

Article

A Sustainable Approach to the Stereoselective Synthesis of Diazaheptacyclic Cage Systems Based on a Multicomponent Strategy in an Ionic Liquid

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Abstract: The microwave-assisted three-component reactions of 3,5-bis(*E*)-arylmethylidene] tetrahydro-4(1*H*)-pyridinones, acenaphthenequinone and cyclic α -amino acids in an ionic liquid, 1-butyl-3-methylimidazolium bromide, occurred through a domino sequence affording structurally intriguing diazaheptacyclic cage-like compounds in excellent yields.

Keywords: diazaheptacyclic cage compounds; multicomponent reactions; ionic liquid; microwave-assisted synthesis

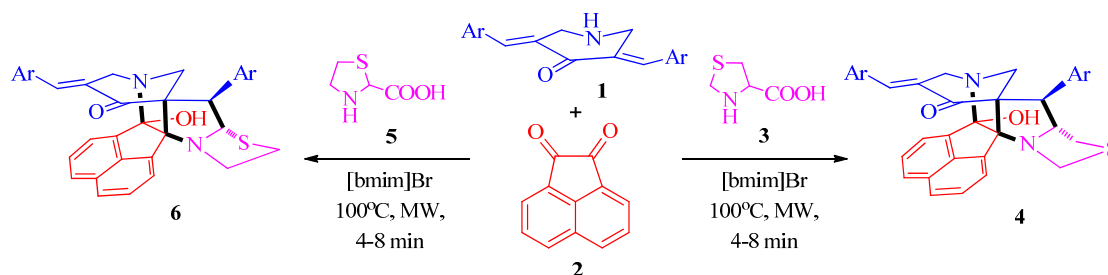
1. Introduction

Achieving molecular complexity and diversity from common starting materials with a minimum number of synthetic steps and short reaction time is a major challenge for synthetic chemists [1–5]. Multi-component reactions (MCR) have proven to be one of the most effective and attractive methods to achieve this goal [6–8]. These reactions allow several bond-forming or bond-breaking transformations to occur in a single step, thereby obviating the time-consuming and costly processes of isolation or purification of various intermediates formed in each step, and also the tedious operations of protection or deprotection of functional groups. Consequently, these reactions are environmentally benign and often proceed with excellent stereoselectivities [9]. Therefore, the design of new selective MCRs for the synthesis of diverse heterocycles of biological significance is a continuing challenge at the forefront of synthetic organic chemistry.

On the other hand, the choice of an appropriate reaction medium is crucial for a successful synthesis. Recently, more emphasis has been focused on the use of eco-friendly solvents. In this regard, ionic liquids are widely recognized as “green” solvents as an alternative to the volatile organic solvents and are suitable for executing diverse organic reactions [10,11]. The development of multicomponent reactions in ionic liquids, although relatively unexplored [12], is of great interest.

Furthermore, microwave-assisted reactions have been reported to proceed in dramatically shortened reaction times as compared to reactions under conventional heating. Under these conditions, the reactions are usually cleaner, affording enhanced product yields and avoiding the formation of unnecessary side products. Microwave-assisted synthesis has significant advantages in several chemical transformations [13,14], including cycloadditions [15].

The synthesis of cage-like compounds has received considerable attention in view of their biological activities and applications as artificial receptors [16]. Gambogic acid, a naturally occurring cage-like compound has been identified as a potent antitumor agent [17] and has recently finished phase IIa clinical trials [18]. The biological evaluation of Gambogic acid derivatives indicated that the peripheral moieties were suitable sites for diverse modification while the α,β -unsaturated moiety in the caged ring was essential for antitumor activity [19]. A recent study from our laboratory revealed that several polycyclic cage compounds embedded with an α,β -unsaturated moiety displayed promising AChE inhibitory activity [20,21]. Several reports pertaining to the synthesis of polycyclic caged structures are available in the literature. However, these methods have mostly relied on multi-step sequences and therefore the development of greener, step-economic routes is imperative. Herein we report the stereoselective synthesis of structurally diverse heptacyclic cage-like frameworks from the three-component domino reactions of 3,5-bis(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **1**, acenaphthenequinone **2** and cyclic α -amino acids **3** or **5** in ionic liquid under microwave conditions (Scheme 1) with the aim of studying their pharmacological profiles in the near future. Furthermore, the present work also stems from our ongoing investigation aimed at synthesizing novel heterocycles employing green chemical protocols [20–31].



Scheme 1. Synthesis of diazaheptacycles **4** and **6**.

2. Results and Discussion

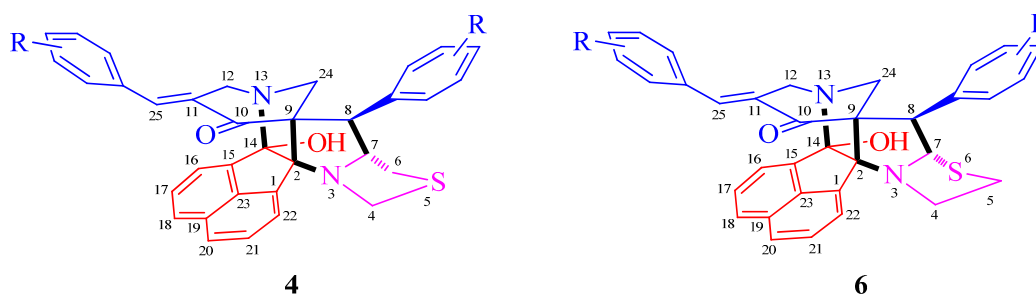
Initially, the precursor 3,5-bis(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **1** was synthesized following a literature method [32]. Then, the optimized reaction condition established in our earlier report for the synthesis of analogous cage-like compounds [23] was employed in the present investigation for the synthesis of two series of novel diazaheptacycles **4** and **6** (Scheme 1 and Table 1). In a typical reaction, an equimolar mixture of the starting materials **1**, **2** and **3** or **5** in 100 mg of ionic liquid [bmim]Br was subjected to microwave irradiation at 100 °C for 4–8 min (Scheme 1 and Table 1). After completion of the reaction, the products **4** and **6** were isolated by extraction and crystallization. After extraction of the product, the ionic liquid [bmim]Br was dried under vacuum, and its recyclability was investigated by successive syntheses of compounds **4** or **6**, which revealed that its efficacy was not significantly diminished after up to three subsequent runs. Furthermore, these reactions gain importance from the viewpoint of green chemistry as the crude reaction products were clean enough to be purified just by crystallization, thereby eliminating the need for chromatography, the main source of waste from synthetic activities.

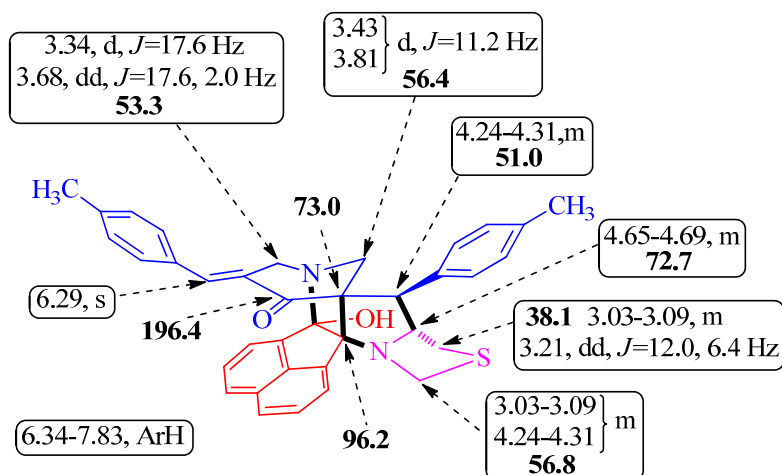
Table 1. Reaction time, yield and melting point of diazaheptacycles **4a–n** and **6a–m**.

Entry	Ar	Comp.	Reaction Time (min)	Yield (%) ^a	m.p. (°C)	Comp.	Reaction Time (min)	Yield (%) ^a	m.p. (°C)
1	C ₆ H ₅	4a	4	92	140–142	6a	4	93	135–137
2	2-CH ₃ C ₆ H ₄	4b	6	90	127–129	6b	6	90	179–181
3	2-OCH ₃ C ₆ H ₄	4c	8	85	166–168	6c	8	84	175–177
4	2-BrC ₆ H ₄	4d	4	91	184–186	6d	4	92	172–174
5	2-ClC ₆ H ₄	4e	4	90	146–148	6e	6	87	134–136
6	2-FC ₆ H ₄	4f	6	88	150–152	6f	6	90	162–164
7	3-NO ₂ C ₆ H ₄	4g	6	91	176–178	6g	4	89	180–182
8	2,4-Cl ₂ C ₆ H ₃	4h	4	90	144–146	6h	6	91	146–147
9	4-CH ₃ C ₆ H ₄	4i	4	93	141–143	6i	6	92	190–192
10	4-OCH ₃ C ₆ H ₄	4j	6	87	137–139	6j	6	86	144–146
11	4-BrC ₆ H ₄	4k	4	92	171–173	6k	4	90	156–158
12	4-ClC ₆ H ₄	4l	4	95	154–156	6l	4	92	164–166
13	4-FC ₆ H ₄	4m	6	93	132–134	6m	6	91	136–138
14	1-Naphthyl	4n	6	89	158–160	-	-	-	-

^a Isolated yield.

