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An efficient non-catalytic, regioselective approach to the synthesis of angularly fused polycyclic systems

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ABSTRACT

A novel approach to the synthesis of partially reduced different ring sizes of PAH analogs with *sec*.amino and nitrile functionalities is delineated through base-induced ring transformation of 4-*sec*.amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles by a carbanion, generated in situ from cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone separately in good yields. An increase in the size of cycloalkanone ring beyond cyclooctanone restricts the ring transformation under analogous reaction conditions possibly due to bulky conformation of higher homologs. The synthetic method provides an efficient general route for the construction of angularly fused partially reduced polycyclic aromatic hydrocarbons: 5-*sec*.amino-2,3,6,7-tetrahydro-1*H*-cyclopenta[*c*]phenanthrene-4-carbonitriles, 6-*sec*.amino-2,3,4,7,8-pentahydro-1*H*-benzo[*c*]phenanthrene-5-carbonitriles, 7-*sec*.amino-2,3,4,5,8,9-hexahydro-1*H*-cyclohepta[*c*]phenanthrene-6-carbonitriles, and 8-*sec*.amino-2,3,4,5,6,9,10-heptahydro-1*H*-cycloocta[*c*]phenanthrene-7-carbonitriles.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitously present as environmental pollutants and most of them are carcinogenic in animal models. Human populations exposed[1,2] to these contaminants, produced by incomplete combustion of fossil fuels, coal, wood burning, and tobacco smoke are real threat and instrumental in causing cancer. It has been observed that PAHs are activated by cytochrome P450 to diol epoxides that covalently bind cellular DNA through C–N linkage and induce tumorigenesis. The steric constraints in the bay region of PAHs significantly enhance the carcinogenicity[3,4] and attenuate[5–8] further with the formation of fjord region diol epoxides. It has been observed that the bay region diol epoxides preferentially bind with amino function of deoxyguanosine residue while fjord region diol epoxides preferably react with amino group of deoxyadenosine of cellular DNA[9,10] to form carcinogen-deoxyadenosine adducts, instrumental in tumor initiation.[11,12] Recent studies have shown that tumorigenic effect of PAHs is influenced by the preferred conformation of the adduct in DNA template. Partial reduction of PAHs brings conformational change in the adduct and thereby reduces the carcinogenicity of the molecule.

Among various carcinogens, benzo[*c*]phenanthrene (BcP) **I** is relatively weak carcinogen[13] present in the environment.[14] The two metabolites of BcP 3,4-dihydrodiol **I** and corresponding diol epoxide **II** are highly carcinogenic[15,16] (Fig. 1). Similar finding has also been reported with benzochrysenes,[17] and dibenzo[*a*,*f*]anthracenes[18] (Fig. 1).

The extensive literature survey revealed that there are limited regioselective routes for the synthesis of different ring sizes of PAH analogs.[16–19] This observation led to the synthesis of partially reduced cycloalkyl[*c*]phenanthrenes **III** with distorted conformation to assess the impact of partial reduction and size of fused alicyclic ring on the degree of distortion and carcinogenicity of the molecule. Our strategy to synthesize planarity distorted PAHs is

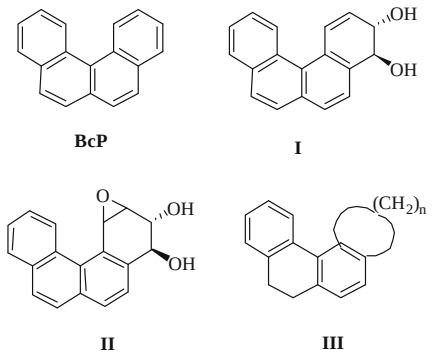

Figure 1.

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either through (i) partial reduction or (ii) increasing the size of the fused alicyclic ring or (iii) through substitution in the overcrowding region of the molecule, or (iv) combination of all.

