ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 11, pp. 1727–1732. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © O.V. Kushnir, N.V. Mel'nichenko, M.V. Vovk, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 11, pp. 1691–1695.

Heterocyclizations of Functionalized Heterocumulenes with C,N-, C,O-, and C,S-Binucleophiles: XIII.* Synthesis of Dialkyl 2-Oxo-3-allyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates and Their Reaction with Arylhydroxymoyl Chlorides

O. V. Kushnir[a], N. V. Mel'nichenko[b], and M. V. Vovk[b]

[a] *Fed'kovich Chernovtsy National University, Chernovtsy, Ukraine*
[b] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine*
Kiev, 02094 Ukraine
e-mail: mvovk@i.com.ua

Received January 26, 2011

Abstract—Dialkyl 2-oxo-3-allyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates obtained by condensation of 1-chlorobenzyl isocyanates with N-allylfumarates reacted regioselectively with arylhydroxymoyl chlorides with the formation of dialkyl 6-aryl-3-[(3-aryl-4,5-dihydro-5-isoxazolyl)methyl]-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates.

DOI: 10.1134/S1070428011110133

3,4-Dihydropyrimidine ring is the structural fragment governing the biological activity of many organic compounds [2–4]. Therewith the useful properties of 3,4-dihydropyrimidine derivatives are essentially affected by the character of substituents at the carbon atoms of the ring. Yet the effect of the substituents at nitrogen atoms remains practically nonstudied to a certain extent because of the lack of methods of the selective functionalization of the nitrogen atoms with biophore moieties. To the latter the isoxazoline heterocycle certainly belongs for among its derivatives substances are found with a wide range of the biologic action [5–8].

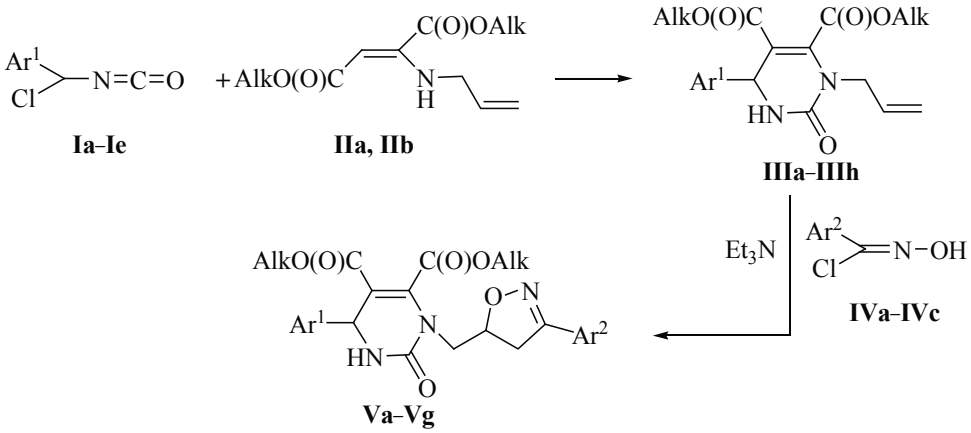
The analysis of publications [9–11] reveals a limited number of isoxazoline derivatives linked to the other heterocycles by a methylene bridge. It was therefore feasible to extend our method [12] of 3-arylpyrimidinedicarboxylates synthesis on their 3-allyl analogs and to use the latter for building up an isoxazoline ring.

It was established that 1-chlorobenzyl isocyanates **Ia–Ie** reacted with previously unknown dialkyl N-allylaminofumarates **IIa, IIb** in toluene solution at room temperature giving dialkyl 2-oxo-3-allyl-6-aryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates **IIIa–IIIh** in 45–83% yields. The structure of the latter is confirmed by ^{1}H and ^{13}C NMR spectra containing typical doublets of protons H^{6} in the range 5.23–5.42 ppm and signals of atoms C^{6} in the range 51.86–53.02 ppm. The presence of the asymmetric carbon center in the position *6* of the heterocycle results in the diastereotopic character of the methylene group of the allyl substituent leading to the complex multiplicity of the signal of allyl protons in the ^{1}H NMR spectrum.

Among the versatile procedures for the preparation of isoxazoline derivatives the version should be specially indicated of 1,3-dipolar addition of nitrile oxides to alkenes, in particular, to functionalized ones, which is characterized by high regioselectivity [13, 14]. We demonstrated that 3-allylpyrimidin-2-ones **IIIb, IIId**, **IIIe–IIIh** also reacted regioselectively with hydroxymoyl chlorides **IVa–IVb** in the presence of triethylamine, i.e.,

* For Communication XII, see [1].

