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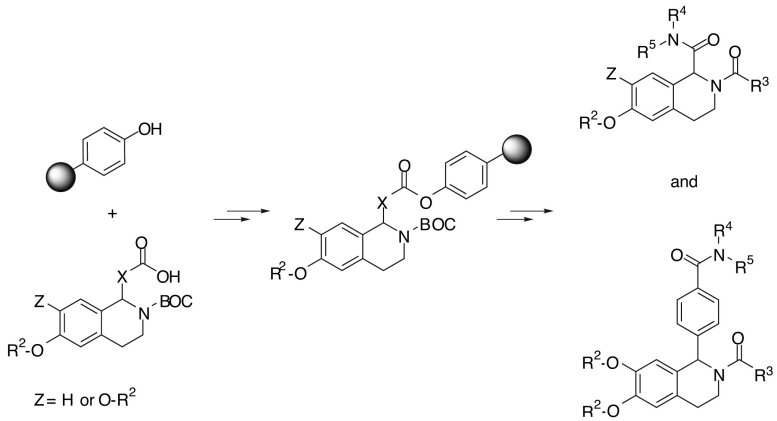

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Solid-Phase Synthesis of 1-Substituted Tetrahydroisoquinoline Derivatives Employing BOC-Protected Tetrahydroisoquinoline Carboxylic Acids

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Compounds containing the tetrahydroisoquinoline ring system were prepared using solid-supported ester derivatives on a nucleophile-sensitive resin, starting from the corresponding BOC-protected amino acids. The key heterocyclic intermediates were obtained from the Pictet−Spengler reaction between ethyl glyoxylate or methyl 4-formylbenzoate and dopamine or 3-hydroxyphenethylamine. After the resulting amino esters were converted to the BOC derivatives, the phenolic hydroxyl groups were alkylated with a series of alkyl halides to afford the corresponding ethers. Ester hydrolysis afforded the BOC-protected tetrahydroisoquinoline carboxylic acid scaffolds, which were then attached to (4-hydroxyphenyl)sulfide resin (Marshall linker) as the corresponding ester. The BOC group was removed under acidic conditions, and the resulting support-bound amine hydrochlorides were converted to the corresponding amides using a set of carboxylic acids. The support-bound amides were liberated with amines to produce the desired tetrahydroisoquinoline carboxamides. Optimization of the resin loading conditions is described in addition to the identification of impurities observed during the development of the optimum conditions for solid-phase synthesis.

Introduction

The combinatorial synthesis of small molecules has quickly evolved from a novel concept[1] to an accepted discipline with broad applications, particularly in the realm of drug discovery.[2] Today, the key synthetic challenge in combinatorial chemistry is to develop general methods that provide rapid access to libraries of biologically relevant and structurally diverse compounds. Preparation of combinatorial libraries based on heterocyclic motifs has become a popular objective in library design, since a substantial number of drugs contain at least one heterocyclic ring system. For this reason, we chose to focus on the tetrahydroisoquinoline ring system for its rich history in biologically active natural products and as a scaffold in drug discovery. Most commonly, this heterocycle has appeared in peptides and peptidomimetics as the constrained unnatural amino acid tetrahydroisoquinoline-3-carboxylic acid [TIC, **1** (Chart 1)].[3] Tetrahydroisoquinoline **2**, the isomeric form of **1**, is also known, but has been less frequently reported in the literature.[4] Examples of biologically active structures containing **1** and **2** as a scaffold are shown in Chart 1. Chemical routes to derivatives of both **1** and **2** generally employ the Pictet−Spengler reaction between the appropriate phenethylamine and aldehyde. As part of a program to generate combinatorial libraries for drug discovery, we chose to prepare peptidomimetic derivatives of **2**, relying on the Pictet−Spengler reaction for synthesis of the key building blocks.[5]

Results and Discussion

Large-Scale Synthesis of BOC-Protected Tetrahydroisoquinoline-1-Carboxylic Acids. The synthetic route employed for the large-scale synthesis of the protected tetrahydroisoquinoline-1-carboxylic acid scaffolds is depicted in Scheme 1. To prepare scaffold **7**, an efficient route to produce kilogram quantities of 3-hydroxyphenethylamine **3** was required, since this material was not commercially available in bulk. Synthetic approaches to various salt forms of **3**, such as catalytic reduction of commercially available norphenylephrine[4] and reduction of 1-(3-hydroxyphenyl)-2-nitroethene were investigated but were ultimately unsatisfactory for the large-scale synthesis of **3**. Instead, compound **3** was conveniently produced on a 6.6-mole scale via demethylation of commercially available 3-methoxyphenethylamine by reaction with 48% hydrobromic acid at reflux.[6] Pictet−Spengler reaction of **3** with ethyl glyoxylate afforded the tetrahydroisoquinoline **5**, which was protected as the BOC derivative **7**[7] then converted to ether derivatives **9a**−**c** using alkyl halides and potassium hydroxide or tetramethylammonium hydroxide as base, the latter being employed for dihydroxytetrahydroisoquinoline **8**. These conditions also converted the ester group of **7** to the corresponding carboxylic acid after acidic workup. Under similar conditions, dopamine hydrochloride (**4**) was converted to the (6,7-dimethoxy)tetrahydroisoquinoline scaffold **10a** via the same sequence. Tetrahydroisoquinoline scaffolds containing a

