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The synthesis, analgesic and anti-inflammatory activity of 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]-azepin-3-yl)acrylonitrile derivatives

Aim. To synthesize, prove the structure and study the analgesic and anti-inflammatory activities of 3-(het)-aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile derivatives.

Results and discussion. Condensation of 2-methoxy-3,4,5,6-tetrahydro-7*H*-azepine with cyanoacetic acid hydrazide leads to formation of 2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acetonitrile. The latter readily reacts with the corresponding (het)arenecarbaldehydes in refluxing ethanol in the presence of catalytic amount of piperidine yielding a series of new 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)-acrylonitrile derivatives. Further functionalization of 3-(4-hydroxy-3-R-phenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)acrylonitriles has been done by modification of the OH group. One of the compounds synthesized, namely 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile, exhibits a high level of the analgesic activity on the “hot plate” model, and a similar level of the activity on the model of “acetic acid-induced writhings” as compared to ketorolac. The results obtained indicate the pronounced antinociceptive activity for the test compound.

Experimental part. ^{1}H NMR spectra of the compounds synthesized were recorded on a Bruker VXR-300 spectrometer (Germany) operating at a frequency of 299.945 MHz, in DMSO-d_6, using tetramethylsilane (TMS) as an internal standard. Melting points were measured using a RNMK 05 device (VEB Analytik, Dresden). The elemental analysis was performed on a EuroEA 3000 elemental analyzer. The analgesic and anti-inflammatory activities of 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile were determined using models of “carrageenan induced paw edema”, ”hot plate” and “acetic acid-induced writhings”, and compared to the reference drug ketorolac.

Conclusions. A series of new 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile derivatives can be easily synthesized by the interaction of 2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acetonitrile with (het)arenecarbaldehydes. The hydroxy group in 3-(4-hydroxy-3-R-phenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitriles can be modified to obtain phenyl esters of aliphatic and aromatic carboxylic acids. The high level of the analgesic activity for 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile has been determined.

***Key words*:** 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile derivatives; ketorolac; analgesic activity; anti-inflammatory activity

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Синтез, анальгетична та протизапальна активність похідних 3-(гет)арил-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрилу

Мета. Синтезувати, довести структуру і дослідити анальгетичну та протизапальну активність похідних 3-(гет)арил-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрилу.

Результати та їх обговорення. Конденсація 2-метокси-3,4,5,6-тетрагідро-7*H*-азепіну з гідразидом ціанооцтової кислоти приводить до утворення 2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)-ацетонітрилу. Останній легко реагує з відповідними (гет)аренкарбальдегідами у присутності каталітичної кількості піперидину у середовищі киплячого етанолу з утворенням серії нових похідних 3-(гет)арил-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрилу. Подальшу функціоналізацію 3-(4-гідрокси-3-R-феніл)-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрилів було проведено шляхом модифікації ОН-групи. Одна із синтезованих сполук – 3-(4-гідроксифеніл)-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрил виявляє високий рівень анальгетичної активності на моделі «гарячої пластинки» та близький до кеторолаку рівень анальгетичної активності на моделі «оцтовокислих корчів». Одержані результати чітко вказують на виражену антиноцицептивну активність цієї сполуки.

Експериментальна частина. ^{1}Н ЯМР-спектри синтезованих сполук було записано на спектрометрі Bruker VXR-300 (Німеччина), робоча частота – 299,945 МГц, в ДМСО-d_6, з використанням тетраметилсилану (TMS) як внутрішнього стандарту. Температури плавлення вимірювали за допомогою пристрою RNMK 05 (VEB Analytik, Дрезден). Елементний аналіз виконували на елементному аналізаторі EuroEA 3000. Анальгетичну та протизапальну активність 3-(4-гідроксифеніл)-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло-[4,3-*a*]азепін-3-іл)акрилонітрилу досліджували на моделях «карагенін-індукованого набряку», «гарячої пластинки» та «оцтовокислих корчів», препарат порівняння – кеторолак.

Висновки. Серія нових похідних 3-(гет)арил-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)-акрилонітрилу може бути легко синтезована взаємодією 2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]-азепін-3-іл)ацетонітрилу з (гет)аренкарбальдегідами. Гідроксигрупа у 3-(4-гідрокси-3-R-феніл)-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрилах може бути модифікована з утворенням фенілових естерів аліфатичних та ароматичних карбонових кислот. Встановлено високий рівень анальгетичної активності для 3-(4-гідроксифеніл)-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)акрилонітрилу.

***Ключові слова*:** похідні 3-(гет)арил-2-(6,7,8,9-тетрагідро-5*H*-[1,2,4]триазоло[4,3-*a*]азепін-3-іл)-акрилонітрилу; кеторолак; анальгетична активність; протизапальна активність

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Синтез, анальгетическая и противовоспалительная активность производных 3-(гет)арил-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила

Цель. Синтезировать, доказать структуру и исследовать анальгетическую и противовоспалительную активность производных 3-(гет)арил-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила.

Результаты и их обсуждение. Конденсация 2-метокси-3,4,5,6-тетрагидро-7*H*-азепина с гидразидом цианоуксусной кислоты приводит к образованию 2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)-ацетонитрила. Последний легко реагирует с соответствующими (гет)аренкарбальдегидами в присутствии каталитического количества пиперидина в среде кипящего этанола с образованием серии новых производных 3-(гет)арил-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила. Дальнейшая функционализация 3-(4-гидрокси-3-R-фенил)-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)-акрилонитрилов была проведена путем модификации ОН-группы. Одно из синтезированных соединений – 3-(4-гидроксифенил)-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрил проявляет высокий уровень анальгетической активности на модели «горячей пластинки» и сравнимый с кеторолаком уровень анальгетической активности на модели «уксуснокислых корчей». Полученные результаты определенно указывают на выраженную антиноцицептивную активность данного соединения.

