ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

Toward Lead-Oriented Synthesis: One-Pot Version of Castagnoli Condensation with Nonactivated Alicyclic Anhydrides

Sergey V. Ryabukhin,*[,†,‡] Dmitriy M. Panov,[‡,§] Dmitry S. Granat,[‡,§] Eugeniy N. Ostapchuk,[§] Dmitriy V. Kryvoruchko,[§] and Oleksandr O. Grygorenko[‡]

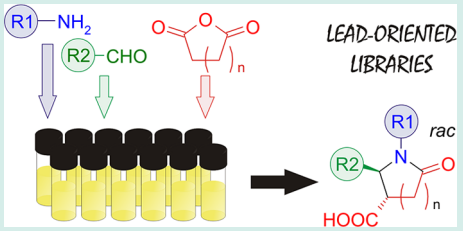
[†]The Institute of High Technologies, Taras Shevchenko National University of Kyiv, Glushkov Street 4, Kyiv 03187, Ukraine

[‡]Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv 01601, Ukraine

[§]Enamine, Ltd., Alexandra Matrosova Street 23, Kyiv 01103, Ukraine

Supporting Information

ABSTRACT: One-pot variation of Castagnoli condensation, that is, reaction of cyclic anhydrides, amines, and aldehydes, has been developed as a combinatorial approach to 1,2-disubstituted 5-oxopyrrolidine- and 6-oxopiperidine-3-carboxylic acids, as well as their benzo-analogues. Utility of the method to multigram preparation of building blocks and synthetic intermediates was also demonstrated. The final products are obtained in high yields and diastereoselectivity. The method fits well in the concept of lead-oriented synthesis; in particular, it can be used for the design of lead-like compound libraries, even if the strictest cut-offs are applied to the physicochemical properties of their members.



KEYWORDS: *multicomponent reaction, condensation, anhydride, aldehyde, amine, lead-oriented synthesis*

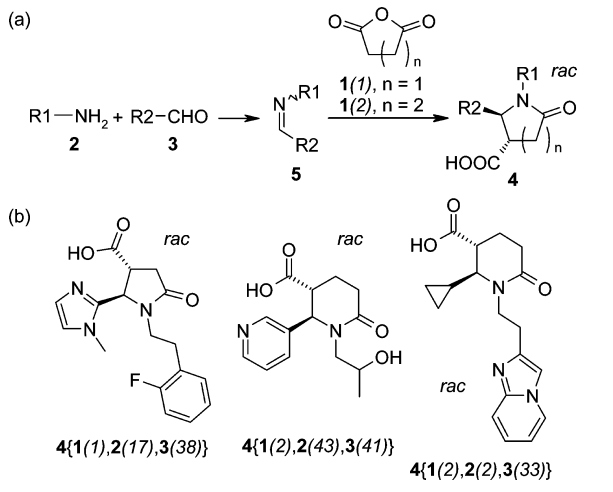
INTRODUCTION

Modern drug discovery relies heavily on the ability of synthetic chemists to provide compounds with favorable physicochemical properties in an efficient manner. Since the cornerstone work of Lipinski and co-workers,[1] the "drug-likeness" concept has evolved significantly: apart from more rigorous restrictions imposed on molecular weight and lipophilicity of the compounds,[2] additional molecular properties are considered such as conformational flexibility[3] and three-dimensionality.[4] As a result, a "lead-likeness" concept emerged in drug discovery.[5]

Although the criteria that define the part of chemical space, which is attractive for starting medicinal chemistry projects, are more or less clear, the synthetic methodology, which would allow navigating this chemical space, is not easily accessible. A challenge of "lead-oriented synthesis"[6] should be addressed by developing approaches to the libraries of highly polar, conformationally restricted, sp^3-enriched compounds with low molecular weight. One of such approaches pursued by us recently[7] relies on design of building blocks with molecular properties vastly shifted to the appropriate part of chemical space; this leaves much room for applying classical combinatorial chemistry modifications (that is, acylation, arylation, alkylation, reductive amination, etc.), which normally increase both MW and LogP. Nevertheless, novel combinatorial reactions producing lead-like libraries from common building blocks might be more beneficial. In particular, advantages of one-pot multicomponent reactions[8] could be used to ensure huge diversity of the compound libraries produced.

In this work, we report a one-pot reaction of alicyclic anhydrides (**1**), primary amines (**2**), and aldehydes (**3**) as a combinatorial approach to 1,2-disubstituted 5-oxopyrrolidine- and 6-oxopiperidine-3-carboxylic acids (**4**) (Scheme 1); the utility of the method for the multigram preparation of building blocks is also demonstrated. The reaction is a modification of Castagnoli condensation, that is, reaction of succinic anhydride (**1**(*1*)) with imines (**5**).[9,10] Compounds **4** and their derivatives have great potential for a broad spectrum of biological

Scheme 1. Condensation of Alicyclic Anhydrides, Primary Amines, and Aldehydes: (a) Castagnoli Reaction and (b) Illustrative Examples of the Products Obtained in This Work



Received: September 29, 2013
Revised: November 21, 2013
Published: January 30, 2014

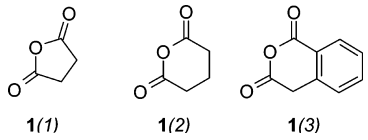


Figure 1. Anhydrides **1**(*1*−*3*) used in this work for the synthesis of carboxylic acids **4**.

activities: they were evaluated as protein tyrosine phosphatase 1B inhibitors,[11] transcription factor inhibitors,[12] antiepileptic,[13] antilipidemic,[14] and antiviral[15] agents, topoisomerase I inhibitors,[16] and progesterone receptor agonists.[17] They were also used in the synthesis of amino acids,[18] alkaloilds[19] and other natural products.[20] Notably, compounds **4** are carboxylic acids, which are hardly accessible via combinatorial methods and are therefore underrepresented in current screening collections.[21]

RESULTS AND DISCUSSION

The classical Castagnoli condensation involving simple alicylic anhydrides gives moderate yields of the products, but includes a preliminary synthesis of an imine;[9] it is therefore unsuitable for parallel synthesis. Milder reaction conditions, including one-pot multicomponent variations, have been developed only for more CH-acidic and hence more reactive substrates, such as (arylthio)succinic[20,22] (generated in situ) and homophtalic anhydrides. The latter reaction was promoted by ionic liquids and $InCl_3$,[23] $Yb(OTf)_3$,[24] $KAl(SO_4)_2{\cdot}12H_2O$,[25] iodine,[26] sulfuric,[27] and sulfonic[28] acid functionalized silica, $ZnCl_2$−$AlCl_3/SiO_2$,[29] and L-proline.[30]

First of all, we have focused on developing a method for introducing simple alicylic anhydrides, that is, succinic **1**(*1*) and glutaric **1**(*2*) (Figure 1), into a one-pot variation of Castagnoli reaction, which would be amendable for parallel synthesis. To demonstrate the scope of the reaction, 44 amines **2**(1−*44*) (Figure 2) and 44 aldehydes **3**(*1*−*44*) (Figure 3) were selected. It was found that the optimal procedure includes sonication of

