Lipid-Lowering Effects of Polymers Derived from Halophenyl Pyrroles

Bruce S. Burnham*[,1], Joshua D. Berkowitz[1], Zachary Orr[1], Bryan McCranor[1], Mardel Cooper[1], Kurt McCann[1], Kyle Pillitteri[1], Jodi Hallback[1], Lisa-Marie Bergh[1], Larisa Gofman[1], Melissa Melendez[1], Justin M. Holub[1], Kenzo Morie[2] and Charles E. Carraher, Jr.[3]

[1]*Department of Chemistry, Biochemistry and Physics, Rider University, Lawrenceville, NJ, USA*

[2]*Department of Engineering, Tokushima University, Tokushima, Japan*

[3]*Department of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, FL, USA*

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Abstract: 2,4-Disubstituted pyrroles were polycondensed and tested for lipid-lowering effects in mice. Fluoro-substituted pyrrole monomers and polymers lowered total serum cholesterol by 30-35% and LDL-cholesterol by 47-64%. The lipid-lowering effects were similar for polymers and their monomers, however, the polymers produced these effects at dosage concentrations 1/8th that of the monomers.

Keywords: Carboxylic acids, cholesterol, lipids, polymers, pyrroles, triglycerides.

INTRODUCTION

Cardiovascular disease (CVD) is prevalent in the United States, affecting approximately 81.1 million Americans [1]. There is a strong correlation between elevated serum lipid concentrations and morbidity from CVD [1,2]. Elevated serum lipid concentrations are defined as total cholesterol greater than 240 mg/dL, with the low-density lipoprotein fraction (LDL) greater than 160 mg/dL, and serum triglycerides greater than 150 mg/dL [1,2]. In contrast, low concentrations of high-density lipoprotein (HDL) in the serum, less than 40 mg/dL, are considered to be a high risk factor for CVD [1,2]. Currently, elevated serum lipids are treated with the statins, either alone, or in combination with a fibric acid, niacin, ω-3 fatty acids, or ezetimibe [2,3]. However, the statins can have the serious life-threatening side effects of liver dysfunction and rhabdomyolysis [4-6]. Because of these issues, our group has been interested in developing new lipid-lowering compounds.

Previous studies from our group have shown that 4'-halophenyl pyrroles lower serum lipid levels in rodents [7]. As an extension of this effort, two 2,4-disubstituted pyrroles, the chloro- and fluoro-derivatives of 4-(4'-halophenyl)-*1H*-pyrrole-2-carboxylic acid, were polymerized using adipoyl chloride or isophthaloyl chloride. Here we report the *in vivo* lipid-lowering effects of the monomeric pyrrole esters and free acids, as well as their respective adipoyl or isophthaloyl polymers in CF-1 male mice.

The use of polymers to treat elevated serum cholesterol began with the bile-sequestrating polymers cholestyramine and colistipol. These polymers work locally in the gut to prevent the reabsorption of bile salts, thus reducing total serum cholesterol [8]. Since lipid-lowering pyrroles are not thought to be bile-sequestering agents, then the following arguments for incorporating these drugs into polymers can be made: 1) The polymer can act as a controlled release agent delivering the drug over an extended period of time. The presence of easily hydrolyzed units should allow slow release of the 4'-halophenyl pyrrole unit. 2) Polymers tend to cling to cell surfaces through physical entrapment that may include primary and secondary interactions. 3) Polymer chains greater than 100 units are typically membrane-impermeable and thus might localize within desired body cavities. This should also reduce the amount of drug that is administered and allowed to flow through the body causing liver and kidney damage. 4) If multiple ligands are desirable for activity, chains containing several units will have a greater potential to bind at multiple sites [9].

RESULTS

The regioselective synthesis of the 2,4-disubstituted pyrrole carboxylic acids was carried out by first preparing the vinamidinium salt using the corresponding phenyl acetic acid, DMF and $POCl_3$ followed by the condensation with glycine methyl or ethyl ester hydrochloride then base-mediated ring closure as previously described [10]. The esters were saponified with NaOH in refluxing 30% MeOH/H_2O (Scheme **1**). Polycondensation products **5-8** were prepared from the pyrrole carboxylic acids, **2** and **4**, and the diacid dichlorides as previously described [9]. The polycondensation products are medium-length polymers of 30-100 units and range from 9-30 kD [9]. It is clear that condensation can occur at either the pyrrole nitrogen, yielding an amide bond, or the carboxylic acid group *via* a mixed acid anhydride, producing polymers of random linkages between the monomeric pyrrole carboxylic acids.

