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Design and Synthesis of New Biprivileged Molecular Scaffolds: Indolo-Fused Benzodiazepinyl/quinoxalinyl benzimidazoles

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Abstract: The present article describes the design and synthesis of new biprivileged molecular scaffolds with diverse structural features. Commercially available, simple heterocyclic building blocks such as 4-fluoro-3-nitrobenzoic acid, 2-chloro-3-nitrobenzoic acid, and indoline were utilized for the synthesis of the novel heterocycles. Pictet–Spengler-type condensation was used as a key step to construct tetracyclic indolo-benzodiazepines and indolo-quinoxalines linked with substituted benzimidazoles. Analysis of single crystals of representative compounds showed that these molecular skeletons have the potential to present various substituents with distinct three-dimensional orientations.

Keywords: drug discovery · heterocycles · Pictet–Spengler-type reactions · privileged structures · synthesis design

Introduction

"Privileged Structures" are highly fascinating molecular scaffolds in pharmaceutical research.[1] Through the modification of various functional groups, a privileged scaffold can provide potent and selective ligands for a range of different biological targets.[2] Over the past twenty years this concept has emerged as a fruitful approach to the discovery of novel lead compounds. A significant amount of drugs currently on the market comprise privileged structures.[3] The main function of the privileged structure in a drug molecule is to position the functional groups in the right direction to achieve an optimal interaction with the desired biomolecules (proteins, enzymes, receptors, or nucleic acids), which are capable of diverse functions ranging from molecular recognition to catalysis because of their precise three-dimensional tertiary or quaternary structures. Hence, small molecules with three-dimensional complex structures that fit best into the active-site crevices of these biopolymers can selectively modulate their functions. By analyzing a database of more than two million compounds, Lovering et al. provided evidence that the complexity of a molecule is a key determinant of its success in the transition from discovery to clinical testing and finally to an approved drug.[4] Increases in the level of molecular complexity of molecules have been correlated with an improved potency of drug candidates,[5] thus highlighting the limitations of the synthesis of flat chemical libraries over diversity-oriented non-flat libraries. Several reports on the combinatorial synthesis of chiral complex libraries have been published.[6] To understand the importance of these molecular scaffolds and to use the concept of privileged structures, the present article describes the design and synthesis of new biprivileged molecular scaffolds **1** and **2** that can provide multiple ligands in distinct three-dimensional orientations (Figure 1).

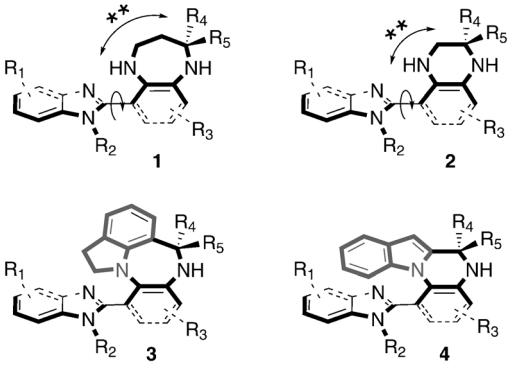

Figure 1. Molecular scaffolds with multiple privileged structures. For structures **1** and **2**, sites for incorporation of additional steric bulk leading to rigid basic skeletons are marked by two asterisks.

To increase the rigidity of the basic skeletons of **1** and **2**, we envisioned to incorporate fused indoline and indole moieties leading to molecules **3** and **4** (Figure 1). Overall, the newly designed skeletons consist of four important privileged structures, namely benzimidazole, benzodiazepine/benzopyrazine, and indole.[7–12] The new molecular scaffolds can be utilized to explore novel dimensions in the drug dis-

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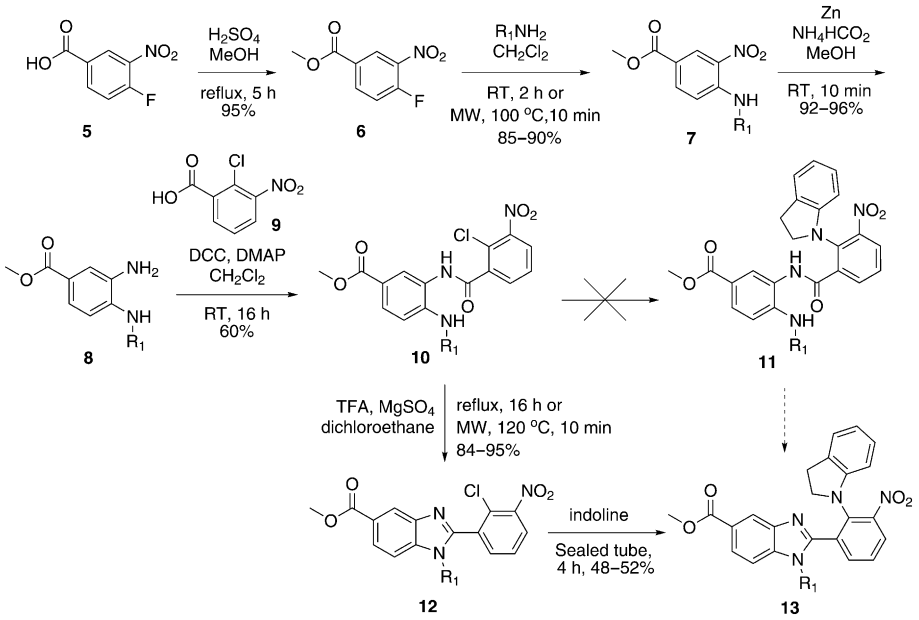
covery process. Increased hit rates at a comparably small library size are expected from such complex skeletons. To the best of our knowledge, the synthesis of such benzimidazole-linked heterocycles with four annulated rings has not been reported. Herein, the synthesis of benzimidazoles[13] and indolo-quinoxalines/benzodiazepines[14] was combined for the synthesis of a library having multiple privileged structures. The real challenge was to devise a synthetic protocol for the scaffold-based synthesis of these highly constrained chimeric skeletons.

Results and Discussion

Commercially available 4-fluoro-3-nitrobenzoic acid (FNBA) **5** was esterified to its methyl ester, which was used as the starting material for the further synthesis. The first point of structural diversity was achieved in the next step by *ipso*-fluoro displacement of the activated aromatic fluoride in **6**, which was conducted at ambient temperature for 2 hours using various primary amines (Scheme 1). The nitro functionality in aniline derivatives **7** was reduced by zinc and ammonium formate leading to diamines **8**.

