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Synthesis and structure of condensed biheterocycles on the basis of 3-amino-1,2,4-triazole

The article is devoted to the development of preparatively convenient methods for the synthesis of new derivatives of 3-amino-1,2,4-triazole with the aim of constructing new condensed systems of industrially important substances. The synthesis of triazolopyrimidines, prepared by three-component condensation of 1,3-dicarbonyl compounds (anilide of acetoacetic acid and acetoacetic ether) with substituted aromatic aldehydes and 3-amino-1,2,4-triazole. It is shown that by melting at 120–140 ºC, in the absence of a solvent in equimolecular amounts of acetylacetyl anilide and acetoacetic ether with a mixture of 3-amino-1,2,4-triazole and substituted aromatic aldehydes (3-ethoxy-4-hydroxybenzaldehyde, salicylic aldehyde), leads to the 7-aryl-5-methyl-N-phenyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxamides and ethyl 7-aryl-5-methyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidin-6-carboxylate-titrate respectively. The structures of the synthesized compounds were studied by ^{1}H and ^{13}C NMR spectroscopy, as well as with the data of the two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C). The values of chemical shifts, multiplicity and integrated intensity of the ^{1}H and ^{13}C signals in one-dimensional NMR spectra are determined. Homo- and heteronuclear interactions were established using spectra in the formats COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), confirming the structure of the compounds under study.

Keywords: 3-amino-1,2,4-triazole, 7-aryl-5-methyl-N-phenyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxamides, aromatic aldehydes, ^{1}H- and ^{13}C NMR-spectra.

Introduction

The growing needs of mankind in new materials predetermine the vector orientation and tasks of organic synthesis, which involve the development of fundamentally new, convenient, economically and technologically sound, safe and competitive synthesis methods, as well as the production of previously unknown chemical products. One of the modern trends in organic synthesis is the using of the polycomponent condensations. Their attractiveness for synthetic chemists is connected with the combinatorial possibilities, the environmentally oriented idea of «green chemistry», one-pot and the rejection of the solvent as the preferred methods of practical implementation, allowing the synthesis of extensive libraries of substances in a short time. Multicomponent reactions involving 1,3-dicarbonyl compounds (1,3-DCC), aldehydes, mono- and bi-N-nucleophiles play an important role in fine organic synthesis and medical chemistry as universal methods for the synthesis of a large number of biologically active compounds, for example, derivatives of pyridines, pyrimidines [1, 2].

Pyrimidines are an important component of nucleic acids, and they have been used as building blocks in pharmaceutical preparations for the synthesis of antiviral [3], anticancer [4], antibacterial and antifungal agents [5].

Previously [6], we synthesized the condensed biheterocycles — tetrazolopyrimidines obtained by three-component condensation of anilide of acetoacetic acid with substituted aromatic aldehydes and the monohydrate of 5-aminotetrazole. The closest structural analogue of 5-aminotetrazole is 3-amino-1,2,4-triazole. It should be noted that derivatives of 1,2,4-triazole have wide range of physiological activity: hepatoprotective, wound healing, antiviral, germicidal, etc. [7, 8]. They are used as additives to high photographic materials, exhibit fungicidal, herbicidal and insecticidal properties [9, 10].

Continuing research into the synthesis of pyrimidine compounds [11, 12] with the aim of constructing new condensed systems, we carried out the reaction of substituted aromatic aldehydes with 3-amino-1,2,4-triazole and 1,3-dicarbonyl compounds (anilide of acetoacetic acid and acetoacetic acid ether), leading to the formation of triazolopyrimidines.

Experimental

The ^{1}H and ^{13}C NMR spectra of compounds (1, 2) were removed in DMSO-d6 using a JNN-ECA 400 spectrometer (400 and 100 MHz on ^{1}H and ^{13}C nuclei) from Jeol, Japan. The survey was carried out at room temperature using a DMSO solvent. Chemical shifts are measured relative to signals of residual protons or carbon atoms of a deuterated solvent.

