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OXAHETEROCYCLES: DI- AND TRIOXABENZO[3,4]CYCLOHEPTA-[1,2 *a*]NAPHTHALENE-6,7-DIONES AND DIBENZO[*a*,*c*]CYCLO-HEPTENE-3-CARBONITRILES

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Dedicated in honor of Dr. Albert Padwa on his 75th birthday.

Abstract – An efficient and convenient synthesis of 9-aryl-11,12-dihydro-13*H*-5,8-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-diones and 9-aryl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-diones has been delineated through base catalyzed condensation-cyclization of 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitriles and 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a,c*]-cycloheptene-3-carbonitriles with aryl methyl ketone separately. We have also reported the synthesis of 2-aryl-4-*sec*-amino-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclo-heptene-3-carbonitriles through ring transformation of 4-*sec*-amino-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitriles with aryl methyl ketones in the presence of powdered KOH/NaOH in DMF. We have successfully synthesized 4-aryl-2-(piperidin-1-yl)-5,6-dihydro-7-oxadibenzo[*a,c*]-cycloheptene-1-carbonitriles as isomeric products through ring transformation of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles by 3,4-dihydro-2*H*-benzo[*b*]-oxepin-5(2*H*)-ones.

INTRODUCTION

An extensive literature survey revealed that the chemistry of 5,8-dioxa- and 5,8,13-trioxabenzo[3,4]-

cyclohepta[1,2-*a*]naphthalene-6,7-diones remains to be explored. The only report available so far on these oxaheteroarenes is the synthesis[1] of pyrano[3,4-*c*]chromene-4,5-dione (**I**) and benzo[*h*]pyrano[3,4-*c*]chromene-1,12-dione (**II**) with their anticancer,[2] antibacterial,[3] photochemical[4] and luminescence[5] properties. As evident from the topography of these molecules, it seems obvious that pharmacological and optical properties are possibly due to the presence of pyranopyrandione substructure. This inspired us to design newer class of molecules with pyranopyrandione substructure fused with 6, 7, 8, 9-tetrahydro-5*H*-benzocycloheptene and 2,3,4,5-tetrahydrobenzo[*b*]oxepine rings resulting **III a, b** for better efficacy as antimicrobial agents (Figure 1).

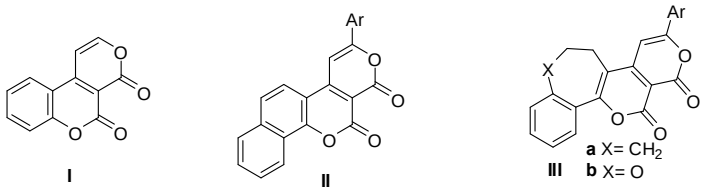
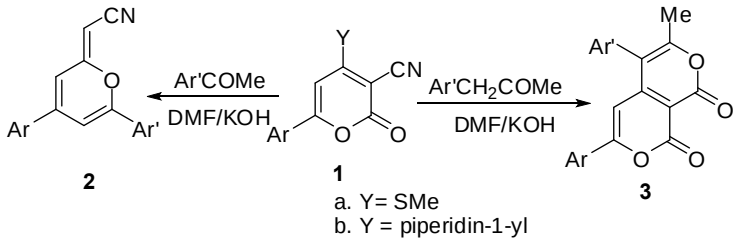


Figure 1. Compounds with pyranopyrandione substructure

Recently, we have reported[6] the non-regioselective synthesis of pyranopyrandiones from the reaction of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile with aryl acetones. However, under analogous conditions, reaction of **1** and aryl methyl ketone gave 4,6-diarylpyran-2-ylidene-2-acetonitrile (**2**) [6b] in lieu of compounds like 3-methyl-4,6-diarylpyrano[3,4-*c*]pyran-1,8-dione (**3**) (Scheme 1). This discrepancy is possibly due to difference in the hardness of carbanion generated in situ from ketones.



Scheme 1

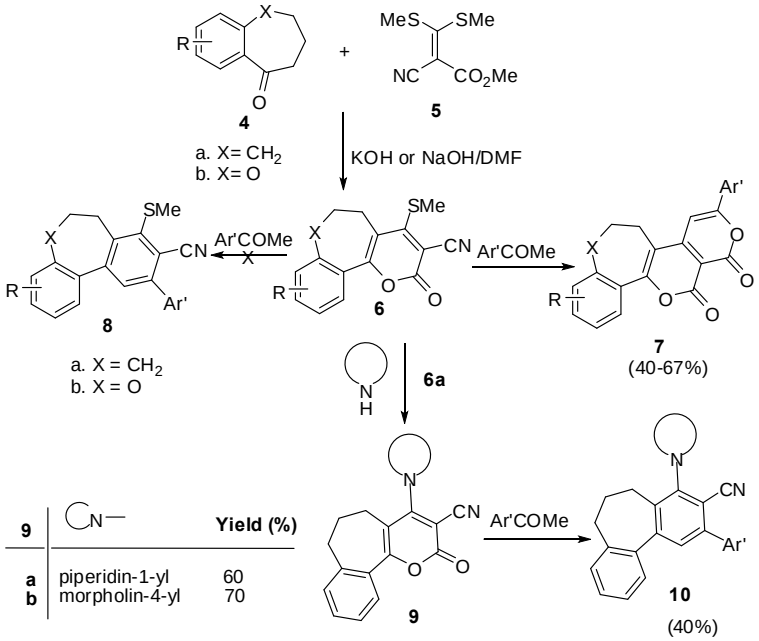
Thus, unpredictability of the course of reactions aroused considerable interest to explore the chemistry of rigid analogs of biaryl systems as depicted in Scheme 2.