Scheme.



I, Ar^1 = Ph (**a**), 3-BrC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**), 4-$NO_2C_6H_4$ (**d**), 3,4-$Cl_2C_6H_3$ (**e**); **II**, Alk = Me (**a**), Et (**b**); **III**, Alk = Me, Ar^1 = Ph (**a**), 3-BrC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**), 4-$NO_2C_6H_4$ (**d**), 3,4-$Cl_2C_6H_3$ (**e**); Alk = Et, Ar = 3-BrC_6H_4 (**f**), 4-$NO_2C_6H_4$ (**g**), 3,4-$Cl_2C_6H_3$ (**h**); **IV**, Ar^2 = Ph (**a**), 4-FC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**); **V**, Alk = Me: Ar^1 = 3-BrC_6H_4, Ar^2 = Ph (**a**), 4-$MeOC_6H_4$ (**b**); Ar^1 = 4-$NO_2C_6H_4$, Ar^2 = 4-FC_6H_4 (**c**); Ar^1 = 3,4-$Cl_2C_6H_3$, Ar^2 = Ph (**d**); Alk = Et: Ar^1 = 3-BrC_6H_4, Ar^2 = 4-$MeOC_6H_4$ (**e**); Ar^1 = 4-$NO_2C_6H_4$, Ar^2 = 4-$MeOC_6H_4$ (**f**); Ar^1 = 3,4-$Cl_2C_6H_3$, Ar^2 = 4-FC_6H_4 (**g**).

under the conditions of generation of the corresponding nitrile oxides leading to the formation of 3-isoxazolinyl methylpyrimidinones **Va–Vg** (see the scheme)

The analysis of crude reaction products by the methods of ^{1}H NMR spectroscopy and GC-MS showed that the content there of the target products reached 79–88%. Therewith compounds **Vc, Ve–Vg** formed as single diastereomers, and compounds **Va, Vb, Vd**, as mixtures of two diastereomers in the ~2:1 ratio. The fractional crystallization of the latter compounds from ethanol made it possible to isolate th major diastereomers in 29–36% yields.

The presence of an isoxazoline ring in the structure of compounds **Va–Vg** was proved by the ^{1}H NMR spectra that contained the multiplet signals of methylene (3.07–3.24 ppm) and methine (4.76–4.85 ppm) protons, and also by ^{13}C NMR spectra where the atoms $C^{4'}$ and $C^{5'}$ gave rise to signals at 37.31–37.59 and 77.68–78.55 ppm respectively.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 in thin film (for compounds **IIa, IIb**) or in pellets with KBr. ^{1}H NMR spectra [of compounds **IIa, IIb** in $CDCl_3$, of the other in $(CD_3)_2SO$] and ^{13}C NMR spectra [in $(CD_3)_2SO$] were registered on a spectrometer Bruker Advance DRX-500 (500.13 and 125.75 MHz respectively), internal reference TMS. GC-MS measurements were performed on an instrument Agilent 1100/DAD/HSD/VLG 119562. Dialkyl N-allylaminofumarates **IIa, IIb** were synthesized as described in [15].

Dimethyl N-allylaminofumarate (IIa). Yield 88%, bp 72°C (0.02 mm Hg). IR spectrum , ν, cm^{-1}: 3240 (NH), 1745 (C=O), 1680, 1645 (C=C). ^{1}H NMR spectrum, δ, ppm: 3.66 s (3H, CH_3O), 3.83 s (3H, CH_3O), 3.96 m (2H, CH_2N), 5.12 s (1H, HC=), 5.12–5.20 m (2H, H_2C=), 5.85 m (1H, HC=), 8.13 s (1H, NH). Found, %: C 54.46; H 6.51; N 7.10. $C_9H_{13}NO_4$. Calculated, %: C 54.26; H 6.58; N 7.03.

Diethyl N-allylaminofumarate (IIb). Yield 72%, bp 92°C (0.04 mm Hg). IR spectrum , ν, cm^{-1}: 3235 (NH), 1750 (C=O), 1675, 1645 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, CH_3, *J* 7.0 Hz), 1.34 t (3H, CH_3, *J* 7.0 Hz), 3.99 m (2H, CH_2N), 4.15 q (2H, CH_2O, *J* 7.0 Hz), 4.29 q (2H, CH_2O, *J* 7.0 Hz), 5.14 s (1H, HC=), 5.16–5.24 m (2H, H_2C=), 5.88 m (1H, HC=), 8.17 s (1H, NH). Found, %: C 58.31; H 7.57; N 6.18. $C_{11}H_{17}NO_4$. Calculated, %: C 58.14; H 7.54; N 6.16.

