Synthesis of fluorescent dibenzopyranones by the Diels-Alder reaction of 4-styrylcoumarins and *N*-phenylmaleimide and in situ aromatization using DDQ

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Abstract

Reaction of 7-substituted-4-styrylcoumarins and *N*-phenylmaleimide in nitrobenzene under reflux conditions affords mainly 7-substituted-2,11-diphenyl-3a,10,11,11a-tetrahydro[1]-benzopyrano[3,4-*e*]isoindole-1,3,4(2*H*)-triones. The same reaction in *o*-dichlorobenzene in the presence of DDQ gives the corresponding aromatized dibenzopyranones. The dibenzopyranones are fluorescent and their UV and fluorescence spectra are reported.

Keywords: Diels-Alder reaction, 4-styrylcoumarin, dibenzopyranone

Introduction

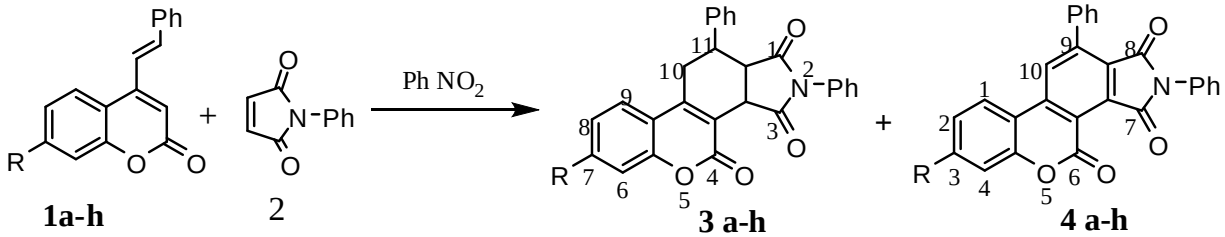
The dibenzopyranone unit is present in many natural products,[1-5] such as alternariol, graphislactones, autumnariol, autumnariniol, and altenuisol, and in many biologically active compounds.[6-7] Such lactones have been used as intermediates in the synthesis of several pharmaceutically interesting compounds including progesterone, androgen, glucocorticoid modulators,[8-10] and endothelial cell proliferation inhibitors.[11] Furthermore, dibenzopyranones occur naturally in many food sources including citrus fruits, herbs, and vegetables.[12] There are several methods available for the synthesis of dibenzopyranones, the most common being Suzuki cross-coupling reaction followed by Lewis acid[13-16] or metal[17] mediated lactonization. More recently, the Diels-Alder cycloaddition of 4-cyanocoumarins (as dienophiles),[18] inverse electron demand Diels-Alder reaction of coumarin fused electron deficient dienes with electron rich dienophiles,[19-21] tert-butyllithium-mediated cyclization of bromobenzylfluorophenyl ethers,[22] and ruthenium-catalyzed cyclotrimerization of aryl diynes[23] have been reported. In 2002, Abbott Laboratories reported a practicable and scalable synthesis of glucocorticoid receptor A-224817.0 through Negishi cross coupling.[24] However, the disadvantages of these methods include low

overall yield, long reaction time, low temperature conditions, multistep sequence, and the need to purify the intermediates.

Diels-Alder reaction of 4-styrylcoumarins with *N*-phenylmaleimide in nitrobenzene is reported to give 7-substituted-2,11-diphenyl-3a,10,11,11a-tetrahydro[1]benzopyrano[3,4-*e*]-isoindole-1,3,4(2*H*)-triones, and no further dehydrogenation is observed.[25-27] Diels-Alder reaction of 4-styrylcoumarins gives an entry to dibenzopyranones. We are hereby reporting a simple route for the synthesis of dibenzopyranones via a tandem Diels-Alder reaction-dehydrogenation of 4-styrylcoumarins (**1**) and *N*-phenylmaleimide (NPMA) (**2**) in the presence of DDQ.

