Synthesis of a Library of 2-Alkyl-3-alkyloxy-2*H*-indazole-6-carboxamides

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A library of 200 2-alkyl-3-alkyloxy-2*H*-indazole-6-carboxamides was synthesized using parallel solution-phase methods. The indazole cyclization reaction was optimized for library production with the best yields resulting from controlled alcohol/water solvent ratios. The key step, a heterocyclization reaction, proceeds by N,N-bond formation and delivers the 2*H*-indazole scaffold. Automated preparative HPLC was utilized to provide pure compounds on a 10+ mg scale.

Introduction

Using both solution- and solid-phase strategies and techniques, pharmaceutical and biotech companies focus on producing arrays of pure compounds for screening in biological assays to identify potential drug canidates.[1,2] Using these tools, the pharmaceutical industry has accumulated huge libraries of compounds that are not accessible to the interested public for understandable reasons. The work presented here is in collaboration with the National Institute of General Medical Sciences (NIGMS) to create pilot-scale diversity libraries. The targeted NIGMS collection will be used for high-throughput biological screening and represents a new approach to collaborative academic/nonprofit research.

Because heterocycles are prevalent in many drugs currently on the market,[3] synthetic chemists are increasingly motivated to discover new methods for rapid construction of pharmacologically important druglike compounds.[4] A recent surge of renewed interest in the construction of indazoles, especially 2*H*-indazoles has emerged[5−9] because these compounds are reported to have pharmacological, agricultural, and industrial applications.[5−7] In continuation of our interest in 2*H*-indazoles work and in compliance with our NIGMS collaboration, we have extended our N,N-bond-forming route to include 2*H*-indazole library construction. Herein, we report optimization of the N,N-bond-forming indazole heterocyclization reaction and its application to the synthesis of a pilot scale library of 2-alkyl-3-alkyloxy-2*H*-indazole-6-carboxamides (Figure 1) via parallel solution-phase techniques starting from 4-bromomethyl-3-nitrobenzoic acid and utilizing automated preparative HPLC to provide 10+ mg of each pure library member to the NIGMS.

Results and Discussion

In recent work, the synthesis of a small set of 2*H*-indazoles (12 compounds with limited diversity) in which a new N,N-bond-forming heterocyclization technique was used to construct the 2*H*-indazole scaffold was reported. In that work, substituent effects on the reaction yield were explored, and it was also found that the heterocyclization reaction proceeded well in methanol.[10]

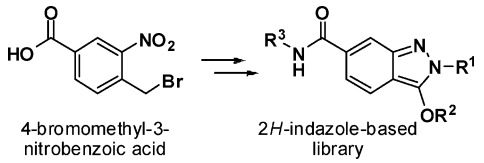
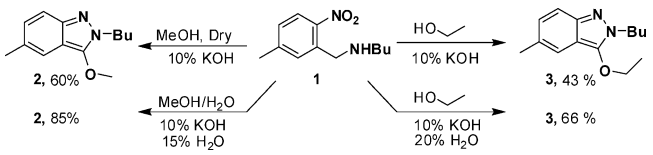


Figure 1. An indazole-based library with three points of diversity.

With the objective of synthesizing a large collection of substituted 2*H*-indazoles, we set out to further optimize the indazole cyclization reaction for new 2*H*-indazole targets that are difficult to prepare otherwise, as well as to achieve better yields and higher purity. Other anhydrous alkoxide solutions in alcoholic solvents were investigated and found not to improve the yield of the cyclization reaction; quite to the contrary, a noticeable drop in yield was observed. These observations led to experiments in adding water to the reaction and monitoring the resulting product yield. Initial findings demonstrated that the addition of a limited quantity of water to the indazole cyclization reaction in MeOH produced a substantial increase in product yield (60% in MeOH → 85% in MeOH/H_2O//85/15; **1** → **2** in Scheme 1).

Scheme 1. Optimization of Indazole Cyclization with Water



This observation was further validated when other alcohols were employed (for example, 43% in EtOH → 66% in EtOH/H_2O//80/20; **1** → **3** in Scheme 1). In the case of less polar alcohols that, at best, gave low yields under anhydrous conditions, adding a limited quantity of water caused the

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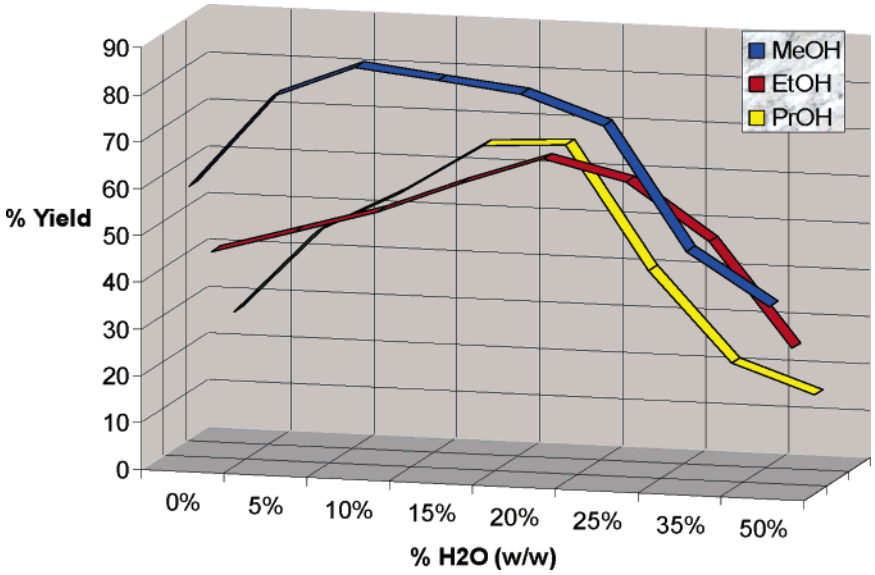


