ChemInform Abstract: Pyrrolidine and Piperidine Based Chiral Spiro and Fused Scaffolds via Build/Couple/Pair Approach.

Article *in* RSC Advances · February 2014

DOI: 10.1039/c3ra47714b

RSC Advances

PAPER

Pyrrolidine and piperidine based chiral spiro and fused scaffolds *via* build/couple/pair approach†

Cite this: *RSC Adv.*, 2014, **4**, 10619

Rajinikanth Mamidala,[b] V. Surendra Babu Damerla,[b] Rambabu Gundla,[b] M. Thirumala Chary,[c] Y. L. N. Murthy[d] and Subhabrata Sen*[a]

Received 17th December 2013
Accepted 1st February 2014

DOI: 10.1039/c3ra47714b

www.rsc.org/advances

A versatile stereoselective diversity oriented synthetic pathway to the possible spiro and fused diverse heterocyclic small molecules is described. The strategy involved the "build–couple–pair" approach involving an S_NAr, Michael addition and Mannich reaction on chiral acyl bicyclic lactams **2a/b**, followed by a cyclization onto the inbuilt scaffold electrophile, thereby leading to asymmetric fused and spirocyclic nitrogen heterocycles. A "post-pair" phase has been incorporated to generate more polar compounds. We used Principal Component Analysis (PCA) and polar moment of inertia to evaluate the shape-space diversity of our scaffolds with respect to a commercial database and observed extraordinary diversity within the scaffold network. We further calculated the polar surface area (PSA) of our molecules which is an indicator for drug cell permeability.

Introduction

Interactive abilities of small molecules with biomacromolecules like DNA and RNA are a critical factor in analysing biological processes.[1] They form the fundamental platform of modern pharmaceutical science. These superficial three-dimensional interactions have inspired diversity oriented synthesis (DOS), to design molecules that mimic them.[2] Due to the unbiased nature of DOS libraries they exhibit a varied range of physicochemical and biological properties, and hence can be used for screening to identify novel compounds.[3]

In recent years, build/couple/pair (B/C/P) algorithm of DOS has evolved as an extremely successful technique to generate architecturally and stereochemically diverse scaffolds.[4] We envisioned a collection of diverse shaped chiral spiro- and fused scaffolds *via* the B/C/P strategy. Scheme 1 illustrates our strategy where the "build" phase generates stereochemically diverse chiral bicyclic lactams **1a** and **1b** as building blocks. In the "couple" phase, the building blocks are equipped with orthogonal functionalities *via* enolisation–substitution and final "pairing" involved intramolecular cyclization onto the inbuilt scaffold electrophile between the embedded functionalities to generate higher order, more complicated structures.

The ready availability of these acyl bicyclic lactam precursors from chiral aminols is key to the success of the B/C/P strategy described in this article. The bicyclic lactams **1a** and **1b** can be generated easily from the condensation of (i) *R*-(6-hydroxymethy)-piperidinone and (ii) *R*-pyroglutaminol with benzaldehyde.[5] Followed by acylation with α-chloroformate to afford **2a** and **2b**.[6,7] These chiral acyl bicyclic lactams, by virtue of their susceptability towards enolate mediated nucleophilic reactions at the carbon α- to the amide bond are extremely popular intermediates to synthesize various nitrogen and oxygen heterocycles.[8] In our case we coupled them (**2a**/**2b**) with appropriate reagents *via* an array of efficient intermolecular reactions such as (i) Michael addition; (ii) aromatic nucleophilic substitution (S_NAr); and (iii) Mannich reaction, to generate more densely functionalized scaffolds. Finally, functional group (FG) pairing afforded skeletally and stereochemically diverse scaffolds containing, disparate physicochemical properties (Scheme 1).

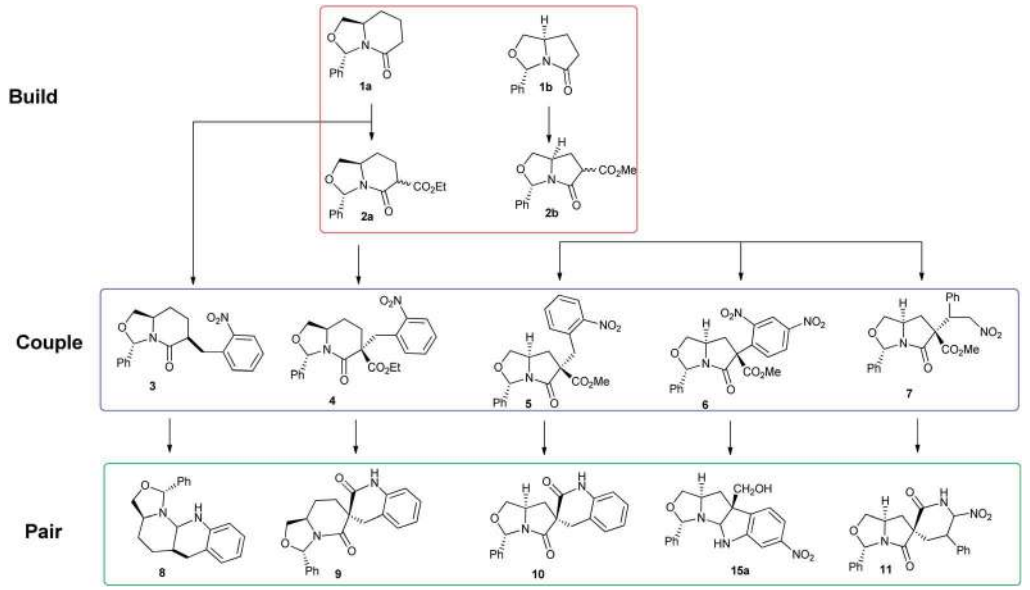
We wanted our scaffolds to abide by the "rule of three" as close as possible ($M < 300$; HBD ≤ 3 and HBA ≤ 3; $c \log P = 3$; number of rotatable bonds ≤ 3; polar surface area $= 60$ Å^2). These are acceptable med-chem attributes for creating fragment based libraries.[9] Chiral synthesis of only cyclotryptamines (**15a**/**15**) have been reported earlier.[10] However, to the best of our knowledge, this is the first B/C/P based DOS methodology that provides access to all of these structurally diverse molecular scaffolds through common intermediates (**1a** and **1b**).

