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ω-(2-Naphthyloxy) amino alkanes as a novel class of anti-hyperglycemic and lipid lowering agents☆

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Dedicated to Dr. Nitya Anand for his constant inspiration for research.

Abstract—ω-(2-Naphthyloxy) amino alkanes, obtained as major by-product during course of synthesis of carbamate esters from ω-(2-naphthyloxy) alkyl halides and amines, showed significant anti-hyperglycemic and lipid lowering activities in various test models as a novel class of compounds. Compounds were tested in rat GLM, SLM, STZ, and STZ-S models at 100 mg/kg dose. Of these compound **13** was found to be the most active which caused lowering of sugar by 33.6%, 31.0%, 28.5%, and 73.8% in GLM, SLM, STZ, STZ-S, and db/db mice models, respectively. It also significantly effected lowering of LDL in rat model and also in Hamster model without reducing HDL. Most of the compounds showing anti-diabetic and lipid lowering activity have shown promising PPAR-α/γ/δ-activity. Compounds **6**, **13**, and **19** have shown very good PPAR-α/γ/δ activity.

1. Introduction

Diabetes[1] is the root cause of several chronic and progressive diseases, which adversely affect a number of organs including the nervous and vascular systems. More than 90% of the diabetic patients suffer from type-2 diabetes, that is, non-insulin dependent diabetes mellitus (NIDDM), which is characterized by insulin resistance and hyperglycemia. Type-2 diabetes is one of the major causes of several chronic diseases such as retinopathy, neuropathy, nephropathy, and cardiovascular diseases.[2] Long term hyperglycemia, caused by insufficient insulin secretion from pancreas and/or insulin resistance in muscle, liver, and adipose tissues, caused an aggravation of diabetes. Therefore, it is important to regulate the blood glucose levels in order to control diabetes.[3] The treatment generally prescribed for NIDDM has been a combination of diet, exercise, and an anti-hyperglycemic agent.[4] One such class of anti-hyperglycemic agents is sulfonylureas. These are insulin secretagogues, which stimulate insulin secretion from pancreatic β-cells but are often known to induce severe hyperglycemia[5] and weight gain. Another major class of anti-hyperglycemic agents is thiazolidine-dione derivatives. These are known to reverse insulin resistance without stimulating insulin release from β-cells.[6] Some of the potential compounds belonging to this class are Pioglitazone[7] **A**, Rosiglitazone[8] **B** (Fig. 1), act through PPAR-γ receptor therefore are well-known PPAR-γ agonists, which have been marketed until 2004. Although these agents have glucose lowering effect and improve the lipid lowering profile like TG, LDL cholesterols, and HDL cholesterols, the crucial side effects like congestive heart failure, edema, fluid retention, and weight gain still remain unresolved.[9] It was visualized that a dual PPAR-α and -γ activator could be an effective drug for insulin resistance, hyperglycemia, and dyslipidemia. Several drugs of such dual activity were in clinical development like Ragaglitazar[10] **C**, KRP-297[11] **D**, Tesaglitazar[12] **E**, Muraglitazar[13] **F**, etc. (Fig. 1). Unfortunately, the first two were discontinued following instances of carcinogenicity in rodent models. The successful PPAR-α, γ dual agonists including Tesaglitazar **E**, Muraglitazar **F** have not been marketed. Besides the above-mentioned potential dual PPAR-α, γ agonists, some other series of potential dual PPAR-α, γ agonists have also been reported recently in compounds **G**,[14] **H**,[15] **I**[16] shown in Figure 1. Nevertheless PPAR- α, γ dual agonist would be well

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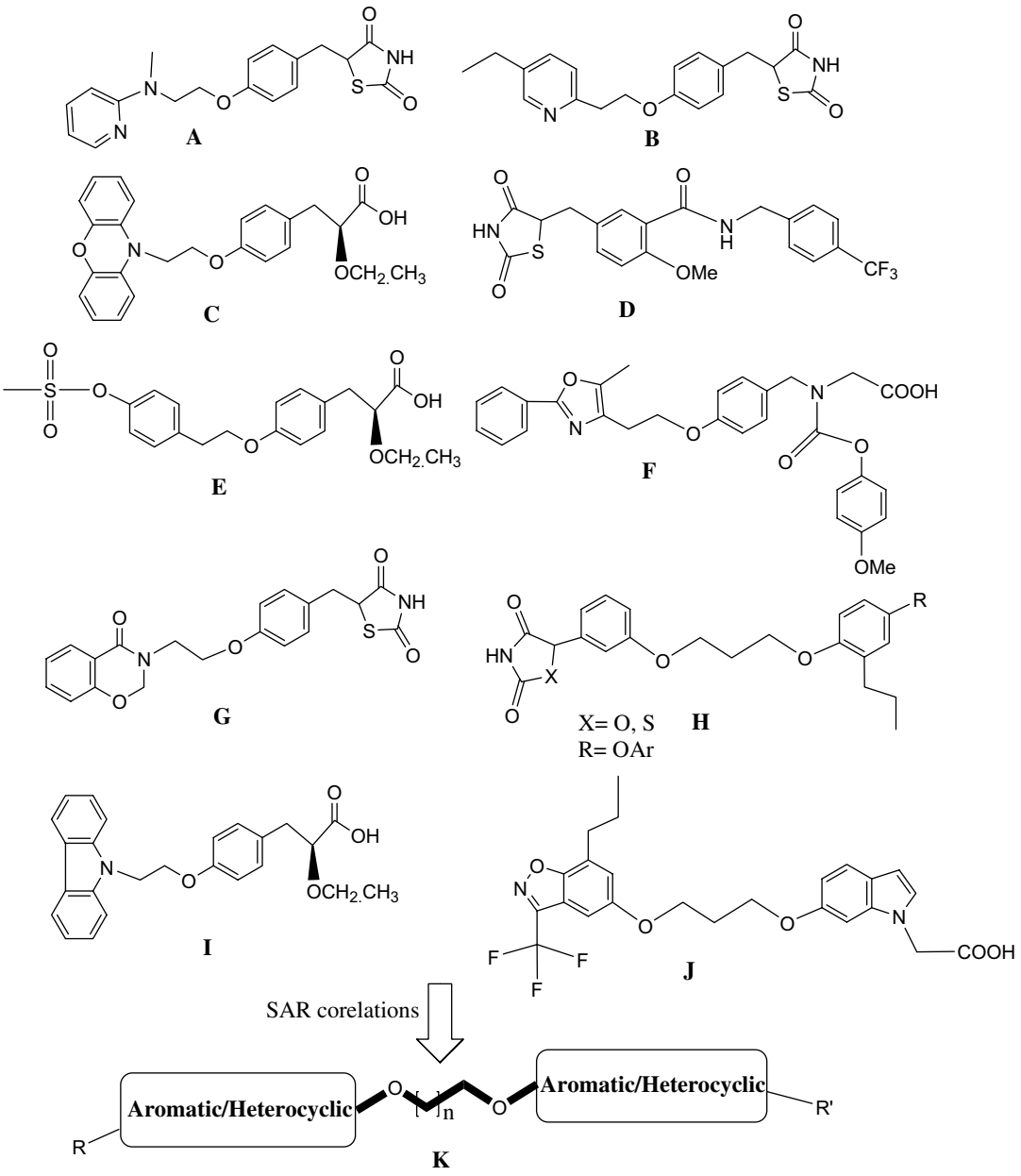