This manuscript describes the synthesis of diverse partially reduced different ring sizes of PAH analogs such as 5-*sec*.amino-2,3,6,7-tetrahydro-1*H*-cyclopenta[*c*]phenanthrene-4-carbonitriles **7**, 6-*sec*.amino-1,2,3,4,7,8-hexahydrobenzo[*c*]phenanthrene-5-carbonitriles **9**, 7-*sec*.amino-2,3,4,5,8,9-hexahydro-1*H*-cyclohepta[*c*]-phenanthrene-6-carbonitriles **11,** and 8-*sec*.amino-2,3,4,5,6,9,10-heptahydro-1*H*-cycloocta[*c*]phenanthrene-7-carbonitriles **13** through base-induced ring transformation of 4-*sec*.amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles by a carbanion, generated in situ from cycloalkanones.

An alternative route to the synthesis of partially reduced cycloalkyl[*c*]phenanthrenes, pendant with secondary amine and nitrile functionalities, necessitated the construction of 2-oxo-4-methylsulfanyl-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitrile **3** as a key step and was obtained from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate **1** with 1-tetralone **2** in the presence of powdered KOH using DMSO as a solvent at room temperature. Amination of **3** with secondary amine in refluxing ethanol gave 4-*sec*.amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** in good yields[20] (Scheme 1) and was used directly as a precursor for the ring transformation study.

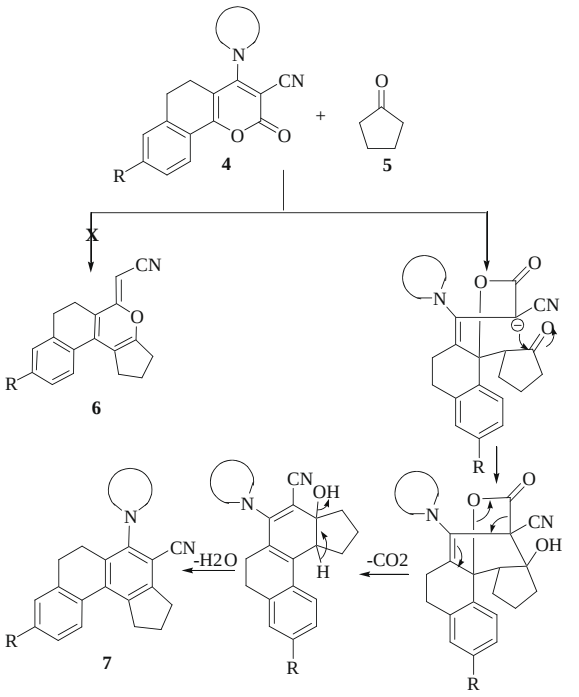
As is evident from the topography of 4-*sec*.amino-2-oxo-5,6-dihydrobenzo[*h*]chromene-3-carbonitriles **4**, that they possess three electrophilic centers C-2, C-4, and C-10b in which the latter is highly susceptible to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing CN substituent at position 3 of the chromene ring. The nucleophiles used for the ring transformation reactions were carbanions, generated in situ from cycloalkanones in the presence of base in DMF. The initial step in the formation of 5-*sec*.amino-2,3,6,7-tetrahydro-1*H*-cyclopenta[*c*]phenanthrene-4-carbonitriles **7** is attack of the carbanion at C-10b of the chromene **4** with formation of Michael adduct followed by ring closure involving carbonyl group of cyclopentanone and C-3 of the chromene with loss of carbon dioxide and water as depicted in Scheme 2.

Under analogous reaction conditions a mixture of **4** with cyclohexanone **8** in the presence of powdered KOH gave a crude product **9** which was purified through neutral alumina column as 6-*sec*.amino-1,2,3,4,7,8-hexahydro benzo[*c*]phenanthrene-5-carbonitriles in very good yields (Scheme 3). In this reaction also carbanion from cyclohexanone initiated the ring transformation following similar course of reaction.

Analogously, a reaction of 2-oxobenzo[*h*]chromene **4** with cycloheptanone **10** produced 7-*sec*.amino-2,3,4,5,8,9-hexahydro-1*H*-cyclohepta[*c*]phenanthrene-6-carbonitriles **11** (Scheme 4).

