Supplementary material for

How accurate are continuum solvation models for drug-like molecules?

by Jacob Kongsted, Pär Söderhjelm, & Ulf Ryde

References (with the same numbering as in the main paper):

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Table S1. Molecules in the calibration set, together with experimental free energies of solvation (ΔG_{solv}, in kJ/mol).

Molecules	ΔG_{solv}	Reference
water, H_2O	-26.40	35
methanol, CH_3OH	-21.38	35
ethanol, CH_3CH_2OH	-20.96	35
para-cresol, *p*-$CH_3C_6H_4OH$	-25.69	35
ammonia, NH_3	-17.95	35
methylamine, CH_3NH_2	-19.08	35
acetamide, CH_3CONH_2	-40.63	35
propionamide	-39.25	35
methane, CH_4	8.37	35
propane, $CH_3CH_2CH_3$	8.20	35
n-butane	8.70	35
isobutane	9.71	35
toluene	-3.72	35
metanthiol, CH_3SH	-5.19	35
methyl-ethyl-thioether, $CH_3SCH_2CH_3$	-6.19	56
3-methylindole	-24.60	56
4-methylimidazole	-42.97	56
N-propyl guanidine	-45.69	19
trifluoroethanol, CF_3CH_2OH	-18.03	35
o-chloro toluene, $ClC_6H_4CH_3$	-4.81	35
H_3O^+	-461.5	57
$CH_3OH_2^+$	-389.1	57
$CH_3NH_3^+$	-319.7	57
$(CH_3)_2NH_2^+$	-287.0	57
$(CH_3)_3NH^+$	-255.6	57
$C_6H_5NH_3^+$	-302.9	57
$CH_3COHNH_2^+$	-309.2	57
$CH_3SHCH_3^+$	-269.9	57
imidazoleH$^+$	-248.9	57
pyridineH$^+$	-255.6	37[a]
OH^-	-438.1	57
CH_3O^-	-397.5	57
m-$CH_3C_6H_4O^-$	-297.5	57
$HCOO^-$	-318.8	57
CH_3COO^-	-324.7	57
$C_6H_5COO^-$	-297.9	57
CH3COCH2$^-$	-318.8	57
CH_3CONH^-	-335.6	57
$C_6H_5NH^-$	-263.2	57
CH_3S^-	-308.8	57

[a] 18.8 kJ/mol was added to the value in ref.37 to use the same value of the absolute solvation energy of a proton as in ref. no. 57.

Table S2. Description of the 20 neutral drug-like molecules. The identifier, name, chemical formula, molecular weight, and starting structure (a PDB structure or conformational search) are listed.

Name	Formula	Mol. Weight	Starting structure
061 (a biphenyl tetrazole)	$C_{26}H_{24}N_6O_2$	452.5	1a8t
caffeine	$C_8H_{10}N_4O_2$	194.2	conformation search
cannabidiol	$C_{21}H_{30}O_2$	314.5	conformation search
TPD (disulphonamide)	$C_9H_{10}N_2O_4S_4$	338.4	1bnw
efavirenz	$C_{14}H_9ClF_3NO_2$	215.7	1jkh
ethoxyresorufin	$C_{14}H_{11}NO_3$	241.3	conformation search
Gal3	$C_{23}H_{30}F_4N_2O_{12}$	602.5	2nn8
MXA (methotrexate analogue)	$C_6H_{14}O_2$	325.4	1dlr
omeprazole	$C_{17}H_{19}N_3O_3S$	345.4	conformation search
paclitaxel (taxol)	$C_{47}H_{51}NO_{14}$	853.9	1jff
paracetamol	$C_8H_9NO_2$	151.2	conformation search
phenolphtalein	$C_{20}H_{14}O_4$	318.3	conformation search
phenylbutazone	$C_{19}H_{20}N_2O_2$	308.4	2bxq
progesterone	$C_{21}H_{30}O_2$	314.5	[90]
quercetin	$C_{15}H_{10}O_7$	302.2	2o3p
R-thalidomide	$C_{13}H_{10}N_2O_4$	258.2	conformation search
SB3 (a diphenyl piperidine)	$C_{28}H_{35}NO_4$	449.6	1fkg
S-warfarin	$C_{19}H_{16}O_4$	308.3	1og5
thiabendazole	$C_{10}H_7N_3S$	201.2	1yvm
Btn4	$C_{13}H_{20}N_2O_5S$	316.4	1avd

Table S3. Free energies of hydration (kJ/mol) calculated for the various molecules in the test set and with the various theoretical methods. The PCM methods are 1 – IEFPCM/UAHF, 2 – DPCM/UAHF, 3 – IEFPCM/UAKS, 4 – DPCM/UAHF, but with 6-31+G* on all atoms. The PB methods are 1 – FF94/Tan2, 2 – FF94/Tan1, 3 – FF94/mbondi, 4 – FF94/Parse, 5 – FF03/Tan2, 6 – MK/Tan2, 7 – MK/mbondi. The GB methods are 1 – GB^{HCT}/FF94/mbondi, 2 – GB^{HCT}/FF03/mbondi, 3 – GB^{HCT}/MK/mbondi, 4 – GB^{OBC1}/FF94/mbondi, 5 – GB^{OBC2}/FF94/mbondi, 6 – GBn/FF94/mbondi, 7 – GBn/FF03/mbondi, 8 – GBn/MK/mbondi, 9 – GBn/FF94/Tan2, 10 – GB*n*/FF94/Tan1, 11 – GBn/FF94/Parse.

