Supporting Information

Nature-inspired 1-phenylpyrrolo[2,1-*a*]isoquinoline scaffold for novel antiproliferative agents circumventing P-glycoprotein-dependent multidrug resistance

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Table of content

Figure S1: ^{1}H and ^{13}C-NMR of (1-(4-methoxyphenyl)-8,9-dimethoxy -5,6- dihydropyrrolo[2,1-*a*]isoquinoline -2- carbaldehyde (**4b**)

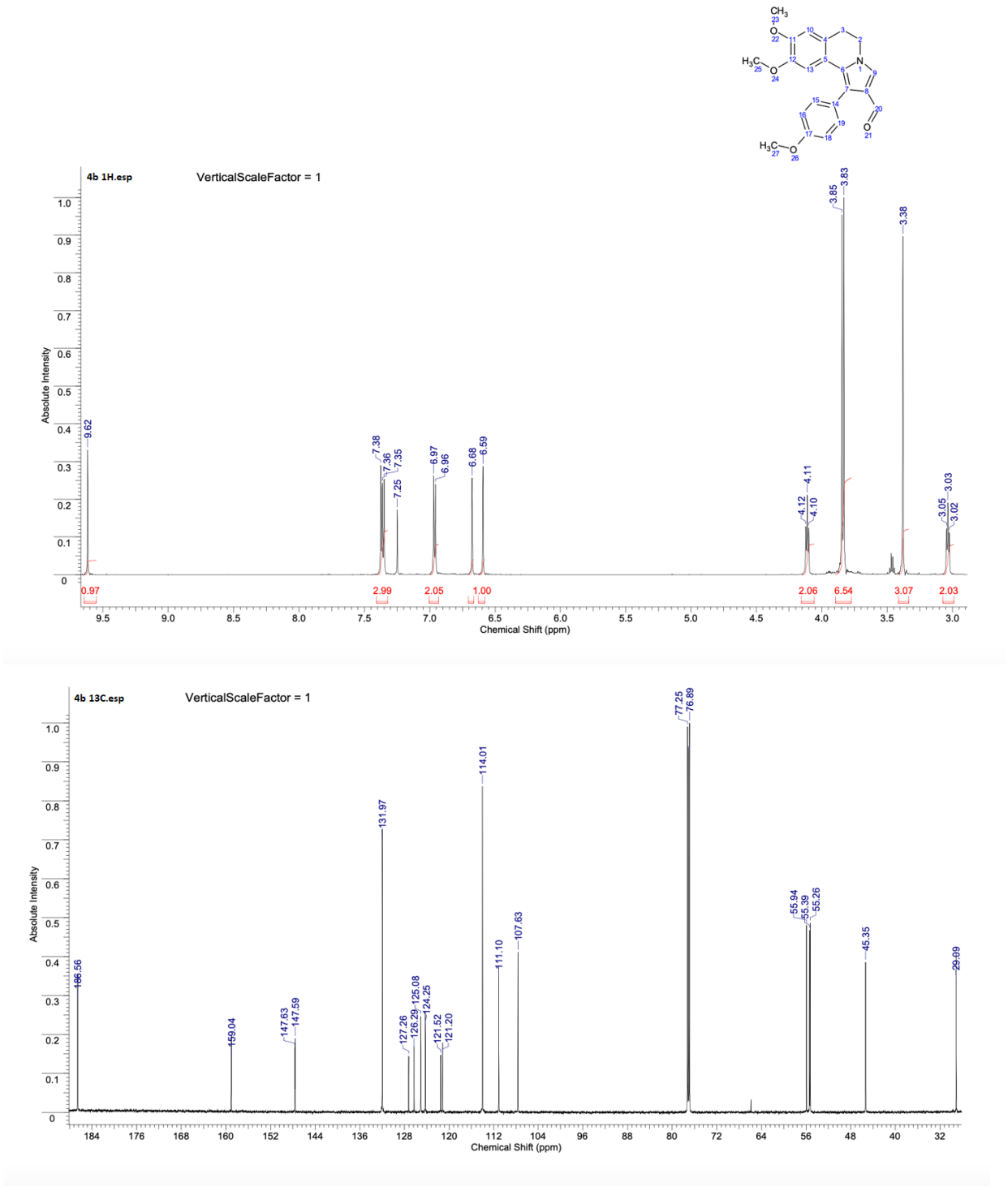


Figure S2: ^{1}H and ^{13}C-NMR of 1-(4-chlorophenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**5a**)