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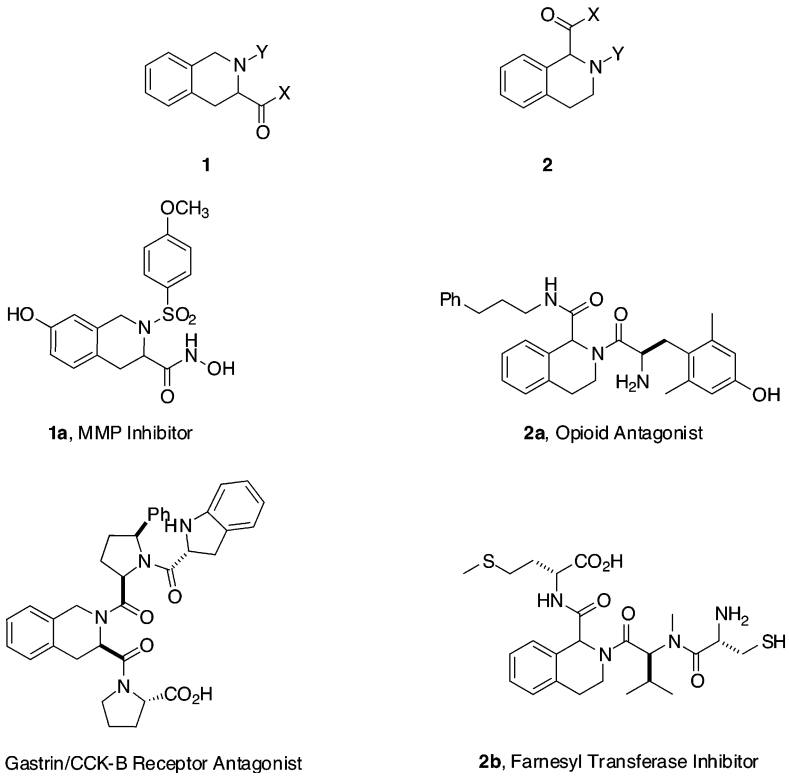
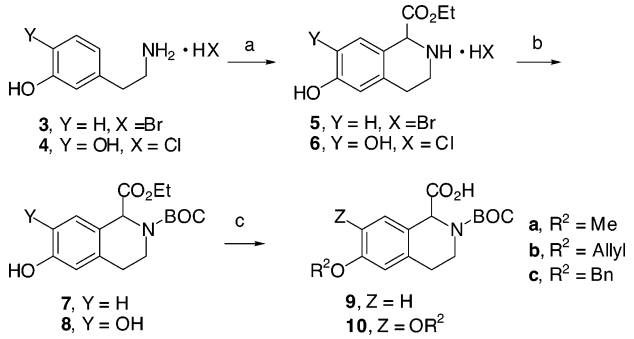
Chart 1. Tetrahydroisoquinoline Carboxylic Acid-Based Scaffolds and Representative Bioactive Structures

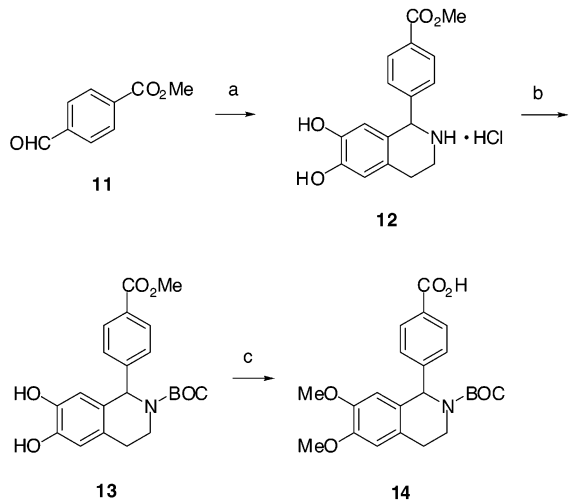


Scheme 1. Synthesis of BOC-Protected Tetrahydroisoquinoline Scaffolds from Ethyl Glyoxylate[a]



[a] Reagents and conditions: (a) EtO_2CCHO (50% in toluene), MeOH−EtOH (3:1), reflux; (b) $(BOC)_2O$, Et_3N, THF, H_2O; (c) 25% aq $Me_4N^+OH^-$ or aq KOH, R^2-X (X = Br or I), DMSO; then 1 N aq HCl.

Scheme 2. Preparation of Tetrahydrosioquinoline 14 via the Pictet−Spengler Reaction[a]



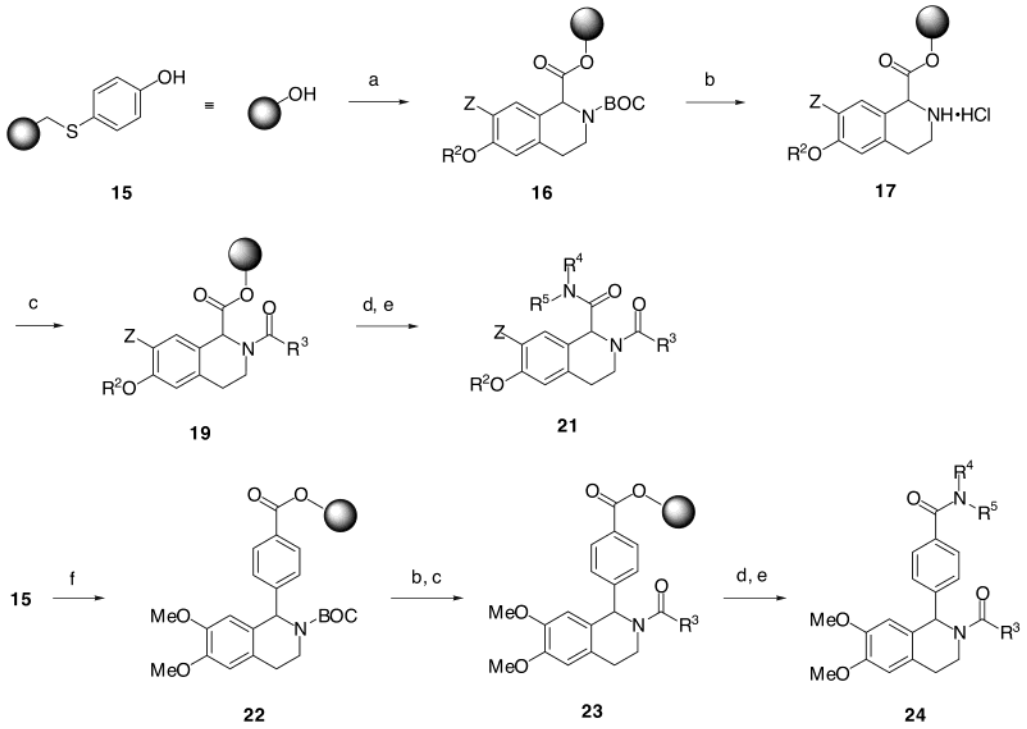
[a] Reagents and conditions: (a) **4**, MeOH−EtOH (1:1), reflux, 48 h; (b) $(BOC)_2O$, Et_3N, THF, H_2O; (c) 25% aq $Me_4N^+OH^-$, MeI, DMSO; then 1 N aq HCl.

phenyl spacer could also be prepared from either **3** or **4** using the same conditions, instead employing methyl 4-formyl benzoate (**11**) as the aldehyde component in the Pictet−Spengler reaction (Scheme 2). Specifically, scaffold **14** was prepared according to this route, using methyl iodide for the alkylation step.

