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A new general approach to 4-substituted-3-halo-2-quinolones

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ABSTRACT

A general procedure for the preparation of 4-substituted-3-halo-2-quinolones (halo = F, Cl, Br) utilizing 2-halo diethylphosphonoacetic acids (halo = F, Cl, Br) and *o*-aminophenylketones as the starting materials is described. The title compounds are obtained by an intramolecular Horner–Wadsworth–Emmons olefination of halogen-containing N-acyl-*o*-aminophenylketones. The transformation process is generally applicable under mild conditions.

1. Introduction

The 2-quinolone skeleton, as an important structure unit, usually presents in a large number of alkaloids and in biologically active compounds [1–3]. There has been considerable interest in developing 2-quinolones as anticancer [4], antibacterial [5], antihypertensive agents [6], and inhibitors of the macrophage colony-stimulating factor-1 receptor (FMS) and p38 Mitogen-activated protein (MAP) kinase [7,8]. Moreover, 2-quinolones are useful precursors to the corresponding quinolines and isoquinolines [9].

In recent years, an increasing interest in the synthesis of functionalized 2-quinolones with promising biological properties has been observed [10]. Especially, 4-substituted-3-halo-2-quinolones have been given more attention, which have been used as cardiac stimulants [11] and herbicides [12]. However, to the best of our knowledge, there is no general method for the synthesis of 4-substituted-3-halo-2-quinolones (halo = F, Cl, Br) reported. Some examples used direct halogenation of 4-substituted-2-quinolones, such as the bromination of 4-substituted-2-quinolones with NBS or bromine dissolved in acetic acid to prepare 4-substituted-3-bromo-2-quinolones [13]. Some used substitution of 4-substituted-2-quinolone derivates, such as $Rh_2(OAc)_4$ catalyzed cyclic diazodicarbonyl compounds with a variety of halides obtaining the corresponding 4-substituted-3-chloro(or 3-bromo)-2-quinolones [14]. And the substitution of 3-bromo-4-trifloxy-quinolin-2(1*H*)-one with $Pd(Cl)_2(PPh)_3$ was used to get 4-substituted-3-bromo-2-quinolones [15]. A frequently employed method is an intramolecular condensation of an N-acyl-*o*-aminophenylketone. For example, the condensation of α-chloro(or bromo)-aroylacetanilides with concentrated sulfuric acid giving the corresponding 4-substituted-3-chloro(or bromo)-2-quinolones [16,17], and the condensation of 2-chloro-2-(2-fluorobenzoyl) acetanilide with 85% KOH in DMF and H_2O giving 3-chloro-4-(2-fluorophenyl)-2(1*H*)-quinolinone [18]. Nevertheless, the limitation of methods reported lies in the difficulty of halogenation due to the difficulty in controlling their regioselectivity, the strong reaction conditions, and the side reactions involving polyhalogenation [19]. Other disadvantages involve the low yields of the reaction, a cumbersome and lengthy process, migration of substituents (rearrangement), and not readily available starting materials. Therefore, it is required to develop a general, effective and simple method to prepare 4-substituted-3-halo-2-quinolones. To pursue the goal, we adopted the strategy shown in Scheme 1. In order to obtain compounds **1** with high yields and easily controlled regioselectivity of reactions, an intramolecular Horner–Wadsworth–Emmons olefination of intermediates **2** was employed. The phosphonoacetate in molecules of intermediates **2** activated the carboxamide α-position, which could be eliminated after cyclization under basic conditions to produce compounds **1**. In this strategy, halogens were previously introduced into intermediates **2** by the acylation of 2-halo diethylphosphonoacetic acids **3** with *o*-aminophenylketones **4**, which could overcome the difficulty in controlling their regioselectivity.

2. Results and discussion

One of the starting materials 2-halo diethylphosphonoacetic acids **3** were easily prepared in good yields by the hydrolysis of triethyl 2-

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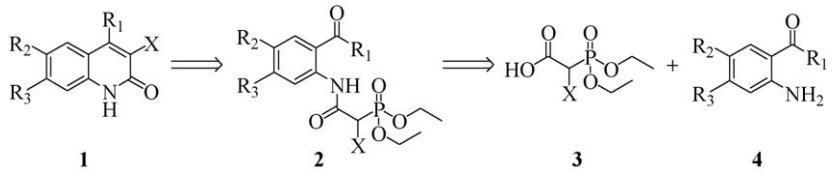
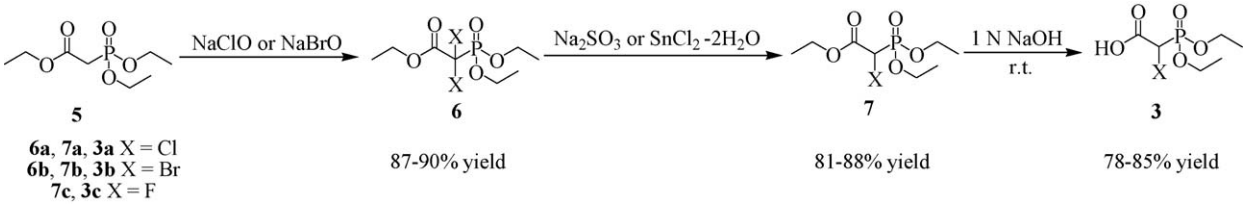
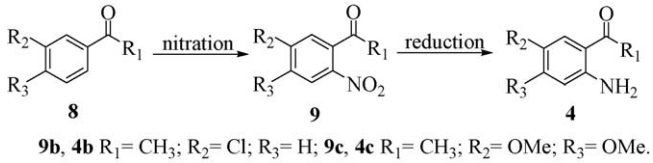


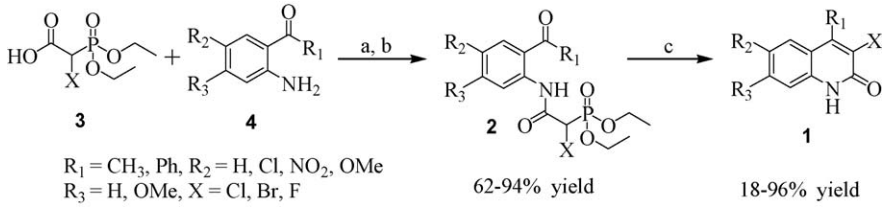
Scheme 1. Strategy for the preparation of 4-substituted-3-halo-2-quinolones.



Scheme 2. Preparation of 2-halo diethylphosphonoacetic acids **3**.



Scheme 3. Preparation of *o*-aminophenylketones.



Scheme 4. Preparation of 4-substituted-3-halo-2-quinolones. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, r.t., 24 h; (b) pyridine, CH_2Cl_2, 0 °C to r.t., 4.5 h; (c) THF, LiCl, DBU, r.t., 2 h.

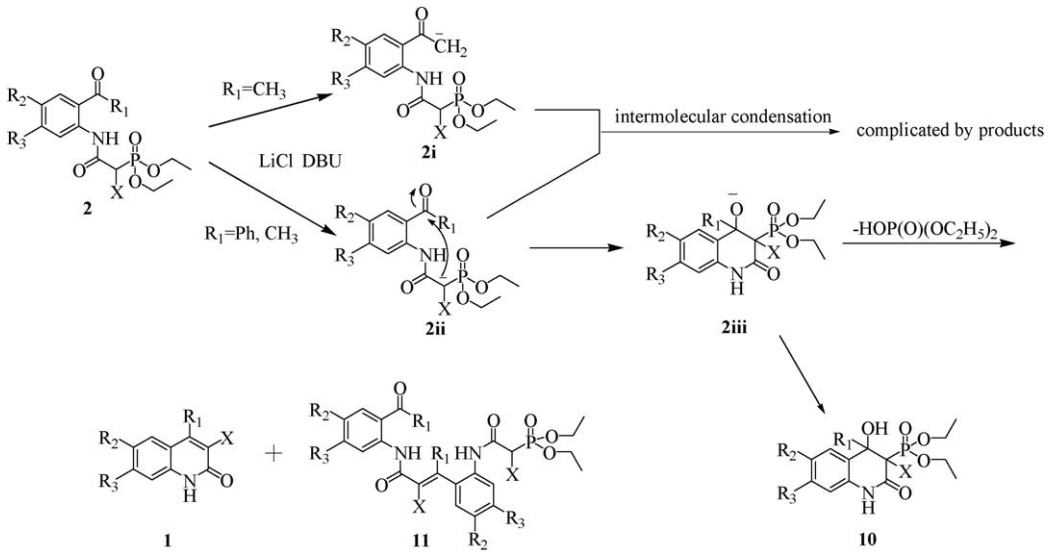
halo phosphonoacetates **7** with 1 N NaOH [20]. Triethyl 2-fluorophosphonoacetate **7c** was commercially available. However, triethyl 2-chlorophosphonoacetate **7a** and triethyl 2-bromophosphonoacetate **7b** were prepared according to literatures [21]. The method is illustrated in Scheme 2. Triethyl 2,2-dichlorophosphonoacetate **6a** was prepared by the chlorination of triethyl phosphonoacetate **5** using sodium hypochlorite, followed by selective reduction to convert the dichloro product to the corresponding triethyl 2-chlorophosphonoacetate **7a** with sodium sulfite. In the same way, triethyl 2,2-dibromophosphonoacetate **6b** was prepared by the bromination of triethyl phosphonoacetate **5** using the freshly prepared sodium hypobromite, followed by selective reduction to convert the dibromo product to the corresponding triethyl 2-bromophosphonoacetate **7b** with $SnCl_2$-$2H_2O$.

