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RESEARCH ARTICLE

5-Pyrenylidene-hydantoin, 2-thiohydantoin derivatives: synthesis, *S*- and *N*-alkylation

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5-Pyrenylidene-2-thiohydantoin derivatives **2a**–**d** were prepared by condensation of pyrene-1-carboxaldehyde with 2-thiohydantoin derivatives. Compounds **2a**,**b** undergo Mannich reaction with formaldehyde and morpholine to give the corresponding Mannich products **3a**,**b** respectively. *S*- and *N*-monoalkyl-5-pyrenylidene-hydantoin derivatives **5a**,**b** and **6a**,**b** were prepared by reaction of 5-pyrenylidene-2-thiohydantoin sodium salts with 1,3-dioxolan-methylsulfate derivatives. Deprotection of the products afforded 5-pyrenylidene-hydantoin (**7**), *S*- and *N*-dihydroxy derivatives **8a**,**b** and **9a**,**b** respectively. Reaction of **2a** with methyl iodide afforded the corresponding *S*-methyl derivative **10**, which reacted with secondary amines such as morpholine and piperidine afforded the glycocymidine derivatives **11a**,**b**. Reaction of **2a** with (2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)bromide afforded a mixture of *S*- and *N*-glucoside derivatives **12** and **13** respectively. Deprotection of **12** afforded compound **7**, while deprotection of **13** furnished 5-Pyrenylidene-3-*D*-glucopyranosyl-2-thiohydantoin (**14**). Reaction of 7 with propargyl chloride in DMF afforded the monoalkynyl- and bis-alkynyl-hydantoin derivatives **15** and **16**, respectively. Reaction of **15** with *p*-bromophenyl-ether derivative **17** yielded the bis-alkynyl derivative **18**.

Keywords: Pyrenylidene-hydantoin; 2-Thiohydantoins alkyl; Alkynyl derivatives

1. Introduction

Hydantoin derivatives have found use in medicine and have mainly been described as anticonvulsant agents [1]. The nucleosides of several 5-arylidene-3-aryl-hydantoin, 2-thiohydantoin show potent activity against the herpes simplex virus (HSV) [2], the human immunodeficiency virus (HIV) [3] and the leukaemia subpanel [4]. Several classes of compounds containing hydroxyl groups in the side chain have been identified as high-specific DNA intercalators [5–8]. 1-*O*−(Pyrenylmethyl)-glycerol stabilizes dsDNA and show discrimination for DNA over RNA [9, 10]. 3-[(*S*)-3,4-dihydroxybutyl]-5-[(pyren-1-yl) methylidene]imidazolidine-2,4-dione upon insertion as a bulge stabilizes a DNA triplex at pH 6.0 and 7.2 as well as a DNA/DNA parallel duplex at pH 6.0 [11].

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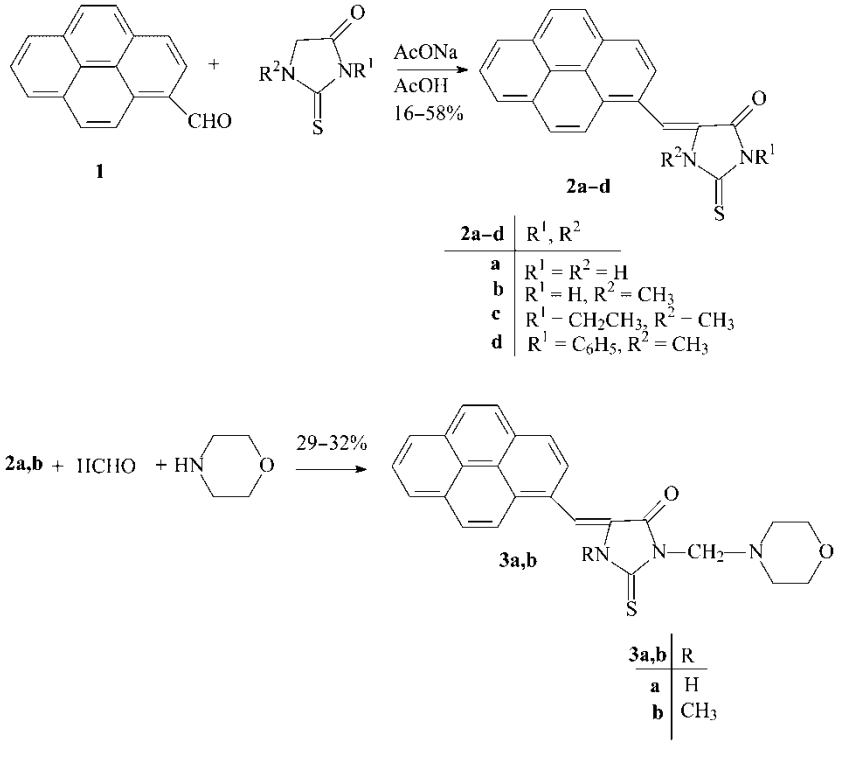
Those results are interesting and encourage me to resume of my interest in the chemistry of hydantoin, 2-thiohydantoin derivatives [12–17]. Herein I report the synthesis of new 5-pyrenylidene-hydantoin, 2-thiohydantoin derivatives and some of there *S*- and *N*-alkyl, alkynyl derivatives. These synthesized compounds may be important for future development of conjugated DNA intercalators.

2. Results and discussion

The 5-pyrenylidene-2-thiohydantoin derivatives **2a**–**d** were prepared in 16–58% yield by reacting 1-formylpyrene (**1**) and 2-thiohydantoin derivatives in glacial acetic acid and freshly fused sodium acetate. The synthesis of Mannich bases derived from 5-substituted-2-thiohydantoin was previously studied and the site attack was reported to be only at position three [18]. Thus, when compounds **2a**,**b** was allowed to react with formaldehyde and morpholine in ethanol afforded the corresponding N^3-morpholinomethyl-imidazolidin-2-thioxo-4-one derivatives **3a**,**b** in yield 29–32% (scheme 1). The structure of compounds **2a**–**d** and **3a**,**b** was established by ^{1}H-NMR, ^{13}C-NMR and microanalytical data.

