Synthesis and Biological Evaluation of Novel Cholesterol Lowering Agents

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ABSTRACT :

Propitious hypolipidemic activity has been reported in droves of 2- substitutedthieno(2,3-d)pyrimidines. Earlier 2-(chloromethyl)-5,6,7,8-tetrahydro(1) benzothieno(2,3-d)pyrimidin-4(3H)-one (I, LM-1554, CAS89567-03-3) have been extensively evaluated pharmacologically and toxicologically for hypolipidemic activities. Its 4-chloro analog (II) recently revealed much supercilious activity to it. Scientific exploration and clinical studies have already archieved the importance of Niacin (Vitamin B3) in reducing blood cholesterol levels and other consequential risk factors in the blood. Further, it also documented to contribute in the repair of artery wall. With this rationalization, the synthesis & biological evaluation of novel mutual prodrugs composing the LM 1554 nucleus and vitamin B3 molecule was ventured through the consecutive synthetic routes.

Keywords: LM-1554; Vitamin B3; Prodrugs; Hypolipidemic activity.

Materials & Methods:

Synthesis of Starting Material (Gewald Reactions)

Synthesis of 2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(*b*) thiophene (I*a*): Method A

Cyclohexanone (9.8 g; 0.1mole), sulfur (3.2 g; 0.1mole), ethyl cyanoacetate (11.7 g; 0.1mole) and ethanol (20ml) were mixed and stirred together. To this well stirred mixture diethylamine (9.14 g; 0.125 mole) was added dropwise for ½ hour and stirring continued for another 3 hours at ambient temperature. The reaction mixture was kept in refrigerator overnight. The solid separated was filtered next day, and washed with 20 ml chilled 50% aqueous methanol. The product (69.9% yield) having m.p 112-114^{0}C (115 ^{0}C)[1] was characterized as 2-Amino-3-carbethoxy-4,5,6,7-tetrahydro benzo(b)thiophene(Ia).

Molecular formula: C¬11H15NO2S

IR (KBr) cm-1 :1649, 2988, 3074, 165(γCOOEt). 3306, 3414 (γNH);

UV (MeOH) λmax : 314.0 nm

TLC; Rf: 0.74

Solvent system (Benzene- 4.5 ml: Methanol- 2 drops)

Synthesis of Chloroacetonitrile (II)[2,3]

Step I: Synthesis of Chloroacetamide

In a 2 litre round-bottomed flask with a mechanical stirrer and surrounded by an ice-bath was placed 215g (1.75 moles) of ethylchloroacetate. Vigorous stirring was started and to the cold ester 200 cc. of chilled aqueous ammonia (sp. gr. 0.9) was added. The solution was stirred in the cold for about fifteen minutes; then another 200 cc. portion of aqueous ammonia was added and the stirring is continued for about fifteen minutes.

The mixture was then allowed to stand for about 30 minutes, filtered with suction and washed with 25 cc. portion of cold water to remove ammonium chloride. The yield of air-dried material melting at 118-119^{0}C is 128-138g. (78-84% of the theoretical amount). This product contained traces of ammonium chloride, which were removed by crystallization from water. When 100g of crude product is recrystalised from 400 cc. of water, about 80g of product is obtained. The recrystalised product melts at 119-120^{0}C.

Step II : Synthesis of chloroacetonitrile

In a 3 litre round-bottomed flask fitted with an efficient mechanical stirrer, a reflux condenser, and a thermometer were placed 170g. (1.2 moles) of phosphorous pentoxide, 187g. (2 moles) of chloroacetamide and 800 ml of dry technical trimethylbenzene. The mixture was refluxed gently with vigorous stirring for 1 hour. The reaction mixture was then allowed to cool to about 100^{0}C with continuous stirring, and the reflux condenser was replaced with a distilling adapter fitted with a thermometer and a water-cooled condenser.

The crude product and part of solvent were distilled at atmospheric pressure. The yield of crude product boiling at 124-128^{0}C is 121-131g (80-87%). In order to obtain a pure product, the crude chloroacetonitrile was mixed with 10g of phosphorous pentoxide and redistilled through an efficient packed fractionating column. The yield of the pure chloroacetonitrile distilling at 123-124^{0}C was 93-106g (62-70%).

