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The synthesis and biological assessment of [[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides with an 1,2,4-oxadiazol cycle in positions 6, 7 and 8

Fused heterocyclic 1,2,4-triazoles have provided much attention due to variety of their interesting biological properties.

Aim. To develop the method for the synthesis of novel 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides and conduct the biological assessment of the compounds synthesized.

Results and discussion. A diverse set of acetamides newly synthesized consists of 32 analogs bearing an 1,2,4-oxadiazole cycle in positions 6, 7 and 8. A convenient scheme of the synthesis starts from commercially available 2-chloropyridine-3-, 2-chloropyridine-4-, 2-chloropyridine-5-carboxylic acids with amidoximes to form the corresponding 2-chloro-[3-R_1-1,2,4-oxadiazol-5-yl]pyridines, then follows the reaction of hydrazinolysis with an excess of hydrazine hydrate. The process continues via the ester formation with the pyridine ring closure, then the amide formations of the end products are obtained by hydrolysis into acetic acid.

Experimental part. A series of new 2-[6-(1,2,4-oxadiazol-5-yl)-, 2-[7-(1,2,4-oxadiazol-5-yl)-, 2-[8-(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides were obtained in good yields, and their structures were proven by the method of ^{1}H NMR spectroscopy. The prognosis and study of their pharmacological activity were also conducted.

Conclusions. The synthetic approach of obtaining the representatives of 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4] triazolo[4,3-a]pyridine-3-yl]acetamides previously unknown can be used as an applicable method for the synthesis of diverse functionalized [1,2,4]triazolo[4,3-a]pyridine derivatives.

Key words: triazolopyridine; (1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine; 1,2,4-oxadiazole

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Синтез та біологічна оцінка [[1,2,4]триазоло[4,3-а]піридин-3-іл]ацетамідів з 1,2,4-оксадіазольним циклом у 6, 7 та 8 положенні

Конденсовані гетероциклічні 1,2,4-триазоли привертають велику увагу до себе різноманітністю цікавих біологічних властивостей.

Мета роботи. Розробити метод синтезу нових 2-[(1,2,4-оксадіазол-5-іл)-[1,2,4]триазоло[4,3-а]піридин-3-іл]ацетамідів та провести біологічну оцінку синтезованих сполук.

Результати та їх обговорення. Синтезовано низку нових похідних ацетамідів, яка складається з 32 аналогів, що містять 1,2,4-оксадіазольний цикл у 6, 7 та 8 положеннях. Зручна схема синтезу починається з комерційно доступних 2-хлоропіридин-3-, 2-хлоропіридин-4-, 2-хлоропіридин-5-карбонових кислот з амідоксимами з утворенням відповідних 2-хлоро-[3-R_1-1,2,4-оксадіазол-5-іл]піридинів, після чого перебігає реакція гідразинолізу з надлишком гідразин гідрату. Процес продовжується шляхом утворення ефіру з закриттям піридинового кільця, потім через гідроліз до оцтової кислоти ми отримуємо амідні утворення кінцевих продуктів.

Експериментальна частина. Ряд нових 2-[6-(1,2,4-оксадіазол-5-іл)-, 2-[7-(1,2,4-оксадіазол-5-іл)-, 2-[8-(1,2,4-оксадіазол-5-іл)-[1,2,4]триазоло[4,3-а]піридин-3-іл]ацетамідів був отриманий з добрими виходами, а їх структури підтверджені методом ЯМР ^{1}Н-спектроскопії. Також було зроблено прогноз та вивчення їх фармакологічної активності.

Висновки. Синтетичний підхід до отримання раніше невідомих представників 2-[(1,2,4-оксадіазол-5-іл)-[1,2,4]триазоло[4,3-а]піридин-3-іл]ацетамідів може бути застосований для синтезу різноманітних функціоналізованих [1,2,4]триазоло[4,3-а]піридинових похідних.

Ключові слова: триазолопіридин; (1,2,4-оксадіазол-5-іл)-[1,2,4]триазоло[4,3-а] піридин; 1,2,4-оксадіазол

В. Р. Карпина, С. С. Коваленко, С. Н. Коваленко, О. В. Заремба, О. В. Силин, Т. Лангер
Синтез и биологическая оценка [[1,2,4]триазоло[4,3-а]пиридин-3-ил]ацетамидов с 1,2,4-оксадиазольным циклом в 6, 7 и 8 положениях

Конденсированные гетероциклические 1,2,4-триазолы привлекают большое внимание разнообразием интересных биологических свойств.

Цель работы. Разработать метод синтеза новых 2-[(1,2,4-оксадиазол-5-ил)- [1,2,4]триазоло[4,3-а] пиридин-3-ил]ацетамидов и провести биологическую оценку синтезированных соединений.