Molecule	PCM					Chem	PB							GB									
	1	2	3	4		Sol	1	2	3	4	5	6	7	1	2	3	4	5	6	7	8	9	10	11
H_2O	-26.4	-26.7	-26.4	-24.1	-25.1	-23.3	-33.4	-24.5	-25.8	-53.4	-45.0	-22.3	-24.5	-53.4	-56.2	-52.0	-56.2	-37.7	-36.5	-30.0	-27.6	-30.0	-28.6	-29.9
CH_3OH	-21.4	-21.1	-21.5	-19.3	-20.0	-18.6	-21.5	-13.1	-12.0	-34.7	-28.3	-12.1	-11.9	-33.3	-30.7	-29.1	-29.4	-24.7	-22.9	-19.6	-17.6	-18.5	-20.3	-19.2
CH_3CH_2OH	-21.0	-21.9	-22.4	-20.4	-21.3	-19.5	-17.4	-9.2	-8.5	-29.1	-24.2	-9.0	-9.0	-29.0	-25.4	-25.0	-25.0	-19.9	-17.9	-14.6	-13.8	-14.9	-14.7	-14.0
p-$CH_3C_6H_4OH$	-25.7	-26.7	-26.2	-24.1	-25.3	-21.9	-23.9	-19.7	-12.6	-34.5	-34.9	-18.7	-19.7	-34.6	-32.1	-31.0	-32.3	-27.0	-24.4	-24.2	-21.7	-24.3	-30.5	-23.5
NH_3	-17.9	-18.2	-18.2	-17.5	-18.3	-16.7	-17.7	-11.0	-10.5	-23.1	-35.4	-8.0	-11.0	-23.1	-33.3	-26.3	-33.3	-35.2	-34.0	-24.5	-19.1	-24.5	-25.0	-24.5
CH_3NH_2	-19.1	-19.6	-20.0	-19.2	-19.9	-18.2	-11.0	-6.9	-5.9	-17.6	-23.9	-5.6	-16.8	-16.4	-18.9	-15.9	-18.0	-24.9	-22.5	-17.9	-15.2	-16.9	-18.6	-17.7
CH_3CONH_2	-40.6	-39.8	-39.3	-37.7	-39.4	-36.4	-43.6	-38.2	-33.3	-38.7	-56.8	-43.5	-37.9	-38.5	-42.8	-46.0	-42.7	-50.3	-46.6	-47.9	-52.1	-47.8	-52.2	-47.4
propionamide	-39.2	-38.2	-38.0	-36.4	-38.4	-35.1	-38.7	-31.9	-27.5	-33.6	-49.7	-36.4	-32.6	-34.5	-36.6	-38.8	-37.8	-43.6	-40.1	-41.0	-44.3	-42.0	-45.0	-40.6
CH_4	8.4	7.8	4.7	4.6	4.5	4.7	7.7	11.6	7.2	6.1	5.8	11.6	11.5	6.0	3.7	3.7	3.6	4.0	3.9	5.9	5.9	5.9	11.0	6.6
propane	8.2	8.3	8.2	8.1	7.9	8.2	8.7	12.7	9.2	8.4	8.0	12.7	12.6	8.2	7.9	7.9	7.6	7.3	7.5	8.1	8.0	8.0	12.3	8.8
n-butane	8.7	8.9	8.9	8.7	8.6	8.9	9.2	13.0	10.0	9.0	8.8	13.0	12.9	8.7	8.1	8.3	7.4	7.5	7.6	8.5	8.4	8.0	12.5	9.5
isobutane	9.7	10.0	9.9	9.8	9.6	10.0	8.7	11.6	9.2	7.5	6.8	11.7	11.8	7.6	5.6	6.0	6.1	4.4	4.7	8.5	8.3	8.4	11.8	9.3
toluene	-3.7	-4.5	-4.5	-3.9	-4.2	-2.1	-6.1	-2.5	0.6	-5.7	-10.8	-1.3	-2.5	-5.8	-5.6	-4.1	-5.7	-9.2	-7.8	-8.8	-6.8	-8.9	-11.1	-8.0
CH_3SH	-5.2	-5.4	-5.7	-6.1	-6.0	-5.4	-4.7	-3.3	-1.2	-10.3	-7.8	-3.8	-2.8	-9.8	-8.6	-9.4	-8.1	-7.6	-6.9	-6.8	-7.5	-6.4	-8.5	-6.4
$CH_3SC_2H_5$	-6.2	-7.0	-7.6	-7.6	-7.6	-6.7	-3.9	1.0	1.9	-1.2	-2.1	0.0	-0.7	-3.6	-0.4	-1.5	-3.3	-2.6	-1.9	-1.5	-2.9	-4.2	-1.7	-0.8
3-methylindol	-24.6	-20.8	-20.6	-24.2	-25.6	-20.8	-24.9	-21.0	-12.7	-22.1	-35.3	-21.9	-21.0	-22.2	-22.0	-22.6	-22.2	-28.1	-25.3	-30.6	-30.9	-30.8	-38.2	-30.0
4-methyl-imidazole	-43.0	-38.4	-37.7	-41.5	-43.1	-39.2	-34.2	-32.0	-25.0	-35.2	-48.6	-37.3	-31.4	-34.6	-36.5	-42.3	-36.0	-42.7	-39.5	-46.5	-52.5	-45.9	-52.6	-45.6
N-propyl guanidine	-45.7	-45.1	-42.0	-39.4	-40.6	-36.9	-24.2	-14.4	-7.9	-36.9	-60.6	-29.4	-14.9	-37.0	-34.5	-32.0	-35.1	-42.3	-36.1	-43.8	-42.2	-44.0	-49.8	-43.2
CF_3CH_2OH	-18.0	-25.4	-25.9	-21.5	-21.3	-20.7	-22.8	-19.8	-17.5	-35.6	-30.9	-18.7	-19.1	-34.8	-34.7	-32.2	-33.3	-26.4	-23.4	-29.0	-24.7	-28.4	-30.7	-28.4
o-Cl-toluene	-4.8	-3.2	-3.3	-2.3	-2.5	-0.5	-7.2	-8.1	-1.4	-4.3	-8.5	-6.9	-8.0	-4.4	-4.8	-3.4	-4.9	-8.3	-7.0	-8.9	-6.9	-9.0	-14.8	-8.1
H_3O^+	-461.5	-442.2	-444.5	-441.6	-447.7	-441.1	-411.7	-407.3	-408.6	-509.2	-455.0	-402.8	-407.4	-509.2	-554.6	-546.4	-554.7	-402.7	-394.4	-376.3	-375.7	-376.3	-375.1	-376.4
$CH_3OH_2^+$	-389.1	-360.8		-370.2	-371.8	-379.7	-371.1	-336.6	-297.2	-296.3	-383.6	-347.5	-303.0	-297.2	-383.7	-402.8	-411.5	-402.9	-326.3	-320.6	-310.0	-314.6	-310.1	-310.7	-309.9
