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RESEARCH ARTICLE

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Divergent Synthesis of Unsymmetrical Annulated Biheterocyclic Compound Libraries: Benzimidazole Linked Indolo-benzodiazepines/quinoxaline

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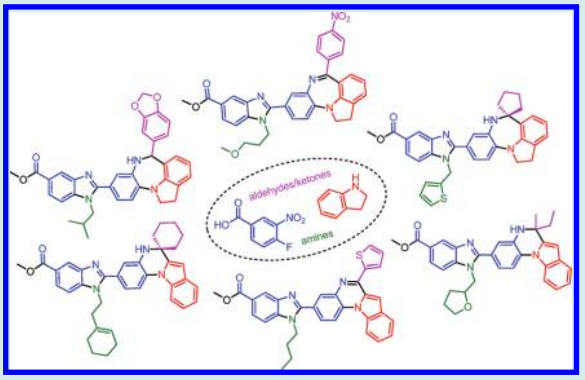
Supporting Information

ABSTRACT: Diversity-oriented synthesis of novel benzimidazole linked indolo-benzodiazepine/quinoxaline ring systems using poly-(ethylene glycol) as soluble polymer support is described. Commercially available 4-fluoro-3-nitrobenzoic acid and indoline were utilized for the construction of these annulated biheterocyclic compound libraries having multiple privileged structures with three-point structural diversity. A reagent based diversification approach coupled with the Pictet−Spengler-type condensation was used to construct the tetracyclic indolo-benzodiazepines/quinoxalines on substituted benzimidazoles.



KEYWORDS: indolo-benzodiazepines/quinoxalines, Pictet−Spengler, diversity-oriented synthesis, PEG

INTRODUCTION

Heterocyclic structures have myriad biomedical applications and play important roles in drug discovery. Many of the best selling drugs currently in use contain one or more heterocyclic rings. Among the various heterocyclic structures, several fused heterocyclic systems[1] as well as biheterocyclic frameworks[2] are known to provide ligand landing zones for more than one type of bioreceptors and are often included in the category of privileged structures. Particularly common in drugs and lead-compounds are the indole, benzimidazole, benzopyrazine, or benzodiazepine groups, and the biheterocyclic phenylimidazole unit is also found in many natural products.[1,3] Several reports on the design and synthesis of new chemical libraries based on these privileged structures have appeared in the recent literature.[4]

A large number of indole fused ring systems with a range of biological activities are known.[5] For example, benzimidazoles are structurally related to indoles as well as to purine bases and are ligands for serotonin receptors (5-HT), histamine (H4) receptors, bradykinin (B2) receptors, and dopamine (D4) receptors.[6] Molecules containing the benzimidazole scaffold exhibit antiarrhythmic, antihistamine, antiulcer, anticancer, inotropic, fungicidal, anthelmintical, and antiviral activities.[7] The related benzopyrazines (quinoxalines) and their derivatives have also received much attention owing to their antimicrobial, antifungal, anticancer, and antihelmentic properties.[4c] Benzodiazepines are the class of compounds to which the term "privileged structure" was first applied by Evans in 1988.[8] The therapeutic applications of benzodiazepines include anxiolytics, antiarrhythmics, vasopressin antagonists, HIV reverse transcriptase inhibitors, and cholecystokinin antagonists.[9]

On the basis of the diverse biological properties of these classes of compounds, the present article describes the design and combinatorial synthesis of new biheterocyclic scaffold having multiple privileged structures. A few reports on linked heterocyclic compounds bearing benzimidazole-like groups have appeared. For example, benzimidazole linked quinoxaline **1** was identified as DNA topoisomerase I inhibitor,[10] and several head-to-head symmetric bisbenzimidazole-based DNA minor groove binding agents **2** demonstrated potential antitumor activity.[11] A new series of benzimidazolyl-thiadiazepines **3** was synthesized and evaluated as antibacterial agents.[12] We earlier reported the synthesis of pharmaceutically interesting angular-bisbenzimidazoles **4** having potential vascular endothelial growth factor receptor 3 inhibition activity.[13] To the best of our knowledge, no report on the synthesis of benzimidazole linked heterocycles with four annulated rings exists in the literature.

Chimeric skeletons of this type, shown in Figure 1, may provide advantages in drug discovery if they can be accessed efficiently. To accelerate the discovery process, we implemented a liquid phase combinatorial synthetic protocol[14] using poly(ethylene glycol) (PEG) as soluble polymer support. Unlike the use of an insoluble matrix, PEG conjugated intermediates remain in homogeneous solution during reactions, and are precipitated when desired by the addition of diethyl ether. After precipitation, unwanted reagents and byproducts are simply filtered away.