Figure 2. 2*H*-Indazole yield vs weight % water.

Table 1. Optimization Data of Indazole Cyclization[a]

ROH	% H_2O	% yield	ROH	% H_2O	% yield	ROH	% H_2O	% yield
MeOH	0	60	EtOH	0	43	PrOH	0	27
MeOH	5	80	EtOH	5	48	PrOH	5	45
MeOH	10	87	EtOH	10	53	PrOH	10	54
MeOH	15	85	EtOH	15	60	PrOH	15	65
MeOH	20	83	EtOH	20	66	PrOH	20	66
MeOH	25	78	EtOH	25	62	PrOH	25	27
MeOH	35	75	EtOH	35	50	PrOH	35	21
MeOH	50	40	EtOH	50	28	PrOH	50	15

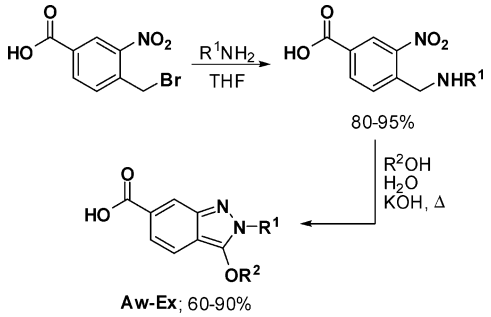
[a] Isolated yields after purification by chromatography.

yield of the reaction to increase dramatically. To quantify this effect, we set up 24 reactions of **1** with 0, 5, 10, 15, 20, 25, 35, and 50% water in MeOH, EtOH, and PrOH (Table 1, Figure 2). Methanol gave the highest yield with 10% (w/w) added water, and both ethanol and propanol gave the best yield with 20% (w/w) added water (Figure 2). However, it should be pointed out that further addition of water beyond these specified limits resulted in a drop in 2*H*-indazole yield. Considering our previously proposed mechanism[11] that involves the formation of ionic intermediates, addition of water increases the dielectric constant of the solvent mixture, which we believe enhances the reaction and gives higher yields.

With these results in hand, we turned to the libary construction. With this objective, our synthesis of the core 2*H*-indazole carboxylic acid was accomplished in two steps (see Aw-Ex in Scheme 2).[10] The first step, alkylation of various volatile alkyl amines[12] with commercially available 4-(bromomethyl)-3-nitrobenzoic acid, introduces R^1 diversity (Scheme 2; see amines A−E in Figure 3) as it delivers the targeted benzylic amines as their corresponding ammonium carboxylates in good to excellent yield (80−95%).

The second step, heterocyclization of *o*-nitrobenzyl amines Aw-Ex, was affected by heating an alcoholic solvent—MeOH or EtOH for this library—with 10% KOH (w/w) plus added water (10% w/w for MeOH and 20% w/w for EtOH). This step installs the R^2 diversity as it affects N,N-bond forming heterocyclization to the targeted 2*H*-indazoles (see Aw-Ex in Scheme 2). Purification of these 2*H*-indazole acids is

Scheme 2. Synthesis of 15 3-Alkoxy-2-alkyl-2*H*-indazole-6-carboxylic Acids



conveniently achieved by acidifying the alcoholic reaction mixture to pH 4, followed by filtration to collect the precipitated acid. A one-pot conversion of 4-(bromomethyl)-3-nitrobenzoic acid to the 3-alkoxy-2-alkyl-2*H*-indazole-6-carboxylic acid was accomplished, but these conditions led to an ~30% drop in overall yield.

As outlined in Scheme 3, the final step in this solution phase array synthesis delivers 3-alkoxy-2-alkyl-2*H*-indazole-6-carboxamides by the EDC-mediated coupling of various amine building blocks (see **5**−**24** in Figure 3). Each coupling reaction was worked up by washing with saturated aq sodium bicarbonate, water, 1 N aq HCl, and brine. Concentration of the organic layer delivered each targeted compound in 45−95% crude yield and 60−95% crude purity. Subsequent purification of each reaction mixture by preparative HPLC delivered 10+ mg of the pure 3-alkoxy-2-alkyl-2*H*-indazole-

