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# Dibenzo-1,5-diazocine-2,6-dione, 2-Iminoindolin-3-one and *N*-(Carbamoylmethyl)-aminobenzoic Acid Ester from Aminobenzoic Acid by Multicomponent Reactions†

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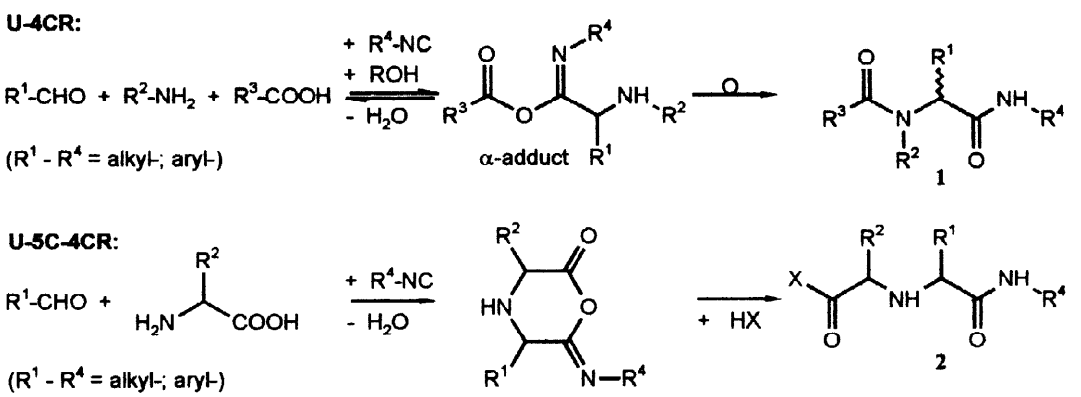
In memoriam of Sir Derek H. R. Barton

**Abstract:** Aminobenzoic acids show different types of multicomponent reactions when treated with a carbonylic component and an isocyanide in an alcoholic solution. Anthranilic acid provides dibenzo-1,5-diazocine-2,6-dione derivatives by a double Ugi four component reaction (U-4CR) or depending on the reaction conditions the U-5C-4CR product, a *N*-(carbamoylmethyl)anthranilic acid ester. Whereas anthranilic acid reacts hardly with ketones in that kind of multicomponent reaction. Instead the preferred reaction with isocyanides is the formation of 2-iminoindolin-3-ones. While 3-aminobenzoic acid shows no reaction, 4-aminobenzoic acid forms the U-5C-4CR product exclusively. 

Multicomponent reactions (MCR) have a long tradition [1,2]. Especially the U-4CR produces a good variety of possible products [3]. An amine, an aldehyde, an acid and an isocyanide form a U-4CR product of the general formula **1** by a one-pot reaction. The structure of the final product depends on the transformation of the α-adduct. The kind of the acid (e.g. carboxylic acid) determines the type of rearrangement. A special case of the U-4CR is the reaction with an α-aminoacid [4,5]. Its α-adduct is not able to rearrange as usual, but the nucleophilic solvent is acylated instead.




**Scheme 1:** Classical U-4CR and U-5C-4CR with α-aminoacids (X: nucleophile like alcohol, sodium hydroxide, 1° and 2° amine).

† MCR 7 (previous articles: MCR 1-6); # Auszug aus der Dissertation [11].

0040-4020/98/$ - see front matter 
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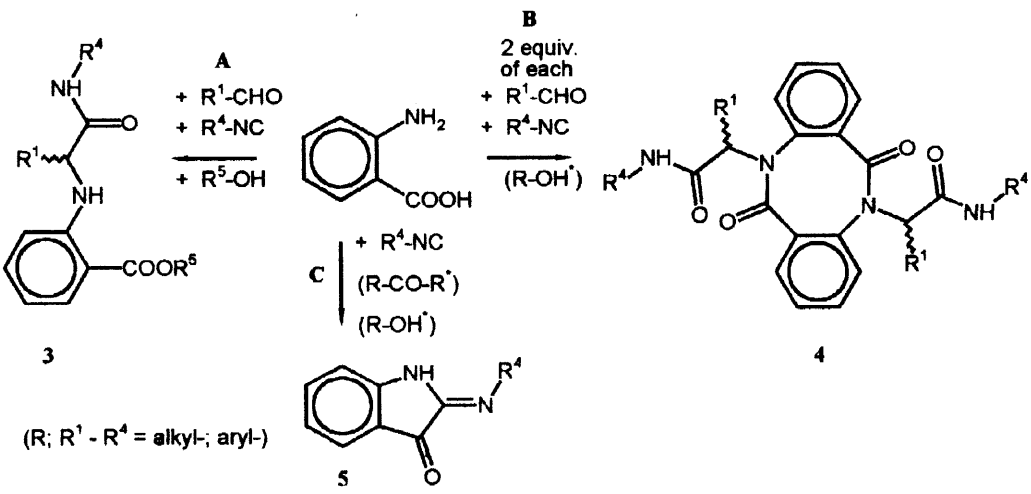
Many benzodiazepines have selective activities against diverse deseases. The 2,5-dioxo derivative *flumazenil* functions as a benzodiazepine antagonist [6]. 1,4-Benzodiazepine-2,5-dione derivatives have also shown promise as antithrombotics [7], as ethanol-intoxication antagonist [8] and as herbicides [9]. Further more they serve as precursors for antitumor antibiotics of the anthramycin family [10]. Their backbone consists of an annelated ring system of benzene and a seven-membered diazepine ring, a basic structure that appears in various natural products. By a U-4CR a similar ring system can be synthesized, with the diazepine ring being enlarged for one carbon atom. The one-pot reaction of anthranilic acid, an aldehyde and an isocyanide yields a dibenzo-1,5-diazocine-2,6-dione [11].

## 1. Multicomponent reactions of anthranilic acid leads to dibenzo-1,5-diazocine-2,6-diones and *N*-(carbamoylmethyl)anthranilic acid esters

Anthranilic acid undergoes MCR when treated with a carbonylic compound and an isocyanide. Equal equivalents of anthranilic acid, a carbonylic compound and an isocyanide react in alcohol, forming dibenzo-1,5diazocine-2,6-diones **4**, *N*-(carbamoylmethyl)anthranilic acid esters **3** or alternatively 2-iminoindolin-3-ones **5** by a one-pot reaction. The transition product, the imine, is condensed *in situ* without need of isolation or purification. Three different routes of reaction are possible.




**Scheme 2:** Reactions of anthranilic acid yielding dibenzo-1,5-diazocine-2,6-diones, *N*-(carbamoylmethyl)anthranilic acid esters or 2-iminoindolin-3-ones; * solvent.

Like α-aminoacids anthranilic acid cannot react in a classical U-4CR. So the expected reaction of anthranilic acid with aldehyde and isocyanide in alcoholic solution is the U-5C-4CR in which the solvent is acylated by the carboxylic group of the acid (see Scheme 1 and Scheme 2, route **A**). But only in case of sterically highly hindered aldehydes (like pivalaldehyde) or in presence of isocyanides carrying an ester function (like isocyano acetic acid methyl ester) the *N*-(carbamoylmethyl)anthranilic acid esters **3** are formed. Molecules like **3** were first synthesized by L. Capuano in 1966 who treated an anthranilic acid or -acid ester with methyl- or phenyl isocyanide and homologues of diazomethane [12].