Synthesis of 2-Chloromethylthieno(2,3-*d*) pyrimidine-4(3*H*)-ones (III*a*-*k*) Reaction of 2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(*b*)thiophene with chloroacetonitrile in the presence of dry hydrogen chloride gas(IIIa)

A stream of dry hydrogen chloride gas was bubbled through an ice-cold mixture of 2-Amino-3-carbethoxy-

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4,5,6,7-tetrahydrobenzo(*b*)thiophene (**I*a***), (11.25 g; 0.05 mole) and chloroacetonitrile (**II**) (5 g; 0.066 mole) in dry dioxane (50 ml) for 6 hours at temperature below 10^0C. The reaction mixture was allowed to stand thereafter at room temperature for 12 hours. Then it was heated on a water bath for 2 to 3 hours, cooled to room temperature and poured onto ice-water mixture (150-200 ml) and neutralized with strong ammonium hydroxide solution (50%v/v). The solid separated was filtered, washed with water and dried. The crude product on recrystallisation from dioxane yielded fine needles (11.49 g; 90.0%), m.p 272-275^{0}C (273-276^{0}C)[4] characterized as 2-Chloromethyl-5,6,7,8-tetrahydrobenzo(*b*)thieno 2,3-*d*)pyrimidin-4(3*H*)-one (**III*a***).

Molecular formula: $C_{11}H_{11}ClN_2OS$

IR (KBr) cm^{-1}: 3015(γ_{ArH}); 1664.72(γ_{CONH}); 937.85(γ_{CH2}); 792, 754, 686(γ_{C-l}).

NMR ($CDCl_3$): 1.62-1.99,4H, m, CH_2 at 6 & 7; 2.78-3.02, 4H, m, CH_2 at 4 & 8; 4.56, 2H, s, CH_2 at 2.

UV (MeOH) λmax : 319 nm

MS m/e: 255(M^+); 221.2, 149

TLC:Rf: 0.78

Solvent system (benzene: 4.5 ml; methanol 0.7 ml)

Synthesis of Sodium Nicotinate (IV)[5]:

The solution of sodium hydroxide (1.62gm) in minimum quantity of water was prepared. Nicotinic acid (5gm) was dissolved in the previously prepared sodium hydroxide solution (equimolar quantities of NaOH & nicotinic acid were taken).Refluxed this mixture for 7-8 hrs in acetone(50ml). Distilled off acetone (by rotary flash evaporator)& removed water by azeotropic distillation (by dean &stark apparatus). The pure sodium nicotinate was obtained (% yield 76.4).

Synthesis of the prodrugs(V*a-k*) Reaction of 2-chloromethyl-5, 6, 7, 8-tetrahydrobenzo(*b*)thieno (2,3-*d*)pyrimidin-4(3*H*)-one with sodium nicotinate (V a)[6]

A solution of 2-chloromethyl -5 ,6 , 7, 8 -tetrahydrobenzo (*b*) thieno (2, 3 -*d*) pyrimidin-4(3*H*)-one **(III*a*)** (1.527gm,0.006mol) & sodium nicotinate(3.624gm,0.024mol) in glacial acetic acid (25ml) was refluxed for 12 hrs., poured into ice-water & basified with dil.ammonium hydroxide(10%v/v).

The precipitate formed was filtered, dried & recrystallised from acetic acid to obtain white powder (1.24gm, 60.6% yield) m.p.296-98^{0}C was characterized as Nicotinic acid -4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno(2,3-*d*) pyrimidin-2-ylmethyl ester **(V*a*)**.

