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PAPER

Inter- and intramolecular Mitsunobu reaction and metal complexation study: synthesis of *S*-amino acids derived chiral 1,2,3,4-tetrahydroquinoxaline, benzo-annulated [9]-N_3 peraza, [12]-N_4 peraza-macrocycles†

Krishnananda Samanta,[a] Nitin Srivastava,[b] Satyen Saha[b] and Gautam Panda*[a]

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Substituted 1,2,3,4-tetrahydroquinoxaline, benzo-annulated unsymmetrical chiral [9]-N_3 peraza, and [12]-N_4 peraza-macrocycles have been synthesized employing an inter- and intramolecular Mitsunobu reaction from an amino acid derived common synthetic intermediate **3**. The metal complexation study of these macrocycles has been investigated by UV-visible spectroscopic technique with binding constant (K_b) value 1.84×10^3 dm^3 mol^{-1} using the Benesi–Hildebrand equation and a Gibbs free energy (ΔG) −19.4 kJ mol^{-1} at 35 °C for **14d** with Co^{2+}. The binding properties of the metal were dependent on the structure of polyaza-macrocycles that were confirmed by the DFT optimized structure of two macrocycles. A detailed investigaton of UV-visible spectra of macrocycles and their complete interpretation with the help of TD-DFT along with the frontier molecular orbital calculations are presented.

Introduction

Substituted 1,2,3,4-tetrahydroquinoxaline core is very a important structural unit, exhibiting a wide range of biological activities such as prostaglandin D2 receptor[1] and vasopressin V2 receptor antagonists.[2] A common method to synthesize tetrahydroquinoxalines involves the reduction of quinoxalines,[3] giving a mixture of diastereoisomers. Asymmetric hydrogenation of quinoxalines in the presence of a chiral catalyst or ligand is also important for the synthesis of optically active tetrahydro-quinoxalines.[4] An alternatative strategy involves the Pd catalyzed reaction of 1,4-butenediols and acetates with 1,2-diaminobenzene furnishing 2-vinyl-1,2,3,4- tetrahydroquinoxalines.[5] However one of the major drawbacks of this strategy is that it is only applicable to symmetrically substituted 1,2-diaminobenzene. Furthermore, other methods involved intermolecular Michael additions,[6] the reduction of nitroarenes and S_N2 cyclization with leaving groups,[7,8] tandem reduction-reductive amination reactions.[9] Eary and co-workers have described the Cp*Ir-complex mediated hydrogen transfer *N*-heterocyclization of anilino alcohols.[10] High temperature and long reaction time are generally required in these methods.

Design and synthesis of chiral macrocycles are important areas of research because of their diverse range of applications such as enantiomeric recognition,[11] asymmetric catalysis[12] and complex formation with transition metal ions.[13] The azamacrocycles 1,4,7-triazacyclononanes have drawn much attention, because of their ability to bind with transition metal ions.[14] Due to the ability to bind with high oxidation state metal ions, 1,4,7-triazacyclononanes are used as redox metalloenzyme mimic,[15] oxidative catalysts for organic transformations,[16] hydrolytic agents for the non-oxidative cleavage of DNA[17] and RNA.[18] Thus, an efficient synthetic route is highly desirable for accessing these chiral 1,4,7-triazacyclononanes. Careful literature search reveals that there are only few synthetic approaches for chiral symmetrical and unsymmetrical 1,4,7-triazacyclononanes[19] and other peraza-macrocycles.[20] Most of the reported procedures used Richman–Atkins cyclization[21] strategy to synthesize chiral 1,4,7-macrocycles. The yield of the reaction is not satisfactory and also high temperature is required. In some cases, ring cyclization has failed.[19a] Similarly, 12-membered 1,4,7,10-tetraaza-macrocycles also have the ability to stabilize high oxidation state metal ions[22,23] The metal complexes of these macrocycles are known to catalyze alkene epoxidation, electrochemical epoxide carboxylation and intramolecular reductive cyclization.[24]

We have been working on the synthesis and biology of *S*-amino acids-based chiral heterocycles and natural product-like molecules.[25] From our previous knowledge,[25k] the Mitsunobu approach has been utilized for the construction of enatiomerically pure amino acids-derived tetrahydroquinoxaline derivatives. Moreover, the Mitsunobu reaction offers the advantage of

[a]*Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow, 226001 UP, India. Fax: 91-522-2623405; Tel: 91-522-2612411-18, Ext. 4385, 4603*
[b]*Department of Chemistry, Banaras Hindu University, Varanasi, 221 005 UP, India. E-mail: gautam.panda@gmail.com, gautam_panda@cdri.res.in*

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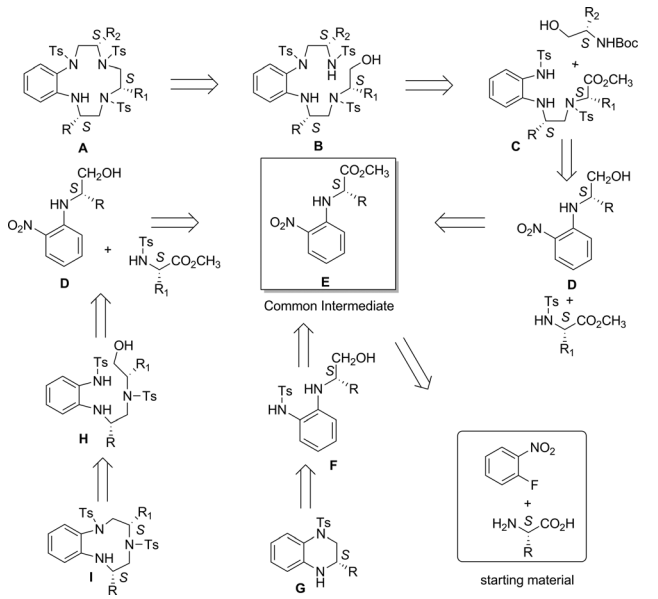


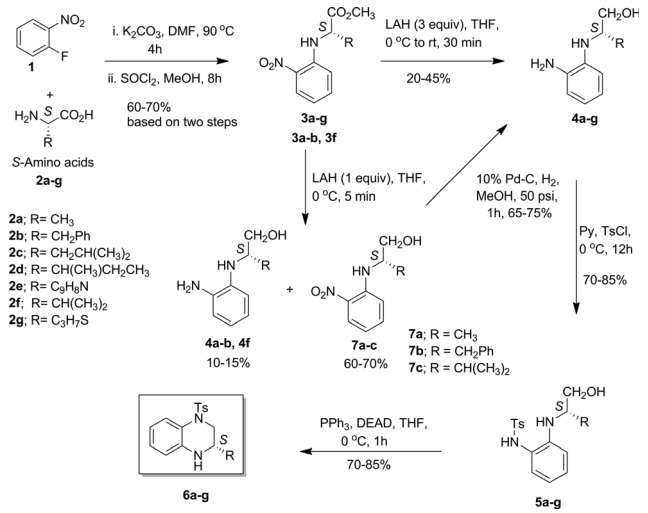
Scheme 1 Retro synthetic analysis of substituted-1,2,3,4-tetrahydroquinoxalines, benzo-annulated chiral [9]-N_3 peraza- and [12]-N_4 peraza-macrocycles.

mild reaction conditions with a short reaction time giving rise to products with excellent yields. Herein, we report the utility of the Mitsunobu approach for the synthesis of tetrahydroquinoxalines and its versatility for accessing new types of unsymmetrical chiral benzo-annulated triaza- and tetraaza-macrocycles derived from *S*-amino acids and the metal complexation study of these macrocycles towards transition and alkaline-earth metal ions by a UV-vis technique with binding constant K_b and Gibbs free energy ΔG values.

Results and discussion

Retrosynthetic analysis and strategy

From a retrosynthetic point of view (Scheme 1), amino acids-based chiral polycycles could be synthesized from a common intermediate **E**. The substituted-1,2,3,4-tetrahydroquinoxalines **G** could be obtained from *N*-Ts-anilino carbinol **F** through intramolecular Mitsunobu cyclization. The anilino carbinol **F** can be obtained from LAH reduction of a common intermediate **E** followed by tosylation. Benzo-annulated triaza-macrocycles **I** could be prepared through an intramolecular Mitsunobu cyclization from an intermediate **H** which could be easily prepared again through an intermolecular Mitsunobu reaction between intermediate **D** and *N*-Ts-amino ester followed by selective ester reduction. Benzo-annulated tetraaza-macrocycles **A** can be easily constructed from **B** through intramolecular Mitsunobu cyclization. **B** could be easily prepared through intermolecular Mitsunobu cyclization of **C** with Boc-protected amino alcohol followed by Boc-deprotection, tosylation and LAH reduction of the ester group. The intermediate **C** can be synthesized easily from **D** through intermolecular Mitsunobu cyclization with *N*-Ts-amino esters. The common intermediate **E** could be easily prepared from S_NAr reaction between commercially available *ortho*-nitrofluorobenzene and amino acids.



Scheme 2 Synthesis of (*S*)-3-s-1-tosyl-1,2,3,4-tetrahydroquinoxalines **6a–g**.

