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Flavone-Based Novel Antidiabetic and Antidyslipidemic Agents

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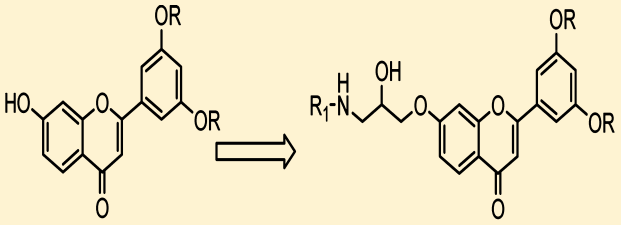
Divisions of [†]Medicinal & Process Chemistry, [‡]Biochemistry, [§]Pharmaceutics, [∥]Pharmacokinetics & Pharmacodynamics, [⊥]Biometry & Statistics and [#]Pharmacology, Central Drug Research Institute (CSIR), Lucknow−226001, India

Supporting Information

ABSTRACT: The hybrid congeners **62**−**90** of 6- and 7-hydroxyflavones with aminopropanol have been synthesized and evaluated for their antidiabetic activity in sucrose-challenged low-dosed streptozotocin (STZ)-induced diabetic rats and *db/db* mice. The optical enantiomers **70a**, **70b**, **90a**, and **90b** of two congeners **70** and **90** exhibiting consistent antidiabetic and antidyslipidemic activities were also prepared, and their antidiabetic activity results indicate its association mainly with S isomers. These compounds also lower cholesterol and TG profiles while improving high-density lipoprotein cholesterol to CHOL ratio in *db/db* mice. The bioavailability of compound **70** and its isomer varies between 27 and 29% whereas that of the more polar compound **90a** is poor as determined in rat by oral and intraperitoneal administrations.



70; R= CH_2Ph, R_1= *tert*-Butyl

90; R=H, R_1= *iso*-Propyl

INTRODUCTION

The sedentary lifestyle and energy-rich diet in the present industrialized world is aggressively contributing to a staggering increase in obesity resulting in insulin resistance. As a result, there is a steady increase in the pathogenesis of type 2 diabetes.[1] Prolonged obesity leads to atherogenicity, whereas diabetes manifests into chronic macrovascular complications such as retinopathy and nephropathy. The majority of previous antiobesity drugs are targeted toward reduction of energy intake (anorectic drugs) whereas antidiabetic drugs rely on either an increase in insulin secretion from pancreatic β-cells by sulphonylureas (e.g., glibenclamide[2]), an enhancement of insulin action by PPAR-γ (peroxisome proliferator activated receptor-γ) agonists[3] (e.g., rosiglitazone), or a reduction of hepatic glucose production (metformin).[4] The current pharmacological option for the treatment of obesity is to increase energy expenditure (thermogenic drugs) by two major hormonal effectors: β-adrenergic agents and thyroid hormone.[5] In the early 1980s, a third β-adrenoceptor (β_3-adrenoceptor) was discovered in rodents. The stimulation of this was found to be associated with marked weight loss as well as antidiabetic properties, mainly by increasing energy expenditure.[6,7] The dual actions of antiobesity and antidiabetic properties make such agonists an attractive choice for the development of drugs with this new mechanism.

Since the discovery of the thermogenic property of the β_3-adrenergic stimulatory mechanism, several highly selective noncatecholic agonists of dual actions, e.g., of phenethanolamine and phenoxypropanolamine series (Figure 1), were discovered. These agents, however, failed in clinical trials mainly because of the lack of favorable pharmacokinetic property.[8] It therefore emphasizes the need for structural improvements in this class of agents. Of the three most potent compounds shown here, **1** and **2** have the aromatic ring attached with the basic pharmacophore but the rings themselves are biologically nonfunctional. Also the presence of 1,4-substitution patterns present in compounds **1** and **3** is generally not preferred in druggable molecules. The compound **3** has a carbazole moiety in place of phenyl, which is biologically functional and present in druglike molecules such as carvedilol.[9] Flavonoids are among the most ubiquitous groups of polyphenolic compounds in foods of plant origin and exhibit biological activities through free radical scavenging.[10] These properties of flavones led us to utilize them for the synthesis of their hybrids with oxypropanolamine moiety and evaluation of their antidiabetic and antidyslipidemic activities in animal models, as well as their pharmacokinetic and pharmacodynamic properties.

RESULTS AND DISCUSSION

Chemistry. The synthesis of 3-amino-2-hydroxypropoxyflavones from hydroxylflavones is outlined in Scheme 1. The hydroxylflavones were prepared by intramolecular cyclization of *o*-hydroxyphenyl-β-diketone, and the latter were prepared from *o*-hydroxyacetophenone and ethylbenzoate following the Cushman and Nagarathnam procedure.[11] Thus 2,4-dihydoxyacetophenone (**4**) or 2,5-dihydroxyacetophenone (**5**) (utilized as a template of ring A) was treated with an excess of lithium

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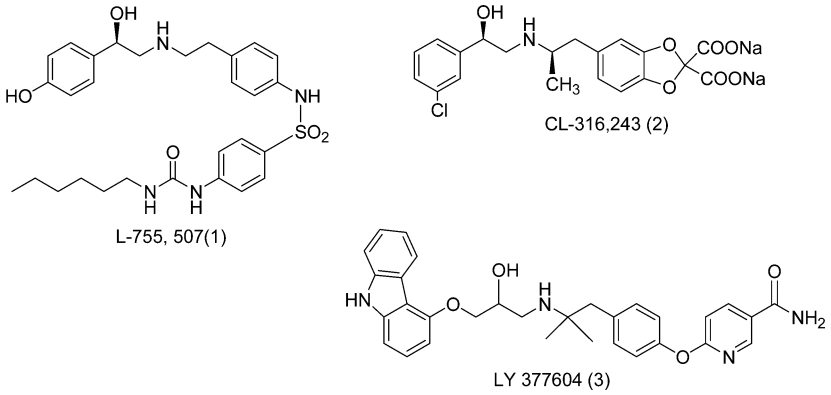
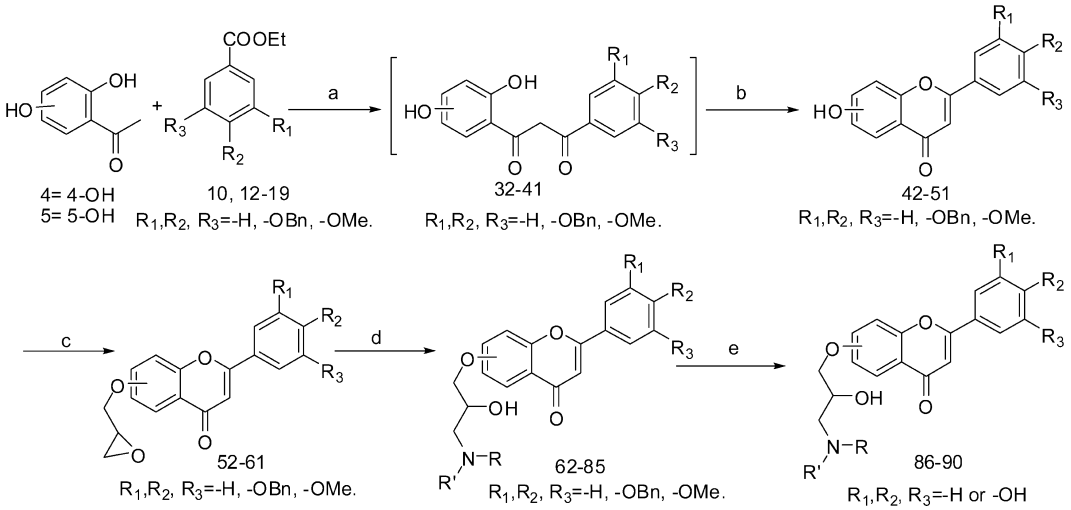


Figure 1. Some thermogenic activators in clinical trials.

Scheme 1. Representative Synthetic Route of 3-Amino-2-hydroxypropoxyflavones[a]

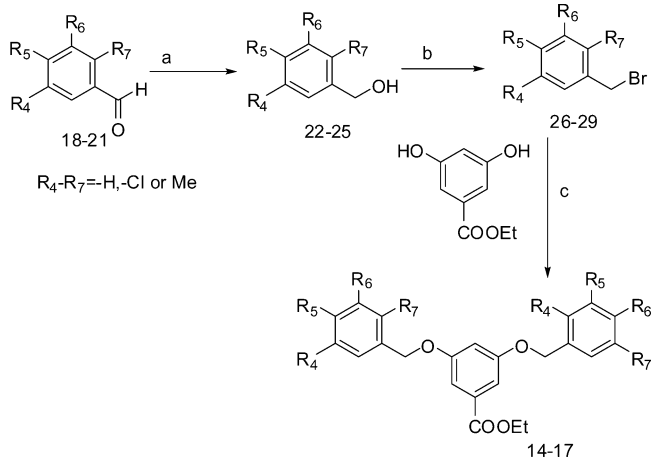


[a]Reagents and conditions: (a) LiHMDS, tetrahydrofuran (THF), −78 °C; (b) Dowex-H^+, 2-propanol, reflux; (c) epichlorohydrin, NaH, DMF, room temperature (r.t.) or K_2CO_3, 110 °C; (d) amine, methanol, reflux; (e) H_2−Pd/C, methanol.

bis(trimethylsilyl)amide (LiHMDS) at −78 °C to generate a polylithiated anionic intermediate that reacted with ester **10** or **12**−**19**, resulting in the intermediate *β*-diketones **32**−**41**.[12] The preparation of ethyl benzoates **16**−**19** having substitution in the benzyloxy groups is given in Scheme 2. The additional benzyl bromides **28**−**31** used in the protection of hydroxy groups of ethyl-3,5-dihydroxybenzoate (**11**) were prepared from the corresponding benzaldehydes. The *β*-diketones **32**−**41** were cyclized to flavones **42**−**51** using Dowex H^+ in isopropanol. The hydroxylflavones **42**−**47** on treatment with epichlorohydrin in the presence of NaH in dry DMF yielded epoxyflavones **52**−**57**, and heating of flavones **48**−**51** with epichlorohydrin and anhydrous K_2CO_3 in DMF afforded epoxyflavones **58**−**61**. The resulting epoxyflavones **52**−**61** on treatment with an appropriate amine under reflux yielded desired compounds **62**−**85**. The debenzylation of **62**−**64**, **70**, and **71** was done with Pd−C under H_2 atmosphere to obtain flavones **86**−**90**.

For the synthesis of optical enantiomers, a different protocol used in the synthesis of Atenolol starting with optically active epichlorohydrin was followed.[13] 7-Hydroxyflavone **46** was heated at ∼120 °C with either *R*- or *S*-enantiomers of epichlorohydrin to give chlorohydrin intermediates **91a** and **91b**, which were then cyclized under basic conditions to provide epoxyflavones **56a** and **56b** with inversion of stereochemistry

Scheme 2. Representative Synthetic Route *O*-Benzylated Benzoic Acid Esters[a]



[a]Reagents and conditions: (a) $NaBH_4$, methanol; (b) PBr_3, benzene, 80 °C; (c) K_2CO_3, acetone, NaI, 70 °C.

(Scheme 3). The optically active *S*- or *R*-isomer of epoxides were refluxed with suitable amines to give aminocarbinols **70a**, **70b**, **71a**, and **71b**, retaining the epoxide's configuration. The

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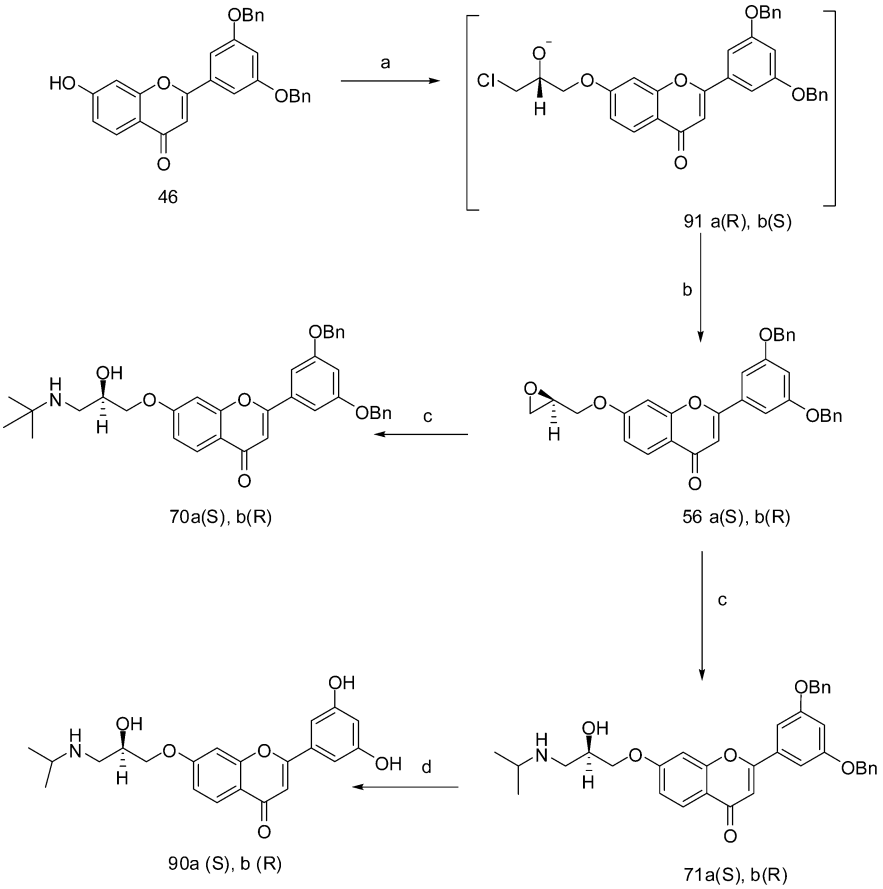
Scheme 3. Synthetic Route for Optical Enantiomers of 3-Amino-2-hydroxypropoxyflavones[a]



[a]Reagent and conditions: (a) *R*-epichlorohydrin or *S*-epichlorohydrin, 110 °C; (b) aq. NaOH, toluene, triethylbenzylammonium chloride; (c) *tert*-butylamine or isopropylamine, methanol, reflux; (d) 10% Pd−C, H_2.

debenzylation of **71a** and **71b** was performed as in the case of racemic compound to obtain compounds **90a** and **90b**. All the purified optically active enantiomers were checked for their purity on HPLC column.

Biological Screening. The compounds synthesized above were tested for their antihyperglycemic and antidyslipidemic effects. The antihyperglycemic activity was evaluated in artificially enhanced blood glucose in albino rats called sucrose-loaded model (SLM) followed by in sucrose-challenged streptozotocin (STZ-S)-induced pancreatic β-cell damaged diabetic rats and finally in C57BL/KsJ-*db*/*db* mice models. These compounds were also simultaneously evaluated for antidyslipidemic effects in triton-induced dyslipidemic male *Wistar*, rats and the activity of the best compounds was then confirmed in a high-fructose and -fat diet (HFD)-fed hamster model. The flavone derivatives **70**, **90**, and their enantiomers found to be effective in repetitive studies were followed for ED_{50} dose estimation and pharmacokinetic behaviors.

The compounds **70**, **72**, **78**, **81**, **82**, **84**, **85**, and **90** showed ∼29.4, 34.6, 39.1, 51.6, 32.0, 25.9, 32.7, and 29.0% antihyperglycemic activity in SLM rat model, respectively, and compounds **63**, **64**, **65**, **68**, **83**, and **89** exhibited a moderate activity of ∼15.9, 17.9, 23.9, 20.7, 15.7, and 19.1%, respectively. The rest of the molecules were inefficient in the lowering of blood glucose in sucrose-loaded rats. These encouraging results led us to further verify the results in a secondary antidiabetic animal model of streptozotocin-induced diabetic rats.

