5,6-Dihydropyrrolo[2,1-α]isoquinolines as Alternative of New Drugs with Cytotoxic Activity

Rosa María Chávez-Santos, a Paul Eduardo Reyes-Gutiérrez, b Rubén Omar Torres-Ochoa, a Maria Teresa Ramírez-Apan, a and Roberto Martínez* a

a Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria; 04510, Cd. México, México; and b Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences; Flemingovo náměstí 542/2, 16610 Prague 6, Czech Republic.

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In this study, the pyrrolo[2,1-α]isoquinolines 4a–n were synthesized in good yields in a three steps synthesis from the corresponding α,β-unsaturated esters starting materials. These compounds were tested on six human cancer cell lines to measure the cytotoxic activity as a function of the electronic properties and aromaticity of the substituent at the C-2 position of the pyrroloisoquinoline. Our results reveal that the cytotoxic activity could be explained in terms of the distribution of electronic density across the ring joined to C-2. Also, this study identified 3-hydroxy (4d) and 3-chloro (4j) derivatives with powerful cytotoxic activities. The IC50 values of these compounds were found to be comparable to those of the commercially available Topotecan, Irinotecan, Etoposide, Tamoxifen, and Cisplatin.

Key words pyrrolo[2,1-α]isoquinoline; synthesis; cytotoxic activity

Results and Discussion

Chemistry The synthetic route to compounds 4a–n is depicted in Chart 1. Compounds 4a–n were synthetized via a three-step procedure starting from α,β-unsaturated esters 1a′, 1b, 1c, 1d′, 1e–j, 1k′, 1l′, 1m and 1n based in our previous synthetic strategy of synthesis of 5,6-pyrrolo[2,1-α]-isoquinolines I–IV with slightly modifications.4,5 Accordingly with our synthetic Chart 1, the reaction between the corresponding aromatic aldehydes and ethyl diethylphosphonoacetate, using a Horner–Wadsworth protocol, gave the starting materials 1c, 1d′, 1e–j, 1l′, 1m and 1n in excellent yields (Chart 2). The ethyl cinnamates 1a′ and 1b were obtained from m-iodobenzoic acid or m-iodoaniline through a Heck reaction4 and a subsequent amidation reaction5 with the corresponding cyclic amines (Chart 3). It should be noted that all the α,β-unsaturated esters prepared were obtained exclusively as the (E)-isomers in good yields (78–96%).

Treatment of the electrophilic alkenes 1a′–n with monomethylated p-toluenesulfonylmethyl isocyanide (TosMIC), prepared from the commercially available TosMIC under phase transfer conditions according to van Leusen’s protocol,7 afforded the 2,3,4-polysubstituted pyrroles 2a′–n in 70–96% yields. The key intermediates 3a′–n were prepared by N-alkylation of the pyrroles 2a′–n using 2-bromo-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate as alkylating agent, which had been prepared from 2-(3,4-dimethoxyphenyl)ethanol in the presence of sodium hydride (NaH) as a base in dry dimethyl sulfoxide (DMSO). Finally, the N-alkyl-pyrroles 3a′–n were cyclized to the corresponding tetrasubstituted-5,6-dihydropyrroloisoquinolines 4a–n using radical oxidative conditions in the presence of tributyltin hydride (n-Bu3SnH) and dilauroyl peroxide (DLP) in toluene.9 The nitro derivative was prepared via a palladium-catalyzed reaction10 used to obtain the tricyclic framework 4g. This step was necessary due to the possibility of a denitration reaction in the presence of tributyltin hydride (Chart 1, conditions iii’).
**Table 1.** The IC$_{50}$ Values (µM) of Compounds I to IV in the Six Cancer Cell Lines$	extsuperscript{a}$

| Compd. | PC-3 (Prostate) | U-251 (CNS) | K-562 (Leukemia) | HCT-15 (Colon) | MCF-7 (Breast) | SKLU-1 (Lung) |
|--------|-----------------|-------------|-------------------|---------------|---------------|---------------|
| I      | 0.16±0.01       | 0.05±0.00   | 0.16±0.01         | 0.02±0.01     | 5.58±0.04     | 0.02±0.00     |
| II     | 18.15±0.60      | 4.86±0.60   | 76.78±7.30        | 0.14±0.06     | 25.20±2.00    | 0.59±0.00     |
| III    | 21.20±1.20      | 5.96±0.50   | 2.50±0.80         | 0.01±0.00     | 1.30±0.10     | 0.10±0.01     |
| IV     | 8.47±0.23       | 6.99±0.67   | 4.07±0.49         | 0.59±0.05     | 7.41±0.09     | 2.13±0.03     |

$	extsuperscript{a}$ Results are expressed as IC$_{50}$ values in units of µM±standard error (S.E.). The values indicate the mean calculated from experiments conducted in triplicate.