Экспериментальная часть. ^{1}Н ЯМР-спектры синтезированных соединений были записаны на спектрометре Bruker VXR-300 (Германия), рабочая частота – 299,945 МГц, в ДМСО-d_6, с использованием тетраметилсилана (TMS) в качестве внутреннего стандарта. Температуры плавления измеряли с помощью устройства RNMK 05 (VEB Analytik, Дрезден). Элементный анализ выполняли на элементном анализаторе EuroEA 3000. Анальгетическую и противовоспалительную активность 3-(4-гидроксифенил)-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила исследовали на моделях «карагенин-индуцированного отека», «горячей пластинки» и «уксуснокислых корчей», препарат сравнения – кеторолак.

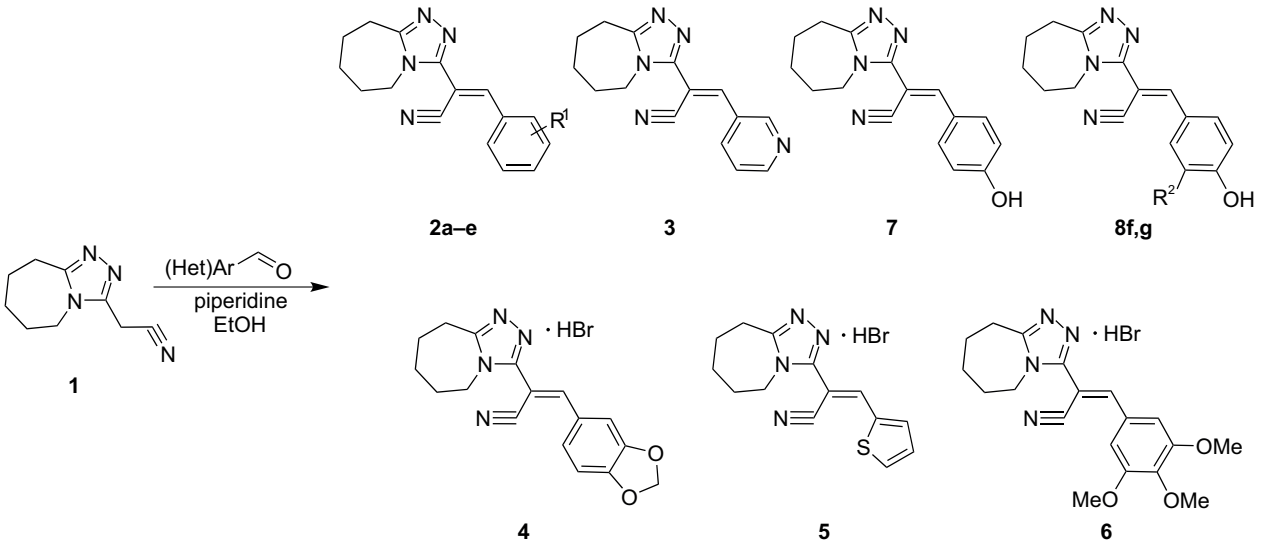
Выводы. Серия новых производных 3-(гет)арил-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила может быть легко синтезирована взаимодействием 2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]-триазоло[4,3-*a*]азепин-3-ил)ацетонитрила с (гет)аренкарбальдегидами. Гидроксигруппа в 3-(4-гидрокси-3-R-фенил)-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрилах может быть модифицирована с образованием фениловых эфиров алифатических и ароматических карбоновых кислот. Установлен высокий уровень анальгетической активности для 3-(4-гидроксифенил)-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила.

***Ключевые слова*:** производные 3-(гет)арил-2-(6,7,8,9-тетрагидро-5*H*-[1,2,4]триазоло[4,3-*a*]азепин-3-ил)акрилонитрила; кеторолак; анальгетическая активность; противовоспалительная активность

Diseases accompanied by inflammation and pain are among most widespread [1]. A wide range of drugs are used for therapy of such pathologies. Among them non-steroid anti-inflammatory drugs (NSAIDs) have occupied the dominant position [2]. They act as cyclooxygenase (COX) inhibitors. Nowadays, there are no NSAIDs, which would fully satisfy clinical requirements. Non-selective COX inhibitors are usually characterized by effectiveness in case of inflammation and/or a weak or moderate pain syndrome. At the same time, they are characterized by a wide range of undesirable side effects (ulcerogenic effect, hepatotoxicity, nephrotoxicity, hematotoxicity, etc.). Selective COX-2 inhibitors (Celecoxib, Valdecoxib, etc.) are characterized by reliably lower risk of the ulcerogenic effect. Nevertheless, because of the weak effect on thromboxane and kidney prostaglandins this group of drugs is characterized by drawbacks for the cardiovascular system and other undesirable reactions [1, 3, 4]. These facts reveal the importance of searching for new NSAIDs, which are safer and more effective than the existing analogs.

In our previous studies, a pronounced analgesic and anti-inflammatory activities for new triazoloazepines were found [5]. Due to this, we set the task to synthesize and prove the structure of substituted 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo-[4,3-*a*]azepine-3-yl)acrylonitriles. We also aimed at assessing their analgesic and anti-inflammatory activities compared to ketorolac, a NSAID with the strongest analgesic activity [6, 7].