Another starting materials **4a**, **4d–f** were purchased from commercial sources. However, 2-amino-5-chloroacetophenone **4b** and 2-amino-4,5-dimethoxyacetophenone **4c** were prepared by ourselves. The method is illustrated in Scheme 3. 3-Chloroacetophenone **8b** was converted to 5-chloro-2-nitroacetophenone **9b** by nitration with fuming HNO_3 and concentrated H_2SO_4 at −20 °C, which was then reduced by iron powder in AcOH to form 2-amino-5-chloroacetophenone **4b** [22]. 3,4-Dimethoxyacetophenone **8c** was converted to 4,5-dimethoxy-2-nitroacetophenone **9c** by nitration with fuming HNO_3 and AcOH at 0 °C, which was then reduced into 2-amino-4,5-dimethoxyacetophenone **4c** by H_2 with PtO_2/C [23].

The intermediates **2** were prepared by the acylation of *o*-aminophenylketones **4a–f** with 2-halo diethylphosphonoacetic acids **3a–c** [8]. The method is illustrated in Scheme 4. In order to realize this transformation, **3** were first converted into acyl

Table 1
The preparation of intermediates **2a–r** using 2-halo diethylphosphonoacetic acids **3** and *o*-aminophenylketones **4**.

Compound	R_1	R_2	R_3	X	Conversion (%)	Yield (%)
2a	CH_3	H	H	Cl	98	94
2b	CH_3	Cl	H	Cl	96	93
2c	CH_3	OCH_3	OCH_3	Cl	95	92
2d	Ph	H	H	Cl	74	70
2e	Ph	Cl	H	Cl	95	90
2f	Ph	NO_2	H	Cl	92	88
2g	CH_3	H	H	Br	95	91
2h	CH_3	Cl	H	Br	96	92
2i	CH_3	OCH_3	OCH_3	Br	94	91
2j	Ph	H	H	Br	69	65
2k	Ph	Cl	H	Br	91	87
2l	Ph	NO_2	H	Br	90	85
2m	CH_3	H	H	F	98	92
2n	CH_3	Cl	H	F	98	92
2o	CH_3	OCH_3	OCH_3	F	96	90
2p	Ph	H	H	F	65	62
2q	Ph	Cl	H	F	94	89
2r	Ph	NO_2	H	F	93	88



Scheme 5. Proposed mechanism for the reaction of N-acyl-*o*-aminophenylketones with LiCl and DBU.

Table 2
The yields of 4-substituted-3-halo-2-quinolones **1** via a Horner–Wadsworth–Emmons route.

Entry	R_1	R_2	R_3	X	Purification methodology	mp (°C)	Yield (%)
1a	CH_3	H	H	Cl	Recrystallization	300–302	88
1b	CH_3	Cl	H	Cl	Recrystallization	272–274	95
1c	CH_3	OCH_3	OCH_3	Cl	Recrystallization	250–252	82
1d	Ph	H	H	Cl	Recrystallization	191–193	94
1e	Ph	Cl	H	Cl	Recrystallization	299–301	95
1f	Ph	NO_2	H	Cl	Recrystallization	221–223	96
1g	CH_3	H	H	Br	Recrystallization	268–269	85
1h	CH_3	Cl	H	Br	Recrystallization	204–206	88
1i	CH_3	OCH_3	OCH_3	Br	Recrystallization	227–229	78
1j	Ph	H	H	Br	Column chromatography	228–230	26
1k	Ph	Cl	H	Br	Column chromatography	218–220	18
1l	Ph	NO_2	H	Br	Column chromatography	202–204	19
1m	CH_3	H	H	F	Column chromatography	179–181	40
1n	CH_3	Cl	H	F	Column chromatography	211–213	38
1o	CH_3	OCH_3	OCH_3	F	Column chromatography	266–268	30
1p	Ph	H	H	F	Recrystallization	254–256	91
1q	Ph	Cl	H	F	Recrystallization	197–199	92
1r	Ph	NO_2	H	F	Recrystallization	188–190	93

halide *in situ* by using $(COCl)_2$ at room temperature, which then reacted with newly added *o*-aminophenylketones **4** in the presence of excessive pyridine to give compounds **2a–r**. The reaction underwent smoothly, and good yields were obtained except 2-aminodiphenyl methanone **4d** as substrate. The results are shown in Table 1. As can be seen from Table 1, the reaction was applicable to a variety of *o*-aminophenylketones **4**. The successful acylation of **4** with **3** was achieved when R_1 = alkyl and aryl, and R_2, R_3 as electron-donating and electron-withdrawing groups. In order to test the generality of this method, we embarked on a systematic study of substituted *o*-aminophenylketones **4** and 2-halo diethylphosphonoacetic acids **3** as starting materials.

Compounds **2** were subjected to cyclization under the mildly basic Masamune–Roush conditions (LiCl/DBU) [24]. As it turned out, the difference of the halogen and substituents had effect on the cyclization of the intermediates **2**. When X = Cl, all the cyclization of intermediates **2a–f** occurred smoothly to produce the expected 2-quinolones **1a–f** in excellent yields (Entries **1a–f**, Table 2).

However, in the case of X = Br, when R_1 = alkyl, the cyclization of intermediates **2g–i** gave the expected 2-quinolones **1g–i** in good yields, but when R_1 = aryl, the reactions were complicated, and the cyclization of intermediates **2j–l** gave **1j–l** only in yields of 18–26%. The expected products were obtained only as the minor products, and the unexpected byproducts **10** were isolated as the main one. Interestingly, the contrast results were observed for the cyclization of intermediates **2** with X = F. When R_1 = aryl, the cyclization of intermediates **2p–r** occurred smoothly to produce the expected 2-quinolones **1p–r** in excellent yields, but when R_1 = alkyl, the cyclization of intermediates **2m–o** gave **1m–o** only in yields of 30–40%, and a few byproducts were observed.

Based on the above results, we proposed the possible mechanism of the cyclization (Scheme 5). Two carbanions **2i** and **2ii** could be formed under basic conditions. Some unexpected products could be formed via carbanions **2i** by inter- and intramolecular condensations. Not only can carbanions **2ii** give expected products **1** and uneliminated products **10**, but also it can form unexpected products **11** by intermolecular condensation.

3. Conclusions

The reaction of *o*-aminophenylketones with 2-halo diethylphosphonoacetic acids provides a general procedure for 4-substituted-3-halo-2-quinolones from readily available starting materials. The

cyclization of halogenated N-acyl-*o*-aminophenylketones is mainly influenced by the halogen. Although some compounds were obtained in low yields, this new method may be considered as new halogen-containing substrates for the synthesis of a wide variety of heterocyclic compounds with potential biological activity. Study of this reaction and the nature of the products are being continued.

4. Experimental

Infrared spectra were measured on a Bruker Tensor 27 IR spectrophotometer. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), ^{31}P NMR (121 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on a Bruker AV-300. The spectra were recorded in $CDCl_3$ and DMSO-d_6 as solvent at room temperature. The chemical shifts (δ) were given in ppm, and the coupling constants (J) in Hz. HRMS spectra were recorded on a high resolution ESI-FTICR and MALDI-FTICR mass spectrometry. Melting points were determined on a X-4 digital display micromelting point apparatus and were uncorrected.

4.1. Triethyl 2-chlorophosphonoacetate (7a) [25]

A solution of 5.25% sodium hypochlorite (31.6 g, 22.3 mmol) was adjusted to pH 7.1 with approximately 2 mL of 3 N HC1. Triethyl phosphonoacetate (1.0 g, 4.5 mmol) was added dropwise at ice-bath temperature with vigorous stirring. After complete addition, the ice-bath was removed, and stirring was continued for an additional 5 min. The turbid solution was extracted with 5 × 5 mL of hexane. The combined hexane extracts were dried ($MgSO_4$), and the solvent was removed in vacuo at 50 °C to give triethyl 2,2-dichlorophosphonoacetate **6a** (1.18 g, 90% yield) as colourless oil. **6a** (1.1 g, 3.8 mmol) was dissolved in EtOH (7.5 mL), and the resulting solution was cooled in an ice-bath. A solution of sodium sulfite (1.0 g, 7.7 mmol) in H_2O (30 mL) was added with stirring at a rate such that the temperature could be maintained below 15 °C (15 min). During addition, the reaction mixture became turbid. After 20 min of further stirring at room temperature, it was extracted with chloroform (5 × 10 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude mixture was partitioned between hexane (20 mL) and 0.1 M $NaHCO_3$ (85 mL). The bicarbonate fractions were combined and re-extracted with chloroform (6 × 5 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to give pure **7a** (0.85 g, 88% yield) as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52 ppm (d, $^{2}J_{P,H}$ = 16.2, 1H, CHCl), 4.35–4.23 ppm (m, 6H, CH_2), 1.43–1.31 ppm (m, 9H, CH_3).