Результаты и их обсуждение. Синтезирован ряд новых производных ацетамидов, который состоит из 32 аналогов, содержащих 1,2,4-оксадиазольный цикл в 6, 7 и 8 положениях. Удобная схема синтеза начинается с коммерчески доступных 2-хлорпиридин-3, 2-хлорпиридин-4, 2-хлорпиридин-5-карбоновых кислот с амидоксимами с образованием соответствующих 2-хлор-[3-R_1-1,2,4-оксадиазол-5-ил]пиридинов, после чего следует реакция гидразинолиза с избытком гидразин гидрата. Процесс продолжается путем образования эфира с закрытием пиридинового кольца, затем через гидролиз к уксусной кислоте мы получаем амидные образования конечных продуктов.

Экспериментальная часть. Ряд новых 2-[6-(1,2,4-оксадиазол-5-ил)-, 2-[7-(1,2,4-оксадиазол-5-ил)-, 2-[8-(1,2,4-оксадиазол-5-ил)-[1,2,4]триазоло[4,3-а] пиридин-3-ил]ацетамидов был получен с хорошими выходами, а их структуры подтверждены методом ЯМР ^{1}H-спектроскопии. Также был проведен прогноз и изучение их фармакологической активности.

Выводы. Синтетический подход получения ранее неизвестных представителей 2-[(1,2,4-оксадиазол-5-ил)-[1,2,4]триазоло4,3-а]пиридин-3-ил]ацетамидов может быть применен для синтеза различных функционализированных [1,2,4]триазоло[4,3-а]пиридиновых производных.

Ключевые слова: триазолопиридин; (1,2,4-оксадиазол-5-ил)-[1,2,4]триазоло [4,3-а]пиридин; 1,2,4-оксадиазол

[1,2,4]Triazolo[4,3-a]pyridine derivatives represent an important class of heteroaromatic compounds having a wide range of pharmaceutical and biological activities, including antibacterial [1, 2], antithrombotic [3], anti-inflammatory [4-7], herbicidal [8], antifungal [2], anticonvulsant [9], anxiolytic [10], antipsychotic ones [11, 12]. A simple, versatile, and widely applicable method for the synthesis of 1,2,4-triazolopyridine is therefore of considerable interest. The available methods for the triazolopyridine preparation are based on heterocyclic hydrazones or hydrazides as precursors [13]. Moreover, the oxidative cyclization of 2-pyridylhydrazones, addition of hydrazine to pyridines bearing a leaving group in position 2 followed by acylation and dehydration under a variety of conditions is the most commonly used method for the synthesis of [1,2,4]triazolo[4,3-a]pyridines [13, 14]. Synthetic methodologies have been also developed using PS-PPh_3/CCl_3 under microwave heating [15], (diacetoxy) iodo-benzene [1], and oxidant chloroamine T [16], as well as by electrochemical methods [17].

In the course of our studies a convenient method for the synthesis of novel [[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides with an 1,2,4-oxadiazole cycle in positions 6, 7 and 8 were developed. In order to predict the pharmacological activity the pharmacophore-based parallel *in silico* screening experiments were performed. Our collection of structure- and ligand-based interaction models was used; it revealed the potential inhibitory activity of the compounds against Cytochrome P 450 (CYP) known to be a heme containing protein superfamily of enzymes metabolizing a broad variety of xenobiotics, including drugs and toxic chemicals. In addition, our experiment also revealed the potential inhibitory activity against 5-HT2C (G-protein coupled receptor) known to be a potential target for the treatment of central nervous system (CNS) disorders.

The antimicrobial activity (bacterial and fungal) of some of the compounds synthesized was studied *in vitro*.

The synthetic process for preparing novel derivatives is described below. The structures were determined using spectroscopy methods, and all compounds were characterized by physical data.

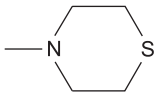
Our new target compounds 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides **f1-32**, as listed in Tab. 1, were prepared by the following the process presented in Scheme.

The reaction sequence started from the known 2-chloropyridine carboxylic acids **a1-3** dissolved in anhydrous DMF (N,N-Dimethylformamide) with an excess of CDI (carbonyldiimidazole). Adding an excess of the corresponding amidoxime resulted in formation of the corresponding 2-chloro-[3-R_1-1,2,4-oxadiazol-5-yl]pyridine **b1-11**. 2-hydrazine-[3-R_1-1,2,4-oxadiazol-5-yl]pyridines **c1-11** were synthesized by hydrazinolysis with hydrazine hydrate and subsequent heating until the end of the reaction in dioxane. Further synthesis of ethyl 2-[(3-R_1-1,2,4-oxadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyridine-3-yl]acetates **d1-11** were performed following the procedure of the ethyl malonylchloride addition to the solution of 2-hydrazine-[3-R_1-1,2,4-oxadiazol-5-yl]pyridines **c1-11** in acetic acid with reflux for 2h. Then products **d1-11** obtained were hydrolyzed with sodium hydroxide in aqueous methanol for 12h and acidified with hydro chloric acid to obtain the corresponding 2-[(3-R_1-1,2,4-oxadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyridine-3-yl]acetic acids **e1-11**. Further products **e1-11** were reacted with CDI in order to activate the carboxyl group for the direct reaction with the corresponding amines via the amide bond formation. As a result, novel 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides **f1-32** were obtained.

