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Isoxazole-Based Derivatives from Baylis–Hillman Chemistry: Assessment of Preliminary Hypolipidemic Activity†

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Abstract—The synthesis of isoxazole-based derivatives utilizing Baylis–Hillman chemistry and results of their preliminary bioevaluation as hypolipidemic agents in triton model are described.

The Baylis–Hillman (BH) chemistry has been expounded tremendously in the last couple of years. This has been mainly due to the unique property of this C–C bond forming reaction to furnish multifunctional derivatives that can be modified as per the requirement.[1] Towards this objective various workers have exemplified the use of BH reaction for the synthesis of a wide spectrum of biodynamic heterocycles and intermediates for natural products.[2] The problem of unusually slow reaction rate associated with BH reaction has been almost overcome by the use of Lewis acids,[3] additives,[4] sonication,[5] supercritical liquid[6] etc. Despite the aggressive exploitation of this reaction for its synthetic utility, only few reports addressing the medicinal use of derivatives obtained from the BH chemistry exist.[7] This could be attributed to the limited spectrum of substrate, which undergoes this reaction. Our interest in the BH chemistry has been mainly associated with our finding that 5-isoxazolecarboxaldehyde undergoes unusually fast DABCO- or Lewis acid-mediated BH reaction.[8] In the present era of developing chemical libraries using combinatorial ways, our major aim is to develop isoxazole-based libraries both in solution and solid phase and screen them in appropriate bioassays. As isoxazole form component of various bioactive molecules, an easy BH reaction of 5-isoxazolecarboxaldehyde has provided a good platform to achieve our objectives.

The cardiovascular diseases affect large populations both in developed and developing countries.[9] Atherosclerosis caused by lipid disorders that in turn results from high levels of cholesterol and oxidized LDL forms the major share of such diseases. The statins have been an excellent choice for control of cholesterol, and LDL indirectly. However, the side effects due to the long-term use have led researchers to look for better options.[10]

Toward these objectives we have earlier reported the synthesis and bioevaluation of 3 amino-hex-2-ene-3-one derivatives as hypolipidemic agents.[11] However their toxicity in vivo at higher doses led us to discard further optimization and evaluation of those derivatives.[12] We reasoned among ourselves that the isoxazole nucleus imbibed those hexenone derivatives in a manner that for now the keto and amino group are in a rigid geometry and the position between the two have swapped (Fig. 1). In addition, the isoxazole-based amide derivatives have earlier been reported to show inhibition of ACAT enzyme that in turn results in decrease of cholesterol levels.[13] Using this information we have evaluated various derivatives obtained from BH chemistry for hypolipidemic activity in the triton model. The details of synthesis and preliminary bioevaluation of these compounds are presented in this communication.

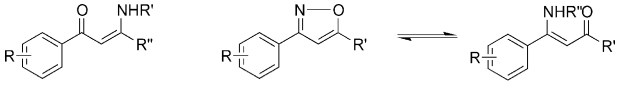

Figure 1.

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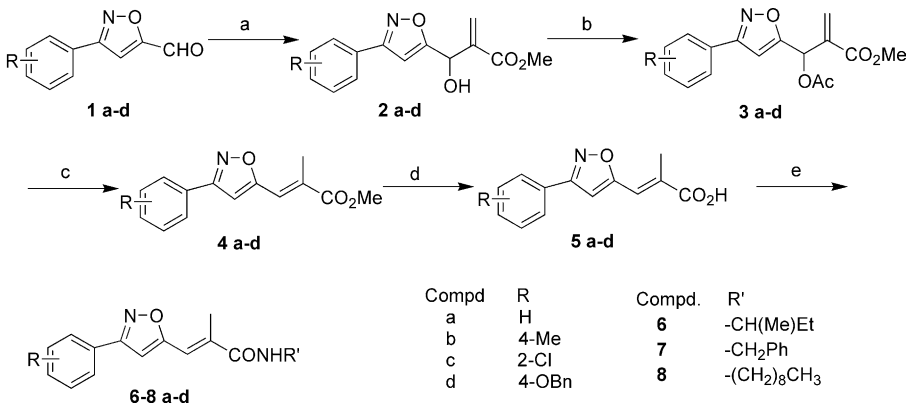
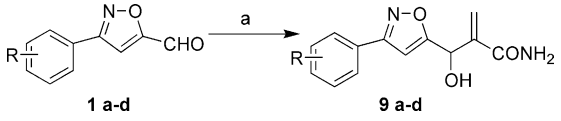


Scheme 1. Reagents and conditions: (a) DABCO (20 mol%), CH_2=$CHCO_2Me$ (1.0 equiv), rt, 30 min; (b) AcCl (1.5 equiv), Pyridine (1.3 equiv), DCM, rt, 3 h; (c) $NaBH_4$ (2.0 equiv), MeOH, rt, 1 h; (d) KOH (2.0 equiv), MeOH: H_2O (4:1), rt, 2 h; (e) R'NH_2 (1.0 equiv), DIC (1.0 equiv), HOBt (1.0 equiv), DCM, rt, 3–4 h.

