Arabian Journal of Chemistry (2016) 9, S395–S403

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis and antihyperlipidemic activity of some novel 4-substituted-2-substitutedmethyltriazino[6,1-*b*]quinazolin-10-ones and 2,4-disubstituted-6,7-dimethoxy quinazoline

M.K. Kathiravan [d,*], Nikhil Vidyasagar [b], Rahul Khiste [c], Aparna Chote [a], Kishor Jain [d]

[a] *AISSMS's College of Pharmacy, Kennedy Road, Near RTO, Pune 411001, India*
[b] *Pad. Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune 411018, India*
[c] *MMM's College of Pharmacy, Thergaon (Kalewadi), Pune 411033, India*
[d] *STES's Sinhgad College of Pharmacy, Vadgaon(Bk), Pune 411041, India*

Received 21 February 2011; accepted 8 May 2011
Available online 14 May 2011

KEYWORDS

Quinazoline;
Triazinoquinazoline;
Antihyperlipidaemic activity;
Cholesterol;
Triglycerides;
HDL

Abstract The synthesis and antihyperlipidemic activity of some novel 4-substituted-2-substitutedmethyltriazino[6,1-*b*]quinazolin-10-ones and 2,4-disubstituted-6,7-dimethoxy quinazoline derivatives are described. Among the series 4-chloro-2-acetoxymethyl-3*H*,11*H*-[1,2,4]triazino[6,1-*b*] quinazoline-4,10-dione **5d** has shown better activity in case of % reduction in serum cholesterol level while 4-chloro-10-oxo-10*H*-[1,2,4]triazino[6,1-*b*]quinazolin-2-yl benzoate **5f** in reducing % serum triglyceride level than that of the standard. 4-Hydroxyquinazolin-2-yl nicotinate **6g** has significantly increased serum HDL level. Among the series compound **6g** has shown promising results over all in lipid profile. These molecules indeed have the potential to be developed as an antihyperlipaemic molecule.

1. Introduction

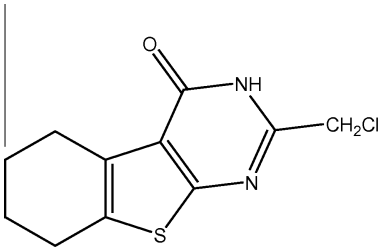
Today in most of the developed and developing countries, hyperlipidemia and thereby atherosclerosis is the leading cause of cardiac illness and deaths (Murray and Lopez, 1997; Rosamond et al., 1998). In 1984 it was demonstrated for the first time that there exists a link between serum cholesterol levels and risk to Coronary Heart Disease (CHD) (McGill, 1985). A 1% drop in serum cholesterol reduces the risk for CHD by 2%. The agents in current use are, however, insufficiently active or are accompanied by unacceptable side effects. A reduction in LDL cholesterol concentration remains the principal desired action, although an elevation in HDL may also be beneficial (Jain et al., 2007).

* Corresponding author. Tel.: +91 9637820823; fax: +91 020 24354720.
E-mail address: drmkkathir@gmail.com (M.K. Kathiravan).
Peer review under responsibility of King Saud University.

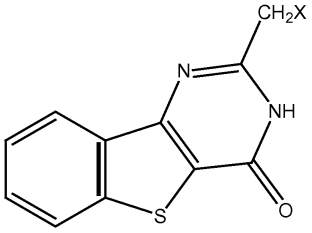
Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2011.05.009

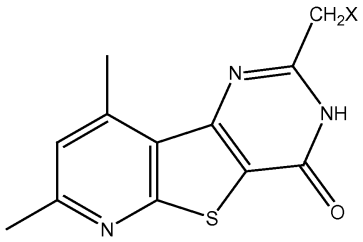
The chemical moiety thienopyrimidin-4-ones, suitably substituted at the 2-position have been looked upon with considerable interest due to their isosterism with the biologically important quinazolin-4-ones (http://www.americanheart.org/statistics, 2001; Sauter, 1972). Earlier, synthesis and antihyperlipidemic activity of a series of 2-substitutedthieno[2,3-*d*] pyrimidin-4(3*H*)-ones have been reported. One of the compounds, 2-chloromethyl-5,6,7,8-tertrahydrobenzo(*b*)thieno[2,3-*d*]pyrimidin-4(3*H*)-one **1** (CAS # 89587-03-3) was found to be most active among the series (Shiroki, 1976; Dave et al., 1980; Shishoo et al., 1990).



1

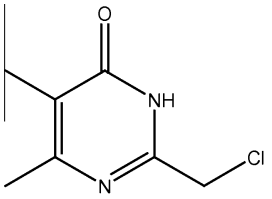


2



3

All these encouraging results have led these workers to undertake a very systematic study into the synthesis and evaluation of various related 2-substitutedthienopyrimidin-4-ones **2** and **3** for antihyperlipidemic activity (Shishoo et al., 1997) Therefore, it is concluded that the 2-chloromethylpyrimidin-4(3*H*)-one nucleus **4** is a potential pharmacophore for antihyperlipaemic activity.



4

Scientific research and clinical studies have already documented particularly the value of vitamin B_3 (nicotinic acid), and other vitamins like vitamin C, vitamin B_5 (pantothenic acid), vitamin E and caronitinin in lowering of elevated cholesterol levels and other secondary risk factors in the blood. Vitamins and other essential nutrients lower the particular rate of cholesterol and other repair molecules in the liver and at the same time, contribute to the repair of the artery wall. These facts ignited a thought to develop novel molecules which are basically comprising of both, vitamin B_3, as well as, 2-chloromethylthienopyrimidin-4-one nucleus, the latter having already demonstrated significant potential to reduce blood cholesterol levels (Shishoo et al., 1984, 1996). On these lines, it was decided to link the active prodrug, thus combining two potential pharmacophores *viz*, 2-chloromethyl-pyrimidines with nicotinic acid to get a mutual prodrug. Recently, we have reported the synthesis and antihyperlipidemic activity of a series of condensed 2-chloroalkyl-4-chloro/hydroxyl-5,6-disubstitutedpyrimidines (Davidson, 2003) In continuation to our ongoing work herein we report a series of condensed pyrimidines and their antihyperlipidemic activity using Triton WR 1339 model (Arya, 1985).

