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SUPPLEMENTARY MATERIAL TO

Structure–activity relationship and *in silico* study of unique bi-heterocycles: 5-[(2-amino-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazole-2-thiol derivatives

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CHARACTERIZATION DATA

*2-(2-Amino-1,3-thiazol-4-yl)acetohydrazide (**2**)*. Yield: 90 %; white crystalline solid; m.p.: 291–292 °C; Anal. Calcd. for $C_5H_8N_4OS_1$ (*FW*: 172.21): C, 34.87; H, 4.68; N, 32.53 %. Found: C, 34.98; H, 4.84; N, 32.69 %; IR (KBr, cm^{-1}): 3358 (NH_2 str.), 3351 (N–H str.), 3032 (C–H str.), 2950 (–CH_2– str.), 1566 (C=C str.), 1587 (C=N str.), 1162 (C–N–C str.), 648 (C–S str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 9.02 (1H, *brs*, 1′–CO–N**H**–NH_2), 6.85 (2H, *brs*, 2-NH_2), 6.23 (1H, *s*, H-5), 4.19 (2H, *brs*, 1′-CO–NH–N**H**$_2$), 3.19 (2H, *s*, CH_2-2′); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.97 (C-1′), 168.51 (C-2), 146.43 (C-4), 102.76 (C-5), 37.32 (C-2′); EI-MS (*m/z* (% rel. abund.)): 172.0 $[M]^+$ (100), 130.16 $(C_4H_6N_2OS)^+$ (18.5), 113.1 $(C_4H_5N_2S)^+$ (80.3), 71 $(C_3H_3S)^+$ (25.7).

*5-[(2-Amino-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazole-2-thiol (**3**)*. Yield: 90 %; bright yellow solid; m.p.: 227–228 °C; Anal. Calcd. for $C_6H_6N_4OS_2$ (*FW*: 214.27): C, 33.63; H, 2.82; N, 26.15 %. Found: C, 33.76; H, 2.99; N, 26.27 %; IR (KBr, cm^{-1}): 3340 (NH_2 str.), 3045 (C–H str.), 2938 (–CH_2– str.), 1577 (C=C str.), 1558 (C=N str.),1182 (C–N–C str.), 613 (C–S str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.05 (2H, *brs*, 2-NH_2), 6.45 (1H, *s*, H-5), 3.93 (2H, *s*, CH_2-6); ^{13}C-NMR 150 MHz, DMSO-d_6, δ / ppm: 178.29 (C-2′), 169.31 (C-5′),

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162.48 (C-2), 143.59 (C-4), 104.06 (C-5), 28.29 (C-6); EI-MS (*m/z* (% rel. abund.)): 214.1 $[M]^+$ (100), 172.2 $(C_5H_4N_2OS_2)^+$ (4.9), 113.1 $(C_4H_5N_2S)^+$ (86.2), 71.0 $(C_3H_3S)^+$ (17.0).

*4-{[5-(Benzylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1,3-thiazol-2-amine (**5a**)*. Yield: 89 %; light brown solid; m.p.: 236–237 °C; Anal. Calcd. for $C_{13}H_{12}N_4OS_2$ (*FW*: 304.39): C, 51.30; H, 3.97; N, 18.41 %. Found: C, 51.41; H, 4.04; N, 18.35 %; IR (KBr, cm^{-1}): 3350 ($-NH_2$ str.), 3052 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1576 (C=C of aromatic ring str.), 1518 (C=N); ^1H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.50 (2H, dist. *dd*, J = 1.4 & 7.4 Hz, H-2″ & H-6″), 7.34 (1H, *dt*, J = 1.5 & 7.5 Hz, H-4″), 7.30 (2H, dist. *t*, J = 7.4, H-3″ & H-5″), 6.99 (2H, *s*, NH_2), 6.41 (1H, *s*, H-5), 4.52 (2H, *s*, CH_2-7″), 4.04 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76 (C-2′), 166.05 (C-5′), 162.39 (C-2), 143.82 (C-4), 133.75 (C-1″), 129.91 (C-4″), 129.58 (C-3″ & C-5″), 127.42 (C-2″ & C-6″), 103.28 (C-5), 34.10 (C-7″), 27.56 (C-6); EI-MS (*m/z* (% rel. abund.)): 304 $[M]^+$ (38.3), 230 $[C_{12}H_{10}N_2OS]^+$ (14.7), 205 $[C_{10}H_9N_2OS]^+$ (44.1), 141 $[C_5H_5N_2OS]^+$ (33.4), 113 $[C_4H_5N_2S]^+$ (88.7), 91 $[C_7H_7]^+$ (100), 77 $(C_6H_5)^+$ (56.8).

*4-({5-[(2-Chlorobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5b**)*. Yield: 83 %; off-white solid; m.p.: 287–288 °C; Anal. Calcd. for $C_{13}H_{11}ClN_4OS_2$ (*FW*: 338.84): C, 46.08; H, 3.27; N, 16.54 %. Found: C, 46.17; H, 3.24; N, 16.59 %; IR (KBr, cm^{-1}): 3344 ($-NH_2$ str.), 3048 (C–H of aromatic ring str.), 2923 ($-CH_2-$ stretching), 1570 (C=C of aromatic ring str.), 1523 (C=N), 584 (C–Cl str.); ^1H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.53 (1H, *brs*, H-6″), 7.37–7.34 (3H, *m*, H-3″, H-4″ & H-5″), 7.02 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.47 (2H, *s*, CH_2-7″), 4.04 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.78 (C-2′), 165.88 (C-5′), 162.73 (C-2), 143.79 (C-4), 139.30 (C-1″), 132.95 (C-2″), 130.33 (C-5″), 128.84 (C-3″), 127.68 (C-4″), 127.64 (C-6″), 103.22 (C-5), 34.90 (C-7″), 27.53 (C-6); EI-MS (*m/z* (% rel. abund.)): 340 $[M+2]^+$ (11.8), 338 $[M]^+$ 33.6), 264 $[C_{12}H_9ClN_2OS]^+$ (18.2), 239 $[C_{10}H_8ClN_2OS]^+$ (21.8), 141 $[C_5H_5N_2OS]^+$ (31.3), 113 $[C_4H_5N_2S]^+$ (100), 125 $[C_7H_6Cl]^+$ (86.7), 111 $[C_6H_4Cl]^+$ (28.9).

*4-({5-[(3-Chlorobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5c**)*. Yield: 88 %; brown solid; m.p.: 283–284 °C; Anal. Calcd. for $C_{13}H_{11}ClN_4OS_2$ (*FW*: 338.84): C, 46.08; H, 3.27; N, 16.54 %. Found: C, 46.11; H, 3.33; N, 16.51 %; IR (KBr, cm^{-1}): 3348 ($-NH_2$ str.), 3173 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1672 (C=C of aromatic ring str.), 1590 (C=N str.), 1159 (C–O–C str.), 588 (C–Cl str.); ^1H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.50 (1H, *brs*, H-2″), 7.46-7.36 (2H, *m*, H-4″ & H-5″), 7.32 (1H, *brd*, J = 7.1 Hz, H-6″), 7.01 (2H, *s*, NH_2), 6.41 (1H, *s*, H-5), 4.47 (2H, *s*, CH_2-7″), 4.04 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76 (C-2′), 165.82 (C-5′), 162.72 (C-2), 143.85 (C-4), 139.21 (C-1″), 132.94 (C-3″), 130.32 (C-4″), 128.76

(C-5″), 127.64 (C-2″), 127.52 (C-6″), 103.25 (C-5), 34.28 (C-7″), 27.58 (C-6); EI-MS (*m/z* (% rel. abund.)): 340 $[M+2]^+$ (9.4), 338 $[M]^+$ (27.9), 264 $[C_{12}H_9ClN_2OS]^+$ (21.7), 239 $[C_{10}H_8ClN_2OS]^+$ (30.5), 141 $[C_5H_5N_2OS]^+$ (44.6), 113 $[C_4H_5N_2S]^+$ (100), 125 $[C_7H_6Cl]^+$ (89.1), 111 $[C_6H_4Cl]^+$ (23.2).

*4-({5-[(4-Chlorobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5d**)*. Yield: 79 %; brown solid; m.p.: 267–268 °C; Anal. Calcd. for $C_{13}H_{11}ClN_4OS_2$ (*FW*: 338.84): C, 46.08; H, 3.27; N, 16.54 %. Found: C, 46.15; H, 3.36; N, 16.46 %; IR (KBr, cm^{-1}): 3351 ($-NH_2$ str.), 3173 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1672 (C=C of aromatic ring str.), 1590 (C=N), 1159 (C–O–C str.), 584 (C–Cl str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.41 (2H, *brd*, J = 8.2 Hz, H-2″ & H-6″), 7.33 (2H, *brd*, J = 8.2 Hz, H-3″ & H-5″), 7.02 (2H, *s*, NH_2), 6.41 (1H, *s*, H-5), 4.42 (2H, *s*, CH_2-7″), 4.03 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76 (C-2′), 165.82 (C-5′), 162.72 (C-2), 143.85 (C-4), 136.34 (C-4″), 132.49 (C-1″), 131.26 (C-3″ & C-5″), 127.64 (C-2″ & C-6″), 103.25 (C-5), 34.28 (C-7″), 27.53 (C-6); EI-MS (*m/z* (% rel. abund.)): 340 $[M+2]^+$ (18.8), 338 $[M]^+$ 54.1), 264 $[C_{12}H_9ClN_2OS]^+$ (17.4), 239 $[C_{10}H_8ClN_2OS]^+$ (27.3), 141 $[C_5H_5N_2OS]^+$ (31.9), 113 $[C_4H_5N_2S]^+$ (100), 125 $[C_7H_6Cl]^+$ (92.3), 111 $[C_6H_4Cl]^+$ (27.5).

*4-({5-[(2-Bromobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5e**)*. Yield: 77 %; light brown solid; m.p.: 236–237 °C; Anal. Calcd. for $C_{13}H_{11}BrN_4OS_2$ (*FW*: 382.29): C, 40.74; H, 2.89; N, 14.62 %. Found: C, 40.71; H, 2.97; N, 14.57 %; IR (KBr, cm^{-1}): 3350 ($-NH_2$ str.), 3173 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1672 (C=C of aromatic ring str.), 1590 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.58 (1H, *brd,* J = 7.6 Hz, H-3″), 7.37–7.34 (3H, *m*, H-4″, H-5″ & H-6″), 7.02 (2H, *s*, NH_2), 6.41 (1H, *s*, H-5), 4.47 (2H, *s*, CH_2-7″), 4.04 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.78 (C-2′), 165.88 (C-5′), 162.73 (C-2), 143.79 (C-4), 136.30 (C-1″), 132.33 (C-3″), 131.84 (C-4″), 129.68 (C-6″), 127.64 (C-5″), 123.95 (C-2″), 103.82 (C-5), 34.90 (C-7″), 27.56 (C-6); EI-MS (*m/z* (% rel. abund.)): 384 $[M+2]^+$ (29.8), 382 $[M]^+$ (30.2), 308 $(C_{12}H_9BrN_2OS)^+$ (16.9), 283 $[C_{10}H_8BrN_2OS]^+$ (10.4), 169 $[C_7H_6Br]^+$ (90.9), 141 $[C_5H_5N_2OS]^+$ (20.8), 113 $[C_4H_5N_2S]^+$ (100).

*4-({5-[(3-Bromobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5f**)*. Yield: 81 %; creamy brown amorphous powder; m.p.: 223–224 °C; Anal. Calcd. for $C_{13}H_{11}BrN_4OS_2$ (*FW*: 382.29): C, 40.74; H, 2.89; N, 14.62 %. Found: C, 40.78; H, 2.93; N, 14.66 %; IR (KBr, cm^{-1}): 3345 ($-NH_2$ str.), 3173 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1672 (C=C of aromatic ring str.), 1590 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.66 (1H, *brs*, H-2″), 7.48 (IH, dist. *dd*, J = 0.6, 8.5 Hz, H-6″), 7.40 (1H, *brd*, J = 7.6 Hz, H-4″), 7.28 (1H, *brt*, J = 7.8 Hz, H-5″), 6.98 (2H, *s*, NH_2), 6.39 (1H, *s*, H-5), 4.45 (2H, *s*, CH_2-7″), 4.03 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76

(C-2′), 165.89 (C-5′), 162.72 (C-2), 143.85 (C-4), 139.57 (C-1″), 131.71 (C-2″), 130.61 (C-4″), 130.52 (C-5″), 128.06 (C-6″), 121.51 (C-3″), 103.21 (C-5), 34.86 (C-7″), 27.55 (C-6); EI-MS (*m/z* (% rel. abund.)): 384 $[M+2]^+$ (27.1), 382 $[M]^+$ (28.3), 308 $(C_{12}H_9BrN_2OS)^+$ (18.5), 283 $[C_{10}H_8BrN_2OS]^+$ (14.8), 169 $[C_7H_6Br]^+$ (94.2), 141 $[C_5H_5N_2OS]^+$ (19.4), 113 $[C_4H_5N_2S]^+$ (100).

*4-({5-[(4-Bromobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5g**)*. Yield: 85 %; brown solid; m.p.: 240–241 °C; Anal. Calcd. for $C_{13}H_{11}BrN_4OS_2$ (*FW*: 382.29): C, 40.74; H, 2.89; N, 14.62 %. Found: C, 40.69; H, 2.94; N, 14.61 %; IR (KBr, cm^{-1}): 3350 ($-NH_2$ str.), 3173 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1672 (C=C of aromatic ring str.), 1590 (C=N str.); ^1H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.51 (2H, *brd*, J = 8.2 Hz, H-2″ & H-6″), 7.35 (2H, *brd*, J = 8.2 Hz, H-3″ & H-5″), 7.02 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.42 (2H, *s*, CH_2-7″), 4.03 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.78 (C-2′), 165.85 (C-5′), 162.68 (C-2), 143.79 (C-4), 136.30 (C-1″), 131.39 (C-3″ & C-5″), 131.28 (C-2″ & C-6″), 120.87 (C-4″), 103.27 (C-5), 34.95 (C-7″), 27.52 (C-6); EI-MS (*m/z* (% rel. abund.)): 384 $[M+2]^+$ (30.4), 382 $[M]^+$ (31.1), 308 $(C_{12}H_9BrN_2OS)^+$ (22.8), 283 $[C_{10}H_8BrN_2OS]^+$ (19.2), 169 $[C_7H_6Br]^+$ (96.6), 141 $[C_5H_5N_2OS]^+$ (22.5), 113 $[C_4H_5N_2S]^+$ (100).

*4-({5-[(4-Fluorobenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5h**)*. Yield: 77 %; lemon yellow solid; m.p.: 297–298 °C; Anal. Calcd. for $C_{13}H_{11}FN_4OS_2$ (*FW*: 322.38): C, 48.43; H, 3.44; N, 17.38 %. Found: C, 48.55; H, 3.38; N, 17.42 %; IR (KBr, cm^{-1}): 3355 ($-NH_2$ str.), 3018 (C–H of aromatic ring str.), 2923 ($-CH_2-$ str.), 1527 (C=C of aromatic ring str.), 1590 (C=N str.); ^1H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.43 (2H, *dd*, J = 5.5 & 8.4 Hz, due to coupling with F_{19}, H-2″ & H-6″), 7.14 (2H, *brt*, J = 8.8 Hz, due to coupling with F_{19}, H-3″ & H-5″),[18,19] 7.00 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.44 (2H, *s*, CH_2-7″), 4.03 (2H, *s*, CH_2-6); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76 (C-2′), 165.83 (C-5′), 162.77 (C-2), 161.55 (*d*, J^* = 243.0 Hz, coupling with F_{19}, C-4″), 143.89 (C-4), 132.95 (*d*, J^* = 3.0 Hz, due to coupling of F_{19}, C-1″), 131.07 (*d*, J^* = 7.5 Hz, due to coupling of F_{19}, C-2″ & C-6″), 115.31 (*d*, J^* = 21.0 Hz, due to coupling of F_{19}, C-3″ & C-5″), 103.26 (C-5), 34.89 (C-7″), 27.54 (C-6); EI-MS (*m/z* (% rel. abund.)): 322 $[M]^+$ (33.1), 248 $[C_{12}H_9FN_2OS]^+$ (11.6), 223 $[C_{10}H_8FN_2OS]^+$ (25.9), 141 $[C_5H_5N_2OS]^+$ (35.6), 113 $[C_4H_5N_2S]^+$ (100), 109 $[C_7H_6F)^+$ (44.8). *Considering the effective frequency of the spectrometer as 150 MHz for the ^{13}C nucleus.

