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Use of tosylated glycerol carbonate to access *N*-glycerylated aza-aromatic species

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ABSTRACT

Tosylated glycerol carbonate was used for *N*-glyceryl functionalization of diverse aza-aromatic systems. Depending on the pK_a of the aza-heterocycle and the reaction conditions applied, original *N*-alkylated or *N*-acylated aza-heterocyclic derivatives were obtained. Those compounds carry an electrophilic appendage—either carbonate or epoxide—which allows further useful transformations.

1. Introduction

The possibility of using glycerol in the creation of value-added chemicals has become increasingly attractive in recent years, partly from the manufacture of biodiesel, where glycerol is formed in large amounts as the main by-product and partly from the renewable aspect of the chemistry developed.[1] Among the readily accessible molecules obtained from glycerol, the cyclic 1,2-carbonate (4-hydroxymethyl-1,3-dioxolan-2-one) **1**—a stable, low vapour pressure, colourless liquid is one major renewable target in glycerol chemistry. Glycerol 1,2-carbonate (GC) is a relatively new and interesting bio-degradable material that can be used as a non-toxic solvent in cosmetics, medicine and industry.[2] In addition to these applications GC, as a bifunctional organic compound, has considerable potential for use as a reagent or a building block in fine chemistry. Five-membered cyclic alkylene carbonates are highly reactive species, which can easily undergo a number of reactions with various nucleophiles, such as amines, alcohols, thiols, and can also take part in ring-opening polymerisation reactions.[3] The primary hydroxyl functionality also broadens the reactivity scope of GC as a nucleophile. Treatment of GC with anhydrides,[4] arylsulfonyl chlorides,[4c] isocyanates[5] readily affords esters, sulfonates and urethanes, respectively. GC nucleophilicity has been used in glycoside synthesis by reaction with saccharides under acid catalysis.[6]

As an inexpensive industrial starting material, GC has been applied in the elaboration of surfactants[4a] and polymeric materials.[5,7] It can easily be converted into glycidol and epichlorohydrin—high value monomers for macromolecular applications.[4b,8] More recently, an advanced building block of GC has been introduced through its conversion into the tosylated form as a new valuable starting material for fine chemistry or polymer applications. Tosylated glycerol 1,2-carbonate (TGC) has also found use as an initiator for cationic ring-opening polymerisations.[9]

The reactivity of *O*-sulfonylated GCs—either mesylate or tosylate—has been explored with various thiols, alcohols and amines as nucleophiles aiming at selectively mono- or bis-functionalised 3-carbon synthons.[10] In this regard, TGC underwent chemoselective reactions (Scheme 1). With aliphatic primary and secondary amines and aliphatic alkoxides, ring-opening of the cyclic carbonate occurred. Aminolysis afforded (2-hydroxy-3-tosylpropyl)carbamates, further transformed into the corresponding glycidyl

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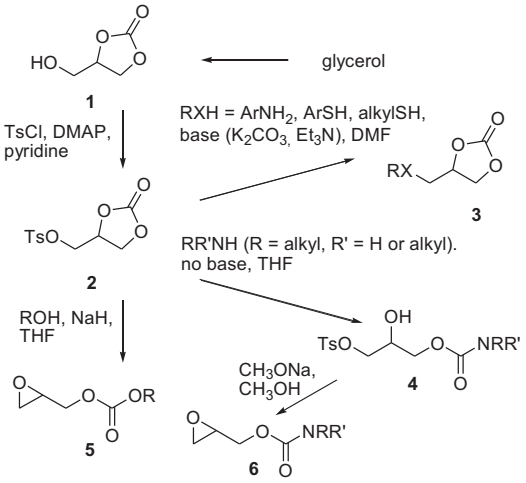
alkylcarbamates, which can be seen as protected intermediates of glycidol derivatives.[10b] Alkoxides reacted to afford glycidyl carbonates, whereas the reactivity observed with softer nucleophiles was centred on the glycerol sulfonylated site.



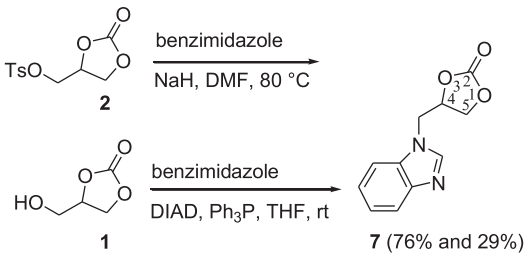
Scheme 1. Reactivity of TGC **2**.

Our current interest in developing TGC seeked for extension of its abilities as a bis-electrophile with involvement of a new family of aza-nucleophiles based on heteroaromatic structures containing an acidic *N*–H bond. In this regard, our aim was to explore the site selectivity and the potentiality to develop new building blocks for fine organic chemistry. Reacting aza-heteroaromatics with TGC would lead to molecular hybrids in which the aryl system is *N*-connected to a glyceryl-derived appendage, thus delivering building blocks of general interest in the preparation of pharmaceuticals and advanced materials particularly.[11]

2. Results and discussion

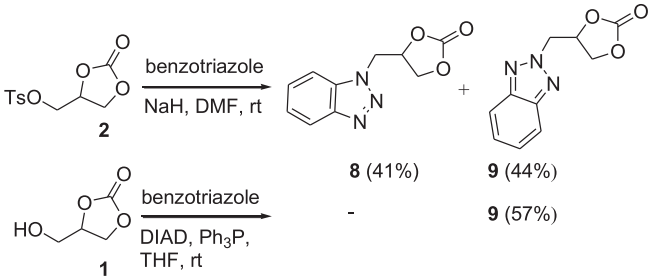
Stable crystalline TGC **2** was prepared in quantitative yield from GC **1** following our previously described procedure (TsCl in the presence of pyridine and DMAP in dichloromethane).[10a] Reagent **2** was confronted to different *N*H-containing aza-heteroaromatics, namely 9*H*-carbazole, 1*H*-indole, 1*H*-benzimidazole and 1*H*-benzotriazole. All of the above mentioned heterocycles are *N*–H acids, with pK_a values (measured in DMSO) ranging between 20.95 (for 1*H*-indole) and 11.9 (for 1*H*-benzotriazole).[12] The direct nucleophilicity of these aromatic *N*H-heterocycles is very weak and requires deprotonating activation to the corresponding anion.[13] The *N*-alkylation of heterocyclic compounds bearing a *N*–H acidic hydrogen atom is accomplished either by treatment of the substrate with a base such as sodium hydride, potassium hydroxide or *n*-BuLi, followed by reaction of the resulting anion with an alkylating agent,[14] or by direct N-alkylation under phase-transfer catalysis conditions.[14a,c,15] Another alternative alkylation method involves Mitsunobu reaction of *N*–H heteroaromatics with alcohols.[16]

