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ORIGINAL PAPER

N-Acylbenzotriazole: convenient approach for protecting group-free monoacylation of symmetric diamines

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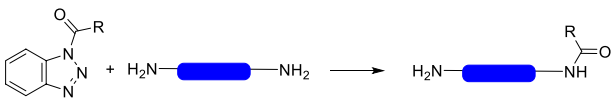
Abstract

An efficient green route for monoacylation of aromatic diamines, namely *o*-phenylenediamine and *p*-phenylenediamine and aliphatic diamines ethylenediamine and piperazine using *N*-acylbenzotriazoles (NABs) in *n*-butanol was developed. The new protocol does not require prior selective protection of the diamine and comprises simple conditions, short reaction times, an easy work up as well as high isolated yields (69–94%). Moreover, the method described herein enable stepwise acylation of aliphatic diamines such as ethylenediamine and piperazine with two different *N*-acylbenzotriazoles affording unsymmetrical substituted diamines that can be used for construction of pharmaceutically important targets such as drugs, foldamers, and drug conjugates.

Graphic abstract



Keywords *N*-Acylbenzotriazole · Monoacylation · Diamine · Piperazine

Introduction

Monoacylated diamines are frequently used building blocks in drug synthesis. *N*-monoacyl-*o*-phenylenediamines are valuable building blocks that have been utilized for construction of a variety of targets such as metal complexing antitumor Schiff bases [1], pyridine-2,6-dicarboxylamide oligoamide foldamers [2], 2- substituted benzimidazoles [3], chemosensors [4], and urolithins B [5]. In addition, *N*-monoacylation of *p*-phenylenediamine enabled the synthesis of amphiphilic gelators [6], antagonists of smoothened receptor [7], and modulators of Wnt/β-catenin signaling [8]. The synthesis of anticancer compounds like aminoacyl-anthraquinone conjugates [9] and 18-β-glycyrrhetinic acid conjugates [10] requires *N*-monoacylation of ethylenediamine. Furthermore, *N*-monoacylpiperazines are the key intermediates for the construction of potent nootropic drugs based on DM235 (sunifiram) (Fig. 1) [11–13].

Planning a synthetic protocol for the synthesis of such compounds requires controlled acylation of one amino group while keeping the other group free. In spite of their widespread use in drug synthesis, reported methods for direct monoacylation of diamines are hampered by the low yields of the monoamides, even in the presence of a large excess of the diamine [14]. Other limitations include, the use of harsh condition and starting materials which are not readily available as well as tedious work up to eliminate diamide

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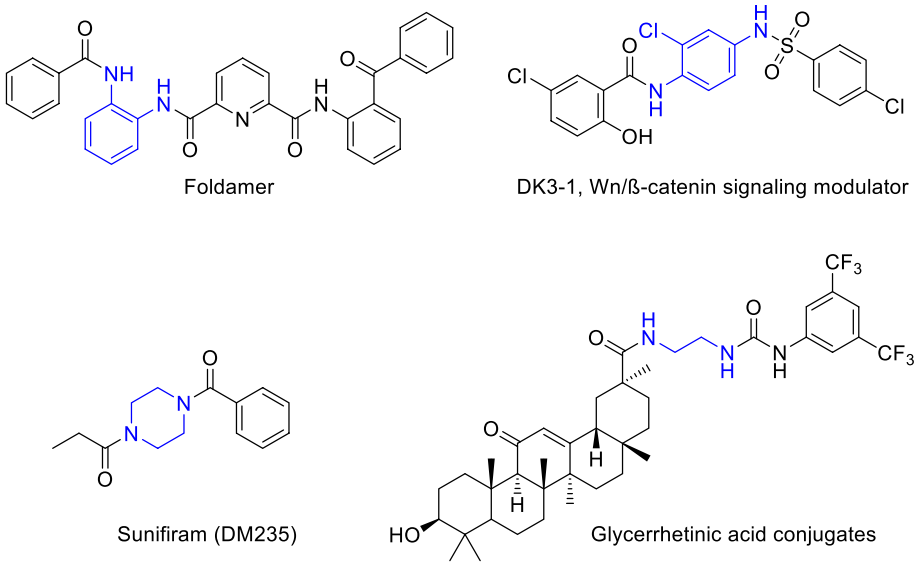


Fig. 1 Some acylated diamines of pharmaceutical interest

products [15–18]. To our knowledge, the most practical method for monoacylation is the *N*-BOC monoprotection of the diamine followed by acylation and deprotection [19, 20]. However, this method adds more steps to the synthesis and may lower the overall yield.

The difficulties faced during the synthesis of monoacylated diamines and the need for notable amount of pure monoacylated products, evoked many research groups to continue searching for more effective protocols for their synthesis. For example, Fang group utilized phenyl esters for monoacylation of diamines. The reaction needed 24 h to reach completion and a tedious chromatographic work up to separate the monoacylated products in low to moderate yields [20]. Also, Kaushik group utilized acyl imidazole as a reagent, although the reported yields was said to be excellent [16] when repeated under the same condition a lower yield was obtained [18]. Selective monoacylation of aliphatic diamines was also accomplished using ionic immobilization of diamines to sulfonic acid functionalized silica gel. However, the method failed to give useful yields [21].

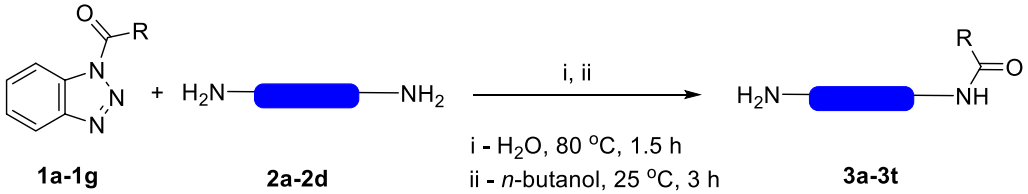
Herein, we report a new strategy for monoacylation of aliphatic and aromatic diamines using *N*-acylbenzotriazoles (NABs). NABs are well known as effective acylating agents for the construction of peptides, peptidomimetics, and drug conjugates [22, 23]. They are easily synthesized, easily handled, isolated in high yields, and chirality is preserved during their preparation and reaction [24].

