Med Chem Res (2013) 22:4286–4292
DOI 10.1007/s00044-012-0263-z

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antihyperlipidemic activity of novel condensed 2-fluoromethylpyrimidines

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Received: 10 April 2012 / Accepted: 27 September 2012 / Published online: 6 January 2013

Abstract A series of novel condensed 2-fluoromethylpyrimidines has been synthesized and evaluated for antihyperlipidemic activity in high fat diet fed hyperlipidemic Sprague–Dawley rats. The aim of this study was to investigate the effect of the fluorine atom at the 2-methyl position of these compounds. Most of the synthesized compounds significantly affected the lipid profile of the test animals. Compound **IIIb** exhibited remarkably best effects in lowering the serum cholesterol and triglyceride levels and elevating the serum HDL levels, of the test animals.

Keywords Antihyperlipidemic · Lipid profile · Condensed 2-fluoromethylpyrimidines

Introduction

Hyperlipidemia is a collective term used to describe elevated human plasma levels of one or more classes of lipids, namely cholesterol, triglycerides, phospholipids, and fatty acids (Jain *et al*., 2007). Hyperlipidemia and atherosclerosis, are two risk factors for stroke and cardiovascular diseases (CVDs); the leading causes of death in many industrialized countries (Jain *et al*., 2007). By 2030, almost 23.6 million people may die from CVDs and stroke (http://www.who.int/mediacentre/factsheets/fs317/en). Elevated lipid levels can be reduced by either the inhibition of the endogenous cholesterol biosynthesis or promoting hepatic cholesterol clearance from the plasma or by inhibiting the absorption of dietary and biliary cholesterol from the intestine (Clader *et al*., 1996).

Earlier, we have reported the synthesis and antihyperlipidemic activity in series of condensed 2-substitutedmethylpyrimidin-4(3*H*)-ones (Kathiravan *et al*., 2007a) (Fig. 1). Compound **1** has already exhibited significant lipid lowering property in various laboratory animals and has been a subject of pharmacokinetic and bioavailability studies (Shishoo *et al*., 1996). The QSAR studies (Shishoo *et al*., 1997; Kathiravan *et al*., 2011; Jain *et al*., 2011) on thieno[3,2-*d*]-pyrimidin-4(3*H*)-ones **2**, **3** and thieno[3,2-*d*]pyrimidines **4** have indicated the direct positive influence of the electron withdrawing groups at the methyl substituent on their antihyperlipidemic activity.

Introducing a spacer (an ethyl group) at position 2- resulted in decrease in activity while, introduction of a chlorine atom at position 4- resulted in better activity (Fig. 2). The "condensed 2-chloromethylpyrimidine" nucleus, is therefore concluded to be a potential pharmacophore for antihyperlipidemic activity.

It was logically thought to introduce a group of higher electronegativity such as fluorine atom on the 2-methyl position of the basic pharmacophore and see its effect on the lipid profiles of test animals. The variations for substitution introduced at positions 5- and 6- at the rings fused to the pyrimidine were aliphatic, aromatic, alicyclic, as well as, electron donating and withdrawing groups.

The fluorine atom, being very electronegative is known to change the charge distribution (polarity) in compounds into which it is placed, thereby altering their biological

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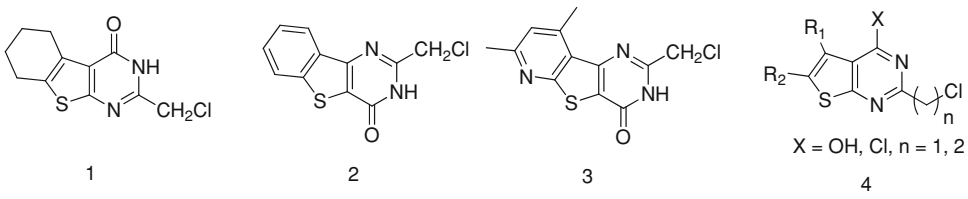
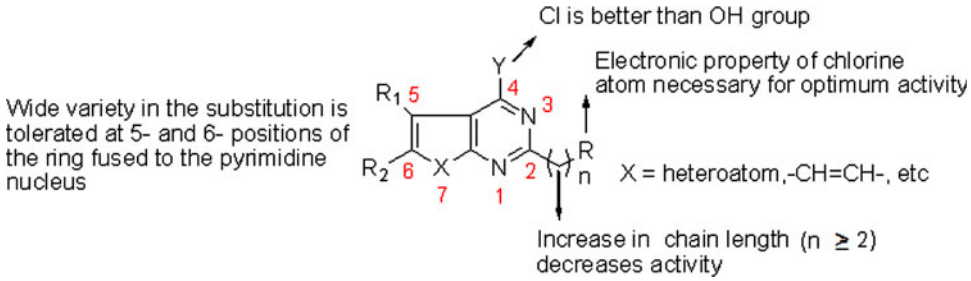
Fig. 1 Structure of lead compounds **1–4**



