Parallel solid-phase synthesis of novel 3,7-diazabicyclo[3.3.1]nonane derivatives starting from natural alkaloid cytisine

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A parallel solid-phase synthesis of combinatorial library of 436 amides of 4-(3,7-diorganyl-3,7-diazabicyclo[3.3.1]nonan-2-yl)butanoic acid has been accomplished starting from natural alcaloid (−)-cytisine. A five-step liquid-phase synthesis resulted in the conversion of cytisine to 7-benzyl-3-[(9*H*-fluoren-9-yl)methyl]-substituted acids, which were further diversified with the use of solid-phase technology on the acid-susceptible amine resins. The combinatorial library obtained is intended for a discovery of new physiologically active compounds.

Key words: alcaloids, cytisine, physiologically active compounds, nicotine acetylcholine receptors, solid-phase synthesis.

Synthetic and natural compounds with 3,7-diazabicyclo[3.3.1]nonane (bispidine) fragment possess highly diverse physiological activity.* Thus, this series includes ion-channel modulators displaying antiunrhythmical properties (for example, drugs Bisaramil and Tedisamil, which are under clinical testing at present),[1] analgesic antagonists of tachichinine receptors NK1,[2] antiepilepsy ligands of γ-aminobutiric acid GABA(B) receptors,[3] *etc*. One of the well known compounds of this type, alcaloid (−)-cytisine (**1**), found in appreciable amounts in the broom kind plants (for example, *Cytisus laburnum L*) and the leguminous family thermopsis (*Thermopsis lanceolata*).[4] Alcaloid **1** and a number of its derivatives are selective ligands of nicotine acetylcholine receptors (nAChR),[5—7] which now are considered as one of the most promising biotargets in the development of new drugs for treatment of neurodegenerative diseases and psychotic states.[8] Taking into account a high potential and wide range of physiological activity of substituted 3,7-diazabicyclo[3.3.1]-nonanes, a design of new compounds of this type seems quite reasonable, as well as a development of methods for their synthesis and creation of corresponding combinatorial libraries for the direct search of compounds-leaders.

Earlier,[9] we have reported on the synthesis of a small test liquid-phase combinatorial library on the basis of 3,7-diazabicyclo[3.3.1]nonane ring. In the framework of our research in the field of highly productive solid-phase synthesis, we used similar technology for the synthesis of more largely scaled combinatorial library on the basis of bispidine core. The major goal of the present work is to synthesize a combinatorial library on the basis of aminoacids suitable for the solid-phase synthesis through the hydrogenation of the pyridone fragment of cytisine, subsequent opening of the lactam ring formed, and introduction of suitable protecting group at the nitrogen atoms.

For this, the starting (−)-cytisine **1** was converted to decahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (tetrahydrocytisine) **2** by the catalytic hydrogenation in water in the presence of platinum(IV) oxide[10—12] (Scheme 1). After alkylation of compound **2** with benzyl bromide and 3-fluorobenzyl bromide, the corresponding 3-substituted lactams **3a,b** were obtained. According to the HPLC/MS data, both the acidic and the basic hydrolyses of these compounds lead to the lactam ring opening and formation of the corresponding aminoacid salts **3´a,b**, however, all attempts to isolate them in the free state resulted in spontaneous dehydration back to the starting lactams. To prevent the reverse cyclization, we carried out methanolysis of compounds **3a,b** catalyzed by HCl, that allowed us to obtain and isolate 7-substituted methyl 4-(3,7-diazabicyclo[3.3.1]non-2-yl)butanoates **4a,b** in form of hydrochlorides. These compounds are rather stable on standing, but on conversion to the free bases also gradually cyclize to the corresponding lactams **3a,b**.