Results and discussion

In the current work, *p*-phenylenediamine (**2a**) and *o*-phenylenediamine (**2b**) (1.5 equivalent) were reacted with *N*-benzoylbenzotriazole (**1a**) [25] in water at 80 °C for 1.5 h to give the targets **3a** and **3b** in 80% and 78% isolated yields, respectively. Repeating the reaction of **2a** and **2b** with NABs **1b**–**1g** under the aforementioned reaction conditions gave monoacylated aromatic diamines in 73-83% isolated yields (Scheme 1, Table 1). On the other hand, the reaction of piperazine and ethylenediamine with *N*-benzoylbenzotriazole (**1a**) in water or ethanol water (1:1) at 25 °C gave low isolated yields of monobenzoylated products (15% for **3c** and 18% for **3d**). This might be attributed to the similarity of the two p*K*a's of the aliphatic diamine and the limited reduction in the nucleophilicity of the second nitrogen upon benzoylation of the first one [26]. However, upon stirring aliphatic diamines **2c** or **2d** with **1a** in *n*-butanol for 3 h afforded *N*-benzoylpiperazine (**3c**) and *N*-benzoylethylenediamine (**3d**) in 69% and 85% isolated yields, respectively. Such improvement in isolated yields may be due to the low solubility of monoacylated piperazines in *n*-butanol.

To gain insight into the outcomes of the reaction in different solvents, we performed LC-Q-TOF–MS analysis for the reaction between *N*-benzoylbenzotriazole and piperazine in water, ethanol: water (1:1), or *n*-butanol (Fig. 2). LC-Q-TOF-MS chromatogram of the reaction in water showed the presence of some monoacylated and diacylated products ($t_R = 2.3$ and 9.4 min, respectively) as well as a number of side products (Fig. 2a). On using ethanol: water (1:1), the LC-Q-TOF-MS chromatogram revealed that the reaction is cleaner, however, the monoacylated product ($t_R = 2.2$ min) is present in a low percentage (Fig. 2b) which justifies the low isolated yield of the monoacylated product. The use of *n*-butanol as a solvent decreased the formation of side products significantly (Fig. 2c) and the extracted ion chromatogram (Fig. 3) revealed that the ratio of monobenzoylpiperazine ($[M+H]^+$: 191.1150) to dibenzoylpiperazine ($[M+H]^+$: 295.1333) was 100:2. This

Scheme 1



2a: *p*-phenylenediamine, **2b**: *o*-phenylenediamine, **2c**: piperazine, **2d**: ethylenediamine

	R
1a	C_6H_5
1b	Cbz-NH-CH_2-
1c	4-$CH_3OC_6H_4$
1d	3,4,5-$(CH_3O)_3C_6H_2$
1e	3-NO_2-C_6H_4
1f	$CH_3(CH_2)_{16}$
1g	2-$NH_2C_6H_4$

confirms that lowering polarity of the solvent enabled a cleaner and a controlled reaction.

n-Butanol was then used as a solvent for acylation of both aliphatic and aromatic diamines **2a**–**2d** with NABs **1a**–**1g** at 25 °C. The reaction in *n*-butanol gave better yields of monoacylated aromatic diamines (82–94%) and high isolated yields of monoacylated aliphatic diamines (69–86%) (Scheme 1, Table 1).

The scope of the current monoacylation protocol included the preparation of interesting monoacylated diamines **3s**, **3t** in high isolated yields (82–86%) via reaction of *p*-phenylenediamine and piperazine with *N*-(2-aminobenzoyl)benzotriazole (**1g**). Such intermediates are valuable for the construction of biologically active compounds [27, 28] and polyamide fibers [29], literature preparation of **3t** requires a multistep solid-phase synthesis and long reaction times [30]. In addition, preparation of **3s** requires the protection of one of the two amino groups of *p*-phenylenediamine [31].

To explore the applications of the new protocol, *N*-benzoylpiperazine (**3c**) was reacted with NAB **1b** and *N*-(Cbz-gly)ethylenediamine (**3h**) was reacted with NABS **1a**, **1c** in *n*-butanol for 1 h to give the unsymmetrical substituted aliphatic diamines **4a**–**4c** in 88–90% isolated yields (Scheme 2). The main advantages of the new approach are (i) high overall yields, (ii) short reaction times, (iii) use of inexpensive starting materials, (iv) use of green solvent, and (v) benzotriazole can be recycled.

This shows the potential of benzotriazole-based monoacylation and unsymmetrical diacylations in the construction of biologically active molecules.

