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FLUOROPHENYL-CONTAINING A-AMINOPHOSPHONATES: SYNTHESIS AND STRUCTURE

Abstract. Novel α-aminophosphonates ***1-3*** were synthesized by the one-pot three component reaction of equimolar quantities of dimethylphosphite, diphenylmethylpiperazine and a carbonyl component (4, 3 or 2-fluorobenzaldehyde) in benzene at reflux conditionsfor 30 h viaKabachnik-Fields reaction in high yields (82.9-90.3%). The progress of the reaction was monitored by thin layer chromatography analysis. The chemical structures were established by the physico-chemical methods as IR, ^{1}H, ^{13}C NMR and elemental analyses.

Key words: α-aminophosphonates, fluorophenyl, Kabachnik-Fields reaction, synthesis, structure.

The α-aminophosphonate fragment is a universal pharmacophoredue to the spectrum of biological activity exhibited by the compounds having this structural unit. Studies are underway to develop new synthetic methods for the preparation of α-aminophosphonates [1-3]. The attractiveness of the chemistry of this family of compounds is explained by the fact that a significant number of derivatives of α-aminophosphonates are used in medicine as antiviral [4] antifungal, antibacterial [5] and antitumor drugs [6-8] inhibitors of enzymes [9], antibiotics and pharmacological agents [10]. It addition theaminophosphonates are valuable intermediates for the preparation of medicinal and agriculture compounds, reagents for the recovery of metal ions, etc.

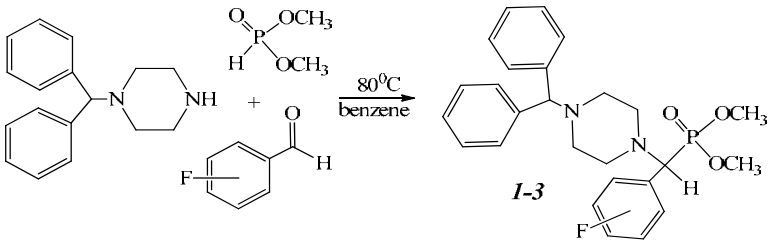
In the present workthe problem of introducing a fluorophenyl group into a molecule having an aminophosphonate fragment is solving.

Interest tofluorophenyl derivatives is dictated by their pharmacological potential – in particular, fluorophenyl is a part of the known neuroleptics haloperidol [11], droperidol [12], melperone [13], some antiseptic and antipsychotic agents. Although organofluorine compounds are practically not found among natural products, it is interesting to note that about 25% of pharmaceutical drugs contain at least one fluorine atom. Thus, there are nine new synthetic preparations out of thirty-one approved in 2002 for pharmaceutical production, contain fluorine [14-16].

Synthesis of aminophosphonic acids derivatives is an active research field, and many methods are currently available. Among the synthetic approaches to aminophosphonates, one of the most important methods is the Kabachnik-Fields reaction [17, 18]. This reliable method for the synthesis of aminophosphonates is

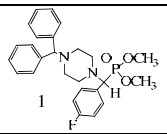
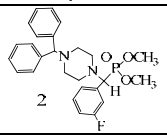
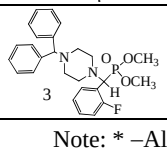
a three-component reaction ofa carbonyl compound, primary or secondary amine and dialkyl or trialkylphosphites.

To continue Research related to the synthetic design of potential bioactive nitrogen heterocycles carried out in the laboratory of the Synthetic and Natural Medicinal Compounds Chemistry, pharmacophorediphenylmethylpiperazine [19] was used as the initial amine component, which is a synthetic analogue of natural alkaloids. The interaction of diphenylmethylpiperazine with *p*-, *m*- or *o*-fluoro-benzaldehydes and dimethylphosphite under the conditionsof the one-pot reactor three-component classical Kabachnik-Fields reaction in benzene at 80°C, using a Dean-Stark trap to divert the obtained water from the reaction zone by distilling its azeotrope– water+benzene, leads to the target α-aminophosphonates ***1-3***:



The yields and physico-chemical characteristics of α-aminophosphonates ***1-3*** are presented in table 1. α-Aminophosphonates 1-3 were prepared with the yields of 82.9-90.3% after long time boiling (for 30 hours).

