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Synthesis of norfloxacin analogues catalyzed by Lewis and Brönsted acids: An alternative pathway

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ABSTRACT

An alternative synthetic pathway to prepare norfloxacin analogues is presented. Three Lewis acids ($CeCl_3{\cdot}7H_2O$, $AlCl_3{\cdot}6H_2O$, $ZnCl_2$) and one Brönsted acid (TsOH) were tested as catalysts in the preparation of 3,4-difluoroacrylate. Cyclization of this acrylate at 55 °C was achieved with the use of Eaton's reagent ($P_2O_5/MeSO_3H$) a known Brönsted acid. The fluoroquinolone–boron complex presented high yields on C-7 nucleophilic substitution of the fluorine atom by different heterocyclic amines with low, medium and strong nucleophilic character.

1. Introduction

Fluoroquinolones are a group of compounds with a broad antibacterial spectrum [1–3]. Ciprofloxacin, norfloxacin and sparfloxacin have gained a wide acceptance for their use in the treatment of numerous diseases [1]. The synthesis of norfloxacin and its derivatives, starting from 3-chloro-4-fluoroaniline and followed by a limited number of reactions already reported [4,5], presented certain disadvantages such as a long time in the condensation reaction, extreme conditions for acrylate cyclization (250 °C) and non-specific fluorine substitution with moderate yields at C-7 only when strong nucleophiles are used.

Recently, evidence of quinolone interaction with several metals such as Mg^{2+}, Ca^{2+}, B^{3+}, Fe^{2+}, Co^{2+}, Zn^{2+}, Ag^{2+}, Cd^{2+} and Bi^{2+} has been presented by other authors [6,7]. Covalent, coordinative or ionic interactions with ketone and carboxylic acid moieties of fluoroquinolone molecule, allowed us to introduce Lewis and Brönsted acids in a catalytic amount in order to promote the Michael addition reaction under mild conditions. $CeCl_3{\cdot}7H_2O$ [8], $AlCl_3{\cdot}6H_2O$ [9,10] and $ZnCl_2$ [11] have been described as Lewis acids with great affinity for the electron pair of oxygen, these interactions are useful for the synthesis of intermediate molecules of norfloxacin analogues.

In spite of the large number of publications, regarding the synthetic applications of polyphosphoric acid (PPA) for cyclization reaction [12,13], little has been established concerning the use of Eaton's reagent [14–16]. This reagent is easily prepared by dissolving phosphorus pentoxide in methanesulfonic acid (CH_3SO_3H) [12]. It provides the advantages of a solution with less viscosity and a better solubility of certain organic molecules [13]. Furthermore, it is a convenient alternative to achieve good yields in the cyclization reaction.

On the other hand, the methodology for introducing different heterocyclic amines by nucleophilic aromatic substitution (S_NAr) at C-7 of 7-chloro-6-fluoroquinolone has not been satisfactory in terms of yield. An alternative reaction has been proposed, which uses the quinolone–boron complex derivative of the fluoroquinolone-3-carboxylic acid [17,18]. The complex obtained, opens the possibility of introducing a heterocyclic amine, as pyrrolidine or piperidine, obtaining the fluoroquinolone-7-substituted in good yields. However, its efficiency against different kinds of nucleophiles has been poorly explored. This strategy is evaluated by introducing different heterocyclic amines as nucleophiles, such as piperazine, morpholine, pyrrolidine, 2-methyl-piperazine, 2-amino-pyrimidine, 3,5-diamino-1,2,4-triazole and 5-amino-uracil.

2. Results and discussion

In the first reaction, the conjugate addition of an amine to α,β-unsaturated esters (Michael reaction) catalyzed by Lewis ($CeCl_3{\cdot}7H_2O$, $AlCl_3{\cdot}6H_2O$, $ZnCl_2$) or Brönsted (TsOH) acids, could be carried out in a solvent-free environment without employing poisonous condensations solvents such as benzene or toluene. The liquid malonate **1** allowed a good interaction at room temperature

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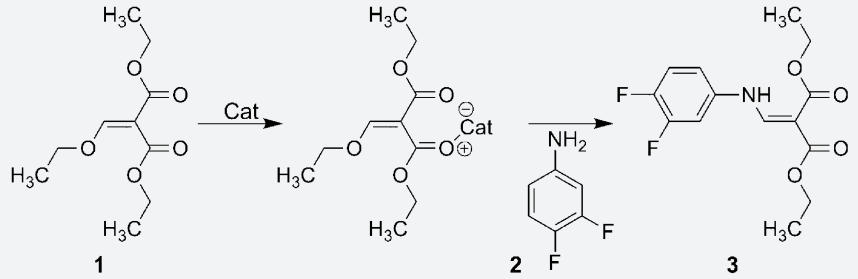
Table 1
Preparation of 3,4-difluoroacrylate **3** using Lewis and Brönsted acids as catalyst.



Sample	Catalyst[a] (mmol)		Yield (%)	mp (°C)	Time (min)
1 [19]	None		74	76–77	80[b]
2 [20]	None		81	80–81	120[c]
3	$CeCl_3$	1:100	54	76–77	120[d]
4	$CeCl_3$	1:100	67	76–77	3[e]
5	$CeCl_3$	1:100	52	76–77	7[f]
6	$CeCl_3$	1:150	55	76–77	1[e]
7	TsOH	1:200	46	72–73	33[e]
8	TsOH	1:150	37	72–73	39[e]
9	TsOH	1:100	60	68–69	28[e]
10	$AlCl_3$	1:100	70	73–74	23[e]
11	$AlCl_3$	1:150	61	74–75	25[e]
12	$AlCl_3$	1:200	60	72–73	27[e]
13	$ZnCl_2$	1:100	45	68–69	20[e]
14	$ZnCl_2$	1:150	43	68–69	10[e]
15	$ZnCl_2$	1:100	43	66–67	41[f]

