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

 Perumal Prabhakaran and Perumal Rajakumar \*

A convenient and efficient method for the regioselective macrocyclization of triazole bridged spiropyrrolidine-oxindole, and bis-spiropyrrrolizidine-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.

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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.<sup>1,2</sup> Further, heteroatom-containing macrocyclic molecules have privileged structural units that are essential in the area of drug discovery.<sup>3</sup> 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.<sup>4,5</sup> 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.<sup>6</sup> Hence, macrocyclic compounds of the following type such as calixarenes,<sup>7,8</sup> cyclodextrin,<sup>9,10</sup> cucurbiturils,<sup>11</sup> resorcinarenes,<sup>12,13</sup> conjugated aromatic systems,<sup>14</sup> and Schiff base macrocycles,<sup>15–17</sup> are important from the synthetic view point. Noncovalent self-assembly<sup>18</sup> of

coordination bonds in organometallics<sup>19,20</sup> functioning as sensors for the recognition of selective ions in host guest chemistry<sup>21</sup> 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.<sup>22</sup> Spirocyclic oxindoles occupy a privileged position in organic and diversity-oriented synthesis,<sup>23</sup> and attract a wide range of natural and synthetic products and display a variety of bioactivities and present in pharmaceutically active compounds.<sup>24,25</sup> In particular multifunctional polycyclic spiropyrrolidine-oxindole and spiropyrrrolizidine-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,<sup>26</sup> such as antibacterial, anticancer, antimicrobial, antimycobacterial, antitumor, antifungal, acetylcholinesterase (AChE) inhibitory properties and cholinesterase inhibitory activity.<sup>27–29</sup> 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.<sup>30</sup> 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.<sup>31</sup>

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

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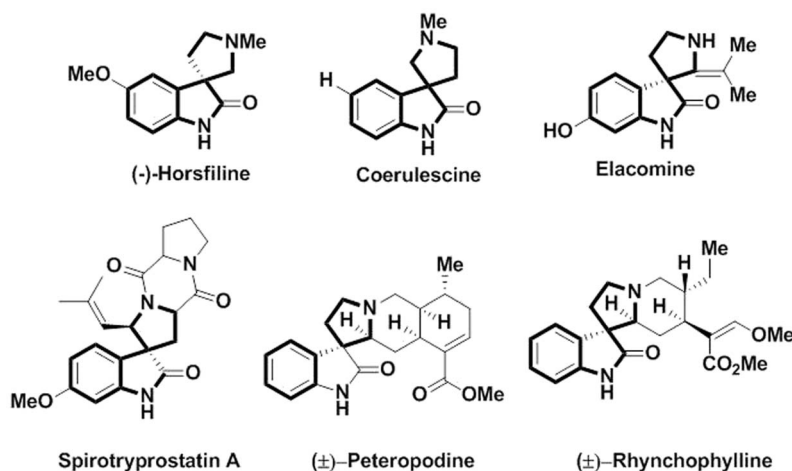


Fig. 1 Representative examples of naturally occurring bioactive spiropyrrolidine-oxindole alkaloids.

1,3-Dipolar cycloaddition<sup>32</sup> of azomethine ylide is a powerful method for the synthesis of biologically significant five-membered 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 pyrrolidine, pyrrolizidine and spirocyclic oxindole molecules.<sup>33</sup> 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.<sup>34</sup> 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-spiropyrrrolizidine-oxindole grafted macrocycles.

We disclose a novel method for the synthesis and electrochemical property and biological activity<sup>35</sup> 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-spiropyrrrolizidine 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  $K_2CO_3$  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  $NaN_3$  in DMF at room temperature (Scheme 2). The structure of the *N*-alkylazidoketone **4** was confirmed from  $^1H$  and  $^{13}C$  NMR spectra. Synthesis of *O*-propargylated chalcone fragments **8a–i** was achieved from salicylaldehyde (**5**) by adopting a reported procedure<sup>35</sup> (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**, 2-methoxyacetophenone **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  $\delta$  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

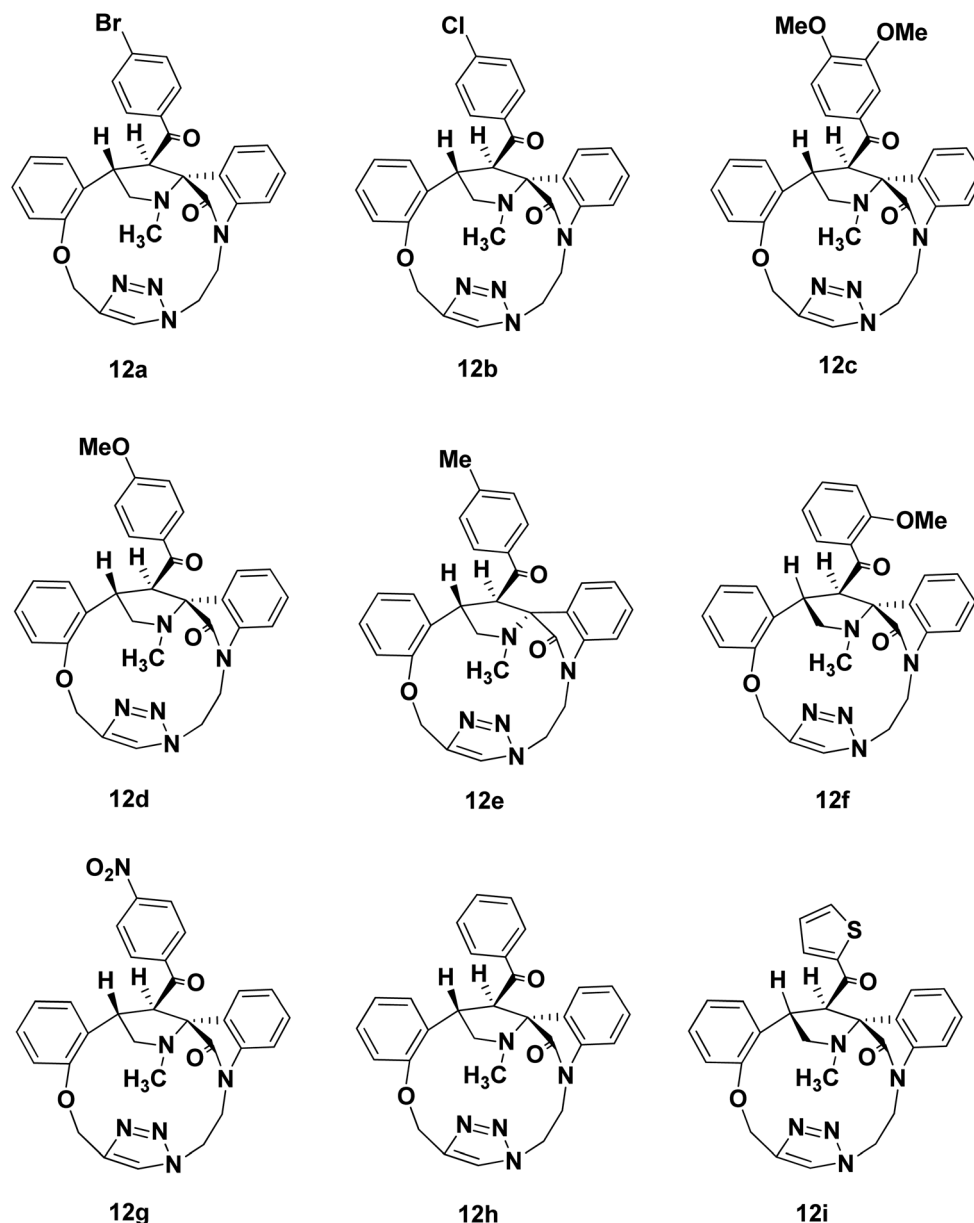


Fig. 2 Molecular structure of spiro[pyrrolidine-oxindole]grafted macrocycles **12a-i**.