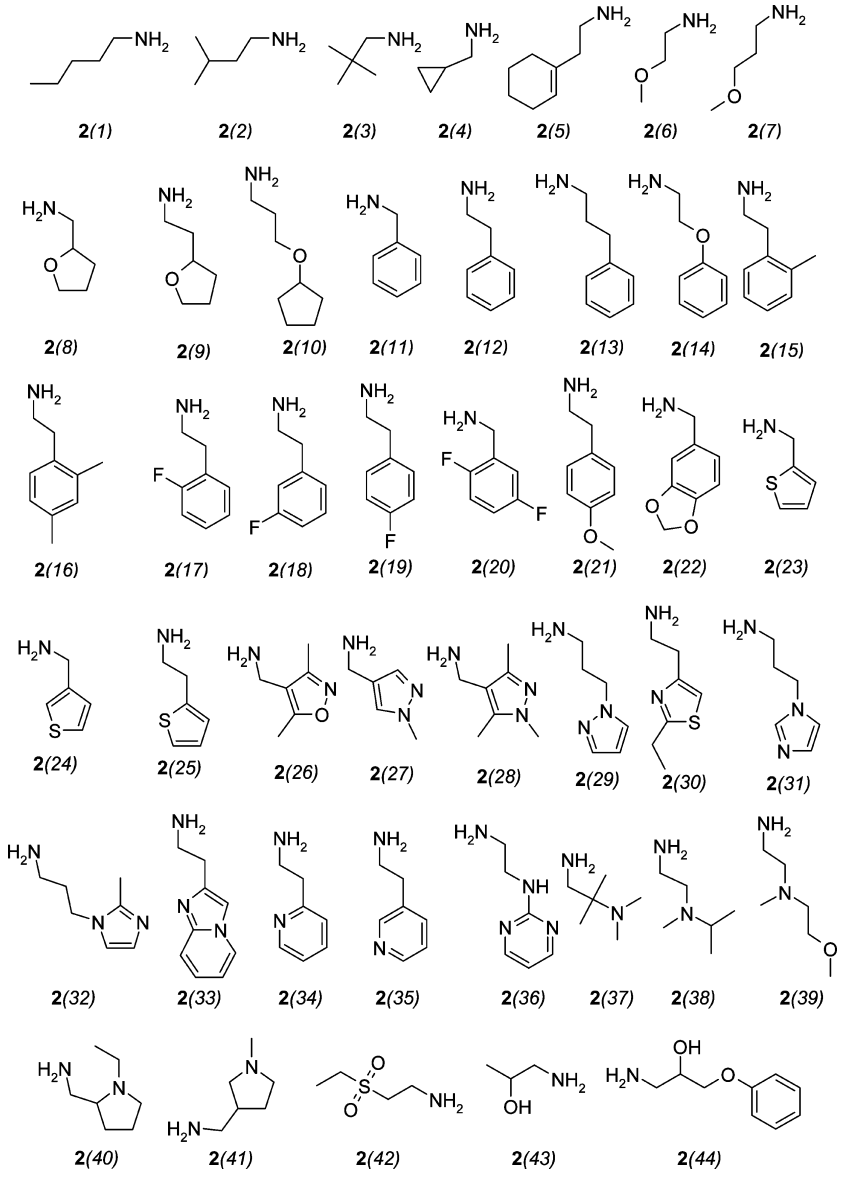


Figure 2. Amines **2**(*1*−*44*) used in this work for the synthesis of carboxylic acids **4**.

dx.doi.org/10.1021/co4001277 | ACS Comb. Sci. 2014, 16, 146−153

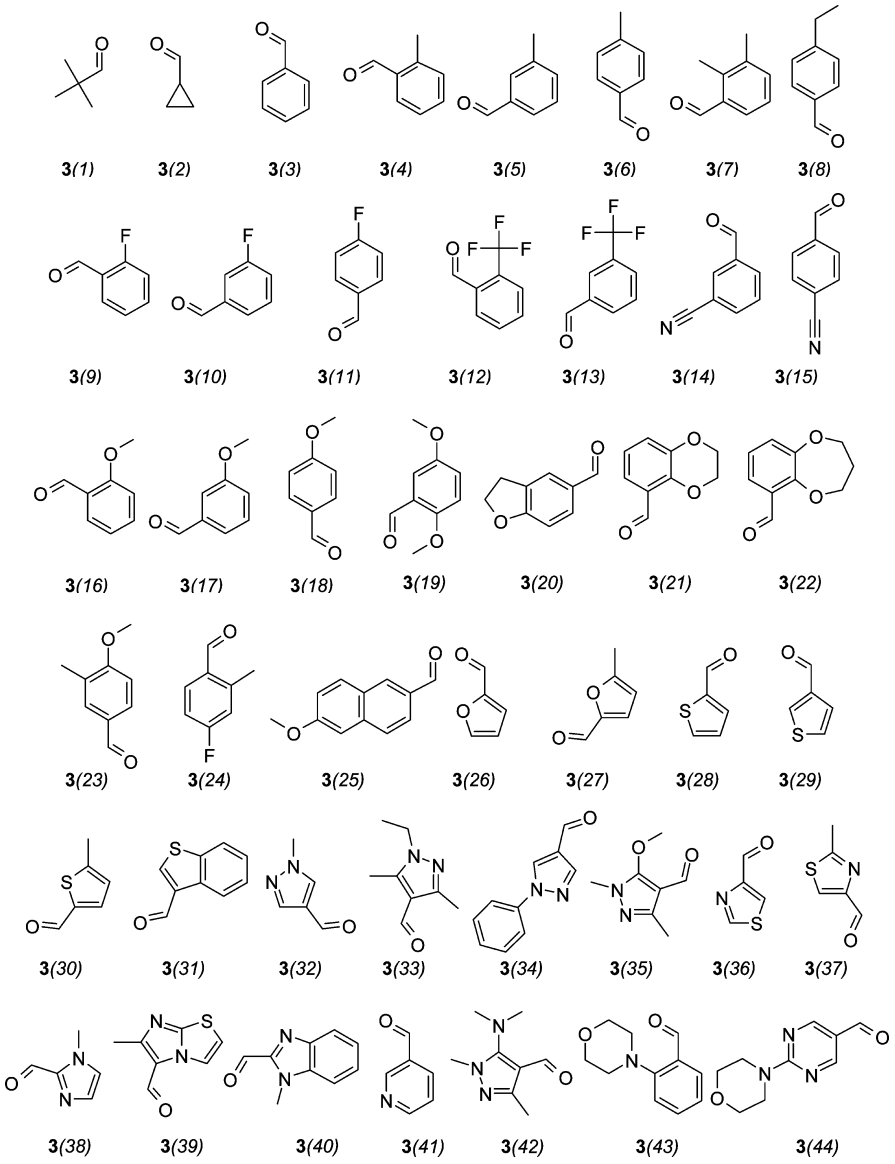


Figure 3. Aldehydes 3(*1*−*44*) used in this work for the synthesis of carboxylic acids **4**.

2(*1*−*44*) and **3**(*1*−*44*) in MeOH for 6 h, evaporation of the solvent in the vacuum drying oven, and heating of the residue with **1**(*1*,*2*) in dry xylenes at 140−180 °C for 6−8 h. 125 products, **4**{**1**(*1*,*2*), **2**(*1*−*44*), **3**(*1*−*44*)} were randomly selected from the virtually possible library to demonstrate the scope of the protocol and were synthesized in 67−88% yields (see Table S1 in the Supporting Information). It should be noted that in most cases the reaction proceeded in a diastereoselective manner, resulting in the formation of the final products with more than 85% of major diastereomer content. In the case of racemic amines containing chiral centers (**2**(*8*,*9*,*40*,*41*,*43*,*44*)), the products were obtained as nearly ∼1:1 mixtures of the diastereomers.