Results and discussion

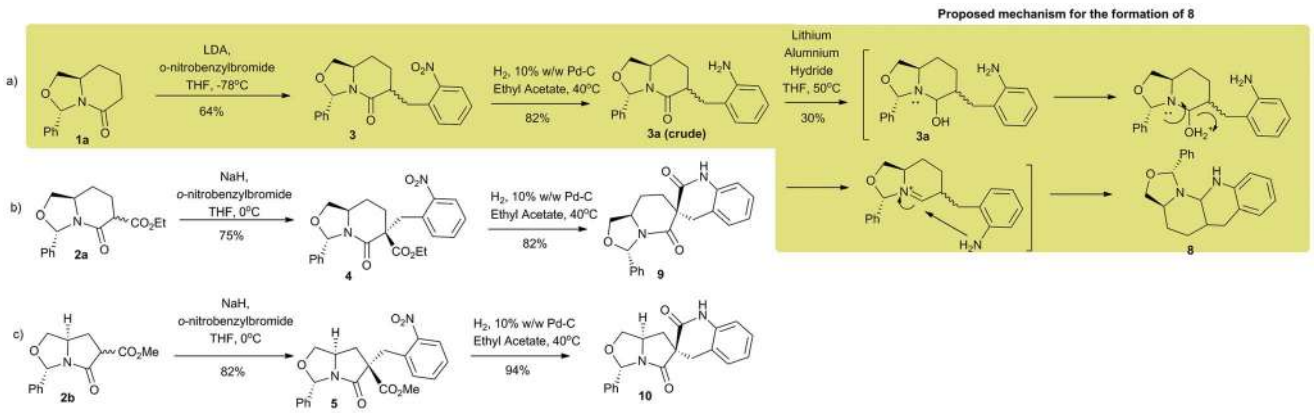
The coupling phase of the strategy initiated with simple alkylation of **1a**, **2a** and **2b** with *o*-nitroarylbenzyl bromide to generate the corresponding alkylated intermediates **3**, **4** and **5** respectively (Scheme 2). *Exo*-**3** which is obtained from

[a]*Department of Chemistry, Shiv Nadar University, Dadri, UP, India. E-mail: subhabrata.sen@snu.edu.in*
[b]*GVK Bioscience, 28A IDA Nacharam, Hyderabad, AP, India*
[c]*JNTU-H College, Nachupally, Karimnagar, AP, India*
[d]*Andhra University, Vishakhapatnam, AP, India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra47714b



Scheme 1 The build/couple/pair strategy for the synthesis of novel spiro- and fused scaffolds.



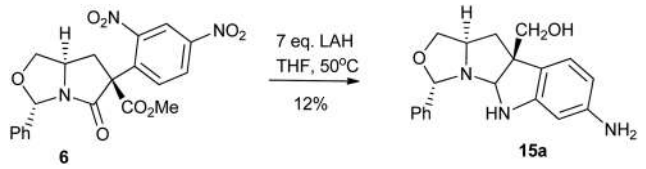
Scheme 2 Scaffold **8**, **9** and **10** from alkylation of chiral bicyclic lactam **1a**, **2a** and **2b**.

o-nitrobenzylation of **1a**, by flash column chromatography of 1 : 1 exo–endo mixture was reduced to amine under hydrogenation condition (10% w/w Pd–C, H_2 at atm. pr.) (Scheme 2). The crude amine was treated with lithium aluminium hydride (LAH) at 50° and was transformed into a tetrafused carbocycle **8**. We envisioned this conversion *via* an acyliminium cation mediated pathway as depicted in the Scheme 2. For representative purpose we chose to move ahead with the *exo*-diastereomer of **3** to generate **8**, as shown in Scheme 2.

Intermediates **4** and **5** were generated with high diastereoselectivity (diastereomeric ratio ~98 : 2). The relative configuration was established *via* NOE (refer ESI†). Hydrogenation of the aryl nitro groups, afforded the amines, which cyclize *in situ* with the built in adjacent electrophilic carbonyl carbon of the ester to generate the spiro-compounds **9** and **10** with no loss of chirality.

For the synthesis of cyclotryptamine **15a** we used arylated intermediate **6**, which was already reported in one of our early publications.[6] There we have also reported the relative configuration of **6** by single crystal X-ray analysis. We used **6** for the synthesis of spiroxoindolinones (*via* Pd–C mediated hydrogenation of the nitro group on the benzene ring that led to an *in situ* lactamization). Such hydrogenation was not an option for our present effort. We envisioned an approach that would initiate with the ester reduction followed by the reduction of the nitro group and finally acylimine cation mediated cyclization of **6**. Careful exploration of reagents (*viz.* diisobutylaluminium hydride [DIBAL-H, no conversion], Red-Al [no conversion], super hydride [no conversion], borane–DMS [no conversion]) prompted us to identify LAH as the most suitable reducing agent which facilitated this transformation to **15a**, all be it in extremely poor yield of 12% and 95 : 5 dr (Scheme 3).

To access **7**, chiral acyl bicyclic lactam **2b** was treated with NaH at 0 °C and the resulting enolate was reacted with nitrostyrene. It was generated in decent yield (~66%) and high diastereoselectivity (~95%). Finally using Mültstadt's

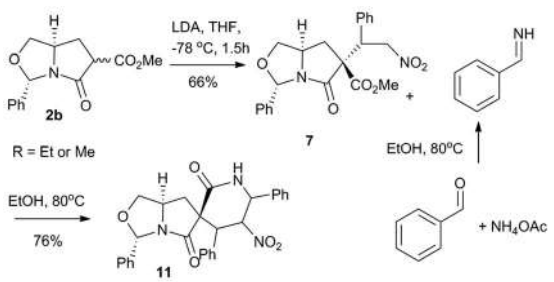


Scheme 3 Synthesis of cyclotryptamine **15a**.

nitro-Mannich lactamization cascade we could transform **7** into the 5-5-6 spiro-scaffold **11**.[11] In this sequence **7** is reacted with benzyl imine generated *in situ* by treating benzaldehyde with ammonium acetate in ethanol at 80 °C to afford the desired product **11** as a single diastereomer (~99%) with 76% yield. The relative configuration of the compound is derived from NOE/^{1}H NMR (refer ESI†) data and is depicted in the scheme below (Scheme 4).

Along with shape, a DOS library should be prudent to possess physical properties for screening and promote follow-up chemistry. Transformational handle such as an alcoholic group is deliberately incorporated in the final compounds (**12–16**). In addition to structural and stereochemical diversity, this is a third diversity attribute in our library imbibed *via* a "post-pairing phase." This polar, alcohol group augment the solubility of these compounds, and will also serve as hydrogen-bonding donors (HBD) and acceptors (HBA), thereby improving binding affinity against bio-macromolecular targets. Last but not the least, this functional group was envisioned to facilitate scaffold proliferation (growing and transformation) into drug-like compounds.