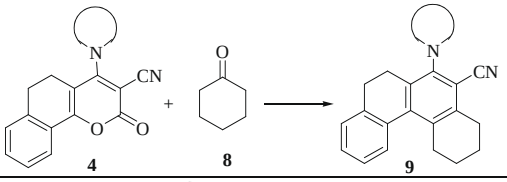
Under similar reaction conditions the ring transformation of **4** with cyclooctanone in the presence of powdered KOH in DMF produced 8-*sec*.amino-2,3,4,5,6,9,10-heptahydro-1*H*-cycloocta[*c*]phenanthrene-7-carbonitriles **13** in moderate yields (Scheme 5).

The ring transformation of **4** by higher homologs of cycloalkanones beyond eight membered did not occur and lactone was always



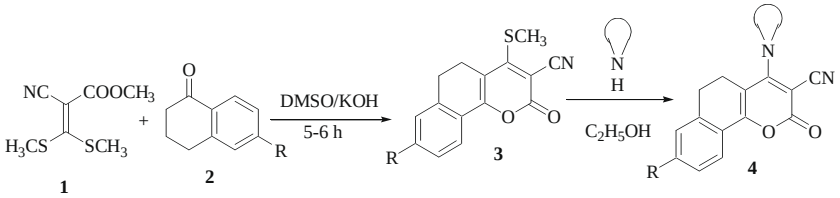
7	N—	R	Yields (%)
a	piperidin-1-yl	H	86
b	4-methylpiperidin-1-yl	H	78
c	tetrahydroisoquinolin-2-yl	H	89
d	4-benzylpiperazin-1-yl	H	91
e	4-[bis(4-fluorophenyl) methyl]piperazin-1-yl	H	73
f	piperidin-1-yl	OCH_3	78

Scheme 2. Synthesis of 5-*sec*.amino-2,3,6,7-tetrahydro-1*H*-cyclopenta-[*c*]phenanthrene-4-carbonitriles **7**.

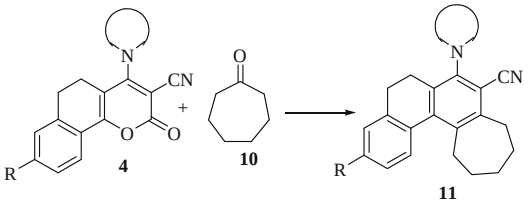


9	N—	Yields (%)
a	4-morpholin-1-yl	88
b	4-(pyridine-2-yl)-piperazin-1-yl	73

Scheme 3. Synthesis of 6-*sec*.amino-1,2,3,4,7,8-hexahydrobenzo[*c*]-phenanthrene-5-carbonitriles **9**.

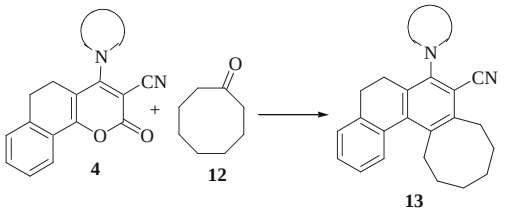


Scheme 1. Two-step synthesis of 2-oxobenzo[*h*]chromene **4**.



11	N—	R	Yields (%)
a	piperidin-1-yl	H	80
b	4-methylpiperidin-1-yl	H	81
c	4-benzylpiperidin-1-yl	H	75
d	4-morpholin-1-yl	H	71
e	tetrahydroisoquinolin-2-yl	H	73
f	piperidin-1-yl	OCH_3	70

Scheme 4. Synthesis of 7-*sec*.amino-2,3,4,5,8,9-hexahydro-1*H*-cyclohepta[*c*]phenanthrene-6-carbonitriles **11**.



