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New benzophenone phosphonate derivatives

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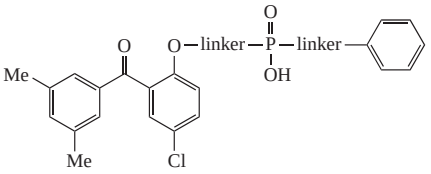
New well-soluble in 10% DMSO phosphonate derivatives of substituted benzophenone have been synthesized using different methods. Preliminary computer modeling of proposed structures in the reverse transcriptase HIV-1 hydrophobic pocket suggested these molecules as potential non-nucleoside inhibitors of this enzyme.



Despite of the numerous efforts, AIDS remains one of the main threats to human health. According to the latest data of the World Health Organization, there were 2.1 million new cases of HIV infection in the world in 2015 and a total of 36.7 million people living with HIV.[1]

Currently, 25 approved individual drugs are used in HIV infection therapy, which act in different stages of the viral life cycle. The most effective treatment for HIV is a highly active antiretroviral therapy, which includes several drugs with different mechanisms of action: obligatory one or more nucleoside inhibitors of HIV reverse transcriptase (RT) plus a non-nucleoside inhibitor of HIV reverse transcriptase (NNRTI) and/or inhibitors of other classes. However, disadvantages of the existing drugs, in particular, side effects, toxicity and the rapid emergence of resistant virus strains lead to the need of the regimen change. Thus, the search for new anti-HIV agents as well as optimization of properties of the existing drugs remain essential.

Compounds containing benzophenone moiety linked to the aromatic or heterocyclic ring (Figure 1) possess inhibitory activity against RT of HIV-1 in nanomolar and subnanomolar concentrations, wich makes them very promising among many classes of NNRTI.[2–4] Unfortunately, benzophenone analogues have not found practical applications yet due to the extremely poor solubility and low bioavailability. In this work we have studied the possibility of introducing a phosphonate fragment to benzophenone-containing compounds in order to find new potential inhibitors of HIV RT. Such modifications may improve solubility but not affect biological properties dramatically.[5]

Herein, we have designed several phosphonates **1**–**6** (see Figure 1) and have proposed the strategy of their synthesis.

Preliminary evaluation of the affinity of new potential non-nucleoside inhibitors to the HIV RT hydrophobic pocket was conducted by computer modeling. Molecular cross-docking was performed by the AutoDock Vina 1.1.2[6] program using standard procedures for the preparation of ligands and receptors. Docking analysis has revealed that the proposed structures are able to reproduce binding modes of the known highly active NNRTIs of biphenyl ether[7] and benzophenone types.[8]

