

Table S1: 2D structure representation of various 4-hydroxyisoleucine derivatives

VAL-L-4HILe 	2R,3S,4S-4HILe 	2R,3S,4R-4HILe 	4HILe-5 	4HILe-Amide-2
ALA-L-4HILe 	2R,3R,4R-4HILe 	4HILe-1 	4HILe-6 	4HILe-Amide-3
THR-L-4HILe 	2S,3S,4S-4HILe 	4HILe-2 	4HILe-7 	2S,3R,4R-4HILe
GLY-L-4HILe 	2R,3R,4S-4HILe 	4HILe-3 	4HILe 	
SER-L-4HILe 	2S,3S,4R-4HILe 	4HILe-4 	4HILe-Amide-1 	

Table S2: Docking score representation of various 4-hydroxyisoleucine derivatives against diabetes targets

Ligand	α -glucosidase (5NN8) Kcal/mol	α -amylase (4GQR) Kcal/mol	Aldose reductase (4QX4) Kcal/mol
Co-crystal	-7.2	-8.2	-7.6
4HILe-Amide-1	-5.9	-7.8	-6.9
4HILe-Amide-2	-7.7	-7.2	-7.7
4HILe-Amide-3	-5.6	-7.3	-6.6
4HILe	-6.8	-9.4	-7.4
4HILe-1	-6.2	-7.9	-6.2
4HILe-2	-6.4	-7.1	-6.1
4HILe-3	-6.4	-7.7	-6.3
4HILe-4	-8.3	-7	-6.6
4HILe-5	-6.1	-6.1	-6.1
4HILe-6	-6.1	-6.5	-6.1
4HILe-7	-6.4	-6.8	-6.4
VAL-L-4HILe	-6	-7.4	-6
ALA-L-4HILe	-6.8	-6	-7
THR-L-4HILe	-7.4	-5.8	-7
SER-L-4HILe	-6.9	-7.3	-6.9
GLY-L-4HILe	-6.1	-6.5	-6.1
2R,3R,4S-4HILe	-6.9	-6.3	-6.9
2S,3R,4R-4HILe	-5.4	-6.4	-6.4
2S,3S,4S-4HILe	-4.1	-6.9	-5.1
2S,3S,4R-4HILe	-6.7	-6.7	-6.7
2R,3S,4R-4HILe	-6.8	-7.9	-6.8
2R,3S,4S-4HILe	-6.7	-7.7	-6.7
2R,3R,4R-4HILe	-4.1	-6.6	-7.1

Table S3: Hydrophobic interactions of 4-hydroxyisoleucine derivatives against various diabetes targets

S.no	ligand	Hydrophobic interactions (4qx4)	Hydrophobic interactions (5nn8)	Hydrophobic interactions (4gqr)
1	4HILe-Amide-1	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 PHE-122 TYR-209 TRP-219 CYS-298	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 PHE-649 LEU-650	TRP-59 TYR-62 LEU-162 LEU-165 ALA-198
2	4HILe-Amide-2	TRP-20 VAL-47 TYR-48	TRP-376 ILE-441 TRP-481	TRP-58 TRP-59 TYR-62

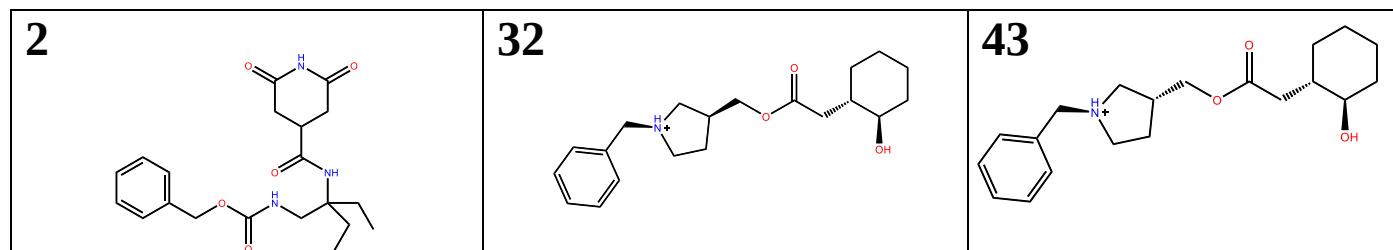
		TRP-79 TRP-111 PHE-122 TYR-209 TRP-219 CYS-298 LEU-300	MET-519 PHE-525 PHE-649 LEU-650	LEU-162 LEU-165 ALA-198
3	4HILe- Amide-3	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 PHE-122 TRP-219 CYS-298 LEU-300 LEU-301	ALA-284 TRP-376 ILE-441 TRP-516 PHE-525 ALA-555 PHE-649	TRP-58 TRP-59 TYR-62 TYR-151 LEU-162
4	4HILe	TRP-20 TYR-48 TRP-79 TRP-111 TRP-219 CYS-298	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 TRP-613 PHE-649	TRP-58 TYR-62 LEU-165
5	4HILe-1	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 TYR-209 CYS-298	TRP-376 TRP-481 TRP-516 MET-519 PHE-649	TRP-58 TYR-62 LEU-162 ALA-198
6	4-HILe-2	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 TYR-209 CYS-298	TRP-516 MET-519 PHE-649	TRP-58 TYR-62 LEU-162 LEU-165 ALA-198
7	4-HILe-3	TYR-209 ILE-260 CYS-298	TRP-376 TRP-516 MET-519 PHE-649	TRP-59 LEU-162 LEU-165 ALA-198 ILE-235
8	4-HILe-4	TRP-20 VAL-47	TRP-376 TRP-516	TRP-58 TRP-59