*4-({5-[(2-Methylbenzyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5i**)*. Yield: 71 %; yellowish solid; m.p.: 189–190 °C; Anal. Calcd. for $C_{14}H_{14}N_4OS_2$ (*FW*: 318.42): C, 52.81; H, 4.43; N, 17.60 %. Found: C, 52.89; H, 4.57; N, 17.55 %; IR (KBr, cm^{-1}): 3341 ($-NH_2$ str.), 3165 (C–H of aromatic ring str.), 2920 ($-CH_2-$ str.), 1670 (C=C of aromatic ring str.), 1600 (C=N str.);

^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.30 (1H, *brd*, J = 7.4 Hz, H-6″), 7.20–7.19 (2H, *m*, H-3″ & H-4″); 7.14–7.11 (1H, *m*, H-5″), 7.01 (2H, *s*, NH_2), 6.41 (1H, *s*, H-5), 4.47 (2H, *s*, CH_2-7″), 4.04 (2H, *s*, CH_2-6), 2.35 (3H, *s*, CH_3-8″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76 (C-2′), 165.82 (C-5′), 162.72 (C-2), 143.85 (C-4), 136.71 (C-1″), 133.74 (C-2″), 130.42 (C-3″), 129.96 (C-4″), 128.14 (C-6″), 126.09 (C-5″), 103.25 (C-5), 34.28 (C-7″), 27.55 (C-6), 18.67 (C-8″); EI-MS (*m/z* (% rel. abund.)): 318 $[M]^+$ (19.4), 244 $[C_{13}H_{12}NO_2S]^+$ (15.5), 219 $[C_{11}H_{11}N_2OS]^+$ (11.3), 192 $[C_9H_8N_2OS]^+$ (73.0), 141 $[C_5H_5N_2OS]^+$, (10.1), 127 $[C_4H_3N_2OS]^+$ (70.2), 113 $(C_4H_5N_2S)^+$ (84.8), 105 $[C_8H_9]^+$ (100).

*4-{[5-(Ethylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1,3-thiazol-2-amine (**5j**)*. Yield: 73 %; dark brown liquid; Anal. Calcd. for $C_8H_{10}N_4OS_2$ (*FW*: 242.32): C, 39.65; H, 4.16; N, 23.12 %. Found: C, 39.73; H, 4.11; N, 23.06 %; IR (KBr, cm^{-1}): 3364 (NH_2 str.), 3057 (C–H of aromatic ring str.), 2920 (–CH_2– str.); 1566 (C=C of aromatic ring str.), 1519 (C=N str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 6.99 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.04 (2H, *s*, CH_2-6), 3.22 (2H, *q*, J = 6.7 Hz, CH_2-1″), 1.44 (3H, *t*, J = 6.7 Hz, CH_3-2″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.74 (C-2′), 165.53 (C-5′), 163.48 (C-2), 143.98 (C-4), 103.14 (C-5), 31.59 (C-1″), 27.13 (C-6), 14.82 (C-2″); EI-MS (*m/z* (% rel. abund.)): 242 $[M]^+$ (45.6) 213 $[C_6H_5N_4OS_2]^+$ (11.2), 168 $[C_7H_8N_2OS]^+$ (33.4), 143 $[C_5H_7N_2OS]^+$ (21.6), 141 $[C_5H_5N_2OS]^+$ (32.1), 113 $[C_4H_5N_2S]^+$ (100).

*4-{[5-(Propylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1,3-thiazol-2-amine (**5k**)*. Yield: 79 %; light brown greasy solid; m.p.: 179–180 °C; Anal. Calcd. for $C_9H_{12}N_4OS_2$ (*FW*: 256.35): C, 42.17; H, 4.72; N, 21.86 %. Found: C, 42.24; H, 4.67; N, 21.77 %; IR (KBr, cm^{-1}): 3361 (NH_2 str.), 3059 (C–H of aromatic ring str.), 2920 (–CH_2– str.); 1574 (C=C of aromatic ring str.), 1525 (C=N str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 6.91 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.04 (2H, *s*, CH_2-6), 3.20 (2H, *t*, J = 7.20 Hz, CH_2-1″), 1.68 (2H, *sext.*, J =7.2 Hz, CH_2-2″), 0.98 (3H, *t*, J = 7.2 Hz, CH_3-3″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.74 (C-2′), 165.53 (C-5′), 163.48 (C-2), 143.98 (C-4), 103.14 (C-5), 33.84 (C-1″), 27.18 (C-6), 22.42 (C-2″), 12.88 (C-3″); EI-MS (*m/z* (% rel. abund.)): 256 $[M]^+$ (18.9), 214 $[C_6H_6N_4OS_2]^+$ (21.7), 182 $[C_8H_{10}N_2OS]^+$ (29.1), 157 $[C_6H_9N_2OS]^+$ (18.4), 141 $[C_5H_5N_2OS]^+$ (34.5), 113 $[C_4H_5N_2S]^+$ (100), 43 $(C_3H_7)^+$ (36.7).

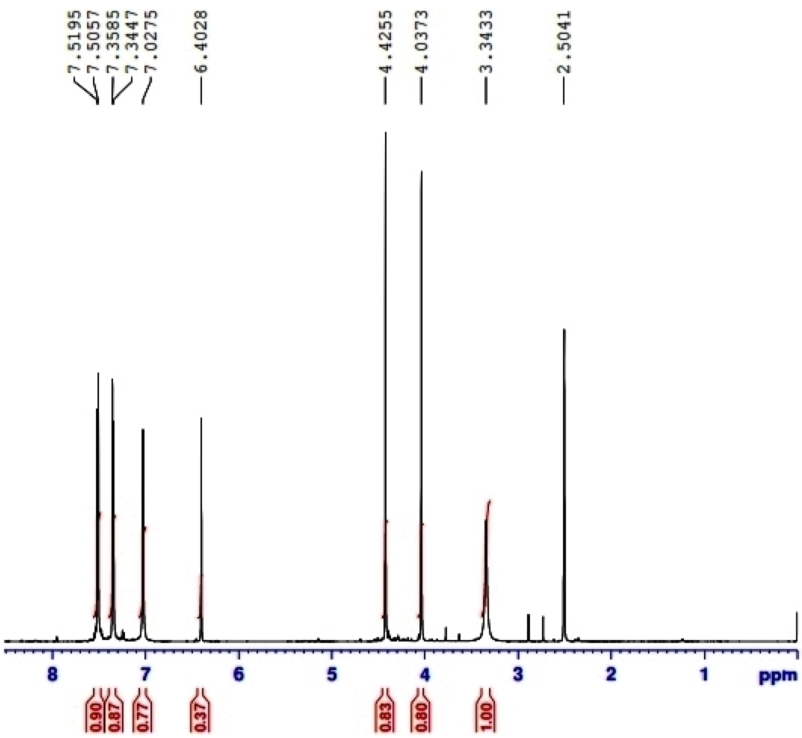
*4-{[5-(Butylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1,3-thiazol-2-amine (**5l**)*. Yield: 84 %; light green greasy liquid; Anal. Calcd. for $C_{10}H_{14}N_4OS_2$ (*FW*: 270.38): C, 44.42; H, 5.22; N, 20.72 %. Found: C, 44.51; H, 5.27; N, 20.68 %; IR (KBr, cm^{-1}): 3366 (NH_2 str.), 3055 (C–H of aromatic ring str.), 2920 (–CH_2– str.), 1520 (C=C of aromatic ring str.), 1582 (C=N str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 6.99 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.04 (2H, *s*, CH_2-6), 3.20 (2H, *t*, *J* = 7.2 CH_2-1″), 1.68 (2H, *quint.*, *J* = 7.2, CH_2-2″), 1.37 (2H, *sext.*, *J* = 7.3 Hz, CH_2-3″), 0.88 (3H, *t*, *J* = 7.3 Hz, CH_3-4″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.74 (C-2′), 165.53 (C-5′), 163.48 (C-2), 143.98 (C-4), 103.14 (C-5), 31.59 (C-1″), 30.92 (C-2″), 27.53 (C-6), 20.87 (C-3″), 13.27 (C-4″); EI-MS (*m/z* (% rel. abund.)): 270 $[M]^+$ (11.3), 214 $[C_6H_6N_4OS_2]^+$ (33.2), 196 $[C_9H_{12}N_2OS]^+$ (17.6), 171 $[C_7H_{11}N_2OS]^+$ (10.8), 141 $[C_5H_5N_2OS]^+$ (29.3), 113 $[C_4H_5N_2S]^+$ (100), 57 $[C_4H_9]^+$ (30.5).

*4-{[5-(Pentylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1,3-thiazol-2-amine (**5m**)*. Yield: 81 %; brown solid; m.p.: 173–174 °C; Anal. Calcd. for $C_{11}H_{16}N_4OS_2$ (*FW*: 284.40): C, 46.45; H, 5.67; N, 19.70 %. Found: C, 46.53; H, 5.74; N, 19.66 %; IR (KBr, cm^{-1}): 3362 (NH_2 str.), 3053 (C–H of aromatic ring), 2920 (–CH_2– str.), 1520 (C=C of aromatic ring str.), 1582 (C=N str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 6.97 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.04 (2H, *s*, CH_2-6), 3.19 (2H, *t*, *J* = 7.2 Hz, CH_2-1″), 1.70 (2H, *quint.*, *J* = 7.2 Hz, CH_2-2″), 1.37–1.33 (2H, *m*, CH_2-3″), 1.32–1.26 (2H, *m*, CH_2-4″), 0.86 (3H, *t*, *J* = 7.2, CH_3-5″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.73 (C-2′), 165.54 (C-5′), 163.48 (C-2), 143.98 (C-4), 103.14 (C-5), 31.86 (C-1″), 29.95 (C-2″), 28.55 (C-3″), 27.53 (C-6), 21.48 (C-4″), 13.73 (C-5″); EI-MS (*m/z* (% rel. abund.)): 284 $[M]^+$ (12.9), 214 $[C_6H_6N_4OS_2]^+$ (27.3), 185 $[C_8H_{13}N_2OS]^+$ (20.1), 141 $[C_5H_5N_2OS]^+$ (35.5), 113 $[C_4H_5N_2S]^+$ (100), 71 $[C_5H_{11}]^+$ (12.6).

*4-{[5-(Heptylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1,3-thiazol-2-amine (**5n**)*. Yield: 73 %; brick red solid; m.p.: 207–208 °C; Anal. Calcd. for $C_{13}H_{20}N_4OS_2$ (*FW*: 312.46): C, 49.97; H, 6.45; N, 17.93 %. Found: C, 49.92; H, 6.55; N, 17.84 %; IR (KBr, cm^{-1}) 3356 (NH_2), 3055 (C–H of aromatic ring str.), 1520 (C=C of aromatic ring str.), 1582 (C=N str.), 2920 (–CH_2– str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 6.95 (2H, *s*, NH_2), 6.40 (1H, *s*, H-5), 4.04 (2H, s, CH_2-6), 3.63 (2H, *t*, *J* = 7.3 CH_2-1″), 1.72 (2H, *quint*, *J* = 7.3 Hz, CH_2-2″), 1.20–1.11 (8H, *m*, CH_2-3″ to CH_2-6″), 0.85 (3H, *t*, *J* = 7.3, CH_3-7″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.74 (C-2′), 165.53 (C-5′), 163.48 (C-2), 143.98 (C-4), 103.14 (C-5), 31.59 (C-1″), 31.24 (C-5″), 30.98 (C-3″), 28.92 (C-2″), 28.14 (C-4″), 27.72 (C-6), 21.96 (C-6″), 13.78 (C-7″); EI-MS (*m/z* (% rel. abund.)): 312 $[M]^+$ (11.5), 214 $[C_6H_6N_4OS_2]^+$ (29.8), 141 $[C_5H_5N_2OS]^+$ (26.4), 113 $[C_4H_5N_2S]^+$ (100), 99 $[C_7H_{15}]^+$ (8.3).

*4-({5-[(3-Phenylpropyl)sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2--amine (**5o**)*. Yield: 91 %; lemon yellow solid; m.p.: 324–325 °C; Anal. Calcd. for $C_{15}H_{16}N_4OS_2$ (*FW*: 332.45): C, 54.19; H, 4.85; N, 16.85 %. Found: C, 54.23; H, 4.89; N, 16.72 %; IR (KBr, cm^{-1}): 3360 (NH_2 str.), 3056 (C–H of aromatic ring str.), 2920 (–CH_2– str.), 1575 (C=C of aromatic ring str.), 1518 (C=N str.); ^{1}H-NMR (600 MHz, DMSO-d_6, δ / ppm): 7.28 (2H, *dist.t*, *J* = 7.5 Hz, H-3″ & H-5″), 7.20–7.17 (3H, *m*, H-2″, H-4″ & H-6″), 7.01 (2H, *s*, NH_2), 6.41 (1H, *s*, H-5), 4.03 (2H, *s*, CH_2-6), 3.20 (2H, *t*, *J* = 7.3 Hz, CH_2-9″), 2.70 (2H, *t*, *J* = 7.4

Hz, CH_2-7″), 2.01 (2H, *quint*., *J* = 7.5 Hz, CH_2-8″); ^{13}C-NMR (150 MHz, DMSO-d_6, δ / ppm): 168.76 (C-2′), 165.57 (C-5′), 163.34 (C-2), 143.79 (C-4), 140.74 (C-1″), 128.36 (C-2″ & C-6), 128.27 (C-3″ & C-5), 125.94 (C-4″), 103.19 (C-5), 33.72 (C-9″), 31.47 (C-7″), 30.49 (C-8″), 27.49 (C-6); EI-MS (*m*/*z* (% rel. abund.)): 332 $[M]^+$ (31.6), 241 $(C_8H_9N_4OS_2)^+$ (17.2), 214 $[C_6H_6N_4OS_2]^+$ (11.5), 141 $[C_5H_5N_2OS]^+$ (32.4), 119 $[C_9H_{11}]^+$ (22.1), 113 $[C_4H_5N_2S]^+$ (94.8), 91 $[C_7H_7]^+$ (100), 77 $[C_6H_5]^+$ (61.8).



Fig, S-1. ^{1}H-NMR spectrum of **5g**.

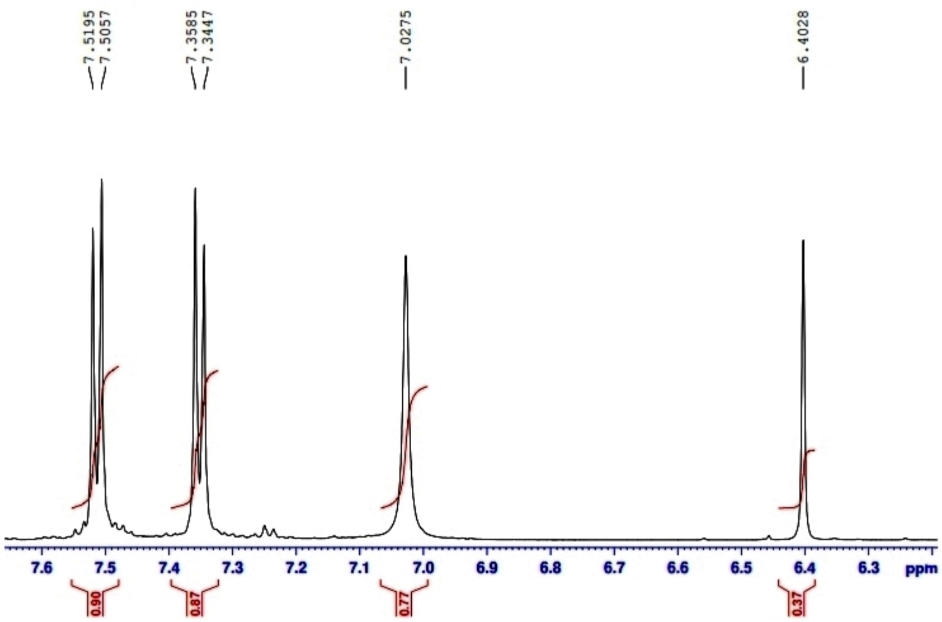


Fig. S-2. Aromatic region of the [1]H-NMR spectrum of **5g**.

