Synthesis and X-ray powder diffraction data of *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline

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The 2,4-diaryl 1,2,3,4-tetrahydroquinoline derivative (1), described in the title (Chemical formula: $C_{23}H_{22}N_2O_3$), was synthesized via the "one-pot" three-component imino Diels–Alder reaction catalyzed by $Cu(OTf)_2$. Molecular characterization was performed by ^1H and ^{13}C NMR, Fourier transform-infrared, and gas chromatography-mass spectrometry. The X-ray powder diffraction pattern for the title compound was analyzed and found to be crystallized in an orthorhombic system with space group $P2_12_12_1$ (No. 19) and refined unit-cell parameters $a = 8.6415(8)$ Å, $b = 12.679(2)$ Å, $c = 17.601(2)$ Å, and $V = 1928.4(2)$ Å^3. © *2013 International Centre for Diffraction Data*.
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Key words: imino Diels–Alder reaction, tetrahydroquinoline, three-component reaction, X-ray powder diffraction

I. INTRODUCTION

Heterocyclic systems with quinoline and tetrahydroquinoline nucleus are known as a remarkable class of natural and synthetic compounds, being privileged moieties in medicinal chemistry. Many pharmaceutical agents and different natural products with significant biological activity are built on the (tetrahydro)quinoline scaffolds (Katritzky *et al.*, 1996; Kouznetsov *et al.*, 1998). A large number of reports showed that these compounds display a wide spectrum of biological activities, including antimalarial activity (Bendale *et al.*, 2007), estrogenic receptor (Wallace *et al.*, 2003; Chen, *et al.*, 2007), anti-inflammatory behavior (Calhoun *et al.* 1995), among others.

In accordance with the importance of the compounds possessing these skeletons, there is a large list of methods developed for their synthesis (Sridharan *et al.*, 2011). Among them, the cycloaddition reactions stand out as powerful reactions to construct rapidly the tetrahydroquinoline systems. The Lewis acid-catalyzed imino Diels–Alder reaction between aldimines and electron-rich alkenes or its three-component version is probably the most powerful and successful synthetic tool to construct rapidly N-containing six-membered heterocyclic compounds, including tetrahydroquinolines (Buonora, *et al.*, 2001; Glushkov and Tolstikov, 2008; Kouznetsov, 2009). Recently, interesting chemical transformation with phenylpropenoid derivatives (electron-rich alkenes, e.g. *trans*-anethole) as dienophiles in this cycloaddition process for obtaining 2,4-diaryl 1,2,3,4-tetrahydroquinoline derivatives under green conditions was reported by our laboratory (Kouznetsov *et al.*, 2007; Kouznetsov *et al.*, 2008) and others (He *et al.*, 2012). In this regard, our ongoing research program focused on the chemistry of the bioactive tetrahydroquinoline derivatives with anethole fragments (Romero *et al.*, 2012). In this work, we report the X-ray powder diffraction (XRPD) data of the compound *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (**1**) prepared using a commercial *trans*-anethole as a dienophile in the "one-pot" three-component imino Diels–Alder reaction (Povarov reaction) catalyzed by the Lewis acid $Cu(OTf)_2$ and starting from the corresponding 4-nitroaniline and benzaldehyde (Romero *et al.*, 2011).

II. EXPERIMENTAL

A. Synthesis

As shown in Figure 1, the title compound was synthesized according to the following experimental procedure: a mixture of 4-nitroaniline (2.90 mmol) and benzaldehyde (3.19 mmol) in anhydrous CH_3CN (15 ml) was stirred at room temperature for 30 min. Then, $Cu(OTf)_2$ (0.29 mmol) was added in solution into the mixture. Over a period of 30 min, a solution of commercial *trans*-anethole (3.48 mmol) in CH_3CN (10 ml) was added dropwise. The resulting mixture was stirred at room temperature for 16 h (overnight). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (30 ml) and extracted with ethyl acetate (3 times × 15 ml). The organic layer was separated and dried (Na_2SO_4), concentrated under vacuum and the crude product was purified by column chromatography using silica gel (between 60 and 120 mesh) and eluted with petroleum ether–ethyl acetate to afford pure title tetrahydroquinoline (**1**) (yield 98%). This compound was obtained as yellow solid with melting point between 203 and 204 °C (uncorrected) recrystallizing by slow evaporation in dichloromethane solution.