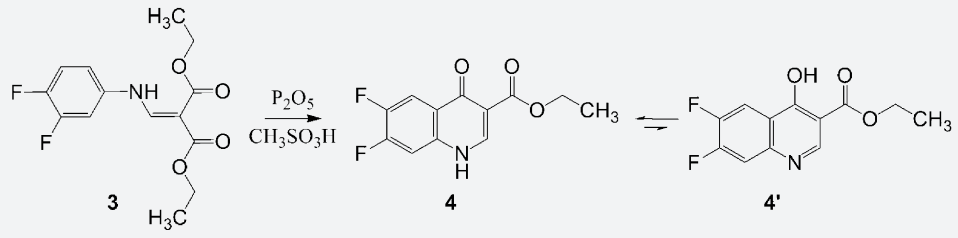
[a] Relationship catalyst:feedstock.
[b] 100 °C.
[c] 110–120 °C.
[d] 80 °C.
[e] rt.
[f] 0 °C.

between oxygen-carbonyl group and the catalyst, forming the complex malonate-Lewis acid that reacted with the liquid 3,4-difluoroaniline **2** in order to obtain a pink solid. This interaction was more efficient with $CeCl_3{\cdot}7H_2O$ than $AlCl_3{\cdot}6H_2O$ followed by TsOH and $ZnCl_2$. A further re-crystallization produced a white solid **3** in fairly good yields (Table 1).

The ionic bonding contributions of Ce^{3+} ion combined with the high Lewis acidity cause the strong oxophilicity shown in the lanthanide cations [21], catalyzing Michael addition reaction in less time over the Al^{3+} ion that possesses a strong affinity toward various heteroatoms due to its low polarizability and small ionic radii. In contrast, the high polarizability of the Zn^{2+} ion exerts a lower force of attraction over the electronic density in a malonate molecule than aluminum or cerium salts, presenting a lower oxophilicity and reacting over a long time. In a similar way, protonation of malonate carbonyl groups by TsOH, resulted in a poor electronic density movement, a longer time of reaction and the lowest yields [22]. Moreover, because of the shortest reaction time and highest purity, according to the melting data, the best catalyst to use in this Michael addition reaction could be Ce^{3+} ion.

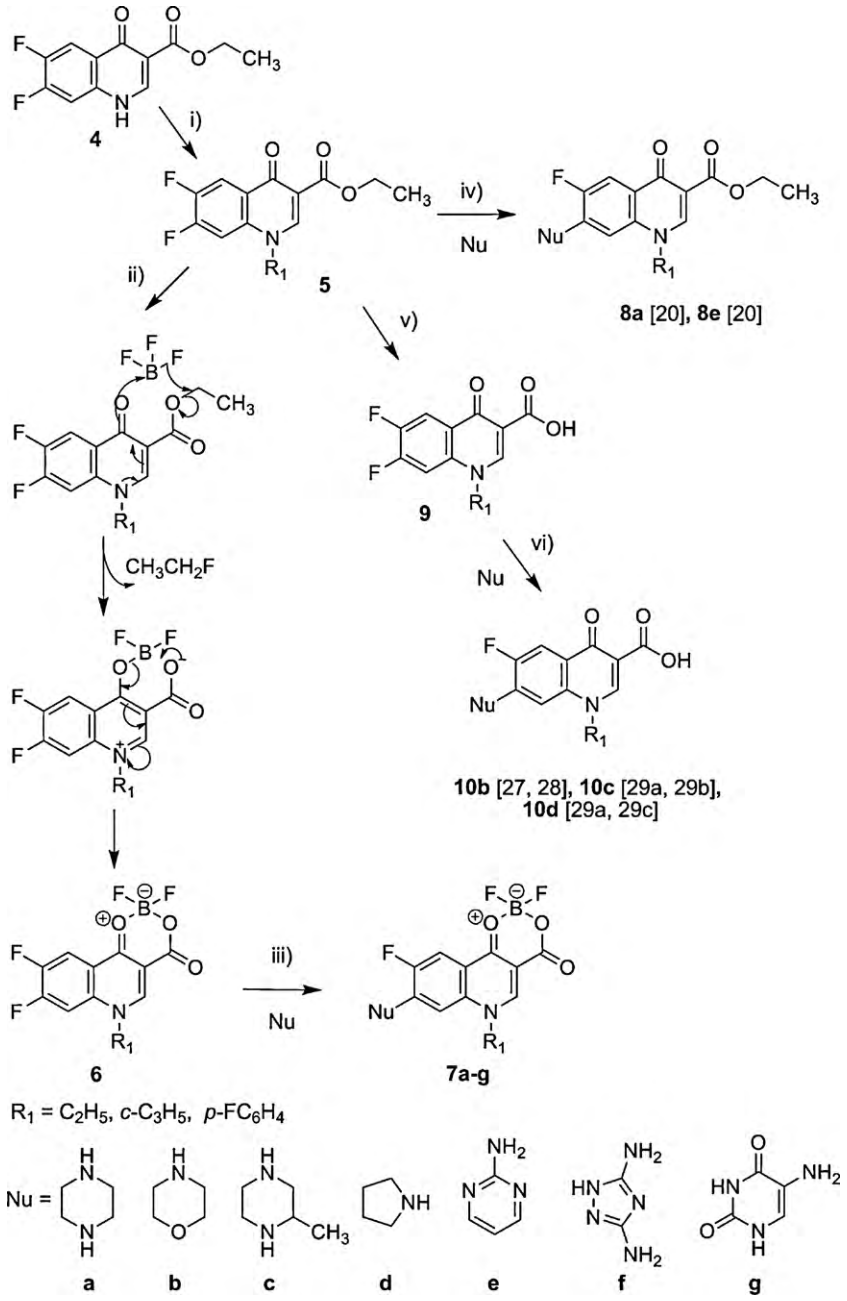
Cyclization of acrylate **3** was achieved with the use of Eaton's reagent decreasing the reported temperature from 250 °C to 55 °C, obtaining the hydroxyquinoline **4** in a 50% yield (Table 2). The reaction probably followed a 2+2+2 electrocyclization upon

Table 2
Preparation of ethyl 6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate **4** using Eaton's reagent.



Sample	Molar ratio[a] (mmol)	Time (h)	Yield (%)	sp[b] (°C)	Temp (°C)
1 [20]	None	6	87	241–242	250
2	5.1:1	168	8	229–230	63
3	3:1	22	17	229–230	55
4	3:1	168	0	–	rt
5	2:1	168	41	220–221	55
6	2.5:1	336	50	218–219	55

[a] Molar ratio (Eaton:acrylate).
[b] sp: sublimation point.



