

## Design, synthesis and biological evaluation of novel bergapten derivatives as potent lipid lowering agents

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### Abstract

The aim of this study was to synthesize novel amide derivatives of bergapten and evaluate their lipid-lowering and triglyceride-lowering activities in mice. Amide derivatives of bergapten were synthesized by using lactone ring opening strategy in DMSO using NaOH as base followed by alkylation in presence of methyl iodide. The compounds were subjected to preliminary *in vivo* screening. Fenofibrate (30 mg/kg/day) was used as positive controls in this assay. The lipid lowering activity was evaluated using *in vivo* Triton model and Triton WR-1339 was used as positive control. Most of the synthesized analogs displayed remarkable plasma triglyceride-lowering activity. Compound 5 showed the best activity with (41%) triglyceride lowering activity. This compound also exhibited the most potent lipid lowering activity displaying 33, 32 and 29% lowering in total cholesterol, phospholipids, and triglycerides, respectively. The other derivatives showed almost comparable activity with that of the parent molecule.

### Introduction

Cardiovascular diseases have been the main cause of mortality since the inception mankind and the most important discoveries for its cure have come from natural products (Memon and Gilani, 1975; Lozano et al., 2012). In USA, more than half the total deaths occur due to cardiovascular complications (Witztum, 1994). Among the predominant risk factors that contribute to cardiovascular diseases; most prominent ones are high LDL-cholesterol, triglyceride and low HDL-cholesterol. For this purpose, current therapies mostly focus on lowering LDL-cholesterol and triglycerides due to various complications associated with their increase in concentration (LaRosa et al., 1999; Evans and Rees, 2002; Anwar-ul-Hassan, 1998). The potential of coumarins in general and bergapten (Figure 1) in particular has not been fully exploited in the field of treatment of cardiovascular diseases, therefore, more efforts need to be invested towards the building of their diverse libraries for better activities and lesser toxicities.

Therefore, it was thought worthwhile to carry out chemical modifications of bergapten with main focus to obtain more potent and less toxic analogs which may qualify as a potential lead compounds as cardiovascular agents. It was envisaged to synthesise a diverse amide series of 5-methoxypsoralen (bergapten) for improving its effectiveness and drug likeness.

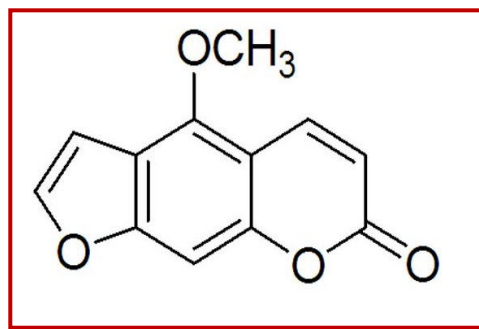


Figure 1: Molecular structure of bergapten



## Materials and Methods

All reagents used for chemical synthesis were purchased from Sigma-Aldrich. Solvents were distilled before use. All the reactions were monitored by TLC on silica gel F254 plates (E. Merck) using 2% ceric ammonium sulfate solution for detection of the spots. Column chromatography was carried out for purification of the products. All NMR spectra were recorded on Bruker DPX 200, DPX 400 and DPX 500 instruments using CDCl<sub>3</sub> as the solvent with TMS as internal standard. The chemical shifts are expressed in delta whereas coupling constants in Hertz. Mass spectra were recorded on ESI-esquire 3000 Bruker Daltonics instrument. IR recorded on FT Bruker (270-30) spectrophotometer. The purity of all the compounds was determined by RP-HPLC. Melting points of compounds were recorded on Buchi melting point apparatus B-542.

