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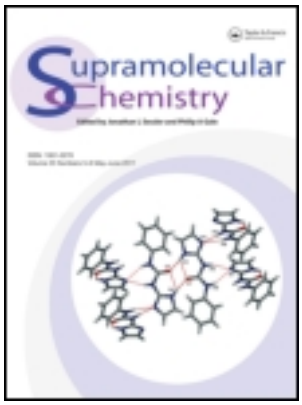

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Novel adamantane-bearing anilines and properties of their supramolecular complexes with β-cyclodextrin

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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 β-cyclodextrin (β-CD) were studied using electrospray ionisation mass spectrometry, 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 β-CD 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

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1. Introduction

Since the first description of the antiviral activity of 1-adamantylamine in 1964 (*1*), various compounds containing the adamantane scaffold have been shown to exhibit antiviral (*2*), anticancer (*3*) and antimicrobial (*4*) activities; such compounds have also been described as hypoglycaemic (*5*), proapoptotic (*6*) and neuroprotective (*7*) agents, as well as possible treatments for hypertension, vascular inflammation (*8*) and tuberculosis (*9*). Adamantane-bearing compounds can also serve as cannabinoid receptor ligands (*10*). 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 β-cyclodextrin (β-CD) (*11*) significantly increases drug's solubility in water. CD drug carrier systems have been studied extensively in terms of solubility, bioavailability and stability (*12*). This attention has yielded several commercial pharmaceutical products based on CD host–guest complexes (*12*). The adamantane-bearing amines are suitable candidates for drug modification, e.g. as ligands in preclinically tested (*3*) platinum derivate LA-12 (Figure 1, left) or as building blocks for displacement of C6 substituent in purvalanol-like promising anticancer drugs (Figure 1, right). However, the steric hindrance of bulky adamantane may lead to attenuation of the desired activity if the scaffold is introduced too close to the active site of the drug (*13*), hence the need for preparation and property investigation of new suitable adamantane-bearing building blocks is justified.

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

2. Results and discussion

2.1 Synthesis of amines

The nitro intermediates were prepared following previously described procedures, including the ketone

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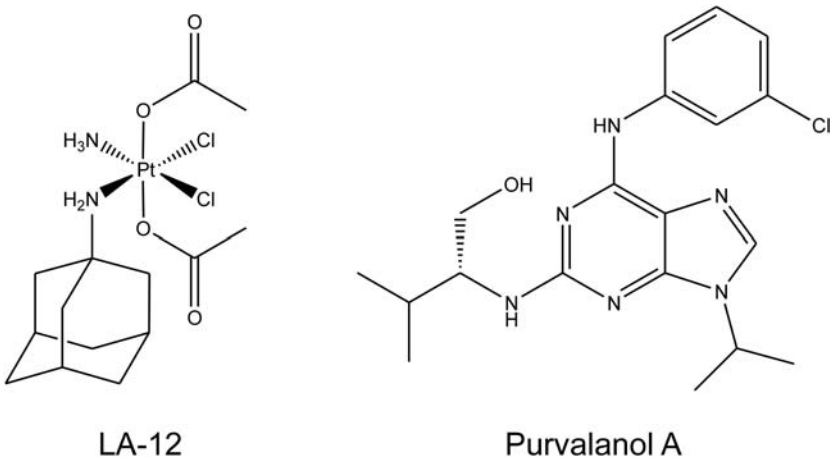

Figure 1. Structural formulas for selected promising anticancer drugs.

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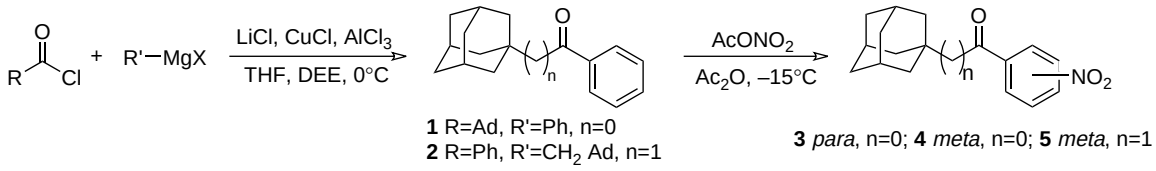
preparation (*16*) and nitration with acetyl nitrate (*17*) as shown in Scheme 1. Regioisomers were separated by column chromatography, and compounds **3**–**5** were used as starting materials for further reactions.

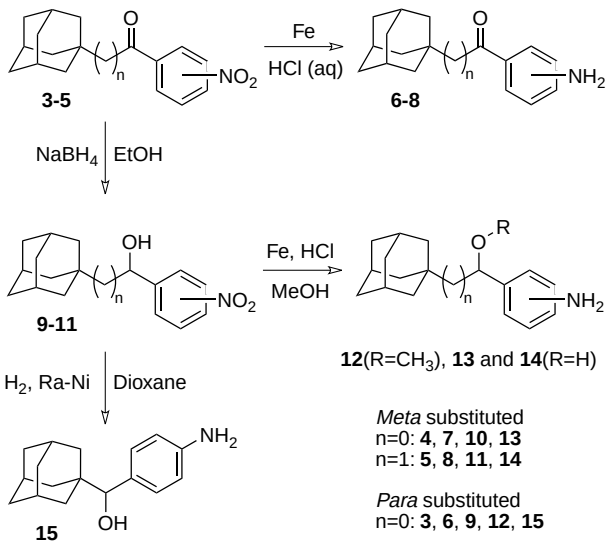
Aminoketones **6**–**8** were prepared in methanolic HCl solution using iron powder as a reducing agent. The iron powder used in this reaction was obtained from iron pentacarbonyl decomposition (purchased from commercial source); use of iron fillings or turnings led to considerably longer reaction times. 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 $NaBH_4$ 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 $LiAlH_4$ or H_2/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 the reduction of the nitro group by iron powder in alcohol/HCl mixture and reduction/desulphurisation with H_2 on Ra–Ni catalyst (Scheme 3). Although the yields of the first step were excellent (about 90% of isolated products **16**–**20**), the following steps were accompanied by some difficulties. Nitrodithiane **18** was treated with Ra–Ni in ethanol under hydrogen atmosphere and was successfully desulphurised. The nitro group was also reduced under these conditions, but an undesirable substitution occurred, and the corresponding *N*-ethyl derivative was identified as the main product. Dithiane **16**, however, afforded required amine **27** under the same conditions. Although the isolated yield was not excellent, no side products were detected by either TLC or GC analysis. Due to the very poor solubility of dithioacetals in hexane, reduction with H_2 could not be performed without the use of a more polar solvent. We attempted the reduction of dithiane **18** in a dioxane/hexane mixture (1/1, v/v), but under such conditions, the nitro group was reduced to an amino group, while the dithiane



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

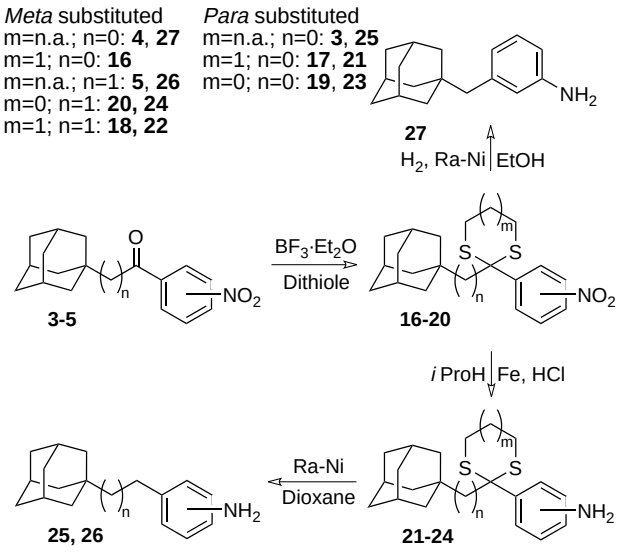


Scheme 2. Synthesis of aminoketones and aminoalcohols.

ring did not react. As a result, the corresponding aminodithiane derivative was isolated. Similarly, nitrodithiane **17** afforded the corresponding aminodithiane in an ethanol/hexane reaction medium. Thus, a two-step procedure was necessary for the smooth transformation of nitrodithianes to the required amines. Iron in *i* PrOH/HCl and Ra–Ni in dioxane were used for nitro group reduction and desulphurisation, respectively (Scheme 3).