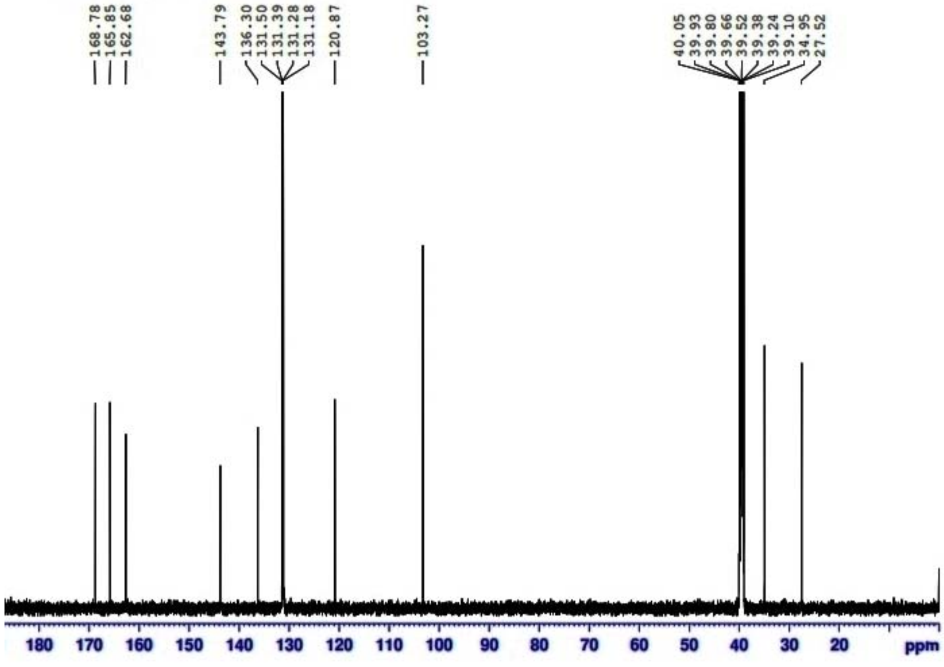


Fig. S-3. [13]C-NMR spectrum of **5g**.

TABLE S-I. Inhibition and IC_{50} for AChE, BChE, urease and α-glucosidase enzymes; all compounds were dissolved in methanol and the experiments performed in triplicate (mean±*SEM*, *n* = 3). AChE = acetylcholinesterase enzyme, BChE = butyrylcholinesterase enzyme

Sample code	AChE		BChE		Urease		α-Glucosidase	
	Inhibition, % at 0.5 mM	IC_{50} / μM	Inhibition, % at 0.5 mM	IC_{50} / μM	Inhibition, % at 0.5 mM	IC_{50} / μM)	Inhibition, % at 0.5 mM	IC_{50} / μM
5a	49.15±0.19	121.17±0.13	45.23±0.19	167.67±0.22	53.51±0.13	149.15±0.45	71.15±0.45	175.11±0.50
5b	64.29±0.14	104.29±0.23	59.82±0.14	99.17±0.29	81.96±0.16	115.40±0.14	73.55±0.15	147.48±0.35
5c	88.26±0.19	14.27±0.19	52.56±0.21	121.45±0.12	84.72±0.19	105.15±0.17	89.17±0.25	123.33±0.20
5d	81.26±0.14	84.71±0.4	78.26±0.14	85.67±0.13	74.59±0.11	145.25±0.17	75.17±0.35	169.29±0.21
5e	45.27±0.13	274.21±0.19	71.28±0.21	193.41±0.14	80.42±0.14	119.45±0.15	83.35±0.15	135.12±0.19
5f	39.17±0.14	248.51±0.11	69.18±0.23	175.37±0.19	51.63±0.13	157.12±0.27	90.29±0.22	46.17±0.14
5g	72.34±0.17	43.71±0.21	67.18±0.21	63.51±0.12	77.89±0.11	121.45±0.19	70.49±0.19	185.26±0.27
5h	61.34±0.11	165.17±0.12	45.11±0.47	251.21±0.11	47.53±0.15	189.22±0.45	67.35±0.17	173.23±0.20
5i	83.34±0.15	48.51±0.11	57.18±0.23	151.67±0.13	76.45±0.13	143.29±0.29	61.29±0.25	195.14±0.29
5j	64.34±0.18	171.42±0.21	71.43±0.19	185.42±0.21	75.23±0.15	159.15±0.11	81.43±0.35	136.16±0.31
5k	42.34±0.13	148.51±0.11	7.22±0.23	–	68.27±0.17	141.33±0.14	55.15±0.45	225.36±0.17
5l	79.34±0.19	71.41±0.12	69.34±0.27	175.65±0.14	29.24±0.14	–	84.17±0.71	117.31±0.24
5m	41.34±0.13	261.51±0.41	72.18±0.17	164.27±0.23	48.34±0.19	179.45±0.15	60.23±0.17	199.24±0.20
5n	85.84±0.14	39.22±0.41	27.34±0.21	–	75.58±0.13	129.09±0.23	53.25±0.29	213.18±0.21
5o	83.18±0.16	46.71±0.52	55.08±0.16	147.27±0.32	60.59±0.11	165.15±0.23	51.27±0.25	234.25±0.24
Eserine	91.27±1.17	0.04±0.0.01	82.82±1.09	0.85±0.01	–	–	–	–
Thiourea	–	–	–	–	98.12±0.18	21.11±0.12	–	–
Acarbose	–	–	–	–	–	–	92.23±0.16	37.38±0.12

DOCKING IMAGES

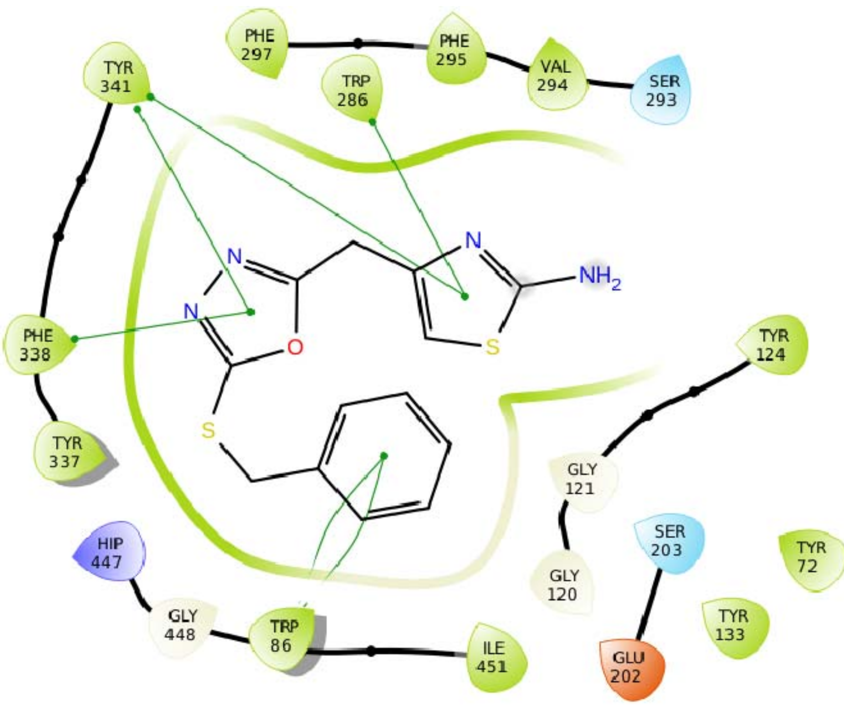


Fig. S-4. Docking image of **5a** against AChE.

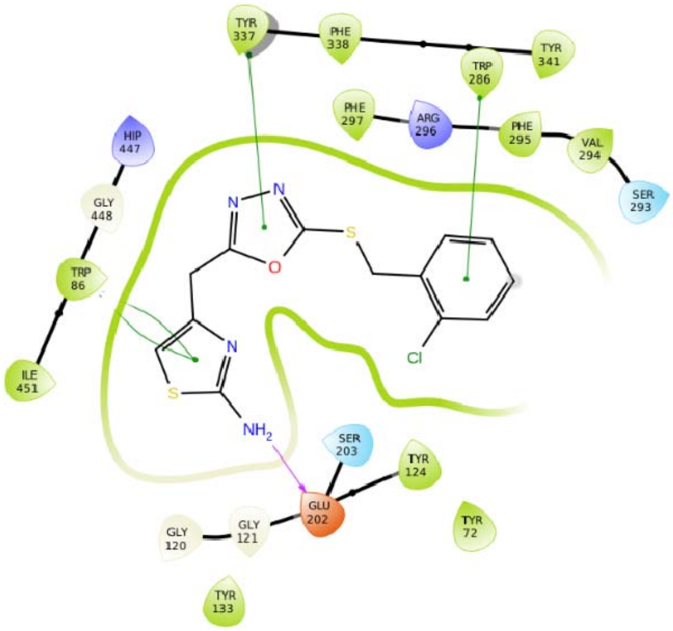


Fig. S-5. Docking image of **5b** against AChE.

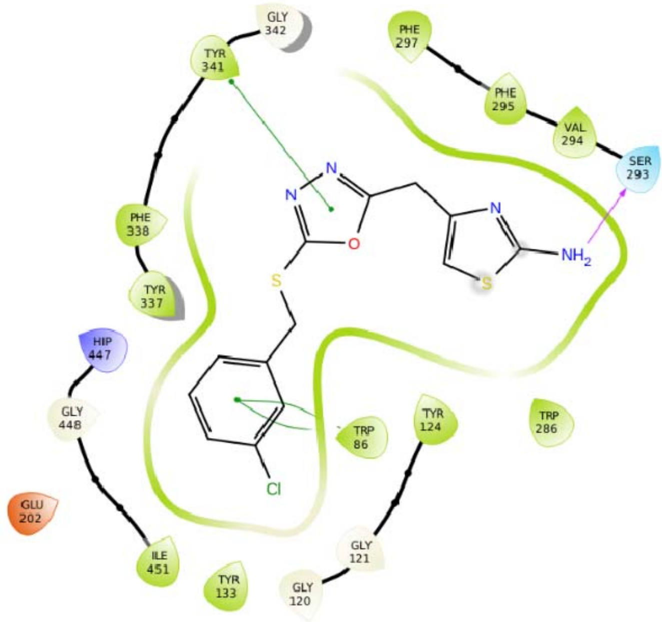


Fig. S-6. Docking image of **5c** against AChE.

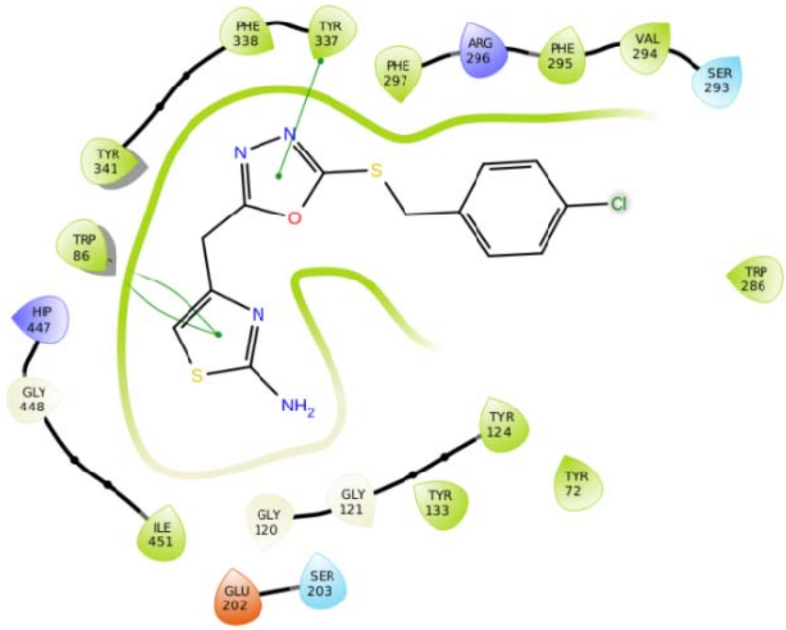


Fig. S-7. Docking image of **5d** against AChE.

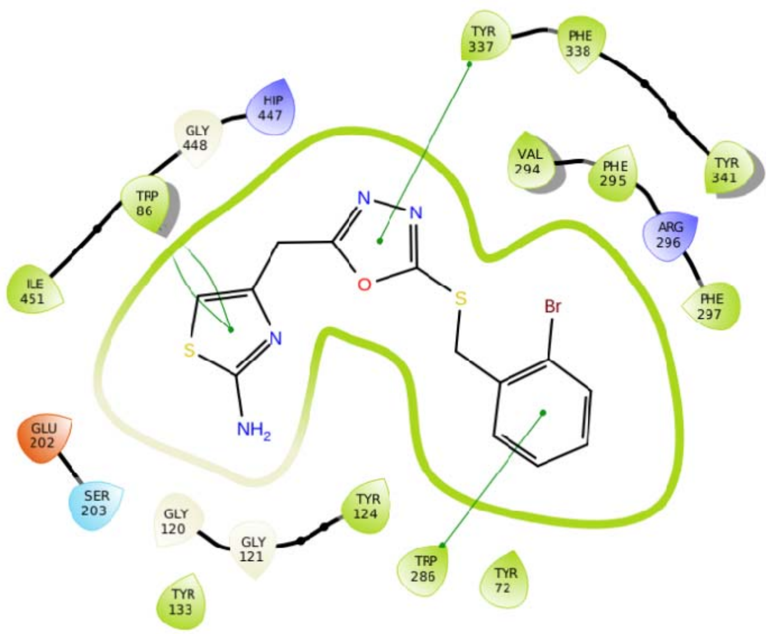


Fig. S-8. Docking image of **5e** against AChE.

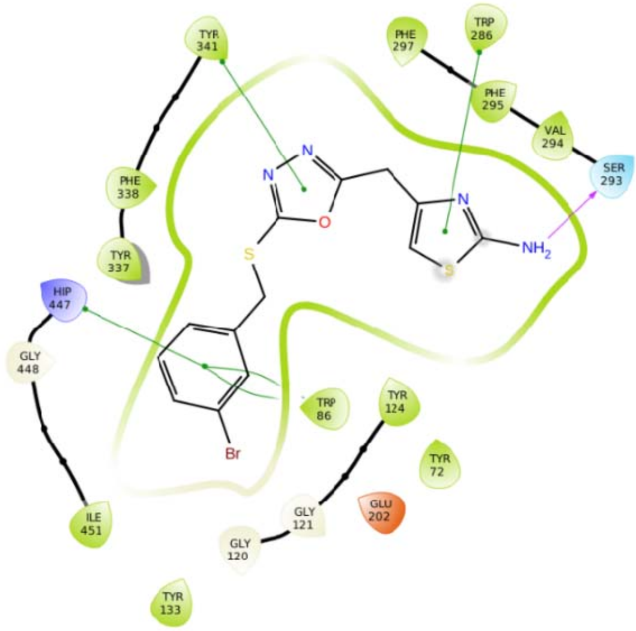


Fig. S-9. Docking image of **5f** against AChE.

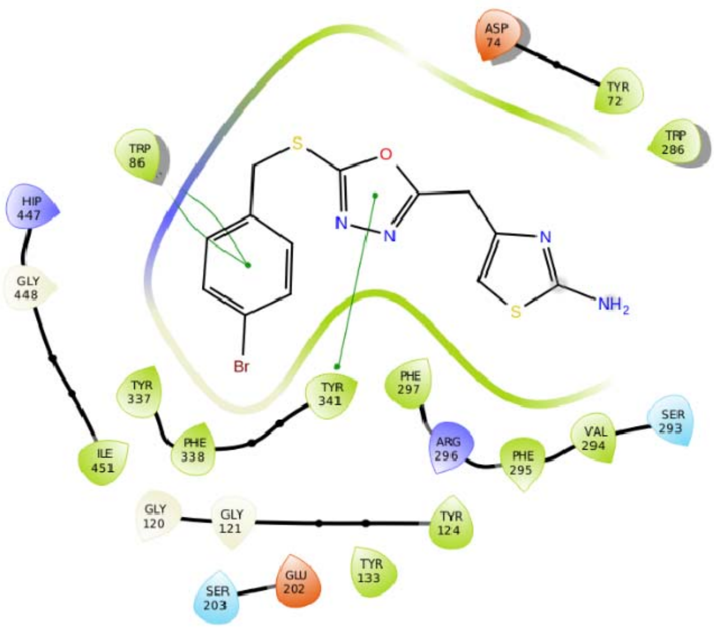


Fig. S-10. Docking image of **5g** against AChE.

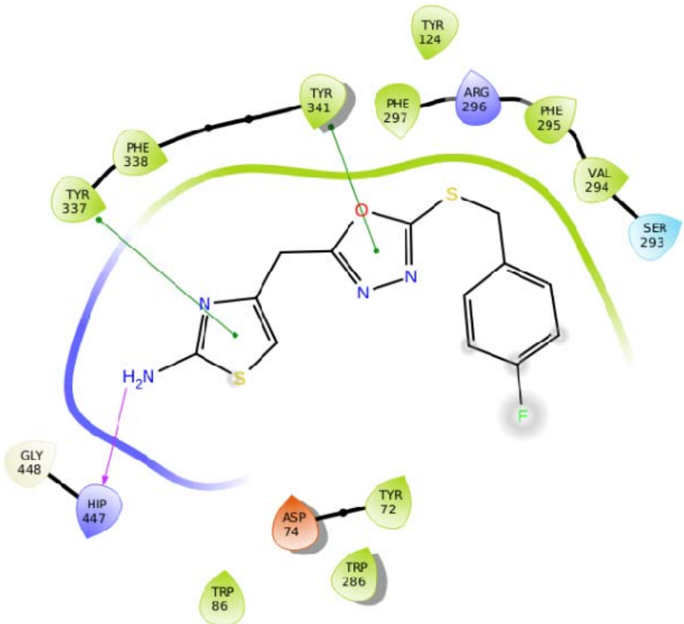


Fig. S-11. Docking image of **5h** against AChE.