### Synthesis of (E)-3-(4,6-dimethoxybenzofuran-5-yl) acrylic acid **2** (Scheme 1)

To a solution of bergapten (**1**) (1 g, 1 eq.) in DMSO (10 mL), crushed NaOH pellets (1.5 g, 1.5 eq.) were added and stirred for 30-40 min at 25 °C. Solution of propargyl bromide (1.1 mL, 1 eq.) in DMSO was then added slowly to the mixture and the suspension was stirred for 2-3 hours. Progress of reaction was monitored using TLC at regular intervals. After the completion of reaction, the reaction mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic layer was dried over sodium sulphate and purified through column chromatography to give pure product **2** in 95% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.81 (3H, s), 3.89 (3H, s), 6.29 (1H, d, J=16Hz), 6.86 (1H, d, J=2.28 Hz), 7.09 (1H, s), 7.44 (1H, d, J=2.65 Hz), 6.29 (1H, d, J=15.55 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 56.33, 60.65, 93.82, 105.66, 112.53, 116.54, 123.36, 135.23, 146.77, 152.57, 156.57, 157.35, 169.01; IR (KBr) max<sup>cm-1</sup>: 2941, 1682, 1608, 1593, 1486, 1384, 1366, 1314, 1266, 1162, ESI-MS (m/z): 249.07 (M+ H)<sup>+</sup>.

### General procedure for synthesis of amide derivatives (**3-10**)

Thionyl chloride (1.2 eq.) freshly prepared was added to compound **2** dissolved in DCM, and the contents were refluxed for 1 hour under nitrogen conditions. Then the contents concentrated on rotavapor and reconstituted in DCM (10 mL). To this, appropriate amines (1 eq.) were added using dry DCM as solvent, and the contents were stirred for 1 hour. Progress of reaction was monitored using TLC at regular intervals. After the completion of reaction, the reaction mixture was extracted with DCM (3 × 30 mL) and the combined organic layer was dried over sodium sulphate and purified through column chromatography to give pure amides (**3-10**) in excellent yields of 90-95%.

### 4-methoxy-7H-furo [3, 2-g] chromen-7-one **1**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.91 (3H, s), 6.26 (1H, d, J=9.45 Hz), 6.93 (1H, d, J=2.21 Hz), 7.09 (1H, s), 7.61 (1H, d, J=2.67 Hz), 7.99 (1H, d, J=9.50 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 59.6, 105.6, 114.7, 118.5, 121.2, 125.6, 130.3, 142.1, 145.2, 146.4, 147.3, 160.0. IR (KBr) max<sup>cm-1</sup>: 1717, 1607, 1500, 1495, 1385, 1365; ESI-MS (m/z): 217.06 (M+ H)<sup>+</sup>.

### (E)-3-(4, 6-dimethoxybenzofuran-5-yl) acrylic acid: **2**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.81 (3H, s), 3.89 (3H, s), 6.29 (1H, d, J=16Hz), 6.86 (1H, d, J=2.28 Hz), 7.09 (1H, s), 7.44 (1H, d, J=2.65 Hz), 6.29 (1H, d, J=15.55 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 56.33, 60.65, 93.82, 105.66, 112.53, 116.54, 123.36, 135.23, 146.77, 152.57, 156.57, 157.35, 169.01; IR (KBr) max<sup>cm-1</sup>: 2941, 1682, 1608, 1593, 1486, 1384, 1366, 1314, 1266, 1162, ESI-MS (m/z): 249.07 (M+ H)<sup>+</sup>.

### (E)-3-(4, 6-dimethoxybenzofuran-5-yl)-1-(piperidin-1-yl) prop-2-en-1-one: **3**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.65 - 1.78 (m, 6H), 3.36 - 3.40 (m, 4H), 3.79 (3H, s), 3.87 (3H, s), 6.69 (1H, d, J=16.04Hz), 7.02 (1H, d, J=2.28 Hz), 7.09 (1H, s), 7.49 (1H, d, J=2.30 Hz), 7.68 (1H, d, J=15.75 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 23.42, 24.78, 24.99, 45.20, 45.59, 56.79, 60.45, 92.82, 105.66, 112.53, 116.54, 123.44, 140.43, 146.77, 153.43, 155.57, 157.75, 168.89; IR (KBr) max<sup>cm-1</sup>: 2915, 2851, 1731, 1637, 1595, 1485, 1443, 1381, 1362, 1091, 1022; ESI-MS (m/z): 316.17 (M+ H)<sup>+</sup>.

