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SYNTHESIS AND ANTIHYPERLIPIDEMIC ACTIVITY OF CERTAIN NICOTINIC ACID DERIVATIVES

Abdel Ghany A. El-Helby and Mohamed H. Abdel-Wahab*

Departments of Pharmaceutical Chemistry, and (Pharmacology and Toxicology), Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt*

تم فى هذا البحث تشييد بعض المركبات الجديدة من نواة البيريدون (نيكوتنيك اسد) وتم أثبات التركيب البنائى للمركبات المشيدة بالتحاليل الدقيقة للعناصر والاشعة دون الحمراء والرنين النووى المغناطيسىومطياف الكتلة وقد تم عمل الإختبار البيولوجى على الفئران لبعض المركبات المشيدة كمخفضات للدهون (الكلوستيرول والتراجلسرايد والدهون ذات الكثافة العالية HDL والدهون ذات الكثافة المنخفضة LDL) فوجد أن للمركبات فاعلية عالية جدا فى تخفيض نسبة الدهون الضارة (LDL) دون أى تأثير على الدهون ذات الكثافة العالية والتى تحمى القلب وهذا بالمقارنة بالموديل والكنترول كما هو مبين بالجدول رقم ٥ وكذلك بالرسم رقم ١،٢،٣،٤.

*3-Ethoxycarbonyl-4,6-dimethyl-2(1H)-pyridone **I** was prepared and converted to the corresponding sodium salt **II**. The latter reacted with certain chloroacetanilides to afford the corresponding ethers **III**. In addition 3-cyano-4,6-dimethyl-2(1H)-pyridone **IV** was prepared and converted to the corresponding potassium salt **V** which was allowed to react with α-chloroacetyl and β-chloropropionyl derivatives of certain aromatic amines to afford **VI**. Furthermore, **IV** was converted to 3-cyano-4,6-dimethyl pyridine-2-thione **IX**. Potassium salt of the latter upon reaction with α-chloroacetyl and β-chloropropionyl derivatives of some aromatic amines gave the expected thioethers **X**. Compounds **III_2, V_4, X_1** and **X_{12}** were selected for testing for antihyperlipidemic effect and revealed promising hypolipidemic effect on cholesterol, triglyceride, LDL and have no effect on HDL.*

INTRODUCTION

Some new derivatives of nicotinonitrile and nicotinamide exhibited antihypertensive β-adrenergic bloking activity.[1-3] Osman *et al.*[4] synthesized some derivatives of 3-ethoxy-carbonyl-4,6-dimethyl-2(1H)-pyridone and evaluated them as antihyperlipidemic agents. Consequently, it was decided to synthesize certain new nicotinic acid derivatives for evaluation as antihyperlipidemic agents aiming to avoid drawbacks of the nicotic acid itself.

EXPERIMENTAL

All meting points were carried out on Geriffin melting point apparatus and are uncorrected. Elemental analysis were performed on CHN analyzer at the Microanalytical unit, Cairo University, Cairo, Egypt. The IR spectra were recorded on a Pye Unicam SP-1000 IR spectrophotometer at Microanalytical Unit., Cairo University. ^{1}HNMR spectra were recorded on a Joel 200 MHz spectrometer at Faculty of Science, Cairo, University, Cairo, Egypt. And Inova 400 Cosy-Chem. buffalo edu. at the Natural Science Complexes, Buffalo, USA. Chemical values were expressed by δ values using TMS as internal standard. Mass spectra were performed on Hewlett Packard 5988 (70 ev) spectrometer at the Microanalytical Unit, Cairo, University.

The following non available intermediates were prepared according to reported procedures: 3-ethoxycarbonyl-4,6-dimethyl-2(1H)-pyridone **I**[4,5] and its sodium salt **II**,[4,5] 3-cyano-4,6-dimethyl 2(1H) pyridone **IV**[6,7] and its potassium salt,[8] 2-chloro-3-cyano-4,6-dimethyl-pyridone **VII**,[4-7,9] chloroacetanilides and β-chloropropionoyl anilides.[10]

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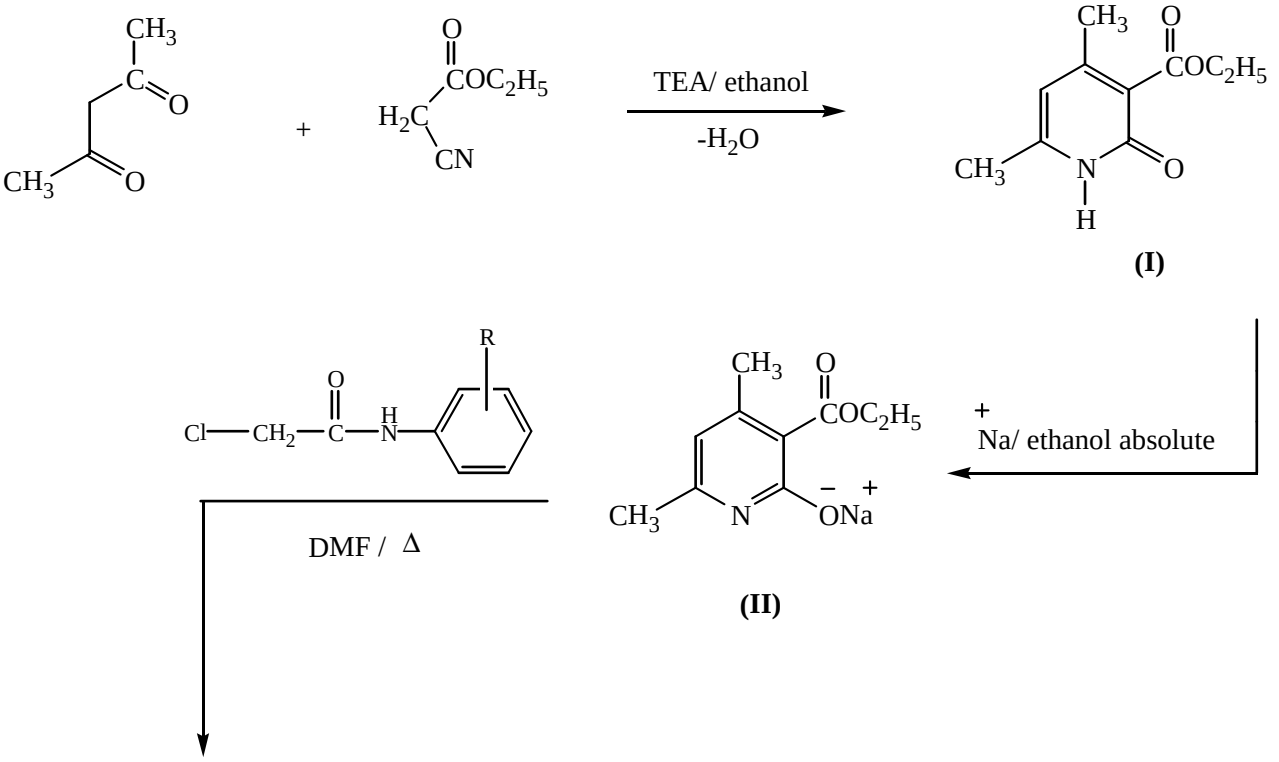


