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Synthesis and bromination of 4-alkylamino-*N*-alkyl-1,8-naphthalimides

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Abstract

4-Alkylamino-*N*-alkyl-1,8-naphthalimides were prepared from 4-chloro-1,8-naphthalic anhydride and from 4-amino-1,8-naphthalimide. It was found that the amino nitrogen of 4-amino-*N*-alkyl-1,8-naphthalimides is nucleophilic enough to participate in nucleophilic displacement reactions without the need for added base, despite being a vinylogous amide. Bromination of 4-alkylamino-*N*-alkyl-1,8-naphthalimides using molecular bromine was found to occur in the absence of a Lewis acid catalyst, and to be regiospecific, yielding only the 3-bromo isomer. Extended reaction times and the use of excess bromine result in dealkylation of the 4-alkylamino substituent, but no polybromination of the naphthalimide ring system. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Naphthalimides; Bromination; Fluorescent; Gabriel synthesis; Dealkylation

1. Introduction

1,8-Naphthalimide derivatives are highly fluorescent and photostable, so they have been used as fluorescent dyes for synthetic polymers and textile materials, in fluorescent solar energy collectors, as liquid-crystal additives, as electro-optically sensitive materials, in laser technology and as fluorescent markers in medicine and biology [1]. The 4-amino-1,8-naphthalimide dyes are probably still the most important yellow components for daylight fluorescent pigments, and most applications of 1,8-naphthalimide derivatives are as fluorescent brighteners in detergents, textiles, paper, plastics and paints [2,3]. 1,8-Naphthalimide derivatives are used as fluorescent dichroic dyes in liquid crystal displays [4–6], and their high fluorescence quantum yield and photostability makes them excellent candidates for dye lasers, where a high quantum yield and low level of re-absorption are extremely important. It has been observed that the fluorescence quantum yield of a 4-alkylamino-*N*-alkyl-1,8-naphthalimide is improved when it is placed in a glass matrix [7–9], such glasses may be important new materials in the development of dye lasers. More recently, 1,8-naphthalimide derivatives have been studied as DNA intercalators [10], and their use proposed for quantitation of paramagnetic transition metal cations by fluorescence emission enhancement [11,12].

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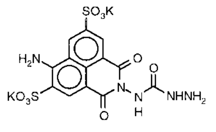
In biology, the most widely used fluorescent probes based on the naphthalimide system are 4-amino-3,6-disulfo-1,8-naphthalimide derivatives Lucifer Yellow CH (**1**) and Lucifer yellow VS (**2**) [13], both of which have been used with considerable success as intracellular markers in a wide variety of systems. Probe **1** is used more often than **2** because the latter is not available commercially. The most frequent application of **1** has been to reveal the shape of neurons since, like other sulfonated dyes, **1** does not cross the membrane of live cells due to the fact that the sulfonic acid group is fully ionized at physiological pH. One important observation was made with **1**: although it is retained by the injected cell, it does migrate to certain adjacent cells, a phenomenon known as "dye-coupling". Dye-coupled cells are known to be electrically coupled to each other [14]. Even though **1** appears innocuous under normal illumination, cell kill under intense illumination has been observed [15], and the possibility of a selective tumoricidal effect was suggested [16]. Lucifer Yellow CH has also served as the starting point for the development of new class of anti-retrovirus agents, with aminodisulfonatonaphthalimide (ADSN) derivatives **3** and **4** reported by Rideout and co-workers (serving as examples) [17].



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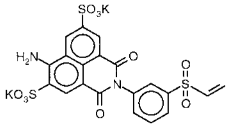

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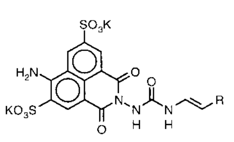
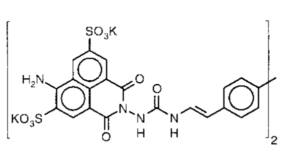


3a: R = C_6H_5
3b: R = (4,4')- O=CH—C_6H_4— C_6H_4
3c: R = *m*-O=CH— C_6H_4



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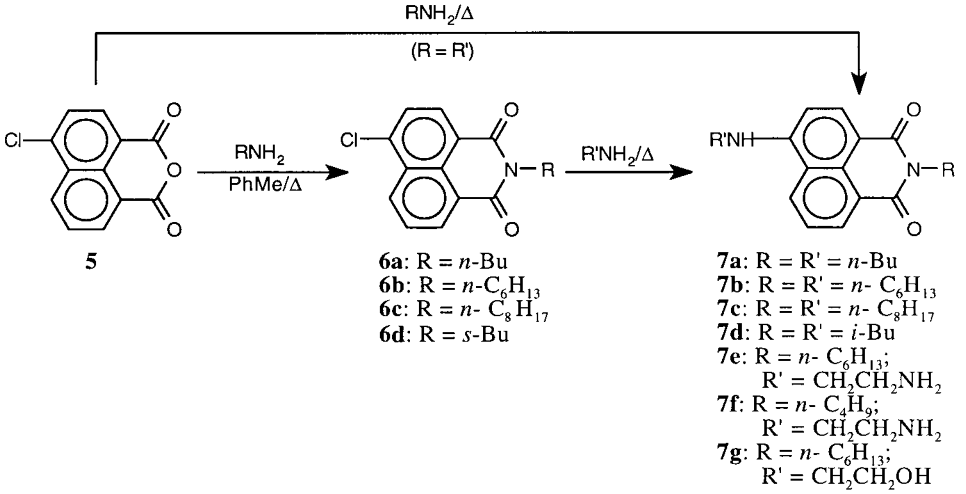
Our initial consideration of naphthalimide dyes arose from an interest in the use of fluorescent dyes to mediate the eradication of pathogenic organisms, including enveloped viruses, from blood using dye-mediated photochemistry. Extending the observations of Miller and Selverston [15] suggested that appropriately substituted 4-amino-1,8-naphthalimides might form the basis for a new class of photochemically active antiviral and anti-tumor agents. In contrast to currently used hematoporphyrin-derived photodynamic agents which are of limited chemical stability and uncertain composition, and difficult to purify, the chemical stability of the naphthalimides under a variety of conditions makes them resistant to degradation and generally amenable to routine purification and analysis. Moreover, their relatively simple synthesis permits a wide variety of substituents to be attached to the parent structure during synthesis, thus enhancing the potential for manipulating the tissue selectivity of these dyes by simply controlling the identity and location of substituents. In addition, a high fluorescence quantum yield makes the 4-amino-1,8-naphthalimide system an ideal candidate for use where the ability to visualize the localization of the therapeutic agent is important.

2. Results and discussion

The first major class of lipid-soluble compounds chosen for study as potential agents for the photodynamic inactivation of tumor cells and enveloped viruses were the 4-alkylamino-*N*-alkyl-1,8-naphthalimides (**7**). The "R_2 class" naphthalimides (**7**, $R = R'$) in this work were synthesized from 4-chloro-1,8-naphthalic anhydride (**5**) and the primary amine by the procedure of Le Pape and Maréchal [18] (see Scheme 1). Good yields of the naphthalimide were obtained with straight chain amines and isobutylamine, but the reaction failed with sec-butylamine, indicating that the Le Pape and Marechal procedure is limited to primary amines bearing the aminomethyl group. The α-branched chain apparently inhibits the displacement of the halogen, as would be expected on the basis of an addition-elimination mechanism.

The "RR′ class" naphthalimides (**7**, $R \neq R'$) were prepared in two steps from **5** (see Scheme 1). Heating the anhydride with a slight excess of the appropriate primary amine in refluxing toluene gave the 4-chloro-*N*-alkyl-1,8-naphthalimides (**6**) uncontaminated by phenolic by-products, unlike the reactions reported in dipolar aprotic solvents [19].



