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Reagent-Based DOS: Developing a Diastereoselective Methodology to Access Spirocyclic- and Fused Heterocyclic Ring Systems**

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In memory of Dr. Albert I Meyers

Abstract: Herein, we report a diversity-oriented-synthesis (DOS) approach for the synthesis of biologically relevant molecular scaffolds. Our methodology enables the facile synthesis of fused N-heterocycles, spirooxoindolones, tetrahydroquinolines, and fused N-heterocycles. The two-step sequence starts with a chiral-bicyclic-lactam-directed enolate-addition/substitution step. This step is followed by a ring-closure onto the built-in scaffold electrophile, thereby leading to stereoselective carbocycle- and spirocycle-formation. We used in silico tools to calibrate our compounds with respect to chemical diversity and selected drug-like properties. We evaluated the biological significance of our scaffolds by screening them in two cancer cell-lines. In summary, our DOS methodology affords new, diverse scaffolds, thereby resulting in compounds that may have significance in medicinal chemistry.

Keywords: bicyclic compounds · biological activity · fused-ring systems · lactams · spiro compounds

Introduction

Small molecules make excellent drugs because of their ability to modulate the functions of proteins in living systems.[1] There is an ongoing effort in the chemical community to discover new chemical scaffolds that will access new chemical space and reveal interesting biological activity. Diversity-oriented synthesis (DOS) provides an ideal platform to access new compounds and has demonstrated great utility in the generation of structurally complex- and skeletally diverse small molecules.[2] Efficient synthetic strategies, coupled with rational design, leads to the generation of small molecules with architectural diversity and complexity, as well as acceptable physicochemical properties. Evans et al.[3a] and later Schreiber[3b] have pioneered library-generation by using the DOS approach. Popular DOS strategies include the build/couple/pair (B/C/P) concept pioneered by Nielsen and Schreiber,[4] the "click, click, cyclize" strategy by Hanson and co-workers,[6] and others by the groups of Park, Shair, and Spring.[5]

Biologically active spirocyclic indoles, tetrahydroquinolines, and N-fused polycyclic ring-systems provide a good platform to demonstrate the utility of our DOS methodology.[7] Spiroxoindolines *Elacomine* and *Horsfiline* (Scheme 1) are known to have multiple biological activities (as antimalarial agents, inhibitors of p53:MDM2 receptors, and as antimicrobial agents for both plant- and human pathogens).[8] 1,2,3,4-tetrahydroquinoline (THQ) structures (such as those present in *Oxamniquine*, *Nicainopril*, and *Virantmycin*, Scheme 1) are present in nature and exhibit antitumor- and antibiotic properties, bradykinin antagonism, and activity against α-adrenergic, histaminergic, and muscarinic receptors.[9] Fused N-heterocycles show promising antiphlogistic activity in rats.[10] We wanted to keep our scaffolds as close to the "rule of three" as possible ($M < 300$; $HBD \leq 3$ and $HBA \leq 3$; $clogP = 3$; number of rotatable bonds ≤ 3; polar surface area $= 60$ Å^2). These parameters are generally accepted to be the most appropriate in creating libraries of fragments.[11] Linear enantioselective syntheses of these scaffolds have been reported previously.[12] However, to the best of our knowledge, this is the first reagent-based DOS methodology that allows access to these structurally diverse molecular scaffolds through common intermediates (**1** and **2**). We achieve skeletal diversity through a sequence that uses either alkylation, Michael addition, or an S_NAr reaction on

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[**] DOS: Diversity-oriented synthesis.

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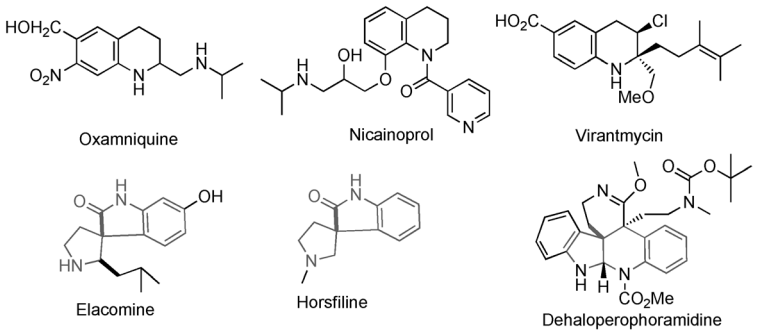


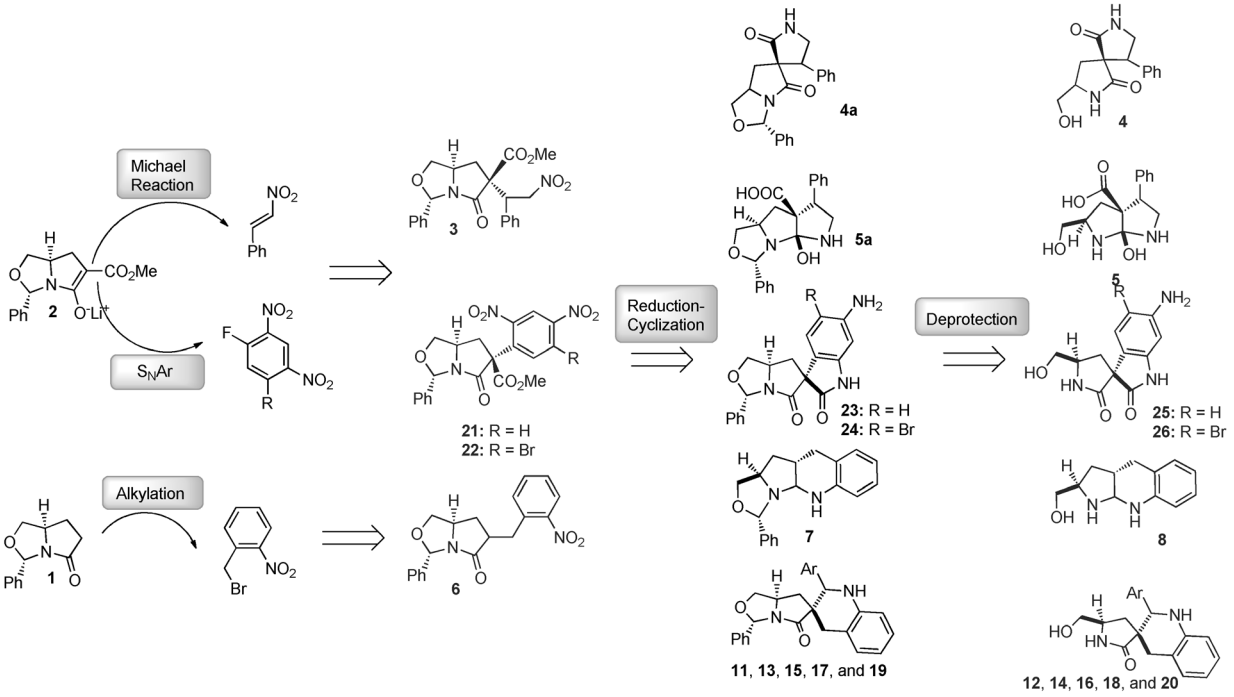
Scheme 1. Biologically active spirooxoindoles, tetrahydroquinolines, and pyrroloquinolinolines.

chiral bicyclic lactams (**1** and **2**), followed by cyclization of the intermediates (after reduction of the nitro group) to give polycyclic systems. The highlight of our methodology is a three-step synthesis of five distinct natural-product-inspired scaffolds. This methodology has an attractive steps-per-scaffold efficiency whilst providing access to chemically complex molecules.

Results and Discussion

Four unique bicyclic-lactam-based intermediates, compounds **3**, **6**, **21**, and **22**, were made according to the procedure shown in Scheme 2. Intermediate **3** was synthesized by Michael addition of the enolate of acyl bicyclic lactam **2** (generated with lithium diisopropylamide (LDA) in THF) to nitrostyrene at −78 °C in approximately 50 % yield and a 9:1 diastereomeric ratio (the diastereomers were separable by column chromatography). In turn, compound **2** was synthesized by acylation of compound **1** with methyl chloroformate and LDA at −78 °C.[13] By using two different hydrogenation conditions, the fused- and spiro templates (**4**, **4a**, **5**, and **5a**) were readily synthesized. Initial hydrogenation of compound **3** (H_2-Pd/C, 10 % w/w), followed by in situ cyclization of the resulting amine, provided the desired spirolactam (**4a**) and fused bispyrrolidine (**5a**). Spirolactam **4a** (70:30) was the major product under neutral hydrogenation condition (with EtOAc or isopropanol as the solvent). On the other hand, during acidic hydrogenation (AcOH), the formation of compound **5a** was favored (60:40). Deprotection of the intermediates (**4a** and **5a**) with TFA generated compounds **4** and **5**, respectively (Scheme 3).