Results and Discussion

7-Methyl-4-styrylcoumarin (**1a**) was prepared by a known method.[28] **1a** was subjected to Diels-Alder reaction with *N*-phenylmaleimide (**2**) (NPMA) in boiling nitrobenzene when adduct **3a** was formed within 10 min. When the reaction was continued further, a small amount of the corresponding dehydrogenated aromatic product **4a** was formed along with **3a**. The reaction was continued up to 24 h to see whether compound **3a** underwent retro Diels-Alder reaction. Instead, **3a** underwent dehydrogenation slowly to form **4a** indicating a nitrobenzene promoted dehydrogenation of **3a**. This was confirmed by aniline produced in the reaction. Dehydrogenation of hydroaromatics under neutral conditions requires high temperature and a catalyst.[29-33] Nitrobenzene is a known dehydrogenating agent, e.g. as in the Skraup synthesis.[34] In the ^{1}H NMR, **4a** showed a multiplet at 7.29-7.55 δ corresponding to aromatic 12 H, a doublet at 8.02 δ for $C_1\underline{H}$, and a singlet at 8.35 δ for $C_{10}\underline{H}$, indicating the dehydrogenation of **3a** to **4a**. No signal was observed for aliphatic protons.



1a-h 2 **3 a-h** **4 a-h**

1a: R=Me **3a**: R=Me **4a**: R=Me

Scheme 1. Diels-Alder reaction of 4-styrylcoumarins with *N*-phenylmaleimide in nitrobenzene.

The dehydrogenation step, i.e. **3** to **4**, was studied further in order to confirm the role of nitrobenzene. **3a** was heated separately in boiling nitrobenzene. The dehydrogenation reaction was very slow and only 9% of **4a** was formed in 24 h. The Diels-Alder adducts **3b** (R=OH), **3c**

(R=OMe) and **3d** (R=H) also gave the corresponding dehydrogenated products **4b**, **4c** and **4d** respectively, in low yield on heating in boiling nitrobenzene (Table 1).

Table 1. Dehydrogenation of Diels-Alder adducts (**3**) in nitrobenzene[a]

Entry	Compound	Time[b] (h)	Product	Yield[c] (%)
1	**3a**	24	**4a**	9
2	**3b**	36	**4b**	13
3	**3c**	36	**4c**	14
4	**3d**	36	**4d**	14

Reaction conditions: **3** (1 mmol); nitrobenzene (5 mL); [a]Reflux temperature; [b]Time for which reaction was continued; [c]Isolated yield.

In order to see the effect of NPMA on the dehydrogenation, we carried out the Diels-Alder reaction with an increasing amount of NPMA. However, the quantity of NPMA was not found to have any effect on the dehydrogenation (Table 2).

Table 2. Effect of increasing quantity of NPMA in the reaction with **1a** on the yield of **4a**

Entry	Equivalent of **2**	Time[b] (h)	Yield[c] of **4a** (%)
1	2	24	6
2	3	24	9
3	4	24	9
4	5	24	10
5	6	24	10

Reaction conditions: **1a** (0.262 g, 1 mmol); nitrobenzene: 5 mL; Temp: Reflux; [b]Time for which reaction was continued; [c]Isolated yield.

The dehydrogenation of **3a** was attempted in the presence of Pd/C (10%), sulfur, napthoquinone, and DDQ, in different solvents (Table 3). DDQ in nitrobenzene and *o*-dichlorobenzene (o-DCB) was found to be the most effective dehydrogenating agent. In xylene, **3a** was partly soluble at the reflux temperature and only a trace of the product was obtained.

Our next objective was to develop a one-pot process, where the Diels-Alder reaction and dehydrogenation would occur subsequently. **1a** was reacted with NPMA in boiling nitrobenzene or o-dichlorobenzene, in the presence of DDQ by varying the mole ratio for NPMA and DDQ (Table 4). Two equivalents of DDQ and three equivalents of NPMA in o-DCB gave 73% yield of **4a** in 1 h. In nitrobenzene, the required time for Diels-Alder-dehydrogenation reaction was shorter, but the yield obtained was 48% and 49% using two and three equivalents of DDQ,

respectively. Surprisingly, though the Diels-Alder reaction in o-DCB was slower as compared to nitrobenzene, the yield in o-DCB was better.