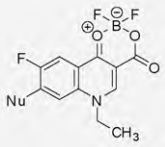
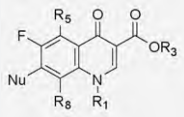
Scheme 1. Nucleophilic aromatic substitution at C-7 of difluoroquinolone ester, carboxylic acid and boron complex rings. (i) CH_3CH_2I, K_2CO_3, $(CH_3)_2NCHO$, 80–90 °C, 10 h. (ii) $BF_3{\cdot}OEt_2$, $(C_6H_5)_2O$, 200 °C, 30 min. (iii) CH_3SOCH_3, $N(C_2H_5)_3$, rt, 24 h. (iv) CH_3CN, reflux, 4 h for piperazine, or NaH 95%, C_5H_5N, reflux, 24 h for 2-aminopyrimidine. (v) (a) NaOH (2N), 110–120 °C, 2 h, (b) HCl (1:1) or H_2SO_4 2N, 80–90 °C, 2 h. (vi) morpholine or 2-methylpiperazine/N-methyl-2-pyrrolidinone, rt, 2 h for R_1 = *p*-FC_6H_4 [27], *c*-C_3H_5 [29a] or excess of pyrrolidine/pyridine, 95 °C, 4 h for $R_1 = C_2H_5$ [28].

protonation and then the hemiketal intermediate decomposed to form the hydroxyquinoline **4**. Variations on the molar ratio Eaton:acrylate influenced the reaction yield. An excess of polyphosphoric acid and temperatures for over 55 °C resulted in a drop regarding yields. Better results could be obtained using Na_2SO_3 as a saturated basic solution instead of water to stop cyclization reaction with moderate yields [23].

A further N-alkylation was carried out for obtaining ethyl 1-ethyl-6,7-difluoroquinolone-3-carboxylate **5** (Scheme 1). Synthesis of fluoroquinolone–boron complex has been performed with excellent results [24], but this method did not prove to be a good choice due to formation of HF as a sub-product when fluoroboric acid is used to convert ester **5** into boron complex **6** [25,26]. In our experimental procedure, the production of the boron chelated **6** was achieved with $BF_3{\cdot}OEt_2$. In this case, the CH_3CH_2F is generated as a sub-product, avoiding the formation of HF. The electron pair on the tertiary amine allows better conjugation with the ketone group on the pyridone ring, this electronic movement promotes the formation of an oxygen anion. Then the oxygen with negative charge can attack the BF_3 molecule, and the adduct is formed. High temperature induced the production of fluoroethane molecule and the corresponding complex **6**.

In this latter intermediate **6** [18] a more positive charge at C-7 is generated. Introduction of a heterocyclic amine (Table 3), classified as a poor nucleophile such as 5-amino-uracil into a fluoroquinolone ring by S_NAr reaction, was performed at room temperature in 24 h of reaction time and a 69% yield.

Table 3
Different heterocyclic amines used as nucleophiles in S_NAr on C-7 of fluoroquinolone–boron complex.

Entry	Nucleophile	Product	Yield (%)	mp (°C)	Product	Yield (%)	mp (°C)
							
1	Piperazine	**7a**	82	268–269	**8a**	46	172–173[a]
2	Morpholine	**7b**	93	269–270	**10b**	56	None[b]
						51	281–283[c]
3	2-Methyl-piperazine	**7c**	74	286–287	**10c**	50	168–169[d]
						52	235–237[e]
						33	225–227[e]
						30	277–280[e]
4	Pyrrolidine	**7d**	75	285–286	**10d**	52	222–223[d]
						56	233–234[f]
5	2-Amino-pyrimidine	**7e**	69	336–338	**8e**	41	266–267[a]
6	3,5-Diamino-1,2,4-triazole	**7f**	54	>400	None	None	None
7	5-Amino-uracil	**7g**	69	>400	None	None	None

[a] $R_1 = C_2H_5$, $R_3 = C_2H_5$, $R_8 = H$ [20].
[b] $R_1 = p\text{-}FC_6H_4$, R_3, R_5 and $R_8 = H$ [27].
[c] $R_1 = C_2H_5$, $R_3 = H$, R_5 and $R_8 = F$ [28].
[d] $R_1 = c\text{-}C_3H_5$, R_3 and $R_5 = H$, $R_8 = OEt$ [29a].
[e] $R_1 = c\text{-}C_3H_5$, $R_3 = H$, $R_8 = F$, $R_5 = F$, Cl, OH [29b].
[f] $R_1 = c\text{-}C_3H_5$, $R_3 = H$, $R_5 = NH_2$, $R_8 = F$ [29c].

Pyrrolidine, morpholine, piperazine and 2-methylpiperazine rings are expected to be good nucleophiles because of their sp^3-hybridized nitrogen. On the other hand, in the 3,5-diamino-1,2,4-triazole, 2-amino-pyrimidine and 5-amino-uracil compounds, the electron pair on the nitrogen is delocalized into the ring atom, since the neighbor carbon is sp^2-hybridized. Therefore, these heterocyclic amines are poor nucleophiles and they reacted under mild conditions giving good substitution yields on C-7 when the fluoroquinolone–boron complex is used. Fluoroquinolone antibacterials are commonly prepared by direct amination of 1-ethyl-6,7-difluoroquinolone-3-carboxylic acid **9** [27,28,29a–c] or ester **5** [20] with heterocyclic amines having low to moderate yields with longer reaction times and higher temperatures.

3. Conclusions

We have synthesized various 7-substituted-6-fluoroquinonolone–boron complexes in moderate yields. The Michael condensation (between 3,4-difluoroaniline and malonate) was catalyzed by Lewis and Brönsted acids in a solvent-free environment in a very short time. Cyclization was performed decreasing the temperature from 250 °C to 55 °C with Eaton's reagent. Then, the S_NAr substitutions in C-7 were realized with poor nucleophiles in a more reactive fluoroquinolone–boron complex to produce norfloxacin analogues. A further treatment with a basic solution (NaOH 2N) could be used to generate the corresponding fluoroquinolone-3-carboxylic acid [30,31]

4. Experimental

4.1. Instruments

The melting points were obtained by using a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Fourier Perkin Elmer, FTIR-1600 spectrophotometer. The NMR spectra were recorded on a Varian 300 MHz spectrometer using TMS as the internal standard. Mass spectrometry was done on a JEOL apparatus using FAB^+ technique.

