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Diversity-oriented approach to novel spirocycles via 1,2,4,5-tetrakis(bromomethyl)benzene under operationally simple reaction conditions

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ABSTRACT

Here, we have established a simple and an efficient methodology for the synthesis of spirocyclic α-amino acids as well as spirosulfones starting with readily available active methylene compounds (AMCs). The key di-bromo building blocks were assembled by reacting various active methylene compounds with 1,2,4,5-tetrakis(bromomethyl)benzene in one step. We have also expanded this strategy to generate a variety of bis-spirocycles by treating the di-bromo intermediates with different AMCs under operationally simple reaction conditions.

1. Introduction

In recent years, spirocycles have elevated the chemical and pharmacological space to a higher level. There are also some other reasons that render them unique, for example, they are the integral parts of several natural as well as non-natural products[1] and also valuable building blocks in thermotropic liquid crystals, which in turn are useful for optical display device.[2] Due to the unique structural and reactivity pattern a great deal of attention has been paid to spirocycles and simple methodologies to these targets are in high demand. Generally, design and synthesis of spirocycles is a difficult task in preparative organic chemistry because of the formation of a spiro-ring junction.[3]

Synthesis of conformationally constrained α-amino acid (AAA) derivatives are in great demand because they are useful for drug discovery and development.[4] Replacement of proteinogenic AAAs by cyclic α-imino acid derivatives or cyclic AAAs is considered to be a useful tactic for the design of peptidomimetics with diverse pharmacological profiles. Recently, usage of peptide drugs have been expanded to a higher level.[5] However, sometimes their applicability is restricted due to various factors such as instability towards proteolytic degradation, poor absorption after oral ingestion, rapid excretion through liver and kidneys, non-selectivity and undesirable side effects because of the interaction of conformational flexibility of peptide(s) with a receptor.[6] To address this problem, incorporation of cyclic AAAs into a given peptide chain alter the conformational rigidity and thus modulate the pharmacological properties.[7] The structures of some interesting constrained AAAs synthesized in our laboratory are shown in Fig. 1.[8]

The sulfone functional group is often present in 'drug-like' small molecules and they are also valuable synthons for the construction of C–C bonds.[9] In addition, they are latent resource of conjugated dienes useful for the Diels–Alder (DA) chemistry.[10] The α-methylene groups in sulfones can be alkylated with various electrophiles due to the electron withdrawing nature of the sulfone moiety and this aspect in combination with the ease of desulfonylation has been explored in the numerous instances for assembling various biologically interesting targets.[11] Furthermore, α-halogenated sulfones are useful precursors suitable for the Ramberg–Bäcklund reaction for the generation of C–C double bonds.[12]

Here, we have demonstrated new strategies to various spirocyclic AAAs, spirosulfone derivatives and architecturally intricate bis-spirocyclic frameworks. Although, several methods are available for synthesis of AAAs and sulfone derivatives, most of them involve multi-step synthetic sequences.[13] Limited number of methods are available for the synthesis of spirocyclic AAAs and spirosulfone derivatives.[14] The importance of spirocycles, cyclic

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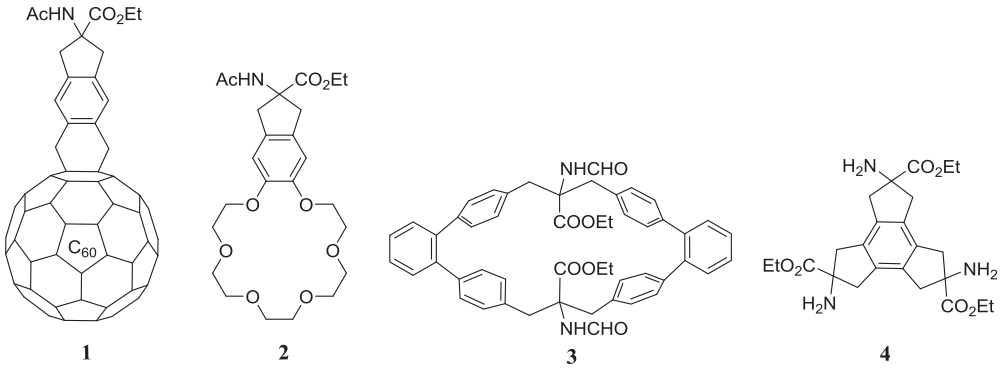


Fig. 1. Some interesting constrained AAAs synthesized in our laboratory.

AAAs as well as sulfone derivatives (Fig. 2)[15] and the documented difficulties in their synthesis prompted us to develop operationally simple methods from the readily available starting materials. To this end, we now report a simple route to spirocyclic AAAs and spirosulfone derivatives including some interesting bis-spirocyclic scaffolds. Here, the key di-bromo intermediates have been assembled by partial alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene with a variety of AMCs. The structures of the AMCs used in our strategy are shown in Fig. 3.

10a–**j** under mild reaction conditions appears to be a good option (Scheme 2).

To achieve this goal, we started our journey with the preparation of 1,2,4,5-tetrakis(bromomethyl)benzene **16** by using the known procedure.[17] Having the tetra-bromo derivative **16** in hand, it was treated with various AMCs (Fig. 3) to assemble the corresponding di-bromo building blocks in a single step. To this end, the compound **10a** on treatment with tetra-bromide **16** gave the desired di-bromo building block **14a** (39%) along with the dimeric

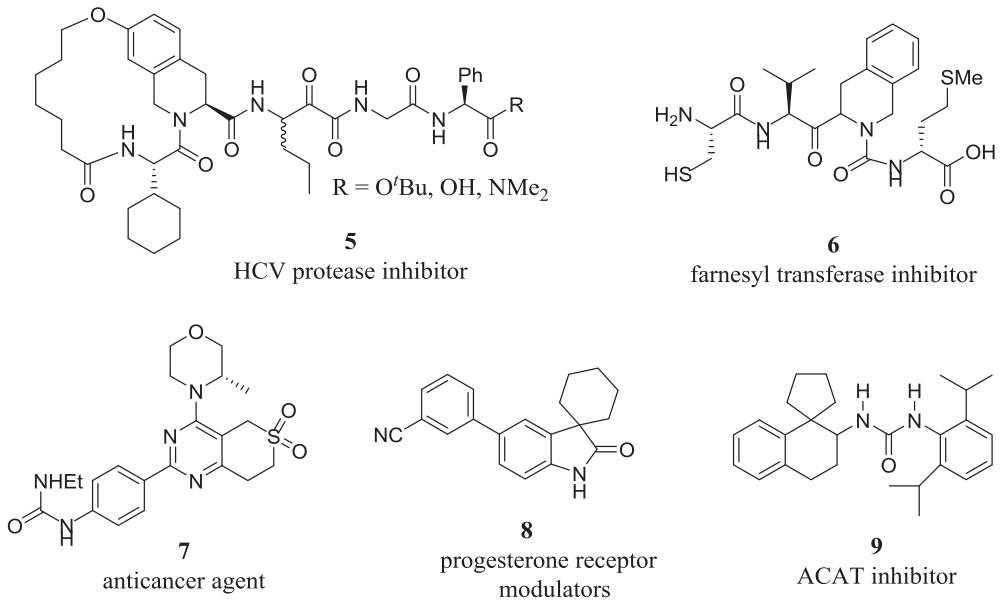


Fig. 2. Structures of some important bioactive AAAs, sulfones and a spirocyclic system.

2. Results and discussion

In view of our interest to generate new methodologies to spirocycles, here we report short and operationally simple strategies. In our earlier report,[16] we have assembled various di-bromo building blocks **14a**–**j** involving three steps: (i) propargylation of AMCs **10a**–**j**; (ii) [2+2+2] cycloaddition reaction of di-propargylated building blocks **11a**–**j** with 2-butyne-1,4-diol **12**; (iii) conversion of diols **13a**–**j** into the di-bromo building blocks **14a**–**j** via PBr_3 reaction (Scheme 1). In this context, conversion of diols into the di-bromo derivatives seems to be problem with sensitive substrates. This aspect forced us to look for an alternate approach. Therefore, it occurred to us that selective one side alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene **16** with AMCs products **17a** (25%) (Scheme 2, Fig. 4 and Fig. 5). Surprisingly, when we treated the tetra-bromide **16** with indane-1,3-dione **10b**, we isolated the desired di-bromo product **14b** in low yield (8%) along with the *C* and *O*-alkylated compounds **14b**′ and **17b** in 30% and 18% yields, respectively (Figs. 4 and 5).