Tetrahydroisoquinolines **5**, **6**, and **12** were prepared in 85−100% yields up to a 7-mole scale according to the routes outlined in Schemes 1 and 2. Protection of the amino group of these compounds as the *tert*-butyloxycarbonyl (BOC) derivatives afforded intermediates **7**, **8**, and **13** in 95−100% crude yield. The optimized one-pot ester hydrolysis/alkylation sequence afforded the target tetrahydroisoquinoline scaffolds **9a**−**c**, **10a**, and **14** in 73−82% isolated yields and purities of >95% by HPLC−UV analysis at 214 nm [area under the curve (AUC)]. The five BOC-protected tetrahydroisoquinoline scaffolds prepared in this manner are shown in Table 1.

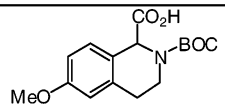
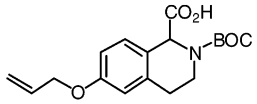
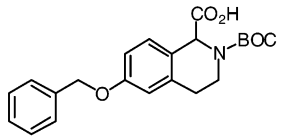
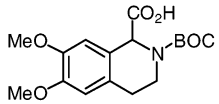
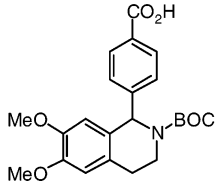
Solid-Phase Synthesis of Tetrahydroisoquinoline Derivatives. Having established reliable synthetic routes for the large-scale synthesis of the tetrahydroisoquinoline scaffolds, development of solid-phase chemistry for the synthesis of the target structures was then pursued. Although several routes to the synthesis of libraries based on the tetrahydroisoquinoline ring system were investigated, the preferred route to library synthesis is shown in Scheme 3. Attachment of the scaffolds to 4-hydroxyphenylsulfide resin **15**[8,9] was performed by a carbodiimide-mediated esterification reaction with scaffolds **9** or **10a** using EDC and DMAP in a mixture of dichloromethane and DMF. Agitation of the resulting

Scheme 3. Solid-Phase Synthesis of Tetrahydroisoquinoline Derivatives[a]



[a] Reagents and conditions: (a) **9** or **10a**, EDC, DMAP, CH_2Cl_2−DMF (1:1), 48 h; (b) 4 N HCl in 1,4-dioxane; (c) R^3CO_2H (**18**), DIC, HOBt, $(i\text{-Pr})_2NEt$; (d) R^4R^5NH (**20**), py, 48 h; (e) amine extraction; (f) **14**, EDC, DMAP, CH_2Cl_2−DMF (1:1), 48 h.

Table 1. Structures and Overall Yields of BOC-Protected Difunctional Tetrahydroisoquinoline Scaffolds Prepared According to Schemes 1 and 2

Compound	Structure	% Yield[a]
9a		100
9b		95
9c		100
10a		75
14		73

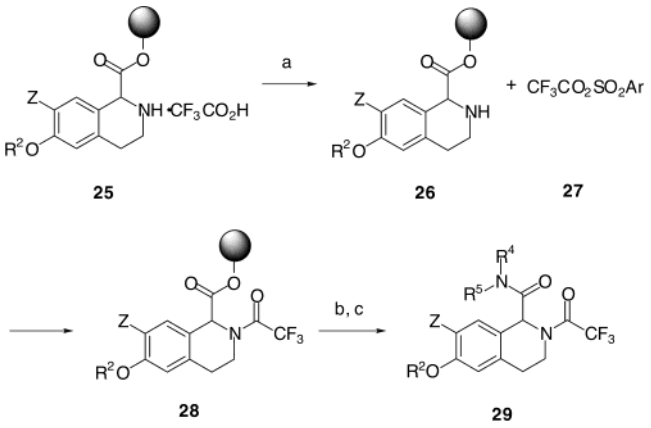
[a] Yield after ester hydrolysis and alkylation.

slurry, followed by washing the resin with organic solvents, afforded the functionalized resin **16**. Deprotection of the BOC group was accomplished with commercially available solution of 4 N HCl in 1,4-dioxane. Acylation of the resulting resin-bound amine hydrochlorides **17** was performed with carboxylic acids by generation of the corresponding active esters using DIC and HOBt. Activation of the carboxylic acids prior to addition to the resin afforded the cleanest products after cleavage from the resin. Similarly, acid **14** was exposed to the same conditions as **9** and **10a** to afford support-bound ester **23**.

The desired amides **21** and **24** were liberated from the resin using 400 mol % of an amine **20** in pyridine. Removal of excess amine was accomplished using solid-supported liquid−liquid extraction (SLE)[10] with diatomaceous earth as support. The choice of aqueous buffer for extraction depended on the physical properties of the amine to be extracted. In general, 2 N aqueous hydrochloric acid was employed for hydrophobic amines, and water was the preferred buffer for removal of hydrophilic amines.

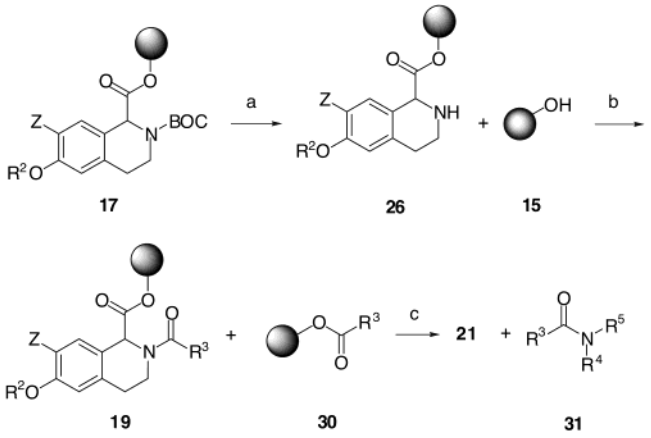
For BOC-deprotection of the support-bound tetrahydroisoquinolines, 4 N HCl in 1,4-dioxane was preferred over TFA, historically preferred for BOC deprotection of amino acids on resin **15**.[9] The presence of TFA, primarily as the salt of the amine, often led to the formation the corresponding trifluoroacetamide **28** as a contaminant. This impurity was observed in significant amounts when sulfonyl chlorides were employed in the acylation of resin **15** (Scheme 4). Formation of the mixed anhydride **26** under these conditions was postulated to be the active species that ultimately afforded **28**. Furthermore, when the support-bound phenyl ester hydrochloride was converted to the free amine after washing the resin with triethylamine, significant amounts of amide **31** were observed (Scheme 5). The formation of this impurity is postulated to arise from base-mediated hydrolysis of the ester **26** to the free phenol **15**, followed by acylation of **15** to give ester **30** and subsequent cleavage with an amine (**20**).

Scheme 4. Formation of the Trifluoroacetamidotetrahydroisoquinoline Impurity during Reaction Optimization[a]



[a] Reagents and conditions: (a) $ArSO_2Cl$, $(i\text{-Pr})_2NEt$; (b) **20**, py; (c) amine extraction.

