

Supplementary Information

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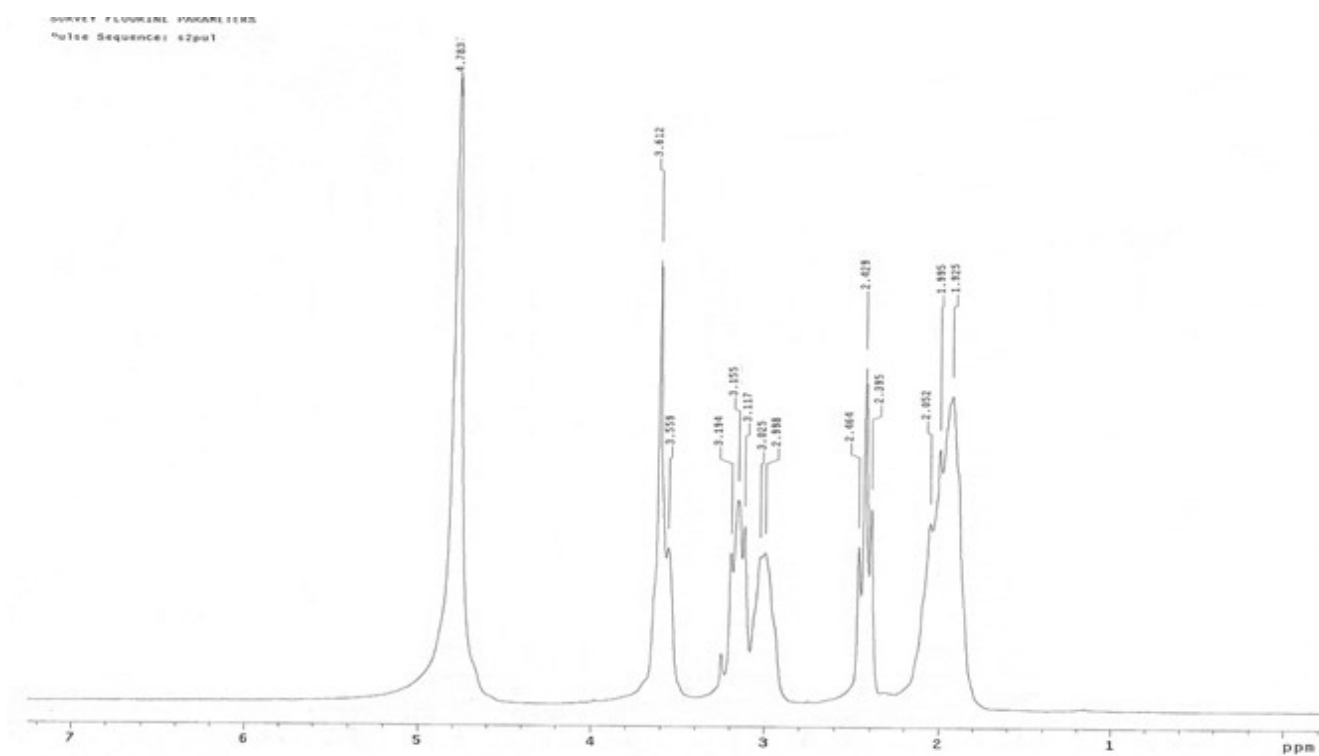
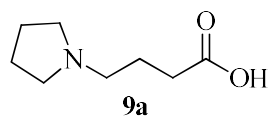


Figure S1. ^1H NMR (D_2O , 200 MHz) of 4-(Pyrrolidin-1-yl)butanoic acid (**9a**).

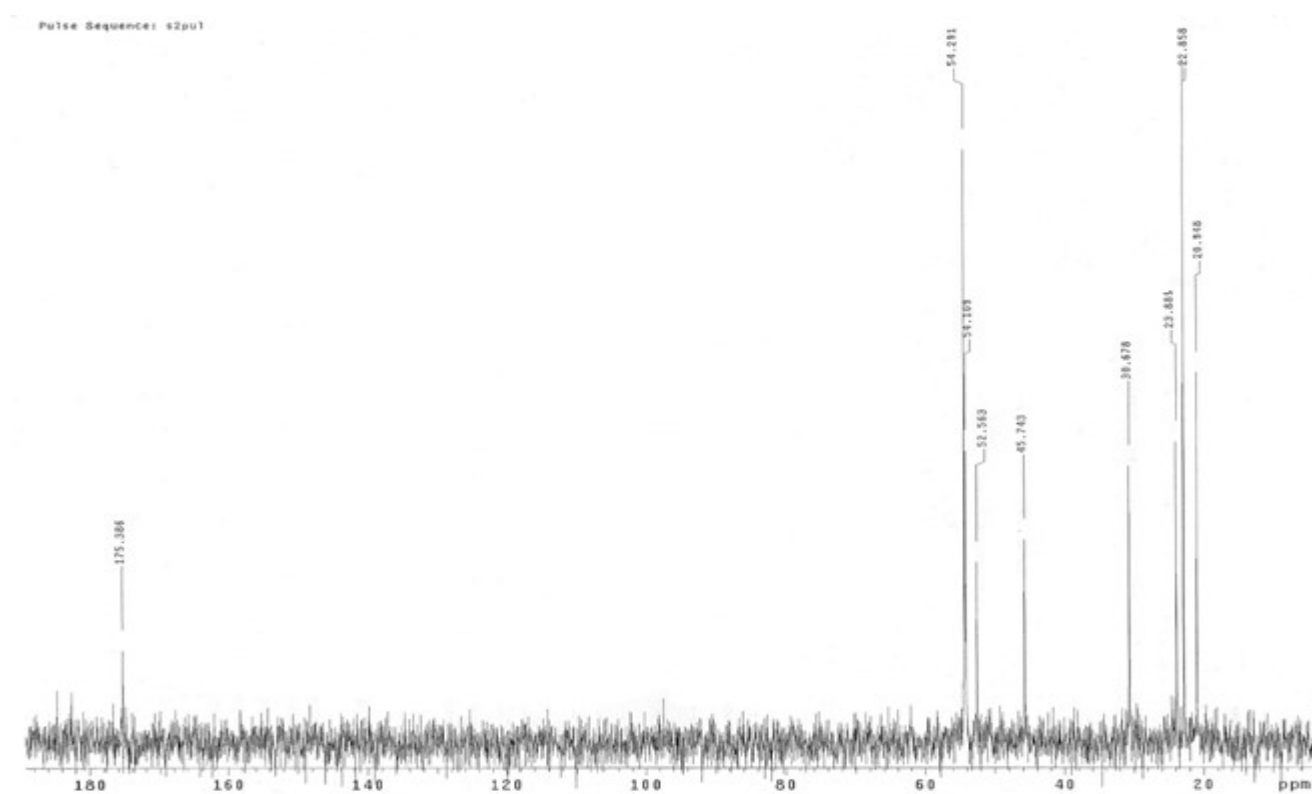
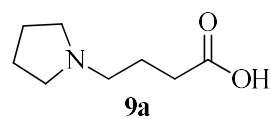
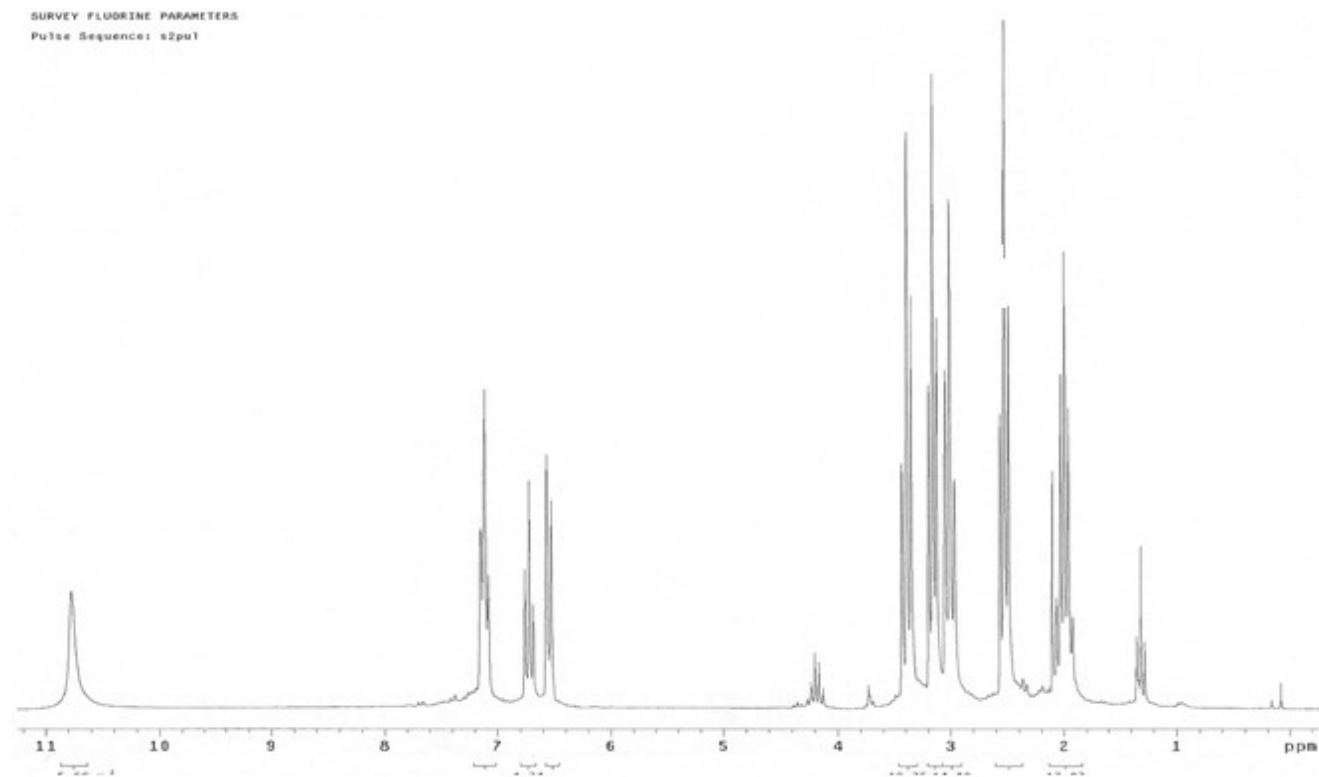


Figure S2. ^{13}C NMR (D_2O , 200 MHz) of 4-(Pyrrolidin-1-yl)butanoic acid (**9a**).



