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Synthesis of Certain New Dibenz[c,e]azepine-5,7-diones of Expected Antihyperlipidemic Activity

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Abstract. The structural requirements for decreasing cholesterol and triglyceride levels remain largely uninvestigated. Thus a systematic investigation of certain N-substituted dibenz[c,e]azepines is necessary. Twenty-four compounds of certain new N-substituted derivatives of dibenz[c,e]azepines-5,7-diones were synthesized and tested for their anticholestesrolemic and antitriglyceridimic activities. The evaluation of antihyperlipidemic activity of dibenz[c,e]azepine-5,7-diones (VII, X-XII) against Triton-WR1339-induced hyperlipidemia in rats showed a significant lowering of serum total cholesterol and triglyceride levels at a dose of 150 mg/kg compared with the control value. The phenyl substituted derivatives of diphenimide have shown a pronounced decrease in both triglyceride and cholesterol levels.

Keywords: Dibenzazepines, Synthesis, Antihyperlipidemics.

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Introduction

The hyperlipidemias are a complex group of diseases that represent the major cause of heart diseases. The therapeutic strategies for treating hyperlipidemia include dietary intervention plus a regimen of drugs. The drugs used in the treatment of hyperlipidemias are generally targeted to: a) decrease production of lipoproteins in the tissues b) increase catabolism of lipoproteins in the plasma, or c) increase removal of cholesterol from the body. Bile acid sequestrants (*e.g.,* cholestyramine), 3-hydroxymethylglutaryl Co-A reductase inhibitors (HMGRIs *e.g.,* statins) and fibrates such as clofibrate are currently used to lower plasma triglycerides and cholesterol. This will lead to a decline in the progression of coronary plaque and a possible regression of pre-existing lesions[1-4].

In searching for a new class of antihyperlipidemic agents, many compounds having open imide or cyclic imide function have been found to possess antihyperlipidemic action via lowering the triglycerides and cholesterol levels. Some dibenz[*c,e*]azepines-5,7-dione derivatives are more superior in many cases than clofibrate[5]. The detailed study of cyclic imides showed that seven-member cyclic imides such as dibenz[c,e]azepines-5,7-diones demonstrated a potent antihyper-lipidemic activity and might be useful in the treatment of hyperlipidemia and arteriosclerosis[6].

Based on the forgoing, and as an extension of our earlier work[7], it was planned to synthesize some new dibenz[*c,e*]azepines-5,7-dione derivatives, VII-XIII, in order to evaluate their antihyperlipidemic activity with the aim of finding more effective antihyperlipidemic compounds. For the preparation of the desired derivatives VII-XIII, Fig. 1 was adopted.

Experimental

All melting points were carried out by a capillary method on a Gallen Kamp melting point apparatus and were uncorrected. Elemental analyses were performed on a Carbon Hydrogen Nitrogen (CHN) analyzer at the Microanalytical unit, Cairo University, Cairo, Egypt. The infrared spectra were recorded on a Pye Unicam SP 1000 IR