6a: R = *n*-Bu
6b: R = *n*-C_6H_{13}
6c: R = *n*- C_8H_{17}
6d: R = *s*-Bu

7a: R = R' = *n*-Bu
7b: R = R' = *n*- C_6H_{13}
7c: R = R' = *n*- C_8H_{17}
7d: R = R' = *i*-Bu
7e: R = *n*- C_6H_{13}; R' = $CH_2CH_2NH_2$
7f: R = *n*- C_4H_9; R' = $CH_2CH_2NH_2$
7g: R = *n*- C_6H_{13}; R' = CH_2CH_2OH

Scheme 1. Synthesis of "R_2 class" (**7a**–**d**) and "RR" class (**7e**–f) naphthalimides.

Replacement of the chloro group was then effected by heating **6** in the appropriate primary amine as the solvent.

The results of initial biological testing of the "R_2 class" naphthalimide **7b** showed that this compound is photochemically active against H-9 cells (a transformed, immortalized *T*-lymphocyte cell line), although the levels of activity observed were marginal. The mechanism by which this biological activity occurred is not known, but as a working hypothesis — now known to be incorrect [20][1] — it was assumed that these naphthalimide dyes functioned by the same mechanism as the porphyrinoid sensitizers and derive their biological activity from the generation of singlet oxygen [21]. To increase the production of the singlet oxygen, it was decided to incorporate a heavy atom, bromine, into these naphthalimide dyes in an effort to enhance intersystem crossing. If the photobiological activity of these dyes were due to sensitization of oxygen, the incorporation of a bromine would increase the photochemical activity of the compounds.

The bromination step was carried out using elemental bromine in carbon tetrachloride, and was complete after 3 h at room temperature. This gave the 3-bromo-1,8-naphthalimide (**8**) as the sole product, indicating that in aminonaphthalimides, as in aminonaphthalenes, the directing effect of the activating amino group dominates the course of the reaction [22]. To further enhance the rate of singlet oxygen generation, an attempt was made to introduce a second bromine into the naphthalimide moiety. However, when the bromination step was allowed to proceed for an extended period of time with excess bromine, a de-alkylation reaction occurred to give 4-amino-3-bromo-1,8-naphthalimide (**9**) rather than introduction of a second bromine atom. Since this reaction occurs in a nonpolar solvent, and since no attempt was made to protect the reaction from oxygen or light, we suggest that the *N*-dealkylation may occur by a free radical rather than an ionic mechanism (Scheme 2).

While testing of brominated naphthalimide **8b** revealed useful biological activity, a method for its synthesis free of other isomers was required in order to be able to assess its biological activity in a more quantitative manner. Because anhydride **5** is contaminated by 5% of the isomeric 3-chloro-1,8-naphthalic anhydride, this leads to contaminants which are extremely difficult to remove. To enhance dye purity, synthesis of naphthalimides **7** by a two-step Gabriel-type alkylation of 4-amino-

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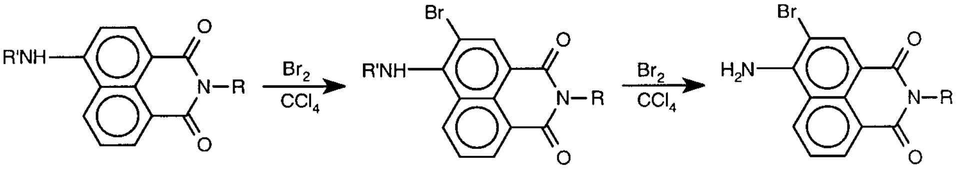
[1] The non-sensitization of oxygen by these dyes was demonstrated by photochemical bleaching of tryptophan in the presence of naphthalimide **8b**. The observed rates of photobleaching of both species was unchanged after the removal of oxygen (three freeze–thaw cycles) from the reaction mixture This suggests that the participation of singlet oxygen in the photobleaching must be, at best, a minor pathway for the photochemistry.



7

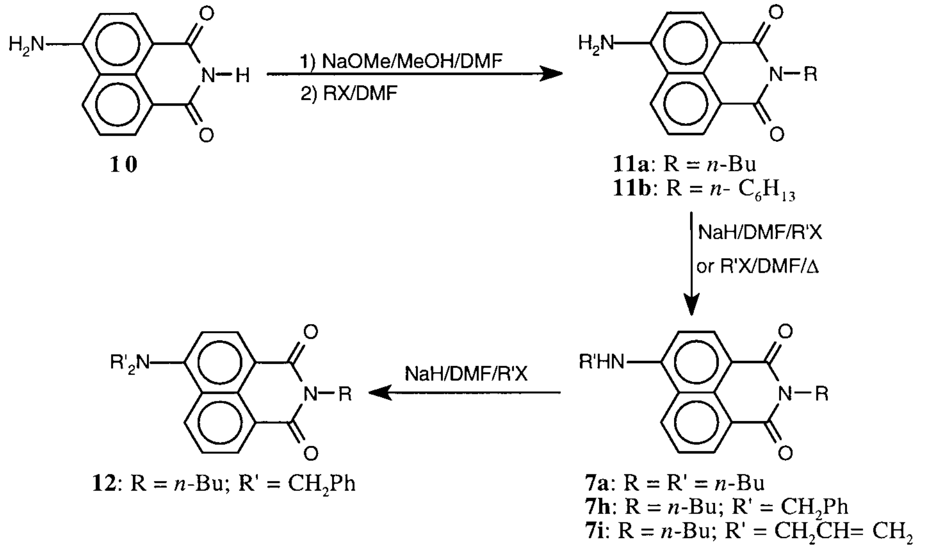
8a: R = R' = n-C_4H_9
8b: R = R' = n- C_6H_{13}
8c: R = R' = n- C_8H_{17}

9a: R = n- C_4H_9
9b: R = n- C_6H_{13}

Scheme 2. Bromination of naphthalimides **7** and **8**.

1,8-naphthalimide (**10**) was explored. The imide nitrogen of **10** was alkylated using sodium methoxide as the deprotonating agent, a procedure developed by Middleton and co-workers [23] for the synthesis of 4-amino-*N*-ω-bromoalkyl-1,8-naphthalimides. In the case of compounds **11**, deprotonation of the amino substituent (formally a vinylogous *N*-acylurea) required sodium hydride as base. When **11a** was treated with sodium hydride and benzyl bromide in DMF, naphthalimide **7h** was obtained, but the product was contaminated with the 4-dibenzylamino compound (**12**) and unchanged starting material. Lowering the reaction temperature to 0°C did not alter the outcome of the reaction substantially.

The alkylation of **11a** by benzyl bromide was then carried out in the absence of base by refluxing the reactants in DMF. Under these conditions, alkylation occurred to yield only the mono-benzylated product **7h**. In a similar manner allyl bromide and 1-iodobutane were employed to give **7i** and **7a**. The reaction with isobutyl iodide, however, failed regardless of the presence or absence of sodium hydride. It appears that this reaction, like the reaction of sec-butylamine and chlorides **6** discussed earlier, is very susceptible to steric factors. Similarly, alkylation of brominated naphthalimide **9a** with a variety of straight-chain primary halides using sodium hydride as base also failed. We suggest that the presence of the bromine at the 3-position presents a steric interaction that makes the alkylation reaction energetically unfavorable. Some evidence of the steric effect introduced by the bromine was afforded by single



10

11a: R = n-Bu
11b: R = n- C_6H_{13}

12: R = n-Bu; R' = CH_2Ph

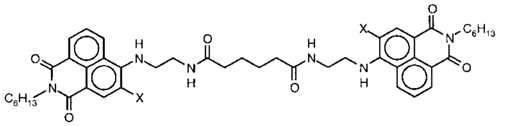
7a: R = R' = n-Bu
7h: R = n-Bu; R' = CH_2Ph
7i: R = n-Bu; R' = CH_2CH= CH_2

Scheme 3. Alternative route to "RR′ class" naphthalimides.

crystal X-ray structure analysis of the brominated compound **8a**, which showed considerable distortion of the geometry about C-4 of the ring system and the amine nitrogen [24] (Scheme 3).

