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Synthesis of bicyclic biaryls as glucose-6-phosphatase inhibitors☆

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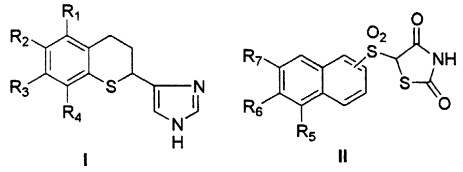
Abstract—Biaryls, 7-naphthyl-5-*s*-amino-2,3-dihydrobenzo[*b*]thiophene-4-carbonitriles (**3a–e**), 8-(1-naphthyl)-6-*s*-amino-isothiochroman-5-carbonitriles (**6a–d**), 4-(1-naphthyl)-2-*s*-aminobezocycloalkene-1-carbonitriles (**6e–j**), 8-naphthyl-6-*s*-amino-2-ethyl-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrle (**6k–n**), 1-naphthyl-3-*s*-amino-10*H*-9-thia-phenantherene-4-carbonitriles (**8a–e**) and 1-(1-naphthyl)-3-*s*-amino-9,10-dihydrophenantherene-4-carbonitriles (**8f–i**) have been prepared through carbanion induced ring transformation reactions of 6-naphthyl-3-cyano-4-*s*-amino-2*H*-pyran-2-ones (**1**) from respective ketones (**2**, **5**, and **7**). These compounds have been evaluated for their glucose-6-phosphatase inhibitory activity and only **6a**, **c**, **j**, **m**, **c**, **d**, **h** displayed significant inhibition of the glucose-6-phosphatase.

1. Introduction

Diabetes mellitus is one of the leading causes of deaths in developing and developed countries, which, arises due to under utilization of blood glucose by metabolic organs. Type 2 is the most common form of diabetes, characterized by resistance in peripheral target tissues to the binding of insulin.[1,2] Gluconeogenesis is a multistep enzymatic process, which maintains the blood glucose homeostasis in normal conditions. Glucose-6-phosphatase, an enzyme operates the penultimate step of gluconeogenesis has been identified as an important antidiabetic target in recent years. Though numerous compounds known to control type 2 diabetes with different mechanism but inhibitors of glucose-6-phosphatase as antihyperglycemic agents are not exploited extensively. The significance of this enzyme was realized in controlling blood glucose level with the discovery of vanadium[3] and pyridine[4] derivatives as inhibitors of glucose-6-phosphatase. From extensive literature survey, it was found that the derivatives of benzothiopyran[5] (**I**) and naphthylthiazolidinedione[5] (**II**) possess potent antidiabetic and antiobesity properties, which led us to synthesize compounds, encompassing these moieties in their molecular make-up to display blood glucose lowering and antiobesity activities. Thus, several dihydrobenzothiophenes (**3**), isothiochromans (**6**), 9-thiaphenanthrenes (**8**) and dihydrophenantherens (**8**) have been designed and synthesized to evaluate their glucose 6-phosphatase inhibitory activity.



I II

2. Chemistry

Several methodologies are available for the synthesis of 2,3-dihydro-1-benzothiophenes (**3**) either by ring contraction[6] of *cis*-3-bromo-7-chloro-3,4-dihydro-2*H*-benzothiopyran-4-ol in presence of imidazole or reductive ring opening of 6a,11a-6*H*-bezotheino[3,2-c]benzopyran[7] with $LiAlH_4$. Such nucleus has also been prepared by Bordwell procedures.[8]

Herein we report an expedient one pot synthesis of 2,3-dihydro-1-benzothiophene derivatives (**3**) through base catalyzed carbanion induced ring transformation of 6-aryl-4-*s*-amino-3-cyano-2*H*-pyran-2-ones (**1**) from dihydro 3(2*H*)-thiophenone (**2**) in DMF-KOH in an inert atmosphere. The precursor (**1**) has been synthesized from the reaction of methyl 3,3′-dimethylthioacrylate with 1-acetonaphthalene followed by reaction with secondary

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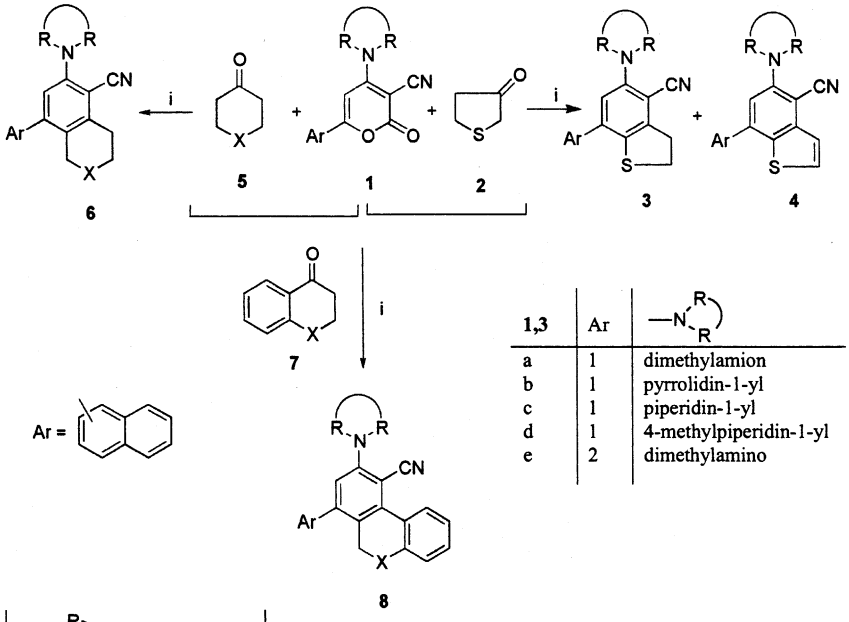
amines under reflux conditions.[9,10] The formation of **3** is possibly by the attack of carbanion generated in situ from ketone (**2**) at position C-6 of the pyran ring, a highly electropositive center due to extended conjugation with electron withdrawing group (CN), present at position 3 in pyran ring, followed by ring opening, decarboxylation and re-cyclization to yield **3** (Scheme 1). This reaction may also proceed via an inverse electron demand Diels–Alder type cyclo-addition reaction with ketone (**2**), followed by elimination of carbon dioxide to yield compounds (**3**). Since the reaction is performed at room temperature (~25 °C) under very mild reaction conditions, the former reaction pathway seems to be highly probable. The beauty of the procedure lies in the creating molecular diversity by synthesizing highly functionalized 2,3-dihydrobenzothiophenes (**3**), which are difficult to obtain in a single step from easily accessible precursors. In one of our experiments we have been able to isolate 5-dimethylamino-7-naphthalen-2-ylbenzo[*b*]thiophene (**4**) beside **3e** from the reaction of 2*H*-pyran-2-one (**1e**) and tetrahydrothiophene-3-one (**2**).