The study was initiated with 1*H*-benzimidazole. Alkylation of ambident benzimidazole anion with alkyl halides or alkyl sulfonates can be readily accomplished in both protic and aprotic solvents.[17] The reaction of TGC **2** with the benzimidazole anion generated with NaH in DMF afforded the crystalline carbonate **7** in 76% yield using a 1:1 stoichiometric ratio of reactants. The formation of the *N*-acylated derivative was not observed. A comparative direct *N*-alkylation of 1*H*-benzimidazole with GC **1** using Mitsunobu reaction conditions (DIAD, Ph_3P, THF) afforded compound **7** in only 29% yield (Scheme 2). Analysis of the unpurified reaction mixture by LC/MS and ^{1}H NMR spectroscopy revealed also the formation of high molecular weight side products. Variations of the reaction parameters such as reaction temperature and time, and the use of DEAD as a Mitsunobu reagent, did not result in a significant improvement of the yield of the target product.



Scheme 2. Reactions of benzimidazole with TGC **2** and GC **1**.

Comparatively, the more acidic 1*H*-benzotriazole was then investigated. It is known that the ambident anion of benzotriazole reacts with electrophiles to afford mixtures of 1- and 2-substituted regioisomers.[18] Reacting TGC **2** at room temperature with the benzotriazolyl anion generated with NaH in DMF afforded an equimolar mixture of *N*-alkylated regioisomers **8** and **9** in 85% global yield. As expected, applying the Mitsunobu reaction to 1*H*-benzotriazole with 1,2-glycerol carbonate **1** regioselectively afforded the 2-substituted product **9** in 57% yield (Scheme 3).



Scheme 3. Reactions of benzotriazole with TGC **2** and GC **1**.

X-ray crystallographic study of **8** (Fig. 1)[19] was performed to ascertain the regioisomeric issue in both reactions.[20]

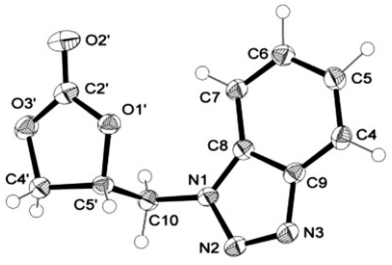


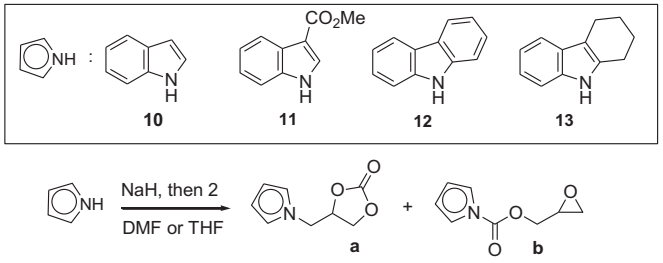
Fig. 1. ORTEP drawing of compound **8**.

Switching to less acidic aza-heterocyclic systems, we now considered the reaction of 1*H*-indole derivatives.[21] Indole **10** has shown in some cases to undergo exclusive *N*-alkylation, whereas different conditions oriented substitution at C-3. The rate and regioselectivity of the reaction mainly depend on the solvent, the counter-cation and on the structure of the electrophilic partner.

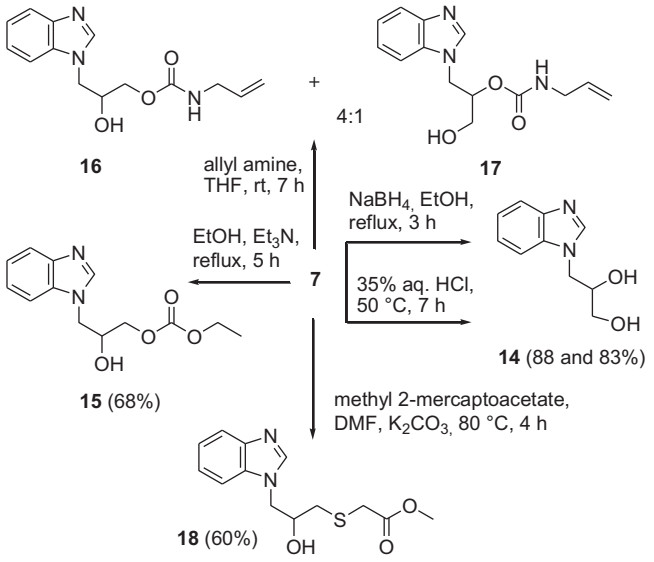
The reaction of TGC **2** with deprotonated 1*H*-indole in DMF exclusively gave *N*-alkylated compound **10a** in 34% yield (Table 1, entry 1). When performed in THF instead of DMF, the reaction afforded compound **10b** in 39% yield (Table 1, entry 2). Low yield of the both reactions can be explained by the tendency of 3-unsubstituted indoles to polymerize (Scheme 4).[22]

Table 1
Products and yields of the reaction of indole derivatives **10**–**13** with TGC **2**

Entry	Substrate	Solvent	Cyclic carbonate **a**	Glycidyl carbamate **b**
1	**10**	DMF	**10a** (34%)	**10b** (–)
2	**10**	THF	**10a** (–)	**10b** (39%)
3	**11**	DMF	**11a** (48%)	**11b** (–)
4	**12**	DMF	**12a** (53%)	**12b** (10%)
5	**12**	THF	**12a** (–)	**12b** (64%)
6	**13**	DMF	**13a** (–)	**13b** (51%)



Scheme 4. Reaction of indole derivatives **10**–**13** with TGC **2**.