It was found that the method gave excellent yields with α-branched aliphatic, aromatic and heteroaromatic aldehydes. The method was equally efficient with aliphatic amines **2**(*1*−*10*), as well as amines bearing aromatic (**2**(*11*−*22*)) and heteroaromatic (**2**(*23*−*36*)) substituents, sulfone (**2**(*42*)) or hydroxy (**2**(*43*,*44*)) groups.

It was also shown that the method works well with homophtalic anhydride **1**(*3*): the corresponding 7 products **4**{**1**(*3*), **2**(*4*,*6*,*7*), and **3**(*4*,*5*,*14*,*36*,*37*)} were obtained in 75−93% yields.

Predicted physicochemical properties of 132 synthesized library members **4**{**1**(*1*,*2*), **2**(*1*−*44*), **3**(*1*−*44*)} are summarized in Figure 4 (see also Figure S1 in the Supporting Information).[31] The value ranges are as follows: molecular weight (MW) 265−349 (average 335), calculated logP −1.25−3.32 (average 1.29), number of H-donors 1−2 (average 1.03), H-acceptors 3−7 (average 4.30), rotatable bonds 4−8 (average 5.20), fraction of sp^3 carbons (F_{sp^3}) 0.25−0.82 (average 0.51), total polar surface area (TPSA) 57.6−109.6 Å (average 75.9 Å).[2] These data show that the one-pot version of Castagnoli condensation developed in this work can be used for the design of lead-like compound libraries, even if the strictest lead-likeness cut-offs[6] are applied.

The method was also applicable for the scaled preparation of building blocks and synthetic intermediates. In particular, reaction of anhydrides **1**(*1*) or **1**(*2*) with aldehydes **3**(*3*), **3**(*18*), **3**(*28*), or **3**(*32*) and methylamine led to the formation of carboxylic acids **6**−**12** in 71−80% yields (Scheme 2). It should be noted that the reaction was performed on a

dx.doi.org/10.1021/co4001277 | ACS Comb. Sci. 2014, 16, 146−153

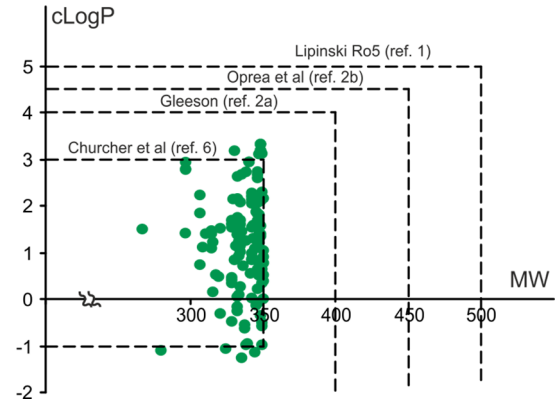
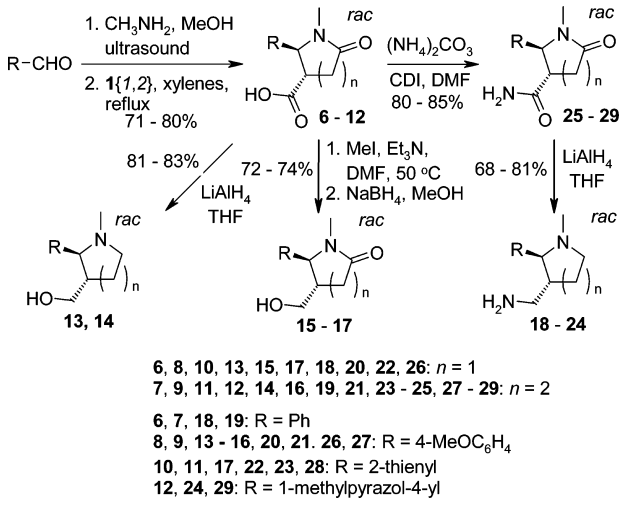


Figure 4. Physicochemical properties of 132 library members **4**{**1**(*1*−*3*), **2**(*1*−*44*), **3**(*1*−*44*)} shown in cLogP−MW plot.

Scheme 2. Preparation of Building-Blocks 6−29

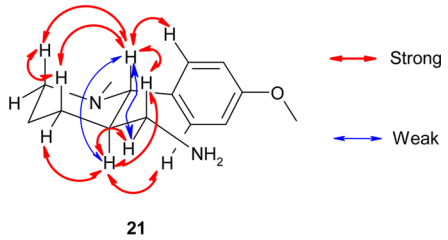


6, **8**, **10**, **13**, **15**, **17**, **18**, **20**, **22**, **26**: *n* = 1
7, **9**, **11**, **12**, **14**, **16**, **19**, **21**, **23** - **25**, **27** - **29**: *n* = 2

6, **7**, **18**, **19**: R = Ph
8, **9**, **13** - **16**, **20**, **21**. **26**, **27**: R = 4-MeOC$_6$H$_4$
10, **11**, **17**, **22**, **23**, **28**: R = 2-thienyl
12, **24**, **29**: R = 1-methylpyrazol-4-yl

multigram scale (up to 100 g) without considerable effect on its outcome. The products **6**−**12** were obtained in a diastereoselective manner (more than 85% of the major diastereomer). The carboxylic acids **6**−**12** can be used for the preparation of other building blocks of potential interest to synthetic and medicinal chemistry, that is, alcohols **13**−**17** (either *via* complete or partial selective reduction) or primary amines **18**−**24** (via reduction of the corresponding amides **25**−**29**).

The relative configuration for the pyrrolidine-derived carboxylic acids **6**, **8**, and **10** was established using an analysis of the coupling constants for the signal of 2-CH proton (observed at 4.7−4.9 ppm) as compared to the literature data for **6** and **8**.[9a,10b] For the major isomers, the value $J \approx 5$ Hz was observed, which is consistent with trans configuration, whereas for the impurities of minor isomers, the corresponding value was $J \approx 9$ Hz − a feature characteristic for the cis stereoisomer. In the case of piperidine-derived compounds **7**, **9**, **11**, and **12**, the corresponding *J* values were not informative since they were ∼4 Hz for both major isomers and impurities, a feature discussed previously in the literature for the trans isomer.[10d] Since no useful correlations were found in NOESY spectrum of the carboxylic acid **7**, NOESY experiment was carried out with the diamine **21** (Figure 5). The spectral data confirmed trans configuration for this compound; the trans configuration can be assumed for all other compounds obtained.



21

Figure 5. Significant correlations in NOESY spectra of compound **21**.

CONCLUSIONS

The classical Castagnoli reaction with alicyclic anhydrides can be adopted for the conditions of the parallel synthesis if it is performed in an one-pot two-step manner, namely, sonication of amine and aldehyde in MeOH, followed by replacing the solvent with xylenes and heating the mixture at 140−180 °C. The target 1,2-disubstituted 5-oxopyrrolidine- and 6-oxopiperidine-3-carboxylic acids were obtained in 67−88% yields in a diastereoselective manner. The method allowed for vast variation of both aldehyde and amine components: α-branched aliphatic, aromatic and heteroaromatic aldehydes, as well as primary amines amines bearing aliphatic, aromatic, heteroaromatic substituents, sulfone or hydroxy groups. Utility of the method to the preparation of building blocks on a 100 g scale was also demonstrated.