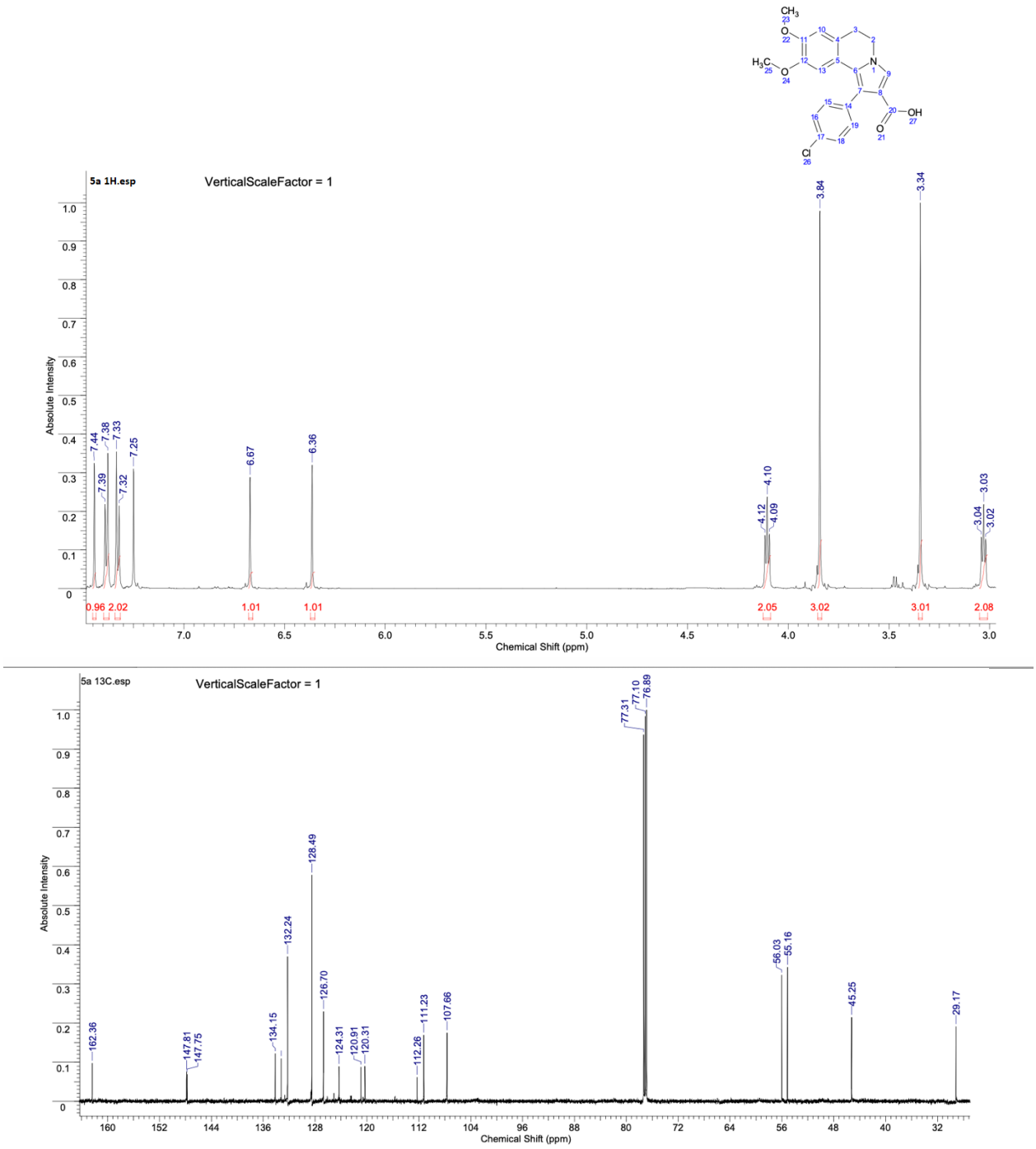


Figure S3: ^{1}H and ^{13}C-NMR of 1-(3,4-diethoxyphenyl)-8,9-diethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid (**5c**)

