Arch Pharm Res Vol 23, No 6, 585-588, 2000

Design and Synthesis of New DNA Photocleavers, 4'-Bromoacetophenone-Pyrrolecarboxamide Hybrid Compounds

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(Received July 22, 2000)

4-Bromoacetophenone-pyrrolecarboxamide conjugates were designed and synthesized as photoinducible DNA cleaving agents which can generate monophenyl radicals capable of causing the hydrogen atom abstraction which initiates the scission of DNA.

Key words: 4-Bromoacetophenone, DNA cleaving agents, Phenyl radical

INTRODUCTION

Small molecules that target specific DNA sequences have the potential to regulate gene expression. There are various approaches to the development of sequence specific DNA cleaving agents using conjugates of DNA cleaver and recognition elements (Bouziane *et al.*, 1995; Boutorine *et al.*, 1996; Nakamura *et al.*, 1996; Frier *et al.*, 1998; Bailly *et al.*, 1998; Hashimoto *et al.*, 1998; Herman *et al.*, 1999). The family of naturally occurring oligopeptides, including netropsin, distamycin, anthelvencin, kikumycin B, amidinomycin and noformycin, has been the focus of research in this area since these oligopeptides exhibit antiviral, antibacterial, and anticancer activities. Netropsin and distamycin and their analogs have attracted particular attention because of a unique biological property related to the AT sequence preferential and their strong minor groove nonintercalative binding ability to DNA (Carrondo *et al.*, 1989; Chen *et al.*, 1992; Edwards *et al.*, 1992).

This is a report on the design and synthesis of 4'-bromoacetophenone-pyrrolecarboxamide hybrid compounds as a sequence specific DNA photocleaver. The phenyl radical precursor, 4-bromoacetophenone has been attached to pyrrole polyamides to create synthetic oligopeptides in order to increase DNA cleaving ability and DNA sequence selectivity. The DNA cleaving moiety and minor groove binders are connected together by a methylene linker to bring some flexibility on this molecule as shown below.

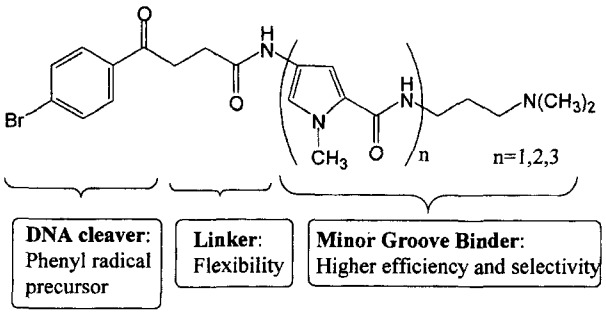

Fig. 1. 4'-Bromoacetophenone-pyrrolecarboxamide conjugates as a photoinducible DNA cleaving agent

MATERIALS AND METHODS

Reagents and solvents

Unless indicated, all reagents and solvents were purchased from Aldrich chemicals. They were used without purification, with the following exceptions. The ethyl ether, tetrahydrofuran, benzene and toluene were distilled over sodium/benzophenone under nitrogen. The acetonitrile, methylene chloride, triethylamine, pyridine, dimethyl formamide, and diisopropylamine were distilled from calcium hydride under nitrogen. The chromatography grade hexanes were distilled through a 50 cm packed column.

Synthesis

1-Methyl-2-trichloroacetylpyrrole (2)

A solution of N-methylpyrrole (20 g, 246 mmol) in 80 mL of anhydrous ethyl ether was added drop by drop to a well-stirred solution of trichloroacetyl chloride (44g, 246 mmol) in 170 mL of ethyl ether in a 500 mL flask,

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over period of 1.5 h. The reaction mixture was stirred for an additional 3 h. The reaction was then quenched by the dropwise addition of a solution of 18 g of potassium carbonate in 70 mL water. The layers were separated, and the ether layer was concentrated *in vacuo* to produce 1-methyl-2-trichloroacetylpyrrole (**2**) (53 g, 234 mmol, 95% yield) as a yellow crystalline solid sufficiently pure to be used without further purification: IR ($CHCl_3$) 1662, 1522, 1456, 1365, 1333 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (dd, J=4.4, 1.7 Hz, 1H), 6.97 (m, 1H), 6.22 (dd, J=4.5, 2.5 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 133.6, 124.0, 121.8, 108.9, 96.3, 38.5.

