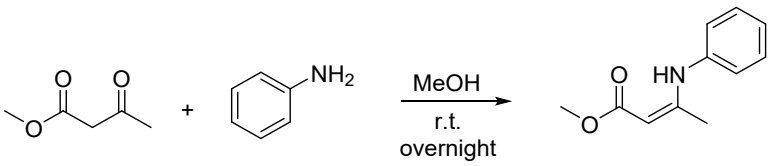
Dynamic exchange in vinylogous urethane vitrimers: computational and experimental approaches to screen structure-property relationships of dynamic bonds

Jacopo Teotonico, Fernando Ruipérez, Nicholas Ballard**

SUPPORTING INFORMATION

Synthetic Procedures

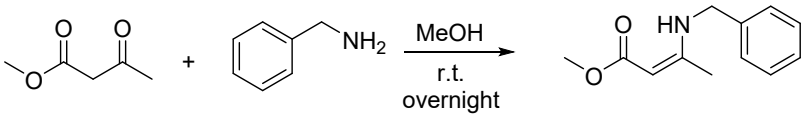
Synthesis of Methyl-3-(phenylamino)but-2-enoate (VU_PhNH$_2$):



The synthesis of VU_PhNH$_2$ was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (5g, 43 mmol) and aniline (8,4g, 90 mmol) were added in 30 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin-layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. The obtained product was purified by flash chromatography using EtOAc/hexane (v/v = 85/15) as the eluent. Yield of methyl-3-(phenylamino)but-2-enoate: 58%, 4.8 g. ^{1}H NMR

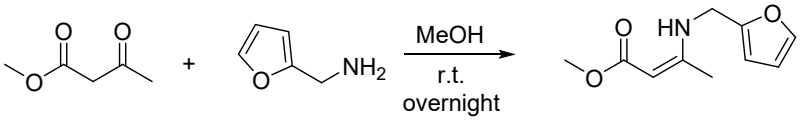
(400 MHz, DMSO-d^6) δ 7.59 – 6.95 (m, 5H), 4.71 (d, J = 0.7 Hz, 1H), 3.59 (s, 3H), 2.01 (d, J = 0.6 Hz, 3H).

Synthesis of Methyl-3-(benzylamino)but-2-enoate (VU_BnNH$_2$):



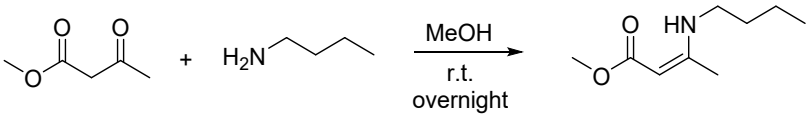
The synthesis of VU_BnNH$_2$ was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and benzylamine (3,6g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin-layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(benzylamino)but-2-enoate: 98%, 3.40g. ^{1}H NMR (400 MHz, DMSO-d^6) δ 8.95 – 8.79 (m, 1H), 7.45 – 7.18 (m, 4H), 4.48 – 4.46 (m, 2H), 4.44 (s, 1H), 3.50 (s, 3H), 1.90 (d, J = 0.6 Hz, 3H).

Synthesis of Methyl-3-(furfurylamino)but-2-enoate (VU_FuNH$_2$):



The synthesis of VU_FuNH$_2$ was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and furfurylamine (3.3g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin-layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(furfurylamino)but-2-enoate: 98%, 3.26g. ^{1}H NMR (400 MHz, DMSO-d^6) δ 8.69 (t, J = 6.2 Hz, 1H), 6.42 (dd, J = 3.2, 1.9 Hz, 1H), 6.30 (dt, J = 3.2, 0.8 Hz, 1H), 4.46 (d, J = 0.7 Hz, 1H), 4.44 (t, J = 0.7 Hz, 2H), 3.48 (s, 3H), 1.97 (d, J = 0.6 Hz, 3H).

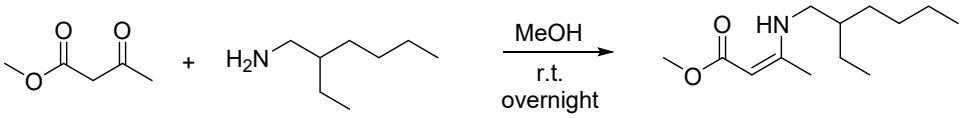
Synthesis of Methyl-3-(butylamino)but-2-enoate (VU_BuNH$_2$):



The synthesis of VU_BuNH$_2$ was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and butylamine (2,5g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin-layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(butylamino)but-2-enoate: 98%, 2.79g. ^{1}H NMR (400 MHz,

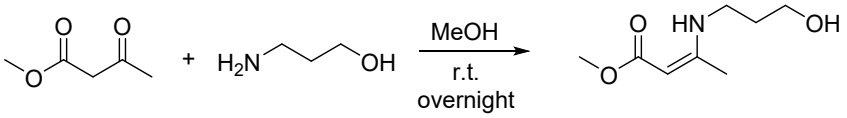
DMSO-d^6) δ 8.50 (s, 1H), 4.35 (d, J = 0.6 Hz, 1H), 3.47 (s, 3H), 3.20 (td, J = 6.9, 5.8 Hz, 2H), 1.89 (d, J = 0.6 Hz, 3H), 1.53 – 1.40 (m, 2H), 1.41 – 1.26 (m, 2H), 0.95 – 0.85 (m, 3H).

Synthesis of Methyl-3-(2-ethylhexylamino)but-2-enoate (VU_2EHA):



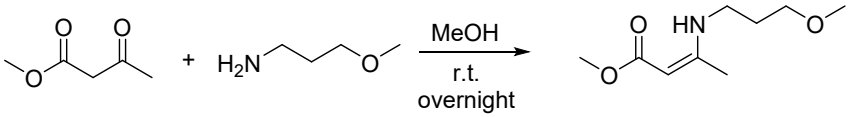
The synthesis of VU_2EHA was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and 2-ethylhexylamine (4,4g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin-layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(2-ethylhexylamino)but-2-enoate: 99%, 3,74g. ^{1}H NMR (400 MHz, DMSO-d^6) δ 8.60 (t, J = 5.8 Hz, 1H), 4.36 (d, J = 0.7 Hz, 1H), 3.48 (s, 3H), 3.13 (td, J = 5.9, 0.8 Hz, 2H), 1.89 (d, J = 0.6 Hz, 4H), 1.39 – 1.19 (m, 13H), 0.92 – 0.79 (m, 7H).

Synthesis of Methyl-3-(3-propanolamino)but-2-enoate (VU_3MET):



The synthesis of VU_3MET was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and 3-aminopropanol (2,55g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin-layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(3-aminopropanol)but-2-enoate: 94%, 2,61g. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 4.43 (s, 1H), 3.71 (t, 1H), 3.59 (s, 5H), 3.33 (t, 1H), 1.92 (s, 5H), 1.86 – 1.71 (m, 1H).

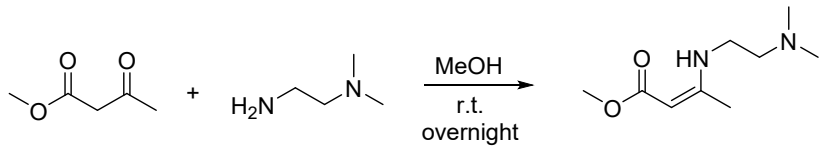
Synthesis of Methyl-3-(3-methoxypropylamino)but-2-enoate (VU_3APO):



The synthesis of VU_3APO was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and 3-methoxypropylamine (3g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(3-methoxypropylamine)but-2-enoate: 97%, 3,07g. ^{1}H NMR

(300 MHz, DMSO) δ 8.52 (s, 1H), 4.37 (s, 1H), 3.49 (s, 4H), 3.37 (t, 2H), 3.32 – 3.27 (m, 1H), 3.25 (s, 4H), 1.90 (s, 4H), 1.77 – 1.67 (m, 1H).

Synthesis of Methyl-3-(N,N-dimethyl-1,3-propanediamino)but-2-enoate (VU_N,NDIAM):



The synthesis of VU_N,NDIAM was based on procedures published by Denissen *et al.*.[1] Methyl acetoacetate (2g, 17 mmol) and N,N-dimethylethylenediamine (3g, 34 mmol) were added in 20 mL of MeOH in a 100 mL round bottom flask. The reaction was stirred overnight at room temperature and the formation of the product was checked with thin layer chromatography (TLC). The solvent was removed in vacuo and the mixture was extracted twice with brine and EtOAc. The combined organic phases were dried with $MgSO_4$ and evaporated, yielding the desired product as a yellowish liquid. Yield of methyl-3-(N,N-dimethyl-1,3-propanediamino)but-2-enoate: 96%, 3,03g. ^{1}H NMR (300 MHz, Chloroform-d) δ 8.63 (s, 1H), 4.47 (d, J = 0.7 Hz, 1H), 3.64 (d, J = 1.2 Hz, 3H), 3.31 (td, J = 6.6, 5.6 Hz, 2H), 2.48 (t, J = 6.6 Hz, 2H), 2.28 (s, 6H), 1.94 (d, J = 0.6 Hz, 3H).