On the other hand, we were pleased to observe that when the tetra-bromo compound **16** was treated with 1,3-dimethylbarbituric acid **10c** the expected product **14c** was obtained in respectable yield (Fig. 4). Along similar lines, treatment of tetra-bromide **16** with 1-indanone **10d** or various tetralone derivatives **10e**–**g** delivered the desired products **14d**–**g** in satisfactory yields (Fig. 4). Later, this strategy has also been extended to some interesting fluorene derivatives. To this end, the compounds **10h**–**j** were treated with tetra-bromide **16** to yield the fluorene-based di-bromo building

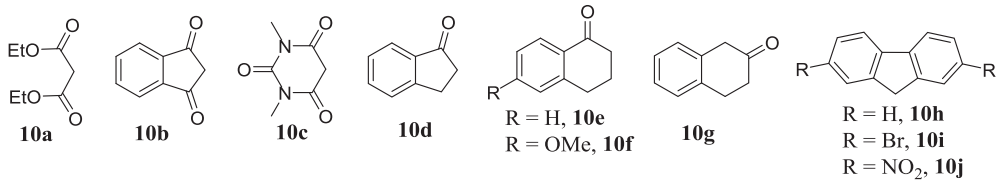
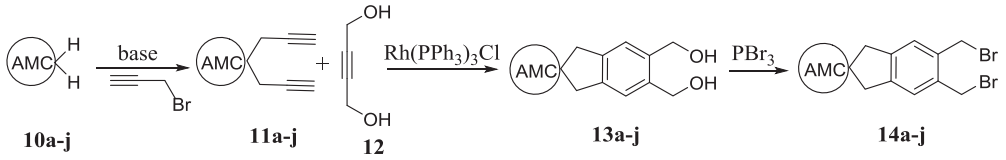
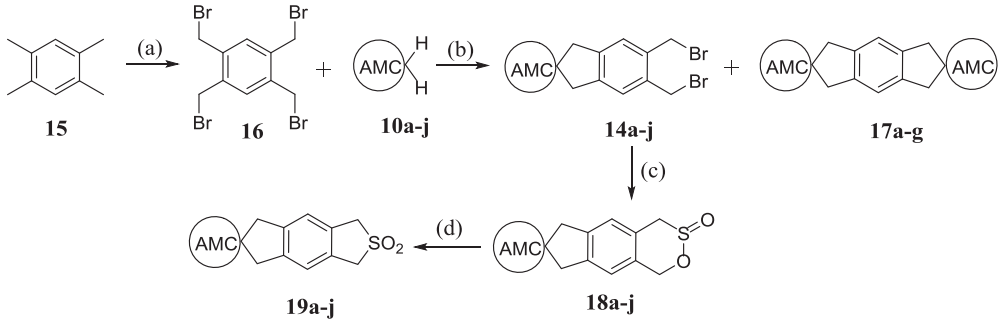


Fig. 3. Diverse active methylene compounds used in our study.



Scheme 1. Synthesis of di-bromo intermediates **14a**–**j** by earlier method.



Scheme 2. General strategy to spirosulfone derivatives. *Reagents and conditions*: (a) NBS, CH_2Cl_2, 500 W lamp, reflux, 20 h, 47%; (b) i) K_2CO_3, tetrabutylammonium hydrogen sulfate (TBAHS), MeCN, rt, 8–12 h, 8–68% (compounds **14b**–**c**, **14g** and **14j**); ii) NaH, THF, rt, 8–24 h, 32–48% (compounds **14a**, **14d**–**f** and **14h**–**i**); (c) rongalite, tetrabutylammonium bromide (TBAB), DMF, 0 °C-rt, 3–6 h, 64–92%, (compounds **18a**–**j**); (d) toluene, reflux, 10–15 h 76–91%, (compounds **19a**–**j**).

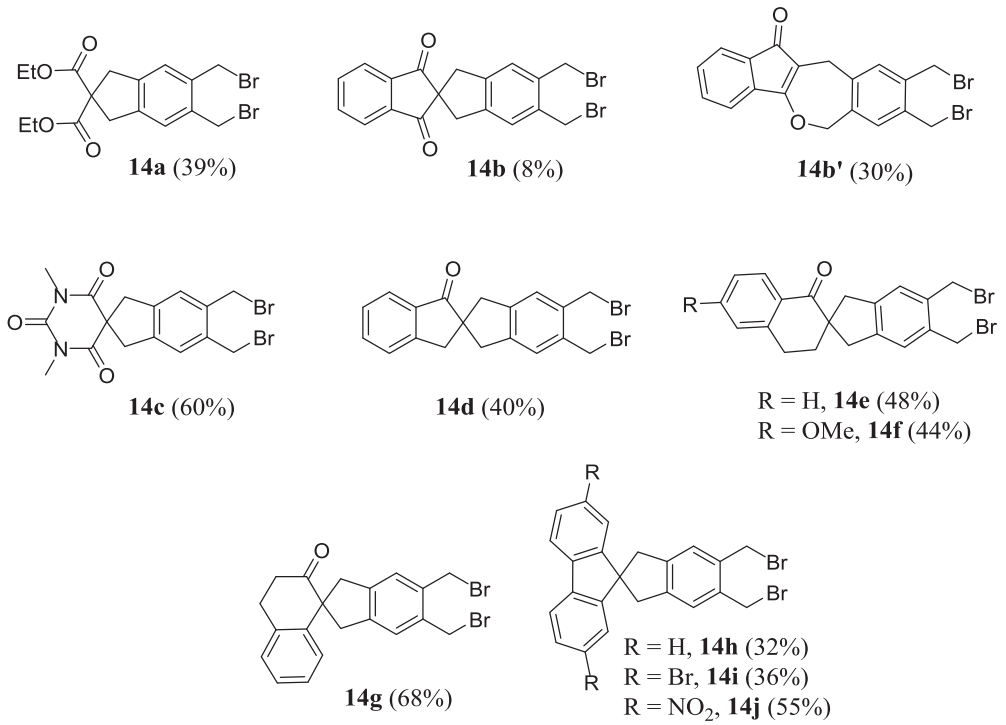


Fig. 4. Diverse di-bromo building blocks assembled in our study.

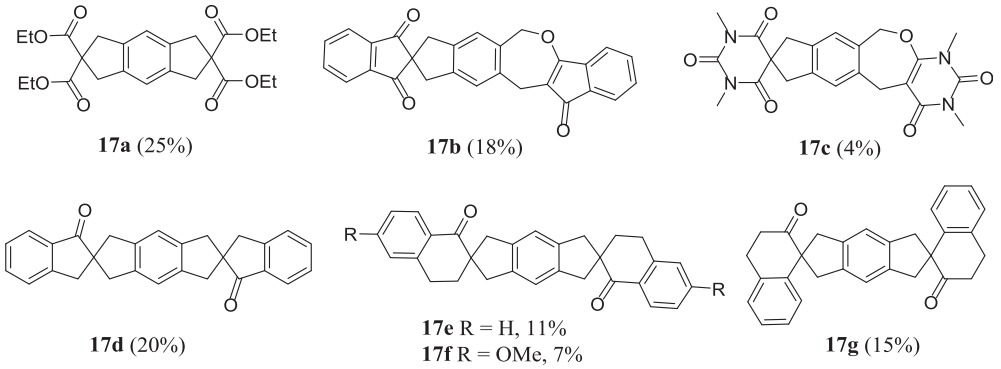


Fig. 5. Structures of bis-alkylated products isolated during the alkylation sequence.

blocks **14h–j** in moderate to good yields (Fig. 4). Having the di-bromo building blocks **14a–j** in hand, they were successfully transformed into the sultine derivatives **18a–j** by using rongalite (Scheme 2 and Fig. 6). The sultine derivatives were then cleanly rearranged to the sulfone derivatives **19a–j** under thermal reaction conditions in good to excellent yields (Scheme 2 and Fig. 7). The mechanism for the formation of sulfone from sultine is described in earlier report.[18]

were treated with diethyl acetamidomalonate (DEAM) by using K_2CO_3 as a base in MeCN at rt to deliver the spiro 1,2,3,4-tetrahydroisoquionline-3-carboxylic acid (Tic) derivatives **20a–e** in good yields (Scheme 3 and Fig. 8). Alternatively, treatment of the di-bromo intermediates **14b–c**, **h–j** with ethyl isocyanoacetate (EICA),[19] a glycine equivalent in the presence of K_2CO_3 gave the isonitrile derivatives, which on hydrolysis with conc. HCl/EtOH gave the non-protected constrained AAA derivatives **21c–e** in

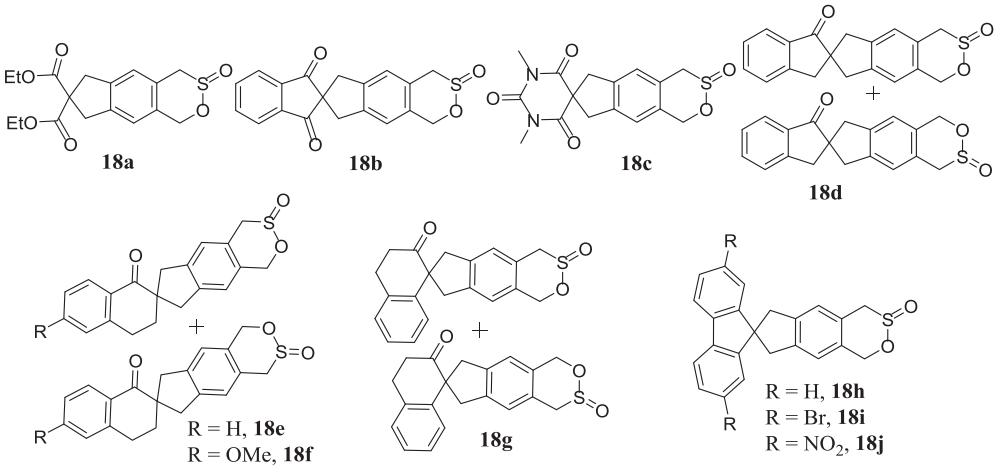


Fig. 6. The structures of sultine derivatives assembled in our study.