1 2 3 4

Fig. 2 Basic pharmacophore requirement for optimum antihyperlipidemic activity



effects, chemical and metabolic stability, as well as bioavailability (Kirk, 2006; O'Hagan, 2010).

Results and discussion

Chemistry

Various *ortho*-amino substrates **Ia–h** were synthesized as per earlier reported methods (Kathiravan *et al*., 2007b; Carpenter *et al*., 1979). The intermediate compounds, condensed 2-chloromethylpyrimidin-4(3*H*)-ones **IIa–h** were synthesized through the facile one pot HCl catalyzed cyclization of appropriate 2-amino-3-carbethoxy/carbmethoxy substrates with slight molar excess of chloroacetonitrile under MWI, by the reported procedure from this laboratory (Jain *et al*., 2009) (Table 1; Scheme 1).

The title compounds condensed 2-fluoromethylpyrimidin-4(3*H*)-ones (**IIIa–h**, Table 1) were synthesized through the nucleophilic halogen exchange reaction of **IIa–h** with NaF in the presence of TEBA-Cl in a dipolar aprotic solvent, dimethyl sulfoxide (DMSO) at 135–140 °C (Atkinson and Lebedev, 2003; Robert, 1981) (Table 1; Scheme 1).

Antihyperlipidemic activity

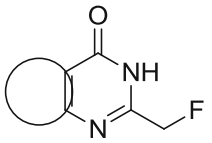
The test compounds **IIIa–h** were evaluated for antihyperlipidemic activity in high fat diet fed Sprague–Dawley rats for 1 week. The test animals were divided broadly into 11 groups. Compounds were administered at dose 50 mg/kg, p.o., whereas, ezetimibe (Kathiravan *et al*., 2009) a well-known cholesterol absorption inhibitor was administered as the standard drug at dose 1 mg/kg p.o. The standard drug, ezetimibe, also has fluoro substituents. Further, the proposed mechanism of action for compounds closely related to the title compounds by interfering in cholesterol reabsorption and to be effective by oral route (Shishoo *et al*., 1997). These points led to the selection of ezetimibe as the standard drug during the biological evaluation of the title compounds.

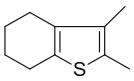
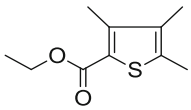
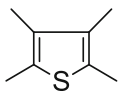
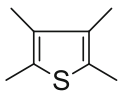
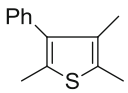
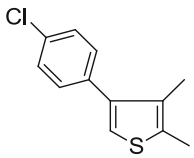
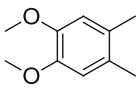
One week after the treatment all the animal groups were fasted for 14 h and blood was withdrawn from retro orbital plexus of the test animals for the evaluation of serum level of total cholesterol, triglyceride, and HDL (Heek *et al*., 2003; Santosh *et al*., 2006; Mali and Bodhankar, 2008).

The obtained results revealed that feeding rats with high fat diet for 7 days significantly elevated the serum levels of total cholesterol and triglycerides, as compared to the normal control rats. Moreover, induction of hyperlipidemia significantly decreased serum HDL levels of these animals as compared to the normal control ones. It was found that the test compounds showed significant changes in lipid profile, i.e., decrease in serum level of total cholesterol and triglycerides and increase in HDL at a dose of 50 mg/kg body weight p.o. as compared with the normal control group.

