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Features of Synthesis and Structure of Ethyl (2*Z*)-3-Hydroxy-(2,3,4,5-tetrafluorophenyl)-propyl-2-enoate

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Abstract—The structure of key intermediates in the synthesis of fluoroquinolone antibiotics: diethyl (2,3,4,5-tetrafluorobenzoyl)malonate and ethyl (2*Z*)-3-hydroxy-(2,3,4,5-tetrafluorophenyl)prop-2-enoate was for first time studied using X-ray diffraction (XRD) and ^{1}H, ^{19}F NMR spectroscopy. In solution both the esters were shown to exist as a mixture of enol and ketone tautomeric forms with predominance of the latter. According to the XRD analysis, ethyl (2*Z*)-3-hydroxy-(2,3,4,5-tetrafluorophenyl)prop-2-enoate in the solid state exists entirely in the enol form.

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Ethyl 3-(2,3,4,5-tetrafluorophenyl)-3-oxopropionate (**I**) is a key intermediate in the organic synthesis of a wide range of polyfluorinated quinolone derivatives [1–5] and benzotiazines [6] exhibiting antiviral [7], antibacterial [8], and antitumor [9] activity. It should be noted in particular that a series of quinolones represents a specific group of modern antibiotics used in medicine, such as ciprofloxacin, ofloxacin, levofloxacin, and others.

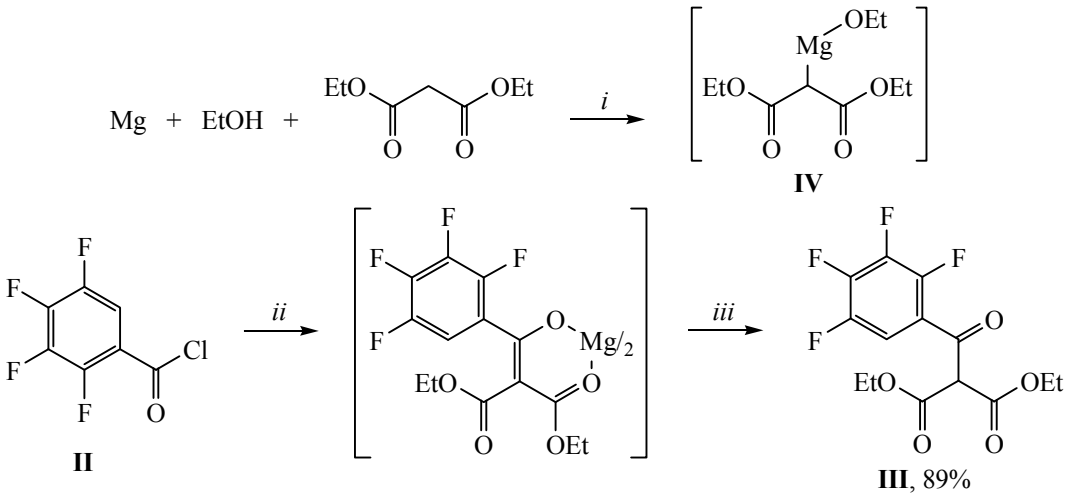
The necessity to find an effective method of synthesis of the 3-oxoester **I** is due to the fact that the polyfluoroaromatic fragment easily undergoes nucleophilic substitution, which limits the use of strong bases [10]. The action of acetoacetic ester on pentafluorobenzoyl chloride or ethyl pentafluorobenzoate leads to transformations with the replacement of fluorine atoms in the *ortho*- and *para*-positions of the aromatic ring [11]. The classic method of obtaining ester **I** is the acylation of malonic ester with 2,3,4,5-tetrafluorobenzoyl chloride (**II**) in the presence of magnesium followed by hydrolysis and decarboxylation of the intermediate tricarbonyl derivative **III** [12]. To increase the yield of 3-oxo ester **I**, the acylation with polyfluorobenzoyl chloride **II** was carried out with the monoethyl malonate in the presence of *n*-butyllithium [13, 14], or with the monoethyl potassium malonate under the action of magnesium chloride and triethylamine [15]. However, the proposed technique requires an additional step of the synthesis of malonic acid monoethyl ester, and implementing specific conditions in the process of the synthesis (low temperature, inert atmosphere). An alternative method for obtaining 3-oxoester **I** is the reaction of tetrafluorobenzonitrile with $BrZnCH_2COOEt$ [16, 17].