Dialkyl 3-allyl-6-aryl-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates IIIa–IIIh. To a solution of 6 mmol of dialkyl N-allylaminofumarate **IIa**, **IIb** in 25 ml of anhydrous toluene was added 6 mmol of isocyanate **Ia–Ie**, and the mixture was left standing

at room temperature for 24 h. The solvent was decanted from the oily precipitate, the precipitate was treated with hexane and left standing for 24 h. The formed solid reaction product was filtered off, dried, and crystallized from ethanol .

Dimethyl 3-allyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIa). Yield 45%, mp 108–109°C. IR spectrum , ν, cm^{-1}: 3250, 3110 (NH), 1740, 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.58 s (3H, CH_3O), 3.86 s (3H, CH_3O), 3.99 d.d, 4.30 d.d (2H, CH_2, *J* 16.5, *J* 5.5 Hz), 5.05 d (1H, HC=, *J* 17.0 Hz), 5.10 d (1H, HC=, *J* 10.0 Hz), 5.23 d (1H, H^6, *J* 3.5 Hz), 5.73 m (1H, HC=), 7.27–7.41 m (5H$_{arom}$), 8.27 d (1H, NH, *J* 3.5 Hz). ^{13}C NMR spectrum, δ, ppm: 45.89 (CH_2), 51.97 (CH_3O), 52.53 (CH_3O), 52.88 (C^6), 102.52 (C^5), 117.32 (H_2C=), 126.10, 127.90, 128.71, 133.36 (C_{Ar}), 142.69 (HC=), 142.88 (C^4), 151.12 (C^2), 162.82 (C=O), 163.90 (C=O). Found, %: C 61.54; H 5.55; N 8.55. [*M* + 1]$^+$ 331. $C_{17}H_{18}N_2O_5$. Calculated, %: C 61.81; H 5.49; N 8.48. *M* 330.3.

Dimethyl 3-allyl-6-(3-bromophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIb). Yield 83%, mp 142–143°C. IR spectrum , ν, cm^{-1}: 3245, 3125 (NH), 1740, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.59 s (3H, CH_3O), 3.80 s (3H, CH_3O), 3.86 d.d, 4.31 d.d (2H, CH_2, *J* 16.5, *J* 5.5 Hz), 5.06 d (1H, HC=, *J* 17.0 Hz), 5.11 d (1H, HC=, *J* 10.5 Hz), 5.23 d (1H, H^6, *J* 3.3 Hz), 5.74 m (1H, HC=), 7.24–7.54 m (4H$_{arom}$), 8.30 d (1H, NH, *J* 3.3 Hz). ^{13}C NMR spectrum, δ, ppm: 45.95 (CH_2), 52.04 (CH_3O), 52.06 (CH_3O), 53.02 (C^6), 101.94 (C^5), 117.16 (H_2C=), 121.92, 125.15, 129.08, 130.85, 131.07, 133.22 (C_{Ar}), 143.27 (HC=), 145.21 (C^4), 150.95 (C^2), 162.68 (C=O), 163.74 (C=O). Found, %: C 50.11; H 4.08; N 6.69. [*M* + 1]$^+$ 410. $C_{17}H_{17}N_2O_5$. Calculated, %: C 49.89; H 4.19; N 6.85. *M* 409.2.

Dimethyl 3-allyl-6-(3-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIc). Yield 49%, mp 138–139°C. IR spectrum , ν, cm^{-1}: 3250, 3130 (NH), 1745, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, CH_3O), 3.87 s (3H, CH_3O), 3.90 d.d, 4.35 d.d (2H, CH_2, *J* 16.5, *J* 5.5 Hz), 5.07 d (1H, HC=, *J* 16.5 Hz), 5.11 d (1H, HC=, *J* 10.0 Hz), 5.42 d (1H, H^6, *J* 3.5 Hz), 5.76 m (1H, HC=), 7.73 m (2H$_{arom}$), 8.15 s (1H$_{arom}$), 8.21 m (1H$_{arom}$), 8.42 d (1H, NH, *J* 3.5 Hz). ^{13}C NMR spectrum, δ, ppm: 46.00 (CH_2), 52.05 (CH_3O), 52.10 (CH_3O), 53.01 (C^6), 101.65 (C^5), 117.18 (H_2C=), 120.95, 122.95, 130.53, 132.81, 133.18, 143.51 (C_{Ar}), 144.74 (HC=), 147.96 (C^4), 150.80 (C^2), 162.53 (C=O), 163.63 (C=O). Found, %: C 54.71; H 4.52; N 11.39. [*M* + 1]$^+$ 376. $C_{17}H_{17}N_3O_7$. Calculated, %: C 54.40; H 4.57; N 11.20. *M* 375.3.