4.2. Triethyl 2-bromophosphonoacetate (7b) [21]

Triethyl phosphonoacetate (1.2 g, 5.4 mmol) was added over 3 min to the freshly prepared, stirred sodium hypobromite solution cooled in an ice-salt bath. The temperature was maintained below 10 °C. When addition was complete, the mixture was immediately extracted with chloroform (4 × 10 mL). The chloroform extracts were washed with water (2 × 2 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was partitioned between hexane (40 mL) and H_2O (2 × 0.5 mL) and the hexane extracts were dried ($MgSO_4$). Removal of the solvent in vacuo left pure triethyl 2,2-dibromophosphonoacetate **6b** (1.78 g, 87% yield) as colourless oil. To **6b** (2.0 g, 5.2 mmol) dissolved in EtOH (5 mL) was added with cooling (ice-bath) a solution of 1.12 g (5.0 mmol) of $SnCl_2$-$2H_2O$ in H_2O (10 mL). The temperature was maintained below 10 °C. When addition was complete (20 min), the reaction mixture was stirred for an additional 5 min at room temperature and then extracted with $CHCl_3$ (4 × 10 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The desired product was isolated by partitioning the crude residue between hexane (20 mL) and H_2O (4 × 5 mL). The aqueous fractions were combined and re-extracted with chloroform (3 × 10 mL). The chloroform extracts were dried ($MgSO_4$) and evaporated at reduced pressure to provide pure **7b** (1.28 g, 81% yield) as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.37 ppm (d, $^{2}J_{P,H}$ = 14.0, 1H, CHBr), 4.33–4.24 ppm (m, 6H, CH_2), 1.40–1.30 ppm (m, 9H, CH_3).

4.3. General procedure for the preparation of 2-halo diethylphosphonoacetic acids 3 [26]

To a solution of sodium hydroxide (0.84 g, 15.0 mmol) in water (15 mL) was added the triethyl 2-halo phosphonoacetate (10.0 mmol). The reaction mixture was stirred for 20 h at r.t. and then washed with CH_2Cl_2 (2 × 10 mL), acidified to pH 2 with 10% HCl and extracted with AcOEt (3 × 15 mL). After drying with $MgSO_4$, the solvent was evaporated under reduced pressure to give the acids **3**.

4.3.1. 2-Chloro diethylphosphonoacetic acid (3a)

1.96 g (85% yield), colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.59 ppm (d, $^{2}J_{P,H}$ = 17.2, 1H, CHCl), 4.40–4.20 ppm (m, 4H, CH_2), 1.42–1.37 ppm (m, 6H, CH_3).

4.3.2. 2-Bromo diethylphosphonoacetic acid (3b)

2.26 g (82% yield), colourless oil. ^{1}H NMR (300 MHz, DMSO): δ 5.01 ppm (d, $^{2}J_{P,H}$ = 14.6, 1H, CHBr), 4.19–3.98 ppm (m, 4H, CH_2), 1.29–1.20 ppm (m, 6H, CH_3).

4.3.3. 2-Fluoro diethylphosphonoacetic acid (3c)

1.67 g (78% yield), colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 ppm (dd, $^{2}J_{P,H}$ = 13.4, $^{2}J_{F,H}$ = 47.1, 1H, CHF), 4.39–4.26 ppm (m, 4H, CH_2), 1.42–1.36 ppm (m, 6H, CH_3).

4.3.4. 5-Chloro-2-nitroacetophenone (9b) [22]

To a rapidly stirred solution fuming HNO_3 (8.5 ml) and concentrated H_2SO_4 (1.3 ml) at −20 °C was added portionwise 3-chloroacetophenone (2.5 g, 16.2 mmol) over 15 min. The reaction mixture was allowed to warm to −10 °C and stirred for 5 h at this temperature after which ice-water (40 ml) was added and the reaction mixture extracted twice with CH_2Cl_2. The organic layers were combined, washed five times with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a pad of silica (eluting with CH_2Cl_2/PE, 4:1) to afford a pale green oil which was recrystallized from Et_2O/PE to give 5-chloro-2-nitroacetophenone (2.52 g, 78% yield), pale yellow crystals, mp 63–65 °C. IR (KBr): ν 1712, 1565, 1520, 1421, 1340, 1307, 1245, 1105, 863 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 ppm (d, J_o = 8.7, 1H, Ar–H), 7.57 ppm (d, J_o = 8.7, 1H, Ar–H), 7.39 ppm (s, 1H, Ar–H), 2.56 ppm (s, 3H, OCH_3).

4.3.5. 2-Amino-5-chloroacetophenone (4b) [27]

A mixture of 5-chloro-2-nitroacetophenone (2.2 g, 11.0 mmol), PtO_2 (20 mg) and charcoal (200 mg) in EtOH (40 ml) was rapidly stirred at r.t. for 4.5 h under 1 atm. of hydrogen. The reaction mixture was filtered through a pad of celite (the residues washed with CH_2Cl_2) and concentrated under reduced pressure. The residues was filtered through a pad of silica (eluting with CH_2Cl_2/PE, 4:1) to afford a pale green oil which was recrystallized from Et_2O/PE to give 2-amino-5-chloroacetophenone (1.35 g, 72% yield), pale green crystals, mp 63–64 °C. IR (KBr): ν 3455, 3320, 1657, 1616, 1570, 1546, 1475, 1361, 1222, 1158, 956, 823, 626 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 ppm (s, 1H, Ar–H), 7.22 ppm (d, J_o = 8.7, 1H, Ar–H), 6.62 ppm (d, J_o = 8.7, 1H, Ar–H), 6.28 ppm (s, 2H, NH_2), 2.57 ppm (s, 3H, OCH_3).

4.3.6. 4,5-Dimethoxy-2-nitroacetophenone (9c) [23]

Fuming nitric acid (6.0 mL, 140 mmol) was added dropwise to a solution of 3,4-dimethoxyacetophenone (3.6 g, 20.0 mmol) in AcOH (14 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 10 min and at room temperature for 20 min. Then it was poured into ice and the separated residue was filtered off and washed with a water solution of $NaHCO_3$ until pH 7 was reached. Recrystallization from EtOH–acetone afforded compound **9c** (2.34 g, 52% yield), yellow needles, mp 135–137 °C. IR (KBr): ν 1702, 1578, 1515, 1464, 1326, 1284, 1225, 1183, 1047, 883, 789 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 ppm (s, 1H, Ar–H), 6.76 ppm (s, 1H, Ar–H), 3.99 ppm (s, 6H, OCH_3), 2.51 ppm (s, 3H, OCH_3).

4.3.7. 2-Amino-4,5-dimethoxyacetophenone (4c) [23]

A mixture of 4,5-dimethoxy-2-nitroacetophenone (2.0 g, 9.0 mmol), iron powder (5.0 g), AcOH (18 mL), water (25 mL), and AcOEt (5 mL) was stirred under reflux for 6 h. After completion of the reaction, the mixture was neutralized with $NaHCO_3$ until pH 7 and filtered off. The residue was washed on the filter with AcOEt (3 × 40 mL). The organic layer was separated and the water layer was extracted with AcOEt (3 × 40 mL). Combined extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was recrystallized from AcOEt–hexane afforded compound **4c** (1.19 g, 68% yield), pale yellow solid, mp 106–108 °C. IR (KBr): ν 3414, 3299, 1629, 1591, 1540, 1511, 1468, 1454, 1406, 1255, 1210, 1164, 1057, 949, 845, 566 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 ppm (s, 1H, Ar–H), 6.26 ppm (s, 2H, NH_2), 6.11 ppm (s, 1H, Ar–H), 3.88 ppm (s, 3H, OCH_3), 3.85 ppm (s, 3H, OCH_3), 2.53 ppm (s, 3H, OCH_3).

4.4. General procedure for the preparation of N-acyl-o-aminophenylketone 2a–r

To a solution of 2-halo-2-diethylphosphonoacetic acids **3a–c** (2.3 mmol) in dichloromethane (2 mL) was added oxalyl chloride (0.40 mL, 4.7 mmol) at 25 °C under argon. The mixture was stirred overnight and then concentrated. The brown oil was diluted with dichloromethane (5 mL), followed by the addition of the corresponding *o*-aminophenylketones **4a–f** (2.3 mmol) in dichloromethane (4 mL). In the case of **4f**, it was dissolved with dichloromethane (30 mL), due to the low solubility. Pyridine (0.38 mL, 4.7 mmol) was slowly added using a ice-water bath over 10 min. After stirring for 4.5 h, the reaction mixture was quenched with 3 N HCl (2 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), and evaporated to obtain the corresponding product which was further purified by column chromatography (silica gel).

4.4.1. Diethyl (2-acetylphenylcarbamoyl)chloromethylphosphonate (2a)

0.75 g (94% yield), purified by column chromatography (dichloromethane:methanol = 90:1), yellowish solid, mp 93–96 °C. IR (KBr): ν 3432, 1682, 1643, 1612, 1595, 1525, 1470, 1451, 1368, 1344, 1269, 1207, 1159, 1038, 1018, 869, 532 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.52 ppm (s, 1H, NH), 8.72 ppm (d, J = 8.4 Hz, 1H, Ar–H), 7.93 ppm (d, J = 7.9 Hz, 1H, Ar–H), 7.57 ppm (t, J = 7.6 Hz, 1H, Ar–H), 7.19 ppm (t, J = 7.6 Hz, 1H, Ar–H), 4.57 ppm (d, $^2J_{P,H}$ = 16.1 Hz, 1H, CHCl), 4.37–4.24 ppm (m, 4H, CH_2), 2.68 ppm (s, 3H, $COCH_3$), 1.39–1.34 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 162.8 ppm (d, $^2J_{P,C}$ = 1.7 Hz), 139.7, 135.0, 131.5, 123.4, 122.4, 120.7, 64.6 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 52.8 ppm (d, $^1J_{P,C}$ = 142.3 Hz), 28.3, 16.3 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 5.38 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{14}H_{19}ClNO_5PNa$: 370.0582; found: 370.0586.