In contrast, the synthesis of the interesting C7-aminoaryl-substituted fused ring system was initiated by alkylation of bicyclic lactam **1** with 2-nitrobenzylbromide in the presence of LDA at −78 °C to generate compound **6** in 80 % yield as a 98:2 diastereomeric mixture (Scheme 4). NOE studies of compound **6** confirmed the absolute configuration at the C7 position as *S* (see the Experimental Section). Reduction of the nitro group with 3 equivalents of LAH, followed by in situ cyclization, generated the desired fused system (**7**) in



Scheme 2. Progression of the DOS methodology.

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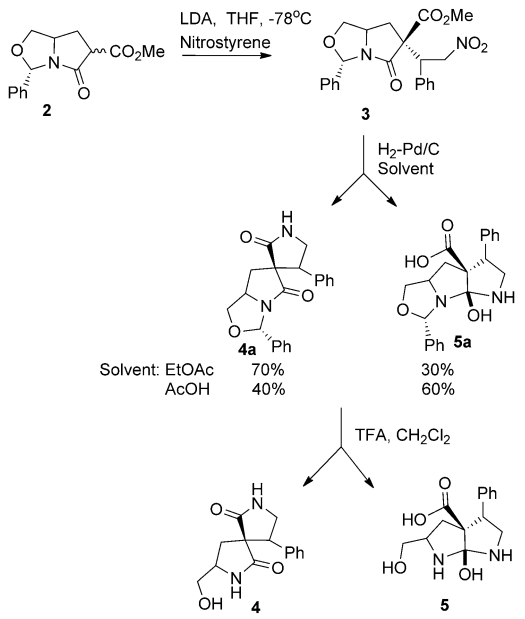
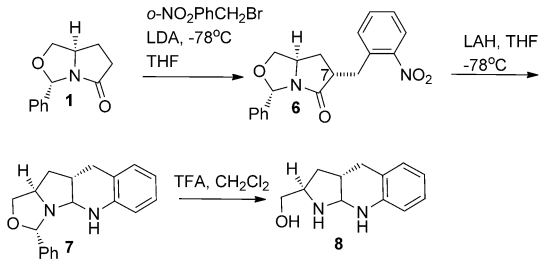


Scheme 3. Michael-addition/cyclization-mediated synthesis of scaffolds **4**, **4a**, **5**, and **5a**.



Scheme 4. Synthesis of rigid pyrroloquinoline scaffolds.

56% yield. Removal of the chiral auxiliary was achieved upon treatment of compound **7** with trifluoroacetic acid (TFA) to generate alcohol **8** in 86% yield.

We attempted to build in more diversity at this stage by reducing compound **6** into the corresponding amine (**9**), converting it into the benzaldehyde imine (**10**), and finally subjecting it to a base-mediated 1,6-ring-closing intramolecular addition to the imine. This process generated the corresponding spirotetrahydroquinoline (**11**), which contained a chiral quaternary C center. We attempted the cyclization of the crude imine (**10**) with various bases (Et_3N, K_2CO_3, Cs_2CO_3, and KH) at various temperatures (70–80 °C) and obtained the desired products in extremely low yield (2–5%). However, by using microwave heating at 160 °C with *t*BuOK as the base, we obtained the desired product, spirotetrahydroquinoline **11**, in 76% yield and 95% *de*. Deprotection with TFA generated alcohol **12** in 67% yield. With the optimized cyclization conditions in hand, we converted several crude imines into their corresponding spirotetrahydroquinolines (**11**–**20**) in decent yields (about 65%) and good diastereoselectivity (>90%). The absolute configuration of these molecules was established by X-ray crystallography of one of the representative compounds (**13**) for which the single crystal was generated in MeCN (Scheme 5).

Our group has previously established that C7-aminoaryl-substituted spiro-oxoindolone systems are readily accessible by nucleophilic aromatic substitution at the C7 position of bicyclic lactam **2**.[13] Accordingly, we reacted lactam **2** with sodium hydride and electron-poor fluorobenzenes (2,4-nitrofluorobenzene and 5-bromo-2,4-dinitrofluorobenzene), which, in turn, generated the desired *exo*-arylated compounds (**21** and **22**). X-ray crystallography analysis of compound **21** (the single crystal was generated in MeCN) allowed its unequivocal assignment (Scheme 6).[13] Reduction of lactams **21** and **22** by using 10% Pd/C and ammonium formate generated the desired spiro-oxoindolones (**23** and **24**, respectively). Final deprotection with TFA generated alcohols **25** and **26**, respectively (Scheme 6).

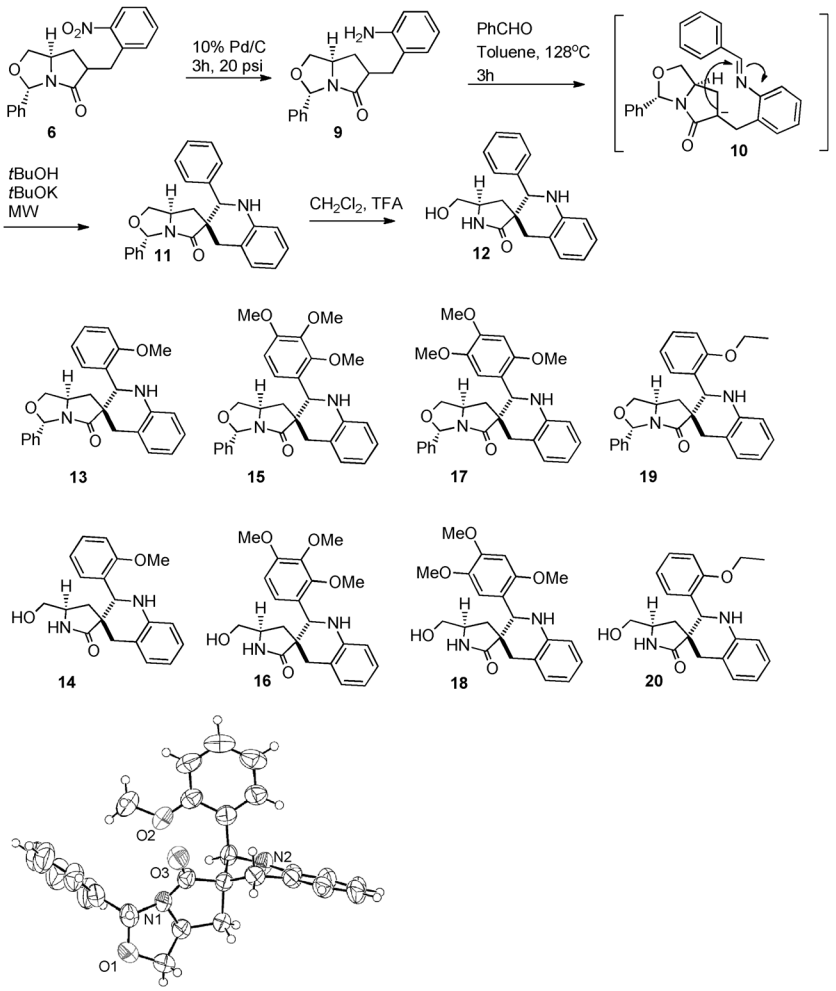
We set out to determine the diversity in the chemical space that was covered by our scaffolds by using in silico algorithms. We wanted to evaluate their diversity quotient with respect to commercial drugs. Thus, we compared our molecules, in a scatter-plot, against 1011 FDA-approved drugs (from our GOSTAR database).[14a]

We evaluated our library in terms of four parameters: hydrogen-bond donors (HBD), -acceptors (HBA), log D, and polar surface area (PSA; Figure 1). Our compounds fell into the most populated areas of the plots. The absence of outliers suggests that this methodology yields compounds that are inclined to have drug-like properties.[14b]

The plots indicate that the end compounds are significantly diverged from the starting bicyclic lactams, thereby exploring new chemical space.