Synthesis of (*S*)-3-substituted-1-tosyl-1,2,3,4-tetrahydroquinoxalines

S-Amino acids and substituted benzene derivatives were used as building blocks for the synthesis of substituted tetrahydroquinoxalines, (Scheme 2). *S*-Amino acids **2a–g** were reacted with *ortho*-nitrofluorobenzene *via* a S_NAr pathway in the presence of K_2CO_3 and DMF at 90 °C to afford 2-nitrobenzene protected amino acids. These amino acid derivatives were converted to their methyl esters **3a–g** in the presence of $SOCl_2$ and MeOH. In addition, it was interesting to know whether any racemization of the amino acids occurred upon nucleophilic aromatic substitution. The chiral HPLC of **3b** and **3f** showed that the nucleophilic aromatic substitution of amino acids on *ortho*-nitrofluorobenzene occurred without any racemization (see ESI).† We used reference compounds {mixture of *S*-**3b** and its enantiomer *R*-**3b**} to prove the condition that was appropriate for the separation of racemic compounds. The lithium aluminum hydride reduction of **3a–g** was interesting.

When 1 equiv of LAH was used at 0 °C in dry THF, the ester was reduced to carbinol along with formation of anilino carbinols in 5 min (10–15% yield). Use of 3 equiv of LAH from 0 °C to room temperature in dry THF for half an hour furnished desired anilino carbinols in 20–45% yield. Alternatively, anilino carbinols could be synthesized from ester reduction of **3a–g** followed by hydrogenolysis (10% Pd/C) of the nitro group. It is noted, a successful Mitsunobu reaction is dependent on the pK_a associated with the incoming nucleophile and is independent of the nucleophilicity of the nucleophile.[26] Thus, the amine functionality of anilino carbinol was selectively converted to its tosyl derivative by treatment with TsCl in pyridine at 0 °C for 12 h (kept in refrigerator) in order to make its proton acidic for Mitsunobu reaction. Interestingly, the tosylated product of the primary carbinol was not detected although primary carbinol was very reactive, indicating selectivity on aromatic amine functionality. The intramolecular Mitsunobu[27] cyclization between the activated sulfonamide and primary carbinol of **5a–g** in the presence of diethylazodicarboxylate (DEAD), triphenylphosphine (PPh_3)

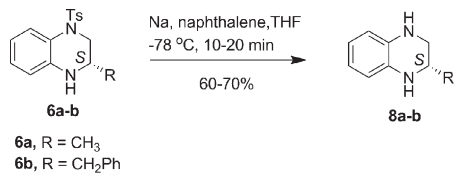
at 0 °C furnished enatiomerically pure substituted 1,2,3,4-tetrahydroquinoxalines **6a–g** (70–85%) along with 8–16% overall yield. The tosyl group of the selected molecules **6a–b** were deprotected (Scheme 3) by using sodium naphthalenide [28] in dry THF with 60–70% yield and the overall yield was 10–11%.

Synthesis of benzo-annulated chiral [9]-N_3 peraza-macrocycles

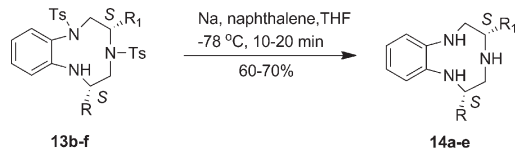
After a successful synthesis of enantiomerically pure 3-substituted-1-(toluene-4-tosyl-1,2,3,4-tetrahydro quinoxalines *via* Mitsunobu cyclization, the advanced synthetic intermediate **7a–c** used in (Scheme 4), was utilized for the construction of benzo-annulated chiral [9]-N_3 peraza-macrocycles. Tosyl derivatives of amino acids methyl ester **9a–d** were synthesized[25d] following two steps: amino acids were transformed to their methyl esters by treatment with $SOCl_2$ and MeOH, followed by treatment with *p*-toluenesulfonyl chloride, triethyl amine in dry DCM. The treatment of **9a–d** with **7a–c** under DEAD/PPh_3 conditions furnished **10a–f** in 70–80% yield. The nitro groups in **10a–f** were converted into its amine by hydrogenolysis and the activated sulfonamides **11a–f** were synthesized by treatment with TsCl in pyridine at 0 °C to make its proton acidic for Mitsunobu reaction. The reduction of the ester group in **11a–f** by LAH gave carbinol **12a–f** in 60–68% yield. The intramolecular Mitsunobu cyclization between the activated sulfonamide and primary carbinol in **12a–f** afforded enantiomerically pure benzo-annulated chiral [9]-N_3 peraza- macrocycles **13a–f** in 70–80% yield. Both tosyl groups of the final molecules **13b–f** were deprotected by using sodium naphthalenide in dry THF with 60–70% yield and the overall yield was 6–10% (Scheme 5).

Synthesis of benzo-annulated [12]-N_4 peraza-macrocycles 20a–b

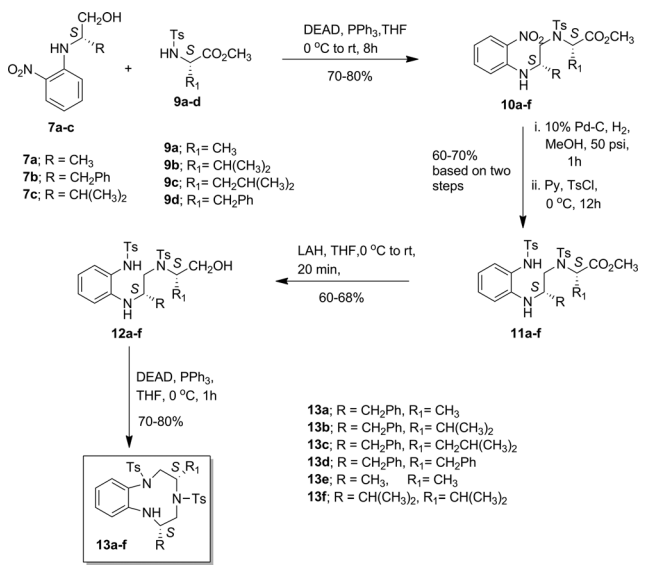
Next, a synthesis of enantiomerically pure benzo-annulated [12]-N_4 peraza-macrocycle was undertaken (Scheme 6). The advanced synthetic intermediate **11b–c** and Boc-protected amino carbinol **15** were used for the synthesis of tetraaza-macrocycles. Boc-protected amino carbinol **15** was synthesized in three steps from our previous reported procedure.[25d] Treatment of **11b–c** with **15** under the Mitsunobu conditions furnished ester derivatives **16a–b** in 60–70% yield. Next, **16a–b** was treated with TFA, instead of Boc-deprotection, salt formation took place. After the neutralization of salt, the starting material was recovered. We circumvented the problem using $SOCl_2$ and MeOH to deprotect[29] the Boc-group, affording free amine hydrochlorides **17a–b** which were again converted to their tosyl derivatives **18a–b** by treatment with tosyl chloride and pyridine at 0 °C in 50–60% yield. The reduction of the ester group of **18a–b** by LAH gave carbinols **19a–b** in 60–70% yield. The intramolecular Mitsunobu cyclization between the sulfonamide and primary carbinol in **19a–b** furnished enantiomerically pure benzo-annulated tetraaza-macrocycles **20a–b** in 50–60% yield along with recovery of 20–30% starting material. The tosyl groups of **20a** were deprotected by using sodium naphthalenide protocol with 66% yield and the overall yield was 1.69% (Scheme 7).



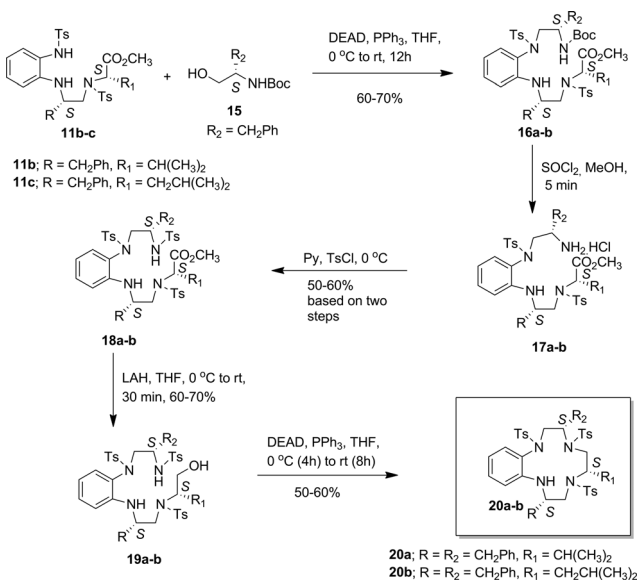
Scheme 3 Deprotection of the tosyl group of **6a–b**.



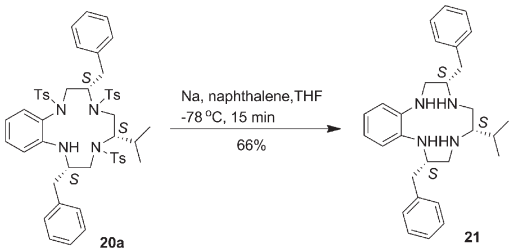
Scheme 5 Deprotection of both tosyl groups of **13b–f**.



Scheme 4 Synthesis of benzo-annulated chiral [9]-N_3 peraza-macro cycles **13a–f**.



Scheme 6 Synthesis of benzo-annulated [12]-N_4 peraza-macrocycles **20a–b**.



Scheme 7 Deprotection of the tosyl groups of **20a**.

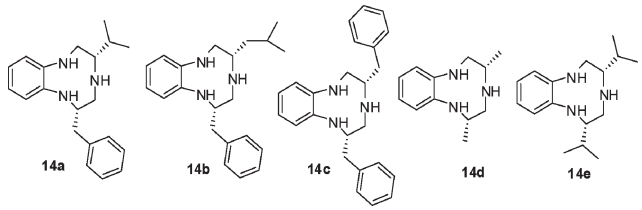


Fig. 1 Metal complexation studies of these macrocycles.

