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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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Keywords:	uracil, thymine, mechanism, NMR, DFT



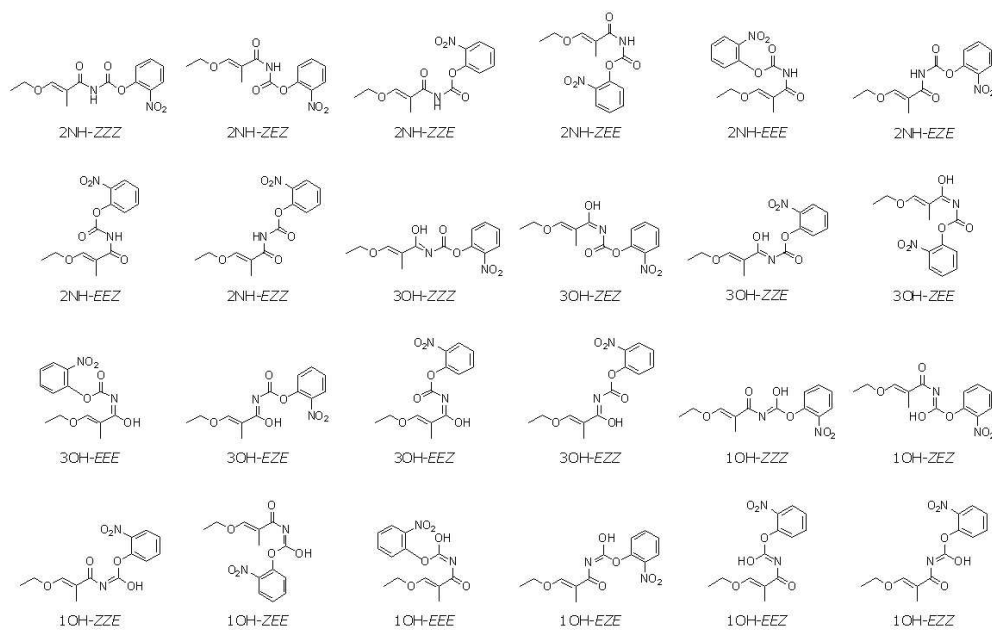


Figure 1. The planar geometries of E-7b investigated by density functional theory calculations.

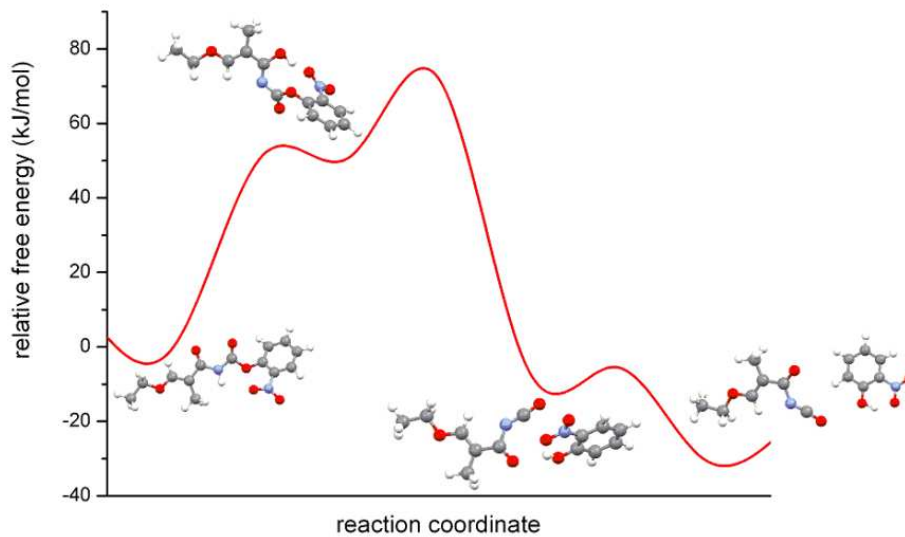
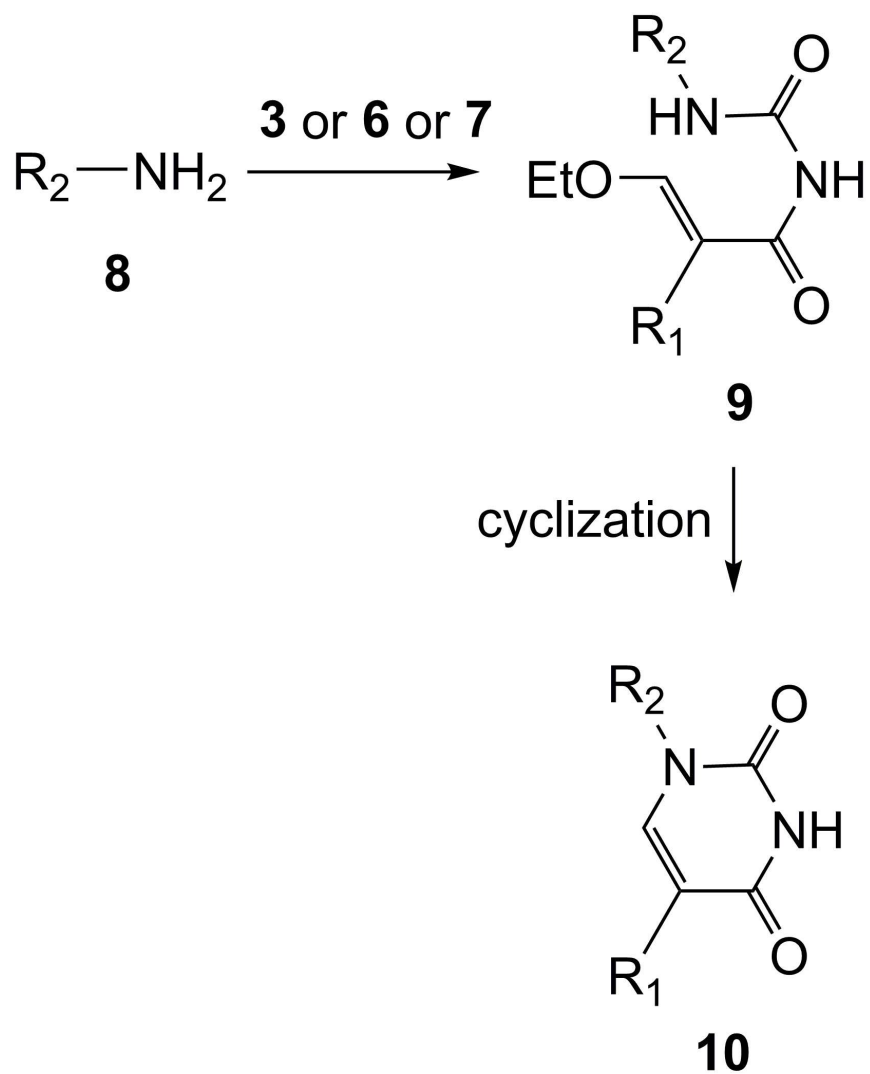


Figure 2. The reaction coordinate for the degradation of E-7b.
80x51mm (300 x 300 DPI)

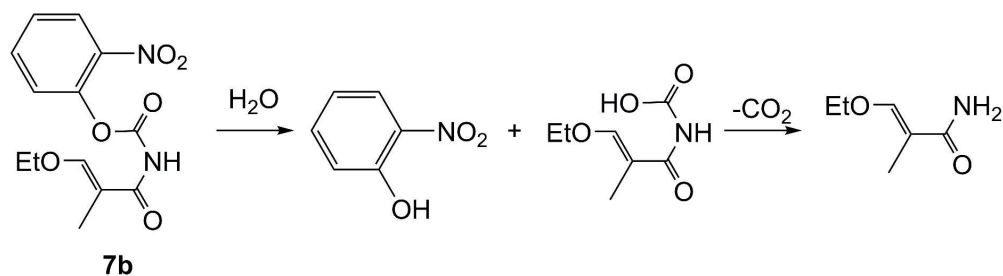
Review



$\text{R}_1 = \text{H, CH}_3$

$\text{R}_2 = \text{alkyl, cycloalkyl, aryl, hetaryl}$

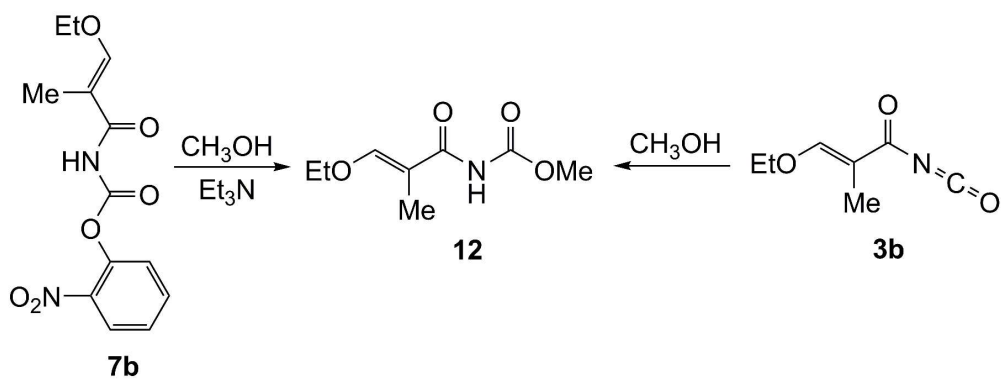
Scheme 2. The reaction of reagents 3, 6 and 7 with amines and subsequent cyclization providing 1-N-substituted pyrimidines.
71x98mm (600 x 600 DPI)



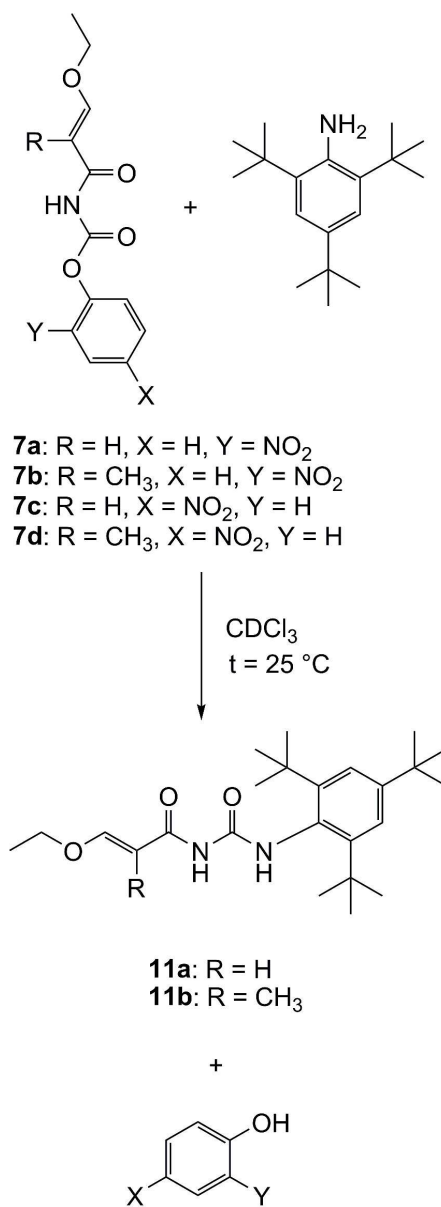
18 Scheme 3. The decomposition of 7b via hydrolysis and decarboxylation.
19 159x43mm (600 x 600 DPI)

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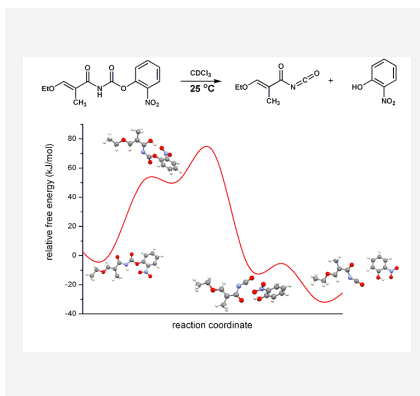


Scheme 4. The chemical proof of 3b structure.
153x58mm (600 x 600 DPI)



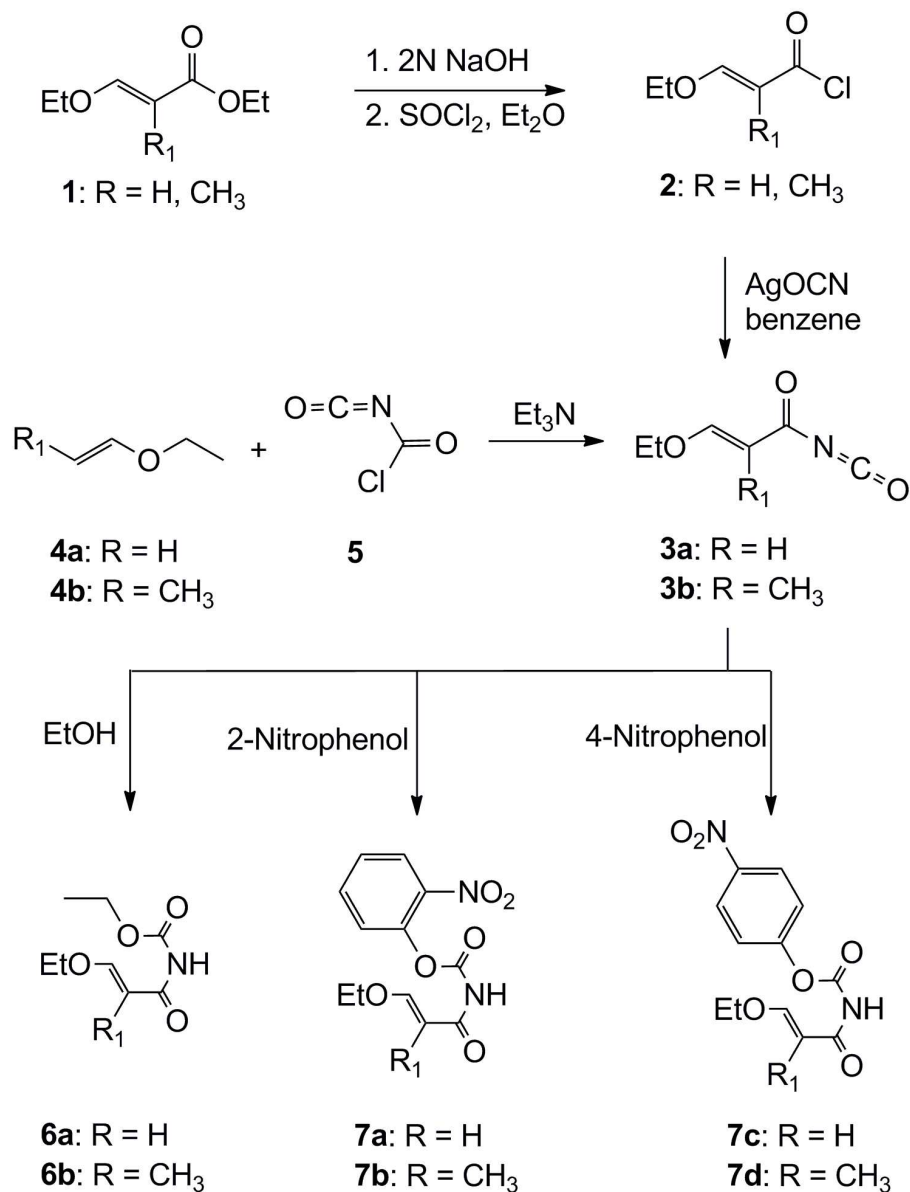
Scheme 6. The reaction of 7a-d with 2,4,6-tri-tert-butylaniline.
72x196mm (600 x 600 DPI)

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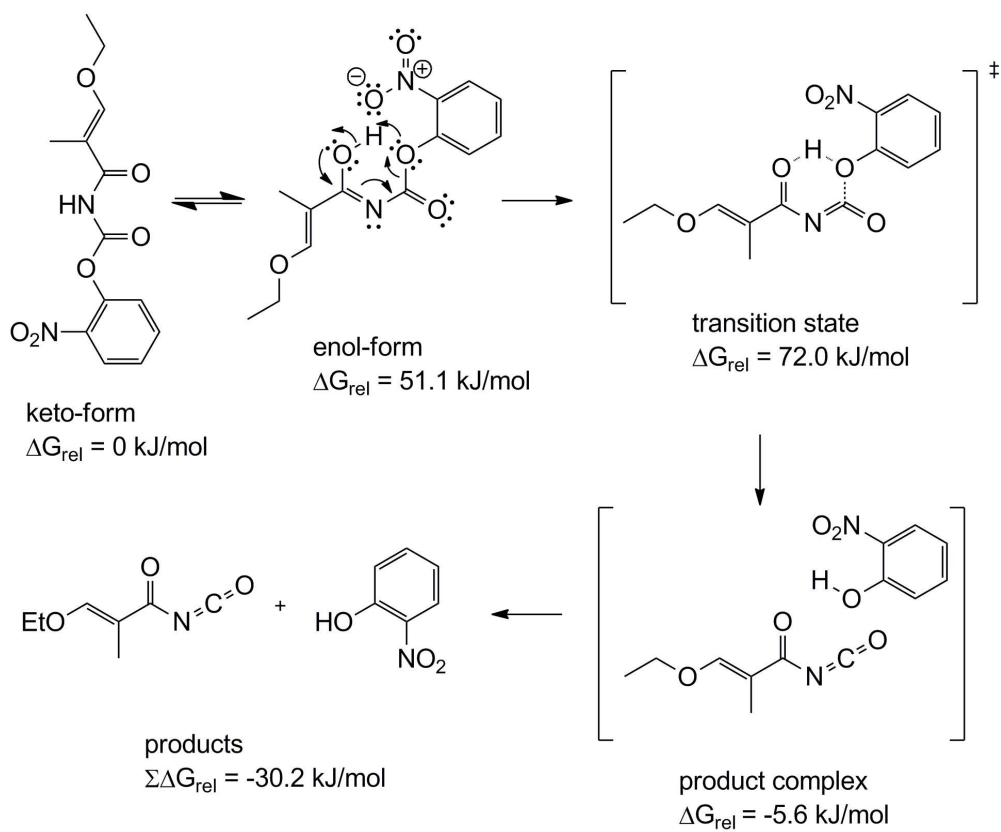


**The Stability and Reactivity of Activated
Acryloylcarbamates as Reagents for the
Synthesis of *N*-1 Substituted Thymine and
Uracil – A NMR and DFT Study**

Radek Pohl,^{*} Lubomír Rulíšek,^{*} and
Dominik Rejman^{*}



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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**

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3 recorded in commercial grade CDCl_3 (see Supporting Info) showed a mixture of at least four
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5 compounds identified as 3-ethoxy-2-methylacryloylcarbamic acid (as the product of reagent
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7 hydrolysis), 3-ethoxy-2-methylacryloylamide (as the product of the decarboxylation of the
8
9 former compound), 2-nitrophenol and reagent **7b** (Scheme 3).

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

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

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

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

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45 The rate of decomposition was estimated based on the ^1H NMR kinetic measurement in dry
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47 CDCl_3 and sealed NMR tube at $25\text{ }^\circ\text{C}$. The concentrations of starting compounds and
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49 decomposition product(s) were obtained by integration of several corresponding signals with
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51 similar relaxation times. The rate constant for the irreversible first order kinetic model was
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53 obtained from plots of the logarithm of the starting compound concentrations versus time,
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55 while rate constant for the reversible first order kinetic model was obtained from plots of the
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57 logarithm of the starting compound concentrations minus equilibrium concentration versus
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59 time and from equilibrium constant. Experimental data for decomposition of **7b** fitted
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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

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3 reagents, **7a**, **7c** and **7d**, and the results have been summarized in Table 1. The decomposition
4 of **7a** was reversible reaction with first order kinetics (Table 1 and supporting material), while
5 compounds **7c** and **7d** were stable and did not decompose at all.
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11 As arises from Table 1, the kinetic measurements demonstrate a surprisingly strong
12 dependence on the reagents and their structure. Reagents **7c** and **7d** (possessing a nitro group
13 in the *para* position) do not undergo any degradation. On the other hand, the derivatives with
14 the *ortho*-nitro group in nitrophenol moiety decompose readily, with the decomposition of the
15 **7b**-bearing methyl group in the acryloyl part of the molecule being approximately fifty times
16 faster than the decomposition of the **7a**-lacking methyl substituent. The different stability of
17 the reaction products reflected in the molecular structure was further explored by DFT
18 calculations.
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27 **Reaction mechanism of decomposition. Theoretical calculations.**

28 We first optimised all sixteen planar geometries for each of **7a–d**, *viz.* all the possible
29 arrangements of four double or partial double bonds in the system (64 molecular geometries
30 in total) at the DFT(PBE)/def2-SVP level with the single-point energy calculated at the
31 DFT(B3LYP)/def2-TZVP level. The solvation effects and corrections to the ZPE energy,
32 enthalpy and entropy (using the ideal gas approximation) were included as well (for details,
33 see Experimental). The results of this extensive conformational search are summarised in
34 Tables S1–S5 (see Supporting Info). As can be seen in Tables S1–S4, the calculations predict
35 (in all cases) the most stable isomers to possess *trans*-configuration on the -C=C- double
36 bond. This fact has been corroborated experimentally by a missing NOE interaction between
37 the Me group and the proton on the double bond for **7a–b** or by a missing NOE between the
38 protons of the double bond for **7c–d**. At the same time we observe NOE between protons of
39 CH₂ group from EtO and H or CH₃ on double bond in alpha position to CO.
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50 With regard to the proposed reaction mechanism, we have also investigated the possible
51 isomers with the proton on either of the oxygens adjacent to the central -NH- group (these
52 calculations were carried out only for the most stable isomers). The results are also listed in
53 Tables S1–S4 (including various terms in overall Gibbs energies), and all twenty-four
54 structures of **7b** (assuming an *E* configuration on the -C=C- double bond) have been
55 schematically depicted in Fig. 1.
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5 Figure 1. The planar geometries of *E-7b* investigated by density functional theory
6 calculations.
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10 The calculations have shown that the 2NH-ZZZ conformer is the most stable structure for the
11 *keto*-tautomer of **7b** whereas 3OH-ZZE is the lowest energy *enol*-form of the same compound.
12 It can be noted that 3OH-ZZE geometry is nicely preorganised to form a six-membered
13 transition state with bifurcated hydrogen bonding.
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17 However, a rather surprising finding is the relatively small difference in energies between all
18 the studied isomers. Considering the planar models depicted in Fig. 1, some of the structures
19 would have been expected to have substantial intramolecular crowding. Even for such
20 structures (e.g. 2NH-ZEE, 2NH-EEE) the energy or free energy differences amount to only
21 ~15-25 kJ.mol⁻¹. This demonstrates a relatively high level of flexibility in the studied
22 molecules (the systems avoid crowding by adopting a helical form). Thus, we had to consider
23 several reaction pathways for the elimination reaction. The lowest saddle points and their
24 energies are summarised in Table 2 for all studied compounds (**7a-7d**) and for the proposed
25 reaction mechanism of degradation shown in Scheme 5. It can be mentioned that all saddle
26 points are characterized by a single imaginary frequency corresponding to the reactive
27 coordinate and are therefore a true transition states for the studied reactions. By small changes
28 of the geometry in the direction of reactant and product we ascertained that it connects the
29 desired reactant and products structures (IRC-like calculation). A more complete listing of the
30 calculated values of activation barriers can be found in Tables S1-S4.
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49 Scheme 5. The degradation of **7b** – a proposed mechanism.
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53 Furthermore, the reaction coordinate with the structures of all the key points on the potential
54 energy surface is depicted in Figure 2.
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60 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

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3 calculation using the same method and software as for the geometry optimisation at the RI-
4 PBE/def2-SV(P) level, 298 K, and 1 atm using the ideal-gas approximation.⁴⁴
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9 **(E)-3-Ethoxy-2-methylacryloyl isocyanate (3b)**

10 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,
11 $J(\text{CH}_3, \text{CH}) = 1.2$ (CH₃); 4.13 q, 2 H, $J(\text{CH}_2, \text{CH}_3) = 7.1$ (OCH₂CH₃); 7.53 q, 1 H, $J(\text{CH}, \text{CH}_3)$
12 = 1.2 (CH=). ¹³C NMR (CDCl₃, 125.7 MHz): 8.79 (CH₃); 15.34 (CH₃CH₂O); 70.98
13 (OCH₂CH₃); 110.19 (C=); 130.47 (NCO); 162.82 (CH=); 165.52 (CO).
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19 **1-(2,4,6-Tri-*tert*-butylphenyl)-3-((E)-3-ethoxyacryloyl)urea (11a)**

20 ¹H NMR (CDCl₃, 500.0 MHz): 1.30 s, 9 H ((CH₃)₃C-4'); 1.32 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$
21 (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
22 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
23 H (H-3); 10.29 bs, 1 H (H-1). ¹³C NMR (CDCl₃, 125.7 MHz): 14.48 (CH₃CH₂O); 31.38
24 ((CH₃)₃C-4'); 31.86 ((CH₃)₃C-2',6'); 34.97 ((CH₃)₃C-4'); 36.19 ((CH₃)₃C-2',6'); 67.87
25 (OCH₂CH₃); 97.48 (C-5); 122.93 (C-3',5'); 129.26 (C-1'); 148.01 (C-2',6'); 149.55 (C-4');
26 154.77 (C-2); 163.84 (C-6); 168.26 (C-4).
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33 HR-MS for C₂₄H₃₉N₂O₃ (M+H)⁺ calcd 403.2955, found 403.2955.
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37 **1-(2,4,6-Tri-*tert*-butylphenyl)-3-((E)-3-ethoxy-2-methylacryloyl)urea (11b)**

38 ¹H NMR (CDCl₃, 500.0 MHz): 1.31 s, 9 H ((CH₃)₃C-4'); 1.33 t, 3 H, $J(\text{CH}_3, \text{CH}_2) = 7.1$
39 (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,
40 $J(\text{CH}_2, \text{CH}_3) = 7.1$ (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
41 bs, 1 H (H-3); 10.45 bs, 1 H (H-1). ¹³C NMR (CDCl₃, 125.7 MHz): 8.83 (5-CH₃); 15.44
42 (CH₃CH₂O); 31.37 ((CH₃)₃C-4'); 31.87 ((CH₃)₃C-2',6'); 34.98 ((CH₃)₃C-4'); 36.20 ((CH₃)₃C-
43 2',6'); 70.54 (OCH₂CH₃); 105.68 (C-5); 123.04 (C-3',5'); 129.30 (C-1'); 147.97 (C-2',6');
44 149.53 (C-4'); 154.33 (C-2); 158.71 (C-6); 169.64 (C-4).
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51 HR-MS for C₂₅H₄₁N₂O₃ (M+H)⁺ calcd 417.3112, found 417.3111.
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56 **Methyl (E)-3-ethoxy-2-methylacryloylcarbamate (12)**

57 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,
58 $J(\text{CH}_3, 6) = 1.2$ (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
59 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-
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3 CH₃); 15.26 (CH₃CH₂O); 52.72 (CH₃O); 70.12 (OCH₂CH₃); 107.09 (C-5); 151.93 (C-2);
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5 157.59 (C-6); 165.97 (C-4).