of 15.9 Hz which confirms the *E* configuration of the double bond. In the <sup>13</sup>C 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 chalcone 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 spiro[pyrrolidine oxindole]grafted macrocycles **12a-i** was unambiguously established from spectroscopic data. In the <sup>1</sup>H NMR spectrum, the cycloadduct **12a** displayed the *N*-methyl protons of the pyrrolidine ring as a singlet at  $\delta$  2.14 and the two diastereotopic *N*-methylene protons of the pyrrolidine moiety resonated as triplets at  $\delta$  3.38 and  $\delta$  3.92 ( $J = 8.1$ ,  $J = 9.6$  Hz).

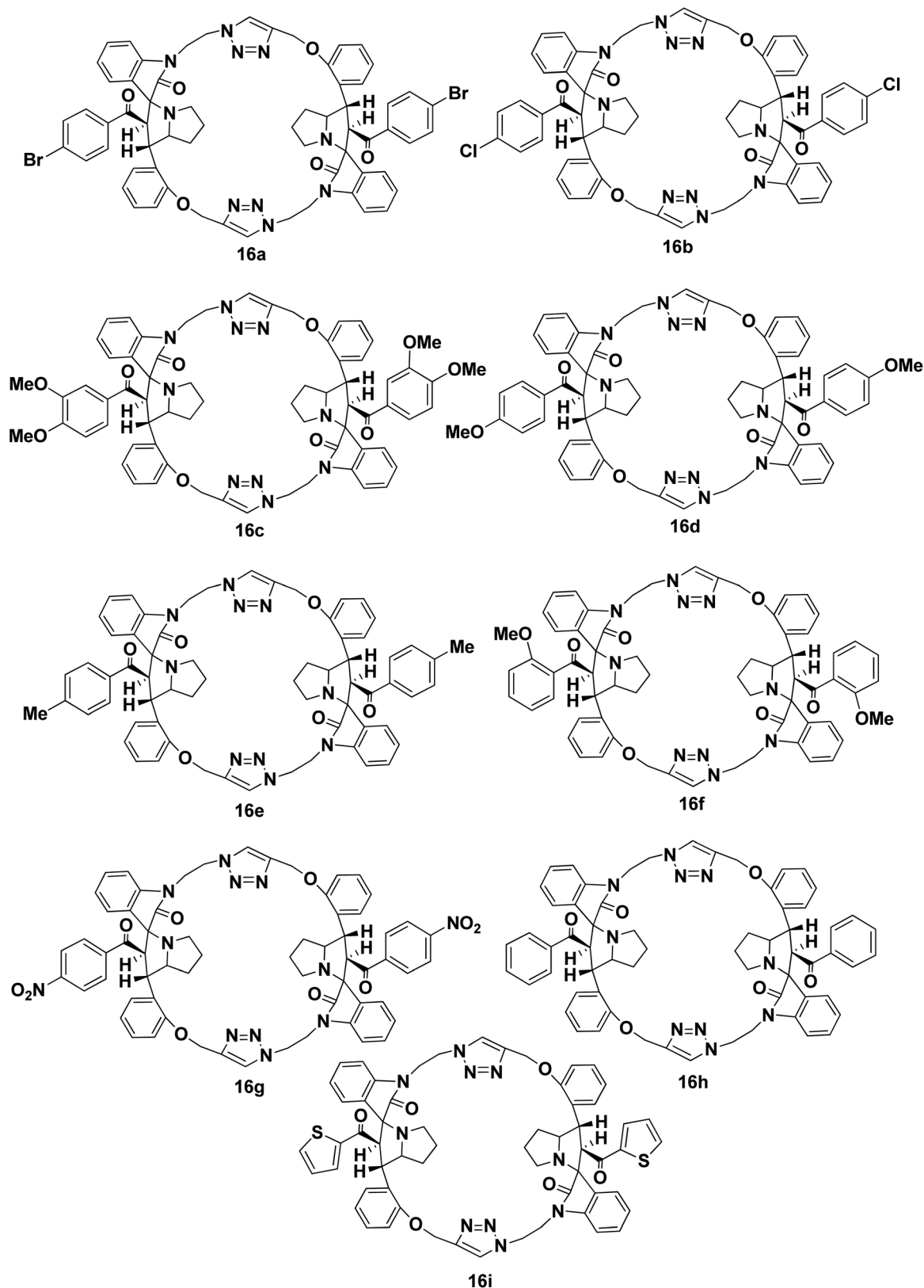
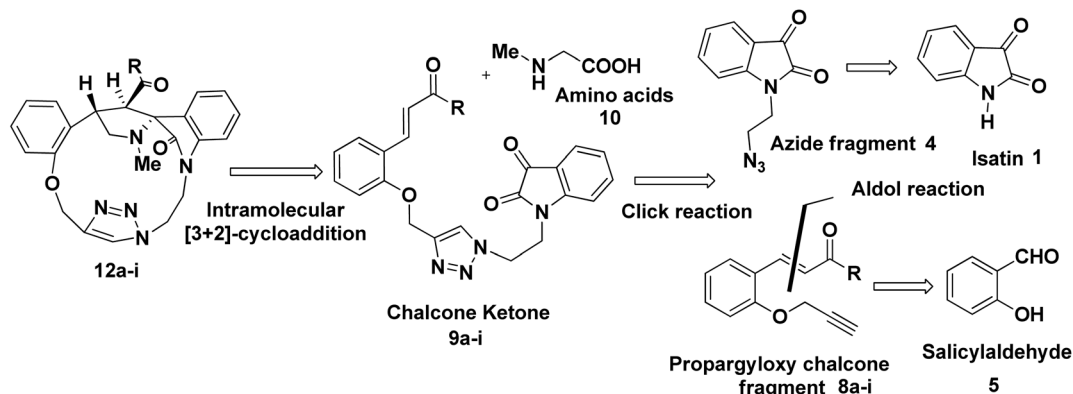