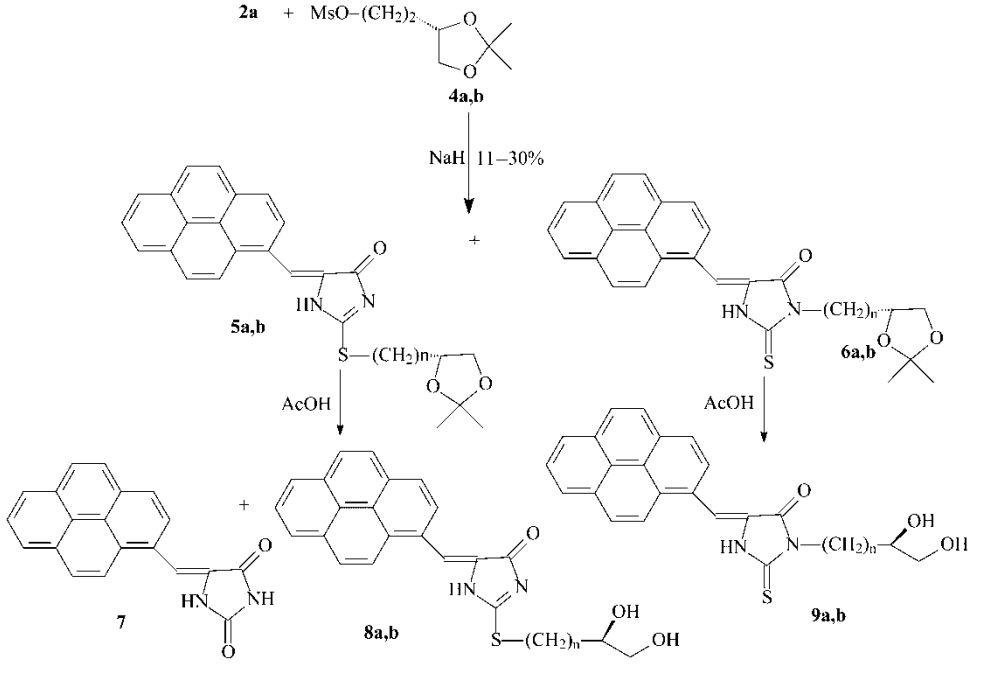
Reaction of the sodium salt of pyrenylidene-2-thiohydantoin (**2a**) with 1,2-*O*-isopropylidene-*D*-glycerol methylsulfate (**4a**) [19] and 2-[(*S*)-2,2-dimethyl[1,3]dioxolane-4-yl]ethyl methanesulfonate (**4b**) [19] in dry DMF under nitrogen afforded the *S*-alkylated 1,3-dioxolanoimidazolidine-4-one derivatives **5a** and **5b** as major products in yield of 26–30% and the N^3-alkylated 1,3-dioxolanoimidazolidine-2-thioxo-4-one derivatives **6a** and **6b** as minor products in yield of 11–13%. The ^{13}C-NMR spectra of compounds **5a** and **5b** showed



SCHEME 1

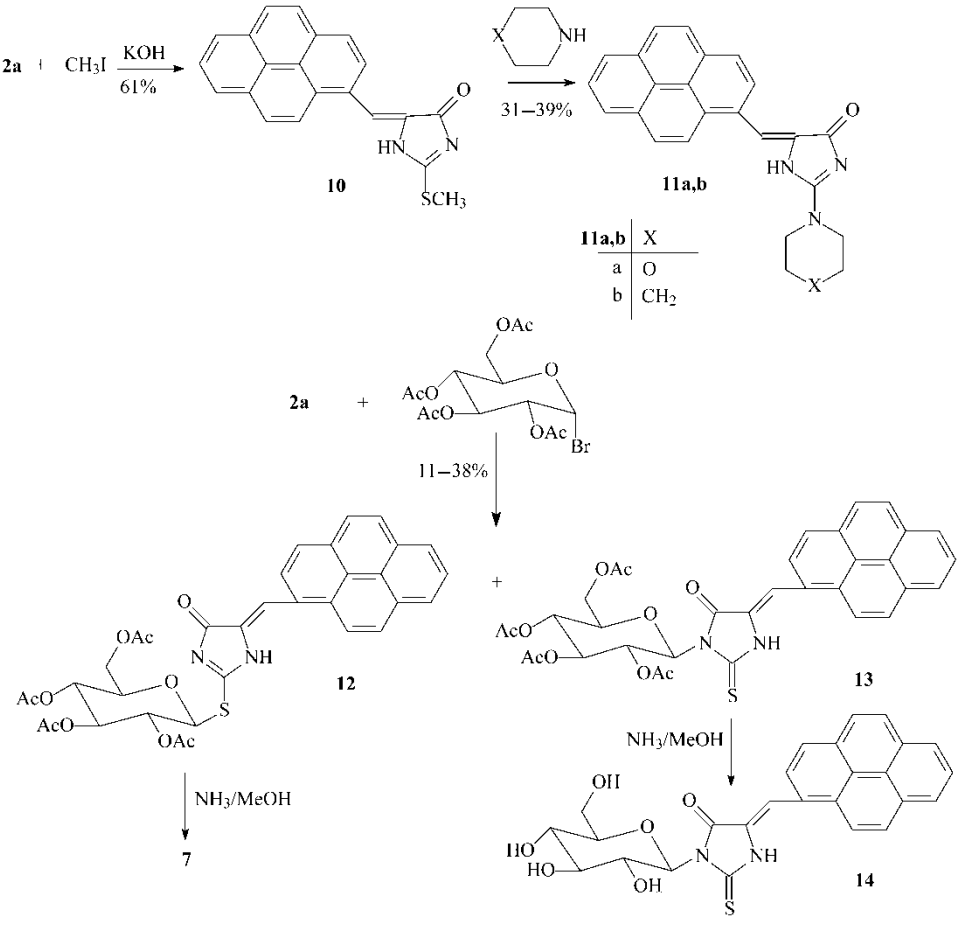
disappearance of C=S signal of **2a** at 179.20 ppm and appearance of C=N at 170.70 and 170.60 ppm respectively, corresponding to *S*-alkylation, while H^1-NMR spectra of **6a** and **6b** showed NH at 9.19 and 9.40 ppm, respectively, corresponding to N^1-H, proving N^3-alkylation [2, 11]. Deprotection of the N^3-alkylated compounds **6a**,**b** were performed by treatment with 80% aqueous acetic acid at room temperature to afford the corresponding N^3-dihydroxy derivatives **9a**,**b**, however the deprotection of *S*-alkylated derivatives **5a**,**b** under the same reaction condition afforded the *S*-dihydroxy derivatives **8a**,**b** and pyrenylidene-hydantoin **7** [11], respectively. The structure of compounds **5a**,**b**, **6a**,**b**, **8a**,**b** and **9a**,**b** was established by ^{1}H-NMR, ^{13}C-NMR and microanalytical data (scheme 2).

Reaction the potassium salt of compound **2** with methyl iodide furnished the *S*-methyl derivative **10** in yield of 61%. Compound **10** was used as starting material for the synthesis of glycocyamidine derivatives **11a**,**b** in yield of 31–39% by reacting compound **10** with secondary amines namely morpholine and piperidine. For the synthesis of glucosyl hydantoins **12** and **13**, compound **2a** was treated with one equiv of aqueous KOH in acetone followed by 2,3,4,6-tetra-*O*-acetyl-α–$_D$-glucopyranosyl bromide, both *S*- and *N*-glucosylation reactions took place with formation of the *S*- and *N*-glucosyl hydantoin derivatives **12** and **13** respectively, in yield of 11–38%. The ^{13}C-NMR spectra of compounds **12** showed disappearance of C=S signal of **2a** at 179.20 ppm and appearance of C=N at 169.23 ppm corresponding to *S*-glucosylation, while ^{13}C–NMR spectra of **13** showed C=S signal at 179.21 ppm corresponding to *N*-glucosylation. Upon deprotection of **13** with ammonia in methanol afforded the N^3-glucosyl-2-thiohydantoin derivative **14** in yield of 65%, however



