Table S1. List of the M^{pro} protein ligand-complexes used for this study. The name of the complex is composed by its PDB name and by the PDB code of the ligand small molecule crystallized within. For each system, it is also reported if the ligand is crystallized inside or outside the orthosteric binding pocket.

Protein-ligand complex	Ligand IN/OUT of the catalytic pocket	Protein-ligand complex	Ligand IN/OUT of the catalytic pocket	Protein-ligand complex	Ligand IN/OUT of the catalytic pocket
5R7Y-JFM	IN	7AVD-S1W	IN	5REA-JGP	OUT
5R7Z-HWH	IN	7AWU-S8B	IN	5REC-T1J	OUT
5R80-RZG	IN	7B83-PK8	IN	5RED-JJG	OUT
5R81-RZJ	IN	7CA8-FNO	IN	5REE-T1M	OUT
5R82-RZS	IN	7JU7-G65	IN	5REF-6SU	OUT
5R83-K0G	IN	7KX5-X7V	IN	5REG-LWA	OUT
5R84-GWS	IN	7L0D-0EN	IN	5REI-T1S	OUT
5RE4-SZY	IN	7L10-XEY	IN	5RF0-T5D	OUT
5RE9-LPZ	IN	7L11-XF1	IN	5RF4-T5Y	OUT
5REB-T0Y	IN	7L12-XF4	IN	5RF5-HV2	OUT
5REH-AWP	IN	7L13-XF7	IN	5RF8-SFY	OUT
5REZ-T54	IN	7L14-XFD	IN	5RF9-S7D	OUT
5RF1-T5G	IN	7L5D-XNJ	IN	5RFA-JGY	OUT
5RF2-HVB	IN	7LDL-XV4	IN	5RFB-K3S	OUT
5RF3-T5V	IN	7LFE-XWS	IN	5RFC-K1Y	OUT
5RF6-NTG	IN	7LMD-Y6A	IN	5RFD-T6J	OUT
5RF7-T67	IN	7LME-Y6J	IN	5RGG-NZD	OUT
5RFE-JGG	IN	7LMF-Y6G	IN	5RGJ-U0S	OUT
5RG1-T9J	IN	7LTJ-YD1	IN	5RGQ-U1V	OUT
5RGH-U0M	IN	7M8M-YSG	IN	5RGS-S7V	OUT
5RGI-U0P	IN	7M8N-YSP	IN	5RH4-UHG	OUT
5RGK-U0V	IN	7M8O-YSM	IN	6YVF-A82	OUT
5RGU-UGD	IN	7M8P-YSJ	IN	7ABU-R6Q	OUT
5RGV-UGG	IN	7M8X-YTJ	IN	7AF0-R9W	OUT
5RGW-UGM	IN	7M8Y-YTM	IN	7AGA-LZE	OUT
5RGX-UGP	IN	7M8Z-YTV	IN	7AMJ-RMZ	OUT
5RGY-UGS	IN	7M90-YTS	IN	7AOL-RQH	OUT
5RGZ-UH1	IN	7M91-YU4	IN	7AQI-QEL	OUT
5RH0-UH4	IN	7MPB-ASC	IN	7AWR-S7W	OUT
5RH1-UGV	IN	7N44-06I	IN	7AWW-CLU	OUT
5RH2-UH7	IN	7N8C-YD1	IN	7AXM-93J	OUT
5RH3-UHA	IN	7NT3-UQZ	IN	7AXO-QCP	OUT
5RH8-UHM	IN	7NUK-USH	IN	7KVL-X4P	OUT
5RHD-US7	IN	7P51-5P9	IN	7KVR-X4V	OUT
6M2N-3WL	IN	7S3K-Z26	IN	7KW5-X4Y	OUT
6W63-X77	IN	7S3S-860	IN	7LDX-R9V	OUT
6W79-X77	IN	7S4B-87H	IN	7LFP-XY4	OUT
7A1U-FUA	IN	5RE5-T0J	OUT		
7ANS-RNW	IN	5RE6-O0S	OUT		
7AP6-RQN	IN	5RE7-T0S	OUT		
7AQE-RV5	IN	5RE8-T0V	OUT		

Table S2. Table showing the result of the solvent exposure analysis for each M^{pro} crystallographic ligand. The pose considered for the calculation was the crystallographic one. The name of the complex is composed by its PDB name and from the PDB code of the ligand small molecule crystallized within. For each system, it is also reported if the ligand is located inside or outside the orthosteric binding pocket.