4.2. Diethyl 2-(3,4-difluoro)-phenyl-aminomethylenemalonate (3)

A measured amount of Lewis acid: $CeCl_3{\cdot}7H_2O$, $AlCl_3{\cdot}6H_2O$, $ZnCl_2$ or Brönsted acid: TsOH (33.4 μmol) was added to diethyl ethoxymethylenemalonate **1** (3.34 mmol) and allowed it to react for 15 min at a room temperature (25 °C). Then, 3,4-difluoroaniline **2** (3.34 mmol) was added. After 3 min of reaction, a pink solid was obtained and poured into warm n-hexane (5 mL) until achieving its complete dissolution. The formation of two phases was observed when the temperature of suspension decreased. The upper phase was removed and the lower one was left to cool down to allow crystallization. The 3,4-difluoroacrylate **3** was obtained as white needles and separated by vacuum filtration in 67% yield, m.p. 76–77 °C. IR (KBr, cm^{-1}): 3263 (N–H, secondary amine), 3175 (N–H, overtone), 1686 and 1645 (C=O, ester), 1629 (C=C, alkene), 1594 and 1522 (C=C, aromatic), 1381 (CH_3), 1300–1200 (C–O), 1250 and 1100 (C–F), 1076 (C–N, secondary amine). ^1H NMR ($CDCl_3$) δ ppm: 10.97 (1H, d, J = 13.50 Hz, amine H), 8.36 (1H, d, J = 13.50 Hz, vinyl H), 7.17 (1H, dd, J = 9.00, 6.50 Hz, aromatic H), 6.98 (1H, m, aromatic H), 6.85 (1H, dd, J = 9.00, 2.50 Hz, aromatic H), 4.31 (2H, q, J = 7.00 Hz, CH_2), 4.25 (2H, q, J = 7.00 Hz, CH_2), 1.38 (3H, t, J = 7.00 Hz, CH_3), 1.33 (3H, t, J = 7.00 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ ppm: 168.94 and 165.41 (C=O ester), 151.67 and 94.67 (vinyl C), 106.64, 149.92, 146.58, 136.18, 118.38 and 113.06 (aromatic C), 60.59 and 60.28 (CH_2), 14.39 and 14.24 (CH_3). The exact mass was 322.0861 amu, the mass observed was 322.0873 amu for $C_{14}H_{15}F_2NO_4Na^+$.

4.3. Ethyl 6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (4)

The Eaton's reagent (2.5 mmol) was added to diethyl 2-(3,4-difluoro)-phenyl-aminomethylenemalonate **3** (1.66 mmol) and allowed to react under stirring for 2 weeks at 55 °C. After then, the reacting mixture was poured into water to yield a yellow solid.

It was filtered, washed twice with ethanol/acetone (1:1) and refluxed with ethanol for 30 min. The hydroxyquinoline **4** was filtered and dried to give a white powder (50% yield) with s.p. 218–219 °C. IR (KBr, cm^{-1}): 1697 (C=O, ester), 1621 (C=C, alkene), 1565 and 1533 (C=C, aromatic), 1495 (CH_2), 1381 (CH_3), 1292 and 1263 (C–O), 1250 and 1100 (C–F), 1082 (C–N, secondary amine). ^{1}H NMR (*DMSO*-d_6) δ ppm: 8.59 (1H, s, vinyl H), 7.99 (1H, dd, J = 8.96, 7.44 Hz, aromatic H), 7.64 (1H, dd, J = 8.96, 7.44 Hz, aromatic H), 4.21 (2H, q, J = 7.00 Hz, CH_2), 1.27 (3H, t, J = 7.00 Hz, CH_3). The exact mass was 276.0442 amu and the mass observed was 276.0440 amu for $C_{12}H_9F_2NO_3Na^+$.

4.4. Ethyl 1-ethyl-6,7-difluoroquinolone-3-carboxylate (5)

The hydroxyquinoline **4** (10 mmol) was added into a flask with K_2CO_3 (24.96 mmol), EtI (50 mmol) and dimethylformamide (20 mL), and refluxed at 80–90 °C for 10 h. The $KHCO_3$ produced was removed by hot filtration and washed with ethanol. After cooling the liquid phase at room temperature, the formation of white rectangular needles was observed. The solid was washed with hot ethanol to give the compound **5**, m.p. 154–155 °C and 85% yield. IR (KBr, cm^{-1}): 1717 (C=O, pyridone), 1686 (C=O, ester), 1618 (C=C, alkene), 1565 and 1497 (C=C, aromatic), 1388 (CH_3), 1290 and 1230 (C–O), 1184 and 1080 (C–F), 1080 (C–N, tertiary amine). ^{1}H NMR (*DMSO*-d_6) δ ppm: 8.69 (1H, s, vinyl H), 8.06 (2H, m, aromatic H), 4.37 (2H, q, J = 7.28 Hz, CH_2), 4.22 (2H, q, J = 7.28 Hz, CH_2), 1.33 (3H, t, J = 7.28 Hz, CH_3), 1.27 (3H, t, J = 7.28 Hz, CH_3). ^{13}C NMR (*DMSO*-d_6) δ ppm: 171.30 (C=O ketone), 164.29 (C=O ester), 149.42 and 110.05 (vinyl C), 153.54, 146.42, 136.04, 125.71, 113.85 and 106.90 (aromatic C), 59.86 and 48.42 (CH_2), 14.25 (CH_3). The exact mass was 304.0755 amu and the mass observed for $C_{14}H_{13}F_2NO_3Na^+$ was 304.0752 amu.

