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A Modular Approach Towards Functionalized Highly Stable Self-complementary Quadruple Hydrogen Bonded Systems†

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Suresh Rayavarapu,[a] Sanjeev Kheria,[a] Dinesh R. Shinde,[b] Rajesh G. Gonnade,[c] and Gangadhar J. Sanjayan*[a]

Self-complementary quadruple hydrogen bonded systems have shown potential as key building blocks for developing various supramolecular polymers. Opportunities for introduction of multiple functionalities would further augment, in principle, their application potential. Herein, we report a novel modular approach to simultaneously introduce two closely aligned side chains into **AADD**-type self-complementary quadruple hydrogen-bonding systems. Dithiane-tethered ureidopyrimidinone has been used as a reactive intermediate to efficiently attach closely aligned side chains by simply reacting with amines to form highly stable molecular duplexes. These duplexes featuring **AADD**-type array of hydrogen bonding codes are highly stable in non-polar solvent (K_{dim} > 1.9 x 10^7 M^{-1} in $CDCl_3$) as well as in polar solvent (K_{dim} > 10^5 in 10% DMSO-d_6/$CDCl_3$). Another notable feature of these self-assembling systems is their insensitivity to prototropy-related issues owing to prototropic degeneracy, which will enhance their application potential in supramolecular chemistry.

Introduction

Multiple hydrogen bonded arrays, particularly, **AADD**-type self complementary systems, have received an increasing attention from the last two decades owing to their specificity, strength, directionality and easy synthetic accessibility.[1] These systems have been used to develop different non-covalent supramolecular architectures that have potential applications in supramolecular polymers,[2] molecular recognition[3] and supramolecular electronics.[4] Construction of these supramolecular assemblies is of fundamental importance for mimicking bimolecular structures and thereby understanding the functions of natural systems.[5] Due to their significance in supramolecular chemistry, different types of quadruple hydrogen bonded systems have been developed and studied extensively.[6]

Amidst the myriad quadruple hydrogen bonding systems developed till date, ureidopyrimidinone-based (UPy) self-assembling systems developed by Meijer group,[7] have been extensively utilized in various applications, due to their high stability and easy synthetic accessibility. Analogous to UPy, deazapterin-based self-assembling systems (DeAP)[8] are also known to form strong **AADD**-type hydrogen bonded duplexes. However, it is noteworthy that these aforementioned heterocyclic-based systems are often associated with the prototropy-related demerits, thereby limiting the applications of these systems in supramolecular chemistry.[7c] Further research in this area by various groups led to the development of new **AADD**-type self-assembling modules devoid of prototropy with promise for diverse applications.[9]

Despite the considerable progress achieved in the last two decades in this field, the synthesis of various supramolecular assemblies has been mainly based on ureidopyrimidinone (UPy) systems which are often associated with tautomerization.[7c] In view of the range of properties required from supramolecular materials, there is a need for developing new quadruple hydrogen bonding systems with attractive features, such as high dimerization constant, easy synthetic accessibility, tailorability and prototropy-free assembly.

Herein we report a new class of UPy-based motif **1** with a unique feature of tethered dithiane unit which can serve as toolbox for the preparation of self-assembled systems **2** featuring inbuilt **AADD**-type self-complementary array (Fig. 1). As proof-of-principle, the dithiane intermediates were reacted with various amines to form highly stable and prototropy-free molecular duplexes - stable in non-polar solvent such as $CDCl_3$ and relatively stable in polar solvents (10% DMSO-d_6/$CDCl_3$).

[a] Organic Chemistry Division, CSIR-National Chemical Laboratory (CSIR-NCL), Dr Homi Bhabha Road, Pune-411008, India. E-mail: gj.sanjayan@ncl.res.in; Fax: +91-20-25902629; Tel: +91-20-25902082.
[b] Central NMR Facility, CSIR-National Chemical Laboratory (CSIR-NCL), Dr Homi Bhabha Road, Pune-411008, India.
[c] Centre for Materials Characterization, CSIR-National Chemical Laboratory (CSIR-NCL), Dr. Homi Bhabha Road, Pune-411008, India

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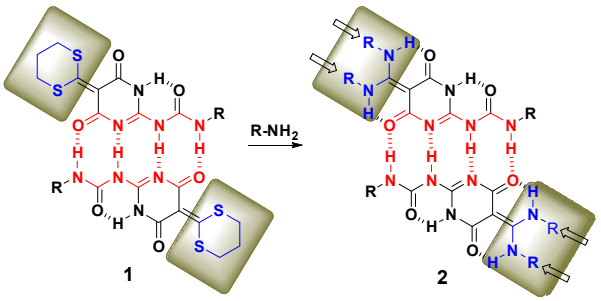
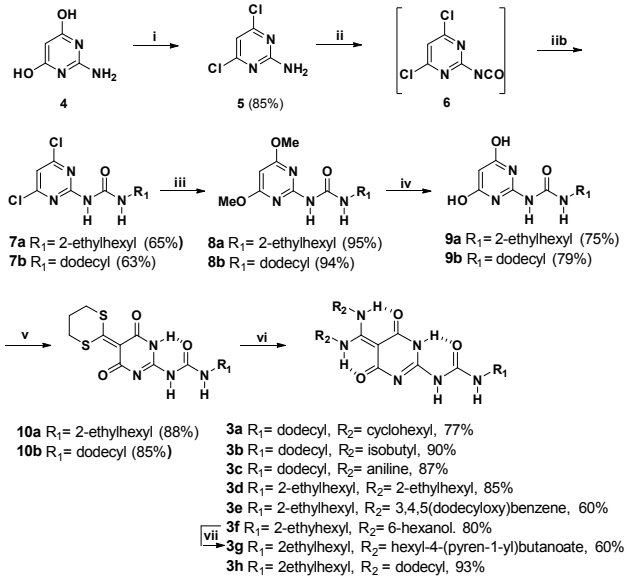


Fig. 1 Dithiane-functionalized reactive AADD-type self-assembling motif (left) and amine-coupled highly stable self-assembled duplex (right), reported in this work. Note: The side chains can be arranged in a parallel fashion on the self-assembling motif, as depicted by the arrows.