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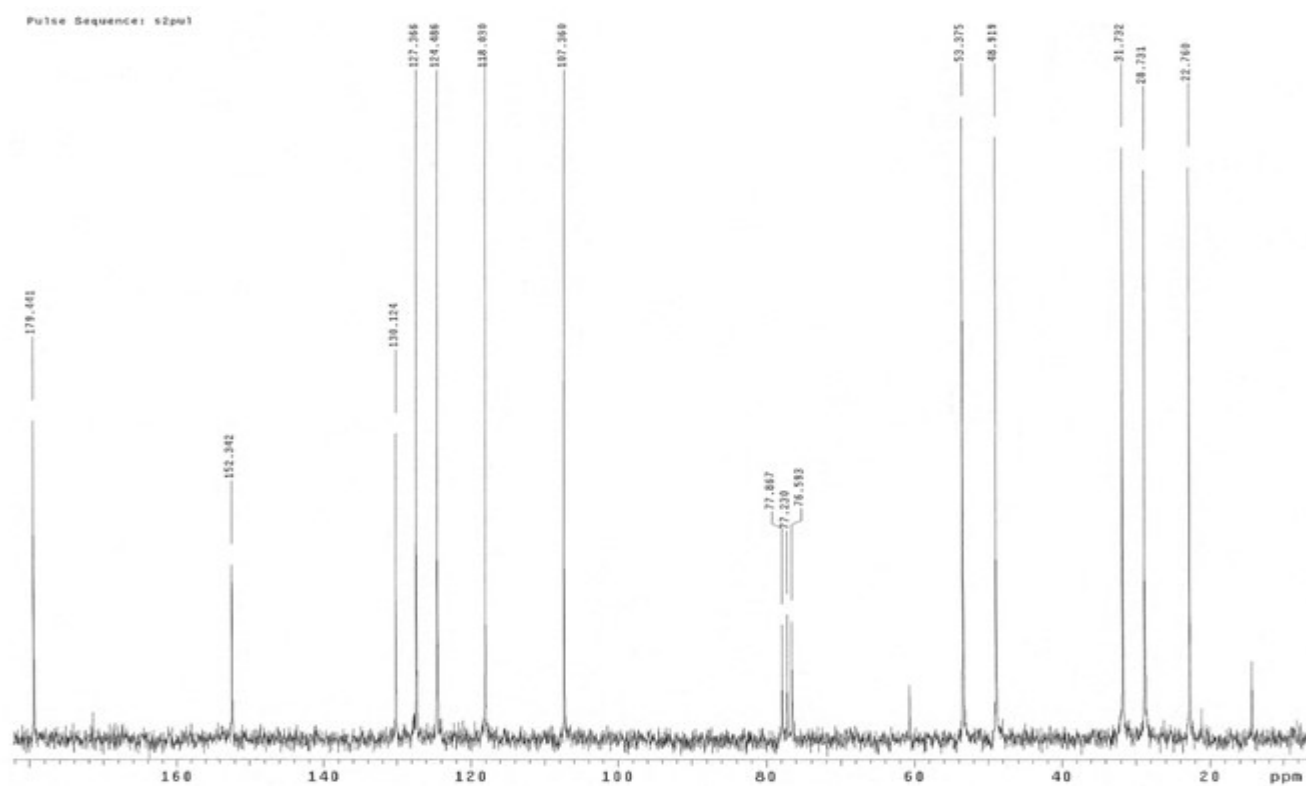
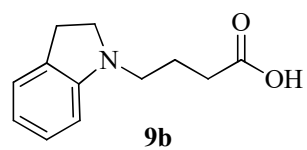


Figure S4. ^{13}C NMR (CDCl_3 , 200 MHz) of 4-(Indolin-1-yl)butanoic acid (**9b**).

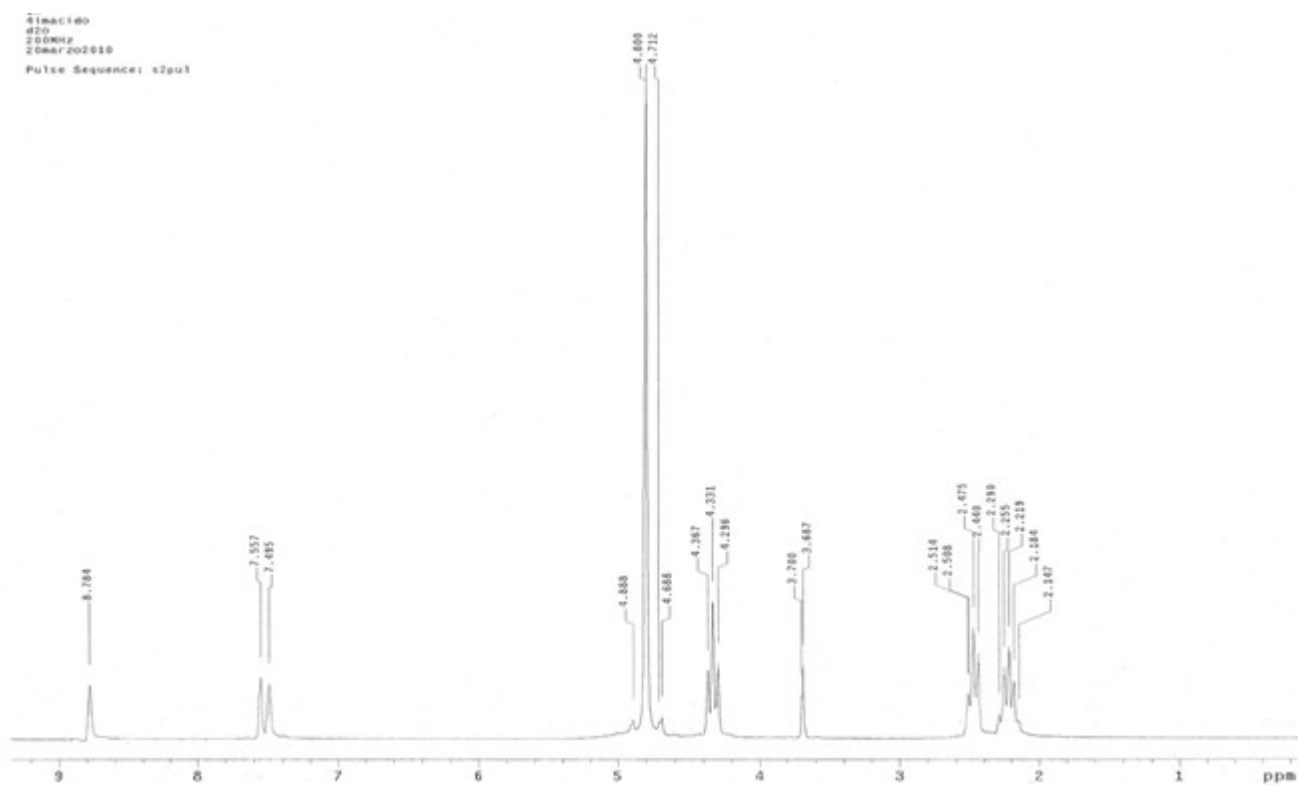
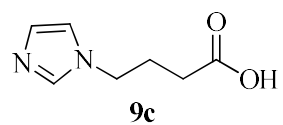


Figure S5. ^1H NMR (D_2O , 200 MHz) of 4-(1*H*-Imidazol-1-yl)butanoic acid (**9c**).

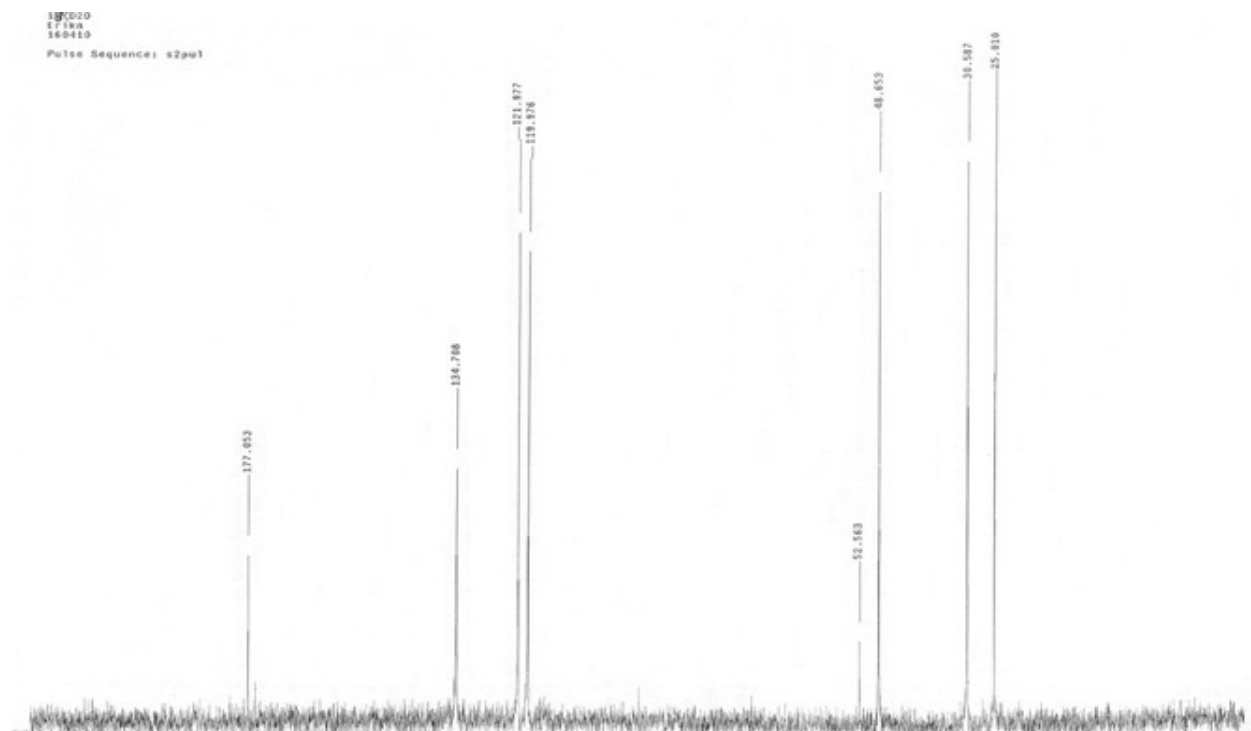
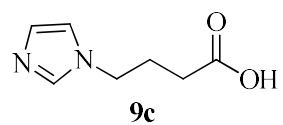


Figure S6. ^{13}C NMR (D_2O , 200 MHz) of 4-(1*H*-Imidazol-1-yl)butanoic acid (**9c**).

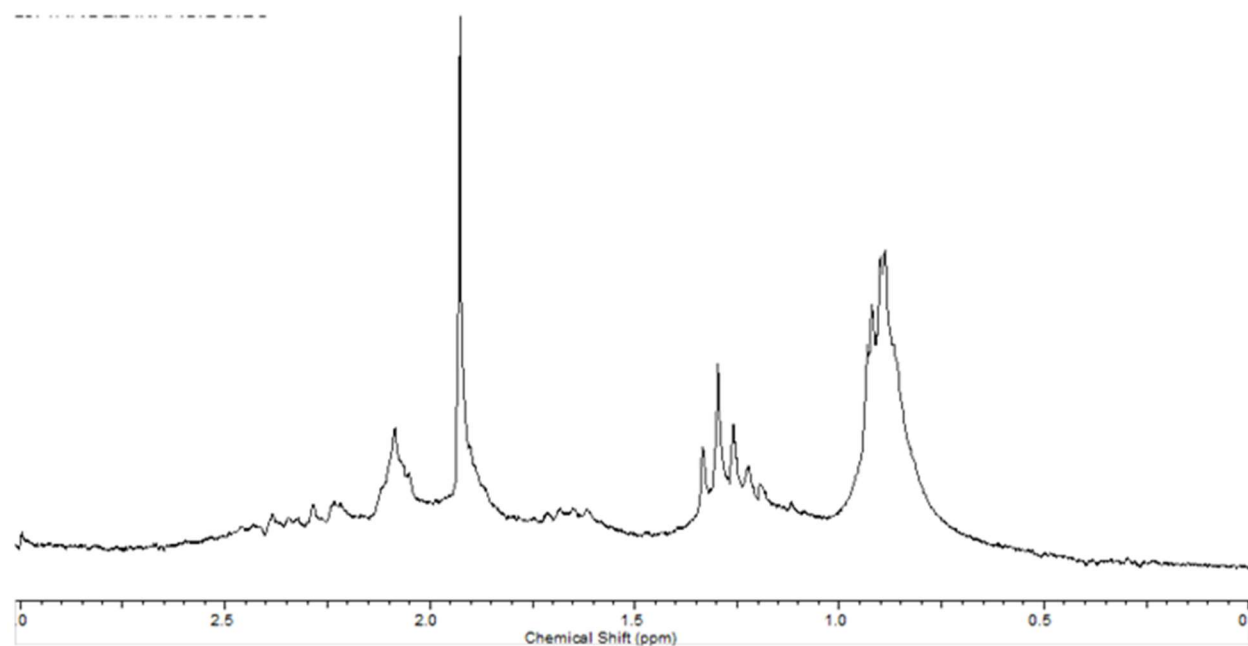
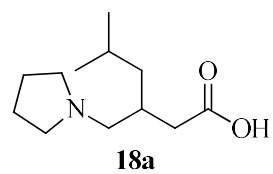


Figure S7. ^1H NMR (D_2O , 200 MHz) of 5-methyl-3-(pyrrolidin-1-ylmethyl)hexanoic acid (**18a**).