Fig. 1. Preliminary SAR of Pyrroloisoquinolines I–IV and Designed Compounds
The piperazinyl compound 4a was prepared from compound 4a' in ethanol using hydrazine hydrate as a deformylating agent.\textsuperscript{11} The pyrroloisoquinoline 4d was prepared after hydrogenolysis of the benzyl ether 4d.\textsuperscript{12} The bromo derivative 4k was synthesized through a Sandmeyer reaction\textsuperscript{13} using the corresponding aniline 4k' as a precursor. Finally, the \(N\)-deprotection of pyrrole 4l' was achieved after applying the reductive conditions described by Sajiko \textit{et al.},\textsuperscript{14} which afforded the pyrroloisoquinoline 4l.

### Cytotoxic Activity and Structure–Activity Relationship (SAR) for Compounds 4a–m

We evaluated the effects of modifying the cyclohexylmethylpiperazinyl group in compound I on the antiproliferative activities (Table 2). The removal of the methylcyclohexyl group from our lead compound I decreased the antiproliferative activity of the synthesized compound 4a in all cell lines compared to the activity of the lead compound I [Table 2, Entry 3]. These results suggested that the methylcyclohexyl group is key to the cytotoxic activity. The influence of the piperazine NH group on the activity of 4a was examined by synthesizing the morpholinyl analog 4b. Surprisingly, 4b did not inhibit proliferation of any of the six cancer lines tested (Table 2, Entry 4). On the other hand, the antiproliferative activity of \(N\)-formylpiperazine 4a' displayed inhibition levels minor to those displayed by 4a. These results could be attributed to effect of the piperazinyl-NH group of 4a on the activity, probably by forming a quaternary ammonium ion \textit{in situ}.

Complete removal of the piperazine ring, in compound 4c (3-CONH\(_2\)), provided a level of growth inhibition in all cell lines tested that exceeded the inhibitory activity of 4a. The antiproliferative activity of 4c was better than that of the lead compound I in the MCF-7 cell line but lesser than in tested: PC-3, U-251, K-562, HCT-15 and SKLU-1 cell lines. The last results suggested that the electronic properties of amide group of compound 4c affected the cytotoxicity to a greater degree than the electronic properties of cyclohexylmethyl-piperazinyl group on I in the MCF-7 cancer cell line.

The electronic effects were further examined by introducing electron-donating groups (4d, 3-OH; 4e, 3-OMe) or electron-withdrawing groups (4f, 3-CN; 4g, 3-NO\(_2\); 4h, 3-CF\(_3\)) at the meta position of the 2-benzene ring. The majority of these changes significantly increased the inhibitory activity compared to the unsubstituted compound II in all cell lines (Table 3). By the contrary, the inhibitory activity of compounds 4d–h...
was lesser than that the lead compound I in all cell lines, with exception in HCT-15 cell line were compound 4d was twice times more active than I. Interestingly, compound 4d (3-OH) was the most active derivative across three of the six cancer lines (Table 3). The nature of the –OH substituent appeared to increase the activity due to the capacity of the substituent to form hydrogen bonds.

The roles of the electronegativity and/or size of the halogen group on the antiproliferative activity were investigated by synthesizing compounds 4i (3-F), 4j (3-Cl), and 4k (4-Br). As shown in Table 3, the chloro derivative 4j was the most active of the halogenated compounds on all the cancer cell lines tested but was lesser than that the lead compound I, with exception in MCF-7 cell line were compound 4j was six times more active than I. These results suggest that derivatization of C-2-phenyl group with an m-chloro substituent is suitable to obtain best anticancer pyrroloisoquinoline compounds.