Protein-ligand complex	Ligand IN/OUT of the catalytic pocket	Percentage of ligand surface area exposed to the solvent
5R7Y-JFM	IN	16,94
5R7Z-HWH	IN	19,16
5R80-RZG	IN	15,57
5R81-RZJ	IN	18,94
5R82-RZS	IN	19,11
5R83-K0G	IN	8,99
5R84-GWS	IN	7,18
5RE4-SZY	IN	13,64
5RE9-LPZ	IN	46,21
5REB-T0Y	IN	19,78
5REH-AWP	IN	51,67
5REZ-T54	IN	16,61
5RF1-T5G	IN	18,89
5RF2-HVB	IN	18,08
5RF3-T5V	IN	13,80
5RF6-NTG	IN	17,35
5RF7-T67	IN	10,46
5RFE-JGG	IN	24,08
5RG1-T9J	IN	13,87
5RGH-U0M	IN	13,30
5RGI-U0P	IN	12,83
5RGK-U0V	IN	51,80
5RGU-UGD	IN	8,71
5RGV-UGG	IN	19,31
5RGW-UGM	IN	9,91
5RGX-UGP	IN	9,81
5RGY-UGS	IN	35,21
5RGZ-UH1	IN	6,98
5RH0-UH4	IN	8,93
5RH1-UGV	IN	11,18
5RH2-UH7	IN	12,30
5RH3-UHA	IN	11,67
5RH8-UHM	IN	12,74
5RHD-US7	IN	17,24
6M2N-3WL	IN	3,69
6W63-X77	IN	15,01
6W79-X77	IN	17,64
7A1U-FUA	IN	35,39
7ANS-RNW	IN	10,39
7AP6-RQN	IN	12,92
7AQE-RV5	IN	17,46
7AVD-S1W	IN	34,92
7AWU-S8B	IN	39,39
7B83-PK8	IN	27,91
7CA8-FNO	IN	18,17
7JU7-G65	IN	22,89
7KX5-X7V	IN	14,10
7L0D-0EN	IN	13,87

7L10-XEY	IN	16,80
7L11-XF1	IN	13,15
7L12-XF4	IN	11,99
7L13-XF7	IN	16,68
7L14-XFD	IN	13,15
7L5D-XNJ	IN	24,72
7LDL-XV4	IN	18,35
7LFE-XWS	IN	13,16
7LMD-Y6A	IN	13,89
7LME-Y6J	IN	14,81
7LMF-Y6G	IN	13,35
7LTJ-YD1	IN	12,08
7M8M-YSG	IN	12,68
7M8N-YSP	IN	15,94
7M8O-YSM	IN	16,77
7M8P-YSJ	IN	15,81
7M8X-YTJ	IN	14,90
7M8Y-YTM	IN	17,74
7M8Z-YTV	IN	15,02
7M90-YTS	IN	15,90
7M91-YU4	IN	12,54
7MPB-ASC	IN	18,89
7N44-06I	IN	9,48
7N8C-YD1	IN	12,33
7NT3-UQZ	IN	20,25
7NUK-USH	IN	18,05
7P51-5P9	IN	15,67
7S3K-Z26	IN	18,78
7S3S-860	IN	15,57
7S4B-87H	IN	15,62
5RE5-T0J	OUT	49,62
5RE6-O0S	OUT	48,87
5RE7-T0S	OUT	38,26
5RE8-T0V	OUT	45,35
5REA-JGP	OUT	70,12
5REC-T1J	OUT	51,69
5RED-JJG	OUT	51,99
5REE-T1M	OUT	33,11
5REF-6SU	OUT	30,60
5REG-LWA	OUT	38,49
5REI-T1S	OUT	56,22
5RF0-T5D	OUT	52,50
5RF4-T5Y	OUT	44,20
5RF5-HV2	OUT	26,78
5RF8-SFY	OUT	60,90
5RF9-S7D	OUT	31,73
5RFA-JGY	OUT	13,99
5RFB-K3S	OUT	51,17
5RFC-K1Y	OUT	49,15
5RFD-T6J	OUT	49,80
5RGG-NZD	OUT	49,33
5RGJ-U0S	OUT	50,88
5RGQ-U1V	OUT	2,48
5RGS-S7V	OUT	31,97

5RH4-UHG	OUT	55,52
6YVF-A82	OUT	51,50
7ABU-R6Q	OUT	59,53
7AF0-R9W	OUT	76,15
7AGA-LZE	OUT	28,37
7AMJ-RMZ	OUT	61,11
7AOL-RQH	OUT	54,82
7AQI-QEL	OUT	58,98
7AWR-S7W	OUT	48,45
7AWW-CLU	OUT	53,95
7AXM-93J	OUT	62,58
7AXO-QCP	OUT	48,20
7KVL-X4P	OUT	40,90
7KVR-X4V	OUT	61,16
7KW5-X4Y	OUT	34,07
7LDX-R9V	OUT	29,89
7LFP-XY4	OUT	38,64