Molecular formula : $C_{17}H_{15}N_3O_3S$

IR (KBr) cm^{-1} : 3070.78(γ_{CH2}); 1685.84 (γ_{CONH}); 1571(γ_{COO^-}) NMR(DMSO.D_6) dppm

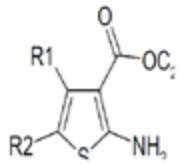
1.163,4H, s,H at 6 & 7; 1.920,4H,s,H at 5 & 8; 4.9,2H,s,H at 2; 7.312,4H,m,H at Ar

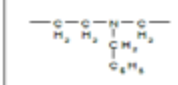
UV (MeOH) λmax : 226nm

TLC Rf value: 0.58 Solvent System (Benzene: 3 ml Methanol: 2 ml).

Results and Discussions:

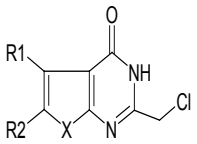
Table I: 2-Amino-3-carbethoxythiophenes (Ia-j)



Sr. No.	R_1	R_3	Yield (%) (method)	M.P. (^{0}C)	Mol. Formula
I*a*	-$(CH_2)_4$-		69.9 (A)	112-114	$C_{11}H_{13}NO_2S$
I*b*	CH_3	CH_3	65.7 (A)	90-93	$C_9H_{13}NO_2S$
I*c*	C_2H_5	CH_3	65.3 (B)	90-93	$C_{10}H_{15}NO_2S$
I*d*	4-ClC_2H_5	H	69.2 (B)	102-104	$C_{13}H_{15}ClNO_2S$
I*e*	CH_3	$COOC_2H_5$	60 (A)	104-107	$C_{11}H_{13}NO_4S$
I*f*	H	C_2H_5	70.7 (C)	65-68	$C_9H_{13}NO_2S$
I*g*	4-CH_3 C_6H_4	H	65.7 (B)	100-103	$C_{14}H_{15}NO_2S$
I*h*			69.2 (A)	98-100	$C_{14}H_{21}N_2O_2S$
I*i*	C_6H_5	H	62 (B)	94-99	$C_{13}H_{13}NO_2S$
I*j*	4-$OCH_3C_6H_4$	H	63 (B)	108-112	$C_{14}H_{15}NO_3S$

Prepared by method A, B,C

Table II : Condensed 2-Chloromethylpyrimidin-4(3*H*)-ones (III*a-k*)



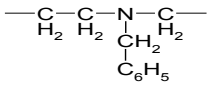
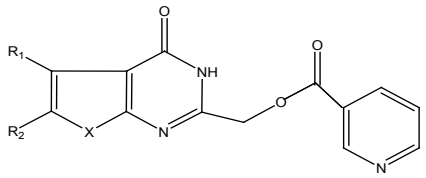
Sr.No.	R_1 R_2	X	Yield (%)	M.P. (°C)	Mol.Formula
III*a*	$-(CH_2)_4-$	S	90	272-275	$C_{11}H_{11}ClN_2OS$
III*b*	CH_3 CH_3	S	92.5	270-273	$C_9H_9ClN_2OS$
III*c*	C_6H_5 CH_3	S	88	242-246	$C_{14}H_{15}ClN_2OS$
III*d*	4-ClC_6H_5 H	S	75.8	213-217	$C_{11}H_9Cl_2N_2OS$
III*e*	CH_3 $COOC_2H_5$	S	89.4	240-243	$C_{11}H_{11}ClN_2O_3S$
III*f*	H C_2H_5	S	82	194-198	$C_9H_9ClN_2OS$
III*g*	4-CH_3 C_6H_4 H	S	76.9	262-265	$C_{14}H_{11}ClN_2OS$
III*h*		S	78	270-275	$C_{17}H_{16}ClN_3OS$
III*i*	C_6H_5 H	S	92	194-199	$C_{13}H_9ClN_2OS$
III*j*	4-$OCH_3C_6H_4$ H	S	79.3	206-210	$C_{14}H_{11}ClN_2O_2S$
III*k*	H H	-CH=CH-	92.6	256-260	$C_9H_7ClN_2O$

Table III : Nicotinic acid-4-oxo-5,6-disubstituted condensed (2,3-d) pyrimidin- 2ylmethyl ester (Va-k)



