An Expeditious Concise Synthesis of Benzo[*b*]pyrano[2,3-*d*]oxepines and Dibenzo[*b*,*d*]oxepines

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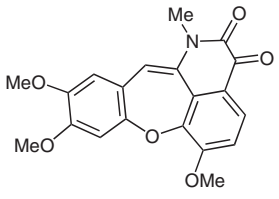
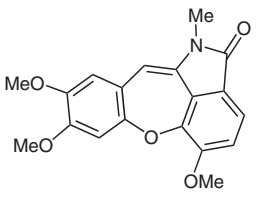
Abstract: An efficient concise synthesis of 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles has been delineated through condensation–cyclization of 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones and methyl 2-cyano-3,3-dimethylthioacrylate in DMF using powdered KOH as a base. A base-induced reaction of 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones and 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitrile in the presence of powdered KOH in DMF gave an isomeric mixture of (*E*)- and (*Z*)-2-(4-phenyl-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepin-2-ylidene)acetonitriles. However, the ring transformation of 6-aryl-4-(*sec*-amino)-2*H*-pyran-2-one-3-carbonitriles from 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones under analogous reaction conditions exclusively gave 8-phenyl-10-(*sec*-amino)-6,7-dihydrodibenzo[*b*,*d*]oxepine-11-carbonitriles.

Keywords: 2-pyranone, benzo[*b*]pyrano[2,3-*d*]oxepine, dibenzo[*b*,*d*]oxepine, ring-transformation reaction

Dibenzoxepine framework is commonly present as substructure in numerous natural products of therapeutic importance.[1] Cularinoids, a group of sixty isoquinoline alkaloids, are characterized by the presence of dibenzoxepine skeleton. The oxidized cularinoids,[2] such as 3,4-dioxocularines **I** and aristocularines **II**, are known to display significant cytotoxic activity against both wild-type and adriamycin-resistant cell lines. They are also effective against H-29 human colon adenocarcinoma and MDA-MB-231 human breast cancer cells[3,4] and found useful as nuclear hormone receptor modulators.[5] Besides these, they are extensively in use for the treatment of anxiety, depression, and schizophrenic psychoses.[6,7]



3,4-dioxocularine (**I**)



aristocularine (**II**)

Figure 1 Natural isoquinoline alkaloids with benzoxepine framework

A comprehensive literature survey revealed that mainly four possible dibenzoxepine ring systems: dibenzo[*b*,*d*]-, dibenzo[*b*,*e*]-, dibenzo[*b*,*f*]-, and dibenzo[*c*,*e*]oxepines are reported depending upon the site of fusion of benzene with oxepine ring. The chemistry and pharmacology of dibenzo[*b*,*e*]-, dibenzo[*b*,*f*]-, and dibenzo[*c*,*e*]oxepines are explored extensively while dibenzo[*b*,*d*]oxepine is still underdeveloped. The diverse pharmacological activities, fascinating chemistry,[8] and meagerly explored ring system necessitated to develop an easy access to the synthesis of dibenzo[*b*,*d*]oxepines to explore their chemistry and biodynamic properties.

Earlier, compounds of this ring system have been synthesized[9] by treatment of biphenyl-2-yloxyacetyl chloride with $AlCl_3$ as dibenzo[*b*,*d*]oxepin-5-one in moderate yield. These are also obtained by thermal decomposition of 2′-phenyldiphenylether-2-sulfonyl chloride at 250–260 °C as tribenzo[*b*,*d*,*f*]oxepines.[10] Junjappa et al. have reported[11,12] the synthesis of this ring system by the reaction of cyclic 2-oxoketenedithioacetals with propargylmagnesium bromide and allylmagnesium bromide separately. These are also obtained by irradiation of 9,10-epoxy-9,10-dihydrophenanthrene under nitrogen blanket in benzene.[13] Further, irradiation of 2-phenethyloxyaryl bromide in acetonitrile[13] also gave similar product.[13]

Recently, dibenzo[*b*,*d*]oxepines have been prepared by intramolecular cyclization of 1-bromo-2-phenethoxy benzene in the presence of a catalyst generated from $Pd(OAc)_2$ and 2-(diphenylphospheno)-2′-(*N*,*N*-dimethylamino)biphenyl.[14] An improved synthesis has also been reported through cyclization of 1-bromo-2-phenethoxybenzenes in the presence of $Pd(OAc)_2$ and $PCY_3{\cdot}HBF_4$ in conjunction with Cs_2CO_3 and 2,2-dimethylpropionic acid in mesitylene at 135 °C.[15] Oxidative coupling of substituted phenyl phenylacetate by thallium(III)trifluoroacetate (TTFA) or phenyl iodine(III)bis(trifluoroacetate) (PIFA) has also been reported as an alternative route[16] for the construction of lactonized benzo[*b*,*d*]oxepines.