RESULTS AND DISCUSSION

The chemistry of rigid analogs of biaryl systems **7**, **10**, prepared through base induced reaction of 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitrile (**6a**), 4-methyl sulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadi-benzo[*a,c*]cycloheptene-3-carbonitriles (**6b-e**) and 4-*sec*-amino-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitriles (**9**) by aryl methyl ketone separately is delineated in Scheme 2.

However, in all the cases reaction of **6a** and **6b-e** with aryl methyl ketone exclusively gave

9-aryl-11,12-dihydro-13*H*-5,8-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (**7a,b**) and 9-aryl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (**7c-j**) respectively.



Scheme 2

Table 1. Yields of Lactons (**6**) in KOH and NaOH

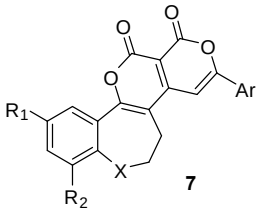
6	R	X	Yields (%) in	
			KOH	NaOH
a	H	CH_2	65	80
b	H	O	59	76
c	10-Me	O	55	72
d	10-OMe	O	65	85
e	8,10-$(Me)_2$	O	21	39

We were also interested to prepare 2-aryl-4-methylsulfanyl-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carbonitrile (**8a**) from the reaction of **6a** with aryl methyl ketone but failed to isolate the right product. Thus, a different synthetic strategy was followed to obtain product analogous to **8** by introducing a *sec*-amino substituent in place of methylsulfanyl group at position 4 of the lactone (**6a**) for preferential attack at position C11b for the ring transformation reactions.

The precursors, 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitrile (**6a**) and 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a,c*]cycloheptene-3-carbonitriles (**6b-e**) were prepared from the base induced condensation-cyclization of 6,7,8,9-tetrahydrobenzocyclohepten-5-one (**4a**) or 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones[7,8] (**4b**), with methyl 2-cyano-3,3-dimethylthioacrylate separately in the presence of powdered KOH or NaOH in DMF. The use of NaOH as a base in the preparation of **6** was found yield wise superior (15-20%) compared to KOH, Scheme 2

(Table 1). 4-*sec*-Amino-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitriles (**9**), required for the construction of 4-*sec*-amino-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carbonitrile (**10**) were obtained by amination[9] of **6a** with different *sec*-amine in boiling ethanol (Scheme 2).

Table 2. Yields and Mp of compounds (**7**)