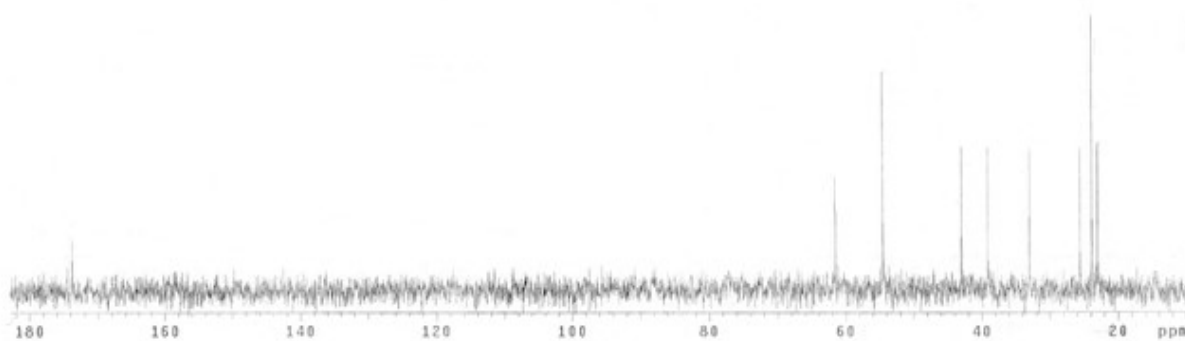
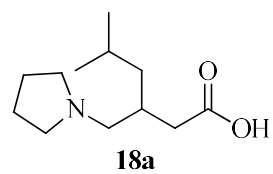


Figure S8. ^{13}C NMR (D_2O , 200 MHz) of 5-methyl-3-(pyrrolidin-1-ylmethyl)hexanoic acid (**18a**).

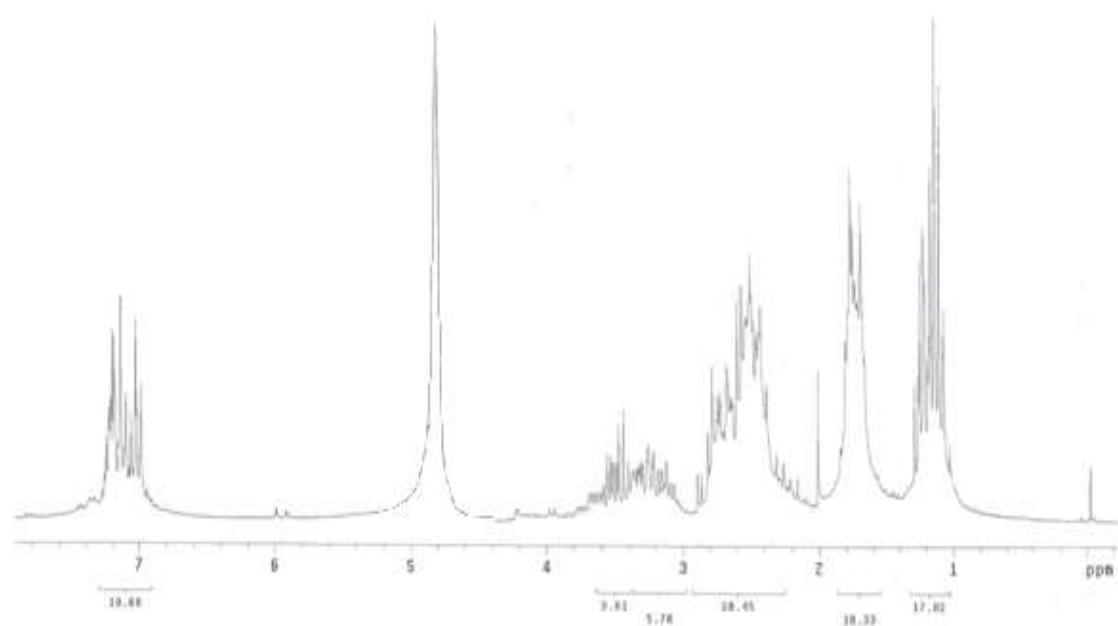
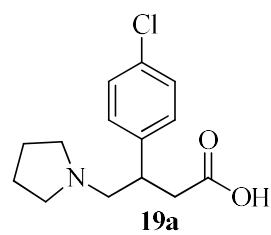


Figure S9. ^1H NMR (D_2O , 200 MHz) of 3-(4-chlorophenyl)-4-(pyrrolidin-1-yl)butanoic acid (**19a**).

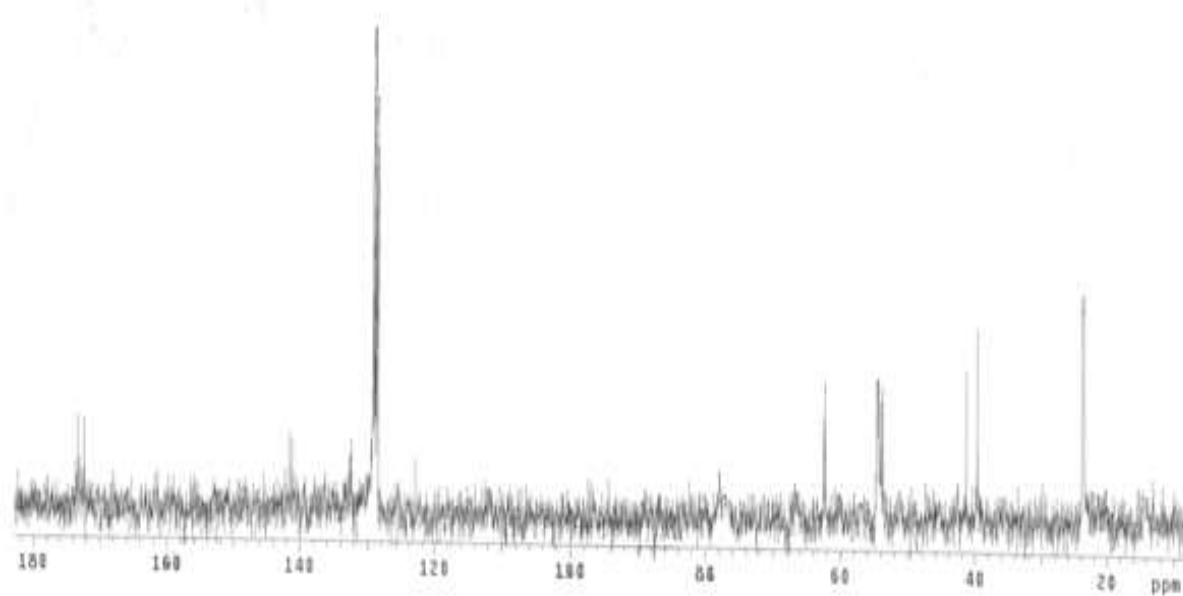
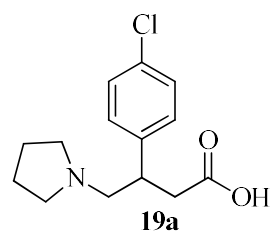


Figure S10. ^{13}C NMR (D_2O , 200 MHz) of 3-(4-chlorophenyl)-4-(pyrrolidin-1-yl)butanoic acid (**19a**).

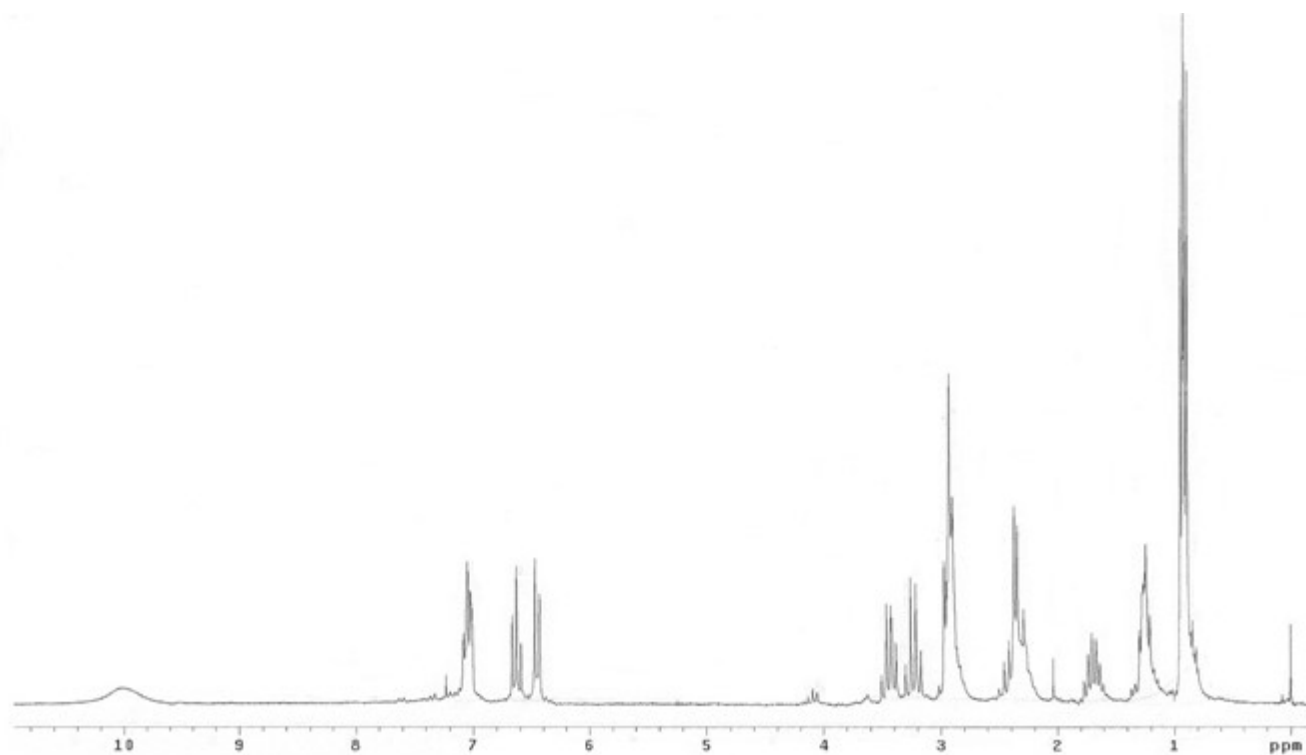
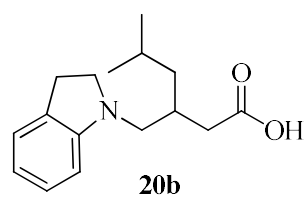


Figure S11. ^1H NMR (CDCl_3 , 200 MHz) of 3-(Indolin-1-ylmethyl)-5-methylhexanoic acid (20b).