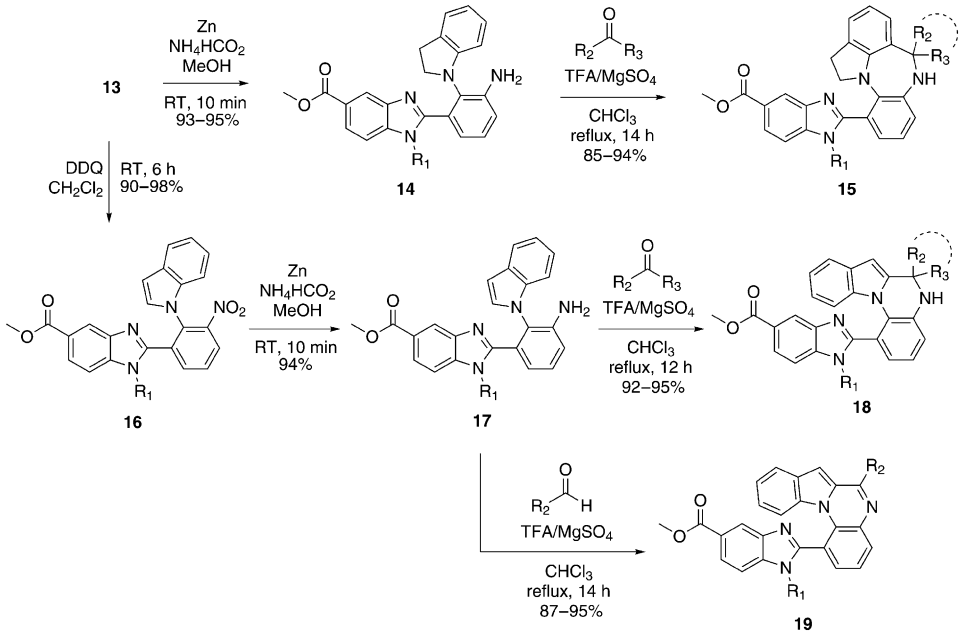


Scheme 1. General strategy for the synthesis of intermediate **13**.

The selective condensation of 2-chloro-3-nitrobenzoic acid **9** with **8** via the in situ generated DCC-activated ester in dichloromethane at room temperature resulted in the formation of anilides **10**. Because of the presence of the ester functionality on the ring, which deactivates the secondary amine and facilitates the amide coupling with the primary amine site, exclusive selectivity was achieved. The selectivity was assessed by ^{1}H NMR spectroscopy, which showed no change in the chemical shift of the R_1 methylene group (R_1 = isobutyl). Efforts to displace the chloro functionality in **10** by indoline to deliver **11** using triethylamine, diisopropylethylamine as well as potassium carbonate as a base under various conditions (heating at reflux, heating in a sealed tube, or microwave irradiation) failed. The reaction was possibly impeded because of steric effects. The desired compound **13** was obtained in an alternative approach in which formation of the benzimidazole ring was carried out first before the actual chloro displacement by indoline, in an anticipation to improve the electrophilicity of the ring for the desired *ipso*-substitution. Intramolecular ring closure through nucleophilic attack of the secondary amine on the amide carbonyl in **10** was brought about in refluxing 1,2-dichloroethane with TFA (10%) and anhydrous $MgSO_4$ to furnish benzimidazole-linked nitrochlorobenzene **12**. As expected, an electron-withdrawing resonance effect was observed in methyl 2-(2-chloro-3-nitrophenyl)-1-isobutyl-1H-benzo[*d*]imidazole-5-carboxylate **12**, as evidenced by the deshielding of the aromatic proton at position 6 of the 2-chloro-3-nitrophenyl moiety of **12** in comparison to that in methyl 3-(2-chloro-3-nitrobenzamido)-4-(isobutylamino)benzoate **10**. Our initial effort to displace the chloro functionality in **12** by indoline applying NaH and Cs_2CO_3 as a base using heat and microwave irradiation conditions were unsuccessful to deliver **13**. The same nucleophilic substitution reaction using organic bases like TEA and DIPEA at reflux temperature, microwave irradiation, and sealed-tube heating conditions resulted in the formation of the desired product **13** in very low yields (5–10%). We therefore focused our attention subsequently towards the metal-catalyzed coupling reaction of indoline with compound **12**. Accordingly, indoline and **12** were subjected to Ullman coupling conditions. Attempts using CuI in combination with Cs_2CO_3 as well as Cs_2CO_3 and 1,10-phenanthroline resulted in the recovery of starting material. The screening of metal-catalyzed coupling reactions under various Buchwald conditions like palladium acetate in the presence of tri(*o*-tolyl)phosphine and palladium acetate in combination with (2-biphenyl)di-*tert*-butylphosphine and sodium *tert*-butoxide did not lead to **13** as well. Hence, we speculated that the coupling reaction requires harsh conditions which can be promoted in solvent-free conditions. Consequently, the hindered chloro displacement by indoline in compound **12** was achieved at heating for 4 hours in a sealed tube, resulting in **13** in a moderate yield. The decrease in the steric effect and an additional electron-withdrawing resonance effect of the benzimidazole ring in **12** as

compared to that in substrate **10** might have promoted the indoline substitution.

Compound **13** was utilized as the common intermediate for the synthesis of indolo-fused benzodiazepinyl and quinoxalinyl benzimidazoles **15**, **18**, and **19** (Scheme 2). The



Scheme 2. Synthesis of indolo-fused benzodiazepinyl and quinoxalinyl benzimidazole derivatives.

nitro functionality in **13** was reduced to amine using Zn and ammonium formate in methanol to yield amino-indolinyl intermediate **14**. On the other hand, the indoline ring of compound **13** was first oxidized to indole-bearing compound **16** using DDQ, and the nitro group in **16** was further reduced by similar reducing conditions to furnish amino-indolyl precursor **17** at room temperature. The key step in this process was to accomplish the Pictet–Spengler-type heterocyclization to furnish the desired highly constrained chimeric skeletons. The indoline-substituted intermediate **14** furnished the desired tetrahydroindolo-benzodiazepinyl benzimidazoles **15** when reacted with various aldehydes and ketones (Table 1) in the presence of TFA and $MgSO_4$ in refluxing chloroform for 12 hours. By contrast, under these acid-catalyzed dehydrating conditions, the amino-indolyl intermediate **17** resulted in dihydroindolo-quinoxalinyl benzimidazoles **18** when reacted with ketones (Table 1, entries **18a** and **18b**).

Similarly, using aldehydes in place of ketones, indolo-quinoxalinyl benzimidazoles **19** were obtained in good yields. The dihydropyrazine ring was found to be easily air-oxidized during this transformation to deliver fully aromatic tetracyclic flat skeletons **19** linked to benzimidazole. During this Pictet–Spengler-type condensation,[15] **14** underwent an electrophilic cyclization with ketones at the phenyl ring,[14b] while compound **17** cyclized onto its electron-rich pyrrole ring[14a] to furnish the required heterocycles in good to excellent yields (Table 1). Various aromatic and heteroaromatic aldehydes and cyclic as well as noncyclic ketones were applied during this unusual Pictet–Spengler-type cyclization.

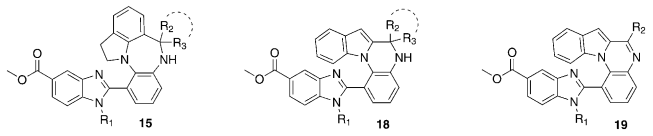
To visualize the importance of these molecular skeletons that have the potential to present various substituents in particular three-dimensional orientations, single crystals of the representative compounds **15i** and **18a** were grown from a hot, saturated, and filtered solution of these compounds in CH_2Cl_2/CH_3OH mixtures. Suitable crystals were obtained by slow evaporation of the solvent at room temperature. Compounds **15i** and **18a** crystallized as yellow and pale yellow crystals, respectively. The best crystals were selected and the X-ray diffraction data were collected.[16] As it can be clearly observed in the ORTEP[17] diagrams (Figure 2), the molecules possess a distinct three-dimensional orientation due to the hindered rotation about the single bond (C1–C14) between the benzimidazole ring and the tetracyclic indolo-benzodiazepine ring (**15i**) or indolo-quinoxaline ring (**18a**).

