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Novel substituted naphthalen-1-yl-methanone derivatives as anti-hyperglycemic agents

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Abstract—A series of aminoalkoxy phenyl-substituted naphthalene-1-yl-methanone was synthesized and tested for its anti-hyperglycemic activity in SLM and STZ-S rat models. Some compounds (**3b**, **4c** and **4h**) of the series were showing significant anti-hyperglycemic activity in male Sprague–Dawley rats in sucrose-loaded model (SLM) as well as in streptozotocin-induced model (STZ-S). Active compounds were also evaluated for relative binding affinity against glucagon receptor.

Diabetes (type-2) is a disease characterised by insulin resistance, hyperglycemia and hyperinsulinemia, leading to impaired secretion of insulin in latter stages.[1] Diabetes is often associated with obesity, dyslipidemia and hypertension, which are collectively known as syndrome X or insulin resistance-associated disorders (IRAD).[2] Current therapies for type-2 diabetes have inherent problems of non-compliance, ineffectiveness and hypoglycemic episodes with insulin and sulfonyl ureas.[3] Different types of peroxisome proliferator-activated receptor (PPAR) agonists (glitazones and glitazars) have been shown to have beneficial effects on the described characteristic of type-2 diabetes. Glitazone type therapeutics are in market but some of them have been reported to have hepatotoxicity.[4] Therefore, there is a greater need for more effective and better-tolerated orally active agents.

Glucagon is a 29-amino acid polypeptide produced in the pancreatic α-cells and secreted in response to falling glucose levels during the fasting period. Glucagon increases glucose production by promoting glycogenolysis and gluconeogenesis in the liver and attenuation of the ability of insulin to inhibit these processes. The combined action of glucagon and insulin is responsible for maintaining glucose homeostasis in the body. Both increased glucagon secretion during the fasting state and the lack of insulin-mediated suppression of glucagon production in postprandial state contribute to the elevated glucagon levels associated with the hyperglycemia observed in the diabetic state. Therefore, reducing circulating glucagon levels and inhibiting glucagon-immunoneutralization of endogenous glucagons with monoclonal glucagons resulted in normalization of hyperglycemic in streptozotocin diabetic rats.[5]

The study gives indication that glucagon receptor antagonists can be effectively used for the treatment of type-2 diabetes. The glucagon receptor is a seven transmembrane G-protein-coupled receptor (GPCR) belonging to the secretin family.[6]

There are some peptide glucagon antagonists known such as DesHIS^{1}[Glu^{9}]-glucagon amide, DesHIS^{1} DesPhe^{6} [Glu^{9}]-glucagon amide and Nleu^{9}Ala^{11,16}-glucagon amide.[7] But oral availability and metabolic stability of these peptide antagonists are question marked. Although very few non-peptide glucagon antagonists were reported in the literature, for example, CP-99,711, NNC-92,1687 and **I**[8] (Fig. 1). This prompted us to design new non-peptide glucagon receptor antagonists.

We describe in this paper the design, synthesis and antidiabetic activities of (substituted aminoalkoxy phenyl) naphthalen-1-yl-methanone derivatives.

The design of naphthalen-1-yl-methanone nucleus was mainly based on CP-99,711, NNC-92,1687 and the

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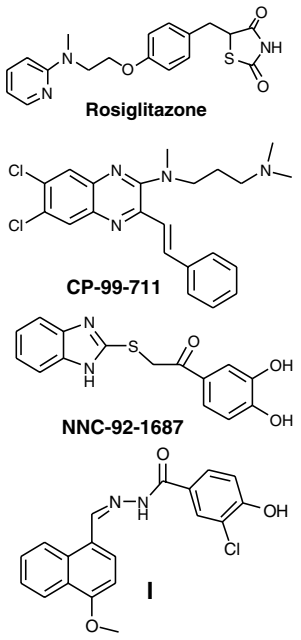


Figure 1.