The arbitrary atom numbering of heptacyclic cage compounds **4** and **6** are shown in Scheme 2. The structures of cage compounds **4** and **6** were elucidated using Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopic studies (vide Supplementary Materials) as discussed for **4i**. In the IR spectrum, the absorptions at 3416, 1723, 1682 and 1594 cm⁻¹ were attributed to the O-H, C=H (arylmethylidene), C=O and C=C (aromatic ring) stretching frequency, respectively. In the ¹H-NMR spectrum of **4i**, the singlet at 6.29 ppm was readily assigned to the arylmethylidene proton (H-25) on the basis of its multiplicity. Furthermore, H-25 showed HMBCs with the carbon signal at 53.3 ppm assignable to C-12 besides showing correlation with C-10 and C-11, the *ipso* and *ortho* carbons of the *p*-methylphenyl ring. From the C,H-COSY correlation of C-12, the doublet at 3.34 ppm (*J* 17.6 Hz) and the doublet of doublets at 3.68 ppm (*J* 17.6, 2.0 Hz) was assigned to H-12a and H-12b, respectively. The other doublets at 3.43 ppm and 3.81 ppm (*J* 11.2 Hz) were due to H-24a and H-24b. The multiplet in the range 4.24–4.31 ppm was due to H-8 and the C,H-COSY assigned the carbon at 51.0 ppm to C-8. The multiplet in the range 4.65–4.69 ppm was assigned to H-7 as it showed H,H-COSY with H-8. The multiplet in the range 3.03–3.09 ppm accounting for two protons was assigned to H-4a and H-6a. The doublet of doublets at 3.21 ppm (*J* 12.0, 6.4 Hz) was assigned to H-6b, whereas H-4b appeared as multiplet in the range 4.24–4.31 ppm. The two CH₃ protons appeared as singlets at 2.23 and 2.33 ppm and the aromatic protons appeared as multiplet in the range 6.34–7.83 ppm. The carbon signals at 73.0 and 96.2 ppm was assigned to the spiro-carbons C-9 and C-2, respectively (Scheme 3). Similarly, the structure of the other heptacyclic cage-like compounds **6** was also assigned using NMR spectroscopy and X-ray crystallographic studies.

**Scheme 2.** Arbitrary atom numbering of **4** and **6**.



Scheme 3. Selected ^1H - and ^{13}C -NMR chemical shifts of **4i**.

The X-ray crystallographic study of a single crystal of **4j** (Figure 1) [33] and **6f** (Figure 2) [34] confirms the structure deduced from NMR spectroscopic studies.

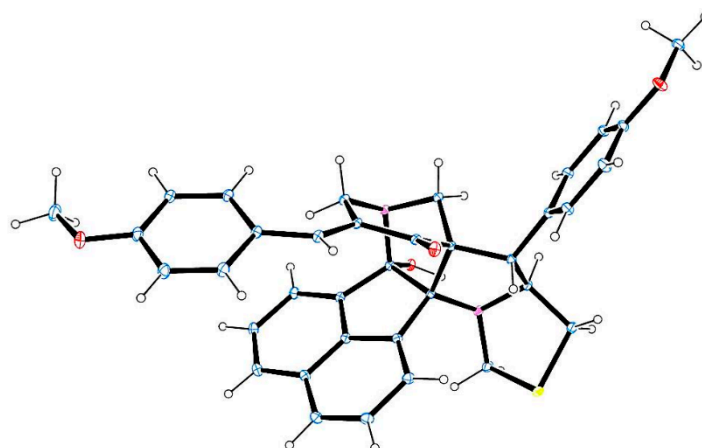


Figure 1. Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of **4j**.

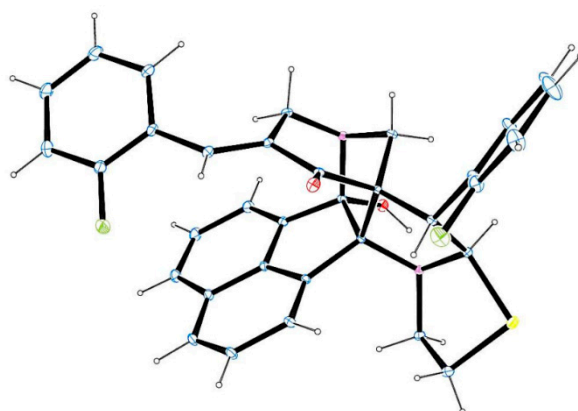
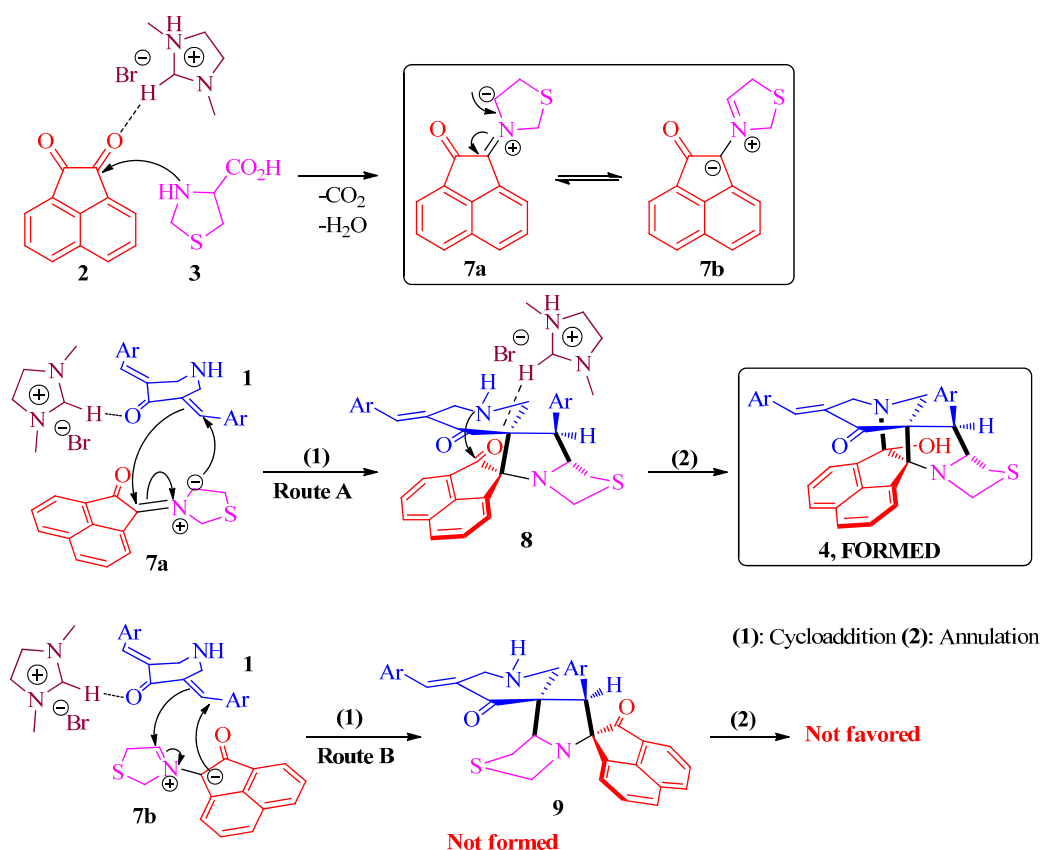


Figure 2. ORTEP diagram of **6f**.

A viable mechanism for the formation of diazaheptacycles **4** and **6** is shown in Scheme 4. Initially, the interaction of [bmim]Br with the carbonyl group of acenaphthenequinone **2** via hydrogen bonding

would increase the electrophilicity of the carbonyl carbon, facilitating the nucleophilic attack of the NH of thiaprolone **3**. Subsequent dehydration and concomitant decarboxylation furnishes azomethine ylide **7**, which may exist in the resonating forms **7a** and **7b** [35]. The interaction of [bmim]Br with the carbonyl group of 3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **1** presumably activates the exocyclic double bond, allowing the initial addition reaction with the azomethine ylide that, in principle, can take place via reaction of **7a** (route A) or **7b** (route B) with the more electron deficient β -carbon of **1** to afford the spiropyrrolothiazoles **8** or **9**, respectively. However, the exclusive formation of **4** in the above reaction proves the selective cycloaddition of **7a** with **1** via route A to form **8**. Subsequently, the interaction of [bmim]Br with the second carbonyl group of the acenaphthenequinone ring of spiropyrrolothiazole **8** presumably increases the electrophilicity of that carbonyl carbon, facilitating further annulation by the reaction of amino function of piperidone ring with the proximate carbonyl group resulting in the formation of the cage framework **4**. In addition, the cycloaddition via route B is also ruled out from the fact that the dispiro intermediate **9** may not favor the subsequent annulation step to afford cage-like compounds in view of the higher distance between the reacting groups in **9**.



