Synthesis of 2-Substituted 4-Quinazolone-5-carboxylic Acids as Inhibitors of DNA-Gyrase

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A series of 4-quinazolone-5-carboxylic acids were designed as bacterial DNA gyrase inhibitors. The syntheses of the target compounds were accomplished by reacting 3-aminophthalimide with aroyl chlorides followed by rearrangement of the resulting 3-acylaminophthalimides under basic conditions. The designed compounds showed moderate DNA gyrase inhibitory activity.

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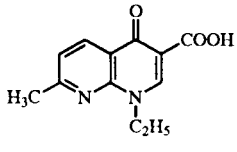
Antibacterial quinolones (*e.g.* nalidixic acid, **1**) have attracted increasing attention as clinically useful drugs [1]. Despite the success of the newer generation quinolones in the clinic, side effects on the central nervous system and articular cartilage limit their use [2-4]. It is possible that the β-keto acid structure in quinolones may be responsible for those side effects. The antibacterial effects of the quinolones are thought to be due to the inhibition of bacterial DNA gyrase [5-7]. In the continuation of our search for novel non-quinolone inhibitors of DNA gyrase [8-10], we uncovered a series of 2-substituted 4-quinazolone-5-carboxylic acids. Herein we report the synthesis and DNA gyrase inhibitory activities of these compounds.



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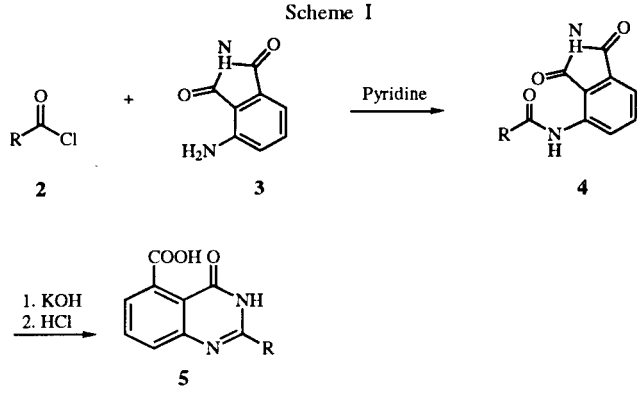
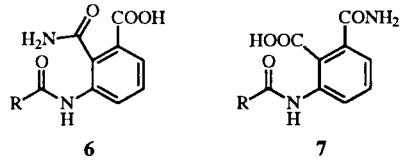
A modification of the procedures described in the literature [11,12] for the synthesis of 5-quinazolinecarboxylic acids was used for the preparation of our target compounds. Reactions of 3-aminophthalimides with the corresponding aroyl chlorides provided 3-aroylaminophthalimides **4**. Purification of **4** was usually not necessary. The 4-quinazolone-5-carboxylic acids **5** were obtained by heating the aroylaminophthalimides **4** in potassium hydroxide, followed by treatment with hydrochloric acid. Apparently the phthalimide ring in **4** was hydrolytically opened when treated with base and subsequently closed to give the final products. To investigate whether the cyclization was effected by the base or hydrochloric acid, we isolated the intermediate in the synthesis of **5d** before adding the acid. The ^{1}H-nmr spectrum of the isolated intermediate was identical with that of the potassium salt of **5d**. This proved that the ring opened intermediates **6** were cyclized to 4-quinazolones under basic conditions (Scheme I). The yields in the conversion of the phthalimides to the 4-quinazolone-5-carboxylic acids were above 50% in most

Scheme I



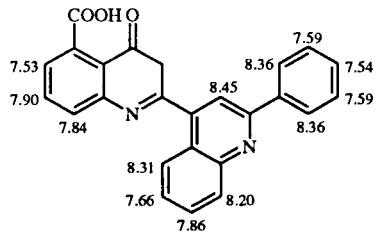
cases. This indicates that in the ring opening of the phthalimide, the formation of the intermediate phthalamic acid **6** is favored over **7**. These results are consistent with the electronic effects of the acylamino group in **4** on the two different carbonyl groups. The nucleophilic attack of hydroxide ion occurs predominantly at the carbonyl *meta* to the acylamino group since it is more electrophilic.