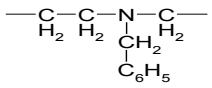
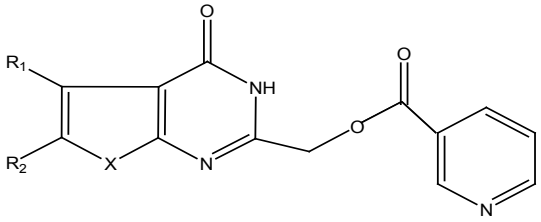
Sr.No.	R_1	R_2	X	Yield (%)	M.P. (°C)	Mol.Formula
V*a*		$-(CH_2)_4-$	S	60.6	296-298	$C_{17}H_{15}N_3O_3S$
V*b*	CH_3	CH_3	S	71	294-99	$C_{15}H_{13}N_3O_3S$
V*c*	C_6H_5	CH_3	S	78	228-32	$C_{20}H_{15}N_3O_3S$
V*d*	4-ClC_6H_5	H	S	74.4	253-57	$C_{19}H_{13}ClN_3O_3S$
V*e*	CH_3	$COOC_2H_5$	S	83	265-70	$C_{17}H_{15}N_3O_5S$
V*f*	H	C_2H_5	S	82.5	285-89	$C_{20}H_{15}N_3O_3S$
V*g*	4-CH_3 C_6H_4	H	S	69	238-42	$C_{20}H_{15}N_3O_3S$
V*h*			S	70.8	270-74	$C_{23}H_{20}N_4O_3S$
V*i*	C_6H_5	H	S	66.7	291-95	$C_{19}H_{13}N_3O_3S$
V*j*	4-$OCH_3C_6H_4$	H	S	78	195-99	$C_{20}H_{15}N_3O_4S$
V*k*	H	H	CH=CH-	84.5	230-34	$C_{15}H_{11}N_3O_3$

Table IV: Spectral data of Nicotinic acid-4-oxo-5.6-disubstitutedthieno(2, 3-*d*) pyrimidin-2ylmethyl ester (V*a-k*)



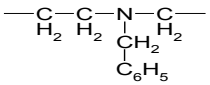
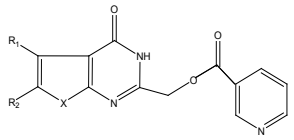
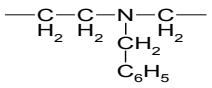
Sr. No.	R_1	R_2	X	UV λmax (nm) (MeOH)	I.R. (cm^1) (KBr)	^1H NMR (δ ppm) (CDCl3/DMSO)	MASS (m/e)
V*a*	-$(CH_2)_4$-		S	226	1685.84[γ_{CONH}]; 3070.78[γ_{CH2}]; 1571[γ_{RCOO^-}]	1.163,4H, s,H at 6 & 7; 1.920,4H,s,H at 5 & 8;4.9,2H,s,H at 2; 7.312,4H,m,H at Ar	-
V*b*	CH_3	CH_3	S	360	1674.27[γ_{CONH}]; 2926.11[γ_{CH2}]; 1553.71[γ_{RCOO^-}]	-	-
V*c*	C_6H_5	CH_3	S	336	1681.98[γ_{CONH}]; 3006.16[γ_{CH2}]; 1590.36[γ_{RCOO^-}]	2.395,3H,s,H at6; 4.402,2H,s,H at 2	377, 290, 271
V*d*	4-ClC_6H_5	H	S	314	1630.87[γ_{CONH}]; 2975.3[γ_{CH2}]; 1584.57[γ_{RCOO^-}]	-	397, 341,310
V*e*	CH_3	$CH_3COOC_2H_5$	S	326	1708.99[γ_{CONH}]; 2989.76[γ_{CH2}]; 1596.15[γ_{RCOO^-}]	1.380,3H,t,H at CH_3;1.977,3H,s,H at 5;4.320,2H,t,H at CH_2;6.075,2H,s,H at 2;7.801,4H,m,H at Ar	-
V*f*	H	C_2H_5	S	360	-	-	-
V*g*	4-CH_3 C_6H_4	H	S	326	1674.27[γ_{CONH}]; 2945.4[γ_{CH2}]; 1590.36[γ_{RCOO^-}]	2.705,3H,s,H at 5; 6.449,2H,s,H at 2; 7.298,4H,m,H at Ar;7.519,4H,m,H at Nico.;7.655,1H,s,H at 3	-
V*h*			S	360	1675.23[γ_{CONH}]; 2925.15[γ_{CH2}]; 1543.10[γ_{RCOO^-}]	-	-
V*i*	C_6H_5	H	S	340	1712.85[γ_{CONH}]; 3030.27[γ_{CH2}]; 1526.71[γ_{RCOO^-}]	-	-
V*j*	4-$OCH_3C_6H_4$	H	S	331	1698.38[γ_{CONH}]; 2730.33[γ_{CH2}]; 1574.93[γ_{RCOO^-}]	-	-
V*k*	H	H	-CH=CH-	240	1683.91[γ_{CONH}]; 2991.69[γ_{CH2}]; 1608.69[γ_{RCOO^-}]	-	-