A perusal of Table 2 reveals that at 50 mg/kg body weight p.o. dose levels, compounds **IIIb** caused significant reduction in serum total cholesterol levels, comparable to that caused by ezetimibe at a dose level of 1 mg/kg body weight p.o. compounds, while compounds **IIIa**, **IIIc**, **IIId**, **IIIe**, and **IIIg** remained moderately effective. The test compounds **IIIb**, **IIIf**, and **IIIa** caused significant reduction in serum triglycerides levels Table 2, comparable to that caused by ezetimibe at a dose level of 1 mg/kg body weight p.o. compounds, while compounds **IIIc**, **IIId**, **IIIe**, **IIIg**, and **IIIh** remained moderately effective. The compounds **IIIf** and **IIIb** also exhibited good HDL levels enhancing activity in the test animals (Table 2), while other compounds **IIIa**, **IIIc**, **IIId**, **IIIe**, **IIIg**, and **IIIh** remained moderately effective in this activity.

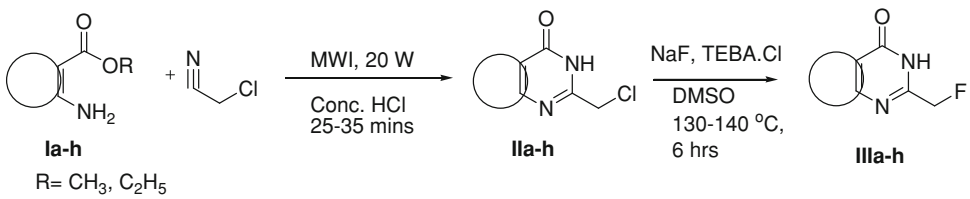
Table 1 Physical data for the condensed 2-fluoromethylpyrimidin-4(3*H*)-ones (**IIIa–h**)



Comp no.	A	M.P (°C) (Solv. of recryst.)	Rf	Yield (%)
IIIa		258–260 (D–M)	0.56	76
IIIb		189–190 (D–M)	0.52	78
IIIc		237–239 (D–M)	0.55	75
IIId		258–260 (D–M)	0.51	75
IIIe		226–227 (D–M)	0.52	73
IIIf		262–264 (D–M)	0.58	74
IIIg		190–192 (D–M)	0.56	71
IIIh		210–212 (D–M)	0.53	67

D dichloromethane, *M* methanol

Scheme 1 Scheme for the synthesis of target compounds



The compounds **IIIb**, **IIIf**, and **IIIa** exhibit good VLDL and LDL reducing activity, comparable to that caused by ezetimibe at a dose level of 1 mg/kg body weight p.o. (Table 2) while compounds **IIIc, IIId**, **IIIe**, **IIIg**, and **IIIh** remained moderately effective. All compounds exhibit good atherogenic index (Normal value of AI = <3.5).

Table 2 Effect of title compounds, **IIIa–h**, on lipid profile in high fat diet fed hyperlipidemic Sprague–Dawley rats