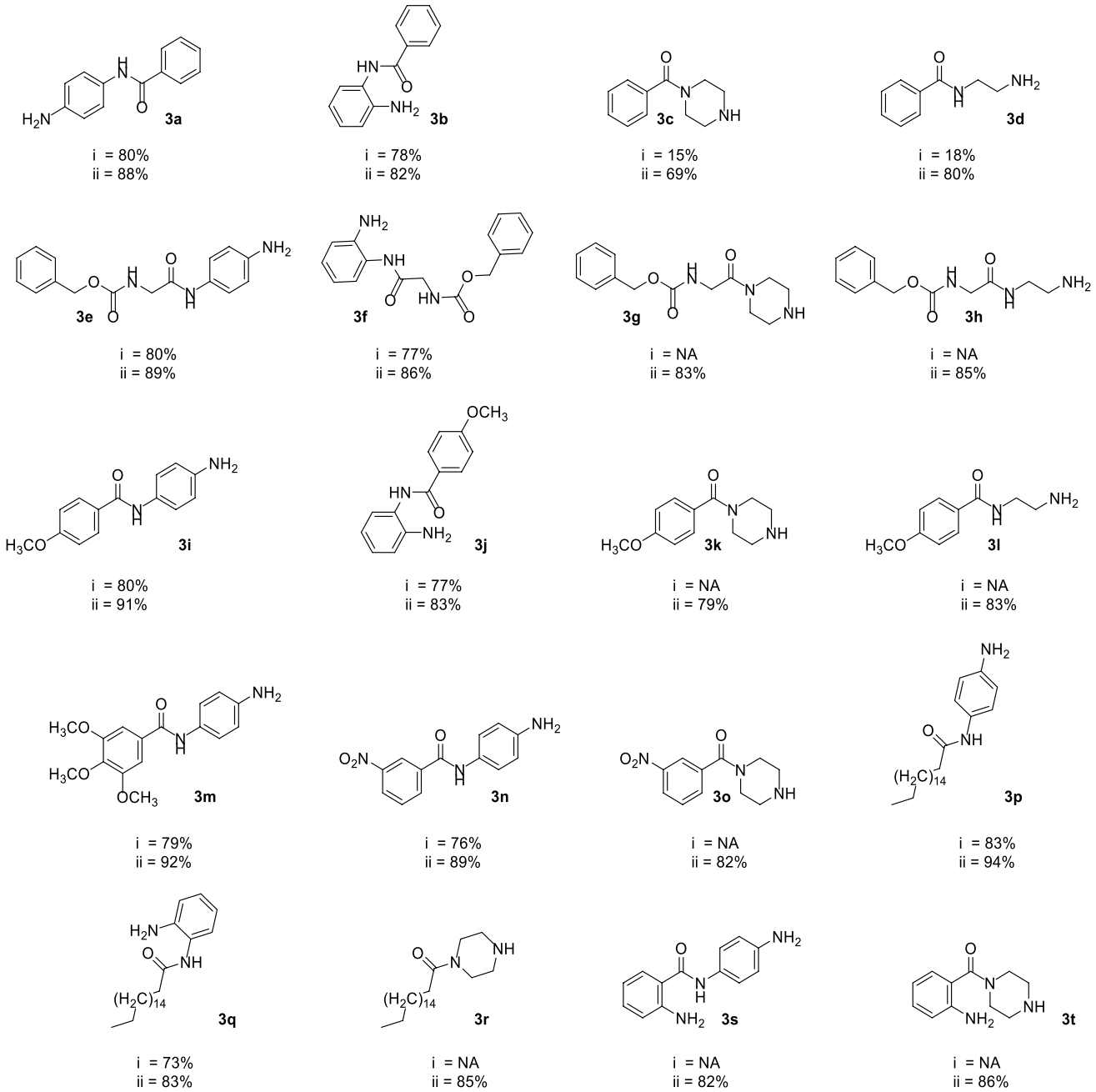
Conclusion

In conclusion, we have demonstrated a simple and high yielding procedure for controlled monoacylation and unsymmetrical diacylation of diamines with various *N*-acylbenzotriazoles. The advantage of this method includes the ease of preparation of NABs, the short reaction time and the use of green *n*-butanol as well as the easy recycling of the leaving group (1*H*-benzotriazole).

Experimental

Starting materials and solvents were purchased from common commercial sources and used without further purification. Melting points were determined on Fisher melting apparatus. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a JEOL 500 MHz NMR spectrometer and using DMSO-d_6 and $CDCl_3$ as solvents, at

Table 1 Monoacylation of diamines using different solvent systems



Reaction conditions: (i)—H_2O, 80 °C (used with *p*-phenylenediamine and *o*-phenylenediamine), (ii)—*n*-butanol, 25 °C, 3 h (optimum solvent for aromatic and aliphatic diamines)

Faculty of Science, Mansoura University. Also Bruker 400 MHz NMR spectrometer at Faculty of Science, Zagazig University and Faculty of Pharmacy, Mansoura University was used. The chemical shift (δ) is reported in ppm, and coupling constants (J) are given in Hz. The LC-Q-TOF-MS system 6530 (Agilent Technologies, Santa Clara, CA, USA) equipped with an autosampler (G7129A), a quat. pump (G7104C), a DAD detector (G7115 A), and a column comp (G7116A) was used for chromatographic separation at Faculty of Pharmacy, Fayoum University. Elemental analysis was performed on the Thermo Fisher Flash 2000 CHNS analyzer at the Regional Center for Mycology and Biotechnology, Al-Azhar University. All reactions were monitored by TLC with visualization by UV irradiation.

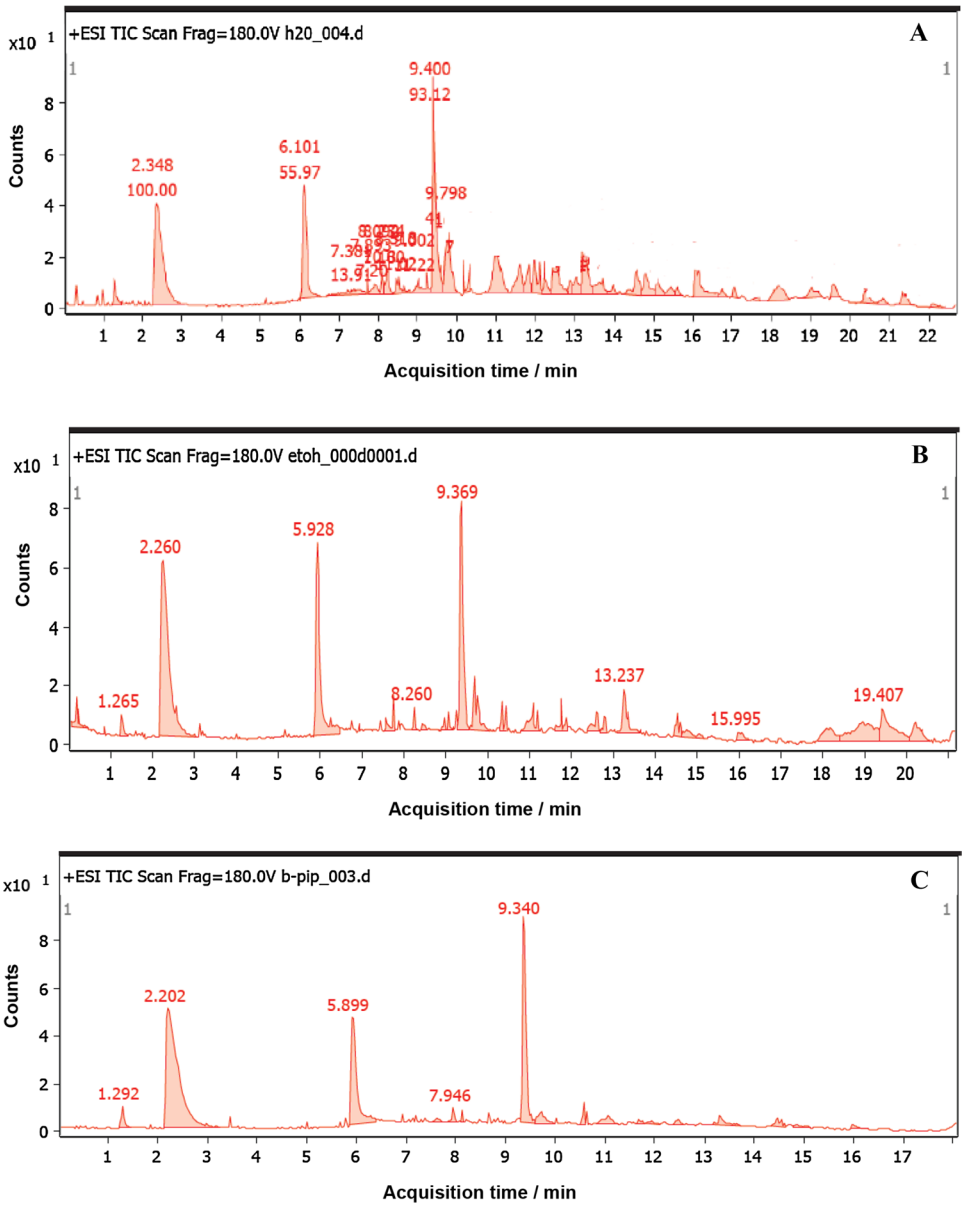


Fig. 2 LC-Q-TOF-MS chromatogram in different solvents: **a** water, **b** ethanol:water (1:1), C: *n*-butanol (monoacylated product around $t_R = 2.2$ min, the diacylated around $t_R = 9.3$ min)