2.2 *ESI-MS analysis*

Solutions of individual amines, as well their 1:1 mixtures with β-CD, were studied by ESI-MS. The dominant ions corresponding to the amines were the pseudomolecular



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

ions $[M + H]^+$, accompanying the signals at *m*/*z* values about two times as high (exactly $[2 \times (M + H) - 1]^+$ or $[2 \times M + 23]^+$). The latter ions were observed when a polar functional group (oxo or hydroxy) was present in the amine molecule, as shown for amine **13** in Figure 2(a). These signals are assumed to be related to associates of dimer linked via hydrogen bonds with a proton or sodium cation, respectively. The formation of analogous dimers in the solid state has been observed for aminoalcohol **15** (*18*). In the amine/β-CD mixtures, the protonated amine and sodium adduct of β-CD, as well as protonated β-CD–amine complex, were detected for all examined amines (Table 1). Figure 2(b) shows a typical spectrum of an equimolar mixture of β-CD and amine **27**. The tandem mass spectrum of the protonated complex showed a characteristic fragmentation pattern, which confirms its identity. The ions at *m*/*z* 1136, 974, 811, 649 and 487 resulted from the successive losses of amine and glucose residues of the β-CD moiety (Figure 2(c)).

2.3 *The geometry of host–guest complexes*

The β-CD is a heptamer built up from glucopyranose units linked by α-1,4-glycosidic bonds with a very well-known structure (*19*) that it is often described as a doughnut with rims of differing diameters. The larger diameter corresponds to the secondary rim where secondary hydroxyl groups at C2 and C3 are located; primary hydroxyl groups at C6 are placed on the opposite smaller primary rim due to the non-alternating orientation of the glucose units. The interior of the cavity has steric constraints due to H3 and H5 protruding into the cavity (*14c*). Schematics with the relevant dimensions of β-CD and the prepared amines are displayed in Figure 3.

The internal diameter of the cavity is likely to be slightly smaller than the diameter of the nearly ball-shaped adamantane moiety, which cannot pass through it easily but still fit well in the interior of the β-CD cavity. As a result, two distinct complexes may form. The adamantane moiety can be located either at the primary rim region or at the secondary rim region. In a solution, a reasonable orientation of a short and, in most cases, charged, substituent bound to adamantane is outside the β-CD cavity (*14c*, *15a*). Occupancy of the primary rim was observed only when the secondary rim was blocked. Higher thermodynamic stabilities were calculated for complexes with the adamantane unit sitting in the secondary rim (*14c*). However, it is reasonable to suppose that a non-polar substituent of appropriate length may thread through the cavity of β-CD. Thus, four possible arrangements of 1:1 adamantane and β-CD complexes should be considered. These arrangements are illustrated in Figure 4.

All examined systems obey the fast exchange mode on the NMR timescale, and thus only one set of signals was

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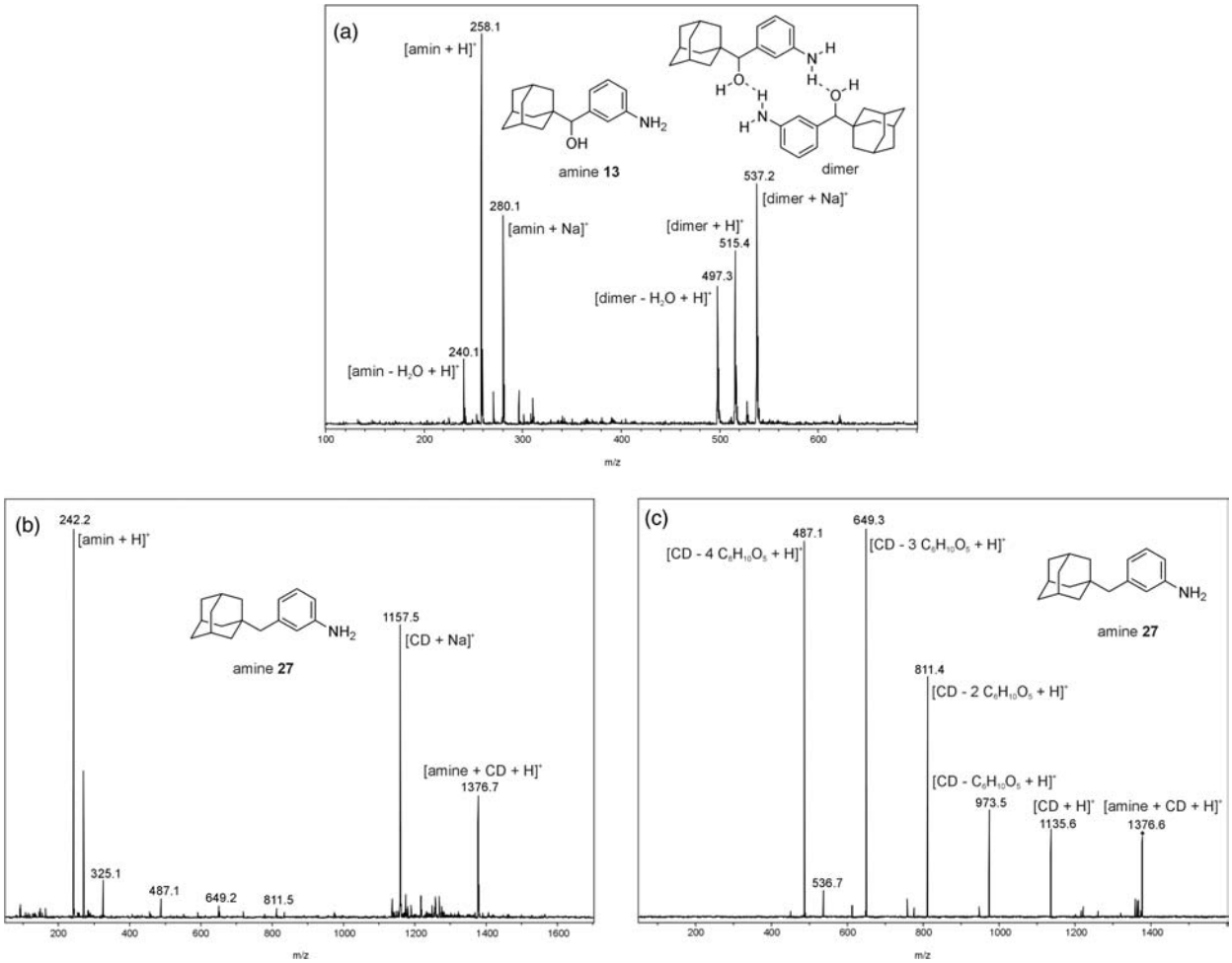

Figure 2. ESI-MS data for amine **13** (a), equimolar mixture of amine **27** with β-CD (b), and MS^2 spectrum of amine **27**–β-CD complex, target mass = 1377 m/z (c).