Group	Comp (mg/kg)	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	AI	CRI
I	Normal control	64.16 ± 1.62	74.71 ± 2.57	38.11 ± 0.84	11.11 ± 0.91	14.94 ± 0.51	0.29 ± 0.02	1.66 ± 0.04
II	CFD control	149.6 ± 2.68† (↑133.16)	175.1 ± 2.39† (↑134.37)	22.29 ± 0.57† (↓41.48)	92.33 ± 3.23† 731.01)	35.02 ± 0.48† 234.40	4.15 ± 0.23†	5.21 ± 1.76†
III	EZ (1)	78.43 ± 2.16$^{@}$ (↓47.57)	83.63 ± 3.73$^{@}$ (↓52.23)	39.00 ± 0.53$^{@}$ (↑74.96)	22.70 ± 2.28$^{@}$ (↓75.41)	16.73 ± 0.75$^{@}$ (↓52.22)	0.58 ± 0.07$^{@}$	2.01 ± 0.08$^{@}$
IV	**IIIa** (50)	84.09 ± 3.61$^{@}$ (↓40.44)	86.29 ± 3.28$^{@}$ (↓50.71)	35.28 ± 0.76$^{@}$ (↑58.27)	31.55 ± 3.76$^{@}$ (↓65.82)	17.26 ± 0.65$^{@}$ (↓50.71)	0.96 ± 0.08$^{@}$	2.39 ± 0.12$^{@}$
V	**IIIb** (50)	65.53 ± 3.18$^{@}$ (↓56.19)	73.94 ± 2.92$^{@}$ (↓57.77)	38.67 ± 0.68$^{@}$ (↑73.48)	12.07 ± 2.42$^{@}$ (↓86.92)	14.79 ± 0.58$^{@}$ (↓57.76)	0.31 ± 0.06$^{@}$	1.69 ± 0.06$^{@}$
VI	**IIIc** (50)	101.0 ± 2.36$^{@}$ (↓32.48)	108.9 ± 6.32$^{@}$ (↓37.80)	32.25 ± 1.03$^{@}$ (↑44.68)	46.94 ± 2.11$^{@}$ (↓45.91)	21.77 ± 1.26$^{@}$ (↓37.83)	1.46 ± 0.01$^{@}$	3.14 ± 0.15*
VII	**IIId** (50)	93.56 ± 1.37$^{@}$ (↓37.45)	88.66 ± 2.77$^{@}$ (↓49.36)	35.64 ± 0.91$^{@}$ (↑46.43)	40.19 ± 0.92$^{@}$ (↓56.47)	17.73 ± 0.55$^{@}$ (↓49.37)	1.13 ± 0.03$^{@}$	2.63 ± 0.05$^{\#}$
VIII	**IIIe** (50)	99.95 ± 2.00$^{@}$ (↓33.18)	105.5 ± 1.76$^{@}$ (↓39.74)	31.50 ± 0.97$^{@}$ (↑41.31)	47.36 ± 1.07$^{@}$ (↓48.70)	21.09 ± 0.35$^{@}$ (↓39.77)	1.51 ± 0.03$^{@}$	3.18 ± 0.03
IX	**IIIf** (50)	82.29 ± 2.00$^{@}$ (↓44.99)	84.19 ± 2.80$^{@}$ (↓51.91)	40.04 ± 0.55$^{@}$ (↑79.63)	25.41 ± 1.6$^{@}$ (↓72.47)	16.84 ± 0.56$^{@}$ (↓51.91)	0.63 ± 0.04$^{@}$	2.05 ± 0.03$^{@}$
X	**IIIg** (50)	92.38 ± 2.96$^{@}$ (↓38.24)	93.15 ± 3.18$^{@}$ (↓46.19)	33.97 ± 1.96$^{@}$ (↑52.40)	39.78 ± 4.73$^{@}$ (↓57.31)	18.63 ± 0.64$^{@}$ (↓46.80)	1.20 ± 0.12$^{@}$	2.75 ± 0.21$^{\#}$
XI	**IIIh** (50)	110.3 ± 4.46$^{@}$ (↓26.27)	94.80 ± 5.92$^{@}$ (↓45.14)	36.21 ± 0.77$^{@}$ (↑62.44)	55.09 ± 4.52$^{@}$ (↓40.26)	18.96 ± 1.18$^{@}$ (↓45.85)	1.53 ± 0.16$^{@}$	3.16 ± 0.18*

Each value represents the mean ± SEM, $n = 5$, ANOVA followed by Tukey's test

CFD cholesterol diet fed control group, *EZ* ezetimibe, *TC* total cholesterol, *TG* triglyceride, *HDL* high density lipoproteins, *LDL* low density lipoproteins, *VLDL* very low density lipoproteins, *AI* atherogenic index, *CRI* coronary risk index

† $P < 0.001$ statistically significant as compared to normal control group; $^{@}P < 0.001$; $^{\#}P < 0.01$; $^{*}P < 0.05$ statistically significant as compared to cholesterol fed diet group. Values in parenthesis indicates, ↓ % reduction and ↑ % rise

Total two test compounds **IIIb** and **IIIf** of the series significantly affect the lipid profile (decreasing total cholesterol and triglycerides and increasing the HDL levels) of the test animals and can be looked upon as potential leads for further development and investigations.