4a,b–9a,b	n
a	1
b	2

SCHEME 2



SCHEME 3

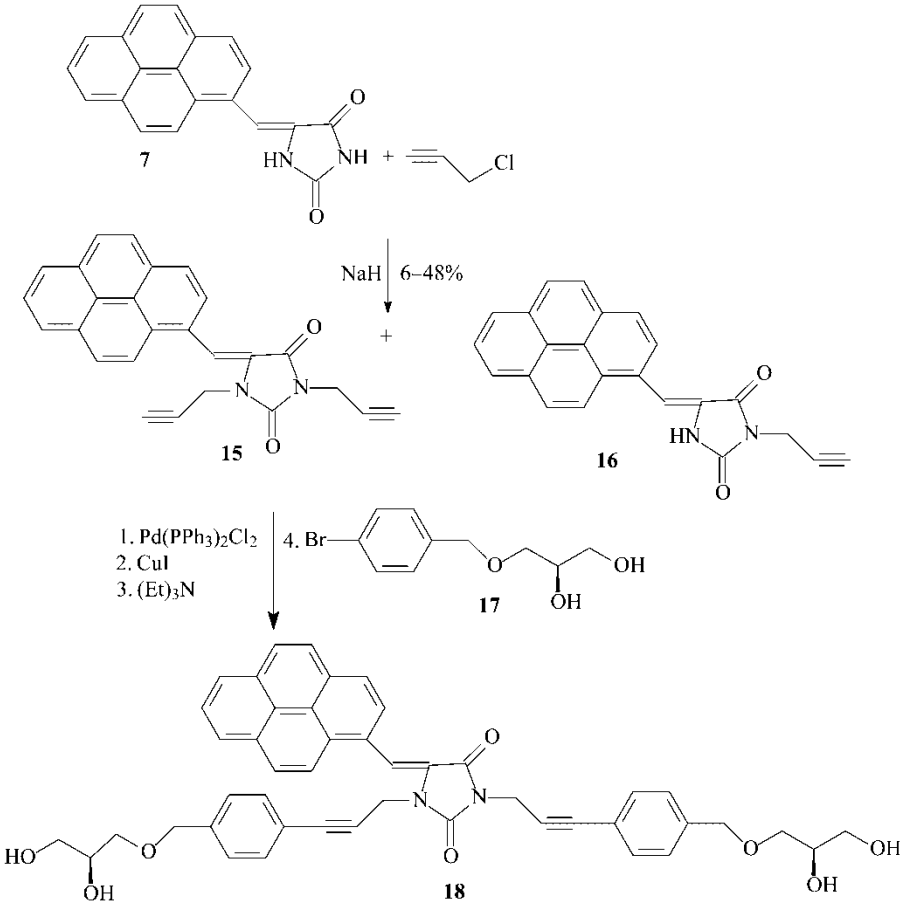
the deprotection of **12** at the same reaction condition, the glucosylthio group was most likely replaced by oxygen atom [2] to give the 2-oxo derivative **7** [11] (scheme 3).

When sodium salt of 5-pyrnylidene-hydantoin (**7**) [11] was treated with propargyl chloride in dry DMF under nitrogen yielded the monoalkynyl-hydantoin derivative **16** in low yield (6%) and the bis-alkynyl-hydantoin derivative **15** in 48% yield. Coupling of **15** with the *p*-bromo-phenyl-ether derivative **17** in the presence of bis(triphenylphosphine)palladium (II) dichloride and CuI in triethylamine as solvent under nitrogen using the condition of Price and Tour [20] afforded the corresponding bis-alkynylphenylether derivative **18** in 38% yield. (scheme 4). H^1-NMR, ^{13}C-NMR and MS spectroscopy were found in agreement with the proposed structure.

3. Experiment

3.1 *General consideration*

All melting points are not corrected. NMR spectra were recorded on a Varian Gemini 2000 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C NMR. TMS was used as an internal



SCHEME 4

standard in ^{1}H NMR spectra. Accurate-ion mass determinations were performed using the 4.7 T Ultima Fourier transform (FT) mass spectrometer (Ion Spec, Irvine, CA). The $(M + H)^+$ and $(M + Na)^+$ ions were peak matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. Thin-layer chromatography (TLC) analyses were carried out with Silica Gel 60 F_{254} TLC plates purchased from E. Merck and were visualized in an UV light (254 nm). The silica gel (0.040–0.063 mm) used for column chromatography was purchased from E. Merck. Solvents used for column chromatography were distilled prior to use, while reagents were used as purchased.

3.2 *General procedure for the preparation of pyenylidend-2-thiohydantoin derivatives 2a–d*

Pyrene-1-carboxaldehyde (4.6 g, 0.02 mol), 2-thio-hydantoin derivatives (0.022 mol), and fused sodium acetate (6 g, 0.72 mol) were dissolved in glacial AcOH (50 mL). The reaction mixture was refluxed for 24 h. The solid formed in the hot mixture was filtered off after cooling, washed with EtOH and dried. The mother layer was refluxed with excess of 2-thio-hydantoin derivatives (0.005 mol) and fused sodium acetate (2 g, 0.24 mol) for another 15 h. and the solid formed on hot was cooled and likewise isolated to yield **2a–d**.

5-[(Pyren-1-yl)methylidene]imidazolidine-2-thioxo-4-one (2a). Yield, 3.8 g, 58%; m.p: 282–284 °C. δ_H (300 MHz, DMSO): 7.35 (1H, s, C*H*=C), 8.07–8.40 (9H, m, H_{ar}), 12.38, 12.49 (2H, 2s, 2N*H*). δ_C (75 MHz, DMSO): 108.21, 122.96, 123.61, 123.85, 124.91, 125.71, 125.87, 126.43, 126.76, 127.23, 127.44, 128.19, 128.38, 129.00, 129.90, 130.20, 130.70, 131.22 (C_{ar}), 165.47 (CO), 179.20 (CS). Calc. for $C_{20}H_{12}N_2OS$ (328): C 73.1, H 3.6, N 8.5; found C 72.8, H 3.4, N 8.2.

5-[(Pyren-1-yl)methylidene]-N^1-methyl-imidazolidine-2-thioxo-4-one (2b). Yield, 2.24 g, 32%; m.p: 296–298 °C. δ_H (300 MHz, DMSO): 3.14 (3H, s, N^1−C*H*$_3$), 7.15 (1H, s, C*H*=C), 8.01-8.33 (9 H, m, H_{ar}), 12.01(1H, s, N*H*). δ_C (75 MHz, DMSO): 26.48 (N^1−*C*H$_3$), 108.11, 122.83, 123.41, 123.81, 124.88, 125.68, 125.81, 126.40, 126.73, 127.13, 127.48, 128.13, 128.31, 129.03, 129.82, 130.18, 130.68, 131.21 (C_{ar}), 165.23 (CO), 179.03 (CS). Calc. for $C_{21}H_{14}N_2OS$ (342): C 73.6, H 4.1, N 8.1; found C 73.3, H 3.8, N 7.8.