Some of the compounds that had promising antihyperglycemic activity are **68**, **70**, **78**, **81**, **82**, **85**, and **90**, which exhibited sugar lowering to the extent of ∼17.4, 21.6, 23.2, 22.8, 26.2, 22.1, and 26.9%, respectively, at 5 h post-treatment with the compounds and ∼19.1, 28.7, 17.2, 11.9, 17.9, 16.2, and 13.2%, respectively, at 24 h post treatment in STZ-S rat model. The marked antihyperglycemic activity at 24 h in these diabetic rats showed that these compounds are efficient in the lowering of blood glucose until 24 h. Compounds **63**, **64**, **65**, **72**, **83**, and **84** exhibited a lowering of ∼11.8, 12.4, 13.8, 14.3, 12.2, and 14.2%, respectively, and thus had marked lowering of blood glucose at 5 h but not at 24 h in the STZ-S rat model. The rest of the compounds were less efficient in the lowering of blood glucose in the aforementioned model. Therefore, compounds **70**, **78**, **81**, **82**, **85**, and **90** were identified as potent blood-glucose-lowering agents in SLM as well as in STZ-S rat model. From a structure−activity relationship (SAR) point of view, these active compounds possess bulky lipophilic substitution on the B ring of flavones as indicated by **70** and **76**−**85** and no bulky attachments at the nitrogen atom. The compounds with *tert*-butyl- and isopropylamine functionality are superior in activity. On the contrary, the molecules reported in the literature (Figure 1) in general had bulky substitution at the amino functionality. Further, the oxygen atoms at the 1,3-positions in the B ring (compounds **70** and **90**) seem necessary because the compounds **86**−**88** with oxygen atoms at the 1,2-positions exhibited inferior activity.

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Table 1. 3-Amino-2-hydroxypropoxyflavones and Their Antidiabetic and Antidyslipidemic Activity

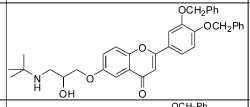
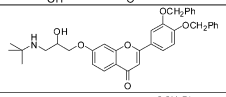
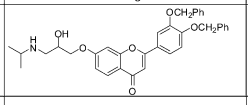
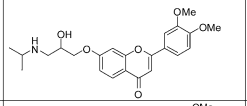
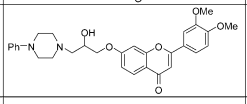
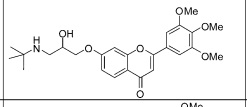
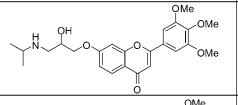
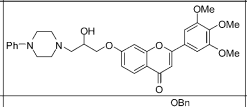
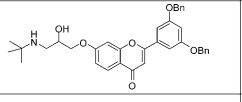
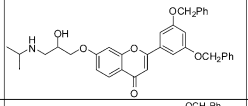
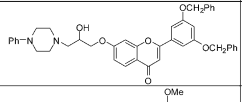
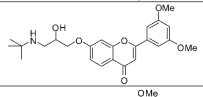
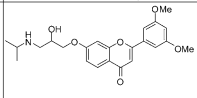
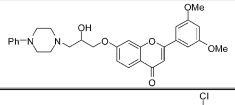
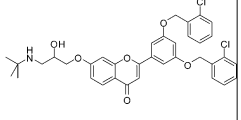
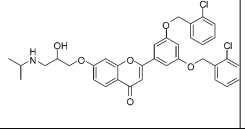
Compound No.	Structure of the compound	% Fall of blood glucose levels[a]			% Fall in lipid profile[b]		
		SLM	STZ-S				
			5 h	24 h	TG	CHOL	PL
62		21.8	14.9	0.36	17.0	21.0	12.0
63		15.9	11.8	0.89	16.0	23.0	12.0
64		17.9	12.4	2.34	14.0	16.0	05.0
65		23.9	13.8	6.83	ND	ND	ND
66		5.45	4.35	2.34	19.0	23.0	22.0
67		Nil	ND	ND	28.0	24.0	26.0
68		20.7	17.4	19.1	19.0	18.0	16.0
69		5.64	2.36	0.24	23.0	19.0	8.0
70		29.4	21.6**	28.7**	9.0	21.0	18.0
71		Nil	7.86	2.23	11.0	13.0	08.0
72		34.6	14.3	2.46	17.0	24.0	21.0
73		Nil	4.86	2.36	17.0	21.0	19.0
74		1.36	Nil	Nil	24.0	17.0	21.0
75		Nil	ND	ND	17.3	14.3	12.8
76		14.8	7.48	Nil	18.7	12.5	11.3
77		12.6	6.83	Nil	30.2	12.1	20.2

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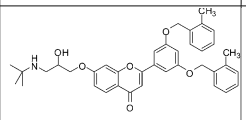
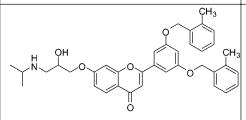
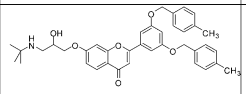
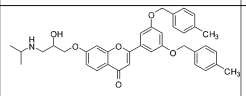
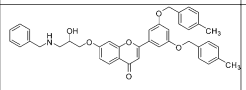
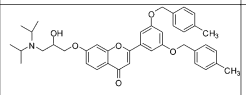
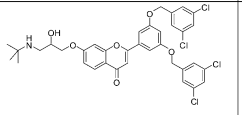
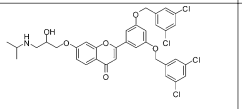
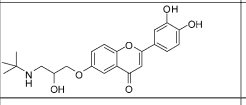
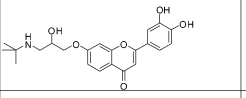
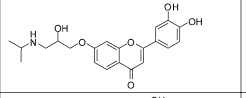
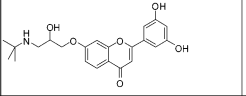
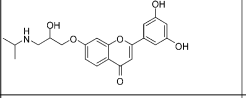
Table 1. continued

Compound No.	Structure of the compound	% Fall of blood glucose levels[a]			% Fall in lipid profile[b]		
		SLM	STZ-S				
			5 h	24 h	TG	CHOL	PL
78		39.1	23.2	17.2	28.2	22.3	12.6
79		4.65	ND	ND	26.2	13.5	24.1
80		13.6	ND	ND	12.8	11.2	16.2
81		51.6	22.8	11.9	25.6	20.3	26.5
82		32.0	26.2	17.9	27.2	16.5	20.8
83		15.7	12.2	Nil	12.1	10.1	4.67
84		25.9	14.2	Nil	11.3	8.93	12.2
85		32.7	22.1	16.2	26.0	22.2	11.8
86		4.96	Nil	Nil	25.0	24.0	23.0
87		Nil	ND	ND	25.0	21.0	23.0
88		Nil	ND	ND	19.0	15.0	13.0
89		19.1	ND	ND	16.0	17.0	04.0
90		29.0	26.9**	13.2*	32.0*	32.0*	28.0*
	Metformin	22.1*	24.3*	19.4*	5.9	4.2	6.2
	Fenofibrate	6.43	1.47	Nil	32.9*	18.9*	30.3*

[a]SLM and STZ experiments were performed using rats of *Wistar* and *Sprague–Dawley* strains, respectively. [b]Lipid-lowering experiments were performed using *Wistar* strain of rats. Values are mean % change in 5 animals of a group; significance: *$p < 0.05$ and **$p < 0.01$; ND = not done; Nil = insignificant.

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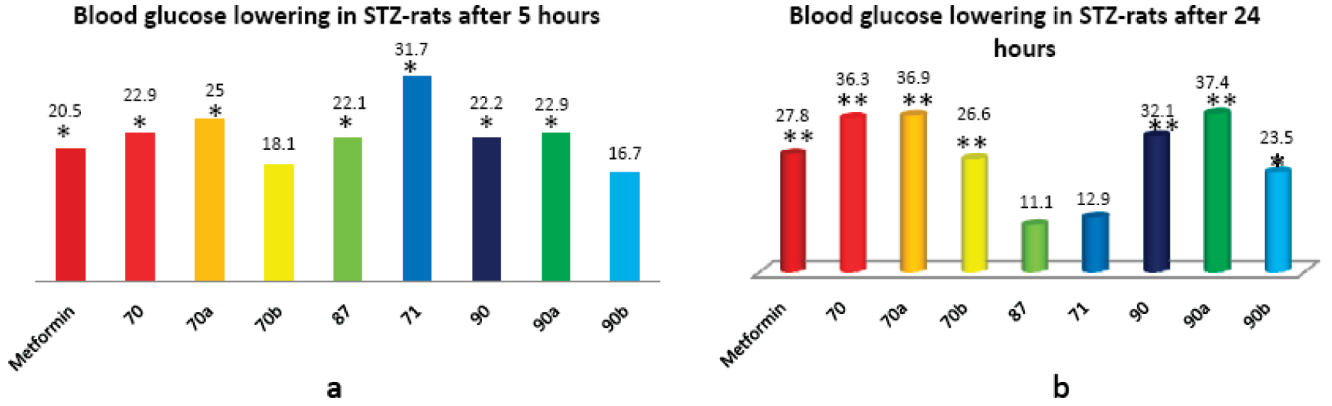

Figure 2. Comparative effects of metformin with compounds **70**, **90**, **87**, and **71** as well as enantiomers **70a**, **70b**, **90a**, and **90b** on blood glucose lowering in streptozotocin-induced diabetic rats: (a) after 5 h and (b) after 24 h. Values are mean % change in 5 animals of each group; significance: $*p < 0.05$ and $**p < 0.01$.

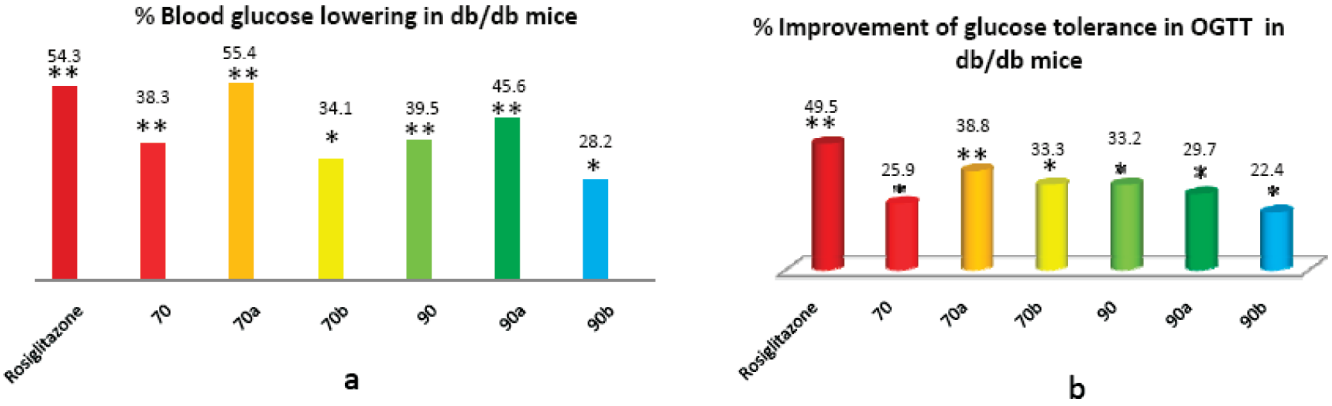

Figure 3. Comparative effects of rosiglitazone, compounds **70** and **90**, and their enantiomers on (a) lowering of glucose and (b) improvement of glucose tolerance in OGTT in *db/db* mice. Values are mean % change in 5 animals of each group; significance: $*p < 0.05$ and $**p < 0.01$.

These compounds were also evaluated for the antidyslipidemic activity in the triton-induced dyslipidemic rats, and some of them showed promising activity. Compounds **67**, 77, **78**, **79**, **81**, **82**, **85**, **86**, **87**, and **90** showed a lowering of ~28.0, 30.2, 28.2, 26.2, 25.6, 27.2, 26.0, 25.0, 25.0, and 32.0%, respectively, in TG concentrations of ~24.0, 12.1, 22.3, 13.5, 20.3, 16.5, 22.2, 24.0, 21.0, and 32%, respectively, in CHOL levels of ~26.0, 20.2, 12.6, 24.1, 26.5, 20.8, 11.8, 23.0, 23.0, and 28.0%, respectively, in phospholipid levels as compared to control dyslipidemic rats. The rest of the compounds had relatively low antidyslipidemic activity.

The compounds **67**, 77, **79**, **86**, and **87** were identified as potent antidyslipidemic agents, but these did not lower blood glucose level either in SLM model or in STZ-S rat model. The compounds **70**, **78**, **81**, **82**, **85**, and **90** were identified as potent antidyslipidemic as well as antihyperglycemic agents.

Antihyperglycemic Activity of Selected Compounds in STZ Rats. Figure 2 shows the antihyperglycemic activity profile of some selected promising compounds **70**, **70a**, **70b**, **90**, **87**, **71**, **90a**, and **90b** on STZ-induced diabetic rats (Supporting Information Tables 1, 5, and 10). Oral administration of these samples at 100 mg/kg of body weight conferred significant inhibition on the blood glucose level in STZ-induced diabetic rats after sucrose load of 2.5 g/kg of body weight as compared to vehicle-treated control group. The decline in glucose (area under curve, AUC) was seen at both 0−5 and 0−24 h after drug administration. The compounds **70**, **70a**, **70b**, **90**, **87**, **71**, **90a**, and **90b** were found to exhibit a decline in glucose (AUC) level ~22.9, 25.0, 18.1, 22.2, 31.7, 22.1, 22.9, and 16.7%, respectively, at 0−5 h, as compared to the vehicle-treated control group, whereas the metformin at 100 mg/kg dose showed ~20.5%. During 0−24 h, the decline was found to be ~36.3, 36.9, 26.6, 32.1, 12.9, 11.1, 37.4, and 23.5%, respectively, whereas metformin showed 27.8% decline as compared to the vehicle-treated control.

Antihyperglycemic Activity in db/db Mice. The data so far collected reveals that the compounds **70** and **90** exhibited significant and repeated activity and, therefore, were selected for detailed study in *db/db* mice. The flavone derivatives **70**, **70a**, **70b**, **90**, **90a**, and **90b** were chosen for detailed study and were tested in hyperglycemic *db/db* mice at a lower dose of 25 mg/kg of body weight administered daily for 10 days. The *S*-enantiomers **70a** and **90a** caused a more significant decline in the hyperglycemia by ~55.4 and 45.6% compared to their *R*-enantiomer, which declined the hyperglycemia by ~34.1 and 28.2%, respectively, whereas the racemic compounds **70** and **90** caused a decline trend of the blood glucose by ~38.3 and 39.5%, respectively, as compared to the vehicle-treated control *db/db* mice (Figure 3a). The standard drug rosiglitazone caused ~54.3% decline in hyperglycemia of *db/db* mice as compared to the vehicle-treated control. Figure 3b shows the antihyperglycemic effect of compounds **70**, **70a**, **70b**, **90**, **90a**, and **90b** on oral glucose tolerance test (OGTT) in *db/db* mice after 10 consecutive days of treatment. The overnight-fasted *db/db* mice were subjected to an oral glucose tolerance test post-3.0 g/kg of body weight of oral glucose load. The fasting baseline blood

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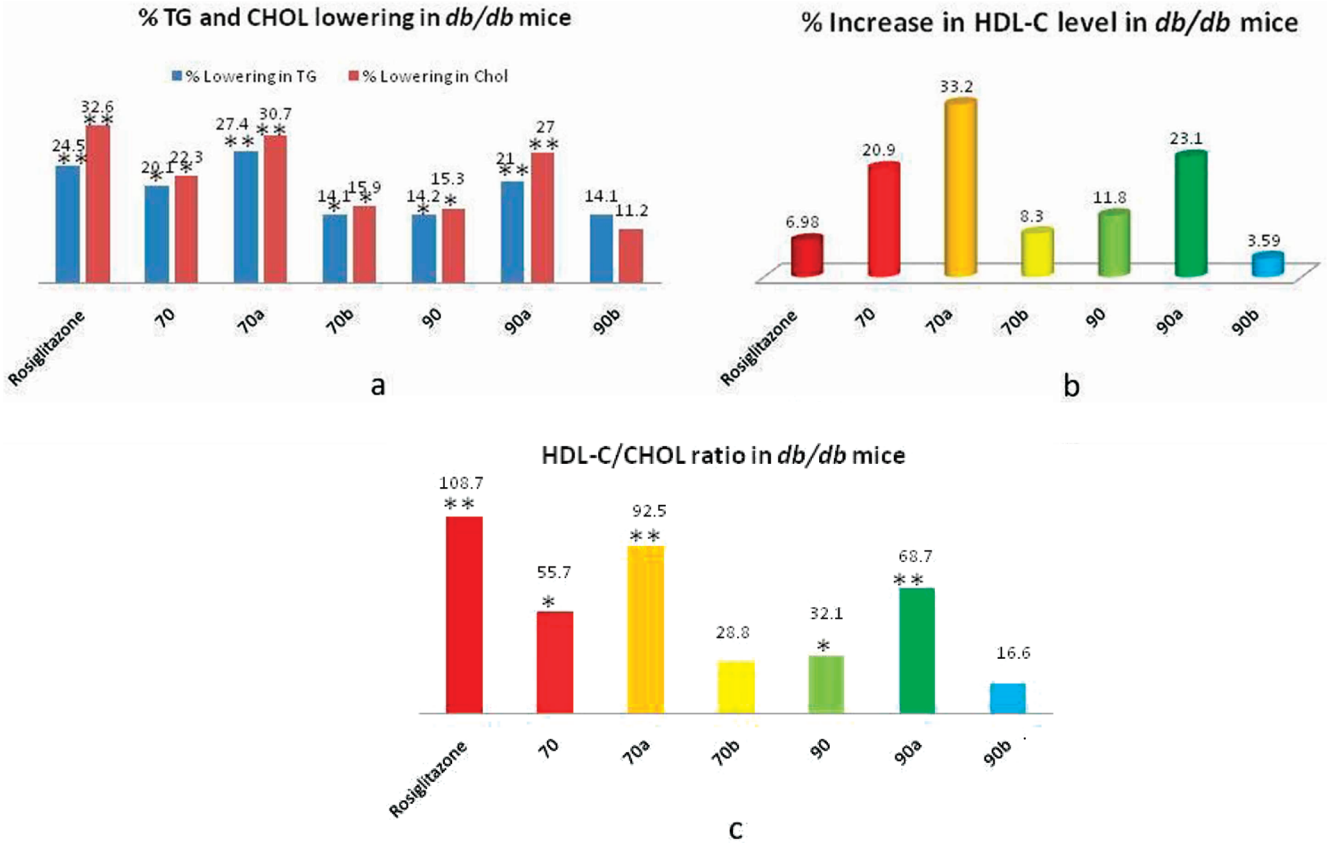