Dimethyl 3-allyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIId). Yield 63%, mp 170–171°C. IR spectrum , ν, cm^{-1}: 3260, 3150 (NH), 1750, 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.58 s (3H, CH_3O), 3.80 s (3H, CH_3O), 3.92 d.d, 4.28 d.d (2H, CH_2, *J* 17.0, *J* 6.7 Hz), 5.06 d (1H, HC=, *J* 15.8 Hz), 5.13 d (1H, HC=, *J* 8.5 Hz), 5.38 d (1H, H^6, *J* 3.3 Hz), 5.74 m (1H, HC=), 7.53 d (2H$_{arom}$, *J* 8.0 Hz), 8.27 d (2H$_{arom}$, *J* 8.0 Hz), 8.40 d (1H, NH, *J* 3.0 Hz). ^{13}C NMR spectrum, δ, ppm: 46.00 (CH_2), 51.98 (CH_3O), 52.22 (CH_3O), 52.91 (C^6), 101.53 (C^5), 117.18 (H_2C=), 124.02, 127.52, 133.21, 143.38 (C_{Ar}), 147.09 (HC=), 149.66 (C^4), 150.71 (C^2), 162.47 (C=O), 163.58 (C=O). Found, %: C 54.19; H 4.63; N 11.39. [*M* + 1]$^+$ 375. $C_{17}H_{17}N_3O_7$. Calculated, %: C 54.40; H 4.57; N 11.20. *M* 375.3.

Dimethyl 3-allyl-2-oxo-6-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIe). Yield 58%, mp 143–144°C. IR spectrum , ν, cm^{-1}: 3255, 3140 (NH), 1740, 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, CH_3O), 3.88 s (3H, CH_3O), 3.97 d.d, 4.30 d.d (2H, CH_2, *J* 16.0, *J* 5.3 Hz), 5.05 d (1H, HC=, *J* 16.5 Hz), 5.12 d (1H, HC=, *J* 10.5 Hz), 5.28 d (1H, H^6, *J* 3.0 Hz), 5.74 m (1H, HC=), 7.24 d (1H$_{arom}$, *J* 8.5 Hz), 7.48 c (1H$_{arom}$), 7.70 d (1H$_{arom}$, *J* 8.5 Hz), 8.34 d (1H, NH, *J* 3.0 Hz). ^{13}C NMR spectrum, δ, ppm: 45.97 (CH_2), 51.69 (CH_3O), 52.04 (CH_3O), 53.00 (C^6), 101.55 (C^5), 117.17 (H_2C=), 126.40, 128.34, 130.9, 131.13, 131.28, 133.20 (C_{Ar}), 143.39 (HC=), 143.55 (C^4), 150.78 (C^2), 162.55 (C=O), 163.63 (C=O). Found, %: C 51.31; H 4.18; N 6.79. [*M* + 1]$^+$ 400. $C_{17}H_{16}Cl_2N_2O_5$. Calculated, %: C 51.14; H 4.04; N 7.02. *M* 399.2.

Diethyl 3-allyl-6-(3-bromophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIf). Yield 47%, mp 97–98°C. IR spectrum , ν, cm^{-1}: 3245, 3125 (NH), 1735, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.10 t (3H, CH_3, *J* 7.2 Hz), 1.26 t (3H, CH_3, *J* 7.2 Hz), 3.81–4.58 m (6H, CH_2 + 2CH_2O), 5.06 d (1H, HC=, *J* 16.0 Hz), 5.14 d (1H, HC=, *J* 10.0 Hz), 5.24 d (1H, H^6, *J* 3.3 Hz), 5.74 m (1H, HC=), 7.25–7.53 m (4H$_{arom}$), 8.29 d (1H, NH, *J* 3.3 Hz). ^{13}C NMR spectrum, δ, ppm: 13.43 (CH_3), 13.72 (CH_3), 45.76 (CH_2), 52.25 (C^6), 60.57 (CH_2O), 60.63 (CH_2O), 101.96 (C^5), 117.01 (H_2C=), 121.73, 125.14, 129.17, 130.69, 130.96, 133.23 (C_{Ar}), 142.99 (HC=), 145.43 (C^4), 150.94 (C^2), 162.05 (C=O), 163.15 (C=O). Found, %: C 52.41; H 4.58; N 6.55. [*M* +

1]$^+$ 438. $C_{19}H_{21}BrN_2O_5$. Calculated, %: C 52.19; H 4.84; N 6.41. *M* 437.3.