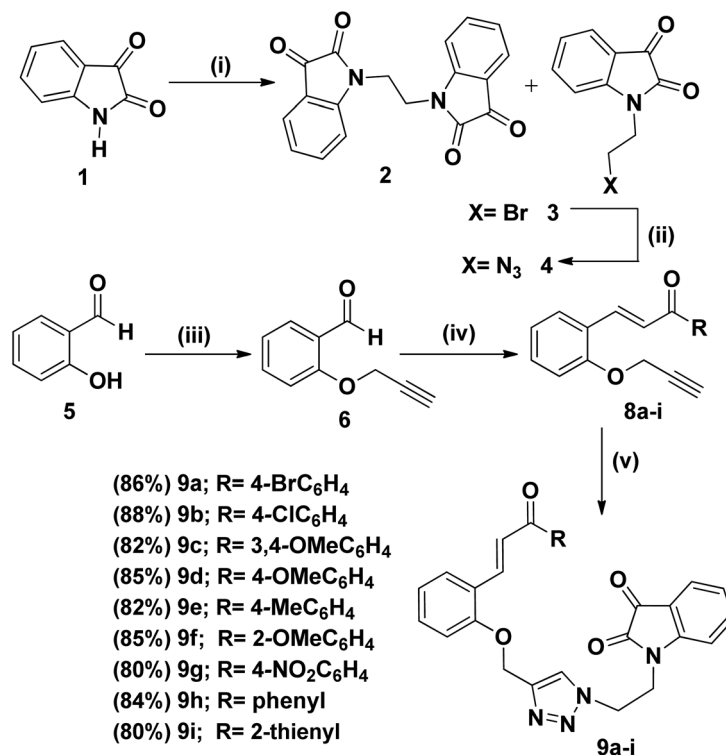
Fig. 3 Molecular structure of bis-spiropyrrolidine-oxindole grafted macrocycles 16a–i.

The two *O*-methylene protons appeared as two doublets at  $\delta$  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  $\delta$  3.57–3.61. The pyrrolidine  $H_b$  proton adjacent to the carbonyl group appeared as a doublet at  $\delta$  5.21 ( $J = 6.9$  Hz), which clearly proved the regiochemistry of the cycloaddition.



Scheme 1 Synthetic plan for spiropyrrolidine-oxindole grafted macrocycles 12a–i.



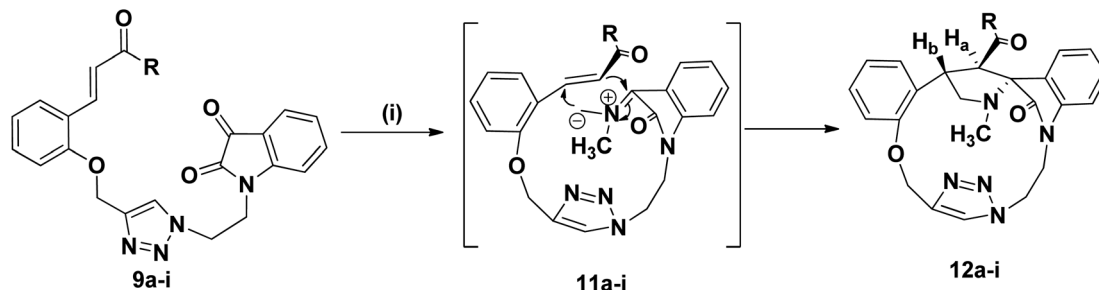
Scheme 2 Synthesis of 1,2,3-triazole bridged chalcone isatin **9a–i**. Reagent and conditions: (i) 1,2-dibromoethane, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 2 h, **2** (24%), **3** (58%); (ii) NaN<sub>3</sub>, DMF, rt, 8 h, **4** (93%); (iii) propargyl bromide, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 12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

Table 1 Optimizing the reaction conditions for the synthesis of cycloadduct **12a**

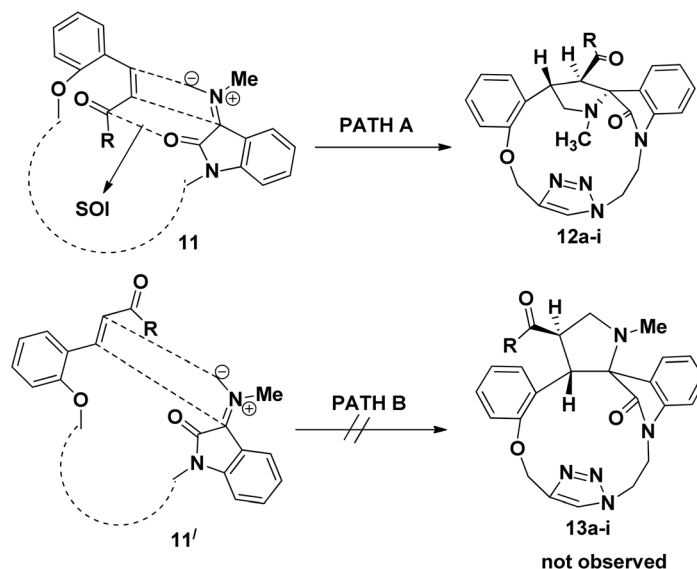
Entry	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	Benzene	Reflux	6	Trace
2	MeOH	Reflux	6	34
3	CH <sub>3</sub> CN	Reflux	6	58
4	Toluene	Reflux	6	74

Further, the triazolyl –CH– proton appeared at  $\delta$  8.12 as a singlet.

In the <sup>13</sup>C NMR spectrum, the cycloadduct **12a** showed the *N*-methyl, *N*-methylene and carbonyl carbons at  $\delta$  34.5, 60.1 and 199.3 ppm respectively. In DEPT-135 <sup>13</sup>C NMR spectrum, the cycloadduct **12a** exhibited the four peaks in the negative region at  $\delta$  39.5, 48.7, 60.1 and 62.3 ppm which confirm the presence of four methylene carbons in **12a**. Moreover, <sup>1</sup>H–<sup>1</sup>H COSY and <sup>1</sup>H–<sup>13</sup>C 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 spiro pyrrolidine-oxindole grafted macrocycles **12a–i**. Reagent and conditions: (i) sarcosine **10**, toluene,  $N_2$  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 transition state that leads to the cycloadduct **12a–i**.

$H^+$  in HRMS (TOF MS  $ES^+$   $3.35 \times 10^7$ ). 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)<sup>36</sup> 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 transition 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 stereocontrolled cycloaddition and the favorable SOI results in the formation of the regioisomer **12a–i** only.

