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SYNTHESIS AND STUDY OF ANTI-INFLAMMATORY ACTIVITY OF HYDROCHLORIDES OF SUBSTITUTED PIPERAZINOPROPIOPHENONES - MANNICH BASES

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By aminomethylation of some p-substituted acetophenones and p-substituted ethanones with paraformaldehyde and substituted phenylpiperazines, the synthesis of 1-(4-substituted phenyl)-3-{4-[2(4)-substituted phenyl]piperazin-1-yl}-2-H(phenyl)propan-1-ones was carried out. The hydrochlorides of the latter were obtained for pharmacological tests. It has been revealed that β-aminoketone hydrochlorides have mild to moderate anti-inflammatory activity.

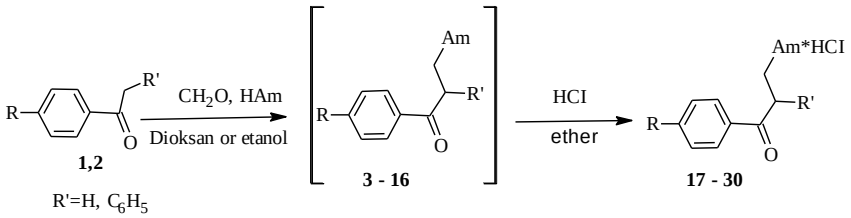
Table 1, referenses 11.

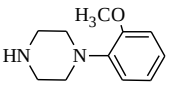
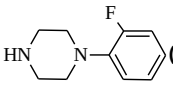
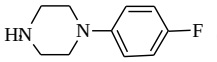
It is known that aminoketone hydrochlorides and their derivatives have a wide range of biological effects [1-6]. The aim of this study is to search for pharmacologically active compounds in a series of new β-amino ketones, and in particular, to study the anti-inflammatory activity of these compounds. The starting compounds for the synthesis were 1-(4-substituted phenyl)ethan-1-ones **1** and 1-(4-butoxyphenyl)-2-phenylethan-1-one **2**, obtained by the Friedel-Kraftz reaction from acetyl chloride or phenylacetic acid chloride with substituted benzenes [2-4]. Aminomethylation of compounds **1** and **2** with paraform-aldehyde and substituted phenylpiperazines in dioxane (pH 1-2) or ethanol (pH 8-9) gave 1-(4-substituted phenyl)-3-{4-[2(4)-substituted phenyl]piperazin-1-yl}-2-H (phenyl)propan-1-ones; some of them **3-5** are stable crystalline substances, and the other part of compounds are thick oily substances **6-16**, the action of which with an ethereal solution of hydrogen chloride afforded hydrochlorides amino ketones **17-30**.

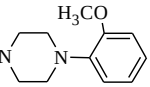
Compounds **17-30** are crystalline substances, the structure of which was confirmed by ^{1}H NMR spectroscopy and IR spectrometry data. In the IR spectra of compounds **17-30**, the absorption band of the carbonyl (C = O)

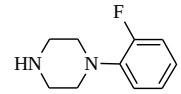
1655-1680 cm^{-1} and carbethoxy (COOEt) 1700-1720 cm^{-1} groups is observed.

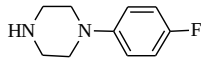
Scheme

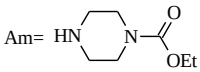


R'= C_6H_5; R=C_4H_9O; Am=  **(17),**  **(18)** ,  **(19)**

R'=H; R=OCH_3 (**20**), OC_3H_7 (**21**), izo C_3H_7 (**22**), izoOC_4H_9 (**23**), Br (**24**) , Am= 