Scheme 4. Probable mechanism for the formation of diazaheptacycles **4**.

3. Experimental Section

3.1. General Methods

Melting points were taken using open capillary tubes and are uncorrected. ¹H, ¹³C and two-dimensional NMR spectra were recorded on a Bruker 400 or 300 MHz instruments (Faellanden, Switzerland) in CDCl₃ using Tetramethylsilane (TMS) as internal standard. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ -scale) and the coupling constants are given in Hertz. IR spectra were recorded on a Perkin Elmer system 2000 FT-IR instrument

(KBr) (Shelton, AL, USA). Single crystal X-ray data set for **4j** and **6f** was collected on Bruker APEXII DUO CCD area detector diffractometer (Karlsruhe, Germany) with Mo K α ($\lambda = 0.71073 \text{ \AA}$) radiation. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer (Waltham, MA, USA).

3.2. General Procedure for the Synthesis of Diazaheptacyclic Cage Compounds **4a–n** or **6a–m**

An equimolar mixture of 3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone **1**, acenaphthenequinone **2** and thiaproline **3** or **5** in 100 mg of [bmim]Br was irradiated in a CEM microwave synthesizer at 100 °C for 4–8 min. After completion of the reaction (TLC), ethyl acetate (10 mL) was added and the reaction mixture stirred for 15 min. The ethyl acetate layer was then separated, washed with water (50 mL) and the solvent evaporated under reduced pressure. The resultant precipitate was dried in vacuum and subjected to crystallization from petroleum ether–ethyl acetate mixture (2:8) to obtain pure **4** or **6**. The ionic liquid [bmim]Br after extraction of the product was dried under vacuum and reused for subsequent reactions.

14-Hydroxy-8-(phenyl)-11-[(E)-phenylmethylidene]-5-thia-3,13-diazaheptacyclo-[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}] tetracos-1(22),15(23),16,18,20-pentaen-10-one (4a) White solid, 92% (0.175 g), m.p. 140–142 °C, IR (KBr) ν_{\max} 3420, 1721, 1685, 1602 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 3.03–3.12 (m, 2H, H-4a and H-6a), 3.22 (dd, $J = 12.0, 6.3 \text{ Hz}$, 1H, H-6b), 3.35 (d, $J = 17.4 \text{ Hz}$, 1H, H-12a), 3.44 (d, $J = 11.4 \text{ Hz}$, 1H, H-24a), 3.68 (dd, $J = 17.4, 1.8 \text{ Hz}$, 1H, H-12b), 3.81 (d, $J = 11.4 \text{ Hz}$, 1H, H-24b), 4.27–4.35 (m, 2H, H-4b and H-8), 4.67–4.73 (m, 1H, H-7), 6.27 (s, 1H, H-25), 6.39–6.42 (m, 2H, ArH), 7.06–7.11 (m, 3H, ArH), 7.25–7.38 (m, 4H, ArH), 7.50–7.60 (m, 5H, ArH), 7.74 (d, $J = 8.1 \text{ Hz}$, 1H, ArH), 7.83 (d, $J = 6.9 \text{ Hz}$, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 38.1, 51.4, 53.4, 56.4, 57.0, 72.7, 73.2, 96.3, 104.1, 121.6, 125.2, 126.2, 126.8, 127.8, 128.0, 128.2, 128.4, 128.8, 129.1, 129.6, 130.0, 131.2, 133.2, 134.2, 134.5, 136.2, 136.9, 137.0, 138.5, 196.7. Anal. calcd for $\text{C}_{34}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$: C, 77.24; H, 5.34; N, 5.30. Found: C, 77.39; H, 5.23; N, 5.38%.

14-Hydroxy-8-(2-methylphenyl)-11-[(E)-(2-methylphenyl)methylidene]-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}] tetracos-1(22),15(23),16,18,20-pentaen-10-one (4b) Pale yellow solid, 90% (0.165 g), m.p. 127–129 °C, IR (KBr) ν_{\max} 3422, 1725, 1680, 1598 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 1.56 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 2.98 (d, $J = 12.3 \text{ Hz}$, 1H, H-6a), 3.14 (dd, $J = 12.3, 6.3 \text{ Hz}$, 1H, H-6b), 3.32–3.44 (m, 3H, H-4a, H-12a and H-24a), 3.72 (d, $J = 17.4 \text{ Hz}$, 1H, H-12b), 3.83 (d, $J = 11.4 \text{ Hz}$, 1H, H-24b), 4.47–4.65 (m, 3H, H-4b and H-8 and H-7), 6.03 (d, $J = 7.5 \text{ Hz}$, 1H, ArH), 6.53 (s, 1H, H-25), 6.84–7.04 (m, 3H, ArH), 7.18–7.45 (m, 5H, ArH), 7.57–7.69 (m, 3H, ArH), 7.78 (d, $J = 8.1 \text{ Hz}$, 1H, ArH), 7.89 (d, $J = 6.9 \text{ Hz}$, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 19.6, 21.2, 37.2, 46.3, 52.8, 56.6, 57.4, 73.9, 74.9, 96.6, 103.8, 121.8, 125.1, 125.4, 126.1, 126.3, 126.8, 126.9, 127.7, 128.2, 128.4, 128.5, 128.9, 130.1, 131.3, 131.8, 132.7, 133.4, 134.4, 135.4, 135.8, 137.1, 137.5, 138.7, 139.3, 196.2. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_2\text{S}$: C, 77.67; H, 5.79; N, 5.03. Found: C, 77.80; H, 5.70; N, 5.12%.

14-Hydroxy-8-(2-methoxyphenyl)-11-[(E)-(2-methoxyphenyl)methylidene]-5-thia-3,13-diazaheptacyclo [13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}] tetracos-1(22),15(23),16,18,20-pentaen-10-one (4c) Pale yellow solid, 85% (0.149 g), m.p. 166–168 °C, IR (KBr) ν_{\max} 3426, 1722, 1683, 1600 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 3.03 (d, $J = 12.0 \text{ Hz}$, 1H, H-6a), 3.12 (dd, $J = 12.0, 6.3 \text{ Hz}$, 1H, H-6b), 3.28–3.40 (m, 3H, H-4a, H-12a and H-24a), 3.56 (s, 3H, OCH_3), 3.68 (dd, $J = 17.7, 2.1 \text{ Hz}$, 1H, H-12b), 3.81 (d, $J = 11.1 \text{ Hz}$, 1H, H-24b), 3.96 (s, 3H, OCH_3), 4.59–4.83 (m, 3H, H-4b and H-8 and H-7), 5.99 (dd, $J = 7.8, 1.2 \text{ Hz}$, 1H, ArH), 6.47 (s, 1H, H-25), 6.57–6.63 (m, 2H, ArH), 6.93–7.11 (m, 3H, ArH), 7.22–7.37 (m, 2H, ArH), 7.48 (dd, $J = 8.1, 1.8 \text{ Hz}$, 1H, ArH), 7.55–7.60 (m, 3H, ArH), 7.74 (d, $J = 8.1 \text{ Hz}$, 1H, ArH), 7.90 (d, $J = 6.9 \text{ Hz}$, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 37.6, 47.1, 53.1, 55.2, 56.2, 56.3, 57.6, 71.8, 73.8, 96.0, 103.5, 110.3, 112.0, 119.8, 121.1, 121.4, 123.4, 125.2, 125.5, 126.0, 126.6, 127.8, 128.3, 129.1, 129.9, 130.4, 131.3, 131.8, 131.9, 133.0, 134.5, 137.1, 138.7, 157.7, 158.9, 196.5. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.63; H, 5.39; N, 4.89%.