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RESULTS AND DISCUSSION

Commercially available 4-fluoro-3-nitrobenzoic acid (FNBA) **6** and indoline **12** were utilized for the construction of these annulated biheterocyclic compound libraries. The stepwise synthesis was initiated by loading FNBA on PEG-6000 using 1,3-dicyclohexylcarbodiimide (DCC) and catalytic 4-dimethylaminopyridine (DMAP). The first point of structural diversity was installed in the next step by the *ipso*-fluoro displacement of the activated aromatic fluoride in PEG ester conjugate **7** using various primary amines (Scheme 1).

Reduction of the aryl nitro group in the resulting derivative **8** was accomplished with a suspension of Zn/NH_4Cl in methanol to afford immobilized diamine **9** at room temperature. These *ortho*-diamino ester conjugates **9** were earlier used for the parallel synthesis of substituted benzimidazoles, amino/thio-benzimidazoles, benzimidazolones, quinoxalinones and benzimidazolyl quinoxalinones.[15] The benzimidazole ring in the present synthesis was constructed using another molecule of FNBA. The selective condensation of FNBA **6** with the aniline conjugates **9** via the in situ generated DCC activated ester in refluxing dichloromethane resulted in the formation of anilide conjugates **10**. The observed selectivity was achieved because of the presence of the ester functionality on the ring, which deactivated the secondary amine and facilitated the amide coupling exclusively with primary amine. Further intramolecular ring closure through the nucleophilic attack of the secondary amine on the amide carbonyl was brought about in refluxing 1,2-dichloroethane in the presence of TFA (10%) and anhydrous $MgSO_4$. The subsequent aromatic substitution on immobilized benzimidazole linked o-fluoro nitrobenzene **11** by indoline **12** was achieved in refluxing acetonitrile. The reaction took 12 h for the complete disappearance of the starting materials. To monitor the progression of reaction, a small portion of the reaction mixture was pulled out, the compound was precipitated and washed with cold ether and dried to record the proton NMR spectrum (Figure 2). Upon completion of the reaction, the polymer bound compound mixtures were purified by the same precipitation and washing protocol.

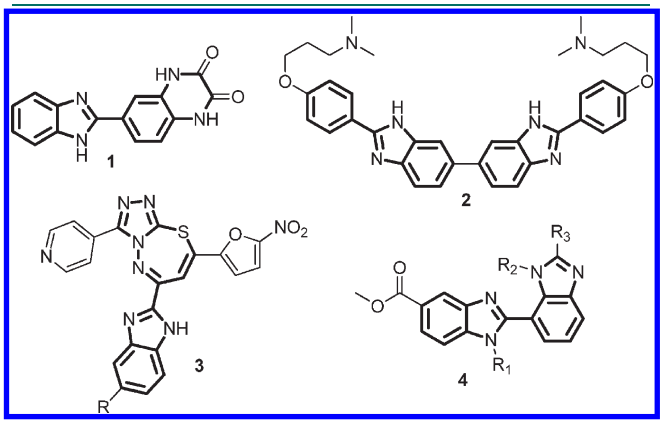


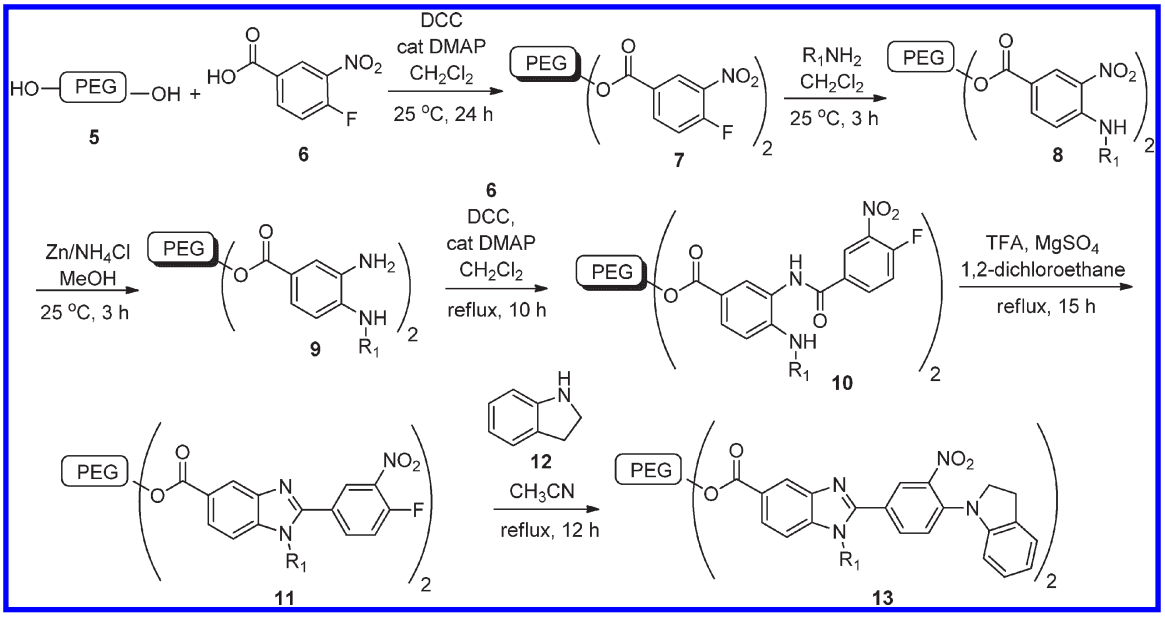
Figure 1. Benzimidazole-linked biologically active compounds.

