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Report

The Synthesis of Homophthalimide and Related Derivatives and Their Hypolipidemic Activity in Rodents

Akula R. K. Murthy,[1] James M. Chapman, Jr.,[1] Steven D. Wyrick,[1] and Iris H. Hall[1,2]

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Homophthalimide and a series of N-alkyl-substituted derivatives were investigated to determine their ability to lower serum cholesterol and triglyceride levels in mice. At 20 mg/kg/day these agents were equally potent or more potent than clofibrate at 150 mg/kg/day. However, the homophthalimide series was not as active as other hypolipidemic cyclic imides investigated by this laboratory. Compounds that caused a greater than 30% reduction of both serum cholesterol and triglyceride levels after 16 days at 20 mg/kg/day ip include the N-propyl, N-phenyl, 3′-methylphenyl, 3′-methoxyphenyl, 3′-chlorophenyl, and the 3′-ethylphenyl derivatives. Substitutions in the 3′ position of the phenyl group afforded the most active compounds for reducing blood lipid levels in rodents.

KEY WORDS: homophthalimide; hypolipidemic agents; cholesterol-lowering agents; triglyceride-lowering agents.

INTRODUCTION

Our original investigation demonstrated that cyclic imides, e.g., phthalimide (1), were potent hypolipidemic agents at the relative low dose of 20 mg/kg/day when compared to clofibrate at 150 mg/kg/day, reducing both serum cholesterol and triglyceride >40%. Further analysis showed that the cyclic imide ring could be chemically modified in a number of ways and still retain good hypolipidemic activity, e.g., saccharin (2), 1,8-naphthalimide (3), indazalones (4), indan-1,3-diones (5), 3-imino-1-oxoisoindolines (6), and finally, to a six-member system, e.g., 2,3-dihydrophthalazine-1,4-dione (7). Consequently, we decided to test another six-member system, specifically homophthalimide (1,2,3,4-tetrahydroisoquinoline-1,3-dione), which demonstrated good activity. Nevertheless, the activity was not as potent as that of phthalimide and saccharin. Thus, a structure activity study was undertaken to determine if an improvement in activity for the homophthalimide series could be achieved, and those results are reported herein.

MATERIALS AND METHODS

Chemistry

Homophthalimide and N-alkyl derivatives were prepared by condensation of ammonia or the appropriate alkyl amine with homophthalic acid, while N-aryl derivatives were prepared by condensation of the appropriate aniline with homophthalic anhydride. In an attempt to oxidize the N-(3-hydroxybutyl) derivative to the N-(3-oxobutyl) with CrO_3, the benzylic carbon was also oxidized to give the tetrahydroisoquinolintrione 27. The physical and chemical characteristics of the N-substituted derivatives can be found in Table I.

Melting points are uncorrected and were determined on a Thomas–Hoover melting point apparatus. Column chromatography was performed with silica gel G-60 (60–200 mesh). ^{1}H-NMR spectra were obtained on a JEOL FX 60-MHZ spectrometer. Elemental analyses were performed by M-H-W Laboratories, Pheonix, Arizona, and are correct within ±0.4%.

Homophthalimide and N-Alkyl Derivatives

General Procedure (1–6)

A mixture of homophthalic acid (0.03 mol) and conc. ammonium hydroxide or 40% alkyl amine (25 ml) was refluxed for 2 hr and the reaction mixture was distilled at atmospheric pressure. The product was recrystallized from the suitable solvent.

N-Arylhomophthalimides

General Procedure (7–25)

A mixture of homophthalic anhydride (0.03 mol) and the suitably substituted aniline (0.04 mol) was heated for 0.5 hr at 180–190°C. The hard mass obtained upon cooling was purified by column chromatography with silica gel (chloroform:ethylacetate, 9:1) and was recrystallized from the appropriate solvent.

[1] Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514.

[2] To whom correspondence should be addressed.

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Table I. Physical Characteristics of N-Substituted Homopthalimides (1,2,3,4-Tetrahydroisoquinoline-1,3-diones and) Related Compounds