1-Methyl-4-nitro-2-trichloroacetylpyrrole (3)

Twenty mL of fuming nitric acid was added drop by drop to a cooled (-40°C) solution of 1-methyl-2-trichloroacetylpyrrole (53 g, 234 mmol) in acetic anhydride 300 mL in a 500 mL flask, while a temperature of -40°C was maintained. The reaction mixture was carefully allowed to warm to room temperature and stirred for an additional 4 h. The mixture was then cooled to -30°C and isopropyl alcohol (300 mL) was added. The solution was stirred at -20°C for 30 min, during which time a white precipitate formed. The solution was allowed to stand for 15 min. The resulting precipitate was collected by vacuum filtration to provide compound **3** (39.4 g, 145 mmol, 62 % yield): IR ($CHCl_3$) 1691, 1538, 1316 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J=1.7 Hz, 1H), 7.76 (d, J=1.7 Hz, 1H), 4.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 135.2, 130.3, 121.3, 117.4, 94.8, 39.7. MS (EI) *m/z* 270 (M^+ ,3), 207 (11), 153 (100), 107 (68), 79 (13). HRMS (EI) *m/z* calcd for $C_7H_5Cl_3N_2O_3$ 269.9366, found 269.9371.

3-(1-Methyl-4-nitropyrrole-2-carboxamido) dimethylaminopropane (4)

A solution of 3-dimethylaminopropylamine (597 mg, 5.85 mmol) in THF (2 mL) was added dropwise to a stirred solution of **3** (1.35 g, 5 mmol) in THF 3 mL at 0°C. The reaction mixture was warmed to room temperature and stirring was continued for 1 h. The solvent was removed *in vacuo* and the residual solid was recrystallized from ethanol to give pale yellow needles of **4** (1.23 g, 4.84 mmol, 96% yield): IR ($CHCl_3$) 1647, 1546, 1305 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.77 (br s, 1H), 7.53 (d, J=1.9 Hz, 1H), 6.91 (d, J=1.9 Hz, 1H), 4.01 (s, 3H), 3.49 (q, J=5.7 Hz, 2H), 2.51 (t, J=5.7 Hz, 2H), 2.32 (s, 6H), 1.75-1.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 135.0, 127.1, 126.4, 106.5, 59.5, 45.3, 40.3, 37.8, 24.5. MS (EI) *m/z* 254(M^+ ,12), 153 (19), 107 (15), 84 (8), 72 (14), 58 (100). HRMS (EI) *m/z* calcd for $C_{11}H_{18}N_4O_3$ 254.1379, found 254.1377.

3-[1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido) pyrrole-2-carboxamido]dimethylaminopropane (6)

A suspension of 10% Pd-C (250 mg) in a solution of **4** (1 g, 3.91 mmol) in MeOH (10 mL) was stirred for 2 h under a current of H_2 at room temperature, and then filtered. The residual catalyst was washed thoroughly with methanol and the combined filtrate and washings were concentrated *in vacuo* to produce a crude amine. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (br s, 1H), 6.27 (d, J=2.0 Hz, 1H), 6.05 (d, J=2.0 Hz, 1H), 3.83 (s, 3H), 3.41 (q, J= 6.0 Hz, 2H), 2.41 (t, J=6.0 Hz, 2H), 2.27 (s, 6H), 1.72-1.68 (m, 2H).

The residual solid was dissolved in DMF (5 mL) and a solution of compound **3** (880 mg, 3.9 mmol) in DMF (5 mL) was stirred in at 0°C. The temperature was allowed to rise to ambient temperature. The solvent was removed *in vacuo* and the residue was purified using column chromatography on silica gel with NH_4OH:MeOH:CH_2Cl_2 (3:10:90) as an eluent to produce **6** (1.25 g, 3.32 mmol, 85% yield): IR ($CHCl_3$) 1657, 1634, 1538, 1310 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (s, 1H), 7.84 (br, 1H), 7.59 (d, J=1.8 Hz, 1H), 7.28 (d, J=1.6 Hz, 1H), 7.18 (d, 1H), 6.47 (d, J=1.8 Hz, 1H), 4.03 (s, 3H), 3.92 (s, 3H), 3.46 (q, J=5.8 Hz, 2H), 2.45 (t, J=6.0 Hz, 2H), 2.29 (s, 6H), 1.74-1.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 159.2, 136.5, 128.5, 128.0, 125.7, 122.4, 120.3, 108.9, 104.6, 60.5, 46.9, 41.1, 39.4, 38.1, 27.1. MS (EI) *m/z* 376 (M^+ ,4), 358 (4), 291 (3), 275 (13), 259 (7), 153 (12), 149 (3), 138(2), 123 (3), 107 (9), 84 (8), 72 (13), 58 (100). HRMS (EI) *m/z* calcd for $C_{17}H_{24}N_6O_4$ 376.1859, found 376.1853.