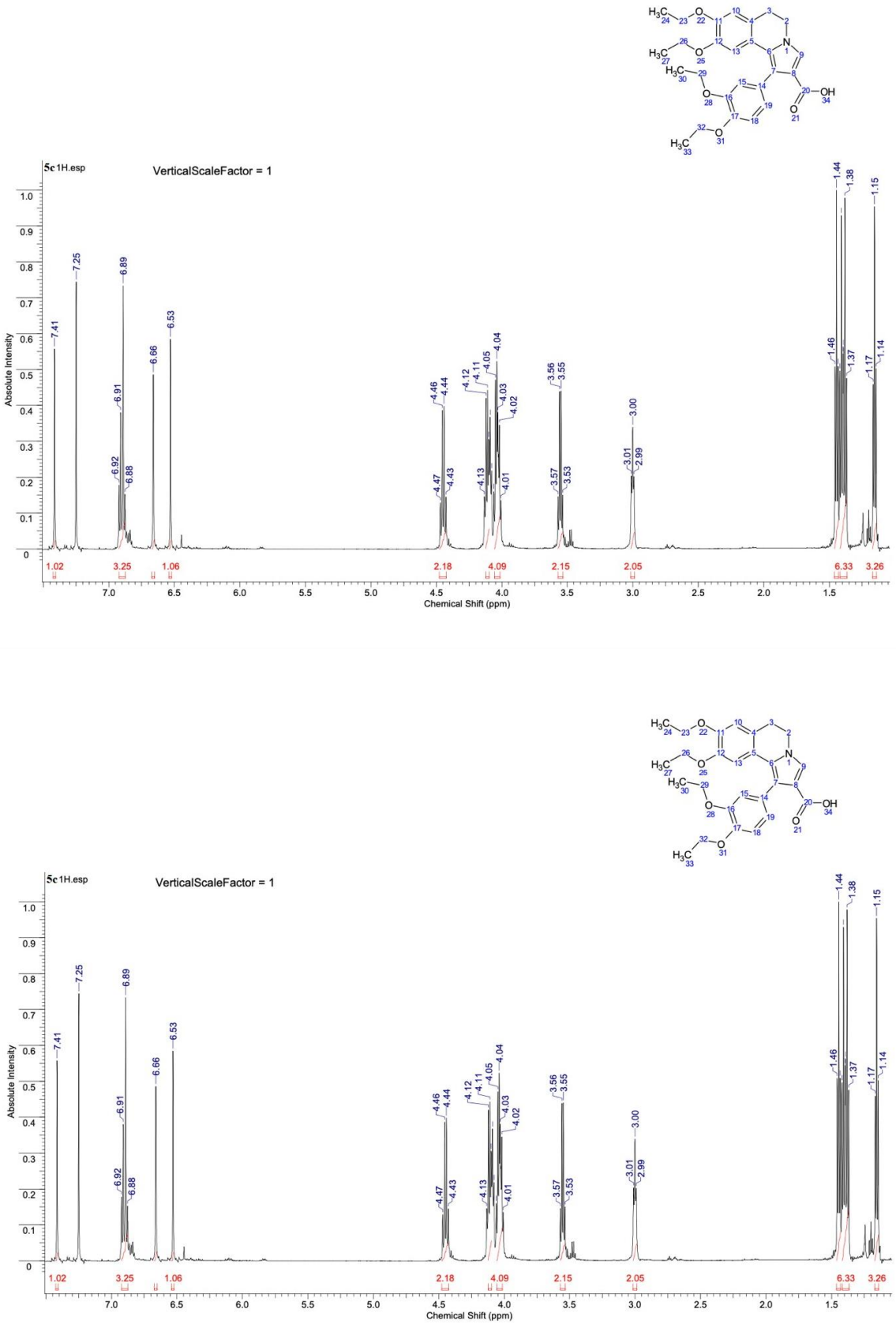


Figure S4: ^{1}H and ^{13}C-NMR of 1-(3,4-diethoxyphenyl)-8,9-diethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbonitrile (**6d**)

