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Modification of Chitosan with Ethoxycarbonyl and 3-Fluoroimidazo[1,2-*a*]pyridine-2-carbonyl Fragments

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Abstract—Reactions of the natural biopolymer chitosan with 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acid hydrochlorides in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate resulted in introduction of ethoxycarbonyl and 3-fluoroimidazo[1,2-*a*]pyridine-2-carbonyl fragments into glucosamine units of the polymer.

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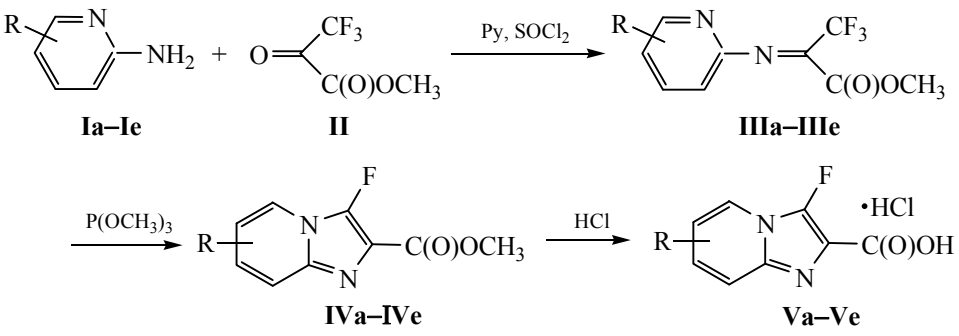
Intentional modification of biologically active compounds underlies one of the main approaches to molecular design of drugs and is thus a quite important problem in medicinal chemistry. The goal of the present study was to introduce 3-fluoroimidazo[1,2-*a*] pyridine substituents into the polymer chain of chitosan which is a natural polysaccharide biopolymer. We believed that such modification should change physicochemical properties and biological activity of the initial biopolymer. Polysaccharide nature of chitosan determines its affinity for living species, and the presence of reactive functional groups in the polymer chain provides the possibility for various chemical modifications, in particular with drug-like clusters [1–3]. As the latter we selected substituted 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acids whose analogs exhibit a broad spectrum of biological activity, e.g., cardiotonic [4], arrhythmic [4], neurotropic [5, 6], cytoprotective, and antitumor [7], and are promising for the treatment of Alzheimer's disease [8].

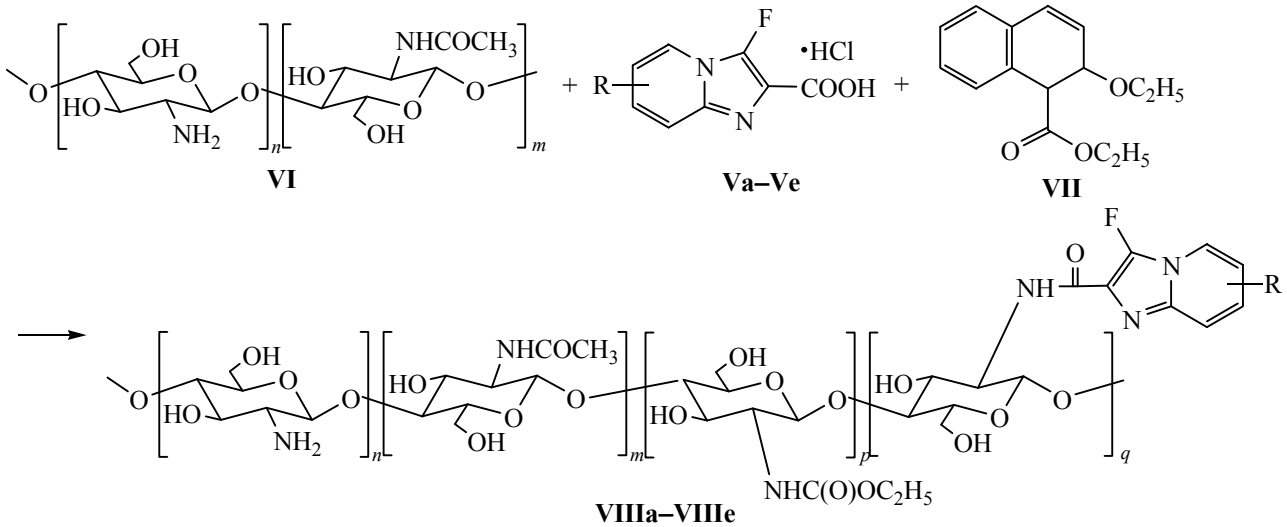
Initial 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acid hydrochlorides **Va**–**Ve** were synthesized by reaction of the corresponding methyl 3,3,3-trifluoro-2-(pyridin-2-ylimino)propionates **IIIa**–**IIIe** with trimethyl phosphite, followed by hydrolysis of methyl 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylates **IVa**–**IVe** [9] thus formed (Scheme 1).

