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Synthesis of 4-Nitro-*N*-phenyl-1,8-naphthalimide Annulated to Thia- and Azacrown Ether Moieties

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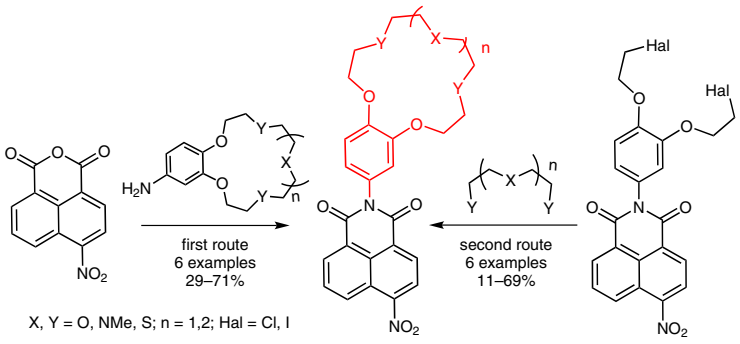

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Abstract Two convenient procedures for the synthesis of thia- and azacrown ether containing 4-nitro-1,8-naphthalimides have been developed. The first procedure is based on the amination of 1,8-naphthalic anhydride with crown-containing anilines. The second procedure includes the macrocyclization reaction of *N*-[1,2-bis(2-haloethoxy)phenyl]naphthalimide derivative with terminal thiols or methylamines. A strategy based on a macrocyclization is flexible and variable and also allows the use of the synthetic approach for more complex compounds.

Key words azacrown ether, thiacrown ether, 1,8-naphthalimide, synthesis, macrocyclization

Determination of the contents of metal cations in environmental objects and biological systems is an important practical task for industry, medicine, and ecology, and for chemical and biochemical studies.[1] Among the known modern physico-chemical methods of analysis, great popularity was gained by optical electron spectroscopy techniques, which is first of all due to relative simplicity of experimental procedure in combination with high sensitivity towards analytes. The spectrophotometric methods are mainly based on ion recognition by molecular optical sensors, which are able to change their optical characteristics upon association with metal spices.[2] A general approach to the development of cation chemosensors consists in coupling of at least two units, each one displaying a precise function: acting as a binding site and as a signaling subunit site. Binding sites and signaling units can be covalently linked.

In this work, we designed and synthesized a series of the novel compounds combining crown ether macrocycles of different size and combinations of O, S, and N atoms and fluorescent naphthalimide subunit (Figure 1). 1,8-Naphthalimide derivatives represent an important class of luminophores with regard to design of optical chemosensors, first, due to the relative ease of synthetic operations for targeted modification of the molecular structure and, second, due to the diversity of photophysical properties of the naphthalimide fluorophore.[3] Currently, a large number of chemosensors based on 1,8-naphthalimide have been prepared.[3,4] Even though crown ether receptors have been extensively used in the construction of fluorescent probes, there have been only few examples of naphthalimide chemosensors bearing crown ether groups as a receptor unit.[5–13]

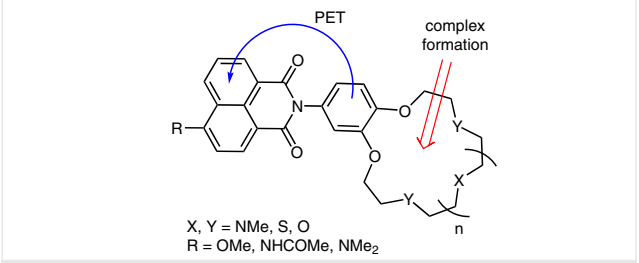
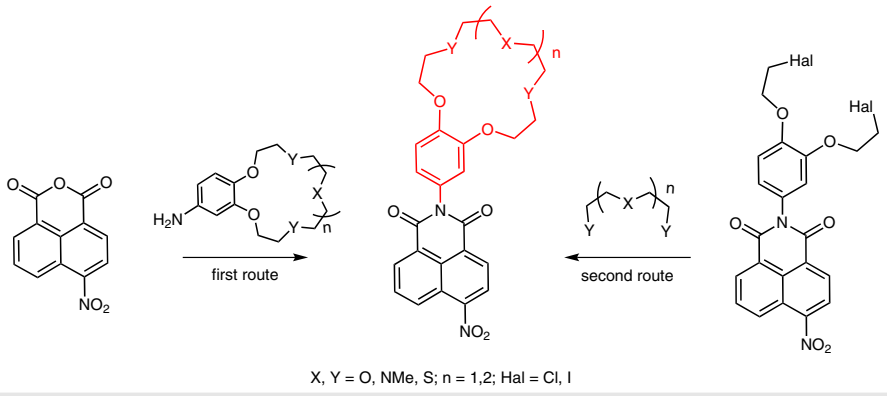


Figure 1 PET process providing the fluorescence respond in crown-containing naphthalimide upon complex formation

The development of effective complexons, which can exhibit high selectivity and high stability constants, provides a new powerful tool for the estimation of the metal cations content in a media. Thia- and azacrown ethers are among the most promising macrocyclic ligands. They have attracted interest due to their ability to form stable complexes with different types of metal ions.[14,15] The selectivity of the ligand can be controlled by changing its size and composition. In addition, these types of the ligands adapt to the coordination sphere of the metal ion. Due to this reason the complexes from macrocyclic ligands are kinetically inert with respect to dissociation and show a good thermodynamic stability as well as higher selectivity in comparison with their acyclic analogues.



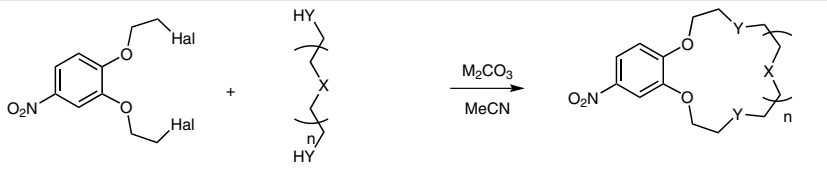
Scheme 1 Approaches to the synthesis of the target crown ether naphthalimides

From synthetic view point, the preparation of thia- and azacrown-containing fluorophores is an urgent task. Thia- and azacrown ethers are not stable at harsh synthetic conditions, this is why the search for appropriate methods is important. Thus, of the known crown-containing naphthalimide derivatives only a few contain thiacrown ether fragments.[3]

In this work, we have developed two synthetic strategies to a series of novel 4-nitro-*N*-phenyl-1,8-naphthalimides containing thia- and azacrown ether fragments in their *N*-phenyl residue (Scheme 1). The nitro group in 4-nitro-*N*-phenyl-1,8-naphthalimide can be easily replaced by required amino- or methoxy substituent. The structure of the naphthalimide derivatives possessing donor group in the 4-position of naphthalene ring provides the occurrence of highly effective PET (Photoinduced Electron Transfer) process from donor benzocrown ether part and electron-acceptor naphthalimide residue.[16,17] This is the reason why such naphthalimide derivatives do not demonstrate high emission quantum yield in the free state. The complex formation through the crown ether prevents the PET resulting in the increase of fluorescence. Thus, 4-nitronaphthalimides containing crown ether fragment in the *N*-phenyl residue present the key compounds of the derivatives, which are considered as promising class of the fluorescent sensor molecules demonstrating a remarkable enhance of fluorescence in the presence of metal ions. Such compounds could be applied as reagents in analytical analysis or sensitive elements in optode analytical equipment.

Herein, we compare two routes for obtaining thia- and azacrown ether derivatives of naphthalimides (Scheme 1). In the first route, the target crown-containing naphthalimides were formed by imidation of 1,8-naphthalic anhydride with crown-containing anilines. The second route includes the macrocyclization reaction of *N*-[1,2-bis(2-haloethoxy)phenyl]naphthalimide derivatives with terminal thiols or methylamines.

According to the first route shown in Scheme 1, the synthesis starts from 1,2-bis(2-haloethoxy)-4-nitrobenzenes and includes the following three stages: i) synthesis of the 4-nitrobenzocrown ethers by cyclization of 1,2-bis(2-haloethoxy)-4-nitrobenzenes and the corresponding terminal thiols or methylamines (Scheme 2); ii) reduction of nitro derivatives giving anilines; and iii) acylation of crown-containing anilines with 4-nitro-1,8-naphthalic anhydride yielding the target crown-containing naphthalimide derivatives (Scheme 3).



