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Synthesis of Anticancer Compounds, I, "Dual Function" Antitumor Agents Based on Bioreduction and *DNA*-Alkylation

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Summary. We report the synthesis of novel anticancer compounds based on bioreductive and *DNA*-alkylating properties. The strategy was to combine a benzoquinone annelated pyrrole with bioreductive properties with a set of *DNA*-alkylating functionalities, thus resulting in bifunctional anticancer compounds. The biological activity of all compounds was evaluated against a number of cancer cell lines. One of the compounds should be emphasized.

Keywords. Antitumor agents; *DNA*; Alkylations; Quinones.

Introduction

The treatment of cancer in humans faces the fundamental problem of selectivity. This means to hit predominantly tumor cells and to avoid damaging healthy cells. One of the possibilities to enhance the accuracy of destroying tumor cell is based on the use of bioreductive drugs [1]. This concept was introduced by *Lin* [2]. Members of this class of compounds are activated to cytotoxic species by reduction. The selective bioactivation of this class of drugs may be due to differences in enzymology (elevated levels of some reductases in certain tumors), or to hypoxia (bioreductive drugs are more toxic to hypoxic cells than to well oxygenated ones). Hypoxia is important in that O_2-content is a key factor in determining the response of a cell to drug, and hypoxic cells are more acidic (lactic acid production). Finally hypoxic cells are "protected" against inhibitors of *topoisomerase* II, the basic principle of many antitumor agents [3]. The most common bioreductive agents are based on quinones and nitroimidazoles. In the biological situation, the reduction of quinones can take place by 1- or 2-electron processes according to which enzyme is involved. The 1-electron reduction is readily reversed by oxygen; the 2-electron reduction leads to hydroquinones and in the following to *DNA*-conjugates, thus causing cell death in the following. The various possibilities of quinone reduction are illustrated in Scheme 1 [3].

A number of bioreductive structures are synthesized in combination with alkylating functions. The rationale, directed primarily toward developing more potent drugs, was that the alkylating agent would serve to locate the drug on *DNA*. The predominant cytotoxicity of these compounds under aerobic conditions is *DNA* monoalkylation, but reductive metabolism converts it into a bifuntional alkylating agent capable of crosslinking *DNA*. Typical "dual function" bioreductive drugs are shown in Scheme 2 [4–7].

Results and Discussion

Syntheses

In accordance with the guidelines discussed above we chose the previously synthesized benzoquinone annelated pyrrole derivative **1** [8]. It has high structural similarity to the EO9 nucleus (see Scheme 2);

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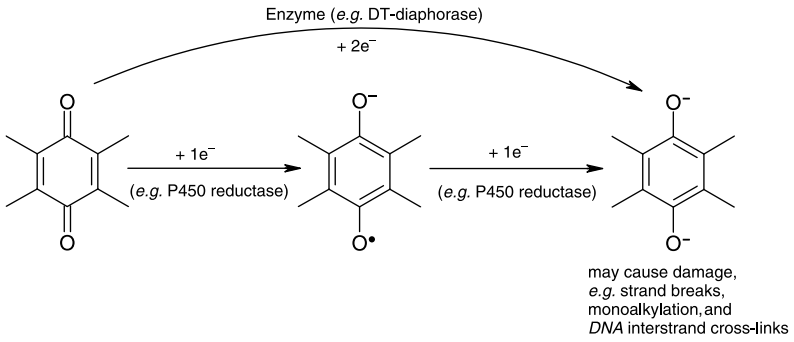
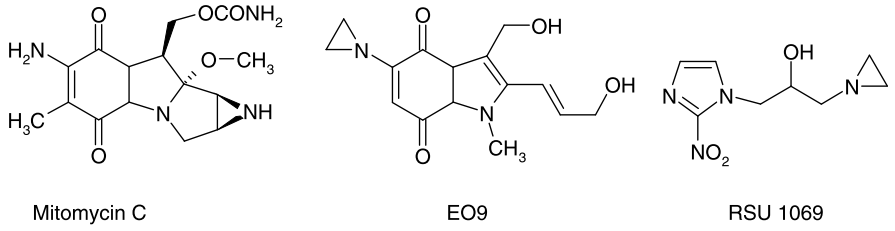
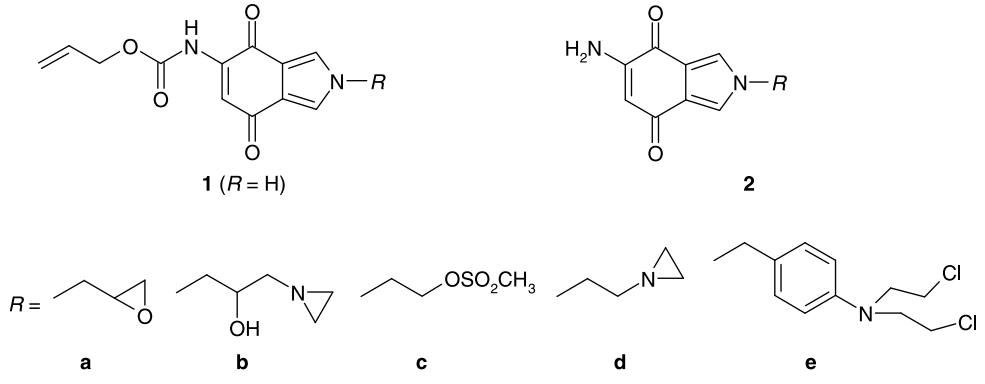