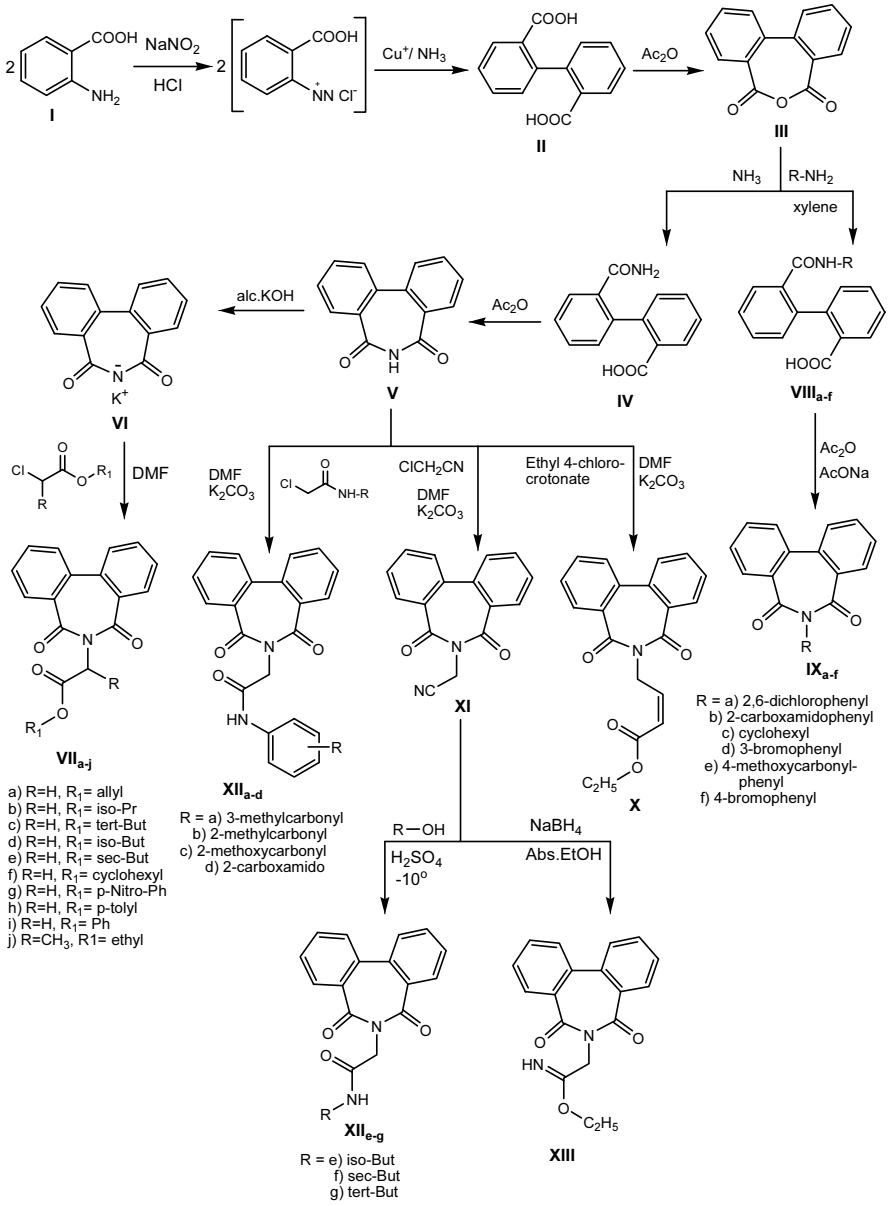


Fig. 1. Synthesis of the target compounds.

spectrophotometer at Microanalytical Unit, Cairo University, Cairo, Egypt. Nuclear magnetic resonance (1HNMR) spectra were obtained on 500 MHz GEQE-300 FT-NMR spectrophotometer at the Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, Virginia, U.S.A. and on a Jeol 200 MHz spectrophotometer at the Faculty of Science, Cairo University, Cairo, Egypt. Tetramethyl Silane (TMS) was used as an internal standard. deuterated **c**hloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-d_6) were used as solvents. The chemical shifts were measured in ppm. Mass spectra were performed on a Hewlett Packard 5988 (70eV) spectrometer at the Microanalytical Unit, Cairo University, Cairo, Egypt. The reactions were monitored by TLC using Merck precoated silica gel 60F 254 plates.

The following compounds were prepared according to reported procedures, diphenic acid (II)[8], dibenz[*c,e*]oxepine-5,7-dione (diphenic anhydride) (III)[9], diphenamic acid (IV)[10], dibenz[*c,e*]azepine-5,7-dione (diphenimide V)[7] and diphenimide potassium salt (VI)[7], 2,6-dichlorophenyl-, 2-carboxamido-phenyl-, cyclohexyl-, 3-bromophenyl-, 4-methoxycarbonylphenyl- and 4-bromophenyl-diphenamic acids (VIII)[10], allyl, iso-propyl, tert-butyl, iso-butyl, sec-butyl, cyclohexyl, *p*-nitrophenyl, *p*-tolyl, phenyl and ethyl chloroacetates[11], 3-methylcarbonyl-, 2-methylcarbonyl-, 2-methoxycarbonyl- and 2-carboxamido-chloroacetamide derivatives[10].

6-(Alkyloxyl/aryloxycarbonylmethyl)dibenz[c,e]azepine-5,7-dione (VIIa-j)

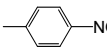
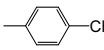
A quantity of the appropriate alkyl/aryl chloroacetate (0.01 mol) was mixed with potassium diphenimide VI (2.6 g, 0.01 mol) in dimethylformamide (50 ml). The mixture was heated for 2 h on a water-bath, then cooled, poured onto ice-cooled water (200 ml) and stirred well for thirty minutes. The obtained solid or oil was filtered or extracted. The substance was then washed with water, dried and crystallized with ethanol (Table 1).

Ethyl 2-Dibenz[c,e]azepine-5,7-dion-6-ylpropionate (VIIa-j)

Yield 65% (3.38 g), m.p. 90-92 ^{o}C. IR (KBr)cm^{-1}: 1732 (C=O ester), 1645 (C=O imide); ^{1}HNMR ($CDCl_3$, ppm): 7.89-7.48 (m, 8H, Ar-H), 5.59-5.53 (q, J=7.0 Hz, 1H, -CH-CH_3), 4.25-4.10 (q, J=7.0 Hz, 2H, -CH_2-

CH_3), 1.66-1.62 (d, J=7.0 Hz, 3H, -CH-CH_3), 1.23-1.15 (t, J=7.0 Hz, 3H, -CH_2-CH_3). MS, m/z (abund %): 323 (8.32) M^+, 250 (25) M-$CO_2CH_2CH_3$, 181 (100) [(M+1)-CO-NCH(CH_3)$CO_2CH_2CH_3$. Anal. for $C_{19}H_{17}NO_4$ (323.34) Calcd. C, 70.58; H, 5.30; N, 4.33; Found C, 70.59; H, 5.16; N, 4.17.

Table 1. 6-(Alkoxy/aryoxycarbonylmethyl)dibenz[c,e]azepine-5,7-diones (VII).