Molecular architecture and biological activity go hand in hand.[12] Hence, screening libraries with higher degree of built-in molecular-shape diversity transcribe into a greater probability of discovering compounds with biological activity. In order to assess the overall diversity level of our library we used a computational method based on the normalized principal moment of inertia (PMI) formalism of Sauer and Schwartz.[13] The PMI calculations involved aligning each molecule to the principal moment axes in SYBYL and the normalized PMI values were calculated by using in-house software. The commercial compounds were the FDA-approved drugs curated from the GOSTAR (GVK Bio Online Structure Activity Relationship)™ database.[14] These compounds along with our scaffolds were imported into DS 3.1 and converted into 3D structures. Energy minimization was performed for all of these



Scheme 4 Conversion of Michael adduct **7** into **11**.

3D structures to identify global/local minima by applying the CHARMm force field. The resulting 3D structures were used to calculate the three principal moments of inertia; the PMI values are sorted in ascending magnitude, that is, I1, I2, and I3. Normalized PMI ratios (NPR) were calculated by dividing the two smaller PMI values (I1 and I2) by the largest PMI value (I3) and generated two characteristic values for each compound (I1/I3 and I2/I3). These values were plotted against each other and the resulting graph formed an isosceles triangle that was defined by its three corners, wherein the vector [I1/I3, I2/I3] was equal to [1, 1], [0.5, 0.5], and [0, 1] (Fig. 1c) The three corners of the isosceles triangle of the PMI plot are dominated by rods, spheres, and discs, respectively (the shapes are representations of the overall shape of the constituent molecules). FDA approved drugs tend to occupy evenly over the shapes between rods and discs. Fig. 1 shows the coverage and distribution of majority of our scaffolds (**1b**, **8–9** and **12–16**).

Our collection of scaffolds can be classified into two types of architectures, spiro- (**9–11** and **13**, **14** and **16**), and fused (**8**, **12**, **15a** and **15**). The figure above illustrates a wide distribution of our scaffolds across the PMI plot. It is noteworthy that majority of the scaffolds (**1b** and **12–14**) from the post pair phase overlay on the same space as the FDA approved drugs, thereby emphasizing their drug like attributes. However there are quite a few outliers *viz.* **8**, **9**, **15** and **16**. Interestingly these outliers consisted of both the spiro- and fused compounds. The advent of these outliers indicates a novel therapeutic domain that is yet to be investigated. We further hope that the similar shapes of some of our scaffolds to those of FDA-approved drugs will increase the likelihood of discovering biologically relevant molecules by using this method.

The polar surface area (PSA) of a molecule is the surface sum of all polar atoms, *viz.* oxygen and nitrogen, and hydrogens attached to them. In pharmaceutical chemistry it is a commonly used metric for evaluating drug's cell permeability and an important contributor to ligand/receptor binding at active sites. In general molecules with a PSA > 140 Å is poor in permeating

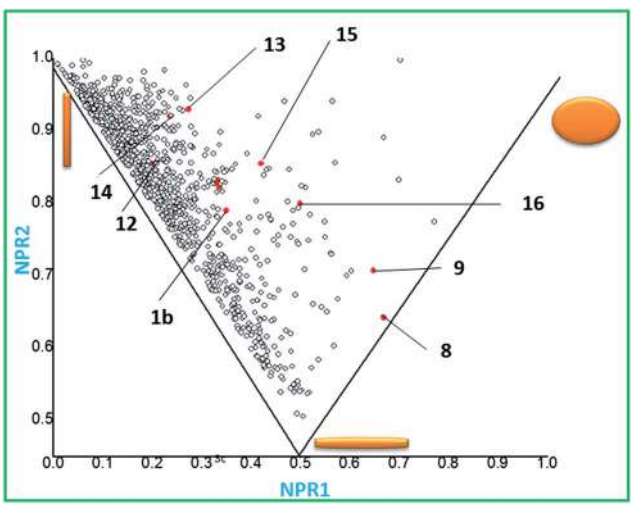


Fig. 1 Assessment of the diversity of our scaffolds *via* polar moment of inertia.

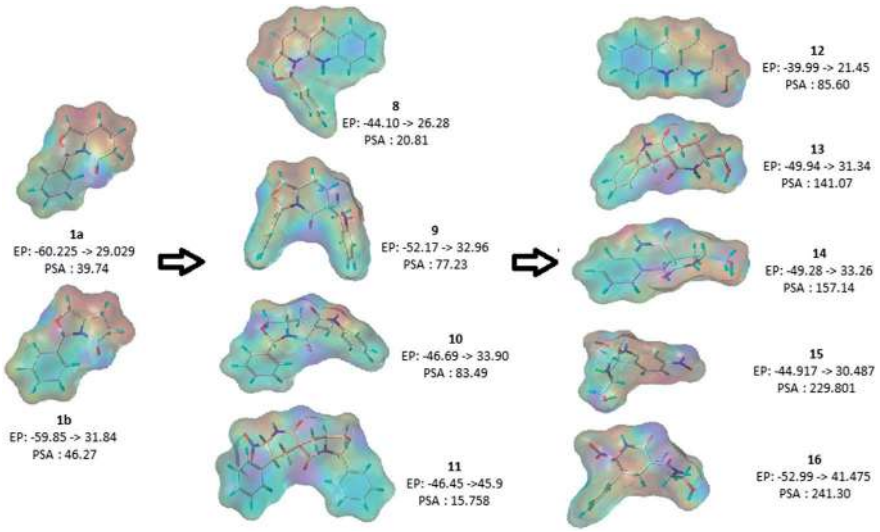


Fig. 2 Polar surface area and electrostatic potential of our scaffolds.

cell membranes. For molecules with PSA < 60 Å are more likely to penetrate the blood–brain barrier and are preferred to act on receptors in the central nervous system. In order to assess the diversity of these scaffolds w.r.t their polar surface area we calculated 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] A wide distribution of PSAs from 15 Å to 240 Å in addition, to diverse 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 (Fig. 2).