Table 1 – The yields and physico-chemical characteristics
of dimethyl[(4-benzhydrylpiperazin-1-yl)(*p*-, *m*- and *o*-fluorophenyl)methyl]phosphonate

Compound	Yield, %	R_f*	$T_{melting,}$ ^0C	Calculated / Found, % for $C_{26}H_{30}FN_2O_3P$				
				C	H	N	P	F
 1	82,9	0,56	72	66,65 66,83	6,45 6,62	5,98 6,03	6,61 6,92	4,06 3,83
 2	85,7	0,53	58	66,65 66,74	6,45 6,69	5,98 6,11	6,61 6,59	4,06 4,10
 3	90,3	0,48	98	66,65 66,56	6,45 6,51	5,98 5,83	6,61 6,77	4,06 3,99
Note: * –Al_2O_3, eluent hexane: chloroform1:3.								

The structure of synthesizedcompounds ***1-3*** were established by IR, ^{1}H and ^{13}C NMR. In the IR spectra (figure 1), the peaks at 1507-1588 cm^{-1}were attributed to the absorption of C = C of the aromatic ring, 1227-1287 cm^{-1} to C-N, 1035 to 1022 cm^{-1} to P = O and 754 to 769 cm^{-1} to -P-C.

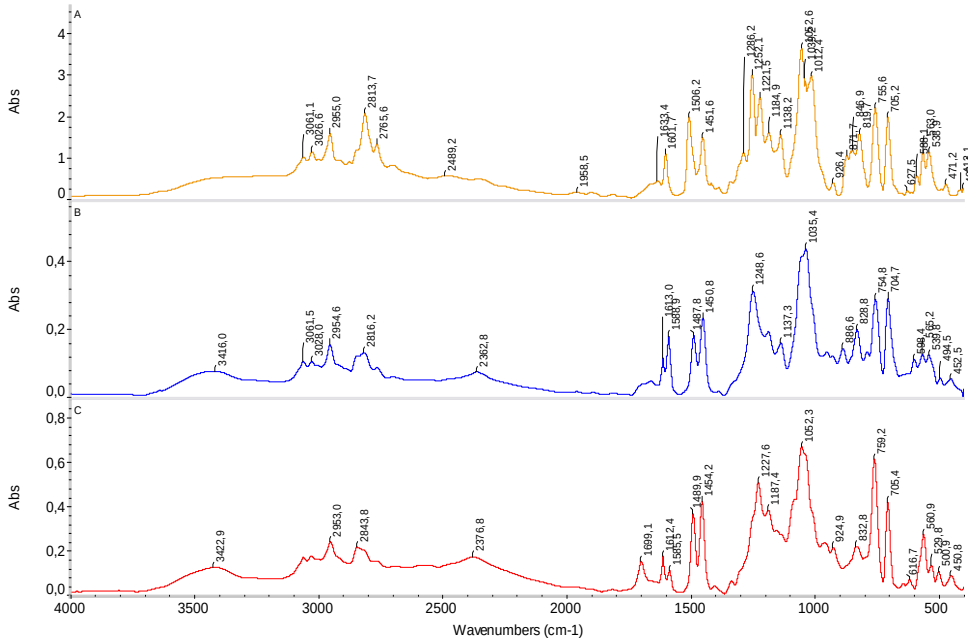


Figure 1 – The IR spectra
of dimethyl[(4-benzhydrylpiperazin-1-yl)(*p*-, *m*- and *o*-fluorophenyl)methyl]phosphonate

The proton (figure 2) and the carbon spectra of fluorophenyl-containing benzhydrylpiperazineaminophosphonates***1-3*** differed by signals of protons and carbons in the "aromatic" region, associated with the position of the fluorine atom in the benzene ring. Signals in the area of 0.75-1.25 ppmwere in the axial protons of the piperazine cycle, the equatorial ones were 2.25-2.75 ppm.

The methoxy protons resonated at 3.75 ppm. The methine proton adjacent to the phosphorus atom resonated in the region of 4.25 ppm, analogous to the benzhydryl group - 5.0 ppm (for *n*- and *m*-F), in the *o*-F signal the signal was shifted to a weaker field (5.8 ppm). All aromatic protons resonated in the region of 7.1-8.0 ppm, but they differed greatly in signalsform.