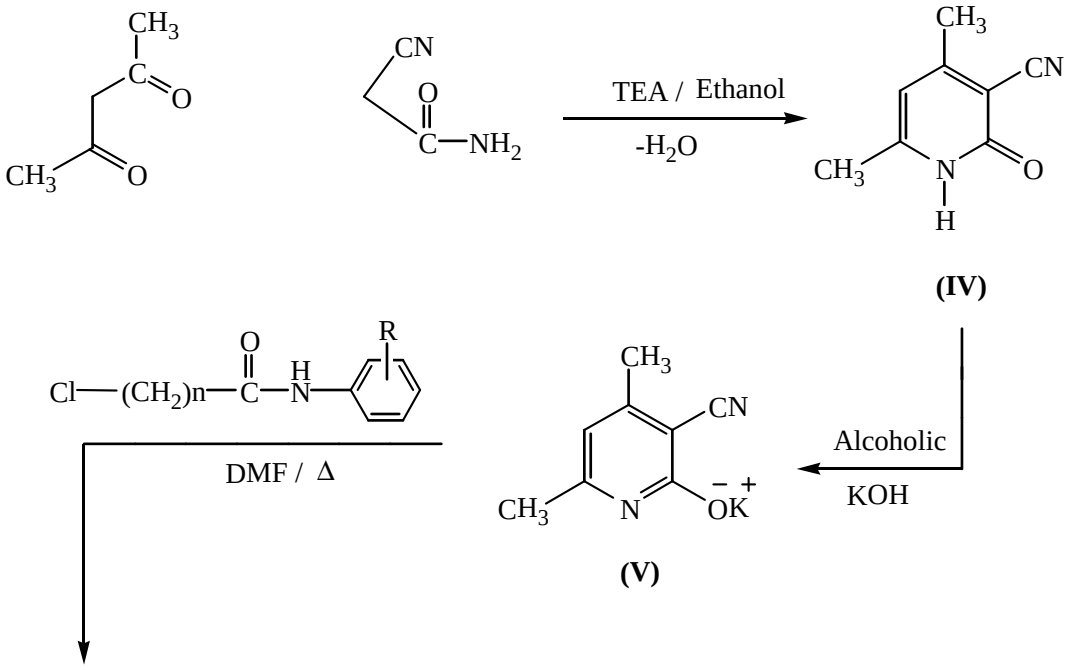
(III_{1-7})

(III_{1-7})

R =

1) H
2) 4-CH_3
3) 4-Cl
4) 2,6-dichloro
5) 4-Br
6) 2-CO_2CH_3
7) 4-$COOCH_3$

Scheme 1



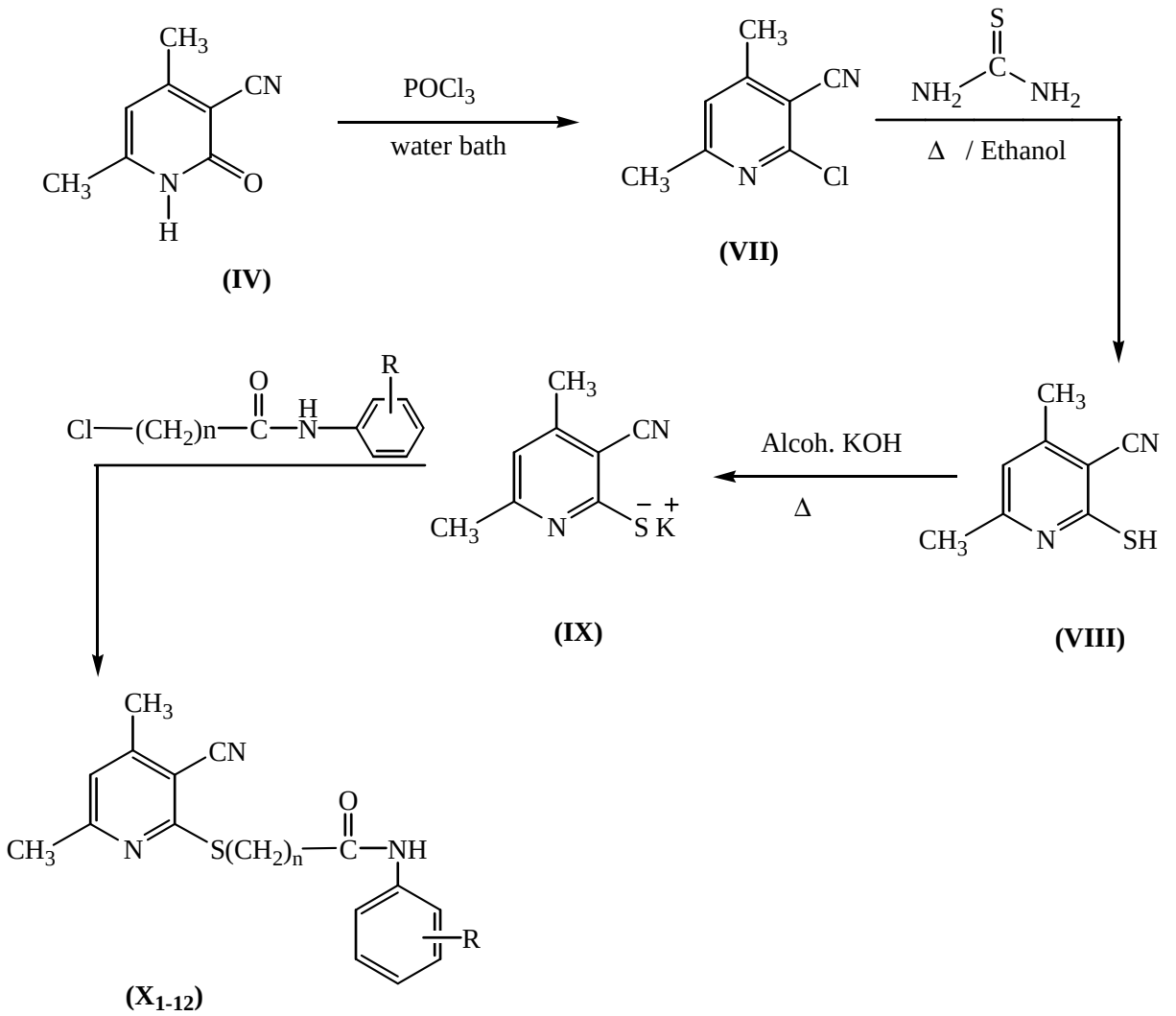
(VI $_{1\text{-}9}$)