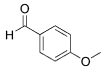
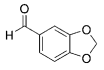
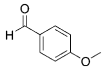
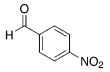
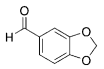
Non-planarity in the basic tetracyclic indolo-benzodiazepine ring system **15i** was also observed as a result of a twist between the two planes comprising the indoline ring and the phenyl ring connected by N3 and C19. This was enforced by the linkage with a tetrahedral carbon (C28) and a nitrogen (N4) atom, resulting in a seven-membered diazepino ring junction that has a partial envelope conformation. A similar non-planarity was also observed in indolo-quinoxaline skeleton **18a**. Suitable solubility and salt-forming properties (important for oral absorption and bioavailability) can be expected from these non-planar heterocycles that contain several basic nitrogen atoms as well as a carboxylate functionality. The carboxylate functionality as well as the aromatic halo/nitro functionalities on several library members can be further utilized according to structure–activity relationship (SAR) requirements.

Conclusions

Novel privileged structures comprising indolo-fused benzodiazepinyl/quinoxalinyl benzimidazoles were synthesized in good to excellent yield. The concept of atropisomerism was used to construct these non-flat skeletal compound libraries. Commercially available 4-fluoro-3-nitrobenzoic acid, 2-chloro-3-nitrobenzoic acid, and indoline were utilized for the synthesis of these complex molecular scaffolds. The various electron densities on the indoline and indole rings of

Table 1. Indolo-fused benzodiazepinyl/quinoxalinyl benzimidazoles **15**, **18**, and **19**.



Entry	R_1	Aldehydes or Ketones	Isolated Yield [%]
15a			94
15b			90
15c			86
15d			92
15e			88
15f			85
15g			90
15h			88
15i			87
15j			88
18a			95
18b			92
19a			95
19b			95
19c			88
19d			87
19e			90
19f			90
19g			92
19h			88

compounds **14** and **17** were utilized for Pictet–Spengler-type cyclization reactions to furnish benzodiazepinyl or quinoxalinyl structural units. Analysis of single crystals of representative compounds demonstrated that these molecular skeletons have the potential to present various substituents with distinct three-dimensional orientations. The compound libraries will be screened against various biological targets.

Experimental Section

General

All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kieselgel 60 F254 plates. Compound purification was carried out by flash chromatography on silica gel 60 (230–400 mesh). IR spectra were recorded using a HORIBA FT-720 FREEXACT-II IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard (TMS). Mass spectra were recorded on a JEOL TMS-HX 110 mass spectrometer; samples were introduced by the infusion method using the electrospray ionization technique. Starting compounds were purchased from Matrix Scientific, Accela ChemBio Inc., and Alfa Aesar, and used without purification.

*Synthesis of Key Intermediate **13***

H_2SO_4 (5 mL, 0.3 M) was added to a solution of 4-fluoro-3-nitrobenzoic acid **5** (5.0 g, 27.0 mmol) in dry MeOH (30 mL), and the reaction mixture was heated to reflux for 5 h. After removal of the solvent under reduced pressure, the mixture was dissolved in EtOAc (150 mL), washed with saturated $NaHCO_3$ (20 mL × 2), water (10 mL × 2), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford methyl 4-fluoro-3-nitrobenzoate **6** (95%) as a white solid. Compound **6** (2.0 g, 10.2 mmol) and a primary amine (3 equiv) in dry CH_2Cl_2 (50 mL) were stirred for 2 h at room temperature or under MW irradiation (100 W, 100 °C) in dry CH_2Cl_2 (5 mL) in a sealed vial for 10 min. Subsequently, the solvents were removed under reduced pressure, and the crude product was purified by flash chromatography to afford amino/nitro benzoates **7** (85 to 90%). For the next step, zinc dust (15 equiv, 71.4 mmol) and ammonium formate (7.5 equiv, 35.7 mmol) were added to a solution of **7** (2.0 g, 4.8 mmol) in dry MeOH (100 mL), and the resulting reaction mixture was stirred for 10 min at room temperature. Subsequently, Zn dust was filtered off through a bed of celite, the solvent was evaporated, and the product was dissolved in CH_2Cl_2 (100 mL). The precipitated ammonium formate was filtered off and the solvent was evaporated to furnish **8** (92–96%). The crude products obtained were used directly for the next step of the synthesis, in which **8** (1.0 g, 4.8 mmol), 2-chloro-3-nitrobenzoic acid (1.3 g, 6.7 mmol), DCC (1.4 g, 6.6 mmol), and catalytic DMAP (0.006 g, 0.05 mmol) in dry CH_2Cl_2 (25 mL) were stirred in a round-bottomed flask for 16 h at 25 °C. After cooling to 0 °C the solid dicyclohexylurea (DCU) formed was filtered off and the solvent was evaporated. The crude product was further purified by precipitation and washing with *n*-hexane (20 mL × 3) to afford amide **10** in 60–70% yield. Next, amide **10** (1.0 g, 2.8 mmol) in 1,2-dichloroethane (50 mL) was heated to reflux for 16 h in the presence 10% trifluoroacetic acid (TFA) (0.43 mL, 5.61 mmol) and $MgSO_4$ (0.5 g, 4.14 mmol) or heated under MW irradiation (100 W, 120 °C) for 10 min in a sealed vial in 1,2-dichloroethane (5 mL) containing five drops of TFA. Subsequently, the volatilities were removed and the crude product purified by flash chromatography to give **12** (84–95%). Nucleophilic aromatic substitution of indoline (10 equiv, 30.0 mmol) with compound **12** (1.0 g, 3.0 mmol) was brought about in a sealed tube by heating for 4 h at 150 °C. The obtained crude product was purified by flash chromatography to afford key intermediate **13** (48–52%).

*Synthesis of Tetrahydroindolo-benzodiazepinyl-benzimidazoles (**15**)*

The nitro functionality in compound **13** was reduced to amine using Zn/ammonium formate as described above to afford compound **14** (93–95%). Next, an aldehyde or ketone (3.0 equiv), anhydrous magnesium

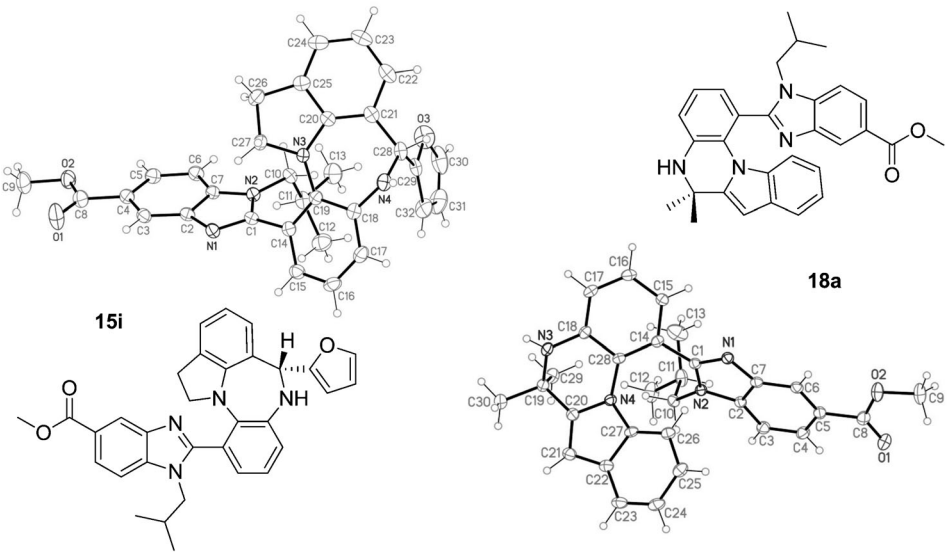


Figure 2. ORTEP view of compounds **15i** and **18a** (No atropselective synthesis was carried out. The relative stereo-chemistries in structures are shown for clarity).

sulfate (20%), and 2 drops of trifluoroacetic acid (TFA) were added to a solution of compound **14** (0.1 g, 0.26 mmol, 1.0 equiv) in $CHCl_3$ (10 mL). The resulting reaction mixture was refluxed for 14 h. Subsequently, the mixture was passed through a thin layer of Celite to remove $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to afford tetrahydroindolo-benzodiazepinyl-benzimidazoles **15** in good to excellent yields (85–94%, Table 1).

