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Scheme_1.cdx Scheme_2.cdx Scheme_3.cdx	

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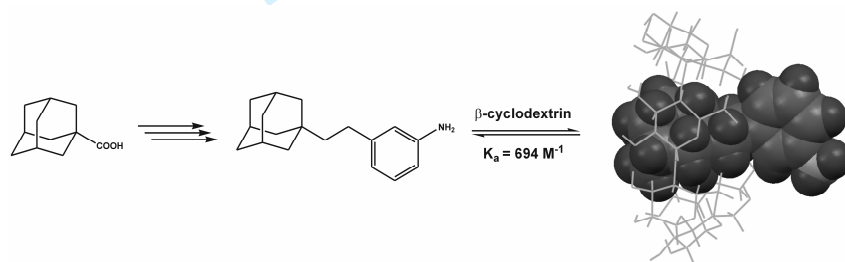
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## Novel Adamantane-Bearing Anilines and Properties of Their Supramolecular Complexes with $\beta$ -Cyclodextrin

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## Novel Adamantane-Bearing Anilines and Properties of Their Supramolecular Complexes with $\beta$ -Cyclodextrin

Several novel anilines bearing 1-adamantyl substituents that are useful for drug modification were synthesised from the corresponding 1-adamantyl (nitrophenyl) ketones. The host-guest systems of these prepared ligands with  $\beta$ -cyclodextrin were studied using ESI-MS, NMR spectroscopy, titration calorimetry, and semi-empirical calculations. The complexes with 1:1 stoichiometry were found to predominantly exist as pseudorotaxane-like threaded structures with the adamantane cage sitting deep in the cavity of  $\beta$ -cyclodextrin close to the wider rim. Such geometry was observed for all examined amines and is independent of their structure and/or presence of protic substituents.

Keywords: adamantane; amines; cyclodextrins; host-guest systems

### 1. Introduction

Since the first description of the antiviral activity of 1-adamantylamine in 1964,<sup>1</sup> various compounds containing the adamantane scaffold have been shown to exhibit antiviral,<sup>2</sup> anticancer<sup>3</sup> and antimicrobial<sup>4</sup> activities; such compounds have also been described as hypoglycaemic,<sup>5</sup> proapoptotic,<sup>6</sup> and neuroprotective<sup>7</sup> agents, as well as possible treatments for hypertension, vascular inflammation<sup>8</sup> and tuberculosis.<sup>9</sup>

Adamantane-bearing compounds can also serve as cannabinoid receptor ligands.<sup>10</sup>

This well-founded interest is related to a unique property of the adamantane cage that can improve the characteristics of biologically active compounds. As a result of its high lipophilicity, adamantane should increase the rate of transfer of a modified drug through cell membranes and thus facilitate the distribution of the drug. On the other hand, the formation of supramolecular complexes with  $\beta$ -cyclodextrin ( $\beta$ -CD)<sup>11</sup> significantly increases drug's solubility in water. Cyclodextrin drug carrier systems have been studied extensively in terms of solubility, bioavailability and stability.<sup>12</sup>

This attention has yielded several commercial pharmaceutical products based on cyclodextrin host-guest complexes.<sup>12b</sup> The adamantane-bearing amines are a suitable

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3 candidates for drug modification e.g. as a ligands in preclinically tested<sup>3b</sup> platinum  
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5 derivate LA-12 (Figure 1, left) or as a building blocks for displacement of C6  
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7 substituent in purvalanol-like promising anticancer drugs (Figure 1, right). However,  
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9 the steric hindrance of bulky adamantane may lead to attenuation of the desired  
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11 activity if the scaffold is introduced too close to the active site of the drug,<sup>13</sup> hence the  
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13 need for preparation and property investigation of new suitable adamantane-bearing  
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15 building blocks is justified.

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17 While inclusion complexes of  $\beta$ -CD with 1-adamantyl-based compounds have  
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19 been studied for a long time, previous efforts have focused on small ionic guests.<sup>14</sup>  
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21 Some structural data have also been published for more complex ligands.<sup>15</sup> In most of  
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23 these cases, the nature of the inclusion complexes is determined by the structure of  
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25 host and/or guest molecule. It is reasonable to suppose that the geometry and stability  
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27 of host-guest complexes are affected by substituents adjacent to the adamantane cage.  
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29 Therefore, we have prepared several new potential building blocks with modulated  
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31 polarity and variable linker length between the adamantane and benzene ring units.  
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33 The host-guest complexes of these prepared anilines and  $\beta$ -CD were investigated  
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35 using electrospray ionisation mass spectrometry (ESI-MS), <sup>1</sup>H and <sup>13</sup>C NMR  
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37 spectroscopy, and titration calorimetry.

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## 40 2. Results and Discussion

### 41 2.1. Synthesis of amines

42 The nitro intermediates were prepared following previously described procedures,  
43  
44 including the ketone preparation<sup>16</sup> and nitration with acetyl nitrate<sup>17</sup> shown in Scheme  
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46 1. Regioisomers were separated by column chromatography, and compounds 3–5  
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48 were used as starting materials for further reactions.  
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Aminoketones **6–8** were prepared in methanolic HCl solution using iron powder as a reducing agent. The iron powder used in this reaction was obtained from iron pentacarbonyl decomposition (purchased from commercial source); use of iron fillings or turnings led to considerably longer reaction times. Amines **6–8** are rather unstable at room temperature as a free base (but may be stored for several months at –10°C) and decompose to dark brown oily products within a few days. Unfortunately, transformation to their corresponding solid hydrochloride salts via introduction of dry gaseous hydrogen chloride into diethyl ether or hexane solution only provided oily, brownish products.

Aminoalcohols **13–15** were prepared from nitroketones in two steps. Selective reduction using NaBH<sub>4</sub> proved to be very effective in our case, and we obtained nitroalcohols **9–11** in excellent yields (~95%) in 30 min. Reduction of the nitro group was carried out using iron powder in a methanol/HCl (1/1, v/v; conc. HCl was used) mixture. Amines **13** and **14** were isolated either as free bases (pH adjustment followed by extraction) or directly as hydrochloride salts. Attempted preparation of aminoalcohol **15** in the same manner failed due to undesirable nucleophilic substitution, and methoxyamine **12** was isolated in 85% yield. Therefore, catalytic hydrogenation on Ra-Ni was employed in the preparation of amine **15** (Scheme 2). Attempts to prepare aminoalcohols from compounds **3–5** in one step using less selective reducing agents such as LiAlH<sub>4</sub> or H<sub>2</sub>/Ra-Ni were not successful, and complex mixtures were obtained.

Amines with non-polar hydrocarbon spacers between the adamantane and benzene ring moieties (**25–27**) were also prepared in two (via 1,3-dithianes) or three (via 1,3-dithiolanes) steps. This synthesis involved the formation of the corresponding *S,S*-acetals, followed by reduction of the nitro group by iron powder in alcohol/HCl



1  
2 mixture and reduction/desulphurisation with H<sub>2</sub> on Ra-Ni catalyst (Scheme 3). While  
3  
4 the yields of the first step were excellent (about 90% of isolated products **16–20**), the  
5  
6 following steps were accompanied by some difficulties. Nitrodithiane **18** was treated  
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8 with Ra-Ni in ethanol under hydrogen atmosphere and was successfully  
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10 desulphurised. The nitro group was also reduced under these conditions, but an  
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12 undesirable substitution occurred, and the corresponding *N*-ethyl derivative was  
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14 identified as the main product. Dithiane **16**, however, afforded required amine **27**  
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16 under the same conditions. Although the isolated yield was not excellent, no side  
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18 products were detected by either TLC or GC analysis. Due to the very poor solubility  
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20 of dithioacetals in hexane, reduction with H<sub>2</sub> could not be performed without the use  
21  
22 of a more polar solvent. We attempted the reduction of dithiane **18** in a  
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24 dioxane/hexane mixture (1/1, v/v), but under such conditions, the nitro group was  
25  
26 reduced to an amino group, while the dithiane ring did not react. As a result, the  
27  
28 corresponding aminodithiane derivative was isolated. Similarly, nitrodithiane **17**  
29  
30 afforded the corresponding aminodithiane in an ethanol/hexane reaction medium.  
31  
32 Thus, a two-step procedure was necessary for the smooth transformation of  
33  
34 nitrodithianes to the required amines. Iron in *i*PrOH/HCl and Ra-Ni in dioxane were  
35  
36 used for nitro group reduction and desulphurisation, respectively (Scheme 3).  
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38

### 39 2.2. ESI-MS analysis

40 Solutions of individual amines, as well their 1:1 mixtures with β-CD, were studied by  
41  
42 ESI-MS. The dominant ions corresponding to the amines were the pseudomolecular  
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44 ions [M+H]<sup>+</sup>, accompanying the signals at *m/z* values about two times as high  
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46 (exactly [2×(M+H)-1]<sup>+</sup> or [2×M+23]<sup>+</sup>). The latter ions were observed when a polar  
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48 functional group (oxo or hydroxy) was present in the amine molecule, as shown for  
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50 amine **13** in Figure 2a. These signals are assumed to be related to associates of dimer  
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2 linked via hydrogen bonds with a proton or sodium cation, respectively. The  
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4 formation of analogous dimers in the solid state has been observed for aminoalcohol  
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6 **15**.<sup>18</sup> In the amine/ $\beta$ -CD mixtures, the protonated amine and sodium adduct of  $\beta$ -CD,  
7  
8 as well as protonated  $\beta$ -CD·amine complex, were detected for all examined amines  
9  
10 (Table 1). Figure 2b shows a typical spectrum of an equimolar mixture of  $\beta$ -CD and  
11  
12 amine **27**. The tandem mass spectrum of the protonated complex showed a  
13  
14 characteristic fragmentation pattern, which confirms its identity. The ions at  $m/z$   
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16 1136, 974, 811, 649, and 487 resulted from the successive losses of amine and  
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18 glucose residues of the  $\beta$ -CD moiety (Figure 2c).  
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### 21 **2.3. The geometry of host-guest complexes**

22 The  $\beta$ -CD is a heptamer built up from glucopyranose units linked by  $\alpha$ -1,4-glycosidic  
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24 bonds with a very well-known structure<sup>19</sup> that it is often described as a doughnut with  
25  
26 rims of differing diameters. The larger diameter corresponds to the secondary rim  
27  
28 where secondary hydroxyl groups at C2 and C3 are located; primary hydroxyl groups  
29  
30 at C6 are placed on the opposite smaller primary rim due to the non-alternating  
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32 orientation of the glucose units. The interior of the cavity has steric constraints due to  
33  
34 H3 and H5 protruding into the cavity.<sup>14c</sup> Schematics with the relevant dimensions of  
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36  $\beta$ -CD and the prepared amines are displayed in Figure 3.  
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39 The internal diameter of the cavity is likely to be slightly smaller than the  
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41 diameter of the nearly ball-shaped adamantane moiety, which cannot pass through it  
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43 easily but still fit well the interior of the  $\beta$ -CD cavity. As a result, two distinct  
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45 complexes may form. The adamantane moiety can be located either at the primary rim  
46  
47 region or at the secondary rim region. In solution, a reasonable orientation of a short  
48  
49 and, in most cases, charged, substituent bound to adamantane is outside the  $\beta$ -CD  
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51 cavity.<sup>14c,15a</sup> Occupancy of the primary rim was observed only when the secondary  
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2 rim was blocked. Higher thermodynamic stabilities were calculated for complexes  
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4 with the adamantane unit sitting in the secondary rim.<sup>14c</sup> However, it is reasonable to  
5  
6 suppose that a non-polar substituent of appropriate length may thread through the  
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8 cavity of  $\beta$ -CD. Thus, four possible arrangements of 1:1 adamantane and  $\beta$ -CD  
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10 complexes should be considered. These arrangements are illustrated in Figure 4.

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12 All examined systems obey the fast exchange mode on the NMR time scale,  
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14 and thus only one set of signals was observed in all cases. Unfortunately, the shifts  
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16 observed upon complexation for the host and guest protons were small ( $\leq 10^{-2}$  ppm),  
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18 and determination of thermodynamic parameters from NMR titrations was generally  
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20 impossible. We observed reproducible complexation-induced shifts of well-resolved  
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23  $^1\text{H}$  NMR signals only for guest **14**. Although the Job plot for the H5 protons (Figure  
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25 S1) of the adamantane guest indicates a 1:1 stoichiometry, the analysis of titration  
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27 data was unsatisfactory. The fitting of experimental data to the theoretical rectangular  
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29 hyperbola using the standard least square regression procedure (MicroCal ORIGIN)  
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31 led to estimation of association constant being  $\sim 40 \text{ M}^{-1}$ , but the systematic discrepancy  
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33 between the theoretical data and best fit curve is too high (Figure S2). We attribute  
34  
35 this discrepancy to the influence of higher ordered, hydrogen-bonded complexes on  
36  
37 the observed chemical shifts. Nevertheless, the down-field shifts for guest protons  
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39 H4-6 (on the adamantane cage) and up-field shifts for H1, H2<sup>A,B</sup>, H14, and H16-18  
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41 were clearly observed (Figure S3).