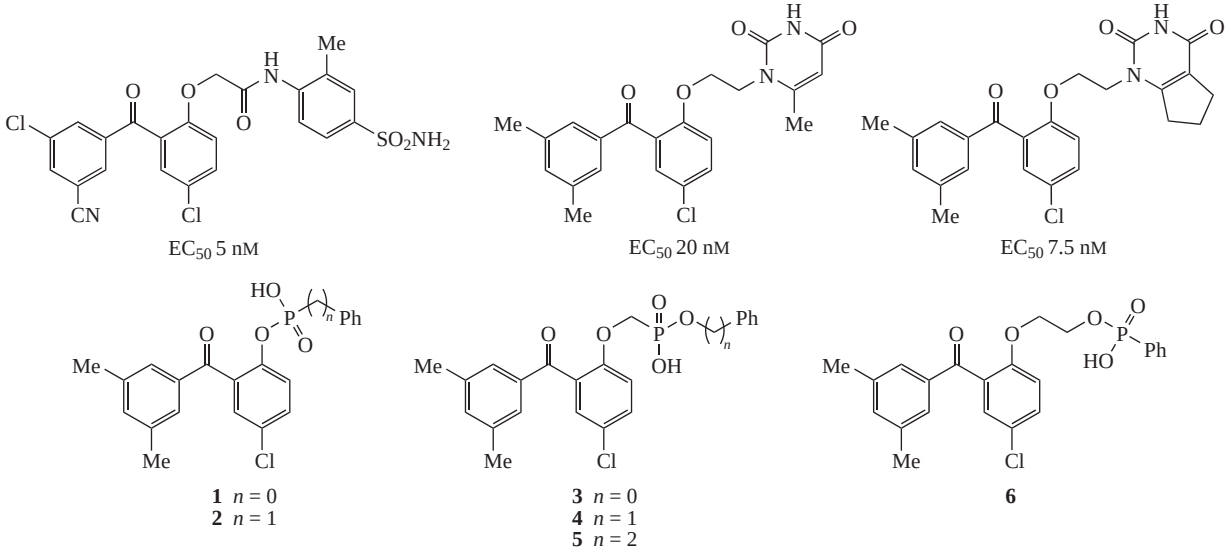
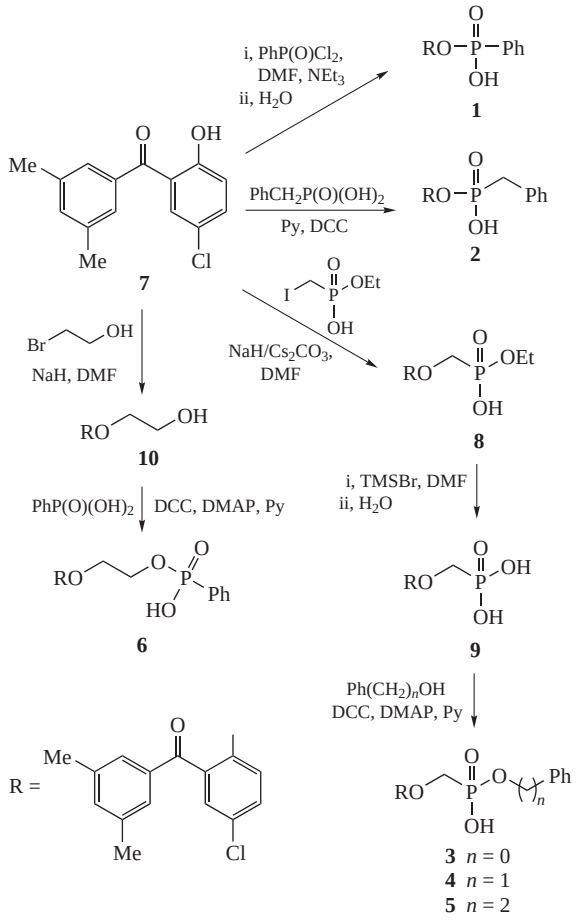


Figure 1 Structures of model and designed (**1**–**6**) compounds.



Scheme 1

The key steps of synthesis of target phosphonates (Scheme 1) were: condensation with phenylphosphonic dichloride (for compound **1**) or with its acid (for compounds **2**, **6**), or reaction with iodomethylphosphonic acid monoethyl ester (for compound **3**). Yields of compounds **1** and **2** after purification were 37 and 58%, respectively.†

To obtain phosphonates **3**–**5**, starting compound **7**, activated with NaH and Cs_2CO_3, was treated with iodomethylphosphonic acid monoethyl ester to give ester **8** (see Scheme 1).‡ Compound **8** can also be synthesized using *p*-tosyloxymethylphosphonic acid monoethyl ester, however in lower yield. Monoethyl ester **8** was isolated on DEAE cellulose and then O-deethylated with Me_3SiBr to afford phosphonic acid **9** which was used without further purification. Acid **9** was then activated with DCC and the corresponding alcohol or phenol was added in the presence of a catalytic amount of DMAP. Yields of phosphonates **3**, **4**, **5** were 56, 74 and 72%, respectively.

To increase the distance between benzophenone and phosphonate fragments, compound **7** was alkylated with 2-bromoethanol, activated with DCC and treated with phenylphosphonic acid (see Scheme 1). Product **6** was obtained in 60% yield.

In summary, six new substituted benzophenone phosphonate derivatives were synthesized. Compounds bear three aromatic fragments construction that is typical of known NNRTIs and differ from each other by the phosphonate linker.