Treatment of compounds **4a,b** with [(9*H*-fluoren-9-yl)methyl]chlorocarbonate (Fmoc-Cl) in aqueous dioxane in the presence of $NaHCO_3$ led to the Fmoc-protected products **5a,b**. After hydrolysis of the ester group in

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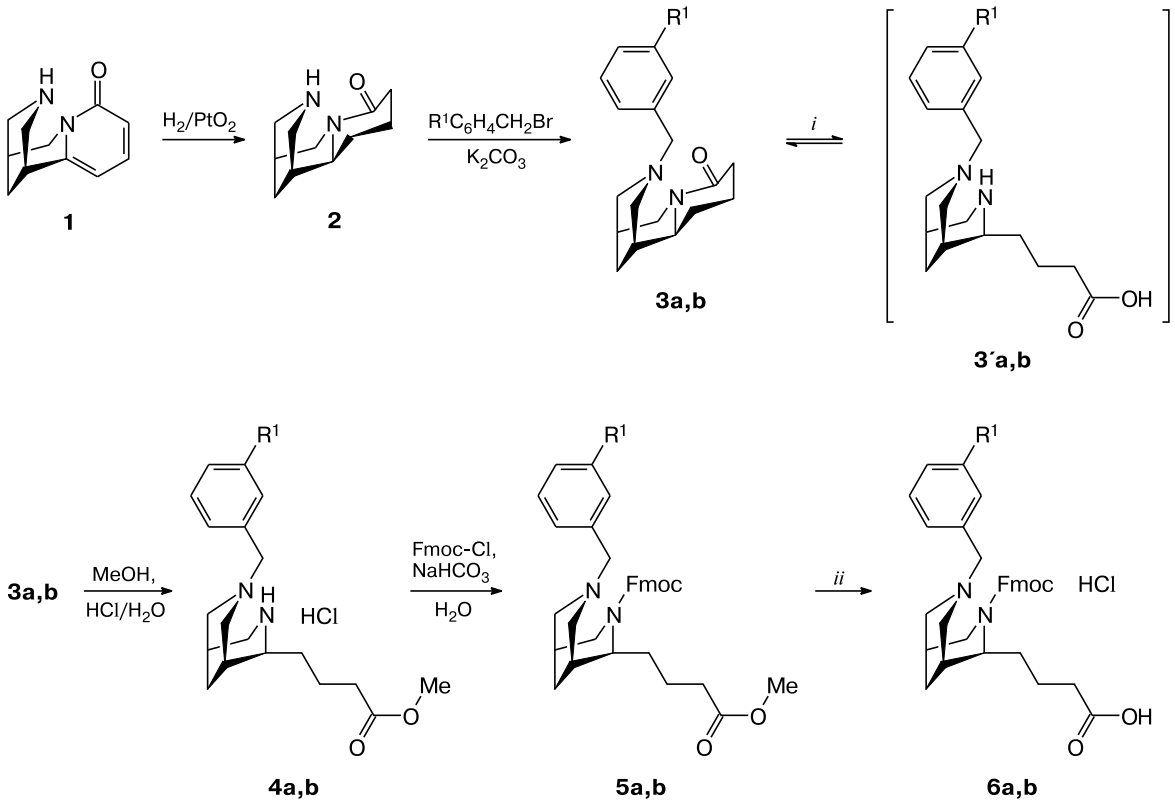
Scheme 1



R^1 = H (**a**), F (**b**)

Reagents and conditions: *i*. H^+ or OH^-; *ii*. HCl, water—dioxane, Δ.

the mixture of dioxane and hydrochloric acid, the Fmoc-protected aminoacids **6a,b** were isolated in form of hydrochlorides. The compounds obtained were used as pre-combinatorial building blocks containing the first point of diversity R^1, which are convenient for the loading on polymeric support in order to carry out subsequent modifications on a solid-phase.

The combinatorial part of the library was performed by the "tea-bags" technology[13] using the substituted acid-labile amine resins **7** on the basis of polystyrene (PS)[14] (Scheme 2).

The reaction of amine resins **7a—h** with Fmoc-aminoacids **6a,b** was carried out in the presence of DIPC.[15] The thus obtained amide resins **8**, already having substituents at two points of diversity, were treated with piperidine in DMF to remove the protecting Fmoc group, then, after washing and drying, they were sealed into the labeled bags made of polypropylene net (the so-called tea-bags).