Figure 4. Comparative effects of standard drug rosiglitazone, compounds **70** and **90**, and their enantiomers on (a) lowering of TG and total CHOL, (b) increase of HDL-C levels in *db/db* mice, and (c) HDL-C/CHOL ratios in *db/db* mice. Values are mean % change in 5 animals of each group; significance: $*p < 0.05$ and $**p < 0.01$.

glucose values at 0 min were found to be lower in all the treated groups as compared to the vehicle-treated control group at the corresponding time. The treatment significantly inhibited the rise in postprandial blood glucose level of *db/db* mice after glucose load of 3.0 g/kg of body weight. The treatment with *S*-isomer **70a** improved the oral glucose tolerance by ~38.8% whereas that with the *R*-isomer **70b** showed improvement on oral glucose by ~33.3%, and the racemic compound **70** showed improvement of glucose tolerance by ~25.9% comparable to rosiglitazone treatment, which showed improvement on oral glucose by ~49.5%. The treatment with **90a** showed antihyperglycemic effect by ~29.7%, and that with **90b** showed ~22.4% antihyperglycemic effect. Racemic compound **90** showed ~33.2% antihyperglycemic effect compared to the vehicle-treated *db/db* mice.

Effect on Lipid Profile of db/db Mice. The effects of **70**, **70a**, **70b**, **90**, **90a**, and **90b** on plasma lipid profiles in *db/db* mice were also studied to see further benefits of antidiabetic treatment. Oral administrations of all six compounds at a dose of 25 mg/kg of body weight for the period of 10 consecutive days significantly lowered the plasma TG by ~20.1, 27.4, 14.1, 14.2, 21.0, and 14.1%, respectively (Figure 4a), while total plasma CHOL level was decreased by ~22.3, 30.7, 15.9, 15.3, 27.0, and 11.2%, respectively, whereas the levels of HDL-C were enhanced by ~20.9, 33.2, 8.30, 11.8, 23.1, and 3.59%, respectively (Figure 4b). Compound **70a** displayed better antidyslipidemic activity as compared to compounds **70** and **70b**. Similarly, compound **90a** displayed better antidyslipidemic activity as compared to **90** and **90b**. The antidyslipidemic activities of these compounds were compared with standard drug rosiglitazone. Rosiglitazone also lowered the TG and total CHOL by ~24.5 and 32.6%, respectively, and enhanced the HDL-C level by ~6.98% as compared to the vehicle-treated control.

The rosiglitazone and test samples treatment also increased the HDL-C to CHOL ratio by ~108.7, 55.7, 92.5, 28.8, 32.1, 68.7, and 16.6%, respectively, as compared to the vehicle-treated control (Figure 4c).

Effect on Plasma Insulin Level & Body Weight of db/db Mice. The effect of compounds **70**, **70a**, **70b**, **90**, **90a**, and **90b** on plasma insulin level in *db/db* mice after 10 consecutive days of treatment was also studied. Repeated oral gavage of test samples at an oral dose of 25 mg/kg of body weight caused a significant decrease in plasma insulin levels by ~30.6, 53.4, 18.0, 22.3, 39.2, and 9.10%, respectively, compared to the vehicle-treated control group, whereas rosiglitazone treatment declined the hyperinsulinemia of *db/db* mice by ~40.5% as compared to control (Figure 5). Compound **70a** decreased the insulin level to a greater extent in comparison to the other test compounds **70** and **70b**. Similarly, compound **90a** displayed a much higher decrease in plasma insulin level as compared to compounds **90** and **90b**. Because these compounds do not increase plasma insulin level, it therefore can be inferred that the compounds improve the sensitivity of insulin, which, however, needs to be further explored.

The effect of these compounds on body weight was also studied, and it has been observed that, in the *db/db* mice treated with *S*-enantiomer **70a**, there was a significant decline (28.2%) in the body weight when compared to the control,

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whereas compounds **70**, **70b**, **90**, **90a**, and **90b** did not show any significant change in body weight. In the same set of experiments, rosiglitazone led to an increase in the body weight by 18.3% as compared to control.

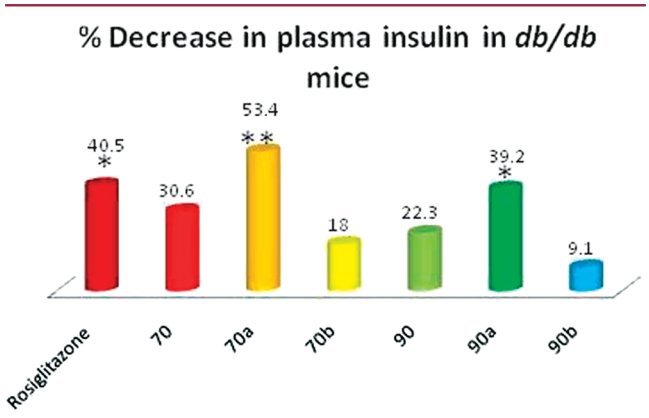

Figure 5. Comparative effects of rosiglitazone, compounds **70** and **90**, and their enantiomers on the lowering of plasma insulin levels in *db/db* mice. Values are mean % change in 5 animals of each group; significance: $*p < 0.05$ and $**p < 0.01$.

*Dose-Dependent Antidiabetic Activity of **70a** and **90a** in db/db Mice.* The *S*-enantiomers **70a** and **90a** were also evaluated to ascertain the lowest dose required for antidiabetic activity in *db/db* mice. Figure 6a shows the effects at doses of 1, 3, 10, 25, and 100 mg/kg on oral glucose tolerance in overnight-fasted *db/db* mice. After 2 h post-administration of compound **70a**, it exhibited ~21.5, 35.1, 39.9, 44.6, and 59.4% improvement in glucose tolerance 0−2 h (AUC), respectively, whereas compound **90a** had ~12.0, 19.7, 30.7, 41.1, and 49.2% improvement in glucose tolerance 0−2 h (AUC), respectively. Figure 6b shows the effect of compounds **70a** and **90a** on postprandial blood glucose profile at doses of 1, 3, 10, 25, and 50 mg/kg after 10 consecutive days of treatment. It was evident that the average decline on postprandial blood glucose was ~14.8, 22.1, 28.8, 38.3, 39.1% for compound **70a** whereas it was ~12.1, 27.1, 31.2, 31.6, and 35.4% for **90a**, respectively. On the basis of these data, the ED_{50} of compound **70a** was estimated to be ~1.72 mg/kg.

*Antidyslipidemic Profile of Compounds **70**, **70a**, **70b**, and **90** in Hamsters.* Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. Our results are in accord with previous reports that HFD-fed hamsters shared some common features of type 2 diabetes, that is, obesity, dyslipidemia, and usually hypertension. In the present study, experiments were carried out to investigate the antidyslipidemic effects of flavone derivatives in the HFD-fed dyslipidemic hamster model. Feeding of high-fructose diet to these hamsters caused an alteration of the plasma lipid profile (Supporting Information Tables 11, 12, and 13). Figure 7

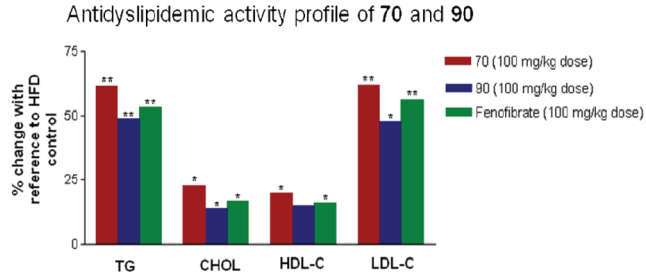

Figure 7. Antidyslipidemic activity profile of **70** and **90**. Data is given as % change with reference to HFD control of six hamsters per group. Significance: $***p < 0.001$, $**p < 0.01$, $*p < 0.05$ as compared to HFD control.

presents the antidyslipidemic profile of flavone derivatives **70** and **90** at the dose of 100 mg/kg in HFD-fed *Syrian golden* hamsters. Compounds **70** and **90** caused significant lowering of TG level by ~61.5 and 48.9%, CHOL level by ~22.9 and 13.8%, and LDL-C concentration by ~61.9 and 47.7%, respectively. Compounds **70** and **90** also displayed a marked elevation of ~20.0 and 14.9%, respectively, in the level of HDL-C, i.e., good cholesterol, which is beneficial and desirable. The antidyslipidemic profiles of compounds **70** and **90** were compared to the standard lipid-lowering drug fenofibrate at the same doses, which caused ~53.4% lowering in TG concentration, ~16.8% lowering in cholesterol level, and ~56.3% lowering in low-density lipoprotein level. Fenofibrate treatment also caused ~16.2% increase in the HDL-C level. The compounds **70**, **90**, and fenofibrate treatment also caused lowering in the body weight, but the effect of **70** was found to be greater as compared to **90** and fenofibrate. The antidyslipidemic activity found after treatment with **70** was more promising than that with flavone **90** or the standard drug fenofibrate (Figure 7). Therefore,

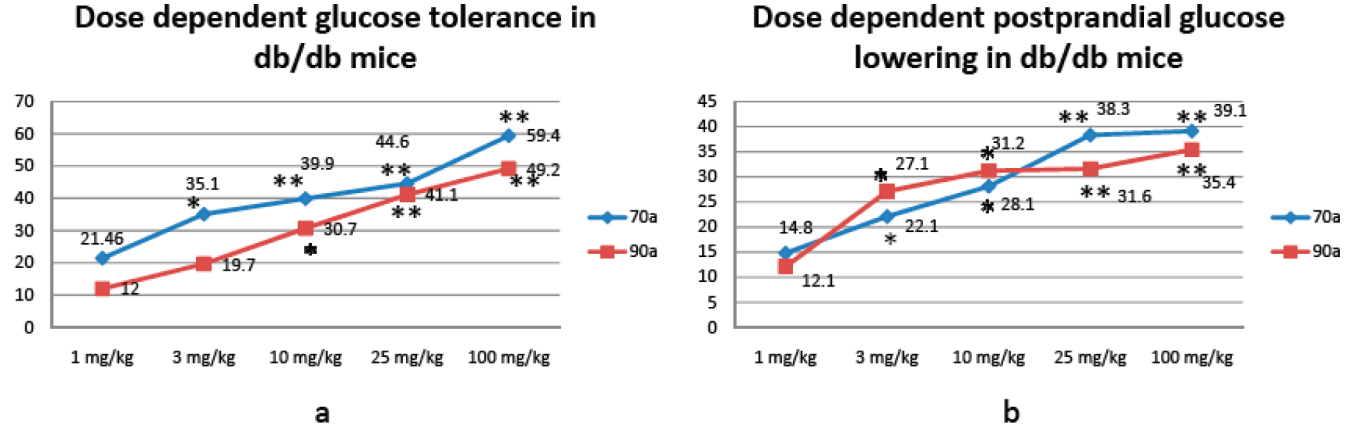

Figure 6. Dose-dependent (a) glucose tolerance in OGTT and (b) lowering of postprandial glucose by **70a** and **90a** in *db/db* mice. Values are mean % change in 5 animals of a group; significance: $*p < 0.05$ and $**p < 0.01$.

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they were selected for further study in HFD-fed hamsters along with optical enantiomers **70a** and **70b** at the dose of 25 mg/kg.

The antidyslipidemic activities of compounds **70a** and **70b** were compared with that of standard drug fenofibrate at the same doses, i.e., 25 mg/kg (Figure 8). The compounds **70**, **70a**,

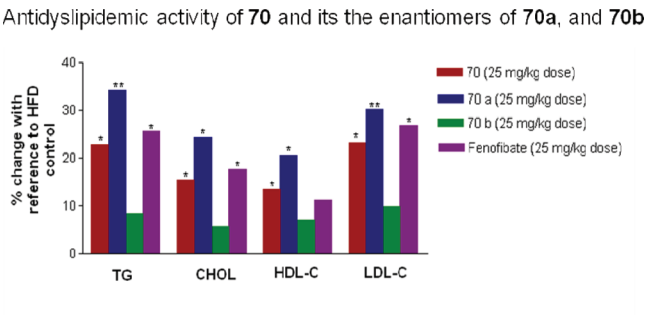

Figure 8. Antidyslipidemic activity of **70**, **70a**, and **70b**. Data is given as % change with reference to HFD control of six hamsters per group. Significance: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ as compared to HFD control.

and **70b** showed triglyceride-lowering activity of ~22.2, 34.7, and 8.40%, respectively. These compounds also caused lowering of ~15.3, 24.4, and 5.52%, respectively, in CHOL level and lowering of ~23.3, 30.1, and 9.78%, respectively, in LDL-C on post-treatment with **70**, **70a**, and **70b**. The treatment with these compounds also caused an increase in the HDL-C level, which was calculated to be ~13.3, 20.5, and 7.08%, respectively. The lipid-lowering activity of the fenofibrate was found to be ~25.5, 17.5, and 26.8% lowering in triglyceride, cholesterol, and LDL-C levels at the same dose. Fenofibrate treatment also caused elevation in HDL-C level of ~11.2%. These enantiomers and fenofibrate showed body-weight-reducing activity, which was found to be ~8.89, 14.3, 3.73, and 6.78% after treatment, respectively.

It was clear from Figure 8 that **70a** showed better antidyslipidemic activity than **70**, **70b**, and fenofibrate at the dose of 25 mg/kg. Finally, compound **70a** was followed for the dose-dependent study in HFD-fed dyslipidemic hamsters and was found to correct dyslipidemia in a dose-dependent manner. It was evident from Figure 9 that the compound **70a** (at the doses

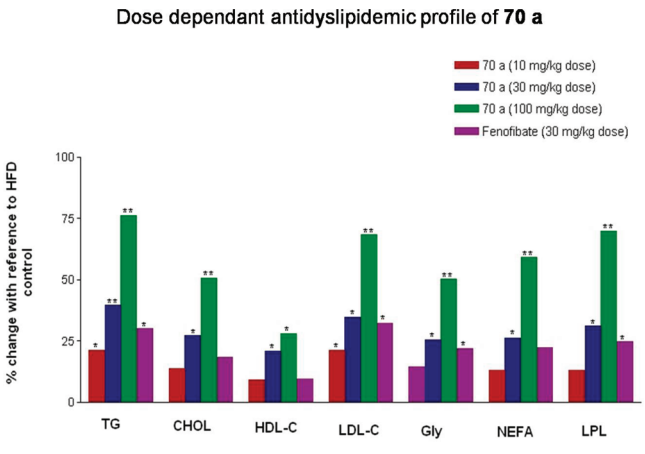

Figure 9. Dose-dependent antidyslipidemic profile of **70a**. Data is given as % change with reference to HFD control of six hamsters per group. Significance: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ as compared to HFD control.

of 10, 30, and 100 mg/kg) exhibited a dose-dependent effect. Compound **70a** at 10 mg/kg dose lowered the TG, CHOL, LDL-C, glycerol, and nonesterified free fatty acid (NEFA) levels and was calculated to be ~21.2, 13.8, 21.1, 14.4, and 13.1%, respectively. Elevation of ~9.37% in HDL-C and ~13.2% increase in lipoprotein lipase activity were observed at this dose. After 7 days after treatment of **70a** at 30 mg/kg, there was a marked decrease in the TG (39.8%), CHOL (27.2%), LDL-C (34.6%), glycerol (25.7%), and NEFA levels (26.3%). An increase in the HDL-C level (21.0%) and an elevation in the lipoprotein lipase (LPL) activity were observed as compared to HFD control (31.2%). The compound **70a** at 100 mg/kg showed a sharp decrease in the TG (76.3%), CHOL (50.7%), LDL-C (68.4%), glycerol (50.5%), and NEFA levels (59.1%). A marked increase in HDL-C level (27.9%) and a marked elevation in LPL activity (69.7%) were observed as compared to HFD control. The standard drug fenofibrate treatment at the dose of 30 mg/kg showed a reduction in TG (30.2%), CHOL (18.5%), LDL-C (32.3%), glycerol (22.1%), and NEFA levels (22.2%). Increases in HDL-C (9.68%) and LPL activity (24.7%) were also observed after treatment of fenofibrate. The interesting feature of compound **70a** was an increase in the level of good cholesterol, i.e., HDL-C. HFD-fed hamsters showed a decrease of LPL activity. Treatment with compound **70a** caused an increase of LPL activity.