Figure 1. Structures of PPAR-γ (**A**, **B**), dual PPAR-α, γ (**C**–**I**), and dual PPAR-α/δ (**J**) agonists with a detailed discussion of structure–activity relationship.

suited for the treatment of diabetes and cardiovascular diseases as long as it could reduce side effects as mentioned above. Therefore, there has been a resurgence of interest in the development of novel dual PPAR-α, γ agonists which could be an effective drug for insulin resistance, hyperglycemia, and dyslipidemia free, from unwanted effects.

Typical structure–activity relationship (SAR) study of most of the potential dual PPAR-α, γ agonists reveals that there should be atleast one substituted aromatic and one hetero-aromatic system inter-connected through atleast 2–3 carbon chain separated through hetero-atom. Moreover, it was realized from the structure of a PPAR-α/δ, agonist, that is, compound **J**,[17] where both of the heterocyclic systems were inter-connected. Hence, it was further concluded that for dual PPAR α/δ agonists both of the hetero-atoms are required. These aromatic and hetero-aromatic systems were further substituted through different kinds of substitutions.

The present invention was aimed at the modification of cyclic and rigid thiazolidine-dione moiety into a non-rigid open chain carbamate moiety (Fig. 2). During the course of synthesis of acyclic carbamate compound reported by our group[18] as shown in Scheme 1, through the condensation of ω-(2-naphthyloxy) alkyl halides with amines, the major by-product obtained was ω-(2-naphthyloxy) alkyl amines. Although the anti-diabetic activity of the designed carbamates was tested, none of the compounds have shown promising anti-diabetic activity. Lateron, It has been realized after careful study

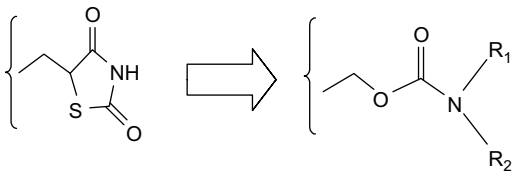


Figure 2. Modification of thiazolidine-dione moiety into carbamate moiety.

of the structure–activity relationship (SAR) of dual PPAR- α/γ and PPAR-α/δ agonists as discussed above (Fig. 1) that the ω-(2-naphthyloxy) alkyl substituted aromatic amines particularly compounds **6–20** have shown very close co-relations with the above-mentioned dual agonists depicted in Figure 3. It became further clear that the two aromatic rings of the substituted amine derivatives were inter-connected with the 2–4 carbon chains separated by O and N heterocycles, respectively. Keeping all the above considerations, we became interested to investigate the anti-diabetic activity profile of these amine derivatives. Interestingly, most of the phenyl substituted amine derivatives have shown promising anti-diabetic activity, indicating the further confirmation about the proposed SAR study. Furthermore, keeping the designing of the dual agonists we have tested these compounds for lipid lowering activity where we have observed promising lipid lowering profile. Thus, we report[19] here evaluation of such ω-(2-naphthyloxy) alkyl amines as a novel class of anti-hyperglycemic and lipid lowering agents. Later on, the synthetic protocol for these amines was changed. These have been simply prepared directly from the condensation of alkyl halides with amines using K_2CO_3 system.

The general structures of the designed prototypes have been mentioned in Figure 4.

2. Chemistry

Initially, these by-products formed during the synthesis of carbamates, that is, ω-(2-naphthyloxy) amino alkanes, were isolated and tested for biological activity. Interestingly, after getting the unexpected promising biological activity in these compounds, we became interested in the preparation of amine derivatives through di-

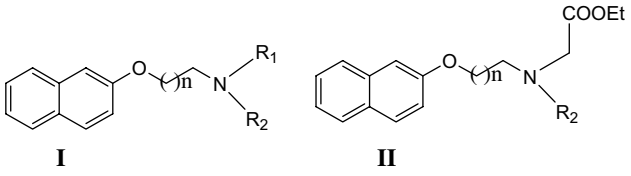
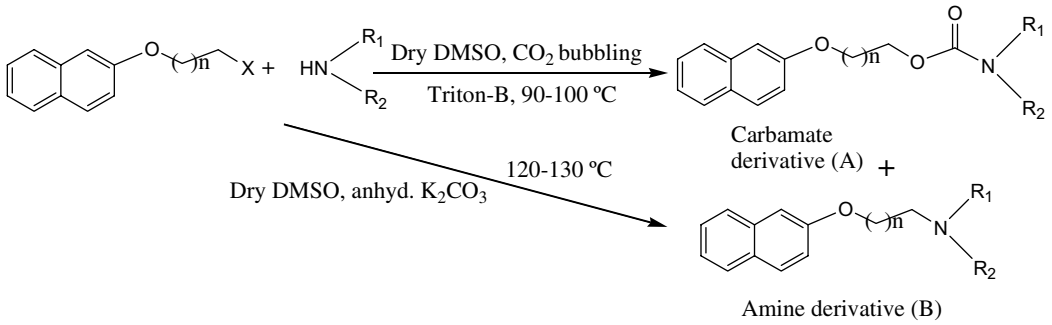
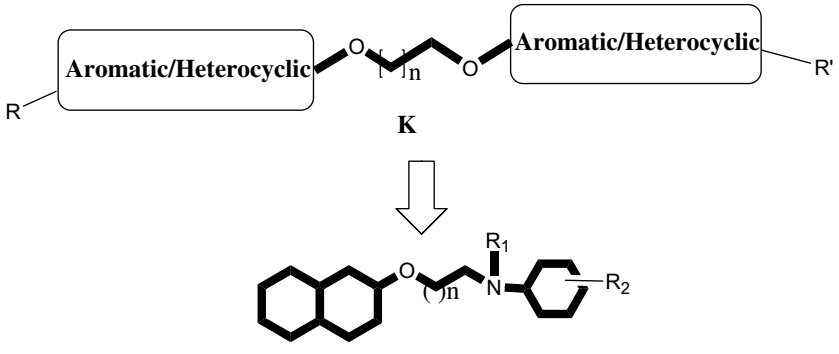


Figure 4. General structure of the prepared prototypes.