Table 3. Conversion of **3a** to **4a** using of different dehydrogenating reagents and solvents

Entry	Reagent (equiv.)	Solvent[a]	Time[b] (h)	Yield[c] of **4a** (%)
1	Pd/C (10 %), (20 wt %)	Glacial AcOH	12	21
2	Pd/C (10 %), (30 wt %)	Glacial AcOH	18	27
3	Sulfur (4)	Nitrobenzene	18	36
4	Sulfur (4)	*o*-Dichlorobenzene	18	29
5	Naphthoquinone (2)	Nitrobenzene	18	27
6	DDQ (2)	Nitrobenzene	5 min	61
7	DDQ (2)	*o*-Dichlorobenzene	5 min	79
8	DDQ (2)	Xylene	18	Traces

Reaction conditions: **3a** (0.435 g, 1 mmol); Solvent (5 mL); [a]Reflux temp; [b]Time for which reaction was continued; [c]Isolated yield.

Table 4. Diels-Alder reaction of **1a** and NPMA using different mole ratios of NPMA and DDQ in nitrobenzene and o-dichlorobenzene (*o*-DCB)

Entry	(DDQ/NPMA)	Mole ratio **1a**: DDQ/NPMA	Solvent[a]	Time[b] (h)	Yield[c] of **4a** (%)
1	DDQ	1	Nitrobenzene	2	27
2	DDQ	2	Nitrobenzene	15 min	48
3	DDQ	3	Nitrobenzene	15 min	49
4	DDQ	1	*o*-DCB	3	42
5	DDQ	2	*o*-DCB	1	73
6	DDQ	3	*o*-DCB	1	75
7	NPMA	2	*o*-DCB	1.5	64
8	NPMA	4	*o*-DCB	1	73
9	NPMA	5	*o*-DCB	1	75

Reaction conditions: **1a** (0.262 g, 1 mmol); Solvent (5 mL); [a]Reflux temperature; [b]Time for which reaction was continued; For entries (1-6) - NPMA used 3 equiv.; For entries (7-9) – DDQ used 2 equiv.; [c]Isolated yield.

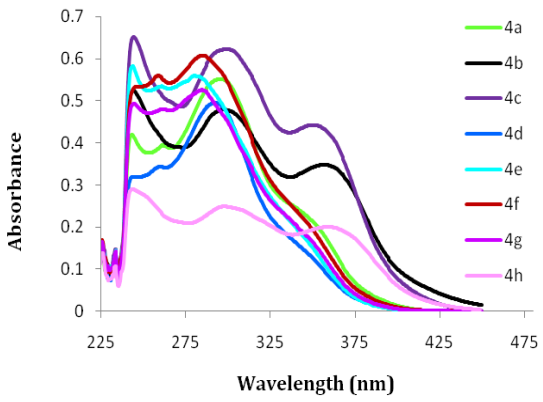
Using the optimized conditions we carried out the reactions for other substrates to study the generality of tandem Diels-Alder-Dehydrogenation reactions. Different 4-styrylcoumarins were prepared by the known procedure.[28] They were reacted with NPMA under the optimized conditions to obtain a series of dibenzopyranones (**4**) (Table 5).

Table 5. Tandem Diels-Alder-dehydrogenation reaction of **1** with NPMA in *o*-dichlorobenzene[a]

Entry	Diene **1**	(R)	Time[b] (min)	Yield[c] of **4**
1	**1a**	Me	60	73
2	**1b**	OH	75	71
3	**1c**	OMe	75	69
4	**1d**	H	70	66
5	**1e**	OTs	85	61
6	**1f**	OAc	85	63
7	**1g**	Cl	80	67
8	**1h**	$NHCO_2Et$	75	72

Reaction conditions: mole ratio **(1**: NPMA) 1:3 equiv.; **1**: DDQ 2 equiv.; [a]Reflux temperature; [b]Time for which reaction was continued; [c]Isolated yield.