As seen, the method using organomagnesium intermediate is the most convenient for the preparative synthesis of 3-oxoester **I**. Analysis of published data showed the absence of detailed information about the effect of the process conditions on the possible formation of by-products, as well as about the structure of tricarbonyl derivative **III** and the oxo ester **I**.

The aim of this work was to study the features of preparation of diethyl (2,3,4,5-tetrafluorobenzoyl) malonate **III** and ethyl 3-(2,3,4,5-tetrafluorophenyl)-3-oxopropionate **I** and their structures.

The first step in the synthesis of compound **I** is obtaining the benzoylmalonate derivative **III** by the reaction of 2,3,4,5-tetrafluorobenzoyl chloride **II** with malonic ester under the action of magnesium ethoxide

Scheme 1.



i, CCl_4 (cat.), toluene; *ii*, **IV**, toluene, 0°C; *iii*, H_2SO_4, H_2O.

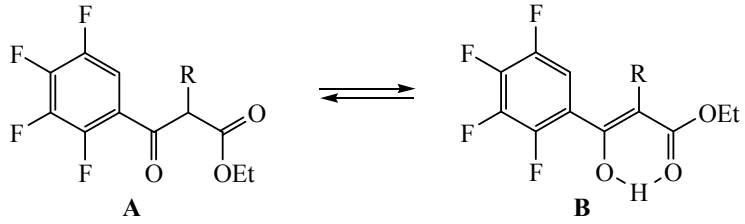
(Scheme 1). According to [11, 18], the formation of the malonic ester magnesium derivative **IV** occurs in ethyl alcohol being initiated by CCl_4 at the subsequent addition of ether as the reaction medium. We found that replacing the ether by toluene has no effect on the formation of the benzoylmalonate derivative **III**. In this case, the gradual addition of alcohol and malonic ester to magnesium in toluene allows controlling the reaction mixture temperature. As a result ethoxymagnesiummalonic ester **IV** formed (Scheme 1). An excess of alcohol can then react with 2,3,4,5-tetrafluorobenzoyl chloride **II**. To avoid the formation of ethyl 2,3,4,5-tetrafluorobenzoate, the homogeneous solution formed after dissolution of magnesium was evacuated and the residual alcohol was removed as a mixture with toluene.

Further 2,3,4,5-tetrafluorobenzoyl chloride **II** was added to the obtained *in situ* malonic ester magnesium derivative **IV** in anhydrous toluene at cooling to 0°C. We performed similar process also without cooling. This led to heating and raising the reaction temperature to 100°C, but the formation of by-products did not occur and the yield of product **III** was 82–89%, the same as with cooling. Hence, the nucleophilic substitution of fluorine atoms in the aromatic ring of the initial substrate in toluene medium does not occur under the influence of ethoxymagnesiummalonic ester in a wide temperature range (0ºC to 100ºC).

We found that for the successful decomposition of the formed magnesium salt the most suitable was a low-temperature regime (5–10°C), which prevents the formation of by-products. For a more complete decomposition the best is to use 15% sulfuric acid. The benzoylmalonate derivative **III** is a liquid substance, which was purified by distillation under a reduced pressure.

The isolation of pure malonate derivative **III** allowed us for the first time to study its structure. The individuality of the diester **III** was confirmed by TLC, its quantitative composition was established by elemental analysis, and structural characteristics were studied using IR and ^1H, ^{19}F NMR spectroscopy. The benzoylmalonate derivative **III** is a prototropic system and can exist in the tautomeric forms of a triketone (**A**) and a diketoenol (**B**) (Scheme 2) called further ketone (**A**) and enol (**B**) for simplicity. According to ^1H and ^{19}F NMR spectra, the diester **III** is as a mixture of ketone (**A**) and enol (**B**) tautomers. The presence of the enol form is indicated by the presence of proton signal of the hydroxy group at 13.82 ppm (in $CDCl_3$ solution). In the spectrum a doublet signal of methine proton in the ketone form **A** at 5.10 ppm ($^5J_{HF}$ 2.6 Hz) and the signals of the tetrafluorophenyl group protons of enol and ketone forms at 7.16 and 7.80 ppm respectively can be easily identified. The signals of ethyl groups of the enol form **B** are not equivalent due to the formation of intramolecular hydrogen bond between the hydroxy proton and the oxygen atom of one of the ester groups. Basing on the assignment of the proton signals to the two forms and the comparison of their integral intensities we conclude that the ketone form predominates (67%) over the enol (33%). The resulting percentage is confirmed by the data of the ^{19}F