8-(2-Bromophenyl)-11-[(E)-(2-bromophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4d**) White solid, 91% (0.144 g), m.p. 184–186 °C, IR (KBr) ν_{\max} 3424, 1725, 1680, 1595 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_{H} 3.11 (dd, $J = 12.3, 6.3$ Hz, 1H, H-6b), 3.20 (d, $J = 12.3$ Hz, 1H, H-6a), 3.36–3.42 (m, 3H, H-4a, H-12a and H-24a), 3.68 (dd, $J = 17.7, 3.0$ Hz, 1H, H-12b), 3.82 (d, $J = 11.4$ Hz, 1H, H-24b), 4.37–5.07 (m, 3H, H-4b and H-8 and H-7), 5.82–5.87 (m, 1H, ArH), 6.51 (s, 1H, H-25), 6.93–7.00 (m, 2H, ArH), 7.12–7.18 (m, 1H, ArH), 7.27–7.50 (m, 4H, ArH), 7.57–7.76 (m, 4H, ArH), 7.82 (d, $J = 8.1$ Hz, 1H, ArH), 7.96 (d, $J = 6.9$ Hz, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃): δ_{C} 36.6, 49.3, 52.4, 56.3, 57.2, 74.0, 74.7, 96.3, 103.5, 121.6, 124.2, 125.4, 126.5, 126.9, 127.4, 127.7, 127.9, 128.2, 128.3, 128.7, 129.3, 129.5, 130.0, 131.5, 132.9, 133.7, 133.9, 134.6, 134.7, 135.3, 137.0, 137.1, 138.5, 195.3. Anal. calcd for C₃₄H₂₆Br₂N₂O₂S: C, 59.49; H, 3.82; N, 4.08. Found: C, 59.64; H, 3.70; N, 4.21%.

8-(2-Chlorophenyl)-11-[(E)-(2-chlorophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4e**) White solid, 90% (0.156 g), m.p. 146–148 °C, IR (KBr) ν_{\max} 3418, 1720, 1681, 1601 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_{H} 3.12–3.14 (m, 2H, H-6a and H-6b), 3.34–3.42 (m, 3H, H-4a, H-12a and H-24a), 3.69 (dd, $J = 17.7, 2.7$ Hz, 1H, H-12b), 3.81 (d, $J = 11.4$ Hz, 1H, H-24b), 4.39–5.06 (m, 3H, H-4b and H-8 and H-7), 5.98 (d, $J = 7.5$ Hz, 1H, ArH), 6.51 (s, 1H, H-25), 6.90–7.13 (m, 3H, ArH), 7.19–7.29 (m, 2H, ArH), 7.37–7.62 (m, 5H, ArH), 7.69 (d, $J = 8.1$ Hz, 1H, ArH), 7.80 (d, $J = 8.4$ Hz, 1H, ArH), 7.95 (d, $J = 6.9$ Hz, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃): δ_{C} 36.9, 46.5, 52.7, 56.3, 57.4, 74.0, 74.4, 96.3, 103.6, 121.6, 125.3, 126.2, 126.5, 127.3, 127.4, 128.0, 128.3, 128.7, 129.0, 129.7, 130.0, 131.2, 131.4, 132.7, 132.9, 133.7, 134.2, 134.4, 135.3, 136.6, 137.0, 138.4, 195.5. Anal. calcd for C₃₄H₂₆Cl₂N₂O₂S: C, 68.34; H, 4.39; N, 4.69. Found: C, 68.50; H, 4.48; N, 4.52%.

8-(2-Fluorophenyl)-11-[(E)-(2-fluorophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4f**) Light brown solid, 88% (0.160 g), m.p. 150–152 °C, IR (KBr) ν_{\max} 3419, 1724, 1680, 1598 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_{H} 3.02 (d, $J = 12.3$ Hz, 1H, H-6a), 3.16–3.31 (m, 3H, H-4a, H-6b and H-12a), 3.43 (d, $J = 11.1$ Hz, 1H, H-24a), 3.67 (dd, $J = 17.7, 1.8$ Hz, 1H, H-12b), 3.82 (d, $J = 11.4$ Hz, 1H, H-24b), 4.46–4.77 (m, 3H, H-4b and H-8 and H-7), 6.12–6.22 (m, 3H, H-25 and ArH), 6.76–6.86 (m, 2H, ArH), 7.08–7.31 (m, 4H, ArH), 7.51–7.62 (m, 4H, ArH), 7.79 (d, $J = 8.4$ Hz, 1H, ArH), 7.88 (d, $J = 6.9$ Hz, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃): δ_{C} 37.7, 46.3, 53.3, 56.3, 57.3, 71.6, 73.8, 96.0, 103.7, 115.5, 116.8, 121.5, 122.1, 123.6, 123.8, 124.7, 125.2, 126.2, 127.1, 127.8, 128.2, 128.5, 129.7, 130.5, 130.9, 131.2, 131.9, 134.1, 135.1, 137.0, 138.4, 159.5, 162.8, 196.2. Anal. calcd for C₃₄H₂₆F₂N₂O₂S: C, 72.32; H, 4.64; N, 4.96. Found: C, 72.20; H, 4.75; N, 4.80%.

14-Hydroxy-8-(3-nitrophenyl)-11-[(E)-(3-nitrophenyl)methylidene]-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4g**) Dark brown solid, 91% (0.154 g), m.p. 176–178 °C, IR (KBr) ν_{\max} 3424, 1716, 1686, 1616 cm^{-1} ; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 3.02–3.09 (m, 2H, H-4a and H-6a), 3.23 (d, $J = 17.6$ Hz, 1H, H-12a), 3.28 (dd, $J = 12.4, 6.4$ Hz, 1H, H-6b), 3.48 (d, $J = 11.6$ Hz, 1H, H-24a), 3.65 (dd, $J = 17.6, 2.8$ Hz, 1H, H-12b), 3.85 (d, $J = 11.6$ Hz, 1H, H-24b), 4.37–4.40 (m, 2H, H-4b and H-8), 4.75–4.80 (m, 1H, H-7), 6.16 (s, 1H, H-25), 6.69 (d, $J = 8.0$ Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.24–7.30 (m, 2H, ArH), 7.50–7.51 (m, 3H, ArH), 7.65–7.69 (m, 1H, ArH), 7.84–7.88 (m, 2H, ArH), 7.95 (d, $J = 7.6$ Hz, 1H, ArH), 7.99 (dd, $J = 8.0, 1.6$ Hz, 1H, ArH), 8.18 (dd, $J = 7.2, 1.2$ Hz, 1H, ArH), 8.46–8.48 (m, 1H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ_{C} 37.9, 50.9, 53.2, 56.4, 56.9, 72.2, 73.5, 96.3, 104.1, 121.8, 123.2, 123.3, 124.2, 124.5, 125.2, 126.2, 127.2, 128.1, 128.7, 129.2, 130.2, 131.3, 133.1, 134.1, 134.9, 135.1, 135.9, 136.0, 136.9, 138.2, 139.0, 148.0, 148.9, 196.4. Anal. calcd for C₃₄H₂₆N₄O₆S: C, 66.01; H, 4.24; N, 9.06. Found: C, 66.19; H, 4.45; N, 9.19%.

8-(2,4-Dichlorophenyl)-11-[(E)-(2,4-dichlorophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4h**) Light brown solid, 90% (0.145 g), m.p. 144–146 °C, IR (KBr) ν_{\max} 3409, 1686, 1605 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_{H} 3.07–3.16 (m, 2H, H-4a and H-6a), 3.27–3.49 (m, 3H, H-6b, H-12a and H-24a), 3.67 (dd, $J = 18.0, 3.0$ Hz, 1H, H-12b), 3.82

(d, $J = 11.4$ Hz, 1H, H-24b), 4.36–4.99 (m, 3H, H-4b, H-7 and H-8), 5.92 (d, $J = 8.4$ Hz, 1H, ArH), 6.40 (s, 1H, H-25), 6.93 (dd, $J = 8.4, 2.1$ Hz, 1H, ArH), 7.15–7.48 (m, 3H, ArH), 7.43–7.48 (m, 1H, ArH), 7.54–7.64 (m, 3H, ArH), 7.71 (d, $J = 8.1$ Hz, 1H, ArH), 7.81 (d, $J = 8.1$ Hz, 1H, ArH), 7.91 (m, $J = 6.6$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{c} 36.8, 46.1, 52.6, 56.3, 57.2, 74.0, 74.2, 96.2, 103.6, 121.6, 125.3, 126.5, 126.7, 127.4, 127.6, 128.2, 128.7, 129.1, 129.6, 130.3, 131.0, 131.1, 131.3, 131.7, 133.5, 133.8, 134.3, 134.6, 135.1, 135.2, 136.9, 137.3, 138.3, 195.3. Anal. calcd for $\text{C}_{34}\text{H}_{24}\text{Cl}_4\text{N}_2\text{O}_2\text{S}$: C, 61.28; H, 3.63; N, 4.20. Found: C, 61.46; H, 3.49; N, 4.33%.