3-{1-Methyl-4-[1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]pyrrole-2-carboxamido}dimethylaminopropane (8)

By using the same procedure that was described for the production of **6**, **8** (407 mg, 0.82 mmol) was obtained from **6** (400 mg, 1.06 mmol), PtO_2 (10 mg), and **3** as a microcrystalline solid in a 77% yield: IR ($CHCl_3$) 1644, 1534, 1310 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.13 (br s, 1H), 8.07 (br, 1H), 7.70 (d, J=1.7 Hz, 1H), 7.60 (d, J =1.7 Hz, 1H), 7.33 (d, J=1.7 Hz, 1H), 7.13 (s, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.48 (d, J=1.7 Hz, 1H), 6.25 (d, J =1.7 Hz, 1H), 4.06 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.54 (q, J = 5.7 Hz, 2H), 2.49 (t, J=6.0 Hz, 2H), 2.31 (s, 6H), 1.81-1.73 (m, 2H). ^{13}C NMR (CD_3OD, 100 MHz) δ 164.2, 161.2, 159.5, 136.1, 128.7, 127.7, 124.6, 124.5, 123.2, 122.9, 120.7, 120.4, 108.7, 106.2, 106.1, 58.0, 45.1, 38.3, 38.1, 36.9, 36.8, 28.0. MS (EI) *m/z* 498 (M^+, 5), 480 (4), 453 (3), 413 (12), 397 (5), 395 (5), 370 (3), 291 (8), 273 (6), 245 (4), 159 (4), 138 (8), 58 (100). HRMS (EI) *m/z* calcd for $C_{23}H_{30}N_8O_5$ 498.2339, found 498.2332.

4-(4-Bromophenyl)-4-oxo-butyric acid (10)

Fifty-five mL of bromobenzene was added all at once to a mixture of anhydrous $AlCl_3$ (26.67 g, 200 mmol) and succinic anhydride (10 g, 100 mmol) in boiling cyclohexane (50 mL), by stirring. After approximately 15 min of further heating, the vigorous evolution of HCl had

ceased. The viscous red reaction mixture was cooled, diluted with toluene and treated with ice and aqueous HCl. The keto acid was extracted from this mixture with hot toluene. The toluene extract was washed with water and then extracted with 2 M aqueous NaOH solution. The basic extract was acidified with aqueous HCl, and the keto acid was extracted with toluene. Rotary evaporation of the toluene extract yielded crude **10**. Recrystallization from a mixture of toluene and *n*-hexane produced 10.1 g (42 mmol, 42%) of 3-(4'-bromobenzoyl) propanoic acid (**10**) as a white solid: IR ($CHCl_3$) 3034, 1699, 1673, 1411 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85, 7.62 (ABq, J= 8.6 Hz, 4H), 3.29 (t, J=6.5 Hz, 2H), 2.82 (t, J=6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.2, 180.6, 137.4, 134.3, 131.8, 130.8, 35.2, 30.0. MS (EI) *m/z* 258, 256 (M^+, 9), 185 (98), 183 (100), 155 (27), 119 (19), 76 (24). HRMS (EI) *m/z* calcd for $C_{10}H_9{}^{81}BrO_3$ 257.9715, found 257.9709. calcd for $C_{10}H_9{}^{79}BrO_3$ 255.9735, found 255.9730.

3-{1-Methyl-4-[3-(4'-bromobenzoyl) propanoylamino] pyrrole-2-carboxamido}dimethylaminopropane (11)

3-(4'-bromobenzoyl)propanoic acid (**10**) (122 mg, 0.51 mmol) and 4-dimethylaminopyridine (63.5 mg, 0.52 mmol) were added to aminopyrrole (90 mg, 0.4 mmol). The mixture was dissolved in dry DMF (1 mL) and then chilled (0°C). This was followed by the addition of a solution of dicyclohexylcarbodiimide(107 mg, 0.52 mmol) in dry DMF (1 mL). The reaction mixture was stirred under a nitrogen atmosphere at 0°C for 15 min and then at room temperature for 17 h. The precipitated urea was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified using flash column chromatography on silica gel with NH_4OH: MeOH: CH_2Cl_2 (1: 10: 90) as an eluent to afford **11**: IR ($CHCl_3$) 1681, 1645, 1585, 1532, 1442, 1400 cm^{-1}. ^1H NMR (DMSO, 300 MHz) δ 9.90 (s, 1H), 8.12 (t, J=5.6 Hz, 1H), 7.91 (d, J=8.6 Hz, 2H), 7.74 (d, J=8.6 Hz, 2H), 7.07 (d, J=1.7 Hz, 1H), 6.70 (d, J=1.7 Hz, 1H), 3.77 (s, 3H), 3.28 (t, J=6.3 Hz, 2H), 3.21 (m, 2H), 2.78 (t, J=7.6 Hz, 2H), 2.65 (t, J= 6.3 Hz, 2H), 2.56 (s, 6H), 1.74 (m, 2H).