A series of 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile derivatives **2–8** was synthesized by the interaction of 2-(6,7,8,9-



2a–e **3** **7** **8f,g**

1 **4** **5** **6**

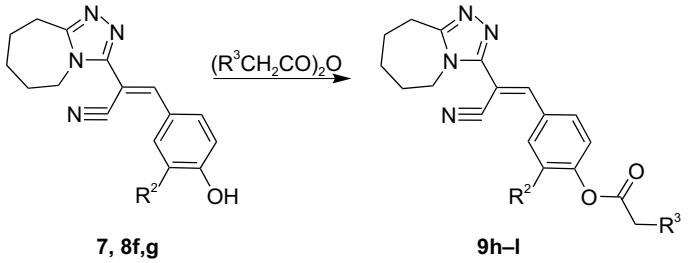
2a: R^1 = 4-OMe; **2b:** R^1 = 4-OEt; **2c:** R^1 = 4-Cl; **2d:** R^1 = 4-Br; **2e:** R^1 = 3-NO_2
8f: R^2 = OMe; **8g:** R^2 = OEt

Scheme 1. The synthesis of 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile derivatives **2–8**

tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acetonitrile **1** with the corresponding (het)arenecarbaldehydes in ethanol in the presence of piperidine (Scheme 1). Further modification of the acrylonitrile derivatives was carried out by acylation of the OH group in 3-(4-hydroxy-3-R-phenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitriles **7**, **8** giving O-acyl derivatives **9**, **10** (Scheme 2).

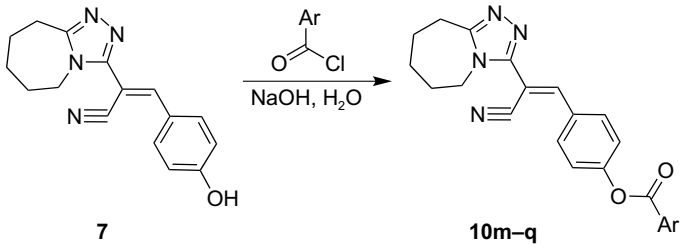
In ^{1}H NMR spectra of the compounds synthesized a singlet at 4.35 ppm characterizing the –CH_2CN group in the starting 2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo-[4,3-*a*]azepin-3-yl)acetonitrile **1** disappears, and a new singlet signal of the methyne group =CH– of the aldehyde moiety appears at 7.76–8.07 ppm. It should be noted that the location of the signal of the methyne proton depends on the nature of the (het)aryliden fragment and substituents attached to it. In this way, in case of the 4-EtO-Ph substituent (compound **2b**) the chemical shift of =CH– proton is 7.76 ppm. Replacement of an electron-donating ethoxy group with an electron-withdrawing NO_2 group (compound **2e**) leads to downfield shifting of the methyne proton, and it is registered at 8.07 ppm.

The analgesic and anti-inflammatory activities were studied on female non-linear white mice weighing 20±2 g from the vivarium of the Institute of Pharma-



7, 8f,g **9h–l**

9h: R^2 = H, R^3 = H; **9i:** R^2 = H, R^3 = Me; **9j:** R^2 = OMe, R^3 = H;
9k: R^2 = OMe, R^3 = Me; **9l:** R^2 = OEt, R^3 = H



7 **10m–q**

10m: Ar = Ph; **10n: Ar** = 2-Me-Ph; **10o: Ar** = 4-Me-Ph;

Scheme 2. Modification of 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitriles

Table 1

The analgesic activity of 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile **7** in the "hot plate" test

Compound	Dose, mg/kg	The latent period of the reaction, M±m, sec		The percent of the latent reaction period change, %
		Output data	60 min	
7	25.0	9.96±1.15	22.14±3.15	+122.3*
Ketorolac	25.0	8.72±1.10	15.46±1.22	+77.29*

Note: * – P<0.05 compared to the output data

cology and Toxicology of the National Academy of Medical Sciences of Ukraine. Animals were fed with a standard diet and had free access to water *ad libitum*. The results obtained are given in Table 1–3.

Test compounds (compound **7** and the reference drug ketorolac) were administered orally on an empty stomach in the dose of 25 mg/kg using the water-alcohol mixture (5% of alcohol) and 5% of Tween-20 as a detergent [8]. The volume of the emulsion administered did not exceed 0.2 mL per animal.

The primary evaluation of the analgesic activity was done by using models of "hot plate" and "acetic acid-induced writhings" [9, 10]. The analgesic activity was assessed in 60 min after introduction of the compounds under research.

A hot-plate analgesia meter (Ugo Basile, Italy) was used for thermal nociceptive stimulation in the "hot plate" model. Mice were divided into two groups (n = 5). The reaction time (paw licking or jumping) was recorded for each mouse at the time interval of 60 min after administration of the test compounds with cut-off time 20 sec to prevent the tissue damage.

For modelling of visceral pain the "acetic acid-induced writhings" test was used. Writhings were induced in mice by intra-peritoneal injection of 0.6% *v*/*v* acetic acid in the dose of 0.1 mL/10 g in 60 min after introduction of the test compounds (the study groups, 7 mice per group) or the solvent (the control group, 10 mice per group). The number of writhings was counted from 5 to 15 min after injection of acetic acid. The percent inhibition of the writhings count of the study group was calculated from the writhings count of the control group.