13	N—	Yields (%)
a	piperidin-1-yl	70
b	4-methylpiperidin-1-yl	68
c	4-benzylpiperidin-1-yl	71
d	4-morpholin-1-yl	73
e	tetrahydroisoquinolin-2-yl	75

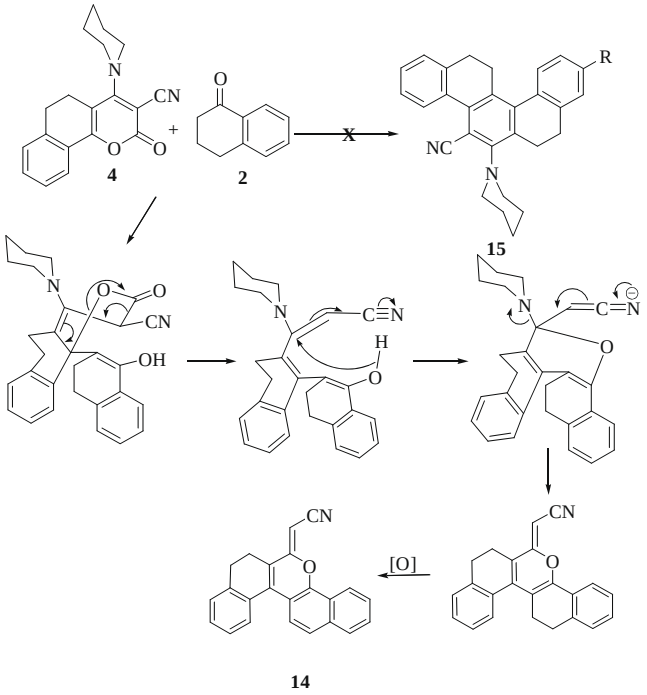
Scheme 5. Synthesis of 8-*sec*.amino-2,3,4,5,6,9,10-heptahydro-1*H*-cycloocta[*c*]phenanthrene-7-carbonitriles **13**.

recovered. The attack at C-10b by bigger size of the carbanion formed from higher homologs of cycloalkanone is hindered.

It is quite interesting that the use of fused cyclic ketones such as 1-tetralone, for the ring transformation of **4** did not follow the same course of reaction under analogous reaction conditions and the product isolated was characterized as (7,8-dihydro-5-oxabenzo[*c*]chrysene-6-ylidene)acetonitrile **14**. In this reaction also carbanion generated in situ from 1-tetralone attacks at C-10b followed by enolate addition to enamine with loss of secondary amine and subsequent oxidation, yields **14**[21] in lieu of usual ring transformed product **15** as depicted in Scheme 6. From this reaction it was concluded that the presence of fused benzene ring in 1-tetralone facilitates the enolization that ultimately participates in the ring closure to yield **14**.

All the synthesized compounds were characterized by spectroscopic analysis.[22]

This is the first non-catalytic approach for the concise synthesis of partially reduced angularly fused polycyclic aromatic hydrocarbons through base-induced ring transformation of 4-*sec*.amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles by a carbanion generated in situ from cycloalkanone in DMF at room temperature. This methodology is very efficient, economical, and provides an easy access for the construction of different ring sizes of PAHs.



Scheme 6. Synthesis of oxachrysene **14** in lieu of usual product benzochrysene **15**.

