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ORIGINAL PAPER

Synthesis of anticancer compounds, III (Bioorg Med Chem Lett 17, 6091, 2007), carbinol derivatives of azanaphthoquinone annelated pyrroles

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Abstract A series of carbinols has been synthesized by attachment of different piperidinyl side chains to the quinone structure of azanaphthoquinone annelated pyrroles. The synthesized compounds were screened for their cytotoxic activities. Compared to previously published results, they exhibited only moderate activities, thus showing that the existence of the quinone moiety seems to be essential for anticancer activities of this group.

Keywords Azanaphthoquinone · Anticancer agents · Heterocycles · Carbinols

Introduction

The anthracene-9,10-dione derivative, mitoxantrone (**1**), plays an important role in fighting cancer. The anticancer activity of mitoxantrone is probably multiplex, including DNA intercalation complexes, interference of topoisomerase II, and free radical intermediate formation [2, 3]. Beside cytotoxic side effects, the major drawback of mitoxantrone (**1**) and related anthraquinone anticancer compounds is cardiotoxicity. Moreover, some results suggest that the cardiotoxicity might be related to the 5,8-dihydroxy substitution pattern in this compound [4]. In the search for analogs with lower cardiotoxicity, BBR 2778 (**2**) was developed as an aza-bioisosteric chemotype of mitoxantrone lacking the 5,8-dihydroxy substitution pattern [4]. This compound is currently in phase III clinical trials in patients with non-Hodgkin's lymphoma and exhibits a better therapeutic index and no cardiotoxicity [5] (Scheme 1).

As a part of the studies on the synthesis of pharmaceutical active compounds as potential anticancer compounds [6–8], azanaphthoquinone annelated pyrrolo oximes **3** were successfully synthesized by our group [1]. With the annelated aromatic systems, oximes **3** should have a sufficiently large planar shape, and therefore these compounds seem to be potentially intercalating agents. But it could be demonstrated by standard DNA intercalating UV experiments that these oximes did not intercalate. Indeed, these compounds exert their antiproliferative/cytotoxic effects by arresting cells in the G2/M phase and activation of apoptosis pathways [1]. The biological evaluation showed remarkable anticancer activities of these oximes. However, the major drawbacks of these oximes were the formation of E and Z isomers, respectively, and in general the easy metabolic cleavage of the oxime group. To overcome these disadvantages, we decided to explore the replacement of the oxime pattern by a piperidinyl carbinol or piperidylidene moiety, respectively, to furnish the proposed target structure of types **4** and **5**. Both modifications should lead to more stable compounds, and moreover, because of the symmetry, no E/Z isomers could exist. Variation of *N*-substituents of the piperidine ring should be investigated in an attempt to improve the potency of activity.

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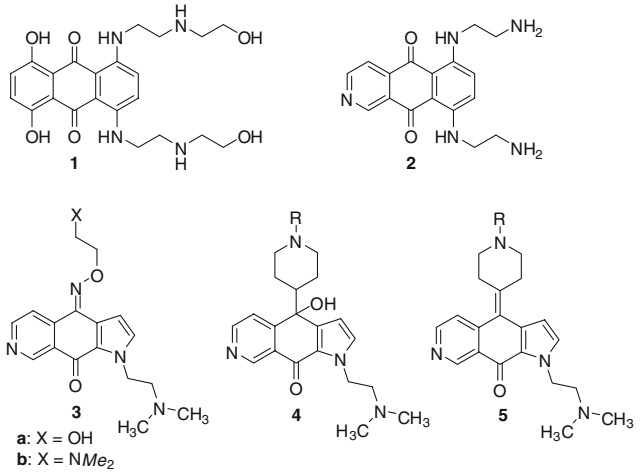
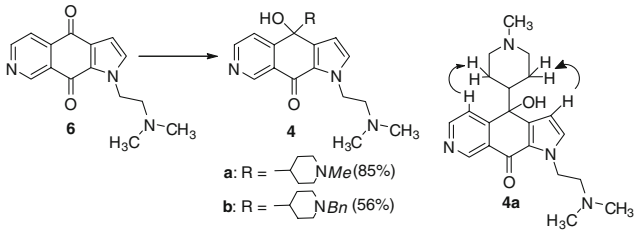