Compounds **4** showed fluorescence. Hence, their UV absorption and emission properties were studied in chloroform + methanol (1:1, v/v) (Figure 1, Table 6). In the same solvent system standards anthracene and fluorescein show fluorescence at 488 and 513 nm respectively. UV (λ_{abs} max) and emission (λ_f max) depended upon the nature of the substituent on the coumarin ring. High stoke shift ($\Delta\lambda_f$-abs) was observed in the case of **4a**, **4b**, and **4c**. This may be ascribed to the increased π-electron density on the coumarin ring, due to the presence of electron donating groups –Me, –OH, -OCH_3. The other substituents showed poor stokes shift.



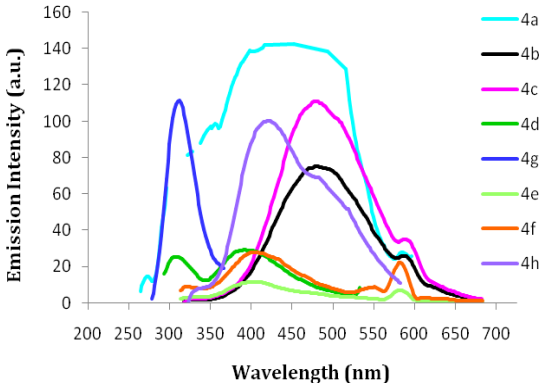


Figure 1. Absorption and emission spectra of **4a-4h.**

Table 6. UV-Vis absorption (λ_{abs} max) and fluorescence (λ_f max) of **4**

Entry	Product	R	λ_{abs} max (nm)	λ_f max (nm)	Extinction coefficient Lit $mol^{-1}cm^{-1}$	$\Delta\lambda f_{-abs}$ (nm)
1	**4a**	Me	295	452	23762	157
2	**4b**	OH	296	478	20745	182
3	**4c**	OMe	297	480	27805	183
4	**4d**	H	292	400	20634	108
5	**4e**	OTs	292	394	32826	102
6	**4f**	OAc	291	396	28862	105
7	**4g**	Cl	284	308	23692	24
8	**4h**	$NHCO_2Et$	300	415	12550	115

Solvent: chloroform + methanol (1:1, v/v); concentration of **4**: 10 ppm; Temperature 28-30 ^oC.

Conclusions

We have developed a protocol for the synthesis of dibenzopyranones by the tandem Diels-Alder dehydrogenation reaction. DDQ in *o*-dichlorobenzene is the best dehydrogenating agent. These dibenzopyranones are pale yellow to yellow in color and show emission under UV light (365 nm).

Experimental Section

General. The melting points were determined on an Analab melting point apparatus (Model-μThermocal 10) in open capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin-Elmer spectrum-100 FTIR spectrophotometer. The ^1H NMR spectra were recorded on Varian Mercury plus 300 (300 MHz) spectrometer in $CDCl_3$/DMSO-d_6 with TMS as an internal standard and the chemical shifts are expressed in δ unit (ppm). The Mass spectra were recorded on a Finnigan LCQ Advantage Max spectrometer. Elemental analysis was carried out on a Thermo finnigan, Flash EA 1112. UV spectra were recorded on a Shimadzu UV-1601, UV–VIS Spectrophotometer. Fluorescence spectra were recorded on a Cary Eclipse fluorescence Spectrophotometer. Absorption and Emission spectra were performed using quartz cell (1 x 1 cm). All compounds are excited at their absorption values shown in table no 6. Emission range

was kept as 250-675 nm. Absorption and Emission spectra were performed using quartz cell (1 x 1 cm). Emission and excitation slit had the width equal to 5 constant for all measurements.

Diels-Alder reaction followed by dehydrogenation reaction of 1a with NPMA (2) without DDQ in nitrobenzene. 1a (0.262 g, 1 mmol) and NPMA (0.519 g, 3 mmol) were refluxed in nitrobenzene (5 mL) for 24 h. The solution was cooled to room temperature, n-hexane (15 mL) was added and the solution stirred for 30 min. The precipitated solid was filtered and subjected to column chromatography to obtain **4a** using silica gel in chloroform.