Results and discussion

The urea intermediate **7** could be efficiently synthesized *via* a three-step process (Scheme 1). The 2-amino-4,6-dichloropyrimidine **5** was obtained by reacting 2-amino-4,6-dihydroxypyrimidine **4** with $POCl_3$ and Et_3N in acetonitrile under reflux conditions. Subsequently, **5** was converted to its isocyanate[10], by treatment with oxalyl chloride, in refluxing benzene. The highly reactive and unstable isocyanate **6** was treated with amines at room temperature to afford urea intermediate **7**. Conversion of **7a**,**b** to **9a**,**b** *via* direct hydrolysis of chloro substituent proved difficult and resulted in mono hydroxy compound. Therefore, an alternative two-step strategy was adopted in which **7a**,**b** were methoxylated followed by demethylation under HBr/acetic acid condition, resulting in good yields of **9a**,**b**.



Scheme 1 Synthesis of compounds **3a-h**. Reagents and conditions: (i) $POCl_3$, Et_3N, CH_3CN, reflux, 1 h; (ii) a) $(COCl)_2$, C_6H_6, reflux, 2 h, b) R_1-amine, C_6H_6, RT, 18 h; (iii) K_2CO_3, MeOH, reflux, 6 h; (iv) HBr in AcOH, reflux, 1 h; (v) Et_3N, CS_2, 1,3-dibromopropane, DMSO, 0 °C-RT, 6 h; (vi) R_2-amine, DMSO, 0 °C-80 °C, 4 h; (vii) 1-pyrenebutyric acid, EDC.HCl, DMAP, DCM, 0 °C-RT, 6 h

The synthesis of **10a**,**b** was accomplished by reacting **9a**,**b** in DMSO with an excess of carbon disulphide and triethylamine at room temperature, followed by the treatment of reaction mixture with 1,3-dibromopropane in DMSO.[11] Further **10a**,**b** were reacted with corresponding amines in DMSO, to get **AADD**-type self-assembling systems **3a-h** in excellent yields.

Formation of the **AADD**-type self-complementary molecular duplex by **3d** and **3e** was studied in detail by ^1H NMR experiments. ^1H and ^{13}C NMR spectra of **3e** in $CDCl_3$ clearly showed a *single set* of well-resolved signals, which suggested the formation of strong molecular duplex (Fig. 2).The formation of strong duplex of **3e** was quickly evident from the downfield shift of urea NHs at 11.52 and 9.78 ppm; suggesting that the urea NH protons are involved in strong intermolecular hydrogen bonding. Additionally, the signals at 13.66, 12.79 and 12.60 ppm are due to intramolecular S(6)-type hydrogen bonding that facilitates self-assembly by the pre-organization of **AADD**-type H-bonding codes.

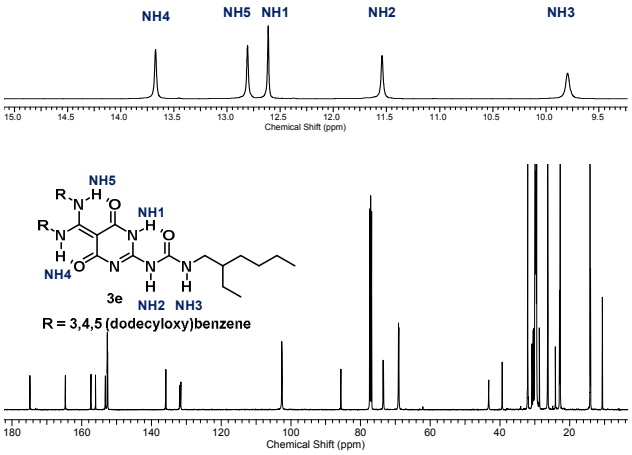


Fig. 2 ^1H excerpts [top (500 MHz)] and ^{13}C [bottom (125 MHz)] spectra of **3e** in CDCl3 showing single set of well-resolved signals.

The dimerization property of compounds **3d** and **3e** were examined by ^1H NMR dilution experiments. Upon dilution of the $CDCl_3$ solution of **3d** from 100 mM to 10 μM, no changes were observed in the chemical shift values of urea protons. Similarly, the dilution of $CDCl_3$ solution of **3e** didn't afford any change in chemical shift of urea protons (ESI,† Fig. S15 and S20 for **3d** and **3e**, respectively). The dilution experiments showed that both **3d** and **3e** remain as dimer with high dimerization constant even at a very low concentration in $CDCl_3$. Assuming a conservative estimate of more than 95% dimer formation at the lowest concentration studied (10 μM), the K_{dim} value of **3d** and **3e** was estimated to be at a lower limit of 1.9×10^7 M^{-1} in $CDCl_3$.

To further support the strong duplex formation of these compounds, we studied the dimerization of **3d**·**3d** and **3e**·**3e** in various DMSO-d_6/$CDCl_3$ mixtures. The K_{dim} values of **3d**·**3d** and **3e**·**3e** were determined quantitatively in the range from 5% to 30% DMSO-d_6/$CDCl_3$ (v/v) mixtures by ^1H NMR dilution experiments (table 1).

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Table 1 Dimerization constants (K_{dim}) of the duplex **3d**·**3d** and **3e**·**3e** in various DMSO-d_6/$CDCl_3$ mixtures at 298 K.