4.4.2. Diethyl (2-acetyl-4-chlorophenylcarbamoyl)chloromethylphosphonate (2b)

0.82 g (93% yield), purified by column chromatography (dichloromethane:methanol = 90:1), yellow oil. IR (KBr): ν 3475, 1681, 1664, 1577, 1512, 1397, 1361, 1304, 1258, 1163, 1020, 961, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.40 ppm (s, 1H, NH), 8.72 ppm (d, J_o = 9.0 Hz, 1H, Ar–H), 7.88 ppm (d, J_m = 2.1 Hz, 1H, Ar–H), 7.54 ppm (dd, J_m = 2.1 Hz, J_o = 9.0 Hz, 1H, Ar–H), 4.57 ppm (d, $^2J_{P,H}$ = 16.2 Hz, 1H, CHCl), 4.37–4.25 ppm (m, 4H, CH_2), 2.68 ppm (s, 3H, $COCH_3$), 1.40–1.35 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 162.9 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 138.2, 134.6, 131.1, 128.4, 123.6, 122.2, 64.7 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 52.8 ppm (d, $^1J_{P,C}$ = 142.3 Hz), 28.3, 16.3 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.01 ppm (s, 1P). HRMS-MALDI: m/z $[M+Na]^+$ calcd for $C_{14}H_{18}Cl_2NO_5PNa$: 404.0192; found: 404.0192.

4.4.3. Diethyl (2-acetyl-4,5-dimethoxyphenylcarbamoyl)chloromethylphosphonate (2c)

0.86 g (92% yield), purified by column chromatography (dichloromethane:methanol = 100:1), yellowish solid, mp 83–85 °C. IR (KBr): ν 3436, 1674, 1658, 1583, 1519, 1451, 1312, 1259, 1165, 1046, 1019, 970, 948, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.79 ppm (s, 1H, NH), 8.49 ppm (s, 1H, Ar–H), 7.30 ppm (s, 1H, Ar–H), 4.59 ppm (d, 1H, $^2J_{P,H}$ = 16.1 Hz, CHCl), 4.36–4.28 ppm (m, 4H, CH_2), 3.98 ppm (s, 3H, OCH_3), 3.93 ppm (s, 3H, OCH_3), 2.64 ppm (s, 3H, $COCH_3$), 1.40–1.35 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 162.6 ppm (d, $^2J_{P,C}$ = 1.7 Hz), 154.1, 144.0, 136.2, 114.8, 113.3, 103.4, 64.6 ppm (d, $^2J_{P,C}$ = 6.7 Hz), 56.1, 56.0, 52.7 ppm (d, $^1J_{P,C}$ = 143.3 Hz), 28.1, 16.2 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 11.71 ppm (s, 1P). HRMS-MALDI: m/z $[M+Na]^+$ calcd for $C_{16}H_{23}ClNO_7PNa$: 430.0793; found: 430.0792.

4.4.4. Diethyl (2-acetophenone-phenylcarbamoyl)chloromethylphosphonate (2d)

0.66 g (70% yield), purified by column chromatography (dichloromethane:methanol = 110:1), yellow oil. IR (KBr): ν 3485, 3278, 1692, 1641, 1583, 1528, 1448, 1317, 1294, 1269, 1163, 1051, 979, 755, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.59 ppm (s, 1H, NH), 8.61 ppm (d, J = 8.7 Hz, 1H, Ar–H), 7.73 ppm (d, J = 7.4 Hz, 2H, Ar–H), 7.63 ppm (s, 1H, Ar–H), 7.59 ppm (d, J = 7.5 Hz, 2H, Ar–H), 7.49 ppm (t, J = 7.4 Hz, 2H, Ar–H), 7.16 ppm (t, J = 7.5 Hz, 1H, Ar–H), 4.59 ppm (d, $^2J_{P,H}$ = 16.1 Hz, 1H, CHCl), 4.36–4.24 ppm (m, 4H, CH_2), 1.40–1.31 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 162.5 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 139.1, 138.1, 134.0, 133.3, 132.5, 129.9 × 2, 128.2 × 2, 124.1, 123.1, 121.5, 64.6 ppm (d, $^2J_{P,C}$ = 6.7 Hz), 52.6 ppm (d, $^1J_{P,C}$ = 142.5 Hz), 16.2 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 10.88 ppm (s, 1P). HRMS-MALDI: m/z $[M+Na]^+$ calcd for $C_{19}H_{21}ClNO_5PNa$: 432.0738; found: 432.0744.

4.4.5. Diethyl (2-acetophenone-4-chlorophenylcarbamoyl)chloromethylphosphonate (2e)

0.92 g (90% yield), purified by column chromatography (dichloromethane:methanol = 100:1), yellow oil. IR (KBr): ν 3427, 3238, 1697, 1663, 1604, 1528, 1482, 1332, 1293, 1274, 1224, 1163, 1043, 955, 697, 534 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.39 ppm (s, 1H, NH), 8.57 ppm (d, J = 9.6 Hz, 1H, Ar–H), 7.74 ppm (d, J = 7.5 Hz, 2H, Ar–H), 7.64 ppm (t, J = 7.3 Hz, 1H, Ar–H), 7.50–7.55 ppm (m, 4H, Ar–H), 4.58 ppm (d, $^2J_{P,H}$ = 16.1 Hz, 1H, CHCl), 4.35–4.23 ppm (m, 4H, CH_2), 1.37–1.31 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 162.5 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 137.5, 137.4, 133.6, 133.0, 132.4, 129.9 × 2, 128.5 × 2, 128.4, 125.6, 123.1, 64.7 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 52.5 ppm (d, $^1J_{P,C}$ = 142.4 Hz), 16.2 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.04 ppm (s, 1P). HRMS-MALDI: m/z $[M+Na]^+$ calcd for $C_{19}H_{20}Cl_2NO_5PNa$: 466.0348; found: 466.0341.

4.4.6. Diethyl (2-acetophenone-4-nitrophenylcarbamoyl)chloromethylphosphonate (2f)

0.92 g (88% yield), purified by column chromatography (dichloromethane:methanol = 110:1), yellow oil. IR (KBr): ν 3471, 3253, 1704, 1648, 1616, 1582, 1541, 1511, 1446, 1413, 1346, 1262, 1157, 1022, 972, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.84 ppm (s, 1H, NH), 8.88 ppm (d, J_o = 9.2 Hz, 1H, Ar–H), 8.51 ppm (s, 1H, Ar–H), 8.45 ppm (dd, J_m = 2.0 Hz, J_o = 9.2 Hz, 1H, Ar–H), 7.77–7.67 ppm (m, 3H, Ar–H), 7.56 ppm (t, J = 7.5 Hz, 2H, Ar–H), 4.64 ppm (d, $^2J_{P,H}$ = 16.4 Hz, 1H, CHCl), 4.37–4.26 ppm (m, 4H, CH_2), 1.39–1.33 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 163.0 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 144.2, 141.9, 136.7, 133.4, 129.8 × 2, 128.6 × 2, 128.5, 128.2, 123.5, 121.5, 64.8 ppm (d, $^2J_{P,C}$ = 6.9 Hz), 52.5 ppm (d, $^1J_{P,C}$ = 141.8 Hz), 16.1 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.20 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{19}H_{20}ClN_2O_7PNa$: 477.0589; found: 477.0585.

4.4.7. Diethyl (2-acetylphenylcarbamoyl)bromomethylphosphonate (2g)

0.82 g (91% yield), purified by column chromatography (dichloromethane:methanol = 90:1), yellowish solid, mp 88–90 °C. IR (KBr): ν 3426, 1669, 1658, 1583, 1516, 1451, 1311, 1258, 1166, 1047, 1018, 968, 948, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.43 ppm (s, 1H, NH), 8.71 ppm (d, J = 8.4 Hz, 1H, Ar–H), 7.93 ppm (d, J = 7.9 Hz, 1H, Ar–H), 7.58 ppm (t, J = 7.4 Hz, 1H, Ar–H), 7.19 ppm (t, J = 7.5 Hz, 1H, Ar–H), 4.44 ppm (d, $^2J_{P,H}$ = 14.5 Hz, 1H, CHBr), 4.38–4.25 ppm (m, 4H, CH_2), 2.69 ppm (s, 3H, $COCH_3$), 1.40–1.35 ppm (t, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2, 162.9, 139.9, 135.0 ppm (d, J = 2.8 Hz), 131.5 ppm (d, J = 2.8 Hz), 123.4 ppm (d, J = 1.8 Hz), 122.5 ppm (d, J = 3.2 Hz), 120.82, 64.76 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 39.8 ppm (d, $^1J_{P,C}$ = 140.0 Hz), 28.4 ppm (d, J = 3.6 Hz), 16.3 ppm (d, $^3J_{P,C}$ = 5.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 13.39 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{14}H_{19}BrNO_5PNa$: 414.0076; found: 414.0081.