Compound **70a** exhibited antidyslipidemic property in a similar manner as fenofibrate. Fenofibrate treatment at the same dose significantly lowered the level of TG and LDL-C and also resulted in an increase of LPL activity.

The epidemiological studies suggest that the consumption of HFD is linked with obesity, which in turn causes development of hyperinsulinemia resulting in type 2 diabetes. The reversal of dyslipidemia and effect on body weight was therefore studied in a hamster model with compound **70a** at different doses (Figure 10).

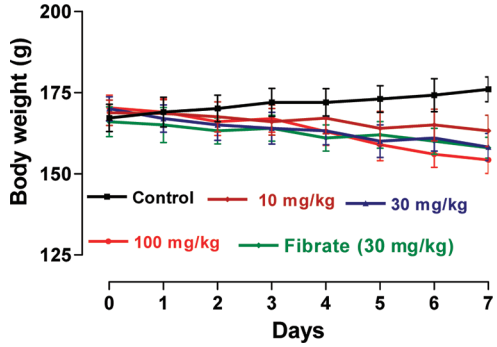

Figure 10. Dose-dependent body-weight-reducing activity of **70a** in HFD-fed dyslipidemic golden hamsters.

Compound **70a** displayed ~7.38, 10.2, and 12.5% reduction in body weight of the treated hamsters at 10, 30, and 100 mg/kg doses, respectively, whereas fenofibrate displayed 10.2% reduction in body weight at 30 mg/kg dose after 7 days of treatment.

*Pharmacokinetic Study of Compounds **70**, **70a**, and **90a**.* The pharmacokinetic parameters were evaluated from plasma concentration–time profile in *Sprague–Dawley* male rats (Table 2).[14] After oral dose administration of compounds **70**, **70a**, and **90a**, the elimination half-lives ($t_{1/2}$) were found to be 19.56, 19.83, and 3.97 h, respectively. The plasma clearances (Cl) of these compounds were found to be 3.42, 3.75, and 3.27 L/h/kg,

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Table 2. Pharmacokinetic Parameter Studies on Compounds 70, 70a, and 90a[a]

compd.	route	C_{max} (ng/mL)	T_{max} (h)	Cl (L/h/kg)	MRT (h)	V_d (L/kg)	AUC (ngh/ml)	$t_{1/2}$ (h)	bioavailability (%)
70	oral	60.93	8.00	3.42	43.20	96.73	3469.28	19.56	29.48
70	intravenous	998.21		3.65	22.77	69.41	2717.5	16.30	
70a	oral	70.30	8.00	3.75	30.26	107.41	1798.22	19.83	27.00
70a	intravenous	523.00		3.72	13.50	50.26	666.00	10.10	
90a	oral	21.17	0.33	3.27	5.96	16.18	39.50	3.39	0.52
90a	intravenous	1813.00		3.30	4.90	16.20	756.00	4.83	

respectively. The oral bioavailabilities of compounds **70**, **70a**, and **90a** on these parameters were estimated to be ∼29.48, 27.00, and 0.52%, respectively, in accordance with their dose-normalized AUC. After oral dosing of both racemic compound **70** and its *S*-enantiomer **70a**, it appears that the absorption was slow as plasma concentrations peaked at 8 h after dose. Multiple peaks were observed in plasma concentration−time profile after oral dose. It may be due to enterohepatic recycling, selective and differential absorption from the gastrointestinal tract, formation of depot on the intestinal wall, and variation in gastrointestinal motility. The higher values of MRT and elimination half-life ($t_{1/2}$) after oral and intravenous doses indicate that compound **70** was retained for longer periods of time and had slow elimination from the body. The oral bioavailability of both racemic compound **70** and its *S*-enantiomer **70a** were nearly similar with values of ∼29.48 and 27.0%, respectively.

CONCLUSION

Thus, these flavones show significant antihyperglycemic as well as antidyslipidemic effects and possess hyperinsulinemia reversal activity with moderate reduction in body weight, with the *S*-enantiomer of both compounds being the most active. The flavonoid derivatives **70** and **90** thus offer promising leads to develop as drug molecules for the management of type 2 diabetes.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 200 or 300 MHz as mentioned using Perkin-Elmer DPX 200 MHz or Bruker Avance DRX-300 spectrometer. Chemical shifts (δ) are quoted in ppm, referenced internally to $CDCl_3$ at 77.0 ppm. All coupling constants (J) are given in Hz. Low- and high-resolution electrospray ionization (ESI) MS was carried out using a Bruker (U.S.A.) Daltronics BioApex II with a 7T superconducting magnet and an analytical ESI source. The purity of the compounds is verified by the HPLC performed on Chira Sphere NT (250 mm × 0.4 mm, 5 μm, Merck) column using a solvent mixture of hexane/isopropanol/methanol/ammonia (in a ratio of 60:40:5:0.5 mL) at the flow rate of 2 mL/min and a peak detection at 240 nm under UV.

General Procedure for Esterification. Concentrated sulphuric acid (2−3 mL) was added dropwise to a solution of required benzoic acid (**6**−**8**, 123 mmol) in absolute ethanol (250 mL), and the reaction mixture was refluxed for ∼8 h. Solvent was removed and the residue was taken up in water and extracted with diethyl ether. The combined ethereal layers were washed with $NaHCO_3$ solution, water, and brine. It was dried over Na_2SO_4 and filtered, and the solvent was removed to get ethyl benzoates **9**−**11**, which crystallized to get purified esters.

Ethyl-3,4-dihydroxybenzoate (9). Yield 82%; mp 133−134 °C; MS (FAB): 183 (M+1); IR (KBr): 3498, 3471, 1819, 1685 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.20 (d, J = 1.9 Hz, 1H, arom. −CH), 7.15 (dd, J = 8.2 Hz, 2.0 Hz, 1H, arom. −CH), 6.65 (d, J = 8.2 Hz, 1H, arom. −CH), 4.04 (q, J = 7.1 Hz, 2H, $-OCH_2$), 1.09 (t, J = 7.1 Hz, 3H, $-CH_3$).

Ethyl-3,4,5-trimethoxybenzoate (10). Yield 75%; mp 56−57 °C; MS (FAB): 241 (M + 1); IR (KBr): 1967, 1708 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (s, 2H, arom. −CH), 4.38 (q, J = 7.1 Hz, 2H, $-OCH_2$), 3.91 (s, 9H, $-OCH_3$), 1.40 (t, J = 7.1 Hz, 3H, $-CH_3$).

Ethyl-3,5-dihydroxybenzoate (11). Yield 75%; mp 128−130 °C; MS (FAB): 183 (M + 1); IR (KBr): 3496, 1819, 1687 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.89 (s, 2H, −OH), 7.06 (d, J = 2.2 Hz, 2H, arom. −CH), 6.69 (t, J = 2.2 Hz, 1H, arom. −CH), 4.48 (q, J = 7.1 Hz, 2H, $-OCH_2$), 1.52 (t, J = 7.1 Hz, 3H, $-CH_3$).

Ethyl-3,4-dimethoxybenzoate (13). Dimethylsulfate (16.4 mL, 130 mmol) and 20% NaOH (in excess) were added dropwise to a solution of 3,4-dihydroxybenzoic acid (**6**, 20.0 g, 130 mmol) in ethanol (250 mL) over a period of 3 h, and the reaction mixture was further stirred at room temperature for 3 h. During this process, esterification also occurred due to the acid generated in situ from dimethyl sulfate. The solvent was removed, and the residue was taken in water and extracted with ether. The combined ethereal layers were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and filtered, and the solvent was removed to afford the required product ethyl-3,4-dimethoxybenzoate (7). Yield 24.5 g (90%); oil; MS (FAB): 211 (M + 1); IR (KBr): 1974, 1712 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 1H, arom. −CH), 7.55 (s, 1H, arom. −CH), 6.88 (d, J = 8.4 Hz, 1H, arom. −CH), 4.36 (q, J = 7.1 Hz, 2H, $-OCH_2$), 3.93 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 1.39 (t, J = 7.1 Hz, 3H, $-CH_3$).

Ethyl-3,5-dimethoxybenzoate (15). Yield 94%; oil; MS (FAB): 211 (M + 1); IR (KBr): 1970, 1716 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18 (d, J = 2.3 Hz, 2H, arom. −CH), 6.64 (d, J = 2.3 Hz, 1H, arom. −CH), 4.36 (q, J = 7.1 Hz, 2H, $-OCH_2$), 3.82 (s, 6H, $-OCH_3$), 1.39 (t, J = 7.1 Hz, 3H, $-CH_3$).

Typical Procedure for Benzylation of Hydroxy Ethyl Benzoates. *Ethyl-3,5-dibenzyloxybenzoate (14).* To a solution of ethyl-3,5-dihydroxybenzoate (**11**, 16.8 g, 92 mmol) in dry acetone (350 mL) were added K_2CO_3 (27.6 g, 200 mmol) and benzyl bromide (23.8 mL, 200 mmol), and the reaction mixture was stirred at room temperature for ∼9 h. On completion of the reaction, it was filtered. The excess reagent and solvent were removed to get the crude product **14**, which was purified by column chromatography. Yield 74%; mp 63−65 °C; MS (FAB): 363 (M + 1); IR (KBr): 1824, 1708 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34−7.35 (m, 10H, −Ph), 7.30 (d, J = 2.3 Hz, 2H, arom. −CH), 6.79 (t, J = 2.2 Hz, 1H, arom. −CH), 5.07 (s, 4H, $-OCH_2$), 4.36 (q, J = 7.1 Hz, 2H, $-OCH_2$), 1.38 (t, J = 7.1 Hz, 3H, $-CH_3$).

Ethyl-3,4-dibenzyloxybenzoate (12). Yield 76%; mp 68−69 °C; MS (FAB): 363 (M + 1); IR (KBr): 1889, 1707 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65 (s, 1H, arom. −CH), 7.63 (dd, J = 8.7 Hz, 1.7 Hz, 1H, arom. −CH), 7.48−7.25 (m, 10H, −Ph), 6.91 (d, J = 8.3 Hz, 1H, arom. −CH), 5.19 (s, 2H, $-OCH_2$), 5.18 (s, 2H, $-OCH_2$), 4.31 (q, J = 7.1 Hz, 2H, $-OCH_2$), 1.35 (t, J = 7.1 Hz, 3H, $-CH_3$).

General Procedure to Prepare Substituted Benzyloxyethyl Benzoates 16−19. In an ice-cooled solution of substituted benzaldehydes **20**−**23** (10 mmol) in dry methanol (100 mL), pellets of sodium borohydride (20 mmol) were added under stirring at room temperature for 2−6 h. On completion of the reaction, the solvent was removed followed by the addition of water to precipitate the crude products, which were filtered, washed, and dried. The resulting benzyl alcohols **24**−**27** (5 mmol) were taken in benzene and cooled in ice water followed by the addition of PBr_3 (6 mmol). The reaction mixture was then refluxed for 6−10 h. On completion of the reaction, it was decomposed by slow addition of water and extracted with

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benzene. The organic layer was dried (Na_2SO_4) and the solvent was removed to obtain the crude products **28**–**31**.

In an ice-cooled solution of 3,5-dihydroxybenzoic acid (**8**, 10 mmol) in absolute ethanol, thionyl chloride (15 mmol) was added dropwise under stirring. On completion of the reaction, the solvent was removed followed by extraction with chloroform, dried (Na_2SO_4), and concentrated to obtain crude product **11**. The resulting ethyl-3,5-dihydroxybenzoate (**11**, 10 mmol) in dry acetone, anhydrous K_2CO_3 (30 mmol), substituted benzyl bromide **28**–**31** (22 mmol) prepared above, and sodium iodide (2 mmol) was refluxed for 4–6 h. On completion of the reaction, K_2CO_3 was filtered, and the solvent was removed. The residue was taken in chloroform, washed with water, and dried (Na_2SO_4), and the solvent was removed to get crude products, which were purified by column chromatography on silica gel.

*Ethyl-3,5-bis(2-chlorobenzyloxy)benzoate (**16**).* Yield 52%; mp 65 °C; ES-MS: 432 (M + 1); $C_{25}H_{26}O_4$; FT-IR(KBr): 1698, 1600, 1452 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.54 (m, 2H, arom. −CH); 7.38 (m, 8H, arom. −CH); 6.82 (d, 1H, J = 2.2 Hz, arom. −CH); 5.16 (s, 4H, $-OCH_2$); 4.35 (q, 2H, $-OCH_2$); 1.39 (t, 3H, $-CH_3$).

*Ethyl-3,5-bis(2-methylbenzyloxy)benzoate (**17**).* Yield 51%; mp 77 °C; ES-MS: 391 (M + 1), $C_{25}H_{26}O_4$; FT-IR(KBr): 1711, 1600, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 2.2 Hz, arom. −CH); 7.24 (m, 6H, arom. −CH); 6.85 (d, 1H, J = 2.2 Hz, arom. −CH); 5.08 (s, 4H, $-OCH_2$); 4.40 (q, 2H, J = 6.9 Hz, $-OCH_2$); 2.41 (s, 6H, $-CH_3$); 1.43 (t, 3H, J = 6.7 Hz, $-CH_3$).

*Ethyl-3,5-bis(4-methylbenzyloxy)benzoate (**18**).* Yield 58%; mp 85 °C; ESMS: 391(M + 1); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.32 (m, 10H, arom. −CH); 6.77 (d, 1H, J = 2.2 Hz, arom. −CH); 5.01 (s, 4H, $-OCH_2$); 4.34 (q, 2H, J = 6.9 Hz, $-OCH_2$); 1.37 (t, 3H, $-CH_3$); 2.35 (s, 6H, $-CH_3$).

*Ethyl-3,5-bis(3,5-dichlorobenzyloxy)benzoate (**19**).* Yield 61%; mp 115 °C; ESMS: 501(M + 1), ^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, 2H, J = 1.8. Hz, arom. −CH); 7.47 (s, 1H, arom. −CH); 7.43 (s, 1H, arom. −CH); 7.23(d, 4H, J = 2.1 Hz, arom. −CH); 6.70 (s, 1H, arom. −CH); 5.02 (s, 4H, $-OCH_2$); 4.38 (q, 2H, $-OCH_2$); 1.44 (t, 3H, $-CH_3$).

Typical Procedure for the Preparation of 6- or 7-Hydroxyflavones 42–51. A solution of LiHMDS (20% in THF, 217.5 mL, 260 mmol) was added dropwise to a well-stirred and cooled (at −78 °C) solution of 2,4-dihydroxyacetophenone (**4**) or 2,5-dihydroxyacetophenone (**5**, 9.88 g, 65 mmol) in THF (150 mL) during ∼30 min under nitrogen atmosphere. The reaction mixture was stirred for 1 h at this temperature and subsequently at −30 °C for 2 h. It was again cooled to −78 °C, and a solution of ethyl benzoates (**10** or **12**–**19**, 65 mmol) in THF (100 mL) was added over a period of 30 min. It was further stirred at room temperature overnight and poured into ice water containing hydrochloric acid. It was extracted with chloroform, dried (Na_2SO_4), and filtered, and the solvent was removed to afford β-diketone intermediates **32**–**41**. The residue was refluxed with Dowex-H^+ (8 g) in 2-propanol for 3–4 h. The solvent was removed under reduced pressure, and the residue was suspended in hot DMF to dissolve the product. Dowex-H^+ was filtered, the solvent was removed, and the solid product was washed with cold MeOH (3 × 200 mL) to afford flavones **42**–**51**.