Scheme 1



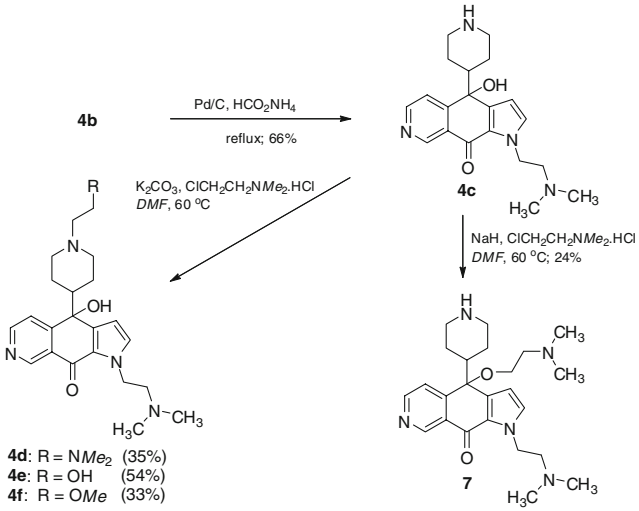
Scheme 2

Results and discussions

Compound **6** was prepared as previously described [1]. Reaction with *Grignard* reagents prepared from 4-chloropiperidine derivatives gave carbinol **4a** and *N*-benzyl protected derivative **4b**, respectively (Scheme 2).

Compound **4a** was investigated for structure elucidation. The structure elucidation was confirmed by nuclear *Overhauser* enhancement (NOE) experiments. Only irradiation at C(3)–H and C(5)–H showed significant enhancements of piperidinyl protons, while there was no such enhancement effect when irradiated at C(8)–H (Scheme 2). These results indicated unambiguously that the Grignard reaction occurred regioselectively at the C-4 carbonyl group of compound **6**. We suggest that steric hindrance caused by the amino ethyl group attached to the pyrrole ring as well as the electronic activation by the *p*-positioned nitrogen of the pyridine ring system favored the attack of the *Grignard* reagent at C-4 of quinone **6**.

To prepare a series with different groups attached at the nitrogen of the piperidine ring, cleavage of the *N*-benzyl protecting group of **4b** has to be worked out. The cleavage of the *N*-benzyl group under traditional high pressure catalytic hydrogenation using H_2/Pd-C in methanol failed. Alternatively, debenzylation was successful by catalytic transfer hydrogenation utilizing anhydrous ammonium

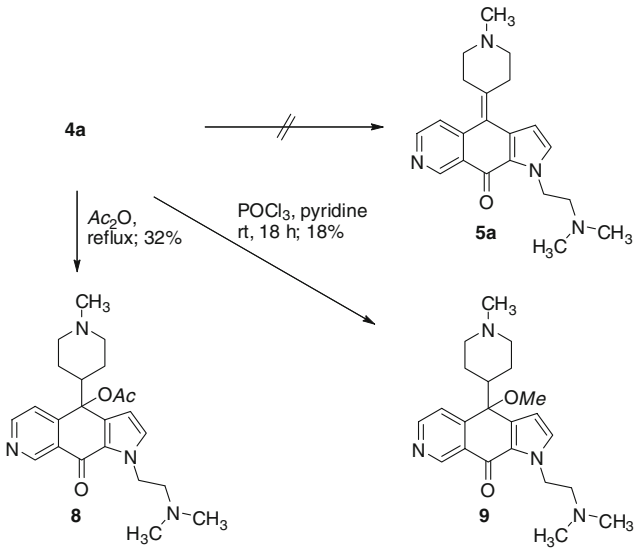


Scheme 3

formate and 10% Pd-C in methanol [9] to give **4c** as shown in Scheme 3. Compound **4c** prompted us to attach side chains at the piperidine ring by *N*-alkylation. However, under strong conditions, sodium hydride in DMF at 60 °C, the reaction of **4c** with *N*,*N*-dimethylaminoethyl chloride gave selectively *O*-alkylation, thus furnishing carbinol ether **7**. In order to obtain the *N*-alkylated product **4d**, we employed the mild conditions using K_2CO_3 in DMF at room temperature for 60 h, thus leading solely to **4d**. This method was also employed for the synthesis of carbinols **4e** and **4f**.