^{13}C NMR (DMSO, 75 MHz) δ 198.3, 168.5, 161.5, 135.6, 131.8, 129.9, 127.2, 122.7, 122.1, 117.6, 103.5, 55.6, 43.3, 36.0, 33.3, 29.5, 25.6. MS (EI) *m/z* 464, 462 (M^+, 4), 446, 444 (2), 388, 386 (3), 363 (4), 361 (4), 241 (4), 239 (4), 185 (2), 183 (3), 139 (4), 123 (4), 101 (5), 72 (12). HRMS (EI) *m/z* calcd for $C_{21}H_{27}{}^{79}BrN_4O_3$ 462.1266, found 462.1266. calcd for $C_{21}H_{27}{}^{81}BrN_4O_3$ 464.1246, found 464.1280.

3-{1-Methyl-4-[1-methyl-4-(3-(4'-bromobenzoyl) propanoylamino)pyrrole-2-carboxamido]pyrrole-2-carboxamido}dimethylaminopropane (12)

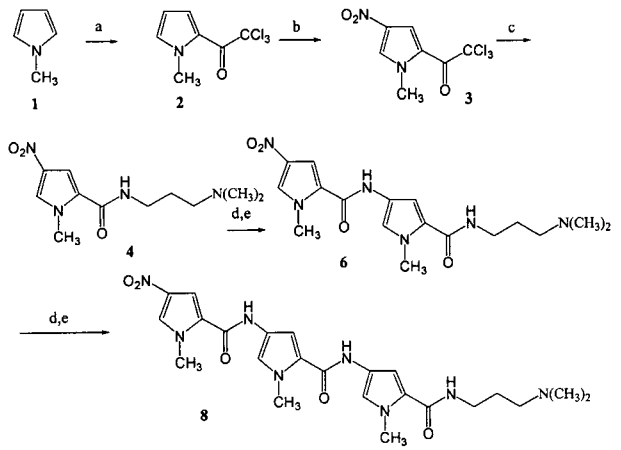
Using the same procedure that was described for **11**, **12** was obtained from dipyrrole amine (153 mg, 0.44 mmol), **10** (107 mg, 0.44 mmol), DCC (119 mg, 0.58 mmol), and DMAP (70 mg, 0.58 mmol): IR ($CHCl_3$) 1682, 1651, 1634, 1585, 1557, 1538, 1466, 1435, 1403 cm^{-1}. ^1H NMR (DMSO, 500 MHz) δ 9.94 (s, 1H), 9.84 (s, 1H), 8.08 (t, J=5.6 Hz, 1H), 7.91 (dd, J=6.8, 2.0 Hz, 2H), 7.73 (d, J=6.8, 2.0 Hz, 2H), 7.17 (d, J=2.0 Hz, 1H), 7.11 (d, J=2.0 Hz, 1H), 6.87 (d, J=2.0 Hz, 1H), 6.83 (d, J=1.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.28 (t, J=6.3 Hz, 2H), 3.19 (m, 2H), 2.65 (t, J=6.3 Hz, 2H), 2.38 (t, J= 7.3 Hz, 2H), 2.24 (s, 6H), 1.64 (m, 2H). ^{13}C NMR (DMSO, 125 MHz) δ 198.4, 168.6, 161.4, 158.5, 135.7, 131.9, 130.0, 127.3, 123.0, 122.8, 122.1, 118.1, 117.9, 104.2, 104.0, 56.7, 44.7, 36.9, 36.2, 36.0, 33.3, 29.5, 26.8. MS (EI) *m/z* 586, 584 (M^+, 1), 568 (4), 566 (4). HRMS (EI) *m/z* calcd for $C_{27}H_{33}{}^{79}BrN_6O_4$ 584.1746, found 584.1760. calcd for $C_{27}H_{33}{}^{81}BrN_6O_4$ 586.1726, found 586.1639.

