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DEVELOPMENT AND SYNTHESIS OF AMINO ACID DERIVATIVES OF *N*-METHYL ANALOGUE OF PROCAINE AND BENZOCAINE BASED ON PHARMACOPHORE FUSION STRATEGY

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Abstract. *We have developed a rational method for the synthesis of amino acid derivatives of N-methyl analogue of procaine and benzocaine using N,N-carbonyl diimidazole method in solutions. Using the PASS software package, we predicted the biological activity of a series of hybrid compounds produced by the fusion of aminoether and aminoanilide anaesthetics. All hybrid compounds have a potential lack of significant hepatotoxicity with an increased median lethal dose for both intraperitoneal and subcutaneous injection routes when the pharmocophor is fused. The synthesised compounds are of interest as potential therapeutic agents with local anaesthetic activity and low toxicity.*

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Introduction

Local anaesthetics refer to medicines widely used in clinics. They induce reversible local anaesthesia through loss of nociception in certain areas of the body by blocking nerve impulse transmission without affecting consciousness. In terms of chemistry, we can distinguish two main groups of local anaesthetics that include a common aniline group, namely aminoether anaesthetics (e.g. benzocaine, procaine, tetracaine, Fig. 1) and aminoamide anaesthetics (e.g. lidocaine, ropivacaine, articaine, Fig. 1) [1]. These drugs molecules have three common structural components: 1) a lipophilic aromatic fragment; 2) an ester or amide binding group; and 3) a tertiary or secondary amine fragment [2].

The strength and duration of action of the local anaesthetics are generally greater for aminoamide anaesthetics compared to aminoether anaesthetics, but at the same time these values are strongly dependent on the length and volume of the alkyl substituents at the secondary or tertiary nitrogen atom in their structure [3]. On the other hand, stability, toxicity, and ability to

cause allergic reactions are determined not only by structure but also by the site of biotransformation of the drug: either by enzymatic hydrolysis in plasma (aminoether anaesthetics) or by degradation in the hepatic system (aminoamide anaesthetics).

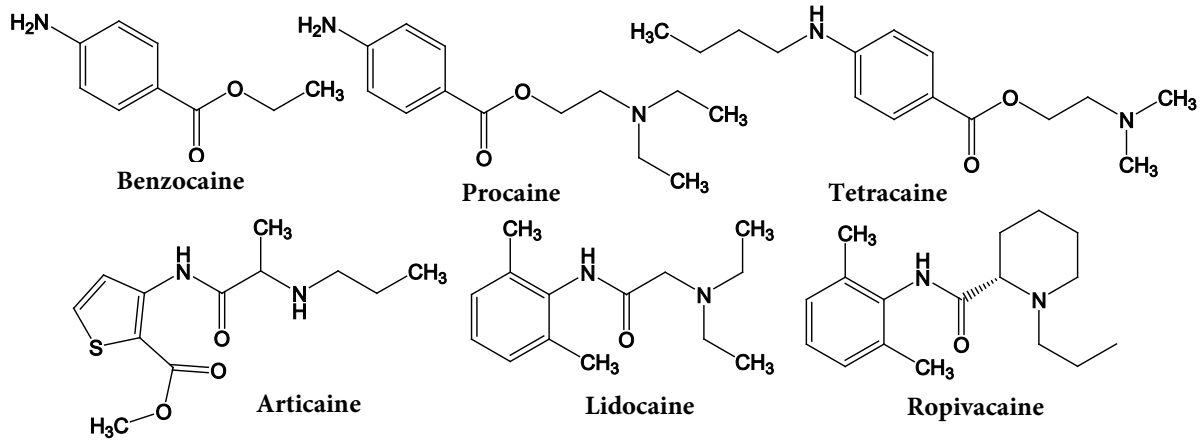


Fig. 1. Structures of some commonly used local anaesthetics

It is important to note that, despite the relative safety of these drugs, they all possess some degree of toxicity to the central nervous and cardiovascular systems (3). Side-effects include the possibility of ischaemic necrosis caused by the irritant nature or large volumes of drug solutions when injected, as well as severe vasoconstriction as a result of the concomitant vasopressor effect (2). Moreover, there is a risk of direct neurotoxicity from injections of solutions containing high concentrations of anaesthetics (such as 4%), especially artichaine and prilocaine (2).