4.5. Difluoroboranyl 1-ethyl-6,7-difluoroquinolone-3-carboxylate (6)

The ethyl 1-ethly-6,7-difluoroquinolone-3-carboxylate 5 (2.29 mmol) and $BF_3{\cdot}OEt_2$ (2.72 mmol) were added into diphenylether (10 mL) at 200 °C and refluxed for 30 min. The solid obtained was separated by filtration and washed with ethyl acetate to afford compound **6** as a white solid in 93% yield and m.p. 292–293 °C. IR (KBr, cm^{-1}): 1715 (C=O, pyridone), 1637 (C=O, ester), 1583 (C=C, alkene), 1554 and 1487 (C=C, aromatic), 1388 (CH_3), 1308 and 1268 (C–O, ester), 1140 and 1040 (C–F), 1075 (C–N, tertiary amine). ^{1}H NMR (*DMSO*-d_6) δ ppm: 9.61 (1H, s, vinyl H), 8.69 (1H, dd, J = 12.44, 6.59 Hz, aromatic H), 8.55 (1H, dd, J = 12.44, 6.59 Hz, aromatic H), 4.88 (2H, q, J = 7.32 Hz, CH_2), 1.48 (3H, t, J = 7.32 Hz, CH_3). ^{13}C NMR (*DMSO*-d_6) δ ppm: 167.50 (C=O ketone), 159.52 (C=O ester), 154.70 and 108.64 (vinyl C), 151.01, 149.60, 137.64, 119.43, 112.71 and 107.13 (aromatic C), 51.73 (CH_2), 14.61 (CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 302 $[M+1]^+$ (16), 289 $[M+1-CH_3+H_2]^+$ (39), 282 $[M-F]^+$ (9), 236 $[M-CH_3-BF_2-H]^+$ (7), 220 $[M-CH_3-BF_2+H_2-F]^+$ (41), 205 $[M-CH_3-BF_2+H_2-F-CH_3]^+$ (16), 167 $[M-BF_2-2CO-C_2H_5]^+$ (25), 137 $[M+2H_2-BF_2-CO_2-C_2H_4-CO-F]^{+\cdot}$ (100), 136 $[M+H_2-BF_2-CO_2-C_2H_4-CO+H-F]^{+\cdot}$ (98), 107 $[M+H_2-BF_2-CO_2-C_2H_4-CO+H-F-C_2H_5]^+$ (51).

4.6. General procedure for difluoroboranyl 1-ethyl-6-fluoro-7-(substituent)-quinolone-3-carboxylate (7a–g)

The corresponding amine (1 mmol) was added into a flask with dimethylsulfoxide (3 mL), triethylamine (138.83 μL) and difluoroboranyl 1-ethyl-6,7-difluoroquinolone-3-carboxylate 6 (665.70 μmol) stirring for 24 h at room temperature. After that, ethanol was added and a solid was formed. The solvent was removed by filtration and the solid was dried under vacuum.

4.6.1. Difluoroboranyl 1-ethyl-6-fluoro-7-(piperazin-1-yl)-quinolone-3-carboxylate (7a)

It was obtained as a yellow solid in 82% yield and m.p. 268–269 °C. IR (KBr, cm^{-1}): 3347 (N–H, secondary amine), 2967–2763 (CH_2), 1704 (C=O, pyridone), 1638 (C=O, ester), 1574 (C=C, alkene), 1529 and 1490 (C=C, aromatic), 1453 (CH_2), 1256 and 1137 (C–O), 1105 and 1038 (C–N, tertiary amine), 1105 (C–F). ^{1}H NMR (*DMSO*-d_6) δ ppm: 9.62 (1H, s, vinyl H), 8.27 (1H, d, J = 13.93 Hz, aromatic H), 7.70 (1H, d, J = 7.32 Hz, aromatic H) 3.64 (4H, t, J = 5.12 Hz, piperazine CH_2), 3.15 (4H, t, J = 5.12 Hz, piperazine CH_2), 3.48 (1H, br s, amine H), 5.20 (2H, q, J = 7.32 Hz, CH_2), 1.83 (3H, t, J = 7.32 Hz, CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 368 $[M+1]^+$ (48), 348 $[M-F]^+$ (7), 320 $[M+H_2-BF_2]^+$ (8), 307 $[M-F+H_2-CH_3-CO]^+$ (41), 289 $[M+2H_2-BF_2-H_2O-CH_3]^+$ (21), 220 $[M+H_2-BF_2-CO_2-CO-C_2H_4]^+$ (10), 155 $[M-OBF_2-C_2H_4-CO-C_5H_7NO+3H_2]^{+\cdot}$ (39), 154 $[M-OBF_2-C_2H_4-CO-C_5H_7NO+2H_2+H]^+$ (100), 136 $[M+H_2-BF_2-CO_2-CO-C_2H_3-N_2C_4H_9]^+$ (95).

4.6.2. Difluoroboranyl 1-ethyl-6-fluoro-7-(morpholin-1-yl)-quinolone-3-carboxylate (7b)

It was obtained as a beige solid in 93% yield and m.p. 269–270 °C. IR (KBr, cm^{-1}): 1726 (C=O, pyridone), 1637 (C=O, ester), 1613 (C=C, alkene), 1581 and 1490 (C=C, aromatic), 1449 and 1414 (CH_2), 1284–1245 (C–O), 1126 (C–N, tertiary amine), 1064 (C–F). ^{1}H NMR (*DMF*-d_7) δ ppm: 9.62 (1H, s, vinyl H), 8.31 (1H, d, J = 14.08 Hz, aromatic H), 7.76 (1H, d, J = 7.31 Hz, aromatic H), 5.21 (2H, q, J = 7.32 Hz, CH_2), 4.04 (4H, t, J = 5.12 Hz, morpholine CH_2), 3.72 (4H, t, J = 5.12 Hz, morpholine CH_2), 1.83 (3H, t, J = 7.32 Hz, CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 369 $[M+1]^+$ (48), 349 $[M-F]^+$ (7), 321 $[M+H_2-BF_2]^+$ (17), 307 $[M-BF_2-CH_3+H_2+H]^+$ (60), 289 $[M-OBF_2-CH_3+H]^+$ (29), 220 $[M-BF_2-CO_2-CO-C_2H_3]^+$ (11), 154 $[M-OBF_2-CO-C_5H_7NO-C_2H_4+2H_2]^{+\cdot}$ (100), 137 $[M-BF_2-CO_2-CO-C_2H_2-C_4H_8NO+H_2]^+$ (100), 136 $[M-BF_2-CO_2-CO-C_2H_2-C_4H_8NO+H]^+$ (100).