Chemistry

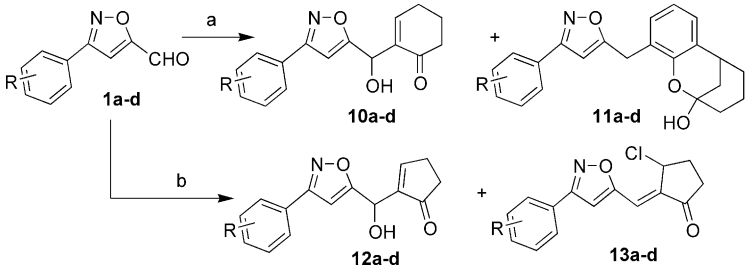
The compounds described herein were obtained from four different synthetic strategies. The amide derivatives (**6–8a–d**) were obtained as described in Scheme 1. The various 3-substituted phenyl-5-isoxazolecarboxaldehydes were subjected to BH reaction with methyl acrylate to obtain the BH adducts (**2a–d**). These were then acetylated using acetyl chloride to obtain acetates (**3a–d**), which upon reduction with sodium borohydride reaction yielded compounds (**4a–d**). The potassium hydroxide-mediated hydrolysis of compounds **4a–d** furnished the acids **5a–d**, which upon coupling reactions with amines yielded amides **6–8a–d**. The *E*-stereochemistry of amides was confirmed on the basis of NOE studies.



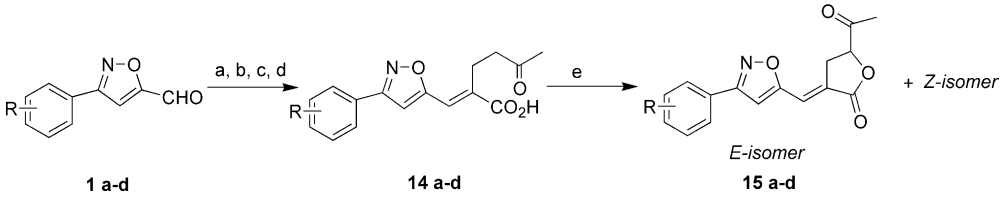
Scheme 2. Reagents and conditions: (a) DABCO (0.5 equiv), acrylamide (1.0 equiv) Dioxane–water (3:2), rt, 5–7 h.

In another strategy compounds **9a–d** were directly obtained from the BH reactions of acrylamide with the aldehydes **1a–d** in excellent yields (Scheme 2). The BH reaction using acrylamide has been described[14] to be complete within 12–48 h depending on the aldehyde employed, but in the case of 5-isoxazolecarboxaldehydes this reaction was completed within 5–7 h.

The compounds **10–12a–d** and **15a–d** were obtained through the synthetic methodologies that have been reported earlier[8b,c] and have been summarized in Schemes 3 and 4. Here it is essential to state that though we have obtained the *E*- and *Z*-isomers of compound **15,** only compounds having *E*-stereochemistry were subjected to biological screening.



Scheme 3. Reagents and conditions: (a) Cyclohexenone (1.5 equiv), $TiCl_4$ (1.0 equiv), DCM, rt, 1.5 h; (b) Cyclopentenone (1.5 equiv), $TiCl_4$ (1.0 equiv), DCM, rt, 1.5 h.



Scheme 4. Reagents and conditions: (a) DABCO (20 mol%), *tert*-Butyl acrylate (1.0 equiv), rt 30 min; (b) AcCl (1.5 equiv), Pyridine (1.3 equiv), DCM, rt, 2 h; (c) Acetylacetone (2.0 equiv), K_2CO_3 (1.5 equiv), EtOH, reflux, 2 h; (d) TFA (25%) in DCM, rt, 6 h; (e) HTIB (1.0 equiv), DCM, rt, 16 h.

Results and Discussion

The hypolipidemic activity data of various compounds is summarized in Tables 1 and 2. The compound guggulsterone, which is the active constituent of the hypolipidemic drug Guggulipid was used as standard for the present study. The plasma levels of TC, PL and TG were observed as 86.29 (±4.78), 86.73 (±6.49) and 81.28 (±9.63) mg/dL, respectively. The level of these parameters after the addition of triton was recorded as 285.41 (±22.96), 248.07 (±35.91) and 266.49 (±51.03) showing an increase of 3.3, 2.86 and 3.27 fold, respectively. It was found that the amides described in Scheme 1 showed significant biological activity. The effect was

Table 1. Hypolipidemic activity data of new compounds

Compd. No.	Bioactivity[a]		
	Cholesterol (TC)	Phospholipids (PL)	Triglycerides (TG)
Guggulsterone	42	34	24
4a	6*	35	33
4b	8**	12	10
4c	17**	12	8
4d	20*	20	22
5a	18**	24	29
5b	7**	34	2
5c	23**	21	23
5d	10**	9	8
6a	14**	17	9
6b	30*	29	30
6c	12**	10	7
6d	16**	16	18
7a	16**	12	22
7b	23**	28	24
7c	28*	29	26
7d	14**	21	19
8a	17**	15	15
8b	14**	27	22
8c	6**	2	7
8d	16*	12	19
9a	25**	25	28
9b	24*	22	18
9c	33*	12	17
9d	28*	11	20

$P^{**} < 0.01$; *0.001.
[a]Triton fed group was compared with control and triton plus compound treated and the values are the % decrease obtained from levels that are mean±S.D. of six rats.