Scheme 1. Formation of side product, that is, amine derivative, during carbamate synthesis from alkyl halides and amines.



n = 1-3

R_1 = H, CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, CH_2COOEt, CH_2COOH

R_2 = methoxy, methyl

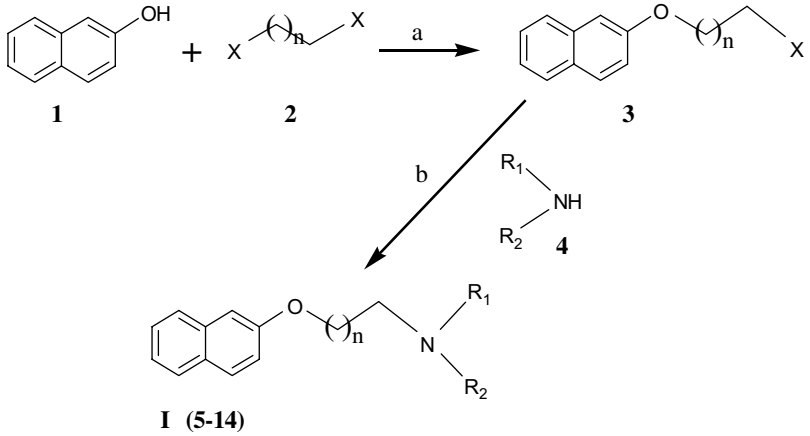
Figure 3. SAR co-relations of dual PPAR-α/γ and PPAR-α/δ agonists with designed substituted amines.

rect condensation of the corresponding ω-(2-naphthyloxy) alkyl halides with various amines. Thus, the synthetic procedure for the preparation of ω-(2-naphthyloxy) amino alkanes and its substituted derivatives is shown in Scheme 2. Reaction of β-naphthol or its derivatives **1** with different dihaloalkanes **2** (where X^1 and X^2 may be same or different halogens) gave halogen substituted compound **3**, which was further reacted with amines **4** to afford desired compounds **5**–**14** of the general structure **I**. All the prepared compounds of structure **I** are shown in Table 1 and were evaluated for their anti-hyperglycemic and lipid lowering activities. Out of the various compounds (**5**–**14**) tested, compound **13** was found to be the most active and has shown very promising anti-diabetic activity and lipid lowering activity compared with the corresponding standard drugs.

To optimize further SAR of **13**, various N-substituted derivatives of compound **13** were prepared. Compound **13** was treated with various alkyl halides to afford *N*-alkyl derivatives of general structure **II** (**15**–**18**) (Scheme 3). Compound **13** was also converted into N-substituted esters using corresponding halo ester. This N-substituted ester was subjected to basic hydrolysis to afford the corresponding N-substituted acid. The activity data of all the compounds are shown in Table 1.

3. Results and discussion

All the compounds synthesized were evaluated for in vivo anti-hyperglycemic activity in male and female albino rats (Sprague–Dawley) of body weight of ~160 g in four different models namely GLM, SLM,

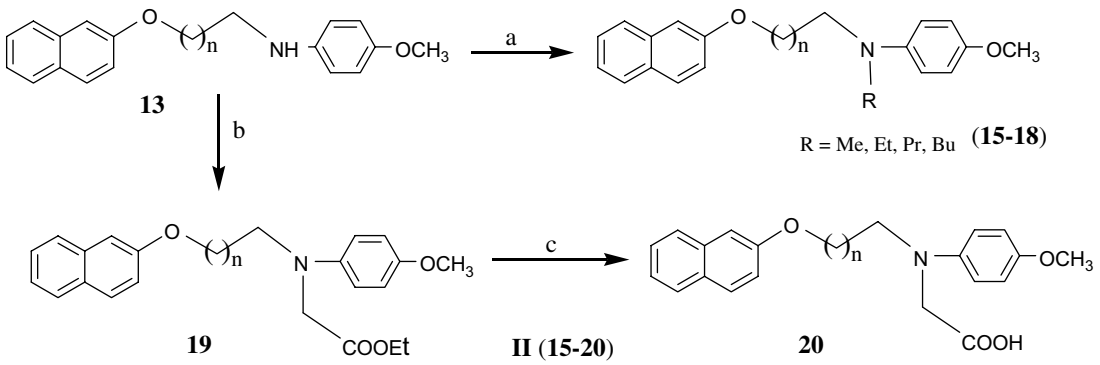


Scheme 2. Reagents and conditions: (a) bromochloro alkane/dihalo alkanes, anhyd K_2CO_3, dry acetone, reflux, 12–15 h; (b) anhyd K_2CO_3, dry DMSO, 130–140 °C, 12–15 h.

Table 1. Anti-hyperglycemic and lipid lowering activity of various derivatives of compound **I** in different models

Entry	R_1	R_2	*n*	Dose: 100 mg/kg						
				Anti-diabetic activity (% inhibition)				Lipid lowering activity (% inhibition) (Triton model)		
				GLM	SLM	STZ	STZ-S	Chol	Phosp	TG
5	H	C_8H_{17}	2	17	32	NT	NT	NT	NT	NT
6	H	$CH_2C_6H_5$	1	37.6	64	13	69.5	31	34	37
7	H	$CH_2C_6H_5$	2	13.8	40.5	NT	NT	NT	NT	NT
8	H	$CH_2C_6H_5$	3	8.89	16.0	NT	NT	10.1	18	5
9	H	*m*-$OCH_3C_6H_4CH_2$	2	1.23	8.30	NT	NT	14	22	22
10	H	*p*-$CH_3C_6H_4$–	1	2.45	6.99	NT	NT	27.0	30	18
11	H	*p*-$CH_3C_6H_4$–	3	3.21	6.90	NT	NT	NT	NT	NT
12	H	*p*-$OCH_3C_6H_4$	1	10.6	19.4	NT	NT	NT	NT	NT
13	H	*p*-$OCH_3C_6H_4$	2	33.6	31	28.5	73.8	32.4	38	28
14	H	*p*-$OCH_3C_6H_4$	3	3.89	5.09	NT	NT	24.0	36	22
15	CH_3	*p*-$OCH_3C_6H_4$	2	8.20	14.5	NT	NT	11.0	19	15
16	C_2H_5	*p*-$OCH_3C_6H_4$	2	6.88	13.5	NT	NT	NT	NT	NT
17	C_3H_7	*p*-$OCH_3C_6H_4$	2	11.6	37.2	NT	NT	14	27	12
18	C_4H_9	*p*-$OCH_3C_6H_4$	2	13.5	4.40	NT	NT	15	25	17
19	CH_2COOEt	*p*-$OCH_3C_6H_4$	2	25.9	45.4	6.9	5.6	21.2	26	15
20	CH_2COOH	*p*-$OCH_3C_6H_4$	2	15.5	21.5	NT	NT	23.8	16.9	13.0
Gybenclamide					33.9	32.8	NT	NA	NA	NA
Glyclazide					44.8	27.7	NT	NA	NA	NA
Gugulipid				NA	NA	NA	NA	34	33	30

NT, not tested; NA, not applicable.