Usually the reaction follows a different route (**B**) with two eqivalents of each component forming a Ugi 8 center 6 component product (U-8C-6C product) **4** in a double U-4CR. This condensation leads to a tricyclus of dibenzo-1,5-diazocine-2,6-diones. These are derivatives of benzodiazepinediones [9] being enlarged for one carbon atom. Instead of the seven-membered ring of the benzodiazepinedione basic structure they show an eight-membered ring structure. The intermolecular condensation of an amino group and a carboxylic group of two different molecules of anthranilic acid could be explained by the strong hydrogen bonds between them.

Ketones prefer to react in a different way (**C**) than aldehydes do. In a one-pot reaction with anthranilic acid, an isocyanide, a ketone and alcohol, the two latter compounds only serve as a solvent, but do not join the condensation. Anthranilic acid and isocyanide form a 2-iminoindolin-3-ones **5**. The yields for the synthesis with acetone and cyclohexanone to the 2-iminoindolin-3-ones lay between 50 and 60 %. The U-5C-4CR and 8C-6CR products are formed as by products (up to15 % each) only if the imine is precondensed in the presence of water withdrawing agents.

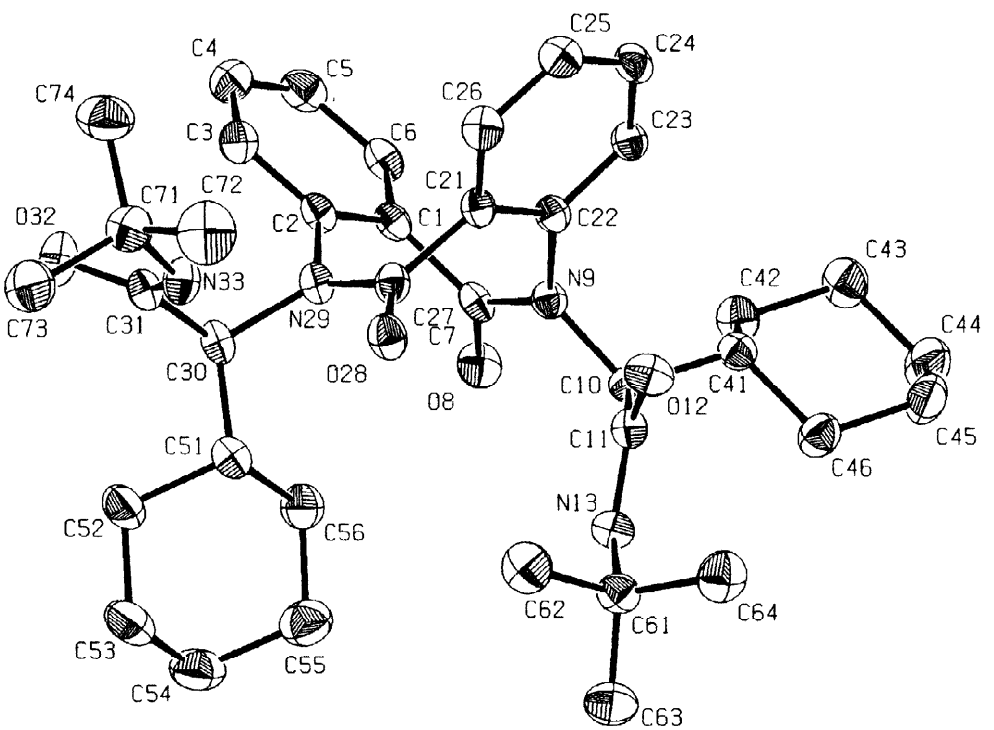
The way the reaction takes place mostly depends on the nature of the carbonylic component. In the presence of an aldehyde the products of both the U-5C-4CR and the U-8C-6CR are synthesized in most of the cases. For sterically highly hindered aldehydes or isocyanides carrying an ester U-5C-4CR products are obtained almost exclusively, while for other educts the double U-4CR is preferred. Usually a mixture of both products is formed. Table 1 shows the products of some selected syntheses with diverse aldehydes and isocyanides.

| **carbonylic component $R^1$-CHO** | **isocyanide $R^4$-NC** | **anthranilic acid mmol/ml solvent** | **reaction conditions time; ΔT: reflux** | **3:4:5 relation; yield (% of the product)** |
|---|---|---|---|---|
| pivalaldehyde | $MeO_2C$-$CH_2$-NC | (10/ 10) ethanol | 3-4 h/ΔT; 20 h/RT | 100:0:0 (**3a**=84 %) |
| pivalaldehyde | Me-NC | (10/ 10) ethanol | 3-4 h/ΔT; 20 h/RT | 100:0:0 (**3b**=68 %) |
| isobutyraldehyde | $EtO_2C$-$CH_2$-NC | (10/ 10) ethanol | 3-4 h/ΔT; 20 h/RT | 100:0:0 (**3c**=80 %) |
| propionealdehyde | $MeO_2C$-$CH_2$-NC | (10/ 10) methanol | 3-4 h/ΔT; 20 h/RT | 100:0:0 (**3d**=64 %) |
| cyclohexyl carbaldehyde | Me-NC | (1/ 5) ethanol | 3-4 h/ΔT; 20 h/RT | 50:50:0 (**3e**=46 %; **4e**=47 %) |
| benzaldehyde | t-Bu-NC | (5/ 75) methanol | 3-4 h/ΔT; 20 h/RT | 40:60:0 (**3f**=22 %; **4f**=32 %) |
| propionealdehyde | Me-NC | (10/ 10) methanol | 3-4 h/ΔT; 20 h/RT | 10:90:0 (**3g**=9 %; **4g**=80 %) |
| cyclohexyl carbaldehyde | t-Bu-NC | (10/ 10) i-propanol | 3-4 h/ΔT; 20 h/RT | 0:100:0 (**4h**=79 %) |
| isobutyraldehyde | t-Bu-NC | (10/ 10) tetrahydrofuran | 6 d/RT | 0:100:0 (**4i**=69 %) by product P-3CR |
| acetone | Me-NC | (5/ 50) ethanol | 1 d/RT | 0:0:100 (**5j**=59 %) |
| cyclohexane | $MeO_2C$-$CH_2$-NC | (5/ 10) methanol | 1 d/RT | 0:0:100 (**5k**=52 %) |
| acetone | Me-NC | (5/ 10) methanol | 3-4 h/ΔT; 1 d/RT | 20:20:60 (**3l**=18 %; **4l**=16 %; **5l**=58 %) |

**Table 1:** Multicomponent reactions with anthranilic acid leading to the products **3**, **4** and **5**.

Solvents like THF can also support the formation of the double U-4CR product. But mainly the ratio of the U-8C-6CR to the U-5C-4CR product is defined by the sterical demands of the aldehyde and the isocyanide. So the nature of the educts' substituents determines the reactions pathway. Beyond that there is a risk of Passerini-3 component reaction instead of U-8C-6CR by using nonpolar solvents.