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

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

observed in all cases. Unfortunately, the shifts observed upon complexation for the host and guest protons were small ($< 10^{-2}$ ppm), and determination of thermodynamic parameters from NMR titrations was generally impossible.

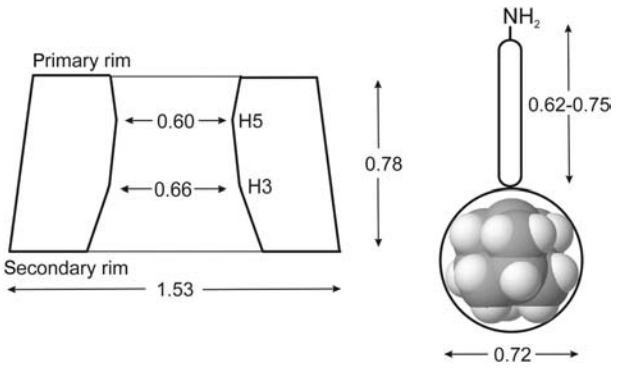

Figure 3. Schematic representations of β-CD and the prepared guest molecules with dimensions shown in nanometres.

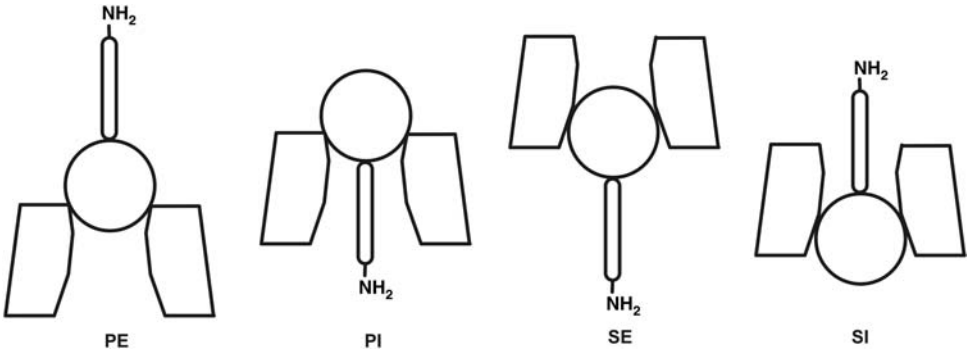

Figure 4. Schematic representations of possible geometries of host–guest systems under consideration. S, secondary; P, primary; I, internal; E, external. (Previously published (*14*) geometric parameters were considered.)

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We observed reproducible complexation-induced shifts of the well-resolved ^{1}H NMR signals only for guest **14**. Although the Job plot for the H5 protons (Figure S1) of the adamantane guest indicates a 1:1 stoichiometry, the analysis of titration data was unsatisfactory. The fitting of experimental data to the theoretical rectangular hyperbola using the standard least square regression procedure (MicroCal ORIGIN) led to an estimation of association constant being $\sim 40\,M^{-1}$, but the systematic discrepancy between the theoretical data and best-fit curve is too high (Figure S2). We attribute this discrepancy to the influence of higher ordered, hydrogen-bonded complexes on the observed chemical shifts. Nevertheless, the downfield shifts for guest protons H4-6 (on the adamantane cage) and upfield shifts for H1, $H2^{A,B}$, H14 and H16–18 were clearly observed (Figure S3).

The observed NOE interactions between guest protons bound to the adamantane cage (H4–6 for guest **14**) and inner hydrogen atoms of the CD cavity suggest the formation of an inclusion complex with adamantane positioned inside the β-CD cavity. The observation of relatively strong NOE interactions between guest protons H2 and β-CD-H5, together with weak (if any) interactions with β-CD-H3, indicates the occupancy of the secondary rim of β-CD by the adamantane cage. Additionally, in the case of all hydroxylated guests (**13**–**15**), the NOE interactions between the inner β-CD hydrogen atoms and $H6_{ax}$ of adamantane are significantly weakened or completely missing from the spectra, whereas those with $H6_{eq}$ are observed. A portion of the NOESY spectrum of a mixture of amine **14** and β-CD is shown in Figure 5 (top). However, ^{1}H NMR signals of β-CD inner protons H3 and protons H6 of the secondary rim were significantly overlapped in dimethyl sulphoxide (DMSO) solution, and interpretation of the observed cross-peaks in standard NOESY spectrum became ambiguous. Therefore, we applied a 2D ^{1}H–^{13}C gs-HMQC–NOESY experiment to increase the spectral resolution by employing a carbon frequency in an indirect dimension to assign the individual NOE contacts unequivocally. A schematic of the host–guest complex **7**·β-CD and its observed interactions are depicted in Figure 5 (bottom). Both the observed interactions of adamantane protons H4 and H5 with β-CD carbons C3 and the absence of interactions between these same protons and β-CD carbons C5 indicate a positioning of the adamantane cage inside the β-CD cavity with bridgehead-substituted carbon C2 located close to the secondary rim of β-CD. In addition, observed interactions of phenyl protons H13 and H17 with β-CD carbons C6 and C5 support the proposed structural model in which the aromatic part of the guest protrudes from the secondary rim of β-CD (Figure 5). According to the notation in Figure 4, the observed arrangement of the examined host–guest complexes is assigned as SI.

The binding properties of prepared guests **6**–**8**, **13**–**15** and **25**–**27** were studied using isothermal titration calorimetry. All three aminoalcohols **13**–**15** exhibited additional heat release during both titration and dilution experiments; therefore, thermodynamic parameters could not be determined. This observation may be reasonably attributed to additional equilibria related to the dissociation of dimers and/or higher associates of guest molecules. In addition, dilution data of these aminoalcohols did not fit the theoretical curve using a simple 'dissociation' model, which takes into account only dimer dissociation. Therefore, it is reasonable to assume additional equilibria involving higher-ordered associations. Anilines **25** and **27** exhibited some exothermic process that very slowly equilibrated. This slow equilibration thwarted the collection of usable data. The obtained values of binding constants, enthalpies, entropies and stoichiometries of the complexes for aminoketones **6**–**8** and amine **26** are listed in Table 2. For the typical raw data, integrated values of heat released and the fitted curve for guest **7**, see Supplementary data, Figure S4.