Scheme 5. Reactivity of carbonate **7**.

Reacting methyl 1*H*-indole-3-carboxylate **11** in DMF under the same conditions selectively afforded the *N*-alkylated compound **11a** in a much better yield than with indole (Table 1, entry 3). This result is consistent with the enhanced mobility of the *N*–H bond under the influence of the EWG in position 3.

The reaction of TGC **2** with deprotonated carbazole **12** in DMF (Table 1, entry 4) afforded a mixture of *N*-alkylated product **12a** and glycidyl carbamate **12b**, with 5:1 selectivity and a 63% overall yield.[23] When performed in THF instead of DMF the reaction afforded compound **12b** in 64% yield (Table 1, entry 5). Finally, the reaction of TGC **2** with deprotonated 1,2,3,4-tetrahydrocyclopenta [*b*]indole **13** in DMF afforded selectively the glycidyl carbamate **13b** in 51% yield (Table 1, entry 6).

Thus it appears that the pK_a of the *N*–H bond in the aza-aromatic moieties stands as a critical parameter in the reaction with TGC **2** in DMF, N-alkylation being privileged over N-acylation for most acidic systems. In other respects, we have shown that selectivity inversion can be induced by use of a less polar solvent, so that involvement of a marked solvation process also has to be considered.

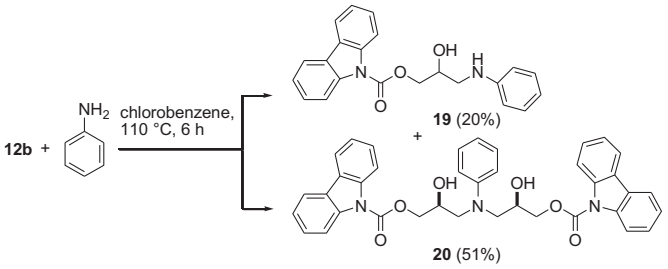
With a view to evaluating the synthetic potential of the elaborated *N*-glycerylated aza-aromatic hybrids as building blocks for the preparation of more complex structures, the reactivity of benzimidazole-derived carbonate **7** was explored under various conditions. Applying either reductive (sodium borohydride in ethanol) or hydrolytic (35% hydrochloric acid) conditions to compound **7** provoked decarboxylative ring cleavage of the cyclic carbonate to deliver the related diol **14** in 88 and 83% yield, respectively (Scheme 5). Compound **14** is an acyclic nucleoside analogue known to possess antiviral activity.[24] It was also used in the synthesis of ATP analogues designed as potential glutamine synthetase inhibitors.[25] The previously reported methods for the preparation of **14** included alkylation reactions of benzimidazole with 3-bromo-1,2-propandiol (yield 57%),[24c] with the corresponding bromoketal and further acidic hydrolysis of the intermediate 1-(1,3-dioxolan-4-ylmethyl)-1*H*-benzimidazole derivative (overall yield of 37% for the two steps)[25] and with allylbromide followed by cis-hydroxylation using a mixture of silver acetate and iodine in acetic acid (overall yield of 24%).[24a]

Ethanolysis of compound **7** in the presence of triethylamine also resulted in ring cleavage of the cyclic carbonate, affording the mixed carbonate **15** in reasonable yield (Scheme 5).

It is known that the cleavage of five-membered carbonate rings using aliphatic amines leads to the formation of carbamate derivatives.[10b] When compound **7** was treated with allylamine in THF at room temperature, TLC monitoring of the reaction showed an apparently clean conversion. However, NMR spectra revealed that the purified product was in fact a non-separable 4:1 mixture of isomeric carbamates **16** and **17** (Scheme 5).

Finally, the softer nucleophile methyl 2-mercaptoacetate was reacted on the cyclic carbonate **7** in DMF under basic conditions. Ring-opening by the thiol occurred regioselectively at the primary position to give the sulfide **18** in 60% yield.

In other respects, the glycidyl carbamates **10b**–**13b** can also be considered for further structural modifications through epoxide ring opening. For example, when reacted with aniline at 110 °C, the glycidyl carbamate **12b** underwent regioselective ring-opening to form the corresponding aminoalcohol **19** in 20% yield, together with the bis-alkylated aniline **20** in 51% yield (Scheme 6).



Scheme 6. Reaction of glycidyl carbamate **12b** with aniline.

3. Conclusion

In summary, tosylated glycerol carbonate **2** has proven to be a useful bis-electrophilic reagent to access *N*-glycerylated aza-aromatic species. Depending on the pK_a of the aza-heterocycle and modulating the reaction conditions, a synthetic way is open to original *N*-alkylated or *N*-acylated benzimidazole, benzotriazole and indoles. In turn, those new aza-aromatic species carry an electrophilic appendage—either carbonate or epoxide—which allows further conversions aimed at building up more complex molecules bearing aza-aromatic tags.

4. Experimental section

4.1. General

Reagents and solvents were purchased from Sigma–Aldrich or Fluka and used without further purification. Reactions were monitored by TLC analysis on precoated silica gel plates (Kieselgel $60F_{254}$, Merck). Compounds were visualized with UV light and charring after 1% $KMnO_4$ solution spray. Column chromatography was performed on silica gel SI 60 (43–60 μm, E. Merck). Melting points were determined in open capillary tubes with a Büchi B-540 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer using potassium bromide pellets; for liquid samples, a thin film between two KRS-5 plates was prepared. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Unity Inova spectrometer and at 400 MHz on a Bruker Avance DPX-400 spectrometer. ^{13}C NMR spectra were registered using the same instruments at 75 and 100 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) downfield from TMS and coupling constants *J* referring to apparent peak multiplicity are reported in hertz (Hz). Mass spectra were recorded on an Agilent 110 (series MS with VL) apparatus. HRMS spectra were recorded on a Bruker maXis 4G spectrometer. Elemental analyses were conducted using an Elemental Analyzer CE-440 (Exeter Analytical, Inc.) by the Microanalytical Laboratory, Department of Organic Chemistry, Kaunas University of Technology.