In this regard, the most modern and clinically used local anaesthetics, primarily in long-term surgical procedures, are derivatives of the mepivacaine derivative family, of which ropivacaine and bupivacaine are the most preferable (4). For these drugs, the pure (*S*)-enantiomeric forms are the safest in practice, as the (*R*)-enantiomeric forms have a higher incidence of cardiac arrest (4).

All these facts impose limitations to some extent on the use of local anaesthetics for clinical practice, especially when repeated administration or high concentrations are required. It indicates the need for further development of both more effective and safer preparations of this group, and improvement of the properties and synthesis methods of already known ones.

For example, the synthesis and *in vivo* results of a series of *N*-alkylprolinanilides have been published, many of which were both more active as surface anaesthetics and had a higher antiarrhythmic index than lidocaine, ropivacaine and bupivacaine [5]. Various enantioselective methods have been developed for the synthesis of (*S*)-2-piperidincarboxylic acid as a key intermediate in the synthesis of anaesthetics of the mepivacaine family, for example based on the chiral additive sultam Opolzer and ethyl-*N*-(diphenylmethylene)glycinate with an enantiomeric excess value > 97% [6]. Alternative clinically important pharmacological properties of lidocaine homologues have been investigated in addition to local anaesthetic and antiarrhythmic effects, namely antihistamine antispasmodic activity (7). The synthesis of a number of adamantan-substituted derivatives of anaesthesin, procaine, procainamide and metoclopramide with improved lipophilicity has been investigated [8]. Glycoside derivatives of anaesthesin have been obtained and their biological activity predicted [9].

Based on the data above, the present paper suggests that new hybrid compounds of common structures **A** and **B** (Fig. 2), derived from the fusion of pharmacophore fragments of aminoamide and aminoether local anesthetics, would not only have improved biological activity as a result of synergistic effects, but would also acquire an improved safety profile as well as a reduced level of drug resistance. The strategy of fusing multiple pharmacophores into a single chemical structure is one of the most attractive concepts in the development of novel therapeutics with different activities, especially in polypharmacology approaches and design of drug molecules with multi-targeted activity [10-14].