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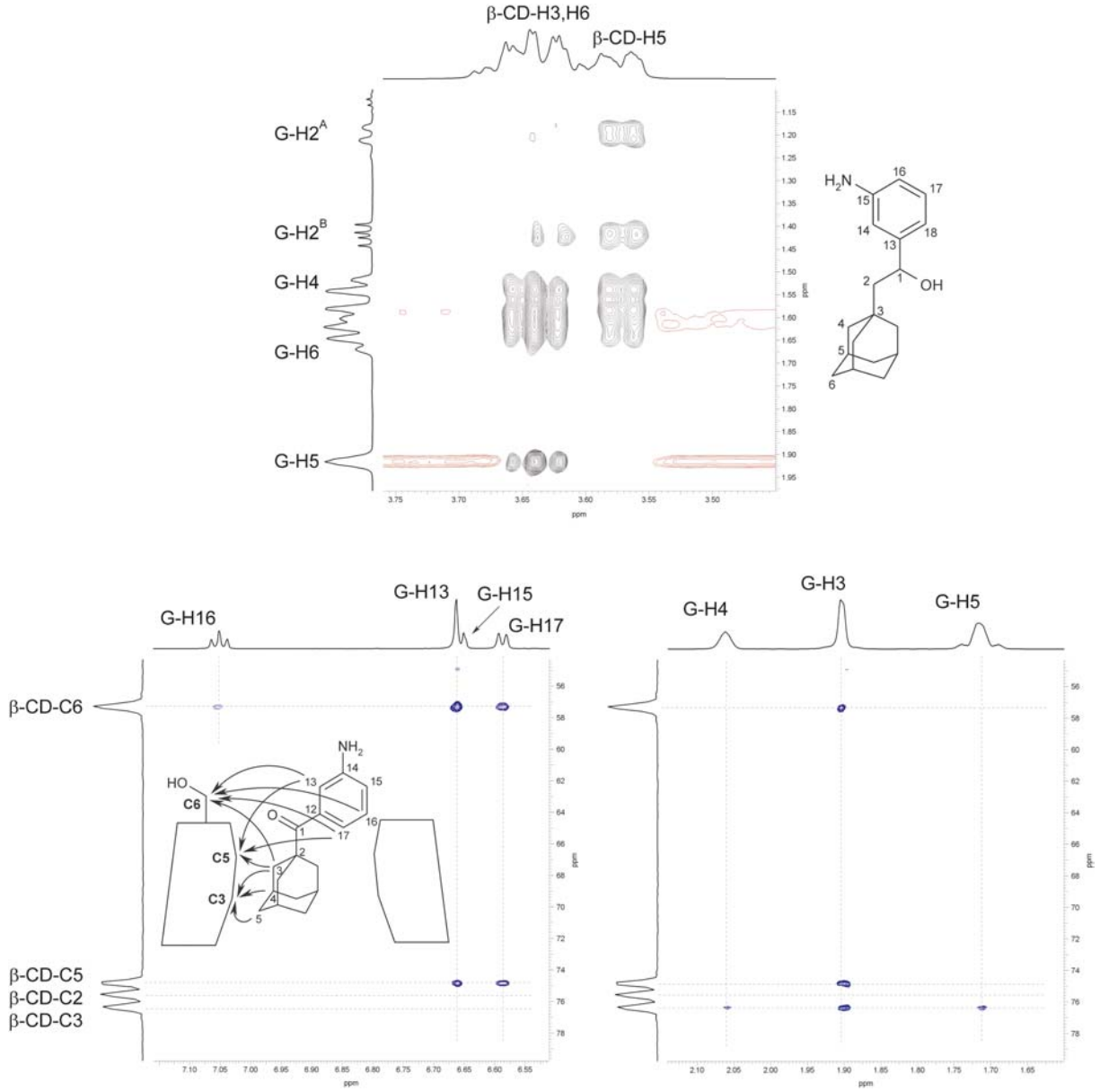

Figure 5. A portion of the NOESY spectrum of a 1:1 mixture of guest **14** with β-CD (top); A portion of the gs-HMQC-NOESY spectrum of a 1:1 mixture of guest **7** with β-CD (bottom). Detailed comment may be found in the text. Signals of host and guest nuclei are labelled as β-CD and G, respectively.

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

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

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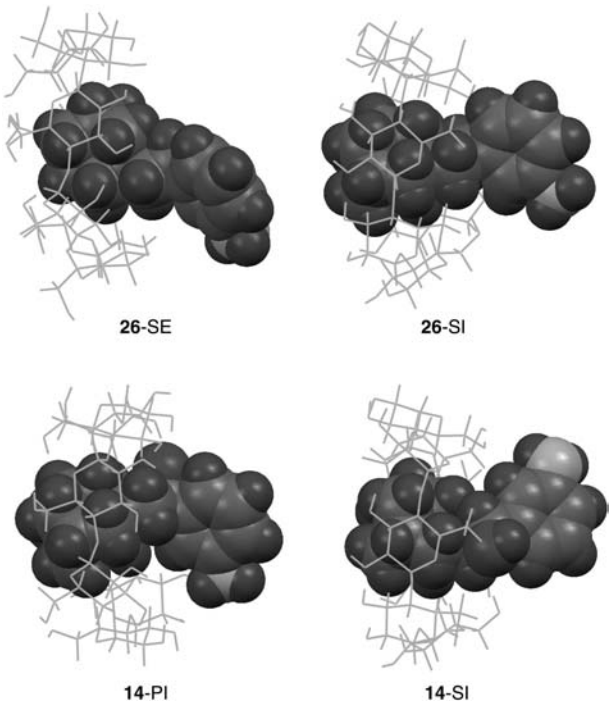

Figure 6. Minimised structures of complexes of β-CD with amine **26** and **14**, respectively.

2.4 Computation

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

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 β-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 β-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.

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 β-CD's hydroxyl groups is beyond our consideration. Although only one initial conformation of the CD 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) (*24*) was virtually threaded through the β-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 intermolecular hydrogen bonds was expected, it is not clearly manifested here. Therefore, we suggest only a

Table 3. Selected geometric parameters and free energies for complexes of amines **14**, **26** and **PH** with β-CD.

Structure	d[nm][a]	l [nm]	α[°]	β[°]	Stabilisation energy [kJ/mol]
14-SI	+0.0295	0.0227	142.48	50.31	−613.62
14-PI	−0.1534	0.1534	163.49	90.00	−604.14
26-SI	+0.0656	0.0622	16.10	71.47	−655.29
26-SE	+0.1173	0.1158	36.74	80.83	−633.66
PH-SI	+0.0930	0.0856	139.54	66.99	−668.04
PH-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, α is $Cg1-Og-Cg2$ angle, β is $Cg1-Og-P$ angle.
[a] The positive or negative sign implies location of adamantane cage in cavity close to the secondary or primary rim, respectively.

