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A simple entry to novel spiro dihydroquinoline-oxindoles using Povarov reaction between 3-*N*-aryliminoisatins and isoeugenol

Vladimir V. Kouznetsov *, Josué S. Bello Forero, Diego F. Amado Torres

Laboratorio de Química Orgánica y Biomolecular, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia

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ABSTRACT

An easy, fast, and cheap way for the synthesis of the new 4′-(4-hydroxy-3-methoxyphenyl)-3′-methyl-3′,4′-dihydro-1′*H*-spiro[indoline-3,2′-quinolin]-2-ones using $BF_3{\cdot}OEt_2$-promoted imino Diels–Alder cycloaddition between ketimine-isatin derivatives and *trans*-isoeugenol.

Tetrahydroquinoline and spiro-quinoline derivatives[1] occupy a special place in organic and medicinal chemistry, because these compounds are well-known as melanocortin receptors (MC4) agonists,[2] antipsychotics,[3] acetylcholinesterase inhibitors (an important target for the treatment of Alzheimer's disease),[4] ligands for estrogen receptors,[5] and protein farnesyltransferase (PTF) inhibitors, important enzyme for the survival of the pathogenic protozoa *Plasmodium falciparum*.[6] The C-3-spiro-oxindol framework system is the core structure of many natural alkaloids (horsfiline **1**, spirotryprostatin A **2**, pretropodine **3**, etc.)[7] and reported pharmacological agents **4** or **5**[8,9] (Fig. 1), which proves that this spiro-bridge with a heterocyclic ring, highly enhances biological activity. With the view that the small rigid molecules containing both the tetrahydroquinoline and oxindole framework connected through a spiro-atom would be of high interest in pharmacological studies, and in continuation of our research on the synthesis of heterocyclic molecules using acid-catalyzed cycloaddition reactions,[10] we herein report a facile reaction of *trans*-isoeugenol with iminoisatin derivatives to provide a novel protocol for the preparation of dihydrospiro[indoline-3,2′-quinolin]-2-one derivatives **6** via $BF_3{\cdot}OEt_2$-catalyzed imino Diels–Alder reaction (Povarov reaction), which is a popular, atom-economical, C–C and C–N bonds forming reaction to construct N-containing six-membered heterocyclic compounds, including tetrahydroquinolines.[11,12]

However, to the best of our knowledge, there have not been reports about the straightforward synthesis of dihydrospiro[indoline-3,2′-quinolin]-2-one derivatives **6**,[13] which are complex and interesting rigid molecules in pharmacological studies. Moreover, this is the first utilization of the Povarov reaction of iminoisatins as azadienes with styrene derivatives as a dienophile.

Bearing these results in mind, we started our study toward dihydrospiro[indoline-3,2′-quinolin]-2-one derivatives preparation from cheap and commercially available isatin **7**. Ketimine precursors **9a–h** were easily obtained using a common procedure for imine formation, condensing isatin with diverse substituted anilines **8** in the presence of AcOH in refluxing methanol,[14,15] or in PEG-400 as a green reaction medium.[16] Further cycloadditions [4+2] through imino Diels–Alder reaction of the ketimines **9a–h** with the *trans*-isoeugenol **10** lead to the novel spiro-cycloadducts **6a–h** as stable solid substances after chromatographic purification in moderate to good yields (Scheme 1, Table 1).[17] This reaction is promoted by the Lewis acid $BF_3{\cdot}OEt_2$ in anhydrous dichloromethane as solvent, at room temperature from 1 to 3 h.

The ^{1}H NMR and ^{13}C NMR analysis of the dihydrospiro[indoline-3,2′-quinolin]-2-ones indicated that the methyl substituent in position C-3′ was *trans* to the aryl ring at C-4′ of the major diastereomers **6**, although three stereocentres are presented in molecules **6**; its *trans*-(3′e,4′e)-form is shown in Scheme 1. This was corroborated by the protons H-3′ and H-4′ coupling constants ($J_{3'a,4'a}$ = 11.2–11.9 Hz), affirmation enough to indicate the axial-axial (*trans*) relationship to the case. The latter form is maintained to all the homologue series. Two broad singlets appeared at 10.55–10.68 ppm to the NH_{Indol} and at 5.30–6.58 ppm to the NH_{THQ} protons, confirming the amide and amine functions, respectively. The new quaternary center or the generated spirocyclic carbon atom

* Corresponding author. Tel./fax: +57 76 349069.
E-mail address: kouznet@uis.edu.co (V. V. Kouznetsov).

