SUPPLEMENTARY MATERIAL

Estimation of passive gastrointestinal absorption and membrane retention using PAMPA test, quantitative structure-permeability and quantitative structure-retention relationship analyses of ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoic acid and 1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl)propanoic acid derivatives

Biljana Tubić[a,1,2], Vladimir Dobričić[a,2,*], Jelena Poljarević[b], Aleksandar Savić[b], Tibor Sabo[b], Bojan Marković[a]

[a] *University of Belgrade-Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11000 Belgrade, Serbia*

[b] *Department of General and Inorganic Chemistry, University of Belgrade – Faculty of Chemistry, Studentski trg 12-16, 11158 Belgrade, Serbia*

*Corresponding author. Tel.: 00381 11 3951 341

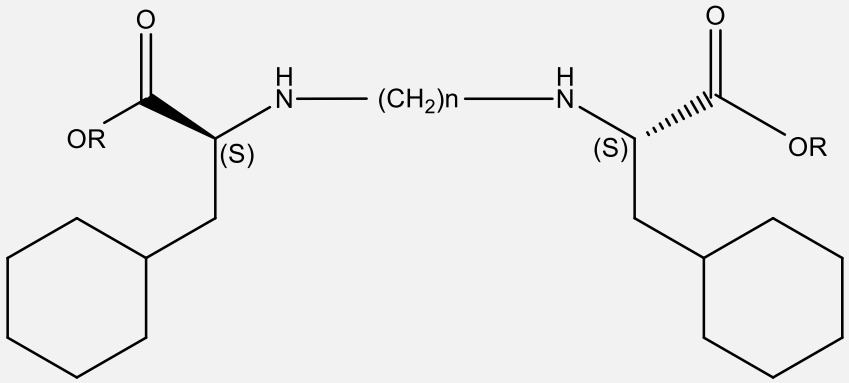
E-mail address: vladimir@pharmacy.bg.ac.rs (V.Dobričić).

[1] Present addresses: Agency for Medicines and Medical Devices of Bosnia and Herzegovina, Veljka Mladjenovica bb, 78000 Banja Luka, Bosnia and Herzegovina; Faculty of Medicine - Department of Pharmacy, University of Banja Luka, Save Mrkalja 14, 78000 Banja Luka, Bosnia and Herzegovina

[2] Both authors contributed equally to this work

Table S1

Derivatives of (*S*,*S*)-ethylenediamine-*N*,*N'*-di-2-(3-cyclohexyl)propanoic acid and (*S*,*S*)-1,3-propanediamine-*N*,*N'*-di-2-(3-cyclohexyl)propanoic acid.



N	Name of compound	Empirical formula	Abbreviation	MW (g/mol)*	R	n	m/z
1.	(*S*,*S*)-ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoic acid dihydrochloride	$C_{20}H_{38}O_4N_2Cl_2$	EDCP	441.43	H	2	369→152** 369→198**
2.	*O,O'*-dimethyl-(*S*,*S*)-ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{22}H_{42}O_4N_2Cl_2$	DM-EDCP	469.48	CH_3	2	397→212**

3.	*O,O'*-diethyl-(*S,S*)-ethylenediamine-*N,N*'-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{24}H_{46}O_4N_2Cl_2$	DE-EDCP	497.54	C_2H_5	2	425→198[**] 425→226[**]
4.	*O,O'*-dipropyl-(*S,S*)-ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{26}H_{50}O_4N_2Cl_2$	DP-EDCP	525.59	C_3H_7	2	453→240[**]
5.	*O,O'*-dibutyl-(*S,S*)-ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{28}H_{54}O_4N_2Cl_2$	DB-EDCP	553.64	C_4H_9	2	481→254[**]
6.	*O,O'*-diisobutyl-(*S,S*)-ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{28}H_{54}O_4N_2Cl_2$	DIB-EDCP	553.64	C_4H_9	2	481→254[**]
7.	(*S,S*)-1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl) propanoic acid dihydrochloride	$C_{21}H_{40}O_4N_2Cl_2$	PDCP	455.46	H	3	383[***]
8.	(*S,S*)-*O,O'*-dimethyl-1,3-propanediamine-	$C_{23}H_{44}O_4N_2Cl_2$	DM-PDCP	483.51	CH_3	3	411[***]