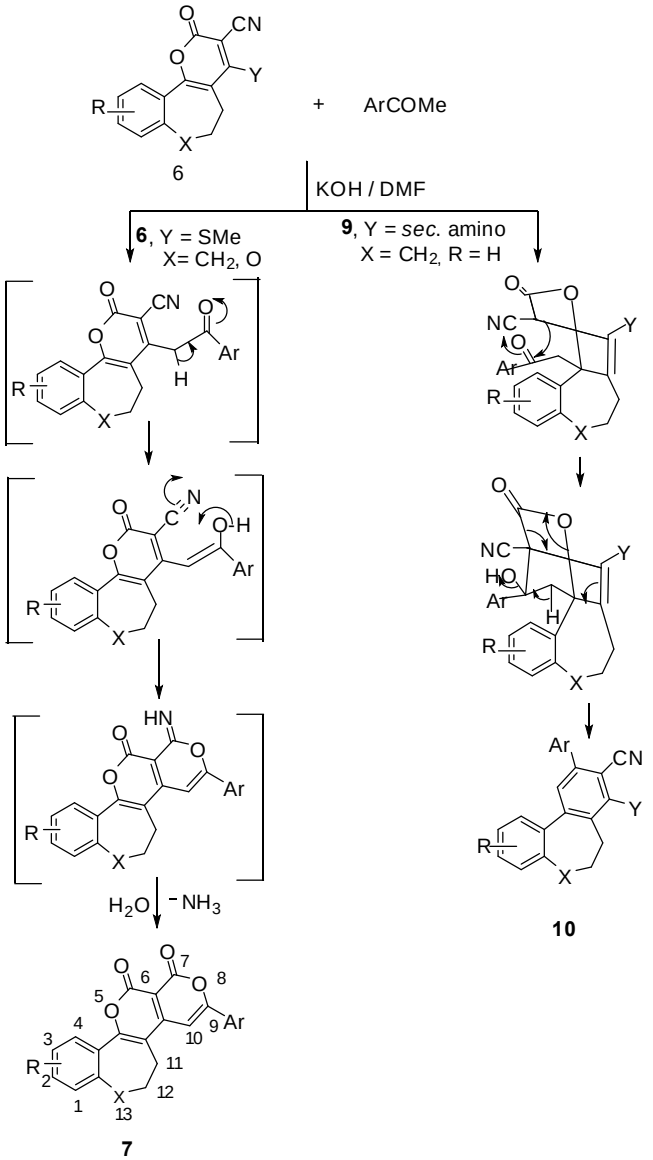


7

7	R_1	R_2	X	Ar	Mp	Yields (%)
a	H	H	CH_2	4-bromophenyl	252	60
b	H	H	CH_2	thiophen-2-yl	220	60
c	MeO	H	O	phenyl	>290	67
d	MeO	H	O	4-chlorophenyl	>290	52
e	MeO	H	O	4-methylphenyl	256	47
f	MeO	H	O	pyridin-4-yl	>290	46
g	MeO	H	O	naphthalen-1-yl	272	42
h	H	H	O	4-chlorophenyl	290	41
i	Me	Me	O	4-chlorophenyl	>290	45
j	Me	H	O	4-chlorophenyl	>290	40

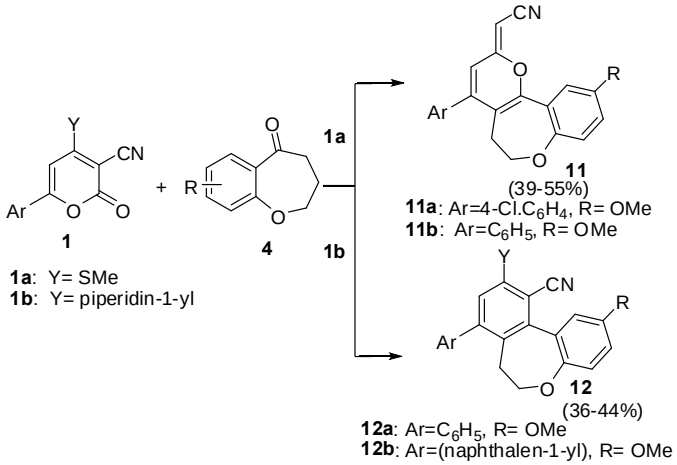
The molecular make up of 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitrile (**6a**) and 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a,c*]cycloheptene-3-carbonitriles (**6b-e**) revealed the presence of three electrophilic sites C2, C4, and C11b in which the latter is likely most electron deficient due to extended conjugation and the presence of an electron-withdrawing CN substituent at position 3 of the lactone ring. However, the electrophilicity of C11b is not enough compared to C4 for preferential nucleophilic attack, possibly due to the presence of methylene bridge at C4a of the lactone. The only option to direct the carbanion attack at C11b was to introduce *sec*-amino function at C4 to reduce its electrophilicity. Under this situation C11b position of the lactone ring becomes susceptible to attack by carbanion, generated in situ either from 6,7,8,9-tetrahydrobenzocycohepten-5-one (**4a**) or 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones (**4b**) in the presence of powdered KOH/NaOH and DMF. The progress of the reaction was clearly evident by evolution of carbon dioxide bubbles. The completion of reaction was monitored by silica gel coated TLC plates. Thus, an equimolar mixture of 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]-

cycloheptene-3-carbonitrile (**6a**) or 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a,c*]cycloheptene-3-carbonitriles (**6b-e**) and aryl methyl ketone was separately stirred with anhydrous powdered KOH in DMF for 8-18 h at room temperature. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% aqueous HCl. The resulting precipitate was filtered, washed with water and dried. The crude product was purified by silica gel column chromatography which exclusively gave 9-aryl-11,12-dihydro-13*H*-5,8-di-oxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-diones (**7a**,**b**) and 9-aryl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (**7c-j**) (Table 2) without any trace formation of expected 2-aryl-4-methylsulfanyl-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carbonitriles (**8**).



Scheme 3. A plausible mechanism for the synthesis of 5,8-dioxa-, 5,8,13-trioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene-6,7-diones (**7**) and 2-aryl-4-*sec*-amino-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carbonitriles (**10**)

A different protocol was followed for the preparation of 2-aryl-4-*sec*-amino-6,7-dihydro-5*H*-dibenzo-[*a*,*c*]cycloheptene-3-carbonitriles (**10**) by using 4-*sec*-amino-2-oxo-2,5-tetrahydro-1-oxadibenzo[*a*,*c*]-cycloheptene-3-carbonitriles (**9**) as a precursor. Thus, an equimolar mixture of **9** and aryl methyl ketone in the presence of powdered KOH in DMF was stirred for 6-8 h at room temperature. Usual work up and silica gel column chromatography exclusively gave 2-aryl-4-*sec*-amino-6,7-dihydro-5*H*-dibenzo[*a*,*c*]-cycloheptene-3-carbonitrile (**10**) in moderate yield. The initial step in the synthesis of **7** is the attack of a carbanion, generated in situ from aryl methyl ketone at C4 of the lactone (**6**), followed by ring closure involving enolate of the ketone intermediate and CN function. The cyclic imine intermediate so formed is hydrolysed to yield **7**. However, the first step in the synthesis of **10** is the formation of Michael adduct with aryl methyl ketone which underwent ring opening in situ followed by recyclization involving C3 of 9 and carbonyl function of aryl methyl ketone. A plausible mechanism of the reaction is illustrated in Scheme 3.