Scheme 5. Proposed Pathway for the Formation of Amide Impurities Observed during Reaction Optimization[a]



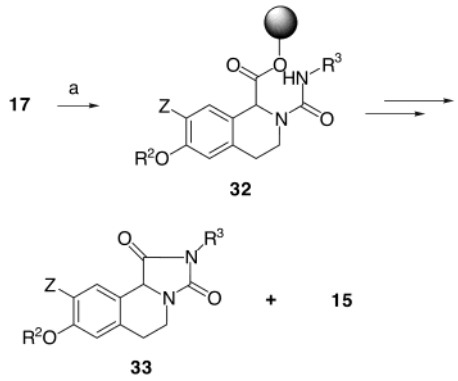
[a] Reagents and conditions: (a) 4 N HCl in 1,4-dioxane, then Et_3N; (b) **18**, DIC, HOBt, $(i\text{-Pr})_2NEt$; (c) **20**, py.

In situ generation of the free amine **25** from the support-bound hydrochloride salt **17** during the acylation reaction suppressed the formation of amide **31**.

Urea formation between isocyanates and resin-bound tetrahydroisoquinoline scaffolds **9** and **10** was complicated by the formation of the corresponding tricyclic hydantoin **33** (Scheme 6), which proceeds via a cyclicative cleavage-type process[11] from the support-bound urea **32**. In fact, formation of hydantoins from α-(ureido)esters on other linkers has been described in the literature.[12] The formation of **33** is facilitated by the more reactive phenyl ester relative to the literature examples for hydantoin formation employing amino esters on Wang or Merrifield resin.[13]

Quantitation of Resin Loading. Resin loading was problematic during development of the solid-phase chemistry, as indicated by low yields of **21** and **24** after cleavage from the resin. While a qualitative assay[9b] for scaffold loading was generally employed for acylation of Marshall resin, a more rigorous measure of scaffold loading was required to allow for optimization of the resin loading in this case.[14] The sterically congested nature of the BOC-amino acids employed here for resin acylation reduced the efficiency of resin loading relative to other examples recently reported

Scheme 6. Formation of Hydantoins from Support-Bound Ureas via a Cyclicative Cleavage Process[a]



[a] Reagents and conditions: (a) R^3−NCO, $(i\text{-Pr})_2Net$.

Table 2. Loading[a] of Resin 15 after One and Two Coupling with Scaffolds **9a**−**c**, **10a** or **14**

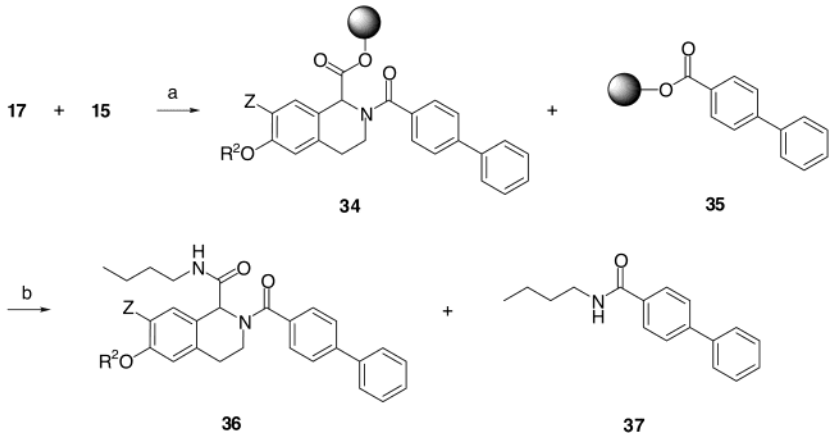
scaffold	% loading after first acylation	% loading after second acylation
9a	84	99
9b	84	99
9c	64	80
10a	87	95
14	100	ND[b]

[a] Determined according to Scheme 7. [b] Not done.

for resin **15**.[9] The best method for determination of loading involved acylation of the functionalized resin with an acid chloride, followed by cleavage with a primary amine. This process converts any unacylated Marshall resin **15** to provide a mixture of desired product and the amide derived from the acid chloride and amine employed for product cleavage from the resin. The relative amounts of each product were determined by HPLC−UV analysis at 214 nm, taking into account the relative extinction coefficients obtained from authentic samples of each product. The chemistry employed for this measure of scaffold loading is shown in Scheme 7, employing 4-phenylbenzoyl chloride as acylator and *n*-butylamine as cleaving amine. The ratio of butylamide **36** to *n*-butyl-4-phenylbenzamide **37** was determined to be a measure of the success of loading of the scaffold onto resin **15**. When this assay showed levels of scaffold loading below 90%, a second coupling of the scaffold was performed exactly as described in Scheme 3, with two minor changes. The second coupling of scaffold employed 300 mol % relative to the measured molar quantity of unacylated sites remaining on resin. Second, DIC was substituted for EDC as the activating reagent. On the basis of the quantitation experiment described above, the scaffolds were loaded onto the resin **15** with >95% conversion after the double coupling. Table 2 shows the results of loading based on the quantitation method described in Scheme 7.

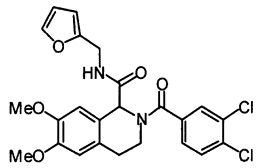
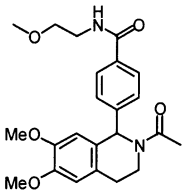
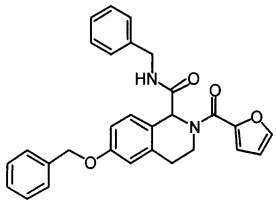
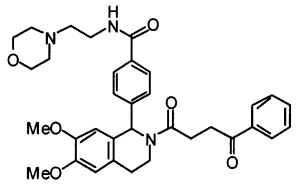
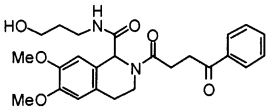
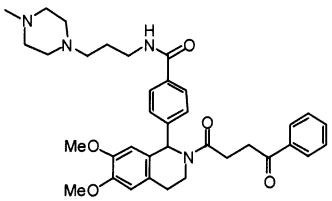
Although several approaches to a tetrahydroisoquinoline library were explored on solid phase and in solution, the route described herein provided the cleanest products, although in modest yields. Representative tetrahydroisoquinoline compounds prepared according to Scheme 3 are reported in Table 3. Purity of these products was assessed by a quantitative purity method,[15] generated by HPLC−UV analysis of solutions containing the compounds reported in

Scheme 7. Reaction Sequence Employed to Determine Scaffold Loading[a]



[a] Reagents and conditions: (a) *p*-PhC_6H_4COCl, $(i\text{-}Pr)_2NEt$; (b) *n*-$BuNH_2$, 1,4-dioxane.

