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A Facile Synthesis of New 5*H*-Indazolo[3,2-*b*]benzo[*d*]-1,3-oxazines via One-Pot Intramolecular Bis-heterocyclizations

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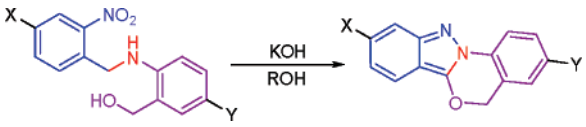

The parent 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine heterocycle as well as a series of novel analogues have been synthesized utilizing two subsequent intramolecular heterocyclizations in one pot. A variety of diversity groups were added to explore the scope of this reaction and to provide a number of new compounds for biological screening.

Introduction

The indazolobenzoxazine ring system **1** (Figure 1) is a rare heterocycle comprised of benzo-1,3-oxazine (**2**) and 2*H*-indazole (**3**) substructures. Indazoles,[1] which encompass both 1*H*- and 2*H*-renditions, are known to display a wide range of biological activities including anti-angiogenic activity,[2] antiviral activity,[3] and strong antihypertensive effects.[4] Of special interest, an indazole derivative has recently been reported to exhibit potential as a male contraceptive.[5] Benzo-1,3-oxazines are also known to be biologically active, demonstrating antianginal activity,[6] antihypertensive affects,[7] and potency as antirheumatic agents.[8] Thus, it is envisioned that indazolobenzoxazines, which contain both the indazole and benzoxazine moieties, may afford unique biological activities.

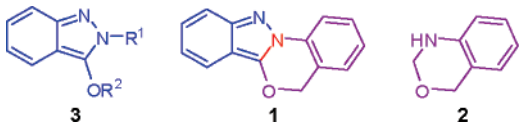

FIGURE 1. Heterocycles of interest: 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (**1**), 2,4-dihydro-1*H*-benzo[*d*]-1,3-oxazine (**2**), and 3-alkoxy-2*H*-indazole (**3**).

While 1*H*- and 2*H*-indazoles and 1*H*-benzo[*d*]-1,3-oxazines[9] are well represented, 5*H*-indazolo[3,2-*b*]benzo-[*d*]-1,3-oxazines are rare in the chemical literature. The related indazolobenzoxazinones have been employed in the synthesis of indazoloindazolediones,[10] and derivatives of indazolobenzoxazines have been used to dope electroluminescent devices.[11] To the best of our knowledge, the parent system (**1**) and substituted indazolobenzoxazines are unknown, which provided the impetus to synthesize these novel compounds.

Previously, it has been demonstrated that 3-alkoxy-2*H*-indazoles (**3**, Figure 1) can be obtained from *o*-nitrobenzylamines via an *N*,*N*-bond-forming heterocyclization reaction

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(1) Stadlbauer, W. *Sci. Synth.* **2002**, *12*, 227−324.
(2) Huang, L.-J.; Shih, M.-L.; Chen, H.-S.; Pan, S.-L.; Teng, C.-M.; Lee, F.-Y.; Kuo, S.-C. *Bioorg. Med. Chem.* **2006**, *14*, 528−536.
(3) Kim, D.; Wang, L.; Caldwell, C. G.; Chen, P.; Finke, P. E.; Oates, B.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Carver, G.; Carella, A.; Holmes, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3103−3106.
(4) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. *J. Med. Chem.* **2007**, *50*, 6−9.
(5) (a) Cheng, C. Y.; Mruk, D.; Silvestrini, B.; Bonanomi, M.; Wong, C.-H.; Siu, M. K. Y.; Lee, N. P. Y.; Lui, W.-Y.; Mo, M-Y. *Contraception* **2005**, *72*, 251−261. (b) Mruk, D. D.; Wong, C.-H.; Silvestrini, B.; Cheng, C. Y. *Nature Med.* **2006**, *12*, 1323−1328.
(6) Benedini, F.; Bertolini, G.; Cereda, R.; Donà, G.; Gromo, G.; Levi, S.; Mizrahi, J.; Sala, A. *J. Med. Chem.* **1995**, *38*, 130−136.
(7) Clark, R. D.; Caroon, J. M.; Kluge, A. F.; Repke, D. B.; Roszkowski, A. P.; Strosberg, A. M.; Baker, S.; Bitter, S. M.; Okada, M. D. *J. Med. Chem.* **1983**, *26*, 657−661.
(8) Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.; Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105−111.

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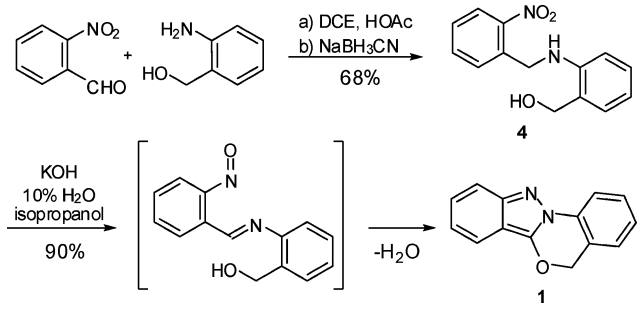
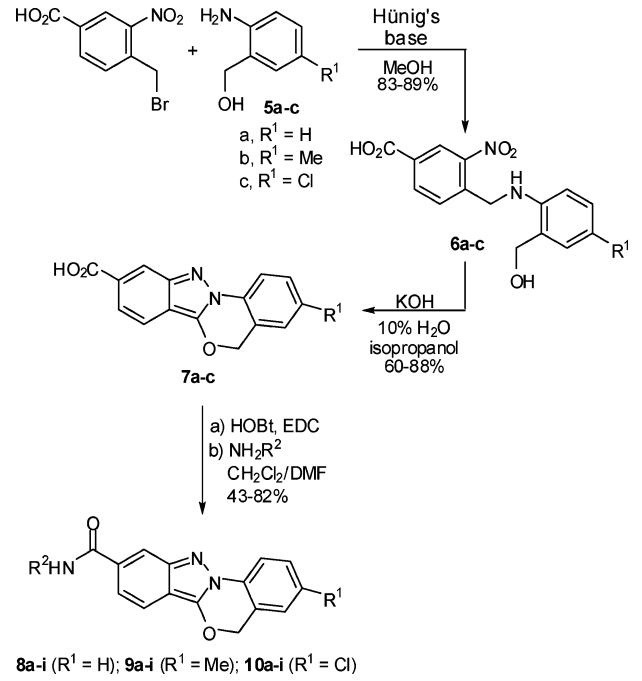
SCHEME 1. Route to Indazolobenzoxazine 1



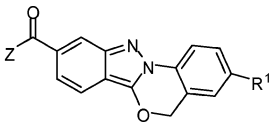
SCHEME 2. Route to Indazolobenzoxazine Carboxamides 8−10

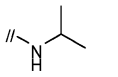
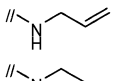
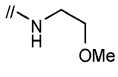
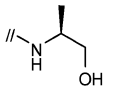
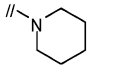
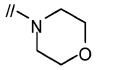
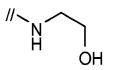
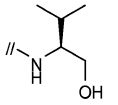
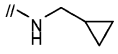


8a-i (R^1 = H); **9a-i** (R^1 = Me); **10a-i** (R^1 = Cl)

mediated by potassium hydroxide in alcoholic solvent; methanol, ethanol, and 1-propanol all work well.[12] On this basis, it was surmised that an intramolecular variant of this reaction would provide an effective entry into indazolobenzoxazines and would further demonstrate the generality of this intriguing heterocyclization. This work reports the synthesis of the parent 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (**1**) system, which culminated in the preparation of a novel library focused on this heterocycle.