The same methodology has been also utilized for the synthesis of isothiochromenes (**6a–d**) benzocycloalkanes (**6e–j**) and tetrahydroisoquinolines (**6k–m**) (Scheme 1) from the reaction of **1** and respective ketones, tetrahydro-4*H*-thiopyran-4-one (**5**), cycloalkanone and *N*-ethyl-4-piperidone (**5**) respectively to explore their glucose-6-phosphatase inhibitory properties. Earlier, compounds of isothiochromene,[11–13] tetrahydroisoquinoline,[14–17] benzo-cycloalkenes ring systems have been prepared by different procedures but these methodologies suffer with demerits of harsh reaction conditions. Similarly 10*H*-9-thia-phenanthren (**8a–e**) and 9,10-dihydrophenanthrenes (**8f–i**) have been prepared through ring transformation of 6-aryl-3-cyano-2*H*-pyran-2-ones (**1**) with respective ketones (**7**), thiochroman-4-one and tetralone. Our synthetic approach is superior to the known literature procedures[18–22] in many ways such as simple reaction conditions, easy work up and cheap raw materials.

3. Results and discussion

Most of the synthesized compounds were evaluated for in vitro glucose-6-phosphatase inhibitory activity. Among the screened compounds, only compounds **6a, c, j, m, 8c, d, h** demonstrated significant inhibitory activity ranging from 48.6–75.3% at 100 μM concentration.



1,3	Ar	—N(R)R
a	1	dimethylamion
b	1	pyrrolidin-1-yl
c	1	piperidin-1-yl
d	1	4-methylpiperidin-1-yl
e	2	dimethylamino

6	Ar	—N(R)R	X
a	1	dimethylamino	S
b	1	pyrrolidin-1-yl	S
c	1	piperidin1-yl	S
d	1	4-methylpiperidin-1-yl	S
e	1	pyrrolidin-1-yl	CH_2
f	1	piperidin-1-yl	CH_2
g	1	pyrrolidin-1-yl	$(CH_2)_2$
h	1	piperidin-1-yl	$(CH_2)_2$
i	1	pyrrolidin-1-yl	$(CH_2)_3$
j	1	piperidin-1yl	$(CH_2)_3$
k	2	dimethylamino	NC_2H_5
l	2	pyrrolidin-1-yl	NC_2H_5
m	2	piperidin-1-yl	NC_2H_5
n	1	4-methylpiperidin-1-yl	NC_2H_5

8	Ar	—N(R)R	X
a	1	dimethylamino	S
b	2	dimethyamino	S
c	1	pyrrolidin-1-yl	S
d	1	piperidin-1-yl	S
e	1	4-methylpiperidin-1-yl	S
f	1	dimethylamino	CH_2
g	2	pyrrolidin-1-yl	CH_2
h	2	piperidin-1-yl	CH_2
i	2	4-methylpiperidin-1-yl	CH_2

Scheme 1. Reagent and condition: (i) DMF/KOH/25 °C/Stirring for 24–30 h.

Table 1. In vitro percent glucose-6-phosphatase inhibitory activity of compounds **3a–d**, **6a–n** and **8a–i** at 100 μM concentration

3,6	% Inhibition[a]	6,8	% Inhibition[a]
3a	31.8	**6k**	24.6
3b	24.1	**6l**	20.2
3c	20.1	**6m**	54.3
3d	17.6	**6n**	12.7
6a	57.4	**8a**	24.6
6b	26.8	**8b**	11.9
6c	75.3	**8c**	56.6
6d	21.3	**8d**	48.6
6e	23.8	**8e**	18.5
6f	23.8	**8f**	8.9
6g	29.8	**8g**	1.0
6h	14.1	**8h**	68.2
6i	54.8	**8i**	28.2
6j	53.8		

[a] Mean of three experiments.

3.1. Glucose-6-phosphatase enzyme assay

Glucose-6-phosphate, EDTA, TCA and NaF were purchased from the Sigma Chemicals Co. (USA). All other chemicals and reagent used were of analytical grade and were purchased from the local suppliers.