recently reported compound **I** (Fig. 1). Our strategy here was to merge the key pharmacophoric motifs of these three series into a hybrid structure of type **II** (**4a**–**k**). These molecules have three important motifs, which are responsible for the biological activity (Fig. 2). Whereas naphthalen-1-yl-methanone molecule has four distinct motifs in which one motif B_a is taken from CP-99,711, motif A_a is taken from **I** and other two motifs (E_a and F_a) are selected from two common motifs of compound I and NNC-92,1687 (E,E_1 and F,F_1). The motif B_a was designed as side chain having substituted alkylamino groups, as present in CP-99,711 (glucagon antagonist). Interestingly similar side chains are also present in rosiglitazone and adrenergic receptor β-$_3$ agonists. The phenolic group motif-F_a was taken from motifs-F/F1 of NNC-92,1687 and compound **I**. In the motif E_a only the carbonyl hinge was kept as present in NNC-92,1687 and Compound **I**. Whereas the main nucleus (motif A_a) was selected as naphthalene moiety. The motifs A/A_1 are having heterocyclic moieties, which were changed into naphthalene moiety. The selection of naphthalene nucleus was based on motif A_2 of compound **I** (Fig. 2). As F_a and B_a motifs together are bulkier therefore, unsubstituted naphthalene (A_a) and only carbonyl hinge (E_a) are selected from motifs E and E_1. The designed phenyl-substituted alkylamino naphthalen-1-yl-methanone nucleus II (**4a–k**) is shown in Figure 3.

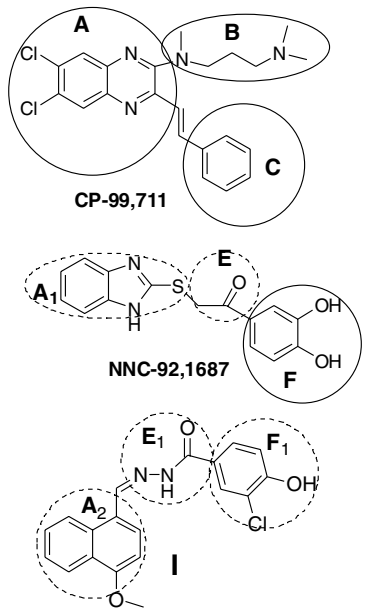


Figure 2. Three main motifs responsible for biological activity of CP-99,711. A, heterocyclic moiety; B, alkyl amino chain; C, phenyl. NNC-92,1687: F, phenolic moiety; E, linker and A_1, heterocyclic moiety; Compound **I**: A_2, naphthalene; E_1, linker; F_1, phenolic moiety.

Synthesis of naphthalen-1-yl[4-(2/3-amino-1-yl-alkoxy)-phenyl]methanone derivatives (**4**) was achieved starting from 1-naphthoic acid (Scheme 1). Friedel Crafts acylation reaction of anisole with 1-naphthoic acid in the presence of $AlCl_3$ or polyphosphoric acid gave 4-methoxy-phenyl naphthophenone (**1**). The reaction gave better results, when polyphosphoric acid was used as catalyst, which on reaction with pyridine hydrochloride

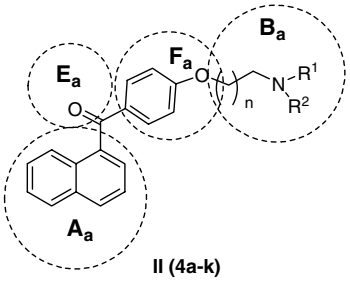
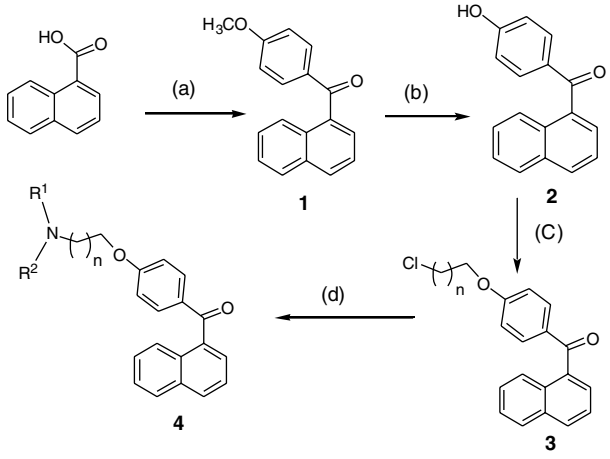


Figure 3. General structure of synthesized compound [substituted naphthalen-1-yl-methanone] **II** (**4a**–**k**).