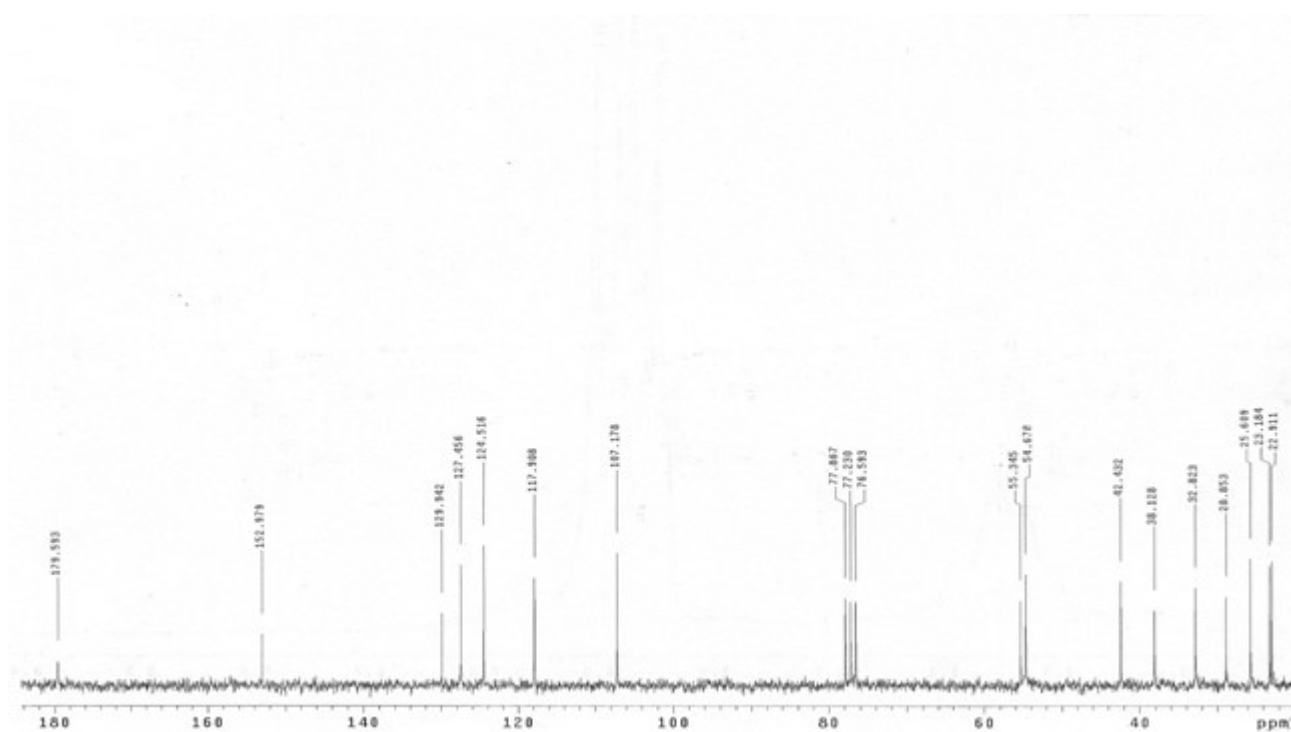
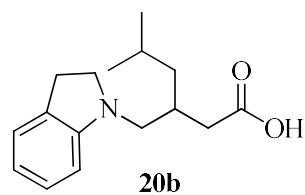
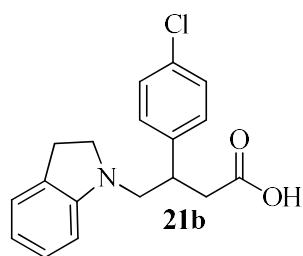


Figure S12. ¹³C NMR (CDCl₃, 200 MHz) of 3-(Indolin-1-ylmethyl)-5-methylhexanoic acid (20b).



15abril2013pClindolinaacido1Hcdcl3good

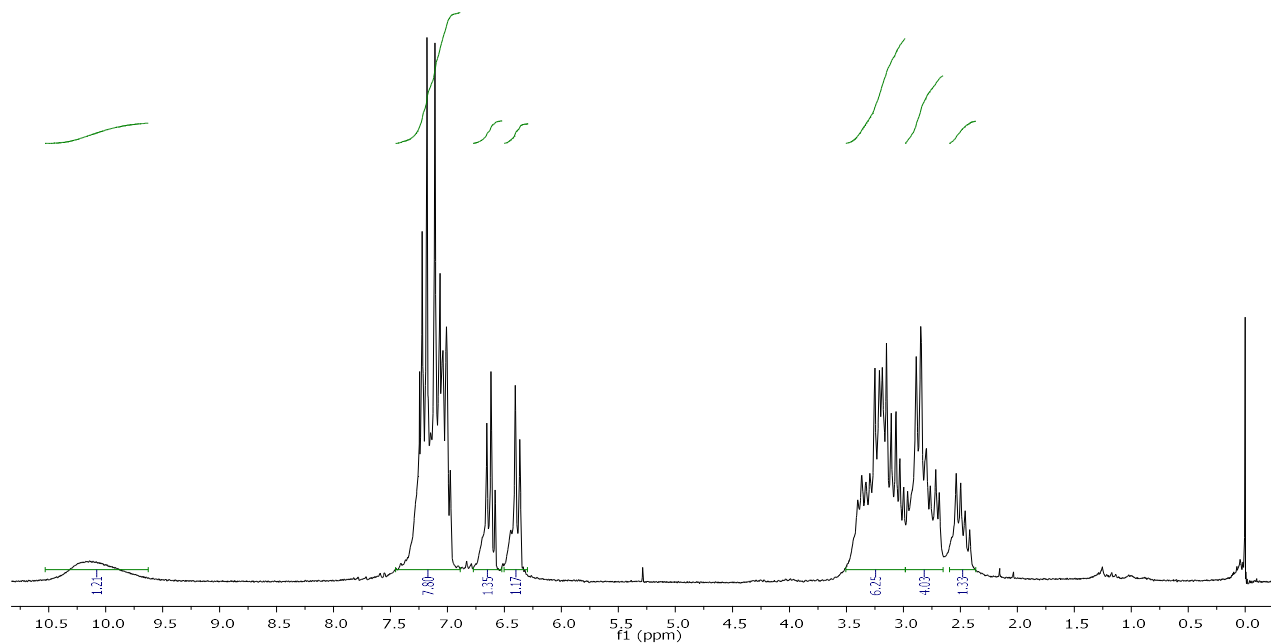


Figure S13. ¹H NMR (CDCl₃, 200 MHz) of 3-(4-chlorophenyl)-4-(indolin-1-yl)butanoic acid (21b).

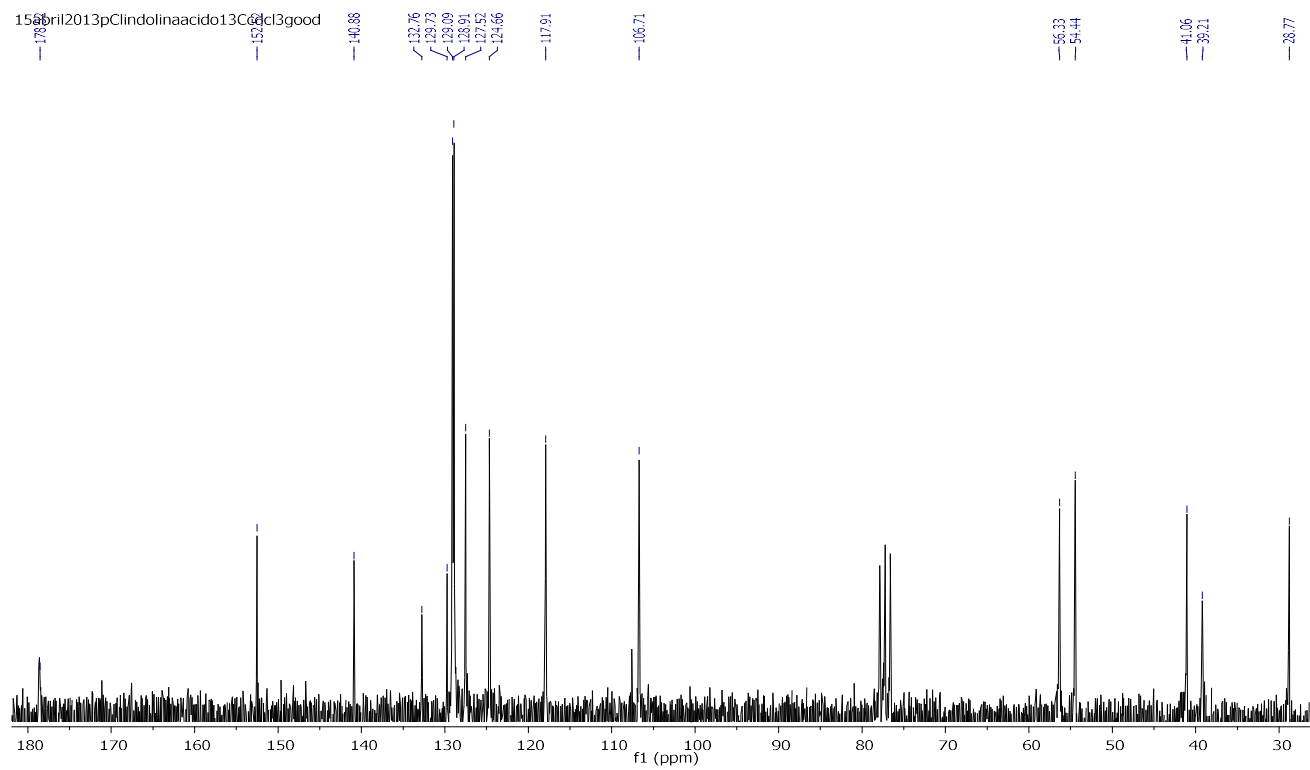
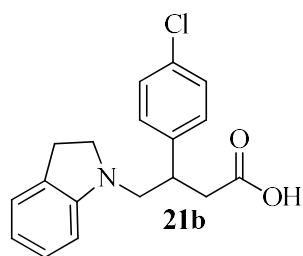


Figure S14. ^{13}C NMR (CDCl_3 , 200 MHz) of 3-(4-Chlorophenyl)-4-(indolin-1-yl)butanoic acid (**21b**).