Finally in a bid to evaluate the diversity quotient of our scaffold library (green squares) we compared them in scattered plots against randomly selected compounds from FDA approved drugs (red circles), macrocyclic natural products (solid blue triangles) natural product database (blue triangles) and from commercial databases such as ChemDiv (green cross) and ChemBridge (blue square). The incorporation of these additional compound sets in the analysis enables us to compare the chemical space covered by the collections and also provides

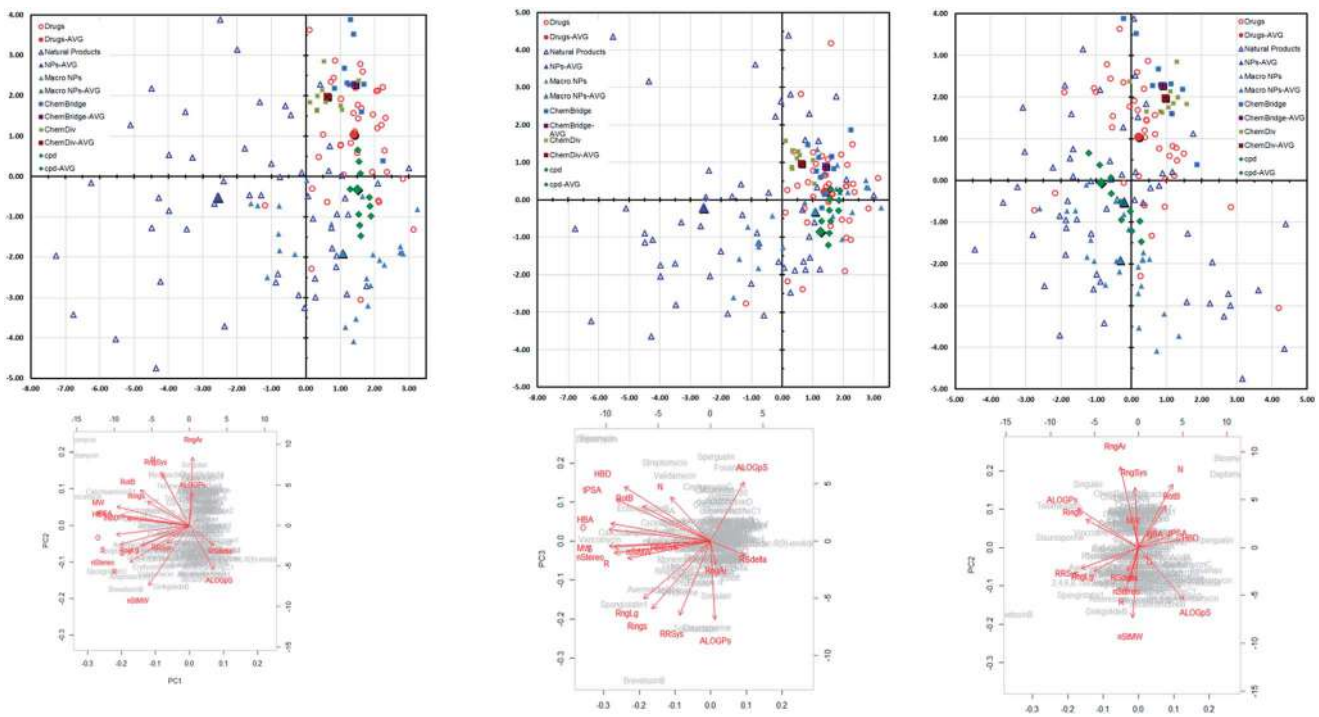
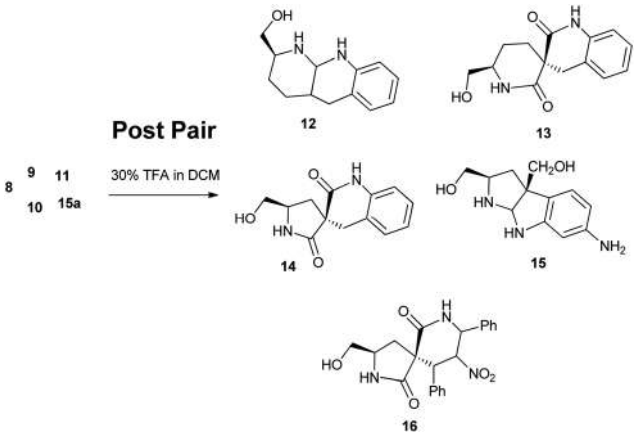


Fig. 3 Principal Component Analysis (PCA) to assess the diversity of our library against various chemical database.



Scheme 5 Post pairing of the scaffolds.

some perspective to the positions of the library compounds in chemical space with respect to known biologically active regions. 2D molecular descriptors (*via* MOE) *viz.* log *P*, PSA, HBA (hydrogen bond acceptor), HBD (hydrogen bond donor) and *etc.* of all these compounds were calculated, followed by principal component analysis (PCA) of the values were obtained.[16] Fig. 3 exhibits a scatter plot of the compound collections. From the plots it is quite obvious that our library compounds cover a relatively large area of chemical space, indicating the successful incorporation of a high degree of molecular diversity into the synthesis.

Conclusions

Herein we have reported B/C/P based facile DOS synthesis of novel and privileged spiro- and fused scaffolds from pyrroldine and piperidine based chiral auxiliaries. The diversity of scaffold library when assessed *via* PMI and PCA against FDA approved drugs demonstrated a wide coverage of chemical space. A post pairing phase generated scaffolds with polar handle that facilitates further proliferation of these scaffolds into novel drug like compounds. The apogee of our methodology is a three-step synthesis of ten distinct natural-product-inspired scaffolds. This methodology has excellent steps per scaffold efficiency of 1.7 whilst generating chemically complex molecules (Scheme 5).

Experimental section

General information

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with a magnetic stirrer. Reactive liquids were transferred by syringe or cannula and were charged to the reaction flask through rubber septa. Common chemicals were obtained from Sigma-Aldrich Chemical Company and used without purification. Compounds **1a**, **1b**, **2a**, **2b**, **3** and **6** were prepared by a standard literature protocol.[16] Lithium hexamethyldisilylamide (LDA) was obtained from Spectrochem Ltd. and used without purification. Tetrahydrofuran (THF) was freshly distilled prior to use from sodium and benzophenone ketyl under nitrogen and methylene chloride was freshly distilled from calcium hydride under nitrogen. Analytical thin layer chromatography was performed with Merck silica gel plates (0.25 mm thickness) with PF_{254} indicator. Compounds were visualized under UV lamp or by iodine treatment. Column chromatography was carried out on 60–120 mesh silica gel with technical grade solvents, which were distilled prior to use. ^{1}H NMR spectra were recorded on Bruker 300 Ultrashield™ at 300 MHz. ^{13}C NMR spectra were obtained on the same instrument at 75.5 MHz in $CDCl_3$ solution with tetramethylsilane (^{1}H NMR spectra) and [D_6]DMSO or $CDCl_3$ (^{13}C NMR spectra) as an internal reference, unless otherwise stated. Chemical shifts (δ) are reported in ppm. All ^{13}C NMR spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet.