Scheme 1. Reagents and conditions: (a) anisole, (PPA) polyphosphoric acid, 80 °C; (b) pyridine hydrochloride 120 °C or BBr_3, 6 h stirring; (c) acetone/K_2CO_3 reflux; (d) acetone/K_2CO_3 reflux or DMF/K_2CO_3, 80 °C.

at 120 °C or boron tribromide at room temperature gave demethylated product 4-hydroxy-phenyl naphthophenone (**2**). Boron tribromide gave better yield than pyridine hydrochloride. The 4-hydroxyl-phenyl naphthophenone (**2**) on Willimson O-alkylation reaction with bromochloroalkanes in the presence of dry K_2CO_3 and acetone transformed into [(2/3-chloro alkoxy)-phenyl]naphthalen-1-yl methanone (**3**) which on treatment with various aliphatic and aromatic amines in acetone/K_2CO_3 under refluxing condition or in DMF/K_2CO_3/DMAP at 80 °C under anhydrous conditions gave the desired product as free base (**4**). Which on treatment with oxalic acid in methanol gave [(2/3-substituted aminoalkoxy phenyl]naphthalen-1-yl-methanone as their oxalate salts (**4a**–**k**). The synthesized compounds were tested for their anti-hyperglycemic activity and are listed in Table 1.

All the synthesized compounds were evaluated for anti-hyperglycemic activity in sucrose-loaded model (SLM) using male Sprague–Dawley rats. Compounds showing promising anti-hyperglycemic activity are **3b** (22%), **4b** (17.2%), **4c** (14.9%), and **4h** 28.8%. But out of these, only activity shown by **3b** and **4h** was significant at $p < 0.05$. The most active compound in the series ($n = 1$) as well as in ($n = 2$) have alkyl pyrrolidine as a side chain. All the compounds then evaluated for anti-hyperglycemic activity in sucrose charged streptozotocin (STZ-S)-induced β-cell damaged diabetic model of Sprague–Dawley strain male albino rat model. Compounds **3b** and **4h** were showing 17% and 27% glucose lowering activity, respectively, at 100 mg/kg dose. It is interesting to report here that compound having alkyl pyrrolidine substitution in both the series [$n = 1$ (17%), $n = 2$ (27%)] was active and most potent compounds in entire series. Whereas alkyl piperidine substitution is showing moderate activity in $n = 1$ series (11.3%) but it is showing insignificant activity in $n = 2$ (6.8%) series. Compounds showing activity in SLM as well as STZ-S models were assayed for competitive binding of ^{125}I-glucagon to the human glucagon receptor.[9] Compounds exhibited moderate activity against the human glucagon receptor binding affinity **4b**: $IC_{50} = 55$ μM, **4h**:$IC_{50} = 17$ μM, and **4k**: $IC_{50} = 35$ μM). All compounds tested were functionally competitive antagonists. Compound 4 h was showing quite comparable anti-hyperglycemic activity with standard drugs (metformin, glibenclamide and glyclazide) in STZ-S rat model (Table 1).