(n=1) (n=2)

R = 1) H
2) 4-CH_3
3) 4-OCH_3
4) 4-Cl
5) 2,6-dichloro
6) 4-Br
7) 2-CO_2CH_3

R = 8) 2,6-dichloro
9) 4-Br

Scheme 2



(IV) **(VII)** **(VIII)** **(IX)** **(X_{1-12})**

(X_{1-8})(n = 1)

R = 1) H
2) 4-CH_3
3) 4-OCH_3
4) 4-Br
5) 4-Cl
6) 2,6-dichloro
7) 2-CO_2CH_3
8) 4-CO_2CH_3

(X_{9-12})(n =2)

R = 9) H
10) 4-CH_3-Br
11) 4-Br
12) 2,6-dichloro

Scheme 3

3-Ethoxycarbonyl-4,6-dimethyl-2-substituted pyridines III_{1-7}

A mixture of 3-ethoxycarbonyl-4,6-dimethyl-2-pyridone sodium salt **II** 2.17 g (0.01 mole), chloroacetanilides 1.7 g (0.01 mole) and dimethylformamide 20 ml was heated on water-bath for 3 hr, the reaction mixture was cooled, poured onto water. The solid so obtained was filtered, washed with water and crystallized from ethanol (Table 1).

Potassium salt of 3-cyano-4,6-dimethyl-2(1H)-pyridone V

3-Cyano-4,6-dimethyl-2(1H)-pyridone **IV** 1.48 g (0.01 mole) was treated with alcoholic solution of potassium hydroxide (0.01 mole) until dissolved, the solution was stirred for 30 min, the potassium salt of the target compound was separated as solid product, filtered, washed several times with absolute ethanol and then dried.

m.p, 265-6° as reported; Yield, 1.86 g (100%) as reported.[8]

3-Cyano-4,6-dimethyl-2-substituted pyridines VI_{1-9}

A mixture of potassium salt **V** 1.86 g (0.01 mole), α-chloroacetyl or β-chloropropionyl aromatic amines (0.01 mole) and dimethyl formamide (20 ml) was heated on water-bath for 3 hr, the reaction mixture was cooled, poured onto water, the precipitate was filtered, washed with water and recrystallized from ethanol (Table 2).

3-Cyano-4,6-dimethylpyridine-2-thione VIII

A mixture of 2-chloro-3-cyano-4,6-dimethylpyridine **VII** 1.66 g (0.01 mole) and thiourea 1.52 g (0.02 mole) was heated under reflux in absolute ethanol (50 ml) for 4 hr. The formed yellow crystals was filtered while hot and washed with ethanol and crystallized from ethanol.

Analysis of $C_8H_8N_2S$, M.Wt., 164.23; m.p, 285-6°; yield 1.4 g (85%).

	C%	H%	N%
Calcd.	58.51	4.91	17.06
Found	58.32	5.00	16.95

Potassium 3-cyano-4,6-dimethylpyridine-2-thiolate IX

3-Cyano-4,6-dimethylpyridine-2-thione **VIII** 1.64 g (0.01 mole) was dissolved in alcholic solution of KOH 0.056 g (0.01 mole) with stirring, the potassium salt of the target compound was immediately precipitated washed with ethanol then dried.

m.p, 280-1°; yield, (2.02 g) 100%.

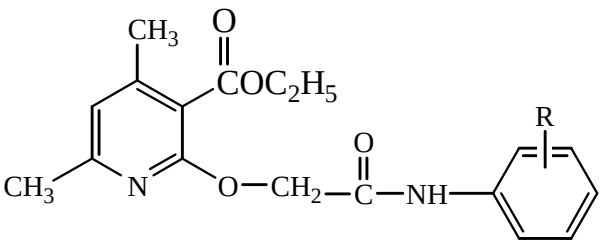
3-Cyano-4,6-dimethyl-2-(substitutedthio) pyridines X_{1-12}

A mixture of the potassium salt **IX** 2.02 g (0.01 mole) and α-chloroacetyl or β-chloropropionyl aromatic amines (0.01 mole) was heated on water-bath for 4 hr in DMF (20 ml). The reaction mixture was cooled, poured onto water, the solid so obtained was filtered and crystallized from ethanol (Table 3).

RESULT AND DISCUSSION

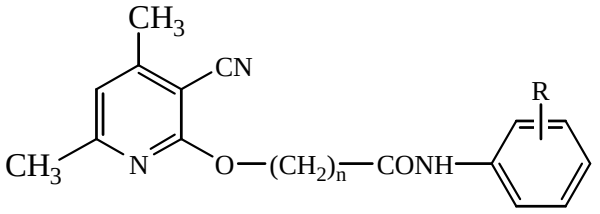
Condensation of acetylacetone and ethyl cyanoacetate in absolute ethanol containing triethylamine (TEA) afforded 3-ethoxy-carbonyl-4,6-dimethyl-2(1H)-pyridone **I**.[4,5] The latter upon reaction with $NaOC_2H_5$ afforded its sodium salt[4] **II**. Reaction of **II** with certain chloroacetanilides afforded the corresponding ethers, ethyl 3-ethoxycarbonyl-4,6-dimethyl-2-substitutedpyridines $\mathbf{III_{1-7}}$. IR spectra of such compounds showed absorption at 1719-1735 cm^{-1} and 3380 cm^{-1} for the ester carbonyl and NH absorption bands respectively. The amide carbonyls of these compounds exhibited bands at 1643-1637 cm^{-1}. The ^{1}HNMR spectra showed the presence of methylene group at δ 4.88-4.92 ppm. The NH proton appeared at δ 9.65- 10.20 ppm. Reaction of acetylacetone and cyanoacetamide in the presence of TEA afforded 3-cyano-4,6-dimethyl-2(1H)-pyridone **IV**, which was converted into the corresponding potassium salt **V** through the reaction with alcoholic KOH.[8] The potassium salt **V**[8] was allowed to react with α-chloroacetyl and β-chloropropionyl derivatives of certain aromatic amines to afforded 3-cyano-4,6-dimethyl-2-substituted pyridines $\mathbf{VI_{1-9}}$. IR spectra of such compounds showed the absorption band at 3270 cm^{-1} for the NH

Table 1: 3-Ethoxycarbonyl-4,6-dimethyl-2-substituted pyridines **III$_{1-7}$**.