Diethyl 3-allyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIg). Yield 48%, mp 113–114°C. IR spectrum , ν, cm^{-1}: 3255, 3150 (NH), 1745, 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, CH_3, *J* 7.2 Hz), 1.26 t (3H, CH_3, *J* 7.2 Hz), 3.91–4.34 m (6H, CH_2 + 2CH_2O), 5.08 d (1H, HC=, *J* 17.0 Hz), 5.14 d (1H, HC=, *J* 10.0 Hz), 5.39 d (1H, H^6, *J* 3.0 Hz), 5.76 m (1H, HC=), 7.53 d (2H$_{arom}$, *J* 8.5 Hz), 8.27 d (2H$_{arom}$, *J* 8.5 Hz), 8.39 d (1H, NH, *J* 3.0 Hz). ^{13}C NMR spectrum, δ, ppm: 13.46 (CH_3), 13.70 (CH_3), 45.96 (CH_2), 52.44 (C^6), 60.72 (CH_2O), 62.25 (CH_2O), 101.56 (C^5), 117.11 (H_2C=), 124.03, 127.66, 133.32, 143.31 (C_{Ar}), 147.10 (HC=), 149.95 (C^4), 150.89 (C^2), 162.01 (C=O), 163.14 (C=O). Found, %: C 56.31; H 5.08; N 10.19. [*M* + 1]$^+$ 404. $C_{19}H_{21}N_3O_7$. Calculated, %: C 56.57; H 5.25; N 10.42. *M* 403.4.

Diethyl 3-allyl-2-oxo-6-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (IIIh). Yield 50%, mp 99–100°C. IR spectrum , ν, cm^{-1}: 3255, 3135 (NH), 1730, 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.10 t (3H, CH_3, *J* 7.2 Hz), 1.26 t (3H, CH_3, *J* 7.2 Hz), 3.82–4.35 m (6H, CH_2 + 2CH_2O), 5.09 d (1H, HC=, *J* 17.4 Hz), 5.14 d (1H, HC=, *J* 10.2 Hz), 5.26 d (1H, H^6, *J* 3.0 Hz), 5.74 m (1H, HC=), 7.25 d (1H$_{arom}$, *J* 8.4 Hz), 7.47 s (1H$_{arom}$), 7.70 d (1H$_{arom}$, *J* 8.4 Hz), 8.32 d (1H, NH, *J* 3.0 Hz). ^{13}C NMR spectrum, δ, ppm: 13.44 (CH_3), 13.73 (CH_3), 45.83 (CH_2), 51.86 (C^6), 60.64 (CH_2O), 62.22 (CH_2O), 101.57 (C^5), 117.06 (H_2C=), 126.44, 128.45, 130.48, 131.06, 131.14, 133.24 (C_{Ar}), 143.18 (HC=), 143.79 (C^4), 150.81 (C^2), 161.99 (C=O), 163.10 (C=O). Found, %: C 53.31; H 4.68; N 6.49. [*M* + 1]$^+$ 428. $C_{19}H_{20}Cl_2N_2O_5$. Calculated, %: C 53.41; H 4.72; N 6.56. *M* 427.3.

Dialkyl 6-aryl-3-[(3-aryl-4,5-dihydro-5-isoxazolyl) methyl]-2-oxo-1,2,3,6-tetrahydro-pyrimidine-4,5-dicarboxylates Va–Vg. To a solution of 2 mmol of dicarboxylate **IIIb, IIId**, **IIIe–IIIh** in 10 ml of dichloromethane cooled to –15° was added at stirring in succession 2 mmol of hydroxymoyl chloride **IVa–IVc** and 2 mmol of triethylamine. The reaction mixture was stirred for 1 h, warmed to room temperature, and left standing for 12 h. Then it was treated with the saturated ammonium chloride solution. The organic layer was separated, dried with magnesium sulfate, and evaporated. The residue was purified by recrystallization from the mixture benzene–hexane, 1 : 2 (compound **Va**) or ethanol (compounds **Vb–Vg**).