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PF -----MSNKTNASLMKRREAAVPRGVGQIHP-IFAESAKNATVTDVEGREFID
EC -----NSNKELMQRRSQAI PRGVGQIHPI-FADRAENCRVWDVEGREYLD
HS -FDYDGPLMKTEVPGPRSQELMKQLNII--QNAEAVHFFCNYEESRGNYLVDVDGNRMLD
JB -FDYDGPLMKTEVPGPRSRELMKQLNII--QNAEAVHFFCNYEESRGNYLVDVDGNRMLD

PF FAGGIAVLNTGHLHPKIIAAVTEQLNKLTH---TCFQVLAYEPYVELCEKVNAK-VPGDF
EC FAGGIAVLNTGHLHPKVVAAVEAQLKKLSH---TCFQVLAYEPYLELCEI-MNQKVP GDF
HS LYSQISSVPIGYSHPALCLKIQQPQNASMFVNRPALGILPPENFVEKLRQSLLSVAPKGM
JB LYSQISSIPIGYSHPALVKLVQQPQNVSTFINRPALGILPPENFVEKLRESLLSVAPKGM

PF AKKTLLVTTGSEA-----VENAVKJARATTGRAGVIAFT
EC AKKTLLVTTGSEAVENA-----VKIARAATKRSGTIAFS
HS -SQLITMACGSCSNENALKTIFMWYRSKERGQRGFSQEELETTCMINQAPGCPDYSILSFM
JB -SQLITMACGSCSNENAFKTI FMWYRSKERGESAFSKEELETTCMINQAPGCPDYSILSFM

PF GAYHGRITMMTLGLTGKVPYPYSAGMGLM--P-GGIFRALYPNELHGVS-V---DDSIAS-I
EC GAYHGRITHTYTLALTGKVNYPYSAGMGL---MPGHVYRALYPCPLHGI----SEDDAIASI-
HS GAFHGRITMGCLATTHSKAIHKIDIPSFWDPIAPFPRLKYPLEEFVKENQQEEARCLEEVE
JB GAFHGRITMGCLATTHSKAIHKIDIPSFWDPIAPFPRLKYPLEEFVKENQQEEARCLEEVE

PF ERIFKNDAEPRDIAAIIIEPVQGEGGFYVAPKAFMKRLRELCDKHGILLIADEVQTGAGR
EC HRIFKNDAAPEDIAAIVIEPVQGEGGFYASSPAFMQRLRALCDEHGIMLIADEVQSGAGR
HS DLIVKYRKKKKTVAGIIVEPIQSEGGDNHASDDFFRKLRLDIARKHGCAFLVDEVQTGGGC
JB DLIVKYRKKKKTVAGIIVEPIQSEGGDNHASDDFFRKLRLDISRKHGCAFLVDEVQTGGGS

PF TGTFFAMEQMGVAA--DLTTFAKSI-AGGFPLAGVCGKAEYMDAIPGGLGTYAGSPIA
EC TGTLFAMEQMGVAP--DLTTFAKSI-AGGFPLAGVTGRAEVM DAVAPGGLGTYAGNP IA
HS TGKFWAHEHWGLDDPADVMTFSKKMMTG GFFH-----K-EEFRPNAPYRI FNTWLGDPSK
JB TGKFWAHEHWGLDDPADVMTFSKKMMTG GFFH-----K-EEFRPNAPYRI FNTWLGDPSK

PF CAAALAVMEVFEEEEHLLDRCKAVGERLVTGLKAIQAKYPVI-GEVRALGAMIALELFEDG
EC CVAALEVLKVFEQENLLQKANDLGQKLKDGLLAIAEKHPEI-GDVRGLGAMIAIELFEDG
HS NLLLAEVINIIKREDLLNNAAHAGKALLTGLLDLQARYPQFISRVRGRGTFC SFDT----
JB NLLLAEVINIIKREDLLSNAAHAGKVLLTGLLDLQARYPQFISRVRGRGTFC SFDT----

PF DSHKPNAAVASVVAKARDKGLILLSCGTYGNVLRVLVPLTSPDEQLDKGLAIEECFSEL-
EC DHNKPDAKLTAIEIVARARDKGLILLSCGPYYNVLRLILVPLTIEDAQIRQGLEIISQCFDEAK
HS ----PDDSIRNKLILIIARNKGVVLGGCGDKSIRFRPTLVFRDHHA--HLFLNIFSDILADFK
JB ----PDESIRNKLISIARNKGVMLGGCGDKSIRFRPTLVFRDHHA--HLFLNIFSDILADFK

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Figure S15 . Alignment of *pseudomonas fluorescens* (PF), *human* (HS), *E. coli* (EC) and *wild boar* (JB). Red and blue color letters corresponds to the residues of the chain A and chain B respectively, that interact with vigabatrin in the 1ohv crystal structure.

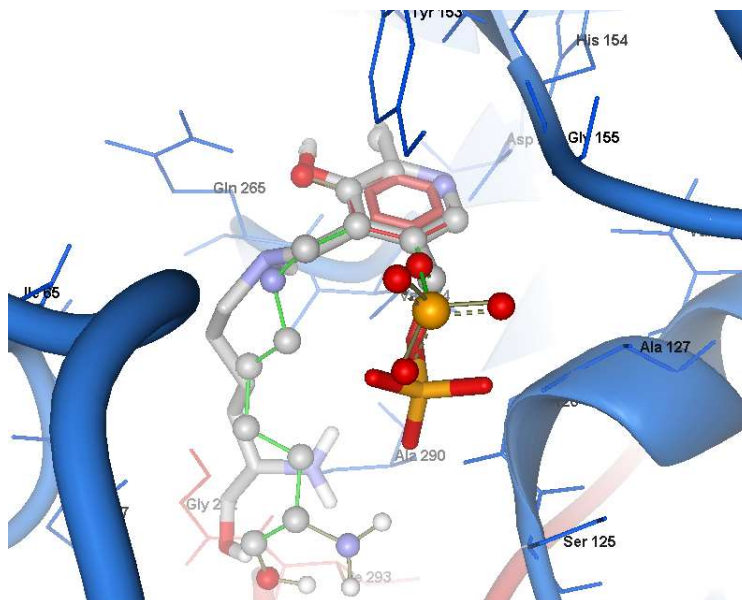


Figure S16. Validation of the molecular docking calculation for the *pseudomonas* model. Ligand in the 3r4t crystal structure was reproduced with a RMSD of 1.7 Å. Ligand experimental and calculated conformations are displayed as thick sticks and ball and stick representation respectively.

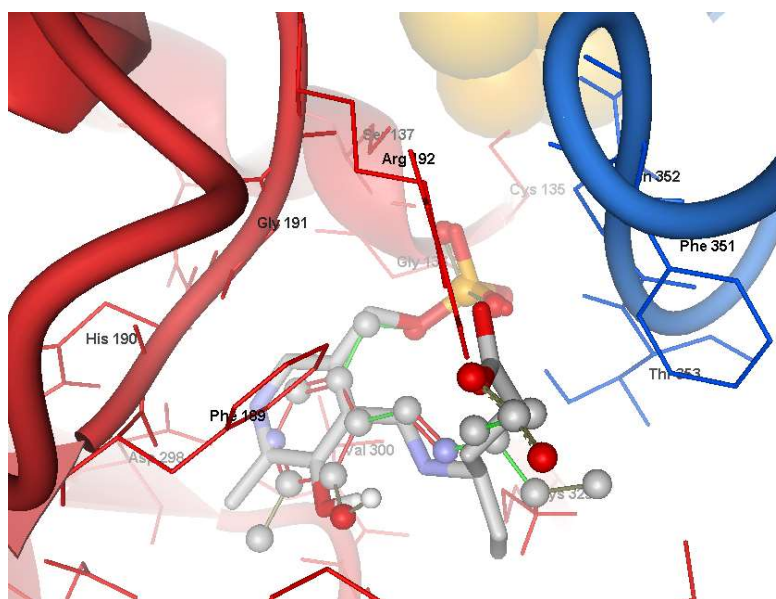


Figure S17. Validation of the molecular docking calculation for the *human* model. Ligand in the 1ohw crystal structure was reproduced with a RMSD of 1.3 Å. Ligand experimental and calculated conformations are displayed as thick sticks and ball and stick representation respectively.

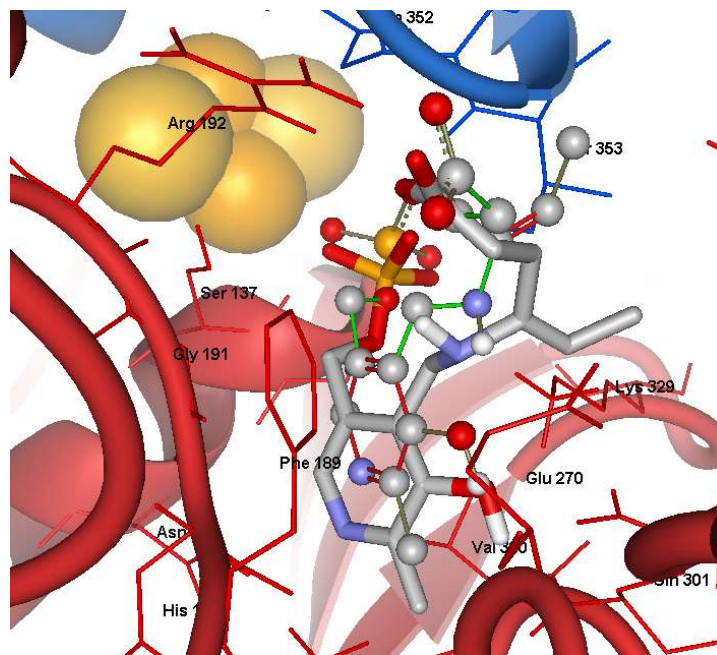
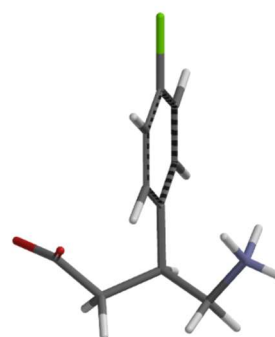
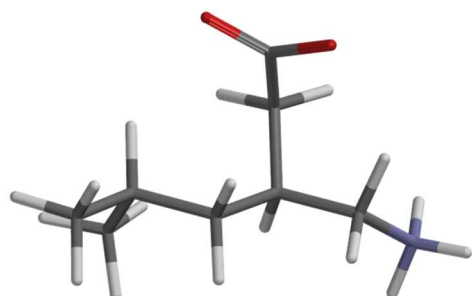
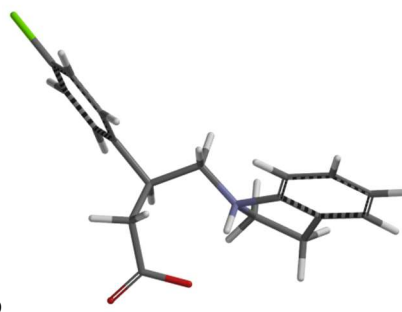
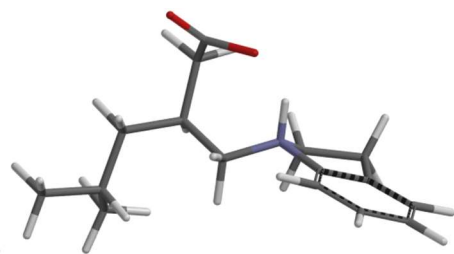
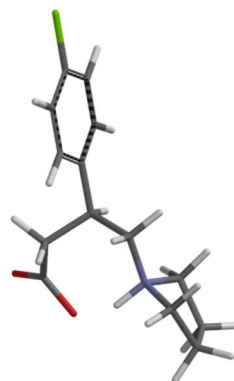
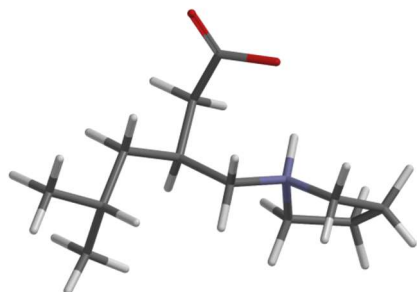
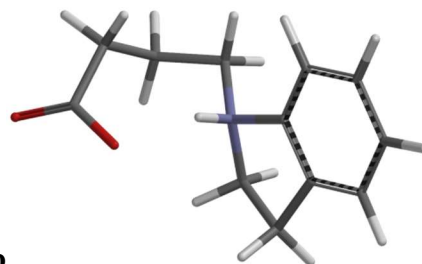
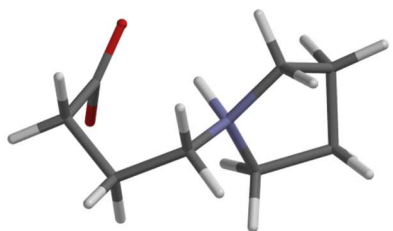
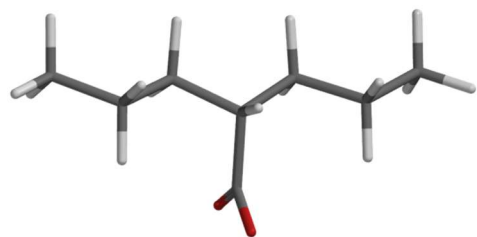
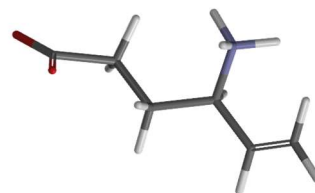


Figure S18. Validation of the molecular docking calculation for the *human* model. Ligand in the 1ohy crystal structure was reproduced with a RMSD of 1.8 Å. Ligand experimental and calculated conformations are displayed as thick sticks and ball and stick representation respectively.