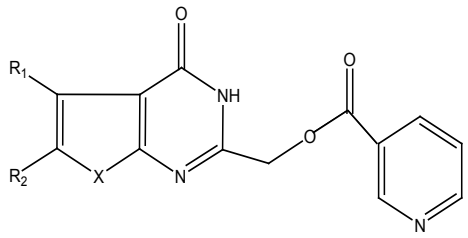
Table V: Antihyperlipidemic activity (reduction in serum cholesterol level) of Nicotinic acid-4-oxo-5.6-disubstitutedthieno (2,3-*d*) pyrimidin-2ylmethyl ester (V*a-k*).

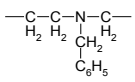


Sr.No.	R_1	R_2	X	Yield (%)	M.P. (°C)	Mol.Formula
III*a*	$-(CH_2)_4-$		S	90	272-275	$C_{11}H_{11}ClN_2OS$
III*b*	CH_3	CH_3	S	92.5	270-273	$C_9H_9ClN_2OS$
III*c*	C_6H_5	CH_3	S	88	242-246	$C_{14}H_{15}ClN_2OS$
III*d*	4-ClC_6H_5	H	S	75.8	213-217	$C_{11}H_9Cl_2N_2OS$
III*e*	CH_3	$COOC_2H_5$	S	89.4	240-243	$C_{11}H_{11}ClN_2O_3S$
III*f*	H	C_2H_5	S	82	194-198	$C_9H_9ClN_2OS$
III*g*	4-CH_3 C_6H_4	H	S	76.9	262-265	$C_{14}H_{11}ClN_2OS$
III*h*			S	78	270-275	$C_{17}H_{16}ClN_3OS$
III*i*	C_6H_5	H	S	92	194-199	$C_{13}H_9ClN_2OS$
III*j*	4-$OCH_3C_6H_4$	H	S	79.3	206-210	$C_{14}H_{11}ClN_2O_2S$
III*k*	H	H	-CH=CH-	92.6	256-260	$C_9H_7ClN_2O$

**Results are expressed as mean* ± standard error, statistically significant (p *<0.05, t test, n=6)*.

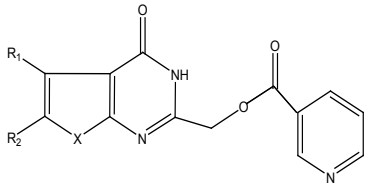
Table VI: Antihyperlipidemic activity (reduction in serum triglycerides) of Nicotinic acid-4-oxo-5.6-disubstituted (2,3-*d*) pyrimidin-2ylmethyl ester (V*a-k*)

