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Introduction

Macrocyclic molecules have received significant attention because of varied ring size and chemical constitution commonly found in natural products and pharmaceutical molecules, and such molecules have potential application in chemistry, biology, nanotechnology and medical fields.^{1,2} Further, heteroatom-containing macrocyclic molecules have privileged structural units that are essential in the area of drug discovery.3 The druglike "rule of five" properties are not obeyed by the macromolecules and the improved binding properties, unique stereochemical and structural feature and conformational flexibility make macrocycle molecules function as important biological targets.^{4,5} Moreover, proteins with various functional groups in preorganized three-dimensional constellation can increase the catalytic efficiency in enzyme active sites and molecular recognition in protein binding sites. Therefore, there is acute necessity for the development of synthetic macrocyclic scaffolds that can be used for the preorganized constellation of functional groups for catalytic and molecular recognition applications.6 Hence, macrocyclic compounds of the following type such as calixarenes,7,8 cyclodextrin,9,10 cucurbiturils,¹¹ resorcinarenes,^{12,13} conjugated aromatic systems,14 and Schiff base macrocycles,15-17 are important from the synthetic view point. Noncovalent self-assembly¹⁸ of

Regio- and stereoselective synthesis of spiropyrrolidine-oxindole and bisspiropyrrolizidine-oxindole grafted macrocycles through [3 + 2] cycloaddition of azomethine ylides[†]

Perumal Prabhakaran and Perumal Rajakumar 回 *

A convenient and efficient method for the regioselective macrocyclization of triazole bridged spiropyrrolidine-oxindole, and bis-spiropyrrolizidine-oxindole derivatives was accomplished through intra and self-intermolecular [3 + 2] cycloaddition of azomethine ylides. The chalcone isatin precursors **9a–i** required for the click reaction were obtained from the reaction of *N*-alkylazidoisatin **4** and propargyloxy chalcone **8a–i** which in turn were obtained by the aldol condensation of propargyloxy salicylaldehyde **6** and substituted methyl ketones **7a–i**. The regio- and stereochemical outcome of the cycloadducts were assigned based on 2D NMR and confirmed by single crystal XRD analysis. High efficiency, mild reaction conditions, high regio- and stereoselectivity, atom economy and operational simplicity are the exemplary advantages of the employed macrocyclization procedure.

coordination bonds in organometallics^{19,20} functioning as sensors for the recognition of selective ions in host gest chemistry²¹ make macrocyclic molecules an important class of supramolecules.

Spiro compounds comprise two rings fused at a central spiro atom, and possess a unique three dimensional architecture. Synthetic chemists have been fascinated by spirocycles for more than hundred years and the first spiran was synthesized by Baeyer in 1900.22 Spirocyclic oxindoles occupy a privileged position in organic and diversity-oriented synthesis,23 and attract a wide range of natural and synthetic products and display a variety of bioactivities and present in pharmaceutically active compounds^{24,25} In particular multifunctional polycyclic spiropyrrolidine-oxindole and spiropyrrolizidine-oxindole are the privileged heterocyclic skeleton which contain spiro stereocenter at the C3 position of the oxindole frequently encountered in natural alkaloids and in important structural moieties exhibiting versatile bioactivities,26 such as antibacterial, anticancer, antimicrobial, antimycobacterial, antitumor, antifungal, acetylcholinesterase (AChE) inhibitory properties and cholinesterase inhibitory activity.27-29 The spirooxindoles unit occurs in several natural products, such as (-)-horsfiline, coerulescene, elacomine, spirotryprostatin A, peteropodine, rhynchophylline, and also in spirooxindole alkaloids (Fig. 1). Spiro pyrrolidine-3,3-oxindole alkaloids also shows anticancer activity and inhibition of p53-MDM2 protein-protein interaction with rapid regression of tumor cells.³⁰ Thus, the anticancer effect of spirooxindole natural products allow more significant non-natural analogues design. Presently, MI-77301 (SAR405838) is yet another promising anticancer drug under clinical trials.31

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai-600 025, Tamil Nadu, India. E-mail: perumalrajakumar@gmail.com

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1.1 Representative examples of naturally occurring bioactive spiropyrrolidine-oxindole alkaloids.

1,3-Dipolar cycloaddition³² of azomethine ylide is a powerful method for the synthesis of biologically significant fivemembered heterocyclic compounds. Electron-deficient alkenes are employed as dipolarophiles in the presence of either transition metals or organo catalysts to achieve highly functionalized and stereochemically enriched pyrroldine, pyrrolizidine and spirocyclic oxindole molecules.33 The simplicity, atomic economy, mild reaction conditions and extension of the scope of substrates make such cycloaddition as the current direction in combinatorial chemistry. Driven thorough literature survey, we are encouraged to construct hybrid macrocyclic systems. However, the extensive applications of 1,3-dipolar cycloaddition for the synthesis of such macrocycles still remains a challenge.34 To the best of our knowledge there is no report in the literature on a one pot self-intermolecular [3 + 2]cycloaddition to give bis-spiropyrrolizidine-oxindole grafted macrocyles.

We disclose a novel method for the synthesis and electrochemical property and biological activity³⁵ of 1,2,3-triazole bridged pyrrolidine grafted macrocycles with high regio- and stereoselectivity *via* [3 + 2] cycloaddition approach. We wish to report herein the synthesis of novel spiropyrrolidine oxindole grafted macrocycles **12a-i** (Fig. 2) and bis-spiropyrrolizidine oxindole grafted macrocycles **16a-i** (Fig. 3) through intra and self-intermolecular [3 + 2] cycloaddition of azomethine ylides (AMY) generated *in situ* by the decarboxylative condensation of cyclic ketones and secondary amino acids.

Results and discussion

The synthetic plan for achieving the spiropyrrolidine-oxindole grafted macrocycles 12a-i is shown in Scheme 1. The macrocyclic spiropyrrolidine-oxindole 12a-i can be obtained by the intramolecular (3 + 2) cycloaddition of chalcone isatins 9a-i with the azomethine ylide generated from the corresponding amino acids. The chalcone isatins 9a-i can be derived from the click reaction of the propargyloxy chalcone 8a-i with the azido fragment derived from isatin. The propargyloxy chalcone 8a-i

can be prepared by the *O*-propargylation of salicylaldehyde with propargyl bromide followed by the aldol condensation using suitable methyl aryl ketone (Scheme 1).

Hence we began the synthesis of the desired azido compound 4 from isatin (1). Reaction of isatin (1) with one equivalent of 1,2-dibromoethane in the presence of K₂CO₃ in DMF at room temperature gave the N-alkylbromo ketone 3 in 58% yield along with the bisalkylated tetraketone 2 in 24% yield. The monobromoketone 3 was smoothly converted to the desired azide 4 in 93% by NaN₃ in DMF at room temperature (Scheme 2). The structure of the N-alkylazidoketone 4 was confirmed from ¹H and ¹³C NMR spectra. Synthesis of O-propargylated chalcone fragments 8a-i was achieved from salicylaldehyde (5) by adopting a reported procedure³⁵ (Scheme 2). Reaction of salicylaldehyde (5) with 1.2 equiv. of propargyl bromide in the presence of potassium carbonate in DMF at room temperature gave propargyloxy salicylaldehyde 6 in 92% yield, which on further aldol condensation with 1.2 equiv. of each of the various substituted aromatic and heteroaromatic methyl ketones viz., 4-bromoacetophenone 7a, 4-chloroacetophenone 7b, 3,4-dimethoxyacetophenone 7c, 4-methoxyacetophenone 7d, 4-methylacetophenone 7e, 2methoxyacetophenone 7f, 4-nitroacetophenone 7g, acetophenone 7h and 2-acetylthiophene 7i in the presence of 20% aqueous NaOH solution in EtOH gave the substituted chalcone derivatives 8a-i in 75-85% yields.