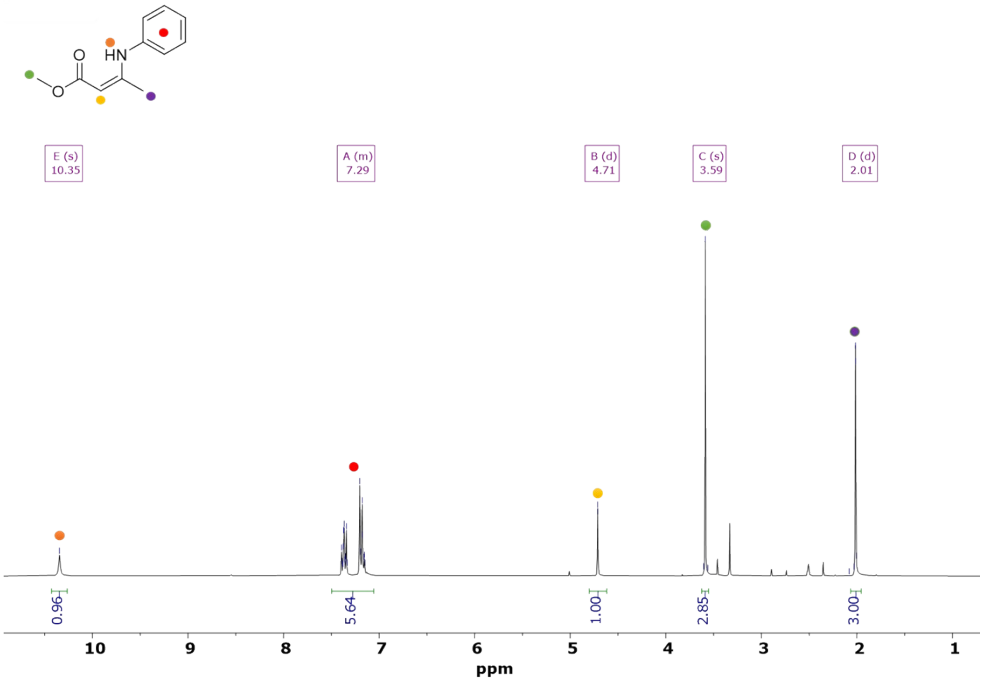


Figure S1: ^{1}H-NMR (400 MHz, dmso-d^{6}) spectrum of VU_PhNH$_2$

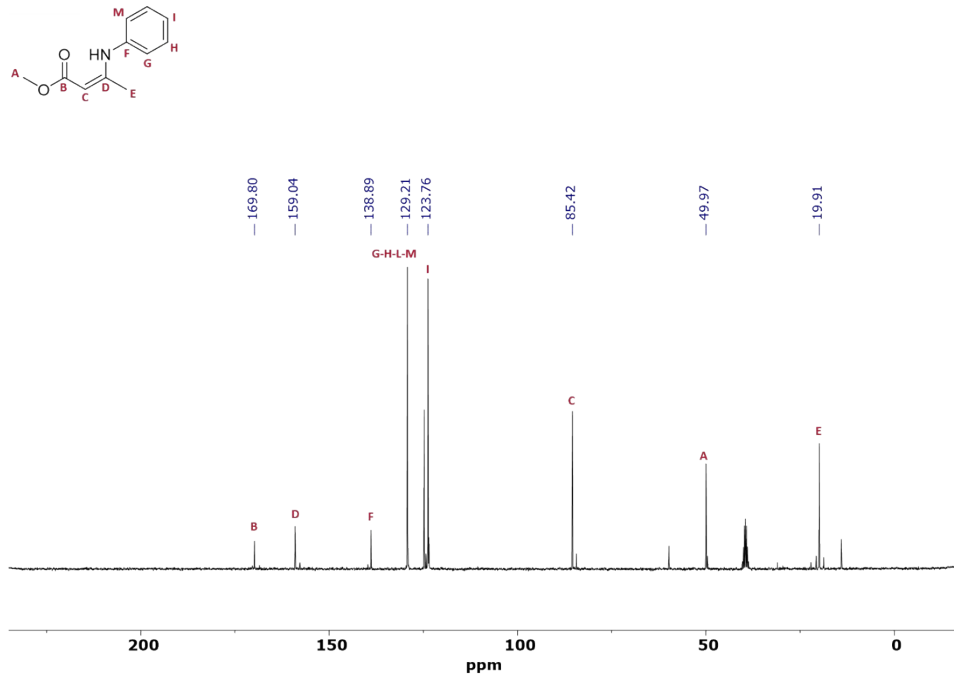


Figure S2: ^{13}C-NMR (400 MHz, dmso-d^{6}) spectrum of VU_PhNH$_2$

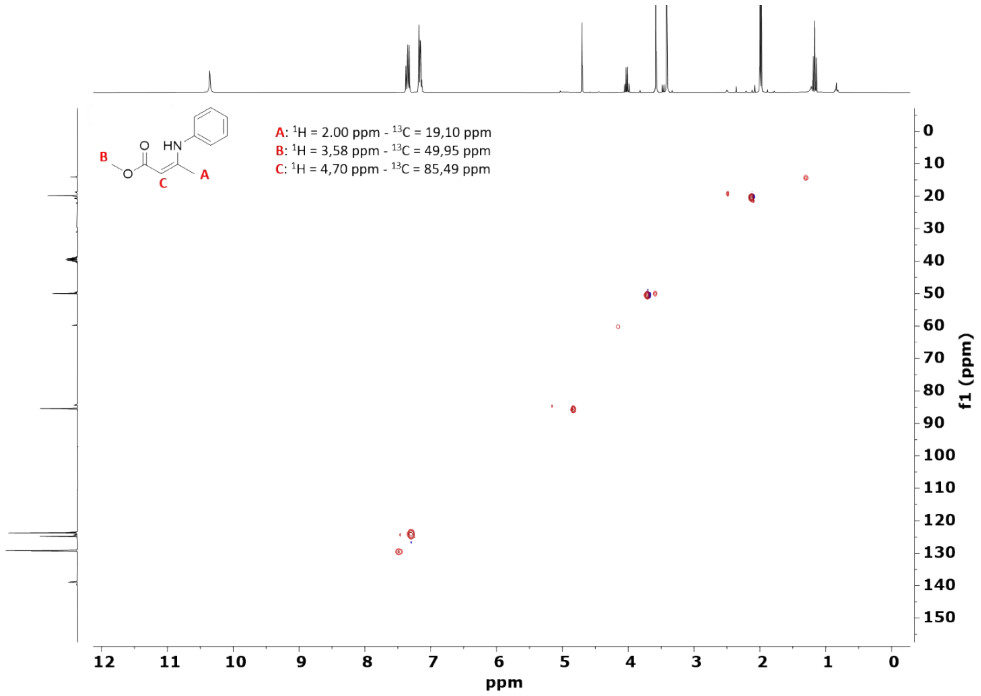


Figure S3: HSQC NMR (400 MHz, dmso-d6) spectrum of VU_PhNH$_2$.

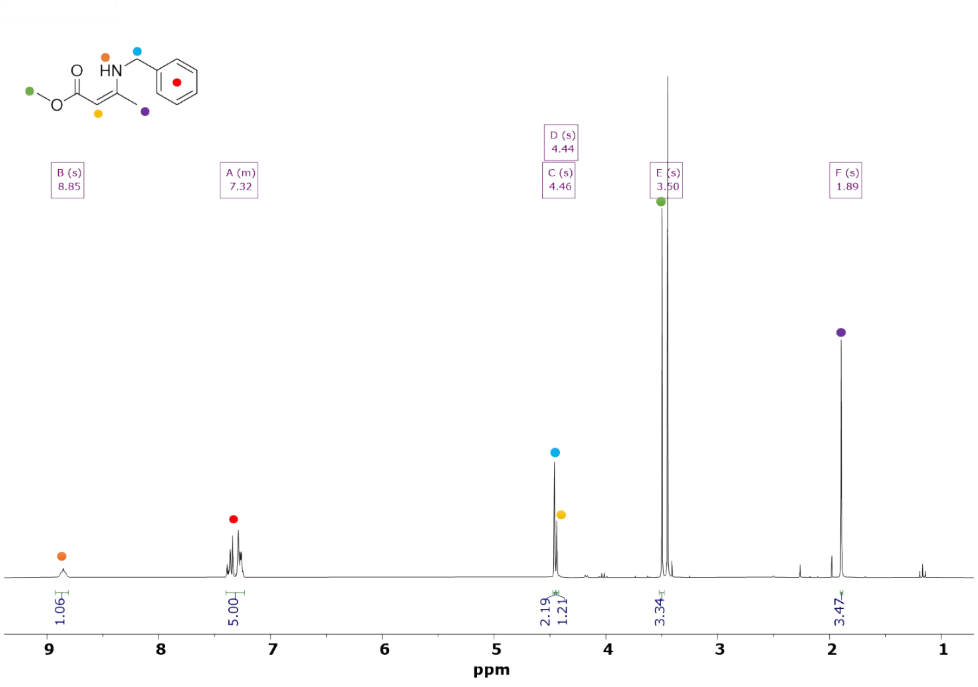


Figure S4: ^{1}H-NMR (400 MHz, dmso-d^6) spectrum of VU_BnNH$_2$.