Table 2. Hypolipidemic activity data of reported compounds[8a,8c]

Compd. No	Bioactivity[a]		
	Cholesterol (TC)	Phospholipids (PL)	Triglycerides (TG)
10a	6**	10	12
10b	9**	8	8
10c	7**	8	18
10d	17**	17	5
11a	28**	24	23
11b	8**	6	9
11c	28*	21	28
11d	36*	33	37
12a	17**	15	15
12b	20**	19	18
12c	9**	34	18
12d	14**	10	9
14a	18**	24	29
14b	14*	19	16
14c	39*	22	30
14d	34*	33	33
15a	ND	ND	ND
15b	38*	20	28
15c	34*	22	30
15d	13**	14	16

$P^{**} < 0.01$; *0.001.
[a]Triton fed group was compared with control and triton plus compound treated and the values are the % decrease obtained from levels that are mean±S.D. of six rats.

pronounced in the compound having 2-chlorophenyl at position 3 of the isoxazole nucleus and benzyl moiety on the NH of the amide (**7c**). Increasing the lipophilicity (**8a–d**) led to total loss in activity. Therefore, it was decided to synthesize the simple amide derivatives utilizing the acrylamide in BH reaction. This led to significant increase in the cholesterol lowering profile of nearly all the derivatives (**9a–d**) though phospholipid and triglycerides were not lowered in proportion. Out of the earlier reported derivatives, the BH adducts derived from cyclohexenone or cyclopentenone did not show any activity but the hemiacetals that were obtained in significant yields elicit potent biological response. The hemiacetal (**11d**) having 4-benzyloxy substitution in the isoxazole moiety was observed to have better hypolipidemic profile. On the other hand for acrylic acids (**14**) and furanones (**15**) in Scheme 4, the biological activity was more concentrated in compounds with 2-chloro substitution on the phenyl ring of the isoxazole. During our studies with 5-isoxazolecarboxaldehyde derivatives we have discovered that these compounds elicit significant in vivo antithrombotic activity,[15] therefore we subjected some of the amides for this activity. However, none of the derivatives show potent biological activity (Table 3).

Conclusion

In conclusion, we have described the preliminary hypolipidemic activity profile of various products derived from the BH chemistry of 5-isoxazolecarbox-aldehydes. During this study it was encouraging to note that hemiacetals and acrylamides show good biological response and their further optimization to modulate and optimize the hypolipidemic activity is under progress.

Experimental

General. Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR spectra were recorded either on a Bruker Avance DRX-300 or Bruker DPX-200 FT spectrometers, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The EIMS were recorded on JEOL-D-300 mass spectrometer at 70 eV while FABMS were recorded on JEOL/SX-102 spectrometer. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer.

Table 3. In vivo antithrombotic activity of amides at 30 μmol/kg

Compound	Protection (%)	Compound	Protection (%)
6a	0	**8a**	20
6b	20	**8b**	0
6c	0	**8c**	20
6d	0	**8d**	ND
7a	0	**9a**	0
7b	20	**9b**	0
7c	0	**9c**	40
7d	0	**9d**	0

Acetylsalicylic acid was used as standard that gives % of protection of 40.

General method for acetates

See ref 8b.

2-[Acetoxy-(3-phenyl-isoxazol-5-yl)-methyl]-acrylic acid methyl ester (3a). 96.7% as yellow oil; IR (Neat) (cm^{-1}) 1700 (CO_2CH_3), 1730 ($OCOCH_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) 2.17 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.11 (s, 1H, $=CH_2$), 6.58 (s, 1H, =CH), 6.60 (s, 1H, $=CH_2$), 6.88 (s, 1H, CH), 7.43–7.46 (m, 3H, Ar–H), 7.76–7.81 (m, 2H, Ar–H); mass (EIMS) m/z 301 (M^+). Anal. calcd. for $C_{16}H_{15}NO_5$ C, 63.78; H, 5.02; N, 4.65. Found C, 63.62; H, 5.22; N, 4.68.

2-[Acetoxy-(3-p-tolyl-isoxazol-5-yl)-methyl]-acrylic acid methyl ester (3b). 82% as white solid, m.p. 97–98 °C; IR (KBr) (cm^{-1}) 1709 (CO_2CH_3) 1745 ($OCOCH_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) 2.17 (s, 3H, CH_3), 2.39 (s, 3H, Ar–CH_3), 3.77 (s, 3H, CH_3), 6.10 (s, 1H, $=CH_2$), 6.56 (s, 1H, $=CH_2$), 6.58 (s, 1H, CH), 6.87 (s, 1H, =CH), 7.24 (d, 2H, $J=8.0$ Hz, Ar–H), 7.67 (d, 2H, $J=8.0$ Hz, Ar–H); Mass (EIMS) m/z 315 (M^+). Anal. calcd. for $C_{17}H_{17}NO_5$ C, 64.75; H, 5.43; N, 4.44. Found C, 64.65; H, 5.28; N, 4.20%.

