Hypolipidemic Agents of Phthalimide Derivatives 6. Effects of Aromatic vs. Non-Aromatic Imides[3]

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Received: January 24, 1984; accepted May 20, 1984.

Abstract: A number of substituted phthalimide, 1, 8-naphthalimide, succinimide and glutarimide derivatives demonstrated significant hypolipidemic activity at 20 mg/kg/day, I.P. after 16 days dosing. The *N*-(*n*-pentyl) succinimide proved to be the most potent analogue of the new compounds, lowering serum triglyceride levels 51 % and serum cholesterol 47 % after 16 days dosing in mice. For the *N*-substituted derivatives, i. e., *n*-butyl, butanone, and propionic acid, of these four cyclic imides, there appeared to be no obvious trend in ability to reduce serum lipid levels. In general, the 1,8-naphthalimide and glutarimide derivatives appeared to be less active than phthalimide and succinimide. However, the α-phenylsuccinimide afforded less activity than the α-phenylglutarimide. Most of the derivatives at 20 mg/kg/day demonstrated improved activity over clofibrate at 150 mg/kg/day.

A series of *N*-substituted analogues of phthalimide and saccharin have been shown to be hypolipidemic agents in mice (1, 2). *N*-Substitutions of four carbon atoms or the replacement of one of the carbons with an oxygen atom afforded compounds which proved to have the best hypolipidemic activity (>35 % reduction). In the current series of compounds, the importance of the aromatic ring was evaluated comparing phthalimide to succinimide, and 1,8-naphthalimide to glutarimide. The hypolipidemic activity of N-substituted derivatives as well as their α-phenyl substituted derivatives were investigated. The dose of 20 mg/kg/day was selected for this SAR study because this dose proved to be the optimum dose when testing phthalimide and 3-*N*-(1′,8′-naphthalimide)propionic acid (1, 2).

Materials and Methods

Chemistry

Phthalimide (**1**), succinimide (**6**), 1,8-naphthalimide (**12**) and glutarimide (**17**) were purchased commercially from Kodak Company or Aldrich Chemical Company. The synthetic procedure for compounds **2** to **5** (2), **7**(3), **8** (6), **9** (5), **10** and **16** (1), **11** (8), **13** (4), **14** (9), **19** (7) and **22** (10) as well as the physical characteristics of these compounds have been published previously.

Melting points were determined using a Mel-Temp apparatus and are uncorrected. NMR data were obtained using a JEOL-FX-60 spectrophotometer. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Arizona, and were within ±0.4 % of theory.

β-[*N*-(1,8-Naphthalimide)] propionic Acid (**15**) – 1,8-Naphthalic anhydride, 19.8 g (0.1 mol), and 8.9 g (0.1 mol) of β-alanine were refluxed in 300 ml DMF for 1.25 hours. The solvent was removed under vacuum, and the residue washed with ethanol to yield 24 g (89 %) of crude 3-*N*-(1,8-naphthalimido) propionic acid. Recrystallization from ethyl acetate afforded pure 3-*N*-(1,8-naphthalimido) propionic acid; mp 231–233°C. NMR: (d_6-DMSO): δ 7.62–8.47 (m 6H, aromatic) δ 4.26 (t, 2H,N-CH_2) δ 2.60 (t, 2H, CH_2C=O). Anal. ($C_{15}H_{11}NO_4$) C,H.

N-*n*-Butylglutarimide (**18**) – Glutaric anhydride, 11.4 g (0.1 mol) was melted at 120°C under N_2. *n*-Butylamine, 7.3 g (0.1 mol) was slowly added, the reaction mixture heated to 170°C under N_2 for 5 hours and the resulting residue distilled under high vacuum yielding *N*-*n*-butylglutarimide; bp 75–76°C/0.15 mm. NMR ($CDCl_3$) δ 3.74 (t, 2H, N-CH_2) 2.67 (t, 4H, CH_2-C=O) 1.98 (m, 2H, CH_2, CH_2C=O) 0.70–1.62 (m, 7H, CH_2-CH_2-CH_3). Anal. ($C_9H_{15}NO_2$) C,H,N.