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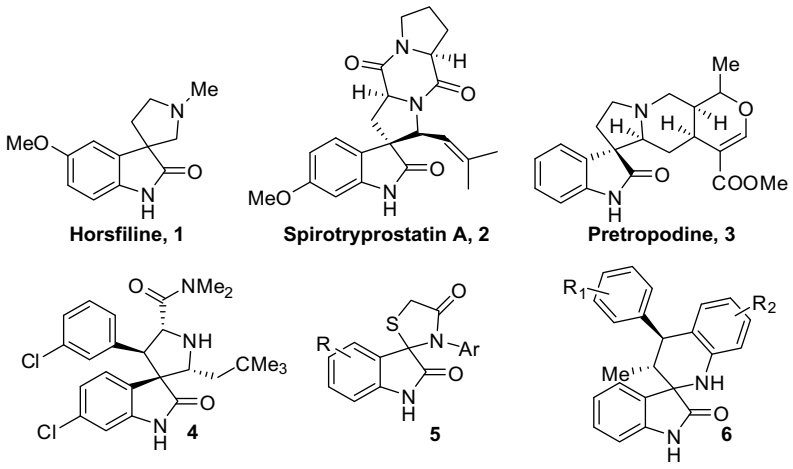
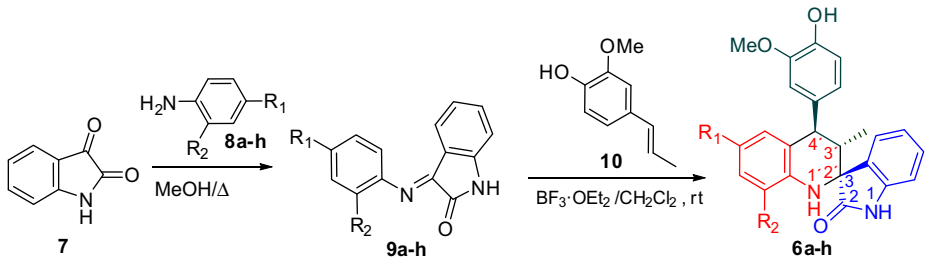


Figure 1. Heterocyclic spiro indolic skeleton of alkaloids **1–3** and synthetic spiro compounds **4–6**.



Scheme 1. Synthesis of the 4′-(4-hydroxy-3-methoxyphenyl)-3′-methyl-3′,4′-dihydro-1′*H*-spiro[indoline-3,2′-quinolin]-2-ones from commercial isatin, anilines and *trans*-isoeugenol.

Table 1
Physical data of dihydrospiro[indoline-3,2′-quinolin]-2-one derivatives **6a–h**

Compounds **6**	R_1	R_2	Mp (°C)	Yield (%)	Molecular formula	Log*P*[a]
a	H	H	280–282	40	$C_{24}H_{22}N_2O_3$	3.22 ± 0.59
b	H	CH_3	252–253	40	$C_{25}H_{24}N_2O_3$	3.68 ± 0.59
c	H	OCH_3	252–253	37	$C_{25}H_{24}N_2O_4$	3.43 ± 0.70
d	CH_3	H	272–273	60	$C_{25}H_{24}N_2O_3$	3.68 ± 0.59
e	Et	H	240–241	64	$C_{26}H_{26}N_2O_3$	4.21 ± 0.59
f	H	Et	263–264	58	$C_{26}H_{26}N_2O_3$	4.21 ± 0.59
g	Cl	H	270–271	55	$C_{24}H_{21}ClN_2O_3$	4.00 ± 0.69
h	Br	H	264–265	35	$C_{24}H_{21}BrN_2O_3$	4.38 ± 0.66

[a] Theoretical values log*P* were calculated using commercially available ACD LAB 6.0 program.

C-2′ was assigned through ^{13}C NMR and DEPT-135 experiments at 64.1–65.4 ppm.[18] These data were also confirmed by homonuclear and inverse detected 2D-NMR.[19] The HMBC correlations of compound **6d,** helpful in the assignment of the chemical shifts of molecules **6**, are shown in Figure 2.