2. Results and discussion

2.1. Synthesis

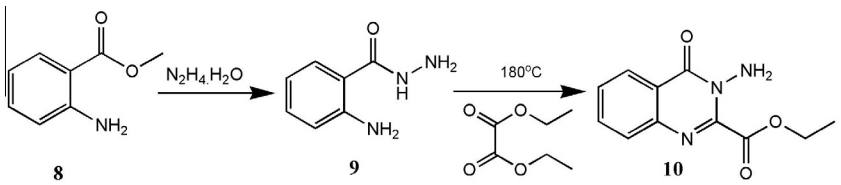
Methyl anthranilate **8** was refluxed with hydrazine hydrate to obtain anthranilic acid hydrazide **9** which on subsequent refluxing with diethyl oxalate yielded 3-amino-2-ethoxycarbonylquinazolin-4-one **10** (Scheme 1).

Vanillin **11** was *o*-methylated with dimethyl sulfate in the presence of aqueous KOH to get the Veratraldehyde **12** which was treated with fuming nitric acid at 0 °C with constant stirring to get 3,4-dimethoxy-6-nitrobenzaldehyde **13** which further oxidized in acetone with potassium permanganate to get the 3,4-dimethoxy-6-nitrobezoic acid **14**. The next step involves the esterification reaction. The dry hydrogen chloride gas was passed in the mixture of 3,4-dimethoxy-6-nitrobenzoic acid **14** in anhydrous methanol for 2–3 h at 0–5 °C to get methyl-3,4-dimethoxy-6-nitrobenzoate **15**. Methyl 2-amino-4,5-dimethoxybenzoate **16** was synthesized (Scheme 2) by reducing 2-nitro-4,5-dimethoxymethylbenzoate 15 with iron powder (activated 80# mesh) and a catalytic amount of concentrated hydrochloric acid in ethanol by refluxing at 80 °C for 8–9 h.

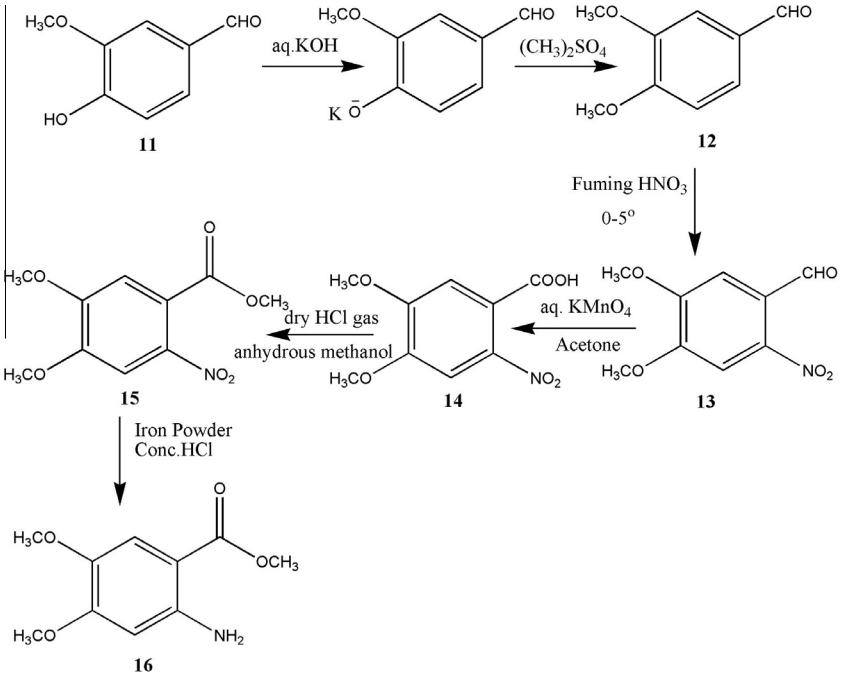
The 2-chloromethyl-3*H*,11*H*-[1,2,4]triazino[6,1-*b*]quinazoline-4,10-dione 5a and 2-(chloromethyl)quinazolin-4-ol 6a were synthesized through the dry HCl gas catalyzed one-pot condensation of the appropriate amino esters and chloroacetonitrile (Scheme 3) as described in our earlier reports (Kathiravan et al., 2007).

2-(Chloromethyl)-6,7-dimethoxyquinazolin-4-ol **7a** was synthesized through the dry HCl gas catalyzed one-pot condensation of the methyl 2-amino-4,5-dimethoxybenzoate **16** and chloroacetonitrile. The 4-chloro-2-chloromethyl-3*H*-[1,2,4]triazino[6,1-*b*]quinazolin-10-one **5b** was synthesized (Scheme 4) using phosphorus oxytrichloride ($POCl_3$) in *N,N*-dimethyl formamide at 0–5 °C (Shvedov et al., 1974).

