Article

Structure-Based Screening of Modified Nucleobase, Nucleoside and Nucleotide Analogues against the SARS-CoV-2 Main Protease: Molecular Docking, Molecular Dynamics and the Limits of Score-Based Ranking

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Supplementary Materials

Table S1. AutoDock Vina docking scores for all 28 compounds against SARS-CoV-2 Mpro.

Figure S1. Ball-and-stick representation of the prepared input structure of Compound 26 (m^7GTP).

Figure S2. Ball-and-stick representations of the prepared input structures of all 28 compounds.

Table S1. AutoDock Vina docking scores (in kcal/mol) for the 28 investigated compounds against the SARS-CoV-2 main protease (Mpro) a.

Compound	Chemical name	Target	Docking score (kcal/mol)
1	7-Deazaguanine	SARS-CoV-2 Mpro	-5.9
2	5-Iodouracil	SARS-CoV-2 Mpro	-4.9
3	5-Bromouracil	SARS-CoV-2 Mpro	-4.9
4	2-Thiouracil	SARS-CoV-2 Mpro	-4.2
5	2-Aminopurine	SARS-CoV-2 Mpro	-5.0
6	2H-Imidazo[4,5-e]benzoxazole	SARS-CoV-2 Mpro	-5.3
7	4-Thiouracil	SARS-CoV-2 Mpro	-4.6
8	2-Thiopurine	SARS-CoV-2 Mpro	-4.7
9	2-Nitro-1H-imidazole	SARS-CoV-2 Mpro	-4.6
10	5-Methylcytosine	SARS-CoV-2 Mpro	-4.8
11	Pyrazolo[1,5-a]pyrimidine	SARS-CoV-2 Mpro	-4.3
12	2'-Fluoro-2'-deoxy-arabino-uridine	SARS-CoV-2 Mpro	-6.0
13	8-Aza-7-deazaadenine	SARS-CoV-2 Mpro	-5.0
14	N6-Methyladenine	SARS-CoV-2 Mpro	-4.7
15	5-Azidomethyluracil	SARS-CoV-2 Mpro	-5.0
16	5-Fluorocytosine	SARS-CoV-2 Mpro	-4.8
17	5-Hydroxymethylcytosine	SARS-CoV-2 Mpro	-4.5
18	1-Etheno-2'-deoxyadenosine	SARS-CoV-2 Mpro	-6.8
19	2-Fluoroadenine	SARS-CoV-2 Mpro	-4.7
20	1,3,5-Triazine	SARS-CoV-2 Mpro	-3.5
21	7-Methyl-7-deazaadenosine	SARS-CoV-2 Mpro	-6.3
22	1-(beta-D-Ribofuranosyl)-4-(2-aminopyridin-3-yl)pyrazole	SARS-CoV-2 Mpro	-6.5
23	Tubercidin (7-deazaadenosine)	SARS-CoV-2 Mpro	-6.5
24	Sangivamycin	SARS-CoV-2 Mpro	-6.6
25	7-Methylguanosine 5'-diphosphate (m7GDP)	SARS-CoV-2 Mpro	-6.7
26	**7-Methylguanosine 5'-triphosphate (m7GTP)**	**SARS-CoV-2 Mpro**	**-7.6**
27	Ribosylthymine-pseudouridine-cytidine-guanosine tetranucleotide phosphate	SARS-CoV-2 Mpro	-8.1
28	[N2-Isobutyryl-N4-p-nitrophenylethyl N-trityl-morpholino guanosine] phosphate	SARS-CoV-2 Mpro	-7.8

a Docking was performed with AutoDock Vina 1.1.2 through PyRx at exhaustiveness 8 (grid centre x = 10.99, y = -0.28, z = 12.05 Å; search volume 7.69 × 23.96 × 25.0 Å). Nine binding modes were generated for each ligand and the score of the best-scoring mode is reported. Compound numbering corresponds to the chemical structures shown in Figure 1 of the main text and does not reflect the docking rank.

b Compound 26, 7-methylguanosine 5′-triphosphate (shown in bold), is the lead compound carried into the molecular dynamics simulations reported in the main text. Compounds 27 and 28 are protected oligonucleotide synthetic intermediates above 1300 Da bearing trityl, nitrophenylethyl and isobutyryl protecting groups.