*Synthesis of Indoloquinoxalinyl-benzimidazoles (**18** and **19**)*

A solution of compound **13** (0.5 g, 1.2 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature in the presence of DDQ (0.80 g, 3.6 mmol) for 6 h. Subsequently, CH_2Cl_2 (50 mL) was added, and the organic layer was washed with NaOH solution (1 N, 10 mL × 3), water (10 mL × 3), and brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated to furnish **16** (90–98%). The nitro functionality in compound **16** was reduced to amine using Zn/ammonium formate as described earlier to afford compound **17** (80–94%). To a solution of compound **17** (0.1 g, 0.26 mmol, 1.0 equiv) in $CHCl_3$ (10 mL), ketone (3.0 equiv), anhydrous magnesium sulfate (20%), and 2 drops of trifluoroacetic acid (TFA) were added. The resulting reaction mixture was refluxed for 14 h. After completion of the reaction, the compound mixtures were passed through a thin layer of Celite to remove $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography to afford dihydroindolo-quinoxalinyl-benzimidazoles **18** in excellent yields (92–95%, Table 1). Compounds **19** were obtained using aldehydes and following a similar protocol as described above.

*Characterization Data for **15a–j**, **18a,b**, and **19a–h***

Methyl 2-[6-(2-fluorophenyl)-1,2,6,7-tetrahydroindolo[1,7-ab][1,5]-benzodiazepin-11-yl]-1-(furan-2-ylmethyl)-1H-benzimidazole-5-carboxylate (**15a**). IR (neat): $\tilde{\nu}$ = 2925, 2852, 2358, 1714 cm^{-1}; ^1H NMR (300 MHz, d_6-Acetone): δ = 8.39 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.08 (m, 3H), 6.99 (m, 2H), 6.81 (t, J = 7.2 Hz, 2H), 6.68 (t, J = 7.2 Hz, 2H), 6.26 (s, 1H), 6.06 (s, 1H), 5.81 (s, 1H), 5.70 (s, 1H), 5.40–5.00 (m, 2H), 3.91 (s, 3H), 3.46 (m, 1H), 3.23 (m, 1H), 2.70 ppm (m, 2H); ^{13}C NMR (75 MHz, d_6-Acetone): δ = 167.2, 162.8, 159.5, 156.6, 149.3, 147.0, 143.8, 143.3, 142.4, 138.7, 136.3, 131.6, 130.6, 130.4, 130.3, 130.3, 129.6, 129.5, 127.8, 127.5, 127.4, 124.8, 124.5, 124.2, 124.1, 124.0, 123.4, 121.9, 121.8, 121.7, 118.8, 115.7, 115.4, 111.2, 110.7, 109.6, 60.1, 59.9, 54.3, 51.8, 41.7, 28.4 ppm; MS (ESI$^+$) m/z: 571.1 $(M+H)^+$; HRMS: calcd for $C_{35}H_{27}FN_4O_3$ m/z: 570.2067; found: 570.2075.

Methyl 2-[6-(2-bromophenyl)-1,2,6,7-tetrahydroindolo[1,7-ab]-[1,5]benzodiazepin-11-yl]-1-(furan-2-ylmethyl)-1H-benzimidazole-5-carboxylate (**15b**). IR (neat): $\tilde{\nu}$ = 2927, 2852, 2381, 2348, 2312 cm^{-1}; ^1H NMR (300 MHz, d_6-Acetone): δ = 8.39 (d, J = 1.2 Hz, 1H), 7.94 (dd, J = 8.5, 1.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 7.9, 0.9 Hz, 1H), 7.26 (s, 1H), 7.03 (d, J = 7.2 Hz, 3H), 6.96 (dd, J = 7.7, 1.7 Hz, 2H), 6.80 (t, J = 7.6 Hz, 2H), 6.66 (t, J = 7.3 Hz, 2H), 6.28 (dd, J = 3.2, 1.9 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.76 (s, 2H), 5.38 (m, 2H), 3.92 (s, 3H), 3.48 (m, 1H), 3.27 (m, 1H), 2.73 ppm (t, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, d_6-Acetone): δ = 167.2, 156.5, 149.3, 146.9, 143.7, 143.4, 142.0, 138.7, 136., 133.3, 131.6, 130.8, 129.5, 127.7, 127.5, 127.4, 124.9, 124.6, 124.3, 124.2, 124.0, 123.7, 121.8, 121.5, 118.8, 111.2, 110.8, 109.6, 64.9, 54.2, 51.8, 41.8, 28.4 ppm; MS (ESI+) m/z: 632.0 $(M+H)^+$; HRMS: calcd for $C_{35}H_{27}BrN_4O_3$ m/z: 630.1267; found: 630.1262.

Methyl 2-[6-(2-bromophenyl)-1,2,6,7-tetrahydroindolo[1,7-ab]-[1,5]benzodiazepin-11-yl]-1-(furan-2-ylmethyl)-1H-benzimidazole-5-carboxylate (**15c**). IR (neat): $\tilde{\nu}$ = 2950, 2925, 2854, 2360, 1714 cm^{-1}; ^1H NMR (300 MHz, d_6-Acetone): δ = 8.36 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.32 (s, 1H), 7.13 (d, J = 8.3 Hz, 2H), 7.01 (m, 4H), 6.84 (t, J = 7.6 Hz, 2H), 6.64 (m, 3H), 6.22 (s, 1H), 5.52 (s, 1H), 5.08 (m, 2H), 3.91 (s, 3H), 3.56 (s, 3H), 3.43 (m, 1H), 3.20 (m, 1H), 2.66 ppm (m, 2H); ^{13}C NMR (75 MHz, d_6-Acetone): δ = 167.2, 158.9, 156.9, 149.4, 146.5, 143.8, 143.1, 138.7, 135.9, 135.4, 131.4, 129.7, 127.7, 126.7, 124.7, 124.0, 123.6, 121.8, 121.7, 118.6, 113.8, 111.2, 110.6, 109.5, 64.0, 60.1, 555.0, 54.7, 54.6, 51.7, 41.5, 28.3 ppm; MS (ESI+) m/z: 583.1 $(M+H)^+$; HRMS: calcd for $C_{36}H_{30}N_4O_4$ m/z: 582.2267; found: 582.2260.