Its structural characterization was achieved by the use of Fourier transform-infrared spectroscopy (FT-IR) and mass spectrometry with electron impact (MS-EI). Analysis revealed the

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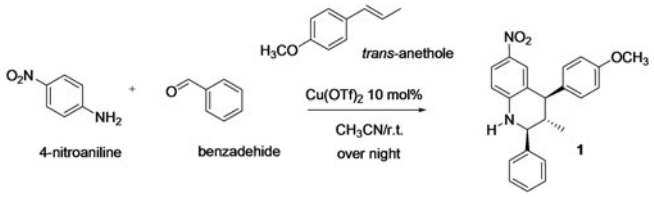

Figure 1. Synthesis of *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (**1**) via "one pot" three-component imino Diels–Alder reaction.

following characteristic absorption bands 3448, 3339, 1610, 1495, and 1305 cm^{-1} (FT-IR) and a molecular peak m/z: = 374 (15, $M^{+\bullet}$) (MS-EI). In addition, nuclear magnetic resonance on protons (^{1}H NMR) (400 MHz, $CDCl_3$ Me_4Si) and nuclear magnetic resonance on carbons (^{13}C-NMR) (100 Hz, $CDCl_3$ Me_4Si), were performed to confirm the molecular structure of the title compound. Proton spectrum revealed the following data: δ (ppm), 0.58 (3H, d, J = 6.5 Hz, –CH_3), 2.15 (1H, m, 3-H), 3.70 (1H, d, J = 11.2 Hz, 2-H), 3.83 (3H, s, Ar-OCH_3), 4.23 (1H, d, J = 10.0 Hz, 4-H), 4.87 (1H, s, NH), 6.44 (1H, d, J = 8.9 Hz, 8-H), 6.90 (2H, d, J = 8.6 Hz, 2′-H_{Ar}), 7.11 (2H, d, J = 8.6 Hz, 3′-H_{Ar}), 7.35–7.40 (5H, m, all-H_{Ar}), 7.48 (1H, br s, 5-H), and 7.90 (1H, dd, J = 8.9, 2.4 Hz, 7-H). Similarly, its carbon spectrum offered the following data: δ (ppm), 158.7, 150.2, 141.2, 138.0, 133.8, 130.1, 128.9, 128.5, 127.7, 126.6, 124.8, 124.2, 114.4, 112.2, 63.6, 55.2, 50.6, 40.1, and 16.2. In this way, both spectroscopy methods established the tetrahydroquinoline structure of the title compound.

B. Powder data collection

A small amount of the compound $C_{23}H_{22}N_2O_3$ was gently ground in an agate mortar and sieved to a grain size of less than 38 μm. The specimen was mounted on a zero-background specimen holder (Buhrke *et al.*, 1998) for the respective measurement. The XRPD data were collected at 295 K with D8 FOCUS BRUKER diffractometer operating in Bragg-Brentano geometry equipped with a Cu-target X-ray tube (40 kV and 40 mA), a nickel filter, and an one-dimensional LynxEye detector. A fixed antiscatter slit of 8 mm, receiving slit of 1 mm, soller slits of 2.5°, and a detector slit of 3 mm were used. The scan range was from 2 to 70° 2θ with a step size of 0.02° 2θ and a counting time of 0.4 s per step.

POWDERX program (Dong, 1999) was used to remove the background (Sonneveld and Visser, 1975), smoothing (Savitzky and Golay, 1964), to eliminate the $K\alpha_2$ component (Rachinger, 1948) and the second derivative method was used to determine the positions and intensities of the diffraction peaks.