Our synthetic strategy is based on the use of 6-aryl-4-methylsulfanyl-2*H*-pyrans-2-one-3-carbonitriles **2** as precursors, obtainable from the reaction of aryl methyl ketone and methyl 2-cyano-3,3-dimethylthioacrylate[17] (**1**). Amination[18] of **2** with *sec*-amine in boiling ethanol afforded 6-aryl-4-(*sec*-amino)-2*H*-pyran-2-one-3-carbonitriles **3** (Scheme 1).

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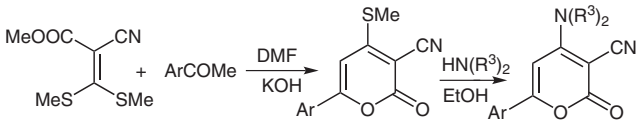
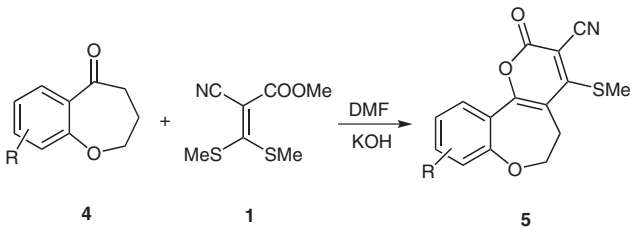
3,4-Dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4**, used as a source of carbanion for the construction of various benzo[*b*]pyrano[2,3-*d*]oxepins have been obtained by the reaction of phenol with γ-butyrolactone with subsequent cyclization of isolated acid in PPA.[19] The benzo[*b*]oxepin-5-ones **4** on reaction with methyl 2-cyano-3,3-dimethylthioacrylate (**1**) at room temperature in the presence of KOH exclusively gave 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles **5** (Scheme 2).



1 **2** **3**

2,3	Ar	$N(R^3)_2$
	Ph	piperidin-1-yl
	4-ClC_6H_4	1,2,3,4-tetrahydroisoquinolin-2-yl
	1-naphthyl	piperidin-1-yl
	2-thienyl	piperidin-1-yl
	4-MeC_6H_4	–

Scheme 1 Synthesis of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles **2** and 6-aryl-4-(*sec*-amino)-2*H*-pyran-2-one-3-carbonitriles **3**



4 **1** **5**

5	R	Yield (%)
a	H	59
b	10-Me	55
c	10-OMe	65
d	8,10-$(Me)_2$	21

Scheme 2 Synthesis of 5,6-dihydro-4-methylthio-2-oxo-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles

The reaction of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles **2** and **4** in DMF using powdered KOH as a base exclusively gave an isomeric mixture (*E*)- and (*Z*)-2-{4-phenyl-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepin-2-ylidene}acetonitriles **7** instead of 8-aryl-10-methylthio-6,7-dihydrobenzo[*b*,*d*]oxepine-11-carbonitriles **6** (R^1 = SMe), by following path B (Scheme 3). Attempts to separate the *E*- (minor) and *Z*-isomer (major) under different reaction conditions failed due to their very close R_f and were identified only by NMR spectroscopy. Use of different bases such as NaH and Na_2CO_3 in lieu of KOH did not change the course of reaction and improved the yield.

A different synthetic strategy was followed to obtain **6** by using 6-aryl-4-*sec*-amino-2*H*-pyran-2-one **3** as a precursor in lieu of **2** for the ring-transformation reaction. Thus, the reaction of 6-aryl-4-s*ec*-amino-2*H*-pyran-2-one **3** and 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4** under analogous reaction conditions exclusively gave 8-phenyl-10-*sec*-amino-1-yl-6,7-dihydrodibenzo[*b*,*d*]oxepine-11-carbonitriles **6** by following path A (Scheme 3).