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7 HR-MS for C₈H₁₃NO₄Na (M+H+Na)⁺ calcd 210.0742, found 210.0741.
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10 **Supporting Information** (see footnote on the first page of this article): Kinetics
11 measurements and computational data including .
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13

14 15 16 **Acknowledgments**

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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 (hr ⁻¹)	$t_{1/2}$ (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			

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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	-	-

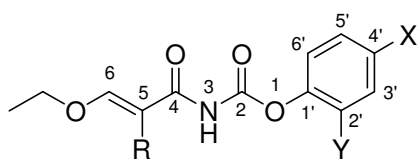
Table 3. The kinetics of the reaction of the reagents **7a–d** with 2,4,6-tri-*tert*-butylaniline in dry CDCl₃ at 25 °C.

Reagent	k (hr ⁻¹)	$t_{1/2}$ (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

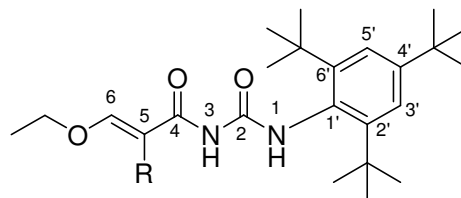
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Supporting Information

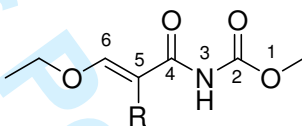
The numbering for NMR assignment:



- 7a:** R = H, X = H, Y = NO₂
7b: R = CH₃, X = H, Y = NO₂
7c: R = H, X = NO₂, Y = H
7d: R = CH₃, X = NO₂, Y = H



- 11a:** R = H
11b: R = CH₃



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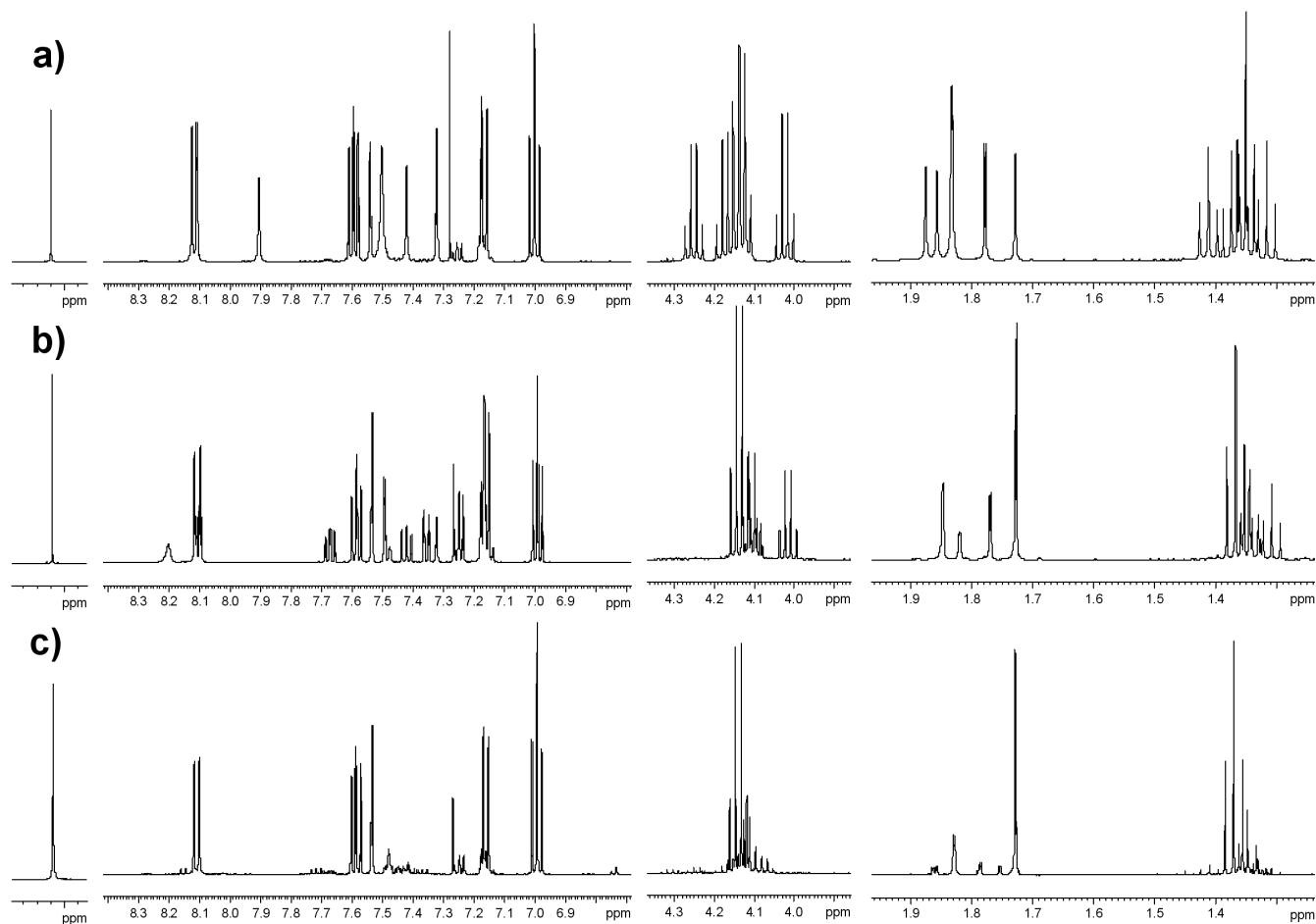


Fig.1. a) The ^1H NMR of **7b** recorded in commercial grade CDCl_3 . b) The ^1H NMR of **7b** recorded in dry CDCl_3 right after dissolution ($t_r = 5$ min). c) The same mixture as b) after 2 hours.

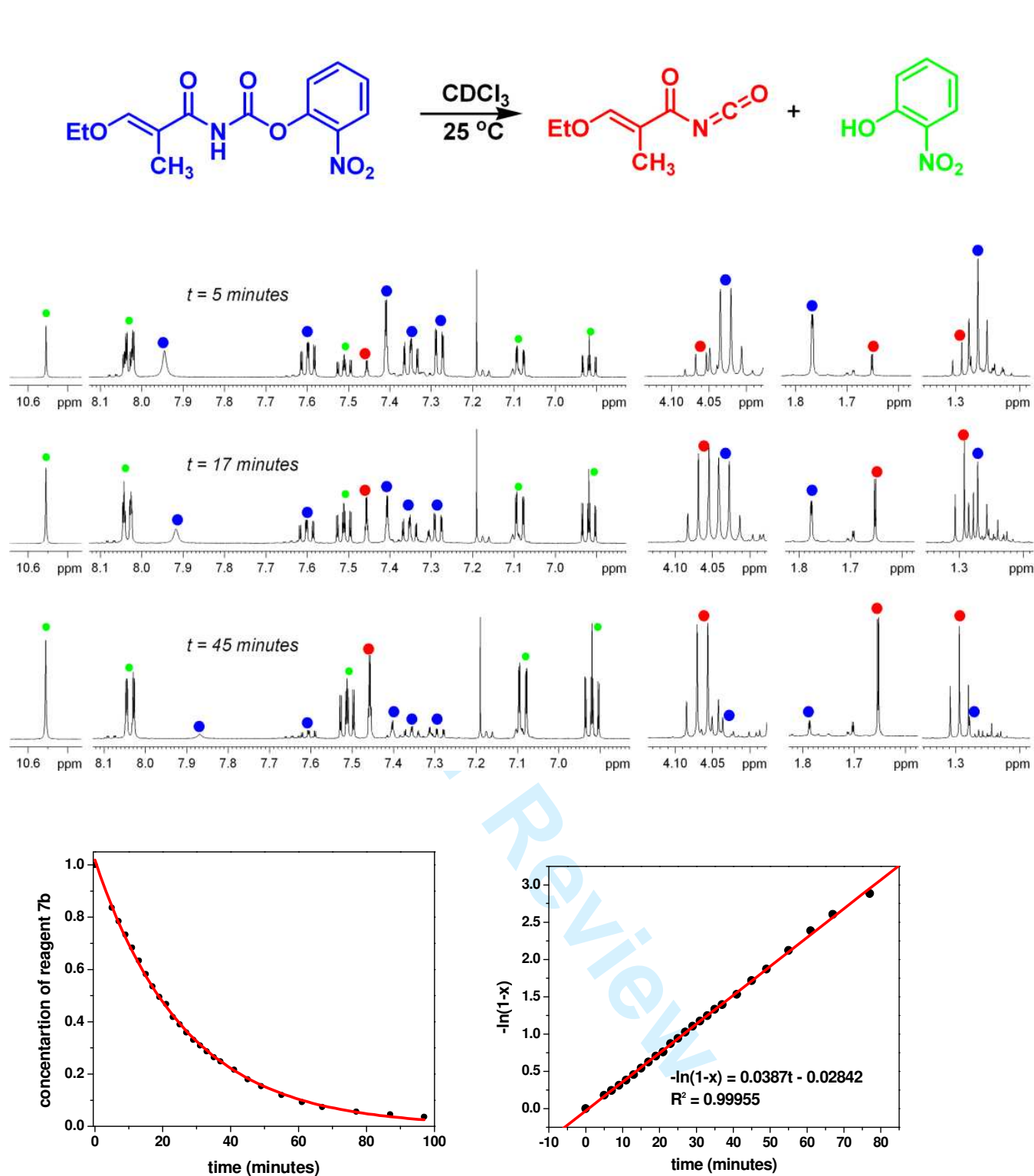


Fig. 2. The kinetics of the decomposition of **7b** in dry CDCl_3 in a sealed NMR tube at 25°C .

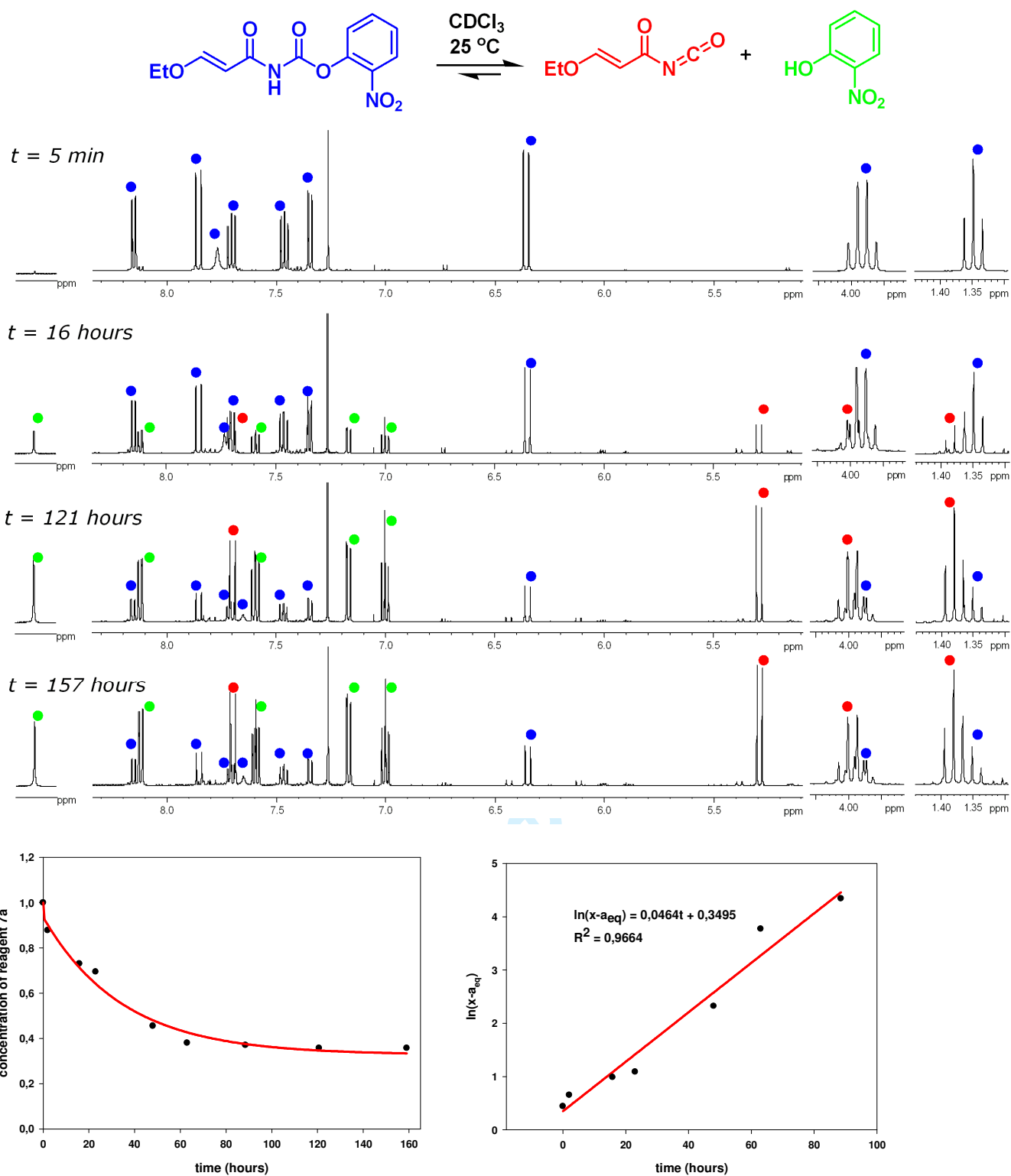


Fig. 3. The kinetics of the decomposition of **7a** in dry CDCl_3 in a sealed NMR tube at $25\text{ }^\circ\text{C}$.

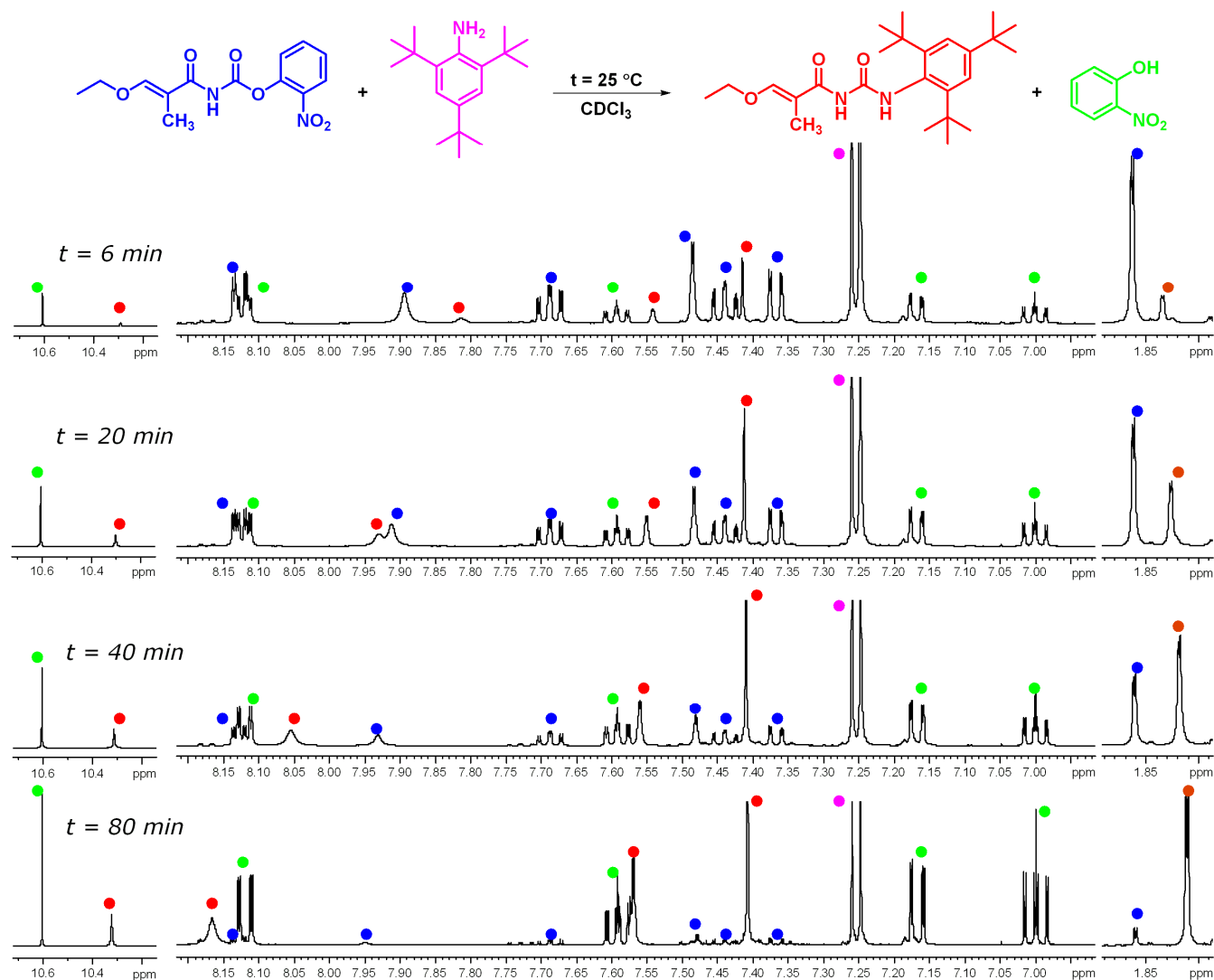


Fig. 4. The course of the reaction of **7b** with 2,4,6-tri-*tert*-butylaniline in dry CDCl₃ in a sealed NMR tube at 25 °C.

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)	$E(\text{PBE})$ def2-SVP	$E(\text{B3LYP})$ def2-TZVP	$E(\text{PBE+D+}$ COSMO) def2-SVP	G_{tot}	ΔG (kJ.mol ⁻¹)	ΔE (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-EZEZ	-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-ZZEE	-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

$E(\text{PBE})$... *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

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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3 ΔE ... relative difference in energy, $E(\text{B3LYP})$, in $\text{kJ}\cdot\text{mol}^{-1}$, with respect to the most stable reactant
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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)	$E(\text{PBE})$ def2-SVP	$E(\text{B3LYP})$ def2-TZVP	$E(\text{PBE+D+}$ COSMO) def2-SVP	G_{tot}	ΔG (kJ.mol ⁻¹)	ΔE (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-EZEZ	-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-ZEZE	-1062.58282	-1064.42597	-1062.62404	-1064.26226	13.6	0.3
2NH-ZEZZ	-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-ZZEZ	-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

$E(\text{PBE})$... *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

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	$E(\text{PBE+D+}$ 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

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3 c -1.40887 -2.75191 1.44095
4 c -2.51561 -3.14526 0.64612
5 o -0.85849 -1.49945 1.44903
6 c -1.71890 -0.38699 1.54644
7 n -0.97584 0.73182 1.26925
8 c -1.36312 2.12464 1.37224
9 c -2.68784 2.50479 0.90080
10 h -3.03861 3.50018 1.21334
11 n -3.14855 -2.23683 -0.32460
12 o -4.34277 -2.39834 -0.56785
13 o -2.88575 -0.48244 1.85016
14 o -2.42808 -1.39006 -0.86402
15 o -0.52197 2.90605 1.79856
16 c -3.41865 1.75670 0.02423
17 o -4.61669 2.13997 -0.41697
18 c -5.24048 1.31969 -1.43022
19 c -6.74370 1.50392 -1.34100
20 h 0.04221 0.60424 1.26900
21 h -3.04404 0.79642 -0.37653
22 h -4.85434 1.64631 -2.42372
23 h -4.94908 0.25539 -1.27753
24 h -7.24302 0.91118 -2.13747
25 h -7.12654 1.16055 -0.35616
26 h -7.02143 2.57173 -1.47326
27 h -3.89987 -4.70181 0.10401
28 h -2.80344 -6.42819 1.58819
29 h -0.80650 -5.76386 2.97597
30 h 0.03476 -3.39317 2.89979
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34 2NH-EEZE
35 E(B3LYP/def2-TZVP)=-1025.112407482
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37 32

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39 c -2.55668 -4.53433 0.03983
40 c -2.48542 -5.31611 1.19731
41 c -1.90140 -4.78258 2.35961
42 c -1.41021 -3.47091 2.36234
43 c -1.47194 -2.67681 1.20462
44 c -2.03980 -3.22797 0.03014
45 o -0.92700 -1.42111 1.29891
46 c -1.69144 -0.34028 0.93383
47 n -0.94165 0.82381 0.90282
48 c 0.40032 1.08173 1.32507
49 c 0.96688 2.33739 0.79408
50 h 1.84214 2.72588 1.33857
51 n -2.06196 -2.50874 -1.26336
52 o -2.86623 -2.89408 -2.10929
53 o -2.87631 -0.38489 0.67929
54 o -1.24558 -1.60024 -1.42917
55 o 1.01382 0.33552 2.07001
56 c 0.57637 2.93682 -0.36313
57 o 1.16183 4.04912 -0.82892
58 c 0.78245 4.48382 -2.14701
59
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2				
3	c	1.40272	5.84502	-2.39857
4	h	-1.49882	1.62275	0.58950
5	h	-0.23594	2.51846	-0.99349
6	h	1.13987	3.73520	-2.89249
7	h	-0.33066	4.52954	-2.21282
8	h	1.13378	6.20070	-3.41611
9	h	1.03942	6.58900	-1.65756
10	h	2.51011	5.79240	-2.32696
11	h	-3.00456	-4.91223	-0.89040
12	h	-2.88272	-6.34321	1.19065
13	h	-1.83594	-5.38893	3.27737
14	h	-0.96511	-3.02067	3.26255

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18 2NH-EEZZ

19 E(B3LYP/def2-TZVP)=-1025.112080149

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21 32

22				
23	c	-3.11615	-3.08811	1.17656
24	c	-1.85887	-2.46460	1.12131
25	c	-0.69949	-3.27075	1.01572
26	c	-0.79204	-4.67148	1.01497
27	c	-2.05095	-5.28057	1.06174
28	c	-3.20971	-4.48666	1.13654
29	o	-1.72550	-1.10817	1.23437
30	c	-2.14205	-0.29842	0.15095
31	o	-3.01400	-0.60099	-0.62029
32	n	0.64662	-2.66997	0.90170
33	o	0.74351	-1.56048	0.36749
34	n	-1.34786	0.82511	0.19719
35	c	-1.46188	1.98040	-0.63734
36	o	-2.51463	2.29453	-1.16544
37	c	-0.20614	2.73941	-0.78659
38	c	1.03867	2.20853	-0.63359
39	o	2.15206	2.92814	-0.82926
40	c	3.40133	2.21323	-0.80639
41	c	4.53164	3.22466	-0.80509
42	h	-0.31749	3.77196	-1.15366
43	o	1.59438	-3.32999	1.32404
44	h	-0.54054	0.74936	0.82120
45	h	1.19695	1.14366	-0.36151
46	h	3.43767	1.56419	0.10035
47	h	3.45546	1.55193	-1.70282
48	h	5.51038	2.69878	-0.80081
49	h	4.48443	3.86944	-1.70863
50	h	4.47845	3.87695	0.09284
51	h	0.13748	-5.25713	0.96663
52	h	-2.12903	-6.37901	1.04104
53	h	-4.20266	-4.96343	1.17261
54	h	-4.01146	-2.45534	1.25684