Finally, the noteworthy results that have been obtained by studying bioisosteric compounds led us to synthesize bioisosters of II by changing the benzene ring to a pyrrolo, a furan or a pyridine ring, creating compounds 4l, 4m, and 4n, respectively. Our results demonstrate that a bioisosteric modification of the C-2 benzene ring of compound II, gives compounds with preserved cytotoxic activity. Moreover, this activity is enhanced by the presence of a furan ring in the PC-3 cell line (compound 4m). However, the inhibitory activ-

Reagents and conditions: (i) NaH, CH₃-TosMIC, diethyl ether–DMSO (2:1), 0°C to RT.; (ii) NaH, DMSO, 2-bromo-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate, RT; (iii) n-Bu₃SnH, DLP, Toluene, reflux; (iii') Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux; (iv) Hydrazine/EtOH, 60°C; (v, vii) H₂, Pd/C EtOH, RT; (vi) t-BuONO, CuBr₂, CH₂CN, 0°C.

Chart 1. Synthetic Route of Compounds 4a–n
The cytotoxic activity of compounds 4l–n was lesser than that of the lead compound I in all cell lines tested. Likewise, the data for compounds II, IV, 4l–m in three of the six cancer lines U-251, HCT-15 and SKLU-1 indicate that the cytotoxic effect was dependent of the kind of aromaticity of the substituent joined to C-2 (Table 4). These findings confirmed that the cytotoxic activity could be explained in terms of the distribution of electronic density across the ring joined to C-2.

The cytotoxic activities of our most active compounds 4d and 4j were compared with those of the commercially available Topotecan,16) Irinotecan,17) Etoposide,18) Tamoxifen,19) and Cisplatin.20) As shown in Table 3, compound 4d (3-OH) was ten times more active than cisplatin in the prostate PC-3 cell line, almost two thousand times more active than irinotecan in the colon HCT-15 cell line. In the lung SKLU-1 cell line, compound 4d (3-OH) was thirty-seven times more active than topotecan, six hundred forty-one times more active than etoposide. Compound 4j (3-Cl) showed more activity in the U-251(CNS) cell line and leukemia K-562 cell line compared to the reference etoposide. Finally, compound 4j (3-Cl) showed a higher activity than tamoxifen in the breast cancer cell line MCF-7.

**Conclusion**

Compounds 4a–n were synthesized through a practical synthetic route involving the van Leusen’s pyrrole construction protocol and an intramolecular radical oxidative cyclization. The inhibitory activities of compounds 4a–n were evaluated using six cancer cell lines. Our results reveal that the cytotoxic activity could be explained in terms of the distribution of electronic density across the ring joined to C-2. Also, the present study enabled the discovery of the novel 3-hydroxy 4d...
and 3-chloro 4j derivatives pyrroloisoquinoline compounds, which displayed excellent cytotoxic activity. The IC_{50} values of these compounds were determined and were found to compare satisfactorily with those of the commercially available drugs topotecan, irinotecan, etoposide, tamoxifen, and cisplatin.

**Experimental Chemistry**

All reported melting points were measured in open capillaries using a Mel-Temp apparatus. 1H-NMR spectra were recorded on a Avance III HD 700 MHz Brucker, Avance III HD 500 MHz Brucker, Avance 400 MHz Brucker, 300 MHz Jeol Eclipse, Fourier 300 MHz Brucker spectrometers in deuterated chloroform (CDCl\textsubscript{3}) solutions using tetramethylsilane (TMS) as the internal standard (δ=0 ppm), 14C-NMR spectra were recorded at 75, 100, 125, 150 and 175 MHz on the same instruments. The chemical shifts are reported in the δ scale in parts per million (ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad signal. The coupling constants (J) are reported in Hertz (Hz). IR spectra were obtained on a Magna-IR spectrometer. Mass spectra were recorded on Jeol JEM-AX505HA spectrometer by electronic impact (EI) detection at 70 eV for low-resolution and on a Jeol 5X102A mass spectrometer (Jeol Ltd.) with fast atom bombardment (FAB+) and EI ionization detection for high-resolution measurements.