2-{Acetoxy-[3-(2-chloro-phenyl)-isoxazol-5-yl]-methyl}-acrylic acid methyl ester (3c). 90% as yellow oil; IR (Neat) (cm^{-1}) 1703 (CO_2CH_3), 1739 ($OCOCH_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) 2.18 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.11 (s, 1H, $=CH_2$), 6.56 (s, 1H, $=CH_2$), 6.58 (s, 1H, =CH), 6.74 (s, 1H, CH), 7.32–7.49 (m, 3H, Ar–H), 7.71–7.74 (m, 1H, Ar–H); Mass (EIMS) m/z 335 (M^+). Anal. calcd. for $C_{16}H_{14}ClNO_5$ C, 57.24; H, 4.20; N, 4.17. Found C, 57.45; H, 3.99; N, 4.08%.

2-{Acetoxy-[3-(4-benzyloxy-phenyl)-isoxazol-5-yl]-methyl}-acrylic acid methyl ester (3d). 95% as white solid, m.p. 95–97 °C; IR (KBr) (cm^{-1}) 1709 (CO_2CH_3), 1744 ($OCOCH_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) 2.16 (s, 3H, $OCOCH_3$), 3.77 (s, 3H, CO_2CH_3), 5.11 (s, 2H, CH_2), 6.10 (s, 1H, $=CH_2$), 6.52 (s, 1H, $=CH_2$), 6.56 (s, 1H, =CH), 6.86 (s, 1H, CH), 7.03 (d, 2H, $J=8.8$ Hz, Ar–H), 7.32–7.46 (m, 5H, Ar–H), 7.72 (d, 2H, $J=8.8$ Hz, Ar–H); Mass (EIMS) m/z 407 (M^+). Anal. calcd. for $C_{23}H_{21}NO_6$ C, 67.80; H, 5.20; N, 3.44. Found C, 67.92; H, 5.34; N, 3.56%.

General procedure for sodium borohydride reduction

To a solution of appropriate compound from **3a–d** (4 mmol) in methanol (5 mL) was added $NaBH_4$ (0.76 g, 8 mmol) with stirring at 0–5 °C. After 15 min. the reaction was decomposed with water and extracted with ethyl acetate (2×30 mL). The organic phase was separated and washed with brine (40 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue upon trituration with hexane furnished the pure product (**4a–d**) as solids.

2-Methyl-3-(3-phenyl-isoxazol-5-yl)-acrylic acid methyl ester (4a). 81% as white solid, mp 88–90 °C; IR (KBr) (cm^{-1}) 1714 (CO_2CH_3); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 6.73 (s, 1H, =CH), 7.52 (s, 1H, =CH), 7.72 (d, 2H, $J=8.0$ Hz, 3×Ar–H and =CH), 7.84 (m, 2H, Ar–H); mass (EIMS) m/z 243 (M^+). Anal. calcd for $C_{14}H_{13}NO_3.H_2O$ C, 64.36; H, 5.79; N, 4.83. Found C, 64.62; H, 5.55; N: 5.06%.

2-Methyl-3-(3-*p*-tolyl-isoxazol-5-yl)-acrylic acid methyl ester (4b). 84% as white solid, mp 105–106 °C; IR (KBr) (cm^{-1}) 1708 (CO_2CH_3); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, CH_3), 2.41 (s, 3H, Ar–CH_3), 3.85 (s, 3H, CH_3), 6.69 (s, 1H, =CH), 7.28 (d, 2H, $J=8.0$ Hz, Ar–H), 7.52 (s, 1H, =CH), 7.72 (d, 2H, $J=8.0$ Hz, Ar–H); mass (EIMS) m/z 206 (M^+-41). Anal. calcd for $C_{15}H_{15}NO_3$ C, 70.02; H, 5.88; N, 5.44. Found C, 70.21; H, 6.09; N, 5.35%.

3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-methyl-acrylic acid methyl ester (4c). 88% as white solid, mp 90–92 °C; IR (KBr) (cm^{-1}) 1719 (CO_2CH_3); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.90 (s, 1H, =CH), 7.49 (m, 4H, 3×Ar–H and =CH), 7.76 (m, 1H, Ar–H); mass (FABMS+) m/z 278 ($M^+ + 1$). Anal. calcd for $C_{14}H_{12}ClNO_3$ C, 60.55; H, 4.36; N, 5.04. Found C, 60.21; H, 4.29; N: 5.35%.

3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-methyl-acrylic acid methyl ester (4d). 77% as white solid, mp 128–130 °C; IR (KBr) (cm^{-1}) 1710 (CO_2CH_3); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.32 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 6.66 (s, 1H, =CH), 7.03 (d, 2H, $J=8.0$ Hz, Ar–H), 7.42 (m, 6H, 5×Ar–H and =CH), 7.76 (d, 2H, $J=8.0$ Hz, Ar–H); mass (FABMS+) m/z 350 ($M^+ + 1$). Anal. calcd for $C_{21}H_{19}NO_4$ C, 72.19; H, 5.48; N, 4.00. Found C, 71.84; H, 5.73; N: 3.67%.

