Antihyperlipidemic Activity of Amine Cyanoboranes, Amine Carboxyboranes, and Related Compounds

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Abstract □ A series of amine cyanoboranes and amine carboxyboranes were observed to be antihyperlipidemic agents in mice; *i.e.*, they lowered serum cholesterol and triglyceride levels significantly. These compounds appeared to inhibit lipid synthesis in the early stages. The ability to lower serum cholesterol levels appeared to correlate with the suppression of the regulatory enzyme of cholesterol synthesis, β-hydroxy-β-methylglutaryl-CoA reductase activity. The reduction of serum triglycerides correlated with the ability of the borane compound to suppress liver fatty acid synthetase activity.

Keyphrases □ Amine carboxyboranes—borane analogs of α-amino acids, evaluation for antihyperlipidemic activity, mice □ Amine cyanoboranes—borane analogs of α-amino acids, evaluation for antihyperlipidemic activity, mice □ Antihyperlipidemic activity—effects of amine cyanoboranes and amine carboxyboranes on serum cholesterol and triglyceride levels in mice

The antineoplastic (1) and anti-inflammatory (2) activities of a series of amine cyanoboranes, amine carboxyboranes (boron analogs of amino acids), and related analogs in mice were reported previously. While studying the metabolic effects of the cyanoborane derivatives in Ehrlich ascites cells, it was noted that a number of these analogs significantly reduced the activity of the regulatory enzymes of cholesterol synthesis. For example, trimethylamine cyanoborane reduced the enzymatic activity of β-hydroxy-β-methylglutaryl-CoA reductase activity by 25%. This observation suggested that the amine cyanoborane and amine carboxyborane analogs should be screened for antihyperlipidemic effects. Those studies are now reported.

EXPERIMENTAL

Compounds—The following reagents were purchased: *tert*-butylamine borane[1] [$(CH_3)_3CNH_2{\cdot}BH_3$] (I), morpholine borane[1] [$O(CH_2CH_2)_2NH{\cdot}BH_3$] (II), trimethylamine borane[2] [$(CH_3)_3N{\cdot}BH_3$] (III), and dimethylamine borane[2] [$(CH_3)_2NH{\cdot}BH_3$] (IV). Trimethylamine cyanoborane [$(CH_3)_3N{\cdot}BH_2CN$] (V), dimethylamine cyanoborane [$(CH_3)_2NH{\cdot}BH_2CN$] (VI), trimethylamine-*N*-ethylamidoborane [$(CH_3)_3N{\cdot}BH_2C(O)N(CH_2CH_3)H$] (VII), trimethylamine carboxyborane [$(CH_3)_3N{\cdot}BH_2COOH$] (VIII), trimethylamine iodoborane [$(CH_3)_3N{\cdot}BH_2I$] (IX), and hexakis(ammonia cyanoborane)sodium iodide {$[Na(NH_3{\cdot}BH_2CN)_6]I$} (X) were prepared by procedures outlined previously (1).

Likewise, the following were prepared by previously outlined procedures (2): *N,N,N′,N′*-tetramethylethylenediamine-bis(cyanoborane) $[CH_2N(CH_3)_2{\cdot}BH_2CN]_2$ (XI), *N,N,N′,N′*-tetramethylethylenediamine-bis(carboxyborane) $[CH_2N(CH_3)_2{\cdot}BH_2COOH]_2$ (XII), *N,N,N′,N′*-tetramethylethylenediamine-bis(*N*-ethylamidoborane) $[CH_2N(CH_3)_2{\cdot}BH_2C(O)NHCH_2CH_3]_2$ (XIII), *N*-methylmorpholine cyanoborane $[O(CH_2CH_2)_2N(CH_3)_2{\cdot}BH_2CN]$ (XIV), pyridine cyanoborane ($C_5H_5N{\cdot}BH_2CN$) (XV), pyridine carboxyborane ($C_5H_5N{\cdot}BH_2COOH$) (XVI), ammonia cyanoborane ($NH_3{\cdot}BH_2CN$) (XVII), trimethylamine carboethoxyborane $[(CH_3)_3N{\cdot}BH_2COOCH_2CH_3]$ (XVIII), 3-dimethylaminoproprionitrile cyanoborane $[NCCH_2CH_2N(CH_3)_2{\cdot}BH_2CN]$ (XIX), and ethylenediamine-bis(cyanoborane) $(CH_2NH_2{\cdot}BH_2CN)_2$ (XX).