Compound No.	R	MP (°C) (lit.)	Yield	Formula
1	Hydrogen[a]	233–235 (234–36)[9,j]	80	—
2	Methyl[b]	108–110 (110)[10]	86	
3	Ethyl[c]	103–104 (105)[11]	70	—
4	Propyl[d]	59–60 (61)[9]	63	—
5	*n*-Butyl[e]	53–54 (49)[8]	56	—
6	*n*-Pentyl	—	65	$C_{14}H_{17}NO_2$
7	Phenyl[b]	181–184	78	$C_{15}H_{11}NO_2$
8	2-Methylphenyl[f]	102–104 (106)[12]	45	—
9	3-Methylphenyl[c]	108–110	65	$C_{16}H_{13}NO_2$
10	4-Methylphenyl[c]	166–168	54	$C_{16}H_{13}NO_2$
11	2-Methoxyphenyl[f]	151–153	56	$C_{16}H_{13}NO_3$
12	3-Methoxyphenyl[f]	162–164	48	$C_{16}H_{13}NO_3$
13	4-Methoxyphenyl[f]	184–186	62	$C_{16}H_{13}NO_3$
14	2-Chlorophenyl[g]	118–120	40	$C_{15}H_{10}NO_2Cl$
15	3-Chlorophenyl[g]	148–150	64	$C_{15}H_{10}NO_2Cl$
16	4-Chlorophenyl[f]	166–168	68	$C_{15}H_{10}NO_2Cl$
17	2-Acetylphenyl[f]	144–146	38	$C_{17}H_{13}NO_3$
18	3-Acetylphenyl[c]	187–189	61	$C_{17}H_{13}NO_3$
19	4-Acetylphenyl[h]	178–181	48	$C_{17}H_{13}NO_3$
20	2,4-Dimethylphenyl[f]	173–175 (178)[13]	72	—
21	2,4-Dimethoxyphenyl[b]	192–195	22	$C_{17}H_{15}NO_4$
22	2,4-Dichlorophenyl[f]	155–157	63	$C_{15}H_9NO_2Cl_2$
23	2-Ethylphenyl[c]	74–76	40	$C_{17}H_{15}NO_2$
24	3-Ethylphenyl[h]	117–119	41	$C_{17}H_{15}NO_2$
25	4-Ethylphenyl[h]	126–128	46	$C_{17}H_{15}NO_2$
26	2-Carboxyethyl[i]	154–155	30	$C_{12}H_{11}NO_4$
27	2-(3-Oxobutyl)	—	20	$C_{13}H_{11}NO_4$

[a] Acetic acid.
[b] Ethanol.
[c] Benzene.
[d] Aqueous ethanol.
[e] Water.
[f] Ethyl acetate.
[g] Methanol.
[h] Benzene/hexane.
[i] Toluene.
[j] Superscripts 9–13, Refs. 9–13.

N-(2'-Carboxyethyl)-homophthalimide (26)

To a suspension of homophthalic anhydride (3.24 g; 0.02 mol) in dry toluene (50 ml) was added β-alanine (1.78 g; 0.02 mol) and the resulting mixture was refluxed until 0.2 ml of H_2O was removed azeotropically using a Dean-Stark apparatus. The solvent was evaporated and the solid was recrystallized from toluene.

N-(3-Oxobutyl)-1,2,3,4-tetrahydroisoquinoline-1,3,4-trione (27)

A mixture of homophthalic anhydride (3.40 g; 0.022 mol) and 4-amino butan-2-ol (2.0 g; 0.02 mol) in dry toluene (50 ml) was refluxed, and 0.4 ml of water was removed azeotropically using a Dean-Stark apparatus. The solvent was removed under vacuum, and the dark residue was purified by column chromatography with silica gel (CH_2Cl_2:EtOAc, 7:3) to afford the alcohol (2.8 g; 57%). A solution of chromium trioxide (1.2 g; 0.012 mol), acetic acid (5.6 ml), and water (1.4 ml) was added slowly to a cooled and stirred solution of alcohol (2.8 g; 0.12 mol) in acetic acid (9.2 ml). The dark mixture was stirred overnight at room temperature. The contents were poured into water (120 ml) and extracted with methylene chloride. The organic layer was dried and evaporated to afford the product, which was purified on a column with CH_2Cl_2:EtOAc = 9:1.

Hypolipidemic Screens

Test compounds were suspended in 1% (carboxymethyl)cellulose–water and administered intraperitoneally to CF_1 male mice (~25 g) for 16 days at a dose of 20 mg/kg/day. On days 9 and 16, blood was collected in nonheparinized microcapillary tubes by tail vein bleeding and the serum was obtained by centrifugation for 3 min. The serum cholesterol levels were determined by a modification of the Liebermann–Burchard reaction (8). Blood was also collected on day 16 in nonheparinized microcapillary tubes and the serum was obtained. Serum triglyceride levels were assayed by a commercial kit from this sample of serum.

RESULTS AND DISCUSSION

A series of N-substituted homophthalimide derivatives proved to be potent hypolipidemic agents in mice after 16 days of dosing at 20 mg/kg/day. Homophthalimide (**1**) 20 mg/kg/day for 16 days reduced serum cholesterol levels 26% (Table II). The N-substituted propyl derivative (**4**) demonstrated an approximately equal hypocholesterolemic activity, i.e., 35%, but did afford improved hypotriglyceridemic activity, with an ~35% reduction. The N-substituted ethyl derivative (**3**) demonstrated a good hypotriglyceridemic activity of 39%; however, the hypocholesterolemic activity was reduced (17%).

The opposite relationship was found with the N-methyl (**2**) derivative, which demonstrated good hypocholesterolemic activity, i.e., 33%, but poor hypotriglyceridemic activity (16%). The N-phenyl derivative (7) showed good hypocholesterolemic (39%) and hypotriglyceridemic activity (31%). Substitution of the phenyl ring with a methyl group, an electron-releasing group, at the 2′ and 3′ position (**8,9**) led to improved hypotriglyceridemic activity of 39 and 46%, respectively. The 4′-substituted methyl group (**10**) led to improved hypocholesterolemic activity of 41% but a loss of the hypotriglyceridemic activity.