Dimethyl 6-(3-bromophenyl)-3-[(3-phenyl-4,5-dihydro-5-isoxazolyl)methyl]-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Va). Yield 29%, mp 154–156°C. IR spectrum , ν, cm^{-1}: 3250, 3130, (NH), 1740, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.15–3.21 m (2H, CH_2), 3.42 m (1H, CH), 3.61 s (3H, CH_3O), 3.80 s, 3.83 s (3H, CH_3O), 4.11 d.d (1H, CH, *J* 10.5, *J* 3.0 Hz), 4.83 m (1H, CH), 5.25 d (1H, H^6, *J* 3.5 Hz), 7.31–7.65 m (9H$_{arom}$), 8.39 d (1H, NH, *J* 3.5 Hz). ^{13}C NMR spectrum, δ, ppm: 37.31 (C$^{4'}$), 46.12 (CH_2N), 52.03 (C^6), 52.26 (CH_3O), 53.10 (CH_3O), 78.02 (C$^{5'}$), 102.50 (C^5), 121.86, 125.20, 126.51, 128.78, 129.01, 130.09, 130.97, 142.91, 143.51 (C_{Ar}), 144.98 (C^4), 151.19 (C$^{3'}$), 156.34 (C^2), 162.75 (C=O), 163.71 (C=O). Found, %: C 54.81; H 4.08; N 7.69. [*M* + 1]$^+$ 529. $C_{24}H_{22}BrN_3O_6$. Calculated, %: C 54.56; H 4.20; N 7.95. *M* 528.3.

Dimethyl 6-(3-bromophenyl)-3-{[3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolyl]methyl}-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Vb). Yield 66%, mp 203–205°C. IR spectrum , ν, cm^{-1}: 3240, 3135 (NH), 1735, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.10–3.18 m (2H, CH_2), 3.41 m (1H, CH), 3.63 s (3H, CH_3O), 3.81 s, 3.83 s (3H, CH_3O),, 4.03 d.d (1H, CH, *J* 10.5, *J* 3.3 Hz) 4.76 m (1H, CH), 5.22 d (1H, H^6, *J* 3.0 Hz), 7.01 d (2H$_{arom}$, *J* 7.5 Hz), 7.36–7.62 m (6H$_{arom}$), 8.34 d (1H, NH, *J* 3.0 Hz). ^{13}C NMR spectrum, δ, ppm: 37.55 (C$^{4'}$), 47.06 (CH_2N), 52.05 (CH_3O), 52.26 (C^6), 53.11 (CH_3O), 55.27 (CH_3O), 77.68 (C$^{5'}$), 102.50 (C^5), 114.22, 121.51, 121.89, 125.27, 128.26, 129.37, 130.85, 131.01, 143.54, 155.79 (C_{Ar}), 145.01 (C^4), 151.30 (C$^{3'}$), 160.66 (C^2), 162.74 (C=O), 163.75 (C=O). Found, %: C 53.41; H 4.28; N 7.79. [*M* + 1]$^+$ 559. $C_{25}H_{24}BrN_3O_7$. Calculated, %: C 53.77; H 4.33; N 7.53. *M* 558.4.

Dimethyl 6-(4-nitrophenyl)-3-{[3-(4-fluorophenyl)-4,5-dihydro-5-isoxazolyl]methyl}-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Vc). Yield 36%, mp 197–199°C. IR spectrum , ν, cm^{-1}: 3245, 3150 (NH), 1730, 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.08–3.24 m (2H, CH_2), 3.42 m (1H, CH), 3.60 s (3H, CH_3O), 3.81 s (3H, CH_3O), 4.18 d.d (2H, CH_2N, *J* 14.8, *J* 3.4 Hz), 4.82 m (1H, CH), 5.37 d (1H, H^6, *J* 2.7 Hz), 7.29–7.67 m (6H$_{arom}$), 8.17 d (2H$_{arom}$, *J* 7.6 Hz), 8.54 d (1H, NH, *J* 2.7 Hz). ^{13}C NMR spectrum, δ, ppm: 37.55 (C$^{4'}$), 45.78 (CH_2N), 51.13 (CH_3O), 52.05 (C^6), 53.31 (CH_3O), 78.55 (C$^{5'}$), 102.88 (C^5), 115.72, 123.89, 125.54, 127.59, 143.32, 146.97 (C_{Ar}), 149.24 (C^4), 151.37 (C$^{3'}$), 155.67 (C^2), 162.67 (C=O), 163.15 d (4-FC_6H_4,

$J_{C\text{-}F}$ 250.6 Hz), 164.04 (C=O). ^{19}F NMR spectrum, δ, ppm: –109.89. Found, %: C 56.51; H 4.18; N 11.00. [*M* + 1]$^+$ 513. $C_{24}H_{21}FN_4O_8$. Calculated, %: C 56.25; H 4.13; N 10.83. *M* 512.4.