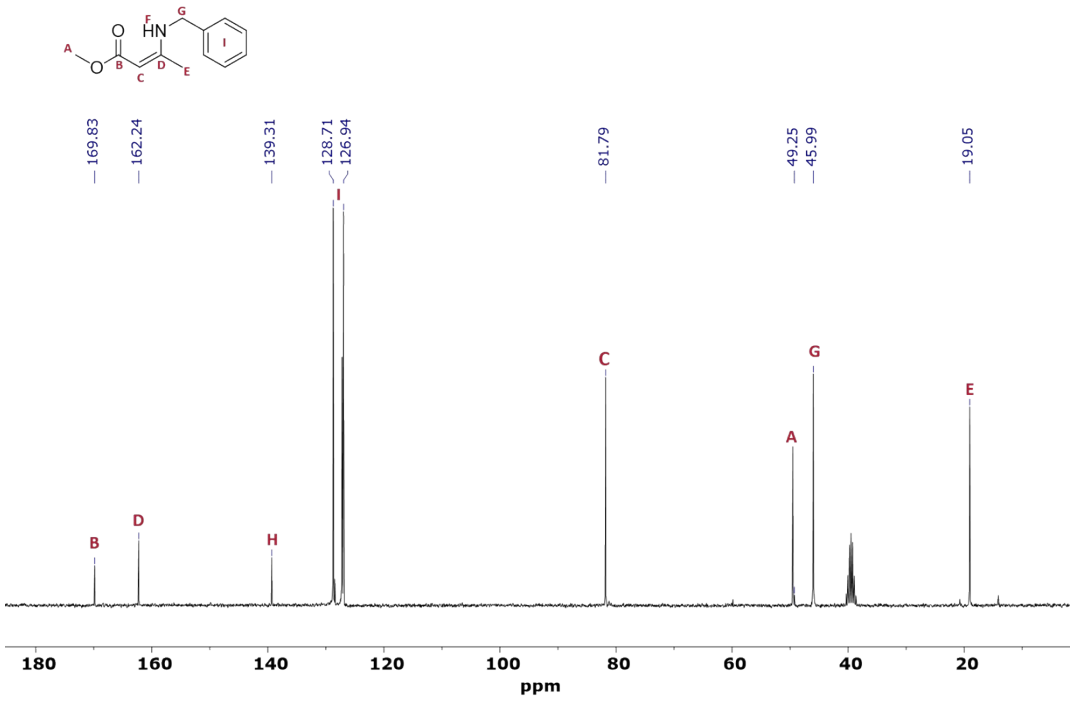


Figure S5: ^{13}C-NMR (400 MHz, dmso-d^6) spectrum of VU_BnNH$_2$.

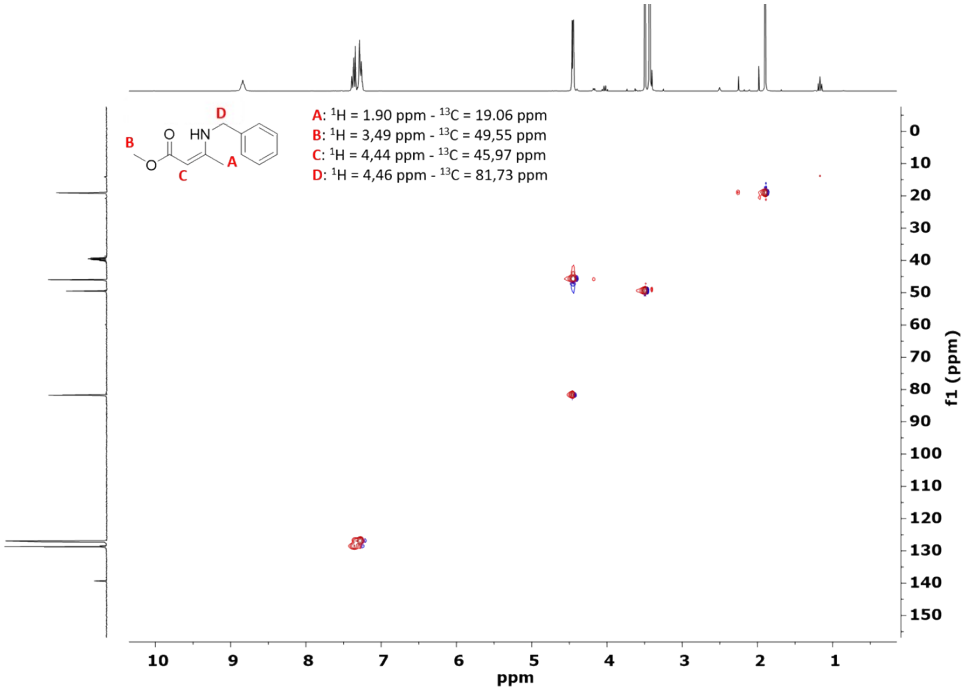


Figure S6: HSQC NMR (400 MHz, dmso-d6) spectrum of VU_BnNH$_2$.

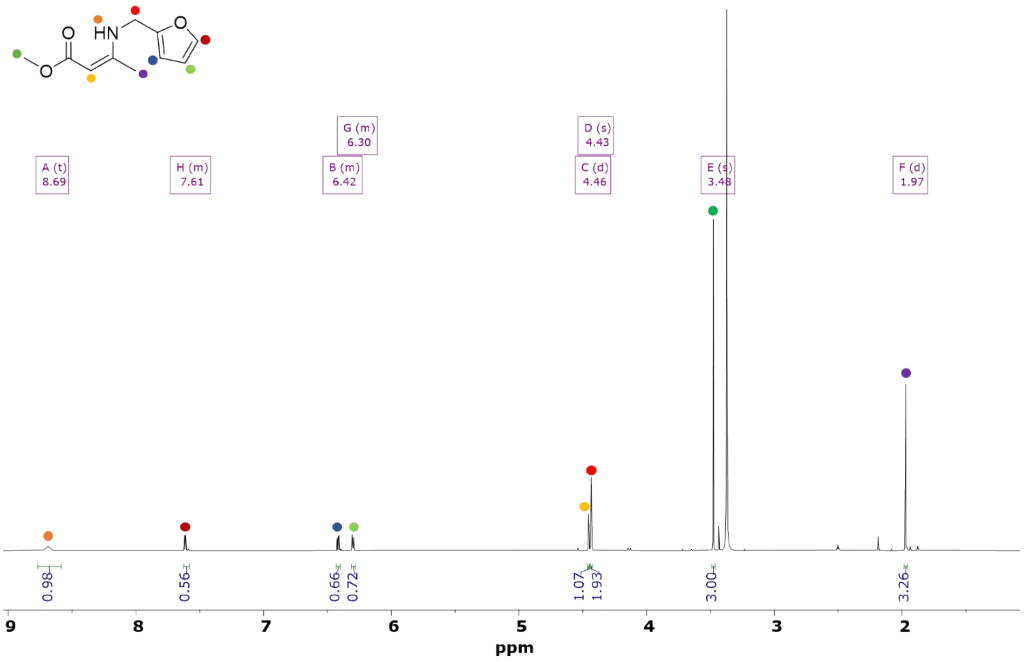


Figure S7: ^{1}H-NMR (400 MHz, dmso-d^{6}) spectrum of VU_FuNH$_2$.

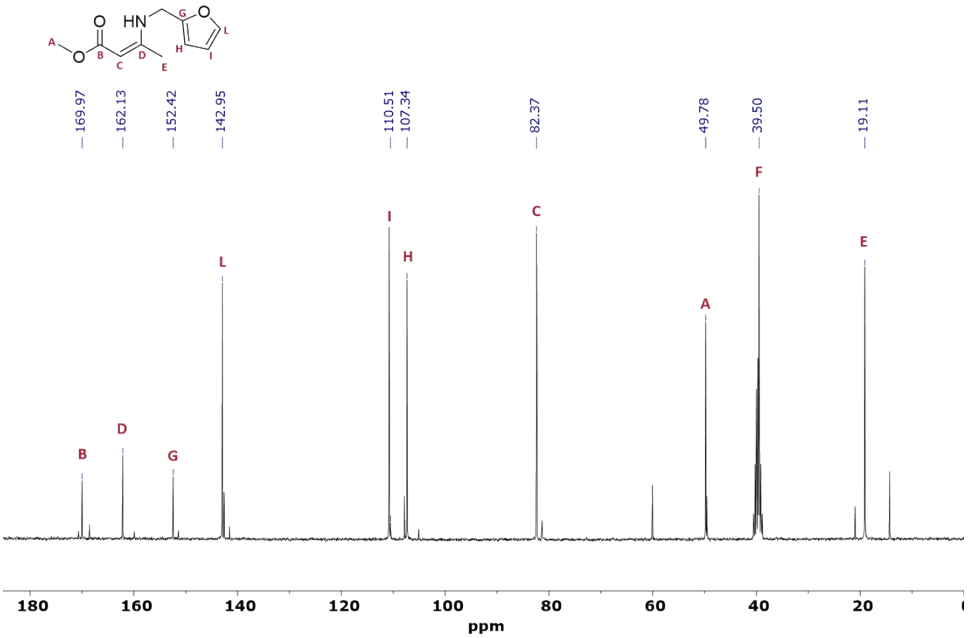


Figure S8: ^{13}C-NMR (400 MHz, dmso-d^{6}) spectrum of VU_FuNH$_2$.

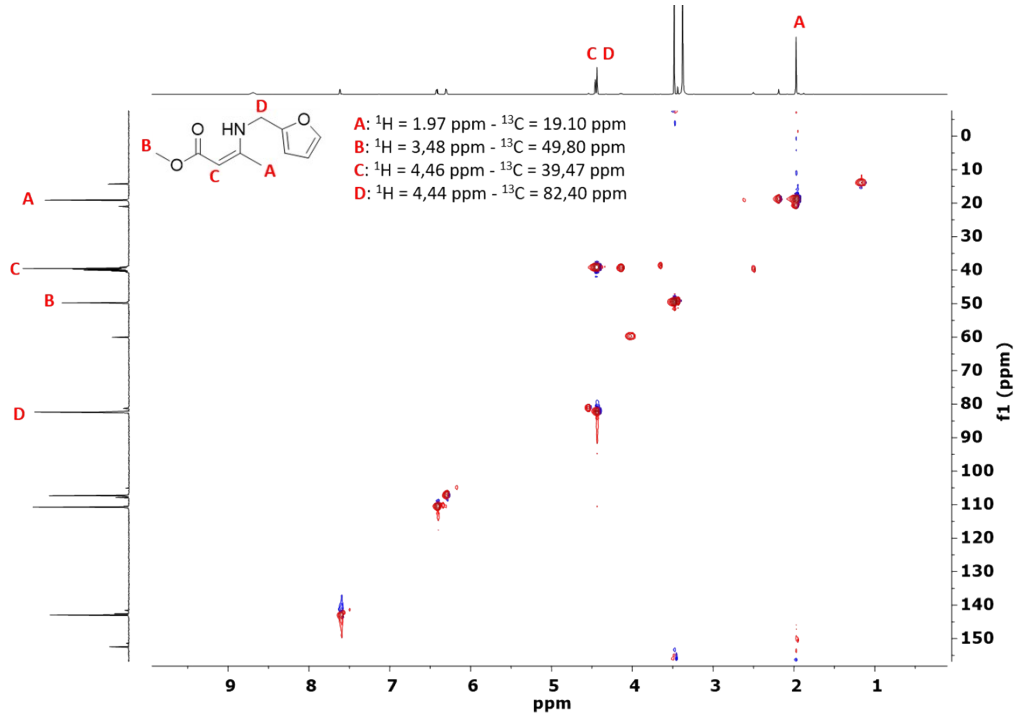


Figure S9: HSQC NMR (400 MHz, dmso-d6) spectrum of VU_FuNH$_2$.