Scheme 3. Reagents and conditions: (a) alkyl halides, dry acetone, reflux; (b) bromo-ethyl acetate, dry acetone, reflux; (c) NaOH, ethanol, reflux, basic hydrolysis.

STZ, and STZ-S. Compounds showing sugar lowering activity (more than 7%) were evaluated for in vivo lipid lowering activity in Triton model taking male Charles Faster rats (200–225 g) and some in hamster model taking male golden Syrian hamster (120–130 g). The anti-diabetic activity profile and lipid lowering activity of compounds are given in Table 1.

Among the **16** compounds screened, compound nos. **5**, **6**, **7**, **8**, **12**, **13**, **15**, **17**, **18**, **19**, and **20** demonstrated anti-hyperglycemic activity (more than 7%) in GLM model, while **5**, **6**, **7**, **8**, **9**, **12**, **13**, **15**, **16**, **17**, **19**, and **20** displayed blood sugar lowering activity in SLM model. In general compounds showing activity in GLM model were also found to be active in SLM model as well.

The most promising compounds **6** and **13** were also assayed in STZ and STZ-S models. Both of the compounds **6**, **13** were found active in STZ and STZ-S models.

Compounds **6**, **9**, **13**, **15**, and **19** showing sugar lowering activity in SLM model were also evaluated for their lipid lowering activity in Triton model. Lipid lowering activity of **6** and **13** was comparable to the standard drug Gugulipid. Compound **13** was also evaluated for lipid lowering activity in hamster model and compared with Fenofibrate (standard drug). Although the activity profile of **13** was inferior to that of Fenofibrate, it showed that the test compound **13** besides having significant sugar lowering activity had the added advantage of anti-hyperlipidemic activity as well.

The promising compounds **6**, **13**, **19** in GLM and SLM models were also assayed in STZ and STZ-S models. Compounds **6** and **13** showed promising activity in STZ and STZ models, while compound **19** could not show promising activity in both the models (Table 1). Those compounds which have shown anti-diabetic activity in STZ as well as STZ-S model were than evaluated for their anti-diabetic activity in db/db mice (degree of mean glucose lowering as percentage of the difference between vehicle treated db/db mice versus lean control mice), PPAR-γ binding activity and only compound **13** has shown promising activity (Table 2).

Structure–activity relationship (SAR) of compounds studied suggested that in the case of benzyl substituent (R_2) on the nitrogen, the anti-hyperglycemic activity of the compounds was maximum with $n = 1$ and decreased on the increasing of their chain length. However, when R_2 is an aryl residue, compounds with $n = 1$ were less active. Most promising activity was encountered with *p*-methoxyphenyl substituent (R_2) on the nitrogen having a three-carbon chain ($n = 2$) (compound no. **13**). In this anisyl series, introduction of an additional alkyl substituent on the nitrogen (R_1) caused lowering in anti-hyperglycemic activity. Shifting of the methoxy substituent on the phenyl to *m*-position or its replacement by a methyl substituent resulted in diminished or total loss of activity. An alkyl/ester/acid substitution on the nitrogen of ω-(2-naphthyloxy) amino alkane compounds (**15**–**20**) was not showing good anti-diabetic activity but these compounds have lipid lowering activity.

It has already been realized from the structural co-relations of ω-(2-naphthyloxy) amino alkanes with the general structural SAR of the dual PPAR-α, γ and PPAR-α, δ agonists that this class of compounds should be promising PPAR dual agonists. Thus, keeping all the above

Table 2. PPAR-γ and lipid lowering activity (in hamster model) of compound nos. **6**, **13**, **19**, and **20**

Entry	Anti-diabetic activity (% inhibition)			Lipid lowering activity (% inhibition, hamster model)					
	db/db mice % efficacy day 3 (100 mg/kg) PPAR-binding			TG	Chol	HDL	GLU	GLY	FFA
	5 h	24 h	PPAR-γ EC_{50} (μM)						
6	7	11.6	0.4	37.0	14.0	13.0	9.5	10	NT
13	22.4	28.9	33.8	48	14	15	31	14	NT
19	12.0	15.4	4.8	68	22	16	34	7.3	48
20	NT	NT	NT	44	21	11	22	23	NT
Fenofibrate			41	77	30	33	33	52	53

considerations the compounds which have shown promising anti-diabetic activity were further tested for PPAR-α/γ/δ agonistic activity. Thus, compounds **5**, **6**, **7**, **8**, **12**, **13**, **14**, **15**, **16**, **17**, **18**, **19**, and **20** were tested for PPAR-α/γ/δ activity using Rosiglitazone and Tesaglitazar as standard drugs (Table 3). It is clear from Table 3 that most of the compounds showing anti-diabetic and lipid lowering activity have shown promising PPAR-α/γ/δ activity. Out of the above-mentioned compounds tested, compounds **6**, **13**, and **19** have shown very good activity.

4. Experimental

4.1. Chemistry

All the reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC plates were visualized by warming the CeSO4 (1% 2 N H_2SO_4) sprayed plates in an oven at 100 °C. Other developers used were iodine vapors and $KMNO_4$ spray. For column chromatography, silica gel (100–200 mesh) was used. The melting points were recorded on electrically heated melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 881 and FTIR 8210 PC Shimadzu spectrophotometers either as KBr disks or neat and the values are expressed in cm^{-1}. ^1H NMR spectra were recorded on Brucker WM 400 MHz spectrometer in deuterated solvents with TMS as internal reference. EI spectra of all the compounds were measured on JEOL JMS-D 300 spectrometer with the ionization potential of 70 eV. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Microanalyses were carried out on Carlo Erba EA-1108 element analyzer.

4.1.1. General procedure for the preparation of ω-naphthyloxy halo alkanes (3a–c). A mixture of β-naphthol **1** (20 g, 0.14 mol), anhydrous K_2CO_3 (100 g, in excess), and bromochloroalkane **2** (0.14 mol) was refluxed in dry acetone (200 mL) for 12–15 h. Reaction mixture was filtered and filtrate was concentrated to get oily compound, which was crystallized with benzene-hexane to give the colorless crystals of pure desired compound.