5-[(Pyren-1-yl)methylidene]-N^1-methyl-N^3-ethyl-imidazolidine-2-thioxo-4-one (2c). Yield 2.2 g, 29%; m.p: 278–280 °C. δ_H (300 MHz, DMSO): 1.34 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 3.14–3.18 (2H, m, C*H*$_2$CH$_3$), 3.23 (3H, s, N^1-C*H*$_3$), 7.23 (1H, s, C*H*=C), 8.11-8.36 (9H, m, H_{ar}). δ_C (75 MHz, DMSO): 14.82 (CH$_3$CH$_2$), 25.22 (N^3−CH$_2$), 26.74 (N^1−CH$_3$), 108.21, 123.13, 123.63, 123.92, 124.81, 125.54, 125.78, 126.44, 126.76, 127.21, 127.32, 128.16, 128.42, 129.10, 129.91, 130.22, 130.73, 131.32 (C_{ar}), 165.33 (CO), 178.78 (CS). Calc. for $C_{23}H_{18}N_2OS$ (370): C 74.5, H 4.9, N 7.5; found C 74.3, H 4.6, N 7.2.

5-[(Pyren-1-yl)methylidene]-N^1-methyl-N^3-phenyl-imidazolidine-2-thioxo-4-one (2d). Yield, 1.4 g, 16%; m.p: 291–293 °C. δ_H (300 MHz, DMSO): 3.12 (3H, s, N^1−C*H*$_3$), 7.26 (1H, s, C*H*=C), 7.46–8.33 (14H, m, H_{ar}). δ_C (75 MHz, DMSO): 26.47 (N^1−CH$_3$), 108.32, 123.03, 123.52, 123.78, 123.92, 124.36, 124.76, 125.16, 125.53, 125.72, 126.43, 126.64, 127.02, 127.43, 128.24, 128.42, 129.12, 129.86, 130.26, 130.71, 131.31, 137.12 (C_{ar}), 165.45 (CO), 178.83 (CS). Calc. for $C_{27}H_{18}N_2OS$ (418): C 77.4, H 4.3, N 6.6; found C 77.2, H 3.9, N 6.4.

3.3 *Reaction of 2a or 2b with formaldehyde and morpholine* (*synthesis of 3a,b*)**:** *General procedure*

A mixture of **2a** or **2b** (0.01 mol), formaldehyde (1.0 mol, 40% solution) and morpholine (0.01 mol) in ethanol (30 mL) was stirred at room temperature for 72 h, the solid formed filtered off washed with ethanol and recrystallized from acetic acid to give **3a** and **3b**.

5-[(Pyren-1-yl)methylidene]-*N*^{3}-morpholinomethyl-imidazolidin-2-thioxo-4-one (3a). Yield, 1.4 g, 32%; m.p: 276–278 °C. δ_H (300 MHz, DMSO): 2.66 (4H, t, *J* 4.6 Hz, 2C*H*$_2$N$_{morph}$), 3.59–3.62 (4H, m, 2C*H*$_2$O$_{morph}$), 4.67 (2H, s, NC*H*$_2$N), 7.23 (1H, s, C*H*=C), 7.87–8.38 (9H, m, H_{ar}), 11.61 (1H, s, N*H*). δ_C (75 MHz, DMSO): 43.40 (s, 2CH$_2$N$_{morph}$), 62.71 (NCH$_2$N), 65.78 (s, 2CH$_2$O$_{morph}$), 108.46 (C−5), 123.01 (CH=C), 123.67, 123.82, 124.72, 125.68, 125.73, 126.23, 126.62, 127.12, 127.32, 128.02, 128.31, 129.03, 129.86, 130.18, 130.76, 131.13 (C_{ar}), 164.96 (CO), 178.81 (CS). Calc. for $C_{25}H_{21}N_3O_2S$ (427); C 70.2, H 4.9, N 9.8; found C 69.9, H 4.7, N 9.5.

5-[(Pyren-1-yl)methylidene]-N^1-methyl-N^3-morpholinomethyl-imidazolidin-2-thioxo-4-one(3a). Yield, 1.3 g, 29%; m.p: 294–296 °C. δ_H (300 MHz, DMSO): 2.43 (4H, t, *J* 4.3 Hz, 2CH_2N$_{morph}$), 3.16 (3H, s, N^1−CH_3), 3.42–3.48 (4H, m, 2CH_2O$_{morph}$), 4.53 (2H, s, NCH_2N), 7.12 (1H, s, C*H*=C), 7.78–8.22 (9H, m, H_{ar}). δ_C (75 MHz, DMSO): 26.36 (N^1−*C*H$_3$), 43.40 (s, 2CH$_2$N$_{morph}$), 62.43 (NCH$_2$N), 65.62 (s, 2CH$_2$O$_{morph}$), 108.62 (C-5), 123.11 (CH=C), 123.69, 123.78, 124.64, 125.59, 125.71, 126.33, 126.64, 127.22, 127.34, 128.06, 128.34, 129.13, 129.88, 130.28, 130.86, 131.17 (C$_{ar}$), 164.86 (CO), 179.01 (CS). Calc. for $C_{26}H_{23}N_3O_2S$ (441): C 70.7, H 5.2, N 9.5; found C 70.4, H 4.9, N 9.28.

3.4 *General procedure for the preparation of 5a,b and 6a,b*

Compound **2a** (1.7 g, 5.2 mmol) was dissolved in dry DMF 20 mL under N_2 and warmed to 60 °C, NaH (0.12 g, 5.25 mmol, 100%) was added, and the mixture stirred for 1 h at 60 °C. NaI (0.78 g, 5.2 mmol) in warm dry DMF 10 mL was added to the reaction mixture. 1,2-*O*-Isopropylidene-*D*-glycerol methylsulfate (**4a**) or 2-[(*S*)-2,2-dimethyl[1,3]dioxolane-4-yl]ethyl methanesulfonate (**4b**) (5.5 mmol) was added and the reaction mixture was stirred at 80 °C for 48 h, then quenched with 1 mL of methanol. The solvent was evaporated *in vacuo* to complete dryness. The residue was extracted with EtOAc 200 mL and filtered. The filtrate was evaporated *in vacuo*, and the residual material was chromatographed on silica gel using ethyl acetate: petroleum ether 60–80 °C (3:7, *v*:*v*) to give the products **5a**,**b** and **6a**,**b**.

2-{2-[(S)-(2,2-Dimethyl-[1,3] dioxolan-4-yl]methylthio}-5-[(1-pyrene-1-yl)methylidene]-imidazolidine-4-one (5a). Yield: 0.6 g, 26%; mp: 202–204 °C. δ_H (300 MHz, DMSO): 1.35, 1.37 (6H, 2s, 2CH_3), 3.48 (2H, d, *J* 6.0 Hz, SCH_2), 3.65 (2H, d, *J* 6.2 Hz, OCH_2), 4.34–4.37 (1H, m, OC*H*), 7.63 (1H, s, C*H*=C), 8.07–8.38 (9H, m, H_{ar}), 11.85 (1H, s, N*H*). δ_C (75 MHz, DMSO): 25.37, 26.73 (2CH$_3$), 32.60 (SCH$_2$), 67.57 (OCH$_2$), 73.86 (OCH), 109.02, [(CH$_3$)$_2$*C*], 115.90 (C−5), 122.30 (CH=C), 123.76, 123.97, 125.02, 125.85, 126.10, 126.50, 127.37, 127.58, 128.62, 128.92, 129.01, 129.96, 130.13, 130.78, 131.54, 139.74 (C$_{ar}$), 164.82, (C=O), 170.70 (C=N). MALDI-MS: m/z = (442, 26%, $C_{26}H_{22}N_2O_3S^+$); (43, 100%, $C_3H_7^+$); (147, 6%, $C_6H_{11}O_2S^+$); (295, 12%, $C_{20}H_{11}N_2O^+$).