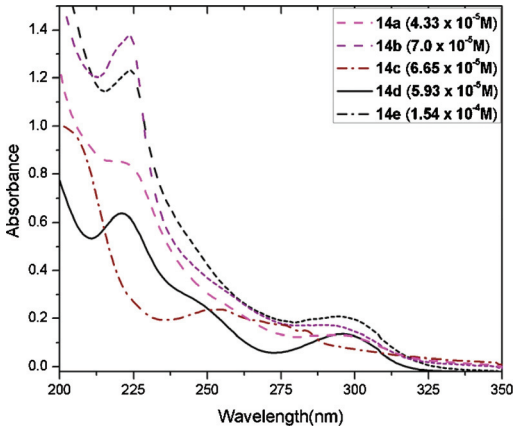


Fig. 2 UV-Visible spectra of different compounds in acetonitrile recorded at laboratory temperature (35 °C).

Table 1 Molar extinction coeffcient (ε) at the lowest energy band maxima for various compounds at laboratory temperature.

Compound	(λ_{max} nm)	ε (M^{-1} cm^{-1}, at λ_{max})
14a	296	3009
14b	293	2414
14c	275	2586
14d	296	2269
14e	295	1344

UV-Visible spectroscopic study

The objective of synthesizing these amino acids derived chiral macrocycles is to study their complexation with metal ions. The metal complexation studies have been reported by various spectroscopic techniques, such as ultraviolet visible (UV-Vis.), NMR, fluorescence, and infrared (IR).[30] UV-Vis spectroscopy is the most popular tool for examination of binding phenomena.[31] The UV-visible spectrum of some of these novel chiral macrocyle derivatives (Fig. 1) have been recorded in dry acetonitrile and are presented in Fig. 2. Among triaza-macrocycles, except the diphenyl substituted derivative **14c**, all derivatives show a broad band in the wavelength region of 275–325 nm having wavelength maxima at 295 nm, which is assigned to π–π* transition in benzene moiety with a considerable overlap from amino groups, along with a sharp band at 222 nm. The absorption peak maxima and the corresponding molar extinction coefficients (ε) are presented in Table 1. The highest ε value is observed for **14a** while the lowest is observed for **14e**. Similar values are obtained for **14b**, **14c** and **14d**. No specific relationship could be observed between the strength of transition and the subsituation in the macrocycle. In case of **14c** derivatives this sharp band is blue shifted to below 210 nm. Since in this low wavelength region (below 190 nm) acetonitrile also absorbs, it was not possible to detect exactly its peak position. In addition, for **14c** the broad band is blue shifted and became structured. This hypsochromic effect is due to the phenyl substitutions which changes the electronic properties as will be discussed in detail in the section 'Quantum chemical calculations: DFT and TD-DFT'.

In fact, an in-depth investigation on the absorption spectra of **14c** and **14d** has been performed with the help of TD-DFT and described in the same section. The solvent polarity sensitivity of these derivatives has also been studied. No noticeable sensitivity is observed (see Fig. S-167 and S-168 in the ESI).† We also have not observed any change in the UV-visible spectrum for any compound due to the change of concentration. Hence the possibility of intermolecular complexation or dimerization can be ruled out. While the low energy band in the UV-visible spectrum of tetraaza-macrocycle derivatives is red shifted (*e.g.*, to 305 nm for **21**, see ESI, S-162)† as compared to that of the triaza-macrocycles discussed above, the high energy band in these derivatives appears as a hump. It is probably due to the inclusion of one amino group which increases the number of electronic energy levels thereby making the electronic energy levels closer. The molar extinction coefficient as tabulated in Table 1 shows no definite trend with substitution. However, the derivatives without any phenyl ring substitution have the lowest molar extinction coefficients (**14e** and **14d**). Due to poor solubility, metal complexation studies could not be performed for tetraaza-macrocycle derivatives.

Studies of complexation with metal salts

As reported elsewhere, on addition of a cation, the low energy absorption band increases with increase in concentration of the cation in solution.[32] During our studies with the synthesized novel macrocycles (Fig. 1), we have found that in some cases there are some significant changes in absorbance at the peak maximum, while in other cases, only a minor change in absorbance followed by a change in the position was observed (see ESI, S-154 to S-161).† Fig. 3 shows a typical enhancement of absorbance of the characteristic band when it binds with the cation. It is interesting to note the appearance of isosbestic points due to complexation, which is generally either not observed or not given importance. The appearance of isosbestic points is far more confirmative of the complex formation than enhancement of absorbance since we found that few of the cations (*e.g.* Ni^{2+}) themselves absorb in the same wavelength range in which the

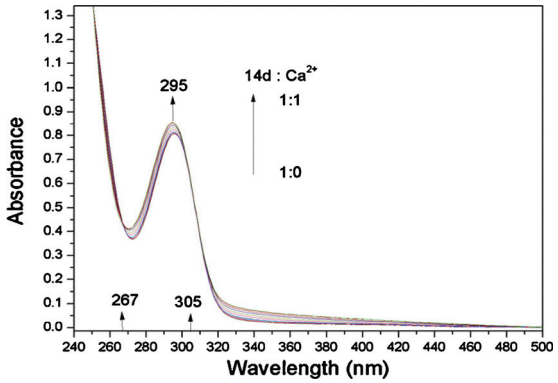


Fig. 3 Change of UV-visible spectra of **14d** with gradual addition of Ca^{2+} in acetonitrile. The concentration of **14d** was 2.8×10^{-4} M while the concentration of Ca^{2+} was varied from 2.8×10^{-5} M to 2.8×10^{-4} M. Isosbestic points are marked on the *x*-axis.

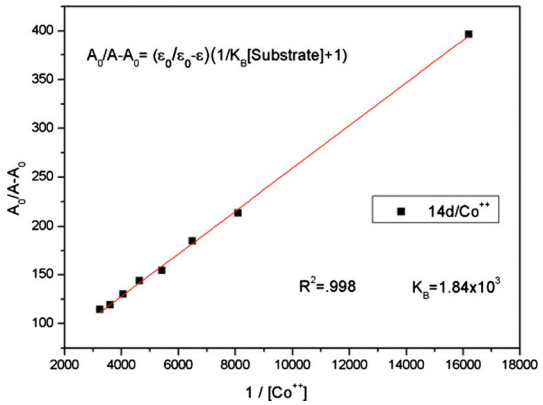


Fig. 4 Bensei-Hildebrand plot for **14d** with Co^{2+}, considering the 1 : 1 complexation. The goodness of the fit is shown by the R^2 value. The equation is also mentioned in the graph.

ligand absorbs. Fig. 3 also shows an appearance of a broad band above 320 nm which increases gradually with the increase in addition of metal salts. This broad band is due to a complex which is evident from the fact that the metal salt has no absorption in these wavelength ranges (see ESI, Fig. S-153).† In general, the appearance of an isosbestic point indicates that two species involved in the complexation are related linearly by stoichiometry, such that the absorbance is invariant for one particular wavelength. The complexation properties of these macrocycles (Fig. 1) have been studied by an UV-visible spectroscopic technique with transition metal ions Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} and an alkaline earth metal ion Ca^{2+}.

Fig. 3 shows representative spectra of the change of absorption spectra on addition of Ca^{2+} solution of various concentrations. It has been observed that a response to the addition of a particular metal ion is different for the different triaza-macrocycles (ESI, Fig. S-154-161).† In some cases there are clear isosbestic points with the in absorbance of the longest wavelength band (*e.g.*, **14e** with Co^{2+}, S-155) while for others the absence of any isosbestic point with enhancement of absorbance are noticed (*e.g.* **14e** with Ni^{2+}, S-160 ESI),† though no definite trend could be established in the structure of the macromolecules. While a slight increase in absorbance of the longest wavelength peak is observed for **14d** and **14e** with gradual addition of Co^{2+} salt solution, the presence of sharp isosbestic points is clearly indicative of complex formation. For both compounds slight blue shifts were observed on complexation. On the other hand, for **14a** and **14b**, no substantial increase in absorbance at peak maxima is observed. Insignificant change of absorbance may be due to the similar values of molar absorptivity of the complexes with that of host molecules alone. The different response of different compounds to the Co^{2+} is due to the different structure of the host molecules. Since the compound containing a phenyl group is found to be less sensitive to the cations, it must be the structure of the host molecule which inhibits proper interaction which is discussed in detail in the section 'Quantum chemial calculation'. Among all the macrocycles studied, the complexation behavior is clearly depicted by **14e** with Co^{2+} which shows a considerable increase in absorbance as well as these isosbestic points (at 274, 298 and 329 nm) (Fig. S-155).† Since there is no clear peak at 295 nm regions (due to overlapping of a low energy peak with high energy) for **14c**, the formation of a complex is evident from the appearance of isosbestic points at 282 and 313 nm (Fig. S-158).† Interestingly, isosbestic points different from that appeared in other derivatives (appear approximately at 295 and 325 nm). This further indicates that the complexation for **14c** is clearly different than that of others and has been explained in the following section taking into consideration the different structure.