Experimental

Chemistry

All reagents and chemicals used were of LR grade and standard quality. Melting points were determined on scientific melting point apparatus in open capillaries and were uncorrected. The ^{1}H NMR spectra were recorded in DMSO-d_6 using NMR Varian Mercury YH-300 MHz spectrometer and chemical shifts are given in units as parts per million, downfield from TMS (tetramethylsilane) as an internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP2010 spectrometer. Elemental analyses were obtained using a Flash EA 1112 Thermofinnigan instrument. The IR spectra of the synthesized compounds were recorded on Perkin Elmer (USA) Spectrum BX_2 FT–IR spectrophotometer in potassium bromide disks.

General synthesis procedure of condensed 2-chloromethylpyrimidin-4(3*H*)-ones (IIa–h)

A mixture of an appropriate *o*-aminoester substrate (0.01 mol), chloroacetonitrile (1.51 g, 0.02 mol), and catalytic amount of HCl were irradiated under microwave for 25–35 min at 20 W. The progress of reaction was monitored (TLC; Toluene: methanol: 4.5: 0.5) at 5 min intervals. After completion of the reaction (25–35 min), the reaction mixture was allowed to cool to room temperature and poured onto ice-water mixture (100 ml). The resultant product was filtered, washed with chilled water, and dried. The crude product on recrystallization from dioxane yielded fine crystals of intermediate compounds. **(IIa–h).**

General synthesis procedure of condensed 2-fluoromethylpyrimidin-4(3*H*)-ones (IIIa–h)

A mixture of appropriate 2-chloromethylpyrimidin-4(3*H*)-one (0.01 mol), sodium fluoride (0.025 mol), and TEBA Chloride (0.002 mol) in DMSO (30 ml) were heated at 130–140 °C for 6–8 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was thereafter cooled to room temperature and poured onto ice-water mixture (100–150 ml). The solid separated was filtered, washed with water, and dried. The crude product on recrystallization from mixture of methanol and

methylene chloride (5 %) yielded crystals of target compounds, **IIIa–h**.

2-Fluoromethyl-5,6,7,8-tetrahydrobenzo(b)thieno-[2, 3-d]pyrimidin-4(3H)-one (IIIa)

IR (KBr) : 3366.81 (γ_{NH}), 2854.42 (γ_{C-H}), 1654.14($\gamma_{C=O}$), 1070.28 (γ_{C-F}). 1H NMR (300 MHz, DMSO):1.72 (4H, s, CH_2 at 6 & 7), 2.71 (2H, s, CH_2 at 8), 2.85 (2H, s, CH_2 at 5), 4.35 (2H, s, CH_2 at 2), 11.97 (1H, s, N*H* at 3). MS (m/e): 238(M^+), 237, 217, 196, 182 and 163. Anal. Calcd. for $C_{11}H_{11}FN_2OS$: C, 55.45; H, 4.65; N, 11.76; Found: C, 55.61; H, 4.85; N, 11.85.

Ethyl 2-fluoromethyl-5-methylthieno[2,3-d]pyrimidine-6-carboxylate (IIIb)

IR (KBr) : 3247.43(γ_{NH}), 2917.69(γ_{C-H}), 1718.02($\gamma_{C=O}$), 1684.32(γ_{CONH}), 1032.64 (γ_{C-F}). 1H NMR (300 MHz, DMSO): 1.41 (3*H*, t, $J = 7.0$, CH_3), 2.95 (3*H*, s, CH_3). 4.38 (2*H*, quartlet, $J = 7.0$, CH_2), 4.57 (2*H*, s, CH_2), 10.62 (1*H*, s, N*H*). MS (m/e): 270 (M^+), Anal. Calcd. for $C_{11}H_{11}FN_2O_3S$: C, 48.88; H, 4.10; N, 10.36; Found: C, 48.97; H, 4.23; N, 10.13.