4.4.8. Diethyl (2-acetyl-4-chlorophenylcarbamoyl)bromomethylphosphonate (2h)

0.90 g (92% yield), purified by column chromatography (dichloromethane:methanol = 90:1), yellowish oil. IR (KBr): ν 3425, 1695, 1652, 1608, 1512, 1397, 1317, 1239, 1167, 1126, 1108, 1051, 1020, 976, 945, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.30 ppm (s, 1H, NH), 8.70 ppm (d, J_o = 9.0 Hz, 1H, Ar–H), 7.87 ppm (s, 1H, Ar–H), 7.53 ppm (dd, J_m = 1.5 Hz, J_o = 9.0 Hz, 1H, Ar–H), 4.43 ppm (d, $^2J_{P,H}$ = 14.6 Hz, 1H, CHBr), 4.37–4.28 ppm (m, 4H, CH_2), 2.68 ppm (s, 3H, $COCH_3$), 1.40–1.35 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.1, 162.9 ppm (d, $^2J_{P,C}$ = 1.7 Hz), 138.4, 134.6, 131.1, 128.4, 123.6, 122.3, 64.8 ppm (d, $^2J_{P,C}$ = 6.9 Hz), 39.57 ppm (d, $^1J_{P,C}$ = 139.8 Hz), 28.4, 16.3 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 4.74 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{14}H_{18}ClBrNO_5PNa$: 447.9687; found: 447.9683.

4.4.9. Diethyl (2-acetyl-4,5-dimethoxyphenylcarbamoyl)bromomethylphosphonate (2i)

0.95 g (91% yield), purified by column chromatography (dichloromethane:methanol = 100:1), yellowish solid, mp 128–130 °C. IR (KBr): ν 3426, 1679, 1641, 1612, 1593, 1524, 1469, 1452, 1367, 1343, 1269, 1206, 1159, 1038, 1018, 980, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.69 ppm (s, 1H, NH), 8.47 ppm (s, 1H, Ar–H), 7.30 ppm (s, 1H, Ar–H), 4.45 ppm (d, $^2J_{P,H}$ = 14.6 Hz, 1H, CHBr), 4.38–4.26 ppm (m, 4H, CH_2), 3.98 ppm (s, 3H, OCH_3), 3.92 ppm (s, 3H, OCH_3), 2.63 ppm (s, 3H, $COCH_3$), 1.39–1.35 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 162.8 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 154.3, 144.1, 136.6, 114.9, 113.4, 103.5, 64.7 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 56.3, 56.2, 39.9 ppm (d, $^1J_{P,C}$ = 140.8 Hz), 28.2, 16.3 ppm (d, $^3J_{P,C}$ = 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.50 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{16}H_{23}BrNO_7PNa$: 474.0288; found: 474.0280.

4.4.10. Diethyl (2-acetophenone-phenylcarbamoyl)bromomethylphosphonate (2j)

0.68 g (65% yield), purified by column chromatography (dichloromethane:methanol = 110:1), yellow oil. IR (KBr): ν 3480, 3274, 1693, 1642, 1601, 1583, 1528, 1447, 1317, 1294, 1267, 1162, 1051, 966, 755, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.44 ppm (s, 1H, NH), 8.57 ppm (d, J = 8.5 Hz, 1H, Ar–H), 7.74 ppm (d, J = 7.6 Hz, 2H, Ar–H), 7.60–7.57 ppm (m, 3H, Ar–H), 7.49 ppm (t, J = 7.4 Hz, 2H, Ar–H), 7.16 ppm (t, J = 7.6 Hz, 1H, Ar–H), 4.45 ppm (d, $^2J_{P,H}$ = 14.5 Hz, 1H, CHBr), 4.36–4.24 ppm (m, 4H, CH_2), 1.40–1.31 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6, 162.5 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 139.2, 138.1, 133.9, 133.2, 132.6, 129.9 × 2, 128.2 × 2, 124.3, 123.1, 121.6, 64.7 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 39.4 ppm (d, $^1J_{P,C}$ = 140.0 Hz), 16.2 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 10.39 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{19}H_{21}BrNO_5PNa$: 476.0233; found: 476.0225.

4.4.11. Diethyl (2-acetophenone-4-chlorophenylcarbamoyl)bromomethylphosphonate (2k)

0.98 g (87% yield), purified by column chromatography (dichloromethane:methanol = 100:1), yellow oil. IR (KBr): ν 3432, 3235, 1692, 1662, 1604, 1528, 1481, 1331, 1293, 1274, 1244, 1223, 1163, 1039, 975, 953, 696, 528 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.24 ppm (s, 1H, NH), 8.54 ppm (d, J = 9.6 Hz, 1H, Ar–H), 7.75 ppm (d, J = 7.6 Hz, 2H, Ar–H), 7.65 ppm (t, J = 7.1 Hz, 1H, Ar–H), 7.56–7.50 ppm (m, 4H, Ar–H), 4.44 ppm (d, $^2J_{P,H}$ = 14.5 Hz, 1H, CHBr), 4.35–4.24 ppm (m, 4H, CH_2), 1.37–1.31 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 162.5 ppm (d, $^2J_{P,C}$ = 1.4 Hz), 137.6, 137.3, 133.5, 133.1, 132.3, 129.9 × 2, 128.5 × 2, 128.4, 125.8, 123.1, 64.8 ppm (d, $^2J_{P,C}$ = 6.8 Hz), 39.3 ppm (d, $^1J_{P,C}$ = 140.0 Hz), 16.2 ppm (d, $^3J_{P,C}$ = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 4.83 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{19}H_{20}ClBrNO_5PNa$: 509.9843; found: 509.9842.

4.4.12. Diethyl (2-acetophenone-4-nitrophenylcarbamoyl)bromomethylphosphonate (2l)

0.98 g (85% yield), purified by column chromatography (dichloromethane:methanol = 110:1), yellow oil. IR (KBr): ν 3472, 3253, 1702, 1650, 1617, 1582, 1541, 1510, 1412, 1346, 1262, 1157, 1021, 971, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.68 ppm (s, 1H, NH), 8.84 ppm (d, J = 9.2 Hz, 1H, Ar–H), 8.49 ppm (s, 1H, Ar–H), 8.44 ppm (d, J = 9.4 Hz, 1H, Ar–H), 7.76 ppm (d, J = 7.7 Hz, 2H, Ar–H), 7.69 ppm (t, J = 7.3 Hz, 1H, Ar–H), 7.55 ppm (t, J = 7.4 Hz, 2H, Ar–H), 4.48 ppm (d, $^2J_{P,H}$ = 14.7 Hz, 1H, CHBr), 4.34–4.25 ppm (m, 4H, CH_2), 1.38–1.31 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 163.2 ppm (d, $^2J_{P,C}$ = 1.6 Hz), 144.6, 142.0, 136.9, 133.6, 130.0 × 2, 128.8 × 2, 128.7, 128.4, 123.7, 121.7, 65.0 ppm (d, $^2J_{P,C}$ = 7.0 Hz), 39.2 ppm (d, $^1J_{P,C}$ = 139.4 Hz), 16.3 ppm (d, $^3J_{P,C}$ = 6.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 3.61 ppm (s, 1P). HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{19}H_{20}BrN_2O_7PNa$: 521.0084; found: 521.0079.

4.4.13. Diethyl (2-acetylphenylcarbamoyl)fluoromethylphosphonate (2m)

0.71 g (92% yield), purified by column chromatography (dichloromethane:methanol = 90:1), white solid, mp 126–129 °C. IR (KBr): ν 3441, 1688, 1655, 1584, 1526, 1451, 1362, 1314, 1258, 1164, 1044, 1017, 981, 959, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.51 ppm (s, 1H, NH), 8.77 ppm (d, J = 8.4 Hz, 1H, Ar–H), 7.94 ppm (d, J = 7.9 Hz, 1H, Ar–H), 7.59 ppm (t, J = 7.6 Hz, 1H, Ar–H),

7.21 ppm (t, J = 7.6 Hz, 1H, Ar–H), 5.27 ppm (dd, $^2J_{P,H}$ = 11.4 Hz, $^2J_{F,H}$ = 46.5 Hz, 1H, CHF), 4.37–4.24 ppm (m, 4H, CH_2), 2.68 ppm (s, 3H, $COCH_3$), 1.41–1.35 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 163.5 ppm (dd, $^2J_{P,C}$ = 1.0 Hz, $^2J_{F,C}$ = 16.8 Hz), 139.3, 135.0 ppm (d, J = 3.3 Hz), 131.6 ppm (d, J = 3.2 Hz), 123.5 ppm (d, J = 2.5 Hz), 122.4, 120.9, 87.0 ppm (dd, $^1J_{P,C}$ = 158.8 Hz, $^1J_{F,C}$ = 201.2 Hz), 64.2 ppm (d, J_1 = 2.5 Hz, J_2 = 6.3 Hz), 28.3 ppm (d, J = 4.6 Hz), 16.3 ppm (dd, J_1 = 1.5 Hz, J_2 = 5.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −204.1 ppm (dd, $^2J_{H,F}$ = 46.5 Hz, $^2J_{P,F}$ = 71.9 Hz, 1F, CHF). ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.79 ppm (d, J_F = 71.9 Hz, 1P). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{14}H_{19}FNO_5PNa$: 354.0877; found: 354.0874.