To introduce combinatorial substituents at position 3-bispidine fragment, the acylation with carboxylic acids in the presence of DIPC was performed, as well as the reactions with isocyanates (the lists of the reagents used are given in the corresponding sections of Experimental) and with sulfonyl chlorides (on the example of ethanesulfonyl chloride).

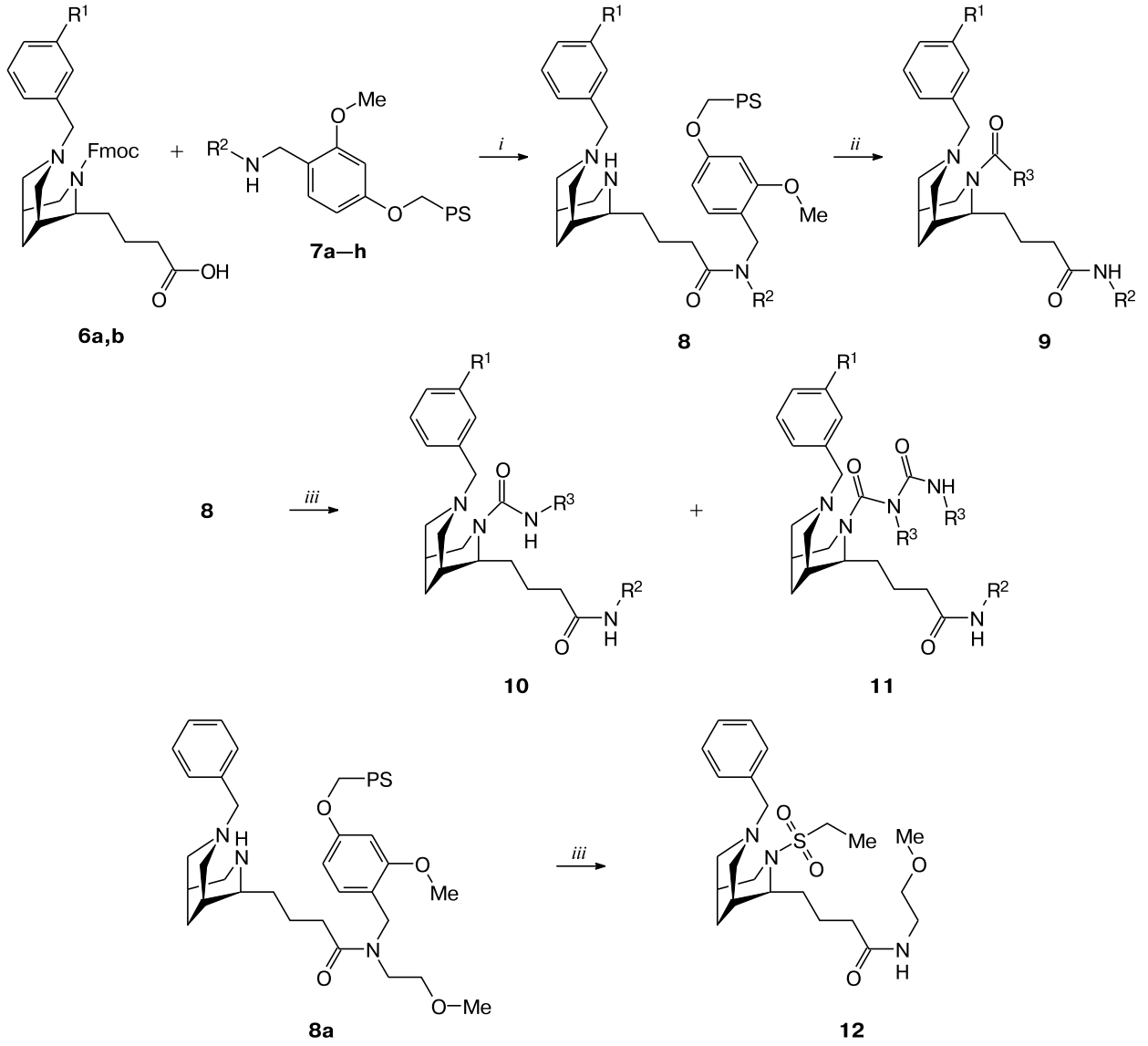
3-Acyl derivatives **9** were obtained with the best results. The nature of amine resins **7** and carboxylic acid R^3COOH (aliphatic, aromatic, and heteroaromatic acids were used) did not have considerable effect on the purity and yield of the combinatorial samples **9**.