The polar surface area of a small molecule is an important contributor to ligand/receptor binding at active sites. PSA has a direct correlation with membrane-permeability and, therefore, serves as a reliable indicator of drug-availability across various biological barriers. Charge-distribution on molecular surfaces also plays a significant role in binding-affinity to active sites. Therefore, we decided to calculate the electrostatic profiles of the surfaces of our molecules by projecting the Gasteiger–Marsili charge-distribution onto the Connolly surface that was generated by using the MOLCAD tool in SYBYL and plotting the PSA distributions.[15] Our scaffolds had PSAs that spanned acceptable values for CNS (central nervous system)- and non-CNS-penetrating orally active drugs.[16] Scheme 7 shows four select scaffolds that have a PSA range of 37–170 $Å^2$. In addition, the surface electrostatic potential maps indicate diverse shapes and electron-densities that allow these scaffolds to be potential biological modulators across a wide spectrum of therapeutic targets.

Another objective of our study was to develop methods to prepare compounds that have the potential to be biologically active. We realize that it is unrealistic to expect to generate potent molecules by using synthetic efforts that are not directed at a particular biological target. However, we

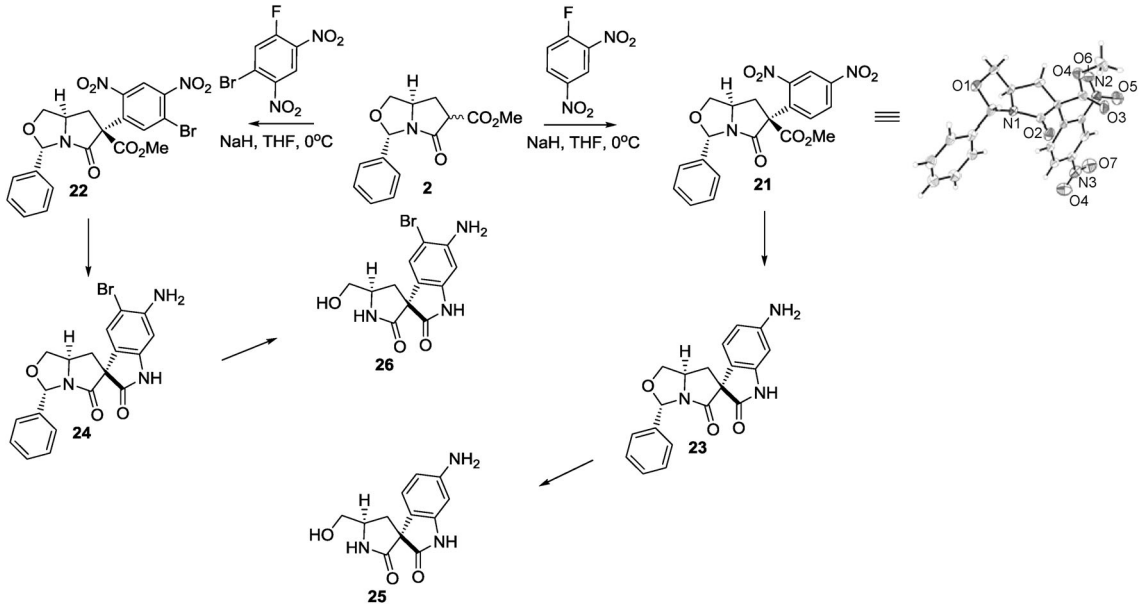


Scheme 5. Synthesis of chiral tetarhydroquinolines from the 1,6-electrocyclization reaction.

hoped that our scaffolds may provide hits that are useful for further elaboration into drug leads. Spirocyclic pyrrolidine frameworks feature in marine alkaloids, some of which show anti-cancer activity. Therefore, we decided to screen our compounds against two cancer cell lines to evaluate if they had any bioactive potential. We used the MCF-7 (breast cancer) and HeLa (human epithelial) cell-lines for biological evaluation.

The cell-lines were procured from the Cell-Line Bank of the National Center for Cellular Sciences (NCCS), Pune, India. These cells were cultured in RPMI –1640, DMEM media that contained 10% fetal bovine serum (FBS) at 37°C in a CO_2 incubator in the presence or absence of test compounds. Cytotoxicity was measured by assay with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), according to the method reported by Mosmann in 1983.[17]

The cells in the exponential phase of growth were exposed to etoposide. The duration of exposure is commonly deter-



Scheme 6. Synthesis of spirooxoindolones.

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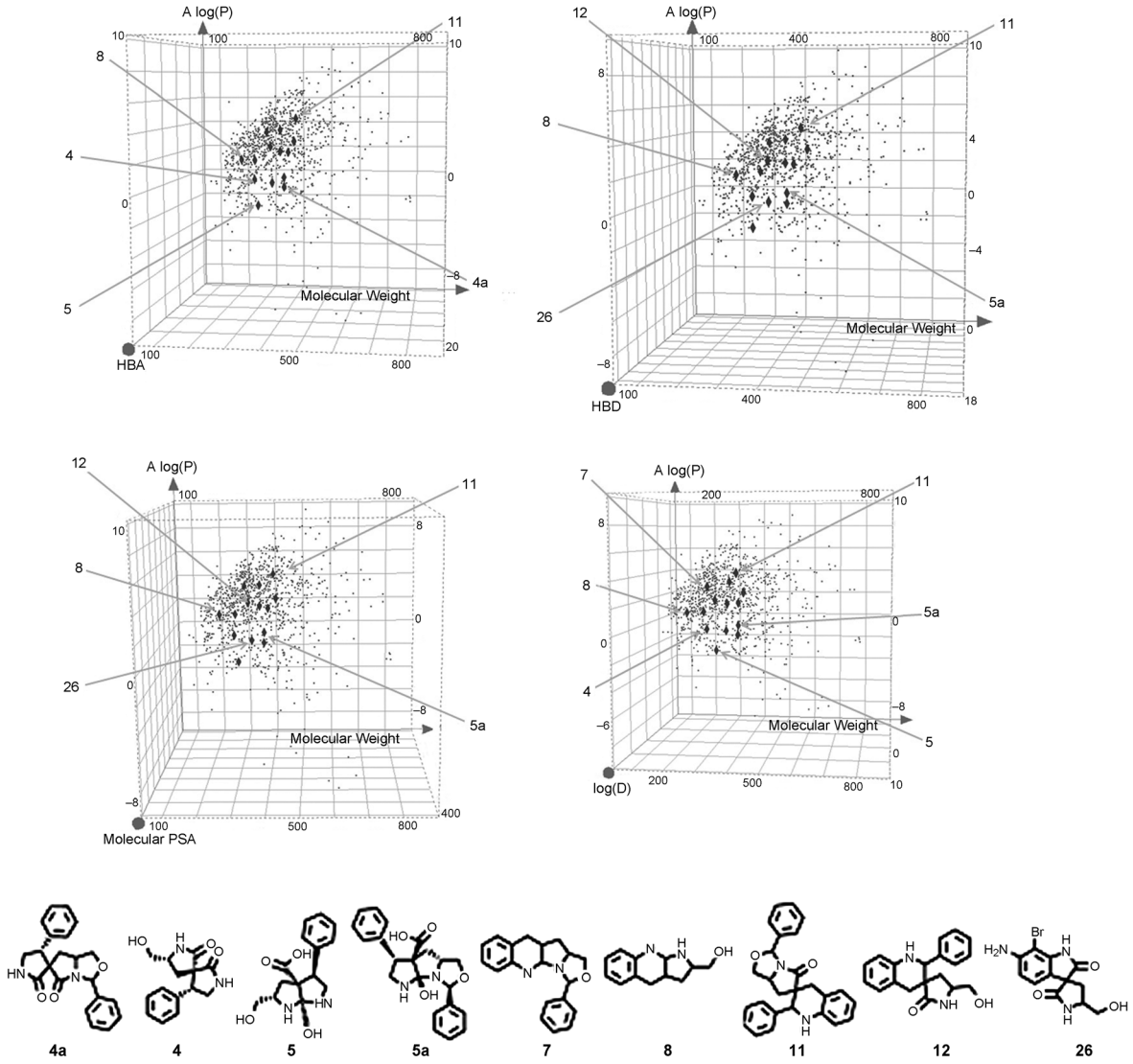
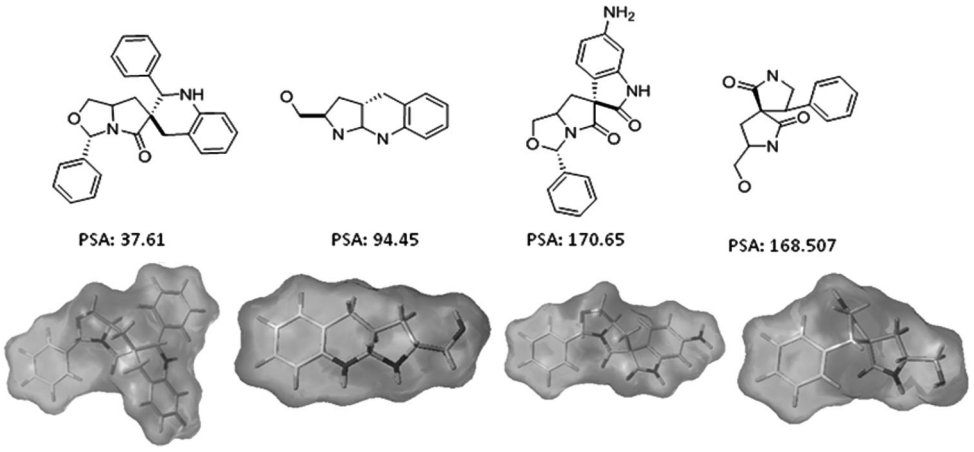