Methyl 1-(furan-2-ylmethyl)-2-[6-(furan-3-yl)-1,2,6,7-tetrahydroindolo-[1,7-ab][1,5] benzodiazepin-11-yl]-1H-benzimidazole-5-carboxylate (**15d**). IR (neat): $\tilde{\nu}$ = 2950, 2852, 2360, 1716, 1616 cm^{-1}; ^1H NMR (300 MHz, d_6-Acetone): δ = 8.39 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 8.5, 1.5 Hz, 1H), 7.30 (s, 1H), 7.20 (s, 1H), 7.14 (d, J = 6.0 Hz, 1H), 7.00 (t, J = 7.6 Hz, 2H), 6.90 (t, J = 7.6 Hz, 2H), 6.66 (d, J = 7.4 Hz, 1H), 6.45 (s, 1H), 6.19 (s, 1H), 5.98 (br, 1H), 5.75 (br, 1H), 5.41 (s, 1H), 5.30–4.85 (m, 2H), 3.91 (s, 3H), 3.42 (m, 1H), 3.20 (m, 1H), 2.63 ppm (m, 2H); ^{13}C NMR (75 MHz, d_6-Acetone): δ = 167.2, 156.8, 149.5, 146.0, 143.9, 143.7, 143.0, 141.1, 138.8, 135.7, 131.6, 129.4, 127.0, 126.8, 124.7, 124.6, 124.1, 123.7, 121.9, 121.8, 121.7, 118.5, 111.2, 110.6, 110.5, 109.2, 57.2, 54.6, 51.8, 41.2, 28.3 ppm; MS (ESI$^+$) m/z: 543.1 $(M+H)^+$; HRMS: calcd for $C_{33}H_{26}N_4O_4$ m/z: 542.1985; found: 542.1959.

Methyl 1-(furan-2-ylmethyl)-2-[6-(thiophen-2-yl)-1,2,6,7-tetrahydroindolo[1,7-ab][1,5] benzodiazepin-11-yl]-1H-benzimidazole-5-carboxylate (**15e**). IR (neat): $\tilde{\nu}$ = 2950, 2925, 2854, 2360, 1714 cm^{-1}; ^1H NMR (300 MHz, d_6-Acetone): δ = 8.37 (d, J = 1.2 Hz, 1H), 7.03 (dd, J = 8.6, 1,5 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.21 (s, 1H), 7.11(dd, J = 7.6 1.6 Hz, 2H), 7.04 (m, 2H), 6.93 (d, J = 7.6 Hz, 2H), 6.69 (t, J = 7.4 Hz, 1H), 6.64 (s, 1H), 6.20 (m, 1H), 5.85 (m, 1H), 5.76 (m, 1H), 5.08 (m, 2H), 3.91 (s, 3H), 3.48 (m, 1H), 3.20 (m, 1H), 2.65 ppm (m, 2H); ^{13}C NMR (75 MHz, d_6-Acetone): δ = 167.2, 156.8, 149.5, 149.4, 148.5, 146.1, 143.8, 143.4, 143.0, 142.2, 138.8, 135.6, 131.8, 127.7, 127.1, 126.5, 125.2, 124.7, 124.1, 124.0, 122.1, 121.9, 121.7, 118.6, 111.3, 110.6, 109.3, 60.6, 60.1, 54.6, 51.8, 41.5, 28.3 ppm; MS (ESI+) m/z: 559.1 $(M+H)^+$; HRMS: calcd for $C_{33}H_{26}N_4O_3S$ m/z: 558.1726; found: 558.1736.

Methyl 2-[6-(1,3-benzodioxol-5-yl)-1,2,6,7-tetrahydroindolo[1,7-ab]-[1,5]benzodiazepin-11-yl]-1-(3-methoxypropyl)-1H-benzimidazole-5-carboxylate (**15f**). IR (neat): $\tilde{\nu}$ = 2952, 2927, 2360, 2316, 1714 cm^{-1}; ^1H NMR

(300 MHz, d_6-Acetone): δ=8.40 (d, J=1.1 Hz, 1H), 7.99 (dd, J=8.6, 1.6 Hz, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.06 (d, J=7.4 Hz, 2H), 6.99 (d, J=7.1 Hz, 1H), 6.89 (d, J=7.5 Hz, 1H), 6.83 (s, 1H), 6.75 (t, J=9.1 Hz, 3H), 6.66 (d, J=7.2 Hz, 1H), 5.96 (s, 2H), 5.49 (s, 1H), 4.25 (m, 1H), 3.93 (s, 4H), 3.40 (m, 1H), 3.15 (br, 1H), 2.64 (m, 3H), 1.73 (m, 1H), 1.48 ppm (br, 1H); ^{13}C NMR (75 MHz, d_6-Acetone): δ=167.3, 156.9, 148.3, 147.0, 146.2, 143.6, 139.0, 137.8, 135.7, 131.4, 127.8, 127.0, 124.5, 124.0, 123.7, 122.4, 122.2, 121.8, 121.7, 118.6, 110.9, 109.0, 108.1, 101.5, 69.0, 64.4, 57.9, 54.4, 51.7, 41.7, 28.4 ppm; MS (ESI$^+$) m/z: 589.2 $(M+H)^+$; HRMS: calcd for $C_{32}H_{34}N_4O_2$ m/z: 588.2373; found: 588.2365.

Methyl 2-[6-(furan-3-yl)-1,2,6,7-tetrahydroindolo[1,7-ab][1,5]-benzodiazepin-11-yl]-1-(3-methoxypropyl)-1H-benzimidazole-5-carboxylate (**15g**). IR (neat): $\tilde{\nu}$=2925, 2852, 2360, 1714, 1612 cm^{-1}; ^{1}H NMR (300 MHz, d_6-Acetone): δ=8.40 (s, 1H), 7.98 (dd, J=8.5, 1.5 Hz, 1H), 7.62 (d, J=8.5 Hz, 1H), 7.46 (s, 1H), 7.13 (dd, J=7.7, 1.7 Hz, 1H), 7.08 (dd, J=7.6, 1.6 Hz, 1H), 6.98 (d, J=7.2 Hz, 1H), 6.92 (t, J=7.6 Hz, 2H), 6.66 (t, J=7.4 Hz, 1H), 6.50 (s, 1H), 5.42 (s, 1H), 4.19 (m, 1H), 3.93 (s, 4H), 3.41 (m, 1H), 3.12 (br, 1H), 2.98 (s, 3H), 2.77 (br, 2H), 2.57 (m, 2H), 1.63 ppm (m, 2H); ^{13}C NMR (75 MHz, CDCl3): δ=168.1, 156.4, 145.6, 144.2, 143.3, 141.2, 138.8, 135.5, 127.7 124.9, 124.7, 124.2, 122.6, 122.4, 122.2, 118.9, 110.2, 110.2, 77.6, 68.8, 58.8, 57.7, 54.5, 52.5, 41.6, 32.3, 30.1, 29.8, 29.6, 28.8, 23.1 ppm; MS (ESI+) m/z: 535.1 $(M+H)^+$; HRMS: calcd for $C_{32}H_{30}N_4O_4$ m/z: 534.2267; found: 534.2263.