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 β-CD were detected using ESI-ion trap MS, and their structures were determined by 2D NMR experiments in dimethyl sulphoxide. In agreement with our experimental NMR data and molecular modelling, the most populated inclusion complex between β-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 β-CD and the substituent protrudes from the primary rim. Association constants of the prepared amines and β-CD were estimated to be on the order of 10^2 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 (*16*) 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 FlashEA 1112. Retention times were determined using TLC plates (Alugram Sil G/UV) from Macherey-Nagel and petroleum ether/ethyl acetate as mobile phase. Three compositions of mobile phases were used (v/v): system a (1/1), system b (4/1) and system c (8/1). NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C), and a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^{1}H) and 75.77 MHz (^{13}C). ^{1}H and ^{13}C NMR chemical shifts were referenced to the signal of solvent (^{1}H: δ(residual $CHCl_3$) = 7.27 ppm, δ(residual DMSO-d_5) = 2.50 ppm; ^{13}C: $\delta(CDCl_3)$ = 77.23 ppm, δ(DMSO-d_6) = 39.52 ppm). The mixing time for NOESY (*25*) experiment was adjusted to 500 ms, and the spin-lock for ROESY was adjusted to 400 ms. The assignment of ^{1}H signals for β-CD was described previously (*19d*). The 2D ^{1}H–^{13}C gs-HMQC–NOESY spectrum (*26*) was measured at resonance frequencies of 600.15 MHz (^{1}H) and 150.67 MHz (^{13}C). The HMQC step was adjusted for $^1J_{H\text{-}C}$ = 145 Hz with a subsequent NOE transfer of 700 ms. The spectrum was recorded in phase-sensitive mode using the echo–antiecho protocol (*27*). The IR spectra were recorded in a KBr disc with a Mattson 3000 FT-IR instrument. GC-MS analyses were run on a Shimadzu QP-2010 instrument using a Supelco SLB-5ms (30 m, 0.25 mm) column. Helium was employed as a carrier gas in a constant linear flow mode (38 cm s^{-1}); 100°C/7 min, 25°C/min to 250°C, hold for the required time. Only peaks of relative abundance exceeding 5% are listed. The electrospray mass spectra were recorded with an Esquire LC ion trap mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an ESI source. Sample solutions (8.8 μM in methanol/water, 1/1, v/v) were introduced into the ion source at a flow rate of 3 μl/min via a metal capillary held at high voltage (± 3.5 kV). The other instrumental conditions were as follows: drying gas temperature, 250°C; drying gas flow, 5 dm^3/min and nebuliser pressure, 41.37 kPa. Nitrogen was used as both nebulising gas and drying gas. The nozzle-skimmer potential and octopole potential were modified and optimised before each experiment. Isothermal titration calorimetry measurements were done in a DMSO/H_2O (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 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.

4.2 Quantum chemical methods

All theoretical calculations were carried out using the SPARTAN'08 software package (*28*). First, the initial geometries of amines **14** and **26** and β-CD were optimised with the PM3 method without imposing any symmetrical restrictions. A hypothetical **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 β-CD was based on available crystallographic data determined by XRD (*19b*). Initial approximations of amine–CD 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 (*Cg*1), the centre of mass of the seven glycosidic oxygen atoms in β-CD (*Og*), centre of mass of the six carbons of the benzene ring (*Cg*2) and the best least squares plane of the seven

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glycosidic oxygen atoms in β-CD (*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 was positioned along the molecular sevenfold axis of β-CD at 11 *Cg*1–*Og* distances ranging from 1.0 to − 1.0 nm in increments of 0.2 nm. The resulting geometries were optimised. These optimised geometries represent the sequential local minima for an amine passing through the CD cavity. The stabilisation energy of complex formation was calculated as the difference between the energy of the complex and the sum of energies of the guest and host calculated independently. The geometry with the absolute minimum energy could in this way be described as the geometry of inclusion complex. On the other hand, the rotation of the guest molecule within the CD's cavity was not tested, as it is known that the optimisation process automatically finds the best relative rotational orientation of the guest and host molecules (*29*). Under real condition, one could expect water-filled central cavity in CDs that must be displaced if a guest is to enter which would stabilise any interaction due to hydrophobic effects. Therefore, it is expected that basic considerations for this virtual experiment are not compromised by neglecting of water molecules in calculations. Because both the CD and the amine have non-equivalent sides following the threading route, two distinct threading processes must be performed with each amine. It was decided to arrange the threading process as adamantane-on into the secondary and primary rim of the CD, respectively.

4.3 General procedure for nitro ketones reduction to amino ketones 6–8

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

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%. ^{1}H NMR ($CDCl_3$): δ 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 ($CDCl_3$): δ 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, 70 eV); *m/z* (%): 65 (8), 79 (9), 92 (9), 93 (7), 120 (100), 121 (8), 135 (11), 255 (M^+, 8).

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. ^{1}H NMR ($CDCl_3$): δ 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 ($CDCl_3$): δ 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, 70 eV); *m/z* (%): 41 (8), 55 (6), 65 (13), 67 (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%. ^{1}H NMR ($CDCl_3$): δ 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 ($CDCl_3$): δ 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, 70 eV); *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).

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

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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 1 m HCl (10 ml) and a pale yellow solid precipitated. Mixture was extracted twice with diethyl ether (10 ml), collected organic portions were washed with brine and dried over Na_2SO_4. Crude product was obtained after removing of the solvent *in vacuo*.

4.4.1 1-Adamantyl-(4-nitrophenyl)methanol (**9**) was purified by crystallisation from methanol to yield 233 mg (96%) of a pale yellow crystals. Mp 191–192°C, R_f 0.11 (system b), anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06%; H, 7.37%; N, 4.87%; O, 16.70; found C, 71.34%; H, 7.45%; N, 4.98%. ^{1}H NMR ($CDCl_3$): δ 1.47–1.72 (m, 12H, CH_2(Ad)), 2.01 (m, 4H, CH(Ad), OH), 4.33 (s, 1H, C**H**OH), 7.44 (d, $J = 8.1$ Hz, 2H, Ph), 8.18 (d, $J = 8.5$ Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.4 (CH), 37.1 (CH_2), 37.7 (C), 38.3 (CH_2), 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^{-1}. GC-MS (EI, 70 eV); *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^+, 4).

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_f 0.20 (system b), anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06%; H, 7.37%; N, 4.87%; found C, 70.83%; H, 7.18%; N, 4.55%. ^{1}H NMR ($CDCl_3$): δ 1.27–1.71 (m, 12H, CH_2(Ad)), 1.99 (m, 3H, CH(Ad)), 2.10 (s, 1H, OH), 4.33 (s, 1H, C**H**OH), 7.49 (m, 1H, Ph), 7.59 (m, 1H, Ph), 8.12 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9 (CH), 32.9 (C), 37.2 (CH_2), 43.3 (CH_2), 54.7 (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): 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) cm^{-1}. GC-MS (EI, 70 eV); *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).

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 $C_{18}H_{23}NO_3$: C, 71.73%; H, 7.69%; N, 4.65%; found C, 71.56%; H, 7.44%; N, 4.83%. ^{1}H NMR ($CDCl_3$): δ 1.50 (d, $J = 2.6$, 1H, AdC**H**$^{\mathbf{A}}$H$^{\mathbf{B}}$), 1.59–1.79 (m, 12H, CH_2(Ad)), 1.88 (d, $J = 3.6$ Hz, 1H, AdCH$^{\mathbf{A}}$**H**$^{\mathbf{B}}$), 2.02 (m, 3H, CH(Ad)), 5.05 (m, 1H, PhC**H**OH), 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}C NMR ($CDCl_3$): δ 28.9 (CH), 32.9 (C), 37.2 (CH_2), 43.3 (CH_2), 54.7 (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) cm^{-1}. GC-MS (EI, 70 eV); *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).

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**.

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_f (free base) 0.27 (system b), anal. calcd for $C_{18}H_{26}ClNO$: C, 70.22%; H, 8.51%; N, 4.55%; found C, 69.94%; H, 8.37%; N, 4.75%. ^{1}H NMR (DMSO-d_6): δ 1.34–1.60 (m, 12H, CH_2(Ad)), 1.89 (m, 3H, CH(Ad)), 3.08 (s, 3H, OCH_3), 3.71 (s, 1H, C**H**OCH_3), 7.27–7.36 (m, 4H, Ph), 10.28 (bs, 3H, NH_3^+) ppm. ^{13}C NMR (DMSO-d_6): δ 27.5 (CH), 36.5 (CH_2), 37.7 (CH_2), 56.9 (CH_3), 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^{-1}. GC-MS (IE, 70 eV); *m/z* (%): 120 (7), 121 (6), 136 (100), 137 (9), 271 (M^+, 2).