Table 3. Structure and Purities of Compounds Prepared According to Scheme 3

Compound/Structure		Yield (%)[a]	Purity (%)[b]	Compound/Structure		Yield (%)[a]	Purity (%)[b]
21a		33	92	**24a**		31	85
21b		13	57	**24b**		42	74
21c		17	60	**24c**		36	76

[a] Yield of crude material. [b] By quantitation against purified and fully characterized samples; see text for details.

Table 3 at a known concentration and comparing these data to calibration curves generated from analytically pure samples of **21** and **24**. The analytical data (NMR, MS, and combustion analysis) for these purified samples are reported in the Experimental Section. In some cases, the lower yields were due to several factors, including poor product solubility and losses of material during solution transfers, especially during the SLE process.

Summary

We have developed a solid-phase approach to compounds containing the tetrahydrosioquinoline ring system, relying on a series of large-scale Pictet−Spengler reactions for scaffold preparation. Attachment of the protected scaffolds to a nucleophile-cleavable resin followed by amine deprotection, acylation and product cleavage from the resin using

amines, afforded the desired library components. Scaffold loading onto resin was determined by an in-process quality control method, which was used to optimize the reaction conditions required for scaffold attachment. Optimization of this step was necessary to improve product yields and to avoid formation of byproducts, such as the amide derived from the carboxylic acid used for acylation of the scaffold and the amine employed for product cleavage. On the basis of these conditions, a series of libraries based on the tetrahydroisoquinoline-1-carboxylic acid scaffold were prepared in good to excellent product purities.

Experimental Section

General. Mass spectral (MS) data was obtained using a Sciex 150 MCA with a 0.5 mL/min flow rate using a binary solvent system of 99:1 water/acetonitrile containing 0.1% acetic acid and 99:1 acetonitrile/water containing 0.1% acetic acid. UV detection was monitored at 214 and 254 nm. Mass detection was performed using a turbo ion spray source on Shimadzu LC-10 and Shimadzu SDD-1 instruments fitted with a Gilson 215 autosampler. HPLC−UV data was obtained using a Hewlett-Packard HP1100 instrument equipped with a Zorbax SB-C18 4.6 mm × 7.5 cm column and diode array detector. Chromatograms were obtained using a 1.0 mL/min flow rate with the following solvent system: 99.9% acetonitrile/0.1% trifluoroacetic acid and 99.9% water/0.1% trifluoroacetic acid. NMR spectra were obtained in DMSO-d_6, unless stated otherwise, at 300 MHz (proton) and 75 MHz (carbon) employing a GE QE 300-MHz spectrometer. Elemental analyses were performed by Robertson Microlit, Madison, NJ or M-H-W Laboratories, Phoenix, AZ.

4-Hydroxyphenylsulfide resin (Marshall resin, **15**) was purchased from MidWest Biotech and was used as received. All other reagents, solvents, and building blocks were purchased from commercial sources and used as received.

6-Hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid Ethyl Ester Hydrobromide (5). To a 12-L round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel was added 48% aqueous hydrobromic acid (7.60 L, 66.1 mol, 1002 mol %). 3-Methoxyphenethylamine (998 g, 6.60 mol) was added slowly over 30 min with vigorous stirring **(CAUTION: exothermic reaction!)** After the addition was complete, the reaction mixture was heated to reflux for 6 h. Complete conversion of the starting material was observed by HPLC analysis. The reaction mixture was concentrated in vacuo and was then coevaporated from a mixture of toluene and ethanol [1:1 (v/v); 4 L]. The resulting off-white solid corresponding to 3-methoxyphenethylamine hydrobromide (**3**) was dissolved in reagent grade ethanol (4 L). The solution was treated with ethyl glyoxylate (50% solution in toluene; 1.44 L, 7.26 mol, 110 mol %) and heated to reflux for 16 h. The reaction mixture was concentrated to remove ∼3.0 L of solvent. The thick mixture was then cooled to room temperature, then to 5 °C for 2 h with moderate agitation to precipitate the product. The slurry was then filtered on a 3-L coarse sintered glass funnel. To minimize potential losses, the mother liquor was employed to transfer residual solids from the reaction flask to the funnel. The off-white filter cake was vacuum-dried, then rinsed with cold (−20 °C) ethanol (2 × 300 mL, then 1 × 200 mL) and again dried on the funnel. The solid was further dried in a vacuum oven to constant weight at 50 °C (N_2 bleed, 25 mmHg) to give 1.69 kg (85% yield) of **5** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.60 (br s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 6.72 (dd, J = 8.2, 2.2 Hz, 1H), 6.62 (d, J = 2.2 Hz, 1H), 5.35 (s, 1H), 4.24 (q, J = 7.0 Hz, 2H), 3.50−3.36 (m, 2H), 2.93 (t, J = 5.9 Hz, 2H), 1.24 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 222 [$(M + H)^+$].

6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid Ethyl Ester Hydrochloride (6). To a 12-L round-bottomed flask was added dopamine hydrochloride (**4**; 401 g, 2.10 mol) and 3.0 L of methanol. To the suspension was added ethyl glyoxylate (50% solution in toluene; 462 mL, 2.10 mol, 110 mol %) and reagent grade ethanol (1 L). The flask was fitted with a reflux condenser and heated to a gentle reflux using a heating mantle. Upon reaching an internal temperature of 50 °C, the reaction mixture changed from a white suspension to a clear yellow solution. The reaction mixture was stirred at reflux overnight for 12−18 h. The solution was cooled to <40 °C and then concentrated to dryness. Reagent grade ethanol (500 mL) was added to the yellow solid, and the resulting suspension was stirred as a slurry at room temperature, then placed in a refrigerator at 5 °C overnight. The precipitate was isolated on a sintered glass funnel, and the mother liquor was employed to transfer residual solids from the reaction flask to the funnel. The filter cake was washed with cold (−20 °C) reagent grade ethanol (500 mL) and air-dried on the funnel. The filtrate was then dried to constant weight in a vacuum oven at 50 °C (N_2 bleed, 25 mmHg), affording 498 g (100% yield) of **6** as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.84 (br s, 1H), 9.25 (d, J = 4.4 Hz, 1H), 9.22 (d, J = 4.4 Hz, 1H), 6.79 (s, 1H), 6.57 (s, 1H), 5.18 (s, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.46−3.35 (m, 2H), 2.81 (t, J = 5.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H); MS (ESI) m/z 238 $[M + H]^+$.