The Benesi–Hildebrand equation[33] for a 1 : 1 complex was employed for the cases where a significant change in absorbance is observed. Fig. 4 represents a case where we could successfully use the above mentioned equation. The binding constant value as determined from the figure was found to be 1.84×10^3 dm^3 mol^{-1} which corresponds to the Gibbs energy change (ΔG) of -19.4 kJ mol^{-1} at 35 °C. This binding constant is found to be less by an order of magnitude as compared to the tetraaza derivatives reported in literature.[32] The highest binding capability is shown by **14b** with Co^{2+} (9.6×10^3) while the lowest was obtained for **14a** with Ni^{2+} (1.7×10^3). The binding constants for Ni^{2+} and Ca^{2+} with various derivatives are found to vary between 1.8–6.2 $\times 10^3$ and 1.7–8.0 $\times 10^3$, respectively. An interesting fact that came out particularly from these two cations with various macromolecules is that symmetrically substituted derivatives like **14d** (dimethyl substituted) and **14c** (dibenzyl substituted) have relatively higher binding constants as compared to others. However, the difference of strength of binding for various derivatives does not vary significantly, therefore no definite conclusion is made. In general, the binding constants for different metal–ligand complexes here vary between 1.7–9.6 $\times 10^3$ dm^3 mol^{-1}.

Quantum chemical calculations: DFT and TD-DFT

In this section the ground state molecular, electronic structure and optical spectra of two of the macrocycles (**14c** and **14d**) are computed in the solution phase (acetonitrile as bulk solvent) using DFT and TD-DFT methods. These studies, as will be seen from the following discussions, lead to an unambiguous interpretation of their optical spectra and to rationalization of the different complexation behaviour of **14c** as compared to the

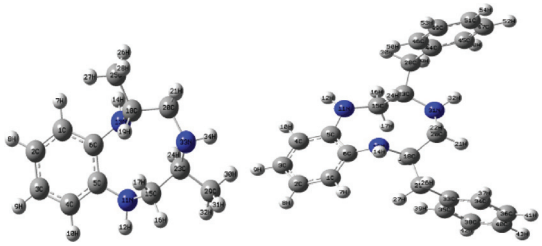
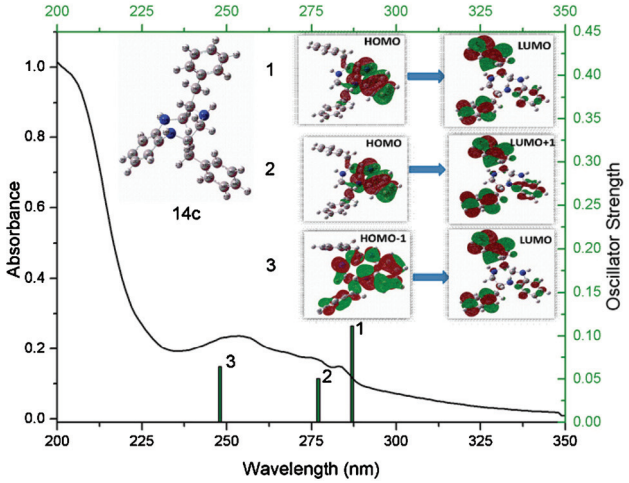


Fig. 5 DFT optimized structures of **14d** (left) and **14c** (right) molecules. The optimizations were done using the polarizable continuum model (PCM) with acetonitrile as the dielectric continuum. Blue spheres indicate nitrogens while the gray stands for carbon atoms.

other macrocycles studied. The solution phase DFT (polarizable continuum model, PCM using acetonitrile as dielectric continuum, see ESI, Fig. S-163 to S-166)† optimized structures of **14d** and **14c** are presented in Fig. 5. While **14d** represents the basic unit of the all the macromolecules studied for the complexation and **14c** is studied due to its different complexation behavior as discussed in the preceding section. It is found that the replacement of a methyl group by phenyl has significantly stabilized **14c** over **14d**, (as is evident from the total energy of the system, −687219 *vs.* −397223 kcal mol^{-1}) which is presumably due to the electronegative nature of phenyl ring.

The main purpose of performing the TD-DFT calculation is to analyse the UV-visible spectra of different compounds and moreover to know the reason for the difference in the spectrum of **14c** with respect to **14d** (which represents other derivatives as well). An overall excellent agreement can be seen between the theoretical and experimental UV-visible spectral data which are shown in Fig. 6 (a and b). The HOMO of **14c** and **14d** are strickingly similar, in both cases this higest occupied molecular orbital is situated mainly on the benzene ring along with the adjacent two nitrogens in spite of the fact that **14c** has two phenyl groups. The main differences are noticed on LUMOs. While the LUMO of **14c** is mainly on the two phenyl groups attached to two aza nitrogens, the same for the **14d** is mainly on the parent benzene ring with minor contributions from adjacent methyl groups. The groups of predicted transitions in **14c** within the wavelength region of 225 nm to 325 nm appear at 287, 277, and 248 nm (indicated in Fig. 6(a), as 1, 2, and 3 respectively). These transitions match reasonably well with experimental values (284, 276 and 253 nm respectively). Similar good agreements, though to a lesser extent have been observed for **14d** as well. While experimental band positions are observed at 296, 249 and 221 nm, the calculated corresponding band positions are 284, 244 and 234 nm. The longest wavelength band (284 nm) is clearly the n–π* transition (HOMO to LUMO). The involvement of a phenyl ring in LUMO is clearly seen in the Frontier Molecular Orbital pictures, emboided in the Fig. 6 (a and b). Hence, it is clear that the difference in nature of the band and peak positions in **14c** as compared to others is because of the presence of phenyl rings in **14c**.

To know the reason for the different types of complexation for **14c** and others, we have optimized the structures of **14c** and **14d** as already mentioned. Though the **14c** molecule containing a phenyl substituent was found to be more symmetrical as compared to **14d**, the binding sites (amino nitrogens) of **14d**



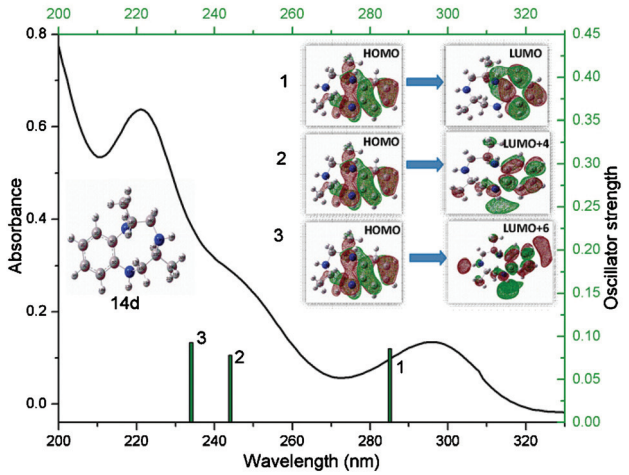


Fig. 6 Experimental UV-visible spectra in acetonitrile along with the TD-DFT calculated spectra of (a) **14c** and (b) **14d**. Frontier Molecular Orbitals involved in predominant transitions are also shown in respectve diagrams. Smooth lines correspond to experimental while vertical lines correspond to calculated transitions with their respective oscillator strength shown on the right axis. The difference in nature of the band and peak positions in **14c** as compared to others is because of the presence of phenyl rings in **14c**.

derivatives were unhindered or exposed for the complexation. On the other hand, one N–H of **14c** was sandwiched between two phenyl rings making it difficult to be accessible for the guest molecules to bind. This initial structural difference might be the reason for a different response of **14c** to the cation. It is necessary to mention here that the observed complexation differences are explained here considering the initial structure of macromolecule as the initial structure will guide the complexation. Another approach of examining the final complex structures is also possible. Since at present, convincing information (like single crystal X-ray diffraction data) on the type of complex formation is unavailable, intution based calculations on the final

complex structure may not produce trustworthy or convincing results.

Conclusion

We have synthesized enantiomerically pure amino acids derived substituted 1,2,3,4-tetrahydroquinoxalines, new types of benzo-annulated unsymmetrical chiral [9]-N_3 peraza- and [12]-N_4 peraza-macrocycles employing an inter- and intramolecular Mitsunobu reaction. The binding phenomena of the macrocycles with metal ion have been investigated by an UV-visible spectroscopic technique. The binding constant (K_b) value 1.84 × $10^3 dm^3$ mol^{-1} using the Benesi–Hildebrand equation and the Gibbs free energy (ΔG) −19.4 kJ mol^{-1} at 35 °C were determined for **14d** with Co^{2+}. UV-Visible along with DFT study reveal that the responses of polyazamacrocycles towards metal ions greatly depend on molecular conformation and substitution. The presence of clear isosbestic points and the increase (in some cases) of absorbance of the longest wavelength peak maxima confirm the formation of 1 : 1 complex with the metal ions.

Experimental

General remarks

IR spectra were recorded on 55 a Perkin-Elmer FT-IR RXI spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker DPX-200 or DPX- 300 spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded on JEOL SX 102 spectrometer. Elemental analyses were done on Varian EL-III CH N analyzer (Germany). The enantiomeric excess was determined by Lichro CART Chiradex column (250 × 4 mm, 5 μm) using 10–100 acetonitrile, water, gradient method, flow rate 1 mL min^{-1} as eluent at 20 °C. The ee value was determined for the compounds **3b** and **3f** (using CHIRAL 1C, hexane/propanol 95 : 5, flow rate 0.50 mL min^{-1}), for **6f** (using CHIRAL 1C, hexane/propanol 95 : 5, flow rate 0.80 mL min^{-1}) and for **13b** (using CHIRAL 1C, hexane/propanol 50 : 50, flow rate 0.60 mL min^{-1}) as eluent at 20 °C. All complexation studies were performed at 35 °C (± 0.2 °C) using the Peltier thermostat. UV-Visible spectra were recorded by CARY 100 BIO UV-Visible spectrophotometer (in the range of 200–800 nm) attached with the Peltier temperature controller, which has photometric linearity till absorbance 3.5 and wavelength resolution of ± 0.2 nm. A pair of Spectrosil quartz cuvette with Teflon stopper was used for the measurements.