EXPERIMENTAL PROCEDURES

Solvents were purified according to the standard procedures. All the starting materials were purchased from Acros, Merck, Fluka, and Ukrorgsyntez. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons, 100.7 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. HPLC-MS analyses were done on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

General Procedure for the Synthesis of Compound Library Members 4. A mixture of aldehyde **2** (1 mmol) and amine **3** (1 mmol) in MeOH (3 mL) was sonicated for 6 h. The solvent was removed in vacuum drying oven, and the residue was dissolved in dry xylenes (3 mL). Anhydride **1** (1 mmol) was added, and the mixture was heated at 140 °C for 6−8 h. The precipitate was filtered to give the product **4**. If the precipitate was not formed, the solvent was removed in vacuum drying oven, the residue was triturated with hexanes, and the precipitate was filtered to give the product **4**.

*1-(2-Methoxyethyl)-6-oxo-2-(2-(trifluoromethyl)phenyl)-piperidine-3-carboxylic Acid (**4**{**1**(2), **2**(6), **3**(12)}).* Yield: 80%. White crystals. mp: 154−155 °C. MS (*m*/*z*, CI): 346 (MH^+). Anal. Calcd. for $C_{16}H_{18}F_3NO_4$: C 55.65, H 5.25, N 4.06. Found: C 55.94, H 4.97, N 4.09. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.91 (s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 5.54 (s, 1H), 3.78 (dt, *J* = 12.6, 6.1 Hz, 1H), 3.34 (t, *J* = 6.2 Hz, 2H), 3.13 (s, 3H), 2.73 (s, 1H), 2.57−2.48 (m, 2H), 2.37−2.24 (m,

dx.doi.org/10.1021/co4001277 | ACS Comb. Sci. 2014, 16, 146−153

1H), 2.04−1.82 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.4, 169.1, 139.4, 133.3, 129.0, 128.6, 127.0 (q, J = 6.1 Hz), 126.9 (q, J = 29.5 Hz), 126.3 (q, J = 116.2 Hz), 69.1, 58.4, 58.3, 45.4, 44.0, 28.8, 18.0.

*2-(Cyclopropylmethyl)-1-oxo-3-(thiazol-4-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**4**{**1**(3), **2**(4), **3**(36)}).* Yield: 78%. White crystals. mp: 218−219 °C. MS (m/z, CI): 329 (MH^+). Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C 62.18, H 4.91, N 8.53, S 9.76. Found: C 61.96, H 4.72, N 8.37, S 9.89. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.99 (d, J = 1.8 Hz, 1H), 7.89 (d, J = 6.8 Hz, 1H), 7.42 (td, J = 7.4, 1.3 Hz, 1H), 7.36 (td, J = 7.5, 1.1 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.21 (d, J = 0.7 Hz, 1H), 5.62 (s, 1H), 4.40 (s, 1H), 3.85 (dd, J = 13.9, 6.8 Hz, 1H), 3.03 (dd, J = 13.9, 7.2 Hz, 1H), 1.10−0.92 (m, J = 5.0 Hz, 1H), 0.56−0.41 (m, J = 17.1 Hz, 1H), 0.39−0.26 (m, 2H), 0.23−0.13 (m, J = 18.0 Hz, 1H). COOH is not observed due to exchange. ^{13}C NMR (126 MHz, DMSO-d_6): δ 172.4, 163.2, 156.1, 155.3, 134.4, 132.1, 129.8, 129.6, 128.1, 127.4, 116.3, 59.2, 50.9, 49.1, 10.3, 4.3, 3.4.

*2-(1-Methyl-1H-imidazol-2-yl)-1-[2-(2-methylphenyl)-ethyl]-5-oxopyrrolidine-3-carboxylic Acid (**4**{**1**(1), **2**(15), **3**(38)}).* Yield: 79%. White crystals. mp: 201−203 °C. MS (m/z, CI): 328 (MH^+). Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C 66.04, H 6.47, N 12.84. Found: C 65.72, H 6.31, N 13.03.^{1}H NMR (500 MHz, DMSO-d_6): δ 7.16 (s, 1H), 7.13−7.05 (m, 3H), 7.03−6.95 (m, 1H), 6.92 (s, 1H), 5.07 (d, J = 5.2 Hz, 1H), 3.64 (s, 3H), 3.52−3.39 (m, 1H), 3.32−3.23 (m, 1H), 2.83−2.72 (m, 1H), 2.72−2.63 (m, 2H), 2.65−2.53 (m, 1H), 2.46−2.35 (m, 1H), 2.12 (s, 3H). COOH and NH are not observed due to exchange. ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.9, 172.3, 137.4, 136.2, 130.6, 129.5, 127.7, 126.9, 126.5, 122.8, 56.1, 43.6, 41.8, 33.1, 32.7, 31.0, 19.0.

*2-(4-Methoxyphenyl)-6-oxo-1-(thiophen-2-ylmethyl)-piperidine-3-carboxylic Acid (**4**{**1**(2), **2**(23), **3**(18)}).* Yield: 79%. White crystals. mp: 192−193 °C. MS (m/z, CI): 346 (MH^+). Anal. Calcd. for $C_{18}H_{19}NO_4S$: C 62.59, H 5.54, N 4.05, S 9.28. Found: C 62.84, H 5.59, N 4.28, S 9.01. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.56 (s, 1H), 7.40 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.92−6.88 (m, 1H), 6.77 (d, J = 3.0 Hz, 1H), 5.16 (d, J = 15.1 Hz, 1H), 4.76 (d, J = 6.4 Hz, 1H), 3.77 (s, 3H), 3.64 (d, J = 15.1 Hz, 1H), 2.79 (dt, J = 11.3, 6.7 Hz, 1H), 2.63−2.53 (m, 1H), 2.48−2.40 (m, 1H), 1.94−1.84 (m, 1H), 1.84−1.72 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.8, 169.2, 159.3, 139.9, 132.4, 128.8, 127.1, 126.8, 126.3, 114.6, 61.4, 55.6, 47.5, 42.4, 30.6, 21.6.

*1-(3-Methylbutyl)-6-oxo-2-(thiophen-2-yl)piperidine-3-carboxylic Acid (**4**{**1**(2), **2**(2), **3**(28)}).* Yield: 73%. White crystals. mp: 158−159 °C. MS (m/z, CI): 296 (MH^+). Anal. Calcd. for $C_{15}H_{21}NO_3S$: C 60.99, H 7.17, N 4.74, S 10.85. Found: C 61.27, H 7.02, N 4.55, S 10.99. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.84 (s, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.15−6.91 (m, 2H), 5.22 (d, J = 3.7 Hz, 1H), 3.87−3.78 (m, 1H), 2.93 (dd, J = 8.5, 4.3 Hz, 1H), 2.60−2.52 (m, 1H), 2.43−2.25 (m, 2H), 1.94 (t, J = 9.4 Hz, 2H), 1.51−1.38 (m, 1H), 1.39−1.21 (m, 2H), 0.82 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.4, 168.2, 145.5, 127.6, 126.2, 125.9, 57.7, 46.7, 43.8, 35.9, 29.6, 25.9, 23.0, 22.7, 20.2.