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56
57 2NH-EZEE

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3 E(B3LYP/def2-TZVP)=-1025.117619883
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7 c -1.38607 -3.55984 1.31552
8 c -2.17226 -4.63414 1.76294
9 c -3.51728 -4.43664 2.09144
10 c -4.07571 -3.15125 1.98450
11 c -3.28594 -2.07220 1.56676
12 c -1.93623 -2.25883 1.22586
13 o -1.25122 -1.15208 0.78718
14 c -0.08146 -0.79966 1.44777
15 o 0.24917 -1.26219 2.51723
16 n -0.00036 -3.86897 0.89723
17 o 0.54762 -3.09191 0.11131
18 n 0.59211 0.20214 0.78106
19 c 0.48980 0.82193 -0.50215
20 o 1.08379 1.88845 -0.64830
21 c -0.24876 0.12310 -1.55839
22 c -0.39332 0.75253 -2.75595
23 o -1.01134 0.18795 -3.79867
24 c -1.09959 0.97319 -5.00160
25 c -1.77007 0.13280 -6.07171
26 h -0.63554 -0.89268 -1.40521
27 o 0.50167 -4.90386 1.32718
28 h 1.31771 0.64268 1.35727
29 h 0.01502 1.77376 -2.89491
30 h -1.68545 1.89872 -4.79001
31 h -0.07399 1.27934 -5.31441
32 h -1.85606 0.71612 -7.01339
33 h -1.17993 -0.78538 -6.27971
34 h -2.78964 -0.17247 -5.75292
35 h -1.69415 -5.62174 1.83472
36 h -4.13001 -5.28658 2.43047
37 h -5.13399 -2.98205 2.24117
38 h -3.69406 -1.05215 1.49977

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40
41 2NH-EZEZ

42 E(B3LYP/def2-TZVP)=-1025.122726203
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45
46 c -1.35059 -3.18314 0.17717
47 c -1.40133 -4.56878 -0.04686
48 c -1.98954 -5.41770 0.89618
49 c -2.54371 -4.87380 2.06786
50 c -2.52125 -3.48949 2.28030
51 c -1.92535 -2.62555 1.34540
52 o -1.92056 -1.28955 1.65814
53 c -2.43640 -0.38049 0.72715
54 o -3.06756 -0.71139 -0.25100
55 n -0.61569 -2.37029 -0.81956
56 o -0.16740 -1.28289 -0.45187
57 n -2.13595 0.88143 1.18194
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3 c -2.44394 2.16649 0.64318
4 o -2.02808 3.14079 1.26713
5 c -3.22262 2.21661 -0.59608
6 c -3.51209 3.44102 -1.11540
7 o -4.21526 3.59923 -2.24058
8 c -4.42051 4.94974 -2.69438
9 c -5.28682 4.90730 -3.93900
10 h -3.54922 1.28935 -1.08755
11 o -0.46168 -2.85430 -1.93815
12 h -1.56295 0.94067 2.03039
13 h -3.16067 4.35729 -0.59953
14 h -4.90908 5.53783 -1.88237
15 h -3.43003 5.41540 -2.90872
16 h -5.46042 5.93819 -4.31531
17 h -4.79456 4.31817 -4.74210
18 h -6.27185 4.44249 -3.71902
19 h -0.95669 -4.95137 -0.97684
20 h -2.01325 -6.50416 0.71747
21 h -3.01033 -5.53125 2.81907
22 h -2.97154 -3.03835 3.17765
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24
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26 2NH-EZZE

27 E(B3LYP/def2-TZVP)=-1025.116667362

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29 32
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31 c -1.95589 -3.99889 0.12443
32 c -2.62423 -5.16419 0.53547
33 c -2.87697 -5.39571 1.89131
34 c -2.46732 -4.44664 2.84407
35 c -1.82708 -3.26984 2.43573
36 c -1.56283 -3.02720 1.07684
37 o -0.89472 -1.86463 0.78717
38 c -1.42283 -1.01399 -0.15156
39 o -2.52833 -1.12228 -0.63841
40 n -1.63477 -3.88587 -1.31647
41 o -0.68883 -3.16465 -1.63696
42 n -0.55427 0.02387 -0.45128
43 c 0.74744 0.33277 0.03327
44 o 1.30000 -0.30221 0.92045
45 c 1.33352 1.50292 -0.65305
46 c 2.57586 1.91420 -0.28475
47 o 3.19540 2.95818 -0.84375
48 c 4.52186 3.25583 -0.36668
49 c 5.01982 4.49532 -1.08534
50 h 0.79356 2.03526 -1.45364
51 o -2.30586 -4.55654 -2.09783
52 h -0.94839 0.64305 -1.16503
53 h 3.11106 1.36576 0.51622
54 h 4.48480 3.41623 0.73629
55 h 5.18385 2.38097 -0.56616
56 h 6.04523 4.74708 -0.73953
57 h 5.05079 4.32948 -2.18348
58 h 4.35727 5.36349 -0.88136
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3 h -2.92710 -5.87866 -0.24334
4 h -3.39063 -6.31820 2.20449
5 h -2.65679 -4.61776 3.91613
6 h -1.51479 -2.50139 3.15902
7
8
9

10 2NH-EZZZ
11 E(B3LYP/def2-TZVP)=-1025.116606729
12

13 32
14

15 c -3.51715 -4.45306 1.54546
16 c -3.11932 -3.11399 1.42605
17 c -1.80219 -2.80127 1.04624
18 c -0.89680 -3.85751 0.79107
19 c -1.28715 -5.19626 0.94817
20 c -2.60458 -5.49670 1.31104
21 o -1.34836 -1.50970 0.99279
22 c -1.99706 -0.58192 0.15766
23 n -1.14945 0.50612 0.07277
24 c -1.43325 1.74241 -0.57139
25 c -0.27181 2.65381 -0.57963
26 h 0.69297 2.36515 -0.13040
27 n 0.48980 -3.59448 0.34298
28 o 1.34166 -4.42705 0.65540
29 o -3.07541 -0.75279 -0.34795
30 o 0.69766 -2.58537 -0.33043
31 o -2.52851 1.99450 -1.05091
32 c -0.41135 3.87025 -1.17096
33 o 0.57439 4.76968 -1.23585
34 c 0.28300 6.00008 -1.92684
35 c 1.50924 6.88969 -1.85498
36 h -0.21633 0.36365 0.47011
37 h -1.38650 4.14035 -1.62456
38 h 0.01550 5.76747 -2.98405
39 h -0.59810 6.48673 -1.44725
40 h 1.31447 7.84620 -2.38574
41 h 1.76941 7.12044 -0.79977
42 h 2.38353 6.39641 -2.33092
43 h -0.53731 -5.98072 0.77021
44 h -2.91925 -6.54706 1.41490
45 h -4.55520 -4.68245 1.83604
46 h -3.82175 -2.29381 1.62842
47
48

49 2NH-ZEEE
50 E(B3LYP/def2-TZVP)=-1025.105315786
51

52 32
53

54 c -1.43228 -5.17152 0.55322
55 c -2.07874 -5.88525 1.56884
56 c -2.48239 -5.21215 2.73362
57 c -2.26316 -3.83493 2.88952
58
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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
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3 o -0.71413 -3.51919 -1.87272
4 h -0.32845 0.52075 1.75116
5 h -4.65585 2.26036 -0.46159
6 h -6.21816 1.20351 0.84713
7 h -5.41895 -0.31173 0.26457
8 h -6.72550 -0.72566 2.39263
9 h -4.96420 -1.01036 2.63871
10 h -5.72539 0.50725 3.24895
11 h -1.38522 -5.45704 -0.69189
12 h -2.40402 -6.71207 1.25307
13 h -2.86652 -5.47832 3.40300
14 h -2.33939 -3.01957 3.56612
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18 2NH-ZEZE
19 E(B3LYP/def2-TZVP)=-1025.115476938
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21 32
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23 c -2.71638 -5.30919 1.63771
24 c -2.47584 -4.48377 2.75006
25 c -1.93464 -3.20445 2.57344
26 c -1.60199 -2.73169 1.29185
27 c -1.82382 -3.57849 0.17825
28 c -2.39440 -4.84984 0.35679
29 o -1.04037 -1.48293 1.23375
30 c -1.57198 -0.55253 0.37187
31 o -2.62187 -0.68781 -0.22184
32 n -1.41484 -3.21797 -1.19748
33 o -0.52003 -2.38136 -1.32844
34 n -0.78897 0.58444 0.28950
35 c 0.43717 0.91863 0.91746
36 o 0.97583 0.23050 1.77085
37 c 1.03228 2.19865 0.45494
38 c 0.59718 3.07065 -0.49294
39 o -0.55737 2.92549 -1.17977
40 c -0.78265 3.79834 -2.30411
41 c -2.20008 3.58781 -2.80051
42 h 1.97451 2.44498 0.96685
43 o -1.96457 -3.81163 -2.12315
44 h -1.16042 1.26699 -0.38421
45 h 1.18437 3.97777 -0.73833
46 h -0.61779 4.85218 -1.97776
47 h -0.03698 3.55889 -3.09721
48 h -2.39175 4.24258 -3.67737
49 h -2.35886 2.53321 -3.11260
50 h -2.93990 3.83508 -2.00946
51 h -2.56510 -5.46196 -0.54049
52 h -3.15123 -6.31271 1.76765
53 h -2.72114 -4.83426 3.76564
54 h -1.75450 -2.53057 3.42470
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58 2NH-ZEZZ
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3 E(B3LYP/def2-TZVP)=-1025.115067365
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7 c -3.58463 -4.36653 1.53588
8 c -3.25424 -3.01155 1.38680
9 c -1.92804 -2.63914 1.10551
10 c -0.95001 -3.65421 0.97145
11 c -1.27313 -5.00572 1.16464
12 c -2.59900 -5.36466 1.43275
13 o -1.52617 -1.33596 1.03828
14 c -2.10309 -0.46491 0.08227
15 n -1.19225 0.55494 -0.07439
16 c -1.33825 1.69356 -0.90840
17 c -0.09521 2.48397 -1.07985
18 h -0.22105 3.35841 -1.73527
19 n 0.44284 -3.31912 0.61606
20 o 1.33309 -4.02867 1.08187
21 o -3.17182 -0.64697 -0.43962
22 o 0.62235 -2.36552 -0.14719
23 o -2.38966 1.99148 -1.45140
24 c 1.14816 2.25855 -0.57404
25 o 1.44283 1.27037 0.29559
26 c 2.82894 0.93611 0.52262
27 c 3.30779 -0.15408 -0.42321
28 h -0.26820 0.40218 0.35325
29 h 1.99647 2.92139 -0.83966
30 h 3.43569 1.86708 0.43052
31 h 2.87147 0.60015 1.57972
32 h 4.36092 -0.42016 -0.18311
33 h 2.68027 -1.06649 -0.32307
34 h 3.27106 0.18775 -1.48081
35 h -0.47083 -5.75402 1.08583
36 h -2.86403 -6.42563 1.56359
37 h -4.62954 -4.64524 1.74802
38 h -4.01355 -2.22425 1.49019

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41 2NH-ZZEE

42 E(B3LYP/def2-TZVP)=-1025.111662524
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46 c -2.12067 -4.82793 1.53832
47 c -3.46675 -4.73485 1.90682
48 c -4.08927 -3.47515 1.94678
49 c -3.36195 -2.31911 1.63473
50 c -2.01180 -2.39937 1.25449
51 c -1.39812 -3.67367 1.19507
52 o -1.38857 -1.22038 0.93026
53 c -0.22190 -0.88594 1.61125
54 n 0.38691 0.21448 1.05100
55 c 0.20315 0.98183 -0.15004
56 c -0.46106 0.31660 -1.27484
57 h -0.65268 -0.76276 -1.21699
58
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2
3 n -0.00881 -3.86545 0.72426
4 o 0.56219 -4.90046 1.05562
5 o 0.14931 -1.45346 2.61526
6 o 0.47433 -2.99621 -0.00654
7 o 0.68257 2.10920 -0.16345
8 c -0.80992 0.94373 -2.43517
9 o -0.66999 2.24932 -2.67304
10 c -1.04299 2.71875 -3.97936
11 c -0.93337 4.23172 -3.98815
12 h 1.09024 0.63670 1.66726
13 h -1.25969 0.34817 -3.25684
14 h -0.36292 2.26278 -4.73707
15 h -2.08418 2.38782 -4.20773
16 h -1.20215 4.62670 -4.99141
17 h -1.61652 4.68049 -3.23589
18 h 0.10335 4.54952 -3.74756
19 h -1.59357 -5.79211 1.49809
20 h -4.02976 -5.64600 2.16293
21 h -5.14874 -3.38831 2.23714
22 h -3.82001 -1.31954 1.68524
23
24
25

26 2NH-ZZEZ

27 E(B3LYP/def2-TZVP)=-1025.117170896

28
29 32
30

31 c -1.72098 -4.90195 0.17263
32 c -2.41986 -5.55169 1.19506
33 c -2.87452 -4.81305 2.30112
34 c -2.64412 -3.43304 2.36881
35 c -1.93576 -2.76856 1.35282
36 c -1.46171 -3.52387 0.25271
37 o -1.73282 -1.42285 1.52369
38 c -2.11399 -0.55069 0.49626
39 n -1.64690 0.69714 0.82544
40 c -1.77434 1.96359 0.16173
41 c -2.52678 1.97976 -1.09343
42 h -2.94474 1.03493 -1.46778
43 n -0.62274 -2.93701 -0.81706
44 o -0.56674 -3.54183 -1.88528
45 o -2.77948 -0.89445 -0.45589
46 o 0.00030 -1.90732 -0.55374
47 o -1.23857 2.92247 0.70480
48 c -2.73630 3.10086 -1.84320
49 o -2.30932 4.32524 -1.53106
50 c -2.56999 5.37014 -2.48383
51 c -2.11991 6.68631 -1.87838
52 h -1.07990 0.76476 1.67744
53 h -3.30796 3.01636 -2.79084
54 h -2.01393 5.15023 -3.42586
55 h -3.65985 5.38732 -2.72299
56 h -2.29799 7.51563 -2.59610
57 h -2.67900 6.90065 -0.94256
58 h -1.03670 6.65451 -1.63489
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3 h -1.34804 -5.44047 -0.71062
4 h -2.60771 -6.63488 1.12934
5 h -3.42623 -5.31207 3.11414
6 h -3.01396 -2.82952 3.21182
7
8
9

10 2NH-ZZZE
11 E(B3LYP/def2-TZVP)=-1025.110324335
12

13 32
14

15 c -2.71091 -5.18300 0.50399
16 c -2.97961 -5.42361 1.85515
17 c -2.56016 -4.49221 2.82107
18 c -1.89442 -3.32369 2.43031
19 c -1.61472 -3.07134 1.07604
20 c -2.01775 -4.02608 0.11058
21 o -0.92435 -1.91822 0.80452
22 c -1.42878 -1.04783 -0.13053
23 n -0.54265 -0.02051 -0.40712
24 c 0.75984 0.27002 0.10950
25 c 1.35843 1.43903 -0.56736
26 h 0.80683 1.94152 -1.37834
27 n -1.68204 -3.90480 -1.32615
28 o -2.36079 -4.55271 -2.12035
29 o -2.53055 -1.13651 -0.63117
30 o -0.71797 -3.20134 -1.63107
31 o 1.28084 -0.37806 1.00105
32 c 2.58361 1.96224 -0.27362
33 o 3.40592 1.49337 0.66463
34 c 4.65232 2.18698 0.84791
35 c 5.44218 1.46279 1.92145
36 h -0.92228 0.61124 -1.11732
37 h 2.94910 2.84201 -0.84378
38 h 5.20810 2.20382 -0.11936
39 h 4.44286 3.24200 1.14497
40 h 6.41197 1.97771 2.09221
41 h 4.87752 1.44359 2.87779
42 h 5.64599 0.41380 1.61835
43 h -3.01998 -5.88392 -0.28464
44 h -3.51341 -6.33927 2.15440
45 h -2.76218 -4.67057 3.88967
46 h -1.57252 -2.56924 3.16405
47
48

49 2NH-ZZZZ
50 E(B3LYP/def2-TZVP)=-1025.110214269
51

52 32
53

54 c -2.70285 -5.32137 1.35821
55 c -3.55058 -4.25434 1.70431
56 c -3.11857 -2.92596 1.58356
57 c -1.83183 -2.64615 1.08852
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1				
2				
3	c	-0.99290	-3.72576	0.72240
4	c	-1.41504	-5.05470	0.88089
5	o	-1.33018	-1.37496	1.02465
6	c	-2.04211	-0.36346	0.34987
7	o	-3.19898	-0.43848	0.02638
8	n	0.35498	-3.49819	0.15300
9	o	0.53916	-2.47739	-0.50969
10	n	-1.14317	0.66791	0.17035
11	c	-1.44319	1.96645	-0.34982
12	o	-2.58220	2.31776	-0.60105
13	c	-0.22287	2.77850	-0.52237
14	c	-0.20618	4.06039	-0.98977
15	o	-1.28856	4.75388	-1.33977
16	c	-1.08009	6.08513	-1.84383
17	c	-2.43606	6.68828	-2.15693
18	h	0.75955	2.34425	-0.27563
19	o	1.19976	-4.37019	0.36006
20	h	-0.17072	0.43645	0.39324
21	h	0.76456	4.58820	-1.09552
22	h	-0.53802	6.68640	-1.07593
23	h	-0.44170	6.03368	-2.75737
24	h	-2.31143	7.71942	-2.55187
25	h	-2.96956	6.07913	-2.91713
26	h	-3.06657	6.73162	-1.24358
27	h	-0.71351	-5.85812	0.61314
28	h	-3.04431	-6.36308	1.46475
29	h	-4.56447	-4.45697	2.08599
30	h	-3.76937	-2.08979	1.87201
31				
32				
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34	3OH-EEZE			
35	E(B3LYP/def2-TZVP)=-1025.102531907			
36				
37	32			
38				
39	c	0.36724	2.63078	3.32665
40	c	0.12467	1.92554	2.14191
41	c	-0.01561	0.52476	2.14592
42	c	0.08900	-0.15140	3.38933
43	c	0.30169	0.56050	4.58349
44	c	0.44986	1.94957	4.55523
45	o	-0.22000	-0.10065	0.95681
46	n	0.02546	-1.61731	3.49557
47	o	-0.26477	-2.10065	4.58284
48	o	0.30950	-2.30353	2.49823
49	c	-1.44820	-0.87859	0.78363
50	n	-1.41905	-1.54987	-0.38851
51	c	-0.36406	-2.15753	-0.88124
52	c	-0.35709	-2.66986	-2.24218
53	c	-1.45142	-2.54997	-3.04362
54	o	-1.47303	-3.00051	-4.30085
55	c	-2.71512	-2.86424	-5.01816
56	c	-2.51111	-3.38562	-6.42791
57	o	-2.33739	-0.78224	1.59667
58	o	0.76860	-2.41830	-0.22043
59				
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3	h	0.55626	-3.16920	-2.59799
4	h	-2.36900	-2.06585	-2.65374
5	h	-3.50634	-3.44165	-4.48561
6	h	-3.01619	-1.79049	-5.02378
7	h	-3.45596	-3.29501	-7.00520
8	h	-1.72133	-2.80709	-6.95329
9	h	-2.21005	-4.45499	-6.41359
10	h	0.35692	-0.00951	5.52208
11	h	0.63061	2.50136	5.49091
12	h	0.48018	3.72657	3.29316
13	h	0.02929	2.44072	1.17389
14	h	0.70507	-2.08908	0.72286
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58				
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60				

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

32

23	c	-0.91007	1.18974	-4.65526
24	c	-0.68912	1.38881	-3.28935
25	c	-0.33850	0.31016	-2.44807
26	c	-0.20271	-0.97864	-3.03504
27	c	-0.43244	-1.16913	-4.41152
28	c	-0.78514	-0.09159	-5.22416
29	o	-0.17935	0.48464	-1.11052
30	n	0.19037	-2.17638	-2.26436
31	o	0.42622	-3.20344	-2.89688
32	o	0.26919	-2.10965	-1.02998
33	c	0.60452	1.60757	-0.57223
34	n	0.52606	1.65593	0.77505
35	c	0.24104	0.65824	1.58742
36	c	0.10082	0.95545	3.00210
37	h	0.25058	2.00145	3.30541
38	o	1.18297	2.35428	-1.32518
39	o	0.10142	-0.63082	1.26662
40	c	-0.19542	-0.00724	3.92047
41	o	-0.31694	0.26552	5.22316
42	c	-0.65951	-0.83286	6.08905
43	c	-0.67452	-0.32660	7.51882
44	h	-0.34283	-1.05954	3.60887
45	h	-1.65798	-1.23088	5.79194
46	h	0.08986	-1.64818	5.95740
47	h	-0.94059	-1.15424	8.21062
48	h	0.32293	0.06714	7.80919
49	h	-1.42088	0.48715	7.64186
50	h	-0.31899	-2.18611	-4.81194
51	h	-0.96512	-0.24870	-6.29922
52	h	-1.18981	2.04974	-5.28526
53	h	-0.78750	2.38877	-2.84662
54	h	0.09395	-0.77999	0.27196

Transition State for EEZE isomer

1
2
3 E(B3LYP/def2-TZVP)=-1025.088955179
4
5

6 32

7 c 0.38521 1.75400 3.44851
8 c 0.32842 0.72085 2.47614
9 c -0.00937 -0.58626 2.95115
10 c -0.24257 -0.82838 4.31938
11 c -0.17032 0.21090 5.24699
12 c 0.14430 1.51106 4.80152
13 o 0.59367 1.04594 1.21011
14 n -0.13404 -1.74082 2.04885
15 o -0.13251 -1.53510 0.82686
16 o -0.24200 -2.86041 2.55070
17 c -0.92205 0.98341 -0.00248
18 o -1.89049 1.23919 0.62349
19 n -0.44230 0.75907 -1.17572
20 c 0.78601 0.30053 -1.51197
21 o 1.73837 0.09208 -0.66421
22 c 1.06386 0.02557 -2.90379
23 c 0.10733 0.18407 -3.86546
24 o 0.33711 -0.08609 -5.14644
25 c -0.72434 0.19014 -6.08659
26 c -0.40301 -0.51020 -7.39225
27 h 2.07302 -0.33149 -3.15691
28 h -0.90482 0.54084 -3.58787
29 h -1.68957 -0.16660 -5.65962
30 h -0.79159 1.29400 -6.22484
31 h -1.19503 -0.29216 -8.14034
32 h 0.56874 -0.15927 -7.80016
33 h -0.34731 -1.61054 -7.24972
34 h -0.48505 -1.85774 4.61929
35 h -0.36227 0.01314 6.31339
36 h 0.19983 2.34360 5.52245
37 h 0.63469 2.76096 3.07991
38 h 1.34357 0.38676 0.33426

39
40
41 Transition State for EZZE isomer

42 E(B3LYP/def2-TZVP)=-1025.088679583
43

44 32

45
46 c -2.85546 -2.39361 1.40905
47 c -2.46863 -2.86977 0.15465
48 c -1.87536 -4.14756 -0.01231
49 c -1.70592 -4.93471 1.16918
50 c -2.08198 -4.44481 2.43475
51 c -2.66111 -3.18149 2.56168
52 o -1.51555 -4.51543 -1.24471
53 n -1.13524 -6.28940 1.12863
54 o -0.75109 -6.78684 2.18810
55 o -1.07787 -6.86901 0.03545
56 c -2.65161 -5.81376 -2.06579
57 n -1.93778 -6.44794 -2.93751
58
59
60

1				
2				
3	c	-0.59582	-6.47822	-3.05223
4	c	-0.05104	-7.35208	-4.06751
5	h	-0.75797	-7.92356	-4.68607
6	o	-3.74131	-5.68103	-1.62925
7	o	0.21640	-5.78352	-2.31364
8	c	1.29824	-7.47767	-4.23517
9	o	1.82737	-8.27708	-5.15751
10	c	3.26823	-8.36906	-5.20306
11	c	3.65385	-9.21519	-6.40049
12	h	1.99748	-6.90538	-3.59364
13	h	3.69343	-7.34150	-5.27716
14	h	3.62570	-8.82599	-4.25152
15	h	4.75945	-9.30980	-6.45357
16	h	3.21862	-10.23406	-6.32093
17	h	3.29487	-8.75313	-7.34486
18	h	-1.90809	-5.09378	3.30489
19	h	-2.96480	-2.81092	3.55337
20	h	-3.31583	-1.39525	1.49370
21	h	-2.60647	-2.26789	-0.75680
22	h	-0.41406	-5.18058	-1.63965
23				
24				