4-(6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-benzoic Acid Methyl Ester Hydrochloride (12). A 22-L round-bottomed flask was charged with **4** (1.40 kg, 7.38 mol), methanol (8.0 L), and ethanol (8.0 L). The resulting suspension was treated with methyl 4-formylbenzoate **11** (1.33 kg, 8.10 mol, 110 mol %), and the reaction mixture was heated to a vigorous reflux. After 2.5 h, the mixture went from a pale yellow suspension to a clear yellow solution. After 48 h, HPLC analysis indicated that the reaction was complete. The reaction mixture was allowed to cool to room temperature, then cooled to 5 °C in a refrigerator for 2 h. The resulting slurry was then filtered through a coarse sintered glass funnel. The mother liquor was employed to transfer residual solids from the reaction flask to the funnel, and the filter cake was washed with cold diethyl ether (1.2 L) to afford 2.11 kg (85% yield) of **12** as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.63 (br s, 1H), 9.36 (d, J = 4.7 Hz, 1H), 9.15 (d, J = 3.7 Hz, 1H), 8.22 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 6.82 (s,

1H), 6.19 (s, 1H), 5.85 (s, 1H), 4.05 (s, 3H), 3.42−3.21 (m, 2H), 3.08−3.01 (m, 2H); MW 299, MS (ESI) *m*/*z* 300 [M + H]$^+$.

General Procedure for BOC Protection: Preparation of Ethyl 6,7-Dihydroxy-3,4-dihydro-1*H*-isoquinoline-1,2-dicarboxylic Acid 2-*tert*-Butyl Ester (8). The hydrochloride salt **6** (693 g, 2.90 mol) was dissolved in THF (8.2 L) and water (3.5 L) in a 22-L round-bottomed flask equipped with a mechanical overhead stirrer. To the stirring solution was added triethylamine (407 mL, 2.90 mol), followed by slow addition (∼1 h) of a solution of liquid di-*tert*-butyl dicarbonate (637.3 g, 2.9 mol) in THF (0.5 L). When the reaction was complete as determined by HPLC analysis (2 h), the mixture was transferred to a 22-L extraction vessel. The two-phase system was diluted with ethyl acetate, and the layers were separated. The organic layer was washed with 1 N HCl (1.0 L), then with saturated aqueous NaCl (1.0 L), and dried (Na_2SO_4). Evaporation of the solvent and drying in vacuo for 4 h afforded the BOC-protected tetrahydroisoquinoline **8** (929 g, 95% yield) as a brittle yellow foam.

BOC-protected tetrahydroisoquinoline intermediates **7** and **13** were prepared in this manner and were obtained in 95−100% crude yields. These materials were taken on the corresponding alkylation products as described below.

General Method for Alkylation and Hydrolysis of 7. Preparation of 2-*tert*-Butyl Ester-6-methoxy-3,4-dihydro-1*H*-isoquinoline-1-carboxylic Acid (9a). To a 3-L round-bottomed flask equipped with a mechanical stirrer and stirblade assembly was added crude **7** (244 g, 770 mmol), followed by 605 mL of DMSO. A previously prepared aqueous solution of potassium hydroxide [129.6 g (2.31 mol) of KOH dissolved in 555 mL of water] was added, then stirring was initiated. After ∼2.5 h, hydrolysis of the ester was complete, as determined by HPLC analysis. The reaction mixture was then treated with iodomethane (83.3 mL, 1.36 mol; 177 mol %). The reaction mixture was stirred vigorously overnight. After the reaction was deemed to be complete as determined by HPLC−UV analysis, KOH (183.4 g, 3.27 mol) was added as a solution in water (200 mL). After stirring for an additional 2−4 h, the reaction mixture was extracted with Et_2O (300 mL). The aqueous phase was acidified to pH 2 by slow addition of concentrated H_3PO_4 and then extracted with ethyl acetate (1 L). The organic phase was washed with water (500 mL) and saturated aqueous NaCl (500 mL), dried (Na_2SO_4), and concentrated in vacuo to give 236 g (100%) **9a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 1H), 6.76 (dd, J = 8.5, 2.5 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 5.50 (s, 1H), 5.33 (s, 1H), 3.78 (s, 3H), 3.81−3.61 (m, 2H), 2.98−2.62 (m, 2H), 1.46 (s, 9H); MS (ESI) *m*/*z* 306 [(M − H)$^-$].

Compounds **9b** and **9c** were prepared in a similar manner.

2-*tert*-Butoxycarbonyl-6-allyloxy-3,4-dihydro-1*H*-isoquinoline-1-carboxylic Acid (9b). Isolated as a yellow oil in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.5, 2.5 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 6.08−5.96 (m, 1H), 5.49 (s, 1H), 5.39 (dd, J = 17.2, 1.5 Hz, 1H), 5.33 (s, 1H), 5.27 (dd, J = 10.4, 1.1 Hz, 1H), 4.50 (d, J = 5.1 Hz, 2H), 3.81−3.61 (m, 2H), 2.97−2.68 (m, 2H), 1.46 (s, 9H); MS (ESI) *m*/*z* 332 [(M − H)$^-$].

2-*tert*-Butoxycarbonyl-6-benzyloxy-3,4-dihydro-1*H*-isoquinoline-1-carboxylic Acid (9c). Isolated as a yellow oil in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.27 (m, 6H), 6.82 (dd, J = 8.4, 2.2 Hz, 1H), 9.75 (d, J = 2.2 Hz, 1H), 5.45 (s, 0.5H), 5.34 (s, 0.5H), 5.03 (s, 2H), 3.78−3.59 (m, 2H), 3.00−2.70 (m, 2H), 1.46 (s, 9H); MS (ESI) *m*/*z* 382 [(M − H)$^-$].

General Method for Alkylation and Hydrolysis of 8. Preparation of 6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinoline-1,2-dicarboxylic Acid 2-*tert*-Butyl Ester (10a). To a 2-L round-bottomed flask equipped with a magnetic stir bar was added crude **8** (136 g, 404 mmol), 25% tetramethylammonium hydroxide solution (506 mL; 1.40 mol, 350 mol %), and water (500 mL). Stirring was initiated, resulting in the formation of an opaque, blood-colored solution. After ∼2.5 h, hydrolysis of the ester was complete, as determined by HPLC analysis. The mixture was then diluted with water (500 mL) and treated with a solution of iodomethane (62.8 mL, 1.01 mol; 250 mol %) in 300 mL of DMSO. The two-phase system was stirred vigorously, resulting in the formation of a white precipitate. The reaction was allowed to stir overnight. After the reaction was deemed to be complete as determined by HPLC−UV analysis, KOH (22.6 g, 404 mmol) in water (50 mL) was added. The reaction mixture was stirred for an additional 2−4 h, then the solution was extracted with Et_2O (1.3 L). The aqueous phase was acidified to pH 2 with slow addition of concentrated H_3PO_4 and extracted with ethyl acetate (2 × 1 L). The combined organic layers were washed with water (2 L) and saturated aqueous NaCl (2 L), dried (Na_2SO_4), and concentrated in vacuo. Trituration of the resulting viscous oil with Et_2O afforded 109 g (80%) of **10a** as a crystalline solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.07 (s, 1H), 6.76 (s, 1H), 5.32 (d, J = 19.8 Hz, 1H), 3.81 (s, 6H), 3.78−3.63 (m, 2H), 2.98−2.68 (m, 2H), 1.48 (s, 9H); MS (ESI) *m*/*z* 336 [(M − H)$^-$].