Scheme 1



Scheme 2



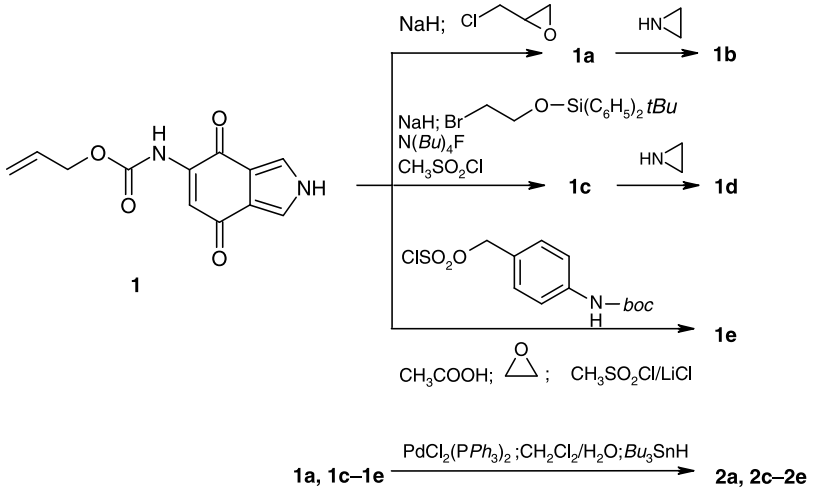
Scheme 3

instead of a [*b*]-annelated pyrrole the core of the new ''dual function'' bioreductive drug is a [*c*]-annelated pyrrole skeleton, which is attached to various alkylating functions. Besides that we tested the influence of the ''free'' amino group *vs.* the *Alloc*-protected amino function. As alkylating functions we chose epoxide, aziridine, mesylate, and bis(chloroethyl)amino groups (Scheme 3).

Compound **1a** was accessable by alkylation with epoxy choloropropane. Subsequently, the reaction with aziridine yielded hydroxy aziridine derivative **1b**. The synthesis of **1c** was realized by alkylation of **1** with *TBDPS*O-protected bromoethanol, subsequent deprotection with *TBAF* [9] and mesylation of the resulting alcohol. Reaction of **1c** with aziridine afforded **1d**. The synthesis of **1e** was realized by alkylation of **1** with *BOC*-protected *p*-aminobenzylmesylate, selective cleavage of the N-*BOC* protecting group and subsequent conversion of the amino function to the bis(chloroethyl)amine group (**1e**). All compounds **1a**–**1e** were treated with $PdCl(PPh_3)_2$ and $SnBu_3H$ [10] giving the amino derivatives **2a** and **2c**–**2e** (**2b** could not be isolated, Scheme 4).