*3′,4′-Dibenzyloxy-6-hydroxyflavone (**42**).* Yield 44%; mp 196–197 °C; MS (FAB): 451 (M + 1); IR (KBr): 3419, 1621 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 10.08 (s, 1H, −OH), 7.75 (s, 1H, H-8), 7.69 (d, J = 8.7 Hz, 1H, H-7), 7.63 (s, 1H, H-3), 7.55–7.22 (m, 13H, H-2′, H-5′, H-5, and -Ph), 6.94 (s, 1H, H-6′), 5.30 (s, 2H, $-OCH_2$), 5.27 (s, 2H, $-OCH_2$).

*3′,4′-Dibenzyloxy-7-hydroxyflavone (**43**).* Yield 24 g (89%); mp 245–247 °C; MS (FAB): 451 (M + 1); IR (KBr): 3426, 1607 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 10.79 (s, 1H, −OH), 7.86 (d, J = 8.6 Hz, 1H, H-5), 7.68 (s, 1H, C-2′), 7.60 (d, J = 8.8 Hz, 1H, C-6′), 7.51–7.30 (m, 10H, −Ph), 7.18 (d, J = 8.5 Hz, 1H, H-6), 6.98 (s, 1H, C-6), 6.91 (d, J = 8.8 Hz, 1H, C-8), 6.83 (s, 1H, H-3), 5.26 (s, 2H, $-OCH_2$), 5.21 (s, 2H, $-OCH_2$).

*3′,4′-Dimethoxy-7-hydroxyflavone (**44**).* Yield 52%; mp 263–265 °C; MS (FAB): 299 (M + 1); IR (KBr): 3452, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 9.83 (s, 1H, −OH), 7.32 (d, J = 8.5 Hz, 1H, H-5), 6.97 (dd, J = 8.5 Hz, 1.7 Hz, 1H, H-2′), 6.83 (d, J = 1.7 Hz, 1H, H-6′), 6.43 (d, J = 8.5 Hz, 1H, H-6), 6.34 (s, 1H, H-8), 6.30 (dd, J = 9.7 Hz, 2.0 Hz, 1H, H-5′), 6.08 (s, 1H, H-3), 3.35 (s, 3H, $-OCH_3$), 3.32 (s, 3H, $-OCH_3$).

*7-Hydroxy-3′,4′,5′-trimethoxyflavone (**45**).* Yield 82%; mp 284–286 °C; MS (FAB): 329 (M + 1); IR (KBr): 3408, 1630 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.86 (d, J = 8.7 Hz, 1H, H-5), 7.29 (s, 2H, H-2′ and H-6′), 7.03 (d, J = 1.8 Hz, 1H, H-8), 6.96 (s, 1H, H-3), 6.92 (d, J = 8.9 Hz, 1H, H-6), 3.89 (s, 6H, $-OCH_3$), 3.79 (s, 3H, $-OCH_3$).

*3′,5′-Dibenzyloxy-7-hydroxyflavone (**46**).* Yield 81%; mp 248–249 °C; MS (FAB): 451 (M + 1); IR (KBr): 3452, 1620 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.84 (d, J = 8.7 Hz, 1H, H-5), 7.52–7.28 (m, 10H, −Ph), 7.23 (d, J = 1.9 Hz, 2H, H-2′, and H-6′), 6.98 (d, J = 2.0 Hz, 1H, H-8), 6.89 (s, 1H, H-3), 6.89 (dd, J = 8.6 Hz, 2.1 Hz, 1H, H-6), 6.82 (s, 1H, H-4′), 5.14 (s, 4H, $-OCH_2$).

*3′,5′-Dimethoxy-7-hydroxyflavone (**47**).* Yield 59%; mp 267–268 °C; MS (FAB): 299 (M + 1); IR (KBr): 3405, 1602 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 10.82 (s, 1H, −OH), 7.89 (d, J = 8.7 Hz, 1H, H-5), 7.17 (d, J = 2.0 Hz, 2H, H-2′, and H-6′), 7.03 (d, J = 1.9 Hz, 1H, H-8), 6.95 (s, 1H, H-3), 6.94 (dd, J = 7.2 Hz, 2.0 Hz, 1H, H-6), 6.71 (s, 1H, H-4′), 3.85 (s, 6H, OCH_3).

*3′, 5′-bis(2″-Chlorobenzyloxy)-7-hydroxyflavone (**48**).* Yield 81%; mp 176 °C; ESMS: 519 (M + 1); 521 (M + 3); ^1H NMR (200 MHz, $CDCl_3$): δ 8.01 (d, 1H, J = 8.4 Hz, H-5); 7.41 (s, 1H); 7.56 (m, 6H,); 7.33 (d, 1H, J = 4.4 Hz); 7.15 (s, 1H); 6.91 (d, 2H); 6.78 (s; 1H, H-6′); 6.68 (s, 1H, H-3); 6.35 (d, 1H, J = 4.4 Hz, H-4′); 5.23 (s, 4H, $-OCH_2$).

*3′,5′-bis(2″-Methylbenzyloxy)-7-hydroxyflavone (**49**).* Yield 71%; mp 195 °C; ES-MS: 479 (M + 1); ^1H NMR (200 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H, H-5′); 7.43 (m, 6H, −Ph, H-2′, and H-6′); 6.95 (s, 1H, H-6); 7.16 (s, 4H, −Ph); 6.69 (s, 1H, H-4′); 5.09 (s, 4H, $-OCH_2$); 2.73 (s, 6H, $-CH_3$).

*3′,5′-bis(4″-Methylbenzyloxy)-7-hydroxyflavone (**50**).* Yield 74%; mp 205 °C; ES-MS: 479 (M + 1); ^1H NMR (200 MHz, $CDCl_3$): δ 8.04 (d, J = 4.5 Hz, 1H, H-5); 7.23–7.39 (m, 9H); 7.19 (m, 4H); 7.01 (d, J = 1.9 Hz, 2H, −CH); 6.93 (m, 2H); 6.77 (m, 1H); 6.66 (s, 1H, H-3); 5.06 (s, 4H, $-OCH_2$); 2.37 (s, 6H, $-CH_3$).

*3′,5′-bis(3″,5″-Dichlorobenzyloxy)-7-hydroxyflavone (**51**).* Yield 55%; mp 225 °C; ES-MS: 589 (M + 1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.1 Hz, 1H, H-5); 7.40 (m, 4H, −Ph); 7.18 (m, 6H, −Ph); 6.72 (m, 2H, H-4′, and H-8); 6.37 (m, 1H, H-6); 6.28 (s, 1H, H-3); 5.01 (s, 4H, $-OCH_2$).

Typical Procedure for 6- or 7-(2,3-Epoxypropoxy)flavones. To a well-stirred solution of 7-hydroxyflavone **42**–**47** (17.8 mmol) in dry DMF (200 mL), NaH (50%, 125 mmol) was added at 0–5 °C, and after 30 min of stirring an excess of epichlorohydrin (107 mmol) was added and the solution was again stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with chloroform. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude products **52**–**57** were purified by column chromatography over silica gel (100–200 mesh).

*3′,4′-Dibenzyloxy-6-(2,3-epoxypropoxy)flavone (**52**).* Yield 81%; mp 147–149 °C; MS (FAB): 507 (M + 1); IR (KBr): 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.57–7.29 (m, 15H, arom. −CH), 7.02 (d, J = 8.6 Hz, 1H, H-4′), 6.66 (s, 1H, H-3), 5.25 (s, 4H, $-OCH_2$), 4.39 (dd, J = 11.0 Hz, 2.6 Hz, 1H, $-OCH_2$), 3.98 (dd, J = 11.0 Hz, 6.0 Hz, 1H, $-OCH_2$), 3.40–3.39 (m, 1H, −OCH), 2.93 (t, J = 4.5 Hz, 4.5 Hz, 1H, $-OCH_2$), 2.78 (dd, J = 4.8 Hz, 2.6 Hz, 1H, $-OCH_2$).

*3′,4′-Dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**53**).* Yield 86%; mp 168–170 °C; MS (FAB): 507 (M + 1); IR (KBr): 1639 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, J = 8.7 Hz, 1H, H-5), 7.50–7.32 (m, 12H, arom. −CH), 7.04–6.93 (m, 3H, H-2′, H-6′, and H-3), 6.61 (s, 1H, H-4′), 5.24 (s, 4H, $-OCH_2$), 4.38 (dd, J = 11.1 Hz, 2.9 Hz, 1H, $-OCH_2$), 4.05 (dd, J = 11.1 Hz, 5.8 Hz, 1H, $-OCH_2$), 3.42–3.40 (m, 1H, −OCH), 2.96 (t, J = 4.5 Hz, 4.5 Hz, 1H, $-OCH_2$), 2.80 (dd, J = 4.8 Hz, 2.6 Hz, 1H, $-OCH_2$).

*3′,4′-Dimethoxy-7-(2,3-epoxypropoxy)flavone (**54**).* Yield 74%; mp 148–149 °C; MS (FAB): 355 (M + 1); IR (KBr): 1632 cm^{-1}; ^1H

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NMR (200 MHz, $CDCl_3$): δ 8.13 (d, J = 9.5 Hz, 1H, H-5), 7.73 (dd, J = 8.5 Hz, 2.0 Hz, 1H, H-8), 7.35 (d, J = 1.9 Hz, 1H, H-6), 7.00 (dd, J = 7.1 Hz, 2.3 Hz, 1H, H-2′), 6.99 (d, J = 2.2 Hz, 1H, H-6′), 6.97 (d, J = 8.5 Hz, 1H, H-5′), 6.68 (s, 1H, H-3), 4.39 (dd, J = 11.1 Hz, 2.9 Hz, 1H, $-OCH_2$), 4.05 (dd, J = 11.1 Hz, 5.8 Hz, 1H, $-OCH_2$), 3.98 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$), 3.44−3.40 (m, 1H, −OCH), 2.96 (t, J = 4.5 Hz, 4.5 Hz, 1H, $-OCH_2$), 2.81 (dd, J = 4.8 Hz, 2.6 Hz, 1H, $-OCH_2$).

*7-(2,3-Epoxypropoxy)-3′,4′,5′-trimethoxyflavone (**55**).* Yield 83%; mp 187−188 °C; MS (FAB): 385 (M + 1); IR (KBr): 1651 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.14 (d, J = 9.3 Hz, 1H, H-5), 7.10 (s, 2H, H-2′, and H-6′), 7.02 (d, J = 7.6 Hz, 1H, H-8), 7.00 (s, 1H, H-6), 6.70 (s, 1H, H-3), 4.39 (dd, J = 11.0 Hz, 2.8 Hz, 1H, $-OCH_2$), 3.98 (dd, J = 11.0 Hz, 5.7 Hz, 1H, $-OCH_2$), 3.43−3.39 (m, 1H, −OCH), 3.96 (s, 6H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 2.97 (t, J = 4.5 Hz, 4.2 Hz, 1H, $-OCH_2$), 2.82 (dd, J = 4.7 Hz, 2.2 Hz, 1H, $-OCH_2$).

*3′,5′-Dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56**).* Yield 79%; mp 172−173 °C; MS (FAB): 507 (M + 1); IR (KBr): 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 1H, H-5), 7.47−7.34 (m, 10H, arom. −CH), 7.11 (d, J = 2.2 Hz, 2H, H-2′, and H-6′), 7.00 (dd, J = 10.9 Hz, 2.1 Hz, 1H, H-4′), 6.97 (d, J = 1.9 Hz, 1H, H-8), 6.77 (d, J = 2.0 Hz, 1H, H-6), 6.69 (s, 3H, H-3), 5.10 (s, 4H, $-OCH_2$), 4.38 (dd, J = 11.1 Hz, 2.8 Hz, 1H, $-OCH_2$), 4.04 (dd, J = 11.1 Hz, 5.8 Hz, 1H, $-OCH_2$), 3.41−3.40 (m, 1H, −OCH), 2.95 (t, J = 4.5 Hz, 4.5 Hz, 1H, $-OCH_2$), 2.80 (dd, J = 4.8 Hz, 2.6 Hz, 1H, $-OCH_2$); ^{13}C NMR: δ 177.9, 163.8, 162.9, 160.7, 158.1, 136.7, 133.9, 129.1, 128.6, 127.9, 127.5, 118.2, 115.1, 108.1, 106.0, 105.4, 101.7, 70.8, 69.7, 50.2, 44.9.

*3′,5′-Dimethoxy-7-(2,3-epoxypropoxy)flavone (**57**).* Yield 72%; mp 181−182 °C; MS (FAB): 355 (M + 1); IR (KBr): 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.14 (dd, J = 8.3 Hz, 0.77 Hz, 1H, H-5), 7.04−6.99 (m, 4H, H-2′, H-6′, H-8, and H-6), 6.73 (s, 1H, H-3), 6.61 (t of dd, J = 2.2 Hz, 2.2 Hz, 2.2 Hz, 1H, H-4′), 4.39 (dd, J = 11.1 Hz, 2.9 Hz, 1H, $-OCH_2$), 4.06 (dd, J = 11.1 Hz, 5.8 Hz, 1H, $-OCH_2$), 3.87 (s, 6H, $-OCH_3$), 3.44−3.39 (m, 1H, −OCH), 2.96 (t, J = 4.5 Hz, 4.5 Hz, 1H, $-OCH_2$), 2.80 (dd, J = 4.8 Hz, 2.6 Hz, 1H, $-OCH_2$).

To a well-stirred solution of substituted 7-hydroxyflavone **48**−**51** (17.8 mmol), an excess of epichlorohydrin was added as well as anhydrous K_2CO_3 (54 mmol), and the reaction mixture was heated at 100−110 °C for 2−6 h. K_2CO_3 was filtered, and the residue was taken in chloroform, washed with water, and the organic layer was dried (Na_2SO_4). The solvent was removed, and the product was purified by column chromatography to afford **58**−**61**.

*3′,5′-bis(2-Chlorobenzyloxy)-7-(2,3-epoxypropoxy)flavone (**58**).* Yield 79%; mp 135 °C; ESMS: 575 (M + 1), 577 (M + 3); ^1H NMR (200 MHz, $CDCl_3$): δ 8.01 (d, 1H, J = 8.4 Hz, H-5); 7.41 (s, 1H); 7.56 (m, 6H, −Ph); 7.33 (d, J = 4.4 Hz, 1H, −Ph); 7.15 (s, 1H, H-4′); 6.91 (d, 2H, −Ph); 6.78 (s; 1H, H-3); 6.68 (s, 1H, H-8); 6.35 (d, J = 4.4 Hz, 1H, H-6); 5.22 (s, 4H, $-OCH_2$); 4.42 (dd, J = 5.6 Hz, 1H, $-OCH_2$); 4.07 (dd, J = 5.6 Hz, 1H, $-OCH_2$); 3.42 (m, 1H, −OCH); 2.87 (m, 1H, $-OCH_2$); 2.82 (m, 1H, $-OCH_2$).

*3′,5′-bis(2-Methylbenzyloxy)-7-(2,3-epoxypropoxy)flavone (**59**).* Yield 67%; mp 115 °C; ESMS: 535 (M + 1), FT-IR(KBr): 1644, 1603, 1440 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz 1H, H-5); 7.21 (m, 6H, −Ph);7.41 (d, J = 5.2 Hz, 2H, −Ph); 7.13 (d, J = 2.0 Hz, 2H, −Ph); 7.02 (d, J = 2.2 Hz, 1H, −Ph); 6.78 (d, J = 2.0 Hz, 1H, −Ph); 6.73 (s, 1H, H-3); 5.07 (s, 4H, $-OCH_2$); 4.35 (d, J = 2.6 Hz, 1H, $-OCH_2$); 4.06 (d, J = 6.0 Hz, 1H, $-OCH_2$); 3.41 (m, 1H, −OCH); 2.93 (d, J = 4.2 Hz, 2H, $-OCH_2$); 2.40 (s, 6H, $-CH_3$).

*3′,5′-bis(4-Methylbenzyloxy)-7-(2,3-epoxypropoxy)flavone (**60**).* Yield 55%; mp 128 °C; ESMS: 535 (M + 1); FT-IR(KBr): 1643, 1603, 1443 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.15 (d, J = 8.7 Hz, 1H, H-5); 7.11−7.36 (m, 10H, −Ph); 6.76 (m, 1H, −Ph); 6.70 (s, 1H, −H-3); 5.06 (s, 4H, $-OCH_2$); 4.41 (dd, J = 8.3 Hz, 3.0 Hz, 1H, $-OCH_2$); 4.0 (m, 2H, $-OCH_2$ and −OCH); 2.96 (m, 1H, $-OCH_2$), 2.81 (m, 1H, OCH_2), 2.37 (s, 6H, $-CH_3$).