4.2. Synthetic procedures

*4.2.1. 4-(1H-Benzimidazol-1-ylmethyl)-1,3-dioxolan-2-one (**7**)*

4.2.1.1. Method A. To a solution of 1*H*-benzimidazole (1.18 g, 10 mmol) in anhydrous DMF (20 mL) NaH (0.40 g, 10 mmol, 60% in mineral oil) was added and the resulting slurry was stirred at rt for 30 min under inert atmosphere. The tosylate **2** (2.72 g, 10 mmol) was then added and the reaction mixture was stirred at 80 °C for 5 h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (100 mL) and water (100 mL). The aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (ethyl acetate) to give compound **7** as white crystals (1.65 g, 76%), mp 143–145 °C. R_f=0.10 (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.32 (dd, 1H, *J*=6.3, 8.8 Hz, H-5b), 4.63–4.73 (m, 3H, H-5a, NCH_2), 5.16–5.22 (m, 1H, H-4), 7.22–7.31 (m, 2H, ArH), 7.68–7.72 (m, 2H, ArH), 8.23 (s, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 46.1 (CH_2N), 66.7 (C-5), 75.4 (C-4), 110.6, 119.4, 121.7, 122.6, 133.9, 143.1, 144.2, 154.2 (C=O). IR (cm^{-1}): 1786 (C=O), 1500, 1485, 1460, 1271, 1165, 1077, 1027, 751. MS (APCI$^+$): *m*/*z* 219.4 [M+H]$^+$. Anal. Calcd for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.34; H, 4.72; N, 13.03.

4.2.1.2. Method B. Diisopropyl azodicarboxylate (263 mg, 0.26 mL, 1.3 mmol) was added dropwise in the dark at rt to a solution containing 1,2-glycerol carbonate **1** (153 mg, 1.3 mmol), 1*H*-benzimidazole (154 mg, 1.3 mmol) and Ph_3P (340 mg, 1.3 mmol) in anhydrous THF (5 mL) under inert atmosphere. After 5 h stirring at rt, water (20 mL) was added and the aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (ethyl acetate) to afford compound **7** (82 mg, 29%).

*4.2.2. 4-(1H-Benzotriazol-1-ylmethyl)-1,3-dioxolan-2-one (**8**) and 4-(2H-benzotriazol-2-ylmethyl)-1,3-dioxolan-2-one (**9**)*

4.2.2.1. Method A. To a solution of 1*H*-benzotriazole (179 mg, 1.5 mmol) in anhydrous DMF (5 mL) NaH (60 mg, 1.5 mmol, 60% in mineral oil) was added and the resulting slurry was stirred at rt for 15 min under inert atmosphere. Tosylate **2** (272 mg, 1.0 mmol) was then added and the reaction mixture was stirred at rt for 5 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate 1:1, v/v) to successively deliver compounds **8** and **9**.

*Compound **8***: white crystals, yield 90 mg (41%), mp 172–174 °C. R_f=0.15 (*n*-hexane/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.39 (dd, 1H, *J*=8.7, 6.0 Hz, H-5*b*), 4.70 (t, 1H, ^2J=^3J=8.7 Hz, H-5*a*), 5.11–5.24 (m, 2H, NCH_2), 5.29–5.37 (m, 1H, H-4), 7.40–7.46 (m, 1H, ArH), 7.57–7.63 (m, 1H, ArH), 7.90–7.94 (m, 1H, ArH), 8.06–8.09 (m, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.2 (CH_2N), 66.7 (C-5), 75.2 (C-4), 110.8, 119.1, 124.2, 127.7, 133.5, 145.0, 154.2 (C=O). IR (cm^{-1}): 1792 (C=O), 1456, 1386, 1317, 1299, 1157, 1147, 1069, 1017, 770, 755. MS (APCI$^+$): *m*/*z* 220.5 [M+H]$^+$. Anal. Calcd for $C_{10}H_9N_3O_3$ (219.20): C, 54.79; H, 4.14; N, 19.17. Found: C, 54.54; H, 4.42; N, 18.90.

*Compound **9***: white crystals, yield 96 mg (44%), mp 124–125 °C. R_f=0.33 (*n*-hexane/ethyl acetate 1:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.45 (dd, 1H, *J*=8.4, 6.0 Hz, H-5*b*), 4.71 (t, 1H, ^2J=^3J=8.4 Hz, H-5*a*), 5.21 (d, 2H, *J*=5.1 Hz, NCH_2), 5.42–5.52 (m, 1H, H-4), 7.43–7.50 (m, 2H, ArH), 7.91–7.98 (m, 2H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 57.2 (CH_2N), 66.7 (C-5), 74.6 (C-4), 117.9, 126.8, 143.8, 154.3 (C=O). IR (cm^{-1}): 1802 and 1792 (C=O), 1451, 1389, 1163, 1112, 1075, 1014, 751. MS (APCI$^+$): *m*/*z* 220.4 [M+H]$^+$. Anal. Calcd for $C_{10}H_9N_3O_3$ (219.20): C, 54.79; H, 4.14; N, 19.17. Found: C, 55.07; H, 4.26; N, 18.91.

4.2.2.2. Method B. 1*H*-Benzotriazole (155 mg, 1.3 mmol) and 1,2-glycerol carbonate **1** (118 mg, 1.0 mmol) were reacted as described for **7** (*method B*) with diisopropyl azodicarboxylate (263 mg, 0.256 mL, 1.3 mmol) and Ph_3P (340 mg, 1.3 mmol) in anhydrous THF (5 mL). Standard workup afforded **9**. Yield 125 mg (57%).