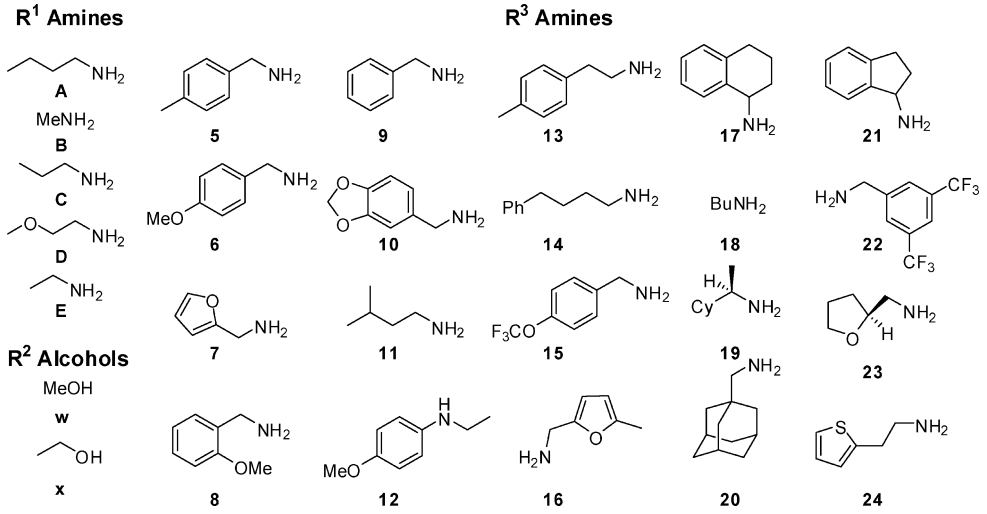
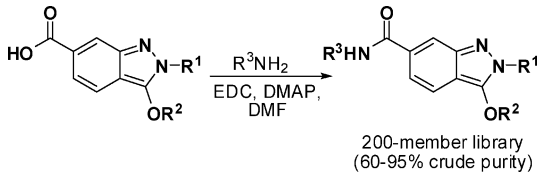


Figure 3. Library building blocks R^1-R^3; see Scheme 3.

Scheme 3. EDC Coupling Completes the 3-Alkoxy-2-alkyl-2*H*-indazole-6-carboxamide Library



6-carboxamide. All compounds were characterized by analytical LC/MS to ensure that their purity was >90% as well as to confirm compound identity. ^{1}H NMR analysis of 20 random members of the library confirmed their correct structures (see Table 2). Two hundred 2*H*-indazole-6-carboxamides have been synthesized via this process.

Conclusion

A high-throughput, efficient route to a library of novel 2-alkyl-3-alkoxy-2*H*-indazole-6-carboxamides has been reported. In an effort to improve the purity and efficiency of the N,N-bond forming 2*H*-indazole heterocyclization reaction, optimized conditions were developed by the addition of limited quantities of water to the alcohol solvent. Use of preparatory HPLC for rapid purification of the final 200-member 2-alkyl-3-alkoxy-2*H*-indazole-6-carboxamides library delivered each product in good to excellent yield with high purity.

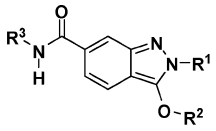
Experimental

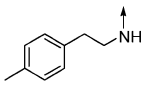
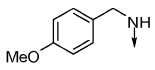
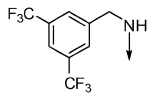
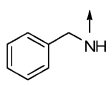
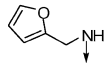
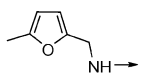
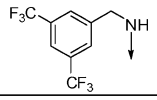
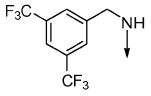
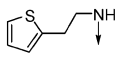
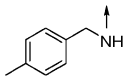
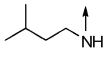
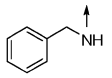
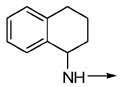
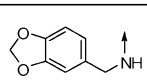
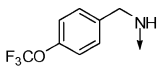
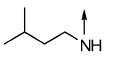
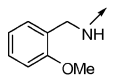
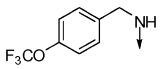
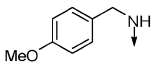
Organic solvents and reagents were purified by the appropriate standard procedures. Thin layer chromatography (TLC) used aluminum sheets coated with silica gel 60 F254 visualized under 254-nm light. Flash chromatography was conducted using silica gel 60 of particle size 0.040−0.063 mm. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with solvent signals used for reference at 7.26 ppm for ^{1}H and 77.16 for ^{13}C NMR; δ values are given in parts per million, and the coupling constants (J) are expressed in Hertz. LC/MS was accomplished using a Waters Alliance equipped with a Nova-Pak C_{18} column (3.9 × 150 mm). Mobile phases were 99.9% CH_3CN with 0.1% TFA and 99.9% water with 0.1% TFA. The separation gradient began at 5% CH_3CN for 4 min, 5−100% CH_3CN over 16 min, 100% CH_3CN for 5 min, 100−0% CH_3CN over 5 min, and held at 5% CH_3CN for 5 min. Samples were run at a constant flow rate of 1 mL/min and a temperature of 25 °C. Detection was at 254 nm. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy. The crude reaction purity after EDC coupling of the amine diversity was good (60−95%). Regardless of the crude reaction purity, and due to purity constraints required by the NIGMS, all 200 library members were purified by preparatory HPLC and characterized by LC/MS to be >90% purity.