Dimethyl 6-(3,4-dichlorophenyl)-3-{[3-(4-phenyl)-4,5-dihydro-5-isoxazolyl]methyl}-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Vd). Yield 31%, mp 168–169°C. IR spectrum , ν, cm^{-1}: 3245, 3135 (NH), 1725, 1690 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.12–3.20 m (2H, CH_2), 3.44 m (1H, CH), 3.62 s (3H, CH_3O), 3.80 s, 3.83 s (3H, CH_3O), 4.16 d.d (2H, CH_2N, *J* 15.2, *J* 3.2 Hz), 4.83 m (1H, CH), 5.28 d (1H, H^6, *J* 3.5 Hz), 7.36–7.68 m (8H$_{arom}$), 8.41 d (1H, NH, *J* 3.5 Hz). ^{13}C NMR spectrum, δ, ppm: 37.31 (C$^{4'}$), 47.18 (CH_2N), 51.80 (C^6), 52.12 (CH_3O), 53.14 (CH_3O), 78.00 (C$^{5'}$), 102.19 (C^5), 126.45, 126.53, 128.61, 128.88, 129.09, 130.14, 130.61, 131.01, 131.36, 143.13 (C_{Ar}), 143.75 (C^4), 151.16 (C$^{3'}$), 156.41 (C^2), 162.66 (C=O), 163.69 (C=O). Found, %: C 55.33; H 4.24; N 8.29. [*M* + 1]$^+$ 519. $C_{24}H_{21}Cl_2N_3O_6$. Calculated, %: C 55.61; H 4.08; N 8.11. *M* 518.3.

Diethyl 6-(3-bromophenyl)-3-{[3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolyl]methyl}-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Ve). Yield 71%, mp 174–175°C. IR spectrum , ν, cm^{-1}: 3240, 3140 (NH), 1735, 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, CH_3, *J* 7.0 Hz), 1.24 t (3H, CH_3, *J* 7.0 Hz), 3.16–3.24 m (2H, CH_2), 3.42 m (1H, CH), 3.80 s (3H, CH_3O), 4.03–4.29 m (5H, $2CH_2O + CH_2$), 4.82 m (1H, CH), 5.24 d (1H, H^6, *J* 3.3 Hz), 7.02 d (2H$_{arom}$, *J* 9.0 Hz), 7.38–7.78 m (6H$_{arom}$), 8.38 d (1H, NH, *J* 3.3 Hz). ^{13}C NMR spectrum, δ, ppm: 13.36 (CH_3), 13.73 (CH_3), 37.59 (C$^{4'}$), 46.26 (CH_2N), 55.26 (C^6), 60.70 (CH_2O), 62.51 (CH_2O), 77.90 (C$^{5'}$), 103.05 (C^5), 114.21, 121.44, 121.73, 125.30, 128.12, 129.36, 130.74, 130.94, 142.72, 155.75 (C_{Ar}), 145.20 (C^4), 151.26 (C$^{3'}$), 160.67 (C^2), 162.22 (C=O), 163.12 (C=O). Found, %: C 55.41; H 4.89; N 7.00. [*M* + 1]$^+$ 587. $C_{27}H_{28}BrN_3O_7$. Calculated, %: C 55.30; H 4.81; N 7.17. *M* 586.4.

Diethyl 6-(4-nitrophenyl)-3-{[3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolyl]methyl}-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Vf). Yield 75%, mp 180–182°C. IR spectrum , ν, cm^{-1}: 3245, 3140 (NH), 1725, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.13 t (3H, CH_3, *J* 7.0 Hz), 1.23 t (3H, CH_3, *J* 7.0 Hz), 3.07–3.18 m (2H, CH_2), 3.42 m (1H, CH), 3.81 s (3H, CH_3O), 4.06–4.32 m (5H, $2CH_2O + CH_2$), 4.82 m (1H, CH), 5.37 d (1H, H^6, *J* 2.7 Hz), 7.00 d (2H$_{arom}$, *J* 8.7 Hz), 7.44–7.77 m (4H$_{arom}$), 8.17 d (1H$_{arom}$, *J* 8.0 Hz), 8.24 d (1H$_{arom}$, *J* 8.0 Hz), 8.49 d (1H, NH, *J* 2.7 Hz). ^{13}C NMR spectrum, δ, ppm: 13.39 (CH_3), 13.75 (CH_3), 37.39 (C$^{4'}$), 46.01 (CH_2N), 55.22 (C^6), 55.24 (CH_3O), 60.82 (CH_2O), 62.53 (CH_2O), 78.02 (C$^{5'}$), 102.82 (C^5), 114.18, 121.38, 123.88, 127.62, 128.04, 143.13, 147.00, 155.88 (C_{Ar}), 149.50 (C^4), 151.38 (C$^{3'}$), 160.68 (C^2), 162.09 (C=O), 163.08 (C=O). Found, %: C 58.41; H 5.22; N 10.39. [*M* + 1]$^+$ 553. $C_{27}H_{28}N_4O_9$. Calculated, %: C 58.69; H 5.11; N 10.14. *M* 552.5.