After 14 days I.P. administration of compounds **1-8** in CF-1 male mice, all of the monomeric pyrrole esters and carboxylic acid derivatives lowered total serum cholesterol concentrations, affording a 20 to 34% reduction from control values (Table **1**, Fig. **1**). All of the polymerized pyrrole derivatives except **7**, demonstrated a lowering of the total se-

*Address correspondence to this author at the Department of Chemistry, Biochemistry and Physics, Rider University, 2083 Lawrenceville Road, Lawrenceville, NJ 08648 USA; Tel: 609-896-5207; Fax: 609-895-5782; E-mail: bburnham@rider.edu

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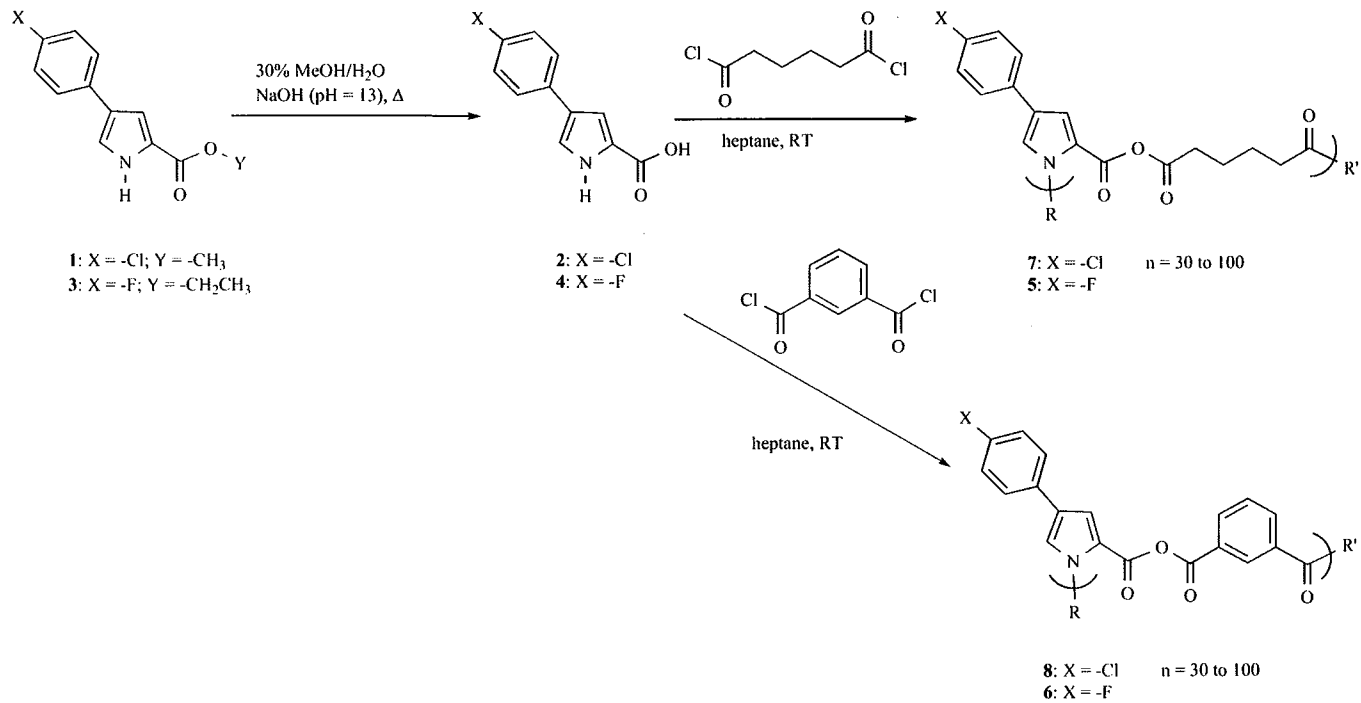

Scheme 1. Synthesis of the halophenyl pyrrole carboxylic acids and products of their condensation with adipoyl chloride and isophthaloyl dichloride. R and R' represent either amide or mixed acid anhydride linkages.

rum cholesterol in the range of 32 to 44%. The serum triglyceride concentrations were relatively unchanged after 14 days for the monomers and polymers except compound **2** lowered serum triglycerides by 64% and compound **6** markedly increased serum triglycerides by 177% (Table **1**, Fig. **2**). The three active polymers, **5, 7** and **8** also lowered serum LDL-cholesterol 55 to 64%. Only the monomeric compound **4** had a lowering effect on the serum LDL-cholesterol, 47%. None of the polymers had a statistically significant effect on the HDL-cholesterol in the serum although there was some lowering observed. However, the monomers all lowered the serum HDL-cholesterol concentrations from 40 to 78% (Table **2**, Fig. **3**). Food consumption was similar for all treated and control groups. Overall, there was an observed larger weight gain for the monomers over the polymers.

