The Stability and Reactivity of Activated Acryloylcarbamates as Reagents for the Synthesis of N-1 Substituted Thymine and Uracil - An NMR and DFT Study

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**The Stability and Reactivity of Activated Acryloylcarbamates
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Keywords:	uracil, thymine, mechanism, NMR, DFT

Figure 1. The planar geometries of E-7b investigated by density functional theory calculations.

Figure 2. The reaction coordinate for the degradation of E-7b.
80x51mm (300 x 300 DPI)

$R_1 = H, CH_3$
 $R_2 = \text{alkyl, cycloalkyl, aryl, hetaryl}$

Scheme 2. The reaction of reagents 3, 6 and 7 with amines and subsequent cyclization providing 1-N-substituted pyrimidines.
71x98mm (600 x 600 DPI)

Scheme 3. The decomposition of 7b via hydrolysis and decarboxylation.
159x43mm (600 x 600 DPI)

Scheme 4. The chemical proof of 3b structure.
153x58mm (600 x 600 DPI)

Scheme 6. The reaction of 7a-d with 2,4,6-tri-tert-butylaniline.
72x196mm (600 x 600 DPI)

The mechanism of the decomposition of acryloylcarbamates yielding highly reactive isocyanates was proposed based on NMR measurements and quantum chemical calculations. Their reactivity with 2,4,6-tri-*tert*-butylaniline showed their usefulness in synthesis of *N*-1 substituted thymines and uracils.

The Stability and Reactivity of Activated Acryloylcarbamates as Reagents for the Synthesis of *N*-1 Substituted Thymine and Uracil – A NMR and DFT Study

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126x167mm (300 x 300 DPI)

163x135mm (300 x 300 DPI)

The Stability and Reactivity of Activated Acryloylcarbamates as Reagents for the Synthesis of *N*-1 Substituted Thymine and Uracil – An NMR and DFT Study

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Keywords: uracil / thymine / nucleosidation / mechanism / NMR / DFT

Abstract:

The mechanism of the decomposition of acryloylcarbamates **7a-b** yielding highly reactive isocyanates **3a-b** was proposed based on NMR measurements and quantum chemical calculations. A good agreement between the experimental kinetic data and DFT calculations allowed us to demonstrate that the stability of **7a-d** depends on the presence of methyl in the acryloyl moiety and the position of nitro group in the nitrophenolic part of the molecule. Furthermore, the reactivity of **7a-d** with weakly nucleophilic and sterically hindered 2,4,6-tri-*tert*-butylaniline was explored by ¹H NMR demonstrating the usefulness of reagents **7a-d** offering access to a variety of 1-*N*-substituted uracils and thymines with potentially interesting biological properties.

Introduction

Many biologically active compounds belong to the class of nucleosides and nucleotides analogues, which play an important role in anticancer therapy¹⁻² or act as antiviral compounds.³ Specific examples also involve carbocyclic nucleosides⁴⁻⁵ (Carbovir®) and acyclic phosphonate nucleotides⁶ (Viread, Cidofovir, Tenofovir, Hepsera), which represent biologically important compounds in which the nucleobase is not connected *via* a glycosidic bond.

From a synthetic point of view, a crucial step in their preparation is the attachment of the nucleobase – the nucleosidation reaction. The most common synthetic routes to purine

nucleoside analogues are represented by direct alkylation of the appropriate nucleobases (adenine, 6-chloropurine or 2-amino-6-chloropurine) with the halo, tosyloxy or mesyloxy derivatives in dipolar aprotic solvents (DMF, DMSO) using cesium carbonate as a base.⁷⁻⁹ Alternatively, Mitsunobu reaction of 6-chloropurine or 2-amino-6-chloropurine with appropriate hydroxyderivative can be used.^{8,10-11} Recently, *N*⁶-bis-Boc-protected adenine was successfully used as a substrate for the Mitsunobu reaction during the synthesis of neplanocin A.¹² However, all of these methods for the introduction of pyrimidine nucleobases (uracil, thymine, and cytosine) suffer from both low regioselectivity and low yield of the 1-*N*-substituted product. The direct alkylation of nucleobases is usually accompanied by a competing elimination reaction, which further decreases the yield of the desired product.⁸⁻⁹ Some improvement (both in regioselectivity and overall yield) can be obtained through the use of 2,4-dimethoxypyrimidine or 2,4-dimethoxy-6-methylpyrimidine for the alkylation instead of uracil or thymine, respectively.¹³⁻¹⁵ As an alternative approach to the pyrimidine nucleoside analogues (e.g. carbocyclic nucleosides), a synthesis of 1-*N*-substituted nucleobases starting from a primary amine and isocyanates **3a-b** or carbamates **6a-b** were described fifty years ago by Shaw and Warrenner.¹⁶ The key isocyanates **3a-b**, accessible through two independent routes¹⁷⁻¹⁸ (Scheme 1), were used as intermediates for the synthesis of carbamates **6a-b** described by Hřebabeký et al.¹⁹

Scheme 1. The reagents for the preparation of 1-*N*-substituted pyrimidine nucleobases.

Isocyanates **3a-b** are an unusually moisture-sensitive species and also very reactive compounds, capable of forming carbamates with free hydroxy groups.²⁰ Therefore, the reaction is usually carried out either with the appropriately protected substrate or without protection at low temperature (<-20 °C). This property seems to be the main factor responsible for the varying yield of the reported uracil and thymine derivatives (usually ~20–80 %, in most cases <60 %) found in the literature.²¹⁻³² The formation of uracil and thymine rings is a two-stage reaction consisting of the aminolysis of carbamates **6a-b** or the addition of amine to isocyanates **3a-b** followed by a cyclization of the acryloylureas **9** formed (Scheme 2).³³

Scheme 2. The reaction of reagents **3**, **6** and **7** with amines and subsequent cyclization providing 1-*N*-substituted pyrimidines.

To date, there has not been any general, high-yield method available for the attachment of uracil and thymine moieties to sterically hindered secondary, tertiary, or even aromatic carbon atoms.

It was the extreme reactivity and moisture sensitivity of isocyanates **3** on the one hand and the low yields of **9** obtained using carbamates **6** on the other that prompted us to develop more advantageous reagents **7**, which proved to be reactive enough with a variety of amines. Moreover, they can be stored for longer time (several months in refrigerator), which enabled us to use them in modular syntheses of uracils and thymines **10**.³⁴ The synthesis of the reagents **7a–d** followed the procedure described for **6**,¹⁹ in whose last step of the ‘one-pot’ synthesis, a 2-nitrophenol solution in dioxane was added instead of ethanol.

The reagents **7a–d** were tested in reactions with a wide variety of amines (including those bonded to secondary, tertiary, and aromatic systems), giving consistently high yields of corresponding 1,3-disubstituted urea derivatives. The desired uracil and thymine derivatives were obtained by the cyclization of the urea intermediates using Dowex 50 in H⁺ form, providing again very high yields.³⁴

In this work, we wish to address an unprecedented decomposition of the reagent **7b** in CDCl₃ solution observed in the ¹H NMR measurements, to analyze and quantitatively characterize the reaction mechanism of the decomposition reaction. To this end, we conducted a series of NMR experiments to yield reliable kinetic data and a series of DFT calculations to provide us with the mechanistic view of the studied reaction. In order to understand the reaction mechanism in detail, we have compared the experimental data with other reagents **7a**, **7c** and **7d**. We have also investigated reaction of **7a–d** with low nucleophilic and sterically hindered 2,4,6-tri-*tert*-butylaniline to ensure that decomposition of **7a–b** does not limit their synthetic usage in preparation of *N*-1 substituted thymines and uracils. These findings represent a useful and successful conjunction of theoretical and experimental efforts extending our understanding of the organic reactions pertinent to this class of compounds.

Results and Discussion

Kinetics of decomposition studied by NMR

Reagents **7a–d** were prepared according Scheme 1 and fully characterized by ¹H and ¹³C NMR, elemental analysis, IR and MS. In the course of the NMR characterization of **7b**, we found that the reagent decomposes, yielding a complex mixture. The ¹H NMR spectrum of **7b**

recorded in commercial grade CDCl_3 (see Supporting Info) showed a mixture of at least four compounds identified as 3-ethoxy-2-methylacryloylcarbamic acid (as the product of reagent hydrolysis), 3-ethoxy-2-methylacryloylamide (as the product of the decarboxylation of the former compound), 2-nitrophenol and reagent **7b** (Scheme 3).

Scheme 3. The decomposition of **7b** *via* hydrolysis and decarboxylation.

To rule out the effect of water, which might be present in regular CDCl_3 , the ^1H NMR spectra were recorded in dried CDCl_3 and a sealed NMR tube (see Experimental). The experiment has again shown the decomposition of compound **7b**, and the final products of decomposition were identified as acryloylisocyanate **3b** and 2-nitrophenol. Reagent **7b** was characterised by NMR only when a high concentration of sample and a short measurement time were applied.

To ascertain that acryloylisocyanate **3b** is the decomposition product, we allowed the decomposed mixture to react with dry methanol, yielding methyl ester **12**, i.e. the same product as that formed through the reaction of **7b** with methanol in the presence of Et_3N (Scheme 4). In addition, isocyanate **3b** was identified by IR measured in dry CHCl_3 (the characteristic band being at 2244 cm^{-1} for asymmetric stretching vibrations of the $-\text{NCO}$ group) and by ^{13}C NMR (with the characteristic chemical shift of $-\text{NCO}$ carbon at 130.47 ppm).

Scheme 4. The chemical proof of **3b** structure.

The rate of decomposition was estimated based on the ^1H NMR kinetic measurement in dry CDCl_3 and sealed NMR tube at $25\text{ }^\circ\text{C}$. The concentrations of starting compounds and decomposition product(s) were obtained by integration of several corresponding signals with similar relaxation times. The rate constant for the irreversible first order kinetic model was obtained from plots of the logarithm of the starting compound concentrations versus time, while rate constant for the reversible first order kinetic model was obtained from plots of the logarithm of the starting compound concentrations minus equilibrium concentration versus time and from equilibrium constant. Experimental data for decomposition of **7b** fitted irreversible reaction with first order kinetics (Table 1 and supporting material) with half life ($t_{1/2}$) of about 18 minutes. The kinetics measurements were also performed for the other

reagents, **7a**, **7c** and **7d**, and the results have been summarized in Table 1. The decomposition of **7a** was reversible reaction with first order kinetics (Table 1 and supporting material), while compounds **7c** and **7d** were stable and did not decompose at all.

As arises from Table 1, the kinetic measurements demonstrate a surprisingly strong dependence on the reagents and their structure. Reagents **7c** and **7d** (possessing a nitro group in the *para* position) do not undergo any degradation. On the other hand, the derivatives with the *ortho*-nitro group in nitrophenol moiety decompose readily, with the decomposition of the **7b**-bearing methyl group in the acryloyl part of the molecule being approximately fifty times faster than the decomposition of the **7a**-lacking methyl substituent. The different stability of the reaction products reflected in the molecular structure was further explored by DFT calculations.

Reaction mechanism of decomposition. Theoretical calculations.

We first optimised all sixteen planar geometries for each of **7a–d**, viz. all the possible arrangements of four double or partial double bonds in the system (64 molecular geometries in total) at the DFT(PBE)/def2-SVP level with the single-point energy calculated at the DFT(B3LYP)/def2-TZVP level. The solvation effects and corrections to the ZPE energy, enthalpy and entropy (using the ideal gas approximation) were included as well (for details, see Experimental). The results of this extensive conformational search are summarised in Tables S1–S5 (see Supporting Info). As can be seen in Tables S1–S4, the calculations predict (in all cases) the most stable isomers to possess *trans*-configuration on the -C=C- double bond. This fact has been corroborated experimentally by a missing NOE interaction between the Me group and the proton on the double bond for **7a–b** or by a missing NOE between the protons of the double bond for **7c–d**. At the same time we observe NOE between protons of CH₂ group from EtO and H or CH₃ on double bond in alpha position to CO.

With regard to the proposed reaction mechanism, we have also investigated the possible isomers with the proton on either of the oxygens adjacent to the central -NH- group (these calculations were carried out only for the most stable isomers). The results are also listed in Tables S1–S4 (including various terms in overall Gibbs energies), and all twenty-four structures of **7b** (assuming an *E* configuration on the -C=C- double bond) have been schematically depicted in Fig. 1.

Figure 1. The planar geometries of *E*-**7b** investigated by density functional theory calculations.

The calculations have shown that the 2NH-ZZZ conformer is the most stable structure for the *keto*-tautomer of **7b** whereas 3OH-ZZE is the lowest energy *enol*-form of the same compound. It can be noted that 3OH-ZZE geometry is nicely preorganised to form a six-membered transition state with bifurcated hydrogen bonding.

However, a rather surprising finding is the relatively small difference in energies between all the studied isomers. Considering the planar models depicted in Fig. 1, some of the structures would have been expected to have substantial intramolecular crowding. Even for such structures (e.g. 2NH-ZEE, 2NH-EEE) the energy or free energy differences amount to only ~15-25 kJ.mol⁻¹. This demonstrates a relatively high level of flexibility in the studied molecules (the systems avoid crowding by adopting a helical form). Thus, we had to consider several reaction pathways for the elimination reaction. The lowest saddle points and their energies are summarised in Table 2 for all studied compounds (**7a–7d**) and for the proposed reaction mechanism of degradation shown in Scheme 5. It can be mentioned that all saddle points are characterized by a single imaginary frequency corresponding to the reactive coordinate and are therefore a true transition states for the studied reactions. By small changes of the geometry in the direction of reactant and product we ascertained that it connects the desired reactant and products structures (IRC-like calculation). A more complete listing of the calculated values of activation barriers can be found in Tables S1–S4.

Scheme 5. The degradation of **7b** – a proposed mechanism.

Furthermore, the reaction coordinate with the structures of all the key points on the potential energy surface is depicted in Figure 2.

Figure 2. The reaction coordinate for the degradation of *E*-**7b**.

As mentioned above, the transition state is characterised by the six-membered ring arrangement and is structurally close to the *enol*-form with activation barriers of 72–88 kJ.mol⁻¹ (Table 2). We have also investigated an alternative pathway starting from the more stable *keto*-form and involving the direct hydrogen transfer from the nitrogen atom to the oxygen atom of the nitrophenol ring. The activation barrier involving a four-membered transition state was considerably higher (~160–180 kJ.mol⁻¹, see Tables S1, S3, S4) for the 2NH-EEZ isomer (which has the most favourable arrangement of the atoms and highest thermodynamic stability of the reactants). This clearly favours the pathways involving the six-membered transition states described above.

As arises from Table 2, the presence of the *ortho*-nitro group plays an important role in the bifurcated hydrogen bond and lowers the free enthalpy of degradation ΔG_{calc} . On the other hand, the methyl group on the -C=C- double bond lowers the free energy of activation, $\Delta G_{\text{calc}}^{\ddagger}$, likely due to the effect of hyperconjugation. The computational results are in good agreement with the experimentally calculated $\Delta G_{\text{exp}}^{\ddagger}$ computed from the rate constants using Eyring equation. Since the accurate *ab initio* determination of the *absolute rate constant* is beyond the scope of this work (for a thorough discussion on the subject, we refer the reader to Ref. 35), we mostly want to highlight the excellent agreement in the relative difference between the two reactions (**7a**, **7b**) for which the comparison is available. $\Delta \Delta G_{\text{exp}}^{\ddagger} = 9.7$ kJ.mol⁻¹, whereas $\Delta \Delta G_{\text{calc}}^{\ddagger} = 11.9$ kJ.mol⁻¹.

NMR characterisation of the reactivity of **7a–d** towards amines

In our previous work,³⁴ we showed that reagents **7a,b** react with a variety of amines, including acyclic, cyclic, and aromatic, and also amino acids. All of the reactions were completed within one hour of stirring at room temperature. Nevertheless, the reaction kinetics were not addressed in detail. Herein, the reactivity of **7a–d** with low nucleophilic and sterically hindered 2,4,6-tri-*tert*-butylaniline is presented (Scheme 6).

Scheme 6. The reaction of **7a–d** with 2,4,6-tri-*tert*-butylaniline.

The kinetic measurements were performed in dry CDCl₃ at 25 °C and monitored by ¹H NMR. The concentrations of starting compounds and products were obtained by integration of

several corresponding signals with similar relaxation times (for example CH₃ on double bond in **7b** and **11b**). The rate constants were obtained from plots of the logarithm of the starting compound concentrations versus time. Obtained data fitted first order kinetics and the results of the measurements are summarized in Table 3. The kinetic data show relatively high difference in reaction rates that might be explained by observed decomposition described above. Similar reaction rates for **7c-d** confirm the finding that these compounds do not decompose and reaction with amine can be viewed as aminolysis of 4-nitrophenyl ester. On the other hand, very fast reaction rate for **7b** corresponds with decomposition of the compound and can be therefore assumed that 2,4,6-tri-*tert*-butylaniline reacts with isocyanate **3b** formed in course of the decomposition **7b**. The only anomaly is reactivity of 2,4,6-tri-*tert*-butylaniline with **7a**. In this case the amine probably reacts either with acryloylcarbamate **7a** or with its decomposition product **3b** and overall reaction rate is indeed anomalous. The reaction was complete for all the studied reagents, providing substituted acryloylureas as products. The results of the kinetics show that novel reagents **7a-d** are capable of reaction even with sterically hindered aromatic amines, which offers access to a variety of 1-*N*-substituted uracils and thymines with potentially interesting biological properties.

Conclusions

It has been shown that the studied reagents **7a-d** are highly reactive even with low-nucleophilic and sterically hindered amines and can be successfully applied for a modular synthesis of various 1-*N*-substituted uracils and thymines, which is difficult to achieve with other synthetic methods. The stability of reagents **7a-d** in dry CDCl₃ was investigated by experimental and theoretical methods. It has been proved that the decomposition of the studied molecules is strongly affected by the presence of the Me-group on the -C=C- double bond and the position of the nitro group on the phenol ring. While the former is assumed to lower the activation barrier of the reaction probably due to hyperconjugation, the latter plays a role in hydrogen bonding and influences the thermodynamics of the reaction. The experimental NMR observations are in good agreement with the results predicted by the DFT calculations, which allowed us to postulate a plausible reaction mechanism, presumably extending our understanding of the reactivity and stability of this class of compounds. It should be noted here that all the reagents are stable enough in the solid state to be stored for a long time. Moreover, the decomposition of the 2-nitrophenyl derivatives **7a** and **7b** yields an

isocyanate product that could react in the same manner as the parent reagents. These compounds could be seen as an 'instant form' of the previously described isocyanates **3a-b**.

Experimental Section

NMR Experiments: NMR spectra were acquired on a Bruker Avance 500 spectrometer (500.0 MHz for ^1H and 125.7 MHz for ^{13}C) in dry CDCl_3 . CDCl_3 was dried prior to use by anhydrous K_2CO_3 and distilled. The measurements were performed in an oven-dried NMR tube, which was sealed after sample preparation. The concentration of the samples was 38 mM and 40mM for the degradation kinetics and kinetics of reaction with amines, respectively. All of the kinetic measurements were performed at 25 °C. Temperature calibration was done using the standard method with an MeOH sample. ^1H and ^{13}C resonances were assigned based on PFG H,C-HSQC and H,C-HMBC experiments (for numbering see Supportin Info). ^1H and ^{13}C NMR of compounds **7a-d** have been already reported.³⁴

Computational Details: All the density functional theory (DFT) calculations reported in the study were carried out using the Turbomole 6.0 program.³⁶ The Perdew-Burke-Ernzerhof (PBE)³⁷ and hybrid three-parameter Becke's³⁸ (B3LYP) functionals were used throughout. The calculations were expedited by expanding the Coulomb integrals in an auxiliary basis set, the resolution-of-identity (RI-J) approximation.³⁹⁻⁴⁰ All the geometry optimisations were conducted using the def2-SVP basis set,⁴¹ whereas the single-point energies were recomputed in the def2-TZVP (triple-zeta valence with two polarisation functions on each atom).⁴² To account for the solvation effects, the conductor-like screening model (COSMO) method⁴¹⁻⁴² was used with the dielectric constant corresponding to chloroform ($\epsilon_r = 4.9$). In order to account for dispersion, we used the DFT+D method (i.e. the DFT method with the empirical dispersion terms) available in Turbomole 6.0.⁴³ The Gibbs free energy was then calculated as the sum of these contributions:

$$G = E_{\text{el}} + G_{\text{solv}} + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}}),$$

where E_{el} is the *in vacuo* energy of the system (at the B3LYP/def2-TZVP level and the geometry optimised at the RI-PBE/def2-SVP level), G_{solv} is the solvation free energy (at the RI-PBE/def2-SVP level), E_{ZPE} is the zero-point energy, and $-RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$ accounts for the entropic terms and the thermal correction to the enthalpy obtained from a frequency

calculation using the same method and software as for the geometry optimisation at the RI-PBE/def2-SV(P) level, 298 K, and 1 atm using the ideal-gas approximation.⁴⁴

(*E*)-3-Ethoxy-2-methylacryloyl isocyanate (3b)

¹H NMR (CDCl₃, 500.0 MHz): 1.36 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.82 d, 3 H, $J(\text{CH}_3, \text{CH}) = 1.2$ (CH₃); 4.13 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.53 q, 1 H, $J(\text{CH}, \text{CH}_3) = 1.2$ (CH=). ¹³C NMR (CDCl₃, 125.7 MHz): 8.79 (CH₃); 15.34 (CH₃CH₂O); 70.98 (OCH₂CH₃); 110.19 (C=); 130.47 (NCO); 162.82 (CH=); 165.52 (CO).

1-(2,4,6-Tri-*tert*-butylphenyl)-3-((*E*)-3-ethoxyacryloyl)urea (11a)

¹H NMR (CDCl₃, 500.0 MHz): 1.30 s, 9 H ((CH₃)₃C-4'); 1.32 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.40 s, 18 H ((CH₃)₃C-2',6'); 3.90 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 5.26 d, 1 H, $J(5,6) = 12.2$ (H-5); 7.40 s, 2 H, (H-3',5'); 7.72 d, 1 H, $J(6,5) = 12.2$ (H-6); 8.54 bs, 1 H (H-3); 10.29 bs, 1 H (H-1). ¹³C NMR (CDCl₃, 125.7 MHz): 14.48 (CH₃CH₂O); 31.38 ((CH₃)₃C-4'); 31.86 ((CH₃)₃C-2',6'); 34.97 ((CH₃)₃C-4'); 36.19 ((CH₃)₃C-2',6'); 67.87 (OCH₂CH₃); 97.48 (C-5); 122.93 (C-3',5'); 129.26 (C-1'); 148.01 (C-2',6'); 149.55 (C-4'); 154.77 (C-2); 163.84 (C-6); 168.26 (C-4).

HR-MS for C₂₄H₃₉N₂O₃ (M+H)⁺ calcd 403.2955, found 403.2955.

1-(2,4,6-Tri-*tert*-butylphenyl)-3-((*E*)-3-ethoxy-2-methylacryloyl)urea (11b)

¹H NMR (CDCl₃, 500.0 MHz): 1.31 s, 9 H ((CH₃)₃C-4'); 1.33 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.42 s, 18 H ((CH₃)₃C-2',6'); 1.84 d, 3 H, $J(\text{CH}_3, 6) = 1.2$ (5-CH₃); 4.04 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.43 s, 2 H, (H-3',5'); 7.58 q, 1 H, $J(6, \text{CH}_3) = 1.2$ (H-6); 7.95 bs, 1 H (H-3); 10.45 bs, 1 H (H-1). ¹³C NMR (CDCl₃, 125.7 MHz): 8.83 (5-CH₃); 15.44 (CH₃CH₂O); 31.37 ((CH₃)₃C-4'); 31.87 ((CH₃)₃C-2',6'); 34.98 ((CH₃)₃C-4'); 36.20 ((CH₃)₃C-2',6'); 70.54 (OCH₂CH₃); 105.68 (C-5); 123.04 (C-3',5'); 129.30 (C-1'); 147.97 (C-2',6'); 149.53 (C-4'); 154.33 (C-2); 158.71 (C-6); 169.64 (C-4).

HR-MS for C₂₅H₄₁N₂O₃ (M+H)⁺ calcd 417.3112, found 417.3111.

Methyl (*E*)-3-ethoxy-2-methylacryloylcarbamate (12)

¹H NMR (CDCl₃, 500.0 MHz): 1.33 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.83 d, 3 H, $J(\text{CH}_3, 6) = 1.2$ (5-CH₃); 3.79 s, 3 H (CH₃O); 4.08 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.42 q, 1 H, $J(6, \text{CH}_3) = 1.2$ (H-6); 7.79 bs, 1 H (H-3). ¹³C NMR (CDCl₃, 125.7 MHz): 9.07 (5-

CH₃); 15.26 (CH₃CH₂O); 52.72 (CH₃O); 70.12 (OCH₂CH₃); 107.09 (C-5); 151.93 (C-2); 157.59 (C-6); 165.97 (C-4).

HR-MS for C₈H₁₃NO₄Na (M+H+Na)⁺ calcd 210.0742, found 210.0741.

Supporting Information (see footnote on the first page of this article): Kinetics measurements and computational data including .

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Table 1. The kinetics of **7a–d** degradation monitored by ¹H NMR.
[a] $k_+ = 1.83\ k_-$

Degradation	Reaction	Kinetics	$k\ (\text{hr}^{-1})$	$t_{1/2}\ (\text{hr})$
7a	reversible	first-order	$3.00 \times 10^{-2[a]}$	23.1
7b	irreversible	first-order	2.32	0.30
7c	no degradation observed			
7d	no degradation observed			

Table 2. The theoretical calculations of reaction free energies and activation barriers carried out using the B3LYP/def2-TZVP//RI-PBE/def2-SVP method. The solvation effects were included through COSMO calculations and the energies corrected for zero-point energies, thermal corrections to enthalpy and entropic terms (using ideal gas approximation) to obtain free energy estimates. The experimental data are shown in the right part of the table ($\Delta G^\ddagger_{\text{exp}}$ were calculated using Eyring equation: $\Delta G^\ddagger = RT[23.76 - \ln(k/T)]$).

Degradation	ΔG_{calc} (kJ.mol ⁻¹)	$\Delta G^\ddagger_{\text{calc}}$ (kJ.mol ⁻¹)	k_{exp} (s ⁻¹)	$\Delta G^\ddagger_{\text{exp}}$ (kJ.mol ⁻¹)
7a	-24.6	84.1	8.33×10^{-6}	102.0
7b	-30.2	72.0	6.44×10^{-4}	91.2
7c	-3.9	88.4	-	-
7d	-15.1	79.1	-	-

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Table 3. The kinetics of the reaction of the reagents **7a–d** with 2,4,6-tri-*tert*-butylaniline in dry CDCl₃ at 25 °C.

Reagent	<i>k</i> (hr ⁻¹)	<i>t</i> _{1/2} (hr)
7a	2.7 × 10 ⁻²	25.7
7b	1.2	0.6
7c	7.4 × 10 ⁻²	9.4
7d	2.7 × 10 ⁻¹	2.6

The numbering for NMR assignment:

7d: R = CH₃, X = NO₂, Y = H

11b: R = CH₃

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Fig.1. a) The ^1H NMR of **7b** recorded in commercial grade CDCl_3 . b) The ^1H NMR of **7b** recorded in dry CDCl_3 right after dissolution ($t_r = 5$ min). c) The same mixture as b) after 2 hours.

Fig. 2. The kinetics of the decomposition of **7b** in dry CDCl_3 in a sealed NMR tube at 25°C .

Fig. 3. The kinetics of the decomposition of **7a** in dry CDCl_3 in a sealed NMR tube at 25°C .

Fig. 4. The course of the reaction of **7b** with 2,4,6-tri-*tert*-butylaniline in dry CDCl_3 in a sealed NMR tube at 25°C .

Table S1: The molecular energies, contributions to free energy and the difference in the total energies and free energies for **7a**. If not explicitly mentioned, the energies are in atomic units (a.u.).

Conformer (Structure)	<i>E</i> (PBE) def2-SVP	<i>E</i> (B3LYP) def2-TZVP	<i>E</i> (PBE+D+ COSMO) def2-SVP	<i>G</i> _{tot}	Δ <i>G</i> (kJ.mol ⁻¹)	Δ <i>E</i> (kJ.mol ⁻¹)
2NH-EEEE	-1023.33987	-1025.10724	-1023.38280	-1024.97035	34.2	40.6
2NH-EEEZ	-1023.34859	-1025.11567	-1023.39021	-1024.97587	19.7	18.5
2NH-EEZE	-1023.34009	-1025.11241	-1023.38208	-1024.97643	18.2	27.1
2NH-EEZZ	-1023.34039	-1025.11208	-1023.38195	-1024.97460	23.0	28.0
2NH-EZEE	-1023.34690	-1025.11762	-1023.38786	-1024.98036	7.9	13.4
2NH-EZEEZ	-1023.35190	-1025.12273	-1023.39140	-1024.98337	0.0	0.0
2NH-EZZE	-1023.34505	-1025.11667	-1023.38653	-1024.98032	8.0	15.9
2NH-EZZZ	-1023.34454	-1025.11661	-1023.38661	-1024.98184	4.0	16.1
2NH-ZEEE	-1023.33878	-1025.10532	-1023.38510	-1024.96851	39.0	45.7
2NH-ZEEZ	-1023.34170	-1025.11103	-1023.38449	-1024.97348	25.9	30.7
2NH-ZEZE	-1023.34533	-1025.11548	-1023.38694	-1024.97854	12.7	19.0
2NH-ZEZZ	-1023.34843	-1025.11507	-1023.39039	-1024.97655	17.9	20.1
2NH-ZZEE	-1023.34136	-1025.11166	-1023.38333	-1024.97520	21.4	29.0
2NH-ZZEEZ	-1023.34660	-1025.11717	-1023.38694	-1024.97938	10.5	14.6
2NH-ZZZE	-1023.33888	-1025.11032	-1023.38172	-1024.97333	26.4	32.6
2NH-ZZZZ	-1023.33844	-1025.11021	-1023.38171	-1024.97799	14.1	32.9
<i>enol-form</i>						
3OH-EEZE	-1023.33077	-1025.10253	-1023.36969	-1024.96243	55.0	53.0
3OH-EZZE	-1023.33072	-1025.10242	-1023.36865	-1024.96292	53.7	53.3
<i>6-Membered Ring Transition States Corresponding to the 3OH → Phenol Hydrogen Transfer</i>						
EEZE	-1023.32247	-1025.08896	-1023.36016	-1024.95135	84.1	88.7
EZZE	-1023.32191	-1025.08868	-1023.35961	-1024.95117	84.5	89.4
<i>Product Complex</i>						
EEZE	-1023.34109	-1025.11742	-1023.37758	-1024.98113	5.9	13.9
EZZE	-1023.34171	-1025.11767	-1023.37771	-1024.98169	4.4	13.3

E(PBE)... *in vacuo* energy of the system optimised at the RI-PBE/def2-SVP level of theory

E(B3LYP) *in vacuo* energy of the system calculated at the B3LYP/def2-TZVP//RI-PBE/def2-SVP level

E(PBE+D+COSMO) energy of the system optimised at the RI-PBE+D+COSMO/def2-SVP level, i.e. with the empirical dispersion correction and COSMO solvation model

$G_{\text{tot}} = E(\text{B3LYP}) + E(\text{PBE+D+COSMO}) - E(\text{PBE}) + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$

Δ*G* ...relative difference in free energy, *G*_{tot}, in kJ.mol⁻¹, with respect to the most stable reactant isomer

Δ*E* ... relative difference in energy, *E*(B3LYP), in kJ.mol⁻¹, with respect to the most stable reactant isomer

Table S2: The molecular energies, contributions to free energy and the difference in the total energies and free energies for **7b**. If not explicitly mentioned, the energies are in atomic units (a.u.).

Conformer (Structure)	<i>E</i> (PBE) def2-SVP	<i>E</i> (B3LYP) def2-TZVP	<i>E</i> (PBE+D+ COSMO) def2-SVP	<i>G</i> _{tot}	ΔG (kJ.mol ⁻¹)	ΔE (kJ.mol ⁻¹)
2NH-EEEE	-1062.56966	-1064.40923	-1062.61547	-1064.25063	25.5	19.3
2NH-EEEZ	-1062.57222	-1064.41566	-1062.61606	-1064.25635	10.5	2.4
2NH-EEZE	-1062.57038	-1064.41490	-1062.61483	-1064.25732	7.9	4.4
2NH-EEZZ	-1062.57069	-1064.41471	-1062.61497	-1064.25778	6.7	4.9
2NH-EZEE	-1062.56928	-1064.41129	-1062.61493	-1064.25165	22.8	13.9
2NH-EZEEZ	-1062.57216	-1064.41546	-1062.61617	-1064.25567	12.3	3.0
2NH-EZZE	-1062.57305	-1064.41658	-1062.61744	-1064.25779	6.7	0.0
2NH-EZZZ	-1062.57274	-1064.41654	-1062.61838	-1064.26034	0.0	0.1
2NH-ZEEE	-1062.56716	-1064.40589	-1062.61644	-1064.25089	24.8	28.1
2NH-ZEEZ	-1062.56959	-1064.41140	-1062.61518	-1064.25165	22.8	13.6
2NH-ZEZE	-1062.57396	-1064.41635	-1062.61797	-1064.25616	11.0	0.6
2NH-ZEZZ	-1062.57630	-1064.41496	-1062.62163	-1064.25606	11.2	4.3
2NH-ZZEE	-1062.56188	-1064.40501	-1062.60753	-1064.24735	34.1	30.4
2NH-ZZEEZ	-1062.56426	-1064.40788	-1062.60869	-1064.24914	29.4	22.9
2NH-ZZZE	-1062.56398	-1064.40750	-1062.60993	-1064.24862	30.8	23.8
2NH-ZZZZ	-1062.56380	-1064.40743	-1062.60998	-1064.25472	14.7	24.0
<i>enol-form</i>						
3OH-EEEE	-1062.53875	-1064.38545	-1062.58516	-1064.22766	85.8	81.7
3OH-EEZE	-1062.55983	-1064.40333	-1062.60157	-1064.24064	51.7	34.8
3OH-EZZE	-1062.55997	-1064.40410	-1062.60174	-1064.24186	48.5	32.8
3OH-ZEZZ	-1062.55519	-1064.39868	-1062.59446	-1064.23455	67.7	47.0
3OH-ZZZZ	-1062.55894	-1064.40408	-1062.60003	-1064.24096	50.9	32.8
<i>Transition State Corresponding to the Direct 2NH → Phenol Hydrogen Transfer</i>						
2NH-EZZZ	-1062.51933	-1064.35661	-1062.55909	-1064.19874	161.7	157.5
<i>6-Membered Ring Transition States Corresponding to the 3OH → Phenol Hydrogen Transfer</i>						
EEZE	-1062.55248	-1064.39108	-1062.59292	-1064.23291	72.0	67.0
EZZE	-1062.55124	-1064.38978	-1062.59181	-1064.23270	72.6	70.4
<i>Product Complex</i>						
EEZE	-1062.57157	-1064.42019	-1062.61069	-1064.26245	-5.6	-9.5
EZZE	-1062.57067	-1064.41848	-1062.60958	-1064.25993	1.1	-5.0

E(PBE)... *in vacuo* energy of the system optimised at the RI-PBE/def2-SVP level of theory

E(B3LYP) *in vacuo* energy of the system calculated at the B3LYP/def2-TZVP//RI-PBE/def2-SVP level

E(PBE+D+COSMO) energy of the system optimised at the RI-PBE+D+COSMO/def2-SVP level, i.e. with the empirical dispersion correction and COSMO solvation model

$$G_{\text{tot}} = E(\text{B3LYP}) + E(\text{PBE+D+COSMO}) - E(\text{PBE}) + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$$

ΔG ...relative difference in free energy, G_{tot} , in kJ.mol⁻¹, with respect to the most stable reactant isomer

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ΔE ... relative difference in energy, $E(\text{B3LYP})$, in $\text{kJ}\cdot\text{mol}^{-1}$, with respect to the most stable reactant isomer

For Peer Review

Table S3: The molecular energies, contributions to free energy and the difference in the total energies and free energies for **7c**. If not explicitly mentioned, the energies are in atomic units (a.u.).

Conformer (Structure)	<i>E</i> (PBE) def2-SVP	<i>E</i> (B3LYP) def2-TZVP	<i>E</i> (PBE+D+ COSMO) def2-SVP	<i>G</i> _{tot}	ΔG (kJ.mol ⁻¹)	ΔE (kJ.mol ⁻¹)
2NH-EEEE	-1023.34634	-1025.11777	-1023.38824	-1024.98412	22.3	36.7
2NH-EEEZ	-1023.35105	-1025.12400	-1023.39024	-1024.98631	16.6	20.4
2NH-EEZE	-1023.34810	-1025.12098	-1023.38817	-1024.98327	24.5	28.3
2NH-EEZZ	-1023.34654	-1025.11967	-1023.38900	-1024.98542	18.9	31.8
2NH-EZEE	-1023.35435	-1025.12678	-1023.39323	-1024.98914	9.1	13.1
2NH-EZEEZ	-1023.35955	-1025.13177	-1023.39767	-1024.99262	0.0	0.0
2NH-EZZE	-1023.35407	-1025.12635	-1023.39280	-1024.98573	18.1	14.2
2NH-EZZZ	-1023.35299	-1025.12545	-1023.39400	-1024.99192	1.8	16.6
2NH-ZEEE	-1023.34758	-1025.11667	-1023.39244	-1024.98249	26.6	39.6
2NH-ZEEZ	-1023.34947	-1025.12080	-1023.39060	-1024.98344	24.1	28.8
2NH-ZEZE	-1023.35427	-1025.12511	-1023.39308	-1024.98410	22.4	17.5
2NH-ZEZZ	-1023.35305	-1025.12357	-1023.39446	-1024.98899	9.5	21.5
2NH-ZZEE	-1023.34839	-1025.12053	-1023.38841	-1024.98335	24.3	29.5
2NH-ZZEEZ	-1023.35428	-1025.12638	-1023.39326	-1024.98748	13.5	14.1
2NH-ZZZE	-1023.34802	-1025.12012	-1023.38805	-1024.98125	29.8	30.6
2NH-ZZZZ	-1023.34686	-1025.11908	-1023.38920	-1024.98549	18.7	33.3
<i>enol-form</i>						
3OH-EEZE	-1023.33490	-1025.10896	-1023.37308	-1024.97026	58.7	59.9
3OH-EZZE	-1023.33313	-1025.10760	-1023.37198	-1024.97013	59.0	63.5
<i>Transition State Corresponding to the Direct 2NH → Phenol Hydrogen Transfer</i>						
2NH-EZZZ	-1023.28790	-1025.05495	-1023.32605	-1024.92399	180.2	201.7
<i>6-Membered Ring Transition States Corresponding to the 3OH → Phenol Hydrogen Transfer</i>						
EEZE	-1023.32768	-1025.09600	-1023.36479	-1024.95812	90.6	93.9
EZZE	-1023.32688	-1025.09529	-1023.36419	-1024.95895	88.4	95.8
<i>Product Complex</i>						
EEZE	-1023.34439	-1025.12327	-1023.38243	-1024.99025	6.2	22.3
EZZE	-1023.34512	-1025.12350	-1023.38253	-1024.98924	8.9	21.7

E(PBE)... *in vacuo* energy of the system optimised at the RI-PBE/def2-SVP level of theory

E(B3LYP) *in vacuo* energy of the system calculated at the B3LYP/def2-TZVP//RI-PBE/def2-SVP level

E(PBE+D+COSMO) energy of the system optimised at the RI-PBE+D+COSMO/def2-SVP level, i.e. with the empirical dispersion correction and COSMO solvation model

$$G_{\text{tot}} = E(\text{B3LYP}) + E(\text{PBE+D+COSMO}) - E(\text{PBE}) + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$$

ΔG ...relative difference in free energy, G_{tot} , in kJ.mol⁻¹, with respect to the most stable reactant isomer

ΔE ... relative difference in energy, *E*(B3LYP), in kJ.mol⁻¹, with respect to the most stable reactant isomer

Table S4: The molecular energies, contributions to free energy and the difference in the total energies and free energies for **7d**. If not explicitly mentioned, the energies are in atomic units (a.u.).