Compound 4. A solution of monoacylated bicyclic lactam **2a** (443 mg, 1.53 mmol), was dissolved in THF (4 mL). Sodium hydride (60% in mineral oil) (55 mg, 2.29 mmol) was added to the reaction mixture at −5 °C. The mixture was stirred at 0 °C for 20 minutes. 2-Nitrobenzylbromide (1.99 mmol, 428 mg) was then added to the reaction mixture at the same temperature under N_2. The mixture was allowed warm to rt and was stirred for 1 h under N_2. Once TLC (thin layer chromatography) confirms the complete consumption of the starting material, the reaction mixture was quenched with water (10 mL). It was then diluted with ethyl acetate (10 mL) and the organic phase was separated, dried with anh. Na_2SO_4, concentrated *in vacuo* and subjected to flash column chromatography (eluted with 20% EtOAc in petroleum ether) to yield **5** (487 mg, 75%) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12–1.19 (t, 3H), 1.99–2.21 (m, 2H), 3.53–3.62 (m, 3H), 3.63–3.95 (m, 3H), 4.21–4.35 (m, 2H), 7.28–7.35 (m, 3H), 7.36–7.42 (m, 5H), 7.43–7.48 (m, 1H), 7.86–7.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.5, 135.2, 137.9, 129.7, 129.7, 128.7, 128.4, 126.0, 125.9, 88.3, 88.1, 71.7, 57.9, 56.9, 53.0, 51.8, 51.0, 27.6, 27.5; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{23}H_{24}N_2O_6$) requires (*m*/z) 425.1634 found (*m*/*z*) 425.50.

Compound 5. A solution of monoacylated bicyclic lactam **2b** (1.53 mmol, 400 mg), was dissolved in THF (4 mL). Sodium hydride (60% in mineral oil) (55 mg, 2.29 mmol) was added to the reaction mixture at −5 °C. The mixture was stirred at 0 °C for 20 minutes. 2-Nitrobenzylbromide (1.99 mmol, 428 mg) was then added to the reaction mixture at the same temperature under N_2. The mixture was allowed warm to rt and was stirred for 1 h under N_2. Once TLC (thin layer chromatography) confirms the complete consumption of the starting material, the reaction mixture was quenched with water (10 mL). It was then diluted with ethyl acetate (10 mL) and the organic phase was separated, dried with anh. Na_2SO_4, concentrated *in vacuo* and subjected to flash column chromatography (eluted with 20% AcOEt in pet. ether) to yield **5** (527 mg, 87%) as a colourless liquid. ^{1}H NMR (400 MHz, CD_3OD): δ 2.39–2.45 (m, 1H), 2.54–2.59 (m, 1H), 3.53–3.62 (m, 3H), 3.74 (s, 1H), 3.77–3.79 (s, 3H), 4.14–4.20 (m, 1H), 6.13 (s, 1H), 7.26–7.29 (m, 2H), 7.33–7.38 (m, 5H), 7.39–7.44 (m, 1H), 7.86–7.88 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.6, 172.5, 151.9, 139.4, 134.1, 133.7, 131.4, 129.8, 129.5, 129.4, 127.1, 125.8, 88.2, 72.9, 63.0, 57.8,

53.6, 35.7, 33.2; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{21}H_{20}N_2O_3$) requires (*m*/*z*) 397.1321, found (*m*/*z*) 397.02.

Compound 7. A solution of **2b** (200 mg, 0.76 mmol) in THF (2 mL) was added to a solution of 1.2 eq. of LDA (98 mg, 0.91 mmol) (freshly prepared from diisopropylamine and *n*-BuLi) at −78 °C. The mixture was stirred at −78 °C for 0.5 h. 1.5 eq. of nitrostyrene (171 mg, 1.14 mmol) was added drop wise at −78 °C under N_2. The mixture was allowed to stir at rt for 1 h under N_2 until the starting material was consumed by TLC analysis. The mixture was diluted with ethyl acetate, extracted with water (2 × 4 mL), dried with anh. Na_2SO_4 concentrated under reduced pressure. The resulting residue was purified by neutral alumina column chromatography (hexane–ethyl acetate = 80/20) to afford pure white solid (245 mg, 0.597 mmol) of **4**, with 78% yield. R_f = 0.6 (PE–AcOEt = 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 (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; HRMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{22}H_{23}N_2O_6$) requires (*m*/*z*) 411.1478, found (*m*/*z*) 411.1476.

Compound 8. Compound **3** (207.91 mg, 0.59 mmol) was added to a solution of 10% Pd–C (40 mg) in methanol (2 mL) at rt under N_2 and the mixture was hydrogenated at 20 psi over a period of 8 h at rt. The suspension was filtered through celite pad concentrated under reduced pressure to yield the crude amine **3a** which, was dissolved in THF (2 mL) and treated with LAH (1 M in THF) (23 mg, 0.60) at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 4 h. Once TLC indicates the total consumption of the starting material the reaction mixture was quenched with ethyl acetate (0.2 mL) filtered through celite pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by neutral alumina column chromatography (hexane–ethyl acetate = 80/20) to afford pure white solid (69 mg, 0.23 mmol), with 30% yield. R_f = 0.42 (hexane–EtOAc = 70 : 30). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62–2.15 (m, 5H), 2.72–2.85 (m, 3H), 3.42–3.52 (m, 1H), 3.78–3.81 (m, 1H), 3.95 (s, 1H), 7.25–7.30 (m, 5H), 7.42–7.48 (m, 1H), 7.51–7.59 (m, 1H), 7.82 (s, 1H), 8.12–8.15 (d, J = 4 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 134.3, 134.2, 129.2, 128.8, 128.6, 127.3, 127.4, 127.0, 62.7, 57.5, 50.9, 33.0, 29.7, 29.6; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{20}H_{22}N_2O$) requires (*m*/*z*) 307.1732 found (*m*/*z*) 306.94.

Compound 9. Compound **4** (200 mg, 0.47 mmol) was added to a solution of 10% Pd–C (20 mg) in methanol (2 mL) at rt under N_2 and the mixture was hydrogenated at 20 psi over a period of 6 h at rt. Once the reaction is over, the suspension was filtered through celite pad, concentrated *in vacuo*. The crude was purified by flash column chromatography with 25% EtOAc–hexane as eluent to afford **9** as colourless gummy solid (134 mg, 0.38 mmol) in 82% yield. R_f = 0.35 (hexane–EtOAc = 75 : 25). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51–1.72 (m, 2H), 1.95–2.15 (m, 4H), 2.81–2.88 (d, J = 24 Hz, 1H), 3.58–3.68 (t, J = 12 Hz, 1H), 3.78–3.82 (d, J = 18 Hz, 1H), 3.95–4.12 (m, 1H), 4.32–4.39 (t, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 6.45 (s, 1H), 6.78–6.88 (d, J = 8 Hz, 1H), 6.98–7.02 (m, 1H), 7.16–7.19 (m, 2H), 7.28–7.42 (m, 3H), 7.51–7.58 (m, 2H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.15, 167.30, 137.99, 135.96, 128.88, 128.68, 128.50, 127.69, 126.73, 126.40, 123.46, 121.54, 114.95, 89.25, 72.64, 56.30, 50.10, 34.72, 28.01, 22.50; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{21}H_{20}N_2O_3$) requires (*m*/*z*) 349.1474, found (*m*/*z*) 349.0.