Scheme 1.



I, **III**, R = H (**a**), 3-Me (**b**), 4-Me (**c**), 5-Br (**d**), 5-Cl (**e**); **IV**, **V**, R = H (**a**), 8-Me (**b**), 7-Me (**c**), 6-Br (**d**), 6-Cl (**e**).

Scheme 2.



VI **Va–Ve** **VII**

VIIIa–VIIIe

VI, n = 98, m = 2; **VIII**, R = H, n = 42, m = 2, p = 21, q = 35 (**a**); R = 8-Me, n = 45, m = 2, p = 22, q = 31 (**b**); R = 7-Me, n = 43, m = 2, p = 23, q = 33 (**c**); R = 6-Br, n = 70, m = 2, p = 12, q = 16 (**d**); R = 6-Cl, n = 42, m = 2, p = 16, q = 40 (**e**).

As substrate we used low-molecular weight chitosan [M_W 7.8 kDa, deacetylation degree (DD) 98%] which was prepared according to modified procedure [10] by acid hydrolysis of high-molecular weight chitosan (M_W 500 kDa, DD 85%). 3-Fluoroimidazo-[1,2-*a*]pyridine fragments were introduced into glucosamine units of chitosan (**VI**) by treatment of the polymer with 3-fluoroimidazo[1,2-*a*]pyridin-2-carboxylic acid hydrochlorides **Va**–**Ve** in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**VII**) in aqueous methanol at pH 5.5 (20°C) according to the procedure described in [11] (Scheme 2). Under these conditions, the reaction was accompanied by ethoxycarbonylation of amino groups in chitosan as side process [12].

Modified chitosans **VIIIa**–**VIIIe** were isolated as hydrochlorides and were amorphous solids. The structure of **VIIIa**–**VIIIe** was confirmed by ^{1}H and ^{19}F NMR spectroscopy. Their ^{1}H NMR spectra characteristically contained signals from methyl protons in the ethoxycarbonyl groups at δ 1.17–1.26 ppm, methyl protons in the acetylamino groups at δ 2.01–2.05 ppm, 2-H in the aminoglucopyranose rings at δ 2.99–3.22 ppm, and protons in the imidazopyridine fragments at δ 7.03–8.96 ppm. In the ^{19}F NMR spectra of **VIIIa**–**VIIIe**, fluorine nuclei in the imidazopyridine fragments resonated at δ_F –66 to –70 ppm. The degree of substitution in polymer units (n, m, p, q) was determined from the signal intensity ratios of aromatic protons (q), 2-H in the aminoglucopyranose rings (n), methyl protons in the acetylamino groups (m), and methyl protons in the ethoxycarbonyl groups (p).

To conclude, we have demonstrated the possibility for modification of chitosan with biologically active fluorine-containing fragments via acylation with 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acids.

EXPERIMENTAL

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200.13 and 188.29 MHz, respectively, using tetramethylsilane (internal) and CF_3COOH (external) as references. Compounds **IIIa**, **IIIc**, **IVa**, **IVc**, and **Vc** were synthesized previously [9]. Initial 2-aminopyridines **Ib**, **Id**, and **Ie**, methyl 3,3,3-trifluoro-2-oxopropionate (**II**), trimethyl phosphite (Aldrich), and chitosan (500 kDa, DD 85%; Heppe Biomaterial GmbH) were commercial products. The molecular weight of chitosan was determined by high-performance liquid chromatography. The weight-average molecular weights (M_W), number-average molecular weights (M_n), and polydispersity indices (M_W/M_n) of low molecular weight chitosans were determined at 30°C using an Ultrahydrogel 500 column (Waters) and 0.05 M acetic acid–0.15 M ammonium acetate (pH 5.2) as eluent (flow rate 0.5 ml/min). The chromatograms were processed with the aid of Multikhrom 1.6 program (Ampersend). The

column was calibrated using dextran standards with molecular weights of 1080, 4440, 9890, 43500, 66700, 123600, and 196300 kDa (Sigma).