TABLE 1. Diversification of Indazolobenzoxazine Carboxamides 8−10



Z =	R^1 = H		R^1 = Me		R^1 = Cl	
	(#)	Yield (%)	(#)	Yield (%)	(#)	Yield (%)
	**8a**	76	**9a**	68	**10a**	70
	**8b**	73	**9b**	75	**10b**	64
	**8c**	68	**9c**	63	**10c**	72
	**8d**	66	**9d**	71	**10d**	69
	**8e**	55	**9e**	57	**10e**	63
	**8f**	59	**9f**	52	**10f**	61
	**8g**	52	**9g**	56	**10g**	43
	**8h**	70	**9h**	75	**10h**	76
	**8i**	82	**9i**	79	**10i**	77

Results and Discussion

Indazolobenzoxazine **1**, the parent heterocycle, was prepared by first performing the reductive amination[13] of 2-nitrobenzaldehyde with 2-aminobenzyl alcohol to yield **4** (Scheme 1). Bis-heterocyclization of **4** to **1**, presumably via a nitroso imine intermediate, was achieved under basic conditions, using aqueous KOH in 2-propanol or methanol. It is interesting to note that intramolecular cyclization **4** → **1** is preferred over the potentially competing intermolecular possibility (e.g., **4** → **3**).[12,14] The two-step overall yield of **1** was 61%, demonstrating this as a viable approach to the synthesis of 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazines.

A demonstration of the scope of this intramolecular bis-heterocyclization reaction was undertaken as outlined in Scheme 2. The diversification potential of this study focused on the indazolo ring of **1** by placing a manipulatable carboxylic acid functional group at C9. Thus, 2-aminobenzyl alcohols **5a−c**

(9) (a) Hoback, J. H.; Crum, J. D.; Carroll, D. W. *W. V. Univ. Bull., Ser.* **1955**, *56*, 40−43. (b) Wagner, G. *Arch. Pharm.* **1957**, *290*, 520−527. (c) Sicker, D.; Schulz, M. *Stud. Nat. Prod. Chem.* **2002**, *27*, 185−232. (d) Pietsch, M.; Guetschow, M. *J. Med. Chem.* **2005**, *48*, 8270−8288. (e) Heydenreich, M.; Koch, A.; Klod, S.; Szatmari, I.; Fueloep, F.; Kleinpeter, E. *Tetrahedron* **2006**, *62*, 11081−11089. (f) Ando, Y.; Ando, K.; Yamaguchi, M.; Kunitomo, J.; Koida, M.; Fukuyama, R.; Nakamuta, H.; Yamashita, M.; Ohta, S.; Ohishi, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5849−5854. (g) Li, J.-R.; Ma, S.-L.; Sun, Y.-J.; Wei, X.-J.; Zhou, Z.-M. *J. Heterocycl. Chem.* **2006**, *43*, 745−748. (h) Basheer, A.; Rappoport, Z. *J. Org. Chem.* **2006**, *71*, 9743−9750. (i) Yadav, L. D. S.; Rai, V. K. *Synlett* **2007**, 1227−1230. (j) Kiskan, B.; Yagci, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1670−1676. (k) Spagnol, G.; Rajca, A.; Rajca, S. *J. Org. Chem.* **2007**, *72*, 1867−1869. (l) Anwar, H. F.; Skattebøl, L.; Hansen, T. V. *Tetrahedron* **2007**, *63*, 9997−10002.

(10) Alkhader, M. A.; Smalley, R. K.; Mohajerani, B. *Synthesis* **1980**, 381−383.

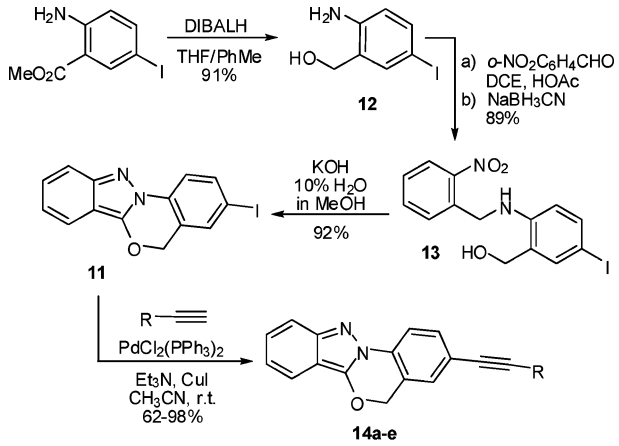
(11) Sato, Y.; Murata, J. (Mitsubishi Chemical Industries Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho 05311162, 1993.

(12) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687−2689.

(13) Koshio, H.; Hirayama, F.; Ishihara, T.; Shiraki, R.; Shigenaga, T.; Taniuchi, Y.; Sato, K.; Moritani, Y.; Iwatsuki, Y.; Kaku, S.; Katayama, N.; Kawasaki, T.; Matsumoto, Y.; Sakamoto, S.; Tsukamoto, S. *Bioorg. Med. Chem.* **2005**, *13*, 1305−1323.

(14) Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M. J. *J. Comb. Chem.* **2007**, *9*, 171−177.