Compound 10. Compound **5** (0.505 mmol, 200 mg) was added to a solution of 10% Pd–C (20 mg) in methanol (2 mL) at rt under N_2 and the mixture was hydrogenated at 20 psi over a period of 6 h at rt. Once the reaction is over, the suspension was filtered through celite pad, concentrated *in vacuo*. The crude was purified by flash column chromatography with 25% EtOAc–hexane as eluent to afford **10** as yellowish gummy solid (160 mg, 0.48 mmol) in 94% yield. R_f = 0.45 (hexane–EtOAc = 75 : 25). ^{1}H NMR (300 MHz, DMSO-D_6): δ 2.15–2.21 (m, 1H), 2.59–2.69 (m, 2H), 3.16–3.20 (m, 1H), 3.51–3.61 (t, J_1 = 6 Hz, J_2 = 8 Hz, 1H), 4.18–4.38 (m, 2H), 6.12 (s, 1H), 6.82–6.95 (m, 2H), 7.05–7.19 (m, 2H), 7.32–7.42 (m, 5H), 10.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) 177.5, 140.2, 138.8, 130.1, 129.7, 129.3, 128.9, 127.4, 124.1, 122.5, 116.0, 88.6, 72.7, 57.6, 56.5, 49.8, 49.7; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{20}H_{18}N_2O_3$) requires (*m*/z) 335.1317, found (*m*/z) 335.01.

Compound 11. Nitro adduct **7** (410 mg, 1.00 mmol), ammonium acetate (5 eq.) and benzaldehyde (0.15 mL, 1.5 mmol) were taken in ethanol (5.4 mL) under nitrogen. The resulting mixture was heated in a sealed vessel and refluxed for 10 h. After which it was cooled to rt. The mixture was diluted with water and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (pet. ether–ethyl acetate = 1/1) to afford 130 mg of pure product **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78–1.82 (t, J = 8 Hz, 1H), 2.01–2.15 (dd, J = 4 Hz, 1H), 2.92–3.01 (m, 1H), 3.81–3.88 (t, J = 4 Hz, 1H), 3.99–4.10 (d, J = 12 Hz, 1H), 4.16–4.21 (m, 1H), 5.10–5.15 (d, J = 1.8 Hz, 1H), 5.98 (s, 1H), 6.51–6.61 (m, 1H), 7.28–7.52 (m, 15H); ^{13}C NMR; 170.2, 161.8, 135.8, 133.1, 130.2, 129.1, 128.8, 128.5, 127.4, 127.3, 127.1, 115.9, 115.7, 115.6, 114.9, 114.7, 92.1, 60.2, 56.1, 53.9, 52.8, 36.7, 28.4, 28.1; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{28}H_{25}N_3O_5$) requires (*m*/*z*) 484.1794, found (*m*/*z*) 483.79.

Compound 12. Compound **8** (153.2 mg, 0.5 mmol) was dissolved in DCM (1 mL) treated with TFA (0.2 mL) at 0 °C and stirred for 1 h at rt. The mixture diluted with dichloromethane (DCM) (10 mL) and was extracted with water (2 × 10 mL). The organic phase was dried (Na_2SO_4), concentrated *in vacuo* and subjected to flash column chromatography (eluted with 70% AcOEt in pet. ether) to yield **12** (60 mg, 55%) as a greyish solid. R_f = 0.12 (hexane–EtOAc = 70 : 30). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72–1.98 (m, 4H), 2.72–2.85 (m, 3H), 3.42–3.52 (m, 1H), 3.81 (s, 2H), 7.51–7.59 (m, 1H), 7.61–7.68 (m, 1H), 7.72–7.78 (m, 1H), 7.81–7.84 (m, 1H), 8.22–8.32 (m, 1H), 9.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.8, 128.5, 127.4, 127.3, 126.4, 124.6, 124.5, 58.2, 55.9, 33.7, 33.1, 27.4, 25.8, 25.2, 23.2; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{13}H_{18}N_2O$) requires (*m*/*z*) 219.1419, found (*m*/*z*) 219.04.

Compound 13. Compound **9** (174 mg, 0.5 mmol) was dissolved in DCM (1 mL) treated with TFA (0.2 mL) at 0 °C and stirred for 1 h at rt. The mixture diluted with dichloromethane (DCM) (10 mL) and was extracted with water (2 × 10 mL). The organic phase was dried (Na_2SO_4), concentrated *in vacuo* and subjected to flash column chromatography (eluted with 70% EtOAc in hexane) to yield **13** (143 mg, 55%) as a white solid. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.88–2.12 (m, 2H), 3.10–3.18 (m, 2H), 3.31–3.42 (m, 1H), 3.55–3.75 (t, J = 14 Hz, 1H), 4.02–4.18 (m, 1H), 4.31–4.41 (m, 1H), 4.42–4.52 (d, J = 10 Hz, 2H), 4.78–4.81 (m, 1H), 7.02–7.42 (m, 5H), 8.02–8.38 (bs, 1H); LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{14}H_{16}N_2O_3$) requires (m/z) 261.1161, found (m/z) 261.32.

Compound 14. Compound **10** (167.2 mg, 0.5 mmol) was dissolved in DCM (1 mL) treated with TFA (0.2 mL) at 0 °C and stirred for 1 h at rt. The mixture diluted with dichloromethane (DCM) (10 mL) and was extracted with water (2 × 10 mL). The organic phase was dried (Na_2SO_4), concentrated *in vacuo* and subjected to flash column chromatography (eluted with 70% AcOEt in pet. ether) to yield **14** (68 mg, 55%) as a white solid. ^{1}H NMR (300 MHz, DMSO-D_6) δ 1.87–1.94 (m, 1H), 2.07–2.13 (m, 1H), 3.14–3.19 (q, 2H, J = 5.1 Hz), 3.32–3.39 (m, 1H), 3.51–3.57 (m, 1H), 4.75–4.79 (t, 1H, J = 5.7 Hz), 6.83–6.93 (m, 2H), 7.11–7.16 (m, 2H), 7.95 (bs, 1H), 10.23 (s, 1H), 10.85–11.1 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 35.0, 36.5, 52.7, 55.0, 66.4, 116.7, 123.2, 124.2, 129.3, 130.0, 138.7, 173.5, 178.3; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{13}H_{14}N_2O_3$) requires (m/z) 247.1004, found (m/z) 247.2.