Product Complex EEZE

E(B3LYP/def2-TZVP)=-1025.117420818

32

31	c	0.27589	1.59575	5.12820
32	c	0.83664	1.74549	3.86210
33	c	0.73556	0.72174	2.88443
34	c	0.03141	-0.46492	3.25896
35	c	-0.53303	-0.60853	4.54450
36	c	-0.41496	0.41351	5.48168
37	o	1.30145	0.94782	1.70042
38	n	-0.12915	-1.56407	2.32144
39	o	-0.75141	-2.56460	2.66415
40	o	0.38565	-1.43442	1.18535
41	c	-1.23381	0.50850	-0.43508
42	n	-0.62256	0.37137	-1.48848
43	c	0.74871	0.13945	-1.83246
44	c	0.98630	-0.01151	-3.26334
45	c	-0.00751	0.05188	-4.19338
46	o	0.22610	-0.08908	-5.50049
47	c	-0.91194	-0.00717	-6.38119
48	c	-0.42577	-0.19387	-7.80552
49	o	-1.93498	0.66370	0.49867
50	o	1.62841	0.08242	-0.98262
51	h	2.02982	-0.18594	-3.56562
52	h	-1.05762	0.22497	-3.88403
53	h	-1.64639	-0.79701	-6.09878
54	h	-1.40241	0.98563	-6.24883
55	h	-1.28424	-0.13555	-8.50845
56	h	0.30700	0.59483	-8.07951
57	h	0.06296	-1.18387	-7.92947
58	h	-1.06125	-1.54702	4.76526
59				
60				

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

35

c	-1.55348	-5.59376	0.90097
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1				
2				
3				
4	c	-1.67437	-6.09667	2.19913
5	c	-1.78244	-5.20137	3.27798
6	c	-1.77824	-3.81695	3.06534
7	c	-1.64399	-3.29418	1.76493
8	c	-1.52240	-4.20566	0.68812
9	o	-1.60800	-1.94390	1.51757
10	c	-2.51873	-1.11407	2.17039
11	n	-2.20627	0.21538	1.97690
12	c	-0.93198	0.83529	1.60776
13	c	-0.42562	0.64635	0.25153
14	c	0.98443	1.09877	-0.01927
15	n	-1.34589	-3.74130	-0.69782
16	o	-1.87398	-4.41133	-1.58844
17	o	-3.46555	-1.51551	2.81411
18	o	-0.66428	-2.73250	-0.87801
19	o	-0.40349	1.55810	2.44402
20	c	-1.26672	0.20798	-0.73662
21	o	-0.88661	0.11837	-2.01074
22	c	-1.85987	-0.24559	-3.00764
23	c	-1.29696	-1.33220	-3.90762
24	h	-2.71462	0.79888	2.65213
25	h	1.22570	1.01980	-1.09781
26	h	1.71435	0.48128	0.55104
27	h	1.13033	2.14969	0.31369
28	h	-2.31602	-0.06590	-0.51643
29	h	-2.79437	-0.58452	-2.50349
30	h	-2.09687	0.67798	-3.58448
31	h	-2.01451	-1.54450	-4.73008
32	h	-0.33583	-1.00582	-4.36016
33	h	-1.12473	-2.26313	-3.32866
34	h	-1.47643	-6.25485	0.02542
35	h	-1.68251	-7.18453	2.37026
36	h	-1.87776	-5.58463	4.30662
37	h	-1.88644	-3.12486	3.91103

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

35

45	c	-2.13512	-5.63856	1.47655
46	c	-2.19442	-4.96600	2.70939
47	c	-1.91531	-3.59511	2.77718
48	c	-1.54806	-2.87511	1.62699
49	c	-1.47019	-3.56444	0.39222
50	c	-1.77961	-4.93281	0.32262
51	o	-1.25959	-1.54580	1.79962
52	c	-1.91465	-0.60381	0.99222
53	o	-2.86300	-0.87830	0.29184
54	n	-0.99957	-2.91963	-0.85583
55	o	-0.30548	-1.90721	-0.74963
56	n	-1.31388	0.61119	1.23367
57	c	-1.31667	1.84463	0.48375
58	o	-0.26702	2.48024	0.50655

1
2
3 c -2.51046 2.32307 -0.22515
4 c -3.76165 1.86497 0.07515
5 o -4.85929 2.36860 -0.50988
6 c -6.11012 1.74422 -0.17283
7 c -7.21795 2.45941 -0.92325
8 c -2.27969 3.45142 -1.19812
9 o -1.29549 -3.46400 -1.91675
10 h -0.43652 0.54101 1.76331
11 h -3.21979 3.72233 -1.71868
12 h -1.51521 3.17081 -1.95523
13 h -1.88610 4.35055 -0.67405
14 h -3.93460 1.06479 0.81279
15 h -6.06367 0.66580 -0.45100
16 h -6.26556 1.80877 0.93035
17 h -8.19921 1.99689 -0.68288
18 h -7.25718 3.53359 -0.64167
19 h -7.05777 2.39167 -2.02064
20 h -1.72135 -5.41955 -0.66175
21 h -2.36311 -6.71417 1.41376
22 h -2.47213 -5.50980 3.62669
23 h -1.97905 -3.04193 3.72675
24
25
26

27 2NH-EEZE
28 E(B3LYP/def2-TZVP)=-1064.414898082
29

30 35
31

32 c -2.48502 -5.28064 1.13663
33 c -1.89636 -4.77068 2.30714
34 c -1.39868 -3.46167 2.33218
35 c -1.45855 -2.64713 1.18872
36 c -2.03100 -3.17446 0.00567
37 c -2.55438 -4.47823 -0.00683
38 o -0.90797 -1.39567 1.30415
39 c -1.66892 -0.30517 0.96111
40 o -2.85358 -0.34096 0.70439
41 n -2.05143 -2.43204 -1.27475
42 o -1.22832 -1.52724 -1.42685
43 n -0.91518 0.85697 0.95313
44 c 0.41951 1.10470 1.39585
45 o 1.01249 0.34629 2.14731
46 c 1.01112 2.37259 0.89046
47 c 0.59422 2.91204 -0.29245
48 o 1.12682 4.04116 -0.79456
49 c 0.77292 4.38061 -2.14513
50 c 1.32775 5.75878 -2.45355
51 c 2.16106 2.94034 1.67754
52 o -2.86124 -2.79613 -2.12480
53 h -1.46648 1.66382 0.65025
54 h 2.73203 3.67651 1.07703
55 h 2.83319 2.11692 2.00069
56 h 1.80690 3.44828 2.60419
57 h -0.18083 2.42746 -0.91874
58 h 1.19472 3.61399 -2.83721
59
60

1				
2				
3	h	-0.33831	4.36119	-2.25052
4	h	1.07360	6.04517	-3.49645
5	h	0.90140	6.51977	-1.76526
6	h	2.43364	5.77141	-2.34640
7	h	-3.00596	-4.83755	-0.94264
8	h	-2.88760	-6.30543	1.11263
9	h	-1.83228	-5.39348	3.21390
10	h	-0.94988	-3.02928	3.23924
11				
12				
13				

2NH-EEZZ

E(B3LYP/def2-TZVP)=-1064.414709522

35

19	c	-1.82717	-2.44763	1.10980
20	o	-1.69556	-1.08956	1.21055
21	c	-2.10991	-0.29274	0.11817
22	n	-1.34379	0.85030	0.17591
23	o	-2.95932	-0.61707	-0.66932
24	c	-1.47930	2.00356	-0.65361
25	c	-0.24205	2.81532	-0.79002
26	o	-2.53885	2.28817	-1.18800
27	c	-0.41508	4.24410	-1.22948
28	c	0.98636	2.23792	-0.63199
29	o	2.12868	2.93284	-0.77960
30	c	3.34726	2.17053	-0.80719
31	c	4.51733	3.13532	-0.76989
32	c	-0.66766	-3.25401	1.01255
33	c	-0.75967	-4.65468	1.02467
34	c	-2.01837	-5.26387	1.07623
35	c	-3.17746	-4.46981	1.14308
36	c	-3.08421	-3.07095	1.16996
37	n	0.67827	-2.65345	0.89401
38	o	1.62520	-3.30745	1.32761
39	o	0.77524	-1.55109	0.34598
40	h	-0.54985	0.80232	0.81918
41	h	0.53144	4.65625	-1.63349
42	h	-0.74174	4.89267	-0.38393
43	h	-1.21060	4.30205	-2.00306
44	h	1.11087	1.15911	-0.40992
45	h	3.36717	1.47610	0.06630
46	h	3.36808	1.55089	-1.73456
47	h	5.47473	2.57216	-0.79803
48	h	4.48996	3.82246	-1.64280
49	h	4.49616	3.74748	0.15720
50	h	0.17015	-5.24031	0.98243
51	h	-2.09602	-6.36248	1.06552
52	h	-4.17031	-4.94649	1.18302
53	h	-3.97998	-2.43796	1.24373

2NH-EZEE

E(B3LYP/def2-TZVP)=-1064.411293140

35

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

35

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

1				
2				
3	c	-4.91413	1.45970	-0.32630
4	n	-0.36478	-2.25775	-0.54942
5	o	0.02501	-2.70499	-1.62541
6	o	-3.01717	-0.76631	-0.35448
7	o	-0.07361	-1.14755	-0.09972
8	o	-1.66725	2.96359	0.80373
9	c	-3.52913	3.35514	-1.20708
10	o	-4.50210	3.70834	-2.05885
11	c	-4.24606	4.84940	-2.89606
12	c	-5.46987	5.09253	-3.75953
13	h	-1.66907	0.89860	1.97491
14	h	-5.78424	2.09510	-0.59674
15	h	-5.09029	1.04304	0.68844
16	h	-4.87673	0.60146	-1.03020
17	h	-2.60963	3.97020	-1.19813
18	h	-4.02506	5.73322	-2.25248
19	h	-3.34576	4.64666	-3.52224
20	h	-5.29908	5.96845	-4.42139
21	h	-5.68519	4.20800	-4.39646
22	h	-6.36304	5.29607	-3.13056
23	h	-0.51295	-4.84821	-0.81642
24	h	-1.74886	-6.51087	0.63483
25	h	-3.14705	-5.66246	2.55434
26	h	-3.31783	-3.18423	2.97054
27				
28				
29				

2NH-EZZE

E(B3LYP/def2-TZVP)=-1064.416583725

35

35	c	-2.58855	-5.16397	0.56608
36	c	-2.80557	-5.38741	1.92947
37	c	-2.38371	-4.42615	2.86453
38	c	-1.76695	-3.24564	2.43154
39	c	-1.53894	-3.01080	1.06477
40	c	-1.94401	-3.99441	0.12983
41	o	-0.89143	-1.84314	0.74991
42	c	-1.45296	-1.00569	-0.18060
43	n	-0.60908	0.04296	-0.51129
44	c	0.69285	0.38210	-0.05485
45	c	1.26806	1.56149	-0.76422
46	c	0.55641	2.29793	-1.87209
47	n	-1.66016	-3.88872	-1.31933
48	o	-2.34435	-4.57131	-2.07882
49	o	-2.56838	-1.13305	-0.64027
50	o	-0.72957	-3.16104	-1.66865
51	o	1.26225	-0.23627	0.83464
52	c	2.51081	1.92712	-0.33612
53	o	3.18511	2.96356	-0.85606
54	c	4.49920	3.20826	-0.32465
55	c	5.06645	4.44295	-0.99949
56	h	-1.03324	0.64383	-1.22256
57	h	1.19492	3.11911	-2.25740
58	h	-0.39877	2.76195	-1.52932

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2
3 h 0.31864 1.63268 -2.73461
4 h 2.99651 1.35229 0.47529
5 h 4.42625 3.35032 0.77924
6 h 5.14062 2.31584 -0.51412
7 h 6.08535 4.65403 -0.60961
8 h 5.13564 4.29586 -2.09864
9 h 4.42566 5.32950 -0.80500
10 h -2.90193 -5.88813 -0.19953
11 h -3.30071 -6.31317 2.26227
12 h -2.54529 -4.59068 3.94217
13 h -1.44501 -2.46833 3.14097
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17 2NH-EZZZ

18 E(B3LYP/def2-TZVP)=-1064.416538143
19

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22 c -3.15636 -3.13016 1.39830
23 c -1.83191 -2.79497 1.06640
24 c -0.91002 -3.83483 0.80177
25 c -1.29204 -5.18122 0.90463
26 c -2.61629 -5.50371 1.22133
27 c -3.54484 -4.47587 1.46310
28 o -1.38705 -1.50006 1.06615
29 c -2.00253 -0.55395 0.22328
30 o -3.07857 -0.69894 -0.29446
31 n 0.48551 -3.54448 0.40120
32 o 0.70252 -2.51201 -0.23376
33 n -1.12214 0.50792 0.15098
34 c -1.36131 1.75526 -0.48612
35 o -2.45790 2.04714 -0.94185
36 c -0.15799 2.63227 -0.52462
37 c -0.35989 3.84203 -1.12250
38 o 0.60733 4.76196 -1.24943
39 c 0.25983 5.97218 -1.94480
40 c 1.46887 6.88843 -1.94384
41 c 1.18238 2.22654 0.03617
42 o 1.33698 -4.37878 0.70957
43 h -0.19567 0.32441 0.54583
44 h 1.93026 3.02559 -0.14373
45 h 1.57285 1.29555 -0.43664
46 h 1.14642 2.05510 1.13803
47 h -1.36147 4.08799 -1.52494
48 h -0.05104 5.71789 -2.98529
49 h -0.60887 6.45003 -1.43428
50 h 1.22990 7.83214 -2.47949
51 h 1.77256 7.14185 -0.90549
52 h 2.33092 6.40575 -2.45221
53 h -0.53100 -5.95366 0.72166
54 h -2.92397 -6.55944 1.28297
55 h -4.58842 -4.72355 1.71639
56 h -3.87081 -2.32193 1.60657
57
58

59 2NH-ZEEE
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2
3 E(B3LYP/def2-TZVP)=-1064.405885218
4
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6 35

7 c -2.03893 -5.90231 1.58221
8 c -2.45482 -5.22441 2.74014
9 c -2.25015 -3.84388 2.88550
10 c -1.59976 -3.11709 1.86978
11 c -1.15960 -3.81795 0.72222
12 c -1.39591 -5.19040 0.56311
13 o -1.34959 -1.76787 1.92114
14 c -2.26029 -0.89079 2.48729
15 o -3.26825 -1.21809 3.07830
16 n -0.42419 -3.12040 -0.34621
17 o 0.53323 -2.42676 -0.01807
18 n -1.82741 0.41375 2.36186
19 c -0.78804 1.04709 1.61359
20 o -0.25787 2.03413 2.11403
21 c -0.45086 0.57540 0.25220
22 c -1.33168 -0.03034 -0.59864
23 o -2.58047 -0.41095 -0.27296
24 c -3.37766 -1.00277 -1.31840
25 c -4.75627 -1.29044 -0.75398
26 c 0.91443 0.98084 -0.24589
27 o -0.81795 -3.29925 -1.50523
28 h -2.25053 1.04050 3.05516
29 h 1.07020 0.66600 -1.29901
30 h 1.71293 0.51030 0.37003
31 h 1.05165 2.08155 -0.17100
32 h -1.02251 -0.24844 -1.63988
33 h -3.43308 -0.29360 -2.17737
34 h -2.87527 -1.93500 -1.66749
35 h -5.38806 -1.77397 -1.52975
36 h -4.69130 -1.97113 0.12218
37 h -5.25536 -0.35352 -0.42610
38 h -1.05946 -5.67986 -0.36323
39 h -2.21165 -6.98453 1.47310
40 h -2.95843 -5.77590 3.55050
41 h -2.60564 -3.31635 3.77862

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43
44 2NH-ZEEZ

45 E(B3LYP/def2-TZVP)=-1064.411404609

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47
48
49 c -2.48514 -4.94612 2.51132
50 c -2.20667 -3.57769 2.62077
51 c -1.59824 -2.87708 1.56431
52 c -1.27656 -3.58448 0.38041
53 c -1.58382 -4.94989 0.26243
54 c -2.18080 -5.63592 1.32498
55 o -1.33604 -1.54912 1.77801
56 c -1.81312 -0.61254 0.84660
57 n -1.23321 0.59368 1.16730
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2				
3	c	-1.33085	1.86002	0.52393
4	c	-2.55041	2.23480	-0.22825
5	c	-2.33267	3.26001	-1.31542
6	n	-0.55106	-2.96012	-0.74993
7	o	-0.63139	-3.51246	-1.84450
8	o	-2.61072	-0.88280	-0.01920
9	o	0.12030	-1.95477	-0.51222
10	o	-0.37017	2.61578	0.63292
11	c	-3.81391	1.84768	0.10718
12	o	-4.12630	1.09213	1.17314
13	c	-5.38833	0.40926	1.12060
14	c	-5.64045	-0.23790	2.46967
15	h	-0.40933	0.53763	1.77697
16	h	-3.28575	3.51549	-1.82549
17	h	-1.61589	2.88796	-2.08105
18	h	-1.89399	4.19182	-0.89555
19	h	-4.67749	2.20665	-0.49127
20	h	-6.19072	1.14461	0.86856
21	h	-5.34650	-0.35585	0.31222
22	h	-6.62146	-0.75987	2.46298
23	h	-4.85045	-0.98528	2.69924
24	h	-5.65144	0.52286	3.27996
25	h	-1.33000	-5.45024	-0.68342
26	h	-2.40577	-6.70965	1.22787
27	h	-2.95416	-5.47475	3.35690
28	h	-2.45568	-3.01107	3.53140
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32	2NH-ZEZE			
33	E(B3LYP/def2-TZVP)=-1064.416351357			
34				
35	35			
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37	c	-2.50797	-4.46180	2.71627
38	c	-1.96419	-3.18148	2.55572
39	c	-1.60569	-2.70310	1.28316
40	c	-1.80469	-3.54560	0.16186
41	c	-2.37727	-4.81835	0.32386
42	c	-2.72484	-5.28320	1.59606
43	o	-1.04311	-1.45439	1.24159
44	c	-1.55874	-0.51996	0.37384
45	n	-0.77317	0.61545	0.30310
46	c	0.45494	0.93568	0.92456
47	c	1.08486	2.21883	0.47389
48	c	2.38698	2.53776	1.16448
49	n	-1.36975	-3.17877	-1.20415
50	o	-1.89805	-3.77194	-2.14266
51	o	-2.60160	-0.65094	-0.23367
52	o	-0.47650	-2.33755	-1.31478
53	o	0.98804	0.23346	1.77198
54	c	0.60081	3.07084	-0.47445
55	o	-0.58317	2.91884	-1.11795
56	c	-0.79741	3.69727	-2.30946
57	c	-2.24319	3.53293	-2.73811
58	h	-1.13894	1.30568	-0.36729
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3	h	2.83266	3.47962	0.77993
4	h	3.11895	1.71221	1.02585
5	h	2.24021	2.63822	2.26273
6	h	1.16973	3.98033	-0.75415
7	h	-0.55654	4.76399	-2.08779
8	h	-0.09778	3.34229	-3.10173
9	h	-2.42865	4.11389	-3.66685
10	h	-2.47771	2.46596	-2.94241
11	h	-2.93563	3.89915	-1.95021
12	h	-2.52882	-5.42693	-0.57926
13	h	-3.16130	-6.28760	1.71315
14	h	-2.77394	-4.81625	3.72525
15	h	-1.80189	-2.51105	3.41324
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2NH-ZEZZ

E(B3LYP/def2-TZVP)=-1064.414956284

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24	c	-3.21875	-3.07221	0.94924
25	c	-1.85405	-2.74149	0.81641
26	c	-0.88974	-3.76149	1.03728
27	c	-1.27150	-5.05898	1.40801
28	c	-2.62856	-5.37972	1.51684
29	c	-3.59100	-4.38275	1.28318
30	o	-1.36417	-1.49577	0.56143
31	c	-2.10655	-0.41500	0.05389
32	o	-3.30036	-0.39838	-0.11160
33	n	0.55543	-3.49574	0.88863
34	o	0.90701	-2.71796	-0.00126
35	n	-1.17112	0.57054	-0.18653
36	c	-1.44407	1.89911	-0.59017
37	o	-2.57900	2.31708	-0.76509
38	c	-0.24586	2.77380	-0.76819
39	c	1.05774	2.40735	-0.59457
40	o	1.48096	1.15760	-0.29728
41	c	2.84486	0.97425	0.13913
42	c	3.36885	-0.35566	-0.36981
43	c	-0.57394	4.18993	-1.17171
44	o	1.31784	-4.09316	1.64817
45	h	-0.18202	0.30834	-0.06198
46	h	0.34288	4.80971	-1.26810
47	h	-1.25085	4.66680	-0.42919
48	h	-1.11812	4.21006	-2.14178
49	h	1.86755	3.15340	-0.72549
50	h	3.45437	1.82649	-0.24215
51	h	2.85522	1.01807	1.25287
52	h	4.40173	-0.51428	0.01030
53	h	2.73580	-1.20399	-0.03021
54	h	3.39997	-0.36860	-1.48051
55	h	-0.48070	-5.79959	1.59764
56	h	-2.93374	-6.40259	1.78740
57	h	-4.66335	-4.62165	1.37232
58	h	-3.97073	-2.29090	0.78668

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5 2NH-ZZEE
6 E(B3LYP/def2-TZVP)=-1064.405006331
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10 c -3.83472 -3.96928 1.60046
11 c -4.14030 -2.71986 1.03383
12 c -3.11129 -1.84493 0.66248
13 c -1.76355 -2.20778 0.82438
14 c -1.46284 -3.47610 1.37547
15 c -2.49712 -4.33783 1.77671
16 o -0.83200 -1.29234 0.39751
17 c 0.15098 -0.88158 1.27979
18 o 0.19069 -1.19824 2.44804
19 n -0.08066 -3.98617 1.50901
20 o 0.77335 -3.53966 0.73919
21 n 1.03890 -0.01292 0.67169
22 c 1.06600 0.64092 -0.59975
23 o 1.62925 1.72347 -0.65711
24 c 0.50947 -0.07992 -1.78436
25 c -0.32839 0.57824 -2.62837
26 o -0.85368 1.79148 -2.36201
27 c -1.39601 2.51294 -3.47149
28 c -2.13506 3.72777 -2.93948
29 c 1.00078 -1.47468 -2.09224
30 o 0.11915 -4.85730 2.35017
31 h 1.64740 0.45400 1.35461
32 h 0.56438 -1.83812 -3.04782
33 h 0.74152 -2.20613 -1.29649
34 h 2.10979 -1.49013 -2.20202
35 h -0.67193 0.09766 -3.56880
36 h -0.56717 2.82003 -4.15301
37 h -2.08143 1.84610 -4.05107
38 h -2.55478 4.31947 -3.78130
39 h -2.96910 3.42235 -2.27153
40 h -1.44650 4.37904 -2.35989
41 h -2.21408 -5.30273 2.22167
42 h -4.63814 -4.65760 1.90625
43 h -5.18979 -2.41562 0.89153
44 h -3.32403 -0.85007 0.24233

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46
47 2NH-ZZEE
48 E(B3LYP/def2-TZVP)=-1064.407877132
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51

52 c -1.82292 -5.37644 0.61384
53 c -2.52263 -4.97190 1.76396
54 c -2.61366 -3.61294 2.09076
55 c -1.98986 -2.63562 1.29582
56 c -1.26960 -3.05314 0.14996
57 c -1.20528 -4.41412 -0.19152
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1				
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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

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35				
36				
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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				
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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
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22 2NH-ZZZZ
23 E(B3LYP/def2-TZVP)=-1064.407425375
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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
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3 h -3.09986 -6.32692 1.39027
4 h -4.61543 -4.41694 2.00949
5 h -3.79379 -2.05321 1.85037
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7
8