4.4.14. Diethyl (2-acetyl-4-chlorophenylcarbamoyl)fluoromethylphosphonate (2n)

0.79 g (92% yield), purified by column chromatography (dichloromethane:methanol = 90:1), white solid, mp 125–127 °C. IR (KBr): ν 3444, 1689, 1659, 1577, 1513, 1397, 1310, 1290, 1257, 1226, 1166, 1112, 1069, 1043, 1013, 973, 954, 761 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.40 ppm (s, 1H, NH), 8.78 ppm (d, J_o = 9.0 Hz, 1H, Ar–H), 7.90 ppm (d, J_m = 2.0 Hz, 1H, Ar–H), 7.56 ppm (dd, J_m = 2.0 Hz, J_o = 9.0 Hz, 1H, Ar–H), 5.28 ppm (dd, $^2J_{P,H}$ = 11.5 Hz, $^2J_{F,H}$ = 46.8 Hz, 1H, CHF), 4.36–4.28 ppm (m, 4H, CH_2), 2.69 ppm (s, 3H, $COCH_3$), 1.43–1.37 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 163.5 ppm (d, $^2J_{F,C}$ = 16.9 Hz), 137.7, 134.6, 131.1, 128.4, 123.4, 122.3, 86.8 ppm (dd, $^1J_{P,C}$ = 158.9 Hz, $^1J_{F,C}$ = 201.0 Hz), 64.3 ppm (dd, J_1 = 2.2 Hz, J_2 = 6.4 Hz,), 28.3, 16.3 ppm (dd, J_1 = 1.2 Hz, J_2 = 5.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −205.5 ppm (dd, $^2J_{H,F}$ = 46.8 Hz, $^2J_{P,F}$ = 71.9 Hz, 1F, CHF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{14}H_{18}ClFNO_5PNa$: 388.0487; found: 388.0489.

4.4.15. Diethyl (2-acetyl-4,5-dimethoxyphenylcarbamoyl)fluoromethylphosphonate (2o)

0.82 g (90% yield), purified by column chromatography (dichloromethane:methanol = 100:1), yellowish solid, mp 75–77 °C. IR (KBr): ν 3445, 1683, 1643, 1613, 1592, 1528, 1406, 1369, 1345, 1269, 1209, 1160, 1067, 1046, 1019 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.77 ppm (s, 1H, NH), 8.51 ppm (s, 1H, Ar–H), 7.30 ppm (s, 1H, Ar–H), 5.26 ppm (dd, $^2J_{P,H}$ = 11.2 Hz, $^2J_{F,H}$ = 46.8 Hz, 1H, CHF), 4.34–4.26 ppm (m, 4H, CH_2), 3.98 ppm (s, 3H, OCH_3), 3.92 ppm (s, 3H, OCH_3), 2.63 ppm (s, 3H, $COCH_3$), 1.41–1.34 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 163.5 ppm (d, $^2J_{F,C}$ = 17.4 Hz), 154.3, 144.2, 136.0, 114.9, 113.4, 103.7, 86.9 ppm (dd, $^1J_{P,C}$ = 159.2 Hz, $^1J_{F,C}$ = 201.6 Hz), 64.3 ppm (dd, J_1 = 2.2 Hz, J_2 = 6.6 Hz), 56.3 × 2, 28.3, 16.4 ppm (d, J = 5.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −204.6 ppm (dd, $^2J_{H,F}$ = 46.8 Hz, $^2J_{P,F}$ = 70.5 Hz, 1F, CHF). ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.06 ppm (d, $^2J_{F,P}$ = 70.5 Hz, 1P). HRMS-MALDI: m/z [M+Na]$^+$ calcd for $C_{16}H_{23}FNO_7PNa$: 414.1088; found: 414.1085.

4.4.16. Diethyl (2-acetophenone-phenylcarbamoyl)fluoromethylphosphonate (2p)

0.57 g (62% yield), purified by column chromatography (dichloromethane:methanol = 110:1), yellow oil. IR (KBr): ν 3481, 3286, 1696, 1641, 1584, 1523, 1450, 1296, 1267, 1163, 1018, 978, 923, 755, 733, 703, 644 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.60 ppm (s, 1H, NH), 8.67 ppm (d, J = 8.6 Hz, 1H, Ar–H), 7.72 ppm (d, J = 7.5 Hz, 2H, Ar–H), 7.61 ppm (t, 3H, J = 6.9 Hz, Ar–H), 7.49 ppm (t, 2H, J = 7.5 Hz, Ar–H), 7.17 ppm (t, 1H, J = 7.3 Hz, Ar–H), 5.28 ppm (dd, $^2J_{P,H}$ = 11.3 Hz, $^2J_{F,H}$ = 47.1 Hz, 1H, CHF), 4.34–4.26 ppm (m, 4H, CH_2), 1.39–1.33 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.1, 163.3 ppm (dd, $^2J_{P,C}$ = 1.0 Hz, $^2J_{F,C}$ = 16.7 Hz), 138.9, 138.2, 134.2, 133.6, 132.6, 129.9 × 2, 128.3 × 2, 123.9, 123.2, 121.7, 86.9 ppm (dd, $^1J_{P,C}$ = 158.8 Hz, $^1J_{F,C}$ = 201.0 Hz), 64.3 ppm (dd, J_1 = 2.0 Hz, J_2 = 6.4 Hz), 16.4 ppm (d, J = 5.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −203.7 ppm (dd, $^2J_{H,F}$ = 47.1 Hz, $^2J_{P,F}$ = 71.3 Hz, 1F, CHF). ^{31}P NMR (121 MHz, $CDCl_3$): δ 5.09 ppm (d, $^2J_{F,P}$ = 71.3 Hz, 1P). HRMS-MALDI: m/z [M+Na]$^+$ calcd for $C_{19}H_{21}FNO_5PNa$: 416.1034; found: 416.1036.

4.4.17. Diethyl (2-acetophenone-4-chlorophenylcarbamoyl)fluoromethylphosphonate (2q)

0.89 g (89% yield), purified by column chromatography (dichloromethane:methanol = 100:1), yellow oil. IR (KBr): ν 3485, 3291, 1703, 1646, 1597, 1579, 1516, 1446, 1397, 1289, 1258, 1162, 1019, 975, 948, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.42 ppm (s, 1H, NH), 8.67 ppm (d, J = 9.6 Hz, 1H, Ar–H), 7.75 ppm (d, J = 7.4 Hz, 2H, Ar–H), 7.67 ppm (t, J = 7.4 Hz, 1H, Ar–H), 7.59–7.52 ppm (m, 4H, Ar–H), 5.29 ppm (dd, $^2J_{P,H}$ = 11.4 Hz, $^2J_{F,H}$ = 46.8 Hz, 1H, CHF), 4.35–4.25 ppm (m, 4H, CH_2), 1.41–1.35 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6, 163.2 ppm (d, $^2J_{F,C}$ = 16.8 Hz), 137.4, 137.2, 133.7, 133.0, 132.6, 129.8 × 2, 128.4 × 2, 128.3, 125.2, 123.1, 86.8 ppm (dd, $^1J_{P,C}$ = 158.9 Hz, $^1J_{F,C}$ = 200.9 Hz), 64.3 ppm (dd, J_1 = 2.6 Hz, J_2 = 6.3 Hz), 16.3 ppm (d, J = 5.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −204.6 ppm (dd, $^2J_{H,F}$ = 46.8 Hz, $^2J_{P,F}$ = 70.5 Hz, CHF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{19}H_{20}ClFNO_5PNa$: 450.0644; found: 450.0642.

4.4.18. Diethyl (2-acetophenone-4-nitrophenylcarbamoyl)fluoromethylphosphonate (2r)

0.90 g (88% yield), purified by column chromatography (dichloromethane:methanol = 110:1), white solid, mp 101–103 °C. IR (KBr): ν 3443, 1706, 1641, 1617, 1581, 1543, 1510, 1351, 1254, 1156, 1100, 1021, cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.88 ppm (s, 1H, NH), 8.97 ppm (d, J_o = 9.2 Hz, 1H, Ar–H), 8.55 ppm (d, J_m = 2.3 Hz, 1H, Ar–H), 8.48 ppm (dd, J_m = 2.3 Hz, J_o = 9.2 Hz, 1H, Ar–H), 7.76 ppm (d, J = 7.6 Hz, 2H, Ar–H), 7.70 ppm (d, J = 7.2 Hz, 1H, Ar–H), 7.58 ppm (t, J = 7.5 Hz, 2H, Ar–H), 5.34 ppm (dd, $^2J_{P,H}$ = 11.8 Hz, $^2J_{F,H}$ = 46.5 Hz, 1H, CHF), 4.37–4.27 ppm (m, 4H, CH_2), 1.43–1.37 ppm (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 164.0 ppm (d, $^2J_{F,C}$ = 16.4 Hz), 144.1, 142.1, 136.9, 133.6, 129.9 × 2, 128.9 × 2, 128.8, 128.6, 123.3, 121.7, 86.9 ppm (dd, $^1J_{P,C}$ = 158.6 Hz, $^1J_{F,C}$ = 200.7 Hz), 64.5 ppm (dd, J_1 = 2.3 Hz, J_2 = 6.4 Hz), 16.3 ppm (d, J = 5.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −204.4 ppm (dd, $^2J_{H,F}$ = 46.5 Hz, $^2J_{P,F}$ = 70.8 Hz, 1 F, CHF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{19}H_{20}FN_2O_7PNa$: 461.0884; found: 461.0881.