**General Procedure for Synthesizing the Pyrroles 2a–n**

A solution containing the alkene (2.6 mmol) and 1-(1-isocyanooethylsulfonyl)-4-methylbenzene (Me-TosMIC) (0.6 g, 2.9 mmol) in Et\textsubscript{2}O–DMSO (2 : 1, 15 mL) was added dropwise to a suspension of NaH (0.23 g, 5.7 mmol, 60% dispersion in mineral oil) in dry ether (5 mL). The mixture was stirred at room temperature for 1 h, then H\textsubscript{2}O (15 mL) was added dropwise and the product was extracted with EtOAc (3 × 30 mL). The organic layer was washed with H\textsubscript{2}O and brine (3 × 10 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to furnish the respective pyrrole. Physical and spectroscopic data of all compounds 2a–n are reported in supplementary material.

**General Procedure for the Synthesis of the N-Alkylpyrroles 3a–n**

NaH (0.2 g, 5.7 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of the corresponding pyrrole (2.3 mmol) and 2-bromo-4,5-dimethoxyphenethyl 4-methyl benzenesulfonate (1.9 g, 4.5 mmol) in dry DMSO (10 mL). The mixture was stirred at room temperature for 6 h, EtOAc (20 mL) was added, and the solution was washed with water and brine (3 × 10 mL). The organic layer was dried with Na\textsubscript{2}SO\textsubscript{4} and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to furnish the respective N-alkylpyrrole. Physical and spectroscopic data of all compounds 3a–n are reported in supplementary material.

**General Procedure for Synthesizing the 5,6-Dihydropyrrolo[2,1-aj]isoquinolines 4a–4n**

To a refluxing solution of the N-alkylpyrrole in degassed dry toluene (10 mL), a solution of n-Bu\textsubscript{3}SnH
(1.0 mL, 3.7 mmol) in toluene (5 mL) was added dropwise (syringe pump) over 7 h. During that time, solid dilauroyl peroxide (DLP) was added portionwise (1.49 g, 3.7 mmol, 0.11 g/30 min). The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography on silica gel. Hexane was first added to remove the n-Bu3SnBr, then hexane–EtOAc–Et3N (70:25:5 to 50:45:5). Physical and spectroscopic data of all compounds 4a–n are reported in supplementary material.

Table 3. Effects of meta-Substituent on 3-Phenyl Moiety on the Antiproliferative Activity and Comparison with the Activities of Commercially Available Drugs

| Compd. | R= | PC-3 | U-251 | K-562 | HCT-15 | MCF-7 | SKLU-1 |
|--------|----|------|-------|-------|--------|-------|--------|
| I      |    | 0.16±0.01 | 0.05±0.00 | 0.16±0.01 | 0.02±0.01 | 5.58±0.04 | 0.02±0.001 |
| II     |    | 18.15±0.60 | 4.86±0.60 | 76.78±7.30 | 0.14±0.06 | 25.20±2.00 | 0.59±0.00 |
| III    |    | 21.20±1.20 | 5.96±0.50 | 2.50±0.80 | 0.01±0.00 | 1.30±0.10 | 0.10±0.00 |
| 4d     |    | 0.76±0.50 | 6.12±0.40 | 5.47±0.70 | 0.01±0.00 | 5.72±0.40 | 0.05±0.01 |
| 4e     |    | 3.26±0.10 | 3.31±0.40 | 2.65±0.10 | 0.69±0.05 | 2.35±0.20 | 0.77±0.08 |
| 4f     |    | 3.86±0.10 | 3.17±0.30 | 1.98±0.05 | 2.53±0.20 | 4.08±0.20 | 2.93±0.08 |
| 4g     |    | 8.26±1.00 | 12.66±0.50 | 8.28±1.10 | 0.10±0.04 | 13.98±0.70 | 1.26±0.30 |
| 4h     |    | 2.30±0.20 | 2.50±0.40 | 3.30±0.20 | 1.90±0.20 | 3.10±0.30 | 1.70±0.10 |
| 4i     |    | 2.20±0.09 | 3.10±0.20 | 1.30±0.20 | 2.50±0.30 | 1.70±0.07 | 3.30±0.10 |
| 4j     |    | 0.91±0.01 | 0.37±0.04 | 0.33±0.03 | 0.25±0.02 | 0.88±0.09 | 0.76±0.07 |
| 4k     |    | 22.90±0.90 | 23.60±0.90 | 5.20±1.20 | 5.60±0.20 | 57.70±1.00 | 3.60±0.60 |