*4.2.3. 4-(1H-Indol-1-ylmethyl)-1,3-dioxolan-2-one (**10a**) and oxiran-2-ylmethyl 1H-indole-1-carboxylate (**10b**)*

4.2.3.1. Reaction in DMF. Reacting 1*H*-indole **10** (176 mg, 1.5 mmol) with NaH (60 mg, 1.5 mmol, 60% in mineral oil), then tosylate **2** (272 mg, 1.0 mmol) in anhydrous DMF (5 mL) as described for **7** (*method A*) delivered compound **10a** as yellowish crystals (74 mg, 34%), mp 90–91 °C (lit. mp 91.4–92.4 °C).[22] R_f=0.24 (*n*-hexane/ethyl acetate 2:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.24 (dd, 1H, *J*=8.4, 6.3 Hz, H-5b), 4.57–4.64 (m, 3H, H-5a, NCH_2), 5.09–5.18 (m, 1H, H-4), 6.50 (dd, 1H, *J*=3.0, 0.3 Hz, H-3-indolyl), 7.02–7.08 (m, 1H, ArH), 7.14–7.20 (m, 1H, ArH), 7.36 (d, 1H, *J*=3.0 Hz, H-2-indolyl), 7.55–7.60 (m, 2H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.3 (CH_2N), 66.7 (C-5), 76.0 (C-4), 101.5, 109.9, 119.3, 120.4, 121.3, 128.0, 129.0, 136.1, 154.4 (C=O). IR (cm^{-1}): 1785 and 1740 (C=O), 1513, 1477, 1461, 1397, 1311, 1244, 1162, 1078, 1049, 765, 741. MS (APCI$^+$): *m*/*z* 218.4 [M+H]$^+$.

4.2.3.2. Reaction in THF. To a solution of 1*H*-indole **10** (117 mg, 1.0 mmol) in anhydrous THF (8 mL), NaH (40 mg, 1.0 mmol, 60% in mineral oil) was added and the resulting slurry was stirred at rt for 15 min under inert atmosphere. The tosylate **2** (408 mg, 1.5 mmol) was then added and the reaction mixture was stirred at rt for 12 h.

The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (20 mL) and water (20 mL). The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate 5:1, v/v) to afford compound **10b** as a yellow liquid (85 mg, 39%). R_f=0.50 (*n*-hexane/ethyl acetate 5:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.79 (dd, 1H, *J*=5.0, 2.6 Hz, H-3b-oxiranyl), 2.88 (t, 1H, *J*=4.8 Hz, H-3a-oxiranyl), 3.42–3.46 (m, 1H, H-2-oxiranyl), 4.21 (dd, 1H, *J*=12.0, 6.3 Hz, COOC*Hb*), 4.79 (dd, 1H, *J*=12.3, 2.7 Hz, COOC*Ha*), 6.76 (d, 1H, *J*=3.6 Hz, H-3-indolyl), 7.24–7.29 (m, 1H, ArH), 7.32–7.38 (m, 1H, ArH), 7.63–7.66 (m, 1H, ArH), 7.72 (d, 1H, *J*=3.7 Hz, H-2-indolyl), 8.09–8.10 (m, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.8, 48.8, 67.5, 108.3, 114.6, 121.2, 123.0, 124.5, 125.8, 130.1, 134.5, 150.1 (C=O). IR (cm^{-1}): 1740 (C=O), 1456, 1387, 1360, 1327, 1244, 1211, 1120, 1082, 1120, 762. ESI-HRMS: [M+H]$^+$, found 218.0810. $C_{12}H_{12}NO_3$ requires 218.0812.

*4.2.4. Methyl 1-[(2-oxo-1,3-dioxolan-4-yl)methyl]-1H-indole-3-carboxylate (**11a**).* Obtained similarly to compound **7** (*method A*) from methyl 1*H*-indole-3-carboxylate **11** (175 mg, 1.0 mmol) and tosylate **2** (272 mg, 1.0 mmol) as white crystals, yield 132 mg (48%), mp 133–134 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 4.30 (dd, 1H, *J*=8.7, 6.3 Hz, 1H, H-5*b*), 4.61–4.69 (m, 3H, H-5*a*, NCH_2), 5.13–5.22 (m, 1H, H-4), 7.22–7.33 (m, 2H, ArH), 7.70–7.73 (m, 1H, ArH), 8.02–8.05 (m, 1H, ArH), 8.16 (s, 1H, H-2-indolyl). ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.9 (CH_2N), 50.7 (OCH_3), 66.7 (C-5), 75.4 (C-4), 106.2, 111.0, 120.6, 121.8, 122.7, 125.9, 135.6, 136.5, 154.2 (C=O carbamate), 164.3 (C=O carboxylate). IR (cm^{-1}): 1786 (C=O), 1694 (C=O), 1538, 1444, 1413, 1274, 1258, 1223, 1192, 1163, 1113, 1079, 1018, 756. MS (APCI$^+$): *m*/*z* 276.3 [M+H]$^+$. Anal. Calcd for $C_{14}H_{13}NO_5$ (275.26): C, 61.09; H, 4.76; N, 5.09. Found: C, 61.43; H, 4.97; N, 5.00.

*4.2.5. 4-(9H-Carbazol-9-ylmethyl)-1,3-dioxolan-2-one (**12a**) and oxiran-2-ylmethyl 9H-carbazole-9-carboxylate (**12b**)*

4.2.5.1. Reaction in DMF. To a solution of 9*H*-carbazole **12** (2.0 g, 12 mmol) in anhydrous DMF (20 mL) NaH (0.48 g, 12 mmol, 60% in mineral oil) was added and the resulting slurry was stirred at rt for 10 min under inert atmosphere. The tosylate **2** (2.0 g, 7.35 mmol) was then added and the reaction mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous phase was extracted with ethyl acetate (3×80 mL). The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 5:1→3:1, v/v) to deliver compounds **12a** and **12b**.