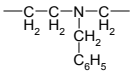


Sr No	R_1	R_2	X	Triglyceride levels in serum (mg/dl)		% Reduction in Serum Triglyceride level
				Initial	Final	
	Cholesterol control			157.88	302.72	
V*a*	$-(CH_2)_4-$		S	179.34	186.68	14.08
V*b*	CH_3	CH_3	S	149.78	241.21	16.02
V*c*	C_6H_5	CH_3	S	187.88	199.24	12.25
V*d*	$4\text{-}ClC_6H_4$	H	S	156.23	266.67	11.01
V*e*	CH_3	$COOC_2H_5$	S	148.06	213.09	25.00
V*f*	H	C_2H_5	S	159.18	280.63	08.18
V*g*	$4\text{-}CH_3C_6H_4$	H	S	141.84	251.61	07.41
V*h*			S	152.95	269.91	08.00
V*i*	C_6H_5	H	S	158.07	270.66	10.80
V*j*	$4\text{-}CH_3OC_6H_4$	H	S	156.08	262.03	12.67
V*k*	H	H	–CH=HC–	150.59	274.24	5.00
Std	Gemfibrozil			150.00	348.60	27.06±5.82

**Results are expressed as mean* ± standard error, statistically significant (p *<0.05, t test, n=6).*

Table VII: Antihyperlipidemic activity (elevation in serum HDL level) of Nicotinic acid-4-oxo-5.6-disubstituted (2,3-*d*) pyrimidin-2ylmethyl ester (V*a-k*)



Sr No	R_1	R_2		HDL levels in serum (mg/dl)		% Change in Serum HDL level
				Initial	Final	
	Cholesterol control		x	50.58	47.58	
V*a*	$-(CH_2)_4-$		S	51.05	57.63	12.88
V*b*	CH_3	CH_3	S	43.58	46.60	07.20
V*c*	C_6H_5	CH_3	S	49.24	55.76	13.53
V*d*	4-ClC_6H_4	H	S	48.04	53.31	10.91
V*e*	CH_3	$COOC_2H_5$	S	49.56	52.67	06.16
V*f*	H	C_2H_5	S	47.40	49.39	04.21
V*g*	4-$CH_3C_6H_4$	H	S	41.48	42.86	03.37
V*h*			S	50.07	51.83	03.49
V*i*	C_6H_5	H	S	43.74	46.41	06.33
V*j*	4-$CH_3OC_6H_4$	H	S	49.68	55.63	12.20
V*k*	H	H	–CH=HC–	45.43	49.09	08.16
Std	Gemfibrozil			56.17	60.39	7.423±0.92

**Results are expressed as mean* ± standard error, statistically significant (p *<0.05, t test, n=6).*

Biological activity:

General conditions of experimental animals:

The experiments were carried out with Wistar Albino rats. The animals were housed at a temperature of 30±5oC and humidity of 40-50% with 12 h light and 12 h dark cycles. The animals were given food and water ad libitum, unless specified otherwise. For all studies animals of either sex were selected at random.

Hyperlipidemia induced by Triton WR 13397

General conditions of experimental animals:

Triton WR 1339, a surfactant, chemically isooctyl phenyl polyethoxyethanal (Tyloxapol) were used to induce hyperlipidemia. Albino rats (120-200 gm) of Wistar strain of either sex were used for the study. The animals were kept at optimum temperature condition(25-30 0C) and humidity of 45% ±RH.

The animals were divided into four groups of six animals each:

1.Control group:The control group received only vehicle (2 % acacia solution).

2.Cholesterol–control group: The cholesterol–control group received Triton WR 1339 (200mg/kg) by i.p.. route and 2% acacia solution.

3.Standard drug treated group: The standard drug treated group received Triton WR 1339 (200 mg./kg, i.p.) as well as standard drug, Gemfibrozil as suspension in 2% acacia (500 mg/kg, p.o).

4.Test group: The test drug treated group received Triton WR 1339 (200 mg./kg, i.p.) as well as test drug as suspension in 2 % acacia solution (400 mg/kg, p.o).

Procedure for screening the test and standard drugs:

Test group and Standard drug treated group received their respective drug one hour prior to Triton injection. The second dose of drug was given 20 hours later. At the end of 24 hours after Triton injection, blood was collected by retro-orbital puncture. The animals were kept fasted throughout the experiment period, but were provided water ad libitum.