Ammonia carboxyborane ($NH_3{\cdot}BH_2COOH$) (XXI), the boron analog of glycine, was prepared by an amine-displacement reaction on $(CH_3)_3N{\cdot}BH_2COOH$ with liquid ammonia (3). Similarly, methylamine carboxyborane ($CH_3NH_2{\cdot}BH_2COOH$) (XXII) and dimethylamine carboxyborane [$(CH_3)_2NH{\cdot}BH_2COOH$] (XXIII) were prepared by amine-displacement reactions on $(CH_3)_3N{\cdot}BH_2COOH$ with the appropriate amine (4). Sodium dimethylaminohydroborate [$Na(CH_3)_2NBH_3$] (XXIV) was obtained commercially[3].

Serum Antihyperlipidemic Effects—CF_1 male mice (~30 g) were fed rodent laboratory food with water *ad libitum* during the experiment. Drugs were suspended in 1% carboxymethylcellulose–water and homogenized. Doses were calculated on weekly weights of the mice (5). Test compounds were administered at 20 mg/kg/day ip. On Days 9 and 16, blood was collected by tail vein bleeding in alkali-free, nonheparinized microcapillary tubes and centrifuged 3 min to obtain the serum. Duplicate 30-μl samples of nonhemolyzed serum were used to determine the serum cholesterol levels (milligram percent) by a modification of the Liebermann–Burchard reaction (6). A separate group of mice were bled on Day 14, and their serum triglyceride levels (milligram percent) were determined by using 25-μl samples (7).

Enzymatic Assays—Compounds were tested *in vitro* at 10^{-5} *M* concentrations for their effects on enzymatic activity of a 10% liver homogenate prepared in 0.25 *M* sucrose and 0.001 *M* ethylenediaminetetraacetic acid, pH 7.2. Adenosine triphosphate citrate-lyase activity was measured by the method of Hoffmann *et al.* (8). Acetyl-CoA synthetase activity was determined by the method of Goodridge (9). The acetyl-CoA formed from each enzymatic reaction was coupled with hydroxylamine to produce acetohydroxamide, which was measured at 540 nm. Acetyl-CoA carboxylase activity was measured by the method of Greenspan and Lowenstein (10), utilizing sodium-[^{3}H]bicarbonate (6.2 mCi/mmole) after 30 min of incubation at 37° for polymerization of the enzymes (11).

Fatty acid synthetase activity was determined by the method of Brady *et al.* (12), utilizing [2′-^{14}C]malonyl-CoA (37.5 mCi/mmole) incorporated into newly synthesized fatty acids. [^{14}C]Acetate (57.8 mCi/mmole) incorporation into cholesterol (β-hydroxy-β-methylglutaryl-CoA reductase activity) was measured as described by Haven *et al.* (13) and extracted by the method of Wada *et al.* (14).

RESULTS AND DISCUSSION

The amine cyanoborane and amine carboxyborane compounds significantly reduced serum cholesterol levels in mice after 16 days of dosing (Table I). Compound XXI demonstrated the best inhibitory effect by causing 56% reduction of serum cholesterol at 20 mg/kg/day. Compounds IV, VII, and VIII caused >40% inhibition while I, II, X, XV, XVIII, XXII, and XXIII caused >30% inhibition of serum cholesterol levels. The serum triglyceride levels also were lowered after 14 days of treatment with the borane derivatives; V, XVIII, XXII, and XXIV caused >40% reduction. Compounds VII, VIII, IX, XII, and XV–XIX reduced the serum triglyceride levels at least 30%, whereas II and XXIII caused a 20% reduction.

With *in vitro* enzymatic assays, it was demonstrated that acetyl-CoA synthetase activity was suppressed >50% by II and XV and 40% by IV, V, X, XVI, XVIII, XIX, XXII, and XXIV (Table II). Compounds VIII, IX, XVII, XX, and XXIII caused at least 30% inhibition. Citrate-lyase activity was inhibited at least 30% by VI, XIV, and XV and 20% by II, III, V, IX–XI, XVII, and XVIII. β-Hydroxy-β-methylglutaryl-CoA reductase activity was inhibited 62% by XXI and 50% by IV. Compounds V, VIII, XI–XV, XVIII, XX, and XXIII suppressed this enzymatic activity by

[1] Alfa Products.
[2] Aldrich Chemical Co.
[3] Callery Chemical Co.