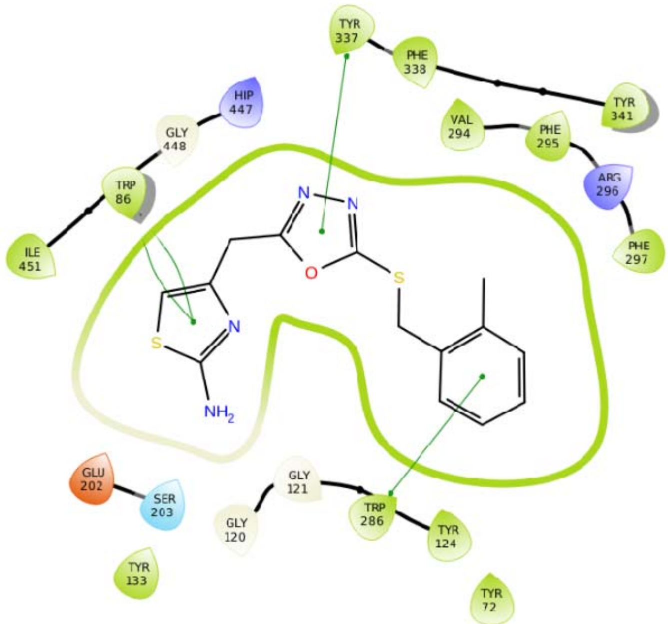


Fig. S-12. Docking image of **5i** against AChE.

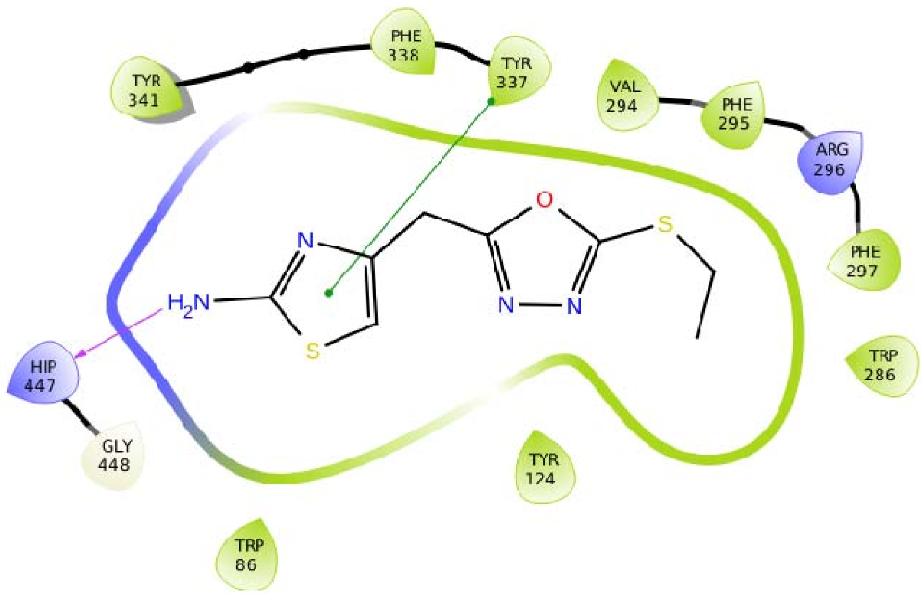


Fig. S-13. Docking image of **5j** against AChE.

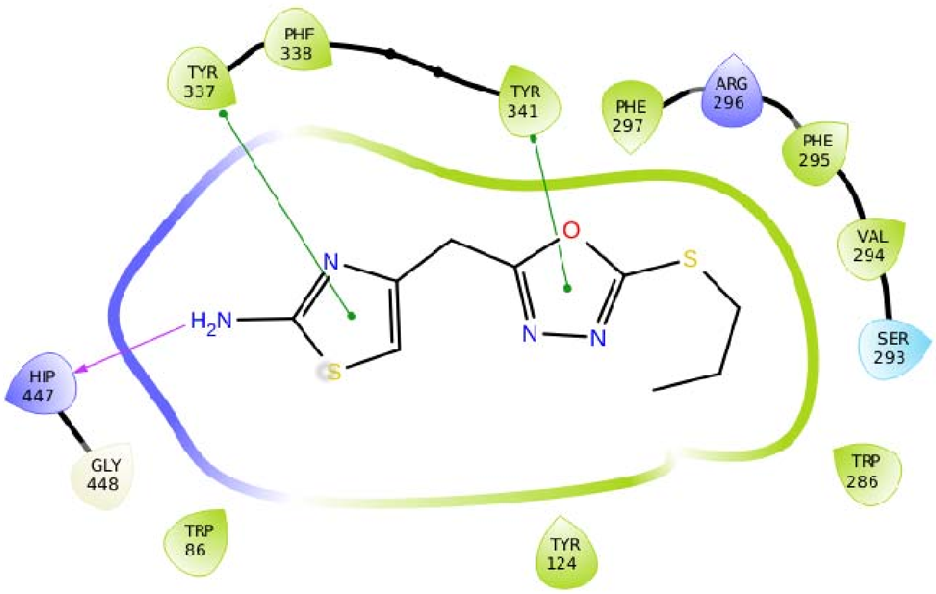


Fig. S-14. Docking image of **5k** against AChE.

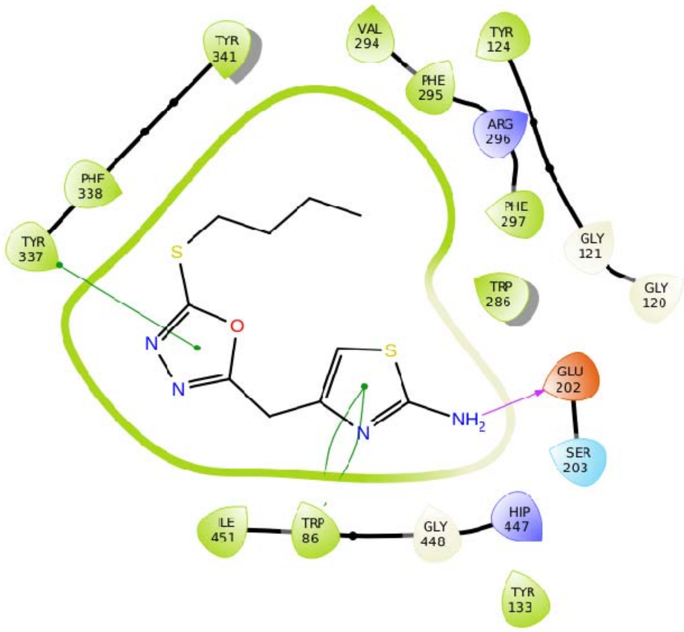


Fig. S-15. Docking image of **5l** against AChE.

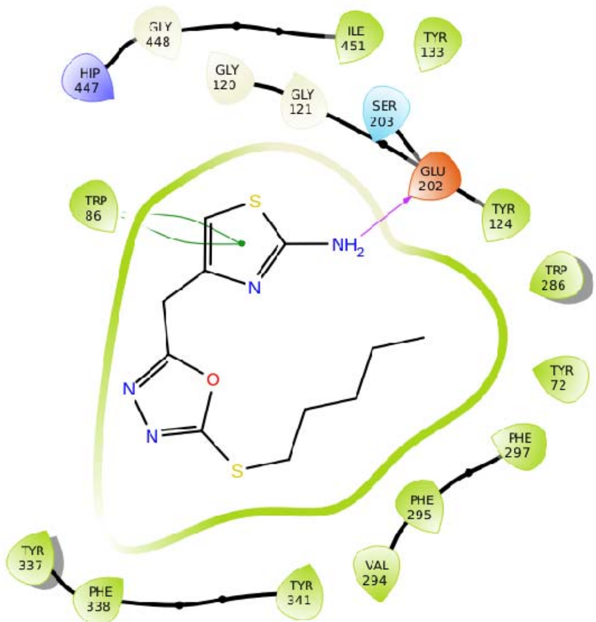


Fig. S-16. Docking image of **5m** against AChE.

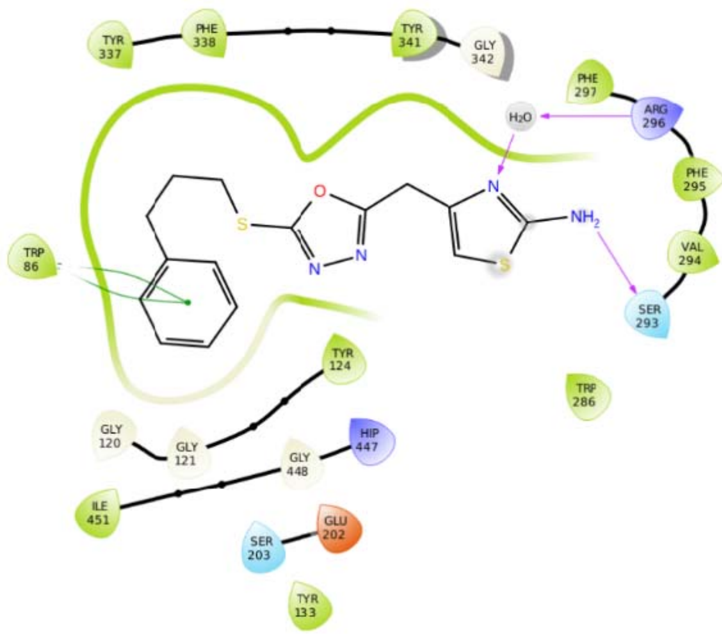


Fig. S-17. Docking image of **5n** against AChE.

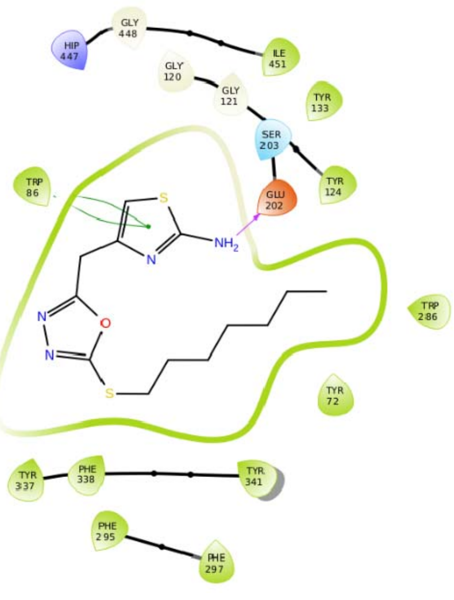


Fig. S-18. Docking image of **5o** against AChE.

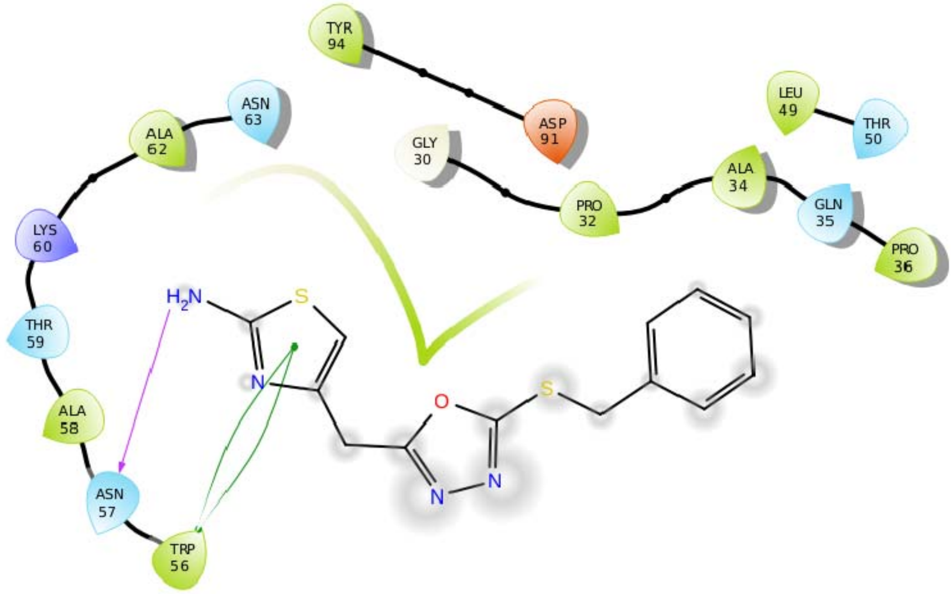


Fig. S-19. Docking image of **5a** against BChE.

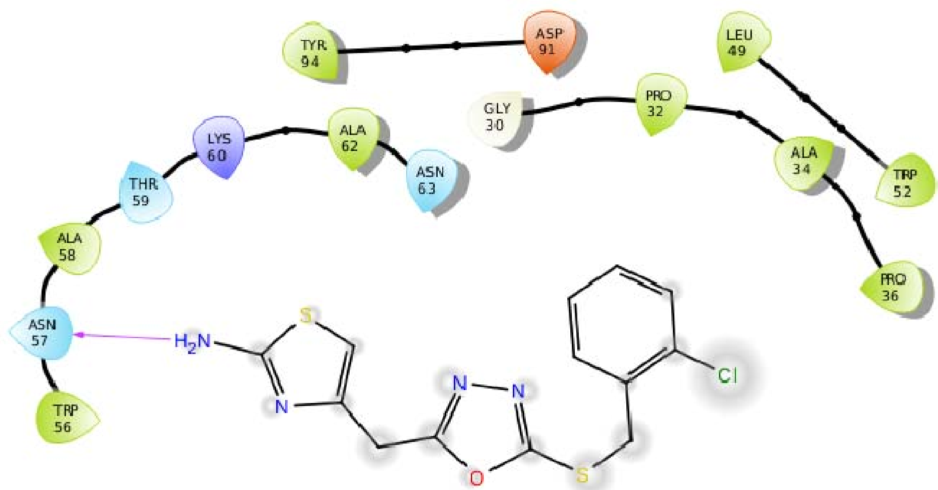


Fig. S-20. Docking image of **5b** against BChE.

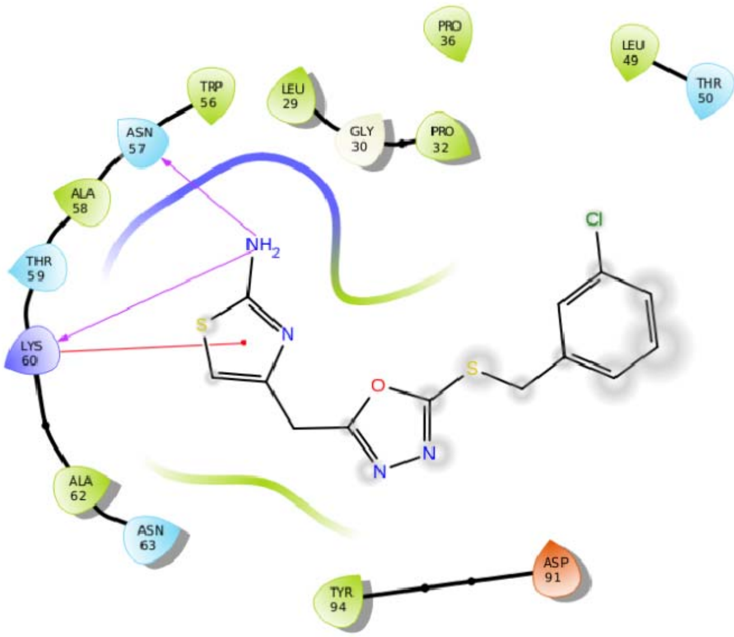


Fig. S-21. Docking image of **5c** against BChE.

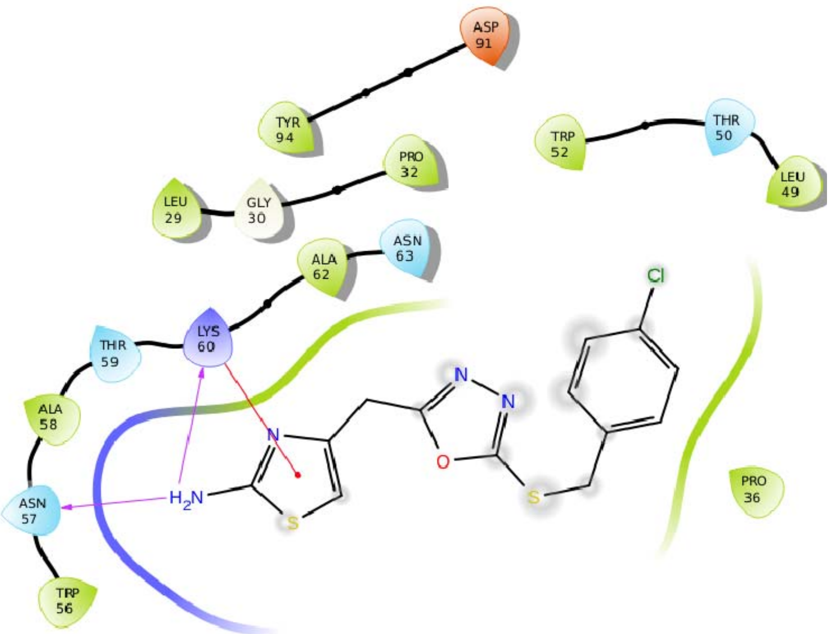


Fig. S-22. Docking image of **5d** against BChE.