General procedure for the preparation of triazolopyrimidines (1–4). A mixture of 1,3-dicarbonyl compound, aromatic aldehyde and 3-amino-1,2,4-triazole in equimolar amounts was held at 130–150 °C for 5–10 minutes until gas evolution ceased. The reaction mixture was cooled to room temperature, treated with ethyl alcohol, and the precipitate was filtered off. The precipitate was recrystallized from acetonitrile.

7-(3-Ethoxy-4-hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (1). The yield of the product (1) was 2.16 g (56 %), m.p. 245–247 ºC.

7-(2-Hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (2). Product yield (2) was 2.6 g (63 %) with m.p. 100–105 °C.

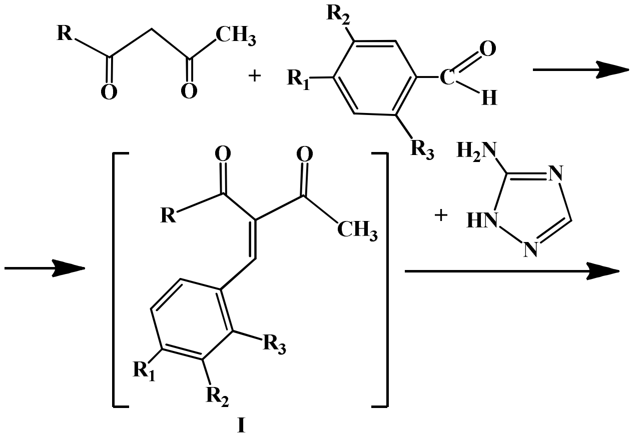
Ethyl 7-(3-ethoxy-4-hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (3). The yield of product (3) was 3.55 g (43 %), m.p. 225–228 ºC.

Ethyl 7-(2-hydroxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (4). The yield of the product (4) was 3 g (83 %), m.p. 145–148 ºC.

Results and discussion

In this paper we present the results of the research of the product of a three-component reaction of the anilide of acetoacetic acid and acetoacetic ether with substituted aromatic aldehydes and 3-amino-1,2,4-triazole in the absence of a solvent and a catalyst. The three-component Biginelli reaction, originally proposed for the synthesis of dihydropyrimidine-2(1*H*)-one by the reaction of aromatic aldehyde, urea and acetoacetic ether, is now used with great success in the synthesis of dihydropyrimidine-2(1*H*)-thione and various annelated pyrimidines [13–23].

We found that the fusion of equimolecular amounts of an acetoacetyl anilide with a mixture of 3-amino-1,2,4-triazole and substituted aromatic aldehydes at 130–150 ºC resulted in 7-aryl-5-methyl-N-phenyl-4,7-dihydro[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxamides (1, 2), and with acetoacetic ether — ethyl 7-aryl-5-methyl-4,7-dihydro-[1,2,4-triazolo[1,5-a]pyrimidine-6-carboxylate (3, 4). The resulting compounds (1–4) are pale yellow powders soluble in DMF, DMSO, heated in ethanol, acetonitrile, insoluble in water.