Table 1. ***In Vivo*** **Hypolipidemic Activity of the Pyrrole Derivatives in CF-1 Male Mice Dosed at 1-8 mg/kg/day, I.P. for 14 Days**

N = 6	Wt. Gain	Food Consum.	Percent of Control (*X*±SD)			
			Day 7		Day 14	
Compound	(g/mouse)	(g/mouse/day)	Cholesterol	Triglycerides	Cholesterol	Triglycerides
1[a]	3.67	3.76	108±10	92±27	72±15*	112±12
2[a]	6.17	4.25	109±13	95±24	80±7*	36±37*
3[a]	2.14	4.64	112±6	98±84	70±10*	93±21
4[a]	3.53	3.72	106±12	78±34	66±16*	95±24
5[b]	0.66	3.63	89±17	87±24	68±12*	107±28
6[b]	1.33	3.52	87±12	85±11	66±12*	277±36*
7[b]	0.83	3.53	52±57*	85±52	84±10	49±38
8[b]	1.44	3.28	76±20	59±9	56±17*	84±43
Gemfibrozil[c]	1.50	3.30	70±27	77±18	73±9*	94±30
Atorvastatin[a]	2.55	2.86	81±22	51±18*	77±13	96±25
Control[d]	-0.88	4.06	100±27[e]	100±33[f]	100±7[g]	100±21[h]

[a]Dosed at 8 mg/kg/day, IP.
[b]Dosed at 1 mg/kg/day, IP.
[c]Dosed at 90 mg/kg/day, IP.
[d]1% CMC, I.P.
[e]183 mg/dL total serum cholesterol.
[f]163 mg/dL serum triglycerides.
[g]166 mg/dL total serum cholesterol.
[h]120 mg/dL serum triglycerides
*$p < 0.005$ (*t*-test)

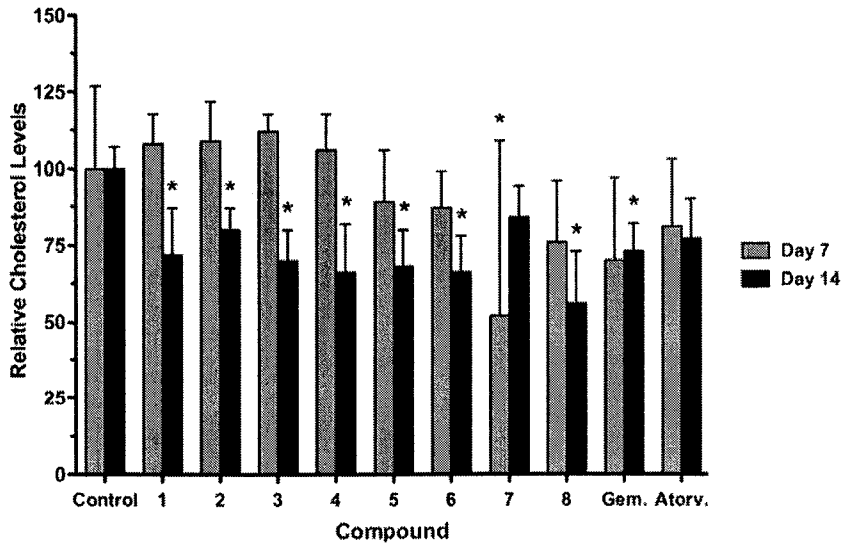

Fig. (1). Relative serum cholesterol levels (% of control) in CF-1 male mice following treatment with compounds **1-8** at 1-8 mg/kg/day, I.P. for 14 days. See Table **1** for full dosing concentrations. Gem.: Gemfibrozil; Atorv.: Atorvastatin. * $p < 0.005$ (*t*-test).