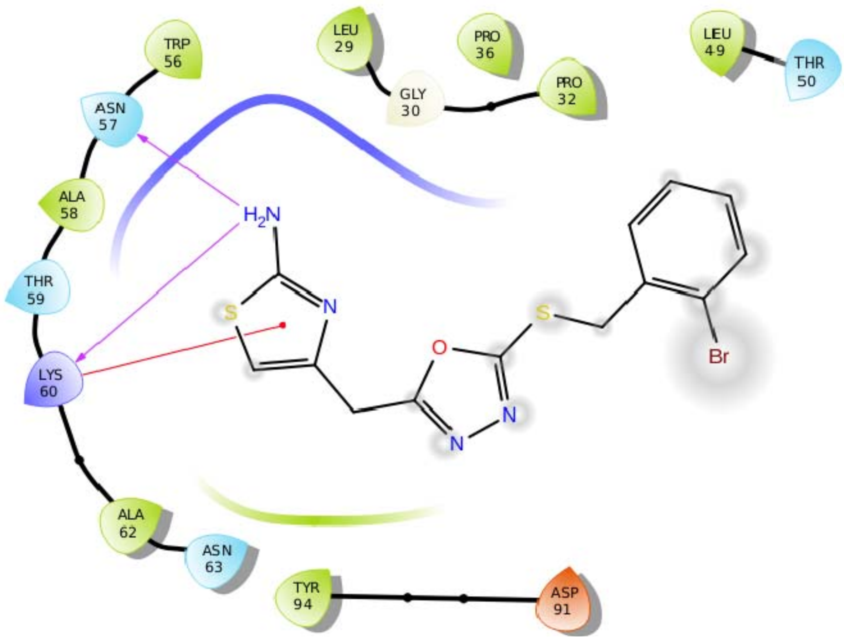


Fig. S-23. Docking image of **5e** against BChE.

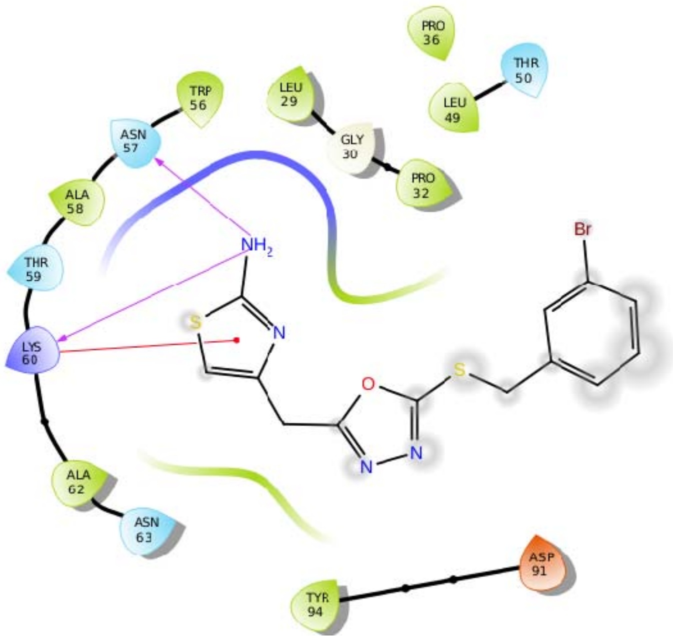


Fig. S-24. Docking image of **5f** against BChE.

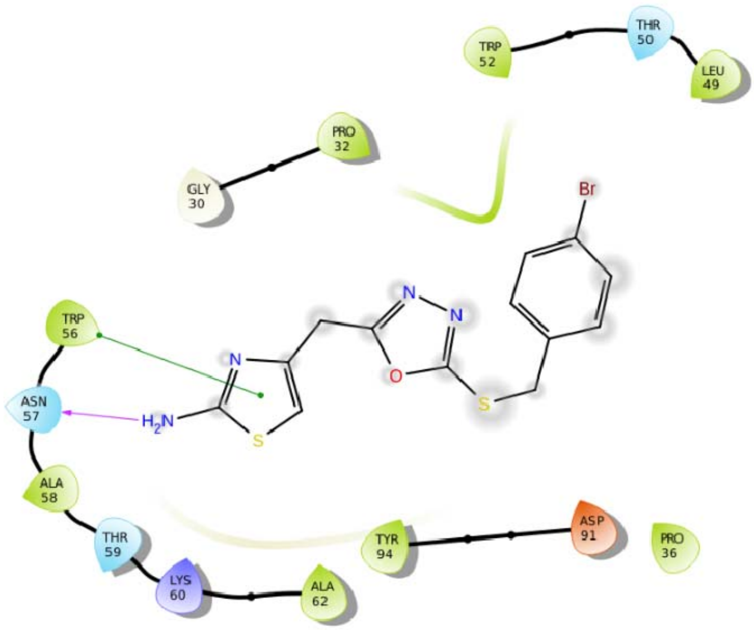


Fig. S-25. Docking image of **5g** against BChE.

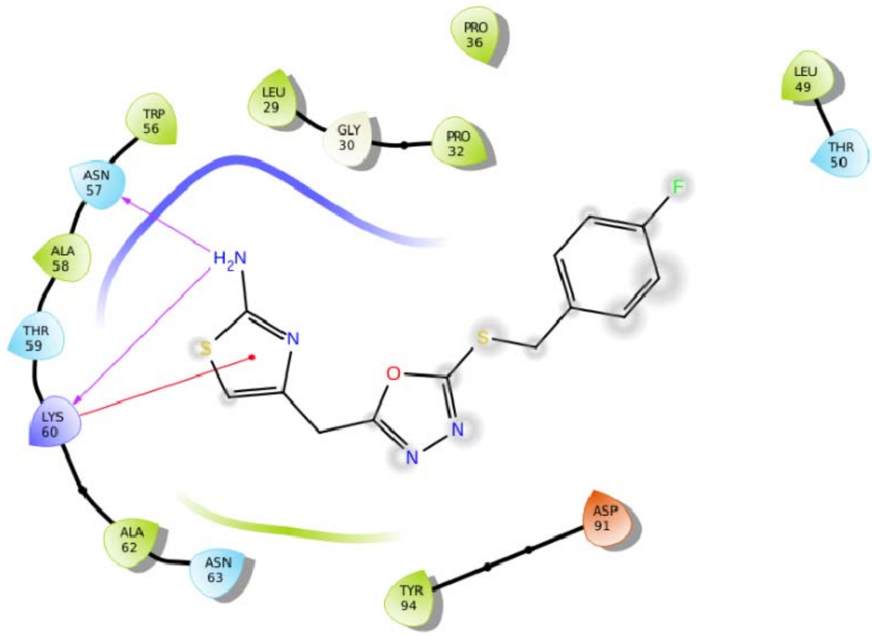


Fig. S-26. Docking image of **5h** against BChE.

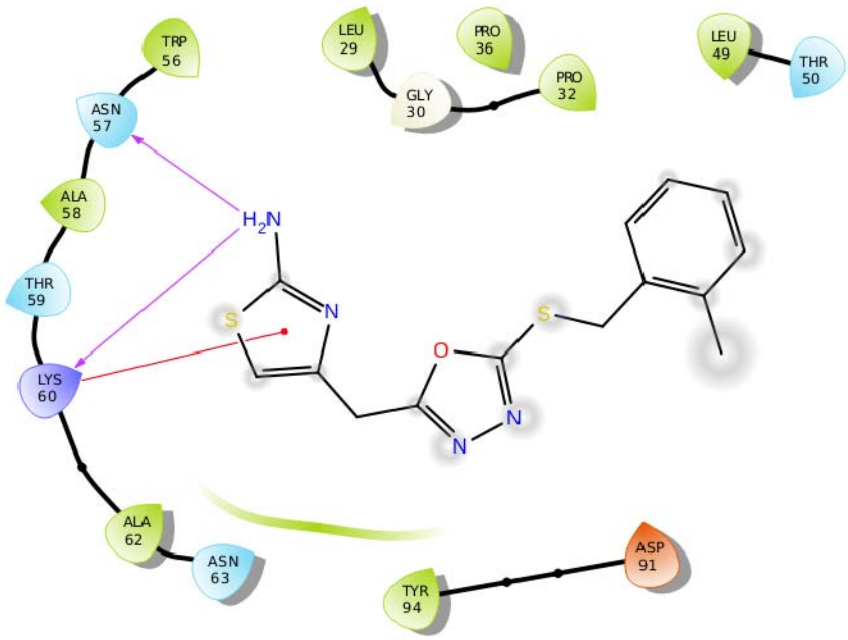


Fig. S-27. Docking image of **5i** against BChE.

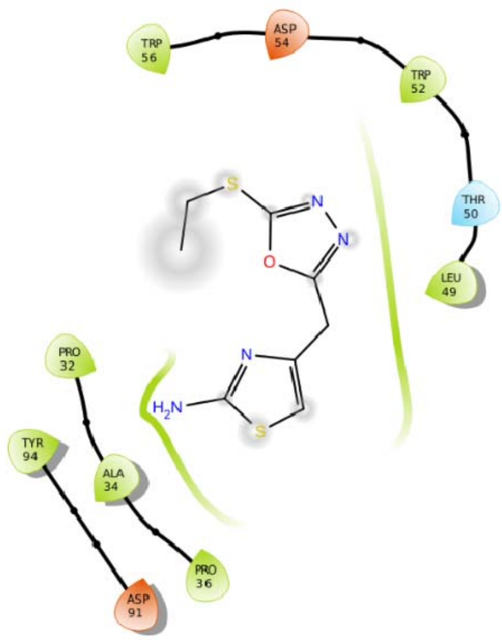


Fig. S-28. Docking image of **5j** against BChE.

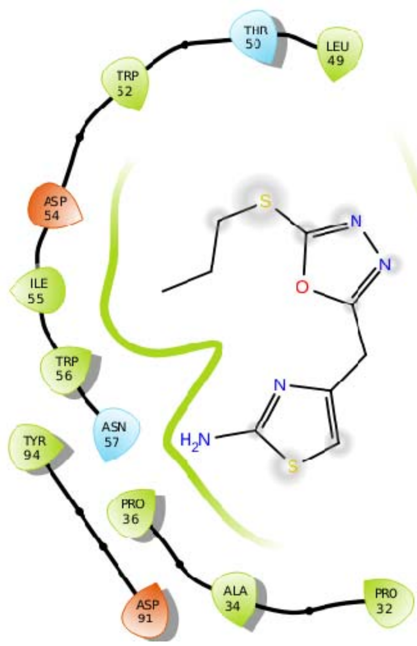


Fig. S-29. Docking image of **5k** against BChE.

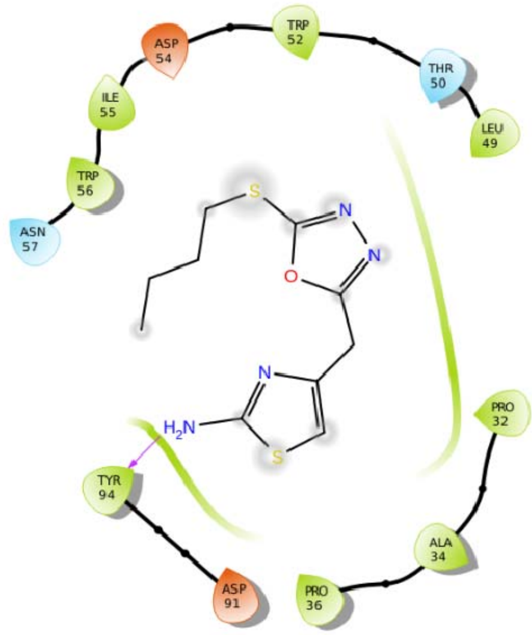


Fig. S-30. Docking image of **5l** against BChE.

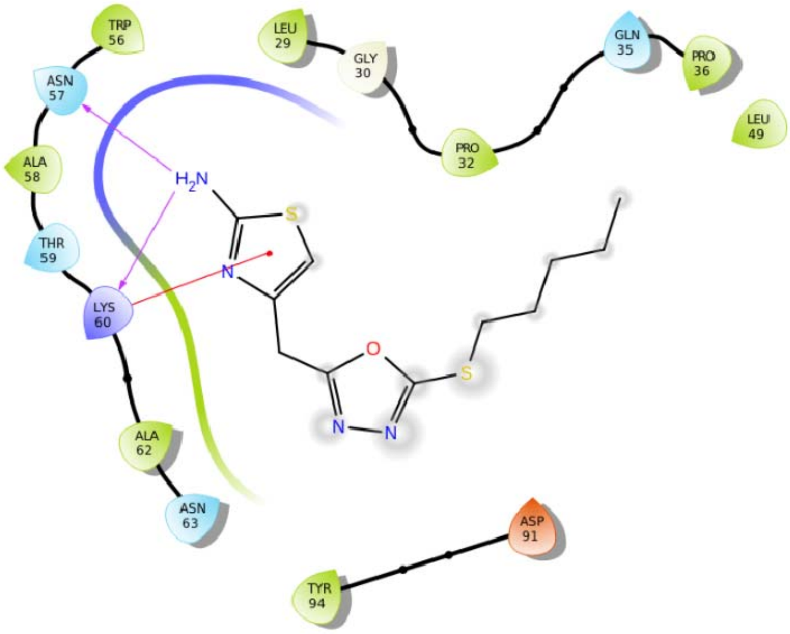


Fig. S-31. Docking image of **5m** against BChE.

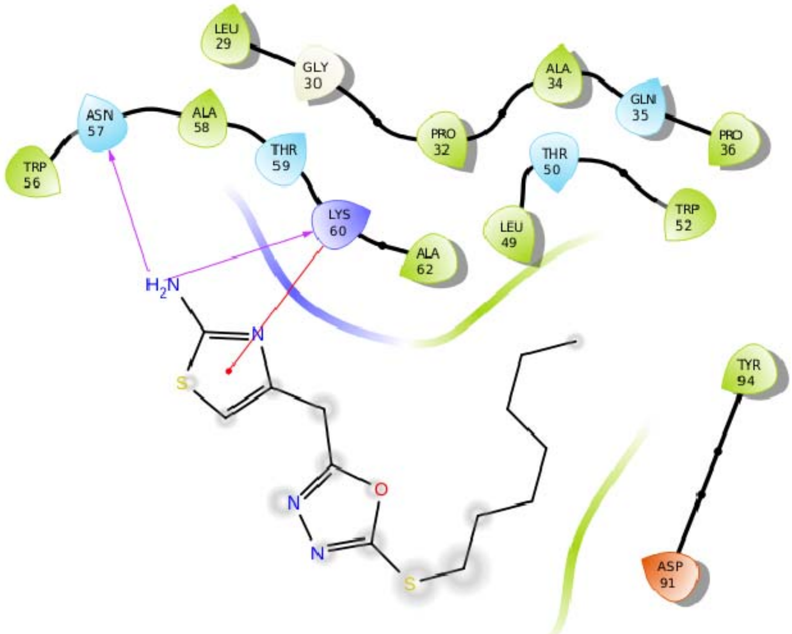


Fig. S-32. Docking image of **5n** against BChE.

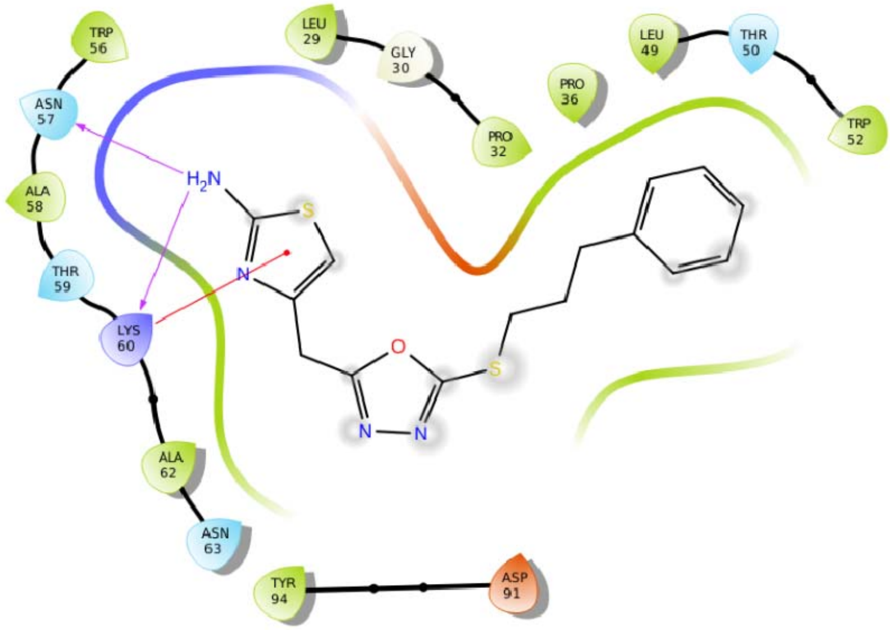


Fig. S-33. Docking image of **5o** against BChE.