Appropriate concentrations of chloride salts of different metal ions in acetonitrile have been prepared as follows

Due to the limited solubility of chloride salts in acetonitrile, initially salts were dissolved in a minimum amount of triple water (less than 7% of the total solution volume). Then an appropriate amount of acetonitrile was added to the water solution to prepare a salt solution of required concentration. This solution of the host molecule was added in the guest solution in such a way that a concentration range of host : guest, starting from 1 : 0 to 1 : 2 was prepared. UV-Visible spectra of these solutions were recorded at laboratory temperature (35 °C) keeping acetonitrile as reference.

Computational method

The Gaussian 03 program[34] was used for the density functional theory (DFT) calculation for two derivatives. The basis set already implemented in the program was used for the different types of calculations. The geometry of the molecule was optimized with 6-31G++(d,p) basis set at the Becke's three parameter hybrid method with LYP correlation (B3LYP) using the PCM model (solvent : acetonitrile). In addition to optimization, a frequency calculation was also performed at the B3LYP level of calculation. The absence of imaginary vibrational frequencies in the vibrational spectrum ensures the presence of a true minimum. The TD-DFT method (time-dependent density functional theory) is also used for calculating transitions. The electronic spectrum is calculated in the polarizable continuum model (PCM) using acetonitrile as dielectric continuum. We have used the same basis set and geometry as we used for optimization.

Experimental procedures and characterization data of the selected examples

General experimental procedure for the synthesis of (3a–g). To a stirred solution of *S*-amino acids **2** (1 equiv) in 30 mL of anhydrous DMF was added K_2CO_3 (1.5 equiv) at 25 °C followed by addition of *ortho*-nitrofluorobenzene (1equiv). The mixture was stirred for 4 h at 90 °C, K_2CO_3 was filtered off, and DMF was removed under vacuum. The residue was diluted with 30 mL MeOH and followed by addition of $SOCl_2$ at 0 °C, and then the reaction mixture was stirred for 3–4 h. After completion of the reaction, the solvent was removed under vacuum, the reaction mixture was diluted with water and then was added excess $NaHCO_3$ to neutralize the HCl and aqueous layer was extracted with ethyl acetate (3 × 50 mL). Removal of the solvent under vacuum and column chromatography of the crude product on silica gel with hexane-ethyl-acetate (8.5 : 1.5) as eluent furnished **3**.

(2*S*)-2-(2-Nitrophenylamino) propionic acid methyl ester (3a). Yellow oil; yield, 67% (based on two steps); R_f 0.51 (8.5/1.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3456, 2926, 2858, 2370, 1744, 1620, 1267, 1163, 744; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32–8.30 (bs, 1H), 8.22 (dd, 1H, J_1 = 1.9, J_2 = 8.8), 7.48–7.42 (m, 1H), 6.76–6.70 (m, 2H), 4.37–4.28 (m, 1H), 3.79 (s, 3H), 1.63 (d, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 143.7, 136.1, 132.5, 126.9, 116.1, 113.6, 52.5, 51.1, 18.5; MS (ESI): m/z 225 $[M + H]^+$; Anal. calcd. (%) for $C_{10}H_{12}N_2O_4$: C 53.57; H 5.39; N 12.49; Found: C 53.61; H 5.49; N 12.53.

(2*S*)-3-Methyl-2-(2-nitrophenylamino)butyric acid methyl ester (3f). Yellow oil; yield, 68% (based on two steps); R_f 0.52 (8.5/1.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3387, 2964, 2366, 1743, 1619, 1512, 1160, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 1H, J = 7.3), 8.20 (dd, 1H, J_1 = 1.5, J_2 = 8.6), 7.46–7.40 (m, 1H), 6.75–6.67 (m, 2H), 4.08–4.04 (m, 1H), 3.76

(s, 3H), 2.38–2.26 (m, 1H), 1.12 (d, 3H, J = 6.8), 1.07 (d, 3H, J = 6.8); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 144.9, 136.7, 133.1, 127.4, 116.5, 114.1, 62.1, 52.6, 31.8, 19.5, 18.9; MS (ESI): m/z 253 $[M + H]^+$; Anal. calcd. (%) for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10; Found: C, 57.23; H, 6.43; N, 11.15.

General experimental procedure for the synthesis of (4a–g). Compound **3** (1 equiv) in anhydrous THF (15 mL) was added to a suspension of LAH (1 M) sol^n (3 equiv) in THF (15 mL) at RT. The reaction mixture was stirred at RT for 30 min. The reaction was quenched by addition of ethyl acetate (30 mL) followed by water (30 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with hexane-ethyl-acetate (6 : 4) as eluent to furnish **4**.

(2*S*)-2-(2-Aminophenylamino)propan-1-ol (4a). Brown oil; yield, 41%; R_f 0.51 (6.5/3.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3653, 3437, 2926, 1633, 1458, 746; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.83–6.70 (m, 4H), 3.76–3.70 (m, 1H), 3.63–3.45 (m, 2H), 2.94–2.87 (m, 4H), 1.19 (d, 3H, J = 6.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 135.0, 120.6, 119.4, 117.0, 113.8, 65.9, 50.5, 17.4; MS (ESI): m/z 167 $[M + H]^+$; Anal. calcd. (%) for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85; Found: C, 65.11; H, 8.46; N, 16.91.

(2*S*)-2-(2-Aminophenylamino)-3-phenylpropan-1-ol (4b). Brown oil; yield, 43%; R_f 0.48 (6.5/3.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3652, 3446, 2929, 2372, 1600, 1514, 747; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 6.89–6.73 (m, 4H), 3.78–3.68 (m, 2H), 3.56–3.50 (m, 1H), 3.16 (bs, 4H), 2.99 (dd, 1H, J_1 = 5.6, J_2 = 13.6), 2.87 (dd, 1H, J_1 = 7.5, J_2 = 13.6); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 136.1, 135.2, 129.3, 128.5, 126.4, 120.7, 119.6, 117.2, 114.1, 62.9, 56.1, 37.6; MS (ESI): m/z 243 $[M + H]^+$; Anal. calcd. (%) for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56; Found: C, 74.33; H, 7.57; N, 11.62.

General experimental procedure for the synthesis of (5a–g). Compound **4** (1 equiv) was dissolved in 5 mL anhydrous pyridine, and then was cooled at 0 °C, followed by addition of *p*-toluenesulfonylchloride (1.2 equiv). Then it was kept in a refrigerator for 12 h. The pyridine was removed under vacuum and diluted with 30 mL water. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the crude product was then chromatographed over silica gel with eluent MeOH-$CHCl_3$ (0.3 : 9.7) to afford the title compound **5**.

(*S*)-*N*-[2-(2-Hydroxy-1-methylethylamino)phenyl]-4-methylbenzenesulfonamide (5a). Brown oil; yield, 77%; R_f 0.51 (6.0/4.0, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3652, 3417, 2927, 2366, 1602, 1326, 1159, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 2H, J = 8.2), 7.24 (d, 2H, J = 8.1), 7.12–7.06 (m, 1H), 6.71 (d, 1H, J = 8.2), 6.43–6.41 (m, 2H), 6.38 (bs, 1H), 3.74 (dd, 1H, J_1 = 3.6, J_2 = 11.1), 3.67–3.61 (m, 1H), 3.46 (dd, 1H, J_1 = 3.5, J_2 = 11.0), 2.41 (s, 3H), 1.16 (d, 3H, J = 6.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 143.6, 135.9, 129.4, 128.8, 128.5, 127.4, 120.9, 116.4, 112.4, 65.3, 49.9, 21.4, 16.9; MS (ESI): m/z 321 $[M + H]^+$; Anal. calcd. (%) for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74; Found: C. 59.93; H, 6.32; N, 8.79.

General experimental procedure for the synthesis of (6a–g). To a stirred solution of **5** (1equiv), and triphenylphosphine (1.2 equiv) in anhydrous THF (10 mL) under N_2 atmosphere, DEAD (1.2 equiv in THF) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for additional 1 h. The organic solvent was removed under vacuum and the column chromatography (eluent = hexane-ethylacetate, 8.5 : 1.5) of crude product over silica gel furnished **6**.

(3*S*)-3-Methyl-1-tosyl-1,2,3,4-tetrahydroquinoxaline (6a). Yellow solid; mp 162–164 °C; yield, 77%; overall yield, 16.3%; R_f 0.52 (8.0/2.0, hexane/EtOAc); $[\alpha]_D^{30}$ −47.3 (*c* 0.11, MeOH), HPLC analysis: ee > 99 (t_R = 5.2 min, CH_3CN/H_2O); IR ν_{max} (KBr, cm^{-1}) 3407, 2930, 2374, 1602, 1344, 1162, 573; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, 1H, J_1 = 1.3, J_2 = 8.2), 7.49–7.46 (m, 2H), 7.22–7.19 (m, 2H), 7.01–6.96 (m, 1H), 6.73–6.67 (m, 1H), 6.47 (dd, 1H, J_1 = 1.4, J_2 = 8.0), 4.26–4.23 (m, 1H), 2.90–2.87 (m, 2H), 2.39 (s, 3H), 1.05 (d, 3H, J = 5.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.8, 136.3, 129.5, 127.0, 126.2, 125.4, 121.2, 116.8, 114.4, 50.1, 43.2, 21.4, 19.1; MS (ESI): m/z 302.9 $[M + H]^+$; Anal. calcd. (%) for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26; Found: C, 63.61; H, 6.10; N, 9.30.