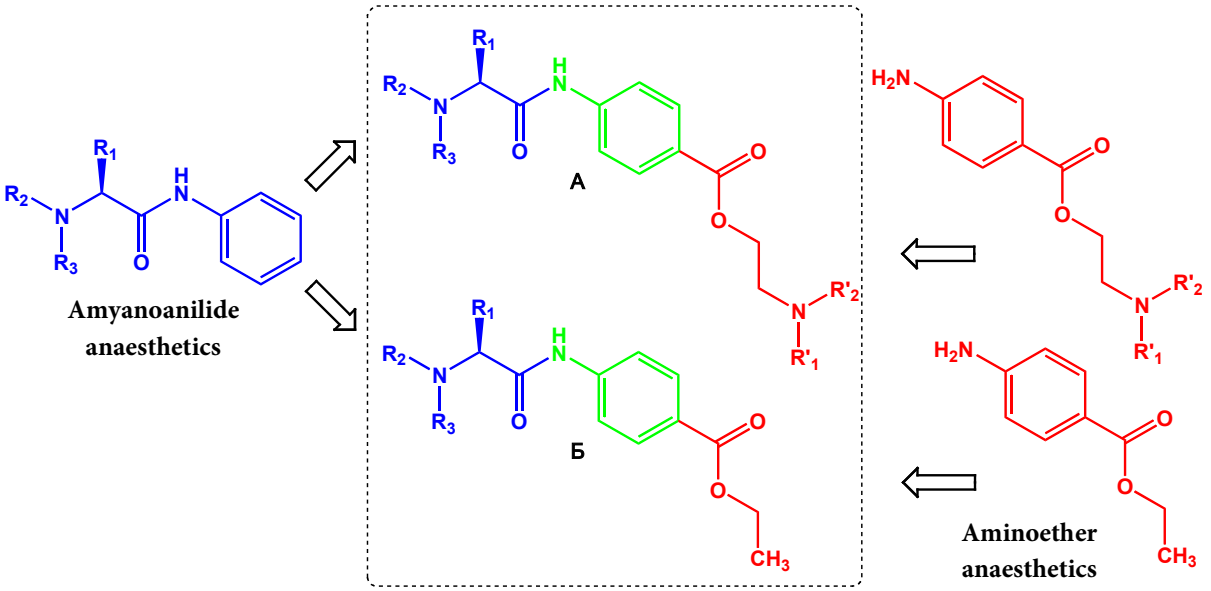


Fig. 2. Structural design of hybrid compounds of general formulas **A** and **B** with potential local anaesthetic activity

At the presynthetic stage we did a prediction of biological activity for a series of hybrid compounds of common structures **A** and **B** using a software package based on PASS (*Prediction of activity spectra for substances*) [15-19]. It allows the online assessment *in silico* for chemical structures of various pharmacological effects, determining their most probable molecular targets, probability of certain side-effects, and acute toxicity. Further, we planned and implemented the synthesis of new compounds with a potentially "attractive" pharmacological profile as local anaesthetics.

Main body

In order to realise this purpose, we initially chose procaine and benzocaine structures as starting aminoether fragments at the structural design stage. However, the replacement of two ethyl radicals at the tertiary nitrogen atom in the procaine molecule by methyl radicals leads to a complete absence of hepatotoxicity while maintaining a high probability of local anesthetic activity and a close value of acute toxicity (Table 1), so in the future only the dimethylamine ethyl radical was considered as a tertiary amine in the aminoether fragment. We chose anilides of α-amino acids with an aliphatic side radical or cyclic structure as aminoamide derivatives of local anaesthetics characterised by a sufficiently high lipophilicity [2].

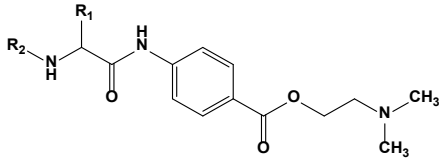
Using this approach, we generated two small series of hybrid compounds of the general formulas **C** and **D**. The probabilities of baseline local anaesthetic, antiarrhythmic activity,

arrhythmia, and hepatotoxicity as side effects and acute toxicity values for intraperitoneal and subcutaneous administration were further determined (see Table 1). We compare the data obtained with the results for commonly used local anaesthetics, namely ropivacaine, lidocaine, benzocaine and procaine. It should be noted here that an assessment of the adverse effects of ropivacaine, and to a lesser extent lidocaine, revealed a high likelihood of cardiovascular problems, P_a(arr.) = 0.844 and 0.649 respectively, which is consistent with the real data reported above, and a fairly pronounced toxicity of ropivacaine when administered subcutaneously.

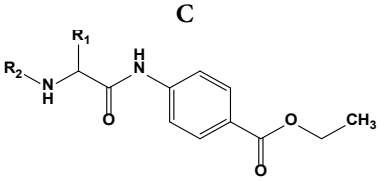
Indeed, the general trend for the hybrid compounds of formula **C** with respect to Me-procaine (2-(dimethylamino)ethyl-4-aminobenzoate) was a slight decrease of about 0.05 units in the probability of local anaesthetic activity with a P_a(l.a.) value > 0.690 with P_i(l.a.) < 0.004, except for the compound with the sarcosine moiety, for which the probability of "being active" was found to be 0.903. For compounds of the general formula **D** a similar situation was observed with P_a(l.a.) > 0.453 with P_i(l.a.) < 0.006, and 0.822 for the probability of "being active" in the sarcosine derivative. A practically important result of the pharmocophor fusion was the potential absence of significant hepatotoxicity in all hybrid compounds except for the proline derivatives. In addition, for these compounds, the average lethal dose was kept or increased for both routes of administration, except for proline derivatives, for which the toxicity increased by a factor of three when administered subcutaneously. The level of possible arrhythmia and anti-arrhythmic effect of the predicted compounds was not clear, as the difference between P_a(arr.) and P_i(arr.) was small, or these values were not given as programming results.