β-(*N*-Glutarimido)propionic Acid (**20**) – Glutaric anhydride, 11.4 g (0.1 mol) was dissolved in 200 ml of toluene and 8.9 g (0.1 mol) β-alanine added. The reaction mixture was heated to reflux for 16 hours, when 0.1 mol of water had been collected by azeotropic distillation. The solvent was removed under vacuum and the resulting residue repeatedly recrystallized from EtOH to yield 1.85 g 3-*N*-glutarimidopropionic acid (10 %); mp 122–123°C. NMR (d_6-DMSO) δ 3.80 (t, 2H, N-CH_2) 2.21–2.72 (m, 6H, CH_2-C=O) 1.85 (m, 2H, CH_2, CH_2-C=O). Anal. ($C_8H_{11}NO_4$)C, H, N.

1-*N*-Glutarimidobutan-3-one (**21**) – A solution of 3-hydroxybutylamine (800 mg, 0.009 mol) in 10 ml toluene was added dropwise to a solution of 1.0 g (0.009 mol) glutaric anhydride in 30 ml toluene and the reaction stirred overnight at reflux using a Dean-Stark trap to remove water. The toluene was removed in vacuo to afford a dark viscous oil. This crude material was dissolved in 6 ml glacial acetic acid and 1.4 ml water and a solution of 900 mg (0.009 mol) CrO_3 in 9 ml glacial acetic acid was added dropwise with cooling. The reaction was stirred overnight at room temperature, poured into 100 ml water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated in vacuo to afford a light green oil which was column chromatographed on silical gel 60 (70–230 mesh) with chloroform-EtOAc 7:3 to afford 200 mg (12 %) of product as a gum. ^{1}H-NMR ($CDCl_3$) δ 4.04 (t, 2H, N-CH_2), 2.65 (t, 6H, CH_2-C=O), 2.16 (s, 3H, CH_3), 2.05(m,2H,$COCH_2CH_2CH_2CO$). Anal ($C_9H_{13}NO_3$) C,H,N.

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[3] J. M. Chapman, Jr., S. D. Wyrick, P. J. Voorstad, J. H. Maguire, G. H. Cocolas, and I. H. Hall, "Hypolipidemic Agents of Phthalimide Derivatives 5. Reduced and Hydrolytic Products of Simple Cyclic Imides", J. Pharm. Sci. (in press) preceding paper in this series.

Analysis for New Compounds

	% Theory	% Found
N-*n*-Butyl succinimide (**7**)	C 61.91	61.74
$C_8H_{13}NO_2$	H 8.44	8.22
3-*N*-(1,8-Naphthalimido) propionic acid (**15**)	C 66.91	66.96
$C_{15}H_{11}NO_4$	H 4.12	4.11
N-*n*-Butylglutarimide (**18**)	C 63.88	63.64
$C_9H_{15}NO_2$	H 8.94	8.68
	N 8.28	8.30
3-*N*-(Glutarimido)propionic acid (**20**)	C 51.89	51.84
$C_8H_{11}NO_4$	H 5.99	5.96
	N 7.56	7.64
1-*N*-(Glutarimido)butan-3-one (**21**)	C 51.89	51.84
$C_9H_{13}NO_3$	H 5.99	5.96
	N 7.56	7.64

Hypolipidemic Activity

Test compounds were suspended in 1 % carboxymethylcellulose-water and administered to CF_1 male mice (~25 g) intraperitoneally for 16 days. On days 9 and 16, blood was obtained by tail vein bleeding and the serum was separated by centrifugation for 3 min. The serum cholesterol was determined by a modification of the Liebermann-Burchard reaction (11). Serum triglyceride levels were determined in blood collected on day 16 by a commercial kit (Biodynamics/bmc).

Results and Discussion

A number of *N*-substituted cyclic imides demonstrated potent hypolipidemic activity in mice at 20 mg/kg/day and were more active than clofibrate at 150 mg/kg/day. Compounds **2, 3, 4, 8, 13, 14,** and **22** demonstrated equal ability to phthalimide in suppressing serum cholesterol levels on day 16 (>40 %). Whereas none of the compounds demonstrated more potent activity than phthalimide in suppressing serum triglyceride levels in mice, e.g., compounds **4, 5, 8, 9, 15,** and **16** produced greater than 40 % reduction but only **8** produced greater than 50 % reduction. The pentyl derivative (**8**) was the most active compound of the succinimide series, whereas the propionic acid (**15**) of the 1,8-naphthalimide series appeared to have the highest activity. The butyl derivative (**18**) of the glutarimide series possessed the best activity of the glutarimide series; however, this activity was not as great as that observed for compounds in the other series. Interestingly, the α-phenyl substituted derivative (**22**) of glutarimide proved to be more active than *N*-substituted derivatives, lowering serum cholesterol 49 % and serum triglyceride 36 %, respectively, after 16 days dosing. The α-phenyl substituted derivative (**11**) of succinimide, on the other hand, did not demonstrate improved activity over the *N*-substituted derivatives of that series.

