Supplementary Material for:

Recent advances on SARS-CoV-2 Mpro inhibitors: from Nirmatrelvir to future perspectives

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**Table 1**. Most relevant SARS-CoV-2 Mpro inhibitors discovered so far.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **Chemical class** | **Structure** | **IC50 (nM)a** | **Mechanism** | **EC50 (M)c** |
| **1**  **NIRMATRELVIR** | **Nitriles** |  | **3.11b** | **Covalent Reversible** | **0.075** |
| **2**  **PF-00835231** | **Hydroxy ketones** |  | **4b** | **Covalent Reversible** | **0.23** |
| **3**  **PF-07304814** | **Hydroxy ketones**  **(phosphate prodrug)** |  | **27.9b** | **Covalent Reversible** | **1.4** |
| **4** | **Nitriles** |  | **27.7b** | **Covalent Reversible** | **1.4** |
| **5** | **Ketones** |  | **230b** | **Covalent Reversible** | **5.6** |
| **6** | **Ketones** |  | **7.93b** | **Covalent Reversible** | **0.9** |
| **7** | **Ketones** |  | **12.1b** | **Covalent Reversible** | **0.85** |
| **8** | **Nitriles** |  | **4b** | **Covalent Reversible** | **0.019** |
| **9** | **Nitriles** |  | **9b** | **Covalent Reversible** | **2.2** |
| **10** | **Nitriles** |  | **18** | **Covalent Reversible** | **0.31** |
| **11** | **Nitriles** |  | **22** | **Covalent**  **Reversible** | **0.17** |
| **12**  **BBH-2** | **Nitriles** |  | **26d** | **Covalent**  **Reversible** | **0.88** |
| **13**  **NBH-2** | **Nitriles** |  | **30d** | **Covalent Reversible** | **1.82** |
| **14** | **Alkynes** |  | **140** | **Covalent**  **Irreversible** | **25.7** |
| **15** | **Alkynes** |  | **230** | **Covalent Irreversible** | **5.1** |
| **16** | **Aldehydes** |  | **53** | **Covalent Reversible** | **0.53** |
| **17** | **Aldehydes** |  | **40** | **Covalent Reversible** | **0.72** |
| **18** | **Aldehydes** |  | **34** | **Covalent Reversible** | **0.29** |
| **19**  **GC-373** | **Aldehydes** |  | **400** | **Covalent Reversible** | **1.5** |
| **20**  **GC-376** | **Aldehydes**  **(phosphate prodrug)** |  | **190** | **Covalent Reversible** | **0.9** |
| **21** | **Aldehydes**  **(phosphate prodrug)** |  | **70** | **Covalent Reversible** | **0.57** |
| **22** | **Aldehydes**  **(phosphate prodrug)** |  | **80** | **Covalent Reversible** | **0.7** |
| **23**  **UAWJ247** | **Aldehydes**  **(phosphate prodrug)** |  | **45** | **Covalent Reversible** | **6.8** |
| **24**  **Coronastat** | **Aldehydes**  **(phosphate prodrug)** |  | **16** | **Covalent Reversible** | **0.006** |
|  |  |  |  |  |  |
| **25**  **MI-09** | **Aldehydes** |  | **15.2** | **Covalent Reversible** | **0.86** |
| **26**  **Mi-23** | **Aldehydes** |  | **7.6** | **Covalent Reversible** | **n.d.** |
| **27**  **MI-30** | **Aldehydes** |  | **17.2** | **Covalent Reversible** | **0.54** |
| **28** | **Aldehydes** |  | **180** | **Covalent Reversible** | **0.035** |
| **29**  **UAWJ9-36-1** | **Aldehydes** |  | **51** | **Covalent Reversible** | **2.6** |
| **30**  **UAWJ9-36-3** | **Aldehydes** |  | **54** | **Covalent Reversible** | **0.37** |
| **31**  **MPI143** | **Aldehydes** |  | **45** | **Covalent Reversible** | **0.4 – 1.0e** |