Methyl 3,3,3-trifluoro-2-(3-methylpyridin-2-ylimino)propionate (IIIb) was synthesized according to the procedure described in [9] from 0.1 mol of 3-methylpyridin-2-amine and 0.1 mol of methyl 3,3,3-trifluoro-2-oxopropionate. Yield 75%, bp 97–98°C (5 mm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.49 s (3H, Me), 3.98 s (3H, MeO), 6.98 t (1H, H_{arom}, J = 6.9 Hz), 7.11 d (1H, H_{arom}, J = 6.9 Hz), 7.75 d (1H, H_{arom}, J = 6.9 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F 8.02 ppm. Found, %: C 48.61; H 3.87; N 11.25. $C_{10}H_9F_3N_2O_2$. Calculated, %: C 48.79; H 3.68; N 11.38.

Methyl 3,3,3-trifluoro-2-(5-bromopyridin-2-ylimino)propionate (IIId) was synthesized according to the procedure described in [9] from 0.1 mol of 5-bromopyridin-2-amine and 0.1 mol of methyl 3,3,3-trifluoro-2-oxopropionate. Yield 75%, bp 81–82°C (1 mm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.89 s (3H, MeO), 6.71 d (1H, H_{arom}, J = 8.2 Hz), 7.53 d (1H, H_{arom}, J = 8.2 Hz), 7.83 s (1H, H_{arom}). ^{19}F NMR spectrum (DMSO-d_6): δ_F 8.19 ppm. Found, %: C 34.92; H 2.12; N 9.23. $C_9H_6BrF_3N_2O_2$. Calculated, %: C 34.75; H 1.94; N 9.01.

Methyl 3,3,3-trifluoro-2-(5-chloropyridin-2-ylimino)propionate (IIIe) was synthesized according to the procedure described in [9] from 0.1 mol of 5-chloropyridin-2-amine and 0.1 mol of methyl 3,3,3-trifluoro-2-oxopropionate. Yield 75%, bp 118–119°C (5 mm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.82 s (3H, MeO), 6.89 d (1H, H_{arom}, J = 8.8 Hz), 7.42 d (1H, H_{arom}, J = 8.8 Hz), 7.91 s (1H, H_{arom}). ^{19}F NMR spectrum (DMSO-d_6): δ_F 8.12 ppm. Found, %: C 40.74; H 2.12; N 10.23. $C_9H_6ClF_3N_2O_2$. Calculated, %: C 40.55; H 2.27; N 10.51.

Methyl 3-fluoro-8-methylimidazo[1,2-*a*]pyridine-2-carboxylate (IVb) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 3,3,3-trifluoro-2-(3-methylpyridin-2-ylimino) propionate and 0.1 mol of trimethyl phosphite. Yield 73%, mp 142–144°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.54 s (3H, Me), 3.93 s (3H, MeO), 6.90 t (1H, H_{arom}, J = 6.7 Hz), 7.05 d (1H, H_{arom}, J = 6.7 Hz), 7.99 d (1H, H_{arom}, J = 6.7 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F –65.59 ppm, d (1F, J = 1.9 Hz). Found, %: C 57.47; H 4.53; N 13.16. $C_{16}H_{12}F_3N_5O_3S$. Calculated, %: C 57.69; H 4.36; N 13.36.

Methyl 6-bromo-3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylate (IVd) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 2-(5-brompyridin-2-ylimino)-3,3,3-trifluoropropionate and 0.1 mol of trimethyl phosphite. Yield 71%, mp 175–177°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.96 s (3H, MeO), 6.83 d (1H, H_{arom}, J = 8.0 Hz), 7.62 d (1H, H_{arom}, J = 8.0 Hz), 7.95 s (1H, H_{arom}). ^{19}F NMR spectrum (DMSO-d_6): δ_F –67.21 ppm, d (1F, J = 1.9 Hz). Found, %: C 39.38; H 2.02; N 10.04. $C_9H_6BrFN_2O_2$. Calculated, %: C 39.59; H 2.21; N 10.26.

Methyl 6-chloro-3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylate (IVe) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 2-(5-chloropyridin-2-ylimino)-3,3,3-trifluoropropionate and 0.1 mol of trimethyl phosphite. Yield 79%, mp 169–171°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.91 d (1H, H_{arom}, J = 8.7 Hz), 7.51 d (1H, H_{arom}, J = 8.7 Hz), 7.89 s (1H, H_{arom}). ^{19}F NMR spectrum (DMSO-d_6): δ_F –66.29 ppm, d (1F, J = 1.8 Hz). Found, %: C 47.52; H 2.81; N 17.16. $C_9H_6ClFN_2O_2$. Calculated, %: C 47.29; H 2.65; N 17.33.