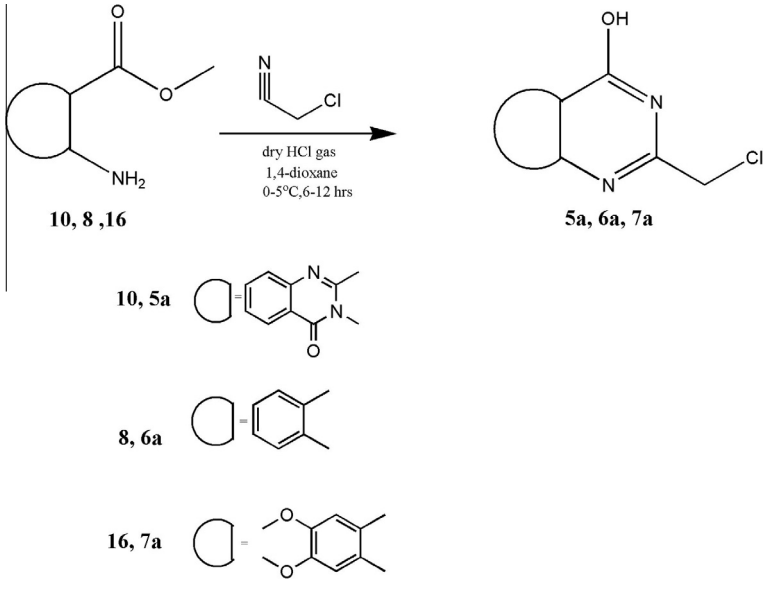
The desired mutual prodrugs namely 2-acetoxymethyl-3*H*,11*H*-[1,2,4] triazino[6,1-*b*] quinazoline-4,10-dione, **5c** 2-benzyloxymethyl-3*H*,11*H*-[1,2,4]triazino[6,1-*b*] quinazoline-4,10-dione, **5e** 2-(2-pyridinylcarboxy)methyl-3*H*,11*H*-[1,2,4]triazino[6,1-*b*] quinazoline-4, 10-dione **5g** from 3*H*,11*H*,-[1,2,4]triazino[6,1-*b*]quinazoline-4,10-dione **5a**, similarly **6c**, **6e**, **6g** from **6a** and **7c**, **7e**, **7g** from **7a** were prepared through the nucleophilic displacement of the chlorine atom of the 2-chloromethyl- (Otera, 2003) with sodium acetate, sodium benzoate and sodium nicotinate using dimethyl sulfoxide as the solvent with stirring for **6h** at room temperature. The workup of the reaction afforded the corresponding desired product in good yields as shown in (Scheme 5).



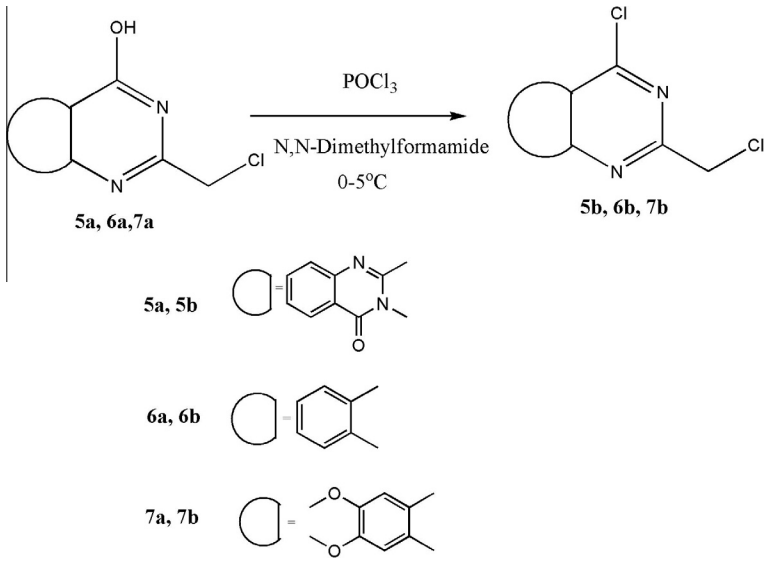
Scheme 1 Synthesis of 3-amino-2-ethoxycarbonylquinazolin-4-one.



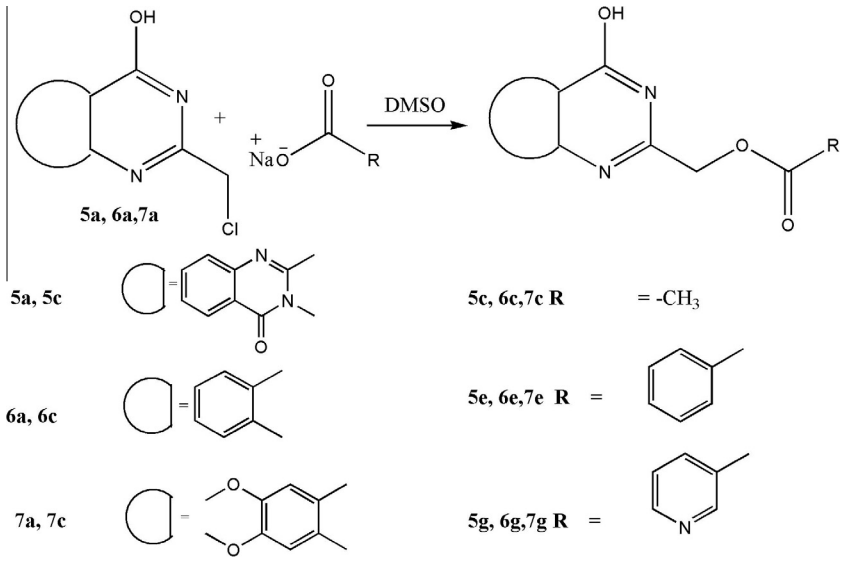
Scheme 2 Synthesis of methyl 2-amino-4,5-dimethoxybenzoate.



Scheme 3 Synthesis of 2-(Chloromethyl)quinazolin-4-ol.



Scheme 4 Synthesis of 4-chloro-2-chloromethyl-3*H*-[1,2,4]triazino[6,1-*b*]quinazolin-10-one.



Scheme 5 Synthesis of mutual prodrugs.

The desired chlorinated products of mutual prodrugs namely 4-chloro-2-acetoxymethyl-3*H*,11*H*-[1,2,4]triazino[6,1-*b*]quinazoline 4,10-dione **5d**, 4-chloro-2-benzyloxymethyl-3*H*,11*H*-[1,2,4]triazino[6,1-*b*]quinazoline 4,10-dione **5f**, 4-chloro-2-(2-pyridinylcarboxy)methyl-3*H*,11*H*-[1,2,4]triazino[6, 1-*b*]quinazoline 4,10-dione **5h**, similarly **6d**, **6f**, **6h** and **7d**, **7f**, **7h** were prepared through chlorination by chlorinating agent phosphorusoxytrichloride ($POCl_3$) in the presence of phosphorus pentachloride (PCl_5) from displacement products in good yields (Scheme 6).