During the reaction of resins **8** with isocyanates R^3NCO, ureas **10** formed additionally reacted with excess of isocyanate giving *N*-carbamoylureas **11**. Aromatic isocyanates underwent this reaction especially readily. An attempt to decrease excess of isocyanate to 1—2 equiv. led to a decrease of product **11** content in the sample, leaving a considerable amount of amine **8** unreacted under these conditions. The formation of such admixtures made purification of the target ureas **10** considerably more difficult, therefore, we refused their large-scale production.

A possibility to obtain 3-sulfonamides has been also demonstrated. After treatment of resins **8a** with ethanesulfonyl chloride and subsequent cleavage, product **12** was isolated.

In some combinatorial samples, impurities of compounds of the type **13** (resulting from acylation or carbam-

Scheme 2



R^2 = (3-pyridyl)methyl (**a**), cyclopentyl (**b**), 1-propyl (**c**), cyclopropyl (**d**), 2-phenylethyl (**e**), 2-methoxyethyl (**f**), ethyl (**g**), 3-methoxypropyl (**h**)

Reagents and conditions: *i*. 1) Diisopropylcarbodiimide (DIPC), DMF; 2) piperidine in DMF. *ii*. 1) R^3COOH/DIPC in DMF; 2) 25% TFA in CH_2Cl_2. *iii*. 1) $EtSO_2Cl$ in DMF; 2) 25% TFA in CH_2Cl_2.

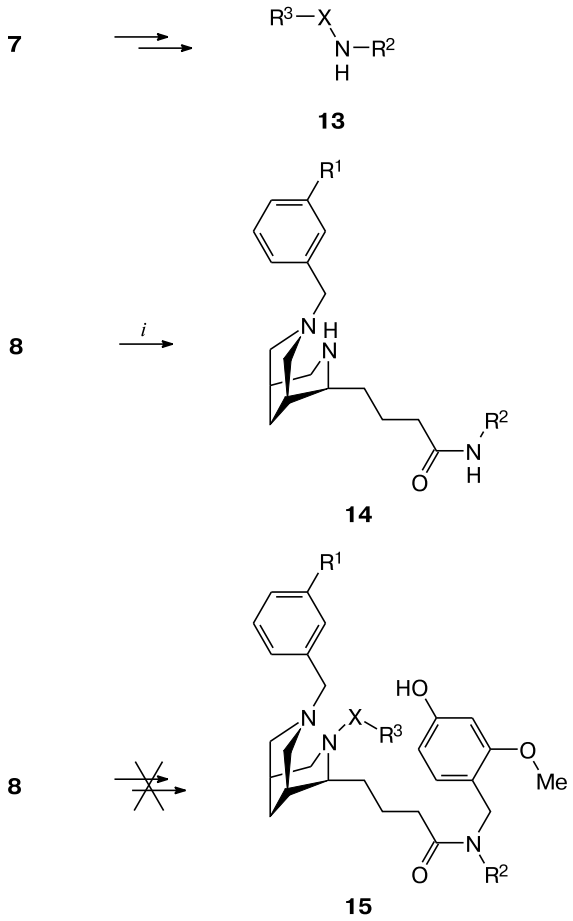
oylation of resins **7**) or unreacted amines **14** were also detected (Scheme 3). Note that the side product of the type **15** known from the literature[16] as forming by the alternative cleavage with the linker fragment was not observed in the reaction mixtures.