3.2. Partial purification of G-6-Pase (D-glucose-6-phosphate phosphorylase; EC 3.1.3.9) from rat liver:

The liver of male rats of Wistar strain was excised. A 10% homogenate was prepared in 150 mM KCl (w/v) using Potter Elvejhem glass homogeniser fiited with Teflon pestle. The homogenate was centrifuged at 1000 *g* for 15 min; supernatant was decanted and used as enzyme source.

The effect of test compounds was studied by pre-incubating 100 μg of the compound in 1.0 mL reaction system for 10 min and then determining the residual glucose-6-phosphatase activity according to the method of Hubscher and West.[23] The 1.0 mL assay system contained 0.3 M citrate buffer (pH 6.0), EDTA 28 mM, NaF 14 mM, 30 mL water, glucose-6-phosphate 200 mM and enzyme protein. The mixture was incubated at 37 °C for 30 min after which 1.0 mL of 10% TCA was added. Estimation of inorganic phosphates (Pi) in protein free supernatant was done according to the method of Taussky and Shorr.[24] Glucose-6-phosphatase activity was defined as μmol Pi released per min per mg protein.

Compounds of all protypes **3**, **6** and **8** were assayed for their glucose-6-phosphatase inhibitory activity (Table 1). In the first series of compounds **3a–d**, variations at positions 5 in *s*-amino group were made to assess their effect on inhibitory property. As evident from the screening results of compounds **3a–d** variation in secondary amino group did not affect the activity profile and it remains in the range of 20.1–31.8%. In attempts to obtain more active compounds and also to assess the effect of increased ring size of annulated 2,3-dihydrothienyl to 1,3,4-trihydrothiopyranyl ring as isothiochroman derivatives (**6a–d**) were prepared and evaluated for their inhibitory activity. In this series only compound **6c** exhibited 75.3% of inhibition followed by **6a** (57.4%) and rest of the compounds remained marginally active. Thus, nature of s-amino group at position 6 in **6a–d** plays an important role on inhibitory activity.

Analogous to sulfur heterocycles, isothiochromans (**6a–d**), nitrogen heterocycle as isoquinoline derivatives (**6k–n**) were synthesized to assess the impact of nitrogen hetero atom on glucose-6-phosphatase inhibitory property. In this series of compounds only **6m** exhibited 54.3% inhibition and rest of them displayed low order of activity. To understand the necessity of hetero atom for inhibitory property, some benzocycloalkenes (**6e–j**) were also synthesized and for evaluating their inhibitory property. In all these compounds only variations in s-amino sustituents and ring size of annulated cycloalkenes were made. As it is evident from the screening results that compounds fused with cyclooctane ring **6i** (54.8%) and **6j** (53.8%) displayed almost same order of inhibition while compounds annulated with cyclohexane and cycloheptane ring (**6e–h**) displayed insignificant activity. In order to synthesize compounds of better activity profile further structural manipulations were carried out by preparing 9-thiaphenanthrene derivatives (**8a–e**). In this series only compounds **8c,d** with pyrrolidinyl and piperidinyl substituents at position 3 displayed 56.6% and 48.6% respectively. Furhter modification in structure led to the synthesis of phenanthrene derivatives **8f–i** to assess the effect of methylene group on inhibitory property. Only compound **8h** with 3-piperidinyl substituent demonstrated 68.2% of inhibition while its sulfur analogue (**8d**) exhibited 48.6%.

It was concluded from the screening results that in most of the cases compounds bearing piperidinyl substituent (**6c, j, m, d, h**) displayed better inhibitory activity followed by dimethylamino substituent **6a**.

4. Experimental

Melting points were determined on Büchi-530 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker WM 200 MHz spectrometer in deuterated solvents with TMS as internal reference. IR spectra of all compounds were recorded on Perkin–Elmer AC-1 spectrometer. Mass spectra of all compounds were measured with Jeol JMS-D 300 spectrometer (70eV). Microanalyses were determined on Carlo Erba EA-1108 element analyzer within ±0.5% of the theoretical values. Thin layer chromatography (TLC) was performed on 7×3 cm precoated silica gel plastic plates. For column chromatography, silica gel of 60–120 mesh from Acme Synthetic Chemicals, Bombay, India, was used.

4.1. General procedure for the preparation of 7-aryl-5-*s*-amino-2,3-dihydrobenzo[*b*]thiophene-4-carbonitriles (3a–e)

An equimolar mixture of 6-naphthyl-4-*s*-amino-2*H*-pyran-2-one-3-carbonitriles **1e** (0.58 g, 2 mmol) and

3(2*H*)-thiophenone **2** (0.20 g, 2 mmol) were stirred in DMF (10 mL) and KOH (0.22 g, 4 mmol) under nitrogen atmosphere for 24–30 h. The reaction mixture was poured into ice chilled water with stirring followed by neutralization with 10% HCl. Precipitate thus obtained was filtered and washed with excess of water. Crude product was purified on silica gel column using hexane/$CHCl_3$ (1:1) as eluent.

In case of a reaction of **1e** with ketone **2** under similar reaction conditions yielded aromatized product, 5-dimethylamino-7-naphthalen-2-yl-benzo[*b*]thiophene-4-carbonitrile (**4**) beside **3e**.

Other compounds of prototypes **6** and **8** were prepared similarly by the reaction of **1** and respective ketones **5** and **7** separately.