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43 The observed nOe interactions between guest protons bound to the  
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45 adamantane cage (H4-6 for guest **14**) and inner hydrogen atoms of the cyclodextrin  
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47 cavity suggest the formation of an inclusion complex with adamantane positioned  
48  
49 inside the  $\beta$ -CD cavity. The observation of relatively strong nOe interactions between  
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51 guest protons H2 and  $\beta$ -CD-H5, together with weak (if any) interactions with  $\beta$ -CD-  
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2 H3, indicates the occupancy of the secondary rim of  $\beta$ -CD by the adamantane cage.

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4 Additionally, in the case of all hydroxylated guests (**13–15**), the nOe interactions

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6 between the inner  $\beta$ -CD hydrogen atoms and H6<sub>ax</sub> of adamantane are significantly

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8 weakened or completely missing from the spectra, whereas those with H6<sub>eq</sub> are

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10 observed. A portion of the NOESY spectrum of a mixture of amine **14** and  $\beta$ -

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12 cyclodextrin is shown in Figure 5 (left). However, <sup>1</sup>H NMR signals of  $\beta$ -CD inner

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14 protons H3 and protons H6 of the secondary rim were significantly overlapped in

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16 DMSO solution, and interpretation of the observed cross-peaks in standard NOESY

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18 spectrum became ambiguous. Therefore, we applied a 2D <sup>1</sup>H-<sup>13</sup>C gs-HMQC-NOESY

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20 experiment to increase the spectral resolution by employing a carbon frequency in an

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22 indirect dimension to assign the individual nOe contacts unequivocally. A schematic

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24 of the host-guest complex **7**- $\beta$ -CD and its observed interactions are depicted in Figure

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26 5 (middle and right). Both the observed interactions of adamantane protons H4 and

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28 H5 with  $\beta$ -CD carbons C3 and the absence of interactions between these same protons

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30 and  $\beta$ -CD carbons C5 indicate a positioning of the adamantane cage inside the  $\beta$ -CD

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32 cavity with bridgehead-substituted carbon C2 located close to the secondary rim of  $\beta$ -

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34 CD. In addition, observed interactions of phenyl protons H13 and H17 with  $\beta$ -CD

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36 carbons C6 and C5 support the proposed structural model in which the aromatic part

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38 of the guest protrudes from the secondary rim of  $\beta$ -CD (Figure 5). According to the

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40 notation in Figure 4, the observed arrangement of the examined host-guest complexes

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42 is assigned as SI.

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45 The binding properties of prepared guests **6-8**, **13-15**, and **25-27** were studied

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47 using isothermal titration calorimetry. All three aminoalcohols **13-15** exhibited

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49 additional heat release during both titration and dilution experiments; therefore,

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51 thermodynamic parameters were not able to be determined. This observation may be

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2 reasonably attributed to additional equilibria related to the dissociation of dimers  
3 and/or higher associates of guest molecules. In addition, dilution data of these  
4 aminoalcohols did not fit the theoretical curve using a simple “dissociation” model,  
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6 which takes into account only dimer dissociation. Therefore, it is reasonable to  
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8 assume additional equilibria involving higher-ordered associations. Anilines **25** and  
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10 **27** exhibited some exothermic process that very slowly equilibrated. This slow  
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12 equilibration thwarted the collection of usable data. The obtained values of binding  
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14 constants, enthalpies, entropies and stoichiometries of the complexes for  
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16 aminoketones **6-8** and amine **26** are listed in Table 2. For the typical raw data,  
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18 integrated values of heat released and the fitted curve for guest **7**, see Supplementary  
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20 data, Figure [S4](#).  
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#### 25 **2.4. Computation**

26 In order to support the structural conclusions about host-guest complexes formulated  
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28 from NMR analysis, we performed the modeling of these complexes for amines **14**  
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30 and **26** with  $\beta$ -CD at a semi-empirical level of theory. Semi-empirical PM3 [method](#)<sup>20</sup>  
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32 proved to perform well across a diverse group of macrocycles, particularly for CDs.<sup>21</sup>  
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34 Moreover, [the](#) PM3 method was selected among available semi-empiricals because of  
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36 its superiority to AM1 in dealing with hydrogen bonded molecules.<sup>22</sup> Although PM3  
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38 method chosen for our preliminary calculations appeared to be a powerful tool in  
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40 conformational studies of supramolecular systems, computed relative energies should  
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42 be handled with the full awareness of the weakness of semi-empiricals in relative  
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44 energy estimations and interpreted along with corroborating experimental data. An  
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46 exhaustive, up-to-date theoretical study may require equilibrium geometries generated  
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48 by PM3, combined with single point energy calculations at higher levels of theory,  
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50 preferably DFT which accounts thermochemistry better than semi-empirical methods,  
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as these sequential methods are reported in recent literature, and successfully applied for CDs.<sup>23</sup>

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A series of calculations, described in detail in the Experimental section, yielded geometries and energies for several examined positions. The most energetically favoured geometries for amines **14** and **26**, for both directions of their virtual threading through the  $\beta$ -CD cavity, are depicted in Figure 6, and selected geometric parameters and energies are collected in Table 2. In the case of amine **14**, the adamantane cage occupies the secondary or primary rim with distances of  $Cg1-Og$  being shorter than 0.16 nm, with the benzene ring positioned on the opposite side of the  $\beta$ -CD. In respect to the orientations defined in Figure 4, they may be called as SI and PI, respectively. In the case of amine **26**, the respective threading resulted in geometries with adamantane located close to the secondary rim with the  $Cg1-Og$  being shorter than 0.12 nm, i.e. SE and SI. For both examined amines, the complex with SI geometry was the most populated in the thermodynamic equilibrium.

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The calculations were performed for molecules *in vacuo*, neglecting the fact that complex formation might be driven by differences in solvation energies of the host-guest complex and its building blocks. Moreover, the large number of possible orientations of the  $\beta$ -CD's hydroxyl groups is beyond our consideration. Although only one initial conformation of the cyclodextrin was used for each minimisation, the method provides a consistent indicator of the hydrogen bond stabilisation effect as well. To assess the importance of hydrogen bonding in the complex formation, a modelling experiment was performed. Non-polar parent hydrocarbon (PH)<sup>24</sup> was virtually threaded through the  $\beta$ -CD's cavity in the same way as described above with the amines. Hence, we obtained analogous results for **PH** and amines **14** and **26**, as shown in Table 3. Although partial stabilisation of this complex geometry via

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intermolecular hydrogen bonds was expected, it is not clearly manifested here.

Therefore, we suggest only a small contribution of intermolecular H-bonds to the stabilisation of the complex in the gas phase.

### 3. Conclusions

Ten new anilines bearing adamantane with linkers of varying polarity and length were synthesised and fully characterised using spectral methods. The inclusion complexes of these anilines with  $\beta$ -CD were detected using ESI-ion trap MS, and their structures were determined by 2D NMR experiments in DMSO. In agreement with our experimental NMR data and molecular modelling, the most populated inclusion complex between  $\beta$ -CD and adamantane guests with a long, uncharged substituent may be characterised as a pseudorotaxane-like structure in which the adamantane group is sitting deep in the CD cavity close to the wider secondary rim of the  $\beta$ -CD and the substituent protrudes from the primary rim. Association constants of the prepared amines and  $\beta$ -CD were estimated to be on the order of  $10^2 \text{ M}^{-1}$  by isothermal calorimetric titrations. These binding properties allowed us to consider the use of these prepared amines in further research on drug modification.

### 4. Experimental Section

#### 4.1. General

All starting compounds, reagents and solvents were purchased from commercial sources in analytical quality and were used without further purification. Adamantane-1-carbonyl chloride<sup>16</sup> was prepared following a previously published procedure.

Melting points were measured on a Kofler block and are uncorrected. Elemental analyses (C, H, N, S) were performed on a Thermo Fisher Scientific Flash EA 1112.

Retention times were determined using TLC plates (Alugram Sil G/UV) from Machrey-Nagel and petroleum ether/ethyl acetate as mobile phase. Three

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2  
3 compositions of mobile phases were used (v/v): system a (1/1), system b (4/1) and  
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5 system c (8/1). NMR spectra were recorded on a Bruker Avance 500 spectrometer  
6  
7 operating at frequencies of 500.13 MHz ( $^1\text{H}$ ) and 125.77 MHz ( $^{13}\text{C}$ ) and a Bruker  
8  
9 Avance 300 spectrometer operating at frequencies of 300.13 MHz ( $^1\text{H}$ ) and 75.77  
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11 MHz ( $^{13}\text{C}$ ).  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR chemical shifts were referenced to the signal of solvent  
12  
13 ( $^1\text{H}$ :  $\delta(\text{residual CHCl}_3) = 7.27$  ppm,  $\delta(\text{residual DMSO-}d_5) = 2.50$  ppm;  $^{13}\text{C}$ :  
14  
15  $\delta(\text{CDCl}_3) = 77.23$  ppm,  $\delta(\text{DMSO-}d_6) = 39.52$  ppm). The mixing time for NOESY<sup>25</sup>  
16  
17 experiment was adjusted to 500 ms, and the spin-lock for ROESY was adjusted to 400  
18  
19 ms. The assignment of  $^1\text{H}$  signals for  $\beta$ -CD was described previously.<sup>19c</sup> The 2D  $^1\text{H}$ -  
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21  $^{13}\text{C}$  gs-HMQC-NOESY spectrum<sup>26</sup> was measured at resonance frequencies of 600.15  
22  
23 MHz ( $^1\text{H}$ ) and 150.67 MHz ( $^{13}\text{C}$ ). The HMQC step was adjusted for  $^1J_{\text{H-C}} = 145$  Hz  
24  
25 with a subsequent nOe transfer of 700 ms. The spectrum was recorded in phase-  
26  
27 sensitive mode using the echo-antiecho protocol.<sup>27</sup> The IR spectra were recorded in a  
28  
29 KBr disc with a Mattson 3000 FT-IR instrument. GC-MS analyses were run on a  
30  
31 Shimadzu QP-2010 instrument using a Supelco SLB-5ms (30 m, 0.25 mm) column.  
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33 Helium was employed as a carrier gas in a constant linear flow mode ( $38 \text{ cm}^3\text{s}^{-1}$ );  
34  
35  $100 \text{ }^\circ\text{C}/7 \text{ min}$ ,  $25 \text{ }^\circ\text{C}/\text{min}$  to  $250 \text{ }^\circ\text{C}$ , hold for the required time. Only peaks of relative  
36  
37 abundance exceeding 5% are listed. The electrospray mass spectra were recorded with  
38  
39 an Esquire LC ion-trap mass spectrometer (Bruker Daltonics, Bremen, Germany)  
40  
41 equipped with an ESI source. Sample solutions ( $8.8 \text{ }\mu\text{M}$  in methanol/water,  $1/1$ , v/v)  
42  
43 were introduced into the ion source at a flow rate of  $3 \text{ }\mu\text{L}/\text{min}$  via a metal capillary  
44  
45 held at high voltage ( $\pm 3.5 \text{ kV}$ ). The other instrumental conditions were as follows:  
46  
47 drying gas temperature,  $250 \text{ }^\circ\text{C}$ ; drying gas flow,  $5 \text{ dm}^3/\text{min}$ ; nebuliser pressure,  $41.37$   
48  
49 kPa. Nitrogen was used as both nebulising gas and drying gas. The nozzle-skimmer  
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51 potential and octopole potential were modified and optimised before each experiment.  
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Deleted: NOESY<sup>28</sup>Deleted: <sup>1</sup>Deleted: <sup>d</sup>Deleted: <sup>1</sup>Deleted: spectrum<sup>29</sup>Deleted: <sup>30</sup>



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Isothermal titration calorimetry measurements were done in a DMSO/H<sub>2</sub>O (3/1 v/v) solvent mixture using a VP-ITC MicroCal instrument at 30 °C. The concentrations of host in the cell and guest in microsyringe were approximately 7.0 mM and 0.6 mM, respectively. The raw experimental data were analysed using MicroCal ORIGIN software. The heats of dilution were taken into account for each guest compound. Data were fitted to a theoretical titration curve using the “one set of binding sites” model.