*Compound **12a***: white crystals, yield 1.04 g (53%), mp 189–190 °C (lit. mp 189.6–191.1 °C).[22] R_f=0.20 (*n*-hexane/ethyl acetate 3:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.33 (dd, 1H, *J*=8.7, 6.9 Hz, H-5b), 4.67–4.91 (m, 3H, H-5a, NCH_2), 5.19–5.28 (m, 1H, H-4), 7.21–7.26 (m, 2H, ArH), 7.44–7.50 (ArH), 7.71–7.74 (m, 2H, ArH), 8.15–8.18 (m, 2H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.7 (CH_2N), 66.9 (C-5), 76.0 (C-4), 109.6 (2C), 119.2 (2C), 120.2 (2C), 122.2 (2C), 125.8 (2C), 140.3 (2C), 154.5 (C=O). IR (cm^{-1}) 1806 and 1780 (C=O), 1483, 1455, 1183, 1164, 1096, 1042, 748. ESI-HRMS: [M+Na]$^+$, found 290.0787. $C_{16}H_{13}NNaO_3$ requires 290.0787.

*Compound **12b***: white crystals, yield 196 mg (10%), mp 86–87 °C. R_f=0.50 (*n*-hexane/ethyl acetate 5:1, v/v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.82 (dd, 1H, *J*=4.8, 2.7 Hz, H-3b-oxiranyl), 2.92 (dd, 1H, *J*=5.1, 4.2 Hz, H-3a-oxiranyl), 3.50–3.56 (m, 1H, H-2-oxiranyl), 4.32 (dd, 1H, *J*=12.0, 6.9 Hz, COOC*Hb*), 4.88 (dd, 1H, *J*=12.0, 2.7 Hz, COOC*Ha*), 7.38–7.44 (m, 2H, ArH), 7.50–7.56 (m, 2H, ArH), 8.15–8.18 (m, 2H, ArH), 8.24–8.26 (m, 2H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.0, 48.8, 67.6, 115.8 (2C), 120.1 (2C), 123.5 (2C), 125.2 (2C), 127.4 (2C), 137.4 (2C), 151.3 (C=O). IR (cm^{-1}) 1727 (C=O), 1490, 1447, 1377, 1324, 1257, 1220, 1205, 1049, 761, 749. Anal. Calcd for $C_{16}H_{13}NO_3$ (267.28) C, 71.90; H, 4.90; N, 5.24. Found: C, 71.80; H, 4.96; N, 5.13. ESI-HRMS: [M+Na]$^+$, found 290.0788. $C_{16}H_{13}NNaO_3$ requires 290.0787.

4.2.5.2. Reaction in THF. Reacting 9*H*-carbazole (167 mg, 1.0 mmol) with tosylate **2** (408 mg, 1.5 mmol) in anhydrous THF (8 mL) as described for **10b** afforded compound **12b** (158 mg, 64% yield).

*4.2.6. Oxiran-2-ylmethyl 2,3-dihydrocyclopenta[b]indole-4(1H)-carboxylate (**13b**).* To a solution of 1,2,3,4-tetrahydrocyclopenta[*b*]indole **13** (118 mg, 0.75 mmol) in anhydrous DMF (4 mL), NaH (30 mg, 0.75 mmol, 60% in mineral oil) was added and the resulting slurry was stirred at rt for 15 min under inert atmosphere. Tosylate **2** (204 mg, 0.75 mmol) was then added and the reaction mixture was stirred at rt for 6 h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (15 mL) and water (15 mL). The aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate 7:1, v/v) to give compound **13b** as white crystals (98 mg, 51%), mp 113–114 °C. R_f=0.50 (*n*-hexane/ethyl acetate 7:1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46–2.58 (m, 2H, $CH_2CH_2CH_2$), 2.75–2.82 (m, 3H, H-3b-oxiranyl, $CH_2CH_2CH_2$), 2.94 (t, 1H, *J*=4.8 Hz, H-3a-oxiranyl), 3.09–3.15 (m, 2H, $CH_2CH_2CH_2$), 3.35–3.41 (m, 1H, H-2-oxiranyl), 4.23 (dd, 1H, *J*=12.3, 6.3 Hz, COOC*Hb*), 4.73 (dd, 1H, *J*=12.3, 3.0 Hz, COOC*Ha*), 7.21–7.32 (m, 2H, ArH), 7.36–7.43 (m, 1H, ArH), 8.17–8.20 (m, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0 (CH_2-cyclopenta), 27.3 (CH_2-cyclopenta), 28.8 (CH_2-cyclopenta), 44.6, 49.2, 66.9, 115.7, 118.6, 123.0, 123.2, 125.5, 127.0, 140.1, 143.5. IR (cm^{-1}): 1729 (C=O), 1615, 1453, 1381, 1323, 1295, 1217, 1114, 1033, 752. MS (APCI$^+$): *m*/*z* 258.5 [M+H]$^+$. Anal. Calcd for $C_{15}H_{15}NO_3$ (257.28): C, 70.02; H, 5.88 N, 5.44. Found: C, 70.04; H, 5.92; N, 5.41.