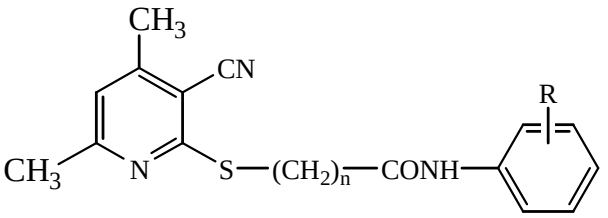
Comp. No.	R	M.P,°	Yield %	Molecular formula M.Wt	Elemental analyses		
					%	Calcd.	Found
III$_1$	H	140-1	72	$C_{18}H_{20}N_2O_4$ 328.36	C H N	65.84 6.14 8.53	66.10 6.40 8.56
III$_2$	4-CH_3	165-6	75	$C_{19}H_{22}N_2O_4$ 342.39	C H N	66.65 6.46 8.18	66.30 6.70 8.13
III$_3$	4-(Cl)	195-6	71	$C_{18}H_{19}ClN_2O_4$ 362.81	C H N	59.59 5.28 7.72	59.34 5.53 7.63
III$_4$	2,6-dichloro	159-61	67	$C_{18}H_{18}Cl_2N_2O_4$ 397.25	C H N	54.42 4.53 7.05	54.10 4.70 6.95
III$_5$	4-(Br)	248-50	70	$C_{18}H_{19}BrN_2O_4$ 407.26	C H N	53.08 4.70 6.88	52.70 4.90 6.82
III$_6$	2-(CO_2CH_3)	150-1	65	$C_{20}H_{22}N_2O_6$ 386.40	C H N	62.17 5.74 7.25	61.80 5.40 7.13
III$_7$	4-(CO_2CH_3)	190-2	71	$C_{20}H_{22}N_2O_6$ 386.40	C H N	62.17 5.74 7.25	62.28 6.00 7.15

Table 2: 3-Cyano-4,6-dimethyl-2-substituted pyridines **VI_{1-9}**.



Comp. No.	R	n	M.P,°	Yield %	Molecular formula M.Wt	Elemental analyses		
						%	Calcd.	Found
VI_1	H	1	229-30	80	$C_{16}H_{15}N_3O_2$ 281.31	C H N	68.31 5.37 14.94	68.28 5.36 14.88
VI_2	4-CH_3	1	214-15	82	$C_{17}H_{17}N_3O_2$ 295.34	C H N	69.14 5.80 14.23	69.10 5.72 14.21
VI_3	4-OCH_3	1	219.20	81	$C_{17}H_{17}N_3O_3$ 311.34	C H N	65.58 5.50 13.50	65.60 5.63 13.40
VI_4	4-(Cl)	1	170-1	75	$C_{16}H_{14}ClN_3O_2$ 315.75	C H N	60.86 4.47 13.31	60.98 4.53 13.25
VI_5	2,6-dichloro	1	319-20	76	$C_{16}H_{13}Cl_2N_3O_2$ 350.20	C H N	54.87 3.74 12.00	54.92 3.75 11.88
VI_6	4-(Br)	1	235-7	72	$C_{16}H_{14}BrN_3O_2$ 360.20	C H N	53.35 3.92 11.67	53.13 3.95 11.56
VI_7	2-CO_2CH_3	1	190-1	79	$C_{18}H_{17}N_3O_4$ 339.35	C H N	63.71 5.05 12.38	63.62 5.03 12.30
VI_8	2,6-dichloro	2	269-71	65	$C_{17}H_{15}Cl_2N_3O_2$ 364.23	C H N	56.06 4.15 11.54	56.12 4.32 11.75
VI_9	4-(Br)	2	200-2	62	$C_{17}H_{16}BrN_3O_2$ 374.23	C H N	54.56 4.31 11.23	54.49 4.20 11.31

Table 3: 3-Cyano-4,6-dimethyl -2-(substitutedthio) pyridines $\mathbf{X_{1\text{-}12}}$.



Comp. No.	R	n	M.P,°	Yield %	Molecular formula M.Wt	Elemental analyses		
						%	Calcd.	Found
X_1	H	1	220-2	75	$C_{16}H_{15}N_3O_2$ 297.38	C H N	64.62 5.08 14.13	64.35 5.15 14.20
X_2	4-CH_3	1	210-11	80	$C_{17}H_{17}N_3OS$ 311.40	C H N	65.57 5.50 13.49	65.70 5.59 13.40
X_3	4-OCH_3	1	265-6	77	$C_{17}H_{17}N_3O_2S$ 327.48	C H N	62.36 5.23 12.83	62.01 5.20 12.66
X_4	4-(Br)	1	229-31	80	$C_{16}H_{14}Br\ N_3OS$ 376.27	C H N	51.07 3.75 11.17	50.85 3.84 11.18
X_5	4-(Cl)	1	214-5	71	$C_{16}H_{14}ClN_3OS$ 331.82	C H N	57.91 4.25 12.66	57.73 4.22 12.55
X_6	2,6-dichloro	1	214-6	81	$C_{16}H_{13}Cl_2N_3OS$ 366.27	C H N	52.47 3.58 11.47	52.49 3.56 11.45
X_7	2-CO_2CH_3	1	235-6	70	$C_{18}H_{17}N_3O_3S$ 355.41	C H N	60.83 4.82 11.82	60.70 4.60 11.75
X_8	4-CO_2CH_3	1	214-5	67	$C_{18}H_{17}N_3O_3S$ 355.41	C H N	60.83 4.82 11.82	61.05 4.90 11.75
X_9	H	2	140-1	65	$C_{17}H_{17}N_3OS$ 311.40	C H N	65.57 5.50 13.49	65.46 5.41 13.52
X_{10}	CH_3	2	120-1	61	$C_{18}H_{19}N_3OS$ 325.43	C H N	66.43 5.88 12.91	66.45 5.72 12.88
X_{11}	4-(Br)	2	140-1	62	$C_{17}H_{16}BrN_3OS$ 390.30	C H N	52.31 4.13 10.77	52.48 4.11 10.89
X_{12}	2,6-dichloro	2	157-8	65	$C_{17}H_{15}Cl_2N_3OS$ 380.20	C H N	53.69 3.98 11.05	53.61 4.01 10.95

Table 4: Spectral data of some new compounds (**III-X**).