Scheme 4

A different synthetic strategy was followed for the construction of 4-aryl-2-methylthio-5,6-dihydro-7-oxadibenzo[*a*,*c*]cycloheptene-1-carbonitriles and 4-aryl-2-(piperidin-1-yl)-5,6-dihydro-7-oxadibenzo-[*a*,*c*]cycloheptene-1-carbonitriles (**12a**,**b**), a structural isomers of **8b** through the ring transformation of **1b** by **4**. However, the interaction of **1a** with **4** did not follow the same course of reaction and the products isolated were characterized[10] as 2-(4-aryl-6,7-dihydro-5*H*-1,7-dioxadibenzocycloheptene-2-ylidene)-acetonitriles (**11a**,**b**) (Scheme 4).

CONCLUSION

In conclusion, we have developed a novel, simple and economical route for the synthesis of various 9-aryl-11,12-dihydro-13*H*-5,8-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-diones (**7a,b**), 9-aryl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-diones (**7c-j**) from the reaction of

4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a,c*]cycloheptene-3-carbonitrile (**6a**) and 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a,c*]cycloheptene-3-carbonitriles (**6b-e**) separately with aryl methyl ketone. A new protocol for the construction of 2-aryl-4-*sec*-amino-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carbonitrile (**10**) has also been developed from the reaction of **9** with aryl methyl ketone in the presence of KOH/NaOH in DMF through C-C insertion, not reported so far. The protocol provides an efficient and concise route for the preparation of new class of annelated oxaheterocycles, reported for the first time.

EXPERIMENTAL

Materials and methods: The reagents and the solvents used in this study were of analytical grade and used without further purification. The melting points were determined on an electrically heated Townson Mercer melting point apparatus and are uncorrected. Commercial reagents were used without purification. ^{1}H and ^{13}CNMR spectra were measured on a Bruker WM-300 (300 MHz) using $CDCl_3$ and DMSO-d_6 solvents. Chemical shift are reported in parts per million shift (δ-value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}CNMR) as the internal standard. Signal patterns are indicate as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constant (*J*) are given in Hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectrophotometer in KBr disc and reported in wave number (cm^{-1}). Fast-atomic bombardment (FAB) and ESIMS spectrometers were used for mass spectra analysis. ^{13}C NMR for all compounds is not reported due to poor solubility of compounds in DMSO-d_6.

General procedure for the synthesis of 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo-[*a*,*c*]cycloheptene-3-carbonitrile (6a) and 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo-[*a*,*c*]cycloheptene-3-carbonitriles (6b): A mixture of 6,7,8,9-tetrahydrobenzocyclohepten-5-one or 3,4-dihydro- 2*H*-benzo[*b*]oxepin-5(2*H*)-one **4** (1 mmol) and methyl 2-cyano-3,3-dimethylthioacrylate **5** (1 mmol) in DMSO (8 mL) was stirred in the presence of powdered KOH (2 mmol) for 5 h and the reaction mixture was poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with 10% HCl (5 mL) and the precipitate obtained was filtered, washed with water and purified on silica gel column, using DCM as eluent.

4-Methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (6a): Light yellow amorphous solid; yield: 65%; mp 166-67 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (t, J = 6.8 Hz, 2H, CH_2), 2.34 (t, J = 6.8Hz, 2H, CH_2), 2.65 (t, J = 6.8Hz, 2H, CH_2), 2.95 (s, 3H, SCH_3), 7.40-7.59 (m, 3H, ArH), 7.60 (d, J = 7.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.4, 23.5, 30.5, 32.8, 93.9, 114.9, 115.9, 126.8, 127.9, 129.4, 131.5, 131.5, 141.0, 157.5, 158.3, 168.7; HRMS (EI, 70 eV) Calcd for $C_{16}H_{13}NO_2S$: 283.0669 (M^+). Found: 283.0658.

4-Methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (6b): White powder; yield: 59%; mp 194 ºC; IR (KBr): 2937, 2212 (CN), 1725 (C=O), 1582, 1488, 1276, 1185, 1126, 1065, 1009, 828, 771, 672, 562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, J = 6 Hz, 2H), 3.01 (s, 3H, SCH_3), 4.50 (t, 2H, J= 6 Hz, OCH_2), 7.08 (m, 1H, ArH), 7.21 (m, 1H, ArH), 7.45 (m, 1H, ArH), 7.95 (m, 1H, ArH); MS (ESI): m/z 286 (M^++1); HRMS (EI, 70 eV) Calcd for $C_{15}H_{11}NO_3S$: 285.0460 (M^+). Found: 285.0451.