	N,N'-di-2-(3-cyclohexyl)propanoate dihydrochloride						
9.	(*S,S*)-*O,O'*-diethyl-1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{25}H_{48}O_4N_2Cl_2$	DE-PDCP	511.56	C_2H_5	3	438***
10.	(*S,S*)-*O,O'*-dipropyl-1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{27}H_{52}O_4N_2Cl_2$	DP-PDCP	539.62	C_3H_7	3	467***
11.	(*S,S*)-*O,O'*-dibutyl-1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{29}H_{56}O_4N_2Cl_2$	DB-PDCP	567.67	C_4H_9	3	495***
12.	(*S,S*)-*O,O'*-diisobutyl-1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{29}H_{56}O_4N_2Cl_2$	DIB-PDCP	567.67	C_4H_9	3	495***
13.	(*S,S*)-*O,O'*-di-*n*-pentyl-1,3-propanediamine-*N,N'*-di-2-(3-	$C_{31}H_{60}O_4N_2Cl_2$	DPE-PDCP	595.72	C_5H_{11}	3	523***

	cyclohexyl)propanoate dihydrochloride						
14.	(*S,S*)-*O,O'*-diisopentyl-1,3-propanediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate dihydrochloride	$C_{31}H_{60}O_4N_2Cl_2$	DIPE-PDCP	595.72	C_5H_{11}	3	523***

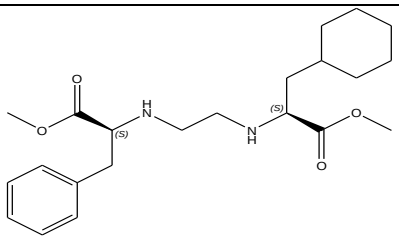
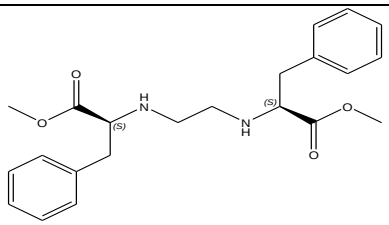
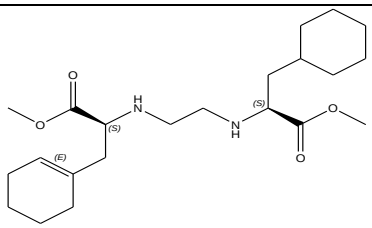
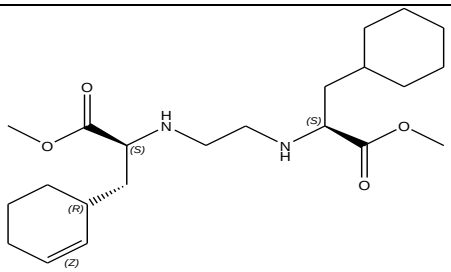
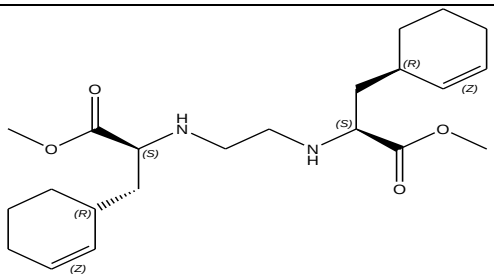
*MW=Molecular Weight;

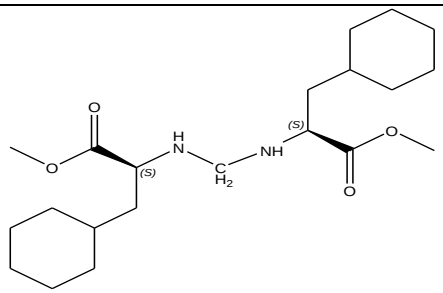
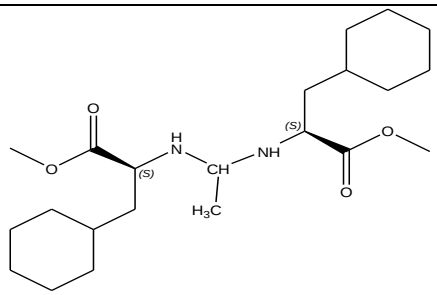
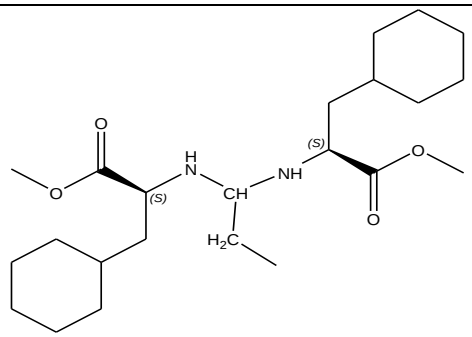
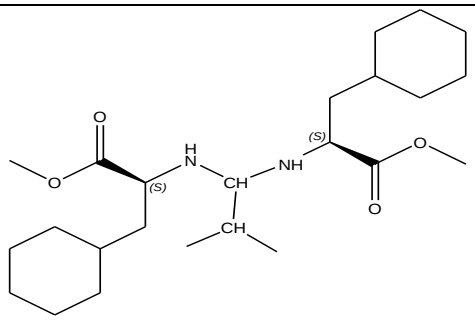
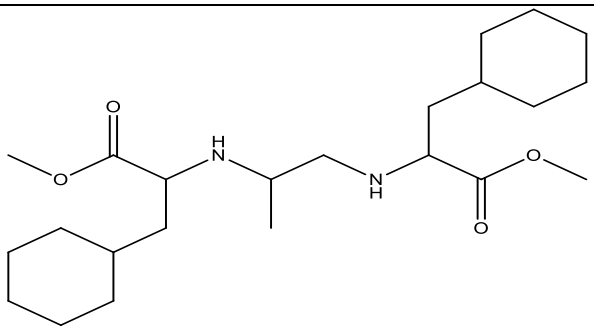
**Selected reaction monitoring (SRM);