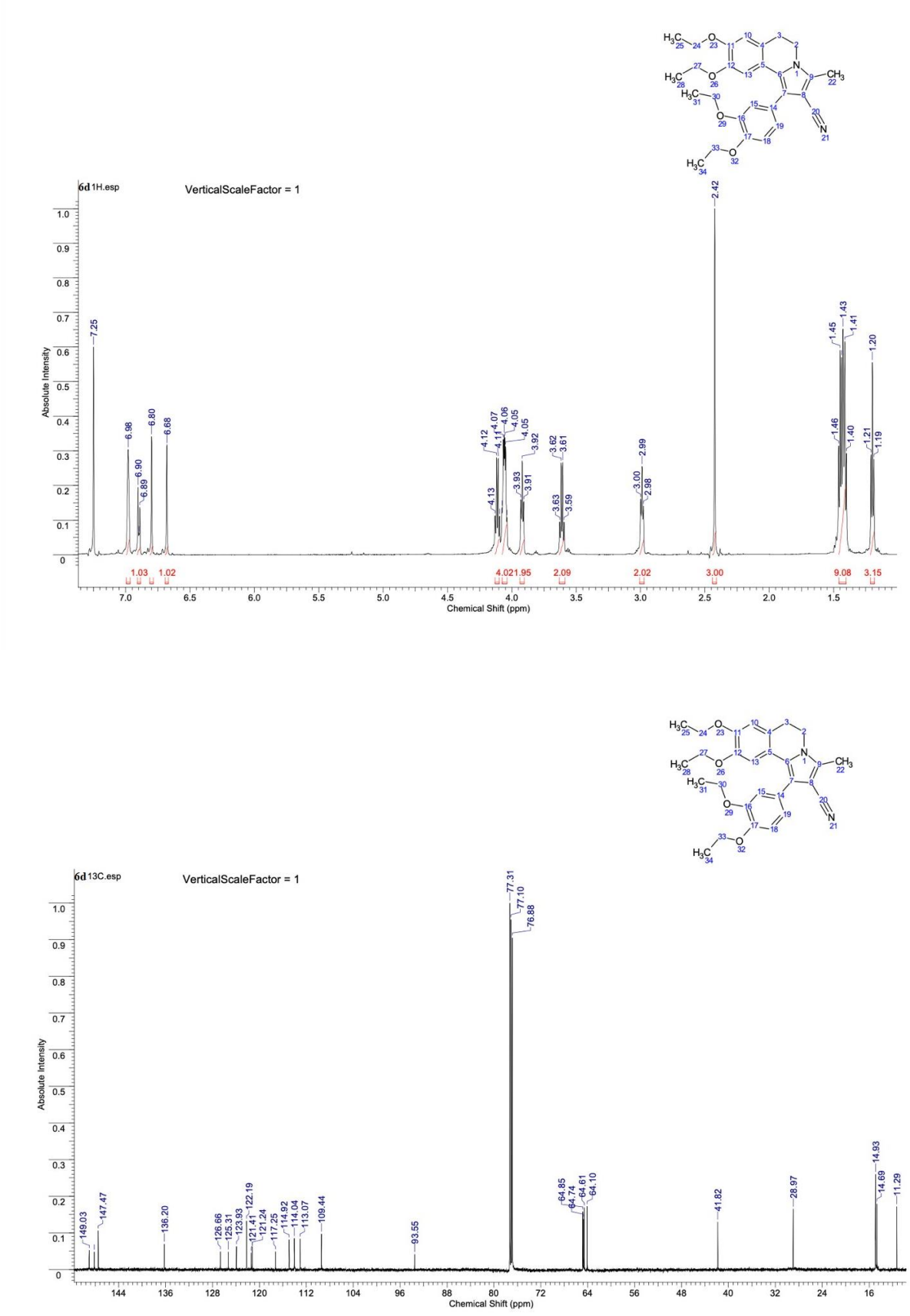
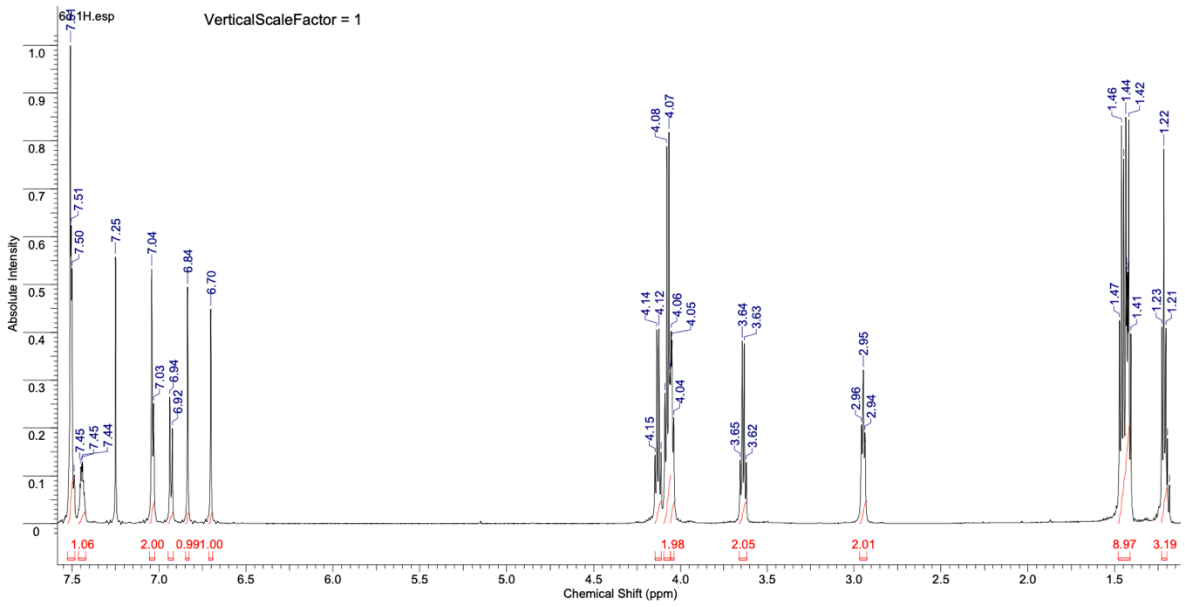
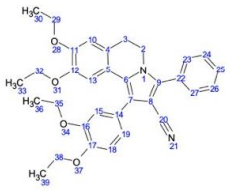


Figure S5: ^{1}H and ^{13}C-NMR of 1-(3,4-diethoxyphenyl)-8,9-diethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbonitrile (**6e**)





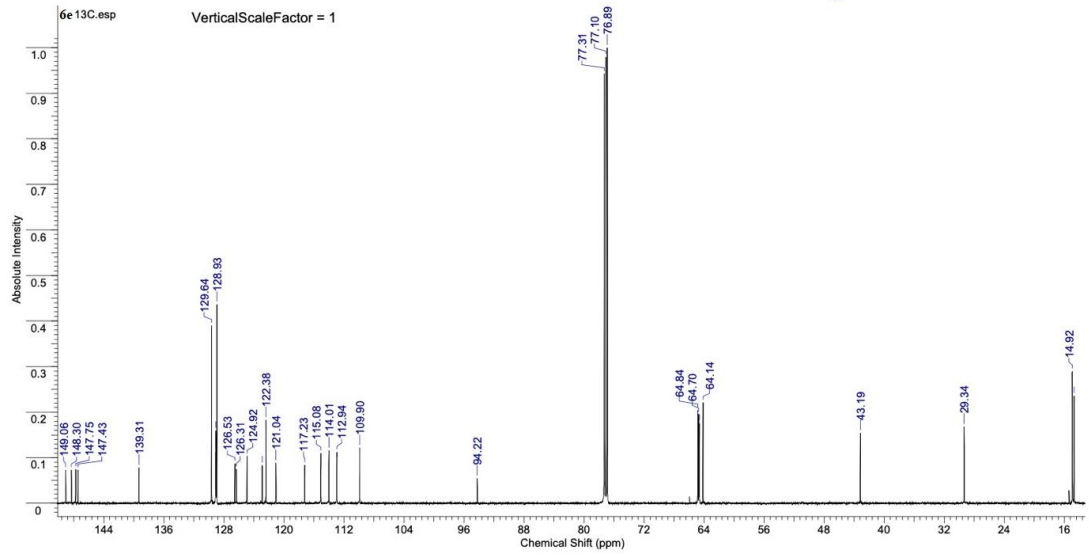


Figure S6: [1]H and [13]C-NMR of ethyl 1-(3,4-diethoxyphenyl)-8,9-diethoxy-5,6-dihydro pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**7c**)