Conformer (Structure)	<i>E</i> (PBE) def2-SVP	<i>E</i> (B3LYP) def2-TZVP	<i>E</i> (PBE+D+ COSMO) def2-SVP	<i>G</i> _{tot}	Δ <i>G</i> (kJ.mol ⁻¹)	Δ <i>E</i> (kJ.mol ⁻¹)
2NH-EEEE	-1062.57643	-1064.42032	-1062.62136	-1064.26353	10.3	15.1
2NH-EEEZ	-1062.58007	-1064.42532	-1062.62243	-1064.26552	5.1	2.0
2NH-EEZE	-1062.57830	-1064.42343	-1062.62089	-1064.26487	6.8	7.0
2NH-EEZZ	-1062.57689	-1064.42216	-1062.62166	-1064.26669	2.0	10.3
2NH-EZEE	-1062.57661	-1064.42119	-1062.62130	-1064.26432	8.2	12.9
2NH-EZEE	-1062.57971	-1064.42467	-1062.62251	-1064.26440	8.0	3.7
2NH-EZZE	-1062.58196	-1064.42608	-1062.62363	-1064.26583	4.3	0.0
2NH-EZZZ	-1062.58096	-1064.42538	-1062.62501	-1064.26745	0.0	1.9
2NH-ZEEE	-1062.57539	-1064.41702	-1062.62309	-1064.26060	18.0	23.8
2NH-ZEEZ	-1062.57723	-1064.42103	-1062.62142	-1064.26111	16.7	13.3
2NH-ZEEZ	-1062.58282	-1064.42597	-1062.62404	-1064.26226	13.6	0.3
2NH-ZEEZ	-1062.58186	-1064.42456	-1062.62535	-1064.26559	4.9	4.0
2NH-ZZEE	-1062.56818	-1064.41336	-1062.61317	-1064.25730	26.7	33.4
2NH-ZZEE	-1062.57188	-1064.41712	-1062.61262	-1064.25591	30.3	23.5
2NH-ZZZE	-1062.57301	-1064.41712	-1062.61617	-1064.25641	29.0	23.5
2NH-ZZZZ	-1062.57196	-1064.41623	-1062.61758	-1064.25854	23.4	25.9
<i>enol-form</i>						
3OH-EEZE	-1062.56408	-1064.40986	-1062.60503	-1064.24885	48.8	42.6
3OH-EZZE	-1062.56274	-1064.40893	-1062.60402	-1064.24928	47.7	45.0
<i>Transition State Corresponding to the Direct 2NH → Phenol Hydrogen Transfer</i>						
2NH-EZZZ	-1062.51848	-1064.35806	-1062.55993	-1064.20568	162.2	178.6
<i>6-Membered Ring Transition States Corresponding to the 3OH → Phenol Hydrogen Transfer</i>						
EEZE	-1062.55750	-1064.39779	-1062.59750	-1064.23883	75.1	74.3
EZZE	-1062.55624	-1064.39655	-1062.59623	-1064.23732	79.1	77.5
<i>Product Complex</i>						
EEZE	-1062.57492	-1064.42598	-1062.61566	-1064.27015	-7.1	0.3
EZZE	-1062.57407	-1064.42449	-1062.61441	-1064.26897	-4.0	4.2

E(PBE)... *in vacuo* energy of the system optimised at the RI-PBE/def2-SVP level of theory

E(B3LYP) *in vacuo* energy of the system calculated at the B3LYP/def2-TZVP//RI-PBE/def2-SVP level

E(PBE+D+COSMO) energy of the system optimised at the RI-PBE+D+COSMO/def2-SVP level, i.e. with the empirical dispersion correction and COSMO solvation model

$G_{\text{tot}} = E(\text{B3LYP}) + E(\text{PBE+D+COSMO}) - E(\text{PBE}) + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$

Δ*G* ...relative difference in free energy, *G*_{tot}, in kJ.mol⁻¹, with respect to the most stable reactant isomer

Δ*E* ... relative difference in energy, *E*(B3LYP), in kJ.mol⁻¹, with respect to the most stable reactant isomer

Table S5: The molecular energies, contributions to free energy and the difference in the total energies and free energies for decomposition products. If not explicitly mentioned, the energies are in atomic units (a.u.).

Conformer (Structure)	$E(\text{PBE})$ def2-SVP	$E(\text{B3LYP})$ def2-TZVP	$E(\text{PBE+D+}$ $\text{COSMO})$ def2-SVP	G_{tot}	ΔG (kJ.mol ⁻¹)	ΔE (kJ.mol ⁻¹)
<i>o</i> -nitrophenol	-511.04060	-511.91856	-511.05604	-511.86260	3.6	0.0
<i>p</i> -nitrophenol	-511.02999	-511.91394	-511.05044	-511.86398	0.0	12.1
3a_EE	-512.29253	-513.19701	-512.31001	-513.13040	0.0	0.5
3a_EZ	-512.29318	-513.19721	-512.31015	-513.13012	0.7	0.0
3a_ZE	-512.28746	-513.19092	-512.30576	-513.12593	11.7	16.5
3a_ZZ	-512.28804	-513.19188	-512.30609	-513.12683	9.4	14.0
3b_EE	-551.52298	-552.49977	-551.54306	-552.41139	0.0	0.0
3b_EZ	-551.52206	-552.49797	-551.54197	-552.40922	5.7	4.7
3b_ZE	-551.51556	-552.49127	-551.53647	-552.40350	20.7	22.3
3b_ZZ	-551.51439	-552.49019	-551.53539	-552.40281	22.5	25.2

$E(\text{PBE})$... *in vacuo* energy of the system optimised at the RI-PBE/def2-SVP level of theory

$E(\text{B3LYP})$ *in vacuo* energy of the system calculated at the B3LYP/def2-TZVP//RI-PBE/def2-SVP level

$E(\text{PBE+D+COSMO})$ energy of the system optimised at the RI-PBE+D+COSMO/def2-SVP level, i.e. with the empirical dispersion correction and COSMO solvation model

$$G_{\text{tot}} = E(\text{B3LYP}) + E(\text{PBE+D+COSMO}) - E(\text{PBE}) + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$$

ΔG ...relative difference in free energy, G_{tot} , in kJ.mol⁻¹, with respect to the most stable reactant isomer

ΔE ... relative difference in energy, $E(\text{B3LYP})$, in kJ.mol⁻¹, with respect to the most stable reactant isomer

Molecular energies (in a.u.) and molecular structures of 7a (Table S1)

2NH-EEEE
E(B3LYP/def2-TZVP)= -1025.107243478

32

c	-1.59810	-4.21913	0.68536
c	-1.61160	-5.60579	0.91284
c	-1.67027	-6.09885	2.21857
c	-1.73205	-5.19467	3.29377
c	-1.74324	-3.81256	3.06910
c	-1.67278	-3.29851	1.75974
o	-1.65100	-1.94928	1.50679
c	-2.51916	-1.11788	2.21345
o	-3.44661	-1.51794	2.88558
n	-1.48882	-3.77234	-0.71330
o	-0.87073	-2.72972	-0.93174
n	-2.19300	0.21073	2.03839
c	-0.93871	0.84320	1.62347
o	-0.40516	1.59479	2.42835
c	-0.48008	0.63483	0.26169
c	-1.27939	0.18584	-0.74969
o	-0.86554	0.13108	-2.01093
c	-1.80503	-0.23296	-3.04210
c	-1.20688	-1.30458	-3.93662
h	0.53263	1.00394	0.03783
o	-2.00120	-4.48607	-1.57766
h	-2.67447	0.78771	2.73832
h	-2.32428	-0.12969	-0.55904
h	-2.75114	-0.58442	-2.56980
h	-2.02956	0.69633	-3.61416
h	-1.89235	-1.50262	-4.78948
h	-0.22916	-0.97129	-4.34611
h	-1.06044	-2.24385	-3.36462
h	-1.57105	-6.27299	0.03963
h	-1.66505	-7.18527	2.39862
h	-1.77644	-5.56893	4.32918
h	-1.81296	-3.11455	3.91406

2NH-EEEZ
E(B3LYP/def2-TZVP)= -1025.115668207

32

c	-3.02370	-4.45287	0.72050
c	-2.41131	-5.40004	1.54684
c	-1.29679	-5.02759	2.31889
c	-0.81428	-3.71332	2.27656

c	-1.40887	-2.75191	1.44095
c	-2.51561	-3.14526	0.64612
o	-0.85849	-1.49945	1.44903
c	-1.71890	-0.38699	1.54644
n	-0.97584	0.73182	1.26925
c	-1.36312	2.12464	1.37224
c	-2.68784	2.50479	0.90080
h	-3.03861	3.50018	1.21334
n	-3.14855	-2.23683	-0.32460
o	-4.34277	-2.39834	-0.56785
o	-2.88575	-0.48244	1.85016
o	-2.42808	-1.39006	-0.86402
o	-0.52197	2.90605	1.79856
c	-3.41865	1.75670	0.02423
o	-4.61669	2.13997	-0.41697
c	-5.24048	1.31969	-1.43022
c	-6.74370	1.50392	-1.34100
h	0.04221	0.60424	1.26900
h	-3.04404	0.79642	-0.37653
h	-4.85434	1.64631	-2.42372
h	-4.94908	0.25539	-1.27753
h	-7.24302	0.91118	-2.13747
h	-7.12654	1.16055	-0.35616
h	-7.02143	2.57173	-1.47326
h	-3.89987	-4.70181	0.10401
h	-2.80344	-6.42819	1.58819
h	-0.80650	-5.76386	2.97597
h	0.03476	-3.39317	2.89979

2NH-EEZE
E(B3LYP/def2-TZVP)=-1025.112407482

32

c	-2.55668	-4.53433	0.03983
c	-2.48542	-5.31611	1.19731
c	-1.90140	-4.78258	2.35961
c	-1.41021	-3.47091	2.36234
c	-1.47194	-2.67681	1.20462
c	-2.03980	-3.22797	0.03014
o	-0.92700	-1.42111	1.29891
c	-1.69144	-0.34028	0.93383
n	-0.94165	0.82381	0.90282
c	0.40032	1.08173	1.32507
c	0.96688	2.33739	0.79408
h	1.84214	2.72588	1.33857
n	-2.06196	-2.50874	-1.26336
o	-2.86623	-2.89408	-2.10929
o	-2.87631	-0.38489	0.67929
o	-1.24558	-1.60024	-1.42917
o	1.01382	0.33552	2.07001
c	0.57637	2.93682	-0.36313
o	1.16183	4.04912	-0.82892
c	0.78245	4.48382	-2.14701

c	1.40272	5.84502	-2.39857
h	-1.49882	1.62275	0.58950
h	-0.23594	2.51846	-0.99349
h	1.13987	3.73520	-2.89249
h	-0.33066	4.52954	-2.21282
h	1.13378	6.20070	-3.41611
h	1.03942	6.58900	-1.65756
h	2.51011	5.79240	-2.32696
h	-3.00456	-4.91223	-0.89040
h	-2.88272	-6.34321	1.19065
h	-1.83594	-5.38893	3.27737
h	-0.96511	-3.02067	3.26255

2NH-EEZZ
E(B3LYP/def2-TZVP)=-1025.112080149

32

c	-3.11615	-3.08811	1.17656
c	-1.85887	-2.46460	1.12131
c	-0.69949	-3.27075	1.01572
c	-0.79204	-4.67148	1.01497
c	-2.05095	-5.28057	1.06174
c	-3.20971	-4.48666	1.13654
o	-1.72550	-1.10817	1.23437
c	-2.14205	-0.29842	0.15095
o	-3.01400	-0.60099	-0.62029
n	0.64662	-2.66997	0.90170
o	0.74351	-1.56048	0.36749
n	-1.34786	0.82511	0.19719
c	-1.46188	1.98040	-0.63734
o	-2.51463	2.29453	-1.16544
c	-0.20614	2.73941	-0.78659
c	1.03867	2.20853	-0.63359
o	2.15206	2.92814	-0.82926
c	3.40133	2.21323	-0.80639
c	4.53164	3.22466	-0.80509
h	-0.31749	3.77196	-1.15366
o	1.59438	-3.32999	1.32404
h	-0.54054	0.74936	0.82120
h	1.19695	1.14366	-0.36151
h	3.43767	1.56419	0.10035
h	3.45546	1.55193	-1.70282
h	5.51038	2.69878	-0.80081
h	4.48443	3.86944	-1.70863
h	4.47845	3.87695	0.09284
h	0.13748	-5.25713	0.96663
h	-2.12903	-6.37901	1.04104
h	-4.20266	-4.96343	1.17261
h	-4.01146	-2.45534	1.25684

2NH-EZEE

E(B3LYP/def2-TZVP)=-1025.117619883

32

c	-1.38607	-3.55984	1.31552
c	-2.17226	-4.63414	1.76294
c	-3.51728	-4.43664	2.09144
c	-4.07571	-3.15125	1.98450
c	-3.28594	-2.07220	1.56676
c	-1.93623	-2.25883	1.22586
o	-1.25122	-1.15208	0.78718
c	-0.08146	-0.79966	1.44777
o	0.24917	-1.26219	2.51723
n	-0.00036	-3.86897	0.89723
o	0.54762	-3.09191	0.11131
n	0.59211	0.20214	0.78106
c	0.48980	0.82193	-0.50215
o	1.08379	1.88845	-0.64830
c	-0.24876	0.12310	-1.55839
c	-0.39332	0.75253	-2.75595
o	-1.01134	0.18795	-3.79867
c	-1.09959	0.97319	-5.00160
c	-1.77007	0.13280	-6.07171
h	-0.63554	-0.89268	-1.40521
o	0.50167	-4.90386	1.32718
h	1.31771	0.64268	1.35727
h	0.01502	1.77376	-2.89491
h	-1.68545	1.89872	-4.79001
h	-0.07399	1.27934	-5.31441
h	-1.85606	0.71612	-7.01339
h	-1.17993	-0.78538	-6.27971
h	-2.78964	-0.17247	-5.75292
h	-1.69415	-5.62174	1.83472
h	-4.13001	-5.28658	2.43047
h	-5.13399	-2.98205	2.24117
h	-3.69406	-1.05215	1.49977

2NH-EZEZ

E(B3LYP/def2-TZVP)=-1025.122726203

32

c	-1.35059	-3.18314	0.17717
c	-1.40133	-4.56878	-0.04686
c	-1.98954	-5.41770	0.89618
c	-2.54371	-4.87380	2.06786
c	-2.52125	-3.48949	2.28030
c	-1.92535	-2.62555	1.34540
o	-1.92056	-1.28955	1.65814
c	-2.43640	-0.38049	0.72715
o	-3.06756	-0.71139	-0.25100
n	-0.61569	-2.37029	-0.81956
o	-0.16740	-1.28289	-0.45187
n	-2.13595	0.88143	1.18194

c	-2.44394	2.16649	0.64318
o	-2.02808	3.14079	1.26713
c	-3.22262	2.21661	-0.59608
c	-3.51209	3.44102	-1.11540
o	-4.21526	3.59923	-2.24058
c	-4.42051	4.94974	-2.69438
c	-5.28682	4.90730	-3.93900
h	-3.54922	1.28935	-1.08755
o	-0.46168	-2.85430	-1.93815
h	-1.56295	0.94067	2.03039
h	-3.16067	4.35729	-0.59953
h	-4.90908	5.53783	-1.88237
h	-3.43003	5.41540	-2.90872
h	-5.46042	5.93819	-4.31531
h	-4.79456	4.31817	-4.74210
h	-6.27185	4.44249	-3.71902
h	-0.95669	-4.95137	-0.97684
h	-2.01325	-6.50416	0.71747
h	-3.01033	-5.53125	2.81907
h	-2.97154	-3.03835	3.17765

2NH-EZZE

E(B3LYP/def2-TZVP)=-1025.116667362

32

c	-1.95589	-3.99889	0.12443
c	-2.62423	-5.16419	0.53547
c	-2.87697	-5.39571	1.89131
c	-2.46732	-4.44664	2.84407
c	-1.82708	-3.26984	2.43573
c	-1.56283	-3.02720	1.07684
o	-0.89472	-1.86463	0.78717
c	-1.42283	-1.01399	-0.15156
o	-2.52833	-1.12228	-0.63841
n	-1.63477	-3.88587	-1.31647
o	-0.68883	-3.16465	-1.63696
n	-0.55427	0.02387	-0.45128
c	0.74744	0.33277	0.03327
o	1.30000	-0.30221	0.92045
c	1.33352	1.50292	-0.65305
c	2.57586	1.91420	-0.28475
o	3.19540	2.95818	-0.84375
c	4.52186	3.25583	-0.36668
c	5.01982	4.49532	-1.08534
h	0.79356	2.03526	-1.45364
o	-2.30586	-4.55654	-2.09783
h	-0.94839	0.64305	-1.16503
h	3.11106	1.36576	0.51622
h	4.48480	3.41623	0.73629
h	5.18385	2.38097	-0.56616
h	6.04523	4.74708	-0.73953
h	5.05079	4.32948	-2.18348
h	4.35727	5.36349	-0.88136

h -2.92710 -5.87866 -0.24334
h -3.39063 -6.31820 2.20449
h -2.65679 -4.61776 3.91613
h -1.51479 -2.50139 3.15902

2NH-EZZZ
E(B3LYP/def2-TZVP)=-1025.116606729

32

c -3.51715 -4.45306 1.54546
c -3.11932 -3.11399 1.42605
c -1.80219 -2.80127 1.04624
c -0.89680 -3.85751 0.79107
c -1.28715 -5.19626 0.94817
c -2.60458 -5.49670 1.31104
o -1.34836 -1.50970 0.99279
c -1.99706 -0.58192 0.15766
n -1.14945 0.50612 0.07277
c -1.43325 1.74241 -0.57139
c -0.27181 2.65381 -0.57963
h 0.69297 2.36515 -0.13040
n 0.48980 -3.59448 0.34298
o 1.34166 -4.42705 0.65540
o -3.07541 -0.75279 -0.34795
o 0.69766 -2.58537 -0.33043
o -2.52851 1.99450 -1.05091
c -0.41135 3.87025 -1.17096
o 0.57439 4.76968 -1.23585
c 0.28300 6.00008 -1.92684
c 1.50924 6.88969 -1.85498
h -0.21633 0.36365 0.47011
h -1.38650 4.14035 -1.62456
h 0.01550 5.76747 -2.98405
h -0.59810 6.48673 -1.44725
h 1.31447 7.84620 -2.38574
h 1.76941 7.12044 -0.79977
h 2.38353 6.39641 -2.33092
h -0.53731 -5.98072 0.77021
h -2.91925 -6.54706 1.41490
h -4.55520 -4.68245 1.83604
h -3.82175 -2.29381 1.62842

2NH-ZEEE
E(B3LYP/def2-TZVP)=-1025.105315786

32

c -1.43228 -5.17152 0.55322
c -2.07874 -5.88525 1.56884
c -2.48239 -5.21215 2.73362
c -2.26316 -3.83493 2.88952

1				
2				
3	c	-1.60976	-3.10590	1.87690
4	c	-1.18096	-3.80299	0.72244
5	o	-1.34495	-1.75945	1.93339
6	c	-2.21975	-0.87756	2.54564
7	n	-1.77623	0.42353	2.41710
8	c	-0.76082	1.05834	1.63333
9	c	-0.49520	0.59106	0.26672
10	h	0.46605	0.93688	-0.14034
11	n	-0.43671	-3.10785	-0.34199
12	o	-0.83600	-3.27222	-1.50204
13	o	-3.20839	-1.19707	3.17252
14	o	0.53345	-2.43473	-0.01176
15	o	-0.20849	2.04253	2.11128
16	c	-1.34757	-0.01493	-0.60625
17	o	-2.57763	-0.44564	-0.28973
18	c	-3.36868	-1.02666	-1.34942
19	c	-4.73399	-1.36850	-0.78413
20	h	-2.16674	1.04659	3.13254
21	h	-1.02942	-0.18910	-1.65285
22	h	-3.44895	-0.29101	-2.18323
23	h	-2.84287	-1.93355	-1.72768
24	h	-5.35988	-1.83979	-1.57209
25	h	-4.64412	-2.07990	0.06501
26	h	-5.25400	-0.45725	-0.41863
27	h	-1.10357	-5.65683	-0.37809
28	h	-2.26289	-6.96472	1.45177
29	h	-2.98794	-5.76467	3.54204
30	h	-2.60969	-3.31159	3.78834
31				
32				
33				
34	2NH-ZEEZ			
35	E(B3LYP/def2-TZVP)=-1025.111030212			
36				
37	32			
38				
39	c	-2.16635	-5.64060	1.34480
40	c	-2.42240	-4.95156	2.54293
41	c	-2.12827	-3.58588	2.64585
42	c	-1.55052	-2.88798	1.57054
43	c	-1.27760	-3.59471	0.37409
44	c	-1.60136	-4.95687	0.26340
45	o	-1.26821	-1.56314	1.77801
46	c	-1.77076	-0.62002	0.86705
47	o	-2.60039	-0.88111	0.02883
48	n	-0.58667	-2.97341	-0.77948
49	o	0.10511	-1.97742	-0.56167
50	n	-1.17225	0.58181	1.17002
51	c	-1.29116	1.85187	0.53260
52	o	-0.33428	2.61357	0.61181
53	c	-2.53579	2.21342	-0.16216
54	c	-3.81339	1.85700	0.13847
55	o	-4.15878	1.07306	1.16744
56	c	-5.44462	0.43534	1.08996
57	c	-5.72924	-0.23426	2.42104
58	h	-2.40042	2.99528	-0.92476
59				
60				

o -0.71413 -3.51919 -1.87272
h -0.32845 0.52075 1.75116
h -4.65585 2.26036 -0.46159
h -6.21816 1.20351 0.84713
h -5.41895 -0.31173 0.26457
h -6.72550 -0.72566 2.39263
h -4.96420 -1.01036 2.63871
h -5.72539 0.50725 3.24895
h -1.38522 -5.45704 -0.69189
h -2.40402 -6.71207 1.25307
h -2.86652 -5.47832 3.40300
h -2.33939 -3.01957 3.56612

2NH-ZEZE
E(B3LYP/def2-TZVP)=-1025.115476938

32

c -2.71638 -5.30919 1.63771
c -2.47584 -4.48377 2.75006
c -1.93464 -3.20445 2.57344
c -1.60199 -2.73169 1.29185
c -1.82382 -3.57849 0.17825
c -2.39440 -4.84984 0.35679
o -1.04037 -1.48293 1.23375
c -1.57198 -0.55253 0.37187
o -2.62187 -0.68781 -0.22184
n -1.41484 -3.21797 -1.19748
o -0.52003 -2.38136 -1.32844
n -0.78897 0.58444 0.28950
c 0.43717 0.91863 0.91746
o 0.97583 0.23050 1.77085
c 1.03228 2.19865 0.45494
c 0.59718 3.07065 -0.49294
o -0.55737 2.92549 -1.17977
c -0.78265 3.79834 -2.30411
c -2.20008 3.58781 -2.80051
h 1.97451 2.44498 0.96685
o -1.96457 -3.81163 -2.12315
h -1.16042 1.26699 -0.38421
h 1.18437 3.97777 -0.73833
h -0.61779 4.85218 -1.97776
h -0.03698 3.55889 -3.09721
h -2.39175 4.24258 -3.67737
h -2.35886 2.53321 -3.11260
h -2.93990 3.83508 -2.00946
h -2.56510 -5.46196 -0.54049
h -3.15123 -6.31271 1.76765
h -2.72114 -4.83426 3.76564
h -1.75450 -2.53057 3.42470

2NH-ZEZZ

E(B3LYP/def2-TZVP)=-1025.115067365

32

c	-3.58463	-4.36653	1.53588
c	-3.25424	-3.01155	1.38680
c	-1.92804	-2.63914	1.10551
c	-0.95001	-3.65421	0.97145
c	-1.27313	-5.00572	1.16464
c	-2.59900	-5.36466	1.43275
o	-1.52617	-1.33596	1.03828
c	-2.10309	-0.46491	0.08227
n	-1.19225	0.55494	-0.07439
c	-1.33825	1.69356	-0.90840
c	-0.09521	2.48397	-1.07985
h	-0.22105	3.35841	-1.73527
n	0.44284	-3.31912	0.61606
o	1.33309	-4.02867	1.08187
o	-3.17182	-0.64697	-0.43962
o	0.62235	-2.36552	-0.14719
o	-2.38966	1.99148	-1.45140
c	1.14816	2.25855	-0.57404
o	1.44283	1.27037	0.29559
c	2.82894	0.93611	0.52262
c	3.30779	-0.15408	-0.42321
h	-0.26820	0.40218	0.35325
h	1.99647	2.92139	-0.83966
h	3.43569	1.86708	0.43052
h	2.87147	0.60015	1.57972
h	4.36092	-0.42016	-0.18311
h	2.68027	-1.06649	-0.32307
h	3.27106	0.18775	-1.48081
h	-0.47083	-5.75402	1.08583
h	-2.86403	-6.42563	1.56359
h	-4.62954	-4.64524	1.74802
h	-4.01355	-2.22425	1.49019

2NH-ZZEE

E(B3LYP/def2-TZVP)=-1025.111662524

32

c	-2.12067	-4.82793	1.53832
c	-3.46675	-4.73485	1.90682
c	-4.08927	-3.47515	1.94678
c	-3.36195	-2.31911	1.63473
c	-2.01180	-2.39937	1.25449
c	-1.39812	-3.67367	1.19507
o	-1.38857	-1.22038	0.93026
c	-0.22190	-0.88594	1.61125
n	0.38691	0.21448	1.05100
c	0.20315	0.98183	-0.15004
c	-0.46106	0.31660	-1.27484
h	-0.65268	-0.76276	-1.21699

n	-0.00881	-3.86545	0.72426
o	0.56219	-4.90046	1.05562
o	0.14931	-1.45346	2.61526
o	0.47433	-2.99621	-0.00654
o	0.68257	2.10920	-0.16345
c	-0.80992	0.94373	-2.43517
o	-0.66999	2.24932	-2.67304
c	-1.04299	2.71875	-3.97936
c	-0.93337	4.23172	-3.98815
h	1.09024	0.63670	1.66726
h	-1.25969	0.34817	-3.25684
h	-0.36292	2.26278	-4.73707
h	-2.08418	2.38782	-4.20773
h	-1.20215	4.62670	-4.99141
h	-1.61652	4.68049	-3.23589
h	0.10335	4.54952	-3.74756
h	-1.59357	-5.79211	1.49809
h	-4.02976	-5.64600	2.16293
h	-5.14874	-3.38831	2.23714
h	-3.82001	-1.31954	1.68524

2NH-ZZEZ

E(B3LYP/def2-TZVP)=-1025.117170896

32

c	-1.72098	-4.90195	0.17263
c	-2.41986	-5.55169	1.19506
c	-2.87452	-4.81305	2.30112
c	-2.64412	-3.43304	2.36881
c	-1.93576	-2.76856	1.35282
c	-1.46171	-3.52387	0.25271
o	-1.73282	-1.42285	1.52369
c	-2.11399	-0.55069	0.49626
n	-1.64690	0.69714	0.82544
c	-1.77434	1.96359	0.16173
c	-2.52678	1.97976	-1.09343
h	-2.94474	1.03493	-1.46778
n	-0.62274	-2.93701	-0.81706
o	-0.56674	-3.54183	-1.88528
o	-2.77948	-0.89445	-0.45589
o	0.00030	-1.90732	-0.55374
o	-1.23857	2.92247	0.70480
c	-2.73630	3.10086	-1.84320
o	-2.30932	4.32524	-1.53106
c	-2.56999	5.37014	-2.48383
c	-2.11991	6.68631	-1.87838
h	-1.07990	0.76476	1.67744
h	-3.30796	3.01636	-2.79084
h	-2.01393	5.15023	-3.42586
h	-3.65985	5.38732	-2.72299
h	-2.29799	7.51563	-2.59610
h	-2.67900	6.90065	-0.94256
h	-1.03670	6.65451	-1.63489

h -1.34804 -5.44047 -0.71062
h -2.60771 -6.63488 1.12934
h -3.42623 -5.31207 3.11414
h -3.01396 -2.82952 3.21182

2NH-ZZZE
E(B3LYP/def2-TZVP)=-1025.110324335

32

c -2.71091 -5.18300 0.50399
c -2.97961 -5.42361 1.85515
c -2.56016 -4.49221 2.82107
c -1.89442 -3.32369 2.43031
c -1.61472 -3.07134 1.07604
c -2.01775 -4.02608 0.11058
o -0.92435 -1.91822 0.80452
c -1.42878 -1.04783 -0.13053
n -0.54265 -0.02051 -0.40712
c 0.75984 0.27002 0.10950
c 1.35843 1.43903 -0.56736
h 0.80683 1.94152 -1.37834
n -1.68204 -3.90480 -1.32615
o -2.36079 -4.55271 -2.12035
o -2.53055 -1.13651 -0.63117
o -0.71797 -3.20134 -1.63107
o 1.28084 -0.37806 1.00105
c 2.58361 1.96224 -0.27362
o 3.40592 1.49337 0.66463
c 4.65232 2.18698 0.84791
c 5.44218 1.46279 1.92145
h -0.92228 0.61124 -1.11732
h 2.94910 2.84201 -0.84378
h 5.20810 2.20382 -0.11936
h 4.44286 3.24200 1.14497
h 6.41197 1.97771 2.09221
h 4.87752 1.44359 2.87779
h 5.64599 0.41380 1.61835
h -3.01998 -5.88392 -0.28464
h -3.51341 -6.33927 2.15440
h -2.76218 -4.67057 3.88967
h -1.57252 -2.56924 3.16405

2NH-ZZZZ
E(B3LYP/def2-TZVP)=-1025.110214269

32

c -2.70285 -5.32137 1.35821
c -3.55058 -4.25434 1.70431
c -3.11857 -2.92596 1.58356
c -1.83183 -2.64615 1.08852

c	-0.99290	-3.72576	0.72240
c	-1.41504	-5.05470	0.88089
o	-1.33018	-1.37496	1.02465
c	-2.04211	-0.36346	0.34987
o	-3.19898	-0.43848	0.02638
n	0.35498	-3.49819	0.15300
o	0.53916	-2.47739	-0.50969
n	-1.14317	0.66791	0.17035
c	-1.44319	1.96645	-0.34982
o	-2.58220	2.31776	-0.60105
c	-0.22287	2.77850	-0.52237
c	-0.20618	4.06039	-0.98977
o	-1.28856	4.75388	-1.33977
c	-1.08009	6.08513	-1.84383
c	-2.43606	6.68828	-2.15693
h	0.75955	2.34425	-0.27563
o	1.19976	-4.37019	0.36006
h	-0.17072	0.43645	0.39324
h	0.76456	4.58820	-1.09552
h	-0.53802	6.68640	-1.07593
h	-0.44170	6.03368	-2.75737
h	-2.31143	7.71942	-2.55187
h	-2.96956	6.07913	-2.91713
h	-3.06657	6.73162	-1.24358
h	-0.71351	-5.85812	0.61314
h	-3.04431	-6.36308	1.46475
h	-4.56447	-4.45697	2.08599
h	-3.76937	-2.08979	1.87201

3OH-EEZE
E(B3LYP/def2-TZVP)=-1025.102531907

32

c	0.36724	2.63078	3.32665
c	0.12467	1.92554	2.14191
c	-0.01561	0.52476	2.14592
c	0.08900	-0.15140	3.38933
c	0.30169	0.56050	4.58349
c	0.44986	1.94957	4.55523
o	-0.22000	-0.10065	0.95681
n	0.02546	-1.61731	3.49557
o	-0.26477	-2.10065	4.58284
o	0.30950	-2.30353	2.49823
c	-1.44820	-0.87859	0.78363
n	-1.41905	-1.54987	-0.38851
c	-0.36406	-2.15753	-0.88124
c	-0.35709	-2.66986	-2.24218
c	-1.45142	-2.54997	-3.04362
o	-1.47303	-3.00051	-4.30085
c	-2.71512	-2.86424	-5.01816
c	-2.51111	-3.38562	-6.42791
o	-2.33739	-0.78224	1.59667
o	0.76860	-2.41830	-0.22043

h	0.55626	-3.16920	-2.59799
h	-2.36900	-2.06585	-2.65374
h	-3.50634	-3.44165	-4.48561
h	-3.01619	-1.79049	-5.02378
h	-3.45596	-3.29501	-7.00520
h	-1.72133	-2.80709	-6.95329
h	-2.21005	-4.45499	-6.41359
h	0.35692	-0.00951	5.52208
h	0.63061	2.50136	5.49091
h	0.48018	3.72657	3.29316
h	0.02929	2.44072	1.17389
h	0.70507	-2.08908	0.72286

3OH-EZEE
E(B3LYP/def2-TZVP)=-1025.102420340

32

c	-0.91007	1.18974	-4.65526
c	-0.68912	1.38881	-3.28935
c	-0.33850	0.31016	-2.44807
c	-0.20271	-0.97864	-3.03504
c	-0.43244	-1.16913	-4.41152
c	-0.78514	-0.09159	-5.22416
o	-0.17935	0.48464	-1.11052
n	0.19037	-2.17638	-2.26436
o	0.42622	-3.20344	-2.89688
o	0.26919	-2.10965	-1.02998
c	0.60452	1.60757	-0.57223
n	0.52606	1.65593	0.77505
c	0.24104	0.65824	1.58742
c	0.10082	0.95545	3.00210
h	0.25058	2.00145	3.30541
o	1.18297	2.35428	-1.32518
o	0.10142	-0.63082	1.26662
c	-0.19542	-0.00724	3.92047
o	-0.31694	0.26552	5.22316
c	-0.65951	-0.83286	6.08905
c	-0.67452	-0.32660	7.51882
h	-0.34283	-1.05954	3.60887
h	-1.65798	-1.23088	5.79194
h	0.08986	-1.64818	5.95740
h	-0.94059	-1.15424	8.21062
h	0.32293	0.06714	7.80919
h	-1.42088	0.48715	7.64186
h	-0.31899	-2.18611	-4.81194
h	-0.96512	-0.24870	-6.29922
h	-1.18981	2.04974	-5.28526
h	-0.78750	2.38877	-2.84662
h	0.09395	-0.77999	0.27196

Transition State for EEZE isomer

E(B3LYP/def2-TZVP)=-1025.088955179

32

c	0.38521	1.75400	3.44851
c	0.32842	0.72085	2.47614
c	-0.00937	-0.58626	2.95115
c	-0.24257	-0.82838	4.31938
c	-0.17032	0.21090	5.24699
c	0.14430	1.51106	4.80152
o	0.59367	1.04594	1.21011
n	-0.13404	-1.74082	2.04885
o	-0.13251	-1.53510	0.82686
o	-0.24200	-2.86041	2.55070
c	-0.92205	0.98341	-0.00248
o	-1.89049	1.23919	0.62349
n	-0.44230	0.75907	-1.17572
c	0.78601	0.30053	-1.51197
o	1.73837	0.09208	-0.66421
c	1.06386	0.02557	-2.90379
c	0.10733	0.18407	-3.86546
o	0.33711	-0.08609	-5.14644
c	-0.72434	0.19014	-6.08659
c	-0.40301	-0.51020	-7.39225
h	2.07302	-0.33149	-3.15691
h	-0.90482	0.54084	-3.58787
h	-1.68957	-0.16660	-5.65962
h	-0.79159	1.29400	-6.22484
h	-1.19503	-0.29216	-8.14034
h	0.56874	-0.15927	-7.80016
h	-0.34731	-1.61054	-7.24972
h	-0.48505	-1.85774	4.61929
h	-0.36227	0.01314	6.31339
h	0.19983	2.34360	5.52245
h	0.63469	2.76096	3.07991
h	1.34357	0.38676	0.33426

Transition State for EZZE isomer

E(B3LYP/def2-TZVP)=-1025.088679583

32

c	-2.85546	-2.39361	1.40905
c	-2.46863	-2.86977	0.15465
c	-1.87536	-4.14756	-0.01231
c	-1.70592	-4.93471	1.16918
c	-2.08198	-4.44481	2.43475
c	-2.66111	-3.18149	2.56168
o	-1.51555	-4.51543	-1.24471
n	-1.13524	-6.28940	1.12863
o	-0.75109	-6.78684	2.18810
o	-1.07787	-6.86901	0.03545
c	-2.65161	-5.81376	-2.06579
n	-1.93778	-6.44794	-2.93751

c	-0.59582	-6.47822	-3.05223
c	-0.05104	-7.35208	-4.06751
h	-0.75797	-7.92356	-4.68607
o	-3.74131	-5.68103	-1.62925
o	0.21640	-5.78352	-2.31364
c	1.29824	-7.47767	-4.23517
o	1.82737	-8.27708	-5.15751
c	3.26823	-8.36906	-5.20306
c	3.65385	-9.21519	-6.40049
h	1.99748	-6.90538	-3.59364
h	3.69343	-7.34150	-5.27716
h	3.62570	-8.82599	-4.25152
h	4.75945	-9.30980	-6.45357
h	3.21862	-10.23406	-6.32093
h	3.29487	-8.75313	-7.34486
h	-1.90809	-5.09378	3.30489
h	-2.96480	-2.81092	3.55337
h	-3.31583	-1.39525	1.49370
h	-2.60647	-2.26789	-0.75680
h	-0.41406	-5.18058	-1.63965

Product Complex EEZE

E(B3LYP/def2-TZVP)=-1025.117420818

32

c	0.27589	1.59575	5.12820
c	0.83664	1.74549	3.86210
c	0.73556	0.72174	2.88443
c	0.03141	-0.46492	3.25896
c	-0.53303	-0.60853	4.54450
c	-0.41496	0.41351	5.48168
o	1.30145	0.94782	1.70042
n	-0.12915	-1.56407	2.32144
o	-0.75141	-2.56460	2.66415
o	0.38565	-1.43442	1.18535
c	-1.23381	0.50850	-0.43508
n	-0.62256	0.37137	-1.48848
c	0.74871	0.13945	-1.83246
c	0.98630	-0.01151	-3.26334
c	-0.00751	0.05188	-4.19338
o	0.22610	-0.08908	-5.50049
c	-0.91194	-0.00717	-6.38119
c	-0.42577	-0.19387	-7.80552
o	-1.93498	0.66370	0.49867
o	1.62841	0.08242	-0.98262
h	2.02982	-0.18594	-3.56562
h	-1.05762	0.22497	-3.88403
h	-1.64639	-0.79701	-6.09878
h	-1.40241	0.98563	-6.24883
h	-1.28424	-0.13555	-8.50845
h	0.30700	0.59483	-8.07951
h	0.06296	-1.18387	-7.92947
h	-1.06125	-1.54702	4.76526

h	-0.85588	0.30040	6.48419
h	0.37590	2.41309	5.86143
h	1.37794	2.65953	3.57345
h	1.19380	0.14208	1.10200

Product Complex EEZE
E(B3LYP/def2-TZVP)=-1025.117669801

32

c	-3.07854	-2.97735	2.60245
c	-2.71968	-2.06282	1.58522
c	-1.98647	-2.47764	0.47582
c	-1.57470	-3.82753	0.32677
c	-1.94693	-4.73768	1.36473
c	-2.69042	-4.30879	2.48494
o	-0.87708	-4.13907	-0.76448
n	-1.57044	-6.14041	1.29728
o	-0.90118	-6.51243	0.30434
o	-1.91103	-6.90049	2.19836
c	-2.70673	-6.59365	-2.12545
o	-3.59772	-6.22576	-1.44860
n	-1.88266	-7.04951	-2.90900
c	-0.47679	-6.93428	-3.09216
o	0.21377	-6.19860	-2.39198
c	0.01511	-7.77063	-4.18564
c	1.34589	-7.76531	-4.47815
o	1.87461	-8.49846	-5.45883
c	3.29936	-8.39413	-5.65605
c	3.68722	-9.29384	-6.81348
h	-0.69310	-8.39198	-4.75432
h	2.03374	-7.12946	-3.88492
h	3.55831	-7.33028	-5.86631
h	3.81748	-8.69763	-4.71674
h	4.78249	-9.23209	-6.98939
h	3.42561	-10.35172	-6.59702
h	3.16446	-8.98752	-7.74475
h	-2.94452	-5.06208	3.24414
h	-3.65890	-2.64396	3.47659
h	-3.02153	-1.00550	1.66670
h	-1.70046	-1.77663	-0.32335
h	-0.61798	-5.11498	-0.74572

Molecular energies (in a.u.) and molecular structures of 7b (Table S2)

2NH-EEEE
E(B3LYP/def2-TZVP)=-1064.409226655

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c	-1.55348	-5.59376	0.90097
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c	-1.67437	-6.09667	2.19913
c	-1.78244	-5.20137	3.27798
c	-1.77824	-3.81695	3.06534
c	-1.64399	-3.29418	1.76493
c	-1.52240	-4.20566	0.68812
o	-1.60800	-1.94390	1.51757
c	-2.51873	-1.11407	2.17039
n	-2.20627	0.21538	1.97690
c	-0.93198	0.83529	1.60776
c	-0.42562	0.64635	0.25153
c	0.98443	1.09877	-0.01927
n	-1.34589	-3.74130	-0.69782
o	-1.87398	-4.41133	-1.58844
o	-3.46555	-1.51551	2.81411
o	-0.66428	-2.73250	-0.87801
o	-0.40349	1.55810	2.44402
c	-1.26672	0.20798	-0.73662
o	-0.88661	0.11837	-2.01074
c	-1.85987	-0.24559	-3.00764
c	-1.29696	-1.33220	-3.90762
h	-2.71462	0.79888	2.65213
h	1.22570	1.01980	-1.09781
h	1.71435	0.48128	0.55104
h	1.13033	2.14969	0.31369
h	-2.31602	-0.06590	-0.51643
h	-2.79437	-0.58452	-2.50349
h	-2.09687	0.67798	-3.58448
h	-2.01451	-1.54450	-4.73008
h	-0.33583	-1.00582	-4.36016
h	-1.12473	-2.26313	-3.32866
h	-1.47643	-6.25485	0.02542
h	-1.68251	-7.18453	2.37026
h	-1.87776	-5.58463	4.30662
h	-1.88644	-3.12486	3.91103

2NH-EEEZ
E(B3LYP/def2-TZVP)=-1064.415662908

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c	-2.13512	-5.63856	1.47655
c	-2.19442	-4.96600	2.70939
c	-1.91531	-3.59511	2.77718
c	-1.54806	-2.87511	1.62699
c	-1.47019	-3.56444	0.39222
c	-1.77961	-4.93281	0.32262
o	-1.25959	-1.54580	1.79962
c	-1.91465	-0.60381	0.99222
o	-2.86300	-0.87830	0.29184
n	-0.99957	-2.91963	-0.85583
o	-0.30548	-1.90721	-0.74963
n	-1.31388	0.61119	1.23367
c	-1.31667	1.84463	0.48375
o	-0.26702	2.48024	0.50655

c	-2.51046	2.32307	-0.22515
c	-3.76165	1.86497	0.07515
o	-4.85929	2.36860	-0.50988
c	-6.11012	1.74422	-0.17283
c	-7.21795	2.45941	-0.92325
c	-2.27969	3.45142	-1.19812
o	-1.29549	-3.46400	-1.91675
h	-0.43652	0.54101	1.76331
h	-3.21979	3.72233	-1.71868
h	-1.51521	3.17081	-1.95523
h	-1.88610	4.35055	-0.67405
h	-3.93460	1.06479	0.81279
h	-6.06367	0.66580	-0.45100
h	-6.26556	1.80877	0.93035
h	-8.19921	1.99689	-0.68288
h	-7.25718	3.53359	-0.64167
h	-7.05777	2.39167	-2.02064
h	-1.72135	-5.41955	-0.66175
h	-2.36311	-6.71417	1.41376
h	-2.47213	-5.50980	3.62669
h	-1.97905	-3.04193	3.72675