4.1.1. 5-Dimethylamino-7-naphthalen-1-yl-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile (3a). Yield 58%; mp 105–106 °C; MS (EI) *m*/*z* 330 (M^+, 100), 317 (16.1), 285 (14.8); IR (KBr) ν 2213 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.98 (s, 6H, $2NCH_3$), 3.32 (t, *J* = 7.4 Hz, 2H, CH_2), 3.56 (t, *J* = 7.4 Hz, 2H, CH_2), 6.77 (s, 1H, ArH), 7.42–7.62 (m, 5H, ArH), 7.88–7.92 (m, 2H, ArH). Anal. calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48. Found: C, 76.41; H, 5.70; N, 8.59.

4.1.2. 7-Naphthalen-1-yl-5-pyrrolidin-1-yl-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile (3b). Yield 56%; mp 172–173 °C; MS (EI) *m*/*z* 356 (M^+, 100), 262 (32.5), 246 (20.8), 239 (26.3), 210 (19.3), 182 (76.1), 168 (52.9); IR (KBr) ν 2199 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.95–2.08 (m, 4H, $2CH_2$, pyrrolidinyl), 3.30 (t, *J* = 7.4 Hz, 2H, CH_2), 3.52–3.60 (m, 6H, $2NCH_2$, CH_2, thienyl), 6.52 (s, 1H, ArH), 7.39–7.70 (m, 5H, ArH), 7.89–8.01 (m, 2H, ArH). Anal. calcd for $C_{23}H_{20}N_2S$: C, 77.49; H, 5.65; N, 7.86. Found: C, 77.31; H, 5.56; N, 7.90.

4.1.3. 7-Naphthalen-1-yl-5-piperidin-1-yl-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile (3c). Yield 54%; mp 140–141 °C; MS (EI) *m*/*z* 370 (M^+, 100), 314 (9.4), 201 (19.7), 166 (10.4); IR (KBr) ν 2217 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.52–1.60 (m, 2H, CH_2), 1.76–1.77 (m, 4H, $2CH_2$, piperidinyl), 3.11–3.12 (m, 4H, $2NCH_2$), 3.32 (t, *J* = 7.4 Hz, 2H, CH_2), 3.56 (t, *J* = 7.4 Hz, 2H, CH_2), 6.84 (s, 1H, ArH), 7.43–7.59 (m, 5H, ArH), 7.92–7.93 (m, 2H, ArH). Anal. calcd for $C_{24}H_{22}N_2S$: C, 77.80; H, 5.98; N, 7.56. Found: C, 77.86; H, 5.77; N, 7.60.

4.1.4. 5-(4-Methylpiperidin-1-yl)-7-naphthalen-1-yl-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile (3d). Yield 61%; mp 142–143 °C; MS (EI) *m*/*z* 384 (M^+, 100), 381 (17.6), 314 (31.7), 285 (26.5), 258 (20.6); IR (KBr) ν 2218 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, *J* = 4.9 Hz, 3H, CH_3), 1.48–1.55 (m, 3H, CH, CH_2, piperidinyl), 1.72–1.76 (m, 2H, CH_2, piperidinyl), 2.72–2.73 (m, 2H, NCH_2), 3.32 (t, *J* = 7.4 Hz, 2H, CH_2), 3.46–3.56 (m, 4H, CH_2, NCH_2), 6.83 (s, 1H, ArH), 7.39–7.64 (m, 5H, ArH), 7.90–7.92 (m, 2H, ArH). Anal. calcd for $C_{25}H_{24}N_2S$: C, 78.09; H, 6.29; N, 7.28. Found: C, 78.17; H, 6.35; N, 7.32.

4.1.5. 5-Dimethylamino-7-naphthalen-2-yl-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile (3e). Yield 60%; mp 110–111 °C; MS (FAB) *m*/*z* 331 ($M^+ + 1$); IR (KBr) ν 2210 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 3.01 (s, 6H, $2NCH_3$), 3.38 (t, *J* = 7.2 Hz, 2H, CH_2), 3.54 (t, *J* = 7.2 Hz, 2H, CH_2), 6.87 (s, 1H, ArH), 7.35–7.64 (m, 4H, ArH), 7.89–7.97 (m, 3H, ArH). Anal. calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48. Found: C, 76.44; H, 5.65; N, 8.54.

4.1.6. 5-dimethylamino-7-naphthalen-2-yl-benzo[*b*]thiophene-4-carbonitrile (4). Yield 32%; mp 128–129 °C; MS (FAB) *m*/*z* 329 ($M^+ + 1$); IR (KBr) ν 2190 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 3.20 (s, 6H, $2CH_3$), 7.06 (s, 1H, ArH), 7.54–7.65 (m, 4H, ArH), 7.75–7.80 (m,1H,ArH), 7.90–8.01 (m, 3H, ArH), 8.16 (s, 1H, ArH). Anal. calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 76.89; H, 4.97; N, 8.65.

4.1.7. 6-Dimethylamino-8-naphthalen-1-yl-isothiochroman-5-carbonitrile (6a). Yield 62%; mp 110–111 °C; MS (EI) *m*/*z* 344 (M^+, 100), 297 (29.4), 281 (31.0), 254 (33.8); IR (KBr) ν 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.93 (s, 6H, $2NCH_3$), 2.83–2.90 (m, 2H, CH_2), 3.16 (s, 2H, CH_2), 3.24 (t, *J* = 6.6 Hz, 2H, CH_2), 6.70 (s, 1H, ArH), 7.36–7.50 (m, 5H, ArH), 7.84 (m, 2H, ArH). Anal. calcd for $C_{22}H_{20}N_2S$: C, 76.71; H, 5.85; N, 8.13. Found: C, 76.60; H, 5.71; N, 8.19.