The molecular makeup of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles **2** revealed the presence of three electrophilic sites C-2, C-4, and C-6 in which the latter is the most electron deficient due to extended conjugation and the presence of an electron-withdrawing CN substituent at position 3 of the pyran ring. Thus, C-6 position of the pyran ring is attacked by carbon nucleophiles, generated in situ from 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4** in the presence of powdered KOH. The progress of the reaction was clearly observed by evolution of carbon dioxide bubbles. The completion of reaction was monitored by silica gel coated TLC plates.

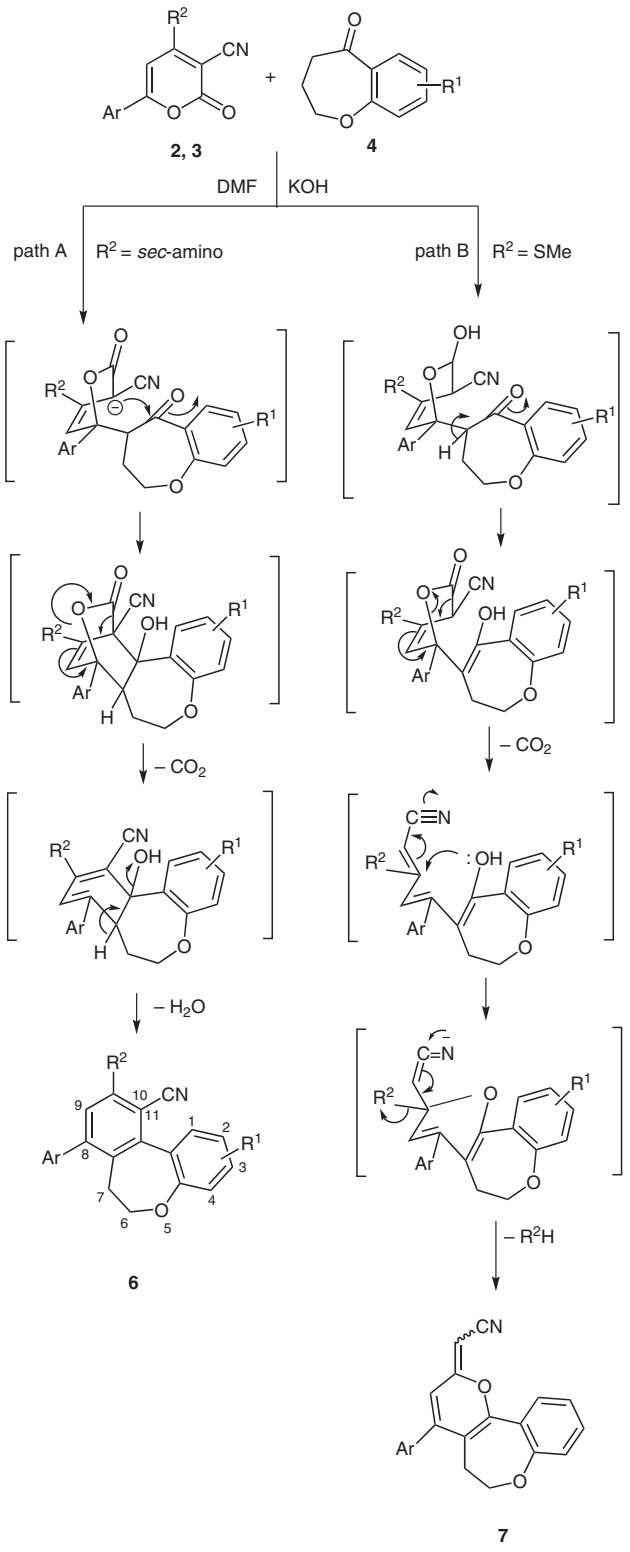
Thus, an equimolar mixture of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles **2** and bicyclic ketone **4** was stirred with anhydrous KOH in DMF for 2–3 hours at room temperature, and the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% aqueous HCl. The resulting precipitate was filtered, washed with water, and dried. The crude product was purified by silica gel column chromatography and compound isolated was identified as an isomeric mixture of (*E*)- and (*Z*)-2-{4-phenyl-5,6-dihydro-2*H*-benzo[*b*]pyrano-[2,3-*d*]oxepin-2-ylidene}acetonitriles **7**. However, compound **6** was obtained by stirring a mixture of 6-aryl-4-s*ec*-amino-2*H*-pyran-2-one **3** and **4** under analogous reaction conditions in the presence of powdered KOH in DMF at room temperature.