| **32**  **MPI144** | **Aldehydes** |  | **59** | **Covalent Reversible** | **0.9 – 2.9e** |
| **33**  **MPI146** | **Aldehydes** |  | **120** | **Covalent Reversible** | **0.8 – 2.3e** |
| **34**  **Calpeptin** | **Aldehydes** |  | **10700** | **Covalent Reversible** | **0.072** |
| **35**  **MPI3** | **Aldehydes** |  | **8.5** | **Covalent Reversible** | **n.d.** |
| **36**  **MPI8** | **Aldehydes** |  | **108** | **Covalent Reversible** | **2.5** |
| **37**  **MGI132** | **Aldehydes** |  | **7500** | **Covalent Reversible** | **n.d.** |
| **38**  **Calpain inhibitor I** | **Aldehydes** |  | **970** | **Covalent Reversible** | **n.d.** |
| **39**  **Calpain inhibitor II** | **Aldehydes** |  | **8600** | **Covalent Reversible** | **2.07** |
| **40**  **MPI16** | **Aldehydes** |  | **105** | **Covalent Reversible** | **0.056** |
|  |  |  |  |  |  |
| **41**  **MPI17** | **Aldehydes** |  | **60** | **Covalent Reversible** | **0.097** |
| **42** | **Ketones** |  | **1.0** | **Covalent Reversible** | **0.16** |
| **43** | **Ketones** |  | **19.0** | **Covalent Reversible** | **0.3** |
| **44** | **Ketones** |  | **14.0** | **Covalent Reversible** | **0.47** |
| **45**  **YH-53** | **Ketones** |  | **130** | **Covalent Reversible** | **2.6** |
| **46**  **TKB245** | **Ketones** |  | **7** | **Covalent Reversible** | **0.03** |
| **47**  **TKB248** | **Ketones** |  | **74** | **Covalent Reversible** | **0.22** |
| **48** | **Ketones** |  | **1650** | **Covalent Reversible** | **0.18** |
| **49**  **BBH1** | **Ketones** |  | **n.d.** | **Covalent Reversible** | **16.1** |
| **50**  **Z-FA-FMK** | **Ketones** |  | **11400** | **Covalent Irreversible** | **0.13** |
| **52** | **Ketones** |  | **n.d.** | **Covalent Reversible** | **12.9f** |
| **53** | **Ketones** |  | **750** | **Covalent Reversible** | **n.d.** |
| **54**  **X77** | **Miscellaneous** |  | **4100** | **Non Covalent** | **n.d.** |
| **55** | **a-haloacetamides** |  | **410** | **Covalent Irreversible** | **n.d.** |
| **56**  **23R** | **Miscellaneous** |  | **200** | **Non Covalent** | **1.4** |
| **57**  **JUN9-62-2R** | **a-haloacetamides** |  | **430** | **Covalent Irreversible** | **0.90** |
| **58**  **JUN9-90-3R** | **a-haloacetamides** |  | **300** | **Covalent Irreversible** | **2.07** |
| **59**  **JUN9-90-4R** | **a-haloacetamides** |  | **460** | **Covalent Irreversible** | **1.10** |
| **60**  **JUN9-88-6R** | **a-haloacetamides** |  | **80** | **Covalent Irreversible** | **0.58** |
| **61** | **a-haloacetamides** |  | **56** | **Covalent Reversible** | **n.d.** |
| **62**  **Y020-9948** | **a-haloacetamides** |  | **8500** | **Covalent Irreversible** | **n.d.** |
| **63**  **MCULE-5948770040** | **Miscellaneous** |  | **4200** | **Non Covalent** | **n.d.** |
| **64**  **GC-14** | **Miscellaneous** |  | **400** | **Non Covalent** | **1.1** |
| **65**  **GD9** | **a-haloacetamides** |  | **180** | **Covalent Irreversible** | **2.6** |
| **66**  **GD13** | **a-haloacetamides** |  | **310** | **Covalent Irreversible** | **4.2** |
|  |  |  |  |  |  |