3-Fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acid hydrochloride (Va) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylate. Yield 87%, mp 215–216°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.26 t (1H, H_{arom}, J = 7.9 Hz), 7.65 m (2H, H_{arom}), 8.52 d (1H, H_{arom}, J = 7.9 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F –63.33 ppm, s (1F) Found, %: C 44.58; H 2.63; N 13.16. $C_8H_5ClFN_2O_2$. Calculated, %: C 44.36; H 2.79; N 12.93.

3-Fluoro-8-methylimidazo[1,2-*a*]pyridine-2-carboxylate hydrochloride (Vb) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 3-fluoro-8-methylimidazo[1,2-*a*]pyridine-2-carboxyylate. Yield 91%, mp 213–214°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.50 s (3H, Me), 7.16 t (1H, H_{arom}, J = 7.9 Hz), 7.40 d (1H, H_{arom}, J = 7.9 Hz), 8.37 d (1H, H_{arom}, J = 7.9 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F –64.59 ppm, d (1F, J = 1.9 Hz). Found, %: C 46.68; H 3.72; N 12.36. $C_9H_7ClFN_2O_2$. Calculated, %: C 46.87; H 3.50; N 12.15.

6-Bromo-3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acid hydrochloride (Vd) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 6-bromo-3-fluoroimidazo[1,2-*a*]-pyridine-2-carboxylate. Yield 93%, mp 265–266°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.59 d (1H, H_{arom},

J = 9.1 Hz,), 7.72 d (1H, H_{arom}, J = 9.1 Hz), 8.83 s (1H, H_{arom}). ^{19}F NMR spectrum (DMSO-d_6): δ_F –63.22 ppm, s (1F). Found, %: C 32.74; H 1.89; N 9.66. $C_8H_4BrClFN_2O_2$. Calculated, %: C 32.52; H 1.71; N 9.48.

6-Chloro-3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acid hydrochloride (Ve) was synthesized according to the procedure described in [9] from 0.1 mol of methyl 6-chloro-3-fluoroimidazo[1,2-*a*]-pyridine-2-carboxylate. Yield 88%, mp 261–262°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.51 d.d (1H, H_{arom}, J = 9.8, 2.1 Hz), 7.69 d (1H, H_{arom}, J = 9.8 Hz), 8.79 s (1H, H_{arom}). ^{19}F NMR spectrum (DMSO-d_6): δ_F –62.59 ppm, s (1F). Found, %: C 38.52; H 2.19; N 11.31. $C_8H_4Cl_2FN_2O_2$. Calculated, %: C 38.28; H 2.01; N 11.16.

Low molecular weight chitosan (VI). A mixture of 15 g of chitosan with M_W 500 kDa (DD 85%) and 120 ml of 6 M hydrochloric acid was stirred for 4 h on heating on a boiling water bath. The precipitate was filtered off and recrystallized twice from 1 M hydrochloric acid. The product was washed with two 70-ml portions of boiling ethanol and dried over P_2O_5 under reduced pressure (5 mm) over a period of 5 h. We thus isolated 8 g (53%) of low molecular weight chitosan hydrochloride. To obtain the corresponding free base, 1 g of chitosan hydrochloride was dissolved in 50 ml of water, the solution was adjusted to pH 9 by adding 5% aqueous ammonia, and the product was purified by dialysis against deionized water over a period of 5 days and liophilized. Yield 60%. ^1H NMR spectrum (DCl), δ, ppm: 2.0 (3H, CH_3CO), 3.15 (1H, 2-H, GluN), 3.67–3.81 (3-H, 6-H, GluN; 3-H, 6-H, 2-H, GluNAc).