General procedure for hydrolysis

To a solution of appropriate compound from **4a–d** (4 mmol) in 80% aqueous methanol (5 ml) was added KOH (0.38 g, 8 mmol) with stirring at rt. After 1 h the reaction was neutralized with cold aqueous HCl (30%) keeping the temperature of reaction mixture below 20 °C. The separated solid was isolated, dried and recrystallized from ethanol, to furnish the pure acid as colourless solid.

2-Methyl-3-(3-phenyl-isoxazol-5-yl)-acrylic acid (5a). 99.5% as white solid, mp 180–182 °C; IR (KBr) (cm^{-1}) 1685 (CO), 3445 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36 (s, 3H, CH_3), 6.78 (s, 1H, =CH), 7.48 (m, 3H, Ar–H), 7.54 (s, 1H, =CH), 7.83 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 20.6, 65.8, 99.1, 125.8, 125.9, 128.1, 128.8, 129.2, 139.2, 141.3, 161.2, 167.9, 172.6; mass (EIMS) m/z 229 (M^+). Anal. calcd for $C_{13}H_{11}NO_3$ C, 68.11; H, 4.83; N, 6.11. Found C, 67.84; H, 5.06; N, 5.82%.

2-Methyl-3-(3-*p*-tolyl-isoxazol-5-yl)-acrylic acid (5b). 98.5% as white solid, mp 204–205 °C (d); IR (KBr) (cm^{-1}) 1687 (CO), 3420 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.35 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.75 (s, 1H, =CH), 7.28 (d, 2H, $J=8.0$ Hz, Ar–H), 7.62 (s, 1H, =CH), 7.73 (d, 2H, $J=8.0$ Hz, Ar–H); mass (EIMS) m/z 243 (M^+). Anal. calcd for $C_{14}H_{13}NO_3$ C, 69.12; H, 5.38; N, 5.75. Found C, 69.35; H, 5.27; N, 5.20%.

3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-methyl-acrylic acid (5c). 99.5% as white solid, mp 155–156 °C; IR (KBr) (cm^{-1}) 1695 (CO), 3440 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.35 (s, 3H, CH_3), 6.95 (s, 1H, =CH), 7.50 (m, 3H, Ar–H), 7.65 (s, 1H, =CH), 7.77 (m, 1H, Ar–H); mass (EIMS) m/z 263 (M^+). Anal. calcd for $C_{13}H_{10}ClNO_3$ C, 59.17; H, 3.81; N, 5.30. Found C, 59.32; H, 4.06; N, 5.22%.

3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-methyl-acrylic acid (5d). 98.5% as white solid, mp 156–158 °C; IR (KBr) (cm^{-1}) 1687 (CO), 3440 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 6.66 (s, 1H, =CH), 7.07 (d, 2H, $J=8.0$ Hz, Ar–H), 7.38 (m, 5H, Ar–H), 7.54 (s, 1H, =CH), 7.74 (d, 2H, $J=8.0$ Hz, Ar–H); mass (EIMS) m/z 335 (M^+). Anal. calcd for $C_{20}H_{17}NO_4$ C, 71.63; H, 5.11; N, 4.18. Found C, 71.86; H, 5.27; N, 4.30%.

General procedure for the synthesis of amides

To a solution of appropriate compound from **5a–d** (4 mmol) in a mixture of dry dichloromethane (10 mL) and dry DMF (1 mL) and was added DIC (0.6 mL, 4 mmol) followed by HOBt (0.5 g, 4 mmol). After 25 min appropriate amine was added dropwise under stirring. The reaction was continued for 3–4 h followed by cooling of the mixture to 0 °C in ice-salt mixture. The separated solid was filtered and the filtrate was washed with 5% aqueous HCl followed by 5% sodium bicarbonate solution. The filtrate was then washed with water and the organic layer after usual work up furnished a residue that was column chromatographed on neutral alumina using hexane–ethyl acetate (3:7, v/v) as eluent to furnish the pure product as colourless solid or oil.

***N*-sec-Butyl-2-methyl-3-(3-phenyl-isoxazol-5-yl)-acrylamide (6a).** 84% as white solid, mp 130–132 °C; IR (KBr) (cm^{-1}) 1624 (CO), 3299 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (t, 3H, $J=7.4$ Hz, CH_3), 1.21 (d, 3H, $J=7.4$ Hz, CH_3), 1.62 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 4.04 (m, 1H, CH), 5.70 (brs, 1H, NH), 6.65 (s, 1H, =CH), 7.16 (s, 1H, =CH), 7.47 (m, 3H, Ar–H), 7.83 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) 10.3, 20.2, 29.5, 47.2, 103.5, 117.6, 126.7, 128.6, 128.9, 130.1, 137.4, 162.4, 167.5 ppm; mass (EIMS) m/z 284 (M^+). Anal. calcd for $C_{17}H_{20}N_2O_2$ C, 71.81; H, 7.09; N, 9.85. Found C, 72.07; H, 6.89; N, 10.14%.