SCHEME 3. Route to Alkynyl Indazolobenzoxazines 14



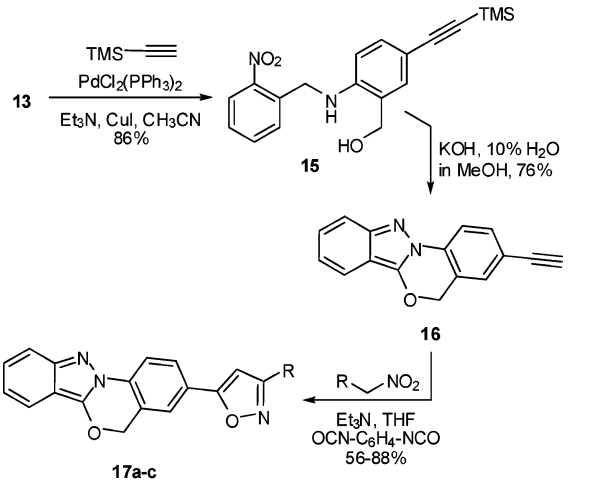
R =	(#)	Yield (%)
//—C_4H_9	**14a**	98
//—C_5H_{11}	**14b**	62
//—cyclopentyl	**14c**	74
//—cyclohexyl	**14d**	74
//—phenyl	**14e**	78[a]

[a] Reaction run at 50 °C.

were efficiently *N*-alkylated with 4-bromomethyl-3-nitrobenzoic acid to generate *N*-(2-nitrobenzyl)anilines **6a**−**c**. Bis-heterocyclizations of these isolated intermediates to indazolobenzoxazines **7a**−**c** were accomplished with aqueous KOH in 2-propanol (or methanol). The resulting indazolocarboxylic acids were purified by aqueous base → aqueous acid precipitation of **7a**−**c** and subsequent filtration. This crucial transformation was performed in good to excellent yields (60−88%). Amidation of the C9 carboxylic acid with primary and secondary amines yielded **8a**−**i**, **9a**−**i**, and **10a**−**i**. These results are delineated in Table 1.

A second indazolobenzoxazine diversification strategy that is focused on the benzoxazine half of **1** is detailed in Scheme 3. The key synthetic intermediate for this protocol, iodoindazolobenzoxazine **11**, was prepared in three steps (75% overall yield) from methyl 5-iodoanthranilate. Applying Stefaniak's procedure,[15] the first step consisted of benzoate ester reduction with DIBALH to benzyl alcohol **12** where diluting the reaction with THF before quenching afforded improved yields. This was followed by step 2, reductive amination of 2-nitrobenzaldehyde with **12**, to give benzylaniline **13**.[13] Bis-heterocyclization of **13**, the third step enroute to **11**, was affected by aqueous potassium hydroxide in 2-propanol. However, it was determined that iodoindazolobenzoxazine **11** was also obtained in methanol and in better yield [92%; none of the anticipated 3-alkoxy-2*H*-indazole (e.g., **3**) byproduct was observed]. Diversification at the benzoxazine subunit was then accomplished by Sonogashira coupling.[16] In the event, coupling of **11** with various terminal alkynes delivered alkynyl indazolobenzoxazines **14a**−**e** in good to excellent yields as summarized in Scheme 3. Indeed, the four-step yield of **14a** from methyl 5-iodoanthranilate is 73% overall.

SCHEME 4. Route to (5-Isoxazolyl)indazolobenzoxazines 17



R =	(#)	Yield (%)
//—CH_3	**17a**	63
//—CH_2CH_3	**17b**	56
//—$CH_2CH_2CH_3$	**17c**	88

A third diversification protocol is delineated in Scheme 4; the strategy here was to again vary the benzoxazino aryl ring—this time with a 5-isoxazoloyl moiety. Sonogashira coupling of **13** with trimethylsilyl acetylene worked beautifully, affording **15** in 86% yield. Subsequent application of the base-mediated bis-heterocyclization was accompanied by concurrent protodesilylation to give **16** in 76% yield. Nitrile oxide (formed in situ from the corresponding nitroalkanes employing 1,4-phenylene diisocyanate)[17] 1,3-dipolarcycloaddition with various nitroalkanes delivered (5-isoxazolyl)indazolobenzoxazines **17a**−**c** in good yields (56−88%). This transformation was most effective when excess base (3 equiv of triethylamine) was employed and the nitroalkane was added dropwise over 6−8 h while heating at 50 °C. These results are summarized in Scheme 4.

Conclusions

In summary, the rare 5*H*-indazolo-[3,2-*b*]benzo[*d*]-1,3-oxazine system has been synthesized utilizing a one-pot, intramolecular bis-heterocyclization reaction. Furthermore, the scope of this reaction was explored with different substrates and the reactivity of its heterocyclic products was investigated via further diversification. The resultant library of novel heterocycles has been submitted to the NIH Molecular Libraries Small Molecule Repository (MLSMR) for high-throughput biological screening.

(15) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1988**, *31*, 2048−2056.

(16) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

(17) Kantorowski, E. J.; Brown, S. P.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 5272−5274.

Experimental Section

General Procedures. All chemicals were purchased from commercial suppliers and used without further purification. Analytical thin layer chromatography was carried out on pre-coated plates (silica gel 60F_{254}, 250 μm thickness) and visualized with UV light. Flash chromatography was performed with 60 Å, 32−63 μm silica gel (Scientific Adsorbents). Concentration refers to rotary evaporation under reduced pressure. ^{1}H NMR spectra were recorded at 300, 400, or 600 MHz at ambient temperature with DMSO-d_6 or $CDCl_3$ as solvents. ^{13}C NMR spectra were recorded at 75, 100, or 150 MHz at ambient temperature with DMSO-d_6 or $CDCl_3$ as solvents. Chemical shifts are reported in parts per million relative to DMSO-d_6 (^{1}H, δ 2.50; ^{13}C, δ 39.52) or $CDCl_3$ (^{1}H, δ 7.26; ^{13}C, δ 77.16). Infrared spectra were recorded on a FTIR spectrophotometer (Mattson Genesis II). The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 150−1500 Da, 20 V cone voltage, and Xterra MS C_{18} column (2.1 mm × 50 mm × 3.5 μm). HOBt refers to 1-hydroxybenzotriazole and EDC refers to *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride.

(2-(2-Nitrobenzylamino)phenyl)methanol (4). 2-Nitrobenzaldehyde (1.0 g, 6.6 mmol) and 2-aminobenzyl alcohol (0.80 g, 6.6 mmol) were added to a dry round-bottomed flask together with 1,2-dichloroethane (33 mL) and the solution was allowed to stir while adding acetic acid (1.5 mL, 26.4 mmol). This solution was allowed to stir under a nitrogen atmosphere at room temperature for 5 h. Sodium cyanoborohydride (2.0 g, 33.1 mmol) was added and the solution was allowed to react for an additional 8 h under a nitrogen atmosphere at room temperature. The solution was concentrated and then diluted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate (100 mL), 1 N HCl (100 mL), water (100 mL), and brine (100 mL). The resulting solution was dried over sodium sulfate and concentrated. The crude material was purified via flash chromatography (1:3 ethyl acetate/hexanes) yielding **4** (1.2 g, 68%). Orange oil: IR (neat) ν_{max} 3403, 3021, 2871, 1613, 1525, 744 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 6.6 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 6.6 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 4.73 (s, 2H), 4.66 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.5, 146.9, 135.9, 133.9, 129.8, 129.5, 128.2, 125.5, 124.8, 117.4, 111.1, 64.7, 45.3; ESI MS *m*/*z* 241 ($-H_2O$, M + H)$^+$. Purity was determined to be 84% by HPLC analysis on the basis of absorption at 214 nm.