### (E)-3-(4,6-dimethoxybenzofuran-5-yl)-N-p-tolylacrylamide: **4**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.33 (s, 3H), 3.80 (3H, s), 3.84 (3H, s), 6.31 (1H, d, J=16.03Hz), 6.67 (1H, d, J=2.34 Hz), 6.98 (1H, s), 7.20 (2H, d, J=8.06 Hz), 7.38 (2H, d, J=7.79 Hz), 7.59 (1H, d, J=2.64 Hz), 7.74 (1H, d, J=15.95 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 21.13, 57.79, 60.65, 88.82, 104.43, 110.47, 116.54, 119.70, 120.08, 129.74, 134.10, 136.37, 138.86, 146.77, 152.57, 156.57, 157.65, 167.89; IR (KBr) max<sup>cm-1</sup>: 2925, 1660, 1605, 1562, 1490, 1442, 1386, 1278, 1248, 1160, 1088, 1026, 830; ESI-MS (m/z): 338.15 (M+ H)<sup>+</sup>.

### (E)-3-(4,6-dimethoxybenzofuran-5-yl)-N-(4-methoxyphenyl) acrylamide: **5**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.79 (s, 3H), 3.83 (3H, s), 3.88 (3H, s), 6.65 (1H, d, J=16.68Hz), 6.66 (1H, d, J=2.59 Hz), 6.87 (1H, s), 6.95 (2H, d, J=8.24 Hz), 7.40 (2H, d, J=8.81 Hz), 7.47 (1H, d, J=2.95Hz), 8.12 (1H, d, J=16.75 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 56.04, 56.79, 60.65, 93.82, 106.66, 112.57, 114.59, 116.54, 120.08, 122.37, 131.19, 138.86, 146.77, 152.57, 156.57, 156.78, 157.35, 166.56; IR (KBr) max<sup>cm-1</sup>: 2935, 2837, 1681, 1620, 1593, 1485, 1462, 1365, 1273, 1247, 1170, 1090; ESI-MS (m/z): 354.12 (M+ H)<sup>+</sup>.

**(E)-3-(4,6-dimethoxybenzofuran-5-yl)-N-phenylacrylamide: 6**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.84 (s, 3H), 3.86 (3H, s), 6.66 (1H, d, J=2.65 Hz), 6.78 (1H, d, J=15.92 Hz), 6.86 (1H, s), 7.01 (1H, m), 7.33 (2H, m), 7.43 (2H, m), 7.45 (1H, d, J=2.78 Hz), 7.97 (1H, d, J=16.05 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 56.79, 59.65, 93.82, 106.66, 112.53, 116.54, 120.08, 121.97, 124.36, 129.14, 137.27, 138.86, 146.77, 152.57, 156.35, 157.95, 166.66; IR (KBr) max<sup>cm-1</sup>: 2998, 2793, 1741, 1617, 1555, 1542, 1497, 1403, 1384, 1366; ESI-MS (m/z): 324.13 (M+ H)<sup>+</sup>.

**(E)-N,N-diisopropyl-3-(4,6-dimethoxybenzofuran-5-yl)acrylamide: 7:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.34 (12H, bs), 3.81 (s, 3H), 3.84 (3H, s), 4.25 (2H, m), 6.70 (1H, d, J=16.12 Hz), 7.01 (1H, s), 7.04 (1H, d, J=2.83 Hz), 7.55 (1H, d, J=16.05 Hz), 7.66 (1H, d, J=2.78 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 21.07, 47.86, 56.10, 56.37, 93.82, 106.42, 112.25, 117.28, 125.34, 142.63, 146.77, 152.57, 156.25, 157.40, 168.36; IR (KBr) max<sup>cm-1</sup>: 2966, 2928, 1732, 1641, 1607, 1484, 1440, 1386, 1373, 1335, 1300, 1270, 1251, 1211, 1161, 1117, 1045, 989; ESI-MS (m/z): 332.15 (M+ H)<sup>+</sup>.

**(E)-N-isobutyl-3-(4,6-dimethoxybenzofuran-5-yl)acrylamide: 8:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.95 (6H, d, J= 6.65 Hz), 2.71(m,1H), 3.21 (2H, d, J= 6.35 Hz), 3.79 (s, 3H), 3.82 (3H, s), 6.36 (1H, d, J=16.81Hz), 6.66 (1H, d, J=2.23 Hz), 6.97 (1H, s), 7.27 (1H, d, J=16.65 Hz), 7.59 (1H, d, J=2.38Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 20.10, 28.18, 48.54, 56.79, 59.65, 94.02, 107.02, 112.53, 116.54, 120.94, 144.30, 147.17, 153.17, 157.15, 158.03, 168.88; IR (KBr) max<sup>cm-1</sup>: 2959, 2871, 1650, 1614, 1594, 1556, 1485, 1386, 1364, 1337, 1272, 1255, 1180, 1170, 1020, 990; ESI-MS (m/z): 304.15 (M+ H)<sup>+</sup>.