14-Hydroxy-8-(4-methylphenyl)-11-[(E)-(4-methylphenyl)methylidene]-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (4i) Light brown solid, 93% (0.170 g), m.p. 141–143 °C, IR (KBr) ν_{max} 3416, 1723, 1682, 1594 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 2.23 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.03–3.09 (m, 2H, H-4a and H-6a), 3.21 (dd, $J = 12.0, 6.4$ Hz, 1H, H-6b), 3.34 (d, $J = 17.6$ Hz, 1H, H-12a), 3.43 (d, $J = 11.2$ Hz, 1H, H-24a), 3.68 (dd, $J = 17.6, 2.0$ Hz, 1H, H-12b), 3.81 (d, $J = 11.2$ Hz, 1H, H-24b), 4.24–4.31 (m, 2H, H-4b and H-8), 4.65–4.69 (m, 1H, H-7), 6.29 (s, 1H, H-25), 6.35 (d, $J = 8.0$ Hz, 2H, ArH), 6.88 (d, $J = 8.0$ Hz, 2H, ArH), 7.17 (d, $J = 8.0$ Hz, 2H, ArH), 7.30–7.34 (m, 1H, ArH), 7.43 (d, $J = 8.0$ Hz, 2H, ArH), 7.52–7.61 (m, 3H, ArH), 7.72 (d, $J = 8.0$ Hz, 1H, ArH), 7.82 (d, $J = 6.8$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ_{c} 21.5, 21.7, 38.1, 51.0, 53.3, 56.4, 56.8, 72.7, 73.0, 96.2, 104.1, 121.5, 125.2, 126.3, 126.7, 127.9, 128.4, 129.0, 129.4, 129.8, 130.2, 131.2, 131.5, 132.1, 133.9, 134.5, 136.5, 137.0, 137.6, 138.5, 139.2, 196.4. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_2\text{S}$: C, 77.67; H, 5.79; N, 5.03. Found: C, 77.79; H, 5.68; N, 5.12%.

14-Hydroxy-8-(4-methoxyphenyl)-11-[(E)-(4-methoxyphenyl)methylidene]-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (4j) Pale yellow solid, 87% (0.152 g), m.p. 137–139 °C, IR (KBr) ν_{max} 3422, 1720, 1684, 1600 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 3.03–3.11 (m, 2H, H-4a and H-6a), 3.22 (dd, $J = 12.0, 6.6$ Hz, 1H, H-6b), 3.34 (d, $J = 17.1$ Hz, 1H, H-12a), 3.42–3.49 (m, 1H, H-24a), 3.68–3.70 (m, 2H, H-12b and H-24b), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.23–4.30 (m, 2H, H-4b and H-8), 4.63–4.68 (m, 1H, H-7), 6.27 (s, 1H, H-25), 6.47 (d, $J = 8.7$ Hz, 2H, ArH), 6.62 (d, $J = 8.7$ Hz, 2H, ArH), 6.89 (d, $J = 8.7$ Hz, 2H, ArH), 7.31–7.36 (m, 1H, ArH), 7.45–7.63 (m, 5H, ArH), 7.71 (d, $J = 8.1$ Hz, 1H, ArH), 7.82 (d, $J = 6.9$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{c} 38.0, 50.6, 53.4, 55.6, 55.7, 56.4, 56.8, 72.7, 72.9, 96.1, 104.1, 113.8, 114.4, 121.5, 125.1, 126.2, 126.6, 127.1, 127.9, 128.3, 129.0, 130.5, 131.0, 131.2, 132.1, 134.7, 136.1, 137.0, 138.6, 159.3, 160.2, 196.7. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.31; H, 5.34; N, 4.87%.

8-(4-Bromophenyl)-11-[(E)-(4-bromophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (4k) Light brown solid, 92% (0.146 g), m.p. 171–173 °C, IR (KBr) ν_{max} 3418, 1724, 1680, 1597 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 3.00–3.06 (m, 2H, H-4a and H-6a), 3.20–3.30 (m, 1H, H-6b and H-12a), 3.44 (d, $J = 11.4$ Hz, 1H, H-24a), 3.63 (dd, $J = 17.7, 2.1$ Hz, 1H, H-12b), 3.81 (d, $J = 11.4$ Hz, 1H, H-24b), 4.22–4.29 (m, 2H, H-4b and H-8), 4.62–4.68 (m, 1H, H-7), 6.16 (s, 1H, H-25), 6.26 (d, $J = 8.4$ Hz, 2H, ArH), 7.21–7.60 (m, 10H, ArH), 7.75 (d, $J = 8.1$ Hz, 1H, ArH), 7.80 (d, $J = 6.9$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{c} 38.0, 50.7, 53.2, 56.4, 56.8, 72.4, 73.1, 96.2, 104.1, 121.7, 122.1, 123.3, 125.1, 126.3, 126.9, 128.1, 128.5, 130.4, 131.2, 131.4, 131.5, 132.2, 133.0, 133.7, 134.9, 135.9, 135.4, 136.9, 138.3, 196.5. Anal. calcd for $\text{C}_{34}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_2\text{S}$: C, 59.49; H, 3.82; N, 4.08. Found: C, 59.62; H, 3.90; N, 4.21%.

8-(4-Chlorophenyl)-11-[(E)-(4-chlorophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (4l) Brown solid, 95% (0.165 g), m.p. 154–156 °C, IR (KBr) ν_{max} 3402, 1719, 1686, 1601 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 2.99–3.04 (m, 2H, H-4a and H-6a), 3.19–3.29 (m, 2H, H-6b and H-12a), 3.43 (d, $J = 11.6$ Hz, 1H, H-24a), 3.62 (dd, $J = 17.6, 2.4$ Hz, 1H, H-12b), 3.80 (d, $J = 11.2$ Hz, 1H, H-24b), 4.23–4.27 (m, 2H, H-4b and H-8), 4.61–4.66 (m, 1H, H-7), 6.17 (s, 1H, H-25), 6.32 (d, $J = 8.4$ Hz, 2H, ArH), 7.05 (d, $J = 8.4$ Hz, 2H, ArH), 7.27–7.35 (m, 3H, ArH), 7.48 (d, $J = 8.4$ Hz, 2H, ArH), 7.55–7.69 (m, 3H, ArH), 7.73 (d, $J = 8.4$ Hz, 1H, ArH), 7.79 (d, $J = 6.8$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ_{c} 38.0, 50.7, 53.2, 56.4, 56.8, 72.4,

73.1, 96.2, 104.1, 121.7, 125.1, 126.3, 126.9, 128.1, 128.4, 128.5, 128.8, 129.3, 130.9, 131.2, 132.5, 133.6, 133.9, 134.3, 134.8, 134.9, 135.4, 136.9, 138.3, 196.5. Anal. calcd for $C_{34}H_{26}Cl_2N_2O_2S$: C, 68.34; H, 4.39; N, 4.69. Found: C, 68.45; H, 4.51; N, 4.78%.

8-(4-Fluorophenyl)-11-[(E)-(4-fluorophenyl)methylidene]-14-hydroxy-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4m**) White solid, 93% (0.169 g), m.p. 132–134 °C, IR (KBr) ν_{\max} 3416, 1682, 1601 cm^{-1} ; ¹H-NMR (400 MHz, CDCl₃): δ_H 3.02–3.09 (m, 2H, H-4a and H-6a), 3.21–3.26 (m, 1H, H-6b), 3.30 (d, $J = 17.6$ Hz, 1H, H-12a), 3.45 (d, $J = 11.2$ Hz, 1H, H-24a), 3.67 (dd, $J = 17.2, 2.0$ Hz, 1H, H-12b), 3.82 (d, $J = 11.6$ Hz, 1H, H-24b), 4.25–4.31 (m, 2H, H-4b and H-8), 4.64–4.68 (m, 1H, H-7), 6.20 (s, 1H, H-25), 6.39–6.42 (m, 2H, ArH), 6.76–6.81 (m, 2H, ArH), 7.04–7.08 (m, 2H, ArH), 7.31–7.34 (m, 1H, ArH), 7.51–7.56 (m, 3H, ArH), 7.59 (d, $J = 6.8$ Hz, 2H, ArH), 7.74 (d, $J = 8.4$ Hz, 1H, ArH), 7.81 (d, $J = 7.2$ Hz, 1H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ_C 38.0, 50.6, 53.3, 56.4, 56.9, 72.6, 73.1, 96.2, 104.1, 115.4, 116.0, 121.6, 125.1, 126.2, 126.8, 128.0, 128.4, 130.3, 131.0, 131.2, 131.9, 132.5, 133.0, 134.5, 135.0, 137.0, 138.4, 161.5, 163.9, 196.7. Anal. calcd for $C_{34}H_{26}F_2N_2O_2S$: C, 72.32; H, 4.64; N, 4.96. Found: C, 73.20; H, 4.79; N, 4.78%.