The anti-inflammatory activity was assessed on the model of "carrageenan-induced paw edema" [6]. The acute inflammation was produced by injecting 0.1 mL of the freshly prepared carrageenan solution (1% *w*/*v*) into the sub-plantar region of the mice paw. The test compounds were injected 30 min before carrageenan injection. The paw volume was measured at the time interval of 3 h after carrageenan injection.

The carrageenan-induced paw edema model characterizes the cyclooxygenase path of inflammation [11]. The results obtained indicate that the derivative of 5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)-acrylonitryle **7** exhibits a moderate, but reliable anti-inflammatory effect (Table 3).

The results obtained were statistically analyzed using the Student's *t*-criterion. Changes with P<0.05 were regarded as reliable [12].

It was found that the derivative of 2-(5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)acrylonitrile **7** showed a reliable antinociceptive effect on the "hot plate" model (122.3%) exceeding the effect of ketorolac (77.29%) (Table 1). Considering the fact that the "hot plate" model reveals supraspinal nociceptive processes the data obtained indicate the central component of the analgesic activity for the compound studied [13].

The level of the peripheral antinociceptive activity was assessed on the "acetic acid-induced writhings" model based on the chemical irritation. On this model the test compound showed the activity close to ketorolac (57.35% and 61.02%, respectively) (Table 2). Considering the fact that intraperitoneal injection of acetic acid contributes to the overall activation of the nociceptive system and local release of bradykinins, histamine, leukotrienes, prostaglandins the data obtained show the presence of the anti-inflammatory component in the antinociceptive action of the test compound [13].

Table 2

The analgesic activity of 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile **7** in the "acetic acid-induced writhings" test

Compound	Dose, mg/kg	The number of writhings in the control, M±m	The number of writhings in the experiment, M±m	The percent of writhing inhibition, %
7	25.0	27.20±2,03	11.60±3.12	–57.35*
Ketorolac	25.0	27.20±2.03	10.60±2.72	–61.02*

Note: * – P<0.05 compared to the output data

Table 3

The anti-inflammatory activity of 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile **7** in the "carrageenan-induced paw edema" test

Compound	Dose, mg/kg	Control, M±m, mg	Experiment, M±m, mg	Percent, %
7	25.0	45.40±2.48	37.00±3.76	–18.50*
Ketorolac	25.0	45.40±2.48	22.80±4.57	–49.77**

Note: * – P<0.05 compared to ketorolac; ** – P<0.05 compared to control

Experimental part

(6,7,8,9-Tetrahydro-*5H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acetonitrile **1** was obtained by the interaction of 2-methoxy-3,4,5,6-tetrahydro-7*H*-azepine with cyanoacetic acid hydrazide [14].

^{1}H NMR spectra were recorded on a Bruker VXR-300 spectrometer (Germany) operating at a frequency of 299.945 MHz, in DMSO-d_6, using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in ppm units using the δ scale. The melting points were measured on a small-sized heating table with a RNMK 05 observation device (VEB Analytik, Dresden). The elemental analysis was performed on a EuroEA 3000 elemental analyzer.

2-(6,7,8,9-Tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]-azepin-3-yl)acetonitrile 1. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 4.35 (2H, s, CH_2CN), 1.55–1.62 (2H, m, 7-CH_2), 1.64–1.72 (2H, m, 8-CH_2), 1.77–1.84 (2H, m, 6-CH_2), 2.86–2.90 (2H, m, 9-CH_2), 3.95–3.98 (2H, m, 5-CH_2).

The general procedure for the synthesis of 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo-[4,3-*a*]azepin-3-yl)acrylonitriles 2a–e, 3, 7, 8f, g. Reflux the mixture of 2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)acetonitrile **1** (0.01 mol) and the corresponding aldehyde (0.01 mol) in 60 mL of ethanol with a few drops of piperidine for 6 h. After cooling filter the solid products, wash with ethanol, then dry in the air and recrystallize from ethanol or propanol-2.

3-(4-Methoxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 2a. Yield – 1.79 g (61%). M. p. 157–158°C (from propanole-2). Anal. Calcd. for $C_{17}H_{18}N_4O$, %: N 19.03. Found, %: N 19.31. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.00 (2H, d, *J* = 9.0 Hz, C_6H_4), 7.79 (1H, s, =CH), 7.15 (2H, d, *J* = 9.0 Hz, C_6H_4), 4.13–4.17 (2H, m, 5-CH_2), 3.87 (3H, s, OCH_3), 2.95–2.98 (2H, m, 9-CH_2), 1.79–1.87 (2H, m, 6-CH_2), 1.72–1.80 (2H, m, 8-CH_2), 1.61–1.68 (2H, m, 7-CH_2).

3-(4-Ethoxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 2b. Yield – 1.94 g (63%). M. p. 182–183°C (from ethanol). Anal. Calcd. for $C_{18}H_{20}N_4O$, %: N 18.17. Found, %: N 18.43. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.98 (2H, d, *J* = 9.0 Hz, C_6H_4), 7.76 (1H, s, =CH), 7.12 (2H, d, *J* = 9.0 Hz, C_6H_4), 4.12–4.19 (4H, m, $OC\underline{H}_2CH_3$ + 5-CH_2), 2.94–2.98 (2H, m, 9-CH_2), 1.78–1.86 (2H, m, 6-CH_2), 1.72–1.79 (2H, m, 8-CH_2), 1.61–1.68 (2H, m, 7-CH_2), 1.37 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$).