(3*S*)-3-Benzyl-1-tosyl-1,2,3,4-tetrahydroquinoxaline (6b). Light yellow semi-solid; yield, 75%; overall yield, 15.9%; R_f 0.53 (8.0/2.0, hexane/EtOAc); $[\alpha]_D^{30}$ −93.3 (*c* 0.13, MeOH), HPLC analysis: ee > 99 (t_R = 12.4 min, CH_3CN/H_2O); IR ν_{max} (KBr, cm^{-1}) 3399, 2926, 1601, 1497, 1349, 1163, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, 1H, J_1 = 1.1, J_2 = 8.2), 7.42–7.28 (m, 5H), 7.22–7.19 (m, 2H), 7.07–7.04 (m, 2H), 7.00–6.94 (m, 1H), 6.74–6.68 (m, 1H), 6.43 (dd, 1H, J_1 = 1.3, J_2 = 8.1), 4.24 (dd, 1H, J_1 = 2.4, J_2 = 13. 9), 3.71 (bs, 1H), 3.06 (dd, 1H, J_1 = 10.1, J_2 = 13.9), 2.86–2.78 (m, 1H), 2.69 (dd, 1H, J_1 = 5.6, J_2 = 13.4), 2.49 (dd, 1H, J_1 = 8.4, J_2 = 13.4), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 137.5, 136.4, 136.1, 129.6, 129.0, 128.7, 127.3, 126.9, 126.3 125.6, 121.9, 117.3, 114.6, 48.9, 48.3, 40.0, 21.5; MS (ESI): m/z 379 $[M + H]^+$; Anal. calcd. (%) for $C_{22}H_{22}N_2O_2S$: C, 69.81; H, 5.86; N, 7.40; Found: C, 69.88; H, 5.92; N, 7.45.

General experimental procedure for the synthesis of (7a–c). Compound **3a–b**, **3f** (1 equiv) in anhydrous THF (15 mL) was added to a suspension of LAH (1 M) sol^n (1 equiv) in THF (15 mL) at 0 °C. The reaction mixture was stirred at RT for 5 min and was quenched by addition of ethyl acetate (30 mL) followed by water (30 mL) at 0 °C. The same work-up procedure was followed as described for **4** and the product was chromatographed on silica gel with hexane-ethylacetate (7 : 3) as eluent to furnish **7a–c**.

(*S*)-2-(2-Nitro-phenylamino)-propan-1-ol (7a). This product was isolated as yellow oil. yield, 64%, R_f 0.49 (7.olour, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3366, 2924, 2366, 1616, 1507, 1227, 770; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1H, J_1 = 1.2, J_2 = 8.5), 7.99–7.97 (m, 1H), 7.34–7.29 (m, 1H), 6.84 (d, 1H, J = 8.7), 6.57–6.52 (m, 1H), 3.84–3.74 (m, 1H), 3.70–3.59 (m, 2H), 1.27 (d, 3H, J = 6.4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 135.9, 127.3, 115.4, 114.1, 66.2, 49.9, 17.6; MS (ESI):

m/z 197 $[M + H]^+$; Anal. calcd. (%) for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N,14.28; Found: C, 55.14; H, 6.23; N, 14.34.

General experimental procedure for the synthesis of (8a–b). Finely chopped sodium metal (10 equiv) and naphthalene (12 equiv) were dissolved in 10 mL dry THF. The reaction mixture was stirred for 2 h, until dark green color appeared. The desired THF solution of **6a–b** was cooled to −78 °C and then Na-napthalenide solution was added dropwise to the reaction mixture *via* a syringe, until dark green color persisted. The reaction mixture was stirred for 10 min at −78 °C and then was quenched by adding 1–2 drops water to discharge the green color. The reaction mixture was diluted with water and then extracted with Et_2O (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and the column chromatography (eluent = hexane/ethylacetate, 7.5 : 2.5) of crude product over silica gel furnished **8**.

(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline (8a). Brown oil; yield, 65%; overall yield, 10.6%; R_f 0.51 (8.0/2.0, hexane/EtOAc); $[\alpha]_D^{30}$ −47.3 (*c* 0.14, MeOH); IR ν_{max} (neat, cm^{-1}) 3441, 2362, 1640, 1217, 767; ^1H NMR (200 MHz, $CDCl_3$) δ 6.61–6.47 (m, 4H), 3.58–3.43 (m, 1H), 3.31 (dd, 1H, J_1 = 2.9, J_2 = 10.7), 3.03 (dd, 1H, J_1 = 8.1, J_2 = 10.7), 1.18 (d, 3H, J = 6.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 133.0, 118.6, 114.4, 114.3, 48.1, 45.6, 19.8; MS (ESI): *m/z* 149 $[M + H]^+$; Anal. calcd. (%) for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90; Found: C, 72.91; H, 8.27; N, 18.96.

General experimental procedure for the synthesis of (10a–f). To a stirred solution of **7a–c** (1 equiv), **9a–d** (1.1 equiv) and triphenylphosphine (1.3 equiv) in anhydrous THF (15 mL) under atmosphere of N_2, DEAD (1.3 equiv) in THF was added dropwise at 0 °C. The same reaction condition and worked-up procedure followed as described in the synthesis of **6a–g**. The column chromatography (eluent = hexane-ethylacetate, 8.5 : 1.5) of crude product over silica gel furnished **10a–f**.

(*S*)-Methyl-2-(4-methyl-*N*-((*S*)-2-(2-nitrophenylamino)-3-phenylpropyl)phenylsulfonamido)propanoate (10a). Yellow oil; yield, 75%; R_f 0.54 (8.5/1.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3022, 2361, 1741, 1509, 1216, 760; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12–8.08 (m, 2H), 7.65–7.62 (m, 2H), 7.45–7.38 (m, 1H), 7.30–7.20 (m, 7H), 7.06 (d, 1H, J = 8.6), 6.65–6.59 (m, 1H), 4.73–4.65 (m, 1H), 4.37–4.30 (m, 1H), 3.58–3.50 (m, 1H), 3.43 (s, 3H), 3.29–3.20 (m, 2H), 2.68 (dd, 1H, J_1 = 8.9, J_2 = 13.8), 2.40 (s, 3H), 1.42 (d, 3H, J = 7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 144.8, 143.9, 137.4, 136.2, 135.8, 132.2, 129.7, 129.5, 129.1, 128.7, 128.6, 127.4, 127.2, 126.9, 126.7, 115.6, 114.3, 56.1, 54.3, 52.2, 49.0, 39.4, 21.5, 16.7; MS (ESI): *m/z* 512 $[M + H]^+$, 534 $[M + Na]^+$; Anal. calcd. (%) for $C_{26}H_{29}N_3O_6S$: C, 61.04; H, 5.71; N, 8.21; Found: C, 61.12; H, 5.74; N, 8.28.

(*S*)-Methyl-3-methyl-2-(4-methyl-*N*-((*S*)-3-methyl-2-(2-nitro phenylamino)butyl)-phenylsulfonamido)butanoate(10f). Yellow oil; yield, 75%; R_f 0.50 (8.0/2.0, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3343, 3021, 2361, 1739, 1509, 1216, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16–8.10 (m, 2H), 7.64–7.61 (m, 2H), 7.36–7.27 (m, 2H), 7.14–7.11 (m, 2H), 6.62–6.56 (m, 1H), 4.09–4.06 (m, 2H), 3.76–3.62 (m, 1H), 3.57–3.50 (m, 1H), 3.52 (s, 3H), 2.32 (s, 3H), 2.16–2.08 (m, 2H), 1.05 (d, 3H, J = 7.0), 0.98–0.90 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1, 145.0, 143.3, 137.0, 135.7, 129.5, 129.2, 127.1, 126.9, 114.9, 114.1, 66.3, 55.6, 51.6, 45.5, 29.1, 28.9, 21.4, 19.6, 19.3, 18.1, 17.1; MS (ESI): *m/z* 492 $[M + H]^+$; Anal. calcd. (%) for $C_{24}H_{33}N_3O_6S$: C, 58.64; H, 6.77; N, 8.55; Found: C, 58.68; H, 6.81; N, 8.59.

General experimental procedure for the synthesis of (11a–f). Compound **10** dissolved in MeOH and added Pd (10% on carbon) in a bottle under nitrogen atmosphere. Then the nitrogen was completely replaced by hydrogen in parr assembly. The reaction was allowed to run for 1 h under pressure of 50 psi of H_2. After completion of the reaction (1 h, TLC monitoring), the catalyst was removed by filtration through celite, the solvent was removed under vacuum, the crude which was directly used for next step. The procedure was followed as described in the synthesis of **5a–g**.

(*S*)-Methyl-2-(4-methyl-*N*-((*S*)-2-(2-(4-methylphenylsulfonamido) phenylamino)-3-phenylpropyl)phenylsulfonamido) propanoate (11a). Brown oil; yield, 63% (based on two steps); R_f 0.52 (7.5/2.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3021, 2361, 1737, 1215, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.69 (m, 2H), 7.51–7.48 (m, 2H), 7.30–7.15 (m, 10H), 7.09–7.04 (m, 1H), 6.93 (d, 1H, J = 8.1), 6.59–6.53 (m, 2H), 4.65–4.62 (m, 2H), 4.13 (dd, 1H, J_1 = 7.2, J_2 = 14.2), 3.88–3.86 (m, 1H), 3.41 (s, 3H), 3.30 (dd, 1H, J_1 = 4.3, J_2 = 15.3), 3.10 (dd, 1H, J_1 = 9.0, J_2 = 15.3), 2.73 (dd, 1H, J_1 = 5.5, J_2 =, 14.2), 2.41 (s, 3H), 2.38 (s, 3H), 1.29 (d, 3H, J = 7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 143.5, 143.4, 143.0, 137.9, 137.1, 136.2, 129.45, 129.39, 129.2, 129.1, 129.0, 128.5, 128.3, 128.0, 127.5, 127.3, 127.2, 126.4, 121.6, 117.0, 111.6, 55.6, 54.2, 52.3, 48.4, 39.2, 21.5, 21.4, 16.1; MS (ESI): *m/z* 636 $[M + H]^+$, 658 $[M + Na]^+$; Anal. calcd. (%) for $C_{33}H_{37}N_3O_6S_2$: C, 62.34; H, 5.87; N, 6.61; Found: C, 62.37; H, 5.82; N, 6.65.