14-Hydroxy-8-(naphthyl)-11-[(E)-naphthylmethylidene]-5-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**4n**) White solid, 89% (0.149 g), m.p. 158–160 °C, IR (KBr) ν_{\max} 3423, 1721, 1684, 1590 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_H 2.96 (d, $J = 12.3$ Hz, 1H, H-6a), 3.13 (dd, $J = 12.3, 6.3$ Hz, 1H, H-6b), 3.30 (d, $J = 18.0$ Hz, 1H, H-12a), 3.41–3.52 (m, 2H, H-4a and H-24a), 3.73 (dd, $J = 18.0, 2.1$ Hz, 1H, H-12b), 3.88 (d, $J = 11.4$ Hz, 1H, H-24b), 4.66–4.77 (m, 2H, H-4b and H-7), 5.32 (d, $J = 10.2$ Hz, 1H, H-8), 6.22 (d, $J = 6.9$ Hz, 1H, ArH), 6.69 (d, $J = 8.4$ Hz, 1H, ArH), 6.93 (s, 1H, H-25), 7.11–7.91 (m, 16H, ArH), 8.15 (d, $J = 6.9$ Hz, 1H, ArH), 8.92 (d, $J = 8.7$ Hz, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃): δ_C 37.6, 44.8, 53.2, 56.6, 57.8, 73.8, 75.5, 97.0, 104.0, 121.6, 124.8, 125.0, 125.2, 125.4, 126.1, 126.3, 126.4, 127.0, 127.1, 128.1, 128.4, 128.5, 128.8, 129.2, 129.4, 131.2, 131.3, 131.4, 133.3, 133.6, 134.0, 134.1, 134.4, 134.7, 134.8, 137.2, 138.5, 196.4. Anal. calcd for $C_{42}H_{32}N_2O_2S$: C, 80.23; H, 5.13; N, 4.46. Found: C, 80.38; H, 5.29; N, 4.35%.

14-Hydroxy-8-(phenyl)-11-[(E)-phenylmethylidene]-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6a**) White solid, 93% (0.178 g), m.p. 135–137 °C, IR (KBr) ν_{\max} 3418, 1721, 1692, 1599 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_H 2.79–2.99 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.40 (d, $J = 17.4$ Hz, 1H, H-12a), 3.67 (dd, $J = 17.4, 2.7$ Hz, 1H, H-12b), 4.25 (dd, $J = 12.6, 2.1$ Hz, 1H, H-5b), 4.91 (d, $J = 6.9$ Hz, 1H, H-8), 5.70 (d, $J = 7.2$ Hz, 1H, H-7), 5.94 (brs, 1H, OH), 6.28 (s, 1H, H-25), 6.40–6.43 (m, 2H, ArH), 7.05–7.15 (m, 3H, ArH), 7.25–7.39 (m, 4H, ArH), 7.51–7.62 (m, 6H, ArH), 7.74 (dd, $J = 6.9, 2.1$ Hz, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃): δ_C 33.9, 53.1, 53.5, 53.9, 57.6, 75.2, 78.0, 95.1, 103.8, 121.7, 124.2, 126.3, 126.8, 127.8, 128.1, 128.2, 128.5, 128.9, 129.0, 129.1, 130.0, 131.2, 133.3, 134.1, 136.0, 136.5, 137.2, 137.3, 138.2, 196.4. Anal. calcd for $C_{34}H_{28}N_2O_2S$: C, 77.24; H, 5.34; N, 5.30. Found: C, 77.43; H, 5.20; N, 5.17%.

14-Hydroxy-8-(2-methylphenyl)-11-[(E)-(2-methylphenyl)methylidene]-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6b**) Pale yellow solid, 90% (0.165 g), m.p. 179–181 °C, IR (KBr) ν_{\max} 3398, 1719, 1680, 1598 cm^{-1} ; ¹H-NMR (300 MHz, CDCl₃): δ_H 1.56 (s, 3H, CH₃), 2.79–2.96 (m, 7H, CH₃, H-4a, H-4b, H-24a and H-24b), 3.23 (d, $J = 12.6$ Hz, 1H, H-5a), 3.38 (d, $J = 18.0$ Hz, 1H, H-12a), 3.77 (dd, $J = 17.7, 2.7$ Hz, 1H, H-12b), 4.63 (d, $J = 12.6$ Hz, 1H, H-5b), 5.07 (d, $J = 7.8$ Hz, 1H, H-8), 5.46 (d, $J = 8.1$ Hz, 1H, H-7), 6.06 (d, $J = 7.5$ Hz, 1H, ArH), 6.55 (s, 1H, H-25), 6.84–6.91 (m, 2H, ArH), 7.00 (d, $J = 7.2$ Hz, 1H, ArH), 7.15–7.26 (m, 3H, ArH), 7.39 (d, $J = 6.9$ Hz, 1H, ArH), 7.44 (d, $J = 7.8$ Hz, 1H, ArH), 7.56–7.62 (m, 3H, ArH), 7.67 (d, $J = 8.1$ Hz, 1H, ArH), 7.78 (dd, $J = 6.3, 2.7$ Hz, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃): δ_C 19.6, 21.0, 33.4, 50.4, 52.8, 53.1, 57.7, 75.7, 80.3, 95.5, 103.6, 121.9, 124.1, 125.4, 126.2, 126.6, 126.8, 127.4, 127.7, 128.3, 128.5, 128.6, 129.0, 130.1, 131.3, 131.7, 132.7, 133.3, 135.7, 135.9, 136.0, 137.3, 137.6, 138.5, 139.1, 195.8. Anal. calcd for $C_{36}H_{32}N_2O_2S$: C, 77.67; H, 5.79; N, 5.03. Found: C, 77.51; H, 5.91; N, 5.15%.

14-Hydroxy-8-(2-methoxyphenyl)-11-[(E)-(2-methoxyphenyl)methylidene]-6-thia-3,13-diazaheptacyclo-tetracos-1(22),15(23),16,18,20-pentaen-10-one (6c) White solid, 84% (0.147 g), m.p. 175–177 °C, IR (KBr) ν_{\max} 3416, 1721, 1681, 1601 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 2.72–2.97 (m, 4H, H-4a, H-4b, H-24a and H-24b), 3.09 (d, $J = 12.6$ Hz, 1H, H-5a), 3.26 (d, $J = 17.4$ Hz, 1H, H-12a), 3.56 (s, 3H, OCH_3), 3.62 (d, $J = 17.4$ Hz, 1H, H-12b), 3.92 (s, 3H, OCH_3), 4.62 (d, $J = 12.6$ Hz, 1H, H-5b), 5.05 (d, $J = 6.9$ Hz, 1H, H-8), 5.96 (d, $J = 6.9$ Hz, 1H, H-7), 6.01 (d, $J = 7.5$ Hz, 1H, ArH), 6.51 (s, 1H, H-25), 6.55–6.62 (m, 2H, ArH), 6.90–7.59 (m, 9H, ArH), 7.66 (d, $J = 6.6$ Hz, 1H, ArH), 7.73 (d, $J = 8.1$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 33.7, 51.8, 52.9, 53.1, 55.2, 55.9, 57.5, 75.7, 76.9, 94.6, 103.5, 110.3, 111.9, 119.8, 121.2, 121.5, 123.3, 124.4, 125.2, 126.1, 126.5, 128.0, 128.4, 129.1, 129.9, 130.5, 131.2, 132.2, 133.0, 136.3, 137.3, 138.5, 157.7, 158.5, 195.9. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.60; H, 5.32; N, 4.68%.

8-(2-Bromophenyl)-11-[(E)-(2-bromophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (6d) White solid, 92% (0.146 g), m.p. 172–174 °C, IR (KBr) ν_{\max} 3396, 1718, 1681, 1602 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 2.83–2.99 (m, 4H, H-4a, H-4b, H-24a and H-24b), 3.29 (d, $J = 12.3$ Hz, 1H, H-5a), 3.40 (d, $J = 17.7$ Hz, 1H, H-12a), 3.68 (dd, $J = 17.7, 2.7$ Hz, 1H, H-12b), 4.65 (d, $J = 12.3$ Hz, 1H, H-5b), 5.37 (d, $J = 8.4$ Hz, 1H, H-8), 5.41 (d, $J = 8.7$ Hz, 1H, H-7), 5.91–5.94 (m, 1H, ArH), 6.11 (brs, 1H, OH), 6.54 (s, 1H, H-25), 6.96–6.99 (m, 2H, ArH), 7.11–7.78 (m, 10H, ArH), 7.82 (d, $J = 7.5$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 33.4, 52.4, 53.1, 53.4, 57.4, 75.6, 79.2, 95.0, 103.4, 121.7, 124.1, 124.3, 126.6, 126.9, 127.2, 127.4, 127.8, 128.4, 128.6, 128.7, 129.3, 129.6, 130.1, 131.5, 133.0, 133.8, 134.5, 134.6, 135.2, 135.7, 136.7, 137.1, 138.3, 194.8. Anal. calcd for $\text{C}_{34}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_2\text{S}$: C, 59.49; H, 3.82; N, 4.08. Found: C, 59.32; H, 3.73; N, 4.17%.