Scheme 2.



R = COOEt (**III**), H (**I**).

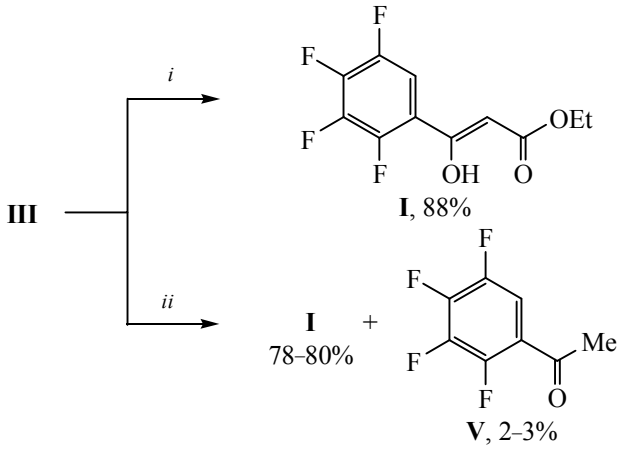
NMR spectrum of compound **III**. The tautomerization is markedly accelerated in the acidic medium. The ^{1}H NMR spectrum of solution of **III** in CD_3COOD shows an increase in the content of the enol form **B**, the tautomers **A** and **B** are formed in approximately equal amounts, 51% and 49%, respectively. In addition to deuteration of the proton of the enol form a slight decrease in the integrated intensity of the methine proton of keto form is observed, apparently due to partial deuteration that indicates its mobility.

Polyfluoroalkyl-substituted benzoylmalonates also exist as a mixture of ketone and enol tautomers, but with a slight predominance of the enol form (54–57%) regardless of polyfluoroalkyl residue [19]. The higher trend to enolization of polyfluoroalkyl analogs compared with 2-tetrafluorobenzoylmalonate **III** probably originates from their high acidity due to the strong electron-withdrawing polyfluoroalkyl substituent.

The IR spectrum of benzoylmalonate **III** taken from a thin layer contains two absorption bands of ester groups at 1739 cm^{-1} and 1703 cm^{-1}. The first one is close to the unperturbed absorption of the ester group due to vibrations of the two ethoxycarbonyl groups in ketone **A**. The band at 1703 cm^{-1} corresponds to vibrations of the free ester group in enol **B**, the observed frequency shift is due to the conjugation of this group with the C=C bond. The band at 1632 cm^{-1} appears in the region of the absorption of chelated 3-oxoesters and is related to the enol form. The absorption bands of C=C and OH groups of the enol form are at 1526 and 2910 cm^{-1}, respectively.

For the synthesis of 3-oxoester **I** one of the ester groups of benzoylmalonate **III** was hydrolyzed under the action of 10% aqueous solution of sulfuric acid followed by decarboxylation (Scheme 3). For complete conversion of starting diester **III** its boiling in the acidic solution was required. Increasing the percentage of acid in solution to 20% leads to the formation of 2,3,4,5-tetrafluorophenyl methyl ketone **V** as an

Scheme 3.



i, H_2SO_4 (10%), 100°C; *ii*, H_2SO_4 (20%), 100°C.

impurity (2–3%, according to GC-MS). According to the literature, in contrast to ester **I,** its pentafluorophenyl analog undergoes the ketone cleavage under more rigid conditions, under the action of a mixture of sulfuric and acetic acids [18].

Structure of 3-oxoester **I** in solid state was studied by XRD and IR spectroscopy and in solution by the method of ^{1}H and ^{19}F NMR spectroscopy.