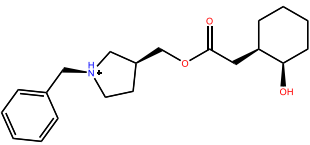
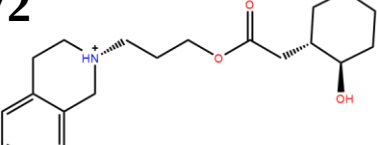
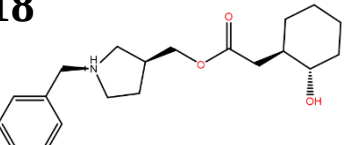
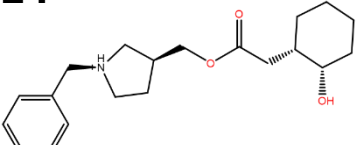
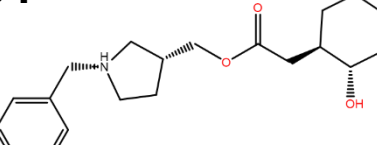
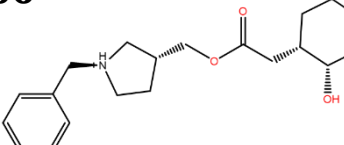
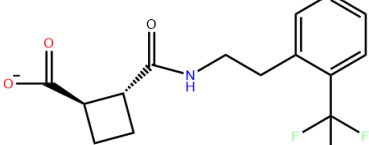
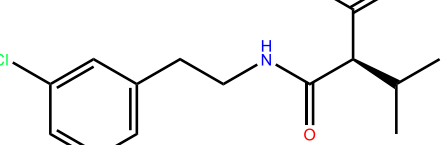
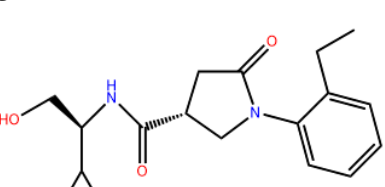
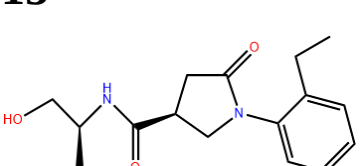
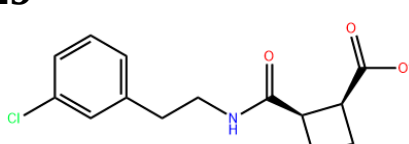
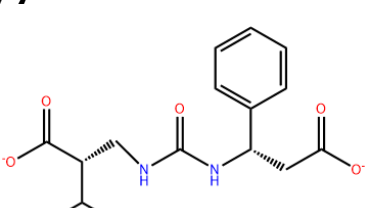
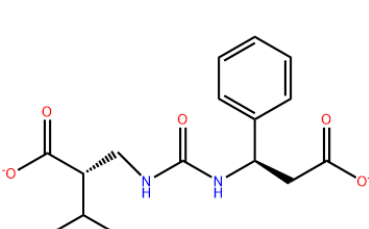
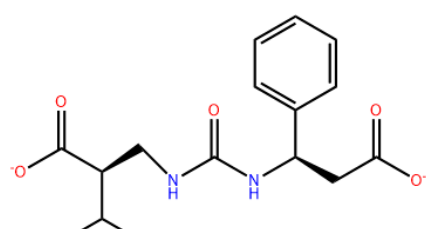
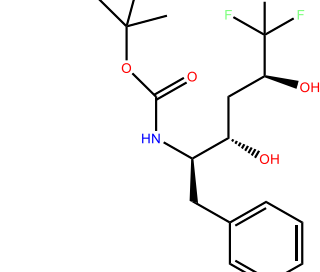
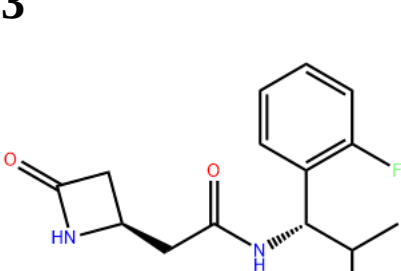
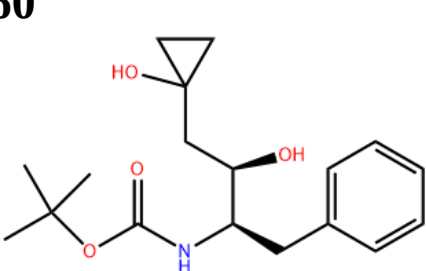
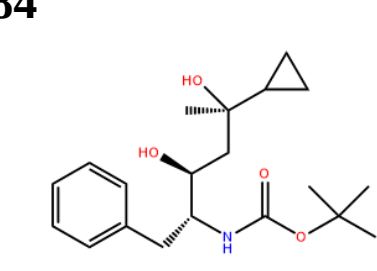
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9	4-HILe-5	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 PHE-122 TRP-219 CYS-298 LEU-300	TRP-376 TRP-516 MET-519 PHE-649 LEU-650	TRP-58 TRP-59 TYR-62 LEU-162 LEU-165 ALA-198 ILE-235
10	4-HILe-6	TRP-20 TYR-48 TRP-79 TRP-111 PHE-122 TYR-209 TRP-219 CYS-298 LEU-300	TRP-376 TRP-516 MET-519 PHE-649 LEU-650 LEU-677 LEU-678	TRP-58 TRP-59 TYR-62 LEU-162 ALA-198 ILE-235
11	4-HILe-7	TRP-20 TYR-48 TRP-111 PHE-122 TYR-209 TRP-219 CYS-298 LEU-300	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 PHE-649 LEU-650 LEU-677	TRP-58 TRP-59 TYR-62 LEU-162 LEU-165 ALA-198