Sucrose-loaded model. Compounds were tested for their effect on glucose tolerance curve in rats of average body weight 169 ± 20 g, an indirect effect of measuring anti-hyperglycemic activity. The blood glucose levels of all animals were checked after an overnight fasting (16 h) by glucostrip (Boehringer–Mannheim). Animals showing blood glucose level between 60 and 80 (mg/dl) (3.33–4.44/mM) were divided into two groups of five to six animals each. Animals of experimental groups were administered the suspension of the synthetic compounds orally (made in 1.0% gum acacia) at a dosage of 100 mg/kg body weight. Animals of 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 postadministration of the test sample/vehicle. Blood glucose of each animal was determined at 30, 60, 90 and 120 min postadministration of sucrose. Food but not water was removed from the cages during the course of experimentation. Quantitative glucose tolerance of each animal was calculated by area under curve (AUC) method. The % fall in blood glucose level was calculated by comparing AUC of experimental and control group. Samples showing significant inhibition ($p < 0.05$) on postprandial hyperglycemia (AUC) were considered as active samples.

Sucrose challenged streptozotocin-induced model. A calculated amount of the fresh solution of streptozotocin (STZ) dissolved in 100 mM citrate buffer (pH 4.5) was injected to overnight fasted rats (60 mg/kg) intraperitoneally. 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 posttest

Table 1. Anti-hyperglycemic activity of aminoalkoxy naphthophenone derivatives **3** (**a**,**b**), **4** (**a**–**k**)[10]

Compound	n	R^1	R^2	% Anti-hyperglycemic activity	
				SLM	STZ-S
3a	1	—	—	24	ND
3b	2	—	—	22	8.5
4a	1	Piperidine	—	15.4	11.3
4b	1	Pyrrolidine	—	17.2	17
4c	1	H	$C_6H_5CH_2$	14.9	5.6
4d	1	H	C_6H_{11}	7.16	Nil
4e	1	H	4-$OCH_3C_6H_5$	9.71	9.2
4f	1	C_2H_5	C_2H_5	7.21	Nil
4g	2	Piperidine	—	7.16	6.8
4h	2	Pyrrolidine	—	28.8 ($p < 0.05$ active)	27
4i	2	H	$C_6H_5CH_2$	8.06	7.5
4j	2	H	C_6H_{11}	11.16	Nil
4k	2	H	4-$OCH_3C_6H_5$	16.17	12.6
Metformin				12.9	19.1
Glibenclamide				33.7	29.0
Glyclazide				40.4	27.7

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 posttest sample/drug administration. Food but not water was withdrawn from the cages during the experiment.

In conclusion, we have described a novel series of naphthalen-1yl-methanone, which is showing promising antihyperglycemic activity in SLM and STZ-S rat models. The most active compound **4h** is showing 28.8% blood sugar lowering activity in SLM model and 27% in STZ-S model and it is also exhibiting glucagon antagonistic activity (IC_{50} = 17 μM). The work has generated a new lead and further optimisation of lead is in progress.