Comp. VII	R_1	M. formula (M. Wt.)	M.P. °C	Yield %	Microanalysis %		
						Calcd.	Found
a	–CH_2CH=CH_2	$C_{19}H_{15}NO_4$ (321.33)	119-21	77	CH N	71.02 4.71 4.36	70.9 5.8 4.12
b	–$CH(CH_3)_2$	$C_{19}H_{17}NO_4$ (323.12)	80-82	83	CH N	70.58 5.3 4.33	70.3 5.71 4.13
c	–$C(CH_3)_3$	$C_{20}H_{19}NO_4$ (337.13)	98-101	93	CH N	71.2 5.68 4.15	71.5 5.5 4.24
d	–$CH_2CH(CH_3)_2$	*$C_{20}H_{19}NO_4$* (337.13)	101-3	90	CH N	71.2 5.68 4.15	70.9 5.76 4.14
e	–$CH(CH_3)CH_2CH_3$	$C_{20}H_{19}NO_4$ (337.13)	110-12	82	CH N	71.2 5.68 4.15	71.27 5.16 4.27
f		$C_{22}H_{21}NO_4$ (363.41)	oil	65	–	–	–
g		$C_{22}H_{14}N_2O_6$ (402.36)	140-42	80	CH N	65.6 3.47 6.9	66.2 5.23 7.3
h		$C_{23}H_{17}NO_4$ (371.12)	150-52	65	CH N	74.3 4.6 3.8	73.81 4.55 3.89
*I**		$C_{22}H_{15}NO_4$ (357.36)	132-34*	72*		–	–

** Reported [10], but not evaluated as antihyperlipidemic*

VII-b: ^{1}HNMR ($CDCl_3$, δ): 7.485-7.923 (m, 8H, Ar-H), 4.87 (s, 2H, CH_2CO), 1.89-1.93 (m, 1H, C<u>H</u>$(CH_3)_2$), 0.871-0.891 (d, J=10 Hz, 6H, CH(<u>CH_3</u>)$_2$.

VII-c: ^{1}HNMR ($CDCl_3$, δ): 7.93-7.50 (m, 8H, Ar-H), 4.76 (s, 2H, CH_2CO), 1.46 (s, 9H, -$C(CH_3)_3$).

VII-d: IR (KBr, cm-1): 1744.1 (C=O ester), 1691 (C=O imide); ^{1}HNMR ($CDCl_3$, δ): [7.88-7.92 & 7.61-7.64 (H-4, H-8 & H-1, H-11), 3.95-3.92 (d, J=15 Hz, 2H, OCH_2-), 1.96-1.83 (sept., 1H, <u>CH</u>$(CH_3)_2$), 0.89-0.85 (d, J=17.5 Hz, 6H, CH(CH3)2).; MS, m/z, (abund. %): 337 (19.3) (M^+), 282 (M-$CH_2CH(CH_3)_2$, 236 (62.01) (M-$CO_2CH_2CH(CH_3)_2$, 193 (100) (M-$HCOCH_2CO_2CH_2CH(CH_3)_2$.

VII-f: ^{1}HNMR ($CDCl_3$, δ): 7.86-7.58 (m, 8H, Ar-H), 4.89 (s, 2H, CH_2CO), 3.45-3.40 (t, J=15 Hz, 1H, OC_6H_{11}); MS, m/z, (abund. %): 363 (6.49) (M^+) 282 (21.67) (M-C_6H_{11}), 209 (79.4) (M-$NCH_2CO_2C_6H_{11}$ and 56 (100) ($COCH_2N^+$).

VII-g: ^{1}HNMR ($CDCl_3$, δ): 7.98-17.18 (m, 12H, Ar-H), 5.15 (s, 2H, CH_2CO).

VII-h: ^{1}HNMR ($CDCl_3$, δ):7.07-9.01 (m, 12H, Ar-H), 5.10 (s, 2H, -CH_2-CO), 2.34 (s, 3H,-CH_3).

Ethyl 4-(Dibenz[c,e]azepine-5,7-dion-6-yl)crotonate (X)

Ethyl 4-chlorocrotonate was added to a solution of diphenimide V (2.6 g, 0.01 mol) in (20 ml) of dimethylformamide containing anhydrous potassium carbonate with continuous stirring. The reaction mixture was heated in a water-bath for 3 h and poured into ice-cold water (300 ml) while being vigorously stirred. The precipitated product was filtered, dried and crystallized from methylene chloride/n-hexane (2:1). Yield 70% (20.5g), m.p. 110-113^{o}C, ^{1}HNMR ($CDCl_3$, ppm): 7.65-7.90 (m, 8H, Ar-H), 7.03-6.96 (dt, J= 15.6 Hz, 1H, CH=CH-COO), 5.78-5.74 (d, J= 15.6 Hz, 1H, CH=CH-COO), 4.83-4.82 (d, J= 5Hz, 2H, -CH_2-CH=CH-), 4.17-4.12 (q, J=7.0 Hz, 2H, -CH_2-CH_3), 1.25-1.21 (t, J=7.0 Hz, 3H, -CH_2-CH_3). Anal.% for $C_{20}H_{17}NO_4$ (335.35) Calcd ;C, 71.63; H, 5.11; N,4.18; Found C, 71.63; H, 5.3; N, 4.28.