The structure elucidations of *O*-alkylated **7** and *N*-alkylated **4d** were based on ^{13}C NMR experiment regarding those of staring material **4c**. In comparison with **4c**, the signal of C-4 in compound **7** showed a significant shift from 73.5 to 80.2 ppm (no shift of C-4 could be observed in **4d**). *N*-alkylated products of type **4** showed a significant shift of the carbon atoms adjacent to the nitrogen of the piperidine ring.

In the following, the carbinol **4a** was submitted to dehydration reaction (Scheme 4). A series of reactions (pyridinium-4-toluene sulfonate (PPTS)/toluene; 4-toluene sulfonic acid in toluene/acetonitrile [10], glacial acetic acid/2 N H_2SO_4 [11]; trifluoroacetic acid/CH_2Cl_2 [12]) have been tried, but unfortunately dehydrated product **5a** could not be obtained. Reaction of **4a** with acetic anhydride for 4 h [13] gave only acetate **8** as shown in Scheme 4. Carbinol **4a** was also treated with $POCl_3$ in pyridine for dehydration [14], but workup via column chromatography (eluting with *Et*OAc/*Me*OH; 1/1) just furnished methyl ether **9**. We suppose that compound **9** was obtained after reaction of the primarily formed chloride intermediate with methanol during the chromatographic separation. After many attempts, it was strongly suggested that dehydration reaction is prohibited due to the rigid and flat structure of



Scheme 4

the envisaged products of type **5**, which exhibit a massive steric hindrance between the aromatic protons of C-3/C-5 and the near methylene groups of the piperidinyl ring.

The synthesized compounds **4a–f**, **7**, **8**, **9**, were screened for antiproliferative activities against three cancer cell lines, cervix cancer (*KB*), brain cancer (*SF*-268), and ovarian carcinoma (*SK-OV*-3), by tetrazolium-based (XXT) cytotoxicity assays. The primary screen was carried out at the concentration of 3.16 μg/cm^3. It was observed in the course of the experiments that these compounds exhibited lower than 50% of inhibition at this concentration. In comparison with compounds of type **3**, it is evident that lack of the quinone moiety of the target structure led to a massive decrease of the biological activity.

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX200 spectrometer (^{1}H 200 MHz, ^{13}C 50 MHz). Chemical shifts are reported in ppm using *TMS* as internal standard. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. Mass spectra were recorded on a Shimadzu DI 50-QP 5000 or Shimadzu GCMS-QP5050A. Melting points were determined using a *Kofler*-type Leica Galen III micro hot-stage microscope. Thin layer chromatography was performed on aluminum-oxide plates from Merck (no. 1.05550: 0.2 mm). Column chromatography was performed on Aluminia B, activity III from ICN. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification.

*General procedure for the synthesis of carbinols **4a** and **4b***

The *Grignard* reagents were generated as described: The alkyl halide (4 mmol) in dry THF (1 cm^3) was added dropwise to Mg turnings (4 mmol) in THF (2 cm^3) under Ar. The mixture was stirred and refluxed for 1 h. The obtained *Grignard* mixture was transferred to a reaction flask and cooled to 0 °C in an ice bath. Compound **6** (1 mmol) in dry THF (5 cm^3) was added dropwise under Ar. The reaction mixture was stirred as described. Then a saturated aqueous solution of NH_4Cl was added. The organic layers were dried (Na_2SO_4), filtered, and concentrated.