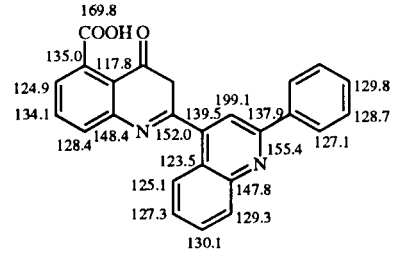
6 **7**

Both electron rich and electron deficient aroyl chlorides gave 4-quinazolone products in satisfactory yields. No distinct substituent effects were observed.

Elemental analyses and spectral data of all the prepared compounds are in accordance with the proposed structures. We have assigned all aromatic signals of the ^{1}H- and ^{13}C-nmr spectra of **5l** by using COSY, NOESY and HETCOR experiments (Figure 1). Furthermore, in the NOESY studies on **5d**, we found an increase in the intensity of the *ortho* proton on the 3-phenyl ring when the exchangeable proton at 12.68 ppm was irradiated. This indicates that these compounds exist in the keto form in solution.



^{1}H-NMR Chemical shifts



^{13}C-NMR Chemical shifts

Figure 1. Assignments of nmr signals of compound **5l**.

Compounds **5** were tested for DNA gyrase inhibitory activity by the bacterial DNA gyrase supercoiling assay as previously reported [10]. Most of the compounds showed inhibitory activities against DNA gyrase. The results are summarized in Table I. The IC_{50} of the best compound (**5l**, IC_{50} = 95 μg/ml) is in the range of first generation antibacterial quinolones such as nalidixic acid (**1**, IC_{50} = 57 μg/ml). In general, a long lipophilic substituent on position **2** of the quinazolone ring appears to enhance the inhibitory activity of the compounds against DNA gyrase. Further biological and antimicrobial studies are in progress.

Table I

DNA Gyrase Inhibitory Activities of 4-Quinazolone-5-carboxylic Acids

Compound	R	IC_{50} (μg/ml)
5a	4-biphenyl	198
5b	3-pyridyl hydrochloride	>1000
5c	2-benzofuranyl	387
5d	3-phenoxyphenyl	484
5e	3,5-bistrifluoromethylphenyl	379
5f	4-styrylphenyl	198
5g	4-(4-phenyl)butylphenyl	181
5h	4-(4-phenylbuten-1-yl)phenyl	121
5i	4-nitrophenyl	>1000
5j	2-naphthyl	>1000
5k	4-(4-ethylphenyl)phenyl	212.5
5l	2-phenylquinolin4-yl	95
1	nalidixic acid	57

EXPERIMENTAL

Melting points were determined on a Meltemp II melting points apparatus and are uncorrected. The nmr were determined with either a GE-300 and a Varian-500 spectrometer with TMS as the internal standard. Elemental analyses (within 0.4% of the theoretical values), ir and mass spectral data were performed by the analytical group at The R. W. Johnson Pharmaceutical Research Institute.

General Procedure for the Preparation of 2-Substituted-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acids **5a-5l**. The Following Procedure for the Preparation of 2-(4-Biphenyl)-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5a**) is a representative example.

To a solution of 4-biphenylcarbonyl chloride (3.25 g, 15 mmoles) in dry pyridine (80 ml) was added α-aminophthalimide (2.0 g, 12 mmoles), prepared by reduction of α-nitro phthalimide [6]. The mixture was heated at reflux temperature for 8 hours. The reaction mixture was then poured into ice-water. The precipitate was collected by filtration and air-dried. The crude solid was transferred to a 250 ml flask and 1*N* potassium hydroxide (60 ml) was added. The mixture was heated at 80° until everything went into solution. The solution was filtered hot into 1*N* hydrochloric acid (80 ml). The precipitated product was collected by filtration and recrystallized from ethanol and water to give 3.6 g (65%) of a yellow solid, mp >300°; ^{1}H nmr (DMSO-d_6): δ 13.15 (bs, 1H, CO_2H), 12.75 (bs, 1H, N*H*), 8.32 (d, 2H, J = 8 Hz, aromatic), 7.84 (m, 6H, aromatic), 7.45 (m, 4H, aromatic); ir (potassium bromide): ν 3087, 1722, 1670, 1593, 1550, 1251 cm^{-1}; ms: (CI) m/z 343 (MH^+).