Figure 1. Comparison of our molecules in terms of six drug-like properties relative to 1011 FDA-approved drugs from the GOSTAR database.



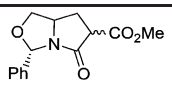
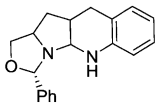
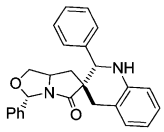
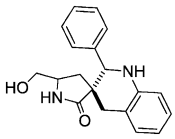
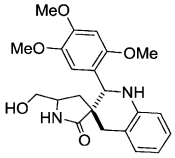
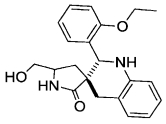
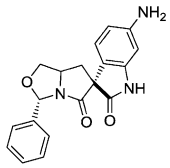
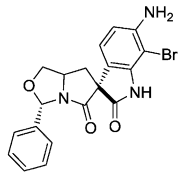
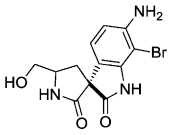
Scheme 7. Surface electrostatic potentials of compounds **4**, **8**, **11**, and **23**. These compounds were mutually aligned as shown. The surface corresponds to the H_2O-accessible Connolly surface and the color indicates the Gasteiger–Marsili charge-distribution: electronegative areas are in red, electropositive areas are in blue.

mined as the time required for minimal damage to occur, but is also influenced by the stability of the drug. After removal of the drug, the cells are allowed to proliferate for between two- and three population-doubling times (PDTs) to distinguish between cells that remain viable and are capable of proliferation and those that remain viable but cannot proliferate. The number of surviving cells is then determined indirectly by reduction of MTT dye. Once the MTT-formazan has been dissolved in a suitable solvent, the amount of MTT-formazan produced is determined spectrophotometrically.

The cells (2×104) were seeded in each well that contained the medium (0.1 mL) in 96-well plates (Greiner CELLSTAR, Sigma–Aldrich, Bangalore, India). After 24 h, different test concentrations (2.5–100 $\mu g\,mL^{-1}$) were added and the cell-viability was assessed. MTT (10 μL per well), at a concentration of 5 $mg\,mL^{-1}$, was added into the wells and the plates were incubated at 37 °C for an additional 4 h. The medium was discarded and formazan blue, which formed in the cells, was dissolved with dimethyl sulfoxide (DMSO; 1 mL). The rate of color production was measured at 570 nm in a spectrophotometer (Spectra MAX Plus; Molecular Devices; supported by SOFTmax PRO-3.0). Etoposide and DMSO were used as positive- and vehicle-controls, respectively. The percentage inhibition of cell-viability was determined with reference to the control values. The data were subjected to linear-regression analysis and the regression lines were plotted to obtain the best straight-line fit. The IC_{50} (inhibition of cell viability) concentrations were calculated by using the respective regression equation.

Of the fourteen compounds that were tested (**2**, **4a**, **7**–**8**, **11**–**20, 23**, **24**, and **26**), nine showed some potency (Table 1). Compounds **2**, **12**, and **26** showed reasonable potency in both cell-lines (7–16 μM). Compounds **20** and **23** were significantly less potent in both cell-lines. Compounds **7**, **18**, and **24** only showed weak potency against MCF-7 cells, whereas compound **11** only showed weak potency against HeLa cells. Whilst the sample size precluded firm determination of the structure activity relationship (SAR), a few trends do emerge: Activity is reasonable for compounds that contain three rings (compounds **2** and **26**), less so for those that contain four rings (compounds **12** and **18**), and falls sharply for compounds that contain five- or six rings (compounds **7**, **11**, and **23**). Bicyclic lactams (except the core, compound **2**) are suboptimal in terms of their potency (**26** versus **23** and **24**; **11** versus **12**). Spirotetrahydroquinolines (**12** versus **18** and **20**) do not appear to tolerate steric hindrance around the phenyl–THQ bond. We plan to use these observations to design better inhibitors.

Table 1. Cellular evaluation of the compounds against the HeLa and MCF-7 cell-lines.

Compound	Structure	M_w	PSA	IC_{50} [μM] HeLa cell-line	IC_{50} [μM] MCF-7 cell-line
2		261.27	55.84	9.3(±0.6)	16.1(±2.5)
7		290.36	24.83	n.a.[a]	47.5(±6.4)
11		396.48	41.57	42.2(±1.7)	n.a.[a]
12		308.37	61.36	7.3(±2.9)	8.9(±5.8)
18		398.45	89.05	n.a.[a]	58.7(±5.5)
20		352.43	70.59	25.4(±7.0)	48.5(±2.4)
23		335.36	84.66	28.5(±2.1)	31.7(±1.0)
24		414.25	84.66	n.a.[a]	63.3(±1.8)
26		326.15	104.45	11.2(±2.2)	16.8(±2.9)

[a] n.a.: not available.

Conclusions

In summary, we have developed a two-step sequence, starting with a chiral-bicyclic-lactam-directed enolate-addition/substitution reaction, thereby leading to the stereoselective formation of carbocycles and spirocycles. A main objective of this work, that is, to explore new- and diverse chemical space, has been achieved (for ESP data, see Scheme 7; for drug-like properties, see Figure 1). In addition, we have demonstrated that these new scaffolds and their derivatives

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show some biological activity in selected cancer cell-lines. This DOS methodology provides hits as starting points for medicinal-chemistry campaigns.

Experimental Section

General Methods

Air- and moisture-sensitive reactions were carried out in oven-dried glassware that were sealed with rubber septa under a positive pressure of dry argon. Sensitive liquids and solutions were transferred by syringe. Reactions were stirred with Teflon-coated magnetic stirrer bars. Elevated temperatures were maintained by using Thermostat-controlled silicon oil baths. Organic solutions were concentrated on a rotary evaporator with a desktop vacuum pump. THF, Et_2O, dioxane, benzene, and toluene were distilled from sodium and benzophenone prior to use. CH_2Cl_2 was distilled from CaH_2 prior to use. Analytical TLC was performed on 0.25 mm silica-gel G plates with a 254 nm fluorescent indicator. The TLC plates were visualized by using UV light and treated with a phosphomolybdic acid stain, followed by gentle heating. Purification of the products was performed by flash chromatography on silica gel and the purified compounds showed a single spot by analytical TLC. The diastereomeric ratio and the regioisomeric ratio were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (ppm) relative to residual solvent peaks ($CDCl_3$: 77.0 ppm).