Antitumor Activities

All compounds were tested against five human cell-lines: cervix cancer (*KB*), lung cancer (*NCI-H*460),



Scheme 4

Table 1. Values in % inhibition of the specified cell lines by a solution of 3.16 $\mu g/cm^3$ of **1a**–**1e** and **2a**–**2e**

	1a	**1b**	**1c**	**1d**	**1e**	**2a**	**2c**	**2d**	**2e**
KB	28.14	13.24	n.d.	11.59	**80.68**	30.20	0.05	16.12	0.88
*NCI-H*460	21.56	n.d.	n.d.	n.d.	**68.88**	36.78	n.d.	2.95	n.d.
*RKOp*27	92.83	13.58	89.97	18.90	**97.44**	45.53	0.68	24.13	0.17
SF-268	41.93	n.d.	n.d.	n.d.	**43.98**	36.53	n.d.	5.85	n.d.
SK-OV-3	n.d.	n.d.	n.d.	n.d.	**56.95**	29.08	4.00	8.87	n.d.

adenocarcinoma colon (*RKOp*27), brain cancer (*SF*-268), and ovarian carcinoma (*SK-OV*-3).

As shown in Table 1 (values in % inhibition of a solution of 3.16 $\mu g/cm^3$) all compounds showed maximum activity against the adenocarcinoma colon cell-line *RKOp*27. Besides that cleavage of the *Alloc*-protecting group results in lower activity. But above all **1e** showed remarkable antitumor activity against all tested human cell-lines and therefore will serve as starting point for further "dual function" bioreductive drugs.

Experimental

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Column chromatography was performed on silica gel 60 from Merck (70–230 mesh ASTM) or on Alumina B, Activity III from ICN. Melting points were determined using a *Kofler*-type Leica Galen III micro hot stage microscope. NMR spectra were recorded on a Bruker AC-80 spectrometer (^{1}H 200 MHz, ^{13}C 50 MHz) and chemical shifts are reported in ppm using *TMS* as internal standard. Mass spectra were recorded on a Shimadzu DI 50-QP 5000 or a Shimadzu GCMS-QP5050A. IR spectra were recorded on a Perkin-Elmer 298 or Perkin-Elmer FT-IR Spektrometer Spectrum 1000.

Allyl [2-(oxiran-2-ylmethyl-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate (**1a**, $C_{15}H_{14}N_2O_5$)

2-Chloromethyloxirane (1.27 cm^3, 16.26 mmol) were added dropwise under Ar to a solution of 500 mg **1** (2.0 mmol) in 4 cm^3 dry *DMSO*. After complete addition 224 cm^3 (4 mmol) pulverized KOH were added and stirring at room temperature was continued for further 2 h. In the following the reaction mixture was treated with 8 cm^3 H_2O and extracted with CH_2Cl_2/*Me*OH (7/3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc/*Me*OH = 7/3) to afford 394 mg **1a** (64%) as yellow crystals. Mp 198–200°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 2.57$ (m, 1H), 2.81 (m, 1H), 3,34 (s, 1H), 4.08 (dd, $J = 6.2$, 14.4 Hz, 1H), 4.38 (dd, $J = 3.5$, 14.5 Hz, 1H), 4.64 (d, $J = 5.3$ Hz, 2H), 5.24 (dd, $J = 1.4$, 10.4 Hz, 1H), 5.40 (dd, $J = 1.6$, 17.2, 1H), 5.85–6.05 (m, 1H), 7.0 (s, 1H), 7.51 (d, $J = 1.6$ Hz, 1H), 7.71 (d, $J = 1.6$ Hz, 1H), 8.83 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 45.0$, 50.3, 51.4, 65.8, 115.5, 118.0, 118.5, 120.6, 124.9, 126.9, 132.4, 142.6, 152.4, 175.4, 181.7 ppm; IR (KBr): $\bar{\nu} = 1194$, 1516, 1601, 1639, 1742, 3290 cm^{-1}; MS: m/z (%) = 302 (M^+, 35), 245 (8), 243 (27), 78 (25), 68 (23), 63 (24), 57 (100), 56 (26), 55 (25).