In U-MCR a new carbon-carbon bond is formed accompanied with the formation of a new chiral center. As it is supposed the U-5C-4CR products are obtained in racemic mixtures. In case of U-8C-6CR to N,N'-di-(t-butylcarbamoylcyclohexylmethyl)dibenzo-1,5-diazocine-2,6-dione only two of four possible diastereomers are synthesized. The purified product was crystallized from methanolic solution. The colourless monoclinic crystals were examined by single crystal X-ray diffraction analysis showing the space group $P2_1/n$ and Z=4. Scheme 3 shows that the eight-membered ring of the dibenzodiazocine backbone has a boat shape, the two aromatic rings facing one level. Furthermore one the opposite side one equivalent of intersticial water is trapped by the two carbonylic groups (O8 and O12), one methanol (O81) and the bulky substituents. The asymmetric unit consists of two more equivalents of methanol (O81/C82; O83/C84). All acidic protons (N13-H; N33-H; $O_wH_2$; $CH_3OH$) are involved in a complex hydrogen bonding system (d O-O/ON: 266 pm - 288 pm) building up a three-dimensional network which will determine and dominate the reaction pathway **B**. In the case of molecule **4h** only the *R,R*- and *S,S*-enantiomeres could be detected.

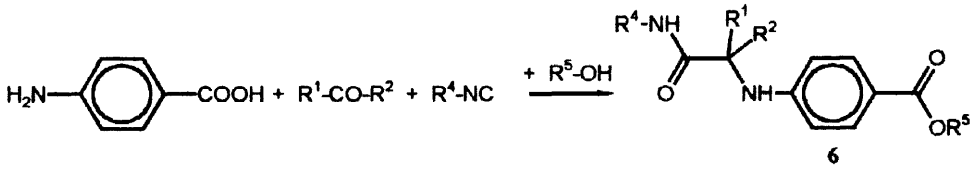



**Scheme 3:** X-ray structure of *N,N'*-{di-1-[*N*-(t-butyl)-carbamoyl]1-cyclohexylmethyl}dibenzodiazocine-2,6-dione **4h**.

## 2. *N*-(Carbamoylmethyl)p-aminobenzoic acid esters by U-5C-4CR with 4-aminobenzoic acid

Imines of aminobenzoic acids, stabilized by a conjugated π-electron system in the protonated state (the carboxylic group being deprotonated), take part in three different MCR with isocyanides in alcoholic solution. Both anthranilic acid and 4-aminobenzoic acid show MCR, whereas 3-aminobenzoic acid does not participate.

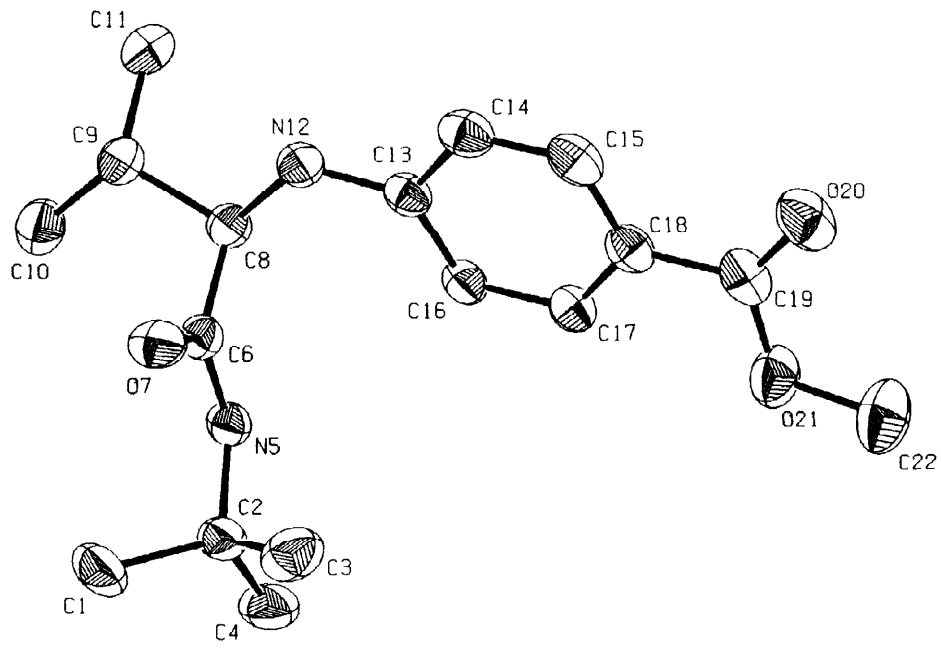
By treating 4-aminobenzoic acid in alcoholic solution with one equivalent of each, aldehyde and isocyanide, the U-5C-4CR product is obtained. The aldehydes and isocyanides can be varied with nearly free choice of the substitution exceptional very reactive aldehydes like furaldehyde or thiophene-2-carbaldehyde. As solvent all homologues of alcohols can be chosen, as long as the excess can be removed at the end of the reaction. In experiments all homologues of alcohol from methanol up to n-hexanol ($R^5$: $-C_6H_{13}$) gave the general U-5C-4CR products **6** in good yields (e.g. 37-80 %).




**6**

**Scheme 4:** 4-Aminobenzoic acid in the U-5C-4CR to *N*-(carbamoylmethyl)p-aminobenzoic acid esters **6** ($R^1$ - $R^5$ = alkyl-, aryl-).

In the absence of chirality inducing agents racemic mixtures are obtained. Isobutyraldehyde and t-butyl isocyanide react as educts in methanolic solution. There two enantiomeres of *N*-(t-butyl carbamoyl-2-methyl propyl)p-aminobenzoic acid methyl esters **6a** are formed. The pale yellow, monoclinic crystals of **6a** were examined by single crystal X-ray diffraction analysis showing a space group $P2_1/n$ and Z=4.




**Scheme 5:** ORTEP-plot of the X-ray structure of *N*-[(1-*N*-t-butylcarbamoyl)2-methylpropyl]4-aminobenzoic acid methyl ester **6a**.

Table 2 gives an overview over selected reactions with educts **6a-h**. Aliphatic aldehydes or isocyanides give high yields and purer products than aromatic compounds even at room temperature, while for the aromatic educts heating under reflux is necessary.

| 6X | carbonylic component $R^1$-CHO | isocyanide $R^4$-NC | alcohol $R^5$-OH | reaction conditions time; ΔT: reflux | yield (%) |
|---|---|---|---|---|---|
| **a** | isobutyraldehyde | t-Bu-NC | methanol | 2d; RT | 80 |
| **b** | propionaldehyde | Me-NC | methanol | 5d; RT; mol. sieves | 66 |
| **c** | isobutyraldehyde | Ph-NC | methanol | 1d; ΔT | 62 |
| **d** | benzaldehyde | $Ph_2CH$-NC | methanol | 3h; ΔT | 42 |
| **e** | anisaldehyde | $MeO_2C$-$CH_2$-NC | methanol | 1d; ΔT | 37 |
| **f** | hexylaldehyde | allyl isocyanide | ethanol | 1d; RT | 44 |
| **g** | cyclohexyl carbaldehyde | t-Bu-NC | isopropanol | 5d; RT; mol. sieves | 50 |
| **h** | cyclohexyl carbaldehyde | t-Bu-NC | hexanol | 1d; RT | 43 |

**Table 2:** Multicomponent reactions with 4-aminobenzoic acid to the products **6a-h**.

## 3. Discussion

Benzodiazocine diones can be synthesized by U-4CR in a one-pot reaction from three starting materials anthranilic acid, aldehydes and isocyanides. With good stereoselectivity only the *R,R* and *S,S*-enantiomers are obtained. As by products the reaction yields also the U-5C-4CR products. Ketones less reactive than aldehydes have to be condensed to the imine before treated with isocyanide. Otherwise 2-iminoindolin-3-ones are built instead of the U-5C-4CR products, the *N*-(carbamoylmethyl)aminobenzoic acid esters.