5*H*-Indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (1). Compound **4** (250 mg, 0.9 mmol) was dissolved in 5.0 mL of a 10% by volume water in 2-propanol solution under a nitrogen atmosphere. Subsequently, KOH (1.2 g, 19.4 mmol) was added and the solution was allowed to stir for 12 h at room temperature. The solution was diluted with ethyl acetate (150 mL) and washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL). The solution was dried over sodium sulfate and concentrated. The resulting solid was purified via flash chromatography (1:5 ethyl acetate/hexanes) yielding a brown solid (183 mg, 90%): mp 96−97 °C; IR (neat) ν_{max} 3052, 2922, 2850, 1634, 1530, 1504, 1463, 1096, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H), 7.49−7.37 (m, 3H), 7.23−7.13 (m, 3H), 6.85 (dd, J = 8.7, 6.6 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 133.8, 130.0, 128.5, 127.0, 125.0, 121.5, 120.6, 119.5, 117.4, 116.2, 106.9; ESI MS *m*/*z* 223 (M + H)$^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for the Synthesis of *o*-Nitro-*p*-methylphenylamino Alcohols: 4-((2-(Hydroxymethyl)phenylamino)methyl)-3-nitrobenzoic Acid (6a). 4-Bromomethyl-3-nitrobenzoic acid (1.0 g, 4.6 mmol) and 2-aminobenzyl alcohol (2.3 g, 18.5 mmol, 4.0) were dissolved in methanol (20 mL) and added to a dry round-bottomed flask containing Hünig's base (1.8 mL, 18.5 mmol). The solution was allowed to stir for 12 h at room temperature under a nitrogen atmosphere, concentrated, and subsequently taken up in ethyl acetate (150 mL). The ethyl acetate solution was washed consecutively with 1 N HCl (100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate, and concentrated yielding orange crystals (1.15 g, 83%): mp 133−135 °C; IR (neat) ν_{max} 3435, 2845, 2607, 2234, 1939, 1696, 1525, 744 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.50 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.57 (t, J = 6.8 Hz, 1H), 6.33 (d, J = 7.9 Hz, 1H), 5.91 (br s, 1H), 5.18 (br s, 1H), 4.78 (d, J = 4.0 Hz, 2H), 4.52 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 148.8, 146.0, 141.4, 134.3, 131.4, 130.4, 128.7, 128.4, 126.8, 126.2, 116.9, 110.5, 62.1, 44.7; ESI MS *m*/*z* 285 ($-H_2O$, M + H)$^+$. Purity was determined to be 85% by HPLC analysis on the basis of absorption at 214 nm.

4-((4-Methyl-2-(hydroxymethyl)phenylamino)methyl)-3-nitrobenzoic Acid (6b). By using the general procedure for synthesis of *o*-nitro-*p*-methylphenylamino alcohols, the target was synthesized yielding orange crystals (1.195 g, 82%): mp 141−142 °C; IR (neat) ν_{max} 3445, 2927, 2617, 2229, 1955, 1696, 1525, 1251, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.60 (s, 1H), 8.49 (s, 1H), 8.14 (d, J = 7.8, 1.5 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 8.7, 2.7 Hz, 1H), 6.33 (d, J = 8.7 Hz, 1H), 6.02 (br s, 1H), 4.77 (s, 2H), 4.51 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 148.7, 144.4, 140.9, 134.4, 131.4, 130.2, 129.0, 127.8, 127.5, 126.3, 120.5, 112.0, 61.0, 44.7; ESI MS *m*/*z* 299 ($-H_2O$, M + H)$^+$. Purity was determined to be 86% by HPLC analysis on the basis of absorption at 214 nm.

4-((4-Chloro-2-(hydroxymethyl)phenylamino)methyl)-3-nitrobenzoic Acid (6c). By using the general procedure for the synthesis of *o*-nitro-*p*-methylphenylamino alcohols, the target was synthesized yielding orange crystals (1.38 g, 89%): mp 150−151 °C; IR (neat) ν_{max} 3083, 2648, 2519, 1701, 1515, 1272, 816, 744 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.50 (d, J = 1.5 Hz, 1H), 8.15 (dd, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.57 (t, J = 6.8 Hz, 1H), 6.33 (d, J = 7.9 Hz, 1H), 5.91 (br s, 1H), 5.18 (br s, 1H), 4.78 (d, J = 4.0 Hz, 2H), 4.52 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 148.8, 146.0, 141.4, 134.3, 131.4, 130.4, 128.7, 128.4, 126.8, 126.2, 116.9, 110.5, 62.1, 44.7; ESI MS *m*/*z* 318 ($-H_2O$, M + H)$^+$. Purity was determined to be 82% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for the Synthesis of Indazolobenzoxazine Carboxylic Acids: 5*H*-Indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxylic Acid (7a). Compound **6a** (1.0 g, 3.3 mmol, 1 equiv) was dissolved in 50 mL of a 10% by volume water in 2-propanol solution under a nitrogen atmosphere. Subsequently, KOH (2.5 g, 42 mmol) was added and the solution was allowed to stir for 12 h at room temperature. The solution was diluted with ethyl acetate (150 mL) and washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL). The solution was dried over sodium sulfate and concentrated. This cyclized product was purified via acid−base precipitation yielding **7a** (780 mg, 88%). Tan crystals: mp 286−287 °C; IR (neat) ν_{max} 2292, 2601, 1696, 1530, 1463, 1204, 739 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.12 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 9.3 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.46 (m, 3H), 5.64 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.2, 147.8, 144.4, 133.2, 131.0, 130.4, 128.4, 126.3, 122.8, 120.8, 120.8, 120.3, 121.1, 116.2, 108.3, 68.8; ESI MS *m*/*z* 267 (M + H)$^+$. Purity was determined to be 89% by HPLC analysis on the basis of absorption at 214 nm.

3-Methyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxylic Acid (7b). By using the general procedure for the synthesis of indazolobenzoxazine carboxylic acids, the target was synthesized yielding tan crystals (669 mg, 75%): mp 293 °C; IR (neat) ν_{max} 2917, 2632, 2539, 1675, 1515, 1235, 816, 744 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.11 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 5.59 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.2, 147.6, 144.1, 138.1, 131.0,

130.8, 130.7, 126.6, 122.8, 120.7, 120.2, 120.0, 116.1, 108.4, 68.8, 21.4; ESI MS *m*/*z* 281 $(M + H)^+$. Purity was determined to be 83% by HPLC analysis on the basis of absorption at 214 nm.