1a,b

1a: Hal = Cl
1b: Hal = I

2a–f

2a: Y = NMe, X = O, n = 1
2b: Y = NMe, X = O, n = 2
2c: Y = S, n = 0
2d: Y = S, X = S, n = 1
2e: Y = S, X = O, n = 1
2f: Y = S, X = O, n = 2

M = K^+, Cs^+

3a–f

3a: Y = NMe, X = O, n = 1 (78%)
3b: Y = NMe, X = O, n = 2 (74%)
3c: Y = S, n = 0 (61%)
3d: Y = S, X = S, n = 1 (63%)
3e: Y = S, X = O, n = 1 (59%)
3f: Y = S, X = O, n = 2 (52%)

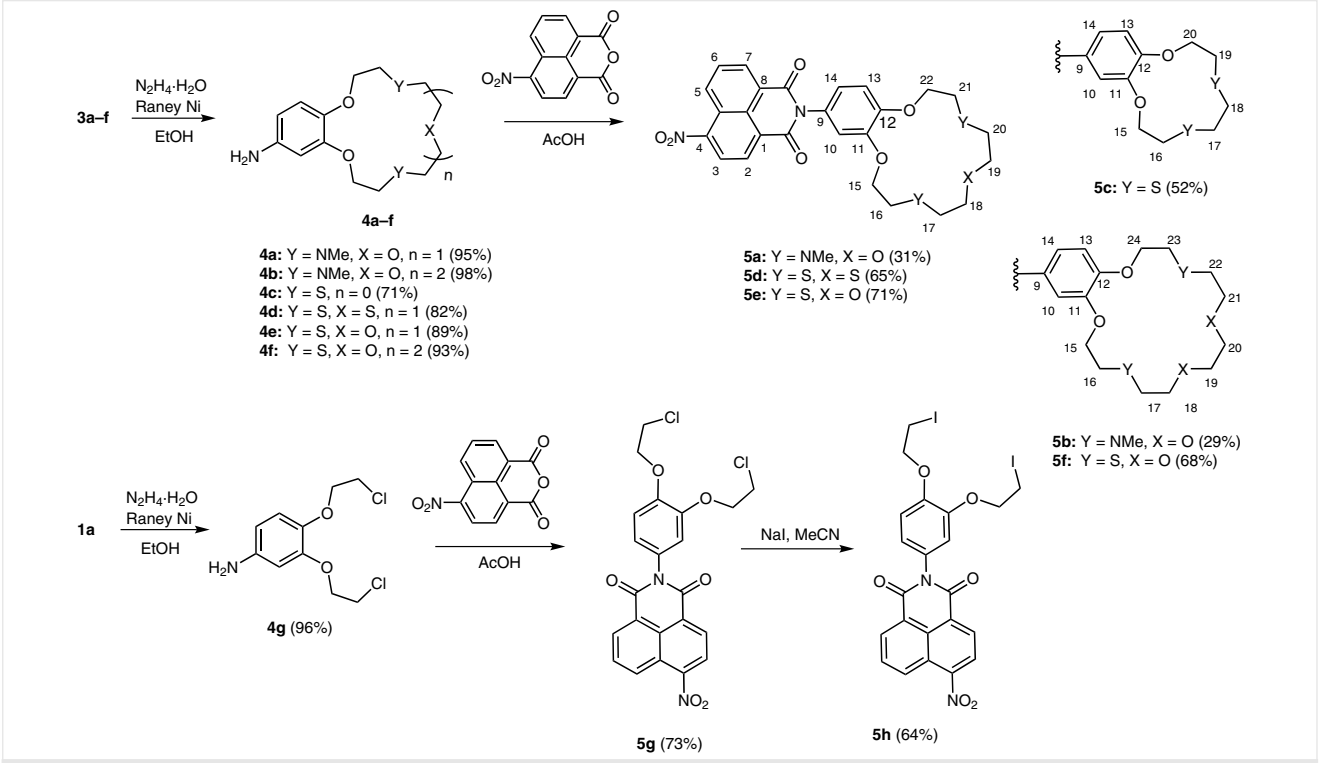
Scheme 2 Synthesis of 4-nitroanilines **3a–f**

The condensation reaction of 1,2-bis(2-haloethoxy)-4-nitrobenzenes **1a**,**b** with terminal (oxa)alkanediamines **2a**,**b** or (oxa)alkanedithiols **2c–f** in the presence of metal carbonates (M_2CO_3) in acetonitrile produced nitrobenzocrown ethers **3a–f** in 52–78% yields (Scheme 2 and experimental section). Reactions occurred in good yields in the case of azacrown ethers **3a**,**b** when 1,2-bis(2-iodoethoxy)-4-nitrobenzene (**1b**) and K_2CO_3 were used.[18] Compounds **3c–f** were successfully obtained from 1,2-bis(2-chloroethoxy)-4-nitrobenzene (**1a**) in the presence of Cs_2CO_3.[19] In both cases, the use of high dilution conditions was not required for carrying out the macrocyclization.

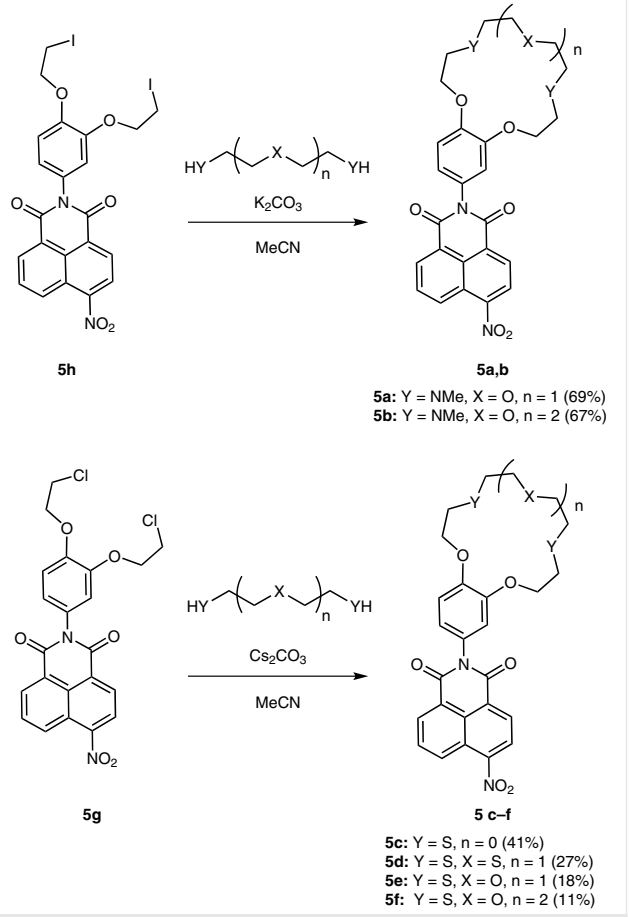
The reduction of nitrobenzocrown ethers **3a–f** and compound **1a** with hydrazine hydrate in the presence of Raney nickel catalyst afforded aniline derivatives **4a–g** in high yields.[20] In order to obtain the target 1,8-naphthalimides **5a–f**, arylamines **4a–f** were acylated with commercially available 4-nitro-1,8-naphthalic anhydride to produce *N*-aryl-1,8-naphthalimides **5a–f** in good or high yields (Scheme 3 and experimental section).[21] Compound **5g** was prepared in a similar way aimed to be used in the synthesis of **5a–f** according to route 2 (Scheme 1).

Similar to route 1 the preparation of **5a–f** through the route 2 (Scheme 1) includes three steps. As described above, the required 1,2-bis(2-chloroethoxy)-4-nitro naphthalimide **5g** was prepared through two-step synthesis (Scheme 3). Iodination of **5g** with NaI in anhydrous acetonitrile under reflux gave compound **5h** in 64% yield (experimental section).[21] At the final step, the cyclization of **5g**,**h** with acyclic α,ω-(oxa)alkanedithiols or α,ω-(oxa)alkane-*N*-methylamines was carried out yielding the target **5a–f** (Scheme 4). The cyclization reactions (Scheme 4) for obtaining **5a–f** were carried out similar to those described for benzocrown ethers **3a–f**. Thus, we applied K_2CO_3 for the preparation of azacrown ethers **5a**,**b**, and Cs_2CO_3 to prepare **5c–f**. Good yields were observed in the case of azacrown ethers **5a**,**b** and moderate yields for **5c–f**. It is important to note that macrocyclization resulting in azacrown-containing naphthalimides **5a**,**b** successfully occurred at ambient temperature.