Table 3. PPAR (α, γ, δ) activities of compounds **5**, **6**, **7**, **8**, **12**, **13**, **14**, **15**, **16**, **17**, **18**, **19**, and **20**

Entry	PPAR (EC_{50}) (% inhibition)		
	PPAR-α (50 μM)	PPAR-γ (1 μM)	PPAR-δ (3 μM)
5	11.4	8.5	7.9
6	36.2	34.6	31.3
7	28.4	27.6	29.1
8	21.3	20.5	22.4
12	22.2	25.3	24.6
13*	44.5	43.5	42.6
14	18.3	17.2	16.3
15	22.5	24.6	19.3
16	20.3	19.4	17.3
17	10.9	11.4	9.6
18	8.5	7.7	8.4
19	33.5	34.9	29.6
20	25.4	22.5	20.2
Tesaglitazar	55.5	59.4	—
Rosiglitazone	—	46.4	—

4.1.1.1. 2-(2-Naphthyloxy)-1-chloroethane (3a). Yield: 27.5 g (96%); mp: 94 °C; IR (KBr, cm^{-1}): ν = 1455 (Ar), 1508 (Ar), 1585 (Ar), 2878 (CH), 2927 (CH); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (t, 2H, CH_2Cl), 4.26 (t, 2H, OCH_2), 6.97–7.64 (m, 7H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.3, 75.1, 105.8, 118.6, 123.6, 126.4, 129.5, 134.5, 157.7 ppm; Mass (EIMS): m/z = 206; Analysis: $C_{12}H_{11}ClO$, Calcd: C, 69.74; H, 5.36; Obsd: C, 70.04, H, 5.66%.

4.1.1.2. 3-(2-Naphthyloxy)-1-chloropropane (3b). Yield: 29.7 g (97%); mp: 98 °C; IR (KBr, cm^{-1}): ν = 1461 (Ar), 1512 (Ar), 1596 (Ar), 2855 (CH), 2940 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.27–2.33 (m, 2H, CH_2), 3.80 (t, 2H, CH_2Cl), 4.25 (t, 2H, OCH_2), 7.12–7.77 (m, 7H, Ar–H) ppm; Mass (EIMS): m/z = 220; Analysis: $C_{13}H_{13}ClO$, Calcd: C, 70.75; H, 5.94; Obsd: C, 70.79; H, 6.21%.

4.1.1.3. 4-(2-Naphthyloxy)-1-chlorobutane (3c). Yield: 32 g (98%); mp: 112 °C; IR (KBr, cm^{-1}):ν = 1464 (Ar), 1510 (Ar), 1599 (Ar), 2887 (CH), 2941 (CH); ^1H NMR ($CDCl_3$): δ = 2.15–2.20 (m, 4H, $CH_2{\cdot}CH_2$), 3.79 (t, 2H, CH_2Cl), 4.24 (t, 2H, OCH_2), 7.13–7.78 (m, 7H, Ar–H) ppm; Mass (EIMS): m/z = 234; Analysis: $C_{14}H_{15}ClO$, Calcd: C, 71.64; H, 6.44; Obsd: C, 71.43; H, 6.31%.

4.1.2. General procedure for the preparation of ω-naphthyloxy amino alkanes (I, compound nos. 5–14). A mixture of anhydrous potassium carbonate (10 g, in excess) and amine (3 mmol) was taken in dry DMSO (40 mL). ω-(2-Naphthyloxy)-1-chloroalkane (0.5 g, 2 mmol) was added to it. Reaction mixture was refluxed at 130–140 °C for 7–9 h when the reaction was completed as checked by TLC. Reaction mixture was poured into distilled water (60 mL) and extracted with ethyl acetate thrice. The organic layer was separated and concentrated to get oily compound, which was later crystallized by benzene-hexane to get the desired compound.

4.1.2.1. *N*-(*n*-Octyl)-(3-(naphthalene-2-yloxy)propyl)-amine (5). Yield: 0.7 g (96.7%); mp: 109 °C; IR (KBr, cm^{-1}): ν = 1470 (Ar), 1527 (Ar), 1623 (Ar), 2874 (CH), 2925 (CH), 3396 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, 3H, CH_3), 1.25–1.30 (m, 8H, CH_2 of *n*-octyl group), 1.30–1.34 (m, 2H, $CH_2{\cdot}CH_3$), 1.38–1.42 (m, 2H, CH_2CH_2N), 1.80–1.83 (m, 2H, O–CH_2 CH_2CH_2N), 2.1 (br, H, NH), 2.53–2.56 (m, 4H, $NHCH_2CH_2$), 2.97 (t, 2H, O–CH_2 CH_2NH), 4.21 (t, 2H, OCH_2-naphthyl), 6.97–7.66 (m, 7H, Ar–H of naphthyloxy); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 23.1, 27.7, 30.6, 32.2, 32.5, 45.8, 49.6, 70.2, 105.8, 118.8, 123.6, 126.7, 129.6, 134.5, 157.6 ppm; Mass (EIMS): m/z = 313; Analysis: $C_{21}H_{31}NO$, Calcd: C, 80.46; H, 9.97; N, 4.47; Obsd: C, 80.93; H, 9.70; N, 4.23%.

4.1.2.2. *N*-Benzyl-[2-naphthalen-2-yloxy]amine (6). Yield: 0.6 g (93%); mp: 94 °C; IR (KBr, cm^{-1}): ν = 1460 (Ar), 1508 (Ar), 1604 (Ar), 2864 (CH), 2927 (CH), 3389 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.2 (br, H, NH), 2.94 (t, 2H, O–CH_2CH_2–N), 3.79–3.82 (m, 2H, CH_2Ph), 4.15 (t, 2H, CH_2–O–naphthyl), 6.97–7.68 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.5, 55.6, 74.5, 105.7, 118.6, 123.6, 126.7, 128.1, 128.7, 129.6, 134.5, 137.2, 157.6 ppm; Mass (EIMS): *m*/*z* = 277; Analysis: $C_{19}H_{19}NO$, Calcd: C, 82.28; H, 6.90; N, 5.05; Obsd: C, 81.97; H, 7.24; N, 4.83%.

4.1.2.3. *N*-Benzyl-[3-(2-naphthyloxy)-propyl]amine (7). Yield: 0.62 g (93.6%); mp: 109 °C; IR (KBr, cm^{-1}): ν = 1467 (Ar), 1522 (Ar), 1609 (Ar), 2874 (CH), 2938 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.84 (m, 2H, O–$CH_2CH_2CH_2N$), 2.3 (br, H, NH), 2.56 (t, 2H, NCH_2), 3.78–3.82 (m, 2H, CH_2Ph), 4.10 (t, 2H, OCH_2), 6.94–7.68 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.5, 45.6, 55.4, 69.7, 105.3, 118.8, 123.8, 126.8, 128.9, 128.8, 129.6, 134.6, 137.5, 157.6 ppm; Mass (EIMS): *m*/*z* = 291; Analysis: $C_{20}H_{21}NO$, Calcd: C, 82.44; H, 7.26; N, 4.81; Obsd: C, 82.69; H, 6.91; N, 4.53%.