† 4-Chloro-2-(3,5-dimethylbenzoyl)phenol **7** was synthesized as described,[9] its physico-chemical characteristics agree with reported ones.[4]

4-Chloro-2-(3,5-dimethylbenzoyl)phenyl hydrogen phenylphosphonate **1**. Triethylamine (132 μl, 0.95 mmol) and phenylphosphonic dichloride (56.3 μl, 0.29 mmol) were added to a solution of 4-chloro-2-(3,5-dimethylbenzoyl)phenol **7** (50 mg, 0.19 mmol) in dry DMF (5 ml) under argon. The mixture was stirred and the conversion was controlled by TLC. Water (5 ml) was added and the solvents were evaporated. The residue was purified by column chromatography on silica gel (eluent $CHCl_3$–MeOH, 4:1) to give product **1** as pale yellow foam (yield 37%). R_f 0.4 ($CHCl_3$–MeOH, 4:1). ^{1}H NMR ($CDCl_3$) δ: 11.9 (s, 1H, OH), 7.56–7.48 (m, 3H, Ar), 7.23–7.22, 7.17–7.12 (m, 8H, Ar), 2.26 (s, 6H, 2Me). ^{31}P NMR ($CDCl_3$) δ: 8.12. HRMS, *m*/*z*: 399.0549 $[M-H]^-$ (calc. for $C_{21}H_{18}O_4PCl$, *m*/*z*: 399.0547).

4-Chloro-2-(3,5-dimethylbenzoyl)phenyl hydrogen benzylphosphonate **2**. Benzylphosphonic acid (50 mg, 0.29 mmol) and DCC (118 mg, 0.57 mmol) were added to a solution of compound **7** (50 mg, 0.19 mmol) in dry pyridine (10 ml) under argon. The mixture was stirred and the conversion was controlled by TLC. Then water (1 ml) was added, the solid residue was removed by filtration. The solvents were evaporated and the residue was purified (eluent $CHCl_3$, $CHCl_3$–MeOH, 4:1) to give product **2** as a yellow foam (yield 58%). R_f 0.4 ($CHCl_3$–MeOH, 4:1). ^{1}H NMR ($CDCl_3$) δ: 11.9 (s, 1H, OH), 7.56–7.55, 7.45–7.42, 7.25–7.24, 7.02–7.00 (m, 11H, Ar), 2.93–2.86 (d, 2H, PCH_2, *J* 28.8 Hz), 2.40 (s, 6H, 2Me). ^{31}P NMR ($CDCl_3$) δ: 14.57. HRMS, *m*/*z*: $[M-H]^-$ 413.0695 (calc. for $C_{22}H_{20}O_4PCl$, *m*/*z*: 413.0704).

‡ *Ethyl hydrogen 4-chloro-2-(3,5-dimethylbenzoyl)phenoxymethylphosphonate* **8**. Sodium hydride (21 mg, 0.87 mmol) and Cs_2CO_3 (151 mg, 0.46 mmol) were added to a solution of 4-chloro-2-(3,5-dimethylbenzoyl)-phenol **7** (150 mg, 0.58 mmol) in dry DMF (10 ml) under argon. After 1 h iodomethylphosphonic acid monoethyl ester (217 mg, 0.87 mmol) was added and the mixture was stirred for 18 h more. The solvent was evaporated and the residue was purified on DEAE Toyopearl eluted with NH_4HCO_3 (0.2 M → 0.4 M) and then NH_4HCO_3–EtOH (0.4 M: 0 → 30%). Product **8** was isolated as a yellow oil in 30% yield. R_f 0.65 (dioxane–NH_3 aq., 4:1). ^{1}H NMR (D_2O) δ: 7.60–7.58, 7.42–7.39 (m, 3H, Ar), 7.29–7.22 (m, 5H, Ar), 7.12–7.09 (m, 2H, Ar), 4.01–3.99 (d, 2H, OCH_2P, *J* 10 Hz), 3.44–3.38 (dd, 2H, $POCH_2$, *J* 8 Hz), 2.16 (s, 6H, $C_6H_3Me_2$), 0.80 (t, 3H, Me, *J* 9 Hz). ^{31}P NMR (D_2O) δ: 14.81.