The biological testing of **8b** (acronym ED66Br [25]) showed that its efficiency as a photochemical inactivator of both H9 cells and enveloped viruses was at least three orders of magnitude higher than the non-brominated compound. This compound could also be converted to an active form by irradiation prior to incubation with cells [25], and in this form the dye was an effective inhibitor of syncytium formation between HIV-1 — infected cells and uninfected T cells. SDS-PAGE electrophoresis [26] of the envelope proteins of HSV-1 indicated that **8b** covalently bonds to proteins on irradiation, and in light of this observation, the synthesis of a dimeric brominated naphthalimide, which might function as a photochemically activated protein cross-linking agent, was undertaken.

Condensation of naphthalimide **7e** with adipoyl chloride afforded the corresponding bis-amide **13** in acceptable yield, and bromination proceeded smoothly to afford the target dibromide **14**. In an effort to expand the flexibility of this approach, the acylation and bromination steps were reversed, but it was found that bromination of naphthalimides **7e** and **7f** gave only an intractable black tar.



13: X = H
14: X = Br

Compound **14** (acronym DiED66Br [27]) proved to be an efficient photochemical inactivator of a variety of enveloped viruses, including HIV-1, as well as an effective inhibitor of syncytium formation between HIV-1–infected cells and uninfected T cells [27]. SDS-PAGE electrophoretic analysis indicated that **14** does, indeed, cross-link viral proteins, and its utility as a photochemical mediator of tissue welding using visible light lasers has also been reported [28,29]. Full details of the biological studies will be reported elsewhere.

3. Conclusions

The synthesis of 4-amino-3-bromo-1,8-naphthalimides, a new class of photochemically activatable antiviral compounds, effected by regiospecific bromination of the corresponding naphthalimides (**7**) which can be prepared from **5** by nucleophilic substitution or by alkylation of both nitrogen atoms of naphthalimide **10**. The brominated naphthalimides (**8**) are resistant to further ring bromination, undergoing dealkylation of the alkylamino substituent to give type **9** naphthalimides, instead. The synthesis of a prototypical brominated naphthalimide dimer (**14**) has also been effected.

Biological testing of **8b** indicates that these compounds are effective photochemical modifiers of proteins, and that **14** is an effective photochemically-activated cross-linker of proteins.

4. Experimental

4.1. General

Melting points were determined using a hot-stage microscope and are uncorrected. Infrared spectra were obtained by diffuse reflectance from KBr using a BioRad FTS 60-A infrared spectrometer. Unless otherwise specified, nuclear magnetic resonance spectra were recorded on $CDCl_3$ or Me_2SO-d_6 solutions at 200 MHz for ^1H or 50 MHz for ^{13}C using a Varian Associates Gemini 200 Spectrometer. Peak positions are reported as δ ppm downfield from internal Me_4Si as standard for ^1H, and relative to the center peak of the solvent (77.1 ppm for $CDCl_3$; 40.5 ppm for Me_2SO) for ^{13}C. Mass spectra were obtained using electron impact at 70 eV or fast atom bombardment from a glycerol-Me_2SO matrix and were recorded using a Kratos MS25 RF Mass Spectrometer with peak intensities as a percentage of base given in parentheses. UV-Visible spectra were obtained using a Perkin–Elmer Lambda 3B UV/VIS Spectrophotometer. Fluorescence spectra were obtained using a Gilford Fluoro IV Spectrofluorometer. Chromatography was performed using Davisil Silica Gel, Grade 710 (Aldrich Chemical Co.), with mixed eluents expressed as % v/v and the less abundant component of mixture listed first. Organic extracts were dried using anhydrous sodium sulfate unless otherwise specified. 4-Chloro-1,8-naphthalic anhydride (technical grade) was obtained from Janssen Chimica and was recrystallized from toluene prior to use and 1-hexylamine and solvents were distilled prior to use. Other reagent chemicals were used as obtained from Aldrich Chemical Company.

4.2. Synthesis

*4.2.1. 2-Alkyl-6-chloro-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-diones* (**6**)

The general procedure involved stirring a mixture of freshly-recrystallized 4-chloro-1,8-naphthalic anhydride (**5**, 1 eq.) and the 1-aminoalkane (10 eq.) in toluene (2–3 ml/mmol) under reflux for 16 h, after which the solution was cooled. The solid deposited was collected by vacuum filtration and recrystallized.

*4.2.2. 2-Butyl-6-chloro-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**6a**)

Compound **6a** was prepared from **5** (6.52 g, 28 mmol) and 1-butylamine (2.05 g, 26 mmol) in toluene (60 ml). The reaction produced (6.68 g, 83%) crude product that was recrystallized from EtOH to give pale yellow crystals, mp 88–90°C (lit. [30] 88–89°C), which exhibited appropriate IR, ^{1}H NMR, ^{13}C NMR, UV-visible and fluorescence spectra.

*4.2.3. 6-Chloro-2-hexyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**6b**)

Compound **6b** was prepared from **5** (4.68 g, 20 mmol) and 1-hexylamine (1.98 g, 20 mmol) in toluene (50 ml). The reaction produced (5.52 g (87%) crude product that was recrystallized from EtOH to give pale yellow crystals, mp 65–68°C (lit. [30] 72–73°C), which exhibited appropriate IR, ^{1}H NMR, ^{13}C NMR, UV-visible and fluorescence spectra. This material was sufficiently pure for subsequent use.

*4.2.4. 6-Chloro-2-octyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**6c**)

Compound **6c** was prepared from **5** (6.15 g, 26 mmol) and 1-octylamine (3.42 g, 26 mmol) in toluene (50 ml). This reaction produced (8.51 g 94%) crude product that was recrystallized from 1-BuOH to give a pale yellow solid. The solid was further purified by flash chromatography (CH_2Cl_2) to afford pale yellow crystals, mp 75–76°C.

IR (ν_{max}) 1697, 1651 cm^{-1}. ^{1}H NMR (δ ppm): 8.60 (1H, d J=7.3 Hz), 8.52 (1H, d J=8.5 Hz), 8.44 (1H, dd J=8.0, 0.8 Hz), 7.80 (1H, dd J=7.3, 8.5 Hz), 7.77 (1H, d J=8.0 Hz, 4.14 (2H, dd J=7.5, 7.8 Hz), 1.9–1.2 (12 H, complex), 0. 87 (3H, t J=6.5 Hz). ^{13}C NMR (δ ppm): 163.5, 163.3, 138.8, 131.8, 130.9, 129.1, 128.8, 127.7, 127.2, 122.9, 121.5, 40.6, 31.8, 29.3, 29.2, 28.0, 27.1, 22.6, 14.1. EIMS (m/z): 345 (^{37}Cl M, 22), 343 (^{35}Cl M, 73). λ_{max} (EtOH): 349 nm (ε_{max} 7.0×10^{3}). Anal.: found: C 69.8, H 6.7, N 4.0; $C_{20}H_{22}ClNO_2$ requires C 69.9, H 6.4, N 4.1.

*4.2.5. 6-Chloro-2-*sec*-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**6d**)

Compound **6d** was prepared from **5** (1.74 g, 7.5 mmol) and *sec*-butylamine (50 ml), and the solution was heated under reflux for 18 h. The resultant red solution was allowed to cool, the amine was removed by evaporation, and the crude product was recrystallized from MeOH to afford **6d** as a pale yellow solid, mp 115–117°C.

IR (ν_{max}: 3094, 3071, 1697, 1659, 1620 cm^{-1}. ^{1}H NMR (δ ppm): 8.64 (1H, dd J=7.2 Hz), 8.57 (1H, dd J=8.5, 1.2 Hz), 8.48 (1H, d J=7.8), 7.85 (1H, ddd J=8.5, 8.4, 1.1 Hz), 7.82 (1H, d J=7.9 Hz), 5.27–5.10 (1H, complex), 2.32–2.10 (1H, complex), 2.05–1.83 (1H, complex), 1.57 (3H, d J=6.9 Hz), 0.91 (3H, br. t J=7.5 Hz). ^{13}C NMR (δ ppm): 164.2, 164.0, 138.6, 133.5, 131.9, 131.0, 130.3, 129.1, 127.8, 127.3, 126.9, 123.5, 122.0, 51.3, 26.4, 18.0, 11.5. λ_{max} (EtOH): 349 nm (ε_{max} 1.3×10^{6}).