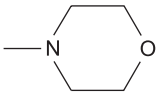
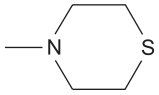
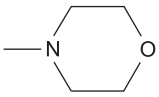
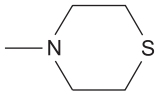
The purity and structures of the compounds synthesized were confirmed by ^{1}H NMR spectroscopy data (Tab. 2). The isolated yields are presented in Tab. 1. The lack of the NH_2 group in intermediate products in their ^{1}H NMR-spectra indicated the completeness of the cyclization reaction of imidazole into oxadiazole. The ^{1}H NMR-spectra of 2-[(1,2,4-oxadiazol-5-yl)-

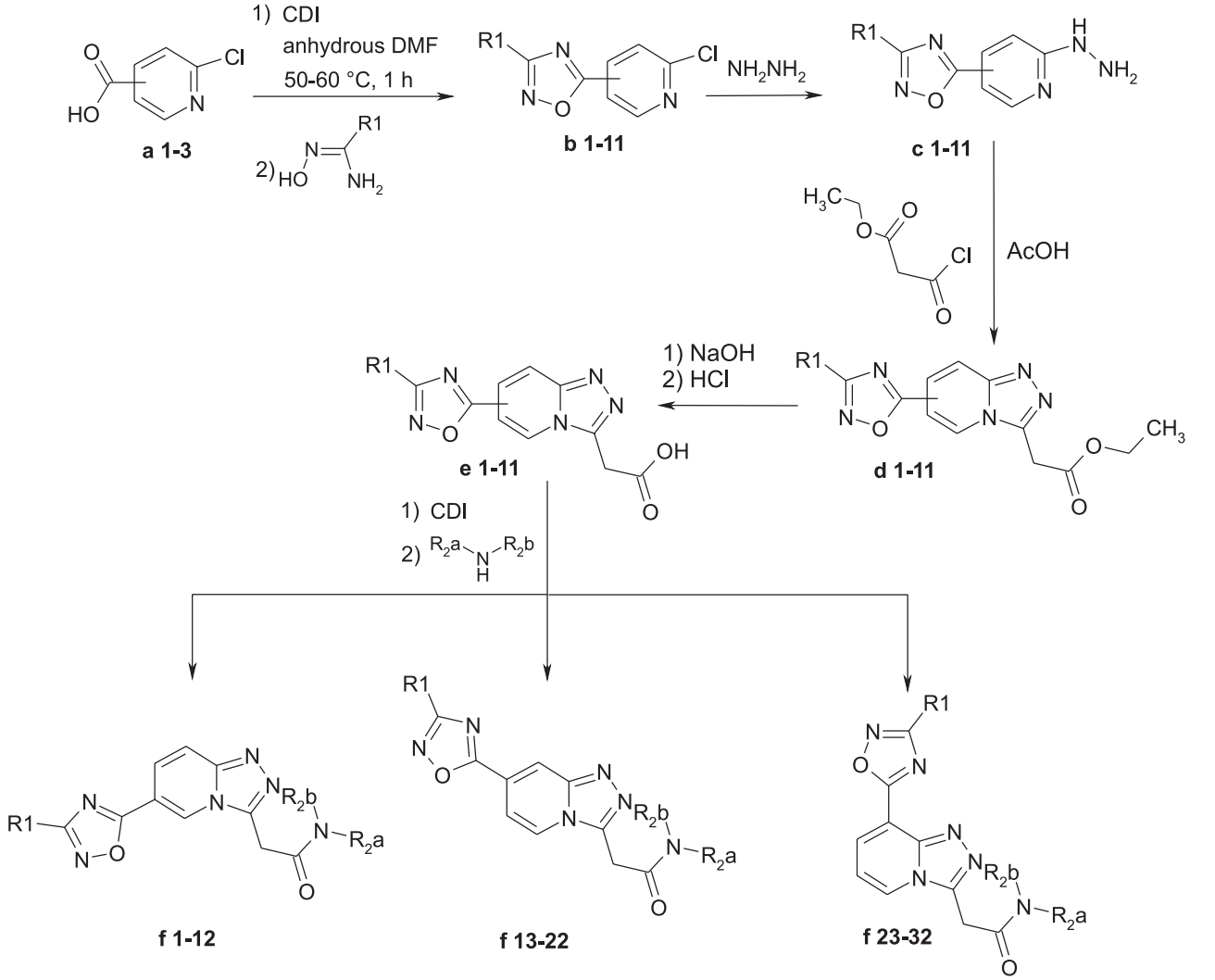
Table 1

The physicochemical properties of compounds **f1-32** synthesized

Compound, No.	R_1	R_{2a}, R_{2b}	Molecular formula, Mw.	Yield, %	M. p., °C
1	2	3	4	5	6
f1	Me	H, 2-MePh	$C_{18}H_{16}N_6O_2$ 348.37	60	147-149
f2	Et	H, Ph	$C_{18}H_{16}N_6O_2$ 348.37	65	165-167
f3	n-Pr	H, Ph	$C_{19}H_{18}N_6O_2$ 362.39	75	163-165
f4	n-Pr	H, 2-MePh	$C_{20}H_{20}N_6O_2$ 376.42	78	170-172
f5	n-Pr	H, 4-FPh	$C_{19}H_{17}FN_6O_2$ 380.38	80	185-187
f6	n-Pr	H, 2-ClPh	$C_{19}H_{17}ClN_6O_2$ 396.84	72	132-134
f7	n-Pr	H, 3F-4MePh	$C_{20}H_{19}FN_6O_2$ 394.41	85	184-186
f8	n-Pr		$C_{17}H_{20}ClN_6O_2S$ 372.45	67	138-140
f9	n-Pr	H, 3,4-diMePh	$C_{21}H_{22}N_6O_2$ 390.45	85	164-166
f10	n-Pr	H, 3,5-diMePh	$C_{21}H_{22}N_6O_2$ 390.45	86	165-167
f11	n-Pr	H, 2-FPh	$C_{19}H_{17}FN_6O_2$ 380.38	82	143-145