DMSO-d_6/$CDCl_3$	K_{dim} (M^{-1})of **3d**·**3d**	K_{dim} (M^{-1}) of **3e**·**3e**
5%	$>10^5$	$>10^5$
10%	$>10^5$	$>10^5$
20%	$>10^5$	$(2.09 \pm 0.195) \times 10^2$
30%	$(2.25 \pm 0.12) \times 10$	-

Nonlinear regression analysis[12] of the chemical shift of **3d** gave a dimerization constant K_{dim} value of (2.25 ± 0.12) x 10 in 30% DMSO-d_6/$CDCl_3$ and (2.09 ± 0.195) x 10^2 for **3e** in 20% DMSO-d_6/$CDCl_3$ (ESI,† Fig. S20 and S25 for **3d** and **3e**, respectively). In case of **3d**, we observed negligible chemical shift changes of urea protons in 5%, 10% and 20% DMSO-d_6/$CDCl_3$ mixtures (ESI,† Figures S16, S17 and S18, respectively). For **3e** in 5% and 10% DMSO-d_6/$CDCl_3$ mixtures (ESI,† Fig. S22, S23), we observed negligible chemical shift changes of urea protons. For **3d** and **3e**, K_{dim} values were estimated to be at a lower limit of 10^5 M^{-1} under these conditions. These findings suggest that the self-assembled duplexes are highly stable even in DMSO-d_6/$CDCl_3$ mixtures without any prototropy issues, although DMSO is considered to be a highly competitive hydrogen bond breaker.

Variable temperature ^{1}H NMR studies carried out in the range 243-323 K provided further evidence for the strong stability of molecular duplexes. Urea protons of these compounds NH2 (-1.85 ppb K^{-1} for **3a**, -1.30 ppb K^{-1} for **3c** and -1.62 ppb K^{-1} for **3d**) and NH3 (-1.20 ppb K^{-1} for **3a**, 2.50 ppb K^{-1} for **3c** and 1.80 ppb K^{-1} for **3d**) showed small temperature coefficients indicative of strong intermolecular hydrogen bonding. These values indicate very high stability of the molecular duplexes (ESI,† Figures S1, S3 and S5 for **3a**, **3c** and **3d**, respectively).

In addition to NMR methods, the stability of these duplexes was also investigated by fluorescence spectroscopy using pyrene-appended self-assembling system **3g**. Pyrene is well known to form an excimer species in solution, featuring emission band that is well separated from its monomer emission band.[13] The dimerization constant of the pyrene labeled **3g** was determined by a method, that was previously reported by the Meijer group.[7b] Concentration-dependent changes in the emission intensities of pyrene eximer band at 490 nm appeared in the range of 10^{-9} to 10^{-7} in chloroform. Non-linear regression analysis of the fluorescence data of compound **3g** gave a dimerization constant K_{dim} value of (3.44 ± 3.11) x 10^8 M^{-1} in chloroform (ESI,† Fig. S27 and S28).[12a]

Compounds **3a**, **3c** and **3f**, indeed form **AADD**-type duplex formation in the solid-state, as clearly evident from their single X-ray crystal analysis (Fig. 3).[14] Comparison of X-ray crystal structures of these compounds reveals that all three compounds form dimers through four C(4)-type intermolecular hydrogen bonds. The urea functionality is in trans-trans geometry, and three intermolecular S(6)-type hydrogen bonds preorganize the AADD array of duplexes.[15] In all cases, the AADD array of duplexes slightly deviates from linearity and outer N-H···O hydrogen bonds being somewhat shorter than inner N-H···N hydrogen bonds.

Dimer formation by **3d** and **3e** was further investigated by 2D NMR and HRMS-ESI studies. 2D NOESY NMR studies of **3d** and **3e** in CDCl3 provided the most diagnostic nOes and these strong nOes suggest the formation of homodimer structures in solution. The characteristic nOe between NH2 and NH3 protons of **3e** suggested their linear arrangement while the cross-strand nOes between NH3 and NH4, and NH3 and aromatic proton confirmed the AADD-type self-complementary dimer formation in solution (ESI,† Figures S12 and S13). In the HRMS-ESI spectrum of **3d**, in addition to protonated molecular ion peak $(M+H)^+$, signals corresponding to the dimer $(2M+H)^+$ was also found, further supporting the duplex formation (ESI,† page S24).

