Research Article

Synthesis of Hybrid Fluoroquinolone-Boron Complexes and Their Evaluation in Cervical Cancer Cell Lines

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Quinolones are a family of antimicrobial agents that have been used in antibacterial and anticancer chemotherapy. Fluoroquinolone targets DNA gyrase and topoisomerase IV enzymes affecting several cellular processes, like cell death and proliferation; the best way to act is in the form of carboxylic acid or, recently, as quinolone-metal complex. In this work, the use of boron is shown as an alternative of metal to form a complex by incorporating to fluoroquinolone as an electron withdrawing substituent to activate the C-7 position chemoselectively for the production of new fluoroquinolone hybrids and test their effects on cell proliferation. Fluoroquinolone-boron complexes were synthesized according to the Gould–Jacobs cyclization method, and five hybrid fluoroquinolone-boron compounds were obtained by $S_N Ar$ reaction, yielding 31 to 46%, at 80°C, and in 10 to 25 hours of reaction. The effect of the five fluoroquinolone-boron hybrids was evaluated in cervical cancer cell lines by cell proliferation assay. 7-hydantoin-fluoroquinolone-boron and 7-dihydropyridine-fluoroquinolone-boron complexes showed the strongest effect according to dose-response assay, respectively. The fluoroquinolone-boron hybrid complex showed proliferation inhibition in SiHa and CasKi cells, opening the possibility to use them as potential agents for the treatment of cancer.

1. Introduction

The antibacterial quinolones are synthetic compounds based on 4-oxo-1,4-dihydroquinoline-3-carboxylic acid skeleton and are used in the treatment of infectious diseases [1]. These quinolones have target as DNA gyrase and topoisomerase IV enzymes [2]. Recently, some studies showed that the family of quinolone antibiotics is promising drugs for the treatment of some cancer diseases [3]. Cervical cancer is one of the most frequent diseases in the world and the second type of cancer that kills most women worldwide, with an estimated global incidence of 470,000 new cases and over 200,000 deaths per year [4]. Cancer treatment is based on radiotherapy and chemotherapy; however, in more than 50 % of the cases, resistance is presented [5]. Therefore, new drugs are important to improve or complement treatments. Several quinolones modifications have been shown to improve properties in cancer treatment. Some modifications

comprise ß-keto and carboxylic acid moiety that are required for hydrogen-bonding interactions with DNA gyrases or/and DNA bases, and therefore, both two functional group moieties are essential [6]. The proximity of the carboxyl and keto groups on the fluoroquinolone molecule would account for good chelating properties [7], suggesting that the interaction of the quinolone complexed to metal is a major step [8].

Metal quinolone chelates play an important role in drug bioavailability, and decreased absorption is produced when it is coadministered with magnesium-aluminum antacids [9] or cations like calcium, iron, or zinc present in multivitamins food [10]. Studies of fluoroquinolone complexed with copper (II), iron, palladium, platinum, and bismuth were found to have higher antibacterial activity than uncomplexed quinolones [11–14]. From these studies, ruthenium, gold, and silver have shown to be interesting molecules for cancer and antiviral therapies [15–17]. Fluoroquinolone metal complex also improved physicochemical properties in quinolones, such as more solubility, pharmacokinetic property and bioavailability [18]. Cervical cancer treatment generally overrides the drugs used; therefore, new compounds with cell proliferation inhibition potential are imperative. Different cellular processes like migration, invasion, apoptosis, and proliferation are altered by complex quinolones. Fluoroquinolone inhibits migration and invasion in colon and breast cancer cell lines [19, 20]. It has been proved that metal incorporation in fluoroquinolone induces HeLa cell death [21]. Interestingly, benzothiazol ring substitution potentialized proliferation inhibition [3]. Synthesis of fluoroquinolone with new modifications represents an opportunity to find new compounds that could be used in cancer treatment.