Diethyl 6-(3,4-dichlorophenyl)-3-{[3-(4-fluorophenyl)-4,5-dihydro-5-isoxazolyl]methyl}-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (Vg). Yield 73%, mp 159–160°C. IR spectrum , ν, cm^{-1}: 3240, 3145 (NH), 1725, 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, CH_3, *J* 7.0 Hz), 1.25 t (3H, CH_3, *J* 7.0 Hz), 3.10–3.21 m (2H, CH_2), 3.34 m (1H, CH), 3.74–4.28 m (5H, $2CH_2O + CH_2$), 4.85 m (1H, CH), 5.25 d (1H, H^6, *J* 2.9 Hz), 7.31–7.74 m (7H$_{arom}$), 8.49 d (1H, NH, *J* 2.9 Hz). ^{13}C NMR spectrum, δ, ppm: 13.40 (CH_3), 13.75 (CH_3), 37.38 (C$^{4'}$), 46.03 (CH_2N), 51.84 (C^6), 60.77 (CH_2O), 62.56 (CH_2O), 78.52 (C$^{5'}$), 102.87 (C^5), 115.77, 125.60, 126.52, 128.65, 128.90, 130.50, 131.18, 142.88, 143.44 (C_{Ar}), 149.25 (C^4), 151.19 (C$^{3'}$), 155.57 (C^2), 162.14 (C=O), 163.28 d (4-FC_6H_4, $J_{C\text{-}F}$ 242.0 Hz), 163.56 (C=O). ^{19}F NMR spectrum, δ, ppm: –109.99. Found, %: C 55.57; H 4.14; N 7.69. [*M* + 1]$^+$ 565. $C_{26}H_{24}Cl_2FN_3O_6$. Calculated, %: C 55.33; H 4.29; N 7.45. *M* 564.4.

REFERENCES

1. Kushnir, O.V. and Vovk, M.V., *Zh. Org. Khim*., 2010, vol. 46, p. 894.
2. Kappe, C.O., *Eur. J. Med. Chem*., 2000, vol. 35, p. 1043.
3. Kappe, C.O., *QSAR Comb. Sci.,* 2003, vol. 22, vol. 630.
4. Dallinger, D., Stadler, A., and Kappe, C.O., *Pure Appl. Chem.,* 2004, vol. 76, p. 1017.
5. Quan, M.L., Pruitt, J.R., Ellis, C.D., Liauw, A.Y., Gallemo, R.A., Stouten, P.F.W., Wityak, J., Knabb, R.M., Thoolen, M.I., Wong, P.C., and Wexler, R.R., *Bioorg. Med. Chem. Lett.,* 1997, vol. 7, p. 2813.
6. Cheng, K.F. and Al-Abed, Y., *J. Bioorg. Med. Chem. Lett*., 2006, vol. 16, p. 3376.
7. Pulkkinen, J.T., Houkekoski, P., Perakyla, M., Berzzi, I., and Laatikainen, R., *J. Med. Chem*., 2008, vol. 51, p. 3562.
8. Gangopadhyay, A.K., Gole, G.V., Jadhav, R.D., and Lal, B., *Synth. Commun*., 2007, vol. 37, p. 4157.

9. Syassi, B., El, Bakkali, B., Benaldelah, G.A., Hassikou, A., Dinia, M.N., Riviete, M., Bougrin, K., and Soutiarui, M., *Tetrahedron Lett*., 1999, vol. 40, p. 7205.
10. Bahloul, A., Sebban, A., Dordari, S., Boudouma, M., Kitana, S., Belghiti, T., and Joly, J.P., *J. Heterocycl. Chem.,* 2003, vol. 40, p. 243.
11. Bouissane, L., El, Kazzouli, S., Rakib, E.M., Khouili, M., Hannioui, A., Benchidmi, M., Essassi, E.M., and Guillaumet, G., *Hetrocycles*, 2004, vol. 63, p. 1651.
12. Vovk, M.V., Kushnir, O.V., Sukach, V.A., and Tsymbal, I.F., *Zh. Org. Khim.,* 2010, vol. 46, p. 716.
13. Huisgen, R., *Angew Chem*., *Int. Ed.,* 1963, vol. 2, p. 633.
14. Caramella, P. and Grunanger, P., *1,3-Dipolar Cycloaddition Chemistry*, New York: Wiley, 1984, vol. 1, p. 291.
15. Domschke, G. and Oelmann, H., *J. Prakt. Chem.,* 1969, vol. 311, p. 787.