In contrast to anthranilic acid 4-aminobenzoic acid reacts in the supposed manner. Here, similar to α-aminoacids, the solvent is involved in the acylation and the U-5C-4CR product is formed.

By a variety of educts of each component large chemical libraries can be created by these varations of the Ugi reaction.

## 4. Experimental

### *General purification of products*

When the convertion was finished, the solvent was removed in vacuum. The residue was solved in dichloro methane and washed with water twice. The organic layer was dried over magnesium sulfate, filtrated and the product was dried under high vacuum.

### *General procedure for the preparation of N-(carbamoylmethyl)anthranilic acid esters 3*

685 mg (5 mmol) of anthranilic acid are solved in absolute alcohol and 5 mmol of each, aldehyde and isocyanide were added. The mixture is stirred by heating under reflux for 3-4 h and another hour at room temperature.

### *Physical data for N-(carbamoylmethyl)anthranilic acid esters 3*

**3a.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.40 (d; 1H; -NH-CH-; J= 4.5 Hz); 7.97 (d; 1H; Ar: -CH- 3; J= 7.8 Hz); 7.35 (t; 1H; Ar: -CH- 5; J= 7.1 Hz); 6.95 (s (broad); 1H; -CO-NH-); 6.70 (t; 1H; Ar: -CH- 4; $J^1$= 7.8 Hz; $J^2$= 7.1 Hz); 6.56 (d; 1H; Ar: -CH- 6; J= 8.4 Hz); 4.34 (q, 2H; -$CH_2$-$CH_3$; J= 7.1 Hz); 4.16 (dd; 1H; -NH-CHH-CO-; $J^1$= 6.5 Hz; $J^2$= 18.2 Hz); 3.84 (dd; 1H; -NH-CHH-CO-; $J^1$= 6.5 Hz; $J^2$= 18.2 Hz); 3.67 (s; 3H; -$CO_2$-$CH_3$); 3.57 (d; 1H; -CH-C($CH_3$)$_3$; J= 4.5 Hz); 1.40 (t; 3H; -$CH_2$-$CH_3$; J= 7.1 Hz); 1.19 (s; 9H; -C($CH_3$)$_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 172.4 (-$CO_2$-$CH_3$); 169.9 (-CO-NH-); 168.7 (Ar-$CO_2$-); 150.2 (Ar: -C- 1); 134.7 (Ar: -C- 5); 131.4 (Ar: -C- 3); 116.3 (Ar: -C- 4); 112.3 (Ar: -C- 6); 111.3 (Ar: -C- 2); 68.0 (-CH-C($CH_3$)$_3$); 60.5 (Ar-$CO_2$-$CH_2$-$CH_3$); 52.0 (-$CO_2$-$CH_3$); 40.8 (-$CH_2$-$CO_2$-$CH_3$); 34.2 (-C($CH_3$)$_3$); 27.2 (-C($CH_3$)$_3$); 14.2 (Ar-$CO_2$-$CH_2$-$CH_3$) ppm. GCMS (EI): m/z for $C_{18}H_{26}N_2O_5$ $M^+$: 350.

**3b.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.33 (s (broad); 1H; -NH-CH-); 7.97 (d; 1H; Ar: -CH- 3; J= 8.5 Hz); 7.34 (t; 1H; Ar: -CH- 5; J= 7.1 Hz); 7.17 (s (broad); 1H; -CO-NH-); 6.72 (t; 1H; Ar: -CH- 4; J= 7.8 Hz); 6.53 (d; 1H; Ar: -CH- 6; J= 8.4 Hz); 4.35 (q; 2H; -$CH_2$-$CH_3$; J= 7.1 Hz); 3.52 (d; 1H; -CH-; J= 3.9 Hz); 2.76 (d; 3H; -NH-$CH_3$; J= 4.5 Hz); 1.41 (t; 3H; -$CH_2$-$CH_3$; J= 7.1 Hz); 1.15 (s; 9H; -C($CH_3$)$_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 172.8 (-$CH_2$-$CO_2$-); 169.9 (-CO-NH-); 167.4 (Ar-$CO_2$-); 141.2 (Ar: -C- 1); 135.3 (Ar: -C- 5); 131.9 (Ar: -C- 3); 117.0 (Ar: -C- 4); 112.6 (Ar: -C- 6); 108.3 (Ar: -C- 2); 68.5 (-NH-$CH_3$); 60.9 (-$CO_2$-$CH_2$-); 37.4 (-C($CH_3$)$_3$); 27.7 (-C($CH_3$)$_3$); 26.3 (-NH-$CH_3$); 14.7 (-$CH_2$-$CH_3$) ppm. GCMS (EI): m/z for $C_{16}H_{24}N_2O_3$ $M^+$: 292.

**3c.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.25 (s; 1H; -NH-CH-); 7.95 (d; 1H; Ar: -CH- 3; J= 8.4 Hz); 7.39 (t; 1H; Ar: -CH- 5; J= 8.4 Hz); 7.08 (s (broad); 1H; -CO-NH-); 6.73 (t; 1H; Ar: -CH- 4; J= 7.8 Hz); 6.59 (d; 1H; Ar: -CH- 6; J= 8.4 Hz); 4.03 (ddd; 2H; -$CH_2$-$CO_2$-; $J^1$= 7.8 Hz; $J^2$= 5.8 Hz; $J^3$= 5.2 Hz); 3.89 (s; 3H; Ar-$CO_2$-$CH_3$); 3.78 (d; 1H; -NH-CH-; J= 4.5 Hz); 3.69 (s; 3H; -$CH_2$-$CO_2$-$CH_3$); 2.09 (ddq; 1H; -CH-CHH-$CH_3$; $J^1$= 7.8 Hz; $J^2$= 7.1 Hz; $J^3$= 4.6 Hz); 1.92 (ddq; 1H; -CH-CHH-$CH_3$; $J^1$= 7.8 Hz; $J^2$= 7.1 Hz; $J^3$= 4.6 Hz); 1.10 (dt; 3H; -CH-$CH_2$-$CH_3$; J= 7.1 Hz) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 173.7 (-$CH_2$-$CO_2$-); 171.5 (-CO-NH-); 169.5 (Ar-$CO_2$-); 149.7 (Ar: -C- 1); 134.5 (Ar: -C- 5); 131.2 (Ar: -C- 3); 116.4 (Ar: -C- 4); 112.3 (Ar: -C- 6); 111.5 (Ar: -C- 2); 59.9 (-NH-CH-); 51.8 (-$CH_2$-$CO_2$-$CH_3$); 51.4 (Ar-$CO_2$-$CH_3$); 40.8 (-$CH_2$-$CO_2$-$CH_3$); 26.4 (-CH-$CH_2$-$CH_3$); 10.1 (-CH-$CH_2$-$CH_3$) ppm. GCMS (FAB), m/z for $C_{15}H_{20}N_2O_5$ $M^+$: 308.