Allyl [2-(3-aziridin-1-2-hydroxypropyl)-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate (**1b**, $C_{17}H_{19}N_3O_5$)
Aziridine (0.46 cm^3, 8.85 mmol) was added under Ar to a solution of 394 mg **1** (1.3 mmol) in 7 cm^3 *Et*OH (cont. 1% triethyl amine). After refluxing for 1 h the reaction mixture was concentrated. The resulting crude product was purified by column chromatography (aluminum oxide, *Et*OAc/*Me*OH = 9/1) to afford 194 mg **1b** (43%) as orange crystals. Mp 164–166°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 1.13$ (m, 2H), 1.60 (m, 2H), 2.0 (dd, $J = 5.4$, 11.9 Hz, 1H), 2.28 (dd, $J = 5.8$, 12.0 Hz, 1H), 3.88–4.25 (m, 3H), 4.63 (d, $J = 5.3$ Hz, 2H), 5.16 (s, 1H), 5.24 (dd, $J = 1.3$, 10.5 Hz, 1H), 5.40 (dd, $J = 1.5$, 17.0 Hz, 1H), 5.85–6.05 (m, 1H), 6.98 (s, 1H), 7.45 (d, $J = 1.5$ Hz), 7.64 (d, $J = 1.5$ Hz, 1H), 8.76 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 26.4$, 26.7, 54.1, 64.3, 65.8, 69.5, 115.5, 118.0, 120.2, 125.2, 127.4, 132.4, 142.5, 152.4, 175.3, 181.7 ppm ; IR (KBr): $\bar{\nu} = 1194$, 1261, 1516, 1636, 1664, 1731, 3113, 3284 cm^{-1}; MS: m/z (%) = 345 (M^+, 2), 86 (24), 69 (15), 58 (21), 57 (85), 56 (100), 55 (27), 45 (16).

2-[5-[[(Allyloxy)carbonyl]amino]-4,7-dioxo-4,7-dihydro-2H-isoindol-2-yl]ethylmethanesulfonate (**1c**, $C_{15}H_{16}N_2O_7S$)

Allyl [2-[2-[[tert-butyl(diphenyl)silyl]oxy]ethyl]-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate ($C_{30}H_{32}N_2O_5Si$)
A solution of 0.5 g **1** (2.03 mmol) in 3.6 cm^3 dry *DMF* was added dropwise to a mixture of 0.07 g (3.05 mmol) NaH (60% dispersion in oil; washed with hexane) in 4.5 cm^3 dry *DMF*. After stirring for 0.5 h at 0°C a solution of 1.12 g 2-(bromoethoxy)(*tert*-butyl)diphenylsilane (3.05 mmol) in 5.1 cm^3 dry *DMF* was added and stirring was continued for 24 h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc/*LP* = 1/1) to afford 850 mg of the N-alkylation product (79%) as yellow crystals. Mp 249–251°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 0.9$ (s, 9H), 3.87 (t, $J = 4.5$ Hz, 2H), 4.21 (t, $J = 4.6$ Hz, 2 H), 4.65 (d, $J = 5.3$ Hz, 2H), 5.24 (dd, $J = 1.7$, 10.5 Hz, 1H), 5.40 (dd, $J = 1.7$, 17.3 Hz, 1H), 5.89–6.01 (m, 1H), 7.02 (s, 1H), 7.33–7.42 (m, 10H), 7.51 (d, $J = 1.7$ Hz, 1H), 7.71 (d, $J = 1.7$ Hz), 8.84 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 18.7$, 26.5, 51.98, 63.2, 65.8, 115.6, 118.0, 118.3, 120.6, 125.1, 127.2, 127.9, 129.9, 132.4, 134.97, 142.6, 152.2, 175.3, 181.7 ppm; IR (KBr): $\bar{\nu} = 1109$, 1192, 1259, 1504, 1632, 1667, 1734, 3355 cm^{-1}; MS: m/z (%) = 529 (M^+, 2), 473 (36), 472 (100), 471 (67), 414 (21), 413 (57), 57 (26), 41 (79).