$CH_3NH_3^+$	-319.7	-293.5	-296.0	-296.2	-297.5	-296.1	-310.7	-245.3	-242.3	-301.9	-302.3	-247.3	-245.3	-301.8	-293.2	-296.8	-293.2	-303.8	-298.4	-317.2	-321.7	-317.2	-320.4	-317.3
$(CH_3)_2NH_2^+$	-287.0	-270.8	-274.1	-274.2	-275.7	-274.2	-283.4	-237.9	-233.4	-265.8	-274.0	-239.4	-238.1	-267.0	-258.8	-262.2	-260.4	-272.1	-267.1	-282.3	-286.7	-283.7	-286.8	-282.3
$(CH_3)_3NH^+$	-255.6	-244.8	-247.8	-247.9	-249.5	-247.8	-262.8	-227.3	-222.1	-237.6	-254.3	-227.9	-227.3	-239.0	-229.0	-230.5	-231.0	-243.5	-238.6	-250.5	-252.4	-252.8	-255.3	-250.1
$C_6H_5NH_3^+$	-302.9	-268.4	-269.7	-267.6	-268.9	-265.7	-282.3	-226.6	-219.2	-260.8	-279.7	-233.2	-226.7	-260.8	-246.4	-257.3	-246.3	-257.0	-250.5	-278.4	-290.4	-278.5	-285.2	-277.9
$CH_3COHNH_2^+$	-309.2	-285.3	-284.7	-282.0	-284.1	-281.4	-286.0	-240.3	-235.5	-300.3	-313.7	-246.5	-241.0	-302.2	-299.8	-297.3	-301.7	-281.8	-275.1	-289.8	-286.5	-290.7	-294.1	-289.2
$CH_3SHCH_3^+$	-269.9	-256.6	-257.2	-257.1	-259.5	-255.8	-262.8	-238.7	-236.9	-270.5	-266.9	-240.5	-237.9	-269.3	-262.4	-266.8	-261.1	-260.3	-255.4	-270.5	-272.7	-269.6	-271.9	-270.1
imidazoleH$^+$	-248.9	-259.5	-261.5	-273.4	-275.1	-272.0	-272.5	-250.2	-241.2	-257.6	-298.6	-249.4	-250.2	-257.6	-256.3	-257.0	-256.3	-269.3	-265.4	-281.5	-281.7	-281.5	-290.1	-281.1
pyridineH$^+$	-255.6	-233.9	-234.9	-241.2	-242.1	-240.0	-257.4	-230.0	-223.9	-237.2	-268.3	-230.8	-230.0	-237.2	-235.3	-237.8	-235.3	-248.2	-244.7	-255.7	-257.8	-255.8	-261.3	-255.2
OH^-	-438.1	-452.4	-440.8	-455.3	-429.1	-452.2	-455.7	-368.9	-370.2	-464.7	-499.9	-371.8	-368.9	-464.7	-491.0	-496.8	-491.0	-497.3	-496.1	-481.8	-488.6	-481.8	-480.3	-481.6
CH_3O^-	-397.5	-393.0	-368.9	-355.1	-347.6	-352.3	-375.0	-304.5	-303.5	-367.2	-381.4	-305.9	-304.5	-367.1	-363.0	-365.4	-363.0	-384.5	-378.0	-376.9	-379.9	-376.9	-377.4	-376.4
m-$CH_3C_6H_4O^-$	-297.5	-298.5	-279.4	-263.6	-265.6	-259.6	-312.0	-236.1	-229.6	-285.3	-299.0	-244.2	-236.1	-285.4	-288.7	-298.6	-289.0	-299.6	-293.7	-297.6	-307.3	-298.0	-303.4	-296.9
$HCOO^-$	-318.8	-321.7	-311.3	-303.2	-296.8	-302.4	-361.4	-411.4	-405.9	-341.7	-364.4	-408.3	-411.5	-341.7	-348.0	-347.4	-348.0	-360.8	-355.2	-356.8	-355.8	-356.8	-361.7	-356.2
$CH_3COO–$	-324.7	-328.6	-315.7	-304.7	-301.1	-303.4	-357.6	-393.4	-388.7	-334.1	-354.8	-398.9	-393.4	-334.2	-339.3	-343.3	-339.4	-351.3	-345.5	-344.7	-349.2	-344.7	-348.7	-344.1
$C_6H_5COO^-$	-297.9	-304.8	-287.5	-271.9	-274.3	-269.6	-330.1	-353.6	-342.9	-304.2	-325.4	-371.0	-353.7	-304.3	-305.7	-320.0	-305.8	-318.8	-311.9	-317.9	-331.8	-317.9	-327.9	-317.2
CH3COCH2$^-$	-318.8	-271.5	-263.3	-266.1	-263.8	-264.2	-331.1	-286.1	-285.3	-319.9	-333.7	-290.3	-286.6	-320.9	-331.6	-337.3	-333.0	-340.9	-335.8	-322.6	-327.0	-323.4	-322.6	-321.8
CH_3CONH^-	-335.6	-311.2	-301.5	-291.7	-291.7	-288.6	-329.8	-298.4	-294.0	-337.8	-357.0	-300.4	-298.5	-337.8	-345.0	-346.0	-345.0	-359.8	-352.6	-345.4	-346.4	-345.4	-349.2	-344.9
$C_6H_5NH^-$	-263.2	-254.3	-251.0	-252.0	-253.0	-247.4	-293.7	-251.6	-245.1	-292.7	-302.7	-257.4	-255.6	-298.5	-296.0	-303.0	-302.5	-309.0	-302.1	-302.4	-309.0	-308.8	-308.3	-301.7
CH_3S^-	-308.8	-315.3	-297.0	-310.7	-291.8	-308.9	-310.6	-420.4	-418.8	-356.5	-343.3	-443.8	-420.4	-356.6	-362.3	-374.9	-362.3	-373.4	-369.1	-359.2	-371.8	-359.2	-360.3	-358.7