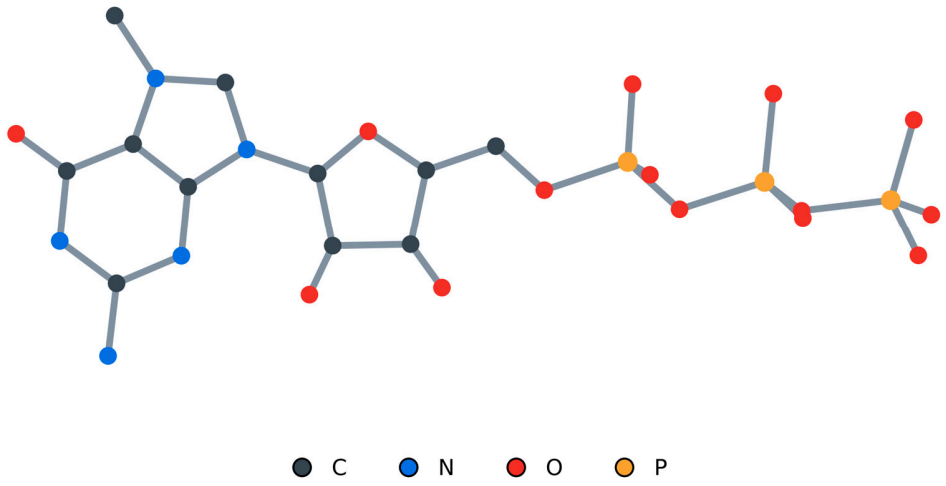
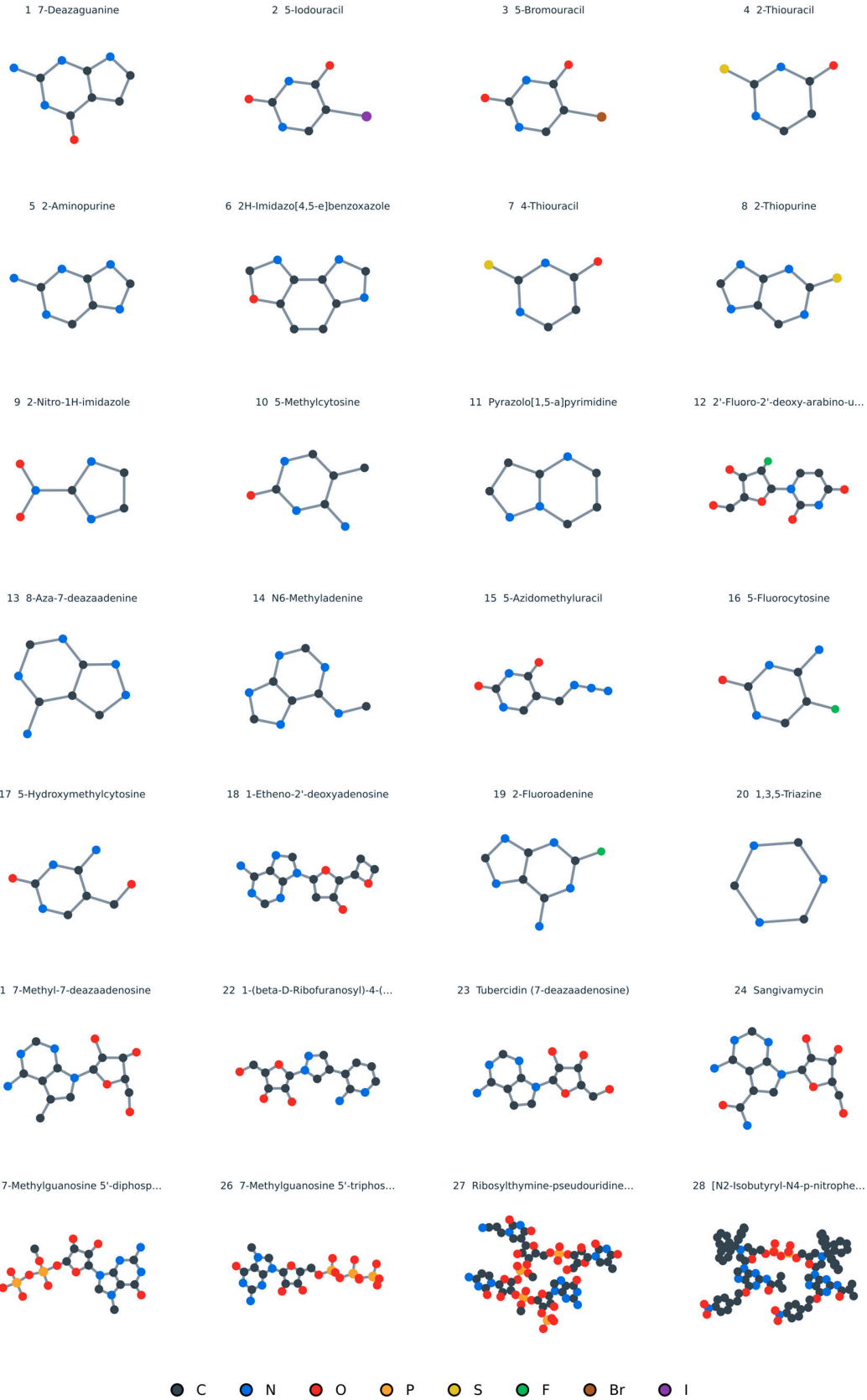


Figure S1. Ball-and-stick representation of the input structure of 7-methylguanosine 5′-triphosphate (m^7GTP, Compound 26), the ligand carried into the molecular dynamics simulations. Heavy atoms are coloured by element and bond connectivity was inferred from interatomic distances. Hydrogen atoms are omitted for clarity. Coordinates are those of the prepared ligand file used for docking.


1 7-Deazaguanine
2 5-Iodouracil
3 5-Bromouracil
4 2-Thiouracil
5 2-Aminopurine
6 2H-Imidazo[4,5-e]benzoxazole
7 4-Thiouracil
8 2-Thiopurine
9 2-Nitro-1H-imidazole
10 5-Methylcytosine
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14 N6-Methyladenine
15 5-Azidomethyluracil
16 5-Fluorocytosine
17 5-Hydroxymethylcytosine
18 1-Etheno-2'-deoxyadenosine
19 2-Fluoroadenine
20 1,3,5-Triazine
21 7-Methyl-7-deazaadenosine
22 1-(beta-D-Ribofuranosyl)-4-(...
23 Tubercidin (7-deazaadenosine)
24 Sangivamycin
25 7-Methylguanosine 5'-diphosp...
26 7-Methylguanosine 5'-triphos...
27 Ribosylthymine-pseudouridine...
28 [N2-Isobutyryl-N4-p-nitrophe...
C
N
O
P
S
F
Br
I

Figure S2. Ball-and-stick representations of the input structures of all 28 investigated compounds, numbered as in Table S1. Heavy atoms are coloured by element and bond connectivity was inferred from interatomic distances; hydrogen atoms are omitted for clarity. Structures are shown in the conformations submitted to docking and are projected onto their principal plane, so apparent bond lengths and angles are foreshortened to differing extents between panels.