In the next step, the nitro functionality in conjugate **13** was reduced to amine using zinc and ammonium formate in methanol at room temperature (Scheme 2). No loss of yield was observed during this reductive transformation, suggesting that the polymer support remained intact. The amino-indolinyl intermediate **14** was used in Pictet-Spengler type heterocyclization reactions with various aldehydes or ketones (Table 1) in the presence of TFA and $MgSO_4$ in refluxing chloroform, to give the desired benzimidazole linked tetrahydro-indolobenzodiazepines **16**.

Different aromatic aldehydes having variable electron densities on the aromatic ring were utilized for this cyclization; aliphatic aldehyde (Table 1, entry **16g**) as well as cyclic (Table 1, entry **16l**) and noncyclic (Table 1, entry **16j**, **16k**) ketones were also incorporated successfully. The use of a cyclic ketone to give spiro compound **16l** was particularly interesting.

One limitation emerged under these acid catalyzed dehydrating conditions for *para*-nitrobenzaldehyde (Table 1, entry **16e**, **16n**, and **16o**), in which cyclization was followed by

Scheme 1. Synthesis of Key Intermediate Ready for Further Diversification



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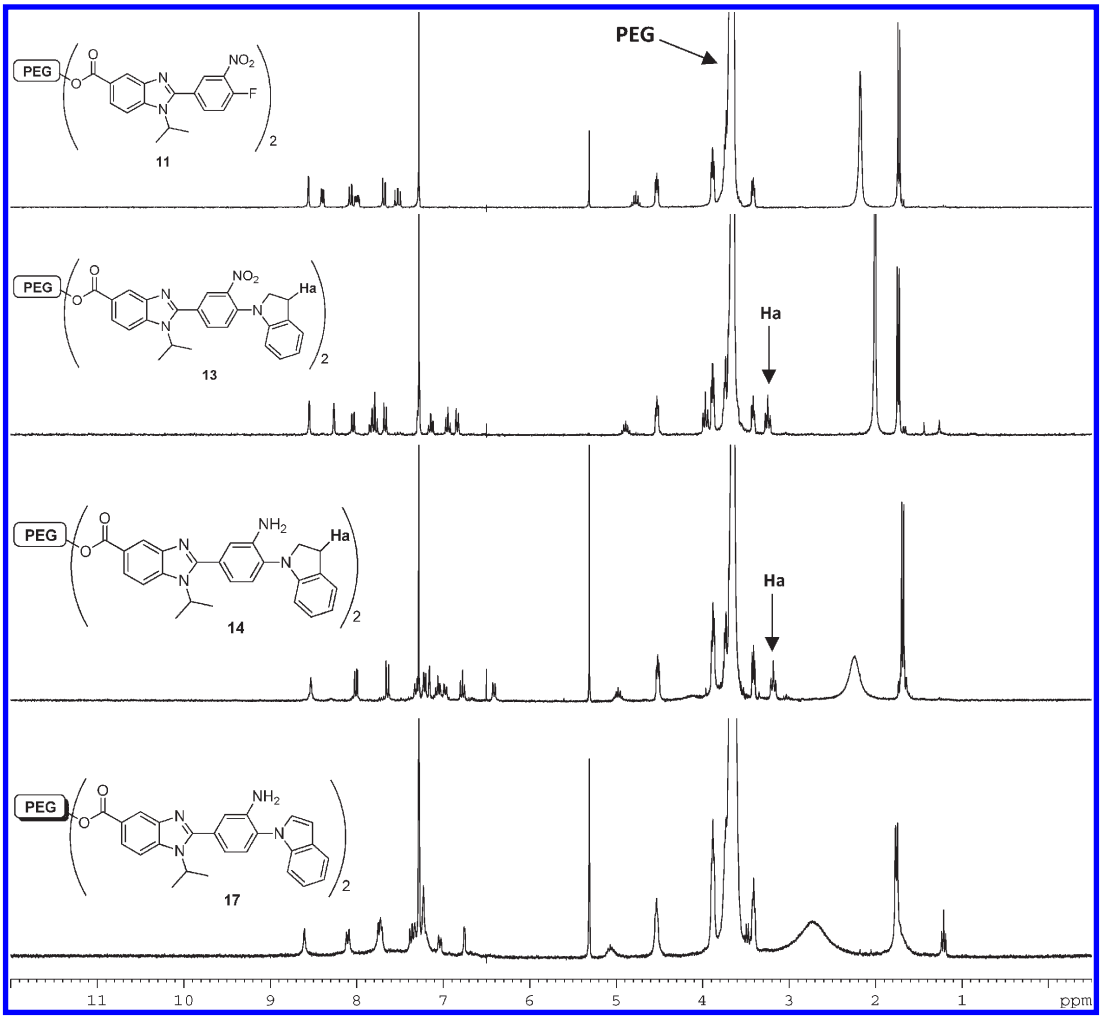
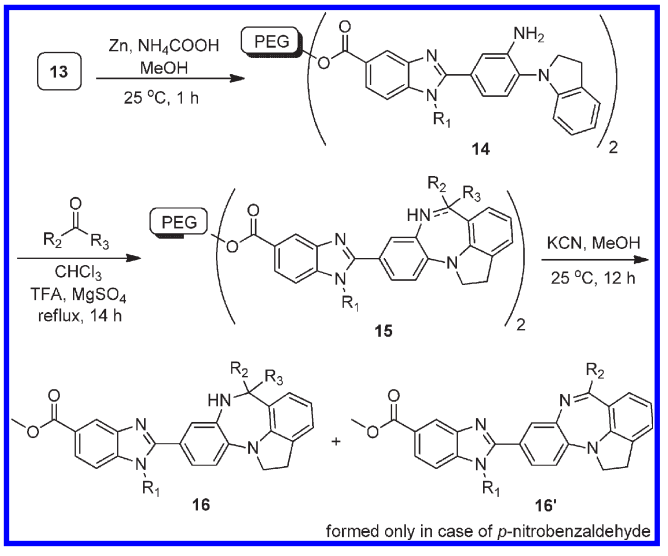


Figure 2. Proton NMR monitoring reaction progress.

Scheme 2. Synthesis of benzimidazole linked indolobenzodiazepines