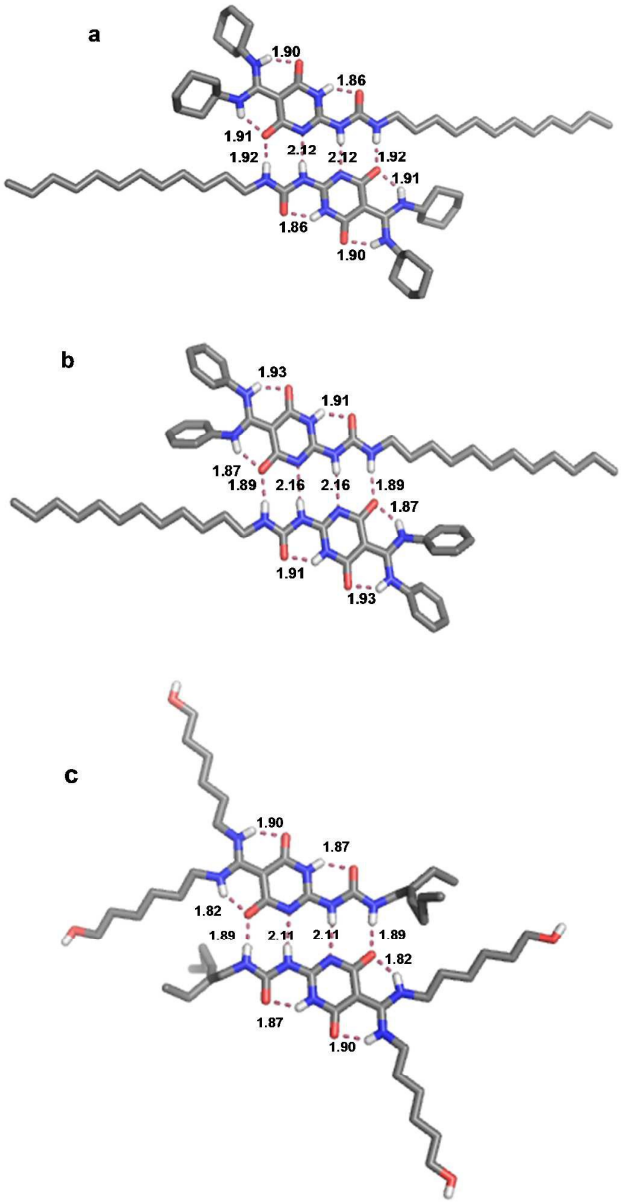

Fig. 3 Single-crystal X-ray structure of dimer **3a** (a), dimer **3c** (b) and dimer **3f** (c). Hydrogen bonding highlighted in dashes (salmon colored), above which hydrogen bond lengths (N-H···O and N-H···N) are displayed in Å. All hydrogens, other than those at the hydrogen-bonding sites, have been removed for clarity.[14]

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Ureidopyrimidone-based self-assembling systems (UPy) are known to form heterodimer with 2,7-diamido-1,8-naphthyridine (Napy).[7a] It had been shown that formation of heterodimers with Napy may have significant applications, owing to the possibility for the construction of supramolecular co-polymers. In this context, we investigated the potential of heterodimerization between **3h** and **11** (Fig. 4).

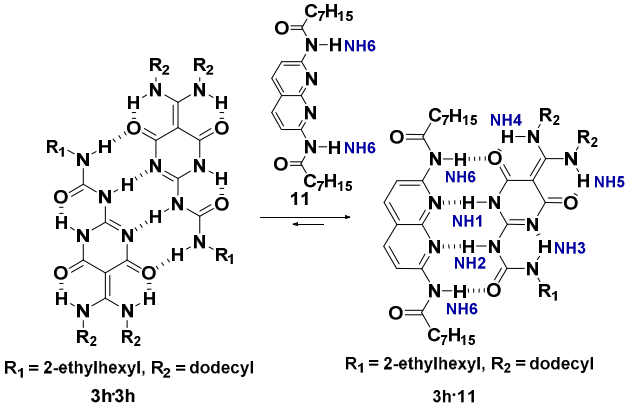

Fig. 4 Formation of heterodimer **3h·11**

Addition of 1 equiv. of 2,7-diamido-1,8-naphthyridine **11** to a solution of homodimer **3h·3h** in $CDCl_3$ caused most of the homodimer to dissociate to form a heterodimer **3h·11**, as evident from the ^{1}H NMR spectrum. ^{1}H NMR clearly showed one set of new signals for heterodimer **3h·11** and another set of signals for homodimer **3h·3h** (ESI,† Figure S7) and the yield of heterodimer **3h·11** was determined to be ~ 75%, at ambient temperature (298 K), based on the relative integrating intensity of methylene protons (attached to NH4 and NH5) signals of both dimers. Dilution of the $CDCl_3$ solution of 1:1 mixture of **3h** and **11** resulted in the up-field shift of NH6 signal of heterodimer **3h·11**. The chemical shift data of NH6 fit well into an 1:1 binding isotherm giving an association constant K_a value of 2.38 x 10^2 M^{-1} in 10% DMSO-d_6/$CDCl_3$ for heterodimer **3h·11** (ESI,† S26).[16]

The formation of heterodimer **3h·11** was further confirmed by 2D NMR studies in $CDCl_3$. 2D ROESY NMR studies of **3h·11** gave the most diagnostic ROE for the formation of heterodimer in solution. The characteristic intermolecular ROE between NH1 and NH6 confirmed the heterodimer formation in the solution state (ESI,† Figure S14). Variable temperature ^{1}H NMR studies (ranging from 243-323 K, ESI,† Figure S8) of **3h·11** provided evidence for high stability of heterodimer. Increasing the solution temperature to 323 K resulted in the sharpening of the NH signals. On the contrary, decreasing the temperature facilitated the formation of heterodimer **3h·11**, as anticipated. The yield of heterodimer **3h·11** was determined to be ~ 92%, at 243 K, based on the relative integrating intensity of the methylene protons (attached to NH4 and NH5) signals of both dimmers.

Conclusions

In conclusion, we have successfully developed a new class of dithiane-tethered **AADD**-type quadruple hydrogen bonding systems, which were further reacted with different amines to form highly stable self–complementary motifs devoid of prototropy. These systems are highly stable in non-polar solvents and relatively stable in polar solvents as well. The dimerization constants of duplexes were determined quantitatively by ^{1}H NMR dilution studies and also by fluorescence spectroscopy. These highly reactive systems having in-built **AADD**-array may have potential application in the preparation of non-covalent supramolecular assemblies. Furthermore, the formation of heterodimers with Napy may have practical applications in constructing supramolecular copolymers. Currently, we are exploring the utility of these systems in constructing different non-covalent assemblies and will report the results in due course.