General Procedure for the Preparation of Carboxylic Acids 6−12. To a solution of aldehyde **2**{3,18,28,32} (0.7 mol) in MeOH (700 mL), $MeNH_2$ (2.2 mol, 25% in MeOH) was added. The mixture was sonicated for 2 h and then evaporated in vacuo. The residue was dissolved in dry xylenes (700 mL), anhydride **1**(1,2) (0.7 mol) was added, and the mixture was refluxed for 6 h. After it was cooled, yellow oil separated from the solution, which solidified upon standing overnight. The precipitate was filtered and washed with hexanes to give carboxylic acid **6−12**.

*1-Methyl-2-oxo-5-phenylpyrrolidine-3-carboxylic Acid (**6**).* Yield: 116 g (76%). White crystals. MS (m/z, CI): 220 (MH^+). Anal. Calcd. for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39. Found: C 65.83, H 6.27, N 6.55. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.75 (s, 1H, COO*H*), 7.42 (t, J = 6.8 Hz, 2H, 3′-C*H* of C_6H_5), 7.36 (t, J = 7.1 Hz, 1H, 4′-C*H* of C_6H_5), 7.29 (d, J = 7.1 Hz, 2H, 2′-C*H* of C_6H_5), 4.72 (d, J = 5.0 Hz, 1H, 5-C*H*), 3.05−2.96 (m, 1H, 4-C*H*), 2.75 (dd, J = 16.7, 10.0 Hz, 1H, 3-C*H*H), 2.56 (dd, J = 16.2, 5.6 Hz, 1H, 3-CH*H*), 2.49 (s, 3H, 1-CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ 174.2 (C═O), 172.5 (C═O), 140.6 (1′-*C* of C_6H_5), 129.4 (3′-CH of C_6H_5), 128.6 (4′-*C*H of C_6H_5), 127.3 (2′-CH of C_6H_5), 66.2 (5-CH), 45.8 (4-*C*H), 33.6 (3-CH_2), 28.1 (1-CH_3).

*1-Methyl-2-oxo-6-phenylpiperidine-3-carboxylic Acid (**7**).* Yield: 129 g (79%). White crystals. MS (m/z, CI): 234 (MH^+). Anal. Calcd. for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N 6.00. Found: C 67.25, H 6.63, N 6.31. ^{1}H NMR (500 MHz, DMSO-d^6): δ 12.72 (s, 1H, COO*H*), 7.40 (t, J = 7.0 Hz, 2H, 3′-C*H* of C_6H_5), 7.31 (t, J = 6.8 Hz, 1H, 4′-C*H* of C_6H_5), 7.23 (d, J = 7.4 Hz, 2H, 2′-C*H* of C_6H_5), 4.86 (d, J = 4.6 Hz, 1H, 6-C*H*), 2.85−2.76 (m, 1H, 5-C*H*), 2.63 (s, J = 13.9 Hz, 3H, 1-CH_3), 2.49−2.41 (m, 1H, 3-C*H*H), 2.38−2.26 (m, 1H, 3-CH*H*), 1.95−1.86 (m, 1H, 4-C*H*H), 1.86−1.76 (m, 1H, 4-CH*H*). ^{13}C NMR (126 MHz, DMSO-d^6): δ 174.0 (*C*═O), 169.1 (*C*═O), 141.0 (1′-*C* of C_6H_5), 129.2 (3′-CH of C_6H_5), 128.1 (4′-CH of C_6H_5), 127.2 (2′-CH of C_6H_5), 64.1 (6-CH), 46.9 (5-CH), 33.7 (1-CH_3), 30.0 (3-CH_2), 20.80 (4-CH_2).

*5-(4-Methoxyphenyl)-1-methyl-2-oxopyrrolidine-3-carboxylic Acid (**8**).* Yield: 123 g (71%). Mixture of isomers, *dr* 87:13. White crystals. MS (m/z, CI): 250 (MH^+). Anal. Calcd. For $C_{13}H_{15}NO_4$: C 62.64, H 6.07, N 5.62. Found: C 62.82, H 5.76, N 5.40. ^{1}H NMR (500 MHz, DMSO-d_6, major isomer): δ 12.64 (s, 1H), 7.22 (d, J = 7.1 Hz, 2H), 6.97 (d, J = 7.2 Hz, 2H), 4.65 (d, J = 5.2 Hz, 1H), 3.77 (s, 3H), 3.00 (dd, J = 8.5, 5.2 Hz, 1H), 2.73 (dd, J = 16.8, 9.9 Hz, 1H), 2.53 (dd, J = 16.3, 6.0 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, major isomer): δ 174.3, 172.4, 159.6, 132.3, 128.7, 114.7, 65.7, 55.6, 45.9, 33.7, 28.0.

*6-(4-Methoxyphenyl)-1-methyl-2-oxopiperidine-3-carboxylic Acid (**9**).* Yield: 132 g (72%). Mixture of isomers, *dr* 88:12. White crystals. MS (m/z, CI): 264 (MH^+). Anal. Calcd. for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32. Found: C 64.06, H 6.32, N 4.99. ^{1}H NMR (500 MHz, DMSO-d_6, major isomer): δ 12.65 (s, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.95 (d, J = 7.6 Hz, 2H), 4.78 (d, J = 3.9 Hz, 1H), 3.75 (s, 3H), 2.80−2.73 (m, 1H), 2.60 (s, 3H), 2.49−2.39 (m, 1H), 2.36−2.27 (m, 1H), 1.94−1.79 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, major isomer): δ 174.0, 169.1, 159.1, 132.8, 128.4, 114.5, 63.7, 55.6, 47.2, 33.5, 30.2, 21.1.

General Procedure for the Preparation of Alcohols 13 and 14. To freshly distilled THF (200 mL), $LiAlH_4$ (0.44 mol) was added portionwise upon vigorous stirring. The resulting suspension was stirred for additional 10 min, and **8** or **9** (0.1 mol) was added in small portions over 1 h. The resulting mixture was refluxed for 2 d, then cooled, and excess of hydride was quenched by dropwise addition of 1: 1 THF−H_2O mixture. The precipitate was filtered off and washed with THF (3 × 300

dx.doi.org/10.1021/co4001277 | ACS Comb. Sci. 2014, 16, 146−153

mL). The combined extracts were evaporated in vacuo, and the crude product was purified by flash chromatography.

*(5-(4-Methoxyphenyl)-1-methylpyrrolidin-3-yl)methanol (**13**).* Yield: 17.9 g (81%). Mixture of isomers, *dr* 92: 8. White crystals. MS (*m*/*z*, CI): 222 (MH^+). Anal. Calcd. for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33. Found C 70.31, H 8.94, N 6.02. ^{1}H NMR (500 MHz, DMSO-d_6, major isomer) δ 7.23 (d, J = 7.2 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 4.52 (s, 1H), 3.74 (s, 3H), 3.41−3.31 (m, 1H), 3.30−3.23 (m, 1H), 3.11−3.04 (m, 1H), 2.67 (d, J = 6.1 Hz, 1H), 2.25−2.16 (m, 1H), 2.01 (s, J = 18.0 Hz, 3H), 1.97−1.89 (m, 2H), 1.68−1.62 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6, major isomer): δ 158.7, 135.3, 129.0, 114.1, 73.1, 62.7, 55.8, 55.43, 51.0, 40.7, 26.9.