oxidation of the benzodiazepine ring to give the benzimidazole-linked dihydro-indolobenzodiazepine skeleton **16′** instead of the tetrahydro-indolobenzodiazepine **16**. Comparatively lower yields were observed for these reactions [Table 1, entry **16e** (62%), **16n** (60%)]. In another *p*-nitrobenzaldehyde case, a small amount of unoxidized product was isolated (Table 1, entry **16o**), and further adjustment of the reaction conditions completely abolished this additional oxidation (Table 1, entry **16r**). Overall, it became apparent that *p*-nitrobenzaldehyde gave structures **16′** when the reaction was carried out for more than 14 h, whereas the unoxidized compound **16** was isolated after 10 h with the reaction being incomplete. The use of *ortho*/*meta*-nitrobenzaldehydes did not produce any oxidized products (Table 1, entry **16f**, **16h**, **16i**) during this reaction.

The highly efficient nature of the benzodiazepine formation during this Pictet-Spengler type condensation reaction deserves some comment. In this step, the iminium ion generated in situ undergoes C−C bond formation with the C-7 of the indoline ring in compound **14** to furnish the indolobenzodiazepine. The success of this step presumably requires the presence of a sufficiently reactive aromatic nucleus (provided by the indoline nitrogen) as well as conformational restrictions induced by the anilinic nature of the substrate (compared to aliphatic amines in the classical Pictet−Spengler isoquinoline synthesis). The final cleavage of the soluble polymer support was achieved using potassium cyanide (1%) in methanol at room temperature to