2NH-EEZE
E(B3LYP/def2-TZVP)=-1064.414898082

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c	-2.48502	-5.28064	1.13663
c	-1.89636	-4.77068	2.30714
c	-1.39868	-3.46167	2.33218
c	-1.45855	-2.64713	1.18872
c	-2.03100	-3.17446	0.00567
c	-2.55438	-4.47823	-0.00683
o	-0.90797	-1.39567	1.30415
c	-1.66892	-0.30517	0.96111
o	-2.85358	-0.34096	0.70439
n	-2.05143	-2.43204	-1.27475
o	-1.22832	-1.52724	-1.42685
n	-0.91518	0.85697	0.95313
c	0.41951	1.10470	1.39585
o	1.01249	0.34629	2.14731
c	1.01112	2.37259	0.89046
c	0.59422	2.91204	-0.29245
o	1.12682	4.04116	-0.79456
c	0.77292	4.38061	-2.14513
c	1.32775	5.75878	-2.45355
c	2.16106	2.94034	1.67754
o	-2.86124	-2.79613	-2.12480
h	-1.46648	1.66382	0.65025
h	2.73203	3.67651	1.07703
h	2.83319	2.11692	2.00069
h	1.80690	3.44828	2.60419
h	-0.18083	2.42746	-0.91874
h	1.19472	3.61399	-2.83721

h	-0.33831	4.36119	-2.25052
h	1.07360	6.04517	-3.49645
h	0.90140	6.51977	-1.76526
h	2.43364	5.77141	-2.34640
h	-3.00596	-4.83755	-0.94264
h	-2.88760	-6.30543	1.11263
h	-1.83228	-5.39348	3.21390
h	-0.94988	-3.02928	3.23924

2NH-EEZZ
E(B3LYP/def2-TZVP)=-1064.414709522

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c	-1.82717	-2.44763	1.10980
o	-1.69556	-1.08956	1.21055
c	-2.10991	-0.29274	0.11817
n	-1.34379	0.85030	0.17591
o	-2.95932	-0.61707	-0.66932
c	-1.47930	2.00356	-0.65361
c	-0.24205	2.81532	-0.79002
o	-2.53885	2.28817	-1.18800
c	-0.41508	4.24410	-1.22948
c	0.98636	2.23792	-0.63199
o	2.12868	2.93284	-0.77960
c	3.34726	2.17053	-0.80719
c	4.51733	3.13532	-0.76989
c	-0.66766	-3.25401	1.01255
c	-0.75967	-4.65468	1.02467
c	-2.01837	-5.26387	1.07623
c	-3.17746	-4.46981	1.14308
c	-3.08421	-3.07095	1.16996
n	0.67827	-2.65345	0.89401
o	1.62520	-3.30745	1.32761
o	0.77524	-1.55109	0.34598
h	-0.54985	0.80232	0.81918
h	0.53144	4.65625	-1.63349
h	-0.74174	4.89267	-0.38393
h	-1.21060	4.30205	-2.00306
h	1.11087	1.15911	-0.40992
h	3.36717	1.47610	0.06630
h	3.36808	1.55089	-1.73456
h	5.47473	2.57216	-0.79803
h	4.48996	3.82246	-1.64280
h	4.49616	3.74748	0.15720
h	0.17015	-5.24031	0.98243
h	-2.09602	-6.36248	1.06552
h	-4.17031	-4.94649	1.18302
h	-3.97998	-2.43796	1.24373

2NH-EZEE
E(B3LYP/def2-TZVP)=-1064.411293140

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c	-2.25060	-4.56877	2.15609
c	-3.62476	-4.31009	2.13171
c	-4.09134	-3.09752	1.59559
c	-3.18395	-2.14999	1.10504
c	-1.80100	-2.40160	1.11390
c	-1.33980	-3.63511	1.63414
o	-1.00489	-1.41785	0.58102
c	0.07589	-0.95563	1.31452
n	0.82130	-0.05054	0.58426
c	0.56859	0.65994	-0.63989
c	0.06780	-0.07848	-1.81875
c	0.19256	-1.56652	-2.03497
n	0.08315	-4.04195	1.60327
o	0.44657	-4.88097	2.42239
o	0.29276	-1.25981	2.46694
o	0.79945	-3.55230	0.72817
o	0.85695	1.85482	-0.64280
c	-0.43806	0.72769	-2.80046
o	-0.88360	0.22551	-3.96125
c	-1.37925	1.16722	-4.92817
c	-1.85747	0.39605	-6.14424
h	1.44750	0.48802	1.19403
h	-0.79692	-2.07449	-2.02756
h	0.81945	-2.05184	-1.26270
h	0.64655	-1.76071	-3.03244
h	-0.48642	1.82465	-2.66433
h	-2.20987	1.75612	-4.47236
h	-0.56288	1.87761	-5.19720
h	-2.24411	1.09969	-6.91219
h	-1.02586	-0.18926	-6.59181
h	-2.67173	-0.30851	-5.87047
h	-1.84276	-5.50194	2.57075
h	-4.33090	-5.05501	2.53076
h	-5.17116	-2.87918	1.57097
h	-3.52299	-1.18127	0.70739

2NH-EZEZ
E(B3LYP/def2-TZVP)=-1064.415459278

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c	-1.13269	-4.52105	0.03088
c	-1.82126	-5.43110	0.83906
c	-2.59893	-4.95657	1.90960
c	-2.69533	-3.58086	2.15393
c	-2.00218	-2.65483	1.35516
c	-1.20507	-3.14233	0.29038
o	-2.12985	-1.33234	1.69361
c	-2.54519	-0.42750	0.70475
n	-2.34807	0.83979	1.20708
c	-2.49367	2.09559	0.53327
c	-3.65203	2.28448	-0.36589

c	-4.91413	1.45970	-0.32630
n	-0.36478	-2.25775	-0.54942
o	0.02501	-2.70499	-1.62541
o	-3.01717	-0.76631	-0.35448
o	-0.07361	-1.14755	-0.09972
o	-1.66725	2.96359	0.80373
c	-3.52913	3.35514	-1.20708
o	-4.50210	3.70834	-2.05885
c	-4.24606	4.84940	-2.89606
c	-5.46987	5.09253	-3.75953
h	-1.66907	0.89860	1.97491
h	-5.78424	2.09510	-0.59674
h	-5.09029	1.04304	0.68844
h	-4.87673	0.60146	-1.03020
h	-2.60963	3.97020	-1.19813
h	-4.02506	5.73322	-2.25248
h	-3.34576	4.64666	-3.52224
h	-5.29908	5.96845	-4.42139
h	-5.68519	4.20800	-4.39646
h	-6.36304	5.29607	-3.13056
h	-0.51295	-4.84821	-0.81642
h	-1.74886	-6.51087	0.63483
h	-3.14705	-5.66246	2.55434
h	-3.31783	-3.18423	2.97054

2NH-EZZE

E(B3LYP/def2-TZVP)=-1064.416583725

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c	-2.58855	-5.16397	0.56608
c	-2.80557	-5.38741	1.92947
c	-2.38371	-4.42615	2.86453
c	-1.76695	-3.24564	2.43154
c	-1.53894	-3.01080	1.06477
c	-1.94401	-3.99441	0.12983
o	-0.89143	-1.84314	0.74991
c	-1.45296	-1.00569	-0.18060
n	-0.60908	0.04296	-0.51129
c	0.69285	0.38210	-0.05485
c	1.26806	1.56149	-0.76422
c	0.55641	2.29793	-1.87209
n	-1.66016	-3.88872	-1.31933
o	-2.34435	-4.57131	-2.07882
o	-2.56838	-1.13305	-0.64027
o	-0.72957	-3.16104	-1.66865
o	1.26225	-0.23627	0.83464
c	2.51081	1.92712	-0.33612
o	3.18511	2.96356	-0.85606
c	4.49920	3.20826	-0.32465
c	5.06645	4.44295	-0.99949
h	-1.03324	0.64383	-1.22256
h	1.19492	3.11911	-2.25740
h	-0.39877	2.76195	-1.52932

h	0.31864	1.63268	-2.73461
h	2.99651	1.35229	0.47529
h	4.42625	3.35032	0.77924
h	5.14062	2.31584	-0.51412
h	6.08535	4.65403	-0.60961
h	5.13564	4.29586	-2.09864
h	4.42566	5.32950	-0.80500
h	-2.90193	-5.88813	-0.19953
h	-3.30071	-6.31317	2.26227
h	-2.54529	-4.59068	3.94217
h	-1.44501	-2.46833	3.14097

2NH-EZZZ

E(B3LYP/def2-TZVP)=-1064.416538143

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c	-3.15636	-3.13016	1.39830
c	-1.83191	-2.79497	1.06640
c	-0.91002	-3.83483	0.80177
c	-1.29204	-5.18122	0.90463
c	-2.61629	-5.50371	1.22133
c	-3.54484	-4.47587	1.46310
o	-1.38705	-1.50006	1.06615
c	-2.00253	-0.55395	0.22328
o	-3.07857	-0.69894	-0.29446
n	0.48551	-3.54448	0.40120
o	0.70252	-2.51201	-0.23376
n	-1.12214	0.50792	0.15098
c	-1.36131	1.75526	-0.48612
o	-2.45790	2.04714	-0.94185
c	-0.15799	2.63227	-0.52462
c	-0.35989	3.84203	-1.12250
o	0.60733	4.76196	-1.24943
c	0.25983	5.97218	-1.94480
c	1.46887	6.88843	-1.94384
c	1.18238	2.22654	0.03617
o	1.33698	-4.37878	0.70957
h	-0.19567	0.32441	0.54583
h	1.93026	3.02559	-0.14373
h	1.57285	1.29555	-0.43664
h	1.14642	2.05510	1.13803
h	-1.36147	4.08799	-1.52494
h	-0.05104	5.71789	-2.98529
h	-0.60887	6.45003	-1.43428
h	1.22990	7.83214	-2.47949
h	1.77256	7.14185	-0.90549
h	2.33092	6.40575	-2.45221
h	-0.53100	-5.95366	0.72166
h	-2.92397	-6.55944	1.28297
h	-4.58842	-4.72355	1.71639
h	-3.87081	-2.32193	1.60657

2NH-ZEEE

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E(B3LYP/def2-TZVP)=-1064.405885218

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c	-2.03893	-5.90231	1.58221
c	-2.45482	-5.22441	2.74014
c	-2.25015	-3.84388	2.88550
c	-1.59976	-3.11709	1.86978
c	-1.15960	-3.81795	0.72222
c	-1.39591	-5.19040	0.56311
o	-1.34959	-1.76787	1.92114
c	-2.26029	-0.89079	2.48729
o	-3.26825	-1.21809	3.07830
n	-0.42419	-3.12040	-0.34621
o	0.53323	-2.42676	-0.01807
n	-1.82741	0.41375	2.36186
c	-0.78804	1.04709	1.61359
o	-0.25787	2.03413	2.11403
c	-0.45086	0.57540	0.25220
c	-1.33168	-0.03034	-0.59864
o	-2.58047	-0.41095	-0.27296
c	-3.37766	-1.00277	-1.31840
c	-4.75627	-1.29044	-0.75398
c	0.91443	0.98084	-0.24589
o	-0.81795	-3.29925	-1.50523
h	-2.25053	1.04050	3.05516
h	1.07020	0.66600	-1.29901
h	1.71293	0.51030	0.37003
h	1.05165	2.08155	-0.17100
h	-1.02251	-0.24844	-1.63988
h	-3.43308	-0.29360	-2.17737
h	-2.87527	-1.93500	-1.66749
h	-5.38806	-1.77397	-1.52975
h	-4.69130	-1.97113	0.12218
h	-5.25536	-0.35352	-0.42610
h	-1.05946	-5.67986	-0.36323
h	-2.21165	-6.98453	1.47310
h	-2.95843	-5.77590	3.55050
h	-2.60564	-3.31635	3.77862

2NH-ZEEZ
E(B3LYP/def2-TZVP)=-1064.411404609

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c	-2.48514	-4.94612	2.51132
c	-2.20667	-3.57769	2.62077
c	-1.59824	-2.87708	1.56431
c	-1.27656	-3.58448	0.38041
c	-1.58382	-4.94989	0.26243
c	-2.18080	-5.63592	1.32498
o	-1.33604	-1.54912	1.77801
c	-1.81312	-0.61254	0.84660
n	-1.23321	0.59368	1.16730

c	-1.33085	1.86002	0.52393
c	-2.55041	2.23480	-0.22825
c	-2.33267	3.26001	-1.31542
n	-0.55106	-2.96012	-0.74993
o	-0.63139	-3.51246	-1.84450
o	-2.61072	-0.88280	-0.01920
o	0.12030	-1.95477	-0.51222
o	-0.37017	2.61578	0.63292
c	-3.81391	1.84768	0.10718
o	-4.12630	1.09213	1.17314
c	-5.38833	0.40926	1.12060
c	-5.64045	-0.23790	2.46967
h	-0.40933	0.53763	1.77697
h	-3.28575	3.51549	-1.82549
h	-1.61589	2.88796	-2.08105
h	-1.89399	4.19182	-0.89555
h	-4.67749	2.20665	-0.49127
h	-6.19072	1.14461	0.86856
h	-5.34650	-0.35585	0.31222
h	-6.62146	-0.75987	2.46298
h	-4.85045	-0.98528	2.69924
h	-5.65144	0.52286	3.27996
h	-1.33000	-5.45024	-0.68342
h	-2.40577	-6.70965	1.22787
h	-2.95416	-5.47475	3.35690
h	-2.45568	-3.01107	3.53140

2NH-ZEZE
E(B3LYP/def2-TZVP)=-1064.416351357

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c	-2.50797	-4.46180	2.71627
c	-1.96419	-3.18148	2.55572
c	-1.60569	-2.70310	1.28316
c	-1.80469	-3.54560	0.16186
c	-2.37727	-4.81835	0.32386
c	-2.72484	-5.28320	1.59606
o	-1.04311	-1.45439	1.24159
c	-1.55874	-0.51996	0.37384
n	-0.77317	0.61545	0.30310
c	0.45494	0.93568	0.92456
c	1.08486	2.21883	0.47389
c	2.38698	2.53776	1.16448
n	-1.36975	-3.17877	-1.20415
o	-1.89805	-3.77194	-2.14266
o	-2.60160	-0.65094	-0.23367
o	-0.47650	-2.33755	-1.31478
o	0.98804	0.23346	1.77198
c	0.60081	3.07084	-0.47445
o	-0.58317	2.91884	-1.11795
c	-0.79741	3.69727	-2.30946
c	-2.24319	3.53293	-2.73811
h	-1.13894	1.30568	-0.36729

h	2.83266	3.47962	0.77993
h	3.11895	1.71221	1.02585
h	2.24021	2.63822	2.26273
h	1.16973	3.98033	-0.75415
h	-0.55654	4.76399	-2.08779
h	-0.09778	3.34229	-3.10173
h	-2.42865	4.11389	-3.66685
h	-2.47771	2.46596	-2.94241
h	-2.93563	3.89915	-1.95021
h	-2.52882	-5.42693	-0.57926
h	-3.16130	-6.28760	1.71315
h	-2.77394	-4.81625	3.72525
h	-1.80189	-2.51105	3.41324

2NH-ZEZZ
E(B3LYP/def2-TZVP)=-1064.414956284

35

c	-3.21875	-3.07221	0.94924
c	-1.85405	-2.74149	0.81641
c	-0.88974	-3.76149	1.03728
c	-1.27150	-5.05898	1.40801
c	-2.62856	-5.37972	1.51684
c	-3.59100	-4.38275	1.28318
o	-1.36417	-1.49577	0.56143
c	-2.10655	-0.41500	0.05389
o	-3.30036	-0.39838	-0.11160
n	0.55543	-3.49574	0.88863
o	0.90701	-2.71796	-0.00126
n	-1.17112	0.57054	-0.18653
c	-1.44407	1.89911	-0.59017
o	-2.57900	2.31708	-0.76509
c	-0.24586	2.77380	-0.76819
c	1.05774	2.40735	-0.59457
o	1.48096	1.15760	-0.29728
c	2.84486	0.97425	0.13913
c	3.36885	-0.35566	-0.36981
c	-0.57394	4.18993	-1.17171
o	1.31784	-4.09316	1.64817
h	-0.18202	0.30834	-0.06198
h	0.34288	4.80971	-1.26810
h	-1.25085	4.66680	-0.42919
h	-1.11812	4.21006	-2.14178
h	1.86755	3.15340	-0.72549
h	3.45437	1.82649	-0.24215
h	2.85522	1.01807	1.25287
h	4.40173	-0.51428	0.01030
h	2.73580	-1.20399	-0.03021
h	3.39997	-0.36860	-1.48051
h	-0.48070	-5.79959	1.59764
h	-2.93374	-6.40259	1.78740
h	-4.66335	-4.62165	1.37232
h	-3.97073	-2.29090	0.78668

2NH-ZZEE

E(B3LYP/def2-TZVP)=-1064.405006331

35

c	-3.83472	-3.96928	1.60046
c	-4.14030	-2.71986	1.03383
c	-3.11129	-1.84493	0.66248
c	-1.76355	-2.20778	0.82438
c	-1.46284	-3.47610	1.37547
c	-2.49712	-4.33783	1.77671
o	-0.83200	-1.29234	0.39751
c	0.15098	-0.88158	1.27979
o	0.19069	-1.19824	2.44804
n	-0.08066	-3.98617	1.50901
o	0.77335	-3.53966	0.73919
n	1.03890	-0.01292	0.67169
c	1.06600	0.64092	-0.59975
o	1.62925	1.72347	-0.65711
c	0.50947	-0.07992	-1.78436
c	-0.32839	0.57824	-2.62837
o	-0.85368	1.79148	-2.36201
c	-1.39601	2.51294	-3.47149
c	-2.13506	3.72777	-2.93948
c	1.00078	-1.47468	-2.09224
o	0.11915	-4.85730	2.35017
h	1.64740	0.45400	1.35461
h	0.56438	-1.83812	-3.04782
h	0.74152	-2.20613	-1.29649
h	2.10979	-1.49013	-2.20202
h	-0.67193	0.09766	-3.56880
h	-0.56717	2.82003	-4.15301
h	-2.08143	1.84610	-4.05107
h	-2.55478	4.31947	-3.78130
h	-2.96910	3.42235	-2.27153
h	-1.44650	4.37904	-2.35989
h	-2.21408	-5.30273	2.22167
h	-4.63814	-4.65760	1.90625
h	-5.18979	-2.41562	0.89153
h	-3.32403	-0.85007	0.24233

2NH-ZZEE

E(B3LYP/def2-TZVP)=-1064.407877132

35

c	-1.82292	-5.37644	0.61384
c	-2.52263	-4.97190	1.76396
c	-2.61366	-3.61294	2.09076
c	-1.98986	-2.63562	1.29582
c	-1.26960	-3.05314	0.14996
c	-1.20528	-4.41412	-0.19152

1				
2				
3				
4	o	-2.10541	-1.33531	1.71568
5	c	-2.58406	-0.37791	0.80920
6	o	-3.09984	-0.65817	-0.24801
7	n	-0.49990	-2.11286	-0.69648
8	o	-0.15769	-1.04062	-0.19444
9	n	-2.39431	0.85698	1.38651
10	c	-2.54217	2.15977	0.79922
11	o	-1.76625	3.02341	1.18370
12	c	-3.66147	2.37666	-0.14873
13	c	-3.51838	3.29519	-1.15160
14	o	-2.39766	3.98012	-1.41056
15	c	-2.38842	4.77981	-2.60074
16	c	-1.09609	5.57461	-2.62899
17	c	-4.99496	1.69015	0.04707
18	o	-0.21355	-2.48226	-1.83280
19	h	-1.72989	0.87195	2.16947
20	h	-5.76409	2.14336	-0.61535
21	h	-5.35561	1.79910	1.09536
22	h	-4.94292	0.60496	-0.18507
23	h	-4.37220	3.49126	-1.83314
24	h	-2.46862	4.11355	-3.49282
25	h	-3.27617	5.45720	-2.59831
26	h	-1.05506	6.20303	-3.54449
27	h	-1.02247	6.23620	-1.73955
28	h	-0.21795	4.89423	-2.62790
29	h	-0.64861	-4.68634	-1.09984
30	h	-1.75628	-6.44229	0.34473
31	h	-3.01409	-5.71943	2.40734
32	h	-3.17760	-3.26990	2.97161
33				
34				

2NH-ZZZE
E(B3LYP/def2-TZVP)=-1064.407500936

35				
36				
37				
38				
39				
40	c	-2.87298	-5.40656	1.88978
41	c	-2.44480	-4.46643	2.84336
42	c	-1.80862	-3.28782	2.43415
43	c	-1.56707	-3.03359	1.07292
44	c	-1.97885	-3.99666	0.11939
45	c	-2.64267	-5.16410	0.53189
46	o	-0.90130	-1.87079	0.78233
47	c	-1.44376	-1.01022	-0.13979
48	o	-2.55903	-1.11636	-0.60687
49	n	-1.68236	-3.87228	-1.32558
50	o	-0.73954	-3.15170	-1.65659
51	n	-0.58301	0.02838	-0.45229
52	c	0.72673	0.34278	0.02595
53	o	1.26073	-0.28665	0.92382
54	c	1.33367	1.50568	-0.68351
55	c	2.57296	1.96285	-0.32014
56	o	3.33480	1.45778	0.65246
57	c	4.59766	2.10144	0.88458
58	c	5.32105	1.34037	1.97968
59				
60				

1
2
3 c 0.61963 2.20246 -1.82241
4 o -2.36907 -4.53409 -2.10118
5 h -0.99773 0.64101 -1.15840
6 h 1.24084 3.02451 -2.23842
7 h -0.34396 2.66745 -1.50358
8 h 0.39604 1.51093 -2.66798
9 h 3.00673 2.82644 -0.86761
10 h 5.18953 2.10416 -0.06160
11 h 4.42006 3.16246 1.18252
12 h 6.30353 1.81559 2.18905
13 h 4.72199 1.33648 2.91497
14 h 5.49391 0.28614 1.67548
15 h -2.96009 -5.87143 -0.24762
16 h -3.38341 -6.33056 2.20387
17 h -2.61693 -4.64600 3.91699
18 h -1.48131 -2.52644 3.15825
19
20
21

22 2NH-ZZZZ
23 E(B3LYP/def2-TZVP)=-1064.407425375
24

25 35
26

27 c -3.59200 -4.21762 1.65225
28 c -3.14556 -2.89149 1.56180
29 c -1.84623 -2.61661 1.09817
30 c -1.01041 -3.69812 0.73051
31 c -1.44719 -5.02541 0.85954
32 c -2.74683 -5.28699 1.30690
33 o -1.33007 -1.35064 1.06581
34 c -2.00576 -0.32379 0.37341
35 n -1.07169 0.67639 0.19854
36 c -1.32393 1.97932 -0.33210
37 c -0.07879 2.76931 -0.53984
38 c 1.28600 2.18441 -0.24378
39 n 0.34976 -3.47239 0.19111
40 o 1.18597 -4.35012 0.40757
41 o -3.15981 -0.37181 0.03639
42 o 0.55260 -2.44680 -0.45958
43 o -2.45670 2.36060 -0.57074
44 c -0.14913 4.05085 -1.01924
45 o -1.27171 4.70374 -1.32577
46 c -1.12667 6.03916 -1.83561
47 c -2.51218 6.58734 -2.12140
48 h -0.11251 0.40466 0.42962
49 h 2.09146 2.90872 -0.49071
50 h 1.49124 1.26251 -0.83694
51 h 1.41517 1.92466 0.83408
52 h 0.79329 4.61754 -1.17526
53 h -0.59334 6.66515 -1.08085
54 h -0.50562 6.01344 -2.76251
55 h -2.43788 7.62233 -2.51896
56 h -3.03611 5.95571 -2.86988
57 h -3.12490 6.60509 -1.19522
58 h -0.74827 -5.83144 0.59297
59
60

h	-3.09986	-6.32692	1.39027
h	-4.61543	-4.41694	2.00949
h	-3.79379	-2.05321	1.85037

3OH-EEEE
E(B3LYP/def2-TZVP)=-1064.385454852

35

c	-1.94905	-5.28329	1.24726
c	-2.11043	-5.82504	2.53519
c	-1.74198	-5.09025	3.66497
c	-1.20940	-3.79798	3.50696
c	-1.06724	-3.24508	2.22906
c	-1.43837	-3.96918	1.08221
o	-1.20973	-3.34602	-0.11898
c	-2.17976	-3.21276	-1.07179
o	-3.41830	-3.35739	-0.55508
n	-2.27480	-6.16397	0.10840
o	-1.87097	-5.82468	-1.01005
n	-1.95491	-2.93083	-2.28564
c	-0.64990	-2.69181	-2.80799
o	-0.01921	-1.68418	-2.50181
c	-0.14393	-3.68733	-3.77425
c	-0.90157	-4.78371	-4.06915
o	-0.49494	-5.74939	-4.91257
c	-1.36306	-6.88536	-5.05721
c	-1.22406	-7.87714	-3.90880
c	1.22017	-3.44062	-4.35773
o	-2.89688	-7.19823	0.33870
h	1.50424	-4.24590	-5.06517
h	1.99010	-3.37721	-3.55637
h	1.24943	-2.46393	-4.89003
h	-1.90426	-4.91083	-3.62094
h	-2.41672	-6.53232	-5.15804
h	-1.06549	-7.34602	-6.02274
h	-1.85369	-8.77309	-4.10580
h	-0.16826	-8.20989	-3.80800
h	-1.54790	-7.43206	-2.94235
h	-2.52153	-6.84176	2.61065
h	-1.86391	-5.52744	4.66829
h	-0.90977	-3.20904	4.38882
h	-0.66820	-2.23036	2.07931
h	-4.03972	-3.23035	-1.30944

3OH-EEZE
E(B3LYP/def2-TZVP)=-1064.403330874

35

c	-1.76843	-4.60902	1.68783
c	-2.38398	-3.84963	2.68604

c	-3.03136	-2.64792	2.34301
c	-3.07176	-2.22224	1.01024
c	-2.44790	-2.96558	-0.01017
c	-1.78168	-4.16522	0.35312
o	-2.50023	-2.48003	-1.27711
c	-3.13916	-3.29999	-2.31118
n	-2.96643	-2.74115	-3.52700
c	-1.86107	-2.16819	-3.94626
c	-1.82511	-1.37886	-5.17930
c	-0.53665	-0.73717	-5.62062
n	-1.04079	-4.98032	-0.62153
o	-0.82505	-6.15287	-0.34186
o	-3.78472	-4.27000	-1.98870
o	-0.62660	-4.44159	-1.66370
o	-0.66648	-2.26643	-3.35223
c	-2.99027	-1.27180	-5.88679
o	-3.07995	-0.55879	-7.01761
c	-4.34197	-0.59688	-7.70745
c	-4.26427	0.34035	-8.89803
h	-0.67995	-0.19325	-6.57589
h	0.26291	-1.49794	-5.76019
h	-0.15951	-0.02015	-4.85778
h	-3.90241	-1.78740	-5.53084
h	-4.54723	-1.64394	-8.03170
h	-5.15171	-0.29049	-7.00448
h	-5.22714	0.32913	-9.45227
h	-4.06029	1.38187	-8.56877
h	-3.45578	0.02912	-9.59364
h	-1.25432	-5.55439	1.91313
h	-2.35877	-4.19395	3.73178
h	-3.52221	-2.04224	3.12205
h	-3.59583	-1.30040	0.71531
h	-0.72800	-2.84807	-2.53859

3OH-EZZE
E(B3LYP/def2-TZVP)=-1064.404100222

35

c	-2.85624	-2.70420	2.46798
c	-2.89226	-2.20614	1.16042
c	-2.40996	-2.96726	0.07850
c	-1.89060	-4.25932	0.35236
c	-1.88550	-4.77235	1.66215
c	-2.35840	-3.99554	2.72271
o	-2.45047	-2.40831	-1.15902
n	-1.29413	-5.10876	-0.69008
o	-1.23242	-6.31348	-0.48086
o	-0.83586	-4.57172	-1.71435
c	-3.18912	-3.09786	-2.21196
n	-3.01116	-2.46497	-3.39440
c	-1.85904	-2.03905	-3.85030
c	-1.83710	-1.18683	-5.03832
c	-3.14628	-0.76898	-5.65091

1
2
3 o -3.90251 -4.03370 -1.93632
4 o -0.65983 -2.35470 -3.33559
5 c -0.62488 -0.80802 -5.54484
6 o -0.51654 -0.01876 -6.62502
7 c 0.81512 0.28871 -7.06907
8 c 0.71769 1.19155 -8.28446
9 h -2.97823 -0.18427 -6.57750
10 h -3.74090 -0.15092 -4.94202
11 h -3.77075 -1.65792 -5.88684
12 h 0.31756 -1.14340 -5.07435
13 h 1.37074 0.78839 -6.24057
14 h 1.34724 -0.66049 -7.31544
15 h 1.73535 1.44822 -8.64912
16 h 0.16652 0.68802 -9.10735
17 h 0.18628 2.13474 -8.03401
18 h -1.49088 -5.78664 1.81804
19 h -2.33839 -4.39648 3.74818
20 h -3.23415 -2.08326 3.29639
21 h -3.30381 -1.21068 0.93404
22 h -0.76377 -2.97336 -2.55608
23
24
25

26 3OH-ZEZZ
27 E(B3LYP/def2-TZVP)=-1064.398680790
28

29 35
30

31 c -3.22273 -2.89605 0.80182
32 c -1.83770 -2.68710 0.71951
33 c -0.94818 -3.73918 1.02211
34 c -1.49470 -4.99012 1.41485
35 c -2.87831 -5.17841 1.52794
36 c -3.75174 -4.13327 1.20505
37 o 0.41336 -3.66363 1.04048
38 c 1.19640 -2.64118 0.55659
39 n 2.49676 -2.97468 0.70197
40 c 3.41759 -2.10865 0.29288
41 c 4.83963 -2.41041 0.38532
42 c 5.82027 -1.33506 -0.01946
43 n -0.62474 -6.14918 1.72156
44 o -0.97597 -6.86856 2.65857
45 o 0.70942 -1.59686 0.07173
46 o 0.35815 -6.33437 1.00787
47 o 3.13246 -0.91122 -0.22490
48 c 5.30707 -3.63806 0.79913
49 o 4.54920 -4.67848 1.11420
50 c 5.15407 -5.86973 1.64199
51 c 4.29709 -7.05574 1.23395
52 h 6.86870 -1.67732 0.11330
53 h 5.68004 -0.40892 0.58113
54 h 5.68512 -1.04174 -1.08452
55 h 6.40513 -3.80107 0.85628
56 h 6.20006 -5.96047 1.26185
57 h 5.19770 -5.76807 2.75116
58 h 4.67278 -7.98205 1.71992
59
60

h 3.23921 -6.89625 1.53575
h 4.31864 -7.20043 0.13256
h -3.24435 -6.15811 1.86860
h -4.84073 -4.28341 1.27323
h -3.90023 -2.06286 0.55300
h -1.42439 -1.71592 0.42298
h 2.10132 -0.87060 -0.23936

3OH-ZZZZ

E(B3LYP/def2-TZVP)=-1064.404075145

35

c -3.51965 -4.07017 1.67051
c -2.59291 -3.50076 2.56096
c -1.25289 -3.35146 2.18161
c -0.80439 -3.78320 0.92046
c -1.74056 -4.37671 0.03816
c -3.08919 -4.49995 0.41096
o 0.53326 -3.62430 0.66580
c 0.94371 -2.98151 -0.48163
o 0.10902 -2.42249 -1.22100
n -1.35459 -4.95285 -1.26948
o -0.18523 -5.31055 -1.41336
n 2.29058 -3.02833 -0.60809
c 2.81727 -2.44433 -1.68717
o 2.10552 -1.82609 -2.61811
c 4.26816 -2.49829 -1.85062
c 4.92995 -1.94365 -2.91733
o 4.36463 -1.27349 -3.92461
c 5.23130 -0.84349 -4.98764
c 4.42551 0.02675 -5.93396
c 5.05770 -3.21334 -0.77966
o -2.24045 -5.07823 -2.11293
h 6.14532 -3.20011 -1.00652
h 4.72804 -4.27003 -0.67930
h 4.89854 -2.74578 0.21633
h 6.03441 -2.04175 -2.96718
h 6.09291 -0.28057 -4.55590
h 5.63465 -1.74149 -5.51238
h 5.06569 0.36505 -6.77688
h 3.56455 -0.53901 -6.34927
h 4.03122 0.92188 -5.40721
h -3.77960 -4.94981 -0.31694
h -4.57700 -4.18253 1.95735
h -2.91699 -3.15840 3.55704
h -0.51306 -2.88848 2.85222
h 1.12269 -1.91197 -2.29758

Transition state for the direct 2NH to Phenol Hydrogen Transfer

E(B3LYP/def2-TZVP)=-1064.356609029

1				
2				
3		35		
4				
5	c	-2.67858	-4.72493	1.65387
6	c	-2.79491	-3.34388	1.78739
7	c	-1.86933	-2.44150	1.17610
8	c	-0.81630	-3.05148	0.40662
9	c	-0.68666	-4.45299	0.30863
10	c	-1.61592	-5.29473	0.91525
11	o	-1.99371	-1.15402	1.37525
12	c	-3.38348	0.32796	0.49911
13	n	-2.23386	0.81741	0.20593
14	c	-2.08200	2.05962	-0.57386
15	c	-0.71767	2.59521	-0.54321
16	c	0.39051	1.99250	0.27954
17	n	0.17312	-2.24656	-0.29927
18	o	1.22520	-2.77970	-0.65580
19	o	-4.52481	0.13793	0.63363
20	o	-0.10030	-1.05383	-0.53817
21	o	-3.06008	2.52412	-1.13568
22	c	-0.54434	3.71069	-1.32232
23	o	0.61874	4.35824	-1.39579
24	c	0.70628	5.46317	-2.31896
25	c	1.97303	6.24057	-2.01699
26	h	-1.53903	-0.05114	0.57537
27	h	1.28948	2.63982	0.23627
28	h	0.66844	0.98009	-0.08935
29	h	0.09367	1.88646	1.34680
30	h	-1.39128	4.10993	-1.91317
31	h	0.71868	5.05634	-3.35658
32	h	-0.19985	6.10267	-2.20817
33	h	2.07497	7.08614	-2.73047
34	h	1.95013	6.65198	-0.98517
35	h	2.86834	5.59034	-2.11604
36	h	0.16024	-4.84645	-0.27203
37	h	-1.52168	-6.38749	0.81763
38	h	-3.42087	-5.37967	2.14087
39	h	-3.60581	-2.89341	2.38149
40				
41				
42				

43 Transition State for EEZE isomer
44 E(B3LYP/def2-TZVP)=-1064.391075000

45		35		
46				
47				
48	c	-2.30025	-2.84137	0.10643
49	c	-1.83382	-4.19399	0.06855
50	c	-1.70190	-4.95334	1.24809
51	c	-2.03882	-4.40698	2.48660
52	c	-2.51171	-3.08009	2.54853
53	c	-2.63969	-2.32208	1.38350
54	n	-1.46716	-4.86378	-1.18888
55	o	-0.93276	-5.97167	-1.12071
56	o	-2.43989	-2.03458	-0.94756
57	c	-3.82962	-2.51348	-2.18590
58	n	-3.49138	-2.02492	-3.32933
59				
60				

c	-2.27823	-1.58630	-3.73352
c	-2.09508	-1.16642	-5.11460
c	-0.74773	-0.65582	-5.54801
o	-4.68202	-3.06824	-1.58311
o	-1.71400	-4.28696	-2.25716
o	-1.24356	-1.51283	-2.95810
c	-3.16842	-1.27203	-5.96138
o	-3.10177	-0.90820	-7.24271
c	-4.28268	-1.11838	-8.04538
c	-4.02305	-0.56133	-9.43153
h	-0.76063	-0.37533	-6.62004
h	0.03853	-1.42636	-5.38846
h	-0.44475	0.23192	-4.94981
h	-4.13257	-1.66910	-5.59088
h	-4.50035	-2.21087	-8.08200
h	-5.14571	-0.60884	-7.55789
h	-4.91665	-0.71648	-10.07305
h	-3.80784	0.52775	-9.38728
h	-3.15809	-1.07113	-9.90705
h	-1.32898	-5.98263	1.15021
h	-1.93786	-5.01089	3.40206
h	-2.78540	-2.63604	3.52006
h	-3.00771	-1.28487	1.40915
h	-1.57992	-1.83460	-1.95335

Transition State for EZZE isomer
E(B3LYP/def2-TZVP)=-1064.389778825

35

c	-2.65169	-2.32878	1.40474
c	-2.29198	-2.84221	0.13015
c	-1.84399	-4.20157	0.09173
c	-1.75007	-4.97274	1.26748
c	-2.10738	-4.43208	2.50259
c	-2.56153	-3.09845	2.56535
o	-2.40457	-2.02902	-0.91983
n	-1.45627	-4.86510	-1.16208
o	-1.66948	-4.27633	-2.23154
o	-0.93687	-5.98007	-1.09131
c	-3.77942	-2.52123	-2.20923
o	-4.63227	-3.08931	-1.62346
n	-3.41859	-2.01702	-3.33878
c	-2.20249	-1.56789	-3.71195
o	-1.18343	-1.49426	-2.91171
c	-2.06311	-1.14936	-5.10015
c	-0.83899	-0.66794	-5.48678
o	-0.59826	-0.26123	-6.73472
c	0.71623	0.26024	-7.01610
c	0.79533	0.57804	-8.49681
c	-3.23479	-1.25809	-6.03928
h	-2.95653	-0.90780	-7.05354
h	-4.09637	-0.65579	-5.67667
h	-3.59245	-2.30844	-6.10908

h	-0.00493	-0.60517	-4.76268
h	0.88023	1.17270	-6.39691
h	1.47728	-0.49956	-6.72301
h	1.79826	0.98833	-8.74200
h	0.63165	-0.33568	-9.10709
h	0.02969	1.33136	-8.78077
h	-1.39087	-6.00681	1.16895
h	-2.03785	-5.04552	3.41461
h	-2.85202	-2.65896	3.53410
h	-3.00733	-1.28721	1.43077
h	-1.53625	-1.82325	-1.91340

Product Complex EEZE
E(B3LYP/def2-TZVP)=-1064.420185736

35

c	0.74271	0.68150	3.07841
c	0.02169	-0.49776	3.44406
c	-0.52755	-0.65146	4.73499
c	-0.37703	0.35280	5.68659
c	0.33152	1.52727	5.34237
c	0.87723	1.68694	4.07095
n	-0.17198	-1.57886	2.49191
o	-0.80798	-2.57311	2.82774
o	1.29561	0.91691	1.89010
c	-1.28967	0.55027	-0.20390
n	-0.69946	0.41519	-1.26889
c	0.65771	0.17083	-1.64497
c	0.88708	0.02631	-3.08665
c	2.30132	-0.22363	-3.53256
o	-1.97165	0.70583	0.74434
o	0.33002	-1.44105	1.35114
o	1.55403	0.09554	-0.81132
c	-0.16851	0.11857	-3.95108
o	-0.02274	-0.00836	-5.27677
c	-1.21192	0.11767	-6.07756
c	-0.83059	-0.07771	-7.53275
h	2.36226	-0.30624	-4.63626
h	2.69865	-1.15833	-3.07838
h	2.97275	0.59644	-3.19414
h	-1.19275	0.30222	-3.57456
h	-1.95467	-0.64696	-5.74972
h	-1.65832	1.12623	-5.91010
h	-1.73151	0.01588	-8.17605
h	-0.08961	0.68574	-7.85288
h	-0.38779	-1.08404	-7.69341
h	-1.07047	-1.58330	4.94812
h	-0.80619	0.23183	6.69328
h	0.45743	2.33050	6.08712
h	1.43171	2.59521	3.78914
h	1.16285	0.12479	1.27869

Product Complex EEZE
E(B3LYP/def2-TZVP)=-1064.418481377

35

c	-2.18630	-2.28419	1.85531
c	-1.88460	-2.81688	0.57493
c	-1.88557	-4.24099	0.44866
c	-2.17406	-5.07512	1.54983
c	-2.46554	-4.52162	2.79305
c	-2.46994	-3.11485	2.93682
o	-1.62645	-1.95059	-0.40347
n	-1.58958	-4.87730	-0.82454
o	-1.32173	-4.13111	-1.79586
o	-1.60884	-6.10161	-0.90603
c	-3.85460	-2.80334	-2.73237
o	-4.44068	-3.34761	-1.86760
n	-3.36714	-2.24822	-3.70925
c	-2.11367	-1.64912	-4.02241
o	-1.21995	-1.55270	-3.18521
c	-2.04165	-1.18036	-5.41657
c	-0.85574	-0.60362	-5.77875
o	-0.62938	-0.12727	-7.00880
c	0.67053	0.43948	-7.25660
c	0.71817	0.91415	-8.69649
c	-3.20291	-1.33988	-6.36093
h	-2.95213	-0.92917	-7.36034
h	-4.10851	-0.81557	-5.98272
h	-3.48266	-2.41001	-6.48146
h	-0.03729	-0.51843	-5.03821
h	0.84016	1.28300	-6.54729
h	1.44781	-0.33574	-7.06152
h	1.71326	1.35678	-8.91633
h	0.54793	0.06885	-9.39715
h	-0.05853	1.68604	-8.88437
h	-2.15903	-6.16137	1.38142
h	-2.69023	-5.17360	3.65129
h	-2.69938	-2.66424	3.91659
h	-2.18531	-1.18763	1.95306
h	-1.39757	-2.44238	-1.25510

Molecular energies (in a.u.) and molecular structures of 7c (Table S3)