Experimental

General information

Unless otherwise stated, all the chemicals and reagents were obtained commercially. Compound **5**,[17] compound **7a**[18] and compound **11**[6a] were synthesized as per the reported procedures. Dry solvents were prepared by the standard procedures. Analytical Thin Layer Chromatography was done on precoated silica gel plates (Kieselgel 60F_{254}, Merck). Column chromatographic purifications were done with 100-200 mesh silica gel. NMR spectra were recorded in $CDCl_3$ on AV 400 MHz, AV 500 MHz and AV 700 MHz Bruker NMR spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), broad singlet (bs), and multiplet (m). The titration studies were done in $CDCl_3$. Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded in $CHCl_3$ using Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi Melting Point B-540. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. MALDI-TOF/TOF mass spectra were obtained from ABSCIEX TOF/TOF™ 5800 mass spectrometer. Yields mentioned are isolated yields.

Synthetic procedures

Compound 7b. Following the same procedure for synthesis of compound **7a**[18] and using dodecylamine (2.54 mL, 11.00 mmol, 1 equiv.), **7b** was synthesized. Purification by column chromatography (eluent: 10% AcOEt/pet. ether, R_f: 0.4) yielded **7b** (2.5 g, 63%) as a white fluffy solid. IR ($CHCl_3$) ν (cm^{-1}): 3416, 3319, 3121, 3018, 2926, 2854, 1696, 1577, 1549, 1498, 1243, 1216, 1102, 771, 667; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.42 (s, 1H), 7.59 (s, 1H), 6.97 (s, 1H), 3.40-3.36 (m, 2H), 1.65-1.59 (m, 2H), 1.41-1.26 (m, 18H), 0.90-0.87 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.9, 157.3, 152.7, 113.5, 40.2, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 26.9, 22.6, 14.0; HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{29}ON_4Cl_2$: 375.1722, found 375.1713.

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Compound 8a. A solution containing **7a** (2 g, 6.287 mmol, 1 equiv.) and K_2CO_3 (2.61 g, 18.861 mmol, 3 equiv.) in 30 ml MeOH was refluxed for 6 h. After completion of reaction, the mixture was concentrated under reduced pressure. The residue was partitioned between DCM and water. The organic layer was separated, washed with water, brine solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (eluent: 3% MeOH/DCM, R_f : 0.4) afforded **8a** (1.89 g, 95%) as a fluffy white solid. IR ($CHCl_3$) *v* (cm^{-1}): 3431, 3291, 3009,2960, 2930, 2873, 1688, 1598, 1548, 1453, 1416, 1375, 1357, 1266, 1216, 1195, 1165, 811, 766, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 7.32 (s, 1H), 5.66 (s, 1H), 3.87 (s, 6H), 3.34-3.29 (m, 2H), 1.50-1.49 (m, 1H), 1.40-1.30 (m, 8H), 0.92-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 156.9, 154.1, 83.1, 54.0, 42.9, 39.6, 31.0, 28.8, 24.1, 23.0, 14.0, 10.7; HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{27}O_3N_4$: 311.2072, found 311.2078.

Compound 8b. Compound **8b** was synthesized following the same procedure for the synthesis of **8a**. Purification was effected by column chromatography (eluent: 3% MeOH/DCM, R_f : 0.4) to yield **8b** (1.85, 94%) as a white fluffy solid. IR ($CHCl_3$) *v* (cm^{-1}):3430, 3290, 3016, 2927, 2855, 1688, 1600, 1550, 1478, 1454, 1416, 1266, 1216, 1196, 1166, 1058, 812, 760, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 7.27 (s, 1H), 5.67 (s, 1H), 3.88 (s, 6H), 3.38-3.33 (m, 2H), 1.59-1.56 (m, 2H), 1.37-1.25 (m, 18H) 0.891-0.86 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 156.8, 154.0, 83.1, 54.0, 40.0, 31.8, 29.8, 29.5, 29.5, 29.3, 27.0, 22.6, 14.0; HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{35}O_3N_4$: 367.2699, found 367.2704, 755.5154 $[2M+Na]^+$.

Compound 9a. A solution of **8a** (1.5 g, 4.835 mmol, 1 equiv.) in 15 ml of HBr in AcOH was refluxed for 1 h. The mixture was cooled to RT and poured into ice water. The resulting solid was filtered and rinsed with cold water and dried under vacuum giving **9a** (1.02 g, 75%) as an off-white solid. The crude product obtained was used for the next step without further purification. mp: >295 °C; IR (Nujol) *v* (cm^{-1}): 3341, 1697, 1641, 1583, 1463, 1435, 1412, 1378, 1321, 1278, 1258, 1237, 1199, 975, 817, 795, 774, 712; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.18 (s, 2H), 9.46 (s, 1H), 7.36 (s, 1H), 4.96 (s, 1H), 3.12-3.04 (m, 2H), 1.42-1.39 (m, 1H), 1.28-1.23 (m, 8H), 0.88-0.83 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.5, 151.5, 83.2, 41.7, 30.3, 28.3, 23.6, 22.4, 13.9, 10.71; HRMS (ESI) calculated $[M+H]^+$ for $C_{13}H_{23}O_3N_4$: 283.1762, found 283.1765, 565.3457 $[2M+H]^+$.

Compound 9b. Compound **9b** was synthesized following the same procedure for synthesis of compound **9a**. The mixture was cooled to RT and poured into ice water. The resulting solid was filtered and rinsed with cold water and dried under vacuum giving **9b** (1.09 g, 79%) as an off-white solid. The crude product obtained was used for the next step without further purification. mp: > 295; IR (Nujol) *v* (cm^{-1}): 3340, 1692, 1643, 1617, 1583, 1463, 1414, 1377, 1326, 1279, 1257, 1237, 1200, 973, 776, 754, 718; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.15 (s, 1H), 9.44 (s, 1H), 7.48 (s, 1H), 4.95 (s, 1H), 3.17-3.06 (m, 2H), 1.44-1.42 (m, 2H), 1.34-1.14 (m, 18H), 0.90-0.78 (t, 3H); HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{31}O_3N_4$: 339.2386, found 339.2391, 677.4709 $[2M+Na]^+$.[#] *Note*: Owing to poor solubility, ^{13}C and DEPT-135 NMR could not be taken in DMSO-d_6.