3-Chloro-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxylic Acid (7c). By using the general procedure for the synthesis of indazolobenzoxazine carboxylic acids, the target was synthesized yielding tan crystals (539 mg, 60%): mp 298−300 °C; IR (neat) ν_{max} 2839, 2632, 2539, 1686, 1520, 1500, 820, 745 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.09 (s, 1H), 7.86 (d, J = 9.3 Hz, 1H), 7.61−7.55 (m, 3H), 7.38 (d, J = 8.7 Hz, 1H), 5.62 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1, 147.9, 144.3, 132.3, 132.1, 131.2, 130.3, 126.3, 124.8, 120.7, 120.3, 120.2, 117.9, 108.3, 68.8; ESI MS *m*/*z* 300 $(M + H)^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for the Synthesis of Indazolobenzoxazine Carboxamides: Isopropyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (8a). Carboxylic acid **7a** (100 mg, 0.3 mmol, 1 equiv), HOBt (40 mg, 0.36 mmol, 1.2 equiv), and EDC (69 mg, 0.36 mmol, 1.2 equiv) were dissolved in a 1:4 DMF/CH_2Cl_2 solution (50 mL) and combined at 0 °C in a dry round-bottomed flask and allowed to stir for 30 min. Isopropylamine was added (0.03 mL, 0.3 mmol, 1 equiv). The solution was allowed to stir under a nitrogen atmosphere for 24 h while warming to 30 °C. The resulting solution was concentrated and taken up in ethyl acetate (50 mL). The solution was then extracted with sodium bicarbonate (100 mL), 1 N HCl (100 mL), water (100 mL), and brine (100 mL). The organic layer was dried over sodium sulfate, concentrated, and purified via flash chromatography (1:1 ethyl acetate/hexanes) resulting in white crystals (70 mg, 76%): mp 219−220 °C; IR (neat) ν_{max} 3279, 2974, 1629, 1520, 759 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 7.9 Hz, 1H), 7.84 (s, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.16−7.28 (m, 3H), 5.92 (br s, 1H), 5.40 (s, 2H), 4.24 (m, 1H), 1.21 (d, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 148.3, 135.2, 133.5, 130.1, 127.4, 124.9, 121.5, 120.0, 118.9, 116.6, 116.3, 107.8, 68.6, 42.1, 29.9, 23.0; ESI MS *m*/*z* 308 $(M + H)^+$. Purity was determined to be 94% by HPLC analysis on the basis of absorption at 214 nm.

***N*-(2-Methoxyethyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (8c).** By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding tan crystals (69 mg, 68%): mp 159−161 °C; IR (neat) ν_{max} 3352, 2927, 2855, 1629, 1536, 1096, 765 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.61 (t, J = 5.4 Hz, 1H), 8.02 (s, 1H), 7.88 (m, 2H), 7.60 (m, 3H), 7.57 (d, J = 9.6, 1H), 5.64 (s, 2H), 3.46−3.43 (m, 4H), 3.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 148.3, 144.1, 134.8, 133.6, 130.1, 127.5, 125.0, 121.6, 120.1, 118.9, 116.9, 116.3, 107.9, 71.4, 68.6, 59.1, 39.9; ESI MS *m*/*z* 324 $(M + H)^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 214 nm.

***N*-(Cyclopropylmethyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (8i).** By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding white crystals (78 mg, 82%): mp 186−187 °C; IR (neat) ν_{max} 3300, 3067, 2912, 1639, 1520, 1266, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.65 (m, 2H), 7.24 (d, J = 9.0 Hz, 1H), 7.18 (t, J = 6.0 Hz, 1H), 7.04−6.99 (m, 2H), 6.94 (d, J = 7.2 Hz, 1H), 6.33 (s, 1H), 5.14 (s, 2H), 3.50 (t, J = 6.0 Hz, 2H), 0.81 (m, 1H), 0.27 (d, J = 7.8 Hz, 2H), 0.00 (d, J = 4.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 148.3, 143.9, 134.9, 134.5, 129.9, 127.4, 124.9, 121.5, 119.9, 118.9, 116.8, 116.2, 107.8, 68.6, 45.2, 10.9, 3.7; ESI MS *m*/*z* 320 $(M + H)^+$. Purity was determined to be 90% by HPLC analysis on the basis of absorption at 214 nm.

***N*-Allyl-3-methyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (9b).** By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding tan crystals (72 mg, 75%): mp 186−187 °C; IR (neat) ν_{max} 2839, 2632, 2539, 1686, 1520, 1500, 820, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.66 (t, J = 5.6 Hz, 1H), 5.89 (m, 1H), 5.31 (s, 2H), 5.22 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.4 Hz, 1H), 4.05 (t, J = 5.6 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 147.9, 143.6, 137.6, 134.5, 134.4, 131.1, 130.4, 125.4, 121.4, 119.9, 118.7, 116.9, 116.6, 116.1, 108.0, 68.6, 42.7, 21.4; ESI MS *m*/*z* 320 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

***N*-(2-Methoxyethyl)-3-methyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (9c).** By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding yellow crystals (64 mg, 63%): mp 187−188 °C; IR (neat) ν_{max} 3336, 2922, 2876, 1639, 1515, 1266, 1106, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.69 (s, 1H), 5.37 (s, 2H), 3.65 (m, 2H), 3.56 (m, 2H), 3.38 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 148.0, 143.7, 137.7, 134.6, 131.2, 130.5, 125.5, 121.5, 119.9, 118.8, 116.9, 116.1, 108.0, 71.4, 68.7, 59.1, 39.9, 21.4; ESI MS *m*/*z* 338 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

Piperidinyl-3-methyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (9e). By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding white crystals (59 mg, 57%): mp 188−189 °C; IR (neat) ν_{max} 2927, 2855, 1618, 1520, 1427, 1375, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H), 7.53−7.51 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 3.69−3.38 (m, 4H), 2.34 (s, 3H), 1.64−1.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.0, 143.8, 137.5, 136.2, 131.2, 130.4, 125.5, 121.4, 120.1, 119.4, 116.0, 115.7, 107.0, 68.6, 46.2, 26.4, 24.8, 21.4; ESI MS *m*/*z* 348 $(M + H)^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 214 nm.

Morpholino-3-methyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (9f). By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding cream-colored crystals (54 mg, 52%): mp 212−214 °C; IR (neat) ν_{max} 2974, 2922, 2855, 1629, 1520, 1427, 1246, 1116, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 6.8 Hz, 1H), 7.02 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 5.39 (s, 2H), 3.69 (m, 8H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 147.8, 143.9, 137.6, 134.9, 131.2, 130.6, 125.5, 121.4, 120.4, 119.3, 116.3, 116.0, 107.2, 68.7, 67.1, 45.6, 21.4; ESI MS *m*/*z* 350 $(M + H)^+$. Purity was determined to be 94% by HPLC analysis on the basis of absorption at 214 nm.