### *General procedure for the preparation of dibenzo-1,5-diazocine-2,6-diones 4*

1370 mg (10 mmol) of anthranilic acid are solved. For solvent and concentration see Table 1. 10 mmol of each aldehyde and isocyanide are added. For the reaction conditions see table 1 and for purification above.

### *Physical data for dibenzo-1,5-diazocine-2,6-diones 4*

**4e.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.34 - 7.00 (m; 8H; Ar: -CH- 3,3',4,4',5,5',6,6'); 4.63 (d; 2H; 2* -CH-c-Hex ; J= 13.7Hz); 2.84 and 2.73 (m; 2H; 2* c-Hex: -CH- 1; J= 10.6 Hz); 2.30 (d; 6H; 2* -NH-$CH_3$); 2.00 - 0.70 (m; 20H; 2* c-Hex: -$CH_2$- 2-6) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 169.6 (2* Ar-CO-NH-); 169.1

(2* -CO-NH-t-Bu); 139.4 (2* Ar: -C- 2); 134.9 (2* Ar: -C- 1); 130.8 (2* Ar: -C- 6); 128.0 (2* Ar: -C- 4); 127.2 (2* Ar: -C- 5); 125.1 (2* Ar: -C- 3); 38.4 (2* -CH-c-Hex); 30.4 (2* c-Hex -CH-); 29.8 (2* c-Hex -$CH_2$- 2.6); 26.3 (-NH-$CH_3$); 26.0 (2* c-Hex -$CH_2$- 3,5); 25.8 (2* c-Hex -$CH_2$- 4) ppm. GCMS (EI), m/z for $C_{32}H_{40}N_4O_4$ $M^+$: 544.

**4f.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.02 - 6.50 (m; 18H; Ar: -CH- 3,3',4,4',5,5',6,6'; 2* Ph); 4.23 (s; 2H; 2* -CH-Ph); 1.38 (s; 18H; 2* t-Bu) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 169.7 (2* Ar-CO-NH-); 169.3 (2* -CO-NH-t-Bu); 139.4 (2* Ar: -C- 2); 134.9 (2* Ar: -C- 1); 130.8 (2* Ar: -C- 6); 128.3 (2* Ar: -C- 4); 127.1 (2* Ar: -C- 5); 125.2 (2* Ar: -C- 3); 64.1 (-CH-Ph); 51.2 (2* -$C(CH_3)_3$); 28.6 (-$C(CH_3)_3$) ppm. GCMS (CI), m/z for $C_{38}H_{40}N_4O_4$ $M^+$: 616.

**4g.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.96 - 6.90 (m; 8H; Ar: -CH- 3,3',4,4',5,5',6,6'); 3.89 (d; 2H; 2* -CH-$CH_2$-$CH_3$ ; J= 10.6 Hz); 2.86 (d; 6H; 2* -NH-$CH_3$; J= 4.9 Hz); 2.28 - 1.99 (m; 4H; 2* -$CH_2$-); 1.12 - 0.84 (m; 6H; -$CH_2$-$CH_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 169.9 (2* Ar-CO-NH-); 169.1 (2* -CO-NH-t-Bu); 139.3 (2* Ar: -C- 2); 134.9 (2* Ar: -C- 1); 130.9 (2* Ar: -C- 6); 128.1 (2* Ar: -C- 4); 127.0 (2* Ar: -C- 5); 125.2 (2* Ar: -C- 3); 60.2 (-CH-$CH_2$-$CH_3$); 26.4 (-NH-$CH_3$); 22.1 (-$CH_2$-); 10.7 (-$CH_2$-$CH_3$) ppm. GCMS (CI), m/z for $C_{24}H_{28}N_4O_4$ $M^+$: 436.

**4h.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.24 - 7.14 (m; 6H; Ar: -CH- 3,3',4,4',5,5'); 7.05 (d; 2H; Ar: -CH- 6,6'; J= 7.5 Hz); 4.07 (d; 2H; 2* -CH-c-Hex ; J= 10.6 Hz); 2.63 (q; 2H; 2* c-Hex: -CH- 1; J= 10.6 Hz); 2.04 - 0.98 (m; 20H; 2* c-Hex: -$CH_2$- 2-6); 1.38 (s; 18H; 2* t-Bu) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 169.6 (2* Ar-CO-NH-); 169.0 (2* -CO-NH-t-Bu); 139.6 (2* Ar: -C- 2); 134.9 (2* Ar: -C- 1); 130.7 (2* Ar: -C- 6); 128.1 (2* Ar: -C- 4); 127.0 (2* Ar: -C- 5); 125.1 (2* Ar: -C- 3); 51.3 (2* -$C(CH_3)_3$); 38.5 (2* -CH-c-Hex); 30.4 (2* c-Hex -CH-); 29.9 (2* c-Hex -$CH_2$- 2.6); 28.9 (-$C(CH_3)_3$); 26.1 (2* c-Hex -$CH_2$- 3,5); 25.6 (2* c-Hex -$CH_2$- 4) ppm. GCMS (EI), m/z for $C_{38}H_{52}N_4O_4$ $M^+$: 628.

**4i.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.24 - 7.15 (m; 6H; Ar: -CH- 3,3',4,4',5,5'); 7.08 (d; 2H; Ar: -CH- 6,6'; J= 7.1 Hz); 3.99 (d; 2H; 2* -CH-i-Pr ; J= 11.0 Hz); 2.98 (sept; 2H; 2* CH-CH-$(CH_3)_2$; $J^1$= 6.5 Hz; $J^2$= 5.8 Hz); 1.39 (s; 18H; 2* t-Bu); 1.16 and 1.04 (d; 12H; -CH-$(CH_3)_2$; J= 6.5 Hz) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 169.7 (2* Ar-CO-NH-); 169.0 (2* -CO-NH-t-Bu); 139.5 (2* Ar: -C- 2); 134.8 (2* Ar: -C- 1); 130.8 (2* Ar: -C- 6); 128.2 (2* Ar: -C- 4); 127.1 (2* Ar: -C- 5); 125.2 (2* Ar: -C- 3); 51.3 (2* -$C(CH_3)_3$); 29.3 (-CH-$(CH_3)_2$); 28.6 (-$C(CH_3)_3$); 20.1 and 19.9 (-CH-$(CH_3)_2$) ppm. GCMS (EI), m/z for $C_{32}H_{44}N_4O_4$ $M^+$: 448.

### *General procedure for the preparation of or 2-iminoindolin-3-ones 5*

685 mg (5 mmol) anthranilic acid are solved in 20 ml of absolute alcohol. Then 5 mmol of the isocyanide are added. The mixture is heated under reflux for one day. For purification see above.

### *Physical data for 2-iminoindolin-3-ones 5*

**5j.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.28 (d; 1H; Ar: -CH- 6; J= 8.0 Hz); 8.16 (s; 1H; -NH-); 7.74 - 7.71 (m; 2H; Ar: -CH- 3,4); 7.48 (m; 1H; Ar: -CH- 5); 3.57 (s; 3H; -$CH_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 171.7 (-CO-); 161.3 (-C=N-); 150.8 (Ar: -C- 1); 134.3 (Ar: -C- 5); 131.8 (Ar: -C- 3); 116.5 (Ar: -C- 4); 116.0 (Ar: -C- 6); 110.3 (Ar: -C- 2); 34.0 (-$CH_3$) ppm. GCMS (EI), m/z for $C_9H_8N_2O$ $M^+$: 160.