Compound 10a. To a solution of **9a** (1 g, 3.543 mmol, 1 equiv.) in 15 ml of dry DMSO at 0 °C, Et_3N (1.038 mL, 7.441 mmol, 2.1 equiv) and CS_2 (0.703 mL, 11.690 mmol, 3.3 eqiv.) were added dropwise and the reaction mixture was stirred for 2 h at room temperature. A solution of 1, 3-dibromopropane (0.359 mL, 3.541 mmol, 1 eqiv.) in DMSO (15 mL) was added drop wise to the above reaction mixture at 0 °C. The reaction mixture was stirred for 4 h at room temperature and then poured in to 200 mL cold water. The resulting solid was filtered and rinsed with cold water and dried under vacuum giving **10a** (1.25 g, 88%) as a yellow solid. mp: compound decomposes above 260 °C; IR (Nujol) *v* (cm^{-1}): 3209, 1697, 1653, 1607, 1526, 1462, 1395, 1378, 1305, 1278, 1251, 1178, 1152, 796, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.59 (s, 1H), 11.57 (s, 1H), 9.56 (s, 1H), 3.23-3.20 (m, 2H), 3.00-2.95 (m, 4H), 2.42-2.35 (p, 2H), 1.44-1.31 (m, 9H), 0.93-0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.9, 170.8, 160.0, 155.5, 155.3, 115.3, 43.3, 39.0, 32.1, 32.0, 30.8, 28.8, 24.3, 24.0, 23.0, 14.1, 10.8; HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{27}O_3N_4S_2$: 399.1520, found 399.1519, 797.2965 $[2M+H]^+$.

Compound 10b. Compound **10b** was synthesized following the same procedure for the synthesis of **10a**. The resulting solid was filtered and rinsed with cold water and dried under vacuum giving **10b** (1.15 g, 85%) as a yellow solid. mp: compound decomposes above 210 °C; IR (Nujol) *v* (cm^{-1}): 3208, 2923, 2854, 1701, 1654, 1607, 1577, 1533, 1462, 1377, 1302, 1254, 1154, 974, 920, 870, 773,722; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.56 (s, 1H), 11.53 (s, 1H), 9.63 (s, 1H), 3.29-3.26 (m, 2H), 3.01-2.96 (m, 4H), 2.40-2.38 (m, 2H), 1.66-1.61 (m, 2H), 1.58-1.52 (m, 16H), 0.91-0.86 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.0, 170.8, 160.0, 155.4, 155.2, 115.3, 40.3, 32.2, 32.0, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3,28.9, 27.0, 24.4, 22.6, 14.1; HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{35}O_3N_4S_2$: 455.2145, found 455.2144, 909.4224 $[2M+H]^+$.

Compound 3a. To a solution of **10b** (0.1 g, 0.220 mmol, 1 equiv.) in DMSO, cyclohexylamine (0.0758 ml, 0.660 mmol, 3 equiv.) was added and stirred at room temperature for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 2% MeOH/DCM, R_f : 0.5) to afford **3a** (0.092 g, 77%) as a white solid. mp: 139-140 °C; IR ($CHCl_3$) *v* (cm^{-1}): 3201, 3014, 2930, 2855, 1699, 1645, 1584, 1469, 1450, 1424, 1402, 1375, 1291, 1217, 1069, 844, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.23 (s, 1H), 11.70 (bs, 1H), 11.48 (s, 1H), 11.11 (bs, 1H), 9.73 (s, 1H), 3.50-3.41 (m, 2H), 3.24-3.19 (m, 2H), 1.98-1.95 (m, 4H), 1.84-1.80 (m, 4H), 1.62-1.56 (m, 4H), 1.49-1.44 (m, 4H), 1.37-1.25 (m, 24H), 0.89-0.86 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 164.5, 160.2, 155.8, 152.4, 85.5, 52.9, 40.0, 33.5, 31.8, 29.6, 29.6, 29.5, 29.4, 29.3, 27.2, 25.3, 24.2, 22.6, 14.0: HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{53}O_3N_6$: 545.4181, found 545.4174, 1089.8275 $[2M+H]^+$.

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Compound 3b. Following the same procedure for synthesis of compound **3a** and using isobutylamine (0.065 ml, 0.660 mmol, 3 equiv.), **3b** was synthesized. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 2% MeOH/DCM, R_f : 0.5) to afford **3b** (0.098 g, 90%) as a fluffy white solid. IR ($CHCl_3$) *v* (cm^{-1}): 3212, 3020, 2962, 2856, 1701, 1644, 1586, 1468, 1395, 1289, 1139,772, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.29 (s, 1H), 11.56 (bs, 1H), 11.46 (s, 1H), 10.96 (bs, 1H), 9.78 (s, 1H), 3.29-3.26 (m, 2H), 3.22-3.17 (m, 2H), 1.95-1.89 (m, 2H), 1.30-1.36(m, 18H), 1.04-1.04 (d, *J* = 6.1 Hz, 12H), 0.90-0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 164.5, 163.7, 155.8, 152.7, 85.3, 53.1, 39.9, 31.9, 29.7, 29.6, 29.4, 29.3, 27.1, 22.6, 20.0, 14.1; HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{49}O_3N_6$: 493.3861, found 493.3861, 985.7649 $[2M+H]^+$.