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Table I—Effects of Boron Analogs on Serum Lipids in Mice (n = 8)

Compound	Formula	Dose, mg/kg	Percent of Control, $\bar{x} \pm SD$ Serum Cholesterol Day 9	Serum Cholesterol Day 16	Serum Triglyceride, Day 14
I	$(CH_3)_3CNH_2{\cdot}BH_3$	10	77 ± 5^a	64 ± 8^a	90 ± 7
II	$O(CH_2CH_2)_2NH{\cdot}BH_3$	20	67 ± 6^a	64 ± 5^a	74 ± 9^a
III	$(CH_3)_3N{\cdot}BH_3$	20	91 ± 7^b	70 ± 3^a	85 ± 5^a
IV	$(CH_3)_2NH{\cdot}BH_3$	20	71 ± 4^a	58 ± 5^a	88 ± 11
V	$(CH_3)_3N{\cdot}BH_2CN$	20	92 ± 8^a	72 ± 6^a	58 ± 9^a
VI	$(CH_3)_2NH{\cdot}BH_2CN$	20	88 ± 5^b	72 ± 7^a	98 ± 9
VII	$(CH_3)_3N{\cdot}BH_2C(O)NHCH_2CH_3$	20	81 ± 5^a	58 ± 6^a	64 ± 7^a
VIII	$(CH_3)_3N{\cdot}BH_2COOH$	20	68 ± 6^a	51 ± 6^a	61 ± 5^a
IX	$(CH_3)_3N{\cdot}BH_2I$	20	100 ± 7	85 ± 5^a	65 ± 8^a
X	$[Na][NH_3{\cdot}BH_2(CN)]_6]I$	20	88 ± 6^b	64 ± 5^a	—
XI	$[CH_2N(CH_3)_2{\cdot}BH_2CN]_2$	20	88 ± 6^b	73 ± 7^a	89 ± 7^b
XII	$[CH_2N(CH_3)_2{\cdot}BH_2COOH]_2$	20	95 ± 4	89 ± 5^c	89 ± 10
XIII	$[CH_2N(CH_3)_2{\cdot}BH_2C(O)NHCH_2CH_3]_2$	20	100 ± 3	90 ± 4^c	68 ± 6^a
XIV	$O(CH_2CH_2)_2NCH_3{\cdot}BH_2CN$	5	84 ± 7^a	73 ± 8^a	95 ± 11
XV	$C_5H_5N{\cdot}BH_2CN$	5	81 ± 8^a	66 ± 3^a	70 ± 7^a
XVI	$C_5H_5N{\cdot}BH_2COOH$	5	82 ± 4^a	71 ± 5^a	60 ± 8^a
XVII	$NH_3{\cdot}BH_2CN$	5	89 ± 7^b	85 ± 5^a	64 ± 4^a
XVIII	$(CH_3)_3N{\cdot}BH_2COOCH_2CH_3$	20	76 ± 7^a	64 ± 6^a	57 ± 5^a
XIX	$NCCH_2CH_2N(CH_3)_2{\cdot}BH_2CN$	20	98 ± 6	76 ± 7	66 ± 9
XX	$(CH_2NH_2{\cdot}BH_2CN)_2$	5	83 ± 7^a	96 ± 7^a	84 ± 4^a
XXI	$NH_3{\cdot}BH_2COOH$	20	56 ± 5	44 ± 6	101 ± 10
XXII	$CH_3NH_2{\cdot}BH_2COOH$	20	66 ± 5^a	66 ± 5^a	55 ± 6^a
XXIII	$(CH_3)_2NH{\cdot}BH_2COOH$	20	65 ± 6^a	63 ± 4^a	77 ± 8^a
XXIV	$Na(CH_3)_2NBH_3$	20	74 ± 4^a	74 ± 5^a	59 ± 9^a
Carboxymethylcellulose (1%)			100 ± 5^e	100 ± 6^e	100 ± 8^f

[a] $p \leq 0.001$. [b] $p \leq 0.025$. [c] $p \leq 0.010$. [d] 115 mg %. [e] 118 mg %. [f] 130 mg %.

Table II—*In Vitro* Effects of Boron Analogs on Regulatory Enzymes of Cholesterol and Triglyceride Synthesis