Compound 15a. To an ice-cooled solution of compound **6** (166.2 mg, 0.389 mmol) in dry THF (3 mL) was added LAH (98 mg, 2.55 mmol) under a stream of nitrogen gas in three almost-equal portions. The ice bath was removed and the reaction mixture was stirred at rt for 1 h and then at 50 °C for next 2 h, by which time, complete consumption of compound **6** had occurred (TLC analysis). Then, the reaction mixture was cooled to 0 °C and EtOAc (3 mL) was added to quench any unreacted LAH. The solution was filtered through a celite plug and thoroughly washed with EtOAc. The filtrate and the washings (about 15 mL) were combined and washed with water (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a crude material (220 mg) that was purified by preparative HPLC (Waters 3100, mass trigger) to afford the desired compounds **15a** (15 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–1.81 (m, 1H), 2.01–2.36 (m, 2H), 3.52–3.78 (m, 2H), 3.81–4.01 (m, 4H), 4.81 (s, 1H), 6.38–6.42 (d, J = 16 Hz, 1H), 6.61–6.75 (m, 1H), 6.88–6.95 (d, 1H), 6.94–7.18 (m, 1H), 7.31–7.42 (m, 5H); ^{13}C NMR 147.0, 139.3, 138.4, 135.7, 128.9, 128.8, 128.4, 127.7, 124.4, 121.5, 118.1, 114.1, 106.4, 92.6, 66.7, 62.9, 60.9, 52.1, 47.8, 46.2, 45.9, 22.7, 21.9, 21.4, 14.1, 8.6; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{19}H_{21}N_3O_2$) requires (m/z) 324.1634, found (m/z) 324.09.

Compound 15. Compound **15a** (12 mg, 0.05 mmol) was dissolved in DCM (1 mL) treated with TFA (0.2 mL) at 0 °C and stirred for 1 h at rt. The mixture diluted with dichloromethane (DCM) (10 mL) and was extracted with water (2 × 10 mL). The organic phase was dried (Na_2SO_4), concentrated *in vacuo* and subjected to flash column chromatography (eluted with 70% AcOEt in pet. ether) to yield **15** (10 mg, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91–2.01 (m, 1H), 2.61–2.79 (m, 1H), 2.81–2.88 (m, 1H), 2.90–3.01 (m, 1H), 3.22–3.32 (d, J = 12 Hz, 1H), 3.58–3.65 (m, 1H), 3.81–3.88 (m, 1H), 6.78–6.84 (m, 12H), 6.99–7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 136.4, 128.9, 128.6, 128.5, 128.4, 127.8, 124.0, 119.8, 111.7, 63.2, 60.8, 54.8, 51.4, 45.9, 29.6, 19.0.

Compound 16. Compound **11** (241 mg, 0.5 mmol) was dissolved in DCM (7 mL) treated with trifluoroacetic acid (TFA) (1.5 mL) at 0 °C and stirred for 1 h at rt. The mixture diluted with dichloromethane (DCM) (25 mL) and was extracted with water (2 × 30 mL). The organic phase was dried (Na_2SO_4), concentrated *in vacuo* and subjected to flash column chromatography (eluted with 70% AcOEt in pet. ether) to yield **16** (130 mg, 80%) as a colourless oil. ^{1}H NMR (300 MHz, DMSO-D_6) 1.41–1.49 (m, 1H), 1.81–1.86 (m, 1H), 2.82–2.92 (m, 1H), 3.80–3.85 (m, 1H), 4.09–4.15 (m, 1H), 4.19–4.21 (d, J = 6 Hz, 1H), 4.98–5.01 (m, 1H), 6.36–6.42 (t, J = 18 Hz, 1H), 7.21–7.59 (m, 10H), 7.82 (s, 1H). ^{13}C NMR 170.5, 164.2, 139.1, 135.8, 128.1, 127.9, 127.6, 126.8, 126.5, 119.1, 118.9, 115.2, 93.8, 63.1, 55.9, 53.6, 53.5, 52.1, 37.6, 29.3, 29.2; LCMS (ES+) exact mass calculated for $[M + H]^+$ ($C_{21}H_{21}N_3O_5$) requires (m/z) 396.1481, found (m/z) 396.1.

Acknowledgements

We acknowledge GVK Bioscience for financial support.

References

1 (*a*) G. B. Bauer and L. F. Povirk, *Nucleic Acids Res.*, 1997, **25**, 1211–1218; (*b*) L. H. Hurley, *Nat. Rev. Cancer*, 2002, **2**, 188–200; (*c*) J. Reedijk, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 3611–3616; (*d*) B. Clement and F. N. Jung, *Drug Metab. Dispos.*, 1994, **22**, 486–497; (*e*) W. A. Remers, *The Chemistry of Antitumor Antibiotics*, Wiley, New York, 1979, p. 1; (*f*) L. D. Williams, M. Egli, G. Qi, P. Bash, G. A. van der Marel, J. H. van Boom, A. Rich and C. A. Frederick, *Proc. Natl. Acad. Sci. U. S. A.*, 1990, **87**, 2225–2229; (*g*) R. Sinha, M. Hossain and G. S. Kumar, *DNA Cell Biol.*, 2009, **28**(4), 209–219; (*h*) E. H. Bayne and R. C. Allshire, *Trends Genet.*, 2005, **21**, 370; (*i*) M. C. Jovanovic and M. O. Hengartner, *Oncogene*, 2006, **25**, 6176; (*j*) G. L. Sen and H. M. Blau, *FASEB J.*, 2006, **20**, 1293; (*k*) L. Manche, S. R. Green, C. Schmedt and M. B. Mathews, *Mol. Cell. Biol.*, 1992, **12**, 5238; (*l*) C. A. Sledz, M. Holko, M. J. de Veer, R. H. Silverman and B. R. Williams, *Nat. Cell Biol.*, 2003, **5**, 834; (*m*) M. J. Fedor and J. R. Williamson, *Nat. Rev. Mol. Cell Biol.*, 2005, **6**, 399; (*n*) J. Drews, *Nat. Biotechnol.*, 1996, **14**, 1516; (*o*) J. Drews and S. Ryser, *Nat. Biotechnol.*, 1997, **15**, 1318; (*p*) A. L. Hopkins and C. R. Groom, *Nat. Rev. Drug Discovery*, 2002, **1**, 727; (*q*) D. S. Wishart, C. Knox, A. C. Guo, S. Shrivastava, M. Hassanali, P. Stothard, P. Z. Chang and J. Woolsey, *Nucleic Acids Res.*, 2006, **34**, D668.

2 (*a*) T. E. Nielsen and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2008, **47**, 48–56; (*b*) B. E. Evans, K. E. Rittle, M. G. Bock,

R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235–2246; (*c*) S. L. Schreiber, *Science*, 2000, **287**, 1964–1969.