A similar character,as similar carbon signals of the piperazine fragment, methine and methoxy groups, only the difference in the signals of aromatic carbons, was observed in the ^{13}C NMR spectra.

The most informative proof of the structure of the synthesized systems werethe carbon ^{13}C NMR spectra of 4-benzhydrylpiperazine aminophosphonates (table 2).

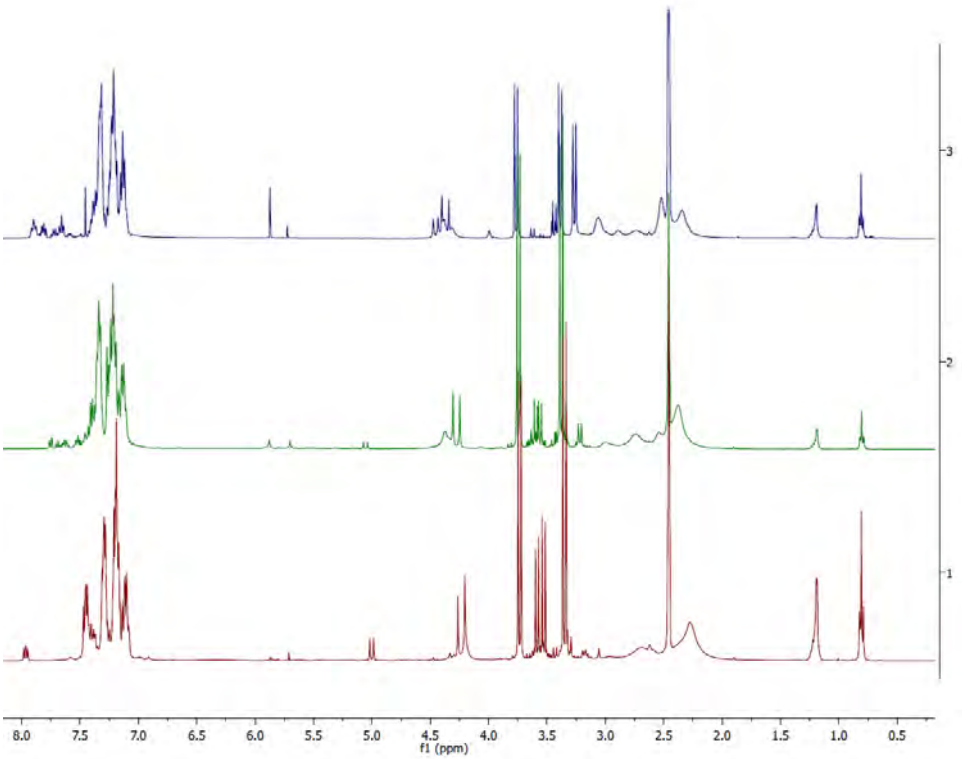


Figure 2 – ^{1}H NMR spectra
of fluorine-containing 4-benzhydrylpiperazine aminophosphonates ***1-3***

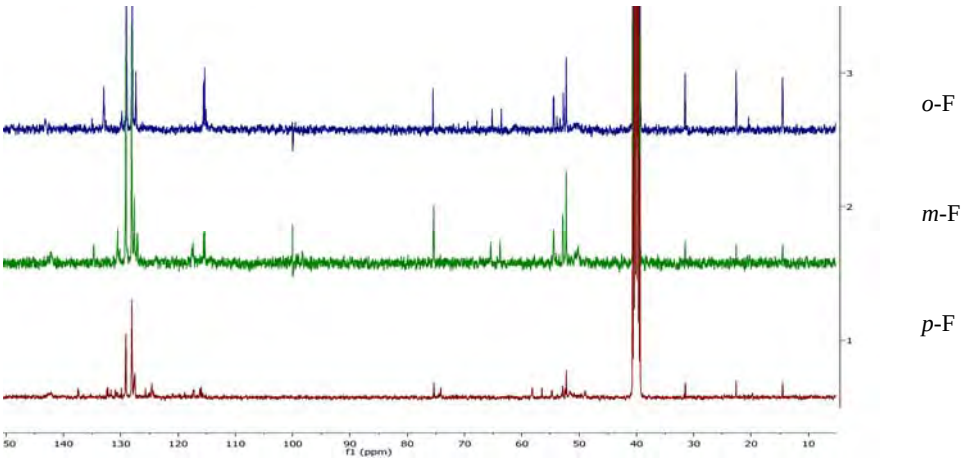
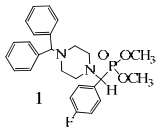
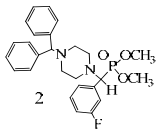
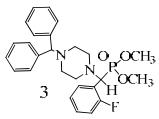