Thus, the presented hybrid compounds, namely sarcosine, glycine, alanine, valine, leucine, phenylalanine, and proline derivatives of Me-procaine and benzocaine of the general formula **C** and **D**, are of considerable interest for synthesis and further biological study as potential local anaesthetics with reduced side effects and toxicity.

The synthesis of compounds of formula **C** based on *p*-aminobenzoic acid was implemented in two different ways, differing in the sequence of amino group and carboxy group functionalisation (Fig. 3).



C



D

By the first version, the synthesis was conducted via three stages. For this purpose at the first stage (*S*)-Boc-α-amino acids were first reacted with *N*,*N*-carbonyl dimidazole in absolute tetrahydrofuran at 60–66 °C to form the corresponding imidazolides *in situ* (conditions **a**, [20]), which were then reacted with *p*-aminobenzoic acid to form the corresponding amido acids (**2.1**-**7**). At the second stage a reaction of the formation of esters between the obtained products and 2-(dimethylamino)ethanol was conducted under similar conditions (conditions **a**), which were further subjected to removal of Boc-protection in an excess of HCl solution in absolute tetrahydrofuran (conditions **b**) at the third stage.

During the second version, benzocaine was first synthesised from *p*-aminobenzoic acid by two stages [21]. The *N*-methyl analogue of procaine was then synthesised with the yield by interesterification and functionalised at the amino group with further removal of the Boc-protection in the same way as described in the first variant.

Table 1.

General formula / amino acid	R_1	R_2	P_a(a.arr.)[1]	P_i(a.arr.)[1]	P_a(l.a.)[2]	P_i(l.a.)[2]	P_a(arr.)[3]	P_i(arr.)[3]	P_a(h.t.)[4]	P_i(h.t.)[4]	LD_{50}(i.in.)[5], mg/kg	LD_{50}(p.i.)[6], mg/kg
Procaine	-	-	0.414	0.014	0.916	0.002	0.428	0.164	0.365	0.086	186	985
Me-Procaine [8]	-	-	0.253	0.042	0.861	0.002	0.474	0.129	n.d.[7]	n.d.	185	816
B/glycine	H	H	0.277	0.034	0.742	0.003	0.489	0.117	n.d.	n.d.	255	1140
B/alanine	Me	H	0.242	0.045	0.816	0.003	0.360	0.222	n.d.	n.d.	163	1480
V/valine	*i*-Pr	H	0.135	0.125	0.737	0.003	0.305	0.297	n.d.	n.d.	177	935
B/leucine	*i*-Bu	H	0.142	0.114	0.816	0.003	0.324	0.265	n.d.	n.d.	212	800
B/Phenylalanine	Bn	H	0.155	0.099	0.691	0.003	0.310	0.290	n.d.	n.d.	360	868
B/sarcosine	H	Me	0.249	0.043	0.905	0.002	0.579	0.057	n.d.	n.d.	150	1055
B/proline	$CH_2CH_2CH_2$		0.164	0.090	0.775	0.003	0.619	0.041	0.403	0.256	179	255
Benzocaine	-	-	n.d.	n.d.	0.621	0.004	n.d.	n.d.	0.425	0.241	721	963
G/Glycine	H	H	0.169	0.086	0.538	0.004	n.d.	n.d.	n.d.	n.d.	605	3691
G/alanine	Me	H	0.131	0.131	0.521	0.004	n.d.	n.d.	n.d.	n.d.	720	3030
G/valine	*i*-Pr	H	n.d.	n.d.	0.453	0.005	n.d.	n.d.	n.d.	n.d.	942	1435
G/leucine	*i*-Bu	H	n.d.	n.d.	0.522	0.004	n.d.	n.d.	n.d.	n.d.	1162	3279
G/Phenylalanine	Bn	H	n.d.	n.d.	0.460	0.005	n.d.	n.d.	n.d.	n.d.	1319	2143
G/sarcosine	H	Me	0.157	0.097	0.822	0.003	0.379	0.203	n.d.	n.d.	213	1573
G/proline	$CH_2CH_2CH_2$		n.d.	n.d.	0.534	0.004	0.392	0.192	0.532	0.179	603	325
Ropivacaine	-	-	0.227	0.051	0.744	0.003	0.844	0.009	n.d.	n.d.	182	118
Lidocaine	-	-	0.549	0.005	0.764	0.003	0.649	0.034	n.d.	n.d.	340	1282