8-(2-Chlorophenyl)-11-[(E)-(2-chlorophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (6e) White solid, 87% (0.150 g), m.p. 134–136 °C, IR (KBr) ν_{\max} 3398, 1725, 1685, 1603 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 2.83–3.02 (m, 4H, H-4a, H-4b, H-24a and H-24b), 3.25 (d, $J = 12.3$ Hz, 1H, H-5a), 3.37 (d, $J = 17.7$ Hz, 1H, H-12a), 3.69 (dd, $J = 17.7, 2.7$ Hz, 1H, H-12b), 4.64 (dd, $J = 12.3, 2.1$ Hz, 1H, H-5b), 5.39 (d, $J = 8.4$ Hz, 1H, H-8), 5.49 (d, $J = 8.1$ Hz, 1H, H-7), 6.03–6.09 (m, 1H, ArH), 6.55 (s, 1H, H-25), 6.91–7.14 (m, 3H, ArH), 7.20–7.63 (m, 8H, ArH), 7.70 (d, $J = 8.1$ Hz, 1H, ArH), 7.81 (d, $J = 7.8$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 33.6, 52.1, 53.5, 53.7, 57.6, 75.5, 79.8, 95.2, 103.6, 121.6, 124.0, 124.2, 126.5, 126.9, 127.1, 127.5, 127.8, 128.2, 128.6, 128.8, 129.5, 129.8, 130.2, 131.7, 133.1, 133.6, 134.3, 134.5, 135.1, 135.8, 136.4, 137.3, 138.6, 194.3. Anal. calcd for $\text{C}_{34}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$: C, 68.34; H, 4.39; N, 4.69. Found: C, 68.47; H, 4.30; N, 4.81%.

8-(2-Fluorophenyl)-11-[(E)-(2-fluorophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (6f) Pale yellow solid, 90% (0.163 g), m.p. 162–164 °C, IR (KBr) ν_{\max} 3418, 1724, 1690, 1599 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ_{H} 2.77–3.01 (m, 4H, H-4a, H-4b, H-24a and H-24b), 3.13 (d, $J = 12.6$ Hz, 1H, H-5a), 3.24 (d, $J = 17.7$ Hz, 1H, H-12a), 3.65 (dd, $J = 17.7, 2.1$ Hz, 1H, H-12b), 4.53 (d, $J = 12.6$ Hz, 1H, H-5b), 4.98 (d, $J = 7.2$ Hz, 1H, H-8), 5.78 (d, $J = 7.2$ Hz, 1H, H-7), 5.96 (brs, 1H, OH), 6.17–6.24 (m, 2H, ArH and H-25), 6.77–6.86 (m, 2H, ArH), 7.08–7.32 (m, 5H, ArH), 7.54–7.64 (m, 5H, ArH), 7.80 (d, $J = 7.8$ Hz, 1H, ArH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ_{C} 33.7, 50.4, 53.1, 53.4, 57.5, 57.6, 75.8, 94.7, 103.7, 115.5, 116.8, 121.6, 122.0, 123.6, 123.9, 124.2, 124.7, 126.3, 127.0, 128.0, 128.5, 129.7, 130.4, 130.5, 130.9, 131.2, 132.5, 135.2, 135.7, 137.3, 138.2, 160.2, 161.7, 195.7. Anal. calcd for $\text{C}_{34}\text{H}_{26}\text{F}_2\text{N}_2\text{O}_2\text{S}$: C, 72.32; H, 4.64; N, 4.96. Found: C, 72.47; H, 4.52; N, 4.87%.

14-Hydroxy-8-(3-nitrophenyl)-11-[(E)-(3-nitrophenyl)methylidene]-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (6g) Dark brown solid, 89% (0.150 g), m.p. 180–182 °C, IR (KBr) ν_{\max} 3416, 1719, 1694, 1601 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 2.76–3.02 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.31 (d, $J = 17.6$ Hz, 1H, H-12a), 3.67 (d, $J = 17.6$ Hz, 1H, H-12b), 4.36 (d, $J = 12.0$ Hz, 1H, H-5b), 4.97 (d, $J = 7.2$ Hz, 1H, H-8), 5.74 (d, $J = 7.2$ Hz, 1H, H-7), 6.15 (s, 1H, H-25), 6.71 (d, $J = 7.2$ Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.23–7.34 (m, 2H, ArH), 7.51–7.73 (m, 4H,

ArH), 7.88 (d, $J = 8.4$ Hz, 1H, ArH), 7.93 (d, $J = 8.0$ Hz, 1H, ArH), 8.00 (d, $J = 8.0$ Hz, 1H, ArH), 8.17–8.24 (m, 2H, ArH), 8.46 (s, 1H, ArH); ^{13}C -NMR (100 MHz, CDCl_3): δ_{C} 34.0, 48.2, 52.9, 53.3, 53.6, 57.6, 75.5, 95.0, 103.9, 121.8, 123.0, 123.3, 123.8, 124.1, 124.5, 124.9, 126.2, 127.0, 128.1, 128.8, 129.3, 130.1, 131.2, 133.2, 133.8, 134.9, 135.6, 136.2, 136.5, 138.0, 139.4, 147.9, 148.7, 196.1. Anal. calcd for $\text{C}_{34}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$: C, 66.01; H, 4.24; N, 9.06. Found: C, 66.15; H, 4.10; N, 9.21%.

8-(2,4-Dichlorophenyl)-11-[(E)-(2,4-dichlorophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6h**) Light brown solid, 91% (0.147 g), m.p. 146–147 °C, IR (KBr) ν_{max} 3380, 1723, 1690, 1601 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3): δ_{H} 2.86–2.99 (m, 4H, H-4a, H-4b, H-24a, and H-24b), 3.21 (d, $J = 12.0$ Hz, 1H, H-5a), 3.33 (d, $J = 18.0$ Hz, 1H, H-12a), 3.66 (dd, $J = 17.6$, 2.8 Hz, 1H, H-12b), 4.59 (d, $J = 12.4$ Hz, 1H, H-5b), 5.30 (d, $J = 8.4$ Hz, 1H, H-8), 5.41 (d, $J = 8.0$ Hz, 1H, H-7), 5.99 (d, $J = 8.4$ Hz, 1H, ArH), 6.43 (s, 1H, H-25), 6.94 (dd, $J = 8.4$, 2.0 Hz, 1H, ArH), 7.15–7.28 (m, 2H, ArH), 7.37 (d, $J = 8.8$ Hz, 1H, ArH), 7.45 (d, $J = 7.2$ Hz, 1H, ArH), 7.51–7.62 (m, 4H, ArH), 7.71 (d, $J = 8.4$ Hz, 1H, ArH), 7.80 (dd, $J = 6.4$, 4.0 Hz, 1H, ArH); ^{13}C -NMR (100 MHz, CDCl_3): δ_{C} 33.5, 50.4, 52.7, 53.1, 57.4, 75.6, 78.7, 95.0, 103.5, 121.7, 124.1, 126.6, 126.7, 127.4, 127.5, 128.4, 128.7, 129.6, 129.8, 130.4, 130.9, 131.0, 131.3, 132.0, 133.6, 134.3, 134.6, 135.1, 135.2, 135.3, 136.9, 137.0, 138.1, 194.8. Anal. calcd for $\text{C}_{34}\text{H}_{24}\text{Cl}_4\text{N}_2\text{O}_2\text{S}$: C, 61.28; H, 3.63; N, 4.20. Found: C, 61.15; H, 3.72; N, 4.35%.

14-hydroxy-8-(4-methylphenyl)-11-[(E)-(4-methylphenyl)methylidene]-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6i**) Orange solid, 92% (0.168 g), m.p. 190–192 °C, IR (KBr) ν_{max} 3394, 1723, 1682, 1598 cm^{-1} ; ^1H -NMR (300 MHz, CDCl_3): δ_{H} 2.23 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.79–2.97 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.40 (d, $J = 17.4$ Hz, 1H, H-12a), 3.67 (dd, $J = 17.4$, 2.8 Hz, 1H, H-12b), 4.23 (d, $J = 12.3$ Hz, 1H, H-5b), 4.87 (d, $J = 7.2$ Hz, 1H, H-8), 5.67 (d, $J = 7.2$ Hz, 1H, H-7), 6.29 (s, 1H, H-25), 6.36 (d, $J = 8.1$ Hz, 2H, ArH), 6.89 (d, $J = 7.8$ Hz, 2H, ArH), 7.15 (d, $J = 8.1$ Hz, 2H, ArH), 7.28–7.33 (m, 1H, ArH), 7.40 (d, $J = 8.1$ Hz, 2H, ArH), 7.52–7.61 (m, 4H, ArH), 7.72 (dd, $J = 6.9$, 1.8 Hz, 1H, ArH); ^{13}C -NMR (75 MHz, CDCl_3): δ_{C} 21.4, 21.7, 33.8, 53.1, 53.5, 53.7, 57.5, 75.0, 78.0, 95.0, 103.8, 121.6, 124.2, 126.3, 126.6, 128.1, 128.4, 128.9, 129.0, 129.7, 130.2, 131.2, 131.5, 132.3, 134.2, 136.1, 136.7, 137.2, 138.4, 139.2, 196.3. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_2\text{S}$: C, 77.67; H, 5.79; N, 5.03. Found: C, 77.84; H, 5.62; N, 5.16%.