(*S*)-Methyl-3-methyl-2-(4-methyl-*N*-((*S*)-2-(2-(4-methyl phenyl-sulfonamido)phenylamino)-3-phenylpropyl)phenyl-sulfonamido) butanoate (11b). Brown oil; yield, 64%, (based on two steps); R_f 0.54 (7.5/2.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3023, 2361, 1742, 1602, 1216, 762; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77–7.74 (m, 2H), 7.55–7.53 (m, 2H), 7.33–7.11 (m, 10H), 7.08–7.02 (m, 1H), 6.63–6.58 (m, 1H), 6.52 (bs, 1H), 6.43 (d, 1H, J = 7.8), 4.60–4.58 (m, 1H), 4.01–3.98 (m, 1H), 3.74–3.73 (m, 1H), 3.64 (dd, 1H, J_1 = 3.7, J_2 = 15.4), 3.36 (s, 3H), 3.12 (dd, 1H, J_1 = 10.3, J_2 = 15.5), 2.69 (dd, 1H, J_1 = 4.2, J_2 = 13.9), 2.43 (s, 3H), 2.37 (s, 3H), 2.05 (dd, 1H, J_1 = 8.4, J_2 = 13.9), 1.85–1.75 (m, 1H), 0.80 (d, 3H, J = 6.4), 0.78 (d, 3H, J = 6.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 143.6, 143.4, 142.3, 137.8, 137.5, 136.4, 129.42, 129.38, 129.0, 128.6. 128.2, 127.6, 127.4, 126.6, 121.4, 116.8, 110.8, 65.9, 53.6, 51.6, 48.0, 39.2, 28.8, 21.6, 21.5, 19.7, 19.4; MS (ESI): *m/z* 664 $[M + H]^+$, 686 $[M + Na]^+$; Anal. calcd. (%) for $C_{35}H_{41}N_3O_6S_2$: C, 63.32; H, 6.23; N, 6.33; Found: C, 63.36; H, 6.28; N, 6.43.

General experimental procedure for the synthesis of (12a–f)

The procedure was followed as described for **4a–g**.

***N*-((*S*)-1-Hydroxy-3-methylbutan-2-yl)-4-methyl-*N*-((*S*)-2-(2-(4-methylphenylsulfonamido)phenylamino)-3-phenyl propyl) benzenesulfonamide (12b).** Brown oil; yield, 64%; R_f 0.52 (7.0/3.0, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3681, 3021, 2359, 1603, 1216, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.51–7.48 (m, 2H), 7.34–7.26 (m, 6H), 7.19–7.17 (m, 2H), 7.02–6.99 (m, 3H), 6.62–6.60 (m, 1H), 6.52–6.44 (m, 2H), 4.10–4.04 (m, 1H), 3.85–3.82 (m, 1H), 3.70–3.56 (m, 2H), 3.49 (dd, 1H, J_1 = 2.7, J_2 = 15.0), 2.95 (dd, 1H, J_1 = 10.8, J_2 = 14.9), 2.89–2.83 (m, 1H), 2.42 (s, 3H), 2.38–2.30 (m, 4H), 1.80–1.73 (m, 1H), 0.92 (d, 3H, J = 6.5), 0.69 (d, 3H, J = 6.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.3, 142.9, 139.2, 138.2, 137.7, 136.5, 129.7, 129.6, 129.3, 129.1, 128.6, 128.4, 127.65, 127.57, 127.1, 126.6, 126.4, 122.4, 117.9, 112.9, 67.0, 62.3, 53.2, 47.4, 39.1, 27.6, 21.6, 21.4, 20.7, 20.2; MS (ESI): m/z 636 $[M + H]^+$, 658 $[M + Na]^+$.; Anal. calcd. (%) for $C_{34}H_{41}N_3O_5S_2$: C, 64.22; H, 6.50; N, 6.61; Found: C, 64.28; H, 6.54; N, 6.71.

General experimental procedure for the synthesis of (13a–f)

The procedure was followed as described for **6a–g**.

(3*S*,6*S*)-6-Benzyl-3-methyl-1,4-ditosyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[b] [1,4,7]triazonine (13a). Colorless semi-solid; yield, 66%, (based on two steps); overall yield, 13.8%; R_f 0.51 (8.0/2.0, hexane/EtOAc); $[\alpha]_D^{30}$ +105.2 (c 0.11, MeOH), HPLC analysis: ee > 99 (t_R = 14.5 min, CH_3CN/H_2O); IR ν_{max} (KBr, cm^{-1}) 3024, 2926, 2363, 1218, 1160, 762; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.72–7.67 (m, 3H), 7.57–7.54 (m, 2H), 7.30–7.17 (m, 8H), 7.06–7.04 (m, 2H), 6.86–6.84 (m, 2H), 4.17–4.12 (m, 1H), 3.62–3.58 (m, 1H), 2.99–2.84 (m, 2H), 2.78 (dd, 1H, J_1 = 3.5, J_2 = 11.9), 2.46 (s, 3H), 2.36–2.33 (m, 1H), 2.30 (s, 3H), 2.18 (dd, 1H, J_1 = 1.1, J_2 = 11.8), 1.85–1.77 (m, 1H), 1.25 (d, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 143.4, 138.2, 137.3, 136.6, 136.5, 134.8, 129.7, 129.6, 128.6, 128.5, 127.2, 127.0, 126.9, 126.7, 124.3, 123.2, 117.8, 60.7, 59.5, 48.7, 44.7, 36.8, 21.5, 21.4, 14.7; MS (ESI): m/z 590 $[M + H]^+$; Anal. calcd. (%) for $C_{32}H_{35}N_3O_4S_2$: C, 65.17; H, 5.98; N, 7.12; Found: C, 65.21; H, 6.02; N, 7.21.

General experimental procedure for the synthesis of (14a–e)

The procedure was followed as described for **8a–b**.

(2*S*,5*S*)-2-Benzyl-5-isopropyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[b] [1,4,7] triazonine (14a). Brown oil; yield 68%; overall yield, 10.1%; R_f 0.51 (0.8/9.2, MeOH/$CHCl_3$); IR ν_{max} (neat, cm^{-1}) 3022, 2369, 1432, 1217, 767; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.13 (m, 3H), 7.08–6.95 (m, 4H), 6.82–6.77 (m, 2H), 3.42–3.37 (m, 1H), 3.21–3.15 (m, 1H), 3.05–2.85 (m, 4H), 2.68–2.55 (m, 2H), 1.94–1.89 (m, 1H), 1.04 (d, 3H, J = 6.7), 1.00 (d, 3H, J = 6.7); MS (ESI): m/z 310 $[M + H]^+$; Anal. calcd. (%) for $C_{20}H_{27}N_3$: C, 77.63; H, 8.79; N, 13.58; Found: C, 77.68; H, 8.72; N, 13.54.

(2*S*,5*S*)-2-Benzyl-5-isobutyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[b] [1,4,7]triazonine (14b). Brown oil; yield 65%; overall yield, 16.6%; R_f 0.58 (0.8/9.2, MeOH/$CHCl_3$); IR ν_{max} (neat, cm^{-1}) 3372, 2925, 2361, 1592, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.13 (m, 4H), 7.06–6.98 (m, 3H), 6.81–6.77 (m, 2H), 3.79–3.67 (m, 1H), 3.44–3.41 (m, 1H), 3.08–2.84 (m, 5H), 2.68–2.64 (m, 1H), 1.76–1.69 (m, 1H), 1.53–1.45 (m, 2H), 0.95–0.93 (m, 6H); MS (ESI): m/z 324 $[M + H]^+$; Anal. calcd. (%) for $C_{21}H_{29}N_3$: C, 77.97; H, 9.04; N, 12.99; Found: C, 77.91; H, 9.11; N, 12.95.

General experimental procedure for the synthesis of (16a–b). To a stirred solution of **11b–c** (1 equiv), Boc-protected amino alcohol **15** (1.2 equiv) and triphenylphosphine (1.5 equiv) in anhydrous THF (15 mL) under atmosphere of N_2, DEAD (1.5 equiv) in THF) was added dropwise at 0 °C. The same reaction condition and worked-up procedure followed as described in the synthesis of **6a–g**. The column chromatography (eluent = hexane-ethylacetate, 8.5 : 1.5) of crude product over silica gel furnished **16a–b**.