Compound 3c. To a solution of **10b** (0.1 g, 0.220 mmol, 1 equiv.) in DMSO, aniline (0.060 ml, 0.660 mmol, 3 equiv.) was added and stirred at 80 °C for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 1% MeOH/ DCM, R_f: 0.5) to afford **3c** (0.102 g, 87%) as a fluffy white solid. IR ($CHCl_3$) *v* (cm^{-1}): 3214. 3020, 2928, 1701, 1641, 1590, 1416, 1245, 929, 772, 669, 608; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.78 (s, 1H), 12.90 (s, 1H), 12.57 (s, 1H), 11.51 (s, 1H), 9.75 (s, 1H), 6.99-6.97 (m, 4H), 6.92-6.88 (m, 2H), 6.86-6.84 (m, 4H), 3.26-3.22 (m, 2H), 1.60-1.52 (m, 2H), 1.28-1.15 (m, 18H), 0.90-0.87 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1, 164.8, 158.2, 155.7, 153.3, 136.2, 128.4, 125.5, 123.5, 123.5, 85.9, 40.2, 31.9, 29.6, 29.5, 29.5, 29.3, 29.3, 28.9, 27.1, 22.7, 14.1; HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{41}O_3N_6$: 533.3243, found 533.3235, 1065.6397 $[2M+H]^+$.

Compound 3d. To a solution of **10a** (0.2 g, 0.502 mmol, 1 equiv.) in DMSO, 2-ethylhexylamine (0.246 ml, 1.506 mmol, 3 equiv.) was added and stirred at room temperature for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 2% MeOH/DCM, R_f: 0.4) to afford **3d** (0.233 g, 85%) as a colorless liquid. IR ($CHCl_3$) *v* (cm^{-1}): 3214, 3019, 2962, 2931, 1710, 1643, 1586, 1531, 1245, 1216, 758, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.30 (s, 1H), 11.58 (bs, 1H), 11.40 (bs, 1H), 10.91 (bs, 1H), 9.65 (s, 1H), 3.41-3.35 (m, 4H), 3.11-3.08 (m, 2H), 1.66-1.53 (m, 3H), 1.48-1.28 (m, 24H), 0.90-0.88 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 164.5, 164.4, 156.0, 152.7, 85.3, 48.2, 43.4, 40.1, 39.3, 30.8, 30.7, 28.8, 24.0, 23.9, 23.1, 22.8, 14.0, 14.0, 10.7; HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{57}O_3N_6$: 549.4489, found 549.4487, 1097.8901 $[2M+H]^+$.

Compound 3e. To a solution of **10a** (0.1 g, 0.251 mmol, 1 equiv.) in DMSO, 3,4,5-(dodecyloxy) aniline (0.486 g, 0.753 mmol, 3 equiv.) was added and stirred at 80 °C for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 1% MeOH/DCM, R_f : 0.5) to afford **3e** (0.240 g, 60%) as a brown colored solid. mp: 35-37 °C; IR ($CHCl_3$) *v* (cm^{-1}): 3207, 3018, 2925, 2854, 1700, 1645, 1592, 1466, 1435, 1348, 1289, 1119, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.64 (s, 1H), 12.81 (s, 1H), 12.59 (s, 1H), 11.54 (s, 1H), 9.75 (s, 1H), 6.09 (s, 4H), 3.76-3.65 (m, 12H), 3.18-3.13 (m, 2H), 1.71-1.66 (m, 13H), 1.42-1.28 (m, 110H), 1.17-1.11 (m, 6H), 0.92-0.87 (m, 18H), 0.80-0.69 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 164.7, 157.3, 155.9, 153.1, 152.6, 152.5, 135.8, 135.8, 131.7, 131.5, 102.5, 85.5, 73.4, 73.3, 69.0, 68.9, 43.1, 39.2, 31.9, 30.7, 30.3, 30.3, 29.8, 29.7, 29.6, 29.5, 29.4, 28.6, 26.2, 24.0, 22.8, 22.6, 14.0, 13.9, 10.5; MALDI-TOF/TOF calculated $[M+H]^+$ for $C_{98}H_{177}N_6O_9$: 1582.36, found 1582.2714.

Compound 3f. To a solution of **10a** (0.1 g, 0.251 mmol, 1 equiv.) in DMSO, 6-amino-1-hexanol (0.88 g, 0.753 mmol, 3 equiv.) was added and stirred at room temperature for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 8% MeOH/ DCM, R_f: 0.4) to afford **3f** (0.105 g, 80%) as a white solid. mp: 122-123 °C; IR ($CHCl_3$) *v* (cm^{-1}): 3623, 3426, 3215, 3019, 2935, 1700, 1643, 1585, 1531,1246, 1216, 766, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.27 (s, 1H), 11.50 (bs, 2H), 10.91 (bs, 1H), 9.60 (s, 1H), 3.66-3.63 (m, 4H), 3.48-3.43 (m, 4H), 3.13-3.08 (m, 2H), 1.85 (bs, 2H), 1.71-1.68 (m, 4H), 1.60-1.57 (m, 4H), 1.49-1.41 (m, 8H), 1.35-1.27 (m, 9H), 0.90-0.86 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 164.5, 163.2, 156.0, 152.6, 85.2, 62.4, 45.0, 43.2, 39.2, 32.3, 30.8, 30.1, 28.8, 26.3, 25.2, 24.0, 23.0, 14.0, 10.7; HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{49}O_5N_6$: 525.3766, found 525.3759, 1049.7445 $[2M+H]^+$.