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#### 4.2. Quantum-Chemical Methods

All theoretical calculations were carried out using the SPARTAN'08 software package.<sup>28</sup> First, the initial geometries of amines **14** and **26** and  $\beta$ -CD were optimised with the PM3 method without imposing any symmetrical restrictions. A hypothetical parent hydrocarbon (**PH**), 1-(1-adamantyl)-2-phenylethane, was used as a non-polar reference to evaluate the effect of hydrogen bonding. This hypothetical parent was constructed and optimised using the same procedure as that used for the amines. The input geometry for the optimisation of  $\beta$ -CD was based on available crystallographic data determined by XRD.<sup>19b</sup> Initial approximations of amine-cyclodextrin complexes were then constructed using the optimised structures of both host and guest molecules. As in the case of their constituents, no restrictions were imposed on the complexes. To characterise the mutual orientations of the molecules, the following values were defined: the centre of mass of the four bridgehead carbons in adamantane skeleton (*Cg1*), the centre of mass of the seven glycosidic oxygen atoms in  $\beta$ -cyclodextrin (*Og*), centre of mass of the six carbons of the benzene ring (*Cg2*), and the best least squares plane of the seven glycosidic oxygen atoms in  $\beta$ -cyclodextrin (*P*). The sign in the half-space according to *P* was defined to be positive close to wider secondary rim and negative close to narrower primary rim. Initially, the amine

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2 was positioned along the molecular sevenfold axis of  $\beta$ -CD at eleven  $Cg1-Og$   
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4 distances ranging from 1.0 to  $-1.0$  nm in increments of 0.2 nm. The resulting  
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6 geometries were optimised. These optimised geometries represent the sequential local  
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8 minima for an amine passing through the CD cavity. The stabilisation energy of  
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10 complex formation was calculated as the difference between the energy of the  
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12 complex and the sum of energies of the guest and host calculated independently. The  
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14 geometry with the absolute minimum energy could in this way be described as the  
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16 geometry of inclusion complex. On the other hand, the rotation of the guest molecule  
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18 within the CD's cavity was not tested, as it is known that the optimisation process  
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20 automatically finds the best relative rotational orientation of the guest and host  
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22 molecules.<sup>29</sup> Under real condition, one could expect water filled central cavity in  
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24 CD's that must be displaced if a guest is to enter which would stabilise any interaction  
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26 due to hydrophobic effects. Therefore it is expected that basic considerations for this  
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28 virtual experiment are not compromised by neglecting of water molecules in  
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30 calculations. Because both the CD and the amine have non-equivalent sides following  
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32 the threading route, two distinct threading processes must be performed with each  
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34 amine. It was decided to arrange the threading process as adamantane-on into the  
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36 secondary and primary rim of the CD, respectively.  
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#### 4.3. General procedure for nitro ketones reduction to amino ketones 6-8

40 The ketone (1.05 mmol) was dissolved in methanol (30 mL) and 6 mL of  
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42 hydrochloric acid/water (v/v, 1/1) was added. Into the refluxed and well stirred  
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44 mixture a portions of an iron powder (2.33 mmol) were added successively unless  
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46 TLC performed after disappearing of each iron portion indicated the consumption of  
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48 all starting material. The mixture was poured onto a 5% solution of NaOH (40 mL)  
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50 and extracted several times with diethyl ether. Combined organic layers were washed  
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with brine and dried over sodium sulphate. The crude product was obtained after evaporation of the solvent in vacuo.

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4.3.1. *1-Adamantyl-(4-aminophenyl)methanone (6)* was purified by column chromatography (silica gel, system a) to yield 257 mg (96%) of a yellow crystalline powder. Mp 79–81 °C,  $R_f$  0.17 (system b), anal. calcd for  $C_{17}H_{21}NO$ : C, 79.96%; H, 8.29%; N 5.49%; found C, 80.05%; H, 8.12%; N, 5.63%.  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.78 (m, 6H,  $CH_2(Ad)$ ), 2.07 (m, 9H,  $CH_2+CH(Ad)$ ), 6.69 (d,  $J=8.6$  Hz, 2H, Ph), 7.72 (d,  $J=8.6$  Hz, 2H, Ph) ppm.  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  28.6 (CH), 37.0 ( $CH_2$ ), 39.9 ( $CH_2$ ), 46.9 (C), 114.4 (CH), 129.3 (C), 131.0 (CH), 148.2 (C), 206.5 (CO) ppm. IR (KBr): 3469 (m), 3347 (s), 2898 (s), 2847 (m), 1629 (s), 1586 (s), 1557 (m), 1517 (w), 1442 (m), 1322 (m), 1271 (s), 1241 (m), 1171 (s), 1112 (m), 986 (w), 929 (w), 841 (m), 751 (w), 643 (w), 614 (m), 511 (w)  $cm^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 65 (8), 79 (9), 92 (9), 93 (7), 120 (100), 121 (8), 135 (11), 255 ( $M^+$ , 8).

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4.3.2. *1-Adamantyl-(3-aminophenyl)methanone (7)* was purified by column chromatography (silica gel, system a) to yield 236 mg (88%) of a colourless crystalline powder. Mp 97–100 °C,  $R_f$  0.20 (system b), anal. calcd for  $C_{17}H_{21}NO$ : C, 79.96%; H, 8.29%; N, 5.49%; found C, 79.89%; H, 8.35%; N, 5.37%.  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.75 (m, 6H,  $CH_2(Ad)$ ), 1.99 (m, 6H,  $CH_2(Ad)$ ), 2.07 (m, 3H,  $CH(Ad)$ ), 3.73 (bs, 2H,  $NH_2$ ), 6.72–6.77 (m, 2H, Ph), 6.91 (d,  $J=7.6$  Hz, 1H, Ph), 7.16 (t,  $J=7.6$  Hz, 1H, Ph) ppm.  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  28.4 (CH), 36.8 ( $CH_2$ ), 39.3 ( $CH_2$ ), 47.1 (C), 113.7 (CH), 116.8 (CH), 117.3 (CH), 128.9 (CH), 141.2 (C), 146.3 (C), 210.9 (CO) ppm. IR (KBr): 3474 (m), 3381 (s), 2900 (s), 2850 (m), 1662 (s), 1626 (m), 1593 (m), 1494 (m), 1446 (m), 1321 (m), 1295 (w), 1219 (m), 1180 (w), 991 (w), 793 (w), 731 (m), 682 (w), 649 (w)  $cm^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (8), 55 (6), 65 (13), 67

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(9), 77 (8), 79 (24), 81 (7), 91 (7), 92 (18), 93 (23), 107 (12), 120 (20), 135 (100), 136 (11), 227 (6), 255 ( $M^+$ , 24), 256 (5).

4.3.3. 2-(1-Adamantyl)-1-(3-aminophenyl)ethanone (**8**) was purified by column chromatography (silica gel, system b) to yield 289 mg (92%) of a pale orange crystalline powder. Mp 66–68 °C,  $R_f$  0.25 (system c), anal. calcd for  $C_{18}H_{23}NO$ : C, 80.26%; H, 8.61%; N, 5.20%; found C, 80.11%; H, 8.49%; N, 5.23%.  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.65 (m, 12H,  $CH_2(Ad)$ ), 1.95 (m, 3H,  $CH(Ad)$ ), 2.67 (s, 2H,  $CH_2CO$ ), 3.80 (s, 2H,  $NH_2$ ), 6.86 (d, 1H,  $J=6.9$  Hz, Ph), 7.20–7.33 (m, 3H, Ph) ppm.  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  29.0 (CH), 34.1 (C), 37.0 ( $CH_2$ ), 43.2 ( $CH_2$ ), 51.5 ( $CH_2$ ), 114.3 (CH), 119.3 (CH), 119.5 (CH), 129.4 (CH), 140.4 (C), 146.8 (C), 200.7 (CO) ppm. IR (KBr): 3459 (m), 3405 (m), 3328 (m), 2899 (s), 2846 (s), 1660 (s), 1627 (m), 1595 (m), 1453 (m), 1326 (m), 1287 (m), 1197 (w), 1162 (w), 1143 (w), 1096 (w), 991 (w), 903 (w), 884 (w), 777 (w), 691 (w), 677 (w)  $cm^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (8), 55 (5), 65 (18), 77 (7), 79 (12), 91 (10), 92 (42), 93 (19), 106 (6), 107 (10), 120 (100), 121 (14), 135 (20), 241 (5), 251 (6), 269 ( $M^+$ , 51), 270 (10).

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#### 4.4. General procedure for nitro ketones reduction to nitro alcohols 9–11

The corresponding ketone (0.84 mmol) was dissolved in warm ethanol (5 mL) and solution was cooled in ice bath. A small portion of starting material formed a soft precipitate. The sodium borohydride (40 mg, 1.04 mmol) was added into this dispersion in one portion at 0 °C. The reaction mixture was vigorously stirred and temperature was allowed to reach 20 °C. After the consumption of all starting material (according to TLC), the mixture was poured onto 1M HCl (10 mL) and a pale yellow solid precipitated. Mixture was extracted twice with diethyl ether (10 mL),

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collected organic portions were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Crude product was obtained after removing of the solvent in vacuo.

4.4.1. *1-Adamantyl-(4-nitrophenyl)methanol (9)* was purified by crystallization from

methanol to yield 233 mg (96%) of a pale yellow crystals. Mp 191–192 °C, R<sub>f</sub> 0.11

(system b), anal. calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: C, 71.06%; H, 7.37%; N, 4.87%; O, 16.70;

found C, 71.34%; H, 7.45%; N, 4.98%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.47–1.72 (m, 12H,

CH<sub>2</sub>(Ad)), 2.01 (m, 4H, CH(Ad), OH), 4.33 (s, 1H, CHOH), 7.44 (d, *J*=8.1 Hz, 2H,

Ph), 8.18 (d, *J*=8.5 Hz, 2H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 28.4 (CH), 37.1 (CH<sub>2</sub>),

37.7 (C), 38.3 (CH<sub>2</sub>), 82.3 (CH), 122.8 (CH), 128.8 (CH), 147.5 (C), 148.8 (C) ppm.

IR (KBr): 3565 (s), 3112 (w), 3081 (w), 2908 (s), 2848 (s), 1600 (m), 1506 (s), 1450

(w), 1346 (s), 1312 (m), 1216 (w), 1168 (w), 1105 (m), 1038 (m), 977 (w), 938 (w),

855 (m), 830 (w), 800 (w), 760 (w), 720 (s), 701 (w), 637 (w), 740 (m) cm<sup>-1</sup>. GC-MS

(EI, 70eV); *m/z* (%): 41 (8), 44 (14), 55 (6), 67 (8), 77 (8), 79 (18), 91 (5), 93 (17),

107 (10), 121 (6), 122 (14), 135 (100), 136 (12), 287 (M<sup>+</sup>, 4).

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4.4.2. *1-Adamantyl-(3-nitrophenyl)methanol (10)* was purified by column

chromatography (silica gel, system b) to yield 234 mg (97%) of a colourless

crystalline powder. Mp 104–106 °C, R<sub>f</sub> 0.20 (system b), anal. calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: C,

71.06%; H, 7.37%; N, 4.87%; found C, 70.83%; H, 7.18%; N, 4.55%. <sup>1</sup>H NMR

(CDCl<sub>3</sub>): δ 1.27–1.71 (m, 12H, CH<sub>2</sub>(Ad)), 1.99 (m, 3H, CH(Ad)), 2.10 (s, 1H, OH),

4.33 (s, 1H, CHOH), 7.49 (m, 1H, Ph), 7.59 (m, 1H, Ph), 8.12 (m, 2H, Ph) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 28.9 (CH), 32.9 (C), 37.2 (CH<sub>2</sub>), 43.3 (CH<sub>2</sub>), 54.7 (CH<sub>2</sub>), 70.3

(CH), 120.9 (CH), 122.4 (CH), 129.6 (CH), 132.1 (CH), 148.6 (C), 149.0 (C) ppm.

IR (KBr): 3543 (m), 3432 (m), 3106 (w), 3092 (w), 2906 (s), 2848 (s), 1525 (s), 1475

(w), 1448 (w), 1349 (s), 1312 (w), 1286 (w), 1194 (w), 1126 (w), 1088 (w), 1036 (m),  
 1021 (m), 982 (w), 930 (w), 909 (w), 896 (w), 813 (m), 722 (m), 693 (m), 661 (w),  
 618 (w)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (10), 55 (7), 67 (10), 77 (13), 78 (5),  
 79 (26), 81 (6), 91 (7), 93 (22), 105 (5), 107 (12), 135 (100), 136 (11).

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4.4.3. 2-(1-Adamantyl)-1-(3-nitrophenyl)ethanol (**11**) was purified by column  
 chromatography (silica gel, system c) to yield 220 mg (87%) of a colourless  
 crystalline powder. Mp 68–69 °C,  $R_f$  0.51 (system c), anal. calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_3$ : C,  
 71.73%; H, 7.69%; N, 4.65%; found C, 71.56%; H, 7.44%; N, 4.83%.  $^1\text{H}$  NMR  
 ( $\text{CDCl}_3$ ):  $\delta$  1.50 (d,  $J=2.6$ , 1H,  $\text{AdCH}^{\text{A}}\text{H}^{\text{B}}$ ), 1.59–1.79 (m, 12H,  $\text{CH}_2(\text{Ad})$ ), 1.88 (d,  
 $J=3.6$  Hz, 1H,  $\text{AdCH}^{\text{A}}\text{H}^{\text{B}}$ ), 2.02 (m, 3H,  $\text{CH}(\text{Ad})$ ), 5.05 (m, 1H,  $\text{PhCHOH}$ ), 7.52 (t,  
 $J=7.9$  Hz, 1H, Ph), 7.70 (d,  $J=7.6$  Hz, 1H, Ph), 8.13 (d,  $J=8.3$  Hz, 1H, Ph), 8.23 (s,  
 1H, Ph) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.9 (CH), 32.9 (C), 37.2 ( $\text{CH}_2$ ), 43.3 ( $\text{CH}_2$ ), 54.7  
 ( $\text{CH}_2$ ), 70.3 (CH), 120.9 (CH), 122.4 (CH), 129.6 (CH), 132.1 (CH), 148.6 (C), 149.0  
 (C) ppm. IR (KBr): 3380 (bs), 3090 (w), 3072 (w), 2899 (s), 2845 (s), 1525 (s), 1445  
 (m), 1349 (s), 1314 (w), 1199 (w), 1160 (w), 1103 (m), 1066 (m), 1014 (w), 969 (w),  
 827 (w), 802 (w), 740 (m), 722 (m), 698 (m), 676 (m)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$   
 (%): 41(17), 43(5), 53(5), 55(12), 65(5), 67(22), 69(7), 77(21), 78(11), 79(35), 80(5),  
 81(21), 91(20), 92(11), 93(43), 94(8), 95(6), 105(13), 106(8), 107(28), 121(8), 134(6),  
 135(100), 136(14), 149(58), 150(15), 152(22), 266(17), 283(14).