**(E)-3-(4,6-dimethoxybenzofuran-5-yl)-N-(3-methoxyphenyl)acrylamide: 9:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.73 (s, 3H), 3.81 (3H, s), 3.84 (3H, s), 6.35 (1H, d, J=16.13Hz), 6.66 (1H, d, J=2.59 Hz), 6.69 (1H, m), 6.93 (1H, m), 6.97 (1H, s), 7.23-7.31 (2H, m), 7.60 (1H, d, J=2.95Hz), 7.65 (1H, d, J=16.75 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 56.14, 57.32, 59.34, 93.82, 105.16, 109.99, 112.53, 114.84, 116.54, 120.08, 129.47, 138.86, 139.25, 146.57, 153.57, 156.17, 157.35, 160.43, 166.56; IR (KBr) max<sup>cm-1</sup>: 2964, 2867, 1651, 1620, 1593, 1462, 1365, 1247, 1170, 1090; ESI-MS (m/z): 354.12 (M+ H)<sup>+</sup>.

**(E)-3-(4,6-dimethoxybenzofuran-5-yl)-N-(2-methoxyphenyl)acrylamide: 10:**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.79 (s, 3H), 3.84 (3H, s), 3.86 (3H, s), 6.65 (1H, d, J=2.35 Hz), 6.76 (1H, d, J=15.93Hz), 6.86 (1H, s), 6.95-7.06 (3H, m), 7.45 (1H, d, J=2.36Hz), 7.55 (1H, m), 7.96 (1H, d, J=16.05 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 56.79, 60.64, 93.82, 105.66,

112.50, 116.54, 120.08, 121.37, 122.52, 125.59, 129.08, 138.16, 146.77, 148.95, 152.57, 156.57, 157.35, 167.09; IR (KBr) max<sup>cm-1</sup>: 2977, 2887, 1681, 1620, 1593, 1462, 1365, 1273, 1247, 1170, 1090; ESI-MS (m/z): 354.12 (M+ H)<sup>+</sup>.

***In vivo plasma triglyceride lowering activity***

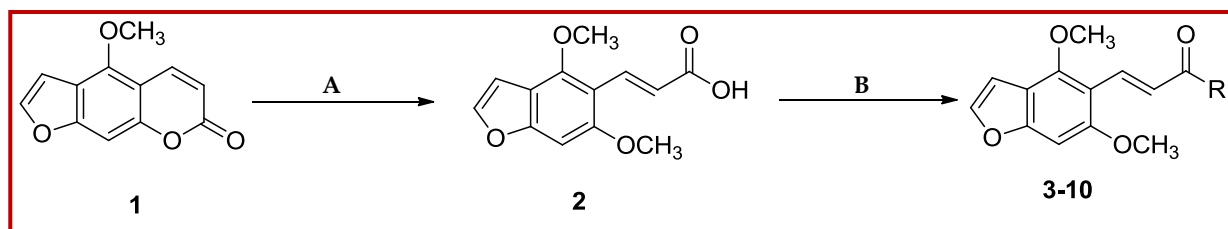
An inbred colony of moderately hypertriglycerimic Swiss Albino mice (SAM) of 20-28 g body weight, have been employ-ed for screening the compounds. Animals (5 per group) were treated orally with 3 mg/kg/day for 6 days. The control animals were treated with the vehicle (0.25% carboxymethyl cellulose, 3 mL/kg) only. Animals were bled through retro orbital sinus on day-1 and day-6 of the experiment. Plasma samples were prepared and triglyceride levels were measured by using a commercial kit (Pointe Scientific, USA). The percent reduction of triglycerides was calculated by the standard method published previously (Reddy et al., 1999). The animals were maintained in accordance with the U.S. National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication 80-23, revised 1996) and all procedures were approved by the Ethical Committee of the General Hospital of Chengdu Military Region.