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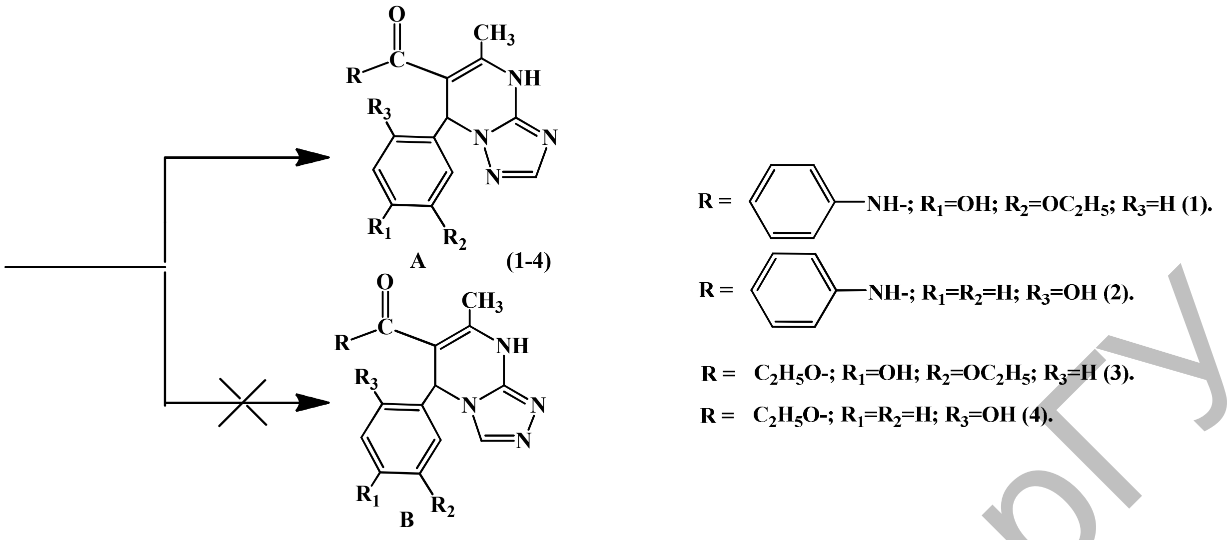
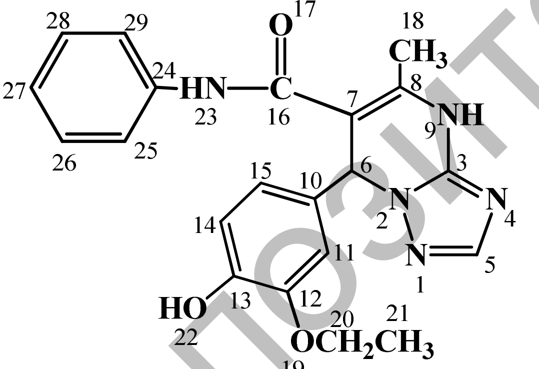


Based on the analysis of the published data [4–6, 11, 12], it is possible to assume that at the first stage of the reaction, as a result of the interaction of the 1,3-dicarbonyl compound with the aromatic aldehyde molecule, an unsaturated compound I is formed, the interaction of which with 3-amino-1,2,4-triazole, leads to the final reaction product. It is shown that in the 3-amino-1,2,4-triazole molecule there are two unequal nitrogen atoms in positions 2 and 4 of the heterocycle, which allows us to consider the two most probabilistic reaction products. However, the main and nucleophilic character of nitrogen in position 2 of the heterocycle, apparently, causes the reaction to proceed in the direction predominantly to form the structure of A.

The proposed mechanism is confirmed by analysis of the IR and NMR spectra of ^{1}H-, ^{13}C. The IR spectra of compounds (1, 2) exhibit bands due to stretching vibrations of amide groups (1672–1684 cm^{-1}) and NH groups (3085–3120 cm^{-1}).

The ^{1}H NMR spectrum of compound (1) is characterized by the presence in the strong-field region of the spectrum at 1.19 ppm triplet signal with an intensity of 3H with ^{3}J 6.9 Hz atoms of the methyl group CH_3^{21} ethyl radical. Another CH_3^{18} methyl radical bound to the C^8 atom of a heterocyclic six-membered ring does not have spin-spin interactions with neighboring protons and is manifested at 2.12 ppm singlet signal with a content of 3H. In this part of the spectrum at 2.46 and 3.32 ppm the presence of solvent signals of DMSO-d6 and residual amounts of water was noted. The methylene protons of the hydroxyethyl radical were resonated with a multiplet signal in the range 3.76–3.89 ppm with an integrated intensity of 2H. The singlet signal with intensity IH at 6.39 ppm corresponds to proton H^6. The protons of the aromatic system H^{15} and H^{14}, which have hydrogen atoms adjacent to each other, which contribute to the splitting of the spectrum, were manifested by doublet signals at 6.56 (^{3}J 7.8 Hz) and 6.56 (^{3}J 8.2 Hz) ppm with intensities IH. The proton H^{11} of the aromatic cycle under consideration, which does not have hydrogen atoms adjacent to it, was indicated by a singlet at 6.71 ppm with an intensity of 1H. For an unsubstituted phenyl radical, all the protons appeared in the aromatic zone of the spectrum. The asymmetric proton H^{27} was manifested in the form of a triplet signal at 6.96 ppm, corresponding to the intensity IH, with ^{3}J 7.3 Hz. Equivalent H^{26,28} protons were manifested by triplet signals at 7.20 ppm with ^{3}J 7.8 Hz with an integrated intensity of 2H, whereas equivalent protons of H^{25,29} were detected by doublet signals at 7.48 ppm with ^{3}J 7.9 Hz with a 2H content. The multiplicity of the signals under consideration, their integrated intensity, and the values of the spin-spin interaction constants are in good agreement with the NMR indices for aromatic systems. The methyl proton H^5 of the five-membered heterocyclic system adjacent to two nitrogen atoms was manifested by the expected singlet at 7.59 ppm with an integrated intensity of 1H. The protons of the hydroxyl group H^{22} and the protons bound to the nitrogen atoms of H^{23} and H^9 were manifested in the form of singlets with an integrated intensity of 1H each at 8.90, 9.66 and 10.10 ppm respectively.