We can conclude that both routes can be applied for obtaining of *N*-phenyl-1,8-naphthalimides annulated with thia- and azacrown ether moieties. The first route through the imidation of 1,8-naphthalic anhydride acid by crown-containing anilines gives better yields for benzothiacrown-naphthalimide derivatives **5c–f**. The second route demonstrates higher yields for benzoazacrown ether naphthalimide derivatives **5a**,**b**. Mild conditions of macrocyclization reaction in the case of **5a**,**b** allow this method to be used for preparation of azacrowned naphthalimide compounds containing different substituents in the molecular skeleton.



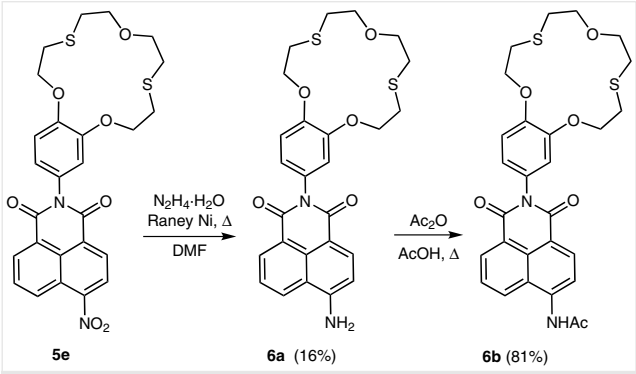
Scheme 3 Synthesis of the crown-containing anilines **4a–g** and 1,8-naphthalimides **5a–g**



Scheme 4 Conditions and yields in the reaction formation of **5a–f** from **5g**,**h**

As described above, the naphthalimide derivative possessing donor group in the 4-position provides the structure of the fluorescent sensor molecule, which should demonstrate a remarkable enhancement of the fluorescence in the presence of metal ions. To prove this, we carried out the synthesis of compound **6b** and checked how the intensity of the fluorescence of this compound changes upon the complex formation.

Preparation of 4-amino- and 4-(acetyl)aminonaphthalimides containing benzodithia-15-crown-5-ether as N-substituent of the aryl moiety was performed starting from 4-nitronaphthalimide **5e** according to Scheme 5. The reduction of amino group was carried out with hydrazine hydrate in the presence of Raney nickel catalyst in DMF. This solvent was applied due to the poor solubility of the initial compound **5e**. The acylation reaction of the amine **6a** with acetic anhydride in acetic acid afforded the desired product **6b** in a good yield (81%). The fluorescence spectra of ligand **6b** were measured without and with a ten-fold excess of various metal perchlorates listed above. The results are shown in Figure 2 in the form of graphs illustrating the degree of fluorescence enhancement (FE) for a particular metal cation. Benzodithiacrown containing acetamide **6b** showed fluorescence enhancement in the presence of mercury cations (Figure 2). The obtained results are in good agreement with known high affinity of dithiacrown ether macrocycles towards the mercury cations.[15]



Scheme 5 Conditions and yields in the reaction formation of **6b** from **5e**

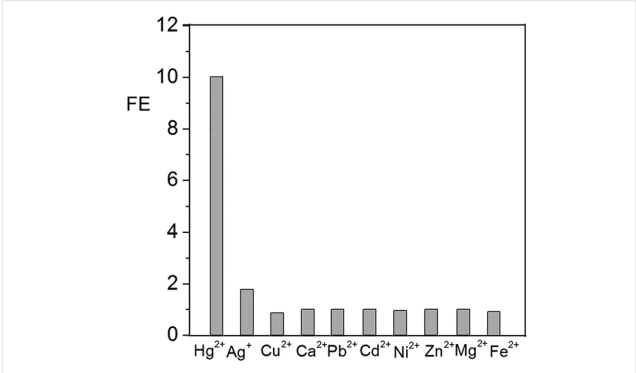


Figure 2 The degree of fluorescence enhancement (FE) of compound **6b** upon the addition of a ten-fold excess of several metal perchlorates in acetonitrile. The concentration of the ligand in solution: $C_L = 2 \cdot 10^{-5}$ mol/L.

Thus, the proposed methods for the synthesis of 1,8-naphthalimide derivatives containing aza- and dithiacrown ether fragments allow to obtain the fluorescence sensor molecules combining effective fluorophoric part and selective macrocyclic receptors.

NMR spectra were recorded on a BrukerAvance 400 and 600 MHz instruments for solutions in $CDCl_3$ and DMSO-d_6 unless otherwise stated; δ values are given in ppm, coupling constants are quoted in Hz. Melting points were not corrected. Amines **2a**,**b**, thiols **3c–f**, K_2CO_3, Na_2CO_3, NaOH, Ni-Al alloy (50% Ni w/w), hydrazine hydrate, and solvents (MeCN, $CHCl_3$, EtOH, AcOH) were purchased from commercial suppliers (Aldrich, Merck, Ekos-1) and used without further purification. The starting 1,2-bis(2-chloroethyl)-4-nitrobenzene (**1a**) was prepared according to the reported procedure.[22] Preparation of 4-nitro-1,8-naphthalic anhydride was described in literature.[23] Mass

spectra were obtained on an Agilent 1100 Series LC/MSD trap interface operated in positive-ion mode. The analyte solution was injected directly into the device. The flow rate was 400 μL/h, the drying gas temperature was 350 °C, and the pressure was 10 psi. The nebulizer needle voltage was 4.5–5.5 kV. The isotope distribution was calculated using the Molecular Weight Calculator software, version 6.73. Electron impact (EI) (70 eV) mass spectra were obtained from Finnigan Polaris Q instrument (ion-trap) in standard conditions.

For complete experimental procedures, analytical data, and NMR spectra, see the Supporting Information.

Iodo Derivatives 1b and 5h; General Procedure

A mixture of dichloride **5g** or **1a** (0.5 g, 1.05 mmol), anhyd NaI (0.95 g, 6.32 mmol), and anhyd MeCN (20.0 mL) was refluxed under stirring for 40 h. Sediments were filtered off and the solvent was removed in vacuo. The solid residue was washed with H_2O and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were concentrated in vacuo.

1,2-Bis(2-iodoethoxy)-4-nitrobenzene (1b)

Prepared from dichloride **1a** (1.85 g, 6.6 mmol) and anhyd NaI (9.84 g, 65.6 mmol) in MeCN (20 mL); yield: 2.57 g (84%); yellow powder; mp 46–49 °C (MeCN).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (m, 4 H, 2 × CH_2I), 4.34–4.40 (m, 4 H, 2 × CH_2O), 6.93 (d, *J* = 8.8 Hz, 1 H, H-6), 7.77 (d, *J* = 2.8 Hz, 1 H, H-3), 7.91 (dd, *J* = 8.8, 2.8 Hz, 1 H, H-5).

2-[3,4-Bis(2-iodoethoxy)phenyl]-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5h)

Prepared from dichloride **5g** (0.5 g, 1.05 mmol) and anhyd NaI (0.95 g, 6.32 mmol) in anhyd MeCN (20.0 mL). After elution with benzene to benzene–EtOH (2:1), **5h** was obtained as a yellow powder; yield: 0.44 g (64%); mp 178–182 °C (MeCN).

^{1}HNMR (400 MHz, $CDCl_3$): δ = 3.45–3.55 (m, 4 H, 2 × CH_2I), 4.30–4.41 (m, 4 H, 2 × CH_2O), 6.88 (s, 1 H, ArH-10), 6.93 (d, *J* = 8.5 Hz, 1 H, ArH-14), 7.07 (d, *J* = 8.5 Hz, 1 H, ArH-13), 8.04 (dd, *J* = 7.3, 8.7 Hz, 1 H, H-6), 8.44 (d, *J* = 8.0 Hz, 1 H, H-3), 8.74 (d, *J* = 8.0 Hz, 1 H, H-2), 8.79 (d, *J* = 7.3 Hz, 1 H, H-7), 8.90 (d, *J* = 8.7 Hz 1 H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.02 (2 × CH_2I), 70.5 (2 × CH_2O), 115.9 (C-13), 116.0 (C-10), 122.3 (C-14), 123.1 (C-4a), 123.9 (C-8), 124.5 (C-3), 127.0 (C-1), 128.4 (C-9), 128.8 (C-8a), 129.7 (C-5), 130.0 (C-2), 130.3 (C-6), 132.9 (C-7), 148.7 (C-12), 148.8 (C-11), 149.9 (C-4), 162.7 (C-8b), 163.5 (C-8c).