***Single ion monitoring (SIM)

Table S2

Chemical structures of all designed derivatives and their predicted -$logP_{app}$ values.

Derivative	Structure	Predicted –$logP_{app}$ values
P1		2.67
P2		2.13
P3		2.57
P4		2.66
P5		2.70

P6		2.12
P7		2.71
P8		2.94
P9		3.29
P10		2.79

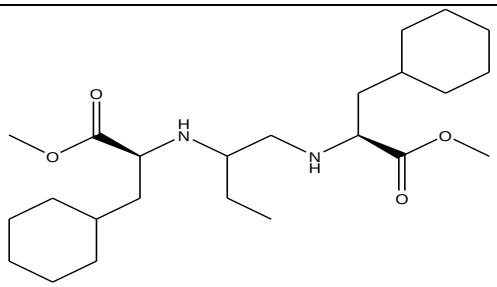
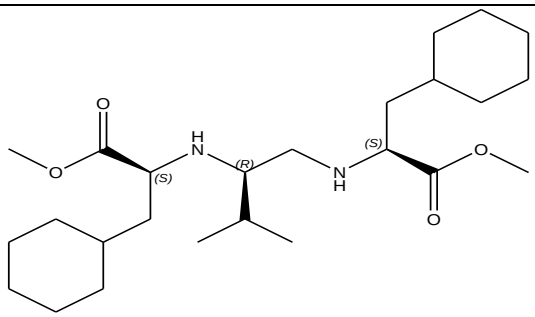
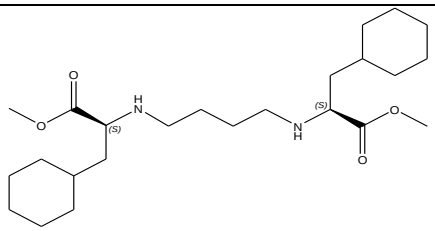
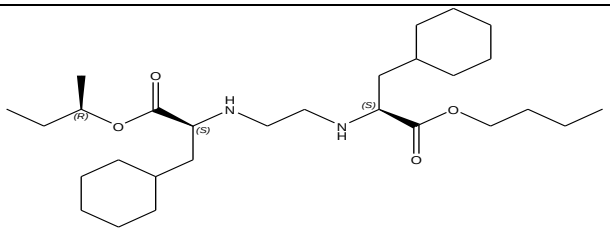