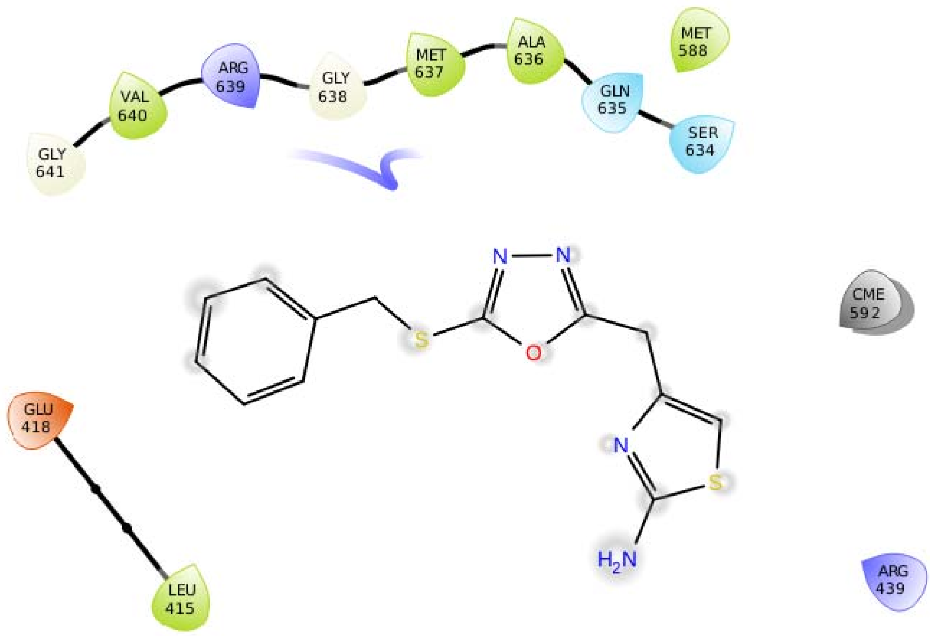


Fig. S-34. Docking image of **5a** against urease.

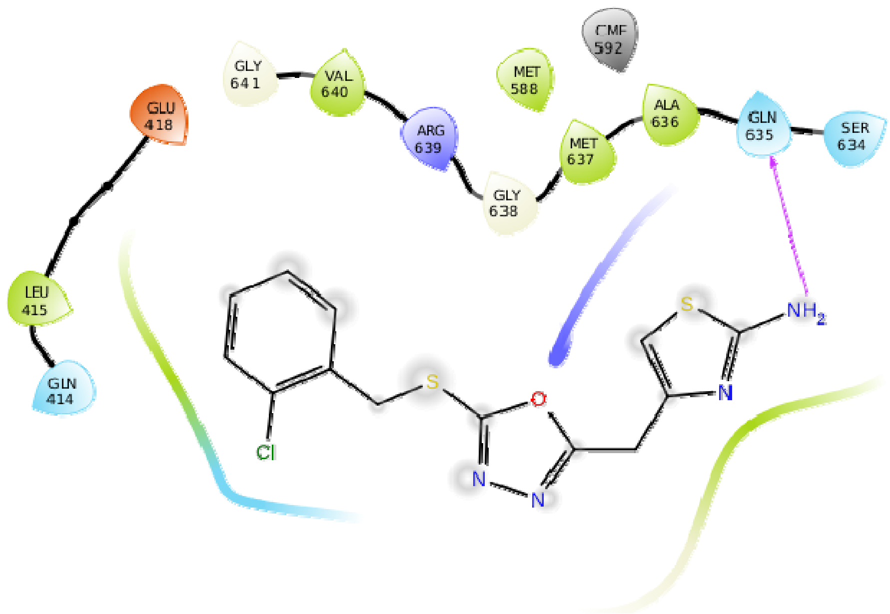


Fig. S-35. Docking image of **5b** against urease.

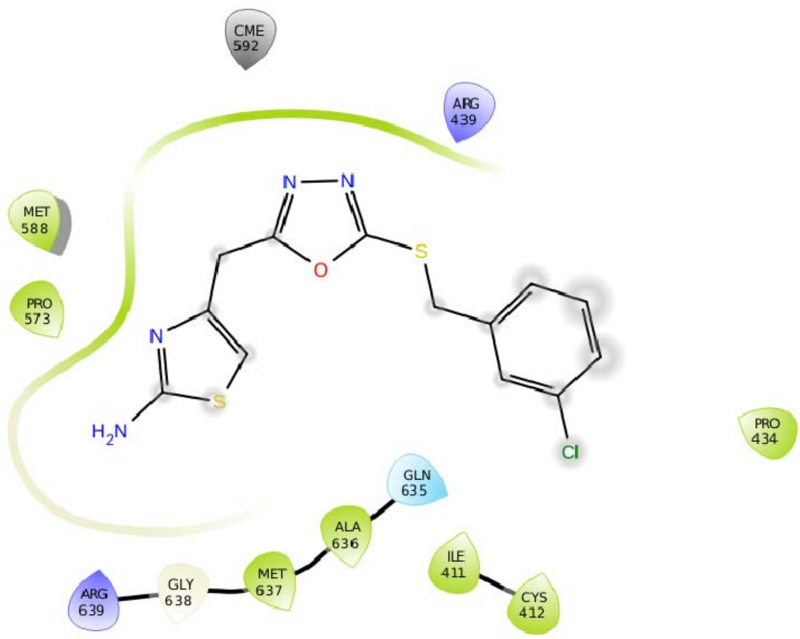


Fig. S-36. Docking image of **5c** against urease.

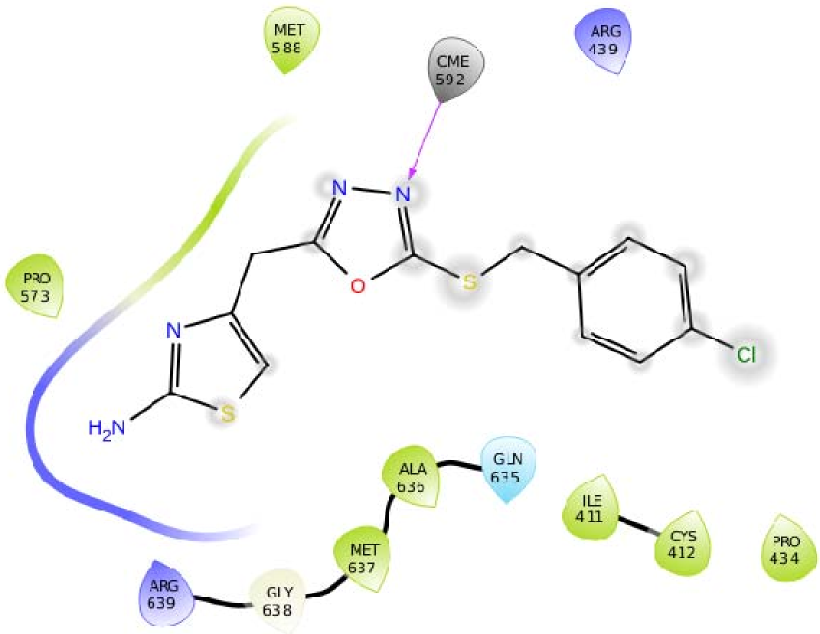


Fig. S-37. Docking image of **5d** against urease.

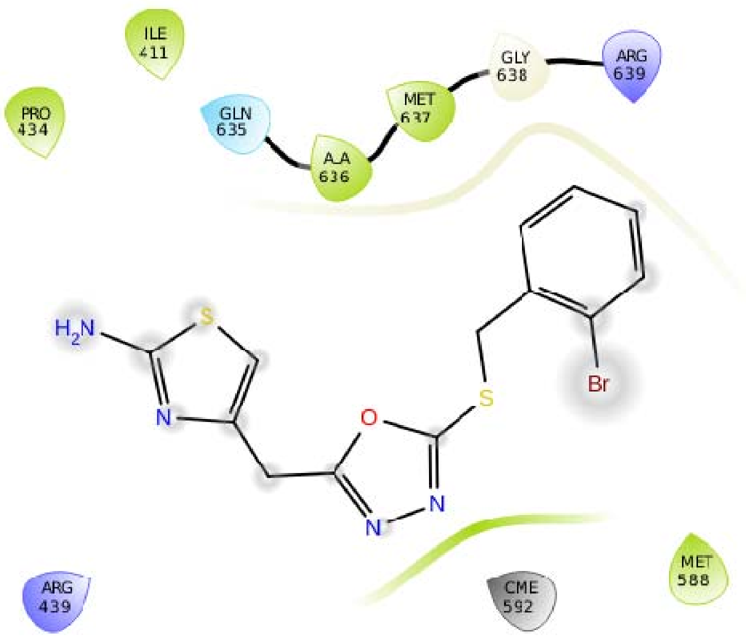


Fig. S-38. Docking image of **5e** against urease.

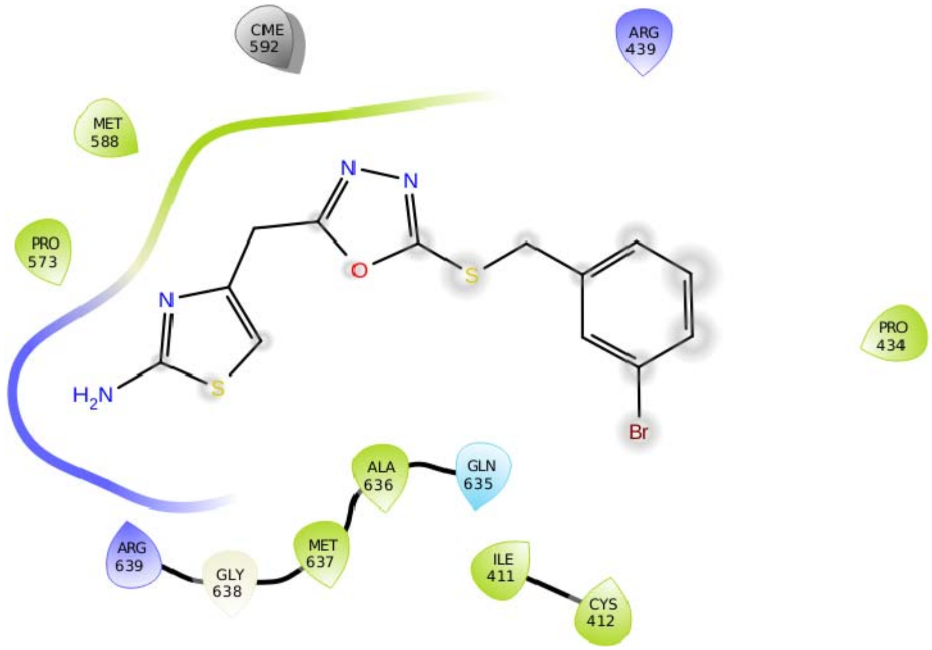


Fig. S-39. Docking image of **5f** against urease.

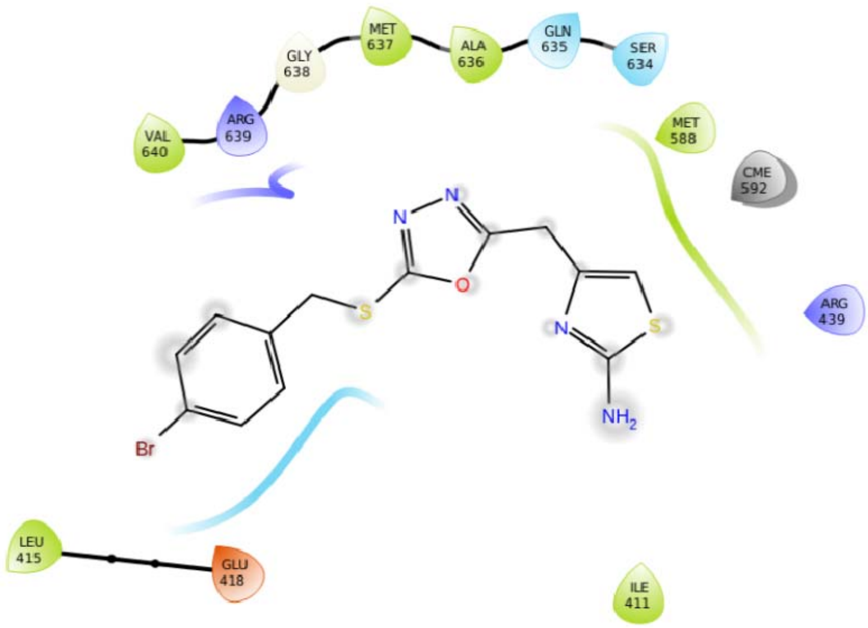


Fig. S-40. Docking image of **5g** against urease.

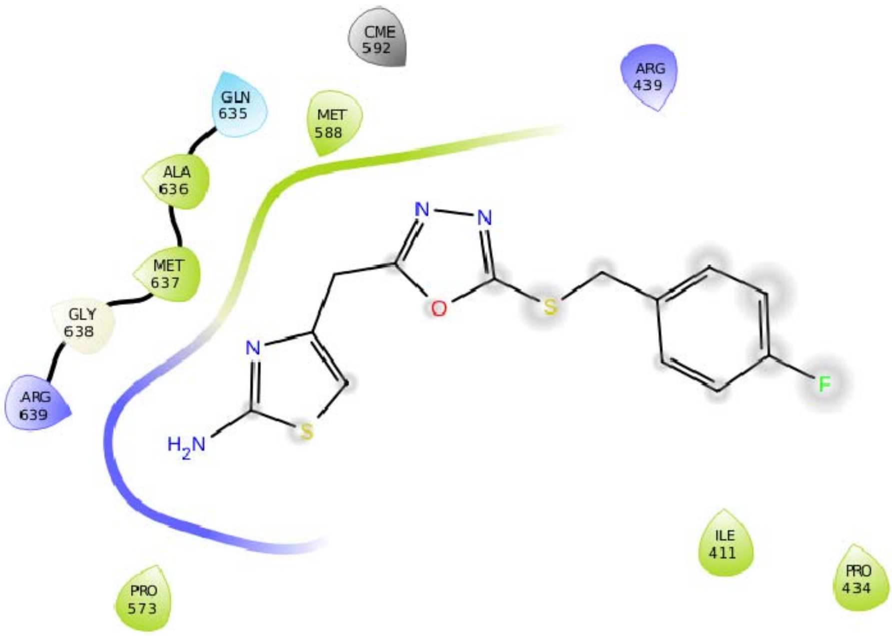


Fig. S-41. Docking image of **5h** against urease.

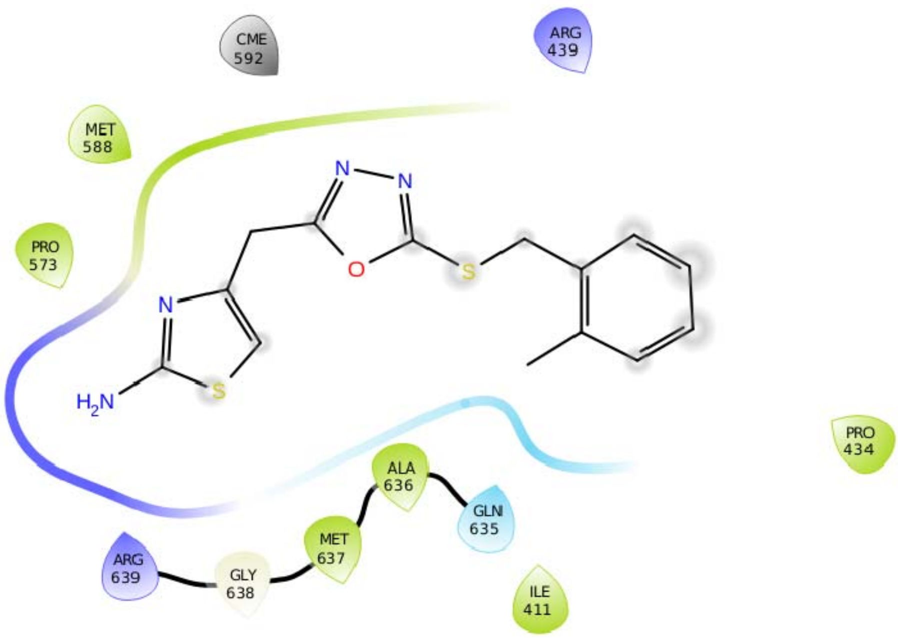


Fig. S-42. Docking image of **5i** against urease.