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_f 0.11 (system b), anal. calcd for $C_{17}H_{23}NO$: C, 79.33%; H, 9.01%; N, 5.44%; found C, 79.57%; H, 9.15%; N, 5.72%.

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^{1}H NMR ($CDCl_3$): δ 1.49–1.66 (m, 12H, CH_2(Ad)), 1.97 (m, 3H, CH(Ad)), 3.62 (bs, 2H, NH_2), 4.12 (s, 1H, C**H**OH), 6.60–6.67 (m, 3H, Ph), 7.10 (t, $J = 7.6$ Hz, 1H, Ph) ppm. ^{1}H NMR (DMSO-d_6): δ 1.37–1.63 (m, 12H, CH_2(Ad)), 1.89 (m, 3H, CH(Ad)), 3.86 (d, $J = 3.8$ Hz, 1H, C**H**OH), 4.77 (d, $J = 3.8$ Hz, 1H, CHO**H**), 4.85 (s, 2H, NH_2), 6.34–6.41 (m, 2H, Ph), 6.46 (s, 1H, Ph), 6.89 (t, $J = 7.6$ Hz, 1H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.6 (CH), 29.9 (C), 37.3 (CH_2), 38.5 (CH_2), 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) cm^{-1}. GC-MS (EI, 70 eV); *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).

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}H NMR ($CDCl_3$): δ 1.50 (d, $J = 2.6$ Hz, 1H, AdC**H**$^{\mathbf{A}}$H$^{\mathbf{B}}$), 1.59–1.79 (m, 12H, CH_2(Ad)), 1.88 (d, $J = 3.6$ Hz, 1H, AdCH$^{\mathbf{A}}$**H**$^{\mathbf{B}}$), 2.02 (m, 3H, CH(Ad)), 5.05 (m, 1H, PhC**H**OH), 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}C NMR ($CDCl_3$): δ 28.9 (CH), 32.9 (C), 37.2 (CH_2), 43.3 (CH_2), 54.7 (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) cm^{-1}. GC-MS (EI, 70 eV); *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).

4.5.4 1-Adamantyl-(4-aminophenyl)methanol (**15**): The nitroalcohol **9** (259 mg, 0.90 mmol) was dissolved in ethanol (40 ml) under 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 Na_2SO_4 and evaporated *in vacuo*. Crude material was purified by column chromatography (silica gel, system a) to yield 227 mg (98%) of a pale yellow crystalline powder. Mp 143–146°C, R_f 0.41 (system a), anal. calcd for $C_{17}H_{23}NO$: C, 79.33%; H, 9.01%; N, 5.44%; found C, 79.09%; H, 9.23%; N, 5.28%. ^{1}H NMR ($CDCl_3$): δ 1.48–1.67 (m, 12H, CH_2(Ad)), 1.97 (m, 3H, CH(Ad)), 3.53 (bs, 2H, NH_2), 4.11 (s, 1H, C**H**OH), 6.64 (d, $J = 8.3$ Hz, 2H, Ph), 7.06 (d, $J = 8.1$ Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.8 (CH), 29.9 (C), 37.5 (CH_2), 38.5 (CH_2), 83.1 (CH), 114.5 (CH), 128.9 (CH), 131.8 (C), 145.8 (C) ppm. IR (KBr): 3378 (m), 2905 (s), 2847 (m), 1615 (m), 1514 (m), 1447 (w), 1265 (m), 1175 (w), 1128 (w), 1046 (m), 844 (w), 811 (w), 572 (m), 535 (w), 481 (w) cm^{-1}. GC-MS (EI, 70 eV); *m/z* (%): 77 (9), 79 (7), 93 (7), 94 (12), 120 (9), 121 (38), 122 (100), 123 (8), 135 (5), 257 (M^+, 4).

4.6 General procedures for nitrodithianes 16–18 and nitrodithiolanes 19, 20 formation

The ketone (0.35 mmol) was dissolved in dichloromethane (2 ml) and corresponding dithiol (1,2-ethanedithiol or 1,3-propanedithiol; 0.55 mmol) was added. The solution was cooled in ice bath to 0°C and stirred for 30 min. After this period, boron trifluoride-diethyl ether (1.00 mmol) was added dropwise and the mixture was stirred at room temperature until TLC indicated complete disappearance of the starting material. The mixture was diluted with CH_2Cl_2 (20 ml) and washed three times with 5% solution of NaOH (10 ml). The organic layer was washed twice with brine, dried over Na_2SO_4 and evaporated *in vacuo*.

4.6.1 2-(1-Adamantyl)-2-(3-nitrophenyl)-1,3-dithiane (**16**) was purified by crystallisation from hexane/CH_2Cl_2 to yield 121 mg (92%) of yellow needles. Mp 191–193°C, R_f 0.42 (system c), anal. calcd for $C_{20}H_{25}NO_2S_2$: 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%. ^{1}H NMR ($CDCl_3$): δ 1.58 (m, 6H, CH_2(Ad)), 1.83 (m, 8H, CH_2(Ad), SCH_2CH_2), 1.97 (m, 3H, CH(Ad)), 2.45 (m, 2H, SCH$^{\mathbf{A}}$H$^{\mathbf{B}}$), 2.67 (m, 1H, SCH$^{\mathbf{C}}$), 2.71 (m, 1H, SCH$^{\mathbf{D}}$), 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. ^{13}C NMR ($CDCl_3$): δ 25.4 (CH_2), 27.8 (CH_2), 28.9 (CH), 36.8 (CH_2), 37.6 (CH_2), 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^{-1}. GC-MS (EI, 70 eV); *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^+, 3).

4.6.2 2-(1-Adamantyl)-2-(4-nitrophenyl)-1,3-dithiane (**17**) was purified by crystallisation from hexane/CH_2Cl_2 to yield 120 mg (91%) of yellow needles. Mp 218–220°C, R_f 0.51 (system b), anal. calcd for $C_{20}H_{25}NO_2S_2$: C,

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63.96%; H, 6.71%; N, 3.73%; S, 17.08%; found C, 63.84%; H, 6.52%; N, 3.46%; S, 16.95%. ^{1}H NMR ($CDCl_3$): δ 1.57 (m, 6H, CH_2(Ad)), 1.83 (m, 8H, CH_2(Ad), $SCH_2C\mathbf{H}_2$), 1.97 (m, 3H, CH(Ad)), 2.46 (m, 2H, SCH^AH^B), 2.67 (m, 1H, SCH^C), 2.71 (m, 1H, SCH^D), 8.20 (m, 4H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 25.3 (CH_2), 27.8 (CH_2), 28.9 (CH), 36.8 (CH_2), 37.6 (CH_2), 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^{-1}. GC-MS (IE, 70 eV); *m/z* (%): 41 (9), 77 (5), 79 (17), 81 (5), 91 (5), 93 (14), 107 (8), 135 (100), 136 (12), 210 (5), 224 (21), 240 (5), 375(M^+, 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_f 0.60 (system b), anal. calcd for $C_{21}H_{27}NO_2S_2$: 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%. ^{1}H NMR ($CDCl_3$): δ 1.36 (m, 6H, CH_2(Ad)), 1.51 (m, 6H, CH_2(Ad)), 1.78 (m, 3H, CH(Ad)), 1.94 (m, 2H, $SCH_2C\mathbf{H}_2$), 2.04 (s, 2H, Ad$C\mathbf{H}_2$), 2.64 (m, 4H, $SC\mathbf{H}_2$), 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. ^{13}C NMR ($CDCl_3$): δ 24.8 (CH_2), 28.1 (CH), 28.9 (CH), 36.1 (C), 36.8 (CH_2), 44.0 (CH_2), 57.6 (C), 59.8 (CH_2), 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^{-1}. GC-MS (EI, 70 eV); *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^+, 6).