The X-ray diffraction analysis of compound **I** (Fig. 1) showed that in the crystal this substance existed as the enol (**B**), ethyl 2-(*Z*)-3-hydroxy-3-(2,3,4,5-tetrafluorophenyl)prop-2-enoate. The oxygen atom O^1 of the ester moiety is involved in an intramolecular hydrogen bond with the hydrogen atom H^3 of the hydroxy group. Thus, the intramolecular distance O^1–H^3 is 1.70(3) Å, and angles $O^1H^3O^3$ and $C^3O^3H^3$ are 105(2)° and 97(1)°, respectively.

The molecules are packed in the crystal at the angles of 39 and 54 degrees to the axes *a* and *b*, respectively, and form the anti-directed parallel layers. The fluoroaromatic fragments of the 3-oxoester **I** in the same layer are directed outwards, while ester groups to each other, providing shortened intermolecular contacts between the hydrogen atom of the OH group and fluorine atom F^4, the methyl group hydrogen atom and fluorine atom F^4, and the hydrogen atom of tetrafluorophenyl ring and the oxygen of the OH group. Some of the distances are shorter than the sum of the van der Waals radii (Fig. 2).

IR spectrum of the ester **I** in solid state also points to its enol structure, since the absorption bands at

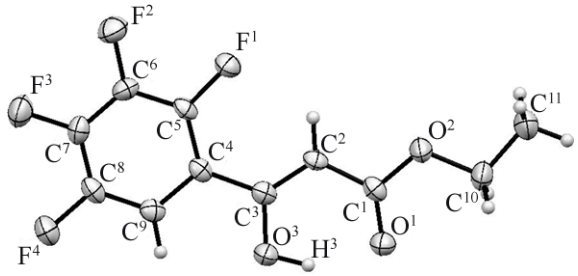


Fig. 1. The general view of the molecule **I**.

2940, 1646 and 1525 cm^{-1} correspond to vibrations of OH, C=C, and C = O fragments, respectively, forming the chelate node.

However, at the dissolution the 3-oxoester **I** undergoes tautomeric transformation. Its ^{1}H and ^{19}F NMR spectra taken from the $CDCl_3$ solution contain a double set of signals corresponding to the enol (**B**) and ketone (**A**) forms (Scheme 2), the ketone form predominating (62%). In other solvents [CD_3OD, CD_3CN, $(CD_3)_2SO$, $(CD_3)_2CO$] the ratio of tautomers remained approximately the same.

Comparing the degree of enolization in the series of 3-oxoesters unsubstituted in 2 position, we conclude that ester **I** occupies an intermediate position between the nonfluorinated acetoacetic (6–8%) and benzoylacetic (20%) esters and the polyfluoroalkyl-containing derivatives (89–100%), like the difluoro-substituted acetoacetic ester (53%) [20]. This distribution agrees well with the data on the acidity of 3-oxoesters, which has a decisive influence on the degree of enolization of carbonyl compounds.