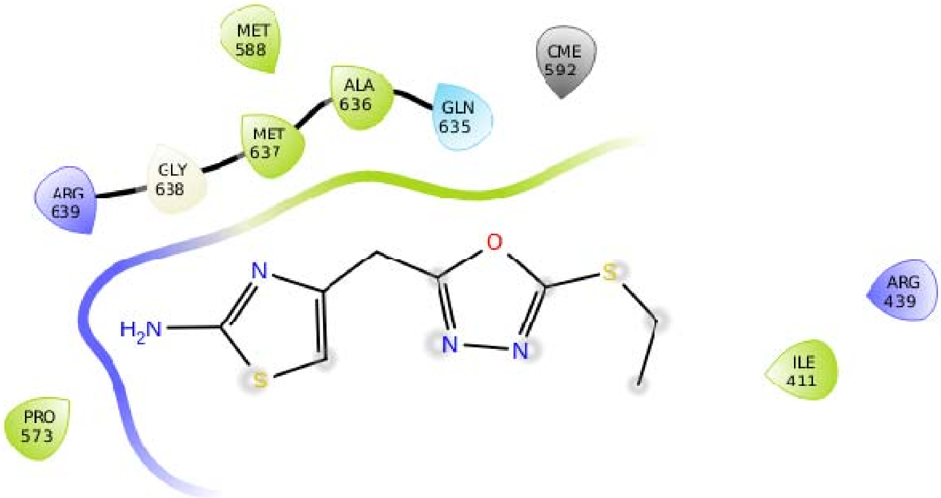


Fig. S-43. Docking image of **5j** against urease.

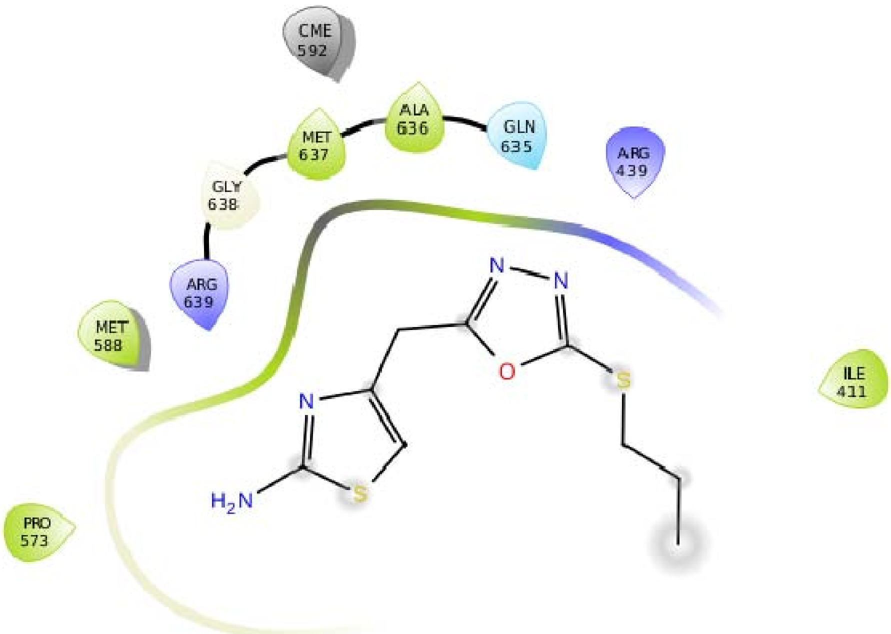


Fig. S-44. Docking image of **5k** against urease.

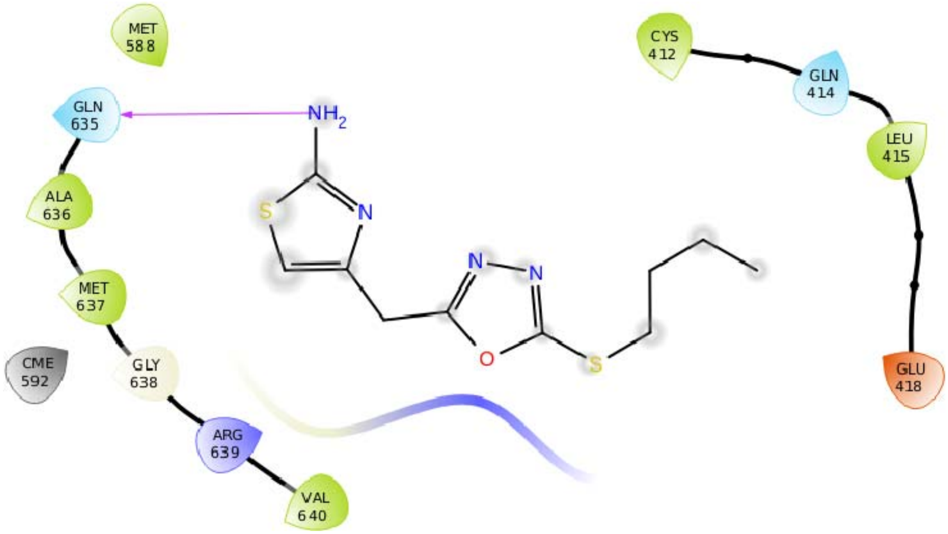


Fig. S-45. Docking image of **5l** against urease.

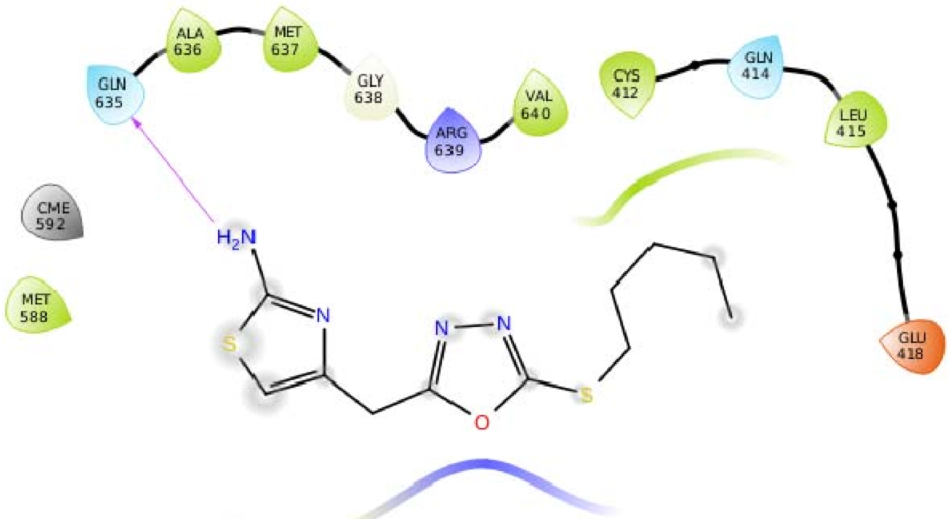


Fig. S-46. Docking image of **5m** against urease.

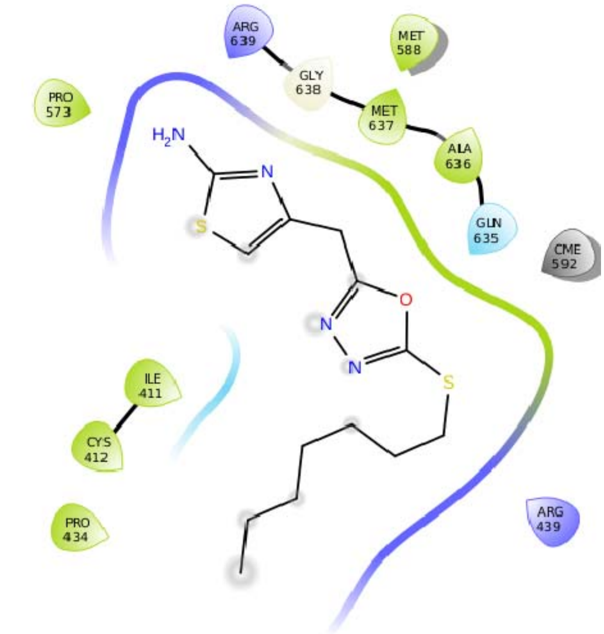


Fig. S-47. Docking image of **5n** against urease.

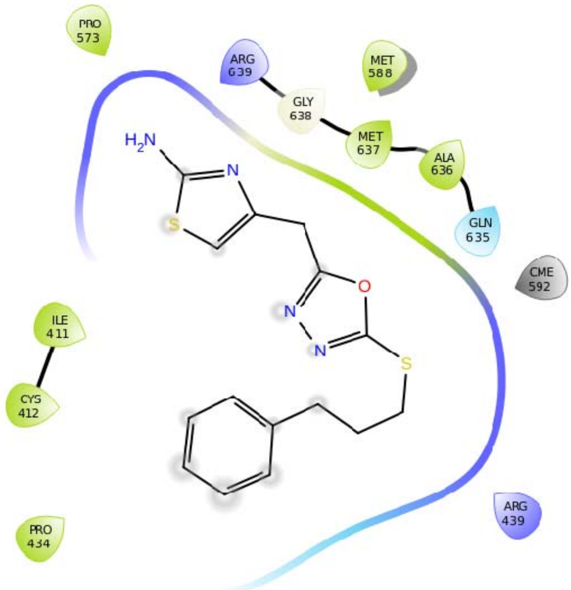


Fig. S-48. Docking image of **5o** against urease.

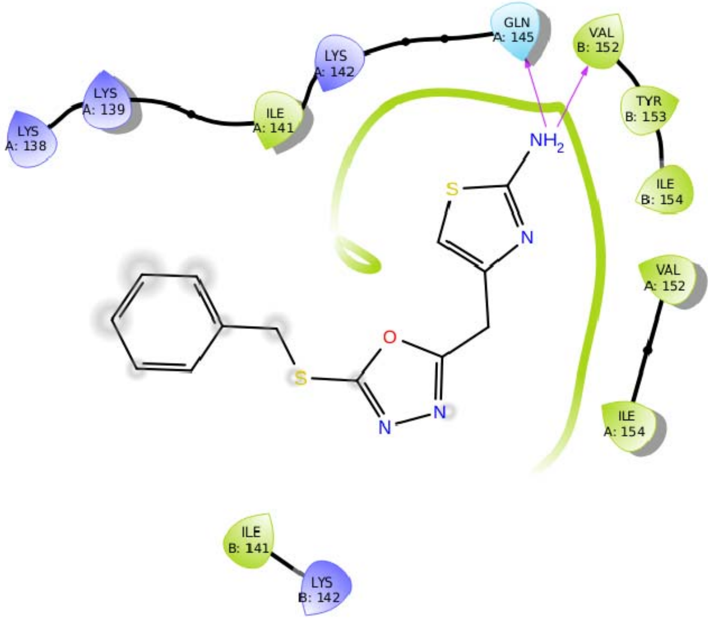


Fig. S-49. Docking image of **5a** against α-glucosidase.

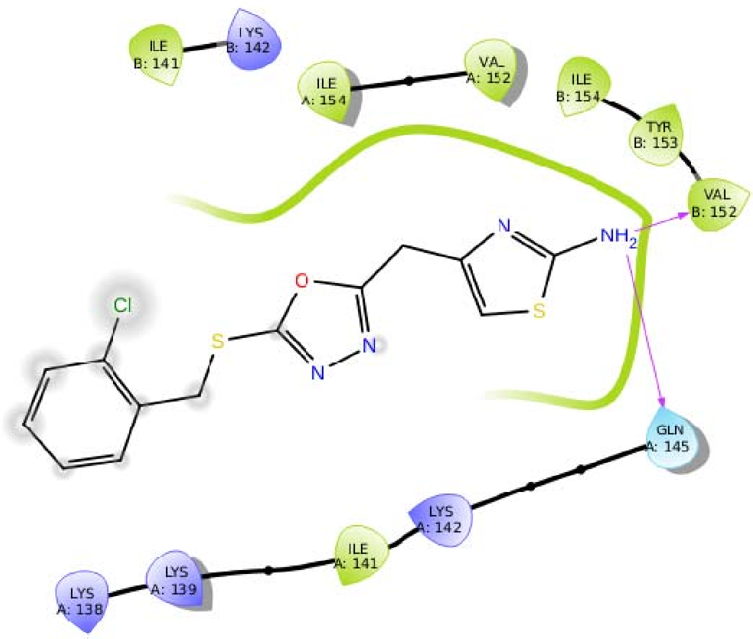


Fig. S-50. Docking image of **5b** against α-glucosidase.

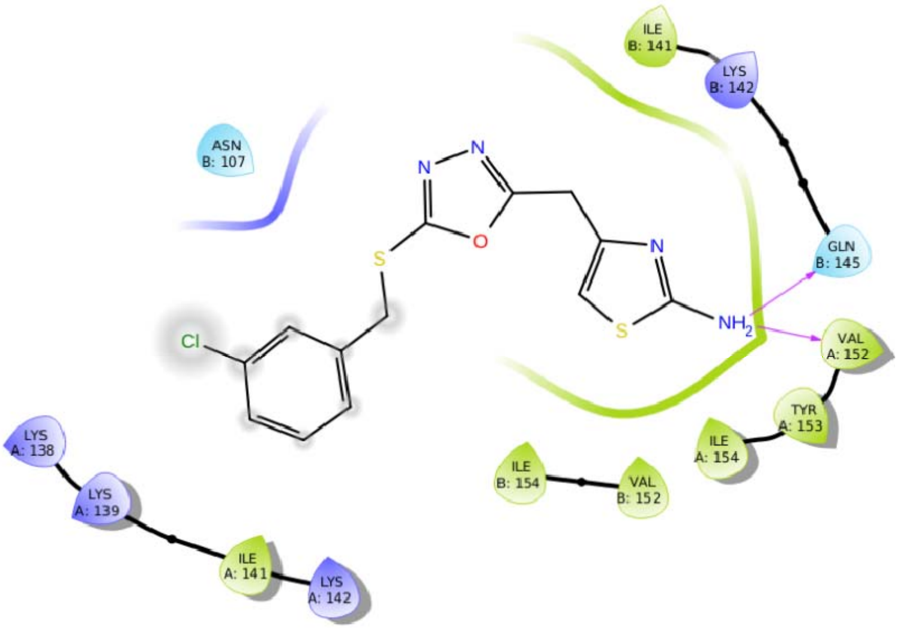


Fig. S-51. Docking image of **5c** against α-glucosidase.

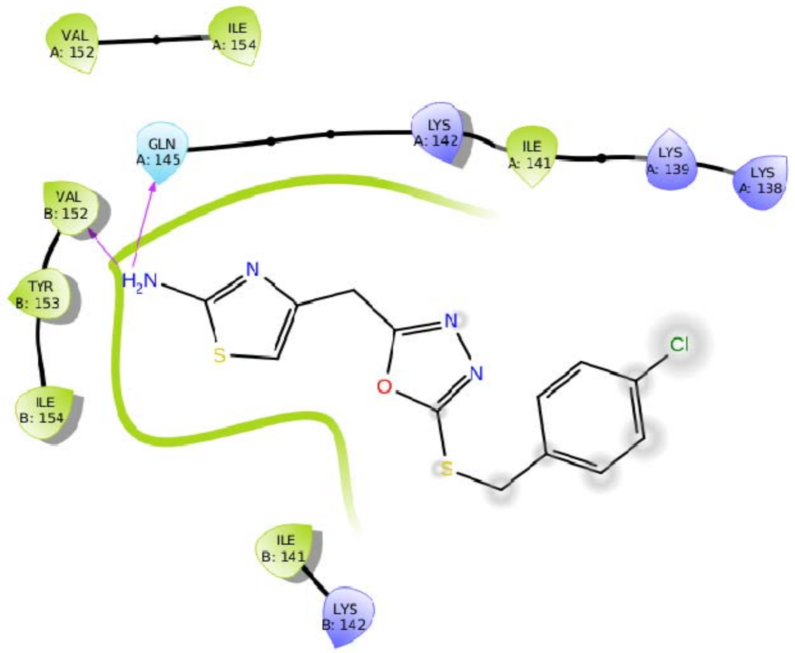


Fig. S-52. Docking image of **5d** against α-glucosidase.