3-(4-Chlorophenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 2c. Yield – 2.06 g (69%). M. p. 190–191°C (from ethanol). Anal. Calcd. for $C_{16}H_{15}ClN_4$, %: N 18.75. Found, %: N 18.95. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.00 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.90 (1H, s, =CH), 7.68 (2H, d, *J* = 8.8 Hz, C_6H_4), 4.16–4.19 (2H, m, 5-CH_2), 2.96–3.00 (2H, m, 9-CH_2), 1.72–1.87 (2H, m, 6-CH_2), 1.73–1.79 (2H, m, 8-CH_2), 1.61–1.68 (2H, m, 7-CH_2).

3-(4-Bromophenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 2d. Yield – 2.57 g (75%). M. p. 208–209°C (from ethanol). Anal. Calcd. for $C_{16}H_{15}BrN_4$, %: N 16.32. Found, %: N 16.39. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.99 (2H, d, *J* = 8.4 Hz, C_6H_4), 7.86 (1H, s, =CH), 7.80 (2H, d, *J* = 8.4 Hz, C_6H_4), 4.15–4.18 (2H, m, 5-CH_2), 2.96–2.99 (2H, m, 9-CH_2), 1.72–1.86 (2H, m, 6-CH_2), 1.73–1.79 (2H, m, 8-CH_2), 1.61–1.69 (2H, m, 7-CH_2).

3-(3-Nitrophenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin3-yl)acrylonitrile 2e. Yield – 2.57 g (77%). M. p. 185–186°C (from ethanol). Anal. Calcd. for $C_{16}H_{15}N_5O_2$, %: N 22.64. Found, %: N 22.38. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.85 (1H, s, C_6H_4), 8.37–8.43 (2H, m, C_6H_4), 8.07 (1H, s, =CH), 7.89 (1H, t, *J* = 8.1 Hz, C_6H_4), 4.20–4.23 (2H, m, 5-CH_2), 2.98–3.02 (2H, m, 9-CH_2), 1.80–1.88 (2H, m, 6-CH_2), 1.76–1.81 (2H, m, 8-CH_2), 1.63–1.70 (2H, m, 7-CH_2).

3-(Pyridin-3-yl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 3. Yield – 1.59 g (60%). M. p. 176–177°C (from propanol-2). Anal. Calcd. for $C_{15}H_{15}N_5$, %: N 26.40. Found, %: N 26.63. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 9.04 (1H, s, C_5H_4N), 8.73 (1H, d, *J* = 3.8 Hz, C_5H_4N), 8.42 (1H, d, *J* = 7.8 Hz, C_5H_4N), 7.95 (1H, s, =CH), 7.61–7.65 (1H, m, C_5H_4N), 4.19–4.22 (2H, m, 5-CH_2), 2.97–3.00 (2H, m, 9-CH_2), 1.79–1.87 (2H, m, 6-CH_2), 1.74–1.80 (2H, m, 8-CH_2), 1.62–1.69 (2H, m, 7-CH_2).

3-(4-Hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 7. Yield – 1.93 g (69%). M. p. 245–247°C (from ethanol). Anal. Calcd. for $C_{16}H_{16}N_4O$, %: N 19.99. Found, %: N 19.83. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 10.50 (1H, s, OH), 7.90 (2H, d, *J* = 8.7 Hz, C_6H_4), 7.70 (1H, s, =CH), 6.95 (2H, d, *J* = 8.7 Hz, C_6H_4), 4.12–4.15 (2H,

m, 5-CH_2), 2.94–2.97 (2H, m, 9-CH_2), 1.78–1.86 (2H, m, 6-CH_2), 1.72–1.79 (2H, m, 8-CH_2), 1.60–1.67 (2H, m, 7-CH_2).

3-(4-Hydroxy-3-methoxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)-acrylonitrile 8f. Yield – 1.95 g (63%). M. p. 214–215°C (from ethanol). Anal. Calcd. for $C_{17}H_{18}N_4O_2$, %: N 18.05. Found, %: N 18.21. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 10.70 (1H, s, OH), 7.88 (1H, s, =CH), 7.76 (1H, s, C_6H_3), 7.59 (1H, d, *J* = 8.4 Hz, C_6H_3), 7.32 (1H, d, *J* = 8.4 Hz, C_6H_3), 4.17–4.20 (2H, m, 5-CH_2), 3.86 (3H, s, OCH_3), 2.96–2.99 (2H, m, 9-CH_2), 1.79–1.87 (2H, m, 6-CH_2), 1.73–1.80 (2H, m, 8-CH_2), 1.62–1.68 (2H, m, 7-CH_2).

3-(4-Hydroxy-3-ethoxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile 8g. Yield – 1.94 g (60%). M. p. 187–188°C (from ethanol). Anal. Calcd. for $C_{18}H_{20}N_4O_2$, %: N 17.27. Found, %: N 17.54. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 10.6 (1H, s, OH), 7.88 (1H, s, =CH), 7.78 (1H, s, C_6H_3), 7.60 (1H, d, *J* = 8.4 Hz, C_6H_3), 7.31 (1H, d, *J* = 8.4 Hz, C_6H_3), 4.16–4.19 (2H, m, 5-CH_2), 4.11 (2H, q, *J* = 6.8 Hz, $OC\underline{H}_2CH_3$), 2.97–3.00 (2H, m, 9-CH_2), 1.79–1.85 (2H, m, 6-CH_2), 1.72–1.80 (2H, m, 8-CH_2), 1.62–1.68 (2H, m, 7-CH_2), 1.33 (3H, t, *J* = 6.8 Hz, $OCH_2\underline{CH}_3$).