R'=H; R=OCH_3 (**25**), izoOC_3H_7 (**26**), Am= 

R'=H; R=OCH_3 (**27**), izoOC_3H_7 (**28**), Am= 

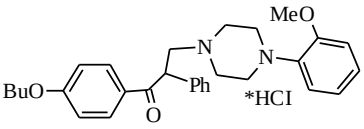
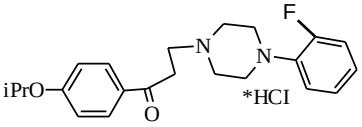
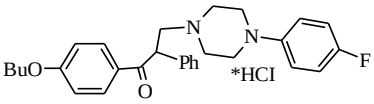
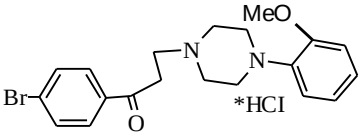
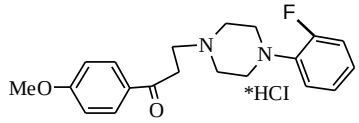
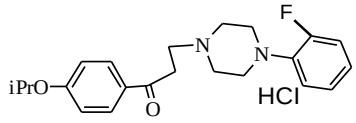
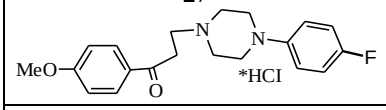
R'=H; R=OC_3H_7 (**29**), izoOC_3H_7 (**30**), Am= 

Experimental pharmacological part

The anti-inflammatory and analgesic properties of the synthesized compounds (**17-19, 24, 25, 26, 27**) were studied. Experiments were carried out on white outbred rats of both sexes weighing 100-120 *g* in a model of acute exudative inflammation caused by subplantar injection of 0.1 *ml* of 1% carrageenin solution into the rat's hind paw [10]. The test substances at doses of 5 and 25 *mg*/*kg* and the reference drug Voltaren at a dose of 10 *mg*/*kg* were administered orally 1 hour before using carrageenan. After 3 *hours*, the amount of paw edema and the pain threshold were determined. The anti-inflammatory activity of the substances was assessed by the degree of decrease in edema, the analgesic activity was assessed by the increase in the pain sensitivity threshold (in % relative to the control). The study of the anti-inflammatory effect of the compounds on chronic proliferative inflammation was carried out using the "Pellet – granuloma" model [10]. The effect of the compounds was determined by the effect on the mass of dry granulomas, which develops within 8 days around the carton as a result of its subcutaneous application. The test compounds and the known control drug indomethacin at a dose of 3 *mg*/*kg* were administered in the last 4 days of the experiment.

Table

Anti-inflammatory and analgesic activity of compounds (17-19, 24, 25, 26, 27) in the model of acute chronic inflammation in rats

Compound	Dose *mg/kg*	Inflammation suppression,%		Pain suppression,%
		Acute(single administration)	Chronic (single administration)	Acute(single administration)
17 	25	49.1*	15.,5	23.5
18 	–	38.7*	12.1	18.9
19 	–	11.7		3.3
24 	–	4.9		3.3
25 	–	5.0		4.6
26 	–	4.9		5.3
27 	–	18.5		4.8
Voltaren	10	63.2*		65.3*
Indomethacin	3	60.8	60.8*	

* P < 0.05 – in relation to control and P > 0.05 – to voltaren

Results and discussion. All studied compounds at a dose of *5 mg/kg* did not have anti-inflammatory and analgesic effects in acute inflammation. The results of studying the effect of compounds on acute and chronic inflammation, as well as their analgesic effect at a dose of *25 mg/kg*, shown in Table 1, indicate that compounds (17-19, 24, 25, 26, 27) have different activities. Moderate anti-inflammatory activity was revealed among 1-(4-butoxyphenyl)-3-{4-[2(4)-substituted phenyl]piperazin-1-yl}-2-phenylpropan-1-ones containing a 4-[2-methoxy (fluoro)phenyl]piperazine fragment (**17, 18**).

Analyzing the results obtained, a definite relationship between the chemical structure of compounds and their biological activity was revealed. So, on the basis of experimental data obtained by 3 different methods, it can be concluded that anti-inflammatory activity appears only in the series of 1-(4-butoxyphenyl)-3-{4-[2 (4)-methoxy(fluoro)phenyl]piperazin-1-yl}-2-phenylpropan-1-ones (**17-19**), that is, the presence of a phenyl fragment at position two of the amino ketone molecule plays a decisive role in the appearance of anti-inflammatory properties (**17-19**), which is confirmed by our previously proposed model pharmacophore. The data obtained indicate the expediency of searching for new, more highly effective compounds in the series of β-amino ketones.