*3′,5′-bis(3,5-Dichlorobenzyloxy)-7-(2,3-epoxypropoxy)flavone (**61**).* Yield 81%; mp 105 °C; ES-MS: 645 (M + 1); ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 7.8 Hz, 1H, H-5); 7.61 (d, J = 2.0 Hz, 2H, H-2′, and H-6′); 7.41 (m, 2H, H-3, and H-4′); 7.12 (m, 4H, −Ph); 6.69 (d, J = 2.2 Hz, 2H, −Ph); 6.60 (m, 1H, H-8); 6.50 (s, 1H, H-6); 4.90 (s, 4H, $-OCH_2$); 3.96 (m, 2H, $-OCH_2$ and −OCH); 3.85 (m, 1H, $-OCH_2$); 2.82 (m, 1H, $-OCH_2$); 2.56 (m, 1H, $-OCH_2$).

Typical Procedure for Epoxide Ring-Opening by Amines. A solution of 7-epoxyflavone (**52**−**61**, 4.9 mmol) and corresponding amine (9.8 mmol) in dry methanol or absolute ethanol (150 mL) was refluxed for 6 h. The solvent was removed, and the products were purified by column chromatography to 6- or 7-(3-amino-2-hydroxypropoxy)flavones **62**−**85**.

*3′,4′-Dibenzyloxy-6-[3-tert-butylamino-2-hydroxypropoxy]-flavone (**62**).* Yield 89%; mp 156−157 °C; MS (FAB): 580 (M + 1); IR (KBr): 3404, 1621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.51−7.26 (m, 15H, −Ph), 6.97 (d, J = 8.9 Hz, 1H, −Ph), 6.62 (s, 1H, H-3), 5.22 (s, 2H, $-OCH_2$), 5.20 (s, 2H, $-OCH_2$), 4.26−4.22 (m, 1H, $-OCH_2$), 4.14−4.10 (m, 2H, $-OCH_2$ and −OCH), 3.07−2.86 (m, 2H, $-NCH_2$), 1.29 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{36}H_{37}NO_6$: C = 74.59; H = 6.43; N = 2.42; found: C = 74.61; H = 6.62; N = 2.36.

*3′,4′-Dibenzyloxy-7-[3-tert-butylamino-2-hydroxypropoxy]-flavone (**63**).* Yield 85%; mp 159−61 °C; MS (FAB): 580 (M + 1); IR (KBr): 3400, 1633 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.08 (d, J = 8.7 Hz, 1H, H-5), 7.50−7.28 (m, 12H, −Ph), 7.02−6.93 (m, 3H, −Ph), 6.60 (s, 1H, H-3), 5.23 (s, 4H, $-OCH_2$), 4.10−3.98 (m, 1H, $-OCH_2$ and −OCH), 2.90 (dd, J = 5.9 Hz, 3.8 Hz, 1H, $-OCH_2$), 2.71 (dd, J = 5.9 Hz, 7.3 Hz, 1H, $-NCH_2$), 2.47 (m, 1H, $-NCH_2$), 1.14 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{36}H_{37}NO_6$: C = 74.59; H = 6.43; N = 2.42; found: C = 73.36; H = 6.62; N = 2.39.

*3′,4′-Dibenzyloxy-7-[3-isopropylamino-2-hydroxypropoxy]-flavone (**64**).* Yield 87%; mp 177−179 °C; MS (FAB): 566 (M + 1); IR (KBr): 3423, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.02 (d, J = 8.5 Hz, 1H, H-5), 7.70−7.32 (m, 12H, −Ph), 7.11−6.98 (m, 3H, −Ph), 6.64 (s, 1H, H-3), 5.24 (s, 2H, $-OCH_2$), 5.23 (s, 2H, $-OCH_2$), 4.14−4.09 (m, 3H, $-OCH_2$ and −OCH), 3.05 (m, 1H, $-NCH_2$), 2.92−2.68 (m, 2H, $-NCH_2$ and −NCH), 1.09 (d, J = 6.2 Hz, 6H, $-CH_3$). Elemental analysis: calculated for $C_{35}H_{35}NO_6$: C = 74.32; H = 6.24; N = 2.48; found: C = 74.46; H = 6.19; N = 2.36.

*3′,4′-Dimethoxy-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**65**).* Yield 83%; mp 144−145 °C; MS (FAB): 414 (M + 1); IR (KBr): 3410, 1634 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, J = 9.5 Hz, 1H, H-5), 7.51 (dd, J = 8.5 Hz, 1.7 Hz, 1H, H-2′), 7.36 (d, J = 1.7 Hz, 1H, H-8), 6.96−6.92 (m, 3H, −Ph), 6.74 (s, 1H, H-3), 4.18−4.12 (m, 3H, $-OCH_2$ and −OCH), 3.97 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$), 3.10−2.75 (m, 3H, $-NCH_2$ and −NCH), 1.23 (d, J = 6.3 Hz, 6H, $-CH_3$). Elemental analysis: calculated for $C_{23}H_{27}NO_6$: C = 66.81; H = 6.58; N = 3.39; found: C = 66.67; H = 6.65; N = 3.53.

*3′,4′-Dimethoxy-7-[3-(4-phenylpiperazin-1-yl)-2-hydroxypropoxy]flavone (**66**).* Yield 94%; mp 191−193 °C; MS (FAB): 517 (M + 1); IR (KBr): 3416, 1627 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, J = 9.5 Hz, 1H, H-5), 7.54 (dd, J = 8.3 Hz, 2.1 Hz, 1H, H-2′), 7.34 (d, J = 1.9 Hz, 1H, H-8), 7.31−7.23 (m, 2H, −Ph), 7.04−6.87 (m, 6H, −Ph), 6.70 (s, 1H, H-3), 4.21−4.16 (m, 3H, $-OCH_2$ and −OCH), 3.99 (s, 3H, $-OCH_3$), 3.97 (s, 3H, $-OCH_3$), 3.28 (t, J = 4.8 Hz, 4H, $-CH_2$), 2.90−2.71 (m, 2H, $-NCH_2$), 2.71 − 2.65 (m, 4H, $-CH_2$). Elemental analysis: calculated for $C_{30}H_{32}N_2O_6$: C = 69.75; H = 6.24; N = 5.42; found: C = 69.96; H = 6.57; N = 5.51.

*3′,4′,5′-Trimethoxy-7-[3-tert-butylamino-2-hydroxypropoxy]-flavone (**67**).* Yield 84%; mp 119−120 °C; MS (FAB): 458 (M + 1); IR (KBr): 3403, 1631 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, J = 9.5 Hz, 1H, H-5), 7.10 (m, 2H, H-6, and H-8), 7.02−6.99 (m, 2H, H-2′, and H-6′), 6.70 (s, 1H, H-3), 4.14−4.11 (m, 3H, $-OCH_2$ and −OCH), 3.96 (s, 6H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 2.86−2.81 (m, 2H, $-NCH_2$), 1.14 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{25}H_{31}NO_7$: C = 65.63; H = 6.83; N = 3.06; found: C = 65.47; H = 6.77; N = 3.12.

*3′,4′,5′-Trimethoxy-7-[3-isopropylamino-2-hydroxypropoxy]-flavone (**68**).* Yield 65%; mp 106−107 °C; MS (FAB): 444 (M + 1); IR (KBr): 3394, 1631 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.09 (d, J = 9.5 Hz, 1H, H-5), 7.10 (m, 2H, H-6, and H-8), 7.10−6.99 (m, 2H, H-2′, and H-6′), 6.71 (s, 1H, H-3), 4.16−4.09 (m, 3H, $-OCH_2$ and

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−OCH), 3.96 (s, 6H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 2.95−2.82 (m, 3H, $-NCH_3$ and −NCH), 1.14 (d, J = 6.2 Hz, 6H, $-CH_3$). Elemental analysis: calculated for $C_{24}H_{29}NO_7$: C = 65.00; H = 6.59; N = 3.16; found: C = 65.16; H = 6.47; N = 3.31.

*3′,4′,5′-Trimethoxy-7-[3-(4-phenylpiperazin-1-yl)-2-hydroxypropoxy]flavone (**69**).* Yield 85%; mp 170−171 °C; MS (FAB): 547 (M + 1); IR (KBr): 3406, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, J = 9.5 Hz, 1H, H-5), 7.27 (t, J = 7.9 Hz, 2H, H-6, and H-8), 7.10 (m, 2H, H-2′, and H-6′), 7.04−7.01 (m, 2H, −Ph), 6.95−6.87 (m, 3H, −Ph), 6.70 (s, 1H, H-3), 4.21−4.12 (m, 3H, $-OCH_2$ and −OCH), 3.95 (s, 6H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 3.23 (t, J = 4.6 Hz, 4H, $-CH_2$), 2.87−2.83 (m, 2H, $-NCH_2$), 2.68−2.65 (m, 4H, $-OCH_2$). Elemental analysis: calculated for $C_{31}H_{34}N_2O_7$: C = 68.12; H = 6.27; N = 5.12; found: C = 68.26; H = 6.37; N = 5.41.

*3′,5′-Dibenzyloxy-7-[3-tert-butylamino-2-hydroxypropoxy]-flavone (**70**).* Yield 93%; mp 170−171 °C; MS (FAB): 580 (M + 1); IR (KBr): 3428, 1648 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.02 (d, J = 8.8 Hz, 1H, H-5), 7.59−7.33 (m, 10H, −Ph), 7.13 (d, J = 1.9 Hz, 2H, H-2′, and H-6′), 7.07 (s, 1H, H-8), 7.01 (dd, J = 9.8 Hz, 2.0 Hz, 1H, H-6), 6.76 (s, 1H, H-4′), 6.71 (s, 1H, H-3), 5.12 (s, 4H, $-OCH_2$), 4.57−4.54 (m, 1H, $-OCH_2$), 4.27−4.16 (m, 2H, $-OCH_2$ and −OCH), 3.24 (d, J = 10.5 Hz, 1H, $-NCH_2$), 3.05 (t, J = 10.6 Hz, 1H, $-NCH_2$), 1.45 (s, 9H, $-CH_3$); ^{13}C NMR: δ 178.3, 163.5, 163.2, 160.7, 158.1, 136.8, 133.9, 129.0, 128.6, 127.9, 127.5, 118.3, 115.2, 108.0, 105.9, 101.5, 72.9, 70.8, 67.5, 54.0, 45.3, 28.1. Elemental analysis: calculated for $C_{36}H_{37}NO_6$: C = 74.59; H = 6.43; N = 2.42; found: C = 74.44; H = 6.35; N = 2.51.

*3′,5′-Dibenzyloxy-7-[3-isopropylamino-2-hydroxypropoxy]-flavone (**71**).* Yield 79%; mp 173−174 °C; MS (FAB): 566 (M + 1); IR (KBr): 3431, 1637 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.05 (d, J = 8.6 Hz, 1H, H-5), 7.59−7.34 (m, 10H, −Ph), 7.15 (d, J = 1.8 Hz, 2H, H-2′, and H-6′), 7.06 (s, 1H, H-8), 7.03 (d, J = 9.4 Hz, 1H, H-6), 6.78 (s, 1H, H-4′), 6.71 (s, 1H, H-3), 5.13 (s, 4H, $-OCH_2$), 4.14−4.11 (m, 3H, $-OCH_2$ and −OCH), 3.18−3.16 (m, 1H, $-NCH_2$), 2.93−2.79 (m, 2H, $-NCH_2$ and −NCH), 1.11 (d, J = 6.2 Hz, 6H, $-OCH_3$); ^{13}C NMR δ 177.9, 163.8, 162.9, 160.6, 158.1, 136.7, 133.9, 128.9, 128.5, 127.8, 127.1, 118.1, 115.3, 108.0, 105.8, 105.3, 101.5, 71.7, 70.7, 68.4, 49.8, 49.3, 23.1, 23.0. Elemental analysis: calculated for $C_{35}H_{35}NO_6$: C = 74.32; H = 6.24; N = 2.48. found: C = 74.16; H = 6.17; N = 2.29.

*3′,5′-Dibenzyloxy-7-[3-(4-phenylpiperazin-1-yl)-2-hydroxypropoxy]flavone (**72**).* Yield 94%; mp 168−170 °C; MS (FAB): 669 (M + 1); IR (KBr): 3389, 1634 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, J = 8.6 Hz, 1H, H-5), 7.46−7.30 (m, 10H, −Ph), 7.26−7.23 (m, 2H, −Ph), 7.11 (d, J = 1.9 Hz, 2H), 7.00 (d, J = 8.5 Hz, 1H, −Ph), 6.98 (s, 1H, H-8), 6.95−6.86 (m, 3H, −Ph), 6.76 (s, 1H, H-4′), 6.69 (s, 1H, H-3), 5.09 (s, 4H, $-OCH_3$), 4.21−4.14 (m, 3H, $-OCH_2$ and −OCH), 3.23 (t, J = 4.7 Hz, 4.6 Hz, 4H, $-CH_2$), 2.91−2.81 (m, 2H, $-NCH_2$), 2.66 (dd, J = 5.2 Hz, 4.1 Hz, 4H, $-CH_2$). Elemental analysis: calculated for $C_{42}H_{40}N_2O_6$: C = 75.43; H = 6.03; N = 4.19; found: C = 75.37; H = 6.20; N = 4.13.

*3′,5′-Dimethoxy-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**73**).* Yield 66%; mp 145−146 °C; MS (FAB): 428 (M + 1); IR (KBr) 3431, 1631 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.93 (d, J = 8.8 Hz, 1H, H-5), 7.32 (d, J = 1.9 Hz, 1H, H-8), 7.15 (d, J = 2.0 Hz, 2H, H-2′. and H-6′), 7.08 (dd, J = 8.9 Hz, 2.0 Hz, 1H, H-6), 6.92 (s, 1H, H-4′), 6.68 (s, 1H, H-3), 4.17−4.01 (m, 3H, $-OCH_2$ and −OCH), 3.82 (s, 6H, $-OCH_3$), 2.77−2.59 (m, 2H, $-NCH_2$), 1.08 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{24}H_{29}NO_6$: C = 67.43; H = 6.84; N = 3.28; found: C = 67.59; H = 6.73; N = 3.39.

*3′,5′-Dimethoxy-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**74**).* Yield 87%; mp 155−156 °C; MS (FAB): 414 (M + 1); IR (KBr): 3426, 1630 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.95 (d, J = 8.9 Hz, 1H, H-5), 7.34 (s, 1H, H-8), 7.18 (d, J = 1.8 Hz, 2H, H-2′, and H-6′), 7.09 (dd, J = 8.9 Hz, 1.9 Hz, 1H, H-6), 6.96 (s, 1H, H-4′), 6.70 (s, 1H, H-3), 4.20−3.90 (m, 3H, $-OCH_2$ and −OCH), 3.85 (s, 6H, $-OCH_3$), 2.84−2.58 (m, 3H, $-NCH_2$ and −NCH), 1.03 (d, J = 6.2 Hz, 6H, $-CH_3$). Elemental analysis: calculated for $C_{23}H_{27}NO_6$: C = 66.81; H = 6.58; N = 3.39; found: C = 66.69; H = 6.13; N = 3.62.

*3′,5′-Dimethoxy-7-[3-(4-phenylpiperazin-1-yl)-2-hydroxypropoxy]flavone (**75**).* Yield 84%; mp 195−196 °C; MS (FAB): 517 (M + 1); IR (KBr): 3417, 1633 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.97 (d, J = 8.8 Hz, 1H, H-5), 7.40 (d, J = 1.9 Hz, 1H, H-8), 7.24 (d, J = 1.9 Hz, 2H, H-2′, and H-6′), 7.20 (d, J = 7.9 Hz, 2H, −Ph), 7.12 (dd, J = 8.9 Hz, 1.9 Hz, 1H, −Ph), 7.04 (s, 1H, H-6), 6.93 (d, J = 8.2 Hz, 2H, −Ph), 6.80 (d, J = 7.1 Hz, 1H, H-4′), 6.74 (s, 1H, H-3), 4.25−4.09 (m, 3H, $-OCH_2$ and −OCH), 3.87 (s, 6H, $-OCH_3$), 3.13 (t, J = 6.5 Hz, 4H, $-CH_2$), 2.63 (d, J = 4.5 Hz, 2H, $-NCH_2$), 2.47−2.43 (m, 4H, $-CH_2$). Elemental analysis: calculated for $C_{30}H_{32}N_2O_6$: C = 69.75; H = 6.24; N = 5.42; found: C = 69.61; H = 6.53; N = 5.61.