Comp. No.	Spectral data IR (cm^{-1}), ^{1}HNMR (δ ppm.), Mass (m/z, %)	
III$_1$	IR ^{1}HNMR ($CDCl_3$)	1639 (CONH), 1735 ($COOC_2H_5$), 3276 (CONHPh) 1.30 (t,3H,$\underline{CH_3}$-CH_2-O-), 2.20 (S,3H,CH_3 at 6- position), 2.45 (s, 3H, CH_3 at 4-position), 4.35 (q, 2H, CH_3-$\underline{CH_2}$-O-), 4.90 (s, 2H,-o-CH_2CO), 6.05 (s,1H, CH at C_5-of pyridine), 7.00-7.50 (m, 5H, aromatic protons), 9.70 (s,1H,NH).
III$_3$	^{1}HNMR ($CDCl_3$)	1.35 (t,3H,CH_3), 2.24 (s,3H, CH_3 at-6-position), 2.51 (s,3H,CH_3 at 4-position), 4.83 (q, 2H, CH_3-$\underline{CH_2}$-O-), 4.83 (s, 2H, OCH_2CO), 6.08 (s, 1H,CH at C_5-of pyridine), 7.17(d,2H, aromatic protons at C_1 and C_6), 7.38 (d, 2H, aromatic protons at C_3 and C_5), 9.62 (s, 1H, NH).
III$_4$	IR ^{1}HNMR (acetone-d_6)	1643 (CONH), 1719 ($COOC_2H_5$), 3194 (CONHPh). 1.26 (t,3H, $\underline{CH_3}$-CH_2-O-), 2.11 (s,3H,CH_3 at 6-position), 2.44 (s,3H, CH_3 at 4-position), 2.24 (q, 2H, CH_3-$\underline{CH_2}$-O-), 5.01 (s,2H, OCH_2CO), 6.07 (s,1H, CH at C_5-of pyridine), 7.33-7.48(m,3H, aromatic protons), 9.38 (s, 1H, NH).
III$_7$	IR ^{1}HNMR ($CDCl_3$)	1739, 1725 ($COOC_2H_5$, p-$COOC_2H_5$), 1637 (CONH), 3280 (CONHPh). 1.31 (t, 3H, $\underline{CH_3}$-CH_2-O-), 2.25 (s, 3H, CH_3 at 6-position), 2.48 (s, 3H, CH_3 at 4-position), 3.86 (s, 3H, p-OCH_3), 3.35 (q,2H,- CH_3-$\underline{CH_2}$-O-), 4.91 (s, 2H,-OCH_2-CO), 6.10 (s, 1H, CH at C_5-of pyridine), 7.44 (d, 2H, aromatic protons at C_2 and C_6), 7.80 (d, 2H, aromatic protons at C_3 and C_5), 10.03 (s,1H, NH).
VI$_1$	^{1}HNMR (DMSO-d_6)	2.36 (s,3H,CH_3 at 6 position), 2.40 (s, 3H, CH_3 at 4 position), 4.89 (s, 2H, OCH_2CO), 6.38 (s, 1H,CH at C_5-of pyridine), 7.10 (t, 1H, aromatic proton at C4-of phenyl ring), 7.35 (t, 2H, aromatic protons at $C_{2,5}$-of phenyl ring), 7.60 (d,2H, aromatic protons at $C_{1,6}$), 10.44 (s,1H, NH).
VI$_2$	^{1}HNMR (DMSO-d_6)	2.26 (s,3H, CH_3 at the p-position), 2.40 (d,6H, $2CH_3$, at 6 and 4-positions), 4.87 (s,2H, -OCH_2CO), 6.38 (s,1H, CH at C_5-of pyridine), 7.15 (d,2H at $C_{3,5}$- of the aromatic ring), 7.45 (d,2H at $C_{2,6}$- of the aromatic ring), 10.26 (s, 1H, NH).
VI$_3$	^{1}HNMR (DMSO-d_6)	2.35 (s, 3H,CH_3 at 6 position), 2.39 (s,3H, CH_3 at 4-position), 3.73 (s,3H, OCH_3 at p-position), 4.86 (s,2H, OCH_2CO), 6.37 (s,1H, CH at C_5-of pyridine), 6.90 (d,2H, at $C_{2,6}$-aromatic protons), 7.50 (d, 2H, at $C_{3,5}$-aromatic position), 10.31 (s,1H,NH).
VI$_4$	^{1}HNMR ($CDCl_3$) Ms	2.43 (d, 6H, $2CH_3$ at 6, 4-positions), 4.94 (s, 2H, OCH_2CO), 6.17 (s, 1H, CH at C_5-of pyridine), 7.12-7.60 (m,5H, aromatic protons and $CDCl_3$ proton), 9.63 (s, 1H, NH). 315, 317 (M^+, M+4, 3.00, 1.21%), 189 (m/e base 100%).
VI$_5$	IR	1671 (CONHPh), 2217 (CN), 3195 (CONHPh).
VI$_6$	^{1}HNMR (acetone d_6)	2.37 (s, 3H, CH_3 at 6-position), 2.48 (s, 3H, CH_3 at 4-position), 4.97 (s, 2H, OCH_2CO), 6.30 (s, 1H, CH at C_5- of pyridine), 7.47 (d, 2H, aromatic at C_2 and C_6), 7.60 (d, 2H, aromatic C_3 , C_5), 9.65 (s, 1H, NH)
VI$_7$	IR ^{1}HNMR ($CDCl_3$)	1693 ($COOCH_3$), 1647 (CONH), 2220 (CN), 3271 (CONHPh). 2.43 (s,6H, $2CH_3$ at 6 and 4 positions), 3.92 (s,3H, o-$COOCH_3$), 4.92(s, CH_3-O-CH_2-CO), 6.13 (s, 1H, CH at C_5- of pyridine), 7.10 (t, 1H, at C_4- of the phenyl ring), 7.25 (s, 1H of $CDCl_3$), 7.50 (t, 1H, at C_5- of phenyl ring), 8.00 (d, 1H, at C_6- of aromatic ring), 8.60 (d, 1H at C_3- of phenyl ring), 11.40 (s, 1H, NH).
VI$_8$	IR ^{1}HNMR (acetone d_6)	1661(CONH), 2216 (CN), 3242 (CONHPh). 2.35 (s, 3H, CH_3 at 6-position), 2.80 (s,3H, CH_3 at 4-position), 2.95 (t, 2H, -CH_2CO), 3.95 (t, 2H, OCH_2-CH_2), 6.12 (s, 1H, CH at C_5-of pyridine), 7.31-7.49 (m, 3H, aromatic), 9.08 (s, 1H, NH).