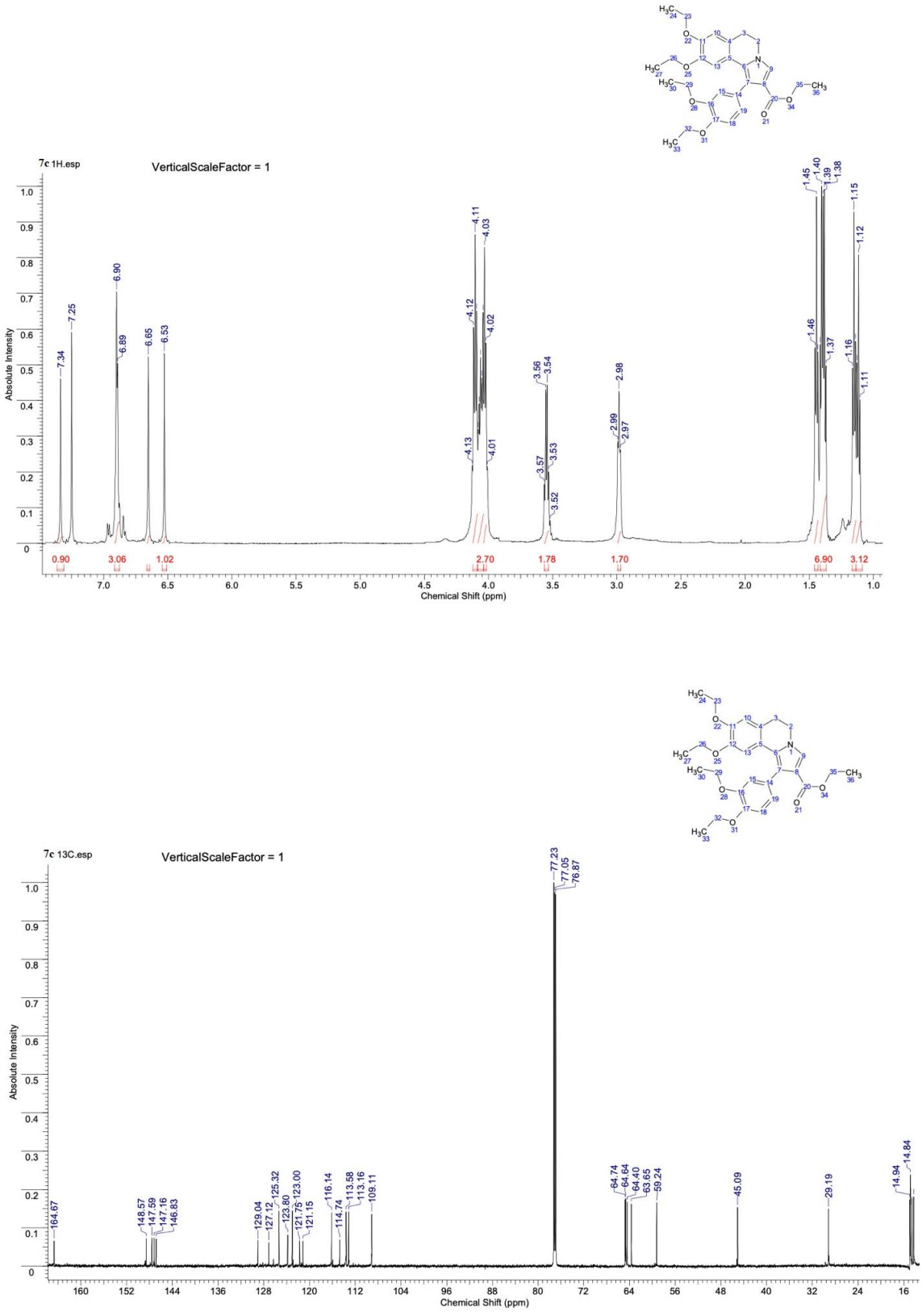
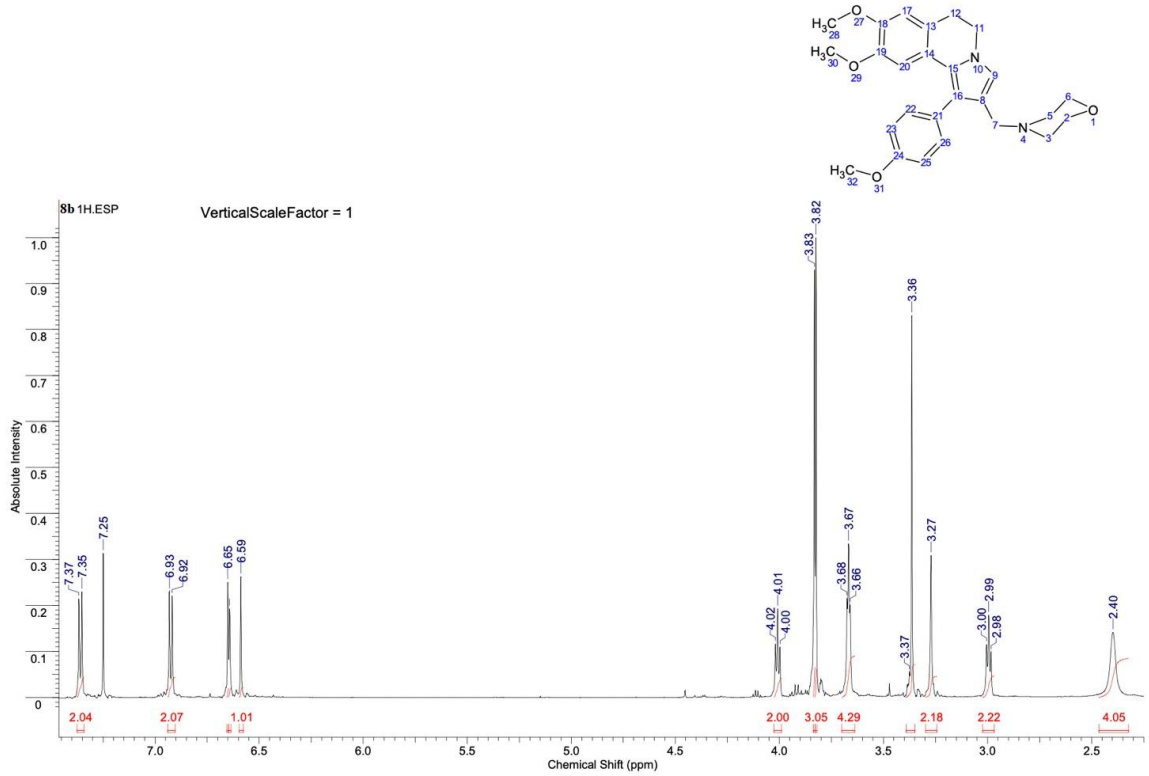