**5k.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.31 (d; 1H; Ar: -CH- 6; J= 8.0 Hz); 8.07 (s; 1H; -NH-); 7.81 - 7.74 (m; 2H; Ar: -CH- 3,4); 7.53 (m; 1H; Ar: -CH- 5); 4.74 (s; 2H; -CH-); 3.81 (s; 3H; -$CO_2CH_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 175.1 (-$CO_2CH_3$); 173.0 (-CO-); 167.7 (-C=N-); 151.0 (Ar: -C- 1); 134.8 (Ar: -C- 5); 132.0

(Ar: -C- 3); 116.7 (Ar: -C- 4); 116.3 (Ar: -C- 6); 110.3 (Ar: -C- 2); 52.9 (-$CO_2CH_3$); 47.3 (-$CH_2$-) ppm. GCMS (EI), m/z for $C_{11}H_{10}N_2O_3$ $M^+$: 218.

**5l. = 5j.**

### *General Procedure for the Preperation of N-(carbamoylmethyl)p-aminobenzoic acid esters 6*

1370 mg (10 mmol) of 4-aminobenzoic acid are solved in 10 ml of absolute alcohol and 10 mmol of each, carbonylic component and isocyanide are added. The mixture is stirred at room temperature one day at minimum. In the presence of aromatic aldehydes or paraformaldehyde heating under reflux is necessary. The complete convertion of the educts is indicated through the missing of the characteristic odour of the isocyanide. (For general purification see above.)

### *Physical data for N-(carbamoylmethyl)p-aminobenzoic acid esters 6*

**6a.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.84 (d; 2H; Ar: -CH- 3,5; J= 8.4 Hz); 6.64 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 6.36 (s (broad); 1H; -NH-CO-); 4.76 (s (broad); 1H; -CH-NH-); 3.85 (s; 3H; -CO-$OCH_3$); 3.60 (d; 1H; -CH-$CH(CH_3)_2$; J= 4.9 Hz); 2.31 (dsept; 1H; -$CH(CH_3)_2$; $J^1$= 4.9 Hz; $J^2$= 6.6 Hz and 6.2 Hz); 1.31 (s; 9H; -$C(CH_3)_3$); 1.03 and 1.04 (d; 6H; -$CH(CH_3)_2$; J= 6.6 Hz and 6.2 Hz) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 171.0 (-NH-CO-); 167.1 (-$CO_2$-$CH_3$); 151.2 (Ar: -C- 1); 131.4 (Ar: -CH- 3,5); 119.3 (Ar: -C- 4); 112.4 (Ar: -CH- 2,6); 64.3 (-CH-$CH(CH_3)_2$); 51.4 (-$OCH_3$); 51.0 (-$C(CH_3)_3$); 31.1 (-$CH(CH_3)_2$); 28.4 (-$CH(CH_3)_3$); 19.3 and 17.8 (-$CH(CH_3)_2$) ppm. GCMS (CI), m/z for $C_{17}H_{26}N_2O_3$ $M^+$: 306.

**6b.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.86 (d; 2H; Ar: -CH- 3,5; J= 8.4 Hz); 6.67 (d; 1H; -CH-NH-; J= 4.4 Hz); 6.58 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 4.65 (d; 1H; -NH-CO-; J= 4.9 Hz); 3.85 (s; 3H; -CO-$OCH_3$); 3.76 (m; 1H; -CH-$CH_2$-$CH_3$; J= 4.4 Hz); 2.79 (d; 3H; -NH-$CH_3$; J= 4.9 Hz); 2.00 (dt; 1H; -CHH-; J= 7.1 Hz); 1.78 (dt; 1H; -CHH-; J= 7.5 Hz); 1.04 (t; 3H; -$CH_2$-$CH_3$; J= 7.5 Hz) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$): δ 173.1 (-NH-CO-); 167.0 (-$CO_2$-$CH_3$); 150.8 (Ar: -C- 1); 131.5 (Ar: -CH- 3,5); 119.9 (Ar: -C- 4); 112.3 (Ar: -CH- 2,6); 59.9 (-CH-$CH_2$-$CH_3$); 51.5 (-$OCH_3$); 26.5 (-$CH_2$-); 26.0 (-NH-$CH_3$); 10.3 (-$CH_2$-$CH_3$) ppm. GCMS (CI), m/z for $C_{13}H_{18}N_2O_3$ $M^+$: 250.

**6c.** $^1$H NMR (360 MHz, $CDCl_3$): δ 8.28 (d; 1H; Ph: -CH- 4; J= 9.3 Hz); 7.88 (d; 2H; Ar: -CH- 3.5; J= 8.4 Hz); 7.48 (2H; Ph: -CH- 2,6; J= 8.0 Hz); 7.11 (t; 2H; Ph: -CH- 3,5; J= 7.5 Hz); 6.68 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 6.37 (m (broad); 1H; -NH-CO-); 4.52 (s (broad); 1H; -CH-NH-); 3.86 (s; 3H; -CO-$OCH_3$); 3.80 (d; 1H; -CH-$CH(CH_3)_2$; J= 4.9 Hz); 2.50 (dsept; 1H; -$CH(CH_3)_2$; $J^1$= 4.9 Hz; $J^2$= 6.6 Hz and 6.2 Hz); 1.11 and 1.07 (d; 6H; -$CH(CH_3)_2$; J= 6.6 Hz and 6.2 Hz) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$) δ 171.2 (-NH-CO-); 167.3 (-CO-$OCH_3$); 151.0 (-CO-$C_6H_4$-NH-: -C- 1); 137.0 (Ph: -C- 1); 131.5 (-CO-$C_6H_4$-NH-: -CH- 3,5); 128.9 (Ph: -C- 2); 124.5 (Ph: -C- 4); 121.0 (Ph: -C- 3); 119.5 (-CO-$C_6H_4$-NH-: -C- 4); 112.6 (-CO-$C_6H_4$-NH-: -CH- 2,6); 64.7 (-CH-$CH(CH_3)_2$); 51.5 (-$OCH_3$); 31.5 (-$CH(CH_3)_2$); 19.4 and 17.9 (-$CH(CH_3)_2$) ppm. GCMS (CI), m/z for $C_{19}H_{22}N_2O_3$ $M^+$: 326.

**6d.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.76 (d; 2H; Ar: -CH- 3,5; J= 8.4 Hz); 7.43 - 6.90 (m; 10H; Ph: -CH-; benzyl: -CH-); 6.50 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 5.50 (s (broad); 1H; -NH-CO-); 4.90 (s; 1H; -CH-NH-); 4.37 and 4.28 (m; 2H; -$CH_2$-); 3.77 (s; 3H; -CO-$OCH_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$) δ 170.4 (-NH-CO-); 167.1 (-CO-$OCH_3$); 150.0 (Ar: -C- 1); 138.2 - 113.7 (Ph; benzyl: -CH-, -C-); 131.5 (Ar: -CH- 3,5); 119.4 (Ar: -C- 4); 112.6 (Ar: -CH- 2,6); 62.2 (-CH-Ph); 51.5 (-$OCH_3$); 43.5 (-$CH_2$-) ppm. GCMS (CI), m/z for $C_{23}H_{22}N_2O_3$ $M^+$: 374.