Acknowledgment

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10. *(4-Methoxy-phenyl)naphthalen-1-yl-methanone (**1**)*. A mixture of 1-naphthoic acid (5 g, 28 mmol), anisole (9 ml, 0.082 mol) and polyphosphoric acid (45 g) was taken in rb flask. The reaction mixture was heated at 80 °C for 8 h. Reaction mixture was poured on ice and extracted with ethyl acetate. Organic layer was concentrated to give (**1**). Which was recrystallised with benzene–hexane.*(4-Hydroxy-phenyl)naphthalen-1-yl-methanone (**2**)*. 4-Methoxy-phenyl naphthophenone (2.5 g, 14 mmol) was taken in dry dichloromethane (30 ml) and stirred for 15 min at 0 °C. Boron tribromide (5 ml, 1 M soln in CH_2Cl_2) was slowly added to the reaction mixture and stirred the solution for 16 h. Reaction mixture was extracted with ethyl acetate and recrystallized with methanol to yield **2**.*General method of O-alkylation: [4-(2-chloro-ethoxy)-phenyl]-naphthalen-1-yl methanone (**3a**)*. (4-Hydroxy-phenyl)-1-naphthlen-1-yl-methanone (**1**) (0.01 mol) and bromochloro ethane (0. 015 mol) were refluxed in dry acetone in the presence of baked K_2CO_3 (1.5 mmol) under anhydrous conditions. After completion of the reaction K_2CO_3 was filtered and acetone was distilled off, and the product was crystallized from ethyl acetate/hexane to give [4-(2-chloro-ethoxy)-phenyl]-naphthalene-1-yl-methanone **3a**. Yield 82%. Mp 75–79 °C; MS (FAB) 311 (M^+1); IR (KBr): 1651 cm^{-1} (C=O), 2965 cm^{-1} (CH_2–H Str); 1600 cm^{-1} (ArH); ^{1}H NMR ($CDCl_3$) δ: 4.26 (t, 2H, O CH_2), 3.83 (t, 2H, CH_2Cl), 6.84 (d, 2H, Ar*H*), 7.42–7.54 (m, 4H, ArH), 7.82–8.15 (m, 5H, ArH).
*[4-(3-Chloro-propoxy)-phenyl]-naphthalen-1-yl-methanone (**3b**)*. Yield 85%; mp 60 °C; IR (KBr): 1651 cm^{-1} (C=O), 2965 cm^{-1} (CH_2–H Str), 1600 cm^{-1} ArH); MS (FAB) (M^++1) 323; ^{1}H NMR ($CDCl_3$) δ: 4.14 (t, 2H, OCH_2), 3.60 (t, 2H, Cl CH_2), 2.13 (m, 2H, CH_2 CH_2 CH_2), 6.82 (m, 2H, Ar*H*), 7.20–7.41 (m, 4H, Ar*H*), 7.72–7.95 (m, 5H, Ar*H*).
*General method of **N**-alkylation: naphthalen-1-yl-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone (**4a**)*. [4-(2-Chloro-ethoxy)-phenyl]-naphthalen-1-yl-methanone (**3a**) (10 mmol), piperidine (15 mmol) and K_2CO_3 (1.0 mol) were taken in acetone (anhydrous) and the reaction mixture was refluxed for 6 h. On completion of reaction, as monitored by TLC. K_2CO_3 was filtered off, in the case of acetone, reaction mixture was distilled off, poured into water (60 ml) and extracted with ethyl acetate thrice. The solvent was distilled off and chromatographed on basic alumina using hexane and ethyl acetate to yield **4a**. Which on treatment with oxalic acid in methanol gave oxalate salt of **4a**. Yield 83%; mp 125 °C; IR (KBr): 1652 (cm^{-1}) C=O, 1600 cm^{-1} ArH, 2929 (CH_2-Str); MS (FAB) (M^++1) 449; ^{1}H NMR ($CDCl_3$) δ: 4.24 (t, 2H, OCH_2), 2.91 (t, 2H, NCH_2), 2.76 (m, 4H, NCH_2) 1.62 (m, 4H-CH_2) 1.24 (p, 2H, CH_2 CH_2 CH_2) 6.84 (d, 2H, Ar*H*), 7.2–7.4 (m, 4H, Ar*H*) 7.7–7.9 (m, 5H, Ar*H*). Anal. Calcd for (**4a**) $C_{26}H_{27}NO_6$: C, 69.48; H, 6.00; N, 3.11. Found: C, 69.17; H, 6.14; N, 3.21.
*Naphthalen-1-yl-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-methanone (**4b**)*. Yield 81%; mp 155 °C, IR (KBr): 1653 (C=O), MS (FAB) (M^++1) 435, ^{1}H NMR ($CDCl_3$) δ: 4.1 (t, 2H, OCH_2), 2.0–2.5 (m, 6H, NCH_2), 1.2–1.6 (m, 4H, H 2,3), 6.8 (d, 2H, Ar*H*), 7.2–7.4 (m, 4H, Ar*H*) 7.7–7.9 (m, 5H, Ar*H*). Anal. Calcd for $C_{25}H_{25}NO_6$: C, 71.7; H, 6.20; N, 3.21. Found: C, 71.5; H, 6.33; N, 3.39.
*[4-(2-Benzylamino-ethoxy)-phenyl]-naphthalen-1yl-methanone (**4c**)*. Yield 72%; mp 220 °C; IR (KBr): 1652 cm^{-1} (C=O), 1600 (Ar-H); MS (FAB) (M+1) 382; ^{1}H NMR ($CDCl_3$) δ: 3.97 (t, 2H OCH_2), 2.54 (t, 2H, NCH_2), 3.84 (s, 1H, $C_6H_5CH_2$), 7.12–7.26 (m, 5H, Ar*H*), 6.85 (d, 2H, Ar*H*) 7.28–7.52 (m 4H, Ar*H*) 7.8–8.3 (m 5H, Ar*H*). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.80; H, 6.56; N, 3.57. Found: C, 81.52; H, 6.32; N, 3.57.
*[4-(2-Cyclohexylamino-ethoxy)-phenyl]-naphthalen-1yl-methanone (**4d**)*. Yield 64%; mp 210 °C; (KBr): 1652 cm^{-1} (C=O), 1600 (Ar-H); MS (FAB) (M^+ + 1) 463; ^{1}H NMR ($CDCl_3$) δ: 4.14 (t, 2H, OCH_2), 2.53 (t, 2H, NCH_2), 2.46 (m, 1H, NH–C*H*), 1.10–1.92 (m, 10H, C_6H_{10}), 6.84 (d, 2H, Ar*H*), 7.22–7.46 (m 4H, Ar*H*), 7.71–7.97 (m, 5H, Ar*H*). Anal. Calcd for $C_{27}H_{29}NO_6$: C, 69.90; H, 6.26; N, 3.00. Found: C, 69.5; H, 5.87; N, 3.36.
*4-[2-(4-Methoxy benzyl amino-ethoxy)-phenyl]-naphthalen-1yl-methanone (**4e**)*. Yield 70%; mp 140 °C; IR (KBr): 1652 cm^{-1} (C=O), 1600 (Ar); MS (FAB) (M^++1) 397; ^{1}H