*4.2.7. 3-(1H-Benzimidazol-1-yl)propane-1,2-diol (**14**)*

4.2.7.1. Via reduction. $NaBH_4$ (57 mg, 1.5 mmol) was added portionwise to a refluxing solution of compound **7** (218 mg, 1.0 mmol) in anhydrous ethanol (6 mL) and reflux was maintained for 3 h under inert atmosphere. After cooling and removal of the solvent under reduced pressure, the residue was subjected to flash chromatography on silica gel (dichloromethane/methanol 10:1, v/v) to afford compound **14** (R_f=0.38) as white crystals (170 mg, 88%), mp 58–59 °C (lit. mp 60–61 °C).[24a] ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.27–3.57 (m, 2H, CH_2OH), 3.76–3.86 (1H, m, CHOH), 4.13 (dd, 1H, *J*=14.4, 7.5 Hz, NC*Hb*), 4.36 (dd, 1H, *J*=14.4, 3.3 Hz, NC*Ha*), 4.90 (br s, 1H, OH), 5.12 (br s, 1H, OH), 7.16–7.27 (m, 2H, ArH), 7.57–7.66 (m, 2H, ArH), 8.13 (s, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 47.4 (CH_2N), 63.2 (CH_2OH), 70.0 (CHOH), 110.6, 119.2, 121.2, 122.0, 134.3, 143.2, 144.7. IR (cm^{-1}): 3345–3100 (O–H), 1499, 1460, 1383, 1262, 1200, 1116, 1043, 744.

4.2.7.2. Via hydrolysis. Compound **7** (109 mg, 0.5 mmol) was dissolved in 35% aq HCl (2 mL) and the mixture was stirred at 50 °C for 7 h. After cooling, the reaction mixture was poured into a saturated Na_2CO_3 solution (5 mL) and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic extract was dried over anhydrous sodium sulfate. After solvent removal under

reduced pressure, the residue was subjected to flash chromatography on silica gel (dichloromethane/methanol, 10:1) to afford **14** (80 mg, 83% yield).

*4.2.8. 3-(1H-Benzimidazol-1-yl)-2-hydroxypropyl ethyl carbonate (**15**).* Triethylamine (505 mg, 0.70 mL, 5.0 mmol) was added dropwise to a refluxing solution of compound **7** (218 mg, 1.0 mmol) in anhydrous ethanol (5 mL) and reflux was maintained for 5 h. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (dichloromethane/methanol 10:1, v/v) to afford compound **15** (R_f=0.54) as a colourless liquid (180 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, 3H, J=7.1 Hz, CH_3), 4.07–4.31 (m, 7H, NCH_2, OCH_2, CH_2CH$_3$, C*H*OH), 7.03–7.09 (m, 1H, ArH), 7.14–7.20 (m, 1H, ArH), 7.31–7.37 (m, 2H, ArH), 7.65 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 48.3 (CH_2N), 64.4, 67.3, 68.5, 109.5, 119.3, 122.3, 123.0, 133.3, 142.3, 143.5, 155.0 (C=O). IR (cm^{-1}) 3650–3100 (O–H), 1814 and 1747 (C=O), 1616, 1501, 1446, 1384, 1275, 1078, 1010, 746. MS (APCI$^+$): m/z 265.4 [M+H]$^+$. Anal. Calcd for $C_{13}H_{16}N_2O_4$ (264.28): C, 59.08; H, 6.10; N, 10.60. Found: C, 59.12; H, 6.31; N, 10.21.

*4.2.9. 3-(1H-Benzimidazol-1-yl)-2-hydroxypropyl prop-2-en-1-ylcarbamate (**16**) and 2-(1H-benzimidazol-1-yl)-3-hydroxypropyl prop-2-en-1-ylcarbamate (**17**).* Allylamine (91 mg, 0.12 mL, 1.60 mmol) was added dropwise to a solution of compound **7** (169 mg, 0.78 mmol) in anhydrous THF (4 mL) under inert atmosphere and the mixture was stirred for 7 h at rt. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (10 mL) and water (15 mL). The aqueous phase was extracted with ethyl acetate (3×10 mL) and the combined organic phase was washed with brine, then dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (dichloromethane/methanol 10:1, v/v) to afford an inseparable mixture of the regioisomeric allylcarbamates **16** and **17** (R_f=0.50) as a white crystalline material (201 mg, 94%). IR (cm^{-1}): 3600–3100 (N–H, O–H), 1709 (C=O), 1645, 1534, 1501, 1461, 1334, 1260, 1150, 746. MS (APCI$^+$): m/z 276.4 [M+H]$^+$. Anal. Calcd for $C_{14}H_{17}N_3O_3$ (275.31): C, 61.08; H, 6.22; N, 15.26. Found: C, 61.46; H, 6.43; N, 15.11.

*Compound **16** (major isomer).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63–3.66 (m, 2H, CH_2NH), 3.85–4.06 (m, 3H, C*H*OH, NCH_2CH), 4.20 (dd, 1H, J=14.4, 7.4 Hz, OC*Hb*), 4.53 (dd, 1H, J=14.4, 3.6 Hz, OC*Ha*), 5.03–5.20 (m, 2H, C=CH_2), 5.43 (d, 1H, J=5.3 Hz, OH), 5.76–5.87 (m, 1H, C=CH), 7.17–7.28 (m, 2H, ArH), 7.47 (t, 1H, J=5.7 Hz, NH), 7.58–7.67 (m, 2H, ArH), 8.14 (s, 1H, H-2-benzimidazolyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.5 (CH_2NH), 47.2 (CH_2N), 65.2 (CH_2O), 67.3 (CHOH), 110.4, 114.9 (C=*C*H_2), 119.2, 121.3, 122.1, 134.1 (C=*C*H), 135.5, 143.2, 144.6, 155.9 (C=O).

*Compound **17** (minor isomer).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46–3.56 (m, 4H, CH_2NH, CH_2OH), 4.40 (1H, dd, J=14.4, 6.8 Hz, OC*Hb*), 4.51 (1H, dd, J=14.8, 4.0 Hz, OC*Ha*), 4.87–4.93 (m, 1H, NCH), 4.97–5.10 (m, 2H, C=CH_2), 5.66–5.76 (m, 1H, C=CH), 7.17–7.28 (m, 2H, ArH), 7.38 (t, 1H, J=5.7 Hz, NH), 7.57–7.67 (m, 2H, ArH), 8.12 (s, 1H, H-2-benzimidazolyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.2 (CH_2NH), 44.5 (CH_2O), 60.1 (CH_2OH), 72.6 (CHN), 110.4, 114.8 (C=*C*H_2), 119.2, 121.4, 122.3, 134.1 (C=*C*H), 135.3, 143.1, 144.4, 155.4 (C=O).