**6e.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.74 (d; 2H; Ar: -CH- 3,5; J= 11.4 Hz); 7.30 (d; 2H; $CH_3O$-Ar: -CH- 3,5; J= 11.4 Hz); 6.80 (d; 2H; $CH_3O$-Ar: -CH- 2,6; J= 10.5 Hz); 6.49 (d; 2H; Ar: -CH- 2,6; J= 11.4 Hz); 5.19 (d; 1H; -CH-NH-; J= 4.4 Hz); 4.79 (d; 1H; -NH-CO-; J= 4.4 Hz); 4.02 (ddd; 2H; $-CH_2-CO_2CH_3$; $J^1$= 7.92 Hz; $J^2$= 7.02 Hz); 3.80 (d; 1H; -NH-CH-; J= 4.4 Hz); 3.74 (s; 3H; -CO-$OCH_3$); 3.68 (s; 3H; Ar-$OCH_3$); 3.61 (s; 3H; $-CH_2-CO_2-CH_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$) δ 171.3 ($-CH_2-CO_2-$); 169.9 (-CO-NH-); 167.1 (Ar-$CO_2-$); 159.8 (Ar-OMe: -C- 1); 129.7 (Ar-OMe: -C- 4); 128.5 (Ar-OMe: -C- 3,5); 114.6 (Ar-$OCH_3$: -C- 2,5); 150.1 (Ar: -C- 1); 131.3 (Ar: -CH- 3,5); 119.7 (Ar: -C- 4); 112.7 (Ar: -CH- 2,6); 61.8 (-NH-CH-); 55.2 (Ar-$OCH_3$); 52.3 ($-CH_2-CO_2CH_3$); 51.6 (Ar-$CO_2CH_3$); 41.2 ($-CH_2-$) ppm. GCMS (CI), m/z for $C_{20}H_{22}N_2O_6$ $M^+$: 386.

**6f.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.87 (d; 2H; Ar: -CH- 3,5; J= 8.4 Hz); 6.94 (s (broad); 1H; -NH-CO-); 6.60 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 5.78 (dokt; 1H; $CH_2=CH-$; $J^1$= 6.2 Hz; $J^2$= 5.7 Hz; $J^3$= 5.3 Hz); 5.13 (s (broad); 1H; -NH-CH-); (dd; 2H; $-CH_2-CH=CH_2$); 5.08 (d; 2H; $CH_2=CH-$; J= 6.2 Hz); 5.03 (s (broad); 1H; -CH-NH-); 4.31 (dq; 2H; -CO-$OCH_2$; $J^1$= 7.1 Hz; $J^2$= 4.4 Hz); 3.86 (t; 1H; -NH-CH-CO-; J= 5.7 Hz); 1.98 (dsex; 1H; -CH-CHH-; $J^1$= 5.7 Hz; $J^2$= 5.3 Hz; $J^3$= 4.9 Hz); 1.73 (dsex; 1H; -CH-CHH-; $J^1$= 5.7 Hz; $J^2$= 5.3 Hz; $J^3$= 4.9 Hz); 1.53 - 1.04 (m; 6H; hexyl: 3* $-CH_2-$); 0.87 (t; 3H; $-CH_2-CH_3$; J= 7.1 Hz); 0.82 (m; 3H; hexyl: $-CH_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$) δ 172.7 (-NH-CO-); 166.6 ($-CO_2-CH_3$); 151.0 (Ar: -C- 1); 132.1($-CH=CH_2$); 131.5 (Ar: -CH- 3,5); 116.2 (Ar: -C- 4); 113.7 ($-CH=CH_2$); 112.4 (Ar: -CH- 2,6); 60.3 ($-CO_2CH_2-$); 58.9 (-NH-CH-); 41.5 ($-CH_2-CH=CH_2$); 33.4 (-CH-$CH_2-$); 31.4 ($-CH-CH_2-CH_2-$); 25.6 ($CH_3-CH_2-CH_2-$); 22.3 ($CH_3-CH_2-$); 14.3 ($-CO_2-CH_2-CH_3$) ppm. GCMS (CI), m/z for $C_{15}H_{26}N_2O_3$ $M^+$: 354.

**6g.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.85 (d; 2H; Ar: -CH- 3,5; J= 8.4 Hz); 6.59 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 6.25 (s (broad); 1H; -NH-CO-); 5.20 (sept; 1H; $-CH-(CH_3)_2$; J= 6.2 Hz); 4.53 (s (broad); 1H; -CH-NH-); 3.53 (dd; 1H; $-CH-C_6H_{11}$; J= 4.4 Hz); 2.0 - 1.1 (m; 11H; $C_6H_{11}$); 1.37 - 1.29 (m, 6H; $-CH-(CH_3)_2$); 1.30 (s; 9H; $-C(CH_3)_3$) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$) δ 170.9 (-NH-CO-); 166.1 ($-CO_2-CH_3$); 151.0 (Ar: -C- 1); 131.4 (Ar: -CH- 3,5); 120.7 (Ar: -C- 4); 112.4 (Ar: -CH- 2,6); 67.4 ($-CO_2-CH-$); 64.3 (-CH-c-Hex); 51.1 ($-C(CH_3)_3$); 41.0 (c-Hex: -CH-); 30.0 (c-Hex: $-CH_2-$ 2.6); 28.7 ($-CH(CH_3)_3$); 26.1 (c-Hex: $-CH_2-$ 3,5); 26.0 (c-Hex: $-CH_2-$ 4); 22.0 ($-CH-(CH_3)_2$) ppm. GCMS (CI), m/z for $C_{22}H_{34}N_2O_3$ $M^+$: 374.

**6h.** $^1$H NMR (360 MHz, $CDCl_3$): δ 7.87 (d; 2H; Ar: -CH- 3,5; J= 8.4 Hz); 6.60 (d; 2H; Ar: -CH- 2,6; J= 8.4 Hz); 6.26 (s (broad); 1H; -NH-CO-); 4.53 (d; 1H; -CH-NH-; J= 4.4 Hz); 4.26 (t; 2H; -CO-$OCH_2-$; J= 6.6 Hz); 3.53 (t; 1H; $-CH-C_6H_{10}$; J= 4.9 Hz); 2.00 - 1.10 (m; 17H; hexyl: 4*-$CH_2-$; $C_6H_{11}$: -CH- and 4*-$CH_2-$); 1.31 (s; 9H; $-C(CH_3)_3$); 1.00 - 0.82 (m; 5H; hexyl: $-CH_3$; $C_6H_{11}$: $-CH_2-$ 4) ppm. $^{13}$C NMR (360 MHz, $CDCl_3$) δ 170.7 (-NH-CO-); 166.6 ($-CO_2-CH_3$); 151.1 (Ar: -C- 1); 131.3 (Ar: -CH- 3,5); 120.2 (Ar: -C- 4); 112.4 (Ar: -CH- 2,6); 64.3 ($-CO_2-CH_2-$); 64.3 (-CH-c-Hex); 51.0 ($-C(CH_3)_3$); 41.0 (c-Hex: -CH-); 31.4 ($-CO_2-CH_2-CH_2-$); 30.0 (c-Hex: $-CH_2-$ 2,6); 28.8 ($-CH(CH_3)_3$); 28.6 ($CH_3-CH_2-CH_2-CH_2-$); 26.1 (c-Hex: $-CH_2-$ 3,5); 26.0 ($CH_3-CH_2-CH_2-$); 25.6 (c-Hex: $-CH_2-$ 4); 22.5 ($CH_3-CH_2-$); 13.9 ($CH_3-CH_2-CH_2-$) ppm. GCMS (CI), m/z for $C_{25}H_{40}N_2O_3$ $M^+$: 416.