*3′,5′-bis(2-Chlorobenzyloxy)-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**76**).* Yield 52%; mp 160 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.14 (d, J = 9.5 Hz, 1H, H-5); 7.57 (d, 2H, J = 4.9 Hz, H-2′,and H-6′); 7.57 (m, 4H, −Ph); 7.19 (m, 4H, −Ph); 7.05 (m, 2H, H-4′,and H-3); 6.78 (d, J = 1.4 Hz, 2H, H-6,and H-8); 5.22 (s, 4H, $-OCH_2$); 4.11(m, 3H, $-OCH_2$); 2.98 (m, 1H, N−CH_2), 2.88 (m, 1H, N−CH_2); 1.16 (s, 9H, $-CH_3$). ES-MS: 648 (M + 1), 650 (M + 3); HRMS: calc. for $C_{36}H_{36}Cl_2NO_6$ = 648.1920; obtained: 648.1925.

*3′,5′-bis(2-Chlorobenzyloxy)-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**77**).* Yield 58%, mp 155 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.07 (d, J = 8.9 Hz, 1H, H-5); 7.67 (s, 1H); 7.61 (d, J = 4.0 Hz, 2H, H-2′, and H-6′); 7.57 (m, 5H, −Ph); 7.19 (m, 2H, H-3, H-4′); 7.05 (m, 2H, H-6, and H-8); 6.80 (d, J = 9.6 Hz, 2H, −Ph); 5.24 (s, 4H, $-OCH_2$); 4.33 (m, 1H, $-OCH_2$), 4.18 (m, 2H, $-OCH_2$); 2.98 (m, 1H, N−CH_2), 2.88 (m, 2H, N−CH_2 and N−CH); 1.28 (d, J = 5.7 Hz, 6H, $-CH_3$). ES-MS: 634 (M + 1), 636 (M + 3); HRMS: calc. for $C_{35}H_{34}Cl_2NO_6$ = 634.1763; obtained = 634.1781.

*3′,5′-bis(2-Methylbenzyloxy)-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**78**).* Yield 61%; mp 175 °C; FT-IR (KBr): 1633, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 3.6 Hz, 1H, H-5); 7.41 (d, J = 4.2 Hz, 2H, H-2′, and H-6′); 7.31 (m, 6H, −Ph); 7.13 (m, 2H, −Ph); 7.00 (m, 2H, H-3, and H-4′); 6.74 (m, 2H, H-6, and H-8); 5.06 (s, 4H, $-OCH_2$); 4.54 (m, 1H, $-OCH_2$); 4.14 (m, 2H, $-OCH_2$ and OCH); 3.37 (m, 1H, N−CH_2); 3.01 (m, 1H, N−CH_2); 2.40 (s, 6H, $-CH_3$); 1.47 (d, 9H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ 159.2, 135.4, 132.9, 129.2, 127.5, 127.2, 125.8, 124.8, 104.1, 103.7, 67.7, 63.9, 55.7, 48.2, 43.5, 24.5, 17.7; ES-MS: 607 (M + 1); HRMS calc. for $C_{38}H_{41}NO_6$ = 608.3010; obtained = 608.3015.

*3′,5′-bis(2-Methylbenzyloxy)-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**79**).* Yield 65%; mp 235 °C; FT-IR (KBr): 3405, 1637, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + CD_3OD): δ 8.05 (d, J = 8.4 Hz, 1H, H-5); 7.29 (d, J = 2.2 Hz, 2H, H-2′, and H-6′); 7.23 (m, 4H, −Ph); 7.18 (d, J = 2.2 Hz, 2H, −Ph); 7.02 (d, J = 2.2 Hz, 2H, H-3, and H-4′); 6.80 (d, J = 2.0 Hz, 1H, H-8); 6.77 (s, 1H, H-6); 5.10 (s, 4H, $-OCH_2$); 4.17 (m, 2H, $-OCH_2$); 3.40 (m, 1H, OCH); 2.93 (d, J = 4.2 Hz, 2H, N−CH_2); 2.41 (s, 6H, $-CH_3$); 1.41 (d, J = 3.3 Hz, 6H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 163.4, 162.9, 160.3, 157.8, 136.7, 133.9, 130.3, 128.7, 126.8,125.9, 117.7, 114.8, 107.3, 105.4, 104.8, 101.0, 70.1, 68.9, 65.0, 50.8, 18.9, 18.7. ES-MS: 594 (M + 1); HRMS: calc. for $C_{37}H_{39}NO_6$ = 594.2856; obtained = 594.2847.

*3′,5′-bis(4-Methylbenzyloxy)-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**80**).* Yield 71%; mp 135 °C; FT-IR (KBr): 1643, 1606, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, J = 8.7 Hz, 1H, H-5); 7.35 (d, J = 4.8 Hz, 4H, -Ph, H-2′, and H-6′); 7.22 (d, J = 4.8 Hz, 4H, −Ph); 7.10 (d, J = 2.1 Hz, 2H, H-3, and H-4′); 7.00 (d, J = 2.1 Hz, 2H, −Ph,); 6.74 (d, J = 1.8 Hz, 1H, H-8); 6.70 (s, 1H, H-6); 5.04 (s, 4H, $-OCH_2$); 3.93 (m, 3H, $-OCH_2$); 2.90 (m, 1H, $-NCH_2$); 2.84 (m, 1H, $-NCH_2$); 2.36 (s, 6H, $-CH_3$); 1.18 (s, 9H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 163.3, 163.1, 160.1, 157.7, 137.8, 133.0, 129.1, 127.5, 126.6, 117.3, 114.8, 107.0, 105.3, 104.9, 100.9, 81.0, 74.8, 71.1, 70.1, 69.5, 68.1, 52.5, 50.7, 28.1, 26.4, 20.8. ESMS: 608 (M + 1), HRMS: calc. for $C_{38}H_{41}NO_6$ = 608.3010; obtained = 608.3015.

*3′,5′-bis(4-Methylbenzyloxy)-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**81**).* Yield 66%; mp 145 °C; ESMS: 594 (M + 1); FT-IR (KBr): 1646, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 8.7 Hz, 1H, H-5); 7.34 (d, J = 4.8 Hz, 4H, −Ph, H-2′ and

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H-6′); 7.21 (d, J = 4.8 Hz, 4H, −Ph) 6.94 (d, J = 2.1 Hz, 2H, H-3, and H-4′); 6.73 (d, J = 1.8 Hz, 1H, H-8); 6.68 (s, 1H, H-6); 5.03 (s, 4H, $-OCH_2$); 4.09 (m, 3H, $-OCH_2$); 2.90 (m, 2H, $-NCH_2$); 2.84 (m, 1H, −NCH); 2.36 (s, 6H, $-CH_3$); 1.12 (d, J = 3.3 Hz, 6H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 163.2, 162.7, 160.3, 157.7, 137.9, 133.5, 133.3, 129.3, 127.7, 126.9, 117.9, 114.6, 107.7, 105.4, 104.9, 101.0, 71.1, 70.3, 67.9, 52.5, 49.0, 22.9, 22.8, 21.2. 594 (M + 1); HRMS: calc. for $C_{37}H_{39}NO_6$ = 594.2856; obtained = 594.2847.

3′,5′-bis(4-Methylbenzyloxy)-7-[3-(2-chlorobenzylamino)-2-hydroxypropoxy]flavone (**82**). Yield 61%; mp 178 °C; FT-IR (KBr): 1645, 1604, 1441 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 8.7 Hz, 1H, H-5); 7.30 (m, −Ph, 10H); 7.14(m, −Ph, 4H); 6.97 (d, J = 6.2 Hz, 2H, H-2′, and H-6′); 6.77 (s, 1H, H-3); 6.72 (s, 1H, H-8); 6.72 (s, 1H, H-6); 5.07 (s, 4H, $-OCH_2$); 4.14 (m, 3H, $-OCH_2$ and $-NCH_2$); 2.90 (m, 2H, OCH_2 and OCH); 2.87 (m, 2H, $-NCH_2$); 2.40 (s, 6H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 163.2, 162.7, 160.3, 157.7, 137.9, 136.4, 133.9, 133.5, 133.3, 130.3, 129.6, 128.8, 127.6, 126.9, 117.9, 114.7, 107.8, 105.4, 105.0, 101.1, 70.9, 70.3, 67.9, 50.9, 50.8, 21.2. ESMS: 676 (M + 1), HRMS: calc. for $C_{41}H_{38}ClNO_6$ = 676.2466; obtained = 676.2445.

3′,5′-bis(4-Methylbenzyloxy)-7-[3-di-isopropylamino-2-hydroxypropoxy]flavone (**83**). Yield 61%; mp 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 8.7 Hz, 1H, H-5); 7.30 (m, 2H, H-2′, and H-6′); 7.14 (m, 4H, −Ph); 6.97 (d, J = 6.2 Hz, 2H, −Ph); 6.77 (s, 1H, H-3); 6.72 (s, 1H, H-8); 6.56 (s, 1H, H-6); 5.07 (s, 4H, $-OCH_2$); 4.57 (m, 1H, $-OCH_2$); 4.34 (m, 1H, $-OCH_2$); 3.98 (m, 1H, OCH); 3.65 (m, 2H, $-NCH_2$); 3.23 (m, 2H, −NCH); 2.37 (s, 6H, $-CH_3$); 1.53 (d, J = 6.2 Hz, 12H, $-CH_3$); ESMS: 636 (M + 1); Elemental analysis: calc. for $C_{40}H_{45}NO_6$: C = 75.56; H = 7.13; N = 2.20; obtained: C = 75.24; H = 7.01; N = 2.01.

3′,5′-bis(3,5-Dichlorobenzyloxy)-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**84**). Yield 54%; mp 143 °C; ES-MS: 718 (M + 1), ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.6 Hz, 1H, H-5); 7.61 (m, 3H, −Ph, H-2′, and H-6′); 7.40 (m, 2H, −Ph); 7.14 (m, 4H, −Ph); 6.78 (d, J = 2.2 Hz, 2H, H-4′, and −Ph); 6.50 (m, 1H, H-3); 6.60 (m, 1H, H-8); 6.50 (s, 1H, H-6); 5.09 (s, 4H, $-OCH_2$); 4.17 (m, 2H, $-OCH_2$ and −OCH); 3.96 (m, 1H, $-OCH_2$); 2.56 (m, 1H, $-NCH_2$); 2.42 (m, 1H, $-NCH_2$); 1.22 (s, 9H, $-CH_3$); Elemental analysis calc. for $C_{36}H_{33}Cl_4NO_6$: C = 60.27; H = 4.64; N = 1.95; obtained, C = 60.57; H = 4.44; N = 1.75.

3′,5′-bis(3,5-Dichlorobenzyloxy)-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**85**). Yield 52%; mp 127 °C; ES-MS: 702 (M + 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 8.8 Hz, 1H, H-5); 7.22 (m, 8H, −Ph, H-2′, and H-6′); 6.98 (m, 4H, −Ph); 6.74 (d, J = 2.2 Hz, 1H, H-8); 6.70 (d, J = 1.2 Hz, 1H, H-6); 5.04 (s, 4H, $-OCH_2$); 4.10 (m, 3H, $-CH_2$ and −OCH); 2.75 (m, 1H, $-NCH_2$); 2.58 (m, 1H, $-NCH_2$); 2.36 (m, 1H, −NCH); 1.02 (d, J = 4.6 Hz, 6H, $-CH_3$); HRMS: calc. for $C_{35}H_{31}Cl_4O_6$ = 702.0985, obtained = 702.0990.

General Procedure of Debenzylation. The suitable flavones **62**−**64** or **70**−**71** (2.2 mmol) were taken in dry methanol (40 mL), and Pd−C (30 mg) was added followed by shaking in Parr hydrogenation assembly at 40 psi of hydrogen atmosphere. On completion of the reaction, the catalyst was filtered and the solvent was removed to get crude flavones **86**−**90**, which were purified by column chromatography.

3′,4′-Dihydroxy-6-[3-tert-butylamino-2-hydroxypropoxy]flavone (**86**). Yield 93%; mp 193 °C (decomposes); MS (FAB): 400 (M + 1); IR (KBr): 3399, 1616 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.93 (s, 1H, H-8), 7.55 (d, J = 9.5 Hz, 1H, H-2′), 7.53 (s, 1H, H-7), 7.39 (d, J = 9.8 Hz, 1H, H-6′), 7.34 (d, J = 8.5 Hz, 1H, H-6), 6.93 (d, J = 8.0 Hz, 1H, H-5′), 6.62 (s, 1H, H-3), 4.41−4.12 (m, 3H, $-OCH_2$ and −OCH), 3.07−2.93 (m, 2H, $-NCH_2$), 1.33 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{22}H_{25}NO_6$: C = 66.15; H = 6.31; N = 3.51; found: C = 66.26; H = 6.47; N = 3.61.

3′,4′-Dihydroxy-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**87**). Yield 97%; mp 165 °C (decomposes); MS (FAB): 400 (M + 1); IR (KBr): 3274, 1623 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.95 (d, J = 8.8 Hz, 1H, H-5), 7.47 (s, 1H, H-8), 7.44 (d, J = 9.4 Hz, 1H, H-2′), 7.29 (s, 1H, H-6), 7.10 (d, J = 8.8 Hz, 1H, H-6′), 6.95 (d, J = 8.1 Hz, 1H, H-5′), 6.68 (s, 1H, H-3), 4.28−4.19 (m, 3H, $-OCH_2$ and −OCH), 3.18−3.14 (m, 1H, $-NCH_2$), 2.97−2.94 (m, 1H, $-NCH_2$), 1.34 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{22}H_{25}NO_6$: C = 66.15; H = 6.31; N = 3.51; found: C = 66.26; H = 6.27; N = 3.27.

3′,4′-Dihydroxy-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**88**). Yield 88%; mp 187 °C (decomposes); MS (FAB): 386 (M + 1); IR (KBr): 3425, 1624 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.96 (d, J = 7.1 Hz, 1H, H-5), 7.47 (s, 1H, H-8), 7.45 (d, J = 8.2 Hz, 1H, H-2′), 7.30 (s, 1H, H-6), 7.10 (d, J = 8.1 Hz, 1H, H-6′), 6.95 (d, J = 7.6 Hz, 1H, H-5′), 6.68 (s, 1H, H-3), 4.23−4.18 (m, 3H, $-OCH_2$ and −OCH), 3.21−3.18 (m, 3H, $-NCH_2$ and −NCH), 1.27 (d, J = 6.2 Hz, 6H, $-CH_3$). Elemental analysis: calculated for $C_{21}H_{23}NO_6$: C = 65.44; H = 6.02; N = 3.63; found: C = 65.37; H = 6.18; N = 3.47.

3′,5′-Dihydroxy-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**89**). Yield 96%; mp 153 °C (decomposes); MS (FAB): 400 (M + 1); IR (KBr): 3401, 1618 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.98 (d, J = 8.8 Hz, 1H, H-5), 7.30 (s, 1H, H-8), 7.13 (d, J = 8.8 Hz, 1H, H-6), 6.90 (d, J = 1.2 Hz, 2H, H-2′, and H-6′), 6.7 (s, 1H, H-3), 6.52 (s, 1H, H-4′), 4.27−4.23 (m, 3H, OCH_2 and −OCH), 3.18−2.99 (m, 2H, $-NCH_2$), 1.32 (s, 9H, $-CH_3$). Elemental analysis: calculated for $C_{22}H_{25}NO_6$: C = 66.15; H = 6.31; N = 3.51; found: C = 66.19; H = 6.47; N = 3.43.

3′,5′-Dihydroxy-7-[3-isopropylamino-2-hydroxypropoxy]flavone (**90**). Yield 95%; mp 185 °C (decomposes); MS (FAB): 386 (M + 1); IR (KBr): 3244, 1623 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.85 (s, 2H, −OH), 7.72 (d, J = 8.8 Hz, 1H, H-5), 7.06 (d, J = 1.7 Hz, 1H, H-8), 6.87 (dd, J = 8.8 Hz, 1.9 Hz, 1H, H-6), 6.66 (d, J = 1.7 Hz, 2H, H-2′, and H-6′), 6.45 (s, 1H, H-3), 6.29 (s, 1H, H-4′), 4.00−3.97 (m, 3H, $-OCH_2$ and −OCH), 3.13−3.03 (m, 1H, $-NCH_2$), 2.94−2.75 (m, 2H, $-NCH_2$ and −NCH), 1.24 (d, J = 5.7 Hz, 6H, CH_3); ^{13}C NMR: δ 176.7, 163.3, 163.1, 159.3, 157.7, 133.2, 126.6, 117.6, 115.4, 106.9, 106.3, 104.6, 101.9, 70.9, 65.3, 50.3, 46.9, 19.0, 18.6. Elemental analysis: calculated for $C_{21}H_{23}NO_6$: C = 65.44; H = 6.02; N = 3.63; found: C = 66.26; H = 6.18; N = 3.44.