General procedure for dehydrogenation of Diels-Alder adduct (3) in nitrobenzene
3 (1 mmol) was refluxed in nitrobenzene (5 mL) for 24 h. The solution was cooled to room temperature. n-Hexane (15 mL) was added and the solution was stirred for 30 min. The precipitated solid was filtered and subjected to column chromatography using silica gel in chloroform.
Tandem Diels-Alder dehydrogenation reaction of 1a in nitrobenzene. 1a (0.262 g, 1 mmol), NPMA (0.519 g, 3 mmol) and DDQ (0.454 g, 2 mmol) were refluxed in nitrobenzene for 15 min. After the completion of reaction, the solution was cooled to room temperature. n-Hexane (15 mL) was added to the solution and stirred for 30 min. The solvent was decanted and the insoluble mass was subjected to column chromatography using silica gel in chloroform.

General procedure for tandem Diels-Alder dehydrogenation reaction in *o*-dichlorobenzene
1 (1 mmol), NPMA (0.519 g, 3 mmol) and DDQ (0.454 g, 2 mmol) were refluxed in *o*-dichlorobenzene for 1 h. After the completion of reaction, the solution was cooled to room temperature. Reduced DDQ was separated from the reaction mixture by filtration. n-Hexane (15 mL) was added to the filtrate and stirred for 30 min. The solvent was decanted and the insoluble mass was subjected to column chromatography using silica gel in chloroform.
***N*-Phenyl-3-methyl-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide (4a).** Pale yellow solid; yield: 73%; mp 272-273 ºC (from MeOH); IR (KBr): 1780, 1754, 1717 (CO), 1606, 1499 (aromatic C=C), 1384 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, $C\underline{H}_3$), 7.29-7.55 (m, 12H, Ar<u>H</u>), 8.02 (d, *J* 8.7 Hz, 1H, C_1H), 8.35 (s, 1H, C_{10}H); MS: *m/z* 432.4 (M+H); Anal. Calcd. for $C_{28}H_{17}NO_4$: C, 77.95; H, 3.97; N, 3.25. Found: C, 77.87; H, 3.73; N, 3.12.
***N*-Phenyl-3-hydroxy-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide (4b).** Yellow solid; yield: 71%; mp 288-289 ºC (from MeOH); IR (KBr): 3120 (OH), 1775, 1742, 1720 (CO), 1611 (aromatic C=C), 1374 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.76 (d, *J* 2 Hz, 1H, $C_4\underline{H}$), 6.83 (dd, *J* 2 and 8 Hz, 1H, $C_2\underline{H}$), 7.42-7.52 (m, 8H, Ar<u>H</u>), 7.72-7.73 (bs, 2H, Ar<u>H</u>), 8.40 (d, *J* 8 Hz, 1H, $C_1\underline{H}$), 8.53 (s, 1H, $C_{10}\underline{H}$), 10.68 (s, 1H, O*H*); MS: *m/z* 434.3 (M+H); *Anal*. Calcd. for $C_{27}H_{15}NO_5$: C, 74.82; H, 3.49; N, 3.23. Found: C, 74.98; H, 3.35; N, 3.16.
***N*-Phenyl-3-methoxy-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide (4c).** Pale yellow solid; yield: 69%; mp 265-266 ºC (from MeOH); IR (KBr): 1777, 1754, 1723 (CO), 1610 (aromatic C=C), 1372 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H, $OC\underline{H}_3$), 6.92 (dd, *J* 2.4

& 8.7 Hz, 1H, C_2H), 6.96 (d, *J* 2.4 Hz, 1H, C_4H), 7.32-7.63 (m, 10H, ArH), 8.00 (d, *J* 8.7, 1H, 1-CH), 8.27 (s, 1H, C_{10}H); MS: *m/z* 448.5 (M+H); *Anal*. Calcd. for $C_{28}H_{17}NO_5$: C, 75.16; H, 3.83; N, 3.13. Found: C, 75.08; H, 3.89; N, 3.16.