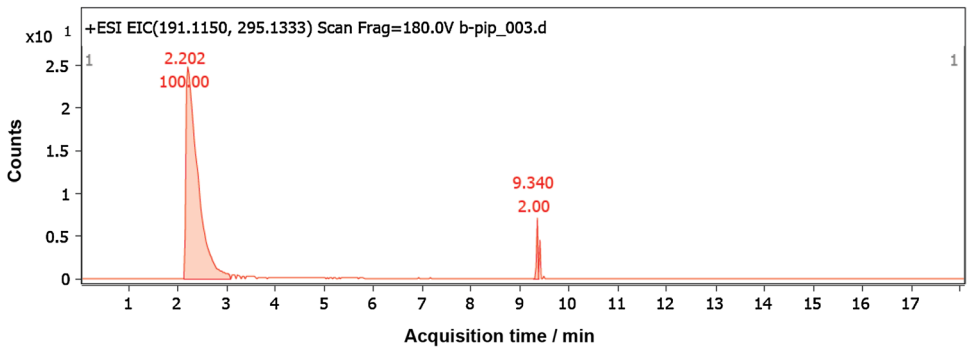
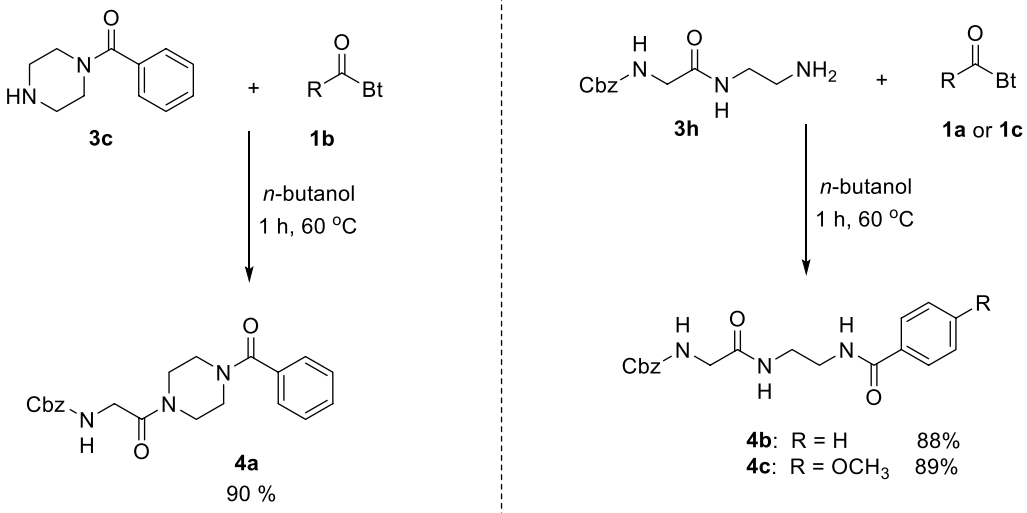


Fig. 3 Ratio between monobenzoylated piperazine $[M+H]^+$ to diacylated piperazine $[M+H]^+$ in *n*-butanol solvent

Scheme 2



General procedure for the synthesis of *N*-acylbenzotriazoles 1a–1g

To 4.76 g BtH (40 mmol) dissolved in 50 cm^3 CH_2Cl_2, 0.73 cm^3 $SOCl_2$ (10 mmol) were added. The mixture was stirred at 25 °C for 30 min, followed by the addition of the corresponding acid (10 mmol) and the reaction was allowed to stir for an additional 3 h at 25 °C. The reaction was diluted with 50 cm^3 CH_2Cl_2 and the organic layer was washed with saturated Na_2CO_3 (3 × 20 cm^3), 20 cm^3 H_2O, and 10 cm^3 brine. The organic layer was dried over anhydrous sodium sulfate, 50 cm^3 hexane was added to the filtrate, and then the solid obtained was dried under vacuum to give compounds **1a**–**1g**.

(1*H*-1,2,3-Benzotriazol-1-yl)(phenyl)methanone (1a) White microcrystals; yield 2.1 g (94%); m.p.: 111–112 °C (Ref. [25] 110–112 °C).

Benzyl [2-(1*H*-benzo[*d*] [1–3] triazol-1-yl)-2-oxoethyl]carbamate (1b) White microcrystals; yield 2.9 g (93%); m.p.: 107–109 °C (Ref. [23] 106–108 °C).

(1*H*-1,2,3-Benzotriazol-1-yl) (4-methoxyphenyl)methanone (1c) White microcrystals; yield 2.4 g (95%); m.p.: 102–104 °C (Ref. [25] 103–104 °C).

(1*H*-1,2,3-Benzotriazol-1-yl) (3,4,5-trimethoxyphenyl)methanone (1d) White microcrystals; yield 2.9 g (93%); m.p.: 126–128 °C (Ref. [25] 126–128 °C).

(1*H*-1,2,3-Benzotriazol-1-yl) (3-nitrophenyl)methanone (1e) White microcrystals; yield 2.4 g (89%); m.p. 157–159 °C (Ref. [23] 159–162 °C).

1-(1*H*-1,2,3-Benzotriazol-1-yl)octadecan-1-one (1f) White microcrystals; yield 3.51 g (91%); m.p.: 58–60 °C (Ref. [25] 58–60 °C).

(2-Aminophenyl)(1*H*-benzo[*d*] [1–3] triazol-1-yl)methanone (1g) Yellow microcrystals; yield 1.5 g (63%); m.p.: 130–132 °C (Ref. [32] 132–133 °C).

General procedure for monoacylation of symmetrical aromatic diamines in water as a solvent

In a round bottom flask, aromatic diamines *p*-phenylenediamine (**2a**) or *o*-phenylenediamine (**2b**) (7.5 mmol), were added to 5 cm^3 water followed by addition of *N*-acylbenzotriazoles **1a**–**1g** (5 mmol). The mixture was heated at 80–100 °C for 30–60 min. Upon completion of the reaction (monitored by TLC, ethylacetate/hexane 1:1), the mixture was cooled. Ethyl acetate (20 cm^3) was added and the organic layer was washed with saturated Na_2CO_3 (3 × 5 cm^3), water (2 × 5 cm^3), and 5 cm^3 brine. After evaporation of ethyl acetate under reduced pressure, the solid separated was dried under vacuum to give the desired monoacylated products (Table 1).