Table S4. Free energies of hydration (kJ/mol) calculated for the drug-like molecules with the various theoretical methods. Ch is the net charge of the molecule. The methods are the same as in Table S3.

Molecule	Ch	PCM					Chem	PB							GB											Av.
		1	2	3	4	5	Sol	1	2	3	4	5	6	7	1	2	3	4	5	6	7	8	9	10	11	
061	0	-64.6	-59.8	-59.7	-61.6	-55.9	-88.9	-99.9	-66.4	-111.4	-131.4	-105.9	-103.6	-117.2	-106.1	-114.7	-111.8	-110.1	-98.1	-126.4	-133.7	-135.3	-158.5	-125.0	-127.0	-76.0
caffeine	0	-39.7	-38.2	-36.2	-36.4	-35.2	-53.1	-63.4	-43.2	-55.5	-70.3	-62.3	-62.5	-54.6	-50.9	-50.4	-50.3	-63.9	-58.3	-63.5	-62.8	-63.3	-83.1	-62.8	-63.8	-44.1
cannabidiol	0	-8.6	-5.1	-4.0	-6.9	-0.4	-25.2	-18.9	-10.6	-39.1	-44.5	-19.9	-20.1	-44.0	-43.2	-46.2	-48.7	-34.4	-30.0	-24.9	-25.6	-28.1	-31.6	-23.3	-25.4	-12.4
TPD	0	-84.5	-87.9	-81.5	-83.2	-78.3	-84.5	-192.0	-161.8	-88.9	-133.1	-178.3	-191.7	-89.4	-78.4	-69.7	-79.2	-93.6	-82.4	-119.1	-106.2	-120.2	-148.6	-118.5	-119.5	-92.4
efavirenz	0	-19.7	-22.7	-22.9	-24.9	-20.4	-51.6	-47.0	-30.7	-40.4	-57.9	-50.4	-47.2	-40.5	-41.7	-43.9	-41.7	-50.7	-45.7	-58.0	-58.5	-58.5	-73.4	-57.0	-58.1	-31.9
ethoxyresorufin	0	-37.5	-36.4	-32.2	-35.6	-30.5	-40.9	-49.7	-29.3	-40.0	-56.9	-54.7	-50.2	-40.6	-39.6	-43.9	-40.0	-50.8	-44.6	-58.6	-61.3	-59.4	-77.9	-57.5	-59.1	-39.4
MXA	0	-77.2	-73.8	-71.3	-74.9	-65.6	-70.6	-80.7	-50.8	-86.1	-117.3	-84.2	-80.1	-85.6	-75.7	-76.8	-75.3	-89.4	-77.7	-112.5	-113.3	-112.5	-141.6	-111.8	-112.9	-78.4
omeprazole	0	-33.2	-30.4	-33.3	-33.4	-29.6	-53.6	-72.7	-46.6	-66.0	-90.9	-71.7	-72.5	-65.6	-56.8	-56.0	-56.4	-70.7	-61.7	-86.8	-85.1	-87.1	-111.7	-85.5	-87.1	-44.3
paclitaxel[a]	0		36.6	48.5	48.3	52.0	-113.7	-134.3	-93.6	-166.7	-197.8	-125.5	-136.5	-171.5	-150.2	-133.7	-155.7	-137.2	-111.6	-103.0	-87.2	-102.6	-142.4	-101.6	-103.4	-6.3
paracetamol	0	-53.0	-52.0	-51.3	-54.2	-48.2	-57.4	-48.6	-36.9	-62.8	-73.2	-52.8	-52.0	-71.1	-61.2	-66.2	-69.6	-60.6	-55.4	-59.8	-63.3	-67.1	-70.8	-59.1	-60.2	-54.5
phenolphtalein	0	-60.9	-56.7	-50.2	-53.4	-45.6	-84.0	-80.9	-58.8	-101.4	-112.1	-84.6	-87.0	-115.6	-98.4	-103.5	-112.5	-90.7	-82.9	-89.6	-88.2	-99.3	-110.9	-88.8	-90.2	-65.1
phenylbutazone	0	-11.4	-11.5	-8.4	-9.3	-5.4	-46.4	-40.3	-27.8	-45.1	-62.9	-39.8	-41.1	-46.2	-43.0	-40.9	-43.9	-56.3	-50.4	-56.2	-52.6	-56.8	-67.3	-54.9	-56.9	-22.0
progesterone	0	-30.2	-30.0	-26.6	-30.0	-25.1	-54.7	-51.9	-32.6	-37.5	-49.1	-56.9	-51.2	-37.0	-36.2	-41.1	-36.2	-46.0	-42.3	-41.2	-46.8	-41.2	-59.4	-40.1	-41.5	-34.8
quercetin	0	-82.6	-75.1	-68.3	-69.0	-64.3	-69.2	-102.1	-68.1	-157.4	-145.2	-101.8	-102.5	-158.1	-161.1	-155.0	-162.1	-107.3	-95.6	-100.3	-93.1	-101.4	-133.7	-99.7	-100.8	-80.0
R-thalidomide	0	-57.4	-59.6	-58.3	-61.9	-56.3	-80.9	-80.9	-57.1	-78.0	-104.7	-79.5	-80.9	-77.8	-77.9	-76.9	-77.8	-94.2	-86.5	-93.9	-91.9	-93.8	-116.9	-93.0	-94.4	-67.7
SB3	0	33.0	36.3	36.5	34.9	40.0	-43.7	-37.2	-22.5	-37.2	-56.1	-34.1	-39.1	-39.9	-40.3	-34.0	-43.5	-53.3	-45.1	-46.8	-40.0	-50.3	-60.2	-45.5	-47.5	10.6
S-warfarin	0	-37.5	-36.4	-29.9	-29.8	-26.1	-76.0	-74.1	-55.8	-86.4	-97.8	-76.1	-74.5	-86.0	-85.3	-86.0	-85.5	-82.7	-74.3	-80.0	-78.9	-80.2	-97.3	-79.0	-80.6	-46.8
thiabendazole	0	-61.7	-59.1	-60.3	-62.3	-56.5	-56.9	-66.2	-44.7	-60.2	-81.8	-76.2	-66.3	-60.4	-58.2	-67.7	-58.4	-69.6	-63.0	-89.8	-100.3	-90.1	-110.4	-88.9	-90.1	-64.1
Btn1	-1	-379.4	-367.7	-344.1	-353.8	-339.7	-391.7	-416.9	-394.1	-350.5	-387.6	-445.2	-416.8	-350.4	-345.6	-367.1	-345.6	-363.8	-353.3	-363.3	-384.6	-363.5	-385.2	-362.4	-363.7	-365.4
Btn2	-1	-372.6	-375.3	-348.1	-362.4	-342.3	-397.1	-419.2	-397.7	-368.1	-407.5	-447.6	-418.4	-367.3	-361.5	-382.3	-361.1	-381.7	-369.6	-379.0	-399.1	-378.6	-399.9	-378.4	-379.4	-371.1
Btn3	-1	-350.8	-347.3	-324.9	-332.7	-321.5	-385.3	-406.5	-389.2	-346.7	-386.0	-426.9	-405.7	-345.7	-344.5	-362.6	-343.6	-363.2	-352.5	-359.6	-377.0	-358.7	-376.2	-358.9	-360.3	-348.6