Allyl [2-(2-hydroxyethyl)-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate ($C_{14}H_{14}N_2O_5$)
A solution of 850 mg (1.61 mmol) of the product obtained above in 9.2 cm^3 dry *THF* and 3.22 cm^3 1 *M TBAF* (3.22 mmol) in *THF* was stirred for 2 h under Ar at room temperature. The reaction mixture was treated with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc/*Me*OH = 9/1) to afford 424 mg of deprotected alcohol (91%) as yellow crystals. Mp 172–174°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 3.69$ (m, 2H), 4.06 (t, $J = 5.1$ Hz), 4.64 (d, $J = 5.3$ Hz), 5.0 (t, $J = 5.1$ Hz), 5.23 (dd, $J = 1.6$, 10.4 Hz, 1H), 5.40 (dd, $J = 1.6$, 17.2 Hz, 1H), 5.85–6.04 (m, 1H), 6.98 (s, 1H), 7.4 (d, $J = 1.8$ Hz, 1H), 7.68 (d, $J = 1.8$ Hz, 1H), 8.77 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 52.4$, 60.3, 65.7, 115.4, 118.0, 120.4, 124.98, 127.0, 132.4, 142.5, 152.4, 175.3, 181.7 ppm; (KBr): $\bar{\nu} = 1045$, 1190, 1516, 1611, 1668, 1731, 3269, 3370 cm^{-1}; MS: m/z (%) = 290 (M^+, 24), 79 (17), 70 (26), 61 (37), 57 (25), 55 (20), 51 (16), 45 (100).

Freshly distilled methanesulfonic acid chloride (0.14 cm^3, 1.76 mmol) was added dropwise under Ar at 0°C to a suspension of 424 mg (1.46 mmol) of the alcohol obtained above and 0.31 cm^3 triethyl amine (2.21 mmol) in 4.7 cm^3 dry CH_2Cl_2. Stirring was continued for 1 h. The reaction mixture was diluted with CH_2Cl_2, extracted with sat. $CuSO_4$-solution and H_2O. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc) to afford 377 mg **1c** (70%) as yellow crystals. Mp 169–170°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 3.14$ (s, 3H), 4.39 (t, $J = 4.6$ Hz, 2H), 4.56 (t, $J = 4.6$ Hz, 2H), 4.64 (d, $J = 5.3$ Hz, 2H), 5.23 (dd, $J = 1.6$, 10.4 Hz, 1H), 5.40 (dd, $J = 1.6$ Hz, 17.2 Hz, 1H), 5.85–6.04 (m, 1H), 7.0 (s, 1H), 7.57 (d, $J = 1.8$ Hz, 1H), 7.77 (d, $J = 1.8$ Hz), 8.8 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 36.6$, 48.8, 65.8, 68.8, 115.5, 118.0, 118.5, 120.7, 124.8, 126.9, 132.4, 142.6, 152.4, 175.3, 181.7 ppm; (KBr): $\bar{\nu} = 1166$, 1190, 1346, 1509, 1639, 1664, 1724, 3277 cm^{-1}; MS: m/z (%) = 368 (M^+, 5), 120 (4), 79 (11), 51 (3), 45 (5), 44 (7), 42 (5), 41 (100).

Allyl [2-(2-aziridin-1-ylethyl)-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate (**1d**, $C_{16}H_{17}N_3O_4$)
Aziridine (3 cm^3, 59 mmol) was added under Ar at room temperature to a suspension of 545 mg **1c** (1.5 mmol) in 6 cm^3 dry acetonitril/triethyl amine (1/1). After stirring for 24 h the reaction mixture was concentrated. The resulting crude product was purified by column chromatography (aluminum oxide, *Et*OAc/*Me*OH = 9/1) to afford 157 mg **1d** (34%) as yellow crystals. Mp 180–182°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.05$ (m, 2H), 1.74 (m, 2H), 2.57 (t, $J = 5.7$ Hz, 2H), 4.12 (t, $J = 5.7$ Hz, 2H), 4.68 (d, $J = 5.8$ Hz, 2H), 5.25–5.40 (m, 2H), 5.86–6.05 (m, 1H), 7.23 (s, 1H), 7.27 (d, $J = 1.9$ Hz, 1H), 7.41 (d, $J = 1.9$ Hz, 1H), 7.89 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 27.1$, 50.99, 61.1, 66.5, 115.9, 119.0, 122.0, 123.98,125.7, 131.7, 141.8, 152.1, 176.1, 182.6 ppm; IR (KBr): $\bar{\nu} = 1045$, 1194, 1519, 1614, 1664, 1721, 3113 cm^{-1}; MS: m/z (%) = 315 (M^+, 11), 70 (8), 69 (8), 57 (13), 56 (100), 43 (7), 42 (7), 41 (23).