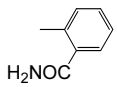
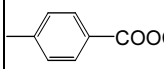
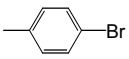
6-(Aryl/cycloalkyl)-dibenz[c,e]azepine-5,7-diones (IX a-f)

A mixture of diphenic anhydride III (2.2 g, 0.01 mol) and the appropriate amine (0.05 mol) in dry xylene (100 ml) was heated under reflux for 3-7 hours with stirring. The mixture was cooled and the solid product (a diphenamic acid derivative VIII a-f) was filtered, dried and transferred to 100 ml round-bottomed flask containing acetic anhydride (20 ml) and fused sodium acetate (2 g) and equipped with a reflux condenser. The mixture was heated with stirring for 3 h, cooled and then poured into 500 ml ice-cooled water. The formed precipitate was filtered, washed thoroughly with water and crystallized from ethanol (Table 2).

6-(Cyanomethyl)dibenz[c,e]azepine-5,7-dione (XI)

To a solution of diphenimide V (2.6 g, 0.01 mol) in dimethylformamide (50 ml), anhydrous K_2CO_3 was added and the reaction mixture was stirred at room temperature. At this temperature chloroacetonitrile (0.75 g, 0.01 mol) was added with continuous stirring for 3 h. The reaction mixture was poured onto-ice-cooled water (200 ml) and stirred well for 30 min. The solid product was filtered, washed with water, dried and crystallized with aqueous ethanol. Yield 78% (25 g); m.p. 121-123°C; IR (KBr, cm^{-1}): 2251 (CN), 1687 and 1655 (C=O imide) ^{1}HNMR ($CDCl_3$, ppm): 7.97-7.51 (m, 8H, Ar-H), 4.950 (s, 2H, CH_2-CN); Anal. % for $C_{16}H_{10}N_2O_2$ (262.26).

Table 2. 6-(Aryl/cycloalkyl)dibenz[c,e]azepine-5,7-dione (IX).

Comp. IX	*R*	M. formula (M. Wt.)	M.P. °C	Yield %	Microanalysis %		
						Calcd.	Found
a		$C_{20}H_{11}Cl_2NO_2$ (367.21)	235-37	73	CH N	65.24 3.01 3.80	66.7 3.5 4.12
b		$C_{21}H_{14}N_2O_3$ (342.35)	210-12	62	CH N	73.68 4.12 8.18	72.8 4.5 8.03
c		$C_{20}H_{19}NO_2$ (305.37)	230-32	85	CH N	78.66 6.27 4.59	75.65 5.53 4.2
d		$C_{20}H_{12}BrNO_2$ (377.22)	217-19	80	CH N	63.51 3.20 3.70	63.3 3.17 3.7
e		$C_{22}H_{15}NO_4$ (357.36)	oil	63	–	–	–
f		$C_{20}H_{12}BrNO_2$ (377.22)	220-22	80	CH N	63.51 3.20 3.70	63.34 3.38 3.67

***IX**-a: [1]HNMR (CDCl$_3$, ppm): 7.26-7.87 (m, 11H, Ar-H); MS (m/z, abund. %): 367 (0.24), 369 (0.20) M$^+$, 180 (100) (M-Cl$_2$C$_6$H$_3$NCO), 152 (56.28) (biphenyl radical cation).*

***IX**-b: IR (KBr, cm^{-1}): 3062 (NH), 1690 (C=O amide), 1668 (C=O imide).*

***IX-c:** MS (m/z, abund.%): 306 (1.91) (M+1), 224 (7.65) (M-C$_6$H$_{11}$), 180 (79.97) (M-C$_6$H$_{11}$NCO), 152 (100) (biphenyl radical cation).*

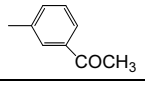
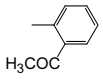
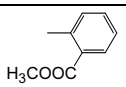
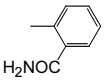
***IX-d:** 377 (8.6), 379 (8.4) (M$^+$), 298 (1.31) (M-Br), 180 (100) (M-BrC$_6$H$_4$NCO), 152 (29.56) (biphenyl radical cation).*

***IX-e:** IR (KBr, cm^{-1}): 1762 (C=O ester), 1756 (C=O imide); [1]HNMR (CDCl$_3$, δ): [7.27-7.32(d, 2H, ortho), 7.85-7.93 (d, 2H, meta) Ar-H p-disubt. Ph], [7.94-7.98, 7.68-7.71 (d, 4H, H-4, H8 & H1,H11), 7.51-7.67 (m, 4H, H3, & H4, H9, H10) Ar-H dibenz. Ring], 2.55 (s, 3H, OCH$_3$); MS (m/z, abund.%): 357 (6.76) (M$^+$), 298 (100) (M-COOCH$_3$), 180 (24) (M-CH$_3$CO$_2$C$_6$H$_4$NCO), 152 (71.42) (biphenyl radical cation).*

6-(Aryl/alkylaminocarbonylmethyl)-dibenz[c,e]azepine-5,7-diones (XII$_{a-d}$)

A quantity of the appropriate chloroacetamide (0.01 mol) was added to a stirred solution of diphenimide V (0.01 mol, 2.2 g) in anhydrous dimethylformamide (20 ml) containing anhydrous K_2CO_3 (1 gm). Stirring at room temperature was continued for 3-4 hrs. The reaction mixture was then poured into ice-water (300 ml). The solid product was filtered, dried and crystallized with methylene chloride / n-hexane mixture (2:1) (Table 3).