*4.2.6. "R_2 class" 2-Alkyl-6-(alkylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-diones* (**7**)

The general procedure involved dissolving freshly recrystallized **5** (1 eq.) in the 1-aminoalkane (5–10 ml/mmol), and heating the solution under reflux. The resultant red solution was allowed to cool, the amine was removed by evaporation, and the crude product was recrystallized. Further purification was effected by flash chromatography as necessary.

*4.2.7. 2-Butyl-6-(butylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7a**)

Compound **7a** was prepared from **5** (5.55 g, 24 mmol) and 1-butylamine (80 ml; 18 h reflux), producing a product that was recrystallized from HoAc and then from EtOH as a bright yellow solid (6.18 g, 80%). Further purification by flash chromatography (99 CH_2Cl_2:1 EtOAc) afforded **7a**, mp 118–120°C (lit. [31] 126–127°C). This material was used without further purification. A second synthesis of **7a** was conducted as follows:

Compound **7a** was prepared from **11a** (1.06 g, 3.95 mmol) and 1-iodobutane (2.41 g, 13.11 mmol). The resultant red-brown paste was recrystallized from EtOH to give 0.74 g (58%).

*4.2.8. 2-Hexyl-6-(hexylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7b**)

Compound **7b** was prepared from **5** (4.32 g, 18.5 mmol) and 1-hexylamine (120 ml; 30 min reflux). The crude yellow product was recrystallized from MeOH to give 5.72 g 81% and was further purified by flash chromatography (CH_2Cl_2). This gave **7b**, mp 118–120°C (lit. [31] 126–127°C), as a bright yellow solid. This material was used without further purification.

*4.2.9. 2-Octyl-6-(octylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7c**)

Compound **7c** was prepared from **5** (1.34 g, 5.8 mmol) and 1-octylamine (25 ml; 18 h reflux). Recrystalization from MeOH gave a bright yellow solid (1.84 g, 73%), mp 86–87°C (lit. [31] 83–85°C).

*4.2.10. 2-Isobutyl-6-(isobutylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7d**)

Compound **7d** was prepared from **5** (2.12 g, 9.1 mmol) and isobutylamine (25 ml; 18 h reflux). Recrystallization from MeOH gave an orange solid (2.31 g, 78%) and subsequent flash chromatography (4 EtOAc:6 CH_2Cl_2) gave **7d** as a yellow solid, mp 126–127°C.

IR (ν_{max}: 3379, 1682, 1643 cm^{-1}. ^1H NMR (δ ppm): 8.56 (1H, d $J = 7.3$ Hz), 8.44 (1H, d $J = 8.5$ Hz), 8.13 (1H, d $J = 8.5$ Hz), 7.56 (1H, dd $J = 8.3$, 8.4 Hz), 6.70 (1H, d $J = 8.5$ Hz), 5.50 (1H, dd $J = 4.9$, 5.1 Hz), 4.02 (2H, d $J = 7.4$ Hz), 3.23 (2H, br. t $J = 6.0$ Hz), 2.35–1.98 (2H, complex), 1.10 (6H, d $J = 6.6$ Hz), 0.97 (6H, d $J = 6.7$ Hz). ^{13}C NMR (d ppm): 165.0, 164.4, 149.5, 134.5, 131.1, 129.8, 125.7, 124.6, 123.0, 120.1, 110.0, 104.3, 51.2, 46.8, 27.8, 27.4, 20.5, 20.3. λ_{max} (EtOH): 439 nm (e_{max} 1.6×10^6). Anal.: found: C 72.2, H 7.7, N 7.9; $C_{20}H_{24}N_2O_2$ requires C 74.0, H 7.5, N 8.6.9; $C_{20}H_{24}N_2O_2 \cdot 0.5$ MeOH requires C 72.3, H 7.7, N 8.2.

*4.2.11. "RR′ class" 2-Alkyl-6-(alkylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-diones*

As a general procedure, naphthalimide **6** (1 eq.) was dissolved in the 1-aminoalkane (5–10 ml/mmol), and the solution was heated under reflux. Afterwards, the amine was removed by evaporation and the crude product was recrystallized. Further purification was effected by flash chromatography as necessary. Compounds carrying 6-(2-aminoethyl)-amino substituents proved difficult to render analytically pure due to solvate and hydrochloride formation.

*4.2.12. 6-(2-Aminoethyl)amino-2-hexyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7e**)

This compound was prepared from **6b** (3.49 g, 11 mmol) and ethylenediamine (50 ml; 16 h reflux). Crystallization of the resultant red oil from MeOH afforded the product (3.57 g, 94%) as an orange solid, mp 87–89°C. The analytical data corresponded to the hemi-methanol solvate of the hemi-hydrochloride salt.

IV ν_{max}: 3333, 1682, 1636 cm^{-1}. ^1H NMR (δ ppm): 8.53 (1H, d $J = 7.3$ Hz), 8.40 (1H, d $J = 8.3$ Hz), 8.17 (1H, d $J = 8.8$ Hz), 7.57 (1H, dd $J = 7.3$, 8.3 Hz), 6.65 (1H, d $J = 8.5$ Hz), 6.22 (1H, br. t), 4.13 (2H, overlapping t $J = 7.3$ Hz), 3.40 (2H, overlapping t $J = 2.5$ Hz), 3.17 (2H, overlapping t $J = 2.5$ Hz), 2.1 (2H, br. s), 1.8–0.7 (11H, complex). ^{13}C NMR (δ ppm): 164.7, 164.2, 149.7, 134.4, 131.1, 130.5, 126.3, 124.6, 123.1, 120.5, 110.3, 104.4, 45.0, 40.2, 31.6, 28.2, 26.9, 22.6, 14.1. Absorption λ_{max} (EtOH): 431 nm (ε_{max} 8.7×10^3). Fluorescence λ_{max} (Ex): 450 nm, λ_{max} (Em): 540 nm. Anal.: found: C 65.5, H 7.4, N 10.8; $C_{20}H_{25}N_3O_2$ requires C 70.8, H 7.4, N 12.4; $(C_{20}H_{25}N_3O_2)_2 \cdot HCl \cdot MeOH$ requires C 65.9, H 7.4, Cl 4.7, N 11.2.

*4.2.13. 6-(2-Aminoethyl)amino-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7f**)

This compound was prepared from **6a** (3.12 g, 10 mmol) and ethylenediamine (2.72 g, 45 mmol) to afford 1.86 g product (55%) which was recrystallized from toluene as an orange solid, mp 129–132°C. Further purification of this chromatographically homogeneous material was ineffective.

IR (ν_{max}) 3348, 3279, 3102, 3063, 3001, 1682, 1636 cm^{-1}. ^{1}H NMR (δ ppm): 8.57 (1H, dd $J=1.0$, 7.3 Hz), 8.45 (1H, $J=8.4$ Hz), 8.16 (1H, dd $J=1.1$, 8.5 Hz), 7.61 (1H, dd $J=7.3$, 8.4 Hz), 6.70 (1H, d $J=8.5$ Hz), 6.15 (1H, br. t), 4.16 (2H, dd $J=8.9$, 7.5 Hz), 3.42 (2H, ddd $J=7.0$, 6.3, 4.8 Hz), 3.19 (2H, dd $J=6.3$, 7.2 Hz), 1.79–1.35 (8H, complex), 0.97 (3H, t $J=7.0$ Hz). ^{13}C NMR (δ ppm): 164.8, 164.3, 149.7, 134.5, 131.2, 129.9, 126.2, 124.8, 123.2, 120.5, 110.5, 104.5, 44.9, 40.2, 40.1, 30.4, 20.5, 14.0. CIMS (*m/z*): 311 (M+, 16). Absorption λ_{max} (EtOH): 434 nm (ε_{max} 2.9×10^3). Fluorescence λ_{max} (Ex): 450 nm, λ_{max} (Em): 540 nm. Anal.: found: C 65.0, H 6.8 N 13.5; $C_{18}H_{21}N_3O_2$ requires C 69.4, H 6.8, N 13.5; $(C_{18}H_{21}N_3O_2)_2\cdot HCl$ requires C 65.6, H 6.6, N 12.7.