A total of 436 compounds of the structures **9** and **10** were synthesized by this technology using two Fmoc-protected aminoacids **6a,b**, eight amine resins **7a—h**, 101 acids, five isocyanates, and ethanesulfonyl chloride. After purification on silica gel, the yields of the target products **9** and **10**, calculated from equivalency of the resins, varied in the range from 5 to 80% with average content of the major substance being 90—95% (HPLC/MS data).

^{1}H NMR spectra of some compounds **9**, their HPLC/MS mass spectra, and yields after purification are given in Table 1.

The solid-phase technology used in this work allowed us to considerably reduce amount of labor on the carrying out and quenching of the reaction due to the convenience of manipulations with tea-bags in comparison with

Scheme 3



i. TFA in CH_2Cl_2.

X = CO, SO_2, NHCO

the liquid reaction mixtures, to increase the total yield, as well as to decrease the cost of purification of compounds obtained since the greater part of impurities can be removed during the washing of the polymer.

In conclusion, we developed a method for the transformation of natural cytisine to Fmoc-protected bispidine aminoacids **6** convenient for the solid-phase combinatorial synthesis. Application of the solid-phase technology with the use of tea-bags allowed us to quickly synthesize and isolate a combinatorial library of compounds **9** and **10** with three points of diversity for performing biological tests.

Experimental

In this work, commercially available materials and reactants were used. Tea-bags (30×40 mm) were made of polypropylene tissue by the SI Corporation production (catalog No. 1004421) and sealed using an AmeriVacS AVP-20 pneumatic blow machine. Analytical TLC was carried out on EM Separations Technology F_{254} silica gel plates. Substances were visualized under the UV light with the wavelength of 254 nm or in a chamber with iodine vapors. Flash chromatography was performed using EM 63 μm silica gel and THF solution (5—10%) in dichloromethane as the eluent. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer (300 MHz) in $CDCl_3$ or DMSO-d_6 with Me_4Si as the internal standard. HPLC/MS spectra were obtained on a chromato-mass spectrometer equipped with a Shimadzu 10Avp liquid chromatograph, a UV detector (λ = 215 and 254 nm), a Sedex 75 detector for the light scattering, and a PE SCIEX API 150EX mass spectrometer (ionization method, ESI), with a C_{18} Synergi 2u Hydro-RP Mercury column (20×2 mm), with a linear gradient of the ratio acetonitrile : water from 5 : 95 to 95 : 5 (vol.) at a flow rate of 0.5 mL min^{-1} and analytical cycle of 4 min.

(1*S*,5*S*)-Decahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (tetrahydrocytisine) (2). A solution of cytisine (20 g, 0.104 mol) in deionized water (100 mL) was hydrogenated under stirring for 24 h at 50 °C and under pressure of 5 atm in the presence of platinum dioxide (0.5 g). The colorless solution obtained was filtered from the platinum precipitate, water was removed on a rotary evaporator at 80 °C until the weight was constant. The yield was 20 g (98%), white powder, m.p. 99—102 °C. ^1H NMR ($CDCl_3$), δ: 4.64 (dt, 1 H, J = 13.8 Hz, J = 1.9 Hz); 3.45—3.56 (m, 1 H); 3.31 (d, 1 H, J = 14.2 Hz); 3.06 (d, 1 H, J = 13.5 Hz); 2.70—3.00 (m, 3 H); 2.15—2.52 (m, 3 H); 1.54—2.05 (m, 7 H); 1.49 (br.s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 169.9, 59.9, 51.9, 46.9, 46.8, 33.5, 33.1, 33.0, 28.5, 28.2, 20.2. HPLC/MS (ESI), m/z: 285 $[M + H]^+$.