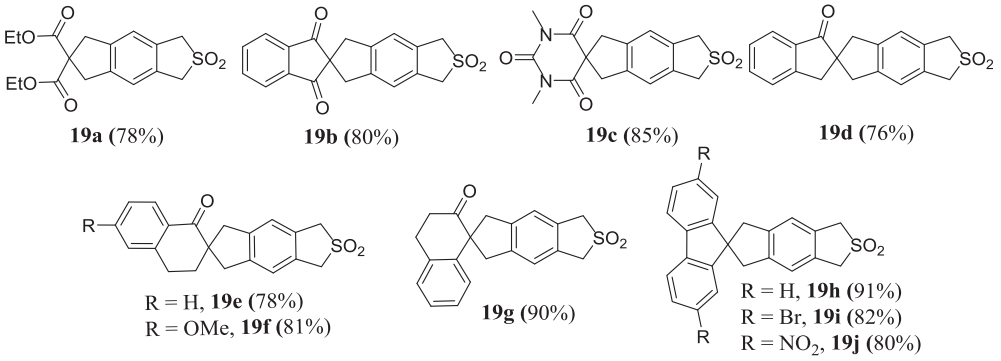
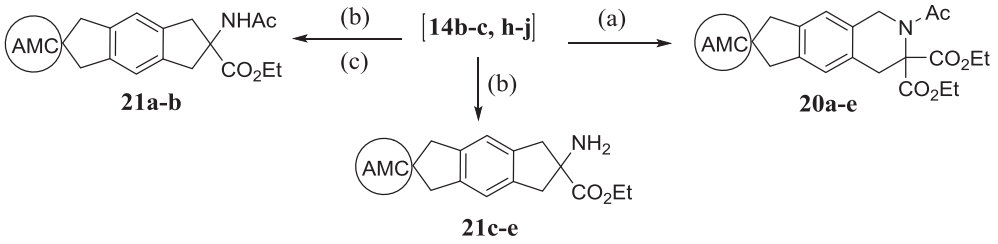


Fig. 7. List of spirosulfone derivatives prepared in our strategy.

Having realized the major portion of Scheme 2, next we extended this strategy to assemble diverse spirocyclic AAA derivatives. In this context, the di-bromo building blocks **14b–c**, **h–j** moderate to good yields (Scheme 3 and Fig. 9). We found that the non-protected AAAs of the di-bromides **14b** and **14c** were difficult to separate by column chromatography, therefore, we synthesized



Scheme 3. General scheme to spirocyclic constrained AAAs and TIC derivatives. *Reagents and conditions*: (a) DEAM, K_2CO_3, TBAHS, MeCN, rt, 15–20 h, 37–66% (compounds **20a**–**e**); (b) EICA, K_2CO_3, TBAHS, MeCN, rt, 14–17 h, 45–59% (compounds **21c**–**e**); (c) acetic anhydride (Ac_2O), MeCN, 29–30 h, 39–42% (compounds **21a** and **21b**).

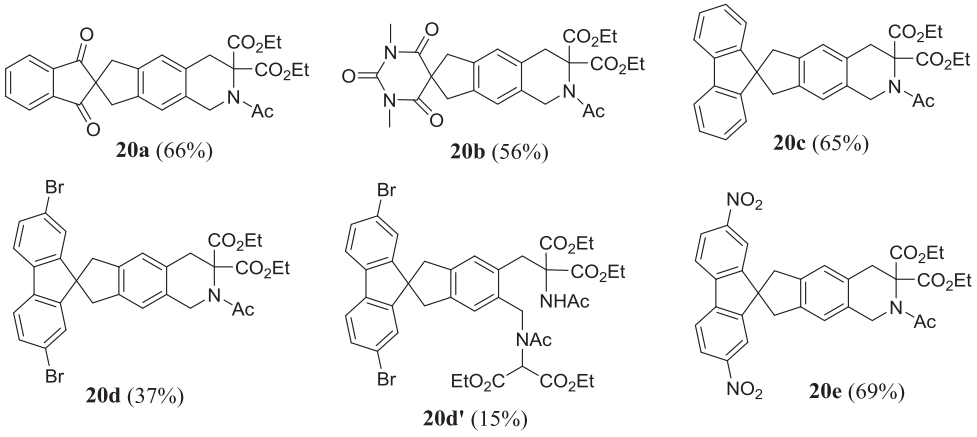


Fig. 8. List of various spirocyclic Tic derivatives assembled in our methodology.

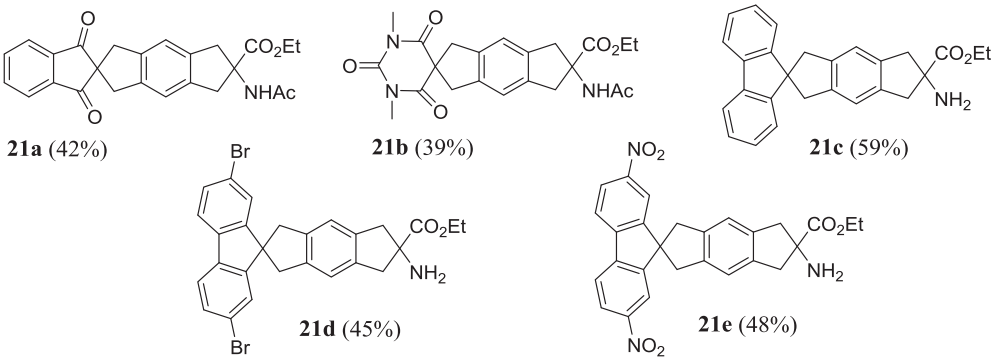
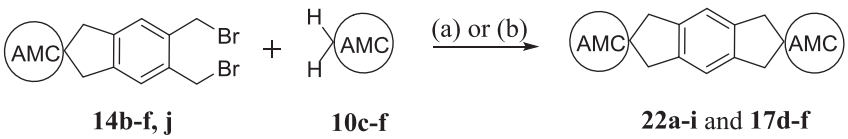


Fig. 9. List of diverse spirocyclic constrained AAAs derivatives.

the *N*-acetyl AAA derivatives **21a** and **21b** under Ac_2O/MeCN reaction conditions (Scheme 3 and Fig. 9). To further expand the utility of this strategy, we have also assembled some architecturally interesting bis-spirocyclic systems **22a**–**i** and **17d**–**f** by using dibromo building blocks **14b**–**f**, **j** and different AMCs **10c**–**f** under operationally simple reaction conditions (Scheme 4, Table 1 and Fig. 10).

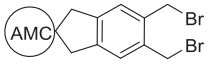
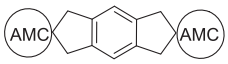
3. Conclusions

In summary, we have shown that partial alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene with active methylene compounds gave the key di-bromo building blocks in moderate to good yields. The di-bromo intermediates were then transformed into the spiro-α-amino acid derivatives as well as spirosulfones under operationally



Scheme 4. General scheme for the synthesis of bis-spirocyclic compounds via alkylation route. *Reagents and conditions*: (a) K_2CO_3, TBAHS, MeCN, rt, 6–12 h, 59–78% (compounds **22a**, **d**, **h**, **i**); (b) NaH, THF, rt, 8–20 h, 56–86% (compounds **17d**–**f** and **22b**–**g**).

Table 1
Synthesis of bis-spirocycles through alkylation method

Entry	 14b-f, j	 10c-f	 22a-i and 17d-f	Yields (%)[a]
1	**14b**	**10c**	**22a**	69
2	**14b**	**10d**	**22b**	81
3	**14b**	**10f**	**22c**	78
4	**14c**	**10d**	**22d**	71
5	**14c**	**10f**	**22e**	86
6	**14d**	**10c**	**22d**	59
7	**14d**	**10d**	**17d**	75
8	**14d**	**10e**	**22f**	65
9	**14d**	**10f**	**22g**	70
10	**14e**	**10c**	**22h**	78
11	**14e**	**10d**	**22f**	84
12	**14e**	**10e**	**17e**	67
13	**14f**	**10f**	**17f**	56
14	**14j**	**10c**	**22i**	68

[a] Yields refers to the isolated yields after column chromatography.

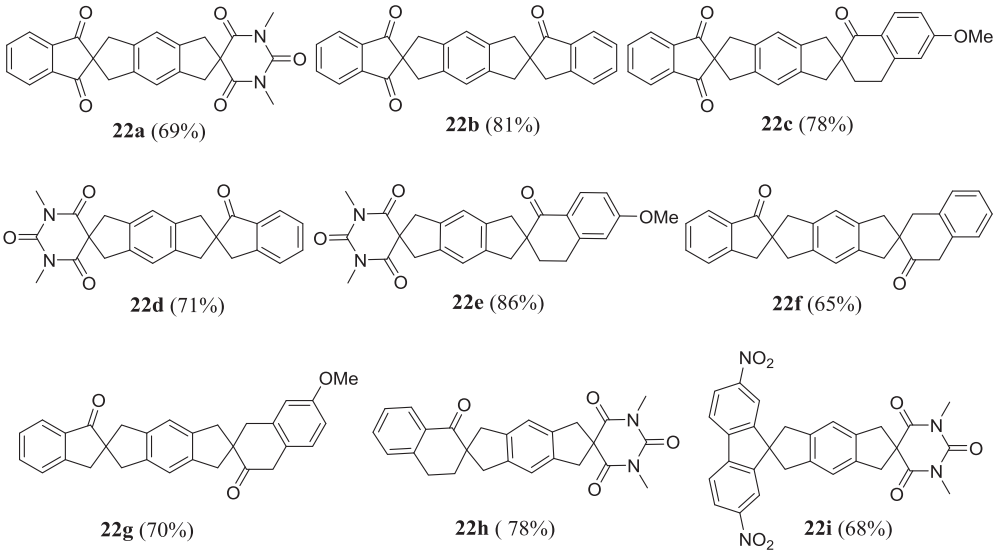


Fig. 10. List of bis-spirocyclic frameworks assembled in our strategy.