Figure 3 – ^{13}C NMR spectra
of fluorine-containing 4-benzhydrylpiperazine aminophosphonates **(*1-3*)**

Table 2 – ^{13}CNMRspectra of 4-benzhydrylpiperazineaminophosphonates ***1-3***

Compound	Chemical shifts ($CDCl_3$), δ, ppm					
	C-2, C-6	C-3, C-5	CH(P) (CH)	(P)OCH_3	C_6H_4F	$(C_6H_5)_2$ (CHN)
 1	51.1	53.8	67.5 (75.4)	53.0-53.9	115.8-166.1	127.8-142.1
 2	51.7	53.3	68.0 (76.1)	52.9-54.5	116.7-164.8	126.1-146.9
 3	52.1	53.7	67.6 (77.5)	52.6-53.8	117.2-163.8	116,2-162,2

The carbon composition completely corresponded to the expected composition of the synthesized dimethyl[(4-benzhydrylpiperazin-1-yl)(*p*-, *m*- and *o*-fluorophenyl)methyl]phosphonates ***1-3***. Strong-field signals of double intensity at 51.1-52.1 and 53.3-53.8 ppm belong to the carbon atoms of the piperazine (C-2, C-6 and C-3 and C-5) cycle. In the same area at 52.6-54.9 ppm the signals of the carbon atom of the dimethylphosphoryl fragment of $P(O)(OCH_3)_2$were observed. The low-field region is "populated" with aromatic carbon atoms. The methine carbon CH(P) resonated at 67.5-68.0 ppm. A similar signal of the benzhydryl group appeared in the region of 116.2-162.2 ppm.

Experimental

The reaction and the individuality of the compounds were monitored by TLC on alumina oxide of III activity (eluent hexane: chloroform 1:3) with the appearance of spots by iodine vapor. The IR spectra were recorded on a Nicolet 5700 spectrometer in a thin layer between the KBr plates. NMR spectra in $CDCl_3$ are recorded on a JNM-ECA400 spectrometer, Jeol (Japan), an operating frequency of 400 MHz (^{1}H) and 100 MHz ($C^{13}C$).

Synthesis of dimethyl[(4-benzhydrylpiperazin-1-yl)(p-fluorophenyl)methyl]-phosphonate (1). 3 g (0.0185mol) 1-Benzhydrylpiperazine, 3.46 g (0.018 mol) of *p*-fluorobenzaldehyde and 1.7 ml of dimethyl phosphate in 185 ml of benzene were placed in a flask equipped with a Dean-Stark trap and a reflux condenser. The mixture was stirred for 20 min at room temperature. With constant stirring, the reaction mixture is heated at the boiling point of benzene. After distillation of the solvent, the residue was repeatedly washed with hot hexane. 4.62 g (82.9% of theory) of dimethyl[(4-benzhydrylpiperazin-1-yl)(*p*-fluorophenyl)methyl]phos-

phonate was isolated from the hexane fraction, m.p. 72°C (transparent needle-like crystals).

*Synthesis of dimethyl[(4-benzhydrylpiperazin-1-yl)(m-fluorophenyl)methyl]-phosphonate (2).*3 g (0.0185 mol) 1-Benzhydrylpiperazine, 3.4 ml (0.018 mol) of *m*-fluorobenzaldehyde and 1.7 ml of dimethyl phosphate in 185 ml ofbenzene were placed in a flask equipped with a Dean-Stark trap and a reflux condenser. The mixture was stirred for 20 minutes at room temperature. With constant stirring, the reaction mixture is heated at the boiling point of benzene. After distillation of the solvent, the residue was repeatedly washed with hot hexane. 3.96 g (85.7% of theory) of dimethyl [(4-benzhydrylpiperazin-1-yl)(*m*-fluorophenyl)methyl]phosphonatewas isolated from the hexane fraction, m.p. 58°C (transparent needle-like crystals).