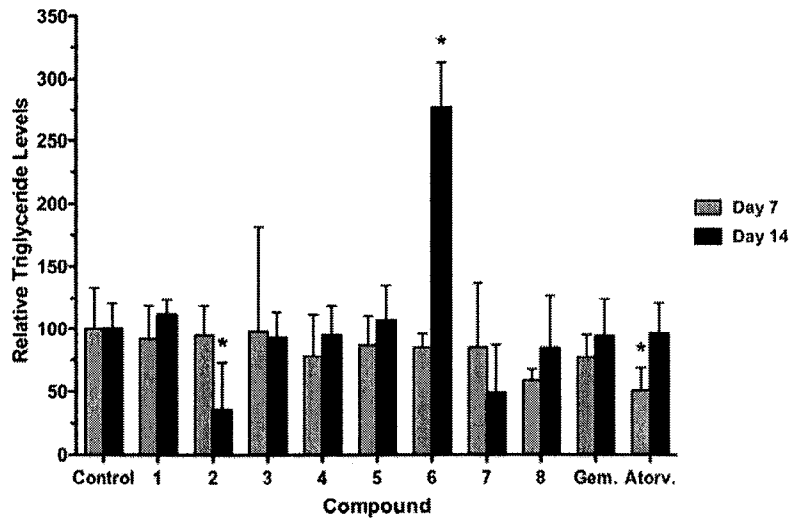

Fig. (2). Relative serum triglyceride levels (% of control) in CF-1 male mice following treatment with compounds **1-8** at 1-8 mg/kg/day, I.P. for 14 days. See Table **1** for full dosing concentrations. Gem.: Gemfibrozil; Atorv.: Atorvastatin. * $p < 0.005$ (*t*-test).

MATERIALS AND METHODS

The synthesis of the polymers has been previously reported [9]. All chemicals and reagents were obtained from Sigma-Aldrich Chemical Company (Milwaukee, WI) or ThermoFisher (Malvern, PA) and used as received. Solvents were stored over 4A molecular sieves and used as received. TLC was performed using silica gel 60F 254 plates (silica gel on plastic, Aldrich Chemical Company). Melting points were obtained on a Thomas-Hoover Uni-melt apparatus (capillary method), and were uncorrected. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer on sodium chloride plates or in a potassium chloride liquid cell in $CHCl_3$ or $CDCl_3$. NMR spectra were obtained on a 300 MHz Bruker Avance FT-NMR spectrometer using tetramethylsilane as an external standard for ^1H and ^{13}C spectra (δ = 0 ppm). HRMS were obtained on a Waters Acquity TQD tandem mass spectrometer. Compounds were dissolved in 5:2.5:2.5 methanol:water:acetonitrile at a final concentration of 10 nM and resolved on a Waters C4 column using a gradient of 5 to 95% solvent A (0.1% formic acid in water) over solvent B (0.1% formic acid in acetonitrile) in 7 min at a flow rate of 0.1 mL/min.

2-(4'-Chlorophenyl)-1,1,5,5,-tetramethyl-1-aza-5-azoniapentadiene Perchlorate

To a 250 ml three neck flask equipped with a mineral oil bubbler, magnetic stirrer and reflux condenser was added 5.0 g (29.3 mmol, 1.0 eq) of 4-chlorophenyl acetic acid and 125 ml of dry DMF under dry N_2. To the stirring solution was

Table 2. ***In Vivo*** **Effects on the Serum Lipoprotein-Cholesterol for the Pyrrole Derivatives in CF-1 Male Mice at 1-8 mg/kg/day, I.P. for 14 Days**

N=6	Percent of Control ($X\pm SD$)	
	Day 14	Day 14
Compound	HDL-C	LDL-C
1[a]	23±60*	66±18
2[a]	38±50*	95±15
3[a]	22±NA	84±65
4[a]	60±43	53±26*
5[b]	65±49	44±28*
6[b]	55±25	36±20*
7[b]	90±19	91±40
8[b]	59±36	45±26*
Gemfibrozil[c]	68±41	40±24*
Atorvastatin[a]	43±31*	30±49*
Control[d]	100±43[f]	100±22[g]

[a]Dosed at 8 mg/kg/day, IP.
[b]Dosed at 1 mg/kg/day, IP.
[c]Dosed at 90 mg/kg/day, IP.
[d]1% CMC, I.P.
[e]38 mg/dL serum HDL-cholesterol.
[f]131 mg/dL serum LDL-cholesterol.
*$p < 0.005$ (*t*-test).