Compound **14** was prepared in a similar manner.

2-*tert*-Butoxycarbonyl-1-(4-carboxyphenyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic Acid (14). Obtained as a white solid in 73% yield from **13**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 6.61 (s, 1H), 6.23 (br s, 1H), 4.01−3.80 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 2.90−2.68 (m, 2H), 1.51 (s, 9H); MW 413; MS (ESI) *m*/*z* 412 [(M − H)$^-$].

Preparation of Support-Bound Tetrahydroisoquinoline Resins (16 and 22). 4-Hydroxyphenylsulfide resin **15** (300 g, 330 mmol, 100 mol %) was swollen with 1 L of dichloromethane. Scaffold **9a**−**c**, **10a**, or **14** (1.00 mol, 303 mol %) and EDC (191 g, 1.00 mol, 303 mol %) were dissolved in a minimum volume of 1:1 dichloromethane/DMF required for complete dissolution. To the resin was added the activated scaffold solution, followed by the addition of a slurry of DMAP (4.16 g, 33.0 mmol, 10 mol %) in 5 mL of dichloromethane. The reaction vessel was capped, then placed on a reciprocal shaker. After 48 h, an aliquot of the resin was washed and exposed to a solution of $FeCl_3$ in pyridine, a qualitative assay for unacylated resin **15**.[9b] The resin was filtered and washed with dichloromethane (2 × 500 mL), DMF (2 × 500 mL), MeOH (2 × 500 mL),

DMF (2 × 500 mL), dichloromethane (2 × 500 mL), MeOH (2 × 500 mL), dichloromethane (2 × 500 mL), and MeOH (2 × 500 mL). The resin was dried in vacuo overnight.

Quantitation of Resin Loading. Resin **16** or **22** (300 mg) was swollen and washed with dichloromethane (3 × 5 mL), then treated with a solution of 4-phenybenzoyl chloride (0.5 M) and diisopropylethylamine (1.0 M) in 5 mL of chloroform for 24 h. After rinsing the resin with dichloromethane (×3), dichloromethane/triethylamine (4:1), MeOH, and 1,4-dioxane (×2), the resin was exposed to a solution of 2.0 M *n*-butylamine in 1,4-dioxane for 24 h. The filtrate was collected, and the ratio of product **36** to amide **37** derived from unacylated resin **15** was determined by HPLC−UV analysis at a wavelength of 214 nm.

BOC Deprotection. Support-bound esters **16** or **22** (125 mg, ∼0.10 mmol) was washed with 1,4-dioxane (2 × 1 mL), then treated with a solution of 4 N HCl in 1,4-dioxane (1 mL). The reaction vessel was sealed, and the resulting slurry was shaken on a reciprocal shaker for 1.5 h. The 4 N HCl in 1,4-dioxane was allowed to drain, and the resin was washed with dichloromethane (2 × 1 mL) and DMF (2 × 1 mL). After the final rinse, excess solvent was removed from the resins prior to the addition of solutions of the activated carboxylic acids.

A carboxylic acid (**18**; 0.375 mmol) was dissolved in anhydrous DMF (0.95 mL) to give a 0.4 M solution. The acid solution was treated with DIC (45.6 mg, 0.375 mmol), followed by HOBt·H_2O (57.2 mg, 0.375 mmol) and *N*,*N*-diisopropylethylamine (0.13 mL, 0.75 mmol). The resulting solution was allowed to stand for 3−7 min to generate the active ester of the carboxylic acid, then the solution was added to resin. The resulting slurry was shaken for 12−36 h at ambient temperature. The resin was then washed using the following solvents: DMF (2 × 1 mL); dichloromethane (2 × 1 mL); 20% triethylamine in DMF (2 × 1 mL); MeOH (2 × 1 mL); dichloromethane (2 × 1 mL); and finally, pyridine (3 × 1 mL).

2-*N*-Acyl-Tetrahydroisoquinoline Carboxamides (21 and 24). The resins obtained as described above were swollen with pyridine, then treated with a 0.5 M solution of an amine **20** in pyridine (1.2 mL; 0.60 mmol, ∼400 mol %). The slurry was shaken on a reciprocal shaker at ambient temperature for 40−56 h. The solution was collected and the resin was washed with methanol (2 × 350 μL). The combined filtrate and washings were concentrated in vacuo. The residue was dissolved in $CHCl_3$ (1 mL) and added to Varian "Chem-Elute Hydromatrix" diatomaceous earth in a fritted reaction vessel, previously treated with either 500 μL of 2 N HCl or with 650 μL of water. The $CHCl_3$ solution was allowed to percolate by gravity through the diatomaceous earth (∼15 min), then the source vessel was washed with $CHCl_3$ (3 × 350 μL), and each wash was transferred to the support. The combined $CHCl_3$ extracts were then concentrated in vacuo. Crude yields and weight-percent purities for products obtained in this manner are given in Table 3. Analytical data for the purified compounds used in the quantitative purity analysis is provided below.

2-(3,4-Dichlorobenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (Furan-2-ylmethyl)-amide (21a). Obtained as a tan powder after purification by flash chromatography on SiO_2 (elution solvent: 30−75% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.69 (m, 1H), 7.56−7.40 (m, 2H), 7.32 (br s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.80 (s, 1H), 6.62 (s, 1H), 6.30 (br s, 1H), 6.19 (br s, 1), 5.96 (s, 1H), 4.53 (dd, J = 15.7, 5.8 Hz, 1H), 4.39−4.33 (m, 1H), 3.96−3.64 (m, 2H), 3.85 (s, 6H), 2.89−2.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.0, 151.2, 148.6, 148.0, 142.1, 135.1, 134.5, 133.1, 130.6, 129.1, 126.1, 122.6, 111.3, 110.4, 110.2, 107.3, 57.0, 55.9, 55.8, 55.7, 44.0, 36.6, 28.5; MS (ESI) *m*/*z* 490.6 $[M + H]^+$. Anal. Calcd for $C_{24}H_{22}Cl_2N_2O_5$: C, 58.91; H, 4.54; N, 5.72. Found: C, 58.81; H, 4.43; N, 5.50.