f12	n-Pr	H, 2-F-5MePh	$C_{20}H_{19}FN_6O_2$ 394.41	90	145-147
f13	c-Pr	H, 2-EtPh	$C_{21}H_{20}N_6O_2$ 388.43	87	182-184
f14	c-Pr	H, 2,3-diMePh	$C_{21}H_{20}N_6O_2$ 388.43	85	220-222
f15	c-Pr	H, 2-OMePh	$C_{20}H_{18}N_6O_3$ 390.40	85	121-131
f16	c-Pr	H, 4-OMePh	$C_{20}H_{18}N_6O_3$ 390.40	86	229-231
f17	c-Pr	H, 2-Me-4-FPh	$C_{20}H_{17}FN_6O_2$ 392.39	75	230-232
f18	i-Pr	H, 2-EtPh	$C_{21}H_{22}N_6O_2$ 390.44	67	165-167
f19	i-Pr	H, 2,3-diMePh	$C_{21}H_{22}N_6O_2$ 390.44	70	214-216
f20	i-Pr	H, 2-OMePh	$C_{20}H_{20}N_6O_3$ 392.42	67	144-146
f21	i-Pr	H, 4-OMePh	$C_{20}H_{20}N_6O_3$ 392.42	75	225-227
f22	i-Pr	H, 2-Me-4-FPh	$C_{20}H_{19}FN_6O_2$ 394.41	78	203-205
f23	n-Pr	H, 4-MePh	$C_{20}H_{20}N_6O_2$ 376.42	79	209 dec
f24	n-Pr	H, 3-FPh	$C_{19}H_{17}FN_6O_2$ 380.38	85	186 dec

Continuation of Table 1

1	2	3	4	5	6
f25	n-Pr	H, 3-F-4MePh	$C_{20}H_{19}FN_6O_2$ 394.41	80	211 dec
f26	n-Pr		$C_{17}H_{20}N_6O_3$ 356.38	65	237 dec
f27	n-Pr		$C_{17}H_{20}N_6O_2S$ 372.44	72	193-195
f28	c-Pr	H, 4-MePh	$C_{20}H_{18}N_6O_2$ 374.40	72	265 dec
f29	c-Pr	H, 3-FPh	$C_{19}H_{15}FN_6O_2$ 378.36	85	222 dec
f30	c-Pr	H, 3-F-4MePh	$C_{20}H_{17}FN_6O_2$ 392.39	82	237 dec
f31	c-Pr		$C_{17}H_{18}N_6O_3$ 354.37	71	255 dec
f32	c-Pr		$C_{17}H_{18}N_6O_2S$ 370.43	70	233 dec



Scheme. The reaction scheme of novel [[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides with an 1,2,4-oxadiazol cycle in positions 6, 7 and 8