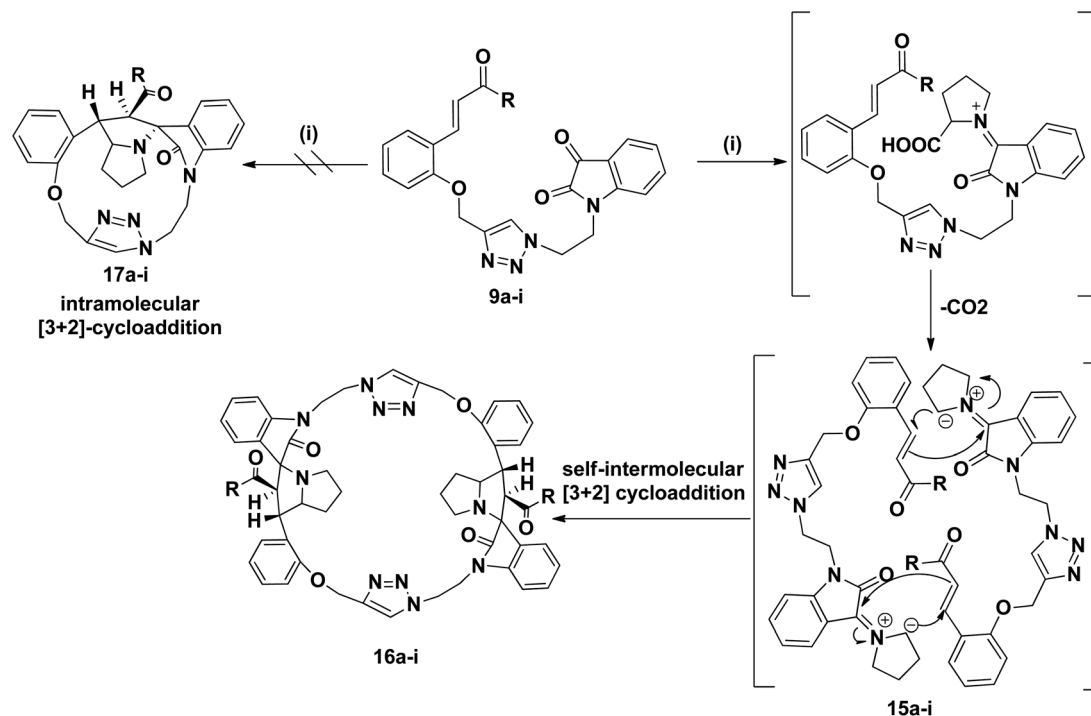
As a logical extension of the methodology, synthesis of bis-spiropyrrolizidine-oxindole grafted macrocycles **16a–i** was then focused. Reaction of the triazole bridged chalcone isatin **9a–i** with *L*-proline (**14**) generated the 1,3-dipolar intermediate

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 macrocycles **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 shown in Table 2. The best optimized yield of 64% is shown 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  $\delta$  1.68–2.69 for the pyrrolizidine ring methylene protons. The  $O-CH_2-$  protons appeared as an  $AB_q$  at  $\delta$  5.24, 5.49 ( $J = 11.7$  Hz). A doublet at  $\delta$  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  $\delta$  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-spiropyrrolidine-oxindole grafted macrocycles **16a-i**. Reagents and conditions: (i) proline (**14**), toluene,  $N_2$  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 ( $^{\circ}C$ )	Time (h)	Isolated yield (%)
1	Benzene	Reflux	6	Trace
2	MeOH	Reflux	6	18
3	$CH_3CN$	Reflux	6	32
4	Toluene	Reflux	6	64

singlet appeared at  $\delta$  9.85 corresponding to triazole  $-CH-$  proton 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  $^1H-^{13}C$  COSY (ESI $^+$ ) experiments. In DEPT-135  $^{13}C$  NMR spectrum, the methylene carbons exhibited six peaks in the negative region at  $\delta$  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  $^{13}C$  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-spiropyrrolidine-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-spiropyrrolidine 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,  $^{13}C$  NMR and DEPT 135 spectra were recorded in  $CDCl_3$  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 ( $\delta_H = CDCl_3$  7.26 ppm, and  $DMSO-d_6$  2.50 ppm;  $\delta_C = CDCl_3$  77.16 ppm, and  $DMSO-d_6$  39.5 ppm). Coupling constants ( $J$ ) are quoted in Hertz (Hz). The HRMS spectra were recorded on Xevo G2s Qtof (ESI) instruments.

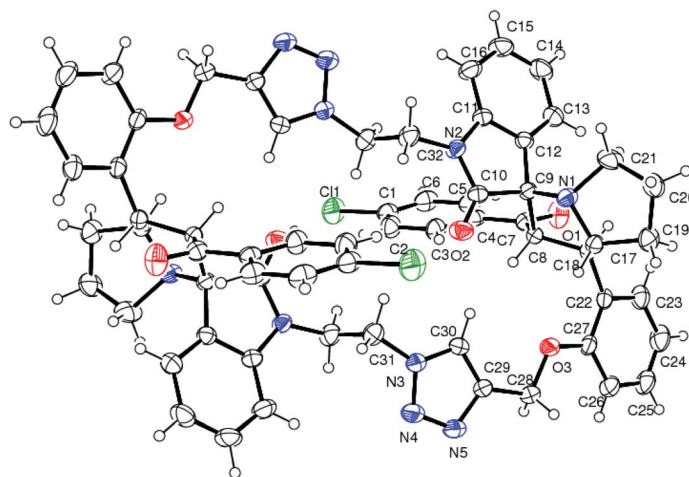


Fig. 5 ORTEP diagram of bis-spiropyrrrolizidine-oxindole grafted macrocycle **16b**.

### 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 H<sub>2</sub>O (20 mL), was added CuSO<sub>4</sub> · 5H<sub>2</sub>O (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 Na<sub>2</sub>SO<sub>4</sub> 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. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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, 131.9, 137.1, 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. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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 9c.** Yield 82%, orange-yellow solid. Mp: 198–200 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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 9e.** Yield 82%. Orange-yellow solid. Mp: 182–184 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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 9f.** Yield 85%, orange-yellow solid. Mp: 128–130 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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 9g.** Yield 80%. Orange-yellow solid. Mp: 180–182 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.21 (t, *J* = 6.0 Hz, 2H); 4.72



(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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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 spiro pyrrolidine-oxindole grafted macrocycles 12a–i/bis-spiro pyrrolidone-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  $\text{N}_2$  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 ( $\text{MgSO}_4$ ) and filtered, concentrated in vacuum. The crude product was purified by column chromatography using hexane/ethyl acetate (1 : 1) as eluent to give the spiro pyrrolidine-oxindole grafted macrocycles **12a–i** and bis-spiro pyrrolidone-oxindole grafted macrocycles **16a–i**.

**Spiro pyrrolidine-oxindole grafted macrocycle 12a.** Yield 74%. White solid. Mp 206–208 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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); 7.03–7.07 (m, 3H); 7.20–7.27 (m, 2H); 7.39 (d,  $J = 8.4$  Hz, 2H); 8.12 (s, 1H).  $^{13}\text{C}$  NMR (70 MHz,  $\text{CDCl}_3$ ):  $\delta$  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  $\text{ES}^+$   $3.35 \times 10^7$ )  $m/z$  calcd for  $\text{C}_{30}\text{H}_{26}\text{BrN}_5\text{O}_5 + \text{H}^+$  [M + H] $^+$  584.1297 found 584.1271.

**Spiro pyrrolidine-oxindole grafted macrocycle 12b.** Yield: 75%; white solid; mp; 146–148 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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  $\text{ES}^+$   $3.36 \times 10^7$ )  $m/z$  calcd for  $\text{C}_{30}\text{H}_{26}\text{ClN}_5\text{O}_5 + \text{H}_2$  [M + 2] $^+$  541.1881 found 541.1859.