2-{2-[(S)-2,2-Dimethyl-[1,3]dioxolan-4-yl]ethylthio}-5-[(1-pyrene-1-yl)methylidene]imidazolidine-4-one (5b). Yield: 0.7 g, 30%; mp: 212–214 °C. δ_H (300 MHz, DMSO): 1.32, 1.38 (6H, 2s, 2CH_3), 3.33–3.38 (2H, m, CH_2CH), 3.42–2.48 (2H, m, SCH_2), 3.67 (2H, d, *J* 6.5 Hz, OCH_2), 4.22–4.26 (1H, m, OC*H*), 7.77 (1H, s, C*H*=C), 8.06–8.60 (9H, m, H_{ar}), 11.98 (1H, s, N*H*). δ_C (75 MHz, DMSO): 25.43, 26.76 (2CH$_3$), 26.03 (CH$_2$), 33.26 (SCH$_2$), 68.08 (OCH$_2$), 74.17 (OCH), 108.19 [(CH$_3$)$_2$*C*], 115.51 (C−5), 122.25 (CH=C), 123.75, 123.93, 124.85, 125.77, 126.03, 126.42, 127.31, 127.62, 128.50, 128.55, 128.92, 129.87, 130.09, 130.74, 131.43, 139.83 (C$_{ar}$), 164.99, (C=O), 170.60 (C=N) ppm.

3-{2-[(S)-2,2-Dimethyl-[1,3]dioxolan-4-yl]methyl}-5-[(1-pyrene-1-yl)methylidene]imidazolidine-2-thioxo-4-one (6a). Yield: 0.25 g, 11%; mp: 140–142 °C. δ_H (300 MHz, CDCl$_3$): 1.34, 1.41 (6H, 2s, 2CH_3), 3.88-3.89 (2H, m, NCH_2), 4.05–4.07 (2H, m, OCH_2), 4.58–4.62 (1H, m, OC*H*), 7.48 (1H, s, C*H*=C), 8.01–8.16 (9H, m, H_{ar}), 9.19 (1H, s, N*H*). δ_C (75 MHz, CDCl$_3$): 25.42, 26.87 (2CH$_3$), 44.37 (NCH$_2$), 67.32 (OCH$_2$), 72.71 (OCH), 109.96 [(CH$_3$)$_2$*C*], 111.63 (C−5), 122.66 (CH=C), 124.16, 124.83, 124.98, 125.43, 126.18, 126.20, 126.36, 126.46, 127.09, 127.28, 128.85, 128.92, 129.76, 130.57, 131.10, 132.19 (C$_{ar}$), 163.46 (C=O),

177.92 (C=S). MALDI-MS: m/z = (442, 29%, $C_{26}H_{22}N_2O_3S^+$); (43, 100%, $C_3H_7^+$); [73, 75%, $C_3H_5O_2^+$ ($^+CH_2COCH_2OH$)]; (240, 53%, $C_{10}H_{13}N_2O_3S^+$); (328, 18%, $C_{20}H_{12}N_2OS^+$).

3-{2-(S)-2,2-Dimethyl-[1,3]dioxolan-4- yl]ethyl}-5-[(1-pyrene-1-yl)methylidene] imidazolid ine-2-thioxo-4-one (6b). Yield: 0.3 g, 13%; mp: 163–165 °C. δ_H (300 MHz, DMSO): 1.31, 1.39 (6H, 2s, $2CH_3$), 2.54–2.56 (2H, m, CH_2), 3.41–3.45 (2H, m, NCH_2), 4.06–4.08 (2H, m, OCH_2), 4.52–4.58 (1H, m, OCH), 7.45 (1H, s, CH=C), 8.06–8.62 (9H, m, H_{ar}), 9.40 (1 H, s, NH). δ_C (75 MHz, DMSO): 25.49, 26.84 ($2CH_3$), 31.25 (CH_2), 44.23 (NCH_2), 68.32 (OCH_2), 73.34 (OCH), 108.23 [$(CH_3)_2C$], 112.65 (C−5), 123.04 (CH=C), 123.64, 123.85, 124.96, 125.76, 125.92, 126.47, 126.53, 127.28, 127.49, 128.24, 128.45, 129.03, 129.95, 130.24, 130.73, 131.26 (C_{ar}), 165.48 (C=O), 179.21 (C=S). MALDI-MS: m/z= (456, 32%, $C_{27}H_{24}N_2O_3S^+$); (43, 100%; $C_3H_7^+$); (87, 82%, $C_4H_7O_2^+$).

3.5 *General procedure for deprotection of compounds 5a,b and 6a–c: (formation of 7, 8a,b and 9a,b)*

Each of compounds **5a**,**b** and **6a**,**b** (2.00 mmol) was dissolved in 80% AcOH (10 mL) and the solution was stirred overnight at room temperature. The solvent was evaporated *in vacuo*, and the residue was coevaporated with water (3 × 5 mL) and finally with EtOH (3 × 5 mL). The products were purified by silica gel column chromatography with ethyl acetate:petroleum ether 60–80 °C (3:7, *v*:*v*) to give **8a**,**b** with 5-[1-pyrene-1-ylmethylidene]-imidazolidine-2,4-dione (**7**) [11] in yield 72% and **9a**,**b**.

2-[(S)-2,3-Dihydroxypropylthio]-5-[(1-pyrene-1-yl)methylidene]imidazolidine-4-one (8a). Yield: 150 mg (18%); m.p: 273–275 °C. δ_H (300 MHz, DMSO): 2.52-2.83 (3H, m, $SCH_2$and OH), 3.36–3.44 (3H, m, CH_2OH and OH), 3.58–3.68 (1H, m, $CHOH$), 7.45 (1 H, s, CH=C), 8.07–8.58 (9H, m, H_{ar}), 9.48 (1H, s, NH). δ_C (75 MHz, DMSO): 33.48 (SCH_2), 65.56 (CH_2OH), 70.10 (CHOH), 114.92 (C−5), 122.31 (CH=C), 123.85, 124.91, 125.14, 125.55, 126.41, 126.61, 127.28, 127.38, 128.18, 128.46, 129.13, 129.85, 130.13, 130.72, 131.36, 140.02 (C_{ar}), 165.32 (C=O), 171.10 (C=N) ppm. Calc. for $C_{23}H_{18}N_2O_3S + 0.5\ H_2O$ (402) C 68.6, H 4.5, N 6.9; found C 67.1, H 4.6, N, 6.8.