In this paper, the use of boron is shown as an alternative to form a complex with metal that is incorporated to fluoroquinolone as electron withdrawing substituent to activate the C-7 position chemoselectively [22–25]. There is no paper reporting the use of fluoroquinolone-boron complexes as antimicrobial or anticancer agents. In the present work, fluoroquinolones were used for the production of new fluoroquinolone hybrids which are proposed here as potential anticancer agents according to theoretical and physicochemical properties and antiproliferative effect [26, 27]. Their effects were proved on SiHa and CasKi cervical cancer cell lines. The five new compounds synthesized herein were evaluated to prove their cell proliferation inhibition capability by dose-response assays, showing dependent and differential effect between them. The most prominent effect on cell proliferation inhibition was reached sequentially with hydantoin-, dihydropyridine-, carbazole-, and benzimidazole-fluoroquinolone complex treatment. Conversely, fluoroquinolone-uracil complex did not show any effect. These new compounds represent an alternative to cancer drug treatments.

2. Materials and Methods

2.1. Instruments.
The melting points were obtained with an Electrothermal, IA 9000 melting point apparatus model. The IR spectra were recorded on a Nicolet iS10 FT-IT (Thermo-Scientific) spectrometer with Smart iTR-ATR

diamond. The NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer using TMS as an internal standard.

2.2. Synthesis.
Fluoroquinolone-boron complex **2** was synthesized according to Leyva et al. method [24]. 332.85 μmol of the fluoroquinolone **2** and 0.5 mmol of the heterocycle (3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine, uracil, 5,5-diphenylhydantoine, benzimidazoleor1,2,3,4-tetrahydrocarbazole) were added in 1.5 mL of DMSO (for **3a–d**, **f**) or CH_3CN (for **3e**) and 69.4 μL of TEA solution. Their action mixture was stirred and heated at 80°C and monitored with thin layer chromatography until reaction was completed. Then, 1 mL of ethanol was added to obtain a solid, which was filtered, washed with cold ethanol, and recrystallized with CH_3CN.

Difluoroboryl 1-ethyl-7-(3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**3a**). Reaction time (10 h), yellow pale solid with an mp of 300-301°C and 31% yield. FTIR-ATR (cm^{-1}): 3066 (C-H, aromatic), 1716 (C=O, ketone, ester), 1617 y 1485 (C=C, Ar), 1561 (C=C, vinyl), 1448 (CH_3, bend), 1360 (C-N, Ar), 1288, 1230 (C-O, ester), 1093, 1041 (C-F, Ar). RMN de ^{1}H NMR δ (DMSO-*d6*, ppm): 9.09 (s, 1H), 8.52 (s, 1H), 8.26 (d, $J_{\text{H-F ortho}}$ = 10.47 Hz, 1H), 7.41 (s, 6H), 4.34 (q, J = 7.30 Hz, 4H), 4.10 (q, J = 7.30 Hz, 2H), 3.10 (s, 2H), 1.91 (t, J = 7.30 Hz, 6H), 1.34 (t, J = 7.30 Hz, 3H).

Difluoroboryl 1-ethyl-7-(5,5-diphenylhydantoin-3-yl)-6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylate (**3b**). Reaction time (15–17 h), white solid with an mp of 307-308°C and 46% yield. FTIR-ATR (cm^{-1}): 3066 (C-H, aromatic), 1717 (C=O, ketone and amide), 1697 (C=O, ketone), 1618 y 1486 (C=C, Ar), 1559 (C=C, vinyl), 1453 (CH_3, bend), 1361 (C-N, Ar), 1289, 1231 (C-O, ester), 1094, 1042 (C-F, Ar). ^{1}H NMR δ (DMSO-*d6*, ppm): 9.09 (s, 1H), 8.47 (d, $J_{\text{H-F meta}}$ = 5.84 Hz, 1H), 8.26 (d, $J_{\text{H-F ortho}}$ = 9.80 Hz, 1H), 7.48 (d, $J_{\text{NH-H}}$ = 3.96 Hz, 1H), 7.40 (t, J = 7.06 Hz, 6H), 7.30 (d, J = 7.06 Hz, 4H), 4.58 (q, J = 7.12 Hz, 2H), 1.41 (t, J = 7.12 Hz, 3H).