In convergent approach, the 1,3-dipolar cycloaddition of propargyloxychalcone derivatives **8a-i** with 1.0 equiv. of *N*-alkylazidoketone **4** under click reaction conditions using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in THF : H_2O as solvent gave the 1,4-triazole bridged chalcone isatin **9a-i** in 80–90% yields (Scheme 2). The structure of the 1,4-triazole bridged chalcone isatin **9a-i** was characterized from spectroscopic methods. In the ¹H NMR spectrum of **9a** the triazole –CH–proton resonated at δ 7.75 as a singlet. The geometry of the olefinic double bond showed the *E* configuration as evidenced from ¹H NMR spectrum. The olefinic protons of the chalcone isatin **9a** appeared as a doublet at 7.99 with a coupling constant











Fig. 2 Molecular structure of spiropyrrolidine-oxindole grafted macrocyles 12a-i.

of 15.9 Hz which confirms the *E* configuration of the double bond. In the ¹³C NMR spectrum of **9a**, the carbonyl carbons exhibited peaks at 182.2 and 189.7 ppm.

To optimize the conditions for 1,3-dipolar cycloaddition, the cycloaddition of the chalcone isatin **9a** and sarcosine was chosen as the model reaction (Table 1). The reaction mixture with equimolar amounts of chacone isatin **9a** and sarcosine (**10**) was tested under various reaction conditions. The effects of solvent and temperature on the 1,3-dipolar cycloaddition was evaluated and from the optimization study the best results were obtained by refluxing the reaction mixture in toluene for 6 h in Dean-Stark apparatus to give the regio- and stereoselective cycloadduct **12a** in 74% yields. Having established suitable reaction conditions (Table 1, entry 4), we tried to extend the scope of the reaction, using a series of various substituted chalcone isatin **9b–i**. Regio- and stereoselective [3 + 2] cycloaddition of azomethine ylide from sarcosine (**10**) with the substituted chalcone isatin **9b–i** gave the cycloadducts **12b–i** in 65–75% yields (Scheme 3). The intramolecular dipolarophile *O*-alkyl enone regioselectively reacts with the azomethine ylide (dipole) in toluene under refluxing conditions for 6 h in Dean–Stark apparatus to give the regio- and stereoselective macrocyclic adducts **12a–i** in 65–75% yields.

The structure and the regiochemistry of the spiropyrrolidine oxindole grafted macrocyles **12a–i** was unambiguously established from spectroscopic data. In the ¹H NMR spectrum, the cycloadduct **12a** displayed the *N*-methyl protons of the pyrrolidine ring as a singlet at δ 2.14 and the two diastereotopic *N*-methylene protons of the pyrrolidine moiety resonated as triplets at δ 3.38 and δ 3.92 (J = 8.1, J = 9.6 Hz).



Fig. 3 Molecular structure of bis-spiropyrrolizidine-oxindole grafted macrocyles 16a-i.

The two *O*-methylene protons appeared as two doublets at δ 5.09 and 5.37 (J = 10.2 Hz, J = 10.5 Hz). The benzylic proton H_b of the pyrrolidine ring appeared as a multiplet in the region

of δ 3.57–3.61. The pyrrolidine H_b proton adjacent to the carbonyl group appeared as a doublet at δ 5.21 (J = 6.9 Hz), which clearly proved the regiochemistry of the cycloaddition.

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Scheme 2 Synthesis of 1,2,3-triazole bridged chalcone isatin 9a-i. Reagent and conditions: (i) 1,2-dibromoethane, K₂CO₃, DMF, rt, 2 h, 2 (24%), 3 (58%); (ii) NaN₃, DMF, rt, 8 h, 4 (93%); (iii) propargyl bromide, K₂CO₃, DMF, rt, 12 h, 6 (92%); (iv) methyl ketones 7a-i, NaOH, EtOH, rt, 6 h 8a-i (75–85%). (v) *N*-Alkylazidoketone 4, CuSO₄·5H₂O, sodium ascorbate, THF : water (1 : 1), rt, 9a-i (80–90%).

Table 1 Optimizing the reaction conditions for the synthesis of cycloadduct $12a\,$

Entry	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	Benzene	Reflux	6	Trace
2	MeOH	Reflux	6	34
3	CH ₃ CN	Reflux	6	58
4	Toluene	Reflux	6	74

Further, the triazolyl –CH– proton appeared at δ 8.12 as a singlet.

In the ¹³C NMR spectrum, the cycloadduct **12a** showed the *N*methyl, *N*-methylene and carbonyl carbons at δ 34.5, 60.1 and 199.3 ppm respectively. In DEPT-135 ¹³C NMR spectrum, the cycloadduct **12a** exhibited the four peaks in the negative region at δ 39.5, 48.7, 60.1 and 62.3 ppm which confirm the presence of four methylene carbons in **12a**. Moreover, ¹H-¹H COSY and ¹H-¹³C COSY experiments were carried out to confirm the structure of regio- and stereoselective isomer **12a** (ESI†). The macrocyclic compound **12a** showed a peak at *m*/z 584.1271 (M +



Scheme 3 Synthesis of spiropyrrolidine-oxindole grafted macrocycles 12a-i. Reagent and conditions: (i) sarcosine 10, toluene, N₂ atm, Dean–Stark water separator, 6 h, 12a (74%), 12b (75%), 12c (68%), 12d (70%), 12e (68%), 12f (65%), 12g (72%), 12h (70%), 12i (65%).



Fig. 4 Regioselectivity due to SOI in the transitions state that leads to the cycloadduct 12a-i.

H)⁺ in HRMS (TOF MS ES⁺ 3.35×10^7). Similarly, the structure of the pyrrolidine grafted macrocycles **12b–i** was confirmed from the spectral and analytical data.

The electron withdrawing or electron donating substituents on the phenyl ring of the dipolarophiles tolerated the reaction conditions, leading to the spirooxindolo pyrrolidine macrocycles in good yields. The regioselectivity of the macrocyclization can be demonstrated by the intramolecular secondary orbital interaction (SOI)³⁶ between the orbital of the dipolarophile carbonyl group and dipole azomethine ylide, as shown in Fig. 4. Formation of the observed regioisomer **12a–i** through path A is favorable because of the SOI, which is not possible in the transitions state **11**['] which could have given the regioisomer **13a–i** (path B). The relative stereochemistry at the positions of spiro center of the macrocycles was observed as highly stereocontroled cycloaddition and the favorable SOI results in the formation of the regioisomer **12a–i** only.

As a logical extension of the methodology, synthesis of bisspiropyrrolizidine-oxindole grafted macrocycles **16a-i** was then focused. Reaction of the triazole bridged chalcone isatin **9a-i** with L-proline (**14**) generated the 1,3-dipolar intermediate which could undergo self-intermolecular [3 + 2] cycloaddition. The azomethine ylides **15a–i** underwent smooth self-intermolecular 1,3-dipolar cycloaddition to give the bis-spiropyrrolizidine oxindole grafted macrocyles **16a–i** in 55–65% yields (Scheme 4).

Optimization of the reaction condition for the formation of the cycloadduct **16a** was then focused. Variation with respect to solvent, temperature and reaction time for the formation of **16a** was carried out and the resulting yield of **16a** is show in Table 2. The best optimized yield of 64% is show in entry 4.