Allyl [2-[4-[bis(2-chloroethyl)amino]benzyl]-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate (**1e**, $C_{23}H_{23}N_3O_4Cl_2$)

1. Allyl [2-[4-[(tert-butoxycarbonyl)amino]benzyl]-4,7-dioxo-4,7dihydro-2H-isoindol-5-yl]carbamate
A solution of 1.40 g **1** (5.69 mmol) in 10 cm^3 dry *DMF* was added under Ar dropwise to a mixture of 0.21 g (8.54 mmol)

NaH (60% dispersion in oil; washed with hexane) in 13 cm^3 dry *DMF*. After stirring for 0.5 h at 0°C a solution of 2.57 g 4-[*tert*-butoxycarbonyl)amino]benzyl methansulfonate (8.54 mmol) in 14.2 cm^3 dry *DMF* was added and stirring was continued for 14 h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc/*LP* = 1/1 + 0.5% triethyl amine) to afford 2.37 g **1a** (92%) as yellow crystals. Mp 191–193°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 1.44$ (s, 9H), 4.62 (d, J = 5.3 Hz, 2H), 5.13 (s, 2H), 5.22 (dd, $J = 1.5$, 10.5 Hz, 1H), 5.40 (dd, $J = 1.6$, 17.2 Hz, 1H), 5.84–6.03 (m, 1H), 6.98 (s, 1H), 7. 29 (d, $J = 8.5$ Hz, 2H), 7.44 (d, $J = 8.5$ Hz, 2H), 7.56 (d, $J = 1.6$ Hz, 1H), 7.78 (d, $J = 1.6$ Hz, 1H), 8.78 (s, 1H), 9.38 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 28.1$, 52.7, 65.7, 79.1, 115.4, 117.96, 118.3, 118.6, 120.8, 124.3, 126.3, 128.7, 130.1, 132.4, 139.6, 142.5, 152.4, 175.3, 181.6 ppm; IR (KBr): $\bar{\nu} = 1162$, 1523, 1632, 1671, 1703, 1738, 3291, 3362 cm^{-1}; MS: m/z (%) = 451 (M^+, 3), 395 (2), 150 (18), 106 (100), 57 (90), 56 (19), 44 (17), 41 (39).

2. Allyl [2-(4-aminobenzyl)-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate

To a solution of 2.37 g (5.25 mmol) of the product obtainded above in 24 cm^3 of dry CH_2Cl_2 were added dropwise under Ar 4.8 cm^3 trifluoroacetic acid (62 mmol). After stirring for 2 h at room temperature the reaction mixture was concentrated. The residue was dissolved in ethyl acetate and the organic layer washed with sat. $NaHCO_3$-solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was purified by column chromatography (aluminum oxide, *Et*OAc/*LP* = 7/3) to afford 1.19 g (65%) of the product as yellow crystals. Mp 194–196°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 4.62$ (d, $J = 5.3$ Hz, 2H), 4.99 (s, 2H), 5.15 (s, 2H), 5.22 (dd, $J = 1.4$, 10.4 Hz, 1H), 5.38 (dd, $J = 1.8$, 17.3 Hz, 1H), 6.53 (d, $J = 8.4$ Hz, 2H), 6.96 (s, 1H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 1.8$ Hz,1H), 7.71, d, $J = 1.8$ Hz, 1H), 8.75 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 53.1$, 65.8, 113.8, 115.4, 118.0, 118.5, 120.7, 123.3, 124.1, 126.1, 129.3, 132.4, 142.5, 148.8, 152.4, 175.3, 181.7 ppm; IR (KBr): $\bar{\nu} = 1155$, 1201, 1519, 1629, 1664, 1728, 3348, 3433 cm^{-1}; MS: m/z (%) = 351 (M^+, 4), 107 (8), 106 (100), 61 (12), 45 (11), 44 (8), 43 (63), 41 (16).