Table 2

The ^{1}H NMR data of compounds f (1-32) synthesized

Compound, No.	^{1}H NMR (δ, ppm)
1	2
f1	2.30 (s, 3H, CH_3); 2.5 (s, 3H, CH_3); 4.0 (s, 2H, CH_2); 7.05 (t, 1H, Ar-H); 7.10-7.20 (m, 2H, Ar-H); 7.50 (d, 1H, Ar-H); 7.95 (d, 1H, Ar-H); 8.18 (d, 1H, Ar-H); 9.55 (s, 1H, Ar-H); 9.70 (s, 1H, NH)
f2	1.30 (t, 3H, CH_3); 2.70-2.90 (s, 2H, CH_2); 4.0 (s, 2H, CH_2); 7.05 (t, 1H, Ar-H); 7.30 (d, 2H, Ar-H); 7.60 (d, 2H, Ar-H); 7.95 (d, 1H, Ar-H); 8.20 (d, 1H, Ar-H); 9.72 (s, 1H, Ar-H); 10.35 (s, 1H, NH)
f3	0.90 (t, 3H, CH3); 1.62-1.85 (m, 2H, CH); 2.75 (t, 2H, CH2); 4.0 (s, 2H, CH2); 7.0 (t, 1H, Ar-H); 7.30 (t, 2H, Ar-H); 7.60 (d, 2H, Ar-H); 7.95 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H); 10.32 (s, 1H, NH)
f4	0.95 (t, 3H, CH_3); 1.65-1.85 (m, 2H, CH_2); 2.25 (s, 3H, CH_3); 2.75 (t, 2H, CH_2); 4.05 (s, 2H, CH_2); 7.0-7.21 (m, 3H, Ar-H); 7.45 (d, 1H, Ar-H); 7.95 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H) 9.80 (s, 1H, NH)
f5	0.90 (t, 3H, CH_3); 1.6-1.85 (m, 2H, CH_2); 2.75 (t, 2H, CH_2); 4.0 (s, 2H, CH_2); 7.12 (t, 2H, Ar-H); 7.60 (t, 2H, Ar-H); 7.92 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H); 10.35 (s, 1H, NH)
f6	0.95 (t, 3H, CH_3); 1.6-1.85 (m, 2H, CH_2); 2.75 (t, 2H, CH_2); 4.15 (s, 2H, CH_2); 7.15 (t, 1H, Ar-H); 7.30 (t, 1H, Ar-H); 7.47 (d, 1H, Ar-H); 7.81 (d, 1H, Ar-H); 7.95 (d, 1H, Ar-H); 8.20 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H); 9.93 (s, 1H, NH)
f7	0.90 (t, 3H, CH_3); 1.61-1.89 (m, 2H, CH_2); 2.12 (s, 3H, CH_3); 2.75 (t, 2H, CH_2); 4.0 (s, 2H, CH_2); 7.20 (s, 2H, Ar-H); 7.50 (d, 1H, Ar-H); 7.95 (d, 1H, Ar-H); 8.12 (d, 1H, Ar-H); 9.70 (s, 1H, Ar-H); 10.42 (s, 1H, NH)
f8	0.92 (t, 3H, CH_3); 1.60-1.85 (m, 2H, CH_2); 2.45-2.69 (m, 4H, $2CH_2$); 2.75 (t, 2H, CH_2); 3.61-3.88 (m, 4H, 2CH2); 4.05 (s, 2H, CH2); 7.95 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.70 (s, 1H, Ar-H)
f9	0.95 (t, 3H, CH_3); 1.62-1.82 (m, 2H, CH_2); 2.12 (s, 6H, $2CH_3$); 2.72 (t, 2H, CH_2); 4.0 (s, 2H, CH_2); 7.0 (d, 1H, Ar-H); 7.31 (d, 2H, Ar-H); 7.91 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H); 10.11 (s, 1H, NH)
f10	0.95 (t, 3H, CH_3); 1.62-1.82 (m, 2H, CH_2); 2.15 (s, 6H, $2CH_3$); 2.72 (t, 2H, CH_2); 4.0 (s, 2H, CH_2); 6.65 (s, 1H, Ar-H); 7.19 (s, 2H, Ar-H); 7.91 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H); 10.15 (s, 1H, NH)
f11	0.95 (t, 3H, CH_3); 1.62-1.82 (m, 2H, CH_2); 2.75 (t, 2H, CH_2); 4.11 (s, 2H, CH_2); 7.09-7.33 (m, 3H, Ar-H); 7.80 (d, 1H, Ar-H); 7.92 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.65 (s, 1H, Ar-H); 10.15 (s, 1H, NH)