[1]a.ar. – antiarrhythmic action; [2]l.a. – localanaesthetic effect; [3]ar. - arrhythmia; [4]h.t. - hepatotoxicity; [5]i.in. – intraperitoneal injection; [6]p.i. - per-cutaneous injection; [7]n.d. - hereinafter "not determined"; [8]Me-procaine - *N*-methyl analogue of procaine, namely 2-(dimethylamino)ethyl-4-aminobenzoate.

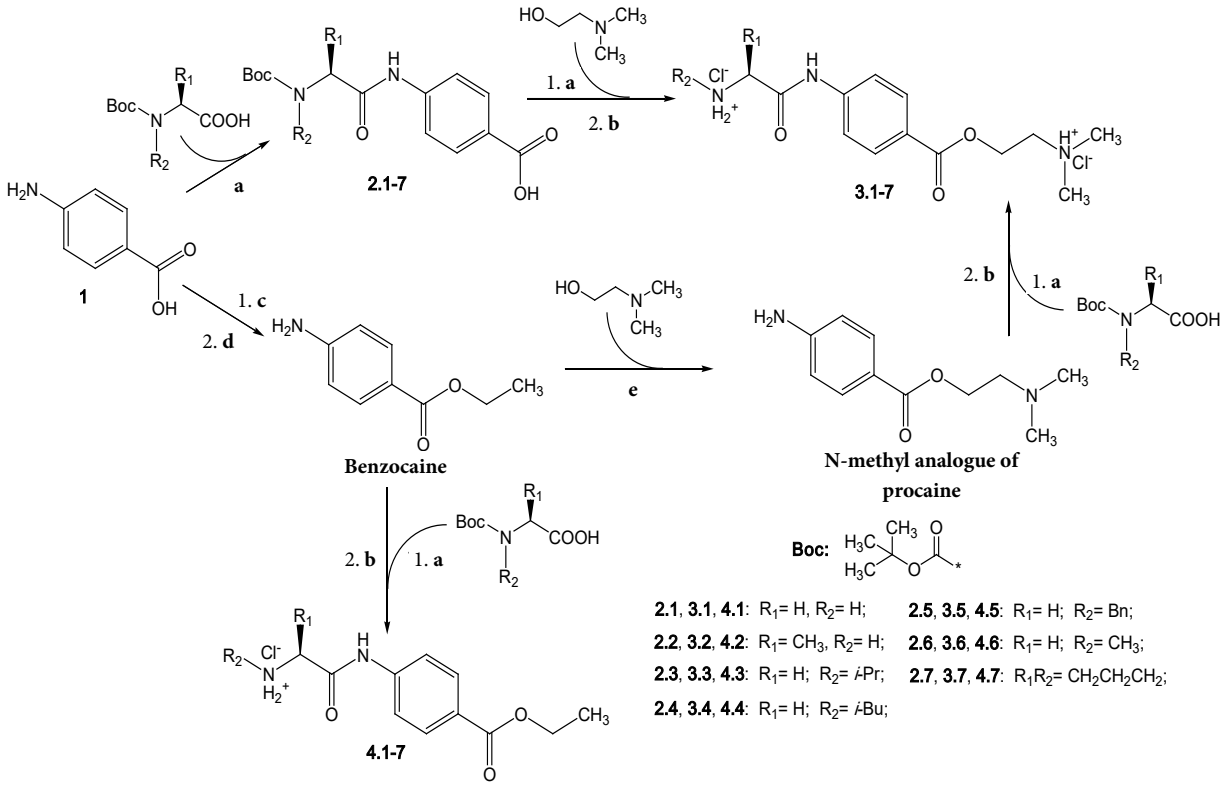


Fig. 3. Layout of the syntheses conducted within this study. Reagents and conditions: **a** – *N*,*N*-carbonyl dimidazole, tetrahydrofuran, 60–66 °C, 3 h; **b** – HCl, tetrahydrofuran, *rt*, 7 h; **c** – AcOH, *rf*, 5 h; **d** – EtOH, H_2SO_4, *rf*, 6 h; **e** – $(Me)_2N(CH_2)_2OK$, *rf*, 5 h

Experimental part

To predict the biological activity of new hybrid compounds, we used the web-based computer information resource Way2Drug [15], which includes the PASS Online computer software application to simultaneously assess over 4000 activities with an average prediction accuracy of over 95% (*www.way2drug.com/passonline*) [17]; GUSAR to assess acute toxicity for various routes of drugs with 92–99% accuracy (*www.way2drug.com/gusar/acutoxpredict*) [16, 18]; and ADVERPred to assess side-effects such as arrhythmia, hepatotoxicity, myocardial infarction, nephrotoxicity, heart failure (*www.way2drug.com/adverpred*) [16]. We pre-recorded the molecular structures as MOL files before evaluating the predicted properties, which we then processed online in appropriate software applications. The resulting probability values for the compounds were in most cases higher than the probability of "being active" (P_a>P_i) and therefore could be taken into account for interpretation, except in cases where these values were not determined by the programme at all, which were interpreted as "inactive". If P_a>0.9, which is very high, compounds are very likely to be known pharmaceutical agents; if P_a>0.7, the probability of experimental pharmacological action is considered high; if Pa is 0.5 <P_a<0.7, the probability of experimental