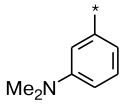
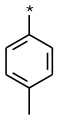
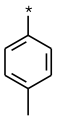
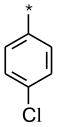
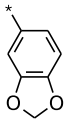
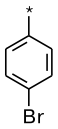
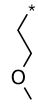
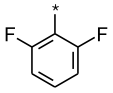
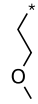
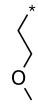
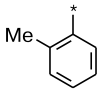
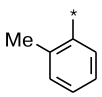
Synthesis of 3-alkyldecahydro-8*H*-1,5-methanopyrido[1,2-*a*]-[1,5]diazocin-8-ones (3-alkyltetrahydrocytisines) 3 (general procedure). A mixture of tetrahydrocytisine **2** (1 equiv.), alkylation agent (1.05 equiv.), dry K_2CO_3 (2.85 equiv.), and anhydrous acetone (2 mL per every mmole of tetrahydrocytisine **2**) was shaken at ~20 °C for 48 h. After filtration and concentration until the weight was constant, compound **3** was obtained, in which, according to the HPLC/MS data, the content of the major substance was >95%.

Synthesis of methyl esters 4 (general procedure). Compound **3** was mixed with methanol (2.5 mL $mmol^{-1}$) and concentrated hydrochloric acid (0.5 mL $mmol^{-1}$). The mixture obtained was refluxed for 24 h. The reaction mixture was treated with excess of dry $NaHCO_3$, filtered, and concentrated on rotary evaporator. To completely remove the salts, the concentrate obtained was diluted with THF, filtered, and again concentrated until the weight was constant. The content of the major substance in compounds **4** obtained exceeded 95% (HPLC/MS data).

Synthesis of Fmoc-methyl esters 5 (general procedure). Sodium hydrogen carbonate (3 equiv.) was added to a solution of the corresponding compound **4** (1 equiv.) in a mixture of dioxane (1 mL $mmol^{-1}$) and water (1 mL $mmol^{-1}$) followed by addition of a solution of Fmoc-Cl (1 equiv.) in dioxane (1 mL $mmol^{-1}$) for 30 min at cooling in an ice-water bath and stirring. The reaction mixture was stirred for 18 h at ~20 °C (TLC monitoring, 20% ethyl acetate in toluene). After the inorganic salts were filtered off, the solution was concentrated *in vacuo*. The residue was used in the next step without additional purification.

Synthesis of Fmoc-carboxylic acids 6 (general procedure). Hydrochloric acid (6 *M*, 8 mL $mmol^{-1}$) was added to a solution of the corresponding compound **5** (1 equiv.) in dioxane (8 mL $mmol^{-1}$) with stirring. The mixture was refluxed for 24 h followed by cooling to ~20 °C. A precipitate formed was filtered

Table 1. ^{1}H NMR spectra, HPLC/MS mass spectra, and yields of some compounds **9** after flash-chromatography