4.6.3. Difluoroboranyl 1-ethyl-6-fluoro-7-(3-methyl-piperazin-1-yl)-quinolone-3-carboxylate (7c)

It was obtained as a yellow solid in 74% yield and m.p. 286–287 °C. IR (KBr, cm^{-1}): 3267 (N–H, secondary amine), 3055 (C–H, alkene and aromatic), 2963 and 2845 (CH_2), 1722 (C=O, pyridone), 1636 (C=O, ester), 1582 (C=C, alkene), 1530 and 1489 (C=C, aromatic), 1450 (CH_2), 1395 (CH_3), 1268 and 1125 (C–O), 1125 and 1082 (C–N, tertiary amine), 1081 (C–F). ^{1}H NMR (*DMF*-d_7) δ ppm: 9.58 (1H, s, vinyl H), 8.27 (1H, d, J = 13.96 Hz, aromatic H), 7.07 (1H, d, J = 7.31 Hz, aromatic H), 5.20 (2H, q, J = 7.32 Hz, CH_2), 3.98 (4H, t, J = 7.97 Hz, piperazine CH_2), 3.22 (2H, td, J = 10.97, 1.63 Hz, piperazine CH_2), 3.13 (2H, m, piperazine CH and amine H), 1.82 (3H, t, J = 7.32 Hz, CH_3), 1.25 (3H, d, J = 6.59 Hz, piperazine CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 382 $[M+1]^+$ (74), 362 $[M-F]^+$ (34), 361 $[M-HF]^+$ (11), 334 $[M-BF_2+H_2]^+$ (7), 316 $[M-BF_2+H_2-H_2O]^+$ (29), 307 $[M-BF_2+H-C_2H_4+H_2]^+$ (43), 289 $[M-BF_2-H_2O-C_2H_5+2H_2]^+$ (22), 279 $[M-BF_2-C_2H_5+2H_2-CO]^+$ (6), 220 $[M-OBF_2-2CO-C_2H_4-CH_3+H_2+H]^+$ (41), 205 $[M-OBF_2-2CO-C_2H_4-C_2H_5+H_2]^+$ (16), 154 $[M-OBF_2-C_2H_3-CO-C_3H_6-C_3H_3NO+2H_2]^+$ (100), 136 $[M-OBF_2-C_2H_3-CO-C_3H_6-C_3H_3NO+2H_2-F+H]^+$ (100).

4.6.4. Difluoroboranyl 1-ethyl-6-fluoro-7-(pyrrolidin-1-yl)-quinolone-3-carboxylate (7d)

It was obtained as a yellow solid in 75% yield and m.p. 285–286 °C. IR (KBr, cm^{-1}): 1700 (C=O, pyridone), 1640 (C=O, ester), 1571 (C=C, alkene), 1540 and 1497 (C=C, aromatic), 1431 (CH_2), 1355 and 1248 (C–O), 1121 and 1100 (C–N, tertiary amine), 1047 (C–F). ^{1}H NMR (*DMF*-d_7) δ ppm: 9.44 (1H, s, vinyl H), 8.15 (1H, d, J = 10.25 Hz, aromatic H), 7.16 (1H, d, J = 7.32 Hz, aromatic H), 5.09 (2H, q, J = 7.32 Hz, CH_2), 3.94 (4H, m, J = 3.66 Hz, pyrrolidine CH_2),

2.22 (4H, m, J = 3.66 Hz, pyrrolidine CH_2), 1.80 (3H, t, J = 7.32 Hz, CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 353 $[M+1]^+$ (31), 333 $[M-F]^+$ (16), 307 $[M-BF_2+2H_2]^+$ (82), 287 $[M-BF_2+H-OH]^+$ (14), 220 $[M-BF_2+2H_2-CO_2-CO-CH_3]^+$ (49), 205 $[M-BF_2+2H_2-CO_2-CO-2CH_3]^+$ (19), 154 $[M-OBF_2-CO-C_2H_4-C_2H_3-C_3H_2O+2H_2]^+$ (100), 137 $[M-OBF_2-CO-C_2H_4-C_2H_3-C_3H_2O-F+3H_2]^+$ (100), 136 $[M-OBF_2-CO-C_2H_4-C_2H_3-C_3H_2O+2H_2-F+H]^+$ (100).

*4.6.5. Difluoroboranyl 1-ethyl-6-fluoro-7-(pyrimidin-2-yl-amino)-quinolone-3-carboxylate (**7e**)*

It was obtained as a brown solid in 69% yield and m.p. 336–338 °C. IR (KBr, cm^{-1}): 1715 (C=O, pyridone), 1636 (C=O, ester), 1583 (C=C, alkene), 1553 and 1509 (C=C, aromatic), 1267–1133 (C–O), 1042 (C–F). ^{1}H NMR (*DMF*-d_7) δ ppm: 9.88 (1H, s, vinyl H), 9.00 (3H, dd, J = 12.48, 6.59 Hz, aromatic H, pyrimidine 2H), 8.76 (2H, dd, J = 10.25, 8.05 Hz, aromatic H, pyrimidine H), 8.18 (1H, br s, amine H), 5.27 (2H, q, J = 7.32 Hz, CH_2), 1.84 (3H, t, J = 7.32 Hz, CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 307 $[M-BF_2+H-OH-H_2]^+$ (32), 238 $[M-OBF_2-CO-C_2H_4-F+H_2]^+$ (8), 154 $[M-OBF_2-CO-C_3H_2O-C_4H_3N_2+2H_2]^+$ (100).