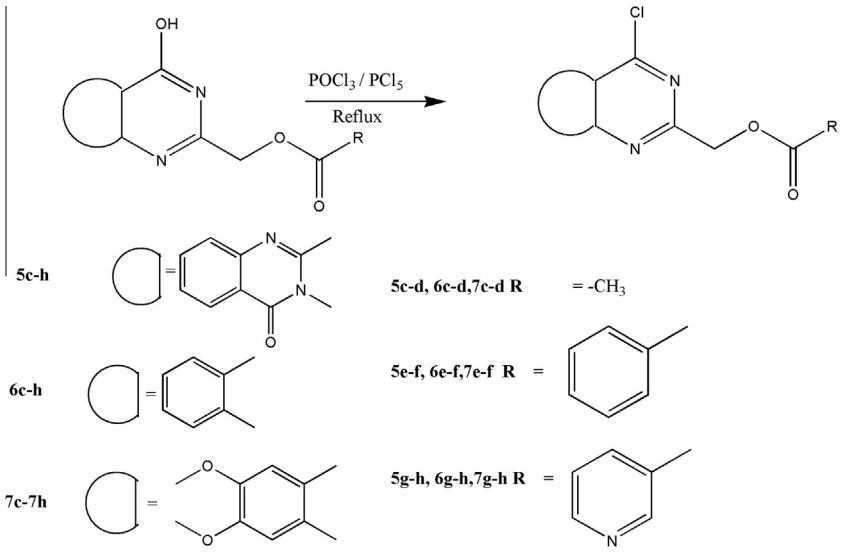
Table 1 summarizes all the products formed and their physical properties.

2.2. Biological activity

The lipid lowering activity of the twenty four synthesized compounds were evaluated using Triton WR 1339 model (Chrysselis et al., 2000). Triton injection causes the accumulation of triglyceride (neutral fat), cholesterol and phospholipids produced in the plasma for about 36 h, after which time a rapid diminution begins. Excess triglyceride begins both to accumulate and to disappear, respectively, before the other two substances. The lipid profile (cholesterol, triglycerides, and HDL) for the hyperlipidemic and control Wistar rats was studied with an oral administration of the test compounds (**5a**–**5h**), (**6a**–**6h**) and (**7a**–**7h**).

It was found that the test compounds showed significant changes in lipid profile, i.e., decrease in total cholesterol, triglycerides and increase in HDL at dose of 400 mg/kg body weigh *p.o.* as compared with the control group.

All the 24 compounds (**5a**–**5h**), (**6a**–**6h**) and (**7a**–**7h**) were tested, out of which compounds (**5d**, **5e**, **7a**, **7g**, **7h**, **6c**, **6g**, **6b**, **6d**, **6h**) were superior in reducing % serum cholesterol level showing (67.90 ± 0.35, 51.98 ± 2.18, 52.34 ± 1.73,



Scheme 6 Chlorination of the mutual prodrugs.

45.21 ± 3.86, 62.07 ± 3.67, 63.27 ± 0.90, 56.35 ± 3.84, 46.56 ± 1.53, 65.68 ± 0.24, and 57.07 ± 5.36%) than the standard drug gemfibrozil (42.42 ± 1.2%).

The test compounds (**5c,** 5f, 5h, 7c, 7e, 7g, 6e, 6g, **6f**) have shown superior activity (46.23 ± 13.05, 58.32 ± 2.16, 50.37 ± 6.45, 39.82 ± 9.79, 57.09 ± 1.84, 54.96 ± 4.96, 55.19 ± 2.08, 48.27 ± 5.98, and 46.86 ± 2.61%) in terms of % reduction in serum triglyceride levels when compared to standard 37.57 ± 1.68. In case of % change in serum HDL level (**6e, 6g, 6f**) compounds showed higher % change in HDL levels (41.48 ± 3.85, 52.73 ± 4.79, 41.24 ± 2.88%) than standard gemfibrozil.

The test compound with superior activity in reducing total serum cholesterol level is **5a**, however, did not show much reduction in triglycerides as well as not much change in HDL levels. The best compound for reducing triglycerides levels among the series is **5f**. The test compounds were found to be uniquely reducing either total serum cholesterol or triglycerides levels such as **5a** and **5f**. The test compound **6g** has increased HDL levels significantly among the series. The SAR reveals that the presence of 2-acetoxy, 4-chloro groups contribute more for reducing total serum cholesterol levels where as 2-benzoxy group may play a key role in reducing triglyceride levels. The incorporation of nicotine moiety as mutual prodrug approach has significantly increased HDL levels such as in **6g**.

Table 2 summarizes all the results for antihyperlipidemic activity.

3. Experimental

The melting points were determined in an open capillary on Veego (model: VMP-D) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Perkin Elmer spectrum BX. FT-IR Spectrophotometer in potassium bromide discs. The ^{1}H NMR spectra were recorded in DMSO-d_6 using NMR Varian-Mercury 300 MHz spectrometer at Punjab University, Chandigarh and chemical shifts are given in units as parts per million, downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on an Electron Impact mass spectrometer at 70 eV ionizing beam and using direct insertion probe. Table 3 summarizes the spectral data for the representative compounds from the series.

3.1. Synthesis of 3-amino-2-ethoxycarbonylquinazolin-4(H)-one ***10***

3.1.1. Synthesis of anthranilic acid hydrazide ***9***

Methyl anthranilate **8** (10 ml, 0.065 mol) and hydrazine hydrate (9.57 ml, 0.2 mol) were refluxed for 2 h. The reaction mixture was cooled avoiding direct exposure to sunlight. Solid crystals of anthranilic acid hydrazide separated out were washed with isopropyl alcohol to yield anthranilic acid hydrazide (**9**, 9.79 g, 97.4%) m.p. 118–120 °C (121–123 °C) (Kathiravan et al., 2007).