f12	0.95 (t, 3H, CH_3); 1.62-1.82 (m, 2H, CH_2); 2.22 (s, 3H, CH_3); 2.75 (t, 2H, CH_2); 4.10 (s, 2H, CH_2); 6.93 (d, 1H, Ar-H); 7.12 (t, 1H, Ar-H); 7.71 (d, 1H, Ar-H); 7.92 (d, 1H, Ar-H); 8.15 (d, 1H, Ar-H); 9.70 (s, 1H, Ar-H); 10.05 (s, 1H, NH)
f13	0.95-1.11 (m, 4H, $2CH_2$); 1.20 (t, 3H, CH_3); 2.17-2.28 (m, 1H, CH); 2.65 (qr, 2H, CH_2); 4.50 (s, 2H, CH_2); 7,09-7.28 (m, 3H, Ar-H); 7.38 (d, 1H, Ar-H); 7.48 (d, 1H, Ar-H); 8.41 (s, 1H, Ar-H); 8.67 (d, 1H, Ar-H); 9.75 (s, 1H, NH)
f14	1.01-1.20 (m, 4H, $2CH_2$); 2.30 (s, 3H, CH_3); 2.09 (s, 3H, CH_3); 2.17-2.25 (m, 1H, CH); 4.45 (s, 2H, CH_2); 7.0 (qr, 2H, Ar-H); 7.15 (d, 1H, Ar-H); 7.45 (d, 1H, Ar-H); 8.40 (s, 1H, Ar-H); 8.65 (d, 1H, Ar-H); 9.80 (s, 1H, NH)
f15	1.01-1.21 (m, 4H, $2CH_2$); 2.18-2.28 (m, 1H, CH); 3.90 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 6.85 (t, 1H, Ar-H); 7.0-7.12 (m, 2H, Ar-H); 7.42 (d, 1H, Ar-H); 7.91 (d, 1H, Ar-H); 8.42 (s, 1H, Ar-H); 8.68 (d, 1H, Ar-H); 9.71 (s, 1H, NH)
f16	1.01-1.20 (m, 4H, $2CH_2$); 2.17-2.28 (m, 1H, CH); 3.71 (s, 3H, CH_3); 4.41 (s, 2H, CH_2); 6.82 (d, 2H, Ar-H); 7.48 (t, 3H, Ar-H); 8.42 (s, 1H, Ar-H); 8.71 (d, 1H, Ar-H); 10.25 (s, 1H, NH)
f17	1.01-1.20 (m, 4H, $2CH_2$); 2.12-2.22 (m, 1H, CH); 2.29 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 6.89-7.05 (m, 2H, Ar-H); 7.38 (t, 1H, Ar-H); 7.48 (d, 1H, Ar-H); 8.42 (s, 1H, Ar-H); 8.67 (d, 1H, Ar-H); 9.75 (s, 1H, NH)
f18	1.15 (t, 3H, CH_3); 1.40 (d, 6H, $2CH_3$); 2.65 (qr, 2H, CH_2); 3.10-3.20 (m, 1H, CH); 4.49 (s, 2H, CH_2); 7.10-7.25 (m, 3H, Ar-H); 7.40 (t, 1H, Ar-H); 7.56 (d, 1H, Ar-H); 8.45 (s, 1H, Ar-H); 8.67 (d, 1H, Ar-H); 9.78 (s, 1H, NH)
f19	1.38 (d, 6H, $2CH_3$); 2.11 (s, 3H, CH_3); 2.29 (s, 3H, CH_3); 3.10-3.20 (m, 1H, CH); 4.45 (s, 2H, CH_2); 6.91-7.05 (qr, 2H, Ar-H); 7.19 (d, 1H, Ar-H); 7.52 (d, 1H, Ar-H); 8.45 (s, 1H, Ar-H); 8.71 (d, 1H, Ar-H); 9.82 (s, 1H, NH)
f20	1.35 (d, 6H, $2CH_3$); 3.10-3.20 (m, 1H, CH); 3.90 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 6.85 (t, 1H, Ar-H); 7.0-7.10 (m, 2H, Ar-H); 7.51 (d, 1H, Ar-H); 7.92 (d, 1H, Ar-H); 8.47 (s, 1H, Ar-H); 8.75 (d, 1H, Ar-H); 9.72 (s, 1H, NH)
f21	1.35 (d, 6H, $2CH_3$); 3.10-3.20 (m, 1H, CH); 3.72 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 6.83 (d, 2H, Ar-H); 7.45 (t, 3H, Ar-H); 8.47 (s, 1H, Ar-H); 8.73 (d, 1H, Ar-H); 10.28 (s, 1H, NH)
f22	1.35 (d, 6H, $2CH_3$); 2.25 (s, 3H, CH_3); 3.10-3.20 (m, 1H, CH); 4.45 (s, 2H, CH_2); 6.86-7.05 (m, 2H, Ar-H); 7.0 (qr, 1H, Ar-H); 7.51 (d, 1H, Ar-H); 8.47 (s, 1H, Ar-H); 8.71 (d, 1H, Ar-H); 9.80 (s, 1H, NH)
f23	1.01 (t, 3H, CH_3); 1.75-1.91 (m, 2H, CH_2); 2.25 (s, 3H, CH_3); 2.8 (t, 2H, CH_2); 4.45 (s, 2H, CH_2); 7.05-7.3 (m, 3H, Ar-H); 7.45 (dd, 2H, Ar-H); 8.25 (d, 1H, Ar-H); 8.85 (d, 1H, Ar-H); 10.35 (s, 1H, NH)