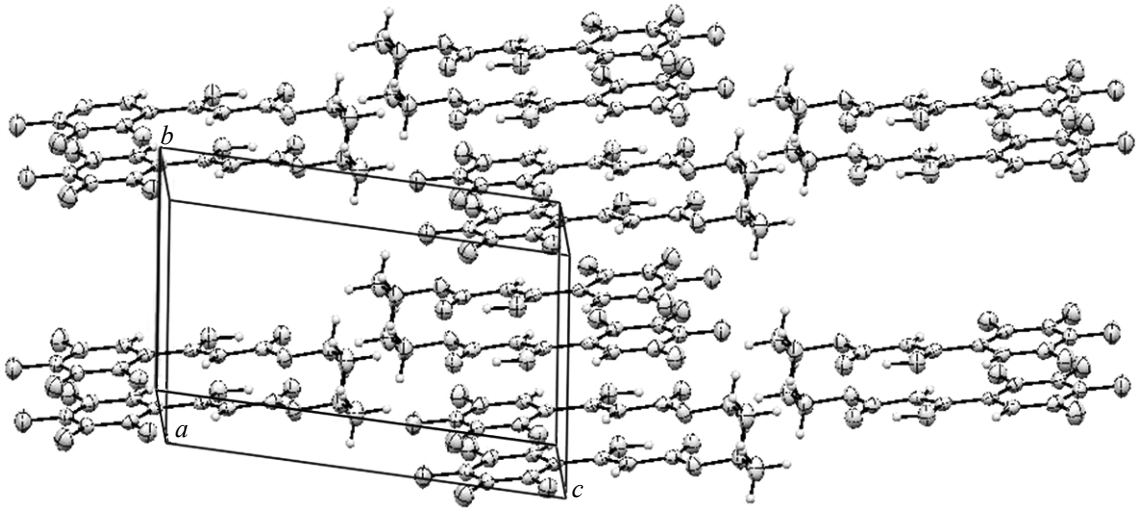


Fig. 2. Packing of molecules **I** in the crystal.

However, the existence of 3-oxoester **I** in solid state as the enol form is due, apparently, only to greater thermodynamic stability of the enol compared to ketone tautomer.

Thus, for the first time was isolated and characterized diethyl (2,3,4,5-tetrafluorobenzoyl)malonate (**III**), the parent compound for the synthesis of 3-oxoester **I**. Esters **I** and **III** in solutions are mixtures of ketone and enol tautomers with a predominance of the former. However, solid 3-oxoester **I** exists exclusively as the enol form, as confirmed by the XRD data.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Spectrum One B spectrophotometer. The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX 400 spectrometer from solutions in $CDCl_3$, the working frequencies 400.1 MHz (^{1}H) and 376.5 MHz (^{19}F), internal references Me_4Si and C_6F_6, respectively. Elemental analysis was performed using an automatic Perkin-Elmer CHN PE 2400 analyzer. The mass spectra were obtained on a gas chromatograph Agilent 7890A with a mass spectrometer 5975 inert XL. The melting points were determined on a Stuart SMP3 device.

Single crystals of 3-oxoester **I** were obtained by crystallization from ethanol. The XRD experiment was carried out on a Xcalibur 3 diffractometer with a CCD detector [graphite monochromator, λMoK_α 0.71073 Å, temperature 145(2) K, ω-scanning]. The structure was solved by the direct method and difference Fourier syntheses with the SHELXS-97 program [21]. Positions and temperature parameters of the non-hydrogen atoms were refined in the anisotropic full-matrix least-squares approximation with the SHELXL-97 program [21].

Crystallographic data of compound **I**: $C_{11}H_8F_4O_3$, *M* 364.17, space group P-1, the crystals are triclinic, *a* = 5.2722(5), *b* = 7.9390(7), *c* = 12.7631(15) Å, α = 99.488(8), β = 93.344(8), γ = 90.083(7)°, *V* = 525.97 (9) Å^3, Z = 2, d_{calc} = 1,668 g cm^{-3} , μ = 0.165 mm^{-1}. The total number of reflections 2996, independent reflections 2058, *R*-factor 0.039, the number of refined parameters 167. Complete crystallographic parameters of compound **I** are available at www.ccdc.cam.ac.uk/conts/retrieving.html (CCDC 797287).