Figure S7: ^{1}H and ^{13}C-NMR of 8,9-dimethoxy-1-(4-methoxyphenyl)-2-(morpholin-4-ylmethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**8b**)



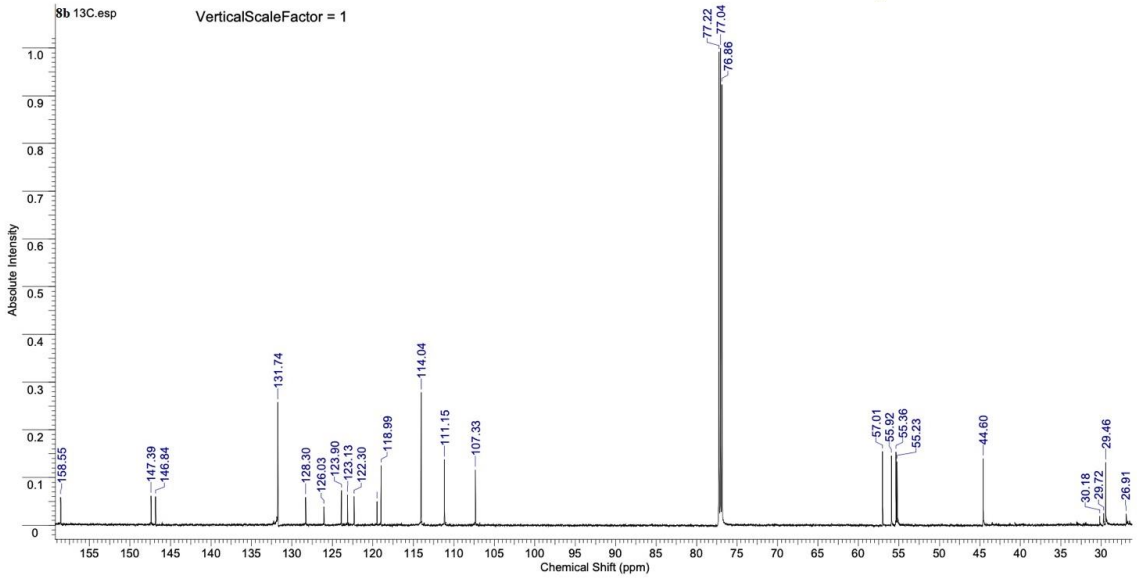


Figure S8: ^{1}H and ^{13}C-NMR of 1-(3,4-diethoxyphenyl)-8,9-diethoxy-2-(morpholin-4-ylmethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**8c**)