2NH-EEEE
E(B3LYP/def2-TZVP)=-1025.117771759

32

c	-1.48823	-3.93508	0.56892
c	-0.92672	-5.22971	0.63009
c	-1.07180	-6.00278	1.78327
c	-1.77902	-5.46901	2.87153
c	-2.33405	-4.18375	2.82358

c	-2.19386	-3.40276	1.66864
n	-1.94034	-6.28471	4.09757
o	-1.45389	-7.41644	4.09235
o	-1.25261	-3.29114	-0.62834
c	-1.84557	-2.11417	-1.02070
n	-1.44511	-1.76337	-2.30282
c	-0.38408	-2.21529	-3.17472
c	-0.19165	-3.64806	-3.39750
h	0.77160	-3.92658	-3.85276
o	-2.60986	-1.44494	-0.35519
o	0.26528	-1.35434	-3.75380
c	-1.15827	-4.59090	-3.23395
o	-0.94767	-5.88250	-3.51593
c	-2.08597	-6.76297	-3.43596
c	-1.60730	-8.18399	-3.66289
o	-2.55087	-5.77853	5.03917
h	-0.37288	-5.60796	-0.24322
h	-1.68406	-0.78465	-2.50264
h	-2.16934	-4.33063	-2.86464
h	-2.56266	-6.65183	-2.43322
h	-2.83084	-6.46150	-4.20894
h	-2.46792	-8.88487	-3.61336
h	-1.12954	-8.28492	-4.66078
h	-0.86742	-8.48161	-2.88929
h	-0.64693	-7.01376	1.86118
h	-2.87591	-3.80473	3.70200
h	-2.62601	-2.39721	1.61202

2NH-EEEZ
E(B3LYP/def2-TZVP)=-1025.124000521

32

c	-1.99519	-3.57996	0.42000
c	-2.22829	-4.95992	0.39625
c	-2.02763	-5.71687	1.55899
c	-1.59167	-5.12738	2.75479
c	-1.36242	-3.74927	2.78230
c	-1.56514	-2.97837	1.62027
n	-2.27799	-7.17691	1.52342
o	-2.08264	-7.81002	2.56150
o	-1.24954	-1.63997	1.73733
c	-1.95736	-0.65470	1.05125
o	-2.92375	-0.86911	0.34962
n	-1.35636	0.54647	1.35697
c	-1.41987	1.85739	0.75671
o	-0.42031	2.55216	0.91179
c	-2.60133	2.33845	0.04779
c	-3.87229	1.84810	0.08804
o	-4.86963	2.47635	-0.54412
c	-6.17307	1.86760	-0.46031
c	-7.14947	2.72323	-1.24462
h	-2.42189	3.28412	-0.48822
o	-2.66475	-7.66013	0.45906

h	-2.14980	-2.97517	-0.48227
h	-0.49428	0.46418	1.90901
h	-4.13763	0.92123	0.62487
h	-6.11795	0.83387	-0.87356
h	-6.47181	1.79538	0.61179
h	-8.16628	2.27790	-1.19646
h	-7.19632	3.75236	-0.82849
h	-6.84646	2.79110	-2.31134
h	-2.56284	-5.46762	-0.51973
h	-1.44359	-5.75836	3.64264
h	-1.02093	-3.24707	3.70030

2NH-EEZE

E(B3LYP/def2-TZVP)=-1025.120976310

32

c	-3.10801	-4.45169	0.54669
c	-2.80628	-5.05098	1.77651
c	-1.70544	-4.60485	2.51889
c	-0.88495	-3.56084	2.06361
c	-1.17996	-2.95927	0.83985
c	-2.28542	-3.40388	0.08411
n	-1.39820	-5.25072	3.81560
o	-0.42479	-4.82981	4.44215
o	-2.42916	-2.73280	-1.11222
c	-3.52088	-2.79857	-1.92176
o	-4.50161	-3.50135	-1.77134
n	-3.36721	-1.95231	-3.01679
c	-2.42385	-0.90527	-3.26542
o	-1.66227	-0.47906	-2.41224
c	-2.45754	-0.37256	-4.64204
c	-2.91910	-1.03441	-5.73737
o	-2.87221	-0.50356	-6.96628
c	-3.24678	-1.35520	-8.06421
c	-3.29709	-0.51473	-9.32557
h	-1.96613	0.60504	-4.77034
o	-2.13487	-6.16673	4.18316
h	-3.96780	-4.78202	-0.04766
h	-4.16259	-2.02652	-3.65628
h	-3.34084	-2.05920	-5.67311
h	-2.49745	-2.17608	-8.15810
h	-4.23938	-1.81726	-7.84813
h	-3.57588	-1.15043	-10.19291
h	-4.04731	0.29909	-9.22903
h	-2.30720	-0.05484	-9.53199
h	-3.41956	-5.87225	2.17456
h	-0.03213	-3.23923	2.67825
h	-0.57302	-2.13393	0.43687

2NH-EEZZ

E(B3LYP/def2-TZVP)=-1025.119671555

32

c	-3.17602	-2.84545	1.23462
c	-1.84466	-2.59115	0.88534
c	-0.97293	-3.67912	0.67176
c	-1.43014	-5.00598	0.80697
c	-2.75860	-5.25669	1.15763
c	-3.61915	-4.16872	1.36601
o	0.36921	-3.54722	0.38644
c	0.86822	-2.46813	-0.35932
n	2.24343	-2.63389	-0.38781
c	3.18783	-1.69592	-0.90862
c	4.57439	-2.19623	-0.99207
h	5.33378	-1.41174	-1.13778
n	-5.02959	-4.42705	1.73717
o	-5.38292	-5.60290	1.83662
o	0.20319	-1.60578	-0.87153
o	2.86664	-0.57019	-1.24598
c	4.95718	-3.50116	-1.01174
o	6.24115	-3.86741	-1.12639
c	6.51296	-5.27203	-1.27835
c	8.01575	-5.47399	-1.23917
o	-5.75571	-3.45015	1.92268
h	-0.72244	-5.83098	0.63314
h	2.59589	-3.44984	0.11917
h	4.22632	-4.33506	-0.95389
h	6.00945	-5.83422	-0.45605
h	6.08603	-5.62211	-2.24759
h	8.25614	-6.55187	-1.35985
h	8.51008	-4.91046	-2.05895
h	8.43610	-5.12512	-0.27181
h	-3.14751	-6.27849	1.27096
h	-3.88625	-2.02528	1.41230
h	-1.48747	-1.56015	0.77197

2NH-EZEE

E(B3LYP/def2-TZVP)=-1025.126778419

32

c	-1.37286	-3.61373	1.71872
c	-2.22907	-4.39028	2.52456
c	-3.61319	-4.21955	2.40439
c	-4.12028	-3.28712	1.48892
c	-3.27417	-2.51372	0.68118
c	-1.89190	-2.67955	0.80103
n	-5.58737	-3.11583	1.36787
o	-6.30046	-3.80805	2.09497
o	0.00376	-3.74591	1.70317
c	0.71889	-4.05645	2.84017
n	2.06942	-4.20447	2.57191
c	2.94423	-4.13637	1.44228
c	2.38357	-3.96404	0.09958
h	1.30206	-3.89807	-0.06962

o	0.24379	-4.17197	3.95023
o	4.14491	-4.24838	1.68549
c	3.25352	-3.89739	-0.94624
o	2.84758	-3.75245	-2.20996
c	3.87412	-3.69143	-3.22036
c	3.20362	-3.53866	-4.57202
o	-5.99602	-2.29379	0.54757
h	-1.81836	-5.11151	3.24204
h	2.60799	-4.37896	3.42839
h	4.34427	-3.96557	-0.76194
h	4.54570	-2.82870	-3.00260
h	4.48349	-4.62396	-3.17467
h	3.97300	-3.48647	-5.37200
h	2.53639	-4.40160	-4.78246
h	2.59610	-2.60926	-4.60923
h	-4.31570	-4.80583	3.01400
h	-3.71368	-1.79391	-0.02376
h	-1.19351	-2.08870	0.18874

2NH-EZEZ

E(B3LYP/def2-TZVP)=-1025.131767374

32

c	-1.31149	-3.25328	0.23412
c	-1.90491	-4.44472	-0.23247
c	-2.55445	-5.28269	0.68205
c	-2.60269	-4.92930	2.03734
c	-2.01082	-3.74843	2.50991
c	-1.36454	-2.90848	1.60042
n	-3.29082	-5.82527	2.99536
o	-3.79804	-6.85371	2.54671
o	-0.59625	-2.37463	-0.55340
c	-0.83109	-2.21520	-1.91544
n	0.10184	-1.30933	-2.37442
c	0.33238	-0.77760	-3.68052
c	-0.53363	-1.23600	-4.76757
h	-1.33625	-1.96115	-4.57485
o	-1.70402	-2.77516	-2.54288
o	1.25213	0.03075	-3.78932
c	-0.30960	-0.73518	-6.01408
o	-1.03865	-1.09243	-7.07368
c	-0.70945	-0.47285	-8.33202
c	-1.61766	-1.05238	-9.39958
o	-3.30905	-5.48236	4.17816
h	-1.86698	-4.70682	-1.29642
h	0.75771	-0.93234	-1.68164
h	0.50608	-0.00242	-6.17818
h	-0.84733	0.62975	-8.23987
h	0.36336	-0.66855	-8.56422
h	-1.38919	-0.58908	-10.38324
h	-1.47448	-2.15070	-9.48675
h	-2.68459	-0.85720	-9.15882
h	-3.02892	-6.22006	0.35790

h -2.06990 -3.50849 3.58096
h -0.88712 -1.97302 1.92977

2NH-EZZE
E(B3LYP/def2-TZVP)=-1025.126351542

32

c -2.11187 -4.18933 0.09330
c -3.29204 -4.68744 0.68410
c -3.39158 -4.69939 2.08171
c -2.33002 -4.22413 2.86258
c -1.15326 -3.72789 2.27918
c -1.04770 -3.71150 0.88817
n -2.45084 -4.24511 4.33794
o -3.49963 -4.67873 4.81654
o -1.85400 -4.10155 -1.25805
c -2.69194 -4.51232 -2.24774
n -2.13232 -4.27140 -3.49962
c -0.89474 -3.68245 -3.89011
c -0.74326 -3.63587 -5.35820
h -1.52214 -4.02571 -6.03475
o -3.78626 -5.02537 -2.11333
o -0.06549 -3.26751 -3.09199
c 0.39234 -3.09445 -5.87520
o 0.62633 -3.00555 -7.18659
c 1.87302 -2.40002 -7.58430
c 1.94377 -2.40647 -9.09906
o -1.49355 -3.82724 4.99129
h -4.11027 -5.05690 0.05538
h -2.75786 -4.58157 -4.24844
h 1.16793 -2.70555 -5.18484
h 1.91536 -1.36099 -7.18206
h 2.71545 -2.97790 -7.13776
h 2.89645 -1.94400 -9.43498
h 1.90017 -3.44450 -9.49280
h 1.10066 -1.83033 -9.53673
h -4.29380 -5.07791 2.58335
h -0.34367 -3.36399 2.92752
h -0.14942 -3.33187 0.37777

2NH-EZZZ
E(B3LYP/def2-TZVP)=-1025.125452800

32

c -3.48864 -4.42923 1.66061
c -3.08653 -3.11169 1.40203
c -1.84323 -2.86775 0.80645
c -1.01641 -3.96224 0.47576
c -1.43226 -5.28406 0.74131
c -2.67204 -5.52310 1.33743

o	0.24775	-3.85260	-0.06091
c	0.64567	-2.76340	-0.84930
o	-0.05749	-1.84606	-1.18634
n	-4.80380	-4.67420	2.29475
o	-5.12236	-5.84533	2.50528
n	1.98024	-2.98425	-1.14761
c	2.81813	-2.14367	-1.93519
o	2.41685	-1.10749	-2.44212
c	4.19091	-2.67283	-2.05537
c	5.09303	-1.96831	-2.79035
o	6.36054	-2.35410	-2.95451
c	7.19039	-1.52325	-3.79142
c	8.60334	-2.07293	-3.75677
h	4.49496	-3.61408	-1.56718
o	-5.49234	-3.69147	2.57195
h	-0.76134	-6.11400	0.47157
h	2.38381	-3.84098	-0.75916
h	4.77259	-1.02527	-3.27775
h	6.77903	-1.53050	-4.82764
h	7.15472	-0.47524	-3.41307
h	9.26525	-1.45444	-4.39992
h	9.00793	-2.06048	-2.72200
h	8.62973	-3.11888	-4.13038
h	-3.02471	-6.54076	1.55689
h	-3.75874	-2.28596	1.67606
h	-1.52144	-1.84172	0.59142

2NH-ZEEE
E(B3LYP/def2-TZVP)=-1025.116673190

32

c	-0.85915	-5.10996	0.65531
c	-1.50803	-5.90445	1.60181
c	-2.46140	-5.31178	2.44410
c	-2.76443	-3.94644	2.35903
c	-2.11423	-3.14246	1.41346
c	-1.16284	-3.73369	0.55320
n	-3.15963	-6.14926	3.44613
o	-3.98735	-5.59649	4.17096
o	-0.45022	-3.08485	-0.42750
c	-0.68194	-1.79376	-0.84182
o	-1.32080	-0.95521	-0.23983
n	-0.00313	-1.54657	-2.02285
c	0.64419	-2.38836	-2.97503
o	1.57254	-1.91639	-3.62055
c	0.12900	-3.74568	-3.23008
c	-1.14792	-4.20843	-3.12450
o	-2.16985	-3.50821	-2.61126
c	-3.44180	-4.17660	-2.49559
c	-4.48344	-3.15071	-2.09192
h	0.84672	-4.39180	-3.75761
o	-2.86775	-7.34538	3.48542
h	-0.10318	-5.53304	-0.02379

h	0.17279	-0.54936	-2.18819
h	-1.39872	-5.22138	-3.49941
h	-3.69400	-4.64836	-3.47419
h	-3.35306	-4.98342	-1.73091
h	-5.47256	-3.64325	-1.97638
h	-4.21321	-2.67493	-1.12475
h	-4.57394	-2.35392	-2.86076
h	-1.29318	-6.97754	1.70473
h	-3.51081	-3.52343	3.04690
h	-2.32571	-2.06915	1.34201

2NH-ZEEZ
E(B3LYP/def2-TZVP)=-1025.120799869

32

c	-2.51381	-5.50616	1.30741
c	-2.37872	-4.94386	2.58466
c	-1.72459	-3.71928	2.78421
c	-1.20330	-3.04596	1.67649
c	-1.33537	-3.60051	0.38725
c	-1.99002	-4.83489	0.19665
n	-2.93700	-5.66237	3.75367
o	-2.79580	-5.13982	4.85988
o	-0.73095	-2.88832	-0.62588
c	-1.26891	-2.84566	-1.91532
n	-0.36767	-2.14404	-2.68971
c	-0.36383	-1.89588	-4.09648
c	-1.63411	-1.79214	-4.82644
h	-1.53864	-1.98397	-5.90596
o	-2.32466	-3.33945	-2.23785
o	0.72705	-1.75648	-4.63759
c	-2.82915	-1.31081	-4.38700
o	-3.04900	-0.84466	-3.15355
c	-4.41864	-0.75079	-2.72363
c	-4.46700	0.06195	-1.44371
o	-3.50537	-6.73410	3.54246
h	-2.09123	-5.26255	-0.80884
h	0.55549	-1.98913	-2.26864
h	-3.68813	-1.24374	-5.08711
h	-5.02163	-0.27293	-3.53293
h	-4.80512	-1.78205	-2.55961
h	-5.51680	0.14768	-1.08996
h	-3.87085	-0.42885	-0.64465
h	-4.06491	1.08521	-1.60571
h	-3.02800	-6.47218	1.20226
h	-1.63845	-3.31556	3.80297
h	-0.68201	-2.08293	1.78799

2NH-ZEZE
E(B3LYP/def2-TZVP)=-1025.125109230

32

c	-3.30034	-4.85218	1.86383
c	-2.38473	-4.39854	2.82240
c	-1.30238	-3.57518	2.47251
c	-1.14404	-3.20407	1.13715
c	-2.06283	-3.65446	0.16415
c	-3.14784	-4.48314	0.52076
n	-2.56223	-4.79511	4.23728
o	-1.73817	-4.37539	5.05140
o	-1.76902	-3.19950	-1.10235
c	-2.49496	-3.46289	-2.22466
n	-1.93672	-2.84324	-3.33572
c	-0.78721	-2.02267	-3.47589
c	-0.53674	-1.55659	-4.86337
h	0.36334	-0.93007	-4.95036
o	-3.50224	-4.14211	-2.29624
o	-0.04886	-1.71369	-2.55248
c	-1.24300	-1.78520	-6.00283
o	-2.38011	-2.51228	-6.05329
c	-2.95715	-2.77113	-7.34921
c	-4.31560	-3.41533	-7.15037
o	-3.52180	-5.51787	4.50992
h	-3.85365	-4.82609	-0.24442
h	-2.47452	-3.02573	-4.19356
h	-0.90793	-1.35899	-6.96873
h	-3.04223	-1.80665	-7.90165
h	-2.27080	-3.43997	-7.91864
h	-4.77515	-3.63441	-8.13782
h	-4.22558	-4.37024	-6.58936
h	-4.99698	-2.74122	-6.58860
h	-4.13158	-5.49625	2.18495
h	-0.60611	-3.24093	3.25457
h	-0.31477	-2.55996	0.80712

2NH-ZEZZ

E(B3LYP/def2-TZVP)=-1025.123573841

32

c	-3.58565	-4.37659	1.22668
c	-3.19962	-3.03316	1.12840
c	-1.84984	-2.70367	0.95278
c	-0.89622	-3.74250	0.87730
c	-1.29904	-5.09272	0.97714
c	-2.64508	-5.41549	1.15382
o	0.46277	-3.57102	0.74698
c	1.06734	-2.37087	0.34082
o	0.48774	-1.36401	0.02184
n	-5.01525	-4.70975	1.41364
o	-5.31260	-5.90239	1.50238
n	2.42884	-2.61046	0.38527
c	3.44903	-1.67386	0.07830
o	3.22151	-0.52634	-0.26666

c	4.83019	-2.20038	0.21495
c	5.25847	-3.43390	0.59299
o	4.43334	-4.45941	0.90252
c	5.03074	-5.66150	1.42772
c	3.96392	-6.73675	1.50293
h	5.60142	-1.45636	-0.03326
o	-5.81454	-3.77455	1.46888
h	-0.52973	-5.87769	0.91406
h	2.72466	-3.55282	0.67135
h	6.34079	-3.66139	0.65338
h	5.86742	-5.96845	0.75764
h	5.45419	-5.44045	2.43508
h	4.40025	-7.67145	1.91518
h	3.12906	-6.42263	2.16605
h	3.55131	-6.95818	0.49520
h	-2.98720	-6.45687	1.23505
h	-3.97046	-2.25175	1.19262
h	-1.53661	-1.65708	0.86523

2NH-ZZEE
E(B3LYP/def2-TZVP)=-1025.120527187

32

c	-2.73489	-4.48030	2.03251
c	-4.11801	-4.41946	1.82552
c	-4.67828	-3.29350	1.20610
c	-3.88656	-2.21610	0.78285
c	-2.50590	-2.27309	0.98991
c	-1.93324	-3.40049	1.61111
n	-6.14323	-3.24045	0.98926
o	-6.59886	-2.23378	0.44547
o	-0.55410	-3.38227	1.69869
c	0.11645	-3.96997	2.75412
o	-0.42010	-4.47771	3.71669
n	1.48754	-3.88965	2.59558
c	2.43087	-3.35317	1.64960
o	3.60204	-3.34241	2.01062
c	1.94318	-2.90982	0.34202
c	2.74427	-2.36174	-0.61960
o	4.04715	-2.12126	-0.48924
c	4.73788	-1.59977	-1.63973
c	6.14842	-1.23386	-1.21958
h	0.88295	-3.02714	0.08971
o	-6.80745	-4.20651	1.36517
h	-2.28361	-5.35122	2.52389
h	1.98392	-4.24674	3.42041
h	2.29545	-2.07670	-1.59426
h	4.74533	-2.37805	-2.43889
h	4.18696	-0.71051	-2.02788
h	6.71450	-0.84208	-2.09178
h	6.13423	-0.45498	-0.42758
h	6.68126	-2.12337	-0.82151
h	-4.77897	-5.24069	2.13765

h -4.36670 -1.35176 0.30263
h -1.84877 -1.44700 0.67777

2NH-ZZEZ
E(B3LYP/def2-TZVP)=-1025.126382228

32

c -1.89390 -4.59113 -0.00297
c -2.57287 -5.26666 1.01759
c -2.81778 -4.61828 2.23580
c -2.39525 -3.30069 2.46543
c -1.71957 -2.62322 1.44786
c -1.46985 -3.26467 0.21783
n -3.53683 -5.34311 3.30893
o -3.73250 -4.74184 4.36592
o -0.74031 -2.52505 -0.68918
c -0.90146 -2.66477 -2.06620
o -1.72491 -3.38031 -2.59657
n 0.02679 -1.83991 -2.66090
c 0.31549 -1.56636 -4.04202
o 1.22334 -0.77348 -4.26174
c -0.50054 -2.25797 -5.03971
c -0.34546 -2.10594 -6.38799
o 0.56022 -1.32237 -6.97206
c 0.55995 -1.28208 -8.41093
c 1.69272 -0.37831 -8.85891
h -1.28812 -2.94195 -4.69411
o -3.89119 -6.49876 3.07436
h -1.70129 -5.08561 -0.96313
h 0.63788 -1.30793 -2.03157
h -1.01235 -2.66921 -7.07353
h 0.68935 -2.31748 -8.80572
h -0.42609 -0.89814 -8.76395
h 1.71757 -0.32254 -9.96825
h 1.55891 0.64792 -8.45552
h 2.67004 -0.76652 -8.50133
h -2.91808 -6.30213 0.88567
h -2.60653 -2.82940 3.43585
h -1.37141 -1.58821 1.58659

2NH-ZZZE
E(B3LYP/def2-TZVP)=-1025.120119075

32

c -3.39944 -4.59889 0.63648
c -3.51028 -4.65423 2.03217
c -2.41559 -4.30836 2.83510
c -1.19361 -3.90127 2.27590
c -1.07607 -3.84312 0.88708
c -2.17381 -4.19001 0.06968

1				
2				
3	n	-2.54929	-4.37351	4.30772
4	o	-1.56515	-4.06262	4.98073
5	o	-1.89739	-4.07804	-1.27521
6	c	-2.77362	-4.33325	-2.28525
7	o	-3.92051	-4.72422	-2.17503
8	n	-2.18487	-4.08767	-3.52084
9	c	-0.88476	-3.60102	-3.87832
10	o	-0.02502	-3.32702	-3.05770
11	c	-0.74372	-3.47889	-5.34285
12	c	0.37190	-3.01517	-5.97799
13	o	1.48793	-2.62375	-5.36617
14	c	2.54012	-2.09760	-6.19561
15	c	3.74906	-1.83587	-5.31802
16	h	-1.57996	-3.76984	-5.99948
17	o	-3.63448	-4.73421	4.76544
18	h	-4.24353	-4.86608	-0.00972
19	h	-2.83934	-4.28429	-4.28295
20	h	0.37787	-2.95259	-7.08632
21	h	2.77581	-2.83398	-6.99982
22	h	2.18322	-1.15826	-6.67986
23	h	4.57701	-1.41629	-5.92873
24	h	3.49983	-1.11114	-4.51430
25	h	4.10104	-2.77562	-4.84169
26	h	-4.44716	-4.96650	2.51537
27	h	-0.35913	-3.63750	2.94089
28	h	-0.14291	-3.52949	0.39468
29				
30				
31				

2NH-ZZZZ

E(B3LYP/def2-TZVP)=-1025.119082019

32

36				
37	c	-2.78892	-5.34281	1.46462
38	c	-3.55122	-4.21526	1.80478
39	c	-3.10734	-2.91692	1.51874
40	c	-1.87765	-2.72677	0.87694
41	c	-1.10617	-3.85552	0.52657
42	c	-1.56350	-5.15754	0.82187
43	n	-4.85246	-4.40325	2.48475
44	o	-5.49500	-3.39313	2.77249
45	o	0.13824	-3.80224	-0.06064
46	c	0.55119	-2.73189	-0.87124
47	n	1.85440	-3.01761	-1.23622
48	c	2.69364	-2.20746	-2.06825
49	c	4.02087	-2.82166	-2.26521
50	h	4.25475	-3.78682	-1.78625
51	o	-0.12382	-1.78135	-1.17278
52	o	2.31698	-1.14799	-2.53506
53	c	5.01833	-2.27669	-3.02146
54	o	4.92361	-1.12589	-3.68366
55	c	6.08706	-0.68466	-4.40767
56	c	5.72384	0.58302	-5.15684
57	o	-5.20732	-5.55983	2.71942
58	h	-0.93579	-6.01557	0.53630
59				
60				

h	2.22994	-3.89751	-0.87299
h	5.98654	-2.81203	-3.11140
h	6.91616	-0.50198	-3.68428
h	6.40913	-1.49060	-5.10857
h	6.60567	0.95630	-5.72034
h	4.89830	0.39235	-5.87489
h	5.39357	1.37417	-4.45089
h	-3.17233	-6.34402	1.70709
h	-3.73679	-2.06307	1.80757
h	-1.52451	-1.71616	0.63997

3OH-EEZE

E(B3LYP/def2-TZVP)=-1025.108962164

32

c	1.17337	-0.40063	3.81617
c	-0.01600	0.02567	4.42512
c	-1.11828	0.44965	3.66882
c	-1.03789	0.45294	2.27224
c	0.15272	0.02401	1.64933
c	1.25221	-0.40528	2.42075
n	-0.10746	0.03148	5.90301
o	-1.16830	0.40510	6.40480
o	0.33235	0.05184	0.28395
o	0.88438	-0.33632	6.53424
c	-0.73506	-0.34269	-0.66152
n	-0.36134	-0.20039	-1.95293
c	0.81885	0.18365	-2.40818
c	1.05271	0.28990	-3.83490
c	0.06458	-0.00577	-4.72812
o	0.24231	0.08538	-6.04460
c	-0.88490	-0.25287	-6.88101
c	-0.46869	-0.08821	-8.32955
o	-1.78929	-0.73881	-0.22718
o	1.88707	0.50202	-1.66906
h	2.16690	-0.74402	1.90933
h	2.04704	0.61758	-4.17288
h	-0.92684	-0.33429	-4.35761
h	-1.19243	-1.30191	-6.66355
h	-1.73665	0.41878	-6.62492
h	-1.32009	-0.34036	-8.99730
h	-0.15955	0.95877	-8.53603
h	0.38122	-0.75985	-8.57624
h	2.01276	-0.72667	4.44656
h	-2.02835	0.77833	4.19078
h	-1.89225	0.77995	1.66616
h	1.60394	0.41256	-0.70703

3OH-EZZE

E(B3LYP/def2-TZVP)=-1025.107598489

1				
2				
3		32		
4				
5	c	0.39457	0.07636	4.42081
6	c	-0.62665	0.89009	3.90922
7	c	-0.88025	0.89671	2.53348
8	c	-0.10421	0.07956	1.68570
9	c	0.91577	-0.73858	2.21304
10	c	1.17363	-0.73841	3.58658
11	o	-0.25439	0.07211	0.31643
12	n	0.66078	0.07855	5.87753
13	o	1.57397	-0.63913	6.28814
14	o	-0.04681	0.79827	6.58300
15	c	-1.58736	0.08701	-0.33342
16	o	-2.57503	0.08412	0.35811
17	n	-1.50918	0.09942	-1.68561
18	c	-0.41206	0.05025	-2.41700
19	o	0.84611	-0.02988	-1.95589
20	c	-0.54890	0.07969	-3.85868
21	c	0.53056	0.04357	-4.69219
22	o	0.40199	0.07523	-6.01971
23	c	1.61466	0.01402	-6.79762
24	c	1.24454	0.11204	-8.26491
25	h	1.49969	-1.37541	1.53007
26	h	-1.57182	0.13496	-4.25762
27	h	1.55921	-0.01216	-4.28492
28	h	2.28367	0.85200	-6.49220
29	h	2.13737	-0.94566	-6.57576
30	h	2.16204	0.06360	-8.88933
31	h	0.57425	-0.72332	-8.55977
32	h	0.72437	1.07025	-8.47841
33	h	1.96256	-1.36232	4.03002
34	h	-1.20890	1.51470	4.60175
35	h	-1.67707	1.52662	2.11746
36	h	0.78067	-0.02088	-0.95085

37
38
39
40 Transition state for the direct 2NH to Phenol Hydrogen Transfer
41 E(B3LYP/def2-TZVP)=-1025.054946518
42

43		32		
44				
45	c	-1.20074	-2.90995	1.02487
46	c	-1.01798	-3.90695	0.02718
47	c	-1.67684	-5.15845	0.17632
48	c	-2.49414	-5.40124	1.27965
49	c	-2.65599	-4.40011	2.25354
50	c	-2.01120	-3.15761	2.13349
51	o	-0.22900	-3.68880	-1.02528
52	c	-0.83004	-3.60704	-3.03212
53	o	-1.32076	-4.55204	-3.52282
54	n	-3.51305	-4.65873	3.42074
55	o	-3.63169	-3.75705	4.25555
56	o	-4.06284	-5.76149	3.49552
57	n	-0.35431	-2.41818	-2.88930
58	c	-0.18505	-1.35809	-3.87846

o	0.32447	-0.31927	-3.49978
c	-0.65262	-1.67210	-5.22533
c	-0.50816	-0.72817	-6.20072
o	-0.91362	-0.92114	-7.45050
c	-0.63973	0.12685	-8.40928
c	-1.40703	-0.17701	-9.68046
h	-1.11070	-2.64519	-5.46228
h	-1.52567	-5.92974	-0.59513
h	-0.08190	-2.55889	-1.71153
h	-0.04008	0.24679	-5.95503
h	-0.94494	1.10490	-7.97167
h	0.45861	0.15474	-8.59475
h	-1.19859	0.60607	-10.44044
h	-1.10423	-1.16004	-10.09988
h	-2.50116	-0.19826	-9.48926
h	-3.01411	-6.36087	1.41394
h	-2.16317	-2.40345	2.91906
h	-0.68145	-1.94407	0.91472

Transition State for EEZE isomer
E(B3LYP/def2-TZVP)=-1025.096002111

32

c	0.16291	-0.20954	4.27651
c	-1.07807	0.26637	3.82403
c	-1.20089	0.72057	2.50857
c	-0.08210	0.69061	1.64079
c	1.16036	0.19997	2.11560
c	1.28604	-0.24234	3.43412
o	-0.19555	1.14336	0.37149
n	0.29262	-0.68279	5.66852
o	1.39933	-1.08757	6.03260
o	-0.71315	-0.64525	6.38075
c	-1.33388	0.26202	-0.78799
o	-2.32733	-0.05432	-0.22439
n	-0.75638	0.23287	-1.94735
c	0.51050	0.59086	-2.27214
o	1.36203	1.09210	-1.43644
c	0.94634	0.40656	-3.63810
c	0.11799	-0.12558	-4.58597
o	0.50493	-0.30502	-5.84381
c	-0.46876	-0.85276	-6.76345
c	0.21396	-1.07980	-8.09747
h	2.02512	0.17286	1.43307
h	1.97387	0.71030	-3.88688
h	-0.91414	-0.42500	-4.31512
h	-0.86546	-1.80457	-6.34177
h	-1.31361	-0.13240	-6.85673
h	-0.51491	-1.49447	-8.82612
h	0.61295	-0.12680	-8.50541
h	1.05537	-1.79798	-7.99550
h	2.23870	-0.62230	3.82999
h	-1.92907	0.27889	4.52017

h -2.15743 1.10926 2.13230
h 0.80125 1.18219 -0.44498

Transition State for EZZE isomer
E(B3LYP/def2-TZVP)=-1025.095291990

32

c -0.63501 0.55911 3.94289
c -0.97909 1.00395 2.66409
c -0.16967 0.66336 1.55236
c 0.99097 -0.12780 1.74923
c 1.33959 -0.56485 3.02840
c 0.52108 -0.21877 4.11581
o -0.48513 1.10769 0.31651
h 1.61338 -0.39574 0.88017
c -2.09298 0.59036 -0.45292
n -1.87287 0.39583 -1.71688
c -0.69296 0.36987 -2.37330
c -0.74891 0.07154 -3.78690
h -1.73428 -0.12400 -4.23359
o -2.95189 0.57645 0.36211
o 0.46001 0.59168 -1.81533
c 0.39031 0.03997 -4.54120
o 0.37174 -0.22355 -5.84321
c 1.64456 -0.27005 -6.52865
c 1.38167 -0.44195 -8.01120
h 1.37486 0.24085 -4.07381
h 2.20041 0.67279 -6.31896
h 2.23564 -1.12159 -6.11916
h 2.34635 -0.49363 -8.55946
h 0.81672 -1.37831 -8.20688
h 0.79550 0.41217 -8.41239
h 2.23525 -1.17636 3.20883
n 0.88776 -0.68171 5.46793
h -1.24456 0.80962 4.82310
h -1.87196 1.62453 2.50478
h 0.23373 0.84141 -0.73378
o 0.15199 -0.35687 6.40250
o 1.90903 -1.36459 5.57969

Product Complex EEZE
E(B3LYP/def2-TZVP)=-1025.123266873

32

c 1.21722 -0.45952 2.95524
c 0.41616 -0.41451 4.10800
c -0.74290 0.38081 4.15622
c -1.10346 1.13428 3.04022
c -0.31136 1.10053 1.86503
c 0.85652 0.29474 1.83691

n	0.79570	-1.21266	5.28320
o	0.06799	-1.14970	6.27843
o	-0.70519	1.84765	0.81803
o	1.81890	-1.89958	5.20459
c	-2.25032	0.56384	-1.43155
n	-1.33496	0.46372	-2.24536
c	0.04198	0.76541	-2.32563
c	0.68077	0.39330	-3.57417
c	0.00738	-0.20501	-4.60100
o	0.60308	-0.53659	-5.74161
c	-0.20919	-1.18058	-6.75019
c	0.64758	-1.40473	-7.98002
o	-3.22287	0.58543	-0.77550
o	0.65868	1.30924	-1.39865
h	1.47683	0.27367	0.92641
h	1.75398	0.61956	-3.66082
h	-1.07402	-0.43165	-4.50852
h	-0.58976	-2.14372	-6.33879
h	-1.08308	-0.52719	-6.97702
h	0.04667	-1.90367	-8.77004
h	1.02402	-0.44015	-8.38238
h	1.51921	-2.05123	-7.74296
h	2.11765	-1.09056	2.95840
h	-1.34159	0.38955	5.07820
h	-2.00541	1.76561	3.04458
h	-0.09417	1.70866	0.02373

Product Complex EEZE

E(B3LYP/def2-TZVP)=-1025.123503031

32

c	-0.18613	0.49057	4.01275
c	-0.80079	1.20329	2.98440
c	-0.36077	1.05484	1.64489
c	0.71377	0.17158	1.36132
c	1.32901	-0.54188	2.39169
c	0.87574	-0.38128	3.71132
o	-0.98364	1.77086	0.69268
h	1.05900	0.05832	0.32102
c	-3.20911	0.68418	-1.04378
n	-2.51769	0.41919	-2.02333
c	-1.18920	0.52581	-2.45874
c	-0.98078	-0.00116	-3.79715
h	-1.83363	-0.42525	-4.34760
o	-4.00204	0.86909	-0.19892
o	-0.29255	1.02530	-1.75651
c	0.26787	0.03807	-4.35018
o	0.52269	-0.42060	-5.56937
c	1.89318	-0.36025	-6.02898
c	1.92604	-0.78464	-7.48355
h	1.11227	0.46864	-3.77452
h	2.27030	0.68011	-5.89863
h	2.50860	-1.03758	-5.39366

h	2.97173	-0.75972	-7.85776
h	1.53648	-1.81798	-7.60318
h	1.31279	-0.10240	-8.11005
h	2.16433	-1.23027	2.19782
n	1.52420	-1.13513	4.79425
h	-0.51166	0.58873	5.05838
h	-1.63494	1.89204	3.18826
h	-0.61846	1.54857	-0.22503
o	1.09652	-0.97486	5.94095
o	2.45807	-1.88478	4.49199

Molecular energies (in a.u.) and molecular structures of 7d (Table S4)

2NH-EEEE
E(B3LYP/def2-TZVP)=-1064.420316614

35

c	-0.98248	-3.74696	0.89429
c	-0.98226	-5.14278	0.86467
c	-1.64964	-5.84098	1.88234
c	-2.30769	-5.17068	2.92182
c	-2.31108	-3.77031	2.95737
c	-1.64558	-3.06201	1.93542
o	-1.52914	-1.68923	1.86224
c	-2.37170	-0.80510	2.49600
o	-3.28831	-1.10318	3.23415
h	-0.46909	-3.15921	0.11710
n	-2.02728	0.50526	2.19181
c	-0.85848	1.08253	1.56764
o	-0.32977	2.03047	2.13571
c	-0.41301	0.56993	0.26079
c	-1.30499	-0.05622	-0.56066
o	-0.96021	-0.52485	-1.77151
c	-2.03262	-0.95674	-2.62863
c	-1.43136	-1.59417	-3.86695
c	0.99835	0.88753	-0.15425
h	-2.45093	1.15955	2.86082
h	1.14989	0.69488	-1.23531
h	1.73264	0.27274	0.41534
h	1.22928	1.95077	0.07038
h	-2.36174	-0.20115	-0.26706
h	-2.67517	-1.68022	-2.07271
h	-2.66053	-0.07463	-2.89613
h	-2.24027	-1.92923	-4.55080
h	-0.79011	-0.86905	-4.41223
h	-0.81115	-2.47608	-3.59811
h	-0.47570	-5.70697	0.06880
n	-1.65540	-7.32210	1.85662
h	-2.81316	-5.76023	3.70019
h	-2.82778	-3.22974	3.75895

o -2.24527 -7.90325 2.76749
o -1.06951 -7.87412 0.92422

2NH-EEEZ
E(B3LYP/def2-TZVP)=-1064.425317291

35

c -2.11683 -4.93177 0.33547
c -2.07617 -5.66853 1.52746
c -1.82523 -5.05456 2.76346
c -1.61835 -3.67325 2.79992
c -1.65996 -2.92243 1.60785
c -1.90719 -3.54821 0.36884
o -1.37796 -1.57937 1.74739
c -1.97860 -0.61102 0.94138
n -1.43527 0.60193 1.31734
c -1.36605 1.86048 0.60918
c -2.50682 2.36283 -0.16338
c -2.21841 3.51358 -1.09310
h -1.93937 -2.95902 -0.55624
o -2.82480 -0.84128 0.10513
o -0.31519 2.48322 0.72770
c -3.77283 1.89671 0.05539
o -4.83636 2.40340 -0.58278
c -6.10950 1.79414 -0.29835
c -7.17119 2.49928 -1.12084
h -0.63619 0.52105 1.95780
h -3.12838 3.80568 -1.65393
h -1.41815 3.24807 -1.81823
h -1.84674 4.39538 -0.52538
h -3.98329 1.08861 0.77512
h -6.05526 0.70981 -0.55043
h -6.32039 1.88502 0.79333
h -8.16662 2.04820 -0.92061
h -7.21742 3.57954 -0.86509
h -6.95604 2.40564 -2.20684
h -2.30942 -5.45788 -0.61053
n -2.29831 -7.13259 1.48104
h -1.79911 -5.66957 3.67424
h -1.41792 -3.15234 3.74866
o -2.50967 -7.63948 0.37894
o -2.25664 -7.74590 2.54818

2NH-EEZE
E(B3LYP/def2-TZVP)=-1064.423425480

35

c -3.13200 -4.54511 0.49779
c -2.38220 -5.34523 1.37001
c -1.26240 -4.84202 2.05091

1				
2				
3	c	-0.89399	-3.51151	1.84745
4	c	-1.64315	-2.69873	0.97060
5	c	-2.76788	-3.20831	0.28943
6	o	-1.13731	-1.42184	0.84656
7	c	-1.81187	-0.36411	0.31868
8	n	-1.04666	0.79595	0.40669
9	c	0.13098	1.08106	1.16469
10	c	0.78181	2.37873	0.83749
11	c	1.70845	2.94076	1.88179
12	h	-3.34567	-2.56427	-0.38373
13	o	-2.91386	-0.38415	-0.19484
14	o	0.55873	0.32880	2.02670
15	c	0.62213	2.96246	-0.38616
16	o	1.21928	4.12261	-0.71203
17	c	1.15560	4.52227	-2.09058
18	c	1.72550	5.92282	-2.21164
19	h	-1.52212	1.58992	-0.02975
20	h	2.36059	3.72974	1.45646
21	h	2.33272	2.12519	2.30512
22	h	1.13951	3.38102	2.73265
23	h	0.01748	2.49640	-1.18967
24	h	1.73774	3.79786	-2.70803
25	h	0.09386	4.48932	-2.43408
26	h	1.69301	6.25522	-3.27128
27	h	1.14096	6.64198	-1.59880
28	h	2.78192	5.94945	-1.86890
29	h	-4.00025	-4.98473	-0.01367
30	n	-2.77904	-6.75678	1.57726
31	h	-0.70243	-5.50211	2.72843
32	h	-0.02711	-3.06386	2.35692
33	o	-3.76356	-7.16643	0.96070
34	o	-2.09793	-7.42935	2.35243

35
36
37
38 2NH-EEZZ
39 E(B3LYP/def2-TZVP)=-1064.422157366

40				
41	35			
42				
43	c	-2.96713	-3.13315	0.74547
44	c	-1.58740	-2.83881	0.74092
45	c	-0.63648	-3.84297	1.01792
46	c	-1.05394	-5.14540	1.30013
47	c	-2.42755	-5.43046	1.29832
48	c	-3.38183	-4.44054	1.02658
49	o	-1.06116	-1.58188	0.53467
50	c	-1.69952	-0.61978	-0.26121
51	o	-2.72207	-0.78372	-0.87483
52	h	0.43196	-3.57823	1.00901
53	n	-0.89950	0.51029	-0.20016
54	c	-1.23388	1.79922	-0.71500
55	o	-2.35845	2.06573	-1.10396
56	c	-0.11906	2.78547	-0.71737
57	c	1.18560	2.38469	-0.73291
58	o	2.20622	3.26123	-0.74729

c	3.51768	2.73203	-0.99760
c	4.53279	3.83595	-0.76779
c	-0.51671	4.23401	-0.80945
h	-0.05852	0.42415	0.37594
h	0.34309	4.86781	-1.10541
h	-0.90636	4.60882	0.16475
h	-1.34012	4.34815	-1.54635
h	1.47723	1.31586	-0.76611
h	3.70218	1.86794	-0.31477
h	3.56528	2.35521	-2.04670
h	5.55825	3.45515	-0.96234
h	4.34304	4.69319	-1.44854
h	4.48646	4.20419	0.27945
h	-0.33824	-5.95032	1.51962
n	-2.87786	-6.80980	1.59414
h	-4.44789	-4.70892	1.04077
h	-3.70411	-2.35198	0.52283
o	-4.09033	-7.02398	1.59275
o	-2.00873	-7.65252	1.82266