6-Benzyloxy-2-(furan-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid Benzylamide (21b). Isolated as a white solid after purification by flash chromatography on SiO_2 (elution solvent: 50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.43−7.12 (m, 11H), 7.05 (s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.79 (s, 1H), 6.49 (s, 1H), 5.87 (s, 1H), 5.04 (s, 2H), 4.41 (t, J = 6.5 Hz, 2H), 4.28−3.84 (m, 2H), 3.02 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 145.0, 143.0, 132.2, 129.2, 123.0, 121.7, 121.1, 114.0, 113.9, 113.3, 112.7, 112.3, 112.2, 112.0, 108.8, 102.1, 99.3, 98.3, 96.3, 54.8, 42.9, 42.8, 28.4, 27.9; MS (ESI) *m*/*z* 465.2 $[M - H]^-$, 467.4 $[M + H]^+$, 489.2 $[M + Na]^+$. Anal. Calcd for $C_{29}H_{26}N_2O_4$: C, 74.66; H, 5.62; N, 6.00. Found: C, 74.45; H, 5.51; N, 5.79.

6,7-Dimethoxy-2-(4-oxo-4-phenylbutyryl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (3-Hydroxypropyl)amide (21c). Isolated as a white powder after purification by reversed-phase preparative HPLC. The purified material was partitioned between dichloromethane and aqueous $NaHCO_3$ to remove residual trifluoroacetic acid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 6.9, 1.5 Hz, 2H), 7.57 (t, J = 1.2 Hz, 1H), 7.47 (t, J = 6.4 Hz, 2H), 7.14 (br t, J = 5.4 Hz, 1H), 6.85 (s, 1H), 6.64 (s, 1H), 5.81 (s, 1H), 3.89 (t, J = 3.7 Hz, 2H), 3.84 (s, 6H), 3.60 (t, J = 5.4 Hz, 2H), 3.38 (t, J = 4.5 Hz, 2H), 3.15−2.87 (m, 4H), 2.65 (t, J = 4.7 Hz, 2H), 1.65 (q, J = 5.9 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 199.9, 172.0, 171.3, 148.6, 147.8, 136.4, 133.5, 128.7, 128.1, 126.4, 123.7, 111.5, 110.8, 59.8, 57.2, 55.9, 42.5, 36.8, 33.8, 31.8, 28.5, 27.2; MS (ESI) *m*/*z* 455.2 $[M + H]^+$. Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.82; H, 6.51; N, 6.06.

4-(2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-*N*-(2-methoxyethyl)benzamide (24a). Isolated as a white powder after purification by reversed-phase HPLC, followed by silica gel chromatography; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 6.87 (s, 1H), 6.66 (s, 1H), 6.57 (br s, 1H), 6.48 (s, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.62 (t, J = 4.5 Hz, 2H), 3.53 (m, 2H), 3.36 (s, 3H), 3.35 (m, 2H), 2.91 (dd, J = 11.2, 5.4 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 167.3, 148.3, 147.8, 146.0, 133.7, 128.9, 127.6, 127.4, 127.0, 126.4, 112.2, 77.3, 71.2, 58.9, 56.0, 54.3, 40.4, 39.7, 28.6, 21.7; MS (ESI) *m*/*z* 413.5 $[M + H]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84: N, 6.79. Found: C, 66.70; H, 6.86; N, 6.66.

4-[6,7-Dimethoxy-2-(4-oxo-4-phenylbutyryl)-1,2,3,4-

tetrahydroisoquinolin-1-yl]-*N*-(2-morpholin-4-yl-ethyl)-benzamide (24b). Isolated as a white powder after purification by reversed-phase HPLC, followed by chromatography on silica gel; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 6.8, 1.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 7.3, 1.7 Hz, 1H), 7.50−7.44 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.85 (s, 1H), 6.76 (t, J = 5.4 Hz, 1H), 6.69 (s, 1H), 6.51 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.72 (t, 4H), 3.58−3.47 (m, 2H), 3.46−3.37 (m, 2H), 3.10−2.95 (m, 2H), 2.86 (t, J = 6.5 Hz, 2H), 2.83−2.72 (m, 2H), 2.58 (t, J = 5.7 Hz, 2H), 2.48 (br t, J = 2.5 Hz, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 99.1, 170.3, 167.1, 148.2, 147.7, 145.9, 136.7, 133.3, 133.1, 128.7, 128.5, 128.1, 127.7, 127.0, 126.6, 126.4, 111.2, 66.3, 57.2, 55.9, 54.7, 53.2, 39.7, 35.6, 33.6, 28.4, 27.4; MS (ESI) m/z 586.0 [(M + H)$^+$]; Anal. Calcd for $C_{34}H_{39}N_3O_6$: C, 69.72; H, 6.71; N, 7.17. Found: C, 69.60; H, 6.76; N, 7.03.

4-[6,7-Dimethoxy-2-(4-oxo-4-phenyl-butyryl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]benzamide (24c). Isolated as a white powder after purification by preparative reversed-phase HPLC. The purified material was partitioned between dichloromethane and aqueous $NaHCO_3$ to remove residual trifluoroacetic acid, then chromatographed again by normal-phase preparative HPLC; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (br s, 1H), 8.00 (dd, J = 8.4, 1.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.85 (s, 1H), 6.68 (s, 1H), 6.50 (s, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.52 (br s, 2H), 3.42 (t, J = 9.9 Hz, 2H), 2.82 (m, 2H), 2.54 (m, 10H), 2.22 (s, 3H), 1.76 (br s, 2H), 1.24 (br s, 2H), 0.85 (m, 2H); ^{13}C NMR, (300 MHz, $CDCl_3$) δ: 199.2, 170.5, 167.3, 148.6, 148.0, 145.9, 137.0, 134.2, 133.3, 128.8, 128.7, 128.3, 127.9, 127.7, 127.3, 126.9, 111.5, 58.2, 56.2, 55.2, 55.0, 53.4, 46.2, 40.7, 39.9, 33.9, 28.7, 27.6, 24.7; MS (ESI) m/z 613.1 [M + H]$^+$. Anal. Calcd for $C_{36}H_{44}N_4O_5$: C, 70.56; H, 7.24; N, 9.14. Found: C, 70.48; H, 7.06; N, 8.92.

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