4.1.8. 8-Naphthalen-1-yl-6-pyrrolidin-1-yl-isothiochroman-5-carbonitrile (6b). Yield 55%; mp 140–141 °C; MS (EI) *m*/*z* 370 (M^+, 100), 262 (18.1), 201 (70.9), 166 (54.2); IR (KBr) ν 2206 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.94–2.01 (m, 4H, pyrrolidinyl), 2.85–2.90 (m, 2H, CH_2), 3.19 (s, 2H, CH_2), 3.26 (t, *J* = 6.6 Hz, 2H, CH_2), 3.59–3.60 (m, 4H, $2NCH_2$), 6.52 (s, 1H, ArH), 7.45–7.48 (m, 5H, ArH), 7.50–7.52 (m, 2H, ArH). Anal. calcd for $C_{24}H_{22}N_2S$: C, 77.80; H, 5.98; N, 7.56. Found: C, 77.71; H, 5.96; N, 7.58.

4.1.9. 8-Naphthalen-1-yl-6-piperidin-1-yl-isothiochroman-5-carbonitrile (6c). Yield 59%; mp 121–122 °C; MS (EI) *m*/*z* 384 (M^+, 100), 262 (10.0), 156 (26.2), 155 (55.0); IR (KBr) ν 2206 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.50–1.62 (m, 2H, CH_2, piperidinyl), 1.65–1.70 (m, 4H, $2CH_2$, piperidinyl), 2.81–2.88 (m, 2H, CH_2), 3.06–3.07 (m, 4H, $2NCH_2$), 3.19 (s, 2H, CH_2), 3.24 (t, *J* = 6.4 Hz, 2H, CH_2), 6.76 (s, 1H, ArH), 7.35–7.50 (m, 5H, ArH), 7.82–7.86 (m, 2H, ArH). Anal. calcd for $C_{25}H_{24}N_2S$: C, 78.09; H, 6.29; N, 7.28. Found: C, 78.20; H, 6.36; N, 7.40.

4.1.10. 6-(4-Methylpiperidin-1-yl)-8-naphthalen-1-yl-isothiochroman-5-carbonitrile (6d). Yield 54%; mp 112–13 °C MS (EI) *m*/*z* 398 (M^+, 100), 262 (28.6), 211 (70.4), 179 (46.2), 151 (57.5); IR (KBr) ν 2217 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, *J* = 4.9 Hz, 3H, CH_3), 1.49–1.55 (m, 3H, CH, CH_2, piperidinyl), 1.73–1.75 (m, 2H, CH_2, piperidinyl), 2.70–2.80 (m, 2H, NCH_2), 2.89–2.97 (m, 2H, CH_2), 3.24 (s, 2H, CH_2), 3.31 (t, *J* = 6.6 Hz, 2H, CH_2), 3.50–3.61 (m, 2H, NCH_2), 6.84 (s, 1H, ArH), 7.42–7.56 (m, 5H, ArH), 7.91–7.92 (m, 2H, ArH). Anal. calcd for $C_{26}H_{26}N_2S$: C, 78.35; H, 6.58; N, 7.03. Found: C, 78.50; H, 6.40; N, 7.18.

4.1.11. 3-Pyrrolidin-1-yl-5,6,7,8-tetrahydro-[1,1′]bina-]binaphthalenyl-4-carbonitrile (6e). Yield 62%; mp 132–133 °C; MS (EI) *m/z* 352 (M^+, 100), 323 (14.9), 254 (20.3), 149 (31.8); IR (KBr) ν 2204 cm^{-1}(CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.58–1.59 (m, 2H, CH_2), 1.77–1.82 (m, 2H, CH_2), 1.92–2.02 (m, 4H, $2CH_2$, pyrrolidinyl), 2.07–2.27 (m, 2H, CH_2), 2.99 (t, $J=6.4$ Hz, 2H, CH_2), 3.56–3.57 (m, 4H, $2NCH_2$), 6.47 (s, 1H, ArH), 7.25–7.54 (m, 5H, ArH), 7.84–7.91 (m, 2H, ArH). Anal. calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 85.20; H, 6.72; N, 7.93.

4.1.12. 3-Piperidin-1-yl-5,6,7,8-tetrahydro[1,1′]binaphthalenyl-4-carbonitrile (6f). Yield 63%; mp 108–109 °C; MS (EI) *m/z* 366 (M^+, 100), 262 (15.4), 201 (55.1), 166 (38.6); IR (KBr) ν 2212 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.56–1.64 (m, 6H, $3CH_2$, piperidinyl), 1.71–1.86 (m, 4H, $2CH_2$, piperidinyl), 2.14–2.26 (m, 2H, CH_2), 3.03–3.11 (m, 6H, CH_2, $2NCH_2$), 6.75 (s, 1H, ArH), 7.25–7.55 (m, 5H, ArH), 7.85–7.92 (m, 2H, ArH). Anal. calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.32; H, 7.21; N, 7.58.

4.1.13. 4-Naphthalen-1-yl-2-pyrrolidin-1-yl-6,7,8,9-tetrahydro 5*H*-benzocycloheptene-1-carbonitrile (6g). Yield 62%; mp 170–171 °C; MS (EI) *m/z* 366 (M^+, 100), 262 (14.4), 166 (10.1), 155 (14.4); IR (KBr) ν 2204 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–1.56 (m, 2H, CH_2), 1.70–1.75 (m, 4H, CH_2), 1.92–1.98 (m, 4H, $2CH_2$, pyrrolidinyl), 2.34 (t, $J=5.8$ Hz, 2H, CH_2), 3.15–3.17 (m, 2H, CH_2), 3.53–3.54 (m, 4H, $2NCH_2$), 6.43 (s, 1H, ArH), 7.38–7.54 (m, 5H, ArH), 7.84–7.92 (m, 2H, ArH). Anal. calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.30; H, 7.21; N, 7.53.