4.5. General procedure for the preparation of the halogenated 2-quinolones 1a–r

In a round-bottomed flask under argon, LiCl (0.13 g, 3 mmol) and N-acyl-*o*-aminophenylketones **2a–r** (1 mmol) was suspended in THF (4 mL). DBU (0.45 mL, 3 mmol) was slowly added for 10 min at r.t., then the mixture was stirred for 2 h. The volatiles were evaporated, the residue was taken up in ethyl acetate, and washed with 3 N HCl and satd $NaHCO_3$. After drying (Na_2SO_4) and evaporation of the solvent, the corresponding compound was isolated from the residue by column chromatography or recrystallization.

4.5.1. 3-Chloro-4-methyl-2-quinolone (1a) [28]

170.4 mg (88% yield), recrystallized from ethanol, white solid; mp 300–302 °C. IR (KBr): ν 3421, 1667, 1606, 1504, 1434, 1381, 746, 633 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.21 ppm (s, 1H, NH), 7.83 ppm (d, J = 8.1 Hz, 1H, Ar–H), 7.56 ppm (t, J = 7.6 Hz, 1H, Ar–H), 7.36 ppm (d, J = 8.1 Hz, 1H, Ar–H), 7.28 ppm (t, J = 7.6 Hz, 1H, Ar–H), 2.60 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.1, 144.3, 136.6, 130.6, 125.3, 125.1, 122.6, 119.2, 115.7, 16.3 ppm.

4.5.2. 3,6-Dichloro-4-methyl-2-quinolone **(1b)** *[16(c)]*

216.7 mg (95% yield), recrystallized from ethanol, white solid; mp 272–274 °C. IR (KBr): ν 3445, 1648, 1603, 1487, 1409, 1146, 1098, 629 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.31 ppm (s, 1H, NH), 7.86 ppm (s, 1H, Ar–H), 7.60 ppm (d, J_o = 8.8 Hz, 1H, Ar–H), 7.36 ppm (d, J_o = 8.7 Hz, 1H, Ar–H), 2.59 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.8, 143.2, 135.4, 130.3, 126.5, 126.4, 124.4, 120.3, 117.4, 16.2 ppm.

4.5.3. 3-Chloro-6,7-dimethoxy-4-methyl-2-quinolone **(1c)**

208.0 mg (82% yield), recrystallized from ethanol, white solid, mp 250–252 °C. IR (KBr): ν 3424, 1655, 1625, 1514, 1414, 1261, 1230, 1205, 1169, 1103, 1035 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.00 ppm (s, 1H, NH), 7.17 ppm (s, 1H, Ar–H), 6.88 ppm (s, 1H, Ar–H), 3.84 ppm (s, 3H, OCH_3), 3.82 ppm (s, 3H, OCH_3), 2.57 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.2, 152.1, 145.4, 144.0, 132.5, 122.5, 112.5, 106.6, 98.1, 56.2, 55.9, 16.7 ppm. HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{12}H_{12}ClNO_3Na$: 276.0398; found: 276.0401.

4.5.4. 3-Chloro-4-phenyl-2-quinolinone **(1d)**

240.4 mg (94% yield), recrystallized from ethanol, white solid, mp 191–193 °C. IR (KBr): ν 3423, 1658, 1611, 1597, 1437, 1072, 750, 631 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.45 ppm (s, 1H, NH), 7.61–7.53 ppm (m, 4H, Ar–H), 7.42 ppm (d, *J* = 8.1 Hz, 1H, Ar–H), 7.36 ppm (s, 1H, Ar–H), 7.34 ppm (s, 1H, Ar–H), 7.14 ppm (t, *J* = 7.7 Hz, 1H, Ar–H), 6.95 ppm (d, *J* = 8.0 Hz, 1H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.4, 153.1, 142.2, 139.8, 135.7, 133.8 × 2, 133.7, 133.6 × 2, 131.6, 129.8, 127.5, 124.5, 120.6 ppm. HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_{10}ClNONa$: 278.0343; found: 278.0345.

4.5.5. 3,6-Dichloro-4-phenyl-2-quinolone **(1e)** *[16(d)]*

275.6 mg (95% yield), recrystallized from ethanol, white solid, mp 299–301 °C. IR (KBr): ν 3420, 1656, 1480, 1407, 1070, 706, 642 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.56 ppm (s, 1H, NH), 7.58–7.50 ppm (m, 4H, Ar–H), 7.39 ppm (d, *J* = 8.8 Hz, 1H, Ar–H), 7.31 ppm (d, *J* = 6.8 Hz, 2H, Ar–H), 6.80 ppm (d, *J* = 1.4 Hz, 1H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.1, 146.8, 136.0, 134.2, 130.4, 128.9, 128.9 × 2, 128.5 × 2, 126.4, 126.3, 125.1, 120.7, 117.6 ppm.

4.5.6. 3-Chloro-6-nitro-4-phenyl-2-quinolone **(1f)**

288.7 mg (96% yield), recrystallized from ethanol, white solid, mp 221–223 °C. IR (KBr): ν 3423, 1655, 1606, 1529, 1486, 1334, 1066, 652 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.01 ppm (s, 1H, NH), 8.40 ppm (dd, J_m = 2.2 Hz, J_o = 9.0 Hz, 1H, Ar–H), 7.77 ppm (d, J_m = 2.1 Hz, 1H, Ar–H), 7.67–7.56 ppm (m, 4H, Ar–H), 7.43 ppm (d, *J* = 6.7 Hz, 2H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.5, 147.5, 141.8, 141.5, 133.7, 129.4, 129.1 × 2, 128.7 × 2, 127.1, 125.2, 122.5, 119.3, 116.9 ppm. HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_9ClN_2O_3Na$: 323.0194; found: 323.0197.

4.5.7. 3-Bromo-4-methyl-2-quinolone **(1g)** *[13(b)]*

202.4 mg (85% yield), recrystallized from ethanol, white solid, mp 268–269 °C. IR (KBr): ν 3440, 1649, 1602, 1502, 1432, 1004, 749, 618 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.16 ppm (s, 1H, NH), 7.82 ppm (d, *J* = 8.1 Hz, 1H, Ar–H), 7.55 ppm (t, *J* = 7.7 Hz, 1H, Ar–H), 7.34 ppm (d, *J* = 8.1 Hz, 1H, Ar–H), 7.24 ppm (t, *J* = 7.7 Hz, 1H, Ar–H), 2.63 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.6, 147.5, 137.3, 131.1, 125.8, 122.8, 119.6, 119.5, 115.9, 19.9 ppm (d, *J* = 1.6 Hz).

4.5.8. 3-Bromo-6-chloro-4-methyl-2-quinolone **(1h)** *[29]*

239.8 mg (88% yield), recrystallized from ethanol, white solid, mp 204–206 °C. IR (KBr): ν 3450, 1648, 1602, 1486, 1142, 1097, 625 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.29 ppm (s, 1H, NH), 7.87 ppm (s, 1H, Ar–H), 7.60 ppm (dd, J_m = 1.6 Hz, J_o = 8.7 Hz, 1H, Ar–H), 7.35 ppm (d, J_o = 8.8 Hz, 1H, Ar–H), 2.63 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.0, 146.2, 135.8, 130.5, 126.4, 124.6, 120.6, 120.3, 117.4, 19.6 ppm.

4.5.9. 3-Bromo-6,7-dimethoxy-4-methyl-2-quinolone **(1i)**

232.5 mg (78% yield), recrystallized from ethanol, white solid, mp 227–229 °C. IR (KBr): ν 3443, 1654, 1514, 1410, 1258, 1230, 1207, 1169 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 11.97 ppm (s, 1H, NH), 7.20 ppm (s, 1H, Ar–H), 6.88 ppm (s, 1H, Ar–H), 3.84 ppm (s, 3H, OCH_3), 3.82 ppm (s, 3H, OCH_3), 2.63 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 152.9, 147.4, 146.0, 133.7, 117.0, 113.3, 107.4, 98.7, 56.8, 56.5, 20.8 ppm. HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{12}H_{12}BrNO_3Na$: 319.9893; found: 319.9889.

4.5.10. 3-Bromo-4-phenyl-2-quinolinone **(1j)** *[17(a)]*

78.0 mg (26% yield), purified by column chromatography (dichloromethane:methanol = 30:1), white solid, mp 228–230 °C. IR (KBr): ν 3444, 1656, 1604, 1110, 1056, 758, 598 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 11–12 ppm (br.s, 1H, NH), 7.59–7.52 ppm (m, 4H, Ar–H), 7.36 ppm (s, 1H, Ar–H), 7.31 ppm (d, *J* = 7.6 Hz, 2H, Ar–H), 7.14 ppm (s, 1H, Ar–H), 7.13 ppm (s, 1H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3, 152.7, 137.3, 137.1, 130.8, 128.7 × 2, 128.5 × 2, 127.2, 123.0, 120.8, 117.9, 116.6 ppm.