14-Hydroxy-8-(4-methoxyphenyl)-11-[(E)-(4-methoxyphenyl)methylidene]-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6j**) White solid, 86% (0.150 g), m.p. 144–146 °C, IR (KBr) ν_{max} 3398, 1719, 1681, 1600 cm^{-1} ; ^1H -NMR (300 MHz, CDCl_3): δ_{H} 2.80–2.99 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.39 (d, $J = 17.4$ Hz, 1H, H-12a), 3.69 (dd, $J = 17.4$, 2.4 Hz, 1H, H-12b), 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.22 (d, $J = 12.6$, 2.1 Hz, 1H, H-5b), 4.85 (d, $J = 7.5$ Hz, 1H, H-8), 5.64 (d, $J = 7.5$ Hz, 1H, H-7), 5.95 (s, 1H, OH), 6.28 (s, 1H, H-25), 6.46 (d, $J = 8.7$ Hz, 2H, ArH), 6.62 (d, $J = 8.7$ Hz, 2H, ArH), 6.88 (d, $J = 8.7$ Hz, 2H, ArH), 7.27–7.35 (m, 1H, ArH), 7.43 (d, $J = 8.7$ Hz, 2H, ArH), 7.51–7.58 (m, 3H, ArH), 7.61 (d, $J = 6.6$ Hz, 1H, ArH), 7.71 (dd, $J = 6.3$, 2.7 Hz, 1H, ArH); ^{13}C -NMR (75 MHz, CDCl_3): δ_{C} 33.8, 53.1, 53.4, 53.5, 55.6, 55.7, 57.4, 74.9, 78.0, 95.0, 103.8, 113.8, 114.4, 121.6, 124.1, 126.3, 126.6, 127.0, 128.1, 128.4, 129.3, 130.0, 131.1, 131.2, 132.1, 136.1, 136.4, 137.2, 138.3, 159.2, 160.3, 196.3. Anal. calcd for $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.59; H, 5.32; N, 4.60%.

8-(4-Bromophenyl)-11-[(E)-(4-bromophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6k**) Brown solid, 90% (0.142 g), m.p. 156–158 °C, IR (KBr) ν_{max} 3390, 1723, 1681, 1603 cm^{-1} ; ^1H -NMR (300 MHz, CDCl_3): δ_{H} 2.83–2.95 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.34 (d, $J = 17.4$ Hz, 1H, H-12a), 3.62 (d, $J = 17.4$, 2.1 Hz, 1H, H-12b), 4.20 (d, $J = 12.6$ Hz, 1H, H-5b), 4.83 (d, $J = 7.2$ Hz, 1H, H-8), 5.63 (d, $J = 7.2$ Hz, 1H, H-7), 6.17 (s, 1H, H-25), 6.27 (d, $J = 8.4$ Hz, 2H, ArH), 7.23 (d, $J = 8.4$ Hz, 2H, ArH), 7.32–7.41 (m, 3H, ArH), 7.49 (d, $J = 8.4$ Hz, 2H, ArH), 7.56–7.61 (m, 4H, ArH), 7.72–7.76 (m, 1H, ArH); ^{13}C -NMR (75 MHz, CDCl_3): δ_{C} 33.9, 53.1, 53.4, 53.5, 57.5, 75.1, 77.6, 95.0, 103.8, 121.8, 121.9, 123.3, 124.2, 126.4, 126.8, 128.3,

128.5, 130.7, 131.2, 131.4, 131.5, 132.2, 132.9, 133.5, 135.1, 135.8, 136.2, 137.1, 138.1, 196.1. Anal. calcd for C₃₄H₂₆Br₂N₂O₂S: C, 59.49; H, 3.82; N, 4.08. Found: C, 59.40; H, 3.71; N, 4.24%.

8-(4-Chlorophenyl)-11-[(E)-(4-chlorophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6l**) Brown solid, 92% (0.160 g), m.p. 164–166 °C, IR (KBr) ν_{\max} 3357, 1719, 1682, 1605 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 2.84–2.94 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.35 (d, *J* = 17.6 Hz, 1H, H-12a), 3.63 (d, *J* = 17.6, 2.4 Hz, 1H, H-12b), 4.28 (d, *J* = 12.4 Hz, 1H, H-5b), 4.83 (d, *J* = 6.4 Hz, 1H, H-8), 5.65 (d, *J* = 6.4 Hz, 1H, H-7), 6.02 (s, 1H, OH), 6.15 (s, 1H, H-25), 6.71 (d, *J* = 7.6 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.23–7.34 (m, 2H, ArH), 7.51–7.73 (m, 4H, ArH), 7.88 (d, *J* = 8.4 Hz, 2H, ArH), 7.93 (d, *J* = 8.0 Hz, 1H, ArH), 8.00 (d, *J* = 8.0 Hz, 1H, ArH), 8.17–8.24 (m, 2H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ_{C} 33.8, 52.7, 53.0, 53.3, 57.3, 75.2, 78.2, 94.7, 103.9, 121.4, 123.8, 126.1, 126.5, 127.9, 128.2, 128.3, 128.8, 130.3, 130.9, 131.0, 132.3, 133.2, 133.9, 134.4, 134.5, 135.9, 136.0, 136.9, 138.2, 196.1. Anal. calcd for C₃₄H₂₆Cl₂N₂O₂S: C, 68.34; H, 4.39; N, 4.69. Found: C, 68.20; H, 4.57; N, 4.60%.

8-(4-Fluorophenyl)-11-[(E)-(4-fluorophenyl)methylidene]-14-hydroxy-6-thia-3,13-diazaheptacyclo[13.7.1.1^{9,13}.0^{2,9}.0^{2,14}.0^{3,7}.0^{19,23}]tetracos-1(22),15(23),16,18,20-pentaen-10-one (**6m**) Light brown solid, 91% (0.165 g), m.p. 136–138 °C, IR (KBr) ν_{\max} 3424, 1723, 1682, 1598 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 2.85–2.99 (m, 5H, H-4a, H-4b, H-5a, H-24a and H-24b), 3.35 (d, *J* = 17.6 Hz, 1H, H-12a), 3.65 (dd, *J* = 17.6, 2.4 Hz, 1H, H-12b), 4.23 (dd, *J* = 12.8, 2.4 Hz, 1H, H-5b), 4.86 (d, *J* = 7.2 Hz, 1H, H-8), 5.64 (d, *J* = 7.6 Hz, 1H, H-7), 6.20 (s, 1H, H-25), 6.39–6.43 (m, 2H, ArH), 6.77–6.82 (m, 2H, ArH), 7.03–7.08 (m, 2H, ArH), 7.27–7.34 (m, 1H, ArH), 7.48–7.62 (m, 6H, ArH), 7.75 (dd, *J* = 6.4, 2.4, 1H, ArH); ¹³C-NMR (100 MHz, CDCl₃): δ_{C} 33.9, 52.6, 53.1, 53.4, 57.6, 75.1, 77.9, 95.0, 103.8, 115.4, 115.9, 121.7, 124.1, 126.3, 126.8, 128.1, 128.4, 130.2, 130.6, 131.2, 131.9, 132.0, 133.1, 135.3, 135.9, 137.2, 138.1, 162.5, 162.9, 196.3. Anal. calcd for C₃₄H₂₆F₂N₂O₂S: C, 72.32; H, 4.64; N, 4.96. Found: C, 73.45; H, 4.73; N, 4.82%.

4. Conclusions

An efficient three-component domino protocol has been achieved for the stereoselective synthesis of novel heptacyclic cage-like compounds in ionic liquid under microwave irradiation conditions. The similar reactivity found for azomethine ylides generated from thiazolidine-2-carboxylic acid and thiazolidine-4-carboxylic acid allowed discarding any influence on dipolar cycloadditions of the well-known [36] carbanion stabilization by adjacent sulfur effect. Further studies on the synthetic applications of this methodology with diverse 1,2-diketones and α -amino acids are currently under progress in our laboratories.

Supplementary Materials: Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/21/2/165/s1>.

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Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds are available from the authors.



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