4.1.14. 4-Naphthalen-1-yl-2-piperidin-1-yl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-1-carbonitrile (6h). Yield 68%; mp 168–169 °C; MS (EI) *m/z* 380 (M^+, 100), 262 (7.3), 155 (10.8), 141 (16.2); IR (KBr) ν 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–1.65 (m, 8H, $4CH_2$, piperidinyl), 1.71–1.76 (m, 4H, $2CH_2$, piperidinyl), 2.38 (t, $J=5.4$ Hz, 2H, CH_2), 3.07–3.08 (m, 4H, $2NCH_2$), 3.16–3.17 (m, 2H, CH_2), 6.72 (s, 1H, ArH), 7.39–7.51 (m, 5H, ArH), 7.85–7.89 (m, 2H, ArH). Anal. calcd for $C_{27}H_{28}N_2$: C, 85.22; H, 7.42; N, 7.36. Found: C, 85.31; H, 7.52; N, 7.43.

4.1.15. 4-Naphthalen-1-yl-2-pyrrolidin-1-yl-5,6,7,8,9,10-hexahydrobenzocyclooctene-1-carbonitrile (6i). Yield 59%; mp 180–181 °C; MS (EI) *m/z* 380 (M^+, 100), 243 (9.6), 205 (15.8); IR (KBr) ν 2210 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–1.35 (m, 4H, $2CH_2$), 1.58–1.60 (m, 2H, CH_2), 1.91–1.98 (m, 4H, $2CH_2$, pyrrolidinyl), 2.24–2.34 (m, 2H, CH_2), 2.44–2.49 (m, 2H, CH_2), 3.03–3.15 (m, 2H, CH_2), 3.55–3.56 (m, 4H, $2NCH_2$), 6.43 (s, 1H, ArH), 7.38–7.53 (m, 5H, ArH), 7.84–7.90 (m, 2H, ArH). Anal. calcd for $C_{27}H_{28}N_2$: C, 85.22; H, 7.42; N, 7.36. Found: C, 85.35; H, 7.31; N, 7.45.

4.1.16. 4-Naphthalen-1-yl-2-piperidin-1-yl-5,6,7,8,9,10-hexahydrobenzocyclooctene-1-carbonitrile (6j). Yield 56%; mp 210 °C; MS (EI) *m/z* 394 (M^+, 100), 366 (6.4), 254 (8,4), 141 (9.81); IR (KBr) ν 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.30–1.38 (m, 4H, $2CH_2$), 1.57–159 (m, 4H, $2CH_2$), 1.74–1.77 (m, 4H, $2CH_2$, piperidinyl), 2.25–2.32 (m, 2H, CH_2), 2.48–2.49 (m, 2H, CH_2), 3.06–3.08 (m, 6H, CH_2, $2NCH_2$), 6.73 (s, 1H, ArH), 7.36–7.54 (m, 5H, ArH), 7.82–7.88 (m, 2H, ArH). Anal. calcd for $C_{28}H_{30}N_2$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.33; H, 7.68; N, 7.12.

4.1.17. 6-Dimethyl-2-ethyl-8-naphthalen-2-yl-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrle (6k). Yield 50%; colorless oil; MS (FAB): 356 ($M^+ + 1$); IR (Neat) 2211 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, $J=7.2$ Hz, 3H, CH_3), 2.44 (q, $J=7.2$ Hz, 2H, CH_2), 2.76 (t, $J=6.0$ Hz, 2H, CH_2), 3.0 (s, 6H, $2NCH_3$), 3.14 (t, $J=6.0$ Hz, 2H, CH_2), 3.37 (s, 2H, CH_2), 6.71 (s, 1H, ArH), 7.35 (d, $J=1.9$ Hz, 1H, ArH), 7.40 (d, $J=1.9$ Hz, 1H, ArH), 7.51–7.55 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.84–7.91 (m, 2H, ArH). Anal. calcd for $C_{24}H_{25}N_3$: C, 81.09; H, 7.09; N, 11.82. Found: C, 81.18; H, 7.20; N, 11.95.

4.1.18. 2-Ethyl-8-naphthalen-2-yl-6-pyrrolidin-1-yl-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (6l). Yield 48%; colorless oil; MS (FAB): 382 ($M^+ + 1$); IR (Neat) 2204 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (t, $J=7.2$ Hz, 3H, CH_3), 1.97–2.00 (m, 4H, $2CH_2$, pyrrolidinyl), 2.44 (q, $J=7.2$ Hz, 2H, CH_2), 2.75 (t, $J=6.0$ Hz, 2H, CH_2), 3.10 (t, $J=6.0$ Hz, 2H, CH_2), 3.32 (s, 2H, CH_2), 3.59–3.63 (m, 4H, $2NCH_2$), 6.46 (s, 1H, ArH), 7.30 (d, $J=1.6$ Hz, 1H, ArH), 7.40 (d, $J=1.6$ Hz, 1H, ArH), 7.49–7.54 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.85–7.89 (m, 2H, ArH). Anal. calcd for $C_{26}H_{27}N_3$: C, 81.85; H, 7.13; N, 11.01. Found: C, 82.01; H, 7.15; N, 11.11.