Satisfactory combustion analyses were obtained for the ethoxycarbonyl derivative of this compound which was prepared as follows: to a suspension of **7f** (1 g, 3.24 mmol) in CH_2Cl_2 (25 ml) was added triethylamine (0.35 g, 3.47 mmol) and ethyl chloroformate (0.46 g, 4.26 mmol). The resultant solution was stirred at ambient temperature for 1 h. The solvent was removed under reduced pressure and the remaining solid was recrystallized from EtOH to afford a yellow solid (0.77 g, 62%) which was purified by flash chromatography (5% Me_2CO/CH_2Cl_2) to afford 6-[(2-ethoxycarbonylamino)ethyl]amino-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione, mp 188–189°C.

IR (ν_{max}): 3356, 3295, 1690, 1643 cm^{-1}. ^{1}H NMR (δ ppm): 8.54 (1H, d $J=7.3$ Hz), 8.40 (1H, d $J=8.3$ Hz), 8.21 (1H, d $J=9.2$ Hz), 7.66 (1H, dd $J=7.7$, 8 Hz), 6.89 (1H, br.s), 6.55 (1H, d $J=8.4$ Hz), 5.40 (1H, br. dd $J=5.9$, 6.2), 4.24–5.21 (4H, complex), 3.68 (2H, ddd $J=5.9$, 5.8, 4.5 Hz), 3.47 (2H, ddd $J=5.1$, 4.4, 4.0 Hz), 1.83–1.58 (2H, complex), 1.77–1.62 (2H, complex), 1.52—1.34 (2H, complex), 1.25 (3H, dd $J=7.2$, 7.0 Hz), 0.96 (3H, br. t $J=7.2$ Hz). ^{13}C NMR (δ ppm): 164.8, 164.3, 159.2, 150.0, 134.5, 131.1, 129.8, 126.9, 124.8, 122.9, 120.4, 110.1, 103.5, 61.8, 46.5, 46.0, 40.0, 30.4, 20.5, 14.7, 14.0, 8.7. EIMS (*m/z*): 383 (M$^+$, 8). Absorption λ_{max} (EtOH): 434 nm (ε_{max} 1.2×10^4). Fluorescence λ_{max} (Ex): 460 nm, λ_{max} (Em): 540 nm. Found: Anal.: C 65.9, H 6.8, N 10.9; $C_{21}H_{25}N_3O_4$ requires C 65.8, H 6.6, N 11.0.

*4.2.14. 6-(2-Hydroxyethyl)amino-2-hexyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7g**)

This compound was prepared from **6b** (1.07 g, 3.38 mmol) and ethanolamine (15 ml; 16 h reflux). The product (1 g, 87%) was recrystallized from MeOH to give an orange solid. Flash chromatography (50% EtOH/hexane) afforded **7g**, mp 147–148°C.

IR ν_{max}: 3295, 1697, 1628, 1613 cm^{-1}. ^{1}H NMR (δ ppm): 8.47 (1H, d $J=7.3$ Hz), 8.34 (1H, d $J=8.4$ Hz), 8.10 (1H, d $J=8.4$ Hz), 7.53 (1H, t $J=7.7$, 8.1 Hz), 6.64 (1H, d $J=8.4$ Hz), 5.77 (1H, br. t $J=4.8$), 4.11 (2H, t $J=7.7$ Hz), 4.08 (2H, br. s), 3.55 (2H, dt $J=5.1$, 4.8 Hz), 2.58 (1H, br. s), 1.73–1.25 (8H, complex), 0.88 (3H, t $J=6.7$ Hz). ^{13}C NMR (δ ppm): 164.5, 164.1, 149.4, 134.2, 131.1, 129.5, 125.9, 124.7, 122.9, 120.2, 110.4, 104.4, 60.4, 45.4, 40.3, 31.6, 28.1, 26.8, 22.6, 14.1. EIMS (*m/z*): 340 (M$^+$, 5). Absorption λ_{max} (EtOH): 432 nm (ε_{max} 7.4×10^3). Fluorescence λ_{max} (Ex): 450 nm, λ_{max} (Em): 540 nm. Anal: found: C 70.7, H 7.4, N 8.1; $C_{20}H_{24}N_2O_3$ requires C 70.6, H 7.1, N 8.2.

*4.2.15. 6-Benzylamino-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7h**)

To a solution of **11a** (1.03 g, 3.83 mmol) in DMF (25 ml) was added benzyl bromide (2.21 g, 12.90 mmol) and NaI (100 mg). This solution was stirred under reflux for 24 h, cooled, and the majority of the DMF was removed under reduced pressure. The brown DMF suspension that remained was dissolved in CH_2Cl_2 (300 ml), and the solution was washed four times with 10% HCl (500 ml), dried, and evaporated to yield a brownish-yellow paste, which crystallized from EtOH to afford a yellow solid (0.90 g, 65%). Flash chromatography (CH_2Cl_2) afforded an analytical sample of **7h** as yellow crystals, mp 171–172°C.

IR (μ_{max}): 3371, 1690, 1636 cm^{-1}. ^{1}H NMR (δ ppm): 8.59 (1H, dd $J=1.0$, 7.3 Hz), 8.47 (1H, d $J=8.4$ Hz), 8.08 (1H, dd $J=1.1$, 8.4 Hz), 7.62 (1H, dd $J=8.4$, 8.3 Hz), 7.45–7.34 (5H, m), 6.76 (1H, d $J=8.4$ Hz), 5.61 (1H, br. t.), 4.62 (2H, d

$J = 5.1$ Hz), 4.16 (2H, dd $J = 7.3$, 7.6 Hz), 1.78–1.62 (2H, complex), 1.53–1.34 (2H, dt, $J = 7.2$, 8.3 Hz), 0.96 (3H, t $J = 7.3$ Hz). ^{13}C NMR (δ ppm): 164.7, 164.2, 149.0, 137.1, 134.4, 131.2, 129.8, 129.1, 128.2, 127.8, 125.9, 125.0, 123.3, 120.3, 111.1, 105.0, 48.1, 40.1, 30.4, 20.5, 14.0. EIMS (*m*/*z*): 358 (M^+, 8). Absorption λ_{max} (EtOH): 432 nm (ε_{max} 1.7×10^4). Fluorescence λ_{max} (Ex): 450 nm, λ_{max} (Em): 530 nm. Anal.: found C 77.3, H 6.5, N 7.7; $C_{23}H_{22}N_2O_2$ requires C 77.1, H 6.2, N 7.8.

4.2.16. *6-Allylamino-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**7i**)

This compound was prepared from **11a** (1.01 g, 3.76 mmol), allyl bromide (0.99 g, 8.15 mmol) and NaI (100 mg) by the same procedure to give the alkylated product (0.71 g, 61%) as a yellow solid. Purification by flash chromatography (30% hexane/CH_2Cl_2) gave **7i** as yellow crystals, mp 157–159°C.