Table 3. 6-(Aryl/alkylaminocarbonylmethyl)-dibenz[c,e]azepine-5,7-diones (XII_{a-d}).

Comp. XII	*R*	M. formula (M. Wt)	M.P. °C	Yield %	Microanalysis %		
						Calcd.	Found
a		$C_{24}H_{18}N_2O_4$ (398.41)	155-157	77	CH N	72.35 4.55 7.03	71.78 4.63 6.94
b		$C_{24}H_{18}N_2O_4$ (398.41)	155-157	77	CH N	72.35 4.55 7.03	71.78 4.63 6.94
c		$C_{24}H_{18}N_2O_5$ (414.41)	168-170	80	CH N	69.56 4.38 6.76	69.85 4.36 6.57
d		$C_{23}H_{17}N_3O_4$ (399.40)	212-14	60	CH N	69.17 4.29 10.52	69.39 4.37 10.38

XII-a: *IR (KBr, cm^{-1}): 3206 (N-H), 1693 (C=O ketone), 1652 (C=O amide), 1609 (C=O imide); ^{1}HNMR (DMSO-d_6, ppm): 10.58(s, 1H, NH), 8.17-7.49 (m, 12H, Ar-H), 4.88 (s, 2H, $\underline{CH_2}CO$), 3.36 (s, 3H, $CO\underline{CH_3}$).*

XII-b: *IR (KBr, cm^{-1}): 3206.7 (NH), 1693.2(C=O ketone), 1652.9 (C=O amide), 1620 (C=O imide); MS (m/z, abound %): 398 (2.15, M^+), 264 (100, M-NHC_6H_3), 193 (4.19, M-$COCH_2CONHC_6H_4CO_2$-CH_3), 56 (9.99, NCH_2CO)*

XII-c: *IR (KBr, cm^{-1}): 3250.8 (NH), 1713.9 (C=O ester), 1690.4 (C=O amide), 1652.7 (C=O imide); ^{1}HNMR ($CDCl_3$, ppm): 10.9 (s, 1H, NH)), 8.22-7.18 (m, 12H, Ar-H), 4.92 (s, 2H, $\underline{CH_2}CO$), 3.76 (s, 3H, $COO\underline{CH_3}$); MS, m/z (abound %): 383 (M+1), 264 (100, M-$NHC_6H_4COOCH_3$), 236 (2.48, M-$CONHC_6H_4COOCH_3$,)*

XII-d: *IR (KBr, cm^{-1}): 3210 (NH_2), 1694 (C=O amide), 1654 (C=O imide), 1606 (C=O, $CONH_2$).*

6-(Alkylaminocarbonymethyl)dibenz[c,e]-azepine-5,7-diones (XII_{e-g})

6-(Cyanomethyl)-dibenz[c,e]azepine-5,7-dione XI (2.62 g, 0.01 mol) was cautiously added while stirring, to sulfuric acid (10 ml) and the mixture was maintained under -10°C with an ice-salt bath. The appropriate secondary or tertiary alcohol (0.01 mol) was added in drops with continuous stirring over a period of 20 min. The mixture was then cautiously poured into ice-cold water while stirring. The solid product was washed with sodium carbonate solution and was filtered or extracted ($CHCl_3$) (Table 4).

Ethyl 2-(Dibenz[c,e]azepine-5,7-dion-6-yl)-acetimidate (XIII)

To a cold solution of 6-(cyanomethyl)dibenz[c,e]azepine-5,7-dione XI (0.75 g, 0.01 mol) in absolute ethanol (50 ml) stirred for 10 min, sodium borohydride (0.38 g, 0.01 mol) was added with continuous stirring at room temperature for 4 h. The reaction mixture was filtered and the residue was washed with absolute ethanol. The combined filtrate and washing were extracted twice with diethyl ether then the solvent was removed under vacuum. The oil residue was purified by chromatography. Yield: 55% (23 g), $C_{18}H_{16}N_2O_3$ (308.33), IR (KBr, cm^{-1}): 3210 (NH),

1694, 1654 (C=O imide). ^{1}HNMR (DMSO-d_6, ppm): 7.83-7.26 (m, 9H, Ar-H & -NH), 4.84 (s, 2H, -CH_2-CO), 4.27-4.16 (q, J=7.2 Hz, 2H, -CH_2-CH_3), 1.26-1.22 (t, J=7.2 Hz, 3H, -CH_2-CH_3). MS (m/z, abound %): 308 (0.12, M^+), 235 (18.16, M-$CNHOCH_2CH_3$), 105 (100, benzoyl radical cation).