The structure and regioselective of self-intermolecular cycloadducts **16a-i** were established from spectroscopic data. The ¹H NMR spectrum of the cycloadduct **16b** displayed a multiplet at δ 1.68–2.69 for the pyrrolizidine ring methylene protons. The O–CH₂– protons appeared as a AB_q at δ 5.24, 5.49 (J = 11.7 Hz). A doublet at δ 5.60 (J = 11.7 Hz) was observed for the benzoyl protons. The benzylic proton of the pyrrolidine ring appeared as a multiplet in the region of δ 4.47–4.58, which clearly showed the stereo- and regiochemistry of the self-intermolecular cycloaddition of azomethine ylides. A neat



Scheme 4 Synthesis of bis-spiropyrrolizidine-oxindole grafted macrocycles 16a-i. Reagents and conditions: (i) proline (14), toluene, N₂ atm, Dean–Stark water separator, 6 h, 16a (64%), 16b (65%), 16c (58%), 16d (60%), 16e (56%), 16f (55%), 16g (62%), 16h (60%), 16i (56%).

Table 2 Optimizing the reaction conditions for the synthesis of cycloadduct $16a\,$

Entry	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	Benzene	Reflux	6	Trace
2	MeOH	Reflux	6	18
3	CH ₃ CN	Reflux	6	32
4	Toluene	Reflux	6	64

singlet appeared at δ 9.85 corresponding to triazole -CHproton which proved the presence of a triazole unit. The stereochemistry of the cycloadduct 16b was also deduced on the basis of 2D ¹H-¹H COSY and ¹H-¹³C COSY (ESI[†]) experiments. In DEPT-135 ¹³C NMR spectrum, the methylene carbons exhibited six peaks in the negative region at δ 28.4, 32.6, 40.0, 46.6, 47.4 and 64.2 ppm which confirms the presence of six methylene carbons in the macrocycle 16b. Furthermore, the presence of molecular ion peak at m/z 1131.3840 (M + 1) in HRMS, also confirmed the structure of the cycloadduct 16b. The carbonyl carbon exhibited a peak at 196.6 ppm in the ¹³C NMR spectrum. The remaining carbons resonated at the corresponding ppm values (ESI⁺). Finally, the structure of the macrocyclic compound 16b was again established from the single crystal XRD analysis (Fig. 5) However, the structure of the bis-spiropyrrolizidine-oxindole grafted macrocycles 16a and 16c-i was confirmed from the spectral and analytical data.

In conclusion, for the first time we have developed an efficient protocol for the macrocyclizations of spiropyrrolidine oxindole and bis-spiropyrrolizidine oxindole with triazole as spacer unit *via* regioselective click reaction, intra and self-intermolecular 1,3-dipolar cycloaddition of azomethine ylide derived from sarcosine and proline under thermal decarboxylative condensation by relatively simple procedure. The [3 + 2] cycloaddition methodology was found to be highly regioselective and the structure of the regio- and stereo isomer was determined from 2D NMR and confirmed by XRD studies.

Experimental

General considerations

All reagents and solvents were of analytical grade and used without further purification as obtained from commercial suppliers. Ethanol, N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene were retrieved from a solvent purification system. Routine monitoring of the reaction was done by thin-layer chromatography (TLC) using hexane/ethyl acetate mixtures as eluent. Column chromatography was carried out on Silica gel (100-200 meshes) by using increasing polarity. All melting points are uncorrected. ¹H NMR, ¹³C NMR and DEPT 135 spectra were recorded in CDCl₃ using TMS as an internal standard on 300 MHz Bruker instrument. 2D NMR spectra were recorded at 500 MHz spectrometer on Bruker instrument. Chemical shifts are reported in ppm relative to deuterated solvent peaks as internal standards ($\delta_{\rm H} = {\rm CDCl}_3$ 7.26 ppm, and DMSO-d₆ 2.50 ppm; $\delta_{\rm C} = \text{CDCl}_3$ 77.16 ppm, and DMSO-d₆ 39.5 ppm). Coupling constants (J) are quoted in Hertz (Hz). The HRMS spectra were recorded on Xevo G2s Qtof (ESI) instruments.





Fig. 5 ORTEP diagram of bis-spiropyrrolizidine-oxindole grafted macrocycle 16b.

Synthesis of 1,2,3-triazole bridged chalcone isatin 9a-i

(i) General procedure. To solution of propargyloxy chalcones 8a-i (1 eq.) and *N*-alkylazidoketones 4 (1 eq.) in a mixture of THF (20 mL), and H₂O (20 mL), was added $CuSO_4 \cdot 5H_2O$ (0.5 eq.) and sodium ascorbate (0.5 eq.). The resulting solution was then stirred for 12 h at room temperature. The solvent was evaporated under vacuum and the residue was dissolved in chloroform (150 mL) and washed with water (50 mL) and brine (50 mL) dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography using hexane : EtOAc (3 : 2) as eluent to give the chalcone isatin **9a-i**.

Chalcone isatin 9a. Yield 86%, orange-yellow solid. Mp: 174– 176 °C. ¹H NMR (300 MHz, CDCl₃): δ 4.23 (t, J = 6.0 Hz, 2H); 4.73 (t, J = 6.0 Hz, 2H); 5.20 (s, 2H); 6.55 (d, J = 7.8 Hz, 1H); 6.97–7.05 (m, 3H); 7.31–7.41 (m, 2H); 7.47–7.51 (m, 1H); 7.56–7.61 (m, 4H); 7.75 (s, 1H); 7.83 (d, J = 8.1 Hz, 2H); 7.99 (d, J = 15.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 40.6, 47.8, 62.4, 109.4, 113.0, 117.5, 121.6, 122.6, 123.9, 124.0, 124.3, 125.5, 127.6, 129.4, 130.1, 131.8, 131.9137.1, 138.4, 140.5, 144.1, 149.9, 157.5, 158.5, 182.2, 189.7.

Chalcone isatin **9b**. Yield 88%. Yellow solid. Mp: 162–164 °C. ¹H NMR (300 MHz, CDCl₃): δ 4.24 (t, J = 5.7 Hz, 2H); 4.72 (t, J = 5.7 Hz, 2H); 5.2 (s, 2H); 6.53 (d, J = 8.1 Hz, 1H); 7.00–7.05 (m, 3H); 7.26–7.41 (m, 2H); 7.43–7.54 (m, 3H); 7.60–7.63 (m, 2H); 7.80 (s, 1H); 7.91 (d, J = 9.9 Hz, 2H); 8.01 (d, J = 15.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 40.6, 47.9, 62.2, 109.4, 112.8, 117.4, 121.5, 122.4, 124.1, 124.2, 125.6, 128.8, 129.3, 129.6, 129.9, 131.9, 136.6, 138.6, 139.1, 140.5, 144.1, 149.9, 157.4, 158.5, 182.3, 189.4.

Chalcone isatin **9***c*. Yield 82%, orange-yellow solid. Mp: 198– 200 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.95 (s, 3H); 3.96 (s, 3H); 4.23 (t, *J* = 6 Hz, 2H); 4.73 (t, *J* = 6 Hz, 2H); 5.22 (s, 2H); 6.50 (d, *J* = 7.8 Hz, 1H); 6.92 (d, *J* = 8.4 Hz, 1H); 6.99–7.05 (m, 3H); 7.31– 7.40 (m, 2H); 7.49 (d, *J* = 7.2 Hz, 1H); 7.57–7.65 (m, 4H); 7.80 (s, 1H); 8.01 (d, *J* = 15.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 40.6, 47.9, 56.09, 56.1, 62.4, 109.3, 110.1, 110.9, 112.9, 117.4, 121.5, 122.5, 123.1, 124.6, 125.6, 128.9, 131.6, 138.5, 139.0, 149.2, 149.9, 153.2, 157.2, 158.5, 182.3, 188.9. *Chalcone isatin* **9d.** Yield 85%, orange solid. Mp: 158–160 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.82 (s, 3H); 4.17 (t, J = 5.4 Hz, 2H); 4.72 (t, J = 5.4 Hz, 2H); 5.13 (s, 2H); 6.47 (d, J = 8.1 Hz, 1H); 6.88– 7.00 (m, 5H); 7.27–7.34 (m, 3H); 7.39 (t, J = 7.2 Hz, 1H); 7.55– 7.60 (m, 2H); 7.90–7.98 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 40.6, 47.8, 55.4, 62.1, 109.5, 112.7, 113.7, 117.3, 121.4, 122.5, 123.9, 124.2, 124.5, 125.3, 129.1, 130.7, 131.0, 131.6, 131.6, 138.5, 138.9, 143.9, 150.0, 157.2, 158.5, 163.3, 182.6, 188.9.