3 (*a*) G. L. Thomas, R. J. Spandl, F. G. Glansdrop, M. Welch, A. Bender, J. Cockfield, J. A. Lindsay, C. Bryant, D. F. Brown, O. Loiseleur, H. Rudyk, M. Ladlow and D. R. Spring, *Angew. Chem.*, 2008, **120**, 2850–2854; *Angew. Chem., Int. Ed.*, 2008, **47**, 2808–2812; (*b*) H. An, S.-J. Eum, M. Koh, S. K. Lee and S. B. Park, *J. Org. Chem.*, 2008, **73**, 1752–1761; (*c*) H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen and M. Shair, *J. Am. Chem. Soc.*, 2001, **123**, 6740–6741; (*d*) D. B. Ramachary, C. Venkaiah, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2009, **7**, 2053–2062.

4 (*a*) T. Uchida, M. Rodriquez and S. L. Schreiber, *Org. Lett.*, 2009, **11**(7), 1559–1562; (*b*) M. E. Fitzgerald, C. A. Mulrooney, J. R. Duvall, J. Wei, B.-C. Suh, L. B. Akella, A. Vrcic, L. A. Marcaurelle, E. Ascic, S. T. Le Quement, M. Ishoey, M. Daugaard and T. E. Nielsen, *ACS Comb. Sci.*, 2012, **14**(4), 253–257.

5 (*a*) C. E. Mills née Davis, T. D. Heightman, S. A. Hermitage, M. G. Moloney and G. A. Woods, *Tetrahedron Lett.*, 1998, **39**(9), 1025–1028; (*b*) S. A. Hermitage and M. G. Moloney, *Tetrahedron: Asymmetry*, 1994, **5**(8), 1463–1464; (*c*) J. H. Bailey, A. T. J. Byfield, P. J. Davis, A. C. Foster, K. Prout, M. Leech, M. G. Moloney and M. Mueller, *Perkin 1*, 2000, **12**, 1977–1982.

6 S. Sen, V. R. Potti, R. Surakanti, Y. L. N. Murthy and R. Pallepogu, *Org. Biomol. Chem.*, 2011, **9**, 358–360.

7 V. S. B. Damerla, C. Tulluri, R. Gundla, L. Naviri, U. Adepally, P. S. Iyer, Y. L. N. Murthy, N. Prabhakar and S. Sen, *Chem. – Asian J.*, 2012, **7**, 2351–2360.

8 (*a*) J. E. Baldwin, M. G. Moloney and S. B. Shim, *Tetrahedron Lett.*, 1991, **32**(10), 1379–1380; (*b*) J. H. Bailey, M. J. Beard, T. D. Cherry, M. G. Moloney, S. B. Shim, K. A. Statham, M. J. Bamford and B. R. Lamont, *Tetrahedron*, 1996, **52**(10), 3719–3740; (*c*) A. R. Cowley, T. J. Hill, M. G. Moloney, R. D. Stevenson, A. L. Thomson and P. Kocis, *Org. Biomol. Chem.*, 2011, **9**(20), 7042–7056; (*d*) M. Amat, J. Hidlago and J. Bosch, *Tetrahedron: Asymmetry*, 1996, **7**(6), 1591–1594; (*e*) M. Amat, N. Llor, J. Hidalgo, J. Bosch, E. Molins and C. Miravitlles, *Tetrahedron: Asymmetry*, 1996, **7**(9), 2501–2504.

9 (*a*) H. Jhoti, G. Williams, D. C. Rees and C. W. Murray, *Nat. Rev. Drug Discovery*, 2013, **12**, 644–679; (*b*) M. Baker, *Nat. Rev. Drug Discovery*, 2013, **12**, 5–7; (*c*) M. Congreve, R. Carr, C. Murray and H. Jhoti, *Drug Discovery Today*, 2003, **8**, 867–877.

10 (*a*) J. E. DeLorbe, D. Horne, R. Jove, S. M. Mennen, S. Nam, F.-L. Zhang and L. E. Overman, *J. Am. Chem. Soc.*, 2013, **135**(10), 4117–4128; (*b*) L. E. Overman and Y. Shin, *Org. Lett.*, 2007, **9**(2), 339–341; (*c*) H. Song, J. Yang, W. Chen and Y. Qin, *Org. Lett.*, 2006, **8**(26), 6011–6014; (*d*) A. Coste, J. Kim, T. C. Adams and M. Movassaghi, *Chem. Sci.*, 2013, **4**, 3191–3197; (*e*) Q. Wei, Y.-Y. Wang, Y.-L. Du and L.-Z. Gong, *Beilstein J. Org. Chem.*, 2013, **9**, 1559–1564; (*f*) M. S. Morales-Rios, N. F. Santos-Sanchez and P. Joseph-Nathan, *J. Nat. Prod.*, 2002, **65**(2), 136–141; (*g*) P. L. Julian and J. Pikl, *J. Am. Chem. Soc.*, 1934, **56**(8), 1797–1801; (*h*) P. L. Julian and J. Pikl, *J. Am. Chem. Soc.*, 1935, **57**(3), 539–544.

11 (*a*) P.-Q. Huang, Z.-Q. Guo and Y.-P. Ruan, *Org. Lett.*, 2006, **8**(7), 1435–1438; (*b*) S. M.-C. Pelletier, P. C. Ray and D. J. Dixon, *Org. Lett.*, 2009, **11**(20), 4512–4515; (*c*) F. Xu, E. Corley, J. A. Murry and D. M. Tschaen, *Org. Lett.*, 2007, **9**(14), 2669–2672; (*d*) P. S. Hynes, P. A. Stupple and D. J. Dixon, *Org. Lett.*, 2008, **10**(7), 1389–1391.

12 (*a*) R. M. Sweet and L. F. Dahl, *J. Am. Chem. Soc.*, 1970, **92**(18), 5489–5507; (*b*) L. Pauling, *Chem. Eng. News*, 1946, **24**(10), 1375–1377; (*c*) F. Diederich, *Chimia*, 2001, **55**, 821–827.

13 W. H. B. Sauer and M. K. Schwartz, *J. Chem. Inf. Model.*, 2003, **43**, 987–1003.

14 Proprietary Database of GVK Bioscience, 28A, IDA Nacharam, Hyderabad, Andhra Pradesh, India.

15 H. Pajouhesh and G. R. Lenz, *NeuroRx*, 2005, **2**, 541–553.

16 Stable 3D structures of all compounds were used to calculate their 2D-med-chem distributors, such as molecular weight, number of hydrogen-bond donors (HBD), number of hydrogen bond acceptors (HBA), $A \log P$, $\log D$, polar surface area (PSA) and *etc.*, these values were calculated by using Discovery Studio 3.1 (Accelrys Inc.).