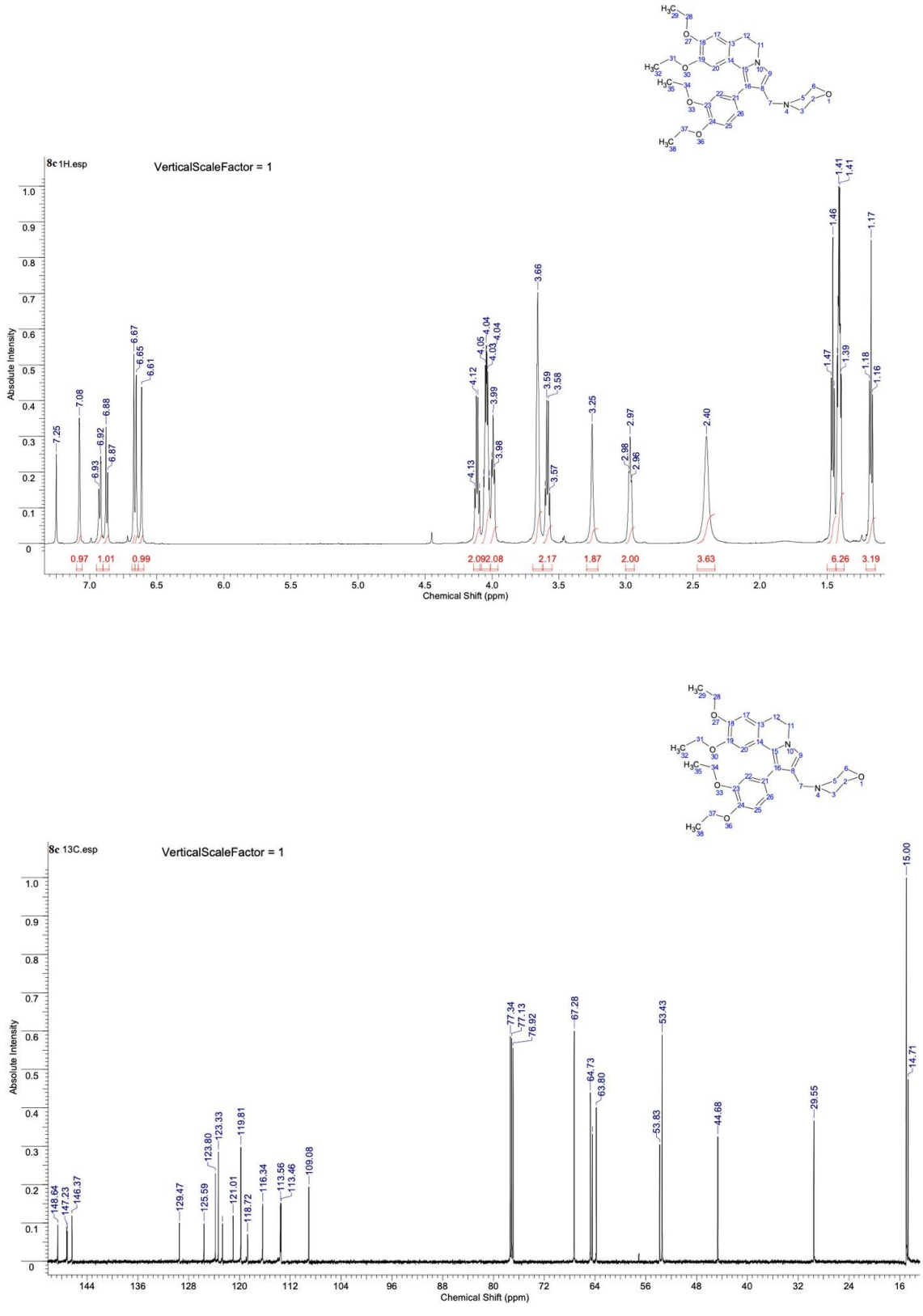


Figure S9: ^{1}H and ^{13}C-NMR of 4-{[1-(3,4-diethoxyphenyl)-8,9-diethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-2-yl]methyl}morpholin-4-ium chloride (**8c·HCl**)