In these reactions 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4** have been employed either as a source of carbanion or as precursors for the construction of various 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]-oxepine-3-carbonitriles **5**.

The common initial step in the synthesis of **6** and **7** is formation of Michael adduct by attack of a carbanion generated in situ from 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4** at C-6 of the pyran ring and thereafter, reaction followed either path A or B depending upon the nature of substrate. The Michael adduct so formed underwent ring opening in situ followed by recyclization involving C-3 of pyran ring and carbonyl function of bicyclic ketone **4** to yield exclusively **6**. In the formation of **7**, the Michael adduct underwent enolization followed by Michael addition with subsequent elimination of methyl mercaptan as depicted in Scheme 3.

All the synthesized compounds were characterized by spectroscopic analyses.[20]

In conclusion, we have developed a novel, simple, and economical synthesis of congested 5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepines **5** from the reaction of 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4** and methyl 2-cyano-3,3-dimethylthioacrylate (**1**) in the presence of KOH in DMF. We have also developed an efficient syn-



Scheme 3 A plausible mechanism for the synthesis of 2-(4-phenyl-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepin-2-ylidene)acetonitriles **7** and 8-phenyl-10-*sec*-amino-6,7-dihydrobenzo[*b*,*d*]oxepine-11-carbonitriles **6**

thesis of dibenzo[*b*,*d*]oxepine **6** and an isomeric mixture of (*E*)- and (*Z*)-2-(4-phenyl-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepin-2-ylidene)acetonitriles **7** by the reaction of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitrile **3** and 6-aryl-4-methylthio-2*H*-pyran-2-one **2** with 3,4-dihydro-2*H*-benzo[*b*]oxepin-5(2*H*)-ones **4** separately through C–C insertion not reported so far.

Table 1 Synthesis of Compounds **6** and **7**

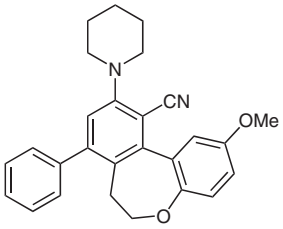
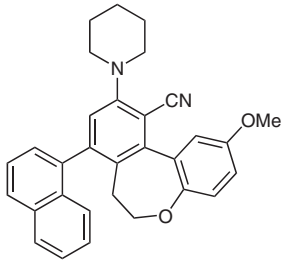
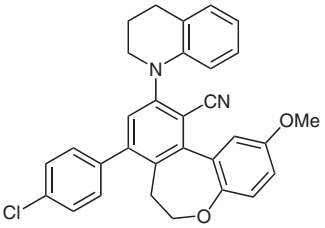
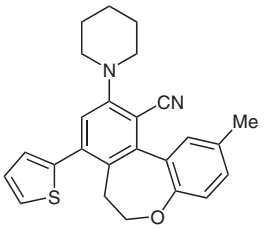
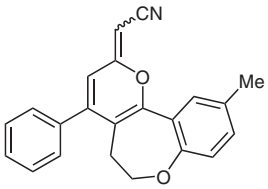
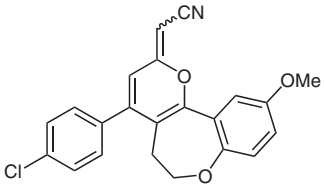
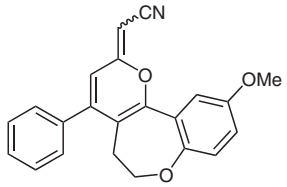
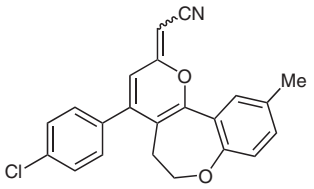
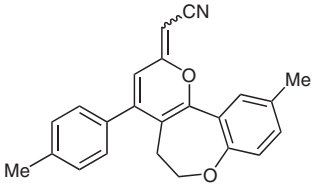
6, **7**	Compound	Mp (°C)	Yield (%)
6a		144	40
6b		188	36
6c		102	38
6d		128	30
7a		116	39
7b		200	55
7c		154	38

Table 1 Synthesis of Compounds **6** and **7** (continued)

6, **7**	Compound	Mp (°C)	Yield (%)
7d		202	39
7e		155	31

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(20) **Data for Compounds**

General Procedure for the Synthesis of 4-Methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (5)

A mixture of 3,4-dihydro-2*H*-benzo[*b*]oxepin-5 (2*H*)-one (1 mmol) and methyl 2-cyano-3,3-dimethylthioacrylate (**1**, 1 mmol) in DMF (8 mL) in the presence of powdered KOH (2 mmol) for 5 h. Excess of DMF was removed under reduced pressure and the residue 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 H_2O, and purified on silica gel column, using 40% hexane in CH_2Cl_2 as eluent.