4.6.4 2-(1-Adamantyl)-2-(4-nitrophenyl)-1,3-dithiolane (**19**) was purified by crystallisation from hexane/CH_2Cl_2 to yield 115 mg (91%) of colourless needles. Mp 185–189°C, R_f 0.51 (system b), anal. calcd for $C_{19}H_{23}NO_2S_2$: 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%. ^{1}H NMR ($CDCl_3$): δ 1.57 (m, 6H, CH_2(Ad)), 1.79 (m, 6H, CH_2(Ad)), 1.99 (m, 3H, CH(Ad)), 2.98 (m, 2H, $SC\mathbf{H}^A\mathrm{H}^B$), 3.27 (m, 2H, $SCH^A\mathbf{H}^B$), 7.97 (m, 2H, Ph), 8.10 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 29.0 (CH), 36.6 (CH_2), 38.8 (CH_2), 39.9 (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) cm^{-1}. GC-MS (EI, 70 eV); *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(M^+, 3).

4.6.5 2-(1-Adamantylmethyl)-2-(3-nitrophenyl)-1,3-dithiolane (**20**) was purified by crystallisation from hexane/CH_2Cl_2 to yield 110 mg (84%) of a pale yellow crystal. Mp 142–148°C, R_f 0.51 (system c), anal. calcd for $C_{20}H_{25}NO_2S_2$: 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}H NMR ($CDCl_3$): δ 1.30 (m, 6H, CH_2(Ad)), 1.51 (m, 6H, CH_2(Ad)), 1.80 (m, 3H, CH(Ad)), 2.52 (s, 2H, $CC\mathbf{H}_2$Ad), 3.06 (m, 2H, $SC\mathbf{H}^A\mathrm{H}^B$), 3.38 (m, 2H, $SCH^A\mathbf{H}^B$), 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}C NMR ($CDCl_3$): δ 28.8 (CH), 35.5 (C), 36.8 (CH_2), 38.9 (CH_2), 43.6 (CH_2), 58.3 (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) cm^{-1}. GC-MS (EI, 70 eV); *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(M^+, 2).

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 and refluxed under hydrogen atmosphere. Further portions of Ra–Ni were added until TLC indicated complete disappearing of the starting material. The Ra–Ni was filtrated off, resulting solution was diluted with water (14 ml) and extracted with diethyl ether (6 × 15 ml) and hexane (1 × 20 ml). Collected organic portions were washed with water (3 × 30 ml), brine (3 × 15 ml) and dried over Na_2SO_4.

4.7.1 2-(1-Adamantyl)-2-(4-aminophenyl)-1,3-dithiane hydrochloride (**21·HCl**) was precipitated from hexane solution of crude **21** by introducing dry HCl. Yield: 146 mg (87%) of a colourless crystalline powder. Mp 140–145°C, R_f (free base) 0.24 (system b), anal. calcd for $C_{20}H_{28}ClNS_2$: C, 62.88%; H, 7.39%; N, 3.67%; S, 16.79%; found C, 62.73%; H, 7.19%; N, 3.62%; S, 16.98%. ^{1}H NMR ($CDCl_3$): δ 1.42–1.60 (m, 8H, CH_2(Ad) + CH_2(dithiane)), 1.75 (m, 6H, CH_2(Ad)), 1.92 (m, 3H, CH(Ad)), 2.34 (m, 2H, CH_2(dithiane)), 2.72 (m, 2H, CH_2(dithiane)), 7.43 (d, J = 8.6 Hz, 2H, Ph), 7.92 (d, J = 8.6 Hz, 2H, Ph), 10.34 (bs, 3H, NH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 24.7 (CH_2), 27.0 (CH_2), 28.0 (CH), 36.3 (CH_2),

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37.0 (CH_2), 41.6 (C), 69.8 (C), 122.4 (CH), 130.8 (C), 133.1 (CH), 136.5 (C) ppm. IR (KBr): 3466 (bs), 2905 (s), 2848 (s), 2597 (m), 1614 (w), 1541 (s), 1504 (m), 1447 (w), 1417 (w), 1359 (w), 1344 (w), 1306 (w), 1279 (w), 1024 (w), 978 (w), 836 (w), 789 (w), 526 (w) cm^{-1}. GC-MS (EI, 70 eV); *m/z* (%): 41 (7), 77 (5), 79 (9), 91 (5), 93 (7), 106 (10), 120 (20), 135 (10), 136 (28), 210 (100), 211 (13), 212 (9), 345 (M^+, 1).

4.7.2 2-(1-Adamantylmethyl)-2-(3-aminophenyl)-1,3-dithiane (**22**) was purified by column chromatography (silica gel, system b) to yield 106 mg (67%) of a pale yellow crystalline powder. Mp 127–132°C, R_f 0.38 (system b), anal. calcd for $C_{21}H_{29}NS_2$: C, 70.14%; H, 8.13%; N, 3.90%; S, 17.83; found C, 70.33%; H, 7.94%; N, 4.25%, S, 18.08%. ^{1}H NMR ($CDCl_3$): δ 1.40–1.58 (m, 12H, CH_2(Ad)), 1.78 (m, 3H, CH(Ad)), 1.85–1.96 (m, 4H, $SCH_2C\mathbf{H}_2$ + $CC\mathbf{H}_2$Ad), 2.57 (m, 2H, $SC\mathbf{H}^AH^B$), 2.78 (m, 2H, $SCH^A\mathbf{H}^B$), 3.68 (bs, 2H, NH_2), 6.58 (d, $J = 7.9$ Hz, 1H, Ph), 7.14 (t, $J = 7.9$ Hz, 1H, Ph), 7.37–7.39 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 25.2 (CH_2), 28.2 (CH_2), 29.0 (CH), 36.0 (C), 37.0 (CH_2), 43.6 (CH_2), 59.6 (CH_2), 113.9 (CH), 116.7 (CH), 120.6 (CH), 129.2 (CH), 143.3 (C), 146.6 (C) ppm. IR (KBr): 3443 (w), 3358 (w), 2363 (w), 1730 (w), 1614 (s), 1598 (s), 1489 (m), 1471 (w), 1448 (s), 1417 (w), 1346 (m), 1313 (m), 1277 (w), 1102 (w), 993 (w), 881 (w), 781 (m), 768 (w), 710 (w), 694 (w), 667 (w), 457 (w) cm^{-1}. GC-MS (EI, 70 eV); *m/z* (%): 41 (17), 53 (5), 55 (14), 65 (7), 67 (17), 77 (13), 79 (44), 81 (13), 91 (25), 92 (5), 93 (36), 106 (7), 107 (19), 117 (10), 118 (30), 119 (7), 135 (100), 136 (30), 210 (81), 211 (11), 212 (8), 224 (6), 251 (5), 252 (13), 253 (7), 284 (10), 285 (70), 286 (15), 359 (M^+, 26), 360 (7).