Difluoroboryl 1-ethyl-6-fluoro-4-oxo-7-uracil-1,4-dihydroquinoline-3-carboxylate (**3c**). Reaction time (20 h), white solid with an mp of 317–319°C and 46% yield. FTIR-ATR (cm^{-1}): 3062 (C-H, aromatic), 1697 (C=O, ketone, ester, and amide), 1614 y 1479 (C=C, Ar), 1558 (C=C, vinyl), 1347 (C-N, Ar), 1387, 1287 (C-O, ester), 1090, 1041 (C-F, Ar). ^{1}H NMR δ (DMSO-*d6*, ppm): 9.13 (s, 1H), 8.47 (d, $J_{\text{H-F meta}}$ = 6.08 Hz, 1H), 8.23 (d, $J_{\text{H-F ortho}}$ = 9.80 Hz, 1H), 7.88 (d, J_{cis} = 7.84 Hz, 1H), 5.86 (d, J_{cis} = 7.84 Hz, 1H), 4.61 (s, 1H), 4.58 (q, J = 7.00 Hz, 2H), 1.43 (t, J = 7.00 Hz, 3H). ^{13}C NMR δ (DMSO-*d6*, ppm): 176.46 (C=O), 163.70 (C=O, amide), 156.34 (C=O), 154.03 (vinyl), 149.88 (C=O, amide), 144.99 (Ar), 142.55 (vinyl, uracil), 135.97 (Ar), 126.47 (Ar), 124.36 (Ar), 120.81 (Ar), 116.08 (vinyl), 107.11 (Ar), 102.25 (vinyl, uracil), 49.61 (CH_2), 14.64 (CH_3).

Difluoroboryl 1-ethyl-7-(1,2,3,4-tetrahydrocarbazol-5-yl)-6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylate (**3d**). Reaction time (20–25 h), yellow pale solid with an mp of 293–300°C and 46% yield. FTIR-ATR (cm^{-1}): 3066 (C-H, Ar), 2993 (C-H, Aliph), 1717 (C=O, ketone), 1618, 1504, 1486,

(C=C, Ar), 1562 (C=C, vinyl), 1451 (CH$_3$, bend), 1361, 1306 (C-N, Ar), 1289, 1230 (C-O, ester), 1093, 1021 (C-F, Ar). ^{1}H NMR δ (DMSO-$d6$, ppm): 8.94 (s, 1H), 8.14 (d, $J_{\text{H-F orto}}$ = 8.95 Hz, 1H), 7.87 (d, $J_{\text{H-F meta}}$ = 5.75 Hz, 1H), 7.80 (d, J = 7.05 Hz, 1H), 7.44 (d, J = 7.05 Hz, 1H), 7.18 (m, 2H), 4.59 (q, J = 7.12 Hz, 2H), 2.77 (t, J = 6.35 Hz, 2H), 2.48 (t, J = 6.35 Hz, 2H), 1.69 (m, 4H), 1.42 (t, J = 7.12 Hz, 3H).

Difluoroboryl 1-ethyl-7-(1H-benzimidazole-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**3e**). Reaction time (10–15 h), white solid with an mp of 316–318°C and 39% yield. FTIR-ATR (cm^{-1}): 3150, 3063, 3037 (C-H, Ar), 2983 (C-H, Aliph), 1705 (C=O, ketone), 1639 (C=O, ester), 1581, 1498, 1476 (C=C, Ar), 1541 (C=C, vinyl), 1450 (CH$_3$, bend), 1360, 1320 (C-N, Ar), 1135 (C-O, ester), 1035 (C-F, Ar). ^{1}H NMR δ (DMSO-$d6$, ppm): 9.08 (s, 1H), 8.65 (s, 1H), 8.54 (d, $J_{\text{H-Fmeta}}$ = 6.12 Hz, 1H), 8.38 (d, $J_{\text{H-F orto}}$ = 10.16 Hz, 1H), 7.54 (m, 1H), 7. 84 (m, 1H), 7.38 (m, 2H), 4.65 (q, J = 7.10 Hz, 2H), 1.44 (t, J = 7.10 Hz, 3H).

2.3. Cell Lines.

The HPV-16 positive cervical tumor lines SiHa and CasKi were grown in Dulbecco's Modified Eagle's Medium (DMEM) (Invitrogen Corporation, Carlsbad CA) enriched with 5% fetal bovine serum (FBS). The cell lines were kindly provided by Ph.D. Gariglio's Lab from CINVESTAV-IPN.

2.4. Cell Proliferation Assay.

The cells were harvested, and 5×10^4 cells were seeded and incubated for 24 hours before treated with the five new compounds at different concentrations and incubated for 72 hours. The cells were harvested and countered in a hemocytometer in triplicate. Floating and adherent cells were collected and included in the counting analysis. Data were subjected to a two-tailed Student's t-test. $P < 0.05$ was considered statistically significant.