pharmacological action is moderate; and if P_a is equal to or less than 0.5, the probability of finding activity is experimentally lower [17]. The result of the acute toxicity assessment was the calculated average lethal dose (LD_{50}) of the compounds expressed in milligrams per kilogram (mg/kg) for the two routes of administration (intraperitoneal and subcutaneous).

^{1}H NMR spectra were recorded by a Varian "VXR-400" in DMSO-d_6 solution. IR spectra were recorded by a Spectrum RX-1 (Perkin Elmer) for substances in suspension in Vaseline oil. The melting temperatures were determined by a BUCHI Melting Point M-560. The homogeneity of obtained compounds was controlled by thin-layer chromatography using analytical plates Sorbfil (Russia) with applied phosphor (254 nm), the eluent used was toluene/acetone = 8 ml/5 ml and the chromatogram was developed under UV-radiation or in iodine vapor.

General methodology for the synthesis of *N*-(*tert*-butoxycarbonyl)-(*S*)-amino acid derivatives of *p*-aminobenzoic acid (**2.1-7**), *N*-methyl analogue of procaine and benzocaine (conditions **a**). We add 1.15 mmol*N*,*N*-carbonyl dimidazole to a solution of 1 mmol *N*-(*tert*-butoxycarbonyl)-(*S*)-amino acids in 10 ml THF.We stirred and heated the reaction mixture to solvent boiling for 1 hour. Then we add 1.20 mmol amine (*p*-aminobenzoic acid, benzocaine or *N*-methyl analogue of procaine) or 1.40 mmol *N*,*N*-dimethylaminoethanol. Stirring was continued under heat for another 3 hours. The reaction mixture was left overnight at room temperature, concentrated to half of its original volume, and then diluted with water to half its volume. Afterwards we add 15-20 ml of methylene chloride to the reaction mixture until the isolated product was completely dissolved, separated the resulting organic layer, dried, evaporated it to a viscous mass, which was then crystallized in a 1:1 ratio *n*-hexane/diethyl ether mixture by volume. The solid products were filtered off and dried on air.