2NH-EZEE

E(B3LYP/def2-TZVP)=-1064.421188748

35

c	-1.30544	-3.44695	1.80554
c	-2.23428	-4.43351	2.15608
c	-3.59777	-4.22309	1.90701
c	-4.06230	-3.04191	1.30979
c	-3.13765	-2.05550	0.95800
c	-1.76470	-2.25745	1.20377
o	-0.93878	-1.24968	0.75255
c	0.27577	-0.97164	1.34833
o	0.65082	-1.41646	2.41204
h	-0.23670	-3.59432	2.00597
n	0.98588	-0.06110	0.58534
c	0.64818	0.65780	-0.61259
o	0.94048	1.84994	-0.64610
c	0.07310	-0.09843	-1.74532
c	-0.46682	0.68452	-2.72785
o	-0.97674	0.15565	-3.84760
c	-1.49539	1.07469	-4.82679
c	-2.03784	0.27151	-5.99372
c	0.15821	-1.59597	-1.91300
h	1.70199	0.42592	1.13608
h	-0.81413	-2.10304	-1.72580
h	0.91212	-2.04170	-1.23205
h	0.45312	-1.84064	-2.95694
h	-0.48790	1.78589	-2.62263
h	-2.29473	1.69399	-4.35640
h	-0.67713	1.75852	-5.15245
h	-2.44406	0.95608	-6.76869
h	-1.23652	-0.34425	-6.45548

h	-2.85274	-0.40716	-5.66247
h	-1.91642	-5.37617	2.62410
n	-4.57238	-5.27450	2.27919
h	-5.14008	-2.91698	1.13372
h	-3.45846	-1.11383	0.48703
o	-5.76197	-5.05001	2.05296
o	-4.12896	-6.30461	2.78807

2NH-EZEZ
E(B3LYP/def2-TZVP)=-1064.424673427

35

c	-1.63780	-3.22889	0.03439
c	-1.48628	-4.61117	-0.12599
c	-1.76787	-5.46940	0.94603
c	-2.19738	-4.97843	2.18782
c	-2.35126	-3.59960	2.35016
c	-2.07449	-2.72743	1.27796
o	-2.20475	-1.38524	1.56804
c	-2.59280	-0.45343	0.60480
o	-2.90978	-0.71982	-0.53199
h	-1.42725	-2.54716	-0.79892
n	-2.53825	0.78733	1.20848
c	-2.66680	2.08172	0.60245
o	-1.92122	2.96113	1.02766
c	-3.71934	2.28133	-0.41447
c	-3.56761	3.42391	-1.15163
o	-4.45325	3.78814	-2.08731
c	-4.20011	5.02551	-2.77753
c	-5.28601	5.22131	-3.81862
c	-4.92570	1.39282	-0.58953
h	-2.00344	0.82588	2.08375
h	-5.79678	2.00472	-0.90689
h	-5.18954	0.88021	0.36004
h	-4.75903	0.60367	-1.35271
h	-2.69792	4.08726	-0.98487
h	-4.19508	5.86022	-2.03765
h	-3.19144	4.97862	-3.25065
h	-5.11748	6.17191	-4.36850
h	-5.28531	4.38638	-4.55183
h	-6.28796	5.26541	-3.34052
h	-1.14721	-5.04193	-1.07893
n	-1.60533	-6.93050	0.76586
h	-2.40637	-5.68608	3.00251
h	-2.68674	-3.17238	3.30743
o	-1.86865	-7.65263	1.72807
o	-1.21727	-7.32703	-0.33367

2NH-EZZE
E(B3LYP/def2-TZVP)=-1064.426084283

35

c	-2.75755	-3.67544	0.26139
c	-3.29674	-4.80146	0.89812
c	-2.74621	-5.25413	2.10451
c	-1.65441	-4.60474	2.70276
c	-1.11108	-3.48426	2.07355
c	-1.65980	-3.02036	0.85812
o	-1.00604	-1.91262	0.36269
c	-1.35483	-1.22880	-0.75951
o	-2.29267	-1.46598	-1.49724
h	-3.17619	-3.30382	-0.68088
n	-0.48054	-0.16969	-0.98851
c	0.66705	0.28396	-0.27943
o	1.07383	-0.25781	0.74046
c	1.30508	1.47213	-0.91452
c	2.42235	1.92453	-0.27359
o	3.12883	2.97905	-0.70214
c	4.28670	3.34094	0.07243
c	4.95513	4.52866	-0.59327
c	0.78053	2.13542	-2.16427
h	-0.74604	0.34505	-1.83248
h	1.41716	3.00347	-2.43209
h	-0.25870	2.51942	-2.03599
h	0.78093	1.44739	-3.04213
h	2.77212	1.40692	0.64026
h	3.96629	3.58848	1.11145
h	4.97737	2.46693	0.12478
h	5.85438	4.83089	-0.01490
h	5.27241	4.27531	-1.62746
h	4.26261	5.39611	-0.64222
h	-4.15124	-5.34213	0.46650
n	-3.32751	-6.44526	2.76396
h	-1.25187	-4.99150	3.64940
h	-0.25353	-2.93902	2.49613
o	-2.82035	-6.80827	3.82668
o	-4.27882	-6.99603	2.20850

2NH-EZZZ

E(B3LYP/def2-TZVP)=-1064.425376873

35

c	-3.56301	-4.39865	1.42279
c	-3.10881	-3.11184	1.11038
c	-1.75021	-2.92699	0.77800
c	-0.85815	-4.01967	0.76386
c	-1.31423	-5.30160	1.07843
c	-2.66779	-5.47706	1.40260
o	-1.17652	-1.70459	0.50406
c	-1.89809	-0.64762	-0.07329
n	-1.00946	0.41192	-0.15209
c	-1.28660	1.70272	-0.68265
c	-0.11387	2.61965	-0.63348

c	1.22721	2.22771	-0.06458
h	0.19577	-3.83967	0.50185
o	-3.04871	-0.69556	-0.42314
o	-2.38674	1.99540	-1.12740
c	-0.34649	3.86097	-1.15138
o	0.58864	4.81936	-1.19338
c	0.19912	6.07586	-1.77914
c	1.38223	7.02252	-1.71243
h	-0.06862	0.22125	0.20191
h	1.93438	3.07958	-0.13161
h	1.68963	1.37571	-0.61648
h	1.16332	1.93945	1.01107
h	-1.34857	4.09907	-1.55739
h	-0.11888	5.90167	-2.83362
h	-0.67512	6.48260	-1.21928
h	1.10879	8.00171	-2.16076
h	1.69312	7.19397	-0.65961
h	2.25015	6.61135	-2.27116
h	-0.64529	-6.17366	1.07480
n	-3.15993	-6.83381	1.73366
h	-4.61420	-4.58292	1.68740
h	-3.80172	-2.26196	1.11380
o	-4.35220	-6.95166	2.01853
o	-2.34367	-7.75591	1.70284

2NH-ZEEE

E(B3LYP/def2-TZVP)=-1064.417018305

35

c	-0.80318	-5.07483	0.86763
c	-1.95099	-5.72096	1.35202
c	-2.91296	-5.03545	2.10536
c	-2.74122	-3.67389	2.38736
c	-1.59587	-3.01254	1.89170
c	-0.62955	-3.71687	1.13904
o	-1.29316	-1.68296	2.06864
c	-2.13205	-0.75808	2.64634
n	-1.66438	0.52217	2.40447
c	-0.69459	1.05427	1.50850
c	-0.47533	0.43399	0.17757
c	0.84222	0.78305	-0.47225
h	0.25572	-3.17160	0.77759
o	-3.09851	-1.00676	3.33744
o	-0.10918	2.07798	1.84656
c	-1.43175	-0.22796	-0.53865
o	-2.66997	-0.51028	-0.09430
c	-3.51857	-1.28442	-0.96138
c	-4.91228	-1.31230	-0.36258
h	-1.99709	1.21190	3.08733
h	0.91789	0.35464	-1.49435
h	1.69983	0.40320	0.12753
h	0.96769	1.88589	-0.53705
h	-1.21399	-0.54652	-1.57836

h	-3.52337	-0.82049	-1.97584
h	-3.09863	-2.31387	-1.05198
h	-5.58552	-1.92391	-1.00058
h	-4.89392	-1.75592	0.65595
h	-5.33203	-0.28626	-0.28856
h	-0.06812	-5.64917	0.28611
n	-2.14663	-7.15957	1.06178
h	-3.79220	-5.58453	2.47235
h	-3.47218	-3.12563	2.99321
o	-1.27319	-7.72837	0.40539
o	-3.17006	-7.69178	1.49287

2NH-ZEEZ

E(B3LYP/def2-TZVP)=-1064.421034889

35

c	-2.14908	-5.63854	1.41379
c	-2.14851	-5.00924	2.66721
c	-1.89918	-3.63566	2.73130
c	-1.65040	-2.90875	1.54994
c	-1.64720	-3.55081	0.29474
c	-1.89914	-4.92595	0.23229
o	-1.35628	-1.57319	1.72343
c	-1.80010	-0.61023	0.81182
o	-2.51848	-0.83907	-0.13333
h	-1.45319	-2.98016	-0.62255
n	-1.26142	0.59182	1.22173
c	-1.32655	1.88128	0.61630
o	-0.37621	2.63403	0.80765
c	-2.50438	2.27650	-0.18673
c	-3.78062	1.86152	0.06157
o	-4.14100	1.05298	1.06963
c	-5.41170	0.39348	0.94285
c	-5.74500	-0.26778	2.26696
c	-2.24246	3.35592	-1.21031
h	-0.51061	0.52959	1.91879
h	-3.17016	3.62558	-1.75824
h	-1.48100	3.03049	-1.95374
h	-1.83967	4.27142	-0.72375
h	-4.61419	2.24285	-0.56482
h	-6.18616	1.14690	0.66027
h	-5.33996	-0.35944	0.12515
h	-6.72982	-0.77794	2.19848
h	-4.97883	-1.02804	2.53162
h	-5.79363	0.48257	3.08537
h	-1.90223	-5.46482	-0.72608
n	-2.41714	-7.09372	1.33760
h	-2.34679	-5.60621	3.56871
h	-1.88924	-3.10217	3.69413
o	-2.40297	-7.61521	0.22219
o	-2.63687	-7.68532	2.39512

2NH-ZEZE
E(B3LYP/def2-TZVP)=-1064.425966201

35

c	-2.67454	-5.29652	1.75000
c	-1.70755	-4.69910	2.57439
c	-1.23401	-3.42937	2.24352
c	-1.72732	-2.76598	1.09892
c	-2.69879	-3.37124	0.27359
c	-3.16856	-4.64740	0.61099
o	-1.15687	-1.52676	0.90933
c	-1.48553	-0.65019	-0.08111
o	-2.32558	-0.81476	-0.94659
h	-3.07517	-2.84549	-0.61133
n	-0.72728	0.51042	0.00193
c	0.29020	0.90428	0.90232
o	0.68164	0.21128	1.83175
c	0.88487	2.25450	0.64261
c	0.52822	3.12305	-0.34744
o	-0.46211	2.90568	-1.24734
c	-0.59330	3.83960	-2.33575
c	-1.87256	3.52492	-3.08790
c	1.98035	2.63728	1.60659
h	-0.96866	1.18744	-0.73504
h	2.40061	3.63830	1.37151
h	2.80469	1.89095	1.58542
h	1.60159	2.64791	2.65218
h	1.04791	4.09580	-0.45087
h	-0.61165	4.87409	-1.91973
h	0.29918	3.74750	-2.99779
h	-1.98914	4.22654	-3.94135
h	-1.85399	2.48887	-3.48942
h	-2.75863	3.62808	-2.42569
h	-3.92437	-5.15601	-0.00451
n	-3.18316	-6.64361	2.09262
h	-1.34514	-5.24127	3.45925
h	-0.47532	-2.91482	2.85266
o	-4.02564	-7.14070	1.34368
o	-2.73100	-7.18082	3.10493

2NH-ZEZZ
E(B3LYP/def2-TZVP)=-1064.424564486

35

c	-3.54689	-4.32630	1.41539
c	-3.16736	-3.03066	1.04284
c	-1.81680	-2.78152	0.71386
c	-0.86500	-3.82484	0.75975
c	-1.24847	-5.11344	1.13236
c	-2.59272	-5.35159	1.45716
o	-1.28900	-1.56073	0.36313
c	-2.05374	-0.43347	0.02420

n	-1.13422	0.56876	-0.22590
c	-1.43433	1.90205	-0.58796
c	-0.24993	2.79617	-0.78908
c	-0.60750	4.20919	-1.17608
h	0.17965	-3.59670	0.49691
o	-3.25670	-0.38844	-0.03062
o	-2.57635	2.31262	-0.72486
c	1.06062	2.44525	-0.65204
o	1.50061	1.19659	-0.35151
c	2.88853	1.05058	0.00041
c	3.21509	-0.42930	0.07095
h	-0.13948	0.31983	-0.13793
h	0.29753	4.84170	-1.29669
h	-1.26816	4.67249	-0.41081
h	-1.18175	4.22549	-2.12854
h	1.86070	3.19535	-0.80866
h	3.50991	1.56536	-0.76933
h	3.06681	1.55166	0.98056
h	4.28061	-0.56738	0.35351
h	2.58616	-0.93934	0.83256
h	3.04696	-0.92044	-0.91150
h	-0.52990	-5.94396	1.17678
n	-3.00793	-6.71527	1.85392
h	-4.58905	-4.55748	1.67939
h	-3.90502	-2.22141	0.99783
o	-4.19467	-6.89062	2.13171
o	-2.13732	-7.58727	1.88106

2NH-ZZEE
E(B3LYP/def2-TZVP)=-1064.413364898

35

c	-2.47449	-4.27795	2.02136
c	-3.77146	-4.00622	1.56461
c	-4.06265	-2.85319	0.82066
c	-3.02979	-1.95768	0.53526
c	-1.72212	-2.22125	0.99104
c	-1.43607	-3.38315	1.73668
o	-0.77975	-1.29566	0.59162
c	0.37950	-1.05490	1.29984
n	1.17997	-0.15050	0.62080
c	0.95593	0.64484	-0.55778
c	0.37256	-0.03241	-1.74497
c	0.74137	-1.46519	-2.06154
h	-0.41897	-3.57664	2.09838
o	0.65206	-1.52746	2.38291
o	1.36102	1.79758	-0.53626
c	-0.39196	0.68051	-2.62473
o	-0.80431	1.93913	-2.42644
c	-1.47086	2.58495	-3.52044
c	-2.02530	3.90850	-3.02720
h	1.88374	0.27165	1.23829

h	0.40592	-1.73515	-3.08619
h	0.28266	-2.19681	-1.36156
h	1.84365	-1.61618	-2.02177
h	-0.74953	0.19596	-3.55768
h	-0.74140	2.74281	-4.34959
h	-2.28550	1.92259	-3.90223
h	-2.53309	4.44204	-3.85917
h	-2.75972	3.74907	-2.20895
h	-1.20803	4.55378	-2.64046
h	-2.29392	-5.19607	2.59855
n	-4.86207	-4.96054	1.87172
h	-5.09358	-2.67883	0.48177
h	-3.21169	-1.04008	-0.04461
o	-4.57259	-5.96136	2.52765
o	-5.98686	-4.68976	1.44883

2NH-ZZEZ
E(B3LYP/def2-TZVP)=-1064.417116111

35

c	-1.57841	-4.56378	-0.28301
c	-1.82004	-5.45166	0.77458
c	-2.18036	-4.99477	2.05088
c	-2.30519	-3.61976	2.26347
c	-2.06857	-2.71815	1.20634
c	-1.70122	-3.18557	-0.07223
o	-2.16128	-1.38354	1.54162
c	-2.60241	-0.42210	0.63167
n	-2.49620	0.80056	1.26233
c	-2.59900	2.12104	0.69744
c	-3.65271	2.36476	-0.31351
c	-4.97288	1.62644	-0.26479
h	-1.52094	-2.48028	-0.89310
o	-3.00162	-0.65817	-0.48698
o	-1.84594	2.96887	1.15653
c	-3.47331	3.35478	-1.24185
o	-2.36507	4.09126	-1.37671
c	-2.31722	4.98763	-2.49735
c	-1.04992	5.81488	-2.39139
h	-1.93587	0.80094	2.12283
h	-5.71197	2.11084	-0.93901
h	-5.40447	1.63841	0.76172
h	-4.86929	0.56576	-0.57790
h	-4.28603	3.56905	-1.96665
h	-2.33146	4.39423	-3.44262
h	-3.22390	5.63871	-2.48735
h	-0.97971	6.51537	-3.25117
h	-1.04393	6.40525	-1.45051
h	-0.15234	5.16036	-2.39584
h	-1.29274	-4.96873	-1.26431
n	-1.68896	-6.90840	0.54063
h	-2.35961	-5.72506	2.85259
h	-2.58607	-3.21864	3.24918

o -1.35720 -7.27431 -0.58755
o -1.92035 -7.65769 1.49024

2NH-ZZZE
E(B3LYP/def2-TZVP)=-1064.417115758

35

c -3.30666 -4.79803 0.84140
c -2.75895 -5.29521 2.03157
c -1.65875 -4.67706 2.64755
c -1.10442 -3.54309 2.05316
c -1.65063 -3.03370 0.85461
c -2.75693 -3.65781 0.24000
o -0.98648 -1.91798 0.39486
c -1.32402 -1.19779 -0.70886
n -0.43799 -0.14406 -0.90671
c 0.73617 0.25744 -0.19196
c 1.37269 1.47230 -0.77526
c 0.76862 2.19915 -1.95829
h -3.17370 -3.25131 -0.68861
o -2.26631 -1.40241 -1.45184
o 1.14818 -0.34849 0.78355
c 2.53551 1.96283 -0.24036
o 3.19794 1.44187 0.79312
c 4.40159 2.11776 1.19608
c 5.01077 1.34876 2.35311
h -0.70585 0.39998 -1.73066
h 1.37486 3.09000 -2.22976
h -0.26275 2.56854 -1.74924
h 0.71922 1.56189 -2.87301
h 2.98891 2.87072 -0.69061
h 5.10381 2.16531 0.32984
h 4.15170 3.16346 1.49483
h 5.94469 1.84684 2.69097
h 4.30381 1.30297 3.20850
h 5.25363 0.30874 2.04822
h -4.16776 -5.31556 0.39496
n -3.35214 -6.49979 2.65395
h -1.25823 -5.09819 3.58026
h -0.23942 -3.02141 2.48997
o -4.30837 -7.02425 2.08091
o -2.85032 -6.90033 3.70553

2NH-ZZZZ
E(B3LYP/def2-TZVP)=-1064.416225655

35

c -2.76742 -5.25911 1.46419
c -3.60431 -4.14162 1.58909
c -3.12749 -2.87230 1.24093

c	-1.80446	-2.74333	0.76660
c	-0.97182	-3.87609	0.64502
c	-1.45015	-5.14012	0.99598
o	-1.20310	-1.54653	0.44816
c	-1.92985	-0.42399	0.01250
o	-3.11492	-0.39964	-0.19749
h	0.05514	-3.74038	0.27257
n	-0.99999	0.59175	-0.12070
c	-1.27708	1.93562	-0.52938
o	-2.40627	2.29510	-0.81079
c	-0.06055	2.79368	-0.56122
c	-0.15764	4.10813	-0.93787
o	-1.28102	4.73063	-1.29418
c	-1.16787	6.11395	-1.67028
c	-2.55439	6.62302	-2.01626
c	1.30237	2.25270	-0.18466
h	-0.03804	0.32996	0.10767
h	2.08077	3.04116	-0.26899
h	1.62786	1.41585	-0.84726
h	1.33942	1.88322	0.86761
h	0.76264	4.72989	-0.95531
h	-0.72672	6.68972	-0.82213
h	-0.47749	6.20087	-2.54269
h	-2.50328	7.69221	-2.31421
h	-2.98711	6.04022	-2.85682
h	-3.23532	6.52905	-1.14390
h	-0.82631	-6.04121	0.91304
n	-3.28166	-6.59575	1.83850
h	-4.62846	-4.28142	1.96389
h	-3.77616	-1.99243	1.32612
o	-2.51497	-7.55256	1.71787
o	-4.44154	-6.66439	2.24714

3OH-EEZE

E(B3LYP/def2-TZVP)=-1064.409859500

35

c	0.07412	0.04846	1.84705
c	1.13660	-0.55077	2.55492
c	1.10231	-0.61268	3.95052
c	-0.00662	-0.07968	4.62387
c	-1.07058	0.51622	3.93143
c	-1.03439	0.58522	2.53448
n	-0.05241	-0.14659	6.10223
o	-1.04005	0.33057	6.66228
o	0.21309	0.12028	0.47906
c	-0.92103	-0.10366	-0.45031
n	-0.55054	-0.01551	-1.74544
c	0.65704	0.23325	-2.22414
c	0.89747	0.27533	-3.66331
c	2.27862	0.57026	-4.18480
o	0.90120	-0.67499	6.67598
o	-2.01417	-0.34043	0.00447

o	1.75504	0.46538	-1.49525
c	-0.17338	0.03210	-4.48324
o	-0.06698	0.04138	-5.81455
c	-1.26345	-0.24662	-6.56592
c	-0.92654	-0.17958	-8.04305
h	1.98623	-0.96930	1.99275
h	-1.16592	-0.18100	-4.04297
h	-1.63350	-1.25856	-6.28035
h	-2.04786	0.49741	-6.29481
h	-1.83269	-0.39959	-8.64710
h	-0.55818	0.83135	-8.32002
h	-0.14265	-0.92230	-8.30440
h	1.91432	-1.07208	4.53182
h	-1.91658	0.92416	4.50294
h	-1.86019	1.04442	1.97692
h	1.47310	0.40150	-0.52941
h	2.28644	0.56138	-5.29318
h	2.63738	1.56377	-3.83571
h	3.01650	-0.17796	-3.81924

3OH-EZZE

E(B3LYP/def2-TZVP)=-1064.408934712

35

c	1.43774	-0.22588	3.81820
c	0.40274	0.22328	4.65131
c	-0.85194	0.58143	4.13730
c	-1.08667	0.49301	2.76084
c	-0.05393	0.03857	1.91432
c	1.20226	-0.32279	2.44434
n	0.64363	0.32430	6.10882
o	-0.28864	0.71390	6.81270
o	-0.18143	-0.02748	0.54457
o	1.76180	0.01269	6.52164
c	-1.42369	-0.48139	-0.12276
n	-1.32701	-0.45719	-1.47323
c	-0.25817	-0.17542	-2.19407
c	-0.38104	-0.20709	-3.64774
c	-1.70738	-0.56787	-4.26043
o	-2.36557	-0.81463	0.55271
o	0.95500	0.13577	-1.70931
c	0.72547	0.09606	-4.39669
o	0.70282	0.08922	-5.73475
c	1.92700	0.43275	-6.41036
c	1.68814	0.34381	-7.90555
h	1.98862	-0.68232	1.76223
h	1.68489	0.35868	-3.91404
h	2.22960	1.46324	-6.11034
h	2.72986	-0.27076	-6.08745
h	2.61831	0.60661	-8.45347
h	1.38773	-0.68517	-8.19739
h	0.88595	1.04522	-8.21997
h	2.40589	-0.49699	4.26244

h	-1.63078	0.93154	4.82963
h	-2.06363	0.76740	2.34377
h	0.86152	0.15211	-0.70697
h	-1.64312	-0.56259	-5.36694
h	-2.03978	-1.57221	-3.91987
h	-2.49902	0.14404	-3.94036

Transition state for the direct 2NH to Phenol Hydrogen Transfer
E(B3LYP/def2-TZVP)=-1064.358055726

35

c	-2.40239	-4.39409	2.02309
c	-1.73785	-3.23073	2.44622
c	-1.06939	-2.44412	1.50734
c	-1.04986	-2.81312	0.13301
c	-1.72300	-4.00159	-0.26578
c	-2.39817	-4.78273	0.67158
o	-0.40429	-2.07096	-0.76627
c	-1.35411	-1.08888	-2.36933
o	-1.89157	-1.72774	-3.18496
n	-3.11322	-5.21902	3.01156
o	-3.68887	-6.23255	2.60511
n	-0.89523	-0.07151	-1.71647
c	-1.06614	1.31328	-2.14381
o	-1.67866	1.56157	-3.16948
c	-0.44273	2.26698	-1.21575
c	-0.58970	3.58169	-1.57271
o	-0.09056	4.58380	-0.84940
c	-0.31713	5.92323	-1.34107
c	0.33073	6.90055	-0.38033
c	0.29424	1.83379	0.02508
o	-3.09272	-4.84796	4.18910
h	-1.69941	-4.29093	-1.32811
h	-0.41574	-0.72228	-0.82918
h	0.69550	2.71764	0.56096
h	1.15064	1.16380	-0.21366
h	-0.36908	1.28332	0.73049
h	-1.14305	3.83978	-2.49653
h	0.11945	6.00812	-2.36301
h	-1.41543	6.09561	-1.41688
h	0.16964	7.94028	-0.73687
h	-0.10801	6.80753	0.63604
h	1.42468	6.72060	-0.30934
h	-2.92817	-5.70207	0.38303
h	-1.76279	-2.96383	3.51271
h	-0.53555	-1.53160	1.82052

Transition State for EEZE isomer
E(B3LYP/def2-TZVP)=-1064.397785941

35

c	1.20004	-0.40966	3.63584
c	0.10496	-0.18106	4.48493
c	-1.06649	0.43730	4.01933
c	-1.14452	0.84180	2.68442
c	-0.05231	0.61956	1.81088
c	1.11745	-0.01574	2.29882
n	0.18915	-0.59921	5.89777
o	-0.79004	-0.38507	6.61598
o	-0.11891	1.02808	0.52446
o	1.23402	-1.13710	6.27246
c	-1.35191	0.25102	-0.60013
n	-0.80260	0.16398	-1.76974
c	0.48437	0.39581	-2.12520
c	0.88748	0.18007	-3.50585
c	2.31413	0.45151	-3.90011
o	-2.35937	0.02887	-0.01530
o	1.39933	0.80498	-1.30241
c	-0.06719	-0.25784	-4.38956
o	0.19875	-0.45544	-5.67889
c	-0.83889	-1.01978	-6.50806
c	-0.60725	-0.58402	-7.94246
h	1.95995	-0.19202	1.61085
h	-1.10096	-0.44914	-4.04334
h	-0.79251	-2.12881	-6.40965
h	-1.83139	-0.67995	-6.13329
h	-1.37352	-1.04300	-8.60340
h	-0.67499	0.52068	-8.03992
h	0.39500	-0.90739	-8.29599
h	2.09701	-0.89851	4.04226
h	-1.89700	0.59896	4.72145
h	-2.04471	1.33845	2.29577
h	0.87181	0.95255	-0.30500
h	2.48132	0.19892	-4.96608
h	2.57561	1.52159	-3.74341
h	3.01976	-0.13935	-3.27606

Transition State for EZZE isomer
E(B3LYP/def2-TZVP)=-1064.396547491

35

c	0.61848	-0.05891	4.30963
c	-0.70152	0.38973	4.14185
c	-1.15657	0.72160	2.86347
c	-0.29295	0.59542	1.74769
c	1.03341	0.13159	1.93889
c	1.49254	-0.18757	3.21806
o	-0.72486	0.92869	0.51190
n	1.10021	-0.40085	5.66197
o	2.26852	-0.78100	5.77241
o	0.30528	-0.28609	6.59739
c	-2.09027	-0.05994	-0.25973
o	-2.91537	-0.31357	0.55103
n	-1.80136	-0.20702	-1.51548

c	-0.66325	0.11424	-2.16886
o	0.35330	0.70006	-1.60745
c	-0.60756	-0.23140	-3.58241
c	0.53406	0.11644	-4.25960
o	0.70475	-0.15557	-5.55341
c	1.93252	0.29611	-6.16413
c	1.95822	-0.18817	-7.60039
h	1.69677	0.02667	1.06509
c	-1.76559	-0.93735	-4.23536
h	1.35734	0.64046	-3.73815
h	1.96970	1.40882	-6.11038
h	2.79353	-0.10879	-5.58346
h	2.89265	0.15258	-8.09536
h	1.92192	-1.29765	-7.64578
h	1.09377	0.21535	-8.16965
h	2.51766	-0.54404	3.39435
h	-1.34785	0.48041	5.02662
h	-2.18142	1.08668	2.70597
h	0.04542	0.88903	-0.53315
h	-1.55709	-1.11922	-5.30876
h	-1.97005	-1.91247	-3.74126
h	-2.69890	-0.33958	-4.14860

Product Complex EEZE

E(B3LYP/def2-TZVP)=-1064.425976133

35

c	-0.86892	0.73392	2.10624
c	0.54963	0.69959	2.06736
c	1.27408	0.28159	3.18531
c	0.58880	-0.10284	4.34941
c	-0.81617	-0.07204	4.40881
c	-1.54001	0.34437	3.29278
n	1.35357	-0.54439	5.52483
o	0.71913	-0.86949	6.53270
o	-1.61598	1.12891	1.06047
o	2.58499	-0.56470	5.43426
o	-0.17887	1.43195	-1.15164
c	-0.39248	0.64736	-2.08926
c	0.39453	0.68477	-3.31804
c	1.48828	1.71258	-3.41255
n	-1.40834	-0.32786	-2.03560
c	-2.26510	-0.72664	-1.25131
o	-3.12623	-1.21979	-0.62421
c	0.11339	-0.20818	-4.31998
o	0.80041	-0.23437	-5.46218
c	0.38270	-1.18935	-6.46190
c	1.35307	-1.11840	-7.62460
h	1.07276	1.00910	1.14802
h	-0.70393	-0.94583	-4.20654
h	0.36926	-2.20599	-6.00537
h	-0.65460	-0.93814	-6.78351
h	1.04909	-1.84040	-8.41228

h	1.36485	-0.10023	-8.06886
h	2.38399	-1.37106	-7.29658
h	2.37301	0.24627	3.18019
h	-1.31449	-0.37907	5.33959
h	-2.64034	0.37875	3.30588
h	-1.03394	1.34633	0.26157
h	1.98025	1.67714	-4.40470
h	1.08500	2.73533	-3.24489
h	2.25838	1.54629	-2.62666

Product Complex EEZE
E(B3LYP/def2-TZVP)=-1064.424492225

35

c	1.00777	-0.09672	4.01097
c	-0.23114	0.51600	4.27128
c	-0.98963	1.00574	3.20932
c	-0.51995	0.88843	1.87671
c	0.73384	0.26860	1.63485
c	1.49372	-0.22081	2.69903
o	-1.28956	1.38180	0.89121
n	1.80953	-0.61330	5.12977
o	2.89340	-1.14197	4.86368
o	1.35113	-0.48835	6.26921
c	-3.14334	-0.26168	-0.85020
o	-3.93351	-0.33531	0.01434
n	-2.43580	-0.27313	-1.85317
c	-1.15568	0.12464	-2.26987
o	-0.39011	0.76615	-1.52828
c	-0.83587	-0.28464	-3.63898
c	0.40200	0.09055	-4.09498
o	0.83495	-0.21182	-5.31799
c	2.15524	0.24817	-5.68300
c	2.46559	-0.25522	-7.07898
h	1.10076	0.17881	0.59972
c	-1.81786	-1.06190	-4.47504
h	1.08240	0.66462	-3.43704
h	2.17025	1.36171	-5.63889
h	2.88854	-0.13939	-4.93872
h	3.48000	0.08078	-7.38245
h	2.43947	-1.36543	-7.11450
h	1.73181	0.13774	-7.81482
h	2.46801	-0.70439	2.53820
h	-0.57588	0.59479	5.31232
h	-1.96417	1.48904	3.37869
h	-0.86473	1.22270	-0.01401
h	-1.36532	-1.33938	-5.44848
h	-2.14176	-1.99241	-3.95944
h	-2.73869	-0.46970	-4.67550

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A convenient, high-yield synthesis of 1-substituted uracil and thymine derivatives

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ABSTRACT

Novel reagents for the synthesis of 1-substituted uracil and thymine derivatives have been developed. The aminolysis of 2- or 4-nitrophenyl 3-ethoxyacryloylcarbamate and 3-ethoxy-2-methylacryloylcarbamate with a variety of primary amino derivatives proceeded smoothly under very mild reaction conditions yielding almost quantitatively the 1,3-disubstituted urea derivatives. Their subsequent cyclization provided the 1-substituted uracil and thymine compounds, in almost quantitative yield.

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1. Introduction

Nucleosidation is often a crucial step in the synthesis of analogues of nucleosides. Purine nucleoside analogues are usually prepared via direct alkylation of the appropriate nucleobases (adenine, 2-amino-6-chloropurine, etc.) with the halo, tosyloxy, or mesyloxy derivatives,^{1–4} or under Mitsunobu conditions.^{2,3} However, all of these methods for the introduction of pyrimidine

a competing elimination reaction which further decreases the yield of the desired compounds. As an alternative approach to the pyrimidine nucleoside analogues (e.g., carbocyclic nucleosides), a synthesis of 1-*N*-substituted nucleobases starting from a primary amine and isocyanate **3** or carbamate **6** was described fifty years ago by Shaw and Warren.⁵ The key isocyanates **3**, accessible by two independent routes^{6,7} (Scheme 1), were used as intermediates for the synthesis of carbamates **6** described by Hřebaběcký.⁸

Scheme 1.

nucleobases (uracil, thymine, and cytosine) suffer from both low regioselectivity and yield of the 1-*N*-substituted product.^{2,3} In some cases, the direct alkylation of nucleobases is accompanied by

Isocyanates **3** are extremely moisture-sensitive species and also very reactive compounds capable of forming carbamates with free hydroxy groups.⁹ The reaction, therefore, is usually carried out either with the appropriately protected substrate or without protection at low temperature.

The formation of uracil and thymine rings is a two-stage reaction consisting of the aminolysis of carbamate **6** or the addition of amine to isocyanate **3** followed by a cyclization of the formed acryloylurea **9**

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(Scheme 2). Both basic (aqueous alkali or ammonia, tertiary amines in organic solvent) and acidic (organic or inorganic acids in either aqueous or organic solvents) conditions were described for the cy-

Scheme 2.

clization of the ureas. Best results were obtained with aqueous sulfuric acid or 15 M aqueous ammonia according to Shealy and Dell.¹⁰

Recently we described the synthesis of pyrrolidine nucleoside analogues using alkylation of purine and pyrimidine nucleobases with various pyrrolidine mesyloxy derivatives.^{2–4} In contrast to the purine nucleobases, the yields and regioselectivity of alkylations of pyrimidine nucleobases are unsatisfactory. Therefore, we attempted to use Hřebabecský's⁸ reagents **6a** and **6b** for the synthesis of uracil and thymine rings to obtain pyrrolidine compounds **10b** and **10n** (Table 1), respectively. While the 'thymine reagent' **6b** provided a moderate yield of **10n**, the 'uracil reagent' **6a** yielded no product **10b** at all. In the latter case, we only

Table 1
Synthesis of uracil and thymine derivatives using reagents **7a** and **7b**

RNH ₂ 8	9 /Yield% R ¹ =H	10 /Yield%	Overall yield U %	9 /Yield% R ¹ =CH ₃	10 /Yield%	Overall yield T %
a	a /85	a /97	82(30) ³	m /96	m /93	89(29) ³
b	b /87	b /90	78	n /99	n /90	89(24) ⁴
c	c /90	c /80	72	—	—	—
d	d /88	d /98	86 (11) ²³	—	—	—
e	e /88	e /99	87	o /82	o /95	77
f	f /99	f /78	77 (40) ²⁴	p /78	p /96	75(18) ²⁴
g	g /95	g /95	90 (15) ²⁵	—	—	—
h	h /88	h /92	81	q /89	q /97	86
i	i /87	i /98	85(69) ²⁶	r /63(76) ^a	r /97	61(45) ²⁷
j	j /94	j /96	90 (63) ²⁸	s /87	s /99	86 (59) ²⁸
k	k /87	k /84	73 (76) ²⁹	—	—	—
l	l /87	l /96	83	—	—	—
m	—	—	—	t /90	t /97	87

Urea derivatives **9a–l** and **9m–t** were synthesized using **7a** and **7b**, respectively. All cyclizations of **9–10** were carried out with Dowex 50 in H⁺ form.

^a When **7d** was used, we obtained **9r** in 76% yield instead of a 64% one obtained with **7b**.

observed the reagent decomposition. We concluded that we needed a reagent more reactive than **6a** and **6b** that would be able to react with the primary amine under milder conditions but which, at the same time, would not be as reactive as the isocyanates **3a–b**. We wanted to avoid the use of these moisture-sensitive and extremely reactive agents, which can react with the unprotected hydroxy groups. This property seems to be a main factor responsible for the varying yield of the reported uracil and thymine derivatives (usually ~20–80%, in most cases <60%) found in the literature.^{11–22} We decided, therefore, to modify the original Hřebabecský's reagents **6**⁸ by exchanging the ethyl ester group for a more reactive nitrophenyl one.

2. Results and discussions

The synthesis of the reagents **7a** and **7b** followed the procedure described for **6**,⁸ whereby in the last step of this 'one pot' synthesis, a 2-nitrophenol solution in dioxane was added instead of ethanol. The reaction mixture was then concentrated in vacuo and the desired product was obtained by a crystallization from a mixture of toluene and petroleum ether. All procedures were carried out under strict exclusion of moisture under an argon atmosphere. By the same synthetic route we also prepared the 4-nitrophenyl esters **7c** but in a lower yield than **7a** (44% and 57%, resp.) due to a more difficult crystallization of **7c**.

The 'uracil reagents' **7a** and **7c** were fully characterized by NMR, MS, and elemental analysis. On the other hand, the characterization of the 'thymine reagent' **7b** appeared to be more difficult due to its unexpectedly high reactivity. The ¹H NMR spectrum of **7b** recorded in commercial grade CDCl₃ showed a mixture of at least four compounds identified as 3-ethoxy-2-methylacryloylcarbamic acid, 3-ethoxy-2-methylacryloylamide (as the product of decarboxylation of the former compound), 2-nitrophenol, and **7b**. If the measurement was performed in CDCl₃ adjusted prior to use by passing it through a short pad of anhydrous potassium carbonate, the spectrum did show the appropriate, expected signals of the reagent **7b** but still in the course of the data acquisition (~1 h), the signals of **7b** gradually disappeared and the signals of 2-nitrophenol and isocyanate **3b** appeared instead. When dry methanol was added to the solution of **7b** in NMR cuvette (in any stage of the NMR measurement), the immediate formation of the methyl ester **11** (~90%) was observed. The IR spectrum recorded in potassium carbonate-treated CDCl₃ showed the presence of the isocyanate moiety (band at 2244, w). These results clearly showed that the high reactivity of **7b** is caused, in fact, by the presence of isocyanate **3b** formed by the spontaneous elimination of 2-nitrophenol from **7b** (Scheme 3). In contrast to **7b**, the 4-nitrophenyl ester **7d** was found to be stable in untreated (commercial grade) CDCl₃ so that NMR spectra could be easily recorded.

Scheme 3.

The mechanism of the instability of **7b** in the solution is unclear. A detailed study on the reaction kinetics, along with the ab initio calculations, which would explain this phenomenon and especially the differences in reactivity of nitrophenyl esters **7a–7d**, is underway.

The prepared reagents **7a** and **7b** were used for the synthesis of desired pyrrolidine nucleosides **10a–c** and **10m,n** in very good yields (see Table 1). A more detailed study on these pyrrolidine

nucleosides, as well as the conformational study, will be published elsewhere. The properties of reagents **7a** and **7b** were further evaluated with a series of commercially available amines **8d–m**. The reactivity of the 4-nitrophenyl 'uracil reagent' **7c** was identical with that of 2-nitrophenyl ester **7a** (data not shown). The reactions were carried out according to the Scheme 2. The results are summarized in Table 1 (yields given in parentheses refer to the cited literature). In all cases, the cyclization was accomplished by heating the respective urea derivatives **9a–t** with Dowex 50 (H⁺ form) in dioxane. Excellent yields of uracil and thymine derivatives were obtained in all cases, as obvious from Table 1.

In the case of free amines, the aminolysis proceeded in dioxane at room temperature. In the case of amine hydrochlorides, the reaction was carried out in DMF with 1 equiv of DBU to release the free amine for the aminolysis. Because of high reactivity of 'thymine reagent' **7b** toward amines bearing free hydroxy groups, the reaction was performed in DMF at –20 °C to suppress potentially competing reaction with hydroxyls and thus obtain optimal results. When performing the reaction at room temperature, the formation of side products was observed. A lower yield (63%) of the urea derivative **9r** originating from 3-aminopropane-1,2-diol (**8i**) seems to be very probably caused by the presence of moisture in the amine **8i**. We repeated the synthesis of **10r** with the reagent **7d**. The aminolysis was carried out in dioxane at rt whereby the urea derivative **9r** was obtained in 76% yield.

Simple amines **8d,e**, as well as the aromatic amines **8j** and **8m**, afforded excellent yields in both aminolysis and cyclization reaction. To show the usefulness of the reagents in the case of amines containing free hydroxy groups, the compounds **8f–i** were selected as a starting material. Amino acid esters **8k,l** were also evaluated, in order to widen the scope of the novel reagent's utility.

3. Conclusion

In conclusion, the synthesis of novel, versatile reagents for uracil (**7a,7c**) and thymine (**7b,7d**) introduction giving consistently high yields has been developed and its practical usefulness proved. The smooth formation of 1,3-disubstituted urea derivatives and, thus, a broad versatility of the prepared carbamates was proved using a variety of structurally diverse amines containing also free hydroxyl functionalities. The reagents are crystalline solids and can be stored for a long time at rt (**7a,7c**, and **7d**) or in freezer (**7b**). The use of the 4-nitrophenyl derivatives **7c** and **7d** is highly recommended for the introduction of uracil and thymine moieties, respectively, because of their optimal reactivity and high stability. The use of the 4-nitrophenyl esters of 2-substituted 3-ethoxyacryloylcarbamates is beneficial for the synthesis of 5-substituted uracil derivatives, because high yields are achieved while the method is preparatively simple.