Methyl 1-(2-methylpropyl)-2-(6-phenyl-1,2,6,7-tetrahydroindolo[1,7-ab]-[1,5] benzodiazepin-11-yl)-1H-benzimidazole-5-carboxylate (**15h**). IR (neat): $\tilde{\nu}$=2956, 2927, 2383, 2360, 1716 cm^{-1}; ^{1}H NMR (300 MHz, d_6-Acetone): δ=8.42 (s, 1H), 7.99 (dd, J=8.5, 1.5 Hz, 1H), 7.69 (d, J=8.6 Hz, 2H), 7.32 (s, 4H), 7.25 (br, 1H), 7.14 (d, J=7.5 Hz, 1H), 7.01 (m, 2H), 6.88 (t, J=7.6 Hz, 1H), 5.55 (s, 1H), 4.112 (dd, J=14.2, 5.5 Hz, 1H), 3.92 (s, 3H), 3.76 (br, 1H), 3.37 (d, J=9.3 Hz, 1H), 3.08 (br, 1H), 2.60 (t, J=7.8 Hz, 2H), 1.91 (m, 1H), 0.63 (d, J=6.8 Hz, 3H), 0.38 ppm (s, 3H); ^{13}C NMR (75 MHz, d_6-Acetone): δ=167.3, 157.0, 146.1, 143.8, 139.2, 135.9, 131.5, 129.1, 128.8, 128.0, 127.4, 124.8, 124.5, 124.0, 123.6, 123.1, 122.2, 121.8, 118.5, 111.2, 54.0, 51.8, 51.7, 28.5, 19.7, 19.4, 13.9, 13.8 ppm; MS (ESI$^+$) m/z: 529.2 $(M+H)^+$; HRMS: calcd for $C_{34}H_{32}N_4O_2$ m/z: 528.2525; found: 528.2529.

Methyl 2-[6-(furan-3-yl)-1,2,6,7-tetrahydroindolo[1,7-ab][1,5]benzodiazepin-11-yl]-1-(3-methoxypropyl)-1H-benzimidazole-5-carboxylate (**15i**). IR (neat): $\tilde{\nu}$=2956, 2927, 2381, 2354, 2310 cm^{-1}; ^{1}H NMR (300 MHz, d_6-Acetone): δ=8.57 (d, J=1.1 Hz, 1H), 8.04 (dd, J=8.5, 1.5 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.24 (dd, J=5.6, 3.6 Hz, 1H), 7.02 (d, J=7.1 Hz, 1H), 6.94 (m, 3H), 6.71 (t, J=7.3 Hz, 1H), 6.14 (br, 1H), 5.77 (br, 1H), 5.50 (s, 1H), 3.98 (s, 4H), 3.85 (dd, J=14.0, 4.6 Hz, 1H), 3.60 (br, 2H), 2.97 (br, 2H), 2.58 (m, 2H), 1.91 (m, 1H), 0.69 (d, J=7.5 Hz, 3H), 0.27 ppm (s, 3H); ^{13}C NMR (75 MHz, d_6-Acetone): δ=168.1, 156.7, 156.5, 145.7, 143.5, 143.0, 138.7, 135.8, 131.9, 128.5, 124.9, 124.7, 124.3, 123.0, 122.9, 122.8, 118.8, 110.5, 110.2, 109.2, 59.6, 54.0, 52.6, 52.1, 34.8, 30.1, 29.0, 28.9, 21.8, 20.3, 19.8 ppm; MS (ESI+) m/z: 519.1 $(M+H)^+$; HRMS: calcd for $C_{32}H_{30}N_4O_3$ m/z: 518.2318; found: 518.2328.

Methyl 1-(furan-2-ylmethyl)-2-[6-(furan-3-yl)-1,2,6,7-tetrahydroindolo-[1,7-ab][1,5] benzodiazepin-11-yl]-1H-benzimidazole-5-carboxylate (**15j**). IR (neat): $\tilde{\nu}$=2954, 2859, 2306, 1714, 1656 cm^{-1}; ^{1}H NMR (300 MHz, d_6-Acetone): δ=8.43 (s, 1H), 7.98 (dd, J=8.5, 1.4 Hz, 1H), 7.68 (d, J=8.5 Hz, 1H), 7.24 (dd, J=7.5 Hz, 1H), 7.16 (dd, J=7.7, 1,5 Hz, 1H), 7.09 (d, J=7.9 Hz, 1H), 7.01 (t, J=7.6 Hz, 1H), 6.66 (t, J=7.5 Hz, 1H), 3.94 (s, 3H), 3.91 (m, 2H), 3.30 (s, 1H), 2.55 (m, 2H), 1.89 (m, 7H), 0.53 ppm (d, J=4.6 Hz, 6H); ^{13}C NMR (75 MHz, d_6-Acetone): δ=167.3, 157.0, 145.5, 143.7, 142.8, 139.4, 136.1, 131.2, 129.6, 127.3, 124.5, 124.4, 124.0, 123.8, 123.0, 122.7, 122.1, 121.8, 118.8, 111.0, 68.8, 54.0, 51.7, 51.7, 28.4, 23.5, 19.5 ppm; MS (ESI$^+$) m/z: 507.2 $(M+H)^+$; HRMS: calcd for $C_{32}H_{34}N_4O_2$ m/z: 506.2682; found: 506.2692.

Methyl 2-(6,6-dimethyl-5,6-dihydroindolo[1,2-a]quinoxalin-1-yl)-1-(2-methylpropyl)-1 H-benzimidazole-5-carboxylate (**18a**). IR (neat): $\tilde{\nu}$= 3342, 2958, 2927, 2362, 1716 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ=7.89 (d, J=8.5 Hz, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.42 (d, J=7.8 Hz, 1H), 7.25(t, J=8.7 Hz, 1H),7.04 (d, J=7.7 Hz, 1H), 6.98 (d, J=8.6 Hz, 1H), 6.79 (t, J=7.6 Hz, 1H), 6.74 (d, J=8.7 Hz, 1H). 6.44 (s, 1H), 6.34 (t, J=7.8 Hz, 1H), 3.99 (s, 3H), 3.02 (d, J=9.4 Hz, 2H), 1.90–1.70 (m, 1H), 1.81 (s, 3H), 15.3 (s, 3H), 0.59 (s, 3H), 0.33 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.2, 155.9, 144.7, 143.7, 139.2, 138.6, 134.4, 129.3, 125.9, 125.2, 124.7, 124.4, 122.4, 122.4, 121.2, 120.6, 120.3, 118.6, 111.3, 110.4, 98.2, 53.8, 52.6, 52.5, 50.9, 28.5, 20.3, 20.0 ppm; MS (EI+) m/z: 478.2 (M^+); HRMS: calcd for $C_{30}H_{30}N_4O_2$ m/z: 478.2369; found: 478.2374.