Acknowledgments

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References and notes

1. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons. Chemistry and Carcinigenesis*; Cambridge University Press: Cambridge, England, 1991. Chapter 3.
2. Harvey, R. G. In *The Handbook of environmental Chemistry: Volume PAHs and related compounds*; Hutzinger, O., Nelson, A., Eds.; Springer: Berlin, Heidelberg, 1977; pp 1–54. Chapter 1.
3. Hetch, S. S.; El-Bayoumy, K.; Rivenson, A.; Amin, S. *Cancer Res.* **1994**, *54*, 21.
4. Hecht, S. S.; Amin, S.; Hulk, K.; Melikian, A. A.; Harvey, R. G. *Cancer Res.* **1987**, *47*, 5310.
5. Levin, W.; Wood, A. W.; Chang, R. L.; Ittah, Y.; Croisy-Delcey, M.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 3910.
6. Amin, S.; Krzeminski, J.; Rivenson, A.; Kurtzke, C.; Hecht, S. S.; El-Bayoumy, K. *Carcinogenesis* **1995**, *16*, 1971.
7. Amin, S.; Desai, D.; Dai, W.; Harvey, R. G.; Hecht, S. S. *Carcinogenesis* **1995**, *16*, 2813.
8. Kumar, S. *J. Org. Chem.* **1997**, *62*, 8535.
9. Dipple, D. M. *Nature* **1987**, *327*, 535.
10. Agarwal, S. K.; Sayer, J. M.; Yeh, H. J.; Pannel, L. K.; Hilton, B. D.; Yagi, H.; erina, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2497.
11. Dipple, A.; Pigott, M. A.; Moschel, R. C.; Costantino, A. *Cancer Res.* **1983**, *43*, 4132.
12. Bigger, C. A. H.; Sawicki, J. T.; Blake, D. M.; Raymond, L. G.; Dipple, A. *Cancer Res.* **1983**, *43*, 5647.
13. Stevenson, J. L.; von Haam, E. *Am. Ind. Hyg. Assoc. J.* **1965**, *26*, 475.
14. Lunde, G.; Bjorscth, A. *Nature* **1977**, *268*, 518.
15. (a) Wood, A. W.; Chang, R. L.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Croisy-Delcey, Y.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 2876; (b) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218.
16. (a) Dipple, A.; Agarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M. *Nature* **1987**, *327*, 535; (b) Ittah, Y.; Thakker, D. R.; Levin, W.; Croisy-Delcey, M.; Ryan, D. E.; Thomas, P. E.; Conney, A. H.; Jerina, D. M. *Chem. Biol. Interact.* **1983**, *45*, 15; (c) Agarwal, S. K.; Sayer, J. M.; Yeh, H. J. C.; Pannell, L. K.; Hilton, B. D.; Pigott, M. A.; Dipple, A.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2497; (d) Pataki, J.; Harvey, R. G. *J. Org. Chem.* **1982**, *47*, 20; (e) Bigger, C. A.; St. John, J.; Yagi, H.; Jerina, D. M.; Dipple, A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 368; (f) Lakshman, M. K.; Kole, P. I.; Chaturnedi, S.; Saugier, J. H.; Yeh, H. J. C.; Glusker, J. P.; Carrell, H. L.; Katz, A. K.; Carol, E. A.; Dashwood, W.-M.; Kenniston, G.; Baird, W. M. *J. Am. Chem. Soc.* **2000**, *122*, 12629.