1-[2-(Dimethylamino)ethyl]-4-hydroxy-4-(1-methylpiperidin-4-yl)-1H-pyrrolo[3,2-g]isoquinolin-9(4H)-one (**4a**, $C_{21}H_{28}N_4O_2$)

The reaction mixture was refluxed for 4 h. After column chromatography (aluminum oxide, *Et*OAc/*Me*OH; 9/1) 0.312 g of **4a** (85%) were obtained as oil. M.p.: 89–91 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.70$–0.95 (m, 1H), 0.96–1.14 (m, 1H), 1.55–1.90 (m, 4H), 2.07 (s, 3H), 2.19 (s, 6H), 2.32–2.48 (m, 1H) 2.50–2.65 (m, 1H), 2.55 (t, $J = 6.8$ Hz, 2H), 2.72–2.92 (m, 1H), 4.27–4.60 (m, 2H), 6.33 (d, $J = 2.6$ Hz, 1H), 6.98 (d, $J = 2.6$ Hz, 1H), 7.66 (d, $J = 5.2$ Hz, 1H), 8.64 (d, $J = 5.2$ Hz, 1H), 9.20 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.2$, 26.6, 45.3, 46.0, 46.6, 49.1, 55.5, 55.8, 59.7, 73.4, 107.8, 120.6, 124.5, 128.0, 131.1, 138.8, 148.1, 152.0, 156.4, 173.8 ppm; IR (KBr): $\bar{\nu} = 3{,}416$, 2,938, 2,788, 1,647, 1,587 cm^{-1}; MS: *m/z* (%) = 368 (M^+, 0.3), 350 (1.3), 272 (2.6), 196 (9.7), 58 (100).

4-(1-Benzylpiperidin-4-yl)-1-[2-(dimethylamino)ethyl]-4-hydroxy-1H-pyrrolo[3,2-g]isoquinolin-9(4H)-one (**4b**, $C_{27}H_{32}N_4O_2$)

The reaction mixture was stirred at 0 °C for 30 min and 45 °C for 18 h. After column chromatography (aluminum oxide, *Et*OAc/*Me*OH; 9/1) 0.250 g of **4b** (56%) was obtained as oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.72$–0.95 (m, 1H), 1.00–1.18 (m, 1H), 1.62–1.97 (m, 4H), 2.26 (s, 6H), 2.62 (t, $J = 6.7$ Hz, 2H), 2.62–2.78 (m, 1H), 2.70–3.08 (m, 2H), 3.38 (s, 2H), 4.30–4.65 (m, 2H), 6.36 (d, $J = 2.6$ Hz, 1H), 7.01 (d, $J = 2.6$ Hz, 1H), 7.12–7.30 (m, 5H), 7.67 (d, $J = 5.2$ Hz, 1H), 8.69 (d, $J = 5.2$ Hz, 1H), 9.25 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.3$, 26.7, 45.3, 46.6, 49.8, 53.5, 53.6, 59.6, 63.1, 73.6, 107.7, 120.6, 124.6, 126.9, 128.0, 128.1, 129.1, 131.1, 137.9, 138.7, 148.1, 151.1, 156.2, 173.8 ppm; IR (KBr): $\bar{\nu} = 3{,}405$, 2,935, 2,799, 1,645, 1,586 cm^{-1}; MS: *m/z*

(%) = 444 (M^+, 0.8), 426 (1.4), 372 (1.0), 272 (5.7), 58 (100).

1-[2-(Dimethylamino)ethyl]-4-hydroxy-4-(piperidin-4-yl)-1H-pyrrolo[3,2-g]isoquinolin-9(4H)-one (**4c**, $C_{20}H_{26}N_4O_2$)

To a stirred suspension of **4b** (0.249 g, 0.56 mmol) and 10% Pd-C (0.301 g) in dry *Me*OH (10 cm^3), anhydrous ammonium formate (0.500 g) was added in a single portion under Ar. The reaction mixture was stirred at reflux for 4 h. Then the catalyst was removed by filtration through celite. The filtrates were removed in vacuo. After chromatographic purification (aluminum oxide, *Et*OAc/*Me*OH; 9/1) **4c** (0.131 g, 66%) was obtained as semisolid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.55–0.80 (m, 1H), 1.00–1.20 (m, 2H), 1.80–2.02 (m, 3H), 2.25 (s, 6H), 2.40–2.58 (m, 1H), 2.59 (t, J = 6.7 Hz, 2H), 2.75–2.90 (m, 1H), 2.94–3.10 (m, 1H), 4.30–4.65 (m, 2H), 6.36 (d, J = 2.5 Hz, 1H), 7.02 (d, J = 2.5 Hz, 1H), 7.68 (d, J = 5.1 Hz, 1H), 8.71 (d, J = 5.1 Hz, 1H), 9.27 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.3, 27.6, 45.4, 46.3, 46.7, 46.5, 50.0, 59.7, 73.5, 107.6, 120.6, 124.6, 128.1, 131.1, 138.8, 148.1, 152.0, 156.3, 173.9 ppm; IR (KBr): $\bar{\nu}$ = 3,412, 2,936, 2,778, 1,645, 1,587 cm^{-1}; MS: *m/z* (%) = 354 (M^+, 1.5), 336 (2.8), 318 (1.6), 58 (100).