Btn4	0	-78.5	-85.7	-80.1	-82.0	-77.3	-93.6	-85.4	-62.5	-85.6	-106.3	-92.7	-85.6	-86.0	-76.7	-82.8	-77.5	-93.8	-85.7	-88.4	-94.3	-89.7	-110.3	-87.4	-88.9	-84.0
Btn5	0	-56.7	-58.7	-54.3	-56.5	-51.1	-37.7	-34.6	-24.7	-46.1	-65.3	-43.6	-34.2	-45.8	-42.2	-46.3	-42.2	-50.2	-44.5	-51.3	-53.8	-51.1	-60.3	-50.4	-51.7	-52.2
Btn6	0	-44.1	-45.1	-41.3	-42.9	-39.8	-54.1	-38.9	-28.5	-37.8	-49.1	-50.4	-38.9	-37.8	-36.8	-41.5	-36.8	-43.3	-39.6	-41.6	-46.4	-41.6	-50.9	-40.5	-41.9	-43.8
Btn7	0	-61.7	-62.8	-61.4	-63.3	-59.2	-52.0	-52.6	-41.1	-43.0	-59.8	-59.2	-52.8	-43.3	-42.6	-48.8	-42.8	-48.6	-45.0	-51.8	-57.4	-52.1	-63.0	-51.4	-52.1	-58.8
FXa39	1		-273.7	-265.1	-246.3	-257.4	-321.2	-401.4	-370.0	-285.6	-343.4	-406.3	-407.8	-288.7	-274.1	-281.9	-277.4	-281.7	-266.8	-304.4	-309.5	-308.2	-334.7	-303.3	-304.9	-278.7
FXa57	1	-198.7	-194.8	-194.1	-194.8	-187.3	-246.9	-332.6	-300.2	-203.9	-269.6	-427.6	-346.5	-210.9	-201.4	-201.5	-209.3	-220.0	-206.7	-239.7	-237.1	-250.2	-271.3	-238.9	-240.4	-215.0
FXa63	1		-273.0	-266.6	-247.7	-258.8	-312.6	-394.2	-364.0	-280.0	-337.4	-399.8	-400.9	-283.5	-270.0	-278.5	-273.5	-276.7	-262.5	-298.9	-304.6	-303.2	-328.1	-298.0	-299.7	-277.4
FXa103	1	-262.8	-271.3	-265.5	-245.7	-257.7	-310.8	-394.4	-363.6	-279.5	-337.5	-400.3	-401.5	-283.1	-269.0	-277.8	-272.6	-276.1	-261.8	-298.4	-304.8	-302.8	-328.2	-297.4	-299.1	-276.7
FXa127	1	-229.3	-226.6	-226.3	-225.3	-221.4	-264.5	-357.0	-337.6	-226.6	-282.6	-366.0	-356.9	-226.9	-216.1	-227.9	-216.8	-233.9	-223.1	-253.3	-264.1	-254.0	-271.8	-252.4	-253.9	-240.0
FXa9	2	-589.4	-590.2	-589.3	-583.2	-582.0	-609.1	-848.9	-812.6	-569.8	-670.5	-850.7	-856.7	-572.6	-553.5	-568.1	-556.6	-578.5	-561.9	-625.6	-636.0	-630.1	-661.2	-624.8	-626.2	-605.9
FXa47	2	-598.0	-596.9	-595.8	-584.5	-587.9	-608.7	-833.7	-800.4	-569.9	-672.8	-839.9	-844.4	-573.4	-552.5	-567.4	-556.2	-578.3	-561.6	-622.8	-633.4	-627.6	-655.3	-622.0	-623.6	-608.6
FXa49	2	-596.8	-595.9	-600.3	-595.3	-593.3	-607.6	-838.8	-803.1	-577.2	-690.5	-838.7	-850.0	-581.7	-561.6	-567.5	-566.0	-590.1	-571.7	-634.5	-636.2	-640.4	-669.7	-634.0	-635.4	-613.5
FXa50	2	-628.1	-623.9	-620.4	-607.2	-611.2	-624.7	-861.0	-823.3	-611.3	-710.0	-867.4	-868.2	-614.4	-595.7	-608.3	-598.9	-608.1	-589.6	-651.6	-660.7	-655.3	-688.7	-651.0	-652.5	-634.1
FXa53	2	-602.3	-601.4	-600.2	-588.9	-592.3	-609.5	-836.8	-803.4	-573.7	-678.0	-843.0	-847.5	-577.5	-556.6	-571.2	-560.3	-582.9	-566.0	-628.3	-638.7	-633.4	-660.9	-627.6	-629.2	-612.7
FXa125	2	-586.6	-593.0	-591.1	-587.7	-583.9	-606.7	-842.5	-810.0	-572.5	-673.2	-840.5	-853.2	-575.4	-554.5	-566.5	-557.7	-581.2	-564.0	-623.8	-631.8	-628.4	-655.8	-623.3	-624.8	-606.5
lactose	0	-135.4	-139.7	-124.5	-132.8	-119.2	-98.8	-115.5	-84.4	-217.5	-191.3	-111.0	-116.2	-218.6	-178.5	-165.4	-179.9	-124.5	-106.5	-85.3	-80.0	-85.6	-116.0	-84.9	-85.9	-124.4
Gal2	0		-147.8	-129.5	-140.5	-123.8	-167.6	-142.9	-112.9	-208.9	-221.2	-146.3	-144.1	-212.1	-182.8	-177.8	-184.7	-159.2	-140.7	-134.0	-131.6	-136.0	-163.0	-133.0	-134.6	-142.7
Gal3	0		-143.3	-122.8	-134.1	-117.5	-171.2	-156.7	-123.6	-211.5	-228.1	-155.3	-157.1	-214.1	-188.0	-182.2	-191.3	-166.0	-146.8	-148.4	-143.4	-149.0	-180.0	-146.9	-148.8	-141.2
Gal4	0		-142.7	-121.1	-129.5	-116.3	-163.8	-151.8	-120.9	-207.1	-221.8	-151.9	-149.4	-209.8	-185.2	-180.3	-188.3	-161.4	-142.7	-145.7	-141.9	-146.4	-175.2	-144.4	-146.3	-137.9
Gal5	0		-147.2	-127.7	-134.9	-122.4	-169.7	-154.7	-124.5	-214.7	-226.7	-155.6	-152.1	-215.5	-188.8	-184.1	-189.7	-164.5	-145.3	-146.9	-144.0	-146.1	-176.1	-145.9	-147.7	-142.9
Gal6	0		-147.5	-132.3	-139.3	-126.1	-161.2	-148.2	-117.3	-208.8	-223.9	-151.5	-148.7	-211.4	-184.8	-179.9	-186.5	-161.6	-142.4	-139.8	-136.9	-141.5	-169.5	-138.7	-140.5	-143.4