10-Methyl-4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (6c): Yellow powder; yield: 55%; mp 180 ºC; IR (KBr): 3020, 2929, 2221 (CN), 1720 (C=O), 1589, 1489, 1216, 1129, 1039, 830, 760, 669, 493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, Me), 2.92 (t, J = 6 Hz, 2H), 3.01 (s, 3H, SCH_3), 4.47 (t, 2H, J= 6 Hz, OCH_2), 7.00 (d, 1H, J=9, Hz, ArH), 7.26 (d, J=9, 1H, ArH), 7.70 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.20, 20.61, 27.80, 29.65, 74.62, 93.67, 114.55, 115.77, 121.83, 122.32, 129.62, 133.44, 134.35, 155.44, 155.90, 158.11; MS (ESI): m/z 300 (M^++1), 301 (M^++2); HRMS (EI, 70 eV) Calcd for $C_{16}H_{13}NO_3S$: 299.06161 (M^+). Found: 299.0628.

10-Methoxy-4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (6d): Yellow amorphous solid; yield: 65%; mp 178 ºC; IR (KBr): 2956, 2216 (CN), 1722 (C=O), 1585, 1489, 1271, 1212, 1037, 840, 761, 668, 502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.87 (t, J = 6 Hz, 2H), 3.01 (s, 3H, SCH_3), 3.83 (s, 3H, OCH_3), 4.47 (t, 2H, J= 6 Hz, OCH_2), 7.03 (s, 1H, ArH), 7.28 (d, J = 9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18, 27, 55, 75, 93, 112 (2C), 114, 115, 120, 123, 124, 150, 155, 158, 168; MS: m/z 315 (M^+); HRMS (ESI) Calcd for $C_{16}H_{13}NO_4S$: 316.0626 (M^++1). Found: 316.0633.

8,10-Dimethyl-4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-1,7-dioxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (6e): Yellow amorphous solid; yield: 65%; mp 210 ºC; IR (KBr): 2936, 2887, 2217 (CN), 1698 (C=O), 1602, 1561, 1485, 1307, 1271, 1226, 1071, 1017, 958, 851, 782, 755, 669, 501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, Me), 2.43 (s, 3H, Me), 2.71 (t, J = 6 Hz, 2H), 3.02 (s, 3H, SCH_3), 4.43 (t, 2H, J= 6 Hz, OCH_2), 6.81 (s, 1H, ArH), 6.93 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.81, 20.37, 21.39, 25.11, 77.87, 93.57, 114.66, 115.27,120.84, 122.49, 128.62, 139.18, 143.66, 155.65, 157.94, 158.32, 167.48; MS (ESI): m/z 314 (M^++1); HRMS (EI, 70 eV) Calcd for $C_{17}H_{15}NO_3S$: 313.0773 (M^+). Found: 313.0761.

General procedure for the synthesis of 9-aryl-11,12-dihydro-13*H*-5,8-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene-6,7-diones (7a,b) and 9-aryl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene-6,7-diones (7c): A mixture of 4-methylsulfanyl-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a*,*c*]cycloheptene- 3-carbonitrile 6 (1.0 mmol) and aryl methyl ketone (1.1 mmol) and powdered KOH (1.2 mmol) in DMF (10 mL) was stirred at room temperature for 8-18 h. After completion, reaction mixture was poured onto crushed ice and neutralized with 10% HCl. The crude

product obtained was filtered, washed with water and finally purified by a silica gel column chromatography using 25% EtOAc in hexane.

9-(4-Bromophenyl)-11,12-dihydro-13*H*-5,8-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7a): White leaflet solid; mp 252 ^{o}C; yield: 40%; IR (KBr): 2926, 2855, 1780 (C=O), 1704 (C=O), 1596, 1461, 1351 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30-2.35 (m, 2H, CH_2), 2.42-2.45 (m, 2H, CH_2), 2.60-2.62 (m, 2H, CH_2), 7.19-7.21 (m, 1H, ArH), 7.38-7.76 (m, 4H, ArH), 8.0 (d, J = 8.4 Hz, 2H, ArH), 8.1 (d, J = 8.4 Hz, 2H, ArH); HRMS (EI, 70 eV) Calcd for $C_{23}H_{15}BrO_4$: 434.0154 (M^+). Found: 434.0155.

9-Thiophen-2-yl-11,12-dihydro-13*H*-5,8-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7b): White leaflet solid; mp 220 ^{o}C; yield: 60%; IR (KBr): 2925, 2853, 1781 (C=O), 1703 (C=O), 1593, 1460, 1352 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25-2.28 (m, 2H, CH_2), 2.45-2.50 (m, 2H, CH_2), 2.63-2.67 (m, 2H, CH_2), 7.20-7.22 (m, 1H, ArH), 7.40-7.46 (m, 4H, ArH), 7.60-7.62 (m, 1H, ArH), 7.73-7.80 (m, 1H, ArH), 8.10-8.12 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.64, 31.93, 33.65, 63.47, 97.03, 100.23, 103.21, 113.00, 126.53, 126.69, 127.97, 128.22, 129.19, 129.40, 129.58, 130.22, 133.31, 140.81, 140.93, 144.14; MS: m/z 360 (M^+), 345, 331, 316; HRMS (EI, 70 eV) Calcd for $C_{21}H_{14}O_4S$: 362.0613 (M^+). Found: 362.0602.