Experimental chemistry

IR spectra were recorded on a NICOLET AVATAR 330 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Mercury VX-300 spectrometer with a resonance frequency of 300.08 MHz, in a DMSO + CF_3COOD solution; internal standard – TMS. The melting point of the obtained substances was determined on a Boetius device. The individuality of the obtained compounds was confirmed by TLC on Silufol-254 plates in the system butanol – ethanol – acetic acid – water (8:2:1:3), the developer was iodine vapor, as well as by elemental analysis data.

1-(4-Substituted phenyl)ethan-1-ones (1) and 1-(4-butoxyphenyl)-2-phenylethan-1-one (2) were obtained by the method [1-4].

Hydrochlorides of 1-(4-substituted phenyl)-3-{4-[2(4)-substituted phenyl]piperazin-1-yl}propan-1-ones (17-30). (**General production method**). A mixture of 0.1 *mol* of 1-(4-substituted phenyl)ethanone, 3.3 *g* (0.11 *mol*) of paraformaldehyde, 0.11 *mol* of amine hydrochloride and 5-6 drops of hydrochloric acid (to pH 1) in dry dioxane was heated on water bath for 8-10 *hours* at a temperature of 85-90°C. After distilling off dioxane, the residue was dissolved in water and extracted with ether (3×100 *ml*) to remove the unreacted ketone. To the aqueous layer 40% sodium hydroxide solution was added to pH 8-9 and extracted with ether (3×100 *ml*). The ether extracts were dried over dry Na_2SO_4 and ether was distilled off. To the

residue **3-16** a saturated solution of hydrogen chloride was slowly added dropwise (to pH 1 using universal indicator paper). The precipitate **17-30** was filtered off, recrystallized from abs. acetone.

1-(4-Butoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropan-1-one hydrochloride (17). Yield 48%, mp 169-170°C, Rf 0.63. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 0.97 (t, 3H, J 7.3 CH_3); 1.48 (tp, 2H, J1 7.6, J2 7.4, CH_2); 1.75 (tt, 2H, J 17.6, J2 6.4, CH_2); 2.81-3.54 (br, 9H, 4CH_2 CH); 3.81 (s, 3H, CH_3); 4.01 (t, 2H, J 6.4, CH_2), 4.01 (br, 1H, CH), 5.94 (br, 1H, CH); 6.79-6.96 (m, 6H, 6CH); 7.17-7.44 (m, 5H, 5CH, Ph); 8.02 (br.d, 2H, J 8.7, 2CH, 1.80 (br, 1H, HCl). $C_{30}H_{36}N_2O_3 \cdot HCl$.

1-(4-Butoxyphenyl)-3-[4-(2-fluorophenyl)piperazin-1-yl]-2-phenyl-propan-1-one hydrochloride (18). Yield 50%, mp 164-167°C, Rf 0.85. IR spectrum, υ, cm^{-1}: 1675 (C = O). ^{1}H NMR spectrum, δ, ppm 0.98 (t, 3H, J 7.4, CH_3); 1.48 (m, 2H, CH_2); 1.75 (m, 2H, CH_2); 2.66 (br, 5H); 2.99 (4H); 3.40 (br, 1H); 4.00 (t, 2H, J 6.4, CH_2), 4, 91 (br, 1H, CH), 6.81 (m, 6H, 6CH, Ar); 7.15 (m, 1H, CH); 7.25 (m, 2H, 2CH); 7.32 (m, 2H, 2CH); 7.25 (m, 2H, 2CH); 7.96 (d, 2H, J 8.8, 2CH), 1.82 (br, 1H, HCl). $C_{29}H_{33}FN_2O_2 \cdot HCl$.