MS (IES): *m*/*z* calcd for $C_{22}H_{16}I_2N_2O_6$: 657.8; found: 658.1 $[M]^+$.

Anal. Calcd for $C_{22}H_{16}I_2N_2O_6$: C, 41.15; H, 2.45. Found: C, 41.21; H, 2.43.

Benzoazaacrown Ethers 3a,b; General Procedure

To a suspension of K_2CO_3 (1.15 mmol) and diiodide **1b** (0.23 mmol) in MeCN (3 mL) was added amine **2a** (or **2b**) (0.23 mmol) under stirring. The reaction mixture was kept for 75 h at r.t. (20 °C) without stirring and then evaporated in vacuo. The residue was extracted with CH_2Cl_2 (3 × 20 mL) and washed with H_2O. The combined organic layers were concentrated in vacuo and the residue was extracted with boiling hexane. Removal of hexane in vacuo gave the product.

4,10-Dimethyl-15-nitro-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,4,10,7,13]trioxadiazacyclopentadecine (3a)

Prepared from diiodide **1b** (107 mg, 0.23 mmol), amine **2a** (28 mg, 0.23 mmol), and K_2CO_3 (159 mg, 1.15 mmol) in MeCN; yield: 61 mg (78%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 6 H, 2 × NCH_3), 2.76 (dd, *J* = 5.7, 5.9 Hz, 4 H, 2 × CH_2N), 2.91 (dd, *J* = 4.4, 4.5 Hz, 4 H, 2 × CH_2N), 3.71–3.73 (m, 4 H, 2 × CH_2O), 4.09–4.13 (m, 4 H, 2 × CH_2O), 6.84 (d, *J* = 8.9 Hz, 1 H, H-6), 7.69 (d, *J* = 2.6 Hz, 1 H, H-2), 7.86 (dd, *J* = 8.9, 2.6 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.6 (C-9, C-14), 55.0 (C-8, C-15), 57.4 (C-10, C-13), 66.6 (C-11, C-12), 68.4 (C-7, C-16), 106.8 (C-3), 110.0 (C-6), 117.3 (C-5), 141.5 (C-4), 147.9 (C-2), 154.3 (C-1).

MS (IES): *m*/*z* calcd for $C_{16}H_{25}N_3O_5$: 339.39; found: 339.54 $[M]^+$.

Anal. Calcd for $C_{16}H_{25}N_3O_5$: C, 56.62; H, 7.42. Found: C, 56.71; H, 7.45.

4,13-Dimethyl-18-nitro-2,3,4,5,6,8,9,11,12,13,14,15-dodecahydrobenzo[*b*][1,4,10,13,7,16]tetraoxadiazacyclooctadecine (3b)

Prepared from diiodide **1b** (107 mg, 0.23 mmol), amine **2b** (41 mg, 0.23 mmol) and K_2CO_3 (159 mg, 1.15 mmol) in MeCN; yield: 65 mg (74%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, NCH_3), 2.35 (s, 3 H, NCH_3), 2,78–2.82 (m, 4 H, 2 × CH_2N), 2.99–3.05 (m, 4 H, 2 × CH_2N), 3.56 (s, CH_2O), 3.58–3.63 (m, 4 H, 2 × CH_2O), 4.09–4.15 (m, 4 H, 2 × CH_2O), 6.83 (d, *J* = 9.0 Hz, 1 H, H-6), 7.66 (d, *J* = 2.6 Hz, 1 H, H-2), 7.82 (dd, *J* = 9.0, 2.6 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.8 (C-9, C-16), 55.2 (C-8, C-17), 57.5 (C-10, C-15), 64.2 (C-11, C-14), 68.8 (C-7, C-18), 70.1 (C-12, C-13), 107.2 (C-3), 110.4 (C-6), 117.5 (C-5), 141.1 (C-4), 148.7 (C-2), 154.2 (C-1).

MS (IES): *m*/*z* calcd for $C_{18}H_{29}N_3O_6$: 383.44; found: 384.36 $[MH]^+$.

Anal. Calcld for $C_{18}H_{29}N_3O_6$: C, 56.38; H, 7.62. Found: C, 56.42; H, 7.59.

Benzoazacrown Naphthalimides 5a,b; General Procedure (Route 2)

To a suspension of K_2CO_3 (1.15 mmol) and diiodide **5h** (0.30 mmol) in MeCN (20 mL) was added a solution of amine **2a** (or **2b**) (0.30 mmol) in MeCN (20 mL) dropwise under stirring. The reaction mixture was stirred at r.t. for 78 h and concentrated in vacuo. Then, H_2O (150 mL) was added to the residue, and the mixture was extracted with $CHCl_3$. The combined organic layers were concentrated in vacuo and the residue was purified by column chromatography on alumina with benzene–EtOH (gradient) as eluent.

2-(4,10-Dimethyl-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,4,10,7,13]trioxadiazacyclopentadecin-15-yl)-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5a)

Prepared from diiodide **5h** (197 mg, 0.30 mmol), amine **2a** (44 mg, 0.33 mmol), and K_2CO_3 (159 mg, 1.15 mmol) in MeCN. After elution with benzene to benzene–EtOH (1:1), **5a** was obtained as a pale-yellow solid; yield: 111 mg (69%); mp 126–129 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3 H, NCH_3), 2.40 (s, 3 H, NCH_3), 2.78–2.84 (m, 4 H, 2 × CH_2N), 2.92 (dd, *J* = 4.5, 4.8 Hz, 2 H, CH_2N), 2.97 (dd, *J* = 4.5, 4.8 Hz, 2 H, CH_2N), 3.75 (dd, *J* = 5.8, 4.8 Hz, 4 H, 2 × CH_2O), 4.07 (t, *J* = 4.8 Hz, 2 H, CH_2O), 4.14 (t, *J* = 4.8 Hz, 2 H, CH_2O), 6.80 (d, *J* = 2.3 Hz 1 H, ArH-10), 6.85 (dd, *J* = 8.4, 2.3 Hz, 1 H, ArH-14), 7.01 (d, *J* = 8.4 Hz, 1 H, ArH-13), 8.01 (dd, *J* = 7.2, 8.4 Hz, 1 H, H-6), 8.42 (d, *J* = 8.0 Hz, 1 H, H-3), 8.71 (d, *J* = 8.0 Hz, 1 H, H-2), 8.78 (d, *J* = 7.2 Hz, 1 H, H-7), 8.88 (d, *J* = 8.4 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 43.8 (C-17, C-22), 55.9 (C-16, C-23), 57.5 (C-18, C-21), 67.1 (C-19, C-20), 68.9 (C-15, C-24), 113.1 (C-13), 113.7 (C-10), 122.0 (C-14), 123.3 (C-4a), 123.8 (C-8), 124.39 (C-3), 127.2 (C-1), 128.3 (C-9), 128.7 (C-8a), 129.4 (C-5), 129.9 (C-2), 130.1 (C-6), 132.7 (C-7), 148.9 (C-12),149.1 (C-11), 149.8 (C-4), 162.7 (C-8b), 163.5 (C-8c).

MS (IES): *m*/*z* calcd for $C_{28}H_{30}N_4O_7$: 534.3; found: 536.1 $[MH]^+$.

Anal. Calcd for $C_{28}H_{30}N_4O_7$: C, 62.91; H, 5.66. Found: C, 62.88; H, 5.62.

