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SYNTHESIS AND THE BIOLOGICAL ACTIVITY OF 4-HYDROXY-2,2-DIOXO-1H-2λ^6,1-BENZOTHIAZIN-3-CARBOXYLIC ACIDS TRIFLUOROMETHYL-SUBSTITUTED ANILIDES

L.A.Petrushova, I.V.Ukrainets, S.P.Dzyubenko*, L.A.Grinevich

National University of Pharmacy
61002, Kharkiv, 53 Pushkinska str. E-mail: uiv-2@mail.ru
* National Pirogov Memorial Medical University

Key words: anilides; 2,1-benzothiazines; synthesis; trifluoromethyl group; analgesic activity; diuretic properties

In order to reveal the regularities of the "structure – biological activity" relationship by interaction of esters of 1-R-4-hydroxy-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxylic acids and trifluoromethyl substituted anilines in boiling xylene with good yields and purity the corresponding N-aryl-4-hydroxy-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxamides have been synthesized. The structure of the compounds obtained has been confirmed by the data of elemental analysis and NMR ^{1}H spectroscopy. It has been shown that the presence of trifluoromethyl groups having the powerful electron-withdrawing properties affects the position of signals of the aniline moiety protons: comparing to the spectra of the model methyl derivatives they undergo a significant paramagnetic shift. According to the results of the pharmacological studies conducted it has been found that the replacement of methyl groups in the anilide moiety of 1-R-4-hydroxy-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxamides to trifluoromethyl has a different effect on their analgesic activity, which can remain at the original level, be completely lost or significantly increase. However, N-aryl-4-hydroxy-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxamides definitely lose the ability to influence in any way on the excretory renal function after this chemical modification.

СИНТЕЗ ТА БІОЛОГІЧНА АКТИВНІСТЬ ТРИФТОРОМЕТИЛЗАМІЩЕНИХ АНІЛІДІВ 4-ГІДРОКСИ-2,2-ДІОКСО-1H-2λ^6,1-БЕНЗОТІАЗИН-3-КАРБОНОВИХ КИСЛОТ

Л.О.Петрушова, І.В.Українець, С.П.Дзюбенко, Л.О.Гріневич

Ключові слова: *аніліди; 2,1-бензотіазини; синтез; трифторометильна группа; аналгетична активність; діуретичні властивості*

З метою виявлення закономірностей зв'язку «структура – біологічна активність» взаємодією естерів 1-R-4-гідрокси-2,2-діоксо-1H-2λ^6,1-бензотіазин-3-карбонових кислот та трифторометилзаміщених анілінів у киплячому ксилолі з добрими виходами і чистотою синтезовані відповідні N-арил-4-гідрокси-2,2-діоксо-1H-2λ^6,1-бензотіазин-3-карбоксаміди. Будова одержаних сполук доведена даними елементного аналізу та спектроскопії ЯМР ^{1}H. Показано, що присутність трифторометильних груп, які виявляють сильні електроноакцепторні властивості, позначається на положенні сигналів протонів анілідних фрагментів – порівняно зі спектрами модельних метильних похідних вони піддаються суттєвому парамагнітному зсуву. За результатам проведених фармакологічних випробовувань знайдено, що заміна метильних груп в анілідному фрагменті 1-R-4-гідрокси-2,2-діоксо-1H-2λ^6,1-бензотіазин-3-карбоксамідів на трифторометильні по-різному впливає на їх аналгетичну активність, яка може залишатися на вихідному рівні, повністю втрачатися або ж значно посилюватися. А ось здатність впливати будь-яким чином на сечовидільну функцію нирок N-арил-4-гідрокси-2,2-діоксо-1H-2λ^6,1-бензотіазин-3-карбоксаміди після зазначеної хімічної модифікації однозначно втрачають.