Removal of the phenyl ring of phthalimide (**1**) resulting in succinimide (**6**) led to less hypolipidemic activity in general, e.g., in the case of succinimide (compare **6** to **1**) and the butanone derivatives of succinimide (compare **10** to **5**). In the case of the butyl derivatives of succinimide, there was improved antitriglyceridemic activity but reduced anticholesterolemic activity (compare **7** to **2**), whereas with the pentyl derivatives (compare **8** to **3**) the loss of the aromatic ring led to improved antitriglyceridemic activity with approximately the same activity with regard to serum cholesterol lowering effect. The propionic acid of succinimide (**9**) had activities comparable to the phthalimide derivative (**4**).

Replacement of the phenyl group of phthalimide with the aromatic system of naphthalimide led, in general, to less hypolipidemic action. Comparing glutarimide to 1,8-naphthalimide, which denotes a loss of the aromatic system (compare **17** to **12**), led to a slight improvement of antitriglyceridemic activity, but a slight loss of anticholesterolemic activity. In the butyl glutarimide **18**, there was a marginal reduction in anticholesterolemic activity (compare **18** to **13**). The pentyl glutarimide (**19**)

Table I. The Hypolipidemic Activity of Cyclic Imides in CF_1 Male Mice at 20 mg/kg/day, I.P.

Compound (N=6)	Percent control 16th Day Serum Triglyceride	9th Day Serum Cholesterol	16th Day Serum Cholesterol
(1) Phthalimide	44 ± 8*	63 ± 8*	57 ± 7*
(2) *N*-*n*-Butylphthalimide	82 ± 7	72 ± 10*	54 ± 6*
(3) *N*-*n*-Pentylphthalimide	75 ± 12	76 ± 5*	58 ± 3*
(4) β-(*N*-Phthalimido) propionic acid	58 ± 10*	74 ± 7*	55 ± 11*
(5) 1-(*N*-Phthalimido)butan-3-one	58 ± 7*	67 ± 11*	63 ± 7*
(6) Succinimide	68 ± 7*	78 ± 9*	73 ± 12*
(7) *N*-*n*-Butyl succinimide	65 ± 4*	103 ± 9	85 ± 10
(8) N-n-Pentyl succinimide	49 ± 10*	83 ± 5*	53 ± 7*
(9) β-(*N*-Succinimido) propionic acid	56 ± 6*	68 ± 6*	61 ± 13*
(10) 1-(*N*-Succinimido)butan-3-one	75 ± 11	88 ± 7	90 ± 9
(11) α-Phenylsuccinimide	73 ± 5*	91 ± 5	79 ± 6*
(12) 1,8-Naphthalimide	87 ± 12	81 ± 6*	61 ± 7*
(13) *N*-*n*-Butyl-1,8-naphthalimide	61 ± 6*	94 ± 8	51 ± 7*
(14) *N*-*n*-Pentyl-1,8-naphthalimide	86 ± 6	61 ± 7*	56 ± 3*
(15) 3-[*N*-(1′,8′-Naphthalimido)] propionic acid	56 ± 4*	90 ± 8	62 ± 6*
(16) 1-*N*-(1′,8′-Naphthalimido)butan-3-one	54 ± 15*	94 ± 12	86 ± 9
(17) Glutarimide	77 ± 6*	80 ± 4*	78 ± 5*
(18) *N*-*n*-Butylglutarimide	64 ± 3*	95 ± 8	70 ± 4*
(19) *N*-*n*-Pentylglutarimide	76 ± 8*	71 ± 9*	71 ± 5*
(20) β-(*N*-Glutarimido propionic acid	84 ± 5	97 ± 4	87 ± 7
(21) 1-*N*-(Glutarimido)butan-3-one	84 ± 8	74 ± 4*	72 ± 4*
(22) α-Phenylglutarimide	64 ± 2*	93 ± 4	51 ± 10*
Clofibrate 150 mg/kg	75 ± 5*	88 ± 6	87 ± 5
1 % Carboxymethylcellulose	100 ± 6[a]	100 ± 5[b]	100 ± 6[c]

[a]118 mg%; [b]122 mg/%; [c]135 mg/dl; *$p \leq 0.001$ (Student's "t" test)

Biological activity on compounds **1** to **6, 10, 12,**and **16** has reported previously, reference 1.

showed an improvement in the antitriglyceridemic activity with a loss of anticholesterolemic activity (compare **19** to **14**). The propionic acid derivative of glutarimide (**20**) showed significantly less antihypolipidemic activity than the corresponding 1,8-naphthalimide derivative (**15**). The butanone derivative of glutarimide (**21**) demonstrated decidedly less antitriglyceridemic activity compared to **16**; nevertheless, **21** showed slightly improved anticholesterolemic activity compared to **16**.