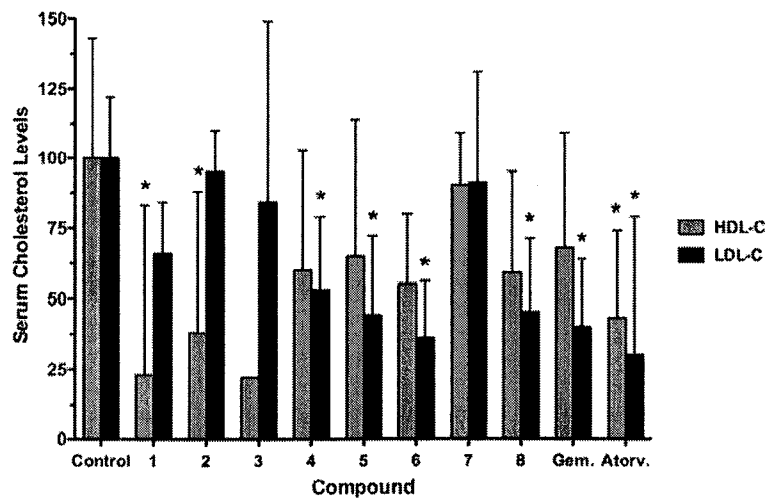

Fig. (3). *In vivo* effects on the serum lipoprotein-cholesterol levels (% of control) in CF-1 male mice following treatment with compounds **1-8** at 1-8 mg/kg/day, I.P. for 14 days. See Table **2** for full dosing concentrations. Gem.: Gemfibrozil; Atorv.: Atorvastatin. * $p < 0.005$ (*t*-test).

slowly added 8.0 ml (87.9 mmol, 3.0 eq) of phosphorusoxychloride. The solution was stirred at rt for 20 mins. then refluxed for 4 hr. The reaction was allowed to cool to rt under N_2 then slowly poured into 120 ml of ice water containing 14.4 g (117 mmol, 4 eq) of sodium perchlorate. The solution was cooled on an ice bath and the resulting precipitate filtered. The solid was then dried under vacuum and stirred with ethyl ether 2 x 75 ml for 20 min. The resulting tan solid (9.3 g 27.5 mmol, 94%) was filtered and dried under vacuum. ^{1}H-NMR (DMSO-d_6) δ = 2.52 (s, 6H), 3.52 (s, 6H), 7.28 (d, 2H, J = 9Hz), 7.42 (d, 2H, J = 9Hz), 7.71 (s, 2H) ppm; ^{13}C-NMR (DMSO-d_6) δ = 40.4, 49.4, 105.5, 129.5, 132.7, 135.2, 135.5, 164.7, 206.6 ppm. HRMS-ESI, calcd for $C_{13}H_{18}ClN_2$ (M^+): *m/z* 237.1153; found: 237.1404.

2-(4'-Flurorphenyl)-1,1,5,5,-tetramethyl-1-aza-5-azoniapentadiene Perchlorate

To a 250 ml three neck flask equipped with a mineral oil bubbler, magnetic stirrer and reflux condenser was added 5.05 g (32.77 mmol, 1.0 eq) of 4-fluorophenyl acetic acid and 125 ml of dry DMF under dry N_2. To the stirring solu-

tion was slowly added 9.0 ml (98.3 mmol, 3.0 eq) of phosphorusoxychloride. The solution was stirred at rt for 20 min then refluxed for 4 hr. The reaction was allowed to cool to rt under N_2 then slowly poured into 120 ml of ice water containing 16.18 g (132.08 mmol, 4 eq) of sodium perchlorate. The solution was cooled on an ice bath and the resulting precipitate filtered. The brown solid was then dried under vacuum and stirred with ethyl ether 2 x 75 ml for 20 min. The resulting tan solid (7.62g, 23.6 mmol, 72%) was filtered and dried under vacuum. ^{1}H-NMR (DMSO-d_6) δ = 2.44 (s, 6H), 3.25 (s, 6H), 7.27 (t, 2H, J = 7Hz), 7.36 (m, 2H), 7.71 (s, 2H) ppm; ^{13}C-NMR (DMSO-d_6) δ = 48.0, 49.9, 104.2, 114.4, 116.6, 133.5, 135.7, 162.3, 164.4 ppm. HRMS-ESI, calcd for $C_{13}H_{18}FN_2$ (M^+): *m/z* 221.1449; found: 221.1764.