1-(4-Butoxyphenyl)-3-[4-(4-fluorophenyl)piperazin-1-yl]-2-phenylpropan-1-one hydrochloride (19). Yield 51%, mp 177-178°C, Rf 0.65 IR spectrum, υ, cm^{-1}: 1675 (C = O) ^{1}H NMR spectrum, δ, ppm 0.97 (t, 3H, J 7.3, CH_3); 1.47 (mt, 2H, J1 7.5, J2 7, 3, CH_2); 1.74 (mt, 2H, J 17.5, J 26.4, CH_2); 2.70-3.65 (br, 9 H, 4CH_2 CH), 4.00 (t, 2H, J 6.4, CH_2); 4.00 (br, 1H, CH), 5.90 (br, 1H, CH); 6.87-6.97 (m, 6H, C_6H_4, 2CH); 7.20 (br.t, 1H, J 7.5, CH); 7.29 (br.t, 2H, J 7.5, 2CH) ; 7.40 (br.d, 2H, J 7.7, 2CH); 8.02 (d, 2H, J 8.7, 2CH), 1.81 (br, 1H, HCl). $C_{29}H_{33}FN_2O_2 \cdot HCl$.

1-(4-Methoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (20). Yield 55%, mp 181-183°C, Rf 0.56. IR spectrum, υ, cm^{-1}: 1675 (C = O). ^{1}H NMR spectrum, δ, ppm 3.34 (br, 2H, CH_2), 3.43-3.54 (m, 6H, 3CH_2), 3.67 (br.d, 2H, J 11.5, CH_2); 3.78 (t, 2H, J 7.5, CH_2); 3.87 (s, 6H, 2CH_3); 4.99 (br, 1H, HCl). 6.86-7.00 (m, 4H, 4CH); 7.00 (d, 2H, J 8.8, 2CH); 7.99 (d, 2H, J 8.8, 2CH); 11.80 (br, 1H, HCl). $C_{21}H_{26}N_2O_3 \cdot HCl$.

3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(4-propoxyphenyl)propan-1-one hydro chloride (21). Yield 56%, mp 183-185°C, Rf 0.56. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, d, ppm 1.05 (t, 3H, J 7.4, CH_3); 1.81 (br.ss, 2H, J 7.0, CH_2); 3.25 (br, 4H, $N(CH_2)_2$); 3.49 (br, 4H, N $(CH_2)_2$); 3.61 (br, 2H, CH_2); 3.68 (br.t, 2H, J 7.5, CH_2); 3.84 (s, 3H, CH_3); 4.03 (t, 2H, J6.5); 6.86-7.00 (m, 4H, C_6H_4); 7.00 (d, 2H, J 8.8, 2CH); 7.99 (d, 2H, J 8.8, 2CH); 11.80 (br, 1H, HCl). $C_{23}H_{30}N_2O_3 \cdot HCl$.

1-(4-Isopropoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (22). Yield 52%, mp 186-188°C, Rf 0.54.

IR spectrum, υ, cm^{-1}: 1670 (C = O). ^{1}H NMR spectrum, δ, ppm 1.34 (d, 6H, J 6.0, $2CH_3$); 3.25 (br, 4H, 2CH2); 3.49 (br, 4H, 2CH2); 3.61 (br, 2H, 2CH2), 3.67 (br.t, 2H, J 7.5, CH2); 3.84 (s, 3H, CH3); 4.75 (sp, 1H, J 6.0, CH); 6.86-7.00 (m, 4H, 4CH); 7.00 d, 2H, J 8.8, CH); 8.00 (d, 2H, J 8.8, 2CH); 12.58 (br, H, HCl). C23H30N2O3 · HCl.

1-(4-Isobutoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (23). Yield 49%, mp 192-193°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 1.05 (d, 6H, J 6.0, $2CH_3$); 3.25 (br, 2H, CH_2); 3.34 (m, 2H, CH_2); 3.43-3.54 (m, 6H, $3CH_2$); 3.67 (br.d, 2H, J 11.5, CH_2); 3.78 (t, 2H, J 7.4, CH_2); 3.87 (s, 3H, CH_3); 4.75 (cn, H, CH); 6.86-6.94 (m, 2H, 2CH); 7.03 (ddd, 1H, J 18.5, J 27.1, J 31.6, CH); 7.10 (dd, 1H, J 17.9, J 21.6, CH); 7.67 (d, 2H, J 8.5, 2CH); 7.98 (d, 2H, J 8.5, 2CH); 9.72 (br, 1H, HCl); 11.96 (br, 1H, HCl). $C_{24}H_{32}N_2O_3 \cdot 2HCl$.