***N*-((*S*)-1-Hydroxy-3-methylbutan-2-yl)-3-methyl-5*H*-indazolo-[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (9h).** By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding tan crystals (82 mg, 75%): mp 202−203 °C; IR (neat) ν_{max} 3435, 3290, 2964, 2876, 1608, 1515, 1360, 1075, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.25−7.21 (m, 2H), 6.98 (s, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 3.95 (m, 1H), 3.80 (m, 2H), 2.36 (s, 3H), 2.02 (m, 1H), 1.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 147.9, 143.7, 137.6, 134.7, 131.1, 130.5, 125.4, 121.5, 119.9, 118.9, 116.6, 116.1, 108.0, 68.6, 63.9, 57.9, 29.5, 21.4, 19.5; ESI MS *m*/*z* 366 $(M + H)^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 214 nm.

Isopropyl-3-chloro-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (10a). By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding white crystals (71 mg, 70%): mp 209−210 °C; IR (neat) ν_{max} 3269, 3062, 2974, 2922, 2860, 1639, 1510, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.91−7.88 (m, 2H), 7.55 (d, J = 9.0 Hz, 1H), 7.47 (dd, J = 8.4, 1.8 Hz, 1H), 7.30 (dd, J = 7.8, 1.2 Hz, 1H), 7.25 (m, 1H), 6.09 (d, J = 7.8 Hz, 1H), 5.43 (s,

2H), 4.30 (m, 1H), 1.28 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 148.2, 143.9, 135.5, 133.1, 131.9, 130.2, 125.2, 122.9, 120.0, 119.2, 117.7, 116.5, 107.8, 68.1, 42.3, 22.9; ESI MS *m/z* 342 $(M + H)^+$. Purity was determined to be 88% by HPLC analysis on the basis of absorption at 214 nm.

Morpholino-3-chloro-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine-9-carboxamide (10f). By using the general procedure for the synthesis of indazolobenzoxazine carboxamides, the target was synthesized yielding yellow crystals (68 mg, 61%): mp 195−196 °C; IR (neat) ν_{max} 2979, 2922, 2855, 1779, 1623, 1504, 1427, 1117, 832, 811 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, $J =$ 8.4 Hz, 1H), 7.59−7.57 (m, 2H), 7.46 (m, 1H), 7.25 (s, 1H), 6.96 (d, $J = 6.6$ Hz, 1H), 6.57 (br s, 1H), 5.43 (s, 2H), 3.8−3.5 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 147.9, 144.3, 135.1, 133.3, 131.7, 130.4, 125.4, 122.9, 120.7, 119.7, 117.7, 116.3, 107.3, 68.2, 67.1, 46.5; ESI MS *m/z* 369 $(M + H)^+$. Purity was determined to be 88% by HPLC analysis on the basis of absorption at 214 nm.

2-Amino-5-iodobenzyl Alcohol (12). Methyl 5-iodoanthranilate (10.0 g, 36.1 mmol) was dissolved in dry THF (25 mL) under an atmosphere of nitrogen. The solution was cooled to −30 °C, and DIBALH (99 mL of a 1.2 M solution in toluene, 120 mmol) was slowly added. After remaining at −30 °C for 1 h, the reaction was allowed to warm to room temperature overnight. Upon completion of the reaction it was diluted with THF (100 mL), cooled to 0 °C, and then quenched by slow addition of methanol (250 mL). Aluminum salts were removed via vacuum filtration and washed several times with ethyl acetate and methanol. The filtrate was concentrated and then purified via flash chromatography (1:49 methanol/chloroform) to afford 8.19 g of **12** (32.9 mmol, 91% yield). Cream-colored solid: mp 120−122 °C (lit.[13] mp 125 °C); IR (neat) ν_{max} 3359, 3191 (br), 2881, 1473, 1392, 1269, 1003, 824 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.35 (d, $J = 1.8$ Hz, 1H), 7.22 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.46 (d, $J = 8.4$ Hz, 1H), 5.11−5.08 (m, 3H), 4.32 (d, $J = 5.4$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 145.8, 135.6, 135.1, 128.4, 117.0, 76.5, 60.0; ESI MS *m/z* 232 $(-H_2O, M + H)^+$, 250 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

(2-(2-Nitrobenzylamino)-5-iodophenyl)methanol (13). 2-Nitrobenzaldehyde (2.55 g, 16.9 mmol) and **12** (4.20 g, 16.9 mmol) were dissolved in 1,2-dichloroethane (90 mL) under an atmosphere of nitrogen. Glacial acetic acid (4.8 mL, 85 mmol) was added, and the reaction was stirred at room temperature for 5 h. Sodium cyanoborohydride (4.25 g, 67.6 mmol) was added to the reaction mixture, and the reaction was stirred an additional 12 h at room temperature. The reaction was quenched by adding 10% aqueous K_2CO_3 (∼150 mL) and then diluted with dichloromethane (∼300 mL). The organic layer was washed twice with 10% aqueous K_2CO_3 and once with brine, then dried with sodium sulfate, filtered, and concentrated. The crude product was purified via flash chromatography (1:2 ethyl acetate/hexanes) to afford 5.58 g of **13** (14.5 mmol, 89% yield). Orange solid: mp 104−106 °C; IR (neat) ν_{max} 3508, 3361, 1575, 1511, 1335, 1273, 998, 802, 723 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, $J = 12$ Hz, 1H), 7.66 (apparent t, $J = 11.4$ Hz, 1H), 7.52 (m, 2H), 7.42 (d, $J = 2.4$ Hz, 1H), 7.23 (dd, $J = 12.9$, 2.7 Hz, 1H), 6.19 (d, $J = 12.6$ Hz, 1H), 5.98 (t, $J = 8.4$ Hz, 1H), 5.28 (t, $J = 7.5$ Hz, 1H), 4.67 (d, $J = 9$ Hz, 2H), 4.46 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.2, 144.9, 135.9, 135.2, 135.1, 133.7, 129.1, 129.0, 128.1, 124.9, 112.5, 77.3, 60.2, 43.5; ESI MS *m/z* 367 $(-H_2O, M + H)^+$, 385 $(M + H)^+$. Purity was determined to be 80% by HPLC analysis on the basis of absorption at 214 nm.