Table S5. MADs for the solvation free energies of the drug-like molecules for each method, calculated relative to the plain average (cf. Table 4 that gives the same results for the method-weighted average). The MADs were calculated either for the 20 neutral drug-like molecules, for all molecules in the three series (avidin, factor Xa, or galectin-3 inhibitors; called "All 3" in the Table), or individually for these three targets (avidin, FXa, and Gal). Moreover, the MADs were calculated for the relative solvation energies, either separately for the avidin, factor Xa, and galectin-3 inhibitors (Target), or separately for each total charge in these three series (Charge; in this case, lactose was omitted from the galectin-3 series).

Method	Neutral	3 Inhibitors				Target	Charges
	drugs	All 3	Avidin	FXa	Gal	All 3	All 3
DPCM/HF	22.3	26.3	8.3	42.6	6.3	6.5	7.2
IEFPCM/HF	28.8	24.2	7.6	40.8	13.0	8.7	4.0
IEFPCM/PBE0/HF	32.8	31.9	17.7	43.1	27.9	11.0	4.4
IEFPCM/PBE0/PBE0	30.4	33.3	13.5	52.9	20.2	10.2	5.5
IEFPCM/B3LYP	36.1	37.2	19.5	50.5	33.3	11.3	4.4
ChemSol	10.6	16.5	12.2	22.0	11.3	18.1	3.8
PB/FF94/Tan2	10.6	77.0	20.2	150.2	9.2	34.5	3.7
PB/FF94/Tan1	22.3	69.8	19.2	118.1	40.2	32.2	4.7
PB/FF94/mbondi	14.8	39.7	10.1	49.0	57.2	14.3	3.2
PB/FF94/Parse	27.5	36.6	16.2	34.2	64.7	7.4	3.7
PB/FF03/Tan2	9.7	86.3	32.3	162.8	8.9	34.4	8.3
PB/MK/Tan2	10.2	80.9	20.0	158.6	9.6	35.1	3.4
PB/MK/mbondi	17.0	38.7	10.3	45.4	59.4	14.5	3.1
GB^{HCT}/FF94/mbondi	14.8	40.2	14.1	62.2	30.5	16.2	2.5
GB^{HCT}/FF03/mbondi	13.2	30.6	2.4	52.1	24.1	13.5	2.6
GB^{HCT}/MK/mbondi	17.1	39.1	14.1	58.5	32.5	16.4	2.5
GB^{OBC1}/FF94/mbondi2	9.6	22.0	3.6	43.8	3.6	12.5	1.9
GB^{OBC2}/FF94/mbondi2	7.6	33.9	8.3	59.4	16.8	13.8	1.8
GBn/FF94/Bondi	11.1	10.7	3.4	9.8	20.8	8.4	1.8
GBn/FF03/Bondi	12.9	10.8	9.2	4.3	24.6	8.3	2.0
GBn/MK/Bondi	12.8	9.1	3.7	6.5	20.1	8.6	2.2
GBn/FF94/Tan2	30.9	17.3	13.9	21.5	13.5	8.1	3.3
GBn/FF94/Tan1	10.5	11.4	3.6	10.6	21.9	8.3	1.8
GBn/FF94/Parse	11.4	10.1	3.2	9.1	20.2	8.4	1.8

Table S6. Standard deviation (Stdev) and ranges among the solvation free energies of either all methods or only the 5 PCM methods. The results are presented as averages over the 20 neutral small molecules, the 20 neutral drug-like molecules, or the three series of inhibitors (avidin, factor Xa, or galectin-3 inhibitors), the latter either individually (called All 3) or individually. In addition, the standard deviations and ranges were calculated also for the relative solvation energies, either separately for the avidin, factor Xa, and galectin-3 inhibitors (Target), or separately for each total charge in these three series (Charge; in this case, lactose was omitted from the galectin-3 series).

Molecules		All methods		PCM	
	Subset	Stdev	Range	Stdev	Range
Neutral small		5.0	19.3	1.2	3.0
Neutral drugs		22.3	80.1	3.8	9.4
Inhibitors	All 3	45.0	155.8	7.8	18.3
	Avidin	25.1	105.4	14.8	34.0
	FXa	48.0	172.1	7.8	19.5
	Galectin-3	30.7	112.3	10.4	23.8
Target	All 3	17.6	61.9	9.3	22.3
Charge	All 3	4.7	19.1	3.0	7.3

Figure S1. Structures of the 20 neutral drug-like molecules (except Gal3 and Btn4, which are shown in Figures S2 and S4, respectively).