Another electron-releasing group, the methoxy group, was substituted in the 2′, 3′, or 4′ position of the phenyl ring. Of the methoxy-substituted derivatives (11–13), the 3′-methoxyphenyl (**12**) demonstrated the best activity, with a 37% reduction of serum cholesterol and a 36% reduction of serum triglyceride levels after 16 days of dosing at 20 mg/kg/day. Of the chloro-substituted derivatives, which are electron-withdrawing groups, the 3′-chlorophenyl derivative (**15**) demonstrated a 31% reduction of cholesterol and a 44% reduction of triglyceride levels. Substitution of acetyl, an electron-withdrawing group, on the phenyl group (**17–19**) afforded compounds which generally were less active at 20 mg/kg/day as hypolipidemic agents. A similar finding was observed when disubstitutions of methyl (**20**), methoxy (**21**), and chlorine (**22**) on the phenyl group were evaluated for hypolipidemic activity. In general, the disubstituted phenyl derivatives were less active in both screens than the monosubstituted phenyl derivatives.

For derivatives where ethyl, an electron-releasing group, was substituted (**23–25**), the 3′-ethylphenyl (**24**) derivatives possessed the best activity, with a 33% reduction of both serum cholesterol and triglyceride levels at 20 mg/kg/day. The N-carboxyethyl substitution (**26**) and the N-(3′-oxobutyl) (**27**) afforded activities in both screens which were less than the N-alkyl and aromatic substitutions.

The homophthalimide derivatives at 20 mg/kg/day were effective hypolipidemic agents, significantly lowering both serum cholesterol and triglycerides. These agents have equal or better hypolipidemic activity than clofibrate at 150 mg/kg/day. Of the N-alkyl-substituted derivatives, the N-propyl homophthalimide had the best activity. This differed from the N-alkyl substitution of phthalamide (1), saccharin (2), and indazalone (4), where the N-butyl derivative demonstrated the highest hypolipidemic activity. N-substitution with the ketone or propionic acid led to less activity. The homophthalimide and N-alkyl-substituted derivatives were not as potent as previously investigated cyclic imides derivates at 20 mg/kg/day. Apparently, the presence of an additional carbon in the cyclic imide ring reduces hypolipidemic activity in rodents.

When substitutions of electron-releasing groups were made on the 3′ position of the phenyl group, improved hypolipidemic activity was afforded. Generally, electron-withdrawing groups substituted on the phenyl ring were less active, with the exception of 3′-chlorophenyl derivative (**15**), which lowered serum triglyceride levels 44%. Disubstitution of the phenyl (**20–22**) ring led to less activity when compared to the monosubstituted derivatives.

Table II. Hypolipidemic Activity of Homophthalimide N-Substituted Derivatives in CF_1 Male Mice at 20 mg/kg/day ip

Compound No.	Percentage control ($\bar{X}$ ± SD)		
	Serum cholesterol		Serum triglyceride
(N = 6)	Day 9	Day 16	Day 16
1	89 ± 8	69 ± 11*	74 ± 6*
2	82 ± 7**	67 ± 6*	84 ± 5**
3	88 ± 7	83 ± 6**	61 ± 4*
4	69 ± 7*	65 ± 6*	65 ± 5*
5	102 ± 4	67 ± 9*	99 ± 6
6	78 ± 6*	70 ± 5*	77 ± 6
7	63 ± 6*	61 ± 5*	69 ± 7*
8	83 ± 7**	67 ± 6*	61 ± 6*
9	64 ± 5*	63 ± 4*	54 ± 5*
10	64 ± 5*	59 ± 5*	73 ± 6*
11	85 ± 6**	80 ± 5*	63 ± 5*
12	65 ± 6*	63 ± 5*	64 ± 5*
13	86 ± 7	74 ± 6*	75 ± 6*
14	72 ± 6*	65 ± 5*	75 ± 6*
15	74 ± 6*	69 ± 6*	56 ± 5*
16	90 ± 7	80 ± 6*	69 ± 4*
17	76 ± 6*	72 ± 6*	72 ± 5*
18	89 ± 10	86 ± 6**	83 ± 4*
19	92 ± 6	89 ± 5	82 ± 6**
20	91 ± 5	89 ± 7	79 ± 5*
21	79 ± 6*	77 ± 6*	75 ± 5*
22	82 ± 7**	71 ± 5*	83 ± 6**
23	76 ± 8*	74 ± 4*	76 ± 5*
24	76 ± 6*	67 ± 6*	67 ± 5*
25	95 ± 7	78 ± 5*	81 ± 6*
26	100 ± 7	77 ± 10**	73 ± 6*
27	86 ± 8	87 ± 7	73 ± 6*
Clofibrate (150 mg/kg)	88 ± 7	87 ± 5**	75 ± 7*
1% Carboxymethylcellulose	100 ± 7[a]	100 ± 6[b]	100 ± 7[c]

[a] 128 mg%.
[b] 129 mg%.
[c] 137 mg%.
* $P \leqq 0.001$.
** $P \leqq 0.005$.

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