СИНТЕЗ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ ТРИФТОРМЕТИЛЗАМЕЩЕННЫХ АНИЛИДОВ 4-ГИДРОКСИ-2,2-ДИОКСО-1H-2λ^6,1-БЕНЗОТИАЗИН-3-КАРБОНОВЫХ КИСЛОТ

Л.А.Петрушова, И.В.Украинец, С.П.Дзюбенко, Л.А.Гриневич

Ключевые слова: *анилиды; 2,1-бензотиазины; синтез; трифторметильная группа; анальгетическая активность; диуретические свойства*

С целью выявления закономерностей связи «структура – биологическая активность» взаимодействием сложных эфиров 1-R-4-гидрокси-2,2-диоксо-1H-2λ^6,1-бензотиазин-3-карбоновых кислот и трифторметилзамещенных анилинов в кипящем ксилоле с хорошими выходами и чистотой синтезированы соответствующие N-арил-4-гидрокси-2,2-диоксо-1H-2λ^6,1-бензотиазин-3-карбоксамиды. Строение полученных соединений подтверждено данными элементного анализа и спектроскопии ЯМР ^{1}H. Показано, что присутствие обладающих мощными электроноакцепторными свойствами трифторметильных групп сказывается на положении сигналов протонов анилидных фрагментов – по сравнению со спектрами модельных метильных производных они претерпевают существенный парамагнитный сдвиг. По результатам проведенных фармакологических испытаний найдено, что замена метильных групп в анилидном фрагменте 1-R-4-гидрокси-2,2-диоксо-1H-2λ^6,1-бензотиазин-3-карбоксамидов на трифторметильные по-разному влияет на их анальгетическую активность, которая может оставаться на исходном уровне, полностью теряться или значительно усиливаться. А вот способность влиять каким-либо образом на мочевыделительную функцию почек N-арил-4-гидрокси-2,2-диоксо-1H-2λ^6,1-бензотиазин-3-карбоксамиды после указанной химической модификации однозначно утрачивают.

Due to its powerful electron-withdrawing properties the trifluoromethyl group is able to enhance reactivity of various electrophilic substrates and affect regioselectivity of reactions involving nucleophiles [1-2]. The presence of this substituent often allows to carry out chemical transformations easily that in its absence do not proceed even in the most rigid conditions; thus, it is widely used in modern preparative organic synthesis. By its intensive development chemistry of trifluoromethylated compounds is obliged to the complex of the desirable properties acquired, such as resistance to external factors – temperature, sunlight, oxidation, etc.

The unique effect of the trifluoromethyl substituents on the properties of the molecule as a whole has not remained without attention of medicinal chemistry – their ability to change significantly the interaction of the active ingredient with the target molecule, peculiarities of its metabolism and other pharmacodynamic and/or pharmacokinetic characteristics has been effectively used for a long time when creating new biologically active substances [3]. As a result, the range of drugs currently used is more than three dozen drugs of different pharmacological groups containing one or even a few of the trifluoromethyl fragments in their structure [4]. It is not surprising that this methodology has not lost its significance, and it is used very widely by modern medicinal chemistry [5-12].

Taking into account these circumstances and in continuation of our studies on the methods of synthesis, chemical and biological properties of derivatives of 2,1-benzothiazines, this message is devoted to trifluoromethyl analogues of the methyl-substituted 4-hydroxy-1-methyl-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxanilides described earlier [13].

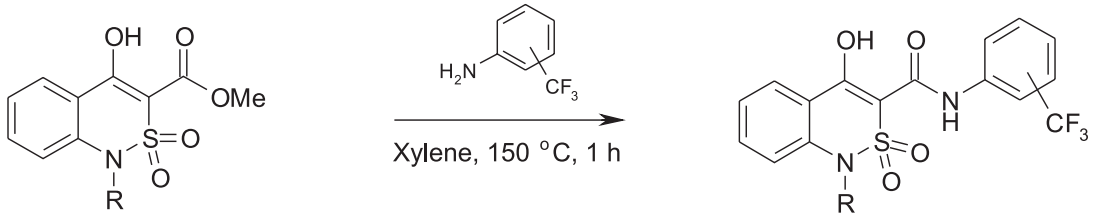
Theoretically, there are several ways of direct trifluoromethylation of organic compounds [14-21]. However, it is quite clear that to obtain the objects of the present study it is advisable to use commercially readily available monotrifluoromethylanilides; in their reaction with esters (**1**) in a boiling xylene the synthesis of the corresponding 1-R-4-hydroxy-1-methyl-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxanilides **2a-f** has been carried out with good yields and purity (Scheme).