3. Results and Discussion

A general procedure for the synthesis of difluoroboryl 1-ethyl-6,7-difluoro-1,4-dihydroquinoline-3-carboxylate **2** is presented as a Gould–Jacobs cyclization process, starting from 2,3-difluoroaniline **1**, followed by *N*-alkylation and ester group moiety transformation into boron complex fluoroquinolone **2**, obtaining a molecule with high regioselectivity in C-7 position (Figure 1) [24].

With the use of fluoroquinolone-boron complex **2**, the S$_N$Ar reaction by addition-elimination was possible for five heterocycles that presents a weak or reduced nucleophilic character and stearic high bulk. The combination of DMSO and TEA, allowed completed reaction at different times, such as **3a** (10 h), **3b** (17 h), **3c** (20 h), and **3d** (25 h), having yields between 31 and 46%. In the particular case of **3e**, it was necessary to replace DMSO for CH$_3$CN to obtain 31% yield in 15 h.

Incorporation of 1,4-dihydropyridine heterocycle into fluoroquinolone-boron complex **2** achieved a broad band at 1715 cm^{-1}, because the number of C=O vibrations of ketone groups increased in **3a** and uracil moiety in **3c** at 1697 cm^{-1}, but in **3b**, hydantoin cycle bonded decreased the intensity of

C=O vibration observed at 1717 cm^{-1}. In the other hand, the C=C aromatic and alkene group were observed at 1616, 1504, and 1561 cm^{-1}, for **3a**; in case of **3e**, these numbers of vibrations were increased and observed at 1638, 1581, 1541, and 1497 cm^{-1}. Another remarkable vibration was aliphatic C-H in **3d** compound that was appreciated due to the tetrahydrocarbazole moiety, while in **3a–c**, **e**, vibrations of C-H aromatic were observed.

The five compounds **3a–e** were also confirmed for ^{1}H NMR, where protons in C-6 and C-8 showed two double signals in the aromatic region, with couple constants of hydrogen and fluorine atoms in ortho and meta positions, vinyl hydrogen at 9.09 ppm (C-3) and ethyl group at 4.58 and 1.41 ppm (N-1); therefore, additional signals were from heterocycles bonded, where **3a** shows a singlet at 3.10 ppm that corresponds to C-4 of pyridine with integration of 2 hydrogens, methyl groups at C-2 and C-6 were observed in 7.41 ppm, as well as the hydrogen for diester group: a quartet at 4.34 ppm and triplet signal at 1.91 ppm.

3b compound was confirmed with a singlet at 7.48 ppm, corresponding to secondary amine, whereas in the aromatic region, a triplet signal at 7.40 ppm and a doublet signal at 7.30 ppm were observed, which belong to diphenyl moiety. On the other hand, **3c** shows a singlet signal from NH at 4.61 ppm and two doublets for hydrogens of the vinyl group at 5.86 and 7.86 ppm with couple constant of J_{cis} = 7.84 Hz. In **3d**, two double signals at 7.80 and 7.44 ppm and a multiple signal at 7.18 ppm were shown, which correspond to benzene moiety of carbazole while 2.77, 2.48 (triplets signal), and 1.69 ppm (multiple signal) for the moiety saturate carbazole. **3e** showed a single signal at 8.65 ppm belonging to hydrogen on C-2 of imidazole and three multiples signals at 7.54, 7.84, and 7.38 ppm, corresponding to benzene fused to imidazole.

The subsequent hydrolysis of **3a–e** to generate the incorporation of carboxylic acid into the quinolone hybrid drastically changed the molecule polarity, limiting its solubility and restraining biological assay performance. This fact confirms that the quinolone-boron complex helps to increase the solubility of the fluoroquinolones.

The **3a–e** compounds were tested on cervical cancer cell lines at different concentrations for 72 h taken in consideration that every 36 h, the cells duplicate their population giving opportunity to obtain at least four cells for each cell. The cervical cancer cell lines SiHa and CasKi were treated with the 5 compounds synthetized at the indicated doses, and proliferation was analyzed. **3b** and **3a** treatment presents the most prominent effect on SiHa and CasKi cell proliferation (Figure 2(a) and 2(b)). However, it should be noted that SiHa cell proliferation inhibition is more potent than in CasKi cells.