2-(4,13-Dimethyl-2,3,4,5,6,8,9,11,12,13,14,15-dodecahydrobenzo[*b*][1,4,10,13,7,16]tetraoxadiazacyclooctadecin-18-yl)-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5b)

Prepared from diiodide **5h** (197 mg, 0.30 mmol), amine **2b** (59 mg, 0.33 mmol), and K_2CO_3 (159 mg, 1.15 mmol) in MeCN. After elution with benzene to benzene–EtOH (1:1), **5b** obtained as a pale-yellow solid; yield: 116 mg (67%); mp 137–142 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 3 H, NCH_3), 2.43 (s, 3 H, NCH_3), 2.82–2.89 (m, 4 H, 2 × CH_2N), 3.00–3.08 (m, 4 H, 2 × CH_2N), 3.63 (s, 4 H, 2 × CH_2O), 3.63–3.70 (m, 4 H, 2 × CH_2O), 4.08–4.12 (m, 2 H, CH_2O), 4.15–4.18 (m, 2 H, CH_2O), 6.79 (s, 1 H, ArH-10), 6.84 (d, *J* = 8.4 Hz, 1 H, ArH-14), 7.01 (d, *J* = 8.4 Hz, 1 H, ArH-13), 8.01 (t, *J* = 7.5 Hz, 1 H, H-6), 8.42 (d, *J* = 8.0 Hz, 1 H, H-3), 8.72 (d, *J* = 8.0 Hz, 1 H, H-2), 8.78 (d, *J* = 7.5 Hz, 1 H, H-7), 8.89 (d, *J* = 8.7 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 43.5 (C-17, C-24), 55.6 (C-16, C-25), 57.2 (C-18, C-23), 67.1 (C-19, C-22), 68.7 (C-15, C-26), 70.5 (C-20, C-21), 113.2 (C-13), 113.6 (C-10), 122.2 (C-14), 123.4 (C-4a), 123.9 (C-8), 124.39 (C-3), 127.1 (C-1), 128.3 (C-9), 128.7 (C-8a), 129.4 (C-5), 129.9 (C-2), 130.1 (C-6), 132.6 (C-7), 148.9 (C-12), 149.2 (C-11), 149.7 (C-4), 162.8 (C-8b), 164.3 (C-8c).

MS (IES): *m*/*z* calcd for $C_{30}H_{34}N_4O_8$: 578.4; found: 578.7 $[M]^+$.

Anal. Calcd for $C_{30}H_{34}N_4O_8$: C, 62.27; H, 5.92. Found: C, 62.30; H, 5.89.

Benzothiacrown Ethers 3c–f and Benzothiacrown Naphthalimides 5c–f; General Procedure (Route 2)

The procedure is a modified synthesis as described earlier.[24] To a suspension of Cs_2CO_3 (1.10 mmol) and dichloride **1a** or **5g** (or diiodide **1b**, **5h** for compounds **3c** and **5c,** respectively) (0.30 mmol) in MeCN (30 mL) was added a solution of dithiol **2c–f** (0.33 mmol) in MeCN (30 mL) dropwise under stirring. The reaction mixture was heated and refluxed for 78 h. Then, it was concentrated in vacuo. H_2O (150 mL) was added to the residue, and the mixture was extracted with $CHCl_3$ (compounds **5c–f** were washed with H_2O). The extracts were concentrated in vacuo, and the residue was purified by silica gel column chromatography with eluent benzene–EtOAc (for **3c–f**) or benzene–EtOH (gradient) (for **5c–f**).

12-Nitro-2,3,5,6,8,9-hexahydrobenzo[*b*][1,4,7,10]dioxadithiacyclododecine (3c)

Prepared from diiodide **1b** (139 mg, 0.30 mmol), dithiol **2c** (31 mg, 0.33 mmol), and Cs_2CO_3 (358 mg, 1.10 mmol) in MeCN: After elution with benzene **3c**, was obtained as a white-yellowish solid; yield: 54 mg (61%); mp 157–159 °C (Lit.[24] mp 159–161 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.99–3.02 (m, 4 H, 2 × CH_2S), 3.07 (s, 4 H, 2 × CH_2S), 4.44–4.47 (m, 4 H, 2 × CH_2OAr), 6.86 (d, *J* = 8.9 Hz, 1 H, H-6), 7.70 (d, *J* = 2.2 Hz, 1 H, H-2), 7.94 (dd, *J* = 8.9, 2.2 Hz, 1 H, H-5).

15-Nitro-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]dioxatrithiacyclopentadecine (3d)

Prepared from dichloride **1a** (84 mg, 0.30 mmol), thiol **2d** (51 mg, 0.33 mmol), and Cs_2CO_3 (358 mg, 1.10 mmol) in MeCN. After elution with benzene–EtOAc (5:1), **3d** was obtained as a yellow solid; yield: 66 mg (63%); mp 157–159 °C (Lit.[25] mp 159–161 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85–2.88 (m, 4 H, 2 × CH_2S), 2.99–3.03 (m, 4 H, 2 × CH_2S), 3.08–3.11 (m, 4 H, 2 × CH_2S), 4.33–4.36 (m, 4 H, 2 × CH_2OAr), 7.21 (d, *J* = 8.9 Hz, 1 H, H-6), 7.77 (d, *J* = 2.5 Hz, 1 H, H-2), 7.93 (dd, *J* = 8.9, 2.5 Hz, 1 H, H-5).

15-Nitro-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,10,7,13]trioxadithiacyclopentadecine (3e)

Prepared from dichloride **1a** (84 mg, 0.30 mmol), thiol **2e** (51 mg, 0.33 mmol), and Cs_2CO_3 (358 mg 1.10 mmol) in MeCN. Ater elution with benzene–EtOAc (5:1), **3e** was obtained as yellow solid; yield: 61 mg (59%); mp 128–130 °C (Lit.[24] mp 129–131 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97–3.01 (m, 4 H, 2 × CH_2S), 3.03–3.07 (m, 4 H, 2 × CH_2S), 4.24–4.28 (m, 4 H, 2 × CH_2OAr), 6.82 (d, *J* = 8.7 Hz, 1 H, H-6), 7.69 (d, *J* = 2.3 Hz, 1 H, H-2), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1 H, H-5).

18-Nitro-2,3,5,6,8,9,11,12,14,15-decahydrobenzo[*b*][1,4,10,13,7,16]tetraoxadithiacyclooctadecine (3f)

Prepared from dichloride **1a** (84 mg, 0.30 mmol), dithiol **2f** (60 mg, 0.33 mmol), and Cs_2CO_3 (358 mg 1.10 mmol) in MeCN. After elution with benzene–EtOAc (10:1), **3f** was obtained as a yellowish solid; yield: 55 mg (52%); mp 128–130 °C (Lit.[24] mp 128–129 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (t, *J* = 6.6 Hz, 2 H, CH_2S), 3.01 (t, *J* = 6.9 Hz, 2 H, CH_2S), 3.15–3.19 (m, 2 H, CH_2S), 3.19 (t, *J* = 6.6 Hz, 2 H, CH_2S), 3.63 (s, 4 H, 2 × CH_2O), 3.74–3.79 (m, 4 H, 2 × CH_2O), 4.25–4.29 (m, 4 H, 2 × CH_2OAr), 6.87 (d, *J* = 8.9 Hz, 1 H, H-6), 7.71 (d, *J* = 2.4 Hz, 1 H, H-2), 7.91 (dd, *J* = 8.9, 2.4 Hz, 1 H, H-5).

2-(2,3,5,6,8,9-Hexahydrobenzo[*b*][1,4,7,10]dioxadithiacyclododecin-12-yl)-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5c)

Prepared from diiodide **5h** (197 mg, 0.30 mmol), dithiol **2c** (31 mg, 0.33 mmol), and Cs_2CO_3 (358 mg 1.10 mmol) in MeCN. After elution with benzene to benzene–EtOH (2:1), **5c** was obtained as a yellow solid; yield: 61 mg (41%); mp 268–269 °C (AcOH).

IR (KBr): 1717 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.90–2.92 (m, 2 H, CH_2-16), 2.95–2.97 (m, 2 H, CH_2-19), 3.02 (s, 4 H, CH_2S-17, 18), 4.22–4.24 (m, 2 H, CH_2OAr-15), 4.36–4.38 (m, 2 H, CH_2OAr-20), 6.95 (dd, ^4J = 2.2 Hz, ^3J = 8.6 Hz, 1 H, ArH-14), 7.05 (d, ^4J = 2.2 Hz, 1 H, ArH-10), 7.09 (d, ^3J = 8.6 Hz, 1 H, ArH-13), 8.13 (dd, ^3J = 7.4 Hz, ^3J = 8.6 Hz, 1 H, H-6), 8.60 (d, ^3J = 8.0 Hz, 1 H, H-3), 8.62 (d, ^3J = 8.0 Hz, 1 H, H-2), 8.64 (d, ^3J = 7.4 Hz, 1 H, H-7), 8.76 (d, ^3J = 8.6 Hz ,1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.8 (C-18, C-17) 33.5 (C-16, C-19), 72.6 (C-15, C-20), 112.9 (C-13), 114.0 (C-10), 121.9 (C-14), 123.3 (C-4a), 123.9 (C-8), 124.8 (C-3), 127.8 (C-1), 128.8 (C-9), 129.2 (C-8a), 129.3 (C-5), 130.1 (C-2), 130.6 (C-6), 132.2 (C-7), 148.4 (C-12),148.5 (C-11), 149.7 (C-4), 163.0 (C-8b), 163.8 (C-8c).