4.1.2.4. *N*-Benzyl-[4-(2-naphthyloxy)-butyl]amine (8). Yield: 0.62 g (95.3%); mp: 105 °C; IR (KBr, cm^{-1}): ν = 1472 (Ar), 1522 (Ar), 1613 (Ar), 2874 (CH), 2939 (CH), 3399 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.42 (m, 2H, $NHCH_2CH_2CH_2CH_2$–O–), 1.70–1.74 (m, 2H, O–$CH_2CH_2CH_2CH_2$–N–), 2.10 (br, H, NH), 2.532–2.56 (m, 2H, $NHCH_2$), 3.80–3.83 (m, 2H, CH_2Ph), 4.21 (t, 2H, OCH_2), 6.95–7.69 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 28.8, 49.6, 55.6, 73.4, 105.7, 118.9, 123.6, 126.5, 128.5, 128.9, 129.5, 134.5, 137.6, 157.5 ppm; Mass (EIMS): *m*/*z* = 305; Analysis: $C_{21}H_{23}NO$, Calcd: C, 82.58; H, 7.59; N, 4.59; Obsd: C, 82.22; H, 7.31; N, 4.27%.

4.1.2.5. *N*-(3-Methoxybenzyl)-[3-(2-naphthyloxy)propyl]amine (9). Yield: 0.68 g (92.8%); mp: 97°C; IR (KBr, cm^{-1}): ν = 1469 (Ar), 1519 (Ar), 1610 (Ar), 2872 (CH), 2934 (CH), 3392 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.81–1.84 (m, 2H, CH_2CH_2NH), 2.21 (br, H, NH), 2.53–2.57 (m, 2H, NCH_2), 3.73 (s, 3H, OCH_3), 3.79–3.85 (m, 2H, CH_2Ph), 4.14 (t, 2H, OCH_2), 6.98–7.66 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.5, 45.4, 55.3, 56.7, 69.7, 105.3, 118.7, 123.8, 126.8, 128.9, 128.8, 129.6, 134.6, 137.5, 157.6 ppm; Mass (EIMS): *m*/*z* = 321; Analysis: $C_{21}H_{23}NO_2$, Calcd: C, 78.47; H, 7.21; N, 4.36; Obsd: C, 78.07; H, 7.75; N, 4.27%.

4.1.2.6. *N*-(4-Methylphenyl)-[2-(2-naphthyloxy)-ethyl]amine (10). Yield: 0.62 g (91.7%); mp: 92 °C; IR (KBr): ν = 1465 (Ar), 1515 (Ar), 1606 (Ar), 2868 (CH), 2931 (CH), 3391 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.43–3.48 (m, 2H, O–CH_2CH_2NH), 4.10 (br, H, NH), 4.21 (t, 2H, CH_2–O–naphthyl), 6.34–7.64 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 51.9, 73.8, 105.9, 112.3, 118.8, 123.5, 126.9, 128.1, 128.4, 129.6, 134.5, 137.5, 157 ppm; Mass (EIMS): *m*/*z* = 277; Analysis: $C_{19}H_{19}NO$, Calcd: C, 82.28; H, 6.90; N, 5.05; Obsd: C, 81.87; H, 7.47; N, 4.83%.

4.1.2.7. *N*-(4-Methylphenyl)-[4-(2-naphthyloxy)butyl]-amine (11). Yield: 0.63 g (97%); mp: 98°C; IR (KBr, cm^{-1}): ν = 1472 (Ar), 1529 (Ar), 1623 (Ar), 2879 (CH), 2940 (CH), 3402 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.52 (m, 2H, $NHCH_2CH_2CH_2CH_2$–O–), 1.91–1.94 (m, 2H, $CH_2CH_2CH_2CH_2NH$), 2.35 (s, 3H, CH_3), 3.01–3.05 (m, 2H, $NHCH_2$), 4.05 (br, H, NH), 4.15 (t, 2H, OCH_2), 6.32–7.66 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 28.3, 29.2, 52.5, 72.5, 105.6, 118.8, 123.7, 126.9, 128.8, 129.6, 134.5, 137.8, 157.6 ppm; Mass (EIMS): *m*/*z* = 293; Analysis: $C_{21}H_{23}NO$, Calcd: C, 82.58; H, 7.59; N, 4.59; Obsd: C, 82.34; H, 7.93; N, 4.73%.

4.1.2.8. *N*-(4-Methoxyphenyl)-[2-(2-naphthyloxy)ethyl]-amine (12). Yield: 0.67 g (94%), mp: 92 °C; IR (KBr, cm^{-1}): ν = 1464 (Ar), 1512 (Ar), 1603 (Ar), 2866 (CH), 2927 (CH), 3388 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.43–3.49 (m, 2H, O–CH_2CH_2NH), 3.73 (s, 3H, OCH_3), 4.12 (br, H, NH), 4.22 (t, 2H, OCH_2), 6.32–7.69 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3, 56.7, 73.8, 105.6, 118.6, 123.6, 126.7, 128.6, 128.8, 129.9, 134.7, 137.5, 157.8 ppm; Mass (EIMS): *m*/*z* = 293; Analysis: $C_{19}H_{19}NO_2$, Calcd: C, 77.79; H, 6.53; N, 4.77; Obsd: C, 77.58; H, 6.99; N, 4.54%.

4.1.2.9. *N*-(4-Methoxyphenyl)-[3-(2-naphthyloxy)propyl]amine (13). Yield: 0.66 g (95.6%); mp: 110 °C; IR (KBr, cm^{-1}): ν = 1468 (Ar), 1521 (Ar), 1611 (Ar), 2874 (CH), 2930 (CH), 3394 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.91–1.94 (m, 2H, O–$CH_2CH_2CH_2NH$), 3.10–3.15 (m, 2H, CH_2NH), 3.75 (s, 3H, OCH_3), 4.01 (br, H, NH), 4.14 (t, 2H, O–CH_2), 6.32–7.64 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.4, 47.9, 56.2, 69.7, 105.7, 118.8, 123.8, 126.5, 128.3, 128.6, 129.9, 134.8, 137.6, 157.6 ppm; Mass (EIMS): *m*/*z* = 307; Analysis: $C_{20}H_{21}NO_2$, Calcd: C, 78.15; H, 6.89; N, 4.56; Obsd: C, 78.59; H, 6.65; N, 4.28%.