*General procedure for the synthesis of carbinols **4d–f***

A solution of the corresponding alkyl halides (0.40 mmol) in DMF (2 cm^3) was added to a suspension mixture of **4c** (0.100 g, 0.28 mmol) and K_2CO_3 (0.128 g, 0.70 mmol) in DMF (2 cm^3) at 0 °C. The reaction mixture was stirred at room temperature until completion of the reaction. Afterward H_2O was added, and all solvents were removed in vacuo. The crude product was purified by column chromatography (aluminum oxide, *Et*OAc/*Me*OH; 9/1).

1-[2-(Dimethylamino)ethyl]-4-{1-[2-(dimethylamino) ethyl]piperidin-4-yl}-4-hydroxy-1H-pyrrolo [3,2-g]isoquinolin-9(4H)-one (**4d**, $C_{24}H_{35}N_5O_2$)

The reaction mixture was stirred at room temperature for 60 h giving **4d** (0.042 g, 35%) as oil. ^{1}H NMR ($CDCl_3$): δ = 0.60–0.95 (m, 1H), 1.00–1.30 (m, 1H), 1.70–1.98 (m, 4H), 2.16 (s, 6H), 2.21 (s, 6H), 2.60 (t, J = 6.6 Hz, 2H), 2.50–2.68 (m, 1H), 2.70–2.85 (m, 1H), 2.90–3.07 (m, 1H), 3.33 (s, 4H), 4.28–4.68 (m, 2H), 6.37 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 7.77 (d, J = 5.2 Hz, 1H), 8.64 (d, J = 5.2 Hz, 1H), 9.20 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ = 26.2, 26.7, 45.3, 45.4, 46.7, 49.4, 52.8, 53.7, 53.8, 59.7, 61.5, 73.5, 107.7, 120.9, 124.5, 128.0, 131.3, 138.8, 148.0, 151.9, 156.0, 173.8; IR (KBr): $\bar{\nu}$ = 3,419, 2,946, 2,788, 1,646, 1,465 cm^{-1}; MS: *m/z* (%) = 425 (M^+, 0.3), 407 (0.8), 367 (5.7), 58 (100).

1-[2-(Dimethylamino)ethyl]-4-hydroxy-4-[1-(2-hydroxyethyl)piper-idin-4-yl]-1H-pyrrolo[3,2-g]isoquinolin-9(4H)-one (**4e**, $C_{22}H_{30}N_4O_3$)

The reaction mixture was stirred at room temperature for 28 h to give **4e** (0.058 g, 54%) as oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.70–0.94 (m, 1H), 0.98–1.14 (m, 1H), 1.70–2.00 (m, 4H), 2.22 (s, 6H), 2.40 (t, J = 5.2 Hz, 2H), 2.50–2.68 (m, 1H), 2.58 (t, J = 6.7 Hz, 2H), 2.67–2.85 (m, 1H), 2.85–3.02 (m, 1H), 3.20–3.65 (br s, 1H), 3.49 (t, J = 5.2 Hz, 2H), 4.25–4.65 (m, 2H), 6.36 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 5.1 Hz, 1H), 8.63 (d, J = 5.1 Hz, 1H), 9.18 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1, 26.5, 45.2, 46.6, 49.4, 53.3, 53.6, 57.7, 59.3, 59.6, 73.4, 107.7, 120.5, 124.6, 128.0, 131.2, 138.4, 148.1, 152.0, 156.2, 173.7 ppm; IR (KBr): $\bar{\nu}$ = 3,422, 2,932, 2,788, 1,734, 1,653 cm^{-1}; MS: *m/z* (%) = 398 (M^+, 0.4), 380 (1.5), 367 (4.8), 350 (3.3), 272 (17.2), 58 (100).