Optimization of the 2*H*-Indazole Cyclization of 1. *N*-(5-Methyl-2-nitrobenzyl)butan-1-amine (**1**[10]; 3.60 mmol) was dissolved in 25 g of MeOH, EtOH, and PrOH, and each was partitioned equally into eight test tubes; these test tubes were labeled 0, 5, 10, 15, 20, 25, 35, and 50%, and the corresponding amount of water (w/w) was added to each. KOH (0.25 g; 10% w/w) was added to each test tube, and each reaction was refluxed with stirring for 6 h and then allowed to cool to room temperature. The crude reaction mixture was concentrated, then taken up in EtOAc (100 mL) and washed with water (100 mL), sodium bicarbonate (100 mL), 1 N HCl (100 mL), and brine (100 mL). Drying over sodium sulfate, concentration, and chromatography afford the 2*H*-indazoles **2**, **3**, and **4** (from MeOH, EtOH, and PrOH, respectively). Reaction yields for all of the optimization reactions are delineated in Table 1. For methanol, 10% (w/w) added water gave the highest yield (87%, Figure 2). For both ethanol and propanol, 20% (w/w) added water gave the highest yields (66%, Figure 2).

2-Butyl-3-methoxy-6-methyl-2*H*-indazole (2). Using the procedure above, **1** in methanol gave **2** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.24 (s, 3H), 4.18 (t, 2H), 2.35 (s, 3H), 1.86 (m, 2H), 1.36 (m, 2H), 0.93 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.1, 145.7, 128.7, 128.5, 117.3, 106.8, 94.3, 60.4, 47.8, 31.9, 21.7, 19.9, 13.6. IR (neat) 3019, 2956, 2935, 2872, 1633, 1530, 1454, 1407, 1347, 1082, 798 cm^{-1}. LC/MS: m/z 219.13 $[M + H]^+$ (C_{18} reversed-phase column, method A, 96.0%, 200−400 nm).

Table 2. Characterization of a random selection of the final library



Cpd #	R1	R2	R3	LCMS	Yield	Cpd #	R1	R2	R3	LCMS	Yield
Dw13	$CH_2CH_2OCH_3$	Me		91	62	Cw20	$CH_2CH_2CH_3$	Me		97	55
Ax6	$CH_2CH_2CH_2CH_3$	Et		92	65	Cw22	$CH_2CH_2CH_3$	Me		98	90
Ax9	$CH_2CH_2CH_2CH_3$	Et		96	50	Cw7	$CH_2CH_2CH_3$	Me		99	61
Dw16	$CH_2CH_2CH_2CH_3$	Me		99	45	Ax22	$CH_2CH_2CH_2CH_3$	Et		99	82
Bw22	CH_3	Me		98	63	Dw24	$CH_2CH_2CH_2CH_3$	Me		99	58
Bw5	CH_3	Me		95	61	Dw11	$CH_2CH_2CH_2CH_3$	Me		99	73
Bx9	CH_3	Et		99	82	Ex17	CH_2CH_3	Et		99	71
Bx10	CH_3	Et		92	53	Ew15	CH_2CH_3	Me		99	66
Bw11	CH_3	Me		99	92	Ex8	CH_2CH_3	Et		99	48
Cw15	$CH_2CH_2CH_3$	Me		99	58	Ex6	CH_2CH_3	Et		99	72

2-Butyl-3-ethoxy-5-methyl-2*H*-indazole (3). Using the procedure above, amine **1** in ethanol gave **3** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.34 (d, J = 8.7, 1H), 7.03 (d, J = 8.7 Hz, 1H), 4.55 (q, 2H), 4.22 (t, 2H), 2.37 (s, 3H), 1.84 (m, 2H), 1.48 (t, 3H), 1.35 (m, 2H), 0.91 (t, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 146.1, 144.9, 128.7, 128.5, 117.4, 117.3, 107.3, 69.2, 47.7, 31.9, 21.7, 19.9, 15.6, 13.6. LC/MS: m/z 233.15 $[M + H]^+$ (C_{18} reversed-phase column, method A, 95.0%, 200−400 nm).

2-Butyl-5-methyl-3-propoxy-2*H*-indazole (4). Using the procedure above, **1** in propanol gave **4** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.41 (d, J = 8.8, 1H), 7.33 (s, 1H), 7.00 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 4.41 (t, 2H), 4.20 (t, 2H), 2.35 (s, 3H), 1.87 (m, 4H), 1.36 (m, 2H), 1.08 (t, 3H), 0.94 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.0, 145.2, 128.7, 128.6, 128.4, 117.5, 117.3, 117.1, 47.9, 31.9, 23.3, 21.7, 19.9, 13.7, 10.4. LC/MS: m/z 247.18 $[M + H]^+$ (C_{18} reversed-phase column, method A, 97.0%, 200−400 nm).