Table 4. 6-(Aryl/alkylaminocarbonylmethyl)-dibenz[c,e]azepine-5,7-diones (XII_{e-g}).

Comp. XII	*R*	M. formula (M. Wt)	M.P. °C	Yield %	Microanalysis %		
						Calcd.	Found
e	$-CH_2\underline{CH}(CH_3)_2$	$C_{19}H_{18}N_2O_3$ (322.36)	oil	72	–	–	–
f	$-CH(CH_3)CH_2CH_3$	$C_{20}H_{20}N_2O_3$ (336.12)	161-163	83	CH N	71.41 5.99 8.33	71.14 5.90 8.14
g	$-C(CH_3)_3$	$C_{20}H_{20}N_2O_3$ (336.38)	180-182	63	CH N	71.41 5.99 8.33	70.75 6.59 8.12

XII-e: *IR (KBr, cm^{-1}): 3282.9 (NH), 1654 (C=O amide), 1597.8 (C=O imide); ^{1}HNMR ($CDCl_3$, ppm): 8.08-7.57 (m, 9H, Ar-H & NH), 4.59 (s, 2H, CH_2CO), 2.83-3.77 (m, 1H, $\underline{CH}(CH_3)_2$), 1.09-0.98 (d, J=33 Hz, 6H, $CH(\underline{CH_3})_2$), MS, m/z (abound %): 322(22, M^+), 264 (100, M-$NHCH(CH_3)_2$), 193 (42.91, M-$COCHCONHCH(CH_3)_2$), 56 (17.54, NCH_2CO).*

XII-f: *^{1}HNMR ($CDCl_3$, ppm): 8.03 (s, 1H, NH), 7.9-7.65 (m, 8H, Ar-H), 4.66-4.65 (s, 2H, $\underline{CH_2}CONH$), 3.74-3.67 (m, 1H, $\underline{CH}(CH_3)_2$), 1.12-1.09 (d, J=7.5 Hz, 3H, -$CH\underline{CH_3}$), 1.49-1.42 (q, J=12 Hz, 2H, -CH-$\underline{CH_2}$-CH_3), 0.92-0.88 (t, J=12 Hz, 3H, CH_2-$\underline{CH_3}$)*

XII-g: *^{1}HNMR ($CDCl_3$, ppm): 11.73 (s, 1H, $\underline{NH}$), 7.93-7.63 (m, 8H, Ar-H), 4.66-4.64 (s, 2H, $\underline{CH_2}CO$), 1.39-1.38(d, J=3 Hz, 9H, $C(\underline{CH_3})_3$).*

Antihyperlipidemic Activity

Twenty-four of the newly synthesized compounds (IXa-f), (VIIa-i), (XIIa-g), VIIj and X were tested for their antihyperlipidemic activity against Triton WR-1339-induced hyperlipidemia in rats following the procedure reported by Kuroda *et al*.[13].

Materials and Apparatus

Triton WR-1339 (*Tyloxapol*, *Sigma*) was used to induce the suitable hyperlipidemia within 24 h. Carboxymethylcellulose sodium (CMC-Na, *Sigma*) was used as a suspending agent. Male Wistar rats (6-7 wks-old, 210-230 g body weight) were used as experimental animals. Spekol-11 apparatus (*Germany*) was used to measure the total triglycerides and total cholesterol (TC) in the serum. Centrifuge (UK) was used to prepare the blood serum samples.

Solutions and Suspension Samples

The test compounds were suspended in carboxymethylcellulose sodium solution in 0.5% in normal saline to give 6% concentrations. Triton was dissolved in normal saline to give 12% solution.

Procedure[13]

One hundred forty rats were arranged in 28 groups (5 animals each) and were deprived of food but were allowed free access to drinking water. Each animal in all groups was injected in the tail vein with a volume of Triton solution equivalent to 300 mg/kg body weight. Animals of one group were orally administered 1 ml of CMC-Na solution and kept as a control group. Animals of the remaining groups were orally given the test compounds at a dose level of 150 mg/kg body weight. After 24 h, blood was taken from each animal and centrifuged to obtain the serum. The plasma TC and total triglyceride (TG) levels were measured and the rates of decrease (%) were calculated using the following equation:

$$\textbf{Rate of decrease (\%)} = (1\text{-}Vt/Vc) \times 100$$

Where Vt and Vc are the value of TC or TG for the test groups and control group respectively. The obtained results and treated values are presented in Table 5.

Discussion

Diphenic anhydride III was synthesized starting with anthranilic acid I, which was diazotized and treated with a reducing mixture formed from ammoniacal cupric sulfate and alkaline hydroxylamine sulfate to give diphenic acid II[8]. The resulting diphenic acid II was then cyclodehydrated with acetic anhydride to yield diphenic anhydride III[9]. Ammonolysis of diphenic anhydride III afforded diphenamic acid IV, which on cyclodehydration produced diphenimide V[7]. Diphenimide V was then converted into its potassium salt VI via treatment with an equivalent amount of ethanolic potassium hydroxide solution and pouring the resulting solution in drops on dry ether.

