the severity of motor deficits.  | FDA approved drug | (4)  |
| Fidaxomicin | SNB19 (EC50: 6 µM, ZG-01; EC50: 6.8 µM MR766), A172 (EC50: 8.8 µM ZG-01), Vero (EC50: 11.7 µM, ZG-01; EC50: 12.4 µM MR766), Huh7 (EC50: 7.7 µM, ZG-01; EC50: 7.3 µM MR766), A549 (EC50: 12.2 µM, ZG-01; EC50: 13 µM MR766), HUVECs (EC50: 14.5 µM, ZG-01)  | Ifnar1−/− C57BL/6 mice (10-20 mg/kg; ZG-01) | Inhibitor of RdRp (*in vitro* & *in silico*). | FDA approved drug  | (5)  |
| Ribavirin | Vero (80 µg/ml could inhibit MR766 replication almost completely), SH-SY5Y (10 µg/ml inhibit MR766 replication strongly), C6/36 (10 µg/ml inhibit MR766 replication significantly) | STAT1-deficient mice (15 mg/day; MR766) | N.D. | FDA approved drug  | (6)  |
| Emetine  | SNB-19 (IC50: 29.8 nM, PRVABC59), HEK293 (IC50: 52.9 nM, MR766), Vero (IC50: 8.74 nM, PRVABC59) | SJL mice (1 mg/kg/day; ZIKVBR), Ifnar1−/− mice (2 mg/kg/day; FSS13025) | Disrupts lysosomal function to prevent virus entry. Inhibitor of RdRp (*in vitro* & *in silico*).  | FDA approved drug  | (7)  |
| Memantine | Neuronal cells (30 µM reduces cell death to ~20 %, HS-2015-BA-01) | IFN-α/βR−/− mice (30 mg/kg twice daily; HS-2015-BA-01) | Blocks N-methyl-D-aspartate receptor (NMDAR). | FDA approved drug | (8)  |
| Novobiocin | Vero (IC50: 42.63 µM, PRVABC59), Huh-7 (IC50: 62.24 µM, PRVABC59) | BALB/c mice (100 mg/kg q12h; PRVABC59) | Inhibitor of NS2B-NS3 protease (*in vitro* & *in silico*). | FDA approved drugs | (9)  |
|  TPB | [Vero](https://www.sciencedirect.com/topics/medicine-and-dentistry/embryonal-carcinoma) (IC50: 94 nM, PRVABC59; 0.5-2 µM, inhibits MR766 growth), HTR-8 (0.5-1 µM, inhibits PRVABC59 growth), NTERRA-2 (0.5-1 µM, inhibits PRVABC59 growth) | BALB/c mice (25 mg/kg; PRVABC59) | Interacts with RdRp (*in silico*). | Non-nucleoside inhibitor | (10)  |
| BCX4430 | Vero (EC50: 11.7 or 8.7 µg/ml, MR766; EC50: 11.5 or 13.8 µg/ml, P 6-740; EC50: 3.8 or 18.2 µg/ml, PRVABC59), Huh-7 (EC50: 5.7 or 6.4 µg/ml, MR766; EC50: 5.5 or 4.9 µg/ml, P 6-740; EC50: 4.7 or 6.7 µg/ml, PRVABC59), RD (EC50: 4.4 or 5.4 µg/ml, MR766; EC50: 4.7 or 10 µg/ml, PRVABC59) | AG129 mice (twice daily at 300 mg/kg/day; P 6-740) |  N.D. | Nucleoside analog | (11)  |
| NITD008 | Vero (EC50: 241 nM, GZ01/2016; EC50: 137 nM, FSS13025; EC50: 0.50 µM, MR766; EC50: 0.56 µM PRVABC59) | A129 mice (50 mg/kg; GZ01/2016) |  N.D. | Nucleoside analog | (12, 13)  |
| 7DMA (7-deaza-2’-C-methyladenosine) | Vero (EC50: 1.3-20 µM, MR766) | AG129 mice (50 mg/kg/day; MR766) |  N.D. | Nucleoside analog (viral polymerase inhibitor) | (14, 15)  |
| N-ter-WDFGSIGGVFNSIGKAVHQVF-C-ter | Vero (IC50: 3.27 µM, H/PF/2013; IC50: 0.07 µM, MRS), Huh-7 (IC50: 0.55 µM, H/PF/2013; IC50: 0.13 µM, MRS) | C57BL/6 mice (50 µM; H/PF/2013) |  N.D. | Peptide (derived from JEV E protein stem region)  | (16)  |