Anilides **2a-f** are white to yellowish white crystalline substances with the narrow melting temperature range (Table 1). They are moderately soluble in DMF, DMSO and ethyl acetate at room temperature, and sparingly soluble in alcohol, are practically insoluble in water, ether and hexane, but readily soluble in hot aqueous alkaline solutions. Their structure was confirmed by elemental analysis and NMR ^{1}H spectroscopy (Tab. 1).

A powerful electron withdrawing effect exhibited by trifluoromethyl groups on the carbon atoms of arylamide moieties, and hence to the protons bound with them, is bound to be reflected in the ^{1}H NMR spectra of anilides **2a-f**. Indeed, compared with the spectra of the model methyl derivatives, resonance signals of the corresponding anilide protons in the spectra of their fluoromethyl analogues **2a-f** undergo a significant paramagnetic shift. Aromatic protons of benzothiazine rings are too far from trifluoromethyl substituents to be affected by them in such a noticeable extent. Therefore, their signals practically do not change their positions in the ^{1}H NMR spectra in going from methyl derivatives to trifluoromethyl ones (see Fig.).

Analgesic properties of the trifluoromethylanilides **2a-f** synthesized were studied in white outbred adult male rats weighing 180-200 g in full compliance with the provisions of the European Convention on Protection of Vertebrates Used for Experimental and Other Scientific Purposes and the Ukrainian Law No. 3447-IV "On protection of animals from severe treatment" (2006).

The standard model of the tail-flick thermal stimulation was used in the study. It allows identifying the central component affecting the nociceptive system in the mechanism of the analgesic effect of the substances studied [22]: the rat's tail tip was immersed in a water bath heated to 54°C, after that the latent period of the tail withdrawal (immersion) expressed in seconds was determined. The substances under research and their structurally similar reference drugs – Meloxicam and Piroxicam – were introduced orally in the form of fine aqueous suspensions stabilized with Tween-80 in the screening dose of 20 mg/kg. The control group received an equivalent amount of water with Tween-80. The analgetic effect (in %) was assessed by the change of the latent period in 1 hour after administration of the test substances.



1 **2a-f**

2: **a** R = H, 2-CF_3; **b** R = H, 3-CF_3; **c** R = H, 4-CF_3; **d** R = Me, 2-CF_3; **e** R = Me, 3-CF_3; **f** R = Me, 4-CF_3

Scheme

Table 1

Characteristics of trifluoromethyl-substituted anilides **2a-f**

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	Yield, %
		C	H	N	S		
2a	$C_{16}H_{11}F_3N_2O_4S$	49.94 / 50.00	2.80 / 2.88	7.37 / 7.29	8.26 / 8.34	181-182	86
2b	$C_{16}H_{11}F_3N_2O_4S$	49.92 / 50.00	2.95 / 2.88	7.35 / 7.29	8.23 / 8.34	226-228	88
2c	$C_{16}H_{11}F_3N_2O_4S$	50.09 / 50.00	2.97 / 2.88	7.38 / 7.29	8.25 / 8.34	245-247	92
2d	$C_{17}H_{13}F_3N_2O_4S$	51.35 / 51.26	3.37 / 3.29	6.95 / 7.03	7.96 / 8.05	157-159	85
2e	$C_{17}H_{13}F_3N_2O_4S$	51.33 / 51.26	3.34/ / 3.29	6.97 / 7.03	7.95 / 8.05	143-145	91
2f	$C_{17}H_{13}F_3N_2O_4S$	51.31 / 51.26	3.36 / 3.29	7.08 / 7.03	7.99 / 8.05	184-186	94

Seven experimental animals were involved to obtain statistically reliable results of each trifluoromethylanilide **2a-f**, reference drugs in testing and control. The results of biological tests were processed by the method of variation statistics using Student's t-criterion.