(1)

In the ^{13}C NMR spectrum of compound (1), the carbon atoms of the methyl groups resonated at 15.15 (C^{21}) and 17.81 (C^{18}) ppm in the strong-field part of the spectrum. Then they showed themselves at 60.47 ppm C^{6} atoms and at 64.43 ppm C^{20} atoms, which have a small screening effect on the carbon nucleus. The other carbons of the bicyclic fragment were resonated at 104.35 (C^{7}), 136.75 (C^{8}), 148.24 (C^{3}), and 150.23 (C^{5}) ppm. Signals with chemical shifts at 113.35 (C^{11}), 115.96 (C^{14}), 120.02 (C^{25,29}), 120.25 (C^{15}), 123.77 (C^{27}), 129.08 (C^{26,28}), 132.17 (C^{10}), 139.58 (C^{24}), 146.86 (C^{12}) and 147.29 (C^{13}) ppm belong to the carbon nuclei of the two aromatic rings. In the most weakly-field region of the spectrum at 165.58 ppm the carbonyl carbon atom C^{16} resonated.

The structure of compound (1) was also confirmed by two-dimensional spectroscopy of COSY (^{1}H-^{1}H) NMR spectroscopy and HMQC (^{1}H-^{13}C), which makes it possible to establish spin-spin interactions of homo- and heteronuclear nature (Fig. 1–4). The observed correlations in the molecule are shown in the diagram. In the spectra of the ^{1}H-^{1}H COSY compound, spin-spin correlations are observed through three proton bonds of neighboring methylene groups H^{25,29}-H^{26,28} (7.47, 7.20 and 7.17, 7.48), H^{26}-H^{27} (7.20, 6.96 and 6.96, 7.21) and H^{27}- H^{28} (6.96, 7.20 and 7.20, 6.96). The coordinates 3.84, 1.18 and 1.16, 3.80 correspond to homolytic interaction through three bonds of neighboring aliphatic protons H^{20} and H^{21}. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^{1}H-^{13}C HMQC spectroscopy for all pairs present in the compound: H^{5}-C^{5} (7.57, 150.23), H^{25,29}-C^{25,29} (7.48, 119.93), H^{26,28}-C^{26,28} (7.19, 129.15), H^{27}-C^{27} (6.94, 123.73), H^{11}-C^{11} (6.70, 113.34), H^{20}-C^{20} (3.82, 64.45), H^{14}-C^{14} (6.65, 120.32), H^{6}-C^{6} (6.37, 60.47), H^{18}-C^{18} (2.11, 17.83) and H^{21}-C^{21} (1.17, 15.05).

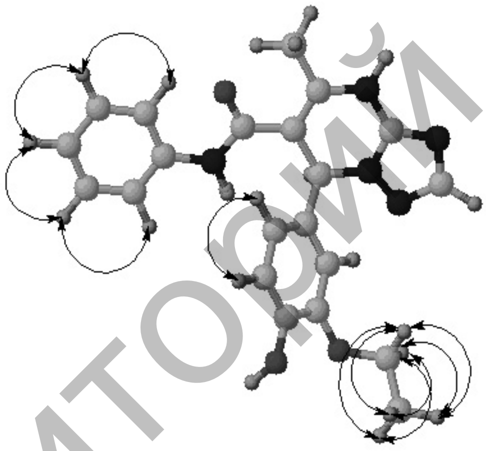


Figure 1. Correlations of COSY (^{1}H-^{1}H) compound (**1**)