| **67**  **(R)-EN82** | **a-haloacetamides** |  | **530** | **Covalent Irreversible** | **n.d.** |
| **68**  **HW-2-010b** | **a-haloacetamides** |  | **14** | **Covalent Irreversible** | **n.d.** |
| **69**  **QUB-00006-Int-07** | **a-haloacetamides** |  | **830** | **Covalent** | **n.d.** |
| **70** | **a-ketoamides** |  | **670** | **Covalent Reversible** | **4-5** |
| **71**  **Y180** | **a-ketoamides** |  | **8.1** | **Covalent Reversible** | **0.011** |
| **72**  **RAY1216** | **a-ketoamides** |  | **8.4b** | **Covalent Reversible** | **0.13** |
| **73** | **a-ketoamides** |  | **1300** | **Covalent Reversible** | **n.d.** |
| **74**  **SY110** | **a-ketoamides** |  | **14.4** | **Covalent Reversible** | **0.38 – 2.8e** |
| **76**  **CINANSERIN** | **Michael Acceptors** |  | **125000** | **Covalent Irreversible** | **20.6** |
| **77** | **Michael Acceptors** |  | **151** | **Covalent Irreversible** | **2.9** |
| **78** | **Michael Acceptors** |  | **47200** | **Covalent Irreversible** | **n.d.** |
| **79** | **Michael Acceptors** |  | **157000** | **Covalent Irreversible** | **n.d.** |
| **80**  **SPR38** | **Michael Acceptors** |  | **260b** | **Covalent Irreversible** | **18.5** |
| **81**  **SPR39** | **Michael Acceptors** |  | **250b** | **Covalent Irreversible** | **1.5** |
| **82**  **SPR41** | **Michael Acceptors** |  | **180b** | **Covalent Irreversible** | **1.8** |
| **83**  **SM141** | **Michael Acceptors** |  | **900** | **Covalent Irreversible** | **0.0082** |
| **84**  **SM142** | **Michael Acceptors** |  | **1800** | **Covalent Irreversible** | **0.0147** |
| **85** | **Michael Acceptors** |  | **1900** | **Covalent Irreversible** | **n.d.** |
| **86** | **Michael Acceptors** |  | **14000** | **Covalent Irreversible** | **5.3f** |
| **87** | **Michael Acceptors** |  | **12400** | **Covalent Irreversible** | **9.1g** |
| **88** | **Michael Acceptors** |  | **10100** | **Covalent Irreversible** | **10.1g** |
| **89** | **Michael Acceptors** |  | **420** | **Covalent Irreversible** | **n.d.** |
| **90** | **Michael Acceptors** |  | **170** | **Covalent Irreversible** | **n.d.** |
| **92** | **Michael Acceptors** |  | **2860** | **Covalent Irreversible** | **n.d.** |
| **93**  **MYRECITIN** | **Michael Acceptors** |  | **200 - 600** | **Covalent Irreversible** | **8** |
| **94** | **Michael Acceptors** |  | **300** | **Covalent Irreversible** | **12.6** |
| **95** | **Michael Acceptors** |  | **260** | **Covalent Irreversible** | **11.5** |
| **96** | **Michael Acceptors** |  | **3100** | **Covalent Irreversible** | **3.2** |
| **97**  **GRL-0920** | **Esters** |  | **250** | **Covalent Irreversible** | **2.8** |
| **98**  **GRL-0820** | **Esters** |  | **73** | **Covalent Irreversible** | **15** |
| **99**  **GRL-1720** | **Esters** |  | **320** | **Covalent Irreversible** | **15** |
| **100** | **Esters** |  | **55** | **Covalent Irreversible** | **n.d.** |
| **101** | **Esters** |  | **34** | **Covalent Irreversible** | **n.d.** |
| **102** | **Esters** |  | **81** | **Covalent Irreversible** | **n.d.** |