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#### 4.5. General procedure for nitro alcohols reduction to amino alcohols 12-15

The alcohols **13** and **14** and methoxy compound **12** were prepared from corresponding  
 nitro alcohols in the same way as the ketones **6–8**.

Deleted: Compound **15** was prepared in dioxane according the same procedure as **27**.

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4.5.1. 4-[1-Adamantyl(methoxy)methyl]anilinium chloride (**12·HCl**) crystallised as the hydrochloride salt directly from reaction mixture and no further purification was necessary. Yield: 275 mg (85%) of a gold-yellow plate crystals. Mp >350 °C, R<sub>f</sub>(free base) 0.27 (system b), anal. calcd for C<sub>18</sub>H<sub>26</sub>ClNO: C, 70.22%; H, 8.51%; N, 4.55%; found C, 69.94%; H, 8.37%; N, 4.75%. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.34–1.60 (m, 12H, CH<sub>2</sub>(Ad)), 1.89 (m, 3H, CH(Ad)), 3.08 (s, 3H, OCH<sub>3</sub>), 3.71 (s, 1H, CHOCH<sub>3</sub>), 7.27–7.36 (m, 4H, Ph), 10.28 (bs, 3H, NH<sub>3</sub><sup>+</sup>) ppm. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 27.5 (CH), 36.5 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 56.9 (CH<sub>3</sub>), 90.8 (CH), 122.0 (CH), 129.3 (CH), 131.0 (C), 137.8 (C) ppm. IR (KBr): 3437 (bs), 2905 (s), 2847 (s), 2562 (s), 1625 (m), 1578 (m), 1556 (m), 1507 (s), 1452 (m), 1360 (w), 1347 (w), 1316 (w), 1241 (w), 1175 (w), 1133 (w), 1085 (s), 997 (w), 826 (w), 529 (m) cm<sup>-1</sup>. GC-MS (IE, 70eV); m/z (%): 120 (7), 121 (6), 136 (100), 137 (9), 271 (M<sup>+</sup>, 2).

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4.5.2. 1-Adamantyl-(3-aminophenyl)methanol (**13**) Crude material was purified by column chromatography (silica gel, system a) to yield 254 mg (94%) of a pale yellow crystalline powder. Mp 137–139 °C, R<sub>f</sub> 0.11 (system b), anal. calcd for C<sub>17</sub>H<sub>23</sub>NO: C, 79.33%; H, 9.01%; N, 5.44%; found C, 79.57%; H, 9.15%; N, 5.72%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.49–1.66 (m, 12H, CH<sub>2</sub>(Ad)), 1.97 (m, 3H, CH(Ad)), 3.62 (bs, 2H, NH<sub>2</sub>), 4.12 (s, 1H, CHOH), 6.60–6.67 (m, 3H, Ph), 7.10 (t, *J*=7.6 Hz, 1H, Ph) ppm. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.37–1.63 (m, 12H, CH<sub>2</sub>(Ad)), 1.89 (m, 3H, CH(Ad)), 3.86 (d, *J*=3.8 Hz, 1H, CHOH), 4.77 (d, *J*=3.8 Hz, 1H, CHOH), 4.85 (s, 2H, NH<sub>2</sub>), 6.34–6.41 (m, 2H, Ph), 6.46 (s, 1H, Ph), 6.89 (t, *J*=7.6 Hz, 1H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 28.6 (CH), 29.9 (C), 37.3 (CH<sub>2</sub>), 38.5 (CH<sub>2</sub>), 83.2 (CH), 114.3 (CH), 114.8 (CH), 118.7 (CH), 128.5 (CH), 142.8 (C), 145.9 (C) ppm. IR (KBr): 3394 (m), 2901 (s), 2847 (m), 2359 (w), 1606 (m), 1490 (w), 1457 (m), 1302 (w), 1125 (w), 1036 (m), 885 (w), 750

(m), 730 (m), 700 (m), 667 (w), 585 (w), 418 (w)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (8), 55 (7), 65 (5), 67 (10), 77 (16), 79 (24), 81 (7), 91 (6), 92 (5), 93 (25), 94 (17), 107 (13), 120 (6), 121 (54), 122 (13), 135 (100), 136 (11), 257 ( $M^+$ , 20), 258 (4).

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4.5.3. 2-(1-Adamantyl)-1-(3-aminophenyl)ethanol (**14**) Crude material was purified by washing with hexane to yield 234 mg (82%) of a colourless crystalline powder. Mp

142–145 °C,  $R_f$  0.57 (system a), anal. calcd for  $C_{18}H_{25}NO$ : C, 79.66%; H, 9.28%; N,

5.16%; found C, 79.73%; H, 9.52%; N, 5.38%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.50 (d,  $J=2.6$

Hz, 1H,  $\text{AdCH}^A\text{H}^B$ ), 1.59–1.79 (m, 12H,  $\text{CH}_2(\text{Ad})$ ), 1.88 (d,  $J=3.6$  Hz, 1H,

$\text{AdCH}^A\text{H}^B$ ), 2.02 (m, 3H,  $\text{CH}(\text{Ad})$ ), 5.05 (m, 1H,  $\text{PhCHOH}$ ), 7.52 (t,  $J=7.9$  Hz, 1H,

Ph), 7.70 (d,  $J=7.6$  Hz, 1H, Ph), 8.13 (d,  $J=8.3$  Hz, 1H, Ph), 8.23 (s, 1H, Ph) ppm.

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.9 (CH), 32.9 (C), 37.2 ( $\text{CH}_2$ ), 43.3 ( $\text{CH}_2$ ), 54.7 ( $\text{CH}_2$ ), 70.3

(CH), 120.9 (CH), 122.4 (CH), 129.6 (CH), 132.1 (CH), 148.6 (C), 149.0 (C) ppm.

IR (KBr): 3380 (bs), 3090 (w), 3072 (w), 2899 (s), 2845 (s), 1525 (s), 1445 (m), 1349

(s), 1314 (w), 1199 (w), 1160 (w), 1103 (m), 1066 (m), 1014 (w), 969 (w), 827 (w),

802 (w), 740 (m), 722 (m), 698 (m), 676 (m)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (8), 55 (5), 65 (5), 67 (7), 77 (17), 79 (11), 81 (5), 91 (7), 92 (5), 93 (15), 94 (72), 95 (7), 107 (6), 120 (6), 121 (20), 122 (100), 123 (9), 135 (7), 253 (5), 271 ( $M^+$ , 28), 272 (6).

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4.5.4. 1-Adamantyl-(4-aminophenyl)methanol (**15**) The nitroalcohol **9** (259 mg, 0.90 mmol) was dissolved in ethanol (40 mL) under  $\text{H}_2$  atmosphere and large excess of Ra-Ni was added portionwise until starting material disappeared. Ra-Ni was filtered off, the filtrate was diluted with water and extracted several times with diethyl ether. Collected organic portions were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and evaporated



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3 | in vacuo. Crude material was purified by column chromatography (silica gel, system  
4 | a) to yield 227 mg (98%) of a pale yellow crystalline powder. Mp 143–146 °C, R<sub>f</sub>  
5 | 0.41 (system a), anal. calcd for C<sub>17</sub>H<sub>23</sub>NO: C, 79.33%; H, 9.01%; N, 5.44%; found C,  
6 | 79.09%; H, 9.23%; N, 5.28%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.48–1.67 (m, 12H, CH<sub>2</sub>(Ad)),  
7 |  
8 | 1.97 (m, 3H, CH(Ad)), 3.53 (bs, 2H, NH<sub>2</sub>), 4.11 (s, 1H, CHOH), 6.64 (d, J=8.3 Hz,  
9 | 2H, Ph), 7.06 (d, J=8.1 Hz, 2H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 28.8 (CH), 29.9 (C),  
10 | 37.5 (CH<sub>2</sub>), 38.5 (CH<sub>2</sub>), 83.1 (CH), 114.5 (CH), 128.9 (CH), 131.8 (C), 145.8 (C)  
11 | ppm. IR (KBr): 3378 (m), 2905 (s), 2847 (m), 1615 (m), 1514 (m), 1447 (w), 1265  
12 | (m), 1175 (w), 1128 (w), 1046 (m), 844 (w), 811 (w), 572 (m), 535 (w), 481 (w) cm<sup>-1</sup>.  
13 | GC-MS (EI, 70eV); m/z (%): 77 (9), 79 (7), 93 (7), 94 (12), 120 (9), 121 (38), 122  
14 | (100), 123 (8), 135 (5), 257 (M<sup>+</sup>, 4).

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#### 4.6. General procedures for nitrodithianes 16-18 and nitrodithiolanes 19, 20

##### formation

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32 The ketone (0.35 mmol) was dissolved in dichloromethane (2 mL) and corresponding  
33 dithiol (1,2-ethanedithiol or 1,3-propanedithiol; 0.55 mmol) was added. The solution  
34 was cooled in ice bath to 0 °C and stirred for 30 min. After this period, boron  
35 trifluoride—diethyl ether (1.00 mmol) was added dropwise and the mixture was  
36 stirred at room temperature until TLC indicated complete disappearing of the starting  
37 material. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed three times with  
38 5% solution of NaOH (10 mL). The organic layer was washed twice with brine, dried  
39 over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo.

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51 4.6.1. 2-(1-Adamantyl)-2-(3-nitrophenyl)-1,3-dithiane (**16**) was purified by  
52 crystallisation from hexane/CH<sub>2</sub>Cl<sub>2</sub> to yield 121 mg (92%) of yellow needles.  
53  
54

Mp 191–193 °C, R<sub>f</sub> 0.42 (system c), anal. calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>2</sub>S<sub>2</sub>: C, 63.96%; H, 6.71%; N, 3.73%; S, 17.08%; found C, 64.23%; H, 6.55%; N, 3.37%; S, 17.12%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.58 (m, 6H, CH<sub>2</sub>(Ad)), 1.83 (m, 8H, CH<sub>2</sub>(Ad), SCH<sub>2</sub>CH<sub>2</sub>), 1.97 (m, 3H, CH(Ad)), 2.45 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 2.67 (m, 1H, SCH<sup>C</sup>), 2.71 (m, 1H, SCH<sup>D</sup>), 7.57 (t, *J*=7.9 Hz, 1H, Ph), 8.15 (d, *J*=8.3 Hz, 1H, Ph), 8.33 (d, *J*=7.9 Hz, 1H, Ph), 8.85 (s, 1H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 25.4 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 28.9 (CH), 36.8 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 41.7 (C), 70.2 (C), 122.0 (CH), 127.4 (CH), 128.7 (CH), 138.6 (CH), 141.0 (C), 148.7 (C) ppm. IR (KBr): 2904 (s), 2846 (s), 1521 (s), 1469 (w), 1447 (w), 1420 (w), 1351 (s), 1310 (w), 1273 (w), 1172 (w), 1093 (w), 1010 (w), 979 (w), 940 (w), 892 (w), 813 (w), 787 (w), 726 (m), 694 (m) cm<sup>-1</sup>. GC-MS (EI, 70eV); m/z (%): 41 (11), 55 (5), 67 (8), 77 (6), 79 (20), 81 (5), 91 (6), 93 (17), 107 (10), 120 (5), 135 (100), 136 (12), 224 (43), 225 (6), 240 (10), 375 (M<sup>+</sup>, 3).

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4.6.2. 2-(1-Adamantyl)-2-(4-nitrophenyl)-1,3-dithiane (**17**) was purified by crystallisation from hexane/CH<sub>2</sub>Cl<sub>2</sub> to yield 120 mg (91%) of yellow needles.