General methodology for the synthesis of (*S*)-amino acid hydrochlorides of *N*-methyl derivatives of procaine (**3.1-5**) and benzocaine (**4.1-5**) (conditions **b**). Under vigorous stirring we add 0.50 mmol *N*-(*tret*-butoxycarbonyl)-*S*-amino acid amino acid derivatives of *N*-methyl

analogue of procaine and benzocaine to 2.5 ml of 2M HCl solution in tetrahydrofuran. We stirred the reaction mixture for 7 hours at room temperature, then the solvent was removed under reduced pressure. We washed the residue with acetone, dried it in a vacuum, and resuspended from water with acetone, then filtered and dried on air.

4-(2-(tret-butoxycarbonylamino)-3-acetamido)benzoic acid (***2.1***)

0.24 g (78%) was obtained. Melting point is 178–180 °C. R_f0.25. IR, *ν*, cm^{-1}: 3379 (N-H), 1712 (C=O), 1670 (C=O), 1617 (C_6H_4),1547 (C=O). ^{1}H NMR, *δ*, ppm.: 12.60 (s, 1H), 10.20 (s, 1H), 7.86 (d, *J*= 10.0 Hz, 2H), 7.72 (d, *J*= 10.0 Hz, 2H), 7.0 (s, 1H), 3.85 (d, *J*= 6.5 Hz, 2H), 1.20 (m. 9H).

4-(2-(tert-butoxycarbonylamino)-3-methylbutanamido)benzoic acid (***2.3***)

0.25 g (76%) was obtained. Melting point is 195–197 °C. R_f0.20. IR, *ν*, cm^{-1}: 3390 (N-H), 2876 (CH_3), 1710 (C=O), 1676 (C=O), 1614 (C_6H_4),1544 (C=O). ^{1}H NMR, *δ*, ppm.: 12.60 (s, 1H), 10.30 (s, 1H), 7.84 (d, *J*= 10.0 Hz, 2H), 7.78 (d, *J*= 10.0 Hz, 2H), 6.80 (s, 1H), 3.9 (dd., *J*= 8.0 Hz, *J*= 9.0 Hz, 1H), 1.8 (m. 1H), 1.2 (m. 9H), 0.8 (m. 6H).

4-(2-(tert-butoxycarbonylamino)-3-methylacetamido)benzoic acid (***2.6***)

0.27 g (78%) was obtained. Melting point is 145–148 °C. R_f0.28. IR, *ν*, cm^{-1}: 3390 (N-H), 1710 (C=O), 1670 (C=O), 1619 (C_6H_4),1547 (C=O). ^{1}H NMR, *δ*, ppm.: 12.50 (s, 1H), 10.40 (s, 1H), 7.68 (d, *J*= 10.0 Hz, 2H), 7.74 (d, *J*= 10.0 Hz, 2H), 3.85 (d, *J*= 6.5 Hz, 2H), 3.10 (s, 3H), 1.20 (m. 9H).

4-(ethyl-(2-amino-N-acetamido))benzoate hydrochloride (**4.1**)

0.21 g (68%) was obtained. Melting point is 111–113 °C. R_f0.11. IR, *ν*, cm^{-1}: 3365 (N-H), 1742 (C=O), 1680 (C=O), 1620 (C_6H_4),1560 (C=O). ^{1}H NMR, *δ*, ppm.: 10.40 (s, 1H), 7.80 (d, *J*= 9.0 Hz, 2H), 7.60 (d, *J*= 9.0 Hz, 2H), 4.5 (s.1H), 4.2 (m, 2H), 3.78 (d, *J*= 6.5 Hz, 2H), 1.28 (s, 3H).