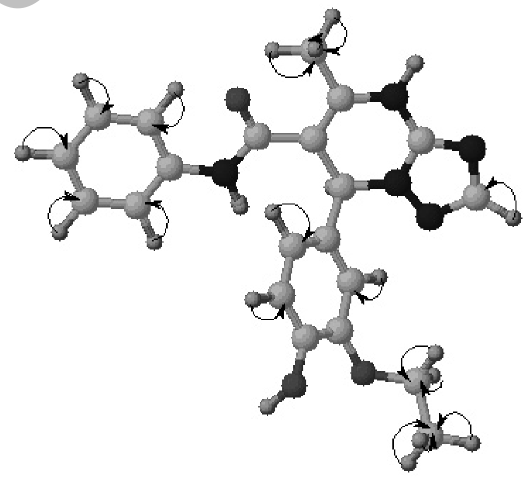


Figure 2. Correlations of HMQC (^{1}H-^{13}C) compound (**1**)

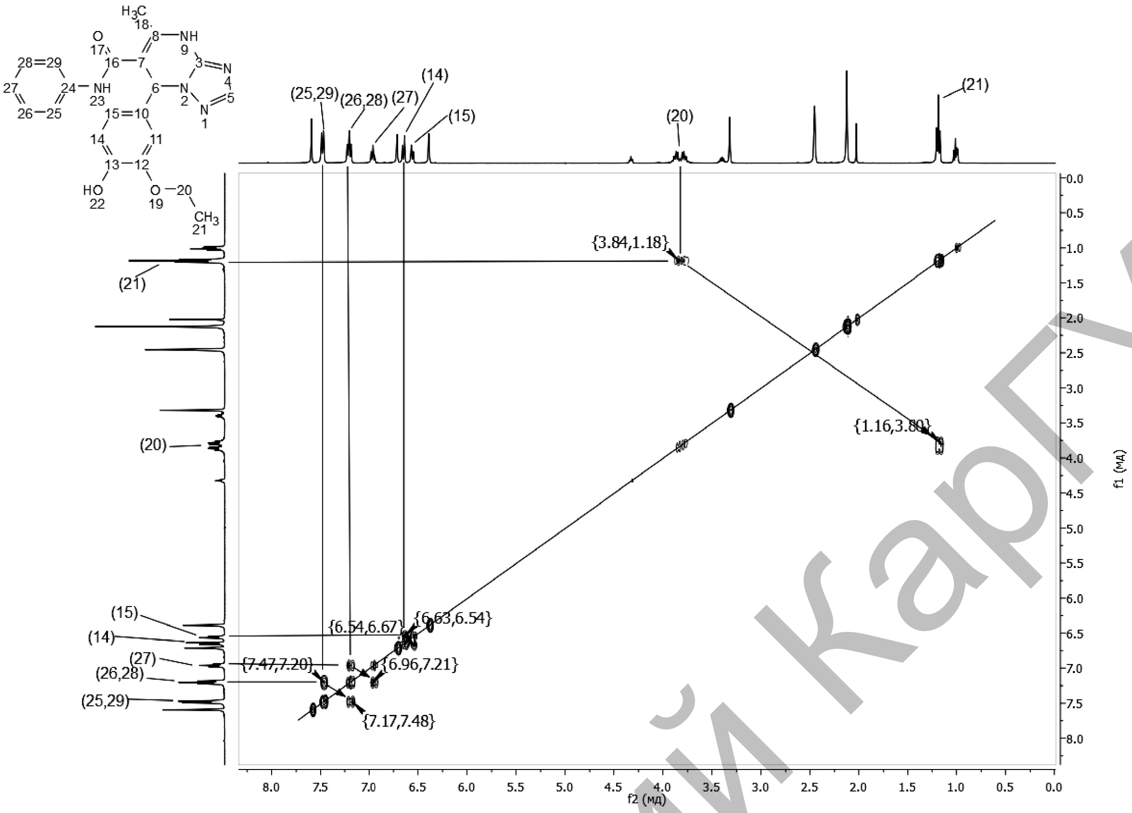


Figure 3. COSY (^1H-^1H) NMR spectrum of compound (**1**)