4.1.2.10. *N*-(4-Methoxyphenyl)-[4-(2-naphthyloxy)-butyl]amine (14). Yield: 0.67 g (97.8%); mp: 95 °C; IR (KBr, cm^{-1}): ν = 1474 (Ar), 1530 (Ar), 1623(Ar), 2880 (CH), 2940 (CH), 3405 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ = 1.91–1.94 (m, 2H, O–CH_2CH_2 CH_2CH_2NH), 3.12–3.16 (m, 2H, O–$CH_2CH_2CH_2$ CH_2NH), 3.73 (s, 3H, OCH_3), 4.05 (br, H, NH), 4.22 (t, 2H, OCH_2), 6.35–7.80 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 28.6, 51.6, 56.3, 72.5, 105.5, 118.6, 123.6, 126.7, 128.6, 128.8, 129.9, 134.7, 137.5, 157.8 ppm; Mass (EIMS): *m*/*z* = 321; Analysis: $C_{21}H_{23}NO_2$, Calcd: C, 78.47; H, 7.21; N, 4.36; Obsd: C, 78.09; H, 7.48; N, 4.21%.

4.1.3. General procedure for the preparation of *N*-alkyl derivatives of compound no. 13. A mixture of (4-methoxyphenyl)-[3-(2-naphthyloxy)propyl]amine (**13**) (0.5 g, 2 mmol) and alkyl iodide (3 mmol) was taken in dry ace-

tone (40 mL). It was refluxed for 10–12 h and the progress of the reaction was checked by TLC. Reaction mixture was filtered and filtrate was concentrated to get oily compound, which was further crystallized using benzene-hexane mixture to get the desired compound.

4.1.3.1. *N*-(4-Methoxyphenyl)-*N*-methyl-[3-(2-naphthyloxy)propyl]amine (15). Yield: 0.5 g (94%); mp: 112 °C; IR (KBr, cm^{-1}): ν = 1464 (Ar), 1512 (Ar), 1600 (Ar), 2864 (CH), 2927 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90–1.94 (m, 2H, O–$CH_2CH_2CH_2N$), 2.85 (s, 3H, N–CH_3), 3.30–3.33 (m, 2H, O–$CH_2CH_2CH_2N$), 3.74 (s, 3H, OCH_3), 4.20 (t, 2H, OCH_2), 6.48–7.64 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 41.4, 54.6, 56.7, 105.6, 118.7, 123.7, 126.6, 128.4, 128.6, 129.8, 134.9, 137.7, 157.5 ppm; Mass (FAB): *m*/*z* = 321; Analysis: $C_{21}H_{23}NO_2$, Calcd: C, 78.47; H, 7.21; N, 4.36; Obsd: C, 78.75; H, 7.69; N, 4.18%.

4.1.3.2. *N*-(4-Methoxyphenyl)-*N*-ethyl-[3-(2-naphthyloxy)propyl]amine (16). Yield: 0.52 g (94.6%); mp: 117 °C; IR (KBr, cm^{-1}): ν = 1470 (Ar), 1519 (Ar), 1612 (Ar), 2872 (CH), 2938 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, 3H, NCH_2CH_3), 1.92–1.97 (m, 2H, O–$CH_2CH_2CH_2N$), 3.31–3.35 (m, 2H, O–$CH_2CH_2CH_2N$), 3.38–3.42 (m, 2H, NCH_2CH_3), 3.76 (s, 3H, OCH_3), 4.22 (t, 2H, OCH_2), 6.50–7.69 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 29.7, 49.1, 52.6, 56.5, 105.2, 118.5, 123.8, 126.7, 128.6, 128.7, 129.6, 134.8, 137.8, 157.5 ppm; Mass (FAB): *m*/*z* = 335; Analysis: $C_{22}H_{25}NO_2$, Calcd: C, 78.77; H, 7.51; N, 4.18; Obsd: C, 78.45; H, 7.96; N, 4.06%.

4.1.3.3. *N*-(4-Methoxyphenyl)-*N*-propyl-[3-(2-naphthyloxy)propyl]amine (17). Yield: 0.55 g (95.7%); mp: 116 °C; IR (KBr, cm^{-1}): ν = 1474 (Ar), 1520 (Ar), 1621 (Ar), 2874 (CH), 2937 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, 3H, $NCH_2CH_2CH_3$), 1.51–1.56 (m, 2H, $NCH_2CH_2CH_3$), 1.92–1.96 (m, 2H, O–$CH_2CH_2CH_2N$), 3.30–3.36 (m, 4H, O–$CH_2CH_2CH_2N$ and $NCH_2CH_2CH_3$), 3.38–3.42 (m, 2H, NCH_2CH_3), 3.75 (s, 3H, OCH_3), 4.24 (t, 2H, OCH_2), 6.51–7.70 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 22.5, 29.8, 49.2, 52.7, 56.6, 105.6, 118.6, 123.9, 126.6, 128.6, 128.7, 129.6, 134.9, 137.8, 157.7 ppm; Mass (FAB): *m*/*z* = 349; Analysis: $C_{23}H_{27}NO_2$, Calcd: C, 79.05; H, 7.79; N, 4.01; Obsd: C, 79.39; H, 7.43; N, 4.15%.

4.1.3.4. *N*-(4-Methoxyphenyl)-*N*-butyl-[3-(2-naphthyloxy)propyl]amine (18). Yield: 0.58 g (98%); mp: 123 °C; IR (KBr, cm^{-1}): ν = 1481 (Ar), 1526 (Ar), 1623 (Ar), 2881 (CH), 2942 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3H, $NCH_2CH_2CH_2CH_3$), 1.51–1.56 (m, 2H, $NCH_2CH_2CH_3$), 1.92–1.96 (m, 2H, O–$CH_2CH_2CH_2N$), 3.30–3.36 (m, 4H, O–$CH_2CH_2CH_2N$ and $NCH_2CH_2CH_3$), 3.38–3.42 (m, 2H, NCH_2CH_3), 3.75 (s, 3H, OCH_3), 4.24 (t, 2H, OCH_2), 6.51–7.70 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 20.5, 29.8, 31.8, 52.7, 56.6, 105.5, 118.7, 123.6, 126.8, 128.7, 128.9, 129.7, 134.8, 137.9, 157.6 ppm; Mass (FAB): *m*/*z* = 363; Analysis: $C_{24}H_{29}NO_2$, Calcd: C, 79.30; H, 8.04; N, 3.85; Obsd: C, 79.58; H, 8.26; N, 4.33%.

4.1.3.5. {*N*-(4-Methoxyphenyl)-[3-(2-naphthyloxy)propyl]amino} acetic acid ethyl ester (19). A mixture of compound 13 (0.5 g, 2 mmol) and ethyl bromoacetate (0.62 mL, 3 mmol) was taken in dry acetone (40 mL). It was refluxed for 10 h and the completion of reaction was checked by TLC. Reaction mixture was filtered and the filtrate was concentrated to get the desired compound.