4.1.19. 2-Ethyl-8-naphthalen-2-yl-6-piperidin-1-yl-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (6m). Yield 54%; colorless oil; MS (FAB) 396 ($M^+ + 1$); IR (Neat) 2216 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.0 (t, $J=7.2$ Hz, 3H, CH_3), 1.57–1.72 (m, 6H, $3CH_2$, piperidinyl), 2.48 (q, $J=7.2$ Hz, 2H, CH_2), 2.78 (t, $J=6.0$ Hz, 2H, CH_2), 3.11–3.13 (m, 6H, CH_2, $2NCH_2$), 3.40 (s, 2H, CH_2), 6.78 (s, 1H, ArH), 7.35 (d, $J=1.6$ Hz, 1H, ArH), 7.40 (d, $J=1.6$ Hz, 1H, ArH), 7.51–7.55 (m, 2H, ArH), 7.70 (s, 1H, ArH), 7.86–7.90 (m, 2H, ArH). Anal. calcd for $C_{27}H_{29}N_3$: C, 81.99; H, 7.39; N, 10.62. Found: C, 81.88; H, 7.54; N, 10.75.

4.1.20. 2-Ethyl-6-(4-methylpiperidin-1-yl)-8-naphthalen-1-yl,1,2,3,4-tetrahydroisoquinoline (6n). Yield 55%; colorless oil; MS (FAB) 410 ($M^+ + 1$); IR (Neat) 2204 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, $J=7.4$ Hz, 3H, CH_3), 0.99 (t, $J=4.9$ Hz, 3H, CH_3), 1.42–1.47 (m, 3H, CH, CH_2, piperidinyl), 1.69–1.70 (m, 2H, CH_2, piperidinyl), 2.34 (q, $J=7.2$ Hz, 2H, CH_2), 2.70–2.76 (m, 2H, NCH_2), 3.05 (s, 2H, CH_2), 3.14–3.22 (m, 4H, $2CH_2$), 3.47–3.59 (m, 2H, NCH_2), 6.74 (s, 1H, ArH), 7.42–7.55 (m, 5H, ArH), 7.87–7.92 (m, 2H, ArH). Anal. calcd for $C_{28}H_{31}N_3$: C, 82.11; H, 7.63; N, 10.26. Found: C, 82.16; H, 7.74; N, 10.39.

4.1.21. 3-Dimethylamino-1-naphthalen-1-yl-10*H*-9-thiaphenanthrene-4-carbonitrile (8a). Yield 63%; mp 220–221 °C; MS (EI) *m/z* 392 (M^+, 100), 263 (61.2), 220

(23.5), 186 (36.0); IR (KBr) ν 2202 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 3.07 (s, 6H, $2NCH_3$), 3.27 (s, 2H, CH_2), 6.93 (s, 1H, ArH), 7.32–7.57 (m, 8H, ArH), 7.93–7.95 (m, 2H, ArH), 8.16–8.20 (m, 1H, ArH). Anal. calcd for $C_{26}H_{20}N_2S$: C, 79.56; H, 5.14; N, 7.14. Found: C, 79.43; H, 5.23; N, 7.12.

4.1.22. 3-Dimethylamino-1-naphthalen-2-yl-10*H*-9-thia-phenanthrene-4-carbonitrile (8b). Yield 60%; mp 211–212 °C; MS (EI) *m/z* 392 (M^+, 100), 376 (7.1), 348 (14.5), 262 (11.0); IR (KBr) ν 2204 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 3.09 (s, 6H, $2NCH_3$), 3.64 (s, 2H, CH_2), 6.98 (s, 1H, ArH), 7.33-7.58 (m, 7H, ArH), 7.81–7.96 (m, 3H, ArH), 8.12–8.20 (m, 1H, ArH). Anal. calcd for $C_{26}H_{20}N_2S$: C, 79.56; H, 5.14; N, 7.14. Found: C, 79.45; H, 5.16; N, 7.25.

4.1.23. 1-Naphthalen-1-yl-3-pyrrolidin-1-yl-10*H*-9-thia-phenanthrene-4-carbonitrile (8c). Yield 55%; mp 122–123 °C; MS (EI) *m/z* 418 (M^+, 100), 390 (11.0), 347 (12.8), 289 (49.7), 155 (18.60; IR (KBr) ν 2200 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.98–2.04 (m, 4H, $2CH_2$, pyrrolidinyl), 3.24 (s, 2H, CH_2), 3.56–3.61 (m, 4H, $2NCH_2$), 6.72 (s, 1H, ArH), 7.28–7.59 (m, 8H, ArH), 7.93–7.95 (m, 2H, ArH), 8.01–8.21 (m, 1H, ArH). Anal. calcd for $C_{28}H_{22}N_2S$: C, 80.35; H, 5.30; N, 6.69. Found: C, 80.33; H, 5.42; N, 6.56.

4.1.24. 1-Naphthalen-1-yl-3-piperidin-1-yl-10*H*-9-thia-phenanthrene-4-carbonitrile (8d). Yield 57%; mp 110–111 °C; MS (EI) *m/z* 432 (M^+, 100), 375 (4.0), 348 (4.7), 262 (3.7), 164 (22.0), 155 (10.1); IR (KBr) ν 2213 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–1.65 (m, 2H, CH_2, piperidinyl), 1.76–1.81 (m, 4H, $2CH_2$, piperidinyl), 3.21–3.22 (m, 4H, $2NCH_2$), 3.29 (s, 2H, CH_2), 6.97 (s, 1H, ArH), 7.30–7.60 (m, 8H, ArH), 7.96–8.22 (m, 2H, ArH), 8.25–8.26 (m, 1H, ArH). Anal. calcd for $C_{29}H_{24}N_2S$: C, 80.52; H, 5.59; N, 6.48. Found: C, 80.38; H, 5.48; N, 6.40.