In the same sense, **3d** and **3e** compounds showed a differential effect between SiHa and CasKi cell proliferation inhibition, the former being more potent. Remarkably, **3d** and **3e** treatment shows a gradual decrease in SiHa cells, whereas abrupt change in CasKi cells was achieved with 0.5 and 0.75 mM. Interestingly, treatment with **3c** did not show the same effect on SiHa and CasKi cell proliferation but a similar trend in all the doses used, suggesting an independent effect
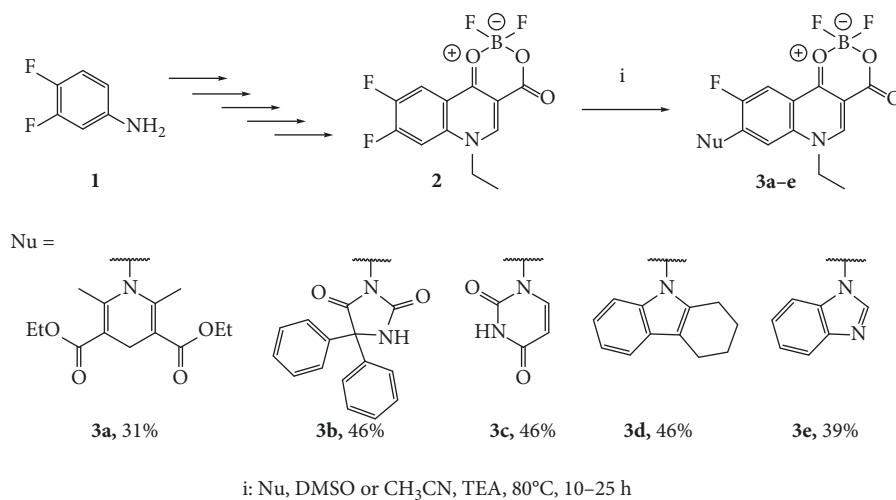
i: Nu, DMSO or CH₃CN, TEA, 80°C, 10–25 h

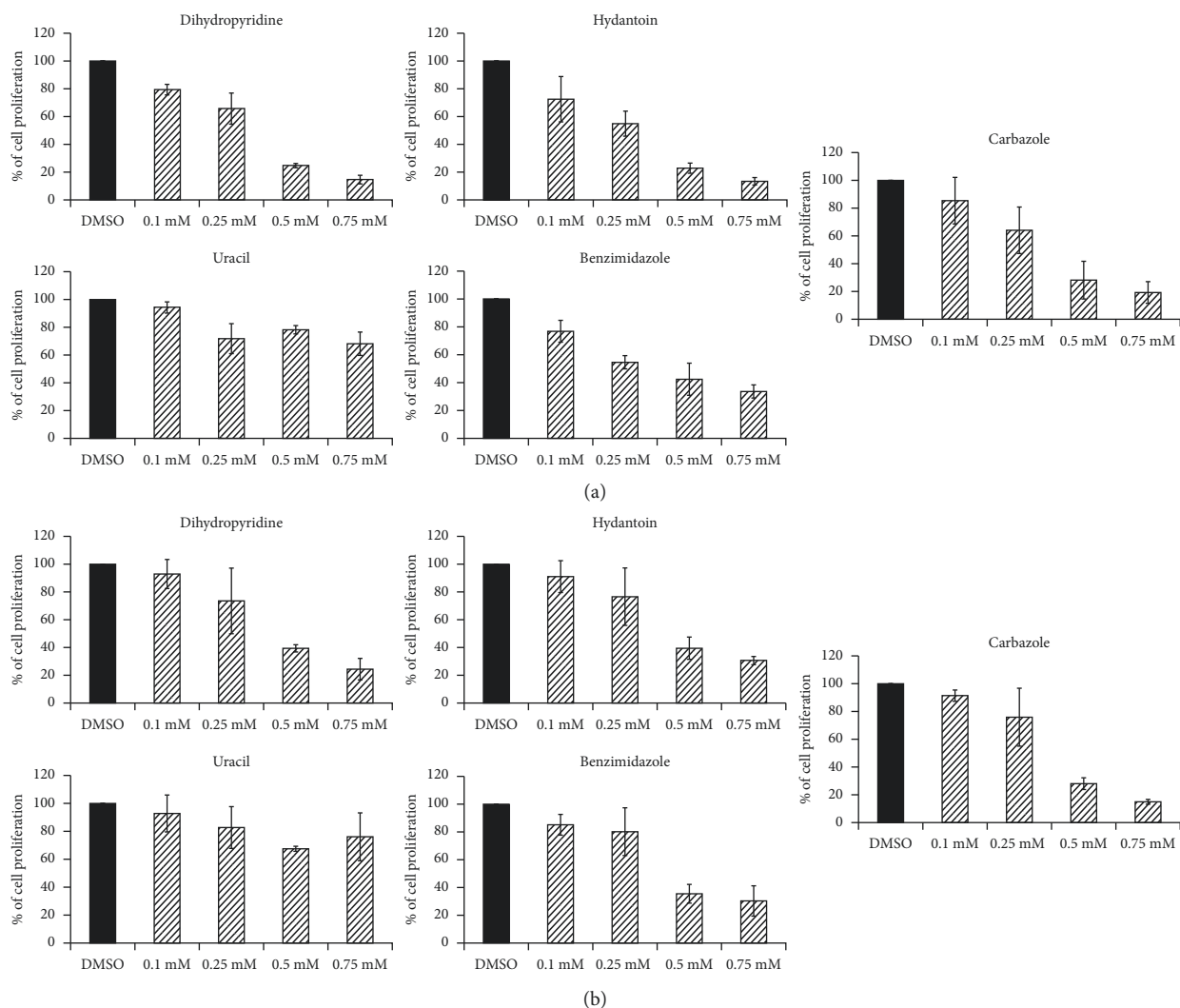Figure 1: Synthesis of hybrid fluoroquinolone-boron complex **3a–e**.