**Spiro pyrrolidine-oxindole grafted macrocycle 12c.** 68%; white solid; mp; 218–220 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  34.6, 39.9, 45.5, 49.0, 52.6, 55.9, 56.0, 60.0, 62.3, 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  $\text{ES}^+$   $9.65 \times 10^8$ )  $m/z$  calcd for  $\text{C}_{32}\text{H}_{31}\text{N}_5\text{O}_5 + \text{H}^+$  [M + H] $^+$  566.2403 found 566.2404.

**Spiro pyrrolidine-oxindole grafted macrocycle 12d.** Yield: 70%; white solid; mp; 232–234 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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  $\text{ES}^+$   $2.50 \times 10^8$ )  $m/z$  calcd for  $\text{C}_{31}\text{H}_{29}\text{N}_5\text{O}_4 + \text{H}^+$  [M + H] $^+$  536.2298 found 536.2377.

**Spiro pyrrolidine-oxindole grafted macrocycle 12e.** Yield: 68%. White solid; mp 184–186 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 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:  $\delta$  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  $\text{ES}^+$   $9.22 \times 10^8$ )  $m/z$  calcd for  $\text{C}_{31}\text{H}_{29}\text{N}_5\text{O}_3 + \text{H}_2$  [M + 2] $^+$  521.2427 found 521.2437.

**Spiro pyrrolidine-oxindole grafted macrocycle 12f.** Yield: 65%; white solid; mp; 196–198 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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);

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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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.

*Spiroyrrolidine-oxindole grafted macrocycle 12g*. Yield: 72%; white solid; mp; 228–230 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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  $\text{ES}^+$   $4.14 \times 10^7$ )  $m/z$  calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_6\text{O}_5 + \text{H}_2$   $[\text{M} + 2]^+$  552.2122 found 552.2100.

*Spiroyrrolidine-oxindole grafted macrocycle 12h*. Yield: 73%; white solid; mp; 216–218 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (70 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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  $\text{ES}^+$   $3.97 \times 10^7$ )  $m/z$  calcd for  $\text{C}_{30}\text{H}_{27}\text{N}_5\text{O}_3 + \text{H}_2$   $[\text{M} + 2]^+$  507.2270 found 507.2260.

*Spiroyrrolidine-oxindole grafted macrocycle 12i*. Yield: 70%; white solid; mp; 238–240 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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-spiroyrrolididine-oxindole grafted macrocycle 16a*. Yield: 64%; white solid; mp; 220–222 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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<sub>q</sub>,  $J = 11.7$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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  $\text{ES}^+$   $2.29 \times 10^8$ )  $m/z$  calcd for  $\text{C}_{64}\text{H}_{56}\text{Br}_2\text{N}_{10}\text{O}_6 + \text{H}^+$   $[\text{M} + \text{H}]^+$  1219.2829 found 1219.2828.

*Bis-spiroyrrolididine-oxindole grafted macrocycle 16b*. Yield: 65%; white solid; mp; 236–238 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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<sub>q</sub>,  $J = 11.7$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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:  $\delta$  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  $\text{ES}^+$   $4.22 \times 10^8$ )  $m/z$  calcd for  $\text{C}_{64}\text{H}_{56}\text{Cl}_2\text{N}_{10}\text{O}_6 + \text{H}^+$   $[\text{M} + \text{H}]^+$  1131.3838 found 1131.3840.

*Bis-spiroyrrolididine-oxindole grafted macrocycle 16c*. Yield: 58%; white solid; mp; 270–272 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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 (m, 4H); 4.46–4.52 (m, 2H); 5.21, 5.35 (AB<sub>q</sub>,  $J = 12$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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  $\text{ES}^+$   $5.86 \times 10^7$ )  $m/z$  calcd for  $\text{C}_{68}\text{H}_{66}\text{N}_{10}\text{O}_{10} + \text{H}^+$   $[\text{M} + \text{H}]^+$  1183.5041 found 1183.5045.

*Bis-spiroyrrolididine-oxindole grafted macrocycle 16d*. Yield: 60%. White solid; mp 250–252 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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<sub>q</sub>,  $J = 11.7$  Hz, 4H); 5.75 (d,  $J = 12$  Hz, 2H); 6.67 (d,  $J = 8.7$  Hz, 4H); 6.89 (d,  $J = 7.5$  Hz, 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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 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:  $\delta$  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  $\text{ES}^+$   $1.24 \times 10^9$ )  $m/z$  calcd for  $\text{C}_{66}\text{H}_{62}\text{N}_{10}\text{O}_8 + \text{H}^+$   $[\text{M} + \text{H}]^+$  1123.4830 found 1123.4847.

*Bis-spiropyrrrolizidine-oxindole grafted macrocycle 16e.* Yield: 56%. White Solid. Mp 238–240 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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<sub>q</sub>, *J* = 11.7 Hz, 4H); 5.67 (d, *J* = 11.4 Hz, 2H); 6.76 (d, *J* = 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, *J* = 7.2 Hz, 2H); 9.87 (s, 2H). <sup>13</sup>C NMR (70 MHz, CDCl<sub>3</sub>): 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<sup>+</sup> 1.21 × 10<sup>9</sup>) *m/z* calcd for C<sub>66</sub>H<sub>62</sub>N<sub>10</sub>O<sub>6</sub> + H<sup>+</sup> [M + H]<sup>+</sup> 1091.4932 found 1091.4944.

*Bis-spiropyrrrolizidine-oxindole grafted macrocycle 16f.* Yield: 55%; white solid; mp; 228–230 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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<sub>q</sub>, *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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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-spiropyrrrolizidine-oxindole grafted macrocycle 16g.* Yield: 62%; white solid; mp; 196–198 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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<sub>q</sub>, *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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sup>+</sup> 9.19 × 10<sup>8</sup>) *m/z* calcd for C<sub>64</sub>H<sub>56</sub>N<sub>12</sub>O<sub>10</sub> + H<sup>+</sup> [M + H]<sup>+</sup> 1153.4320 found 1153.4332.

*Bis-spiropyrrrolizidine-oxindole grafted macrocycle 16h.* 60%; white solid; mp; 208–210 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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<sub>q</sub>, *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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sup>+</sup> 4.89 × 10<sup>7</sup>) *m/z* calcd for C<sub>29</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub> + H<sup>+</sup> [M + H]<sup>+</sup> 1063.4619 found 1063.4640.