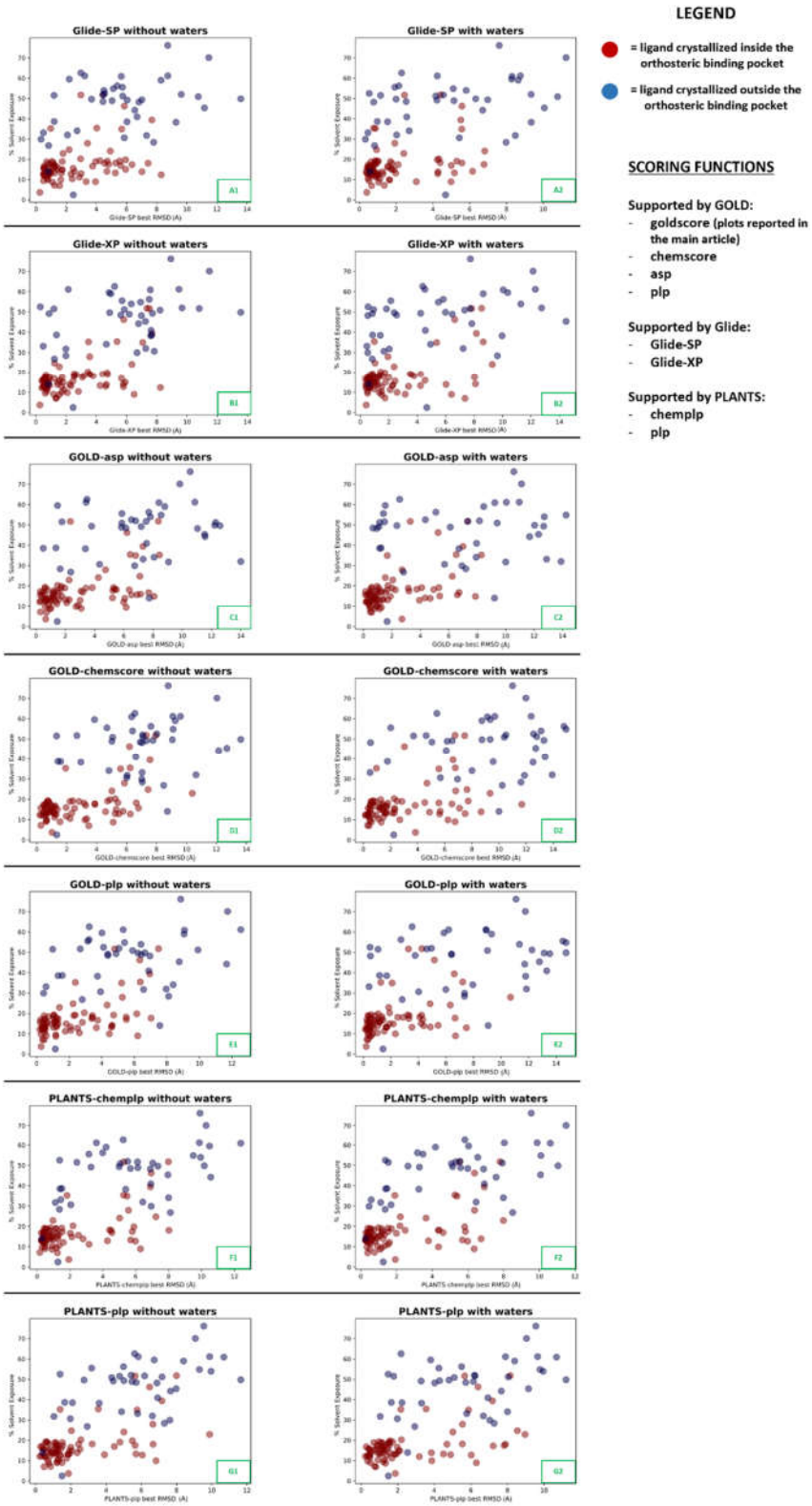

Figure S1. Scatter plots showing the different distribution of the RMSD values between the coordinates of the best pose from the different docking program-scoring function pairs (coming from the molecular docking experiments executed in this study) in function of the solvent exposure of the crystallographic ligand conformation. Each couple of plots (indicated with the same capital letter in green) represents the outcomes in the two "scenarios" considered, so all the graphs marked with number "1" correspond to the docking experiments in which the crystallographic water molecules were not considered in the calculation, while the plots with number "2" show the results for the case in which also water molecules 5 Å or nearer to the ligand are considered in the docking runs. In each plot, the x-axis represents the RMSD value between the coordinates of the best pose given by the docking experiment for a ligand in comparison with the coordinates of its crystallographic conformation. The y-axis represents the exposure to the solvent of the crystallographic ligand pose. The red dots represent the ligands that are originally crystallized inside the catalytic pocket, while the blue dots represent the ligands crystallized in the other parts of M^{pro}. As can be noticed, in all the plots the molecules showing the best values of RMSD are tendentially located inside the orthosteric pocket and characterized by a low solvent exposure of the original crystallographic pose.