12	VAL-L-4HILe	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 PHE-122 TYR-209 TRP-219 LEU-300	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 PHE-649	TRP-58 TYR-62 LEU-162 LEU-165 ALA-198 ILE-235
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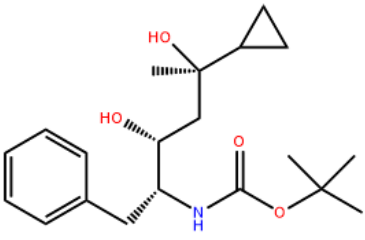
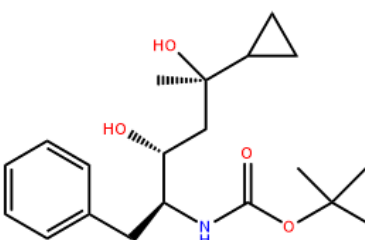
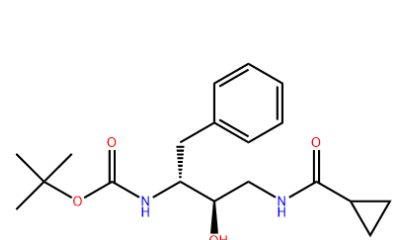
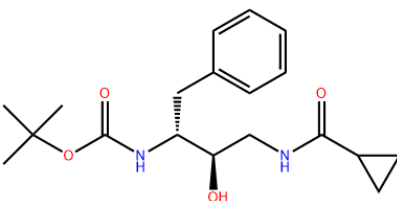
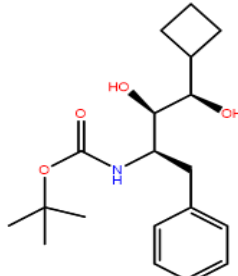
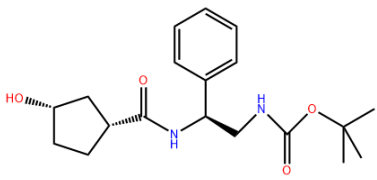
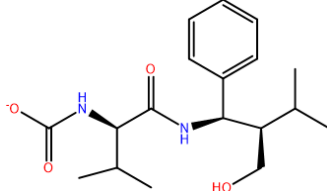
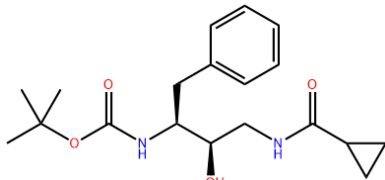
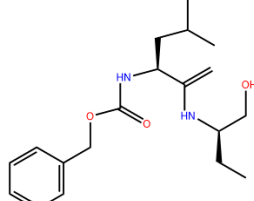
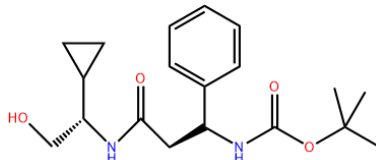
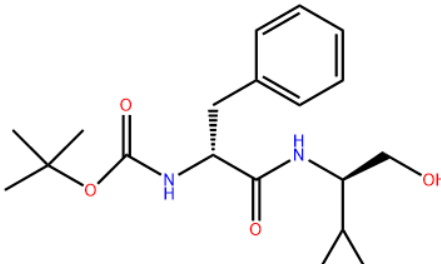
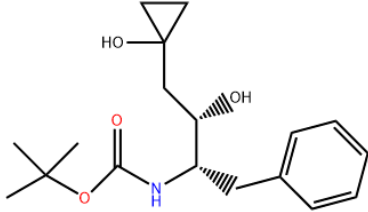
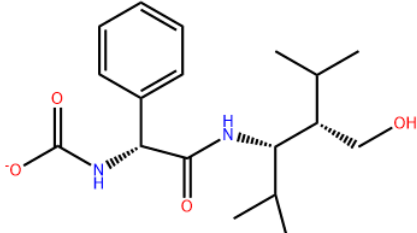
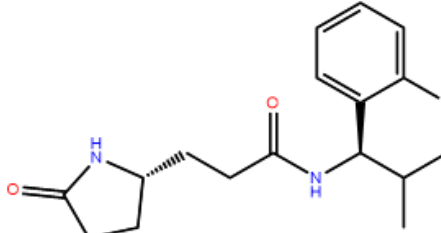
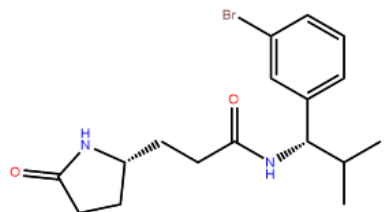
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15	SER-L-4HILe	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 TYR-209 TRP-219 CYS-298	TRP-481 TRP-516 MET-519 TRP-613 PHE-649	TRP-58 TRP- 59 TYR-62 LEU-162
16	GLY-L-4HILe	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 PHE-122 TYR-209 TRP-219 LEU-300	ILE-283 ALA-284 TRP-376 ILE-441 TRP-481 MET-519	TRP-58 TYR-62 LEU-162 ALA-198
17	2R,3R,4S-4HILe	TYR-48 TRP-79 TRP-111 TYR-209 CYS-298 LEU-300	TRP-376 ILE-441 TRP-481 TRP-516 TRP-613 PHE-649	TRP-58 TYR-62
18	2S,3R,4R-4HILe	TYR-48 TRP-79 TRP-111	TRP-376 ILE-441 TRP-481 TRP-516 MET-519 PHE-649	TRP-58 TYR-62 LEU-162