Chalcone isatin **9***e*. Yield 82%. Orange-yellow solid. Mp: 182–184 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.38 (s, 3H); 4.19 (t, J = 5.4 Hz, 2H); 4.73 (t, J = 5.4 Hz, 2H); 5.16 (s, 2H); 6.47 (d, J = 7.8 Hz, 1H); 6.91–7.02 (m, 3H). 7.24 (d, J = 7.8 Hz, 2H); 7.28–7.32 (m, 2H); 7.42 (d, J = 7.5 Hz, 1H); 7.55–7.61 (m, 2H); 7.84 (d, J = 8.1 Hz, 2H); 7.94 (s, 1H); 7.99 (d, J = 15.6 Hz, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 21.6, 40.6, 47.9, 62.2, 109.4, 112.7, 117.3, 121.4, 122.6, 124.0, 124.1, 124.5, 125.4, 128.6, 129.0, 129.3, 131.7, 135.6, 138.5, 139.4, 143.6, 150.0, 157.3, 158.6, 182.5, 189.9.

Chalcone isatin **9***f*. Yield 85%, orange-yellow solid. Mp: 128– 130 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.86, (s, 3H); 4.23 (t, *J* = 6.0 Hz, 2H); 4.69 (t, *J* = 6.0 Hz, 2H); 5.20 (s, 2H); 6.56 (d, *J* = 8.1 Hz, 1H); 6.97–7.04 (m, 5H); 7.29–7.33 (m, 1H); 7.36–7.43 (m, 2H); 7.45–7.48 (m, 1H); 7.53 (d, *J* = 7.5 Hz, 1H); 7.56–7.59 (m, 2H); 7.63 (s, 1H). 7.89 (d, *J* = 15.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 40.6, 47.8, 55.8, 62.7, 109.4, 111.9, 113.1, 117.5, 120.7, 121.6, 123.7, 124.1, 124.8, 125.5, 127.7, 128.4, 129.7, 130.3, 131.5, 132.6, 138.1, 138.5, 149.9, 157.2, 158.5, 186.4, 193.1.

Chalcone isatin **9***g*. Yield 80%. Orange-yellow solid. Mp: 180– 182 °C. ¹H NMR (300, MHz, CDCl₃): δ 4.26 (t, J = 4.7 Hz, 2H); 4.75 (t, J = 6.0 Hz, 2H); 5.22 (s, 2H); 6.60 (d, J = 8.1 Hz, 1H); 7.00– 7.06 (m, 3H); 7.36–7.43 (m, 2H); 7.51 (d, J = 7.2 Hz, 1H); 7.60– 7.63 (m, 2H); 7.78 (s, 1H); 8.03 (d, J = 15.6 Hz, 1H); 8.11–8.14 (m, 2H); 8.31 (d, J = 8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 40.5, 47.7, 62.0, 109.5, 112.7, 117.9, 121.6, 122.4, 124.1, 124.2, 123.7, 125.6, 129.6, 130.1, 132.4, 138.6, 142.1, 143.9, 149.9, 150.1, 157.6, 158.5, 182.2, 189.4.

Chalcone isatin 9h. Yield 84%. Orange-yellow solid. Mp: 82–84 °C. ¹H NMR (300 MHz, CDCl₃): δ 4.21 (t, *J* = 6.0 Hz, 2H); 4.72

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(t, J = 6.0 Hz, 2H); 5.18 (s, 2H); 6.49 (d, J = 7.8 Hz, 1H); 6.94–7.04 (m, 3H); 7.31–7.37 (m, 2H); 7.40–7.48 (m, 4H); 7.52–7.56 (m, 1H); 7.61–7.63 (m, 1H); 7.86 (s, 1H); 7.93–7.95 (m, 2H); 8.02 (d, J = 15.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 40.6, 47.92, 62.3, 109.4, 112.8, 117.4, 121.5, 122.7, 124.1, 124.2, 124.3, 125.5, 128.1, 128.5, 128.6, 129.1, 131.8, 132.7, 138.3, 138.5, 139.8, 144.1, 150.0, 157.3, 158.6, 182.4, 190.7.

Chalcone isatin 9i. Yield 80%, yellow solid. Mp: 110–112 °C. ¹H NMR (300 MHz, CDCl₃): δ 4.24 (t, J = 6.0 Hz, 2H); 4.71 (t, J = 6.0 Hz, 2H); 5.23 (s, 2H); 6.55 (d, J = 8.1 Hz, 1H); 6.98–7.06 (m, 2H); 7.14–7.17 (m, 1H); 7.34–7.49 (m, 3H); 7.49–7.53 (m, 2H); 7.60–7.65 (m, 2H); 7.72 (s, 1H); 7.82 (d, J = 3.6 Hz, 1H); 8.05 (J = 15.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 31.6, 40.6, 47.9, 60.4, 62.3, 69.7, 69.9, 70.1, 72.7, 80.7, 109.5, 112.8, 117.4, 121.5, 124.0, 124.1, 124.3, 124.5, 125.6, 128.8, 131.3, 135.8, 138.6, 144.2, 150.0, 157.2, 158.6, 182.4, 193.5.

Synthesis of 1,2,3-triazole bridged spiropyrrolidine-oxindole grafted macrocycles 12a-i/bis-spiropyrrolizidne-oxindole grafted macrocycles 16a-i

(ii) General procedure. A solution of the chalcone isatins 9a-i (1 mmol) and sarcosine (10)/proline (14) (2.5 mmol) was refluxed in dry toluene under N₂ atmosphere for 12 h at 120 °C using Dean–Stark apparatus. After the completion of reaction as indicated by TLC, toluene was evaporated under reduced pressure. The crude product was washed with water and extracted with dichloromethane (4 \times 20 mL). The combined organic layer was dried (MgSO₄) and filtered, concentrated in vacuum. The crude product was purified by column chromatography using hexane/ethyl acetate (1:1) as eluent to give the spiropyrrolizidine-oxindole grafted macrocycles 12a-i and bisspiropyrrolizidine-oxindole grafted macrocycles 16a-i.

Spiropyrrolidine-oxindole grafted macrocycle **12a**. Yield 74%. White solid. Mp 206–208 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.14 (s, 3H); 3.38 (t, *J* = 8.1 Hz, 1H); 3.56–3.60 (m, 1H); 3.92 (t, *J* = 9.1 Hz, 1H); 4.44–4.52 (m, 1H); 4.56–4.72 (m, 2H); 4.81–4.88 (m, 1H); 5.09 (d, *J* = 10.2 Hz, 1H); 5.21 (d, *J* = 6.9 Hz, 1H); 5.37 (d, *J* = 10.5 Hz, 1H); 6.58 (d, *J* = 7.8 Hz, 1H); 6.77 (t, *J* = 7.2 Hz, 1H); 6.86–6.93 (m, 2H); 6.99 (t, *J* = 8.7 Hz, 1H); 7.03–707 (m, 3H); 7.20–7.27 (m, 2H); 7.39 (d, *J* = 8.4 Hz, 2H); 8.12 (s, 1H). ¹³C NMR (70 MHz, CDCl₃): δ 34.5, 39.5, 44.8, 48.7, 52.1, 60.1, 62.3, 73.8, 107.0, 112.6, 121.1, 122.8, 125.5, 126.2, 126.6, 126.8, 127.5, 128.3, 129.2, 129.4, 131.3, 133.0, 136.6, 142.9, 144.3, 156.9, 178.2, 199.3. DEPT135: 34.5, 39.5, 44.8, 48.7, 52.1, 60.1, 62.3, 107.0, 112.6, 121.1, 122.8, 126.6, 126.8, 128.3, 129.3, 129.4, 131.3, 133.0. HRMS (TOF MS ES⁺ 3.35 × 10⁷) *m/z* calcd for C₃₀H₂₆BrN₅O₅ + H⁺ [M + H]⁺ 584.1297 found 584.1271.