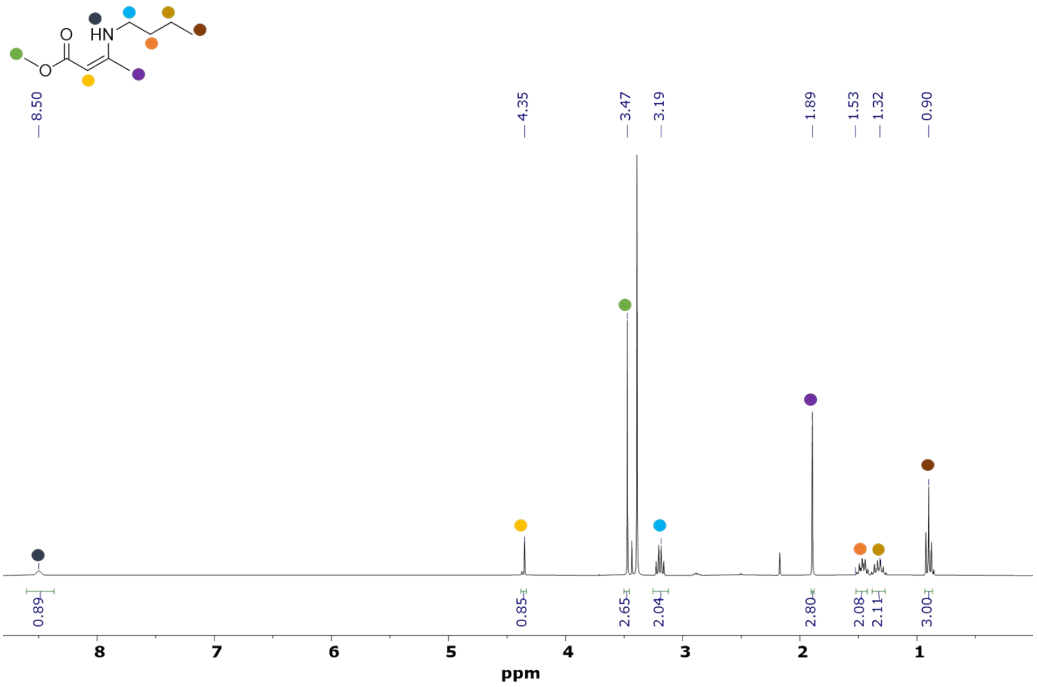


Figure S10: ^{1}H-NMR (400 MHz, dmso-d^{6}) spectrum of VU_BuNH$_2$.

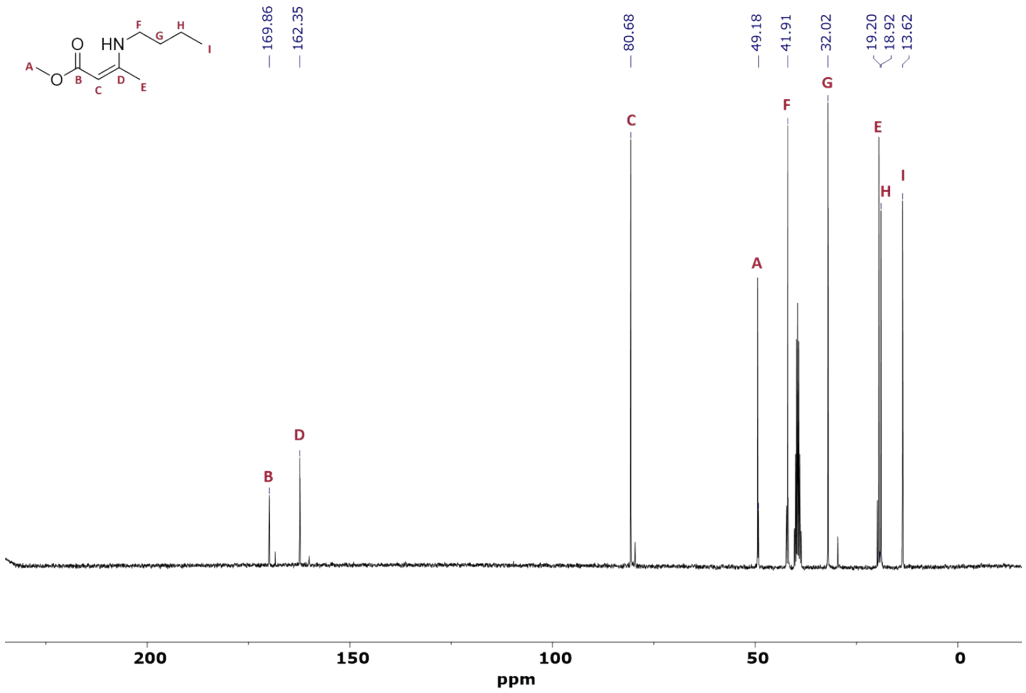


Figure S11: ^{13}C-NMR (400 MHz, dmso-d^6) spectrum of VU_BuNH$_2$.

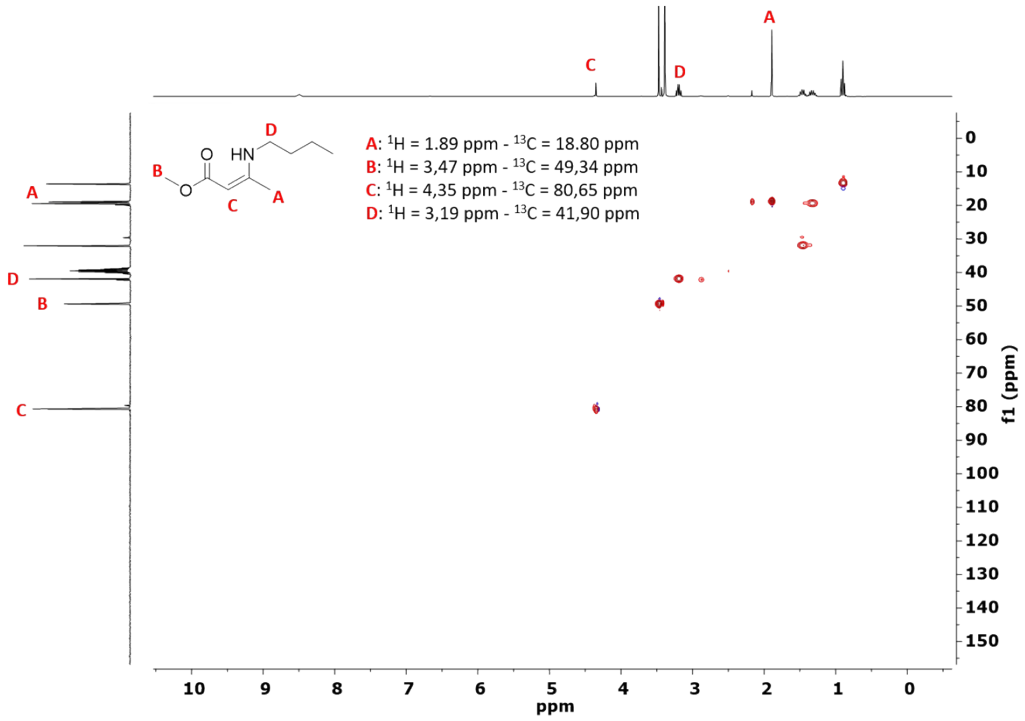


Figure S12: HSQC NMR (400 MHz, dmso-d^6) spectrum of VU_BuNH$_2$.

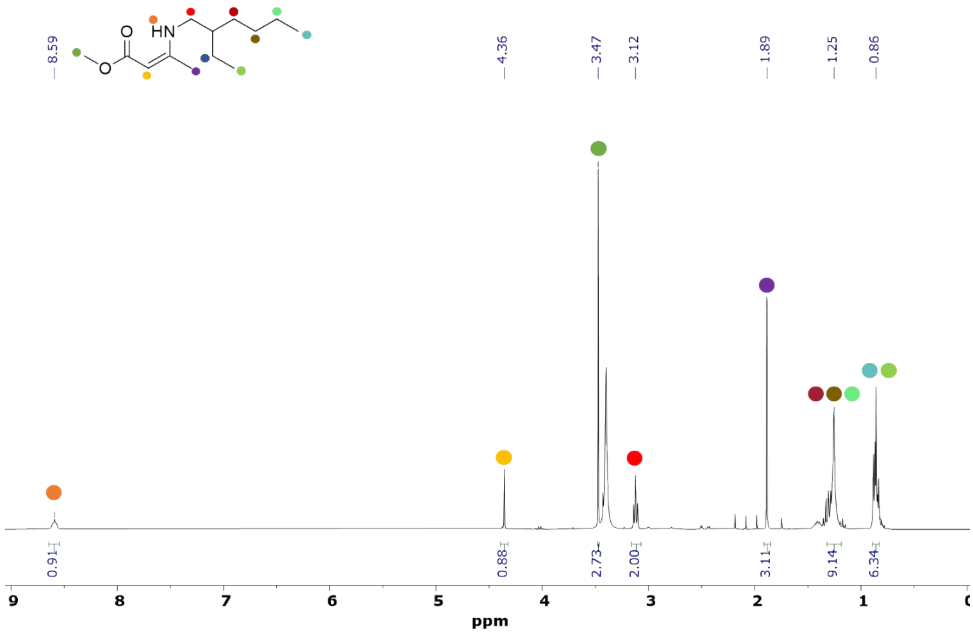


Figure S13: ^{1}H-NMR (400 MHz, dmso-d^{6}) spectrum of VU_2EHA.