Compound	Percent of Control, $\bar{x} \pm SD$ Acetyl-CoA Synthetase	Citrate-lyase	β-Hydroxy-β-methylglutaryl CoA Reductase	Acetyl-CoA Carboxylase	Fatty Acid Synthetase
I	78 ± 6^a	97 ± 6	79 ± 8^a	95 ± 6	100 ± 10
II	43 ± 5^a	79 ± 5^a	118 ± 9	82 ± 7^b	92 ± 9^a
III	77 ± 8^a	72 ± 6^a	74 ± 8^a	86 ± 7^c	79 ± 10^b
IV	59 ± 7^a	96 ± 7	50 ± 5^a	83 ± 6^b	98 ± 9
V	50 ± 7^a	79 ± 8^a	64 ± 7^a	100 ± 9	64 ± 7^a
VI	71 ± 8^a	67 ± 7^a	106 ± 8^a	100 ± 4	77 ± 8^a
VII	—	—	—	—	—
VIII	60 ± 9^a	100 ± 8	61 ± 9^a	100 ± 5	62 ± 5^d
IX	69 ± 5^a	77 ± 5^a	89 ± 7^c	79 ± 6^a	76 ± 7^a
X	50 ± 7^a	71 ± 7^a	74 ± 8^a	—	—
XI	76 ± 5^a	70 ± 6^a	58 ± 6^a	103 ± 8	100 ± 9
XII	89 ± 8^c	99 ± 5	62 ± 4^a	106 ± 7	100 ± 11
XIII	80 ± 9^a	80 ± 7^a	64 ± 6^a	113 ± 7	65 ± 8^a
XIV	77 ± 7^a	67 ± 7^a	62 ± 5^a	118 ± 9	89 ± 7^c
XV	49 ± 6^a	67 ± 8^a	58 ± 7^a	78 ± 8^b	102 ± 8
XVI	50 ± 4^a	86 ± 4^a	72 ± 8^a	82 ± 5^b	92 ± 6
XVII	61 ± 7^a	78 ± 10^a	74 ± 7^a	94 ± 6	100 ± 11
XVIII	55 ± 8^a	72 ± 5^a	61 ± 6^a	65 ± 4^a	92 ± 9
XIX	54 ± 5^a	94 ± 6	78 ± 6^a	100 ± 7	87 ± 8^c
XX	66 ± 6^a	102 ± 5	56 ± 5^a	100 ± 7	99 ± 10
XXI	—	100 ± 4	38 ± 7^a	101 ± 8	70 ± 7^a
XXII	55 ± 7^a	100 ± 8	100 ± 8	40 ± 6^a	72 ± 7^a
XXIII	63 ± 4^a	100 ± 11	60 ± 5^a	75 ± 5^a	83 ± 9^c
XXIV	53 ± 7^a	93 ± 9	87 ± 4^a	101 ± 8	100 ± 10
Carboxymethylcellulose (1%)	100 ± 5^d	100 ± 4^e	100 ± 4^f	100 ± 7^g	100 ± 6^h

[a] $p \leq 0.001$. [b] $p \leq 0.010$. [c] $p \leq 0.025$. [d] 28.5 mg of acetyl-CoA formed/g of wet tissue in 30 min. [e] 30.5 mg of citrate hydrolyzed/g of wet tissue in 30 min. [f] 1,142,065 dpm/g of wet tissue in 60 min. [g] 32,010 dpm/g of wet tissue in 30 min. [h] 37,656 dpm/g of wet tissue in 30 min.

at least 35%; I, III, X, XVI, XVII, and XIX suppressed this activity by 20%. Acetyl-CoA carboxylase activity was inhibited >20% by IX, XV, and XXIII, whereas XXII caused 60% inhibition of enzymatic activity. Fatty acid synthetase activity was suppressed >30% by V, VIII, and XIII and 20% by III, VI, IX, XXI, and XXII.

The ability to lower serum cholesterol levels appeared to correlate positively with the suppression of the regulatory enzyme of cholesterol synthesis, β-hydroxy-β-methylglutaryl-CoA reductase. For example, XXI lowered serum cholesterol levels and β-hydroxy-β-methylglutaryl-CoA reductase activity maximally. Compound IV followed the same pattern. The ability to lower serum triglyceride levels appeared to correlate positively with the inhibition of fatty acid synthetase activity, as seen with V, VIII, and XIII. Fatty acid synthetase is required for fatty acid synthesis, which is needed for triglyceride synthesis. Specific boron analogs inhibited acetyl-CoA carboxylase, the regulatory enzyme of fatty acid synthesis, and adenosine triphosphate citrate-lyase, a hydrolytic enzyme needed for the cleavage of citrate from the mitochondria to acetyl-CoA. However, the inhibition of neither enzyme seemed to correlate directly with the ability of the boron analogs to suppress serum cholesterol and triglyceride levels.

The ability to lower acetyl-CoA synthetase enzymatic activity appeared to be linked to both the ability to lower serum cholesterol and triglyceride levels, as observed with II, IV, V, VIII, XV, XVI, XVIII, and XXII–XXIV. Acetyl-CoA synthetase is required in the activation of acetate in the cytoplasm for the synthesis of cholesterol and fatty acids. Thus, it was demonstrated that the amine cyanoborane and carboxyborane an-

alogs were potent antihyperlipidemic agents in mice by suppressing both cholesterol and triglyceride levels. The probable site of action of the boron analogs is in the early synthesis of lipids.