2-[(S)-3,4-Dihydroxybutylthio]-5-[(1-pyrene-1-yl)methylidene]imidazolidine-4-one (8b). Yield: 130 mg (16%); m.p: 280–282 °C. δ_H (300 MHz, DMSO): 2.61–2.68 (2H, m, CH_2CH), 3.36–3.38 (2H, m, SCH_2), 4.12–4.16 (2H, m, CH_2OH), 4.18 (2H, br, $2OH$), 4.42-4.46 (1H, m, $CHOH$), 7.24 (1H, s, CH=C), 8.10–8.46 (9H, m, H_{ar}), 9.56 (1H, s, NH). δ_C (75 MHz, DMSO): 26.75 (CH_2CH), 33.49 (SCH_2), 65.69 (CH_2OH), 70.05 (CHOH), 115.09 (C−5), 122.32 (CH=C), 123.98, 124.99, 125.11, 125.78, 126.46, 126.69, 127.28, 127.35, 127.99, 128.49, 128.55, 128.64, 129.84, 130.79, 131.39, 140.08 (C_{ar}), 165.34 (C=O), 171.05 (C=N). Calc. for $C_{24}H_{20}N_2O_3S + 0.25\ H_2O$ (416) C 69.2, H 4.8, N 6.7; found C 68.9, H 4.5, N 6.5.

3-[(S)-2,3-Dihydroxypropyl)]-5-[(1-pyrene-1-yl)methylidene]imidazolidine-2-thioxo-4-one (9a). Yield: 0.5 g (62%); m.p: 208–210 °C. δ_H (300 MHz, DMSO): 3.39–3.46 (2H, m, NCH_2), 3.89–3.95 (2H, br, $2OH$), 4.08–4.09 (2H, m, CH_2OH), 4.95–4.99 (1H, m, $CHOH$), 7.47 (1H, s, CH=C), 8.10–8.39 (9H, m, H_{ar}), 12.53 (1H, s, NH). δ_C (75 MHz, DMSO): 44.53 (NCH_2), 64.21 (CH_2OH), 68.17 (CHOH), 109.12 (C−5), 123.04 (CH=C), 123.66, 123.91, 124.99, 125.81, 125.98, 126.56, 127.30, 127.56, 128.30, 128.48, 128.60, 129.07, 129.32,

130.26, 130.75, 131.33 (C_{ar}), 164.18 (C=O), 179.17 (C=S) ppm. Calc. for $C_{23}H_{18}N_2O_3S$ (402) C 68.6, H 4.5, N 6.9; found C 68.3, H 4.2, N 6.6.

3-[(S)-3,4-Dihydroxybutyl)-5-[(1-pyrene-1-yl) methylidene]imidazolidine-2-thioxo-4-one (9b). Yield: 0.5 g (62%); m.p: 217–219 °C. δ_H (300 MHz, DMSO): 2.06–2.10 (2H, m, CH_2CH), 3.33–3.39 (2H, m, NCH_2), 3.93–3.98 (2H, m, CH_2OH), 4.01–4.08 (2H, br, 2OH), 4.67–4.69 (1H, m, CHOH), 7.46 (1H, s, CH=C), 8.07-8.51 (9H, m, H_{ar}), 12.38 (1H, s, NH). δ_C (75 MHz, DMSO): 31.73 (CH_2CH), 38.27 (NCH_2), 65.76 (CH_2OH), 69.36 (CHOH), 108.87 (C−5), 122.95 (CH=C), 123.64, 123.87, 124.90, 125.69, 125.85, 126.44, 126.67, 127.25, 127.62, 128.16, 128.35, 128.98, 130.21, 130.65, 130.72, 131.18 (C_{ar}), 164.14 (C=O), 178.95 (C=S). Calc. for $C_{24}H_{20}N_2O_3S$ (416) C 69.2, H 4.8, N 6.73; found C 68.9, H 4.5, N 6.4.

3.6 *Reaction of 2a with methyl iodide (synthesis of 10)*

Potassium hydroxide solution (0.56 g, 0.01 mol in 10 mL water) was added to suspended solution of compound **2a** (3.3 g, 0.01 mol) in 30 mL ethanol. Methyl iodide (0.03 mol) in 10 mL ethanol was added dropewise. The reaction mixture was kept under stirring for 20 h. The solid formed filtered off, washed with water and ethyl alcohol and purified by silica gel column chromatography with ethyl acetate:petroleum ether 60–80 °C (3:7, *v*:*v*) to give compound **10**.

2-Methylthio-5-[(1-pyrene-1-yl)methylidene]imidazolidine-4-one (10). Yield, 2.1 g, 61%; m.p: 144–146 °C. δ_H (300 MHz, DMSO): 2.76 (3H, s, SCH_3), 7.77 (1H, s, CH=C), 8.07–8.61 (9 H, m, H_{ar}), 12.02 (1H, s, NH). δ_C (75 MHz, DMSO): 12.32 (SCH_3), 115.40 (C−5), 122.28 (CH=C), 123.74, 123.94, 124.93, 125.03, 125.78, 126.03, 126.45, 127.34, 128.49, 128.55, 128.97, 129.86, 130.11, 130.75, 131.42, 139.89 (C_{ar}), 165.82 (CO), 170.79 (C=N). Calc. for $C_{21}H_{14}N_2OS$ (342) C 73.6, H 4.1, N 8.1; found C 73.3, H 3.8, N 7.7.

3.7 *Reaction of 10 with morpholine and piperidine (synthesis of 11a,b)*

A mixture of **10** (3.3 g, 0.01 mol) in 50 mL ethanol and morpholine or piperidine (0.015 mol) was refluxed until the starting material was consumed. The reaction mixture was evaporated under *vacuum* and the residue was purified by silica gel column chromatography with ethyl acetate:petroleum ether 60–80 °C (3:7, *v*:*v*) to give compound **11a**,**b**.

2-Morpholino-5-[(1-pyrene-1-yl)methylidene]glycocyamidine (11a): Yield, 1.5 g, 39%; m.p: 195–197 °C. δ_H (300 MHz, DMSO): 3.28–3.46 (4H, m, 2NCH_2), 3.65–3.74 (4H, m, 2OCH_2), 7.43 (1H, s, 1H, CH=C), 8.06–8.58 (9 H, m, H_{ar}), 9.63 (1H, s, NH). δ_C (75 MHz, DMSO): 44.61 (s, 2NCH_2), 65.53 (s, 2OCH_2), 106.31 (C−5), 122.48 (CH=C), 124.05, 124.13, 124.96, 125.15, 125.42, 126.26, 127.19, 127.38, 127.42, 127.76, 127.93, 128.47, 129.60, 129.91, 130.31, 130.93 (C_{ar}), 161.82 (CO), 170.41 (C=N). Calc. for $C_{24}H_{19}N_3O_2$ (381) C 75.5, H 5.0, N 11.0; found C 75.2, H 4.8, N 10.7.

2-Piperidino-5-[(1-pyrene-1-yl)methylidene)glycocyamidine (11b): Yield, 1.2 g, 31%; m.p: 293–295 °C. δ_H (300 MHz, DMSO): 1.41–1.53 (6H, m, H_{piper}), 3.52–3.60 (4H, m, H_{piper}), 7.22 (1H, s, CH=C), 8.03–8.47 (9H, m, H_{ar}), 9.37 (1H, s, NH). δ_C (75 MHz, DMSO): 23.62,

25.21 (2s, 3 CH_{2piper}), 45.59 (s, 2NCH_{2piper}), 104.18 (C−5), 122.55 (CH=C), 124.16, 124.80, 124.95, 125.18, 125.99, 126.15, 126.97, 127.23, 127.34, 127.44, 127.74, 128.09, 129.44, 130.32, 130.36, 130.97, (C_{ar}), 161.50 (CO), 174.13 (C=N).