The comparative analysis of the experimental data given in Tab. 3 with the results of the previous studies [13] shows that the replacement of the methyl group in the anilide moiety of 1-R-4-hydroxy-2,2-dioxo-1H-2λ⁶,1-benzothiazin-3-carboxamides to the trifluoromethyl one affects quite ambiguously the ability to suppress the pain reaction. In the case of anilide **2a** it has no effect on this ability, but in the cases of anilides **2b, d, f** it leads to its complete loss. At the same time there are some positive examples, in particular, trifluoromethyl substituted anilides **2c,e** show a significant increase in activity compared to their methyl analogues [13]. According to the level of the analgesic effect revealed they significantly exceed Piroxicam, and are almost as good as Meloxicam.

The effect of trifluoromethylanilides **2a-f** on the urinary function of the kidneys was studied according to the classical method [23] on white outbred rats of both sexes weighing 180-200 g in parallel and compared with Hydrochlorothiazide. All animals received water load in the amount of 25 ml/kg by gavage. The compounds studied were administered orally in the form of a thin aqueous suspension stabilized with Tween-80 in the screening dose of 10 mg/kg, and Hydrochlorothiazide was taken in its effective dose (40 mg/kg). The control group received only simi-

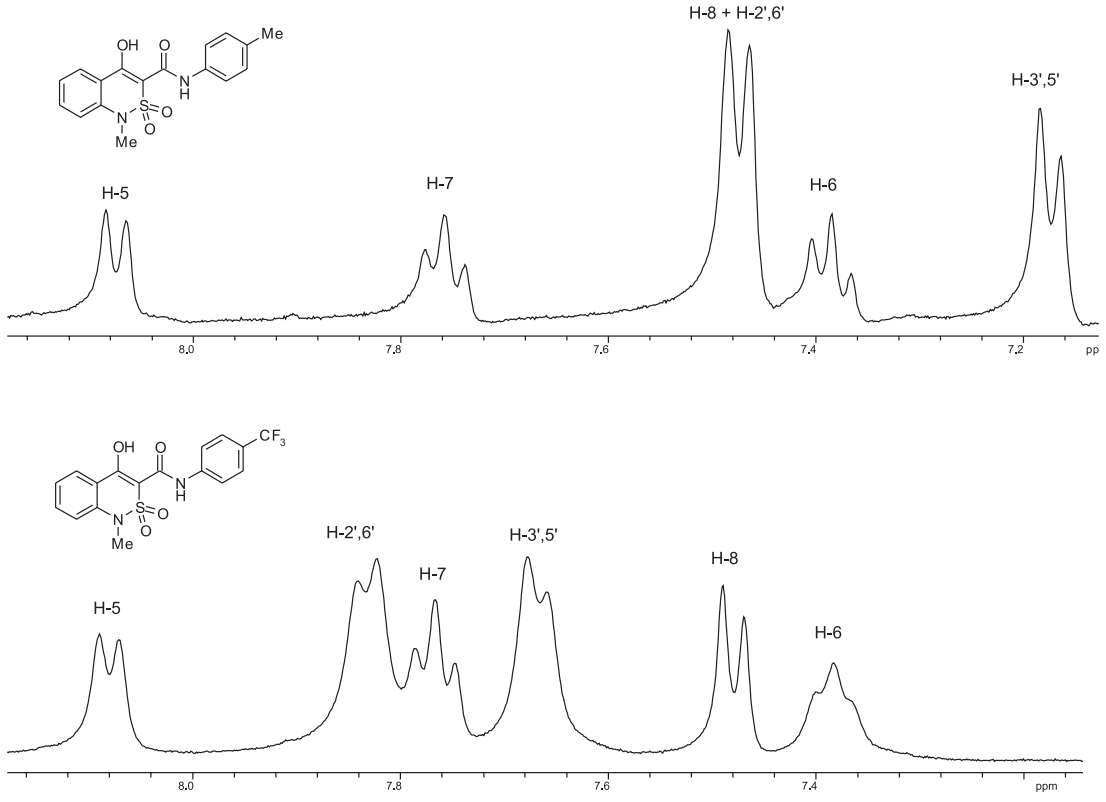


Fig. Fragments of the ^{1}H NMR spectra (signals of aromatic protons) of 4-methyl anilide of 4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazin-3-carboxylic acid [13] and its 4-trifluoromethyl substituted analogue **2f**.

Table 2

^{1}H NMR Spectra of trifluoromethyl-substituted anilides **2a-f**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