(*S*)-Methyl-2-(*N*-((*S*)-2-(2-(*N*-((*S*)-2-(*tert*-butoxycarbonyl amino)-3-phenylpropyl)-4-methylphenylsulfonamido) phenyl amino)-3-phenylpropyl)-4-methylphenylsulfonamido)-3-methylbutanoate (16a). Colorless oil; 65%; R_f 0.54, (7.5/2.5, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3403, 3022, 2977, 1737, 1703, 1513, 1342, 1216, 765; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 8.1), 7.67 (d, 1H, J = 8.1), 7.54–7.49 (m, 2H), 7.32–7.16 (m, 14H), 6.94 (d, 1H, J = 8.1), 6.81 (bs, 1H), 6.47–6.40 (m, 2H), 5.18 (bs, 1H), 4.67–4.64 (m, 1H), 4.48 (bs, 1H), 4.37–4.30 (m, 1H), 4.19–4.06 (m, 2H), 3.96–3.87 (m, 1H), 3.74–3.67 (m, 1H), 3.57–3.51 (m, 2H), 3.45 (s, 3H), 3.32–3.26 (m, 1H), 3.21 (bs, 1H), 2.95–2.90 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 1.64–1.55 (m, 1H), 1.34 (s, 9H), 0.98 (d, 3H, J = 5.8), 0.93 (d, 3H, J = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.6, 145.8, 143.7, 143.6, 143.4, 138.0, 135.8, 129.5, 129.45, 129.36, 129.3, 128.5, 128.3, 128.2, 128.0, 127.8, 126.3, 126.1, 116.3, 111.9, 66.4, 53.1, 52.5, 51.5, 51.2, 48.8, 39.1, 28.4, 21.5, 20.3, 19.5, 19.4; MS(ESI): m/z 797 $[M - Boc]^+$, 897 $[M + H]^+$, 919 $[M + Na]^+$; Anal. calcd. (%) for $C_{49}H_{60}N_4O_8S_2$: C, 65.60; H, 6.74; N, 6.24; Found: C, 65.68; H, 6.73; N, 6.35.

General experimental procedure for the synthesis of (18a–b). Compound **16** (1 equiv) was dissolved in 20 mL MeOH and followed by addition of $SOCl_2$ (3 equiv) at RT for 5 min. Removal of the solvent under vacuum and the crude were directly used for next step. The procedure was followed as described in the synthesis of **5a–g**.

(*S*)-Methyl-3-methyl-2-(4-methyl-*N*-((*S*)-2-(2-(4-methyl-*N*-((*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropyl)phenyl sulfonamido)phenylamino)-3-phenylpropyl)phenylsulfona mido) butanoate (18a). Brown oil; yield, 55%, (based on two steps); R_f 0.52 (7.0/3.0, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3390, 3024, 1738, 1343, 1217, 1160, 758; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 1H, J = 8.1), 7.67 (d, 1H, J = 8.1), 7.56–7.47 (m, 3H), 7.39 (d, 1H, J = 8.2), 7.32–7.04 (m, 15H), 6.92 (d, 1H, J = 8.2), 6.84–6.80 (m, 1H), 6.57–6.47 (m, 3H), 6.37–6.21 (m, 1H), 5.15–5.10 (m, 1H), 4.33–4.25 (m, 1H), 4.24–4.22 (m, 1H), 4.19–4.10 (m, 1H), 4.02–3.89 (m, 1H), 3.60 (dd, 1H, J_1 = 7.8, J_2 = 13.2), 3.54–3.52 (m, 1H), 3.41 (s, 3H), 3.30 (dd, 1H, J_1 = 3.2, J_2 = 13.4), 3.22 (bs, 1H), 3.16–3.12 (m, 1H), 2.88–2.83 (m, 1H), 2.75–2.69 (m, 1H), 2.63–2.56 (m, 1H), 2.44 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 1.66–1.51 (m, 1H), 0.91–0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 146.0, 143.9, 143.3, 142.9, 138.4, 136.7, 136.4, 136.1, 135.9, 134.1, 129.4, 129.34,

129.27, 129.0, 128.5, 128.4, 128.3, 128.2, 127.8, 127.1, 126.22, 126.16, 125.5, 116.3, 112.2, 66.1, 54.2, 53.3, 52.9, 51.4, 48.3, 38.9, 38.1, 29.0, 21.5, 21.4, 21.3, 20.1, 19.3; MS (ESI): *m/z* 951 $[M + H]^+$, 973 $[M + Na]^+$; Anal. calcd. (%) for $C_{51}H_{58}N_4O_8S_3$: C 64.40; H, 6.15; N, 5.89; Found: C, 64.48; H, 6.21; N, 5.91

General experimental procedure for the synthesis of (19a–b)

The procedure was followed as described for **4a–g**.

***N*-((*S*)-1-Hydroxy-3-methylbutan-2-yl)-4-methyl-*N*-((*S*)-2-(2-(4-methyl-*N*-((*S*)-2-(4-methylphenyl-sulfonamido)-3-phenyl propyl) phenylsulfonamido)phenylamino)-3-phenylpropyl) benzenesulfonamide (19a).** Brown oil; yield, 63%; R_f 0.45 (7.0/3.0, hexane/EtOAc); IR ν_{max} (neat, cm^{-1}) 3657, 3424, 3022, 2361, 1642, 1216, 762; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 8.1), 7.63–7.57 (m, 1H), 7.51–7.49 (m, 2H), 7.32–7.05 (m, 18H), 6.93 (d, 1H, J = 6.3), 6.75–6.64 (m, 2H), 6.59–6.54 (m, 1H), 6.31–6.20 (m, 1H), 5.12–5.10 (m, 1H), 4.22–4.12 (m, 1H), 3.94 (bs, 1H), 3.77–3.70 (m, 1H), 3.62 (bs, 1H), 3.56–3.48 (m, 1H), 3.37–3.27 (m, 1H), 3.22–3.15 (m, 1H), 3.06–2.96 (m, 2H), 2.89–2.80 (m, 1H), 2.75–2.66 (m, 1H), 2.47–2.42 (m, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.26 (s, 3H), 1.67–1.51 (m, 1H), 0.93–0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 143.2, 142.7, 138.5, 137.0, 136.3, 135.7, 133.4, 129.6, 129.5, 129.4, 129.3, 129.1, 128.9, 128.6, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 126.8, 126.5, 126.3, 125.8, 116.3, 112.3, 63.1, 54.9, 52.6, 52.4, 38.9, 38.4, 30.9, 21.6, 21.4, 21.3, 20.9, 20.1; MS (ESI): *m/z* 923 $[M + H]^+$; Anal. calcd. (%) for $C_{50}H_{58}N_4O_7S_3$: C, 65.05; H, 6.33; N, 6.07; Found: C 65.13; H 6.39; N 6.18.

General experimental procedure for the synthesis of (20a–b)

The procedure was followed as described for **6a–g**.

(3*S*,6*S*,9*S*)-3,9-Dibenzyl-6-isopropyl-1,4,7-tritosyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7,10] tetraaza-cyclododecine (20a). Light brown, semi-solid; yield, 56%; R_f 0.51 (8.0/2.0, hexane/EtOAc); $[\alpha]_D^{30}$ −201.9 (*c* 0.11, MeOH), HPLC analysis: ee > 99 (t_R = 17.1 min, CH_3CN/H_2O); IR ν_{max} (KBr, cm^{-1}) 3021, 2360, 1595, 1216, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.46–7.37 (m, 4H), 7.34–7.17 (m, 11H), 7.10–7.00 (m, 4H), 6.97–6.94 (m, 2H), 6.86–6.84 (m, 2H), 6.58 (d, 1H, J = 7.2), 5.11–5.09 (m, 1H), 4.17–4.10 (m, 1H), 3.84–3.73 (m, 2H), 3.63–3.47 (m, 3H), 3.42–3.34 (m, 1H), 3.11 (dd, 1H, J_1 = 4.8, J_2 = 14.2), 2.97 (dd, 1H, J_1 = 10.7, J_2 = 14.4), 2.74–2.62 (m, 2H), 2.46 (s, 6H), 2.41–2.35 (m, 1H), 2.26 (s, 3H), 2.18–2.14 (m, 1H), 1.64–1.54 (m, 1H), 0.99 (d, 3H, J = 6.6), 0.89 (d, 3H, J = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 144.1, 143.5, 142.7, 138.7, 138.1, 137.6, 136.5, 135.8, 134.9, 129.6, 129.5, 129.4, 129.0, 128.9, 128.7, 128.5, 128.4, 127.1, 127.0, 126.9, 126.6, 126.1, 125.4, 60.4, 60.3, 60.2, 55.4, 55.3, 52.0, 38.1, 36.6, 29.6, 21.5, 21.4, 21.3, 21.2, 21.1; MS (ESI): *m/z* 905 $[M + H]^+$; Anal. calcd. (%) for $C_{50}H_{56}N_4O_6S_3$: C, 66.34; H, 6.24; N, 6.19; Found: C, 66.58; H, 6.19; N, 6.25.

General experimental procedure for the synthesis of (2*S*,5*S*,8*S*)-2,8-Dibenzyl-5-isopropyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7,10]tetraazacyclodod-ecine (21)

The procedure was followed as described for **8a–b**.

Brown oil; yield, 66%; overall yield, 1.7%; R_f 0.51 (1.5/8.5, MeOH/$CHCl_3$); IR ν_{max} (neat, cm^{-1}) 3430, 3023, 2953, 1610, 1218, 765; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.00 (m, 14H), 3.41–3.28 (m, 3H), 2.98–2.89 (m, 5H), 2.66–2.59 (m, 5H), 1.76–1.61 (m, 1H), 1.05 (d, 3H, J = 6.4), 0.99 (d, 3H, J = 6.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 136.3, 129.6, 129.25, 129.16, 128.6, 128.2, 126.8, 117.1, 54.1, 39.0, 29.6, 19.4, 19.1; MS (ESI): *m/z* 443 $[M + H]^+$; Anal. calcd. (%) for $C_{29}H_{38}N_4$: C, 78.69; H, 8.65; N, 12.66; Found: C, 78.76; H, 8.61; N, 12.72.

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