IR ν_{max}: 3395, 1674, 1643, 1613 cm^{-1}. ^{1}H NMR (δ ppm): 8.51 (1H, dd $J = 7.3$, 1.1 Hz), 8.38 (1H, d $J = 8.4$ Hz), 8.05 (1H, dd $J = 8.5$, 1.0 Hz), 7.55 (1H, ddd $J = 8.4$, 8.3, 1.1 Hz), 6.65 (1H, d $J = 8.5$ Hz), 5.97 (1H, m $J = 17.2$, 10.2, 5.4 Hz), 5.36 (1H, dd $J = 3.0$, 1.6 Hz), 5.27 (1H, br. t.), 5.21 (1H, dd $J = 2.7$, 1.4 Hz), 4.09 (2H, dd $J = 7.6$, 7.3 Hz), 4.01 (2H, t $J = 5.4$ Hz), 1.71–1.56 (2H, m), 1.46–1.27 (2H, m) 0.89 (3H, t $J = 7.25$ Hz). ^{13}C NMR (δ ppm): 164.7, 164.2, 149.1, 134.4, 133.1, 131.2, 129.8, 125.8, 124.9, 123.3, 120.3, 118.0, 110.9, 104.9, 46.1, 40.1, 30.4, 20.5, 14.0. EIMS (*m*/*z*): 308 (M^+, 77). Absorption λ_{max} (EtOH): 433 nm (ε_{max} 1.5×10^4). Fluorescence λ_{max} (Ex): 450 nm, λ_{max} (Em): 530 nm. Anal.: found C 73.8, H 6.7, N 8.9; $C_{19}H_{20}N_2O_2$ requires C 74.0, H 6.5, N 9.1.

4.2.17. *Bromination of 4-alkylamino-*N*-alkyl-1,8-naphthalimides* (**8**)

As the general procedure to a solution of naphthalimide **7** (1 eq.) in an appropriate solvent (15–20 ml/mmol). The solution was stirred at ambient temperature until TLC analysis indicated that compound **7** had been consumed. The solvent and excess bromine were removed by evaporation under reduced pressure, and the crude product was recrystallized. Further purification was effected by flash chromatography.

4.2.18. *5-Bromo-2-butyl-6-(butylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**8a**)

This compound was prepared from **6a** (4.54 g, 14 mmol) and bromine (2.52 g, 16 mmol) in CH_2Cl_2 (200 ml; 3.5 h stirring). The product (5.15 g, 91%) was recrystallized from MeOH as a bright yellow solid, and further purified by flash chromatography (40% hexane/CH_2Cl_2) to afford **8a**, mp 170–172°C. Slow evaporation of an EtOAc solution of this **8a** material provided single crystals suitable for X-ray structure analysis.

IR (ν_{max}: 3456, 3341, 3233, 1705, 1628 cm^{-1}. ^{1}H NMR (δ ppm): 8.58 (1H, s), 8.54 (1H, dd $J = 7.3$, 0.9 Hz), 8.41 (1H, d $J = 8.6$ Hz), 7.60 (1H, dd $J = 7.3$, 8.6 Hz), 4.96 (1H, br.), 4.13 (2H, overlapping t $J = 7.3$ Hz), 3.64 (2H, br.),1.68 (4H, m), 1.44 (4H, m) 0.95 (6H, t $J = 7.1$ Hz). ^{13}C NMR (δ ppm): 164.6, 163.5, 150.1, 135.9, 131.8, 131.0, 130.1, 125.6, 123.7, 114.7, 112.8, 110.3, 51.2, 40.6, 34.1, 30.7, 20.9, 20.5, 14.3, 14.2. EIMS (*m*/*z*): 404 (^{81}Br M^+, 5), 402 (^{79}Br M^+, 5). Absorption λ_{max} (EtOH): 416 nm (ε_{max} 1770). Fluorescence λ_{max} (Ex): 420 nm, λ_{max} (Em): 530 nm. Anal.: found C 59.1, H 6.1, N 6.9, Br 16.1; $C_{20}H_{23}N_2O_2Br$ requires C 59.6, H 5.7, N 6.9, Br 19.8.

When the reaction was allowed to continue, 6-amino-5-bromo-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione (**9a**) was obtained as a yellow solid. Recrystallization from MeOH yielded bright yellow crystals, mp 190–191°C, exhibiting satisfactory spectroscopic data. An analytical sample was prepared by flash chromatography (CH_2Cl_2) and recrystallization from MeOH. Slow evaporation of a mesitylene solution of **9a** provided single crystals suitable for X-ray structure analysis.

IR ν_{max}: 3472, 3356, 3233, 1690, 1627 cm^{-1}. ^{1}H NMR (δ ppm): 8.60 (1H, s), 8.58 (1H, dd $J = 7.3$, 1.1 Hz), 8.10 (1H, dd $J = 8.4$, 1.1 Hz), 7.67 (1H, dd $J = 7.4$, 8.4 Hz), 5.48 (2H, br. s), 4.15 (2H, dd $J = 7.3$, 7.5 Hz), 1.69 (2H, m), 1.43 (2H, m), 0.97 (3H, t $J = 7.2$ Hz). ^{13}C NMR (δ ppm): 164.6, 163.6, 146.3, 136.6, 131.8, 127.2, 126.5, 123.9, 120.8, 104.7, 40.7, 30.7, 20.9, 14.3. EIMS (*m*/*z*): 348 (^{81}Br M^+, 16), 346 (^{79}Br M^+, 14). Absorption λ_{max} (EtOH): 416 nm (ε_{max} 1.8×10^4). Fluorescence λ_{max} (Ex): 420 nm, λ_{max} (Em): 510 nm. Anal.: found C 54.2, H 4.5, N 8.0, Br 23.3; $C_{16}H_{15}N_2O_2Br$ requires

C 55.3, H 4.4, N 8.1, Br 23.0; $C_{16}H_{15}N_2O_2Br{\cdot}0.5$ MeOH requires C 54.6, H 4.7, N 7.7, Br 22.0.

*4.2.19. 5-Bromo-2-hexyl-6-(hexylamino)-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**8b**)

This compound was prepared from **6b** (0.531 g, 1.40 mmol) and bromine (0.240 g, 1.5 mmol) in CCl_4 (20 ml; 3.5 h stirring). Recrystallization of the crude product from MeOH yielded **8b** as bright yellow needles with a metallic sheen (0.435 g, 66%). Flash chromatography (40% hexane/CH_2Cl_2) and recrystallization from MeOH afforded an analytical sample, mp 58–60°C.

IR ν_{max}: 3450, 3334, 3233, 1705, 1694 cm^{-1}. ^1H NMR ppm): 8.64 (1H, s), 8.59 (1H, dd $J=7.3$, 1.1 Hz), 8.45 (1H, dd $J=8.6$, 1.1 Hz), 7.65 (1H, dd $J=7.3$, 8.6 Hz), 4.14 (2H, overlapping t $J=7.4$ Hz), 3.66 (2H, t $J=7.0$ Hz), 1.8–1.2 (22H, complex) 1.0–0.80 (6H, complex). ^{13}C NMR (δ ppm): 164.1, 163.0, 145.8, 136.2, 135.5, 131.4, 130.9, 126.6, 126.0, 125.5, 123.6, 123.4, 40.5, 31.6, 31.4, 31.3, 28.1, 26.9, 26.8, 26.5, 22.6, 22.5, 14.1, 14.0. CIMS (*m*/*z*): 461 ($^{81}Br\ M^+$, 82), 459 ($^{79}Br\ M^+$, 100). Absorption λ_{max} (EtOH): 416 (ε_{max} 5.1×10^3). Fluorescence λ_{max} (Ex): 425 nm, λ_{max} (Em): 530 nm. Anal.: found: C 61.7, H 6.9, N 6.2, Br 16.1. $C_{24}H_{31}N_2O_2Br$ requires C 62.7, H 6.8, N 6.1, Br 17.4; $C_{24}H_{31}N_2O_2Br{\cdot}$MeOH requires C 61.1, H 7.2, N 5.7, Br 16.3.

When the reaction was allowed to continue, 6-amino-5-bromo-2-hexyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione (**9b**) was isolated as a minor product. Recrystallization from MeOH afforded **9b** as bright yellow crystals, mp 200–201°C, which were purified by flash chromatography (CH_2Cl_2) and recrystallization from MeOH.