3.1.2. Synthesis of 3-amino-2-ethoxycarbonylquinazolin-4(3H)-one ***10***

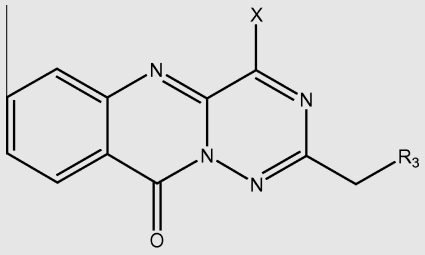
A mixture of anthranilic acid hydrazide (**9**, 9.79 g, 0.06 mol) and diethyl oxalate (19.5 g, 0.13 mol) was refluxed with stirring in an oil bath at 180° for 6 h. The excess of diethyl oxalate was removed in *vacuo* to give a semi-solid product which became crystalline on treatment with ethanol. The product obtained was recrystallized from dichloromethane to yield 3-amino-2-ethoxycarbonylquinazolin-4(3*H*)-one (**10**, 9.6 g, 62.2%) m.p. 132–135 °C (137–138 °C) (George et al., 1971).

3.2. Synthesis of methyl-2-amino-4,5-dimethoxybenzoate ***16*** *(Carpenter et al., 1979)*

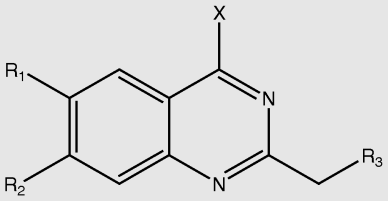
3.2.1. Synthesis of 3,4-dimethoxybenzaldehyde ***12***

An aqueous solution of KOH (30.3 g in 49.5 ml water) was added drop wise into the melted vanillin **11** (50.0 g, 0.3 mol) with constant stirring. Simultaneously dimethyl sulfate (52.8 g, 0.39 mol) was added drop wise with continuous stirring till the addition was complete. The mixture was transferred to porcelain dish and kept overnight, then washed with ice cold water (50 ml), filtered under suction and dried in vacuum desiccators. The product obtained was recrystallized from methanol to yield 3,4-dimethoxybenzaldehyde (**12**, 51.0 g, 93.4%) m.p. 43–45 °C (44 °C).

Table 1 Chemical structures and properties of 4-substituted-2-substitutedmethyltriazino[6,1-*b*]quinazolin-10-ones and 2,4-disubstituted-6,7-dimethoxyquinazoline.



5



6,7

Compound	R_1	R_2	R_3	X	% Yield[a]	Melting point[*]	Mol. formula	Recrystn. solvent	Reference
5a	–	–	Cl	OH	54	240–242	$C_{11}H_7ClN_4O_2$	Methanol–Chloroform	–
5b	–	–	Cl	Cl	60	133–135	$C_{11}H_8Cl_2N_4O$	Benzene–Methanol	–
5c	–	–	$OCOCH_3$	OH	73	108–110	$C_{13}H_{10}N_4O_4$	Methanol–Chloroform	–
5d	–	–	$OCOCH_3$	Cl	62	>300	$C_{13}H_9ClN_4O_3$	Benzene–Methanol	–
5e	–	–	$OCOC_6H_5$	OH	83.12	172–175	$C_{18}H_{12}N_4O_4$	Methanol–Chloroform	–
5f	–	–	$OCOC_6H_5$	Cl	53	200–202	$C_{18}H_{11}ClN_4O_3$	Benzene–Methanol	–
5g	–	–	$OCOC_5H_5N$	OH	80	203–205	$C_{17}H_{11}N_5O_4$	Methanol–Chloroform	–
5h	–	–	$OCOC_5H_5N$	Cl	58	140–143	$C_{17}H_{10}ClN_5O_3$	Methanol–Chloroform	–
6a	H	H	Cl	OH	92	248–250	$C_9H_7ClN_2O$	Ethanol–Chloroform	–
6b	H	H	Cl	Cl	64.30	108–110	$C_9H_6Cl_2N_2$	Benzene–Methanol	–
6c	H	H	$OCOCH_3$	OH	82.40	210–212	$C_{11}H_{10}N_2O_3$	Methanol–Chloroform	–
6d	H	H	$OCOCH_3$	Cl	43.80	148–150	$C_{11}H_9ClN_2O_2$	Benzene–Methanol	–
6e	H	H	$OCOC_6H_5$	OH	76.30	120–124	$C_{16}H_{12}N_2O_3$	Methanol–Chloroform	–
6f	H	H	$OCOC_6H_5$	Cl	32.30	104–106	$C_{16}H_{11}ClN_2O_2$	Benzene–Methanol	–
6g	H	H	$OCOC_5H_4N$	OH	80.00	290–294	$C_{15}H_{11}N_3O_3$	Methanol–Chloroform	–
6h	H	H	$OCOC_5H_4N$	Cl	39.60	132–134	$C_{15}H_{10}ClN_3O_2$	Benzene–Methanol	–
7a	OCH_3	OCH_3	Cl	OH	84	242–245(242–244)	$C_{11}H_{11}ClN_2O_3$	Ethanol–Chloroform	Shishoo et al. (1984)
7b	OCH_3	OCH_3	Cl	Cl	42.80	162–164	$C_{11}H_{10}Cl_2N_2O_2$	Hexane	–
7c	OCH_3	OCH_3	$OCOCH_3$	OH	80.16	224–226	$C_{13}H_{14}N_2O_5$	Methanol–Chloroform	–
7d	OCH_3	OCH_3	$OCOCH_3$	Cl	34.30	140–142	$C_{13}H_{13}ClN_2O_4$	Benzene–Methanol	–
7e	OCH_3	OCH_3	$OCOC_6H_5$	OH	64.50	256–258	$C_{18}H_{16}N_2O_5$	Methanol–Chloroform	–
7f	OCH_3	OCH_3	$OCOC_6H_5$	Cl	38.40	122–124	$C_{18}H_{15}ClN_2O_4$	Benzene–Methanol	–
7g	OCH_3	OCH_3	$OCOC_5H_4N$	OH	54.60	280–282	$C_{17}H_{15}N_3O_5$	Methanol–Chloroform	–
7h	OCH_3	OCH_3	$OCOC_5H_4N$	Cl	42.60	134–136	$C_{17}H_{14}ClN_3O_4$	Methanol–Chloroform	–

[a] Isolated yields.
[*] Melting points are uncorrected.