1-[2-(Dimethylamino)ethyl]-4-hydroxy-4-[1-(2-methoxyethyl)pipe-ridin-4-yl]-1H-pyrrolo[3,2-g]isoquinolin-9(4H)-one (**4f**, $C_{23}H_{32}N_4O_3$)

The reaction mixture was stirred at room temperature for 30 h to provide **4f** (0.040 g, 33%) as oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95–1.12 (m, 2H), 1.40–1.65 (m, 1H), 1.78–2.18 (m, 4H), 2.33 (s, 6H), 2.56 (t, J = 5.3 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 2.82–3.00 (m, 1H), 3.02–3.20 (m, 1H), 3.27 (s, 3H), 3.48 (t, J = 5.3 Hz, 2H), 4.35–4.70 (m, 2H), 6.38 (d, J = 2.5 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 7.68 (d, J = 5.2 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 9.24 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ = 25.5, 25.9, 45.2, 46.4, 49.1, 53.8, 54.1, 57.6, 58.8, 59.5, 69.3, 73.6, 107.9, 120.4, 124.6, 127.9, 131.4, 138.0, 148.2, 152.3, 155.8, 173.8 ppm; IR (KBr): $\bar{\nu}$ = 3,418, 2,938, 2,819, 1,647, 1,588 cm^{-1}; MS: *m/z* (%) = 413 (M^++1, 0.7), 394 (1.8), 367 (27.8), 310 (4.7), 58 (100).

4-[2-(Dimethylamino)ethoxy]-1-[2-(dimethylamino)ethyl]-4-(piperidinyl)-1H-pyrrolo[3,2-g]isoquinolin-9(4H)-one (**7**, $C_{24}H_{35}N_5O_2$)

NaH (60% suspension in mineral oil, 0.089 g, 1.1 mmol) was washed three times with dry hexane under Ar before suspended in DMF (1 cm^3). The mixture was cooled to 0 °C, and then **4c** (0.149 g, 0.42 mmol) in DMF (1.5 cm^3) was added dropwise. The reaction mixture was stirred at 0 °C for an additional 0.5 h. *N*,*N*-dimethylaminoethyl chloride (0.091 g, 0.63 mmol) in DMF (2 cm^3) was added slowly. The reaction mixture was stirred at 60 °C for 4 h. Then it was diluted with water. All solvents were concentrated in vacuo. The crude product was purified by column chromatography (aluminum oxide, *Et*OAc to *Et*OAc/*Me*OH, 7/3). Compound **7** (0.043 g, 24%) was obtained as oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.52–0.90 (m, 2H), 0.92–1.18 (m, 2H), 1.80–2.00 (m, 2H), 2.17 (s, 6H), 2.28 (s, 6H), 2.43 (t, J = 6.1 Hz, 2H), 2.46–2.58

(m, 1H), 2.68 (t, $J = 6.7$ Hz, 2H), 2.75–2.88 (m, 1H), 2.90–3.10 (m, 2H), 3.14–3.30 (m, 1H), 4.30–4.65 (m, 2H), 6.26 (d, $J = 2.5$ Hz, 1H), 7.02 (d, $J = 2.5$ Hz, 1H), 7.58 (d, $J = 5.2$ Hz, 1H), 8.74 (d, $J = 5.2$ Hz, 1H), 9.35 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 27.4$, 27.6, 45.7, 45.9, 46.4, 46.7, 47.3, 50.3, 59.2, 60.0, 62.9, 80.2, 107.9, 120.3, 126.3, 129.8, 131.3, 135.2, 148.7, 152.1, 153.5, 173.8 ppm; IR (KBr): $\overline{\nu} = 3{,}415$, 2,935, 2,769, 1,647, 1,585, 1,456 cm^{-1}; MS: *m/z* (%) = 426 ($M^+ + 1$, 0.7), 338 (18.3), 293 (1.5), 58 (100).