Compound **5c**: yellow solid; yield 65%; mp 178 °C; IR (KBr): 2956, 2361, 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, 2 H), 3.01 (s, 3 H, SCH_3), 3.83 (s, 3 H, OCH_3), 4.47 (t, 2 H, *J* = 6.0 Hz, OCH_2), 7.03 (s, 1 H, ArH), 7.28 (d, *J* = 9 Hz, 2 H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 18, 27, 55, 75, 93, 112 (2 C), 114, 115, 120, 123, 124, 150, 155, 158, 168. MS: *m/z* = 315 [M^+]. ESI-HRMS: *m/z* calcd for $C_{16}H_{14}NO_4S$: 316.0626 [M^+ + 1]; found: 316.0643.

General Procedure for the Synthesis of 8-Phenyl-10-(*sec*-amino)-6,7-dihydrodibenzo[*b*,*d*]oxepine-11-carbonitriles (6)

A mixture of 3,4-dihydrobenzo[*b*]oxepine-5 (2*H*)-ones **4** (1 mmol) and 6-phenyl-4-(*sec*-amino)-2*H*-pyran-2-one-3-carbonitriles **3** (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 H_2O, and dried. The crude product was purified through silica gel column using a mixture of hexane–CH_2Cl_2 (7:3) as eluent and repurified by abs. MeOH.

Compound **6a**: white solid; yield 44%; mp 144 °C. IR (KBr): 3069, 2934, 2850, 2804, 2370, 2218 (CN), 1573, 1496, 1439 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.52–1.69 (m, 6 H), 3.06 (m, 2 H), 3.20 (m, 4 H), 3.79 (s, 3 H), 4.24 (m, 2 H), 6.97–7.03 (m, 2 H), 7.08 (s, 1 H), 7.24 (d, 1 H, *J* = 3.0 Hz), 7.38–7.48 (m, 5 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 24, 26 (2 C), 28, 53 (2 C), 55, 78, 105, 115, 116, 118, 119, 122, 127 (2 C), 128 (3 C), 132 (2 C), 140, 143, 146, 148, 155, 156. MS: *m/z* = 411 [M^+ + 1], 412 [M^+ + 2]. ESI-HRMS: *m/z* calcd for $C_{27}H_{27}N_2O_2$: 411.20725 [M^+ + 1]; found: 411.20728.

General Procedure for the Synthesis of 2-{4-Phenyl-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-d]oxepin-2-ylidene}-acetonitriles (7)

A mixture of 3,4-dihydrobenzo[*b*]oxepine-5 (2*H*)-ones **4** (1 mmol), 6-(4-phenyl-4-methylthio)-2-oxo-2*H*-pyran-3-

carbonitriles **2** (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 H_2O, and purified on silica gel column using hexane–CH_2Cl_2 mixture (7:3) as eluent.

Compound **7b**: red colored solid; yield 55%; mp 200 °C; IR (KBr): 3077, 2927, 2834, 2368, 2189 (CN), 1639, 1570, 1490, 1404 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (*Z*-isomer, 70%) = 2.50 (s, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 4.26 (s, 2 H, OCH_2), 6.18 (s, 1 H, CH), 6.65–7.43 (m, 8 H, ArH); δ (*E*-isomer, 30%) = 2.41 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 4.35 (s, 2 H, OCH_2), 6.65 (s, 1 H, CH), 6.65–7.43 (m, 8 H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 31, 55, 65, 72, 110, 112, 115, 116, 117, 118, 119, 122 (2 C), 129 (2 C), 135 (2 C), 146, 150, 151, 155, 164. MS: *m/z* = 378 [M^+], 380 [M^+ + 2]. ESI-HRMS: *m/z* calcd for $C_{22}H_{17}ClNO_3$: 378.0897 [M^+ + 1]; found: 378.0889.

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