3-Iodo-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (11). Potassium hydroxide was dissolved (10.2 g, 182 mmol) in water (20 mL). This solution was added to **13** (5.17 g, 14.0 mmol) in methanol (180 mL). The reaction mixture was heated at 50 °C overnight, quenched with 1 M aqueous HCl (∼150 mL), and then diluted with water (∼200 mL). The product was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and then concentrated. The crude product was purified via flash chromatography (1:3 ethyl acetate/hexanes) to afford 4.48 g of **11** (12.7 mmol, 92% yield). Pale yellow solid: mp 193−194 °C; IR (neat) ν_{max} 1633, 1500, 1370, 1303, 818, 740 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90−7.86 (m, 2H), 7.65 (d, $J = 8.1$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 9.3$ Hz, 1H), 7.26 (apparent t, $J = 7.7$ Hz, 1H), 6.93 (dd, $J =$ 8.6, 6.5 Hz, 1H), 5.59 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.3, 143.5, 138.2, 134.0, 132.5, 128.3, 124.1, 120.3, 119.3, 117.2, 117.0, 106.0, 91.8, 67.0; ESI MS *m/z* 349 $(M + H)^+$. Purity was determined to be 90% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for the Synthesis of Alkynyl Indazolobenzoxazines: 3-(1-Hexynyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (14a). 1-Hexyne (76 μL, 0.66 mmol) was added under a nitrogen atmosphere to **11** (209 mg, 0.60 mmol) in dry acetonitrile (8 mL). To this was added $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), copper(I) iodide (12 mg, 0.06 mmol), and finally triethylamine (417 μL, 3.0 mmol). The reaction mixture was stirred overnight at room temperature, quenched with saturated aqueous NH_4Cl (∼4 mL), and then diluted with water (∼10 mL). The product was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and then concentrated. The crude product was purified via flash chromatography (1:9 ethyl acetate/hexanes) to afford 178 mg of **14a** (0.59 mmol, 98% yield). White solid: mp 107−108 °C; IR (neat) ν_{max} 2957, 2935, 2858, 1634, 1508, 1377, 822, 745 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 (d, $J = 8.4$ Hz, 1H), 7.51−7.46 (m, 4H), 7.25 (ddd, $J = 8.4$, 6.6, 1.2 Hz, 1H), 6.92 (dd, $J =$ 8.4, 6.6 Hz, 1H), 5.59 (s, 2H), 2.44 (t, $J = 7.2$ Hz, 2H), 1.56−1.51 (m, 2H), 1.48−1.43 (m, 2H), 0.92 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.4, 143.5, 132.5, 132.0, 128.3, 128.2, 122.2, 121.8, 120.3, 119.2, 117.0, 115.4, 106.0, 92.0, 79.8, 67.6, 30.2, 21.4, 18.3, 13.5; ESI MS *m/z* 303 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 214 nm.

3-(1-Octynyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (14b). The general procedure for the synthesis of alkynyl indazolobenzoxazines was employed with use of 1-octyne to afford 122 mg of **14b** (0.37 mmol, 62%). Pale yellow solid: mp 96−97 °C; IR (neat) ν_{max} 3054, 2943, 2847, 1644, 1540, 1520, 1501, 1389, 839, 732 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 (d, $J = 8.4$ Hz, 1H), 7.55−7.47 (m, 4H), 7.26 (apparent t, $J = 7.8$ Hz, 1H), 6.93 (apparent t, $J = 7.5$ Hz, 1H), 5.60 (s, 2H), 2.45 (t, $J = 7.2$ Hz, 2H), 1.57−1.52 (m, 2H), 1.45−1.41 (m, 2H), 1.33−1.29 (m, 4H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.4, 143.6, 132.5, 132.0, 128.3, 128.2, 122.3, 121.8, 120.3, 119.3, 117.0, 115.4, 106.0, 92.0, 79.8, 67.6, 30.8, 28.1, 28.0, 22.0, 18.7, 14.0; ESI MS *m/z* 331 $(M + H)^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 214 nm.

3-(2-Cyclopentylethynyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (14c). The general procedure for the synthesis of alkynyl indazolobenzoxazines was employed with use of cyclopentyl acetylene to afford 139 mg of **14c** (0.44 mmol, 74%). Pale yellow solid: mp 143−144 °C; IR (neat) ν_{max} 2941, 2868, 1630, 1525, 1376, 975, 825, 746 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.80 (d, $J = 8.4$ Hz, 1H), 7.54−7.46 (m, 4H), 7.25 (apparent t, $J = 7.5$ Hz, 1H), 6.92 (dd, $J = 8.4$, 6.6 Hz, 1H), 5.59 (s, 2H), 2.91−2.86 (m, 1H), 2.01−1.97 (m, 2H), 1.73−1.69 (m, 2H), 1.65−1.57 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.4, 143.5, 132.5, 132.0, 128.3, 128.2, 122.2, 121.8, 120.3, 119.3, 117.0, 115.4, 106.0, 96.0, 79.3, 67.6, 33.4, 30.0, 24.6; ESI MS *m/z* 315 $(M + H)^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 214 nm.

3-(2-Cyclohexylethynyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (14d). The general procedure for the synthesis of alkynyl indazolobenzoxazines was employed with use of cyclohexyl acetylene to afford 146 mg of **14d** (0.44 mmol, 74%). Pale yellow solid: mp 159−160 °C; IR (neat) ν_{max} 2929, 2851, 1631, 1526,

1375, 838, 744 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 (d, J = 7.8 Hz, 1H), 7.54−7.47 (m, 4H), 7.25 (apparent t, J = 7.5 Hz, 1H), 6.93 (dd, J = 7.8, 6.6 Hz, 1H), 5.59 (s, 2H), 2.68−2.66 (m, 1H), 1.84−1.82 (m, 2H), 1.71−1.68 (m, 2H), 1.51−1.46 (m, 3H), 1.38−1.34 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.0, 144.2, 133.2, 132.7, 129.0, 128.9, 122.9, 122.4, 121.0, 119.9, 117.6, 116.1, 106.6, 96.3, 80.5, 68.3, 32.8, 29.4, 26.0, 24.9; ESI MS m/z 329 (M + H)$^+$. Purity was determined to be 92% by HPLC analysis on the basis of absorption at 214 nm.

3-(2-Phenylethynyl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (14e). The general procedure for the synthesis of alkynyl indazolobenzoxazines was employed with use of phenyl acetylene (while heating at 50 °C) to afford 145 mg of **14e** (0.45 mmol, 78%). Peach-colored solid: mp 154−156 °C; IR (neat) ν_{max} 2918, 1621, 1519, 1494, 1388, 833, 747, 721, 702 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.90 (d, J = 8.2 Hz, 1H), 7.72 (dd, J = 8.2, 1.5 Hz, 1H), 7.68 (s, 1H), 7.59−7.55 (m, 3H), 7.49 (d, J = 8.9 Hz, 1H), 7.47−7.45 (m, 3H), 7.28−7.26 (m, 1H), 6.94 (dd, J = 8.3, 6.6 Hz, 1H), 5.65 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.5, 143.7, 132.8, 132.7, 131.4, 129.1, 128.9, 128.5, 128.4, 122.4, 122.0, 120.7, 120.4, 119.3, 119.2, 117.0, 116.9, 115.6, 106.0, 90.4, 88.5, 67.6; ESI MS m/z 323 (M + H)$^+$. Purity was determined to be 91% by HPLC analysis on the basis of absorption at 214 nm.