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Inhibition of Histidine Decarboxylase by Imidazole Derivatives

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Abstract □ A series of 4-imidazolylmethyl arylsulfides, sulfoxides, and sulfones and two carbon isosteres of 4-imidazolylmethylphenyl sulfide (I) were synthesized and tested for inhibition of histidine decarboxylase from rat stomach. None of these analogs of I met the criterion of a potent and specific inhibitor of histidine decarboxylase.

Keyphrases □ Imidazoles, 4-substituted—synthesis and evaluation for inhibition of histidine decarboxylase □ Histidine decarboxylase—inhibition, synthesis and evaluation of 4-substituted imidazoles □ Structure–activity relationships—synthesis and evaluation of 4-substituted imidazoles for inhibition of histidine decarboxylase

Due to the implication of histamine in many physiological processes (1, 2), there has been interest in regulating its *de novo* biosynthesis by inhibiting histidine decarboxylase (EC 4.1.1.22) (3–7). A specific and potent inhibitor of this enzyme would be important as a new type of antihistamine and as a useful research tool. The authors previously reported on some derivatives of histidine as candidate inhibitors of histidine decarboxylase from rat stomach (3, 4). This paper summarizes the synthesis and evaluation of some 4-substituted imidazoles as inhibitors of this pharmacologically important enzyme.

DISCUSSION

The imidazolyl sulfides in Table I were prepared by reaction of the appropriate 4-imidazolylalkyl chloride with a mercaptan by a modification of a literature method (7, 8). Oxidation of I or II with hydrogen peroxide gave the sulfoxides VI and VIII or sulfones VII and IX. If the reactions were heated, partial decomposition occurred and the yields were diminished. Application of the Wittig reaction to 4-(*N*-triphenylmethyl)imidazolecarboxaldehyde (4), followed by removal of the trityl group and catalytic hydrogenation, gave IV and V.

Inhibition of histidine decarboxylase was measured as described previously (3). The inhibition obtained with I and II was in close agreement with reported values (7). Varying the nature of the bridge between the imidazole and phenyl rings resulted in a loss in inhibition relative to I (II–IX in Table II). Insertion of nitrogen in the phenyl ring (X and XI) also was deleterious to activity. Substitution of a methyl group on the bridge (XII) gave some enhancement in inhibition with an I_{50} of $4.7 \pm 0.3 \times 10^{-5}$ *M*. Extending the chain length (XIII and XIV) resulted in a loss in inhibition.

In conclusion, several alterations in the structure of I were made, but none of the analogs met the criteria of a potent and specific inhibitor of histidine decarboxylase.

EXPERIMENTAL[1]

Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. The analytical samples gave combustion values for carbon, hydrogen, and nitrogen within 0.4% of the theoretical values.

4-Imidazolylmethylphenyl Sulfide Hydrochloride (I)—*Method A*—To an ice bath-cooled solution of 3.24 g (60.0 mmoles) of sodium methoxide in 100 ml of ethanol was added 6.15 ml (60.0 mmoles) of thiophenol, followed by the addition of 4.45 g (29.0 mmoles) of 4-chloromethylimidazole hydrochloride (8, 9) in 25 ml of ethanol. After 1 hr, the ice bath was removed, and the reaction was stirred at ambient temperature for several hours. The mixture was filtered, and the filtrates were spin evaporated *in vacuo*.

The residue was dissolved in 10% HCl and extracted with ether to remove the excess thiol. The aqueous solution was adjusted to pH 8–9 with 1 *M* NaOH and extracted with ether. The combined extracts were washed with water and brine and then dried. Spin evaporation gave an oil, which was converted to the solid hydrochloride and recrystallized.

Method B—The reaction was carried out with an equimolar quantity of mercaptan. The reaction mixture was spin evaporated to give a residue. This residue was dissolved in chloroform, washed with water, dried, and reevaporated prior to hydrochloride formation.

4-Imidazolylmethylphenyl Sulfone Hydrochloride (VII): *Method C*—A solution of 3.13 g (13.8 mmoles) of I and 15 ml of 30% aqueous hydrogen peroxide in 20 ml of acetic acid was stirred at ambient temperature for 20 hr. The reaction was poured over 200 ml of ether containing 10 ml of hydrogen chloride-saturated ethanol, and the mixture was stirred vigorously to induce the oil to solidify. The solvent was decanted from the semisolid, a moderate amount of ethanol was added, and the mixture was stirred until a crystalline solid was formed. The product was collected, washed with ether, and recrystallized.

1-(4-Imidazolyl)-2-phenylethylene Hydrochloride (IV)—To a

[1] Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected.

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