*Experimental Procedures and Characterization Data for the Michael-Addition/Cyclization-Mediated Synthesis of Scaffolds **3**, **4**, **4a**, **5**, and **5a***

*Compound **3***

A solution of compound **2** (200 mg, 0.76 mmol) in THF (2 mL) was added to a solution of LDA in THF (5 mL) (1.2 equiv, 98 mg, 0.91 mmol, freshly prepared from diisopropylamine and *n*BuLi (1 M in *n*-hexane) at -78°C. The mixture was stirred at −78°C for 0.5 h. Nitrostyrene (1.5 equiv, 171 mg, 1.14 mmol) was added dropwise at −78°C under a N_2 atmosphere. The mixture was stirred at RT for 1 h under a N_2 atmosphere until the starting material was completely consumed (determined by TLC analysis). The mixture was diluted with EtOAc, extracted with water (2×4 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc, 80:20) to afford compound **3** (245 mg, 0.597 mmol, 78% yield) as a white solid. R_f = 0.6 (petroleum ether/EtOAc, 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.00 (m, 1H), 2.61–2.81 (m, 2H), 3.8 (s, 3H), 3.91–3.92 (m, 1H), 4.11- 4.18 (m, 1H), 4.21–4.31 (t, J = 2.6 Hz, 1H), 4.95–5.00 (m, 1H), 5.29–5.40 (m, 1H), 6.21 (s, 1H), 7.23–7.40 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7, 46.9, 53.4, 55.8, 63.5, 71.3, 86.9, 87.1, 125.9, 126.0, 128.5, 128.7, 128.8, 128.86, 128.9 129.22, 129.25,135.4, 137.5, 170.4, 171.7 ppm); HRMS (ES+): *m*/*z* calcd for $C_{22}H_{23}N_2O_6$: 411.1478 $[M+H]^+$; found: 411.1476; *ee* (92%) was determined by HPLC on a chiral stationary phase (ChiralpakAD, *n*-hexane/isopropanol = 60:40, 1 mL min^{-1}, t_R = 6.47 min (major), 5.57 min (minor)).

*Compounds **4a** and **5a***

Compound **3** (0.15 g, 0.37 mmol) was added to a solution of 10% Pd/C (20 mg) in MeOH (2 mL) at RT under a N_2 atmosphere and the mixture was hydrogenated at 20 psi for 6 h at RT. The suspension was filtered through a pad of Celite and concentrated under reduced pressure. The resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc, 80:20) and on EtOAc to afford compounds **4a** (61 mg, 0.175 mmol, 48% yield) and **5a** (37 mg, 0.10 mmol, 28% yield) as white solids. **4a**: R_f = 0.7 (petroleum ether/EtOAc, 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06–2.12 (dd, ^1J = 2.1 Hz, ^2J = 2.4 Hz, 1H), 2.21–2.23 (t, J = 7.6 Hz, 1H), 2.65–2.68 (m, 1H), 3.39–3.41 (m, 1H), 3.54–3.61 (m, 1H), 3.85–4.01 (m, 3H), 5.63 (s, 1H), 7.21–7.23 (m, 2H), 7.32–7.41 (m, 6H), 7.43–7.45 (m, 2H), 8.39 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8, 44.0, 51.06, 55.93, 62.0, 70.7, 86.42, 125.97,127.93, 128.39, 128.47, 128.71, 129.65, 135.99, 138.90, 173.60, 174.57 ppm; HRMS (ES+): *m*/*z* calcd for $C_{21}H_{21}N_2O_3$: 349.147 $[M+H]^+$; found: 349.149. **5a**: R_f = 0.1 (petroleum ether/EtOAc, 50:50); ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.19–2.26 (m, 1H), 2.34–2.40 (m, 1H), 2.83 (m, 1H), 3.62–3.67 (m, 2H), 3.95–4.07 (m, 2H), 4.21–4.25 (m, 1H), 5.60 (s, 1H), 7.20–7.28 (m, 2H), 7.30–7.41 (m, 6H), 7.42–7.48 (m, 2H), 10.2 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 179.54, 145.65, 142.69, 130.41, 129.53, 129.22, 127.85, 127.25, 126.26, 123.18, 119.15, 118.06, 87.98. 74.06, 60.90, 58.37, 40.31, 33.12, 27.25 ppm; HRMS (ES+): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$: 367.158 $[M+H]^+$; found: 367.153.

*Compound **4***

Compound **4a** (50 mg, 0.143 mmol) was dissolved in CH_2Cl_2 (0.5 mL). TFA (32 mg, 0.280 mmol) was added to the reaction at 0°C and the mixture was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 70:30) to afford compound **4** (28 mg, 0.107 mmol, 75% yield) as a pale-yellow syrup. R_f = 0.1 (petroleum ether/EtOAc, 70:30) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06–2.12 (dd, ^1J = 2.1 Hz, ^2J = 2.4 Hz, 1H), 2.21–2.23 (t, J = 6.6 Hz, 1H), 2.65–2.68 (m, 1H), 3.39–3.41 (m, 1H), 3.54–3.61 (m, 1H), 3.85–4.01 (m, 3H), 7.21–7.23 (m, 2H), 7.35–7.41 (m, 1H), 7.45–7.55 (m, 2H), 7.95 (s, 1H), 8.41 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 44.1, 51.1, 55.9, 62.1, 70.8, 126.0, 128.5, 128.7, 136.0, 173.6, 174.5 ppm; HRMS (ES+): *m*/*z* calcd for $C_{14}H_{17}N_2O_3$: 261.116 $[M+H]^+$; found: 261.119.

*Compound **5***

Compound **5a** (100 mg, 0.272 mmol) was dissolved in CH_2Cl_2 (1 mL). TFA (61 mg, 0.544 mmol) was added at 0°C and the mixture was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 20:80) to afford compound **5** (47 mg, 0.169 mmol, 62% yield) as a white solid. R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19–2.26 (m, 1H), 2.34–2.40 (m, 1H), 2.83 (m, 1H), 3.61–3.65 (m, 2H), 3.95–4.05 (m, 2H), 4.21–4.25 (m, 1H), 7.20–7.28 (m, 2H), 7.35–7.41 (m, 1H), 7.42–7.48 (m, 2H), 10.2 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 48.4, 51.5, 56.1, 71.1, 86.8, 125.9, 126.1, 128.0, 128.7, 129.9, 133.7, 181.9 PPM; HRMS (ES+): *m*/*z* calcd for $C_{14}H_{19}N_2O_4$: 279.1267 $[M+H]^+$; found: 279.0199.

*Compound **6***

A solution of bicyclic lactam **1** (500 mg, 2.46 mmol) in THF (2 mL) was added to a solution of LDA in THF (5 mL) (2 equiv, 0.52 g, 4.92 mmol, freshly prepared from diisopropylamine and *n*BuLi in *n*-hexane) at −78°C. The mixture was stirred at −78°C for 0.5 h followed by the addition of 2-nitrobenzyl bromide (1.1 equiv, 0.58 g, 2.70 mmol) at −78°C under a N_2 atmosphere. The mixture was stirred at the same temperature for 30 min under a N_2 atmosphere, slowly warmed to RT, and stirred at RT until the starting material was completely consumed (by TLC analysis). The mixture was diluted with EtOAc, extracted with water (2× 4 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc, 80:20) to afford compound **6** (0.55 g, 1.62 mmol, 67% yield) as a pale-yellow liquid. R_f = 0.5 (petroleum ether/EtOAc, 70:30); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.06–2.15 (m, 2H), 3.05–3.15 (m, 2H), 3.40–3.46 (m, 2H), 4.06–4.17 (m, 2H), 6.15 (s, 1H), 7.29–7.44 (m, 7H), 7.52–7.56 (t, J = 7.6 Hz, 1H), 7.91–7.93 ppm (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 29.02, 35.60, 47.34, 58.90, 72.23, 88.47, 125.82, 127.12, 129.07, 129.42, 129.64, 133.79, 134.18, 134.71, 140.19, 150.94, 181.20 ppm; HRMS (ES+): *m*/*z* calcd for $C_{19}H_{19}N_2O_4$: 339.1267 $[M+H]^+$; found: 339.1096.

Compound ***7***

Compound **6** (200 mg, 0.59 mmol) was added to a solution of 10% Pd/C (40 mg) in MeOH (2 mL) at RT under a N_2 atmosphere and the mixture was hydrogenated at 20 psi for 8 h at RT. The suspension was filtered through a pad of Celite and concentrated under reduced pressure to yield the crude amine. The amine was dissolved in THF (2 mL) and treated with $LiAlH_4$ (1 M in THF, 0.60 mmol, 23 mg) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 4 h. Once the starting material was completely consumed (by TLC analysis), the reaction mixture was quenched with EtOAc (0.2 mL), filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc, 80:20) to afford compound **7** (69 mg, 0.236 mmol, 40% yield) as a white solid. $R_f = 0.5$ (petroleum ether/EtOAc, 70:30); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.81$–1.98 (m, 1H), 2.41–2.61 (m, 2H), 2.91–3.01 (m, 1H), 3.31–3.48 (m, 2H), 3.62–3.72 (m, 1H), 3.80–3.90 (d, $J = 8.9$ Hz, 1H), 3.98–4.02 (m, 1H), 4.41–4.58 (m, 1H), 5.58–5.65 (d, $J = 1.8$ Hz, 1H), 7.02–7.15 (m, 2H), 7.21–7.42 ppm (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.27$, 128.94, 128.50, 128.15, 127.63, 127.41, 127.15, 127.07, 125.08, 123.94, 123.34, 114.60, 62.77, 61.25, 60.33, 58.42, 53.94, 45.02, 29.40, 28.97, 22.29, 22.06 ppm; HRMS (ES+): *m*/*z* calcd for $C_{19}H_{21}N_2O$: 293.157 $[M+H]^+$; found: 293.160. The *ee* (99.5%) was determined by HPLC on a chiral stationary phase (ChiralpakAD, *n*-hexane/isopropanol = 70:30, 1 mL min^{-1}, $t_R = 9.14$ min (major)).