General Procedure for the Synthesis of the 2-Alkyl-3-alkoxy-2*H*-indazole-6-carboxylic Acids. 4-(Bromomethyl)-3-nitrobenzoic acid (5.00 g, 19.3 mmol) was dissolved in THF (20 mL) and added dropwise to a 40% (w/w) solution of diversity amine (A-E, 675 mmol) in water. The reaction was allowed to stir for 4 h, then concentrated. The ammonium salt was precipitated by the addition of ether, followed by trituration with methanol.

This salt was transferred to a 100-mL, round-bottom flask fitted with a reflux condenser, followed by the addition of diversity alcohol (w or x, 38 g), water (10% by weight for MeOH, 20% by weight for EtOH), and 10% KOH (w/w). The resulting mixture was refluxed for 12 h and then allowed to cool to room temperature. The solution was neutralized with 6 N aq HCl to pH 4−5, which caused the neutral

2-alkyl-3-alkoxy-2*H*-indazole to precipitate from the alcohol solvent. The supernate was concentrated, and the remaining precipitate was combined with the original. The solid was collected by filtration and dried to afford the 2*H*-indazole carboxylic acid.

2-Butyl-3-methoxy-2*H*-indazole-6-carboxylic Acid (Aw). ^{1}H NMR (300 MHz, CD_3OD): δ 8.16 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 4.36 (s, 3H), 4.32 (t, 2H), 1.88 (m, 2H), 1.31 (m, 2H), 0.92 (t, 3H). LC/MS: *m*/*z* 249.15 $[M + H]^+$ (Nova-Pak C_{18} column, 86%, 200−400 nm).

2-Butyl-3-ethoxy-2*H*-indazole-6-carboxylic Acid (Ax). ^{1}H NMR (300 MHz, CD_3OD): δ 8.14 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 4.71 (q, 2H), 4.31 (t, 2H), 1.87 (m, 2H), 1.53 (t, 3H), 1.30 (m, 2H), 0.90 (t, 3H). LC/MS: *m*/*z* 263.23 $[M + H]^+$ (Nova-Pak C_{18} column, 91%, 200−400 nm).

3-Methoxy-2-methyl-2*H*-indazole-6-carboxylic Acid (Bw). ^{1}H NMR (300 MHz, CD_3OD): δ 8.14 (s, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.51 (dd, J = 9.0 Hz, J = 0.9, 1H), 4.38 (s, 3H), 3.95 (s, 3H). LC/MS: *m*/*z* 207.01 $[M + H]^+$ (Nova-Pak C_{18} column, 93%, 200−400 nm).

3-Ethoxy-2-methyl-2*H*-indazole-6-carboxylic Acid (Bx). ^{1}H NMR (300 MHz, CD_3OD): δ 8.12 (m, 2H), 7.79 (d, J = 9.0 Hz, 1H), 4.95 (q, 2H), 4.03 (s, 3H), 1.59 (t, 3H). LC/MS: *m*/*z* 221.31 $[M + H]^+$ (Nova-Pak C_{18} column, 89%, 200−400 nm).

3-Methoxy-2-propyl-2*H*-indazole-6-carboxylic Acid (Cw). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.60 (dd, J = 9.0 Hz, J = 1.2, 1H), 4.41−4.28 (m, 4H), 1.97 (m, 2H), 0.92 (t, 3H). LC/MS: *m*/*z* 235.14 $[M + H]^+$ (Nova-Pak C_{18} column, 81%, 200−400 nm).

3-Ethoxy-2-propyl-2*H*-indazole-6-carboxylic Acid (Cx). ^{1}H NMR (600 MHz, CD_3SOCD_3): δ 8.05 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 9.0 Hz, J = 1.2 Hz, 1H), 4.61 (q, 2H), 4.19 (t, 2H), 1.85 (m, 2H), 1.42 (t, 3H), 0.84 (t, 3H). LC/MS: *m*/*z* 249.21 $[M + H]^+$ (Nova-Pak C_{18} column, 85%, 200−400 nm).

3-Methoxy-2-(2-methoxyethyl)-2*H*-indazole-6-carboxylic Acid (Dw). ^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 4.52 (t, 2H), 4.35 (s, 3H), 3.90 (t, 2H), 3.31 (s, 3H). LC/MS: *m*/*z* 251.32 $[M + H]^+$ (Nova-Pak C_{18} column, 88%, 200−400 nm).

3-Ethoxy-2-(2-methoxyethyl)-2*H*-indazole-6-carboxylic Acid (Dx). ^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (s, 1H), 7.79 (dd, J = 8.8 Hz, J = 0.8 Hz, 1H), 7.51 (dd, J = 8.8 Hz, J = 1.2, 1H), 4.65 (q, 2H), 4.37 (t, 2H), 3.83 (t, 2H), 3.29 (s, 3H), 1.49 (t, 3H). LC/MS: *m*/*z* 265.43 $[M + H]^+$ (Nova-Pak C_{18} column, 90%, 200−400 nm).