General procedure for monoacylation of symmetrical aromatic diamines in *n*-butanol

In a round bottom flask, *p*-phenylenediamine (**2a**) or *o*-phenylenediamine (**2b**) (7.5 mmol), were dissolved in 5 cm^3 of *n*-butanol at 25 °C. The corresponding *N*-acylbenzotriazole **1a**–**1g** (5 mmol) was then added to the solution and the mixture was stirred at room temperature for 3 h. Upon completion of the reaction (monitored by TLC ethylacetate/hexane 1:1) *n*-butanol was evaporated. The semisolid was dissolved in 20 cm^3 ethyl acetate and the organic layer was washed with saturated Na_2CO_3 (3 × 5 cm^3), water (2 × 5 cm^3), and 5 cm^3 brine. After evaporation of ethyl acetate under reduced pressure, the solid separated was dried under vacuum to give the desired monoacylated products (Table 1).

General procedure for monoacylation of aliphatic diamines in *n*-butanol

In a round bottom flask, piperazine (**2c**) or ethylenediamine (**2d**) (15 mmol) were dissolved in 10 cm^3 *n*-butanol. To the dissolved solution the corresponding *N*-acylbenzotriazoles **1a**–**1g** (10 mmol) were added. The mixture was stirred at 25 °C for 3 h. The reaction mixture was filtered and the *n*-butanol was removed under reduced pressure. The residue was dissolved in 2 cm^3 methanol and loaded on a silica gel column. A mixture of hexane—ethylacetate—methanol (2:3:5) was used for elution of the pure monoacylated products which were dried under reduced pressure (Table 1).

The LC–MS-based study of the reaction outcome

The LC-Q-TOF–MS system 6530 (Agilent Technologies, Santa Clara, CA, USA) equipped with an autosampler (G7129A), a quat. Pump (G7104C), a DAD detector (G7115 A), and a column comp)G7116A) was used for chromatographic separation. A Q-TOF mass spectrometer (G6530C) was applied for the identification and determination of 1-benzoylpiperazine and 1,4-dibenzoylpiperazine in the reaction mixture. The injection volume was 1 mm^3. The reaction mixture components were separated on a Zorbax RP-18 column from Agilent Technologies (dimensions: 150 mm × 3 mm, $dp = 2.7$ µm) in a flow rate of 0.5 cm^3/min. The mobile phase consisted of a combination of solvent A (water + 0.1% formic acid) and solvent B (acetonitrile + 0.1% formic acid). The gradient elution was as follows: $t = 0$ min, 10% B; $t = 1$ min, 10% B; $t = 16$ min, 100% B. Mass spectra were simultaneously acquired using ESI in positive ionization modes with a capillary voltage of 4000 V. The mass spectra were recorded in the *m/z* range of 50–1700. The gas temperature and drying gas flow were 325 °C and 10 dm^3/min, respectively. The skimmer and fragmentator voltages were set at 45 and 180 V, respectively. The nebulization pressure was 20 psig.

***N*-(4-Aminophenyl)benzamide (3a, $C_{13}H_{12}N_2O$)** Brown microcrystals; yield 0.93 g (88%); m.p.: 103–105 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.86$ (s, 1H, NH), 7.91 (d, $J = 7.2$ Hz, 2H, Ar–H), 7.56–7.47 (m, 3H, Ar–H), 7.37 (d, $J = 8.0$ Hz, 2H, Ar–H), 6.54 (d, $J = 8.0$ Hz, 2H, Ar–H), 4.92 (s, 2H, NH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 164.7$ (CO), 145.2 (=C–NH_2), 135.3 (=C–CO), 131.1 (Ar–C), 128.3 (Ar–C), 127.4 (Ar–C), 122.3 (Ar–C), 120.7 (Ar–C), 113.7 (Ar–C) ppm.

***N*-(2-Aminophenyl)benzamide (3b, $C_{13}H_{12}N_2O$)** Buff microcrystals; yield 0.87 g (82%); m.p.: 133–135 °C;^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 9.67$ (s, 1H, NH), 7.98 (d, $J = 7.0$ Hz, 2H, Ar–H), 7.57 (t, $J = 7.2$ Hz, 1H, Ar–H), 7.51 (t, $J = 7.5$ Hz, 2H, Ar–H), 7.16 (d, $J = 7.5$ Hz, 1H, Ar–H), 6.97 (t, $J = 6.8$ Hz, 1H, Ar–H), 6.78 (d, $J = 8.0$ Hz, 1H, Ar–H), 6.59 (t, $J = 7.0$ Hz, 1H, Ar–H), 4.90 (s, 2H, NH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 165.3$ (CO), 143.2 (=C–NH_2), 134.6 (=C–CO–), 131.4 (Ar–C), 128.3 (Ar–C), 127.8 (Ar–C), 126.5 (Ar–C), 123.3 (Ar–C), 117.3 (Ar–C), 116.3 (Ar–C), 114.5 (Ar–C) ppm.

Phenyl(piperazin-1-yl)methanone (3c) Oil; yield 1.31 g (69%); ^{1}H NMR spectrum was found to conform with the one described in Ref. [15].

***N*-(2-Aminoethyl)benzamide (3d)** Yellow microcrystals; yield 1.32 g (80%); m.p.: 65–67 °C; ^{1}H NMR spectrum was found to conform with the one described in Ref. [33].

Benzyl [2-[(4-aminophenyl)amino]-2-oxoethyl]carbamate (3e, $C_{16}H_{17}N_3O_3$) Brown microcrystals; yield 1.33 g (89%); m.p.: 111–113 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.56$ (s, 1H, N<u>H</u>), 7.55 (s, 1H, OCON<u>H</u>), 7.39–7.23 (m, 7H, Ar–H), 6.54 (d, $J = 7.2$ Hz, 2H, Ar–H), 5.07 (s, 2H, OCH_2), 4.87 (s, 2H, NH_2), 3.76 (s, 2H, $NHCH_2$) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 166.9$ (CO), 156.6 (OCO), 144.8 (C–NH_2), 137.1 (OCH_2C), 134.4 (Ar–C), 128.4 (Ar–C), 127.7 (Ar–C), 120.9 (Ar–C), 119.5 (Ar–C), 113.8 (Ar–C), 65.5 (OCH_2), 43.9 ($NHCH_2$) ppm.