***N*-*sec*-Butyl-2-methyl-3-(3-p-tolyl-isoxazol-5-yl)-acrylamide (6b).** 92.5% as white solid, mp 160–161 °C; IR (KBr) (cm^{-1}) 1622 (CO), 3276 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, 3H, $J=7.8$ Hz, CH_3), 1.20 (d, 3H, $J=6.6$ Hz, CH_3), 1.63 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.03 (m, 1H, CH), 5.69 (brd, 1H, $J=7.8$ Hz, NH), 6.63 (s, 1H, =CH), 7.08 (s, 1H, =CH), 7.28 (d, 2H, $J=8.0$ Hz, Ar–H), 7.81 (d, 2H, $J=8.0$ Hz,

Ar–H); mass (EIMS) *m/z* 298 (M^+). Anal. calcd for $C_{18}H_{22}N_2O_2$ C, 72.16; H, 7.43; N, 9.39. Found C, 72.18; H, 7.56; N, 9.14%.

***N*-*sec*-Butyl-3-[3-(2-chloro-phenyl)-isoxazol-5-yl]-2-methyl-acrylamide (6c).** 80.5% as white solid, mp 110–112 °C; IR (KBr) (cm^{-1}) 1618 (CO), 3285 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (t, 3H, *J* = 7.4 Hz, CH_3), 1.21 (d, 3H, *J* = 7.4 Hz, CH_3), 1.58 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 4.06 (m, 1H, CH), 5.75 (brd, 1H, *J* = 7.2 Hz, NH), 6.82 (s, 1H, =CH), 7.19 (s, 1H, =CH), 7.36–7.52 (m, 3H, Ar–H), 7.72–7.77 (m, 1H, Ar–H); mass (FABMS+) *m/z* 319 ($M^+ + 1$). Anal. calcd for $C_{17}H_{19}ClN_2O_2$ C, 64.06; H, 6.01; N, 8.78. Found C, 64.16; H, 6.38; N, 8.52%.

3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-*N*-*sec*-butyl-2-methyl-acrylamide (6d). 70.6% as white solid, mp 122–124 °C; IR (KBr) (cm^{-1}) 1621 (CO), 3285 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, 3H, *J* = 7.4 Hz, CH_3), 1.14 (d, 3H, *J* = 6.2 Hz, CH_3), 1.58 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 3.84 (m, 1H, CH), 5.12 (s, 2H, CH_2), 5.78 (brd, 1H, *J* = 7.2 Hz, NH), 6.66 (s, 1H, =CH), 7.08 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.17 (s, 1H, =CH), 7.40 (m, 5H, Ar–H), 7.76 (d, 2H, *J* = 8.0 Hz, Ar–H); mass (FABMS+) *m/z* 391 ($M^+ + 1$). Anal. calcd for $C_{24}H_{26}N_2O_3$ C, 73.82; H, 6.71; N, 7.17. Found C, 73.57; H, 6.81; N, 7.17%.

***N*-Benzyl-2-methyl-3-(3-phenyl-isoxazol-5-yl)-acrylamide (7a).** 90% as white solid, mp 120–121 °C; IR (KBr) (cm^{-1}) 1624 (CO), 3292 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.37 (s, 3H, CH_3), 4.58 (d, 2H, *J* = 5.6 Hz, CH_2), 6.21 (brs, 1H, NH), 6.66 (s, 1H, =CH), 7.30 (s, 1H, =CH), 7.33 (m, 5H, Ar–H), 7.46 (m, 3H, Ar–H), 7.82 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 15.1, 44.0, 103.8, 118.2, 126.7, 127.5, 127.7, 128.0, 128.5, 128.9, 130.1, 136.7, 137.8, 162.4, 167.4, 168.0; mass (EIMS) *m/z* 318 (M^+). Anal. calcd for $C_{20}H_{18}N_2O_2$ C, 75.45; H, 5.69; N, 8.79. Found C, 75.17; H, 5.87; N, 8.83%..

***N*-Benzyl-2-methyl-3-(3-p-tolyl-isoxazol-5-yl)-acrylamide (7b).** 92% as white solid, mp 148–150 °C; IR (KBr) (cm^{-1}) 1625 (CONH), 3301 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.58 (d, 2H, *J* = 5.6 Hz, CH_2), 6.22 (brs, 1H, NH), 6.63 (s, 1H, =CH), 7.29 (m, 3H, 2×Ar–H and =CH), 7.35 (m, 5H, Ar–H), 7.71 (d, 2H, *J* = 8.0 Hz, Ar–H); mass (EIMS) *m/z* 332 (M^+). Anal. calcd for $C_{21}H_{20}N_2O_2$ C, 75.88; H, 6.06; N, 8.42. Found C, 75.76; H, 6.22; N, 8.45%.

***N*-Benzyl-3-[3-(2-chloro-phenyl)-isoxazol-5-yl]-2-methyl-acrylamide (7c).** 89% as white solid, mp 130–131 °C; IR (KBr) (cm^{-1}) 1656 (CO), 3289 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36 (s, 3H, CH_3), 4.58 (d, 2H, *J* = 5.6 Hz, CH_2), 6.25 (brs, 1H, NH), 6.82 (s, 1H, =CH),), 7.41 (m, 4H, 3×Ar–H and =CH), 7.52 (m, 5H, Ar–H), 7.74 (m, 1H, Ar–H); mass (EIMS) *m/z* 352 (M^+). Anal. calcd for $C_{20}H_{17}ClN_2O_2$ C, 68.08; H, 4.85; N, 7.93. Found C, 67.97; H, 5.16; N, 7.74%.