Table 4: continued

Comp. No.	Spectral data IR (cm^{-1}), ^{1}HNMR (δ ppm.), Mass (m/z, %)	
VI_9	^{1}HNMR ($CDCl_3$)	2.30 (s, 3H, CH at 6-position), 2.51 (s, 3H, CH_3 at 4-position), 2.81 (t, 2H, CH_2CO), 4.27 (t, 2H, OCH_2), 6.00 (s, 1H, CH at C_5-of pyridine), 7.10-7.80 (m, 4-aromatic protons), 9.82 (s, 1H, NH).
VIII	IR ^{1}HNMR ($DMSO-d_6$) Ms	2216 (CN), 3356 (SH) 2.35 (s, 6H, $2CH_3$ at 6.4 position), 6.69 (s, 1H, CH at C_5-of pyridine), 13.80 (s, 1H, SH). m/z 164 (M^+, 9.21%), M/z 55 (base 100%).
X_1	^{1}HNMR ($DMSO-d_6$)	2.52 (s, 3H, CH_3 at 6-position), 2.81 (s, 3H, CH_3 at 4-position), 6.91 (s,2H, s-CH_2CO), 6.98 (s, 1H,-H of pyridine), 7.07-7.75 (m, 7H, aromatic protons and -SCH_2 -protons), 9.42 (s, 1H, NH).
X_2	^{1}HNMR ($DMSO-d_6$)	2.28 (s,3H, CH_3 at p-position of aromatic ring), 2.52 (s, 3H, CH_3 at 6-position), 2.75 (s, 3H, CH_3 at 4-position), 6.95 (s, 2H, SCH_2CO), 7.05 (s, 1H at 5-position), 7.15 (d, 2H aromatic protons at $C_{3,5}$), 7.58 (d, 2H, aromatic protons at $C_{2,6}$), 9.34 (s, 1H, NH).
X_4	IR ^{1}HNMR ($DMSO-d_6$)	1643 (CONH), 3320 (NH), 3468 (SCH_2) 2.51 (s, 3H, CH_3 at 6-position), 2.74 (s, 3H, CH_3 at 4-positions), 3.42 (s, 2H, SCH_2CO), 7.03 (s, 1H, CH of pyridine), 7.51 (d, 2H, at $C_{2,5}$- of aromatic), 7.60 (d, 2H, at $C_{3,5}$- of aromatic), 9.51 (s, 1H, NH).
X_4	^{1}HNMR ($CDCl_3$)	2.60 (s, 3H, CH_3 at 6-position), 2.76 (s, 3H, CH_3 at 4-positions), 6.47 (s, 2H, SCH_2CO), 6.90 (s, 1H, CH of pyridine), 7.14 (s,1H,NH), 7.46-7.47 (m, 4H, aromatic protons).
X_5	^{1}HNMR (acetone d_6) Ms	2.51 (s, 3H, CH_3 at 6-position), 2.81 (s, 3H, CH_3, at 4-position), 6.93 (s, 2H, SCH_2CO), 7.03 (s, 1H, CH of pyridine), 7.32 (d, 2H, aromatic at C_2 and C_6), 7.78 (d, 2H, aromatic at C_3 and C_5), 8.74 (s, 1H, NH). 331, 335 (M, M^+4, 3.00, 0.72% respectively), 218 (base 100%).
X_7	IR ^{1}HNMR ($DMSO-d_6$)	1699 ($COOCH_3$), 1594 (CONH), 3319 (CONHPh), 3482 (SCH_2). 2.51 (s, 3H, CH_3 at 6-position), 2.76 (s, 3H, CH_3 at 4-position), 3.96 (s, 3H, o-CO_2CH_3 of phenyl ring), 7.01 (s, 2H, SCH_2CO), 7.07 (s, 1H, CH of pyridine), 7.22 (t, 1H at C_5-of aromatic ring), 7.58 (t, 1H, at 4-aromatic position), 8.04 (d, 1H, at C_6- of the aromatic ring), 8.29 (d, 1H at C_3-aromatic position), 11.01 (s, 1H, NH).
X_8	^{1}HNMR ($CDCl_3$)	2.61 (s, 3H, CH_3, at 6-position), 2.77 (s, 3H, CH3 at 4-position), 3.91 (s, 3H, p-OCH_3), 6.53 (s, 2H, SCH_2CO), 6.92 (s, 1H, CH of pyridine), 7.26 (s, 1H, $CDCl_3$), 7.28 (s, 1H, NH), 7.69 (d, 2H, aromatic at C_2 and C_6), 8.05 (d, 2H, aromatic at C_3,C_5).
X_9	IR ^{1}HNMR ($CDCl_3$)	1662 (CONH), 2214 (CN), 3334 (CONHPh). 2.42 (s, 3H, CH_3 at 6-position), 2.15 (s, 3H, CH_3 at 4-position), 2.81 (t, 2H, SCH_2), 3.61 (t, 2H, SCH_2CO), 6.79 (s, 1H, CH of pyridine), 7.10-7.49 (m, 7H, 5-aromatic protons, NH and $CDCl_3$).
X_{10}	^{1}HNMR ($CDCl_3$)	2.29 (s, 3H, CH_3 at 6-position), 2.39 (s, 3H, CH_3 at 4-position), 2.49 (s, 3H, CH_3 at p-position), 2.80 (t, 2H, SCH_2-CH_2-CO), 3.58 (t, 2H, SCH_2-CH_2-CO), 6.87 (s, 1H, CH of pyridine), 6.90-7.60 (m, 4H aromatic protons), 7.73 (s, 1H, NH).
X_{11}	^{1}HNMR ($CDCl_3$)	2.42 (s, 3H, CH_3 at 6-position), 2.51 (s, 3H, CH_3, at 4-position), 2.81 (t, 2H, SCH_2CH_2), 3.61(t, 2H, SCH_2CH_2CO), 6.79 (s, 1H, CH of pyridine), 7.14-7.27 (m, 6H, 4-aromatic protons, NH and $CDCl_3$).
X_{12}	^{1}HNMR ($CDCl_3$)	2.42 (s, 3H, CH_3, at 6 position), 2.47 (s, 3H, CH_3 at 4 position), 2.88 (t, 2H, SCH_2CH_2), 3.59 (t, 2H,-SCH_2CH_2-CO), 6.80 (s, 1H, CH of pyridine), 7.10-7.35 (m, 3H, aromatic protons at 3,4 and 5-positions), 7.77 (s, 1H, NH).