*Bis-spiropyrrrolizidine-oxindole grafted macrocycle 16i.* Yield: 56%; white solid; mp; 202–204 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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<sub>q</sub>, *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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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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## References

- (a) A. K. Yudin, *Chem. Sci.*, 2015, **6**, 30–49; (b) *Practical Medicinal Chemistry with Macrocycles: Design, Synthesis, and Studies*, ed. E. Marsault and M. L. Peterson, Wiley & Sons, Hoboken, 2017; (c) F. Davis and S. Higson, *Macrocycles: Construction, Chemistry and Nanotechnology Applications*, Wiley & Sons, Chichester, U.K., 2011; (d) E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608–624; (e) J. Mallinson and I. Collins, *Future Med. Chem.*, 2012, **4**, 1409–1438; (f) D. Krahn, C. Ottmann and M. Kaiser, *Curr. Med. Chem.*, 2011, **18**, 5052–5060.
- (a) V. Balzani, A. Credi, F. M. Raymo and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2000, **39**, 3349–3391; (b) C. P. Collier, G. Mattersteig, E. W. Wong, Y. Luo, K. Beverley, J. Sampaio, F. M. Raymo, J. F. Stoddart and J. R. Heath, *Science*, 2000, **289**, 1172–1175; (c) X. -J. Wanga, J. Liu, C.-X. Zhang, D.-L. Gong, H. Zhang, J.-D. Wang, Y.-J. Yan and W.-S. Xiang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5145–5148; (d) T. Berg, *Angew. Chem., Int. Ed.*, 2003, **42**, 2462–2481; (e) S. Purushothaman, R. Prasanna and R. Raghunathan, *Tetrahedron Lett.*, 2013, **54**, 6450–6454.

- 3 (a) S. Purushothaman, R. Prasanna, P. Niranjana, R. Raghunathan, S. Nagaraj and R. Rengasamy, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7288–7291; (b) J. R. Liddell, *Nat. Prod. Rep.*, 1996, **13**, 187; (c) J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 535–552; (d) D. J. Robins, *Nat. Prod. Rep.*, 1995, **12**, 413–418; (e) W. Glassco, J. Suchocki, C. George, B. R. Martin and E. L. May, *J. Med. Chem.*, 1993, **36**, 3381–3385; (f) B. B. Snider, Y. Ahn and B. M. Foxman, *Tetrahedron Lett.*, 1999, **40**, 3339–3342; (g) J. A. Nieman and M. D. Ennis, *Org. Lett.*, 2000, **2**, 1395–1397; (h) S. R. Angle, D. Bensa and D. S. Belanger, *J. Org. Chem.*, 2007, **72**, 5592–5597.
- 4 (a) K. Zheng and R. Hong, *Nat. Prod. Rep.*, 2019, **36**, 1546–1575; (b) L.-S. You, R. An, K. Liang, B. Cui and X.-H. Wang, *Curr. Pharm. Des.*, 2016, **22**, 4086–4093; (c) F. Giordanetto and J. Kihlberg, *J. Med. Chem.*, 2014, **57**, 278–295; (d) C. Heinis, *Nat. Chem. Biol.*, 2014, **10**, 696–698; (e) J. Mallinson and I. Collins, *Future Med. Chem.*, 2012, **4**, 1409–1438.
- 5 (a) X. Yu and D. Sun, *Molecules*, 2013, **18**, 6230–6268; (b) C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Deliv. Rev.*, 2001, **46**, 3–26; (c) E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608–624; (d) E. Marsault and M. L. Peterson, *J. Med. Chem.*, 2011, **54**, 1961–2004.
- 6 (a) Q. Zhao and C. E. Schafmeister, *J. Org. Chem.*, 2015, **80**, 8968–8978; (b) P. T. Quinn, P. D. Atwood, J. M. Tanski, T. F. Moore and F. Folmer-Andersen, *J. Org. Chem.*, 2011, **76**, 10020–10030; (c) S. Guo, G. Wang and L. Ai, *Tetrahedron: Asymmetry*, 2013, **24**, 480–491.
- 7 (a) C. D. Gutsche, A. E. Rowan, S. J. Rowan and T. Aida, *Calixarenes: An Introduction*, The Royal Society of Chemistry, Cambridge, U.K., 2008; (b) D. M. Homden and C. Redshaw, *Chem. Rev.*, 2008, **108**, 5086–5130; (c) F. Yang, H. Guo and J. Vicens, *J. Inclusion Phenom. Macrocyclic Chem.*, 2014, **80**, 177–186; (d) E. V. Ukhatskaya, S. V. Kurkov, S. E. Matthews and T. J. Loftsson, *J. Pharmaceut. Sci.*, 2013, **102**, 3485–3512; (e) J. S. Kim and D. T. Quang, *Chem. Rev.*, 2007, **107**, 3780–3799.
- 8 (a) A. Dondoni and A. Marra, *Chem. Rev.*, 2010, **110**, 4949; (b) J. S. Kim and D. T. Quang, *Chem. Rev.*, 2007, **107**, 3780–3799; (c) V. M. Centelles, M. D. Pandey, M. Isabel Burguete and S. V. Luis, *Chem. Rev.*, 2015, **115**, 8736–8834.
- 9 (a) S. Hu, J. Li, J. Xiang, J. Pan, S. Luo and J.-P. Cheng, *J. Am. Chem. Soc.*, 2010, **132**, 7216–7228; (b) R. Breslow, J. B. Doherty, G. Guillot and C. Lipsey, *J. Am. Chem. Soc.*, 1978, **100**, 3227–3322; (c) E. Anslyn and R. Breslow, *J. Am. Chem. Soc.*, 1989, **111**, 8931–8932; (d) A. Douhal, *Chem. Rev.*, 2004, **104**, 1955–1976.
- 10 (a) J. Li and X. J. Loh, Cyclodextrin- Based Supramolecular Architectures: Syntheses, Structures, and Applications for Drug and Gene Delivery, *Adv. Drug Delivery Rev.*, 2008, **60**, 1000–1017; (b) G. Crini, Review: A History of Cyclodextrins, *Chem. Rev.*, 2014, **114**, 10940–10975; (c) E. M. Martin Del Valle, Cyclodextrins and Their Uses: a Review, *Process Biochem.*, 2004, **39**, 1033–1046.
- 11 (a) J. W. Lee, S. Samal, N. Selvapalam, H. Kim and K. Kim, *Acc. Chem. Res.*, 2003, **36**, 621–630; (b) J. Lagona, P. Mukhopadhyay, S. Chakrabarti and L. Isaacs, *Angew. Chem., Int. Ed.*, 2005, **44**, 4844–4870; (c) K. I. Assaf and W. M. Nau, *Chem. Soc. Rev.*, 2015, **44**, 394–418; (d) F. Seidi, A. A. Shamsabadi, M. Amini, M. Shabanian and D. Crespy, *Polym. Chem.*, 2019, **10**, 3674–3711.
- 12 (a) J. L. Atwood and L. R. MacGillivray, *Nature*, 1997, **389**, 469–472; (b) J. R. Moran, S. Karbach and D. J. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 5826–5828; (c) F. R. Pinacho Crisóstomo, A. Lledó, S. R. Shenoy, T. Iwasawa and J. Rebek, *J. Am. Chem. Soc.*, 2009, **131**, 7402–7410; (d) M. M. D. Cominetti, D. L. Hughesb and S. E. Matthews, *Org. Biomol. Chem.*, 2016, **14**, 10161–10164.
- 13 (a) N. Natarajan, E. Brenner, D. Sémeril, D. Matt and J. Harrowfield, *Eur. J. Org. Chem.*, 2017, 6100–6113; (b) N. Li, F. Yang, H. A. Stock, D. V. Dearden, J. D. Lamb and R. G. Harrison, *Org. Biomol. Chem.*, 2012, **10**, 7392–7401; (c) B. A. Roberts, G. W. V. Cave, C. L. Rastonb and J. L. Scott, *Green Chem.*, 2001, **3**, 280–284.
- 14 (a) M. Li, F.-G. Klärner, J. Sakamoto and A. D. Schlüter, *Chem.–Eur. J.*, 2013, **19**, 13348–13354; (b) S. Lee, C.-H. Chen and A. H. Flood, *Nat. Chem.*, 2013, **5**, 704–710; (c) M. Fritzsche, A. Bohle, D. Dudenko, U. Baumeister, D. Sebastiani, G. Richardt, H. W. Spiess, M. R. Hansen and S. Höger, *Angew. Chem., Int. Ed.*, 2011, **50**, 3030–3033; (d) L.-l. Tian, C. Wang, S. Dawn, M. D. Smith, J. A. Krause and L. S. Shimizu, *J. Am. Chem. Soc.*, 2009, **131**, 17620–17629.
- 15 (a) M. Bru, I. Alfonso, M. Bolte, M. I. Burguete and S. V. Luis, *Chem. Commun.*, 2011, **47**, 283–285; (b) A. J. Gallant, M. Yun, M. Sauer, C. S. Yeung and M. J. MacLachlan, *Org. Lett.*, 2005, **7**, 4827–4830; (c) J. Gawronski, K. Gawronska, J. Grajewski, M. Kwit, A. Plutecka and U. Rychlewska, *Chem.–Eur. J.*, 2006, **12**, 1807–1817; (d) S. Guieu, A. K. Crane and M. J. MacLachlan, *Chem. Commun.*, 2011, **47**, 1169–1171.
- 16 (a) A.-M. Stadler, J.-J. Jiang, H.-P. Wang and C. Bailly, *Chem. Commun.*, 2013, **49**, 3784–3786; (b) J. Jiang and M. J. MacLachlan, *Org. Lett.*, 2010, **12**, 1020–1023; (c) M. Kwit, A. Plutecka, U. Rychlewska, J. Gawronski, A. F. Khlebnikov, S. I. Kozhushkov, K. Rauch and A. de Meijere, *Chem.–Eur. J.*, 2007, **13**, 8688–8695.
- 17 (a) A. M. Lopez-Periago, C. A. Garcia-Gonzalez and C. Domingo, *Chem. Commun.*, 2010, **46**, 4315–4317; (b) A. Sarnicka, P. Starynowicz and J. Lisowski, *Chem. Commun.*, 2012, **48**, 2237–2239; (c) J. W. Leeland, F. J. White and J. B. Love, *J. Am. Chem. Soc.*, 2011, **133**, 7320–7323.
- 18 (a) Y. Yamauchi, D. Ajami, J.-Y. Lee and J. Rebek, *Angew. Chem., Int. Ed.*, 2011, **50**, 9150–9153; (b) M. Chas and P. Ballester, *Chem. Sci.*, 2012, **3**, 186–191; (c) A. Asadi, D. Ajami and J. Rebek, *J. Am. Chem. Soc.*, 2011, **133**, 10682–10684; (d) H. Dube and J. Rebek, *Angew. Chem., Int. Ed.*, 2012, **51**, 3207–3210; (e) K. Tiefenbacher and J. Rebek, *J. Am. Chem. Soc.*, 2012, **134**, 2914–2917.
- 19 (a) P. Ballester, *Chem. Soc. Rev.*, 2010, **39**, 3810–3830; (b) P. Mal, D. Schultz, K. Beyeh, K. Rissanen and J. R. Nitschke, *Angew. Chem., Int. Ed.*, 2008, **47**, 8297–8301;