***N*-Benzyl-3-[3-(4-benzyloxy-phenyl)-isoxazol-5-yl]-2-methyl-acrylamide (7d).** 84% as white solid, mp 140–142 °C; IR (KBr) (cm^{-1}) 1628 (CO), 3278 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.35 (s, 3H, CH_3), 4.59 (d, 2H, *J* = 4.8 Hz, CH_2), 5.12 (s, 2H, CH_2), 6.25 (brs, 1H, NH), 6.67 (s, 1H, =CH), 7.05 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.36 (m, 6H, 5×Ar–H and =CH), 7.41 (m, 5H, Ar–H), 7.74 (d, 2H, *J* = 8.0 Hz, Ar–H); mass (FABMS+) *m/z* 425 ($M^+ + 1$). Anal. calcd for $C_{27}H_{24}N_2O_3$ C, 76.39; H, 5.70; N, 6.60. Found C, 76.57; H, 5.85; N, 6.82%.

2-Methyl-*N*-nonyl-3-(3-phenyl-isoxazol-5-yl)-acrylamide (8a). 98% as white solid, mp 90–92 °C; IR (KBr) (cm^{-1}) 1614 (CO), 3296 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.29 (m, 12H, 6×CH_2), 1.58 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 3.38 (m, 2H, CH_2), 6.13 (brs, 1H, NH), 6.65 (s, 1H, =CH), 7.21 (s, 1H, =CH), 7.46 (m, 3H, Ar–H), 7.82 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 14.0, 15.1, 22.3, 22.6, 23.4, 26.9, 29.1, 29.2, 29.4, 31.8, 40.2, 41.8, 103.6, 117.8, 126.7, 128.6, 128.9, 130.1, 137.2, 157.2, 162.4, 167.6, 168.1; mass (FABMS+) *m/z* 355 ($M^+ + 1$). Anal. calcd for $C_{22}H_{30}N_2O_2$ C, 72.69; H, 8.59; N, 7.77. Found C, 72.74; H, 8.79; N, 7.57%.

2-Methyl-*N*-nonyl-3-(3-p-tolyl-isoxazol-5-yl)-acrylamide (8b). 95% as white solid, mp 118–120 °C; IR (KBr) (cm^{-1}) 1612 (CO), 3298 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.27 (m, 14H, 7×CH_2), 2.34 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.37 (m, 2H, CH_2), 6.13 (brs, 1H, NH), 6.62 (s, 1H, =CH), 7.20 (s, 1H, =CH), 7.28 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.71 (d, 2H, *J* = 8.0 Hz, Ar–H); mass (EIMS) *m/z* 368 (M^+). Anal. calcd for $C_{23}H_{32}N_2O_2$ C, 74.96; H, 8.75; N, 7.60. Found C, 74.76; H, 8.59; N, 7.70%.

3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-methyl-*N*-nonyl-acrylamide (8c). 89% as colourless oil; IR (Neat) (cm^{-1}) 1614 (CO), 3302 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.27 (m, 12H, 6×CH_2), 1.58 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 3.37 (m, 2H, CH_2), 6.01 (brs, 1H, NH), 6.82 (s, 1H, =CH), 7.21 (s, 1H, =CH), 7.45 (m, 3H, Ar–H), 7.75 (m, 1H, Ar–H); mass (FABMS+) *m/z* 389 ($M^+ + 1$). Anal. calcd for $C_{22}H_{29}ClN_2O_2$ C, 67.94; H, 7.52; N, 9.12. Found C, 67.59; H, 7.38; N, 9.12%.

3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-methyl-*N*-nonyl-acrylamide (8d). 74% as white solid, mp 135–136 °C; IR (KBr) (cm^{-1}) 1616 (CO), 3286 (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.27 (m, 12H, 6×CH_2), 1.61 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 3.32–3.42 (m, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.13 (brs, 1H, NH), 6.66 (s, 1H, =CH), 7.05 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.19 (s, 1H, =CH), 7.40 (m, 5H, Ar–H), 7.75 (d, 2H, *J* = 8.0 Hz, Ar–H); mass (FABMS+) *m/z* 461 ($M^+ + 1$). Anal. calcd for $C_{29}H_{36}N_2O_2$ C, 75.62; H, 7.88; N, 6.08. Found C, 75.76; H, 7.97; N, 5.96%.