4-Chloro-2-(3,5-dimethylbenzoyl)phenoxymethylphosphonic acid **9**. Bromotrimethylsilane (163 μl, 1.26 mmol) was added to a solution of compound **8** (319 mg, 0.09 mmol) in dry DMF (10 ml). The mixture was stirred for 3 h followed by the addition of water (1 ml). The solvents were evaporated and product **9** was used without further purification. R_f 0.6 (Pr^iOH–NH_3 aq.–H_2O, 7:2:2). ^{1}H NMR (D_2O) δ: 7.52–7.50 (m, 1H, Ar), 7.39–7.35 (m, 3H, Ar), 7.24–7.19 (m, 2H, Ar), 4.01–3.99 (d, 2H, OCH_2P, *J* 8.8 Hz), 2.26 (s, 6H, 2Me). ^{31}P NMR (D_2O) δ: 13.34.

4-Chloro-2-(2-hydroxyethoxy)-3',5'-dimethylbenzophenone **10**. Sodium hydride (46 mg, 1.92 mmol) was added to a solution of compound **7** (250 mg, 0.96 mmol) in dry DMF (10 ml) under argon. After 1 h of stirring, 2-bromoethanol (103 μl, 1.44 mmol) was added, and the mixture was refluxed for 1 h. The solvents were evaporated and the residue was purified by column chromatography (eluent hexane–EtOAc, 9:1 → 3:2) to afford product **10** as a transparent oil (yield 30%). R_f 0.45 (hexane–EtOAc, 3:2). ^{1}H NMR (CD_3OD) δ: 7.42–7.38 (m, 4H, Ar), 7.35–7.34 (m, 1H, Ar), 6.94–6.92 (d, 1H, Ar, *J* 8 Hz), 4.04–4.02 (t, 2H, $ArOCH_2$, *J* 4.4 Hz), 3.95 (s, 1H, OH), 3.66–3.65 (m, 2H, CH_2OH), 2.34 (s, 6H, 2Me).

Phenyl hydrogen 4-chloro-2-(3,5-dimethylbenzoyl)phenoxymethylphosphonate **3**. Phenol (20 mg, 0.21 mmol), DCC (87 mg, 0.42 mmol) and DMAP (1.7 mg, 0.014 mmol) were added to a solution of compound **9** (50 mg, 0.14 mmol) in dry pyridine (5 ml). The mixture was stirred and the conversion was controlled by TLC. Then water (1 ml) was added, the solid residue was removed by filtration. The solvents were evaporated and the residue was purified as above (eluent hexane–EtOAc, 1:3, then EtOAc–MeOH–NH_3 aq., 8:0.2:0.5) to give product **3** as a white foam (yield 56%). R_f 0.55 (dioxane–NH_3 aq., 4:1). ^{1}H NMR (CD_3OD) δ: 7.49–7.46, 7.39–7.38 (m, 3H, Ar), 7.31–7.29, 7.24–7.21 (m, 3H, Ar), 7.13–7.09 (m, 2H, Ar), 7.00–6.96 (m, 1H, Ar), 6.88–6.85 (m, 2H, Ar), 4.13–4.11 (d, 2H, CH_2, *J* 8 Hz), 2.30 (s, 6H, 2Me). ^{31}P NMR (CD_3OD) δ: 11.82. HRMS, *m*/*z*: 429.0654 $[M-H]^-$ (calc. for $C_{22}H_{20}O_5PCl$, *m*/*z*: 429.0653).