| **103** | **Thioesters** |  | **11** | **Covalent Irreversible** | **0.11** |
| **104** | **Thioesters** |  | **88** | **Covalent Irreversible** | **0.73** |
| **105** | **Thioesters** |  | **n.d.** | **n.d.** | **0.1** |
| **106** | **Thioesters** |  | **n.d.** | **n.d.** | **0.44** |
| **107** | **Thioesters** |  | **n.d.** | **n.d.** | **0.66** |
| **108** | **Thioesters** |  | **n.d.** | **n.d.** | **0.038** |
| **109** | **Thioesters** |  | **n.d.** | **n.d.** | **0.045** |
| **110**  **EBSELEN** | **Selenium-based compounds** |  | **670** | **Covalent** | **4.67** |
| **111** | **Selenium-based compounds** |  | **25.7** | **Covalent** | **n.d.** |
| **112** | **Selenium-based compounds** |  | **27.9** | **Covalent** | **n.d.** |
| **113** | **Selenium-based compounds** |  | **15.2** | **Covalent** | **n.d.** |
| **114** | **Selenium-based compounds** |  | **27.4** | **Covalent** | **n.d.** |
| **115** | **Selenium-based compounds** |  | **900** | **Covalent** | **11.2** |
| **116** | **Selenium-based compounds** |  | **680** | **Covalent** | **11.7** |
| **117** | **Selenium-based compounds** |  | **640** | **Covalent** | **18.2** |
| **118** | **Selenium-based compounds** |  | **380** | **Covalent** | **2.0** |
| **119** | **Selenium-based compounds** |  | **2800** | **Covalent** | **0.8** |
| **120**  **MR6-7-2** | **Selenium-based compounds** |  | **360** | **Covalent** | **4.5** |
| **121**  **MR6-18-4** | **Selenium-based compounds** |  | **340** | **Covalent** | **3.7** |
| **122**  **MR6-17-1** | **Selenium-based compounds** |  | **700** | **Covalent** | **n.a.** |
| **123**  **MR6-26-2** | **Selenium-based compounds** |  | **470** | **Covalent** | **3.2** |
| **124**  **MR6-31-2** | **Selenium-based compounds** |  | **820** | **Covalent** | **1.8** |
| **125**  **EBSULFUR** | **Sulfur-based compounds** |  | **490** | **Covalent** | **n.d.** |
| **126** | **Sulfur-based compounds** |  | **110** | **Covalent** | **n.d.** |
| **127** | **Selenium-based compounds** |  | **74** | **Covalent** | **n.d.** |
| **128** | **Sulfur-based compounds** |  | **190** | **Covalent** | **n.d.** |
| **129** | **Sulfur-based compounds** |  | **160** | **Covalent** | **n.d.** |
| **130** | **Sulfur-based compounds** |  | **180** | **Covalent** | **n.d.** |
| **131** | **Sulfur-based compounds** |  | **140** | **Covalent** | **n.d.** |
| **132** | **Sulfur-based compounds** |  | **150** | **Covalent** | **n.d.** |
| **133** | **Sulfur-based compounds** |  | **150** | **Covalent** | **n.d.** |
| **134** | **Sulfur-based compounds** |  | **120** | **Covalent** | **n.d.** |
| **135** | **Sulfur-based compounds** |  | **116** | **Covalent** | **n.d.** |
| **136** | **Sulfur-based compounds** |  | **165** | **Covalent** | **n.d.** |
| **137** | **Sulfur-based compounds** |  | **165** | **Covalent** | **n.d.** |
| **138** | **Miscellaneous** |  | **8600** | **Non Covalent** | **n.d.** |
| **139** | **Miscellaneous** |  | **96** | **Non Covalent** | **12.5** |
| **140**  **S-217622** | **Miscellaneous** |  | **13** | **Non Covalent** | **0.5 – 0.29e** |