From the inverse detected 2D-NMR data it can be seen that the major diastereomers **6** resulting from the imino Diels–Alder cycloaddition reaction orient exclusively the 3′-Me group *cis* to the oxindole carbonyl in all the cases.[20,21]

The synthesized molecules partition coefficient log*P* values (Table 1) between 2.99 and 4.38 are in agreement with the estimated values (less than 5.0, up to 2.0) for a good lipophilicity and solubility, which is a useful parameter in drug discovery and development, a good predictor of the molecules transport properties across cell membranes, and an indicator of protein binding characteristics, according to the spiro-compounds activities discussed above.[22]

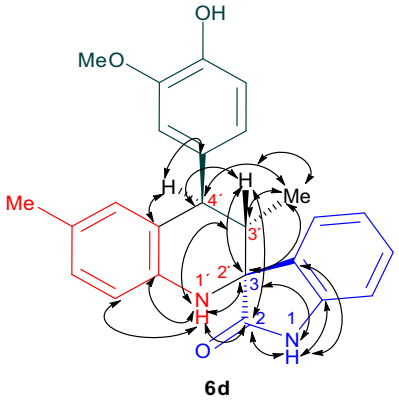


Figure 2. HMBC correlations of the spiro molecule **6d**.

In conclusion, we described in this letter the two-step synthesis of an interesting rigid heterosystem with a strategy that allows the development of a new series of novel -(4-hydroxy-3-methoxyphenyl)-3′-methyl-3′,4′-dihydro-1′*H*-spiro[indoline-3,2′-quinolin]-2-ones in a fast, safe, and cheap way through catalyzed cycloadditions between ketimines from isatin and aromatic anilines, and *trans*-isoeugenol. The coupling of two biologically relevant systems as they are the indole ring along with the tetrahydroquinoline system spiro-joined allows excellent candidates to bioactivity trials.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.096.