9 3OH-EEEE
10 E(B3LYP/def2-TZVP)=-1064.385454852
11

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13

14 c -1.94905 -5.28329 1.24726
15 c -2.11043 -5.82504 2.53519
16 c -1.74198 -5.09025 3.66497
17 c -1.20940 -3.79798 3.50696
18 c -1.06724 -3.24508 2.22906
19 c -1.43837 -3.96918 1.08221
20 o -1.20973 -3.34602 -0.11898
21 c -2.17976 -3.21276 -1.07179
22 o -3.41830 -3.35739 -0.55508
23 n -2.27480 -6.16397 0.10840
24 o -1.87097 -5.82468 -1.01005
25 n -1.95491 -2.93083 -2.28564
26 c -0.64990 -2.69181 -2.80799
27 o -0.01921 -1.68418 -2.50181
28 c -0.14393 -3.68733 -3.77425
29 c -0.90157 -4.78371 -4.06915
30 o -0.49494 -5.74939 -4.91257
31 c -1.36306 -6.88536 -5.05721
32 c -1.22406 -7.87714 -3.90880
33 c 1.22017 -3.44062 -4.35773
34 o -2.89688 -7.19823 0.33870
35 h 1.50424 -4.24590 -5.06517
36 h 1.99010 -3.37721 -3.55637
37 h 1.24943 -2.46393 -4.89003
38 h -1.90426 -4.91083 -3.62094
39 h -2.41672 -6.53232 -5.15804
40 h -1.06549 -7.34602 -6.02274
41 h -1.85369 -8.77309 -4.10580
42 h -0.16826 -8.20989 -3.80800
43 h -1.54790 -7.43206 -2.94235
44 h -2.52153 -6.84176 2.61065
45 h -1.86391 -5.52744 4.66829
46 h -0.90977 -3.20904 4.38882
47 h -0.66820 -2.23036 2.07931
48 h -4.03972 -3.23035 -1.30944
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51 3OH-EEZE
52 E(B3LYP/def2-TZVP)=-1064.403330874
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56 c -1.76843 -4.60902 1.68783
57 c -2.38398 -3.84963 2.68604
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3 c -3.03136 -2.64792 2.34301
4 c -3.07176 -2.22224 1.01024
5 c -2.44790 -2.96558 -0.01017
6 c -1.78168 -4.16522 0.35312
7 o -2.50023 -2.48003 -1.27711
8 c -3.13916 -3.29999 -2.31118
9 n -2.96643 -2.74115 -3.52700
10 c -1.86107 -2.16819 -3.94626
11 c -1.82511 -1.37886 -5.17930
12 c -0.53665 -0.73717 -5.62062
13 n -1.04079 -4.98032 -0.62153
14 o -0.82505 -6.15287 -0.34186
15 o -3.78472 -4.27000 -1.98870
16 o -0.62660 -4.44159 -1.66370
17 o -0.66648 -2.26643 -3.35223
18 c -2.99027 -1.27180 -5.88679
19 o -3.07995 -0.55879 -7.01761
20 c -4.34197 -0.59688 -7.70745
21 c -4.26427 0.34035 -8.89803
22 h -0.67995 -0.19325 -6.57589
23 h 0.26291 -1.49794 -5.76019
24 h -0.15951 -0.02015 -4.85778
25 h -3.90241 -1.78740 -5.53084
26 h -4.54723 -1.64394 -8.03170
27 h -5.15171 -0.29049 -7.00448
28 h -5.22714 0.32913 -9.45227
29 h -4.06029 1.38187 -8.56877
30 h -3.45578 0.02912 -9.59364
31 h -1.25432 -5.55439 1.91313
32 h -2.35877 -4.19395 3.73178
33 h -3.52221 -2.04224 3.12205
34 h -3.59583 -1.30040 0.71531
35 h -0.72800 -2.84807 -2.53859

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39 3OH-EZZE
40 E(B3LYP/def2-TZVP)=-1064.404100222

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43 c -2.85624 -2.70420 2.46798
44 c -2.89226 -2.20614 1.16042
45 c -2.40996 -2.96726 0.07850
46 c -1.89060 -4.25932 0.35236
47 c -1.88550 -4.77235 1.66215
48 c -2.35840 -3.99554 2.72271
49 o -2.45047 -2.40831 -1.15902
50 n -1.29413 -5.10876 -0.69008
51 o -1.23242 -6.31348 -0.48086
52 o -0.83586 -4.57172 -1.71435
53 c -3.18912 -3.09786 -2.21196
54 n -3.01116 -2.46497 -3.39440
55 c -1.85904 -2.03905 -3.85030
56 c -1.83710 -1.18683 -5.03832
57 c -3.14628 -0.76898 -5.65091
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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
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26 3OH-ZEZZ

27 E(B3LYP/def2-TZVP)=-1064.398680790

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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
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3 h 3.23921 -6.89625 1.53575
4 h 4.31864 -7.20043 0.13256
5 h -3.24435 -6.15811 1.86860
6 h -4.84073 -4.28341 1.27323
7 h -3.90023 -2.06286 0.55300
8 h -1.42439 -1.71592 0.42298
9 h 2.10132 -0.87060 -0.23936
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13 3OH-ZZZZ
14 E(B3LYP/def2-TZVP)=-1064.404075145
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17
18 c -3.51965 -4.07017 1.67051
19 c -2.59291 -3.50076 2.56096
20 c -1.25289 -3.35146 2.18161
21 c -0.80439 -3.78320 0.92046
22 c -1.74056 -4.37671 0.03816
23 c -3.08919 -4.49995 0.41096
24 o 0.53326 -3.62430 0.66580
25 c 0.94371 -2.98151 -0.48163
26 o 0.10902 -2.42249 -1.22100
27 n -1.35459 -4.95285 -1.26948
28 o -0.18523 -5.31055 -1.41336
29 n 2.29058 -3.02833 -0.60809
30 c 2.81727 -2.44433 -1.68717
31 o 2.10552 -1.82609 -2.61811
32 c 4.26816 -2.49829 -1.85062
33 c 4.92995 -1.94365 -2.91733
34 o 4.36463 -1.27349 -3.92461
35 c 5.23130 -0.84349 -4.98764
36 c 4.42551 0.02675 -5.93396
37 c 5.05770 -3.21334 -0.77966
38 o -2.24045 -5.07823 -2.11293
39 h 6.14532 -3.20011 -1.00652
40 h 4.72804 -4.27003 -0.67930
41 h 4.89854 -2.74578 0.21633
42 h 6.03441 -2.04175 -2.96718
43 h 6.09291 -0.28057 -4.55590
44 h 5.63465 -1.74149 -5.51238
45 h 5.06569 0.36505 -6.77688
46 h 3.56455 -0.53901 -6.34927
47 h 4.03122 0.92188 -5.40721
48 h -3.77960 -4.94981 -0.31694
49 h -4.57700 -4.18253 1.95735
50 h -2.91699 -3.15840 3.55704
51 h -0.51306 -2.88848 2.85222
52 h 1.12269 -1.91197 -2.29758
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55 Transition state for the direct 2NH to Phenol Hydrogen Transfer
56 E(B3LYP/def2-TZVP)=-1064.356609029
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c	-2.67858	-4.72493	1.65387	
c	-2.79491	-3.34388	1.78739	
c	-1.86933	-2.44150	1.17610	
c	-0.81630	-3.05148	0.40662	
c	-0.68666	-4.45299	0.30863	
c	-1.61592	-5.29473	0.91525	
o	-1.99371	-1.15402	1.37525	
c	-3.38348	0.32796	0.49911	
n	-2.23386	0.81741	0.20593	
c	-2.08200	2.05962	-0.57386	
c	-0.71767	2.59521	-0.54321	
c	0.39051	1.99250	0.27954	
n	0.17312	-2.24656	-0.29927	
o	1.22520	-2.77970	-0.65580	
o	-4.52481	0.13793	0.63363	
o	-0.10030	-1.05383	-0.53817	
o	-3.06008	2.52412	-1.13568	
c	-0.54434	3.71069	-1.32232	
o	0.61874	4.35824	-1.39579	
c	0.70628	5.46317	-2.31896	
c	1.97303	6.24057	-2.01699	
h	-1.53903	-0.05114	0.57537	
h	1.28948	2.63982	0.23627	
h	0.66844	0.98009	-0.08935	
h	0.09367	1.88646	1.34680	
h	-1.39128	4.10993	-1.91317	
h	0.71868	5.05634	-3.35658	
h	-0.19985	6.10267	-2.20817	
h	2.07497	7.08614	-2.73047	
h	1.95013	6.65198	-0.98517	
h	2.86834	5.59034	-2.11604	
h	0.16024	-4.84645	-0.27203	
h	-1.52168	-6.38749	0.81763	
h	-3.42087	-5.37967	2.14087	
h	-3.60581	-2.89341	2.38149	

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

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c	-2.30025	-2.84137	0.10643	
c	-1.83382	-4.19399	0.06855	
c	-1.70190	-4.95334	1.24809	
c	-2.03882	-4.40698	2.48660	
c	-2.51171	-3.08009	2.54853	
c	-2.63969	-2.32208	1.38350	
n	-1.46716	-4.86378	-1.18888	
o	-0.93276	-5.97167	-1.12071	
o	-2.43989	-2.03458	-0.94756	
c	-3.82962	-2.51348	-2.18590	
n	-3.49138	-2.02492	-3.32933	

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3				
4	c	-2.27823	-1.58630	-3.73352
5	c	-2.09508	-1.16642	-5.11460
6	c	-0.74773	-0.65582	-5.54801
7	o	-4.68202	-3.06824	-1.58311
8	o	-1.71400	-4.28696	-2.25716
9	o	-1.24356	-1.51283	-2.95810
10	c	-3.16842	-1.27203	-5.96138
11	o	-3.10177	-0.90820	-7.24271
12	c	-4.28268	-1.11838	-8.04538
13	c	-4.02305	-0.56133	-9.43153
14	h	-0.76063	-0.37533	-6.62004
15	h	0.03853	-1.42636	-5.38846
16	h	-0.44475	0.23192	-4.94981
17	h	-4.13257	-1.66910	-5.59088
18	h	-4.50035	-2.21087	-8.08200
19	h	-5.14571	-0.60884	-7.55789
20	h	-4.91665	-0.71648	-10.07305
21	h	-3.80784	0.52775	-9.38728
22	h	-3.15809	-1.07113	-9.90705
23	h	-1.32898	-5.98263	1.15021
24	h	-1.93786	-5.01089	3.40206
25	h	-2.78540	-2.63604	3.52006
26	h	-3.00771	-1.28487	1.40915
27	h	-1.57992	-1.83460	-1.95335
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29				

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

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34				
35	c	-2.65169	-2.32878	1.40474
36	c	-2.29198	-2.84221	0.13015
37	c	-1.84399	-4.20157	0.09173
38	c	-1.75007	-4.97274	1.26748
39	c	-2.10738	-4.43208	2.50259
40	c	-2.56153	-3.09845	2.56535
41	o	-2.40457	-2.02902	-0.91983
42	n	-1.45627	-4.86510	-1.16208
43	o	-1.66948	-4.27633	-2.23154
44	o	-0.93687	-5.98007	-1.09131
45	c	-3.77942	-2.52123	-2.20923
46	o	-4.63227	-3.08931	-1.62346
47	n	-3.41859	-2.01702	-3.33878
48	c	-2.20249	-1.56789	-3.71195
49	o	-1.18343	-1.49426	-2.91171
50	c	-2.06311	-1.14936	-5.10015
51	c	-0.83899	-0.66794	-5.48678
52	o	-0.59826	-0.26123	-6.73472
53	c	0.71623	0.26024	-7.01610
54	c	0.79533	0.57804	-8.49681
55	c	-3.23479	-1.25809	-6.03928
56	h	-2.95653	-0.90780	-7.05354
57	h	-4.09637	-0.65579	-5.67667
58	h	-3.59245	-2.30844	-6.10908
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2				
3	h	-0.00493	-0.60517	-4.76268
4	h	0.88023	1.17270	-6.39691
5	h	1.47728	-0.49956	-6.72301
6	h	1.79826	0.98833	-8.74200
7	h	0.63165	-0.33568	-9.10709
8	h	0.02969	1.33136	-8.78077
9	h	-1.39087	-6.00681	1.16895
10	h	-2.03785	-5.04552	3.41461
11	h	-2.85202	-2.65896	3.53410
12	h	-3.00733	-1.28721	1.43077
13	h	-1.53625	-1.82325	-1.91340
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Product Complex EEZE

E(B3LYP/def2-TZVP)=-1064.420185736

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22	c	0.74271	0.68150	3.07841
23	c	0.02169	-0.49776	3.44406
24	c	-0.52755	-0.65146	4.73499
25	c	-0.37703	0.35280	5.68659
26	c	0.33152	1.52727	5.34237
27	c	0.87723	1.68694	4.07095
28	n	-0.17198	-1.57886	2.49191
29	o	-0.80798	-2.57311	2.82774
30	o	1.29561	0.91691	1.89010
31	c	-1.28967	0.55027	-0.20390
32	n	-0.69946	0.41519	-1.26889
33	c	0.65771	0.17083	-1.64497
34	c	0.88708	0.02631	-3.08665
35	c	2.30132	-0.22363	-3.53256
36	o	-1.97165	0.70583	0.74434
37	o	0.33002	-1.44105	1.35114
38	o	1.55403	0.09554	-0.81132
39	c	-0.16851	0.11857	-3.95108
40	o	-0.02274	-0.00836	-5.27677
41	c	-1.21192	0.11767	-6.07756
42	c	-0.83059	-0.07771	-7.53275
43	h	2.36226	-0.30624	-4.63626
44	h	2.69865	-1.15833	-3.07838
45	h	2.97275	0.59644	-3.19414
46	h	-1.19275	0.30222	-3.57456
47	h	-1.95467	-0.64696	-5.74972
48	h	-1.65832	1.12623	-5.91010
49	h	-1.73151	0.01588	-8.17605
50	h	-0.08961	0.68574	-7.85288
51	h	-0.38779	-1.08404	-7.69341
52	h	-1.07047	-1.58330	4.94812
53	h	-0.80619	0.23183	6.69328
54	h	0.45743	2.33050	6.08712
55	h	1.43171	2.59521	3.78914
56	h	1.16285	0.12479	1.27869

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

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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

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2				
3	c	-2.19386	-3.40276	1.66864
4	n	-1.94034	-6.28471	4.09757
5	o	-1.45389	-7.41644	4.09235
6	o	-1.25261	-3.29114	-0.62834
7	c	-1.84557	-2.11417	-1.02070
8	n	-1.44511	-1.76337	-2.30282
9	c	-0.38408	-2.21529	-3.17472
10	c	-0.19165	-3.64806	-3.39750
11	h	0.77160	-3.92658	-3.85276
12	o	-2.60986	-1.44494	-0.35519
13	o	0.26528	-1.35434	-3.75380
14	c	-1.15827	-4.59090	-3.23395
15	o	-0.94767	-5.88250	-3.51593
16	c	-2.08597	-6.76297	-3.43596
17	c	-1.60730	-8.18399	-3.66289
18	o	-2.55087	-5.77853	5.03917
19	h	-0.37288	-5.60796	-0.24322
20	h	-1.68406	-0.78465	-2.50264
21	h	-2.16934	-4.33063	-2.86464
22	h	-2.56266	-6.65183	-2.43322
23	h	-2.83084	-6.46150	-4.20894
24	h	-2.46792	-8.88487	-3.61336
25	h	-1.12954	-8.28492	-4.66078
26	h	-0.86742	-8.48161	-2.88929
27	h	-0.64693	-7.01376	1.86118
28	h	-2.87591	-3.80473	3.70200
29	h	-2.62601	-2.39721	1.61202
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2NH-EEEZ

E(B3LYP/def2-TZVP)=-1025.124000521

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37				
38	c	-1.99519	-3.57996	0.42000
39	c	-2.22829	-4.95992	0.39625
40	c	-2.02763	-5.71687	1.55899
41	c	-1.59167	-5.12738	2.75479
42	c	-1.36242	-3.74927	2.78230
43	c	-1.56514	-2.97837	1.62027
44	n	-2.27799	-7.17691	1.52342
45	o	-2.08264	-7.81002	2.56150
46	o	-1.24954	-1.63997	1.73733
47	c	-1.95736	-0.65470	1.05125
48	o	-2.92375	-0.86911	0.34962
49	n	-1.35636	0.54647	1.35697
50	c	-1.41987	1.85739	0.75671
51	o	-0.42031	2.55216	0.91179
52	c	-2.60133	2.33845	0.04779
53	c	-3.87229	1.84810	0.08804
54	o	-4.86963	2.47635	-0.54412
55	c	-6.17307	1.86760	-0.46031
56	c	-7.14947	2.72323	-1.24462
57	h	-2.42189	3.28412	-0.48822
58	o	-2.66475	-7.66013	0.45906
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2
3 h -2.14980 -2.97517 -0.48227
4 h -0.49428 0.46418 1.90901
5 h -4.13763 0.92123 0.62487
6 h -6.11795 0.83387 -0.87356
7 h -6.47181 1.79538 0.61179
8 h -8.16628 2.27790 -1.19646
9 h -7.19632 3.75236 -0.82849
10 h -6.84646 2.79110 -2.31134
11 h -2.56284 -5.46762 -0.51973
12 h -1.44359 -5.75836 3.64264
13 h -1.02093 -3.24707 3.70030
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17 2NH-EEZE
18 E(B3LYP/def2-TZVP)=-1025.120976310
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22 c -3.10801 -4.45169 0.54669
23 c -2.80628 -5.05098 1.77651
24 c -1.70544 -4.60485 2.51889
25 c -0.88495 -3.56084 2.06361
26 c -1.17996 -2.95927 0.83985
27 c -2.28542 -3.40388 0.08411
28 n -1.39820 -5.25072 3.81560
29 o -0.42479 -4.82981 4.44215
30 o -2.42916 -2.73280 -1.11222
31 c -3.52088 -2.79857 -1.92176
32 o -4.50161 -3.50135 -1.77134
33 n -3.36721 -1.95231 -3.01679
34 c -2.42385 -0.90527 -3.26542
35 o -1.66227 -0.47906 -2.41224
36 c -2.45754 -0.37256 -4.64204
37 c -2.91910 -1.03441 -5.73737
38 o -2.87221 -0.50356 -6.96628
39 c -3.24678 -1.35520 -8.06421
40 c -3.29709 -0.51473 -9.32557
41 h -1.96613 0.60504 -4.77034
42 o -2.13487 -6.16673 4.18316
43 h -3.96780 -4.78202 -0.04766
44 h -4.16259 -2.02652 -3.65628
45 h -3.34084 -2.05920 -5.67311
46 h -2.49745 -2.17608 -8.15810
47 h -4.23938 -1.81726 -7.84813
48 h -3.57588 -1.15043 -10.19291
49 h -4.04731 0.29909 -9.22903
50 h -2.30720 -0.05484 -9.53199
51 h -3.41956 -5.87225 2.17456
52 h -0.03213 -3.23923 2.67825
53 h -0.57302 -2.13393 0.43687
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56 2NH-EEZZ
57 E(B3LYP/def2-TZVP)=-1025.119671555
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	32			
5	c	-3.17602	-2.84545	1.23462
6	c	-1.84466	-2.59115	0.88534
7	c	-0.97293	-3.67912	0.67176
8	c	-1.43014	-5.00598	0.80697
9	c	-2.75860	-5.25669	1.15763
10	c	-3.61915	-4.16872	1.36601
11	o	0.36921	-3.54722	0.38644
12	c	0.86822	-2.46813	-0.35932
13	n	2.24343	-2.63389	-0.38781
14	c	3.18783	-1.69592	-0.90862
15	c	4.57439	-2.19623	-0.99207
16	h	5.33378	-1.41174	-1.13778
17	n	-5.02959	-4.42705	1.73717
18	o	-5.38292	-5.60290	1.83662
19	o	0.20319	-1.60578	-0.87153
20	o	2.86664	-0.57019	-1.24598
21	c	4.95718	-3.50116	-1.01174
22	o	6.24115	-3.86741	-1.12639
23	c	6.51296	-5.27203	-1.27835
24	c	8.01575	-5.47399	-1.23917
25	o	-5.75571	-3.45015	1.92268
26	h	-0.72244	-5.83098	0.63314
27	h	2.59589	-3.44984	0.11917
28	h	4.22632	-4.33506	-0.95389
29	h	6.00945	-5.83422	-0.45605
30	h	6.08603	-5.62211	-2.24759
31	h	8.25614	-6.55187	-1.35985
32	h	8.51008	-4.91046	-2.05895
33	h	8.43610	-5.12512	-0.27181
34	h	-3.14751	-6.27849	1.27096
35	h	-3.88625	-2.02528	1.41230
36	h	-1.48747	-1.56015	0.77197

2NH-EZEE
E(B3LYP/def2-TZVP)=-1025.126778419

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	32			
45	c	-1.37286	-3.61373	1.71872
46	c	-2.22907	-4.39028	2.52456
47	c	-3.61319	-4.21955	2.40439
48	c	-4.12028	-3.28712	1.48892
49	c	-3.27417	-2.51372	0.68118
50	c	-1.89190	-2.67955	0.80103
51	n	-5.58737	-3.11583	1.36787
52	o	-6.30046	-3.80805	2.09497
53	o	0.00376	-3.74591	1.70317
54	c	0.71889	-4.05645	2.84017
55	n	2.06942	-4.20447	2.57191
56	c	2.94423	-4.13637	1.44228
57	c	2.38357	-3.96404	0.09958
58	h	1.30206	-3.89807	-0.06962

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2
3 o 0.24379 -4.17197 3.95023
4 o 4.14491 -4.24838 1.68549
5 c 3.25352 -3.89739 -0.94624
6 o 2.84758 -3.75245 -2.20996
7 c 3.87412 -3.69143 -3.22036
8 c 3.20362 -3.53866 -4.57202
9 o -5.99602 -2.29379 0.54757
10 h -1.81836 -5.11151 3.24204
11 h 2.60799 -4.37896 3.42839
12 h 4.34427 -3.96557 -0.76194
13 h 4.54570 -2.82870 -3.00260
14 h 4.48349 -4.62396 -3.17467
15 h 3.97300 -3.48647 -5.37200
16 h 2.53639 -4.40160 -4.78246
17 h 2.59610 -2.60926 -4.60923
18 h -4.31570 -4.80583 3.01400
19 h -3.71368 -1.79391 -0.02376
20 h -1.19351 -2.08870 0.18874
21
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24 2NH-EZEZ

25 E(B3LYP/def2-TZVP)=-1025.131767374
26

27 32
28

29 c -1.31149 -3.25328 0.23412
30 c -1.90491 -4.44472 -0.23247
31 c -2.55445 -5.28269 0.68205
32 c -2.60269 -4.92930 2.03734
33 c -2.01082 -3.74843 2.50991
34 c -1.36454 -2.90848 1.60042
35 n -3.29082 -5.82527 2.99536
36 o -3.79804 -6.85371 2.54671
37 o -0.59625 -2.37463 -0.55340
38 c -0.83109 -2.21520 -1.91544
39 n 0.10184 -1.30933 -2.37442
40 c 0.33238 -0.77760 -3.68052
41 c -0.53363 -1.23600 -4.76757
42 h -1.33625 -1.96115 -4.57485
43 o -1.70402 -2.77516 -2.54288
44 o 1.25213 0.03075 -3.78932
45 c -0.30960 -0.73518 -6.01408
46 o -1.03865 -1.09243 -7.07368
47 c -0.70945 -0.47285 -8.33202
48 c -1.61766 -1.05238 -9.39958
49 o -3.30905 -5.48236 4.17816
50 h -1.86698 -4.70682 -1.29642
51 h 0.75771 -0.93234 -1.68164
52 h 0.50608 -0.00242 -6.17818
53 h -0.84733 0.62975 -8.23987
54 h 0.36336 -0.66855 -8.56422
55 h -1.38919 -0.58908 -10.38324
56 h -1.47448 -2.15070 -9.48675
57 h -2.68459 -0.85720 -9.15882
58 h -3.02892 -6.22006 0.35790
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3 h -2.06990 -3.50849 3.58096
4 h -0.88712 -1.97302 1.92977
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8 2NH-EZZE
9 E(B3LYP/def2-TZVP)=-1025.126351542
10

11 32
12

13 c -2.11187 -4.18933 0.09330
14 c -3.29204 -4.68744 0.68410
15 c -3.39158 -4.69939 2.08171
16 c -2.33002 -4.22413 2.86258
17 c -1.15326 -3.72789 2.27918
18 c -1.04770 -3.71150 0.88817
19 n -2.45084 -4.24511 4.33794
20 o -3.49963 -4.67873 4.81654
21 o -1.85400 -4.10155 -1.25805
22 c -2.69194 -4.51232 -2.24774
23 n -2.13232 -4.27140 -3.49962
24 c -0.89474 -3.68245 -3.89011
25 c -0.74326 -3.63587 -5.35820
26 h -1.52214 -4.02571 -6.03475
27 o -3.78626 -5.02537 -2.11333
28 o -0.06549 -3.26751 -3.09199
29 c 0.39234 -3.09445 -5.87520
30 o 0.62633 -3.00555 -7.18659
31 c 1.87302 -2.40002 -7.58430
32 c 1.94377 -2.40647 -9.09906
33 o -1.49355 -3.82724 4.99129
34 h -4.11027 -5.05690 0.05538
35 h -2.75786 -4.58157 -4.24844
36 h 1.16793 -2.70555 -5.18484
37 h 1.91536 -1.36099 -7.18206
38 h 2.71545 -2.97790 -7.13776
39 h 2.89645 -1.94400 -9.43498
40 h 1.90017 -3.44450 -9.49280
41 h 1.10066 -1.83033 -9.53673
42 h -4.29380 -5.07791 2.58335
43 h -0.34367 -3.36399 2.92752
44 h -0.14942 -3.33187 0.37777
45
46
47