III. RESULTS AND DISCUSSION

The XRPD pattern of *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline is shown in Figure 2 and the data for this compound are given in Table I. The XRPD pattern was successfully indexed using the DICVOL06 program (Boultif and Louër, 2006) on an orthorhombic cell with an absolute error of ±0.03°2θ in the calculations. The space group, $P2_12_12_1$ (No. 19), was estimated by the CHEKCELL program (Laugier and Bochu, 2002) that was compatible with the systematic absences and with the crystal density, 1.288 g/cm^3. The unit-cell parameters were refined with the NBS*AIDS83 program (Mighell *et al.*, 1981). The crystal data, X-ray density as well as figures of merit M_{20} (de Wolff, 1968) and F_{20} (Smith and Snyder, 1979) are compiled in Table II.

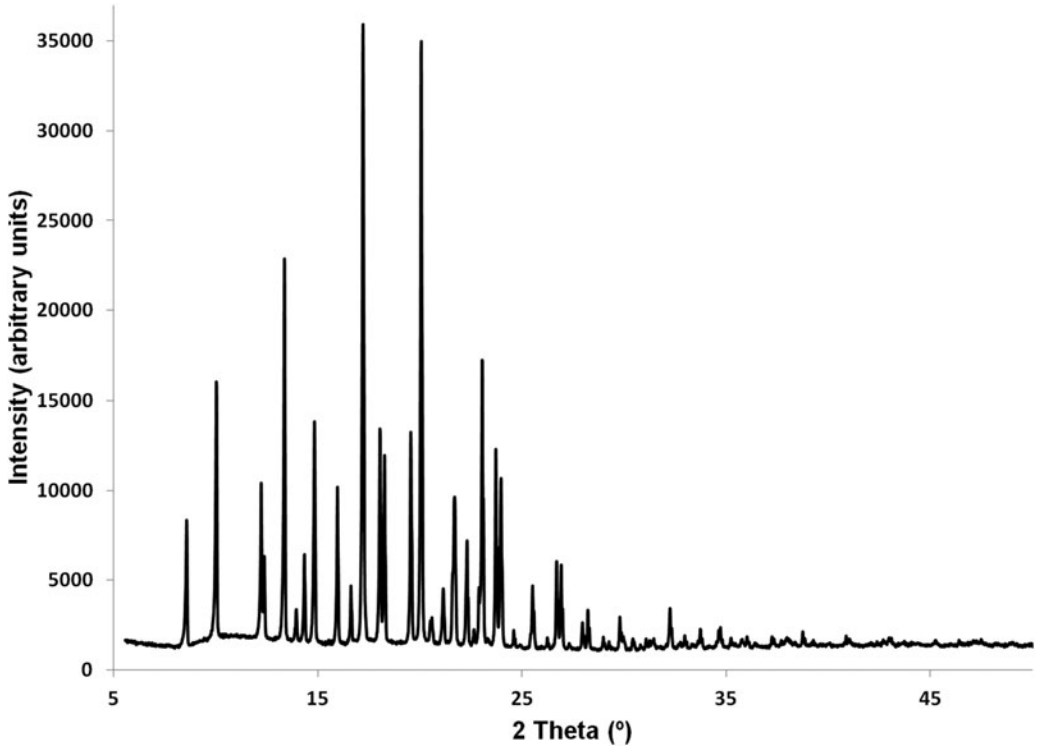

Figure 2. X-ray powder diffraction pattern of *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (**1**).

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TABLE I. X-ray powder diffraction data of *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (**1**). Cu$K\alpha_1$ radiation ($\lambda = 1.5406$ Å).