Synthesis of diethyl (2,3,4,5-tetrafluorobenzoyl) malonate (III). To the iodine-activated magnesium turnings (4.6 g, 0.20 mol) was added 1 ml of anhydrous CCl_4, 7 ml of anhydrous ethanol (99.9%), and then a mixture of diethyl malonate (32 g, 0.20 mol) with 100 ml of anhydrous toluene. After the magnesium dissolution, the resulting homogeneous solution was evacuated until the formation of a viscous residue, to which was added 150 ml of anhydrous toluene. The reaction mixture was cooled to 0°C and a solution of 2,3,4,5-tetrafluorobenzoyl chloride **II** (40 g, 0.20 mol) in 70 ml of anhydrous toluene was added and the mixture was kept for 3 h. Then 250 ml of 10% solution of H_2SO_4 was added to it. Organic layer was separated and washed with water. The solvent was evaporated under a reduced pressure, the residue was distilled in a vacuum. 59.81 g of product **III** was isolated, yield 89%, bp 140–143°C (3 Torr). IR spectrum (from a layer between the KBr plates, ν, cm^{-1}): 3079, 2987, 2942, 2910 (O–H, CH); 1739 (C=O-ketone) 1703 (C=O-enol) 1632 (C=O-enol) 1526 (C=C) 1485, 1448, 1407, 1365 (Ar); 1277, 1236 (CF). ^{1}H NMR spectrum (δ, ppm, *J*, Hz): **A,** 1.30 t (3H, Me, *J* = 7.1); 4.30 q (2H, CH_2, *J* = 7.1); 5.10 d (1H, CH, *J* = 2.6); d.d.d.d 7.67 (1H, C_6F_4H, *J* = 10.4, 8.4, 6.1, 2.5); **B,** 1.15 and 1.38 two t (3H, Me, *J* = 7.1); 4.12 and 4.37 two q (2H, CH_2, *J* = 7.1); 7.67 m (1H, C_6F_4H), 13.83 s (1H, OH). ^{19}F NMR spectrum (δ, ppm): **A,** 8.83 m (1F); 17.00 m (1F); 25.82 m (1F); 26.40 m (1F); **B,** 7.46 m (1F); 10.73 m (1F); 23.81 d.d.d.d (1F, *J* = 21.1, 12.7, 9.9, 3.2); 24.68 t.d.d (1F, *J* = 18.4, 12.0, 5.9). Found, %: C 49.87, H 3.47; F 22.49. $C_{14}H_{12}F_4O_5$. Calculated, %: C 50.01, H 3.60; F 22.60.

Synthesis of ethyl (2*Z*)-3-hydroxy-(2,3,4,5-tetrafluorophenyl)prop-2-enoate (I). To 50 g (0.15 mol) of compound **III** was added 200 ml of 10% solution of sulfuric acid. The reaction mixture was refluxed for 3–4 h, then organic layer was separated and washed with sodium hydrogen carbonate solution until neutral reaction. The solvent was evaporated, the residue was distilled at a reduced pressure. 33.4 g (85%) of compound **I** was obtained as white transparent crystals, mp 40–41°C (mp 41–42°C [22]). bp 117–119°C (3 Torr). IR spectrum, ν, cm^{-1}: 3080 (C–H), 2940 (OH), 1646 (C=O-enol) 1525 (C=C-enol) 1485, 1450, 1407, 1365 (Ar); 1277 , 1236 (CF). ^{1}H NMR spectrum (δ, ppm, *J*, Hz): **A,** 1.28 t (3H, Me, *J* = 7.1); 3.97 d (2H, CH_2, *J* = 3.7); 4.23 q (2H, CH_2, *J* = 7.1); 7.62 d.d.d.d (1H, C_6F_4H, *J* = 10.4, 8.4, 6.1, 2.5); (**B**): 1.35 t (3H, Me, *J* = 7.1); 4.29 q (2H, CH_2, *J* = 7.1); 5.83 s (1H, CH), 7.54 m (1H, C_6F_4H), 12.72 s (1H, OH). ^{19}F NMR spectrum, δ, ppm: (**A**): 8.64 t.t (1F, *J* = 19.8,

2.7); 16.13 t.d.d (1F, J = 21.3, 19.1, 8.6); 25.33 m (1F); 26.09 m (1F); (B): 7.27 t.t (1F , J = 19.8, 2.7); 10.86 m (1F); 23.69 m (1F); 24.85 t.d.d (1F, J = 19.9, 13.3, 6.8). Found, %: C 49.64, H 3.17; F 28.67. $C_{11}H_8F_4O_3$. Calculated, %: C 50.01, H 3.05; F 28.77. Retention time 14.91 min. Mass spectrum, *m/z* (*I*, %): 264 (11) $[M]^{+\bullet}$, 218 (9) $[M - EtOH]^{+\bullet}$, 177 (100) $[HC_6F_4C(O)]^{+\bullet}$, 149 (15) $[HC_6F_4]^{+\bullet}$.