Compound	R^1	R^2	R^3	Yield (%)*	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)	MS (ESI), *m/z* $[M + H]^+$
9a	H			12	7.28—7.40 (m, 5 H); 7.22 (t, 1 H, *J* = 8.1); 6.73 (d, 1 H, *J* = 8.3); 6.67 (s, 1 H); 6.63 (d, 1 H, *J* = 7.3); 6.36 (br.s, 1 H); 3.90—4.02, 3.70—3.84 (both m, 1 H each); 3.35—3.65 (m, 3 H); 3.05—3.24 (m, 2 H); 2.96 (s, 6 H); 1.52—2.68 (m, 12 H); 1.46 (q, 2 H, *J* = 7.3); 1.21—1.40 (m, 2 H); 0.86 (t, 3 H, *J* = 7.3)	491
9b	F			9	7.23—7.32 (m, 3 H); 7.20 (d, 2 H, *J* = 7.7); 7.00—7.10 (m, 2 H); 6.96 (t, 1 H, *J* = 8.2); 6.24 (br.s, 1 H); 4.73—5.00, 3.71—3.93 (both m, 1 H each); 3.35—3.59 (m, 3 H); 3.15—3.32 (m, 2 H); 2.90—3.04, 2.47—2.58 (both m, 1 H each); 2.38 (s, 3 H); 1.90—2.25 (m, 7 H); 1.50—1.86 (m, 4 H); 1.33—1.44 (m, 1 H); 1.06 (t, 3 H, *J* = 7.1)	466
9c	F			25	7.41 (d, 1 H, *J* = 6.0); 7.10—7.34 (m, 7 H); 6.72 (br.s, 1 H); 4.54—4.79 (m, 1 H); 4.19 (d, 1 H, *J* = 12.6); 4.11 (d, 1 H, *J* = 12.6); 3.05—3.99, 2.40—2.85 (both m, 4 H each); 2.38 (s, 3 H); 2.19—2.33 (m, 3 H); 1.43—2.12 (m, 6 H); 0.64—0.76, 0.43—0.52 (both m, 2 H each)	478
9d	H			41	7.39—7.53 (m, 5 H); 7.30—7.39 (m, 4 H); 6.47 (br.s, 1 H); 4.56—4.77, 4.24—4.37 (both m, 1 H each); 4.17 (d, 1 H, *J* = 12.2); 3.76—3.92 (m, 2 H); 3.64 (d, 1 H, *J* = 12.2); 3.38—3.50 (m, 5 H); 3.32 (s, 3 H); 2.59—2.78, 2.40—2.54 (both m, 2 H each); 2.15—2.38 (m, 3 H); 1.38—2.12 (m, 5 H)	498, 500
9e	H			37	7.37—7.53 (m, 5 H); 6.74—6.97 (m, 3 H); 6.44 (br.s, 1 H); 5.99 (s, 2 H); 4.52—4.69 (m, 1 H); 4.08—4.33 (m, 2 H); 3.82—3.98 (m, 1 H); 3.51—3.82 (m, 2 H); 3.37—3.48 (m, 4 H); 3.33 (s, 3 H); 3.19—3.36 (m, 1 H); 2.63—2.82 (m, 2 H); 2.08—2.51, 1.35—2.08 (both m, 5 H each)	508
9f	H			49	7.51 (d, 2 H, *J* = 8.0); 7.37—7.48 (m, 5 H); 7.23—7.33 (m, 2 H); 6.56 (br.s, 1 H); 4.54—4.73, 4.30—4.44 (both m, 1 H each); 4.20 (d, 1 H, *J* = 10.8); 3.73—4.00 (m, 2 H); 3.65 (d, 1 H, *J* = 10.8); 3.35—3.49 (m, 5 H); 3.31 (s, 3 H); 2.66—2.83, 2.42—2.53 (both m, 2 H each); 2.13—2.39 (m, 3 H); 1.38—2.12 (m, 5 H)	542, 544
9g	H			77	7.29—7.51 (m, 6 H); 6.88—7.03 (m, 2 H); 6.82 (br.s, 1 H); 4.66—4.84 (m, 1 H); 4.39, 4.20 (both d, 1 H each, *J* = 12.2); 3.36—3.96 (m, 8 H); 3.31 (s, 3 H); 2.79—2.90 (m, 2 H); 2.14—2.62, 1.38—2.06 (both m, 5 H each)	500
9h	H			52	7.14—7.51 (m, 9 H); 6.67 (br.s, 1 H); 4.57—4.98 (m, 1 H); 4.34, 4.20 (both d, 1 H each, *J* = 10.6); 3.53—3.78 (m, 3 H); 3.37—3.50 (m, 5 H); 3.32 (s, 3 H); 2.65—2.84 (m, 2 H); 2.19—2.58, 1.35—2.09 (both m, 5 H each)	498, 500
9i	H			76	7.33—7.52 (m, 6 H); 7.11—7.31 (m, 2 H); 6.76 (br.s, 1 H); 4.55—4.95 (m, 1 H); 4.42, 4.22 (both d, 1 H each, *J* = 11.9); 3.52—4.01 (m, 3 H); 3.37—3.50 (m, 5 H); 3.31 (s, 3 H); 2.68—2.89 (m, 2 H); 2.19—2.61 (m, 4 H); 1.34—2.14 (m, 6 H)	532, 534, 536
9j	H			7	7.41—7.54 (m, 5 H); 7.31 (d, 1 H, *J* = 6.9); 7.17—7.26 (m, 2 H); 7.09 (d, 1 H, *J* = 6.9); 6.73 (br.s, 1 H); 4.75—4.90 (m, 1 H); 4.45, 4.29 (both d, 1 H each, *J* = 12.6); 3.62—3.89 (m, 3 H); 3.42—3.57 (m, 5 H); 3.34 (s, 3 H); 2.70—2.88 (m, 2 H); 2.52—2.64 (m, 1 H); 2.32—2.49 (m, 3 H); 2.27 (s, 3 H); 1.38—2.10 (m, 6 H)	478