2-Carbomethoxy-4-(4'-chlorophenyl)-1H-pyrrole (1)

To a 250 ml three neck flask equipped with a mineral oil bubbler, magnetic stirrer and reflux condenser under nitrogen was added 0.57 g (14.24 mmol, 2.4 eq) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride was washed with hexanes (3 x 15 ml), which was removed *via* syringe. Slowly, 75 ml of dry ethanol was added and the solution stirred 15 min. Glycine methyl ester hydrochloride (0.930 g, 5.94 mmol, 1.25 eq) was then added to the solution stirred 25 min. 2.0 g (5.97 mmol, 1 eq) of the 2-(4'-chlorophenyl)vinamidinium salt was then added. The mixture was then refluxed 4 hr. then cooled to rt and the solvent removed under reduced pressure. The solid was then washed with water (100 ml) and extracted into ethyl acetate (3 x 80 ml). The organic extracts were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting residue was passed through a silica gel column with a 70% hexanes 30% ethyl acetate mobile phase. The appropriate fraction was collected and reduced to yield a slightly yellow solid in 75% yield (1.05 g, 4.45 mmol). R_f = 0.07 (ethyl acetate); mp: 167-170°C; ^{1}H-NMR ($CDCl_3$) δ = 9.22 (s, 1H), 7.36 (d, 2H, J = 9Hz), 7.25 (d, 2H, J = 9Hz), 7.14 (m, 1H), 7.08 (m, 1H), 3.82 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$) δ = 161.8, 133.3, 132.3, 129.3, 126.9, 126.1, 124.0, 119.9, 112.8, 52.1 ppm. HRMS-ESI, calcd for $C_{12}H_{11}ClNO_2$ $(M+H)^+$: *m/z* 236.0478; found: 236.5600.

2-Carbethoxy-4-(4'-fluorophenyl)-1H-pyrrole (3)

To a 250 ml three neck flask equipped with a mineral oil bubbler, magnetic stirrer and reflux condenser under nitrogen was added 1.17 g (29 mmol, 2.4 eq) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride was washed with hexanes (3 x 15 ml), which was removed *via* syringe. Slowly, 125 ml of dry ethanol was added and the solution stirred 15 min. Glycine ethyl ester hydrochloride (1.83 g, 14.6 mmol, 1.25 eq) was added then the solution stirred for 25 min. 3.76 g (11.7 mmol, 1 eq) of the 2-(4'-fluorophenyl)vinamidinium salt was then added. The mixture was then refluxed 6 hrs. then allowed to cool to rt and the solvent removed under reduced pressure. The solid was then washed with water (100 ml) and extracted into ethyl acetate (3 x 80 ml). The organic extracts were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting residue was passed through a silica gel column with a 70% hexanes 30% ethyl acetate mobile phase. The appropriate fraction was collected and reduced to yield a slightly yellow solid in 68% yield (1.74 g, 7.96 mmol). R_f = 0.10 (ethyl acetate); mp: 129-130°C; ^{1}H-NMR ($CDCl_3$) δ = 9.2 (br.s., 1H), 7.4 (m, 2H), 7.08 (m, 2H), 6.97 (t, 2H, J = 9Hz), 4.28 (q, 2H, J = 7Hz) 1.31 (t, 3H, J = 7Hz) ppm; ^{13}C-NMR ($CDCl_3$) δ = 163.6, 161.5, 160.4, 131.1, 127.2, 126.3, 124.22, 119.5, 116.0, 112.7, 60.9, 14.8 ppm. HRMS-ESI, calcd for $C_{13}H_{13}FNO_2{\cdot}H_2O$ $(M+H)^+$: *m/z* 252.1036; found: 252.0995.

4-(4'-Chlorophenyl)-1H-pyrrole-2-carboxylic Acid (2)

2-Carbethoxy-4-(4'-chlorophenyl)-1H-pyrrole, 1.0 g (4.0 mmol), was dissolved in a minimum amount of methanol and added to a 30% methanol/water solution adjusted to pH 13 with NaOH. The solution was refluxed for 6 hr then allowed to stir overnight. The methanol was removed and to the resulting suspension was added to water (50 ml) and the solution neutralized with glacial acetic acid. The solution was stirred for 1 hr then filtered and washed with cold water to yield an off white powder in 99% yield (0.88g, 3.96 mmol). mp = 245°C (dec); ^{1}H-NMR ($CDCl_3$) δ = 12.20 (s, 1H), 7.84 (d, 2H, J = 8Hz), 7.62 (s, 1H), 7.55 (d, 2H, J = 8Hz), 7.24 (s, 1H), 2.72 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$) δ = 163.0, 134.5, 130.0, 128.8, 126.6, 123.5, 120.0, 110.9 ppm. HRMS-ESI, calcd for $C_{11}H_9ClNO_2$ $(M+H)^+$: *m/z* 221.0244; found: 221.1475.