Valproate



Vigabatrin

Figure S19. Optimized structures of all GABA analogues **9a**, **9b**, (*S*)-**18a**, (*S*)-**19a**, (*S*)-**20b**, (*S*)-**21b**, Baclofen, Pregabalin, Valproate and Vigabatrin molecules.

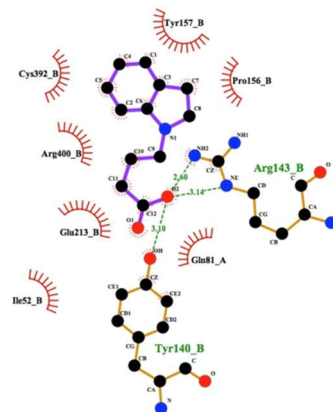
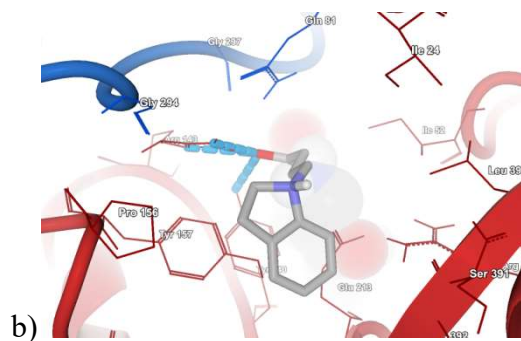
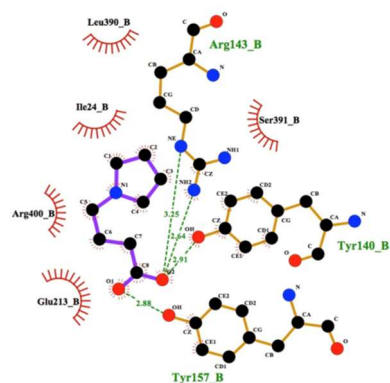
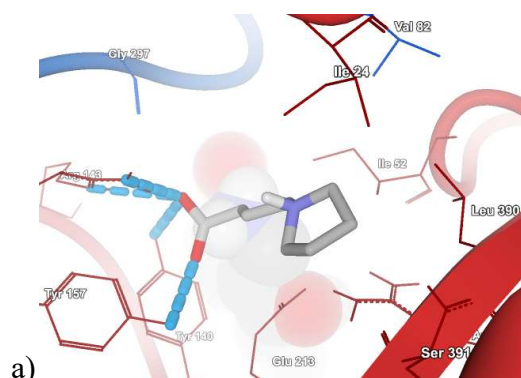


Figure S20. a) **9a** hydrogen bond interactions (blue dashed lines) with pseudomonas GABA-AT in a 3D and 2D representation. b) **9b** hydrogen bond interactions (blue dashed lines) with pseudomonas GABA-AT. PLP prosthetic group is showed as spacefill model. The images were made with Molegro and LigPlot programs.

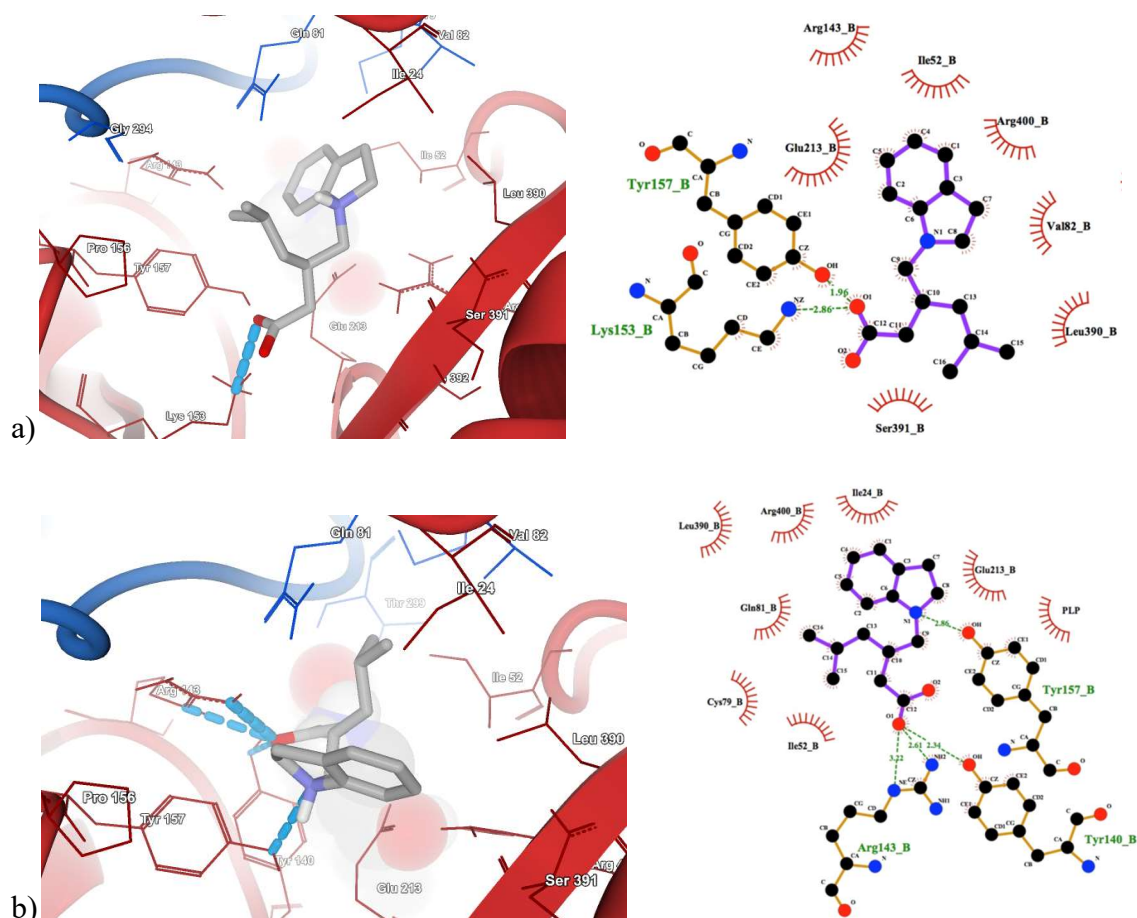


Figure S21. a) (*R*)-**20b** hydrogen bond interactions (blue dashed lines) with pseudomonas GABA-AT in a 3D and 2D representation. b) (*S*)-**20b** hydrogen bond interactions (blue dashed lines) with pseudomonas GABA-AT. PLP prosthetic group is showed as spacefill model. The images were made with Molegro and LigPlot programs.

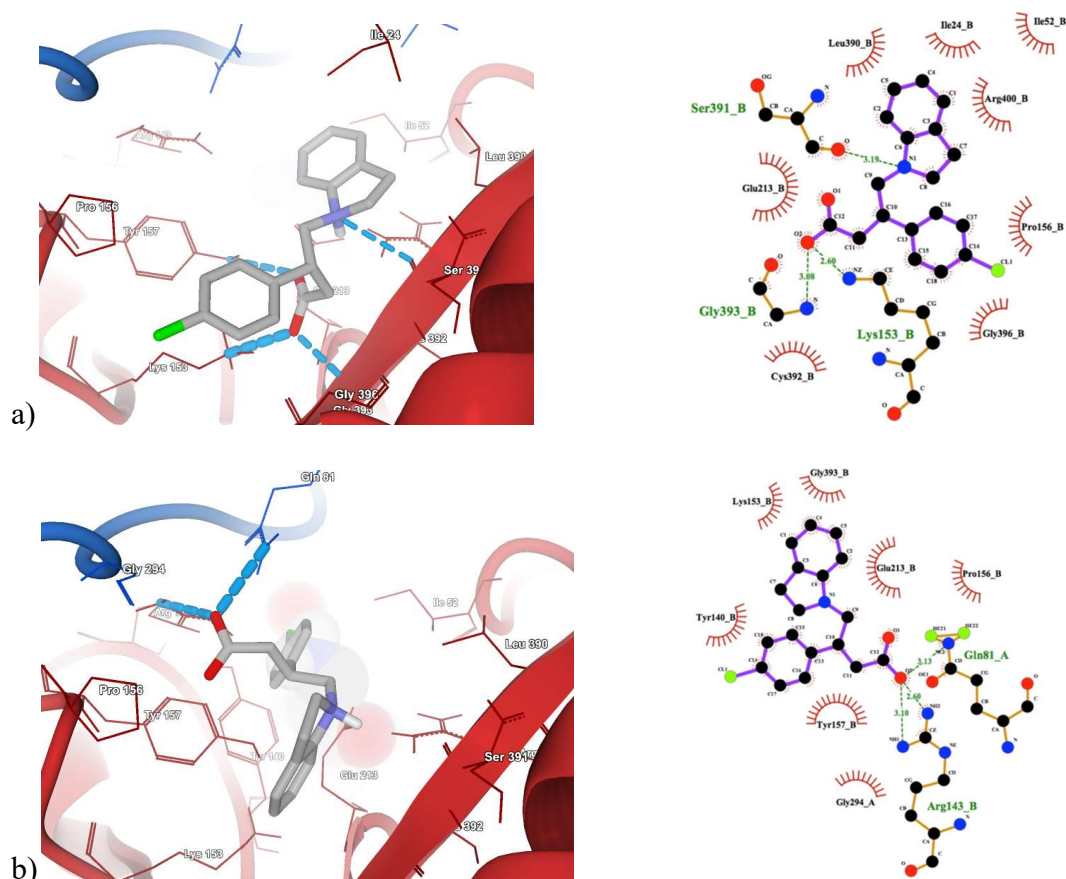
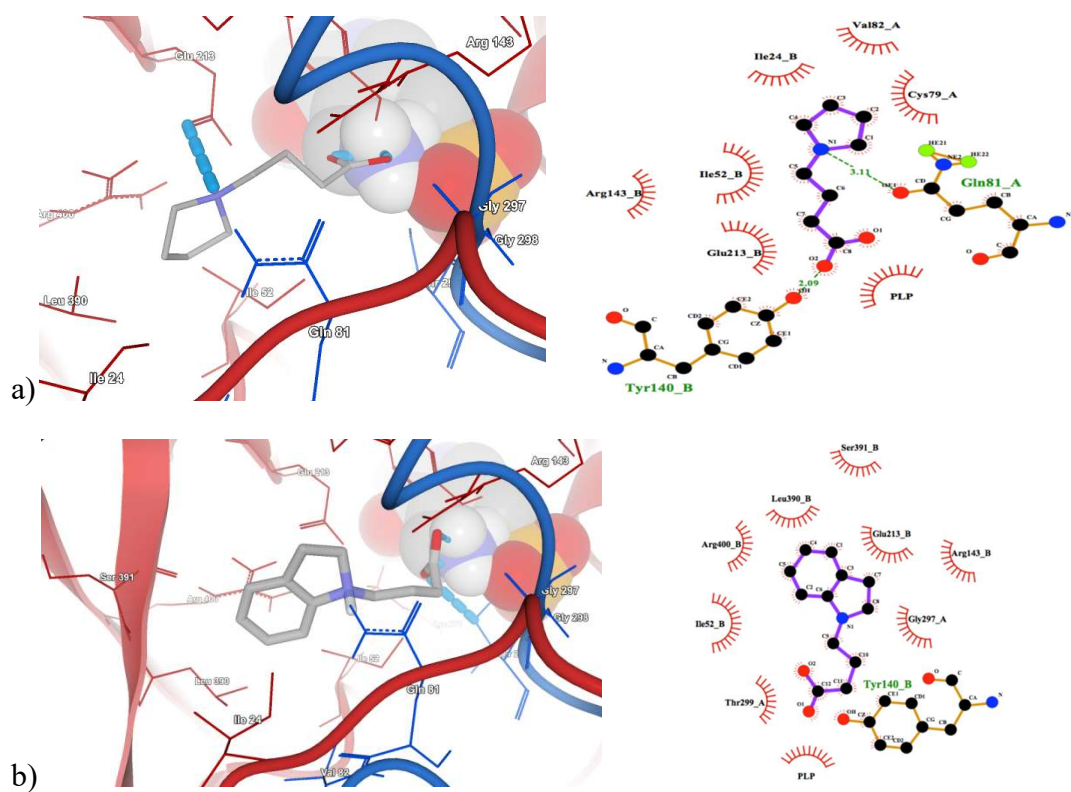
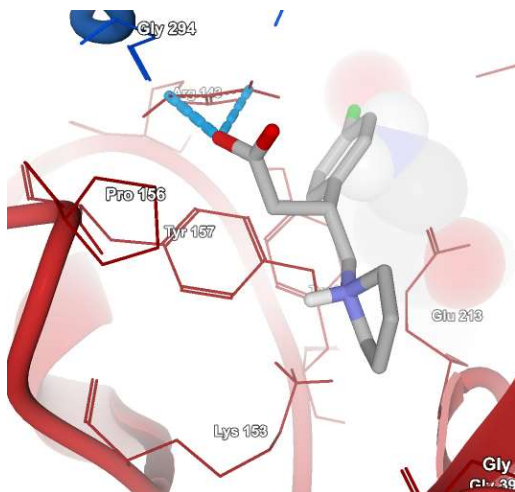