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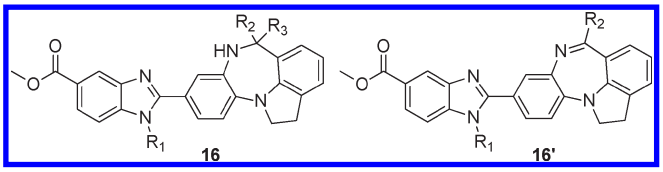
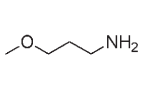
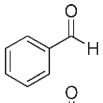
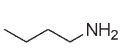
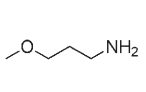
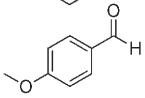
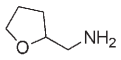
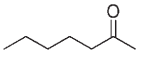
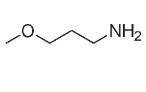
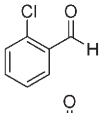
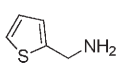
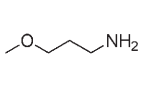
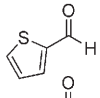
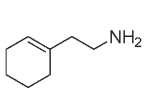
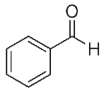
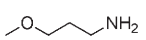
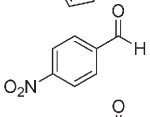
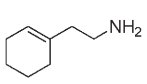
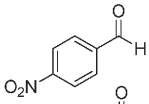
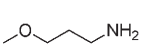
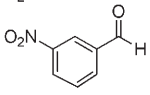
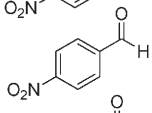
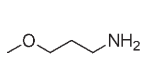
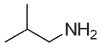
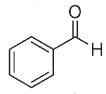
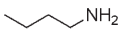
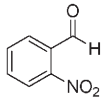
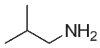
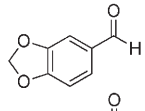
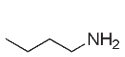
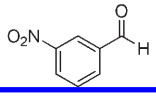
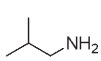
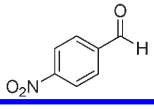
Table 1. Benzimidazole-Linked Indolo-benzodiazepine Conjugate Library



Entry	R_1NH_2	R_2COR_3	LRMS[a]	Yield[b] (%)	Purity[c] (%)	Entry	R_1NH_2	R_2COR_3	LRMS[a]	Yield[b] (%)	Purity[c] (%)
16a			545	77	76	**16j**			494	75	72
16b			575	86	91	**16k**			564	75	69
16c			578	74	69	**16l**			546	67	71
16d			550	87	92	**16m**			622	81	83
16e'[d]			588	62	67	**16n'**[d]			624	60	64
16f			588	72	69	**16o/16o'**[e]			557	63	80[f]
16g			525	69	74	**16p**			529	84	90
16h			573	78	80	**16q**			579	78	78
16i			573	70	69	**16r**[g]			574	82	87

[a] $[M + H]^+$. [b] Isolated yields determined on weight of purified samples. [c] HPLC recorded after the cleavage f1ollowed by precipitation and washing. [d] Only the oxidized product (**16′**) was isolated. [e] Mixture of both **16** and **16′** compounds formed. [f] Aggregrate purity; **16′**/**16**: 57/23. [g] Reaction was carried out for 10 h; no **16r′** formed.

obtain polymer-free benzimidazole linked indolobenzodiazepines **16** and **16′** in good to excellent yields (60−87%, Table 1).

Using a similar synthetic sequence via indole instead of indoline, benzimidazole linked indoloquinoxalinones were also synthesized (Scheme 3).[16] Treatment of conjugate **13** with palladium catalyst and cyclohexene in refluxing ethanol yielded indole-substituted aniline conjugate **17** by transfer hydrogenation, both reducing the nitro group and dehydrogenating the indoline to indole[17] in one step. The amino-indolyl intermediate **17** could also be obtained by the oxidation of the indoline ring in polymer conjugate **14** through the application of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Treatment of **17** with various aldehydes (Table 2) in the presence of TFA and $MgSO_4$ in refluxing chloroform gave the desired benzimidazole-linked indoloquinoxalines **20** in moderate to good yields (62−89%, Table 2). The intermediate dihydropyrazine ring was found to be easily air oxidized during this transformation to deliver the more stable fully aromatic skeleton. During these condensation reactions, the iminium ion generated in situ undergoes C−C bond formation with the electron rich C-2 of the indole ring in **17**. When ketones were employed in place of aldehydes, the corresponding dihydroindoloquinoxaline scaffold **21** was produced on the polymer support. The polymer free final products (75−90%, Table 3) were obtained as before using potassium cyanide (1%) in methanol at room temperature. Complete cleavage during this reaction was verified by ^1H NMR of the recovered polymer support.