MS: *m*/*z* (%) = 496.08 (100.0), 497.08 (28.0), 498.07 (9.1), 498.08 (5.1), 499.08 (2.8).

Anal. Calcd for $C_{24}H_{20}N_2O_6S_2$: C, 58.05; H, 4.06; N, 5.64. Found: C, 57.99; H, 4.08; N, 5.61.

6-Nitro-2-(2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]dioxatrithiacyclopentadecin-15-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5d)

Prepared from dichloride **5g** (143 mg, 0.30 mmol), thiol **2d** (51 mg, 0.33 mmol), and Cs_2CO_3 (358 mg, 1.10 mmol) in MeCN. After elution with benzene to benzene–EtOH (1:1), **5d** was obtained as a gray solid; yield: 45 mg (27%); mp 235–237 °C (AcOH).

IR (KBr): 1716 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.87–2.89 (m, 4 H, CH_2-18,19), 3.02–3.04 (m, 4 H, CH_2-16, 21), 3.08–3.11 (m, 4 H, CH_2S-17, 20), 4.13 (br s, 2 H, CH_2OAr-15), 4.28 (br s, 2 H, CH_2OAr-22), 6.96 (dd, ^4J = 2.2 Hz, ^3J = 8.6 Hz, 1 H, ArH-14), 7.09 (d, ^4J = 2.2 Hz, 1 H, ArH-10), 7.12 (d, ^3J = 8.6 Hz, 1 H, ArH-13), 8.13 (dd, ^3J = 7.4 Hz, ^3J = 8.6 Hz, 1 H, H-6), 8.58 (d, ^3J = 8.0 Hz, 1 H, H-3), 8.60 (d, ^3J = 8.0 Hz, 1 H, H-2), 8.63 (d, ^3J = 7.4 Hz, 1 H, H-7), 8.74 (d, ^3J = 8.6 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.2 (C-17, C-20) 32.0 (C-18, C-19), 40.1 (C-16, C-21), 72.2 (C-15, C-22), 113.0 (C-13), 114.0 (C-10), 121.9 (C-14), 123.3 (C-4a), 123.9 (C-8), 124.8 (C-3), 127.8 (C-1), 128.8 (C-9), 129.2 (C-8a), 129.3 (C-5), 130.0 (C-2), 130.5 (C-6), 132.2 (C-7), 148.4 (C-12),148.5 (C-11), 149.7 (C-4), 163.0 (C-8b), 163.8 (C-8c).

MS (IES): *m*/*z* calcd for $C_{26}H_{24}N_2O_6S_3$: 556.08; found: 557.08 $[MH]^+$.

Calculated for $C_{26}H_{24}N_2O_6S_3$: C, 56.10; H, 4.35; N, 5.03. Found: C, 56.09; H, 4.38; N, 5.01.

6-Nitro-2-(2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,10,7,13]trioxadithiacyclopentadecin-15-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5e)

Prepared from dichloride **5g** (143 mg, 0.30 mmol), dithiol **2e** (46 mg, 0.33 mmol), and Cs_2CO_3 (358 mg 1.10 mmol) in MeCN. After elution with benzene to benzene–EtOH (2:1), **5e** was obtained as a gray solid; yield: 29 mg (18%); mp 228–230 °C (AcOH).

^1H NMR (400 MHz, DMSO-d_6): δ = 2.88–2.92 (m, 8 H, CH_2-16, CH_2-17, CH_2-20, CH_2-21), 3.71–3.76 (m, 4 H, CH_2-18, CH_2-19) 4.11–4.13 (m, 2 H, CH_2OAr-15), 4.24–4.27 (m, 2 H, CH_2OAr-22), 6.96 (dd, ^4J = 2.2 Hz, ^3J = 8.6 Hz, 1 H, ArH-10), 7.09 (d, *J* = 2.2 Hz, 1 H, ArH-14), 7.12 (d, ^3J = 8.6 Hz, 1 H, ArH-13), 8.13 (dd, ^3J = 7.4 Hz, ^3J = 8.6 Hz, 1 H, H-6), 8.58 (d, ^3J = 8.0 Hz, 1 H, H-3), 8.61 (d, ^3J = 8.0 Hz, 1 H, H-2), 8.64 (d, ^3J = 7.4 Hz, 1 H, H-7), 8.75 (d, ^3J = 8.6 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.3 (CH_2S), 30.4 (CH_2S), 30.7 (2 × CH_2S), 70.6 (CH_2O), 70.7 (CH_2O), 71.0 (2 × CH_2O), 113.0 (C-13), 114.1 (C-10), 121.5 (C-14), 122.9 (C-4a), 123.4 (C-8), 124.3 (C-3), 127.3 (C-1), 128.4 (C-9), 128.7 (C-8a), 128.9 (C-5), 129.6 (C-2), 130.2 (C-6), 131.7 (C-7), 148.1 (C-12), 148.2 (C-11), 149.2 (C-4), 162.5 (C-8b), 163.3 (C-8c).

MS (IES): *m*/*z* calcd for $C_{26}H_{24}N_2O_7S_2 + Ag^+$, $C_{26}H_{24}N_2O_7S_2 + Ag^{2+}$: 647.01 ($[M + Ag]^+$), 649.00 ($[M + Ag + 2]^+$); found: 647.02 ($[M + Ag]^+$), 648.94 ($[M + Ag + 2]^+$).

Anal. Calcd for $C_{26}H_{24}N_2O_7S_2$: C, 57.76; H, 4.47; N, 5.18; S, 11.86. Found: C, 57.79; H, 4.46; N, 5.14; S, 11.62.

2-(2,3,5,6,8,9,11,12,14,15-Decahydrobenzo[*b*][1,4,10,13,7,16]tetraoxadithiacyclooctadecin-18-yl)-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5f)

Prepared from dichloride **5g** (143 mg, 0.30 mmol), dithiol **2f** (60 mg, 0.33 mmol), and Cs_2CO_3 (358 mg 1.10 mmol) in MeCN. After elution with benzene to benzene–EtOH (1:1), **5f** was obtained as a light-brown solid; yield: 21 mg (11%); mp 204–207 °C (AcOH).

IR (KBr): 1714 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.89–2.92 (m, 4 H, CH_2-17, 22), 3.05–3.09 (m, 4 H, CH_2S-16, 23), 3.54–3.56 (m, 4 H, CH_2O-19, 20), 3.64–3.66 (m, 4 H, CH_2O-18, 21), 4.06–4.08 (m, 2 H, CH_2OAr-15), 4.20–4.22 (m, 2 H, CH_2OAr-22), 6.96 (dd, ^4J = 2.3 Hz, ^3J = 8.6 Hz, 1 H, ArH-14), 7.07 (d, ^4J = 2.3 Hz, 1 H, ArH-10), 7.18 (d, ^3J = 8.6 Hz, 1 H, ArH-13), 8.14 (dd, ^3J = 7.4 Hz, ^3J = 8.6 Hz, 1 H, H-6), 8.60 (d, ^3J = 8.0 Hz, 1 H, H-3), 8.62 (d, ^3J = 8.0 Hz, 1 H, H-2), 8.65 (d, ^3J = 7.4 Hz, 1 H, H-7), 8.77 (d, ^3J = 8.6 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.5 (C-16, C-23), 31.3 (C-17, C-22), 53.0 (C-19, C-20), 63.5 (C-18, C-21), 72.2 (C-15, C-24), 113.1 (C-13), 114.2 (C-10), 121.6 (C-14), 123.3 (C-4a), 123.9 (C-8), 124.8 (C-3), 127.8 (C-1), 128.8 (C-9), 129.2 (C-8a), 129.3 (C-5), 130.1 (C-2), 130.6 (C-6), 132.2 (C-7), 148.1 (C-12), 148.5 (C-11), 149.7 (C-4), 163.0 (C-8b), 163.8 (C-8c).