(R)-(−)-3′,5′-Dibenzyloxy-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**70b**). A mixture of 3′,5′-dibenzyloxy-7-hydroxyflavone (**46**, 1.0 g, 2.2 mmol) and (*S*)-(+)-epichlorohydrin (1.0 mL, 12.0 m mol) was heated at 120 °C for ∼2 h. The cooled reaction mixture was taken in toluene, and a solution of aq. NaOH (10 mg, 0.0.25 mmol) and benzyltriethyl ammonium chloride (10 mg, 0.04 mmol) were added followed by stirring at room temperature for 2 h. On completion, the organic layer was separated and dried and the solvent was evaporated at reduced pressure to give crude 3′,5′-dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56b**) of *R*-configuration (yield 0.9 g, 80%). The thus-obtained (*R*)-3′,5′-dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56b**, 600 mg, 4.9 mmol) and *tert*-butyl amine (0.26 mL, 9.8 mmol) in dry methanol (50 mL) were refluxed for ∼6 h. The solvent was evaporated at reduced pressure, and the crude product was purified by column chromatography to afford (*R*)-(−)-3′,5′-dibenzyloxy-7-(3-*tert*-butylamino-2-hydroxypropoxy)flavone (**70b**). Yield = 0.65 g, 93%; mp = 158 °C; $[\alpha]_D$ = −8.6° (c = 1.5%, $CHCl_3$).

(S)-(+)-3′,5′-Dibenzyloxy-7-[3-tert-butylamino-2-hydroxypropoxy]flavone (**70a**). A mixture of 3′,5′-dibenzyloxy-7-hydroxyflavone (**46**, 1.2 g, 2.6 mmol) and (*R*)-(−)-epichlorohydrin (1.12 mL, 15.0 mmol) was heated at 120 °C for ∼2 h. The cooled reaction mixture was taken in toluene, and a solution of aq. NaOH (15 mg, 0.37 mmol) and benzyltriethylammonium chloride (15 mg, 0.06 mmol) were added and stirred at room temperature for 2 h. The organic layer was separated and dried, and the solvent was removed at reduced pressure to give crude (*S*)-(+)-7-(2,3-epoxypropoxy)-3′,5′-dibenzyloxyflavone (**56a**) (yield 1.12 g, 83%). The solution of the (*S*)-3′,5′-dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56a**, 500 mg, 4.9 mmol) in dry methanol (50 mL) and *tert*-butyl amine (0.2 mL, 9.8 mmol) was refluxed for ∼6 h. The solvent was removed at reduced pressure, and the crude product was purified by column chromatography to afford (*S*)-(+)-3′,5′-dibenzyloxy-7-(3-*tert*-butylamino-2-hydroxypropoxy)flavone (**70a**). Yield = 0.52 g, 93%; mp = 165 °C; $[\alpha]_D$ = +9.0° (c = 20 mg/7.5 mL of $CHCl_3$).

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*(R)-(−)-3′,5′-Dihydroxy-7-[3-isopropylamino-2-hydroxypropoxy]-flavone (**90b**).* A mixture of 3′,5′-dibenzyloxy-7-hydroxyflavone (**46**, 1.0 g, 2.2 mmol) and *S*-(+)-epichlorohydrin (1.0 mL, 12.0 mmol) was heated at 120 °C for ∼2 h. The cooled mixture was taken in toluene, and a solution of aq. NaOH (10 mg, 0.25 mmol) and benzyltriethylammonium chloride (10 mg, 0.04 mmol) were added and stirred at room temperature for 2 h. The organic layer was separated, dried, and evaporated at reduced pressure to give crude (*R*)-3′,5′-dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56b**) (yield 0.9 g, 80%). A solution of (*R*)-3′,5′-dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56b**, 0.6 g, 4.9 mmol) and isopropylamine (0.5 mL,14.7 mmol) in dry methanol (50 mL) was refluxed for ∼6 h. The solvent was removed at reduced pressure, and the crude product obtained was purified by column chromatography to give (*R*)-3′,5′-dibenzyloxy-7-(3-isopropylamino-2-hydroxypropoxy)flavone (**71b**) (yield 0.55 g, 79%). (*R*)-3′,5′-Dibenzyloxy-7-(3-isopropylamino-2-hydroxypropoxy)flavone (**71b**, 300 mg, 2.12 mmol) was shaken in dry methanol (40 mL) with 10% Pd/C (quantity sufficient) under hydrogen atmosphere (40 psi). The catalyst was filtered, and the solvent was removed at reduced pressure to give the product (*R*)-(+)-3′,5′-dihydroxy-7-(3-isopropylamino-2-hydroxypropoxy)flavone (**90b**). Yield = 0.2 g, 98%; mp = 124 °C; $[\alpha]_D$ = −9.0° (*c* = 20 mg/7.5 mL of 2% $CHCl_3$/MeOH).

*(S)-(+)-3′,5′-Dihydroxy-7-[3-isopropylamino-2-hydroxypropoxy]-flavone (**90a**).* A mixture of 3′,5′-dibenzyloxy-7-hydroxyflavone (**46**, 1.2 g, 2.6 mmol) and *R*-epichlorohydrin (1.2 mL, 15.0 mmol) was refluxed at 120 °C for ∼2 h. The cooled reaction mixture was taken in toluene, and a solution of aq. NaOH (15 mg, 0.37 mol) and benzyltriethylammonium chloride (15 mg, 0.06 mmol) were added to water and allowed to stir at room temperature for 2 h. The organic layer was separated, dried, and concentrated at reduced pressure to give crude (*S*)-3′,5′-dibenzyloxy-7-(2,3-epoxypropoxy)flavone (**56a**) (yield 1.12 g, 83%). A solution of (*S*)-7-(2,3-epoxypropoxy)-3′,5′-dibenzyloxyflavone (**56a**, 500 mg, 4.9 mmol) and isopropylamine (0.3 mL,14.7 mmol) in dry methanol (50 mL) was refluxed at 120 °C for ∼6 h. The solvent was removed at reduced pressure to get crude product and was subjected to column chromatography to afford (*S*)-3′,5′-dibenzyloxy-7-(3-isopropylamino-2-hydroxypropoxy)flavone (**71a**) (yield 0.44 g, 79%). (*S*)-3′,5′-Dibenzyloxy-7-(3-isopropylamino-2-hydroxypropoxy)flavone (**71a**, 250 mg, 2.12 mmol) in dry methanol (40 mL) and 10% Pd/C (quantity sufficient) was shaken in hydrogen atmosphere at ∼40 psi. The catalyst was filtered, and the solvent was removed to give the product (*S*)-(+)-3′,5′-dihydroxy-7-[3-(isopropylamino)-2-hydroxypropoxy]flavone (**90a**). Yield = 0.16 g, 98%; mp = 130 °C; $[\alpha]_D$ = +15.4° (*c* = 20 mg/7.5 mL of 2% $CHCl_3$/MeOH).

In Vivo Antihyperglycemic and Antidyslipidemic Activity Evaluation. *Sucrose-Loaded Rat Model (SLM).* Male albino rats of Charles Foster/Wistar strain of average body weight (160 ± 20 g) were selected for this study. The blood glucose level of each animal was checked by glucometer using glucostrips (Boehringer Mannheim) after 16 h of starvation. Animals showing blood glucose levels between 60 and 80 mg/dL were divided into groups of 5−6 animals in each. Animals of the experimental group were administered on suspension of the desired synthetic compound orally (made in 1.0% gum acacia) at a dose of 100 mg/kg of body weight. Animals of the control group were given an equal amount of 1.0% gum acacia. A sucrose load (10.0 g/kg) was given to each animal orally exactly after 30 min post-administration of the test sample/vehicle. Blood glucose profile of each rat was again determined at 30, 60, 90, and 120 min after administration of sucrose by glucometer. Food but not water was withheld from the cages during the course of experimentation.[15] Quantitative glucose tolerance of each animal was calculated by the area under curve (AUC) method (Prism Software). Comparing the AUC of experimental and control groups determined the percentage of antihyperglycemic activity.

Sucrose-Challenged Streptozotocin-Induced Diabetic Rat Model (STZ-S). Male *albino* rats of *Sprague−Dawley* (SD) strain of body weight 160 ± 20 g were selected for the antihyperglycemic activity evaluation in sucrose-challenged low-dose streptozotocin-induced rat model. Streptozotocin (Sigma, U.S.A.) was dissolved in 100 mM citrate buffer, pH 4.5, and the calculated amount of the fresh solution was injected intraperitoneally to the over-fasted rats at the dose 60 mg/kg. Blood glucose was checked 48 h later by glucostrips (Boehringer Mannheim), and animals showing blood glucose value between 160 and 300 mg/dl were selected and grouped, with each group consisting of 5−6 animals. Oral sucrose load (2.5 g/kg) was given simultaneously with compounds **70**, **70a**, or **90** or with metformin. The experimental groups were dosed at 100 mg/kg, and the control group was given n equal volume of 1% gum acacia. The blood glucose profile was measured at 0, 30, 60, 90, 120, 180, 240, and 300 min, respectively, after the sucrose challenge.[16] Food was withdrawn during the period 0−5 h only. Animals received water ad lib.

Antihyperglycemic and Antidyslipidemic Activity in Diabetic db/db Mice. C57BL/KsJ *db/db* mice 12−18 weeks, 40−50 g, bred in the animal house of CDRI, Lucknow, were used for the evaluation of antihyperglycemic activity. Mice showing blood glucose level 200−350 mg/dL, triglyceride level 170−250 mg/dL, cholesterol level 170−250 mg/dL, and HDL-C level 32−40 mg/dL were selected for the study. The mice were housed in groups of 5 (same sex) in a room controlled for temperature (23 ± 2.0 °C) and 12-h/12-h light/dark cycle (lights on at 6.00 A.M.). Body weight was measured daily from day 1 to day 10. All animals had free access to fresh water and to a normal diet except on the day of the postprandial protocol (day 6) and during the overnight fast before the OGTT on day 10.[17] The animals always had access to water during experimental periods. Blood glucose was checked every morning up until day 9. On day 10 an oral glucose tolerance test (OGTT) was performed after an overnight fasting. Blood glucose was measured at −30.0 min, and test compounds were administered. The blood glucose was again measured at 0 min just after treatment, and at this juncture glucose solution was given at a dose of 3 g/kg to all the groups including the vehicle-treated group. The blood glucose levels were checked at 30, 60, 90, and 120 min after glucose administration.[18] The data was analyzed for its area under curve (AUC) and significance on Prism software. The ED_{50} is the effective dose that produces on average response in 50% of animal population. On the 11th day blood was withdrawn from retro-orbital plexus of the mice for the estimation of plasma triglyceride, cholesterol, HDL cholesterol, and insulin levels. Statistical analysis between groups was made by Student *t* test.

Antihyperlipidemic Activity Evaluation in Triton-Induced Dyslipidemic Rat Model. A total of 8−10 weeks old male *Wistar* strain of rats of average body weight 160 g were taken from the animal colony of the Institute and divided into groups consisting of 10 animals in each. Each group was housed in plastic cages and was fed ad lib the normal pellet diet and water. Hyperlipidemia in rats was induced by intraperitoneal administration of Triton X-100 (Sigma Chemical Co., U.S.A.) at the dose of 400 mg/kg. Flavone-derived compounds were fed orally to the said rats at the dose of 100 mg/kg, respectively, prepared in 1% gum acacia. Control animals received the same amount of 1% gum acacia. Exactly 18 h after administration of Triton-X-100, the blood of each animal was withdrawn from the retro-orbital plexus. Serum was separated after centrifugation at 1500*g* for 10 min. Total triglycerides and total cholesterol content in serum samples were determined using the assay kits as supplied by Randox/Roche. The results are expressed as the mean ± SEM. The statistical significance between groups is determined by analysis of variance and subsequent Dunnet test.

Antidyslipidemic Activity. Antidyslipidemic activity evaluation of compounds in *Syrian golden* hamsters (body weight 100−120 g, age 6−8 weeks old) was fed with high-fructose, high-fat diet (55% fructose, 13% fats) for 1 month for the development of dyslipidaemia in these hamsters.[19] Dyslipidemic hamsters were selected and grouped for the evaluation of antidyslipidemic activity of the compounds. The group first was treated as sham-treated control group and was given 1% gum acacia. Other groups were treated as treatment groups and were dosed at 10, 30, and 100 mg/kg of body weight of compounds. The standard drug-treated group was given fenofibrate at the 30 mg/kg dose. Dose-dependent antidyslipidemic activities were also studied in these hamsters, and the desired compound was dosed at 10, 30, and 100 mg/kg to their respective groups. Treatments were done for 7 days. Body weight

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was measured daily to study the body-weight-reducing activity of compounds. At the end of the experiment, blood was withdrawn from the retro-orbital plexus of the eye for the estimations of serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipoprotein lipase, and fasting serum glucose by using Roche diagnostic kits. Glycerol and nonesterified free fatty acid were estimated using Randox kits

Pharmacokinetic Study in Sprague–Dawley Rats. The pharmacokinetic behavior was studied to estimate the relative bioavailability of the compounds following the literature or in-house protocols. Young and healthy male *Sprague–Dawley* rats weighing 225 ± 25 g (obtained from Laboratory Animal Division of Institute) were housed in well-ventilated cages and kept at room temperature on a regular 12-h light–dark cycle. The intravenous dosing formulation of compounds **70** was prepared in DMF/PG/water (5:4:1, v/v) and finally filtered through 0.2 μ filter before administration of 10 mg/kg dose, which was administered through tail vein in rat. Blood samples were collected at different times ranging from 0.08 to 48 h post i.v. dose in heparinized glass tube. For the oral pharmacokinetic study, the aqueous suspension of compound **70** with 0.5% methyl cellulose was administered by oral feeding needle in rats at dose 40 mg/kg. The animals were fasted for 10–12 h prior to dose. Blood samples were collected at different times ranging from 0.25 to 120 h after oral dose. The plasma was separated by centrifuging at 2000*g* for 10 min at 4 °C and stored at −60 °C. Sample analysis was done by LC-MS/MS method, and the linearity range was taken to be 0.78–400 ng/mL. Pharmacokinetic parameters were determined by using WinNonlin version 5.1 (Pharsight Corp, U.S.A.).

The single-dose pharmacokinetic study of compound **70a** at dose 25 mg/kg was done after oral administration in rats. The intravenous dosing formulation of compound **70a** was administered at 2.5 mg/kg dose. The intravenous dosing formulation of compound **90a** was prepared in DMF/PG/water (2:4:4 v/v) and finally filtered through 0.2 μ filter before administration of 2.5 mg/kg dose. For the oral pharmacokinetic study, the aqueous suspension of compound **90a** with 0.5% methyl cellulose was administered by oral feeding needle in rats at dose 25 mg/kg. Blood samples were collected at different times ranging from 0.08 to 48 h after oral and intravenous dose. Sample analysis was done by LC-MS/MS method, and the linearity range was taken to be 0.78–400 ng/mL. Pharmacokinetic parameters were determined by using WinNonlin version 5.1 (Pharsight Corp, U.S.A.).

Male albino rats of Sprague–Dawley (SD) strain of body weight 160 ± 20 g were selected for the antihyperglycemic activity evaluation in sucrose-challenged low-dose streptozotocin-induced rat model. Streptozotocin (Sigma, U.S.A.) was dissolved in 100 mM citrate buffer, pH 4.5, and the calculated amount of the fresh solution was injected intraperitoneally to the overfasted rats at the dose 60 mg/kg. Blood glucose was checked 48 h later by glucostrips (Boehringer Mannheim), and animals showing blood glucose value between 160 and 300 mg/dL were selected and grouped, with each group consisting of 5–6 animals. Oral sucrose load (2.5 g/kg) was given simultaneously with compounds **70**, **70a**, or **90a** or with metformin. The experimental groups were dosed at 100 mg/kg, and the control group was given an equal volume of 1% gum acacia. Blood glucose profile was measured at 0, 30, 60, 90, 120, 180, 240, and 300 min, respectively, after sucrose challenge. Food was withdrawn during the period 0–5 h only. Animals received water ad lib.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information includes general experimental procedures for synthesis, spectral data for characterization, chromatographic data, biological experimental results, and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

HDL-C,high-density lipoprotein cholesterol; LDL-C,low-density lipoprotein cholesterol; DMF,*N*,*N*-dimethylformamide; HPLC,high-performance liquid chromatography; STZ,streptozotocin; TG,triglycerides; CHOL,cholesterol; PL,phospholipids; AUC,area under curve; ED_{50},effective dose for desired response in 50% population; NEFA,nonesterified fatty acids; LPL,lipoprotein lipase; MRT,maximum retention time; ESM-S,electron spray mass spectroscopy; HRMS,high-resolution mass spectroscopy; NMR,nuclear magnetic resonance; DMSO,-dimethylsulfoxide; FAB-MS,fast atomic bombardment mass spectroscopy

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