Continuation of Table 2

1	2
f24	1.01 (t, 3H, CH_3); 1.75-1.91 (m, 2H, CH_2); 2.75 (t, 2H, CH_2); 4.45 (s, 2H, CH_2); 6.72-6.89 (m, 1H, Ar-H); 7.15-7.35 (m, 3H, Ar-H); 7.55 (dd, 1H, Ar-H); 8.27 (d, 1H, Ar-H); 8.82 (d, 1H, Ar-H); 10.61 (s, 1H, NH)
f25	1.01 (t, 3H, CH_3); 1.75-1.91 (m, 2H, CH_2); 2.18 (s, 3H, CH_3); 2.8 (t, 2H, CH_2); 4.45 (s, 2H, CH_2); 7.09-7.27 (m, 3H, Ar-H); 7.45 (dd, 1H, Ar-H); 8.25 (d, 1H, Ar-H); 8.82 (d, 1H, Ar-H); 10.52 (s, 1H, NH)
f26	1.01 (t, 3H, CH_3); 1.75-1.91 (m, 2H, CH_2); 2.75 (t, 2H, CH_2); 3.40-3.75 (m, 8H, $4CH_2$); 4.47 (s, 2H, CH_2); 7.15 (dd, 1H, Ar-H); 8.22 (d, 1H, Ar-H); 8.61 (d, 1H, Ar-H)
f27	1.01 (t, 3H, CH_3); 1.77-1.92 (m, 2H, CH_2); 2.58-2.79 (m, 4H, $2CH_2$); 3.70-3.92 (m, 4H, $2CH_2$); 4.50 (s, 2H, CH_2); 7.15 (dd, 1H, Ar-H); 8.22 (d, 1H, Ar-H); 8.61 (d, 1H, Ar-H)
f28	1.02-1.20 (m, 4H, CH_2); 2.15-2.25 (m, 1H, CH); 2.35 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 7.01-7.31 (m, 3H, Ar-H); 7.45 (dd, 2H, Ar-H); 8.20 (d, 1H, Ar-H); 8.78 (d, 1H, Ar-H); 10.31 (s, 1H, NH)
f29	1.02-1.20 (m, 4H, $2CH_2$); 2.19-2.30 (m, 1H, CH); 4.45 (s, 2H, CH_2); 6.76-6.89 (m, 1H, Ar-H); 7.15-7.35 (m, 3H, Ar-H); 7.55 (dd, 1H, Ar-H); 8.22 (d, 1H, Ar-H); 8.81 (d, 1H, Ar-H); 10.63 (s, 1H, NH)
f30	1.02-1.20 (m, 4H, $2CH_2$); 2.20-2.32 (m, 1H, CH); 2.15 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 7.10-7.29 (m, 3H, Ar-H); 7.43 (dd, 1H, Ar-H); 8.20 (d, 1H, Ar-H); 8.77 (d, 1H, Ar-H); 10.52 (s, 1H, NH)
f31	1.02-1.20 (m, 4H, $2CH_2$); 2.17-2.30 (m, 1H, CH); 3.40-3.75 (m, 8H, $4CH_2$); 4.45 (s, 2H, CH_2); 7.15 (dd, 1H, Ar-H); 8.18 (d, 1H, Ar-H); 8.61 (d, 1H, Ar-H);
f32	1.02-1.20 (m, 4H, $2CH_2$); 2.17-2.30 (m, 1H, CH); 2.58-2.79 (m, 4H, $2CH_2$); 3.70-3.92 (m, 4H, $2CH_2$); 4.50 (s, 2H, CH_2); 7.15 (dd, 1H, Ar-H); 8.22 (d, 1H, Ar-H); 8.61 (d, 1H, Ar-H)

[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides **f1-32** were characterized by the presence of the signals for three protons of the aromatic nucleus. Three protons in the aromatic nucleus for compounds **f1-12** with an 1,2,4-oxadiazol cycle in position 6 were observed as a doublet, a doublet and a singlet at range from 7.92 to 9.72 ppm; for compounds **f13-22** with an 1,2,4-oxadiazol cycle in position 7 as a doublet, a singlet and a doublet at 7.45-8.75 ppm; for compounds **f23-32** with an 1,2,4-oxadiazol cycle in position 8 as two doublets and one doublet doublet at **7**.15-8.85 ppm. The two-proton singlet of the CH_2-group acetamides **f1-32** was observed at 4.0-4.50 ppm. The ^{1}H NMR-spectra of compounds **f1-7**, **f9-25**, **f13-22** and **f28-30** were also characterized by the presence of NH-group proton signals at 9.70-10.63 ppm.