NMR ($CDCl_3$) δ: 3.73 (s, 3H, OC*H*$_3$), 4.15 (t, 2H, OC*H*$_2$), 3.56 (t, 2H, NC*H*$_2$),6.67 (d, 2H, ArH), 6.78 (d, 2H, ArH) 6.86 (d, 2H, Ar*H*), 7.21–7.45 (m 4H, Ar*H*), 7.7–7.93 (m, 5H, Ar*H*). Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.58; H, 5.79; N, 3.52. Found: C, 78.14; H, 5.69; N, 3.72.

*[4-(2-Diethylamino-ethoxy)-phenyl]-naphthalen-1yl-methanone (**4f**)*. Yield 80%; mp 171 °C; IR (KBr): 1652 cm^{-1} (C=O), 1600 (Ar-H); MS (FAB) (M^++1) 437; ^{1}H NMR ($CDCl_3$) δ: 1.12 {t, 6H, CH_2-(CH_3)$_2$}, 4.15 (t, 2H, OC*H*$_2$), 2.5–2.96 (m, 6H, NC*H*$_2$), 6.81–6.92 (d, 2H, Ar*H*), 7.42–7.56 (m, 4H, Ar*H*), 7.83–8.24 (m, 5H, Ar*H*). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.64; H, 6.17; N, 3.40. Found: C, 66.72; H, 5.71; N, 3.29.

*Naphthalen-1-yl-[4-(2-piperidin-1-yl-propoxy)-phenyl]-methanone (**4g**)*. Yield 82%; mp 165 °C; IR (KBr): 1652 (cm^{-1}) C=O, 1600 cm^{-1} ArH, 2929 (CH_2-Str); MS (FAB) (M^++1) 463; ^{1}H NMR ($CDCl_3$) δ: 4.24 (t, 2H, OC*H*$_2$), 2.96 (t, 2H, NC*H*$_2$), 2.73 (m, 4H, NC*H*$_2$) 1.65 (m, 4H-C*H*$_2$) 1.24 (p, 4H, CH_2 C*H*$_2$ CH_2). 6.86 (d, 2H, Ar*H*), 7.21–7.46 (m, 4H, Ar*H*), 7.73–7.98 (m, 5H, Ar*H*). Anal. Calcd for $C_{27}H_{29}NO_6$ C, 69.9; H, 6.22; N, 3.02. Found: C, 69.56; H, 6.33; N, 3.37.