Benzyl [2-[(2-aminophenyl)amino]-2-oxoethyl]carbamate (3f, $C_{16}H_{17}N_3O_3$) Brown microcrystals; yield 1.29 g (86%); m.p.: 106–108 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.91$ (s, 1H, NH), 7.53 (d, $J = 5$ Hz, 1H, OCON<u>H</u>), 7.43 (d, $J = 7.0$ Hz, 1H, Ar–H), 7.38–7.36 (m, 4H, Ar–H), 7.33–7.29 (m, 1H, Ar–H), 7.16-7.09 (m, 3H, Ar–H), 5.07 (s, 2H, NH_2), 5.05 (s, 2H, OCH_2), 4.42 (d, $J = 5.0$ Hz, 2H, $COCH_2$) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 169.3$ (CO), 157.3

(OCO), 153.1 (H_2N–C), 137.3 (OCH_2C–), 129.1 (Ar–C), 128.6 (Ar–C), 128.4 (Ar–C), 128.3 (Ar–C), 127.5 (Ar–C), 122.5 (Ar–C), 118.8 (Ar–C), 112.0 (Ar–C), 66.5 (OCH_2), 44.6 (CH_2) ppm.

Benzyl [2-oxo-2-(piperazin-1-yl)ethyl]carbamate (3g, $C_{14}H_{19}N_3O_3$) Oil; yield 2.3 g (83%); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.35–7.27$ (m, 6H, Ar–H, –CO–NH–), 5.02 (s, 2H, OCH_2), 3.83 (s, 2H, CH_2CO), 3.32 [d, br, 4H, $CON(CH_2–)_2–$], 2.62 [d, br, 4H, $HN(CH_2)_2–$], 1.67 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 167.1$ (CO), 156.6 (OCO), 137.2 (OCH_2C), 128.5 (Ar–C), 127.9 (Ar–C), 127.8 (Ar–C), 65.5 (OCH_2), 45.8 [$CON(CH_2–)_2–$], 45.5 [$HN(CH_2)_2–$], 42.1 ($COCH_2$) ppm.

Benzyl [2-[(2-aminoethyl)amino]-2-oxoethyl]carbamate (3h, $C_{12}H_{17}N_3O_3$) Buff microcrystals; yield 2.14 g (85%); m.p.: 131–133 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.92$ (s, 1H, OCONH), 7.41 (s, 1H, NH), 7.34–7.27 (m, 5H, Ar–H), 4.99 (s, 2H, OCH_2), 3.54 (s, 2H, $COCH_2$), 3.04 (t, $J = 5.5$ Hz, 2H, $NHCH_2$), 2.53 (t, $J = 5.5$ Hz, 2H, $NHCH_2CH_2$), 1.71(s, 2H, NH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 169.1$ ($NHCOCH_2$), 156.5 (OCO), 137.1 (Ar–C), 128.4 (Ar–C), 127.8 (Ar–C), 127.7 (Ar–C), 65.5 (OCH_2), 43.6 ($COCH_2$), 41.0 ($CONHCH_2$), 38.3 (CH_2NH_2) ppm.

***N*-(4-Aminophenyl)-4-methoxybenzamide (3i, $C_{14}H_{14}N_2O_2$)** Buff microcrystals; yield 1.1 g (91%); m.p.: 169–171 °C;^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 9.71$ (s, 1H, NH), 7.90 (d, $J = 8.7$ Hz, 2H, Ar–H), 7.34 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.02 (d, $J = 8.7$ Hz, 2H, Ar–H), 6.52 (d, $J = 8.5$ Hz, 2H, Ar–H), 4.90 (s, 2H, NH_2), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 164.1$ (C=O), 161.5 (C–OCH_3), 145.1 (C–NH_2), 129.3 (Ar–C), 128.3 (Ar–C), 127.4 (Ar–C), 122.3 (Ar–C), 113.7 (Ar–C), 113.5 (Ar–C), 55.4 (OCH_3) ppm.

***N*-(2-Aminophenyl)-4-methoxybenzamide (3j, $C_{14}H_{14}N_2O_2$)** Buff microcrystals; yield 1 g (83%); m.p.: 135–137 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 9.55$ (s, 1H, NH), 7.97 (d, $J = 7.5$ Hz, 2H, Ar–H), 7.15-6.96 (m, 4H, Ar–H), 6.77 (d, $J = 7.5$ Hz, 2H, Ar–H), 4.87 (s, 2H, NH_2), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 173.2$ (CO), 167.6 (=C–OCH_3), 158.9 (=C–NH_2), 128.9 (Ar–C), 127.2(Ar–C), 123.6 (Ar–C), 121.0 (Ar–C), 118.8 (Ar–C), 118.4 (Ar–C), 117.2 (Ar–C), 116.0 (Ar–C), 53.5 (OCH_3) ppm.

(4-Methoxyphenyl)(piperazin-1-yl)methanone (3k, $C_{12}H_{16}N_2O_2$) Oil; yield 1.74 g (79%); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.32$ (d, $J = 8.3$ Hz, 2H, Ar–H), 6.96 (d, $J = 8.3$ Hz, 2H, Ar–H), 3.77 (s, 3H, OCH_3), 3.29 [br s, 4H, $–CON(CH_2)_2–$], 2.65 [br s, 4H, $–CON(CH_2)_2(CH_2)_2–$] ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 169.0$ (CO), 160.1 [=C–OCH_3], 129.0 (Ar–C), 128.1 (Ar–C), 113.7 (Ar–C), 60.3 (OCH_3), 55.3 [$–N(CH_2)_2–$], 45.8 [$HN–(CH_2)_2–$] ppm.

***N*-(2-Aminoethyl)-4-methoxybenzamide (3l, $C_{10}H_{14}N_2O_2$)** Yellow microcrystals; yield 1.61 g (83%); m.p.: 89–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.5$ Hz, 2H, Ar–H), 6.98 (s, 1H, NH), 6.90 (d, $J = 8.5$ Hz, 2H, Ar–H), 3.83 (s, 3H, OCH_3), 3.53 (t, $J = 5.5$ Hz, 2H, –$CONHCH_2$), 2.98 (t, $J = 5.3$ Hz, 2H, –CH_2NH_2), 1.25 (s, 2H, NH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.3$ (C=O), 162.0 (C–OCH_3), 128.7 (Ar–C), 126.5 (Ar–C), 113.6 (Ar–C), 55.3 (OCH_3), 40.9 (CH_2NH_2), 29.6 ($CONHCH_2$) ppm.

***N*-(4-Aminophenyl)-3,4,5-trimethoxybenzamide (3m, $C_{16}H_{18}N_2O_4$)** Gray microcrystals; yield 1.39 g (92%); m.p.: 204–206 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 9.77$ (s, 1H, NH), 7.31 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.24 (s, 2H, Ar–H), 6.55 (d, $J = 8.5$ Hz, 2H, Ar–H), 4.95 (s, 2H, NH_2), 3.85 (s, 6H, 2*m*-(OCH_3)), 3.71 (s, 3H, *p*-(OCH_3)) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 164.1$ (C=O), 152.6 (C-*m*-(OCH_3), 145.4 (C–NH_2), 139.9 (C-*p*-(OCH_3), 130.4 (Ar–C), 127.9 (Ar–C), 122.7 (Ar–C), 113.7 (Ar–C), 105.0 (Ar–C), 60.1 (*p*-OCH_3), 56.0 (*m*-OCH_3) ppm.