*Synthesis of dimethyl [(4-benzhydrylpiperazin-1-yl) (o-fluorophenyl)methyl] phosphonate (3).*3 g (0.0185 mol) 1-Benzhydrylpiperazine, 3.4 ml (0.018 mol) of of*o*-fluorobenzaldehydeand 1.7 ml of dimethyl phosphite in 185 ml of benzene were placed in a flask equipped with a Dean-Stark trap and a reflux condenser. The mixture was stirred for 20 minutes at room temperature. With constant stirring, the reaction mixture is heated at the boiling point of benzene. After distillation of the solvent, the residue was repeatedly washed with hot hexane.5.03 g (90.3% of theory) of dimethyl[(4-benzhydrylpiperazin-1-yl)(*o*-fluorophenyl)methyl]phosphonate was isolatedfrom the hexane fraction, m.p. 98°C (transparent needle-like crystals).

Conclusion. Novel α-aminophosphonates with fluorophenyl moiety by the reaction of aldehyde, 1-benzhydrylpiperazine and dimethyl phosphatehave been synthesized. These fluorinated aminophosphonates could be very interesting for their biological activity, because α-aminophosphonate derivatives are important building blocks in organic synthesis of biologically active compounds.

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REFERENCES

[1] Kafaraki P., Lejczak B., Biological Activity of Aminophosphonic Acid//Phosphorus Sulfur Silicon Relat. Elem. 1991. N 63. P. 191.

[2] Panl A.B., Willam B.K. Phosphinic acid dipeptide analogs: potent, slow-binding inhibitors of aspartic peptidases // J. Am. Chem. Soc. 1984. N 106. P. 4282.

[3] Vo-Quang Y., Gravey A. M., Stmonneau, R., Towards new inhibitors of D-alanine:D-alanine ligase: The synthesis of 3-amino butenylphosphonic and aminophosphonamidicacids // Tetrahedron Lett. 1987. N 28. P. 6167.

[4] Baylis E.K., Campbell C.D., Dingwall J.G. 1-Aminoalkylphosphonous acids. Part 1. Isosteres of the protein amino acids // J ChemSoc Perkin Trans 1. 1984. P. 2845-2853.

[5] Prasad G.S., Krishna J.R., Manjunath M., Reddy O.V.S., Krishnaiah M., Reddy C.S., Puranikd V.G., Synthesis, NMR, X-ray crystallography and bioactivity of some α-aminophosphonates // *ARKIVOC*. 2007. N 13. P. 133.

[6] Jing-Zi L., Bao-An S., Hui-Tao F., Bhadury P.S., Wan W.-T., Yang S., Xu W., Wu J., Jin L.-H., Wei X., Hu D.-Y., Zeng S. Synthesis and in vitro study of pseudo-peptide thioureas containing α-aminophosphonate moiety as potential antitumor agents // Eur. J. Med. Chem. 2010. N 45. P. 5108-5112.

[7] Bloemink M.J., Diederen J.J.H., Dorenbos J.P., Heetebrij R.J., Keppler B.K., Reedijik J., Calcium Ions Do Accelerate the DNA Binding of New Antitumor-Active Platinum Aminophosphonate // Complexes Eur. J. Inorg. Chem. 1999. N 10. P. 1655-1657.

[8] Rao X., Song Z., He L. Synthesis and antitumor activity of novel α-aminophosphonates from diterpenicdehydroabietylamine // Heteroatom. Chem. 2008. N 19. P. 512-516.

[9] Allen M.C., Fuhrer W., Tuck B., Wade R., Wood J.M. Renin inhibitors. Synthesis of transition-state analog inhibitors containing phosphorus acid derivatives at the scissile bond // J. Med. Chem. 1989. Vol. 32, N 7. P. 1652-1661.