Topotecan | 0.50±0.05 | 0.10±0.02 | 2.00±0.10
Irinotecan | 33.09±3.40 | 34.62±2.30
Etoposide | 1.70±0.30 | 11.30±2.50 | 4.10±0.60
Tamoxifen | 12.80±1.10
Cisplatin | 8.30±0.70 | 3.30±0.60

(continued)

a) Results are expressed as IC50 values in units of µM±S.E. The values indicate the mean calculated from experiments conducted in triplicate. The bold numbers represent the highest activities of the compounds tested.
culture and assay for activity PC-3, U-251, K-562, HCT-15, MFC-7, and SKUL-1, were supplied by The National Cancer Institute (NCI), U.S.A. The cytotoxicity of tumors cells with the test compounds was determined using the protein-binding dye sulforhodamine B (SBR) in microculture assay to measure cell growth. The cell lines were cultured in RPMI-1640 (Sigma Chemical Co., Ltd., St. Louis, MO, U.S.A.) supplemented with 10% fetal bovine serum which was purchased from Invitrogen Corporation, 2 mM L-glutamine, 10000 units/mL of penicillin G, 10000 µg/mL streptomycin and 0.25 µg/mL Fungizone (Gibco). They were maintained at 37°C in a 5% CO2 atmosphere with 95% humidity. For the assay, 5·10⁴ cell/mL (K-562, MCF-7), 7·5·10⁴ cell/mL (U-251, PC-3) and 1·0·10⁵ cell/mL (SKLU-1, HCT-15), and 100 µL/well of these cells suspension was seeded in a 96-well microtiter plates and incubated to allow for cell attachment. After 24 h, 100 µL of each test compounds and positive substances were added to each well. Later 48 h, adherent cell cultures were fixed in situ by adding 50 µL of cold 50% (w/v) trichloroacetic acid (TCA) and incubated for 60 min at 4°C. The supernatant was discarded and the plates were washed three times with water and air dried. Cultured fixed with TCA were stained for 30 min with 100 µL of 0.4% SRB solution. Protein-bounded dye was extracted with 10 mM unbuffered tris base and the optical densities were read on a Microplate Reader Synergy HT (Elx 808, BIOTEK Instruments, Inc., U.S.A.), with a test wavelength of 515 nm. Results were expressed as IC50 values, they were calculated according to the protocol of Monks, were a dose-response curve was plotted for each compound, and the concentration giving 50% inhibition (IC50) was estimated from non-linear regression equations. The IC50 value (mean standard error S.E.).

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials

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Table 4. Effects of Aromaticity of C-2 Substituent on the Antiproliferative Activity

| Compd. | R= | PC-3 IC50 (µM±S.E.) | U-251 IC50 (µM±S.E.) | K-562 IC50 (µM±S.E.) | HCT-15 IC50 (µM±S.E.) | MCF-7 IC50 (µM±S.E.) | SKLU-1 IC50 (µM±S.E.) |
|--------|----|---------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|
| I      |    | 0.16±0.01           | 0.05±0.00            | 0.16±0.01            | 0.02±0.01             | 5.58±0.04             | 0.02±0.00             |
| II     |    | 18.15±0.60          | 4.86±0.60            | 76.78±7.30           | 0.14±0.06             | 25.20±2.00            | 0.59±0.00             |
| IV     |    | 8.47±0.23           | 6.99±0.67            | 4.07±0.49            | 0.59±0.05             | 7.41±0.09             | 2.13±0.03             |
| 4l     | 10.50±0.24          | 8.99±0.68            | 6.50±0.67            | 0.90±0.06             | 13.60±0.60            | 5.60±0.05             |
| 4m     | 2.97±0.10           | 8.67±0.10            | 8.54±0.50            | 1.72±0.20             | 14.70±1.00            | 6.76±0.09             |
| 4n     | 21.70±0.20          | 24.70±1.10           | 9.10±0.90            | 14.00±1.40            | 23.70±1.00            | 15.60±1.20            |

a) Results are expressed as IC50 values in units of µM±S.E. The values indicate the mean calculated from experiments conducted in triplicate. The bold numbers represent the highest activities of the compounds tested.
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