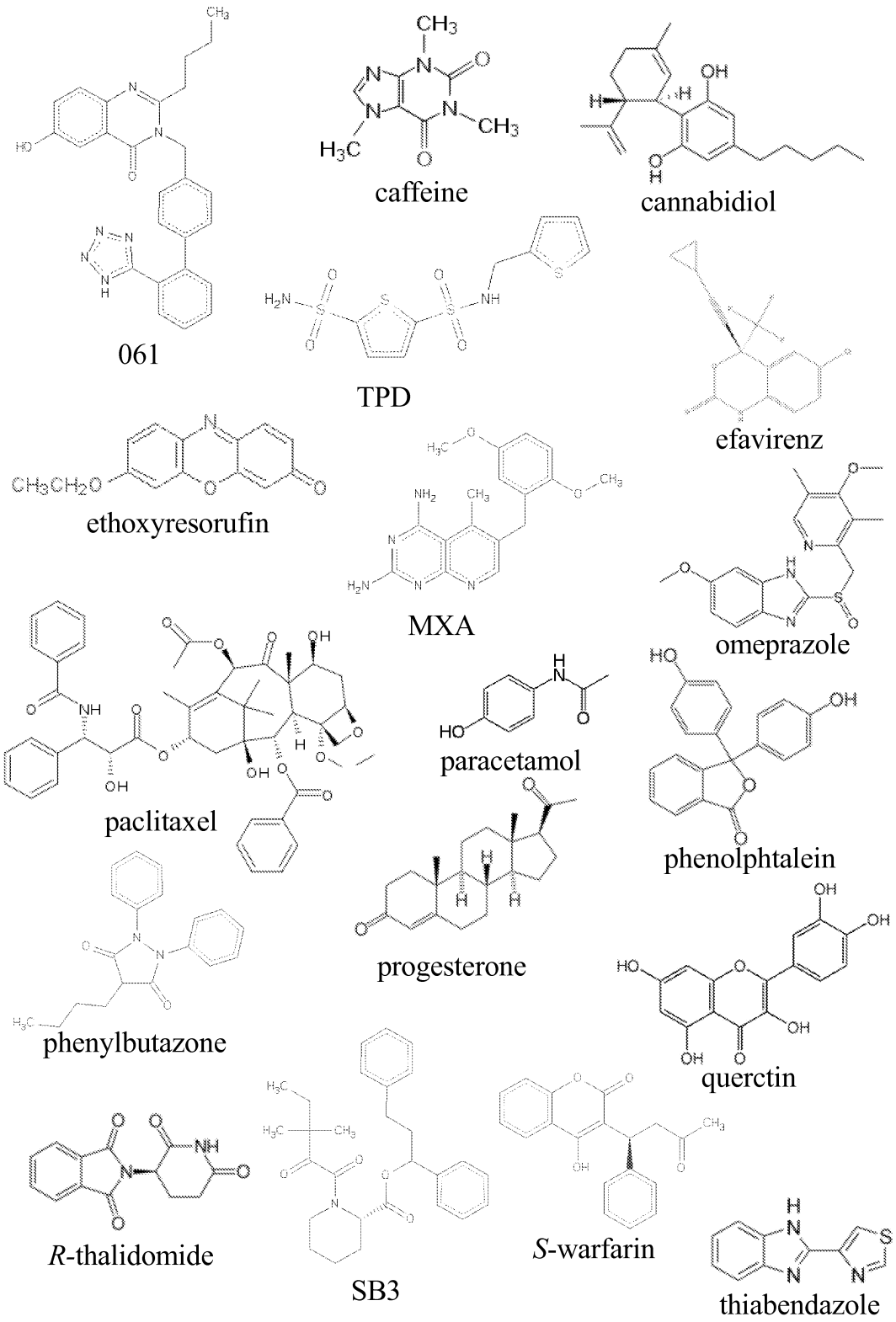


Figure S2. Structures of the seven biotin analogues studied: a) biotin (BTN1), b) 2'-iminobiotin (BTN2), c) desthiobiotin (BTN3), d) 1'-N-methoxycarbonylbiotin methyl ester (BTN4), e) *D*-4-*n*-hexyl-2-iminoimidazolidine (BTN5), f) *D*-4-*n*-hexyloxazolidone (BTN6), and g) imidazolidone (BTN7).