*3.2.2. Nitration of 3,4-dimethoxybenzaldehyde **13***

To a stirred solution of conc. HNO_3 (310 ml) in an ice water bath (0–5 °C), veratraldehyde **12** (50.0 g, 0.3 mol) was added over a period of 45 min. After the addition, the reaction mixture was allowed to stand at 15 °C for 30 min in dark and then poured in ice cold water (1 l). The yellow voluminous precipitated product was obtained which was then filtered at suction, washed with ice cold water, dried and recrystallized from methanol to yield yellow crystalline product. The product obtained was 3,4-dimethoxy-6-nitrobenzaldehyde (**13**, 40.0 g, 62.6%) m.p. 132–134 °C (133 °C).

*3.2.3. Oxidation to 3,4-dimethoxy-6-nitrobenzoic acid **14***

In a conical flask it 3,4-dimethoxy-6-nitrobenzaldehyde **13** (40 g, 0.01 mol) was dissolved in acetone (25 ml) at RT. An aq. solution of potassium permanganate (100 g in 25 ml water) was charged drop wise over a period of 20 min. The solution was stirred at RT for another 2 h. The reaction mass changed from dark gray to violet at the end of the addition, then the reaction mass was filtered and washed with hot water. The filtrate was concentrated to remove excess of acetone and acidified with conc. HCl. The precipitate formed was filtered, washed with cold water and dried under vacuum to give yellow solid. The product obtained was recrystallized from methanol to yield 3,4-dimethoxy-6-nitrobenzoic acid (**14**, 25.6 g, 75%) m.p. 191–194 °C (192–194 °C).

*3.2.4. Esterification to methyl-3,4-dimethoxy-6-nitrobenzoate **15***

To a solution of 3,4-dimethoxy-6-nitrobenzoic acid **14** (25 g, 0.01 mol) in methanol (100 ml) dry HCl gas was bubbled over

Table 2 Triton induced antihyperlipidemic activity of 4-substituted-2-substitutedmethyl triazino [6,1-*b*]quinazolin-10-ones and 2,4-disubstituted-6,7-dimethoxyquinazoline.

Compound	% Reduction in serum levels of total cholesterol	% Reduction in serum levels of triglyceride	% Change in serum levels of HDL
5a	32.06 ± 2.64	29.74 ± 2.98	8.02 ± 2.81
5b	36.48 ± 0.65	31.35 ± 0.65	15.10 ± 1.01
5c	11.38 ± 3.45**	46.23 ± 13.05	23.29 ± 2.60
5d	67.90 ± 0.35**	14.69 ± 1.03*	8.69 ± 1.98
5e	51.98 ± 2.18	19.93 ± 1.77	9.86 ± 1.95
5f	35.16 ± 1.90	58.32 ± 2.16	20.89 ± 2.82
5g	42.15 ± 2.46	29.80 ± 13.8	20.60 ± 4.16
5h	4.39 ± 3.39**	50.37 ± 6.45	5.18 ± 3.54
6a	22.44 ± 2.56**	19.37 ± 2.17	10.89 ± 2.01
6b	46.56 ± 1.53	36.68 ± 0.45	14.20 ± 2.80
6c	63.27 ± 0.90**	3.16 ± 0.92**	16.02 ± 3.29
6d	65.68 ± 0.24**	2.99 ± 2.12**	3.09 ± 1.29*
6e	14.03 ± 1.22**	55.19 ± 2.08	41.48 ± 3.85**
6f	15.08 ± 1.78**	46.86 ± 2.61	41.24 ± 2.88**
6g	56.35 ± 3.84**	48.27 ± 5.98	52.73 ± 4.79**
6h	57.07 ± 5.36	38.42 ± 4.57	3.16 ± 0.94*
7a	52.34 ± 1.73	21.41 ± 3.12	25.93 ± 1.91
7b	21.81 ± 2.65**	38.39 ± 3.06	29.40 ± 5.58**
7c	4.00 ± 2.69**	39.82 ± 9.79	3.50 ± 2.12
7d	30.09 ± 2.39*	38.09 ± 2.40	32.47 ± 2.79**
7e	20.12 ± 1.47**	57.09 ± 1.84	22.06 ± 3.05
7f	25.08 ± 1.92**	26.41 ± 3.58	22.73 ± 2.63
7g	45.21 ± 3.86	54.96 ± 4.96	21.69 ± 2.20
7h	62.07 ± 3.67**	42.06 ± 3.23	1.08 ± 0.39**
Gemfibrozil	42.42 ± 1.2	37.57 ± 1.68	15.1 ± 1.3

Each value is the mean ± SEM of five mice.
** $p < 0.01$.
* $p < 0.05$ compared with control, Statistical analysis by one way ANOVA followed by Dunnett's test.

Table 3 Spectral data of representative compounds from the series.