Compound ***8***

Compound **7** (100 mg, 0.341 mmol) was dissolved in CH_2Cl_2 (1 mL). TFA (77 mg, 0.682 mmol) was added to the reaction at 0 °C and the mixture was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 60:40) to afford compound **8** (42 mg, 0.204 mmol, 60% yield) as a colorless syrup. $R_f = 0.5$ (petroleum ether/EtOAc, 50:50); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.81$–1.98 (m, 1H), 2.41–2.61 (m, 3H), 2.91–3.01 (dd, $^1J = 8.8$ Hz, $^2J = 6.5$ Hz, 1H), 3.31–3.48 (m, 2H), 3.62–3.72 (dd, $^1J = 2.1$ Hz, $^2J = 2.7$ Hz, 1H), 3.80–3.90 (d, $J = 8.9$ Hz, 1H), 3.98–4.02 (m, 1H), 4.41–4.58 (dd, $^1J = 1.2$ Hz, $^2J = 1.2$ Hz, 1H), 7.20–7.51 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.9$, 29.4, 45.2, 53.9, 61.2, 81.2, 118.5, 121.3, 121.9, 125.0, 128.9, 137.3 ppm; HRMS (ES+): *m*/*z* calcd for $C_{12}H_{17}N_2O$: 205.1263 $[M+H]^+$; found: 205.1265.

Compound ***9***

To a dried three-necked flask was added a solution of compound **6** (1 g, 2.95 mmol) in MeOH (10 mL) under an argon atmosphere and 10% Pd/C (0.5 g) at RT. The reaction mixture was stirred at the same temperature for 3 h under a hydrogen atmosphere at 20 psi. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc, 70:30) to afford compound **9** (0.79 g, 2.581 mmol, 87% yield) as a yellow syrup. $R_f = 0.5$ (petroleum ether/EtOAc, 50:50); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 2.01$–2.04 (t, $J = 5.6$ Hz, 2H), 2.64–2.72 (m, 1H), 2.87–2.99 (m, 2H), 3.38–3.42 (t, $J = 8.8$ Hz, 1H), 4.02–4.18 (m, 2H), 4.86 (s, 2H), 6.09 (s, 1H), 6.47–6.51 (t, $J = 14.8$ Hz, 1H), 6.61–6.63 (d, $J = 7.2$ Hz, 1H), 6.89–6.94 (m, 2H), 7.3–7.4 ppm (m, 5H); HRMS (ES+): *m*/*z* calcd for $C_{19}H_{21}N_2O_2$: 309.152 $[M+H]^+$; found: 309.157.

General Procedure for the Synthesis of Chiral Tetrahydroquinolines

To a dried three-necked flask fitted with a reflux condenser was added compound **9** (1.00 mmol) and aryl benzaldehyde (2–3 equiv) in toluene (7.5 mL) under an argon atmosphere. The reaction mixture was heated at reflux (120 °C) for 2–3 h and concentrated under reduced pressure. The resulting residue was dissolved in *tert*-butanol (0.6 mL). Potassium *tert*-butoxide (1 equiv) was added to the reaction at RT and the mixture was stirred for 15 min at RT before being transferred into a microwavable vial and heated in a microwave at 160 °C for 20–30 min. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc) to afford the product.

Compound ***11***

Compound **9** (0.250 g, 0811 mmol) and benzaldehyde (0.172 g, 1.622 mmol) were mixed in toluene (6.25 mL) under an argon atmosphere. The reaction mixture was heated at reflux (120 °C) for 2 h and concentrated under reduced pressure. The resulting residue was dissolved in *tert*-butanol (0.5 mL). Finally, potassium *tert*-butoxide (0.090 g, 0.811 mmol) was added and the reaction mixture was heated in a microwave. The mixture was purified by column chromatography on neutral alumina (petroleum ether/EtOAc, 95:5) to afford compound **11** (225 mg, 70% yield). $R_f = 0.6$ (petroleum ether/EtOAc, 80:20); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.71$–1.76 (m, 1H), 2.39–2.44 (m, 1H), 2.88–2.93 (d, $J = 16.8$ Hz, 1H), 3.47–3.51 (t, $J = 8.4$ Hz, 1H), 3.84–3.88 (t, $J = 6.8$ Hz, 1H), 4.09–4.12 (t, $J = 7.2$ Hz, 1H), 4.52 (s, 1H), 6.05 (s, 1H), 6.48–6.62 (m, 3H), 6.91–6.94 (m, 2H), 7.09–7.23 (m, 5H), 7.30–7.44 ppm (m, 5H); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.71$–1.76 (m, 1H), 2.41–2.45 (m, 1H), 2.89–2.93 (d, $J = 16.0$ Hz, 1H), 3.47–3.51 (t, $J = 8.0$ Hz, 2H), 3.81–3.84 (t, $J = 6.8$ Hz, 1H), 4.09–4.13 (t, $J = 7.6$ Hz, 1H), 4.52 (s, 1H), 6.04 (s, 1H), 6.50–6.54 (t, $J = 7.2$ Hz, 1H), 6.60–6.62 (d, $J = 8.4$ Hz, 1H), 6.92–6.96 (m, 2H), 7.09–7.24 (m, 5H), 7.31–7.45 ppm (m, 5H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 34.66$, 39.37, 52.86, 56.87, 61.96, 73.71, 87.95, 114.33, 117.73, 119.12, 127.03, 127.36, 128.00, 128.66, 128.86, 128.90, 129.36, 129.55, 129.70, 130.02, 130.25, 139.91, 142.79, 145.29, 179.04 ppm; HRMS (ES+): *m*/*z* calcd for $C_{26}H_{25}N_2O_2$: 397.183 $[M+H]^+$; found: 397.181.

Compound ***13***

Compound **9** (0.250 g, 0811 mmol) and 2-methoxy benzaldehyde (0.275 g, 2.029 mmol) were stirred in toluene (6.25 mL) under an argon atmosphere. The reaction mixture was heated at reflux (120 °C) for 2.5 h and concentrated under reduced pressure. The resulting residue was dissolved in *tert*-butanol (0.5 mL). Potassium *tert*-butoxide (0.090 g, 0.811 mmol) was added and the reaction mixture was heated in a microwave. The mixture was purified by column chromatography on neutral alumina (petroleum ether/EtOAc, 80:20) to afford compound **13** (262 mg, 76% yield). $R_f = 0.5$ (petroleum ether/EtOAc, 70:30); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.70$–1.76 (m, 1H), 2.50–2.56 (d, $J = 16.2$ Hz, 1H), 2.64–2.71 (m, 1H), 3.13–3.19 (d, $J = 16.2$ Hz, 1H), 3.33 (s, 3H), 3.40–3.45 (t, $J = 8.1$ Hz, 1H), 3.97–4.01 (m, 1H), 4.22–4.30 (m, 2H), 5.06 (s, 1H), 6.23 (s, 1H), 6.55–6.58 (d, $J = 7.8$ Hz, 1H), 6.65–6.76 (m, 3H), 7.01–7.07 (m, 2H), 7.15–7.20 (m, 2H), 7.32–7.39 (m, 3H), 7.44–7.47 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 34.48$, 38.97, 51.78, 53.76, 55.05, 57.13, 74.22, 88.83, 110.73, 113.94, 113.04, 117.33, 118.40, 121.08, 127.95, 128.25, 128.97, 129.41, 129.45, 129.87, 130.63, 131.80, 140.62, 145.49, 157.96, 179.77 ppm; HRMS (ES+): *m*/*z* calcd for $C_{27}H_{27}N_2O_3$: 427.194 $[M+H]^+$; found: 427.190.