*(6-(4-Methoxyphenyl)-1-methylpiperidin-3-yl)methanol (**14**).* Yield: 19.5 g (83%). Mixture of isomers, *dr* 88: 12. White crystals. MS (*m*/*z*, CI): 236 (MH^+). Anal. Calcd. for $C_{14}H_{21}NO_2$: C 71.46, H 8.99, N 5.95. Found C 71.27, H 9.08, N 5.83. ^{1}H NMR (500 MHz, DMSO-d_6, major isomer): δ 7.21−7.13 (d, J = 7.7 Hz, 2H), 6.87 (d, J = 7.7 Hz, 2H), 4.19 (s, 1H), 3.74 (s, 3H), 2.97 (d, J = 9.6 Hz, 1H), 2.93−2.82 (m, 2H), 2.51 (s, 2H), 2.05−1.92 (m, 2H), 1.81 (s, 3H), 1.73−1.57 (m, 1H), 1.56−1.46 (m, 1H), 1.16 (qd, J = 12.6, 3.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6, major isomer): δ 158.6, 135.4, 129.3, 113.9, 71.3, 63.4, 57.1, 55.4, 45.8, 44.8, 28.4, 25.4.

General Procedure for the Preparation of Alcohols 15−17. To a solution of carboxylic acid **6−12** (0.1 mol) and Et_3N (0.12 mol) in DMF (150 mL), MeI (0.11 mol) was added dropwise. The resulting mixture was stirred at 50 °C for 1 d, then cooled, poured into H_2O and extracted with CH_2Cl_2. The combined extracts were washed with H_2O, evaporated, and the residue was dissolved in THF (200 mL). To this solution, $NaBH_4$ (0.1 mol) was added, followed by dry MeOH (∼20 mL). The resulting mixture was refluxed for 1 h, then cooled and evaporated in vacuo. CH_2Cl_2 (200 mL) was added, and the mixture was washed with H_2O (3 × 100 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from Et_2O to give **15−17**.

*3-(Hydroxymethyl)-5-(4-methoxyphenyl)-1-methylpyrrolidin-2-one (**15**).* Yield: 17.4 g (74%). White crystals. MS (*m*/*z*, CI): 236 (MH^+). Anal. Calcd. for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95. Found: 66.24, H 7.40, N 5.69. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.16 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 4.86 (s, 1H), 4.27 (d, J = 4.4 Hz, 1H), 3.76 (s, 3H), 3.41 (s, 2H), 2.48 (s, 3H), 2.21−2.09 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.8, 159.3, 133.4, 128.4, 114.7, 65.6, 62.4, 55.6, 44.0, 33.4, 28.0.

*3-(Hydroxymethyl)-6-(4-methoxyphenyl)-1-methylpiperidin-2-one (**16**).* Yield 17.9 g (72%). White crystals. MS (*m*/*z*, CI): 250 (MH^+). Anal. Calcd. for $C_{14}H_{19}NO_3$: C 67.45, H 7.68, N 5.62. Found: C 67.49, H 7.36, N 5.90. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.13 (d, J = 6.9 Hz, 2H), 6.95 (d, J = 6.7 Hz, 2H), 4.75 (s, 1H), 4.28 (d, J = 4.7 Hz, 1H), 3.76 (s, 3H), 3.45−3.38 (m, 1H), 3.32−3.23 (m, 1H), 2.56−2.52 (m, 3H), 2.43−2.27 (m, 2H), 1.79 (m, 2H), 1.61−1.51 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.8, 158.9, 134.1, 128.5, 114.5, 64.1, 61.8, 55.5, 44.6, 33.4, 30.6, 21.4.

General Procedure for the Preparation of Amides 25−29. Compound **6−12** (0.5 mol) was dissolved in DMF (750 mL), and CDI (0.52 mol) was added. The mixture was kept at 50 °C for 1 h, then $(NH_4)_2CO_3$ (1.5 mol) was added, and the resulting mixture was heated at 70 °C for 2 d. DMF was removed in vacuo, the residue was triturated with H_2O, filtered, and dried to give **25−29**.

*5-(4-Methoxyphenyl)-1-methyl-2-oxopyrrolidine-3-carboxamide (**26**).* Yield: 101 g (82%). White crystals. MS (*m*/*z*, CI): 249 (MH^+). Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C 62.89, H 6.50, N 11.28. Found: C 63.07, H 6.43, N 10.81. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.41 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.03 (s, 1H), 6.97 (d, J = 7.5 Hz, 2H), 4.57 (d, J = 5.7 Hz, 1H), 3.77 (s, 3H), 2.86 (dd, J = 14.5, 7.3 Hz, 1H), 2.67 (dd, J = 16.4, 9.6 Hz, 1H), 2.47 (s, 3H), 2.40 (dd, J = 16.6, 7.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 174.2, 172.7, 159.5, 132.5, 128.6, 114.7, 66.3, 55.6, 46.7, 34.8, 28.1.

*6-(4-Methoxyphenyl)-1-methyl-2-oxopiperidine-3-carboxamide (**27**).* Yield: 111 g (85%). White crystals. MS (*m*/*z*, CI): 263 (MH^+). Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C 64.11, H 6.92, N 10.68. Found: C 63.74, H 6.59, N 10.40. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 (s, 1H), 7.12 (d, J = 6.5 Hz, 2H), 6.93 (d, J = 6.5 Hz, 2H), 6.91 (s, 1H), 4.68 (d, J = 5.1 Hz, 1H), 3.75 (s, 3H), 2.63−2.57 (m, 1H), 2.54 (s, 3H), 2.41−2.31 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 174.0, 169.4, 159.0, 133.4, 128.5, 114.4, 64.1, 55.5, 48.6, 33.1, 31.0, 23.1.

General Procedure for the Preparation of Amines 18−24. To freshly distilled THF (500 mL), $LiAlH_4$ (1.3 mol) was added portion-wise upon vigorous stirring. The resulting suspension was stirred for additional 10 min, and amide **25−29** (0.3 mol) was added in small portions over 1 h. The resulting mixture was refluxed for 2 d, then cooled, and excess of hydride was quenched by dropwise addition of 1:1 THF−H_2O mixture. The precipitate was filtered off and washed with THF (3 × 180 mL). The combined extracts were evaporated in vacuo, and the crude product was purified by flash chromatography. Compound **18** was isolated as dihydrochloride.

*3-(Aminomethyl)-5-(4-methoxyphenyl)-1-methylpyrrolidin-2-one (**20**).* Yield: 52.8 g (80%). White crystals. MS (*m*/*z*, CI): 221 (MH^+). Anal. Calcd. for $C_{13}H_{20}N_2O$: C 70.87, H 9.15, N 12.72. Found: C 70.53, H 9.11, N 12.52. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.24 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 3.74 (s, 3H), 3.09 (t, J = 7.9 Hz, 1H), 2.60 (d, J = 8.1 Hz, 1H), 2.54 (dd, J = 12.3, 3.4 Hz, 1H), 2.40 (dd, J = 11.9, 8.3 Hz, 1H), 2.20 (dd, J = 17.3, 8.5 Hz, 1H), 1.99 (s, 3H), 1.97−1.91 (m, 1H), 1.90−1.82 (m, 1H), 1.64−1.53 (m, 1H). NH_2 is not observed due to exchange. ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.8, 135.3, 129.1, 114.1, 74.6, 55.7, 55.4, 51.8, 44.8, 40.6, 27.4.