Mp 218–220 °C, R<sub>f</sub> 0.51 (system b), anal. calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>2</sub>S<sub>2</sub>: C, 63.96%; H, 6.71%; N, 3.73%; S, 17.08%; found C, 63.84%; H, 6.52%; N, 3.46%; S, 16.95%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.57 (m, 6H, CH<sub>2</sub>(Ad)), 1.83 (m, 8H, CH<sub>2</sub>(Ad), SCH<sub>2</sub>CH<sub>2</sub>), 1.97 (m, 3H, CH(Ad)), 2.46 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 2.67 (m, 1H, SCH<sup>C</sup>), 2.71 (m, 1H, SCH<sup>D</sup>), 8.20 (m, 4H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 25.3 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 28.9 (CH), 36.8 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 41.7 (C), 70.4 (C), 122.9 (CH), 133.6 (CH), 146.1 (C), 146.6 (C) ppm. IR (KBr): 2908 (s), 2848 (s), 1598 (m), 1515 (s), 1447 (w), 1413 (w), 1349 (s), 1308 (s), 1283 (w), 1264 (w), 1110 (m), 1066 (w), 1011 (w), 976 (w), 930 (w), 855 (m), 839 (m), 794 (w), 727 (m), 696 (w) cm<sup>-1</sup>. GC-MS (IE, 70eV); m/z (%): 41 (9), 77

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(5), 79 (17), 81 (5), 91 (5), 93 (14), 107 (8), 135 (100), 136 (12), 210 (5), 224 (21),  
240 (5), 375(M<sup>+</sup>, 4).

4.6.3. 2-(1-Adamantylmethyl)-2-(3-nitrophenyl)-1,3-dithiane (**18**) was purified by  
crystallisation from hexane to yield 125 mg (92%) of yellow needles. Mp 174–  
176 °C, R<sub>f</sub> 0.60 (system b), anal. calcd for C<sub>21</sub>H<sub>27</sub>NO<sub>2</sub>S<sub>2</sub>: C, 64.74%; H, 6.99%; N,  
3.60%; S, 16.46%; found C, 64.58%; H, 7.17%; N, 3.87%; S, 16.72%. <sup>1</sup>H NMR  
(CDCl<sub>3</sub>): δ 1.36 (m, 6H, CH<sub>2</sub>(Ad)), 1.51 (m, 6H, CH<sub>2</sub>(Ad)), 1.78 (m, 3H, CH(Ad)),  
1.94 (m, 2H, SCH<sub>2</sub>CH<sub>2</sub>), 2.04 (s, 2H, AdCH<sub>2</sub>), 2.64 (m, 4H, SCH<sub>2</sub>), 7.54 (t, J=7.9 Hz,  
1H, Ph), 8.13 (d, J=7.9 Hz, 1H, Ph), 8.33 (d, J=9.2 Hz, 1H, Ph), 8.86 (s, 1H, Ph) ppm.  
<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 24.8 (CH<sub>2</sub>), 28.1 (CH), 28.9 (CH), 36.1 (C), 36.8 (CH<sub>2</sub>), 44.0  
(CH<sub>2</sub>), 57.6 (C), 59.8 (CH<sub>2</sub>), 122.2 (CH), 125.1 (CH), 129.3 (CH), 136.0 (CH), 145.7  
(C), 148.7 (C) ppm. IR (KBr): 3083 (w), 2899 (s), 2845 (s), 2672 (w), 1573 (w), 1523  
(s), 1470 (w), 1448 (w), 1422 (m), 1350 (s), 1311 (m), 1281 (w), 1270 (m), 1101 (m),  
1091 (w), 1079 (w), 1032 (w), 996 (w), 863 (w), 802 (m), 776 (w), 733 (m), 707 (w),  
687 (m) cm<sup>-1</sup>. GC-MS (EI, 70eV); m/z (%): 41 (11), 55 (11), 67 (13), 69 (5), 77 (8),  
79 (28), 81 (10), 91 (10), 93 (24), 107 (18), 135 (100), 136 (13), 239 (43), 315 (7),  
389 (M<sup>+</sup>, 6).

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4.6.4. 2-(1-Adamantyl)-2-(4-nitrophenyl)-1,3-dithiolane (**19**) was purified by  
crystallisation from hexane/CH<sub>2</sub>Cl<sub>2</sub> to yield 115 mg (91%) of colourless needles. Mp  
185–189 °C, R<sub>f</sub> 0.51 (system b), anal. calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>2</sub>S<sub>2</sub>: C, 63.12%; H, 6.41%;  
N, 3.87%; S, 17.74%; found C, 63.41%; H, 6.51%; N, 4.12%; S, 17.45%. <sup>1</sup>H NMR  
(CDCl<sub>3</sub>): δ 1.57 (m, 6H, CH<sub>2</sub>(Ad)), 1.79 (m, 6H, CH<sub>2</sub>(Ad)), 1.99 (m, 3H, CH(Ad)),  
2.98 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 3.27 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 7.97 (m, 2H, Ph), 8.10 (m, 2H, Ph)

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ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  29.0 (CH), 36.6 ( $\text{CH}_2$ ), 38.8 ( $\text{CH}_2$ ), 39.9 ( $\text{CH}_2$ ), 41.3 (C), 86.4 (C), 121.6 (CH), 132.0 (CH), 146.8 (C), 151.6 (C) ppm. IR (KBr): 2903 (s), 2845 (m), 1600 (m), 1515 (s), 1447 (w), 1400 (w), 1345 (s), 1308 (w), 1145 (w), 1110 (m), 1014 (w), 979 (m), 853 (m), 842 (m), 809 (w), 728 (m), 697 (m), 638 (w), 503 (w)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (6), 67 (7), 77 (5), 79 (18), 81 (5), 91 (5), 93 (17), 107 (10), 135 (100), 136 (13), 196 (10), 210 (8), 361( $\text{M}^+$ , 3).

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4.6.5. 2-(1-Adamantylmethyl)-2-(3-nitrophenyl)-1,3-dithiolane (**20**) was purified by crystallisation from hexane/ $\text{CH}_2\text{Cl}_2$  to yield 110 mg (84%) of a pale yellow crystals. Mp 142–148°C,  $R_f$  0.51 (system c), anal. calcd for  $\text{C}_{20}\text{H}_{25}\text{NO}_2\text{S}_2$ : C, 63.96%; H, 6.71%; N, 3.73%; S, 17.08%; found C, 63.98%; H, 6.58%; N, 3.95%; S, 16.82% .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (m, 6H,  $\text{CH}_2(\text{Ad})$ ), 1.51 (m, 6H,  $\text{CH}_2(\text{Ad})$ ), 1.80 (m, 3H,  $\text{CH}(\text{Ad})$ ), 2.52 (s, 2H,  $\text{CCH}_2\text{Ad}$ ), 3.06 (m, 2H,  $\text{SCH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.38 (m, 2H,  $\text{SCH}^{\text{A}}\text{H}^{\text{B}}$ ), 7.46 (t,  $J=7.9$  Hz, 1H, Ph), 8.07 (d,  $J=7.9$  Hz, 1H, Ph), 8.15 (d,  $J=7.9$  Hz, 1H, Ph), 8.71 (s, 1H, Ph) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.8 (CH), 35.5 (C), 36.8 ( $\text{CH}_2$ ), 38.9 ( $\text{CH}_2$ ), 43.6 ( $\text{CH}_2$ ), 58.3 ( $\text{CH}_2$ ), 72.5 (C), 122.2 (CH), 123.0 (CH), 128.7 (CH), 134.1 (CH), 148.0 (C), 149.1 (C) ppm. IR (KBr): 3077 (w), 2921 (s), 2902 (s), 2888 (s), 2841 (s), 1524 (s), 1447 (w), 1348 (s), 1314 (w), 1277 (w), 1100 (w), 898 (w), 804 (w), 736 (m), 685 (m), 588 (w)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (8), 55 (8), 67 (9), 79 (23), 93 (18), 107 (9), 135 (35), 149 (6), 180 (6), 226 (100), 227 (12), 228 (10), 375( $\text{M}^+$ , 2).

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#### 4.7. General procedure for preparation of aminodithianes **21** and **22**

The corresponding nitrodithiane (0.44 mmol) was dissolved in dioxane (7 mL) and a suspension of Ra-Ni in hexane was added to this solution. The mixture was stirred

1  
2 and refluxed under hydrogen atmosphere. Further portions of Ra-Ni were added until  
3  
4 TLC indicated complete disappearing of the starting material. The Ra-Ni was filtrated  
5  
6 off, resulting solution was diluted with water (14 mL) and extracted with diethyl ether  
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8 (6 × 15 mL) and hexane (1 × 20 mL). Collected organic portions were washed with  
9  
10 water (3 × 30 mL), brine (3 × 15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>.

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15 4.7.1. 2-(1-Adamantyl)-2-(4-aminophenyl)-1,3-dithiane hydrochloride (**21·HCl**) was  
16 precipitated from hexane solution of crude **21** by introducing of dry HCl. Yield: 146  
17 mg (87%) of a colourless crystalline powder. Mp 140–145 °C, R<sub>f</sub>(free base) 0.24  
18 (system b), anal. calcd for C<sub>20</sub>H<sub>28</sub>CINS<sub>2</sub>: C, 62.88%; H, 7.39%; N, 3.67%; S, 16.79%;  
19 found C, 62.73%; H, 7.19%; N, 3.62%; S, 16.98%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42–1.60  
20 (m, 8H, CH<sub>2</sub>(Ad)+CH<sub>2</sub>(dithiane)), 1.75 (m, 6H, CH<sub>2</sub>(Ad)), 1.92 (m, 3H, CH(Ad)),  
21 2.34 (m, 2H, CH<sub>2</sub>(dithiane)), 2.72 (m, 2H, CH<sub>2</sub>(dithiane)), 7.43 (d, *J*=8.6 Hz, 2H, Ph),  
22 7.92 (d, *J*=8.6 Hz, 2H, Ph), 10.34 (bs, 3H, NH<sub>3</sub>) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 24.7  
23 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 28.0 (CH), 36.3 (CH<sub>2</sub>), 37.0 (CH<sub>2</sub>), 41.6 (C), 69.8 (C), 122.4 (CH),  
24 130.8 (C), 133.1 (CH), 136.5 (C) ppm. IR (KBr): 3466 (bs), 2905 (s), 2848 (s), 2597  
25 (m), 1614 (w), 1541 (s), 1504 (m), 1447 (w), 1417 (w), 1359 (w), 1344 (w), 1306 (w),  
26 1279 (w), 1024 (w), 978 (w), 836 (w), 789 (w), 526 (w) cm<sup>-1</sup>. GC-MS (EI, 70eV); m/z  
27 (%): 41 (7), 77 (5), 79 (9), 91 (5), 93 (7), 106 (10), 120 (20), 135 (10), 136 (28), 210  
28 (100), 211 (13), 212 (9), 345 (M<sup>+</sup>, 1).  
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45 4.7.2. 2-(1-Adamantylmethyl)-2-(3-aminophenyl)-1,3-dithiane (**22**) was purified by  
46 column chromatography (silica gel, system b) to yield 106 mg (67%) of a pale yellow  
47 crystalline powder. Mp 127–132°C, R<sub>f</sub> 0.38 (system b), anal. calcd for C<sub>21</sub>H<sub>29</sub>NS<sub>2</sub>: C,  
48 70.14%; H, 8.13%; N, 3.90%; S, 17.83; found C, 70.33%; H, 7.94%; N, 4.25%, S,  
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2 18.08%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.40–1.58 (m, 12H,  $\text{CH}_2(\text{Ad})$ ), 1.78 (m, 3H,  $\text{CH}(\text{Ad})$ ),  
3  
4 1.85–1.96 (m, 4H,  $\text{SCH}_2\text{CH}_2+\text{CCH}_2\text{Ad}$ ), 2.57 (m, 2H,  $\text{SCH}^{\text{A}}\text{H}^{\text{B}}$ ), 2.78 (m, 2H,  
5  
6  $\text{SCH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.68 (bs, 2H,  $\text{NH}_2$ ), 6.58 (d,  $J=7.9$  Hz, 1H, Ph), 7.14 (t,  $J=7.9$  Hz, 1H, Ph),  
7  
8 7.37–7.39 (m, 2H, Ph) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  25.2 ( $\text{CH}_2$ ), 28.2 ( $\text{CH}_2$ ), 29.0 (CH),  
9  
10 36.0 (C), 37.0 ( $\text{CH}_2$ ), 43.6 ( $\text{CH}_2$ ), 59.6 ( $\text{CH}_2$ ), 113.9 (CH), 116.7 (CH), 120.6 (CH),  
11  
12 129.2 (CH), 143.3 (C), 146.6 (C) ppm. IR (KBr): 3443 (w), 3358 (w), 2363 (w), 1730  
13  
14 (w), 1614 (s), 1598 (s), 1489 (m), 1471 (w), 1448 (s), 1417 (w), 1346 (m), 1313 (m),  
15  
16 1277 (w), 1102 (w), 993 (w), 881 (w), 781 (m), 768 (w), 710 (w), 694 (w), 667 (w),  
17  
18 457 (w)  $\text{cm}^{-1}$ . GC-MS (EI, 70eV);  $m/z$  (%): 41 (17), 53 (5), 55 (14), 65 (7), 67 (17),  
19  
20 77 (13), 79 (44), 81 (13), 91 (25), 92 (5), 93 (36), 106 (7), 107 (19), 117 (10), 118  
21  
22 (30), 119 (7), 135 (100), 136 (30), 210 (81), 211 (11), 212 (8), 224 (6), 251 (5), 252  
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24 (13), 253 (7), 284 (10), 285 (70), 286 (15), 359 ( $\text{M}^+$ , 26), 360 (7).  
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#### 30 4.8. General procedure for preparation of amino dithiolanes 23 and 24

31  
32 The corresponding nitrodithiolane (3.37 mmol) was dissolved in *i*PrOH (125 mL) and  
33  
34 hydrochloric acid/water (1/1, v/v, 20 mL) and an iron powder (424 mg, 7.59 mmol)  
35  
36 was added. Into well stirred and refluxed mixture, further portions of an iron powder  
37  
38 (424 mg, 7.59 mmol) were added until TLC indicated complete disappearing of the  
39  
40 starting material. The mixture was poured onto a 5% solution of NaOH (120 mL) and  
41  
42 extracted several times with diethyl ether. Combined organic layers were washed  
43  
44 three times with water ( $3 \times 15$  mL) and dried over  $\text{Na}_2\text{SO}_4$  overnight. The crude  
45  
46 product was obtained after evaporation of the solvent in vacuo.  
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51 4.8.1. 2-(1-Adamantyl)-2-(4-aminophenyl)-1,3-dithiolane (23) was purified by column  
52  
53 chromatography (silica gel,  $\text{CHCl}_3$ ) to yield 827 mg (74%) of a pale orange crystalline  
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2 powder. Mp 121–124°C, R<sub>f</sub> 0.31 (system b), anal. calcd for C<sub>19</sub>H<sub>25</sub>NS<sub>2</sub>: C, 68.83%; H,  
3 7.60%; N, 4.22%; S, 19.34; found C, 68.73%; H, 7.45%; N, 4.53%; S, 19.02%.