3. Allyl [2-[4-[bis(2-hydroxyethyl)amino]benzyl]-4,7-dioxo-4,7-dihydro-2H-isoindol-5-yl]carbamate

To a solution of 1.19 g (3.39 mmol) of the product obtained above in 64 cm^3 *Et*OH/H_2O (3/1) were added 1.5 cm^3 ethylene oxide at 0°C. After refluxing for 24 h a portion of 1 cm^3 ethylene oxide was added and refluxing was continued for further 15 h. In the following the reaction mixture was concentrated and the residue was dissolved in ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc) to afford 1.15 g (77%) of the product as yellow crystals. Mp 184–186°C; ^{1}H NMR (200 MHz, d_6-*DMSO*): $\delta = 3.38$ (m, 4H), 3.49 (m, 4H), 4.62 (d, $J = 5.3$ Hz, 2H), 4.71 (t, $J = 5.3$ Hz, 2H), 5.03 (s, 2H), 5.23 (dd, $J = 1.4$, 10.4 Hz, 1H), 5.39 (dd, $J = 1.6$, 17.2 Hz, 1H), 5.84–6.03 (m, 1H), 6.64 (d, $J = 8.8$ Hz, 2H), 6.96 (s, 1H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.53 (d, $J = 1.8$ Hz, 1H), 7.75 (d, $J = 1.8$ Hz, 1H), 8.77 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 52.8$, 53.2, 58.1, 65.7, 111.2, 115.4, 117.98, 118.5, 120.7, 122.7, 124.1, 126.0, 129.5, 132.4, 142.5, 147.9, 152.4, 175.3, 181.4 ppm; IR (KBr): $\bar{\nu} = 1049$, 1194, 1517, 1615, 1636, 1738, 3355 cm^{-1}; MS: m/z (%) = 439 (M^+, 0.05), 176 (7), 162 (14), 118 (17), 58 (14), 57 (71), 44 (100), 41 (29).

4. To a solution of 210 mg (0.48 mmol) of the diol obtainded above in 2.2 cm^3 dry CH_2Cl_2 and 0.17 cm^3 triethyl amine (1.2 mmol) were added under Ar at 0°C 0.08 cm^3 methaneslufonic acid chloride (1.07 mmol). After 15 min the reaction mixture was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was purified by column chromatography (silica gel, *Et*OAc/LP = 1/1) to afford 193 mg **1e** (85%) as yellow crystals. Mp 185–187°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.64$ (m, 4H), 3.72 (m, 4H), 4.68 (d, $J = 5.8$ Hz, 2H), 4.98 (s, 2H), 5.25–5.41 (m, 2H), 5.85–6.05 (d, $J = 5.8$ Hz, 2H), 6.66 (d, $J = 8.7$ Hz, 2H), 7.13 (d, $J = 8.7$ Hz, 2H), 7.19 (d, $J = 1.9$ Hz, 1H), 7.21 (s, 1H), 7.30 (d, $J = 1.9$ Hz, 1H), 7.87 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 40.2$, 53.3, 54.0, 66.5, 112.2, 115.9, 118.9, 119.1, 121.98, 122.95, 123.5, 124,95, 129.96, 131.7, 141.7, 146.5, 152.1, 176.1, 182.6 ppm; IR (KBr): $\bar{\nu} = 1190$, 1512, 1615, 1643, 1735, 3333 cm^{-1}; MS: m/z (%) = 475 (M^+, 10), 428 (17), 426 (47), 232 (55), 230 (74), 118 (100), 63 (17), 41 (46).

General Procedure for the Cleavage of the Alloc-Protecting Group

A portion of 1.1 equ. of tributyltin hydride was added under Ar to a suspension of 1 equivalent of **1a**, or **1c**–**1e**, respectively, 0.02 equ. of bis(triphenylphosphin)palladium chloride, 2 equ. of H_2O, and 0.3 equ. of CH_2Cl_2. After stirring for 15 min at room temperature the reaction mixture was concentrated and subsequently purified.