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14. *General experimental procedure for the synthesis of the ketimines*: Isatin **7** (6.8 mmol) was dissolved in anhydrous methanol (50 mL) and the proper arylamines **8a–h** were added (8.16 mmol) and then, the acid catalyst, AcOH (0.1–7.4 mL). The reaction mixture was refluxed, stirring constantly, for 3–8 h monitoring through TLC. After the reaction mixture reached room temperature, the precipitated solid was filtered and washed with petroleum ether, and then vacuum dried to get the ketimines **9a–h** in good to excellent yields (50–86%).
15. *Selected spectral data of ketimines* **9**: Ketimine **9b**, R_f = 0.43 (2:1 petroleum ether/ethyl acetate); mp 184–185 °C; IR (KBr): 3251 $\nu_{(NH)}$, 1747 $\nu_{(NC=O)}$, 1666 $\nu_{(NH)}$, 1612 $\nu_{(C=N)}$, 1461 $\nu_{(C=C)}$, 1338 $\nu_{(C-N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 9.72 (1H, br. s, H–N), 7.32–7.28 (2H, m, 6-H_{Indol}, 5′-H_{Ar}), 7.23 (1H, d, J = 7.5 Hz, 6′-H_{Ar}), 7.16 (1H, dd, J = 7.8, 7.3 Hz, 5-H_{Indol}), 6.95 (1H, d, J = 7.8 Hz, 4-H_{Indol}), 6.85 (1H, d, J = 7.6 Hz, 3′-H_{Ar}), 6.74 (1H, dd, J = 7.6, 8.3 Hz, 4′-H_{Ar}), 6.5 (1H, d, J = 7.7 Hz, 7-H_{Indol}), 2.16 (3H, s, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ 165.4, 154.7, 149.1, 145.4, 134.3 (+), 130.9, 126.7 (+), 126.2 (+), 126.1 (+), 125.3 (+), 123 (+), 116.6 (+), 111.8 (+), 17.7 (+) ppm. GC–MS: R_t: 23.54 min; m/z (%): 236 (M^+, 51), 208 (100), 180 (16), 118 (6), 91 (19), 65 (26). Anal. calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.49; H, 5.03; N, 11.67. Ketimine **9c**, R_f = 0.33 (2:1 petroleum ether/ethyl acetate); mp 177–179 °C; IR (KBr): 3170 $\nu_{(NH)}$, 1735 $\nu_{(NC=O)}$, 1654 $\nu_{(NH)}$, 1612 $\nu_{(C=N)}$, 1461 $\nu_{(C=C)}$, 1334 $\nu_{(C-N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 9.78 (1H, br. s, H–N), 7.29 (1H, dd, J = 8.0, 6.9 Hz, 6-H_{Indol}), 7.23 (1H, dd, J = 6.2, 8.0 Hz, 5-H_{Indol}), 6.93 (1H, d, J = 7.8 Hz, 3′-H_{Ar}), 7.0–6.9 (3H, m, 4-H_{Indol}, 4′- and 5′-H_{Ar}), 6.76–6.75 (2H, m, 7-H_{Indol} and 4′-H_{Ar}), 3.76 (3H, s, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ 165.3, 155.3, 148.1, 145.2, 134.2 (+), 126.5 (+), 125.8 (+), 122.7 (+), 121.2 (+), 121.0 (+), 119.3 (+), 117.1 (+), 111.8 (+), 111.6 (+), 55.6 (+) ppm. GC–MS: R_t: 24.67 min; m/z (%): 252 (M^+, 67), 237 (9), 224 (36), 195 (100), 180 (34), 117 (36), 92 (17), 77 (24). Anal. calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.23; H, 4.95; N, 11.05.
16. *General experimental procedure for the synthesis of the ketimine* ***9b*** *in PEG 400:* In a round-bottom flask, the isatin **7** (2.04 mmol) was dissolved in PEG 400 (5 mL) and the arylamine 8 b was added (2.44 mmol) stirring and heating at 80 °C for 3 h. The product formation is monitored by TLC comparing to the standard protocol of ketimine.
17. *General experimental procedure for the synthesis of the dihydrospiro[indoline-3,2′-quinolin]-2-ones*: In a Schlenck flask, the ketimines **9a–h** (1.8 mmol) were dissolved in anhydrous dichloromethane with inert nitrogen atmosphere. The $BF_3{\cdot}OEt_2$ (1.98 mmol) was added stirring constantly. Fifteen minutes later, the *trans*-isoeugenol (2.7 mmol) was added. The reaction mixture was monitored through TLC. The reaction mass was then treated with 20 mL of $NaHCO_3$ solution and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried on anhydrous Na_2SO_4 and then concentrated by vacuum. The pure compounds **6a–h** were obtained after recrystallization from heptanes/AcOEt (1/1) or silica gel column chromatography with petroleum ether and ethyl acetate as eluents (Table 1). It is important to note that trying to heat the reaction over the room temperature (25 °C) resulted in the ketimine rupture and the complete failure of the synthesis.