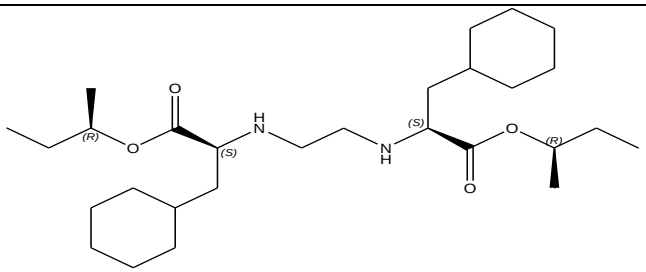
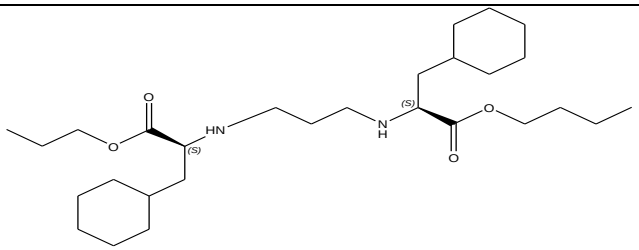
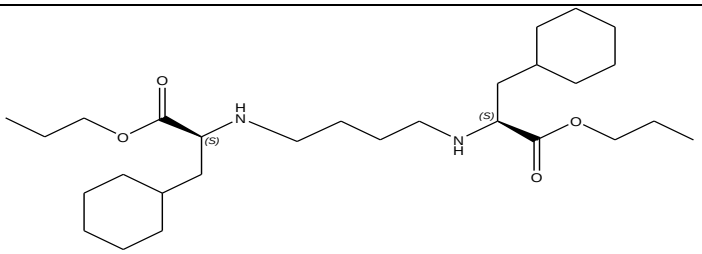
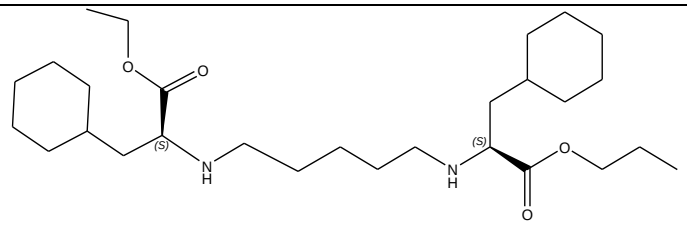
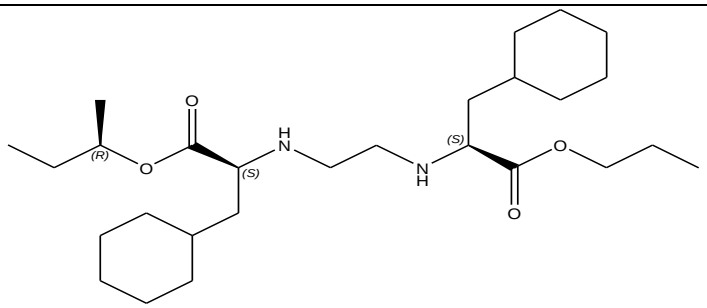
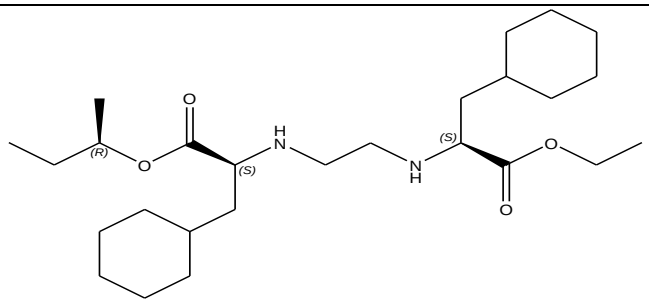
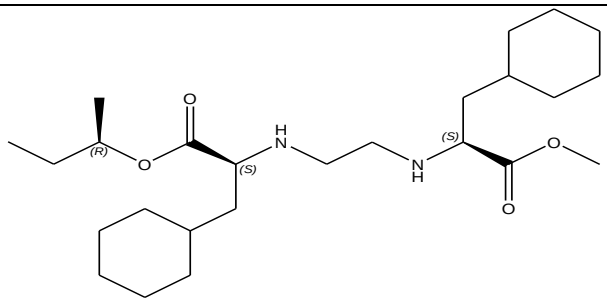
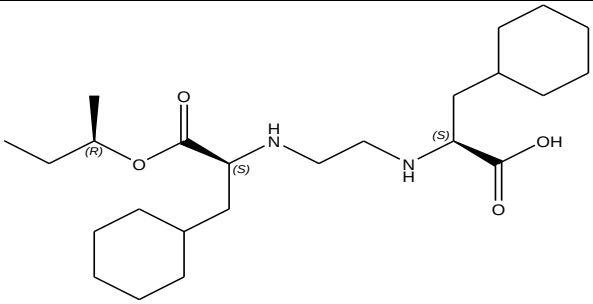
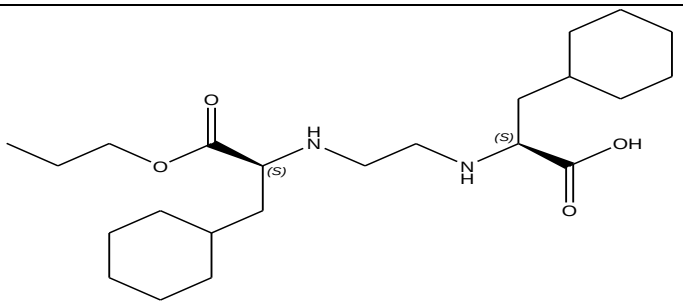
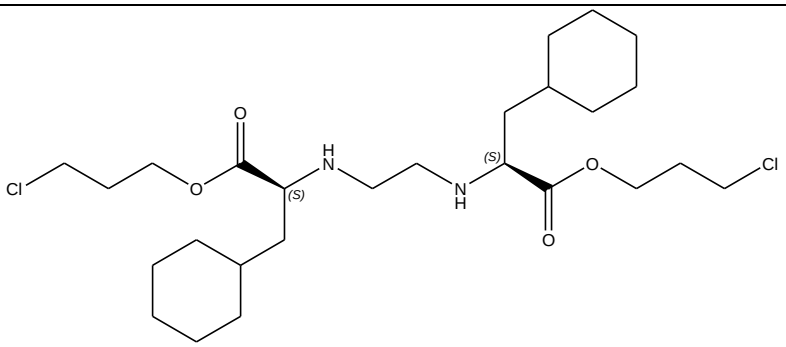
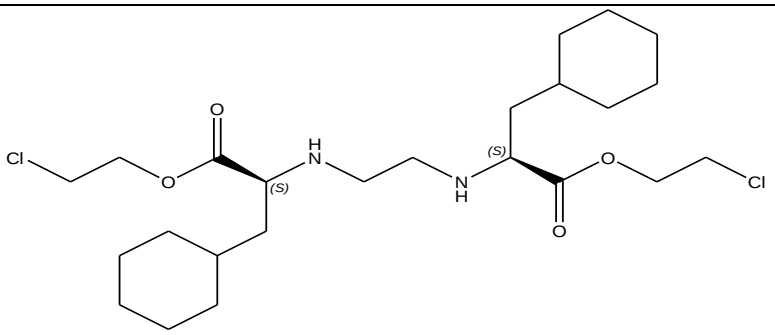