Compound	Spectral data
10	IR, $\tilde{\nu}/cm^{-1}$: 3340, 3279 (NH), 1739 (COOEt), 1685 (N–C═O). ^{1}H NMR (DMSO-d_6), δ: 1.41 (t, 3H, $COOCHCH_3$), 4.50 (q, 2H, $COOCH_2CH_3$), 5.30 (s, 2H, NH_2), 7.3–7.7 (m, 4H, Ar-H). MS, *m/z*: 233 (M^+). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.52; H, 4.64; N, 18.00
5a	IR, $\tilde{\nu}/cm^{-1}$: 2896 (C–H), 1688 (CONH), 778 (C–Cl). ^{1}H NMR (DMSO-d_6), δ: 4.2 (s, 2H, CH_2), 7–8 (m, 5H, Ar-H) 12.5 (s, 1H, NH). MS, *m/z*: 262 (M^+). Anal. Calcd for $C_{11}H_7ClN_4O_2$: C, 50.30; H, 2.69; N, 21.33. Found: C, 50.11; H, 2.51; N, 21.17
5b	IR, $\tilde{\nu}/cm^{-1}$: 1608 (N–C═O), 715–764 (C–Cl). ^{1}H NMR (DMSO-d_6), δ: 4.5 (s, 2H, CH_2), 7–8 (m, 5H, Ar-H & NH). MS, *m/z*: 282 (M^+). Anal. Calcd for $C_{11}H_8Cl_2N_4O$: C, 47.00; H, 2.15; N, 19.93. Found: C, 47.18; H, 2.31; N, 19.99
5g	IR, $\tilde{\nu}/cm^{-1}$: 1726 ($OCOC_5H_5N$), 1672 (N–C═O). ^{1}H NMR (DMSO-d_6), δ: 5.3 (s, 2H, CH_2), 7.6–7.8 (m, 4H, Ar-H). MS, *m/z*: 349 (M^+). Anal. Calcd for $C_{17}H_{11}N_5O_4$: C, 58.45; H, 3.17; N, 20.05. Found: C, 58.69; H, 3.29; N, 20.24
7c	IR, $\tilde{\nu}/cm^{-1}$: 3409 (NH), 1673 (CONH), 1741 ($OCOCH_3$), 864 (C–Cl). ^{1}H NMR (DMSO-d_6), δ: 3.90 (s, 6H, OCH_3), 5.23 (s, 2H, H), 7.59 (t, 1H, H), 8.81(d, 1H, H), 9.13 (s, 1H, H), 12.35 (s, 1H, NH). MS, *m/z*: 278 (M^+). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.75; H, 4.71; N, 10.79
7g	IR, $\tilde{\nu}/cm^{-1}$: 2847 ($COCH_3$), 673 (CONH), 1741 ($OCOC_5H_4N$), 737 (C–Cl). ^{1}H NMR (DMSO-d_6), δ: 3.90 (s, 6H, OCH_3), 5.23 (s, 2H, H), 7.59 (t, 1H, H), 8.81 (d, 1H, H), 9.13 (s, 1H, H), 12.53 (s, 1H, NH). MS, *m/z*: 341 (M^+). Anal. Calcd for $C_{17}H_{15}N_3O_5$: C, 58.72; H, 4.00; N, 12.84. Found: C, 58.54; H, 4.09; N, 12.68
7h	IR, $\tilde{\nu}/cm^{-1}$: 2922 ($COCH_3$), 1722 ($OCOC_5H_4N$). ^{1}H NMR (DMSO-d_6), δ: 4.01 (s, 6H, OCH_3), 4.85 (s, 2H, H), 7.36 (s, 1H, H), 7.43 (s, 1H, H). MS, *m/z*: 359 (M^+). Anal. Calcd for $C_{17}H_{14}ClN_3O_4$: C, 55.58; H, 3.50; N, 12.15. Found: C, 55.74; H, 3.81; N, 12.22

a period of 1–1.5 h, at 0 °C. A yellow color solid precipitate was observed after 2–3 h. Then the solution was concentrated to half of its original volume. The reaction mixture was extracted with chloroform, washed with aq. $NaHCO_3$ solution (10% w/v), dried and concentrated to give a yellow colored solid. The product obtained was the yield recrystallized from methanol to 6-nitro-3,4-dimethoxymethylbenzoate (**15**, 16 g, 79%) m.p. 141–142 °C (142–143 °C).

3.2.5. Synthesis of methyl 2-amino-4,5-dimethoxybenzoate 16

A mixture of iron (24 g, 0.62 mol), ethanol (100 ml) and conc. HCl (9 ml.) was stirred with mechanical stirrer and refluxed for 30 min. To the above mixture 6-nitro-4,5-dimethoxymethylbenzoate (16 g, 0.019 mol) was added. The reaction mixture was allowed to reflux with stirring for 12 h and the progress of reaction was monitored by TLC. The reaction mixture was cooled to RT, neutralized with aq sodium carbonate (10% w/v) and filtered. The filtrate was concentrated to 20 ml, cooled and poured in ice–water mixture (100 ml). The solid obtained was filtered and washed with cold water followed by washing with aq. potassium thiocyanate solution (10% w/v) to remove iron impurities. The product obtained was methyl 2-amino-4,5-dimethoxymethylbenzoate (**16**, 3.2 g, 74%) m.p. 120–122 °C (120–121 °C). recrystallized from methanol.

3.3. Synthesis of 2-(chloromethyl)quinazolin-4-ol – general procedures

A stream of dry hydrogen chloride gas was bubbled into anice-cold solution of 3-amino-2-ethoxycarbonylester (0.0085 mol) and chloroacetonitrile (0.017 mol) in dry dioxane (30 ml) for 6 h. The reaction mixture was poured into ice–water mixture and neutralized with strong ammonium hydroxide solution (10% v/v). The precipitate separated was filtered, washed with cold water and dried. The product obtained was recrystallized from methanol–chloroform to yield 2-chloromethyl-compound.

3.4. Synthesis of 4-chloro-2-chloromethylquinazoline – general procedures

2-(Chloromethyl)quinazolin-4-ol (0.0038 mol) was dissolved in 10 ml of dry DMF. To this solution $POCl_3$ (5 ml) was added drop wise with continuous stirring at 0–5 °C for 30 min. The progress of the reaction was monitored by TLC. On

completion the reaction mixture was poured onto ice–water mixture to get the solid. The product obtained was recrystallized from benzene methanol (Shvedov et al., 1974).

3.5. Synthesis of prodrugs of 2-(chloromethyl)quinazolin-4-ol – general procedures

To a solution of sodium acetate or benzoate or nicotinate (0.09 mol) in DMSO (50 ml), 2-(chloromethyl)quinazolin-4-ol (0.023 mol) was added and the reaction mixture was allowed to stir for 6 h at RT. The reaction mixture was thereafter poured onto ice water mixture (150 ml) where upon solid separated out. The product obtained was recrystallized from methanol–chloroform.

3.6. Synthesis of 4-chloro derivatives of prodrugs – general procedures

2-Acetoxy/benzyloxy/pyridinylcarboxymethyl derivatives (0.0069 mol) was added to $POCl_3$ (0.017 mol) with continuous stirring maintaining the temp at 0–5 °C for 30 min. PCl_5 (0.017 mol) was then added and the solution was stirred for further 30 min at 0–5 °C. The solution was refluxed further for 4–5 h. The progress of the reaction was monitored by TLC. The reaction mixture was poured into ice water to get crude solid which was filtered, dried. The product obtained was recrystallized from benzene–methanol.