- (c) J.-F. Ayme, J. E. Beves, D. A. Leigh, R. T. McBurney, K. Rissanen and D. Schultz, *Nat. Chem.*, 2011, **4**, 15–20; (d) Y. Wang, J. Xiang and H. Jiang, *Chem.–Eur. J.*, 2011, **17**, 613–619.
- 20 (a) H. Li, R. Aneja and I. Chaiken, *Molecules*, 2013, **18**, 9797–9817; (b) C. Chu and R. Liu, *Chem. Soc. Rev.*, 2011, **40**, 2177–2188; (c) D. Astruc, L. Liang, A. Rapakousiou and J. Ruiz, *Acc. Chem. Res.*, 2012, **45**, 630–640; (d) J. Shang, N. M. Gallagher, F. Bie, Q. Li, Y. Che, Y. Wang and H. Jiang, *J. Org. Chem.*, 2014, **79**, 5134–5144.
- 21 (a) C. NfflÇez, A. Aldrey, V. Garca, R. Bastida, A. Macas and C. Lodeiro, *Inorg. Chim. Acta*, 2012, **381**, 85–94; (b) C. Bazzicalupi, A. Bencini, I. Matera, S. Puccioni and B. Valtancoli, *Inorg. Chim. Acta*, 2012, **381**, 162–169; (c) J. Beckmann, A. Duthie, G. Reeske and M. Schürmann, *Organometallics*, 2005, **24**, 3629–3633; (d) T. Berg, *Angew. Chem., Int. Ed.*, 2003, **42**, 2462–2481; (e) J. A. Wells and L. McClendon, *Nature*, 2007, **450**, 1001–1009; (f) Ahsanullah and J. Rademann, *Angew. Chem., Int. Ed.*, 2010, **49**, 5378–5382.
- 22 (a) A. Von Baeyer, *Ber. Dtsch. Chem. Ges.*, 1900, **33**, 3771–3775; (b) J. Pospíšilová, V. Krchňák and E. Schütznerová, *ACS Comb. Sci.*, 2019, **21**, 1–5.
- 23 (a) S.-S. Li, S. Zhu, C. Chen, K. Duan, Q. Liu and J. Xiao, *Org. Lett.*, 2019, **21**, 1058–1062; (b) Y.-B. Shen, S.-S. Li, X. Liu, L. Yu, Y.-M. Sun, Q. Liu and J. Xiao, *J. Org. Chem.*, 2019, **84**, 3990–3999; (c) Y.-B. Shen, S.-S. Li, X. Liu, L. Yu, Q. Liu and J. Xiao, *Adv. Synth. Catal.*, 2019, **361**, 1453–1458.
- 24 (a) J. S. Bindra, Oxindole Alkaloids, in *Alkaloid Chemistry and Physiology*, ed. R. H. F. Manske, Academic Press, New York, 1973, p. 14; (b) A. Padwa and W. H. Pearson, *Synthetic Applications of 1,3 Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, New York, 2002; (c) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104–6155; (d) N. Lashgari and G. M. Ziarani, *Arkivoc*, 2012, 277–320.
- 25 (a) X. Fang and C.-J. Wang, *Org. Biomol. Chem.*, 2018, **16**, 2591–2601; (b) I. J. Enyedy, W. A. Zaman, S. Sakamuri, A. P. Kozikowski, K. M. Johnson and S. Wang, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1113; (c) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758; (d) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139–165; (e) N. Deppermann, H. Thomanek, A. H. G. P. Prenzel and W. Maison, *J. Org. Chem.*, 2010, **75**, 5994–6000.
- 26 (a) M. Ochi, K. Kawasaki, H. Kataoka, Y. Uchio and H. Nishi, *Biochem. Biophys. Res. Commun.*, 2001, **283**, 1118–1123; (b) A. Czarna, B. Beck, S. Srivastava, G. M. Popowicz, S. Wolf, Y. Huang, M. Bista, T. A. Holak and A. Dömling, *Angew. Chem., Int. Ed.*, 2010, **49**, 5352–5356; (c) S. Crosignani, C. Jorand-Lebrun, P. Page, G. Campbell, V. Colovray, M. Missotten, Y. Humbert, C. Cleva, J.-F. Arrighi, M. Gaudet, Z. Johnson, P. Ferro and A. Chollet, *ACS Med. Chem. Lett.*, 2011, **2**, 644–649; (d) J. I. Jimenez, U. Huber, R. E. Moore and G. M. L. J. Patterson, *Nat. Prod.*, 1999, **62**, 569–572; (e) S. Rana and A. Natarajan, *Org. Biomol. Chem.*, 2013, **11**, 244–247; (f) B.-D. Cui, J. Zuo, J.-Q. Zhao, M.-Q. Zhou, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.*, 2014, **79**, 5305–5314.
- 27 (a) P. C. Mhaske, S. H. Shelke, R. P. Jadhav, H. N. Raundal, S. V. Patil, A. A. Patil and V. D. Bobade, *J. Heterocycl. Chem.*, 2010, **47**, 1415–1420; (b) P. Prasanna, K. Balamurugan, S. Perumal, P. Yogeewari and D. Sriram, *Eur. J. Med. Chem.*, 2010, **45**, 5653–5661; (c) S. Purushothaman, R. Prasanna, S. Lavanya and R. Raghunathan, *Tetrahedron Lett.*, 2013, **54**, 5744–5747; (d) T. Usui, M. Kondoh, C. B. Cui, T. Mayumi and H. Osada, *Biochem. J.*, 1998, **333**, 543–548.
- 28 (a) G. Periyasami, R. Raghunathan, G. Surendiran and N. Mathivanan, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2342–23425; (b) G. Bhaskar, Y. Arun, C. Balachandran, C. Saikumar and P. T. Perumal, *Eur. J. Med. Chem.*, 2012, **51**, 79–91; (c) S. Haddad, S. Boudriga, F. Porzio, A. Soldera, M. Askri, M. Knorr, Y. Rousselin, M. M. Kubicki, C. Golz and C. Strohmann, *J. Org. Chem.*, 2015, **80**, 9064–9075.
- 29 (a) M. A. Ali, R. Ismail, T. S. Choon, Y. K. Yoon, A. C. Wei, S. Pandian, R. S. Kumar, H. Osman and E. Manogaran, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7064–7066; (b) Y. Kia, H. Osman, R. S. Kumar, V. Murugaiyah, A. Basiri, S. Perumal and I. A. Razak, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2979–2983; (c) A. S. Filatov, N. A. Knyazev, A. P. Molchanov, T. L. Panikorovsky, R. R. Kostikov, A. G. Larina, V. M. Boitsov and A. V. Stepanov, *J. Org. Chem.*, 2017, **82**, 959–975.
- 30 (a) C. J. A. Ribeiro, C. M. P. Rodrigues, R. Moreira and M. M. M. Santos, *Pharmaceuticals*, 2016, **9**, 25–57; (b) S. Nag, X. Zhang, K. S. Srivenugopal, M.-H. Wang, W. Wang and R. Zhang, *Curr. Med. Chem.*, 2014, **21**, 553–574.
- 31 (a) A. A. Akaev, E. V. Villemson, N. S. Vorobyeva, A. G. Majouga, E. M. Budynina and M. Y. Melnikov, *J. Org. Chem.*, 2017, **82**, 5689–5701; (b) Y. Zhao, A. Aguilar, D. Bernard and S. Wang, *J. Med. Chem.*, 2015, **58**, 1038–1052; (c) Y. Zhao, S. Yu, W. Sun, L. Liu, J. Lu, D. McEachern, S. Shargary, D. Bernard, X. Li, T. Zhao, P. Zou, D. Sun and S. Wang, *J. Med. Chem.*, 2013, **56**, 5553–5561.
- 32 (a) F. Shi, R. Mancuso and R. T. Larock, *Tetrahedron Lett.*, 2009, **50**, 4067–4070; (b) C. E. P. Galvis and V. V. Kouznetsov, *Org. Biomol. Chem.*, 2013, **11**, 7372–7386; (c) N. Lashgari and G. M. Ziarani, *ARKIVOC*, 2012, 277–320; (d) S. Kamalraj and J. Muthumary, *Eur. J. Med. Chem.*, 2011, **46**, 600–607; (e) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2810; (f) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484–4517; (g) M. Naodovic and H. Yamamoto, *Chem. Rev.*, 2008, **108**, 3132–3148; (h) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2011, **47**, 6784–6794.
- 33 (a) J. Nájera and M. Sansano, *Angew. Chem., Int. Ed.*, 2005, **44**, 6272–6276; (b) V. Nair and D. T. Suja, *Tetrahedron*, 2007, **63**, 12247–12275; (c) H. Pellissier, *Tetrahedron*, 2007, **63**, 3235–3285; (d) K. Anita and R. M. Marie, *Chem. Soc. Rev.*, 2010, **39**, 845–883; (e) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887–2902; (f) A. Moyano and R. Rios, *Chem.*