4.1.25. 3-(4-Methylpiperidin-1-yl)-1-naphthalen-1-yl-10*H*-9-thia-phenanthrene-4-carbonitrile (8e). Yield 54%; mp 220–221 °C; MS (EI) *m/z* 446 (M^+, 100), 375 (6.2), 346 (7.8), 314 (10.1), 262 (35.8); IR (KBr) ν 2212 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.0 (d, $J = 5.2$ Hz, 3H, CH_3), 1.48–1.54 (m, 3H, CH, CH_2, piperidinyl), 1.70–1.72 (m, 2H, CH_2, piperidinyl), 2.78–2.82 (m, 2H, NCH_2), 3.28 (s, 2H, CH_2), 3.56–3.60 (m, 2H, NCH_2), 6.97 (s, 1H, ArH), 7.41–7.56 (m, 8H, ArH), 7.92–7.96 (m, 2H, ArH), 8.21–8.23 (m, 1H, ArH). Anal. calcd for $C_{30}H_{26}N_2S$: C, 80.68; H, 5.87; N, 6.27. Found: C, 80.60; H, 5.81; N, 6.23.

4.1.26. 3-Dimethylamino-1-naphthalen-1-yl-9,10-dihydro-phenanthrene-4-carbonitrile (8f). Yield 59%; mp 152–153 °C; MS (EI) *m/z* 374 (M^+, 100), 358 (12.3), 328 (10.5), 314 (8.6); IR (KBr) ν 2203 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.28–2.31 (m, 2H, CH_2), 2.56–2.59 (m, 2H, CH_2), 3.04 (s, 6H, $2NCH_3$), 6.89 (s, 1H, ArH), 7.25–8.31 (m, 8H, ArH), 7.90–7.95 (m, 2H, ArH), 8.25–8.31 (m, 1H, ArH). Anal. calcd for $C_{27}H_{22}N_2$: C, 86.60; H, 5.92; N, 7.48. Found: C, 86.51; H, 5.53; N, 7.33.

4.1.27. 1-Naphthalen-2-yl-3-pyrrolidin-1-yl-9,10-dihydro-phenanthrene-4-carbonitrile (8g). Yield 52%; mp 128–129 °C; MS (EI) *m/z* 400 (M^+,100), 370 (19.5), 305 (8.0), 287 (10.7); IR (KBr) ν 2203 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.99–2.05 (m, 4H, $2CH_2$, pyrrolidinyl), 2.62–2.63 (m, 4H, $2CH_2$), 3.61–3.67 (m, 4H, $2NCH_2$), 6.73 (s, 1H, ArH), 7.30–7.46 (m, 6H, ArH), 7.80–7.92 (m, 4H, ArH), 8.19–8.23 (m, 1H, ArH). Anal. calcd for $C_{29}H_{24}N_2$: C, 86.97; H, 6.04; N, 6.99. Found: C, 80.87; H, 5.88; N, 6.88.

4.1.28. 1-Naphthalen-1-yl-3-piperidin-1-yl-9,10-dihydro-phenanthrene-4-carbonitrile (8h). Yield 61%; mp 170–171 °C; MS (EI) *m/z* 414 (M^+, 100), 387 (5.3), 359 (6.4), 330 (7.6), 300 (7.6), 171 (15.8); IR (KBr) ν 2193 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.54–1.66 (m, 2H, CH_2, piperidinyl), 1.78–1.89 (m, 4H, $2CH_2$, piperidinyl), 2.66–2.68 (m, 4H, $2CH_2$), 3.19–3.25 (m, 4H, $2NCH_2$) 6.98 (s, 1H, ArH), 7.27–7.56 (m, 6H, ArH), 7.78–7.79 (m, 1H, ArH), 7.89–7.93 (m, 3H, ArH), 8.27–8.30 (m, 1H, ArH). Anal. calcd for $C_{30}H_{26}N_2$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.86; H, 6.30; N, 6.64.

4.1.29. 3-(4-Methylpiperidin-1-yl)-1-naphthalen-2-yl-9,10-dihydrophenanthrene-4-carbonitrile (8i). Yield 58%; mp 98–99 °C; MS (EI) *m/z* 428 (M^+, 100), 348 (55.8), 211 (18.5), 182 (25.1); IR (KBr) ν 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (d, $J = 5.2$ Hz, 3H, CH_3), 1.60–1.62 (m, 3H, CH, CH_2, piperidinyl), 1.77–1.82 (m, 2H, CH_2, piperidinyl), 2.62–2.66 (m, 4H, CH_2), 2.76–2.90 (m, 2H, NCH_2), 3.61–3.67 (m, 2H, NCH_2), 7.00 (s, 1H, ArH), 7.31–7.56 (m, 6H, ArH), 7.77–7.89 (s, 1H, ArH), 7.89–7.93 (m, 3H, ArH), 8.26–8.31 (m, 1H, ArH). Anal. calcd for $C_{31}H_{28}N_2$: C, 86.88; H, 6.59; N, 6.54. Found: C, 86.76; H, 6.44; N, 6.50.

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