(2-(2-Nitrobenzylamino)-5-(2-(trimethylsilyl)ethynyl)phenyl)-methanol (15). Trimethylsilylacetylene (169 μL, 1.20 mmol) was added under nitrogen to **13** (404 mg, 1.09 mmol) in dry acetonitrile (15 mL). To this was added $PdCl_2(PPh_3)_2$ (38 mg, 0.055 mmol), copper(I) iodide (21 mg, 0.11 mmol), and finally triethylamine (757 μL, 5.45 mmol). The reaction mixture was stirred overnight at room temperature, quenched with saturated aqueous NH_4Cl (∼10 mL), and then diluted with water (∼20 mL). The product was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and then concentrated. The crude product was purified via flash chromatography (1:3 ethyl acetate/hexanes) to afford 333 mg of **15** (0.94 mmol, 86% yield). Orange-brown oil: IR (neat) ν_{max} 3398, 2957, 2142, 1608, 1513, 1247, 838 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 8.4 Hz, 1H), 7.66 (apparent t, J = 7.2 Hz, 1H), 7.54−7.50 (m, 2H), 7.24 (d, J = 1.6 Hz, 1H), 7.05 (dd, J = 8.4, 2.0 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 6.22 (t, J = 6.0 Hz, 1H), 5.24 (t, J = 5.6 Hz, 1H), 4.72 (d, J = 6.0 Hz, 2H), 4.48 (d, J = 5.6 Hz, 2H), 0.17 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.1, 145.9, 135.0, 133.7, 131.6, 131.0, 129.0, 128.2, 126.1, 125.0, 109.7, 108.9, 107.1, 90.6, 60.6, 43.5, 0.2; ESI MS m/z 265 (−H_2O, −TMS, M + H)$^+$, 283 (−TMS, M + H)$^+$, 337 (−H_2O, M + H)$^+$, 355 (M + H)$^+$. Purity was determined to be 84% by HPLC analysis on the basis of absorption at 214 nm.

3-Ethynyl-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (16). Potassium hydroxide was dissolved (675 mg, 12.0 mmol) in water (15 mL). This was added to **15** (328 mg, 0.925 mmol) in 13.5 mL of methanol. The reaction mixture was heated at 50 °C overnight, quenched with 1 M aqueous HCl (∼10 mL), and then filtered. The precipitate was dissolved in ethyl acetate, dried with sodium sulfate, filtered, and then concentrated. The crude product was purified via flash chromatography (1:9 ethyl acetate/hexanes) to afford 174 mg of **16** (0.71 mmol, 76% yield). White solid: mp 177−178 °C; IR (neat) ν_{max} 3250, 1633, 1504, 824, 750 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.26 (apparent t, J = 7.8 Hz, 1H), 6.93 (dd, J = 8.4, 6.4 Hz, 1H), 5.62 (s, 2H), 4.34 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.2, 144.4, 133.8, 133.5, 129.5, 129.0, 123.0, 121.0, 120.8, 120.0, 117.6, 116.1, 106.6, 83.3, 82.6, 68.2; ESI MS m/z 247 (M + H)$^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for the Synthesis of (5-Isoxazolyl)indazolobenzoxazines: 3-(3-Methylisoxazol-5-yl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (17a). 1,4-Phenylene diisocyanate (144 mg, 0.90 mmol) was added to **16** (74 mg, 0.30 mmol) in dry tetrahydrofuran (4 mL). Triethylamine (125 μL, 0.90 mmol) was added to the reaction mixture and this was heated to 50 °C. Nitroethane (65 μL, 0.90 mmol) was added in portions over a period of 6−8 h, and then the reaction was heated an additional 2 h. The reaction was quenched with water (2 mL) and allowed to stir at room temperature for 1 h. 1,4-Phenylene diisocyanate was removed by filtration over celite (washing several times with ethyl acetate), and the filtrate was then concentrated and subjected to flash chromatography (2:3 ethyl acetate/hexanes) to afford 57 mg of **17a** (0.19 mmol, 63% yield). White solid: mp 217−218 °C; IR (neat) ν_{max} 1636, 1620, 1531, 1513, 1426, 1381, 828, 803, 732 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.99−7.95 (m, 3H), 7.56 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.27 (apparent t, J = 5.4 Hz, 1H), 6.95−6.92 (m, 2H), 5.70 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.6, 160.6, 148.6, 143.8, 133.8, 128.5, 127.0, 125.4, 122.8, 122.7, 120.4, 119.3, 117.0, 115.9, 106.0, 101.5, 67.8, 11.13; ESI MS m/z 304 (M + H)$^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 214 nm.

3-(3-Ethylisoxazol-5-yl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (17b). The general procedure for the synthesis of (5-isoxazolyl)indazolobenzoxazines was employed to afford 87 mg of **17b** (0.17 mmol, 56% yield). White solid: mp 164−165 °C; IR (neat) ν_{max} 2973, 1637, 1619, 1530, 1511, 1433, 1377, 803, 730 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.00−7.95 (m, 3H), 7.55 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.28−7.25 (m, 1H), 6.99 (s, 1H), 6.94 (dd, J = 8.2, 6.7 Hz, 1H), 5.69 (s, 2H), 2.69 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.6, 165.8, 148.5, 143.8, 133.8, 128.4, 127.0, 125.5, 122.8, 122.7, 120.4, 119.3, 117.0, 115.9, 106.0, 100.3, 67.8, 19.0, 12.5; ESI MS m/z 318 (M + H)$^+$. Purity was determined to be 90% by HPLC analysis on the basis of absorption at 214 nm.

3-(3-Propylisoxazol-5-yl)-5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (17c). The general procedure for the synthesis of (5-isoxazolyl)indazolobenzoxazines was employed to afford 87 mg of **17c** (0.26 mmol, 88% yield). White solid: mp 149−150 °C; IR (neat) ν_{max} 2954, 1634, 1614, 1529, 1512, 1419, 1375, 983, 818, 734 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.00−7.95 (m, 3H), 7.55 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.27 (apparent t, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.94 (apparent t, J = 7.5 Hz, 1H), 5.69 (s, 2H), 2.64 (t, J = 7.4 Hz, 2H), 1.68 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.6, 164.5, 148.6, 143.8, 133.8, 128.5, 127.0, 125.5, 122.8, 122.7, 120.4, 119.3, 117.0, 115.9, 106.0, 100.5, 67.8, 27.3, 21.0, 13.6; ESI MS m/z 332 (M + H)$^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 214 nm.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of intermediates and selected library members as well as a summary of LC/MS data for all other library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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