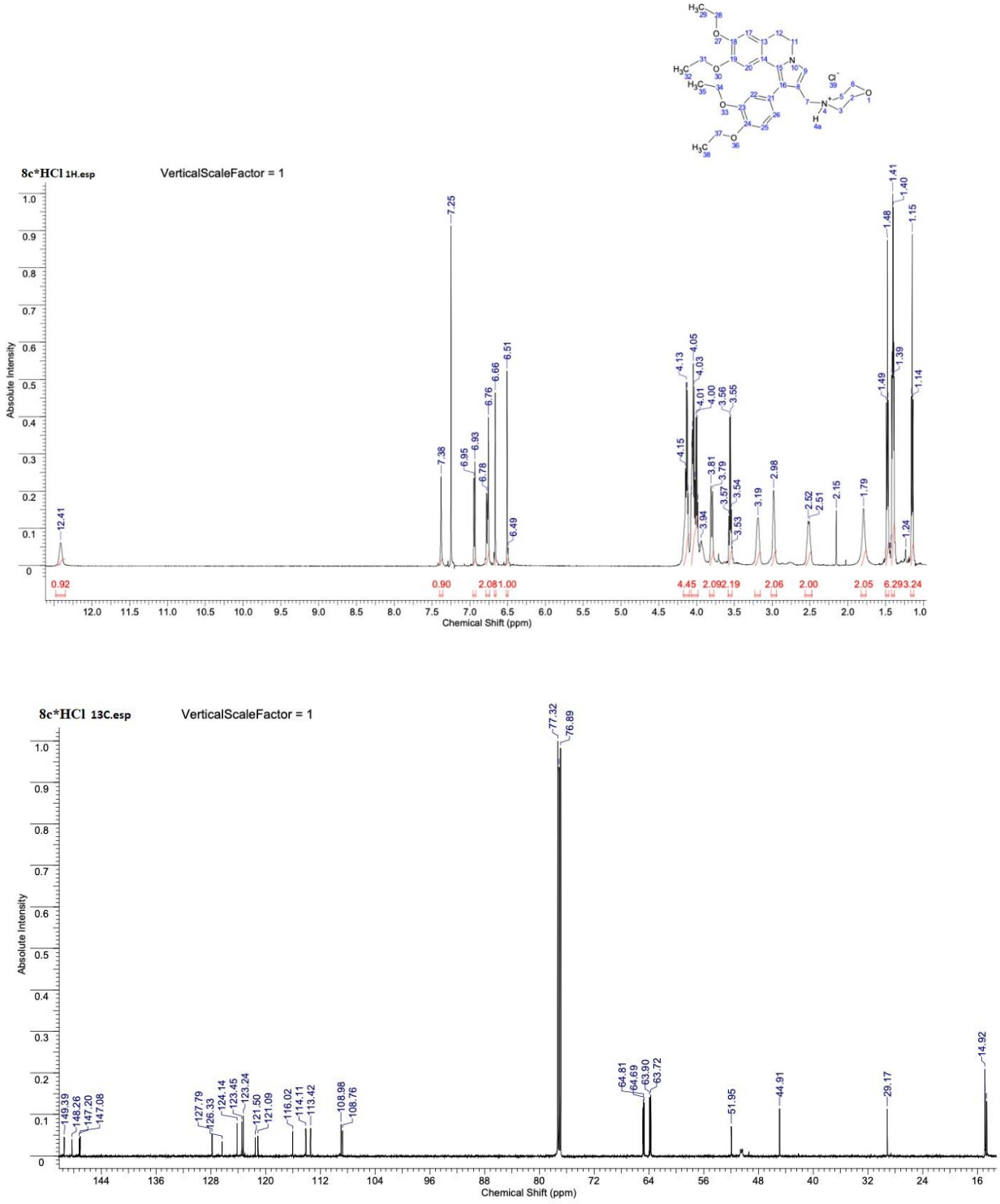


Figure S10. Plot of the P-gp inhibition potency (-log IC_{50}) versus free energy of binding (FEB, kcal·mol^{-1}); data are correlated through a trend of binomial nonlinear relationship (r^2 = 0.879).

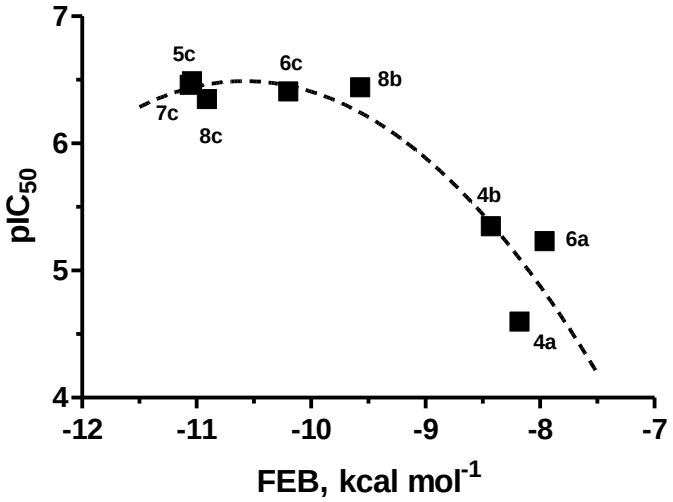


Table S1. Squared correlation matrix (r^2) of the biochemical/biophysical data[a] and physicochemical parameters[b] listed in Table 2.

	P-gp	**MRP1**	**HSA**	**log S**	**clog P**	**log *k*'$_w$**
P-gp	1					
MRP1	0.001	1				
HSA	0.381	0.284	1			
log S	0.147	0.502	0.497	1		
clog P	0.255	0.135	0.029	0.017	1	
log *k*'$_w$	0.237	0.272	0.003	0.041	0.791	1

[a] P-gp (P-glycoprotein) and MRP1 (multidrug-resistance-associated protein-1) inhibition potency data are expressed by -log IC_{50} (mol·L^{-1}) values; for compounds showing IC_{50}s > 100 μM 'truncated' values of -log IC_{50} equal to 4.00 were used in correlation analysis. HSA (human serum albumin) binding affinity is expressed as $\log_{10}$ of the equilibrium dissociation constant (K_D, mol·L^{-1}) determined by a surface plasmon resonance (SPR) technique. [b] Log S is the $\log_{10}$ of the compound solubility (mol·L^{-1}) in PBS (50 mM, pH 7.4, 0.15 M KCl) at 25±1 °C; clog P is the 1-octanol/water partition coefficient calculated by ACDLabs software (release 10.0, Advanced Chemistry Development, Inc., Toronto, Canada); log *k*'$_w$ is the $\log_{10}$ of the polycratic capacity factor determined by a reversed phase (RP) HPLC technique.