Benzyl hydrogen 4-chloro-2-(3,5-dimethylbenzoyl)phenoxymethylphosphonate **4**. Compound **4** was synthesized and purified (eluent $CHCl_3$–MeOH, 4:1) according to the procedure described for compound **3**, using reactant **9** (25 mg, 0.07 mmol), benzyl alcohol (11 μl, 0.11 mmol), DCC (43.3 mg, 0.21 mmol) and DMAP (0.86 mg, 0.007 mmol). Yield of product **4** as a pale yellow oil was 74%. R_f 0.6 ($CHCl_3$–MeOH, 4:1). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.08 (m, 3H, Ar), 7.00–6.99 (m, 3H, Ar), 6.87–6.86 (m, 5H, Ar), 4.69–4.67 (d, 2H, OCH_2P, *J* 8.8 Hz), 4.23–4.18 (d, 2H, CH_2Ph, *J* 8 Hz), 2.18 (s, 6H, 2Me). ^{31}P NMR ($CDCl_3$) δ: 8.52. HRMS, *m*/*z*: 443.0810 $[M-H]^-$ (calc. for $C_{23}H_{22}O_5PCl$, *m*/*z*: 443.0810).

The estimated solubility in 100 ml of 10% DMSO for compounds **1**, **2** was higher than 100 mg, and for compounds **3** and **6** it was 80 mg. Compounds **4** and **5** were more hydrophobic with solubility of 50 and 80 mg, respectively, in 100 ml of 10% DMSO. To compare with the prototype benzophenone derivatives which have the solubility of 5–15 mg in 100 ml of 10% DMSO, all new compounds possess improved properties.

Preliminary computer modeling of the affinity of the new compounds to the target enzyme hydrophobic pocket allows us to suggest that phosphonates **1**–**6** may be potential non-nucleoside RT HIV inhibitors. Experiments to determine their inhibitory activity against RT HIV will be performed and data will be published elsewhere.

2-Phenylethyl hydrogen 4-chloro-2-(3,5-dimethylbenzoyl)phenoxymethylphosphonate **5**. Compound **5** was synthesized and purified according to the procedure described for compound **3**, using reactant **9** (50 mg, 0.14 mmol), 2-phenylethanol (26 μl, 0.21 mmol), DCC (87 mg, 0.42 mmol) and DMAP (1.7 mg, 0.014 mmol). Yield of product **5** as a white foam was 72%. R_f 0.5 (dioxane–NH_3 aq., 4 : 1). ^{1}H NMR (CD_3OD) δ: 7.48–7.45, 7.34 (m, 3H, Ar), 7.24–7.19, 7.17–7.10 (m, 8H, Ar), 4.07–4.04 (d, 2H, CH_2P, *J* 12 Hz), 3.81–3.75 (dd, 2H, $POCH_2$, *J* 8 Hz), 2.68–2.65 (t, 2H, CH_2Ph, *J* 8 Hz), 2.26 (s, 6H, 2Me). ^{31}P NMR (CD_3OD) δ: 15.08. HRMS, *m*/*z*: 457.0966 $[M-H]^-$ (calc. for $C_{24}H_{24}O_5PCl$, *m*/*z*: 457.0966).

2-[4-Chloro-2-(3,5-dimethylbenzoyl)phenoxy]ethyl hydrogen phenylphosphonate **6**. Phenylphosphonic acid (45 mg, 0.29 mmol), DCC (118 mg, 0.57 mmol) and DMAP (2.32 mg, 0.019 mmol) were added to a solution of reactant **10** (58 mg, 0.19 mmol) in dry pyridine (10 ml) under argon. The mixture was stirred and the conversion was controlled by TLC. Then water (1 ml) was added, the solid precipitate was removed by filtration. The solvents were evaporated and the residue was purified using PLC (eluent dioxane–NH_3 aq., 4 : 1) to give product **6** as a white foam (yield 60%). R_f 0.6 (dioxane–NH_3 aq., 4 : 1). ^{1}H NMR (DMSO-d_6) δ: 7.55–7.50 (m, 3H, Ar), 7.31–7.26 (m, 8H, Ar), 4.00–3.98 (t, 2H, $ArOCH_2$, *J* 4.4 Hz), 3.51–3.50 (d, 2H, CH_2OP, *J* 3.6 Hz), 2.27 (d, 6H, 2Me). ^{31}P NMR (DMSO-d_6) δ: 11.85. HRMS, *m*/*z*: 443.0807 $[M-H]^-$ (calc. for $C_{23}H_{22}O_5PCl$, *m*/*z*: 443.0810).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.07.008.

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