4-(ethyl-(2-amino-N-methylbutanamido))benzoate hydrochloride (**4.3**)

0.21 g (66%) was obtained. Melting point is 123–125 °C. R_f0.13. IR, *ν*, cm^{-1}: 3390 (N-H), 2876 (CH_3), 1745 (C=O), 1678 (C=O), 1620 (C_6H_4),1540 (C=O). ^{1}H NMR, *δ*, ppm.: 10.35 (c, 1H), 7.94 (d, *J*= 10.0 Hz, 2H), 7.65 (d, *J*= 10.0 Hz, 2H), 4.4 (s, 1H), 3.8 (dd, *J*= 7.0 Hz, *J*=8.0 Hz, 1H), 1.8 (m. 1H), 0.8 (m. 6H).

4-(ethyl-(2-amino-N-methylacetamido))benzoate hydrochloride (**4.6**)

0.23 g (59%) was obtained. Melting point is 90–92 °C. R_f0.18. IR, *ν*, cm^{-1}: 3390 (N-H), 1748 (C=O), 1660 (C=O), 1612 (C_6H_4),1549 (C=O). ^{1}H NMR, *δ*, ppm.: 10.60 (s, 1H), 7.87 (d, *J*=9.0 Hz, 2H), 7.78 (d, *J*=9.0 Hz, 2H), 4.2 (s, 1H), 3.85 (d, *J*=6.5 Hz, 2H), 3.15 (s, 3H).

*4-(2-aminoacetamide)-N-[2-(dimethylamino)ethyl]benzamide dihydrochloride (**3.1**)*

0.19 g (56%) was obtained. Melting point is 88–90 °C. R_f0.32. IR, *ν*, cm^{-1}: 3390 (N-H), 1745 (C=O), 1680 (C=O), 1621 (C_6H_4),1555 (C=O). ^{1}H NMR, *δ*, ppm.: 10.8 (s, 1H), 8.05 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*= 8.5 Hz, 2H), 4.6 (br. s, 1H), 4,4 (br. s, 1H), 4.30 (tr, *J*= 6.9 Hz, 2H), 3.80 (s, 2H), 2.82 (tr, *J*= 6.9 Hz, 2H), 2.29 (s. 6H).

*4-(2-aminomethylbutanamide)-N-[2-(dimethylamino)ethyl]benzamide dihydrochloride (**3.3**)*

0.16 g (53%) was obtained. Melting point is 80–83 °C. R_f0.35. IR, *ν*, cm^{-1}: 3375 (N-H), 1746 (C=O), 1679 (C=O), 1619 (C_6H_4),1556 (C=O). ^{1}H NMR, *δ*, ppm.: 10.2 (s, 1H), 8.05 (d, *J*= 8.5 Hz,

2H), 7.35 (d, *J*= 8.5 Hz, 2H), 4.5 (br.s., 1H), 4,3 (br.s., 1H), 4.30 (tr, *J*= 6.9 Hz, 2H), 3.52 (d, *J*= 5.1 Hz, 1H), 2.82 (tr, *J*= 6.9 Hz, 2H), 2.29 (s. 6H), 1.95 (m,1H), 0.78-0.89 (m, 6H).

*4-(2-amino-N-methylacetamide)-N¹-[2-(dimethylamino)ethyl]benzamide dihydrochloride (**3.6**)*

0.15 g (51%) was obtained. Melting point is 94–96 °C. R_f0.29. IR, *ν*, cm^{-1}: 3379 (N-H), 1738 (C=O), 1685 (C=O), 1617 (C_6H_4),1551 (C=O). ^{1}H NMR, *δ*, ppm.: 10.1 (s, 1H), 7.85 (d, *J*=8.5 Hz, 2H), 7.34 (d, *J*= 8.5 Hz, 2H), 4.8 (br.s., 1H), 4,6 (br.s., 1H), 4.28 (tr, *J*= 7.0 Hz, 2H), 3.78 (s, 2H), 2.81 (tr, *J*= 6.9 Hz, 2H), 2.34 (s, 3H), 2.28 (s. 6H).

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