*4.2.10. Methyl {[3-(1H-benzimidazol-1-yl)-2-hydroxypropyl]sulfanyl}acetate (**18**).* A solution of compound **7** (196 mg, 0.90 mmol) in anhydrous DMF (3 mL) was cooled down to 0 °C under inert atmosphere. Potassium carbonate (149 mg, 1.08 mmol) and methyl 2-mercaptoacetate (119 mg, 0.10 mL, 1.12 mmol) were then added and the reaction mixture was stirred at 80 °C for 4 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous phase was extracted with dichloromethane (3×10 mL) and the combined organic phase was washed with brine, then dried over anhydrous sodium sulfate. After solvent removal under reduced pressure, the residue was subjected to flash chromatography on silica gel (dichloromethane/methanol 10:1, v/v) to afford compound **18** (R_f=0.53) as a yellow liquid (151 mg, 60%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.62–2.75 (m, 2H, SCH_2CH), 3.45 (s, 2H, SCH_2CO), 3.61 (s, 3H, OCH_3), 3.92–4.03 (m, 1H, C*H*OH), 4.17 (dd, 1H, J=14.4, 7.8 Hz, NC*Hb*), 4.36 (dd, 1H, J=14.3, 3.3 Hz, NC*Ha*), 5.43 (d, 1H, J=5.4 Hz, OH), 7.16–7.28 (m, 2H, ArH), 7.58–7.66 (m, 2H, ArH), 8.13 (s, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.4, 36.4 (CH_2S), 49.2 (CH_2N), 52.0 (OCH_3), 68.6 (CHOH), 110.5, 119.3, 121.3, 122.1, 134.2, 143.2, 144.6, 170.7 (C=O). IR (cm^{-1}): 3600–3100 (O–H), 1733 (C=O), 1500, 1461, 1437, 1290, 1203, 1164, 1136, 1007, 746. ESI-HRMS: [M+H]$^+$, found 281.0954. $C_{13}H_{17}N_2O_3S$ requires 281.0954.

*4.2.11. 2-Hydroxy-3-(phenylamino)propyl 9H-carbazole-9-carboxylate (**19**) and (phenylimino)bis-2-hydroxypropane-3,1-diyl bis(9H-carbazole-9-carboxylate), (**20**, mixture of diastereomers).* The glycidyl carbamate **12b** (188 mg, 0.70 mmol), aniline (32 mg, 0.35 mmol) and a few drops of chlorobenzene were heated at 110 °C for 6 h. After cooling, the mixture was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate 3:1, v/v) to successively afford compounds **19** (R_f=0.3) and **20** (R_f=0.43).

*Compound **19***: white solid, yield 50 mg (20%), mp 117–118 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.16–3.34 (m, 2H, CH_2N), 4.13–4.23 (m, 1H, C*H*OH), 4.49 (dd, 1H, J=11.1, 6.3 Hz, OC*Hb*), 4.61 (dd, 1H, J=11.1, 3.6 Hz, OC*Ha*), 5.51 (d, 1H, J=5.1 Hz, OH), 5.73 (t, 1H, J=5.9 Hz, NH), 6.51–6.56 (m, 1H, ArH), 6.63–6.66 (m, 2H, ArH), 7.05–7.10 (m, 2H, ArH), 7.38–7.43 (m, 2H, ArH), 7.49–7.54 (m, 2H, ArH), 8.16–8.18 (m, 2H, ArH), 8.32–8.35 (m, 2H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 46.1 (CH_2N), 66.8 (CH_2O), 69.2 (CHOH), 112.1 (2C), 115.8, 116.0 (2C), 120.1 (2C), 123.4 (2C), 125.2 (2C), 127.4 (2C), 128.9 (2C), 137.6 (2C), 148.7, 151.8 (C=O). IR (cm^{-1}): 3520 (O–H), 3349 (N–H), 1730 (C=O), 1601, 1514, 1448, 1329, 1302, 1220, 1205, 1124, 1043, 762, 753. MS (APCI$^+$): m/z 361.3 [M+H]$^+$. Anal. Calcd for $C_{22}H_{20}N_2O_3$ (360.41): C, 73.31; H, 5.59; N, 7.77. Found: C, 73.59; H, 5.45; N, 7.60.

*Compound **20***: white solid, yield 113 mg (51%), mp 162–164 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.50–3.88 (m, 4H, 2×CH_2N), 4.24–4.33 (m, 2H, 2×C*H*OH), 4.42–4.49 (m, 2H, 2×OCH*H*b), 4.55–4.64 (m, 2H, 2×OCH*Ha*), 5.55 (d, 1H, J=5.1 Hz, OH), 5.69 (d, 1H, J=5.1 Hz, OH), 6.55–6.68 (m, 1H, ArH), 6.82–6.86 (m, 2H, ArH), 7.05–7.14 (m, 2H, ArH), 7.33–7.40 (m, 4H, ArH), 7.45–7.52 (m, 4H, ArH), 8.09–8.15 (m, 4H, ArH), 8.31–8.35 (m, 4H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.7 (2×CH_2N), 66.0 (2×CH_2O), 69.2 (2×CHOH), 112.1 (2C), 112.3, 116.0 (4C), 120.1 (4C), 123.4 (4C), 125.2 (4C), 127.4 (4C), 129.0 (2C), 137.5 (4C), 147.7, 151.8 (2×C=O). IR (cm^{-1}): 3388 (N–H), 1732 and 1699 (C=O), 1600, 1506, 1446, 1403, 1330, 1304, 1249, 1219, 1202, 1116, 1043, 760, 749. MS (APCI$^+$): m/z 628.2 [M+H]$^+$. Anal. Calcd for $C_{38}H_{33}N_3O_6$ (627.70): C, 72.71; H, 5.30; N, 6.69. Found: C, 72.89; H, 5.14; N, 6.35.

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