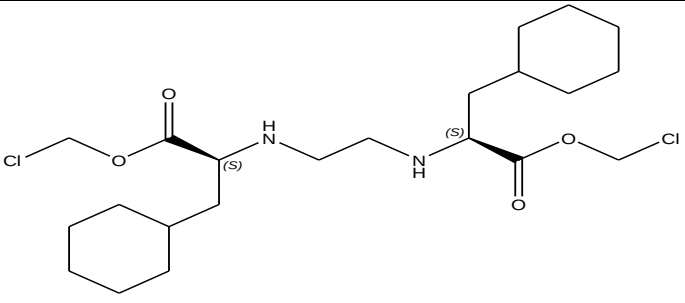
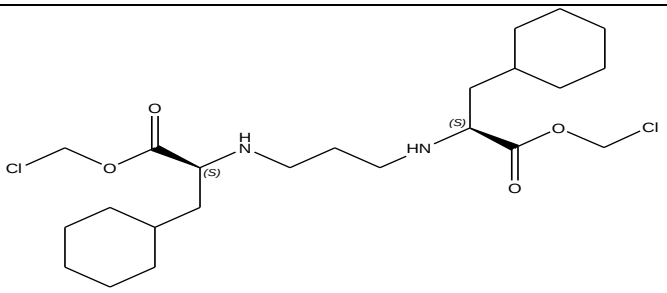
P11		3.07
P12		3.18

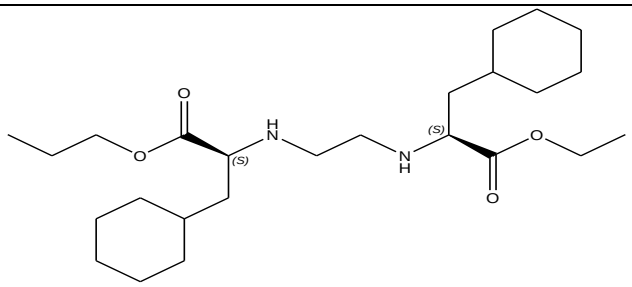
Table S3

Chemical structures of all designed derivatives and their predicted *R* values.

Derivative	Structure	Predicted *R* values
R1		88.84
R2		65.53
R3		65.53
R4		65.53
R5		65.53

R6		65.53
R7		78.18
R8		87.34
R9		91.27
R10		88.70

R11		79.44
R12		54.30
R13		80.29
R14		91.01
R15		88.40

R16		91.27