Methyl 1-(2-methylpropyl)-2-(5′H-spiro[cyclohexane-1,6′-indolo[1,2-a]quinoxalin]-1′-yl)-1 H-benzimidazole-5-carboxylate (**18b**). IR (neat): $\tilde{\nu}$=2931, 2856, 2360, 1716, 1612 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ=8.63 (s, 1H), 7.86 (d, J=8.3 Hz, 1H), 7.54 (d, J=7.7 Hz, 1H), 7.33–7.23 (2H), 7.42 (d, J=7.6 Hz, 1H), 6.98 (d, J=8.6 Hz, 1H), 6.87–6.66 (2H), 6.48 (s, 1H), 6.34 (d, J=7.6 Hz, 1H), 3.99 (s, 1H), 3.15–2.88 (2H), 2.38–2.21 (m, 1H), 2.13–1.41 (10H), 0.85 (s, 1H), 0.33 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl3): δ=168.2, 155.9, 145.3, 143.6, 138.6, 138.6, 134.3, 129.3, 125.9, 125.8, 125.6, 124.7, 124.4, 122.4, 122.4, 121.2, 120.6, 120.3, 118.7, 111.2, 110.4, 98.6, 53.9, 52.5, 50.9, 28.4, 25.6, 22.2, 21.9, 20.3, 19.9 ppm; MS (EI+) m/z: 518.3 (M^+); HRMS: calcd for $C_{33}H_{34}N_4O_2$ m/z: 518.2682; found: 518.2685.

Methyl 2-[6-(4-methoxyphenyl)indolo[1,2-a]quinoxalin-1-yl]-1-(2-methylpropyl)-1 H-benzimidazole-5-carboxylate (**19a**). IR (neat): $\tilde{\nu}$=2954, 2360, 1718, 1606, 1504 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.71 (d, J=1.1 Hz, 1H), 8.21 (dd, J=7.8, 1.5 Hz, 1H), 8.13 (d, J=8.8 Hz, 2H), 8.06 (dd, J=7.8, 1.5 Hz, 1H), 7.95 (dd, J=8.5, 1.5 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.64 (t, J=7.8 Hz, 1H), 7.34 (s, 1H), 7.14 (d, J=8.9 Hz, 1H), 7.08 (d, J=9.7 Hz, 1H), 7.01 (d, J=8.6 Hz, 1H), 6.56 (t, J=7.9 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 2.96 (m, 1H), 2.41 (m, 1H), 1.41 (m, 1H), 0.43 (d, J=6.1 Hz, 3H), 0.15 ppm (d, J=6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168., 162.0, 156.2, 155., 143.6, 138.8, 138.5, 135.0, 133.3, 131.9, 130.4, 130.1, 129.2, 127.3, 125.7, 125.0, 124.7, 124.3, 123.4, 122.7, 122.2, 119.1, 114.6, 113.6, 110.4, 104.7, 52.6, 51.3, 30.1, 28.5, 20.2, 19.9 ppm; MS (ESI+) m/z: 555.2 $(M+H)^+$; HRMS: calcd for $C_{35}H_{30}N_4O_3$ m/z: 554.2318; found: 554.2315..

Methyl 1-(2-methylpropyl)-2-[6-(4-nitrophenyl)indolo[1,2-a]quinoxalin-1-yl]-1 H-benzimidazole-5-carboxylate (**19b**). IR (neat): $\tilde{\nu}$=2954, 2925, 2856, 2381, 2346 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.54 (d, J=8.8 Hz, 1H), 8.34 (d, J=8.8 Hz, 2H), 8.26 (dd, J=7.8, 1.6 Hz, 1H), 8.15 (dd, J=7.7, 1.6 Hz, 1H), 7.97 (dd, J=8.6, 1.5 Hz, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.71 (t, J=7.8 Hz, 1H), 7.31 (s, 1H), 7.11 (t, J=8.6 Hz, 2H), 6.59 (t, J=5.3 Hz, 1H), 4.02 (s, 3H), 3.05–2.90 (1H), 2.50–2.30 (1H), 1.45 (quint, 1H), 0.46 (d, J=5.8 Hz, 3H), 0.17 ppm (d, J=5.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ=168.0, 155.0, 154.4, 149.4, 143.8, 143.6, 138.8, 138.0, 135.2, 134.6, 132.4, 130.0, 129.5, 129.1, 127.6, 126.0, 124.9, 124.5, 123.8, 122.8, 122.4, 119.4, 113.7, 110.5, 104.5, 51.3, 28.6, 20.2 ppm; MS (EI+) m/z: 569.3(M^+); HRMS: calcd for $C_{34}H_{27}N_5O_4$ m/z: 569.2063; found: 569.2057.

Methyl 2-[6-(4-bromophenyl)indolo[1,2-a]quinoxalin-1-yl]-1-(2-methylpropyl)-1 H-benzimidazole-5-carboxylate (**19c**). IR (neat): $\tilde{\nu}$=2954, 1716, 1616, 1590, 1527 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.71 (s, 1H), 8.22 (d, J=7.8 Hz, 1H), 8.10 (d, J=7.7 Hz, 1H), 8.02 (d, J=8.2 Hz, 2H), 7.96 (d, J=8.5 Hz, 1H), 7.85–7.70 (m, 1H), 7.76 (d, J=8.5 Hz, 2H), 7.66 (t, J=7.8 Hz, 1H), 7.29 (s, 1H), 7.08 (t, J=7.8 Hz, 2H), 7.02 (d, J=8.6 Hz, 1H), 6.56 (t, J=7.8 Hz, 1H), 4.01(s, 1H), 3.05–2.85 (m, 1H), 2.50–2.26 (m, 1H), 1.41 (quint., 1H), 0.43 (d, J=5.2 Hz, 3H), 0.15 ppm (d, J=5.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.0, 155.6, 155.2, 143.5, 138.8, 138.2, 1, 135.1, 133.9, 132.4, 132.1, 130.5, 129.7, 129.2, 127.4, 125.8, 125.3, 125.1, 124.8, 124.6, 123.6, 122.7, 122.3, 119.2, 113.6, 110.4, 104.6, 52.6, 51.3, 28.5, 20.2, 20.0 ppm; MS (EI+) m/z: 602.1 (M^+); HRMS: calcd for $C_{34}H_{27}BrN_4O_2$ m/z: 602.1317; found: 602.1326.

Methyl 2-[6-(furan-2-yl)indolo[1,2-a]quinoxalin-1-yl]-1-(2-methylpropyl)-1 H-benzimidazole-5-carboxylate (**19d**). IR (neat): $\tilde{\nu}$=2954, 2925, 2312, 1716, 1614 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ=8.71 (d, J=1.2 Hz, 1H), 8.22 (dd, J=7.9, 1.6 Hz, 1H), 8.06 (dd, J=7.7, 1.5 Hz, 1H), 7.95 (dd, J=8.5, 1.5 Hz, 1H), 7.90 (s, 1H), 7.84 (d, J=1.1 Hz, 1H), 7.82 (d, J=7.9 Hz, 1H), 7.65 (t, J=7.8 Hz, 1H), 7.59 (d, J=3.5 Hz, 1H), 7.10 (t, J=8.0 Hz, 1H), 6.76 (dd, J=3.5, 1.8 Hz, 1H), 6.55 (t, J=7.1 Hz, 1H), 4.02 (s, 3H), 2.86 (m, 1H), 2.31 (m, 1H), 1.42 (m, 1H), 0.40 (d, J=6.4 Hz, 1H), 0.10 ppm (d, J=6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.1, 155.3, 152.2, 145.5, 143.6, 138.7, 138.0 134.6, 133.6, 131.8, 129.4,

127.9, 127.5, 125.7, 125.1, 124.7, 124.3, 123.5, 122.7, 122.3, 119.0, 114.3 113.6, 112.8, 110.4, 104.4, 52.6, 51.1, 28.5, 20.1, 19.9 ppm; MS (EI+) *m/z*: 514.0 (M^+); HRMS: calcd for $C_{32}H_{26}N_4O_3$ *m/z*: 514.2005; found: 514.2011.