4-(4'-Fluorophenyl)-1H-pyrrole-2-carboxylic Acid (4)

2-Carbethoxy-4-(4'-fluorophenyl)-1H-pyrrole, 1.20 g (5.1 mmol), was dissolved in a minimum amount of methanol and added to a 30% methanol/water solution adjusted to pH 13 with NaOH. The solution was refluxed for 6 hr then allowed to stir overnight. The methanol was removed and 50 mL water was added to the resulting suspension. This solution was then neutralized with glacial acetic acid. The mixture was stirred 1 hr then filtered and washed with cold water to yield an off white powder in 100% yield (1.05g, 5.1 mmol). mp = 195-200°C; ^{1}H-NMR ($CDCl_3$) δ = 11.90 (s, 1H), 7.67 (m, 2H), 7.46 (s, 1H), 7.17 (m, 3H), 2.56 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$) δ = 162.3, 160.5, 131.7, 126.8, 124.7, 124.2, 120.6, 115.7, 111.8 ppm. HRMS-ESI, calcd for $C_{11}H_9FNO_2$ $(M+H)^+$: *m/z* 206.0617; found: 206.1826.

HYPOLIPIDEMIC STUDIES

CF-1 male mice were purchased from Harlan (Indianapolis, IN) and acclimated to their new environment for at least 14 days prior to treatment. Animals were housed in 12 hr light-dark cycles at 68 °F. Food (5015 mouse diet, PMI Nutrition International) and water were given *ad libitum* in accordance to procedures approved by the Institutional Animal Care and Use Committee. Healthy CF-1 male mice (30-40 g) were administered I.P. either 1 or 8 mg/kg of the pyrrole monomers **1-4** or polymer derivatives **5-8**, 90 mg/kg/day of gemfibrozil (Teva) or 8 mg/kg/day of atorvastatin (Pfizer), dissolved in 1% CMC daily for 14 days. These dosage levels represent the therapuetic doses for the known drugs. The pyrroles were administered at the dosage range of the statins. Blood (~0.5 mL) was collected on day 7 and 14 from the

suborbital vein under CO_2 anesthesia. The mice were euthanatized with CO_2 after 14 days upon completion of the study.

Serum was separated by centrifugation at 5,000 rpm x 3 min. Total serum cholesterol (Infinity®), triglyceride (Infinity®), HDL-cholesterol (HDL-C Plus®) and LDL-cholesterol (LDL-C Plus®) concentrations were determined by commercial enzymatic assays (ThermoDMA, Louisville, CO) and analyzed on a Perkin-Elmer l-25 UV-Vis spectrometer.

STATISTICAL ANALYSIS

Data is displayed in tables as the mean ± standard deviation of the mean expressed as a percentage of the control value. *N* is the number of samples per group. The Student's "*t*"-test was used to determine the probable level of significance (p) between test samples and control samples. Values of $p < 0.005$ were considered to be significant.

CONCLUSION

In summary, we report here the lipid-lowering effects of a novel class of pyrrole-based polymers. We have expanded on our previous report, which outlined the synthesis of the intermediate monomers and polymers in acceptable yields (2-53%) [9]. The pyrrole monomers and polymers lowered total serum cholesterol to a similar degree as the clinically used pyrrole-based drug atorvastatin (Lipitor®). A lipid-lowering effect similar to that of atorvastatin was observed in the LDL-cholesterol fraction for the polymers **5, 6** and **8**. These observations suggest that the polymers of 4-(4'halophenyl)pyrrole-2-carboxylates have significant lipid-lowering properties. The undesirable lowering of the HDL-cholesterol fraction, albeit not statistically significant, would indicate that further optimization of these compounds is necessary in order to develop a viable drug candidate.

The polymers were dosed at 1/8th the dosage level of the pyrrole esters and acids, and achieved a similar lowering of the total serum cholesterol levels. These data suggest that the polymers reported herein are more potent than their monomeric counterparts at lowering total serum cholesterol levels.

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