Estimation of lipid profile

Analytical Procedure for the Estimation of Serum Cholesterol:

The sample were analysed for serum cholesterol (total) levels using Infinite liquid

cholesterol solution ready to use reagent (ACCUREX Biomedical Pvt. Ltd., India).

The working reagent solution (1ml) was added to the serum sample (0.1ml) and the mixture incubated at 37 oC for 5 minutes. Absorbance measured at 510nm, using working reagent solution as blank. The absorbance of the serum samples was compared with that of the standard cholesterol solution and the serum concentration of cholesterol in the samples was determined as follows,

Cu =[Au / As] x Cs

Cu = Conc. of standard cholesterol (200mg/dl)

Au = Conc. of cholesterol in serum sample

As = Absorbance of standard

Cs = Absorbance of sample

Biological activity was calculated as % decrease in Blood Cholesterol Levels, this was further converted into B.A. = (% Reduction/ 100-% Reduction) and its log value i.e., Log (BA) which was finally correlated with the physiochemical parameters.

Analytical Procedures for the Estimation of Serum Triglyceride:

The samples were analysed for Serum Triglyceride (total) levels using Infinite liquid Triglyceride solution ready to use reagent (ACCUREX Biomedical Pvt Ltd., India). The working reagent solution (1ml) was added to the serum sample (0.1ml) and the mixture was incubated at 37 oC for 10min. or at R.T. (25-30 0C) for 20 minutes. Absorbance was measured at 510nm, using working reagent solution as blank. The absorbance of the serum samples was compared with that of the standard cholesterol solution and the serum concentration of cholesterol in the samples was determined as follows

Cu =[Au / As] x Cs

Cu = Conc. of standard triglyceride (200mg/dl)

Au = Conc. of triglyceride in serum sample

As = Absorbance of standard

Cs = Absorbance of sample,

Biological activity was calculated as % decrease in Blood Triglyceride levels.

Analytical Procedures for the Estimation of Serum Cholesterol–HDL (Total)

The samples were analysed for Serum Cholesterol-HDL(-total) levels using Infinite liquid cholesterol solution ready to use reagent (ACCUREX Biomedical Pvt Ltd., India) and HDL precipitating agent (0.5 ml.) were added to the serum samples (0.5 ml.).

The samples were then centrifuged at 4000 rpm. for 10 minutes to obtain a clear supernatant. The working reagent solution (1ml) were added to the supernatant (0.05 ml.) obtained and the standard solution and the mixture was incubated at 37 oC for 10 minutes. Absorbance was measured at 510nm, using working reagent solution as blank. The absorbance of the serum samples was compared with that of the standard cholesterol solution and the serum concentration of cholesterol in the samples was determined as follows

Cu = Au / As x Cs

Cu = Conc. of Standard HDL (100mg/dl)

Au = Conc. of HDL-cholesterol in serum sample

As = Absorbance of standard

Cs = Absorbance of sample

Biological activity was calculated as % change in HDL-cholesterol level.

Conclusions:

A series of 2-Chloromethylthieno[2,3-d]pyrimidines-4(3H)-ones has been synthe- sized through the condensation of 2-Amino-3-carbethoxybenzo(b)thiophenes with various nitriles under the influence of dry hydrogen chloride gas. Displacement reaction of 2-Chloromethylthieno[2,3-d]pyrimidines-4(3H)-ones with sodium nicotinate to get the target compounds. All the newly synthesized compounds have been characterized by spectral data (IR, UV, NMR and Mass spectra). All the test compounds

were screened for antihyperlipidemic activity (% reduction in serum cholesterol levels, % reduction in serum triglyceride levels & % Change in HDL Levels) in wistar albino rats Triton WR 1339 model. In comparing the overall lipid lowering property of the test compounds i.e.%
reduction in serum cholesterol level, % reduction in serum triglyceride level & % increase in HDL levels, the drug (Vd) has shown comparable level in % reduction in serum cholesterol with the standard drug Gemfibrozil. But the test compound has not shown promising % reduction in serum triglyceride level, but has increased HDL levels than the standard drug Gemfibrozil.

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