General procedure for BH reaction with acrylamide

A mixture of appropriate compound from **1a–d** (4 mmol), DABCO (20 mol%) and acrylamide (4 mmol) in 5 mL of dioxane–water (3: 2, v/v) mixture was stirred at

rt for 5–7 h. Thereafter the reaction mixture was extracted with ethyl acetate. The usual work up of the organic layer furnished a residue that upon filtration through a small band of silica gel using hexane–ethyl acetate (4: 6, v/v) as eluent yielded the pure products as solids. The compound **9d** was obtained as colourless solid directly from the reaction mixture

2-[Hydroxy-(3-phenyl-isoxazol-5-yl)-methyl]-acrylamide (9a). 85% as white solid, mp 127–128 °C; IR (KBr) (cm^{-1}) 1625 (CO), 3386 (OH), 3200 (NH_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 4.72 (d, 1H, $J=7.4$ Hz, OH), 5.62 (d, 1H, $J=7.4$ Hz, CH), 5.78 (s, 1H $=CH_2$), 5.99 (s, 1H $=CH_2$), 6.65 (s, 1H, =CH), 7.47 (m, 3H, Ar–H), 7.79 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 103.4, 120.8, 125.8, 127.6, 128.0, 129.2, 133.2, 161.5, 166.6, 168.0; mass (FABMS+) m/z 245 ($M^+ + 1$). Anal. calcd. for $C_{13}H_{12}N_2O_3$ C, 59.53, H, 5.38; N 10.68. Found C, 59.26; H, 5.37; N, 10.48%.

2-[Hydroxy-(3-*p*-tolyl-isoxazol-5-yl)-methyl]-acrylamide (9b). 90% as white solid, mp 144–145 °C; IR (KBr) (cm^{-1}) 1624 (CO), 3382 (OH), 3200 (NH_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.38 (s, 3H, CH_3), 4.81 (s, 1H, OH), 5.63 (s, 1H, CH), 5.78 (s, 1H $=CH_2$), 6.02 (s, 1H $=CH_2$), 6.61 (s, 1H, =CH), 7.24 (d, 2H, $J=8.0$ Hz, Ar–H), 7.71 (d, 2H, $J=8.0$ Hz, Ar–H); mass (FAB+) m/z 259 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{14}N_2O_3$ C, 65.11; H, 5.46; N, 10.85. Found C, 64.99; H, 5.61; N, 10.81%.

2-{[3-(2-Chloro-phenyl)-isoxazol-5-yl]-hydroxy-methyl}-acrylamide (9c). 83% as white solid, mp 124–126 °C; IR (KBr) (cm^{-1}) 1679 (CO), 3360 (OH), 3204 (NH_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 4.72 (d, 1H, $J=7.4$ Hz, OH), 5.62 (d, 1H, $J=7.4$ Hz, CH), 5.78 (s, 1H $=CH_2$), 5.99 (s, 1H $=CH_2$), 6.65 (s, 1H, =CH), 7.46 (m, 3H, Ar–H), 7.73 (m, 1H, Ar–H); mass (FAB+) m/z 279 ($M^+ + 1$). Anal. calcd. for $C_{13}H_{11}ClN_2O_3$ C, 56.02; H, 3.97; N, 10.05. Found C, 56.05; H, 4.08; N, 10.45%.

2-{[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-hydroxy-methyl}-acrylamide (9d). 88% as white solid, mp 150–152 °C; IR (KBr) (cm^{-1}) 1625 (CO), 3390 (OH), 3201 (NH_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.10 (d, 2H, $J=8.0$ Hz, s of OCH_2 merged with d of OH), 5.69 (d, 1H, $J=6.0$ Hz, CH), 5.77 (s, 1H $=CH_2$), 6.13 (s, 1H $=CH_2$), 6.53 (s, 1H, =CH), 7.03 (d, 2H, $J=8.0$ Hz, Ar–H), 7.37 (m, 5H, Ar–H), 7.71 (d, 2H, $J=8.0$ Hz, Ar–H); mass (FAB+) m/z 359 ($M^+ + 1$). Anal. calcd for $C_{20}H_{18}N_2O_4$ C, 68.56; H, 5.18; N, 8.00. Found C, 68.81; H, 5.31; N, 7.88%.

Bioassays

Hypolipidemic. Charles Foster rats (200–225 g) bred in the animal house of the institute were divided in control, triton and triton plus drug treated groups containing six rats in each. Triton WR-1339 (Sigma, USA) was administered (200 mg/kg b. wt.) by intraperitoneal injection for 18 h. The compounds and guggulsterone were macerated with 2% aqueous gum acacia suspension and fed orally (100 mg/kg b. wt.) simultaneously with triton. At the end of the experiment, rats were fasted overnight and blood was withdrawn from retro-orbital plexus. Serum was separated by centrifugation at low speed and assayed for total cholesterol, phospholipid and triglycerides by standard procedure reported earlier.[11,16].

Antithrombotic. All the new amides were evaluated for their antithrombotic activity in vivo. Swiss mice (20–25 g, from CDRI animal colony) were used in a group of at least 10 animals each. Thrombosis was induced by infusion of a mixture of 15 μg collagen and 5 μg adrenaline in a volume of 100 μL into the tail vein of each mouse. This resulted in either death or hind limb paralysis of 100% animals. The compounds were administered at 30 μmol/kg by oral route 1 h prior to the thrombotic challenge. The antithrombotic effects of these compounds were assessed by the percentage protection offered by these agents to mice from death or paralysis following thrombotic challenge using acetylsalicyclic acid as a standard.

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