The general procedure for the synthesis of 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile hydrobromide derivatives 4–6. Reflux the mixture of 2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)-acetonitrile **1** (0.01 mol) and the corresponding aldehyde (0.01 mol) in 60 mL of ethanol with a few drops of piperidine for 6 h. After cooling evaporate the solvent and add the solution of 1 mL of hydrobromic acid in 40 mL of propanol-2. Filter the solid products **4–6**, wash with propanol-2, then dry in air and recrystallize from propanol-2.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)-acrylonitrile hydrobromide 4. Yield – 2.30 g (57%). M. p. 228–229°C (from propanol-2). Anal. Calcd. for $C_{17}H_{17}BrN_4O_2$, %: N 14.39. Found, %: N 14.28. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.88 (1H, s, =CH), 7.67 (1H, s, C_6H_3), 7.57 (1H, d, *J* = 8.4 Hz, C_6H_3), 7.18 (1H, d, *J* = 8.7 Hz, C_6H_3), 6.21 (2H, s, –OCH_2O–), 5.29–5.39 (1H, br. s, HBr), 4.27–4.30 (2H, m, 5-CH_2), 3.09–3.13 (2H, m, 9-CH_2), 1.82–1.89 (4H, m, 6-CH_2, 8-CH_2), 1.70–1.77 (2H, m, 7-CH_2),

2-(6,7,8,9-Tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]-azepin-3-yl)-3-(thiophen-2-yl)acrylonitrile hydrobromide 5. Yield – 1.93 g (55%). M. p. 236–237°C (from propanol-2). Anal. Calcd. for $C_{14}H_{15}BrN_4S$, %: N 15.95. Found, %: N 16.23. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.29 (1H, s, =CH), 8.18 (1H, d, *J* = 5.0 Hz, C_6H_3S), 7.98 (1H, d, *J* = 3.5 Hz, C_6H_3S), 7.35–7.38 (1H, m, C_6H_3S), 6.08–6.21 (1H, br. s, HBr), 4.29–4.33 (2H, m, 5-CH_2), 3.11–3.15 (2H, m, 9-CH_2), 1.83–1.91 (4H, m, 6-CH_2, 8-CH_2), 1.71–1.79 (2H, m, 7-CH_2).

2-(6,7,8,9-Tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]-azepin-3-yl)-3-(3,4,5-trimethoxyphenyl)acrylonitrile hydrobromide 6. Yield – 2.61 g (60%). M. p. 155–156°C (from propanol-2). Anal. Calcd. for $C_{19}H_{23}BrN_4O_3$, %: N 12.87. Found, %: N 13.13. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.93 (1H, s, =CH), 7.45 (2H, s, C_6H_2), 4.81–4.99 (1H, br. s, HBr), 4.29–4.33 (2H, m, 5-CH_2), 3.85 (6H, s, 3,5-di-OCH_3), 3.79 (3H, s, 4-OCH_3), 3.10–3.13 (2H, m, 9-CH_2), 1.84–1.89 (4H, m, 6-CH_2, 8-CH_2), 1.71–1.77 (2H, m, 7-CH_2).

The general procedure for the synthesis of 4-(2-cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl acetates (propionates) 9h–l. Reflux the corresponding hydroxy derivatives **7** or **8f, g** (0.01 mol) in 5 mL of acetic (or propionic) anhydride for 2 h. After cooling pour the reaction mixture into 100 mL of water. Filter the solid products **9h–l**, wash with propanol-2, then dry in air and recrystallize from propanol-2 or ethanol.

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl acetate 9h. Yield – 2.54 g (79%). M. p. 175–176°C (from propanol-2). Anal. Calcd. for $C_{18}H_{18}N_4O_2$, %: N 17.38. Found, %: N 17.57. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.03 (2H, d, *J* = 8.7 Hz, C_6H_4), 7.88 (1H, s, =CH), 7.37 (2H, d, *J* = 8.7 Hz, C_6H_4), 4.15–4.19 (2H, m, 5-CH_2), 2.95–2.99 (2H, m, 9-CH_2), 2.31 (3H, s, CH_3CO), 1.79–1.86 (2H, m, 6-CH_2), 1.73–1.80 (2H, m, 8-CH_2), 1.62–1.68 (2H, m, 7-CH_2).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl propionate 9i. Yield – 2.52 g (75%). M. p. 128–129°C (from propanol-2). Anal. Calcd. for $C_{19}H_{20}N_4O_2$, %: N 16.66. Found, %: N 16.73. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.04 (2H, d, *J* = 8.7 Hz, C_6H_4), 7.89 (1H, s, =CH), 7.37 (2H, d, *J* = 8.7 Hz, C_6H_4), 4.16–4.19 (2H, m, 5-CH_2), 2.96–2.99 (2H, m, 9-CH_2), 2.65 (2H, q, *J* = 7.5 Hz, $CH_3C\underline{H}_2CO$), 1.78–1.86 (2H, m, 6-CH_2), 1.74–1.79 (2H, m, 8-CH_2), 1.61–1.68 (2H, m, 7-CH_2), 1.16 (3H, t, *J* = 7.5 Hz, $C\underline{H}_3CH_2CO$).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)-2-methoxyphenyl acetate 9j. Yield – 2.39 g (68%). M. p. 158–159°C (from propanol-2). Anal. Calcd. for $C_{19}H_{20}N_4O_3$, %: N 15.90. Found, %: N 15.67. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.86 (1H, s, =CH), 7.77 (1H, s, C_6H_3), 7.60 (1H, d, *J* = 8.4 Hz, C_6H_3), 7.31 (1H, d, *J* = 8.4 Hz, C_6H_3), 4.16–4.19 (2H, m, 5-CH_2), 3.85 (3H, s, OCH_3), 2.96–2.99 (2H, m, 9-CH_2), 2.30 (3H, s, CH_3CO), 1.79–1.87 (2H, m, 6-CH_2), 1.74–1.80 (2H, m, 8-CH_2), 1.62–1.69 (2H, m, 7-CH_2).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)vinyl)-2-methoxyphenyl propionate 9k. Yield – 2.38 g (65%). M. p. 152–153°C