***N*-(4-Aminophenyl)-3-nitrobenzamide (3n, $C_{13}H_{11}N_3O_3$)** Orange microcrystals; yield 1.14 g (89%); m.p.: 221–223 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 10.23$ (s, 1H, NH), 8.75 (s, 1H, Ar–H), 8.40 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.36 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.80 (t, $J = 7.8$ Hz, 1H, Ar–H), 7.38 (d, $J = 8.5$ Hz, 2H, Ar–H), 6.55 (d, $J = 8.5$ Hz, 2H, Ar–H), 5.00 (s, 2H, NH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 156.5$ (C=O), 152.4 (=C–NO_2), 143.1 (=C–NH_2), 137.0 (=C–CO–), 134.3 (Ar–C), 128.4 (Ar–C), 127.9 (Ar–C), 127.8 (Ar–C), 121.8 (Ar–C), 121.1 (Ar–C), 118.4 (Ar–C) ppm.

(3-Nitrophenyl)(piperazin-1-yl)methanone (3o, $C_{11}H_{13}N_3O_3$) Yellow microcrystals; yield 1.92 g (82%); m.p.: 64–66 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.65$ (s, 1H, Ar–H), 8.36 (d, $J = 9.0$ Hz, 1H, Ar–H), 8.19 (d, $J = 7.5$ Hz, 1H, Ar–H), 7.65 (t, $J = 7.7$ Hz, 1H, Ar–H), 3.54 [t, $J = 5.7$ Hz, 4H, $CON(CH_2–)_2–$], 3.00 [t, $J = 5.7$ Hz,, 4H, $HN(CH_2)_2–$], 0.87 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 164.2$ (C = O), 147.8 (C–NO_2), 136.0 (Ar–C), 133.8 (Ar–C), 130.1(Ar–C), 125.8 (Ar–C), 122.0 (Ar–C), 43.02 [$CON(CH_2–)_2–$], 41.0 [$HN(CH_2)_2–$] ppm.

***N*-(4-Aminophenyl)stearamide (3p, $C_{24}H_{42}N_2O$)** White microcrystals; yield 1.76 g (94%); m.p.: 117–119 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 9.39$ (s, 1H, NH), 7.18 (d, $J = 8.5$ Hz, 2H, Ar–H), 6.46 (d, $J = 8.5$ Hz, 2H, Ar–H), 4.80 (s, 2H, NH_2), 2.18 (t, $J = 7.5$ Hz, 2H, –CH_2–CO–),

1.54–1.51 (m, 2H, –CH_2–CH_2–CO–), 1.28–1.20 (m, 28H, Aliph-H), 0.84 (t, J = 6.7 Hz, 3H, –CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.2 (CO), 144.5 (=C–NH_2), 128.6 (=C–NH–CO–), 120.8 (Ar–C), 113.8 (Ar–C), 36.2 (–CH_2–CO–), 31.3 (Aliph-C), 29.1 (Aliph-C), 29.0 (Aliph-C), 28.8 (Aliph-C), 28.7 (Aliph-C), 25.3(Aliph-C), 22.1 (Aliph-C), 14.0 (CH_3) ppm.

***N*-(2-Aminophenyl)stearamide (3q, $C_{24}H_{42}N_2O$)** Dark gray microcrystals; yield 1.55 g (83%); m.p.: 78–80 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.11 (s, 1H, NH), 7.14 (d, J = 7.5 Hz, 1H, Ar–H), 6.87 (t, J = 7.5 Hz, 1H, Ar–H), 6.70 (d, J = 7.5 Hz, 1H, Ar–H), 6.52 (t, J = 7.5 Hz, 1H, Ar–H), 4.81 (s, 2H, NH_2), 2.29 (t, J = 7.3 Hz, 2H, –$COCH_2$–), 1.60–1.56 (m, 2H, –$COCH_2CH_2$–), 1.32–1.17 (m, 28H, Aliph-H), 0.85 (t, J = 6.5 Hz, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.2 (CO), 141.9 (=C–NH_2), 125.6 (Ar–C), 125.2 (Ar–C), 123.6 (Ar–C), 116.1 (Ar–C), 115.9 (Ar–C), 35.8 (Aliph-C), 31.3 (Aliph-C), 29.1 (Aliph-C), 29.0 (Aliph-C), 28.9 (Aliph-C), 28.8 (Aliph-C), 28.74 (Aliph-C), 28.71 (Aliph-C), 28.5 (Aliph-C), 27.6 (Aliph-C), 25.3 (Aliph-C), 22.1 (Aliph-C), 14.0 (Aliph-C) ppm.

1-(Piperazin-1-yl)octadecan-1-one (3r, $C_{22}H_{44}N_2O$) Sticky; yield 3 g (85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59–3.44 (m, 4H, –$CON(CH_2)_2$–), 2.86–2.81 (m, 4H, –$CON(CH_2)_2(CH_2)_2$–), 2.30 (t, J = 7.7 Hz, 2H, –$COCH_2$–), 1.64–1.58 (m, 2H, –$COCH_2CH_2$–), 1.34–1.22 (m, 28H, Aliph-H), 0.87 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (CO), 47.0 (–$N(CH_2)_2$–), 42.7 ($NH(CH_2)_2$, 33.5 (Aliph-C), 32.1 (Aliph-C), 29.82 (Aliph-C), 29.79 (Aliph-C), 29.76 (Aliph-C), 29.7 (Aliph-C), 29.6 (Aliph-C), 29.5 (Aliph-C), 25.5 (Aliph-C), 25.40 (Aliph-C), 25.39 (Aliph-C), 22.8 (Aliph-C), 14.3 (CH_3) ppm.

2-Amino-*N*-(4-aminophenyl)benzamide (3s, $C_{13}H_{13}N_3O$) Brown microcrystals; yield 0.93 g (82%); m.p.: 75–77 °C; ^{1}H NMR (400 MHz, DMSO): δ = 9.65 (s, 1H, –NH), 7.58 (d, J = 8.0 Hz, 1H, –CO–(*o*-Ar–H)), 7.32 (d, J = 8.0 Hz, 2H, –NH–(*o*-Ar–H)), 7.17 (t, J = 7.6 Hz, 1H, Ar–H), 6.73 (d, J = 8.0 Hz, 1H, Ar–H), 6.59–6.54 (m, 3H, Ar–H), 6.29 (s, 2H, NH_2), 4.92 (s, 2H, NH_2) ppm; ^{13}C NMR (101 MHz, DMSO): δ = 167.7 (CO), 150.0 (=C–NH_2), 145.5 (=C–NH_2), 132.1 (Ar–C), 128.9 (Ar–C), 128.6 (Ar–C), 123.0 (Ar–C), 116.7 (Ar–C), 116.3 (Ar–C), 115.2 (Ar–C), 114.1 (Ar–C) ppm; HRMS (ESI): *m/z* cald for $C_{13}H_{14}N_3O$ ([M + H^+]) 228.1159, found 228.1157.