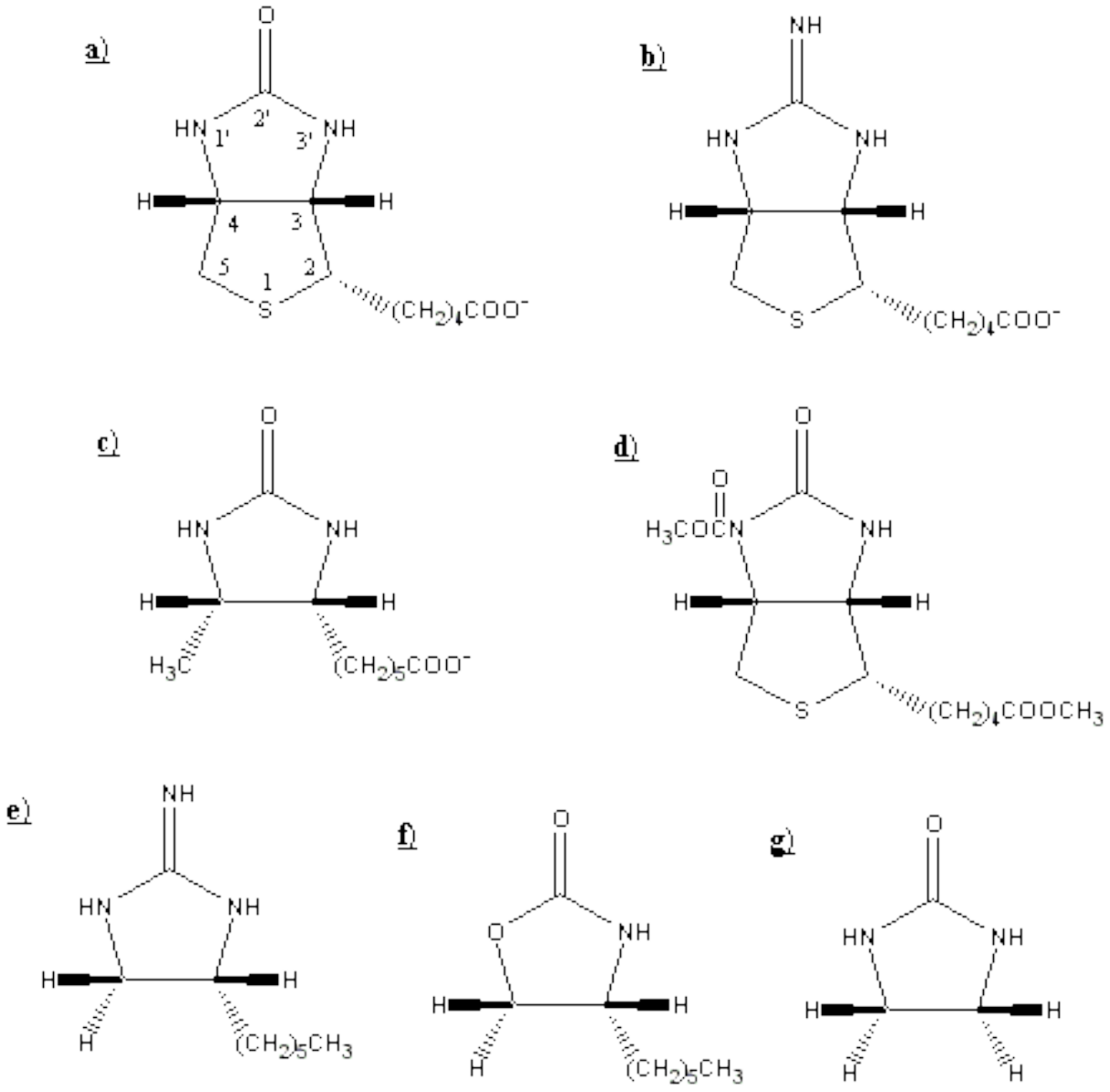
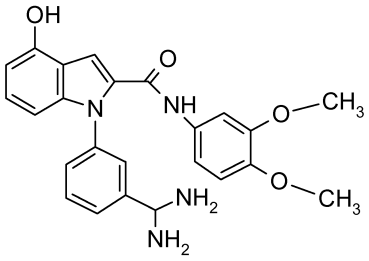
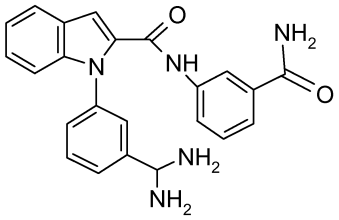


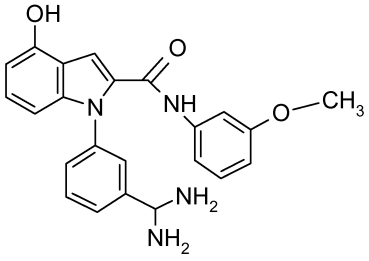
Figure S3. Structures of the eleven factor Xa inhibitors studied. FXa39, 57, 63, 103, and 127 (left) have a single positive charge, whereas the other six (right) have a double positive charge.



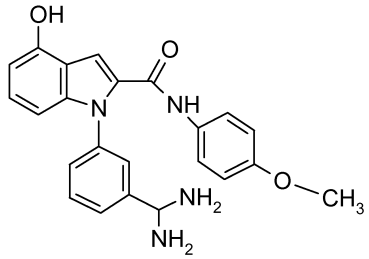
FXa39



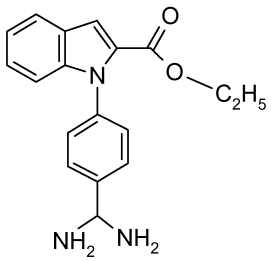
FXa57



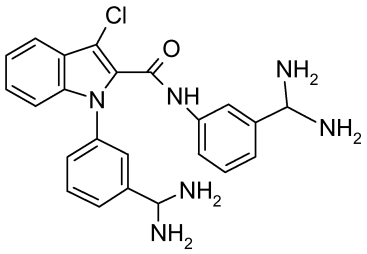
FXa63



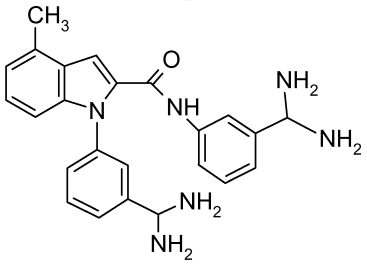
FXa103



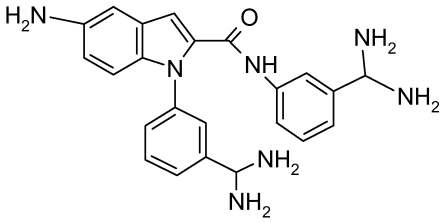
FXa127



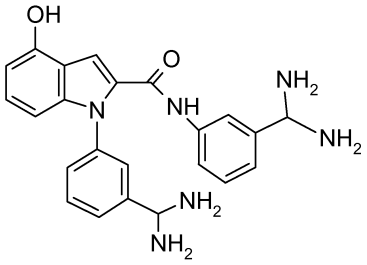
FXa9



FXa47



FXa49



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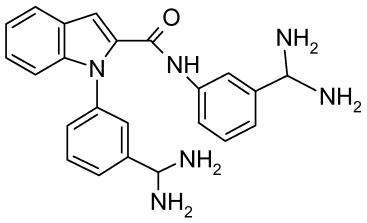

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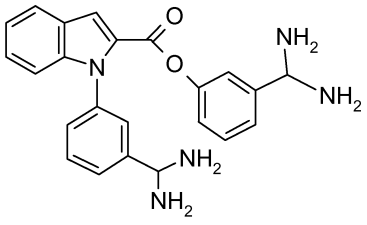

FXa125

Figure S4. Structures of the six galectin-3 inhibitors studied, lactose and Gal2–Gal6.