4  
5  
6 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.56 (m, 6H, CH<sub>2</sub>(Ad)), 1.81 (m, 6H, CH<sub>2</sub>(Ad)), 1.96 (m, 3H,  
7 CH(Ad)), 2.99 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 3.23 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 3.64 (s, 2H, NH<sub>2</sub>), 6.58 (d,  
8 J=8.6 Hz, 2H, Ph), 7.55 (d, J=8.6 Hz, 2H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 29.1(CH),  
9 36.8 (CH<sub>2</sub>), 38.4 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 41.4 (C), 87.3 (C), 113.2 (CH), 131.9 (CH),  
10 133.2 (C), 145.0 (C) ppm. IR (KBr): 3417 (w), 2902 (s), 2370 (m), 2341 (m), 1622  
11 (m), 1507 (m), 1280 (w), 1186 (w), 977 (w), 835 (w), 652 (w), 531 (w) cm<sup>-1</sup>. GC-MS  
12 (EI, 70eV); m/z (%): 79 (6), 93 (5), 124 (5), 136 (20), 196 (100), 197 (12), 198 (9),  
13 331 (M<sup>+</sup>, 1).  
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25 4.8.2. 2-(1-Adamantylmethyl)-2-(3-aminophenyl)-1,3-dithiolane (**24**) was purified by  
26 column chromatography (silica gel, system b) to yield 1013 mg (87%) of a pale  
27 yellow crystalline powder. Mp 115–120°C, R<sub>f</sub> 0.29 (system b), anal. calcd for  
28 C<sub>20</sub>H<sub>27</sub>NS<sub>2</sub>: C, 69.51%; H, 7.88%; N, 4.05%; S, 18.56; found C, 69.64%; H, 8.15%;  
29 N, 4.27%; S, 18.33%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35 (m, 6H, CH<sub>2</sub>(Ad)), 1.53 (m, 6H,  
30 CH<sub>2</sub>(Ad)), 1.80 (s, 3H, CH(Ad)), 2.44 (s, 2H, AdCH<sub>2</sub>C), 3.10 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>),  
31 3.32 (m, 2H, SCH<sup>A</sup>H<sup>B</sup>), 3.65 (s, 2H, NH<sub>2</sub>), 6.52 (d, J=7.9 Hz, 1H, Ph), 7.05 (t, J=7.9  
32 Hz, 1H, Ph), 7.18 (m, 2H, Ph) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 28.9 (CH), 35.4 (C), 36.9  
33 (CH<sub>2</sub>), 38.5 (CH<sub>2</sub>), 43.2 (CH<sub>2</sub>), 58.4 (CH<sub>2</sub>), 73.7 (C), 113.8 (CH), 115.0 (CH), 118.7  
34 (CH), 128.6 (CH), 145.8 (C), 146.9 (C) ppm. IR (KBr): 3420 (w), 3345 (w), 2896 (s),  
35 2844 (s), 1615 (m), 1597 (m), 1489 (m), 1445 (m), 1416 (w), 1363 (w), 1346 (w),  
36 1313 (m), 1273 (w), 1103 (w), 994 (w), 781 (m), 694 (m), 452 (w) cm<sup>-1</sup>. GC-MS (EI,  
37 70eV); m/z (%): 41 (6), 55 (6), 67 (6), 79 (17), 81 (5), 91 (8), 93 (13), 107 (6), 135  
38 (23), 136 (12), 196 (100), 197 (12), 198 (9), 345(M<sup>+</sup>, 5).  
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#### 4.9. General procedure for preparation of anilines 25 and 26

The corresponding aminodithiolane (2.37 mmol) was dissolved in dioxane (10 mL) and large excess of Ra-Ni was added. The mixture was stirred and refluxed under an Ar atmosphere. If repeated GC analysis showed no significant progress, further portions of Ra-Ni were added until the starting material was completely consumed. Ra-Ni was filtered off, the filtrate was diluted with water and extracted several times with diethyl ether. Collected organic portions were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo. The desired crude product obtained as orange oil was subsequently converted to the hydrochloride.

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4.9.1. 4-(1-Adamantylmethyl)anilinium chloride (**25·HCl**) The crude product was dissolved in hexane/diethyl ether and **25·HCl** precipitated when dry HCl was introduced into solution. Yield: 579 mg (88%) of a colourless microcrystalline powder. Mp 178–188 °C, R<sub>f</sub>(free base) 0.28 (system b), anal. calcd for C<sub>17</sub>H<sub>24</sub>ClN: C, 73.49%; H, 8.71%; N, 5.04%; found C, 73.22%; H, 8.53%; N, 4.81%. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.43 (m, 6H, CH<sub>2</sub>(Ad)), 1.57 (m, 6H, CH<sub>2</sub>(Ad)), 1.90 (m, 3H, CH(Ad)), 2.38 (s, 2H, AdCH<sub>2</sub>Ph), 7.19 (d, *J*=7.9 Hz, 2H, Ph), 7.31 (d, *J*=7.9 Hz, 2H, Ph), 10.43 (bs, 3H, NH<sub>3</sub><sup>+</sup>) ppm. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 27.9 (CH), 32.9 (C), 36.4 (CH<sub>2</sub>), 41.6 (CH<sub>2</sub>), 49.5 (CH<sub>2</sub>), 122.5 (CH), 129.4 (C), 131.3 (CH), 137.7 (C) ppm. IR (KBr): 2902 (s), 2848 (s), 1613 (w), 1573 (w), 1509 (m), 1450 (w), 1314 (w), 1205 (w), 817 (w), 601 (m), 526 (w), 485 (m) cm<sup>-1</sup>. GC-MS (EI, 70eV); m/z (%): 41 (6), 55 (5), 67 (7), 77 (12), 79 (23), 81 (5), 91 (6), 93 (18), 106 (100), 107 (20), 135 (69), 136 (8), 241 (M<sup>+</sup>, 35), 242 (7).

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4.9.2. 3-[2-(1-Adamantyl)ethyl]anilinium chloride (**26·HCl**) The crude product was dissolved in hexane and **26·HCl** precipitated when dry HCl was introduced into solution. Yield: 491 mg (71%) of a colourless microcrystalline powder. Mp 142–150°C,  $R_f$ (free base) 0.25 (system b), anal. calcd for  $C_{18}H_{26}ClN$ : C, 74.07%; H, 8.98%; N, 4.80%; found C, 73.86%; H, 9.17%; N, 4.63%.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  1.30 (m, 2H, AdCH<sub>2</sub>), 1.52 (m, 6H, CH<sub>2</sub>(Ad)), 1.65 (m, 3H, CH<sub>2</sub>(Ad)), 1.94 (s, 3H, CH(Ad)), 2.55 (m, 2H, PhCH<sub>2</sub>), 7.22 (m, 3H, Ph), 7.36 (t,  $J=7.9$  Hz, 1H, Ph), 10.37 (bs, 3H, NH<sub>3</sub>) ppm.  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  28.1 (CH), 28.2 (CH<sub>2</sub>), 32.0 (CH), 36.6 (CH<sub>2</sub>), 41.7 (CH<sub>2</sub>), 46.0 (CH<sub>2</sub>), 120.3 (CH), 122.7 (CH), 127.8 (CH), 129.5 (CH), 131.8 (C), 145.1 (C) ppm. IR (KBr): 3429 (w), 2901 (s), 2845 (s), 2676 (w), 2605 (m), 2362 (w), 1964 (w), 1598 (m), 1576 (w), 1518 (w), 1490 (m), 1451 (m), 1359 (w), 1314 (w), 1243 (w), 1101 (w), 1046 (w), 790 (w), 691 (m), 524 (w), 437 (w) cm<sup>-1</sup>. GC-MS (EI, 70eV);  $m/z$  (%): 41 (15), 53 (7), 55 (11), 67 (15), 77 (23), 78 (6), 79 (42), 80 (5), 91 (16), 93 (34), 94 (7), 105 (5), 106 (46), 107 (67), 119 (22), 120 (49), 121 (7), 135 (59), 136 (7), 149 (8), 255 ( $M^+$ , 100), 256 (21).

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4.9.3. 3-(1-Adamantylmethyl)anilinium chloride (**27·HCl**) was prepared according to the procedure used for previous amines. The nitrodithiane **16** (338 mg, 0.90 mmol) was dissolved in ethanol (40 mL) under H<sub>2</sub> atmosphere and large excess of Ra-Ni was added portionwise until starting material disappeared. The crude product was dissolved in hexane and **27·HCl** precipitated when dry HCl was introduced into solution. Yield: 188 mg (75%) of a colourless microcrystalline powder. Mp 182–187 °C,  $R_f$ (free base) 0.42 (system b), anal. calcd for  $C_{17}H_{24}ClN$ : C, 73.49%; H, 8.71%; N, 5.04%; found C, 73.62%; H, 8.51%; N, 5.24%.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  1.44 (m, 6H, CH<sub>2</sub>(Ad)), 1.50–1.66 (m, 6H, CH<sub>2</sub>(Ad)), 1.91 (m, 3H, CH(Ad)), 2.38 (s,

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2H, AdCH<sub>2</sub>Ph), 7.07–7.11 (m, 2H, Ph), 7.20 (d, *J*=7.9 Hz, 1H, Ph), 7.37 (t, *J*=7.9 Hz, 1H, Ph), 10.14 (bs, 3H, NH<sub>3</sub><sup>+</sup>) ppm. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 27.9 (CH), 32.9 (C), 36.4 (CH<sub>2</sub>), 41.6 (CH<sub>2</sub>), 49.8 (CH<sub>2</sub>), 120.3 (CH), 124.4 (CH), 128.7 (CH), 129.6 (CH), 131.8 (C), 139.4 (C) ppm. IR (KBr): 3421 (m), 2901 (s), 2846 (s), 2604 (m), 1602 (w), 1578 (m), 1518 (w), 1487 (m), 1452 (m), 1105 (w), 795 (m), 742 (w), 716 (w), 694 (m) cm<sup>-1</sup>. GC-MS (EI, 70eV); *m/z* (%): 41 (6), 67 (8), 77 (8), 79 (19), 91 (5), 93 (16), 106 (11), 107 (13), 135 (100), 136 (11), 241 (M<sup>+</sup>, 35), 242 (7).

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### Supplementary material

Supplementary data associated with this article can be found in online version at ...

These data include NMR data obtained from titration of guest **15** by β-CD and data obtained from isothermal titration calorimetry for guest **7**.

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Table 1. Results of MS analyses – ionic species observed for amine with and without the presence of  $\beta$ -CD

Amine	Exact mass					
	[amine+H] <sup>+</sup>		[2-amine+Na] <sup>+</sup>		[ $\beta$ -CD+amine+H] <sup>+</sup>	
	calc.	found	calc.	found	calc.	found
<b>6</b>	256.2	256.1	533.4	533.3	1390.6	1390.6
<b>7</b>	256.2	256.1	533.4	533.3	1390.6	1390.6
<b>8</b>	270.2	270.1	561.4	561.3	1404.6	1404.6
<b>12</b>	272.2	272.1	565.4	-	1406.6	1406.6
<b>13</b>	258.2	258.1	537.4	537.2	1392.6	1392.6
<b>14</b>	272.2	272.1	565.4	565.4	1406.6	1406.7
<b>15</b>	258.2	258.1	537.4	537.2	1392.6	1392.6
<b>21</b>	346.2	346.1	714.4	-	1480.6	1480.7
<b>22</b>	360.2	360.2	742.4	-	1494.6	1494.7
<b>24</b>	346.2	346.3	714.4	-	1480.6	1480.8
<b>25</b>	242.2	242.8	505.4	-	1376.6	1376.7
<b>26</b>	256.2	256.3	533.4	-	1390.6	1390.7
<b>27</b>	242.2	242.1	505.4	-	1376.6	1376.6

Table 2. Thermodynamic parameters for inclusion complex formation of guest molecules and  $\beta$ -CD, derived from calorimetric titration experiments in DMSO/water (3/1, v/v) mixture at 30 °C.

guest	K [M <sup>-1</sup> ]	$-\Delta H$ [kJ·mol <sup>-1</sup> ]	$-\Delta S$ [J·K <sup>-1</sup> ·mol <sup>-1</sup> ]	n
<b>6</b>	186±23	35±14	71	1.1±0.4
<b>7</b>	226±25	46±15	105	1.0±0.3
<b>8</b>	313±55	38±17	75	1.0±0.4
<b>26</b>	694±28	44±3	88	0.93±0.05



Table 3. Selected geometric parameters and free energies for complexes of amines **14**, **26** and parent hydrocarbon **PH** with  $\beta$ -CD.