[10] Atherton F.R., Hassall C.H., Lambert R.W. Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl)phosphonic acid and (aminomethyl)phosphonic acid // J. Med. Chem. 1986. Vol. 29, N1. P. 29-40.

[11] Hyung-Jun Yoon, Kyoung-Min Park, Won-Jung Choi, Soo-Hee Choi, Jin-Young Park, Jae-Jin Kim, Jeong-Ho Seok. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium // BMC Psychiatry. 2013. N 13. P. 240.

[12] Sneyd J.R. Droperidol: past, present and future // Anaesthesia. 2009. N 64. P. 1161–1164. doi:10.1111/j.1365-2044.2009.06124.x

[13] Sumiyoshi T., Jayathilake K., Meltzer H.Y. The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia // Schizophrenia Research. 2003. Vol. 59, N 1. P. 7-16.

[14] Groult H., Leroux F., Tressaud A. Modern Synthesis Processes and Reactivity of Fluorinated Compounds: Progress in Fluorine Science. London: Academic Press, 2016. P. 500-501.

[15] Bohm H.J., Banner D., Bendels S., Kansy M., Kuhn B., Muller K., Obst-Sander U., Stahl M. Fluorine in Medicinal Chemistry // ChemBioChem: Wiley-VCH Verlag GmbH & Co. KGaA. Weinheim. 2004. Vol. 5, N 5. P. 637-643.

[16] Strunecka A., Patocka J., Connett P. Fluorine in medicine // Journal of Applied Biomedicine. 2004. N 2. P. 141-150.

[17] Kabachnik M.I., Bear T.Ya. A new method for the synthesis of α-aminophosphonic acids. Doklady Akademii Nauk SSSR. 1952. P. 689.

[18] Fields E.K. Substituted hydroxymethanephosphonic esters // J. Am. Chem. Soc. 1952. Vol. 74, N 6. P. 1528-1531.

[19] Akhmetova G.S., Ibraimbek A.K., Sadyrbaeva F.M., Otesh A., Yu V.K., Praliev K.D., Ilyin A.I., Leonova N.V., Seilkhanov T.M., Idrisova R. 1-(2-Phenylethyl)-4-ketoximipiperidine fluorobenzoate with antimicrobial activity // News of Scientific and Technical Society "Kazakh". Ser. chem. 2015. N 3. P. 4-9.

Резюме

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ФТОРФЕНИЛДІ α-АМИНОФОСФОНАТТАР:
СИНТЕЗІ ЖӘНЕ ҚҰРЫЛЫСЫ

Жаңа α-аминофосфонаттар ***1-3*** үш компонентті «*one-pot*» реакциясы бойынша эквимолярлы мөлшердегі диметилфосфиттің, дифенилметилпиперазиннің және карбонильді компоненттің (4, 3 немесе 2-фторбензальдегид) бензолда 30 сағ. Кабачник-Филдс реакциясы жағдайында қайнату арқылы жоғары шығымммен (82,9-90,3%) синтезделді. Реакция бағытыжұқа қабатты хроматография әдісімен бақыланды. Химиялыққұрылым ИҚ, ^{1}Н, ^{13}С ЯМР және элементтісараптама сияқты физика-химиялық әдістермен анықталды.

Түйін сөздер: α-аминофосфонаттар, фторфенил, Кабачник-Филдс реакциясы, синтез, құрылым.

Резюме

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ФТОРФЕНИЛСОДЕРЖАЩИЕ α-АМИНОФОСФОНАТЫ:
СИНТЕЗ И СТРОЕНИЕ

Новые α-аминофосфонаты ***1-3*** были синтезированы с высокими выходами (82,9-90,3%) из эквимолярных количеств диметилфосфита, дифенилметилпиперазина и карбонильного компонента (4, 3 или 2-фторбензальдегида) в условиях одно-реакторной трехкомпонентной классической реакции Кабачника-Филдса, кипячением в бензоле в течение 30 ч. Ход реакции контролировали методом ТСХ. Химическая структура была установлена физико-химическими методами – ИК, ^{1}Н, ^{13}С ЯМР и элементный анализ.

Ключевые слова: α-аминофосфонаты, фторфенил, реакция Кабачника-Филдса, синтез, строение.