*4.6.6. Difluoroboranyl 1-ethyl-6-fluoro-7-(5-amino-1H-[1,2,4]-triazol-3-yl-amino)-quinolone-3-carboxylate (**7f**)*

It was obtained as an orange needles in 54% yield and m.p. >400 °C. IR (KBr, cm^{-1}): 3316 and 3133 (N–H, primary amine), 1709 (C=O, pyridone), 1656 (C=N–C, heterocycle), 1625 (C=O, ester), 1540 (C=C, alkene), 1581, 1485 and 1412 (C=N, heterocycle), 1288–1258 (C–O), 1048 (C–F). ^{1}H NMR (*DMF*-d_7) δ ppm: 9.86 (1H, s, vinyl H), 8.80 (1H, d, J = 10.25 Hz, aromatic H), 8.59 (1H, d, J = 6.59 Hz, aromatic H), 8.18 (1H, s, amine H), 6.99 (2H, s, amine H), 5.67 (1H, s, amine H), 5.31 (2H, q, J = 7.32 Hz, CH_2), 1.87 (3H, t, J = 7.32 Hz, CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 381 $[M+1]^+$ (32), 361 $[M-F]^+$ (18), 307 $[M-CH_3N_3-CH_3-H]^+$ (23), 289 $[M-CH_3N_3-CH_3-F]^+$ (21), 254 $[M-BF_2-C_2H_5+2H_2-OH-NH_2-F+H_2]^+$ (10), 154 $[M-OBF_2-CO-C_2H_5-C_3H_2O-C_2H_2N_4+2H_2]^+$ (100), 136 $[M-OBF_2-CO-C_2H_5-C_3H_2O-C_2H_2N_4+2H_2-F+H]^+$ (81).

*4.6.7. Difluoroboranyl 1-ethyl-6-fluoro-7-(2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl-amino)-quinolone-3-carboxylate (**7g**)*

It was obtained as a dark goldenrod solid in 69% yield and m.p. >400 °C. IR (KBr, cm^{-1}): 3374 and 3200 (N–H, amide), 1710 (C=O, pyridone and amide), 1639 (C=O, ester), 1583 (C=C, alkene), 1553 and 1485 (C=C, aromatic) 1480 (C–N, heterocycle), 1318 and 1279 (C–O), 1047 (C–F). ^{1}H NMR (*DMF*-d_7) δ ppm: 9.53 (1H, s, amine H), 9.48 (1H, s, amine H) 9.36 (1H, s, vinyl H), 8.48 (1H, d, J = 10.25 Hz, aromatic H), 7.63 (1H, d, J = 8.05 Hz, aromatic H), 6.83 (1H, s, amine H), 5.07 (1H, d, J = 6.59 Hz, (uracil) vinyl H), 4.94 (2H, q, J = 7.23 Hz, CH_2), 1.71 (3H, t, J = 7.23 Hz, CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 391 $[M-F+H_2]^+$ (48), 307 $[M-BF_2-CO-C_2H_4+2H_2]^+$ (31), 289 $[M-OBF_2-CO-C_2H_4+H_2]^+$ (14), 220 $[M-OBF_2-CO-C_3H_2O-CHNO+H_2]^+$ (28), 205 $[M-OBF_2-CO-C_3H_2O-CHNO+H_2-CH_3]^+$ (20), 154 $[M-OBF_2-CO-C_3H_2O-C_4H_2N_2O_2+H_2+H]^+$ (100).

*4.7. Ethyl 1-ethyl-6-fluoro-7-(piperazin-1-yl)-quinolone-3-carboxylate (**8a**)*

A mixture of difluoroquinonolone ester **5** (1.78 mmol) and piperazine (7.12 mmol) in 14 mL of CH_3CN was heated under reflux for 4 h, cooled, and concentrated. 12 mL of CH_2Cl_2 was poured into the residue and then, 6 mL of deionized H_2O was added. The organic phase was dried with Na_2SO_4 and concentrated to give a yellow solid, which was re-crystallized in $CHCl_3$/CH_3CH_2OH (70:30) resulting in a white solid (46%) and m.p. 172–173 °C. IR (KBr, cm^{-1}): 3650–3100 (N–H, secondary amine), 1709 (C=O, ester), 1617 (C=O, pyridone), 1584 and 1483 (C=C, aromatic), 1312 and 1251 (C–O, ester). ^{1}H NMR (CD_2Cl_2) δ ppm: 8.49 (1H, s, vinyl H), 8.15 (1H, d, J = 10.26 Hz, aromatic H), 6.82 (1H, d, J = 7.47 Hz, aromatic H), 4.48 (2H, q, J = 7.32 Hz, CH_2), 4.29 (2H, q, J = 7.32 Hz, CH_2), 3.31 (4H, br s, piperazine CH_2), 3.19 (4H, br s, piperazine CH_2), 2.02 (1H, br s, amine H), 1.63 (3H, t, J = 7.32 Hz, CH_3), 1.50 (3H, t, J = 7.32 Hz, CH_3). ^{13}C NMR (CD_3COCD_3) δ ppm: 175.73 (C=O ketone), 168.58 (C=O ester), 150.58 and 106.39 (vinyl C), 147.85, 138.81, 126.47, 116.50, 116.22 and 113.27 (aromatic C), 63.46, 53.96, 51.59 and 48.68 (CH_2), 17.07 (CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 348 $[M+1]^+$ (100), 303 $[M-C_2H_5O+H]^+$ (13), 302 $[M-C_2H_5OH+H]^+$ (99). The mass exact of $C_{18}H_{22}FN_3O_3Na^+$ was 370.1543 amu, the observed mass was 370.1535 amu.

*4.8. Ethyl 1-ethyl-6-fluoro-7-(pyrimidin-2-yl-amino)-quinolone-3-carboxylate (**8e**)*

The difluoroquinolone ester **5** (1.28 mmol) was added to a suspension of 2-amino-pyrimidine (3.84 mmol), 95% NaH (4.44 mmol) and pyridine (15 mL). The reaction mixture was refluxed for 24 h under nitrogen atmosphere, cooled, and concentrated. The residue was dissolved in 30 mL of ethanol, boiled for 5 min, and concentrated to a yellow solid. It was chromatographed on silica gel with 95:5 $CH_3CO_2CH_2CH_3$/$CHCl_3$ to give yellow crystals in 41% yield and mp 266–267 °C. IR (KBr, cm^{-1}): 3400 (N–H, secondary amine), 1715 (C=O, ester), 1662 (C=O, pyridone), 1581, 1560 and 1491 (pyrimidine), 1309 and 1225 (C–O, ester). ^{1}H NMR (CD_2Cl_2) δ ppm: 9.47 (2H, br s, pyrimidine H), 8.68 (2H, br s, vinyl H, pyrimidine H), 8.10 (2H, br s, aromatic H), 4.96 (2H, q, J = 7.32 Hz, CH_2), 4.75 (2H, q, J = 7.32 Hz, CH_2), 1.83 (3H, t, J = 7.32 Hz, CH_3), 1.62 (3H, t, J = 7.32 Hz, CH_3). ^{13}C NMR (CD_3COCD_3) δ ppm: 174.06 (C=O ketone), 165.04 (C=O ester), 140.31 and 110.21 (vinyl C), 169.42, 151.73 and 111.40 (pyrimidine C), 122.74, 121.53, 118.96, 116.55, 115.18 and 108.42 (aromatic C), 67.97 and 56.43 (CH_2), 17.05 and 16.15 (CH_3). MS FAB$^+$ (probe) 70 eV, m/z (rel. int.): 305 $[M-C_2H_5-F-2H_2+H]^+$ (32), 304 $[M-C_2H_5-F-2H_2]^+$ (100), 236 $[M-C_2H_5-CO_2-C_2H_4-F]^+$ (85).