***N*-Ethoxycarbonyl-*N*-(3-fluoroimidazo[1,2-*a*]pyridin-2-ylcarbonyl)chitosan (VIIIa).** A suspension of 0.2 g of chitosan (**VI**, free base; 1.24 mmol of NH_2 groups) and 1.33 mmol of 3-fluoroimidazo[1,2-*a*]-pyridine-2-carboxylic acid hydrochloride (**Va**) in 10 ml of water was stirred until the mixture became homogeneous (pH 3.2–4.5), 10 ml of methanol was added, the mixture was titrated with a saturated solution of $NaHCO_3$ to pH 5.5, and 0.33 g (1.33 mmol) of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**VII**) was added. The mixture was stirred for 24 h at 20°C, adjusted to pH 2.0 with 0.5 M hydrochloric acid, stirred for 2 h at 20°C, filtered through a 5-μm membrane, dialyzed against deionized water over a period of 5 days, and liophilized. Yield 0.19 g. ^1H NMR spectrum (D_2O), δ, ppm: 1.19 t (1.18H, CH_3CH_2OCONH), 2.05 s (0.04H, CH_3CONH), 2.99 m (1.19H, 2-H, GluN), 7.03 d (1H, H_{arom}), 7.37–7.48 m (2H, H_{arom}), 8,15 d (1H, H_{arom}). ^{19}F NMR spectrum (D_2O): δ_F –69.70 ppm.

***N*-Ethoxycarbonyl-*N*-(3-fluoro-8-methylimidazo-[1,2-*a*]pyridin-2-ylcarbonyl)chitosan (VIIIb)** was synthesized in a similar way from 0.2 g of chitosan (**VI**), 1.33 mmol of 3-fluoro-8-methylimidazo[1,2-*a*]-pyridine-2-carboxylic acid hydrochloride (**Vb**), and 1.33 mmol of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**VII**). Yield 0.19 g. ^1H NMR spectrum (D_2O), δ, ppm: 1.26 t (2.13H, CH_3CH_2OCONH), 2.03 s (0.04H, CH_3CONH), 2.67 s (3H, Me), 2.99 (1.39H, 2-H, GluN), 7,57 d (1H, H_{arom}), 7,91 t (1H, H_{arom}), 8,52 d (1H, H_{arom}). ^{19}F NMR spectrum (D_2O): δ_F –66.80 ppm.

***N*-Ethoxycarbonyl-*N*-(3-fluoro-7-methylimidazo-[1,2-*a*]pyridin-2-ylcarbonyl)chitosan (VIIIc)** was synthesized in a similar way from 0.2 g of chitosan (**VI**), 1.33 mmol of 3-fluoro-7-methylimidazo[1,2-*a*]-pyridine-2-carboxylic acid hydrochloride (**Vc**), and 1.33 mmol of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**VII**). Yield 0.20 g. ^1H NMR spectrum (D_2O), δ, ppm: 1.25 t (2.21H, CH_3CH_2OCONH), 2.01 s (0.04H, CH_3CONH), 2.62 s (3H, Me), 3.22 (1.28H, 2-H, GluN), 7.51 d (1H, H_{arom}), 7.75 s (1H, H_{arom}), 8.55 d (1H, H_{arom}). ^{19}F NMR spectrum (D_2O): δ_F –68.27 ppm.

***N*-(6-Bromo-3-fluoroimidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-ethoxycarbonylchitosan (VIIId)** was synthesized in a similar way from 0.2 g of chitosan (**VI**), 1.33 mmol of 6-bromo-3-fluoroimidazo[1,2-*a*]-pyridine-2-carboxylic acid hydrochloride (**Vd**), and 1.33 mmol of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**VII**). Yield 0.15 g. ^1H NMR spectrum (D_2O), δ, ppm: 1.17 (2.3H, CH_3CH_2OCONH), 2.03 (0.04H, CH_3CONH), 3.18 (4.42H, 2-H, GluN), 7.88 d (1H, H_{arom}), 8.18d (1H, H_{arom}), 8.96 s(1H, H_{arom}). ^{19}F NMR spectrum (D_2O): δ_F –66.36 ppm.

***N*-(6-Chloro-3-fluoroimidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-ethoxycarbonylchitosan (VIIIe)** was synthesized in a similar way from 0.2 g of chitosan (**VI**), 1.33 mmol of 6-chloro-3-fluoroimidazo[1,2-*a*]-pyridine-2-carboxylic acid hydrochloride (**Ve**), and 1.33 mmol of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**VII**). Yield 0.17 g. ^1H NMR spectrum (D_2O), δ, ppm: 1.24 (3H, CH_3CH_2OCONH), 2.05 (3H, CH_3CONH), 3.19 (1H, 2-H, GluN), 7.98 d (1H, H_{arom}), 8.11 d (1H, H_{arom}), 8.90 s (1H, H_{arom}). ^{19}F NMR spectrum (D_2O): δ_F –66.20 ppm.

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