Anal. Calcd. for $C_{21}H_{14}N_2O_3$•0.10 H_2O: C, 73.29; H, 4.16; N, 8.14. Found: C, 72.95; H, 4.28; N, 7.86.

2-(3-Pyridyl)-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid Hydrochloride (**5b**).

Compound **5b** was obtained in 50% yield as a light yellow solid (ethanol/2*N* hydrochloric acid), mp >300°, from nicotinoyl chloride hydrochloride (2.67 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 9.38 (d, 1H, Py-*H*), 8.87 (dd, 1H, J = 1 Hz, 5 Hz, Py-*H*), 8.71 (dt, 1H, J = 1 Hz, 8 Hz, Py-*H*), 7.78-7.89 (m, 3H, 2 Phenyl-*H* and 1 Py-*H*), 7.48 (dd, 1H, J = 2 Hz, 7 Hz, Phenyl-*H*); ir (potassium bromide): ν 2903, 2600, 1728, 1658, 1588, 1553 cm^{-1}; ms: (CI) m/z 268 (MH^+).

Anal. Calcd. for $C_{14}H_9N_3O_3$•HCl•0.30 H_2O: C, 54.40; H, 3.46; N, 13.59. Found: C, 54.27; H, 3.38; N, 13.48.

2-(2-Benzofuranyl)-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5c**).

Compound **5c** was obtained in 62% yield as a white solid (ethanol), mp >300°, from coumariloyl chloride (2.71 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.15 (bs, 1H, CO_2H), 12.92 (bs, 1H, N*H*), 8.11 (s, 1H, H of benzofuran), 7.86 (m, 3H, aromatic), 7.77 (d, 1H, J = 8 Hz, aromatic), 7.49 (m, 2H, aromatic), 7.38 (m, 1H, aromatic); ir (potassium bromide): ν 3068, 1719, 1671, 1617, 1590 cm^{-1}; ms: (CI) m/z 307 (MH^+).

Anal. Calcd. for $C_{17}H_{10}N_2O_4$•0.10 H_2O: C, 66.28; H, 3.34; N, 9.09. Found: C, 66.14; H, 3.00; N, 8.88.

2-(3-Phenoxyphenyl)-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5d**).

Compound **5d** was obtained in 66% yield as a brown solid (DMSO/water), mp 279-280°, from 3-phenoxybenzoyl chloride (3.73 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.12 (bs, 1H, CO_2H), 12.71 (bs, 1H, NH), 7.99 (d, 1H, J = 8 Hz, aromatic), 7.85 (m, 3H, aromatic), 7.55 (t, 1H, J = 8 Hz, aromatic), 7.45 (m, 3H, aromatic), 7.22 (m, 2H, aromatic), 7.10 (d, 2H, J = 8 Hz, aromatic); ir (potassium bromide): ν 3440, 3064, 1710, 1667, 1610, 1577, 1483 cm^{-1}; ms: (CI) m/z 359 (MH^+).

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82. Found: C, 70.08; H, 3.71; N, 7.65.

2-[3,5-Bis(trifluoromethyl)phenyl]-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5e**).

Compound **5e** was obtained in 62% yield as a white solid (ethanol/water), mp >300°, from 3,5-bis(trifluoromethyl)benzoyl chloride (4.15 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.15 (bs, 2H, CO_2H, NH), 8.90 (s, 2H, aromatic), 8.35 (s, 1H, aromatic), 7.90 (m, 2H, aromatic), 7.71 (m, 1H, aromatic); ir (potassium bromide): ν 3098, 1703, 1686, 1630 cm^{-1}; ms: (CI) m/z 403 (MH^+).