4.5.11. 3-Bromo-6-chloro-4-phenyl-2-quinolone **(1k)**

60.2 mg (18% yield), purified by column chromatography (dichloromethane:methanol = 30:1), white solid, mp 218–220 °C. IR (KBr): ν 3442, 1665, 1056, 1028, 1008, 823, 761 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.55 ppm (s, 1H, NH), 7.62–7.53 ppm (m, 4H, Ar–H), 7.42 ppm (d, *J* = 8.8 Hz, 1H, Ar–H). 7.32 ppm (d, *J* = 6.8 Hz, 2H, Ar–H), 6.80 ppm (s, 1H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.4, 150.0, 136.5, 136.4, 130.7, 129.0 × 2, 128.9, 128.2 × 2, 126.2, 125.4, 120.9, 120.4, 117.6 ppm. HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_9BrClNONa$: 355.9448; found: 355.9444.

4.5.12. 3-Bromo-6-nitro-4-phenyl-2-quinolone **(1l)**

65.6 mg (19% yield), purified by column chromatography (dichloromethane:methanol = 30:1), white solid, mp 202–204 °C. IR (KBr): ν 3440, 1669, 1058, 1028, 823, 761, 624 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.97 ppm (s, 1H, NH), 8.39 ppm (dd, J_m = 2.2 Hz, J_o = 9.0 Hz, 1H, Ar–H), 7.74 ppm (d, J_m = 2.1 Hz, 1H, Ar–H), 7.67–7.60 ppm (m, 3H, Ar–H), 7.56 ppm (d, J_o = 9.1 Hz, 1H, Ar–H), 7.40 ppm (d, *J* = 6.5 Hz, 2H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.7, 150.7, 142.0, 141.7, 135.9, 129.2, 129.0 × 2, 128.4 × 2, 125.4, 122.7, 121.1, 119.4, 116.8 ppm. HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_9BrN_2O_3Na$: 366.9689; found: 366.9682.

4.5.13. 3-Fluoro-4-methyl-2-quinolone **(1m)**

70.9 mg (40% yield), purified by column chromatography (dichloromethane:methanol = 30:1), white solid, mp 179–181 °C. IR (KBr): ν 3444, 1666, 1629, 1577, 1437, 1204, 749, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.15 ppm (s, 1H, NH), 7.70 ppm (d, *J* = 7.3 Hz, 1H, Ar–H), 7.46 ppm (d, *J* = 6.9 Hz, 1H, Ar–H), 7.32 ppm (d, *J* = 7.8 Hz, 1H, Ar–H), 7.25 ppm (d, *J* = 6.4 Hz, 1H, Ar–H), 2.35 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.4 ppm (d, $^2J_{F,C}$ = 28.2 Hz), 148.6 ppm (d, $^1J_{F,C}$ = 243.6 Hz), 135.6, 129.6 ppm (d, *J* = 2.0 Hz), 127.7 ppm (d, $^2J_{F,C}$ = 12.8 Hz), 125.1 ppm (d, *J* = 6.4 Hz), 122.8, 119.3 ppm (d, *J* = 4.5 Hz), 115.8, 10.1 ppm (d, $^3J_{F,C}$ = 4.4 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ −133.1 ppm (s, 1F, CF).

4.5.14. 6-Chloro-3-fluoro-4-methyl-2-quinolone **(1n)**

80.4 mg (38% yield), purified by column chromatography (dichloromethane:methanol = 30:1), white solid, mp 211–213 °C. IR (KBr): ν 3445, 1664, 1631, 1574, 1492, 1422, 1202, 645 cm^{-1}. ^1H

NMR (300 MHz, DMSO-d_6): δ 12.29 ppm (s, 1H, NH), 7.76 ppm (s, 1H, Ar–H), 7.54 ppm (d, J_o = 8.8 Hz, 1H, Ar–H), 7.33 ppm (d, J_o = 8.8 Hz, 1H, Ar–H), 2.36 ppm (s, J = 2.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.8 ppm (d, $^2J_{F,C}$ = 28.3 Hz), 148.8 ppm (d, $^1J_{F,C}$ = 245.2 Hz), 134.0 ppm (d, J = 2.0 Hz), 129.3 ppm (d, J = 2.5 Hz), 126.8 ppm (d, $^2J_{F,C}$ = 13.7 Hz), 126.7, 124.0 ppm (d, J = 6.5 Hz), 120.5 ppm (d, J = 5.1 Hz), 117.3, 9.8 ppm (d, $^3J_{F,C}$ = 4.2 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ −129.93 ppm (s, 1F, CF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{10}H_7ClFNONa$: 234.0092; found: 234.0093.

4.5.15. 3-Fluoro-6,7-dimethoxy-4-methyl-2-quinolone **(1o)**

71.8 mg (30% yield), purified by column chromatography (dichloromethane:methanol = 30:1), white solid, mp 266–268 °C. IR (KBr): ν 3422, 1657, 1623, 1516, 1423, 1271, 1215, 1169, cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.96 ppm (s, 1H, NH), 7.11 ppm (s, 1H, Ar–H), 6.89 ppm (s, 1H, Ar–H), 3.84 ppm (s, 3H, OCH_3), 3.80 ppm (s, 3H, OCH_3), 2.50 ppm (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.7 ppm (d, $^2J_{F,C}$ = 28.1 Hz), 150.8 ppm (d, J = 2.5 Hz), 147.1 ppm (d, $^1J_{F,C}$ = 239.1 Hz), 145.3, 130.4, 127.6 ppm (d, $^2J_{F,C}$ = 14.2 Hz), 111.7 ppm (d, J = 4.2 Hz), 105.9 ppm (d, J = 5.6 Hz), 98.0, 55.9, 55.5, 10.1 ppm (d, $^3J_{F,C}$ = 4.6 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ −136.6 ppm (s, 1F, CF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{12}H_{12}FNO_3Na$: 260.0693; found: 260.0686.

4.5.16. 3-Fluoro-4-phenyl-2-quinolinone **(1p)**

217.7 mg (91% yield), recrystallized from ethanol, white solid, mp 254–256 °C. IR (KBr): ν 3444, 1669, 1617, 1568, 1283, 755, 701 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.45 ppm (s, 1H, NH), 7.59–7.50 ppm (m, 4H, Ar–H), 7.46–7.41 ppm (m, 3H, Ar–H), 7.21–7.14 ppm (m, 2H, Ar–H). ^{13}C NMR (75 MHz, DMSO–d_6): δ 155.3 ppm (d, $^2J_{F,C}$ = 28.0 Hz), 147.0 ppm (d, $^1J_{F,C}$ = 246.6 Hz), 135.7 ppm (d, J = 2.0 Hz), 131.5 ppm (d, $^2J_{F,C}$ = 12.8 Hz), 130.1, 129.5 ppm (d, J = 2.6 Hz), 129.4, 129.3, 129.0, 128.8 × 2, 125.9 ppm (d, J = 6.5 Hz), 122.6, 118.6 ppm (d, J = 2.8 Hz), 115.7. ^{19}F NMR (282 MHz, DMSO-d_6): δ −130.9 ppm (s, 1F, CF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{15}H_{10}FNONa$: 262.0639; found: 262.0643.

4.5.17. 6-Chloro-3-fluoro-4-phenyl-2-quinolone **(1q)**

251.8 mg (92% yield), recrystallized from ethanol, white solid, mp 197–199 °C. IR (KBr): ν 3445, 1661, 1620, 1569, 1484, 1414, 1271, 1203, 700, 664 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11–14 ppm (br.s, 1H, NH), 7.61–7.55 ppm (m, 4H, Ar–H), 7.47–7.42 ppm (m, 3H, Ar–H), 7.04 ppm (s, 1H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.1 ppm (d, $^2J_{F,C}$ = 28.0 Hz), 147.7 ppm (d, $^1J_{F,C}$ = 249.0 Hz), 134.5 ppm (d, J = 3.4 Hz), 130.5 ppm (d, $^2J_{F,C}$ = 13.8 Hz), 129.5, 129.4 ppm (d, J = 2.6 Hz), 129.3 × 3, 129.0 × 2, 126.6, 124.6 ppm (d, J = 6.5 Hz), 120.1 ppm (d, J = 3.4 Hz), 117.7 ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ −127.56 ppm (s, 1F, CF). HRMS-MALDI: m/z [M+Na]$^+$ calcd for $C_{15}H_9ClFNONa$: 296.0249; found: 296.0256.

4.5.18. 3-Fluoro-6-nitro-4-phenyl-2-quinolone **(1r)**

264.3 mg (93% yield), recrystallized from ethanol, white solid, mp 188–190 °C. IR (KBr): ν 3443, 1666, 1629, 1575, 1535, 1487, 1380, 1336, 1272, 1206, 832, 731 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 ppm (d, J = 8.9 Hz, 1H, Ar–H), 7.95 ppm (s, 1H, Ar–H), 7.64–7.62 ppm (m, 3H, Ar–H), 7.54–7.49 ppm (m, 3H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6 ppm (d, $^2J_{F,C}$ = 28.0 Hz), 148.0 (d, $^1J_{F,C}$ = 250.6 Hz), 142.0, 140.3 ppm (d, J = 1.7 Hz), 131.0 ppm (d, $^2J_{F,C}$ = 13.9 Hz), 129.7, 129.5 × 2, 129.1 × 2, 129.1, 124.2 ppm (d, J = 2.2 Hz), 121.9 ppm (d, J = 7.0 Hz), 118.7 ppm (d, J = 3.8 Hz), 117.0 ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ −127.0 ppm (s, 1F, CF). HRMS-ESI: m/z [M+Na]$^+$ calcd for $C_{15}H_9FN_2O_3Na$: 307.0489; found: 307.0493.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2010.01.008.

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