The use of relatively hindered ketones (3-methylbutan-2-one and 1-(thiophen-2-yl)ethanone, Table 3, entries **21e** and **21f**) illustrated a limitation to the reaction, giving none of the desired products under standard conditions even after prolonged reaction time (48 h reflux). These substrates were incorporated by heating the reaction mixtures in a sealed tube for 20 h. Lower yields (56−61%), as well as poor HPLC purity (50%), are the result of the harsh reaction conditions, which could not be further improved. Nonplanarity in the annulated indoloquinoxaline

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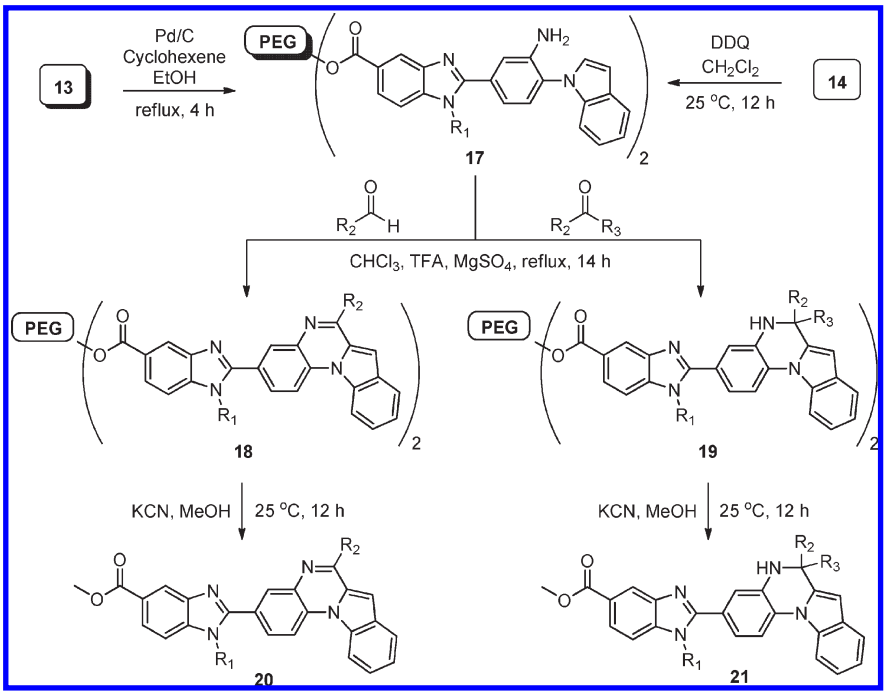
Scheme 3. Synthesis of Benzimidazole-Linked Indoloquinoxalines



skeleton was clearly indicated by X-ray crystallographic analysis of spiro compound **21h** (ORTEP[18] diagram shown in Figure 3).

CONCLUSION

A reagent-based diversification approach coupled with the Pictet−Spengler type condensation was used to construct tetracyclic indolo-benzodiazepines/quinoxalines on substituted benzimidazoles in a divergent fashion. A small library of these unsymmetrical annulated biheterocyclic compounds were prepared in good to excellent yield, with methods that provide three points of structural diversity. The use of a soluble polymer supported was found to be effective and convenient, and the scaffolds and methods provide ample opportunities for further functionalization.

EXPERIMENTAL PROCEDURES

General Remarks. 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 Kiselgel 60 F254 plates. Compound purification was carried out using flash chromatography grade silica gel 60 (230−400 mesh). IR spectra were recorded on an FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a 300 and 75 MHz spectrometer, respectively. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard. Mass spectra were recorded on a time-of-flight mass spectrometer, samples being introduced by infusion method using the electrospray ionization technique. All starting compounds were purchased from commercial sources and used without purification. To monitor the progression of reaction on a polymer support, a small portion of the reaction mixture was pulled out, compound was precipitated and washed with cold ether, subsequently dried and proton NMR spectrum was recorded. The reaction progress and the stepwise transformations on a polymer support after each stage of the synthetic sequence from 4-fluoro-3-nitrobenzoic acid to the desired products were cleanly observed in proton NMR spectra (Figure 2).