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References

[1] V.T. Andriole, The Quinolones, 2nd ed., Academic Press, San Diego, CA, 1998.
[2] P. Ball, J. Antimicrob. Chemother. 46 (2000) 17–24.
[3] B.K. Srivastava, M. Solanki, B. Mishra, R. Soni, S. Jayadev, D. Valani, M. Jain, P.R. Patel, Bioorg. Med. Chem. Lett. 17 (2007) 1924–1929.
[4] H. Koga, A. Itoh, S. Murayama, S. Suzue, T. Irikura, J. Med. Chem. 23 (1980) 1358–1363.
[5] A.V. Shindikar, C.L. Viswanathan, Bioorg. Med. Chem. Lett. 15 (2005) 1803–1806.
[6] Z.-F. Chen, R.-G. Xiong, J.-L. Zuo, Z. Guo, X.-Z. You, H.-K. Fun, J. Chem. Soc. Dalton Trans. 22 (2000) 4013–4014.
[7] I. Turel, Coord. Chem. Rev. 232 (2002) 27–47.
[8] O. Muñoz-Muñiz, M. Quintanar-Audelo, E. Juaristi, J. Org. Chem. 68 (2003) 1622–1625.
[9] H. Yamamoto, Lewis Acid Reagent. A Practical Approach, Oxford University Press, London, 1998, reprint 2003.
[10] J.P. Cornard, J.C. Merlin, J. Inorg. Biochem. 92 (2002) 19–27.
[11] S.Y. Dike, J.R. Merchant, N.Y. Sapre, Tetrahedron 47 (1991) 4775–4786.
[12] P.E. Eaton, G.R. Carlson, J.T. Lee, J. Org. Chem. 38 (1973) 4071–4073.
[13] Y.-H. So, J.P. Heeschen, J. Org. Chem. 62 (1997) 3552–3561.
[14] D. Zhao, D.L. Hughes, D.R. Bender, A.M. DeMarco, P.J. Reider, J. Org. Chem. 56 (1991) 3001–3006.
[15] S.M.P. Gaudêncio, Synlett 16 (2005) 2545–2546.
[16] M.G. Zolotukhin, M.C.G. Hernández, A.M. López, L. Fomina, G. Cedillo, A. Nogales, T. Ezquerra, D. Rueda, H.M. Colquhoun, K.M. Fromm, A. Ruiz-Treviño, M. Ree, Macromolecule 39 (2006) 4696–4703.
[17] Y. Li, M.-Q. Chang, F. Gao, W.T. Gao, J. Chem. Res. (2008) 640–641.

[18] G. Anquetin, M. Rouquayrol, N. Mahmoudi, M. Santillana-Hayat, R. Gozalbes, J. Greiner, K. Farhati, F. Derouin, R. Guedj, P. Vierling, Bioorg. Med. Chem. Lett. 14 (2004) 2773–2776.
[19] A. Sagredo, B.Sc. Thesis, University of San Luis Potosí, México, 2001.
[20] S. Leyva, Ph.D. Thesis, University of San Luis Potosí, México, 2006.
[21] S. Cotton, Lanthanide and Actinide Chemistry, 2nd ed., Wiley, England, 2006.
[22] S. Kobayashi, 1st ed., Lanthanides: Chemistry and Use in Organic Synthesis, vol. 2, Springer, Germany, 1999.
[23] D. Zewge, C.-Y. Chen, C. Deer, P.G. Dormer, D.L. Hughes, J. Org. Chem. 72 (2007) 4276–4279.
[24] S. Deloisy, A. Olesker, G. Lukacs, Heterocycles 41 (1995) 259–265.
[25] V. Cecchetti, A. Fravolini, M. Palumbo, C. Sissi, O. Tabarrini, P. Terni, T. Xin, J. Med. Chem. 39 (1996) 4952–4957.
[26] X. Li, R.K. Russell, Org. Process Res. Dev. 12 (2008) 464–466.
[27] D.T.W. Chu, P.B. Fernandes, A.K. Claiborne, E. Pihuleac, C.W. Nordeen, R.E. Maleczka, A.G. Pernet, J. Med. Chem. 28 (1985) 1558–1564.
[28] D.B. Moran, C.B. Ziegler, T.S. Dunne, N.A. Kuck, Y.-I. Lin, J. Med. Chem. 32 (1989) 1313–1318.
[29] (a) J.P. Sanchez, R.D.G. Gogliotti, J.M. Domagala, S.J. Gracheck, M.D. Huband, J.A. Sesnie, M.A. Cohen, M.A. Shapiro, J. Med. Chem. 38 (1995) 4478–4487;
(b) T. Miyamoto, J. Matsumoto, K. Chiba, H. Egawa, K. Shibamori, A. Minamida, Y. Nishimura, H. Okada, M. Kataoka, J. Med. Chem. 33 (1990) 1645–1656;
(c) J.M. Domagala, S.E. Hagen, C.L. Heifetz, M.P. Hutt, T.F. Mich, J.P. Sanchez, A.K. Trehan, J. Med. Chem. 31 (1988) 503–506.
[30] D.T.W. Chu, P.B. Fernandes, R.E. Maleczka, C.W. Nordeen, A.G. Pernet, J. Med. Chem. 30 (1987) 504–509.
[31] M.M. Heravi, N. Nami, H.A. Oskooie, R. Hekmatshoar, Z. Jaddi, Phosphorus Sulfur Silicon 181 (2006) 797–801.