(from propanol-2). Anal. Calcd. for $C_{20}H_{22}N_4O_3$, %: N 15.29. Found, %: N 15.53. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.87 (1H, s, =CH), 7.31–7.78 (3H, m, C_6H_3), 4.16–4.19 (2H, m, 5-CH_2), 3.84 (3H, s, OCH_3), 2.96–2.99 (2H, m, 9-CH_2), 2.63 (2H, q, *J* = 7.5 Hz, $CH_3C\underline{H}_2CO$), 1.79–1.86 (2H, m, 6-CH_2), 1.74–1.80 (2H, m, 8-CH_2), 1.62–1.69 (2H, m, 7-CH_2), 1.16 (3H, t, *J* = 7.5 Hz, $C\underline{H}_3CH_2CO$).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)-2-ethoxyphenyl acetate 9l. Yield – 2.42 g (66%). M. p. 123–124°C (from propanol-2). Anal. Calcd. for $C_{20}H_{22}N_4O_3$, %: N 15.29. Found, %: N 15.47. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.87 (1H, s, =CH), 7.77 (1H, s, C_6H_3), 7.59 (1H, d, *J* = 8.4 Hz, C_6H_3), 7.32 (1H, d, *J* = 8.4 Hz, C_6H_3), 4.15 – 4.19 (2H, m, 5-CH_2), 4.12 (2H, q, *J* = 6.8 Hz, $OC\underline{H}_2CH_3$), 2.96–2.99 (2H, m, 9-CH_2), 2.30 (3H, s, OCH_3), 1.79–1.86 (2H, m, 6-CH_2), 1.73–1.80 (2H, m, 8-CH_2), 1.61–1.68 (2H, m, 7-CH_2), 1.34 (3H, t, *J* = 6.8 Hz, $OCH_2C\underline{H}_3$).

The general procedure for the synthesis of benzoic (or substituted benzoic) acid 4-(2-cyano-2-(6,7,8,9-tetrahydro-*5H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl ester 10m–q. To the suspension of 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)acrylonitrile **7** (0.01 mol) in 20 mL of 10% sodium hydroxide solution add 0.015 mol of the corresponding benzoyl chloride at ambient temperature. Shake the reaction mixture vigorously for several minutes and leave for 5 h at ambient temperature. Pour the reaction mixture into 100 mL of water. Filter the solid products **10m–q**, wash with water, then dry in the air and recrystallize from ethanol.

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl benzoate 10m. Yield – 3.11 g (81%). M. p. 175–176°C (from ethanol). Anal. Calcd. for $C_{23}H_{20}N_4O_2$, %: N 14.57. Found, %: N 14.41. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.17 (2H, d, *J* = 7.2 Hz, C_6H_5), 8.10 (2H, d, *J* = 8.7 Hz, C_6H_4), 7.94 (1H, s, =CH), 7.79 (1H, t, *J* = 7.5 Hz, C_6H_5), 7.64 (2H, t, *J* = 7.8 Hz, C_6H_5), 7.56 (2H, d, *J* = 8.7 Hz, C_6H_4), 4.17–4.21 (2H, m, 5-CH_2), 2.97–3.00 (2H, m, 9-CH_2), 1.80–1.87 (2H, m, 6-CH_2), 1.74–1.81 (2H, m, 8-CH_2), 1.62–1.69 (2H, m, 7-CH_2).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl 2-methylbenzoate 10n. Yield – 2.99 g (75%). M. p. 190–191°C (from ethanol). Anal. Calcd. for $C_{24}H_{22}N_4O_2$, %: N 14.06. Found, %: N 14.30. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.41–8.14 (8H, m, C_6H_4 + C_6H_4), 7.93 (1H, s, =CH), 4.17–4.21 (2H, m, 5-CH_2), 2.97–3.00 (2H, m, 9-CH_2), 2.62 (3H, s, CH_3), 1.80–1.87 (2H, m, 6-CH_2), 1.75–1.81 (2H, m, 8-CH_2), 1.63–1.69 (2H, m, 7-CH_2).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl 4-methylbenzoate 10o. Yield – 3.07 g (77%). M. p. 187–188°C (from ethanol). Anal. Calcd. for $C_{24}H_{22}N_4O_2$, %: N 14.06. Found, %: N 13.32. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.09 (2H, d, *J* = 8.8 Hz, C_6H_4), 8.06 (2H, d, *J* = 8.1 Hz, C_6H_4), 7.93 (1H, s, =CH), 7.53 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.44 (2H, d, *J* = 8.1 Hz, C_6H_4), 4.17–4.20 (2H, m, 5-CH_2), 2.97–3.00 (2H, m, 9-CH_2), 2.44 (3H, s, CH_3), 1.80–1.88 (2H, m, 6-CH_2), 1.74–1.81 (2H, m, 8-CH_2), 1.62–1.69 (2H, m, 7-CH_2).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl 2-methoxybenzoate 10p. Yield – 2.73 g (66%). M. p. 136–137°C (from ethanol). Anal. Calcd. for $C_{24}H_{22}N_4O_3$, %: N 13.52. Found, %: N 13.34. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 8.09 (2H, d, *J* = 8.7 Hz, C_6H_4), 7.96 (1H, d, *J* = 7.1 Hz, C_6H_4), 7.93 (1H, s, =CH), 7.68 (1H, t, *J* = 7.9 Hz, C_6H_4), 7.50 (2H, d, *J* = 8.7 Hz, C_6H_4), 7.26 (1H, d, *J* = 8.2 Hz, C_6H_4), 7.13 (1H, t, *J* = 7.1 Hz, C_6H_4), 4.16–4.21 (2H, m, 5-CH_2), 3.90 (3H, s, OCH_3), 2.96–3.01 (2H, m, 9-CH_2), 1.79–1.88 (2H, m, 6-CH_2), 1.74–1.80 (2H, m, 8-CH_2), 1.61–1.68 (2H, m, 7-CH_2).