MS (IES): *m*/*z* calcd for $C_{28}H_{28}N_2O_8S_2$: 584.13; found: 585.14 $[MH]^+$.

Anal. Calcd for $C_{28}H_{28}N_2O_8S_2$: C, 57.52; H, 4.83; N, 4.79. Found: C, 57.49; H, 4.85; N, 4.71.

Nickel Catalyst

In a 250 mL beaker a slurry of Ni-Al alloy (50% Ni w/w, 11.0 g) was prepared in H_2O (110 mL). Solid KOH was added without any external cooling of the mixture. The addition was continued until further portions of KOH caused a visible reaction (about 22–25 g total). When the reaction had settled the mixture was maintained at r.t. for 10–15 min and transferred to a 70 °C water bath for 30 min. Then, H_2O was decanted, and the precipitate was washed with distilled H_2O (3 ×) followed by a triple wash with EtOH. The obtained powder was stored under EtOH.[20]

Reduction of 4-Nitro Derivatives of *N*-Phenyl Azacrown Ethers 3a–f to Amines 4a–f with Raney Nickel; General Procedure

The procedure was a modified synthesis described earlier.[20] Hydrazine hydrate (100%, 0.7 mL) was added to a refluxing solution of nitro derivative **3** (1 mmol) in EtOH or DMF (30 mL). Then, the Ni catalyst was added until the next successive portion caused a visible reaction. The mixture was maintained at reflux for 1 day, the catalyst was filtered off, and the filtrate was evaporated in vacuo.

4,10-Dimethyl-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,4,10,7,13]trioxadiazacyclopentadecin-15-amine (4a)

Prepared from **3a** (60 mg, 0.18 mmol); yield: 52 mg (95%); yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.34–2.37 (m, 6 H, 2 × NCH_3), 2.75–2.77 (m, 4 H, 2 × CH_2N), 2.90–2.93 (m, 4 H, 2 × CH_2N), 3.67–3.70 (m, 4 H, 2 × CH_2O), 3.99–4.03 (m, 4 H, 2 × CH_2O), 6.23 (dd, *J* = 8.3, 2.4 Hz, 1 H, H-6), 6.28 (s, 1 H, H-2), 6.70 (dd, *J* = 8.3, 2.4 Hz, 1 H, H-5).

MS (IES): *m*/*z* calcd for $C_{16}H_{27}N_3O_3$: 309; found: 310 $[MH]^+$.

Anal. Calcd for $C_{16}H_{27}N_3O_3$: C, 62.11; H, 8.80. Found: C, 62.56; H, 8.68.

4,13-Dimethyl-2,3,4,5,6,8,9,11,12,13,14,15-dodecahydrobenzo[*b*][1,4,10,13,7,16]tetraoxadiazacyclooctadecin-18-amine (4b)

Prepared from **3b** (60 mg, 0.15 mmol); yield: 54 mg (98%); yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.31–2.35 (m, 6 H, 2 × NCH_3), 2.72–2.75 (m, 4 H, 2 × CH_2N), 2.87–3.91 (m, 4 H, 2 × CH_2N), 3.52–3.56 (m, 4 H, 2 × CH_2O), 3.94–4.00 (m, 4 H, 2 × CH_2O), 6.25 (dd, *J* = 8.4, 2.5 Hz, 1 H, H-6), 6.30 (s, 1 H, H-2), 6.70 (dd, *J* = 8.4, 2.5 Hz, 1 H, H-5).

MS (IES): *m*/*z* calcd for $C_{18}H_{31}N_3O_4$: 353; found: 354 $[MH]^+$.

Anal. Calcd for $C_{18}H_{31}N_3O_4$: C, 61.17; H, 8.84. Found: C, 61.08; H, 8.81.

2,3,5,6,8,9-Hexahydrobenzo[*b*][1,4,7,10]dioxadithiacyclododecin-12-amine (4c)

Prepared from **3c** (54 mg, 0.18 mmol); yield: 35 mg (71%); colorless oil.[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.90–2.94 (m, 4 H, 2 × CH_2S), 3.07–3.10 (m, 4 H, 2 × CH_2S), 4.29–4.32 (m, 4 H, 2 × CH_2OAr), 6.25 (dd, *J* = 8.4, 2.5 Hz, 1 H, H-6), 6.27 (s, 1 H, H-2), 6.68 (d, *J* = 8.4 Hz, 1 H, H-5).

2,3,5,6,8,9,11,12-Octahydrobenzo[*b*][1,4,7,10,13]dioxatrithiacyclopentadecin-15-amine (4d)

Prepared from **3d** (58 mg, 0.16 mmol); yield: 44 mg (82%); colorless oil.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.87–2.91 (m, 4 H, 2 × CH_2S), 3.02–3.05 (m, 4 H, 2 × CH_2S), 3.09–3.13 (m, 4 H, 2 × CH_2S), 4.29–4.32 (m, 4 H, 2 × CH_2OAr), 6.22 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-6), 6.30 (s, 1 H, H-2), 6.79 (d, *J* = 8.5 Hz, 1 H, H-5).

2,3,5,6,8,9,11,12-Octahydrobenzo[*b*][1,4,10,7,13]trioxadithiacyclopentadecin-15-amine (4e)

Prepared from **3e** (53 mg, 0.15 mmol); yield: 43 mg (89%); grey oil.[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.90 (t, *J* = 6.1 Hz, 2 H, CH_2S), 2.96 (t, *J* = 6.6 Hz, 2 H, CH_2S), 3.04–3.08 (m, 4 H, 2 × CH_2S), 3.78–3.83 (m, 4 H, 2 × CH_2O), 4.14–4.17 (m, 2 H, CH_2OAr), 4.20–4.24 (m, 4 H, 2 × CH_2OAr) 6.25 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-6), 6.30 (d, *J* = 2.4 Hz, 1 H, H-2), 6.74 (d, *J* = 8.5 Hz, 1 H, H-5).

2,3,5,6,8,9,11,12,14,15-Decahydrobenzo[*b*][1,4,10,13,7,16]tetraoxadithiacyclooctadecin-18-amine (4f)

Prepared from **3f** (54 mg, 0.14 mmol); yield: 46 mg (93%); grey oil.[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93–2.97 (m, 4 H, 2 × CH_2S), 3.07–3.10 (m, 4 H, 2 × CH_2S), 3.64 (s, 4 H, 2 × CH_2O), 3.73–3.77 (m, 4 H, 2 × CH_2O), 4.12–4.16 (m, 4 H, 2 × CH_2OAr), 6.22 (dd, *J* = 8.5, 2.3 Hz, 1 H, H-6), 6.30 (d, *J* = 2.3 Hz, 1 H, H-2), 6.71 (d, *J* = 8.5 Hz, 1 H, H-5).

3,4-Bis(2-chloroethoxy)aniline (4g)

Prepared from **1a** (0.2 g, 0.71 mmol); yield: 0.17 g (96%); grey oil.[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79–3.83 (m, 4 H, 2 × CH_2Cl), 4.28–4.32 (m, 4 H, 2 × CH_2O), 6.24 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-6), 6.29 (d, *J* = 2.4 Hz, 1 H, H-2), 6.81 (d, *J* = 8.5 Hz, 1 H, H-5).

Acylation of Arylamines 4a–g with 4-Nitro-1,8-naphthalic Anhydride; General Procedure (Route 1)

The procedure was a modified synthesis described earlier.[21] A suspension of 4-nitro-1,8-naphthalic anhydride (0.35 mmol) and equimolar quantity of the corresponding amine **4** in glacial AcOH (40 mL) was heated under reflux for 4 h. The hot reaction mixture was filtered to remove the unreacted starting anhydride. The filtrate was cooled to r.t. and a solid precipitate appeared. The precipitate was collected by filtration, washed with aq 5% HCl, hot 10% aq Na_2CO_3, H_2O, EtOH, and dried.

Products **5a–f** prepared by route 1 were identical with **5a–f** prepared by the cyclization reactions of **5g**,**h** as shown in Scheme 4 (route 2). See above for details as well as for the analytical and spectral data of **5a–g**.

5a

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) and amine **4a** (0.108 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene–EtOH (2:1) on Al_2O_3, **5a** was obtained as a pale-yellow solid; yield: 0.058 g (31%).