Spiropyrrolidine-oxindole grafted macrocycle **12b**. Yield: 75%; white solid; mp; 146–148 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.14 (S, 3H); 3.38 (t, *J* = 7.8 Hz, 1H); 3.57–3.61 (m, 1H); 3.92 (t, *J* = 7.5 Hz, 1H); 4.45–4.53 (m, 1H); 4.57–4.72 (m, 2H); 4.81–4.91 (m, 1H); 5.10, (d, *J* = 10.5 Hz, 1H); 5.22 (d, *J* = 6.6 Hz, 1H); 5.38 (d, *J* = 10.5 Hz, 1H); 6.58 (d, *J* = 7.8 Hz, 1H); 6.77 (t, *J* = 7.5 Hz, 1H); 6.87–6.93 (m, 2H); 6.96–7.04 (m, 2H); 7.13 (d, *J* = 8.4 Hz, 2H); 7.21–7.26 (m, 4H); 8.13 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 34.5, 39.5, 44.8, 48.7, 52.1, 60.1, 62.3, 73.8, 107.0, 112.6, 121.1, 122.8,

125.5, 126.2, 126.6, 126.8, 128.3, 129.2, 129.3, 133.0, 136.2, 138.7, 142.9, 144.3, 156.9, 178.2, 199.1 DEPT135: 34.5, 39.5, 44.8, 48.7, 52.1, 60.1, 62.3, 107.0, 112.6, 121.1, 122.8, 126.6, 126.8, 128.3, 129.2, 129.3, 133.0 ppm. HRMS (TOF MS ES⁺ 3.36 \times 10⁷) *m/z* calcd for C₃₀H₂₆ClN₅O₅ + H₂ [M + 2]⁺ 541.1881 found 541.1859.

Spiropyrrolidine-oxindole grafted macrocycle **12c.** 68%; white solid; mp; 218–220 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.15 (s, 3H); 3.36 (t, J = 8.1 Hz, 1H); 3.55–3.59 (m, 1H); 3.78 (s, 3H); 3.87 (s, 3H); 3.90–3.96 (m, 1H); 4.41–4.52 (m, 3H); 4.88–4.92 (m, 1H); 5.12 (d, J = 10.5 Hz, 1H); 5.31 (d, J = 6.9 Hz, 1H); 5.43 (d, J = 10.5 Hz, 1H); 6.57 (d, J = 8.1 Hz, 1H); 6.67–6.76 (m, 2H); 6.82–6.91 (m, 2H); 6.96–6.98 (m, 2H); 7.01–7.07 (m, 2H); 7.21–7.27 (m, 2H); 8.08 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 34.6, 39.9, 45.5, 49.0, 52.6, 55.9, 56.0, 60.0, 62.3, 73.9, 106.7, 109.3, 110.3, 112.5, 121.1, 122.2, 122.6, 125.9, 126.3, 126.5, 127.2, 128.3, 129.0, 131.9, 133.1, 142.9, 148.6, 152.7, 157.0, 178.3, 199.4. DEPT135: δ 34.6, 39.9, 45.5, 49.0, 52.6, 55.9, 56.0, 60.0, 62.3, 73.9, 106.7, 109.3, 110.3, 112.5, 121.1, 122.2, 122.6, 126.5, 127.2, 128.3, 129.1, 133.1. HRMS (TOF MS ES⁺ 9.65 × 10⁸) *m*/*z* calcd for C₃₂H₃₁N₅O₅ + H⁺ [M + H]⁺ 566.2403 found 566.2404.

Spiropyrrolidine-oxindole grafted macrocycle **12d.** Yield: 70%; white solid; mp; 232–234 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.14 (s, 3H); 3.36 (t, *J* = 8.1 Hz, 1H); 3.58 (t, *J* = 6.3 Hz, 1H); 3.77 (s, 3H); 3.89–3.96 (m, 1H); 4.43–4.41 (m, 1H); 4.52–4.61 (m, 2H); 4.87–4.92 (m, 1H); 5.12 (d, *J* = 10.2 Hz, 1H); 5.27 (d, *J* = 6.9 Hz, 1H); 5.41 (d, *J* = 10.2 Hz, 1H); 6.57 (d, *J* = 7.8 Hz, 1H); 6.72 (d, *J* = 8.7 Hz, 2H); 6.81 (t, *J* = 8.1 Hz, 1H); 6.86–6.91 (m, 1H); 6.97–7.04 (m, 3H); 7.21–7.27 (m, 4H); 8.09 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 34.6, 39.8, 45.3, 48.9, 52.2, 55.4, 60.0, 62.3, 73.9, 106.7, 112.5, 113.7, 121.1, 122.7, 125.8, 126.4, 126.5, 127.1, 128.2, 129.0, 130.1, 131.4, 133.1, 142.9, 144.4, 157.1, 157.0, 162.8, 178.3, 198.7. DEPT135: δ 34.6, 39.8, 45.3, 49.0, 52.2, 55.4, 60.0, 62.3, 106.7, 112.5, 113.7, 121.1, 126.5, 127.1, 128.3, 129.1, 130.1, 133.1. HRMS (TOF MS ES⁺ 2.50 × 10⁸) *m*/*z* calcd for C₃₁H₂₉N₅O₄ + H⁺ [M + H]⁺ 536.2298 found 536.2377.

Spiropyrolidine-oxindole grafted macrocycle **12e**. Yield: 68%. White solid; mp 184–186 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.14 (s, 3H); 2.26 (s, 3H); 3.34 (t, J = 7.8 Hz, 1H); 3.51–3.61 (m, 1H); 3.90–3.96 (m, 1H); 4.41–4.52 (m, 3H); 4.91 (d, J = 10.2 Hz, 1H); 5.09 (d, J = 10.5 Hz, 1H); 5.34 (d, J = 6.9 Hz, 1H); 5.48 (d, J = 10.5 Hz, 1H); 6.56 (d, J = 8.1 Hz, 1H); 6.81–6.90 (m, 2H); 6.98–7.12 (m, 5H); 7.10 (d, J = 8.1 Hz, 2H); 7.22–7.26 (m, 3H); 7.99 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): 21.5, 34.55, 40.1, 45.7, 49.2, 52.8, 59.9, 62.4, 73.8, 106.7, 112.5, 121.1, 122.7, 125.9, 126.2, 126.4, 127.3, 127.7, 128.3, 128.7, 129.0, 133.1, 136.1, 142.9, 143.0, 144.5, 157.1, 178.2, 210.4. DEPT135: δ 21.5, 34.6, 40.1, 45.7, 49.2, 52.8, 59.9, 62.4, 106.7, 112.5, 121.1, 122.3, 126.4, 127.3, 128.4, 128.7, 129.0, 133.2. HRMS (TOF MS ES⁺ 9.22 × 10⁸) m/z calcd for C₃₁H₂₉N₅O₃ + H₂ [M + 2]⁺ 521.2427 found 521.2437.