3-{1-Methyl-4-[1-Methyl-4-<1-methyl-4-(3-(4'-bromobenzoyl)propanoylamino)pyrrole-2-carboxamido> pyrrole-2-carboxamido]pyrrole-2-carboxamido} dimethylaminopropane (13)

Using the same procedure that was described for **12**, **13** was obtained from tripyrroleamine (355 mg, 0.758 mmol), **10** (183 mg, 0.7582 mmol), DCC (203 mg, 0.98 mmol), and DMAP (120 mg, 0.98 mmol): IR ($CHCl_3$) 1682, 1674, 1668, 1659, 1652, 1644, 1634, 1585, 1557, 1538, 1464, 1434, 1403 cm^{-1}. ^1H NMR (DMSO, 500 MHz) δ 9.93 (s, 1H), 9.89 (s, 1H), 9.88 (s, 1H), 8.08 (t, J=5.4 Hz, 1H), 7.92 (dd, J=6.8, 2.0 Hz, 2H), 7.75 (d, J=6.8, 2.0 Hz, 2H), 7.23 (d, J=1.5 Hz, 1H), 7.18 (d, J=2.0 Hz, 1H), 7.12 (d, J=1.5 Hz, 1H), 7.03 (d, J=1.5 Hz, 1H), 6.89 (d, J=2.0 Hz, 1H), 6.82 (d, J=2.0 Hz, 1H) 3.84 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.29 (t, J=6.3 Hz, 2H), 3.19 (m, 2H), 2.66 (t, J=6.3 Hz, 2H), 2.25 (t, J= 6.8 Hz, 2H), 2.15 (s, 6H), 1.61 (m, 2H). ^{13}C NMR (DMSO, 125 MHz) δ 198.3, 168.5,161.2, 158.5, 135.6, 131.8, 129.9, 127.2, 123.0, 122.8, 122.7, 122.1, 118.4, 118.0, 117.7, 104.7, 104.0, 103.9, 57.1, 45.2, 37.1, 36.1, 35.9, 33.3, 29.5, 27.1. MS (+LSIMS) *m/z* 709, 707 (MH^+), 643, 533, 483, 369, 329, 232.

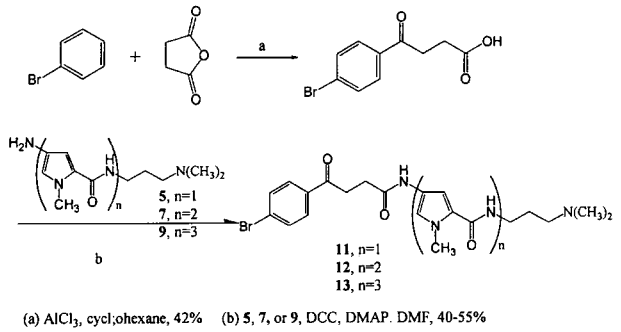
RESULTS AND DISCUSSION

The peptide-linked 4'-bromoacetophenones were synthesized as shown in Scheme 1 and 2. The oligo-*N*-methyl pyrrole carboxamides were prepared according to Shibuyas method (Nishiwaki *et al.*, 1988). The commercially available *N*-methylpyrrole was chlorinated, and then the nitration of trichloroacetylpyrrole (**2**) provided the desired 4-nitro isomer **3**. Condensation of the trichloroacetylpyrrole with 3-dimethylaminopropylamine yielded the corresponding amide **4**. The reduction of the nitro group of pyrrole amide **4** to the amine **5** was followed by condensation with **3** to yield the dipeptide **6**. The reduction-condensation process was then repeated, leading to the tripeptide **8** (Scheme 1).



(a) Cl_3CCOCl, Et_2O, 95% (b) HNO_3, Ac_2O, 62% (c) $H_2N(CH_2)_3N(CH_3)_2$, THF, 96%
(d) 10% Pd-C/H_2, MeOH (e) **3**, DMF, 85% for **6**, 77% for **8** (two steps)

Scheme 1. Preparation of pyrrolecarboxamides



(a) $AlCl_3$, cycl;ohexane, 42% (b) **5**, **7**, or **9**, DCC, DMAP. DMF, 40-55%

Scheme 2. Preparation of 4'-bromoacetophenone-pyrrolecarboxamide hybrids

On the other hand, the DNA cleaving unit, 3-(4-bromobenzoyl)propanoic acid, was prepared using the Friedel-Crafts succinoylation of bromobenzene, and then coupled with pyrrole polyamides to obtain 4'-bromoacetophenone-pyrrolecarboxamide hybrid compounds, **11**, **12**, and **13**.

In summary, the 4'-bromoacetophenone-pyrrolecarboxamide conjugates have been designed and synthesized as a novel sequence specific DNA cleavers, with the expectation of a higher level of affinity between the simple phenyl radical species and DNA. The DNA cleaving activity and sequence selectivity of the new photoinducible DNA cleaving agents will be described in the following paper.

ACKNOWLEDGEMENTS

Financial support was provided by the Korean Science and Engineering Foundation.

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