Figure 2: SiHa and CasKi cells were treated with the five hybrid fluoroquinolones **3a–e** at different doses. (a) SiHa cells treatment shows a gradual inhibitory effect with compounds **3a**, **3b**, **3d**, and **3e**. (b) CasKi cells treatment shows a gradual effect with **3a** while the abrupt effect was noticed with **3b**, **3d**, and **3e**.

on SiHa and CasKi cell proliferation. In contrast, the structure seems not to influence the effect recorded in **3a**, **3b**, **3d**, and **3e**. Compounds **3a** and **3b** have completely different structure despite sharing similar effect on SiHa and CasKi cell proliferation. Nevertheless, it should be observed that **3d** and **3e** demonstrate a significant and promising effect on cancer cell proliferation inhibition. One of the marks that trigger cancer development is the reproduction of millions and millions of cells forming the tumor [28]; therefore, inhibiting this multiplication is imperative for cervical cancer treatment. It should be noted that cervical cancer is one of the principal carcinomas that kill women around the world [4]. One of the ways that we have to study cancer progression is the use of a multistep model to have the tool to diagnose on time and predict the evolution of sickness and to have therapeutic agents. Our group has proposed a multistep model in cervical cancer [29] that should be tested with the use of **3a**, **3b**, **3d**, and **3e**. The incorporation of these compounds to the clinic is a process that presents different steps before they reach general population for its application highlighting the potential of **3b**, **3a**, **3d**, and **3e** compounds as new alternatives for cervical treatment.

4. Conclusions

With the use of fluoroquinolone-boron, complex **2** was able to synthesize the hybrid fluoroquinolone-boron complexes **2** and **3a–c**, with yields of 31 to 46%, mild conditions of reaction, and easy procedure of purification. The compounds **3a–c** have purity and better solubility than fluoroquinolone with carboxylic acid moiety. **3c** compound did not present effect in SiHa and Caski cell lines in contrast to **3b**, **3a**, **3d**, and **3e** that inhibited cell proliferation in a dose response-dependent manner, indicating specific effect of these compounds and opening the possibility to use them as potential agents for the treatment of cancer.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

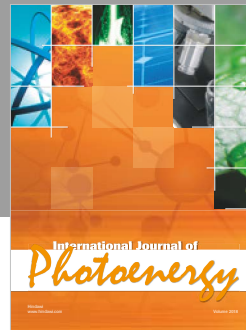The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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