1-[2-(Dimethylamino)ethyl]-4-(1-methylpiperidin-4-yl)-9-oxo-4,9-dihydro-1H-pyrrolo[3,2-g]isoquinolin-4-yl acetate (**8**, $C_{23}H_{30}N_4O_3$)

The carbinol **4a** (0.260 g, 0.76 mmol) was dissolved in dry Ac_2O (10 cm^3). The reaction mixture was stirred and refluxed for 4 h. Ac_2O was removed in vacuo. The crude product was purified by column chromatography (aluminum oxide, *EtOAc/MeOH*, 9/1 → 8/2) to give compound **8** (0.100 g, 32%) as oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.70$–1.10 (m, 2H), 1.32–1.50 (m, 1H), 1.55–1.70 (m, 1H), 1.72–1.98 (m, 3H), 2.02 (s, 3H), 2.11 (s, 3H), 2.26 (s, 6H), 2.66 (t, $J = 6.8$ Hz, 2H), 2.50–2.70 (m, 1H), 2.75–2.90 (m, 1H), 4.25–4.65 (m, 2H), 6.11 (d, $J = 2.5$ Hz, 1H), 6.98 (d, $J = 2.5$ Hz, 1H), 7.30 (d, $J = 5.2$ Hz, 1H), 8.66 (d, $J = 5.2$ Hz, 1H), 9.35 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.4$, 25.6, 26.1, 45.6, 45.9, 47.2, 48.3, 55.2, 55.5, 59.9, 79.4, 106.1, 118.1, 124.9, 127.9, 131.1, 134.8, 148.8, 152.0, 152.6, 168.4, 173.6 ppm; IR (KBr): $\overline{\nu} = 3{,}423$, 2,939, 2,782, 1,747, 1,646, 1,587 cm^{-1}; MS: *m/z* (%) = 411 ($M^+ + 1$, 0.2), 350 (19.4), 280 (3.0), 58 (100).

1-[2-(Dimethylamino)ethyl]-4-methoxy-4-(1-methylpiperidin-4-yl)-1H-pyrrolo[3,2-g] isoquinolin-9(4H)-one (**9**, $C_{22}H_{30}N_4O_2$)

The carbinol **4a** (0.282 g, 0.77 mmol) was dissolved in absolute pyridine (5 cm^3). $POCl_3$ (0.6 cm^3, 2.13 mmol) was added dropwise under Ar at 0 °C. The mixture was stirred at room temperature for 18 h. Pyridine was removed in vacuo, and the crude product was purified by column chromatography (aluminum oxide, *Et*OA*c* to *Et*OA*c*/*Me*OH, 1/1). The starting material (0.050 g, 18%) was recovered, and **9** (0.035 g, 12%) was obtained as oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.70$–1.10 (m, 2H), 1.20–1.44 (m, 1H), 1.55–1.97 (m, 4H), 2.11 (s, 3H), 2.29 (s, 6H), 2.50–2.65 (m, 1H), 2.68 (t, $J = 6.8$ Hz, 2H), 2.75–2.90 (m, 1H), 2.93 (s, 3H), 4.35–4.60 (m, 2H), 6.25 (d, $J = 2.5$ Hz, 1H), 7.05 (d, $J = 2{,}5$ Hz, 1H), 7.54 (d, $J = 5.2$ Hz, 1H), 8.74 (d, $J = 5.2$ Hz, 1H), 9.37 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.4$, 26.7, 45.7, 46.1, 47.3, 49.6, 52.4, 55.6, 55.9, 60.0, 80.6, 108.0, 120.2, 126.4, 130.0, 131.3, 134.8, 148.8, 152.2, 153.1, 173.8 ppm; IR (KBr):$\overline{\nu} = 3{,}425$, 2,923, 2,852, 1,653 cm^{-1}; MS: *m/z* (%) = 382 (M^+, 3.7), 350 (4.9), 286 (2.9), 58 (100).

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