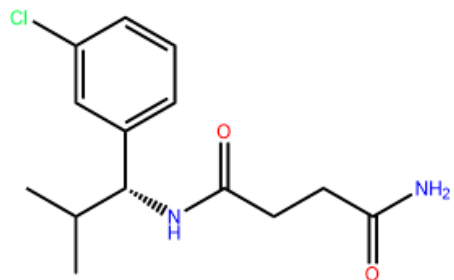
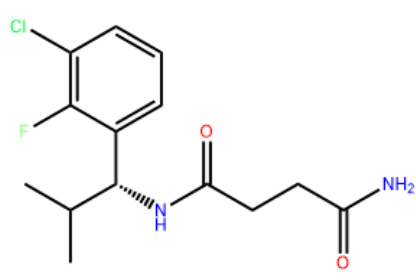
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20	2S,3S,4R-4HILe	TRP-20 TYR-48 TRP-111 TYR-209 TRP-219 CYS-298	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 PHE-649	TRP-58 TYR-62 LEU-162 ALA-198
21	2R,3S,4R-4HILe	TRP-20 TYR-48 TYR-209 ILE-260 CYS-298 LEU-300	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 TRP-613 PHE-649	TYR-62 LEU-162
22	2R,3S,4S-4HILe	TRP-20 VAL-47 TYR-48 TRP-79 TRP-111 CYS-298	TRP-376 LEU-405 TRP-481 TRP-516 MET-519 TRP-613 PHE-649	TYR-62 LEU-162
23	2R,3R,4R-4HILe	TRP-20 TYR-48 TRP-79 TRP-111 TYR-209 CYS-298	TRP-376 LEU-405 ILE-441 TRP-481 TRP-516 MET-519 TRP-613 PHE-649	TRP-58 TYR-62 LEU-162 ALA-198

Table S4: AI Generative model scaffolds



65 	72 	18 
24 	94 	66 
4 	27 	6 
15 	29 	77 
98 	52 	28 
3 	60 	84 

14 	30 	92 
96 	5 	22 
97 	54 	33 
41 	63 	16 
7 	88 	68 

9**23****36**