simple reaction conditions. Additionally, we assebmbled diverse architecturally interesting bis-spirocyclic systems under mild reaction conditions. The new chemical library generated here expand the spiro chemical space for additional studies. The unique capability of tetra-bromo derivative **16** usage significantly increase the diversity[20] of spirocyclic molecules for further studies without the involvement of a [2+2+2] cycloaddition.[21]

4. Experimental section

4.1. General

Commercially accessible reagents were used without purification and reactions involving air sensitive catalysts or reagents were performed in degassed solvents. Moisture sensitive materials were transferred by using syringe-septum techniques and the reactions were maintained under nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed on (7.5×2.5 cm) glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder) by using a suitable mixture of EtOAc and petroleum ether for development. Column chromatography was performed by using Acme's silica gel (100–200 mesh) with an appropriate mixture of EtOAc and petroleum ether. The coupling constants (J) are given in hertz (Hz) and chemical shifts are denoted in parts per million (ppm) downfield from internal reference, tetramethylsilane (TMS). The abbreviations s, d, t, q, m, dd and td, refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublet, and triplet of doublet respectively. Yields refer to the isolated yields after column chromatography technique. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT IR spectrometer in $CHCl_3$. Proton nuclear magnetic resonance (^1H NMR, 400 MHz and 500 MHz) spectra and carbon nuclear magnetic resonance (^{13}C NMR, 100 MHz and 125 MHz) spectra were recorded on a Bruker spectrometer. The high-resolution mass measurements were carried out by using electrospray ionization (ESI, Q-ToF) spectrometer. Melting points were recorded on a Veggo melting point apparatus.

4.2. Preparation of compound 16

This compound has been prepared by the known procedure and the ^1H, ^{13}C NMR data matched with the literature reported spectral data.[15]

4.3. General procedure for the synthesis of 14b–c, 14g and 14j

To a solution of compounds **10b–c**, **10g** or **10j**, K_2CO_3 (5 equiv) and TBAHS (0.5 equiv) in dry MeCN (25 mL), tetra-bromo derivative **16** (1.2 equiv) was added and the reaction mixture was stirred at rt for 12–16 h. At the conclusion of reaction (TLC monitoring), excess amount of K_2CO_3 was filtered through the sintered glass funnel and the aqueous layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to deliver the expected products **14b** (8%, 355 mg from 1.5 g of **10b**, 8 h), **14b′** (30%, 1.33 g from 1.5 g of **10b**, 8 h), **14c** (60%, 853 mg from 500 mg of **10c**, 12 h), **14g** (68%, 404 mg from 250 mg of **10g**, 8 h), and **14j** (55%, 350 mg from 300 mg of **10j**, 8 h), along with the dimeric products **17b–c**, and **17g**. The ^1H and ^{13}C NMR spectra of these compounds matched with the reported spectral data.[14]

4.4. General procedure for the synthesis of compounds 14a, 14d–f and 14h–i

To a suspension of sodium hydride (3 equiv) in dry THF (20 mL), compounds **10a**, **10d–f** or **10h–i** were added and the reaction

mixture was stirred at rt for 10 min. Later, tetra-bromo compound **16** (1.2 equiv) was added and the stirring was continued at the same temperature for 8–12 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with EtOAc and the solvent was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 and the crude products were purified using appropriate mixtures of EtOAc-petroleum ether to deliver the expected products **14a** (39%, 1.09 g from 1 g of **10a**, 12 h), **14d** (40%, 636 mg from 500 mg of **10d**, 8 h), **14e** (48%, 285 mg from 200 mg of **10e**, 12 h), **14f** (44%, 580 mg from 500 mg of **10f**, 20 h), **14h** (32%, 175 mg from 200 mg of **10h**, 24 h) and **14i** (36%, 204 mg from 300 mg of **10i**, 15 h), along with the dimeric products **17a** and **17d–f** products. The ^1H and ^{13}C NMR spectra of these compounds matched with the literature reported spectral data.[14b]

4.5. Compound 17a

White solid; yield=25% (697 mg, starting from 1 g of **10a**); reaction time=12 h; mp 139–141 °C; R_f=0.49 (silica gel, 10% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ=1.24 (t, J=7.12 Hz, 12H), 3.51 (s, 8H), 4.18 (q, J_1=7.08 Hz, J_2=14.20 Hz, 8H), 7.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.12, 40.15, 60.75, 61.76, 120.10, 139.01, 171.76; HRMS (ESI, Q-Tof) calculated for $C_{24}H_{30}NaO_8$ $[M+Na]^+$ 469.1833, found: 469.1835; IR ($CHCl_3$): υ_{max}: 1255, 1679, 1730, 2983, 3054 cm^{-1}.

4.6. Compound 17b

The ^1H and ^{13}C NMR spectra matched with the reported spectral data.[14c]

4.7. Compound 17c

White solid; yield=4% (56 mg, starting from 500 mg of **10c**); reaction time=12 h; mp 157–158 °C; R_f=0.55 (silica gel, 50% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ=3.28–3.36 (m, 12H), 3.58 (d, J=7.29 Hz, 4H), 3.99 (s, 2H), 5.41 (s, 2H), 7.18 (d, J=7.45 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=27.37, 28.59, 29.13, 29.20, 43.67, 44.50, 56.25, 72.10, 89.30, 124.47, 124.58, 132.50, 138.52, 140.46, 141.41, 150.74, 151.30, 157.31, 163.56, 171.91, 172.01; HRMS (ESI, Q-Tof) calculated for $C_{22}H_{22}N_4NaO_6$ $[M+Na]^+$ 461.1432, found: 461.1427; IR ($CHCl_3$): υ_{max}: 1681, 1750, 2837, 2934, 2961, 3020 cm^{-1}.

4.8. Compound 17d

White solid; yield=20% (295 mg, starting from 500 mg of **10d**); reaction time=8 h; mp 230 °C (decomposed); R_f=0.51 (silica gel, 25% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ=2.78–2.83 (m, 4H), 3.20 (d, J=5.05 Hz, 4H), 3.44–3.49 (m, 4H), 7.06 (s, 2H), 7.39–7.46 (m, 4H), 7.63 (t, J=7.52 Hz, 2H), 7.82 (d, J=7.60 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=44.24, 44.59, 58.07, 120.56, 120.68, 124.49, 126.72, 127.72, 135.07, 136.40, 140.43, 152.76, 209.18; HRMS (ESI, Q-Tof) calculated for $C_{28}H_{22}NaO_2$ $[M+Na]^+$ 413.1512 found: 413.1515; IR ($CHCl_3$): υ_{max}: 1608, 1710, 2922, 3077, 3301 cm^{-1}.

4.9. Compound 17e

White solid; yield=11% (63 mg, starting from 200 mg of **10e**); reaction time=12 h; mp 171–173 °C; R_f=0.55 (silica gel, 25% EtOAc-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ=2.27 (t, J=6.20 Hz, 4H), 2.96–3.00 (m, 4H), 3.13 (t, J=6.15 Hz, 4H), 3.47–3.52 (m, 4H), 7.07 (d, J=7.40 Hz, 2H), 7.30–7.32 (m, 2H), 7.38 (t, J=4.40 Hz, 2H), 7.54 (dt, J_1=1.30 Hz, J_2=7.14 Hz, 2H), 8.11–8.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.27, 34.08, 41.10, 41.19, 54.02, 120.96, 126.83, 126.88, 128.33, 128.39, 128.81, 128.87, 131.85, 133.33, 139.85, 143.41, 200.73; HRMS (ESI, Q-Tof) calculated for $C_{30}H_{26}NaO_2$ $[M+Na]^+$ 441.1825 found: 441.1827; IR ($CHCl_3$): υ_{max}: 1216, 1454, 1601, 1680, 2854, 2930, 3016 cm^{-1}.

4.10. Compound 17f

White solid; yield=7% (95 mg, starting from 500 mg of **10f**); reaction time=20 h; mp 182–183 °C; R_f=0.50 (silica gel, 25% EtOAc-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ=2.17 (t, J=6.20 Hz, 4H), 2.86 (d, J=15.16 Hz, 4H), 3.02 (t, J=6.12 Hz, 4H), 3.43 (d, J=15.16 Hz, 4H), 3.86 (s, 6H), 6.69 (d, J=2.44 Hz, 2H), 6.82 (dd, J_1=2.52 Hz, J_2=8.76 Hz, 2H), 6.99 (s, 2H), 8.03 (d, J=8.76 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.61, 34.14, 41.27, 53.74, 55.53, 112.50, 113.40, 120.90, 125.44, 130.74, 139.88, 145.83, 163.55, 199.58; HRMS (ESI, Q-Tof) calculated for $C_{32}H_{31}O_4$ $[M+H]^+$ 479.2217 found: 479.2214; IR ($CHCl_3$): υ_{max}: 1216, 1600, 1681, 2929, 3019 cm^{-1}.

4.11. Compound 17g

White solid; yield=15% (107 mg, starting from 250 mg of **10g**); reaction time=8 h; mp 210–211 °C; R_f=0.59 (silica gel, 25% EtOAc-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ=2.76 (t, J=7.15 Hz, 4H), 3.13–3.19 (m, 8H), 3.75 (d, J=15.45 Hz, 4H), 7.00 (s, 2H), 7.13–3.20 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=28.81, 37.58, 44.81, 59.42, 120.09, 126.25, 126.83, 127.50, 128.12, 135.32, 139.94, 143.30, 212.97; HRMS (ESI, Q-Tof) calculated for $C_{30}H_{26}NaO_2$ $[M+Na]^+$ 441.1825 found: 441.1828; IR ($CHCl_3$): υ_{max}: 665, 1265, 1706, 2856, 2932, 3033 cm^{-1}.