3-Methoxy-9-phenyl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7c): Yellow amorphous solid; yield: 67%; mp >290 ^{o}C; IR (KBr): 3058, 2935, 1763 (C=O), 1701 (C=O), 1628, 1560, 1492 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.00 (t, J=6 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.54 (t, J=6 Hz, 2H, OCH_2), 6.86 (s, 1H), 7.04 (s, 1H, ArH), 7.27 (s, 1H, ArH), 7.54 (m, 4H, ArH), 7.97 (m, 2H, ArH); MS (ESI): m/z 388 (M^+); HRMS (ESI) Calcd for $C_{23}H_{16}O_6$: 389.0980 (M^++1). Found 389.0973.

9-(4-Chlorophenyl)-3-methoxy-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7d): Yellow powder; yield: 52%; mp >290 ^{o}C; IR (KBr): 3201, 3113, 2941, 1763 (C=O), 1701 (C=O), 1623, 1520, 1488, 1468, 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (t, J=6, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.49 (t, J=6 Hz, 2H, OCH_2), 7.13 (m, 2H, ArH), 7.30 (s, 1H), 7.49 (s, 1H, ArH), 7.68 (d, J=8.1 Hz, 2H, ArH), 8.15 (d, J=8.1 Hz, 2H, ArH); MS (ESI): m/z 423 (M^+); HRMS (ESI) Calcd for $C_{23}H_{15}ClO_6$: 423.0606 (M^++1). Found: 423.0615.

3-Methoxy-9-p-tolyl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7e): Yellow amorphous solid; yield: 47%; mp 256 ^{o}C; IR (KBr): 2934, 1763 (C=O), 1696 (C=O), 1619, 1555, 1486, 1380, 1264, 1204, 1100, 1039, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.41 (s, 3H, Me), 3.03 (bs, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.49 (bs, 2H, OCH_2), 7.13 (m, 2H, ArH), 7.31 (s, 1H), 7.41 (m, 3H, ArH), 8.04 (d, J=7.2 Hz, 2H, ArH); MS (ESI): m/z 402 (M^+); HRMS (ESI) Calcd for $C_{24}H_{18}O_6$: 403.1137 (M^++1). Found 403.1145.

3-Methoxy-9-pyridin-4-yl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7f): Yellow amorphous solid; yield: 46%; mp >290 °C; IR (KBr): 3052, 2934, 1763 (C=O), 1702 (C=O), 1633, 1566, 1497, 1405, 1272, 1207, 1088, 1025, 818, 783 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.06 (bs, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.51 (bs, 2H, OCH_2), 7.14 (bs, 2H, ArH), 7.32 (s, 1H), 7.66 (s, 1H, ArH), 8.04 (bs, 2H, ArH), 8.83 (bs, 2H, ArH); MS (ESI): m/z 389 (M^+); HRMS (ESI) Calcd for $C_{22}H_{15}NO_6$: 390.0933 (M^++1). Found: 390.0921.

3-Methoxy-9-naphthalen-1-yl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7g): Yellow powder; yield: 42%; mp 272 °C; IR (KBr): 3046, 2959, 1769 (C=O), 1713 (C=O), 1571, 1491, 1381, 1246, 1212, 1099, 1041, 938, 793, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.00 (bs, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.45 (bs, 2H, OCH_2), 7.13 (m, 2H, ArH), 7.25 (s, 1H), 7.36 (s, 1H, ArH), 7.67 (m, 3H, ArH), 7.94 (m, 1H, ArH), 8.09 (m, 1H, ArH), 8.20 (m, 1H, ArH), 8.29 (m, 1H, ArH); MS (ESI): m/z 438 (M^+); HRMS (ESI) Calcd for $C_{27}H_{18}O_6$: 439.1137 (M^++1). Found: 439.1120.

9-(4-Chlorophenyl)-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7h): Yellow powder; yield: 41%; mp 290 °C; IR (KBr): 3090, 2931, 2891, 1764 (C=O), 1702 (C=O), 1580, 1492, 1401, 1258, 1214, 1094, 1008, 824, 769, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.06 (bs, 2H, CH_2), 4.54 (bs, 2H, OCH_2), 6.83 (s, 1H), 7.10 (d, J=7.8 Hz, 1H, ArH), 7.21 (m, 1H, ArH), 7.44 (d, J=6.9Hz, 1H, ArH), 7.51 (d, J=8.1Hz, 2H, ArH), 7.91 (d, J=8.1Hz, 2H, ArH), 8.19 (d, J=8.1Hz, 1H, ArH); MS (ESI): m/z 392 (M^+); HRMS (ESI) Calcd for $C_{23}H_{13}ClO_5$: 393.0485 (M^++1). Found: 393.0479.

9-(4-Chlorophenyl)-1,3-dimethyl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7i): White leaflet solid; yield: 45%; mp >290 °C; IR (KBr): 3089, 2943, 1762 (C=O), 1701 (C=O), 1591, 1500, 1428, 1400, 1286, 1207, 1121, 1071, 1001, 891, 827, 801 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz): δ 2.36 (s, 3H, 8-Me), 2.48 (s, 3H, 10-Me), 2.72 (bs, 2H, CH_2), 4.51 (bs, 2H, OCH_2), 6.84 (s, 1H, ArH), 6.87 (s, 1H, ArH), 6.95 (s, 1H), 7.52 (d, J=8.1Hz, 2H, ArH), 7.93 (d, J=8.1Hz, 2H, ArH); MS (ESI): m/z 420 (M^+); HRMS (ESI) Calcd for $C_{24}H_{17}ClO_5$: 421.0798 (M^++1). Found: 421.0782.