4.8 General procedure for preparation of amino dithiolanes 23 and 24

The corresponding nitrodithiolane (3.37 mmol) was dissolved in *i*PrOH (125 ml) and hydrochloric acid/water (1/1, v/v, 20 ml) and an iron powder (424 mg, 7.59 mmol) was added. Into the well-stirred and refluxed mixture, further portions of an iron powder (424 mg, 7.59 mmol) were added until TLC indicated complete disappearing of the starting material. The mixture was poured onto a 5% solution of NaOH (120 ml) and extracted several times with diethyl ether. Combined organic layers were washed three times with water (3 × 15 ml) and dried over Na_2SO_4 overnight. The crude product was obtained after evaporation of the solvent *in vacuo*.

4.8.1 2-(1-Adamantyl)-2-(4-aminophenyl)-1,3-dithiolane (**23**) was purified by column chromatography (silica gel, $CHCl_3$) to yield 827 mg (74%) of a pale orange crystalline powder. Mp 121–124°C, R_f 0.31 (system b), anal. calcd for $C_{19}H_{25}NS_2$: C, 68.83%; H, 7.60%; N, 4.22%; S, 19.34; found C, 68.73%; H, 7.45%; N, 4.53%; S, 19.02%. ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 6H, CH_2(Ad)), 1.81 (m, 6H, CH_2(Ad)), 1.96 (m, 3H, CH(Ad)), 2.99 (m, 2H, $SC\mathbf{H}^AH^B$), 3.23 (m, 2H, $SCH^A\mathbf{H}^B$), 3.64 (s, 2H, NH_2), 6.58 (d, $J = 8.6$ Hz, 2H, Ph), 7.55 (d, $J = 8.6$ Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 29.1(CH), 36.8 (CH_2), 38.4 (CH_2), 40.0 (CH_2), 41.4 (C), 87.3 (C), 113.2 (CH), 131.9 (CH), 133.2 (C), 145.0 (C) ppm. IR (KBr): 3417 (w), 2902 (s), 2370 (m), 2341 (m), 1622 (m), 1507 (m), 1280 (w), 1186 (w), 977 (w), 835 (w), 652 (w), 531 (w) cm^{-1}. GC-MS (EI, 70 eV); *m/z* (%): 79 (6), 93 (5), 124 (5), 136 (20), 196 (100), 197 (12), 198 (9), 331 (M^+, 1).

4.8.2 2-(1-Adamantylmethyl)-2-(3-aminophenyl)-1,3-dithiolane (**24**) was purified by column chromatography (silica gel, system b) to yield 1013 mg (87%) of a pale yellow crystalline powder. Mp 115–120°C, R_f 0.29 (system b), anal. calcd for $C_{20}H_{27}NS_2$: C, 69.51%; H, 7.88%; N, 4.05%; S, 18.56; found C, 69.64%; H, 8.15%; N, 4.27%; S, 18.33%. ^{1}H NMR ($CDCl_3$): δ 1.35 (m, 6H, CH_2(Ad)), 1.53 (m, 6H, CH_2(Ad)), 1.80 (s, 3H, CH(Ad)), 2.44 (s, 2H, Ad$C\mathbf{H}_2$C), 3.10 (m, 2H, $SC\mathbf{H}^AH^B$), 3.32 (m, 2H, $SCH^A\mathbf{H}^B$), 3.65 (s, 2H, NH_2), 6.52 (d, $J = 7.9$ Hz, 1H, Ph), 7.05 (t, $J = 7.9$ Hz, 1H, Ph), 7.18 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9 (CH), 35.4 (C), 36.9 (CH_2), 38.5 (CH_2), 43.2 (CH_2), 58.4 (CH_2), 73.7 (C), 113.8 (CH), 115.0 (CH), 118.7 (CH), 128.6 (CH), 145.8 (C), 146.9 (C) ppm. IR (KBr): 3420 (w), 3345 (w), 2896 (s), 2844 (s), 1615 (m), 1597 (m), 1489 (m), 1445 (m), 1416 (w), 1363 (w), 1346 (w), 1313 (m), 1273 (w), 1103 (w), 994 (w), 781 (m), 694 (m), 452 (w) cm^{-1}. GC-MS (EI, 70 eV); *m/z* (%): 41 (6), 55 (6), 67 (6), 79 (17), 81 (5), 91 (8), 93 (13), 107 (6), 135 (23), 136 (12), 196 (100), 197 (12), 198 (9), 345(M^+, 5).

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_2SO_4 and evaporated *in vacuo*. The desired crude product obtained as orange oil was subsequently converted to the hydrochloride.

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_f (free base) 0.28 (system b), anal. calcd for $C_{17}H_{24}ClN$: C, 73.49%; H, 8.71%; N, 5.04%; found C, 73.22%; H, 8.53%; N, 4.81%. ^{1}H NMR (DMSO-d_6): δ 1.43 (m, 6H, CH_2(Ad)), 1.57 (m, 6H, CH_2(Ad)), 1.90 (m, 3H, CH(Ad)), 2.38 (s, 2H, AdC**H**$_2$Ph), 7.19 (d, $J = 7.9$ Hz, 2H, Ph), 7.31 (d, $J = 7.9$ Hz, 2H, Ph), 10.43 (bs, 3H, NH_3^+) ppm. ^{13}C NMR (DMSO-d_6): δ 27.9 (CH), 32.9 (C), 36.4 (CH_2), 41.6 (CH_2), 49.5 (CH_2), 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^{-1}. GC-MS (EI, 70 eV); *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^+, 35), 242 (7).

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%. ^{1}H NMR (DMSO-d_6): δ 1.30 (m, 2H, AdC**H**$_2$), 1.52 (m, 6H, CH_2(Ad)), 1.65 (m, 3H, CH_2(Ad), 1.94 (s, 3H, CH(Ad)), 2.55 (m, 2H, PhC**H**$_2$), 7.22 (m, 3H, Ph), 7.36 (t, $J = 7.9$ Hz, 1H, Ph), 10.37 (bs, 3H, NH_3) ppm. ^{13}C NMR (DMSO-d_6): δ 28.1 (CH), 28.2 (CH_2), 32.0 (C), 36.6 (CH_2), 41.7 (CH_2), 46.0 (CH_2), 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^{-1}. GC-MS (EI, 70 eV); *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).

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_2 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%. ^{1}H NMR (DMSO-d_6): δ 1.44 (m, 6H, CH_2(Ad)), 1.50–1,66 (m, 6H, CH_2(Ad)), 1.91 (m, 3H, CH(Ad)), 2.38 (s, 2H, AdC**H**$_2$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_3^+) ppm. ^{13}C NMR (DMSO-d_6): δ 27.9 (CH), 32.9 (C), 36.4 (CH_2), 41.6 (CH_2), 49.8 (CH_2), 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^{-1}. GC-MS (EI, 70 eV); *m/z* (%): 41 (6), 67 (8), 77 (8), 79 (19), 91 (5), 93 (16), 106 (11), 107 (13), 135 (100), 136 (11), 241 (M^+, 35), 242 (7).

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