Synthesis of Key Intermediate (13). PEG 6000 (1.2 g, 0.2 mmol), FNBA **6** (0.222 g, 1.2 mmol), DCC (0.247 g, 1.2 mmol), and DMAP (0.015 g, 0.12 mmol) in dry CH_2Cl_2 (15 mL) were stirred in a round-bottom flask at 25 °C for 24 h. Upon completion of the reaction, CH_2Cl_2 (10 mL) was added, and the reaction mixture was cooled to 0 °C. The solid dicyclohexylurea (DCU) formed was filtered off and CH_2Cl_2 layer was evaporated. To this crude material, cold diethyl ether (10 mL) was added to precipitate the PEG-bound fluoro-nitro aryl intermediate **7**. The precipitate was then collected on a sintered glass funnel and thoroughly washed with diethyl ether (10 mL × 2) to remove the excess reagents and dried. This PEG supported aryl fluoride **7** (1.14 g, 0.18 mmol) and isobutylamine (0.066 g, 0.90 mmol) were stirred in 10 mL of CH_2Cl_2 for 3 h. After completion of reaction, the solution was concentrated by rotary evaporation and reaction mixture was precipitated by slow addition of cold diethyl ether with stirring. Polymer bound product was then filtered under aspirator pressure using a flitted funnel and washed several times with cold ether and dried in vacuo. Zinc dust (0.11 g, 1.7 mmoL, 10.0 equiv) and NH_4Cl (0.045 g, 0.85 mmoL, 5.0 equiv) were added to the solution of polymer bound fluoro-nitro aryl intermediate **8** (1.1 g, 0.17 mmol) in MeOH (20 mL), and the resulting suspension was stirred at 25 °C for 3 h. The heterogeneous catalyst was removed by filtration during the workup and the polymer-bound diamine **9** was purified by precipitation and dried in vacuum. To the solution of PEG bound aniline conjugate **9** (1.02 g, 0.16 mmol) and FNBA **6** (0.30 g, 1.6 mmol) in CH_2Cl_2 15 mL, were added DCC (0.66 g, 3.2 mmol) and DMAP (0.04 g, 0.32 mmol) and the resulting reaction mixture was refluxed for 10 h. The crude anilide conjugate

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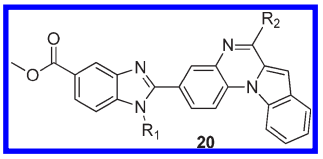
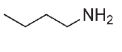
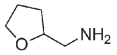
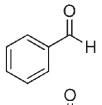
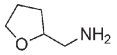
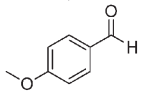
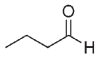
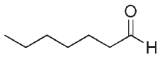
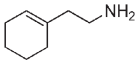
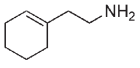
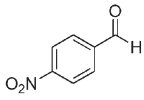
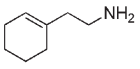
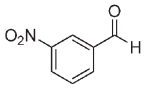
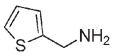
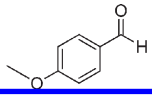
Table 2. Benzimidazole-Linked Indoloquinoxaline Conjugate Library Using aldehydes

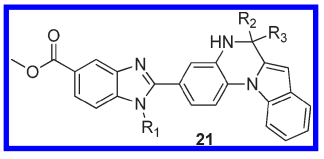


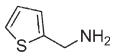
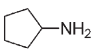
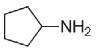
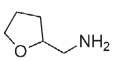
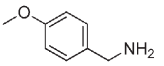
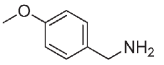
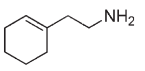
Entry	R_1NH_2	R_2COR_3	LRMS[a]	Yield[b] (%)	Purity[c] (%)
20a			531	87	90
20b			553	84	86
20c			583	86	89
20d			477	87	89
20e			519	78	75
20f			611	71	65
20g			622	89	91
20h			567	62	77
20i			537	84	87
20j			582	78	89
20k			503	76	73
20l			595	73	85

[a] $[M + H]^+$. [b] Isolated yields determined on weight of purified samples. [c] HPLC recorded after the cleavage followed by precipitation and washing.

10 was obtained using the same procedure as described earlier. The anilide conjugate **10** (1.00 g, 0.15 mmol), in the presence of TFA (0.1 mL) and $MgSO_4$ (0.5 g) was further refluxed in 1,2-dichloroethane (10 mL) for 15 h. After completion of the reaction, $MgSO_4$ was removed by the filtration through Celite. The reaction mixtures were precipitated by slow addition of excess of cold ether (100 mL) and filtered through a fritted funnel to obtain compound **11** in high purity. To this crude material **11** (1.00 g, 0.15 mmol) in dry CH_3CN (10 mL) was added indoline **12** (0.09 g, 0.75 mmol), and the reaction mixture was refluxed for overnight. The crude

Table 3. Benzimidazole-Linked Indoloquinoxaline Conjugate Library Using Ketones



Entry	R_1NH_2	R_2COR_3	LRMS[a]	Yield[b] (%)	Purity[c] (%)
21a			519	80	80
21b			491	90	93
21c			505	75	93
21d			521	80	87
21e[d]			571	61	50
21f[d]			671	56	50
21g			557	81	83
21h			571	84	88

[a] $[M + H]^+$. [b] Isolated yields determined on weight of purified samples. [c] HPLC recorded after the cleavage followed by precipitation and washing. [d] Reaction mixtures were heated in sealed tube for 20 h

Figure 3. ORTEP view of compound **21h**.

product **13** (1.05 g) was purified by precipitating and washing with excess cold ether (20 mL × 3) and dried in vacuo. This was used as it is for the further transformations.