4.12. Compound 18a–j

These compound have been prepared by the known procedure and the ^1H, ^{13}C NMR spectra matched with the literature reported spectral data.[14]

4.13. General procedure for the synthesis of sulfones 19a–j

The solution of compounds **18a–j** in toluene (20 mL) was refluxed for 9–14 h. At the conclusion of reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography (50–70% EtOAc-petroleum ether) to afford the sulfones **19a–j**.

4.14. Compound 19a

White solid; yield=78% (39 mg, starting from 50 mg of **18a**); reaction time=12 h; mp 196–198 °C; R_f=0.66 (silica gel, 50% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ=1.26 (t, J=7.12 Hz, 6H), 3.57 (s, 4H), 4.21 (q, J_1=7.12 Hz, J_2=14.20 Hz, 4H), 4.31 (s, 4H), 7.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.18, 40.33, 57.02, 60.53, 62.11, 122.10, 129.94, 141.34, 171.35; HRMS (ESI, Q-Tof) calculated for $C_{17}H_{20}KO_6S$ $[M+K]^+$ 391.0612, found: 391.0617; IR ($CHCl_3$): υ_{max}: 1603, 1732, 2854, 2936, 3033 cm^{-1}.

4.15. Compound 19b

White solid; yield=80% (64 mg, starting from 80 mg of **18b**); reaction time=9 h; mp 222–224 °C; R_f=0.58 (silica gel, 50% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ=3.35 (s, 4H), 4.36 (s, 4H), 7.18 (s, 2H), 7.91 (dd, J_1=3.08 Hz, J_2=5.68 Hz, 2H), 8.03 (dd, J_1=3.12 Hz, J_2=5.64 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=40.44, 57.09, 58.86, 122.08, 123.98, 130.26, 136.32, 141.50, 141.68, 202.53; HRMS (ESI, Q-Tof) calculated for $C_{19}H_{14}NaO_4S$ $[M+Na]^+$ 361.0505, found: 361.0505; IR ($CHCl_3$): υ_{max}: 1216, 1598, 1743, 2846, 2936, 3020 cm^{-1}.

4.16. Compound 19c

White solid; yield=85% (34 mg, starting from 40 mg of **18c**); reaction time=12 h; mp 195 °C (decomposed); R_f=0.38 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.34 (s, 6H), 3.61 (s, 4H), 4.33 (s, 4H), 7.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=29.29, 44.14, 56.29, 57.03, 121.92, 130.47, 140.67, 151.32, 171.82; HRMS (ESI, Q-Tof) calculated for $C_{16}H_{17}N_2O_5S$ $[M+H]^+$ 349.0858, found: 349.0850; IR ($CHCl_3$): υ_{max}: 1453, 1681, 1744, 2850, 2922 cm^{-1}.

4.17. Compound 19d

White solid; yield=76% (42 mg, starting from 55 mg of **18d**); reaction time=12 h; mp 176–178 °C; R_f=0.57 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.80 (d, J=15.08 Hz, 2H), 3.12 (s, 2H), 3.41 (d, J=15.81 Hz, 2H), 4.25, 4.31 (ABq, J=15.61 Hz, 4H), 7.10 (s, 2H), 7.34–7.39 (m, 2H), 7.57 (td, J_1=1.12 Hz, J_2=7.52 Hz, 1H), 7.76 (d, J=7.64 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=43.68, 44.57, 57.14, 57.63, 122.28, 124.64, 126.82, 127.97, 129.73, 135.42, 136.09, 142.92, 152.52, 208.62; HRMS (ESI, Q-Tof) calculated for $C_{19}H_{16}NaO_3S$ $[M+Na]^+$ 347.0718, found: 347.0707; IR ($CHCl_3$): υ_{max}: 1216, 1602, 1701, 2846, 2926, 3020 cm^{-1}.

4.18. Compound 19e

White solid; yield=90% (45 mg, starting from 50 mg of **18e**); reaction time=10 h; mp 246–247 °C; R_f=0.55 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.37 (t, J=6.20 Hz, 2H), 3.11 (d, J=16.15 Hz, 2H), 3.22 (t, J=6.15 Hz, 2H), 3.59 (d, J=16.17 Hz, 2H), 4.42, 4.45 (ABq, J=15.70 Hz, 4H), 7.25 (s, 2H), 7.40 (d, J=3.00 Hz, 1H), 7.46 (t, J=7.55 Hz, 1H), 7.63 (t, J=7.35 Hz, 1H), 8.16 (8, J=7.80 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.26, 34.08, 41.26, 53.79, 57.04, 122.27, 126.98, 128.31, 128.87, 129.50, 131.27, 133.61, 142.54, 143.33, 200.25; HRMS (ESI, Q-Tof) calculated for $C_{20}H_{18}NaO_3S$ $[M+Na]^+$ 361.0869, found: 361.0862; IR ($CHCl_3$): υ_{max}: 1215, 1594, 1687, 2854, 2930, 3016 cm^{-1}.

4.19. Compound 19f

White solid; yield=81% (57 mg, starting from 70 mg of **18f**); reaction time=12 h; mp 270–271 °C; R_f=0.57 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.20 (t, J=6.28 Hz, 2H), 2.95 (d, J=16.09 Hz, 2H), 3.03 (t, J=6.20 Hz, 2H), 3.46 (d, J=16.09 Hz, 2H), 3.87 (s, 3H), 4.28, 4.33 (ABq, J=15.68 Hz, 4H), 6.71 (d, J=2.40 Hz, 1H), 6.85 (dd, J_1=2.52 Hz, J_2=8.76 Hz, 1H), 7.12 (s, 2H), 8.01 (d, J=8.76 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=26.69, 34.22, 41.50, 53.58, 55.62, 57.09, 112.56, 113.64, 122.28, 124.87, 129.43, 130.81, 142.74, 145.83, 163.80, 199.16; HRMS (ESI, Q-Tof) calculated for $C_{21}H_{20}NaO_4S$ $[M+Na]^+$ 391.0975, found: 391.0975; IR ($CHCl_3$): υ_{max}: 1259, 1451, 1598, 1670, 2935, 2962 cm^{-1}.

4.20. Compound 19g

White solid; yield=90% (90 mg, starting from 100 mg of **18g**); reaction time=12 h; mp 146–148 °C; R_f=0.52 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.77 (t, J=7.15 Hz, 2H), 3.16–3.23 (m, 4H), 3.76 (d, J=16.35 Hz, 2H), 4.29, 4.32 (ABq, J=15.72 Hz, 4H), 7.06 (d, J=7.65 Hz, 1H), 7.13–7.21 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=28.69, 37.31, 44.65, 57.06, 59.11, 121.99, 125.96, 127.12, 127.49, 128.38, 129.92, 135.54, 142.14, 142.24, 212.19; HRMS (ESI, Q-Tof) calculated for $C_{20}H_{18}NaO_3S$ $[M+Na]^+$ 361.0869, found: 361.0864; IR ($CHCl_3$): υ_{max}: 1219, 1484, 2851, 2923, 3021 cm^{-1}.

4.21. Compound 19h

White solid; yield=91% (82 mg, starting from 90 mg of **18h**); reaction time=10 h; mp 210 °C (decomposed); R_f=0.49 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.41 (s, 4H), 4.41 (s, 4H), 7.21–7.24 (m, 6H), 7.36 (t, J=6.44 Hz, 2H), 7.74 (d, J=7.44 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=45.17, 57.17, 57.42, 120.07, 122.35, 122.41, 127.75, 129.75, 139.70, 144.20, 151.74; HRMS (ESI, Q-Tof) calculated for $C_{23}H_{18}NaO_2S$ $[M+Na]^+$ 381.0920, found: 381.0919; IR ($CHCl_3$): υ_{max}: 1476, 1577, 2840, 2928, 3021 cm^{-1}.

4.22. Compound 19i

White solid; yield=82% (246 mg, starting from 300 mg of **18i**); reaction time=12 h; mp 198 °C (decomposed); R_f=0.47 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.40 (s, 4H), 4.43 (s, 4H), 7.25 (d, J=1.52 Hz, 2H), 7.32 (d, J=1.60 Hz, 2H), 7.48 (dd, J_1=1.72 Hz, J_2=8.12 Hz, 2H), 7.55 (d, J=8.12 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=45.04, 57.18, 57.38, 121.55, 121.93, 122.63, 125.83, 130.28, 131.18, 137.74, 143.16, 153.67; HRMS (ESI, Q-Tof) calculated for $C_{23}H^{79}_{16}Br_2NaO_2S$ $[M+Na]^+$ 536.9120, found: 536.9127; IR ($CHCl_3$): υ_{max}: 1216, 1449, 1522, 1600, 2846, 2927, 3019 cm^{-1}.