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_0)_{obs}$	h	k	l	$2\theta_{calc}$ (°)	d_{calc} (Å)	$\Delta 2\theta$ (°)
8.583	10.2937	23	0	1	1	8.588	10.2876	0.005
10.040	8.8031	45	0	0	2	10.043	8.8006	0.003
12.237	7.2271	29	0	1	2	12.233	7.2296	−0.004
12.382	7.1428	17	1	1	0	12.386	7.1406	0.004
13.375	6.6146	64	1	1	1	13.370	6.6169	−0.005
13.955	6.3410	9	0	2	0	13.958	6.3394	0.003
14.355	6.1652	18	1	0	2	14.353	6.1659	−0.002
14.848	5.9616	38	0	2	1	14.841	5.9644	−0.007
15.974	5.5438	28	1	1	2	15.971	5.5450	−0.003
16.637	5.3243	12	0	1	3	16.636	5.3246	−0.001
17.225	5.1439	100	0	2	2	17.225	5.1438	0.000
18.058	4.9084	38	1	2	1	18.057	4.9087	−0.001
18.272	4.8514	33	1	0	3	18.262	4.8540	−0.010
19.568	4.5329	37	1	1	3	19.567	4.5331	−0.001
20.075	4.4196	99	1	2	2	20.073	4.4200	−0.002
20.522	4.3243	7	2	0	0	20.539	4.3207	0.017
20.597	4.3087	7	0	2	3	20.610	4.3060	0.013
21.154	4.1965	13	2	0	1	21.156	4.1961	0.002
21.615	4.1080	14	0	3	1	21.607	4.1095	−0.008
21.707	4.0908	27	2	1	0	21.713	4.0898	0.006
22.316	3.9806	20	2	1	1	22.299	3.9836	−0.017
22.659	3.9211	6	1	0	4	22.658	3.9212	−0.001
22.919	3.8772	12	2	0	2	22.911	3.8785	−0.008
23.064	3.8531	50	1	2	3	23.059	3.8540	−0.005
23.319	3.8116	5	0	3	2	23.330	3.8097	0.011
23.731	3.7463	34	1	1	4	23.732	3.7461	0.001
			1	3	1	23.959	3.7112	
23.977	3.7084	30	2	1	2	23.974	3.7088	−0.003
24.607	3.6149	6	0	2	4	24.608	3.6148	0.001
24.906	3.5722	4	2	2	0	24.919	3.5703	0.013
25.437	3.4988	5	2	2	1	25.435	3.4991	−0.002
25.532	3.4860	13	1	3	2	25.532	3.4860	0.000
26.251	3.3921	4	0	1	5	26.253	3.3919	0.002
26.711	3.3347	17	1	2	4	26.710	3.3348	−0.001
26.930	3.3081	16	2	2	2	26.927	3.3084	−0.003
27.319	3.2619	4	1	0	5	27.334	3.2601	0.015
27.973	3.1871	7	1	3	3	27.970	3.1874	−0.003
28.239	3.1577	10	1	1	5	28.242	3.1574	0.003
28.992	3.0774	5	0	2	5	28.990	3.0776	−0.002
			2	2	3	29.258	3.0500	
29.270	3.0488	4	0	3	4	29.277	3.0481	0.007
29.805	2.9952	8	2	1	4	29.801	2.9957	−0.004
			0	4	2	29.939	2.9822	
29.967	2.9794	5	2	3	1	29.984	2.9777	0.017
			1	4	0	30.004	2.9758	
30.440	2.9342	4	1	4	1	30.440	2.9342	0.000
			0	0	6	30.447	2.9335	
30.812	2.8996	4	1	2	5	30.816	2.8992	0.004
31.091	2.8742	4	1	3	4	31.088	2.8745	−0.003
31.272	2.8580	4	0	1	6	31.272	2.8580	0.000
			2	3	2	31.277	2.8576	
31.463	2.8411	5	3	0	1	31.445	2.8427	−0.018
			3	1	1	32.247	2.7738	
32.260	2.7727	9	2	2	4	32.262	2.7725	0.002
32.984	2.7135	5	1	1	6	32.984	2.7135	0.000
33.625	2.6632	4	0	2	6	33.636	2.6623	0.011
33.746	2.6539	6	1	4	3	33.745	2.6540	−0.001
34.544	2.5944	4	3	2	1	34.552	2.5938	0.008
34.641	2.5874	6	3	0	3	34.664	2.5857	0.023
34.731	2.5809	6	1	3	5	34.724	2.5813	−0.007
35.247	2.5443	5	1	2	6	35.246	2.5443	−0.001
			0	5	1	35.746	2.5099	
35.783	2.5074	4	2	2	5	35.793	2.5067	0.010
36.027	2.4909	5	2	3	4	36.031	2.4907	0.004