Table 5. Antihyperlipidemic activity of dibenzazepine derivatives versus control in rats.

Comp. no.	Total Triglycerides (TG)		Total Cholesterol (TC)	
	(mg/dl)	% Decrease	(mg/dl)	% Decrease
Normal (CMC-Na)	56.9	–	54.6	–
Control (Triton WR)	522.5	–	181.25	–
IXa	416.8	79.70 ± 36.23	103.8	57.269 ± 34.87
IXb	441.9	84.57 ± 38.31	33.45	18.45 ± 45.74
IXc	407.7	78.02 ± 35.49	45.5	25.1 ± 42.39
IXd	361.4	69.16 ± 31.79	71.05	39.2 ± 37.9
IXe	391.7	74.96 ± 34.19	112.25	61.93 ± 35.13
IXf	387.1	74.08 ± 33.8	76.4	42.15 ± 36.8
VIIa	377.25	72.20 ± 33.039	70.79	39.05 ± 38.01
VIIb	428.5	82.10 ± 37.2	102.85	56.74 ± 35.14
VIIc	183.8	35.17 ± 20.15	84.25	46.4 ± 36.18
VIId	335.9	64.28 ± 29.83	66.45	36.66 ± 38.7
VIIe	237.9	45.53 ± 22.3	76.95	42.4 ± 37.1
VIIf	399.2	76.40 ± 34.8	112.25	61.93 ± 35.2
VIIg	217.5	41.60 ± 21.86	48.75	26.89 ± 42.09
VIIh	414.18	79.26 ± 36.02	9.25	5.1 ± 52.35
VIIi	403.3	77.18 ± 35.1	92.25	50.89 ± 35.6
XIIa	396.7	70.75 ± 32.2	–	–
XIIb	428.3	81.97 ± 37.18	98.25	54.2 ± 35.3
XIIc	380.3	72.70 ± 33.28	58.5	32.27 ± 49.78
XIId	325.5	62.29 ± 29.05	61.3	33.79 ± 39.5
XIIe	261.1	49.90 ± 24.5	16.25	8.96 ± 50.37
XIIf	392.9	75.20 ± 34.2	29.75	16.4 ± 4.6
XIIg	324.6	62.10 ± 28.9	49.25	27.17 ± 42.02
VIIj	420.9	80.50 ± 36.57	53.25	29.37 ± 40.86
X	30.5	58.47 ± 27.57	56.25	31.03 ± 40.55

On the other hand, treatment of diphenic anhydride III with the appropriate aryl and cyclohexylamine in dry xylene produced N-substituted diphenamic acids VIII a-f. They were cyclized under the effect of acetic anhydride in the presence of fused sodium acetate to give several new 6-(substituted) dibenz[*c,e*]azepine-5,7-diones IX_{a-f}.

In addition, several chloroacetates, which are not available, have been prepared through the reaction of chloroacetyl chloride with different alcohols and phenols. Condensation of the produced chloroacetates with the potassium salt of diphenimide VI in dimethylformamide produced the desired esters VII_{a-i}. It was observed that condensation of ethyl 2-chloropropionate with potassium diphenimide VI in dimethylformamide produced ethyl 2-(dibenz[*c,e*]azepine-5,7-dion-6-yl)-propionate VII_j. However, the same reaction failed to give the corresponding ester when ethyl 2-chloro-2-methylpropionate was used. The presence of two methyl groups on the carbon bearing chlorine hindered the condensation process due to the steric clash between the methyl groups and the two carbonyl groups of the dibenzazepine nucleus. Furthermore, condensation of ethyl 4-chlorocrotonate with diphenimide V in dimethylformamide containing anhydrous potassium carbonate produced ethyl 4-(dibenz[*c,e*]-azepine-5,7-dion-6-yl)-crotonate X.

Certain unavailable N-aryl chloroacetamide derivatives were prepared by amidation of chloroacetyl chloride with different aryl amines. Condensation of diphenimide V with the different N-aryl chloroacetamide derivatives in DMF containing anhydrous potassium carbonate afforded some new arylaminocarbonylmethyldibenz [*c,e*]azepines XII_{a-d}. Other derivatives of such amides XII_{e-g} have been obtained through alcoholysis of 6-(cyanomethyl)dibenz[*c,e*]azepine-5,7-dione XI obtained by condensation of chloroacetonitrile with diphenimide V in dimethylformamide containing anhydrous K_2CO_3. The alcoholysis was achieved by treating the nitrile compound XI with iso-propanol, sec-butanol and tert-butanol in the presence of sulfuric acid at low temperature (-10^{o}C) using salt-ice bath.

When 6-(cyanomethyl)dibenz[*c,e*]azepine-5,7-dione XI was suspended in absolute ethanol, it treated with sodium borohydride yielded ethyl 2-(dibenz[*c,e*]-azepine-5,7-dion-6-yl)-acetimidate XIII. The reaction could be observed as a modified Pinner reaction[12] in which the nitrile group at α-position to a heteroatom partially reduced to imidate.