17. (a) Zhang, F.-J.; Cortez, C.; Harvey, R. G. *J. Org. Chem.* **2000**, *65*, 3952; (b) Sharma, A. K.; Kumar, S.; Amin, S. *J. Org. Chem.* **2004**, *69*, 3979; (c) Butch, E. R.; Yagi, H.; Jerina, D. M. *Polycyclic Aromat. Compd.* **1994**, *6*, 63.
18. (a) Chowdhary, S.; Zhao, B.; Snieckus, V. *Polycyclic Aromat. Compd.* **1994**, *5*, 27; (b) Harvey, R. G.; Dai, W.; Zhang, J.-T.; Cortez, C. *J. Org. Chem.* **1998**, *63*, 8118; (c) Agarwal, S. K.; Boyd, D. R.; McGuckin, M. R.; Jennings, W. B.; Howarth, O. W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1972.
19. Cheung, J.; Field, L. D.; Regalia, F.; Stemhell, S. *Aust. J. Chem.* **1995**, *48*, 1707.
20. Pratap, R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 2755.
21. Pratap, R.; Kumar, R.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 3311.
22. *General procedure for the synthesis of cycloalkyl[c]phenanthrene* (**6**): An equimolar mixture of 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol), cycloalkanone (0.6 mmol), and KOH (0.7 mmol) in DMF (4 mL) was stirred for 2–3 h. Completion of reaction was monitored by TLC. Thereafter, reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered, washed with water, dried, and purified by neutral alumina column using 3% ethyl acetate in hexane as eluent. (**7b**) White powder; yield: 78%; mp: 140–142 °C; IR (KBr): 2926, 2856, 2372, 2221, 1453, 1272, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J = 6.67 Hz, 3H, CH_3), 1.33–1.44 (m, 2H, CH_2), 1.49–1.59 (m, 1H, CH), 1.69–1.73 (m, 2H, CH_2), 2.05–2.14 (m, 2H, CH_2), 2.69–2.73 (m, 2H, CH_2), 2.80–2.83 (m, 2H, CH_2), 3.07 (t, J = 7.35 Hz, 2H, CH_2), 3.19 (t, J = 7.14 Hz, 2H, CH_2), 3.30–3.33 (m, 2H, CH_2), 7.25–7.32 (m, 3H, ArH), 7.61–7.64 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 24.7, 28.2, 29.4, 31.8, 34.1, 50.5, 117.3, 124.9, 125.7, 126.3, 126.7, 133.2, 133.4, 135.2, 135.5, 138.2, 148.1, 150.1; MS m/z 345 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{24}H_{26}N_2$ 342.20960 (M^+) found for m/z 342.20942. (**9a**). White powder; yield: 88%; mp: 186–188 °C; IR (KBr): 2364, 2207, 1626, 1567, 1460, 1220, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.64–1.70 (m, 2H, CH_2), 1.86–1.94 (m, 2H, CH_2), 2.65–2.69 (m, 2H, CH_2), 2.74–2.78 (m, 2H, CH_2), 2.95 (t, J = 5.98 Hz, 2H, CH_2), 3.02 (t, J = 6.81 Hz, 2H, CH_2), 3.27 (br s, 4H, CH_2), 3.85 (t, J = 4.38 Hz, 4H, CH_2), 7.23–7.32 (m, 3H, ArH), 7.54–7.60 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.04, 21.91, 24.05, 27.35, 28.23, 29.49, 49.79, 66.51, 107.56, 116.72, 124.40, 126.04, 126.04, 126.64, 127.49, 131.12, 132.39, 134.06, 139.02, 139.33, 139.52, 148.18; MS m/z 345 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{23}H_{24}N_2O$ 344.18886 (M^+) found for m/z 344.18862. (**11d**). White powder; yield: 71%; mp: 186–188 °C; IR (KBr): 2935, 2213, 1490, 1404, 1200, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.79–1.81 (m, 4H, CH_2), 1.90–1.92 (m, 2H, CH_2), 2.68–2.73 (m, 4H, CH_2), 3.0–3.04 (m, 2H, CH_2), 3.13–3.17 (m, 4H, CH_2), 3.21–3.24 (m, 2H, CH_2), 3.86 (br s, 4H, CH_2), 7.27–7.32 (m, 3H, ArH), 7.36–7.39 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 26.0, 26.8, 28.3, 30.4, 30.5, 32.4, 49.7, 66.6, 107.8, 117.8, 124.7, 126.1, 126.5, 127.5, 133.1, 134.5, 136.4, 138.8, 139.2, 146.4, 147.3; MS m/z 359 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{24}H_{26}N_2O$ 358.20451 (M^+) found for m/z 358.20403. (**13a**). White powder; yield: 70%; mp: 110–112 °C; IR (KBr): 2903, 2211, 1570, 1400, 1229, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.47 (br m, 4H, CH_2), 1.62–1.65 (m, 2H, CH_2), 1.70–1.74 (m, 6H, CH_2), 1.90–1.93 (m, 2H, CH_2), 2.59–2.63 (m, 2H, CH_2), 2.70–2.71 (m, 2H, CH_2), 3.01–3.08 (m, 4H, CH_2), 3.22 (br s, 4H, CH_2), 7.22–7.30 (m, 3H, ArH), 7.57–7.59 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.99, 24.51, 24.65, 25.20, 25.62, 27.75, 28.58, 28.74, 29.10, 31.92, 51.09, 106.86, 117.65, 124.47, 125.92, 126.28, 127.23, 133.37, 133.51, 134.98, 139.27, 139.46, 143.75, 150.15; MS m/z 371 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{26}H_{30}N_2$ 370.24090 (M^+) found for m/z 370.24111.