Spiropyrrolidine-oxindole grafted macrocycle **12f**. Yield: 65%; white solid; mp; 196–198 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.11 (s, 3H); 3.14 (s, 3H); 3.38–3.52 (m, 1H); 3.52–3.61 (m, 1H); 3.75–3.88 (m, 1H); 4.01–4.11 (m, 1H); 4.20–4.29 (m, 1H); 4.76–4.80 (m, 1H); 4.89 (d, *J* = 10.5, Hz, 1H); 5.45–5.53 (m, 3H); 6.57–6.63 (m, 2H); 6.69 (d, *J* = 8.4 Hz, 1H); 6.78 (s, 1H); 6.89–6.94 (m, 1H);

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7.02 (d, J = 7.8 Hz, 1H); 7.14–7.19 (m, 2H); 7.21–7.24 (m, 3H); 7.24–7.28 (m, 1H); 7.31–7.33 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 34.3, 40.8, 47.8, 50.0, 56.4, 58.9, 59.3, 63.3, 73.3, 106.4, 112.0, 112.7, 121.1, 121.2, 123.1, 126.0, 126.4, 126.5, 126.8, 127.1, 128.3, 128.4, 129.1, 131.2, 133.2, 134.1, 143.8, 144.7, 156.2, 158.4, 178.0, 205.2. DEPT135: δ 34.3, 40.8, 47.7, 50.0, 56.4, 58.9, 59.3, 63.3, 106.4, 112.0, 112.7, 121.1, 121.2, 123.1, 126.0, 126.3, 128.3, 128.4, 129.1, 131.2, 133.2.

Spiropyrrolidine-oxindole grafted macrocycle **12g**. Yield: 72%; white solid; mp; 228–230 °C. ¹H NMR (300 MHz, CDCl3): δ 2.14 (s, 3H); 3.41 (t, J = 8.1 Hz, 1H); 3.58–3.62 (m, 1H); 3.88–3.95 (m, 1H); 4.52–4.55 (m, 1H); 4.75–4.83 (m, 3H); 5.12 (d, J = 10.5 Hz, 1H); 5.19 (d, J = 6.6 Hz, 1H); 5.35 (d, J = 10.5 Hz, 1H); 6.57 (d, J = 7.8 Hz, 1H); 6.74 (t, J = 7.5 Hz, 1H); 6.85–6.87 (m, 1H); 6.91–6.97 (m, 3H); 7.01–7.26 (m, 2H); 7.35 (d, J = 8.4 Hz, 2H); 8.10 (d, J = 8.4 Hz, 2H); 8.22 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 34.4, 39.2, 44.3, 48.3, 52.1, 60.2, 62.3, 73.8, 107.2, 112.7, 121.2, 122.9, 123.2, 125.2, 125.9, 126.7, 126.8, 128.4, 129.2, 129.5, 133.0, 142.9, 144.3, 149.6, 157.0, 178.1, 198.7 ppm. DEPT135: δ 34.4, 39.2, 44.3, 48.3, 52.1, 60.2, 62.3, 107.2, 112.7, 121.14, 122.8, 123.2.126.7, 126.8, 128.4, 129.2, 129.5, 133.0. HRMS (TOF MS ES⁺ 4.14 × 10⁷) *m*/z calcd for C₃₀H₂₆N₆O₅ + H₂ [M + 2]⁺ 552.2122 found 552.2100.

Spiropyrrolidine-oxindole grafted macrocycle **12h**. Yield: 73%; white solid; mp; 216–218 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.14 (s, 3H); 3.34 (t, J = 8.1 Hz, 1H); 3.52–3.56 (m, 1H); 3.90–3.96 (m, 1H); 4.39–4.50 (m, 3H); 4.87–4.91 (m, 1H); 5.09, (d, J = 10.5 Hz, 1H); 5.38 (d; J = 7.2 Hz, 1H); 5.43 (d, J = 10.5 Hz, 1H); 6.54 (d, J = 7.8 Hz, 1H); 6.82–6.91 (m, 2H); 6.98–7.05 (m, 3H); 7.15 (d, J = 7.2 Hz, 2H); 7.20–7.26 (m, 4H); 7.29–7.34 (m, 1H); 7.94 (s, 1H). ¹³C NMR (70 MHz, CDCl₃): δ 34.5, 40.1, 45.6, 49.2, 53.2, 59.9, 62.4, 73.8, 106.7, 112.6, 121.6, 122.8, 125.9, 126.2, 126.4, 127.2, 127.5, 128.0, 128.4, 129.1, 132.1, 133.1, 138.9, 143.0, 144.5, 157.1, 178.2, 200.9. DEPT135: δ 34.5, 40.1, 45.6, 49.2, 53.2, 59.8, 62.4, 106.7, 112.5, 121.1, 122.8, 126.4, 127.2, 127.4, 128.0, 128.4, 129.1, 132.2, 133.2. HRMS (TOF MS ES⁺ 3.97 × 10⁷) m/z calcd for $C_{30}H_{27}N_5O_3 + H_2 [M + 2]^+$ 507.2270 found 507.2260.

Spiropyrrolidine-oxindole grafted macrocycle **12i**. Yield: 70%; white solid; mp; 238–240 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.14 (s, 3H); 3.33 (t, *J* = 8.1 Hz, 1H); 3.58–3.71 (m, 1H); 3.92–3.98 (m, 1H); 4.45–4.51 (m, 1H); 4.56–4.62 (m, 1H); 4.85–4.95 (m, 1H); 4.99 (d, *J* = 6.6 Hz, 1H); 5.11 (d, *J* = 10.5 Hz, 1H); 5.40 (d, *J* = 10.5 Hz, 1H); 6.61 (d, *J* = 7.5 Hz, 1H); 6.81 (t, *J* = 7.5 Hz, 1H); 6.86–6.89 (m, 1H); 6.92–6.98 (m, 1H); 7.00–7.21 (m, 2H); 7.21–7.26 (m, 4H); 7.40 (d, *J* = 4.8 Hz, 1H) 8.23 (s, 1H). ¹³C NMR (75 MHz,CDCl₃): δ 34.6, 40.1, 44.9, 49.0, 54.7, 62.2, 73.9, 106.8, 112.5, 121.1, 122.8, 126.8, 127.1, 127.9, 128.4, 129.4, 132.3, 133.0, 133.1, 142.6, 144.8, 157.0, 178.2, 199.3. DEPT 135: δ 34.6, 44.9, 49.0, 54.7, 59.7, 62.2, 106.8, 112.5, 121.1, 121.5, 122.8, 126.8, 127.1, 127.9, 128.4, 129.2, 132.3, 133.1, 133.3.

Bis-spiropyrolizidine-oxindole grafted macrocycle **16a**. Yield: 64%; white solid; mp; 220–222 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.63–1.77 (m, 4H); 1.79–1.94 (m, 4H); 2.43–2.65 (m, 4H); 3.77– 3.83 (m, 2H); 3.86–3.97 (m, 4H); 4.38–4.40 (m, 2H); 4.41–4.53 (m, 2H); 4.59–4.67 (m, 2H); 5.24, 5.49 (AB_q, *J* = 11.7 Hz, 4H); 5.60 (d; *J* = 11.7 Hz, 2H); 6.79 (d, *J* = 7.5 Hz, 2H); 6.95–7.02 (m, 8H); 7.14 (t, *J* = 7.5 Hz, 2H); 7.23–7.25 (m, 8H); 7.32–7.35 (m, 2H); 7.47 (d, J = 6.9 Hz, 2H); 9.85 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 28.4, 32.6, 40.0, 46.6, 47.4, 53.3, 61.6, 64.3, 67.8, 74.1, 108.6, 112.5, 121.7, 122.8, 124.9, 125.4, 126.3, 127.3, 127.6, 128.8, 129.3, 129.9, 131.1, 133.5, 136.4, 141.9, 145.2, 156.8, 179.2, 196.8. DEPT135: δ 28.4, 32.6, 40.0, 46.6, 47.4, 53.3, 61.6, 64.2, 67.8, 108.7, 112.5, 121.7, 122.9, 125.4, 127.3, 128.8, 129.3, 129.9, 131.1, 133.5. HRMS (TOF MS ES⁺ 2.29 × 10⁸) *m/z* calcd for

 $C_{64}H_{56}Br_2N_{10}O_6 + H^+ [M + H]^+ 1219.2829$ found 1219.2828.