48 2NH-EZZZ
49 E(B3LYP/def2-TZVP)=-1025.125452800
50

51 32
52

53 c -3.48864 -4.42923 1.66061
54 c -3.08653 -3.11169 1.40203
55 c -1.84323 -2.86775 0.80645
56 c -1.01641 -3.96224 0.47576
57 c -1.43226 -5.28406 0.74131
58 c -2.67204 -5.52310 1.33743
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3 o 0.24775 -3.85260 -0.06091
4 c 0.64567 -2.76340 -0.84930
5 o -0.05749 -1.84606 -1.18634
6 n -4.80380 -4.67420 2.29475
7 o -5.12236 -5.84533 2.50528
8 n 1.98024 -2.98425 -1.14761
9 c 2.81813 -2.14367 -1.93519
10 o 2.41685 -1.10749 -2.44212
11 c 4.19091 -2.67283 -2.05537
12 c 5.09303 -1.96831 -2.79035
13 o 6.36054 -2.35410 -2.95451
14 c 7.19039 -1.52325 -3.79142
15 c 8.60334 -2.07293 -3.75677
16 h 4.49496 -3.61408 -1.56718
17 o -5.49234 -3.69147 2.57195
18 h -0.76134 -6.11400 0.47157
19 h 2.38381 -3.84098 -0.75916
20 h 4.77259 -1.02527 -3.27775
21 h 6.77903 -1.53050 -4.82764
22 h 7.15472 -0.47524 -3.41307
23 h 9.26525 -1.45444 -4.39992
24 h 9.00793 -2.06048 -2.72200
25 h 8.62973 -3.11888 -4.13038
26 h -3.02471 -6.54076 1.55689
27 h -3.75874 -2.28596 1.67606
28 h -1.52144 -1.84172 0.59142
29
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32 2NH-ZEEE
33 E(B3LYP/def2-TZVP)=-1025.116673190
34

35 32

36
37 c -0.85915 -5.10996 0.65531
38 c -1.50803 -5.90445 1.60181
39 c -2.46140 -5.31178 2.44410
40 c -2.76443 -3.94644 2.35903
41 c -2.11423 -3.14246 1.41346
42 c -1.16284 -3.73369 0.55320
43 n -3.15963 -6.14926 3.44613
44 o -3.98735 -5.59649 4.17096
45 o -0.45022 -3.08485 -0.42750
46 c -0.68194 -1.79376 -0.84182
47 o -1.32080 -0.95521 -0.23983
48 n -0.00313 -1.54657 -2.02285
49 c 0.64419 -2.38836 -2.97503
50 o 1.57254 -1.91639 -3.62055
51 c 0.12900 -3.74568 -3.23008
52 c -1.14792 -4.20843 -3.12450
53 o -2.16985 -3.50821 -2.61126
54 c -3.44180 -4.17660 -2.49559
55 c -4.48344 -3.15071 -2.09192
56 h 0.84672 -4.39180 -3.75761
57 o -2.86775 -7.34538 3.48542
58 h -0.10318 -5.53304 -0.02379
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3 h 0.17279 -0.54936 -2.18819
4 h -1.39872 -5.22138 -3.49941
5 h -3.69400 -4.64836 -3.47419
6 h -3.35306 -4.98342 -1.73091
7 h -5.47256 -3.64325 -1.97638
8 h -4.21321 -2.67493 -1.12475
9 h -4.57394 -2.35392 -2.86076
10 h -1.29318 -6.97754 1.70473
11 h -3.51081 -3.52343 3.04690
12 h -2.32571 -2.06915 1.34201
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16 2NH-ZEEZ

17 E(B3LYP/def2-TZVP)=-1025.120799869

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19 32
20

21 c -2.51381 -5.50616 1.30741
22 c -2.37872 -4.94386 2.58466
23 c -1.72459 -3.71928 2.78421
24 c -1.20330 -3.04596 1.67649
25 c -1.33537 -3.60051 0.38725
26 c -1.99002 -4.83489 0.19665
27 n -2.93700 -5.66237 3.75367
28 o -2.79580 -5.13982 4.85988
29 o -0.73095 -2.88832 -0.62588
30 c -1.26891 -2.84566 -1.91532
31 n -0.36767 -2.14404 -2.68971
32 c -0.36383 -1.89588 -4.09648
33 c -1.63411 -1.79214 -4.82644
34 h -1.53864 -1.98397 -5.90596
35 o -2.32466 -3.33945 -2.23785
36 o 0.72705 -1.75648 -4.63759
37 c -2.82915 -1.31081 -4.38700
38 o -3.04900 -0.84466 -3.15355
39 c -4.41864 -0.75079 -2.72363
40 c -4.46700 0.06195 -1.44371
41 o -3.50537 -6.73410 3.54246
42 h -2.09123 -5.26255 -0.80884
43 h 0.55549 -1.98913 -2.26864
44 h -3.68813 -1.24374 -5.08711
45 h -5.02163 -0.27293 -3.53293
46 h -4.80512 -1.78205 -2.55961
47 h -5.51680 0.14768 -1.08996
48 h -3.87085 -0.42885 -0.64465
49 h -4.06491 1.08521 -1.60571
50 h -3.02800 -6.47218 1.20226
51 h -1.63845 -3.31556 3.80297
52 h -0.68201 -2.08293 1.78799
53
54

55 2NH-ZEZE

56 E(B3LYP/def2-TZVP)=-1025.125109230
57
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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

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2				
3	c	4.83019	-2.20038	0.21495
4	c	5.25847	-3.43390	0.59299
5	o	4.43334	-4.45941	0.90252
6	c	5.03074	-5.66150	1.42772
7	c	3.96392	-6.73675	1.50293
8	h	5.60142	-1.45636	-0.03326
9	o	-5.81454	-3.77455	1.46888
10	h	-0.52973	-5.87769	0.91406
11	h	2.72466	-3.55282	0.67135
12	h	6.34079	-3.66139	0.65338
13	h	5.86742	-5.96845	0.75764
14	h	5.45419	-5.44045	2.43508
15	h	4.40025	-7.67145	1.91518
16	h	3.12906	-6.42263	2.16605
17	h	3.55131	-6.95818	0.49520
18	h	-2.98720	-6.45687	1.23505
19	h	-3.97046	-2.25175	1.19262
20	h	-1.53661	-1.65708	0.86523
21				
22				
23				

2NH-ZZEE

E(B3LYP/def2-TZVP)=-1025.120527187

32

29	c	-2.73489	-4.48030	2.03251
30	c	-4.11801	-4.41946	1.82552
31	c	-4.67828	-3.29350	1.20610
32	c	-3.88656	-2.21610	0.78285
33	c	-2.50590	-2.27309	0.98991
34	c	-1.93324	-3.40049	1.61111
35	n	-6.14323	-3.24045	0.98926
36	o	-6.59886	-2.23378	0.44547
37	o	-0.55410	-3.38227	1.69869
38	c	0.11645	-3.96997	2.75412
39	o	-0.42010	-4.47771	3.71669
40	n	1.48754	-3.88965	2.59558
41	c	2.43087	-3.35317	1.64960
42	o	3.60204	-3.34241	2.01062
43	c	1.94318	-2.90982	0.34202
44	c	2.74427	-2.36174	-0.61960
45	o	4.04715	-2.12126	-0.48924
46	c	4.73788	-1.59977	-1.63973
47	c	6.14842	-1.23386	-1.21958
48	h	0.88295	-3.02714	0.08971
49	o	-6.80745	-4.20651	1.36517
50	h	-2.28361	-5.35122	2.52389
51	h	1.98392	-4.24674	3.42041
52	h	2.29545	-2.07670	-1.59426
53	h	4.74533	-2.37805	-2.43889
54	h	4.18696	-0.71051	-2.02788
55	h	6.71450	-0.84208	-2.09178
56	h	6.13423	-0.45498	-0.42758
57	h	6.68126	-2.12337	-0.82151
58	h	-4.77897	-5.24069	2.13765

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3 h -4.36670 -1.35176 0.30263
4 h -1.84877 -1.44700 0.67777
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8 2NH-ZZEZ
9 E(B3LYP/def2-TZVP)=-1025.126382228
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13 c -1.89390 -4.59113 -0.00297
14 c -2.57287 -5.26666 1.01759
15 c -2.81778 -4.61828 2.23580
16 c -2.39525 -3.30069 2.46543
17 c -1.71957 -2.62322 1.44786
18 c -1.46985 -3.26467 0.21783
19 n -3.53683 -5.34311 3.30893
20 o -3.73250 -4.74184 4.36592
21 o -0.74031 -2.52505 -0.68918
22 c -0.90146 -2.66477 -2.06620
23 o -1.72491 -3.38031 -2.59657
24 n 0.02679 -1.83991 -2.66090
25 c 0.31549 -1.56636 -4.04202
26 o 1.22334 -0.77348 -4.26174
27 c -0.50054 -2.25797 -5.03971
28 c -0.34546 -2.10594 -6.38799
29 o 0.56022 -1.32237 -6.97206
30 c 0.55995 -1.28208 -8.41093
31 c 1.69272 -0.37831 -8.85891
32 h -1.28812 -2.94195 -4.69411
33 o -3.89119 -6.49876 3.07436
34 h -1.70129 -5.08561 -0.96313
35 h 0.63788 -1.30793 -2.03157
36 h -1.01235 -2.66921 -7.07353
37 h 0.68935 -2.31748 -8.80572
38 h -0.42609 -0.89814 -8.76395
39 h 1.71757 -0.32254 -9.96825
40 h 1.55891 0.64792 -8.45552
41 h 2.67004 -0.76652 -8.50133
42 h -2.91808 -6.30213 0.88567
43 h -2.60653 -2.82940 3.43585
44 h -1.37141 -1.58821 1.58659
45
46
47

48 2NH-ZZZE
49 E(B3LYP/def2-TZVP)=-1025.120119075
50

51 32
52

53 c -3.39944 -4.59889 0.63648
54 c -3.51028 -4.65423 2.03217
55 c -2.41559 -4.30836 2.83510
56 c -1.19361 -3.90127 2.27590
57 c -1.07607 -3.84312 0.88708
58 c -2.17381 -4.19001 0.06968
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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				
32	2NH-ZZZZ			
33	E(B3LYP/def2-TZVP)=-1025.119082019			
34				
35	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				
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2
3 h 2.22994 -3.89751 -0.87299
4 h 5.98654 -2.81203 -3.11140
5 h 6.91616 -0.50198 -3.68428
6 h 6.40913 -1.49060 -5.10857
7 h 6.60567 0.95630 -5.72034
8 h 4.89830 0.39235 -5.87489
9 h 5.39357 1.37417 -4.45089
10 h -3.17233 -6.34402 1.70709
11 h -3.73679 -2.06307 1.80757
12 h -1.52451 -1.71616 0.63997
13
14
15

16 3OH-EEZE
17 E(B3LYP/def2-TZVP)=-1025.108962164
18

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21 c 1.17337 -0.40063 3.81617
22 c -0.01600 0.02567 4.42512
23 c -1.11828 0.44965 3.66882
24 c -1.03789 0.45294 2.27224
25 c 0.15272 0.02401 1.64933
26 c 1.25221 -0.40528 2.42075
27 n -0.10746 0.03148 5.90301
28 o -1.16830 0.40510 6.40480
29 o 0.33235 0.05184 0.28395
30 o 0.88438 -0.33632 6.53424
31 c -0.73506 -0.34269 -0.66152
32 n -0.36134 -0.20039 -1.95293
33 c 0.81885 0.18365 -2.40818
34 c 1.05271 0.28990 -3.83490
35 c 0.06458 -0.00577 -4.72812
36 o 0.24231 0.08538 -6.04460
37 c -0.88490 -0.25287 -6.88101
38 c -0.46869 -0.08821 -8.32955
39 o -1.78929 -0.73881 -0.22718
40 o 1.88707 0.50202 -1.66906
41 h 2.16690 -0.74402 1.90933
42 h 2.04704 0.61758 -4.17288
43 h -0.92684 -0.33429 -4.35761
44 h -1.19243 -1.30191 -6.66355
45 h -1.73665 0.41878 -6.62492
46 h -1.32009 -0.34036 -8.99730
47 h -0.15955 0.95877 -8.53603
48 h 0.38122 -0.75985 -8.57624
49 h 2.01276 -0.72667 4.44656
50 h -2.02835 0.77833 4.19078
51 h -1.89225 0.77995 1.66616
52 h 1.60394 0.41256 -0.70703
53
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55 3OH-EZZE
56 E(B3LYP/def2-TZVP)=-1025.107598489
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	32			
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

Transition state for the direct 2NH to Phenol Hydrogen Transfer
E(B3LYP/def2-TZVP)=-1025.054946518

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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

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2
3 o 0.32447 -0.31927 -3.49978
4 c -0.65262 -1.67210 -5.22533
5 c -0.50816 -0.72817 -6.20072
6 o -0.91362 -0.92114 -7.45050
7 c -0.63973 0.12685 -8.40928
8 c -1.40703 -0.17701 -9.68046
9 h -1.11070 -2.64519 -5.46228
10 h -1.52567 -5.92974 -0.59513
11 h -0.08190 -2.55889 -1.71153
12 h -0.04008 0.24679 -5.95503
13 h -0.94494 1.10490 -7.97167
14 h 0.45861 0.15474 -8.59475
15 h -1.19859 0.60607 -10.44044
16 h -1.10423 -1.16004 -10.09988
17 h -2.50116 -0.19826 -9.48926
18 h -3.01411 -6.36087 1.41394
19 h -2.16317 -2.40345 2.91906
20 h -0.68145 -1.94407 0.91472
21
22
23

24 Transition State for EEZE isomer
25 E(B3LYP/def2-TZVP)=-1025.096002111
26

27 32

28
29 c 0.16291 -0.20954 4.27651
30 c -1.07807 0.26637 3.82403
31 c -1.20089 0.72057 2.50857
32 c -0.08210 0.69061 1.64079
33 c 1.16036 0.19997 2.11560
34 c 1.28604 -0.24234 3.43412
35 o -0.19555 1.14336 0.37149
36 n 0.29262 -0.68279 5.66852
37 o 1.39933 -1.08757 6.03260
38 o -0.71315 -0.64525 6.38075
39 c -1.33388 0.26202 -0.78799
40 o -2.32733 -0.05432 -0.22439
41 n -0.75638 0.23287 -1.94735
42 c 0.51050 0.59086 -2.27214
43 o 1.36203 1.09210 -1.43644
44 c 0.94634 0.40656 -3.63810
45 c 0.11799 -0.12558 -4.58597
46 o 0.50493 -0.30502 -5.84381
47 c -0.46876 -0.85276 -6.76345
48 c 0.21396 -1.07980 -8.09747
49 h 2.02512 0.17286 1.43307
50 h 1.97387 0.71030 -3.88688
51 h -0.91414 -0.42500 -4.31512
52 h -0.86546 -1.80457 -6.34177
53 h -1.31361 -0.13240 -6.85673
54 h -0.51491 -1.49447 -8.82612
55 h 0.61295 -0.12680 -8.50541
56 h 1.05537 -1.79798 -7.99550
57 h 2.23870 -0.62230 3.82999
58 h -1.92907 0.27889 4.52017
59
60

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2
3 h -2.15743 1.10926 2.13230
4 h 0.80125 1.18219 -0.44498
5
6
7

8 Transition State for EZZE isomer
9 E(B3LYP/def2-TZVP)=-1025.095291990
10

11 32
12

13 c -0.63501 0.55911 3.94289
14 c -0.97909 1.00395 2.66409
15 c -0.16967 0.66336 1.55236
16 c 0.99097 -0.12780 1.74923
17 c 1.33959 -0.56485 3.02840
18 c 0.52108 -0.21877 4.11581
19 o -0.48513 1.10769 0.31651
20 h 1.61338 -0.39574 0.88017
21 c -2.09298 0.59036 -0.45292
22 n -1.87287 0.39583 -1.71688
23 c -0.69296 0.36987 -2.37330
24 c -0.74891 0.07154 -3.78690
25 h -1.73428 -0.12400 -4.23359
26 o -2.95189 0.57645 0.36211
27 o 0.46001 0.59168 -1.81533
28 c 0.39031 0.03997 -4.54120
29 o 0.37174 -0.22355 -5.84321
30 c 1.64456 -0.27005 -6.52865
31 c 1.38167 -0.44195 -8.01120
32 h 1.37486 0.24085 -4.07381
33 h 2.20041 0.67279 -6.31896
34 h 2.23564 -1.12159 -6.11916
35 h 2.34635 -0.49363 -8.55946
36 h 0.81672 -1.37831 -8.20688
37 h 0.79550 0.41217 -8.41239
38 h 2.23525 -1.17636 3.20883
39 n 0.88776 -0.68171 5.46793
40 h -1.24456 0.80962 4.82310
41 h -1.87196 1.62453 2.50478
42 h 0.23373 0.84141 -0.73378
43 o 0.15199 -0.35687 6.40250
44 o 1.90903 -1.36459 5.57969
45
46
47

48 Product Complex EEZE
49 E(B3LYP/def2-TZVP)=-1025.123266873
50

51 32
52

53 c 1.21722 -0.45952 2.95524
54 c 0.41616 -0.41451 4.10800
55 c -0.74290 0.38081 4.15622
56 c -1.10346 1.13428 3.04022
57 c -0.31136 1.10053 1.86503
58 c 0.85652 0.29474 1.83691
59
60

1				
2				
3	n	0.79570	-1.21266	5.28320
4	o	0.06799	-1.14970	6.27843
5	o	-0.70519	1.84765	0.81803
6	o	1.81890	-1.89958	5.20459
7	c	-2.25032	0.56384	-1.43155
8	n	-1.33496	0.46372	-2.24536
9	c	0.04198	0.76541	-2.32563
10	c	0.68077	0.39330	-3.57417
11	c	0.00738	-0.20501	-4.60100
12	o	0.60308	-0.53659	-5.74161
13	c	-0.20919	-1.18058	-6.75019
14	c	0.64758	-1.40473	-7.98002
15	o	-3.22287	0.58543	-0.77550
16	o	0.65868	1.30924	-1.39865
17	h	1.47683	0.27367	0.92641
18	h	1.75398	0.61956	-3.66082
19	h	-1.07402	-0.43165	-4.50852
20	h	-0.58976	-2.14372	-6.33879
21	h	-1.08308	-0.52719	-6.97702
22	h	0.04667	-1.90367	-8.77004
23	h	1.02402	-0.44015	-8.38238
24	h	1.51921	-2.05123	-7.74296
25	h	2.11765	-1.09056	2.95840
26	h	-1.34159	0.38955	5.07820
27	h	-2.00541	1.76561	3.04458
28	h	-0.09417	1.70866	0.02373
29				
30				
31				
32	Product Complex EEZE			
33	E(B3LYP/def2-TZVP)=-1025.123503031			
34				
35	32			
36				
37	c	-0.18613	0.49057	4.01275
38	c	-0.80079	1.20329	2.98440
39	c	-0.36077	1.05484	1.64489
40	c	0.71377	0.17158	1.36132
41	c	1.32901	-0.54188	2.39169
42	c	0.87574	-0.38128	3.71132
43	o	-0.98364	1.77086	0.69268
44	h	1.05900	0.05832	0.32102
45	c	-3.20911	0.68418	-1.04378
46	n	-2.51769	0.41919	-2.02333
47	c	-1.18920	0.52581	-2.45874
48	c	-0.98078	-0.00116	-3.79715
49	h	-1.83363	-0.42525	-4.34760
50	o	-4.00204	0.86909	-0.19892
51	o	-0.29255	1.02530	-1.75651
52	c	0.26787	0.03807	-4.35018
53	o	0.52269	-0.42060	-5.56937
54	c	1.89318	-0.36025	-6.02898
55	c	1.92604	-0.78464	-7.48355
56	h	1.11227	0.46864	-3.77452
57	h	2.27030	0.68011	-5.89863
58	h	2.50860	-1.03758	-5.39366
59				
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2				
3	h	2.97173	-0.75972	-7.85776
4	h	1.53648	-1.81798	-7.60318
5	h	1.31279	-0.10240	-8.11005
6	h	2.16433	-1.23027	2.19782
7	n	1.52420	-1.13513	4.79425
8	h	-0.51166	0.58873	5.05838
9	h	-1.63494	1.89204	3.18826
10	h	-0.61846	1.54857	-0.22503
11	o	1.09652	-0.97486	5.94095
12	o	2.45807	-1.88478	4.49199
13				
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15				

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

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

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26	c	-0.98248	-3.74696	0.89429
27	c	-0.98226	-5.14278	0.86467
28	c	-1.64964	-5.84098	1.88234
29	c	-2.30769	-5.17068	2.92182
30	c	-2.31108	-3.77031	2.95737
31	c	-1.64558	-3.06201	1.93542
32	o	-1.52914	-1.68923	1.86224
33	c	-2.37170	-0.80510	2.49600
34	o	-3.28831	-1.10318	3.23415
35	h	-0.46909	-3.15921	0.11710
36	n	-2.02728	0.50526	2.19181
37	c	-0.85848	1.08253	1.56764
38	o	-0.32977	2.03047	2.13571
39	c	-0.41301	0.56993	0.26079
40	c	-1.30499	-0.05622	-0.56066
41	o	-0.96021	-0.52485	-1.77151
42	c	-2.03262	-0.95674	-2.62863
43	c	-1.43136	-1.59417	-3.86695
44	c	0.99835	0.88753	-0.15425
45	h	-2.45093	1.15955	2.86082
46	h	1.14989	0.69488	-1.23531
47	h	1.73264	0.27274	0.41534
48	h	1.22928	1.95077	0.07038
49	h	-2.36174	-0.20115	-0.26706
50	h	-2.67517	-1.68022	-2.07271
51	h	-2.66053	-0.07463	-2.89613
52	h	-2.24027	-1.92923	-4.55080
53	h	-0.79011	-0.86905	-4.41223
54	h	-0.81115	-2.47608	-3.59811
55	h	-0.47570	-5.70697	0.06880
56	n	-1.65540	-7.32210	1.85662
57	h	-2.81316	-5.76023	3.70019
58	h	-2.82778	-3.22974	3.75895

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2
3 o -2.24527 -7.90325 2.76749
4 o -1.06951 -7.87412 0.92422
5
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8 2NH-EEEZ
9 E(B3LYP/def2-TZVP)=-1064.425317291
10

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12

13 c -2.11683 -4.93177 0.33547
14 c -2.07617 -5.66853 1.52746
15 c -1.82523 -5.05456 2.76346
16 c -1.61835 -3.67325 2.79992
17 c -1.65996 -2.92243 1.60785
18 c -1.90719 -3.54821 0.36884
19 o -1.37796 -1.57937 1.74739
20 c -1.97860 -0.61102 0.94138
21 n -1.43527 0.60193 1.31734
22 c -1.36605 1.86048 0.60918
23 c -2.50682 2.36283 -0.16338
24 c -2.21841 3.51358 -1.09310
25 h -1.93937 -2.95902 -0.55624
26 o -2.82480 -0.84128 0.10513
27 o -0.31519 2.48322 0.72770
28 c -3.77283 1.89671 0.05539
29 o -4.83636 2.40340 -0.58278
30 c -6.10950 1.79414 -0.29835
31 c -7.17119 2.49928 -1.12084
32 h -0.63619 0.52105 1.95780
33 h -3.12838 3.80568 -1.65393
34 h -1.41815 3.24807 -1.81823
35 h -1.84674 4.39538 -0.52538
36 h -3.98329 1.08861 0.77512
37 h -6.05526 0.70981 -0.55043
38 h -6.32039 1.88502 0.79333
39 h -8.16662 2.04820 -0.92061
40 h -7.21742 3.57954 -0.86509
41 h -6.95604 2.40564 -2.20684
42 h -2.30942 -5.45788 -0.61053
43 n -2.29831 -7.13259 1.48104
44 h -1.79911 -5.66957 3.67424
45 h -1.41792 -3.15234 3.74866
46 o -2.50967 -7.63948 0.37894
47 o -2.25664 -7.74590 2.54818
48
49

50 2NH-EEZE
51 E(B3LYP/def2-TZVP)=-1064.423425480
52

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54

55 c -3.13200 -4.54511 0.49779
56 c -2.38220 -5.34523 1.37001
57 c -1.26240 -4.84202 2.05091
58
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60

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

2NH-EEZZ

E(B3LYP/def2-TZVP)=-1064.422157366

35

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

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2
3 c 3.51768 2.73203 -0.99760
4 c 4.53279 3.83595 -0.76779
5 c -0.51671 4.23401 -0.80945
6 h -0.05852 0.42415 0.37594
7 h 0.34309 4.86781 -1.10541
8 h -0.90636 4.60882 0.16475
9 h -1.34012 4.34815 -1.54635
10 h 1.47723 1.31586 -0.76611
11 h 3.70218 1.86794 -0.31477
12 h 3.56528 2.35521 -2.04670
13 h 5.55825 3.45515 -0.96234
14 h 4.34304 4.69319 -1.44854
15 h 4.48646 4.20419 0.27945
16 h -0.33824 -5.95032 1.51962
17 n -2.87786 -6.80980 1.59414
18 h -4.44789 -4.70892 1.04077
19 h -3.70411 -2.35198 0.52283
20 o -4.09033 -7.02398 1.59275
21 o -2.00873 -7.65252 1.82266
22
23
24