Anal. Calcd. for $C_{17}H_8N_2O3F_6$: C, 50.76; H, 2.00; N, 6.96. Found: C, 50.53; H, 1.93; N, 6.84.

2-(4-Styrylphenyl)-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5f**).

Compound **5f** was obtained in 56% yield as a yellow solid (DMSO/water), mp >300°, from 4-styrylbenzoyl chloride (3.64 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.15 (bs, 1H, CO_2H), 12.65 (bs, 1H, NH), 8.24 (d, 2H, J = 8 Hz, aromatic), 7.81 (m, 4H, aromatic and CH=), 7.66 (d, 2H, J = 7 Hz, aromatic), 7.44 (m, 6H, aromatic and CH=); ir (potassium bromide): ν 3169, 1668, 1593 cm^{-1}; ms: (CI) m/z 369 (MH^+).

Anal. Calcd. for $C_{23}H_{16}N_2O_3$•0.50 H_2O: C, 73.20; H, 4.54; N, 7.42. Found: C, 72.88; H, 4.25; N, 7.37.

2-[4-(4-Phenyl)butylphenyl]-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5g**).

Compound **5g** was obtained in 59% yield as a brown solid (DMSO/water), mp 195-197°C, from 4-(4-phenyl)butylbenzoyl chloride (4.09 g, 15 mmol) and a-amino-phthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.07 (bs, 1H, CO_2H), 12.58 (bs, 1H, NH), 8.11 (d, 2H, J = 8 Hz, aromatic), 7.81 (m, 2H, aromatic), 7.43 (m, 3H, aromatic), 7.38 (m, 2H, aromatic), 7.19 (m, 3H, aromatic), 2.70 (t, 2H, J = 7 Hz, $PhCH_2$), 2.62 (t, 2H, J = 7 Hz, $PhCH_2$), 1.62 (m, 4H, $PhCH_2CH_2$); ir (potassium bromide): ν 3207, 1670, 1579 cm^{-1}; ms: (CI) m/z 399 (MH^+).

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.40; H, 5.89; N, 6.77.

2-[4-(4-Phenylbuten-1-yl)phenyl]-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5h**).

Compound **5h** was obtained in 16% yield as a yellow solid (tetrahydrofuran/water), mp 263-265°, from 4-(4-phenylbuten-1-yl)benzoyl chloride (4.06 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 mL). 1H nmr (DMSO-d_6): δ 13.15 (bs, 1H, CO_2H), 12.61 (bs, 1H, NH), 8.16 (d, 2H, J = 8 Hz, aromatic), 7.81 (m, 2H, aromatic), 7.55 (d, 2H, J = 8 Hz, aromatic), 7.45 (m, 1H, aromatic), 7.30 (m, 5H, aromatic), 6.53 (m, 2H, CH=CH), 2.80 (t, 2H, J = 7 Hz, $PhCH_2$), 2.56 (m, 2H, $CHCH_2$); ir (potassium bromide): ν 3108, 1716, 1669, 1592, 1557 cm^{-1}; ms: (CI) m/z 397 (MH^+).

Anal. Calcd. for $C_{25}H_{20}N_2O_3$•0.20 H_2O: C, 75.02; H, 5.14; N, 7.00. Found: C, 74.79; H, 4.77; N, 6.80.

2-(4-Nitrophenyl)4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5i**).

Compound **5i** was obtained in 60% yield as a yellow solid (DMSO/water), mp 117°, from 4-nitrobenzoyl chloride (2.78 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80ml); ^{1}H nmr (DMSO-d_6): δ 13.16 (bs, 1H, CO_2H), 12.95 (bs, 1H, NH), 8.41 (m, 4H, aromatic), 7.85 (m, 2H, aromatic), 7.51 (d, 1H, J = 1 Hz, aromatic); ir (potassium bromide): ν 3108, 1725, 1676, 1584, 1523, 1346 cm^{-1}; ms: (CI) m/z 312 (MH^+).