Bis-spiropyrrolizidine-oxindole grafted macrocycle 16b. Yield: 65%; white solid; mp; 236–238 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.68-1.78 (m, 4H); 1.90-2.0 (m, 4H); 2.43-2.5 (m, 2H); 2.67-2.69 (m, 2H); 3.79-3.85 (m, 2H); 3.87-3.97 (m, 4H); 4.35-4.44 (m, 2H); 4.47–4.58 (m, 2H); 4.62–4.67 (m, 2H); 5.24, 5.49 (AB a, J = 11.7 Hz, 4H); 5.60 (d, *J* = 11.7 Hz, 2H); 6.58 (d, *J* = 7.8 Hz, 2H); 6.94–7.01 (m, 4H); 7.05–7.09 (m, 8H); 7.14 (t, J = 7.8 Hz, 2H); 7.26–7.30 (m, 4H); 7.31–7.35 (m, 2H); 7.47 (d, J = 7.5 Hz, 2H); 9.85 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 28.4, 31.6, 32.6, 40.0, 46.6, 47.4, 53.3, 61.7, 64.3, 67.8, 74.1, 108.6, 112.5, 121.7, 122.8, 125.0, 125.4, 126.3, 127.3, 128.1, 128.8, 129.2, 129.9, 133.5, 135.9, 138.9, 141.9, 145.2, 156.8, 179.3, 196.6. DEPT135: δ 28.4, 31.6, 32.6, 40.0, 46.6, 47.4, 53.3, 61.7, 64.3, 67.8, 108.6, 112.5, 121.7, 122.9, 125.4, 127.3, 128.2, 128.8, 129.2, 129.9, 133.5. HRMS (TOF MS ES⁺ 4.22 \times 10⁸) m/z calcd for C₆₄H₅₆Cl₂N₁₀O₆ + $H^{+}[M + H]^{+}$ 1131.3838 found 1131.3840.

Bis-spiropyrrolizidine-oxindole grafted macrocycle 16c. Yield: 58%; white solid; mp; 270–272 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.61–1.75 (m, 4H); 1.79–1.90 (m, 4H); 2.50 (t, J = 6.3 Hz, 4H); 3.54 (s, 6H); 3.74 (s, 6H); 3.79-3.83 (m, 4H); 4.17-4.27 (m, 2H); $4.33-4.44 \text{ (m, 4H)}; 4.46-4.52 \text{ (m, 2H)}; 5.21, 5.35 \text{ (AB}_{q}, J = 12 \text{ Hz},$ 4H); 5.67 (d, *J* = 11.7 Hz, 2H); 6.58 (d, *J* = 7.2 Hz, 2H); 6.71–6.72 (m, 2H); 6.80 (d, J = 7.8 Hz, 2H); 6.86–6.89 (m, 2H); 6.93 (d, J = 7.5 Hz, 4H); 7.09 (t, J = 7.5 Hz, 2H); 7.19–7.24 (m, 4H); 7.33 (d, J = 7.2 Hz, 2H); 7.40–7.43 (m, 2H); 9.65 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 27.6, 31.6, 39.2, 45.6, 48.1, 54.5, 55.5, 56.1, 60.1, 63.8, 67.5, 74.2, 108.3, 109.8, 110.4, 111.8, 121.7, 121.9, 122.8, 124.7, 125.3, 126.0, 127.6, 128.7, 129.7, 130.5, 133.8, 141.5, 144.8, 148.4, 153.1, 156.7, 179.4, 195.7. DEPT135: 27.6, 31.6, 39.2, 45.6, 48.2, 54.4, 55.5, 56.1, 60.2, 63.8, 67.5, 108.3, 109.7, 110.4, 111.8, 121.7, 121.9, 122.8, 124.7, 127.6, 128.7, 129.7, 133.8. HRMS (TOF MS ES⁺ 5.86 × 10⁷) m/z calcd for C₆₈H₆₆N₁₀O₁₀ + H⁺ [M + H]⁺ 1183.5041 found 1183.5045.

Bis-spiropyrrolizidine-oxindole grafted macrocycle 16d. Yield: 60%. White solid; mp 250–252 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.73–1.83 (m, 4H); 1.86–1.98 (m, 4H); 2.59 (t, J = 6.3 Hz, 4H); 3.73 (s, 6H); 3.74-3.76 (m, 2H); 3.86 (t, J = 8.1 Hz, 2H); 4.39-4.48 $(m, 4H); 4.54-4.60 (m, 4H); 5.33, 5.42 (AB_{g}J = 11.7 Hz, 4H); 5.75$ (d, J = 12 Hz, 2H); 6.67 (d, J = 8.7 Hz, 4H); 6.89 (d, J = 7.5 Hz, 4H); 2H); 6.98-7.02 (m, 4H); 7.17-7.23 (m, 6H); 7.28-7.35 (m, 4H); 7.41 (d, J = 7.5 Hz, 2H); 7.49–7.52 (m, 2H); 9.73 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): 27.7, 29.7, 31.6, 39.4, 45.6, 48.2, 54.3, 55.4, 60.4, 63.7, 67.6, 74.3, 108.4, 111.7, 113.1, 121.7, 122.8, 124.6, 125.3, 126.0, 127.5, 128.6, 129.8, 130.1, 130.4, 133.8, 141.4, 145.0, 156.6, 163.4, 179.2, 195.7. DEPT135: δ 27.7, 29.7, 31.6, 39.4, 45.6, 48.2, 54.3, 55.4, 60.4, 63.7, 67.6, 108.4, 111.7, 113.1, 121.7, 122.8, 124.6, 127.5, 128.6, 129.8, 130.1, 133.8. HRMS (TOF MS ES⁺ 1.24 \times 10⁹) *m*/*z* calcd for C₆₆H₆₂N₁₀O₈ + H⁺ [M + H]⁺ 1123.4830 found 1123.4847.

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Bis-spiropyrrolizidine-oxindole grafted macrocycle 16e. Yield 56%. White Solid. Mp 238–240 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.69–1.75 (m, 4H); 1.92–1.94 (m, 4H); 2.22 (s, 6H); 2.49 (t, J = 3 Hz, 2H); 2.62 (t, J = 2.4 Hz, 2H); 3.72–3.80 (m, 2H); 3.90–3.97 (m, 4H); 4.26-4.33 (m, 2H); 4.52-4.57 (m, 4H); 5.25, 5.49 (AB_q, J = 11.7 Hz, 4H); 5.67 (d, I = 11.4 Hz, 2H); 6.76 (d, I = 7.8 Hz, 2H); 6.90-6.97 (m, 4H); 6.99-7.02 (m, 4H); 7.01-7.10 (m, 4H); 7.13-7.16 (m, 2H); 7.25–7.30 (m, 4H); 7.34–7.36 (m, 2H); 7.49 (d, I =7.2 Hz, 2H); 9.87 (s, 2H). ¹³C NMR (70 MHz, CDCl₃): δ 21.5, 28.1, 32.4, 40.2, 46.4, 47.6, 53.6, 61.3, 64.1, 67.7, 74.1, 108.5, 112.3, 121.7, 122.7, 125.2, 125.3, 126.5, 127.3, 127.8, 128.6, 128.7, 129.7, 133.7, 135.2, 141.9, 143.4, 152.3, 156.8, 179.4, 197.3. DEPT135: 21.5, 28.1, 32.4, 40.2, 46.4, 47.6, 53.6, 61.3, 64.1, 67.7, 108.5, 112.3, 121.7, 122.7, 125.3, 127.3, 127.8, 128.5, 128.6, 128.7, 129.7, 133.7. HRMS (TOF MS ES⁺ 1.21×10^9) m/z calcd for $C_{66}H_{62}N_{10}O_6 + H^+ [M + H]^+$ 1091.4932 found 1091.4944.