2-Fluoromethyl-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (IIIc)

IR (KBr) : 3394.19(γ_{NH}), 2851.08(γ_{C-H}), 1654.82($\gamma_{C=O}$), 1037.99 (γ_{C-F}). 1H NMR (300 MHz, DMSO): 2.33 (3*H*, s, CH_3), 2.36 (3*H*, s, CH_3), 4.35 (2*H*, s, CH_2), 11.95(1*H*, s, br, N*H*). MS m/e: 212 (M^+), 210, 192, 181, 166, 153, 138. Anal. Calcd. for $C_9H_9FN_2OS$: C, 50.93; H, 4.27; N, 13.20; Found: C, 51.03; H, 4.38; N, 13.36.

2-Fluoromethyl-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (IIId)

IR (KBr) : 3101.24(γ_{NH}), 2849.80(γ_{C-H}), 1663.33(γ_{CONH}), 1051.09 (γ_{C-F}). ^{1}H NMR (300 MHz, DMSO): 4.42 (2*H*, s, CH_2,), 7.36–7.54 (5*H*, m, Ar–*H* and 1*H* at 6 position), 12.11 (1*H*, s, br, N*H*). MS m/e: 260(M^+), 258, 239. Anal. Calcd. for $C_{13}H_9FN_2OS$: C, 59.99; H, 3.49; N, 10.76; Found: C, 60.12; H, 3.58; N, 10.85.

2-Fluoromethyl-6-methyl-5-phenylthieno [2,3-d]pyrimidin-4(3H)-one (IIIe)

IR (KBr) : 3134.36[γ_{ArH}]; 2921.68(γ_{C-H}), 1664.10[γ_{CONH}]; 1055.33 (γ_{C-F}). ^{1}H NMR (300 MHz, DMSO): 2.40 (3*H*, s, CH_3), 4.42 (2*H*, s, CH_2), 7.38–7.44 (5*H*, m, Ar–*H*). MS (m/e): 274 (M^+), Anal. Calcd. for $C_{14}H_{11}FN_2OS$; C, 61.30; H, 4.04; N, 10.21; Found: C, 61.25; H, 4.18; N, 10.30.

2-Fluoromethyl-5-(4-chlorophenyl)thieno[2,3-d]pyrimidin-4(3H)-one (IIIf)

IR (KBr) : 3091.64 [γ_{ArH}]; 1670.11 [γ_{CONH}]; 1037.15 (γ_{C-F}). ^{1}H NMR (300 MHz, DMSO):4.48 (2*H*, s, CH_2,), 7.41–7.56 (4*H*, m, Ar–*H* and 1*H* at 6 position), 11.69 (1*H*, s, br, N*H*). MS (m/e): 294 (M^+). Anal. Calcd. for: $C_{13}H_8ClFN_2OS$: C, 52.98; H, 2.74; Cl, 12.03; N, 9.50; Found: C, 53.09; H, 2.65; N, 9.69.

2-Fluoromethylquinazolin-4(3H)-one (IIIg)

IR (KBr) : 3064.10[γ_{ArH}]; 2847.86(γ_{C-H}), 1676.17(γ_{CONH}), 1130.02 (γ_{C-F}). ^{1}H NMR (300 MHz, DMSO): 4.35 (2*H*, s, CH_2), 7.2–7.5 (4*H*, m, Ar*H*), 10.36 (1*H*, s, N*H*). MS (m/e): 178 (M^+). Anal. Calcd. for: $C_9H_7FN_2O$: C, 60.67; H, 3.96; N, 15.72; Found: C, 60.75; H, 4.12; N, 15.81.

2-Fluoromethyl-6,7-dimethoxyquinazolin-4(3H)-one (IIIh)

IR (KBr) : 2927.25(γ_{C-H}), 1669.99[γ_{CONH}]; 1097.53 (γ_{C-F}). ^{1}H NMR (300 MHz, DMSO):2.5–2.8 (6*H*, s, CH_3); 4.3 (2*H*, s, CH_2 at 6); 7.2–7.5 (2*H*, m, Ar*H*). MS (m/e): 238 (M^+). Anal. Calcd. for $C_11H_{11}FN_2O_3$: C, 55.46; H, 4.65; N, 11.76; Found: C, 55.54; H, 4.78; N, 11.87.