(2-Aminophenyl)(piperazin-1-yl)methanone (3t, $C_{11}H_{15}N_3O$) Oil; yield 1.77 g (86%); ^{1}H NMR (400 MHz, DMSO): δ = 7.08 (t, J = 7.6 Hz, 1H, Ar–H), 6.96 (d, J = 7.2 Hz, 1H, Ar–H), 6.71 (d, J = 8.0 Hz, 1H, Ar–H), 6.56 (t, J = 7.2 Hz, 1H, Ar–H), 5.14 (s, 2H, NH_2), 3.43 (s, br, 4H, –CO–$N(CH_2)_2$–), 2.77 (s, br, 4H, –$NH(CH_2)_2$–) ppm; ^{13}C NMR (101 MHz, DMSO): δ = 169.0 (CO), 146.2 (=C–NH_2), 130.3 (Ar–C), 128.0 (Ar–C), 120.0 (Ar–C), 116.0 (Ar–C), 115.9 (Ar–C), 46.2 (–$CON(CH_2)_2$–), 44.8 ($HN(CH_2)_2$–) ppm; HRMS (ESI): *m/z* cald for $C_{11}H_{16}N_3O$ ([M + H^+]) 206.1315, found 206.1311.

General procedure for synthesis of compounds 4a–4c

In a round bottom flask, monoacylated aliphatic diamines **3c**, **3h** (1 mmol) were added to 5 cm^3 *n*-butanol followed by addition of the corresponding *N*-acylbenzotriazole **1b** for **3c** or **1a**, **1c** for **3h** (1 mmol). The mixture was heated at 60 °C for 1 h. Upon completion of the reaction (monitored by TLC, ethylacetate/hexane 1:1), the organic solvent was evaporated. The semisolid was dissolved in 20 cm^3 ethyl acetate and washed with saturated Na_2CO_3 (3 × 5 cm^3), water (2 × 5 cm^3), and 5 cm^3 brine. The organic layer was dried over anhydrous sodium sulfate. Hexane (20 cm^3) was added to the filtrate, and then the product obtained was dried under vacuum to give the target compounds **4a**–**4c**.

Benzyl [2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]carbamate (4a, $C_{21}H_{23}N_3O_4$) Oil; yield 0.305 g (80%); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.95 (d, J = 7.0 Hz, 1H, NH), 7.48–7.42 (m, 5H, Ar–H), 7.38–7.31 (m, 5H, Ar–H), 5.03 (s, 2H, OCH_2), 3.89 (s, 2H, $NHCH_2$), 3.49 (t, J = 5.25 Hz, 4H, –$CH_2CON(CH_2)_2$–), 3.41 (t, J = 5.25 Hz, 4H, –$CH_2CON(CH_2)_2$–($CH_2)_2$–) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.3 (=C–CO–), 167.5 (–CH_2–CO–), 156.5 (OCO), 137.1 (Ar–C), 132.9 (Ar–C), 129.7 (Ar–C), 129.3 (Ar–C), 128.5 (Ar–C), 128.4(Ar–C), 127.7 (Ar–C), 127.0 (Ar–C), 72.3 (OCH_2), 65.4 (=C–CO–$N(CH_2)_2$–, 60.3 (–CH_2–CO–$N(CH_2)_2$–, 42.1 ($COCH_2$) ppm.

Benzyl [2-[(2-benzamidoethyl)amino]-2-oxoethyl]carbamate (4b, $C_{19}H_{21}N_3O_4$) Buff microcrystals; yield 0.312 g (88%); m.p.: 207–209 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.91 (s, 2H, 2NH), 7.43 (d, J = 6.0 Hz, 1H, OCONH), 7.37–7.29 (m, 10H, Ar–H), 5.02 (s, 2H, OCH_2), 3.57 (d, J = 6.0 Hz, 2H, $OCONHCH_2$), 3.38 (br s, 1H, $CH_2CONHCH_2$), 3.32 (br s, 1H, $CH_2CONHCH_2$), 3.10 (br s, 2H, $CH_2CONHCH_2CH_2$) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.3 (=C–CO–), 156.5 (–HN–CO–CH_2–), 155.4 (OCO), 137.0 (Ar–C), 128.4(Ar–C), 128.3(Ar–C), 127.83 (Ar–C), 127.78 (Ar–C), 127.6 (Ar–C), 127.2 (Ar–C), 127.1 (Ar–C), 65.5 (OCH_2), 43.6 (CO–CH_2), 39.0 (=C–CO–NH–CH_2–CH_2–), 38.3 (=C–CO–NH–CH_2–CH_2–) ppm.

Benzyl [2-[[2-(4-methoxybenzamido)ethyl]amino]-2-oxoethyl]carbamate (4c, $C_{20}H_{23}N_3O_5$) White microcrystals; yield 0.347 g (90%); m.p.: 178–180 °C; ^{1}H NMR

(500 MHz, DMSO-d_6): $\delta = 8.35$ (s, 1H, = C–CO–NH), 8.03 (d, $J = 6.0$ Hz, 1H, $NHCH_2CO$–), 7.81 (d, $J = 10.0$ Hz, 2H, Ar–H), 7.46 (s, 1H, -$CH_2CONHCH_2$), 7.38-7.31 (m, 5H, Ar–H), 6.98 (d, $J = 10.0$ Hz, 2H, Ar–H), 5.02 (s, 2H, –CH_2O–), 3.80 (s, 3H, OCH_3), 3.60 (d, $J = 6.0$ Hz, 2H, –$OCONHCH_2$–), 3.29 (t, $J = 5.5$ Hz, 2H, –$CH_2CONHCH_2CH_2$–), 3.23 (t, $J = 5.5$ Hz, 2H, –$CH_2CONHCH_2CH_2$–) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 169.4$ (=C–CO–), 165.9 (=C–OCH_3), 161.5 (–CH_2–CO–), 156.5 (OCO–), 137.0 (Ar–C), 129.0 (Ar–C), 128.4 (Ar–C), 127.7 (Ar–C), 127.1 (Ar–C), 126.7 (Ar–C), 113.4 (Ar–C), 65.5 (OCH_2), 55.3 (OCH_3), 43.6 (–$NHCH_2CO$–), 38.5 (=C–CO–NH–CH_2–), 38.3 (=C–CO–NH–CH_2–CH_2–) ppm.

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