5-Amino-2-(oxiran-2-ylmethyl)-2H-isoindole-4,7-dione (**2a**, $C_{11}H_{10}N_2O_3$)

Column chromatography (aluminum oxide; *Et*OAc/*Me*OH = 9/1) afforded 51% yield of **2a** as orange crystals. Mp 210°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.55$ (m, 1H), 2.80 (t, $J = 4.5$ Hz,1H), 3.32 (s, 1H), 4.01 (dd, $J = 6.2$, 14.4 Hz, 1H), 4.32 (dd, $J = 3.5$, 14.3 Hz, 1H), 5.46 (s, 1H), 6.78 (s, 2H), 7.24 (d, $J = 1.6$ Hz, 1H), 7.55 (d, $J = 1.6$ Hz, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 45.0$, 50.5, 51.3, 102.4, 122.6, 123.2, 125.98, 152.0, 177.5, 180.9 ppm; IR (KBr): $\bar{\nu} = 1169$, 1205, 1537, 1597, 1618, 3376 cm^{-1}; MS: m/z (%) = 218 (M^+, 100), 161 (7), 69 (42), 65 (43), 57 (100), 55 (71), 51 (43), 45 (40).

2-(5-Amino-4,7-dioxo-4,7-dihydro-2H-isoindol-2-yl)ethyl methanesulfonate (**2c**, $C_{11}H_{12}N_2O_5S$)

Column chromatography (aluminum oxide; *Et*OAc/*Me*OH = 9/1) afforded 59% yield of **2c** as orange crystals. Mp 179–181°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.13$ (s, 3H), 4.33 (t, $J = 4.6$ Hz, 2H), 4.53 (t, $J = 4.6$ Hz, 2H), 5.45 (d, $J = 0.7$ Hz,

1H), 6.76 (s, 2H), 7.31 (s, 1H), 7.62 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 36.6$, 48.6, 68.9, 102.4, 119.2, 122.7, 123.0, 125.98, 151.96, 177.4, 180.8 ppm; IR (KBr): $\bar{\nu} = 1166$, 1335, 1537, 1611, 3312, 3433 cm^{-1}; MS: m/z (%) = 285 ($M^+ + 1$, 100), 225(4), 208 (6), 207 (47), 191 (6), 97 (5), 71 (4), 69 (4).

5-Amino-2-(2-aziridin-1-ylethyl)-2H-isoindole-4,7-dione (**2d**, $C_{12}H_{13}N_3O_2$)

Column chromatography (aluminum oxide; *Et*OAc/*Me*OH = 9/1 + 0.5% triethyl amine) afforded 64% of **2d** as orange crystals. Mp 135–137°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.04$ (m, 2H), 1.50 (m, 2H), 2.42 (t, $J = 5.9$ Hz, 2H), 4.04 (t, $J = 5.9$ Hz, 2H), 5.4 (s, 1H), 6.69 (s, 2H), 7.22 (d, $J = 1.5$ Hz, 1H), 7.54 (d, $J = 1.5$ Hz, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 26.3$, 49.7, 60.5, 102.3, 118.9, 122.4, 123.3, 126.1, 151.98, 177.4, 181.0 ppm; IR (KBr): $\bar{\nu} = 1173$, 1205, 1537, 1604, 1629, 3390 cm^{-1}; MS: m/z (%) = 231 (M^+, 14), 175 (2), 56 (91), 51 (10), 45 (12), 43 (100), 42 (54), 41 (41).

5-Amino-2-[4-[bis(2-chloroethyl)amino]benzyl]-2H-isoindole-4,7-dione (**2e**, $C_{19}H_{19}N_3O_2Cl_2$)

Column chromatography (aluminum oxide; *Et*OAc/*LP* = 97/3) afforded 68% yield of **2e** as orange crystals. Mp 208–210°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.64$ (m, 4H), 3.72 (m, 4H), 4.95 (s, 2H), 5.01 (s, 2H), 5.66 (s, 1H), 6.66 (d, $J = 8.8$ Hz, 2H), 7.11 (m, 3H), 7.25 (s, 1H) ppm; ^{13}C NMR (50 MHz, d_6-*DMSO*): $\delta = 41.0$, 51.98, 52.4, 102.2, 111.8, 119.1, 122.4, 122.7, 124.9, 125.2, 129.7, 146.2, 151.9, 177.3, 180.8 ppm; IR (KBr): $\bar{\nu} = 1162$, 1194, 1371, 1526, 1579, 1608, 3411 cm^{-1}; MS: m/z (%) = 391 (M^+, 18), 342 (29), 232 (45), 230 (64), 118 (100), 63 (25), 57 (53), 43 (40).

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