9-(4-Chlorophenyl)-3-methyl-11,12-dihydro-5,8,13-trioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-6,7-dione (7j): White leaflet solid; yield: 40%; mp >290 °C; IR (KBr): 3092, 2968, 1763 (C=O), 1704 (C=O), 1617, 1562, 1489, 1400, 1307, 1255, 1216, 1086, 1090, 1029, 886, 823 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.36 (s, 3H, 8-Me), 3.08 (bs, 2H, CH_2), 4.50 (bs, 2H, OCH_2), 7.06 (d, J=8.1Hz, 1H, ArH), 7.36 (d, J=8.4Hz, 1H, ArH), 7.48 (s, 1H), 7.70 (m, 3H, ArH), 8.15 (d, J=8.1Hz, 2H, ArH); MS (ESI): m/z 406 (M^+); HRMS (EI, 70 eV) Calcd for $C_{23}H_{15}ClO_5S$: 406.0608 (M^+). Found: 406.0614.

General procedure for the synthesis of 4-*sec*-amino-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a*,*c*]cycloheptene-3-carbonitriles (9): A mixture of **6** (1 mmol) and *sec*-amine (1.1 mmol) was

refluxed in absolute EtOH for 6 h. During this period precipitate separated out which was filtered after cooling, washed with cold EtOH and finally crystallized with acetone.

4-(Piperidin-1-yl)-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (9a): Light yellow amorphous solid; yield: 60%; mp 168 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.65 (bs, 6H, CH_2), 2.09 (t, J = 6.8 Hz, 2H, CH_2), 2.22 (t, J = 6.8 Hz, 2H, CH_2), 2.65 (t, J = 6.8 Hz, 2H, CH_2), 3.53-3.54 (m, 4H, NCH_2), 7.36-7.47 (m, 3H, ArH), 7.53-7.56 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.78, 24.67, 26.0, 31.3, 33.9, 52.9, 53.0, 77.7, 99.5, 111.8, 117.2, 126.8, 127.9, 129.3, 131.4, 132.0, 141.5, 159.8, 161.8, 167.4; HRMS: (CI) Calcd for $C_{20}H_{20}N_2O_2$: 320.1525 (M^+). Found: 320.1539.

4-(Morpholin-4-yl)-2-oxo-2,5,6,7-tetrahydro-1-oxadibenzo[*a*,*c*]cycloheptene-3-carbonitrile (9b): Light yellow amorphous solid; yield: 70%; mp 175 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (t, J = 6.8 Hz, 2H, CH_2), 2.22 (p, J = 6.8 Hz, 2H, CH_2), 2.65 (t, J= 6.8 Hz, 2H, CH_2), 3.63 (t, J = 4.8 Hz, 4H, NCH_2), 3.94 (t, J = 4.8 Hz, 4H, OCH_2), 7.37-7.47 (m, 3H, ArH), 7.54-7.56 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.65, 31.2, 33.9, 51.9, 66.4, 78.1, 111.5, 117.2, 126.8, 127.9, 129.3, 131.5, 131.8, 141.5, 160.2, 161.5, 166.9; HRMS (CI) Calcd for $C_{19}H_{18}N_2O_3$: 322.1317 (M^+). Found for m/z 322.1312.

General procedure for the synthesis of 2-aryl-4-*sec*-amino-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-3-carbonitrile (10): An equimolar mixture of **9** (1 mmol) and aryl methyl ketone was stirred in DMF (8 mL) in the presence of powdered KOH (1.5 mmol) at room temperature for 6-8 h. Thereafter, the reaction mixture was poured onto crushed ice and the precipitate separated was filtered, washed with water and dried. The crude product was purified by silica gel column chromatography using 25% EtOAc in hexane.

2-(4-Bromophenyl)-4-piperidin-1-yl-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-3-carbonitrile (10): Viscous liquid; yield: 40%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23-2.24 (m, 2H, CH_2), 2.42-2.45 (m, 2H, CH_2), 2.60-2.62 (m, 2H, CH_2), 3.20-3.51 (m, 6H, CH_2), 3.88-3.92 (m, 4H, CH_2), 7.17 (s, 1H), 7.23-7.37 (m, 2H, ArH), 7.42-7.45 (m, 2H, ArH), 7.58-7.60 (m, 2H, ArH), 7.42-7.45 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.67, 25.29, 25.50, 26.92, 31.35, 31.60, 32.75, 34.67, 67.81, 109.42, 118.04, 123.02, 126.80, 127.0, 128.3, 128.7, 128.9, 130.5, 131.8, 137.28, 137.95, 139.3, 139.5, 144.1, 147.7, 153.2; MS (CI): m/z 456 (M^+), 458 (M^++2); HRMS (CI) Calcd for $C_{27}H_{25}BrN_2$: 456.1201 (M^+). Found: 456.1190.