2-Ethyl-3-methoxy-2*H*-indazole-6-carboxylic Acid (Ew). ^{1}H NMR (400 MHz, CD_3OD): δ 8.15 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.8 Hz, J = 1.2 Hz, 1H), 4.37 (s, 3H), 4.30 (q, 2H), 1.45 (t, 3H). LC/MS: *m*/*z* 221.31 $[M + H]^+$ (Nova-Pak C_{18} column, 92%, 200−400 nm).

3-Ethoxy-2-ethyl-2*H*-indazole-6-carboxylic Acid (Ex). ^{1}H NMR (300 MHz, CD_3OD): δ 8.17 (s, 1H), 7.86 (dd, J = 8.7 Hz, J = 0.6 Hz, 1H), 7.51 (dd, J = 9.0 Hz, J = 1.2 Hz, 1H), 4.67 (q, 2H), 4.34 (q, 2H), 1.48 (m, 6H). LC/MS: *m*/*z* 235.20 $[M + H]^+$ (Nova-Pak C_{18} column, 87%, 200−400 nm).

General Procedure for EDC Coupling To Give 2-Alkyl-3-alkoxy-2*H*-indazole-6-carboxamide. The 2*H*-indazole carboxylic acid (0.200 mmol) was combined with a diversity amine (**1**−**20**, 0.350 mmol) in a dry test tube. DMF (4 mL) was added, and the reagents were cooled to 0 °C over 30 min. EDC [*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, 0.350 mmol] was added, and the reaction was allowed to warm to room temperature with stirring for 24 h. The resulting reaction mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with aq sodium bicarbonate, water, 1 N aq HCl, and brine; dried over sodium sulfate; and concentrated to give the crude material in 60−95% purity. Purification by preparative HPLC delivered the 2-alkyl-3-alkoxy-2*H*-indazole-6-carboxamide.

3-Methoxy-2-(2-methoxyethyl)-*N*-(4-methylphenethyl)-2*H*-indazole-6-carboxamide (Dw13). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.36 (d, 9.0 = Hz, 1H), 7.14 (s, 4H), 6.21 (s, 1H), 4.47 (t, 2H), 4.34 (s, 3H), 3.86 (t, 2H), 3.71 (m, 2H), 3.3 (s, 3H), 2.90 (t, 2H), 2.33 (s, 3H). LC/MS: *m*/*z* 294.1 $[M + H]^+$ (Nova-Pak C_{18} column, 91.0%, 200−400 nm).

2-Butyl-3-ethoxy-*N*-(4-methoxybenzyl)-2*H*-indazole-6-carboxamide (Ax6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.72 (d, J = 9.6 Hz, 1H), 7.48 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 7.29 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.75 (s, 1H), 4.70 (q, 2H), 4.32 (t, 2H), 3.79 (s, 3H), 1.88 (m, 2H), 1.55 (t, 3H), 1.33 (m, 2H), 0.94 (t, 3H). LC/MS: *m*/*z* 382.3 $[M + H]^+$ (Nova-Pak C_{18} column, 91.8%, 200−400 nm).

***N*-Benzyl-2-butyl-3-ethoxy-2*H*-indazole-6-carboxamide (Ax9).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.98 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.47 (dd, J = 9.0 Hz, 1H), 7.36−7.26 (m, 5H), 6.78 (s, 1H), 4.70 (m, 4H), 4.31 (t, 2H), 1.89 (m, 2H), 1.55 (t, 3H), 1.33 (m, 2H), 0.94 (t, 3H). LC/MS: *m*/*z* 352.3 $[M + H]^+$ (Nova-Pak C_{18} column, 96%, 200−400 nm).

3-Methoxy-2-(2-methoxyethyl)-*N*-((5-methylfuran-2-yl)-methyl)-2*H*-indazole-6-carboxamide (Dw16). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 9.0, 1.8 Hz, 1H), 6.81 (s, 1H), 6.17 (d, J = 3 Hz, 1H), 5.90 (dd, J = 3.0, 0.3 Hz, 1H), 4.58 (d, 2H), 4.49 (t, 2H), 4.37 (s, 3H), 3.82 (t, 3H), 3.29 (s, 3H), 2.26 (s, 3H). LC/MS: *m*/*z* 344.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

***N*-(3,5-Bis(trifluoromethyl)benzyl)-3-methoxy-2-methyl-2*H*-indazole-6-carboxamide (Bw22).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.84−7.79 (m, 4H), 7.55 (d, J = 9.0, 1H), 7.21 (s, 1H), 4.77 (d, 2H), 4.52 (s, 3H), 4.01 (s, 3H). LC/MS: *m*/*z* 432.1 $[M + H]^+$ (Nova-Pak C_{18} column, 98%, 200−400 nm).

3-Methoxy-2-methyl-*N*-(4-methylbenzyl)-2*H*-indazole-6-carboxamide (Bw5). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 9.0, 1H), 7.26 (dd, J = 8.4 Hz, J = 1.8 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.68 (s, 1H), 4.60 (d, 2H), 4.36 (s, 3H), 3.95 (s, 3H),

2.33 (s, 3H). LC/MS: *m*/*z* 310.2 $[M + H]^+$ (Nova-Pak C_{18} column, 95%, 200−400 nm).