4. Experimental

4.1. General

Unless stated otherwise, all used solvents were anhydrous. Amines **8d–m** were purchased from Sigma-Aldrich (Czech Republic) and used directly. TLC was performed on UV 254 silica gel

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pre-coated aluminum plates (Merck). Compounds were detected by UV light (254 nm) and/or by spraying with 1% ethanolic solution of ninhydrin to visualize amines. Preparative column chromatography was carried out on silica gel (40–60 μ m; Fluka), and the elution was performed at the flow rate of 40 ml/min. The following solvent systems were used for TLC and the preparative chromatography: toluene/ethyl acetate 1:1 (T); chloroform/ethanol 9:1 (C1). The concentrations of solvent systems are stated in volume percents. Analytical RP HPLC was performed on LC5000 Liquid Chromatograph (INGOS-PIKRON, Czech Republic) using Luna C18 (2) column (4.6 $\times$ 150 mm) at a flow rate of 1 ml/min under gradient elution of methanol in 0.1 M TEAA pH 7.5 (A=0.1 M TEAA; B=0.1 M TEAA in 50% aqueous methanol; C=methanol). Mass spectra were recorded on LTQ Orbitrap XL (Thermo Fisher Scientific) instrument using ESI method. Bruker AVANCE 500 (^1H at 500 MHz, ^{13}C at 125.7 MHz) and Bruker AVANCE 600 (^1H at 600.1 MHz, ^{13}C at 150.9 MHz) spectrometers were used for NMR spectra measurement. Chemical shifts (in ppm, δ scale) were referenced to TMS as internal standard or to a solvent signal; coupling constants (J) are given in Hz. Complete assignment of protons and carbons was done by analysis of correlated homonuclear 2D-COSY and heteronuclear ^1H – ^{13}C HSQC and ^1H – ^{13}C HMBC spectra. Relative configuration was checked using DPGSE-NOE and 2D-ROESY techniques. Nucleobase atom numbering was used also in the case of linear intermediates:

4.2. General method for aminolysis A

Reagent **7a**, **7c** or **7d** (1.1 equiv) or **7b** (1.3 equiv) was added to the solution of amine in dioxane (10 ml/mmol), and the reaction mixture was stirred at rt for 20 min. Solvent was removed in vacuo and the product was obtained by column chromatography on silica gel using a linear gradient of ethyl acetate in toluene.

4.3. General method for aminolysis B

Reagent **7b** (1.3 equiv) was added to the solution of amine in DMF (10 ml/mmol) at -20°C . The reaction mixture was stirred at -20°C for 20 min. Solvent was removed in vacuo and the product was recovered using column chromatography on silica gel under a linear gradient of ethyl acetate in toluene.

4.4. General method for aminolysis C

Reagent **7a** (1.1 equiv) or **7b** (1.3 equiv) was added to the solution of amine and DBU (1 equiv) in DMF (10 ml/mmol). The reaction mixture was stirred at rt for 20 min. Solvent was removed in vacuo and the product was obtained by column chromatography on silica gel using a linear gradient of ethyl acetate in toluene.

4.5. General method for aminolysis D

Reagent **7b** (1.3 equiv) was added to the solution of amine and DBU (1 equiv) in DMF (10 ml/mmol) at -20°C . The reaction mixture was stirred at -20°C for 20 min. Solvent was removed in vacuo and the product was obtained by column chromatography on silica gel using a linear gradient of ethyl acetate in toluene.

4.6. General method for cyclization E

Dowex 50 in H^+ form (2 g/mmol) was added to the solution of **9** in dioxane (10 ml/mmol). The reaction mixture was heated to 90°C for 3 h.

4.6.1. 2-Nitrophenyl 3-ethoxyacryloylcarbamate (7a). Ethoxyethylene (19 ml, 200 mmol) in dioxane (150 ml) was added to a solution of chlorocarbonylisocyanate (15 g, 142 mmol) in dioxane (200 ml) at 10°C under an argon atmosphere during 20 min followed by triethylamine (20 ml, 142 mmol) in dioxane (150 ml) at 10°C during 20 min (a white thick precipitate of triethylamine hydrochloride appeared). To this suspension, a solution of 2-nitrophenol (25 g, 180 mmol), [co-evaporated with toluene (2×100 ml) and dioxane (2×100 ml)], in dry dioxane (200 ml) was added at 10°C under argon atmosphere during 30 min. The reaction mixture was stirred at 10°C for 30 min, filtered under argon atmosphere, and the filtrate was concentrated in vacuo. The residue was triturated with 20% petroleum ether in toluene (250 ml). The yellowish crystals were immediately filtered off (under argon atmosphere), washed with 20% petroleum ether in toluene (2×50 ml) and then with petroleum ether (100 ml), and finally dried in vacuo over phosphorus pentoxide. The desired reagent **7a** was obtained in 57% yield (22.6 g, 80.65 mmol) in the form of yellowish crystals (mp 124.6°C), ν_{max} (CHCl_3) 3400 (m), 3127 (w), 1808 (w, sh), 1783 (s), 1689 (s), 1621 (s, sh), 1605 (vs), 1534 (vs), 1490 (m), 1450 (s, sh), 1376 (m), 1350 (s), 1316 (m), 1251 (m), 1169 (vs), 1152 (vs), 1087 (s), 1023 (m), 980 (w, sh), 961 (m), 867 (w), 815 (w), 692 (m), 655 (w), 555 (vw), 508 (w), 448 (vw). δ_{H} (500.0 MHz, CDCl_3) 1.34 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_3), 3.98 (2H, qd, $J(\text{CH}_2, \text{CH}_3)=7.1$, $J(\text{CH}_2, 6)=0.5$, OCH_2CH_3), 6.36 (1H, d, $J(5,6)=12.3$, H-5), 7.35 (1H, dd, $J(6',5')=8.2$, $J(6',4')=1.3$, H-6'), 7.45 (1H, ddd, $J(4',3')=8.2$, $J(4',5')=7.4$, $J(4',6')=1.3$, H-4'), 7.69 (1H, ddd, $J(5',6')=8.2$, $J(5',4')=7.4$, $J(5',3')=1.6$, H-5'), 7.85 (1H, dt, $J(6,5)=12.3$, $J(6, \text{CH}_2)=0.5$, H-6), 8.13 (1H, dd, $J(3',4')=8.2$, $J(3',5')=1.6$, H-3'), 8.39 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl_3) 14.24 (CH_3), 67.31 (OCH_2CH_3), 96.27 (C-5), 125.37 (C-6'), 125.88 (C-3'), 127.09 (C-4'), 134.87 (C-5'), 141.69 (C-2'), 143.15 (C-1'), 149.51 (C-2), 165.47 (C-6), 167.28 (C-4). For $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_6$ (280.23) calcd: 51.43% C, 4.32H, 10.00% N; found: 51.36% C, 4.33% H, 9.82% N. HRMS for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$ calcd 281.0768, found 281.0763.

4.6.2. 2-Nitrophenyl 3-ethoxy-2-methylacryloylcarbamate (7b). The title compound was prepared from 1-ethoxypropene (22 ml, 200 mmol) using the same procedure as for compound **7a** in 59% yield (24.66 g, 83.8 mmol) of yellowish crystals. Crystallization of the product **7b** proceeded in the refrigerator overnight (mp 139 – 143°C), ν_{max} (KBr) 3293 (s), 3183 (w), 3104 (w), 3084 (w), 3048 (w), 1787 (vs), 1762 (s), 1678 (s), 1648 (s), 1621 (m), 1605 (m), 1605 (m), 1591 (m), 1533 (vs), 1524 (vs, sh), 1511 (s, sh), 1478 (s), 1450 (m), 1388 (m), 1369 (m, sh), 1352 (s), 1316 (m, sh), 1305 (s), 1211 (vs), 1184 (vs), 1160 (s), 1147 (s), 1122 (s), 1084 (s), 1026 (m), 975 (m), 959 (w, sh), 870 (w), 858 (w), 777 (m, sh), 761 (m), 747 (m), 704 (m), 688 (m), 629 (m), 559 (w), 435 (w). δ_{H} (600.1 MHz, CDCl_3) 1.33 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_3), 1.83 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 4.09 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 7.35 (1H, dd, $J(6',5')=8.2$, $J(6',4')=1.3$, H-6'), 7.42 (1H, ddd, $J(4',3')=8.2$, $J(4',5')=7.4$, $J(4',6')=1.3$, H-4'), 7.50 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 7.67 (1H, ddd, $J(5',6')=8.2$, $J(5',4')=7.4$, $J(5',3')=1.6$, H-5'), 8.09 (1H, dd, $J(3',4')=8.2$, $J(3',5')=1.6$, H-3'), 8.17 (1H, br s, H-3). δ_{C} (150.9 MHz, CDCl_3) 9.10 (5- CH_3), 15.32 ($\text{CH}_3\text{CH}_2\text{O}$), 70.44 (OCH_2CH_3), 107.04 (C-5), 125.49 (C-6'), 125.76 (C-3'), 126.89 (C-4'), 134.85 (C-5'), 141.63 (C-2'), 143.26 (C-1'), 148.23 (C-2), 158.68 (C-6), 165.99 (C-4). Note: CDCl_3 must be made anhydrous by treating with K_2CO_3 and the NMR spectra must be measured as fast as possible because of the instability of the reagent!!

4.6.3. 4-Nitrophenyl 3-ethoxyacryloylcarbamate (7c). The title compound was prepared from 1-ethoxyethylene (19 ml, 200 mmol)

using the same procedure as for compound **7a** in 44% yield (17.5 g, 62.48 mmol) of light beige crystals. Crystallization of the product **7c** proceeded in the refrigerator overnight (mp 131.3 °C), $\nu_{\max}(\text{KBr})$ 3316 (m), 3266 (s), 3195 (m), 3116 (m), 3090 (m), 3060 (m), 3029 (w), 2996 (m), 2956 (w), 2912 (w), 2858 (w), 1802 (vs, sh), 1793 (vs), 1766 (m, sh), 1707 (m), 1691 (s), 1629 (vs, br), 1615 (vs, sh), 1595 (s), 1532 (vs, sh), 1516 (vs, br), 1491 (vs), 1473 (s, sh), 1450 (m), 1402 (m), 1362 (vs), 1354 (vs), 1331 (s), 1302 (m), 1259 (vs), 1207 (vs, sh), 1193 (vs, br), 1177 (s, sh), 1143 (vs, br), 1110 (s), 1107 (s), 1094 (m, sh), 1052 (w), 1021 (s), 978 (vs), 970 (s, sh), 954 (m), 871 (vs), 862 (vs), 749 (s), 719 (s), 678 (s), 633 (w), 529 (w), 494 (m). δ_{H} (500.0 MHz, CDCl_3) 1.37 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 4.02 (2H, qd, $J(\text{CH}_2, \text{CH}_3)=7.1$, $J(\text{CH}_2, 6)=0.5$, OCH_2CH_3), 6.40 (1H, d, $J(5,6)=12.3$, H-5), 7.37 (2H, m, H-2',6'), 7.87 (1H, dt, $J(6,5)=12.3$, $J(6, \text{CH}_2)=0.6$, H-6), 8.30 (2H, m, H-3',5'), 8.34 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl_3) 14.28 ($\text{CH}_3\text{CH}_2\text{O}$), 67.51 (OCH_2CH_3), 96.23 (C-5), 122.33 (C-2',6'), 125.12 (C-3',5'), 145.50 (C-4'), 149.50 (C-2), 154.53 (C-1'), 165.67 (C-6), 167.37 (C-4). HRMS for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}^+$) calcd 281.0768, found 281.0763.

4.6.4. 4-Nitrophenyl 3-ethoxy-2-methylacryloylcarbamate (7d). The title compound was prepared from 1-ethoxypropene (7.3 ml, 66.36 mmol) using the same procedure as for compound **7a** in 60% yield (8.43 g, 28.65 mmol) of white crystals. Crystallization of the product **7c** proceeded in the refrigerator overnight (mp 92.4 °C), $\nu_{\max}(\text{KBr})$ 3330 (m, br, sh), 3244 (m), 3173 (m), 3117 (m), 3083 (m), 3053 (w), 1824 (w), 1780 (vs), 1770 (vs), 1758 (s), 1677 (s, sh), 1661 (s), 1649 (vs), 1615 (m), 1592 (m), 1526 (vs, br), 1488 (vs), 1449 (m), 1388 (w), 1373 (m), 1347 (vs), 1305 (s), 1227 (vs, sh), 1218 (vs), 1185 (vs, br), 1114 (vs), 1093 (m, sh), 863 (m, sh), 857 (s), 764 (m), 746 (m), 709 (m), 681 (m), 610–615 (w, br), 540 (w), 532 (w), 500 (w). δ_{H} (499.8 MHz, CDCl_3) 1.34 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, $\text{CH}_3\text{CH}_2\text{O}$), 1.84 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 4.10 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 7.33 (2H, m, H-2',6'), 7.53 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 8.24 (2H, m, H-3',5'), 8.30 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl_3) 9.00 (5- CH_3), 15.25 ($\text{CH}_3\text{CH}_2\text{O}$), 70.54 (OCH_2CH_3), 106.95 (C-5), 122.10 (C-2',6'), 125.12 (C-3',5'), 145.25 (C-4'), 148.23 (C-2), 154.55 (C-1'), 158.82 (C-6), 166.29 (C-4). For $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_6$ (294.09) calcd: 53.06% C, 4.80% H, 9.52% N; found: 53.00% C, 4.80% H, 9.43% N.

4.6.5. (3R)-3-Amino-1-N-Boc-pyrrolidine (8a). A mixture of (3S)-1-N-Boc-3-mesyloxy-pyrrolidine³ (4.87 g, 18.35 mmol) and sodium azide (6.5 g, 100 mmol) in DMF (150 ml) was stirred at 110 °C for 5 h. DMF was removed in vacuo and the crude azido derivative [HRMS for $\text{C}_9\text{H}_{16}\text{N}_4\text{O}_2$ ($\text{M}+\text{Na}^+$) calcd 235.1165, found 235.1166] was purified using column chromatography on silica gel employing a linear gradient of ethyl acetate in toluene. The obtained azido derivative was dissolved in ethanol (200 ml) and on addition of Pd/C (0.4 g), it was hydrogenated at 10 psi overnight. Pd catalyst was filtered over Celite. Ethanol was then evaporated giving a 73% (2.5 g, 13.49 mmol) overall yield of title compound in the form of yellowish oil, which needed no further purification (NMR checking). $\nu_{\max}(\text{CHCl}_3)$ 3379 (w), 3315 (w), 3165 (w, br), 2980 (vs), 1685 (vs, vbr), 1478 (s), 1455 (s), 1413 (vs, vbr), 1390 (vs, sh), 1367 (vs), 1249 (s), 1168 (vs, br), 1130 (vs, sh), 1123 (vs), 461 (w). δ_{H} (500.0 MHz, $\text{DMSO}-d_6$ mixture of two amidic isomers 1:1) 1.38 (18H, s, $(\text{CH}_3)_3\text{C}$), 1.51 and 1.85 (2×2H, 2×br m, H-4), 2.87 (2H, dd, $J_{\text{gem}}=10.6$, $J(2b,3)=4.8$, H-2b), 3.14–3.22 (2H, m, H-5b), 3.26–3.34 (4H, m, H-2a,5a), 3.37 and 3.38 (2×2H, 2×m, H-3). δ_{C} (125.7 MHz, $\text{DMSO}-d_6$, mixture of two amidic isomers 1:1) 28.44 ($(\text{CH}_3)_3\text{C}$), 33.64 and 34.39 (C-4), 44.26 and 44.47 (C-5), 50.30 and 51.18 (C-3), 54.06 and 54.35 (C-2), 78.20 ($\text{C}(\text{CH}_3)_3$), 153.85 and 153.90 (CO). HRMS for $\text{C}_9\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$) calcd 187.1441, found 187.1439.

4.6.6. (3S,4R)-4-Amino-1-N-Boc-3-dimethoxytrityloxy-pyrrolidine (8b). A mixture of (3S,4S)-1-N-Boc-4-dimethoxytrityloxy-3-mesyloxy-pyrrolidine⁴ (8 g, 13.69 mmol) and sodium azide (4.3 g,

66 mmol) in DMF (130 ml) was stirred at 110 °C for 5 h. DMF was removed in vacuo, the residue was dissolved in ethyl acetate, and the solution filtered through a pad of Celite and finally submitted to flash chromatography on silica gel using linear gradient of ethyl acetate in toluene. The obtained crude azido derivative was dissolved, without further purification in ethanol (200 ml), the Pd/C catalyst (0.4 g) was added, and the whole was hydrogenated at 10 psi for 6 h. The catalyst was then filtered off using Celite, ethanol was evaporated, and the title compound was obtained by column chromatography on silica gel using a linear gradient of ethanol in chloroform in 72% yield (4.98 g, 9.87 mmol) in the form of white foam. $\nu_{\max}(\text{KBr})$ 3057 (w), 3036 (w), 3000 (w), 2972 (m), 2836 (w), 1695 (vs), 1608 (m), 1582 (w), 1509 (s), 1492 (w, sh), 1477 (w), 1463 (m), 1456 (m), 1446 (m), 1408 (s), 1391 (m, sh), 1365 (m), 1302 (m), 1252 (s), 1177 (s), 1155 (m, sh), 1117 (w), 1088 (s), 1034 (m), 1015 (w, sh), 1000 (w), 912 (w), 829 (m), 755 (w), 702 (w), 627 (w). δ_{H} (500.0 MHz, $\text{DMSO}-d_6$ mixture of two amidic isomers 1:1) 1.28 and 1.32 (2×9H, 2×s, $(\text{CH}_3)_3\text{C}$), 2.44 (1H, dd, $J_{\text{gem}}=10.8$, $J(2b,3)=6.6$, H-2b), 2.64 (1H, dd, $J_{\text{gem}}=10.8$, $J(2a,3)=7.3$, H-2a), 2.71 (1H, m, H-4), 2.72 (1H, dd, $J_{\text{gem}}=10.9$, $J(2b,3)=7.2$, H-2b), 2.86 (1H, dd, $J_{\text{gem}}=10.8$, $J(2a,3)=7.8$, H-2a), 2.90–2.99 (3H, m, H-4 and 2×H-5b), 3.02–3.07 (2H, m, 2×H-5a), 3.73 (12H, s, $\text{CH}_3\text{O}-\text{DMTr}$), 3.83 (1H, ddd, $J(3,2)=7.3$, 6.6, $J(3,4)=4.4$, H-3), 3.86 (1H, ddd, $J(3,2)=7.8$, 7.2, $J(3,4)=4.6$, H-3), 6.90 (8H, m, H-m- C_6H_4 -DMTr), 7.23 (2H, m, H-p- C_6H_5 -DMTr), 7.29–7.36 (12H, m, H-o- C_6H_4 -DMTr and H-m- C_6H_5 -DMTr), 7.44 and 7.47 (2×2H, 2×m, H-o- C_6H_5 -DMTr). δ_{C} (125.7 MHz, $\text{DMSO}-d_6$, mixture of two amidic isomers 1:1) 28.26 and 28.35 ($(\text{CH}_3)_3\text{C}$), 47.64 and 47.95 (C-2), 51.32 (C-5), 51.75 (C-4), 51.89 (C-5), 52.04 (C-4), 55.27 and 55.29 ($\text{CH}_3\text{O}-\text{DMTr}$), 73.21 and 73.72 (C-3), 78.17 and 78.36 ($\text{C}(\text{CH}_3)_3$), 86.17 (C-DMTr), 113.57 (C-m- C_6H_4 -DMTr), 126.96 and 127.04 (C-p- C_6H_5 -DMTr), 127.79 and 127.86 (C-o- C_6H_5 -DMTr), 128.19 (C-m- C_6H_5 -DMTr), 129.94, 129.99 and 130.05 (C-o- C_6H_4 -DMTr), 136.30, 136.51 and 136.64 (C-i- C_6H_4 -DMTr), 145.79 and 145.83 (C-i- C_6H_5 -DMTr), 153.71 and 153.82 (CO), 158.44 and 158.53 (C-p- C_6H_4 -DMTr). HRMS for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$) calcd 527.2516, found 527.2512.

4.6.7. (3S,4S)-4-Amino-1-N-Boc-3-dimethoxytrityloxy-pyrrolidine (8c). A mixture of (3R,4S)-1-N-Boc-4-dimethoxytrityloxy-3-mesyloxy-pyrrolidine⁴ (4.28 g, 7.33 mmol) and sodium azide (2.38 g, 37 mmol) in DMF (80 ml) was stirred at 110 °C for 5 h. DMF was removed in vacuo, and the residue was dissolved in ethyl acetate and filtered through a pad of Celite followed by purification on silica gel using a linear gradient of ethyl acetate in toluene. The obtained crude azido derivative was dissolved in ethanol (200 ml), Pd/C (0.2 g) was added, and the whole was hydrogenated for 6 h. The catalyst was filtered off over Celite, ethanol was evaporated, and the title compound was recovered using column chromatography on silica gel under linear gradient of ethanol in chloroform in a 68% yield (2.53 g, 5.01 mmol) in the form of white foam. $\nu_{\max}(\text{KBr})$ 3382 (w), 3322 (w), 3057 (w), 3036 (w), 3000 (w), 2973 (m), 2836 (w), 1736 (m), 1694 (vs), 1608 (s), 1582 (w), 1509 (vs), 1491 (m, sh), 1478 (m), 1463 (m), 1456 (m), 1446 (m), 1408 (vs), 1392 (s, sh), 1365 (m), 1301 (m), 1252 (vs), 1175 (vs), 1155 (s, sh), 1114 (s), 1034 (s), 1009 (m), 1002 (w, sh), 912 (w), 828 (s), 770 (m), 754 (m), 702 (m), 627 (w). δ_{H} (500.0 MHz, $\text{DMSO}-d_6$ mixture of two amidic isomers 1:1) 1.29 and 1.37 (2×9H, 2×s, $(\text{CH}_3)_3\text{C}$), 2.39 (1H, dd, $J_{\text{gem}}=11.7$, $J(2b,3)=2.4$, H-2b), 2.65 (1H, dd, $J_{\text{gem}}=11.7$, $J(2b,3)=1.9$, H-2b), 2.77 (1H, dd, $J_{\text{gem}}=11.7$, $J(2a,3)=4.8$, H-2a), 2.87 (1H, dd, $J_{\text{gem}}=10.9$, $J(5b,4)=3.0$, H-5b), 2.89 (1H, dt, $J(4,5)=5.0$, 2.5, $J(4,3)=2.5$, H-4), 2.92 (1H, dd, $J_{\text{gem}}=10.5$, $J(5b,4)=2.5$, H-5b), 2.96 (1H, dd, $J_{\text{gem}}=11.7$, $J(2a,3)=4.9$, H-2a), 3.01 (1H, dt, $J(4,5)=5.6$, 3.0, $J(4,3)=3.0$, H-4), 3.37 (1H, dd, $J_{\text{gem}}=10.9$, $J(5a,4)=5.6$, H-5a), 3.39 (1H, dd, $J_{\text{gem}}=10.5$, $J(5a,4)=5.0$, H-5a), 3.69 (1H, ddd, $J(3,2)=4.8$, 2.4, $J(3,4)=3.0$, H-3), 3.71 (1H, ddd, $J(3,2)=4.9$, 1.9, $J(3,4)=2.5$, H-3), 3.730, 3.732 and

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3.736 (12H, 3×s, CH₃O-DMTr), 6.90 (8H, m, H-*m*-C₆H₄-DMTr), 7.20–7.33 (14H, m, H-*o*-C₆H₄-DMTr and H-*m,p*-C₆H₅-DMTr), 7.39 and 7.42 (2×2H, 2×m, H-*o*-C₆H₅-DMTr). δ_C (125.7 MHz, DMSO-*d*₆, mixture of two amidic isomers 1:1) 28.27 and 28.40 ((CH₃)₃C), 50.28 and 50.49 (C-2), 51.77 and 52.27 (C-5), 55.25 (CH₃O-DMTr), 55.58 and 56.53 (C-4), 77.98 (C-3), 78.10 and 78.34 (C(CH₃)₃), 78.50 (C-3), 86.18 and 86.28 (C-DMTr), 113.48 and 113.51 (C-*m*-C₆H₄-DMTr), 126.94 and 127.01 (C-*p*-C₆H₅-DMTr), 127.99 and 128.12 (C-*o,m*-C₆H₅-DMTr), 130.15 (C-*o*-C₆H₄-DMTr), 136.32, 136.49 and 136.60 (C-*i*-C₆H₄-DMTr), 145.80 (C-*i*-C₆H₅-DMTr), 153.93 and 153.95 (CO), 158.39, 158.47 and 158.48 (C-*p*-C₆H₄-DMTr). HRMS for C₃₀H₃₆N₂O₅Na (M+Na)⁺ calcd 527.2516, found 527.2512.

4.6.8. 1-((3*R*)-1-*N*-Boc-3-Pyrrolidinyl)-3-(3-ethoxyacryloyl)urea (**9a**). The title compound was prepared according to general method A from compound **8a** (1.15 g, 6.2 mmol) using reagent **7a**. Yield, 85% (1.72 g, 5.254 mmol) of yellowish foam. $\nu_{\max}$ (CHCl₃) 3428 (w), 3268 (w, br, sh), 3236 (w), 3132 (w, sh), 3102 (w), 2983 (m), 1700 (s, sh), 1685 (vs, sh), 1676 (vs), 1624 (s), 1611 (s), 1548 (s), 1498 (m, sh), 1487 (m), 1476 (m), 1456 (m), 1412 (s), 1395 (s, sh), 1368 (m), 1248 (m), 1167 (s), 1132 (s), 977 (w), 960 (w), 846 (w). δ_H (500.0 MHz, CDCl₃, mixture of two amidic isomers 1:1) 1.36 (6H, t, J(CH₃,CH₂)=7.1, CH₃), 1.46 (18H, s, (CH₃)₃C), 1.89 (2H, br m, H-4'b), 2.17 (2H, dddd, $J_{gem}=13.2$, J(4'a,5')=7.8, 5.9, J(4'a,3')=6.3, H-4'a), 3.21 and 3.30 (2×1H, 2×bdd, $J_{gem}=10.9$, J(2'b,3')=5.0, H-2'b), 3.39–3.70 (4H, br m, H-5'), 3.63–3.70 (2H, br m, H-2'a), 3.98 (4H, q, J(CH₂,CH₃)=7.1, OCH₂CH₃), 4.39 (2H, m, H-3'), 5.32 (2H, d, J(5,6)=12.2, H-5), 7.63 (2H, d, J(6,5)=12.2, H-6), 8.84 (2H, br d, J(1,3')=7.0, H-1), 9.27 and 9.40 (2×1H, 2×br s, H-3). δ_C (125.7 MHz, CDCl₃, mixture of two amidic isomers 1:1) 14.50 (CH₃), 28.46 ((CH₃)₃C), 31.07 and 31.81 (C-4'), 43.74 and 44.07 (C-5'), 48.97 and 49.69 (C-3'), 51.25 and 51.57 (C-2'), 67.68 (OCH₂CH₃), 79.49 (C(CH₃)₃), 97.82 (C-5), 154.42 and 154.82 (C-2 and CO), 162.93 and 163.04 (C-6), 168.17 (C-4). HRMS for C₁₅H₂₅N₃O₅Na (M+Na)⁺ calcd 350.1686, found 350.1687.

4.6.9. 1-((3*S*,4*R*)-1-*N*-Boc-3-Dimethoxytrityloxy-4-pyrrolidinyl)-3-(3-ethoxyacryloyl)urea (**9b**). The title compound was prepared according to general method A from compound **8b** (0.95 g, 1.88 mmol) and reagent **7a** in 93% yield (1.13 g, 1.13 mmol) of yellowish foam. $\nu_{\max}$ (KBr) 3261 (w, br), 3101 (w, br), 2976 (m), 2837 (w), 1701 (vs), 1679 (vs), 1628 (m, sh), 1610 (s), 1577 (w, sh), 1540 (s, br), 1510 (vs), 1492 (m, sh), 1477 (m), 1465 (m, sh), 1446 (m), 1404 (s), 1393 (m, sh), 1366 (m), 1303 (m), 1252 (s), 1222 (m, sh), 1176 (s), 1176 (s), 1093 (m), 1035 (m), 1017 (m, sh), 978 (w), 913 (vw), 829 (m), 771 (w), 701 (w). δ_H (500.0 MHz, CDCl₃, mixture of two amidic isomers 1:1) 1.36 (6H, t, J(CH₃,CH₂)=7.1, CH₃), 1.46 (18H, s, (CH₃)₃C), 2.75 (1H, dd, $J_{gem}=11.6$, J(2'b,3')=7.2, H-2'b), 2.88 (1H, dd, $J_{gem}=11.6$, J(2'a,3')=7.7, H-2'a), 3.16 (1H, dd, $J_{gem}=11.6$, J(2'b,3')=7.7, H-2'b), 3.22–3.32 (3H, m, H-2'a and 2×5'b), 3.46 (1H, br m, H-4'), 3.49 and 3.54 (2×1H, 2×dd, $J_{gem}=11.8$, J(5'a,4')=2.8, H-5'a), 3.75 and 3.76 (2×6H, 2×s, CH₃O-DMTr), 3.80 (1H, br m, H-4'), 3.917 and 3.923 (2×2H, 2×q, J(CH₂,CH₃)=7.1, OCH₂CH₃), 4.12 and 4.15 (2×1H, 2×br m, H-3'), 5.27 and 5.31 (2×1H, 2×d, J(5,6)=12.1, H-5), 6.81 and 6.83 (2×4H, 2×m, H-*m*-C₆H₄-DMTr), 7.20 (2H, m, H-*p*-C₆H₅-DMTr), 7.28 (4H, br m, H-*m*-C₆H₅-DMTr), 7.40 (8H, br m, H-*o*-C₆H₄-DMTr), 7.50 and 7.52 (2×2H, 2×m, H-*o*-C₆H₅-DMTr), 7.67 (2H, d, J(6,5)=12.1, H-6), 9.03 (1H, br s, H-3), 9.28 (2H, br d, J(1,4')=5.6, H-1), 9.31 (1H, br s, H-3). δ_C (125.7 MHz, CDCl₃, mixture of two amidic isomers 1:1) 14.50 (CH₃), 28.32 and 28.37 ((CH₃)₃C), 48.52 and 48.81 (C-2'), 49.47 and 50.34 (C-5'), 51.27 and 51.74 (C-4'), 55.16 (CH₃O-DMTr), 67.42 and 67.50 (OCH₂CH₃), 71.28 and 71.80 (C-3'), 79.26 and 79.41 (C(CH₃)₃), 87.08 and 87.15 (C-DMTr), 97.92 and 97.99 (C-5), 113.24 (C-*m*-C₆H₄-DMTr), 126.96 and 127.04 (C-*p*-C₆H₅-DMTr), 127.99 (C-*m*-C₆H₅-DMTr), 128.04 and 128.14 (C-*o*-C₆H₅-DMTr), 129.97 and 130.01 (C-*o*-C₆H₄-DMTr),

136.06, 136.17 and 136.22 (C-*i*-C₆H₄-DMTr), 144.87 and 144.95 (C-*i*-C₆H₅-DMTr), 154.08 and 154.23 (CO), 155.07 and 155.14 (C-2), 158.67 and 158.72 (C-*p*-C₆H₄-DMTr), 162.70 and 162.81 (C-6), 167.50 and 167.80 (C-4). HRMS for C₃₆H₄₃N₃O₈Na (M+Na)⁺ calcd 668.2942, found 668.2942.

4.6.10. 1-((3*S*,4*S*)-1-*N*-Boc-3-Dimethoxytrityloxy-4-pyrrolidinyl)-3-(3-ethoxyacryloyl)urea (**9c**). The title compound was prepared according to general method A from compound **8c** (0.9 g, 1.84 mmol) and reagent **7a** in 78% yield (1.04 g, 1.612 mmol) of yellowish foam. $\nu_{\max}$ (KBr) 3416 (w, vbr), 3261 (w, br), 3089 (w, br), 2976 (m), 2837 (w), 1699 (vs), 1681 (vs), 1628 (m, sh), 1610 (s), 1578 (w, sh), 1549 (s, br), 1509 (s), 1492 (m, sh), 1475 (m), 1466 (m), 1446 (m), 1404 (m, br), 1394 (m, sh), 1367 (m), 1303 (m), 1251 (s), 1174 (s), 1111 (m, sh), 1089 (m), 1035 (m), 1018 (w, sh), 976 (w), 913 (vw), 829 (m), 769 (w), 756 (w), 703 (w). δ_H (500.0 MHz, CDCl₃, mixture of two amidic isomers 1:1) 1.33 (6H, t, J(CH₃,CH₂)=7.1, CH₃), 1.36 and 1.42 (2×9H, 2×s, (CH₃)₃C), 2.48 (1H, dd, $J_{gem}=12.3$, J(2'b,3')=3.4, H-2'b), 2.66 (1H, dd, $J_{gem}=12.3$, J(2'a,3')=5.3, H-2'a), 2.91 (1H, dd, $J_{gem}=12.2$, J(2'b,3')=4.2, H-2'b), 2.99 (1H, dd, $J_{gem}=12.2$, J(2'a,3')=5.9, H-2'a), 3.19 (1H, dd, $J_{gem}=11.7$, J(5'b,4')=4.8, H-5'b), 3.24 (1H, dd, $J_{gem}=11.4$, J(5'b,4')=4.5, H-5'b), 3.70 (1H, dd, $J_{gem}=11.7$, J(5'a,4')=6.1, H-5'a), 3.75 and 3.76 (2×6H, 2×s, CH₃O-DMTr), 3.78 (1H, dd, $J_{gem}=11.4$, J(5'a,4')=6.4, H-5'a), 3.96 (4H, q, J(CH₂,CH₃)=7.1, OCH₂CH₃), 4.03–4.13 (2H, br m, H-3'), 4.20 and 4.36 (2×1H, 2×br m, H-4'), 5.33 and 5.35 (2×1H, 2×d, J(5,6)=12.2, H-5), 6.80 and 6.82 (2×4H, 2×br m, H-*m*-C₆H₄-DMTr), 7.15–7.22 (2H, m, H-*p*-C₆H₅-DMTr), 7.23–7.29 (4H, m, H-*m*-C₆H₅-DMTr), 7.31–7.38 (8H, m, H-*o*-C₆H₄-DMTr), 7.44 and 7.46 (2×2H, 2×m, H-*o*-C₆H₅-DMTr), 7.63 (2H, d, J(6,5)=12.1, H-6), 8.68 and 8.77 (2×1H, 2×br d, J(1,4')=8.2, H-1), 9.33 and 9.47 (2×1H, 2×br s, H-3). δ_C (125.7 MHz, CDCl₃, mixture of two amidic isomers 1:1) 14.49 (CH₃), 28.30 and 28.41 ((CH₃)₃C), 48.86 and 49.39 (C-5'), 50.13 (C-2'), 54.54 (C-4'), 55.13 and 55.14 (CH₃O-DMTr), 67.68 and 67.74 (OCH₂CH₃), 75.40 and 76.08 (C-3'), 79.24 and 79.47 (C(CH₃)₃), 86.95 and 87.03 (C-DMTr), 97.81 (C-5), 113.24 and 113.28 (C-*m*-C₆H₄-DMTr), 126.96 and 127.01 (C-*p*-C₆H₅-DMTr), 127.92 (C-*m*-C₆H₅-DMTr), 128.10 and 128.24 (C-*o*-C₆H₅-DMTr), 130.10 and 130.13 (C-*o*-C₆H₄-DMTr), 136.00, 136.17 and 136.36 (C-*i*-C₆H₄-DMTr), 145.04 (C-*i*-C₆H₅-DMTr), 154.20, 154.38 and 154.58 (C-2 and CO), 158.67 and 158.73 (C-*p*-C₆H₄-DMTr), 162.97 (C-6), 167.95 and 168.11 (C-4). HRMS for C₃₆H₄₃N₃O₈Na (M+Na)⁺ calcd 668.2942, found 668.2941.

4.6.11. 1-Cyclopentyl-3-(3-ethoxyacryloyl)urea (**9d**). The title compound was prepared according to general method A from compound **8d** (0.2 g, 2.348 mmol) and reagent **7a** in 88% yield (0.47 g, 2.079 mmol) of white solid. $\nu_{\max}$ (KBr) 3422 (w, vbr), 3258 (m), 3235 (m), 3133 (w, sh), 3103 (m), 2985 (m, sh), 2962 (m), 2940 (m, sh), 2869 (w), 1695 (s, sh), 1681 (vs), 1613 (s), 1550 (vs), 1501 (m), 1453 (w), 1473 (m), 1396 (w), 1367 (w), 1326 (w), 1242 (m), 1166 (s), 973 (w). δ_H (600.1 MHz, DMSO-*d*₆) 1.24 (3H, t, J(CH₃,CH₂)=7.0, CH₃), 1.38 (2H, m, H-2'a and H-5'a), 1.50–1.65 (4H, m, H-3' and H-4'), 1.84 (2H, m, H-2'b and H-5'b), 3.93 (2H, q, J(CH₂,CH₃)=7.0, OCH₂CH₃), 3.98 (1H, m, H-1'), 5.49 (1H, d, J(5,6)=12.3, H-5), 7.54 (1H, d, J(6,5)=12.3, H-6), 8.52 (1H, br d, J(1,1')=7.2, H-1), 10.00 (1H, br s, H-3). δ_C (150.9 MHz, DMSO-*d*₆) 14.68 (CH₃), 23.39 (C-3' and C-4'), 32.97 (C-2' and C-5'), 50.93 (C-1'), 67.52 (OCH₂CH₃), 98.57 (C-5), 153.54 (C-2), 162.32 (C-6), 168.15 (C-4). HRMS for C₁₁H₁₈N₂O₃Na (M+Na)⁺ calcd 249.1210, found 249.1210.

4.6.12. 1-Cyclohexyl-3-(3-ethoxyacryloyl)urea (**9e**). The title compound was prepared according to general method A from compound **8e** (0.233 g, 2.348 mmol) and reagent **7a** in 88% yield (0.5 g, 2.08 mmol) of white solid. $\nu_{\max}$ (KBr) 3382 (w, vbr), 3256 (m), 3237 (m), 3095 (m), 3060 (m), 2984 (m), 2977 (m), 2938 (s), 2930 (s), 2853 (m), 1698 (s), 1681 (vs), 1613 (vs), 1550 (vs), 1499 (m), 1473

(m), 1394 (w), 1446 (m), 1367 (w), 1326 (m), 1317 (m), 1252 (m), 1242 (s), 1227 (m), 1168 (vs), 998 (m), 955 (w). δ_{H} (500.0 MHz, DMSO- d_6) 1.24 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.0$, CH_3), 1.16–1.35 (5H, m, H-2'ax, 3'ax, 4'ax, 5'ax and H-6'ax), 1.51 (1H, m, H-4'eq), 1.61 (2H, m, H-3'eq and H-5'eq), 1.78 (2H, m, H-2'eq and H-6'eq), 3.55 (1H, m, H-1'), 3.94 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 5.49 (1H, d, $J(5,6)=12.3$, H-5), 7.55 (1H, d, $J(6,5)=12.3$, H-6), 8.52 (1H, br d, $J(1,1')=7.6$, H-1), 10.00 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 14.60 (CH_3), 24.25 (C-4'), 25.29 (C-3' and C-5'), 32.58 (C-2' and C-6'), 47.63 (C-1'), 67.45 (OCH_2CH_3), 98.57 (C-5), 153.11 (C-2), 162.20 (C-6), 168.07 (C-4). HRMS for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 263.1366, found 263.1366.

4.6.13. 1-(Ethoxyacryloyl)-3-(trans-2-hydroxycyclohexyl)urea (9f). The title compound was prepared according to general method C from compound **8f** (0.197 g, 1.3 mmol) and reagent **7a** in 99% yield (0.33 g, 1.287 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3512 (m), 3379 (m, vbr), 3260 (s, vbr), 3135 (m), 3096 (m), 2975 (m), 2936 (s), 2859 (s), 1702 (vs), 1672 (vs, br), 1643 (s, sh), 1620 (vs), 1610 (vs), 1565 (vs, br), 1489 (m), 1474 (m), 1450 (m), 1397 (m), 1372 (w), 1327 (s, sh), 1318 (s), 1252 (s), 1235 (s), 1170 (vs), 1042 (m), 977 (m). δ_{H} (499.8 MHz, DMSO- d_6) 1.07–1.28 (4H, m, H-3'ax, 4'ax, 5'ax and H-6'ax), 1.24 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_3), 1.52 (1H, m, H-5'eq), 1.60 (1H, m, H-4'eq), 1.80 (1H, m, H-6'eq), 1.95 (1H, m, H-3'eq), 3.23 (1H, m, H-1'), 3.35 (1H, m, H-2'), 3.94 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 4.75 (1H, d, $J(\text{OH}, 1')=5.4$, OH), 5.50 (1H, d, $J(5,6)=12.4$, H-5), 7.54 (1H, d, $J(6,5)=12.4$, H-6), 8.56 (1H, br d, $J(1,2')=7.4$, H-1), 9.97 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 14.58 (CH_3), 23.58 (C-5'), 24.01 (C-4'), 30.99 (C-3'), 34.07 (C-6'), 54.60 (C-2'), 67.37 (OCH_2CH_3), 71.25 (C-1'), 98.64 (C-5), 153.82 (C-2), 162.01 (C-6), 167.87 (C-4). HRMS for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 279.1315, found 279.1316.