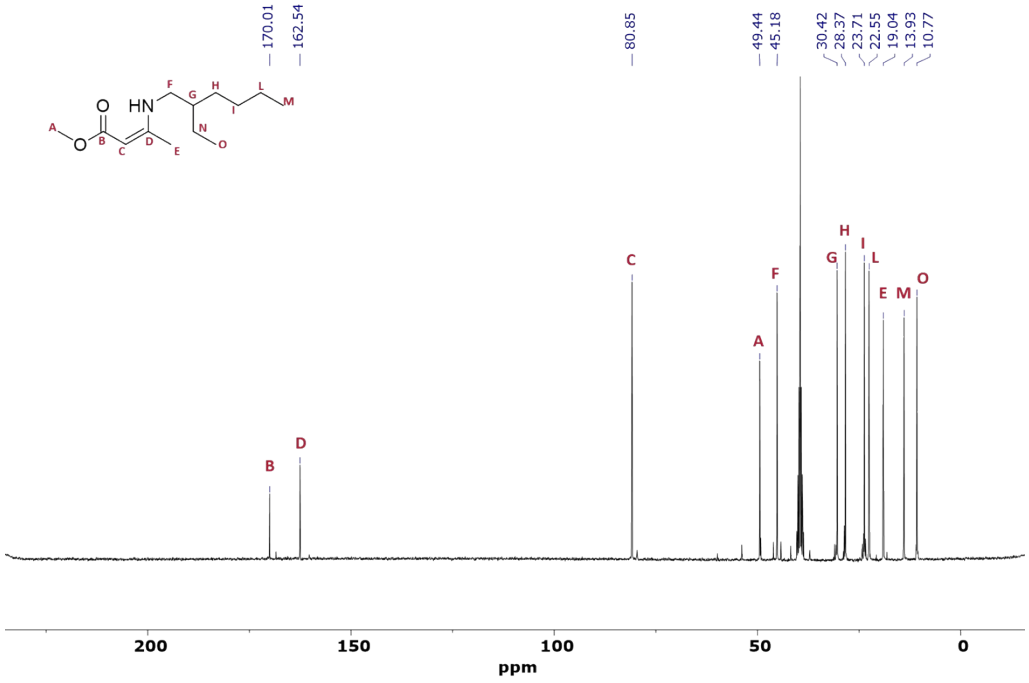


Figure S14: ^{13}C-NMR (400 MHz, dmso-d^{6}) spectrum of VU_2EHA.

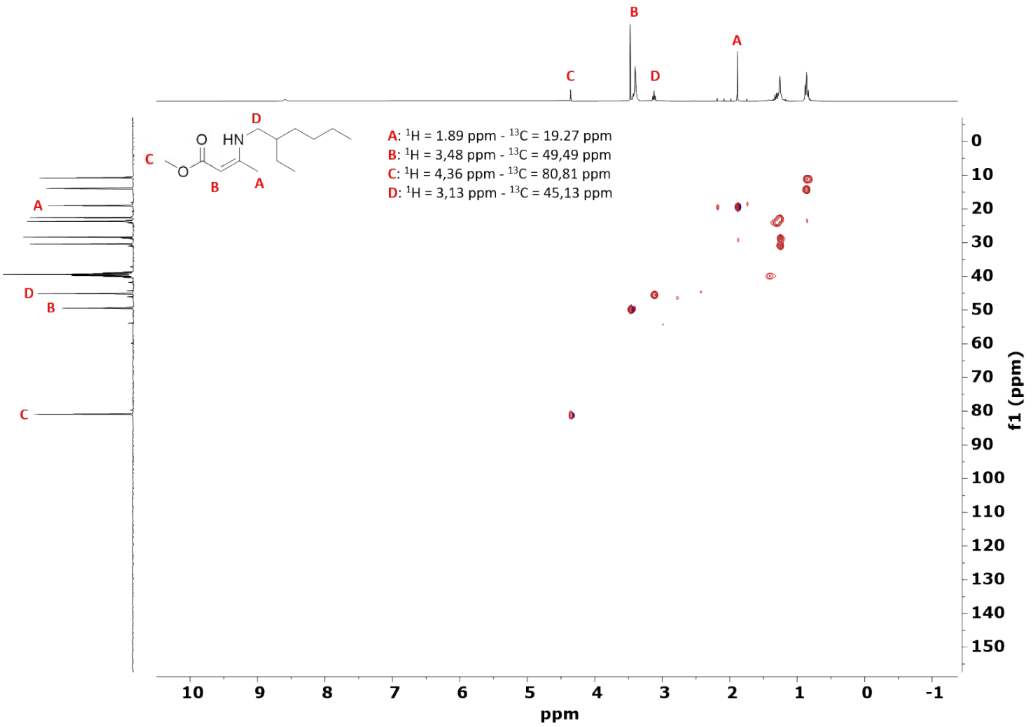


Figure S15: HSQC NMR (400 MHz, dmso-d^6) spectrum of VU_2EHA.

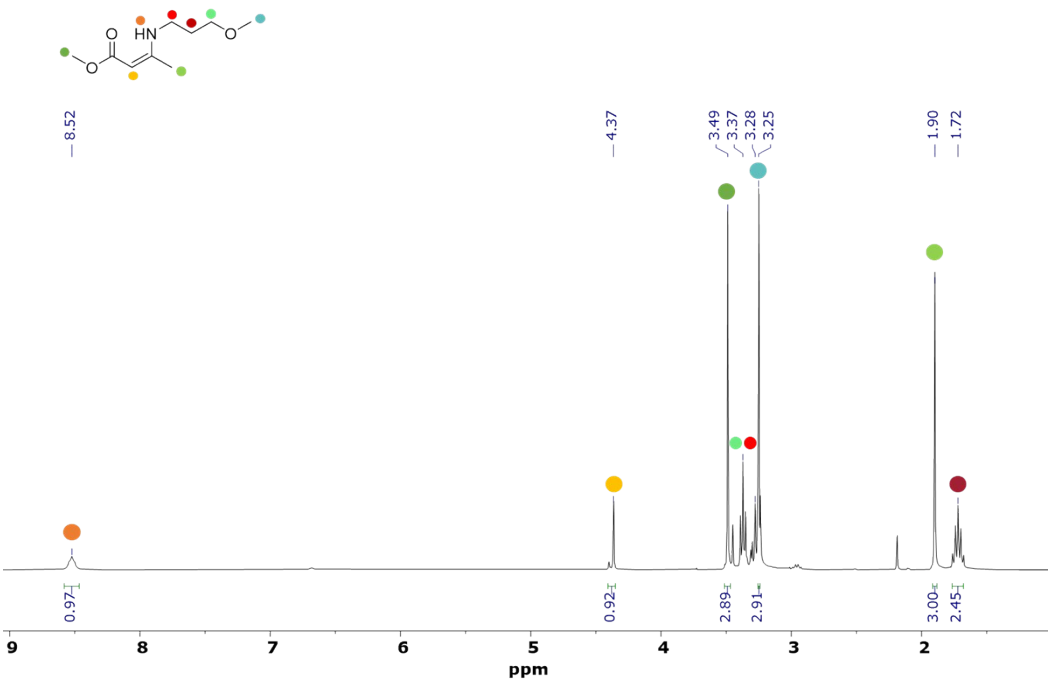


Figure S16 : ^{1}H-NMR (400 MHz, dmso-d^6) spectrum of VU_3MET.

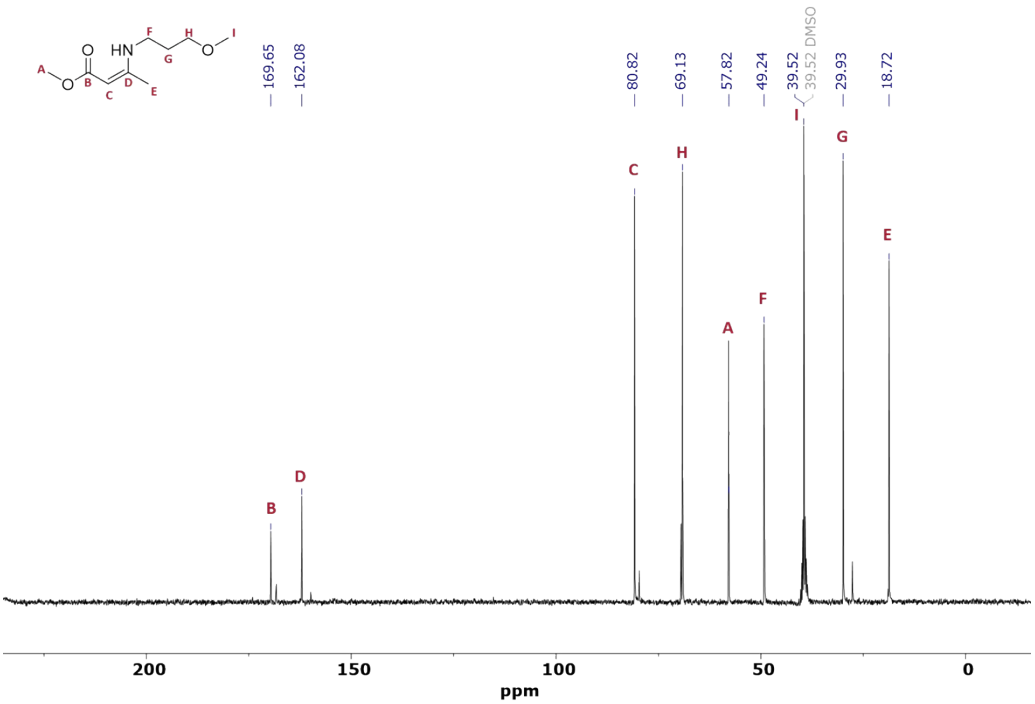


Figure S17: ^{13}C-NMR (400 MHz, dmso-d^6) spectrum of VU_3MET.