***N*-Benzyl-3-ethoxy-2-methyl-2*H*-indazole-6-carboxamide (Bx9).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.75 (d, $J = 9.5$ Hz, 1H), 7.55 (d, $J = 9.0$ Hz, 1H), 7.39−7.29 (m, 5H), 7.26 (d, $J = 1.8$ Hz, 1H), 4.74 (q, 2H), 4.66 (d, 2H), 3.83 (t, 2H), 4.03 (s, 3H), 1.57 (t, 3H). LC/MS: *m*/*z* 310.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-ethoxy-2-methyl-2*H*-indazole-6-carbox-amide (Bx10).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.54 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.36 (bs, 1H), 6.92 (s, 1H), 6.86−6.76 (m, 3H), 5.93 (s, 2H), 4.75 (q, 2H), 4.55 (d, 2H), 4.03 (s, 3H), 1.57 (t, 3H). LC/MS: *m*/*z* 354.1 $[M + H]^+$ (Nova-Pak C_{18} column, 92%, 200−400 nm).

***N*-Isopentyl-3-methoxy-2-methyl-2*H*-indazole-6-carboxamide (Bw11).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.40 (dd, $J = 9.0$, 1.2 Hz, 1H), 6.26 (s, 1H), 4.38 (s, 3H), 3.98 (s, 3H), 3.50 (m, 2H), 1.71 (m, 1H), 1.52 (m, 2H), 0.96 (d, 6H). LC/MS: *m*/*z* 276.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

3-Methoxy-2-propyl-*N*-(4-(trifluoromethoxy)benzyl)-2*H*-indazole-6-carboxamide (Cw15). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.42−7.37 (m, 3H), 7.17 (d, $J = 8.4$ Hz, 2H), 6.75 (s, 1H), 4.64 (d, 2H), 4.36 (s, 3H), 4.23 (m, 2H), 1.92 (m, 2H), 0.91 (t, 3H). LC/MS: *m*/*z* 408.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

3-Methoxy-*N*-adamantanemethyl-2-propyl-2*H*-indazole-6-carboxamide (Cw20). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.80 (dd, $J = 9.0$ Hz, $J = 0.6$ Hz, 1H), 7.47 (dd, $J = 9.0$ Hz, $J = 1.8$ Hz, 1H), 6.42 (s, 1H), 4.41 (s, 3H), 4.27 (t, 2H), 3.17 (d, 2H), 1.99 (s, 3H), 1.93 (m, 2H), 1.71 (d, 3H), 1.65 (d, 3H), 1.56 (s, 6H), 0.92 (t, 3H). LC/MS: *m*/*z* 382.2 $[M + H]^+$ (Nova-Pak C_{18} column, 97%, 200−400 nm).

***N*-(3,5-Bis(trifluoromethyl)benzyl)-3-methoxy-2-propyl-2*H*-indazole-6-carboxamide (Cw22).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.79 (s, 2H), 7.76 (d, $J = 9.0$ Hz, 2H), 7.43 (dd, $J = 9.0$ Hz, $J = 1.2$ Hz, 1H), 7.19 (s, 1H), 4.75 (d, 2H), 4.37 (s, 3H), 4.23 (t, 2H), 1.91 (m, 2H), 0.92 (t, 3H). LC/MS: *m*/*z* 460.2 $[M + H]^+$ (Nova-Pak C_{18} column, 98%, 200−400 nm).

***N*-(Furan-2-ylmethyl)-3-methoxy-2-propyl-2*H*-indazole-6-carboxamide (Cw7).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.80 (dd, $J = 8.4$ Hz, $J = 0.6$ Hz, 1H), 7.50 (dd, $J = 9.0$ Hz, $J = 1.8$ Hz, 1H), 7.37 (dd, $J = 1.8$ Hz, $J = 0.6$ Hz, 1H), 6.89 (s, 1H), 6.34 (m, 1H), 6.31 (m, 1H), 4.65 (d, 2H), 4.18 (s, 3H), 4.29 (t, 2H), 1.93 (m, 2H), 0.92 (t, 3H). LC/MS: *m*/*z* 314.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

***N*-(3,5-Bis(trifluoromethyl)benzyl)-2-butyl-3-ethoxy-2*H*-indazole-6-carboxamide (Ax22).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.78 (s, 2H), 7.75 (s, 1H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.53 (t, $J = 6.0$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 1H), 6.63 (bs, 1H), 4.72 (d, 2H), 4.69 (q, 2H), 4.28 (t, 2H), 1.86 (m, 2H), 1.55 (t, 3H), 1.32 (m, 2H), 0.92 (t, 3H). LC/MS: *m*/*z* 488.2 $[M + H]^+$ (Nova-Pak C_{18} column, 200−400 nm).