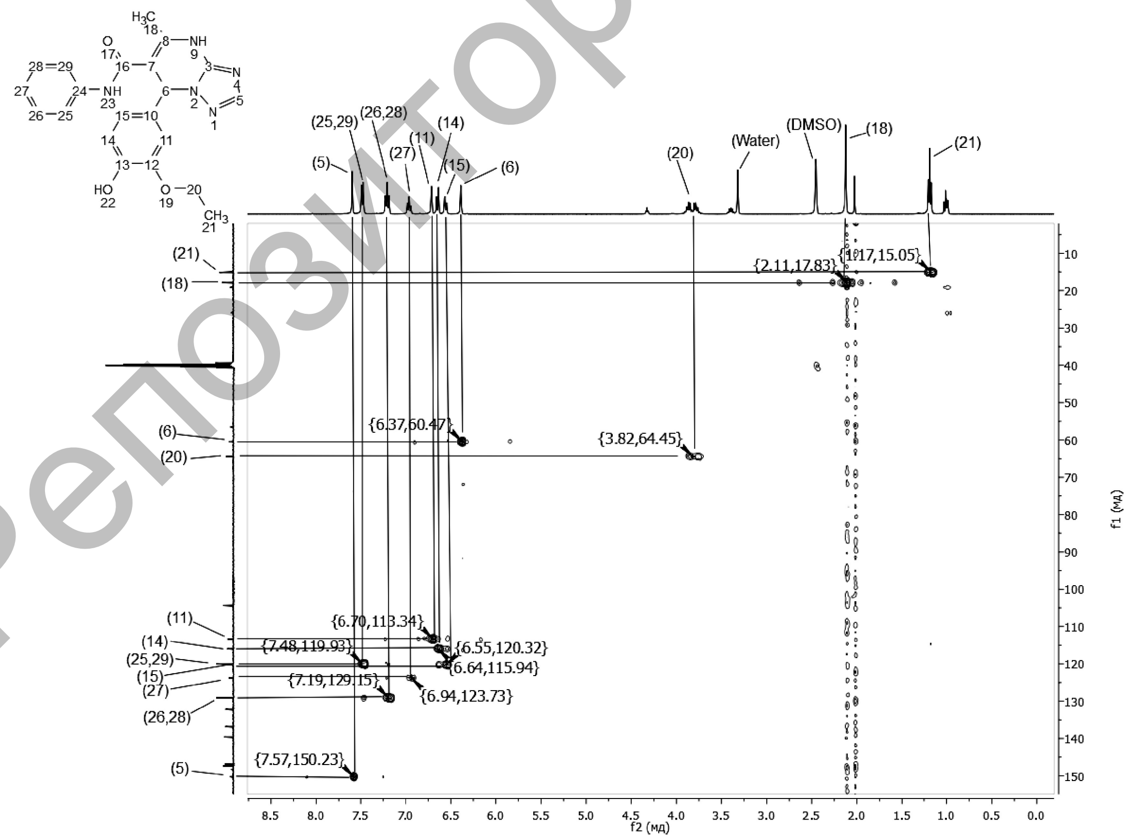


Figure 4. HMQC (^1H-^{13}C) NMR spectrum of compound (**1**)

The structures of other compounds (2), (3), and (4) are also confirmed by single-dimensional ^{1}H NMR and ^{13}C NMR spectroscopy (Table) and homo- and heteronuclear correlations of COSY and HMQC NMR.

Table

^{1}H and ^{13}C NMR spectroscopy data for compounds (1–4)