4.23. Compound 19j

Orange solid; yield=80% (32 mg, starting from 40 mg of **18j**); reaction time=14 h; 270 °C (decomposed); R_f=0.44 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.53 (s, 4H), 4.46 (s, 4H), 7.32 (s, 2H), 7.96 (d, J=8.40 Hz, 2H), 8.13 (s, 2H), 8.35 (dd, J_1=2.08 Hz, J_2=8.40 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=44.73, 57.13, 57.81, 118.29, 121.96, 122.87, 124.40, 130.99, 142.20, 143.40, 148.80, 154.46; HRMS (ESI, Q-Tof) calculated for $C_{23}H_{16}N_2NaO_6S$ $[M+Na]^+$ 471.0621, found: 471.0623; IR ($CHCl_3$): υ_{max}: 1212, 1341, 1514, 1640, 2847, 2917, 3021 cm^{-1}.

4.24. General procedure for the synthesis of compounds 20a–e

The solution of DEAM (1 equiv), TBAHS (0.25 equiv) and K_2CO_3 (5 equiv) in dry MeCN (10–25 mL), was stirred at rt for 15 min. Later, compound **14b–c**, or **14h–j** was added and stirring was continued for 15–20 h at the same temperature. At the conclusion of the reaction (TLC monitoring), K_2CO_3 was filtered through the glass sintered funnel and the solvent was removed under reduced pressure. The crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to give the desired products **20a–e**.

4.25. Compound 20a

White solid; yield=66% (52 mg, starting from 70 mg of **14b**); reaction time=16 h; mp 257–260 °C; R_f=0.31 (silica gel, 60% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.20 (t, J=7.07 Hz, 6H), 2.29 (s, 3H), 3.31 (s, 4H), 3.41 (s, 2H), 4.18 (q, J_1=2.50 Hz, J_2=6.92 Hz, 4H), 4.66 (s, 2H), 7.02 (s, 2H), 7.90 (dd, J_1=3.08 Hz, J_2=5.64 Hz, 2H), 8.02 (dd, J_1=3.08 Hz, J_2=5.08 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.11, 22.59, 37.68, 40.47, 48.18, 58.95, 62.10, 68.22, 122.08, 123.71, 123.88, 131.55, 131.93, 136.18, 139.90, 140.35, 141.56, 168.08, 171.01, 202.84; HRMS (ESI, Q-Tof) calculated for $C_{28}H_{27}NNaO_7$ $[M+Na]^+$ 512.1680, found: 512.1678; IR ($CHCl_3$): υ_{max}: 1415, 1654, 1709, 1742, 2252, 2944, 3121 cm^{-1}.

4.26. Compound 20b

White solid; yield=56% (31 mg, starting from 50 mg of **14c**); reaction time=18 h; mp 293 °C (decomposed); R_f=0.17 (silica gel,

60% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.19 (t, J=7.12 Hz, 6H), 2.28 (s, 3H), 3.31 (s, 6H), 3.39 (s, 2H), 3.57 (s, 4H), 4.17 (q, J_1=3.52 Hz, J_2=7.04 Hz, 4H), 4.64 (s, 2H), 7.00 (d, J=3.88 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.12, 22.61, 29.27, 37.63, 44.05, 44.19, 48.14, 56.39, 62.15, 68.20, 121.93, 123.59, 131.81, 132.15, 138.83, 139.36, 151.45, 168.07, 171.00, 172.02; HRMS (ESI, Q-Tof) calculated for $C_{25}H_{30}N_3O_8$ $[M+H]^+$ 500.2027, found: 500.2026; IR ($CHCl_3$): υ_{max}: 1217, 1374, 1734, 2399, 2923, 2978, 3020 cm^{-1}.

4.27. Compound 20c

White solid; yield=65% (110 mg, starting from 150 mg of **14h**); reaction time=15 h; mp 215–218 °C; R_f=0.25 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.23 (t, J=7.12 Hz, 6H), 2.32 (s, 3H), 3.36 (s, 4H), 3.47 (s, 2H), 4.18–4.25 (m, 4H), 4.72 (s, 2H), 7.11–7.21 (m, 6H), 7.34 (t, J=6.96 Hz, 2H), 7.73 (d, J=7.56 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.19, 22.64, 37.77, 45.06, 45.13, 48.31, 57.65, 62.07, 68.41, 120.03, 122.33, 122.60, 124.20, 127.62, 131.12, 131.59, 139.73, 142.49, 142.93, 152.08, 168.18, 171.06; HRMS (ESI, Q-Tof) calculated for $C_{32}H_{31}NNaO_5$ $[M+Na]^+$ 532.2094, found: 532.2092; IR ($CHCl_3$): υ_{max}: 1399, 1444, 1666, 1727, 1747, 2938, 2982 cm^{-1}.

4.28. Compound 20d

White solid; yield=37% (189 mg, starting from 470 mg of **14i**); reaction time=20 h; mp 230–231 °C; R_f=0.22 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.23 (t, J=7.16 Hz, 6H), 2.31 (s, 3H), 3.32 (s, 4H), 3.46 (s, 2H), 4.18–4.23 (m, 4H), 4.72 (s, 2H), 7.10 (s, 2H), 7.25 (d, J=1.40 Hz, 2H), 7.45 (dd, J_1=1.44 Hz, J_2=8.08 Hz, 2H), 7.52 (d, J=8.10 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.20, 22.58, 37.72, 44.80, 44.85, 48.20, 57.56, 62.10, 68.26, 121.43, 121.73, 122.69, 124.23, 125.72, 130.94, 131.53, 131.90, 137.64, 141.32, 141.77, 153.86, 168.04, 171.05; HRMS (ESI, Q-Tof) calculated for $C_{32}H_{29}^{79}Br_2NNaO_5$ $[M+Na]^+$ 688.0305, found: 688.0308; IR ($CHCl_3$): υ_{max}: 1660, 1737, 2265, 2851, 2927, 3051 cm^{-1}.

4.29. Compounds 20d′

White solid; yield=15% (102 mg, starting from 470 mg of **14i**); reaction time=20 h; mp 223–225 °C; R_f=0.19 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.24 (t, J=7.12 Hz, 6H), 1.28 (t, J=7.20 Hz, 6H), 2.08 (s, 3H), 2.32 (s, 3H), 3.35 (s, 4H), 3.47 (s, 2H), 4.19–4.31 (m, 8H), 4.74 (s, 2H), 5.16 (d, J=7.00 Hz, 1H), 6.51 (br s, 1H), 7.12 (s, 2H), 7.47 (dd, J_1=1.72 Hz, J_1=8.12 Hz, 3H). 7.55 (d, J=8.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.11, 14.21, 22.58, 22.89, 37.73, 44.83, 44.88, 48.21, 56.56, 57.59, 62.09, 62.75, 68.27, 121.44, 121.75, 122.70, 124.25, 125.74, 130.96, 131.56, 131.92, 137.67, 141.34, 141.78, 153.89, 166.54, 168.05, 169.93, 171.03; HRMS (ESI, Q-Tof) calculated for $C_{41}H_{44}^{79}Br_2N_2NaO_{10}$ $[M+Na]^+$ 905.1255, found: 905.1252; IR ($CHCl_3$): υ_{max}: 1267, 1680, 1736, 2255, 2928, 3020 cm^{-1}.

4.30. Compound 20e

White solid; yield=69% (46 mg, starting from 60 mg of **14j**); reaction time=15 h; mp 227–230 °C; R_f=0.23 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.25 (t, J=7.12 Hz, 6H), 2.32 (s, 3H), 3.48 (s, 4H), 3.51 (s, 2H), 4.19–4.28 (m, 4H), 4.77 (s, 2H), 7.17 (d, J=4.36 Hz, 2H), 7.96 (d, J=8.44 Hz, 2H), 8.10 (d, J=1.96 Hz, 2H), 8.33 (dd, J_1=2.04 Hz, J_2=8.40 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.21, 22.66, 37.73, 44.56, 44.63, 48.24, 58.06, 62.24, 68.22, 118.26, 121.88, 122.88, 124.26, 124.50, 132.26, 132.52, 140.43, 140.90, 143.40, 148.73, 154.73, 168.09, 171.07; HRMS (ESI, Q-Tof) calculated for $C_{32}H_{29}N_3NaO_9$ $[M+Na]^+$ 622.1796, found: 622.1797; IR ($CHCl_3$): υ_{max}: 1344, 1525, 1662, 1742, 2305, 2856, 2986, 3055 cm^{-1}.

4.31. General procedure for the synthesis of 21a–e

The solution of compounds **14b–c**, **h–j**, EICA (1.2 equiv), TBAHS (0.25 equiv) and K_2CO_3 (5 equiv) in dry MeCN (20–25 mL) was refluxed for 14–20 h. At the conclusion of reaction (TLC monitoring), K_2CO_3 was filtered through glass sintered funnel and the solvent was removed under reduced pressure. The crude products were then dissolved in EtOH (20 mL), conc. HCl (0.50 mL) was added slowly and the reaction was stirred at rt for 1–2 h. The reaction mixture was made neutral by adding liq. NH_3 solution. Later, the solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to afford the unprotected **21c–e** AAAs derivatives. Later, the crude products were dissolved in MeCN (15 mL), acetic anhydride (Ac_2O, 3 mL) was added to it and the reaction mixture was stirred at rt for 12–13 h. The solvent was removed under the reduced pressure and the crude products were purified by silica gel column chromatography using (60% EtOAc-petroleum ether) to deliver the protected AAAs derivatives **21a** and **21b**.