3.8 *Reaction of 2a with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (synthesis of 12 and 13)*

To a solution of **2a** (3.3 g, 0.01 mol) in aqueous potassium hydroxide (0.56 g, 0.01 mol, in 6 mL water), a solution of 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl bromide (4.1 g, 0.012 mol in 30 mL acetone) was added. The reaction mixture stirred at room temperature for 30 h. The solvent was evaporated under reduced pressure at 40 °C and the residue was chromatographed by silica gel column chromatography with chloroform:methanol (99:1, *v*:*v*) to give compound **12** and **13**.

5-[(1-pyrene-1-yl)methylidene]-2-(2′, 3′, 4′, 6′-tetra-O-acetyl-*β*–*D*-thioglucopyranosyl)-imidazolidine-4-one (12). Yield, 2.5 g, 38%; m.p: 183–185 °C. δ_H (300 MHz, DMSO): 2.06, 2.12, 2.13, 2.14 (12H, 4s, 4 CH_3), 4.06–4.27 (2H, m, 6′-*H*), 5.18 (1H, d-d, *J* 9.7 Hz, 4′-*H*), 5.41 (1H, d-d, *J* 10.0 Hz, 2′-*H*), 5.74 (1H, d-d, *J* 9.3 Hz, 3′-*H*), 6.19 (1H, d, *J* 10.3 Hz, 1′-*H*), 7.87 (1H, s, C*H*=C), 8.15–8.71 (9H, m, H_{ar}), 12.07 (1H, s, N*H*). δ_C (75 MHz, DMSO): 20.11, 20.25, 20.28, 20.40 (4s, 4CH_3), 61.70 (C-6′), 67.99 (C-2′), 68.99 (C-3′), 72.76 (C-4′), 75.29 (C−5′), 79.91 (C-1′), 117.19 (C−5), 122.20 (CH=C), 123.72, 123.89, 125.31, 125.90, 126.14, 126.47, 127.31, 128.69, 128.71, 128.76, 129.69, 130.06, 130.13, 130.71, 131.74, 139.32 (C_{ar}), 161.21 (C-4), 169.23 (C=N), 169.34, 169.48, 169.71, 170.21 (4s, 4CO acetyl).

5-[(1-pyrene-1-yl)methylidene]-3-(2′, 3′, 4′, 6′-tetra-O-acetyl-*β*-*D*-glucopyranosyl)-imidazolidine-2-thioxo-4-one (13). Yield, 0.75 g, 11%; m.p: 171–173 °C. δ_H (300 MHz, DMSO): 1.88, 1.92, 1.94, 1.97 (12H, 4s, 4CH_3), 3.97–4.13 (2H, m, 6′-*H*), 4.87 (1H, d-d, *J* 9.9, Hz, 4′-*H*), 5.38 (1H, d-d, *J* 10.2 Hz, 2′-*H*), 5.92 (1H, d-d, *J* 9.4 Hz, 3′-*H*), 6.16 (1H, d, *J* 10.2 Hz, 1′-*H*), 7.47 (1H, s, C*H*=C), 8.05-8.34 (9H, m, H_{ar}), 12.28 (1H, s, N*H*). δ_C (75 MHz, DMSO): 20.12, 20.26, 20.30, 20.41 (4s, 4CH_3), 61.71 (C-6′), 68.01 (C-2′), 69.00 (C-3′), 72.76 (C-4′), 75.29 (C−5′), 79.92 (C-1′), 108.19 (C−5), 122.21 (CH=C), 123.62, 123.87, 124.92, 125.72, 125.89, 126.48, 127.25, 127.47, 128.21, 128.40, 129.01, 129.92, 130.22, 130.71, 131.24, 131.75 (C_{ar}), 165.45 (C-4), 169.35, 169.49, 169.80, 170.21 (4s, 4CO acetyl), 179.21 (C=S).

3.9 *General procedure for depacetylation of glucosides 12 and 13 (synthesis of 14 and 7)*

To a suspension of the glucoside **12** and **13** (0.001 mol) in methanol (50 mL), a saturated solution of ammonia in methanol (20 mL) was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated to dryness under vacuum and the residue was chromatographed using chloroform:methanol (99:1, *v*:*v*) to give compound **14** and **7** [11].

5-[(1-pyrene-1-yl)methylidene]-3-*D*-glucopyranosyl-imidazolidine-2-thioxo-4-one (14). Yield, 0.32 g, 65%; m.p: 183–185 °C. δ_H (300 MHz, DMSO): 3.09–3.12 (1H, m, 4′-*H*), 3.33–3.36 (1H, m, 3′-*H*), 3.43–3.47 (3H, m, 5′−*H*, 6′−*H*, O*H*), 3.73 (1H, d, *J* 11.1 Hz, 6′-*H*), 4.34–4.36 (1H, m, 2′-*H*), 4.59–4.63 (1H, br, O*H*), 4.88–5.12 (3H, m, br, 1′−*H*, 2O*H*), 7.32

(1H, s, C*H*=C), 8.02–8.39 (9H, m, H_{ar}), 9.98 (1H, s, N*H*). δ_C (75 MHz, DMSO): 61.16 (C-6′), 69.55 (C-4′), 71.79 (C-2′), 77.97 (C−5′), 81.16 (C-3′), 82.20 (C-1′), 104.81 (C−5), 123.04 (CH=C), 124.99, 125.56, 125.73, 126.48, 126.71, 127.28, 127.37, 127.88, 128.20, 128.33, 128.63, 130.19, 130.28, 130.71, 130.79, 130.92 (C_{ar}), 165.30 (CO), 178.91 (C=S).

3.10 *Reaction of 5-[(1-pyrene-1-yl)methylidene]imidazolidine-2,4-dione (7) with propargyl chloride (synthesis 15 and 16).*

Compound **7** (5.2 mmol, 1.6 g) was dissolved in dry DMF (30 mL). NaH (5.2 mmol, 0.21 g) was added dropwise and the reaction mixture was heated to 60 °C for 1 h. Propargyl chloride (5.5 mmol, 0.41 g) was added and the reaction mixture was heated at 80 °C for 72 h. DMF was evapourated under reduced pressure to complete dryness and the residue was chromatographed with ethyl acetate:petroleum ether 60–80 °C (3:7, *v*:*v*) to give compound **15** and **16**.

3-propnyl-5-[(1-pyrene-1-yl)methylidene]imidazolidine-2,4-dione (16). Yield: 100 mg, 6%; m.p: 226–228 °C. δ_H (300 MHz, DMSO): 2.74 (1H, s, $H_{acetylene}$), 4.03 (2H, s, NCH_2), 7.48 (1H, s, C*H*=C), 8.00–8.36 (9H, m, H_{ar}), 11.85 (1 H, s, N*H*). δ_C (75 MHz, DMSO): 30.85(NCH_2), 74.37, 77.20 (2s, 2$C_{acetylene}$), 109.35 (C−5), 123.58 (CH=C), 123.59, 124.14, 124.21, 125.63, 125.68, 126.46, 126.96, 127.22, 127.63, 127.83, 128.15, 129.04, 129.98, 130.30, 130.72, 130.82 (C_{ar}), 155.02, 164.93 (2s, 2C=O). HRMS-MALDI: *m*/*z* found 350.1046 (M^+, $C_{23}H_{14}N_2O_2$); calc. 350.1050.