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TABLE I. Continued

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_0)_{obs}$	h	k	l	$2\theta_{calc}$ (°)	d_{calc} (Å)	$\Delta 2\theta$ (°)
36.403	2.4661	4	0	1	7	36.398	2.4664	−0.005
			1	4	4	36.419	2.4650	
			1	0	7	37.212	2.4143	
37.259	2.4114	5	1	5	1	37.277	2.4103	0.018
			3	0	4	37.280	2.4100	
			0	3	6	37.283	2.4099	
37.708	2.3837	4	2	1	6	37.707	2.3837	−0.001
37.987	2.3668	5	3	1	4	37.973	2.3676	−0.014
38.760	2.3214	6	1	3	6	38.761	2.3213	0.001
39.275	2.2921	4	2	3	5	39.265	2.2927	−0.010
40.883	2.2056	5	3	3	3	40.882	2.2056	−0.001
			2	3	6	42.938	2.1047	
			3	2	5	42.973	2.1030	
42.989	2.1023	5	1	1	8	42.982	2.1026	−0.007
			0	6	1	43.079	2.0981	
43.108	2.0968	5	1	3	7	43.116	2.0964	0.008
			4	1	2	43.695	2.0699	
43.734	2.0682	4	2	4	5	43.735	2.0682	0.001
			3	4	3	45.220	2.0036	
			4	1	3	45.262	2.0019	
45.266	2.0017	4	1	5	5	45.268	2.0016	0.002
46.420	1.9546	4	3	2	6	46.406	1.9551	−0.014
47.499	1.9127	5	4	3	1	47.510	1.9122	0.011

TABLE II. Crystal-structure data for *cis*-4-(4-methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (**1**).

a (Å)	8.6415 (8)
b (Å)	12.679 (2)
c (Å)	17.601 (2)
V (Å^3)	1928.4 (2)
Z	4
M_{20}	58.7
F_{30}	153.0 (0.0053, 37)
D_m	1.288 g/cm^3

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Bendale, P., Olepu, S., Kumar, S. P., Buldule, V., Rivas, K., Nallan, L., Smart, B., Yokoyama, K., Ankala, S., Pendyala, P. R., Floyd, D., Lombardo, L. J., Williams, D. K., Buckner, F. S., Chakrabarti, D., Verlinde, C. L. M. J., Van Voorhis, W. C., and Gelb, M. H. (**2007**). "Second generation tetrahydroquinoline-based protein farnesyltransferase inhibitors as antimalarials," J. Med. Chem. **50**, 4585–4605.

Boultif, A. and Louër, D. (**2006**). "Indexing of powder diffraction patterns of low symmetry lattices by successive dichotomy method," J. Appl. Crystallogr. **37**, 724–731.

Buhrke, V., Jenkins, R., and Smith, D. (**1998**). *Preparation of Specimens for X-ray Fluorescence and X-ray Diffraction Analysis* (Wiley, New York), pp. 141–142.

Buonora, P., Olsen, J-C., and Oh, T. (**2001**). "Recent developments in imino Diels–Alder reactions," Tetrahedron. **57**, 6099–6138.

Calhoun, W., Carlson, R. P., Crossley, R., Datko, L. J., Dietrich, S., Heatherington, K., Marshall, L. A., Meade, P. J., Opalko, A., and Shepherd, R. G. (**1995**). "Synthesis and antiinflammatory activity of certain 5,6,7,8-tetrahydroquinolines and related compounds," J. Med. Chem. **38**, 1473–1481.

Chen, W., Lin, Z., Ning, M., Yang, C., Yan, X., Xie, Y., Shen, X., and Wang, M. W. (**2007**). "Aza analogues of equol: novel ligands for estrogen receptor beta," Bioorg. Med. Chem. **15**, 5828–5836.

de Wolff, P. M. (**1968**). "A simplified criterion for the reliability of a powder pattern," J. Appl. Crystallogr. **1**, 108–113.

Dong, C. (**1999**). "PowderX: Windows-95-based program for poder X-ray diffraction data processing," J. Appl. Crystallogr. **32**, 838–838.

Glushkov, V. A., and Tolstikov, A. G. (**2008**). "Synthesis of substituted 1,2,3,4-tetrahydroquinones by the Povarov reaction. New potentials of the classical reaction," Russ. Chem. Rev. (Engl. Transl.) **77**, 137–159.