^1H NMR (δ ppm): 8.62 (1H, s), 8.60 (1H, dd $J=7.3$, 1.1 Hz), 8.10 (1H, dd $J=8.5$, 1.1 Hz), 7.70 (1H, dd $J=8.5$, 1.1 Hz), 5.43 (1H, br.), 4.14 (2H, overlapping t $J=7.5$, 7.7 Hz), 1.78–1.51 (2H, m), 1.45–1.25 (6H, m,) 0.88 (3H, t $J=7.0$ Hz). ^{13}C NMR (δ ppm): 164.1, 163.1, 145.8, 136.2, 131.3, 128.5, 126.7, 126.0, 123.5, 120.3, 113.0, 104.2, 40.4, 31.6, 28.1, 26.8, 22.6, 14.1. EIMS (*m*/*z*): 376 ($^{81}Br\ M^+$, 2), 374 ($^{79}Br\ M^+$, 2). Absorption λ_{max} (EtOH): 416 nm (ε_{max} 5.6×10^3). Fluorescence λ_{max} (Ex): 420 nm, λ_{max} (Em): 510 nm. Anal.: found: C 57.6, H 5.1, N 7.5, Br 21.9; $C_{18}H_{19}N_2O_2Br$ requires C 57.6, H 5.1, N 7.5, Br 21.3.

*4.2.20. 5-Bromo-2-octyl-6-octylamino-1*H*-benz-[*de*]isoquinoline-1,3-(2*H*)-dione* (**8c**)

This compound was prepared from 4-(octylamino)-*N*-octyl-1,8-naphthalimide (0.58 g, 1.3 mmol) and bromine (0.22 g, 1.4 mmol) in CCl_4 (13.5 ml) to afford the product (0.58 g, 85%) which was recrystallized from MeOH as a bright yellow solid, mp 66–67°C. An analytical sample was prepared by flash chromatography (40% hexane/CH_2Cl_2) and recrystallization from MeOH.

IR ν_{max}: 3364, 1690, 1659 cm^{-1}. ^1H NMR (δ ppm): 8.64 (1H, s), 8.59 (1H, dd $J=7.2$, 1.0 Hz), 8.45 (1H, dd $J=8.6$, 1.1 Hz), 7.64 (1H, dd $J=8.5$, 1.2 Hz), 4.99 (1H, br. s.), 4.14 (2H, overlapping t $J=7.5$ Hz), 3.66 (2H, t $J=7.0$ Hz), 1.8–1.3 (24H, complex) 9.0–0.84 (6H, complex). ^{13}C NMR (δ ppm): 164.2, 163.0, 179.7, 135.5, 131.3, 130.6, 129.7, 125.2, 123.4, 123.3, 109.8, 51.1, 40.4, 31.8, 31.7, 31.6, 29.4, 29.2, 29.1, 28.1, 27.1, 26.8, 24.6, 22.6, 14.1. EIMS (*m*/*z*): 516 ($^{81}Br\ M^+$, 82), 514 ($^{79}Br\ M^+$, 63). Absorption λ_{max} (EtOH): 419 nm (ε_{max} 6.8×10^3). Fluorescence λ_{max} (Ex): 425 nm, λ_{max} (Em): 520 nm. Anal.: found C 64.6, H 7.7, N 5.3, Br 15.3; $C_{28}H_{39}N_2O_2Br$ requires C 65.2, H 7.6, N 5.4, Br 15.5; $C_{28}H_{39}N_2O_2Br{\cdot}0.5$ MeOH requires C 64.4, H 7.8, N 5.3, Br 15.0.

*4.2.21. N,N′-bis-{2-[2-hexyl-1*H*-benz[*de*]isoquinolin-1,3-(2*H*)-dionyl-6-yl)amino]ethyl}-hexanediamide* (**13**)

To a solution of **7e** (590 mg, 2.0 mmol) and pyridine (50 ml) in CH_2Cl_2 (140 ml) was added adipoyl chloride (150 mg, 0.8 mmol). The solution was allowed to stir at ambient temperature for 3 h. After this time, the reaction mixture was poured into water and the organic layer was collected. The organic layer was then washed with 10% HCl (1×50 ml), dried, and the solvent was removed by evaporation under reduced pressure to afford the crude product as a brick-red solid. Recrystallization from 1-BuOH gave **13** (0.34 g, 52%) as red crystals, mp 237–239°C, exhibiting hyperchromism in its UV-visible spectrum.

IR ν_{max}: 3325, 1690, 1651 cm^{-1}. ^1H NMR (Me_2SO-d_6, δ ppm): 8.54 (1H, d $J=8.4$ Hz), 8.40 (1H, d $J=7.3$ Hz), 8.20 (1H, d $J=8.5$ Hz), 8.12 (1H, br. t), 7.82 (1H, br. t) 7.66 (1H, dd $J=8.1$, 7.6

Hz), 6.80 (1H, d $J = 8.7$ Hz), 3.95 (2H, dd $J = 7.0$, 7.3 Hz), 3.38 (4H, s), 2.51 (2H, t $J = 1.8$ Hz), 2.08 (2H, s), 1.56–1.48 (2H, complex), 1.28 (6H, s), 0.85 (3H, t $J = 6.3$ Hz). ^{13}C NMR (Me_2SO-d_6, δ ppm): 172.8, 163.5, 162.7, 150.4, 134.0, 130.5, 129.2, 128.1, 124.2, 121.8, 119.9, 107.7, 103.5, 42.8, 42.7, 37.2, 35.1, 30.9, 27.4, 26.1, 24.7, 21.9, 13.8. EIMS (*m*/*z*): 296 (100). Absorption λ_{max} (EtOH): 436 nm (ε_{max} 1.7×10^4) [c = 7.6×10^{-6} M]; 432 nm (ε_{max} 2.6×10^6) [$c = 7.6 \times 10^{-9}$ M]. Fluorescence λ_{max} (Ex): 460 nm, λ_{max} (Em): 560 nm. Anal.: found C 69.8, H 7.3, N 10.5; $C_{46}H_{56}N_6O_6$ requires C 70.0, H 7.2, N 10.7.

*4.2.22. N,N′-bis-{2-[5-bromo-2-hexyl-1*H*-benz-[*de*]isoquinolin-1,3-(2*H*)-dionyl-6-yl)amino]-ethyl}hexanediamide* (**14**)

To a solution of amide **13** (2.81 g, 4 mmol) in CH_2Cl_2 (100 ml) was added bromine (3.46 g, 21.6 mmol). The solution was allowed to stir at ambient temperature and monitored by TLC. After 3 h, TLC (1:1/Hx:EtOAc) indicated that all the starting material had been consumed, and the excess bromine and the solvent were removed by evaporation under reduced pressure. The brick-red solid was recrystallized from 1-BuOH to give **14** as an amorphous red solid (1.3 g, 34%), mp 144–145°C (dec), exhibiting hyperchromism in its UV-visible spectrum.

IR ν_{max}: 3295, 3078, 1690, 1651 cm^{-1}. ^{1}H NMR (δ ppm): 8.53 (2H, s); 8.51 (2H, d $J = 7.4$ Hz); 8.34 (2H, d $J = 8.4$ Hz); 7.61 (2H, dd $J = 8.4$, 7.4 Hz); 6.30 (2H, br. t $J = 5.5$ Hz); 4.08 (4H, dd J = 7.4, 7.7 Hz); 3.76 (4H, br. t $J = 5.4$ Hz); 3.55 (4H, br. t $J = 5.4$ Hz); 3.46 (2H, br.); 2.1–2.3 (4H, br. m); 1.2–1.75 (20H, complex); 0.85 (6H, br. t $J = 6.7$ Hz). ^{13}C NMR (δ ppm): 173.7, 163.9, 162.9, 149.1, 135.7, 131.4, 131.0, 129.9, 125.9, 124.0, 123.3, 115.3, 110.0, 50.4, 40.7, 40.5, 35.7, 31.6, 28.1, 26.8, 24.6, 22.6, 14.1. FABMS (*m*/*z*): 420 (10), 418 (10). Absorption λ_{max} (EtOH): 418 nm (ε_{max} 6.1×10^4) [$c = 8.4 \times 10^{-8}$ M]; 420 nm (ε_{max} 1.4×10^6) [$c = 8.4 \times 10^{-9}$ M]. Fluorescence λ_{max} (Ex): 430 nm, λ_{max} (Em): 540 nm. Anal.: found C 55.1, H 5.8, N 8.0, Br 16.8; $C_{46}H_{54}N_6O_6Br_2$ requires C 58.4, H 5.7, N 8.9, Br 16.9; $C_{46}H_{54}N_6O_6Br_2 \cdot 3H_2O$ requires C 55.2, H 6.0, N 8.4, Br 16.0.