Antihyperlipidemic activity

The experiments were carried on Sprague–Dawley rats (150–200 g) of either sex. The animals were housed at a temperature of 20 ± 2 °C with relative humidity of 50 ± 10 % with 12 h light and dark cycles. All the study protocols were reviewed and approved (SCOP/IAEC/Approval/2010-11/02) by the Institutional Animal ethical committee. Acute toxicity studies were done according to OECD guidelines GL-423. Ezetimibe (1 mg/kg) was used as standard for the comparison antihyperlipidemic activity. Normal diet was made available for 7 days to Group I (normal control) and vehicle (2 % acacia solution. p.o.) was administered for 7 days. Hyperlipidemia was induced to Group II (cholesterol fed diet control) by orally administering with a suspension of cholesterol (500 mg/kg) and cholic acid (250 mg/kg) in groundnut oil (10 ml/kg) daily for 7 days. Standard treatment groups (Group III) were orally administered ezetimibe at dose 1 mg/kg p.o., respectively for 7 days daily in cholesterol fed animals. Test groups (Groups IV–XI) were orally administered eight synthesized compounds at dose 50 mg/kg, respectively for 7 days daily in high fat diet fed animals.

The blood was collected on 8th day; animals were kept on fasting 14 h before the blood withdrawal. The blood was withdrawn by retro orbital method under light ether anesthesia and serum was separated by centrifugation at 3,000 rpm for 10 min and evaluated for serum total cholesterol, triglyceride, and HDL level using commercial diagnostic kits (Biolabs Pvt. Ltd., Mumbai, India) whereas atherogenic index, coronary risk index, serum LDL, and VLDL levels were calculated by the reported formulae (Mali and Bodhankar, 2008; Friedewald *et al*., 1972; Stern *et al*., 2000).

Statistical analysis

All the values were expressed as the mean ± SEM and were subjected to one-way analysis of variance (ANOVA) followed by Tukey's test, where $P < 0.001$ was considered as statistical significant.

Structure activity relationship

- The synthesized compounds have shown good antihyperlipidemic activity by significantly affecting the lipid profile (decreasing total cholesterol and triglycerides and increasing the HDL levels) of the test animals.
- The 2-halo or 2-chloromethylpyrimidin-4-one is the basic structural requirement for optimum antihyperlipidemic activity. The rings fused to the scaffold at its 5- and 6- position as junction also play a significant role in the potency of the title compound.
- The fluoro substitution on 2- position of basic scaffold has resulted in decreasing total cholesterol and triglycerides as well as increasing the HDL levels due to its high electronegativity.
- The 5- and 6- substituents on the ring fused to the pyrimidine scaffold play a significant role on altering the lipid profile. While, an aryl ring bearing a para-chloro substituent at the 5- position and a carbethoxy substituent at the 6- position have definite positive influence, alkyl or alkoxy substituent have negligible effects. Similarly, cycloalkyl rings fused across the 5- and 6- position have moderate positive effect in altering the lipid profile.

Conclusion

In summary, the newly synthesized condensed 2-fluoromethylpyrimidin-4(*3H*)-ones **(IIIa–h)** were evaluated for antihyperlipidemic activity. Although most of the compounds showed good antihyperlipidemic activity by significantly affecting the lipid profile of the test animals, compounds **IIIb** and **IIIf**, showed the best activity in reducing serum cholesterol and triglyceride levels. Compound **IIIf** showed the most significant HDL enhancing effects. Overall, the title compounds **IIIb** and **IIIf** can be looked upon as potential leads for further development and investigations.

Research highlights

- Condensed 2-fluoromethylpyrimidines were synthesized.
- Their antihyperlipidemic activity was evaluated.
- The presence of fluorine atom at 2-methyl position is important.
- At 5- and 6- positions electron withdrawing groups are favorable.

Acknowledgments The authors acknowledge the contributions of Prof. M. N. Navale, President, and Dr. (Mrs.) S. M. Navale, Secretary, Sinhgad Technical Education Society, Pune and University of Pune for providing necessary facilities to carry out the research & spectral analysis.

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