| **141**  **Z1244904919** | **Miscellaneous** |  | **730** | **Non Covalent** | **5** |
| **142**  **Z1759961356** | **Miscellaneous** |  | **690** | **Non Covalent** | **8.5** |
| **144**  **CCF981** | **Miscellaneous** |  | **68** | **Non Covalent** | **0.5** |
| **145** | **Miscellaneous** |  | **450** | **Non Covalent** | **0.77** |
| **146** | **Miscellaneous** |  | **110** | **Non Covalent** | **0.11** |
| **149** | **Miscellaneous** |  | **77** | **Non Covalent** | **0.11** |
| **150**  **ZINC000373659060** | **Miscellaneous** |  | **58000** | **Non Covalent** | **n.d.** |
| **151**  **ZINC000636416501** | **Miscellaneous** |  | **93000** | **Non Covalent** | **n.d.** |
| **152**  **Z228770960** | **Miscellaneous** |  | **4000** | **Non Covalent** | **n.d.** |
| **153**  **Z393665558** | **Miscellaneous** |  | **6000** | **Non Covalent** | **n.d.** |
| **154**  **Z225602086** | **Miscellaneous** |  | **7400** | **Non Covalent** | **n.d.** |
| **155**  **Z222979552** | **Miscellaneous** |  | **1000** | **Non Covalent** | **n.d.** |
| **156**  **Z228166018** | **Miscellaneous** |  | **1600** | **Non Covalent** | **n.d.** |
| **157**  **Z222977344** | **Miscellaneous** |  | **2000** | **Non Covalent** | **n.d.** |
| **158**  **Z222978028** | **Miscellaneous** |  | **5800** | **Non Covalent** | **n.d.** |
|  |  |  |  |  |  |
| **160** | **Miscellaneous** |  | **83** | **Non Covalent** | **1.1** |
| **161** | **Miscellaneous** |  | **100** | **Non Covalent** | **2.1** |
| **162** | **Miscellaneous** |  | **4100** | **Non Covalent** | **n.d.** |
| **163**  **Neoechinulin A** | **Miscellaneous** |  | **470** | **Non Covalent** | **n.d.** |
| **164**  **Shikonin** | **Miscellaneous** |  | **1570** | **Non Covalent** | **n.d.** |
| **165**  **C1** | **Miscellaneous** |  | **1500** | **Non Covalent** | **n.d.** |
| **166**  **C2** | **Miscellaneous** |  | **1800** | **Non Covalent** | **n.d.** |
| **167**  **Pelitinib** | **Miscellaneous** |  | **n.d.** | **Allosteric** | **1.25** |
| **168**  **Ifenprodil** | **Miscellaneous** |  | **n.d.** | **Allosteric** | **47** |
| **169**  **RS-102895** | **Miscellaneous** |  | **n.d.** | **Allosteric** | **19.8** |
| **170**  **AT7519** | **Miscellaneous** |  | **n.d.** | **Allosteric** | **25.2** |
| **171**  **JMX0286** | **Miscellaneous** |  | **4800** | **Allosteric** | **2.3** |
| **172**  **JMX0301** | **Miscellaneous** |  | **4500** | **Allosteric** | **2.4** |
| **173**  **JMX0941** | **Miscellaneous** |  | **3900** | **Allosteric** | **1.7** |
| **174**  **Apixaban** | **Miscellaneous** |  | **9.7** | **Allosteric** | **1.8** |

Notes: a IC50 value refers to the inhibition of SARS-CoV-2 Mpro. b K*i* value refers to the inhibition of SARS-CoV-2 Mpro.

c EC50 refers to *in vitro* inhibition of SARS-CoV-2. d K*d* value refers to the inhibition of SARS-CoV-2 Mpro

e EC50 refers to *in vitro* inhibition of several variants of SARS-CoV-2.

f EC50 refers to *in vitro* inhibition of several variants of hCoV-229E.

g EC50 refers to *in vitro* inhibition of several variants of hCoV-OC43.

n.d. = not determined

n.a. = not active