Yield: 0.62 g (96%), mp: oil; IR (neat, cm^{-1}): ν = 1479 (Ar), 1519 (Ar), 1617 (Ar), 1689 (C═O), 2877 (CH), 2937 (CH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (9t, 2H, $COOCH_2CH_3$), 1.92–1.96 (m, 2H, O–$CH_2CH_2CH_2$–N–), 3.35 (t, 2H, O–$CH_2CH_2CH_2N$), 3.73 (s, 3H, OCH_3), 4.22 (t, 2H, OCH_2), 4.25–4.30(m, 2H, $COOCH_2CH_3$), 4.33 (s, 2H, NCH_2COOEt), 6.50–7.66 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 29.6, 52.7, 56.6, 59.6, 105.5, 118.7, 123.6, 126.8, 128.7, 128.9, 129.7, 134.8, 137.9, 157.8, 171.5 ppm; Mass (FAB): *m*/*z* = 393; Analysis: $C_{24}H_{27}NO_4$, Calcd: C, 73.26; H, 6.92; N, 3.56; Obsd: C, 73.59; H, 7.34; N, 3.48%.

4.1.3.6. {*N*-(4-Methoxyphenyl)-[3-(2-naphthyloxy)propyl]amino} acetic acid (20). Compound **19** (0.5 g) was taken in ethanol (30 mL) and to this stirring solution NaOH (80 mg) in ethanol (15 mL) was added and refluxed for 1 h to afford acid **20**. Yield: 200 mg, ^1H NMR (400 MHz, $CDCl_3$): δ = 1.92–1.96 (m, 2H, $OCH_2CH_2CH_2N$), 3.32–3.35 (m, 2H, $OCH_2CH_2CH_2N$), 3.76 (s, 3H, OMe), 4.05–4.11 (t, 2H, CH_2–O–naphthyl), 4.25–4.31 (s, 2H, NCH_2COOH), 6.48–7.66 (m, 12H, Ar–H of naphthyloxy and phenyl ring) ppm, Mass (FAB): *m*/*z* = 365; Analysis: $C_{22}H_{23}NO_4$, Calcd: C, 72.31, 6.34, N, 3.83; Obsd: C, 72.69, H, 5.64, N, 3.49%.

4.2. Biological assay

4.2.1. Anti-diabetic activity. Activity of various compounds was tested in different four models as discussed one by one.

4.2.1.1. Glucose-loaded model (GLM). Overnight fasted male Sprague–Dawley rats were used for the glucose-loaded experiment. Blood was collected initially and thereafter test compounds were given to the test group consisting of five rats by oral gavage at a dose of 100 mg/kg body weight. After half an hour post-test sample treatment, a glucose-load of 2 g/kg body weight was given to each rat. The blood was collected at 30, 60, 90, and 120 min. post glucose-load. The % fall in blood glucose level was calculated according to the AUC method.

4.2.1.2. Sucrose-loaded model (SLM). Overnight fasted male Sprague–Dawley rats were used for the sucrose-loaded experiment. Blood was collected initially and thereafter test compounds were given to the test group consisting of five rats by oral gavage at a dose

of 100 mg/kg body weight. After half an hour post-test sample treatment, a sucrose-load of 100 g/kg body weight was given to each rat. The blood was collected at 30, 60, 90, and 120 min post sucrose-load. The % fall in blood glucose level was calculated according to the AUC method.

4.2.1.3. Streptozotocin model (STZ). A solution of streptozotocin (60 mg/kg) in 100 mM citrate buffer, pH 4.5, was prepared and calculated amount of the fresh solution was dosed to overnight fasted rats (60 mg/kg) intra-peritoneally. The blood sugar level was measured after 48 h by glucometer. Animals showing 200–400 mg/dl were selected for anti-diabetic screening. The diabetic animals were divided into groups of six animals each. Rats of experimental group were administered a suspension of desired sample (prepared in 1% gum acacia) orally (100 mg/kg body weight). Controlled group animals were also fed with 1% gum acacia. The blood glucose levels were measured at 1-, 2-, 3-, 4-, 5-, 6-, 7-, and 24-h intervals. The percentage fall in the blood glucose in 1–24 h by test sample was calculated according to the area under curve (AUC) method. The average fall in AUC in experimental group compared to control group provided % anti-hyperglycemic activity.

4.2.1.4. Sucrose challenged streptozotocin-induced (STZ-S) model. A calculated amount of the fresh solution of STZ dissolved in 100 mM citrate buffer (pH 4.5) was injected to overnight fasted rats (60 mg/kg) intra-peritoneally. Blood was checked for glucose content 48 h later by glucometer and animals showing blood glucose profile between 150 and 250 mg/dl were selected and were divided into different groups. Half an hour post-test sample treatment, a sucrose-load of 2.5 g/kg body weight was given to each rat. Blood glucose levels were again tested at 30, 60, 90, 120, 180, 240, 300 min, and 24 h post-test sample/drug administration. Food but not water was withdrawn from the cages during the experiment.

4.2.2. Lipid lowering activity. This activity was evaluated in two different models in vivo.

4.2.2.1. Triton model. Male Charles Foster rats (200–225 g) bred in the animal house of the institute were divided into control, Triton, and Triton plus drug treated groups containing six rats in each. Triton WR-1339 (Sigma, USA) was administered (200 mg/kg body weight) by intra-peritoneal injection for 18 h. The compounds/Gugulipid (standard drug) macerated with 2% aqueous gum acacia suspension were fed orally (100 mg/kg body weight) simultaneously with triton. Control animals received same amount of vehicle. At the end of the experiment, rats were fasted overnight and blood was withdrawn from retro-orbital plexus. Serum was separated by centrifugation at low speed and assayed for total cholesterol, phospholipids, and triglyceride by standard procedure reported earlier. The data are reported in Table 1.

4.2.2.2. Hamster model. Male Golden Syrian hamsters weighing 120–130 g were divided into control, dyslipidemic, and dyslipidemic plus drug treated groups of 8 animals each. Dyslipidemia was produced by feeding with fructose-rich high fat diet (HFD). Dyslipidemic hamsters had free access to HFD and were ad. Lib for 10 days (day 1 to day 100). Compounds (300 μmol/kg)/Fenofibrate (1000 μmol/kg) macerated in vehicle containing 0.2% CMC + 0.4% Tween-80 in distilled water were fed orally from day 4 to day 10 simultaneously with HFD feeding to hamster. Control animals received same amount of vehicle. At the end of the experiment on 10th day, blood was withdrawn and plasma was used for assay of triglyceride (Tg), cholesterol (chol), High density lipo-protien (HDL), glucose, glycerol, and free fatty acids (FFA) by standard spectrophotometric methods on auto analyzer. The data are reported in Table 2.

5. Conclusion

ω-(2-Naphthyloxy) amino alkanes and its substituted derivatives were conveniently prepared in two steps starting from β-naphthol, providing a novel class of compounds showing significant anti-diabetic activity with the added advantage of their effect in lipid lowering. Most of the compounds showing anti-diabetic activity have shown promising PPAR-α/γ/δ agonistic activity. Compound **13** has been picked-up for detailed evaluation.

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