25 2NH-EZEE
26 E(B3LYP/def2-TZVP)=-1064.421188748
27

28 35
29

30 c -1.30544 -3.44695 1.80554
31 c -2.23428 -4.43351 2.15608
32 c -3.59777 -4.22309 1.90701
33 c -4.06230 -3.04191 1.30979
34 c -3.13765 -2.05550 0.95800
35 c -1.76470 -2.25745 1.20377
36 o -0.93878 -1.24968 0.75255
37 c 0.27577 -0.97164 1.34833
38 o 0.65082 -1.41646 2.41204
39 h -0.23670 -3.59432 2.00597
40 n 0.98588 -0.06110 0.58534
41 c 0.64818 0.65780 -0.61259
42 o 0.94048 1.84994 -0.64610
43 c 0.07310 -0.09843 -1.74532
44 c -0.46682 0.68452 -2.72785
45 o -0.97674 0.15565 -3.84760
46 c -1.49539 1.07469 -4.82679
47 c -2.03784 0.27151 -5.99372
48 c 0.15821 -1.59597 -1.91300
49 h 1.70199 0.42592 1.13608
50 h -0.81413 -2.10304 -1.72580
51 h 0.91212 -2.04170 -1.23205
52 h 0.45312 -1.84064 -2.95694
53 h -0.48790 1.78589 -2.62263
54
55 h -2.29473 1.69399 -4.35640
56 h -0.67713 1.75852 -5.15245
57 h -2.44406 0.95608 -6.76869
58 h -1.23652 -0.34425 -6.45548
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2
3 h -2.85274 -0.40716 -5.66247
4 h -1.91642 -5.37617 2.62410
5 n -4.57238 -5.27450 2.27919
6 h -5.14008 -2.91698 1.13372
7 h -3.45846 -1.11383 0.48703
8 o -5.76197 -5.05001 2.05296
9 o -4.12896 -6.30461 2.78807
10

11
12
13 2NH-EZEZ
14 E(B3LYP/def2-TZVP)=-1064.424673427
15

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17

18 c -1.63780 -3.22889 0.03439
19 c -1.48628 -4.61117 -0.12599
20 c -1.76787 -5.46940 0.94603
21 c -2.19738 -4.97843 2.18782
22 c -2.35126 -3.59960 2.35016
23 c -2.07449 -2.72743 1.27796
24 o -2.20475 -1.38524 1.56804
25 c -2.59280 -0.45343 0.60480
26 o -2.90978 -0.71982 -0.53199
27 h -1.42725 -2.54716 -0.79892
28 n -2.53825 0.78733 1.20848
29 c -2.66680 2.08172 0.60245
30 o -1.92122 2.96113 1.02766
31 c -3.71934 2.28133 -0.41447
32 c -3.56761 3.42391 -1.15163
33 o -4.45325 3.78814 -2.08731
34 c -4.20011 5.02551 -2.77753
35 c -5.28601 5.22131 -3.81862
36 c -4.92570 1.39282 -0.58953
37 h -2.00344 0.82588 2.08375
38 h -5.79678 2.00472 -0.90689
39 h -5.18954 0.88021 0.36004
40 h -4.75903 0.60367 -1.35271
41 h -2.69792 4.08726 -0.98487
42 h -4.19508 5.86022 -2.03765
43 h -3.19144 4.97862 -3.25065
44 h -5.11748 6.17191 -4.36850
45 h -5.28531 4.38638 -4.55183
46 h -6.28796 5.26541 -3.34052
47 h -1.14721 -5.04193 -1.07893
48 n -1.60533 -6.93050 0.76586
49 h -2.40637 -5.68608 3.00251
50 h -2.68674 -3.17238 3.30743
51 o -1.86865 -7.65263 1.72807
52 o -1.21727 -7.32703 -0.33367
53
54

55 2NH-EZZE
56 E(B3LYP/def2-TZVP)=-1064.426084283
57
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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

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2				
3	c	1.22721	2.22771	-0.06458
4	h	0.19577	-3.83967	0.50185
5	o	-3.04871	-0.69556	-0.42314
6	o	-2.38674	1.99540	-1.12740
7	c	-0.34649	3.86097	-1.15138
8	o	0.58864	4.81936	-1.19338
9	c	0.19912	6.07586	-1.77914
10	c	1.38223	7.02252	-1.71243
11	h	-0.06862	0.22125	0.20191
12	h	1.93438	3.07958	-0.13161
13	h	1.68963	1.37571	-0.61648
14	h	1.16332	1.93945	1.01107
15	h	-1.34857	4.09907	-1.55739
16	h	-0.11888	5.90167	-2.83362
17	h	-0.67512	6.48260	-1.21928
18	h	1.10879	8.00171	-2.16076
19	h	1.69312	7.19397	-0.65961
20	h	2.25015	6.61135	-2.27116
21	h	-0.64529	-6.17366	1.07480
22	n	-3.15993	-6.83381	1.73366
23	h	-4.61420	-4.58292	1.68740
24	h	-3.80172	-2.26196	1.11380
25	o	-4.35220	-6.95166	2.01853
26	o	-2.34367	-7.75591	1.70284
27				
28				
29				

2NH-ZEEE

E(B3LYP/def2-TZVP)=-1064.417018305

35

35	c	-0.80318	-5.07483	0.86763
36	c	-1.95099	-5.72096	1.35202
37	c	-2.91296	-5.03545	2.10536
38	c	-2.74122	-3.67389	2.38736
39	c	-1.59587	-3.01254	1.89170
40	c	-0.62955	-3.71687	1.13904
41	o	-1.29316	-1.68296	2.06864
42	c	-2.13205	-0.75808	2.64634
43	n	-1.66438	0.52217	2.40447
44	c	-0.69459	1.05427	1.50850
45	c	-0.47533	0.43399	0.17757
46	c	0.84222	0.78305	-0.47225
47	h	0.25572	-3.17160	0.77759
48	o	-3.09851	-1.00676	3.33744
49	o	-0.10918	2.07798	1.84656
50	c	-1.43175	-0.22796	-0.53865
51	o	-2.66997	-0.51028	-0.09430
52	c	-3.51857	-1.28442	-0.96138
53	c	-4.91228	-1.31230	-0.36258
54	h	-1.99709	1.21190	3.08733
55	h	0.91789	0.35464	-1.49435
56	h	1.69983	0.40320	0.12753
57	h	0.96769	1.88589	-0.53705
58	h	-1.21399	-0.54652	-1.57836
59				
60				

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2
3 h -3.52337 -0.82049 -1.97584
4 h -3.09863 -2.31387 -1.05198
5 h -5.58552 -1.92391 -1.00058
6 h -4.89392 -1.75592 0.65595
7 h -5.33203 -0.28626 -0.28856
8 h -0.06812 -5.64917 0.28611
9 n -2.14663 -7.15957 1.06178
10 h -3.79220 -5.58453 2.47235
11 h -3.47218 -3.12563 2.99321
12 o -1.27319 -7.72837 0.40539
13 o -3.17006 -7.69178 1.49287
14
15
16

17 2NH-ZEEZ
18 E(B3LYP/def2-TZVP)=-1064.421034889
19

20 35
21

22 c -2.14908 -5.63854 1.41379
23 c -2.14851 -5.00924 2.66721
24 c -1.89918 -3.63566 2.73130
25 c -1.65040 -2.90875 1.54994
26 c -1.64720 -3.55081 0.29474
27 c -1.89914 -4.92595 0.23229
28 o -1.35628 -1.57319 1.72343
29 c -1.80010 -0.61023 0.81182
30 o -2.51848 -0.83907 -0.13333
31 h -1.45319 -2.98016 -0.62255
32 n -1.26142 0.59182 1.22173
33 c -1.32655 1.88128 0.61630
34 o -0.37621 2.63403 0.80765
35 c -2.50438 2.27650 -0.18673
36 c -3.78062 1.86152 0.06157
37 o -4.14100 1.05298 1.06963
38 c -5.41170 0.39348 0.94285
39 c -5.74500 -0.26778 2.26696
40 c -2.24246 3.35592 -1.21031
41 h -0.51061 0.52959 1.91879
42 h -3.17016 3.62558 -1.75824
43 h -1.48100 3.03049 -1.95374
44 h -1.83967 4.27142 -0.72375
45 h -4.61419 2.24285 -0.56482
46 h -6.18616 1.14690 0.66027
47 h -5.33996 -0.35944 0.12515
48 h -6.72982 -0.77794 2.19848
49 h -4.97883 -1.02804 2.53162
50 h -5.79363 0.48257 3.08537
51 h -1.90223 -5.46482 -0.72608
52 n -2.41714 -7.09372 1.33760
53 h -2.34679 -5.60621 3.56871
54 h -1.88924 -3.10217 3.69413
55 o -2.40297 -7.61521 0.22219
56 o -2.63687 -7.68532 2.39512
57
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2
3 2NH-ZEZE
4 E(B3LYP/def2-TZVP)=-1064.425966201
5

6 35
7

8	c	-2.67454	-5.29652	1.75000
9	c	-1.70755	-4.69910	2.57439
10	c	-1.23401	-3.42937	2.24352
11	c	-1.72732	-2.76598	1.09892
12	c	-2.69879	-3.37124	0.27359
13	c	-3.16856	-4.64740	0.61099
14	o	-1.15687	-1.52676	0.90933
15	c	-1.48553	-0.65019	-0.08111
16	o	-2.32558	-0.81476	-0.94659
17	h	-3.07517	-2.84549	-0.61133
18	n	-0.72728	0.51042	0.00193
19	c	0.29020	0.90428	0.90232
20	o	0.68164	0.21128	1.83175
21	c	0.88487	2.25450	0.64261
22	c	0.52822	3.12305	-0.34744
23	o	-0.46211	2.90568	-1.24734
24	c	-0.59330	3.83960	-2.33575
25	c	-1.87256	3.52492	-3.08790
26	c	1.98035	2.63728	1.60659
27	h	-0.96866	1.18744	-0.73504
28	h	2.40061	3.63830	1.37151
29	h	2.80469	1.89095	1.58542
30	h	1.60159	2.64791	2.65218
31	h	1.04791	4.09580	-0.45087
32	h	-0.61165	4.87409	-1.91973
33	h	0.29918	3.74750	-2.99779
34	h	-1.98914	4.22654	-3.94135
35	h	-1.85399	2.48887	-3.48942
36	h	-2.75863	3.62808	-2.42569
37	h	-3.92437	-5.15601	-0.00451
38	n	-3.18316	-6.64361	2.09262
39	h	-1.34514	-5.24127	3.45925
40	h	-0.47532	-2.91482	2.85266
41	o	-4.02564	-7.14070	1.34368
42	o	-2.73100	-7.18082	3.10493

43
44
45 2NH-ZEZZ
46 E(B3LYP/def2-TZVP)=-1064.424564486
47

48 35
49

50	c	-3.54689	-4.32630	1.41539
51	c	-3.16736	-3.03066	1.04284
52	c	-1.81680	-2.78152	0.71386
53	c	-0.86500	-3.82484	0.75975
54	c	-1.24847	-5.11344	1.13236
55	c	-2.59272	-5.35159	1.45716
56	o	-1.28900	-1.56073	0.36313
57	c	-2.05374	-0.43347	0.02420

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2				
3	n	-1.13422	0.56876	-0.22590
4	c	-1.43433	1.90205	-0.58796
5	c	-0.24993	2.79617	-0.78908
6	c	-0.60750	4.20919	-1.17608
7	h	0.17965	-3.59670	0.49691
8	o	-3.25670	-0.38844	-0.03062
9	o	-2.57635	2.31262	-0.72486
10	c	1.06062	2.44525	-0.65204
11	o	1.50061	1.19659	-0.35151
12	c	2.88853	1.05058	0.00041
13	c	3.21509	-0.42930	0.07095
14	h	-0.13948	0.31983	-0.13793
15	h	0.29753	4.84170	-1.29669
16	h	-1.26816	4.67249	-0.41081
17	h	-1.18175	4.22549	-2.12854
18	h	1.86070	3.19535	-0.80866
19	h	3.50991	1.56536	-0.76933
20	h	3.06681	1.55166	0.98056
21	h	4.28061	-0.56738	0.35351
22	h	2.58616	-0.93934	0.83256
23	h	3.04696	-0.92044	-0.91150
24				
25	h	-0.52990	-5.94396	1.17678
26	n	-3.00793	-6.71527	1.85392
27	h	-4.58905	-4.55748	1.67939
28	h	-3.90502	-2.22141	0.99783
29	o	-4.19467	-6.89062	2.13171
30	o	-2.13732	-7.58727	1.88106
31				
32				
33				
34	2NH-ZZEE			
35	E(B3LYP/def2-TZVP)=-1064.413364898			
36				
37	35			
38				
39	c	-2.47449	-4.27795	2.02136
40	c	-3.77146	-4.00622	1.56461
41	c	-4.06265	-2.85319	0.82066
42	c	-3.02979	-1.95768	0.53526
43	c	-1.72212	-2.22125	0.99104
44	c	-1.43607	-3.38315	1.73668
45	o	-0.77975	-1.29566	0.59162
46	c	0.37950	-1.05490	1.29984
47	n	1.17997	-0.15050	0.62080
48	c	0.95593	0.64484	-0.55778
49	c	0.37256	-0.03241	-1.74497
50	c	0.74137	-1.46519	-2.06154
51	h	-0.41897	-3.57664	2.09838
52	o	0.65206	-1.52746	2.38291
53	o	1.36102	1.79758	-0.53626
54	c	-0.39196	0.68051	-2.62473
55	o	-0.80431	1.93913	-2.42644
56	c	-1.47086	2.58495	-3.52044
57	c	-2.02530	3.90850	-3.02720
58	h	1.88374	0.27165	1.23829
59				
60				

1
2
3 h 0.40592 -1.73515 -3.08619
4 h 0.28266 -2.19681 -1.36156
5 h 1.84365 -1.61618 -2.02177
6 h -0.74953 0.19596 -3.55768
7 h -0.74140 2.74281 -4.34959
8 h -2.28550 1.92259 -3.90223
9 h -2.53309 4.44204 -3.85917
10 h -2.75972 3.74907 -2.20895
11 h -1.20803 4.55378 -2.64046
12 h -2.29392 -5.19607 2.59855
13 n -4.86207 -4.96054 1.87172
14 h -5.09358 -2.67883 0.48177
15 h -3.21169 -1.04008 -0.04461
16 o -4.57259 -5.96136 2.52765
17 o -5.98686 -4.68976 1.44883
18
19
20

21 2NH-ZZEZ

22 E(B3LYP/def2-TZVP)=-1064.417116111
23

24 35
25

26 c -1.57841 -4.56378 -0.28301
27 c -1.82004 -5.45166 0.77458
28 c -2.18036 -4.99477 2.05088
29 c -2.30519 -3.61976 2.26347
30 c -2.06857 -2.71815 1.20634
31 c -1.70122 -3.18557 -0.07223
32 o -2.16128 -1.38354 1.54162
33 c -2.60241 -0.42210 0.63167
34 n -2.49620 0.80056 1.26233
35 c -2.59900 2.12104 0.69744
36 c -3.65271 2.36476 -0.31351
37 c -4.97288 1.62644 -0.26479
38 h -1.52094 -2.48028 -0.89310
39 o -3.00162 -0.65817 -0.48698
40 o -1.84594 2.96887 1.15653
41 c -3.47331 3.35478 -1.24185
42 o -2.36507 4.09126 -1.37671
43 c -2.31722 4.98763 -2.49735
44 c -1.04992 5.81488 -2.39139
45 h -1.93587 0.80094 2.12283
46 h -5.71197 2.11084 -0.93901
47 h -5.40447 1.63841 0.76172
48 h -4.86929 0.56576 -0.57790
49 h -4.28603 3.56905 -1.96665
50 h -2.33146 4.39423 -3.44262
51 h -3.22390 5.63871 -2.48735
52 h -0.97971 6.51537 -3.25117
53 h -1.04393 6.40525 -1.45051
54 h -0.15234 5.16036 -2.39584
55 h -1.29274 -4.96873 -1.26431
56 n -1.68896 -6.90840 0.54063
57 h -2.35961 -5.72506 2.85259
58 h -2.58607 -3.21864 3.24918
59
60

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2
3 o -1.35720 -7.27431 -0.58755
4 o -1.92035 -7.65769 1.49024
5
6
7

8 2NH-ZZZE
9 E(B3LYP/def2-TZVP)=-1064.417115758
10

11 35
12

13 c -3.30666 -4.79803 0.84140
14 c -2.75895 -5.29521 2.03157
15 c -1.65875 -4.67706 2.64755
16 c -1.10442 -3.54309 2.05316
17 c -1.65063 -3.03370 0.85461
18 c -2.75693 -3.65781 0.24000
19 o -0.98648 -1.91798 0.39486
20 c -1.32402 -1.19779 -0.70886
21 n -0.43799 -0.14406 -0.90671
22 c 0.73617 0.25744 -0.19196
23 c 1.37269 1.47230 -0.77526
24 c 0.76862 2.19915 -1.95829
25 h -3.17370 -3.25131 -0.68861
26 o -2.26631 -1.40241 -1.45184
27 o 1.14818 -0.34849 0.78355
28 c 2.53551 1.96283 -0.24036
29 o 3.19794 1.44187 0.79312
30 c 4.40159 2.11776 1.19608
31 c 5.01077 1.34876 2.35311
32 h -0.70585 0.39998 -1.73066
33 h 1.37486 3.09000 -2.22976
34 h -0.26275 2.56854 -1.74924
35 h 0.71922 1.56189 -2.87301
36 h 2.98891 2.87072 -0.69061
37 h 5.10381 2.16531 0.32984
38 h 4.15170 3.16346 1.49483
39 h 5.94469 1.84684 2.69097
40 h 4.30381 1.30297 3.20850
41 h 5.25363 0.30874 2.04822
42 h -4.16776 -5.31556 0.39496
43 n -3.35214 -6.49979 2.65395
44 h -1.25823 -5.09819 3.58026
45 h -0.23942 -3.02141 2.48997
46 o -4.30837 -7.02425 2.08091
47 o -2.85032 -6.90033 3.70553
48
49

50 2NH-ZZZZ
51 E(B3LYP/def2-TZVP)=-1064.416225655
52

53 35
54

55 c -2.76742 -5.25911 1.46419
56 c -3.60431 -4.14162 1.58909
57 c -3.12749 -2.87230 1.24093
58
59
60

1				
2				
3	c	-1.80446	-2.74333	0.76660
4	c	-0.97182	-3.87609	0.64502
5	c	-1.45015	-5.14012	0.99598
6	o	-1.20310	-1.54653	0.44816
7	c	-1.92985	-0.42399	0.01250
8	o	-3.11492	-0.39964	-0.19749
9	h	0.05514	-3.74038	0.27257
10	n	-0.99999	0.59175	-0.12070
11	c	-1.27708	1.93562	-0.52938
12	o	-2.40627	2.29510	-0.81079
13	c	-0.06055	2.79368	-0.56122
14	c	-0.15764	4.10813	-0.93787
15	o	-1.28102	4.73063	-1.29418
16	c	-1.16787	6.11395	-1.67028
17	c	-2.55439	6.62302	-2.01626
18	c	1.30237	2.25270	-0.18466
19	h	-0.03804	0.32996	0.10767
20	h	2.08077	3.04116	-0.26899
21	h	1.62786	1.41585	-0.84726
22	h	1.33942	1.88322	0.86761
23	h	0.76264	4.72989	-0.95531
24	h	-0.72672	6.68972	-0.82213
25	h	-0.47749	6.20087	-2.54269
26	h	-2.50328	7.69221	-2.31421
27	h	-2.98711	6.04022	-2.85682
28	h	-3.23532	6.52905	-1.14390
29	h	-0.82631	-6.04121	0.91304
30	n	-3.28166	-6.59575	1.83850
31	h	-4.62846	-4.28142	1.96389
32	h	-3.77616	-1.99243	1.32612
33	o	-2.51497	-7.55256	1.71787
34	o	-4.44154	-6.66439	2.24714
35				
36				
37				
38				
39				
40				
41				
42				
43	c	0.07412	0.04846	1.84705
44	c	1.13660	-0.55077	2.55492
45	c	1.10231	-0.61268	3.95052
46	c	-0.00662	-0.07968	4.62387
47	c	-1.07058	0.51622	3.93143
48	c	-1.03439	0.58522	2.53448
49	n	-0.05241	-0.14659	6.10223
50	o	-1.04005	0.33057	6.66228
51	o	0.21309	0.12028	0.47906
52	c	-0.92103	-0.10366	-0.45031
53	n	-0.55054	-0.01551	-1.74544
54	c	0.65704	0.23325	-2.22414
55	c	0.89747	0.27533	-3.66331
56	c	2.27862	0.57026	-4.18480
57	o	0.90120	-0.67499	6.67598
58	o	-2.01417	-0.34043	0.00447
59				
60				

3OH-EEZE

E(B3LYP/def2-TZVP)=-1064.409859500

35

42				
43	c	0.07412	0.04846	1.84705
44	c	1.13660	-0.55077	2.55492
45	c	1.10231	-0.61268	3.95052
46	c	-0.00662	-0.07968	4.62387
47	c	-1.07058	0.51622	3.93143
48	c	-1.03439	0.58522	2.53448
49	n	-0.05241	-0.14659	6.10223
50	o	-1.04005	0.33057	6.66228
51	o	0.21309	0.12028	0.47906
52	c	-0.92103	-0.10366	-0.45031
53	n	-0.55054	-0.01551	-1.74544
54	c	0.65704	0.23325	-2.22414
55	c	0.89747	0.27533	-3.66331
56	c	2.27862	0.57026	-4.18480
57	o	0.90120	-0.67499	6.67598
58	o	-2.01417	-0.34043	0.00447
59				
60				

1
2
3 o 1.75504 0.46538 -1.49525
4 c -0.17338 0.03210 -4.48324
5 o -0.06698 0.04138 -5.81455
6 c -1.26345 -0.24662 -6.56592
7 c -0.92654 -0.17958 -8.04305
8 h 1.98623 -0.96930 1.99275
9 h -1.16592 -0.18100 -4.04297
10 h -1.63350 -1.25856 -6.28035
11 h -2.04786 0.49741 -6.29481
12 h -1.83269 -0.39959 -8.64710
13 h -0.55818 0.83135 -8.32002
14 h -0.14265 -0.92230 -8.30440
15 h 1.91432 -1.07208 4.53182
16 h -1.91658 0.92416 4.50294
17 h -1.86019 1.04442 1.97692
18 h 1.47310 0.40150 -0.52941
19 h 2.28644 0.56138 -5.29318
20 h 2.63738 1.56377 -3.83571
21 h 3.01650 -0.17796 -3.81924
22
23
24

25 3OH-EZZE
26 E(B3LYP/def2-TZVP)=-1064.408934712
27

28 35
29

30 c 1.43774 -0.22588 3.81820
31 c 0.40274 0.22328 4.65131
32 c -0.85194 0.58143 4.13730
33 c -1.08667 0.49301 2.76084
34 c -0.05393 0.03857 1.91432
35 c 1.20226 -0.32279 2.44434
36 n 0.64363 0.32430 6.10882
37 o -0.28864 0.71390 6.81270
38 o -0.18143 -0.02748 0.54457
39 o 1.76180 0.01269 6.52164
40 c -1.42369 -0.48139 -0.12276
41 n -1.32701 -0.45719 -1.47323
42 c -0.25817 -0.17542 -2.19407
43 c -0.38104 -0.20709 -3.64774
44 c -1.70738 -0.56787 -4.26043
45 o -2.36557 -0.81463 0.55271
46 o 0.95500 0.13577 -1.70931
47 c 0.72547 0.09606 -4.39669
48 o 0.70282 0.08922 -5.73475
49 c 1.92700 0.43275 -6.41036
50 c 1.68814 0.34381 -7.90555
51 h 1.98862 -0.68232 1.76223
52 h 1.68489 0.35868 -3.91404
53 h 2.22960 1.46324 -6.11034
54 h 2.72986 -0.27076 -6.08745
55 h 2.61831 0.60661 -8.45347
56 h 1.38773 -0.68517 -8.19739
57 h 0.88595 1.04522 -8.21997
58 h 2.40589 -0.49699 4.26244
59
60

1				
2				
3	h	-1.63078	0.93154	4.82963
4	h	-2.06363	0.76740	2.34377
5	h	0.86152	0.15211	-0.70697
6	h	-1.64312	-0.56259	-5.36694
7	h	-2.03978	-1.57221	-3.91987
8	h	-2.49902	0.14404	-3.94036
9				
10				
11				