2a	15.15 (1H, br. s, OH); 12.28 (1H, br. s, SO_2NH); 9.63 (1H, s, CONH); 8.03-7.98 (2H, m, H-5.6′); 7.75 (1H, d, *J* = 7.8, H-3′); 7.70 (1H, t, *J* = 7.7, H-4′); 7,64 (1H, t, *J* = 7.7, H-7); 7.46 (1H, t, *J* = 7.7, H-5′); 7.28 (1H, t, *J* = 7.7, H-6); 7.22 (1H, d, *J* = 8.3, H-8)
2b	15.18 (1H, br. s, OH); 12.30 (1H, br. s, SO_2NH); 9.71 (1H, s, CONH); 8.06 (1H, s, H-2′); 8.01 (1H, d, *J* = 7.9, H-5); 7.80 (1H, d, *J* = 7.9, H-6′); 7.63 (1H, t, *J* = 7.6, H-7); 7.58 (1H, t, *J* = 7.9, H-5′); 7.47 (1H, d, *J* = 7.5, H-4′); 7.28 (1H, t, *J* = 7.6, H-6); 7.21 (1H, d, *J* = 8.3, H-8)
2c	15.16 (1H, br. s, OH); 12.28 (1H, br. s, SO_2NH); 9.79 (1H, s, CONH); 8.00 (1H, d, *J* = 7.9, H-5); 7.84 (2H, d, *J* = 8.0, H-2′,6′); 7.67 (2H, d, *J* = 8.0, H-3′,5′); 7.62 (1H, t, *J* = 7.7, H-7); 7.27 (1H, t, *J* = 7.6, H-6); 7.21 (1H, d, *J* = 8.1, H-8)
2d	14.93 (1H, br. s, OH); 9.66 (1H, s, CONH); 8.09 (1H, d, *J* = 7.9, H-5); 7.99 (1H, d, *J* = 8.0, H-6′); 7.78 (1H, t, *J* = 7.9, H-4′); 7.74 (1H, d, *J* = 7.9, H-3′); 7.70 (1H, t, *J* = 7.9, H-7); 7.49 (1H, d, *J* = 8.4, H-8); 7.44 (1H, t, *J* = 7.9, H-5′); 7.39 (1H, t, *J* = 7.5, H-6); 3.51 (3H, s, N-Me)
2e	14.98 (1H, br. s, OH); 9.82 (1H, s, CONH); 8.09 (1H, d, *J* = 7.9, H-5); 8.05 (1H, s, H-2′); 7.81 (1H, d, *J* = 7.9, H-6′); 7.76 (1H, t, *J* = 7.8, H-7); 7.59 (1H, t, *J* = 7.9, H-5′); 7.50-7.45 (2H, m, H-8.4′); 7.38 (1H, t, *J* = 7.6, H-6); 3.50 (3H, s, N-Me)
2f	15.02 (1H, br. s, OH); 9.80 (1H, s, CONH); 8.08 (1H, d, *J* = 7.9, H-5); 7.83 (2H, d, *J* = 8.0, H-2′,6′); 7.77 (1H, t, *J* = 7.7, H-7); 7.66 (2H, d, *J* = 8.0, H-3′,5′); 7.48 (1H, d, *J* = 8.3, H-8); 7.38 (1H, t, *J* = 7.4, H-6); 3.50 (3H, s, N-Me)