Structure	$d$ [nm] <sup>a</sup>	$l$ [nm]	$\alpha$ [°]	$\beta$ [°]	Stabilisation energy [kJ/mol]
<b>14</b> -SI	+0.0295	0.0227	142.48	50.31	-613.62
<b>14</b> -PI	-0.1534	0.1534	163.49	90.00	-604.14
<b>26</b> -SI	+0.0656	0.0622	16.10	71.47	-655.29
<b>26</b> -SE	+0.1173	0.1158	36.74	80.83	-633.66
<b>PH</b> -SI	+0.0930	0.0856	139.54	66.99	-668.04
<b>PH</b> -SE	+0.2223	0.2199	30.25	81.57	-650.19

For the definition of  $Cg1$ ,  $Cg2$ ,  $Og$ , and  $P$ , see the experimental part.  $d$  is  $Cg1-Og$  distance,  $l$  is  $Cg1-P$  distance,  $\alpha$  is  $Cg1-Og-Cg2$  angle,  $\beta$  is  $Cg1-Og-P$  angle. <sup>a</sup> The positive or negative sign implies location of adamantane cage in cavity close to the secondary or primary rim, respectively.

**Deleted:**  $Cg1$  is centre of mass of four bridgehead carbons in adamantane;  $Og$  and  $P$  are centres of mass and the best least squares plane of seven glycosidic oxygen atoms in  $\beta$ -cyclodextrin, respectively;  $Cg2$  is centre of mass of six carbons in benzene ring

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Scheme 1. Reaction pathway leading to 1-adamantyl (nitrophenyl) ketones.

Scheme 2. Synthesis of aminoketones and aminoalcohols.

Scheme 3. Synthesis of anilines with non-polar linker.

Figure 1. Structural formulas for selected promising anticancer drugs.

Figure 2. Typical ESI-MS data for studied amines (a), mixtures of amine and  $\beta$ -CD (b), and MS<sup>2</sup> spectrum of amine- $\beta$ -CD complexes (c).

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Figure 3. Schematic representations of  $\beta$ -CD and the prepared guest molecules with dimensions shown in nm.

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Figure 4. Schematic representations of possible geometries of host-guest systems under consideration. S = secondary, P = primary, I = internal, E = external. (Previously published<sup>14c</sup> geometric parameters were considered.)

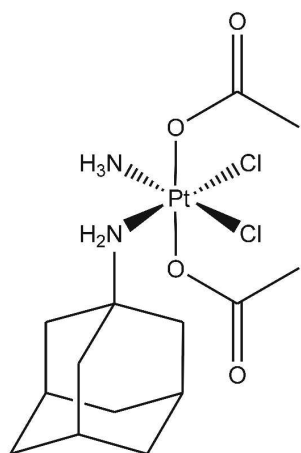
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Figure 5. A portion of the NOESY spectrum of a 1:1 mixture of guest **14** with  $\beta$ -CD (left); A portion of the gs-HMQC-NOESY spectrum of a 1:1 mixture of guest **7** with  $\beta$ -CD (middle and right). Detailed comment may be found in the text. Signals of host and guest nuclei are labelled as  $\beta$ -CD and G, respectively.

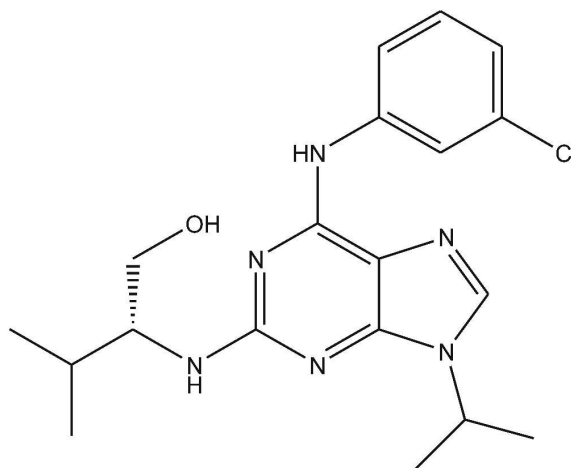
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Figure 6. Minimised structures of complexes of  $\beta$ -CD with amine **26** and **14**, respectively.

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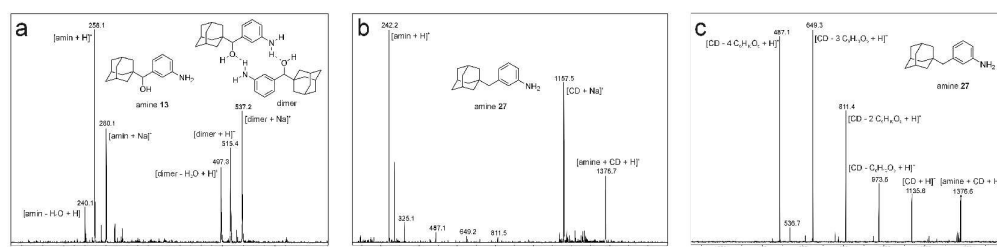


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Typical ESI-MS data for studied amines (a), mixtures of amine and  $\beta$ -CD (b), and MS2 spectrum of amine• $\beta$ -CD complexes (c).

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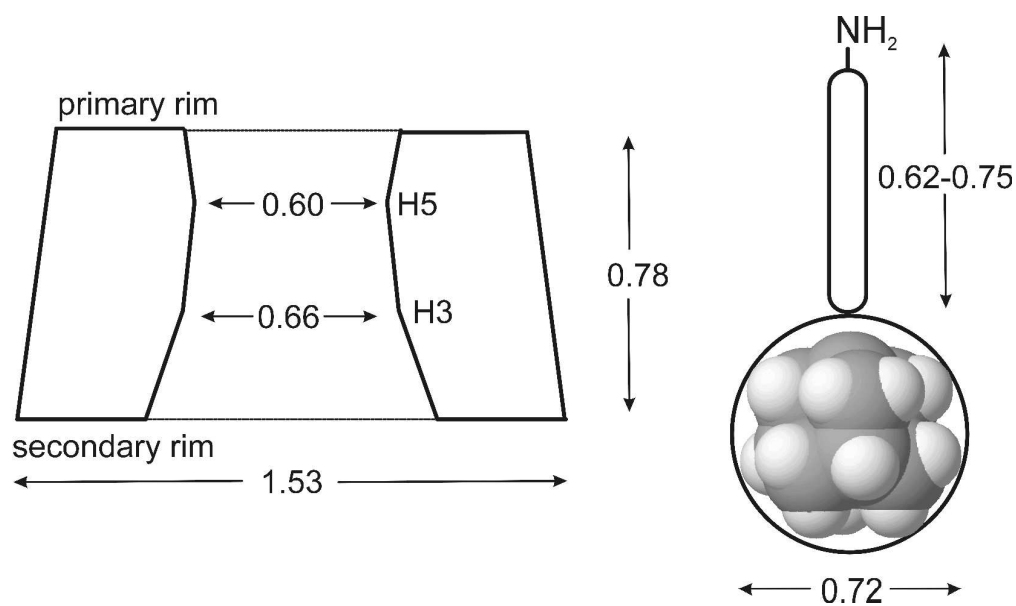
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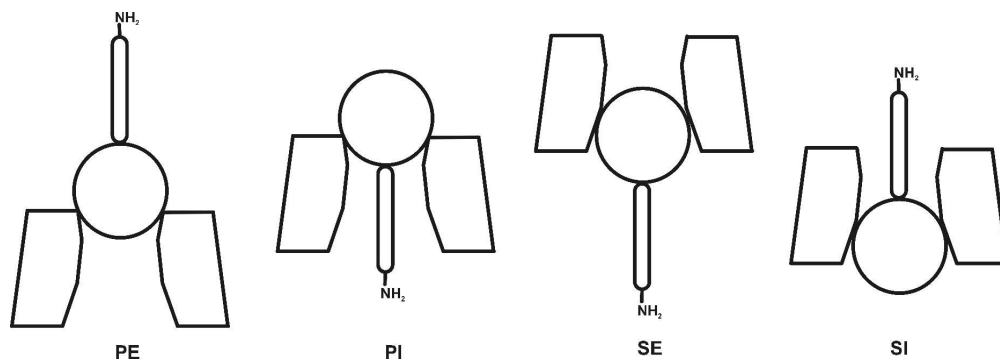
Typical ESI-MS data for studied amines (a), mixtures of amine and  $\beta$ -CD (b), and MS2 spectrum of amine• $\beta$ -CD complexes (c).

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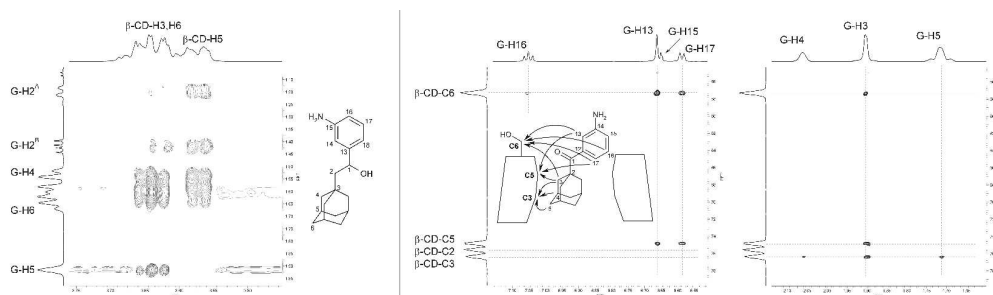
Schematic representations of  $\beta$ -CD and the prepared guest molecules with dimensions shown in nm.



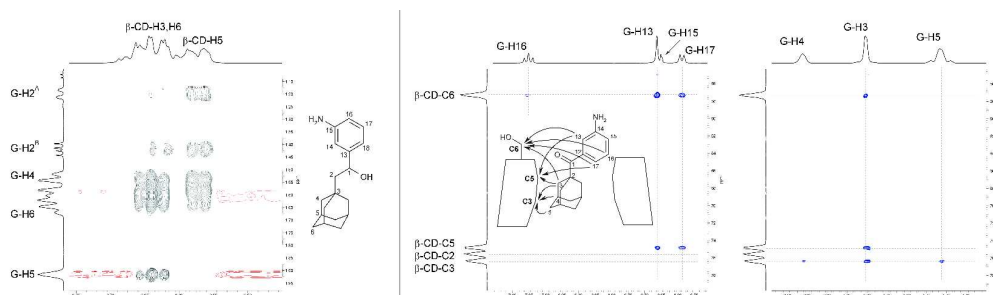


Schematic representations of possible geometries of host-guest systems under consideration. S = secondary, P = primary, I = internal, E = external. (Previously published<sup>14c</sup> geometric parameters were considered.)

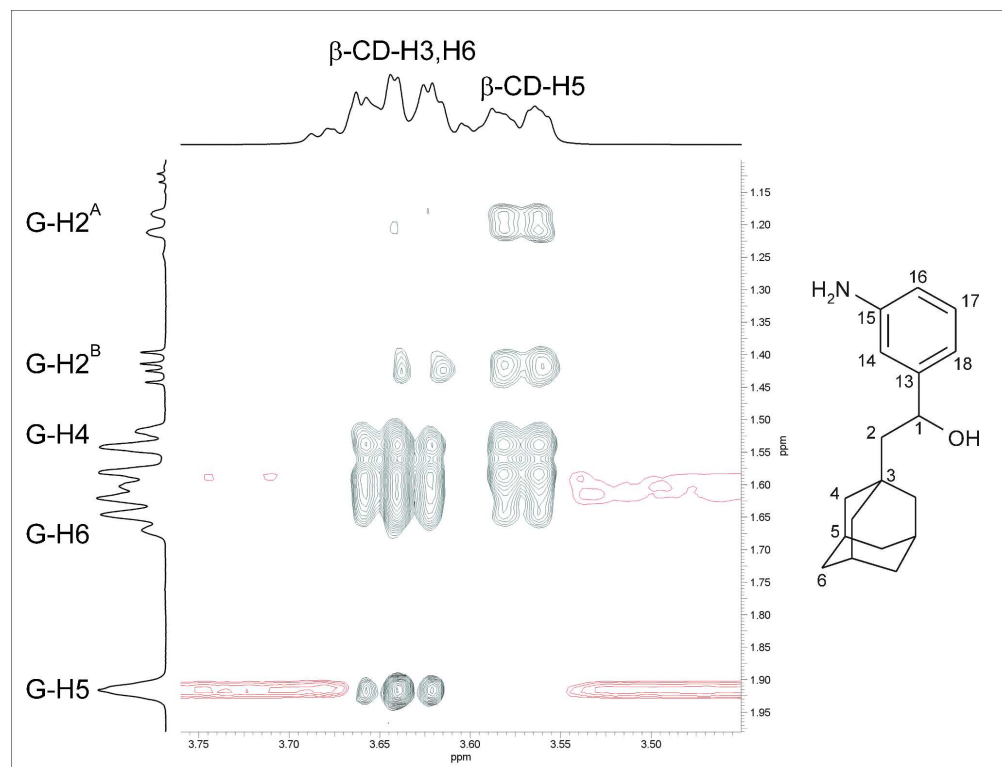
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A portion of the NOESY spectrum of a 1:1 mixture of guest 14 with  $\beta$ -CD (left); A portion of the gs-HMQC-NOESY spectrum of a 1:1 mixture of guest 7 with  $\beta$ -CD (middle and right). Detailed comment may be found in the text. Signals of host and guest nuclei are labelled as  $\beta$ -CD and G, respectively.