4.32. Compound 21a

White solid; yield=42% (81 mg, starting from 200 mg of **14b**); reaction time=(15+2+13) h; mp 283–285 °C; R_f=0.17 (silica gel, 60% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.27 (t, J=7.20 Hz, 3H), 1.93 (s, 3H), 3.16–3.33 (m, 6H), 3.61 (d, J=16.48 Hz, 2H), 4.23 (q, J_1=6.96 Hz, J_2=14.04 Hz, 2H), 6.23 (br s, 1H), 7.03 (s, 2H), 7.88 (dd, J_1=2.96 Hz, J_2=5.20 Hz, 2H), 8.01 (d, J=3.52 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.29, 23.20, 40.38, 43.23, 59.28, 61.77, 66.53, 120.60, 123.82, 123.86, 136.08, 136.12, 139.33, 139.58, 141.51, 141.62, 170.49, 172.90, 202.96, 203.19; HRMS (ESI, Q-Tof) calculated for $C_{25}H_{23}NNaO_5$ $[M+Na]^+$ 440.1468, found: 440.1457; IR ($CHCl_3$): υ_{max}: 1225, 1589, 1659, 1704, 1731, 2851, 2928, 3020, 3238 cm^{-1}.

4.33. Compound 21b

White solid; yield=39% (94 mg, starting from 250 mg of **14c**); reaction time=(12+2+12) h; mp>300 °C; R_f=0.25 (silica gel, 70% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.24 (t, J=6.64 Hz, 3H), 1.88 (s, 3H), 3.14 (d, J=16.48 Hz, 2H), 3.28–3.42 (m, 8H), 3.52–3.58 (m, 4H), 4.19 (q, J_1=6.88 Hz, J_2=14.24 Hz, 2H), 6.39 (br s, 1H), 6.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.27, 23.11, 29.16, 29.22, 43.05, 43.16, 44.13, 56.46, 61.77, 66.47, 120.41, 138.52, 138.65, 139.41, 139.59, 151.46, 170.49, 172.17, 172.49, 172.86; HRMS (ESI, Q-Tof) calculated for $C_{22}H_{25}N_3NaO_6$ $[M+Na]^+$ 450.1636, found: 450.1634; IR ($CHCl_3$): υ_{max}: 1216, 1374, 1734, 2399, 2923, 2978, 3020 cm^{-1}.

4.34. Compound 21c

White solid; yield=59% (103 mg, starting from 200 mg of **14h**); reaction time=17 h; mp 157 °C (decomposed); R_f=0.18 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.32 (t, J=7.12 Hz, 3H), 1.97 (br s, 2H), 2.91 (d, J=15.97 Hz, 2H), 3.33, 3.48 (ABq, J_1=7.78 Hz, J_2=15.64 Hz, 4H), 3.60 (d, J=15.93 Hz, 2H), 4.26 (q, J_1=7.00 Hz, J_2=14.12 Hz, 2H), 7.14–7.35 (m, 8H), 7.72 (d, J=7.52 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.40, 45.16, 46.04, 57.70, 61.55, 65.49, 119.89, 121.26, 122.44, 122.66, 127.42, 127.60, 127.68, 139.33, 139.64, 139.71, 141.82, 152.48, 152.87, 176.76; HRMS (ESI, Q-Tof) calculated for $C_{27}H_{26}NO_2$ $[M+H]^+$ 396.1958, found: 396.1956; IR ($CHCl_3$): υ_{max}: 1216, 1447, 1478, 1726, 2309, 2835, 2928, 3018, 3373 cm^{-1}.

4.35. Compound 21d

White solid; yield=45% (57 mg, starting from 140 mg of **14i**); reaction time=14 h; mp 270 °C (decomposed); R_f=0.16 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.32 (t, J=7.12 Hz, 3H), 2.17 (br s, 2H), 2.92 (d, J=15.97 Hz, 2H), 3.23, 3.33 (ABq, J_1=7.78 Hz, J_2=16.01 Hz, 4H), 3.60 (d, J=15.93 Hz, 2H), 4.26 (q, J_1=7.08 Hz, J_2=14.20 Hz, 2H), 7.11 (s, 2H), 7.30 (d, J=1.48 Hz, 2H), 7.33–7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.36, 44.88, 45.90, 57.60, 61.48, 65.44, 121.28, 121.67, 121.73, 125.69, 125.99, 130.70, 130.72, 137.45, 137.65, 139.76, 140.60, 154.12, 154.82, 176.53; HRMS (ESI, Q-Tof) calculated for $C_{27}H_{23}NNaO_2^{79}Br_2$ $[M+Na]^+$ 573.9988, found: 573.9988; IR ($CHCl_3$): υ_{max}: 1218, 1447, 1478, 1622, 1728, 2254, 2841, 2940, 3020, 3528 cm^{-1}.

4.36. Compound 21e

White solid; yield=48% (86 mg, starting from 200 mg of **14j**); reaction time=17 h; mp 230 °C (decomposed); R_f=0.16 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.34 (t, J=7.22 Hz, 3H), 1.79 (br s, 2H), 2.95 (d, J=15.96 Hz, 2H), 3.39, 3.52 (ABq, J_1=7.89 Hz, J_2=16.08 Hz, 4H), 3.63 (d, J=15.93 Hz, 2H), 4.29 (q, J_1=7.08 Hz, J_2=14.20 Hz, 2H), 7.19 (s, 2H), 7.94 (dd, J_1=2.16 Hz, J_2=8.36 Hz, 2H), 8.10 (d, J=1.84 Hz, 1H), 8.22 (d, J=1.80 Hz, 1H), 8.31–8.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.42, 44.66, 46.03, 58.28, 61.62, 65.65, 118.25, 118.63, 121.57, 121.68, 121.73, 124.06, 139.78, 140.60, 143.24, 143.52, 148.76, 154.90, 155.69, 176.56; HRMS (ESI, Q-Tof) calculated for $C_{27}H_{24}N_3O_6$ $[M+H]^+$ 486.1660, found: 486.1660; IR ($CHCl_3$): υ_{max}: 1517, 1583, 1725, 2401, 2851, 2923, 3016 cm^{-1}.

4.37. General procedure for the synthesis of 22a, 22d, 22h and 22i

To a solution of compound **10c**, K_2CO_3 (5 equiv) and TBAHS (0.5 equiv) in dry MeCN (25 mL), compounds **14a**, **b**, **e**, **j** (1.1 equiv) were added and stirred the reaction mixture at rt for 6–12 h. At the conclusion of reaction (TLC monitoring), excess amount of K_2CO_3 was filtered through the sintered funnel and the aqueous layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to deliver the products **22a**, **22d**, **22h** and **22i** (Fig. 10).

4.38. General procedure for the synthesis of 17d–f and 22b–g

To a suspension of sodium hydride (3 equiv) in dry THF (20 mL), was added the compounds **10b–f** and the reaction mixture was stirred at rt for 10 min. Later, compounds **14c–f** (1.1 equiv) were added and the stirring was continued for 8–20 h at the same temperature. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with saturated aq NH_4Cl (5 mL) solution. Aqueous layer was then extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to afford the desired products **17d** (75%, 104 mg from 150 mg of **14d**, 6 h), **17e** (67%, 65 mg from 100 mg of **14e**, 12 h), **17f** (56%, 34 mg from 60 mg of **14f**, 20 h) and **22b–g** (Fig. 10). The spectral data of compounds **17d–f** prepared by this route matched with earlier route (Scheme 2 and Fig. 5).

4.39. Compound 22a

White solid; yield=69% (68 mg, starting from 100 mg of **14b**); reaction time=12 h; mp 290 °C (decomposed); R_f=0.46 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.29 (s, 4H), 3.33 (s, 6H), 3.56 (s, 4H), 7.03 (s, 2H), 7.87 (dd, J_1=3.10 Hz, J_2=5.65 Hz, 2H), 8.01 (dd, J_1=2.60 Hz, J_2=5.65 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=29.25, 40.39, 43.93, 56.89, 59.36, 119.99, 123.88, 136.07, 138.76, 140.09, 141.62, 151.62, 172.16, 203.01; HRMS (ESI, Q-Tof) calculated for $C_{25}H_{20}KN_2O_5$ $[M+K]^+$ 467.1004 found: 467.1009; IR ($CHCl_3$): υ_{max}: 1216, 1420, 1683, 1709, 1742, 2400, 2857, 2925, 3020 cm^{-1}.

4.40. Compound 22b

White solid; yield=81% (75 mg, starting from 100 mg of **14b**); reaction time=8 h; mp 239–241 °C; R_f=0.56 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.79 (d, J=15.45 Hz, 2H), 3.19 (s, 2H), 3.32, 3.35 (ABq, J=15.50 Hz, 4H), 3.46 (d, J=15.45 Hz, 2H), 7.06 (s, 2H), 7.41 (t, J=7.45 Hz, 1H), 7.45 (d, J=7.60 Hz, 1H), 7.62 (t, J=7.05 Hz, 1H), 7.82 (d, J=7.60 Hz, 1H), 7.88 (dd, J_1=3.05 Hz, J_2=5.45 Hz, 2H), 8.02–8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=40.48, 44.22, 44.59, 58.25, 59.40, 120.38, 123.81, 123.90, 124.51, 126.82, 127.74, 135.13, 136.02, 136.08, 136.44, 139.24, 141.07, 141.60, 141.66, 152.86, 203.03, 203.34, 209.22; HRMS (ESI, Q-Tof) calculated for $C_{28}H_{20}NaO_3$ $[M+Na]^+$ 427.1305 found: 427.1308; IR ($CHCl_3$): υ_{max}: 1276, 1465, 1596, 1701, 1735, 2854, 2918, 3013 cm^{-1}.