Compound ***15***

Compound **9** (0.10 g, 0.324 mmol) and 2,3,4-tri-methoxy benzaldehyde (0.127 g, 0.647 mmol) were stirred in toluene (2.5 mL) under an argon atmosphere. The reaction mixture was heated at reflux (120 °C) for 3 h and concentrated under reduced pressure. The resulting residue was dissolved in *tert*-butanol (0.2 mL). Potassium *tert*-butoxide (0.036 g, 0.324 mmol) was added and the reaction mixture was heated in a microwave. The mixture was purified by column chromatography on neutral alumina (petroleum ether/EtOAc, 80:20) to afford compound **15** (102 mg, 65% yield). $R_f = 0.5$ (petroleum ether/EtOAc, 50:50); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.56$–1.61 (m, 1H), 2.53–2.57 (d, $J = 16.0$ Hz, 1H), 2.91–2.94 (m, 1H), 3.33–3.38 (m, 1H), 3.51–3.54 (m, 1H), 3.60 (s, 6H), 3.81–3.83 (m, 1H), 3.90 (s, 3H), 4.01–4.05 (m, 1H), 4.89 (s, 1H), 6.04 (s, 1H), 6.56–6.64 (m, 2H), 6.81–6.83 (d, $J = 8.8$ Hz, 1H), 6.87–6.89 (m, 2H), 6.93–6.99 (m, 2H), 7.19–7.25 (m, 3H), 7.48–7.50 ppm (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 33.11$, 40.31, 53.65, 53.79, 56.53, 58.37, 60.89, 61.47, 74.05, 87.97, 108.03, 114.98, 118.05, 119.15, 123.18, 126.25, 127.24, 127.85, 129.22, 129.52, 130.40, 139.53, 142.68, 145.65, 153.41, 155.07, 179.50 ppm; HRMS (ES+): *m*/*z* calcd for $C_{29}H_{31}N_2O_5$: 487.215 $[M+H]^+$; found: 487.210.

Compound ***17***

Compound **9** (0.20 g, 0.649 mmol) and 2,4,5-tri-methoxy benzaldehyde (0.32 g, 1.62 mmol) were stirred in toluene (5 mL) under an argon atmosphere. The reaction mixture was heated at reflux (120 °C) for 3 h and concentrated under reduced pressure. The resulting residue was dissolved in *tert*-butanol (0.4 mL). Potassium *tert*-butoxide (0.072 g, 0.649 mmol) was added and the reaction mixture was heated in a microwave. The mixture was purified by column chromatography on neutral alumina (petroleum ether/EtOAc, 70:30) to afford compound **17** (199 mg, 63 % yield). R_f = 0.5 (petroleum ether/EtOAc, 50:50); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.71–1.76 (m, 1H), 2.51–2.55 (d, J = 16 Hz, 1H), 2.68–2.73 (m, 1H), 3.04–3.08 (d, J = 16 Hz, 1H), 3.32 (s, 3H), 3.36 (s, 3H), 345–3.49 (t, J = 8.4 Hz, 1H), 3.80 (s, 3H), 4.07–4.10 (m, 1H), 4.23–4.26 (m, 1H), 4.94 (s, 1H), 6.07 (s, 1H), 6.49 (s, 1H), 6.54–6.61 (m, 2H), 6.75 (s, 1H), 6.94–6.98 (m, 2H), 7.34–7.41 ppm (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): δ = 35.27, 38.93, 52.28, 53.81, 55.96, 56.63, 56.92, 57.27, 74.12, 88.91, 98.01, 114.15, 114.17, 117.54, 118.86, 122.90, 127.90, 128.12, 129.49, 129.87, 130.43, 140.47, 143.85, 145.59, 150.50, 152.76, 179.82 ppm; HRMS (ES+): m/z calcd for $C_{29}H_{31}N_2O_5$: 487.215 $[M+H]^+$; found: 487.211.

Compound ***19***

Compound **9** (0.250 g, 0.811 mmol) and 2-ethoxybenzaldehyde (0.243 g, 1.623 mmol) were stirred in toluene (6.25 mL) under an argon atmosphere. The reaction mixture was heated at reflux (120 °C) for 3 h and concentrated under reduced pressure. The resulting residue was dissolved in *tert*-butanol (0.5 mL). Potassium *tert*-butoxide (0.090 g, 0.811 mmol) was added and the reaction mixture was heated in a microwave. The mixture was purified by column chromatography on neutral alumina (petroleum ether/EtOAc, 80:20) to afford compound **19** (264 mg, 74 % yield). R_f = 0.7 (petroleum ether/EtOAc, 50:50); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.93–0.97 (t, J = 6.8 Hz, 3H), 1.71–1.76 (m, 1H), 2.50–2.55 (d, J = 16.4 Hz, 1H), 2.62–2.67 (m, 1H), 3.09–3.13 (d, J = 16.0 Hz, 1H), 3.42–3.46 (t, J = 8 Hz, 1H), 3.67–3.71 (m, 1H), 3.78–3.82 (m, 1H), 3.89–3.93 (m, 1H), 4.21–4.24 (m, 1H), 5.09 (s, 1H), 6.09 (s, 1H), 6.55–6.58 (m, 2H), 6.67–6.70 (t, J = 7.6 Hz, 1H), 6.78–6.80 (d, J = 7.6 Hz, 1H), 6.94–6.98 (m, 2H), 7.11–7.16 (m, 2H), 7.33–7.42 ppm (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.87, 35.50, 38.63, 51.86, 54.15, 56.99, 64.53, 74.13, 88.75, 111.92, 114.18, 117.44, 118.81, 121.14,127.64, 128.08, 129.32, 129.43, 129.70, 130.44, 131.63, 140.32, 145.69, 157.38, 180.02 ppm; HRMS (ES+): m/z calcd for $C_{28}H_{29}N_2O_3$: 441.210 $[M+H]^+$; found: 441.212.

General Procedure for Opening a Chiral Auxiliary of Tetrahydroquinolines

The tetrahydroquinoline (**11, 13, 15, 17**, or **19**; 1 mmol) was dissolved in CH_2Cl_2 (1 mL). TFA (0.1–0.3 mL) was added to the reaction at 0 °C and the mixture was stirred at RT for 2–3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 60:40) to afford the product.

Compound ***12***

Compound **11** (0.1 g, 0.252 mmol) was dissolved in CH_2Cl_2 (1 mL). TFA (0.1 mL) was added and the mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc, 75:25) to afford compound **12** (62 mg, 80 % yield). R_f = 0.4 (petroleum ether/EtOAc, 70:30); ^{1}H NMR (300 MHz, CD_3OD): δ = 1.56–1.64 (m, 1H), 2.26–2.33 (m, 1H), 2.60–2.69 (m, 1H), 2.96–3.04 (d, J = 15.2 Hz, 1H), 3.09–3.16 (m, 1H), 3.28–3.36 (m, 1H), 3.43–3.49 (m, 1H), 4.32 (s, 1H), 6.53–6.59 (m, 2H), 6.92–6.96 (m, 2H), 7.22–7.32 ppm (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): δ = 35.61, 37.73, 47.15, 53.77, 62.14, 65.94, 114.42, 117.61, 119.71, 127.81, 128.49, 128.73, 128.94, 129.11, 129.33, 129.47, 130.16, 143.05, 145.55, 180.46 ppm; HRMS (ES+): m/z calcd for $C_{19}H_{21}N_2O_2$: 309.152 $[M+H]^+$; found: 309.150.

Compound ***14***

Compound **13** (0.2 g, 0.469 mmol) was dissolved in CH_2Cl_2 (2 mL) and TFA (0.2 mL) was added. The mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70:30) to afford compound **14** (116 mg, 73 % yield). R_f = 0.2 (petroleum ether/EtOAc, 70:30); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.35–1.38 (m, 1H), 2.10–2.20 (m,2H), 2.78–2.82 (d, J = 16.0 Hz, 1H), 3.50–354 (m, 1H), 3.69 (s, 3H), 4.66–4.69 (t, J = 5.2 Hz, 1H), 4.79 (s, 1H), 6.36–6.37 (m, 1H), 6.43–6.47 (t, J = 7.2 Hz, 1H), 6.53–6.55 (d, J = 8.4 Hz, 1H), 6.75–6.79 (t, J = 8.0 Hz, 1H), 6.83–6.85 (d, J = 8.4 Hz, 1H), 6.88–6.96 (m, 2H), 7.12–7.16 (t, J = 7.2 Hz, 1H), 7.48 ppm (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 33.90, 38.04, 52.52, 54.04, 55.40, 66.09, 78.79, 110.77, 113.77, 117.07, 118.62, 121.15, 128.08, 128.72, 129.20, 130.45, 132.38, 145.37, 158.24, 180.90 ppm; HRMS (ES+): m/z calcd for $C_{20}H_{23}N_2O_3$: 339.163 $[M+H]^+$; found: 339.167.