- Rev.*, 2011, **111**, 4703–4832; (g) C.-S. Wang, R.-Y. Zhu, J. Zheng, F. Shi and S.-J. Tu, *J. Org. Chem.*, 2015, **80**, 512–520.
- 34 (a) R. Prasanna, S. Purushothaman and R. Raghunathan, *Org. Biomol. Chem.*, 2014, **12**, 9375–9383; (b) G. Venkataramana, P. Dongare, L. N. Dawe, D. W. Thompson, Y. Zhao and G. J. Bodwell, *Org. Lett.*, 2011, **13**, 2240–2243; (c) I.-S. Tamgho, J. T. Engle and C. J. Ziegler, *J. Org. Chem.*, 2012, **77**, 11372–11376; (d) B. Lewandowski and S. Jarosz, *Org. Lett.*, 2010, **12**, 2532–2535.
- 35 P. Prabhakaran, M. Subaraja and P. Rajakumar, *ChemistrySelect*, 2018, **3**, 4687–4693.
- 36 (a) H. Ardill, M. J. R. Dorrity, R. Grigg, M. S. Leon-Ling, J. F. Malone, V. Sridharan and S. Thianpatanagul, *Tetrahedron*, 1990, **46**, 6433–6448; (b) G. Subramaniyan, R. Raghunathan and M. Nethaji, *Tetrahedron*, 2002, **58**, 9075–9079; (c) J.-M. Yang, Y. Hu, Q. Li, F. Yu, J. Cao, D. Fang, Z.-B. Huang and D.-Q. Shi, *ACS Comb. Sci.*, 2014, **16**, 139–145.