He, L., Bekkaye, M., Retailleau, P., and Masson, G. (**2012**). "Chiral phosphoric acid catalyzed inverse electron-demand aza-Diels–Alder reaction of isoeugenol derivatives," Org. Lett. **14**, 3158–3161.

Katritzky, A. R., Rachwal, S., and Rachwal, B. (**1996**). "Recent progress in the synthesis of 1,2,3,4 tetrahydroquinolines," Tetrahedron. **52**, 15031–15070.

Kouznetsov, V. V. (**2009**). "Recent synthetic developments in a powerful imino Diels–Alder reaction (Povarov Reaction): application to the synthesis of N-polyheterocycles and related alkaloids," Tetrahedron **65**, 2721–2750.

Kouznetsov, V. V., Palma, A., Ewert, C., and Varlamov, A. (**1998**). "Some aspects of reduced quinoline chemistry," J. Heterocycl. Chem. **35**, 761–785.

Kouznetsov, V. V., Romero Bohórquez, A. R., and Stashenko, E. E., (**2007**). "Three-component imino Diels–Alder reaction with essential oil and seeds of anise: generation of new tetrahydroquinolines," Tetrahedron Lett. **48**, 8855–8860.

Kouznetsov, V. V., Merchan, A. D., and Romero, B. A. R. (**2008**). "PEG-400 as green reaction medium for Lewis acid-promoted cycloaddition reactions with isoeugenol and anethole," Tetrahedron Lett. **49**, 3097–3100.

Laugier, J. and Bochu, B. (**2002**). *CHEKCELL*. "LMGP-Suite Suite of Programs for the interpretation of X-ray. Experiments," ENSP/Laboratoire des Matériaux et du Génie Physique, BP 46. 38042 Saint Martin d'Hères, France. http://www.inpg.fr/LMGP and http://www.ccp14.ac.uk/tutorial/lmgp/.

Miguell, A. D., Hubberd, C. R., and Stalick, J. K. (**1981**). "NBS* AIDS80: A FORTRAN program for crystallographic data evaluation," National Bureau of Standards (USA), Tech. Note 1141.

Rachinger, W. A. (**1948**). "A correction for the α_1 α_2 doublet in the measurement of widths of X-ray diffraction lines," J. Sci. Instrum. **25**, 254.

Romero Bohórquez, A. R., Kouznetsov, V. V., and Doyle, M. P. (**2011**). "*Cu (OTf)$_2$*-Catalyzed three-component imino Diels–Alder reaction using propenylbenzenes: synthesis of 2,4-diaryl tetrahydroquinoline derivatives," Lett. Org. Chem. **8**, 5–11.

Romero Bohórquez, A. R., Escobar, P., Leal, S. M., and Kouznetsov, V. V. (**2012**). "*In vitro* activity against *Trypanosoma cruzi* and *Leishmania chagasi* Parasites of 2,4-Diaryl 1,2,3,4-Tetrahydroquinoline derivatives," Lett. Drug Des. Discov. **9**, 802–808.

Saviztky, A. and Golay, M. J. (**1964**). "Smoothing and differentiation of data by simplified least squares procedures," Anal. Chem. **36**, 1627–1639.

Smith, G. S. and Snyder, R. L. (**1979**). "F_N: a criterion for rating powder diffraction patterns and evaluating the reliability of powder-pattern indexing," J. Appl. Crystallogr. **12**, 60–65.

Sonneveld, E. J. and Visser, J. W. (**1975**). "Automatic collection of powder diffraction data from photographs," J. Appl. Crystallogr. **8**, 1–7.

Sridharan, V., Suryavanshi, P. A. and Menéndez, J. C. (**2011**). "Advances in the chemistry of tetrahydroquinolines," Chem. Rev. **111**, 7157–7259.

Wallace, O. B., Lauwers, K. S., Jones, S. A. and Dodge, J. A. (**2003**). "Tetrahydroquinoline-based selective estrogen receptor modulators (SERMs)," Bioorg. Med. Chem. Lett. **13**, 1907–1910.

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