Bis-spiropyrrolizidine-oxindole grafted macrocycle 16f. Yield: 55%; white solid; mp; 228-230 °C. ¹H NMR (300 MHz, CDCl3): δ 1.58–1.75 (m, 4H); 1.71–1.94 (m, 4H); 2.32–2.40 (m, 2H); 2.50– 2.55 (m, 2H); 3.33 (s, 6H); 3.44-3.53 (m, 2H); 3.78-3.89 (m, 4H); 4.21–4.28 (m, 2H); 4.41–4.51 (m, 4H); 5.27, 5.47 (AB_a, J =12.0 Hz, 4H); 5.93 (d, J = 11.7 Hz, 2H); 6.14 (d, J = 6.6 Hz, 2H); 6.52-6.57 (m, 4H); 6.84 (d, J = 7.8 Hz, 2H); 6.96 (t, J = 7.2 Hz, 2H); 7.02 (d, J = 8.4 Hz, 2H); 7.12–7.16 (m, 4H); 7.28 (d, J =9.3 Hz, 2H); 7.35 (d, J = 7.8 Hz, 4H); 7.49 (d, J = 7.2 Hz, 2H); 9.81 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 28.1, 32.5, 40.1, 46.7, 47.2, 53.0, 55.3, 64.0, 64.2, 67.8, 73.6, 108.5, 110.8, 112.0, 119.8, 121.5, 122.6, 125.7, 127.0, 127.2, 128.5, 128.9, 129.1, 129.7, 132.2, 133.7, 142.7, 145.1, 156.8, 157.5, 178.8, 199.6 ppm. DEPT135: δ 28.1, 32.4, 40.1, 46.7, 47.2, 53.0, 55.3, 64.0, 64.2, 67.8, 108.4, 110.8, 112.0, 119.8, 121.5, 122.6, 125.7, 127.2, 128.5, 128.9, 129.7, 132.2, 133.7.

Bis-spiropyrrolizidine-oxindole grafted macrocycle 16g. Yield: 62%; white solid; mp; 196-198 °C. ¹H NMR (300 MHz, CDCl3): δ 1.69–1.81 (m, 4H); 1.94–2.01 (m, 4H); 2.45–2.53 (m, 2H); 2.65– 2.72 (m, 2H); 3.64-3.77 (m, 4H); 3.92-3.97 (m, 2H); 4.39-4.55 (m, 4H); 4.61–4.71 (m, 2H); 5.22, 5.50 (AB_a , J = 12 Hz, 4H); 5.63 (d, J = 11.7 Hz, 2H); 6.76 (d, J = 7.8 Hz, 2H); 6.95-7.02 (m, 4H);7.16 (t, J = 7.5 Hz, 2H); 7.25–7.31 (m, 8H); 7.33–7.35 (m, 2H); 7.46–7.49 (m, 2H); 7.94 (d, J = 8.7 Hz, 4H); 9.81 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 28.4, 29.7, 32.8, 39.8, 46.7, 47.3, 53.2, 62.2, 64.4, 67.8, 73.9, 108.7, 112.6, 121.8, 122.9, 123.1, 124.8, 125.5, 126.0, 127.3, 128.8, 129.0, 130.2, 133.5, 141.8, 142.2, 145.1, 149.8, 156.8, 179.1, 196.5. DEPT135: δ 28.4, 29.7, 32.8, 39.8, 46.7, 47.3, 53.2, 62.3, 64.4, 67.8, 108.7, 112.6, 121.8, 122.9, 123.1, 125.5, 127.3, 128.8, 129.1, 130.2, 133.5. HRMS (TOF MS ES⁺ 9.19 $\times 10^{8}$) m/z calcd for C₆₄H₅₆N₁₂O₁₀ + H⁺ [M + H]⁺ 1153.4320 found 1153.4332.

Bis-spiropyrrolizidine-oxindole grafted macrocycle **16h**. 60%; white solid; mp; 208–210 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.79–1.76 (m, 8H); 2.59 (t, J = 6.0 Hz, 4H); 3.47–3.54 (m, 2H); 3.79–3.86 (m, 2H); 4.37–4.44 (m, 4H); 4.50–4.59 (m, 4H); 5.29, 5.43 (AB _q, J = 11.7 Hz, 4H); 5.80 (d, J = 11.7 Hz, 2H); 6.86 (d, J = 7.8 Hz, 2H); 6.9–7.03 (m, 4H); 7.10–7.14 (m, 8H); 7.16–7.20 (m, 2H); 7.29–7.34 (m, 4H); 7.37–7.40 (m, 4H); 7.53 (d, J = 6 Hz, 2H); 9.69 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 27.6, 31.5, 39.4, 45.6,

48.2, 54.1, 60.9, 63.7, 67.7, 74.1, 108.5, 111.8, 121.7, 122.9, 124.7, 125.1, 125.9, 127.3, 127.7, 127.8, 127.9, 128.7, 129.9, 132.6, 133.8, 137.7, 141.5, 144.9, 156.6, 178.9, 197.9. DEPT135: δ 27.6, 31.5, 39.4, 45.6, 48.2, 54.1, 60.9, 63.7, 67.7, 108.5, 111.8, 121.7, 122.9, 124.6, 127.3, 127.7, 127.8, 127.9, 128.7, 129.9, 132.6, 133.8. HRMS (TOF MS ES⁺ 4.89 × 10⁷) *m*/*z* calcd for C₂₉H₂₇N₅O₅ + H⁺ [M + H]⁺ 1063.4619 found 1063.4640.

Bis-spiropyrrolizidine-oxindole grafted macrocycle **16i**. Yield: 56%; white solid; mp; 202–204 °C. ¹H NMR (300 MHz, CDCl3): δ 1.67–1.83 (m, 4H); 1.81–2.04 (m, 4H); 2.61 (t, J = 6 Hz, 4H); 3.84–3.93 (m, 4H); 4.49–4.65 (m, 8H); 5.27, 5.39 (AB _q, J = 11.7 Hz, 4H); 5.62 (d, J = 12 Hz, 2H); 6.84 (t, J = 7.8 Hz, 2H); 6.97 (t, J = 7.5 Hz, 6H); 7.18 (t, J = 7.5 Hz, 2H); 7.25–7.36 (m, 8H); 7.40–7.45 (m, 4H); 9.70 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 27.8, 31.7, 39.8, 45.8, 48.1, 54.3, 61.9, 63.9, 67.7, 74.8, 108.6, 111.9, 121.8, 123.1, 124.7, 125.3, 125.8, 127.0, 127.7, 128.8, 130.0, 131.5, 133.9, 134.2, 141.5, 144.6, 145.1, 156.8, 179.5, 188.7. DEPT135: δ 27.8, 31.7, 39.8, 45.8, 48.1, 54.3, 61.9, 63.9, 67.7, 108.6, 111.9, 121.8, 123.1, 124.7, 127.0, 127.8, 128.8, 130.0, 131.5, 133.8, 134.2.

Conflicts of interest

The authors have no conflicts of interest.

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