4.41. Compound 22c

White solid; yield=78% (80 mg, starting from 100 mg of **14b**); reaction time=16 h; mp 252–253 °C; R_f=0.50 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.14 (t, J=6.25 Hz, 2H), 2.85 (d, J=15.80 Hz, 2H), 2.98 (t, J=6.20 Hz, 2H), 3.19–3.29 (m, 4H), 3.38 (d, J=15.81 Hz, 2H), 3.81 (s, 3H), 6.65 (d, J=2.40 Hz, 1H), 6.79 (dd, J_1=2.55 Hz, J_2=8.75 Hz, 1H), 7.25 (s, 1H), 6.97 (s, 1H), 7.81–7.85 (m, 2H), 7.96–7.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.70, 34.21, 40.52, 41.29, 53.93, 55.61, 59.43, 112.55, 113.50, 120.51, 123.82, 123.85, 125.41, 130.83, 135.97, 136.01, 139.00, 140.79, 141.59, 141.73, 145.97, 163.63, 199.71, 203.03, 203.38; HRMS (ESI, Q-Tof) calculated for $C_{30}H_{24}NaO_4$ $[M+Na]^+$ 471.1567 found: 471.1568; IR ($CHCl_3$): υ_{max}: 1598, 1681, 1706, 1737, 2852, 2924, 3016 cm^{-1}.

4.42. Compound 22d

White solid; yield=71% (33 mg, starting from 50 mg of **14c**); reaction time=10 h; mp 235 °C (decomposed); R_f=0.40 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.77 (d, J=15.07 Hz, 2H), 3.16 (s, 2H), 3.33 (s, 6H), 3.43 (d, J=15.48 Hz, 2H), 3.53, 3.59 (ABq, J=15.80 Hz, 4H), 7.03 (s, 2H), 7.39–7.44 (m, 2H), 7.59 (dt, J_1=1.05 Hz, J_2=7.55 Hz, 1H), 7.80 (d, J=7.60 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=29.16, 29.19, 43.99, 44.12, 44.51, 56.74, 58.12, 120.17, 124.47, 126.76, 127.72, 135.11, 136.35, 138.11, 141.23, 151.55, 152.75, 172.12, 172.33, 209.05; HRMS (ESI, Q-Tof) calculated for $C_{25}H_{22}N_2NaO_4$ $[M+Na]^+$ 437.1472 found: 437.1476; IR ($CHCl_3$): υ_{max}: 1619, 1701, 1745, 2355, 3019 cm^{-1}.

4.43. Compound 22e

White solid; yield=86% (89 mg, starting from 100 mg of **14c**); reaction time=20 h; mp >300 °C; R_f=0.38 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.15 (t, J=6.20 Hz, 2H), 2.85 (d, J=15.80 Hz, 2H), 2.99 (t, J=6.15 Hz, 2H), 3.30 (d, J=3.55 Hz, 6H), 3.38 (d, J=15.80 Hz, 2H), 3.54, 3.83 (ABq, J=15.80 Hz, 4H), 3.84 (s, 3H), 6.66 (d, J=2.15 Hz, 1H), 6.81 (dd, J_1=2.40 Hz, J_2=8.70 Hz, 1H), 6.98 (s, 2H), 7.99 (d, J=8.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.69, 29.19, 29.26, 34.22, 41.28, 44.04, 53.90, 55.61, 56.85, 112.55, 113.52, 120.43, 125.35, 130.83, 137.88, 141.02, 145.93, 151.64, 163.66, 172.10, 172.42, 199.63; HRMS (ESI, Q-Tof) calculated for $C_{27}H_{26}N_2NaO_5$ $[M+Na]^+$ 481.1734 found: 481.1735; IR ($CHCl_3$): υ_{max}: 1216, 1449, 1682, 1735, 2850, 2928, 3020 cm^{-1}.

4.44. Alternate route for the synthesis of compound 22d

White solid; yield=59% (29 mg, starting from 50 mg of **14d**); reaction time=16 h. The ^{1}H, ^{13}C NMR spectra of this compound is identical to that of the compound **22d** prepared by earlier route.

4.45. Compound 22f

White solid; yield=65% (112 mg, starting from 180 mg of **14d**); reaction time=12 h; mp 210–213 °C; R_f=0.55 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.23 (t, J=6.24 Hz, 2H), 2.75 (d, J=15.44 Hz, 2H), 2.92 (d, J=15.76 Hz, 2H), 3.06 (t, J=6.20 Hz, 2H), 3.17 (s, 2H), 3.42–3.47 (m, 4H), 7.03 (s, 2H), 7.25 (d, J=2.16 Hz, 1H), 7.31 (t, J=7.68 Hz, 1H), 7.38–7.49 (m, 3H), 7.70 (dt, J_1=1.08 Hz, J_2=7.52 Hz, 1H), 7.81 (d, J=7.64 Hz, 1H), 8.04 (dd, J_1=1.04 Hz, J_2=7.84 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.33, 34.29, 41.14, 44.30, 44.67, 54.01, 58.17, 120.74, 124.48, 126.74, 126.83, 126.88, 127.70, 128.39, 128.80, 131.69, 133.34, 135.04, 136.51, 140.01, 140.06, 140.28, 143.39, 152.77, 200.69, 209.13; HRMS (ESI, Q-Tof) calculated for $C_{29}H_{25}O_2$ $[M+H]^+$ 405.1849 found: 405.1846; IR ($CHCl_3$): υ_{max}: 1602, 1680, 1706, 2852, 2927, 3016 cm^{-1}.

4.46. Compound 22g

White solid; yield=70% (72 mg, starting from 100 mg of **14d**); reaction time=15 h; mp 232–233 °C; R_f=0.53 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.21 (t, J=5.85 Hz, 2H), 2.76 (d, J=15.30 Hz, 2H), 2.91 (d, J=15.75 Hz, 2H), 3.03 (t, J=5.65 Hz, 2H), 3.18 (s, 2H), 3.45 (dd, J_1=5.65 Hz, J_2=15.50 Hz, 4H), 3.86 (s, 3H), 6.70 (s, 1H), 6.84 (d, J=7.20 Hz, 1H), 7.03 (s, 2H), 7.39–7.44 (m, 2H), 7.61 (t, J=7.15 Hz, 1H), 7.81 (d, J=7.45 Hz, 1H), 8.04 (d, J=8.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.74, 34.40, 41.36, 44.33, 44.69, 53.78, 55.59, 58.20, 112.55, 113.45, 120.75, 124.50, 125.31, 126.75, 127.72, 130.83, 135.05, 136.54, 140.22, 145.86, 152.80, 163.60, 199.65, 209.19; HRMS (ESI, Q-Tof) calculated for $C_{30}H_{27}O_3$ $[M+H]^+$ 435.1955 found: 435.1952; IR ($CHCl_3$): υ_{max}: 1216, 1432, 1617, 1683, 1707, 2855, 2933, 3020 cm^{-1}.

4.47. Compound 22h

White solid; yield=78% (77 mg, starting from 100 mg of **14e**); reaction time=12 h; mp >300 °C; R_f=0.42 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.21 (t, J=6.20 Hz, 2H), 2.90 (d, J=15.80 Hz, 2H), 3.05 (t, J=6.15 Hz, 2H), 3.32 (d, J=3.60 Hz, 6H), 3.42 (d, J=15.85 Hz, 2H), 3.49, 3.57 (ABq, J=15.75 Hz, 4H), 6.99 (s, 2H), 7.24 (d, J=7.70 Hz, 1H), 7.31 (t, J=7.45 Hz, 1H), 7.58 (dt, J_1=1.25 Hz, J_2=6.20 Hz, 1H), 8.03 (dd, J_1=0.90 Hz, J_2=7.85 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=26.29, 29.18, 29.25, 34.13, 41.07, 44.03, 54.13, 56.83, 120.34, 126.91, 128.39, 128.86, 131.72, 133.42, 137.96, 140.87, 143.47, 151.63, 172.09, 172.40, 200.72; HRMS (ESI, Q-Tof) calculated for $C_{26}H_{24}N_2NaO_4$ $[M+Na]^+$ 451.1628 found: 451.1634; IR ($CHCl_3$): υ_{max}: 1216, 1452, 1621, 1680, 1743, 2400, 2854, 2928, 3021 cm^{-1}.

4.48. Alternate route for the synthesis of compound 22f

White solid; yield=84% (39 mg, starting from 50 mg of **14e**); reaction time=12 h. The ^{1}H, ^{13}C NMR spectra of this compound is identical to that of the compound **22f**.

4.49. Compound 22i

White solid; yield=68% (67 mg, starting from 100 mg of **14j**); reaction time=8 h; mp 213–215 °C; R_f=0.42 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.37 (s, 6H), 3.46 (s, 4H), 3.66 (s, 4H), 7.16 (s, 2H), 7.94 (d, J=8.40 Hz, 2H), 8.15 (s, 2H), 8.32 (d, J=8.40 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=29.25, 43.94, 44.55, 56.99, 58.30, 118.41, 120.76, 121.72, 124.08, 139.38, 140.47, 143.34, 148.73, 151.59, 155.09, 172.04; HRMS (ESI, Q-Tof) calculated for $C_{29}H_{22}N_4KO_7$ $[M+K]^+$ 577.1120 found: 577.1124; IR ($CHCl_3$): υ_{max}: 1601, 1737, 2360, 2855, 2928, 3035 cm^{-1}.

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Supplementary data

Supplementary data (The copies of ^{1}H and ^{13}C NMR for all the new compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.07.008.

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