Compound 3g. To a solution of **3f** (0.075 g, 0.143 mmol, 1 equiv.) in dry DCM (4 mL), 1-pyrenebutyric acid (0.090 g, 0.314 mmol, 2.2 equiv.), EDC.HCl (0.082 g, 0.429 mmol, 3 equiv.) and DMAP (0.01747 g, 0.143 mmol, 1 equiv.) were added and stirred at room temperature for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 5% MeOH/ DCM, R_f: 0.3) to afford **3g** (0.090 g, 60%) as a pale-yellow solid. mp: 98-100 °C; IR ($CHCl_3$) ν (cm^{-1}): 3210, 3019, 2936, 1725, 1702, 1643, 1586, 1531, 1245, 1216, 846, 753, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.28 (s, 1H), 11.41 (bs, 2H), 10.88 (bs, 1H), 9.60 (s, 1H), 8.30-8.28 (m, 2H), 8.16-8.13 (m, 4H), 8.11-8.09 (m, 4H), 8.03-7.96 (m, 6H), 7.86-7.84 (m, 2H), 4.10-4.07 (t, *J* = 6.7 Hz, 4H), 3.40-3.37 (m, 4H), 3.35-3.30 (m, 4H), 3.16-3.07 (m, 2H), 2.48-2.45 (t, *J* = 6.7 Hz, 4H), 2.22-2.18 (quint, *J* = 7.3 Hz, 4H), 1.65-1.55 (m, 8H), 1.55-1.50 (m,

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1H), 1.41-1.33 (m, 8H), 1.32-1.27 (m, 8H), 0.90-0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 173.4, 164.4, 163.2, 155.9, 152.5, 135.6, 131.3, 130.8, 129.9, 128.6, 127.4, 127.3, 127.2, 126.6, 125.7, 125.0, 124.9, 124.8, 124.7, 124.7, 123.2, 85.1, 64.1, 45.0, 43.2, 39.2, 33.8, 32.7, 30.8, 30.0, 28.8, 28.4, 26.7, 26.3, 25.5, 24.0, 23.0, 14.1, 10.7; MALDI-TOF/TOF calculated $[M+H]^+$ for $C_{66}H_{77}N_6O_7$: 1065.58, found 1065.7872, 1087.7468 $[M+Na]^+$.

Compound 3h. To a solution of **10a** (0.2 g, 0.502 mmol, 1 equiv.) in DMSO, dodecylamine (0.279 g, 0.150 mmol, 3 equiv.) was added and stirred at room temperature for 6 h. After completion of the reaction, the reaction mixture was diluted with DCM and was sequentially washed with $KHSO_4$, water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue obtained was purified by column chromatography (eluent: 2% MeOH/ DCM, R_f : 0.6) to afford **3h** (0.310 g, 93%) as a white solid. mp: 55-57 °C; IR ($CHCl_3$) *v* (cm^{-1}): 3209, 3016, 2927, 2856, 1701, 1645, 1587, 1531, 1290, 1245, 1216, 839, 759, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.27 (s, 1H), 11.55 (bs, 1H), 11.50 (bs, 1H), 10.91 (s, 1H), 9.64 (s, 1H), 3.46-3.41 (m, 4H), 3.17-3.09 (m, 2H), 1.71-1.64 (m, 4H), 1.58-1.52 (m, 1H), 1.42-1.26 (m, 44H), 0.91-0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 164.4, 163.2, 156.0, 152.6, 85.2, 45.2, 43.2, 39.2, 31.8, 30.8, 30.2, 29.6, 29.5, 29.4, 29.3, 29.1, 28.8, 26.7, 24.0, 23.1, 22.6, 14.0, 10.7; MALDI-TOF/TOF calculated $[M+H]^+$ for $C_{38}H_{73}N_6O_3$: 661.57, found 661.1044, 683.0699 $[M+Na]^+$, 699.0304 $[M+K]^+$.

Conflicts of interest

There are no conflicts to declare.

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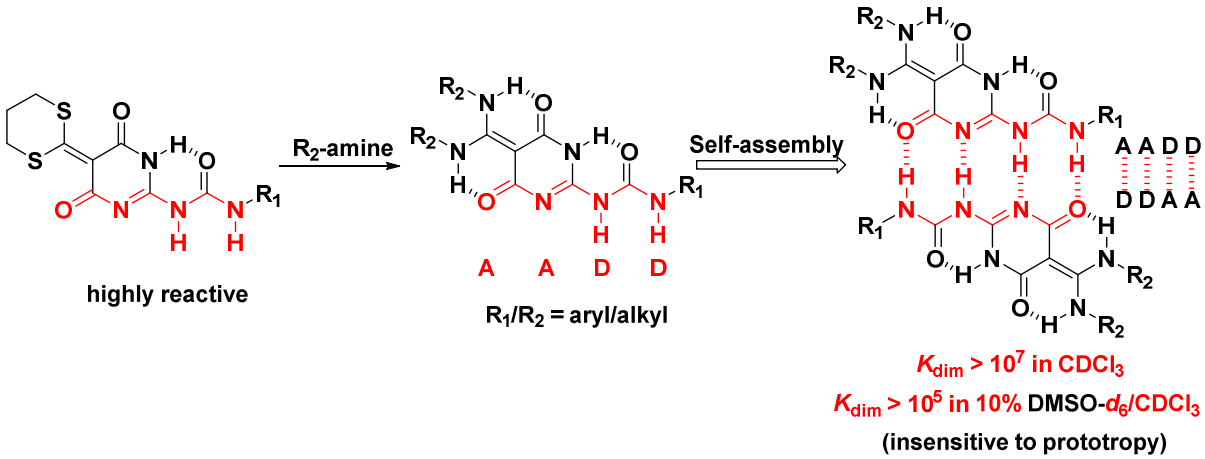

This article reports a new class of highly reactive dithiane-tethered quadruple hydrogen-bonded systems having in-built **AADD**-type self-complementary array. These systems further reacted with different amines to form highly stable molecular duplexes in non-polar (K_{dim} > 1.9 x 10^7 M^{-1} in $CDCl_3$) as well as in polar solvents (K_{dim} > 10^5 in 10% DMSO-d_6/$CDCl_3$) without having prototropy-related issues.