General procedure for the synthesis of 2-(4-aryl-6,7-dihydro-5*H*-1,7-dioxadibenzo[*a*,*c*]cycloheptene-2-ylidene)acetonitriles (11): A mixture of 3,4-dihydrobenzo[*b*]oxepine-5(2*H*)-ones **4** (1 mmol), 6-aryl-4- methylthio-2-oxo-2H-pyran-3-carbonitriles **1a** (1 mmol) and powdered KOH (2 mmol) in DMF (8 mL) was stirred for 3 h.The reaction mixture was poured onto crushed ice with vigorous stirring. The aqueous phase was neutralized with 10% HCl and the precipitate obtained was filtered, washed with water and purified on silica gel column using hexane:DCM mixture (7:3) as eluent.

[4-(4-Chlorophenyl)-10-methoxy-5,6-dihydro-1,7-dioxadibenzo[*a*,*c*]cyclohepten-2-ylidene]acetonitrile (11a): Reddish amorphous solid; yield: 55%; mp 200 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (Z-isomer, 70%) 2.50 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.26 (s, 2H, OCH_2), 6.18 (s, 1H, CH), 6.65-7.43 (m, 8H, ArH); δ (E-isomer, 30%) 2.41 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.35 (s, 2H, OCH_2), 6.65 (s, 1H, CH), 6.65-7.43 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31, 55, 65, 72, 110, 112, 115, 116, 117, 118, 119, 122(2C), 129(2C), 135(2C), 146, 150, 151, 155, 164; MS (ESI): m/z 378 (M^+), 380 (M^++2); HRMS (ESI) Calcd for $C_{22}H_{16}ClNO_3$: 378.0897 (M^++1). Found: 378.0889.

2-(10-Methoxy-4-phenyl-5,6-dihydro-5*H*-1,7-dioxadibenzo[*a*,*c*]cycloheptene-2-ylidene)acetonitrile (11b): Reddish amorphous solid; yield: 39%; mp 116 ^{o}C; IR (KBr): 2933, 2513, 2223 (CN), 2187, 1637, 1571, 1487, 1399 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, Me), 2.43 (s, 3H, Me), 2.71 (t, 2H, CH_2 J=6 Hz), 3.02 (s, 3H, SMe), 4.43 (t, 2H, OCH_2, J=6 Hz), 6.81(s, 1H, Ar-H), 6.93 (s, 1H, Ar-H); MS (ESI): m/z 344 (M^++1); HRMS (ESI) Calcd for $C_{22}H_{17}NO_3$: 344.1142 (M^++1). Found: 344.1138.

General procedure for the synthesis of 4-aryl-2-(piperidin-1-yl)-5,6-dihydro-7-oxadibenzo[*a*,*c*]-cycloheptene-1-carbonitriles (12): A mixture of 3,4-dihydrobenzo[*b*]oxepine-5(2*H*)-ones **4** (1 mmol) and 6-aryl-4-(*sec*-amino)-2*H*-pyran-2-one-3-carbonitrile **1b** (1 mmol) in DMF (6 mL) was stirred for 3 h in the presence of powdered KOH (2 mmol). After completion of the reaction, content was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and dried. The crude product was purified through silica gel column using a mixture of hexane: DCM (7:3) as eluent.

2-Methoxy-8-phenyl-10-piperidin-1-yl-6,7-dihydro-5-oxadibenzo[*a*,*c*]cycloheptene-11-carbonitrile (12a): White solid; yield: 44%; mp 144 ^{o}C; IR (KBr): 3069, 2934, 2850, 2804, 2218 (CN), 1573, 1496, 1439 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52-1.69 (m, 6H), 3.06 (m, 2H), 3.20 (m, 4H), 3.79 (s, 3H), 4.24 (m, 2H), 6.97-7.03 (m, 2H), 7.08 (s, 1H), 7.24 (d, 1H, J=3 Hz), 7.38-7.48 (m, 5H); ^{13}C NMR (75 MHz, CDC_3): δ 24, 26(2C), 28, 53(2C), 55, 78, 105, 115, 116, 118, 119, 122, 127(2C), 128(3C), 132(2C), 140, 143, 146, 148, 155, 156; MS (ESI): m/z 411 (M^++1), 412 (M^++2); HRMS (ESI) Calcd for $C_{27}H_{26}N_2O_2$: 411.20725 (M^++1). Found: 411.20728.

2-Methoxy-8-naphthalen-1-yl-10-piperidin-1-yl-6,7-dihydro-5-oxadibenzo[*a*,*c*]cycloheptene-11-carbonitrile (12b): Light yellow solid; yield: 36%; mp 188 ^{o}C; IR (KBr): 2938, 2217 (CN), 1640, 1496, 1459 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60-2.49 (m, 6H), 3.18 (m, 2H), 3.82 (s, 3H), 3.91-4.16 (m, 4H), 4.73 (m, 2H), 6.80-7.07 (m, 3H), 7.23-7.81 (m, 6H), 7.92-7.94 (m, 2H); MS (ESI): m/z 461 (M^++1), 462 (M^++2); HRMS (ESI) Calcd for $C_{31}H_{28}N_2O_2$: 461.2184 (M^++1). Found: 461.2179.

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