18. *Selected spectral data for some compounds* **6**: *4′-(4-Hydroxy-3-methoxyphenyl)-3′-methyl-3′,4′-dihydro-1′H-spiro[indoline-3,2′-quinolin]-2-one* (**6a**): white yellow solid, mp 280–282 °C; IR (KBr): 3455 $\nu_{(NH-indol)}$, 3336 $\nu_{(NH-THQ)}$, 1712 $\nu_{(NC=O)}$, 1600 $\nu_{(NH)}$, 1265 $\nu_{(ArC-O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 7.80 (1H, s, 4″-OH_{Ar}), 7.27 (1H, td, J = 7.9, 0.9 Hz, 5′-H_{THQ}), 7.14 (1H, d, J = 7.4 Hz, 7-H_{Indol}), 7.03–6.99 (2H, m, 4-H_{Indol} and 7′-H_{THQ}), 6.91 (1H, d, J = 7.7 Hz, 6-H_{Indol}), 6.80 (1H, d, J = 8.0 Hz, 5-H_{Indol}), 6.75 (1H, dd, J = 8.0, 1.7 Hz, 8′-H_{THQ}), 6.70–6.63 (3H, m, 6′-H_{THQ}, 2″-H_{Ar} and 5″-H_{Ar}), 6.59 (1H, d, J = 8.0 Hz, 6″-H_{Ar}), 5.54 (1H, s, NH_{THQ}), 3.86 (1H, d, J = 11.1 Hz, 4′-H), 3.80 (3H, s, 3″-OMe), 2.64 (1H, dq, J = 11.8, 6.6 Hz, 3′-H), 0.53 (3H, d, J = 6.6 Hz, 3′-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ 178.6 (C(O)N), 146.9, 144.5, 142.3, 139.9, 135.2, 131.5, 130.1 (+), 129.1 (+), 127.3 (+), 125.0, 124.8 (+), 123.4 (+), 123.3 (+), 118.8 (+), 115.5 (+), 113.8 (+), 111.0 (+), 109.9 (+), 65.4 (spiro), 56.0 (+), 47.3 (+), 40.8 (+), 13.3 (+) ppm. GC–MS: R_t: 53.34 min; m/z (%): 386 (M^+, 13), 343 (4), 254 (7), 235 (100), 115 (5). Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.78; H, 5.89; N, 7.16. *4′-(4-Hydroxy-3-methoxyphenyl)-3′6′-dimethyl-3′,4′-dihydro-1′H-spiro[indoline-3,2′-quinolin]-2-one* (**6b**): white yellow solid, mp 252–253 °C; IR (KBr): 3540 $\nu_{(NH-indol)}$, 3344 $\nu_{(NH-THQ)}$, 1710 $\nu_{(NC=O)}$, 1592 $\nu_{(NH)}$, 1276 $\nu_{(ArC-O)}$ cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si): δ 10.46 (1H, s, NH_{Indol}), 8.79 (1H, s, 4″-OH_{Ar}), 7.19 (1H, td, J = 7.6, 1.1 Hz, 6-H_{Indol}), 6.96 (1H, t, J = 7.0 Hz, 4-H_{Indol}), 6.90 (1H, t, J = 7.4 Hz, 5-H_{Indol}), 6.85 (1H, d, J = 7.7 Hz, 5″-H_{Ar}), 6.79 (1H, d, J = 6.3 Hz, 5′-H_{THQ}), 6.72 (1H, d, J = 8.0 Hz, 6″-H_{Ar}), 6.66 (1H, s, 2″-H_{Ar}), 6.50 (1H, d, J = 8.0 Hz, 7′-H_{THQ}), 6.40–6.34 (2H, m, 6′-H_{THQ} and 7-H_{Indol}), 5.75 (1H, s, NH_{THQ}), 3.80 (1H, d, J = 12.0 Hz, 4′-H), 3.68 (3H, s, 3″-OMe), 2.32 (1H, dq, J = 12.0, 6.6 Hz, 3′-H), 2.01 (3H, s, 8′-Me), 0.31 (3H, d, J = 6.6 Hz, 3′-Me) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si): δ 178.1 (C(O)N), 147.5, 144.9, 141.7, 141.4, 134.6, 132.4, 128.2 (+), 128.0 (+), 127.1 (+), 123.7 (+), 123.5, 121.7 (+), 121.6 (+), 121.0, 115.8 (+), 115.4 (+), 112.9 (+), 109.2 (+), 64.2 (spiro), 55.5 (+), 46.4 (+), 39.9 (+), 17.6 (+), 13.1 (+) ppm. Anal. calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.74; H, 6.23; N, 7.13.
19. *2D-NMR data of 1′H-spiro[indoline-3,2′-quinolin]-2-one* **6d:** COSY correlations: 0.32 (3′-Me)/2.33; 2.02 (6′-Me)/6.32; 2.33 (3′-H)/0.32/3.76; 3.76 (4′-H)/ 2.33/6.32; 6.32 (5′-H)/2.02/3.76; 6.86 (5-H)/7.20; 6.90 (6-H)/6.86/7.20; 6.96 (4-H)/6.86; 7.20 (7-H)/6.86/6.90. HMQC correlations: 0.32 (3′-Me)/13.2; 2.02 (6′-Me)/20.2; 2.33 (3′-H)/33.8; 3.70 (3″-OMe)/55.6; 3.76 (4′-H)/46.5; 6.32 (5′-H)/129.4; 6.45 (8′-H)/114.2; 6.56 (6″-H)/121.4; 6.86 (5-H)/109.3; 6.90 (6-H)/121.8; 6.96 (4-H)/123.8; 7.20(7-H)/128.3. HMBC correlations: 0.32(3′-Me)/38.8/46.5; 2.02 (6′-Me)/124.6/128.3; 2.33 (3′-H)/13.1/33.8/46.5/64.1/ 132.1/177.7; 3.70 (3″-OMe)/147.4; 3.76 (4′-H)/ 13.1/33.8/46.5/64.1/113.0/ 129.4/134.6; 6.25 (NH_{THQ})/ 33.8/64.1/114.2/177.7; 6.32 (5′-H)/20.2/46.5/ 127.4; 8.83 (4″-OH)/115.5/147.4; 6.45 (8′-H)/124.6/146.8; 6.56 (6″-H)/46.5/ 113.0/144.9; 6.86 (5-H)/132.1; 6.90 (6-H)/109.3/132.1; 6.96 (4-H)/64.1/ 128.3/141.5; 7.20 (7-H)/109.3/123.8/141.5; 10.50 (NH_{Indol})/64.1/132.1/141.5/ 177.7.
20. The configuration of the oxindole moiety was assigned with aid of the NOE-experiments (the irradiation of protons 3′-H_a and 4-H_{Indol} was carried out). The similar case of the stereochemistry at the quaternary spiro and adjacent alkyl centers of spiro[pyrroline-3,3′-oxindoles] has been reported, see: Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711–713.
21. See, recent works on complex isatin-3-spiranes: (a) Sridhar, G.; Gunasundari, T.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 319–322; (b) Kumar, R. S.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 7164–7168; (c) Kumar, R. S.; Perumal, S. *Tetrahedron* **2007**, *63*, 12220–12231.
22. Their antifungal and cytotoxic properties are under way. These results will be published soon elsewhere.