### *X-ray analyses*

Single crystals of **4h** suitable for an X-ray diffraction study were grown by slow evaporation of a methanolic solution of the compound. The diffraction study was carried out at -100±3 °C (173±3 K) on a CAD4 (Nonius) diffractometer, using graphite-monochromated Mo-$K_\alpha$ radiation, λ=71.073 pm. *Crystal data*: $C_{38}H_{52}N_4O_4*H_2O*2CH_3OH$, *M*=711, monoclinic, colorless crystal of 0.5*0.2*0.2 mm, space group $P2_1/n$ (No.

14), $a$=1676.7(5), $b$= 842.5(1), $c$=2928.3(8) pm, β=104.717(13)°, V=4001(2)*$10^6$ $pm^3$ (from 25 setting reflections with 18.0°<Θ<22.4°), Z=4, $D_c$=1.180 g $cm^{-3}$, F(000)=1544, μ=0.8 $cm^{-1}$. A set of 8073 data was collected in ω scan mode width (0.85 + 0.15*tanΘ)° ± 25% for background determination, of these 7792 were unique ($R_{int}$=0.0214), 4793 observed with I>2.0*σ(I). The structure was solved by direct methods and refined by full-matrix least squares (51 non-H atoms anisotropic, 56 H atoms refined isotropically, 684 variables) of all data, converging at R1(F, obs. data)=0.0476, wR2($F^2$, all data)=0.1247, goodness of fit 1.026; residual electron density $\Delta\rho_{max}$=0.22, $\Delta\rho_{min}$=-0.24 $eA^{-3}$. SHELXS-86 and L-93 software were used [13].

Single crystals of **6a** suitable for an X-ray diffraction study were grown by slow evaporation of a methanolic solution of the compound. The diffraction study was carried out at -110±3 °C (163±3 K) on a CAD4 (Nonius) diffractometer, using graphite-monochromated Cu-$K_\alpha$ radiation, λ=154.184 pm. *Crystal data*: $C_{17}H_{26}N_2O_3$, $M$=306, monoclinic, pale yellow crystal fragment of 0.84*0.51*0.38 mm, space group $P2_1/n$ (No. 14), $a$=936.7(1), $b$= 1302.3(1), $c$=1513.2(2) pm, β=105.126(6)°, V=1781.9(3)*$10^6$ $pm^3$ (from 25 setting reflections with 81.5°<2Θ<96.2°), Z=4, $D_c$=1.142 g $cm^{-3}$, F(000)=664, μ=6.3 $cm^{-1}$. A set of 3681 data was collected in Θ/2Θ scan mode width (1.00+0.20*tanΘ)° ± 25% for background determination, of these 3380 were unique ($R_{int}$=0.0198), 2821 observed with I>2.0*σ(I). The structure was solved by direct methods and refined by full-matrix least squares (22 non-H atoms anisotropic, 26 H atoms refined isotropically, 303 variables) of all data, converging at R1(F, obs. data)=0.0537, wR2($F^2$, all data)=0.1483, goodness of fit 1.085; residual electron density $\Delta\rho_{max}$=0.23, $\Delta\rho_{min}$=-0.29 $eA^{-3}$. SIR-92, MoleN and SHELXL-93 software were used [13].

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## 6. References

(1) A. Dömling, I. Ugi, *Angew. Chem.*, **1993**, *105*, 634. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 563.

(2) I. Ugi, A. Dömling, W. Hörl, *Endeavour*, **1994**, *18*, 115; I. Ugi, *J. prakt. Chem.*, **1997**, *339*, 499.

(3) I. Ugi, M. Goebel, M. Heilingbrunner, C. Heiß, W. Hörl, O. Kern, M. Starnecker, A. Dömling, *Res. Chem. Intermed.*, **1996**, *22*, 625; A. Dömling, *Combinatorial Chemistry High Throuput Screening*, **1998**, *1*, 1.

(4) I. Ugi, *Isonitrile Chemistry*, Academic Press: *Vol. 20*, New York, **1971**.

(5) A. Demharter, W. Hörl, E. Herdtweck, I. Ugi, *Angew. Chem.*, **1996**, *108*, 185; *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 173.

(6) H. J. Rost, H. Fenner, *Pharmazeutische Chemie III - Arzneistoffe*, Georg Thieme Verlag: 2° *Ed.* New York, **1994**; W. Hunkeler, *Chimia*, **1993**, *47*, 141.

(7) R. R. Webb, P. R. Barker, M. Baier, M. E. Reynolds, K. D. Robarge, B. K. Blackburn, M. H. Tichler, K. Weese, *Tetrahedron Lett.*, **1994**, *35*, 2113; R. S. McDowell, T. R. Gadek, L. R. McGee, T. Rawson, M. Reynolds, K. D. Robarge, T. C. Somers, E. D. Thorsett, M. Tischler, R. R. Webb, M. C. Venuti, *J. Am. Chem. Soc.* **1994**, *116*, 5077.

(8) P. D. Suzdak, J. R. Glowa, J. N. Crawley, R. D. Schwartz, P. Skolnick, S. M. Paul, *Br. J. Pharmacol.*, **1986**, *234*, 1243; P. Polc, J. G. Richarks, *Br. J. Pharmacol.*, **1985**, *86*, 465; O. Malminiemi, E. R. Korpi, *Eur. J. Pharmacol.*, **1989**, *169*, 53; E. P. Bonetti, W. P. Burkard, M. Gabl, H. Mohler, J. G. Richards, *Br. J. Pharmacol.*, **1985**, *86*, 463.

(9) G. M. Karp, *J. Org. Chem.*, **1995**, *60*, 5814.

(10) M. Ishikura, M. Mori, M. Terashima, Y. Ban, *J. Chem. Soc., Chem. Commun.*, **1982**, 741; M. Mori, Y. Uozumi, M. Kimura, Y. Ban, *Tetrahedron*, **1986**, *42*, 3793; J. N. Reed, V. Snieckus, *Tetrahedron*, **1984**, *25*, 5505; T. Kaneko, H. Wong, T. W. Doyle, *Tetrahedron Lett.*, **1983**, *24*, 5165; R. V. Stevens, R. M. Cory, S. Rossen, *J. Chem. Soc., Chem. Commun.*, **1975**, 742; P. N. Confalone, E. M. Huie, S. S. Ko, G. M. Cole, *J. Org. Chem.*, **1988**, *53*, 482; M. R. Peña, J. K. Stille, *Tetrahedron Lett.*, **1987**, *28*, 6573; M. R. Peña, J. K. Stille, *J. Am. Chem. Soc.*, **1989**, *111*, 5417.

(11) B. M. Ebert, *Dissertation*, TU München, **1998**.

(12) L. Capuano, M. Zander, *Chem. Ber.*, **1966**, *89*, 3085; *Liebigs Ann. Chem.*, **1968**, *712*, 73.

(13) Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographiy Data Centre as supplementary publication no. CCDC-XXX-XXX (4H) and CCDC-YYY (6A). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223)336033; e-mail: deposit@chemcrys.cam.ac.uk).