* Calculated from the theoretical loading of resins.

off, washed with water, and dried in air and *in vacuo*. The total yield calculated from compound **4** was 70—75%.

Amine resins 7a—h were synthesized according to the procedure described earlier.[14]

Synthesis of amide resins 8 (general procedure). Triethylamine (0.162 mol) was added to a suspension of compound **6** (0.162 mol) in dichloromethane (350 mL). The mixture was shaken until dissolution, after which the corresponding resins **7** (0.108 mol) and DIPC (0.162 mol) were added. The reaction mixture was shaken for 48 h at ~20 °C. The resins were filtered off and washed two times each with DMF, dichloromethane, methanol, dichloromethane, and methanol, and dried *in vacuo*. To remove the Fmoc groups, the resins obtained (10 g, ~8.5 mmol) were shaken for 1 h with a solution of piperidine in DMF (20% (v/v), 500 mL). The polymer was filtered off, washed two times each with DMF, methanol, dichloromethane, and methanol; dried in air and *in vacuo*.

Synthesis of amides 9 (general procedure). Resins **8** (200 mg, 0.210 mmol) were placed into tea-bags and a combinatorial series was formed from them consisting of 16 tea-bags (in each of them, the resins have a unique combination of substituents R^1 and R^2, R^1 = H, F; R^2 = (3-pyridyl)methyl, cyclopentyl, 1-propyl, cyclopropyl, 2-phenylethyl, 2-methoxyethyl, ethyl, 3-methoxypropyl), then they were placed into a solution of the corresponding acid R^3COOH (10.0 mmol, 3 equiv.) and DIPC (10.0 mmol) in DMF (160 mL) prior kept for 1 h at ~20 °C. The tea-bags were shaken in the reaction solution for 48 h at ~20 °C, then the liquid was decanted, the tea-bags were washed on a shaker sequentially two times each with DMF, dichloromethane, methanol, dichloromethane, hexane and dried *in vacuo*. A single washing cycle time was 3—5 min with the solvent volume being 120—160 mL. Then, the resins were transferred from the tea-bags into test-tubes to provide an efficient stirring during cleavage of the product from the polymer and treated with a 10% solution of TFA in dichloromethane (3 mL) at ~20 °C for 2 h.* The resins were filtered off and washed with some methanol. After the solvent was removed, compounds **9** were obtained as viscous oil (see Table 1). If needed, the compounds obtained were purified on silica gel with THF (5—10%) in dichloromethane as the eluent.

Ureas 10 were synthesized similarly to amides **9** carrying out the reaction with a solution of the corresponding isocyanate (10.0 mmol) in DMF (160 mL). Cyclohexylisocyanate, benzylisocyanate, 3-methoxypropyl-1-isocyanate, 3-ethoxypropyl-1-isocyanate, and isobutylisocyanate were used in the reaction.

* Though the transfer of resins from a tea-bag into a test-tube often increases product yields, this additional step, as a rule, is not used in our laboratory and treatment of resins is performed with a large volume of TFA solution directly in a tea-bag. However, taking into account exceptionally high cost of starting cytisine, we decided that application of this version of cleavage is economically justified in this case.

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