A portion of the NOESY spectrum of a 1:1 mixture of guest 14 with  $\beta$ -CD (left); A portion of the gs-HMQC-NOESY spectrum of a 1:1 mixture of guest 7 with  $\beta$ -CD (middle and right). Detailed comment may be found in the text. Signals of host and guest nuclei are labelled as  $\beta$ -CD and G, respectively.



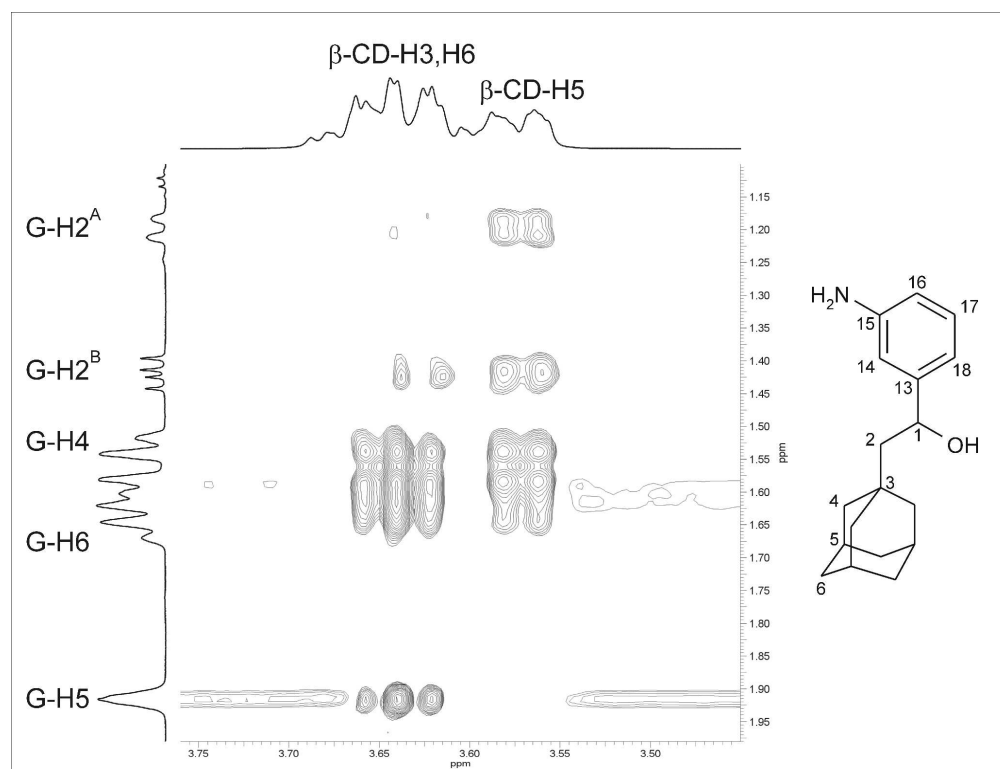
A portion of the NOESY spectrum of a 1:1 mixture of guest 14 with  $\beta$ -CD (left); A portion of the g-HMQC-NOESY spectrum of a 1:1 mixture of guest 7 with  $\beta$ -CD (middle and right). Detailed comment may be found in the text. Signals of host and guest nuclei are labelled as  $\beta$ -CD and G, respectively.

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A portion of the NOESY spectrum of a 1:1 mixture of guest 14 with  $\beta$ -CD (left); A portion of the g-HMQC-NOESY spectrum of a 1:1 mixture of guest 7 with  $\beta$ -CD (middle and right). Detailed comment may be found in the text. Signals of host and guest nuclei are labelled as  $\beta$ -CD and G, respectively.

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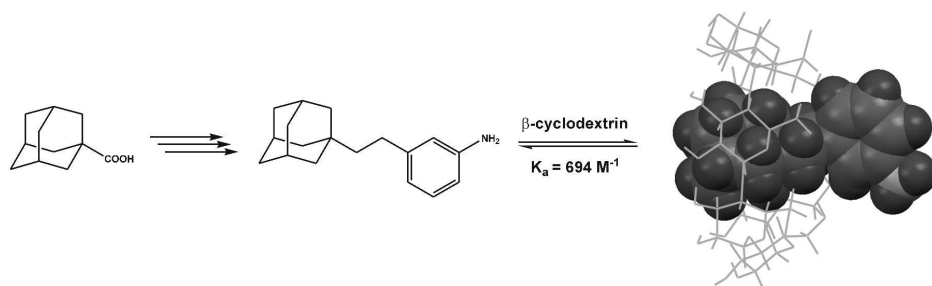
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Minimised structures of complexes of  $\beta$ -CD with amine **26** and **14**, respectively.

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## Supporting information

NMR-based estimation of association constant is shown in following figures. The Job plot for guest **14** (protons H5) is shown in Figure S1. The position of maximum indicates the 1:1 stoichiometry of complex. Titration curves obtained for protons H5 and H1 together with standard least-square regressions are shown in Figure S2. Measurements were carried out in DMSO-*d*<sub>6</sub>/D<sub>2</sub>O 3/1 v/v. Solution of guest (22 mM) was titrated with 74 mM stock solution of host at 303 K.

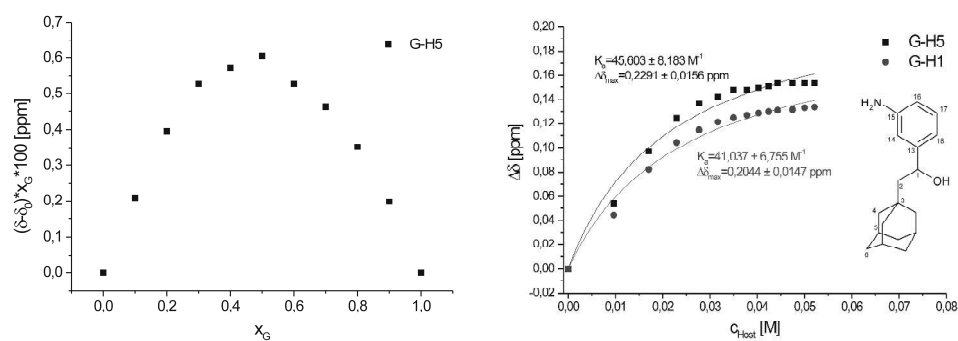


Figure S1

Figure S2

Overlay picture of successively recorded <sup>1</sup>H NMR spectra during NMR titration is shown in Figure S3. Whereas the complexation induced shifts (CIS) of host protons signals are imperceptible, the down-field CIS for guest H4-6 and up-field CIS for H1, H2, H14, and H16-18 may be observed.

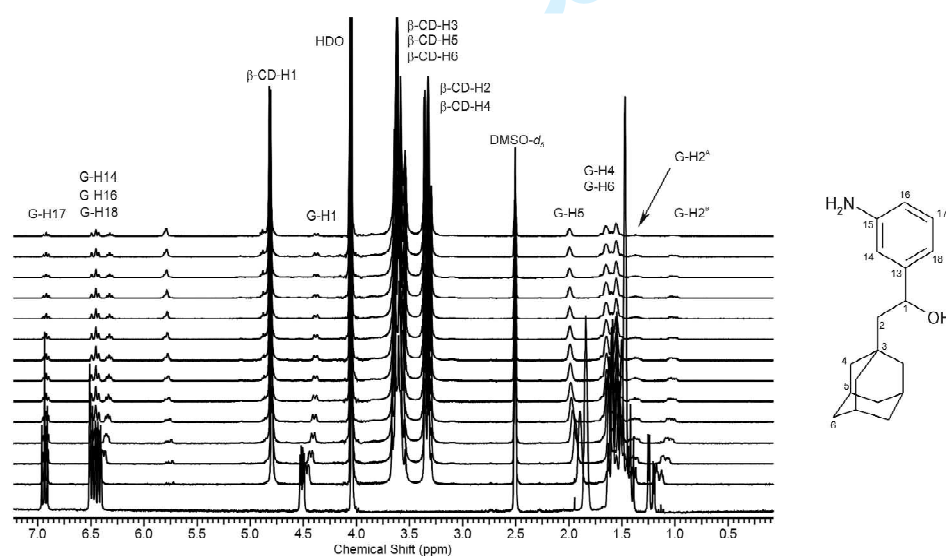
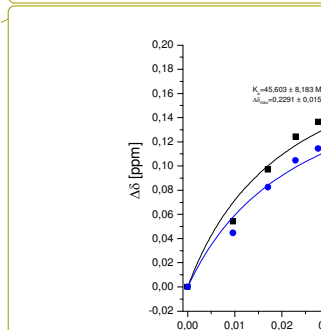
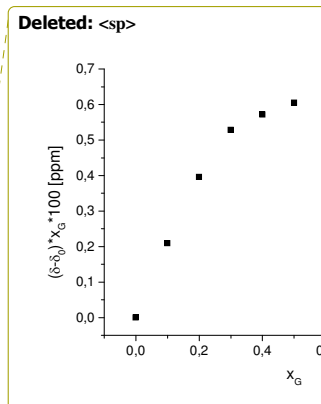
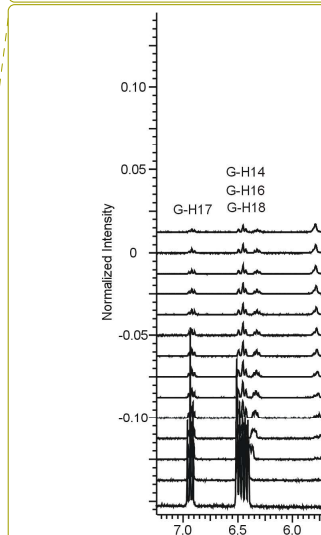


Figure S3



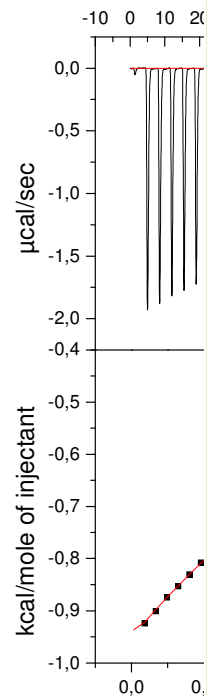
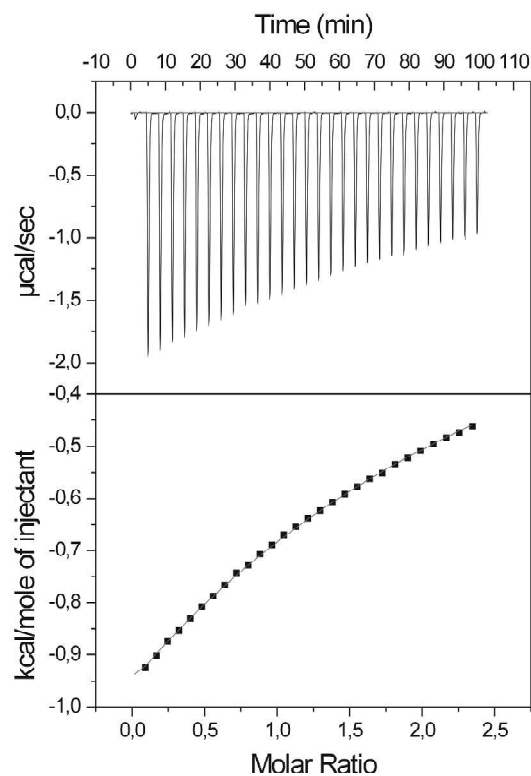
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Isothermal titration calorimetry measurements were performed using MicroCal VP-ITC instrument. In individual titrations, injections of 10 $\mu$ L of guest were added from 250 $\mu$ L syringe at an interval of 210 seconds into solution of  $\beta$ -cyclodextrin in water/DMSO (1/3, v/v) mixture. Typical result of isothermal titration calorimetry experiment for guest **7** is shown in Figure S4



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Figure S4