***In vivo lipid lowering activity***

Adult male Charles Foster rats (200-225 g) bred in the institutional animal house of were used for the lipid lowering activity. Rats were divided in control, triton induced, triton plus com-pounds and gemfibrozil (100 mg/kg) treated groups containing six rats in each. Hyperlipidemia was developed by administration of triton WR-1339 (Sigma chemical Co., St. Louis, USA) at a dose of 400 mg/kg body wt. intraperitoneally to animals of all groups except the control. Compounds **1-10** were macerated with gum acacia (0.2% w/v), suspended in water and fed simultaneously with triton at a dose of 100 mg/kg p.o. to the animals of treated groups. Animals of the control and triton group without treatment with test compounds were given same amount of gum acacia suspension (vehicle). After 18 hours of treatment (50 mg/kg) 1.0 mL blood was withdrawn from retro-orbital sinus using glass capillary in EDTA coated eppendorf tube (3.0 mg/mL blood). The blood was centrifuged (at 2,500 xg) at 4°C for 10 min and the plasma was separated. Plasma was diluted with normal saline (ratio 1:3) and used for analysis of total cholesterol, phospholipids, triglycerides and post heparin lipolytic activity (PHLA) using spectrophotometer, Beckmann auto-analyzer and standard kits purchased from Beckmann Coulter International, USA.

**Results**

Initially, 5-methoxy psoralen (bergapten) **1** as starting material was subjected to lactone ring opening in



Scheme 1: Reagents and conditions: (A) aq. NaOH/DMSO, CH<sub>3</sub>I, rt, 2 hours (B) SOCl<sub>2</sub>/DCM, reflux, amines

DMSO using NaOH as base yielding a *trans* (E) product which simultaneously undergoes alkylation at OH group in presence of methyl iodide to form *trans* (E)-3-(4,6-dimethoxybenzofuran-5-yl)acrylic acid **2**. The proposed structure (**2**) was confirmed by spectral data analysis. The *trans* (E) behaviour of the protons of  $\alpha$ ,  $\beta$ -unsaturated system was depicted by the presence of two doublets at  $\delta$  6.29 and 7.81 with the coupling constant (*J*) of 16.04 Hz each. Compound **2** under reflux conditions was allowed to react with thionyl chloride in DCM (i.e. conversion of acid to acid chloride) and the contents concentrated on rotavapor and *in situ* appropriate addition of various amines in DCM under dry conditions resulting in the formation of different amides (**3-10**) in good to excellent yields (Scheme 1).

The target compounds **3-10** were synthesized as depicted in (Scheme 1). This work provides the initial report on structure activity relationship of lactone ring opened bergapten (**1**).

Moderately hypertriglycerimic Swiss Albino Mice (SAM) weighing 20-28 g were used to screen the newly synthesized amide derivatives of bergapten. Animals (5 per group) were treated orally with 3 mg/kg/day of analogs for 6 days. The control animals were treated with the vehicle (0.25% carboxymethyl cellulose, 3 mL/kg) only. Animals were bled through retro orbital sinus on day 1 and day 6 of the experiment. Plasma samples were prepared and triglyceride levels were measured by using a commercial kit (Pointe Scientific, USA). The standard method (Reddy et al., 1999) used for calculation of percentage in the reduction of triglycerides was applied. Fenofibrate (30 mg/kg/day) was used as positive controls in this assay.

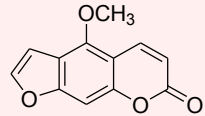
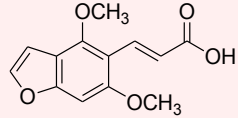

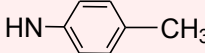
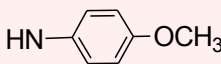
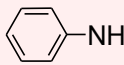
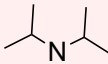
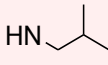
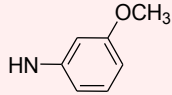
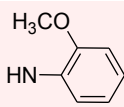
The results indicate that the parent molecule, bergapten (**1**) has moderate plasma triglyceride lowering activity, while as, its ring opened product (**2**) exhibited more than two fold increase in its activity. Most of the synthesized analogs displayed significant plasma triglyceride lowering activity. All the synthesised analogs were screened for plasma triglyceride lowering activity at 3 mg/kg oral dose as shown in Table I. Among all the tested analogs, compound **5** displayed the best activity with overall triglyceride lowering activity of 41%. Compound **4** also showed good (32%) triglyceride lowering activity. Other derivatives displayed moderate plasma triglyceride lowering activity (Table I). As