1-(4-Bromophenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (24). Yield 40%, mp 193-195°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 3.34 (m, 2H, CH_2); 3.43-3.54 (m, 6H, $3CH_2$); 3.67 (br.d, 2H, J 11.5, CH_2); 3.78 (t, 2H, J 7.4, CH_2); 3.87 (s, 3H, CH_3); 6.86-6.94 (m, 2H, 2CH), 7.03 (ddd, 1H, J 18.5, J 27.1, J 31.6, CH); 7.10 (dd, 1H, J 17.9, J 21.6, CH); 7.67 (d, 2H, J 8.5, 2CH); 7.98 (d, 2H, J 8.5, 2CH); 12.44 (br, 1H, HCl). $C_{20}H_{23}BrN_2O_2 \cdot HCl$.

3-[4-(2-Fluorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one hydrochloride (25). Yield 58%, mp 202-205°C, Rf 0.55. IR spectrum, υ, cm^{-1}: 1660 (C = O). ^{1}H NMR spectrum, d, ppm 3.25 (br, 4H, 2CH2), 3.49 (br, 4H, $2CH_2$), 3.62 (br, 2H, CH_2), 3.69 (br.t, 2H, J 7.5, CH_2); 3.84 (s, 3H, CH_3); 6.98-7.03 (m, 4H, 4CH); 7.03 (d, 2H, J 8.8, 2CH); 8.00 (d, 2H, J 8.8, 2CH); 11, 80 (br, 1H, HCl). $C_{20}H_{23}FN_2O_2 \cdot HCl$.

3-[4-(2-Fluorophenyl)piperazin-1-yl]-1-(4-isopropoxyphenyl)propan-1-one hydro chloride (26). Yield 48%, mp 190-191°C, Rf 0.55. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 1.34 (d, 6H, J 6.0, $2CH_3$); 3.20-3.70 (m, 12H, $6CH_2$); 4.75 (sp, 1H, J 6.0, CH); 6.98 (d, 2H, J 8.9, 2CH); 6.95-7.15 (m, 4H, C_6H_4); 7.98 (d, 2H, J 8.9, 2CH); 11.78 (br, 1H, HCl). $C_{22}H_{27}FN_2O_2 \cdot HCl$.

3-[4-(4-Fluorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one dihydro chloride (27). Yield 56%, mp 198-199°C, Rf 0.54. IR spectrum, υ, cm^{-1}:1670 (C = O). ^{1}H NMR spectrum, d, ppm 3.10-3.78 (br, 12H, 6 CH_2); 3.84 (s, 3H, CH_3); 6.86-7.29 (m, 8H, 8CH); 8.00 (d, 2H, J 8.9, 2CH); 9.72 (br, 1H, HCl); 11.96 (br, 1H, HCl). $C_{20}H_{23}FN_2O_2 \cdot 2HCl$.

3-[4-(4-Fluorophenyl)piperazin-1-yl]-1-(4-isopropoxyphenyl)propan-1-one dihydro chloride (28). Yield 52%. mp 187-189°C. Rf 0.54. IR spectrum, υ, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum; d, ppm 1.34 (d, 6H, J 6.0, $2CH_3$), 3.10-3.78 (m, 12H, $6CH_2$), 6.86-7.29 (m, 8H, 8CH); 9.72 (br, 1H, HCl); 11.96 (br, 1H, HCl). $C_{22}H_{27}FN_2O_2 \cdot 2HCl$.