*3-(Aminomethyl)-6-(4-methoxyphenyl)-1-methylpiperidin-2-one (**21**).* Yield: 51.9 g (74%). White crystals. MS (*m*/*z*, CI): 235 (MH^+). Anal. Calcd. for $C_{14}H_{22}N_2O$: C 71.76, H 9.46, N 11.95. Found: C 71.92, H 9.17, N 12.24. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.18 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 7.7 Hz, 2H), 3.74 (s, 3H), 2.91 (d, J = 10.9 Hz, 1H), 2.44 (d, J = 9.9 Hz, 1H), 2.14 (dd, J = 12.4, 3.1 Hz, 1H), 2.06−1.89 (m, 3H), 1.80 (s, 3H), 1.72−1.55 (m, 2H), 1.43 (s, 1H), 1.05 (qd, J = 12.8, 3.9 Hz, 1H). NH_2 is not observed due to exchange. ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.6, 135.4, 129.4, 114.0, 72.7, 57.1, 55.4, 45.8, 44.8, 44.7, 28.5, 25.5.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Compound characterization data, copies of ^{1}H, ^{13}C, and 2D NMR spectra, and Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/co4001277 | ACS Comb. Sci. 2014, 16, 146−153

AUTHOR INFORMATION

Corresponding Author

*E-mail: s.v.ryabukhin@gmail.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Mr. Vitaliy V. Polovinko for NMR measurements and Prof. Igor V. Komarov for his help with Instant JChem calculations.

REFERENCES

(1) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Del. Rev.* **2001**, *46*, 3−26.

(2) (a) Gleeson, M. P. Generation of a set of simple, interpretable ADMET rules of thumb. *J. Med. Chem.* **2008**, *51*, 817−834. (b) Oprea, T. I.; Davis, A. M.; Teague, S. J.; Leeson, P. D. Is there a difference between leads and drugs? A historical perspective. *J. Chem. Inf. Comp. Sci.* **2001**, *41*, 1308−1315. (c) Leeson, P. D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discovery* **2007**, *6*, 881−890 and references therein.

(3) Mann, A. Conformational restriction and/or steric hindrance in medicinal chemistry. In *Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Academic Press/Elsevier: Amsterdam, 2008; pp 363−379.

(4) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from flatland: Increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009**, *52*, 6752−6756. (b) Kingwell, K. Medicinal chemistry: Exploring the third dimension. *Nat. Rev. Drug Discovery 8*, 931. (c) Nicholls, A.; McGaughey, G. B.; Sheridan, R. P.; Good, A. C.; Warren, G.; Mathieu, M.; Muchmore, S. W.; Brown, S. P.; Grant, J. A.; Haigh, J. A.; Nevins, N.; Jain, A. N.; Kelley, B. Molecular shape and medicinal chemistry: A perspective. *J. Med. Chem.* **2010**, *53*, 3862−3886. (d) Feher, M.; Schmidt, J. M. Property distributions: Differences between drugs, natural products, and molecules from combinatorial chemistry. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218−227.

(5) Polinsky, A. Lead-likeness and drug-likeness. In *Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Academic Press/Elsevier: Amsterdam, 2008; pp 244−254.

(6) Nadin, A.; Hattotuwagama, C.; Churcher, I. Lead-oriented synthesis: A new opportunity for synthetic chemistry. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114−1122.

(7) (a) Liubchak, K.; Tolmachev, A. A.; Grygorenko, O. O.; Nazarenko, K. G. An approach to alicyclic ring-fused xanthenes. *Tetrahedron* **2012**, *68*, 8564−8571. (b) Mityuk, A. P.; Denisenko, A. V.; Grygorenko, O. O.; Tolmachev, A. A. Synthesis of dihydro-2*H*-pyran-3(4*H*)-one. *Arkivoc* **2012**, 226−230. (c) Shevchuk, N. V.; Liubchak, K.; Nazarenko, K. G.; Yurchenko, A. A.; Volochnyuk, D. M.; Grygorenko, O. O.; Tolmachev, A. A. A convenient synthesis of (1*H*-azol-1-yl)piperidines. *Synthesis* **2012**, *44*, 2041−2048. (d) Borisov, A. V.; Voloshchuk, V. V.; Nechayev, M. A.; Grygorenko, O. O. 5,6,7,8-Tetrahydropyrido[4,3-*c*]pyridazine: a lead-oriented scaffold with two diversity points. *Synthesis* **2013**, *45*, 2413−2416. (e) Yaremenko, A. G.; Volochnyuk, D. M.; Shelyakin, V. V.; Grygorenko, O. O. Tetrahydropyrido[*d*]pyridazinones—Promising scaffolds for drug discovery. *Tetrahedron* **2013**, *69*, 6799−6803.

(8) (a) Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. Multiple-component condensation strategies for combinatorial library synthesis. *Acc. Chem. Res.* **1996**, *29*, 123−131. (c) Dax, S. L.; McNally, J. J.; Youngman, M. A. Multi-component methodologies in solidphase organic synthesis. *Curr. Med. Chem.* **1999**, *6*, 255−270. (d) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing synthetic efficiency: Multi-component transformations lead the way. *Chem.—Eur. J.* **2000**, *6*, 3321−3329. (e) Ugi, I.; Heck, S. The multicomponent reactions and their libraries for natural and preparative chemistry. *Comb. Chem. High Throughput Screen* **2001**, *4*, 1−34.

(9) (a) Castagnoli, N., Jr. Condensation of succinic anhydride with *N*-benzylidene-*N*-methylamine. Stereoselective synthesis of *trans*- and *cis*-1-methyl-4-carboxy-5-phenyl-2-pyrrolidinone. *J. Org. Chem.* **1969**, *34*, 3187−3189. (b) Cushman, M.; Castagnoli, N., Jr. Condensation of succinic anhydrides with Schiff bases. Scope and mechanism. *J. Org. Chem.* **1971**, *36*, 3404−3411. (c) González-López, M.; Shaw, J. T. Cyclic anhydrides in formal cycloadditions and multicomponent reactions. *Chem. Rev.* **2009**, *109*, 164−189.

(10) (a) Burdzhiev, N. T.; Stanoeva, E. R. Reaction between glutaric anhydride and *N*-benzylidenebenzylamine, and further transformations to new substituted piperidin-2-ones. *Tetrahedron* **2006**, *62*, 8318−8326. (b) Piwowarczyk, K.; Zawadzka, A.; Roszkowski, P.; Szawkalo, J.; Leniewski, A.; Maurin, J. K.; Kranz, D.; Czarnocki, Z. Enantiomers of (2*R**,3*R**)-1-methyl-5-oxo-2-phenylpyrrolidine-3-carboxylic acid as novel chiral resolving agents. *Tetrahedron: Asymmetry* **2008**, *19*, 309−317. (c) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K. O; Urbanczyk-Lipkowska, Z. Highly accelerated reactions in microwave oven: synthesis of heterocycles. *Heterocycles* **1990**, *30*, 741−744. (d) Burdzhiev, N. T.; Stanoeva, E. R. Synthesis of new polysubstituted pyrrolidinones with potential biological activity. *Z. Naturforsch. B* **2008**, *63*, 313−320.