***N*-Phenyl-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide (4d).** Pale yellow solid; yield: 66%; mp 289-290 ºC (from $CHCl_3$); IR (KBr): 1782, 1761, 1720 (CO), 1608, 1503 (aromatic C=C), 1373 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.65 (m, 13H, ArH), 8.13 (d, *J* 8.21 Hz, 1H, C_1H), 8.42 (s, 1H, C_{10}H); MS: *m/z* 418.3 (M+H); *Anal*. Calcd. for $C_{27}H_{15}NO_4$: C, 77.69; H, 3.62; N, 3.36. Found: C, 77.50; H, 3.58; N, 3.21.

***N*-Phenyl-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide-3-yl tosylate (4e).** Pale yellow solid; yield: 61%; mp 275-276 ºC (from MeOH); IR (KBr): 1772, 1763, 1720 (CO), 1614, 1500 (aromatic C=C), 1376 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3), 6.95 (d, *J* 2.1 Hz, 1H, C_4H), 7.19 (dd, *J* 2.1 and 8.7 Hz, 1H, C_2H), 7.35-7.62 (m, 12H, ArH), 7.76 (d, 2H, ArH), 8.09 (d, *J* 8.7 Hz, 1H, C_1H), 8.33 (s, 1H, C_{10}H); MS: *m/z* 588.6 (M+H); *Anal*. Calcd. for $C_{34}H_{21}NO_7S$: C, 69.50; H, 3.60; N, 2.38. Found: C, 69.38; H, 3.51; N, 2.48.

***N*-Phenyl-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide-7-yl acetate (4f).** Yellow solid; yield: 63%; mp 284-285 ºC (from MeOH); IR (KBr): 1780, 1761, 1721 (CO), 1609 (aromatic C=C), 1379 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CO-CH_3), 7.17 (dd, *J* 2.4 and 8.7 Hz, 1H, C_2H), 7.25 (d, *J* 2.4 Hz, 1H, C_4H), 7.36-7.64 (m, 10H, ArH), 8.12 (d, *J* 8.7 Hz, 1H, C_1H); 8.35 (s, 1H, C_{10}H); MS: *m/z* 476.6 (M+H); *Anal*. Calcd. for $C_{29}H_{17}NO_6$: C, 73.26; H, 3.60; N, 2.95. Found: C, 73.41; H, 3.44; N, 2.82.

***N*-Phenyl-3-chloro-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide (4g).** Pale yellow solid; yield: 67%; mp 296-297 ºC (from MeOH); IR (KBr): 1777, 1760, 1724 (CO), 1607, 1500 (aromatic C=C), 1373 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42-7.52 (m, 9H, ArH), 7.64 (bs, 1H, ArH), 7.74 (bs, 2H, ArH), 8.66 (d, *J* 6.6 Hz, 1H, C_1H), 8.73 (s, 1H, C_{10}H); MS: *m/z* 452.8 (M+H). *Anal*. Calcd. for $C_{27}H_{14}ClNO_4$: C, 71.77; H, 3.12; N, 3.10. Found: C, 71.63; H, 3.19; N, 3.12.

***N*-Phenyl-9-phenyl-6-oxo-6*H*-dibenzo[*b,d*]pyran-7,8-dicarboximide-7-yl-ethylcarbamate (4h).** Yellow solid; yield: 72%; mp > 300 ºC (from MeOH); IR (KBr): 3512 (NH), 1777, 1755, 1731 (CO), 1614, 1548 (aromatic C=C), 1367, 1234 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* 6 Hz, 3H, CH_3), 3.93 (s, 1H, NH), 4.19 (q, *J* 6 Hz, 2H, CH_2), 7.32-7.56 (m, 12H, ArH), 7.97 (d, *J* 8 Hz, 1H, C_1H), 8.27 (s, 1H, C_{10}H); MS: *m/z* 505.3 (M+H). *Anal*. Calcd. for $C_{30}H_{20}N_2O_6$: C, 71.42; H, 4.00; N, 5.55. Found: C, 71.32; H, 3.88; N, 5.42.

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