4-[3-oxo-3-(4-propoxyphenyl)propyl]piperazine-1-carboxylic acid ethyl ester dihydro chloride (29). Yield 42%, mp 185-187°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1660 (C = O), 1700 (COO). ^{1}H NMR spectrum, d, ppm 1.05 (t, 3H, J 7.4, CH_3); 1.26 (t, 3H, J 7.1, CH_3); 1.81 (br. ss, 2H, J 7.0, CH_2); 3.41 (br.t, 2H, J 7.2, CH_2); 3.50 (br, 4H, $2CH_2$); 3.63 (br.t, 2H, J 7.2, CH_2); 4.03 (t, 2H, J 6.5, CH_2); 4.10 (q, 2H, J 7.1, CH_2); 6.99 (d, 2H, J 8.8, 2CH); 7.97 (d, 2H, J 8.8, 2CH); 11.87 (br, 1H, HCl). $C_{19}H_{28}N_2O_4 \cdot HCl$.

4-[3-(4-isopropoxyphenyl)-3-oxopropyl]piperazine-1-carboxylic acid ethyl ester dihydrochloride (30). Yield 45%, mp 182-184°C, Rf 0.55. IR spectrum, υ, cm^{-1}: 1660 (C = O), 1700 (COO). ^{1}H NMR spectrum, d, ppm 1.15 (t, 3H, J 7.4, CH_3); 1.34 (d, 6H, J 6.0, $2CH_3$); 3.41 (br.t, 2H, J 7.0, CH_2); 3.50 (br.t, 4H, CH_2); 3.63 (br.t, 2H, J 7.2, CH_2); 4.03 (t, 2H, J 6.5, CH_2); 4.10 (q, 2H, J 7.1, CH_2); 6.99 (d, 2H, J 8.8, 2CH); 7.97 (d, 2H, J 8.8, 2CH); 11.87 (br, 1H, HCl); 12.68 (br, 1H, HCl). $C_{19}H_{28}N_2O_4 \cdot 2HCl$.

ՄԱՆՆԻԽԻ ՀԻՄՔԵՐԻ ԵՎ ՏԵՂԱԿԱԼՎԱԾ ՊԻՊԵՌԱԶԻՆԱՊՐՈՊԻՈՖԵՆՈՆՆԵՐԻ ՀԻԴՐՈՔԼՈՐԻԴՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ՀԱԿԱԲՈՐԲՈՔԱՅԻՆ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆՆԵՐԸ

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Պարաֆորմալդեհիդի, տեղակալված ֆենիլպիպերազինների և p-տեղակալված ացետոֆենոնների (p-տեղակալված էթանոնների) ամինամեթիլացման միջոցով սինթեզվել են 1-(4-տեղակալված ֆենիլ)-3- {4-[2(4)-տեղակալված)ֆենիլ]պիպերա զին-1-իլ)-2-H(ֆենիլ)պրոպանոններ՝ Մաննիխի հիմքեր: Դեղաբանական հետա զոտուԹյունների համար ստացվել են վերջիններիս հիդրոքլորիդները: Բացահայտվել է, որ որոշ β-ամինակետոնների հիդրոքլորիդներ ունեն մեղմ թուլյլ կամ միջին արտահայտված հակաբորբոքային ակտիվուԹյուն:

СИНТЕЗ И ИЗУЧЕНИЕ ПРОТИВОВОСПАЛИТЕЛЬНОЙ АКТИВНОСТИ ГИДРОХЛОРИДОВ ЗАМЕЩЕННЫХ ПИПЕРАЗИНОПРОПИОФЕНОНОВ – ОСНОВАНИЙ МАННИХА

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Аминометилированием некоторых *n*-замещенных ацетофенонов и *n*-замещенных этанонов параформальдегидом и замещенными фенилпиперазинами осуществлен синтез 1-(4-замещенных фенил)-3-{4-[2(4)-замещенных фенил]пиперазин-1-ил}-2-Н(фенил)пропан-1-онов. Для проведения фармакологических испытаний получены гидрохлориды последних. Выявлено, что гидрохлориды β-аминокетонов обладают от слабой до умеренно-выраженной противовоспалительной активности.

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