Whereas none of the new derivatives were as potent as the parent compound, phthalimide (**1**), in hypolipidemic activity, several agents demonstrated potent activity. The pentyl derivative of succinimide (**8**) demonstrated the most consistent activity and was impressive compared to clofibrate. This analogue warrants further study as a possible hypolipidemic agent.

Acknowledgement

The authors wish to thank Greg Webb for his technical assistance. This research was conducted with the financial support from the National Heart, Lung and Blood Institute 2ROI HL25680 grant.

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In Vitro Antimicrobial Activity of Benzoquinolinediones

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Received: February 9, 1984; accepted: May 25, 1984.

Abstract: The *in vitro* antibacterial and antifungal activity of benz[*g*]isoquinoline-5,10-dione (**1**), benzo[*g*]quinoline-5, 10-dione (**2**), benzo[*g*]quinoline-5,6-dione (**3**), and anthraquinone (**4**) was determined using the agar well-diffusion assay. The minimum inhibitory concentrations (MIC's) of each of the active compounds (**1–3**) was determined using the two-fold serial dilution technique. Of the four compounds tested, benz[*g*]isoquinoline-5,10-dione exhibited the best overall activity against both bacteria and fungi. Particularly noteworthy was its significant antifungal activity which was comparable to the activity of the standard antifungal antibiotic amphotericin B.

Walton (1) first reported in 1981 that commercial reagent grade samples of acridine were teratogenic to the cricket, *Acheta domesticus* (L.), and that the teratogenicity was due to impurities in the samples. The substance primarily responsible for the teratogenicity of commercial reagent grade acridine was later isolated and identified as benz[*g*]isoquinoline-5, 10-dione (**1**), a benzoquinolinedione isomer, which was estimated to be present at a concentration of only 20 ppm (2). In another study (3), compound **1** was shown to have potent teratogenic and embryotoxic activity in *A. domesticus*. At a dose of 0.1 ng/egg, compound **1** was capable of producing morphological abnormalities in cricket embryos. Furthermore, of three structurally related compounds (**2, 3** and **4**) tested for their teratogenicity, only benz[*h*]quinoline-5,6-dione (**3**) has been shown to be moderately active.

Elsewhere, it has been reported (4) that compound **3** showed relatively good *in vitro* activity against Ehrlich ascites tumor cells and Sarcoma 180 ascites tumor cells. It was also reported (5) that compound **3** was moderately active against certain strains of *Staphylococcus, Shigella* and *Salmonella.*

As one part of a study to ascertain the complete spectrum of biological activity of compound I and related benzoquinolinediones, the antimicrobial activities of each of the compounds was determined.

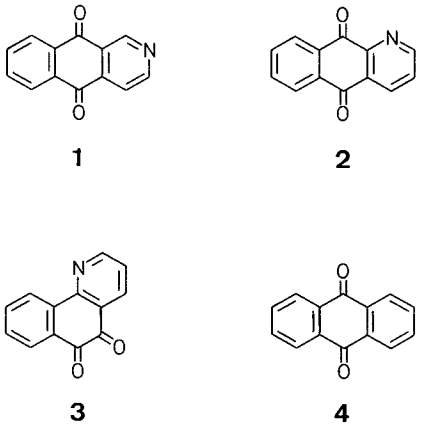

Fig. 1 Structures of benz[*g*]isoquinoline-5, 10-dione, benzoquinolinediones and anthraquinone.

Materials and Methods

Source of compounds: Benz[*g*]isoquinoline-5,10-dione (**1**) and benzo[*g*]-quinoline-5,10-dione (**2**) were synthesized using the method of Philips (6). The synthesis of benzo[*h*]quinoline-5, 10-dione (**3**) was carried out according to Skraup and Cobenzl (7). Anthraquinone (**4**) was obtained from Aldrich Chemical Company (Milwaukee, Wisconsin). All compounds were purified by preparative high pressure liquid chromatography to 99% or more, and

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