The antimicrobial screening was performed by CO-ADD (the Community for Antimicrobial Drug Discovery) funded by the Wellcome Trust (UK) and the University of Queensland (Australia). The growth inhibition was measured against 5 bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and 2 fungi: *Candida albicans* and *Cryptococcus neoformans*. Unfortunately, the compounds deemed active in the Primary Screen (≤ 32 μg/mL) were not confirmed hits (≤ 16 μg/mL) in the dose response assay; therefore, further development was not prioritized.

Experimental part

Melting points were measured using an open capillary tube. The ^{1}H NMR-spectra were recorded on a Varian Gemini-300 (300 MHz) spectrometer. For all NMR spectra, DMSO-d_6 was used as a solvent; chemical shifts were in ppm, the internal standard was TMS. Thin-layer chromatography was performed on Silufol UV254 aluminum plates pre-coated with silica gel.

Starting compounds 2-chloropyridine-3-, 2-chloropyridine-4-, 2-chloropyridine-5-carboxylic acids **a1-3** and methylamidoxime, ethylamidoxime, N-hydroxybutyramidine, N-hydroxy-isobutyramidine, N-hydroxycyclopropanecarboxamidine were commercially available.

The general procedure for the synthesis of.

2-Chloro-[3-R_1-1,2,4-oxadiazol-5-yl]pyridine (b1-11). Dissolve 2-chloropyridine carboxylic acid **a1-3** (1 mmol) in anhydrous DMF (2 ml), and add CDI (1.1 mmol). Heat the mixture at 70-80 °C for 30 min (TLC control). Then add an excess of the corresponding amidoxime (1.1 mmol), stir and heat the reaction mixture at 70-90 °C till the end of the reaction (TLC control). Then cool the solution to an ambient temperature and dilute with the mixture of i-propanol:water (50 : 50). Filter the precipitate formed, wash three times with the mixture of i-propanol: water (50 : 50) and dry. Yield – 60-70 %.

2-Hydrazine-[3-R_1-1,2,4-oxadiazol-5-yl]pyridine (c1-11). Dissolve the corresponding 2-chloro-[3-R_1-1,2,4-oxadiazol-5-yl]pyridine **b1-11** (1 mmol) in dioxane (5 ml), then add dropwise hydrazine hydrate (5 mmol) with vigorous stirring. Heat the reaction mixture at 40-50 °C till the end of the reaction (TLC control). Then cool the solution to an ambient temperature and dilute with water. Filter the precipitate formed, wash three times with water and dry. Yield – 68-75%.

Ethyl 2-[(3-R_1-1,2,4-oxadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyridine-3-yl]acetate (d1-11). Add ethyl malonylchloride (1 mmol) to the solution of the corresponding compound **c1-11** (1 mmol) in ace-

tic acid (5 ml). Reflux the mixture for 2h (TLC control). Then cool the solution to an ambient temperature and dilute with water. Filter the precipitate formed, wash three times with water and dry. Yield – 73-82 %.

2-[(3-R_1-1,2,4-Oxadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyridine-3-yl]acetic acid (e1-11). Mix the solution of the corresponding compound **d1-11** (1 mmol) with sodium hydroxide (2 mmol) and dissolve in an aqueous methanol (10 ml). Stir the mixture at room temperature for 12 h (TLC control). Then cool the mixture to an ambient temperature, dilute with water, and extract with dichloromethane to remove impurities. Acidify the aqueous layer with hydrochloric acid to a slightly acidic environment, i.e. pH 5.5. Filter the precipitate formed, wash three times with water and dry. Yield – 65-80 %.

2-[(1,2,4-Oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides (f1-32). To the solution of the corresponding compound **e1-11** (1 mmol) in 2 ml of dioxane add CDI (1 mmol) and stir at room temperature for 1h. After that add the corresponding amine and heat at 60-70 °C by stirring from 1 to 6 h (TLC control). Then cool the solution to an ambient temperature and dilute with water. Filter the precipitate formed, wash with water and dry. The final compounds were obtained in good yields (60-90 %).

Conclusions

1. In this study an efficient and convenient approach for the synthesis of new 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides has been described; it can be used as an applicable method for the synthesis of diverse functionalized [1,2,4]triazolo[4,3-a]pyridine derivatives. Such type of scaffold can possess a wide range of the pharmacological activity.

2. The *in silico* screening has demonstrated the potential inhibitory activity of the compounds against Cytochrome P 450 (CYP) and 5-HT2C (G-protein coupled receptor).

3. The *in vitro* screening of the antibacterial and antifungal activity has revealed active compounds in the Primary Screen, which were not confirmed hits in the dose response assay. Thus, the search of new biologically active substances among [[1,2,4]triazolo [4,3-a]pyridine-3-yl]acetamide derivatives will be continued.

Conflict of interests: authors have no conflict of interests to declare.

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