far as the structural features are concerned, these results demonstrate that the compounds bearing electron donating groups at para position in phenyl group of R moiety have effective triglyceride lowering efficiency. The compound bearing para methoxyphenyl moiety in the R group (**5**) showed the best activity, while as, the analogs bearing ortho (**10**) and meta methoxyphenyl (**9**) moieties in the R group were less active as compared to **5**. Additionally, the compound bearing para methylphenyl moiety in the R group (**4**) also displayed appreciable activity. The compounds bearing phenyl moiety in the R group seem to be essential for attaining the better activity, while as, the compounds bearing isobutyl, piperidyl and diisopropyl groups in R moieties were totally inactive towards lowering the triglyceride levels. From the above results, we come to the conclusion that it is not only the effect of a particular group (electron donating moieties) but also its position plays a significant role on the triglyceride lowering activity.

The lipid lowering activity of bergapten analogs (**2-10**) was evaluated using *in vivo* Triton model (Table II) (Deeg and Ziegehorn, 1983). Introduction of Triton WR-1339 in rats induced appreciable hyperlipidemia by increasing the plasma level of total cholesterol (2.75-fold), phospholipids (3.0-fold) and triglyceride (3.35-fold). Upon treatment with the synthesised analogs at the dose of 100 mg/kg po, the plasma lipid levels of hyperlipidemic rats got reversed to a large extent. Bergapten **1** displayed moderate lipid lowering activity, while as, its derivatives exhibited interesting lipid lowering activity. Among these analogs, compound **4** significantly lowered the total cholesterol, phospholipids, and triglycerides by 24, 26 and 25% respectively. However compound **5** exhibited the most potent activity displaying 33, 32, and 29% lowering in total cholesterol, phospholipids, and triglycerides, respectively. The compounds **6**, **9** and **10** showed mild activity, while as, compounds **3**, **7** and **8** were inactive towards lowering the plasma total cholesterol, phospholipids and triglycerides levels.

## Discussion

The results indicate that the compound **5** has comparable activity with that of the standard drug gemfibrozil

Table I			
Physical and biological data of bergapten derivatives			
Entry	SM/R	M. P. °C	<sup>a</sup> Triglycerides
1		187	5 ± 2
2		181	11 ± 2
3		152	NE
4		161	32 ± 1
5		167	41 ± 1
6		155	25 ± 2
7		145	NE
8		160	NE
9		171	14 ± 2
10		168	27 ± 2
11	Fenofibrate		36 (at 30 mg/kg)

SM= Starting material (1) and intermediate (2); <sup>a</sup>Triglyceride lowering activity (%). Test compounds were administered at 3 mg/kg for 6 days; NE = Not effective

at the dose of 100 mg/kg. These observations also indicate that para methoxyphenyl moiety in compound 5 is essential for obtaining better activity, while as, paramethylphenyl moiety in compound 4 also enhances the activity significantly. The compounds bearing isobutyl, piperidyl and diisopropyl groups in R moieties were again inactive towards lowering the plasma lipid levels. From the above results, we come to the conclusion that it is not only the effect of a particular group (electron donating moieties) but also its position plays a significant role in achieving the better activity. The study revealed that such bergapten derived analogs

Table II			
Lipid lowering activity of novel bergapten analogs (100 mg/kg) in triton treated hyperlipidemic rats			
Entry	Total cholesterol	Phospholipids	Triglycerides
	%Decrease		
1	11	9	6
2	14	10	7
3	NE	NE	NE
4	24	26	25
5	33	32	29
6	20	18	15
7	NE	NE	NE
8	NE	NE	NE
9	13	11	7
10	24	22	18
Gem-fibrozil	36	35	31

Test compounds were administered at 100 mg/kg; NE = Not effective

might result in identification of new lead compounds for the development of novel lipid lowering agents for the treatment of cardiovascular diseases.

In conclusion, the current study seems to be the first report involving design and synthesis of novel amide derivatives of bergapten and their plasma triglyceride lowering activity and lipid lowering activity.

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