4.6.14. 1-(3-Ethoxyacryloyl)-3-(cis-2-hydroxycyclopentyl)urea (9g). The title compound was prepared according to general method C from compound **8g** (0.179 g, 1.3 mmol) and reagent **7a** in 95% yield (0.30 g, 1.238 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3435 (s, br), 3293 (m), 3237 (m, br), 3141 (m), 3096 (m), 2983 (m), 2964 (m), 2942 (m), 2872 (w), 1698 (vs), 1676 (vs), 1610 (vs), 1535 (s), 1486 (s), 1474 (m), 1458 (m), 1395 (w), 1368 (w, sh), 1322 (m), 1246 (m), 1185 (s), 1163 (s), 1014 (m), 973 (m). δ_{H} (499.8 MHz, DMSO- d_6) 1.24 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.0$, CH_3), 1.40–1.48 (2H, m, H-3'a and H-4'a), 1.54 (1H, m, H-5'a), 1.66–1.80 (2H, m, H-4'b and H-5'b), 1.84 (1H, m, H-3'b), 3.80 (1H, m, H-2'), 3.92 (1H, m, H-1'), 3.94 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.0$, OCH_2CH_3), 4.89 (1H, d, $J(\text{OH}, 1')=4.5$, OH), 5.51 (1H, d, $J(5,6)=12.3$, H-5), 7.53 (1H, d, $J(6,5)=12.3$, H-6), 8.72 (1H, br d, $J(1,2')=7.9$, H-1), 9.92 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 14.59 (CH_3), 20.22 (C-4'), 29.51 (C-3'), 32.73 (C-5'), 54.05 (C-2'), 67.33 (OCH_2CH_3), 70.85 (C-1'), 98.69 (C-5), 153.58 (C-2), 161.91 (C-6), 167.56 (C-4). HRMS for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 265.1159, found 265.1159.

4.6.15. (RS)-1-(3-(3-Ethoxyacryloyl)ureido)-1-hydroxymethylcyclopentane 9h. The title compound was prepared according to general method A from compound **8h** (0.27 g, 2.348 mmol) and reagent **7a** in 88% yield (0.53 g, 2.069 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3415 (m, br), 3273 (m, br, sh), 3220 (m, br), 3127 (m), 3093 (m), 3065 (w), 2980 (m, sh), 2965 (m), 2879 (w), 1701 (m, sh), 1677 (vs), 1610 (s), 1567 (s, sh), 1556 (s), 1488 (m), 1473 (m), 1448 (w), 1396 (w), 1373 (w), 1328 (m), 1246 (m), 1179 (s), 1156 (s), 990 (w, sh). δ_{H} (600.1 MHz, DMSO- d_6) 1.24 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.0$, CH_3), 1.52 (2H, m, H-3'a and H-4'a), 1.61–1.67 (4H, m, H-3'b, 4'b, 2'a and H-5'a), 1.77 (2H, m, H-2'b and H-5'b), 3.43 (2H, d, $J(\text{CH}_2, \text{OH})=5.5$, CH_2OH), 3.93 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.0$, OCH_2CH_3), 4.90 (1H, t, $J(\text{OH}, \text{CH}_2)=5.5$, OH), 5.50 (1H, d, $J(5,6)=12.3$, H-5), 7.53 (1H, d, $J(6,5)=12.3$, H-6), 8.64 (1H, br s, H-1), 9.85 (1H, br s, H-3). δ_{C} (150.9 MHz, DMSO- d_6)

14.65 (CH_3), 24.21 (C-3' and C-4'), 34.39 (C-2' and C-5'), 64.63 (C-1'), 64.88 (CH_2OH), 67.42 (OCH_2CH_3), 98.67 (C-5), 153.06 (C-2), 162.07 (C-6), 168.01 (C-4). HRMS for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 279.1315, found 279.1316.

4.6.16. 1-(2,3-Dihydroxypropyl)-3-(3-ethoxy-2-methylacryloyl)urea (9i). The title compound was prepared according to general method A from compound **8i** (0.118 g, 1.3 mmol) and reagent **7a** in 87% yield (0.26 g, 1.12 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3304 (s), 3237 (s, br, sh), 3145 (s, br, sh), 2984 (m), 1688 (vs), 1635 (m, sh), 1609 (vs), 1545 (vs), 1500 (m), 1476 (m), 1394 (w), 1365 (m), 1332 (m), 1250 (s), 1225 (m), 1162 (vs), 1095 (s), 1063 (s), 972 (m). δ_{H} (500.0 MHz, DMSO- d_6) 1.24 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.0$, CH_3), 3.02 (1H, m, H-1'a), 3.24 (1H, m, H-3'a), 3.31–3.38 (2H, m, H-1'b and H-3'b), 3.50 (1H, m, H-2'), 3.94 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.0$, OCH_2CH_3), 4.65 (1H, t, $J(\text{OH}, 3')=5.6$, 3'-OH), 4.90 (1H, d, $J(\text{OH}, 2')=5.0$, 2'-OH), 5.50 (1H, d, $J(5,6)=12.3$, H-5), 7.55 (1H, d, $J(6,5)=12.3$, H-6), 8.63 (1H, bt, $J(1,1')=5.3$, H-1), 10.01 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 14.63 (CH_3), 42.50 (C-1'), 63.88 (C-3'), 67.44 (OCH_2CH_3), 70.27 (C-2'), 98.63 (C-5), 154.20 (C-2), 162.13 (C-6), 167.76 (C-4). HRMS for $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 255.0951, found 255.0952.

4.6.17. 1-(3-Ethoxyacryloyl)-3-phenylurea (9j). The title compound was prepared according to general method A from compound **8j** (0.091 ml, 1 mmol) and reagent **7a** in 94% yield (0.22 g, 0.94 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3404 (w, br), 3242 (w), 3230 (w, br), 3132 (m, br), 3096 (m), 3063 (m), 3029 (w), 2980 (m), 2936 (w), 1710 (s), 1682 (vs), 1673 (s, sh), 1621 (vs), 1607 (s, sh), 1597 (vs), 1560 (vs), 1500 (m), 1495 (m, sh), 1472 (w), 1448 (m), 1393 (w), 1367 (vw), 1305 (w, sh), 1262 (m), 1245 (s), 1230 (m), 1159 (vs), 1084 (vw), 1018 (w), 1002 (w), 987 (w), 847 (w), 758 (m), 689 (w), 616 (vw), 512 (w). δ_{H} (500.0 MHz, CDCl_3) 1.38 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_3), 3.98 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 5.43 (1H, d, $J(5,6)=12.3$, H-5), 7.11 (1H, m, H-*p*-Ph), 7.31 (2H, m, H-*m*-Ph), 7.55 (2H, m, H-*o*-Ph), 7.73 (1H, d, $J(6,5)=12.3$, H-6), 9.61 and 10.85 (2×1H, 2×br s, H-1,3). δ_{C} (125.7 MHz, CDCl_3) 14.41 (CH_3), 67.22 (OCH_2CH_3), 97.65 (C-5), 120.31 (C-*o*-Ph), 124.16 (C-*p*-Ph), 128.87 (C-*m*-Ph), 137.39 (C-*i*-Ph), 152.86 (C-2), 163.18 (C-6), 168.39 (C-4). HRMS for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 257.0897, found 257.0894.

4.6.18. Methyl 2-(3-(3-ethoxyacryloyl)ureido)acetate (9k). The title compound was prepared according to general method C from compound **8k** (0.5 g, 3.98 mmol) and reagent **7a** in 87% yield (0.8 g, 3.475 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3387 (w, vbr), 3309 (m, br), 3238 (m, br), 3138 (m, sh), 3111 (m), 3095 (m, sh), 2984 (m), 1749 (vs), 1702 (vs), 1686 (s), 1673 (vs), 1616 (vs), 1570 (vs), 1504 (m), 1476 (w), 1437 (m), 1401 (m), 1385 (w), 1180 (vs), 983 (w). δ_{H} (500.0 MHz, CDCl_3) 1.36 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.0$, CH_3), 3.76 (3H, s, CH_3O), 3.97 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.0$, OCH_2CH_3), 4.09 (2H, d, $J(\text{CH}_2, 1)=5.6$, CH_2), 5.34 (1H, d, $J(5,6)=12.2$, H-5), 7.66 (1H, d, $J(6,5)=12.2$, H-6), 9.10 (1H, bt, $J(1, \text{CH}_2)=5.6$, H-1), 9.66 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl_3) 14.46 (CH_3), 41.53 (CH_2), 52.28 (CH_3O), 67.49 (OCH_2CH_3), 97.90 (C-5), 155.51 (C-2), 162.99 (C-6), 168.13 (C-4), 169.86 (COO). HRMS for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 253.0795, found 253.0793.

4.6.19. Ethyl 2(R)-3-(3-ethoxyacryloyl)ureido)propanoate (9l). The title compound was prepared according to general method C from compound **8l** (0.5 g, 3.25 mmol) and reagent **7a** in 87% yield (0.73 g, 2.83 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3375 (m, sh, br), 3241 (s, br), 3132 (s), 3107 (s, sh), 2983 (s), 2940 (s), 1742 (vs), 1683 (vs, vbr), 1619 (vs, br), 1560 (vs, sh), 1543 (vs, vbr), 1497 (s), 1473 (s), 1396 (s), 1377 (s), 1367 (s), 1211 (vs), 1177 (vs), 1110 (s), 1096 (s, sh), 983 (m), 973 (m, sh). δ_{H} (500.0 MHz, DMSO- d_6) 1.19 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, $\text{CH}_3\text{CH}_2\text{O-Val}$), 1.25 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.0$,

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$\text{CH}_3\text{CH}_2\text{O}$), 1.33 (3H, d, $J(\text{CH}_3, \text{CH})=7.2$, $\text{CH}_3\text{-Val}$), 3.96 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.0$, OCH_2CH_3), 4.11 (2H, m, $\text{CH}_3\text{CH}_2\text{O-Val}$), 4.30 (1H, p, $J(\text{CH}, \text{CH}_3)=J(\text{CH}, 1)=7.2$, CH-Val), 5.51 (1H, d, $J(5,6)=12.3$, H-5), 7.59 (1H, d, $J(6,5)=12.3$, H-6), 8.87 (1H, br d, $J(1, \text{CH})=7.1$, H-1), 10.17 (1H, br s, H-3). δ_{C} (125.7 MHz, $\text{DMSO}-d_6$) 14.23 ($\text{CH}_3\text{CH}_2\text{O-Val}$), 14.62 ($\text{CH}_3\text{CH}_2\text{O}$), 18.04 ($\text{CH}_3\text{-Val}$), 48.25 (CH-Val), 60.99 ($\text{CH}_3\text{CH}_2\text{O-Val}$), 67.59 (OCH_2CH_3), 98.40 (C-5), 153.51 (C-2), 162.57 (C-6), 168.05 (C-4), 172.55 (COO-Val). HRMS for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 281.1108, found 281.1108.

4.6.20. 1-(1-*N*-Boc-3-pyrrolidinyl)-3-(3-ethoxy-2-methylacryloyl)urea (9m). The title compound was prepared according to general method A from compound **8a** (0.45 g, 2.42 mmol) and reagent **7b** in 96% yield (0.79 g, 2.314 mmol) of white solid. $\nu_{\text{max}}(\text{CHCl}_3)$ 3439 (w), 3270 (m, br), 2983 (m), 1689 (vs, br), 1655 (s, sh), 1614 (s), 1545 (s), 1487 (m, sh), 1476 (s), 1459 (s), 1412 (s), 1392 (s, sh), 1368 (s), 1165 (s), 1137 (s), 1122 (s), 462 (w). δ_{H} (500.0 MHz, CDCl_3 , mixture of two amidic isomers 1:1) 1.36 (6H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, OCH_2CH_3), 1.46 (18H, s, $(\text{CH}_3)_3\text{C}$), 1.78 (6H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 1.89 (2H, br m, H-4'b), 2.16 (2H, dtd, $J_{\text{gem}}=12.8$, $J(4'a, 3')=7.4$, $J(4'a, 5')=7.4$, 6.0, H-4'a), 3.21 and 3.30 (2×1H, 2×bdd, $J_{\text{gem}}=11.0$, $J(2'b, 3')=4.9$, H-2'b), 3.39–3.53 (4H, br m, H-5'), 3.65 (2H, dd, $J_{\text{gem}}=11.0$, $J(2'a, 3')=6.4$, H-2'a), 4.09 (4H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 4.39 (2H, br m, H-3'), 7.43 (2H, q, $J(6, \text{CH}_3)=1.2$, H-6), 8.17 and 8.21 (2×1H, 2×br s, H-3), 8.93 (2H, br d, $J(1, 3')=6.1$, H-1). δ_{C} (125.7 MHz, CDCl_3 , mixture of two amidic isomers 1:1) 8.82 (5- CH_3), 15.35 (OCH_2CH_3), 28.44 ($(\text{CH}_3)_3\text{C}$), 31.07 and 31.89 (C-4'), 43.71 and 44.08 (C-5'), 48.99 and 49.74 (C-3'), 51.27 and 51.62 (C-2'), 70.31 (OCH_2CH_3), 79.46 ($\text{C}(\text{CH}_3)_3$), 106.54 and 106.64 (C-5), 153.96 and 154.39 (C-2 and CO), 157.50 and 157.59 (CH-6), 169.53 (C-4). HRMS for $\text{C}_{16}\text{H}_{27}\text{N}_3\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 364.1843, found 364.1842.

4.6.21. 1-(1-(3*S*,4*R*)-1-*N*-Boc-3-dimethoxytrityloxy-4-pyrrolidinyl)-3-(3-ethoxy-2-methylacryloyl)urea (9n). The title compound was prepared according to general method A from compound **8b** (0.4 g, 0.79 mmol) and reagent **7b** in 99% yield (0.52 g, 0.79 mmol) of yellowish foam. $\nu_{\text{max}}(\text{KBr})$ 3360 (w, br, sh), 3255 (m, br), 3130 (w, br), 2976 (m), 2836 (m), 1699 (vs), 1680 (vs, sh), 1663 (s), 1609 (s), 1578 (m), 1538 (s, br), 1510 (vs), 1495 (s, sh), 1476 (s), 1465 (s), 1458 (m, sh), 1446 (m), 1404 (s), 1392 (s, sh), 1366 (m), 1252 (s), 1211 (s), 1176 (s), 1130 (s), 1091 (s), 1034 (s), 1002 (m), 911 (w), 768 (m), 698 (m). δ_{H} (500.0 MHz, CDCl_3 , mixture of two amidic isomers 1:1) 1.35 (6H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, OCH_2CH_3), 1.36 and 1.38 (2×9H, 2×s, $(\text{CH}_3)_3\text{C}$), 1.80 and 1.82 (2×3H, 2×br s, 5- CH_3), 2.76 (1H, dd, $J_{\text{gem}}=11.8$, $J(2'b, 3')=7.0$, H-2'b), 2.89 (1H, dd, $J_{\text{gem}}=11.8$, $J(2'a, 3')=7.7$, H-2'a), 3.18 (1H, dd, $J_{\text{gem}}=11.3$, $J(2'b, 3')=7.6$, H-2'b), 3.25 and 3.28 (2×1H, 2×dd, $J_{\text{gem}}=11.8$, $J(5'b, 4')=5.2$, H-5'b), 3.31 (1H, dd, $J_{\text{gem}}=11.3$, $J(2'a, 3')=7.2$, H-2'a), 3.40 (1H, m, H-4'), 3.49 and 3.52 (2×1H, 2×dd, $J_{\text{gem}}=11.8$, $J(5'a, 4')=2.8$, H-5'a), 3.777 and 3.780 (2×6H, 2×s, $\text{CH}_3\text{O-DMTr}$), 3.81 (1H, br m, H-4'), 4.09 (4H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 4.13 and 4.16 (2×2H, 2×br m, H-3'), 6.82 (8H, m, H-*m*- $\text{C}_6\text{H}_4\text{-DMTr}$), 7.21 (2H, m, H-*p*- $\text{C}_6\text{H}_5\text{-DMTr}$), 7.28 (4H, br m, H-*m*- $\text{C}_6\text{H}_5\text{-DMTr}$), 7.40 (8H, br m, H-*o*- $\text{C}_6\text{H}_4\text{-DMTr}$), 7.44 (2H, q, $J(6, \text{CH}_3)=1.2$, H-6), 7.50 and 7.51 (2×2H, 2×m, H-*o*- $\text{C}_6\text{H}_5\text{-DMTr}$), 7.53 and 7.63 (2×1H, 2×br s, H-3), 9.28 (1H, br d, $J(1, 4')=6.4$, H-1), 9.30 (1H, br d, $J(1, 4')=5.6$, H-1). δ_{C} (125.7 MHz, CDCl_3 , mixture of two amidic isomers 1:1) 8.94 (5- CH_3), 15.39 (OCH_2CH_3), 28.33 and 28.39 ($(\text{CH}_3)_3\text{C}$), 48.47 and 48.88 (C-2'), 49.58 and 50.43 (C-5'), 51.29 and 51.78 (C-4'), 55.19 ($\text{CH}_3\text{O-DMTr}$), 70.33 (OCH_2CH_3), 71.28 and 71.79 (C-3'), 79.26 and 79.38 ($\text{C}(\text{CH}_3)_3$), 87.05 and 87.18 (C-DMTr), 106.20 and 106.38 (C-5), 113.25 (C-*m*- $\text{C}_6\text{H}_4\text{-DMTr}$), 126.96 and 127.04 (C-*p*- $\text{C}_6\text{H}_5\text{-DMTr}$), 127.92 (C-*m*- $\text{C}_6\text{H}_5\text{-DMTr}$), 128.06 and 128.13 (C-*o*- $\text{C}_6\text{H}_5\text{-DMTr}$), 130.00 and 130.05 (C-*o*- $\text{C}_6\text{H}_4\text{-DMTr}$), 136.02, 136.10 and 136.20 (C-*i*- $\text{C}_6\text{H}_4\text{-DMTr}$), 144.91 and 145.00 (C-*i*- $\text{C}_6\text{H}_5\text{-DMTr}$), 153.83 and 153.94 (C-2), 154.12 and 154.27 (CO), 157.44 and 157.53 (C-6),

158.73 (C-*p*- $\text{C}_6\text{H}_4\text{-DMTr}$), 168.59 and 168.87 (C-4). HRMS for $\text{C}_{37}\text{H}_{45}\text{N}_3\text{O}_8\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 682.3099, found 682.3096.

4.6.22. 1-Cyclohexyl-3-(3-ethoxy-2-methylacryloyl)urea (9o). The title compound was prepared according to general method A from **8e** (0.128 g, 1.3 mmol) and reagent **7b** in 82% yield (0.27 g, 1.062 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3352 (m), 3261 (s), 3141 (m), 3089 (w), 2986 (m), 2934 (s), 2903 (m), 2854 (m), 1678 (vs), 1657 (vs), 1628 (m, sh), 1612 (m, sh), 1547 (vs), 1490 (m), 1476 (s), 1466 (s), 1454 (s), 1388 (m), 1368 (m), 1295 (s), 1218 (vs), 1040 (m), 764 (m). δ_{H} (499.8 MHz, CDCl_3) 1.34 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, OCH_2CH_3), 1.20–1.40 (5H, m, H-2', 3', 4', 5', 6'ax), 1.58 (1H, m, H-4'eq), 1.71 (2H, m, H-3'eq and H-5'eq), 1.78 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 1.92 (2H, m, H-2'eq and H-6'eq), 3.72 (1H, m, H-1'), 4.08 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 7.45 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 8.33 (1H, br s, H-3), 8.73 (1H, br d, $J(1, 1')=7.8$, H-1). δ_{C} (125.7 MHz, CDCl_3) 8.85 (5- CH_3), 15.38 (OCH_2CH_3), 24.54 (C-3' and C-5'), 25.51 (C-4'), 32.88 (C-2' and C-6'), 48.40 (C-1'), 70.09 (OCH_2CH_3), 107.04 (C-5), 153.52 (C-2), 157.05 (C-6), 169.64 (C-4). HRMS $\text{C}_{13}\text{H}_{23}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$)⁺ calcd 255.1703, found 255.1704.

4.6.23. 1-(3-Ethoxy-2-methylacryloyl)-3-(trans-2-hydroxycyclohexyl)urea (9p). The title compound was prepared according to general method D from compound **8f** (0.128 g, 1.3 mmol) and reagent **7b** in 96% yield (0.26 g, 0.962 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3432 (s), 3264 (s), 3161 (m), 2983 (w), 2940 (m), 2929 (m), 2904 (m), 2861 (m), 1695 (vs), 1687 (vs, sh), 1666 (s), 1607 (m), 1590 (m), 1543 (s), 1532 (s, sh), 1477 (s), 1467 (m, sh), 1451 (m), 1396 (w), 1388 (w, sh), 1370 (w), 1302 (w, sh), 1292 (w), 1215 (s), 1039 (m), 766 (m). δ_{H} (499.8 MHz, $\text{DMSO}-d_6$) 1.08–1.26 (4H, m, H-3'ax, 4'ax, 5'ax and H-6'ax), 1.25 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_2CH_3), 1.53 (1H, m, H-5'eq), 1.61 (1H, m, H-4'eq), 1.62 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 1.80 (1H, m, H-6'eq), 1.96 (1H, m, H-3'eq), 3.24 (1H, m, H-1'), 3.38 (1H, m, H-2'), 4.05 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 4.75 (1H, d, $J(\text{OH}, 1')=5.4$, OH), 7.53 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 8.69 (1H, br d, $J(1, 2')=7.3$, H-1), 9.64 (1H, br s, H-3). δ_{C} (125.7 MHz, $\text{DMSO}-d_6$) 9.12 (5- CH_3), 15.46 (CH_2CH_3), 23.59 (C-5'), 24.01 (C-4'), 31.00 (C-3'), 34.08 (C-6'), 54.63 (C-2'), 69.49 (OCH_2CH_3), 71.24 (C-1'), 107.10 (C-5), 153.88 (C-2), 156.71 (C-6), 169.83 (C-4). HRMS $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 293.1472, found 293.1473.

4.6.24. 1-(3-Ethoxy-2-methylacryloyl)-3-(1-hydroxymethylcyclopentyl)urea (9q). The title compound was prepared according to general method B from compound **8h** (0.115 g, 1.0 mmol) and reagent **7b** in 89% yield (0.24 g, 0.888 mmol) of white solid. $\nu_{\text{max}}(\text{KBr})$ 3282 (s, sh), 3255 (s), 3210 (s, br, sh), 3112 (m), 3085 (m, sh), 2959 (s), 2930 (m), 2870 (m), 1685 (vs), 1655 (vs), 1612 (m, sh), 1556 (vs), 1492 (m), 1477 (m), 1461 (m), 1452 (m), 1389 (m), 1367 (m), 1312 (m, sh), 1300 (s), 1226 (s), 1208 (s), 1051 (m), 1034 (m), 767 (m). δ_{H} (500.0 MHz, CDCl_3) 1.33 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_2CH_3), 1.68 (2H, m, H-3'a and H-4'a), 1.77 (2H, m, H-3'b and H-4'b), 1.79 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 1.83–1.87 (4H, m, H-2' and H-5'), 3.71 (2H, br s, CH_2OH), 4.09 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 4.28 (1H, br s, OH), 7.40 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 8.10 (1H, br s, H-1), 9.11 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl_3) 8.80 (5- CH_3), 15.31 (CH_2CH_3), 23.74 (C-3' and C-4'), 35.69 (C-2' and C-5'), 66.27 (C-1'), 69.13 (CH_2OH), 70.34 (OCH_2CH_3), 106.57 (C-5), 154.80 (C-2), 157.58 (C-6), 169.70 (C-4). HRMS $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺ calcd 293.1472, found 293.1472.

4.6.25. 1-(2,3-Dihydroxypropyl)-3-(3-ethoxy-2-methylacryloyl)urea (9r). A) The title compound was prepared according to general method B from compound **8i** (0.118 g, 1.3 mmol) and reagent **7b** in 63% yield (0.20 g, 0.813 mmol) of white solid. B) The title compound was prepared according to general method A from compound **8i** (0.177 g, 1.95 mmol) and reagent **7d** in 76% yield (0.38 g, 1.54 mmol). $\nu_{\text{max}}(\text{KBr})$ 3405 (m, vbr), 3259 (m, br), 3160 (m, br, sh), 2986 (w), 2937 (w), 2893 (w), 1700 (s, sh), 1687 (vs), 1663 (s), 1638

(m), 1623 (m, sh), 1591 (m), 1559 (s), 1542 (m, sh), 1506 (w), 1477 (m), 1388 (w, sh), 1368 (w), 1300 (m), 1235 (m, sh), 1212 (s), 1102 (m), 1066 (m), 1035 (m), 761 (m). δ_{H} (499.8 MHz, DMSO- d_6) 1.25 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_2CH_3), 1.63 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 3.04 (1H, ddd, $J_{\text{gem}}=13.3$, $J(1'a, 2')=7.1$, $J(1'a, 1)=4.9$, H-1'a), 3.25 (1H, dt, $J_{\text{gem}}=10.9$, $J(3'a, \text{OH})=J(3'a, 2')=6.2$, H-3'a), 3.31–3.40 (2H, m, H-1'b and H-3'b), 3.51 (1H, m, H-2'), 4.05 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 4.61 (1H, t, $J(\text{OH}, 3')=5.7$, 3'-OH), 4.87 (1H, d, $J(\text{OH}, 2')=5.1$, 2'-OH), 7.53 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 8.75 (1H, bdd, $J(1, 1'b)=6.0$, $J(1, 1'a)=5.2$, H-1), 9.67 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 9.16 (5- CH_3), 15.49 (CH_2CH_3), 42.56 (C-1'), 63.88 (C-3'), 69.53 (OCH_2CH_3), 70.27 (C-2'), 107.11 (C-5), 154.29 (C-2), 156.77 (C-6), 169.69 (C-4). HRMS for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$ (M+Na) $^{+}$ calcd 269.1108, found 269.1107.

4.6.26. 1-(3-Ethoxy-2-methylacryloyl)-3-phenylurea (9s). The title compound was prepared according to general method A from compound **8j** (0.118 g, 1.3 mmol) and reagent **7b** in 87% yield (0.28 g, 1.129 mmol) of white solid. ν_{max} (KBr) 3284 (m), 3197 (w), 3142 (w), 3088 (w), 3059 (w), 2986 (w), 2937 (w), 2887 (w), 1702 (vs), 1676 (s), 1617 (m), 1605 (s, sh), 1592 (vs), 1557 (s), 1541 (s, sh), 1501 (m), 1488 (m, sh), 1475 (m), 1455 (s), 1396 (m), 1388 (m, sh), 1312 (w), 1226 (s, sh), 1210 (vs), 1179 (w), 1155 (w, sh), 1037 (m), 1002 (w, sh), 916 (m), 848 (vw), 757 (s), 690 (m), 618 (vw), 513 (w). δ_{H} (499.8 MHz, CDCl_3) 1.29 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_2CH_3), 1.84 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 4.02 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 7.10 (1H, m, H-4'), 7.32 (2H, m, H-3'), 7.50 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 7.52 (2H, m, H-2'), 8.53 (1H, br s, H-3), 10.97 (1H, br s, H-1). δ_{C} (125.7 MHz, CDCl_3) 8.87 (5- CH_3), 15.33 (CH_2CH_3), 70.37 (OCH_2CH_3), 106.78 (C-5), 120.55 (C-2'), 124.13 (C-4'), 128.91 (C-3'), 137.40 (C-1'), 152.00 (C-2), 157.83 (C-6), 169.87 (C-4). HRMS for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3\text{Na}$ (M+Na) $^{+}$ calcd 271.1053, found 271.1055.

4.6.27. 1-(3-Ethoxy-2-methylacryloyl)-3-naphthalen-2-ylurea (9t). The title compound was prepared according to general method A from compound **8m** (0.186 g, 1.3 mmol) and reagent **7b** in 90% yield (0.35 g, 1.174 mmol) of white solid. ν_{max} (KBr) 3268 (m), 3171 (s), 3150 (w), 3054 (w), 2986 (w), 2939 (w), 2898 (w), 1702 (vs), 1668 (s), 1655 (m, sh), 1617 (m), 1605 (m), 1588 (s), 1572 (s), 1512 (w), 1493 (w, sh), 1471 (m), 1396 (w), 1388 (w, sh), 1361 (w), 1286 (w), 1260 (w), 1216 (vs), 1180 (m), 1123 (s), 1042 (w), 1013 (w), 882 (w), 848 (w), 806 (w), 753 (w), 739 (w), 616 (vw), 469 (w). δ_{H} (499.8 MHz, CDCl_3) 1.26 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH_2CH_3), 1.87 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5- CH_3), 4.02 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH_2CH_3), 7.40 (1H, m, H-6'), 7.46 (1H, m, H-7'), 7.52 (1H, dd, $J(3', 4')=8.7$, $J(3', 1')=2.2$, H-3'), 7.52 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 7.77–7.81 (3H, m, H-4', H-5' and H-8'), 8.15 (1H, d, $J(1', 3')=2.1$, H-1'), 8.37 (1H, br s, H-3), 11.14 (1H, br s, H-1). δ_{C} (125.7 MHz, CDCl_3) 8.90 (5- CH_3), 15.28 (CH_2CH_3), 70.45 (OCH_2CH_3), 106.57 (C-5), 117.08 (C-1'), 120.58 (C-3'), 124.92 (C-6'), 126.43 (C-7'), 127.54 and 127.58 (C-5' and C-8'), 128.69 (C-4'), 130.60 (C-4'a), 133.86 (C-8'a), 134.89 (C-2'), 151.92 (C-2), 158.03 (C-6), 169.80 (C-4). HRMS for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{Na}$ (M+Na) $^{+}$ calcd 321.1210, found 321.1209.

4.6.28. (R)-1-(Pyrrolidin-3-yl)uracil (10a). The title compound was prepared from **9a** (1.72 g, 5.254 mmol) according to general method E in 97% yield (0.92 g, 5.08 mmol) of white solid. NMR and HRMS spectra were identical to those in Ref. 3.

4.6.29. 1-((3R,4S)-4-Hydroxypyrrolidin-3-yl)uracil (10b). The title compound was prepared from **9b** (1.13 g, 1.75 mmol) according to general method E and was re-purified using preparative reversed-phase HPLC in 90% yield (0.31 g, 1.575 mmol) of white solid. ν_{max} (KBr) 3397 (m), 3312 (m), 2599 (w, vbr), 1698 (vs), 1677 (s), 1620 (w, sh), 1467 (w), 1388 (m), 1270 (m), 1084 (w), 1053 (w), 802 (m), 768 (w). δ_{H} (600.1 MHz, D_2O) 3.00 (1H, dd, $J_{\text{gem}}=12.9$,

$J(5'b, 4')=2.8$, H-5'b), 3.24 (1H, dd, $J_{\text{gem}}=12.2$, $J(2'b, 3')=8.6$, H-2'b), 3.35 (1H, dd, $J_{\text{gem}}=12.9$, $J(5'a, 4')=5.4$, H-5'a), 3.36 (1H, dd, $J_{\text{gem}}=12.2$, $J(2'a, 3')=8.4$, H-2'a), 4.48 (1H, ddd, $J(4', 3')=5.7$, $J(4', 5')=5.4$, 2.8, H-4'), 4.90 (1H, ddd, $J(3', 2')=8.6$, 8.4, $J(3', 4')=5.7$, H-3'), 5.82 (1H, d, $J(5, 6)=8.0$, H-5), 7.68 (1H, d, $J(6, 5)=8.0$, H-6). δ_{C} (150.9 MHz, D_2O) 48.60 (C-2'), 55.19 (C-5'), 61.16 (C-3'), 72.05 (C-4'), 103.60 (C-5), 147.94 (C-6), 156.38 (C-2), 170.46 (C-4). HRMS for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}_3$ (M+H) $^{+}$ calcd 198.0873, found 198.0873.

4.6.30. 1-((3S,4S)-4-Hydroxypyrrolidin-3-yl)uracil (10c). The title compound was prepared from **9c** (0.4 g, 0.635 mmol) according to general method E in 80% yield (0.1 g, 0.51 mmol) of white solid. ν_{max} (KBr) 3406 (m, br), 3185 (m, vbr), 1687 (vs, br), 1628 (m, sh), 1459 (m), 1420 (m), 1382 (m), 1270 (m), 1078 (w, br), 810 (w), 764 (w). δ_{H} (500.0 MHz, D_2O) 2.94 (1H, dd, $J_{\text{gem}}=12.3$, $J(5'b, 4')=5.2$, H-5'b), 3.16 (1H, dd, $J_{\text{gem}}=12.7$, $J(2'b, 3')=5.9$, H-2'b), 3.38 (1H, dd, $J_{\text{gem}}=12.3$, $J(5'a, 4')=5.9$, H-5'a), 3.51 (1H, dd, $J_{\text{gem}}=12.7$, $J(2'a, 3')=8.1$, H-2'a), 4.59 (1H, ddd, $J(4', 5')=5.9$, 5.2, $J(4', 3')=2.7$, H-4'), 4.61 (1H, ddd, $J(3', 2')=8.1$, 5.9, $J(3', 4')=2.7$, H-3'), 5.83 (1H, d, $J(5, 6)=7.9$, H-5), 7.59 (1H, d, $J(6, 5)=7.9$, H-6). δ_{C} (125.7 MHz, D_2O) 50.55 (C-2'), 54.68 (C-5'), 69.47 (C-3'), 77.63 (C-4'), 104.74 (C-5), 147.76 (C-6), 156.16 (C-2), 170.98 (C-4). HRMS for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}_3$ (M+H) $^{+}$ calcd 198.0873, found 198.0868.

4.6.31. 1-Cyclopropyluracil (10d). The title compound was prepared from **9d** (0.45 g, 1.988 mmol) according to general method E in 97% yield (0.35 g, 1.944 mmol) of white solid. ν_{max} (KBr) 3145 (w, br), 2998 (m, br), 2954 (m), 2876 (m), 1714 (s, sh), 1700 (vs), 1678 (vs), 1615 (m), 1472 (m), 1453 (w, sh), 1430 (w), 1421 (m), 1384 (m), 1268 (s), 765 (w). δ_{H} (500.0 MHz, DMSO- d_6) 1.52–1.65 (4H, m, H-2'a, 3'a, 4'a and H-5'a), 1.75 (2H, m, H-3'b and H-4'b), 1.91 (2H, m, H-2'b and H-5'b), 4.70 (1H, m, H-1'), 5.56 (1H, dd, $J(5, 6)=8.0$, $J(5, 3)=2.3$, H-5), 7.65 (1H, d, $J(6, 5)=8.0$, H-6), 11.22 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 23.84 (C-3' and C-4'), 30.72 (C-2' and C-5'), 56.50 (C-1'), 101.59 (C-5), 142.74 (C-6), 151.32 (C-2), 163.51 (C-4). HRMS for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2$ (M+H) $^{+}$ calcd 181.0972, found 181.0972.

4.6.32. 1-Cyclohexyluracil (10e). The title compound was prepared from **9e** (0.50 g, 2.08 mmol) according to general method E in 99% yield (0.40 g, 2.061 mmol) of white solid. ν_{max} (KBr) 2930 (s), 2865 (m), 1714 (vs, sh), 1690 (vs, br), 1676 (vs, br), 1616 (s), 1470 (s), 1452 (m), 1428 (m), 1419 (s), 1379 (s), 1268 (s), 763 (m). δ_{H} (500.0 MHz, DMSO- d_6) 1.13 (1H, qt, $J_{\text{gem}}=J(4'ax, 3'ax)=J(4'ax, 5'ax)=13.0$, $J(4'ax, 3'eq)=J(4'ax, 5'eq)=3.6$, H-4'ax), 1.32 (2H, qt, $J_{\text{gem}}=J(3'ax, 2'ax)=J(3'ax, 4'ax)=13.2$, $J(3'ax, 2'eq)=J(3'ax, 4'eq)=3.4$, H-3'ax and H-5'ax), 1.54 (2H, qd, $J_{\text{gem}}=J(2'ax, 1')=J(2'ax, 3'ax)=12.4$, $J(2'ax, 3'eq)=3.7$, H-2'ax and H-6'ax), 1.61 (1H, dm, $J_{\text{gem}}=12.9$, H-4'eq), 1.69 (2H, m, H-2'eq and H-6'eq), 1.78 (2H, dm, $J_{\text{gem}}=13.5$, H-3'eq and H-5'eq), 4.23 (1H, tt, $J(1', 2'ax)=J(1', 6'ax)=12.2$, $J(1', 2'eq)=J(1', 6'eq)=3.8$, H-1'), 5.55 (1H, dd, $J(5, 6)=8.0$, $J(5, 3)=2.3$, H-5), 7.70 (1H, d, $J(6, 5)=8.0$, H-6), 11.22 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 24.85 (C-4'), 25.56 (C-3' and C-5'), 31.06 (C-2' and C-6'), 54.25 (C-1'), 101.33 (C-5), 142.40 (C-6), 151.10 (C-2), 163.43 (C-4). HRMS for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}$ (M+Na) $^{+}$ calcd 217.0947, found 217.0948.

4.6.33. 1-(trans-2-Hydroxycyclohexyl)uracil (10f). The title compound was prepared from **9f** (0.33 g, 1.28 mmol) according to general method E in 78% yield (0.210 g, 0.998 mmol) of white solid. ν_{max} (KBr) 3348 (s), 3287 (m, br, sh), 3162 (m, br), 3021 (m, br), 2937 (s), 2862 (m), 1728 (s), 1694 (vs, br), 1662 (s, sh), 1625 (s), 1474 (s), 1427 (m), 1457 (m), 1388 (s), 1271 (s), 1074 (m), 764 (w). δ_{H} (499.8 MHz, DMSO- d_6) 1.21–1.29 (3H, m, H-3'a, 4'a and H-5'a), 1.56 (1H, br s, H-6'a), 1.62–1.71 (3H, m, H-4'b, 5'b and H-6'b), 1.94 (1H, m, H-3'b), 3.64 (1H, br s, H-2'), 4.06 (1H, br s, H-1'), 4.89 (1H, br d, $J(\text{OH}, 2')=5.0$, OH), 5.54 (1H, d, $J(5, 6)=7.9$, H-5), 7.67 (1H, d, $J(6, 5)=7.9$, H-6), 11.12 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6)

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24.02 (C-4'), 25.02 (C-5'), 30.08 (C-6'), 35.14 (C-3'), 60.36 (C-1'), 69.00 (C-2'), 100.98 (C-5), 142.86 (C-6), 151.61 (C-2), 163.46 (C-4). HRMS for $C_{10}H_{15}N_2O_3$ (M+H)⁺ calcd 211.1077, found 211.1078.

4.6.34. 1-(*cis*-2-Hydroxycyclopentyl)uracil (**10g**). The title compound was prepared from **9g** (0.28 g, 1.155 mmol) according to general method E in 95% yield (0.215 g, 0.153 mmol) of white solid. $\nu_{\max}$ (KBr) 3470 (m), 3418 (m, br), 3288 (w, br, sh), 3165 (m), 3024 (m, br), 2964 (m), 2873 (w), 1701 (vs), 1691 (vs), 1665 (s, sh), 1619 (m), 1473 (m), 1453 (w, sh), 1425 (w), 1393 (w), 1277 (m), 1015 (w), 762 (w). δ_H (499.8 MHz, DMSO- d_6) 1.48–1.61 (2H, m, H-3'a and H-4'a), 1.75–1.83 (2H, m, H-4'b and H-5'a), 1.85–1.95 (2H, m, H-3'b and H-5'b), 4.03 (1H, m, H-2'), 4.50 (1H, m, H-1'), 4.93 (1H, br d, J (OH,2')=4.2, OH), 5.48 (1H, dd, J (5,6)=8.0, J (5,3)=2.3, H-5), 7.60 (1H, d, J (6,5)=8.1, H-6), 11.16 (1H, br s, H-3). δ_C (125.7 MHz, DMSO- d_6) 20.05 (C-4'), 26.05 (C-5'), 32.79 (C-3'), 58.56 (C-1'), 69.62 (C-2'), 99.63 (C-5), 144.22 (C-6), 151.71 (C-2), 163.56 (C-4). HRMS for $C_9H_{12}N_2O_3Na$ (M+Na)⁺ calcd 219.0740, found 219.0741.

4.6.35. 1-(1-(Hydroxymethyl)cyclopentyl)uracil (**10h**). The title compound was prepared from **9h** (0.53 g, 2.067 mmol) according to general method E in 92% yield (0.402 g, 1.914 mmol) of white solid. $\nu_{\max}$ (KBr) 3404 (s), 3176 (m), 3054 (m, br), 2956 (m), 2879 (m), 1705 (vs), 1689 (vs), 1662 (vs), 1617 (w), 1465 (m), 1415 (m), 1387 (m), 1265 (w), 1062 (m), 764 (m). δ_H (500.0 MHz, DMSO- d_6) 1.55 (2H, m, H-3'a and H-4'a), 1.65 (2H, m, H-3'b and H-4'b), 1.78 (2H, m, H-2'a and H-5'a), 2.15 (2H, m, H-2'b and H-5'b), 3.49 (2H, s, CH₂O), 5.06 (1H, br s, OH), 5.41 (1H, dd, J (5,6)=8.1, J (5,3)=2.5, H-5), 7.47 (1H, d, J (6,5)=8.2, H-6), 11.01 (1H, br d, J (3,5)=2.2, H-3). δ_C (125.7 MHz, DMSO- d_6) 22.35 (C-3' and C-4'), 33.78 (C-2' and C-5'), 61.59 (CH₂OH), 73.42 (C-1'), 99.49 (C-5), 145.75 (C-6), 151.37 (C-2), 164.00 (C-4). HRMS $C_{10}H_{14}N_2O_3Na$ (M+Na)⁺ calcd 233.0897, found 233.0896.

4.6.36. 1-(2,3-Dihydroxypropyl)uracil (**10i**). The title compound was prepared from **9i** (0.37 g, 1.59 mmol) according to general method E in 97% yield (0.29 g, 1.559 mmol) of white solid. $\nu_{\max}$ (KBr) 3424 (br), 3375 (s, br), 3150 (m, br, sh), 3101 (m), 1689 (vs, sh), 1663 (vs, br), 1620 (s), 1469 (m), 1429 (s), 1391 (m), 1250 (m), 1085 or 1068 (m), 1047 (m), 764 (m). δ_H (500.0 MHz, DMSO- d_6) 3.29 (1H, dd, J_{gem} =11.1, J (3'a,2')=5.9, H-3'a), 3.36 (1H, dd, J_{gem} =11.1, J (3'b,2')=5.2, H-3'b), 3.36 (1H, dd, J_{gem} =13.7, J (1'a,2')=8.8, H-1'a), 3.67 (1H, m, H-2'), 3.92 (1H, dd, J_{gem} =13.7, J (1'b,2')=3.5, H-1'b), 5.50 (1H, dd, J (5,6)=7.8, J (5,3)=2.3, H-5), 7.49 (1H, d, J (6,5)=7.9, H-6), 11.22 (1H, br d, J (3,5)=2.1, H-3). δ_C (125.7 MHz, DMSO- d_6) 51.38 (C-1'), 63.92 (C-3'), 69.30 (C-2'), 100.28 (C-5), 147.36 (C-6), 151.40 (C-2), 164.25 (C-4). HRMS $C_7H_{10}N_2O_4Na$ (M+Na)⁺ calcd 209.0533, found 209.0534.