| AH-D peptide (alpha helix and D enantiomer)  | Neuronal cells from C57BL/6J (IC50: 0.0119 µM; MR766, HS-2015-BA-01) | Ifn-α/βR−/− SV129 (25 mg/kg twice daily; HS-2015-BA-01) | Penetrates blood brain barrier to prevent brain damage and neurodegeneration. | Peptide  | (17)  |
| NSC157058 | hfNPCs (IC50: ~50 µM, FSS13025) | [SJL mice](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/swiss-james-lambert-mouse) (30 mg/kg/day; PA259459) | Inhibitor of NS2B-NS3 protease (*in vitro* & *in silico*). | Small molecule | (18)  |
| 25HC (25-hydroxycholesterol) | Vero (IC50: 188 nm, GZ01/2016), human cortical organoids (2.5 µM reduces 90% ZIKV RNA of PRVABC59) | BALB/c (50 mg/kg; GZ01/2016), A129 (50 mg/kg; GZ01/2016); Rhesus monkeys \_Macaca mulatta (1.5 mg/kg/day; GZ01/2016) | Blocks viral entry to host cell and protect from microcephaly. | Enzymatic product of cholesterol-25-hydroxylase | (19)  |
| Cinnamic acid | Vero (EC50: 49.55 µM, Asian\_KU963796), Huh-7 (EC50: 83.96 µM, Asian\_KU963796), A549 (EC50: 103.8 µM, Asian\_KU963796) | AG6 (75 or 150 mg/kg; Asian\_KU963796) | Inhibitor of RdRp (*in vitro* & *in silico*). | Organic acid | (20)  |
| Methyl 5-chloro-3-(4-hydroxy-3,5-dimethoxybenzoyl)-1H-indole-2-carboxylate | Huh-7 (EC50: 13.9 µM, 976 Uganda) | ICR suckling mouse (1 mg/kg at 1,3 and 5 dpi; 976 Uganda) | Inhibitor (allosteric) of NS2B-NS3 protease (*in vitro* & *in silico*). Inhibits RNA synthesis and protein production. Inhibits brain damage. | Small molecule | (21)  |
| JMX0207 | A549 (EC50: 0.30 µM, PRVABC59), hNPCs (7.5 µM, protects from PRVABC59 infection), cortical organoids (1.5 µM, completely protected from PRVABC59 infection) | A129 (20 mg/kg/day; PRVABC59) | Inhibit the molecular interaction between NS3 and NS2B. Inhibitor of NS2B-NS3 protease (*in vitro*). | Niclosamide derivative | (22) |
| Erythrosin B | A549 (EC50: 0.62 µM, PRVABC59), HPEC (EC50: 0.60 µM, PRVABC59), HPNC (EC50: 1.39 µM, PRVABC59), forebrain organoid (3 µmol/L, significantly reduces ZIKV infection, ZIKV-Venus) | A129 (200 mg/kg/day; PRVABC59) | Disrupts the interaction between NS2B and NS3 protease. Inhibitor of NS2B-NS3 protease (*in vitro* & *in silico*). | FDA approved food additive | (23, 24) |
| Cephaeline | HEK 293 (IC50: 26.4 nM, MR766), SNB-19 (IC50: 3.11 nM), astrocytoma cells (IC50: 7.60 nM, MR766; IC50: 10.51 nM, PRVABC59) | Ifnar1-/- (2mg/kg/day; FS13025) | Inhibitor of NS5 RdRp | Emetine analog | (7)  |
| 6-bromo-1,2-naphthalenedione | Vero (50 µM, 150-fold reduction in MR766) | AG129 (50 µg/day; MR766) | Inhibitor of NS2B-NS3 protease (*in vitro*) | Small molecule | (25) |

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