Figure S22. a) (*R*)-**21b** hydrogen bond interactions (blue dashed lines) with *pseudomonas* GABA-AT in a 3D and 2D representation. b) (*S*)-**21b** hydrogen bond interactions (blue dashed lines) with *pseudomonas* GABA-AT. PLP prosthetic group is showed as spacefill model. The images were made with Molegro and LigPlot programs.

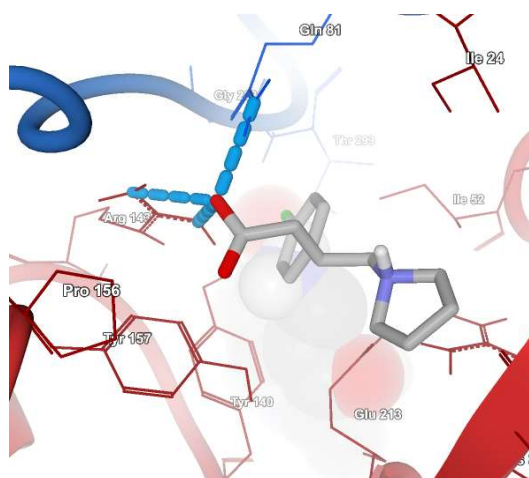
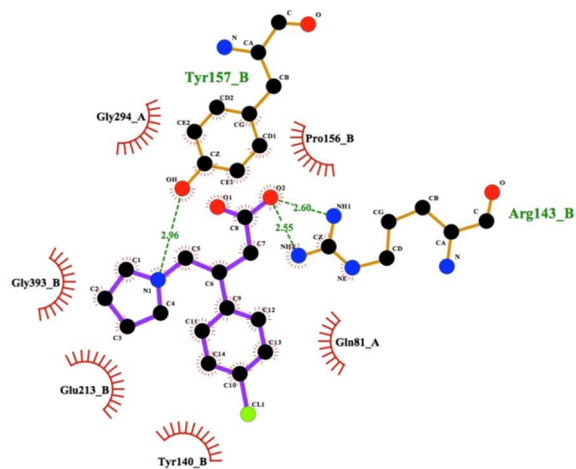
Table S1. Energy interactions values obtained from the docking calculations of all GABA derivatives and *pseudomonas* GABA-AT model. All the values are in kcal/mol.

Ligand	MolDock Score	Electro	HBond	Internal	LE
9a	-69.41	-2.39	-8.82	-2.17	-6.31
9b	-80.05	-1.13	-6.78	4.17	-5.34
(<i>R</i>)- 18a	-71.30	-4.51	-0.08	-9.08	-4.75
(<i>S</i>)- 18a	-82.63	-8.15	-6.96	-4.60	-5.51
(<i>R</i>)- 19a	-27.88	-5.49	-1.97	-1.95	-1.55
(<i>S</i>)- 19a	-91.07	-5.27	-6.65	-1.46	-5.06
(<i>R</i>)- 20b	-81.00	-1.65	-5.55	1.87	-4.26
(<i>S</i>)- 20b	-89.51	-6.91	-0.42	-2.89	-4.71
(<i>R</i>)- 21b	-96.82	-4.44	-4.75	5.13	-4.40
(<i>S</i>)- 21b	-102.18	-6.99	-6.50	1.64	-4.65

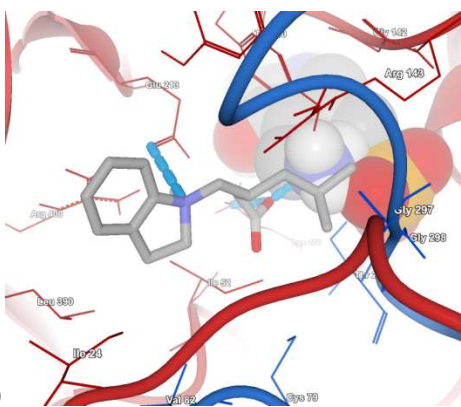
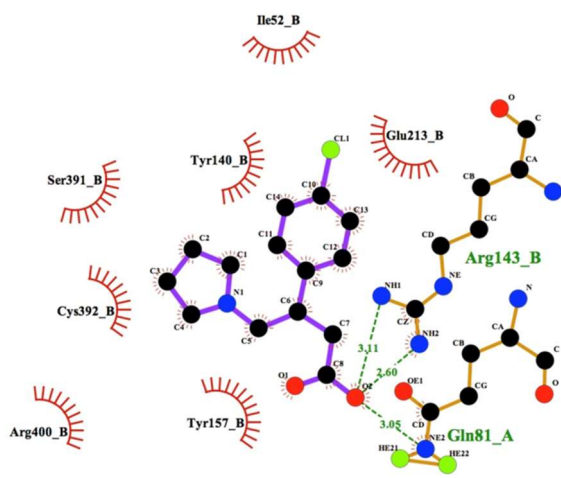




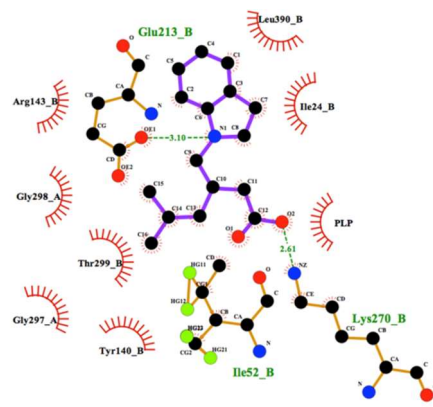
a)



b)



c)



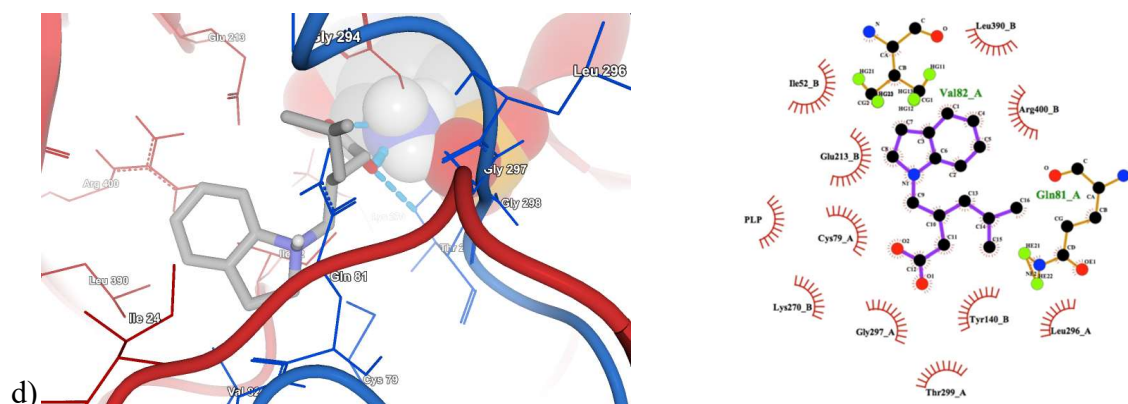


Figure S24. a) (*R*)-**18a** hydrogen bond interactions (blue dashed lines) with *human* GABA-AT. b) (*S*)-**18a** hydrogen bond interactions (blue dashed lines) with *human* GABA-AT. c) (*R*)-**20b** hydrogen bond interactions (blue dashed lines) with *human* GABA-AT in a 3D and 2D representation. d) (*S*)-**20b** hydrogen bond interactions (blue dashed lines) with *human* GABA-AT. PLP prosthetic group is showed as spacefill model. The images were made with Molegro and LigPlot programs.