Compound ***16***

Compound **15** (0.15 g, 0.308 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and TFA (0.15 mL) was added to the reaction mixture at 0 °C. The mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc, 60:40) to afford compound **16** (85 mg, 69 % yield). R_f = 0.4 (petroleum ether/EtOAc, 30:70); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.33–1.39 (m, 1H), 2.00–2.06 (m, 1H), 2.42–2.46 (d, J = 16 Hz, 1H), 2.53–2.59 (m, 1H), 2.81–2.84 (m, 1H), 3.21–3.25 (m, 1H), 3.36–3.41 (m, 2H), 3.78 (s, 3H), 3.85 (s, 6H), 4.88 (s, 1H), 6.53–6.62 (m, 2H), 6.76–6.78 (d, J = 8.8 Hz, 1H), 6.91–6.95 (m, 2H), 7.40–7.42 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 33.11, 40.31, 53.63, 53.79, 56.53, 58.37, 60.89, 61.47, 74.05, 108.03, 114.98, 118.05, 119.15, 126.25, 127.24, 127.83, 129.22, 129.52, 142.63, 145.65, 153.41, 155.07, 179.53 ppm; HRMS (ES+): m/z calcd for $C_{22}H_{27}N_2O_5$: 399.184 $[M+H]^+$; found: 399.180.

Compound ***18***

Compound **17** (0.10 g, 0.205 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and TFA (0.1 mL) was added. The mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc, 60:40) to afford compound **18** (56 mg, 68 % yield). R_f = 0.3 (petroleum ether/EtOAc, 30:70); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.49–1.55 (m, 1H), 2.00–2.04 (m, 1H), 2.33–2.38 (m, 1H), 2.42–2.47 (d, J = 16.4 Hz, 1H), 2.99–3.03 (d, J = 16.4 Hz, 1H), 3.35–3.39 (m, 1H), 3.45–3.49 (m, 2H), 3.56 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 4.88 (s, 1H), 6.52–6.60 (m, 3H), 6.84 (s, 1H), 6.93–6.97 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 35.27,38.93, 52.28, 53.81, 55.96, 56.63, 56.92, 57.27, 74.12, 98.01, 114.15, 114.17, 117.54, 118.86, 122.90, 129.49, 129.87, 130.43, 143.85, 145.59, 150.50, 152.76, 179.82 ppm; HRMS (ES+): m/z calcd for $C_{22}H_{27}N_2O_5$: 399.184 $[M+H]^+$; found: 399.188.

Compound ***20***

Compound **19** (0.20 g, 0.454 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and TFA (0.2 mL) was added to the reaction mixture at 0 °C. The mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70:30) to afford compound **20** (140 mg, 88 % yield). R_f = 0.6 (petroleum ether/EtOAc, 50:50); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.87–0.93 (t, J = 7.6 Hz, 3H), 1.50–1.61 (m, 2H), 2.01–2.06 (m, 1H), 2.30–2.40 (m, 2H), 3.03–3.07 (d, J = 16.0 Hz, 1H), 3.39–3.43 (m, 1H), 3.56–3.59 (m, 1H), 3.69–3.75 (m, 1H), 3.96–4.02 (q, J = 6.8 Hz, 2H), 5.03 (s, 1H), 6.51–6.62 (m, 2H), 6.75–6.81 (m, 2H), 6.91–6.99 (m, 2H), 7.10–7.15 ppm (m, 2H); ^{13}C NMR (400 MHz, CD_3OD): δ = 14.87, 35.50, 38.63, 51.86, 54.16, 56.99, 64.53, 74.25, 111.92, 114.18, 117.44, 118.81, 121.14, 129.32, 129.45, 129.70, 130.44, 131.63, 145.69, 157.38, 180.02 ppm; HRMS (ES+): m/z calcd for $C_{21}H_{25}N_2O_3$: 353.178 $[M+H]^+$; found: 353.171.

Compound ***24***

Compound **22** (0.20 g, 0.395 mmol) was dissolved in THF (2 mL). Ammonium formate (37 mg, 0.592 mmol) and 10 % Pd/C (40 mg) was added to the reaction and the mixture was heated at reflux for 12 h. Once the starting material was completely consumed (by TLC analysis), the reaction was exposed to air and filtered through a pad of Celite. The filtrate was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous sodium sulfate, evaporated under reduced pressure, and the resulting residue was purified by column chromatography on neutral alumina (*n*-hexane/EtOAc, 50:50) to afford compound **24** (109 mg, 0.263 mmol, 67 % yield) as a white solid. R_f = 0.4 (EtOAc);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41–2.61 (m, 2H), 3.61–3.68 (t, J = 8 Hz, 1H), 4.26–4.32 (m, 1H), 4.41–4.52 (m, 1H), 5.12–5.45 (brs, 1H), 6.15 (s, 1H), 6.92–6.93 (d, J = 4 Hz, 1H), 7.25–7.35 (m, 5H), 10.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.44, 174.41, 149.84, 143.01, 138.74, 128.68, 128.44, 126.17, 123.25, 116.88, 103.94, 96.00, 86.71, 71.50, 61.36, 56.74, 33.45 ppm; HRMS (ES+): m/z calcd for $C_{19}H_{17}N_3O_3Br$: 414.037 $[M+H]^+$; found: 414.040.

Compound ***26***

Compound **25** (0.10 g, 0.241 mmol) was dissolved in CH_2Cl_2 (1.0 mL). TFA (0.2 mL) was added to the reaction at 0 °C and the mixture was stirred at RT for 2.5 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 30:70) to afford compound **26** as a syrup in 80% yield. R_f = 0.2 (n-hexane/EtOAc 30:70); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.18–2.24 (m, 2H), 3.40–3.48 (m, 2H), 3.71–3.82 (m, 1H), 4.78–4.85 (m, 1H), 5.34 (s, 1H), 6.34 (s, 1H), 7.18 (s, 1H), 8.20 (s, 1H), 10.41 ppm (s, 1H); ^{13}C NMR (400 Hz, CD_3OD): δ = 14.87, 35.50, 38.63, 51.86, 54.16, 56.99, 64.53, 74.25, 111.92, 114.18, 117.44, 118.81, 121.14, 129.32, 129.45, 129.70, 130.44, 131.63, 145.69, 157.38, 180.02 ppm; HRMS (ES+): m/z calcd for $C_{12}H_{13}N_3O_3Br$: 326.006 $[M+H]^+$; found: 326.009.

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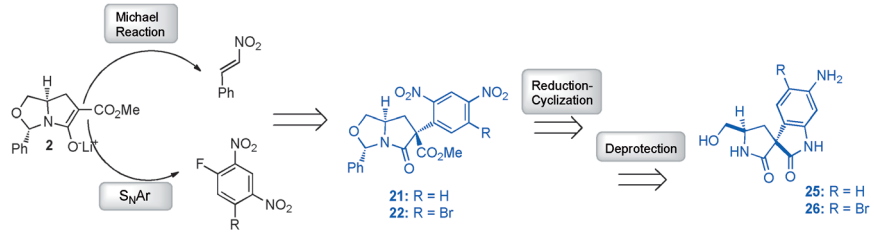

Uno, DOS, tres: An enolate-mediated strategy was used to synthesize biologically relevant cyclic scaffolds. In silico analysis was used to evaluate the compounds in terms of, for example, polar surface area and chemical diversity.

Diversity-Oriented Synthesis

*V. Surendra Babu Damerla, Chiranjeevi Tulluri, Rambabu Gundla, Lava Naviri, Uma Adepally, Pravin S. Iyer, Y. L. N. Murthy, Nampally Prabhakar, Subhabrata Sen** ____ ■■■■–■■■■

Reagent-Based DOS: Developing a Diastereoselective Methodology to Access Spirocyclic- and Fused Heterocyclic Ring Systems