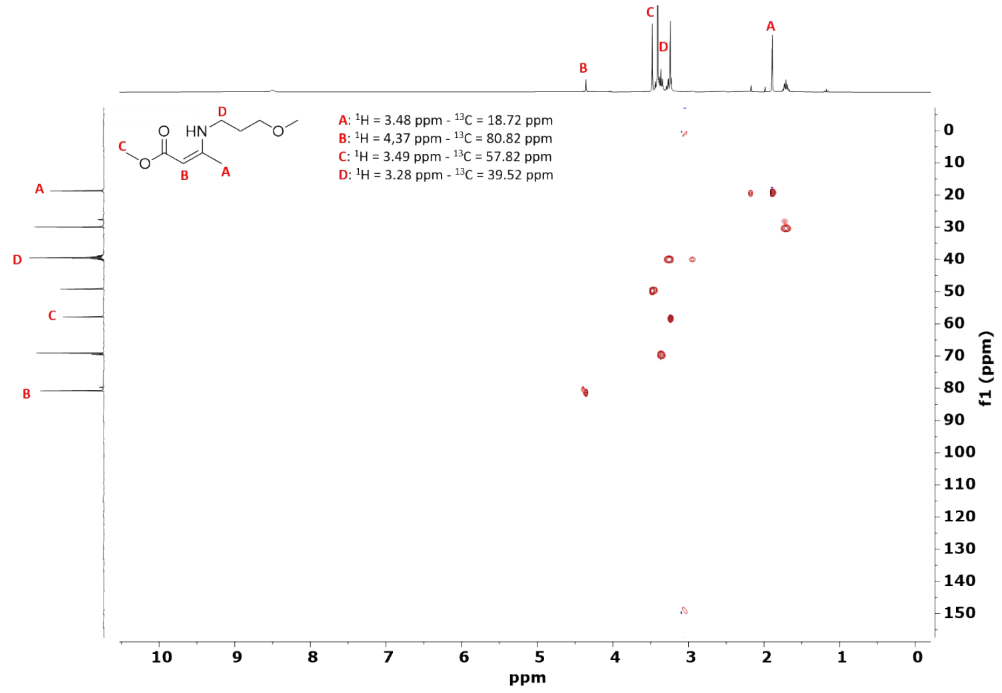


Figure S18: HSQC NMR (400 MHz, dmso-d^6) spectrum of VU_3MET.

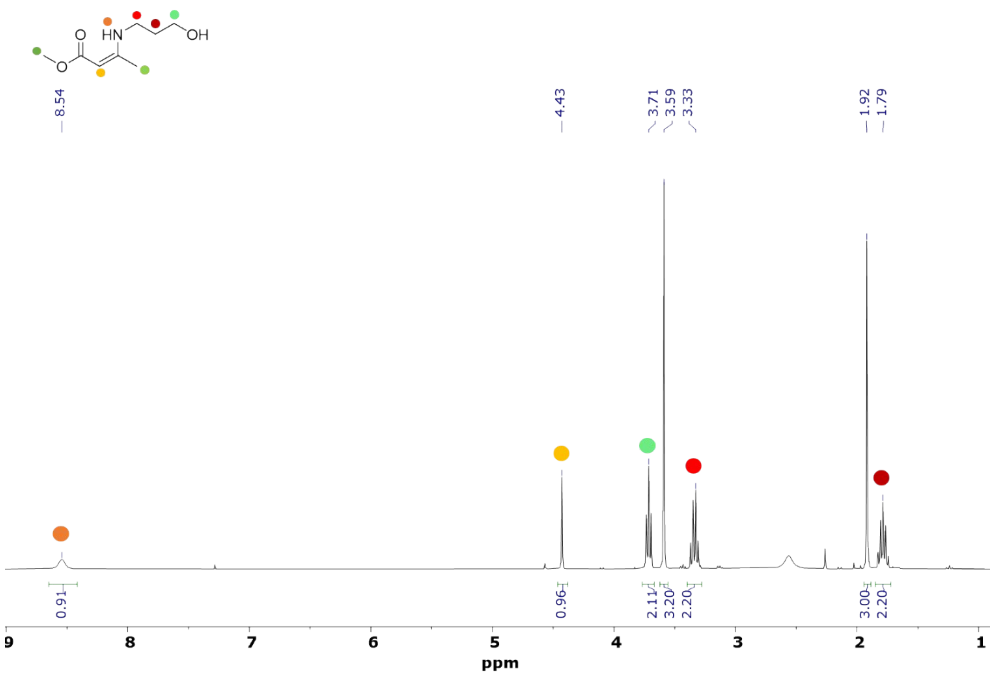


Figure S19: [1]H-NMR (400 MHz, dmso-d[6]) spectrum of VU_3APO.

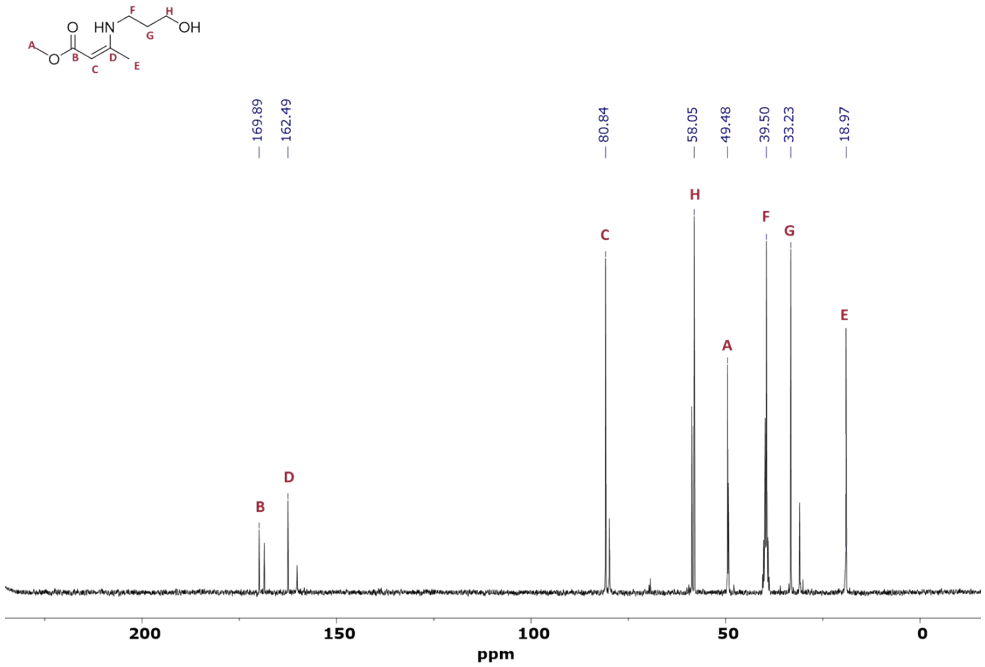


Figure S20: [13]C-NMR (400 MHz, dmso-d[6]) spectrum of VU_3APO.

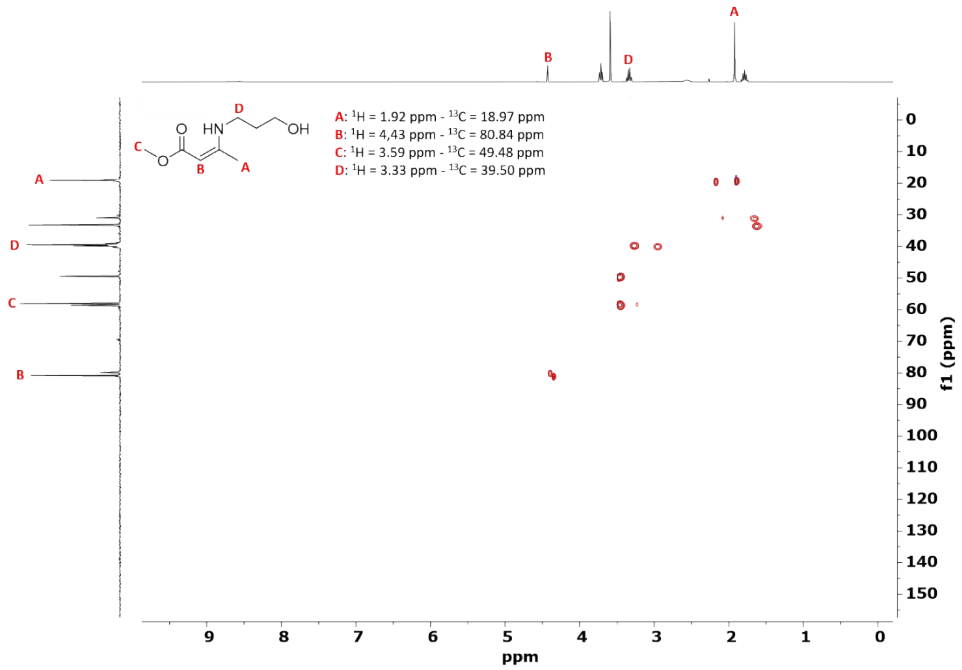


Figure S21: HSQC NMR (400 MHz, dmso-d^{6}) spectrum of VU_3APO.