In the reaction of **III** with 20% aqueous solution of sulfuric acid the product **I** contained 2% of 2,3,4,5-tetrafluorophenyl methyl ketone **IV** (determined by GC-MS). Retention time: 8.20 min. Mass spectrum, *m/z* (*I*, %): 192 (15) $[M]^{+\bullet}$, 177 (100) $[HC_6F_4C(O)]^{+\bullet}$, 149 (15) $[HC_6F_4]^{+\bullet}$, 43 (7) $[CH_3C(O)]^{+\bullet}$.

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REFERENCES

1. Hayakawa, I., Hiramitsu, T., and Tanaka, Y., *Chem. Pharm. Bull*., 1984, vol. 32, no. 12, p. 4907 .
2. Atarashi, S., Yokohama, S., Yamazaki, K., Sakano, K.-I., Imamura, M., and Hayakawa, I., *Chem. Pharm. Bull*., 1987, vol. 35, no. 5, p. 1896.
3. Langer, O., Mitterhauser, M., Wadsak, W., Brunner, M., Müller, U., Kletter, K., and Müller, M., *J. Label. Compd. Radiopharm*., 2003, vol. 46, p. 715.
4. Na, Y., *Bull. Korean Chem*. Soc., 2005, vol. 26, no. 12, p. 2047.
5. Dinakaran, M., Senthilkumar, P., Yogeeswari, P., China, A., Nagaraja, V., Sriram, D., *Bioorganic & Medicinal Chemistry Letters*, 2008, vol. 18, no. 3, p. 1229.
6. Cecchetti, V., Fravolini, A., Fringuelli, R., Schiaffella, F., Lorenzini, M.C., *J. Heterocyclic Chem*., 1993, vol. 30, no. 4, p. 1143.
7. DE Patent no. 4425648, 1996, *C. A*., 1996, vol. 124, 289570.
8. Asahina, Y., Takei, M., Kimura, T., and Fukuda, Y., *J. Med. Chem*., 2008, vol. 51, no. 11, p. 3238.
9. USA Patent no. 5318965, 1994, *C. A*., 1995, vol. 122, 160653.
10. Prudchenko, A.T., Shchegoleva, G.S., Barkhash, V.A., and Vorozhtsov, N.N., Jr., *Zh. Obshch. Khim*., 1967, vol. 37, no. 11, p. 2487.
11. Prudchenko, A.T., Barkhash, V.A., and Vorozhtsov, N.N., Jr., *Izv. Akad. Nauk SSSR, Ser. Khim*., 1965. p. 1798.
12. DE Patent no. 3318145, 1984, *C. A*., 1985, vol. 102, 78744.
13. Chu, D.T.W., Fernandes, P.B., Claiborn, A.K., Pihuleac, E., Nordeen, C.W., Maleczka, R.E., Jr., and Pernet, A.G., *J. Med. Chem*., 1985, vol. 28, no. 11, p. 1558.
14. Chu, D.T.W., Fernandes, P.B., Claiborn, A.K., Gracey, E.H., and Pernet, A.G., *J. Med. Chem*., 1986, vol. 29, no. 11, p. 2363.
15. Chu, D.T.W., Fernandes, P.B., Maleczka, R.E., Jr., Nordeen, C.W., and Pernet, A.G., *J. Med. Chem*., 1987, vol. 30, no. 3, p. 504.
16. Clay, R.J., Collom, T.A., Karrick, G.L., and Wemple, J., *Synthesis,* 1993, p. 290.
17. WO Patent no. 2003033469, 2003, *C. A*., 2003, vol. 138, 337993.
18. Filler, R., Rao, Y.S., Biezais, A., Miller, F.N., and Beaucaire, V.D., *J. Org. Chem*., 1970, vol. 35, no. 4, p. 930.
19. Krokhalev, V.M., Saloutin, V.I., Romas', A.D., Ershov, B.A., and Pashkevich, K.I., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, no. 2, p. 376.
20. Pashkevich, K.I. and Saloutin, V.I., *Usp. Khim*., 1985, vol. 54, no. 12, p. 1997.
21. Scheldrik, G.M., *SHELXS 97 and SHELXL 97*, University of Göttingen, Germany, 1997.
22. China Patent no. 101362693, 2009, *C. A*., 2009, vol. 150, 282562.