absorption, 2220 cm^{-1} for CN and at 1671-1661 cm^{-1} for carbonyl absorption. Reaction of 3-cyano-4,6-dimethylpyridine **IV** with $POCl_3$ on water-bath gave 2-chloro-3-cyano-4,6-dimethylpyridine **VII**. The latter upon reaction with thiourea in ethanol for 3 hr. afforded the expected, 3-cyano-4,6-dimethylpyridine-2-thione **VIII**. The mass spectrum of this compound is characterized by the appearance of molecular ion peak (M^+) at 164, the ^{1}HNMR showed singlet aromatic proton of pyridine at δ 6.69 ppm, the SH proton appear singlet at δ 13.80 ppm. Compound **VIII** when reacted with alcoholic KOH afforded the potassium salt **IX**, which when allowed to reacted with α-chloroacetyl and β-chloropropionyl derivatives of some aromatic amines gave the expected thioethers,3-cyano-4,6-dimethyl-2-(substituted-thio) pyridines $\mathbf{X_{1-12}}$. The IR spectra of these compounds showed the CN absorption at 2221 cm^{-1} and the NH absorption at 3320-3270 cm^{-1}, 1643-1594 cm^{-1} for carbonyl absorption. ^{1}HNMR spectra of X showed the methylene group SCH_2CO- desheileded at δ 7.00-7.20 ppm and the pyridine proton at δ 6.78-7.15 ppm.

Anti-hyperlipidemic effect

Induction of hyperlipidemia

Hyperlipidemia can be induced by three times weekly administration by gavage of 10 ml/kg body weight for two weeks of a cocktail containing in 1 L peanut oil: 100 gm cholesterol, 30 g propylthiouracil and 100 g cholic acid.[11] Rats were maintained at constant environmental condition throughout the whole experimental period.

Design of the experimental work

Thirty six of adult male rats, weighing 120-140 g, were divided into six groups (6 rats for each). The first group served as control group. The second group served as model group. The remaining groups from 3-6 were given an oral doses of the hyperlipidemic cocktail by gavage of 10 ml/kg body weight 3 times weekly for two weeks perior to the tested compounds ($\mathbf{III_2}$, $\mathbf{V_4}$, $\mathbf{X_1}$ and $\mathbf{X_{12}}$) then blood samples of all groups were taken from the orbital fissures of the eye by using heparanized capillary tubes. After clotting of the blood, the samples were centrifuged for 15 min. at 3000 rpm. The above serum layer was decanted in other epindorf tubes and subjected for estimation of lipid profil (cholestyol, triglyceride HDL and LDL) using enzymatic kits methods. For total cholesterol CHOD-PAP. (SPINREACT), SPAIN. For triglyceride (GPO-POD. Ensimatica colorimetica) (SPINREACT) SPAIN, for HDL precipitant PEG 6000 (Dasa-Ragister), Roma.

Table 5: Effect of the synthesized compounds $\mathbf{III_2}$, $\mathbf{V_4}$, $\mathbf{X_1}$ and $\mathbf{X_{12}}$ on the hyperlipideamic rats.

Group Lipids	Control	Model (Cocktail)	Compound $\mathbf{III_2}$	Compound $\mathbf{V_4}$	Compound $\mathbf{X_1}$	Compound $\mathbf{X_{12}}$
Total cholesterol	58.3±2.4	0.155±14.0[a]	75.6±8.1[b]	71.9±4.2[b]	71.1±3.8[b]	63.5±0.9[b]
Trigly-ceride	9.21±2.4	82.6±3.2[a]	47.7±5.5[ab]	54.5±1.2[ab]	45.5±1.5[ab]	63.3±2.6[ab]
HDL	8.42±2.0	31.7±2.6[a]	35.6±4.6[a]	26.9±2.5[a]	29.4±1.7[a]	28.2±1.7[a]
LDL	10.1±2.6	100.8±17.4[a]	30.5±8.3[b]	34.0±5.8[b]	32.6±4.3[b]	29.3±2.6[b]

Data are presented as M ± SEM

a: Significant from control

b: Significant from model

Statistical analysis was done using one way ANOVA followed by Tukey-Kramer as post ANOVA test.

Description of results

Oral administration of hyperlipidemic cocktail to rats significantly increased the total cholesterol level by 265% compared with control group (Table 5, Fig 1). Oral administration of new synthesized hypolipidemic compounds **III_2, V_4, X_1** and **X_{12}**. structurally related to Niacin (hypolipidemic agent) in a dose level of 400 mg/kg body weight daily for 7 days, significantly lowered the total cholesterol level by 49%, 46%, 46% and 41% respectively compared with the model group (Table 5, Fig. 1).

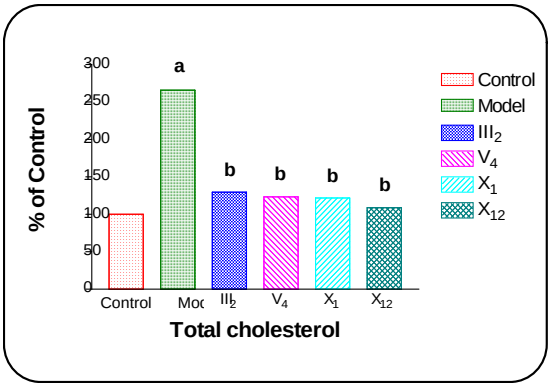


Fig. 1: Effect of some synthesized compounds on serum total cholesterol level.
Data were presented as mean ± SEM.
a: Significant from control.
b: Significant from model.

Concerning the triglyceride level, oral administration of the hyperlipidimic cocktail to rats significantly increased the serum triglyceride by 377% compared with control group. Oral injection of compounds (**III_2, V_4, X_1** and **X_{12}**) significantly decreased serum triglyceride by 58%, 66%, 55% and 44% compared with the model group (Table 5, Fig. 2).

Also the serum HDL was increased by hyperlipidemic cocktail by 74% compared with control group. The previous compounds have no effect on HDL level compared with the model (Table 5, Fig. 3).

Similarly, the serum level of LDL was significantly increased by 100% compared with control group. Oral injection of compounds (III_2, V_4, X_1 and X_{12}) significantly decreased the serum LDL by 31%, 34%, 33% and 29% respectively compared with the model group but still higher than the normal control group (Table 5, Fig. 4).