3-Methoxy-2-(2-methoxyethyl)-*N*-(2-(thiophen-2-yl)-ethyl)-2*H*-indazole-6-carboxamide (Dw24). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (bs, 1H), 7.90 (s, 1H), 7.79 (dd, $J = 9.0$ Hz, $J = 0.6$ Hz, 1H), 7.47 (dd, $J = 9.0$ Hz, $J = 1.8$ Hz, 1H), 7.17 (dd, $J = 4.8$, $J = 1.2$ Hz, 1H), 6.95 (m, 1H), 6.88 (m, 1H), 6.78 (s, 1H), 4.51 (t, 2H), 4.39 (s, 3H), 3.82 (t, 2H), 3.72 (q, 2H), 3.29 (s, 3H), 3.16 (t, 2H). LC/MS: *m*/*z* 360.1 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

***N*-Isopentyl-3-methoxy-2-(2-methoxyethyl)-2*H*-indazole-6-carboxamide (Dw11).** ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 6.45 (s, 1H), 4.48 (t, 2H), 4.36 (s, 3H), 3.82 (t, 2H), 3.48 (q, 2H), 3.29 (s, 3H), 1.71 (m, 1H), 1.51 (m, 2H), 0.95 (d, 6H). LC/MS: *m*/*z* 320.2 $[M + H]^+$ (Nova-Pak C_{18} column, 200−400 nm).

3-Ethoxy-2-ethyl-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-2*H*-indazole-6-carboxamide (Ex17). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.49 (dd, $J = 8.4$ Hz, $J = 1.2$ Hz, 1H), 7.32 (d, $J = 6.6$ Hz, 1H), 7.20−7.15 (m, 2H), 7.11 (d, $J = 7.8$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 5.37 (m, 2H), 4.72 (q, 2H), 4.39 (q, 2H), 2.86−2.77 (m, 2H), 2.15 (m, 1H), 2.17−1.86 (m, 3H), 1.55 (t, 3H), 1.49 (t, 3H). LC/MS: *m*/*z* 364.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

2-Ethyl-3-methoxy-*N*-(4-(trifluoromethoxy)benzyl)-2*H*-indazole-6-carboxamide (Ew15). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.73 (d, $J = 9.0$ Hz, 2H), 7.37 (m, 3H), 7.17 (d, $J = 9.0$ Hz, 2H), 6.82 (s, 1H), 4.64 (d, 2H), 4.35 (s, 3H), 4.30 (q, 2H), 1.47 (t, 3H). LC/MS: *m*/*z* 409.1 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

3-Ethoxy-2-ethyl-*N*-(2-methoxybenzyl)-2*H*-indazole-6-carboxamide (Ex8). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.96 (s, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.54 (dd, $J = 9.0$ Hz, $J = 1.2$ Hz, 1H), 7.33 (dd, $J = 7.2$ Hz, $J = 1.2$ Hz, 1H), 7.27 (m, 1H), 7.22 (s, 1H), 6.93 (d, $J = 7.8$, 1H), 6.90 (d, $J = 9.0$ Hz, 1H), 4.77 (q, 2H), 4.64 (d, 2H), 4.41 (q, 2H), 3.89 (s, 3H), 1.56 (t, 3H), 1.51 (t, 3H). LC/MS: *m*/*z* 354.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

3-Ethoxy-2-ethyl-*N*-(4-methoxybenzyl)-2*H*-indazole-6-carboxamide (Ex6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.96 (s, 1H), 7.68 (d, $J = 9.0$ Hz, 1H), 7.46 (d, $J = 8.6$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.11 (s, 1H), 6.83 (d, $J = 7.8$ Hz, 2H), 4.71 (q, 2H), 4.53 (d, 2H), 4.35 (q, 2H), 3.75 (s, 3H), 1.53 (t, 3H), 1.46 (t, 3H). LC/MS: *m*/*z* 354.2 $[M + H]^+$ (Nova-Pak C_{18} column, 99%, 200−400 nm).

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Supporting Information Available. Spectra data for 20 members of the library, including ^{1}HNMR, and LC/MS data.

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References and Notes

(1) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600.
(2) *Combinatoral Chemistry and Technology*; Miertus, S., Fassina, G., Eds.; Marcel Dekker: New York, 1999.
(3) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141.
(4) Padwa, A. *Prog. Heterocycl. Chem.* **1994**, *6*, 36.
(5) Grimmet, M. R.; Barton, S. D.; Ollis, W. D. *Comprehensive Organic Chemistry*; Pregamon Press: New York, 1997; Vol. 4, p 357.
(6) Stadlbauer, W. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; 2002; Vol. 12, p 227.
(7) Huang, L.; Shih, M.; Chem, H.; Pan, S.; Teng, C.; Lee, F.; Kuo, S. *Bioorg. Chem. Lett.* **2006**, *14*, 528.
(8) (a) Shirtcliff, L. D.; Hayes, A. G.; Haley, M. M.; Kohler, F.; Hess, K.; Herges, R. *J. Am. Chem. Soc.* **2006**, *128*, in press. (b) Shirtcliff, L. D.; Rivers, J.; Haley, M. M. *J. Org. Chem.* **2006**, *71*, in press.
(9) Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392.
(10) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687.
(11) Kurth, M. J.; Olmstead, M. M.; Haddadin, M. J. *J. Org. Chem.* **2005**, *70*, 1060.
(12) The use of volatile amine facilitates purification of the ammonium carboxylate, because they can be removed by concentration.

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