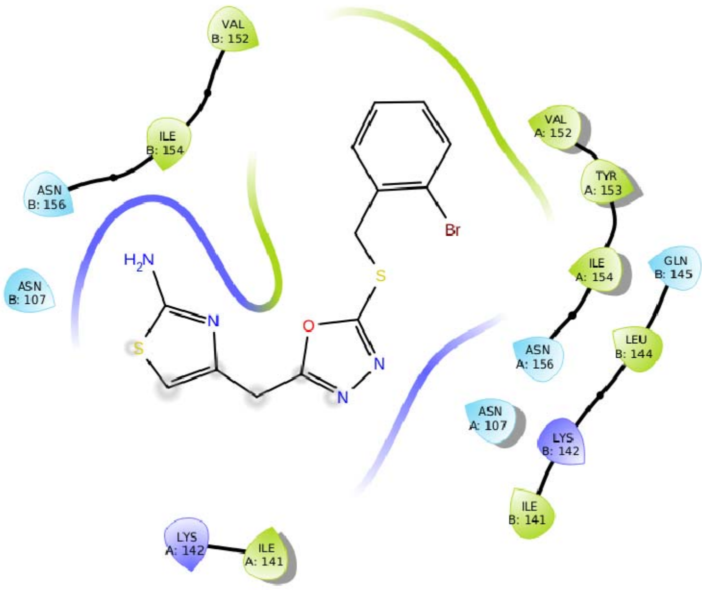


Fig. S-53. Docking image of **5e** against α-glucosidase.

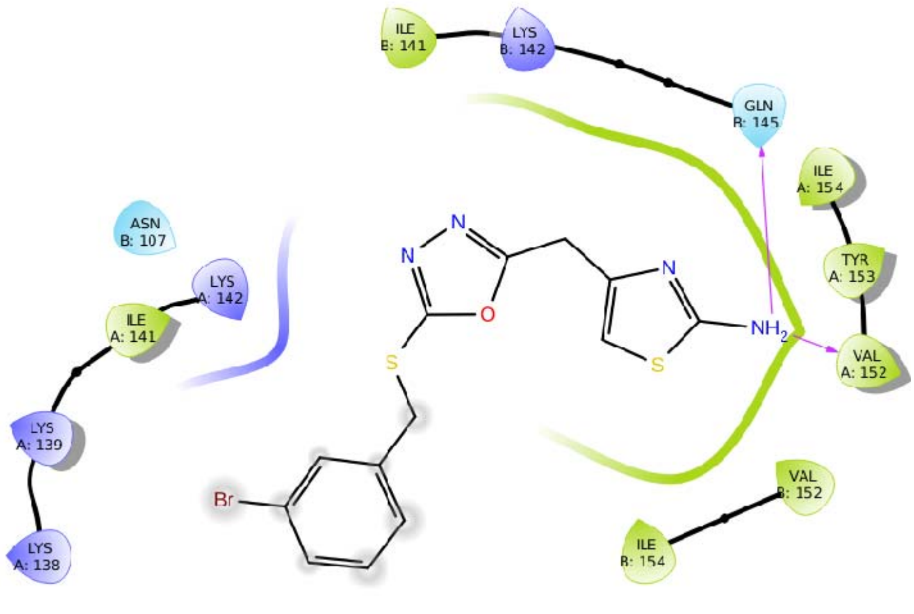


Fig. S-54. Docking image of **5f** against α-glucosidase.

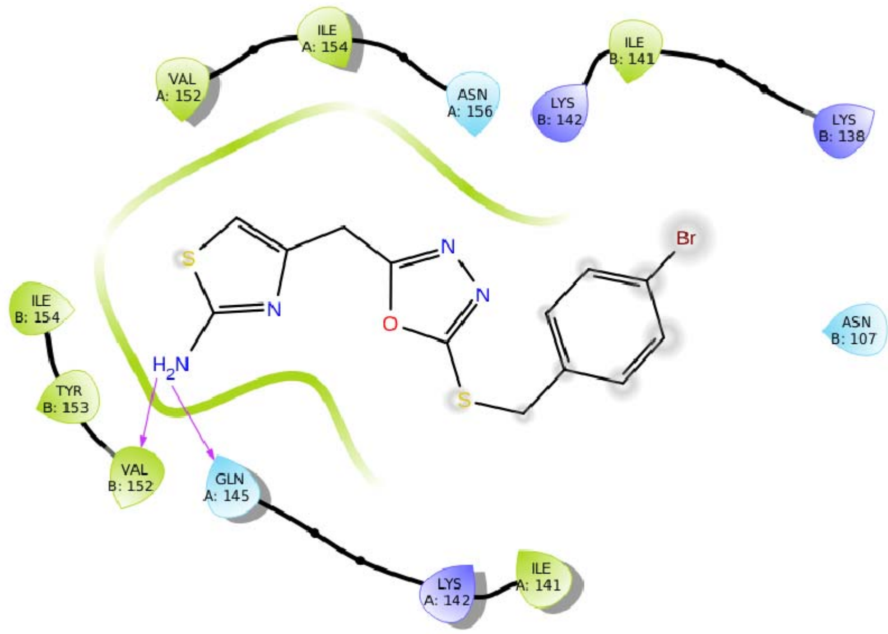


Fig. S-55. Docking image of **5g** against α-glucosidase.

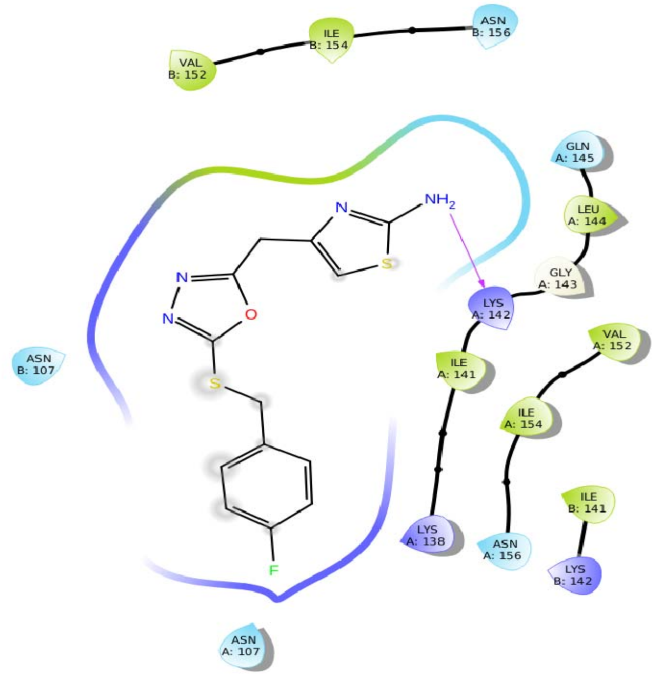


Fig. S-56. Docking image of **5h** against α-glucosidase.

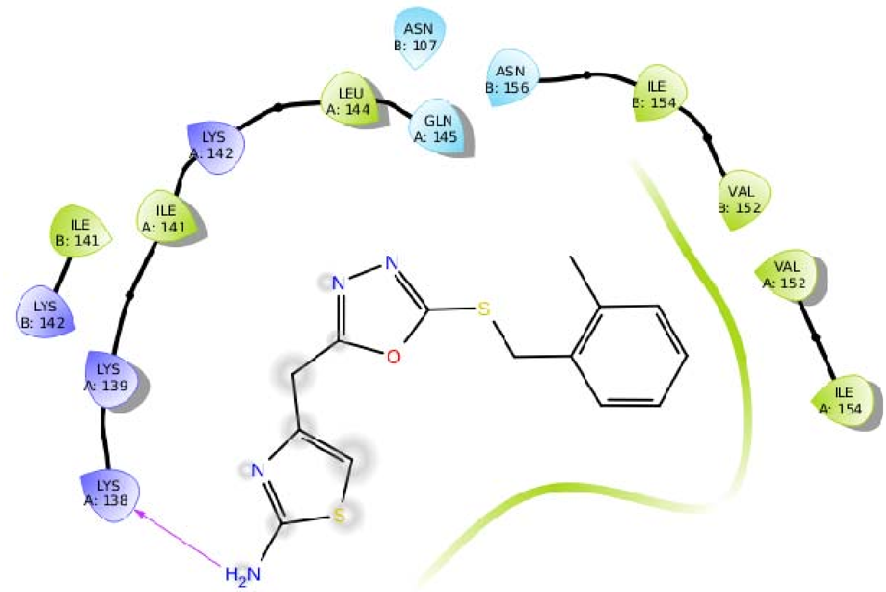


Fig. S-57. Docking image of **5i** against α-glucosidase.

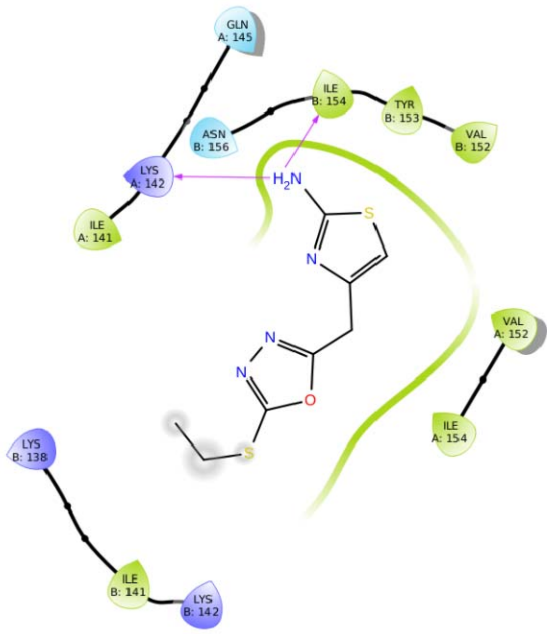


Fig. S-58. Docking image of **5j** against α-glucosidase.

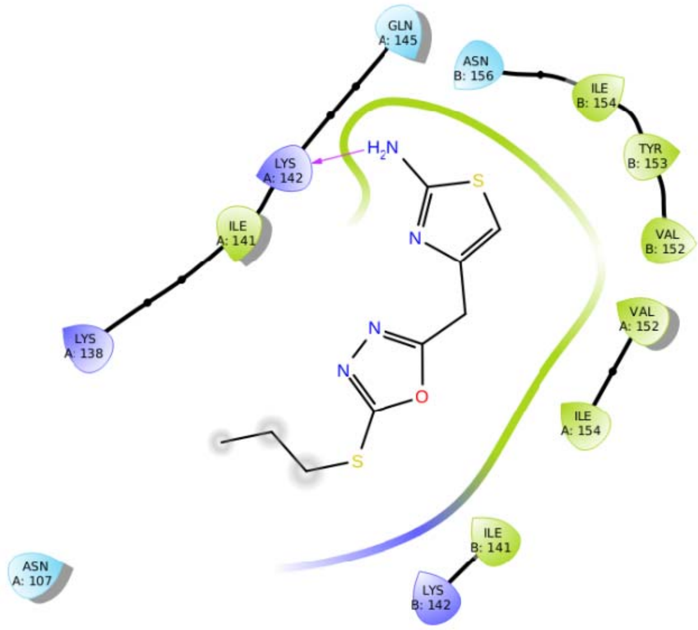


Fig. S-59. Docking image of **5k** against α-glucosidase.

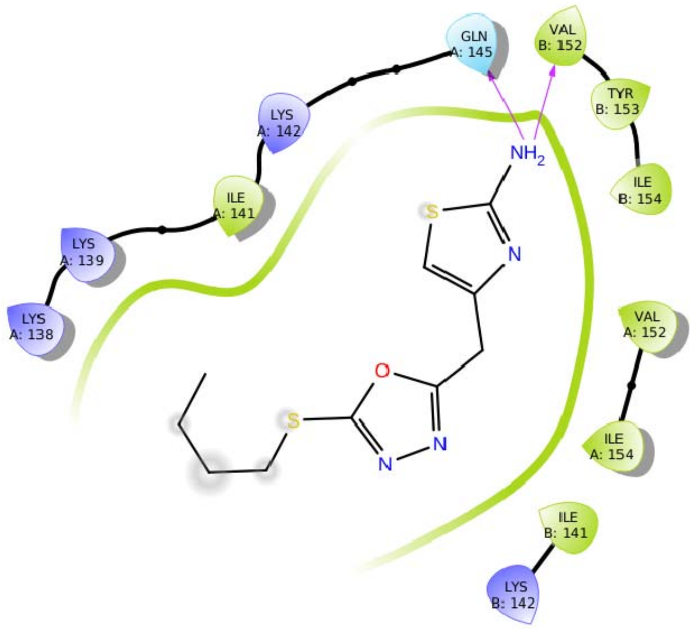


Fig. S-60. Docking image of **5l** against α-glucosidase.

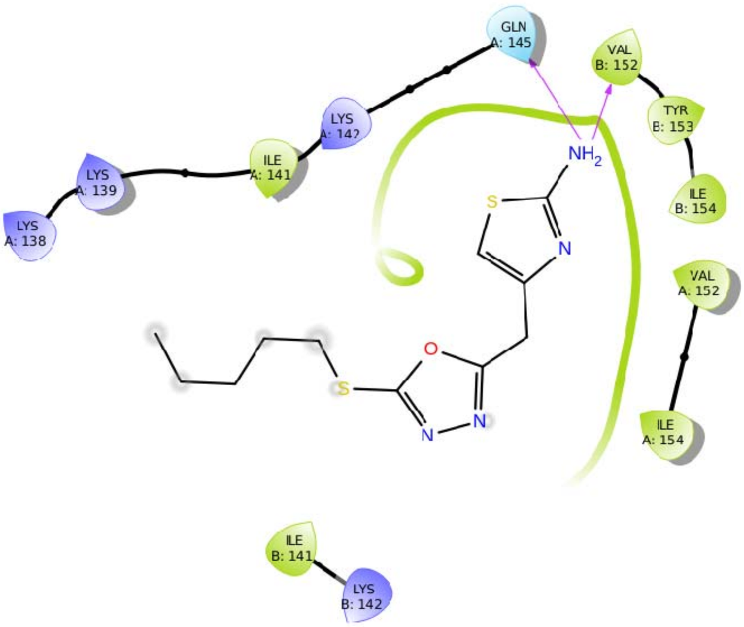


Fig. S-61. Docking image of **5m** against α-glucosidase.

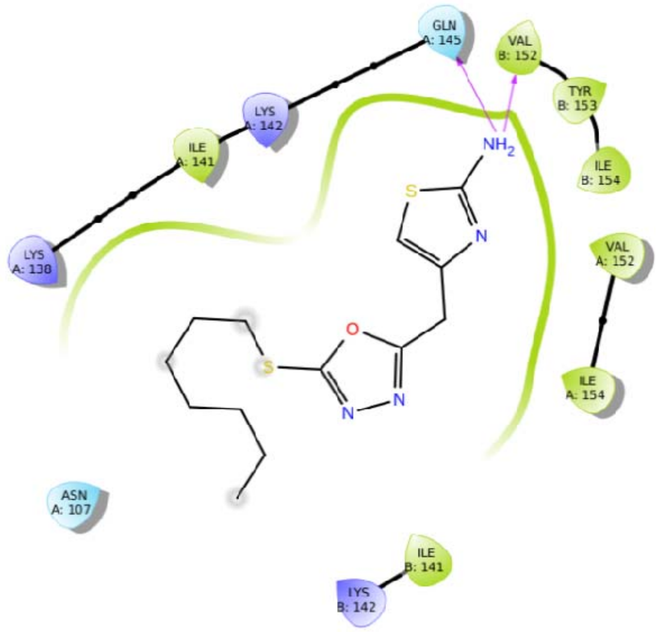


Fig. S-62. Docking image of **5n** against α-glucosidase.

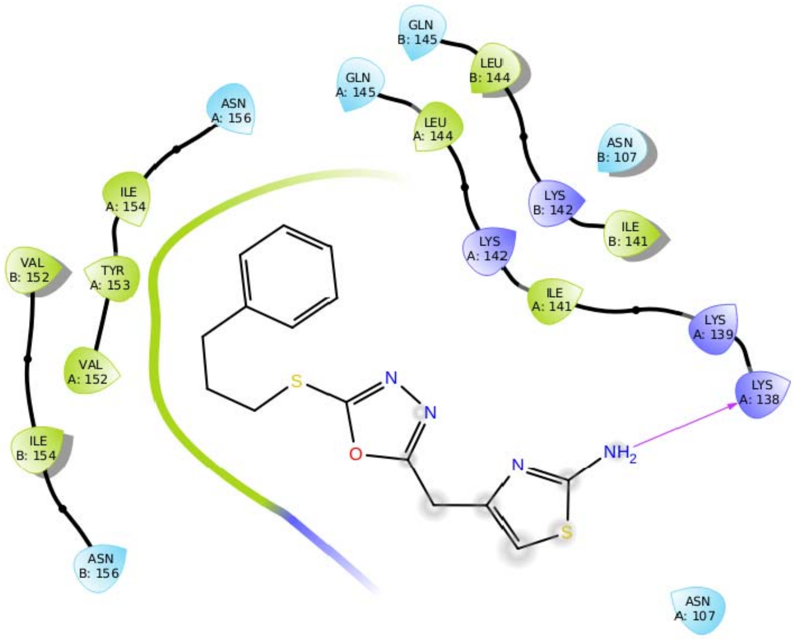


Fig. S-63. Docking image of **5o** against α-glucosidase.