lar amount of water with Tween-80. After that the experimental animals were placed in "metabolism cages". The amount of urine excreted by the animals within 4 hours was the indicator of the intensity of uropoiesis. The results obtained (Tab. 4) show that when transferring from the methyl derivatives to trifluoromethyl ones the ability of *N*-aryl-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazin-3-carboxamides to increase or, conversely, inhibit diuresis is completely lost. Therefore, in the search for new potential diuretics our chemical modification is impractical.

Experimental Part

^{1}H NMR spectra of the compounds synthesized were recorded on a Varian Mercury-400 device (with the operating frequency of 400 MHz) in the solution of DMSO-d_6, the TMS internal standard. Elemental analysis was performed by an EuroVector EA-3000 microanalyzer. Melting points were determined in the capillary on a SMP10 Stuart digital analyzer of the melting point. The initial esters of 1-R-4-hydroxy-1-methyl-2,2-dioxo-1H-2λ^6,1-benzothiazin-3-carboxylate (**3**) were synthesized by the method described earlier [24].

Trifluromethyl anilides of 1-R-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazin-3-carboxylic acids (2a-f). General Procedure. Thoroughly stir the mixture of 0.01 mol of ester **1** and 0.01 mol of the corresponding trifluoromethyl substituted aniline in 5 ml of a dry xylene and heat on a metal bath at 150°C for 1 h. Cool the reaction mixture, add 5 ml of ethanol and allow to stand for several hours at room temperature. Filter the resulting crystals of trifluoromethylanilide **2a-f**,

Table 3

The analgesic properties of anilides **2a-f** on the "tail-flick" model in rats

Compound	R	Position CF_3	The latent period in 1 h after administration of the compounds, s	Change of the latent period, compared to control, %
2a	H	2	3.14±0.11	0
2b	H	3	3.15 ±0.10	0
2c	H	4	4.84 ±0.14*	+ 54.0
2d	Me	2	3.69±0.12*	+17.6
2e	Me	3	4.50 ±0.15*	+43.2
2f	Me	4	3.40±0.12	+8.3
Meloxicam	-	-	4.91±0.17*	+56.3
Piroxicam	-	-	3.96±0.15*	+ 26.1
Control	-	-	3.14±0.14	-

* – differences were significant at p<0.05 compared to the control.

Table 4

The diuretic activity for anilides **2a-f** and Hydrochlorothiazide

Compound	Diuresis within 4 h, ml	Diuretic activity * %
2a	4.04±0.26	–5
2b	4.89±0.32	+15
2c	4.77±0.30	+12
2d	3.96±0.25	–7
2e	4.38±0.31	+3
2f	4.56±0.35	+7
Hydrochlorothiazide	6.43±0.38**	+51
Control	4.26±0.33	-

* "+" – increase, "–" – inhibition of diuresis compared to the control taken as 100%; ** – differences were significant at p<0.05 compared to the control.

wash with cold ethanol and dry. Crystallize from the mixture of DMF/ethanol.

Conclusions

1. Triflurомethyl-substituted anilides of 4-hydroxy-2,2-dioxo-1*H*-2λ⁶,1-benzothiazin-3-carboxylic acids have been synthesized in order to identify the structural and biological regularities that are important for the subsequent search for new analgesics and diuretics in a series of 2,1-benzothiazine.

2. As a result of the pharmacological screening it has been found that the presence of trifluoromethyl groups in the anilide moiety of *N*-aryl-4-hydroxy-2,2-dioxo-1H-2λ⁶,1-benzothiazin-3-carboxamides positively affects their analgesic properties, but it does not provide the diuretic activity.

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