Anal. Calcd. for $C_{15}H_9N_3O_5$: C, 57.88; H, 2.91; N, 13.50. Found: C, 58.14; H, 2.85; N, 13.28.

2-(2-Naphthyl)4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5j**).

Compound **5j** was obtained in 60% yield as a light brown solid (DMSO/water), mp >300°, from 2-naphthoyl chloride (2.86 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.12 (bs, 1H, CO_2H), 12.79 (bs, 1H, NH), 8.84 (s, 1H, aromatic), 8.31 (d, 1H, J = 9 Hz, aromatic), 8.08 (m, 3H, aromatic), 7.86 (m, 2H, aromatic), 7.65 (m, 2H, aromatic), 7.47 (m, 1H, aromatic); ir (potassium bromide): ν 3193, 1720, 1660, 1590, 1307 cm^{-1}; ms: (CI) m/z 317 (MH^+).

Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: C, 72.18; H, 3.77; N, 8.71.

2-[4-(4-Ethylphenyl)phenyl]-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5k**).

Compound **5k** was obtained in 62% yield as an brown solid (DMSO/water), mp 300-301°, from 4-(4-ethylphenyl)benzoyl chloride (3.67 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.19 (bs, 1H, CO_2H), 12.75 (bs, 1H, NH), 8.30 (d, 2H, J = 9 Hz, aromatic), 7.84 (m, 4H, aromatic), 7.70 (d, 2H, J = 8 Hz, aromatic), 7.46 (d, 1H, J = 2 Hz, aromatic), 7.35 (d, 2H, J = 8 Hz, aromatic), 2.67 (q, 2H, J = 8 Hz, CH_2), 1.22 (t, 3H, J = 8 Hz, CH_3); ir (potassium bromide): ν 1716, 1670, 1593, 1561 cm^{-1}; ms: m/z 371 (MH^+).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$•0.1H_2O: C, 74.22; H, 4.93; N, 7.53. Found: C, 73.86; H, 5.14; N, 7.22.

2-(2-Phenylquinolin-4-yl)-4-oxo-5(3*H*,4*H*)-quinazolinecarboxylic Acid (**5l**).

Compound **5l** was obtained in 55% yield as a brown solid (DMSO/water), mp 284-285°, from 2-phenyl-4-quinolinecarbonyl chloride (4.02 g, 15 mmoles) and α-aminophthalimide (2.0 g, 12 mmoles) in pyridine (80 ml); ^{1}H nmr (DMSO-d_6): δ 13.01 (bs, 1H, CO_2H), 8.45 (s, 1H), 8.36 (d, 2H, J = 8 Hz), 8.31 (d, 1H, J = 8 Hz), 8.20 (d, 1H, J = 8 Hz), 7.90 (t, 1H, J = 8 Hz), 7.86 (t, 1H, J = 8 Hz), 7.84 (d, 1H, J = 8 Hz), 7.66 (t, 1H, J = 8 Hz), 7.59 (t, 2H, J = 8 Hz), 7.54 (t, 1H, J = 8 Hz), 7.53 (d, 1H, J = 8 Hz); ^{13}C nmr (DMSO-d_6): δ 169.8, 155.4, 152.0, 148.4, 147.8, 139.5, 137.9, 135.0, 134.1, 130.1, 129.8, 129.3, 128.7, 128.4, 127.3, 127.1, 125.1, 124.9, 123.5, 119.1, 117.1; ir (potassium bromide): ν 1702, 1585, 1547, 1243 cm^{-1}; ms: m/z 394 (MH^+).

Anal. Calcd. for $C_{24}H_{15}N_3O_3 \cdot 0.6H_2O$: C, 71.32; H, 4.04; N, 10.40. Found: C, 71.09; H, 4.02; N, 10.11.

Acknowledgement

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