Synthesis of Benzimidazole, Indoline/Indole Substituted Aniline Conjugates (14) and (17) from Intermediate (13): Reagent-Based Diversification. Zinc dust (10.0 equiv, 0.1 g, 1.5 mmol) and ammonium formate (10.0 equiv, 0.09 g, 1.5 mmol) were added to a solution of polymer bound benzimidazole linked fluoro-nitro aryl intermediate **13** (1.0 g, 0.15 mmol) in MeOH (20 mL), and the reaction mixture was stirred at room temperature for 1 h. Upon completion of reaction, the mixtures were filtered through Celite to remove insoluble zinc dust, and the filtrate was collected and concentrated under reduced pressure. Dichloromethane (15 mL) was added to precipitate ammonium formate, and the mixture was again passed through a thin layer of Celite to remove ammonium formate. The organic layer was concentrated and the crude product (**14**) obtained was used as it is for the further transformations. In another experiment, to the solution of intermediate **13** (1.0 g, 0.15 mmol) in EtOH (20 mL) was added 10% Pd/C (0.1 g, 10 Wt % of **13**) followed by cyclohexene (2 mL) was added, and the reaction mixture was refluxed for 4 h. The solid palladium on charcoal was filtered off and the solvent was evaporated. PEG-bound aniline conjugate **17** was isolated by the same precipitation and washing technique using diethyl ether. Compound **17** was also obtained from intermediate **14**. The solution of compound **14** (1.0 g, 0.15 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature in the presence of DDQ (0.17 g, 0.75 mmol) for overnight. The reaction mixture was filtered and the precipitate was washed with CH_2Cl_2 (50 mL). The combined organic layers were concentrated; compound obtained was dried and used as it is for the further transformations.

General Procedure for the Pictet−Spengler Cyclization and Cleavage from Support. To a solution of indoline/indole-substituted aniline conjugates **14** or **17** (1.0 equiv) in $CHCl_3$ (10 mL), aldehyde or 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 diluted with slow addition of excess of cold ether (50 mL). The precipitated PEG linked biheterocyclic conjugates (**15**, **18**, or **19**) were filtered through a fritted funnel and washed with excess cold ether (20 mL × 3) and dried in vacuo. Potassium cyanide (0.01 equiv.) was added to a solution of these conjugates (**15**, **18**, or **19**) in methanol (10 mL). The mixtures were stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure, and the mixtures were precipitated and washed with ether (50 mL × 3). The filtrates were collected, and products **16**, **16′**, **20**, or **21** were obtained in good yields and purity (Tables 1−3).[19]

1-(3-Methoxy-propyl)-2-(6-phenyl-1,2,6,7-tetrahydro-benzo-[2,3][1,4]diazepino[6,7,1-hi]indol-9-yl)-1*H*-benzoimidazole-5-carboxylic Acid Methyl Ester (16a). IR (neat): 2924, 1713, 1471, 1302 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, J = 1.1 Hz, 1H), 7.97 (dd, J = 8.5, 1.1 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.35−7.10 (m, 6H), 7.05 (s, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.53−6.48 (m, 2H), 5.34 (s, 1H), 4.25 (m, 2H), 4.12 (t, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.20 (m, 4H), 3.16 (s, 3H), 1.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 155.4, 144.5, 143.0, 142.4, 139.6, 139.2, 137.8, 131.7, 129.0 (2C), 128.6 (2C), 128.0, 127.9, 125.1, 124.3, 124.2, 124.0, 122.9, 121.9, 121.7, 120.5, 119.2, 115.7, 110.0, 69.1, 65.4, 59.0, 52.4, 42.2, 31.3, 30.2, 27.8. MS (ESI): m/z 545 (MH^+). HRMS Calcd for $C_{34}H_{33}N_4O_3$: m/z 545.2553; Found 545.2551.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data for all the synthesized compounds, copies of HPLC, ^1H and ^{13}C NMR, MS, HRMS and IR spectra. X-ray crystallographic data for **21h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Characterization data for **16b**−**16r**, **20a**−**20l**, and **21a**−**21h** is included in Supporting Information.