4-(2-Cyano-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)vinyl)phenyl 2-chlorobenzoate 10q. Yield – 2.93 g (70%). M. p. 205–206°C (from ethanol). Anal. Calcd. for $C_{23}H_{19}ClN_4O_2$, %: N 13.38. Found, %: N 13.27. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.56–8.16 (8H, m, C_6H_4+ C_6H_4), 7.95 (1H, s, =CH), 4.17–4.21 (2H, m, 5-CH_2), 2.97–3.00 (2H, m, 9-CH_2), 1.80–1.88 (2H, m, 6-CH_2), 1.75–1.81 (2H, m, 8-CH_2), 1.62–1.69 (2H, m, 7-CH_2).

Conclusions

1. A series of new 3-(het)aryl-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)acrylonitrile derivatives can be easily synthesized by the interaction of 2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]-azepin-3-yl)acetonitrile with (het)arenecarbaldehydes.

2. The hydroxy group in 3-(4-hydroxy-3-R-phenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]-azepin-3-yl)acrylonitriles can be modified to obtain phenyl esters of aliphatic and aromatic carboxylic acids.

3. The high level of the analgesic activity for 3-(4-hydroxyphenyl)-2-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[4,3-*a*]azepin-3-yl)acrylonitrile has been determined.

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References

1. Kaplan, B.; Swain, R. A. NSAIDs: Are There Any Differences? *Archives of Family Medicine* **1993,** *2* (11), 1167–1174.
2. Bacchi, S.; Palumbo, P.; Sponta, A.; Coppolino, M. F. Clinical Pharmacology of Non-Steroidal Anti-Inflammatory Drugs: A Review. *Anti-Inflammatory Anti-Allergy Agents Med. Chem.* **2012,** *11* (1), 52–64. http://dx.doi.org/10.2174/187152312803476255.
3. Sostres, C.; Gargallo, C. J.; Arroyo, M. T.; Lanas, A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract. Res., Clin. Gastroenterol.* **2010,** *24* (2), 121–132. https://doi.org/10.1016/j.bpg.2009.11.005.

4. Conaghan, P. G. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol. Int.* **2012,** *32* (6), 1491–1502. https://doi.org/10.1007/s00296-011-2263-6.
5. Demchenko, S. A.; Yeromina, H. O.; Perekhoda, L. O.; Bukhtiarova, T. A.; Bobkova, L. S.; Demchenko, A. M. Synthesis and analgesic properties of (3-allyl-4-aryl-3*H*-thiazol-2-ylidene)-[4-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepin-3-yl)phenyl]amine derivatives. *Farm. Zh.* **2018**, 1, 67–73. https://doi.org/10.32352/0367-3057.1.17.09.
6. Демченко, С. А.; Ядловський, О. Є.; Бухтіарова, Т. А.; Серединська, Н. М.; Голубов, М. І.; Демченко, А. М. 3-(4-Гідроксифеніл)-2-(6,7,8,9-тетрагідро-5*H*-[4,3-*a*]азепін-3-іл)акрилонітрил, що проявляє анальгетичну та протизапальну активності. Патент України 120416, Листоп 25, 2019.
7. Lyon, C.; Claus, L. W. Less is more when it comes to ketorolac for pain. *The Journal of Family Practice* **2019,** 1, 41–42.
8. Стефанов, В. *Доклінічні дослідження лікарських засобів*; Авіценна: Київ, 2001.
9. Komlos, E.; Porszasz, J.; Knoll, J. Morfin–prostigmin synergismus. *Acta Physiol. Acad. Sci. Hung.* **1950**, *1* (1), 77–90.
10. Wood, P. L. Animal models in analgesic testing. In *Analgesics: Neurochemical, Behavioral and Clinical Perspectives*; Kuhar, M., Pasternak, J., Eds.; Raven Press: New-York, 1984; Vol. 42, pp 175–194.
11. Тринус, Ф. П.; Мохорт, Н. А.; Клебанов, Б. М. *Нестероидные противовоспалительные средства*; Здоров'я: Київ, 1975.
12. Лапач, С. Н.; Чубенко, А. В.; Бабич, П. Н. *Статистика в науке и бизнесе*; Морион: Київ, 2002.
13. Vogel, H. G. *Drug Discovery and Evaluation: Pharmacological Assays*. 2 ed.; Springer-Verlag Berlin Heidelberg: New York, 2002. https://doi.org/10.1007/3-540-29837-1.
14. Petersen, S.; Tietze, E. Reaktionen Cyclischer Lactimäther mit Acylierten Hydrazinderivaten. *Chem. Ber.* **1957,** *90* (6), 909–921. https://doi.org/10.1002/cber.19570900609.

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