4.6.37. 1-Phenyluracil (**10j**). The title compound was prepared from **9j** (0.4 g, 0.635 mmol) according to general method E in 96% yield (0.17 g, 0.603 mmol) of white solid. $\nu_{\max}$ (KBr) 3159 (w, br), 1779 (m), 1745 (s), 1716 (m), 1692 (vs), 1663 (m, sh), 1628 (m), 1601 (m), 1579 (w, sh), 1494 (w), 1460 (w), 1440 (m), 1423 (m), 1384 (s), 1321 (vw), 1258 (m), 1182 (vw), 1075 (w), 1034 (w), 999 (w), 909 (w), 824 (m), 757 (m), 688 (m), 507 (w). δ_H (500.0 MHz, CDCl₃) 5.83 (1H, dd, J (5,6)=8.0, J (5,3)=2.2, H-5), 7.34 (1H, d, J (6,5)=8.0, H-6), 7.35 (2H, m, H-o-Ph), 7.45 (1H, m, H-p-Ph), 7.50 (2H, m, H-m-Ph), 8.39 (1H, br s, H-3). δ_C (125.7 MHz, CDCl₃) 102.65 (C-5), 126.26 (C-o-Ph), 129.05 (C-p-Ph), 129.70 (C-m-Ph), 138.32 (C-i-Ph), 144.64 (C-6), 149.96 (C-2), 162.95 (C-4). HRMS for $C_{10}H_9N_2O_2$ (M+H)⁺ calcd 189.0659, found 189.0658.

4.6.38. Methyl 2-(1-uracilyl)acetate (**10k**). The title compound was prepared from **9k** (0.74 g, 3.21 mmol) according to general method E in 78% yield (0.46 g, 2.5 mmol) of white solid. $\nu_{\max}$ (KBr) 3183 (m, br), 1739 (vs), 1700 (vs, br), 1634 (s), 1454 (s), 1440 (m, sh), 1419 (m), 1381 (m), 1250 (s, sh), 1235 (s), 1223 (s), 822 (m), 768 (m), 760 (m). δ_H (500.0 MHz, DMSO- d_6) 3.68 (3H, s, CH₃O), 4.52 (2H, s, CH₂N),

5.62 (1H, dd, J (5,6)=7.9, J (5,3)=2.2, H-5), 7.61 (1H, d, J (6,5)=7.9, H-6), 11.42 (1H, br d, J (3,5)=2.2, H-3). δ_C (125.7 MHz, DMSO- d_6) 48.33 (CH₂N), 52.62 (CH₃O), 101.42 (C-5), 146.18 (C-6), 151.25 (C-2), 164.09 (C-4), 168.97 (CO). HRMS for $C_7H_8N_2O_4Na$ (M+H+Na)⁺ calcd 207.0376, found 207.0377.

4.6.39. (*R*)-Ethyl 2-(1-uracilyl)propanoate (**10l**). The title compound was prepared from **9l** (0.73 g, 2.83 mmol) according to general method E in 96% yield (0.58 g, 2.73 mmol) of white solid. $\nu_{\max}$ (KBr) 3150 (m, br), 1754 (s), 1746 (vs), 1713 (vs), 1672 (vs), 1617 (s, sh), 1480 (m), 1471 (m), 1459 (m), 1415 (m), 1399 (m), 1380 (s), 1272 (s), 1203 (s, sh), 1191 (s), 1115 (w), 1097 (w, sh), 830 (m), 822 (m), 679 (w), 760 (w). δ_H (500.0 MHz, DMSO- d_6) 1.17 (3H, t, J (CH₃,CH₂)=7.1, CH₃CH₂O), 1.52 (3H, d, J (CH₃,CH)=7.3, CH₃), 4.13 (2H, m, CH₃CH₂O), 4.98 (1H, q, J (CH,CH₃)=7.3, CH), 5.60 (1H, dd, J (5,6)=8.0, J (5,3)=2.2, H-5), 7.66 (1H, d, J (6,5)=8.0, H-6), 11.32 (1H, br s, H-3). δ_C (125.7 MHz, DMSO- d_6) 14.16 (CH₃CH₂O), 15.46 (CH₃), 54.94 (CH), 61.46 (CH₃CH₂O), 101.38 (C-5), 144.15 (C-6), 150.92 (C-2), 163.58 (C-4), 170.19 (CO). HRMS for $C_9H_{12}N_2O_4Na$ (M+H+Na)⁺ calcd 235.0689, found 235.0689.

4.6.40. (*R*)-1-(Pyrrolidin-3-yl)thymine (**10m**). The title compound was prepared from **9m** (0.79 g, 2.314 mmol) according to general method E in 93% yield (0.42 g, 2.15 mmol) of white solid. NMR and HRMS spectra were identical to those in Ref. 3.

4.6.41. 1-((3*R*,4*S*)-4-Hydroxypyrrolidin-3-yl)thymine (**10n**). The title compound was prepared from **9n** (0.52 g, 0.79 mmol) according to general method E and was re-purified using preparative reverse phase HPLC in 90% yield (0.15 g, 0.71 mmol) of white solid. NMR and HRMS spectra were identical to those in Ref. 4.

4.6.42. 1-Cyclohexylthymine (**10o**). The title compound was prepared from **9o** (0.27 g, 1.06 mmol) according to general method E in 95% yield (0.21 g, 1.008 mmol) of white solid. $\nu_{\max}$ (KBr) 3395 (w), 3167 (s), 3100 (s, br), 3042 (s, br), 2931 (s), 2858 (s), 1692 (vs, br), 1661 (vs, br), 1517 (w), 1473 (s), 1451 (s), 1419 (m), 1392 (s), 1368 (m), 1271 (vs), 1046 (w), 759 (m). δ_H (500.0 MHz, CDCl₃) 1.18 (1H, m, H-4'ax), 1.39–1.50 (4H, m, H-2'ax, 3'ax, 5'ax and H-6'ax), 1.74 (1H, dm, J_{gem} =13.2, H-4'eq), 1.86–1.92 (4H, m, H-2'eq, 3'eq, 4'eq and H-6'eq), 1.93 (3H, d, J (CH₃,6)=1.2, CH₃), 4.46 (1H, m, H-1'), 7.06 (1H, q, J (6,CH₃)=1.2, H-6), 9.34 (1H, br s, H-3). δ_C (125.7 MHz, CDCl₃) 12.54 (CH₃), 25.12 (C-4'), 25.53 (C-3' and C-5'), 31.87 (C-2' and C-6'), 54.33 (C-1'), 110.44 (C-5), 136.51 (C-6), 151.03 (C-2), 163.79 (C-4). HRMS $C_{11}H_{17}N_2O_2$ (M+H)⁺ calcd 209.1285, found 209.1284.

4.6.43. 1-(*trans*-2-Hydroxycyclohexyl)thymine (**10p**). The title compound was prepared from **9p** (0.25 g, 0.924 mmol) according to general method E in 96% yield (0.20 g, 0.892 mmol) of white solid. $\nu_{\max}$ (KBr) 3459 (s), 3335 (w, br, sh), 3150 (m, br), 3021 (m, br), 2939 (m), 2858 (m), 1696 (vs, sh), 1685 (vs), 1663 (vs), 1514 (w), 1477 (m), 1454 (m), 1428 (m), 1390 (m), 1374 (m), 1271 (s), 1068 (m), 1046 (w, sh), 764 (w), 758 (w). δ_H (499.8 MHz, DMSO- d_6) 1.20–1.31 (3H, m, H-3'a, 4'a and H-5'a), 1.58 (1H, br s, H-6'a), 1.62–1.71 (3H, m, H-4'b, 5'b and H-6'b), 1.77 (3H, br s, CH₃), 1.94 (1H, m, H-3'b), 3.65 (1H, br s, H-2'), 4.06 (1H, br s, H-1'), 4.73 (1H, br s, OH), 7.56 (1H, br s, H-6), 11.07 (1H, br s, H-3). δ_C (125.7 MHz, DMSO- d_6) 12.29 (CH₃), 24.07 (C-4'), 25.05 (C-5'), 30.09 (C-6'), 35.14 (C-3'), 59.45 (C-1'), 68.97 (C-2'), 108.53 (C-5), 138.47 (C-6), 151.58 (C-2), 164.03 (C-4). HRMS $C_{11}H_{17}N_2O_3$ (M+H)⁺ calcd 225.1234, found 225.1234.

4.6.44. 1-(1-(Hydroxymethyl)cyclopentyl)thymine (**10q**). The title compound was prepared from **9q** (0.30 g, 0.90 mmol) according to general method E in 97% yield (0.195 g, 0.870 mmol) of white solid. $\nu_{\max}$ (KBr) 3428 (m, sh), 3355 (s), 3150 (m), 3090 (m), 3027 (s), 2954 (s), 2880 (m), 1716 (vs), 1664 (vs), 1478 (m), 1465 (m), 1451 (m),

1424 (m), 1389 (m), 1365 (m), 1268 (m), 1054 (s), 1037 (m), 763 (m), 758 (m). δ_{H} (499.8 MHz, DMSO- d_6) 1.55 (2H, m, H-3'a and H-4'a), 1.65 (2H, m, H-3'b and H-4'b), 1.75 (3H, d, $J(\text{CH}_3, 6)=1.1$, CH₃), 1.80 (2H, m, H-2'a and H-5'a), 2.17 (2H, m, H-2'b and H-5'b), 3.50 (2H, d, $J(\text{CH}_2, \text{OH})=5.9$, CH₂O), 4.97 (1H, t, $J(\text{OH}, \text{CH}_2)=5.9$, OH), 7.33 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 10.96 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 12.37 (CH₃), 22.34 (C-3' and C-4'), 33.83 (C-2' and C-5'), 61.60 (CH₂OH), 73.07 (C-1'), 106.71 (C-5), 141.34 (C-6), 151.25 (C-2), 164.42 (C-4). HRMS $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_3$ (M+H)⁺ calcd 225.1234, found 225.1234.

4.6.45. *1-(2,3-Dihydroxypropyl)thymine (10r)*. The title compound was prepared from **9r** (0.19 g, 0.90 mmol) according to general method E in 97% yield (0.195 g, 0.870 mmol) of white solid. ν_{max} (KBr) 3494 (s), 3392 (s, br), 3280 (m, br, sh), 3145 (m, br), 1700 (s, sh), 1678 (vs), 1642 (s, sh), 1520 (vw), 1482 (m), 1429 (m), 1389 (m), 1096 (s), 1044 (m), 763 (m). δ_{H} (499.8 MHz, DMSO- d_6) 1.74 (3H, d, $J(\text{CH}_3, 6)=1.2$, CH₃), 3.30 (1H, dd, $J_{\text{gem}}=11.1$, $J(3'a, 2')=5.8$, H-3'a), 3.36 (1H, dd, $J_{\text{gem}}=11.1$, $J(3'b, 2')=5.2$, H-3'b), 3.36 (1H, dd, $J_{\text{gem}}=13.7$, $J(1'a, 2')=8.6$, H-1'a), 3.68 (1H, m, H-2'), 3.87 (1H, dd, $J_{\text{gem}}=13.7$, $J(1'b, 2')=3.6$, H-1'b), 7.38 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 11.17 (1H, br s, H-3). δ_{C} (125.7 MHz, DMSO- d_6) 12.18 (CH₃), 51.11 (C-1'), 63.88 (C-3'), 69.34 (C-2'), 107.66 (C-5), 143.11 (C-6), 151.31 (C-2), 164.65 (C-4). HRMS $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4$ (M+H)⁺ calcd 199.0713, found 199.0722.

4.6.46. *1-Phenylthymine (10s)*. The title compound was prepared from **9s** (0.26 g, 1.04 mmol) according to general method E in 97% yield (0.205 g, 1.014 mmol) of white solid. ν_{max} (KBr) 3166 (s, br), 3101 (m), 3038 (s, br), 1700 (vs, br), 1664 (vs, br), 1650 (vs, br), 1595 (vs), 1508 (m), 1491 (vs), 1478 (s), 1469 (s), 1446 (s), 1432 (s), 1419 (s), 1385 (m), 1371 (s), 1318 (s), 1279 (vs), 1172 (m), 1156 (w), 1080 (w), 1036 (s), 1006 (w), 965 (w), 916 (s), 841 (m), 761 (s), 692 (s), 615 (w), 515 (m). δ_{H} (499.8 MHz, CDCl₃) 1.97 (3H, d, $J(\text{CH}_3, 6)=1.3$, CH₃), 7.18 (1H, q, $J(6, \text{CH}_3)=1.3$, H-6), 7.34 (2H, m, H-2'), 7.41 (1H, m, H-4'), 7.48 (2H, m, H-3'), 9.09 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl₃) 12.23 (CH₃), 111.08 (C-5), 126.28 (C-2'), 128.66 (C-4'), 129.51 (C-3'), 138.57 (C-1'), 140.66 (C-6), 150.26 (C-2), 164.15 (C-4). HRMS for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_2$ (M+H)⁺ calcd 203.0815, found 203.0815.

4.6.47. *1-(2-Naphthyl)thymine (10t)*. The title compound was prepared from **9t** (0.33 g, 1.106 mmol) according to general method E in 97% yield (0.27 g, 1.071 mmol) of white solid. ν_{max} (KBr) 3170 (s, br), 3049 (s, br), 1704 (vs, br), 1684 (vs, br), 1655 (vs, sh), 1631 (s), 1598 (s), 1508 (s), 1468 (s), 1455 (s), 1437 (s), 1423 (s), 1373 (s), 1377 (s), 1359 (m), 1293 (vs), 1272 (s), 1142 (w), 1127 (m), 1043 (m), 1019 (w), 955 (w), 946 (w), 887 (m, sh), 866 (s), 810 (s), 772 (m), 765 (s), 753 (s), 649 (m), 629 (w), 527 (w), 477 (s). δ_{H} (499.8 MHz, CDCl₃) 2.04 (3H, d, $J(\text{CH}_3, 6)=1.3$, CH₃), 7.29 (1H, q, $J(6, \text{CH}_3)=1.3$, H-6), 7.46 (1H, dd, $J(3', 4')=8.7$, $J(3', 1')=2.2$, H-3'), 7.54–7.58 (2H, m, H-6' and H-7'), 7.80 (1H, d, $J(1', 3')=2.3$, H-1'), 7.85–7.91 (2H, m, H-5' and H-8'), 7.95 (1H, d, $J(4', 3')=8.7$, H-4'), 8.60 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl₃) 12.30 (CH₃), 111.20 (C-5), 124.05 (C-3'), 124.87 (C-1'), 127.11 and 127.19 (C-6' and C-7'), 127.83 and 128.01 (C-5' and C-8'), 129.59 (C-4'), 132.78 (C-4'a), 133.26 (C-8'a), 136.06 (C-2'), 140.88 (C-6), 150.29 (C-2), 163.92 (C-4). HRMS for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2$ (M+H)⁺ calcd 253.0972, found 253.0972.

4.6.48. *Methyl 3-ethoxy-2-methylacryloylcarbamate (11)*. A sample of **7b** was dissolved in 5 ml of anhydrous methanol. Few drops of triethylamine was added. The mixture was evaporated and

dissolved in CDCl₃. δ_{H} (500.0 MHz, CDCl₃) 1.33 (3H, t, $J(\text{CH}_3, \text{CH}_2)=7.1$, CH₃), 1.83 (3H, d, $J(\text{CH}_3, 6)=1.2$, 5-CH₃), 3.79 (3H, s, CH₃O), 4.08 (2H, q, $J(\text{CH}_2, \text{CH}_3)=7.1$, OCH₂CH₃), 7.42 (1H, q, $J(6, \text{CH}_3)=1.2$, H-6), 7.79 (1H, br s, H-3). δ_{C} (125.7 MHz, CDCl₃) 9.07 (5-CH₃), 15.26 (CH₃), 52.72 (CH₃O), 70.12 (OCH₂CH₃), 107.09 (C-5), 151.93 (C-2), 157.59 (C-6), 165.97 (C-4). HRMS for $\text{C}_8\text{H}_{13}\text{NO}_4\text{Na}$ (M+H+Na)⁺ calcd 210.0742, found 210.0741.

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The Stability and Reactivity of Activated Acryloylcarbamates as Reagents for the Synthesis of *N*-1 Substituted Thymine and Uracil – An NMR and DFT Study

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Abstract:

The mechanism of the decomposition of acryloylcarbamates **7a-b** yielding highly reactive isocyanates **3a-b** was proposed based on NMR measurements and quantum chemical calculations. A good agreement between the experimental kinetic data and DFT calculations allowed us to demonstrate that the stability of **7a-d** depends on the presence of methyl in the acryloyl moiety and the position of the nitro group in the nitrophenolic part of the molecule. Furthermore, the reactivity of **7a-d** with weakly nucleophilic and sterically hindered 2,4,6-tri-*tert*-butylaniline was explored by ¹H NMR demonstrating the usefulness of reagents **7a-d** offering access to a variety of 1-*N*-substituted uracils and thymines with potentially interesting biological properties.

Introduction

Many biologically active compounds belong to the class of nucleosides and nucleotides analogues, which play an important role in anticancer therapy¹⁻² or act as antiviral compounds.³ Specific examples also involve carbocyclic nucleosides⁴⁻⁵ (Carbovir®) and acyclic phosphonate nucleotides⁶ (Viread, Cidofovir, Tenofovir, Hepsera), which represent biologically important compounds in which the nucleobase is not connected *via* a glycosidic bond.

From a synthetic point of view, a crucial step in their preparation is the attachment of the nucleobase – the nucleosidation reaction. The most common synthetic routes to purine

nucleoside analogues are represented by direct alkylation of the appropriate nucleobases (adenine, 6-chloropurine or 2-amino-6-chloropurine) with the halo, tosyloxy or mesyloxy derivatives in dipolar aprotic solvents (DMF, DMSO) using cesium carbonate as a base.⁷⁻⁹ Alternatively, Mitsunobu reaction of 6-chloropurine or 2-amino-6-chloropurine with appropriate hydroxyderivative can be used.^{8,10-11} Recently, *N*⁶-bis-Boc-protected adenine was successfully used as a substrate for the Mitsunobu reaction during the synthesis of neplanocin A.¹² However, all of these methods for the introduction of pyrimidine nucleobases (uracil, thymine, and cytosine) suffer from both low regioselectivity and low yield of the 1-*N*-substituted product. The direct alkylation of nucleobases is usually accompanied by a competing elimination reaction, which further decreases the yield of the desired product.⁸⁻⁹ Some improvement (both in regioselectivity and overall yield) can be obtained through the use of 2,4-dimethoxypyrimidine or 2,4-dimethoxy-6-methylpyrimidine for the alkylation instead of uracil or thymine, respectively.¹³⁻¹⁵ As an alternative approach to the pyrimidine nucleoside analogues (e.g. carbocyclic nucleosides), a synthesis of 1-*N*-substituted nucleobases starting from a primary amine and isocyanates **3a-b** or carbamates **6a-b** were described fifty years ago by Shaw and Warrenner.¹⁶ The key isocyanates **3a-b**, accessible through two independent routes¹⁷⁻¹⁸ (Scheme 1), were used as intermediates for the synthesis of carbamates **6a-b** described by Hřebabeký et al.¹⁹

Scheme 1. The reagents for the preparation of 1-*N*-substituted pyrimidine nucleobases.

Isocyanates **3a-b** are an unusually moisture-sensitive species and also very reactive compounds, capable of forming carbamates with free hydroxy groups.²⁰ Therefore, the reaction is usually carried out either with the appropriately protected substrate or without protection at low temperature (<-20 °C). This property seems to be the main factor responsible for the varying yield of the reported uracil and thymine derivatives (usually ~20–80 %, in most cases <60 %) found in the literature.²¹⁻³² The formation of uracil and thymine rings is a two-stage reaction consisting of the aminolysis of carbamates **6a-b** or the addition of amine to isocyanates **3a-b** followed by a cyclization of the acryloylureas **9** formed (Scheme 2).³³

Scheme 2. The reaction of reagents **3**, **6** and **7** with amines and subsequent cyclization providing 1-*N*-substituted pyrimidines.

To date, there has not been any general, high-yield method available for the attachment of uracil and thymine moieties to sterically hindered secondary, tertiary, or even aromatic carbon atoms.

It was the extreme reactivity and moisture sensitivity of isocyanates **3** on the one hand and the low yields of **9** obtained using carbamates **6** on the other that prompted us to develop more advantageous reagents **7**, which proved to be reactive enough with a variety of amines. Moreover, they can be stored for longer time (several months in refrigerator), which enabled us to use them in modular syntheses of uracils and thymines **10**.³⁴ The synthesis of the reagents **7a–d** followed the procedure described for **6**,¹⁹ in whose last step of the ‘one-pot’ synthesis, a 2-nitrophenol solution in dioxane was added instead of ethanol.

The reagents **7a–d** were tested in reactions with a wide variety of amines (including those bonded to secondary, tertiary, and aromatic systems), giving consistently high yields of corresponding 1,3-disubstituted urea derivatives. The desired uracil and thymine derivatives were obtained by the cyclization of the urea intermediates using Dowex 50 in H⁺ form, providing again very high yields.³⁴

In this work, we wish to address an unprecedented decomposition of the reagent **7b** in CDCl₃ solution observed in the ¹H NMR measurements, to analyze and quantitatively characterize the reaction mechanism of the decomposition reaction. To this end, we conducted a series of NMR experiments to yield reliable kinetic data and a series of DFT calculations to provide a plausible mechanistic view of the studied reaction. In order to understand the reaction mechanism in detail, we have compared the experimental data with other reagents **7a**, **7c** and **7d**. We have also investigated the reaction of **7a–d** with low nucleophilic and sterically hindered 2,4,6-tri-*tert*-butylaniline to ensure that decomposition of **7a–b** does not limit their synthetic usage in preparation of *N*-1 substituted thymines and uracils. These findings represent a useful and successful conjunction of theoretical and experimental efforts extending our understanding of the organic reactions pertinent to this class of compounds.

Results and Discussion

Kinetics of decomposition studied by NMR

Reagents **7a–d** were prepared according Scheme 1 and fully characterized by ¹H and ¹³C NMR, elemental analysis, IR and MS. In the course of the NMR characterization of **7b**, we found that the reagent decomposes, yielding a complex mixture. The ¹H NMR spectrum of **7b**

recorded in commercial grade CDCl_3 (see Supporting Information) showed a mixture of at least four compounds identified as 3-ethoxy-2-methylacryloylcarbamic acid (as the product of reagent hydrolysis), 3-ethoxy-2-methylacryloylamide (i.e. the product of the decarboxylation of the former compound), 2-nitrophenol and reagent **7b** (Scheme 3).

Scheme 3. The decomposition of **7b** *via* hydrolysis and decarboxylation.

To rule out the effect of water, which might be present in regular CDCl_3 , the ^1H NMR spectra were recorded in dried CDCl_3 and a sealed NMR tube (see Experimental). The experiment has again shown the decomposition of compound **7b**, and the final products of decomposition were identified as acryloylisocyanate **3b** and 2-nitrophenol. Reagent **7b** was characterised by NMR only when a high concentration of sample and a short measurement time were applied.

To ascertain that acryloylisocyanate **3b** is the decomposition product, we allowed the decomposed mixture to react with dry methanol, yielding methyl ester **12**, i.e. the same product as that formed through the reaction of **7b** with methanol in the presence of Et_3N (Scheme 4). In addition, isocyanate **3b** was identified by IR measured in dry CHCl_3 (the characteristic band being at 2244 cm^{-1} for asymmetric stretching vibrations of the $-\text{NCO}$ group) and by ^{13}C NMR (with the characteristic chemical shift of $-\text{NCO}$ carbon at 130.47 ppm).

Scheme 4. The chemical proof of **3b** structure.

The rate of decomposition was estimated based on the ^1H NMR kinetic measurement in dry CDCl_3 and sealed NMR tube at $25\text{ }^\circ\text{C}$. The concentrations of starting compounds and decomposition product(s) were obtained by integration of several corresponding signals with similar relaxation times. The rate constant for the irreversible first order kinetic model was obtained from plots of the logarithm of the starting compound concentrations versus time, while rate constant for the reversible first order kinetic model was obtained from plots of the logarithm of the starting compound concentrations minus equilibrium concentration versus time and from equilibrium constant. Experimental data for decomposition of **7b** fitted irreversible reaction with first order kinetics (Table 1 and Supporting Information) with half life ($t_{1/2}$) of about 18 minutes. The kinetics measurements were also performed for the other

reagents, **7a**, **7c** and **7d**, and the results have been summarized in Table 1. The decomposition of **7a** was reversible reaction with first order kinetics (Table 1 and Supporting Information), while compounds **7c** and **7d** were stable and did not decompose at all.

As arises from Table 1, the kinetic measurements demonstrate a surprisingly strong dependence on the reagents and their structure. Reagents **7c** and **7d** (possessing a nitro group in the *para* position) do not undergo any degradation. On the other hand, the derivatives with the *ortho*-nitro group in nitrophenol moiety decompose readily, with the decomposition of the **7b**-bearing methyl group in the acryloyl part of the molecule being approximately fifty times faster than the decomposition of the **7a**-lacking methyl substituent. The different stability of the reaction products reflected in the molecular structure was further explored by DFT calculations.

Reaction mechanism of decomposition. Theoretical calculations.

We first optimised all sixteen planar geometries for each of **7a–d**, viz. all the possible arrangements of four double or partial double bonds in the system (64 molecular geometries in total) at the DFT(PBE)/def2-SVP level with the single-point energy calculated at the DFT(B3LYP)/def2-TZVP level. The solvation effects and corrections to the ZPE energy, enthalpy and entropy (using the ideal gas approximation) were included as well (for details, see Experimental). The results of this extensive conformational search are summarised in Tables S1–S5 (see Supporting Information). As can be seen in Tables S1–S4, the calculations predict (in all cases) the most stable isomers to possess *trans*-configuration on the -C=C- double bond. This fact has been corroborated experimentally by a missing NOE interaction between the Me group and the proton on the double bond for **7a–b** or by a missing NOE between the protons of the double bond for **7c–d**. At the same time we observe NOE between protons of CH₂ group from EtO and H or CH₃ on double bond in alpha position to CO.

With regard to the proposed reaction mechanism, we have also investigated the possible isomers with the proton on either of the oxygens adjacent to the central -NH- group (these calculations were carried out only for the most stable isomers). The results are also listed in Tables S1–S4 (including various terms in overall Gibbs energies), and all twenty-four structures of **7b** (assuming an *E* configuration on the -C=C- double bond) have been schematically depicted in Fig. 1.

Figure 1. The planar geometries of *E*-**7b** investigated by density functional theory calculations.

The calculations have shown that the 2NH-ZZZ conformer is the most stable structure for the *keto*-tautomer of **7b** whereas 3OH-ZZE is the lowest energy *enol*-form of the same compound. It can be noted that 3OH-ZZE geometry is nicely preorganised to form a six-membered transition state with bifurcated hydrogen bonding.

However, a rather surprising finding is the relatively small difference in energies between all the studied isomers. Considering the planar models depicted in Fig. 1, some of the structures would have been expected to have substantial intramolecular crowding. Even for such structures (e.g. 2NH-ZEE, 2NH-EEE) the energy or free energy differences amount to only ~15-25 kJ.mol⁻¹. This demonstrates a relatively high level of flexibility in the studied molecules (the systems avoid crowding by adopting a helical form). Thus, we had to consider several reaction pathways for the elimination reaction. The lowest saddle points and their energies are summarised in Table 2 for all studied compounds (**7a–7d**) and for the proposed reaction mechanism of degradation shown in Scheme 5. It can be mentioned that all saddle points are characterized by a single imaginary frequency corresponding to the reactive coordinate and are therefore true transition states for the studied reactions. By small changes of the geometry in the direction of reactant and product we ascertained that it connects the desired reactant and products structures (IRC-like calculation). A more complete listing of the calculated values of activation barriers can be found in Tables S1–S4.

Scheme 5. The degradation of **7b** – a proposed mechanism.

Furthermore, the reaction coordinate with the structures of all the key points on the potential energy surface is depicted in Figure 2.

Figure 2. The reaction coordinate for the degradation of *E*-**7b**.

As mentioned above, the transition state is characterised by the six-membered ring arrangement and is structurally close to the *enol*-form with activation barriers of 72–88 kJ.mol⁻¹ (Table 2). We have also investigated an alternative pathway starting from the more stable *keto*-form and involving the direct hydrogen transfer from the nitrogen atom to the oxygen atom of the nitrophenol ring. The activation barrier involving a four-membered transition state was considerably higher (~160-180 kJ.mol⁻¹, see Tables S1, S3, S4) for the 2NH-EEZ isomer (which has the most favourable arrangement of the atoms and highest thermodynamic stability of the reactants). This clearly favours the pathways involving the six-membered transition states described above.

As arises from Table 2, the presence of the *ortho*-nitro group plays an important role in the bifurcated hydrogen bond and lowers the free enthalpy of degradation ΔG_{calc} . On the other hand, the methyl group on the -C=C- double bond lowers the free energy of activation, $\Delta G_{\text{calc}}^{\ddagger}$, likely due to the effect of hyperconjugation. The computational results are in good agreement with the experimentally calculated $\Delta G_{\text{exp}}^{\ddagger}$ computed from the rate constants using Eyring equation. Since the accurate *ab initio* determination of the *absolute rate constant* is beyond the scope of this work (for a thorough discussion on the subject, we refer the reader to Ref. 35), we mostly want to highlight the excellent agreement in the relative difference between the two reactions (**7a**, **7b**) for which the comparison is available. $\Delta \Delta G_{\text{exp}}^{\ddagger} = 9.7$ kJ.mol⁻¹, whereas $\Delta \Delta G_{\text{calc}}^{\ddagger} = 11.9$ kJ.mol⁻¹.

NMR characterisation of the reactivity of **7a–d** towards amines

In our previous work,³⁴ we showed that reagents **7a,b** react with a variety of amines, including acyclic, cyclic, and aromatic, and also amino acids. All of the reactions were completed within one hour at room temperature. Nevertheless, the reaction kinetics were not addressed in detail. Herein, the reactivity of **7a–d** with low nucleophilic and sterically hindered 2,4,6-tri-*tert*-butylaniline is presented (Scheme 6).

Scheme 6. The reaction of **7a–d** with 2,4,6-tri-*tert*-butylaniline.

The kinetic measurements were performed in dry CDCl₃ at 25 °C and monitored by ¹H NMR. The concentrations of starting compounds and products were obtained by integration of

several corresponding signals with similar relaxation times (for example CH₃ on double bond in **7b** and **11b**). The rate constants were obtained from plots of the logarithm of the starting compound concentrations versus time. Obtained data fitted first order kinetics and the results of the measurements are summarized in Table 3. The kinetic data show relatively high difference in reaction rates that might be explained by observed decomposition described above. Similar reaction rates for **7c-d** confirm the finding that these compounds do not decompose and reaction with amine can be viewed as aminolysis of 4-nitrophenyl ester. On the other hand, very fast reaction rate for **7b** corresponds with decomposition of the compound and can be therefore assumed that 2,4,6-tri-*tert*-butylaniline reacts with isocyanate **3b** formed in course of the decomposition **7b**. The only anomaly is reactivity of 2,4,6-tri-*tert*-butylaniline with **7a**. In this case the amine probably reacts either with acryloylcarbamate **7a** or with its decomposition product **3b** and overall reaction rate is indeed anomalous. The reaction was complete for all the studied reagents, providing substituted acryloylureas as products. The results of the kinetics show that novel reagents **7a-d** are capable of reaction even with sterically hindered aromatic amines, which offers access to a variety of 1-*N*-substituted uracils and thymines with potentially interesting biological properties.

Conclusions

It has been shown that the studied reagents **7a-d** are highly reactive even with low-nucleophilic and sterically hindered amines and can be successfully applied for a modular synthesis of various 1-*N*-substituted uracils and thymines, which is difficult to achieve with other synthetic methods. The stability of reagents **7a-d** in dry CDCl₃ was investigated by experimental and theoretical methods. It has been proved that the decomposition of the studied molecules is strongly affected by the presence of the Me-group on the -C=C- double bond and the position of the nitro group on the phenol ring. While the former is assumed to lower the activation barrier of the reaction probably due to hyperconjugation, the latter plays a role in hydrogen bonding and influences the thermodynamics of the reaction. The experimental NMR observations are in good agreement with the results predicted by the DFT calculations, which allowed us to postulate a plausible reaction mechanism, presumably extending our understanding of the reactivity and stability of this class of compounds. It should be noted here that all the reagents are stable enough in the solid state to be stored for a long time. Moreover, the decomposition of the 2-nitrophenyl derivatives **7a** and **7b** yields an

isocyanate product that could react in the same manner as the parent reagents. These compounds could be seen as an 'instant form' of the previously described isocyanates **3a-b**.

Experimental Section

NMR Experiments: NMR spectra were acquired on a Bruker Avance 500 spectrometer (500.0 MHz for ^1H and 125.7 MHz for ^{13}C) in dry CDCl_3 . CDCl_3 was dried prior to use by anhydrous K_2CO_3 and distilled. The measurements were performed in an oven-dried NMR tube, which was sealed after sample preparation. The concentration of the samples was 38 mM and 40mM for the degradation kinetics and kinetics of reaction with amines, respectively. All of the kinetic measurements were performed at 25 °C. Temperature calibration was done using the standard method with an MeOH sample. ^1H and ^{13}C resonances were assigned based on PFG H,C-HSQC and H,C-HMBC experiments (for numbering see Supportin Info). ^1H and ^{13}C NMR of compounds **7a-d** have been already reported.³⁴

Computational Details: All the density functional theory (DFT) calculations reported in the study were carried out using the Turbomole 6.0 program.³⁶ The Perdew-Burke-Ernzerhof (PBE)³⁷ and hybrid three-parameter Becke's³⁸ (B3LYP) functionals were used throughout. The calculations were expedited by expanding the Coulomb integrals in an auxiliary basis set, the resolution-of-identity (RI-J) approximation.³⁹⁻⁴⁰ All the geometry optimisations were conducted using the def2-SVP basis set,⁴¹ whereas the single-point energies were recomputed in the def2-TZVP (triple-zeta valence with two polarisation functions on each atom).⁴² To account for the solvation effects, the conductor-like screening model (COSMO) method⁴¹⁻⁴² was used with the dielectric constant corresponding to chloroform ($\epsilon_r = 4.9$). In order to account for dispersion, we used the DFT+D method (i.e. the DFT method with the empirical dispersion terms) available in Turbomole 6.0.⁴³ The Gibbs free energy was then calculated as the sum of these contributions:

$$G = E_{\text{el}} + G_{\text{solv}} + E_{\text{ZPE}} - RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}}),$$

where E_{el} is the *in vacuo* energy of the system (at the B3LYP/def2-TZVP level and the geometry optimised at the RI-PBE/def2-SVP level), G_{solv} is the solvation free energy (at the RI-PBE/def2-SVP level), E_{ZPE} is the zero-point energy, and $-RT \ln(q_{\text{trans}} q_{\text{rot}} q_{\text{vib}})$ accounts for the entropic terms and the thermal correction to the enthalpy obtained from a frequency

calculation using the same method and software as for the geometry optimisation at the RI-PBE/def2-SV(P) level, 298 K, and 1 atm using the ideal-gas approximation.⁴⁴

(*E*)-3-Ethoxy-2-methylacryloyl isocyanate (3b)

¹H NMR (CDCl₃, 500.0 MHz): 1.36 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.82 d, 3 H, $J(\text{CH}_3, \text{CH}) = 1.2$ (CH₃); 4.13 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.53 q, 1 H, $J(\text{CH}, \text{CH}_3) = 1.2$ (CH=). ¹³C NMR (CDCl₃, 125.7 MHz): 8.79 (CH₃); 15.34 (CH₃CH₂O); 70.98 (OCH₂CH₃); 110.19 (C=); 130.47 (NCO); 162.82 (CH=); 165.52 (CO).

1-(2,4,6-Tri-*tert*-butylphenyl)-3-((*E*)-3-ethoxyacryloyl)urea (11a)

¹H NMR (CDCl₃, 500.0 MHz): 1.30 s, 9 H ((CH₃)₃C-4'); 1.32 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.40 s, 18 H ((CH₃)₃C-2',6'); 3.90 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 5.26 d, 1 H, $J(5,6) = 12.2$ (H-5); 7.40 s, 2 H, (H-3',5'); 7.72 d, 1 H, $J(6,5) = 12.2$ (H-6); 8.54 bs, 1 H (H-3); 10.29 bs, 1 H (H-1). ¹³C NMR (CDCl₃, 125.7 MHz): 14.48 (CH₃CH₂O); 31.38 ((CH₃)₃C-4'); 31.86 ((CH₃)₃C-2',6'); 34.97 ((CH₃)₃C-4'); 36.19 ((CH₃)₃C-2',6'); 67.87 (OCH₂CH₃); 97.48 (C-5); 122.93 (C-3',5'); 129.26 (C-1'); 148.01 (C-2',6'); 149.55 (C-4'); 154.77 (C-2); 163.84 (C-6); 168.26 (C-4).

HR-MS for C₂₄H₃₉N₂O₃ (M+H)⁺ calcd 403.2955, found 403.2955.

1-(2,4,6-Tri-*tert*-butylphenyl)-3-((*E*)-3-ethoxy-2-methylacryloyl)urea (11b)

¹H NMR (CDCl₃, 500.0 MHz): 1.31 s, 9 H ((CH₃)₃C-4'); 1.33 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.42 s, 18 H ((CH₃)₃C-2',6'); 1.84 d, 3 H, $J(\text{CH}_3, 6) = 1.2$ (5-CH₃); 4.04 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.43 s, 2 H, (H-3',5'); 7.58 q, 1 H, $J(6, \text{CH}_3) = 1.2$ (H-6); 7.95 bs, 1 H (H-3); 10.45 bs, 1 H (H-1). ¹³C NMR (CDCl₃, 125.7 MHz): 8.83 (5-CH₃); 15.44 (CH₃CH₂O); 31.37 ((CH₃)₃C-4'); 31.87 ((CH₃)₃C-2',6'); 34.98 ((CH₃)₃C-4'); 36.20 ((CH₃)₃C-2',6'); 70.54 (OCH₂CH₃); 105.68 (C-5); 123.04 (C-3',5'); 129.30 (C-1'); 147.97 (C-2',6'); 149.53 (C-4'); 154.33 (C-2); 158.71 (C-6); 169.64 (C-4).

HR-MS for C₂₅H₄₁N₂O₃ (M+H)⁺ calcd 417.3112, found 417.3111.

Methyl (*E*)-3-ethoxy-2-methylacryloylcarbamate (12)

¹H NMR (CDCl₃, 500.0 MHz): 1.33 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$ (CH₃CH₂O); 1.83 d, 3 H, $J(\text{CH}_3, 6) = 1.2$ (5-CH₃); 3.79 s, 3 H (CH₃O); 4.08 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.42 q, 1 H, $J(6, \text{CH}_3) = 1.2$ (H-6); 7.79 bs, 1 H (H-3). ¹³C NMR (CDCl₃, 125.7 MHz): 9.07 (5-

CH₃); 15.26 (CH₃CH₂O); 52.72 (CH₃O); 70.12 (OCH₂CH₃); 107.09 (C-5); 151.93 (C-2); 157.59 (C-6); 165.97 (C-4).

HR-MS for C₈H₁₃NO₄Na (M+H+Na)⁺ calcd 210.0742, found 210.0741.

Supporting Information (see footnote on the first page of this article): Kinetics measurements and computational data including .

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Table 1. The kinetics of **7a–d** degradation monitored by ¹H NMR.
[a] $k_+ = 1.83\ k_-$

Degradation	Reaction	Kinetics	$k\ (\text{hr}^{-1})$	$t_{1/2}\ (\text{hr})$
7a	reversible	first-order	$3.00 \times 10^{-2[a]}$	23.1
7b	irreversible	first-order	2.32	0.30
7c	no degradation observed			
7d	no degradation observed			

Table 2. The theoretical calculations of reaction free energies and activation barriers carried out using the B3LYP/def2-TZVP//RI-PBE/def2-SVP method. The solvation effects were included through COSMO calculations and the energies corrected for zero-point energies, thermal corrections to enthalpy and entropic terms (using ideal gas approximation) to obtain free energy estimates. The experimental data are shown in the right part of the table ($\Delta G_{\text{exp}}^{\ddagger}$ were calculated using Eyring equation: $\Delta G^{\ddagger} = RT[23.76 - \ln(k/T)]$).

Degradation	ΔG_{calc} (kJ.mol ⁻¹)	$\Delta G_{\text{calc}}^{\ddagger}$ (kJ.mol ⁻¹)	k_{exp} (s ⁻¹)	$\Delta G_{\text{exp}}^{\ddagger}$ (kJ.mol ⁻¹)
7a	-24.6	84.1	8.33×10^{-6}	102.0
7b	-30.2	72.0	6.44×10^{-4}	91.2
7c	-3.9	88.4	-	-
7d	-15.1	79.1	-	-

Table 3. The kinetics of the reaction of the reagents **7a–d** with 2,4,6-tri-*tert*-butylaniline in dry CDCl₃ at 25 °C.

Reagent	<i>k</i> (hr ⁻¹)	<i>t</i> _{1/2} (hr)
7a	2.7 × 10 ⁻²	25.7
7b	1.2	0.6
7c	7.4 × 10 ⁻²	9.4
7d	2.7 × 10 ⁻¹	2.6