*4.2.23. 6-Amino-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**11a**)

This compound was prepared from **10** (2.53 g, 11.9 mmol) and 1-bromobutane (6.82 g, 49.8 mmol) in DMF (75 ml). Recrystallization of the crude product from HOAc afforded **1a** (2.89 g, 90%) as an orange solid, mp 186–187°C (lit. [33] 184–185°C).

*4.2.24. 6-Amino-2-hexyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**11b**)

To a bright yellow suspension of **10** (2.54 g, 12 mmol) in DMF (72 ml) was added methanolic NaOMe solution (6 M, 3.0 ml). The red solution was stirred at ambient temperature for 15 min, and 1-bromohexane (6.67 g, 40 mmol) was added. The solution was stirred at ambient temperature for 1 h, and the dark green solution was poured into ice/water (750 ml). The yellow precipitate was collected by vacuum filtration and recrystallized from glacial HOAc to afford **11b** (2.61 g, 73%) as an orange solid, mp 178–180°C (lit. [32] 180–181°C).

*4.2.25. 6-Amino-5-bromo-2-butyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione* (**9a**)

To a solution of **11a** (1.01 g, 3.77 mmol) in DMF (20 ml) was added bromine (0.67 g, 4.22 mmol). This solution was stirred at room temperature for 3 h and the solvent and excess bromine were then removed under reduced pressure. The solid that remained was triturated in hot MeOH to yield **9a** (0.97 g, 74%).

*4.2.26. 6-Amino-5-bromo-2-hexyl-1*H*-benz[*de*]-isoquinoline-1,3-(2*H*)-dione* (**9b**)

This compound was prepared from **11b** (1.04 g, 3.49 mmol) and bromine (0.89 g, 5.56 mmol) by the above procedure to afford a crude product that was purified by trituration in hot MeOh to yield **9b** (1.10 g, 84%).

*4.2.27. 2-Butyl-6-(dibenzylamino)-1*H*-benz[*de*]-isoquinoline-1,3-(2*H*)-dione* (**12**)

To a solution of **7h** (0.27 g, 1 mmol) in anhydrous DMF (10 ml) was added NaH (0.35 g, 8.82 mmol). The resultant red solution was stirred at ambient temperature for 15 min and benzyl bromide (0.48 g, 2.83 mmol) was then added dropwise. The final solution was stirred at ambient temperature for 1 h and then poured into ice/water (400 ml). The product was extracted with Et_2O (100 ml) and the extract was washed four times with water (500 ml), dried, and evaporated under reduced pressure to afford a bright yellow solid (0.38, 85%).

IR ν_{max}: 3062, 3032, 1697, 1659 cm^{-1}. ^1H NMR (δ ppm): 8.62 (1H, d $J = 8.4$ Hz), 8.54 (1H, d $J = 7.3$ Hz), 8.33 (1H, d $J = 8.1$ Hz), 7.66 (1H, dd $J = 8.1$, 7.6 Hz), 7.29–7.12 (10H), 7.00 (1H, d $J = 8.2$ Hz), 4.41–4.30 (4H, m), 4.09 (2H, dd $J = 7.6$, 7.2 Hz), 1.71–1.49 (2H, m), 1.43–1.28 (2H, m) 0.90 (3H, t $J = 7.3$ Hz). ^{13}C NMR (δ ppm): 164.6, 164.1, 154.5, 136.9, 132.0, 131.2, 130.3, 128.7, 128.5, 128.2, 127.9, 127.2, 127.6, 126.8, 125.9, 123.5, 118.2, 116.6, 72.2, 57.4, 40.2, 30.4, 29.8, 20.5, 14.0. Absorption λ_{max} (EtOH): 407 nm (ε_{max} 1.1×10^4). Fluorescence λ_{max} (Ex): 430 nm, λ_{max} (Em): 540 nm.

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References

[1] Grabtchev I, Philipova T, Méallier P, Guittonneau S. Dyes and Pigments 1996;31:31.

[2] Dorlars A, Schellhammer C-W, Schroeder J. Angew Chem Int Ed Engl 1975;14:665.

[3] Gold H. In: Venkataraman, K., editor. The chemistry of synthetic dyes. New York: Academic Press, 1971. Vol. V, p. 535–679.

[4] Wolarz E, Moryson H, Bauman D. Displays 1992;13:171.

[5] Marty'nski T, Mykowska E, Bauman D. J Mol Struct 1994;325:161.

[6] Marty'nski T, Mykowska A, Stolarski R, Bauman D. Dyes and Pigments 1994;25:115.

[7] Reifeld R. J Phys Colloq 1987;C7:423.

[8] Thomas WRL, Drake JM, Lesiecki ML. Appl Optics 1983;22:3440.

[9] Lesiecki ML, Drake JM. Appl Optics 1982;21:557.

[10] Tao Z-F, Qian X, Tang J. Dyes and Pigments 1996;30:247.

[11] Chang S-C, Utecht RE, Lewis DE, Judy MM. In: Tons AL, editor. Condition monitoring: the 1990's and beyond. Proc. Intl. JOAP Conf. Department of Defense, 1992.

[12] Mitchell KA, Brown RG, Yuan D, Chang S-C, Utecht RE, Lewis DE. J Photochem Photobiol A: Chem 1998;115:157.

[13] Stewart WW. Nature 1981;292:17.

[14] Stewart WW. Cell 1978;14:741.

[15] Miller JP, Selverson AI. Science 1979;206:702.

[16] Yamasaki H, Katoh F. Cancer Res 1988;48:3203.

[17] Rideout D, Schinazi R, Pauza CD, Lovelace K, Chiang L-C, Calogeropoulou T, McCarthy M, Elder JH. J Cell Biochem 1988;51:446.

[18] Le Pape A, Maréchal E. Comptes Rend 1977;284:561.

[19] Alexiou M, Tyman J, Wilson I. Tetrahedron Lett 1981;22:2303.

[20] Boriack R, Skiles HL, Judy MM, Matthews JL. unpublished results.

[21] Henderson BW, Dougherty TJ. Photochem Photobiol 1992;55:145.

[22] Hodgson HH, Elliott RT. J Chem Soc 1934:1705.

[23] Hodgkiss RJ, Jones GW, Long A, Middleton RW, Parrick J, Stratford MRL, Wardman P, Wilson GD. J Med Chem 1991;34:2268.

[24] Baughman RG, Chang S-C, Utecht RE, Lewis DE. Acta Cryst C 1995;C51:1189.

[25] Chanh TC, Lewis DE, Judy MM, Sogandares-Bernal F, Michalek GR, Utecht RE, Skiles H, Chang S-C, Matthews JL. Antivir Res 1994;25:133.

[26] For a discussion of SDS-PAGE, see: Voet D, Voet JG. Biochemistry, 2nd ed. New York: Wiley, 1995. p. 95.

[27] Chanh TC, Lewis DE, Allan JS, Sogandares-Bernal F, Judy MM, Utecht RE, Matthews JL. AIDS Res Human Retrovir 1993;9:891.

[28] Judy MM, Fuh L, Matthews JL, Lewis DE, Utecht R. SPIE Proc 1994;2128:506.

[29] Judy MM, Chen L, Fuh L, Nosir H, Jackson RW, Matthews JL, Lewis DE, Utecht RE, Yuan D. SPIE Proc 1996;2681:53.

[30] Karishin AP, Baklan VF. Zh Obshch Khim 1959;29:3048.

[31] Tyman JHP. UK Patent No. 2,183,667, 1987.

[32] Zhou C, Cai J. Tianjin Daxue Xuebo, 1991:52–57.

[33] Lecher HZ, Scalera M, Joyce AW, Forster WS. US Patent No. 2,474,185, 1949.