Compound No.	δ, ppm.	
	^{1}H	^{13}C
1	1.19 t (3H, CH_3^{14}, ^3J 6.9 Hz), 2.12 s (3H, CH_3^{18}), 3.76–3.89 m (2H, CH_2^{20}), 6.39 s (1H, H^6), 6.56 d (1H, H^{15}, ^3J 7.8 Hz), 6.65 d (1H, H^{14}, ^3J 8.2 Hz), 6.71 s (1H, H^{11}), 6.96 t (1H. H^{27}, ^3J 7.3 Hz), 7.20 t (2H, $H^{26,28}$, ^3J 7.8 Hz), 7.48 d (2H, $H^{25,29}$, ^3J 7.8 Hz), 8.90 s (1H, OH^{22}), 9.66 s (1H, NH^{23}). 10.10 s (1H, NH^9)	15.15 (C^{21}), 17.81 (C^{18}), 60.47 (C^6), 64.43 (C^{20}), 104.35 (C^7), 113.35 (C^{11}), 115.96 (C^{14}), 120.02 ($C^{25,29}$), 120.25 (C^{15}), 123.77 (C^{27}), 129.08 ($C^{26,28}$), 132.17 (C^{10}), 136.75 (C^8), 139.58 (C^{24}), 146.86 (C^{12}), 147.29 (C^{13}), 148.24 (C^3), 150.23 (C^5), 165.58 (C^{16})
2	2.26 s (3H, CH_3^{18}), 5.78 s (1H, H^3), 6.70 t (1H, H^{13}), 6.95 d (1H, H^{12}), 7.15–7.26 m (3H, $H^{14,24,26}$), 7.36–7.59 m (3H, $H^{22,23,25}$), 7.87 d (1H, H^{15}), 9.64 s (1H, OH^{19}), 9.99 s (1H, NH^6). 10.37 s (1H, NH^{20})	19.20 (C^{18}), 60.29 (C^3), 118.86 ($C^{22,26}$), 119.18 (C^{12}), 119.71 (C^{13}), 120.19 (C^{24}), 128.06 (C^{10}), 128.81 (C^{15}), 129.02 (C^{14}), 129.09 ($C^{23,25}$), 129.32 (C^{21}), 150.18 (C^5), 151.22 (C^9), 152.38 (C^7), 156.43 (C^{21}), 170.88 (C^{16})
3	1.01 t (3H, CH_3^{25}, ^3J 7.0 Hz), 1.24 t (3H, CH_3^{21}, ^3J 7.0 Hz), 2.35 s (3H, CH_3^{18}), 3.87–3.98 m (4H, CH_2^{20}, CH_2^{22}), 6.11 s (1H, H^6), 6.50 dd (1H, H^{15}, ^3J 8.2, 1.8 Hz), 6.64 d (1H, H^{14}, ^3J 8.2 Hz), 6.72 s (1H, H^{11}), 6.96 t (1H. H^{27}, ^3J 7.3 Hz), 7.20 t (2H, $H^{26,28}$, ^3J 7.8 Hz), 7.48 d (2H, $H^{25,29}$, ^3J 7.8 Hz), 8.90 s (1H, OH^{22}), 9.66 s (1H, NH^{23}). 10.10 s (1H, NH^9)	14.49 (C^{25}), 15.21 (C^{21}), 18.88 (C^{18}). 59.62 (C^6), 59.82 (C^{24}), 64.41 (C^{20}), 98.08 (C^7), 113.41 (C^{11}), 115.91 (C^{14}), 119.80 (C^{15}), 133.70 (C^{10}), 146.70 ($C^{3,8}$), 147.09 (C^{12}), 147.41 (C^{13}), 150.45 (C^5), 165.75 (C^{16})
4	1.16 t (3H, CH_3^{22}, ^3J 6.9 Hz), 2.26 s (3H, CH_3^{18}), 3.99 k (2H, CH_2^{21}, ^3J 7.0 Hz), 6.76 d (1H, H^{12}, ^3J 8.8 Hz), 6.80 s (1H, H^3), 6.93 t (1H, H^{13}, ^3J 6.3 Hz), 7.06 t (1H, H^{14}, ^3J 7.3 Hz), 7.68 d (1H, H^{15}, ^3J 8.2 Hz), 9.38 s (1H, OH^{19}), 9.65 s (1H, NH^6)	14.32 (C^{22}), 19.18 (C^{18}), 44.87 (C^3), 61.06 (C^{21}), 98.67 (C^4), 120.01 (C^{12}), 122.79 (C^{13}), 125.44 (C^{10}), 127.07 (C^{15}), 128.87 (C^{14}), 147.60 (C^9), 150.20 (C^5), 151.19 (C^7), 156.42 (C^{11}), 165.39 (C^{16})

Conclusions

The studies carried out for the first time the synthesis of novel 7-aryl-5-methyl-N-phenyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxyethylamidesi and 7-aryl-5-methyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxylates. On basis of analysis of spectral data of their structure and methods NMR ^{1}H- and ^{13}C-spectroscopy as well as two-dimensional spectra data COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) provided a mechanism of the reaction whereby the formation of the final product takes place through the intermediate step of reacting 1,3-dicarbonyl compounds with molecules of aromatic aldehyde.