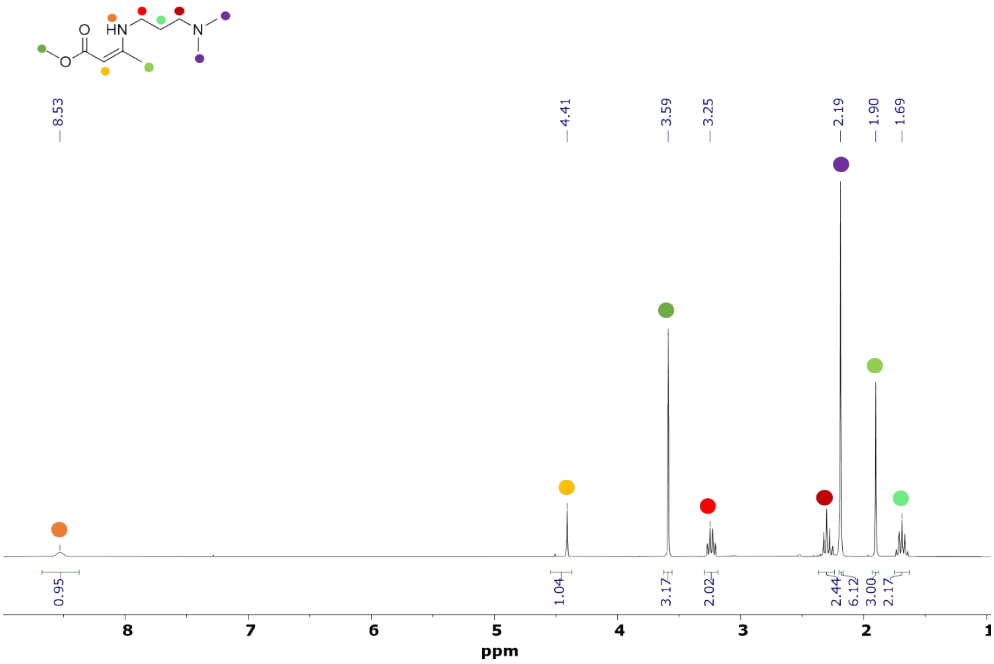


Figure S22: ^{1}H-NMR (400 MHz, dmso-d^{6}) spectrum of VU_N,NDIAM.

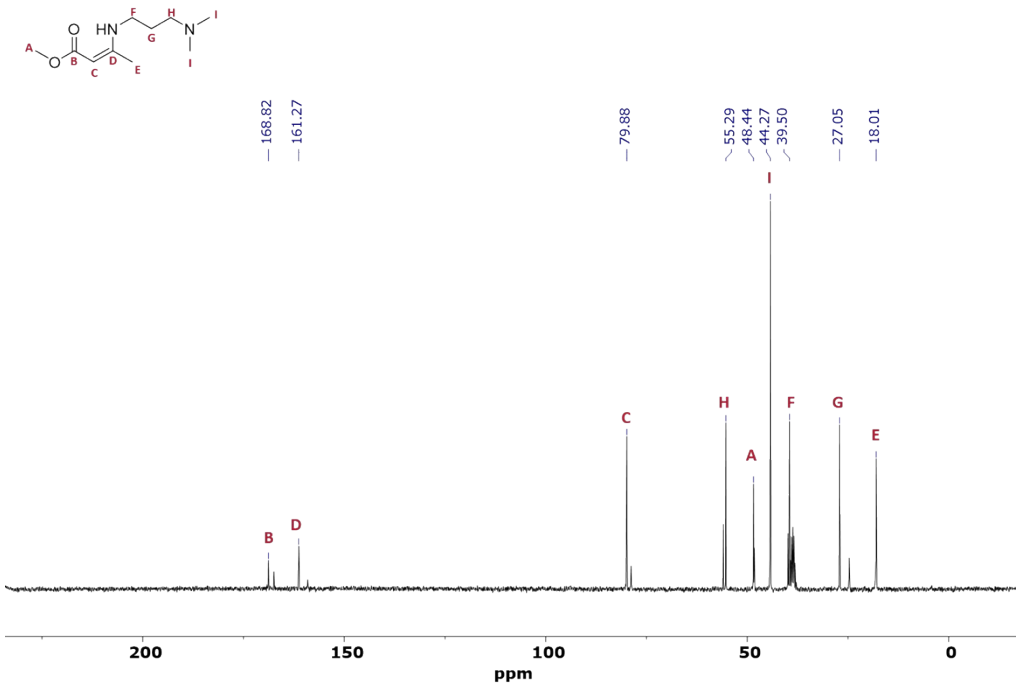


Figure S23: ^{13}C-NMR (400 MHz, dmso-d^6) spectrum of VU_N,NDIAM.

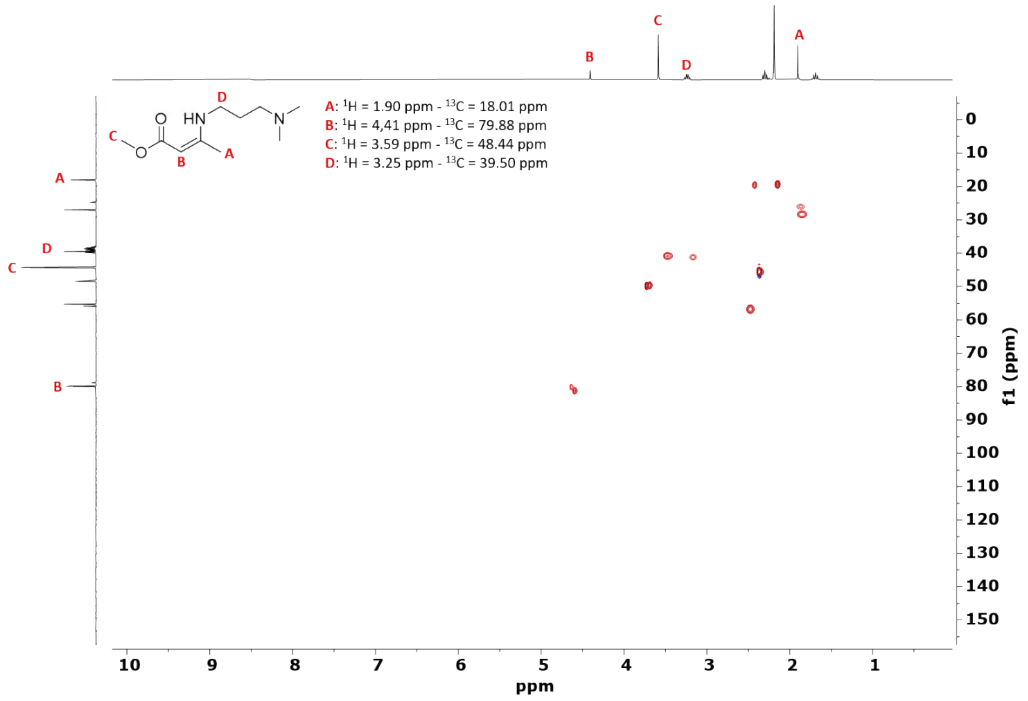


Figure S24: HSQC NMR (400 MHz, dmso-d^6) spectrum of VU_N,NDIAM.

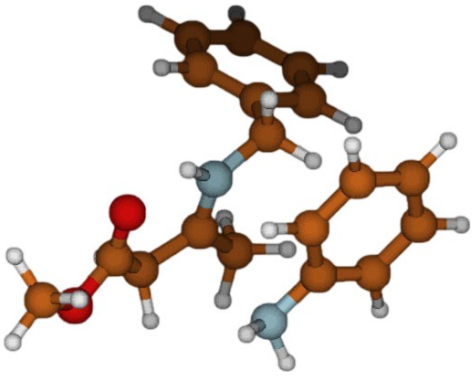


Figure S25: Example of INT3 in cis-conformation. This conformation is stabilized by hydrogen bonding between the NH group and the oxygen of the carbonyl group.

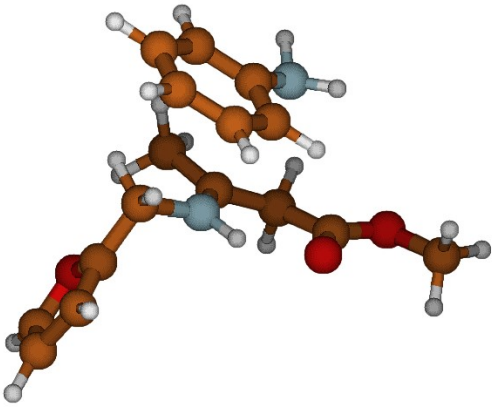


Figure S26: INT3 of the exchange between VU_PhNH2 and $FuNH_2$. The vinylogous urethane structure is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.840 Å). The NH group of the aniline is distant 3.178 Å from the methylene carbon of the vinylogous urethane from which it will later abstract the proton (TS4).

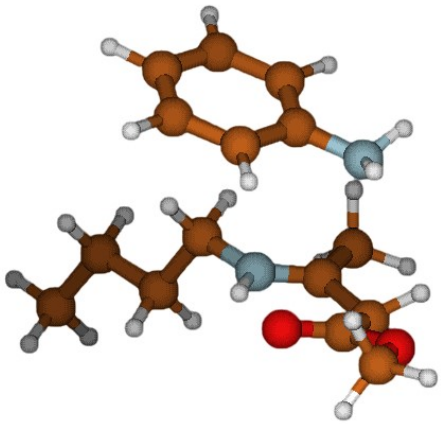


Figure S27: INT3 of the exchange between VU_$PhNH_2$ and $BuNH_2$. The vinylogous urethane structure is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.839 Å). The NH group of the aniline is distant 3.16 Å from the methylene carbon of the vinylogous urethane from which it will later abstract the proton (TS4).