The results presented in Table 5 reveal that the test compounds showed a significant activity in lowering the triglyceride level by 84-35% from the control value, while the TC level was lowered by the same compounds by 61-5.1% from the controlled one. The most promising derivative in lowering the triglyceride level is IXb, where it produced a 84% decrease. On the other hand, the most promising derivative in lowering the TC level is IXe, where it showed 61% decrease. This indicates that such dibenzazepine derivatives possess antitriglyceride activity more than anticholesterolemic action.

Conclusion

It is clear from the results obtained from this antihyperlipidemic evaluation that the dibenz[*c,e*]azepine nucleus represents a good matrix for building up a new class of the antihyperlipidemic compounds which may be useful in the treatment of human hyperlipidemia, one of the most prevalent causes of vascular and heart diseases.

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References

[1] **Mycek MJ, Harvey RA, Champe PC, Fischer BD.** In: Lippincott S. Illustrated Reviews: *Pharmacology: Antihyperlipidemic Drugs*, 2nd ed., New Jersey: Lippincott Williams Wilkins, 2000. 207-211.

[2] **Kumar P, Clark M.** In: Clinical Medicine: *Disorders of Lipid Metabolism*, 4th ed. London: W. B. Saunders, 1998. 989-996.

[3] **Laurence DR, Bennett PN.** In: Clinical Pharmacology: *Hyperlipidemias*, 7th ed. London: Churchill Livingstone, 1992. 453-457.

[4] **Williams DA, Lemke TL.** In: Antilipidemic Drugs: *Foye's Principles of Medicinal Chemistry*. 4th ed., New York: Lippincott Williams Wilkins, 2002. 586-600.

[5] **Voorstad PI, Chapman Jr JM, Cocolas GH, Wyrick SD, Hall IH**, Comparison of the hypolipidemic activity of cyclic vs. acyclic imides. *J Med Chem* 1985; **28**(1): 9-12

[6] **Hall IH, Wong OT, Murthy AR, Day PA, Calvin J.** The hypolipidemic activity of N(4-methyl-phenyl)diphenimide in rodents. *Pharmacol Res Commun* 1987; **19**(12): 839-858.

[7] **Barakat SE-S, El-Zahabi MA, Radwan MF.** Synthesis and hypolipidemic activity of some new Dibenz[c,e]azepine derivatives. *Saudi Pharm J* 2000; **8**(2-3): 110-115.

[8] **El-Helby AA, El-Zahabi MA, Amin MA, Ibrahim MK, Abdel-Hameed SG, Ebaid AM.** Design and Synthesis of Dibenz[c,e]azepine-5,7-diones as anticonvulsant agents. *Egypt J Biomed Sci* 2003; **11**, 90-105.

[9] **Ossman AR, Osman AN, Khalifa M, El-Zahaby MA.** Synthesis of dibenz[c,e]azepine-5,7-dione derivatives. *Egypt J Chem* 1991; **34**(1): 51-64.

[10] **El-Helby AA, El-Zahabi MA, Amin MA, Ibrahim MK, Abdel-Hameed SG, Ebaid AM**. Synthesis of some new nitrogenous compounds for biological activity. *Egypt J Biomed Sci* 2003; 11: 90-105.

[11] **Murthy AR, Wyrick SD, Voorstad PJ, Hall IH.** Hypolipidemic activity of N-substituted diphenimides in rodents. *Eur J Med Chem* 1985; 20(6): 547-550.

[12] **Neilson DG.** In: Patai, *The Chemistry of Amidines and Imidates*, New York: Wiley, 1975. 385-489.

[13] **Kuroda M**, **Tanzawa K**, **Tsujita Y**, **Endo A**. Mechanism for elevation of hepatic cholesterol synthesis and serum cholesterol levels in triton WR-1339-induced hyperlipidemia. *Biochim Biophys Acta* 1977; **489**(1): 119-125..

تصميم وتشييد بعض المركبات الجديدة من نواة داي بنز [سي،إي] أزيبين-٥ و٧- دايون كمثبطات لمستوى دهون الدم

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المستخلص. تم في هذا البحث تشييد بعض المركبات الجديدة من نواة داي بنز[سي، إي] أزيبين-٥ ، ٧- دايون بطرق مختلفة، وقد تم إثبات التركيب البنائي لهذه المركبات بوسائل مختلفة، مثل الأشعة دون الحمراء، الرنين النووي المغناطيسي، والتحليل الدقيق للعناصر المكونة لهذه المركبات، بالإضافة إلى مطياف الكتلة. وقد تم اختيار بعض المركبات المشيدة لعمل الاختبار الأقربازيني المبدئي، وقد تبين من خلال الدراسة أن بعض المركبات قد أبدت فاعلية تفوق في بعض الأحيان، فاعلية مادة الكلوفيبرات في تقليل نسبة الدهون المستحثة بمادة الترايتون في الفئران، ولذلك يمكن القول بأن المشتقات التي تم تحضيرها من مادة داى بنز [سي، إي] أزيبين-٥، ٧- دايون لها نشاط ملحوظ كمثبطات لمستوى دهون الدم.