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3-Амино-1,2,4-триазол негізінде конденсирленген бигетероциклдердің синтезі мен құрылымы

Мақала 3-амино-1,2,4-триазолдың жаңа туындыларын синтездеуде препаратты тиімді әдістерін дамытып, өндіріске қажетті жаңа конденсирленген жүйелерді құру мақсатына арналған. 1,3-дикарбонилді қосылыстардың (ацетосірке қышқылының анилиді және ацетосірке қышқылы), орынауыстырылған ароматтық альдегидтер және 3-амино-1,2,4-триазолымен үшкомпонентті конденсациясы арқылы алынатын триазоло-пиримидиндерді синтездеу туралы мәліметтер келтірілді. Еріткішсіз эквимолекулярлық мөлшерде ацетосірке қышқылының анилиді мен ацетосірке қышқылын қоспасымен 3-амино-1,2,4-триазол және орынауыстырылған ароматтық альдегидтер (3-этокси-4-гидроксибензальдегид, салицил альдегид) қоспасымен 120–140 ºС-да балқыту арқылы сәйкесінше

7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксамидтер мен этил 7-арил-5-метил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксилаттар алынуы көрсетілді. Синтезделген қосылыстардың құрылымы ЯМР ^{1}Н- мен^{13}С-спектроскопия, екі кеңістікті COSY (^{1}Н-^{1}Н) және HMQC (^{1}Н-^{13}С) әдістерімен зерттеліді. Бір кеңістікті ЯМР спектрлерінде химиялық қозғалыстардың сандық мәндері, мултиплеттілігі және ^{1}Н, ^{13}С сигналдарының интегралды қарқындылығы анықталды. Зерттелген қосылыстардың құрылымы COSY (^{1}Н-^{1}Н) и HMQC (^{1}Н-^{13}С) спектрлері көмегімен гомо- и гетероядролық арақатынасын анықтау арқылы дәлелденді.

Кілт сөздер: 3-амино-1,2,4-триазол, 7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксамидтер, ароматтық альдегидтер, ЯМР^{1}Н- и ^{13}С-спектрлер.

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Синтез и строение конденсированных бигетероциклов на основе 3-амино-1,2,4-триазола

Статья посвящена разработке препаративно удобных способов синтеза новых производных 3-амино-1,2,4-триазола с целью построения новых конденсированных систем промышленно важных веществ. Приведены данные по синтезу триазолопиримидинов, полученных трехкомпонентной конденсацией 1,3-дикарбонильных соединений (анилид ацетоуксусной кислоты и ацетоуксусный эфир) с замещенными ароматическими альдегидами и 3-амино-1,2,4-триазолом. Показано, что сплавление при 120–140 ºС в отсутствие растворителя эквимолекулярных количеств анилида ацетоуксусной кислоты и ацетоуксусного эфира со смесью 3-амино-1,2,4-триазола и замещенных ароматических альдегидов (3-этокси-4-гидроксибензальдегид, салициловый альдегид) приводит к 7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксамидам и этил 7-арил-5-метил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксилатам соответственно. Исследовано строение синтезированных соединений методами ЯМР ^{1}Н- и ^{13}С-спектроскопии, а также данными двумерных спектров COSY (^{1}Н-^{1}Н) и HMQC (^{1}Н-^{13}С). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}Н и ^{13}С в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}Н-^{1}Н) и HMQC (^{1}Н-^{13}С) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений.

Ключевые слова: 3-амино-1,2,4-триазол, 7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*] пиримидин-6-карбоксамиды, ароматические альдегиды, ЯМР^{1}Н- и ^{13}С-спектры.

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