(11) Basu, S.; Barawkar, D. A.; De, S.; Palle, V. P.; Menon, S.; Patel, M.; Thorat, S.; Singh, U. P.; Sarma, K. D.; Waman, Y.; Niranjan, S.; Pathade, V.; Gaur, A.; Reddy, S.; Ansari, S.; Prasad, U. V. Discovery of novel and potent heterocyclic carboxylic acid derivatives as protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2843−2849.

(12) Ng, P. Y.; Tang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. Synthesis of diverse lactam carboxamides leading to the discovery of a new transcription-factor inhibitor. *Angew. Chem., Int. Ed.* **2007**, *46*, 5352−5355.

(13) Kenda, B. M.; Matagne, A. C.; Talaga, P. E.; Pasau, P. M.; Differding, E.; Lallemand, B. I.; Frycia, A. M.; Moureau, F. G.; Klitgaard, H. V.; Gillard, M. R.; Fuks, B.; Michel, P. Discovery of 4-substituted pyrrolidone butanamides as new agents with significant antiepileptic activity. *J. Med. Chem.* **2004**, *47*, 530−549.

(14) Ohno, T.; Yano, S.; Yamada, H.; Shirasaka, T.; Yamamoto, A.; Kobayashi, K.; Ogawa, K. Synthesis of the optical isomers of 4-[1-(4-*tert*-butylphenyl)-2-oxo-pyrrolidine-4-yl]methyloxybenzoic acid (S-2) and their biological evaluation as antilipidemic agent. *Chem. Pharm. Bull.* **1999**, *47*, 1549−1554.

(15) Kolocouris, N.; Kolocouris, A.; Foscolos, G. B.; Fytas, G.; Neyts, J.; Padalko, E.; Balzarini, J.; Snoeck, R.; Andrei, G.; De Clercq, E. Synthesis and antiviral activity evaluation of some new aminoadamantane derivatives. 2. *J. Med. Chem.* **1996**, *39*, 3307−3318.

(16) Cinelli, M. A.; Reddy, P. V. N.; Lv, P.-C.; Liang, J.-H.; Cushman, M.; Chen, L.; Van Breemen, R. B.; Agama, K.; Pommier, Y. Identification, synthesis, and biological evaluation of metabolites of the experimental cancer treatment drugs Indotecan (LMP400) and Indimitecan (LMP 776) and investigation of isomerically hydroxylated indenoisoquinoline analogues as topoisomerase I poisons. *J. Med. Chem.* **2012**, *55*, 10844−10862.

(17) Dols, P. P. M. A.; Folmer, B. J. B.; Hamersma, H.; Kuil, C. W.; Lucas, H.; Ollero, L.; Rewinkel, J. B. M.; Hermkens, P. H. H. SAR study of 2,3,4,14b-tetrahydro-1*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]-oxazepines as progesterone receptor agonists. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1461−1467.

(18) Nielsen, L.; Brehm, L.; Krogsgaard-Larsen, P. GABA agonists and uptake inhibitors. Synthesis, absolute stereochemistry, and enantioselectivity of (*R*)-(−)- and (*S*)-(+)-homo-*β*-proline. *J. Med. Chem.* **1990**, *33*, 71−77.

(19) (a) Perard-Viret, J.; Souquet, F.; Manisse, M.-L.; Royer, J. An expeditious total synthesis of (±)-jamtine using condensation between imine and acid anhydride. *Tetrahedron Lett.* **2010**, *51*, 96−98. (b) Ng, P. Y.; Masse, C. E.; Shaw, J. T. Cycloaddition reactions of imines with

3-thiosuccinic anhydrides: Synthesis of the tricyclic core of martinellic acid. *Org. Lett.* **2006**, *8*, 3999−4002.
(20) Younai, A.; Chin, G. F.; Shaw, J. T. Diastereoselective synthesis of (±)-heliotropamide by a one-pot, four-component reaction. *J. Org. Chem.* **2010**, *75*, 8333−8336.
(21) Hann, M. M.; Oprea, T. I. Pursuing the leadlikeness concept in pharmaceutical research. *Curr. Opin. Chem. Biol.* **2004**, *8*, 255−263.
(22) (a) Younai, A.; Fettinger, J. C.; Shaw, J. T. Influence of chiral thiols on the diastereoselective synthesis of γ-lactams from cyclic anhydrides. *Tetrahedron* **2012**, *68*, 4320−4327. (b) Biggs-Houck, J. E.; Davis, R. L.; Wei, J.; Mercado, B. Q.; Olmstead, M. M.; Tantillo, D. J.; Shaw, J. T. Carbon−carbon bond-forming reactions of α-thioaryl carbonyl compounds for the synthesis of complex heterocyclic molecules. *J. Org. Chem.* **2012**, *77*, 160−172.
(23) Yadav, J. S.; Reddy, B. V. S.; Raj, K. S.; Prasad, A. R. Room temperature ionic liquids promoted three-component coupling reactions: a facile synthesis of *cis*-isoquinolonic acids. *Tetrahedron* **2003**, *59*, 1805−1810.
(24) Wang, L.; Liu, J.; Tian, H.; Qian, C.; Sun, J. One-pot synthesis of *cis*-isoquinolonic acid derivatives via three-component reaction of homophthalic anhydride with aldehydes and amines using ytterbium(III) triflate as catalyst. *Adv. Synth. Catal.* **2005**, *347*, 689−694.
(25) Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. A stereoselective three-component reaction: $KAl(SO_4)_2{\cdot}12H_2O$, an efficient and reusable catalyst for the one-pot synthesis of *cis*-isoquinolonic acids. *J. Org. Chem.* **2005**, *70*, 350−352.
(26) Yadav, J. S.; Reddy, B. V. S.; Reddy, A. R.; Narsaiah, A. V. Iodine as a mild, efficient, and cost-effective reagent for the synthesis of *cis*-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids. *Synthesis* **2007**, 3191−3194.
(27) Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. A stereoselective three-component reaction: one-pot synthesis of *cis*-isoquinolonic acids catalyzed by silica sulfuric acid under mild and heterogeneous conditions. *J. Heterocycl. Chem.* **2006**, *43*, 187−190.
(28) Karimi, A. R.; Pashazadeh, R. Sulfonic acid functionalized silica: a mild, reusable and efficient heterogeneous catalyst for the highly diastereoselective synthesis of *cis*-isoquinolonic acids. *Synthesis* **2010**, 437−442.
(29) Mohammadi, M. H.; Mohammadi, A. A. One-pot, three-component synthesis of *cis*-isoquinolonic acids using $ZnCl_2$, $AlCl_3$−SiO_2 as catalyst. *Synth. Commun.* **2011**, *41*, 523−527.
(30) Karimi, A. R.; Pashazadeh, R.; Momeni, H. R. L-Proline-catalyzed diastereoselective synthesis of *cis*-isoquinolonic acids and evaluation of their neuroprotective effects. *Tetrahedron Lett.* **2012**, *53*, 3440−3443.
(31) Instant JChem was used for prediction of the physico-chemical properties of the library members. ChemAxon. Instant JChem 5.10.3, 2012. http://www.chemaxon.com.