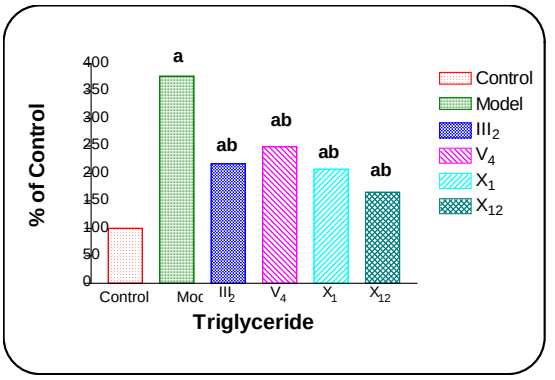


Fig. 2: Effect of some synthesized compounds on serum Triglyceride level.
Data were presented as mean ± SEM.
a: Significant from control.
b: Significant from model.

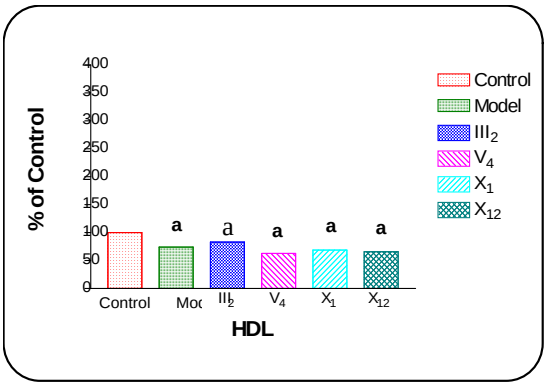


Fig. 3: Effect of some synthesized compounds on serum HDL level.
Data were presented as mean ± SEM.
a: Significant from control.
b: Significant from model.

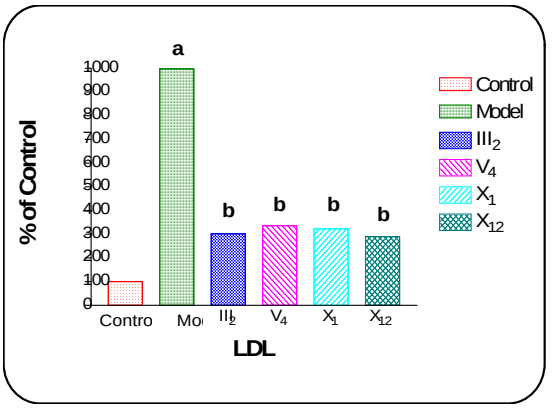


Fig. 4: Effect of some synthesized compounds on serum LDL level.
Data were presented as mean ± SEM.
a: Significant from control.
b: Significant from model.

Discussion of antihyperlipidemic results

The new synthesized hypolipidimic compounds in this study had been found to decrease the serum levels of cholesterol, triglyceride, HDL and LDL. This results are in the same direction with the study of Tapan *et al.*[12] who reported that niacin in a dose level of 400-4000 mg/kg has been found to lower blood lipid. The mechanism underlying the cocktail induced-hyperlipideamia may be due to thiouracil contained in this cocktail has antithyroid effect, this leads to sensetization of blood vessels to the effect of adrenaline.[12] The mechanism underlying the synthetic compounds lowering blood levels of cholesterol, triglyceride HDL and LDL may be due to increase steroid excretion and inhibition of cholesterol synthesis from active acitate.[13,14] In addition, nicotinic acid revealed significant antilipolytic effect by inhibiting the release of NEFA and glycerol from adipose tissues and decrease the synthesis and release of VLDL - TG from liver.[15] Because our new synthesized compounds (**III_2, V_4, X_1** and **X_{12}**) have structuraly similarity to nicotinic acid we suggest that these compound lower blood lipid profil may be throughout the above mechanisms.

Conclusion

The new synthesized compounds (**III_2, V_4, X_1** and **X_{12}**) have marked lowering effects on serum cholesterol, triglyceride, HDL and LDL. Moreover they have the same relative potency in this manner.

REFERENCES

1- J. B. John, C. L. William, F. L. George, S. P. Gerald, W. R. Andrew, L. E. Edward and H. Ralph, J. Med. Chem., 22 (11), 1284-1987 (1979).

2- J. B. John, L. E. Edward, H. Ralph, S. P. Gerald, G. A. Joseph, K. W. Burton, S. S. Charles and S. Alexander, J. Med. Chem., 23, 65-70 (1980).

3- E. M. David, J. B. John, C. R. William, F. L. Thomas, K. Mesler, G. F. Lundell, A. W. Raad, G. E. Dennis, A. R. Dwin, S. S. Charles and W. Michoel, J. Med. Chem., 26, 649-657 (1983).

4- A. N. Osman, M. M. Ismail and M. A. Barakat, Egypt. J. Pharm. Sci., 28, (1-4) 87-98 (1987).

5- J. L. Simonsen and M. Nayak, J. Chem. Soc., 107, 792-8 (1915).

6- A. N. Osman, M. A. Shaban, Mohsen M. Ismail and A. A. El-Gendy, Bull Fac. Pharm. Cairo, Univ., 28, 2, 25-28 (1990).

7- Mohsen M. Ismail and K. M. Ghoneim, Bull. Fac. Pharm. Cairo, Univ., 32 (2), 171-175, (1994).

8- G. Karl and J. Hans, Ger (East) 107, 287 (Cl.C 07d) 20 Jul.,1974, Appl. 172 688,01 Aug (1973).??

9- H. Jahine, H. A. Zaher, A. A. Sayed and M. J. F. Seada, Prakt. Chemie, 316, 2, 337-343 (1974).

10- S. El-Mogahazy, Egypt. J. Pharm. Sci., 33, (3-4), 527-538 (1992).

11- L. C. Fillios, Andrus Stb, G. V. Mann and F. J. Stare, J. Exper. Med., 104, 539 (1956).

12- K. Tapan, Basu and Sarabjit Mann, J. Nutr. 127 (1), 117-121 (1997).

13- S. M. Grundy, H. Y. I. Mok, L. Zech, M. Berman, J. Lipid Res., 22, 24-26 (1981).

14- L. Kaijser, B. Eklund, A. G. Olson and L. A. Carlson, Med. Biol., 57, 114-117 (1979).

15- G. P. Ellis and G. B. West, "Progress in Medicinal Chemistry 11", North-Holland, Publishing company Amsterdam oxford, 1975, p. 124.