*Naphthalen-1-yl-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-methanone (**4h**)*. Yield 80%; mp 158 °C; IR (KBr): 1653 (C=O); MS (FAB) (M^++1) 449; ^{1}H NMR ($CDCl_3$) δ: 4.12 (t, 2H, OC*H*$_2$), 2.11–2.53 (m, 6H, NC*H*$_2$), 1.23–1.64 (m, 4H, C*H*$_2$), 6.88 (d, 2H, Ar*H*), 7.22–7.47 (m, 4H, Ar*H*) 7.72–7.96 (m, 5H, Ar*H*). Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.48; H, 6.0; N, 3.11. Found: C, 69.42; H, 5.87; N, 3.21.

*[4-(2-Benzylamino-propoxy)-phenyl]-naphthalen-1yl-methanone (**4i**)*. Yield 70%; mp 210 °C; IR (KBr): 1652 cm^{-1} (C=O), 1600 (Ar-H); MS (FAB) (M+1) 396, ^{1}H NMR ($CDCl_3$) δ: 3.94 (t, 2H OC*H*$_2$), 2.54 (t, 2H, NC*H*$_2$), 1.83 (m, 2H CH_2 C*H*$_2$ CH_2) 3.86 (s, 1H, C_6H_5C*H*$_2$), 7.10–7.21 (m, 5H, Ar*H*), 6.86 (d, 2H, Ar H) 7.82–8.12 (m, 5H, Ar*H*), 7.21–7.47 (m, 4H, ArH). Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.02; H, 6.32; N, 3.54, Found: C, 82.23; H, 6.22; N, 3.45.

*[4-(2-Cyclohexylamino-propoxy)-phenyl]-naphthalen-1yl-methanone (**4j**)*. Yield 60%; mp, 165 °C; IR (KBr):1652 cm^{-1} (C=O), 1600 (Ar-H); MS (FAB) (M^++1) 477; ^{1}H NMR ($CDCl_3$) δ: 4.14 (t, 2H, OC*H*$_2$), 2.53 (t, 2H, NC*H*$_2$), 2.46 (m,1H, NH-C*H*), 1.12–1.87 (m,10H, C_6H_{10}), 1.95 (m, 2H, CH_2 C*H*$_2$ CH_2), 6.86 (d, 2H, Ar*H*), 7.21–7.44 (m 4H, Ar*H*), 7.73–7.97 (m, 5H, Ar*H*). Anal. Calcd for $C_{28}H_{31}NO_6$: C, 75.16; H, 6.4; N, 2.93. Found: C, 75.23; H, 6.26; N, 3.10.

*{4-[2-(4-Methoxybenzylamino-propoxy)-phenyl]-naphthalen-1yl-methanone} (**4k**)*. Yield 72%; mp 130 °C; IR (KBr) 1652 cm^{-1} (C=O), 1600 (Ar-H); MS (FAB) (M^++1) 411; ^{1}HNMR ($CDCl_3$) δ: 3.76 (s, 3H, OC*H*$_3$), 4.14 (t, 2H, OCH_2), 3.56 (t, 2H, NC*H*$_2$), 1.94 (m, 2H, CH_2 C*H*$_2$ CH_2), 6.68 (d, 2H, Ar*H*), 6.76 (d, 2H, ArH) 6.85 (d, 2H, ArH), 7.23–7.49 (m 4H, ArH), 7.72–7.97 (m, 5H, Ar*H*). Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.83; H, 6.08; N, 3.40. Found: C, 78.53; H, 6.48; N, 3.10.