Methyl 1-(3-methoxypropyl)-2-(6-phenylindolo[1,2-a]quinoxalin-1-yl)-1H-benzimidazole-5-carboxylate (**19e**). IR (neat): $\tilde{\nu}$=2925, 2856, 2360, 1714, 1614 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ=8.69 (d, *J*=1.0 Hz, 1H), 8.25 (dd, *J*=7.9, 1.4 Hz, 1H), 8.18–8.10 (m, 2H), 8.06 (dd, *J*=7.6, 1.5 Hz, 1H), 7.98 (dd, *J*=8.5, 1.4 Hz, 1H), 7.70–7.60 (m, 4H), 7.31 (s, 1H), 7.13 (t, *J*=7.7 Hz, 1H), 7.08 (t, *J*=7.7 Hz, 1H), 6.59 (t, *J*=7.9 Hz, 1H), 4.01 (s, 3H), 3.35–3.00 (m, 2H), 2.84–2.60 (m, 2H), 1.20–1.00 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.1, 156.9, 155.3, 143.6, 138.7, 138.5, 137.9, 135.1, 133.4, 132.2, 130.9, 130.4, 129.2, 128.9, 127.7, 125.6, 125.1, 124.9, 124.4, 123.4, 122.7, 122.3, 118.7, 113.6, 110.3, 104.8, 68.5, 58.8. 52.6, 40.9, 29.0 ppm; MS (EI+) *m/z*: 540.3(M^+); HRMS: calcd for $C_{34}H_{28}N_4O_3$ *m/z*: 540.2161; found: 540.2170.

Methyl 1-(3-methoxypropyl)-2-[6-(thiophen-2-yl)indolo[1,2-a]quinoxalin-1-yl]-1H-benzimidazole-5-carboxylate (**19f**). IR (neat): $\tilde{\nu}$=2923, 2852, 2377, 2312, 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.69 (s, 1H), 8.21 (d, *J*=8.0 Hz, 1H), 8.14 (d, *J*=3.7 Hz, 1H), 8.04 (d, *J*=6.8 Hz, 1H), 7.97 (d, *J*=8.6 Hz, 1H), 7.79 (d, *J*=7.8 Hz, 1H), 7.67 (d, *J*=2.3 Hz, 1H), 7.65 (s, 2H), 7.32 (d, *J*=4.4 Hz, 1H), 7.17 (d, *J*=8.9 Hz, 1H), 7.11 (t, *J*=3.5 Hz, 1H), 7.89 (d, *J*=3.5 Hz, 1H), 6.60 (t, *J*=7.9 Hz, 1H), 4.01 (s, 3H), 3.20 (m, 1H), 3.01 (m, 1H), 2.87 (s, 3H), 2.68 (m, 2H), 1.08 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.1, 155.3, 149.8, 143.6, 141.9, 138.7, 138.2, 1345.0, 133.3, 131.8, 130.1, 129.4 129.3, 129.1, 128.4, 127.4, 125.6, 125.1, 124.8, 124.4, 123.5, 122.7, 122.3, 118.8, 113.6, 110.3, 103.8, 68.4, 58.7, 52.6, 40.8, 29.0 ppm; MS (EI+) *m/z*: 546.3 (M^+); HRMS: calcd for $C_{32}H_{26}N_4O_3S$ *m/z*: 546.1726; found: 546.1729.

Methyl 2-[6-(1,3-benzodioxol-5-yl)indolo[1,2-a]quinoxalin-1-yl]-1-cycloheptyl-1H-benzimidazole-5-carboxylate (**19g**). IR (neat): $\tilde{\nu}$=3747, 3677, 2925, 2856 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ=8.24 (d, *J*=7.9 Hz, 1H), 7.96 (d, *J*=8.7 Hz, 1H), 7.94 (d, *J*=9.0 Hz, 1H), 7.82 (d, *J*=8.0 Hz, 1H), 7.76 (t, *J*=7.8 Hz, 1H), 7.68 (d, *J*=8.1 Hz, 1H), 7.57 (m, 2H), 7.45 (s, 1H), 7.22 (d, *J*=8.7 Hz, 1H), 7.13 (d, *J*=7.2 Hz, 1H), 7.11 (d, *J*=8.0 Hz, 1H), 6.67 (d, *J*=7.5 Hz, 1H), 6.15(s, 1H), 3.99 (s, 3H), 3.49 (m, 1H), 1.89 (m, 2H), 1.60–0.80 (m, 8H), 0.68–0.46 (m, 1H), 0.36–0.20 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.9, 155.9, 154.6, 150.1, 148.6, 143.1, 138.2, 136.5, 135.6, 132.2, 131.8, 130.4, 129.2, 127.6, 125.8, 125.2, 124.7, 124.5, 123.5, 123.4, 122.4, 118.0, 113.6, 112.6, 109.2, 109.0, 104.8, 102.0, 59.8, 52.6, 35, 31.7, 27.8, 26.7, 26.0, 25.8 ppm; MS (EI+) *m/z*: 608.3(M^+); HRMS: calcd for $C_{38}H_{32}N_4O_4$ *m/z*: 608.2424; found: 608.2418.

Methyl 1-cycloheptyl-2-[6-(5-nitrofuran-2-yl)indolo[1,2-a]quinoxalin-1-yl]-1H-benzimidazole-5-carboxylate (**19h**). IR (neat): $\tilde{\nu}$=2929, 2857, 1716, 1616, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.66 (s, 1H), 8.21 (d, *J*=7.7 Hz, 1H), 8.06 (s, 1H), 8.00 (d, *J*=7.4 Hz, 1H), 7.93 (d, *J*=8.8 Hz, 1H), 7.88 (d, *J*=8.0 Hz, 1H), 7.72 (s, 1H), 7.80–7.64 (m, 1H), 7.61 (s, 1H), 7.38–7.21 (m, 3H), 7.15 (t, *J*=7.3 Hz, 1H), 6.64 (t, *J*=7.7 Hz, 1H), 4.01 (s, 3H), 3.23 (m, 1H), 1.68 (m, 2H), 1.38 (m, 1H), 1.23 (m, 6H), 0.95 (m, 1H), 0.33 (m, 1H), 0.07 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.0,154.5, 153.8, 152.9, 144.2, 143.3, 137.5, 136.8, 135.3, 135.0, 132.5, 129.6, 128.3, 127.2, 125.8, 124.9, 124.5, 124.0, 122.9, 122.7, 119.2, 115.2, 114.0, 113.5, 104.8, 59.9, 52.6, 34.9, 31.7, 27.9, 26.7, 26.0, 25.6 ppm; MS (ESI+) *m/z*: 599.2 $(M+H)^+$; HRMS: calcd for $C_{35}H_{29}N_5O_5$ *m/z*: 599.2169; found: 599.2178.

Crystallographic Data

CCDC 861548 (**15i**) and CCDC 861536 (**18a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] A single crystal was selected by using an Olympus stereo zoom microscope and the X-ray diffraction data were collected on a Bruker X8 APEX CCD diffractometer with omega and phi scan mode, $k_{MoK\alpha}$=0.71073 Å at *T*=100(2) K. All data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least-squares on F2 using SHELXTL software package, see: G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122. Hydrogen atoms were included in the refinement as per the riding model.
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