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

35

17	c	-2.40239	-4.39409	2.02309
18	c	-1.73785	-3.23073	2.44622
19	c	-1.06939	-2.44412	1.50734
20	c	-1.04986	-2.81312	0.13301
21	c	-1.72300	-4.00159	-0.26578
22	c	-2.39817	-4.78273	0.67158
23	o	-0.40429	-2.07096	-0.76627
24	c	-1.35411	-1.08888	-2.36933
25	o	-1.89157	-1.72774	-3.18496
26	n	-3.11322	-5.21902	3.01156
27	o	-3.68887	-6.23255	2.60511
28	n	-0.89523	-0.07151	-1.71647
29	c	-1.06614	1.31328	-2.14381
30	o	-1.67866	1.56157	-3.16948
31	c	-0.44273	2.26698	-1.21575
32	c	-0.58970	3.58169	-1.57271
33	o	-0.09056	4.58380	-0.84940
34	c	-0.31713	5.92323	-1.34107
35	c	0.33073	6.90055	-0.38033
36	c	0.29424	1.83379	0.02508
37	o	-3.09272	-4.84796	4.18910
38	h	-1.69941	-4.29093	-1.32811
39	h	-0.41574	-0.72228	-0.82918
40	h	0.69550	2.71764	0.56096
41	h	1.15064	1.16380	-0.21366
42	h	-0.36908	1.28332	0.73049
43	h	-1.14305	3.83978	-2.49653
44	h	0.11945	6.00812	-2.36301
45	h	-1.41543	6.09561	-1.41688
46	h	0.16964	7.94028	-0.73687
47	h	-0.10801	6.80753	0.63604
48	h	1.42468	6.72060	-0.30934
49	h	-2.92817	-5.70207	0.38303
50	h	-1.76279	-2.96383	3.51271
51	h	-0.53555	-1.53160	1.82052
52				
53				
54				

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

35

1				
2				
3	c	1.20004	-0.40966	3.63584
4	c	0.10496	-0.18106	4.48493
5	c	-1.06649	0.43730	4.01933
6	c	-1.14452	0.84180	2.68442
7	c	-0.05231	0.61956	1.81088
8	c	1.11745	-0.01574	2.29882
9	n	0.18915	-0.59921	5.89777
10	o	-0.79004	-0.38507	6.61598
11	o	-0.11891	1.02808	0.52446
12	o	1.23402	-1.13710	6.27246
13	c	-1.35191	0.25102	-0.60013
14	n	-0.80260	0.16398	-1.76974
15	c	0.48437	0.39581	-2.12520
16	c	0.88748	0.18007	-3.50585
17	c	2.31413	0.45151	-3.90011
18	o	-2.35937	0.02887	-0.01530
19	o	1.39933	0.80498	-1.30241
20	c	-0.06719	-0.25784	-4.38956
21	o	0.19875	-0.45544	-5.67889
22	c	-0.83889	-1.01978	-6.50806
23	c	-0.60725	-0.58402	-7.94246
24	h	1.95995	-0.19202	1.61085
25	h	-1.10096	-0.44914	-4.04334
26	h	-0.79251	-2.12881	-6.40965
27	h	-1.83139	-0.67995	-6.13329
28	h	-1.37352	-1.04300	-8.60340
29	h	-0.67499	0.52068	-8.03992
30	h	0.39500	-0.90739	-8.29599
31	h	2.09701	-0.89851	4.04226
32	h	-1.89700	0.59896	4.72145
33	h	-2.04471	1.33845	2.29577
34	h	0.87181	0.95255	-0.30500
35	h	2.48132	0.19892	-4.96608
36	h	2.57561	1.52159	-3.74341
37	h	3.01976	-0.13935	-3.27606
38				
39				
40				
41				
42				
43				
44				
45				
46	c	0.61848	-0.05891	4.30963
47	c	-0.70152	0.38973	4.14185
48	c	-1.15657	0.72160	2.86347
49	c	-0.29295	0.59542	1.74769
50	c	1.03341	0.13159	1.93889
51	c	1.49254	-0.18757	3.21806
52	o	-0.72486	0.92869	0.51190
53	n	1.10021	-0.40085	5.66197
54	o	2.26852	-0.78100	5.77241
55	o	0.30528	-0.28609	6.59739
56	c	-2.09027	-0.05994	-0.25973
57	o	-2.91537	-0.31357	0.55103
58	n	-1.80136	-0.20702	-1.51548
59				
60				

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

35

45				
46	c	0.61848	-0.05891	4.30963
47	c	-0.70152	0.38973	4.14185
48	c	-1.15657	0.72160	2.86347
49	c	-0.29295	0.59542	1.74769
50	c	1.03341	0.13159	1.93889
51	c	1.49254	-0.18757	3.21806
52	o	-0.72486	0.92869	0.51190
53	n	1.10021	-0.40085	5.66197
54	o	2.26852	-0.78100	5.77241
55	o	0.30528	-0.28609	6.59739
56	c	-2.09027	-0.05994	-0.25973
57	o	-2.91537	-0.31357	0.55103
58	n	-1.80136	-0.20702	-1.51548
59				
60				

1				
2				
3	c	-0.66325	0.11424	-2.16886
4	o	0.35330	0.70006	-1.60745
5	c	-0.60756	-0.23140	-3.58241
6	c	0.53406	0.11644	-4.25960
7	o	0.70475	-0.15557	-5.55341
8	c	1.93252	0.29611	-6.16413
9	c	1.95822	-0.18817	-7.60039
10	h	1.69677	0.02667	1.06509
11	c	-1.76559	-0.93735	-4.23536
12	h	1.35734	0.64046	-3.73815
13	h	1.96970	1.40882	-6.11038
14	h	2.79353	-0.10879	-5.58346
15	h	2.89265	0.15258	-8.09536
16	h	1.92192	-1.29765	-7.64578
17	h	1.09377	0.21535	-8.16965
18	h	2.51766	-0.54404	3.39435
19	h	-1.34785	0.48041	5.02662
20	h	-2.18142	1.08668	2.70597
21	h	0.04542	0.88903	-0.53315
22	h	-1.55709	-1.11922	-5.30876
23	h	-1.97005	-1.91247	-3.74126
24	h	-2.69890	-0.33958	-4.14860
25				
26				
27				

Product Complex EEZE

E(B3LYP/def2-TZVP)=-1064.425976133

35

32				
33	c	-0.86892	0.73392	2.10624
34	c	0.54963	0.69959	2.06736
35	c	1.27408	0.28159	3.18531
36	c	0.58880	-0.10284	4.34941
37	c	-0.81617	-0.07204	4.40881
38	c	-1.54001	0.34437	3.29278
39	n	1.35357	-0.54439	5.52483
40	o	0.71913	-0.86949	6.53270
41	o	-1.61598	1.12891	1.06047
42	o	2.58499	-0.56470	5.43426
43	o	-0.17887	1.43195	-1.15164
44	c	-0.39248	0.64736	-2.08926
45	c	0.39453	0.68477	-3.31804
46	c	1.48828	1.71258	-3.41255
47	n	-1.40834	-0.32786	-2.03560
48	c	-2.26510	-0.72664	-1.25131
49	o	-3.12623	-1.21979	-0.62421
50	c	0.11339	-0.20818	-4.31998
51	o	0.80041	-0.23437	-5.46218
52	c	0.38270	-1.18935	-6.46190
53	c	1.35307	-1.11840	-7.62460
54	h	1.07276	1.00910	1.14802
55	h	-0.70393	-0.94583	-4.20654
56	h	0.36926	-2.20599	-6.00537
57	h	-0.65460	-0.93814	-6.78351
58	h	1.04909	-1.84040	-8.41228
59				
60				

1
2
3 h 1.36485 -0.10023 -8.06886
4 h 2.38399 -1.37106 -7.29658
5 h 2.37301 0.24627 3.18019
6 h -1.31449 -0.37907 5.33959
7 h -2.64034 0.37875 3.30588
8 h -1.03394 1.34633 0.26157
9 h 1.98025 1.67714 -4.40470
10 h 1.08500 2.73533 -3.24489
11 h 2.25838 1.54629 -2.62666
12
13
14

15 Product Complex EEZE
16 E(B3LYP/def2-TZVP)=-1064.424492225
17

18 35
19

20 c 1.00777 -0.09672 4.01097
21 c -0.23114 0.51600 4.27128
22 c -0.98963 1.00574 3.20932
23 c -0.51995 0.88843 1.87671
24 c 0.73384 0.26860 1.63485
25 c 1.49372 -0.22081 2.69903
26 o -1.28956 1.38180 0.89121
27 n 1.80953 -0.61330 5.12977
28 o 2.89340 -1.14197 4.86368
29 o 1.35113 -0.48835 6.26921
30 c -3.14334 -0.26168 -0.85020
31 o -3.93351 -0.33531 0.01434
32 n -2.43580 -0.27313 -1.85317
33 c -1.15568 0.12464 -2.26987
34 o -0.39011 0.76615 -1.52828
35 c -0.83587 -0.28464 -3.63898
36 c 0.40200 0.09055 -4.09498
37 o 0.83495 -0.21182 -5.31799
38 c 2.15524 0.24817 -5.68300
39 c 2.46559 -0.25522 -7.07898
40 h 1.10076 0.17881 0.59972
41 c -1.81786 -1.06190 -4.47504
42 h 1.08240 0.66462 -3.43704
43 h 2.17025 1.36171 -5.63889
44 h 2.88854 -0.13939 -4.93872
45 h 3.48000 0.08078 -7.38245
46 h 2.43947 -1.36543 -7.11450
47 h 1.73181 0.13774 -7.81482
48 h 2.46801 -0.70439 2.53820
49 h -0.57588 0.59479 5.31232
50 h -1.96417 1.48904 3.37869
51 h -0.86473 1.22270 -0.01401
52 h -1.36532 -1.33938 -5.44848
53 h -2.14176 -1.99241 -3.95944
54 h -2.73869 -0.46970 -4.67550
55
56
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A convenient, high-yield synthesis of 1-substituted uracil and thymine derivatives

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ABSTRACT

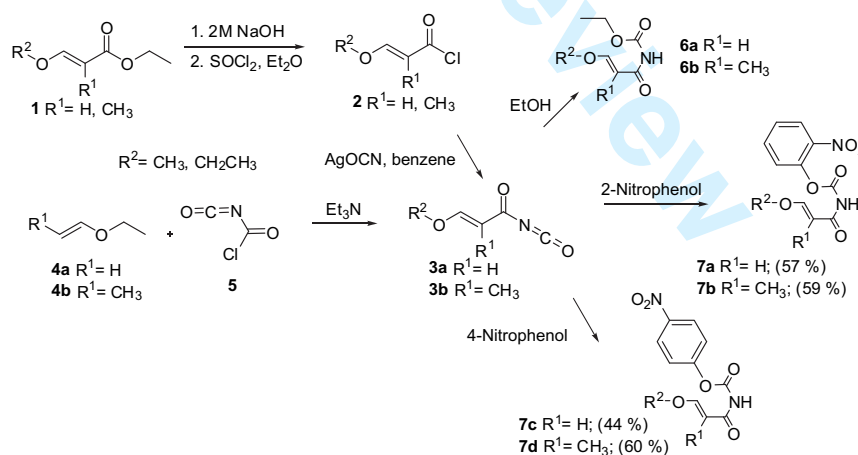
Novel reagents for the synthesis of 1-substituted uracil and thymine derivatives have been developed. The aminolysis of 2- or 4-nitrophenyl 3-ethoxyacryloylcarbamate and 3-ethoxy-2-methylacryloylcarbamate with a variety of primary amino derivatives proceeded smoothly under very mild reaction conditions 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 Hřebabecký.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**

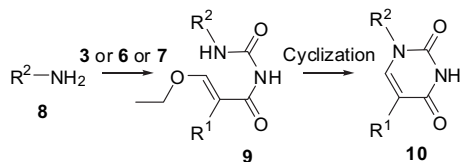
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(Scheme 2). Both basic (aqueous alkali or ammonia, tertiary amines in organic solvent) and acidic (organic or inorganic acids in either aqueous or organic solvents) conditions were described for the cy-



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 Hřebabecý'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 /85	a /97	82(30) ³	m /96	m /93	89(29) ³
	b /87	b /90	78	n /99	n /90	89(24) ⁴
	c /90	c /80	72	—	—	—
	d /88	d /98	86 (11) ²³	—	—	—
	e /88	e /99	87	o /82	o /95	77
	f /99	f /78	77 (40) ²⁴	p /78	p /96	75(18) ²⁴
	g /95	g /95	90 (15) ²⁵	—	—	—
	h /88	h /92	81	q /89	q /97	86
	i /87	i /98	85(69) ²⁶	r /63(76) ^a	r /97	61(45) ²⁷
	j /94	j /96	90 (63) ²⁸	s /87	s /99	86 (59) ²⁸
	k /87	k /84	73 (76) ²⁹	—	—	—
	l /87	l /96	83	—	—	—
	—	—	—	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.

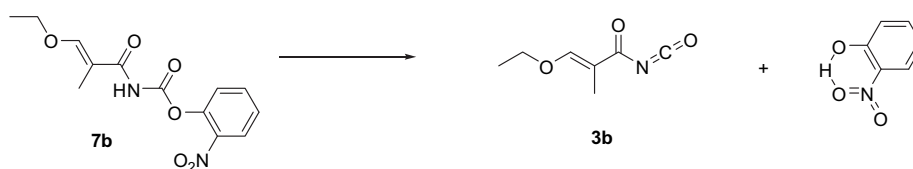
^a When **7d** was used, we obtained **9r** in 76% yield instead of a 64% one obtained with **7b**.

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 Hřebabecký'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

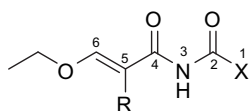
4.1. General

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 μm ; 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 $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_6$ (280.23) calcd: 51.43% C, 4.32% H, 10.00% N; found: 51.36% C, 4.33% H, 9.82% N. HRMS for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_6$ (M+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, $J(\text{CH}_3, \text{CH}_2)=7.1$, $\text{CH}_3\text{CH}_3\text{O}$), 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 $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_6$ (M+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, $J(\text{CH}_3, \text{CH}_2)=7.1$, $\text{CH}_3\text{CH}_3\text{O}$), 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 $\text{C}_9\text{H}_{16}\text{N}_4\text{O}_2$ (M+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, 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, 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 $\text{C}_9\text{H}_{19}\text{N}_2\text{O}_2$ (M+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, 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, $\text{CH}_3\text{O-DMTr}$), 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- $m\text{-C}_6\text{H}_4\text{-DMTr}$), 7.23 (2H, m, H- $p\text{-C}_6\text{H}_5\text{-DMTr}$), 7.29–7.36 (12H, m, H- $o\text{-C}_6\text{H}_4\text{-DMTr}$ and H- $m\text{-C}_6\text{H}_5\text{-DMTr}$), 7.44 and 7.47 (2×2H, 2×m, H- $o\text{-C}_6\text{H}_5\text{-DMTr}$). δ_{C} (125.7 MHz, 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 ($\text{CH}_3\text{O-DMTr}$), 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- $m\text{-C}_6\text{H}_4\text{-DMTr}$), 126.96 and 127.04 (C- $p\text{-C}_6\text{H}_5\text{-DMTr}$), 127.79 and 127.86 (C- $o\text{-C}_6\text{H}_5\text{-DMTr}$), 128.19 (C- $m\text{-C}_6\text{H}_5\text{-DMTr}$), 129.94, 129.99 and 130.05 (C- $o\text{-C}_6\text{H}_4\text{-DMTr}$), 136.30, 136.51 and 136.64 (C- $i\text{-C}_6\text{H}_4\text{-DMTr}$), 145.79 and 145.83 (C- $i\text{-C}_6\text{H}_5\text{-DMTr}$), 153.71 and 153.82 (CO), 158.44 and 158.53 (C- $p\text{-C}_6\text{H}_4\text{-DMTr}$). HRMS for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_5\text{Na}$ (M+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, 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. ν_{\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. ν_{\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. ν_{\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. ν_{\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. ν_{\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 $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$ (M+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 \times 1H, 2 \times 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 \times 1H, 2 \times 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 $\text{C}_{16}\text{H}_{27}\text{N}_3\text{O}_5\text{Na}$ (M+Na)⁺ calcd 364.1843, found 364.1842.

4.6.21. *1-(3S,4R)-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 \times 9H, 2 \times s, $(\text{CH}_3)_3\text{C}$), 1.80 and 1.82 (2 \times 3H, 2 \times 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 \times 1H, 2 \times 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 \times 1H, 2 \times dd, $J_{\text{gem}}=11.8$, $J(5'a, 4')=2.8$, H-5'a), 3.777 and 3.780 (2 \times 6H, 2 \times 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 \times 2H, 2 \times 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 \times 2H, 2 \times m, H- $o\text{-C}_6\text{H}_5\text{-DMTr}$), 7.53 and 7.63 (2 \times 1H, 2 \times 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 $\text{C}_{37}\text{H}_{45}\text{N}_3\text{O}_8\text{Na}$ (M+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, $J(1, 4')=7.8$, 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 $\text{C}_{13}\text{H}_{23}\text{N}_2\text{O}_3$ (M+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 $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ (M+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 $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ (M+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 (w), 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-((3*R*,4*S*)-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-((3*S*,4*S*)-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, 2.061 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. ν_{\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. ν_{\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. ν_{\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, 0.903 mmol) of white solid. ν_{\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. ν_{\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. ν_{\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, $J(CH_3,CH_2)=7.1$, CH₃CH₂O), 1.52 (3H, d, $J(CH_3,CH)=7.3$, CH₃), 4.13 (2H, m, CH₃CH₂O), 4.98 (1H, q, $J(CH,CH_3)=7.3$, 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-((3R,4S)-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. ν_{\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, $J(CH_3,6)=1.2$, CH₃), 4.46 (1H, m, H-1'), 7.06 (1H, q, $J(6,CH_3)=1.2$, 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. ν_{\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. ν_{\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 C₁₁H₁₇N₂O₃ (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 C₈H₁₁N₂O₄ (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 C₁₁H₁₁N₂O₂ (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 C₁₅H₁₃N₂O₂ (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 C₈H₁₃NO₄Na (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 Warren.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**

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3 recorded in commercial grade CDCl_3 (see Supporting Information) showed a mixture of at
4 least four compounds identified as 3-ethoxy-2-methylacryloylcarbamic acid (as the product of
5 reagent hydrolysis), 3-ethoxy-2-methylacryloylamide (i.e. the product of the decarboxylation
6 of the former compound), 2-nitrophenol and reagent **7b** (Scheme 3).
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14 Scheme 3. The decomposition of **7b** *via* hydrolysis and decarboxylation.
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17 To rule out the effect of water, which might be present in regular CDCl_3 , the ^1H NMR spectra
18 were recorded in dried CDCl_3 and a sealed NMR tube (see Experimental). The experiment has
19 again shown the decomposition of compound **7b**, and the final products of decomposition
20 were identified as acryloylisocyanate **3b** and 2-nitrophenol. Reagent **7b** was characterised by
21 NMR only when a high concentration of sample and a short measurement time were applied.
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26 To ascertain that acryloylisocyanate **3b** is the decomposition product, we allowed the
27 decomposed mixture to react with dry methanol, yielding methyl ester **12**, i.e. the same
28 product as that formed through the reaction of **7b** with methanol in the presence of Et_3N
29 (Scheme 4). In addition, isocyanate **3b** was identified by IR measured in dry CHCl_3 (the
30 characteristic band being at 2244 cm^{-1} for asymmetric stretching vibrations of the $-\text{NCO}$
31 group) and by ^{13}C NMR (with the characteristic chemical shift of $-\text{NCO}$ carbon at 130.47
32 ppm).
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42 Scheme 4. The chemical proof of **3b** structure.
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45 The rate of decomposition was estimated based on the ^1H NMR kinetic measurement in dry
46 CDCl_3 and sealed NMR tube at $25\text{ }^\circ\text{C}$. The concentrations of starting compounds and
47 decomposition product(s) were obtained by integration of several corresponding signals with
48 similar relaxation times. The rate constant for the irreversible first order kinetic model was
49 obtained from plots of the logarithm of the starting compound concentrations versus time,
50 while rate constant for the reversible first order kinetic model was obtained from plots of the
51 logarithm of the starting compound concentrations minus equilibrium concentration versus
52 time and from equilibrium constant. Experimental data for decomposition of **7b** fitted
53 irreversible reaction with first order kinetics (Table 1 and Supporting Information) with half
54 life ($t_{1/2}$) of about 18 minutes. The kinetics measurements were also performed for the other
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3 reagents, **7a**, **7c** and **7d**, and the results have been summarized in Table 1. The decomposition
4 of **7a** was reversible reaction with first order kinetics (Table 1 and Supporting Information),
5 while compounds **7c** and **7d** were stable and did not decompose at all.
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11 As arises from Table 1, the kinetic measurements demonstrate a surprisingly strong
12 dependence on the reagents and their structure. Reagents **7c** and **7d** (possessing a nitro group
13 in the *para* position) do not undergo any degradation. On the other hand, the derivatives with
14 the *ortho*-nitro group in nitrophenol moiety decompose readily, with the decomposition of the
15 **7b**-bearing methyl group in the acryloyl part of the molecule being approximately fifty times
16 faster than the decomposition of the **7a**-lacking methyl substituent. The different stability of
17 the reaction products reflected in the molecular structure was further explored by DFT
18 calculations.
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27 **Reaction mechanism of decomposition. Theoretical calculations.**

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29 We first optimised all sixteen planar geometries for each of **7a–d**, *viz.* all the possible
30 arrangements of four double or partial double bonds in the system (64 molecular geometries
31 in total) at the DFT(PBE)/def2-SVP level with the single-point energy calculated at the
32 DFT(B3LYP)/def2-TZVP level. The solvation effects and corrections to the ZPE energy,
33 enthalpy and entropy (using the ideal gas approximation) were included as well (for details,
34 see Experimental). The results of this extensive conformational search are summarised in
35 Tables S1–S5 (see Supporting Information). As can be seen in Tables S1–S4, the calculations
36 predict (in all cases) the most stable isomers to possess *trans*-configuration on the -C=C-
37 double bond. This fact has been corroborated experimentally by a missing NOE interaction
38 between the Me group and the proton on the double bond for **7a–b** or by a missing NOE
39 between the protons of the double bond for **7c–d**. At the same time we observe NOE between
40 protons of CH₂ group from EtO and H or CH₃ on double bond in alpha position to CO.
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50 With regard to the proposed reaction mechanism, we have also investigated the possible
51 isomers with the proton on either of the oxygens adjacent to the central -NH- group (these
52 calculations were carried out only for the most stable isomers). The results are also listed in
53 Tables S1–S4 (including various terms in overall Gibbs energies), and all twenty-four
54 structures of **7b** (assuming an *E* configuration on the -C=C- double bond) have been
55 schematically depicted in Fig. 1.
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5 Figure 1. The planar geometries of *E-7b* investigated by density functional theory
6 calculations.
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10 The calculations have shown that the 2NH-ZZZ conformer is the most stable structure for the
11 *keto*-tautomer of **7b** whereas 3OH-ZZE is the lowest energy *enol*-form of the same compound.
12 It can be noted that 3OH-ZZE geometry is nicely preorganised to form a six-membered
13 transition state with bifurcated hydrogen bonding.
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17 However, a rather surprising finding is the relatively small difference in energies between all
18 the studied isomers. Considering the planar models depicted in Fig. 1, some of the structures
19 would have been expected to have substantial intramolecular crowding. Even for such
20 structures (e.g. 2NH-ZEE, 2NH-EEE) the energy or free energy differences amount to only
21 ~15-25 kJ.mol⁻¹. This demonstrates a relatively high level of flexibility in the studied
22 molecules (the systems avoid crowding by adopting a helical form). Thus, we had to consider
23 several reaction pathways for the elimination reaction. The lowest saddle points and their
24 energies are summarised in Table 2 for all studied compounds (**7a-7d**) and for the proposed
25 reaction mechanism of degradation shown in Scheme 5. It can be mentioned that all saddle
26 points are characterized by a single imaginary frequency corresponding to the reactive
27 coordinate and are therefore true transition states for the studied reactions. By small changes
28 of the geometry in the direction of reactant and product we ascertained that it connects the
29 desired reactant and products structures (IRC-like calculation). A more complete listing of the
30 calculated values of activation barriers can be found in Tables S1-S4.
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49 Scheme 5. The degradation of **7b** – a proposed mechanism.
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53 Furthermore, the reaction coordinate with the structures of all the key points on the potential
54 energy surface is depicted in Figure 2.
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60 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-

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

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7 HR-MS for C₈H₁₃NO₄Na (M+H+Na)⁺ calcd 210.0742, found 210.0741.
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10 **Supporting Information** (see footnote on the first page of this article): Kinetics
11 measurements and computational data including .
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13

14 15 16 **Acknowledgments**

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

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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: $\Delta G_{\text{exp}}^{\ddagger} = RT[23.76 - \ln(k/T)]$).

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	k (hr ⁻¹)	$t_{1/2}$ (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

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