3.7. Biological screening

3.7.1. General conditions of experimental animals

The experiments were carried out with Wistar Albino rats. The animals were housed at a temperature of 30 ± 5 °C 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.

3.7.2. Triton–induced hyperlipidemic rat model (Triton WR 1339)

3.7.2.1. General conditions of experimental animals. Albino rats (150–200 g) of Wistar strain of either sex were used for the study. The animals were kept at optimum temperature condition (25–30 °C) and humidity of 45% ± RH.

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

3.7.2.2. Control group. The control group received only vehicle (2% acacia solution as well as normal saline).

3.7.2.3. Cholesterol-control group. The cholesterol-control group received Triton WR 1339 (200 mg/kg) by *i.p.* route in normal saline solution.

3.7.2.4. 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 (400 mg/kg, *p.o.*).

3.7.2.5. Standard group. Standard group received Triton WR 1339 (200 mg/kg *i.p.*) as well as gemfibrozil (400 mg/kg, *p.o.*) as suspension in 2% acacia.

3.7.3. Procedure for screening the test and standard drugs

Test group received their respective compound 1 h prior (400 mg/kg, *p.o.*) to Triton injection. The second dose of test compound was given 20 h later (400 mg/kg, *p.o.*). At the end of 24 h 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*. The samples were analyzed for serum cholesterol (total) levels, triglycerides and HDL levels as per our previous method (Kathiravan et al., 2007) (IAEC Reg. No. 616/02/ac/CPCSEA).

4. Conclusions

In summary, the newly synthesized 4-substituted-2-substitutedmethyltriazino[6,1-*b*] quinazolin-10-ones and 2,4-disubstituted-6,7-dimethoxy quinazoline derivatives were evaluated for antihyperlipidemic activity. Many synthesized compounds exhibited promising antihyperlipidemic activity against triton induced hyperlipidemia. Compound **5d** showed the best activity in reducing % serum cholesterol level while compound **5f** in reducing % serum triglyceride level. Compound **6g** is giving best activity in case of % change in serum HDL level than standard drug gemfibrozil. The results indicate that quinazoline nucleus shows better activity in reducing total cholesterol as well as triglyceride level when compared with quinazoline nucleus. Also there is significant increase in activity in case of 4-chloro compounds emphasizing the importance of an electronegative atom. However, quinazoline nucleus hybridized with nicotinate has shown better results in increasing HDL level.

Thus, we are able to improve our earlier results considerably and compound **5d** has exhibited excellent % reduction in serum cholesterol where as **5f** exhibited excellent % reduction in triglyceride levels were as comparable in case of serum total cholesterol levels. Among the series compound **6g** has shown promising results in lipid profile. These molecules indeed have the potential to be developed as an antihyperlipaemic molecule.

References

Arya, V.P., 1985. Drugs Future 10, 123–127.
Carpenter, P.D., Peesapati, V., Proctor, G.R., 1979. J. Chem. Soc., Perkin Tran. 1, 10.
Chrysselis, M.C., Rekka, E.A., Kourounakis, P.N., 2000. J. Med. Chem. 43, 609–612. http://dx.doi.org/10.1021/jm991039.
Dave, K.G., Shishoo, C.J., Devnai, M., Kalyanaraman, B.R., Ananthan, S., Ullas, G.V., Bhadti, V.S., 1980. J. Heterocycl. Chem. 17, 1497–1500. http://dx.doi.org/10.1002/jhet.5570170727.
Davidson, M.H., 2003. Curr. Atheroscler. Rep. 5, 418–422.
George, T., Mehta, D.V., Tahilramani, R., 1971. Ind. J. Chem. 19B, 755–759.
http://www.americanheart.org/statistics. American Heart Association: 2001 Heart and Stroke Statistical Update. Dallas Texas: American Heart Association, 2000.
Jain, K.S., Kathiravan, M.K., Shishoo, C.J., Somani, R.S., 2007. Bioorg. Med. Chem. 15, 4674–4699. http://dx.doi.org/10.1016/j.bmc.2007.04.031.
Kathiravan, M.K., Shishoo, C.J., Kumar, K.G., Roy, S.K., Mahadik, K.R., Kadam, S.S., Jain, K.S., 2007. Arzneim.-Forsch./Drug Res. 57 (9), 599–606.
McGill Jr., H.C., 1985. Geographical Pathology of Atheroslclerosis. Williams and Wilken Co., Baltimore.
Murray, C.J., Lopez, A.D., 1997. Lancet 349, 1269–1276.

Otera, J., 2003. Esterification Methods Reactions and Application. Wiley-VCH, Weinheim, Germany, p. 303.

Rosamond, W., Chambless, L., Folsom, A., Cooper, L., Conwill, D., Clegg, L., Wang, C., Heiss, G., 1998. N. Engl. J. Med. 339, 861–867.

Sauter, F., 1972. Ger. Offen., 221003. Chem. Abstr., 1972, 77, 164752.

Shiroki, M., 1976. Japan Kokai., 7643796. Chem. Abstr. 1976, 85, 94398.

Shishoo, C.J., Devani, M.B., Pathak, U.S., Ananthan, S., Bhadti, V.S., Ullas, G.V., Jain, K.S., Rathod, I.S., Talati, D.S., Doshi, N.H., 1984a. J. Heterocycl. Chem. 21, 375.

Shishoo, C.J., Devani, M.B., Bhadti, V.S., 1984. Indian Pat. 151, 496; Chem. Abstr. 1981, 100, 209858.

Shishoo, C.J., Devani, M.B., Bhadti, V.S., Jain, K.S., 1990. Arzneim.-Forsch./Drug Res. 40, 56–58.

Shishoo, C.J., Jain, K.S., Rathod, I.S., Thakkar, B.J., 1996. Arzneim.-Forsch./Drug Res. 46, 273–278.

Shishoo, C.J., Jain, K.S., Goyal, R.K., Rathod, I.S., Shah, T.R., 1997. Arzneim.-Forsch./Drug Res. 47, 1125–1129.

Shvedov, V.I., Kharizomenova, I.A., Grinev, A.N., 1974. Chem. Heterocycl. Compd., 1045–1047.