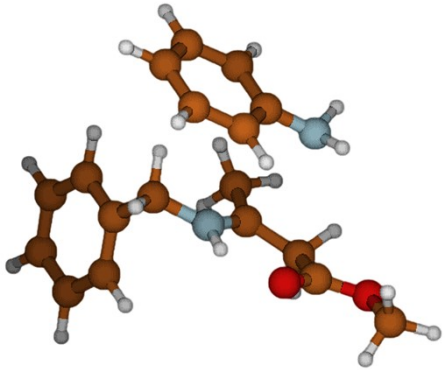


Figure S28: INT3 of the exchange between VU_$PhNH_2$ and $BnNH_2$. The vinylogous urethane structure is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.830 Å). The NH group of the aniline is distant 2.943 Å from the methylene carbon of the vinylogous urethane from which it will later abstract the proton (TS4).

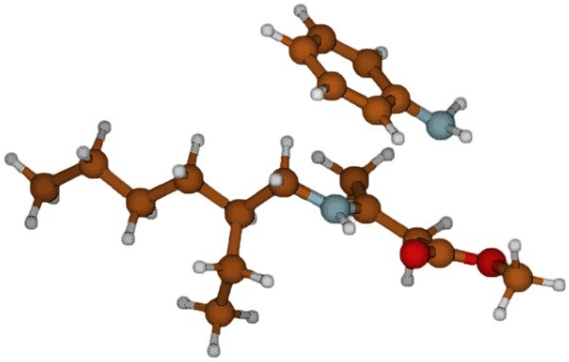


Figure S29: INT3 of the exchange between VU_$PhNH_2$ and 2-EHA. The vinylogous urethane structure is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.843 Å). The NH group of the aniline is distant 3.168 Å from the methylene carbon of the vinylogous urethane from which it will later abstract the proton (TS4).

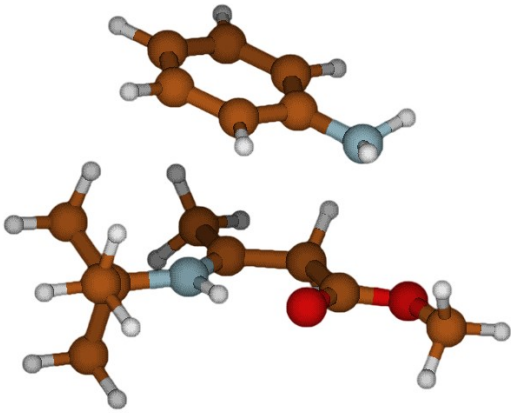


Figure S30: INT3 of the exchange between VU_$PhNH_2$ and $tBuNH_2$. The vinylogous urethane structure is in a cis-conformation stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.770 Å). However, the NH group of the aniline is distant 3.295 Å from the methylene carbon of the vinylogous urethane from which it will later abstract the proton (TS4).

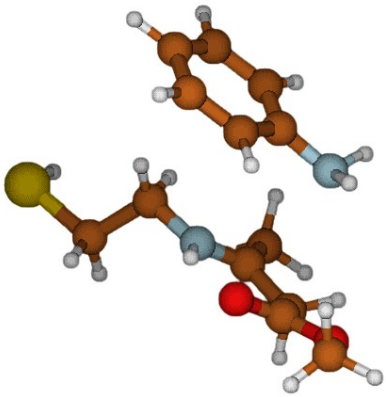


Figure S31: INT3 of the exchange between VU_$PhNH_2$ and Cys. The vinylogous urethane structure (-23 kcal/mol) is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.803 Å). The NH group of the aniline is distant 3.161 Å from the methylene carbon of the vinylogous urethane from which it will later subtract the proton (TS4).

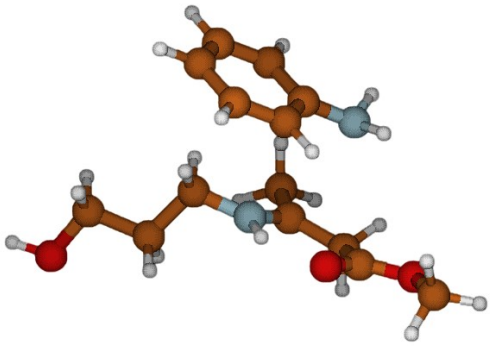


Figure S32: INT3 of the exchange between VU_$PhNH_2$ and 3-APO. The vinylogous urethane structure (-20.3 kcal/mol) is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.835 Å). The NH group of the aniline is distant 3.169 Å from the methylene carbon of the vinylogous urethane from which it will later subtract the proton (TS4).

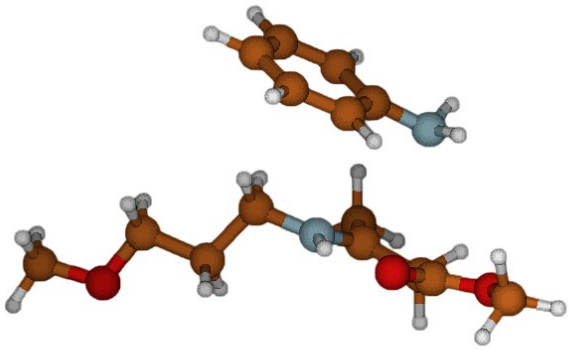


Figure S33: INT3 of the exchange between VU_$PhNH_2$ and 3-MET. The vinylogous urethane structure (-20.11 kcal/mol) is stabilized by the hydrogen bonding between the NH group and the oxygen of the carbonyl group (1.836 Å). The NH group of the aniline is distant 3.168 Å from the methylene carbon of the vinylogous urethane from which it will later subtract the proton (TS4).

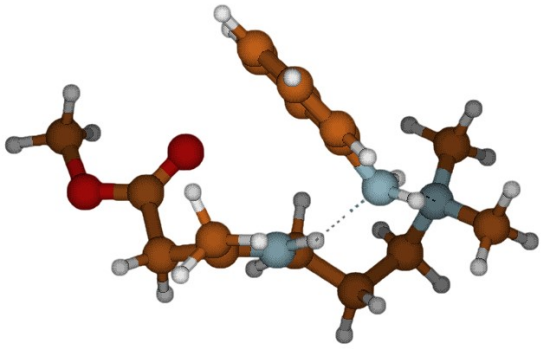


Figure S34: INT3 of the exchange between VU_PhNH$_2$ and N,N-Diam. The vinylogous urethane structure (-19.87 kcal/mol) adopts a twisted conformation where the NH group cannot establish hydrogen bonding with the carbonyl oxygen due to interaction with the amino group of the aniline, which in turn interacts with the dimethyl-substituted nitrogen group present in the aliphatic chain.

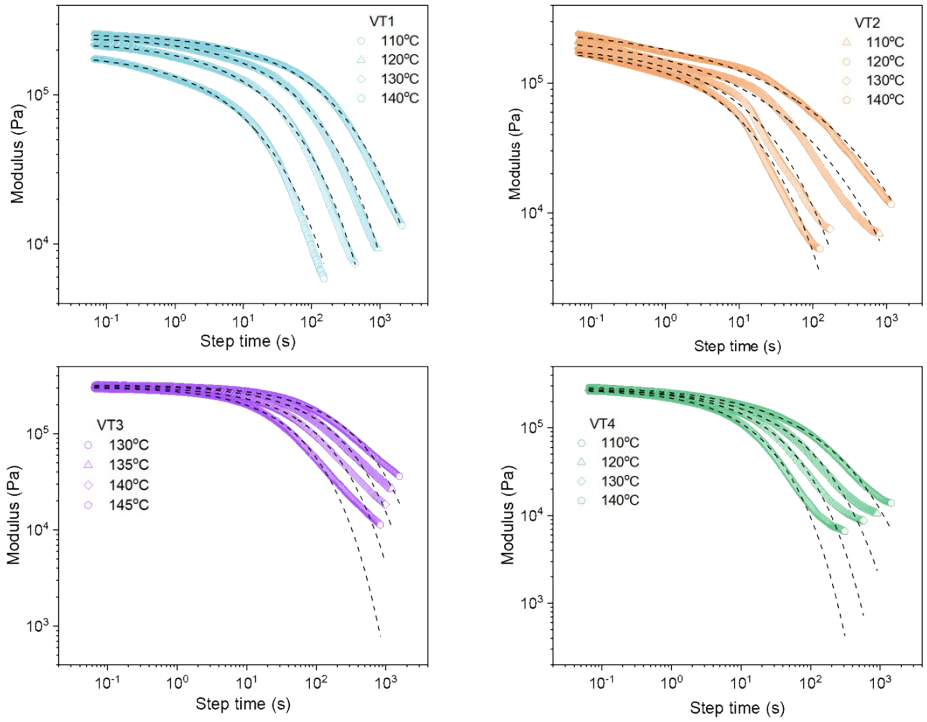


Figure S35: Stress relaxation measurements of network VT1, VT2, VT3, and VT4 carried out at various temperatures. The full lines correspond to fits of the data to a stretched exponential of the form $\sigma(t) = \sigma_0 e^{-\left(\frac{t}{\tau}\right)^{\beta}}$.

(1) Denissen, W.; Rivero, G.; Nicolaÿ, R.; Leibler, L.; Winne, J. M.; Du Prez, F. E. Vinylogous urethane vitrimers *Adv. Funct. Mater.* **2015**, *25*, 2451–2457.