5b

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) and amine **4b** (0.124 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene–EtOH (2:1) on Al_2O_3, **5b** was obtained as a pale-yellow solid; yield: 0.059 g (29%).

5c

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) and amine **4c** (0.095 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene–EtOH (2:1) on Al_2O_3, **5c** was obtained as pale-yellow solid; yield: 0.090 g (52%).

5d

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) amine **4d** (0.116 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene–EtOH (2:1) on Al_2O_3, **5d** was obtained as a pale-yellow solid; yield: 0.127 g (65%).

5e

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) and amine **4e** (0.110 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene-EtOH (2:1) on Al_2O_3, **5e** was obtained as a pale-yellow solid; yield: 0.134 g (71%).

5f

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) and amine **4f** (0.126 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene–EtOH (2:1) on Al_2O_3, **5f** was obtained as a pale-yellow solid; yield: 0.139 g (68%).

2-[3,4-Bis(2-chloroethoxy)phenyl]-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5g)

Prepared from 4-nitro-1,8-naphthalic anhydride (0.085 g, 0.35 mmol) and amine **4g** (0.088 g, 0.35 mmol) in glacial AcOH (20 mL). After elution with benzene to benzene–EtOH (2:1) on Al_2O_3, **5g** was obtained as a pale-yellow solid; yield: 0.12 g (73%); mp 205–207 °C (AcOH).

^{1}HNMR (400 MHz, $CDCl_3$): δ = 3.76–3.83 (m, 4 H, 2 × CH_2Cl), 4.23–4.32 (m, 4 H, 2 × CH_2O), 6.82 (s., 1 H, ArH-10′), 6.86 (d, *J* = 8.4 Hz, 1 H, ArH-14′), 7.07 (d, *J* = 8.4 Hz, 1 H, Ar H-13′), 7.97 (dd, *J* = 7.6, 8.6 Hz, 1 H, H-6), 8.37 (d, *J* = 8.1 Hz, 1 H, H-3), 8.66 (d, *J* = 8.1 Hz, 1 H, H-2), 8.70 (d, *J* = 7.4 Hz, 1 H, H-7), 8.81 (d, *J* = 8.6 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.1 (CH_2Cl), 42.2 (CH_2Cl), 70.2 (2 × CH_2O), 116.1 (C-13), 116.6 (C-10), 122.7 (C-14), 123.1 (C-4a) 124.1 (C-8), 124.5 (C-3), 127.1 (C-1), 128.5 (C-9), 128.9 (C-8a), 129.8 (C-5), 130.2 (C-6), 132.8 (C-7), 132.9 (C-7), 146.4 (C-12), 149.3 (C-11), 150.1 (C-4), 160.7 (C-8b), 165.3 (C-8c).

MS (IES): *m*/*z* calcd for $C_{22}H_{16}C_{l2}N_2O_6$: 475.3; found: 475.4 $[M]^+$.

Anal. Calcd for $C_{22}H_{16}Cl_2N_2O_6$: C, 55.60; H, 3.39. Found: C, 55.56; H, 3.41.

6-Amino-2-(2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,10,7,13]trioxadithiacyclopentadecin-15-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (6a)

According to the general procedure for the reduction of 4-nitro derivatives of naphthalimide with Raney Ni, **5e** (150 mg, 0.28 mmol) afforded the product **6a**; yield: 23 mg (16%); mp 249–250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.85–3.10 (m, 8 H, CH_2-16, 17, 20, 21), 3.67–3.79 (m, 4 H, CH_2-18, 19), 4.07–4.17 (m, 2 H, CH_2OAr), 4.19–4.29 (m, 2 H, CH_2OAr), 6.82 (dd, ^4J = 2.2 Hz, ^3J = 8.6 Hz, 1 H, H-14), 6.86 (d, ^3J = 8.4 Hz, 1 H, H-3), 6.95 (d, ^4J = 2.2 Hz, 1 H, H-10), 7.05 (d, ^3J = 8.6 Hz, 1 H, H-13), 7.49 (s, 2 H, NH_2), 7.63–7.72 (m, 1 H, H-6), 8.18 (d, ^3J = 8.4 Hz, 1 H, H-2), 8.42 (d, ^3J = 7.3 Hz, 1 H, H-7), 8.65 (d, ^3J = 8.5 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.31 (CH_2S), 30.40 (CH_2S), 30.72 (2 × CH_2S), 70.66 (CH_2O), 70.69 (CH_2O), 70.94 (CH_2O), 70.98 (CH_2O), 107.92 (C-1), 108.20 (C-3), 112.95 (C-13), 114.48 (C-10), 119.48 (C-4a), 121.67 (C-14), 122.33 (C-8), 124.03 (C-6), 129.43 (C-9), 129.66 (C-5), 130.17 (C-8a), 131.10 (C-7), 133.99 (C-2), 147.64 (C-12), 148.16 (C-11), 152.76 (C-4), 163.29 (C-8b), 164.15 (C-8c).

MS (IES): *m*/*z* calcd for $C_{26}H_{26}N_2O_5S_2$ + Ag^+, $C_{26}H_{26}N_2O_5S_2$ + Ag^{2+}: 617.03 ([M + Ag]$^+$), 619.02 ([M + Ag + 2]$^+$); found: 617.08 ([M + Ag]$^+$), 618.97 ([M + Ag + 2]$^+$).

Anal Calcd for $C_{26}H_{26}N_2O_5S_2$: C, 61.16; H, 5.13; N, 5.49. Found: C, 61.32; H, 5.18; N, 5.45.

***N*-[2-(2,3,5,6,8,9,11,12-Octahydrobenzo[*b*][1,4,10,7,13]trioxadithiacyclopentadecin-15-yl)-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-6-yl)acetamide (6b)**

According to the general procedure for the acylation of arylamines by 4-nitro-1,8-naphthalic anhydride, compound **6a** (25 mg, 0.049 mmol) and Ac_2O (0.2 mL) in glacial AcOH (0.5 mL) afforded compound **6b** as a pale yellow solid; yield: 22 mg (81%); mp 264–267 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.30 (s, 3 H, CH_3), 2.84–3.11 (m, 8 H, CH_2-16, 17, 20, 21), 3.65–3.81 (m, 4 H, CH_2-18, 19), 4.06–4.18 (m, 2 H, CH_2OAr), 4.19–4.31 (m, 2 H, CH_2OAr), 6.91 (dd, ^4J = 1.8 Hz, ^3J = 8.6 Hz, 1 H, H-14), 7.05 (d, ^4J = 1.8 Hz, 1 H, H-10), 7.08 (d, ^3J = 8.6 Hz, 1 H, H-13), 7.86–7.98 (m, 1 H, H-6), 8.34 (d, ^3J = 8.2 Hz, 1 H, H-3), 8.48 (d, ^3J = 8.2 Hz, 1 H, H-2), 8.53 (d, ^3J = 7.3 Hz, 1 H, H-7), 8.75 (d, ^3J = 8.5 Hz, 1 H, H-5), 10.46 (s, 1 H, NHCO).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 24.11 (CH_3CO), 30.30 (CH_2S), 30.40 (CH_2S), 30.72 (CH_2S), 30.74 (CH_2S), 70.64 (CH_2O), 70.69 (CH_2O), 70.95 (CH_2O), 70.97 (CH_2O), 112.98 (C-13), 114.34 (C-10), 118.04 (C-1), 119.44 (C-3), 121.63 (C-14), 122.90 (C-8), 124.16 (C-4a), 126.42 (C-6), 128.77 (C-8a), 129.02 (C-9), 129.33 (C-5), 130.90 (C-7), 131.64 (C-2), 140.36 (C-4), 147.87 (C-12), 148.19 (C-11), 163.31 (C-8b), 163.87 (C-8c), 169.95 (CH_3CO).

MS (IES): *m*/*z* calcd for $C_{28}H_{28}N_2O_6S_2$ + Ag^+, $C_{26}H_{26}N_2O_5S_2$ + Ag^{2+}: 659.04 ([M + Ag]$^+$), 661.03 ([M + Ag + 2]$^+$); found: 659.11 ([M + Ag]$^+$), 661.00 ([M + Ag + 2]$^+$).

Anal. Calcd for $C_{28}H_{28}N_2O_6S_2$: C, 60.85; H, 5.11; N, 5.07. Found: C, 60.90; H, 5.14; N, 5.03.

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Supporting Information

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