1,3-Bis-propnyl-5-[(1-pyrene-1-yl)methylidene]imidazolidine-2,4-dione (15). Yield: 1.8 g, 48%; m.p: 140–142 °C. δ_H (300 MHz, DMSO): 2.52, 2.77 (2H, 2s, $H_{acetylene}$), 4.09, 4.46 (4H, 2s, N^1CH_2 and N^3CH_2), 7.64 (1H, s, C*H*=C), 8.07–8.41 (9H, m, H_{ar}). δ_C (75 MHz, DMSO): 28.06, 31.41 (2s, 2NCH_2), 74.39, 74.77, 76.90, 77.65 (4s, 4$C_{acetylene}$), 111.40 (C−5), 123.51 (CH=C), 124.44, 124.47, 125.70, 125.76, 126.49, 126.58, 127.19, 127.58, 127.96, 128.23, 128.42, 129.06, 129.98, 130.26, 130.69, 130.98 (C_{ar}), 153.49, 161.62 (2s, 2C=O). HRMS-MALDI: *m*/*z* found 411.1096 ($M + Na^+$, $C_{26}H_{16}N_2O_2Na$); calc. 411.1104.

3.11 *Reaction of compound 15 with p-bromo-(2,3-dihydroxy-propyloxymethyl)benzene* (*17*) *Synthesis of 18*

Compounds **15** (1.42 mmol, 0.53 g) was dissolved in triethylamine (50 mL) under N_2 and bis(triphenylphosphine)palladium (II) dichloride (0.03 g, 0.042 mmol), CuI (0.016 g, 0.085 mmol) were added. The reaction mixture was stirred for 15 min and *p*-bromo-(2,3-dihydroxy-propyloxymethyl)benzene (**17**) (0.86 g, 2.8 mmol) was added. The reaction mixture was heated at 70 °C for 36 hours, cooled and filtered. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel with chloroform/methanol (*v*:*v* = 9:1) to give **18**.

1,3-Bis-[p-(2,3-dihydroxy-propyloxymethyl)phenyl-propnyl]-5-[(1-pyrene-1-yl)methylidene]imidazolidine-2,4-dione (18). Yield: 0.4 g, 38%; yellow fome. δ_H (300 MHz, $CDCl_3$): 2.75, 3.15 (2H, 2s, br, 2CH_2OH), 3.09–3.15 (4H, m, 2CH_2OH), 3.41, 3.49 (2H, 2q, *J* 2.9 Hz, 2C*H*OH), 3.58–3.64 (4H, m, 2OCH_2CH), 3.85 (2H, br, 2CHO*H*), 4.30, 4.37 (4H, 2s, 2PhCH_2O), 4.48, 4.70 (4H, 2s, N^1CH_2 and N^3CH_2), 6.50, 6.75, 7.23, 7.43 (4H, 4d, *J* 8.1 Hz, H_{ar}), 7.75 (1H, s, C*H*=C), 7.88–8.19 (9 H, m, H_{pyrene}). δ_C (75 MHz, $CDCl_3$): 29.30, 32.74

(2s, 2NCH_2), 63.91 (s, 2CH_2OH), 70.63, 70.68 (2s, 2CH.OH), 71.63, 71.73 (2OCH_2CH), 72.78, 72.95 (2s, 2$PhCH_2O$), 82.25, 82.55, 83.23, 83.62 (4s, 4$C_{acetylene}$), 113.24, 123.91, 120.84, 121.61, 124.16, 124.33, 124.42, 125.60, 125.74, 126.21, 126.75, 126.99, 127.37, 127.42, 128.20, 128.39, 128.63, 129.78, 130.73, 131.16, 131.41, 131.64, 132.04, 132.09, 137.78, 138.35 (C_{ar}), 154.00, 162.32 (2s, 2C=O). HRMS-MALDI: m/z found 771.2641 ($M + Na^+$, $C_{46}H_{40}N_2O_8Na$); calc. 771.2677.

References

[1] A. Sinks, W.S. Waring. *Prog. Med. Chem.*, **3**, 313 (1963).
[2] A.A. El-Barbary, A.I. Khodair, E.B. Pedersen, C. Nielsen. *J. Med. Chem.*, **37**, 73 (1994).
[3] A.I. Khodair, H.I. El-Subbagh, A.A. El-Emam. *Boll. Chim. Farm.*, **136**, 561 (1997).
[4] A.A. Al-Obaid, H.I. El-Subbagh, A.I. Khodair, M.M. El-Mazar. *Anti-Cancer Drugs*, **7**, 873 (1996).
[5] V.V Filichev, B. Vester, E.B. Pedersen. *Bioorg. Med. Chem.*, **12**, 2843 (2004).
[6] V.V. Filichev, E.B. Pedersen. *Bioorg. Med. Chem. Lett.*, **14**, 581 (2004).
[7] U.B. Christensen, E.B. Pedersen. *Helv. Chim. Acta.*, **86**, 2090 (2003).
[8] C.B. Nielsen, M. Petersen, E.B. Pedersen, P.E. Hansen, U.B. Christensen. *Bioconj. Chem.*, **15**, 260 (2004).
[9] U.B. Christensen, E.B. Pedersen. *Nucleic Acid Res.*, **30**, 4918 (2002).
[10] K.W. Bair, R.T. Tuttel, V.C. Knich, M. Cory, D.D. Mckee. *J. Med. Chem.*, **33**, 2385 (1990).
[11] Y.L. Aly, M. Wamberg, E.B. Pedersen. *Helv. Chim. Acta.*, **88**, 3137 (2005).
[12] Y.L. Aly. *Phosphorus, Sulfur Silicon*, **180**, 1 (2005).
[13] Y.L. Aly, A.A. El-Barbary, A.A. El-Shehway. *Phosphorus, Sulfur Silicon*, **179**, 185 (2003).
[14] A.A. El-Barbary, Y.L. Aly, A.M. Hashem, A.A. El-Shehway. *Phosphorus, Sulfur Silicon*, **160**, 77 (2000).
[15] Y.L. Aly. *Delta J. Sci.*, **16**, 65 (1992).
[16] Y.L. Aly, E.B. Pedersen. *Nucleosides, Nucleotides, and Nucleic Acid*, **25**, 1335 (2006).
[17] Y.L. Aly. *Afinidad*, **63** (522), 143 (2006).
[18] A.F. Shalaby, H.A. Daboun and A. Abd-Elaziz. *Z. Naturforch*, **31b**, 111 (1976).
[19] H.S. Kim, D. Barak, T.K. Harden, J.L. Boyer, K.A. Jacobson. *J. Med. Chem.*, **44**, 3092 (2001).
[20] D.W. Price, Jr, J.M. Tour. *Tetrahedron*, **59**, 3131(2003).