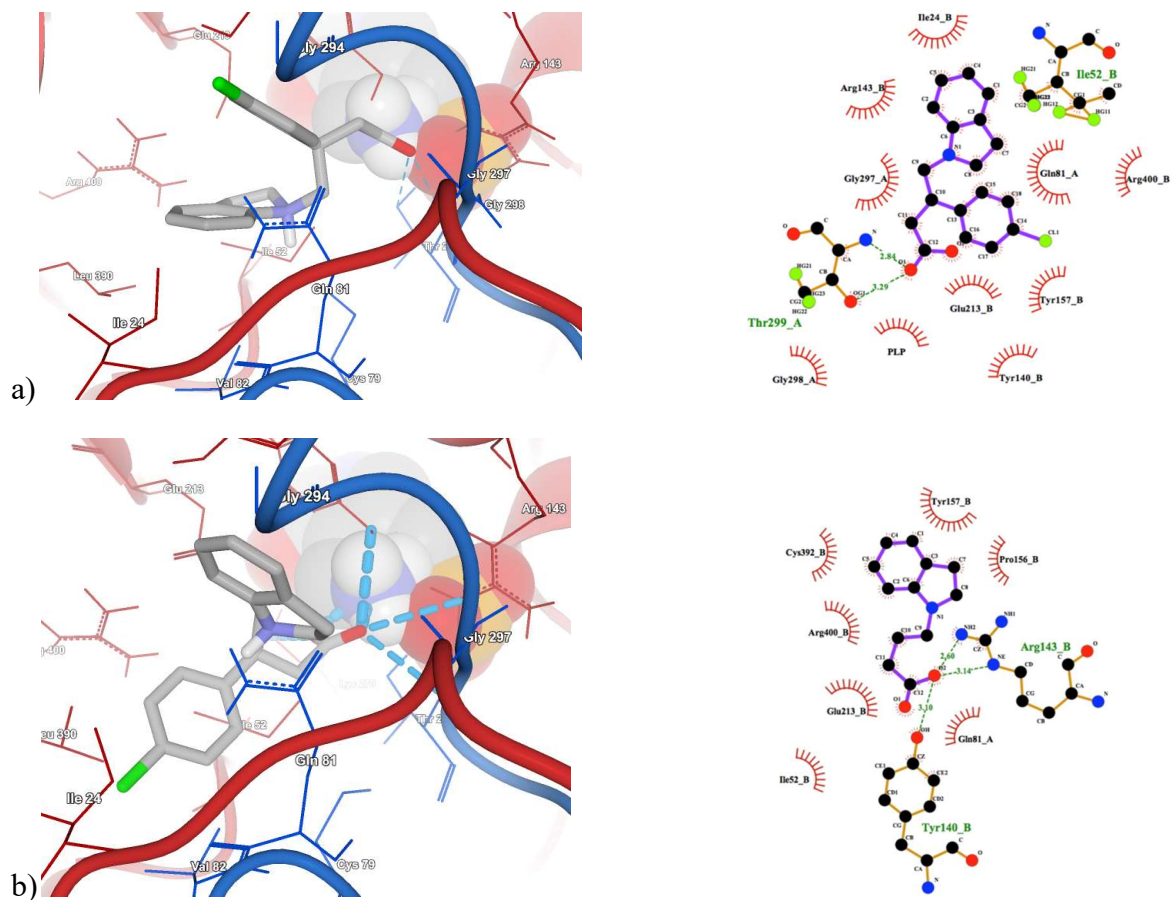


Figure S25. a) (*R*)-**21b** hydrogen bond interactions (blue dashed lines) with *human* GABA-AT in a 3D and 2D representation. b) (*S*)-**21b** hydrogen bond interactions (blue dashed lines) with *human* GABA-AT. PLP prosthetic group is showed as spacefill model. The images were made with Molegro and LigPlot programs.

Table S2. Energy interactions values obtained from the docking calculations of all GABA derivatives and *human* GABA-AT model. All the values are in kcal/mol.

Ligand	MolDock Score	Electro	HBond	Internal	LE
9a	-74.12	-2.31	-0.58	0.57	-6.74
9b	-91.25	-4.18	2.53	3.22	-6.08
(R)-18a	-76.06	-4.82	3.26	-3.15	-5.07
(S)-18a	-78.72	-5.35	-4.59	-6.57	-5.25
(R)-19a	-108.12	-5.32	4.23	3.721	-6.01
(S)-19a	-111.73	-1.97	-8.95	0.78	-6.21
(R)-20b	-80.93	-7.00	-4.94	1.72	-4.26
(S)-20b	-84.63	-0.61	-0.29	-2.00	-4.45
(R)-21b	-98.09	-0.94	0.42	-1.66	-4.46
(S)-21b	-21.54	-5.56	-5.72	6.96	-0.98

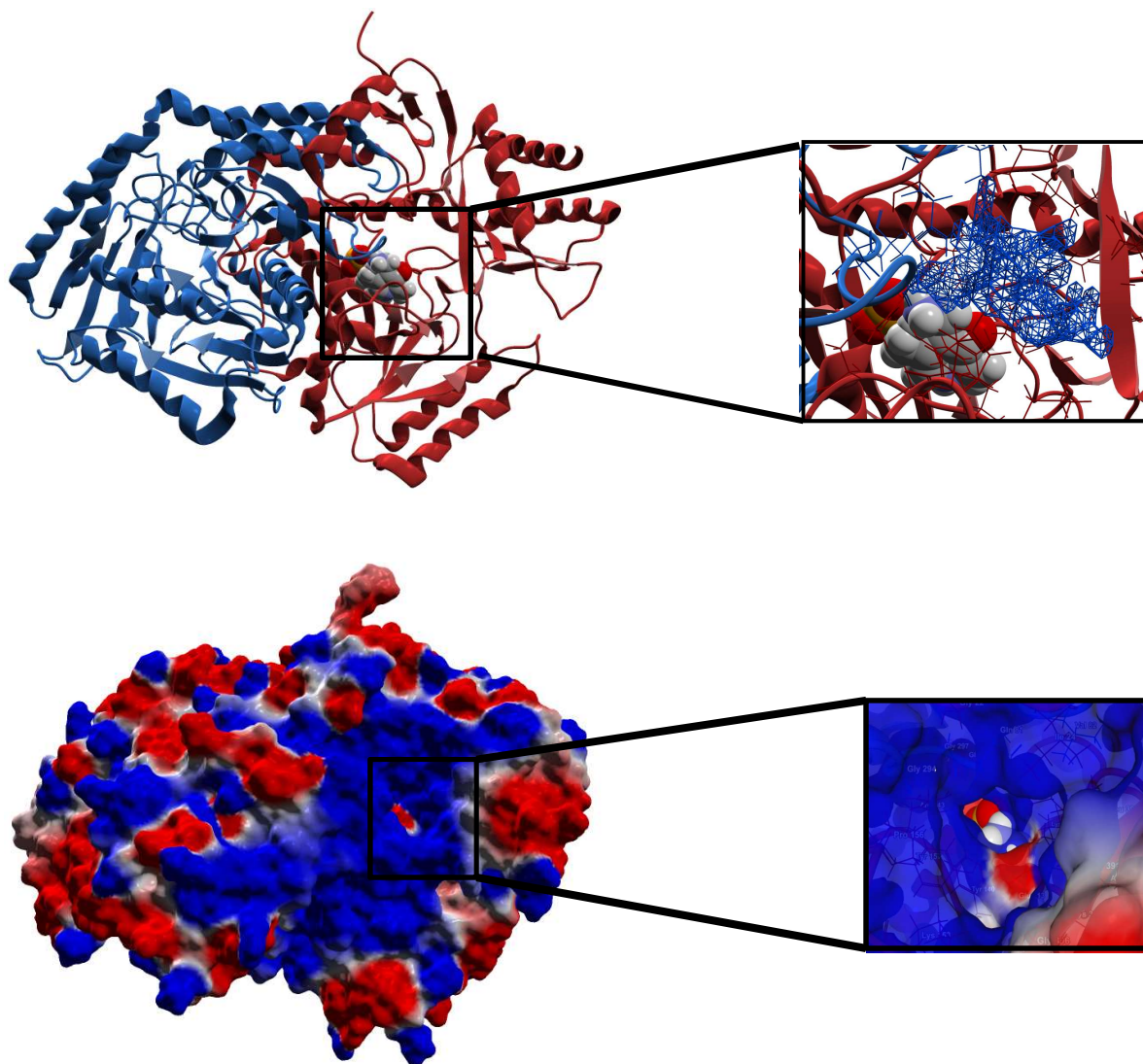


Figure S26. Homology model of *Pseudomonas* GABA-AT. The active site and protein cavity (blue color) is displayed. Electrostatic potential map of *Pseudomonas* GABA-AT. Blue, red and white colors represent regions with positive, negative and neutral electrostatic potential value, respectively. PLP prosthetic group is shown as spacefill model.

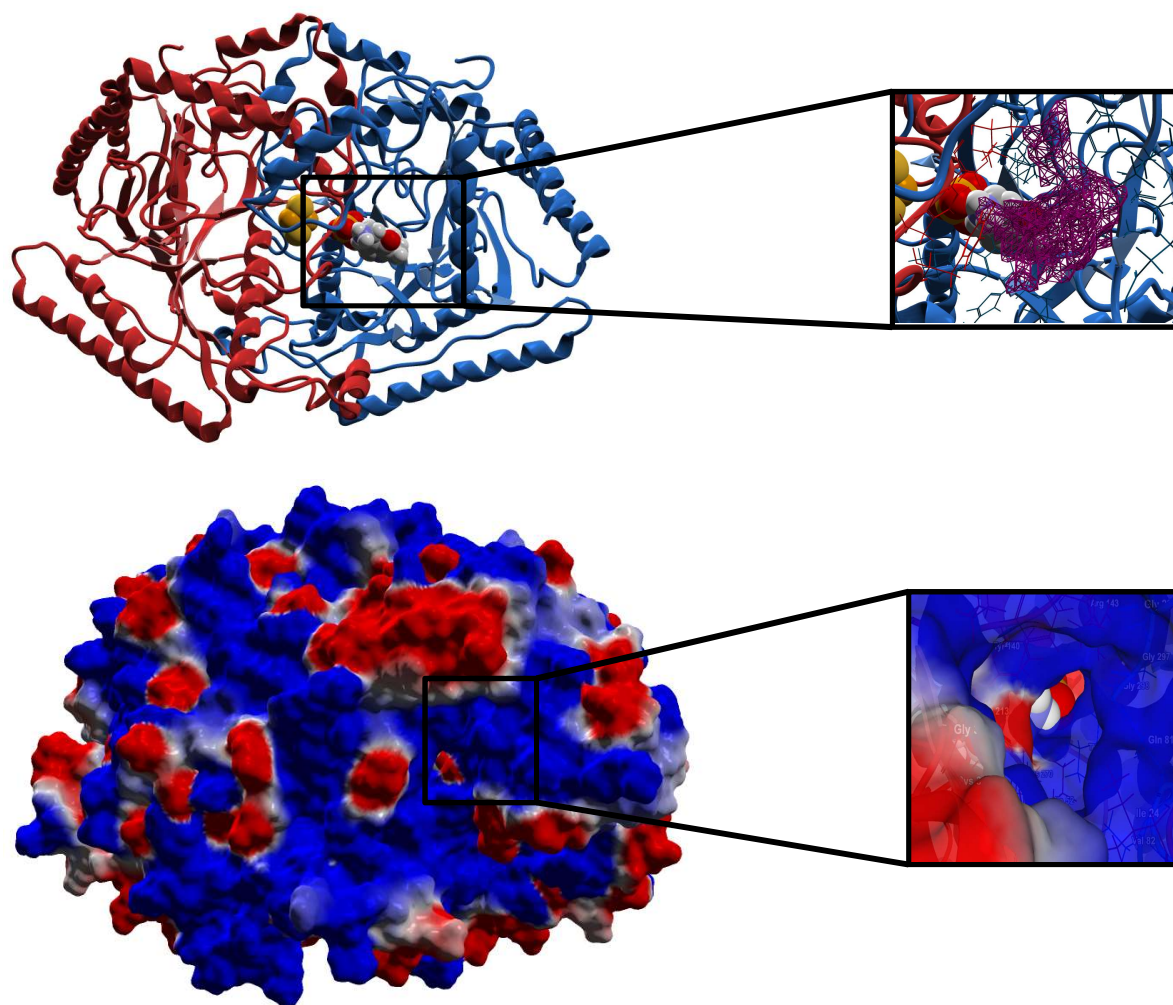


Figure S27. Homology model of human GABA-AT, the active site and protein cavity (purple color) is displayed. Electrostatic potential map of human GABA-AT. Blue, red and white colors represent regions with positive, negative and neutral electrostatic potential value, respectively. PLP prosthetic group and Fe₂/S₂ cluster are shown as spacefill model.